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Synthesis of 7-Fluoro-B-homo-19-norcholest-5(10)-en-3β-ol Acetate

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The synthesis of 7-fluoro-B-homo-19-norcholest-5(10)-en-3β-ol acetate (**1**) was examined by utilizing diethyl(2-chloro-1,1,2-trifluoroethyl)amine (FAR), diethylaminosulfur trifluoride (DAST), and/or hexafluoropropene-diethylamine (FPA) as fluorinating agents for cholest-5-en-3β,19-diol 3-acetate (**2**), 6β-hydroxymethyl-19-norcholest-5(10)-en-3β-ol 3-acetate (**9**), 7β-hydroxy-B-homo-19-norcholest-5(10)-en-3β-ol 3-acetate (**12**), and 3β-acetoxy-6β-hydroxy-5β,19-cyclocholestane (**13**). The treatment of **2** and **9** with these fluorinating agents gave the 7-fluoro-B-homo-5(10)-ene (**1**) in poor yield together with the cyclopropane products, 3β-acetoxy-5β,6β-methanocholest-1(10)-ene (**3**) and 3β-acetoxy-5β,6β-methanocholest-9-ene (**4**). When **12** was allowed to react with FAR at −78°C, the required **1** was produced in 43% yield. The most satisfactory result, however, was obtained by the reaction of **13** with FAR at −78°C, which afforded the 7-fluoro-B-homo-5(10)-ene (**1**) in 64% yield.

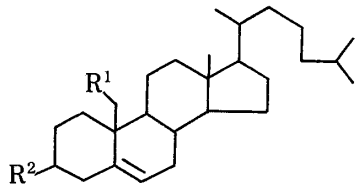
Keywords——fluorination; diethyl(2-chloro-1,1,2-trifluoroethyl)amine; diethylaminosulfur trifluoride; hexafluoropropene–diethylamine; 7-fluoro-B-homo-19-norcholest-5(10)-en-3β-ol acetate

The radioiodine-labeled analog of 6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (NCL-6-I), which is a homoallylic rearrangement product of 19-iodocholesterol, is widely used as a scintiscanning agent for the adrenal gland in clinical diagnosis.[1–3] The modification of NCL-6-I at its C_6 substituent, with the object of improving adrenal affinity, was carried out, leading to the 6β-chloromethyl and 6β-bromomethyl analogs.[4] Other structural changes have included the introduction of a methoxy group and fluorine at the C_3 position, the addition of an ethyl group at the C_{24} position, and configurational change of the C_3 hydroxy group.[5] ^{18}F-Labeled radiopharmaceuticals have also attracted considerable interest because of the short physical half-life of ^{18}F ($T_{1/2}$=110 min, β^+ decay) and its ability to be imaged with positron imaging equipment. Therefore, 19-norcholesterol analogs labeled with this nuclide are expected to have diagnostic value in the adrenals. Thus, 6β-fluoromethyl-19-norcholest-5(10)-en-3β-ol (NCL-6-F) was an obvious candidate for synthesis with ^{18}F, but our initial attempts to prepare NCL-6-F by the reaction of 6β-*p*-toluenesulfonyloxymethyl-19-norcholest-5(10)-en-3β-ol with potassium fluoride, cesium fluoride or tetrabutylammonium fluoride in various solvents were unsuccessful.

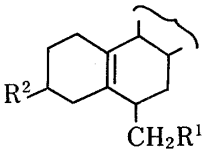
Diethyl(2-chloro-1,1,2-trifluoroethyl)amine (FAR)[6] and diethylaminosulfur trifluoride (DAST)[7] are known as mild fluorinating agents which can replace a hydroxy group with a fluorine atom, and the reaction of 19-hydroxy-5-ene steroids with FAR has been reported to afford the 7-fluoro-B-homo-5(10)-ene derivative together with two kinds of cyclopropane products, 5β,6β-methano-1(10)-ene and 5β,6β-methano-9-ene derivatives.[8,9] Therefore, we turned our attention to the preparation of 7-fluoro-B-homo-19-norcholest-5(10)-en-3β-ol acetate (**1**) from readily accessible cholest-5-en-3β,19-diol 3-acetate (**2**)[10] by using FAR and DAST.

Treatment of **2** with an excess of FAR in dry methylene chloride at room temperature for 24 h gave a mixture of the cyclopropane products (40%), 5β,6β-methano-1(10)-ene (**3**) and 5β,6β-methano-9-ene (**4**), accompanied by a complex mixture of unidentified products. The structures of **3** and **4** were determined by conversion into the corresponding alcohols **5** and

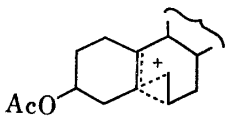
6 after hydrolysis (see Experimental section), because an attempt to obtain pure **3** and **4** from the reaction mixture was unsuccessful. When the same reaction was carried out at lower temperature (−20°C or −78°C), the desired **1** was produced in modest yield together with **3** and **4** and/or the chlorofluoroacetate ester (**7**) in the yields listed in Table I. On the other hand, the use of DAST instead of FAR failed to increase the yield of **1**.



2: R^1=OH, R^2=OAc
7: R^1=OCOCHClF, R^2=OAc
8: R^1=OCOCHFCF$_3$, R^2=OAc



9: R^1=OH, R^2=OAc
10: R^1=OH, R^2=OH
11: R^1=OAc, R^2=OAc



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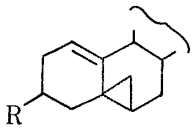
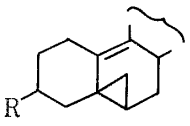
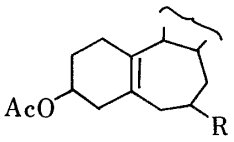


3: R=OAc
5: R=OH



4: R=OAc
6: R=OH



1: R=F
12: R=OH

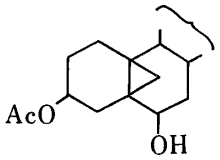


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Chart 1

TABLE I. Fluorination of Steroidal Alcohols (**2**, **9**, **12** and **13**) with FAR, DAST and FPA[a]

Compound	Fluorinating agents	Temp. (°C)	Time (h)	Products (%)[b]				
				1	**3**	**4**	**7**	**8**
2	FAR	r.t.	24		21	19		
2	FAR	−20	24	38[c]	18	11		
2	FAR	−78	48	18	27	15	6[c]	
2	DAST	3	24	10	31	14		
2	FPA	r.t.	48	5	24	7		25[c]
9	FAR	−20	24	35[c]	14	8		
9	DAST	3	24	23	32	12		
12	FAR	−78	48	43[c]	9	6		
13	FAR	−78	48	64[c]	8	15		

a) All reactions were carried out in dry methylene chloride. FAR: diethyl(2-chloro-1,1,2-trifluoroethyl)amine. DAST: diethyl aminosulfur trifluoride. FPA: reaction products of hexafluoropropene and diethylamine.[11]
b) Yields were calculated from the ^{1}H NMR spectra of mixtures, unless otherwise noted.
c) Isolated yields.
r.t., room temperature.

Recently hexafluoropropene–diethylamine (FPA)[11] has been introduced as a mild fluorinating agent for alcohol under neutral conditions. We were thus prompted to examine the use of this reagent with **2**, but the result was again disappointing, giving only 5% yield of **1**, together with **3** and **4** in addition to the 19-tetrafluoropropionate (**8**).

Our second attempt at the synthesis of the 7-fluoro-B-homo-5(10)-ene (**1**) utilized 6β-hydroxymethyl-19-norcholest-5(10)-en-3β-ol 3-acetate (**9**) as a steroidal alcohol. The compound **9** was prepared by the following sequence of reactions; solvolysis of cholest-5-en-3β,19-diol 19-toluene-*p*-sulfonate[10] in Ac_2O–AcOH followed by basic hydrolysis of the crude acetate

led to the isolation of 6β-hydroxymethyl-19-norcholest-5(10)-en-3β-ol (**10**) in 68% yield, and on acetylation this gave the diacetate (**11**). The required **9** was obtained by the selective hydrolysis of **11** in the presence of one equivalent of NaOH in 29% yield. Treatment of **9** with FAR at −20°C or DAST at 3°C in dry methylene chloride led to the formation of the 7-fluoro-B-homo-5(10)-ene (**1**) and the cyclopropane products (**3** and **4**), as shown in Table I, though the yield of **1** could not be improved.

As described above, the yield of the 7-fluoro-B-homo-5(10)-ene (**1**) obtained by the action of FAR, DAST, or FPA on both the 19-hydroxy-5-ene (**2**) and the 6-hydroxymethyl-5-(10)-ene (**9**) was too low for the method to be of preparative value, apparently owing to the predominant formation of **3** and **4**. Furthermore, these approaches are extremely difficult to use as procedures to obtain useful amounts of ^{18}F-labeled 7-fluoro-B-homo-5(10)-ene (**1**). The use of a fluorinating agent such as FAR or DAST, however, is attractive for the preparation of an ^{18}F-labeled steroid. In a further attempt to obtain a satisfactory yield of **1** based on the use of FAR, our attention was next directed to the use of 7β-hydroxy-B-homo-19-norcholest-5(10)-en-3β-ol 3-acetate (**12**) and 3β-acetoxy-6β-hydroxy-5β,19-cyclocholestane (**13**) as steroidal alcohols. These steroids were prepared by solvolytic reaction of cholest-5-en-3β,19-diol 3-acetate 19-toluene-*p*-sulfonate[10] and 19-iodocholest-5-en-3β-ol acetate,[12] respectively, as described in the Experimental section.

When the 7-hydroxy-B-homo-5(10)-ene (**12**) was allowed to react with FAR at −78°C for 48 h, the 7-fluoro-B-homo-5(10)-ene (**1**) was produced in 43% yield together with **3** and **4**. Furthermore, the transformation to the 7-fluoro-B-homo-5(10)-ene (**1**) was achieved in 64% yield by treatment of **13** with FAR at −78°C for 48 h. The yield of **1** was significantly improved by the use of **13**, which is readily accessble in five steps from cholesterol acetate. Thus, this route provide a useful method to label the 7-fluoro-B-homo-5(10)-ene (**1**) with ^{18}F.

In view of the reactivity of the steroidal alcohols (**2**, **9**, **12**, and **13**), the fact that **1**, **3**, and **4** were commonly produced by all the reactions described here implies the intervention of a well known homoallylic cation such as **14** under the present conditions, as was suggested.[8,9,13] The formation of **1** may occur by the low energy pathway involving nucleophilic attack of the fluoride anion on the original C_6 position of **14**. A study on the labeling of **1** with ^{18}F is in progress.

Experimental

All melting points are uncorrected. The ^{1}H nuclear magnetic resonance (NMR) spectra were obtained with a JNM PS-100 spectrometer for solutions in $CDCl_3$ with tetramethylsilane as an internal reference. The mass spectra (MS) were measured with a JEOL-JMS-OISG mass spectrometer. The infrared (IR) spectra were taken on a JASCO DS-701G spectrometer. The ultraviolet (UV) spectra were measured with a Hitachi 139 UV-VIS spectrometer. Optical rotations were determined with a JASCO DIP-SL automatic polarimeter. Elemental analyses were performed by the staff of the microanalytical section of Kyushu University. Column chromatography was carried out on silica gel (200 mesh, Kanto Chemical Co., Japan) with the solvent system specified. Organic extracts were dried over sodium sulfate and solvents were removed under reduced pressure on a rotary evaporator.

6β-Hydroxymethyl-19-norcholest-5(10)-en-3β-ol (**10**)——A solution of 556 mg of cholest-5-en-3β,19-diol 19-toluene-*p*-sulfonate[10] in 1 ml of acetic anhydride and 20 ml of acetic acid was heated with stirring at 95—100°C for 70 min and poured into ice water. The mixture was extracted with ether. The ether extract was washed with 5% K_2CO_3 and water, then dried. After removal of the ether, 485 mg of residue was obtained. The residue was dissolved in 20 ml of dioxane, and a solution of NaOH (264 mg) in 20% aqueous methanol (25 ml) was added under cooling in an ice-bath. The mixture was stirred for 24 h at room temperature, then evaporated to dryness. The residue was extracted with ether and the extract was washed with water and dried. After removal of the solvent, the residue was chromatographed on silica gel using chloroform–acetone (95: 5) as the eluent to give 274 mg (68%) of **10** as a colorless solid, after recrystallization from acetone, mp 141—142°C. IR ν_{max}^{KBr} cm^{-1}: 3320 (OH). ^{1}H NMR δ: 0.64 (3H, s, 18-CH_3), 1.96 (2H, m, 3-OH and 6-CH_2OH, D_2O-exchangeable), 3.64 (2H, m, 6-CH_2), 3.96 (1H, m, 3-H). *Anal.* Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.32; H, 11.67.

6β-Hydroxymethyl-19-norcholest-5(10)-en-3β-ol Diacetate (11)——A solution of 133 mg of **10** in 3 ml of dry pyridine containing 0.3 ml of acetic anhydride was stirred overnight at room temperature and poured into ice water. The mixture was extracted with ether and the extract was washed with 5% K_2CO_3 and water, then dried. After removal of the ether, the residue was chromatographed on silica gel with benzene–petroleum ether (1: 1) to give 140 mg (87%) of **11** as colorless needles, mp 68—69°C. IR ν_{max}^{KBr} cm^{-1}: 1743, 1740 (CO). ^1H NMR δ: 0.75 (3H, s, 18-CH_3), 1.97 (3H, s, OCOCH_3), 1.99 (3H, s, OCOCH_3), 4.01 (2H, m, 6-CH_2), 4.70 (1H, m, 3-H). MS *m/e*: 486 (M^+). *Anal.* Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.43; H, 10.32.

6β-Hydroxymethyl-19-norcholest-5(10)-en-3β-ol 3-Acetate (9)——A solution of 1.10 g of **11** and 90 mg of NaOH in 20 ml of ethanol–ether (1: 1) containing 0.3 ml of water was stirred for 2 h at room temperature. After most of the solvent had been removed, the residue was extracted with ether and the extract was washed with water, dried, and concentrated. The resulting oil was chromatographed on silica gel with benzene–chloroform (9: 1) to afford 340 mg (29%) of **9** as an oil, which crystallized on standing, mp 89—90°C. IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1735 (CO). ^1H NMR δ: 0.70 (3H, s, 18-CH_3), 2.00 (3H, s, OCOCH_3), 3.58 (2H, m, 6-CH_2), 4.88 (1H, m, 3-H). MS *m/e*: 444 (M^+). *Anal.* Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.11; H, 10.62.

7β-Hydroxy-B-homo-19-norcholest-5(10)-en-3β-ol 3-Acetate (12)——A solution of 536 mg of cholest-5-en-3β,19-diol 3-acetate 19-toluene-*p*-sulfonate[10] in 25 ml of acetonitrile containing 5 ml of water was gently refluxed for 1 h. After removal of the solvent, the residue was extracted with ether and the extract was washed with water, dried, and concentrated. The residue was chromatographed on silica gel with ethyl acetate–*n*-hexane (1: 6) as the eluent to give 330 mg (88%) of **12** as colorless needles, mp 47—48°C. $[\alpha]_D^{18}$ −62.3° (*c*=0.55, cyclohexane). IR ν_{max}^{Nujol} cm^{-1}: 3380 (OH), 1740 (CO). ^1H NMR δ: 0.72 (3H, s, 18-CH_3), 2.04 (3H, s, OCOCH_3), 4.02 (1H, m, 7-H), 4.72 (1H, m, 3-H). *Anal.* Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 77.80; H, 10.84.

3β-Acetoxy-6β-hydroxy-5β,19-methanocholestane (13)——A solution of 534 mg of 19-iodocholest-5-en-3β-ol acetate[12] in 90 ml of acetone containing 6.4 ml of water was stirred at room temperature in the presence of 325 mg of silver carbonate for 90 min in the dark. The mixture was filtered through celite and concentrated. The residue was extracted with ether and the extract was washed with water and dried. After removal of the ether, the residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (6: 1) to give crude **13**. The ^1H NMR spectrum of the crude **13** suggested the presence of a small amount of the 6α-isomer of **13**[13] [δ 3.76 (m, $W_1/_2$=14 Hz, 6-H)]. Recrystallization of the crude **13** from acetonitrile gave 312 mg (73%) of pure **13** as colorless needles, mp 108—109°C. $[\alpha]_D^{17}$ +57° (*c*=1.00, cyclohexane). IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1730 (CO). ^1H NMR δ: 0.28 (1H, d, *J*=5 Hz, cyclopropyl proton), 0.64 (3H, s, 18-CH_3), 2.01 (3H, s, OCOCH_3), 4.11 (1H, m, $W_1/_2$=6 Hz, 6-H), 4.72 (1H, m, 3-H). *Anal.* Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.36; H, 10.86.

Reaction of Cholest-5-en-3β,19-diol 3-Acetate (2) **with Diethyl(2-chloro-1,1,2-trifluoroethyl)amine (FAR)**——A) A mixture of 500 mg of **2**, 1 ml of FAR, and 30 ml of dry methylene chloride was allowed to stand for 24 h at room temperature. The reaction mixture was poured into ice water and extracted with methylene chloride. The extracts were washed with 5% K_2CO_3 and water, then dried. After removal of the solvent, the residue was chromatographed on silica gel with benzene–petroleum ether (1: 1) as the eluent to give 194 mg of a mixture of 3β-acetoxy-5β,6β-methanocholest-1(10)-ene (**3**) and 3β-acetoxy-5β,6β-methanocholest-9-ene (**4**) as an oil. The ^1H NMR spectrum of the oil showed characteristic signals at δ 0.63 (s, 18-CH_3), 0.67 (s, 18-CH_3), 1.97 (s, OCOCH_3), 4.99 (br m, 3-H), and 5.36 (m, olefinic). The mixture was dissolved in 20 ml of ethanol containing 100 mg of KOH and 2 ml of water, and the whole was stirred for 6 h at room temperature, then concentrated. The residue was extracted with ether and the ether was washed with water and dried. The ether was removed, and the residue was chromatographed on silica gel with benzene–chloroform (9: 1) as the eluent. The first fraction gave 3β-hydroxy-5β,6β-methanocholest-1(10)-ene (**5**) (84 mg) as needles, after recrystallization from methanol, mp 139—140°C. $[\alpha]_D^{18}$ +36° (*c*=0.53 cyclohexane). UV $\lambda_{max}^{cyclohexane}$ nm (ε): 210 (5460). IR ν_{max}^{KBr} cm^{-1}: 3280 (OH). ^1H NMR δ: 0.61 (3H, s, 18-CH_3), 4.14 (1H, m, 3-H), 5.46 (1H, m, olefinic). *Anal.* Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.40; H, 11.38. Further elution with the same solvent system gave 3β-hydroxy-5β,6β-methanocholest-9-ene (**6**) (67 mg) as needles, after recrystallization from methanol, mp 96—97°C. $[\alpha]_D^{24.5}$ +29.4° (*c*=0.37, cyclohexane). UV $\lambda_{max}^{cyclohexane}$ nm (ε): 220 (10300). IR ν_{max}^{KBr} cm^{-1}: 3340 (OH). ^1H NMR δ: 0.69 (3H, s, 18-CH_3), 1.72 (1H, s, 3-OH), 4.14 (1H, m, 3-H). *Anal.* Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.38; H, 11 64.

B) A mixture of 500 mg of **2**, 1 ml of FAR, and 10 ml of dry methylene chloride was allowed to stand for 24 h at −20°C. Work-up was carried out as described in part A and the resulting oil was chromatographed on silica gel with benzene–petroleum ether (1: 3). The first fraction gave a mixture of **3** and **4** (141 mg) as characterized by ^1H NMR spectroscopy, and the ratio of **3** and **4** was estimated from the spectrum. The analysis consisted of determining the ratio of the areas under the signals due to the olefinic proton of **3** (δ 5.36) and the C_{18} methyl protons of **3** and **4** (δ 0.63 and 0.67). Further elution with the same solvent system gave 189 mg (38%) of 7-fluoro-B-homo-19-norcholest-5(10)-en-3β-ol acetate (**1**) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1743 (CO). ^1H NMR δ: 0.72 (3H, s, 18-CH_3), 1.99 (3H, s, OCOCH_3), 4.64 (1H, dm, J_{HF}= 50 Hz, 7-H), 4.80 (1H, m, 3-H). *Anal.* Calcd for $C_{29}H_{47}FO_2$: C, 77.98; H, 10.61. Found: C, 77.66; H, 10.46.

C) A mixture of 320 mg of **2**, 1 ml of FAR, and 10 ml of dry methylene chloride was allowed to stand for 48 h at −78°C. After work-up as described in part A and chromatography on silica gel with benzene–petroleum ether (1: 1) as the eluent, the first fraction gave 184 mg of a mixture of **1** (18%), **3** (27%), and **4** (15%). The yields were calculated from the ^{1}H NMR spectrum of the mixture by integration of the C_{18} methyl protons (δ 0.63, 0.67 and 0.72) and the olefinic proton (δ 5.36) as described in part B. Further elution with the same solvent system gave 23 mg of cholest-5-en-3β,19-diol 3-acetate 19-chlorofluoroacetate (**7**) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1765, 1745 (CO). ^{1}H NMR δ: 0.68 (3H, s, 18-CH_3), 1.96 (3H, s, $OCOCH_3$), 4.10 and 4.65 (2H, dd, J=12, 4 Hz, 19-CH_2), 4.50 (1H, m, 3-H), 5.64 (1H, m, olefinic), 6.15 (1H, d, J=50 Hz, 19-OCOCHFCl). MS *m/e*: 538 (M^+). *Anal.* Calcd for $C_{31}H_{48}ClFO_4$: C, 69.19; H, 8.99. Found: C, 69.34; H, 9.13.

Reaction of Cholest-5-en-3β,19-diol 3-Acetate (2) with Diethylaminosulfur Trifluoride (DAST)——A mixture of 312 mg of **2**, 0.5 ml of DAST[7] and 10 ml of dry methylene chloride was allowed to stand for 24 h at 3°C in a refrigerator. After work-up as described above, chromatography of the mixture on silica gel with benzene–petroleum ether (1: 1) as the eluent gave 167 mg of a mixture of **1** (10%), **3** (31%), and **4** (14%). The yields were calculated from the ^{1}H NMR spectrum.

Reaction of Cholest-5-en-3β,19-diol 3-Acetate (2) with Hexafluoropropene-diethylamine (FPA)——A solution of 500 mg of **2** and 1.5 ml of FPA[11] in 10 ml of dry methylene chloride was allowed to stand for 48 h at room temperature. After the same procedure as described above, the mixture was chromatographed on silica gel with benzene–petroleum ether (2: 1). The first fraction gave 188 mg of a mixture of **1**, **3** and **4** in the yields listed in Table 1. The second fraction gave cholest-5-en-3β,19-diol 3-acetate 19-(1,1,1,2-tetrafluoro)propionate (**8**) (161 mg) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1765, 1740 (CO). ^{1}H NMR δ: 0.68 (3H, s, 18-CH_3), 1.98 (3H, s, $OCOCH_3$), 4.20 (1H, d, J=12 Hz, one proton of 19-CH_2), 4.88 (2H, m, 3-H and one proton of 19-CH_2), 4.75 and 5.23 (1H, dm, J=50 Hz, $OCOCHFCF_3$), 5.65 (1H, m, olefinic). *Anal.* Calcd for $C_{32}H_{47}F_4O_4$: C, 67.22; H, 8.30. Found: C, 67.58; H, 8.19.

Reaction of 6β-Hydroxymethyl-19-norcholest-5(10)-en-3β-ol 3-Acetate (9) with FAR and DAST——A) A mixture of 316 mg of **9**, 1 ml of FAR, and 10 ml of dry methylene chloride was allowed to stand for 24 h at −20°C. After work-up as described for the reaction of **2** with FAR, the yellowish oil was chromatographed on silica gel with benzene–petroleum ether (1: 2). The first fraction gave a mixture of **3** (14%) and **4** (8%) (67 mg) as characterized by ^{1}H NMR spectroscopy. Further elution with the same solvent system gave 110 mg of **1** (35%) as a colorless oil.

B) The reaction of **9** with DAST at 3°C for 24 h was carried out by the same procedure as described in part A, and the yields are shown in Table I.

Reaction of 7β-Hydroxy-B-homo-19-norcholest-5(10)-en-3β-ol 3-Acetate (12) with FAR——A mixture of 370 mg of **12**, 0.3 ml of FAR, and 5 ml of dry methylene chloride was allowed to stand for 48 h at −78°C. After work-up as described for the reaction of **2** with FAR, the yellowish oil was chromatographed on silica gel with benzene–petroleum ether (1: 3). The first fraction gave 54 mg of a mixture of **3** and **4**. The second fraction gave 161 mg of **1** (43%), which was identical with **1** obtained by the reaction of **9** with FAR.

Reaction of 3β-Acetoxy-6β-hydroxy-5β,19-cyclocholestane (13) with FAR——A mixture of 70 mg of **13**, 0.3 ml of FAR, and 5 ml of dry methylene chloride was allowed to stand for 48 h at −78°C. After work-up as described for the reaction of **2** with FAR, the resulting oil was chromatographed on silica gel with benzene–petroleum ether (1: 3). The first fraction gave 16 mg of a mixture of **3** and **4**. The second fraction gave 45 mg of **1** (64%) as a colorless oil, which was identical with **1** obtained by the reaction of **2** with FAR.

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