Pergamon

Tetrahedron 56 (2000) 9967–9974

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 2[1]

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Received 28 July 2000; revised 10 October 2000; accepted 11 October 2000

Abstract—Fragmentation of the A ring of the steroid hormone testosterone to yield the 10-formyl-5-oxo-des A intermediate was achieved by lactolization, lactonization, ozonolysis, and oxidation of the resulting methylol group. The reconstruction of the A ring was carried out via a Wittig synthesis with triphenylphosphoranylidene-2-propanone-$^{13}C_3$. Syntheses of the ylide, of the $^{13}C_3$-testosterone, and of $^{13}C_3$-progesterone took place in acceptable yields.

Use of ^{13}C labeled steroid compounds as tracers in clinical investigations is superior in comparison to ^{14}C-labeled analogs because of the absence of ionizing radiation. Detection, on the other hand, has to rely on mass spectroscopy. In order to take care for a sufficient difference in intensity to heavier ions resulting from natural abundance, at least three ^{13}C atoms should be introduced into the tracer. A larger number of labels offers no great advantage and will only raise the cost of the material.

In our attempts to prepare ^{13}C labeled steroid hormones, we therefore decided to partially degrade the A ring of commercially available starting compounds without losing the configurational information, subsequently reconstructing the ring with a $^{13}C_3$ synthon. Our aim was to develop a synthesis which could be used with small changes for a number of different steroids. Various possibilities of A ring degradation were investigated; part of this work has been reported in the preceding paper.[1] Here we report an additional way for A ring fragmentation, and the synthesis of the 2,3,4-$^{13}C_3$ steroid hormones testosterone, progesterone and androstendione.

Results and Discussion

In an alternative to the synthesis of 10-formyl-5-oxo-des A testosterone described in the preceding paper[1] a reaction sequence depicted in Scheme 1 via lactol **2**[2] and lactone **3**[2] was carried out. Owing to the poor solubility of the lactol rather large amounts of solvent were necessary to separate **2** from the crown ether and to obtain satisfactory yields of **2**, making scale-up somewhat troublesome. Crucial step in the synthesis was the ozonolysis of the lactone **3** to the ring-opened product **4**; conditions had to be carefully optimized for the reaction to take place in acceptable yields within a reasonable time (see Experimental Section). The procedure was successful both with 17β-protected (**3b**, **3c**) or with the 17-OH (**3a**) compounds. In the latter case the secoalcohol **4a** (R=H) was oxidized in the subsequent oxidation step D to the oxo-compound **5d**, and the following reactions took place with the keto compound.

If progesterone was used as starting material of the reaction sequence, enolate formation of the C-20 keto group led to hydroxylation at C-17 via a peroxide so that 10-formyl-5-oxo-des A progesterone (**5e**) could not be obtained by this route. Either the method described in the preceding paper[1] was used to prepare **5e**, or a stigmastene side chain could be used initially and be converted to the progesterone side chain at a later stage.[3]

A few methods for the reconstruction of the A ring starting with 1,5-secosteroids were available in the literature.[4,5] However, if the aim of the synthesis is the introduction of three ^{13}C atoms, most of these techniques would use the labeled component in large molar excess or as a solvent, thus lowering the yields of the product relative to the expensive labeled starting materials. The most promising method was reaction with a Wittig reagent[5] 1-triphenylphosphoranylidene-$^{13}C_3$-2-propanone (**6**), which could be prepared from commercially available ^{13}C-methyl-triphenylphosphonium iodide and $^{13}C_2$-acetyl chloride in 75% yield. The synthesis takes place via an intermediate thioester (Scheme 2); the ethane thiol is removed from the reaction mixture by

Keywords: steroids; degradation; labeling.

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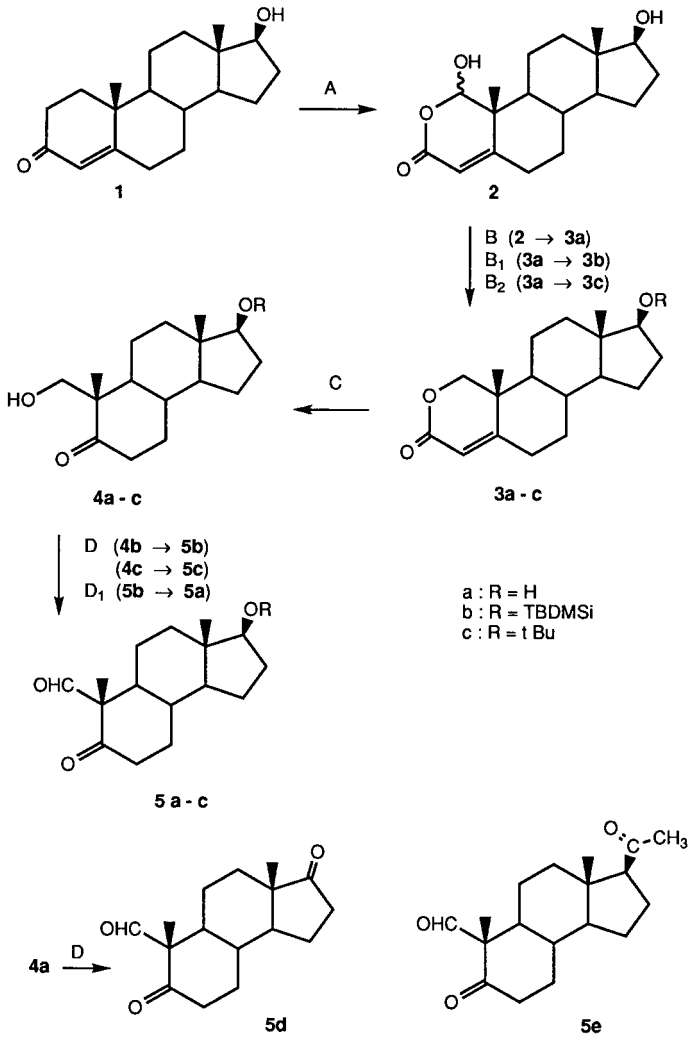
PII: S0040-4020(00)00967-4

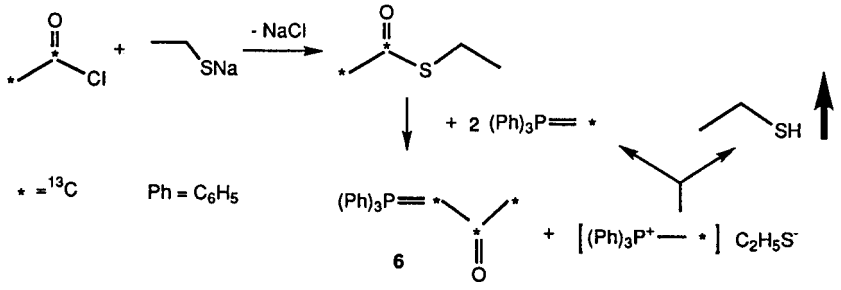


Scheme 1. *Reagents and conditions*: A: O_2, 18-crown-6, t-BuOK, toluene, −30°C, 6 h; RT, 2–3 d. B: $NaBH_4$, $CHCl_3$, H_2O/OH^-. B_1: TBDMSiCl, imidazole, DMF, 12 h. B_2: H_3PO_4/BF_3, $CH_2C(CH_3)_2$. C: O_3, −78°C, EtOAc/CH_3OH; H_2O; 10% aqu. K_2CO_3/H_2O. D: SO_3·pyridine, DMSO, Et_3N. D_1: CH_3COOH, reflux, 20 min.

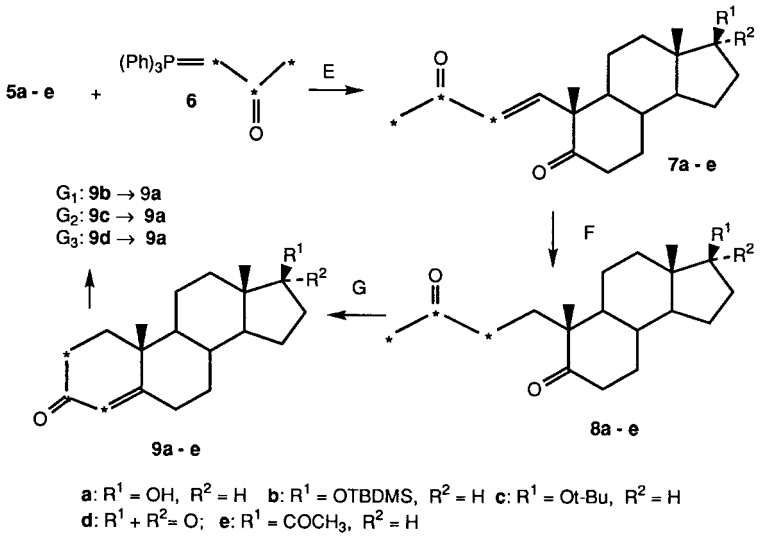
distillation and the starting ylide is regenerated, shifting the equilibrium towards the desired product.[6]

Only the more reactive aldehyde group of the secosteroids **5** reacted with the ylide (Scheme 3).[5] Heating in xylene gave compounds **7**. No retroaldol reactions[3,7] were observed.

Selective hydrogenation of the double bond in the side chain of **7** was possible with a palladium catalyst at slightly elevated pressure. No reduction of the keto groups took place. The protective TBDMSi group of **7b** was split off in a very minor extent (~5% in 5 h). This is unimportant, since the protective group has to be cleaved in any case, and the free 17-OH does not adversely influence the following aldol reaction. Absence of impurities, however, appears to be crucial. If hydrogenation is not complete after a few hours, catalyst and solvent must be replaced with new reagents, or else side product formation can lead to drastically diminished yields of **8**. Mainly 3-ethoxylated products were identified among other products in a long time experiment with **7c** over a catalyst intentionally poisoned with dimethyl sulfide.[3]



Scheme 2.



Scheme 3. *Reagents and conditions*: E: xylene, reflux, 7 d. F: H_2, Pd(10%)/C, EtOH. G: 10% KOH, CH_3OH. G_1: CH_3COOH, reflux, 20 min. G_2: CF_3COOH, RT 1 h; LiOH/CH_3OH, 30 min. G_3: CH_3OH, $NaBH_4$, 0°C, 6 h.

The crude products **8** were cyclized with potassium hydroxide in methanol at room temperature. The protective groups (TBDMSi in **9b** and the *tert* butyl group in **9c**) were removed to give **9**. The 17-keto group of 4-androsten-3,17-dione (**9d**) could be selectively reduced to the 17β-alcohol **9a**; less than 5% of the 3β,17β-diol were formed. Overall yields of the labeled steroid hormones **9a**, **9d** and **9e** relative to the starting $^{13}C_2$-acetyl chloride are shown in Table 1. Yields for testosterone are quite similar independent of starting compound **5**; slightly better yields in the Wittig reaction step for **5b** and **5c** are compensated by the additional step necessary to remove the protective groups.

In summary, the synthetic sequence starting with commercially available testosterone or progesterone to the 2,3,4-$^{13}C_3$-labeled steroids testosterone, adrostendione and progesterone, respectively, can be carried out in between 9 to 11 steps, only 4 to 5 of which involve the labeled material. The ^{13}C of the starting material $^{13}C_2$-acetyl chloride is recovered in approximately 40% yield in the labelled steroids, which allows synthesis of the materials in the gram-amounts needed for clinical investigations even at the considerable cost of ^{13}C materials.

Experimental

General procedures

Melting points were determined using a Reichert Kofler melting point microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AM 400 in $CDCl_3$ unless otherwise indicated; internal references were $(CH_3)_4Si$ (δ 0.00) and $CDCl_3$ (δ 77.00), respectively. Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institut für Physikalische Chemie der Universität Wien. Mass spectra were generally 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 ionisation energy (EI), scan 50–600. The mass spectrum of the ylide **6** was recorded on a mass spectrometer 8230 (Finnigan, MAT) with direct inlet and 70 eV ionisation energy (EI).

Table 1. Yields of products

Starting **5**	CH_3COCl→**7** [a]	**7**→**9**	Total [a]
5a	**7a**: 58	**9a**: 72	**9a**: 42
5b	**7b**: 60	**9a**: 68	**9a**: 41
5c	**7c**: 64	**9a**: 66	**9a**: 42
5d	**7d**: 54	**9d**: 77, **9a**: 72	**9d**: 42, **9a**: 39
5e	**7e**: 50	**9e**: 82	**9e**: 38

[a] Percent of theoretical yield, relative to acetyl chloride. Values are averages of three runs, with ^{12}C-material.

Preparative chromatography was carried out either by flash chromatography using Merck silica gel 60 (0.040–0.063 mm) or by radial chromatography 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). Results were similar with both techniques; the method selected depended on the amounts of sample. If more than 2 g had to be separated, flash chromatography was used. Solvent mixtures were generally ethyl acetate and petroleum ether. The ratios are reported with the individual steps.

Ozonolysis was performed by a Welsbach ozonisator using dry air as oxygen source, producing 10 g ozone/h with dry air feed.

Solvents were purified by standard methodology. Reactions requiring anhydrous conditions were carried out under either dry nitrogen or argon atmospheres. Chemicals were obtained from Aldrich or Sigma and were used without further purification unless otherwise indicated. $^{13}C_2$-Acetyl chloride was purchased from Stable Isotopes, CEA-France.

Content of ^{13}C isotope was determined for the labeled end

products **9a**, **9d** and **9e** by integration of the M^+ regions of the mass spectra and by integration of the ^{13}C NMR spectra. Quantitative evaluation of the mass spectra was achieved by dividing the abundance of the M^+-1 peak (the $^{13}C_2$ compounds) by the sum of M^+ (i.e. the $^{13}C_3$) and M^+-1. Values of $2\pm0.1\%$ M^+-1 were obtained for the three steroids.

In the ^{13}C NMR spectra of **9**, the signals for the ^{13}C enriched carbons 2, 3 and 4 were split into doublets of doublets by the coupling with the neighboring ^{13}C atoms through one and two bonds, respectively. If the regions for ^{13}C-2 and ^{13}C-4 were expanded, additional small doublets could be assigned, corresponding to the coupling in the $^{13}C_2$ compounds with either only ^{13}C-3 or ^{13}C-2 (for ^{13}C-4) and ^{13}C-4 (for ^{13}C-2), respectively. Integration of these doublets relative to the total area of the C-2- and C-4-regions, respectively, indicated an abundance of 99 ± 0.5 % for each of the three positions. This is in satisfactory agreement with the isotopic enrichment of the commercial ^{13}C starting materials specified by the suppliers.

A similar evaluation of the ^{13}C NMR spectrum of **6** was problematic due to the additional carbon–phosphorus coupling; the signals of the doublets of doublets due to one neighboring ^{13}C and one ^{31}P were too small to be reliably integrated. The mass spectrum of the unlabeled analogue of **6** gave an M^+-1 peak (m/z=317) of rather similar intensity to the M^+-peak (m/z=318) (18.9 vs. 24.2%), so these signals could not be used to assess the extent of the labelling in **6** (m/z 320:321=20.0:21.2). However, the ^{13}C-content in each position is reflected in the end products **9**.

1ξ,17β-Dihydroxy-2-oxaandrost-4-en-3-one (2).[2] A solution of testosterone (**1**) (3.64 g, 12.6 mmol) and 18-crown-6 (5.00 g) in 1 L toluene (previously distilled from sodium) was cooled to −27°C (±3°C). Freshly sublimated *tert*-BuOK (4.3 g) was added, and the solution was saturated with oxygen (dried over sulfuric acid, silica gel and potassium hydroxide) for 2 min. Oxygen was then slowly passed through the solution which was kept at −27°C until TLC (acetone: petroleum ether=1:3) showed complete reaction of **1** (~3 h). The mixture was brought to room temperature and stirred while continuously passing through a slow stream of oxygen. After ~90 h TLC showed only **2**. The mixture was neutralized by addition of 10% aqueous hydrochloric acid and 1 L diethyl ether was added. The organic layer was washed with 10% aqueous sodium hydrogen carbonate, the washings were acidified with hydrochloric acid and extracted with diethyl ether. The organic phases were united, dried over magnesium sulfate and the solvent was distilled off. Lactol **2** was recrystallized from ethyl acetate. Yield 3.48 g (90%). Mp 238–241°C (literature[2] mp 248°C). Spectroscopic data agreed with the values in the literature.[2]

17β-Hydroxy-2-oxaandrost-4-en-3-one (3a).[2] To a solution of **2** (1.00 g, 3.3 mmol) in 500 mL chloroform a solution of sodium borohydride (1.00 g, 26.4 mmol) in 140 mL water and 1 mL 10% aqueous sodium hydroxide was slowly added. The mixture was stirred vigorously at room temperature for ~5 h; progress of the reaction was followed by TLC (acetone:petroleum ether=1:2). The phases were separated, and the organic layer was washed with 5% aqueous sodium hydroxide and dried over magnesium sulfate. The solvent was distilled off. To the aqueous phase another 500 mL chloroform was added, and the mixture was stirred over night. The reaction was then quenched by addition of 10% aqueous hydrochloric acid. The organic layer was worked up as described above. The unified products **3a** were purified by chromatography (ethyl acetate:petroleum ether=1:3). Yield 855 mg (90 %). Mp 201–203°C (literature[2] mp 201–202°C). Spectroscopic data agreed with the values in the literature.[2]

17β-*tert*-Butyldimethylsilyloxy-2-oxaandrost-4-en-3-one (3b). A solution of **3a** (1 g, 3.45 mmol), *tert*-butyldimethylchlorosilane (725 mg, 5 mmol) and imidazole (470 mg, 7.9 mmol) in dimethylformamide (10 mL) was stirred at room temperature for 12 h. The reaction was quenched with water, and the mixture was extracted with diethyl ether. The organic layer was washed with 5% aqueous hydrochloric acid and then with 10% aqueous sodium chloride. The diethyl ether solution was dried over magnesium sulfate and the solvent was distilled off at diminished pressure. The crude **3b** was purified chromatographically (ethyl acetate:petroleum ether=1:6). Yield 1.25 g (88%). Mp 136–137°C. (Found: C, 71.14; H, 10.05. $C_{24}H_{40}O_3Si$ requires: C, 71.23; H, 9.96%). δ_H (400 MHz, $CDCl_3$/TMS) 5.56 (s, 1H, 4-H), 4.12 (d, 1H, 1-H), 3.88 (d, 1H, 1-H), 3.45 (t, 1H, 17-H), 1.11 (s, 3H, 19-CH_3), 0.78 (s, 9H, $C(CH_3)_3$), 0.64 (s, 3H, 18-CH_3), −0.09 (s, 6H, $Si(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$/TMS) 167.6 (C-3), 164.3 (C-5), 113.2 (C-4), 81.4 (C-17), 76.7 (C-1), 25.6 ($C(\mathbf{C}H_3)_3$), 17.8 ($\mathbf{C}(CH_3)_3$), 16.2 (C-19), 11.0 (C-18), −4.6, −4.9 ($Si(\mathbf{C}H_3)_2$).

17β-*tert*-Butoxy-2-oxaandrost-4-en-3-one (3c). Isobutene (Aldrich, 99%) (4 mL) was condensed in a vessel cooled with liquid nitrogen, and was slowly added to a suspension of **3a** (290 mg, 1 mmol) in 4 mL dichloromethane (dried over 4 Å molecular sieves) at approx. −30°C. A mixture of boron trifluoride diethyl etherate and phosphoric acid (0.1 mL; ratio=1:1) was added, and the mixture was stirred at room temperature for 20 h in a pressure resistant stoppered flask (the joint was protected by a teflon sleeve). Unreacted isobutene was evaporated, the residue was purged by a stream of dry nitrogen, and the dichloromethane solution was washed with 5% aqueous sodium hydrogen carbonate. The washings were extracted with dichloromethane, the organic layers were united, dried over magnesium sulfate and the solvent was distilled off. The crude **3c** was purified chromatographically (ethyl acetate:petroleum ether=1:3).Yield 322 mg (92%). Mp 176–177°C. (Found: C, 76.17; H, 9.95. $C_{22}H_{34}O_3$ requires: C, 76.26; H, 9.89%). δ_H (400 MHz, $CDCl_3$/TMS) 5.56 (s, 1H, 4-H), 4.13 (d, 1H, 1-H), 3.89 (d, 1H, 1-H), 3.28 (t, 1H, 17-H), 1.16 (s, 3H, 19-CH_3), 1.07 (s, 9H, $C(CH_3)_3$), 0.66 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 168.0 (C-3), 164.8 (C-5), 113.4 (C-4), 80.5 (C-17), 77.0 (C-1), 72.2 ($\mathbf{C}(CH_3)_3$), 28.7 ($C(\mathbf{C}H_3)_3$), 16.4 (C-19), 11.5 (C-18).

Optimization of ozonolysis reaction 3→4 with 3c. A solution of **3c** (200 mg) in the solvent listed in Table 2 was cooled to −78°C. Ozone was passed through the solution until starting material was no longer visible on TLC (ethyl

Table 2.

Solvent	R	t (h)	Yield **4c** (%)
CH_2Cl_2	10 mL 10% aqu. K_2CO_3	15	68
CH_2Cl_2	10 mL 1% aqu. KOH	5	55
CH_2Cl_2	5 mL 5% aqu. H_2SO_4	5	28
CH_2Cl_2/CH_3OH	10 mL 10% aqu. K_2CO_3	15	59
CH_2Cl_2/CH_3OH	10 mL 1% aqu. KOH	5	52
CH_2Cl_2/CH_3OH	5 mL 5% aqu. H_2SO_4	5	24
AcOEt	10 mL 10% aqu. K_2CO_3	15	75
AcOEt	10 mL 1% aqu. KOH	5	65
AcOEt/CH_3OH	10 mL 10% aqu. K_2CO_3	15	93

acetate:dichloromethane=1:5) and a blue color of ozone persisted. The residual ozone was purged from the solution by a stream of dry nitrogen, 1 mL of dimethyl sulfide was added, and the solution was stirred for 3 h at room temperature. The solvent was distilled off at reduced pressure and the residue was dissolved in diethyl ether.

Reagent 'R' (Table 2) was added and the mixture was stirred for several hours. The phases were separated, the aqueous phase was extracted with diethyl ether, the organic layers were united, washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The solvent was distilled off and the products were separated by chromatography (ethyl acetate:petroleum ether=1:5 to 1:1). Yields of **4c** see Table 2.

Ozonolysis reaction 3a→1,17β-dihydroxy-1,5-secoandrostan-5-one (4a), 3b→17β-*tert*-butyldimethylsilyloxy-1-hydroxy-1,5-secoandrostan-5-one (4b), 3c→ 17β-*tert*-butoxy-1-hydroxy-1,5-secoandrostan-5-one (4c). The lactone **3** (3.5 mmol) was dissolved in 100 mL ethyl acetate:methanol=1:1. and ozone was passed through the solution at −78°C until a blue color persisted (~13 min with flow 100 L/min; current intensity 0.6 A) and control by TLC showed no starting **3**. Residual ozone was purged with dry nitrogen, 3 mL dimethyl sulfide was added and the mixture was stirred at room temperature for 2 h. The solvent was distilled off at 50°C at reduced pressure and the residue was dissolved in 100 mL diethyl ether. Aqueous 10% potassium carbonate (100 mL) was added and the mixture was stirred vigorously over night at room temperature. The aqueous phase was extracted repeatedly with diethyl ether, the ether phases were united and dried over magnesium sulfate. The crude products were purified by chromatography.

4a: Chrom. solvent ethyl acetate:petroleum ether=1:3. Yield 88%. Mp 155–158°C. (Found: C, 72.08; H, 9.95. $C_{16}H_{26}O_3$ requires: C, 72.14; H, 9.84%). δ_H (400 MHz, $CDCl_3$/TMS) 3.72 (d, 1H, 1-H), 3.41 (d, 1H, 1-H), 3.43 (t, 1H, 17-H), 1.02 (s, 3H, 19-CH_3), 0.77 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 217.9 (C-5), 81.0 (C-17), 64.7 (C-1), 52.5 (C-10), 15.5 (C-19), 10.9 (C-18).

4b: Chrom. solvent ethyl acetate:petroleum ether=1:6. Yield 87%. Mp 141–144°C. (Found: C, 69.50; H, 10.63. $C_{22}H_{40}O_3Si$ requires: C, 69.42; H, 10.59%). δ_H (400 MHz, $CDCl_3$/TMS) 3.80 (d, 1H, 1-H), 3.43 (d, 1H, 1-H), 3.54 (t, 1H, 17-H), 1.04 (s, 3H, 19-CH_3), 0.85 (s, 9H, $C(CH_3)_3$), 0.74 (s, 3H, 18-CH_3), −0.02 (s, 6H, $Si(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$/TMS) 217.5 (C-5), 81.4 (C-17), 65.4 (C-1), 52.8 (C-10), 25.6 ($C(\mathbf{C}H_3)_3$), 17.8 ($\mathbf{C}(CH_3)_3$), 15.7 (C-19), 11.3 (C-18), −5.0, −4.7 ($Si(\mathbf{C}H_3)_2$).

4c: Chrom. solvent ethyl acetate:petroleum ether=1:5. Yield 93%. Mp 130–132°C (literature[5] mp 130–131°C). Spectroscopic data agreed with the values in the literature.[5]

Oxidation of 4a to 10-formyl-des-A-androstan-5,17-dione (5d), 4b to 17β-*tert*-butyldimethylsilyloxy-10-formyl-des-A-androstan-5-one (5b), 4c to 17β-*tert*-butoxy-10-formyl-des-A-androstan-5-one (5c). To a stirred solution of secoalcohol **4** (0.91 mmol) and 1.83 g triethylamine (18.1 mmol) in anhydrous dimethyl sulfoxide (12 mL) a solution of 920 mg sulfur trioxide/pyridine (5.8 mmol) in anhydrous dimethyl sulfoxide (8 mL) was slowly added at room temperature. Stirring was continued for 1.5 h after addition was complete. After addition of diethyl ether the layers were separated. The ether layer was washed with 10% aqueous sodium chloride solution. To the dimethyl sulfoxide layer a cold 10% aqueous solution of sodium chloride was carefully added, and the resulting mixture was extracted with diethyl ether (precipitates were left in the aqueous phase). The combined washings were extracted with diethyl ether, the combined ether phases were dried over magnesium sulfate or sodium sulfate and the diethyl ether was distilled off. Products were purified by chromatography. As for **5a**[1] and **5e**,[1] no trace of the M^+-peak could be detected in the mass spectra. The peak with the largest mass in each corresponded to the loss of a fragment with mass 28.

5d: Chrom. solvent ethyl acetate:petroleum ether=1:3. Yield 88%. Mp 135–138°C. (Found: C, 73.17; H, 8.51. $C_{16}H_{22}O_3$ requires: C, 73.25; H, 8.45%). MS (EI), *m/z* (%)=234 (100) M^+-28, 190 (28), 136 (39), 121 (55). δ_H (400 MHz, $CDCl_3$/TMS) 9.44 (s, 1H, 1-H), 1.21 (s, 3H, 19-CH_3), 0.85 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 219.1 (C-17), 211.9 (C-5), 201.0 (C-1), 62.1 (C-10), 13.5 (C-18), 12.3 (C-19).

5b: Chrom. solvent ethyl acetate:petroleum ether=1:8. Yield 92%. Mp 122–124°C. (Found: C, 69.70; H, 10.21. $C_{22}H_{38}O_3Si$ requires: C, 69.79; H, 10.12%). MS (EI), *m/z* (%)=350 (13) M^+-28, 321 (81), 217 (57), 75 (100). δ_H (400 MHz, $CDCl_3$/TMS) 9.48 (s, 1H, 1-H), 3.56 (t, 1H, 17-H), 1.24 (s, 3H, 19-CH_3), 0.84 (s, 9H, $C(CH_3)_3$), 0.73 (s, 3H, 18-CH_3), −0.03 (s, 6H, $Si(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$/ TMS) 212.8 (C-5), 201.5 (C-1), 81.2 (C-17), 62.5 (C-10), 25.7 ($C(CH_3)_3$), 17.9 ($C(CH_3)_3$), 12.9 (C-19), 11.3 (C-18), −5.1, −4.7 ($Si(CH_3)_2$).

5c: Chrom. solvent ethyl acetate:petroleum ether=1:4. Yield 90%. Mp 148–150°C (literature[5] mp 149–150.5°C). ^1H NMR spectral data agreed with the values in the literature.[5] In the mass spectrum, in contrast,[5] the M^+-peak could not be detected. MS (EI), *m/z* (%)=292 (22.5) M^+-28, 236 (24.2), 57 (100).

Cleavage of TBDMS protecting group of 5b to 10-formyl-17β-hydroxy-des-A-androstan-5-one (5a). To a solution of **5b** (455 mg, 1.2 mmol) in tetrahydrofuran (10 mL)

acetic acid (30 mL) and water (10 mL) was added and the mixture was heated to reflux for 1 h. The cooled mixture was diluted with water (30 mL) and repeatedly extracted with $CHCl_3$. The chloroform phases were united, the solvent was distilled off and residual acetic acid was distilled off by azeotropic distillation with toluene. Compound **5a** was obtained in quantitative yield after purification by chromatography (ethyl acetate:petroleum ether=1:5). Mp 132–134°C (mp and spectroscopic data were identical with Ref. 1).

Synthesis of 1-triphenylphosphoranylidene-$^{13}C_3$-2-propanone (6). (a) $^{13}C_2$-Thioacetic acid S-ethyl ester. To a solution of $^{13}C_2$-acetyl chloride (1.00 g, 12.4 mmol, isotopic purity >99% for each position) in benzene (distilled from sodium) under argon, sodium thioethylate (1.32 g, 16.2 mmol) was added at 6°C. The reaction was complete after 10 min. **(b) Methylenetriphenylphosphorane-*methylene*-^{13}C.** Methyl-triphenylphosphonium-*methyl*-^{13}C-iodide (5.20 g, 12.8 mmol, isotopic purity >99%) was suspended in dry benzene (80 mL). Sodium amide (0.53 g, 13.6 mmol) was added, and the mixture was heated to reflux under argon for 5 h. A yellow color of the ylide developed after some time. **(c) 1-Triphenylphosphoranylidene-$^{13}C_3$-2-propanone (6).** The benzene solution of the thioester (a) was transferred via a syringe to the solution (b), which had been filtered through a sintered glass filter disk under argon. Solids were washed with small amounts of benzene and this was also added. The resulting benzene solution was heated to reflux under argon for 12 h. The solvent was distilled off, and the remaining white material was used directly in the syntheses of **7**. Yield 2.93 g (75% relative to $^{13}C_2$-acetyl chloride). Mass and NMR-spectra were recorded with a small amount purified by column chromatography (aluminum oxide 90 (70–230 mesh) with ethyl acetate). $^{12}C_{18}{}^{13}C_3H_{19}PO$: MS (EI), *m/z* (%)=321 (21.2) M^+, 320 (20.0), 305 (100) $M^+-{}^{13}CH_3$. δ_H (400 MHz, $CDCl_3$/TMS) 7.3–7.8 (m, 15H, C_6H_5), 3.72 (dd, 1H, =CH–, $^1J_{C-H}$= 164 Hz, $^2J_{P-H}$=32 Hz), 2.12 (3H, CH_3; d, $^1J_{C-H}$=126 Hz, of d, *J*=5 Hz of d, *J*=2 Hz of d, *J*=2 Hz). δ_C (100.6 MHz, $CDCl_3$/TMS) 190.9 (**C**O, ddd, $^1J_{=CCO}$=64 Hz, $^1J_{CH3CO}$= 41 Hz, $^2J_{PC}$=2 Hz), 133.0 (arom. C-2, d, *J*=10.1 Hz), 131.9 (arom. C-4, d, *J*=2.9 Hz), 128.8 (arom. C-3, d, *J*= 12.3 Hz), 127.2 (arom. C-1, d, *J*=90.6 Hz), 51.8 (=**C**H–, ddd, $^1J_{PC}$=108 Hz, $^1J_{=CCQ}$=64 Hz, $^2J_{CH3CH}$=9 Hz), 28.4 (CH_3,ddd, $^1J_{CH3CO}$=41 Hz, $^2J_{CH3CH}$=19 Hz, $^3J_{PC}$=16 Hz).

Wittig-reaction 5→7. 5a→2,3,4-$^{13}C_3$-17β-Hydroxy-4,5-seco-1-androsten-3,5-dione (7a), 5b→2,3,4-$^{13}C_3$-17β-*tert*-butyldimethylsilyloxy-4,5-seco-1-androsten-3,5-dione (7b), 5c→2,3,4-$^{13}C_3$-17β-*tert*-butoxy-4,5-seco-1-androsten-3,5-dione (7c), 5d→2,3,4-$^{13}C_3$-4,5-seco-1-androsten-3,5,17-trione (7d), 5e[1]→2,3,4-$^{13}C_3$-4,5-seco-1-pregnen-3,5,20-trione (7e). A solution of **5** (5 mmol) and of the crude **6** (1.28 g, 4 mmol) in xylene (30 mL) was heated to reflux for several days. The solvent was distilled off under diminished pressure, and the residue was chromatographed to give products **7** as oils. Yields see Table 1.

7a: Reaction time 3 d. Chrom. solvent ethyl acetate:petroleum ether=1:3. δ_H (400 MHz, $CDCl_3$/TMS) 6.76 (dd, 1H, 1-H), 6.00 (ddd, 1H, 2-H, J_{2C-2H}=160.0 Hz), 3.64 (t, 1H, 17-CH), 2.62 and 2.33 (dt, ddd respectively, 1H each, 6-CH_2), 2.28 (dd, 3H, 4-H, J_{4C-4H}=127.5 Hz, J_{3C-4H}= 6.0 Hz), 1.29 (s, 3H, 19-CH_3), 0.78 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 212.5 (C-5), 198.0 (C-3, d, 53.0, of d, 42.5), 150.4 (C-1, d, 70.0, of d, 2.5), 131.0 (C-2, d, 53.0, of d, 15), 81.1 (C-17), 54.4 (C-10), 26.6 (C-4, d, 42,5 of d, 15), 15.2 (C-19), 11.0 (C-18).

7b: Reaction time 3 d. Chrom. solvent ethyl acetate:petroleum ether=1:6. δ_H (400 MHz, $CDCl_3$/TMS) 6.73 (dd, 1H, 1-H), 5.99 (ddd, 1H, 2-H, J_{2C-2H}=160.0 Hz), 3.48 (t, 1H, 17-CH), 2.61 and 2.32 (dt, ddd respectively, 1H each, 6-CH_2), 2.24 (dd, 3H, 4-H, J_{4C-4H}=128.0 Hz, J_{3C-4H}=6.0 Hz), 1.25 (s, 3H, 19-CH_3), 0.82 (s, 9H, $C(CH_3)_3$), 0.71 (s, 3H, 18-CH_3), −0.04 (s, 6H, $Si(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$/TMS) 212.8 (C-5), 198.1 (C-3, d, 53, of d, 42.5), 150.6 (C-1, d, 70.0, of d, 2.5), 130.7 (C-2, d, 53.0, of d, 14.7), 81.2 (C-17), 54.5 (C-10), 26.4 (C-4, d, 42.5 of d, 14.7), 25.7 ($C(CH_3)_3$), 17.9 ($C(CH_3)_3$), 15.3 (C-19), 11.3 (C-18), −5.0, −4.6 ($Si(CH_3)_2$).

7c: Reaction time 3 d. Chrom. solvent ethyl acetate:petroleum ether=1:7. δ_H (400 MHz, $CDCl_3$/TMS) 6.73 (dd, 1H, 1-H), 5.97 (ddd, 1H, 2-H, J_{2C-2H}=159.0 Hz), 3.32 (t, 1H, 17-CH), 2.62 and 2.32 (dt, ddd respectively, 1H each, 6-CH_2), 2.24 (dd, 3H, 4-H, J_{4C-4H}=127.5 Hz, J_{3C-4H}= 5.9 Hz), 1.24 (s, 3H, 19-CH_3), 1.06 (s, 9H, $C(CH_3)_3$), 0.71 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 213.0 (C-5), 198.3 (C-3, d, 53.0, of d, 42.5), 151.1 (C-1, d, 71.0, of d, 2.5), 130.8 (C-2, d, 53, of d, 14.7), 80.3 (C-17), 72.2 ($C(CH_3)_3$), 54.5 (C-10), 28.6 ($C(CH_3)_3$), 26.8 (C-4, d, 42.5 of d, 14.7), 15.3 (C-19), 11.6 (C-18).

7d: Reaction time 3 d. Chrom. solvent ethyl acetate:petroleum ether=1:2. δ_H (400 MHz, $CDCl_3$/TMS) 6.73 (dd, 1H, 1-H), 5.98 (ddd, 1H, 2-H, J_{2C-2H}=158.0 Hz), 2.60 and 2.31 (dt, ddd respectively, 1H each, 6-CH_2), 2.25 (dd, 3H, 4-H, J_{4C-4H}=128.0 Hz, J_{3C-4H}=6.0 Hz), 1.20 (s, 3H, 19-CH_3), 0.82 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 219.2 (C-17), 211.9 (C-5), 198.0 (C-3, d, 53.0, of d, 42.5), 150.2 (C-1, d, 71.0, of d, 2.5), 131.1 (C-2, d, 53.0, of d, 14.7), 54.4 (C-10), 26.9 (C-4, d, 42.5 of d, 15.0), 15.2 (C-19), 14.0 (C-18).

7e: Reaction time 4 d. Chrom. solvent ethyl acetate:petroleum ether=1:3. δ_H (400 MHz, $CDCl_3$/ TMS) 6.73 (dd, 1H, 1-H), 5.97 (ddd, 1H, 2-H, J_{2C-2H}=159.0 Hz), 2.58 and 2.29 (dt, ddd respectively, 1H each, 6-CH_2), 2.47 (t, 1H, 17-H), 2.23 (dd, 3H, 4-H, J_{4C-4H}=128.0 Hz, J_{3C-4H}=6.0 Hz), 2.04 (s, 3H, 21-CH_3), 1.22 (s, 3H, 19-CH_3), 0.62 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 212.5 (C-5), 208.9 (C-20), 198.3 (C-3, d, 53, of d, 42.5), 150.8 (C-1, d, 71.0, of d, 2.5), 131.0 (C-2, d, 53.0, of d, 14.7), 63.3 (C-17), 54.5 (C-10), 26.9 (C-4, d, 42.5 of d, 14.7), 15.3 (C-19), 13.4 (C-18).

Reduction of C–C-double bond (7→8). 7a→2,3,4-$^{13}C_3$-17β-hydroxy-4,5-seco-androstan-3,5-dione (8a), 7b→2,3,4-$^{13}C_3$-17β-*tert*-butyldimethylsilyloxy-4,5-seco-androstan-3,5-dione (8b), 7c→2,3,4-$^{13}C_3$-17β-*tert*-butoxy-4,5-seco-androstan-3,5-dione (8c), 7d→2,3,4-$^{13}C_3$-4,5-seco-androstan-3,5,17-trione (8d), 7e→2,3,4-$^{13}C_3$-4,5-seco-pregnan-3,5,20-trione (8e). To a solution of enone **7** (2.75 mmol) in ethanol (20 mL) catalyst Pd/C (10%, 210 mg) was added and the mixture was shaken under

hydrogen (pressure 3 bar) on a Parr low pressure hydrogenator for several hours. (If hydrogenation had not taken place after that time, the catalyst was filtered off, the solvent was evaporated at reduced pressure and solvent and catalyst were replaced with new reagents.) The catalyst was filtered by passing over a short column with silica gel, and the solvent was distilled off. Products could be obtained pure by chromatography (see below) as colorless oils, or else the crude products were used in the next step (**8→9**).

8a: Hydrogenation time 5 h. Chrom. solvent ethyl acetate: petroleum ether=1:3. Yield 91%. δ_H (400 MHz, $CDCl_3$/TMS) 3.59 (t, 1H, 17-CH), 2.01 (dd, 3H, 4-H, J_{4C-4H}= 128.0 Hz, J_{3C-4H}=5.6 Hz), 1.03 (s, 3H, 19-CH_3), 0.72 (s, 3H,18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 214.3 (C-5), 209.1 (C-3, d, 40.2, of d, 39.8), 81.1 (C-17), 38.7 (C-2, d, 39.8, of d, 14.6), 30.0 (C-4, d, 40.2 of d, 14.6), 20.3 (C-19), 11.0 (C-18).

8b: Hydrogenation time 2 h. Chrom. solvent ethyl acetate: petroleum ether=1:7. Yield 84%; ~ 5% of **8a** is formed and is not separated for the synthesis of **9a**. δ_H (400 MHz, $CDCl_3$/TMS) 3.49 (t, 1H, 17-CH), 2.01 (dd, 3H, 4-H, J_{4C-4H}=127.5 Hz, J_{3C-4H}=5.8 Hz), 1.04 (s, 3H, 19-CH_3), 0.81 (s, 9H, $C(CH_3)_3$), 0.70 (s, 3H, 18-CH_3), −0.06 (s, 6H, $Si(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$/TMS) 214.6 (C-5), 208.6 (C-3, d, 40.3, of d, 39.8), 130.7 (C-2, d, 53.0, of d, 14.7), 81.4 (C-17), 50.3 (C-10), 29.6 (C-4, d, 40.3 of d, 14.7), 25.7 ($C(CH_3)_3$), 20.4 (C-19), 17.9 ($C(CH_3)_3$), 11.2 (C-18), −5.0, −4.6 ($Si(CH_3)_2$).

8c: Hydrogenation time 2 h. Chrom. solvent ethyl acetate: petroleum ether=1:6. Yield 94%. δ_H (400 MHz, $CDCl_3$/ TMS) 3.32 (t, 1H, 17-CH), 2.05 (dd, 3H, 4-H, J_{4C-4H}= 128.0 Hz, J_{3C-4H}=5.6 Hz), 1.04 (s, 3H, 19-CH_3), 1.03 (s, 9H, $C(CH_3)_3$), 0.68 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 214.8 (C-5), 208.9 (C-3, d, 40.3, of d, 39.9), 80.3 (C-17), 72.1 ($C(CH_3)_3$), 50.2 (C-10), 38.6 (C-2, d, 39.9, of d, 14.6), 29.6 (C-4, d, 40.3 of d, 14.6), 28.6 ($C(CH_3)_3$), 20.4 (C-19), 11.4 (C-18).

8d: Hydrogenation time 4 h. Chrom. solvent ethyl acetate: petroleum ether=1:2. Yield 92%. δ_H (400 MHz, $CDCl_3$/ TMS) 2.02 (dd, 3H, 4-H, J_{4C-4H}=128.0 Hz, J_{3C-4H}= 5.5 Hz), 1.01 (s, 3H, 19-CH_3), 0.80 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 219.6 (C-17), 213.9 (C-5), 208.6 (C-3, d, 40.3, of d, 39.5), 50.1 (C-10), 38.4 (C-2, d, 39.5, of d, 14.5), 29.6 (C-4, d, 40.3 of d, 14.5), 20.2 (C-19), 13.5 (C-18).

8e: Hydrogenation time 3 h. Chrom. solvent ethyl acetate: petroleum ether=1:4. Yield 93%. δ_H (400 MHz, $CDCl_3$/ TMS) 2.12 (dd, 3H, 4-H, J_{4C-4H}=128.0 Hz, J_{3C-4H}= 5.6 Hz), 2.04 (s, 3H, 21-CH_3), 1.03 (s, 3H, 19-CH_3), 0.63 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 214.6 (C-5), 208.7 (C-3, d, 53, of d, 42.5), 208.6 (C-20), 63.2 (C-17), 50.3 (C-10), 38.6 (C-2, d, 53.0, of d, 14.7), 31.3 (C-21), 29.7 (C-4, d, 42.5 of d, 14.7), 20.4 (C-19), 13.3 (C-18).

Aldol reaction with 8 to steroids 9. 8a→2,3,4-$^{13}C_3$-testosterone (9a), 8b→2,3,4-$^{13}C_3$-17β-*tert*-butyldimethylsilyloxy-4-androsten-3-one (9b), 8c→2,3,4-$^{13}C_3$-17β-*tert*-butoxy-4-androsten-3-one (9c), 8d→2,3,4-$^{13}C_3$-androstendione (9d), 8e→2,3,4-$^{13}C_3$-progesterone (9e). To a solution of crude **8** of the above step in 40 mL methanol 4 mL of 10% aqueous potassium hydroxide solution was added and the mixture was stirred at room temperature for several hours under a protective atmosphere of argon. After addition of a small amount of sodium chloride the methanol was distilled off at reduced pressure and the residue was extracted with chloroform. The organic layer was washed with a 5% aqueous solution of sodium chloride, dried over magnesium sulfate and the solvent was evaporated. The products were obtained pure by chromatography (see below).

9a: Reaction time 3 h. Chrom. solvent ethyl acetate:petroleum ether=1:3. Yield 80%. Mp 153–154°C (mp of commercial testosterone 152–154°C). $^{12}C_{16}{}^{13}C_3H_{28}O_2$: MS (EI), *m/z* (%)=291 (33) M^+, 247 (31), 204 (23), 147 (29), 127 (100). δ_H (400 MHz, $CDCl_3$/ TMS) 5.66 (d, 1H, 4-H, J_{4C-4H}=159.0 Hz), 3.55 (t, 1H, 17-CH), 1.11 (s, 3H, 19-CH_3), 0.71 (s, 3H,18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 199.3 (C-3, d, 52.0, of d, 39.0), 171.3 (C-5), 123.5 (C-4, d, 52,0 of d, 11.8), 81.1 (C-17), 33.6 (C-2, d, 39.0, of d, 11.8), 17.2 (C-19), 10.9 (C-18).

9b: Reaction time 3 h. Chrom. solvent ethyl acetate:petroleum ether=1:8. Yield 81%. Mp 122–125°C. $^{12}C_{22}{}^{13}C_3H_{42}O_2Si$: MS (EI), *m/z* (%)=405 (<1) M^+, 390 (2.2) M^+-CH_3, 348 (100) $M^+-C(CH_3)_3$. δ_H (400 MHz, $CDCl_3$/TMS) 5.64 (d, 1H, 4-H, J_{4C-4H}=161.0 Hz), 3.48 (t, 1H, 17-CH), 1.12 (s, 3H, 19-CH_3), 0.80 (s, 9H, $C(CH_3)_3$), 0.67 (s, 3H, 18-CH_3), −0.07 (s, 6H, $Si(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$/TMS) 199.2 (C-3, d, 52.0, of d, 40.0), 171.2 (C-5), 123.7 (C-4, d, 52,0 of d, 11.8), 81.4 (C-17), 33.8 (C-2, d, 40.0, of d, 11.8), 25.7 ($C(CH_3)_3$), 17.9 ($C(CH_3)_3$), 17.3 (C-19), 13.7 (C-18), −5.0, −4.6 ($Si(CH_3)_2$).

9c: Reaction time 2 h. Chrom. solvent ethyl acetate:petroleum ether=1:4. Yield 85%. Mp 165–167°C (literature[5] mp of ^{12}C-analogue 168.5–169°C). $^{12}C_{20}{}^{13}C_3H_{36}O_2$: MS (EI), *m/z* (%)=347 (3.62) M^+, 291 (100), 127 (32.0). δ_H (400 MHz, $CDCl_3$/TMS) 5.66 (d, 1H, 4-H, J_{4C-4H}= 161.0 Hz), 3.35 (t, 1H, 17-CH), 1.12 (s, 3H, 19-CH_3), 1.05 (s, 9H, $C(CH_3)_3$), 0.69 (s, 3H, 18-CH_3); δ_C (100.6 MHz, $CDCl_3$/ TMS) 199.3 (C-3, d, 52.0, of d, 40.0), 171.3 (C-5), 123.6 (C-4, d, 52,0 of d, 11.8), 80.5 (C-17), 72.0 ($C(CH_3)_3$), 33.8 (C-2, d, 40.0, of d, 12.0), 28.6 ($C(CH_3)_3$), 17.3 (C-19), 11.5 (C-18).

9d: Reaction time 1 h. Chrom. solvent ethyl acetate:petroleum ether=1:8. Yield 87%. Mp 169–171°C (literature[8] mp of ^{12}C-analogue 173–174°C). $^{12}C_{16}{}^{13}C_3H_{26}O_2$: MS (EI), *m/z* (%)= 289 (100) M^+, 245 (33), 149 (54), 127 (85). δ_H (400 MHz, $CDCl_3$/ TMS) 5.68 (d, 1H, 4-H, J_{4C-4H}= 161.0 Hz), 1.12 (s, 3H, 19-CH_3), 0.83 (s, 3H,18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 220.2 (C-17), 199.1 (C-3, d, 52.0, of d, 40.0), 170.2 (C-5), 124.0 (C-4, d, 52,0 of d, 12.0), 33.8 (C-2, d, 40.0, of d, 12.0), 17.3 (C-19), 13.6 (C-18).

9e: Reaction time 4 h. Chrom. solvent ethyl acetate:petroleum ether=1:4. Yield 82%. Mp 121–122.5°C (literature[9] mp of lower melting modification of ^{12}C-analogue 121–122°C).

$^{12}C_{18}{}^{13}C_3H_{30}O_2$: MS (EI), *m/z* (%)=317 (31) M^+, 273 (35), 230 (34), 127 (100). δ_H (400 MHz, $CDCl_3$/TMS) 5.70 (d, 1H, 4-H, J_{4C-4H}=160.0 Hz), 2.13 (s, 3H, 21-CH_3), 1.18 (s, 3H, 19-CH_3), 0.68 (s, 3H,18-CH_3); δ_C (100.6 MHz, $CDCl_3$/TMS) 208.3 (C-20), 198.8 (C-3, d, 51.9, of d, 39.4), 169.7 (C-5), 123.6 (C-4, d, 51,9 of d, 11.9), 63.3 (C-17), 33.8 (C-2, d, 39.4, of d, 11.9), 17.3 (C-19), 13.2 (C-18).

Removal of 17β-*tert*-butyldimethylsilyl protecting group (9b→9a). To a solution of **9b** (1.2 mmol) in tetrahydrofuran (10 mL) acetic acid (30 mL) and water (10 mL) were added and the mixture was heated to reflux for 1 h. The mixture was cooled, water (30 mL) was added, the aqueous phase was extracted with chloroform, the organic layer was dried and the solvent evaporated. Remaining acetic acid was distilled off under reduced pressure with toluene as an azeotrope. Yield of **9a** 95%.

Removal of 17β-*tert*-butyl protecting group (9c→9a). The *tert*-butyl group was hydrolyzed with trifluoro acetic acid as described in the literature.[5] Yield of **9a** was 86%.

Reduction of the 17-keto group to the 17β-alcohol (9d→9a). To a solution of sodium borohydride in methanol (25 mL) and dichloromethane (20 mL), stirred at room temperature for 3 min and brought to −78°C **9d** (200 mg dissolved in methanol/dichloromethane) was added. After 6 h the reaction was quenched with acetone, and the solution was extracted with a 10% aqueous solution of sodium hydrogen carbonate at room temperature. The organic layer was dried over sodium sulfate and the solvent was evaporated. Yield of **9a** 182 mg (92%).

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