Rearrangement of 4β,5β-methylenepregnanes: a simple approach to A-homopregnanes and 5β-methylpregnanes

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Dedicated to Prof. Rosa Lederkremer on her 70th anniversary

Abstract
A-homopregnanes and 5β-methylpregnanes were prepared from the easily available 3β-hydroxy-20β-acetoxy-4β,5β-methylenepregnane by cationic and radical rearrangements respectively. The A-homopregnane was formed in a single step upon spontaneous rearrangement and elimination by treatment of the cyclopropyl alcohol with $BF_3 \cdot Et_2O$. The 5β-methylpregnane was obtained by cleavage of the hydrazone of the corresponding cyclopropylketone followed by rearrangement mediated by mercury(II) hydrides.

Keywords: Cyclopropylcarbinyl radical; cyclopropylcarbinyl cation; A-homopregnane; 5β-methylpregnane

Introduction

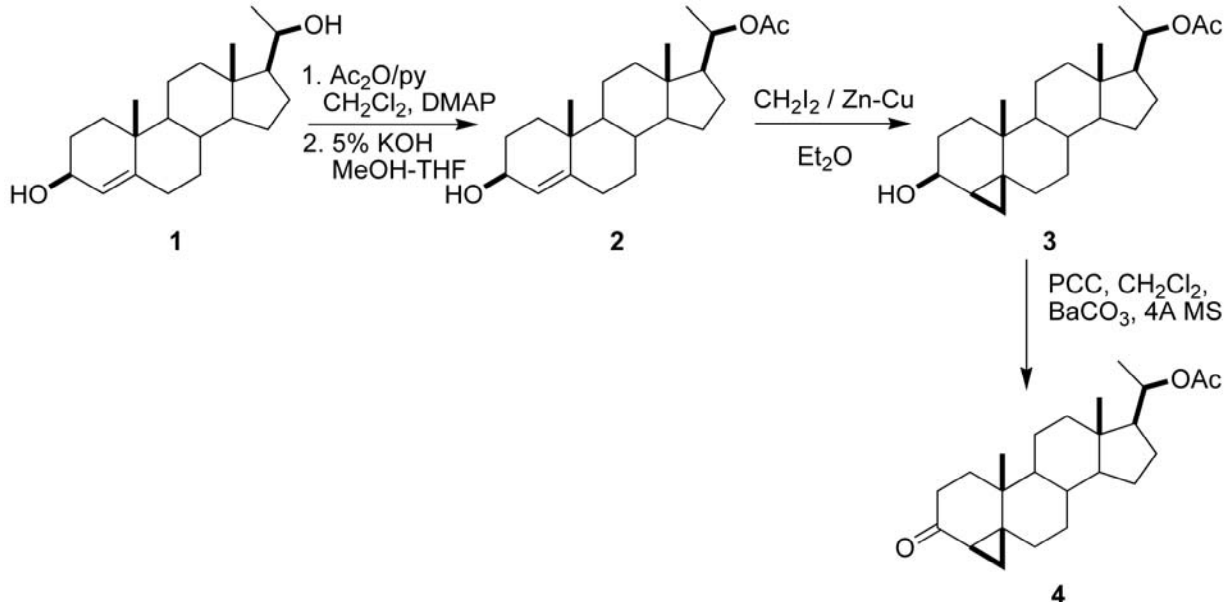
Ring-expansion is a popular approach to medium and large rings, which can be achieved by ionic or radical reactions. In particular, the interest in developing expansion reactions for the construction of seven-membered rings, derives from the common occurrence of these frameworks in biologically active natural products and the preparation of synthetic homologues of active compounds.[1] Ionic and radical expansion reactions, usually follow different paths giving different distributions of products, which may be envisaged and promoted by a judicious choice of conditions. This fact has been used, for example, to easily differentiate between radical and ionic enzymatic mechanisms.[2]

The acid catalyzed rearrangement of cyclopropylcarbinols and analogous systems is well documented.[3,4] The reaction proceeds through the initial formation of a cyclopropylcarbinyl cation followed by either ring expansion or ring fusion. In previous publications we have

reported the synthesis of steroids with expanded C and D rings by means of anionic and radical rearrangements of steroidal cyclopropylketones.[5,6] In a similar way cationic rearrangements of cyclopropane rings fused to the steroidal skeleton may lead to expanded rings. In this work we describe a short synthesis of an A-homopregnane based on the latter. Furthermore an analogous rearrangement under radical conditions was used to obtain a 5β-methylpregnane.

Results and Discussion

The precursor 4β,5β-methylenepregnanes, were obtained from steroidal diol **1** which is readily available in good yield by reduction of progesterone (Scheme 1).[7] Thus, acetylation of **1** with acetic anhydride/pyridine in the presence of DMAP followed by selective removal of the more reactive C-3 acetate gave the allylic alcohol **2** in 82% yield. Introduction of the fused cyclopropane ring in ring A was achieved in 80% yield by a Simmons Smith reaction,[8] to give 4β,5β-methylenepregnane **3**. Oxidation of **3** with PCC gave the corresponding ketone **4**.

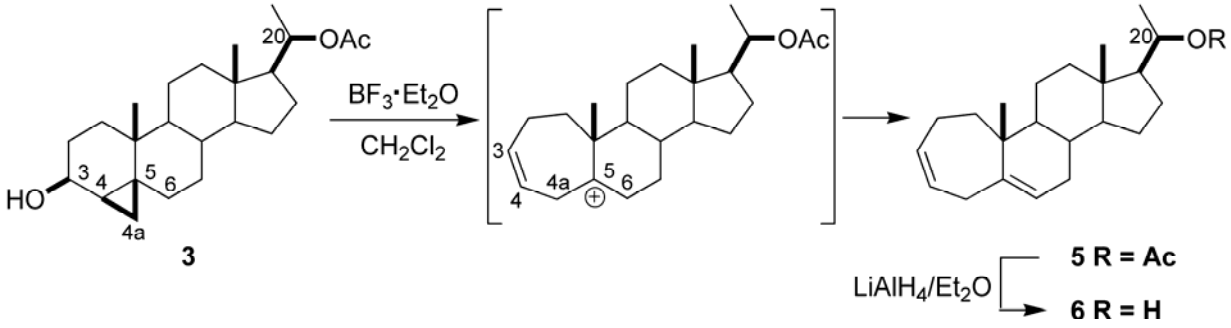


1 **2** **3** **4**

Scheme 1

Cationic rearrangement. Treatment of cyclopropyl alcohol **3** with $BF_3 \cdot Et_2O$ in dichloromethane at 0°C gave the A-homopregnadiene **5** in 60% yield (Scheme 2). The rearrangement would be initiated by the eliminative fission of the endocyclic cyclopropane bond promoted by the Lewis acid, to give the tertiary carbocation at C-5. Loss of a proton from C-6 should give the non-conjugated diene **5**. Removal of the acetate group at C-20 with $LiAlH_4$ gave the 20-alcohol **6**. The structure of **6** was confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. Diagnostic signals in the ^{13}C spectrum include the four olefinic carbons (three disubstituted and

one trisubstituted) at δ 122.5, 129.4, 130.2 and 144.9. This resonances indicate a non-conjugated diene. In the ^{1}HNMR spectrum, the resonances of the mutually coupled hydrogens at C-4a appear at δ 3.04 and 2.47. The latter, assigned to the α-H, appeared as a double doublet with a 7.3 Hz coupling with H-4, while the β-H was observed as a broad doublet with a negligible coupling to H-4 (AM1 calculations predict a *ca.* 90º dihedral angle between these hydrogens).



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Scheme 2

The formation of the conjugated diene was not observed, in agreement with semiempirical AM1 calculations on the intermediate carbocation (Figure 1) that show that in the most stable conformer, only H-6β has the proper orientation (perpendicular to the plane of the carbocation) to be eliminated and give the double bond.

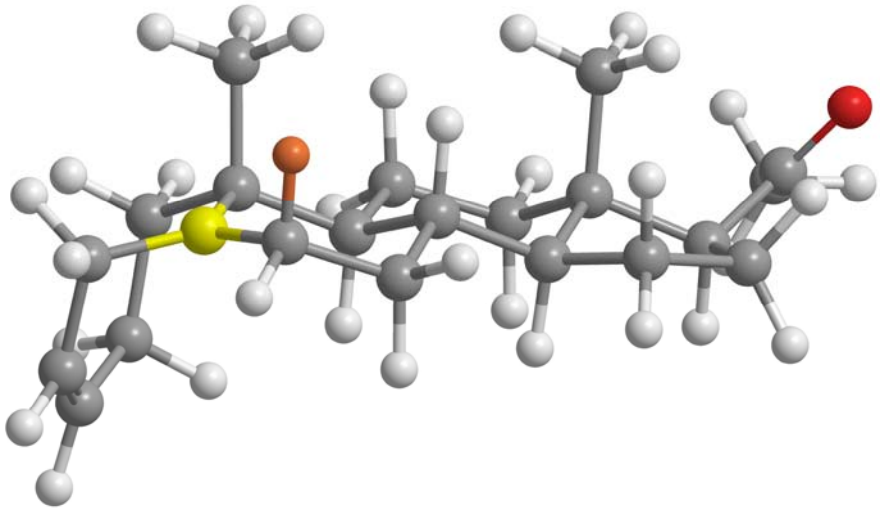
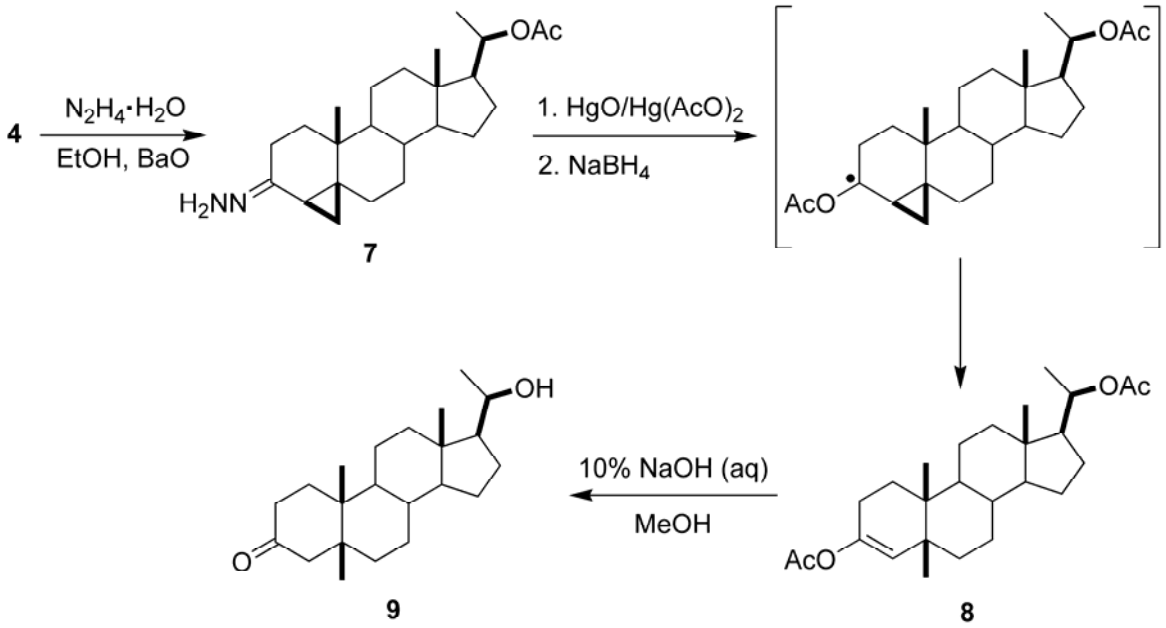


Figure 1. Lowest energy conformer (from AM1 calculations) of the intermediate carbocation in the cationic rearrangement of **3**, showing the carbocation plane (yellow) and H-6β (orange).

Radical rearrangement. The cyclopropylcarbinyl radical at C-3 was generated from the cyclopropylketone **4** via the alkylmercury (II) hydride.[5] Thus ketone **4** was converted to the

hydrazone (**7**) upon reaction with hydrazine hydrate in ethanol in the presence of BaO (Scheme 3). Treatment of **7** with $Hg(AcO)_2$/HgO followed by reduction with aqueous $NaBH_4$ gave the unstable alkylmercury(II) hydride that decomposes spontaneously to the cyclopropylcarbinyl radical. Rearrangement of the latter occurred with regioselective cleavage of the C(4)–C(4a) bond of the cyclopropane ring, to give enol acetate **8**. Alkaline hydrolysis of enol acetate **8** gave 5β-methylpregnane **9** in 21% overall yield from progesterone. The previous synthesis reported for this compound had a 14% yield and required separation of 5α and 5β isomers.[9]



Scheme 3

Ab initio calculations performed on a simplified model of the cyclopropylcarbinyl radical intermediate, show the high radical character of C-4a that leads to cleavage of the C(4)–C(4a) bond (Figure 2). The overlapping of the latter bond with the SOMO at C-3 accounts for the regiospecificity of the rearrangement.[5] This is in contrast to the cationic rearrangement which is directed by the stability of the intermediate carbocation.

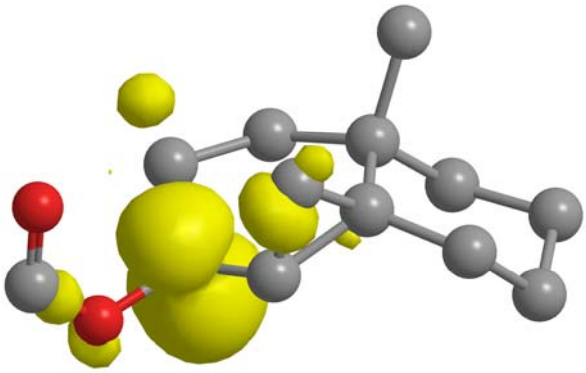


Figure 2. Spin density surface for the lowest energy conformation of a simplified model of the intermediate ciclopropylcarbinyl radical (*ab initio* UHF/6-31G**, isospin surface 0.02 a.u.). In order to reduce the calculation time, only rings A and B of the steroid were used and the acetate was replaced by a formate.

Conclusions

The scope of the rearrangement of cyclopropane rings fused to the steroid skeleton has now been extended to obtain A-homopregnanes from progesterone in 5 steps, using a cationic rearrangement. The radical rearrangement provided in this case, a straightforward preparation of 5β-methylpregnanes. The outcome of the rearrangements may be predicted by semiempirical (ionic) or *ab initio* (radical) calculations. Work is in progress to obtain steroid hormone and neurosteroid analogues from **6**.

Experimental Section

General Procedures. Melting points were taken on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded in thin films using KBr disks on a Nicolet Magna IR 550 FT-IR spectrophotometer. ^{1}H NMR spectra (200 or 500 MHz) and ^{13}C NMR spectra (50 or 125 MHz) were recorded on Bruker AC-200 or Bruker AM-500 NMR spectrometers respectively, in deuteriochloroform solution. Chemical shifts are given from TMS (0 ppm) as internal standard, *J* values are given in Hz. NMR spectra were assigned by analysis of the DEPT, COSY 45 and HETCOSY spectra. The electron impact mass spectra (EI) and high resolution mass spectra (HRMS) were measured on Shimadzu QP-5000 and ZAB SEQ mass spectrometers respectively (70 eV by direct inlet). All solvents used were reagent grade. Solvents were evaporated at *ca.* 45 ºC under vacuum. Column chromatography was performed on silica gel Merck 9385 (0.0040-0.0063 mm). TLC analysis was performed on silica gel 60 F254 (0.2 mm thick). The

homogeneity of all compounds was confirmed by TLC and NMR. 3β,20β-Dihydroxy-4-pregnene **1** was obtained by reduction of progesterone with $LiAlH_4$ in ether.[7]

3β-Hydroxy-20β-acetyloxypregn-4-ene (2). To a solution of 3β,20β-dihydroxypregn-4-ene **1** (1.39 g, 4.40 mmol) in acetic anhydride (3.5 ml) and pyridine (1.4 ml) was added DMAP (15 mg, 0.12 mmol), the solution was stirred for 1.5 h at room temperature, then diluted with dichloromethane and washed with 5% HCl, 5% $NaHCO_3$ and finally with water, the organic layer was dried with Na_2SO_4, filtered and the solvent evaporated. The solid residue was dissolved in THF (62 ml) and methanol (62 ml), to this solution was added 5% aqueous KOH (6 ml) and the mixture was stirred for 1.5 hs at room temperature, concentrated to 1/3 of its volume, diluted with water and extracted with dichloromethane. The organic layer was dried, filtered and evaporated. The amorphous solid was purified by flash chromatography to give compound **2** (1.28 g, 82 %), mp 158-160°C; *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.51; H, 10.08. IR (cm^{-1}) 3327, 2935, 2870, 1718, 1448, 1375, 1249, 1028. ^{1}H NMR (200 MHz) δ 0.65 (3H, s, H-18), 1.04 (3H, s, H-19), 1.14 (3H, d, *J* = 6.2 Hz, H-21), 2.01 (3H, s, acetate), 4.13 (1H, m, H-3) , 4.82 (1H, m, H-20), 5.27 (1H, br s, H-4). ^{13}C NMR (50 MHz) δ 12.4 (C-18), 18.9 (C-19), 19.9 (**C**H_3COO), 20.9 (C-11), 21.5 (C-21), 24.2 (C-15), 25.4 (C-2), 29.5 (C-7), 32.1 (C-16), 33.1 (C-1), 35.3 (C-6), 35.7 (C-8), 37.3 (C-10), 39.2 (C-12), 42.2 (C-13), 54.5 (C-9), 54.9 (C-17), 55.5 (C-14), 67.9 (C-3), 72.2 (C-20), 123.4 (C-4), 147.5 (C-5), 170.4 (CH_3**C**OO). MS *m/z*: 360 (M^+, 4%), 342 (M-H_2O, 2%), 300 (M- AcOH, 12%), 230 (21%), 55 (40%), 43 (100%).

3β-Hydroxy-20β-acetyloxy-4β,5β-methylenepregnane (3). To a suspension of Zn-Cu couple (1.80 g) in anhydrous ether (10 ml) was added slowly diiodomethane (0.86 ml, 10.6 mmol). The reaction mixture was heated under reflux for 1.5 h, cooled to room temperature and a solution of compound **2** (0.382 g, 1.06 mmol) in ether (17 ml) added dropwise. The resulting mixture was heated under reflux for 1 h, poured onto sat. NH_4Cl solution and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), filtered and evaporated. The solid obtained was purified by flash chromatography to give cyclopropylalcohol **3** (0.317 g, 80%), mp 118-120 °C. *Anal.* Calcd. for $C_{24}H_{38}O_3.1/2H_2O$: C, 75.15; H, 10.24. Found: C, 75.02; H, 10.52. IR (cm^{-1}) 2933, 2873, 1732, 1375, 1244 y 1031; ^{1}H NMR (200 MHz) δ 0.07 (1H, dd, *J* = 9.5, 4.8 Hz, H-4a), 0.64 (3H, s, H-18), 0.97 (3H, s, H-19), 1.15 (3H, d, *J* = 6.3 Hz, H-21), 2.00 (3H, s, acetate), 4.36 (1H, t, *J* = 7.0 Hz, H-3), 4.86 (1H, m, H-20); ^{13}C NMR (50 MHz) δ 10.6 (C-4a), 12.3 (C-18), 19.8 (C-19), 21.2 (CH_3COO), 21.4 (C-21), 24.2 (C-15), 25.4 (C-16), 26.3 (C-7), 26.4 (C-6), 27.3 (C-4), 30.3 (C-5), 30.7 (C-2), 32.9 (C-10), 34.1 (C-1), 35.4 (C-8), 39.4 (C-12), 42.1 (C-13), 46.0 (C-9), 55.0 (C-17), 55.8 (C-14), 63.7 (C-3), 72.7 (C-20), 170.4 (CH_3**C**OO); MS *m/z*: 374 (M^+, 6%), 356 (M-H_2O, 4%), 314 (M-AcOH, 10%), 296 (8%), 121 (22%), 43 (100%).

20β-Acetyloxy-4β,5β-methylenepregnan-3-one (4). To a suspension of PCC (0.542 g, 2.5 mmol), $BaCO_3$ (0.337 g, 1.71 mmol) and 4Å molecular sieves (0.413 g) in dry dichloromethane (12 ml), was added a solution of cyclopropylalcohol **3** (0.236 g, 0.63 mmol) in dichloromethane (2 ml). The mixture was stirred 40 minutes at room temperature, diluted with ether and filtered through a silica gel column (dichloromethane-ether 1:1). The solvent was evaporated and the

residue was purified by flash chromatography to give cyclopropylketone **4** (0.186 g, 79%) as a white crystalline solid, mp 145-147°C (hexane-AcOEt); *Anal.* Calcd. for $C_{24}H_{36}O_3.1/2H_2O$: C, 75.55; H, 9.77; Found: C, 75.50; H, 9.72; IR (cm^{-1}) 2933, 2872, 1730, 1686, 1375, 1246, 1030. ^1H NMR (200 MHz) δ 0.64 (3H, s, H-18), 0.85 (1H, dd, *J* = 10.6, 6.6 Hz, H-4a), 1.07 (3H, s, H-19), 1.14 (3H, d, *J* = 6.3 Hz, H-21), 2.00 (3H, s, acetate), 2.13 (1H, t, *J* = 6.3 Hz, H-2α), 4.84 (1H, m, H-20); ^{13}C NMR (50 MHz) δ 12.4 (C-18), 17.9 (C-4a), 19.8 (C-19), 20.6 (**C**H_3COO), 21.4 (C21), 21.6 (C-11), 24.2 (C-15), 25.4 (C-6), 27.6 (C-7), 30.1 (C-2), 32.2 (C-1), 32.4 (C-16), 34.3 (C-10), 35.1 (C-4), 35.4 (C-8), 36.8 (C-5), 39.1 (C-12), 42.2 (C-13), 46.0 (C-9), 55.0 (C-14), 55.5 (C-17), 72.8 (C-20), 170.4 (CH_3**C**OO), 209.9 (C-3); MS *m/z*: 372 (M^+, 5%), 344 (1%), 312 (M-AcOH, 16%), 242 (7%), 121 (25%), 43 (100%).

20β-Acetyloxy-A-homopregna-3,5-diene (5). To a solution of cyclopropyl alcohol **3** (0.178 g, 0.47 mmol) in dichloromethane (27 ml) at 0°C under a nitrogen atmosphere, was added slowly $BF_3{\cdot}Et_2O$ (88.2 µl, 0.47 mmol). The solution was stirred for 30 min, poured onto 5% $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography to give the A-homo steroid **5** (0.107 g, 63 %) as an amorphous solid. IR (cm^{-1}) 2935, 1732, 1460, 1375, 1244, 1072, 1022. ^1H NMR (500 MHz) δ 0.64 (3H, s, H-18), 0.97 (3H, s, H-19), 1.16 (3H, d, *J* = 6.2 Hz, H-21), 2.02 (3H, s, acetate), 2.47 (1H, dd, *J* = 7.3, 15.3 Hz, H-4aα), 3.03 (1H, br d, *J* = 15.3 Hz, H-4aβ), 4.83 (1H, m, H-20), 5.35 (1H, d, *J* = 4.0 Hz, H-6), 5.59 (2H, m, H-3 and H-4). ^{13}C NMR (125 MHz) δ 12.5 (C-18), 19.9 (C-21), 21.3 (C-11), 21.5 (CH_3COO), 22.9 (C-19), 24.0 (C-2), 24.2 (C-15), 25.5 (C-16), 31.4 (C-7), 31.8 (C-8), 34.2 (C-4a), 35.2 (C-1), 39.3 (C-12), 40.4 (C-10), 42.2 (C-13), 43.0 (C-9), 55.0 (C-17), 56.5 (C-14), 72.9 (C-20), 122.4 (C-6), 129.4 (C-4), 130.1 (C-3), 144.9 (C-5), 170.4 (CH_3**C**OO); MS *m/z*: 356 (M^+, 12%), 341 (1%), 296 (M-AcOH, 7%), 281 (10%), 267 (4%), 189 (16%), 121 (22%), 105 (27%), 91 (32%), 43 (100%); HRMS Calcd.$C_{24}H_{36}O_2$: 356.2715. Found: 356.2721

20β-Hydroxy-A-homopregn-3,5-diene (6). To a solution of acetate **5** (0.120g, 0.337 mmol) in ether (5 ml) under a nitrogen atmosphere was added $LiAlH_4$ (0.038 g, 0.99 mmol), the suspension was stirred at room temperature for 1 h, after addition of HCl 1N (1 ml) the mixture was poured onto an aqueous saturated solution of sodium and potassium tartrate and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), evaporated and the residue was purified by flash chromatography to give alcohol **6** (0.078 g, 74%) as a white crystalline solid. mp 138-139°C (hexane-AcOEt); *Anal.* Calcd. for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 83.93; H 11.16; IR (cm^{-1}) 3385, 2925, 2362, 1473, 1450, 1087, 1020. ^1H NMR (200 MHz) δ 0.79 (3H, s, H-18), 0.99 (3H, s, H-19), 1.15 (d, *J* = 6.1 Hz, H-21), 2.47 (1H, dd, *J* = 7.3, 15.3 Hz, H-4aα), 3.04 (1H, br d, *J* = 15.3 Hz, H-4aβ), 3.74 (1H, m, H-20), 5.37 (1H, d, *J* = 4.0 Hz, H-6), 5.61 (2H, m, H-3 and H-4); ^{13}C NMR (50 MHz) δ 12.5 (C-18), 21.3 (C-11), 22.9 (C-21), 23.6 (C-19), 24.1 (C-2), 24.5 (C-15), 25.7 (C-16), 31.5 (C-7), 31.8 (C-8), 34.2 (C-4a), 35.3 (C-1), 40.0 (C-12), 40.5 (C-10), 42.2 (C-13), 43.0 (C-9), 56.6 (C-17), 58.5 (C-14), 70.6 (C-20), 122.5 (C-6), 129.4 (C-4), 130.2 (C-3), 144.9 (C-5); MS *m/z*: 314 (M^+, 28), 299 (5), 281 (5), 233 (7), 189 (24), 91 (52), 45 (100).

20β-Acetyloxy-4β,5β-methylenepregnan-3-one hydrazone (7). To a solution of cyclopropyl ketone **4** (0.125 g, 0.33mmol) in ethanol (6.2 ml) were added hydrazine hydrate (80%, 0.87ml, 12.2 mmol) and barium oxide (5 mg, 0.03 mmol). The mixture was heated under reflux until disappearance of the starting ketone (TLC, *ca.* 1.5 h), poured over water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give hydrazone **7** (0.125 g, 97 %) as a white amorphous solid; *Anal.* Calcd. for $C_{24}H_{38}O_2N_2$: C, 74.57; H, 9.91; Found: C, 75.01; H, 10.10; IR (cm^{-1}) 3389, 2929, 2872, 1732, 1615, 1377, 1246, 1072; ^{1}H NMR (200 MHz) δ 0.47 (1H, dd, *J* = 10.1, 6.6 Hz, H-4a), 0.64 (3H, s, H-18), 1.02 (3H, s, H-19), 1.15 (3H, d, *J* = 6.3 Hz, H-21), 2.00 (3H, s, acetate), 4.82 (1H, m, H-20); ^{13}C NMR (50 MHz) δ 12.4 (C-18), 15.3 (C-4a), 19.0 (C-2), 19.8 (C-19), 20.4 (**C**H_3COO), 21.4 (C-21), 21.6 (C-11), 24.2 (C-15), 25.4 (C-6), 26.9 (C-7), 27.7 (C-4), 30.3 (C-1), 30.5 (C-5), 32.9 (C-16), 34.0 (C-10), 35.4 (C-8), 39.1 (C-12), 42.2 (C-13), 45.4 (C-9), 55.0 (C-17), 55.4 (C-14), 72.8 (C-20), 153.8 (C-3), 170.4 (CH_3**C**OO); MS *m/z*: 386 (M^+, 5%), 370 (M-NH_2, 4%), 326 (M-AcOH, 2%), 295 (4%), 110 (14%), 84 (18%), 55 (26%), 43 (100%).

3,20β-Diacetoxy-5β-methylpregn-3-ene (8). A solution of hydrazone **7** (0.130 g, 0.33 mmol) in anhydrous THF (3 ml) was added at room temperature under nitrogen to a suspension of HgO (0.073g, 0.33 mmol) and $Hg(OAc)_2$ (0.215 g, 0.67 mmol) in anhydrous THF (3 ml). The reaction mixture was vigorously stirred until it turned yellow (*ca* 15 min) and was placed in an ice bath. A cold solution of $NaBH_4$ (0.165 g, 4.3 mmol) was added slowly and the suspension stirred until the gas evolution ceased (*ca* 0.5 h). The reaction mixture was filtered, diluted with water and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), evaporated and the residue purified by flash chromatography to give enol acetate **8** (0.070 g, 50 %) as a white, amorphous solid; *Anal.* Calcd. for $C_{26}H_{40}O_4.1/2H_2O$: C, 73.37; H, 9.71; Found: C, 73.52; H, 10.11; IR (cm^{-1}) 2929, 1755, 1732, 1367, 1246, 1219, 1026; ^{1}H NMR (200 MHz) δ 0.62 (3, s, H-18), 0.85 (3H, s, 5-CH_3), 0.94 (3H, s, H-19), 1.13 (d, *J* = 6.2 Hz, H-21), 2.00 (3H, s, 20-acetate), 2.11 (3H, s, 3-acetate), 4.82 (1H, m, H-20), 4.98 (1H, br s, H-4); ^{13}C NMR (50 MHz) δ 12.4 (C-18), 16.4 (C-19), 19.9 (CH_3COO), 21.0 (CH_3COO), 21.5 (C-21), 21.9 (C-11), 23.8 (C-6), 24.2 (C-16), 25.4 (C-15), 26.6 (C-4a), 28.6 (C-7), 28.9 (C-1), 35.4 (C-8), 36.3 (C-2), 36.6 (C-10), 39.2 (C-5), 39.5 (C-12), 42.1 (C-9), 54.9 (C-14), 55.8 (C-17), 72.9 (C-20), 124.3 (C-4), 147.0 (C-3), 169.5 (CH_3COO), 170.5 (CH_3COO); MS *m/z*: 416 (M^+, 0.5%), 401 (M-CH_3, 1%), 359 (30%), 356 (M-AcOH, 4%), 299 (4%), 109 (15%), 55 (21%), 43 (100%)

20β-Hydroxy-5β-methylpregnan-3-one (9). To a solution of enol acetate **8** (0.07 g, 0.17 mmol) in methanol (4 ml) was added at room temperature under a nitrogen atmosphere, 10% NaOH solution (0.25 ml). The reaction mixture was stirred for 24 h, diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), evaporated and the residue was purified by flash chromatography to give ketone **9** (0.053g, 95%) as a white crystalline solid. The spectroscopic data (NMR) were identical to those reported for 20β-hydroxy-5β-methylpregnan-3-one.[9]

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