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Synthesis of γ-Lactone Ring Fused to Steroidal Ring D of Salamander Alkaloids

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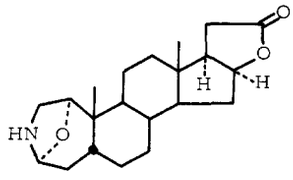
Synthesis of steroids with a γ-lactone ring fused to ring D is described with a view to total synthesis of the salamander alkaloids such as samandaridine (**1**) and cycloneosamandaridine (**2**) and its revised structure **3**. Reformatsky reaction of 3β,16β-diacetoxy-5-androsten-17-one (**4**) with methyl bromoacetate gave 17α-substituted ester **6a**. Dehydration and catalytic hydrogenation of **6b** afforded 17β-substituted ester **10**, which was cyclized to give 3β-acetoxy-16β-hydroxy-5α-pregnan-21-oic acid γ-lactone (**11**). The same product was obtained from 16α-acetoxy ketone **12**. In this case, cyclization of hydroxy carboxylic acid **17b** proceeded under more vigorous conditions of high temperature and strong acid catalysis.

The biologically active salamander alkaloids[1] consist of steroidal ring systems which are distinguished by a nitrogen-containing ring A and substituents on ring D. Previous synthetic studies have been concerned with the construction of the ring A. However, little effort has been devoted to the introduction of ring D substituents. Conversion of samandarone to samandaridine (**1**) by Habermehl[2] and our



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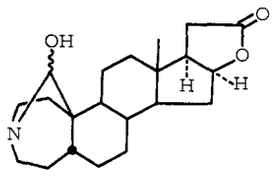

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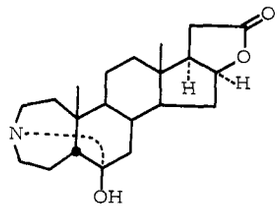

3

transformation of the 17-oxo function to the 16 position in the total synthesis of samandarone[3] are rare instances. The five-membered lactone ring fused to ring D of samandaridine (**1**) has been derived from a steroid which contains an oxygen function at the 16 position, but not from the normal 17-oxo steroid. Our purpose of synthesis and confirmation of the proposed structure of cycloneosamandaridine (**2**)[4] required stereospecific construction of this β-oriented γ-lactone ring. In this paper we wish to report the preparation of 3β-acetoxy-16β-hydroxy-5α-pregnan-21-oic acid γ-lactone (**11**) from both 3β,16β-diacetoxy-5-androsten-17-one (**4**)[5] and 3β,16α-diacetoxy-5α-androstan-17-one (**12**).[6] The results mentioned in this paper were useful for our synthesis of structure **2**, earlier assigned to cycloneosamandaridine, and will also be applicable to the synthesis of the newly proposed structure **3**.[7]

Reformatsky reaction of 16α- and 16β-acetoxy-17-oxo steroids with methyl bromoacetate was considered to be a suitable method for preparation of the two carbon unit attached to the 17 position.[8] The use of both C-16 isomers seemed indispensable for proving the stereochemistry of the fused γ-lactone ring at the late stage of our sequence, as it would be difficult to determine the configuration at position 17 by spectroscopic means before and after the lactonization.

Reformatsky reaction of **4**, which was obtained from dehydroepiandrosterone,[5] with methyl bromoacetate afforded two glycols. The less polar glycol **5a** was easily converted to an acetonide **7** and a diacetate **5b**. The NMR spectrum of **5a** exhibited a one-proton singlet at 3.23 ppm, while in **5b** this signal was observed in the lower field at 4.47 ppm. The most likely explanation for **5a** is methoxycarbonylmethylation from the less hindered 16α side after the regioisomerization of **4**, with the configuration of the vicinal hydroxyl groups having a β cis relationship. The more polar glycol **6a** showed a triplet at 3.90 ppm which was attributed to the 16α hydrogen. This compound was readily converted to an acetonide **8** and a diacetate **6b**, wherein the resonance attributed to the 16α hydrogen shifted downfield to 4.90 ppm (quartet). These facts clearly showed the glycol **6a** to be the desired 17α-substituted derivative.

Dehydration of **6b** was achieved to afford an unsaturated ester **9**. Although the details of the geometrical isomerism are not clearly known, **9** consisted of one isomer and showed a one-proton doublet at 5.66 ppm which was attributed to an olefinic hydrogen adjacent to the carboxyl group. Catalytic hydrogenation of **9** gave **10**. It is reasonable to assume that the stereochemistry is 5α as is usually the case in steroid chemistry.[9] Hydrogenolysis at the 17 position must have proceeded by means of the less hindered α-site attack. This is further confirmed by the next stage of the sequence where the lactonization between the 16β-hydroxyl group and the γ-carboxylic group proceeded quite readily. Thus, **10** was hydro-

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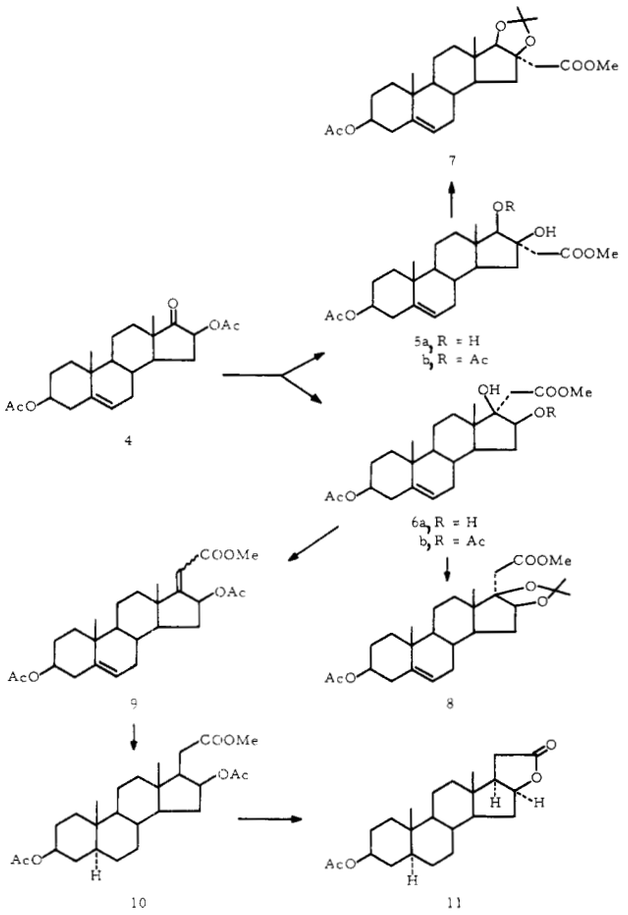
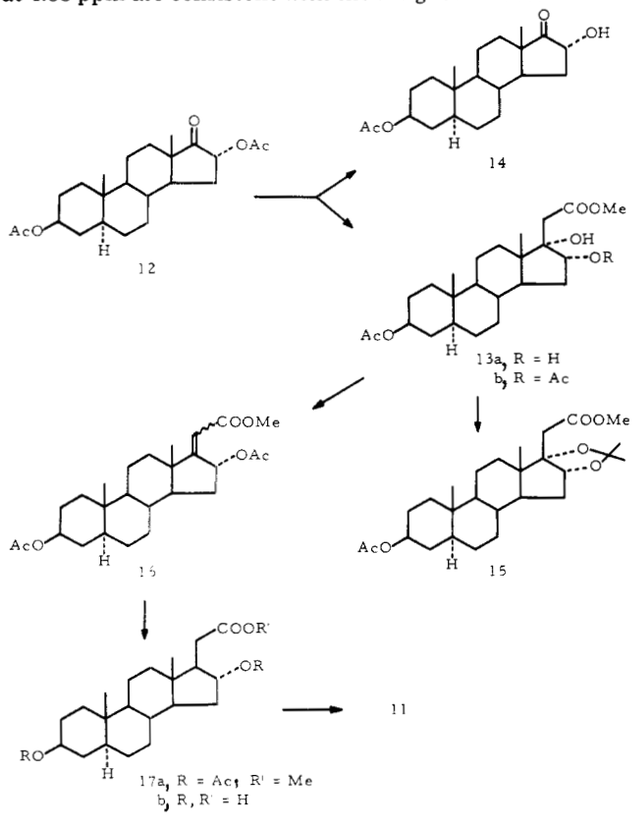


lyzed to achieve an immediate lactonization which was easily observed on TLC in terms of a considerable increase in R_f value. Isolation of the seco carboxylic acid failed. Reacetylation of the 3β-hydroxyl group gave a γ-lactone **11.** The carbonyl stretching band at 1770 cm^{-1} and the signals of the 20-methylene hydrogens at 2.45 ppm and the 16α-hydrogen at 4.88 ppm are consistent with the assigned structure.



Our next objective was the preparation of a γ-lactone from the 16α-acetoxy ketone **12,** which was prepared from epiandrosterone.[6] Reformatsky reaction of **12** gave the desired glycol **13a** and a small amount of a ketol **14.** The structure of the latter product was identified by reacetylation to **12.** Formation of an acetonide **15** from **13a** showed clearly that the vicinal hydroxyl groups are in a cis relationship and that the alkyl substituent at position 17 is β oriented.

The acetate **13b** prepared from **13a** was dehydrated to give an unsaturated ester **16.** The signal of an olefinic proton at 5.69 ppm showed that the material consisted of one geometrical isomer. Catalytic hydrogenation of **16** afforded **17a,** of which the configuration at the 17 position was assigned as β owing to the fact that a hydroxy carboxylic acid **17b** was fairly stable at room temperature and did not afford a lactone in spite of the presence of mineral acid. The lactonization of **17b** was achieved by refluxing in acetic acid containing hydrogen chloride to give the γ-lactone **11,** which was identified with the sample prepared from the 16β-acetoxy ketone described above. This resistance to lactonization indicated an inconvenient configuration of the vicinal substituents of **17b.** It is probable that the participation by the γ-carboxy group may promote the cyclization to the 5,5 system with 16,17 cis orientation.

Thus, our purpose to construct the β-oriented γ-lactone ring on steroidal ring D was complete, and the method has been applied to the total synthesis of the proposed structure of cycloneosamandaridine (**2**).[7] This method will be also applicable to the synthesis of samandaridine (**1**) and the revised structure of cycloneosamandaridine (**3**).

Experimental Section

IR spectra were taken on a Hitachi EPR-50 spectrometer using KBr tablets and are given in cm^{-1}. NMR spectra were determined in $CDCl_3$ on a JEOL-4H-100 spectrometer; chemical shifts are given in ppm from Me_4Si. Melting points were obtained on a Yanagimoto apparatus and are uncorrected. Microanalyses were performed by Microanalytical Center, Tokyo College of Pharmacy.

Reformatsky Reaction of 3β,16β-Diacetoxy-5-androsten-17-one (4). To a solution of 500 mg of **4** in 20 mL of an absolute 1:1 mixture of Et_2O–C_6H_6 was added 1 mL of methyl bromoacetate, 800 mg of granulated zinc metal, and 20 mg of iodine. The mixture was heated at reflux temperature for 1.5 h. After cooling in ice water, 1 mL of a 1:1 mixture of MeOH–AcOH was added dropwise, and the mixture was made basic with $NaHCO_3$ solution, extracted with EtOAc, dried (Na_2SO_4), and evaporated in vacuo. The resulting oil was chromatographed on a 30 g silica gel column (1% Me_2CO in C_6H_6) to yield 103 mg of 3β-acetoxy-16β,17β-dihydroxy-16α-(methoxycarbonylmethyl)-5-androstene (**5a**). Recrystallization from *n*-hexane–EtOAc afforded 78 mg of needles: mp 157–159 °C; IR 3571, 1724 cm^{-1}; NMR 0.86 (s, 3 H), 1.02 (s, 3 H), 2.01 (s, 3 H), 2.50 (d, J = 17.5 Hz, 1 H), 2.70 (d, J = 17.5 Hz, 1 H), 3.23 (s, 1 H), 4.60 (m, 1 H), 5.35 (d, J = 5.0 Hz, 1 H) ppm. Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.72.

Further elution gave 310 mg of 3β-acetoxy-16β,17β-dihydroxy-17α-(methoxycarbonylmethyl)-5-androstene (**6a**), which was recrystallized from EtOAc to give 218 mg of needles: mp 188–190 °C; IR 3597, 3509, 1727 cm^{-1}; NMR 0.88 (s, 3 H), 1.02 (s, 3 H), 2.00 (s, 3 H), 2.34 (d, J = 15.0 Hz, 1 H), 2.65 (d, J = 15.0 Hz, 1 H), 3.70 (s, 3 H), 3.90 (t, J = 6.1 Hz, 1 H), 4.60 (m, 1 H), 5.37 (d, J = 5.1 Hz, 1 H) ppm. Anal. Calcd for $C_{24}H_{36}O_6$:C, 68.54; H, 8.63. Found: C, 68.59; H, 8.77.

3β,17β-Diacetoxy-16β-hydroxy-16α-(methoxycarbonylmethyl)-5-androstene (5b). The glycol **5a** (60 mg) was acetylated with 1 mL of Ac_2O and 0.5 mL of pyridine in the usual manner. Recrystallization from a mixture of *n*-hexane–EtOAc gave 45 mg of needles: mp 203–204 °C; IR 3584, 1730 cm^{-1}; NMR 0.94 (s, 3 H), 1.00 (s, 3 H), 1.99 (s, 3 H), 2.10 (s, 3 H), 2.60 (s, 2 H), 3.63 (s, 3 H), 4.47 (s, 1 H), 4.61 (m, 1 H), 5.35 (m, 1 H) ppm. Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.83; H, 8.10.

3β,16β-Diacetoxy-17β-hydroxy-17α-(methoxycarbonylmethyl)-5-androstene (6b). The glycol **6a** (250 mg) was acetylated with 1 mL of Ac_2O and 1 mL of pyridine in the usual manner. Recrystallization from a mixture of Me_2CO–EtOAc gave 178 mg of needles: mp 181–184 °C; IR 3597, 1730, 1720 cm^{-1}; NMR 0.93 (s, 3 H), 1.01 (s, 3 H), 2.00 (s, 3 H), 2.06 (s, 3 H), 2.45 (d, J = 16.0 Hz, 1 H), 2.58 (d, J =

16.0 Hz, 1 H), 3.71 (s, 3 H), 4.59 (m, 1 H), 4.90 (q, J = 8.0 and 6.0 Hz, 1 H), 5.36 (m, 1 H) ppm. Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.49; H, 8.19.

3β-Acetoxy-16β,17β-isopropylidenedioxy-16α-(methoxycarbonylmethyl)-5-androstene (7). The glycol **5a** (20 mg) was treated with 1% HCl in Me_2CO for 30 min. Evaporation and recrystallization from n-hexane afforded 10 mg of prisms: mp 114–115 °C; IR 1736 cm^{-1}; NMR 0.88 (s, 3 H), 1.02 (s, 3 H), 1.42 (s, 3 H), 1.48 (s, 3 H), 2.02 (s, 3 H), 2.63 (d, J = 16.3 Hz, 1 H), 2.86 (d, J = 16.3 Hz, 1 H), 3.69 (s, 3 H), 3.90 (s, 1 H), 4.60 (m, 1 H), 5.36 (m, 1 H) ppm. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.28; H, 9.01.

3β-Acetoxy-16β,17β-isopropylidenedioxy-17α-(methoxycarbonylmethyl)-5-androstene (8). The glycol **6a** (20 mg) was treated with 1% HCl in Me_2CO to give **8** as a colorless oil: IR 1730 cm^{-1}; NMR 0.99 (s, 3 H), 1.03 (s, 3 H), 1.28 (s, 3 H), 1.50 (s, 3 H), 2.02 (s, 3 H), 2.58 (d, J = 13.8 Hz, 1 H), 2.82 (d, J = 13.8 Hz, 1 H), 3.67 (s, 3 H), 4.58 (m, 1 H), 4.72 (q, J = 7.5 and 3.0 Hz, 1 H), 5.37 (m, 1 H) ppm. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.59; H, 8.76.

Methyl 3β,16β-Diacetoxy-5,17-pregnadien-21-oate (9). The diacetate **6b** (200 mg) and 5 mg of p-TsOH·H_2O in 5 mL of toluene were refluxed for 30 min, and the solvent was removed in vacuo. The resulting oily material was purified on a 5 g silica gel column (25% n-hexane in C_6H_6) to give 180 mg of **9** which was recrystallized from n-hexane to give 135 mg of prisms: mp 135–137 °C; IR 1730, 1669 cm^{-1}; NMR 1.00 (s, 3 H), 1.05 (s, 3 H), 2.01 (s, 6 H), 3.66 (s, 3 H), 4.60 (m, 1 H), 5.37 (m, 1 H), 5.66 (d, J = 1.8 Hz, 1 H), 6.00 (sextet, J = 6.0 and 1.8 Hz, 1 H) ppm. Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24, H, 8.16. Found: C, 70.25; H, 7.88.

Methyl 3β,16β-Diacetoxy-5α-pregnan-21-oate (10). The olefin **9** (150 mg) in 5 mL of AcOH was hydrogenated in the usual manner using 30 mg of platinum catalyst for 1 h at room temperature. Recrystallization from a mixture of n-hexane and Me_2CO gave 105 mg of needles: mp 192–195 °C; IR 1730 cm^{-1}; NMR 0.75 (s, 3 H), 0.83 (s, 3 H), 1.99 (s, 3 H), 2.01 (s, 3 H), 2.40 (m, 2 H), 3.62 (s, 3 H), 4.70 (m, 1 H), 5.25 (m, 1 H) ppm. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.72; H, 9.01.

3β-Acetoxy-16β-hydroxy-5α-pregnan-21-oic Acid γ-Lactone (11). (A) From the Ester 10. To a solution of 100 mg of **10** in 3 mL of MeOH was added 0.5 mL of 50% NaOH solution. The mixture was kept at 50 °C for 1 h. After cooling, the resulting alkaline solution was acidified with 5% HCl and extracted with $CHCl_3$. The solvent was removed in vacuo, and the residue was reacetylated with Ac_2O and pyridine at room temperature overnight. Addition of 2 mL of MeOH and removal of the solvent afforded the crystalline residue which on recrystallization from isopropyl ether gave 70 mg of needles: mp 215–217 °C; IR 1770, 1724 cm^{-1}; NMR 0.72 (s, 3 H), 0.82 (s, 3 H), 1.98 (s, 3 H), 2.45 (m, 2 H), 4.62 (m, 1 H), 4.88 (m, 1 H) ppm. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.58; H, 9.23.

(B) From the Hydroxy Carboxylic Acid 17b. A solution of 100 mg of **17b** in a mixture of 2 mL of concentrated HCl and 5 ml of AcOH was heated at reflux temperature for 2 h. The mixture was cooled, made basic with $NaHCO_3$ solution, extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated to dryness. The resulting residue was chromatographed on a 3 g silica gel column (1% Me_2CO in C_6H_6) and recrystallized from isopropyl ether to give 55 mg of needles: mp 215–216 °C, which was completely identical (mixture melting point, TLC, IR, NMR) with the sample obtained by method **A.**

Reformatsky Reaction of 3β,16α-Diacetoxy-5α-androstan-17-one (12). Diacetoxy ketone **12** (300 mg) was treated with methyl bromoacetate as described for **4.** In this case, however, it was necessary that the addition of 10 mg of iodine be repeated each time the violet color disappeared during the 2 h of refluxing. Purification on a 15 g silica gel column (1% Me_2CO in C_6H_6) afforded 195 mg of methyl 3β-acetoxy-16α,17α-dihydroxy-5α-pregnan-21-oate (**13a**), which was recrystallized from isopropyl ether to give 140 mg of plates: mp 158–160 °C; IR 3521, 1736, 1724 cm^{-1}; NMR 0.66 (s, 3 H), 0.80 (s, 3 H), 1.99 (s, 3 H), 2.48 (d, J = 16.3 Hz, 1 H), 2.73 (d, J = 16.3 Hz, 1 H), 3.69 (s, 3 H), 4.30 (m, 1 H), 4.62 (m, 1 H) ppm. Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.41; H, 9.25.

Further elution with 2% Me_2CO in C_6H_6 gave 45 mg of **14,** which was reacetylated with Ac_2O and pyridine to afford **12:** mp 186–187 °C; identical with the authentic sample (mixture melting point and IR).

Methyl 3β,16α-Diacetoxy-17α-hydroxy-5α-pregnan-21-oate (13b). The glycol **13a** (170 mg) was acetylated with 1 mL of Ac_2O and 0.5 mL of pyridine in the usual manner. Recrystallization from isopropyl ether gave 110 mg of needles: mp 184–185 °C; IR 3610, 1742 cm^{-1}; NMR 0.75 (s, 3 H), 0.82 (s, 3 H), 2.01 (s, 3 H), 2.08 (s, 3 H), 2.54 (s, 2 H), 3.66 (s, 3 H), 4.68 (m, 1 H), 5.24 (q, J = 8.8 and 2.7 Hz, 1 H) ppm. Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.19; H, 8.45.

Methyl 3β-Acetoxy-16α,17α-isopropylidenedioxy-5α-pregnan-21-oate (15). The glycol **13a** (15 mg) was treated with 1% HCl in Me_2CO at room temperature for 10 min. Removal of the solvent and recrystallization from n-hexane gave 7 mg of needles: mp 162–163 °C; IR 1736 cm^{-1}; NMR 0.81 (s, 3 H), 0.83 (s, 3 H), 1.47 (s, 6 H), 2.00 (s, 3 H), 2.75 (s, 2 H), 3.62 (s, 3 H), 4.49 (d, J = 5.0 Hz, 1 H), 4.65 (m, 1 H) ppm. Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.33; H, 9.02.

Methyl 3β,16α-Diacetoxy-5α-pregnan-17-en-21-oate (16). The diacetate **13b** (150 mg) in 4 mL of toluene was heated at reflux temperature for 30 min in the presence of 3 mg of p-TsOH·H_2O. The mixture was cooled, washed with 5% $NaHCO_3$, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from n-hexane to give 95 mg of prisms: mp 175–178 °C; IR 1736, 1724, 1656 cm^{-1}; NMR 0.83 (s, 3 H), 2.00 (s, 6 H), 3.67 (s, 3 H), 4.70 (m, 1 H), 5.69 (d, J = 1.5 Hz, 1 H), 6.13 (m, 1 H) ppm. Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.08; H, 8.60.

Methyl 3β,16α-Diacetoxy-5α-pregnan-21-oate (17a). The olefin **16** (140 mg) in 5 mL of AcOH was hydrogenated at room temperature for 15 min in the presence of 20 mg of platinum catalyst. After the usual workup, recrystallization from n-hexane gave 80 mg of plates: mp 129–131 °C; IR 1751, 1730 cm^{-1}; NMR 0.67 (s, 3 H), 0.83 (s, 3 H), 2.01 (s, 6 H), 2.38 (d, J = 7.5 Hz, 2 H), 3.66 (s, 3 H), 4.70 (m, 1 H), 4.97 (m, 1 H) ppm. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.50; H, 9.08.

3β,16α-Dihydroxy-5α-pregnan-21-oic Acid (17b). To a solution of 130 mg of **17a** in 5 mL of MeOH was added 1 mL of 50% KOH solution, and the mixture was heated at reflux temperature for 30 min. The mixture was concentrated in vacuo and acidified with 5% HCl to yield crystals which were recrystallized from Me_2CO to give 71 mg of prisms: mp 263–264 °C; IR 3450, 3400–2400, 1736 cm^{-1}. Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.68; H, 9.63.

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Registry No.—**4,** 16597-57-2; **5a,** 67556-43-8; **5b,** 67556-44-9; **6a,** 67556-45-0; **6b,** 67556-46-1; **7,** 67556-47-2; **8,** 67556-48-3; **9,** 67556-49-4; **10,** 67556-50-7; **11,** 67556-51-8; **12,** 10459-28-6; **13a,** 67556-52-9; **13b,** 67556-53-0; **14,** 67596-87-6; **15,** 67556-54-1; **16,** 67556-55-2; **17,** 67556-56-3; **18,** 67556-57-4; methyl bromoacetate, 96-32-2.

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