Synthesis of New Formyl and Aminomethyl Steroids *via* Homogeneous Catalysis

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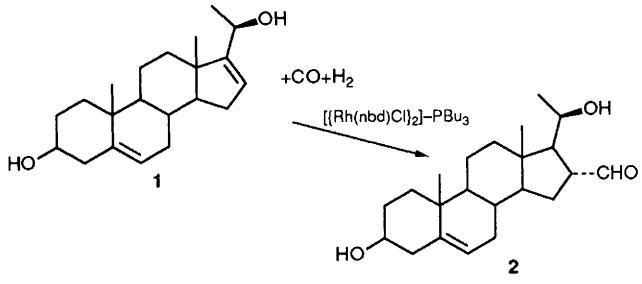
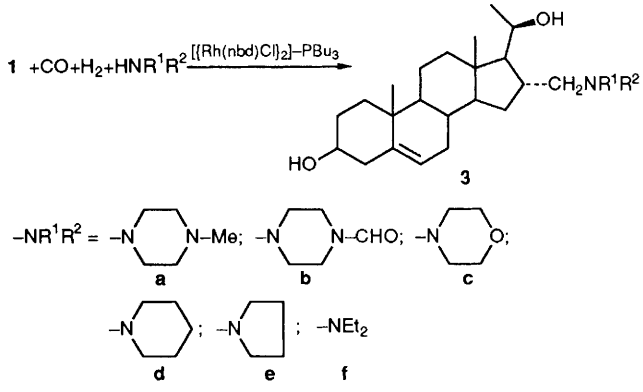
New formyl-pregnene, formyl-androstene and the corresponding aminomethyl derivatives are synthesised selectively *via* hydroformylation with a rhodium–phosphine catalyst prepared *in situ*.

Homogeneous catalysis is a well established method for selective addition, but except for hydrogenation[1] only a little information is available on this type of reaction of steroids.[2,3] Catalysts prepared *in situ* from $[\{Rh(diene)Cl\}_2]$ and tertiary phosphines are efficient in selective hydroformylation of unsaturated steroids.[4] In this paper we report the highly selective syntheses of (20*R*)-3β,20β-dihydroxy-16α-formyl-pregn-5-ene **2** and other formyl-androstane derivatives. The starting compound **1** was prepared in 82% yield by reduction of 3β-acetoxypregna-5,16-dien-20-one {$[\alpha]_D$ −70.3 (*c* 0.9, chloroform, 25 °C), m.p. 168–171 °C;[5] ^{1}H NMR (60 MHz; $CDCl_3$–CD_3OD): δ 0.90 (s, 3H, 18-CH_3), 1.06 (s, 3H, 19-CH_3), 1.28 (d, 3H, 21-CH_3), 3.4 (m, 1H, 3α-H), 4.3 (m, 1H, 20-H), 5.3 (m, 1H, 6-H) and 5.6 (m, 1H, 16-H)}.

In the hydroformylation of **1** (Scheme 1) the double bond in position 5 remains intact even under relatively severe reaction conditions because of steric hindrance. The reaction of the 16, 17 double bond was carried out with high chemo- and regio-selectivity. In a typical experiment the solid substrate **1** (10 mmol) and a solution of $[\{Rh(nbd)Cl\}_2]$ (0.05 mmol; nbd = norbornadiene), PBu_3 (0.22 mmol) and Et_3N (0.5 mmol) in benzene (50 ml) under argon was heated under pressure in an autoclave. The product was obtained by fractional crystallization in 80% yield, and its structure (the stereochemistry of the formyl group at C-16) was based on mass spectral and NMR data using the DEPT, COSY90, HETCOR and $^1H\{^1H\}$ NOE methods† [^{1}H NMR (300 MHz; $CDCl_3$): δ 0.87 (s, 3H, 18-CH_3), 1.02 (s, 3H, 19-CH_3), 1.14 (d, *J* 6.2 Hz, 3H, 21-CH_3), 2.48 (m, $^3J_{16\beta,CHO}$ *ca.* 3.2, $^3J_{16\beta,17\alpha}$ *ca.* 11.2, $^3J_{16\beta,15\alpha}$ *ca.* 2.8, $^3J_{16\beta,15\beta}$ *ca.* 8.4 Hz, 1H, 16β-H), 3.52 (m, 1H, 3α-H), 3.86 (m, 1H, 20-H), 5.34 (dd, 1H, 6-H) and 9.63 (d, *J* 3.2 Hz, 1H, 16-CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (18-CH_3), 19.4 (19-CH_3), 23.9 (21-CH_3), 121.0 (6-CH), 140.9 (5-C) and 203.0 (16-CHO)]. Irradiation at different positions gives the following NOEs proving the 16α-formyl structure: CHO:

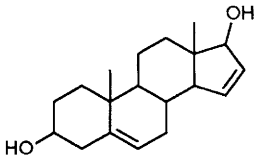


Scheme 1 *Conditions*: 120 °C, 100–120 bar



Scheme 2 *Conditions*: 120 °C, 120 bar

† *Abbreviations used*: DEPT = Distortionless enhancement of polarisation transfer; COSY90 = correlation spectroscopy; HETCOR = heteronuclear correlation spectroscopy; NOE = nuclear Overhauser effect.



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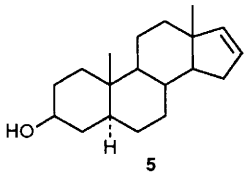

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16-H_β (3.1%), 15-H_α and 17-H_α (5.3%); 16-H_β: CHO (2.5%), 20-H (4.2%), 15-H_β (5.7%), 21-H (1.7%) 18-H (1.8%); 18-H: 20-H (4.5%), 12-H_β (1.0%), 8-H_β, 11-H_β and 15-H_β (6.6%), 16-H_β (1.4%); *m/z*: 346 (60.4), 328 (83.0), 313 (30.2), 310 (20.8), 295 (32.1), 217 (58.5), and 107 (100%); m.p. 171–173 °C.

Hydroformylation of **1** in presence of several secondary amines resulted in the reductive amination of **2** (Scheme 2), *i.e.* in simultaneous formation of new aminomethyl steroids **3a–f** in 47–82% yield. Similar compounds have been prepared previously in multi-step classical syntheses.[6] Characterization of these aminomethyl derivatives was based on mass spectral and NMR data: **3a**: ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.69 (s, 3H, 18-CH_3), 1.01 (s, 3H, 19-CH_3), 1.18 (d, *J* 6.3 Hz, 3H, 21-CH_3), 2.26 (m, 1H, 16β-H), 3.52 (m, 1H, 3α-H), 3.81 (m, 1H, 20-H), 5.34 (dd, 1H, 6-H) and 2.23 (s, 3H, N-CH_3); ^{13}C NMR: (75 MHz; $CDCl_3$): δ 15.1 (18-CH_3), 19.5 (19-CH_3), 22.3 (21-CH_3), 121.4 (6-CH), 141.1 (5-C), 66.8 (CH_2N), 45.8 (NCH_3); *m/z*: 430 (8) and 113 (100%); m.p. 197 °C.

We also succeeded in the hydroformylation of 3β,17β-dihydroxyandrosta-5,15-diene **4**. The double bond in ring *B* remained intact similarly, but the transformation of the double bond in ring *D* resulted in a mixture of four aldehyde isomers in the ratio 45 : 45 : 5 : 5 (^{13}C and ^{1}H NMR data). In the hydroformylation of the 3β-hydroxy-5α-androst-16-ene **5**, mainly (72%) the 16α-formyl compound (^{1}H NMR: δ 9.63, *J* 2.1 Hz) was detected, but we have not yet been able to separate it from a second aldehyde isomer (28%, δ 9.74, *J* 1.2 Hz).

Hydroformylation of the androstene derivatives **4** and **5** in presence of secondary amines produced directly the corresponding aminomethyl isomers (NMR data). The limited selectivity of the latter reactions clearly proves that the substituent at C-17 in the pregnadiene **1** has a direct influence on stereoselectivity.

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