Pergamon

Tetrahedron 56 (2000) 9957–9965

TETRAHEDRON

Novel Partial Synthetic Approaches to Replace Carbons 2,3,4 of Steroids. A Methodology to Label Testosterone and Progesterone with ^{13}C in the Steroid A Ring. Part 1

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Received 10 January 2000; revised 10 October 2000; accepted 11 October 2000

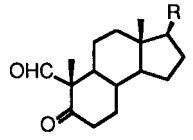
Abstract—A synthetic route to replace A ring carbon atoms 2, 3 and 4 of steroid hormones is described. Readily available testosterone propionate or progesterone, respectively, are degraded to the corresponding 10-formyl-5-oxo-des-A intermediates, in a first stage to the preparation of 2,3,4-($^{13}C_3$)-labeled steroids.

Stable isotope labeled compounds are widely employed in pharmacological and clinical research. Their emergence as first-choice tracers and standards results from their ethical acceptability compared to the radioactive analogs and from the sensitivity of the methods in which they are employed.[1,2] Stable isotope labeled steroid hormones are needed in the development of definitive gas chromatography–mass spectrometry quantitation methods and are used in metabolic, kinetic and clinical studies, especially in those conducted with human subjects.[3] It is essential that the labels are retained during metabolic processes, during chemical and analytical treatment of the samples, and that isotopic effects are negligible. Therefore, the choice of the label and its site are of first importance. In most cases ^{13}C is the ideal label, especially if it is introduced into the steroid skeleton rather than into the more susceptible 17-side chain.

Two general approaches may be considered when synthesizing steroid hormones labeled with ^{13}C: partial synthesis, in which part of the steroid nucleus is replaced with a labeled synthon, or total synthesis. Partial synthesis labeling procedures offer the advantage of shorter synthetic pathways and readily available steroid starting materials. By these procedures, however, not more than two ^{13}C atoms have been previously introduced in the steroid A ring,[4] a most attractive labeling site. We now describe a novel partial synthesis developed for the preparation of (2,3,4-$^{13}C_3$) testosterone and progesterone.

Results and Discussion

The route of synthesis described here comprises the cleavage of the steroid A ring of testosterone and progesterone, respectively, and the degradation of three carbon atoms to the key 10-formyl-5-oxo-des-A intermediates **1** and **2**. Reconstruction of the steroidal A ring is then achieved by incorporation of a C_3 unit[5] unto these intermediates by reaction with the stabilized ylide, 1-triphenyl-phosphoranylidene-2-propanone. The use of a ^{13}C labeled reagent conveniently leads to the desired labeled compounds. The reconstruction of the ^{13}C labeled steroid hormones is described in the following paper in this issue.[6]



1 : R = OH
2 : R = Ac

Our initial attempt to degrade the A ring of testosterone to the 10-formyl-5-oxo-des-A derivate is depicted in Scheme 1. Ozonolysis of testosterone propionate **3** was conducted in ethyl acetate at −78°C, followed by overnight treatment with hydrogen peroxide, produced the keto acid **4**.[7] The key step in this route is the oxidative decarboxylation[8] of the keto acid **4**, leading to the terminal alkene **5**, which after another ozonolysis would generate the desired intermediate **6**. Our initial attempt for oxidative decarboxylation was by lead tetraacetate in the presence of catalytic amounts of cupric acetate and pyridine, which had been successfully applied in steroid synthesis.[9] Low yields of the conversions (16–42%) after many attempts of optimization discouraged us from this route. An alternative procedure for oxidative

Keywords: steroids; degradation; labeling.

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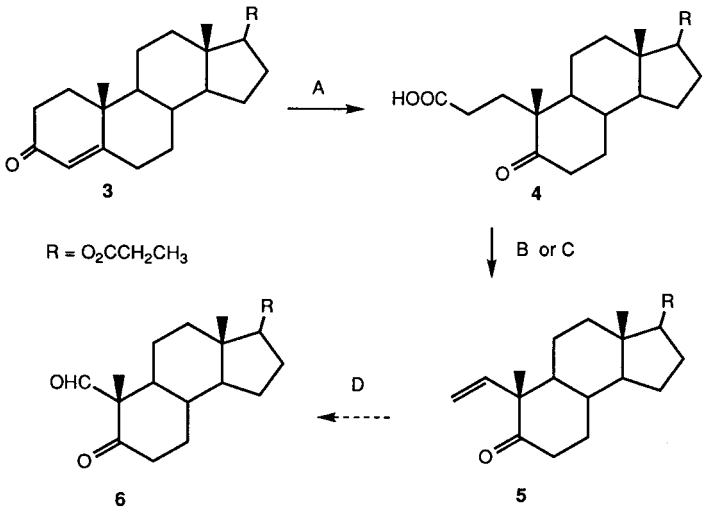
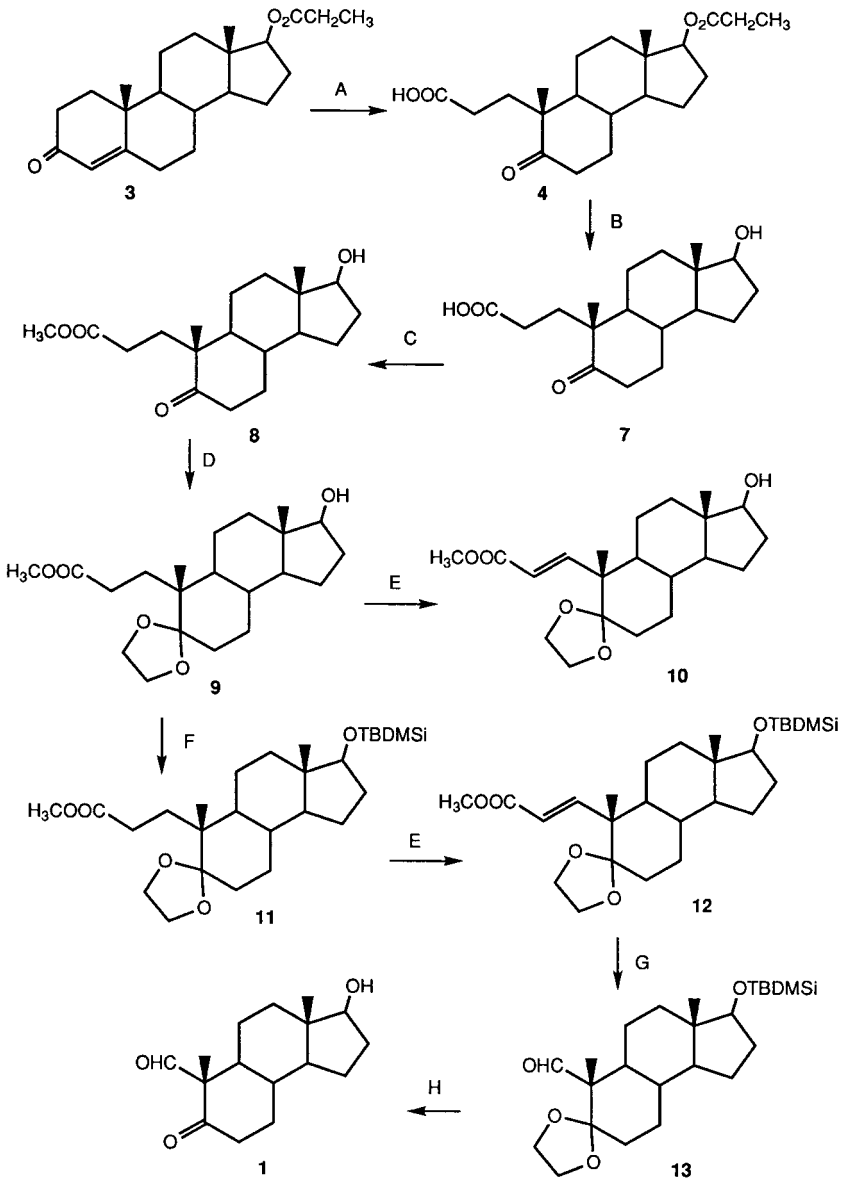
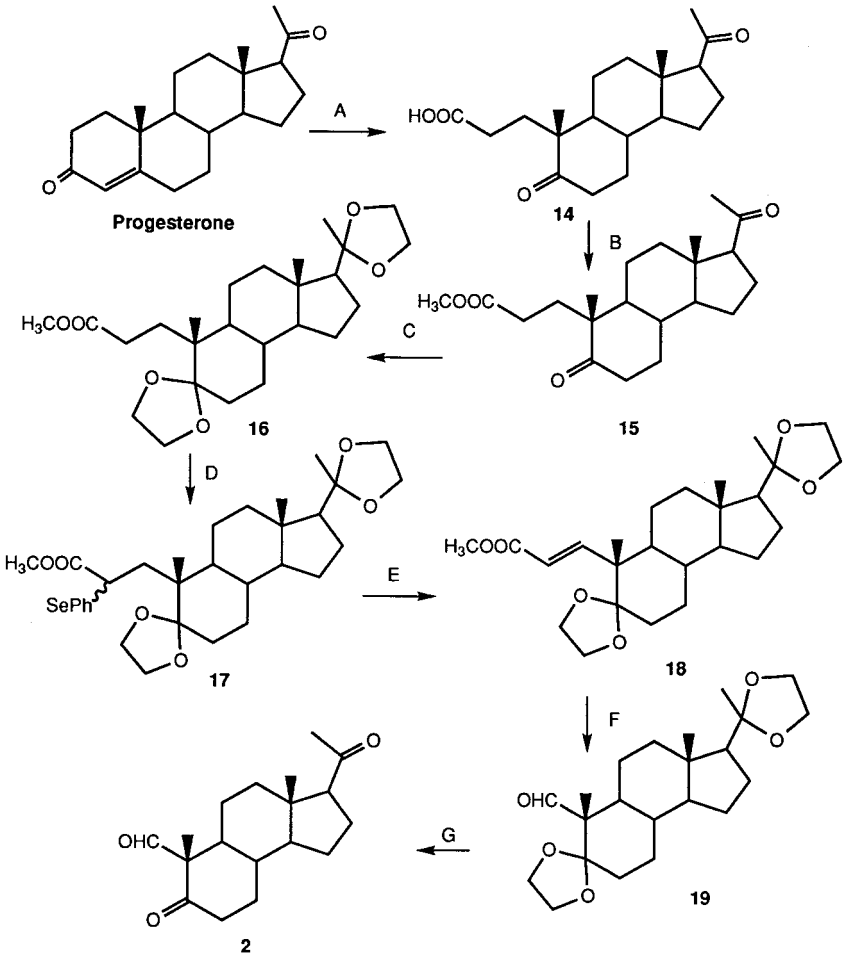


Scheme 1. *Reagents and conditions*: A: O_3, then H_2O_2. B: $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine, refluxing benzene. C: IBDA, $Cu(OAc)_2$, pyridine, refluxing benzene. D: O_3, Me_2S.



Scheme 2. *Reagents and conditions*: A: O_3, then H_2O_2. B: KOH, CH_3OH/H_2O, reflux. C: CH_2N_2. D: $HOCH_2CH_2OH$, $(CH_3O)_3CH$, PTSA. E: LDA, PhSeSePh, then H_2O_2. F: TBDMSiCl, imidazole. G: O_3, Me_2S. H: CH_3CO_2H/H_2O, reflux.



Scheme 3. *Reagents and conditions*: A: O_3, then H_2O_2. B: CH_2N_2. C: $HOCH_2CH_2OH$, $(CH_3O)_3CH$, PTSA. D: LDA, PhSeSePh. E: CH_2Cl_2–H_2O_2, pyridine. F: O_3, Me_2S. G: CH_3CO_2H/H_2O, reflux

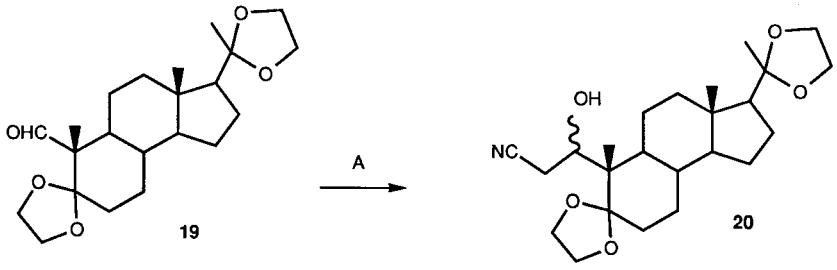
decarboxylation with iodosobenzene diacetate (IBDA) and catalytic amounts of cupric acetate (previously used to prepare alkenes from primary and secondary carboxylic acids derivates of steroidal substrates[10]) also afforded a very modest yield (34%).

Another synthetic route was therefore employed for the removal of the three adjacent carbons of the steroid nucleus to obtain the desired intermediate **1** (Scheme 2). Starting with testosterone propionate **3**, ozonolysis of the enone moiety followed by hydrolysis of the 17β-propionate group of **4** gave the keto acid **7** in good overall yield (76%). Reaction of this product with diazomethane quantitatively afforded the keto ester **8**. The 5-keto group was protected as an ethylenedioxyacetal group giving the ketal ester **9** (74%). Dehydrogenation of the ketal ester **9** would lead to an α,β-unsaturated carboxylic functionality, from which a second ozonolysis would effect the necessary further cleavage of two carbon atoms to obtain a 10-formyl group.

Conversion of ketones and esters to their α,β-unsaturated derivates can be done at mild conditions and in high yields by selenation followed by selenoxide elimination.[11] In our case selenation of ketal ester **9** with diphenyldiselenide, followed by oxidation of the crude selenated material,[12] led to a mixture of predominantly starting material and only about 20% of the desired α,β-unsaturated ketal ester **10** (ratio estimated by ^{1}H NMR).

Protection of the 17β-hydroxy group by treatment of **9** with dimethyl-*tert*-butylsilyl chloride and imidazole in dimethylformamide[13] afforded the silyl ether **11** (99%). Treatment of this compound with lithium diisopropylamide and reaction of the lithium enolate with diphenyldiselenide followed by oxidation with hydrogen peroxide yielded the unsaturated ester **12** (94%). Two-carbon-degradation to the 10-formyl derivate was achieved by ozonolysis of **12** followed by reductive treatment of the ozonide with dimethyl sulfide. Compound **13** was obtained in 85% yield. Simultaneous deacetalization of the C-5 carbonyl and cleavage of the dimethyl-*tert*-butylsilyl ether to the corresponding alcohol was done by treatment of **13** with aqueous acetic acid at reflux temperature,[14] providing compound **1** in excellent yield (98%). The overall yield of 10-formyl-5-oxo-des-A-testosterone **1** from **3** by the above procedure was 44%.

An analogous procedure was employed for the A ring degradation of progesterone (Scheme 3). Ozonolysis of the enone group accounts for the removal of the first carbon. The crude keto acid **14** was treated with diazomethane in methanol and the keto ester **15** was isolated in 79% yield after



Scheme 4. *Reagents and conditions*: A: $LiCH_2CN$.

chromatography. Protection of the keto groups at C-5 and C-20 was accomplished by reaction with ethylene glycol, trimethyl orthoformate and *p*-toluenesulfonic acid.[15] The diketal ester **16** was isolated as a white crystalline solid after radial chromatography on silica gel in 84% yield. Selenation of compound **16** was accomplished by reaction with lithium diisopropylamide in dry THF and treatment of the resulting enolate with diphenyldiselenide. The α-phenylseleno ester **17** was isolated after radial chromatography in 91% yield as a mixture of diastereomers. Oxidation of **17** with subsequent selenoxide elimination to give the α,β-unsaturated ester was performed using pyridine as a buffer to avoid hydrolysis of the C-20 ketal group under the slightly acidic aqueous condition of the oxidation. The desired α,β-unsaturated diketal ester **18** was isolated in 84% yield after radial chromatography. Further degradation of the A ring residue to the 10-formyl diketal derivate was accomplished by ozonolysis of **18** followed by treatment of the ozonide with dimethyl sulfide. Compound **19** was obtained in 96% yield after radial chromatography.

Deprotection of the carbonyl groups at C-5 and C-20 could be acchieved by refluxing compound **19** in 50% aqueous acetic acid solution to give 10-formyl-5-oxo-des-A-progesterone **2**, in 85% yield. The overall yield of **2** from progesterone was 41%.

The three-step procedure employed to accomplish A-ring reconstruction starting with the formyl ketones **1** and **2** is described in the following paper in this issue[6]. The use of compound **19** as an alternative starting material for the reconstruction of ring A of progesterone was also considered. Attempts to condense aldehyde **19** with 1-triphenylphosphoranylidene-2-propanone in xylene under reflux were unsuccessful. Reaction of **19** with diethyl 2-oxopropylphosphonate, which was attempted in a variety of procedures, also met with failure; the unreacted ketal aldehyde **19** was recovered from the reaction mixtures.

Reconstruction of the ring A starting by reaction of **19** with lithium ethyl acetate[16] with subsequent incorporation of a third carbon was also considered, but conversion of the carbonyl compound **19** into the corresponding β-hydroxy ester could not be achieved.

Since the addition to the 10-formyl group of **19** appeared to be seriously disfavored by steric hindrance, it seemed reasonable that a smaller and sterically less demanding nucleophile like acetonitrile anion[17] would be more effective in performing the addition. In fact, treatment of **19** with cyanomethyllithium gave the anticipated adduct **20** (39% yield) (Scheme 4). The low yield of this conversion, however, discouraged us from further attempts towards the potential route dehydration–hydrogenation–methylation and finally deprotection and cyclization.

In summary, we think that the synthetic routes presented here are an efficient way to eliminate the carbon atoms 2, 3 and 4 in the A rings of testosterone and progesterone. The reaction sequence can be easily adapted for use with a number of other steroid hormones. The 10-formyl-5-oxo-des A derivatives are well suited for reconstruction of the A rings; if suitably labeled components are used, this leads to ^{13}C-labeled testosterone and progesterone.[6]

Experimental

Melting points were determined using a Reichert Kofler melting point microscope and are uncorrected. NMR spectra were recorded at room temperature (in $CDCl_3$ unless otherwise indicated); internal references were $(CH_3)_4Si$ (δ 0.00) and $CDCl_3$ (δ 77.00), respectively. ^1H NMR spectra were recorded on either a Bruker WM 250 or a Bruker AM 400 operating at 250 MHz and 400 MHz, respectively. ^{13}C NMR spectra (62.9 and 100 MHz) were also recorded on these instruments. Mass spectra were recorded on a quadrupole mass spectrometer MS 800 (Frisons Instruments) connected to a gas chromatograph GC 800 series (Carlo Erba Instruments). Column was a DB-1 fused silica capillary column (15 m×0.32 mm ID), film thickness 0.25 μm. MS-conditions were 70 eV ionization energy, scan 50–600. The high resolution mass spectrum of **2** was recorded on a mass spectrometer 8230 (Finnigan, MAT) with direct inlet and 70 eV ionization energy (EI).

Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institut für Physikalische Chemie der Universität Wien.

Solvents were purified by standard methodology. Reactions requiring anhydrous conditions were carried out under either dry nitrogen or argon atmospheres. THF was distilled from sodium-benzophenone prior to use. Flash chromatography was performed using Merck silica gel 0.040–0.063 mm. Radial chromatography was carried out on a Chromatotron 8924 from Harrison Research, using rotors coated with Merck silica gel 60 PF-254 with calcium sulfate in various layer thickness (1,2 or 4 mm). Ozonolysis was performed by a Welsbach ozonizator using dry air as oxygen source.

17β-Propionoxy-5-oxo-3,5-*seco*-4-norandrostan-3-oic acid (4). A solution of testosterone propionate (2.028 g, 5.89 mmol) in ethyl acetate (100 mL) was oxidized by passing ozone through the solution at −78°C. The progress of the reaction was followed by TLC. As soon as the testosterone propionate had reacted, the excess ozone was flushed by a stream of nitrogen. To the ozonized solution hydrogen peroxide (30%, 25 mL) and water (5 mL) were added and the biphasic reaction mixture was stirred overnight at room temperature. The aqueous phase was then removed, the organic phase was washed with water (2×30 mL), extracted with ice cold 1% sodium hydroxide solution (4×25 mL). Each portion of the basic extract was immediately acidified with cold 5% hydrochloric acid solution and the resulting suspension was extracted with diethyl ether (3×80 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, the solvent was evaporated and the product was dried under vacuum to give a crystalline white solid (1.863 g, 87%). The product was used in the next step without further purification; δ_H (400 MHz, $CDCl_3$/TMS) 0.83 (s, 3H, 18-CH_3), 1.09 (s, 3H, 19-CH_3), 4.60 (t, 1H, 17-CH); δ_C (100.6 MHz) 214.5 (C-5), 179.3 (C-3), 174.5 (O*C*=OCH_2CH_3), 82.1 (C-17).

17β-Propionoxy-2, 5-*seco*-3, 4-dinorandrost-1-en-5-one (5). (a) Oxidative decarboxylation of acid **4** with lead tetraacetate. In a three neck round bottom flask equipped with condenser, the acid **4** (0.226 g, 0.620 mmol), cupric acetate (0.34 mmol), pyridine (0.3 mL) and dry benzene were stirred at room temperature under dry nitrogen. To the mixture the first portion of lead tetraacetate (0.560 g, 1.26 mmol) was added. The resulting dark green solution was stirred at room temperature in the dark for 30 min. The mixture was heated to reflux for 1 h and 45 min, then the second portion of lead tetraacetate was added (0.289 g, 0.652 mmol). The reaction mixture was refluxed for an additional 1 h and 45 min and the third portion of lead tetraacetate (0.264 g, 0.569 mmol) was added; heating was continued for another 1 h and 30 min. The mixture was allowed to cool to room temperature and 2.5 mL of ethylene glycol and water (20 mL) were added. The organic phase was separated, diluted with ethyl acetate (30 mL), washed with 10% solution of nitric acid (3×20 mL) and water (3×15 mL). The unchanged acid **4** was recovered by extracting the organic phase with ice cold 1% sodium hydroxide solution followed by reacidification and solvent extraction. The organic neutral extract, containing the desired alkene **5** was dried over anhydrous magnesium sulfate, filtered, evaporated and the residue chromatographed (silica gel, elution with 5% ethyl acetate in petroleum ether) to yield 83 mg (0.26 mmol, 42%) of **5** as an oil that crystallized on standing, mp (prisms from benzene–pentane) 119–122°C (Found: C, 75.17; H, 9.46. $C_{20}H_{30}O_3$ requires: C, 75.43; H, 9.50%), δ_H (400 MHz, $CDCl_3$/ TMS) 0.84 (s, 3H, 18-CH_3), 4.59 (t, 1H, 17-CH), 5.02 (d, 1H, 2-CH), 5.24 (d, 1H, 2-CH), 5.76 (dd, 1H, 1-CH); δ_C (100.6 MHz, $CDCl_3$/ TMS) 214.1 (C-5), 174.4 ($O_2CCH_2CH_3$), 141.6 (C-1), 114.5 (C-2), 82.0 (C-17). From the organic acidic extract 78 mg of unchanged acid **4** were recovered.

(b) Oxidative decarboxylation of acid **4** with iodosobenzene diacetate (IBDA). The acid **4** (0.565 g, 1.55 mmol), cupric acetate (0.060 g, 0.33 mmol) and pyridine (1,1 mmol) were mixed in dry benzene (40 mL) under an atmosphere of dry nitrogen. The reagents were stirred for 15 min at room temperature to effect solution. The first portion of IBDA (0.500 g, 1.55 mmol) was then added and the reaction mixture was heated to reflux. To the reaction mixture four additional portions of IBDA (0.505 g, 1.57 mmol; 0.500 g, 1.55 mmol; 0.517 g, 1.60 mmol and 0.513, 1.59 mmol) were added every 90 min, and the mixture was refluxed for 8 h. The reaction mixture was then washed with 5% hydrochloric acid solution (3×20 mL) and water (2×20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was submitted to flash chromatography (silica gel, elution with 5–50% ethyl acetate in petroleum ether) to yield 0.167 g (0.524 mmol, 34%) of alkene **5.** The methyl ester of the acid **4**, *methyl* 17β-*propionoxy*-5-*oxo*-3,5-*seco*-4-*norandrostan*-3-*oate*, was also isolated from the reaction mixture as an oil (0.175 g, 0.462 mmol, 30%), δ_H (400 MHz, $CDCl_3$/ TMS) 3.65 (s, 3H, CH_3O), 4.60 (t, 1H, 17-CH); δ_C (62.9 MHz, $CDCl_3$/ TMS) 214.2 (C-5), 174.4 (C-3), 174.3 (O*C*OCH_2CH_3), 82.1 (C-17), 51.5 (CH_3O).

17β-Hydroxy-5-oxo-3, 5-*seco*-4-norandrostan-3-oic acid (7). To the acid **4** (1.498 g, 4.11 mmol), prepared as described above, 70 mL of a solution of potassium hydroxide (1.0 g) in aqueous methanol (60 mL methanol, 10 mL water) was added. The mixture was heated to reflux for 3 h under nitrogen. The mixture was diluted with distilled water (140 mL), the resulting mixture was acidified and extracted with ether (4×100 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, the solvent evaporated to yield 1.116 g (3,62 mmol, 88%) of the product **7** as a white crystalline solid. Overall yield from testosterone propionate was 76%. The product was used in the next step without further purification. An analytical specimen was obtained by recrystallization from ethyl acetate–petroleum ether, colorless crystals, mp 203–205°C (literature,[7] mp 195–197°C, literature,[18] mp 204–205°C); δ_H (400 MHz, $CDCl_3$/ TMS) 3.58 (t, 1H, 17-CH), 1.07 (s, 3H, 19-CH_3), 0.74 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 215.4 (C-5), 176,9 (C-3), 81.1 (C-17), 17.5 (C-19), 10.9 (C-18).

Methyl 17β-hydroxy-5-oxo-3, 5-*seco*-4-norandrostan-3-oate (8). To a solution of the keto acid **7** (0.720 g, 2.33 mmol) in methanol (15 mL) a solution of diazomethane in diethyl ether was added until the bright yellow color persisted. The excess diazomethane was removed by passing a stream of dry nitrogen through the solution, and the mixture was concentrated. The residue was submitted to chromatography on silica gel (20 g of silica gel, elution with 20–40% ethyl acetate in petroleum ether) to give the keto ester **8** as a viscous colorless oil in quantitative yield: $C_{19}H_{30}O_4$ MS (EI): *m/z*: 322 (M^+,1.00%), 236 (100%); δ_H (400 MHz, $CDCl_3$/ TMS) 3.62 (s, 3H, MeO), 3.59 (t, 1H, 17-CH), 1.07 (s, 3H, 19-CH_3), 0.77 (s, 3H, 18-CH_3). δ_C (100.6 MHz, $CDCl_3$/ TMS) 214.4 (C-5), 174.3 (C-3), 81.2 (C-17), 56.5 (MeO), 20.3 (C-19), 10.9 (C-18).

Methyl 17β-hydroxy-5, 5-ethylenedioxy-3,5-*seco*-4-norandrostan-3-oate(9). The keto ester **8** (2.815 g, 8.73 mmol) was stirred overnight at room temperature with trimethyl orthoformate (20 mL), ethylene glycol

(20 mL) and *p*-toluenesulfonic acid (0.150 g). The mixture was diluted with ethyl acetate and the solution was washed with 5% sodium hydrogen carbonate solution. The organic phase was dried over anhydrous magnesium sulfate, filtered, concentrated and the residue was chromatographed (silica gel, elution with 18% ethyl acetate in petroleum ether) affording 2.371 g (6.45 mmol, 74%) of ketal ester **9**, mp (colorless crystals from benzene–pentane) 152–154°C (Found: C, 68.81; H 9.36. $C_{21}H_{34}O_5$ requires: C, 68.82; H, 9.35%); δ_H (400 MHz, $CDCl_3$/ TMS) 3.88 (m, 4H, $-OCH_2CH_2O-$), 3.61 (s, 3H, OMe), 3.59 (t, 1H, 17-CH), 2.54 (m, 1H, 2-CH), 2.29 (m, 1H, 2-CH), 0.969 (s, 3H, 19-CH_3), 0.715 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 175.3 (C-3), 113.7 (C-5), 81.7 (C-17), 64.1 and 63.9 ($-OCH_2CH_2O-$), 51.4 (CH_3O), 18.0 (C-19), 11.1 (C-18).

Methyl 17β-(*tert*-butyldimethylsilyloxy)-5,5-ethylenedioxy-3,5-*seco*-4-norandrostan-3-oate (11). To a stirred solution of the ketal ester **9** (1.329 g, 3.63 mmol) in dimethylformamide (14 mL), imidazole (0.957 g, 14.05 mmol) and *tert*-butyldimethylsilyl chloride (1.06 g, 7.03 mmol) were added. The mixture was stirred overnight at room temperature. Water (15 mL) was added and the mixture was extracted with ethyl acetate. The organic extract was washed with 1 N hydrochloric acid (30 mL), water (20 mL) and brine (20 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated. The oily residue was chromatographed (silica gel, elution with 5% ethyl acetate in petroleum ether) yielding 1.722 g of product **11** (3.58 mmol, 99 %) as a colorless oil which crystallized when left standing, mp (colorless crystals from pentane) 87–89°C (Found: C, 67.61; H, 10.23. $C_{27}H_{48}O_5Si$ requires: C, 67.45; H, 10.06%). δ_H (400 MHz, $CDCl_3$/ TMS) 3.90 (m, 4H, $-OCH_2CH_2O-$), 3.64 (s, 3H, OMe), 3.55 (t, 1H, 17-CH), 2.57 (m, 1H, 2-CH) and 2.32 (m, 1H, 2-C–H), 0.99 (s, 3H, 19-CH_3), 0.86 (s, 9H, Me_3–C–Si), 0.70 (s, 3H, 18-CH_3), 0.0007 and −0.0060 (2s, 3H each, Me_2–Si); δ_C (100.6 MHz, $CDCl_3$/ TMS) 175.4 (C-3), 113.9 (C-5), 81.7 (C-17), 64.2 and 64.0 ($-OCH_2CH_2O-$), 51.4 (OMe), 25.8 (Me_3–C–Si), 18.2 (C-19), 18.1 (Me_3–C–Si), 11.4 (C-18), −4.5 and −4.8 (Me_2–Si).

Methyl 17β-(*tert*-butyldimethylsilyloxy)-5,5-ethylenedioxy-3,5-*seco*-4-norandrost-1-en-3-oate (12). (a) Preparation of the α-phenylseleno carboxylic ester derivate, 17β *(tert-butyldimethylsilyloxy)*-2-*phenylseleno*-5,5-*ethylenedioxy*-3,5-*seco*-4-*norandrostan*-3-*oate*: To a three-necked round bottom flask equipped with two septa inlets, magnetic stirring, addition funnel and nitrogen inlet were added freshly distilled anhydrous THF (4 mL) and diisopropylamine (0.4 mL, 2.85 mmol). The solution was cooled in a dry ice–isopropanol bath, and was treated with *n*-butyllithium in hexane (15% solution, 1.75 mL, 2.87 mmol) for 25 min. The saturated ketal ester **11** (1.106 g, 2.30 mmol) in 4 mL THF was then slowly added dropwise. After stirring for 25 min, diphenyldiselenide (0.888 g, 2.84 mmol) in 4 mL dry THF was added quickly. The solution was stirred at −78°C for 30 min and then allowed to come to room temperature over a 2 h period. The reaction was then quenched by adding saturated ammonium chloride solution (30 mL), extracted with ethyl acetate, washed with 1 N hydrochloric acid (30 mL), water (30 mL), 5% sodium hydrogen carbonate solution (30 mL), saturated sodium chloride solution (30 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to yield a bright orange crystalline solid. The crude product weighed 1.869 g. In another run, the phenylseleno intermediate, *methyl* 17β-*(tert-butyldimethylsilyloxy)*-2-*phenylseleno*-5,5-*ethylenedioxy*-3,5-*seco*-4-*norandrostan*-3-*oate*, was purified by radial chromatography (4 mm silica gel coated rotor, elution with 5% ethyl acetate in petroleum ether) and isolated as yellow crystals: δ_H (400 MHz, $CDCl_3$/TMS) 7.60–7.58 (m, 2H, aromatic protons), 7.27–7.25 (m, 3H, aromatic protons) 3.92–3.63 (m, 4H, $-OCH_2CH_2O-$) 3.53 (s, 3H, MeO), 3.48 (t, 1H, 17-CH), 2.58 (dd, 1H, 2-CH), 0.93 (s, 3H, 19-CH_3), 0.86 (s, 9H, Me_3–C–Si), 0.65 (s, 3H, 18-CH_3), 0.0001 and −0.0015 (2s, 3H each, Me_2–Si); δ_C (100.6 MHz, $CDCl_3$/ TMS) 174.4 (C-3), 135.8, 129.2, 128.9, 128.4 (aromatic carbons), 113.1 (C-5), 81.7 (C-17), 63.4 and 63.4 ($-OCH_2CH_2O-$), 51.7 (MeO), 25.9 (Me_3–C–Si), 18.1 (Me_3–C–Si), 17.7 (C-19), 11.3 (C-18), −4.5 and −4.8 (Me_2–Si).

Oxidation/elimination of the phenylseleno group. A solution of the crude α-phenylseleno ester derivate (1.869 g) in dichloromethane (15 mL) was stirred in a three necked round bottom flask equipped with thermometer, reflux condenser and addition funnel. It was cooled in an ice bath and a solution of hydrogen peroxide (30%, 2 mL) in water (2 mL) was added dropwise. After addition was complete, the temperature of the reaction mixture rose quickly to 20°C, dropping thereafter. The ice bath was removed and the reaction mixture was stirred briefly at room temperature. Progress of the reaction was checked by TLC. The reaction mixture was transferred to a separation funnel with 5% sodium hydrogen carbonate solution (30 mL) and extracted with dichloromethane. The extract was dried over magnesium sulfate, filtered, evaporated, and the residue was submitted to radial chromatography (rotor coated with silica gel, 4 mm layer, elution with 5–10% ethyl acetate in petroleum ether) to yield 1.032 g (2.15 mmol, 94%) of product **12**, mp (colorless crystals from pentane) 85–88°C (Found: C, 67.69; H 9.91. $C_{27}H_{46}O_5Si$ requires: C, 67.74; H 9.68%); δ_H (400 MHz, $CDCl_3$/ TMS) 7.00 (d, 1H, 1-CH, J=16 Hz), 5.80 (d, 1H, 2-CH, J=16 Hz), 3.82 (m, 4H, $-OCH_2CH_2O-$), 3.71 (s, 3H, OMe), 3.52 (t, 1H, 17-CH), 1.14 (s, 3H, 19-CH_3), 0.85 (s, 9H, Me_3–C–Si), 0.67 (s, 3H, 18-CH_3), −0.022 (s, 6H, Me_2–Si); δ_C (100.6 MHz, $CDCl_3$/ TMS) 167.3 (C-3), 155.4 (C-1), 121.0 (C-2), 112.5 (C-5), 81.6 (C-17), 65.2 ($-OCH_2CH_2O-$), 51.4 (OMe), 25.8 (Me_3–C–Si), 18.1 (Me_3–C–Si), 13.6 (C-19), 11.4 (C-18), −4.5 and −4,8 (Me_2–Si).

17β-(*tert*-Butyldimethylsilyloxy)-10-formyl-5,5-ethylenedioxy-des-A-androstane (13). A solution of the α,β-unsaturated ketal ester **12** (0.164 g, 0.343 mmol) in dichloromethane–methanol solution (2:1.15 mL) was treated with ozone at −78°C until all starting material had been consumed, as indicated by TLC. After excess ozone had been removed by a stream of nitrogen, an excess of dimethyl sulfide (2 mL, 27 mmol) was added and the reaction mixture was allowed to warm gradually and was then stirred overnight at room temperature[19]. The mixture was then diluted with dichloromethane, washed with 5% sodium hydrogen carbonate solution (2×20 mL) and brine, dried over anhydrous magnesium sulfate, filtered and the

solvent was evaporated. The residue, a crystalline white solid, was chromatographed (silica gel, elution with 5% ethyl acetate in petroleum ether) to give 0.123 g (0.291 mmol, 85%) of the aldehyde **13**, a crystalline white solid, mp (colorless needles from pentane) 144–145°C (Found: C, 68.13; H, 9.91. $C_{24}H_{42}O_4Si$ requires: C, 68.20; H, 10.02%); δ_H (400 MHz, $CDCl_3$/ TMS) 9.65 (s, 1H, aldehydic proton at C-1), 3.93–3.78 (m, 4H, $-OCH_2CH_2O-$), 3.55 (t, 1H, 17-CH), 1.12 (s, 3H, 19-CH_3), 0.853 (s, 9H, Me_3-C-Si), 0.68 (s, 3H, 18-CH_3), −0.02 (s, 6H, Me_2-Si); δ_C (100.6 MHz, $CDCl_3$/ TMS) 207.2 (C-1), 113.0 (C-5), 81.6 (C-17, 64.7 and 64.6 ($-OCH_2CH_2O-$), 25.8 (Me_3-C-Si), 18.0 (Me_3-C-Si), 11.4 (C-19), 10.6 (C-18), −4.53 and −4.9 (Me_2-Si).

17β-Hydroxy-10-formyl-5-oxo-des-A-androstane (10-formyl-5-oxo-des-A-testosterone) (1). The ketal aldehyde **13** (0.1134 g, 0.268 mmol) was suspended in a mixture of glacial acetic acid, THF and water (3:1:1; 4.5 mL) and stirred overnight. Aqueous acetic acid was added (50% solution, 2 mL) and the mixture was heated to reflux (oil bath temperature 120°C) for 40 min, after which no more starting protected aldehyde could be detected by TLC. The mixture was allowed to cool to room temperature, brine (20 mL) was added and the mixture was thoroughly extracted with ethyl acetate. The organic extract was washed with 5% sodium hydrogen carbonate solution (15 mL), dried over magnesium sulfate, filtered, concentrated and the residue was chromatographed (silica gel, elution with 20% ethyl acetate in petroleum ether) to afford **1** (69.8 mg, 0.264 mmol, 98%) as a white crystalline solid, mp (colorless crystals from benzene) 133–134°C (Found: C, 72.61; H, 8.96. $C_{16}H_{24}O_3$ requires: C, 72.69; H, 9.15%). MS (EI), *m/z* (%)=236 (100) M^+-28, 221 (56), 218 (19), 185 (14). No trace of the M^+-peak could be detected. δ_H (400 MHz, $CDCl_3$/ TMS) 9.51 (s, 1H, CHO), 3.67 (t, 1H, 17-CH), 2.52 and 2.34 (dt, ddd respectively, 1H each, 6-CH_2), 1.27 (s, 3H, 19-CH_3), 0.79 (s, 3H,18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 212.4 (C-5), 201.1 (C-1), 81.1 (C-17), 62.0 (C-10), 49.9 (C-14), 46.0 (C-9), 42.8 (C-13), 37.9 (C-6), 35.6 (C-12), 34.8 (C-8), 30.6 (C-7), 29.8 (C-16), 23.2 (C-15), 21.3 (C-11), 12.7 (C-19), 11.0 (C-18).

Methyl 5,20-dioxo-3,5-*seco*-4-norpregnan-3-oate (15). A solution of progesterone (3.02 g, 9.60 mmol) in ethyl acetate (100 mL) was treated with a stream of ozone until no starting material could be detected by TLC (30 min). The excess ozone was purged with air, and hydrogen peroxide (30% solution, 25 mL) and water (5 mL) were added to the reaction mixture. The biphasic mixture was stirred over night at room temperature. The organic layer was then separated, washed with water, concentrated to 1/3 of its initial volume and extracted with saturated sodium carbonate solution (3×30 mL). The basic extract was acidified with 10% hydrochloric acid solution and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated to yield the keto acid **14** as a white foam. The crude keto acid was dissolved in methanol (20 mL) and treated with diazomethane until the bright yellow color of the solution persisted. The excess of diazomethane was discharged, the solvent was evaporated and the residue submitted to chromatography (silica gel; elution with 10–25% ethyl acetate in petroleum ether) giving 2.652 g (7.612 mmol, 79%) of the keto ester **15** as a colorless oil. $C_{21}H_{32}O_4$: MS (EI), *m/z* (%)=348 (M^+ 1.55%), 262 (100%); δ_H (400 MHz, $CDCl_3$/ TM) 3.59 (s, 3H, OMe), 205 (s, 3H, 21-CH_3), 1.04 (s, 3H, 19-CH_3), 0.61 (s, 3H, 18-CH_3). δ_C (100.6 MHz, $CDCl_3$/ TMS) 214.0 (C-5), 208.9 (C-20), 174.1 (C-3), 63.3 (C-17), 51.4 (OMe), 20.2 (C-19), 13.2 (C-18).

Methyl 5,5,20,20-bis (ethylenedioxy)-3,5-*seco*-4-norpregnan-3-oate (16). The diketo ester **15** (2.350 g, 6.74 mmol) was stirred overnight at room temperature with trimethyl orthoformate (15 mL), ethylene glycol (15 mL) and *p*-toluenesulfonic acid (65 mg). The mixture was then diluted with dichloromethane and washed with 5% sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, filtered, concentrated and the residue was submitted to radial chromatography on silica gel (4 mm layer rotor coated with silica gel, elution with 5–15% ethyl acetate in petroleum ether) affording 2.475 g (5.67 mmol, 84%) of the bisketal ester **16** as a crystalline white solid, mp (colorless crystals from pentane) 115–117°C (Found: C, 68.60; H, 9.43. $C_{25}H_{40}O_6$ requires: C, 68.78; H, 9.23%); δ_H (400 MHz, $CDCl_3$/TMS) 3.87 (m, 8H, $-OCH_2CH_2O-$), 3.60 (s, 3H, OMe), 2.52 and 2.29 (m both, 1H each, 2-CH_2), 1.24 (s, 3H, 21-CH_3), 0.91 (s, 3H, 19-CH3), 0.72 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 175.2 (C-3), 113.7 (C-5), 11.7 (C-20), 65.1, 64.0, 63.8 and 63.1 (2×$-OCH_2CH_2O-$), 58.2 (C-17), 51.2 (OMe), 18.0 (C-19), 12.9 (C-18).

Methyl 2-phenylseleno-5,5,20,20-bis(ethylenedioxy)-3,5-*seco*-4-norpregnan-3-oate (17). To a three-neck round bottom flask equipped with septum inlet, magnetic stirring, addition funnel and nitrogen inlet were added anhydrous THF (4 mL) and diisopropyl amine (0.45 mL, 3.19 mmol). The resulting solution was cooled in a dry ice–isopropanol bath and treated with *n*-butyllithium in hexane (15% solution, 2.0 mL, 3.28 mmol) for 30 min. The bisketal ester **16** (0.997 g, 2.28 mmol) in THF (5 mL) was then added dropwise and the reaction mixture was stirred at −78°C for another 30 min. Diphenyldiselenide (0.995 g, 3.19 mmol) in THF (2 mL) was quickly added and the reaction mixture was stirred at −78°C for 1 h, allowed to warm slowly to room temperature (over 1 h period), and then quenched by adding saturated ammonium chloride solution. After extraction with ethyl acetate the organic phase was washed with 5% sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, filtered and the residue was submitted to radial chromatography (silica gel coated rotor, 4 mm layer, elution with 5–30% ethyl acetate in petroleum ether), giving 1.225 g (2.071 mmol, 91%) of compound **17** as a pale yellow solid. Compound **17** was isolated as a diastereoisomeric mixture, in which the two diastereoisomers are approximately in a ratio of 4 to 1: δ_H (400 MHz, $CDCl_3$/TMS) 7.61–7.58 (m, 2H, aromatic protons), 7.29–7.26 (m, 3H aromatic protons), 3.98–3.77 (m, 8H, $-OCH_2CH_2O-$), 3.53 and 3.48 (both s, 3H OMe, relative proportion 4: 1), 2.58 (dd, 1H, C*H*–SePh), and 2.3 (dd, 1H, CH–SePh),1.28 and 1.26 (both s, 3H, 21-CH_3), 0.96 and 0.95 (both s, 3H, 19-CH_3), 0.74 and 0.73 (both s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS; relative intensities, in a maximum of 10.00, are given) C-3, 174.8 (0.38) and 174.5 (1.73); C-5, 113.5 (0.72) and 113.1 (2.24); C-20,

111.8 (2.94); C-17, 58.2 (5.18) and 58.2 (1.48); OMe, 51.7 (1.02) and 51.7 (3.73); C-19 17.4 (2.56) and 16.6 (1.28); C-18, 13.4 (1.35) and 12.9 (5.12). Aromatic carbons: 135.7 (8.89), 135.7 (2.80), 129.1 (0.85), 128.8 (10.00) and 128.8 (3.69), 128.4 (5.24). Ethylenedioxy groups are also to some extent affected, since 6 signals were detected: 65.2 (4.77), 64.0 (2.90), 63.4 (5.40), 63.3 (5.24), 63.2 (6.04), 63.1 (2.49).

Methyl 5,5,20,20-bis (ethylenedioxy)-3,5-*seco*-4-nor-pregn-1-en-3-oate (18). To a solution of the α-phenyl-seleno ester **17** (1.164 g, 1.97 mmol) in dichloromethane (15 mL) in a three necked round bottom flask (equipped with condenser, thermometer, addition funnel, magnetic stirring) pyridine was added (0.5 mL) and the solution was cooled in an ice bath. To the cooled mixture a solution of hydrogen peroxide (30% solution, 2 mL) in water (1 mL) was added dropwise. When the addition was complete, the temperature of the reaction mixture rose rapidly to 10°C, dropping thereafter. The cooling bath was removed and stirring was continued at room temperature for 30 min. The mixture was diluted with dichloromethane and washed with 5% sodium hydrogen carbonate solution. The organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated to give an off-white solid. The crude product was then submitted to radial chromatography on silica gel–silver nitrate coated rotor (2 mm layer, elution with 5–10% ethyl acetate in petroleum ether) to give 0.717 g (1.65 mmol, 84%) of the α,β-unsaturated ester **18** as a white powder: mp (colorless crystals from benzene–pentane) 188–190°C (Found: C, 68.88; H, 8.58. $C_{25}H_{38}O_6$ requires: C, 69.10; H, 8.81%.); δ_H (400 MHz, $CDCl_3$/ TMS) 7.01 (d, 1H, J 16.2, 1-HC═), 5,08 (d, 1H, J=16.2 Hz, 2-HC═), 3.96–3,81 (m, 8H, $-OCH_2CH_2O-$), 3.71 (s, 3H, OMe), 1.26 (s, 3H, 21-CH_3), 1.14 (s, 3H, 19-CH_3), 0.73 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 167.3 (C-3), 155.4 (C-1), 121.0 (C-2), 112.5 (C-5), 111.8 (C-20), 65.2 and 63.1 ($-OCH_2CH_2O-$), 58.1 (C-17), 51.3 (OMe), 13.0 (C-18).

10-Formyl-5,5,20,20-bis(ethylenedioxy)-des-A-pregnane (19). The α,β-unsaturated keto ester **18** (0.565 g, 1.30 mmol) in a dichloromethane–methanol solution (2:1, 15 mL) was cooled in a dry ice–isopropanol bath and treated with a stream of ozone until no starting material remained (30 min). Excess ozone was then removed by a stream of nitrogen, dimethyl sulphide (2.0 mL, 27.2 mmol) was added to the solution at −78°C, and the resulting mixture was allowed to come to room temperature and was stirred overnight. The mixture was then diluted with dichloromethane (30 mL), washed with 5% sodium hydrogen carbonate solution (30 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to yield a white crystalline solid. The crude ozonolysis product was submitted to radial chromatography (silica gel coated rotor, 2 mm layer, elution with 5–10% ethyl acetate in petroleum ether), yielding 0.471 g (1.24 mmol, 96%) of the ketal aldehyde **19** as a white crystalline solid: mp (colorless crystals from benzene–pentane) 160–162°C (Found: C, 69.64; H, 9.28. $C_{22}H_{34}O_5$ requires: C, 69.81; H, 9.05%); δ_H (400 MHz, $CDCl_3$/ TMS) 9.96 (s, 1H, CHO), 3.91–3.79 (m, 8H, 2×$-OCH_2CH_2O-$), 1.26 (s, 3H, 21-CH_3), 1.11 (s, 3H, 19-CH_3) and 0.74 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 207.3 (C-1), 113.0 (C-5), 111.8 (C-20), 65.1, 64.7, 64.5, 63.1 (2×$-OCH_2CH_2O-$), 58.1 (C-17), 13.0 (C-19) and 10.6 (C-18).

10-Formyl-5,20-dioxo-des-A-pregnane (10-formyl-5-oxo-des-A-progesterone) (2). The bisketal aldehyde **19** (0.755 g, 1.99 mmol) was suspended in a 50% aqueous solution of acetic acid (14 mL) and heated to reflux until all the starting material had been consumed (oil bath temperature 125°C, 30 min). The mixture was then diluted with ethyl acetate and washed with brine (30 mL), with 5% sodium hydrogen carbonate solution (2×30 mL), dried over magnesium sulfate, filtered and concentrated. The residue was submitted to chromatography on silica gel (flash chromatography, 20 g silica gel, elution with 10–15% ethyl acetate in petroleum ether) to give 0.492 g (1.69 mmol, 85%) of the bis-keto aldehyde **2** as a white crystalline solid: mp (colorless crystals from benzene–pentane) 140–142°C (Found: C, 74.16; H, 9.24. $C_{18}H_{26}O_3$ requires: C, 74.45; H, 9.02%). MS (EI), m/z (%)=262 (100) M^+-28, 247 (52), 201 (46). As for **1**, no trace of the M^+-peak could be detected. For both compounds the largest peak was due to the loss of a fragment with mass 28. High resolution mass spectrometry for **2** showed this fragment to correspond to $C_{17}H_{26}O_2$ (calculated 262.1927; found 262.1933) and thus resulting from the loss of CO. δ_H (400 MHz, $CDCl_3$/ TMS) 9.51 (s, 1H, CHO), 2.54 (m, 2H, 17-CH and 6-H), 2.34 (ddd, 1H, the other 6-H), 2.10 (s, 3H, 21-CH_3), 1.25 (s, 3H, 19-CH_3), 0.66 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 212.5 (C-5), 208.8 (C-20), 201.4 (C-1), 63.1 (C-17), 62.3 (C-10), 55.6 (C-14), 45.6 (C-9), 44.0 (C-13), 38.1 (C-6), 37.9 (C-12), 34.0 (C-8), 31.3 (C-21), 30.6 (C-7), 24.2 (C-15), 22.6 (C-16), 22.2 (C-11), 13.2 (C-18), 12.3 (C-19). The assignments for C-6 and C-12 are uncertain.

1-Hydroxy-2-cyano-5,5,20,20-bis(ethylenedioxy)-2,5-*seco*-3,4-dinor-pregnane (20). To a three neck round bottom flask equipped with septa inlet, magnetic stirring and addition funnel freshly distilled anhydrous THF (1 mL) was added under an atmosphere of dry nitrogen. The flask was cooled by a dry ice–isopropanol bath, and *n*-butyl-lithium (15% solution in hexane, 0.50 mL, 0.82 mmol) was added, followed by 10% acetonitrile solution in anhydrous THF (0.40 mL, 0.75 mmol). The mixture was stirred for 45 min and the ketal aldehyde **19** (0.220 g, 0.581 mmol), in THF (2 mL), was added dropwise. Stirring was continued for 45 min and the reaction was quenched with 10% ammonium chloride solution (10 mL) and extracted with ether (2×25 mL). The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was submitted to radial chromatography (silica gel coated rotor, 2 mm layer, elution with 15–30% ethyl acetate in petroleum ether) affording 0.096 g of the adduct **20** (0.229 mmol, 39%, diastereoisomeric mixture) as a colorless oil: δ_H (400 MHz, $CDCl_3$/TMS) 4.2 to 3.9 (m, 9H, 1-C–(OH)–*H*and $-OCH_2-CH_2O-$), 2.95 to 2.5 (m, 2H, CH_2-CN), 1.25 (s, 3H, 21-CH_3), 1.15 (s, 3H, 19-CH_3), 0.75 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 119.4 and 115.3 (CN), 114.0 and 113.6 (C-5), 111.7 and 111.6 (C-20), 73.2 and 72.8 (C-1), 65.1, 65.0, 63.8, 63.6, 63.17, 63.13, 63.09, and 63.07 ($-OCH_2-CH_2O-$), 15.6 and 15.3 (C-19), 12.9 and 12.8 (C-18), and unchanged compound **19** (85 mg, 0.224 mmol). Yield based on unrecovered bisketal aldehyde **19** is 64%.

References

1. Thompson, G. N.; Pacy, P. J.; Ford, G. C.; Halliday, D. *Biomed. Environ. Mass Spectrom.* **1989**, *18*, 321–327.
2. Baillie, T. *Pharmacol. Rev.* **1981**, *33*, 81–132.
3. (a) Gambert, P.; Lallemant, C.; Archambault, A.; Maume, B. F.; Padieu, P. *J. Chromatogr.* **1979**, *162*, 1–6. (b) Sabot, J. F.; Deruaz, D.; Dechaud, H.; Bernard, P.; Pinatel, H. *J. Chromatogr.* **1985**, *339*, 233–242. (c) Chapman, T. E.; Kraan, G. P. B.; Drayer, N. M.; Nagel, G. T.; Wolthers, B. G. *Biomed. Environ. Mass Spectrom.* **1987**, *14*, 73–82. (d) Vierhapper, H.; Nowotny, P.; Waldhäusl, W. *J. Steroid Biochem.* **1988**, *29*, 105–109. (e) Shackleton, C. H. L.; Reid, S. *Clin. Chem.* **1989**, *35*, 1906–1910. (f) Kraan, G. P. B.; Drayer, N. M. *Steroids* **1990**, *55*, 159–164. (g) Vierhapper, H. *Steroids* **1990**, *55*, 177–180. (h) Chapman, T. E.; Kraan, G. P. B.; Nagel, G. T.; Wolthers, B. G.; Drayer, N. M. *J. Steroid Biochem. Mol. Biol.* **1991**, *38*, 489–496. (i) Ostlund, Jr., R. E.; Matthews, D. E. *J. Lipid Res.* **1993**, *34*, 1825–1831. (j) Dehennin, L. *J. Steroid Biochem. Mol. Biol.* **1993**, *44*, 171–177.
4. Zomer, G.; Stavenuiter, J. F. C. *Steroids* **1990**, *55*, 440–442.
5. Ihara, M.; Tokunaga, Y.; Taniguchi, N.; Fukumoto, K. *Tetrahedron* **1991**, *33*, 6635–6648.
6. Kockert, K.; Vierhapper, F. W. *Tetrahedron* **2000**, 9967–9974.
7. Hartshorn, M. P.; Jones, E. R. H. *J. Chem. Soc.* **1962**, 1312–1313.
8. Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215–2226.
9. (a) Vaidya, A. S.; Dixit, S. M.; Rao, A. S. *Tetrahedron Lett.* **1968**, *50*, 5173– 5174. (b) Keana, J. F. W.; Schumaker, R. R. *J. Org. Chem.* **1976**, *41*, 3840–3846. (c) Frith, R. G.; Phillipou, G.; Seaborn, C. J. *Tetrahedron Lett.* **1977**, *38*, 3403–3404. (d) Mícková, R. *Collect. Czech. Chem. Commun.* **1984**, *49*, 1617–1621.
10. Concepción, J. I.; Francisco, C. G.; Freire, R.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1986**, *51*, 402–404.
11. (a) Reich, H. J.; Renga, J. M.; Reich, L. I. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139.
12. Holt, D. A.; Levy, M. A.; Brandt, M.; Metcalf, B. W. *Steroids* **1986**, *48*, 213–222.
13. Corey, E. J.; Venkateswarklu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
14. Ando, M.; Wada, T.; Kusaka, H.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 4792–4796.
15. Yuan, S. *Steroids* **1982**, *39*, 279–289.
16. Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222–3223.
17. Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613–615.
18. Rodewald, W. J.; Rotuska, T. *Roczniki. Chem.* **1966**, *40*, 1255; *Chem. Abstr.* **1967**, Abstract 66: 38109t.
19. Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, *48*, 4273–4378.