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CONVENIENT PREPARATIVE ROUTES TO 19-HYDROXY, 19-OXO-, 19-OIC-, AND 19-NOR-DEOXYCORTICOSTERONE

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Abstract — Practical synthetic routes to 19-hydroxy-, 19-oxo-, 19-oic-, and 19-nor-deoxycorticosterone were developed. 19-Hydroxydeoxycorticosterone (11) and its 21-acetate 10 were first prepared by two routes via O-protected 19-oxygenated intermediates 6 and 17 starting from readily available pregnenolone acetate (1) and dehydroepiandrosterone acetate (12). The key step in the first route is the application of Henbest acetoxylation at C-21 to the enamine 7 derived from 6. The second route involves introduction of a hydroxyacetyl side chain at C-17 starting with base-catalyzed condensation of 17 with methoxyacetic ester. 19-Oxo- and 19-oic-deoxycorticosterone (23 and 25) and their 21-acetates 22 and 24 were obtained via chromium trioxide oxidation of 10 under different controlled conditions. Alkaline hydrolysis of 22 under decarbonylation led to 19-nor-deoxycorticosterone (26). Alternatively, a short-step synthesis of the latter steroid from estrone methyl ether (27) was achieved by utilizing the same procedure for construction of the corticoid side chain.

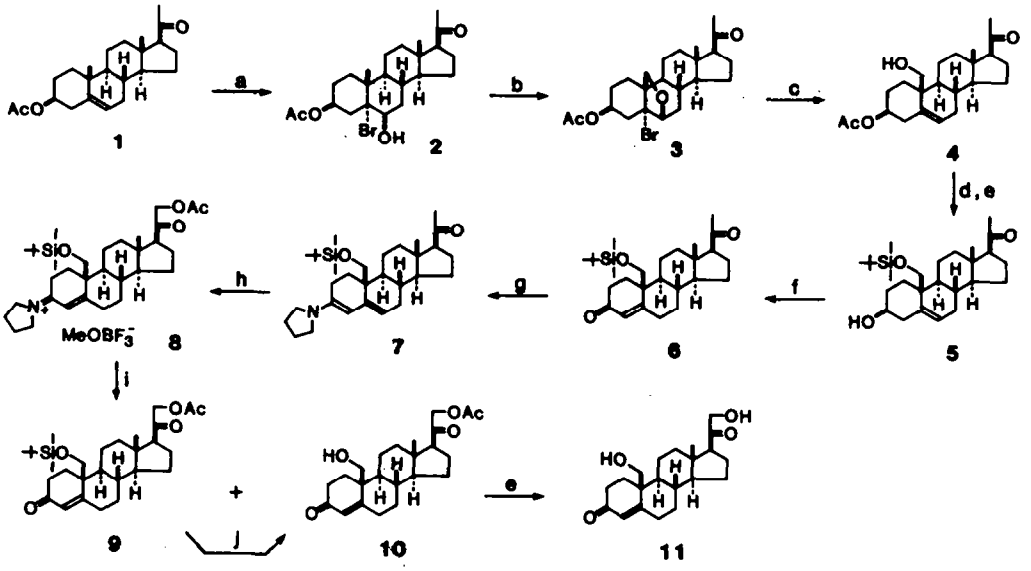
19-Nordeoxycorticosterone (19-nor-DOC) is a mineralocorticoid with potent sodium-retaining activity comparable to that of aldosterone, which has recently been the focus of attention in connection with low renin hypertension.[1] It was first isolated by Gomez-Sanchez et al. from the urine of rats with adrenal regeneration hypertension[2] and later identified by Dale et al. in human urine.[3] More recently, Gomez-Sanchez et al. reported the isolation and identification of 19-hydroxy-, 19-oxo-, and 19-oic-deoxycorticosterone (19-OH-, 19-oxo-, and 19-oic-DOC) as metabolites of deoxycorticosterone (DOC) by rat adrenals.[4] These 19-oxygenated products may be crucial intermediates in the biosynthesis of 19-nor-DOC from DOC. However, 19-OH-DOC and 19-oxo-DOC have little or weak sodium-retaining activity,[5] and the physiological significance of the intra-adrenal formation of 19-oxygenated steroids is as yet unknown.

In order to fully investigate the metabolism of DOC and the structure-activity relationship of this series of deoxycorticoids, large quantities of the title steroids are needed. Since previously published syntheses[5-7] of these compounds were unsatisfactory for our preparative purposes, we developed improved synthetic routes as convenient alternatives. Here we describe the preparative synthesis of 19-OH-DOC, the conversion of 19-OH-DOC to 19-oxo-, 19-oic-, and then 19-nor-DOC, and an alternative facile synthesis of 19-nor-DOC.

19-OH-DOC (11)

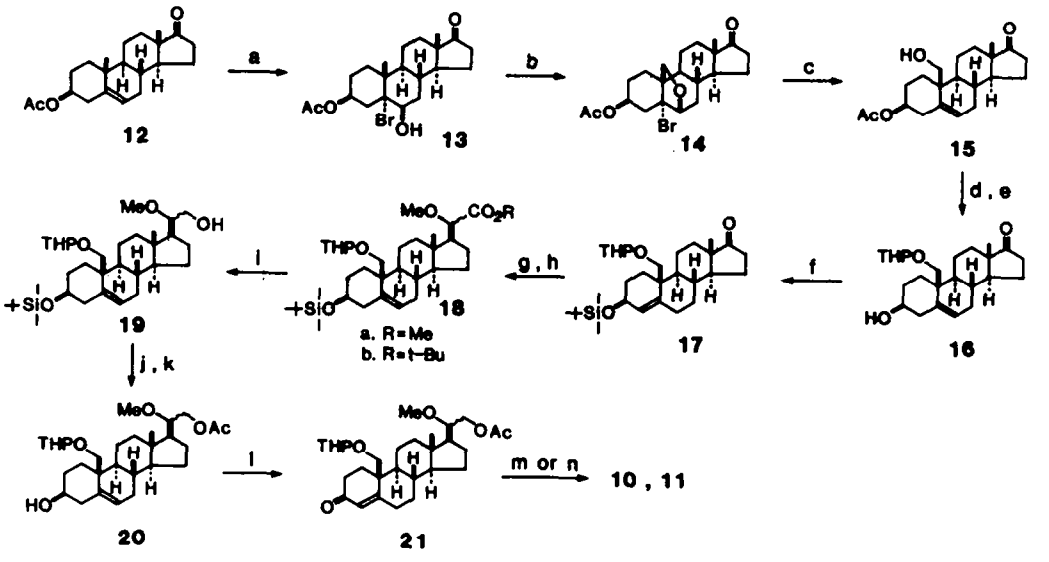
Synthesis of 19-OH-DOC (11) was initially undertaken by two routes starting with readily available materials. The first approach[8] utilized pregnenolone acetate (1) which was converted into 5α,6β-bromohydrin 2 by addition of hypobromous acid (Scheme I). Treatment of 2 with lead tetraacetate and iodine under irradiation (the hypoiodite reaction)[9] afforded the 6β,19-epoxide 3.[8,10-12] Successive reduction of 3 with activated zinc and acetic acid gave the known 19-hydroxy derivative 4[12] which was obtained, after chromatography, in an overall yield of 35.4% from 1. Protection of the 19-hydroxy group as the *t*-butyldimethylsilyl ether followed by alkaline hydrolysis of the 3-acetoxy group converted 4 to the selectively

Scheme I



(a) NBA, 0.5 N-$HClO_4$, dioxane, rt; (b) $Pb(OAc)_4$, I_2, $CaCO_3$, cyclohexane, hν, reflux; (c) Zn, $HOAc-H_2O$ (15:1), rt; (d) t-$BuMe_2SiCl$, imidazole, DMF, rt; (e) K_2CO_3, $MeOH-H_2O$ (10:1), rt; (f) $Al(i-PrO)_3$, N-methyl-4-piperidone, toluene, reflux; (g) pyrrolidine, MeOH, Ar, 60°C; (h) $Pb(OAc)_4$, $BF_3 \cdot Et_2O$, PhH–MeOH(95:5), N_2, rt; (i) EtOH, aq $NaHCO_3$, N_2, rt; (j) n-Bu_4NF, THF, rt.

Scheme II



(a) NBA, 70%-$HClO_4$, aq dioxane, rt; (b) $Pb(OAc)_4$, I_2, $CaCO_3$, cyclohexane, hν, reflux; (c) Zn, $HOAc-H_2O$ (15:1), 45°C; (d) dihydropyran, p-$TsOH \cdot H_2O$, CH_2Cl_2, rt; (e) K_2CO_3, $MeOH-H_2O$ (10:1), rt; (f) t-$BuMe_2SiCl$, imidazole, DMF, rt; (g) LDA (10 eq), $MeOCH_2CO_2R$ (8 eq), THF, -70°C; (h) $SOCl_2$, Py, -20°C; (i) i-Bu_2AlH, toluene, -20°C; (j) Ac_2O, Py, rt; (k) n-Bu_4NF, THF, rt; (l) $Al(i-PrO)_3$, N-methyl-4-piperidone, toluene, reflux; (m) conc HCl, acetone, 0°C: (n) 4 N-HCl, acetone, rt.

protected diol **5**. Oxidation of **5** by a modified Oppenauer procedure[13] led to the O-protected 19-hydroxyprogesterone **6** as a key intermediate, which was thus obtained in 76.8% overall yield from **4**. In order to introduce an acetoxy group at C-21, the enamine **7**, quantitatively prepared from **6**, was treated with excess lead tetraacetate in 5% methanol-benzene containing boron trifluoride etherate (the Henbest procedure).[14,15] The resulting eniminium salt **8** was hydrolyzed with aqueous ethanolic sodium bicarbonate and gave 19-OH-DOC 21-acetate (19-OH-DOCA) (**10**)[8] (9.5%) and its O-protected derivative **9** (24.1%). The latter was deprotected with tetrabutylammonium fluoride and **10** was again obtained. Fianlly, mild alkaline hydrolysis of **10** furnished pure 19-OH-DOC (**11**)[5,8] in 73.4% yield.

The second approach started with dehydroepiandrosterone acetate (**12**) which was similarly converted via the bromohydrin **13** and the epoxide **14** into the known 19-hydroxy derivative **15**[16] in 35.6% overall yield (Scheme II). The 19-hydroxy group was protected as the tetrahydropyranyl ether and the 3-hydroxy group formed on alkaline hydrolysis, as the *t*-butyldimethylsilyl ether. The O-protected diol **17** as a key intermediate was thus prepared in 83.7% overall yield from **15**. To build the corticoid side chain at C-17, we applied an efficient and straightforward method developed by the Schering group.[17] The process involved base-catalyzed condensation with methoxyacetic ester. Addition of excess methyl or *t*-butyl lithiomethoxyacetate, generated in situ from the corresponding ester and lithium diisopropylamide, to the 17-ketone **17** at $-70°C$ followed by dehydration with thionyl chloride in pyridine at $-20°C$ gave the unsaturated ester **18a** or **18b** in identical yields of 70.7%. The product in either case was formed as a mixture of E- and Z-isomers (E/Z ratio: 1/1.3 for **18a** and 1.6/1 for **18b** by NMR as indicated below). The isomers could not be separated by TLC and HPLC and were subjected to further transformation. Their reduction with diisobutylaluminium hydride in toluene at $-20°C$ yielded the same 21-alcohol **19**. The 21-hydroxy group was acetylated and then the 3-silyl group was deprotected. The resulting 3-alcohol **20** was converted by Oppenauer oxidation into the enone **21**. As the final step, smooth conversion of **21** to 19-OH-DOCA (**10**) and 19-OH-DOC (**11**) was achieved in one step by acid hydrolysis under controlled conditions. When aqueous oxalic acid and aqueous hydrochloric acid were employed at room temperature for the hydrolysis, the 19-tetrahydropyranyl group was easily deprotected but, contrary to expectation, the 20-enol ether grouping was incompletely cleaved. The forced conditions required for the complete hydrolysis further induced concomitant removal of the 21-acetoxy group. Thus, exposure of **21** to aqueous 4 N-hydrochloric acid in acetone at room temperature for 39 h directly led to 19-OH-DOC (**11**) in an overall yield of 60.6% from **18a**. On the other hand, treatment of **21** with conc hydrochloric acid in acetone at 0°C caused no appreciable hydrolysis of the 21-acetoxy group, providing solely 19-OH-DOCA (**10**) which was thus obtained in 65.3% and 64.4% overall yields from **18a** and **18b**, respectively.

*19-Oxo-DOC (**23**) and 19-Oic-DOC (**25**)*

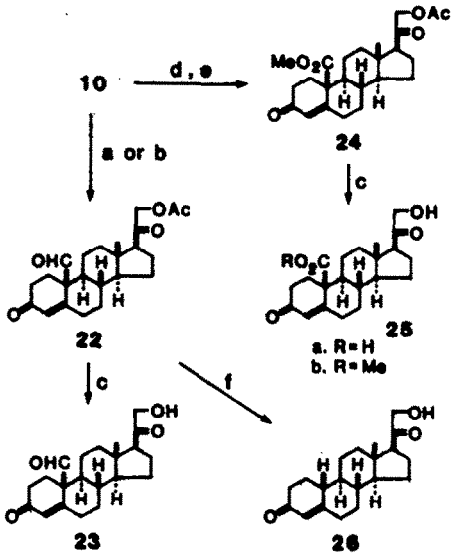
19-Oxo- and 19-oic-DOC (**23** and **25**) were derived from 19-OH-DOCA (**10**) without difficulty (Scheme III). Oxidation of **10** with chromium trioxide in warm aqueous pyridine furnished 19-oxo-DOCA (**22**)[5,8] in 72.6% yield. The latter compound was also obtained by oxidation with pyridinium chlorochromate. Subsequent mild hydrolysis of the product with sodium bicarbonate in aqueous methanol led to 19-oxo-DOC (**23**)[5] in 72.4% overall yield from **10**. On the other hand, oxidation of **10** with a large excess of Jones reagent in acetone and subsequent treatment with diazomethane gave 19-oic-DOCA methyl ester (**24**) as crystals in 73.1% yield. Selective saponification with sodium bicarbonate in aqueous methanol smoothly converted **24** to 19-oic-DOC methyl ester (**25b**) in 84.5% yield.

*19-Nor-DOC (**26**)*

On treatment with methanolic potassium hydroxide at room temperature, 19-oxo-DOCA (**22**) readily underwent decarbonylation to afford the desired 19-nor-DOC (**26**)[6,8] in an overall yield of 67.2% from **10**. However, this synthesis via the intermediate steroid, 19-OH-DOCA (**10**) appeared quite circuitous for the sole preparation of 19-nor-DOC (**26**). Thus, we pursued an alternative facile route to the potent corticoid.

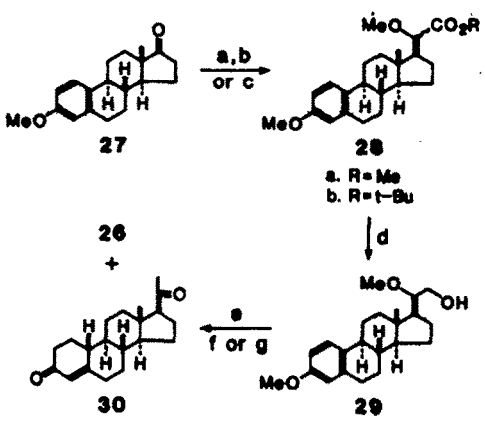
Estrone methyl ether (**27**) was chosen as the starting material, to which the procedure described above for introduction of the hydroxyacetyl side chain was applied (Scheme IV). Addition of excess methyl lithiomethoxyacetate to **27** and subsequent dehydration gave the expected methyl ester **28a** in 72% yield. In a similar manner, the *t*-butyl ester **28b** was obtained in 68.7% yield. In both cases, the product isomers

Scheme III



(a) CrO_3, Py–H_2O (2:1), 60°C; (b) PCC, CH_2Cl_2, rt; (c) $NaHCO_3$, MeOH–H_2O (9:1), N_2, rt; (d) Jones reagent, acetone, 0°C; (e) CH_2N_2, Et_2O–MeOH (4:1), rt; (f) KOH, MeOH (H_2O), Ar, rt.

Scheme IV



(a) LDA (10 eq), $MeOCH_2CO_2R$ (8 eq), THF, −70°C; (b) $SOCl_2$, Py, −20°C; (c) Zn, Et_2AlCl, $MeOCCl_2CO_2Me$, THF, rt→60°C; (d) i-Bu_2AlH, toluene, −20°C; (e) Li, NH_3, EtOH, Et_2O–THF (9:1); (f) $(CO_2H)_2 \cdot H_2O$, MeOH–H_2O (10:1), 50°C; (g) 3N-HCl, MeOH, 60°C.

were successfully isolated in crystalline forms by preparative HPLC, with the Z-isomer being formed almost exclusively or predominantly (E/Z ratio: 1/88 for **28a** and 1/17 for **28b**). We also examined the Reformatsky-type condensation of **27** with methyl dichloromethoxyacetate and zinc in the presence of diethylaluminium chloride.[18] The same ester **28a** was obtained in one step, albeit in a low to moderate yield, with the E-isomer being predominant (E/Z ratio: 2.6/1). The stereochemistry of both isomers could be established on the basis of their UV, CD, and NMR data in comparison with literature data.[18,19] The UV and CD data showed that the E-type compound, in general, has a relatively small molar extinction coefficient (ε) and a larger molecular ellipticity (θ) than the Z-type compound. Inspection of the NMR data also suggested that the 13-methyl signal of the E-isomer shifts to a slightly lower field (~0.1 ppm) than that of the Z-isomer. The crystalline Z-isomer of **28a**, readily obtained in large quantities, was used for the further conversion. Reduction of diisobutylaluminium hydride converted **28a** to the corresponding alcohol **29** in 91.4% yield. Birch reduction of **29** with lithium and alcohol in liquid ammonia followed by acid hydrolysis gave, after chromatography, the desired 19-nor-DOC (**26**) as the major product together with 19-norprogesterone (**30**).[20,21] The by-product **30** presumably resulted from reductive cleavage of the allylic C–O bond, which would be facilitated by enhancing the reducing ability of the dissolving metal by increasing its concentration. For instance, when the reduction was carried out with 63 equivalents of lithium metal, **26** and **30** were produced in 61.7% and 18.5% yields, respectively. In contrast, using 47 equivalents of lithium metal improved the product selectivity, providing **26** and **30** in 51.0% and 5.3% overall yields, respectively, from **28**.

The structures of all compounds synthesized in this work were confirmed from their spectral characteristics (UV, NMR, IR, MS) (see Experimental). The published data were also compared for the already known compounds.

EXPERIMENTAL

Unless otherwise stated, melting points were determined on a calibrated Yanagimoto Micro Melting Point Apparatus. Infrared spectra (IR) were recorded on a Model 260-10 Hitachi spectrophotometer. Ultraviolet spectra (UV) were obtained with a Hitachi 323 spectrophotometer. Circular Dichroism spectra (CD) were recorded using a JASCO J-40 spectrometer. Nuclear magnetic resonance spectra (NMR) were taken on a Varian EM-390 90 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectral analyses were carried out on a Hitachi RMU-6 mass spectrometer. A Varian XL-200 200 MHz spectrometer

was also used for analysis of product ratio. Precoated TLC plates (Silica gel 60 F-254, 20 x 20 x 0.05 cm, Merck) were used for preparative thin-layer chromatography (TLC). Silica gel 60 (Kieselgel 60) (grain size 0.063-0.2 mm, Merck) was used for ordinary column chromatography. Preparative high-performance liquid chromatography (HPLC) was performed using some prepacked silica gel columns (Merck). Usual workup means washing extracts with water and then brine, drying (Na_2SO_4), filtration, and evaporation in vacuo.

3β-Acetoxy-19-hydroxypregn-5-en-20-one (4)

To a stirred suspension of 7.17 g (0.02 mol) of pregnenolone acetate (1) in 60 ml of dioxane and 11 ml of 0.5 N-perchloric acid was added in portions 4.14 g (0.03 mol) of N-bromoacetamide at 10–15°C in the dark. After stirring was continued at room temperature for 2 h, 10 ml of 10% aqueous sodium sulfite solution was added at 5–10°C until KI-starch paper was no longer blued. The mixture was poured into 70 ml of dichloromethane and 30 g of crushed ice. The organic layer separated was washed with cold water and dried (Na_2SO_4). The solvent was evaporated in vacuo below 40°C, leaving the crude bromohydrin 2 (9.5 g) as a viscous syrup. A stirred mixture of the bromohydrin, 2 l of cyclohexane, 49.18 g (0.111 mol) of commercial lead tetraacetate, 16.09 g (0.154 mol) of powdered calcium carbonate, and 9.55 g (0.0376 mol) of iodine was heated at reflux by irradiation with a 500-watt lamp. After the iodine color faded (70 min), the stirred mixture was cooled to room temperature and filtered through celite followed by rinsing with ether. The filtrate was washed with 10% aqueous sodium thiosulfate solution and then water, dried (Na_2SO_4), and evaporated in vacuo. The residue (the crude epoxide 3) was dissolved in 260 ml of acetic acid and 17 ml of water and then 50 g of activated zinc dust was carefully added in portions under stirring. After stirring at room temperature overnight (16 h), the excess zinc was filtered off and the filtrate was concentrated in vacuo. The residue was extracted with 3:1 ether-dichloromethane followed by usual workup. Crystallization of the crude product from ether-pentane afforded 2.29 g of the pure alcohol 4 as a crystalline solid, mp 168-171°C. The mother liquor residue was further subjected to purification by preparative HPLC (Lobar Size C, 4:1 benzene-EtOAc) which separated additional 0.36 g of 4, mp 163–167°C (ether-pentane). The total yield was 2.65 g (overall 35.4%). The pure material showed ν_{max} ($CHCl_3$) 3510 (OH), 1725 (OAc), and 1700 cm^{-1} (COMe); δ ($CDCl_3$–D_2O) 0.67 (s, 3H, 13–Me), 2.02 (s, 3H, OAc), 2.10 (s, 3H, COMe), 3.60, 3.84 (ABq, 2H, J = 12 Hz, 10–CH_2), 4.4–4.9 (m, 1H, 3–H), and 5.74 (bd, 1H, J = 4.5 Hz, 6–H).

19-t-Butyldimethylsilyloxyprogesterone (6)

A stirred solution of 239.7 mg (0.64 mmol) of the 19-alcohol 4, 289.4 mg (1.92 mmol) of *t*-butyldimethylsilyl chloride, and 217.9 mg (3.2 mmol) of imidazole in 10 ml of dry dimethylformamide was allowed to stand at room temperature overnight (24 h). The mixture, diluted with 3:1 ether-dichloromethane, was washed with aqueous saline followed by usual workup. The crystalline residue was dissolved in 40 ml of 10:1 methanol-water and 400 mg of potassium carbonate was added. The suspension was stirred at room temperature for 2 h. The resulting clear solution was concentrated in vacuo and the residue was extracted with dichloromethane. The crude product (the 3-alcohol 5), obtained after usual workup, was dissolved in 40 ml of dry toluene containing 1.18 ml of N-methyl-4-piperidone (9.6 mmol). The resulting solution was heated at reflux using a Dean-Stark apparatus with molecular sieve 4A. The first 8 ml of distillate was discarded and then 130.7 mg (0.64 mmol) of aluminium isopropoxide was charged. After 1 h, additional 196.1 mg (0.96 mmol) of aluminium isopropoxide was added. Refluxing was continued for further 3 h. After most of the solvent was evaporated, the residue was extracted with dichloromethane. The extract was washed successively with 1 N-HCl and satd. aqueous sodium bicarbonate solution and followed by usual workup. The crystalline residue was triturated with ether-pentane to give 170 mg of the silyl enone 6, mp 138–139°C. The mother liquor residue was further purified by preparative TLC (3:1 benzene–EtOAc) which afforded 48.6 mg of the second crop, mp 137–139°C. The total yield was 218.6 mg (76.8%). Recrystallization from dichloromethane-ether-pentane provided an analytical sample, mp 139–140°C: ν_{max} ($CHCl_3$) 1700 (COMe), 1660, and 1620 cm^{-1} (conj. C=O); δ ($CDCl_3$) 0.66 (s, 3H, 13-Me), 0.83 (s, 9H, Sit-Bu), 2.09 (s, 3H, 20-Me), 3.85 (s, 2H, 10-CH_2), and 5.83 (s, 1H, 4-H); m/e 444 (M^+).

19-t-Butyldimethylsilyloxy-3-(N-pyrrolidinyl)-pregna-3,5-dien-20-one (7)

Pyrrolidine (0.15 ml, 1.8 mmol) was added to a solution of 400 mg (0.9 mmol) of the enone 6 in 9 ml of methanol warmed at 60°C under argon. After stirring was continued at the same temperature for 1 h, the mixture was cooled to 0–5°C. The resulting crystalline precipitate was collected by filtration to give 415.4 mg (92.8%) of the dienamine 7, mp 145–150°C: ν_{max} ($CHCl_3$) 1690 (COMe) 1627, and 1600 cm^{-1} (diene); δ ($CDCl_3$) 0.67 (s, 3H, 13-Me), 0.87 (s, 9H, Sit-Bu), 2.11 (s, 3H, 20-Me), 3.0–3.3 (m, 4H, N-CH_2), 3.58, 3.70 (ABq, 2H, J = 10.5 Hz, 10-CH_2), 4.74 (s, 1H, 4-H), and 5.14 (m, 1H, 6-H).

19-t-Butyldimetylsilyloxydeoxycorticosterone 21-Acetate (9)

To a stirred solution of 415 mg (0.834 mmol) of the dienamine 7 in 12.5 ml of 95:5 benzene–methanol containing 2.3 ml (18.7 mmol) of boron trifluoride-diethyl ether was added 666 mg (1.5 mmol) of lead tetraacetate at room temperature under nitrogen. After stirring was continued for 4 h, the mixture was poured into ice-water and extracted with dichloromethane. The extract was worked up as usual to leave the crude salt 8 as a gummy residue. This was dissolved in 47 ml of ethanol and 4 ml of water and 0.2 ml of satd. aqueous sodium bicarbonate solution was added. The mixture was stirred at room temperature for 2 h under nitrogen. Then the mixture was acidified (pH 5) with 10% aqueous acetic acid (1 ml) and evaporated to dryness in vacuo below 30°C. The residue was poured into ice-water and extracted with dichloromethane. The crude syrupy product, obtained after usual workup, was subjected to purification by preparative HPLC (Lobar Size B, 4:1 benzene–EtOAc) which afforded 100.8 mg (24.1%) of the silyloxy enone 9, mp 111–114°C (Et_2O-pentane) together with 30.7 mg (9.5%) of 19-OH-DOCA (10), mp 195–198°C (Et_2O-pentane), identical with a sample obtained below. The major compound showed ν_{max} ($CHCl_3$) 1740 (OAc), 1720 (C=O), 1660, and 1615 cm^{-1} (conj. C=O); δ ($CDCl_3$) 0.70 (s, 3H, 13-Me), 0.83 (s, 9H, Sit-Bu), 2.15 (s, 3H, OAc), 3.87 (s, 3H, 10-CH_2), 4.51, 4.69 (ABq, 2H, J = 17 Hz, 20-CH_2), and 5.86 (s, 1H, 4-H); m/e 502 (M^+).

19-Hydroxydeoxycorticosterone 21-Acetate (19-OH-DOCA) (10)

(a) From the silyl ether 9. A solution of 131 mg (0.26 mmol) of the silyl ether 9 in 2.5 ml of dry tetrahydrofuran containing 204 mg (0.78 mmol) of *n*-tetrabutylammonium fluoride was stirred at room temperature for 4 h. The mixture was poured into ice-water and extracted with chloroform followed by usual workup. The crude product was purified by preparative TLC (5:1 chloroform–acetone with double

development), giving 270.8 mg (69.7%) of 19-OH-DOCA (10) as a crystalline solid, mp 199–200°C (ether-pentane). Recrystallization from acetone-pentane afforded an analytical specimen, mp 202–204°C: ν_{max} ($CHCl_3$) 3625 (OH), 1664, 1620 (conj. C=O), 1725, and 1750 cm^{-1} (C=O and OAc); λ_{max} (EtOH) 243.5 nm (ε 14400); δ ($CDCl_3$) 0.70 (s, 3H, 13-Me), 2.14 (s, 3H, OAc), 3.88, 4.02 (ABq, 2H, J = 10.5 Hz, 10-CH_2), 4.49, 4.68 (ABq, 2H, J = 16.5 Hz, 20-CH_2), and 5.92 (s, 1H, 4-H); m/e 388 (M+).

(b) From the ester 18. To a stirred solution of 530 mg (0.84 mmol) of the *t*-butyl ester 18b in 14 ml of dry toluene cooled to –20°C was added 3.17 ml (3.36 mmol) of 1.06 M diisobutylaluminium hydride solution in toluene. Stirring was continued at the same temperature for 1 h and then water (ca. 2-3 ml) was added at 0-5°C. After 0.5 h-stirring, the mixture, diluted with additional water, was extracted with 3:1 ether-dichloromethane followed by usual workup to give a syrupy residue (504 mg), which was acetylated with 2.5 ml of acetic anhydride in 6 ml of dry pyridine on standing at room temperature overnight. The crude acetate, obtained by usual workup, was dissolved in 3 ml of dry tetrahydrofuran and then 4.2 ml (4.2 mmol) of 1 M *n*-tetrabutylammonium fluoride solution in THF was added. The solution was stirred at room temperature for 2 h. The mixture, diluted with 3:1 ether-dichloromethane was washed with aq saline. Usual workup gave the crude alcohol 20 (500 mg) as a viscous syrup. A stirred solution of the alcohol in 50 ml of dry toluene containing 1.55 ml of N-methyl-4-piperidone (1.43 g, 12.6 mmol) was heated at reflux using a Dean-Stark apparatus with molecular sieve 4A. The first 10 ml of distillate was discarded and then 257.4 mg (1.26 mmol) of aluminium isopropoxide was added. After 1 h, additional 85.8 mg (0.42 mmol) of aluminium isopropoxide was added. Refluxing was continued for total 2 h. The solvent was removed in vacuo and the residue was taken in dichloromethane. The organic phase was worked up as usual to give the crude enone 21 (886 mg). The pure material, obtained on purification by preparative TLC (2:1 benzene-EtOAc) in another experiment, showed δ ($CDCl_3$) (200 MHz NMR) 0.93 (s, 3H, 13-Me), 2.09 (s, 3H, OAc), 3.49 (s, 3H, OMe), 4.58, 4.65 (ABq, 2H, J = 12 Hz, 10-CH_2), and 5.90 (d, 1H, J = 6 Hz, 4-H). The enone 21 was dissolved in 35 ml of acetone and 3 ml of conc HCl was added at 0°C. The solution was stirred at 0°C for 1.5 h, then poured into cold satd aq $NaHCO_3$ solution (65 ml) and extracted with dichloromethane. The product (365 mg), obtained after usual workup, was chromatographed on 2 g of Kieselgel 60. The fractions eluted with 1:2 benzene–chloroform, chloroform, and 9:1 chloroform–methanol were combined and evaporated. The residue was triturated with ether-pentane to give 161.3 mg of 19-OH-DOCA (10) as a crystalline solid, mp 199-202°C, identical with that obtained above. The mother liquor residue was further purified by preparative TLC (5:1 chloroform–acetone with double development), giving an additional crop of 48.9 mg, mp 191–197°C. The total yield was 210.2 mg (overall 64.4%). In the same manner, the corresponding methyl ester 18a was led to 19-OH-DOCA (10) in 65.3% overall yield.

19-Hydroxydeoxycorticosterone (19-OH-DOC) (11)

(a) From 19-OH-DOCA (10). A suspension of 97.1 mg (0.25 mmol) of the acetate 10 and 97.1 mg of potassium carbonate in 9.7 ml of methanol containing 0.97 ml of water was stirred under nitrogen. The mixture became a clear solution after 1 h. After 4 h-stirring, the solution was poured into ice-water and extracted with dichloromethane. The extract was worked up as usual. The residue was purified by preparative TLC (3:2 cyclohexane–acetone with double development), giving 63.6 mg (73.4%) of 19-OH-DOC (11), mp 157–160°C (ether). Recrystallization from acetone-pentane provided an analytical sample, mp 160–163°C: ν_{max} ($CHCl_3$) 3620, 3480 (OH), 1707 (C=O) 1664, and 1620 cm^{-1} (conj. C=O); δ ($CDCl_3$-D_2O) 0.67 (s, 3H, 13-Me), 3.88, 4.02 (ABq, 2H, J = 10.5 Hz, 10-CH_2), 4.16 (s, 2H, 20-CH_2), and 5.91 (s, 1H, 4-H); m/e 346 (M+).

(b) From Diether 21. The crude ether 21 (788 mg), derived from 360 mg (0.61 mmol) of the methyl ester 18a, was dissolved in 36 ml of acetone containing 18 ml of 4 N-HCl. The stirred solution was allowed to stand at room temperature for 39 h. The mixture was poured into ice-water and extracted with dichloromethane. The extract was washed with satd aq $NaHCO_3$ solution and followed by usual workup. The crude product (247 mg) was purified by preparative TLC (3:1 chloroform–acetone with double development) which furnished 128.0 mg (60.6%) of 19-OH-DOC (11) as a crystalline solid, mp 158–160°C (acetone-pentane), identical with that obtained above.

3β-Acetoxy-19-hydroxyandrost-5-en-17-one (15)

To a stirred solution of 16.5 g (50 mmol) of dehydroepiandrosterone acetate (12) in 125 ml of dioxane and 25 ml of water containing 2.5 ml of 70% perchloric acid was added a suspension of 7.59 g (55 mmol) of N-bromoacetamide in 12.5 ml of water. After stirring was continued at room temperature for 2 h, the mixture was poured into ice-water and extracted with chloroform. The extract was washed successively with 5% aqueous sodium thiosulfate solution, satd aqueous sodium bicarbonate solution, and aq saline, dried (Na_2SO_4), and evaporated below 40°C. The residue was crystallized from acetone-hexane, giving 11.6 g (54.3%) of the bromohydrin 13, mp 173–175°C: ν_{max} ($CHCl_3$) 1728 cm^{-1} (C=O); δ ($CDCl_3$-CD_3OD 4:1) 0.80 (s, 3H, 13-Me), 1.35 (s, 3H, 10-Me), 2.03 (s, 3H, OAc), 3.3–3.4 (m, 1H, 6-H), and 5.3–5.7 (m, 1H, 3-H).

A stirred suspension of 11.6 g (27.14 mmol) of the bromohydrin, 50.17 g (101.8 mmol) of commercial lead tetraacetate, 22.8 g (228 mmol) of powdered calcium carbonate, and 14.75 g (58.1 mmol) of iodine in 2 l of cyclohexane was heated at reflux by irradiation with a 500-watt lamp. After 1 h, the mixture was cooled to room temperature, filtered through celite (10 g) followed by washing with benzene. The filtrate was washed with 5% aqueous sodium thiosulfate solution and aq saline, dried (Na_2SO_4), and evaporated in vacuo below 45°C. The crude epoxide 14 obtained was dissolved in 360 ml of 15:1 acetic acid–water. Zinc dust (65 g) was added in portions to the stirred resultant solution warmed at 45°C. Stirring was continued at the same temperature for 1 h. The excess zinc was filtered off and the filtrate was concentrated in vacuo below 50°C. Extraction with 4:1 ether–dichloromethane followed by washing with water and satd aqueous sodium bicarbonate solution, drying, and evaporation in vacuo left a syrupy residue. Crystallization from ether gave 3.28 g of the alcohol 15, 157–161°C. The mother liquor residue was purified by repeated preparative HPLC (Lobar Size B, 3:1 benzene–EtOAc and then 3:1 cyclohexane–acetone) which afforded 2.88 g of 15 as an additional crop, mp 159–162°C (dichloromethane–ether-hexane). The total yield was 6.16 g (overall 65.5%). Recrystallization from ether-hexane gave the pure material, mp 161–164°C: ν_{max} ($CHCl_3$) 3400–3600 (OH) and 1730 cm^{-1} (OAc and C=O); δ($CDCl_3$) 0.93 (s, 3H, 13-Me), 2.02 (s, 3H, OAc), 3.63, 3.87 (ABq, 2H, J = 11 Hz, 10-CH_2), 4.4–4.9 (m, 1H, 3-H), and 5.7–5.9 (m, 1H, 6-H).

3β-t-Butyldimethylsilyloxy-19-(2-tetrahydropyranyloxy)-androst-5-en-17-one (17)

2,3-Dihydropyran (4.13 ml, 45.3 mmol) was added to a stirred solution of 3.923 g (11.3 mmol) of the 19-alcohol **15** and 196 mg of *p*-toluenesulfonic acid monohydrate in 120 ml of dry dichloromethane. After 45 min, the solution was washed with satd aq sodium bicarbonate solution and followed by usual workup. The oily residue was dissolved in 130 ml of methanol and 13 ml of water and 3.13 g (22.6 mmol) of potassium carbonate. The mixture was stirred at room temperature for 2 h, then poured into ice-water, and extracted with dichloromethane. The extract was worked up as usual to give the crude 3-alcohol **16** as a syrupy residue which was dissolved in 167 ml of dry dimethylformamide. To it was added at 0°C 4.75 g (31.5 mmol) of *t*-butyldimethylsilyl chloride and 5.36 g (78.7 mmol) of imidazole. The mixture was stirred at room temperature for 16 h, then poured into ice-water, and extracted with 4:1 ether–dichloromethane. Usual workup left a viscous oily residue which was crystallised from aq methanol, giving 3.256 g of the diether **17** mp 102–104°C. The mother liquor residue was eluted through a column of silica gel (Kieselgel 60) with *n*-hexane (80 ml), 1:1 *n*-hexane–benzene (60 ml), benzene (45 ml), and 1:1 benzene–dichloromethane (60 ml). The eluted fractions were collected, evaporated, and the residue was crystallized from methanol, furnishing 0.812 g of **17** as a second crop, mp 98–112°C. The non-crystalline residue was further purified by preparative HPLC (Lobar Size B, 20:1 benzene–EtOAc) which afforded 0.696 g of **17** as a third crop, mp 97–100°C. The total yield was 4.764 g (overall 83.7%). Recrystallization from pentane or aq methanol provided an analytical sample, mp 115–120°C: ν_{max} ($CHCl_3$) 1730 cm^{-1} (C=O); δ ($CDCl_3$) 0.87 (s, 9H, Sit-Bu), 0.90 (s, 3H, 13-Me), 3.25, 4.06 (ABq, 2H, J = 10.5 Hz, 10-CH_2), 4.58 (m, 1H, 3-H), and 5.58 (m, 1H, 6-H); m/e 502 (M+).

Methyl 3β-t-Butyldimethylsilyloxy-19-(2-tetrahydropyranyloxy)-20-methoxypregna-5,17(20)-dien-21-oate (**18a**)

To a stirred cold (0–5°C) solution of 0.42 ml (304 mg, 3 mmol) of diisopropylamine in 3 ml of dry tetrahydrofuran was added dropwise 1.9 ml (3 mmol) of 1.58 N *n*-butyllithium solution in hexane under nitrogen. The stirred mixture was kept at room temperature for 15 min and then cooled to –75°C. To it was added dropwise within 10 min a solution of 0.24 ml (250 mg, 2.4 mmol) of methyl methoxyacetate in 0.8 ml of dry tetrahydrofuran. Then a solution of 150.8 mg (0.3 mmol) of the ketone **17** in 1 ml of dry tetrahydrofuran was added during 10 min at the same temperature. Stirring was continued at –75– –70°C for 3 h and then 1 ml of satd aq ammonium chloride solution was added at the same temperature. The mixture was poured into cold water and extracted with dichloromethane. The extract was washed with aq saline, dried, and evaporated in vacuo. The residue, dissolved in 1 ml of dry pyridine was treated with 0.1 ml of freshly distilled thionyl chloride at –20°C for 40 min under stirring. The mixture was poured into ice-water and extracted with dichloromethane. The extract was worked up as usual and the crude product was purified by preparative TLC (9:1 cyclohexane–EtOAc with double development) which afforded 124.9 mg (70.7%) of the methyl ester **18a** (1:1.3 E–Z isomeric mixture by 200 MHz NMR), mp 96–97°C (MeOH): ν_{max} ($CHCl_3$) 1705 and 1630 cm^{-1} (conj. ester); δ ($CDCl_3$) (200 MHz) 0.89 (s, 9H, Sit-Bu), 0.96 (s, 1.7H, 13-Me in Z-isomer), 1.00 (s, 1.3H, 13-Me in E-isomer), 3.55 (s, 3H, OMe), 3.77 (s, 3H, CO_2Me), 4.56 (dd, 1H, J = 16 and 4 Hz, 3-H), and 5.55 (bs, 1H, 6-H); m/e 588 (M+).

t-*Butyl 3β-t-Butyldimethylsilyloxy-19-(2-tetrahydropyranyloxy)-20-methoxypregna-5,17(20)-dien-21-oate* (**18b**)

Similarly, a solution of 351 mg (2.4 mmol) of *t*-butyl methoxyacetate in 0.8 ml of dry tetrahydrofuran was added dropwise during 10 min to a stirred solution of lithium diisopropylamide prepared from 0.42 ml (304 mg, 3 mmol) of diisopropylamine and 1.9 ml (3 mmol) of 1.58 N *n*-butyllithium solution in hexane in 3 ml of THF cooled to –75°C. Then, a solution of 150.8 mg (0.3 mmol) of the ketone **17** in 1.0 ml of dry tetrahydrofuran was added during 10 min at the same temperature. The mixture was stirred at –75– –70°C for 1.5 h and 1 ml of satd aq ammonium chloride solution was added at the same temperature. The residue, obtained by extraction as above, was treated with 0.2 ml of thionyl chloride in 2 ml of dry pyridine for 1.5 h under stirring. The mixture was worked up as above and the crude product was roughly chromatographed on 1 g of silica gel (Kieselgel 60) by successive elution with benzene (15 ml), 4:1 benzene–$CHCl_3$ (10 ml), and 1:1 benzene–$CHCl_3$ (20 ml). The combined fraction was evaporated and the syrupy residue was crystallized from aq MeOH, giving 126 mg of the *t*-butyl ester **18b** (1.6:1 E-Z isomeric mixture by 200 MHz NMR), mp 170–172°C The mother liquor residue was further purified by preparative TLC (20:1 benzene–EtOAc) which separated 7.9 mg of **18b** as a second crop. The total yield was 133.9 mg (70.7%). Recrystallization from MeOH furnished an analytical sample, mp 171–173°C. The pure material showed δ ($CDCl_3$) (200 MHz NMR) 0.89 (s, 9H, Si-*t*-Bu), 0.95 (s, 1.15H, 13-Me in Z-isomer), 0.99 (s, 1.85H, 13-Me in E-isomer), 3.55 (s, 3H, OMe), 4.56 (dd, 1H, J = 16 and 4 Hz, 3-H), and 5.55 (bs, 1H, 6-H); m/e 630 (M+).

19-Oxodeoxycorticosterone 21-Acetate (19-Oxo-DOCA) (**22**)

The alcohol **10** (50 mg, 0.129 mmol) was dissolved in 1.5 ml of pyridine and a solution of 90 mg (0.9 mmol) of chromium trioxide in 3 ml of pyridine and 1.5 ml of water was added. The mixture was stirred at 60°C for 90 min, then poured into ice-water, and extracted with 4:1 ether–dichloromethane. The extract was worked up as usual. The residue was purified by preparative TLC (3:2 cyclohexane–acetone) which gave, on crystallization from acetone–pentane, 36.1 mg (72.6%) of the aldehyde, mp 121–124°C. Recrystallization from the same solvent afforded an analytical sample, mp 124–125.5°C: ν ($CHCl_3$) 1745, 1725 (CHO, C=O, OAc), 1675, and 1620 cm^{-1} (conj. C=O); δ ($CDCl_3$) 0.69 (s, 3H, 13-Me), 2.15 (s, 3H, OAc), 4.48, 4.65 (ABq, 2H, J = 16.5 Hz, 20-CH_2), 5.95 (d, 1H, J = 2 Hz, 4-H), and 9.91 (s, 1H, CHO); m/e 386 (M+).

19-Oxodeoxycorticosterone (19-Oxo-DOC) (**23**)

To a stirred solution of 58.3 mg (0.15 mmol) of the alcohol **10** in 1 ml of dichloromethane was added 48.5 mg (0.225 mmol) of pyridinium chlorochromate. The mixture was stirred at room temperature for 2 h and then poured into cold water. Extraction with dichloromethane followed by usual workup left a foamy residue (the crude **22**). This was dissolved in 9 ml of 90% aqueous methanol and 120 mg (1.42 mmol) of sodium bicarbonate was added. The mixture was stirred at room temperature under nitrogen for 4 h and then poured into cold water. Extraction with 3:1 ether–dichloromethane followed by usual workup left a viscous syrup which was purified by preparative TLC (9:1 chloroform-acetone), giving 37.4 mg (72.4%) of the aldehyde **23** as a crystalline solid, mp 157–160°C (ether-pentane). The analytical sample was obtained by recrystallization from acetone-pentane, mp 160–162°C: ν_{max} ($CHCl_3$) 3490 (OH), 1717 (sh), 1710 (CO_2Me and C=O), 1673, and 1619 cm-1 (conj. C=O); λ_{max} (EtOH) 247 nm (ε 11900); δ ($CDCl_3$) 0.67 (s, 3H,

13-Me), 3.20 (t, 1H, J = 4.5 Hz, 21-OH), 4.16 (d, 2H, J = 4.5 Hz, 20-CH_2), 5.95 (d, 1H, J = 2 Hz, 4-H), and 9.92 (s, 1H, CHO); m/e 344 (M+).

19-Oicdeoxycorticosterone Methyl Ester 21-Acetate (19-Oic-DOCA Methyl Ester) (**24**)

Jones chromic acid reagent (0.25 ml) was added dropwise to a stirred solution of 50 mg (0.129 mmol) of the alcohol **10** in 2.5 ml of acetone at 0°C. The mixture was stirred at 0°C for 2 h, then the excess of chromic acid was destroyed with isopropanol, and poured into ice-water. Extraction with dichloromethane followed by usual workup. A solution of the crude acid (19-oic-DOC) obtained in 2.5 ml of 4:1 ether-methanol was treated with excess of a diazomethane solution in ether. After 0.5 h, the solution was evaporated and the oily residue was purified by preparative TLC (3:2 cyclohexane-EtOAc with double development) gave, on trituration with ether-pentane, 39.2 mg (73.1%) of the ester **24**, mp 118–120°C. Recrystallization from the same solvent afforded an analytical specimen, mp 119–120°C: ν_{max} ($CHCl_3$) 1747, 1726 (CO_2Me and $COCH_2OAc$), 1668, and 1620 cm^{-1} (conj. C=O); δ ($CDCl_3$) 0.68 (s, 3H, 13-Me), 2.15 (s, 3H, OAc), 3.72 (s, 3H, CO_2Me), 4.49, 4.67 (ABq, 2H, J = 16.5 Hz, 20-CH_2), and 5.85 (d, 1H, J = 2 Hz, 4-H); m/e 416 (M+).

19-Oicdeoxycorticosterone Methyl Ester (19-Oic-DOC Methyl Ester) (**25b**)

To a stirred solution of 20.8 mg (0.05 mmol) of the acetate **24** in 3 ml of 90% aqueous methanol was added 0.6 ml of 10% aqueous sodium bicarbonate solution. The mixture was stirred at room temperature under nitrogen for 2 h and then poured into cold water. Extraction with dichloromethane followed by usual workup left a viscous syrupy residue. Crystallization from ether-pentane gave 15.8 mg (84.5%) of the alcohol **25** as a crystalline solid, mp 141–144°C. Recrystallization from acetone-pentane afforded an analytical sample, mp 141.5–144.5°C: ν_{max} ($CHCl_3$) 3490 (OH), 1723 (CO_2Me), 1708 (C=O), 1667, and 1618 cm^{-1} (conj. C=O); λ_{max} (EtOH) 243 nm (ε 14900); δ 0.67 (s, 3H, 13-Me), 3.22 (t, 1H, J = 4.5 Hz, 21-OH), 3.72 (s, 3H, CO_2Me), 4.14 (d, 2H, J = 4.5 Hz, 20-CH_2), and 5.84 (d, 1H, J = 2 Hz, 4-H); m/e 374 (M+).

19-Nordeoxycorticosterone (19-Nor-DOC) (**26**)

(a) From 19-OH-DOCA (**10**). To a stirred solution of 116.5 mg (0.3 mmol) of the alcohol **10** in 3 ml of dichloromethane was added 129 mg (0.6 mmol) of pyridinium chlorochromate. After stirring was continued for 1.5 h, the mixture was poured onto a column of Florisil (100–200 mesh, 1 g) and followed by elution with ether (50 ml). The oily residue (102 mg) (the crude **22**), obtained after evaporation of the solvent, was dissolved in 25 ml of methanol containing 25 mg of potassium hydroxide dissolved in 0.023 ml of water was added. The mixture was stirred at room temperature for 2 h under argon, then neutralized by adding a few drops of acetic acid, and concentrated in vacuo. The residue was purified by preparative TLC (1:1 cyclohexane–EtOAc) which furnished 63.8 mg (67.2%) of 19-nor-DOC (**26**), mp 133–136°C (acetone-pentane). The analytical sample was obtained by recrystallization from the same solvent, mp 137–139°C: ν_{max} ($CHCl_3$) 3460 (OH), 1705 (C=O), 1663, and 1618 cm^{-1} (conj. C=O); δ ($CDCl_3$) 0.70 (s, 3H, 13-Me), 3.22 (t, 1H, J = 4.5 Hz, OH), 4.16 (d, 2H, J = 4.5 Hz, 20-CH_2), and 5.81 (bs, 1H, 4-H); m/e 316 (M+). The acetate (19-nor-DOCA) was obtained by usual acetylation with Ac_2O and pyridine (81.7%), mp 173–175°C (acetone-ether): ν_{max} ($CHCl_3$) 1748 (OAc), 1725 (20-C=O), 1665, and 1620 cm^{-1} (conj. C=O); λ_{max} (EtOH) 240.5 nm (ε 17300); δ ($CDCl_3$) 0.71 (s, 3H, 13-Me), 2.15 (s, 3H, OAc), 4.51, 4.71 (ABq, 2H, J = 16.5 Hz, 20-CH_2)and 5.82 (bs, 1H, 4-H); m/e 358 (M+).

(b) From the tetraene **29**. Lithium metal (200 mg, 29 mmol) was added in small portions to 12 ml of redistilled liquid ammonia cooled to –75°C and stirring was continued for 0.5 h. To the blue solution was added dropwise 159 mg (0.464 mmol) of the tetraene **29** in 10 ml of 9:1 dry ether-THF followed by slow addition of dry alcohol (20 ml) until the blue color disappeared (1 h). The ammonia was evaporated and the residue was poured into cold water and extracted with 3:1 ether–dichloromethane. The extract was worked up as usual to leave a colorless syrup which was dissolved in 10 ml of methanol and 1 ml of water and 877 mg (6.96 mmol) of oxalic acid monohydrate was added. The mixture was heated at 50°C for 2 h and then allowed to stand at room temperature overnight. Extraction with 3:1 ether–dichloromethane and washing with satd aq sodium bicarbonate solution followed by usual workup gave a crystalline residue which was purified by preparative TLC (2:1 benzene–EtOAc), yielding 25.8 mg (18.5%) of 19-norprogesterone (**30**), mp 140–144°C (ether-pentane) and 90.7 mg (61.7%) of 19-nor-DOC (**26**), mp 135–136°C (ether-pentane). Both analytical samples were obtained by recrystallization from acetone-hexane. The major product had mp 137–139°C, identical with the authentic sample obtained above. The minor product, 19-norprogesterone (**30**) showed mp 144–146°C: ν_{max} ($CHCl_3$) 1700 (20-C=O), 1660, and 1610 cm^{-1} (conj. C=O); δ ($CDCl_3$) 0.68 (s, 3H, 13-Me), 2.12 (s, 3H, 20-Me), and 5.81 (bs, 1H, 4-H); m/e 300 (M+).

Similarly, the crude tetraene **29**, obtained from 281.6 mg (0.76 mmol) of the parent ester **28a**, in 15 ml of 9:1 ether-THF was reduced with 249 mg (36 mmol) of lithium in 20 ml of liquid ammonia followed by quenching with alcohol. The reduction product was dissolved in 6 ml of methanol containing 2 ml of 3 N-HCl. The mixture was stirred at 60°C for 1 h. The crude product, obtained by usual extractive workup, was purified by preparative TLC (3:1 benzene–EtOAc) which afforded 12.0 mg (overall 5.3%) of 19-norprogesterone (**30**), mp 139–143°C (ether-pentane) and 122.6 mg (overall 51.0%) of 19-nor-DOC (**26**), mp 133–137°C (ether-pentane).

Methyl 3,20-Dimethoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-oate (**28a**)

(a) By condensation with methyl methoxyacetate. To a stirred cold (0–5°C) solution of 1.4 ml (1.01 g, 10 mmol) of diisopropylamine in 12 ml of dry tetrahydrofuran was added 6.5 ml (10.3 mmol) of 1.58 N *n*-butyllithium solution in hexane under nitrogen. The mixture was kept at room temperature for 10 min and then cooled to –75°C. To it was added dropwise with stirring in an interval of 10 min a solution of 0.75 ml (0.79 g, 7.6 mmol) of methyl methoxyacetate **22** in 1.5 ml of dry tetrahydrofuran. Then a solution of 284.4 mg (1 mmol) of estrone methyl ether (**27**) in 6 ml of 3:1 dry tetrahydrofuran-dioxane was added dropwise during 15 min at the same temperature. After stirring was continued at –70°C for 3 h, 1 ml of satd aq NH_4Cl solution was added at the same temperature. The mixture, poured into ice-water, was extracted with dichloromethane. Usual workup left a syrupy residue which was dissolved in 3 ml of dry pyridine and treated with 0.3 ml of freshly distilled thionyl chloride at –20°C under stirring. After 1 h, the mixture was poured into ice-water and extracted with dichloromethane followed by usual workup. The crude product contained the E- and Z-isomers of the unsaturated ester **28a**. Crystallization from ether-pentane gave 222.1

mg (60.0%) of the Z-isomer, mp 130–134°C. The mother liquor residue was further purified by preparative TLC (20:1 benzene–EtOAc with double development) which separated 3.0 mg (0.8%) of the E-isomer, mp 107–110°C (pentane) and 41.8 mg (11.3%) of the Z-isomer, mp 128–132°C (ether-pentane). The analytical samples of the E- and Z-isomers were obtained by recrystallization from ether-pentane. The major Z-isomer had mp 133–134°C: ν_{max} (Nujol) 1716, 1636 (unsatd ester), 1608, 1581, and 1501 cm^{-1} (arom.); λ_{max} (EtOH) 231 nm (ε 18700); λ 250 nm ([θ] +5690); δ ($CDCl_3$) 0.94 (s, 3H, 13-Me), 3.56 (s, 3H, 20-OMe), 3.73 (s, 3H, 21-OMe), 3.75 (s, 3H, 3-OMe), 6.61 (bs, 1H, 4-H), 6.68 (dd, 1H, J = 8 and 2.5 Hz, 2-H), and 7.17 (d, 1H, J = 8 Hz, 1-H); m/e 370 (M+). The minor E-isomer had mp 110–112°C: ν_{max} (Nujol) 1718, 1631 (unsatd ester), 1607, 1578, and 1500 cm^{-1} (arom.); λ_{max} (EtOH) 225 (ε 13800) and 230 nm (sh) (ε 13600); λ 249 nm ([θ] +20300); δ ($CDCl_3$) 1.02 (s, 3H, 13-Me), 3.53 (s, 3H, 20-OMe), 3.77 (s, 3H, 3-OMe), 3.81 (s, 3H, 21-OMe), 6.64 (bs, 1H, 4-H), 6.71 (dd, 1H, J = 8 and 2.5 Hz, 2-H), and 7.19 (d, 1 H, J = 8 Hz, 1-H); m/e 370 (M+).

(b) By Reformatsky-type reaction with methyl dichloromethoxyacetate. To a stirred solution of 262 mg (4 mmol) of zinc dust and 1.14 ml (1.9 mmol) of 20% diethylaluminium chloride solution in hexane in 4 ml of dry tetrahydrofuran, was added dropwise a solution of 346 mg (2 mmol) of methyl dichloromethoxyacetate and 284.4 mg (1 mmol) of estrone methyl ether (**27**) in 7 ml of dry tetrahydrofuran at room temperature during 40 min. Stirring was continued at room temperature for 0.5 h and then at 60°C for 2 h. A mixture of water and pyridine (4:1, 2 ml) was added on ice-cooling. The mixture was poured into ice-water and extracted with ether. The extract was worked up as usual to leave a gummy residue which was purified by preparative HPLC (Lobar Size B, 20:1 benzene–EtOAc), giving 85.0 mg (22.9%) of the E-isomer, mp 106–109°C (ether-pentane) and 33.1 mg (8.9%) of the Z-isomer, mp 130–133°C (ether-pentane), together with 109.7 mg (38.6%) of the recovered estrone methyl ether (**27**).

t-Butyl 3,20-Dimethoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-oate (**28b**)

In a similar reaction carried out using *t*-butyl methoxyacetate,[23] the crude product, obtained from 199 mg (0.7 mmol) of estrone methyl ether (**27**), was purified by preparative TLC (40:1 benzene–ethyl acetate with double development), furnishing 11.0 mg (3.8%) of the E-isomer of **28b** in a crystalline form, mp 108–110°C (ether-pentane) and 187.3 mg (64.9%) of the Z-isomer as a crystalline solid, mp 122–123°C (ether-pentane). The minor E-isomer showed λ_{max} (EtOH) 224 nm (ε 12800) and 230 nm (sh) (ε 12400); λ 252 nm ([θ] +9760); δ ($CDCl_3$) (200 MHz) 1.02 (s, 3H, 13-Me), 1.55 (s, 9H, *t*-Bu), 3.54 (s, 3H, CO_2Me), 3.77 (s, 3H, 3-OMe), 6.63 (bs, 1H, 4-H), 6.71 (dd, 1H, J = 8 and 2.5 Hz, 2-H), and 7.19 (d, 1H, J = 8 Hz, 1-H); m/e 412 (M+). The major Z-isomer showed λ_{max} (EtOH) 231.5 nm (ε 18700); λ 255 nm ([θ] +8430); δ ($CDCl_3$) (200 MHz) 0.94 (s, 3H, 13-Me), 1.53 (s, 9H, *t*-Bu), 3.57 (s, 3H, CO_2Me), 3.76 (s, 3H, 3-OMe), 6.62 (bs, 1H, 4-H), 6.70 (dd, 1H, J = 8 and 2.5 Hz, 2-H), and 7.20 (d, 1H, J = 8 Hz, 1-H); m/e 412 (M+).

(Z)-3,20-Dimethoxy-21-hydroxy-19-norpregna-1,3,5(10),17(20)-tetraene (**29**)

To a stirred solution of 200 mg (0.54 mmol) of the ester **28a** (Z-isomer) in 6 ml of dry toluene cooled to –20°C, was added dropwise 2 ml (2.54 mmol) of 1.27 M diisobutylaluminium hydride solution in toluene. The mixture was stirred at the same temperature for 0.5 h and then water (1 ml) was added at 0–5°C. After stirring was continued for additional 0.5 h, the mixture was poured into cold water and extracted with 3:1 ether–dichlorometane. The extract was worked up as usual to leave a viscous syrup (195 mg) which afforded on trituration with ether-pentane 142.0 mg of the alcohol **29**, mp 107–109°C. The mother liquor residue was further purified by preparative TLC (3:1 cyclohexane–dimethoxyethane) which gave additional 27.0 mg of **29**, mp 107–109°C (ether-pentane). The total yield was 169.0 mg (91.4%). The analytical sample was obtained by recrystallization from the same solvent as a crystalline solid, mp 109–111°C: ν_{max} ($CHCl_3$) 1680 (C=C–OMe), 1615, 1580, and 1500 cm^{-1} (arom.); m/e 342 (M+).

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