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An Efficient Hemisynthesis of 20- and 21-[^{13}C]-Labeled Cortexolone: A Model for the Study of Skin Sensitization to Corticosteroids

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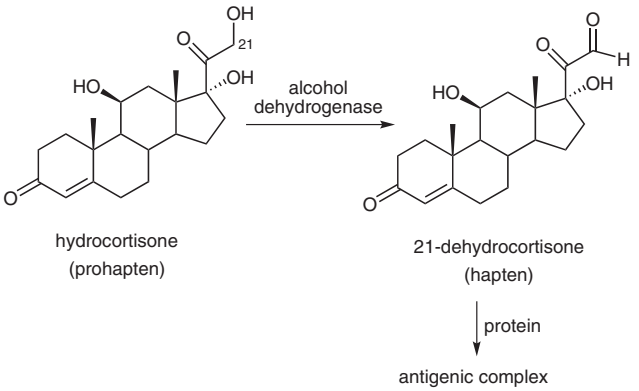
Abstract: A method is described for the synthesis of isotopomers of cortexolone from the commercially available andros-4-ene-3,17-dione. The strategy is based on the use of K^{13}CN for labeling at position 20 and of $^{13}CH_3MgI$, generated in situ, for labeling at position 21. Because of the early introduction of the [^{13}C] labeling, our efforts aimed at reproducible experimental procedures giving high yields with respect to the isotope containing precursors. During the development of this hemisynthesis, we noted that judicious choice of protective groups was essential as this could lead not only to mixtures or unstable intermediates but also influence considerably the output of reactions.

Key words: steroids, medicinal chemistry, isotope labeled, allergen synthesis, protecting groups



Scheme 1 Potential skin metabolism of corticosteroids

Steroids continue to attract much attention because of their special biological activities and strong anti-inflammatory and immunosuppressive properties. These have led to their extensive use in rheumatology, traumatology, and dermatology.[1] Nevertheless, despite many beneficial effects, corticosteroids have also been associated with allergic contact dermatitis (ACD) reactions when applied topically.[2] The frequency of positive ACD reactions to corticosteroid in eczematous patients has thus been estimated between 3–5.9% in northern European countries where the use of topical corticosteroids is high.[3]

From a molecular point of view, ACD is a common disease induced by the chemical modification of skin proteins by low molecular weight molecules or haptens.[4] These modified proteins recognized as foreign by the skin immune system,[5] result from the reaction of an electrophilic function of the hapten with nucleophilic residues present on the proteins. Even if several mechanisms have been identified for the formation of hapten-protein bonds, in the case of corticosteroids they are still hypothetical. In many reports, it has been suggested that these drugs are indeed prohaptens needing a skin metabolic step to form reactive intermediates.[6] Thus, corticosteroids such as hydrocortisone, could be oxidized into 21-dehydro derivatives, which are highly reactive α-keto aldehydes toward nucleophilic amino acids such as arginine (Scheme 1).[7]

In order to investigate the molecular mechanism of ACD to corticosteroids and better characterize the nature of hapten-protein coupling by nuclear magnetic resonance, we were interested in the synthesis of the 20-[^{13}C]- and 21-[^{13}C]-labeled cortexolone. The use of ^{13}C-labeled molecules in association with NMR techniques is a powerful tool for the investigation of hapten-protein interactions and best results are obtained when labeling the reactive sites of the molecule.[8] In the case of corticosteroids, the labeling sites should be either on position 20 or 21 of the side chain (Scheme 1).

The literature about the synthesis of corticosteroids is abundant, but to the best of our knowledge, there had been no report on the synthesis of labeled molecules at these two positions. Since the works of Sarett,[9] compounds of the androstan-17-one group seem to be good precursors for the synthesis of the side chain. Different synthetic approaches have thus been developed essentially based on two strategies: the direct introduction of a two carbons unit[10] or the introduction of the two carbons one by one.[10b,11] Unfortunately, even if these strategies could lead to the corticosteroids structure, they could not be applied for the preparation of labeled derivatives as labeled reagents were not available, their preparations led to mixtures of labeled products, or yields after insertion of labeled unit were low.

In this article, we report an efficient hemisynthesis of 20- and 21-[^{13}C]-labeled cortexolones (Figure 1) from the commercially available andros-4-ene-3,17-dione.

The preparation of [^{13}C]-labeled molecules very often means the development of new syntheses due to the use of a restricted number of available precursors and the very

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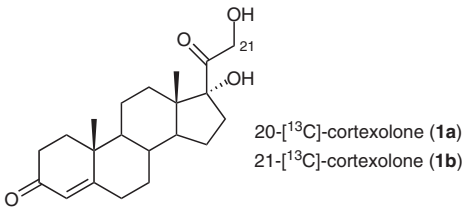
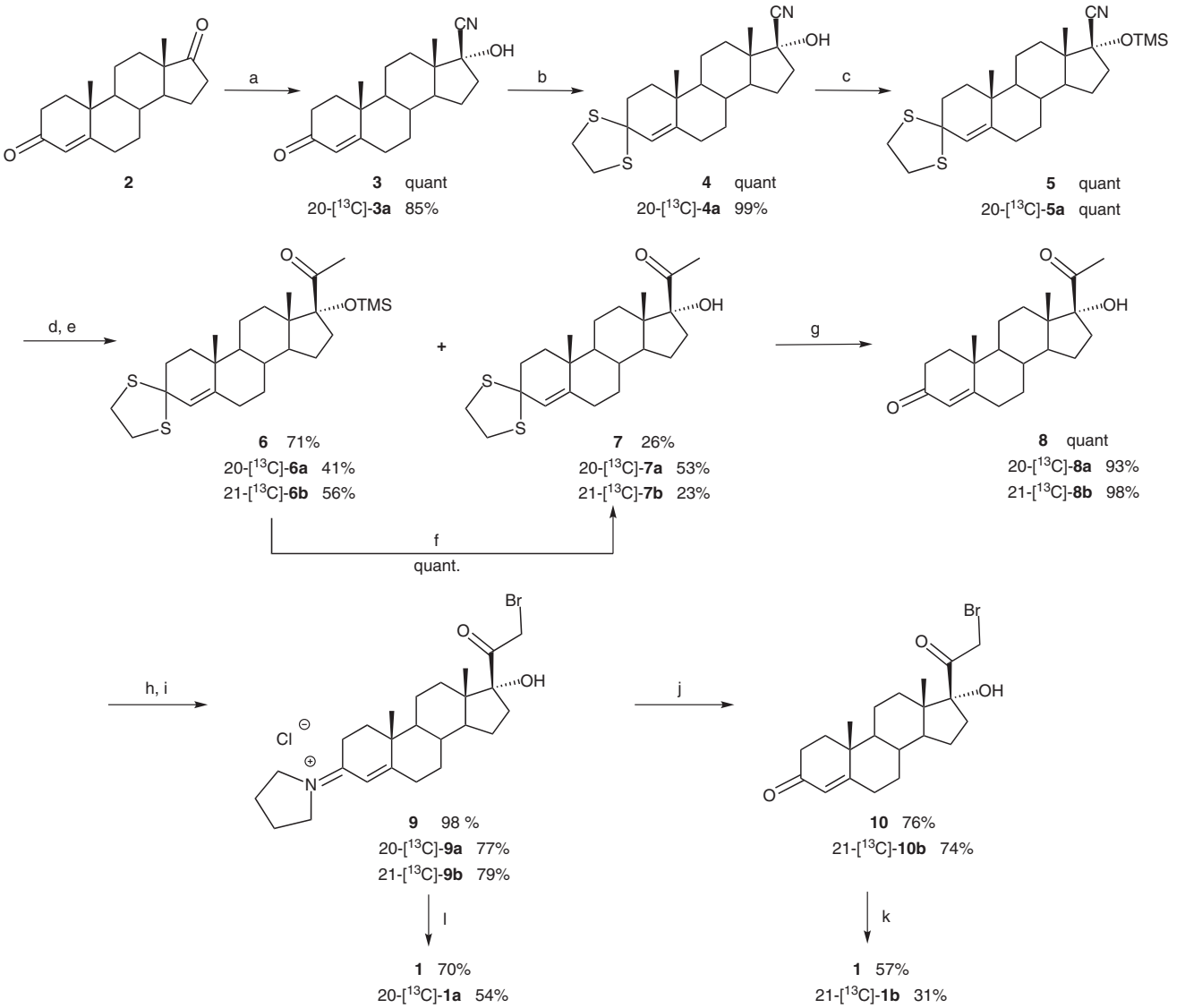


Figure 1 Structure of cortexolones **1a** and **1b**

high cost of starting material that requires optimized reactions.

Our approach to the synthesis of the labeled cortexolones is described in Scheme 2. The strategy is based on the used of $K^{13}CN$ for labeling at position 20 and the used of $^{13}CH_3MgI$, generated in situ, for labeling at position 21. Because of the early introduction of the [^{13}C] labeling, our efforts were aimed at reproducible experimental procedures giving high-yield products with respect to the isotope-containing precursors.

The hemisynthesis started by a regio- and stereoselective cyanation of the commercially available diketone **2** as previously described.[11h] The β-cyanosteroid **3** was obtained in almost quantitative yield, but the use of an excess of KCN (4.2 equiv) was necessary for a good stereoselectivity. Before the introduction of the second carbon unit, the enone function was blocked by a thioketal group and the hydroxy at position 17 was protected by a silyl group to form **5** in very high yield. In this sequence leading to the formation of **4** it is interesting to note that the steps could be reversed. Thus, a regioselective protection of the A-ring enone followed by a regio- and stereoselective cyanation afforded **4** with an overall yield of 95%. In this case, we also tried a direct conversion of **2** into the 3-cyclic ket-



Scheme 2 *Reagents and conditions*: (a) KCN or $K^{13}CN$, AcOH, MeOH, r.t., 2 h; (b) $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$, MeOH, r.t., 2 h; (c) TMSCl, DMF, imidazole, r.t., 19 h; (d) MeMgBr or $^{13}CH_3MgI$, toluene–Et_2O (4:1), 60 °C, 26 h; (e) aq 10% HCl THF–acetone (50:50), r.t., 20 h; (f) from **6a** or **6b**: TBAF, THF, r.t., 19 h; (g) MeI, $CaCO_3$, EtOH, H_2O, Δ, 20 h; (h) pyrrolidine, MeOH, Δ, 2 h; (i) Br_2, HCl, EtOH, r.t., 4 h; (j) K_2CO_3, EtOH–H_2O (87:17), r.t., 1 h; (k) K_2CO_3, acetone–H_2O (60:40), r.t., 0.5 h; (l) K_2CO_3, acetone–H_2O (60:40), r.t., 3 d.

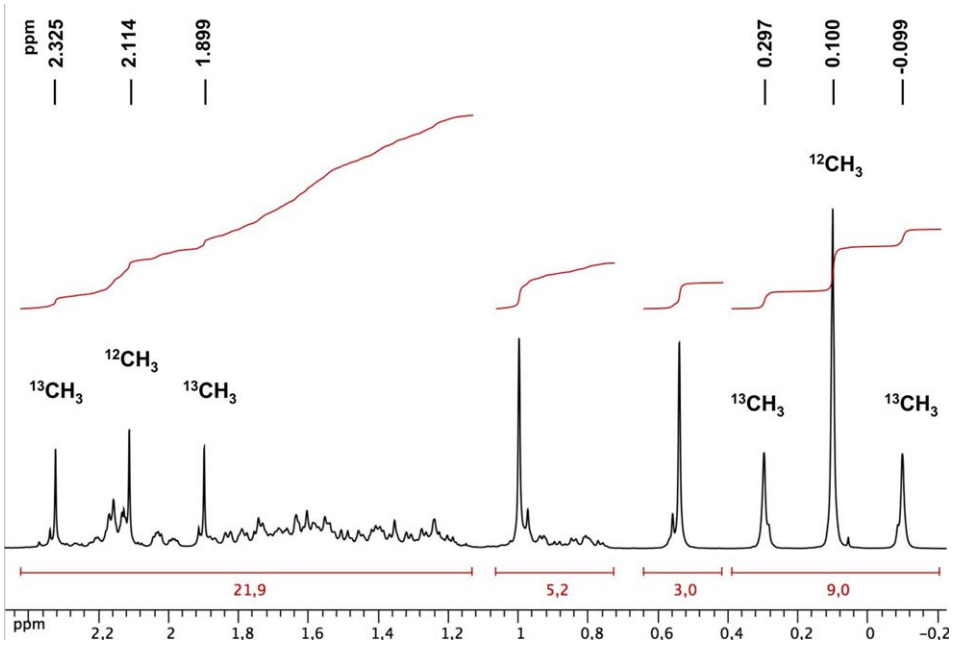
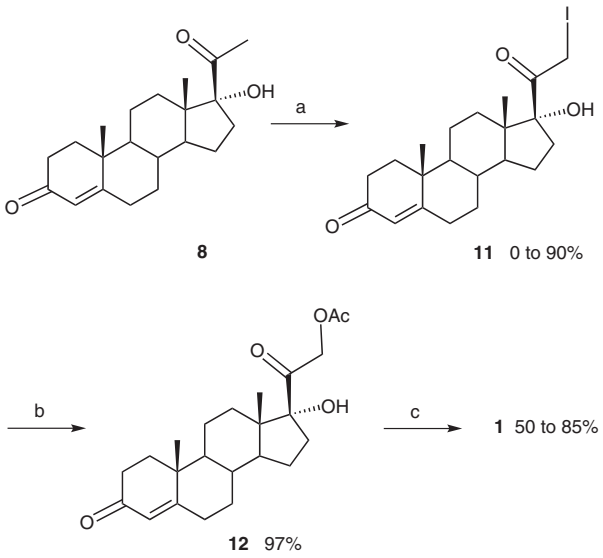


Figure 2 ^{1}H NMR spectrum of 21-[13-C]-**6b**: 21-methyl and OTMS parts

al derivative (instead of a 3-thioketal derivative) via literature procedures,[12] but only a mixture of the expected 3-ketal together with the 3,17-bis-ketal could be obtained.

Introduction of the second carbon was achieved by the addition of an organometallic compound on the protected cyanhydrin **5**. The addition of a Grignard reagent to cyanohydrin *O*-silyl ethers is indeed a very efficient method for the synthesis α-hydroxy ketones,[13] and the labeling on position 21 could be done using [^{13}C]-methylmagnesium iodide (99 atom% ^{13}C), formed in situ. Then, addition of 2.5 equivalents of MeMgI to **5** in toluene–Et_2O (4:1) at 60 °C for 26 hours, followed by acidic hydrolysis, gave a mixture of **6** and **7** (Scheme 2) with a combined yield of 94% for 20-[^{13}C]-labeled compounds and of 79% for 21-[^{13}C]-labeled compounds. However, as we have previously reported,[14] ^{1}H NMR (Figure 2) and MS analysis of the 21-[^{13}C]-**6b** and -**7b** mixture clearly indicated that the 21-methyl position was only partially labeled (60 ± 5 atom% ^{13}C) and that methyl groups on silicon were also partially labeled (30 atom% ^{13}C). This reaction is very interesting from a mechanistic point of view, however, induced a decrease in the expected ^{13}C content.

Then, treatment of **6** with TBAF, followed by deprotection of the thioketal group led to the expected methyl ketone **8** in almost quantitative yields. To convert this methyl ketone into cortexolone (**1**), an additional hydroxy group had to be introduced at position 21. Three methods were investigated: a direct hydroxylation, a Stork's iodination procedure (Scheme 3) or a bromination after an iminium protection (Scheme 2). Various direct hydroxylations of methyl ketones exist in the literature, but few of them have been used on corticosteroids and more particularly on derived pregnenes. We have thus tested a number of direct hydroxylation on the methyl ketone **8** using organohypervalent iodine like phenyliodoso diacetate [$PhI(OAc)_2$][15] or *o*-iodosylbenzoic acid (HOOCPhIO),[16] but we obtained only a mixture of starting material **8** and degradation products.



Scheme 3 *Reagents and conditions*: (a) I_2, CaO, AIBN (cat.), 'aged' THF–MeOH (50:50), r.t. 5 h; (b) AcOH, Et_3N, acetone, Δ, 5 h; (c) K_2CO_3, MeOH, H_2O, r.t., 3 h.

The iodination procedure of 20-ketopregnene by reaction with iodine and calcium oxide,[17] followed by the reaction of the 21-iodo intermediate with triethylammonium acetate[18] is the most reported synthetic methods for the formation of the α-keto functionalized side chain in corticosteroids. The iodination is generally carried out with a large excess of iodine, in a mixture of methanol and 'aged' tetrahydrofuran,[19] containing a certain amount of calcium oxide. The mechanism of this reaction is not com-

pletely elucidated and discussions are still open between a radical process[17] and an ionic one.[20] The Stork's iodination was performed on the methyl ketone **8** under a range of conditions and the reaction proved to be somewhat capricious. Indeed, treatment of **8** with a large excess of iodine (5 equiv) and calcium oxide (22 equiv) gave the best results. As previously descibed,[17c] the introduction of small amounts of a radical initiator (AIBN) is important to accelerate the reaction and then to prevent the slower and spontaneous deiodination in solution. Thus, no reaction occurred in freshly distilled THF and a concentration of peroxide of 5.4×10^{-2} M had been calculated in 'aged' THF. But in every case, we were not able to obtain reproducible outputs (Scheme 3) even when iodine uptake seemed to occur rapidly. Thus, yields ranging from 0 to 90% were obtained without explanation. Conversion of the 21-iodo derivative **11** into the 21-acetate under Moreland's procedure,[18] followed by the acetate hydrolysis to give cortexolone (**1**) proceeded readily, but with a low overall yield from **8**.

In contrast to the iodination process, the conversion of the methyl ketone **8** into the bromo derivative **9** proceeded in good and reproducible yields according to literature procedure.[21] This sequence involves the selective protection of the enone as its eniminium salt, which is inert in neutral or acid conditions towards a broad panel of electrophilic reagents. Thus, pregnene **8** was converted into its pyrrolidinyl dienamine**,** and the crude material was protonated and brominated in situ to give the dienamine salt, which in turn gave bromide **9** in almost quantitative yield. Then, the free α,β-unsaturated ketone group was regenerated by treatment with potassium carbonate (2.8 equiv) in a mixture of ethanol and water to give the 21-[^{13}C]-bromide **10b** in good yields.[21a] Finally, the replacement of the bromine by a hydroxy group could be achieved by treatment with potassium carbonate (1 equiv) in a mixture of acetone and water to obtain **1b** with a moderate yield.[22] In these two last steps, it is interesting to note that the reaction conditions are very similar and differ only by the amount of potassium carbonate added and the nature of the solvent used. Thus, in order to reduce the number of steps, we tried to combine them by treatment of **9** with an excess of potassium carbonate (3.8 equiv) in a mixture of acetone and water. This reaction needed three days to reach completion, but the 20-[^{13}C]-cortexolone (**1a**) was easily obtained in a yield of 54% from **9a**. In this case, the use of acetone instead of ethanol as co-solvent increased the yield of the reaction.

In summary, the synthesis of 20- and 21-[^{13}C]-labeled 21-cortexolones (**1a** and **1b**), representing an important intermediate for the preparation of the potent allergenic agent 21-dehydrocortexolone, has been completed from the commercially available andros-4-ene-3,17-dione. Generally, we noted, during the development of this hemisynthesis that the correct choice of the protective groups is essential as this can lead not only to mixture or unstable intermediates but also influences considerably the output of reactions. Then, the development of this general method, which could be applied to other substrates like precursors of hydrocortisone, is of particular interest.

All air- or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon. All solvents used were of reagent grade. Anhyd solvents were freshly distilled before use. THF and Et_2O were distilled from sodium/benzophenone. CH_2Cl_2 was dried over P_2O_5 before distillation. Petroleum ether (PE) used refers to the fraction boiling in the range 35–60 °C. Unless otherwise noted, reactions were magnetically stirred and monitored by TLC with 0.25 mm Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 mm) supplied by Merck, Geduran. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in ppm (δ) and $CHCl_3$ was used as internal standard (δ = 7.26). IR spectra were obtained on a Perkin-Elmer FT-IR 1600 spectrometer; peaks are reported in cm^{-1}. Melting points were determined on a Büchi Tottoli 510 apparatus and are uncorrected. Elemental analyses were collected at the Service de microanalyse of the University of Strasbourg (France).

Caution! Skin contact with cortexolone derivatives must be avoided. As potential sensitizing substances, these compounds must be handled with care.

17β-Cyano-cyclic-3-(1,2-ethanediylmercapto)-17α-hydroxyandrost-4-ene (4)

To a suspension of cyanohydrin **3** (4.36 g, 13.91 mmol) in MeOH (133 mL) were added ethane dithiol (1.8 mL, 20.87 mmol, 1.5 equiv) and $BF_3{\cdot}OEt_2$ (2.1 mL, 16.69 mmol, 1.2 equiv). The reaction mixture was stirred at r.t. for 2 h and solvents were removed under reduced pressure. The white residue was taken up in hot EtOAc (75 mL) and the resulting organic layer was washed with aq sat. $NaHCO_3$ (3 × 100 mL), H_2O (100 mL), dried ($MgSO_4$), and concentrated under vacuum to give **4** (5.42 g, 13.91 mmol, quant) as a white solid; mp 204–205 °C; $[\alpha]_D^{20}$ +139 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$): 3586 (OH), 2360 cm^{-1} (C≡N).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.67–0.99 (m, 2 H), 0.93 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 1.14–2.24 (m, 16 H), 2.38 (ddd, J_1 = 2.9 Hz, J_2 = 11.5 Hz, J_{AB} = 14.6 Hz, 1 H, H-16β), 2.83 (br s, 1 H, OH-17), 3.16–3.39 (m, 4 H, SCH_2CH_2S), 5.48 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (C-18), 18.5 (C-19), 20.6 (C-11), 23.9 (C-15), 29.5, 31.8, 32.6, 36.1 (C-8), 36.5 (C-10), 37.3, 37.9, 38.1, 39.5, 40.0, 47.7 (C-14), 49.2 (C-13), 53.4 (C-9), 65.6 (C-3), 77.9 (C-17), 121.0 (C-20), 124.5 (C-4), 145.7 (C-5).

Anal. Calcd for $C_{22}H_{31}NOS_2$ (389.61): C, 66.76; H, 8.02; N 3,59. Found: C, 66.53; H, 8.26; N 3.57.

[20-^{13}C]-17β-Cyano-cyclic-3-(1,2-ethanediylmercapto)-17α-hydroxyandrost-4-ene (4a)

Starting from **3a** (4.44 g, 14.12 mmol) and using the same procedure as for the synthesis of **4** gave **4a** (5.45 g, 13.95 mmol, 99%) as a white solid; mp 198–199 °C; $[\alpha]_D^{20}$ +142 (*c* 2.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76–0.99 (m, 2 H), 0.93 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 1.22–1.85 (m, 11 H), 1.91–2.22 (m, 5 H), 2.39 [dddd, ^3J (^{13}C,H) = 3.3 Hz, J_1 = 3.3 Hz, J_2 = 11.5 Hz, J_{AB} = 14.6 Hz, 1H, H-16β], 2.50 (br s, 1 H, OH-17), 3.17–3.39 (m, 4 H, SCH_2CH_2S), 5.48 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (C-18), 18.5 (C-19), 20.6 (C-11), 23.9 [d, ^3J (^{13}C,C) = 3.1 Hz, C-15], 29.5, 31.8, 32.6, 36.1 (C-8), 36.5 (C-10), 37.3, 37.9, 38.1, 39.5, 40.0, 47.7 [d, ^3J (^{13}C,C) = 3.1 Hz, C-14], 49.2 (C-13), 53.4 (C-9), 65.6 (C-3), 77.9 [d, ^1J (^{13}C,C) = 62.9 Hz, C-17], 121.0 (^{13}C-20), 124.5 (C-4), 145.7 (C-5).

17β-Cyano-cyclic-3-(1,2-ethanediylmercapto)-17α-trimethylsilyloxyandrost-4-ene (5)[14]

To a suspension of **4** (3.22 g, 8.26 mmol) in DMF (45 mL) and anhyd $MgSO_4$ (~2 g) were added imidazole (2.70 g, 39.69 mmol, 4.8 equiv) and TMSCl (3.0 mL, 23.47 mmol, 2.8 equiv). The reaction mixture was stirred at r.t. for 22 h, hydrolyzed by aq sat. $NaHCO_3$ (200 mL), and extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with H_2O (3 × 150 mL), brine (150 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give **5** (3.81 g, 8.26 mmol, quant) as a white solid; mp 162–163 °C; $[\alpha]_D^{20}$ +119 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$): 2360 (C≡N), 858 cm^{-1} (C–Si).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 [s, 9 H, $Si(CH_3)_3$], 0.74–1.00 (m, 2 H), 0.89 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 1.17–2.24 (m, 16 H), 2.32 (ddd, J_1 = 3.1 Hz, J_2 = 11.5 Hz, J_{AB} = 14.6 Hz, 1 H, H-16β), 3.18–3.56 (m, 4 H, SCH_2CH_2S), 5.48 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.7 [$Si(CH_3)_3$], 16.0 (C-18), 18.5 (C-19), 20.6 (C-11), 24.0 (C-15), 29.7, 31.9, 32.7, 36.2 (C-8), 36.6 (C-10), 37.3, 38.0, 38.7, 39.5, 40.0, 47.7 (C-14), 50.1 (C-13), 53.4 (C-9), 65.7 (C-3), 78.7 (C-17), 121.0 (C-20), 124.4 (C-4), 146.0 (C-5).

Anal. Calcd for $C_{25}H_{39}NOS_2Si$ (461.79): C, 65.02; H, 8.51. Found: C, 65.24; H, 8.50.

[20-^{13}C]-17β-Cyano-cyclic-3-(1,2-ethanediylmercapto)-17α-trimethylsilyloxyandrost-4-ene (5a)

Starting from **4a** (5.45 g, 13.95 mmol) and using the same procedure as for the synthesis of **5** gave **5a** (6.45 g, 13.94 mmol, quant) as a white solid; mp 154–155 °C; $[\alpha]_D^{20}$ +110 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 [s, 9 H, $Si(CH_3)_3$], 0.74–0.99 (m, 2 H), 0.89 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 1.22–1.81 (m, 11 H), 1.90–2.23 (m, 5 H), 2.32 [dddd, ^3J (^{13}C,H) = 3.3 Hz, J_1 = 3.3 Hz, J_2 = 11.5 Hz, J_{AB} = 14.6 Hz, 1 H, H-16β], 3.18–3.39 (m, 4 H, SCH_2CH_2S), 5.48 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.7 [$Si(CH_3)_3$], 16.0 (C-18), 18.5 (C-19), 20.6 (C-11), 24.0 [d, ^3J (^{13}C,C) = 3.7 Hz, C-15], 29.7, 31.9, 32.7, 36.2 (C-8), 36.6 (C-10), 37.3, 38.0, 38.8, 39.5, 40.0, 47.7 [d, ^3J (^{13}C,C) = 3.1 Hz, C-14], 50.1 (C-13), 53.4 (C-9), 65.7 (C-3), 78.6 [d, ^1J (^{13}C,C) = 62.3 Hz, C-17], 121.0 (^{13}C-20), 124.4 (C-4), 146.0 (C-5).

Cyclic-3-(1,2-ethanediylmercapto)-17α-trimethylsilyloxypregn-4-en-20-one (6) and Cyclic-3-(1,2-ethanediylmercapto)-17α-hydroxypregn-4-en-20-one (7)

Step A: To a suspension of Mg turnings (0.11 g, 4.5 mmol, 2.37 equiv) in anhyd Et_2O (2 mL) was added MeI (0.32 mL, 5.14 mmol, 2.48 equiv). After complete consumption of Mg, cyanohydrin **5** (0.957 g, 2.07 mmol) in toluene (6 mL) was added. The flask was sealed with a septum and heated at 59–61 °C for 26 h, cooled down, and hydrolyzed with aq 10% HCl (50 mL). THF (25 mL) and acetone (25 mL) were added, the solution stirred for 14 h and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with aq sat. $NaHCO_3$ (150 mL), H_2O (2 × 100 mL), and dried ($MgSO_4$). Solvents were concentrated under reduced pressure and the residue purified by column chromatography over silica gel (PE, EtOAc 5%, then PE, EtOAc 15%) to give **6** (704 mg, 1.47 mmol, 71%) and **7** (215 mg, 0.53 mmol, 26%).

Step B: To a solution of **6** (704 mg, 1.47 mmol) in THF (10 mL) cooled at 0 °C was added a 1 M solution of TBAF in THF (2.35 mL, 2.35 mmol, 1.6 equiv). The solution was stirred at r.t. for 20 h, filtered over silica gel, which was washed with CH_2Cl_2 (100 mL) and Et_2O (100 mL). The combined organic solvents were concentrated under reduced pressure and the residue purified by column chromatography over silica gel (PE, EtOAc 10%, then PE, EtOAc 20%) to give **7** (598 mg, 1.47 mmol, quant) as a white solid.

6

Mp 170–171 °C; $[\alpha]_D^{20}$ +119 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$): 1702 (C=O), 852 cm^{-1} (C–Si).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 [s, 9 H, $Si(CH_3)_3$], 0.54 (s, 3 H, H-18), 0.76–1.02 (m, 2 H), 1.00 (s, 3 H, H-19), 1.15–1.90 (m, 12 H), 1.97–2.32 (m, 4 H), 2.11 (s, 3 H, H-21), 2.69–2.79 (m, 1 H, H-16β), 3.17–3.40 (m, 4 H, SCH_2CH_2S), 5.47 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.2 [$Si(CH_3)_3$], 14.5 (C-18), 18.5 (C-19), 21.0 (C-11), 23.4 (C-15), 26.6 (C-21), 30.9, 31.0, 32.0, 32.7, 35.9 (C-8), 36.6 (C-10), 37.3, 38.0, 39.5, 40.0, 47.8 (C-13), 50.4 (C-14), 53.6 (C-9), 65.8 (C-3), 93.3 (C-17), 124.2 (C-4), 146.3 (C-5), 210.7 (C-20).

Anal. Calcd for $C_{26}H_{42}O_2S_2Si$ (478.84): C, 65.21; H, 8.80. Found: C, 65.13; H, 8.95.

7

Mp 164–165 °C; $[\alpha]_D^{20}$ +114 (*c* 1.7, $CHCl_3$).

IR ($CHCl_3$): 3685 (OH), 1697 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (s, 3 H, H-18), 0.77–1.04 (m, 2 H), 1.00 (s, 3 H, H-19), 1.21–1.83 (m, 12 H), 1.98–2.18 (m, 4 H), 2.24 (s, 3 H, H-21), 2.59–2.69 (m, 1 H, H-16β), 2.69 (s, 1 H, OH-17), 3.16–3.39 (m, 4 H, SCH_2CH_2S), 5.48 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (C-18), 18.5 (C-19), 20.7 (C-11), 23.9 (C-15), 27.9 (C-21), 30.1, 32.0, 32.7, 33.5, 35.6 (C-8), 36.6 (C-10), 37.3, 38.0, 39.5, 40.0, 48.3 (C-13), 50.1 (C-14), 53.6 (C-9), 65.7 (C-3), 90.0 (C-17), 124.3 (C-4), 146.1 (C-5), 211.7 (C-20).

Anal. Calcd for $C_{23}H_{34}O_2S_2$ (406.66): C, 67.97; H, 8.43. Found: C, 68.06; H, 8.57.

[20-^{13}C]-Cyclic-3-(1,2-ethanediylmercapto)-17α-trimethylsilyloxypregn-4-en-20-one (6a) and [20-^{13}C]-Cyclic-3-(1,2-ethanediylmercapto)-17α-hydroxypregn-4-en-20-one (7a)

Starting from **5a** (2.00 g, 4.32 mmol) and MeI (0.67 mL, 10.76 mmol, 2.49 equiv) and using the same procedure as for the synthesis of **6** and **7** gave **6a** (844 mg, 1.76 mmol, 41%) and **7a** (934 mg, 2.29 mmol, 53%). Then, **6a** was converted into **7a** (716 mg, 1.76 mmol, quant) as in Step B above.

6a

$[\alpha]_D^{20}$ +119 (*c* 2.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 [s, 9 H, $Si(CH_3)_3$], 0.54 (s, 3 H, H-18), 0.76–1.02 (m, 2 H), 1.00 (s, 3 H, H-19), 1.18–2.20 (m, 16 H), 2.11 [d, ^2J (^{13}C,H) = 3.0 Hz, 3 H, H-21], 2.69–2.79 (m, 1 H, H-16β), 3.17–3.40 (m, 4 H, SCH_2CH_2S), 5.47 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.2 [$Si(CH_3)_3$], 14.5 (C-18), 18.5 (C-19), 21.0 (C-11), 23.4 (C-15), 26.6 [d, ^1J (^{13}C,C) = 50.0 Hz, C-21], 30.9, 31.0, 32.0, 32.7, 35.9 (C-8), 36.6 (C-10), 37.3, 38.0, 39.5, 40.0, 47.8 (C-13), 50.4 (C-14), 53.6 (C-9), 65.8 (C-3), 93.3 [d, ^1J (^{13}C,C) = 50.0 Hz, C-17], 124.2 (C-4), 146.3 (C-5), 210.7 (^{13}C-20).

7a

Mp 164–165 °C; $[\alpha]_D^{20}$ +112 (*c* 2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.69 (s, 3 H, H-18), 0.76–1.03 (m, 2 H), 0.99 (s, 3 H, H-19), 1.18–1.82 (m, 12 H), 1.97–2.19 (m, 3 H), 2.23 [d, ^2J (^{13}C,H)= 5.9 Hz, 3 H, H-21], 2.44–2.49 (m, 1 H), 2.64 [dddd, ^3J (^{13}C,H) = 2.9 Hz, J_1 = 2.9 Hz, J_2 = 11.5 Hz, J_{AB} = 14.8 Hz, 1 H, H-16β], 2.74 (s, 1 H, OH-17), 3.15–3.38 (m, 4 H, SCH_2CH_2S), 5.47 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (C-18), 18.5 (C-19), 20.7 (C-11), 23.9 (C-15), 27.8 [d, ^1J (^{13}C,C) = 40.7 Hz, C-21], 30.2, 32.0, 32.7, 33.5, 35.6 (C-8), 36.5 (C-10), 37.3, 38.0, 39.5, 40.0, 48.2 (C-

13), 50.1 (C-14), 53.6 (C-9), 65.7 (C-3), 89.9 [d, ^1J (^{13}C,C) = 44.4 Hz, C-17], 124.3 (C-4), 146.1 (C-5), 211.7 (^{13}C-20).

[21-^{13}C]-Cyclic-3-(1,2-ethanediylmercapto)-17α-trimethylsilyloxypregn-4-en-20-one (6b) and [21-^{13}C]-Cyclic-3-(1,2-ethanediylmercapto)-17α-hydroxypregn-4-en-20-one (7b)

Starting from **5** (0.957 g, 2.07 mmol) and [^{13}C]-MeI (0.35 mL, 5.58 mmol, 2.70 equiv), and using the same procedure as for the synthesis of **6** and **7** gave **6b** (555 mg, 1.16 mmol, 56%) and **7b** (192 mg, 0.47 mmol, 23%). Then, **6b** was converted into **7b** (473 mg, 1.16 mmol, quant) as in step B above.

6b[14]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 9 H, $Si(CH_3)_3$], 0.54 (s, 3 H, H-18), 0.76–0.97 (m, 2 H), 1.00 (s, 3 H, H-19), 1.15–1.92 (m, 12 H), 1.97–2.37 (m, 4 H), 2.11 [d, ^1J (^{13}C,H) = 127.8 Hz, 3 H, H-21], 2.70–2.80 (m, 1 H, H-16β), 2.99–3.40 (m, 4 H, SCH_2CH_2S), 5.49 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.2 [$Si(CH_3)_3$], 14.5 (C-18), 18.5 (C-19), 21.0 (C-11), 23.4 (C-15), 26.7 (^{13}C-21), 30.9, 31.0, 32.0, 32.7, 35.9 (C-8), 36.6 (C-10), 37.3, 38.0, 39.5, 40.0, 47.8 (C-13), 50.4 (C-14), 53.6 (C-9), 65.8 (C-3), 93.3 [d, ^2J (^{13}C,C) = 11.3 Hz, C-17], 124.2 (C-4), 146.3 (C-5), 210.7 [d, ^1J (^{13}C,C) = 39.8 Hz, C-20].

7b[14]

Mp 161–162 °C; $[\alpha]_D^{20}$ +108 (*c* 2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 (s, 3 H, H-18), 0.78–1.05 (m, 2 H), 1.01 (s, 3 H, H-19), 1.19–1.84 (m, 12 H), 1.98–2.23 (m, 4 H), 2.24 [d, ^1J (^{13}C,H) = 127.8 Hz, 3 H, H-21], 2.60–2.70 (m, 2 H, H-16β, and OH-17), 3.17–3.39 (m, 4 H, SCH_2CH_2S), 5.48 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (C-18), 18.6 (C-19), 20.7 (C-11), 24.0 (C-15), 27.9 (^{13}C-21), 30.2, 32.0, 32.7, 33.5, 35.7 (C-8), 36.6 (C-10), 37.3, 38.0, 39.5, 40.0, 48.3 (C-13), 50.1 (C-14), 53.6 (C-9), 65.7 (C-3), 90.0 [d, ^2J (^{13}C,C) = 11.1 Hz, C-17], 124.3 (C-4), 146.1 (C-5), 211.7 [d, ^1J (^{13}C,C) = 40.1 Hz, C-20].

[20-^{13}C]-17α-Hydroxypregn-4-ene-3,20-dione (8a)

Starting from **7a** (2.42 g, 5.94 mmol) and using the same procedure as for the synthesis of **8** gave **8a** (1.83 g, 5.52 mmol, 93%) as a white solid (cf. Supporting Information); mp 208–209 °C; $[\alpha]_D^{20}$ +70 (*c* 2.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (s, 3 H, H-18), 0.74–1.89 (m, 14 H), 1.16 (s, 3 H, H-19), 2.24 [d, ^2J (^{13}C,H) = 5.9 Hz, 3 H, H-21], 2.26–2.46 (m, 4 H), 2.67 [dddd, ^3J (^{13}C,H) = 2.9 Hz, ^3J = 2.9 Hz, ^3J = 11.5 Hz, ^2J = 14.7 Hz, 1 H, H-16β], 3.00 (br s, 1 H, OH-17), 5.71 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (C-18), 17.3 (C-19), 20.5 (C-11), 23.9 (C-15), 27.8 [d, ^1J (^{13}C,C) = 40.1 Hz, C-21], 30.0, 32.0, 32.8, 33.4, 33.9, 35.4 (C-8), 35.7, 38.5 (C-10), 48.0 (C-13), 50.0 (C-14), 53.3 (C-9), 89.8 [d, ^1J (^{13}C,C) = 44.4 Hz, C-17], 123.9 (C-4), 171.1 (C-5), 199.6 (C-3), 211.6 (^{13}C-20).

[21-^{13}C]-17α-Hydroxypregn-4-ene-3,20-dione (8b)

Starting from **7b** (1.44 g, 3.54 mmol) and using the same procedure as for the synthesis of **8** gave **8b** (1.15 g, 3.47 mmol, 98%) as a white solid (cf. Supporting Information); mp 207–208 °C; $[\alpha]_D^{20}$ +87 (*c* 2.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (s, 3 H, H-18), 0.87–2.04 (m, 14 H), 1.16 (s, 3 H, H-19), 2.22–2.44 (m, 4 H), 2.24 [d, ^1J (^{13}C,H) = 127.8 Hz, 3 H, H-21], 2.66 (m, 1 H, H-16β), 3.01 (s, 1 H, OH-17), 5.70 (d, *J* = 1.5 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (C-18), 17.3 (C-19), 20.5 (C-11), 23.8 (C-15), 28.0 (^{13}C-21), 30.0, 32.0, 32.8, 33.4, 33.9, 35.4 (C-8), 35.6, 38.5 (C-10), 48.0 (C-13), 49.9 (C-14), 53.3 (C-9), 89.8 [d, ^2J (^{13}C,C) = 11.1 Hz, C-17], 123.8 (C-4), 171.2 (C-5), 199.6 (C-3), 211.6 [d, ^1J (^{13}C,C) = 40.1 Hz, C-20].

[20-^{13}C]-21-Bromo-17α-hydroxy-3-(1-pyrrolidinium-1-ylidene)pregn-5-en-20-one Chloride (9a)

Starting from **8a** (520 mg, 1.57 mmol) and using the same procedure as for the synthesis of **9** gave **9a** (603 mg, 1.21 mmol, 77%) as a yellow solid (cf. Supporting Information).

^{1}H NMR (300 MHz, $CDCl_3$–DMSO-d_6): δ = 0.49 (s, 3 H, H-18), 0.92–2.14 (m, 18 H), 1.06 (s, 3 H, H-19), 2.41–2.44 (m, 2 H), 2.47–2.59 (m, 1 H, H-16β), 2.67–2.87 (m, 2 H), 3.71–3.95 (m, 5 H, 2 × H-1′, 2 × H-4′, and OH-17), 4.07 [A part of an AB system, J_{AB} = 15.1 Hz, ^2J (^{13}C,C) = 4.2 Hz, 1 H, H-21], 4.36 [B part of an AB system, J_{AB} = 15.1 Hz, ^2J (^{13}C,H) = 4.2 Hz, 1 H, H-21], 6.19 (s, 1 H, H-4).

[21-^{13}C]-21-Bromo-17α-hydroxy-3-(1-pyrrolidinium-1-ylidene)pregn-5-en-20-one Chloride (9b)

Starting from **8b** (769 mg, 2.32 mmol) and using the same procedure as for the synthesis of **9** gave **9b** (916 mg, 1.83 mmol, 79%) as a yellow solid (cf. Supporting Information).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.55 (s, 3 H, H-18), 0.92–2.68 (m, 21 H), 1.11 (s, 3 H, H-19), 2.73–2.96 (m, 2 H), 3.70–4.05 (m, 4 H, 2 × H-1′, 2 × H-4′), 4.35 [A part of an AB system, J_{AB} = 15.0 Hz, ^1J (^{13}C,H) = 150.3 Hz, 1 H, H-21], 4.36 [B part of an AB system, J_{AB} = 15.0 Hz, ^1J (^{13}C,H) = 150.3 Hz, 1 H, H-21], 5.60 (br s, 1 H, OH-17), 6.50 (s, 1 H, H-4).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.6 (C-18), 16.8 (C-19), 20.3 (C-11), 23.1 (C-15), 23.9 (C-2′ or C-3′), 24.1 (C-2′ or C-3′), 26.1, 30.0, 31.7, 32.8, 33.1 (2 C), 34.8 (C-8), 36.2 (^{13}C-21), 40.3 (C-10), 46.8 (C-13), 48.6 (C-9 or C-14), 52.1 (C-9 or C-14), 52.2 (C-1′ or C-4′), 52.5 (C-1′ or C-4′), 89.2 [d, ^2J (^{13}C,C) = 14.2 Hz, C-17], 115.6 (C-4), 171.4 (C-3 or C-5), 180.0 (C-3 or C-5), 203.5 [d, ^1J (^{13}C,C) = 38.3 Hz, C-20].

[21-^{13}C]-21-Bromo-17α-hydroxypregn-4-ene-3,20-dione (10b)

Starting from **9b** (876 mg, 1.75 mmol) and using the same procedure as for the synthesis of **10** gave **10b** (533 mg, 1.30 mmol, 74%) as a white solid (cf. Supporting Information).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.72 (s, 3 H, H-18), 0.74–2.18 (m, 14 H), 1.18 (s, 3 H, H-19), 2.33–2.49 (m, 4 H), 2.64–2.84 (m, 2 H, H-16β and OH-17), 4.16 [A part of an AB system, J_{AB} = 14.9 Hz, ^1J (^{13}C,H) = 150.0 Hz, 1 H, H-21], 4.39 [B part of an AB system, J_{AB} = 14.9 Hz, ^1J (^{13}C,H) = 150.0 Hz, 1H, H-21], 5.73 (s, 1 H, H-4).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14,8 (C-18), 17.1 (C-19), 20.4 (C-11), 23.3 (C-15), 30.2, 31.7, 32.5, 33.6, 33.9, 35.3, 35.4 (C-8), 35.6 (^{13}C-21), 38.3 (C-10), 47.3 (C-13), 49.8 (C-14), 52.9 (C-9), 89.8 [d, ^2J (^{13}C,C)= 14.1 Hz, C-17], 123.5 (C-4), 171.1 (C-5), 199.3 (C-3), 203.6 [d, ^1J (^{13}C,C) = 38.0 Hz, C-20].

17α,21-Dihydroxypregn-4-ene-3,20-dione (1)

*From **9***: To a solution of **9** (185 mg, 0.37 mmol) in acetone and H_2O (60:40, 100 mL) was added K_2CO_3 (195 mg, 1.41 mmol, 3.8 equiv). The reaction mixture was stirred at r.t. for 3 days and acetone was evaporated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with aq 10% HCl (30 mL), brine (2 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give **1** (90 mg, 0.26 mmol, 70%) as a white solid.

*From **10***: Product **1** was obtained in 57% yield according to the procedure described by Numazawa and Nagaoka.[22]

Mp 201–202 °C [Lit.[22,23] mp 196–199 °C (acetone) or 207–208 °C (acetone)]; $[\alpha]_D^{20}$ +123 (*c* 1.0, $CHCl_3$) {Lit.[24] $[\alpha]_D^{20}$ +126 (*c* 1.0, $CHCl_3$)}.

IR (KBr): 3509 (OH), 3461 (OH), 1711 (C=O), 1664 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (s, 3 H, H-18), 0.74–2.05 (m, 14 H), 1.16 (s, 3 H, H-19), 2.19–2.46 (m, 4 H), 2.62–2.71 (m, 1 H, H-16β), 2.84 (br s, 2 H, OH-17 and OH-21), 4.28 (A part of an AB system, J_{AB} = 19.8 Hz, 1 H, H-21), 4.66 (B part of an AB system, J_{AB} = 19.8 Hz, 1 H, H-21), 5.71 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0 (C-18), 17.3 (C-19), 20.5 (C-11), 23.7 (C-15), 30.1, 32.0, 32.8, 33.9, 34.5, 35.6 (C-8), 35.7, 38.6 (C-10), 48.5 (C-13), 50.3 (C-14), 53.3 (C-9), 67.4 (C-21), 89.0 (C-17), 123.9 (C-4), 171.3 (C-5), 199.8 (C-3), 212.5 (C-20).

[20-^{13}C]-17α,21-Dihydroxypregn-4-ene-3,20-dione (1a)

Starting from **9a** (370 mg, 0.74 mmol) and using the same procedure as for the synthesis of **1** gave **1a** (140 mg, 0.40 mmol, 54%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (s, 3 H, H-18), 0.90–2.05 (m, 14 H), 1.17 (s, 3 H, H-19), 2.24–2.47 (m, 4 H), 2.63–2.71 (m, 1 H, H-16β), 2.84 (br s, 2 H, OH-17 and OH-21), 4.28 [A part of an AB system, J_{AB} = 19.8 Hz, ^2J (^{13}C,H) = 3.9 Hz, 1 H, H-21], 4.66 [B part of an AB system, J_{AB} = 19.8 Hz, ^2J (^{13}C,H) = 3.9 Hz, 1 H, H-21], 5.71 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0 (C-18), 17.4 (C-19), 20.5 (C-11), 23.7 (C-15), 30.1, 32.0, 32.8, 33.9, 34.6, 35.6 (C-8), 35.7, 38.6 (C-10), 48.6 (C-13), 50.3 (C-14), 53.3 (C-9), 67.4 [d, ^1J (^{13}C,H) = 37.5 Hz, C-21], 89.0 [d, ^1J (^{13}C,C) = 46.5 Hz, C-17], 124.0 (C-4), 170.9 (C-5), 199.6 (C-3), 212.3 (^{13}C-20).

[21-^{13}C]-17α,21-Dihydroxypregn-4-ene-3,20-dione (1b)

Starting from **10b** (533 mg, 1.30 mmol) and using the same procedure as for the synthesis of **1** according to the procedure described by Numazawa and Nagaoka[22] and gave **1b** (139 mg, 0.40 mmol, 31%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.67 (s, 3 H, H-18), 0.87–2.03 (m, 14 H), 1.16 (s, 3 H, H-19), 2.23–2.46 (m, 4 H), 2.61–2.70 (m, 1 H, H-16β), 3.00 (br s, 2 H, OH-17 and OH-21), 4.24 [A part of an AB system, J_{AB} = 19.8 Hz, ^1J (^{13}C,H) = 147.0 Hz, 1 H, H-21], 4.68 [B part of an AB system, J_{AB} = 19.8 Hz, ^2J (^{13}C,H) = 147.0 Hz, 1 H, H-21], 5.70 (s, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (C-18), 17.3 (C-19), 20.5 (C-11), 23.7 (C-15), 30.1, 32.0, 32.8, 33.8, 34.5, 35.6 (C-8), 35.7, 38.6 (C-10), 48.5 (C-13), 50.3 (C-14), 53.3 (C-9), 67.4 (^{13}C-21), 89.0 [d, ^2J (^{13}C,C) = 10.4 Hz, C-17], 123.8 (C-4), 171.4 (C-5), 199.8 (C-3), 212.4 [d, ^1J (^{13}C,C) = 37.0 Hz, C-20].

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are: experimental procedures and characterization details for the intermediates **3**, **3a**, **8**, **9**, **10**, and NMR spectra for compounds **1a** and **1b**.

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References

(1) Schimmer, B. P.; Parker, K. L. In *Goodman & Gilman's : The Pharmacological Basis of Therapeutics, 11th ed.*; Brunton, L. L.; Lazo, J. S.; Parker, K. L., Eds.; McGraw Hill: New York, **2006**, 1587–1612.

(2) (a) Wilkinson, S. M.; Cartwright, P. H.; English, J. S. C. *Lancet* **1991**, *337*, 761. (b) Lauerma, A. I. *Contact Dermatitis* **1991**, *24*, 123. (c) Dooms-Goossens, A.; Morren, M. *Contact Dermatitis* **1992**, *26*, 182. (d) Matura, M.; Goossens, A. *Allergy* **2000**, *55*, 698. (e) Hennge, U. R.; Ruzicka, T.; Schwartz, R. A.; Cork, M. J. *J. Am. Acad. Dermatol.* **2006**, *54*, 1.

(3) (a) Lepoittevin, J.-P.; Drieghes, J.; Goossens, A. *Arch Dermatol.* **1995**, *131*, 31. (b) Bircher, A. J.; Thürlimann, W.; Hunziker, T. h.; Pasche-Koo, F.; Hunziker, N.; Perrenoud, D.; Elsner, P.; Schultheiss, R. *Dermatology* **1995**, *191*, 109; the author list also includes members of the Swiss contact dermatitis research group. (c) Isaksson, M.; Andersen, K. E.; Brandão, F. M.; Bruynzeel, D. P.; Bruze, M.; Camarasa, J. G.; Diepgen, T.; Ducombs, G.; Frosch, P. J.; Goossens, A.; Lahti, A.; Menné, T.; Rycroft, R. J. G.; Seidenari, S.; Shaw, S.; Tosti, A.; Wahlberg, J. E.; White, I. R.; Wilkinson, J. D. *Contact Dermatitis* **2000**, *42*, 27.

(4) Rustemeyer, T.; van Hoogstraten, I. M. W.; von Blomberg, B. M. E.; Scheper, R. J. In *Textbook of Contact Dermatitis*; Rycroft, R. J. G.; Menné, T.; Frosch, P. J.; Lepoittevin, J.-P., Eds.; Springer-Verlag: Berlin, **2001**, 13–58.

(5) Lepoittevin, J.-P. In *Textbook of Contact Dermatitis*; Rycroft, R. J. G.; Menné, T.; Frosch, P. J.; Lepoittevin, J.-P., Eds.; Springer-Verlag: Berlin, **2001**, 59–89.

(6) (a) Bundgaard, H. *Arch. Pharm. Chem., Sci. Ed.* **1980**, *8*, 83. (b) Matura, M.; Lepoittevin, J.-P.; Arbez-Gindre, C.; Goossens, A. *Contact Dermatitis* **1998**, *38*, 106.

(7) (a) Demoulin, J. D.; Armbruster, A.-M.; Pullman, B. *J. Quantum Chem.* **1979**, *16*, 631. (b) Lo, T. W. C.; Westwood, M. E.; McLellan, A. C.; Selwood, T.; Thornalley, P. J. *J. Biol. Chem.* **1994**, *269*, 32299. (c) Wilkinson, S. M.; Jones, M. F. *Br. J. Dermatol.* **1996**, *165*, 225.

(8) (a) Franot, C.; Benezra, C.; Lepoittevin, J.-P. *Bioorg. Med. Chem.* **1993**, *1*, 389. (b) Goetz, G.; Meschkat, E.; Lepoittevin, J.-P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1141.

(9) Patchett, A. A. In *Biographical Memoirs, National Academy of Sciences*, Vol. 81; The National Academy Press: Washington, **2002**, 278–293.

(10) (a) Andrews, D. R.; Giusto, R. A.; Sudhakar, A. R. *Tetrahedron Lett.* **1996**, *37*, 3417. (b) Batist, J. N. M.; Marx, A. F.; van Zoest, W. J.; Kapur, J. C. European Patent, EP 0263569, **1987**; *Chem. Abstr.* **1988**, *109*, 129460. (c) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1981**, 774. (d) Daniewski, A. R.; Wojciechowska, W. *Synthesis* **1984**, 132. (e) Murahashi, S.-I.; Saito, T. S.; Hanaoka, H.; Murakami, Y.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *J. Org. Chem.* **1993**, *58*, 2929. (f) Lett, R.; Melnyk, O. US Patent, US 5723638, **1998**; *Chem. Abstr.* **1996**, *124*, 176619.

(11) (a) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Org. Synth.* **1995**, *73*, 123. (b) Batist, J. N. M.; Barendse, N. C. M. E.; Marx, A. F. *Steroids* **1990**, *55*, 109. (c) VanRheenen, V. H. US Patent, US 4500461, **1985**; *Chem. Abstr.* **1985**, *103*, 22844. (d) Livingston, D. A.; Petre, J. E.; Bergh, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 6449. (e) Reid, J. G.; Debiak-Krook, T. *Tetrahedron Lett.* **1990**, *31*, 3669. (f) VanRheenen, V. H. European Patent, EP 0153001, **1985**; *Chem. Abstr.* **1986**, *105*, 60816. (g) Carruthers, N. I.; Andrews, D. R.; Garshasb, S.; Giusto, R. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1195. (h) Nitta, I.; Fujimori, S.; Ueno, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 978. (i) Carruthers, N. I.; Garshasb, S. *J. Org. Chem.* **1992**, *57*, 961.

(12) (a) Dauben, H. J.; Löken, B.; Ringold, H. J. *J. Am. Chem. Soc.* **1954**, *76*, 1359. (b) Nitz, T. J.; Paquette, L. A. *Tetrahedron Lett.* **1984**, *25*, 3047.

(13) (a) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045. (b) Luly, J. R.; Hsiao, C. N.; BaMaung, N.; Plattner, J. J. *J. Org. Chem.* **1988**, *53*, 6109.
(14) Arbez-Gindre, C.; Berl, V.; Lepoittevin, J.-P. *Chem. Commun.* **1999**, 431.
(15) Moriarty, R. M.; John, L. S.; Du, P. C. *J. Chem. Soc., Chem. Commun.* **1981**, 641.
(16) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893.
(17) (a) Ringold, H. J.; Stork, G. *J. Am. Chem. Soc.* **1958**, *80*, 250. (b) Ringold, H. J.; Perez Ruelas, J.; Batres, E.; Djerassi, C. *J. Am. Chem. Soc.* **1959**, *81*, 3712. (c) Rothman, E. S.; Perlstein, T.; Wall, M. E. *J. Org. Chem.* **1960**, *25*, 1966. (d) Nitta, I.; Fujimori, S.; Ueno, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 978.
(18) Moreland, W. T. *J. Org. Chem.* **1956**, *21*, 820.
(19) THF containing a certain amount of peroxide (titration with KI and thiosulfate) was prepared as follows: In a typical procedure, THF was exposed to sunlight in an open bottle until the peroxide content reached the expected value. Alternatively, THF could be first distilled from CaO before exposure to sunlight. Fresh and aged THF may be combined to give the proper peroxide content.
(20) Bodor, N.; Fey, L.; Kircz, M.; Hodosan, F. *Rev. Roum. Chim.* **1964**, *9*, 147; *Chem. Abstr.* **1964**, *61*, 61819.
(21) (a) Gadsby, B.; Leeming, M. R. G. US Patent, US 3646012, **1972**; *Chem. Abstr.* **1969**, *71*, 81648. (b) Bradford, H. W. US Patent, US 3444160, **1969**; *Chem. Abstr.* **1969**, *71*, 61687.
(22) Numazawa, M.; Nagaoka, M. *J. Org. Chem.* **1985**, *50*, 81.
(23) Julian, P. L.; Meyer, E. W.; Ryden, I. *J. Am. Chem. Soc.* **1950**, *72*, 367.
(24) Ringold, H. J.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc.* **1956**, *78*, 820.