Journal of Fluorine Chemistry 129 (2008) 881–887

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of fluorinated analogues of the neurosteroid $GABA_A$ receptor antagonist, 17-PA

Gildas Deniau [a], Keith T. Sillar [b], David O'Hagan [a,*]

[a] School of Chemistry and Centre for Biomolecular Sciences, University of St-Andrews, St-Andrews, Fife, Scotland KY16 9ST, UK
[b] School of Biology, Bute Building, University of St-Andrews, St-Andrews, Fife KY16 9TS, Scotland KY16 9ST, UK

ARTICLE INFO

Article history:
Received 30 January 2008
Received in revised form 9 March 2008
Accepted 11 March 2008
Available online 21 March 2008

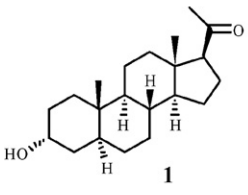
Keywords:
Neurosteroids
17-PA
γ-Aminobutyric acid receptors
Medicinal chemistry

ABSTRACT

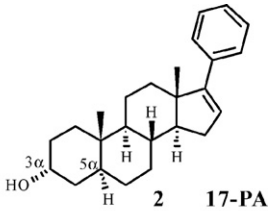
The steroid 17-PA is a $GABA_A$ receptor antagonist which is finding use as a tool in evaluating agonistic/antagonistic activity at $GABA_A$ receptors. Compounds with improved efficacy over 17-PA would be are advantageous for such studies. Accordingly a series of novel analogues of the neurosteroid 17-PA have been prepared and a convenient two-step route is presented which is amenable to the synthesis of analogues with electron-donating *para*-aromatic substituents including fluorine. However, for the *meta*-fluoro analogue then the original four-step route to 17-PA remains more efficient overall. The paper describes these syntheses and discusses the electronic factors which influence this synthetic chemistry.

1. Introduction

$GABA_A$ receptors are chloride ion channels that mediate the fast synaptic inhibition of the main inhibitory neurotransmitter GABA. They play a key role in the central nervous system and they are also the targets for a variety of clinically important therapeutic drugs, such as benzodiazepines, barbiturates and neuroactive steroids. The anaesthetic action of endogenous steroids was first observed in 1941 [1] and their ability to enhance neuronal inhibition *via* the $GABA_A$ receptor was subsequently demonstrated [2,3]. One of the most potent neurosteroids in this regard is allopregnanolone **1** which has potential therapeutic applications as an anaesthetic [4]. However, the steroid-mediated potentiation of $GABA_A$ receptors is complex and has been clarified only very recently. Indeed, there is now direct evidence that neurosteroids bind multiple distinct binding sites on the $GABA_A$ receptors and two of them have been precisely located on the receptor by selective mutation studies [5].



1



2 **17-PA**

In 2004, the first selective steroid antagonist (3α,5α)-17-phenylandrost-16-en-3-ol (17-PA) **2** was reported to antagonise the effects of 5α-reduced neurosteroids at $GABA_A$ receptors whereas 5β-reduced steroids were only weakly affected [6]. This study suggested the presence of at least two steroid binding sites (5α and 5β) on the receptor. To date, 17-PA remains the only selective steroid antagonist known and therefore, it represents an attractive pharmaceutical tool to explore the delineation of different neurosteroids effects and to investigate the pharmacophore of the different steroid binding sites. In this paper we describe the synthesis of some fluorinated analogues of 17-PA in an effort to increase the efficacy of 17-PA as a neurosteroid antagonist.

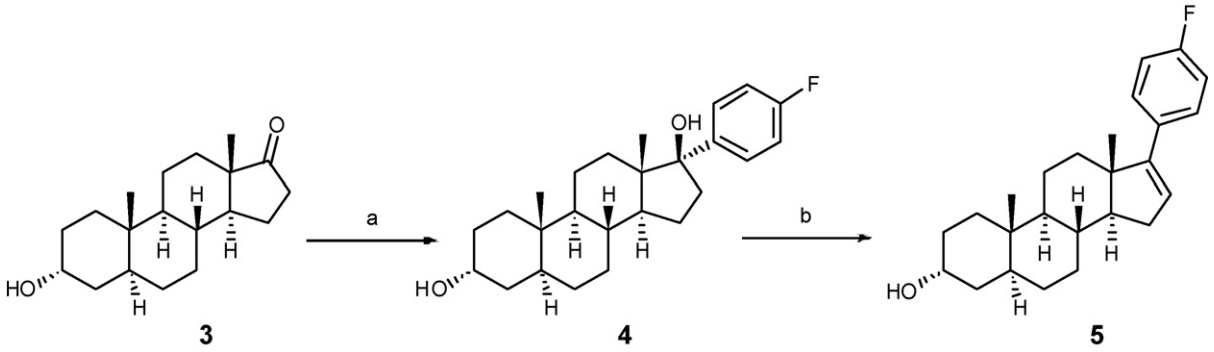
2. Results and discussion

Our initial efforts focused on introducing substituents on the aromatic ring of 17-PA. We decided first to introduce a fluorine atom in the *para*- and *meta*-positions on the phenyl ring. To this end, the analogues **4**–**5** were prepared by a modification of the previous route to 17-PA [6].

4-Fluorophenyllithium was prepared by a metal-bromine exchange reaction of 4-fluorobromobenzene with *n*-BuLi at −78 °C in Et_2O and was added to a solution of androsterone **3** in THF to generate (3α,5α,17β)-17-(*p*-fluorophenyl)androstane-3,17-diol **4** in a modest yield after purification. The formation of a strongly UV-active compound after leaving **4** in $CHCl_3$ for a few days was an indication that the tertiary hydroxyl group was not stable under acidic conditions and was prone to elimination. Therefore, compound **4** was subjected to a pTSA-catalysed

* Corresponding author. Tel.: +44 1334 467176; fax: +44 1334 463808.
E-mail addresses: do1@st-and.ac.uk, do1@st-andrews.ac.uk (D. O'Hagan).

0022-1139/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2008.03.004



Scheme 1. Reagents and conditions: (a) 4-Fluorobromobenzene, *n*-BuLi, Et_2O, −78 to 25 °C, 12 h, 40%; (b) pTSA, DCM, reflux, 4 h, 60%.

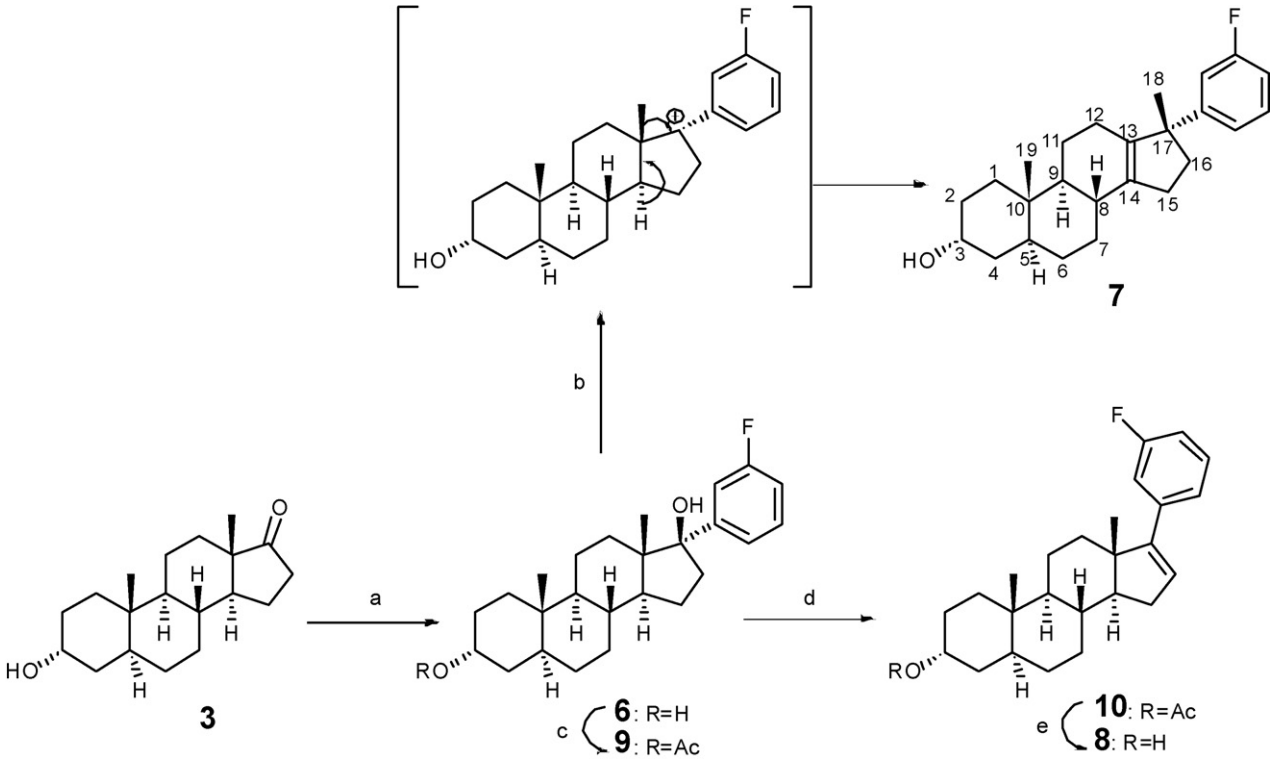
dehydration, which generated **5** in a 60% yield. Accordingly the synthesis of the *para*-fluoro analogue of 17-PA **5** (Scheme 1) could be reduced to two straightforward steps and is a more direct approach than the published route to 17-PA [6].

The synthesis of the *meta*-fluoro analogue of 17-PA was attempted following the sequence described above for the preparation of **5**. Intermediate **6** was prepared by reaction of 3-fluorophenyllithium with androsterone. However, the tertiary hydroxyl group in **6** proved more resistant to elimination under acidic conditions than that experienced for the *para*-fluorophenyl steroid **4**. More forcing conditions (*i.e.* two equivalents of pTSA and heating under reflux of DCM for 5 h) were necessary to achieve complete dehydration of **6** but in this case, a mixture of two isomeric products was obtained, **7** (major) and **8** (minor) as illustrated in Scheme 2.

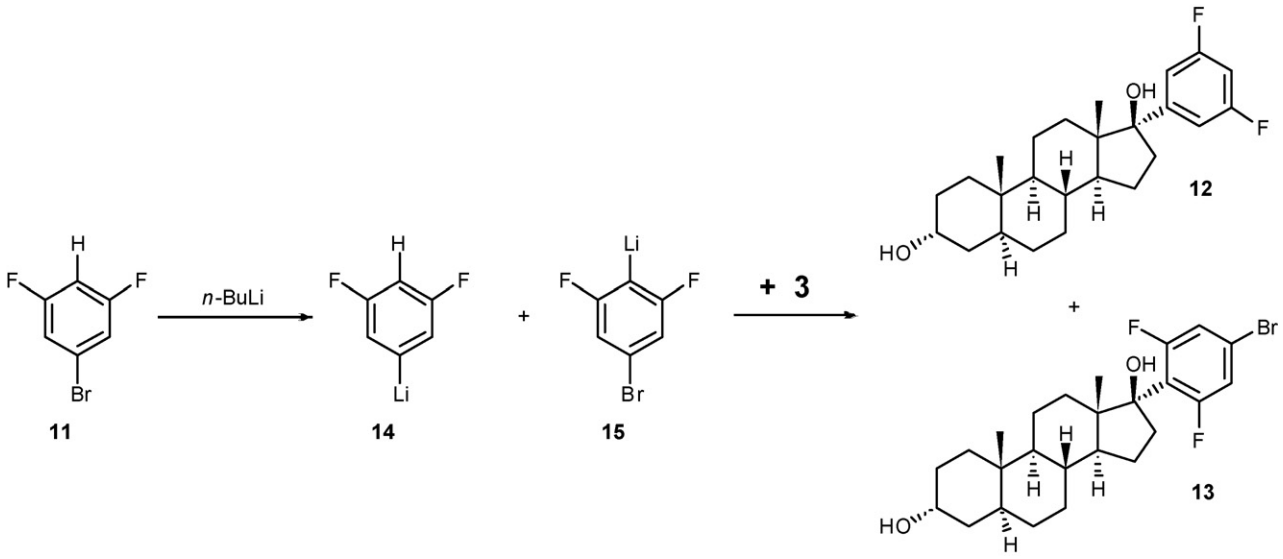
This rearrangement to **7** has precedent in related steroids [7–12]. The reactivity of *meta*-**6** is noticeably different to that of the *para*-fluorophenyl steroid **4**. It seems that the *meta*- fluorine atom inductively destabilises a developing carbocation at C [17] and promotes the rearrangement whereas the *para*-fluorine in **5** provides mesomeric stabilisation and promotes a straightforward E1-elimination.

In the event the *meta*-fluoro analogue **8** of 17-PA was successfully obtained by following the published route to 17-PA [6]. Treatment of **6** with acetic anhydride generated acetate **9** and subsequent dehydration of the tertiary alcohol and then hydrolysis of the acetate, furnished **8** in 15% overall yield (Scheme 2).

The synthesis of the *meta*-difluorophenyl analogue was also addressed, again starting with a metal exchange reaction of 3,5-difluorobromobenzene **11** with *n*-BuLi (Et_2O, −78 °C) and then addition to androsterone **3**. In our hands, this reaction gave a complex mixture from which compounds **12** and **13** could be identified by NMR and mass spectrometry, but they were not purified. The increased acidity of the hydrogen atom *ortho* to the



Scheme 2. Preparation of **8** and formation of **7** by Wagner–Meerwein rearrangement under acidic conditions. Reagents and conditions: (a) 3-fluorobromobenzene, *n*-BuLi, Et_2O, −78 °C to 25 °C, 15 h, 31%; (b): pTSA (2 eq), DCM, 40 °C, 5 h, 52%; (c) Ac_2O, pyridine, DMAP, 25 °C, 15 min, 80%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min, 67%; (e) NaOH, H_2O, MeOH, 65 °C, 1 h, 90%.



Scheme 3. The combined electron withdrawing effect of the two fluorine atoms render the *ortho* hydrogen susceptible to exchange, leading to a mixture of **12** and **13**.

fluorine atoms clearly results in a competing lithium-hydrogen exchange, leading to a mixture of 1,3-difluorophenyl-5-lithium **14** and 1,3-difluorophenyl-2-lithium **15** giving rise to product mixture of **12** and **13** after reaction with androsterone (Scheme 3). Generally, fluorinated phenyllithiums are stable only at low temperature and in the case of *ortho*-fluorophenyllithiums, LiF elimination occurs above −50 °C to generate benzynes [13–16]. Thus this proved to be an inefficient reaction.

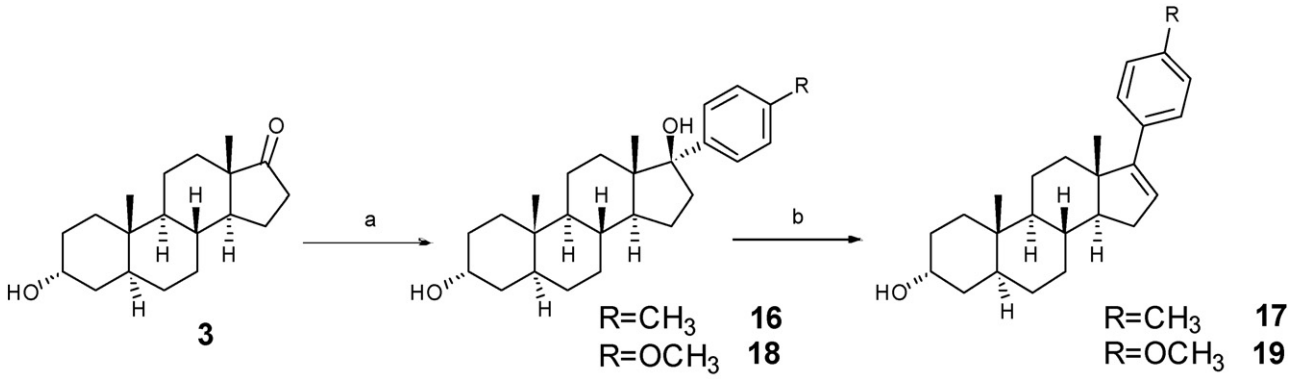
The striking difference in the elimination behaviour between **4** and **6** prompted us to investigate the effects of electron-donating groups on the aromatic ring, with the idea that they will favour dehydration of the tertiary alcohol. To this end, *para*-methylphenyl **17** and *para*-methoxyphenyl **19** derivatives were prepared by the two-step sequence show in Scheme 4.

As anticipated E1 elimination was promoted by both of these donors and dehydration of **16** with a catalytic amount of pTSA in DCM resulted in an efficient conversion to (3α,5α)-(17-*p*-toluene)androst-16-en-3-ol **17**, which was recovered in good yield (71%) with recovery of the rearranged product (5%) as a minor component. In the case of the *para*-methoxyl analogue it is noteworthy that the tertiary alcohol **18** could not be held in solution at all and dehydrated rapidly, consistent with the increased donor ability of the *p*-methoxyl group. Dehydration of **18** furnished (3α,5α)-17-(*p*-methoxyphenyl)androst-16-en-3-ol (**19**) in 90% yield, and there was no evidence of any rearranged product in this case.

In summary we have developed a convenient two-step procedure for the preparation of the *p*-fluoro-, *p*-methyl-**17** and *p*-methoxyl **19** analogues of 17-PA, a development on the published [6] four-step route to 17-PA in those cases. However, in circumstances where significant rearrangement occurs during tertiary alcohol dehydration, then product ratios can be biased against the desired product and separation of the isomers is difficult. Therefore, the four-step procedure e.g. to generate the *meta*-fluoro analogue **8**, is advantageous.

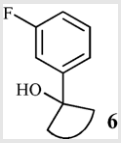
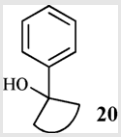
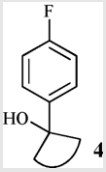
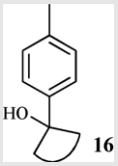
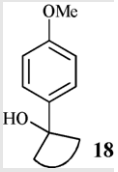
It is tempting to correlate the extent of rearranged product to the Hammett parameter of the substituent (Table 1).

Table 1 indicates that the more electron-donating the substituent, then E1 elimination is promoted and methyl migration is suppressed. Although the Hammett parameter of fluorine in the *para*-position of an aromatic ring is positive, it appears from Table 1 that it acts to stabilise the carbocation at C [17] of **4** similar to that of *para*-hydrogen in **20**. In fact, it is recognised by both theoretical and experimental observations that *para*-fluorine has an ability to stabilise a benzylic positive charge due, to its albeit limited π-donor ability which overcomes the –I effect [18–20]. Conversely at the *meta*-position in **6**, only a –I effect is observed.



Scheme 4. Reagents and conditions: (a) 4-bromotoluene (R = CH_3) or 4-bromoanisole (R = OCH_3), *n*-BuLi, Et_2O, RT, 12 h; (b) pTSA, DCM, RT.

Table 1
Influence of the aromatic substituent on dehydration under acidic conditions

Structure	 6	 20	 4	 16	 18
% Of rearranged product	~75	30	15	~5	0
σ	+0.34	0	+0.06 (or +0.15) [17]	−0.17	−0.29

Finally to add some structural diversity in this series of 17-PA analogues, hydrogenation of the double bond was explored. In this event, the *para*-methyl **17** and *para*-methoxyl **19** analogues of 17-PA were hydrogenated using palladium on carbon as a catalyst. This furnished the saturated compounds **21** and **22** in good yields and as single stereoisomers (Scheme 5). The stereo-chemistry at C [17] was confirmed by ^{1}H NMR-NOESY experiments on **21**, which clearly indicated that the protons of the C [18] methyl group are close to the aromatic ring protons and are not *syn* to the methine hydrogen –H [17].

A set of seven analogues of 17-PA, bearing different substituents on the aromatic ring has been prepared. These compounds are currently under investigation as neurosteroid antagonists on $GABA_A$ receptors, although preliminary assays have been confounded by solubility problems, similar to that experienced for 17-PA. However, the solubility problems of 17-PA in the original assays [6] have recently been partially addressed by dissolution of the steroid with β-cyclodextrins [21].

3. Experimental

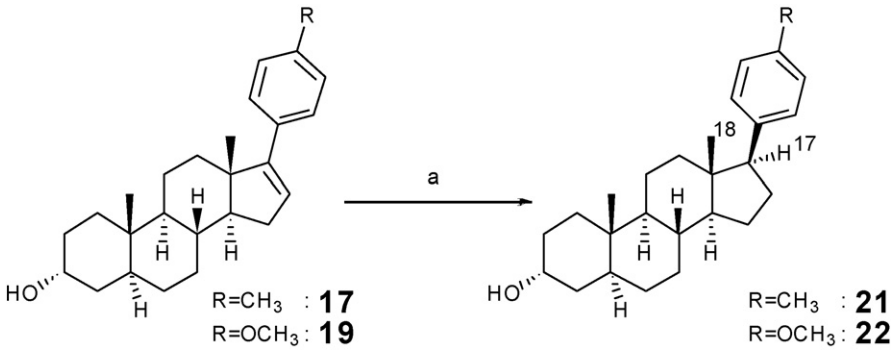
3.1. General experimental procedures

All moisture sensitive reactions were carried out under a positive pressure of nitrogen. Solvents were dried prior to use and column chromatography was performed using silica gel 60 (40–63 μm) from Apollo Scientific Ltd. High-resolution mass spectrometry was performed on a Waters LCT or GCT time-of-flight mass spectrometer. NMR spectra were recorded on either Bruker AV-300 (^{1}H at 300.06 MHz, ^{13}C at 75.45 MHz, ^{19}F at 282.34 MHz), or Bruker AV-500 (^{1}H at 499.90 MHz, ^{19}F at 470.33 MHz). Chemical shifts δ are reported in parts per million (ppm) and quoted relative to internal standard Me_4Si for ^{1}H and ^{13}C and to external standard $CFCl_3$ for ^{19}F. Melting points were measured using a GallenKamp Griffin MPA350.BM2.5 melting point apparatus and are uncorrected. Optical rotations were determined using a A-1000 polarimeter (Optical Polarimeter Ltd.) $[\alpha]_D$ values are measured at 589 nm and given in 10^{-1}deg cm^2 g^{-1}. Elemental analyses were carried out on a CE instrument EA 1110 CHNS analyser. IR spectra were recorded on a PerkinElmer Spectrum GX FT-IR system as KBr disc or as thin film on NaCl plates.

3.2. (3α,5α,17β)-17-(p-Fluorophenyl)androstane-3,17-diol (4)

n-BuLi (3.8 cm^3, 2.5 M in hexane, 9.5 mmol) was added at −78 °C under N_2 to a solution of 4-fluoro-bromobenzene (1.1 cm^3, 10.0 mmol) in dry diethyl ether (10 cm^3). The mixture was stirred for 3 h at −78 °C and then 3 h at −40 °C. The solution was then added dropwise *via* cannula at −40 °C to a solution of androsterone (300 mg, 1.0 mmol) in dry THF (15 cm^3). The reaction mixture was stirred for 8 h at −40 °C and the temperature was allowed to warm to RT over 12 h. A saturated solution of NH_4Cl (10 cm^3) was added and the organic phase was extracted into EtOAc (3 × 50 cm^3). The combined organic extracts were dried and evaporated and the product was purified over silica gel (hexane/EtOAc 6:1) to give compound **4** as a colourless solid (158 mg, 40%).

Mp: 173–176 °C (from $CHCl_3$); $[\alpha]_D^{20}$ + 18.0 (c 1.5, $CHCl_3$); ν_{max} (KBr plate)/cm^{-1} 3464 (br), 2932, 2855, 1603, 1508, 1226, 1162, 1075, 1016, 1005, 832; δ_H (300 MHz, $CDCl_3$) 7.23 (2 H, dd, *J* = 5.6 Hz, *J* = 8.8 Hz, Ar-*H*), 6.91 (2 H, dd, *J* = 8.8 Hz, *J* = 8.8 Hz, Ar-*H*), 3.94–3.99 (1 H, m, C^3*H*), 2.24 (1 H, ddd, *J* = 5.2 Hz, *J* = 9.7 Hz, *J* = 14.7 Hz, C$^{16}H_A$), 1.93–2.05 (1 H, m, C$^{16}H_B$), 0.72–1.77 (20 H, m), 0.95 (3 H, s, C$^{18}H_3$), 0.67 (3 H, s, C$^{19}H_3$); 0.20–0.39 (2 H, m); δ_C (75 MHz, $CDCl_3$) 162.1 (d, *J* = 245.2 Hz, *Ar*-F), 142.1 (d, *J* = 3.1 Hz, *Ar*), 129.3 (2 × C, d, *J* = 7.8 Hz, *Ar*), 114.3 (2 × C, d, *J* = 20.9 Hz, *Ar*), 86.1 (C^{17}), 66.8 (*C*H), 54.1 (*C*H), 49.5 (*C*H), 47.0 (C^{13}), 39.4 (*C*H), 39.1 (*C*H$_2$), 36.6 (*C*H), 36.4 (C^{10}), 36.1 (*C*H$_2$), 33.9 (*C*H$_2$), 32.4 (*C*H$_2$), 32.0 (*C*H$_2$), 29.3 (*C*H$_2$), 28.8 (*C*H$_2$), 24.6 (*C*H$_2$), 20.7 (*C*H$_2$), 15.2 (*C*H$_3$), 11.5 (*C*H$_3$); δ_F (282 MHz, $CDCl_3$) −117.0 (1 F, tt, *J* = 5.4 Hz, *J* = 8.6 Hz); *m*/*z* (+ES), found (M + Na$^+$): 409.2517, $C_{25}H_{35}O_2NaF$ requires 409.2519 (−0.4 ppm).



Scheme 5. Reagents and conditions: (a) Pd/C, H_2 (1 atm), EtOAc, 91–93%.

3.3. (3α,5α)-17-(p-Fluorophenyl)androst-16-en-3-ol (5)

p-Toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) was added at RT to a solution of (3α,5α,17β)-17-(*p*-fluorophenyl)androstane-3,17β-diol **4** (120 mg, 0.31 mmol) in dry DCM (20 cm^3). The reaction solution was heated under reflux for 4 h and stirred at RT for 2 h. The reaction solution was washed with a 10% solution of $NaHCO_3$ (10 cm^3) and the organic phase was extracted into diethyl ether (2 × 40 cm^3). The combined organic extracts were dried and the solvent was removed under reduced pressure. The residue was purified over silica gel (hexane/EtOAc 8:1) to give title compound **5** as a colourless solid (65 mg, 57%).

Mp: 182–187 °C (from $CHCl_3$); $[\alpha]_D^{18}$ + 18.0 (c 1.5, $CHCl_3$); ν_{max} (KBr plate)/cm^{-1} 3332 (br), 2929, 2858, 1601, 1505, 1442, 1230, 1218, 1034, 1005, 810; δ_H (300 MHz, $CDCl_3$) 7.28–7.33 (2 H, m, Ar-*H*), 6.94–7.00 (2 H, m, Ar-*H*), 5.83 (1 H, dd, *J* = 1.8 Hz, *J* = 3.2 Hz, $C^{16}H$), 4.03–4.07 (1 H, m, C^3H), 2.19 (1 H, ddd, *J* = 3.3 Hz, *J* = 6.2 Hz, *J* = 15.4 Hz, $C^{15}H_A$), 1.92–2.04 (2 H, m), 0.73–1.77 (18 H, m), 0.99 (3 H, s, $C^{18}H_3$), 0.83 (3 H, s, $C^{19}H_3$); δ_C (75 MHz, $CDCl_3$) 162.3 (d, *J* = 245.4 Hz, *Ar*), 154.3 (C^{17}), 133.9 (d, *J* = 3.2 Hz, *Ar*), 128.6 (2 × C, d, *J* = 7.7 Hz, *Ar*), 127.5 (C^{16}), 115.3 (2 × C, d, *J* = 21.1 Hz, *Ar*), 67.0 (*C*H), 58.0 (*C*H), 55.0 (*C*H), 47.8 (C^{13}), 39.7 (*C*H), 36.7 (C^{10}), 36.3 (CH_2), 35.9 (CH_2), 34.5 (*C*H), 32.4 (CH_2), 32.2 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 21.2 (CH_2), 17.1 (CH_3), 11.6 (CH_3); δ_F (282 MHz, $CDCl_3$) −116.7 (1 F, tt, *J* = 5.5 Hz, *J* = 8.7 Hz); *m*/*z* (+CI), found MH^+: 369.2585, $C_{25}H_{34}OF$ requires 369.2594 (−2.3 ppm).

3.4. (3α,5α,17β)-17-(m-Fluorophenyl)androstane-3,17-diol (6)

n-BuLi (2.0 cm^3, 2.5 M in hexane, 5.0 mmol) was added at −78 °C under N_2 to a solution of 3-fluoro-bromobenzene (0.55 cm^3, 5.0 mmol) in dry diethyl ether (5 cm^3). The mixture was stirred for 30 min at −78 °C and added dropwise *via* cannula over 10 min to a solution of androsterone (300 mg, 1.0 mmol) in dry THF (20 cm^3). The reaction mixture was stirred 3 h at −78 °C and the temperature was allowed to warm to RT over 15 h. A saturated solution of NH_4Cl (10 cm^3) was added and the organic phase was extracted into EtOAc (3 × 50 cm^3). The combined organic extracts were washed with brine and dried. After evaporation of the solvent, the product was purified over silica gel (hexane/EtOAc 6:1) to give compound **6** as a colourless solid (125 mg, 31%).

Mp: 182–188 °C (from hexane/EtOAc); $[\alpha]_D^{20}$ + 25.3 (c 0.4, $CHCl_3$); ν_{max} (KBr plate)/cm^{-1} 3422 (br), 2926, 2854, 1613, 1586, 1437, 1262, 1096, 1016, 804; δ_H (300 MHz, $CDCl_3$) 6.92–7.45 (4 H, m, Ar-*H*), 3.95–4.01 (1 H, m, C^3H), 2.33 (1 H, ddd, *J* = 5.3 Hz, *J* = 9.7 Hz, *J* = 14.4 Hz, $C^{16}H_A$), 2.08 (1 H, ddd, *J* = 4.4 Hz, *J* = 12.5 Hz, *J* = 14.4 Hz, $C^{16}H_B$), 0.53–1.87 (20 H, m), 1.03 (3 H, s, $C^{18}H_3$), 0.76 (3 H, s, $C^{19}H_3$), 0.29–0.49 (2 H, m); δ_C (75 MHz, $CDCl_3$) 162.6 (d, *J* = 244.2 Hz, *Ar*-F), 149.5 (d, *J* = 6.4 Hz, *Ar*), 128.9 (d, *J* = 8.1 Hz, *Ar*), 123.4 (d, *J* = 2.4 Hz, *Ar*), 115.0 (d, *J* = 22.1 Hz, *Ar*), 113.9 (d, *J* = 21.1 Hz, *Ar*), 86.3 (C^{17}), 66.8 (*C*H), 54.1 (*C*H), 49.5 (*C*H), 47.2 (C^{13}), 39.4 (*C*H), 39.1 (CH_2), 36.6 (*C*H), 36.4 (C^{10}), 36.2 (CH_2), 34.0 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 24.7 (CH_2), 20.7 (CH_2), 15.3 (CH_3), 11.6 (CH_3); δ_F (282 MHz, $CDCl_3$) −114.6 (1 F, ddd, *J* = 6.1 Hz, *J* = 8.4 Hz, *J* = 11.0 Hz); *m*/*z* (+ES), found ($M + Na^+$): 409.2512, $C_{25}H_{35}O_2NaF$ requires 409.2519 (−1.8 ppm).

3.5. 17α-(m-Fluorophenyl)-17β-methyl-5α-androsten-13-3α-ol (7)

p-Toluenesulfonic acid monohydrate (40 mg, 0.26 mmol) was added at RT to a solution of (3α,5α,17β)-17-(*m*-fluorophenyl)androstane-3,17-diol **6** (50 mg, 0.13 mmol) in dry DCM (10 cm^3). The mixture was heated under reflux for 5 h, cooled down to RT, 1 M $NaHCO_3$ (5 cm^3) was added and the solution was stirred for 15 min. The product was extracted into DCM (2 × 20 cm^3), the combined organic extracts were dried and the solvent was evaporated under reduced pressure. The product was purified over silica gel (hexane/EtOAc 10:1) to give title compound **7** as a colourless oil (25 mg, 52%).

δ_H (500 MHz, $CDCl_3$) 7.23 (1 H, ddd, *J* = 6.4 Hz, *J* = 8.0 Hz, *J* = 8.0 Hz, Ar-*H*), 7.03 (1 H, ddd, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 7.9 Hz, Ar-*H*), 6.95 (1 H, ddd, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 11.1 Hz, Ar-*H*), 6.84 (1 H, ddd, *J* = 2.5 Hz, *J* = 8.3 Hz, *J* = 8.4 Hz, Ar-*H*), 4.06–4.08 (1 H, m, C^3H), 2.32–2.40 (1 H, m, $C^{15}H_A$), 2.12–2.21 (2 H, m, $C^{15}H_B$ + C^8H), 1.80–2.02 (5 H, m), 1.04–1.77 (14 H, m), 1.40 (3 H, $C^{18}H_3$), 0.78 (3 H, $C^{19}H_3$); δ_C (75 MHz, $CDCl_3$) 163.0 (d, *J* = 244.2 Hz, *Ar*), 152.0 (d, *J* = 6.2 Hz, *Ar*), 139.9 (C^{14}), 139.6 (C^{13}), 129.3 (d, *J* = 8.2 Hz, *Ar*), 121.6 (d, *J* = 2.3 Hz, *Ar*), 113.0 (d, *J* = 21.4 Hz, *Ar*), 112.1 (d, *J* = 21.2 Hz, *Ar*), 66.6 (C^3), 53.1 (C^{17}), 51.8 (C^9), 42.2 (C^{16}), 39.1 (C^5), 36.9 (C^8), 36.1 (C^{10}), 35.7 (C^4), 31.9 (C^1), 31.5 (C^7), 30.5 (C^{15}), 29.0 (C^6 + C^2), 24.2 (C^{18}), 22.9 (C^{12}), 22.2 (C^{11}), 10.7 (C^{19}); δ_F (282 MHz, $CDCl_3$) −114.3 (1 F, ddd, *J* = 6.3 Hz, *J* = 8.5 Hz, *J* = 11.2 Hz); *m*/*z* (+CI), found MH^+: 369.2594, $C_{25}H_{34}OF$ requires 369.2594 (+0.2 ppm).

3.6. (3α,5α,17β)-17-(m-Fluorophenyl)androstane-3,17-diol, 3-acetate (9)

Ac_2O (0.2 cm^3) and 4-DMAP (8 mg) were added to a solution of (3α,5α,17β)-17-(*m*-fluorophenyl)androstane-3,17-diol **6** (62 mg, 0.16 mmol) in pyridine (0.5 cm^3). The mixture was stirred at RT for 15 min and poured into 10% $NaHCO_3$ (8 cm^3). After further stirring for 20 min, the product was extracted into EtOAc (3 × 20 cm^3). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified over silica gel (hexane/EtOAc 10:1) to give compound **9** as a colourless solid (55 mg, 80%).

Mp: 195–197 °C (from $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 6.92–7.31 (4 H, Ar-*H*), 4.93–4.98 (1 H, m, C^3H), 2.34 (1 H, ddd, *J* = 5.3 Hz, *J* = 9.7 Hz, *J* = 14.5 Hz, $C^{16}H_A$), 2.09 (1 H, ddd, *J* = 4.2 Hz, *J* = 12.4 Hz, *J* = 14.4 Hz, $C^{16}H_B$), 1.99 (3 H, s, CH_3CO_2), 0.57–1.94 (19 H, m), 1.04 (3 H, s, $C^{18}H_3$), 0.77 (3 H, s, $C^{19}H_3$), 0.31–0.51 (2 H, m); δ_C (75 MHz, $CDCl_3$) 171.1 (CO_2), 162.6 (d, *J* = 244.3 Hz, *Ar*-F), 149.5 (d, *J* = 6.3 Hz, *Ar*), 128.9 (d, *J* = 8.1 Hz, *Ar*), 123.4 (d, *J* = 2.4 Hz, *Ar*), 115.0 (d, *J* = 22.1 Hz, *Ar*), 113.9 (d, *J* = 21.0 Hz, *Ar*), 86.3 (C^{17}), 70.5 (*C*H), 54.0 (*C*H), 49.5 (CH_2), 47.3 (C^{13}), 40.3 (*C*H), 39.1 (CH_2), 36.6 (*C*H), 36.2 (C^{10}), 34.0 (CH_2), 33.2 (CH_2), 33.1 (CH_2), 31.9 (CH_2), 28.6 (CH_2), 26.4 (CH_2), 24.7 (CH_2), 21.9 (CH_3CO_2), 20.7 (CH_2), 15.3 (CH_3), 11.7 (CH_3); δ_F (282 MHz, $CDCl_3$) −114.6 (1 F, ddd, *J* = 6.1 Hz, *J* = 8.4 Hz, *J* = 11.1 Hz).

3.7. (3α,5α)-17-(m-Fluorophenyl)androst-16-en-3-ol acetate (10)

Et_3N (0.2 cm^3) and MsCl (60 μL, 0.77 mmol) were added at 0 °C to a solution of (3α,5α,17β)-17-(*m*-fluorophenyl)androstane-3,17-diol, 3-acetate **9** (50 mg, 0.12 mmol) in dry DCM (5 cm^3). The solution was stirred for 45 min at 0 °C and DCM was removed under reduced pressure. The crude product was purified over silica gel (hexane/EtOac 15:1) to give compound **10** as a colourless solid (32 mg, 67%).

Mp: 148–150 °C (from $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.20–7.28 (1 H, m, Ar-*H*), 7.12–7.16 (1 H, m, Ar-*H*), 7.03–7.09 (1 H, m, Ar-*H*), 6.87–6.94 (1 H, m, Ar-*H*), 5.94 (1 H, dd, *J* = 1.8 Hz, *J* = 3.2 Hz, $C^{16}H$), 5.00–5.04 (1 H, m, C^3H), 2.21 (1 H, ddd, *J* = 3.3 Hz, *J* = 6.3 Hz, *J* = 15.7 Hz, $C^{15}H_A$), 1.94–2.08 (2 H, m), 2.06 (3 H, s, CH_3CO_2), 0.78–1.78 (17 H, m), 1.01 (3 H, s, $C^{18}H_3$), 0.85 (3 H, s, $C^{19}H_3$); δ_C (75 MHz, $CDCl_3$) 171.2 (CH_3CO_2), 163.1 (d, *J* = 244.4 Hz, *Ar*-F), 154.2 (d, *J* = 1.9 Hz, C^{17}), 140.0 (d, *J* = 7.7 Hz, *Ar*), 129.8 (d, *J* = 8.4 Hz, *Ar*), 128.9 (C^{16}), 122.7 (d, *J* = 2.6 Hz, *Ar*), 113.8 (d, *J* = 21.5 Hz, *Ar*), 113.8 (d, *J* = 21.1 Hz, *Ar*), 70.5 (*C*H), 58.0 (*C*H), 54.9 (CH_2), 47.8 (C^{13}), 40.6

(*C*H), 36.4 (C^{10}), 35.8 (CH_2), 34.4 (*C*H), 33.3 (CH_2), 33.1 (CH_2), 32.2 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 26.5 (CH_2), 22.0 (CH_3CO_2), 21.2 (CH_2), 17.2 (CH_3), 11.7 (CH_3); δ_F (282 MHz, $CDCl_3$) −114.3 (1 F, ddd, J = 6.1 Hz, J = 8.6 Hz, J = 10.6 Hz); *m*/*z* (+ES), found ($M + Na^+$): 433.2516, $C_{27}H_{35}O_2FNa$ requires 433.2519 (−0.7 ppm).

3.8. (3α,5α)-17-(m-Fluorophenyl)androst-16-en-3-ol (8)

5 N NaOH (0.15 cm^3) was added at RT to a solution of (3α,5α)-17-(*m*-fluorophenyl)androst-16-en-3-ol acetate **10** (21 mg, 0.05 mmol) in MeOH (2.5 cm^3). The mixture was heated under reflux for 1 h and cooled to RT. Water (2 cm^3) was added and the product was extracted into DCM (3 × 10 cm^3). The combined organic extracts were dried and the solvent removed under reduced pressure. The product was purified over silica gel (hexane/EtOAc 9:1) to give title compound **8** as a colourless solid (17 mg, 90%).

Mp: 179–184 °C (from $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.20–7.27 (1 H, m, Ar-*H*), 7.12–7.15 (1 H, m, Ar-*H*), 7.03–7.08 (1 H, m, Ar-*H*), 6.87–6.94 (1 H, m, Ar-*H*), 5.93 (1 H, J = 1.8 Hz, J = 3.1 Hz, $C^{16}H$), 4.04–4.07 (1 H, m, C^3H), 2.21 (1 H, ddd, J = 3.3 Hz, J = 6.2 Hz, J = 15.6 Hz, $C^{15}H_A$), 1.94–2.01 (2 H, m), 0.75–1.78 (18 H, m), 1.01 (3 H, s, $C^{18}H_3$), 0.84 (3 H, s, $C^{19}H_3$); δ_C (75 MHz, $CDCl_3$) 163.1 (d, J = 244.5 Hz, *Ar*-F), 154.3 (d, J = 2.0 Hz, C^{17}), 140.0 (d, J = 7.8 Hz, *Ar*), 129.8 (d, J = 8.5 Hz, *Ar*), 128.9 (C^{16}), 122.7 (d, J = 2.6 Hz, *Ar*), 113.8 (d, J = 21.5 Hz, *Ar*), 113.7 (d, J = 21.1 Hz, *Ar*), 67.0 (*C*H), 58.0 (*C*H), 55.0 (*C*H), 47.8 (C^{13}), 39.7 (*C*H), 36.7 (C^{10}), 36.3 (CH_2), 35.8 (CH_2), 34.4 (*C*H), 32.4 (CH_2), 32.2 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 21.2 (CH_2), 17.2 (CH_3), 11.6 (CH_3); δ_F (282 MHz, $CDCl_3$) −114.3 (1 F, ddd, J = 6.2 Hz, J = 8.7 Hz, J = 10.7 Hz); *m*/*z* (+CI), found MH^+: 369.2599, $C_{25}H_{34}OF$ requires 369.2594 (+1.3 ppm).

3.9. (3α,5α,17β)-(17-p-Toluene)androstane-3,17-diol (16)

n-BuLi (2 cm^3, 2.5 M in hexane, 5.0 mmol) was added at RT under N_2 to a solution of *p*-bromotoluene (860 mg, 5.0 mmol) in dry diethyl ether (5 cm^3). The mixture was stirred for 2 h at RT and added dropwise *via* cannula to a solution of androsterone (262 mg, 0.9 mmol) in dry THF (10 cm^3). The reaction mixture was stirred for 15 h at RT and then a 10% solution of NH_4Cl (10 cm^3) was added. The reaction mixture was extracted into EtOAc (3 × 40 cm^3) and the combined extracts were washed with brine and dried. After evaporation of the solvent under reduced pressure, the product was purified over silica gel (hexane/EtOAc 7:1) to give compound **16** as a colourless solid (148 mg, 43%).

Mp: 173–174 °C (from $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.22 (2 H, d, J = 8.0 Hz, Ar-*H*), 7.11 (2 H, d, J = 8.0 Hz, Ar-*H*), 3.94–3.96 (1 H, m, C^3H), 2.29–2.35 (1 H, ddd, J = 5.2 Hz, J = 9.8 Hz, J = 14.4 Hz, $C^{16}H_A$), 2.33 (3 H, s, PhCH_3), 2.03–2.09 (1 H, m, $C^{16}H_B$), 0.82–1.92 (20 H, m), 1.02 (3 H, s, $C^{18}H_3$), 0.74 (3 H, s, $C^{19}H_3$), 0.34–0.44 (2 H, m); δ_C (75 MHz, $CDCl_3$) 143.6 (*Ar*), 136.6 (*Ar*), 128.3 (2 × C, *Ar*), 127.6 (2 × C, *Ar*), 86.2 (C^{17}), 66.8 (C^3), 54.0 (C^9), 49.5 (C^{14}), 47.0 (C^{13}), 39.4 (C^5), 39.0 (C^{16}), 36.6 (C^8), 36.4 (C^{10}), 36.2 (C^4), 34.0 (C^{12}), 32.4 (C^1), 32.1 (C^7), 29.3 (C^2), 28.9 (C^6), 24.8 (C^{15}), 21.4 (C^{24}), 20.7 (C^{11}), 15.3 (C^{18}), 11.6 (C^{19}); *m*/*z* (+ES), found ($M + Na^+$): 405.2766, $C_{26}H_{38}O_2Na$ requires 405.2770 (−0.8 ppm).

3.10. (3α,5α)-(17-p-Toluene)androst-16-en-3-ol (17)

p-Toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) was added at RT to a solution of (3α,5α,17β)-(17-*p*-toluene)androstane-3,17β-diol **16** (140 mg, 0.37 mmol) in dry DCM (20 cm^3) and the reaction mixture was stirred at RT for 2 days. A 10% solution of $NaHCO_3$ (5 cm^3) was then added, the organic phase was separated and the aqueous phase extracted into DCM (2 × 20 cm^3). The combined organic extracts were dried and the solvent was removed under reduced pressure. The residue was purified over silica gel (hexane/EtOAc 7:1) to give title compound **17** as a colourless solid (95 mg, 71%).

Mp: 182–185 °C (from $CHCl_3$); $[\alpha]_D^{18}$ + 25.1 (c 1.5, $CHCl_3$); (Found: C, 85.41; H, 10.38%, $C_{26}H_{36}O$ requires C, 85.66; H, 9.95%); ν_{max} (KBr plate)/cm^{-1} 3333 (br), 3048, 2924, 2846, 1508, 1443, 1368, 1357, 1001, 794; δ_H (300 MHz, $CDCl_3$) 7.26 (2 H, d, J = 8.0 Hz), 7.10 (2 H, d, J = 8.0 Hz), 5.84 (1 H, dd, J = 1.8 Hz, J = 3.2 Hz, $C^{16}H$), 4.03–4.07 (1 H, m, C^3H), 2.33 (3 H, s, PhCH_3), 2.18 (1 H, ddd, J = 3.3 Hz, J = 6.3 Hz, J = 15.4 Hz, $C^{15}H_A$), 1.92–2.07 (2 H, m), 0.77–1.77 (18 H, m), 1.00 (3 H, s, $C^{18}H_3$), 0.83 (3 H, s, $C^{19}H_3$); δ_C (75 MHz, $CDCl_3$) 154.7 (C^{17}), 136.3 (*Ar*), 134.5 (*Ar*), 128.9 (2 × C, *Ar*), 126.6 (2 × C, *Ar*), 126.4 (C^{16}), 66.6 (C^3), 57.7 (C^{14}), 54.7 (C^9), 47.4 (C^{13}), 39.4 (C^5), 36.3 (C^{10}), 35.9 (C^4), 35.6 (C^{12}), 34.1 (C^8), 32.1 (C^1), 31.9 (C^7), 31.5 (C^{15}), 29.1 (C^2), 28.6 (C^6), 21.1 (PhCH_3), 20.8 (C^{11}), 16.8 (C^{18}), 11.2 (C^{19}); *m*/*z* (+CI), found MH^+: 365.2856, $C_{26}H_{37}O$ requires 365.2844 (3.0 ppm).

3.11. (3α,5α,17β)-17-(p-Methoxyphenyl)androstane-3,17-diol (18)

n-BuLi (2 cm^3, 2.5 M in hexane, 5.0 mmol) was added at RT under N_2 to a solution of 4-bromoanisole (0.63 cm^3, 5.0 mmol) in dry diethyl ether (5 cm^3). The mixture was stirred for 2 h at RT and added dropwise *via* cannula to a solution of androsterone (300 mg, 1.0 mmol) in dry THF (10 cm^3). The reaction mixture was stirred at RT for 15 h. A 10% solution of NH_4Cl (10 cm^3) was added and the organic phase was extracted into Et_2O (3 × 40 cm^3). The combined organic extracts were dried and after evaporation of the solvent under reduced pressure, the product was purified over silica gel (hexane/EtOAc 5:1) to give compound **18** as a white foam (122 mg, 30%). *Note*: **18** was not stable in solution and rapidly dehydrated to **19**.

δ_H (300 MHz, $CDCl_3$) 7.27 (2 H, J = 9.0 Hz, Ar-*H*), 6.86 (2 H, d, J = 9.0 Hz, Ar-*H*), 3.97–4.01 (1 H, m, C^3H), 3.82 (3 H, s, OCH_3), 2.33 (1 H, ddd, J = 5.2 Hz, J = 9.8 Hz, J = 14.6 Hz, $C^{16}H_A$), 2.02–2.13 (1 H, m, $C^{16}H_B$), 0.81–1.83 (20 H, m), 1.03 (3 H, s, $C^{18}H_3$), 0.76 (3 H, s, $C^{19}H_3$); 0.34–0.52 (2 H, m); δ_C (75 MHz, $CDCl_3$) 158.7 (*Ar*), 138.5 (*Ar*), 128.8 (2 × C, *Ar*), 112.9 (2 × C, *Ar*), 86.1 (C^{17}), 66.9 (*C*H), 55.6 (OCH_3), 54.1 (*C*H), 49.5 (CH_2), 47.1 (C^{13}), 39.5 (*C*H), 39.1 (CH_2), 36.6 (*C*H), 36.5 (C^{10}), 36.2 (CH_2), 34.0 (CH_2), 32.4 (CH_2), 32.1 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 24.7 (CH_2), 20.7 (CH_2), 15.3 (CH_3), 11.6 (CH_3); *m*/*z* (+ES), found ($M + Na^+$): 421.2730, $C_{26}H_{38}O_3Na$ requires 421.2719 (+2.7 ppm).

3.12. (3α,5α)-17-(p-Methoxyphenyl)androst-16-en-3-ol (19)

p-Toluenesulfonic acid monohydrate (2 mg) was added at RT to a solution of (3α,5α,17β)-17-(*p*-methoxyphenyl)androstane-3,17-diol **18** (55 mg, 0.14 mmol) in dry DCM (5 cm^3). The mixture turned pink very rapidly. After 8 h the colour had disappeared and DCM was removed under reduced pressure. The residue was purified over silica gel (petroleum ether/diethyl ether 3:1) to give title compound **19** as a colourless solid (47 mg, 90%).

Mp: 171–176 °C (from $CHCl_3$); $[\alpha]_D^{20}$ + 27.4 (c 1.5, $CHCl_3$); (Found: C, 81.50; H, 9.85%, $C_{26}H_{36}O_2$ requires C, 82.06; H, 9.53%); ν_{max} (KBr plate)/cm^{-1} 3322 (br), 2924, 2846, 1600, 1508, 1443, 1362, 1253, 1242, 1175, 1108, 1035; δ_H (300 MHz, $CDCl_3$) 7.30 (2 H, d, J = 8.8 Hz, Ar-*H*), 6.83 (2 H, d, J = 8.8 Hz, Ar-*H*), 5.79 (1 H, dd, J = 1.7 Hz, J = 3.1 Hz, $C^{16}H$), 4.02–4.06 (1 H, m, C^3H), 3.80 (3 H, s, OCH_3), 2.18 (1 H, ddd, J = 3.2 Hz, J = 6.2 Hz, J = 15.3 Hz, $C^{15}H_A$), 1.91–2.06 (2 H, m), 0.77–1.76 (18 H, m), 0.99 (3 H, s, $C^{18}H_3$), 0.83 (3 H, s, $C^{19}H_3$); δ_C (75 MHz, $CDCl_3$) 158.9 (*Ar*), 154.7 (C^{17}), 130.5 (*Ar*), 128.2 (2 × C, *Ar*), 126.0 (C^{16}), 113.9 (2 × C, *Ar*), 67.0 (*C*H), 58.0 (*C*H),

55.7 (OCH_3), 55.1 (*C*H), 47.8 (C^{13}), 39.8 (*C*H), 36.7 (C^{10}), 36.3 (CH_2), 36.0 (CH_2), 34.5 (*C*H), 32.5 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 21.2 (CH_2), 17.1 (CH_3), 11.6 (CH_3); *m*/*z* (+CI), found MH^+: 381.2796, $C_{26}H_{37}O_2$ requires 381.2794 (+0.6 ppm).

3.13. (3α,5α)-(17β-p-Toluene)androstan-3-ol (21)

Pd/C 5% (5 mg) was added to a solution of (3α,5α)-(17-*p*-toluene)androst-16-en-3-ol **17** (12 mg, 0.03 mmol) in EtOAc (5 cm^3). The mixture was stirred at RT under a positive atmosphere of H_2. After 12 h, the reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. The product was purified over silica gel (hexane/EtOAc 6:1) to give title compound **21** as a colourless solid (11 mg, 91%).

Mp: 230–234 °C (from hexane/EtOAc); $[\alpha]_D^{20} + 7.4$ (c 0.65, $CHCl_3$); (Found: C, 84.97; H, 10.82%, $C_{26}H_{38}O$ requires C, 85.19; H, 10.45%); ν_{max} (KBr plate)/cm^{-1} 3289 (br), 2931, 2869, 2842, 1514, 1446, 1262, 1098, 1035, 1002, 807; δ_H (300 MHz, $CDCl_3$) 7.00–7.05 (4 H, dd, Ar-*H*), 4.03–4.06 (1 H, m, C^3H), 2.63 (1 H, t, *J* = 9.9 Hz, $C^{17}H$), 2.32 (3 H, s, PhCH_3), 2.01–2.09 (1 H, m, $C^{16}H_A$), 1.88–1.96 (1 H, m, $C^{16}H_B$), 0.74–1.80 (21 H, m), 0.77 (3 H, s, $C^{19}H_3$), 0.45 (3 H, s, $C^{18}H_3$); δ_C (75 MHz, $CDCl_3$) 138.6 (*Ar*), 135.7 (*Ar*), 129.0 (2 × C, *Ar*), 128.8 (2 × C, *Ar*), 67.0 (*C*H), 57.1 (C^{17}), 56.7 (*C*H), 55.0 (*C*H), 44.6 (C^{13}), 39.7 (*C*H), 38.2 (CH_2), 36.6 (C^{10}), 36.4 (*C*H), 36.3 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 26.6 (CH_2), 24.8 (CH_2), 21.4 ($PhCH_3$), 20.9 (CH_2), 13.2 (CH_3), 11.7 (CH_3); *m*/*z* (+CI), found MH^+: 367.2992, $C_{26}H_{39}O$ requires 367.3001 (−2.4 ppm).

3.14. (3α,5α)-(17β-p-Methoxyphenyl)androstan-3-ol (22)

Pd/C 5% (5 mg) was added to a solution of (3α,5α)-(17-*p*-methoxyphenyl)androst-16-en-3-ol **19** (50 mg, 0.13 mmol) in EtOAc (10 cm^3). The mixture was stirred at RT under a positive atmosphere of H_2. After 12 h, the reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. The product was purified over silica gel (petroleum ether/diethyl ether 2:1) to give title compound **22** as a colourless solid (47 mg, 93%).

Mp: 224–231 °C (from $CHCl_3$); $[\alpha]_D^{20} + 8.0$ (c 0.8, $CHCl_3$); (Found: C, 81.76; H, 10.29%, $C_{26}H_{38}O_2$ requires C, 81.63; H, 10.01%); ν_{max} (KBr plate)/cm^{-1} 3522 (br), 3457 (br), 2930, 2914, 1609, 1512, 1463, 1249, 1238, 1028; δ_H (300 MHz, $CDCl_3$) 7.12 (2 H, d, *J* = 8.6 Hz, Ar-*H*), 6.82 (2 H, d, *J* = 8.6 Hz, Ar-*H*), 4.02–4.06 (1 H, m, C^3H), 3.79 (3 H, s, OCH_3), 2.61 (1 H, t, *J* = 9.8 Hz, $C^{17}H$), 1.87–2.08 (2 H, m), 0.80–1.81 (21 H, m), 0.77 (3 H, s, $C^{19}H_3$), 0.44 (3 H, s, $C^{18}H_3$); δ_C (75 MHz, $CDCl_3$) 158.2 (*Ar*), 133.7 (*Ar*), 129.9 (2 × C, *Ar*), 113.4 (2 × C, *Ar*), 67.0 (C^3), 56.6 (C^{14} + C^{17}), 55.6 (OCH_3), 55.0 (C^9), 44.5 (C^{13}), 39.7 (C^5), 38.2 (C^{12}), 36.6 (C^{10}), 36.4 (C^8), 36.3 (C^4), 32.6 (C^1), 32.5 (C^7), 29.4 (C^2), 29.0 (C^6), 26.8 (C^{16}), 24.8 (C^{15}), 20.9 (C^{11}), 13.2 (C^{18}), 11.7 (C^{19}); *m*/*z* (+CI), found MH^+: 383.2952, $C_{26}H_{39}O_2$ requires 383.2950 (+0.5 ppm).

Acknowledgements

We thank the University of St. Andrews for an Interdisciplinary Studentship (GD).

References

[1] H. Selye, Proc. Soc. Exp. Biol. Med. 46 (1941) 116–121.
[2] N.L. Harrison, M.A. Simmonds, Brain Res. 323 (1984) 287–292.
[3] M.D. Majewska, N.L. Harrison, R.D. Schwartz, J.L. Barker, S.M. Paul, Science 232 (1986) 1004–1007.
[4] D. Bitran, R.J. Hilvers, C.K. Kellogg, Brain Res. 561 (1991) 157–161.
[5] A.M. Hosie, M.E. Wilkins, H.M.A. da Silva, T.G. Smart, Nature 444 (2006) 486–489.
[6] S. Mennerick, Y. He, X. Jiang, B.D. Manion, M. Wang, A. Shute, A. Benz, A.S. Evers, D.F. Covey, C.F. Zorumski, Mol. Pharmacol. 65 (2004) 1191–1197.
[7] P. Tapolcsanyi, J. Welfling, E. Mernyak, G. Schneider, Monatsh. Chem. 135 (2004) 1129–1136.
[8] P. Tapolcsanyi, J. Wolfling, G. Schneider, Steroids 66 (2001) 623–635.
[9] P. Bydal, K.-M. Sam, D. Poirier, Steroids 61 (1996) 349–353.
[10] V. Kumar, C. Rodger, M.R. Bell, J. Org. Chem. 60 (1995) 4591–4594.
[11] D.G. Loughhead, J. Org. Chem. 50 (1985) 3931–3934.
[12] G. Ortar, I. Torrini, Tetrahedron 33 (1977) 859–863.
[13] M. Schlosser, Angew. Chem. Int. Ed. 44 (2005) 376–393.
[14] M. Schlosser, C. Heiss, Eur. J. Org. Chem. (2003) 4618–4624.
[15] W.F. Bailey, J.J. Patricia, J. Organomet. Chem. 352 (1988) 1–46.
[16] H. Gilman, R.D. Gorsich, J. Am. Chem. Soc. 78 (1956) 2217–2222.
[17] M. Sjostrom, S. Wold, Chem. Scr. 9 (1976) 200–210.
[18] R. Yamdagni, P. Kebarle, J. Am. Chem. Soc. 98 (1976) 1320–1324.
[19] T.X. Carroll, T.D. Thomas, H. Bergersen, K.J. Borve, L.J. Sthre, J. Org. Chem. 71 (2006) 1961–1968.
[20] Z.B. Maksic, B. Kovacevic, D. Kovacek, J. Phys. Chem. A 101 (1997) 7446–7453.
[21] S.P. Kelley, J.K. Alan, T.K. O'Buckley, S. Mennerick, K. Krishnan, D.F. Covey, A. Leslie Morrow, Eur. J. Pharmacol. 572 (2007) 94–101.