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Equine Metabolites of Norethandrolone: Synthesis of a Series of 19-Nor-17α-pregnanediols and 19-Nor-17α-pregnanetriols

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A range of 19-nor-17α-pregnanediols and 19-nor-17α-pregnanetriols have been synthesized and used to confirm the structures of major equine urinary metabolites of the synthetic anabolic steroid norethandrolone (1). 19-Nor-5α,17α-pregnane-3α,17β-diol (2), 19-nor-5α,17α-pregnane-3β,17β-diol (4), 19-nor-5β,17α-pregnane-3α,17β-diol (6), and 19-nor-5β,17α-pregnane-3β,17β-diol (7) were prepared by stereoselective reduction of the 3-ene-4-one of norethandrolone. The 19-nor-5α,17α-pregnane-3β,16α,17β-triol (8) and 19-nor-5α,17α-pregnane-3β,16β,17β-triol (9) were prepared from 19-nortestosterone (11) by multistep processes in which the critical step involved Grignard additions to 16-acetoxy-17-ones. The triols (20*R*)-19-nor-5α,17α-pregnane-3β,17β,20-triol (22) and (20*S*)-19-nor-5α,17α-pregnane-3β,17β,20-triol (23) were prepared from norethindrone (24) by initial selective A-ring reduction, then subsequent modification of the 17-ethynyl group. By comparison of these compounds with post-administration equine urine samples it was possible to establish A-ring reduction with 3β,5α stereochemistry as well as non-stereospecific 16-hydroxylation and 20-hydroxylation as significant metabolic pathways affecting norethandrolone in the horse.

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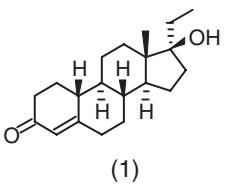
Introduction

Anabolic steroids are classed as prohibited substances in Australian horse racing, and an understanding of the metabolic processes affecting them in the horse, as well as the production of appropriate reference materials for drug testing procedures, are of considerable importance to regulatory authorities. To this end, a recent study of the equine metabolism of the synthetic anabolic steroid norethandrolone (1) (Diagram 1) revealed the presence of a large number of reduced and/or hydroxylated metabolites.[1] The most abundant of these comprised a 19-nor-17α-pregnane-3,17-diol, a pair of 19-nor-17α-pregnane-3,16,17-triols, and a pair of compounds exhibiting mass spectroscopic characteristics consistent with a 19-nor-17α-pregnane-3,17,20- or -3,17,21-triol. The absolute stereochemistry and, in the latter case, the exact regiochemistry of the metabolites were not discernible by mass spectroscopic analysis. Hence the preparation of key compounds for comparative analysis was desirable.



(1)

Diagram 1.

The simplest of the aforementioned metabolites is the 19-nor-17α-pregnane-3,17-diol. Formed by complete reduction of the α,β-unsaturated ketone function, this compound possesses two new stereocentres at C3 and C5 giving rise to four possibilities for its A-ring stereochemistry. Previous studies of anabolic steroid metabolism in the horse have reported 3β,5α as the major stereochemistry arising from this reduction,[2] although the number of steroids studied is limited and other stereochemistries have also been reported. The only way to confirm which was present in this case was to synthesize all four candidates and make an assignment based on gas chromatographic retention times. A similar approach was used by Brooks et al.[3] in determining the stereochemistry of the 19-nor-17α-pregnane-3,17-diols observed as metabolites of (1) in humans.

The 19-nor-17α-pregnane-3,16,17-triols are more complex, with a third unknown stereocentre at C16 giving rise to eight possible steroisomers. Metabolic 16-hydroxylation has been reported in the horse for a number of anabolic steroids,[4,2b,2d] although the precise stereochemistry of the process has never been rigorously investigated. The inherent inefficiency involved in the production of large numbers of surplus isomers mitigated against an exhaustive examination as proposed for the 3,17-diol metabolite. Instead, it was considered reasonable to assume that the A-ring stereochemistry of the major 3,16,17-triol metabolites would match that observed for the 3,17-diol. Thus the number of target

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compounds for synthesis could at least initially be reduced from eight to two.

The remaining compounds of interest were the sidechain-hydroxylated triols. Metabolic 21-hydroxylation of (1) has previously been reported in humans and marmoset monkeys,[5] although comparison of mass spectroscopic data from the equine compounds with that published for the primates and the subsequent synthesis of some 19-nor-17α-pregnane-3,17,21-triols[6] suggested that this was not the case in the horse. It was thus decided to pursue the synthesis of some 19-nor-17α-pregnane-3,17,20-triols. As with the 3,16,17-triols, the A-ring stereochemistry previously established for the 3,17-diol metabolite was utilized to reduce the number of target compounds for initial investigation.

The first aim of the present work was to establish unequivocally the A-ring stereochemistry of the 19-nor-17α-pregnane-3,17-diol observed as a metabolite of (1) in the horse by the synthesis of all four possible C3/C5 stereoisomers. Secondly, it was planned to incorporate the information so obtained into the synthesis of two proposed 19-nor-17α-pregnane-3,16,17-triol and two proposed 19-nor-17α-pregnane-3,17,20-triol metabolites. In this manner it was hoped that valuable information could be obtained as to the metabolic disposition of (1) and related anabolic steroids in the horse.

Results and Discussion

19-Nor-17α-pregnane-3,17-diols

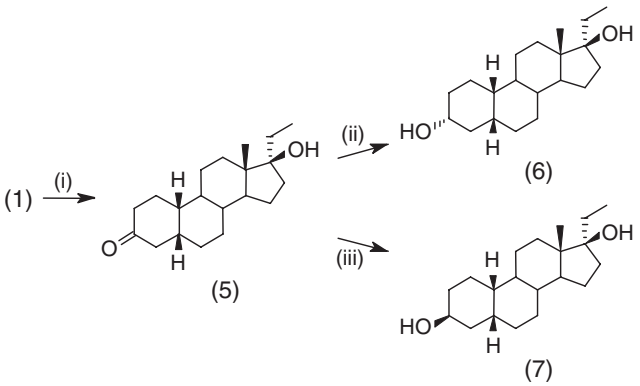
The four C3/C5 stereoisomers of 19-nor-17α-pregnane-3,17-diol were synthesized from (1) by sequential stereoselective reductions. The first to be prepared were the 5α-isomers (Scheme 1). A lithium–ammonia reduction carried out with a methanol quench according to the procedure of Bowers et al.[7] led to complete reduction of the α,β-unsaturated ketone to give 19-nor-5α,17α-pregnane-3β,17β-diol (2) as the sole product. Oxidation of (2) with chromium (VI) oxide then gave the 3-ketone (3), which was reduced with potassium tri(*s*-butyl)borohydride to give 19-nor-5α,17α-pregnane-3α,17β-diol (4) and its 3-epimer (2) in a 7.6 : 1 ratio.

To prepare the 5β-isomers, norethandrolone (1) was reduced (Pd/C) in the presence of aqueous potassium hydroxide as described by Gabbard and Segaloff[8] and produced the 3-ketone (5) as well as its 5-epimer (3) in 16.2 : 1 ratio (Scheme 2). Reduction of (5) with lithium aluminium hydride gave 19-nor-5β,17α-pregnane-3α,17β-diol (6) and its 3-epimer (7) in 9.9 : 1 ratio, while reduction with potassium tri(*s*-butyl)borohydride gave 19-nor-5β,17α-pregnane-3β,17β-diol (7) and its 3-epimer (6) in 20.8 : 1 ratio.

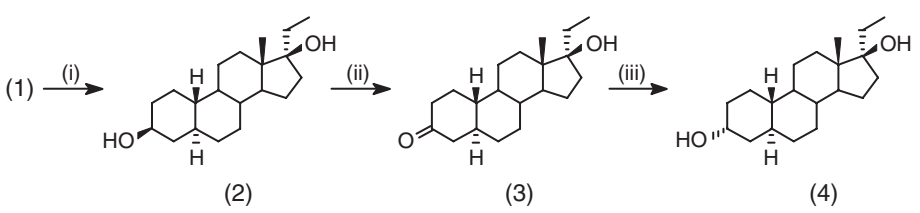
Once the 3,17-diols had been synthesized, they were analysed by gas chromatography–mass spectrometry as their bis(trimethylsilyl ether) derivatives. All four showed identical mass spectra to the 3,17-diol observed in a post-administration urine sample, but only one gave a retention time match. This was the 3β,5α-isomer (2). The remaining isomers (4), (6), and (7), were all clearly resolved from the urinary 3,17-diol under the conditions used (Table 1). Hence the metabolic reduction of (1) in the horse in the absence of other phase I metabolism was shown to proceed with 3β,5α stereochemistry.

19-Nor-17α-pregnane-3,16,17-triols

Given the 3β,5α stereochemistry established for the metabolic reduction of (1) without additional hydroxylation, it was decided to pursue the synthesis of the 16-hydroxylated compounds 19-nor-5α,17α-pregnane-3β,16α,17β-triol (8) and 19-nor-5α,17α-pregnane-3β,16β,17β-triol (9). Procedures for the addition of 16α- and 16β-hydroxy functions to 17-ketosteroids are well established, and proceed in each case via the enol acetate. One protocol, developed by Leeds et al.[9] involves treatment of the enol acetate with a peracid to give an epoxide, which is then hydrolyzed under acidic conditions and acetylated to give the 16α-acetoxy-17-ketone. Another protocol, developed by Johnson et al.[10] uses lead (IV) acetate in acetic acid to form the 16β-acetoxy-17-ketone directly. Treatment of these acetoxyketones with Grignard



Scheme 2. Reagents and conditions: (i) Pd/C/H_2/KOH, 3 atm, 2 h, room temperature; (ii) $LiAlH_4$, 1 h, room temperature; (iii) $K(Bu^s)_3BH$, THF, 1 h, room temperature.



Scheme 1. Reagents and conditions: (i) Li/NH_3; (ii) CrO_3, HOAc, 30 min, room temperature; (iii) $K(Bu^s)_3BH$, THF, 1 h, room temperature.

reagents should then furnish the required tertiary centre at C17.

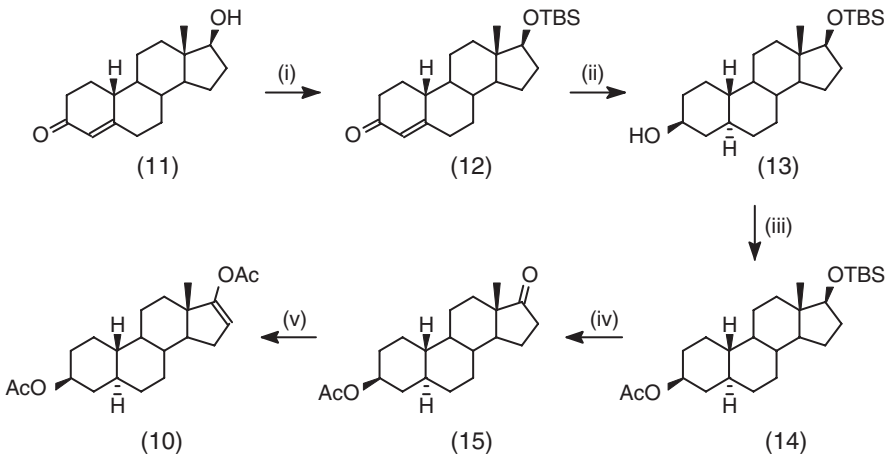
The first objective in the present syntheses was the formation of 5α-estr-16-ene-3β,17-diyl diacetate (10). This was prepared in five steps (Scheme 3) from 19-nortestosterone (11), which was chosen as the most suitable starting material on the grounds of availability and cost. The first step of the synthesis was the protection of the 17β-hydroxyl as the *t*-butyldimethylsilyl ether (12).[11] The α,β-unsaturated ketone was then reduced with lithium–ammonia as described previously to give the mono-protected 3,17-diol (13) with the required A-ring stereochemistry. Acetylation of (13) afforded the monoacetate (14), after which the silyl protecting group was oxidatively cleaved by treatment with potassium fluoride and Jones reagent[12] to give 19-norepiandrosterone acetate (15) in 51% overall yield. Treatment of (15) with isopropenyl acetate under acidic conditions then gave the required enol diacetate (10).

The synthesis now diverged with the insertion of the 16-hydroxy functions. To prepare the 16α-epimer (Scheme 4), the enol diacetate (10) was treated with 3-chloroperbenzoic acid and gave an unstable epoxide, which was immediately hydrolyzed with ice-cold sulfuric acid in methanol as described by Nambara et al.[13] This minor variation on Leeds' procedure[9] was found to open the epoxide rapidly to give the 16α-hydroxy-17-ketone (16) as virtually the sole product. Longer treatment with sulfuric acid lead to partial cleavage of the 3β-acetate, while treatment at room temperature was found to give a mixture of 16α-hydroxy and 16α-acetoxy products, the latter deriving from an acid catalyzed rearrangement.

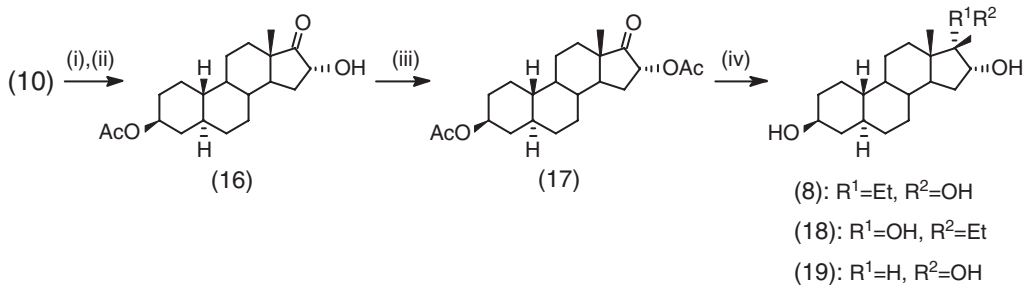
Table 1. Analytical data for synthesized steroids[A]

Steroid	Relative retention time[B]	Mass spectrum[C]
3,17-diols:		
(2)	1.017	421 (16), 241 (9), 157 (100), 144 (52)
(4)	0.975	421 (15), 241 (9), 157 (100), 144 (50)
(6)	0.997	421 (16), 241 (9), 157 (100), 144 (51)
(7)	0.996	421 (16), 241 (10), 157 (100), 144 (52)
3,16,17-triols:		
(8)	1.084	538 (2), 245 (10), 232 (100)
(9)	1.122	538 (2), 245 (11), 232 (100)
(18)	1.065	538 (1), 245 (13), 232 (100)
3,17,20-triols:		
(22)	1.089	538 (5), 421 (63), 331 (13), 241 (100)
(23)	1.058	538 (5), 421 (63), 331 (13), 241 (100)

[A] Per(trimethylsilyl) ether derivatives.
[B] Relative to the bis(trimethylsilyl) ether derivative of 17α-methyl-5α-androstane-3β,17β-diol.
[C] Relative intensities in parentheses.



Scheme 3. Reagents and conditions: (i) Bu^tMe_2SiCl/imidazole, DMF, 12 h, room temperature; (ii) Li/NH_3; (iii) Ac_2O/pyridine, 18 h, room temperature; (iv) CrO_3/KF, acetone, 1 h, 0°C; (v) isopropenyl acetate/H_2SO_4, 4 h, reflux.



Scheme 4. Reagents and conditions: (i) 3-$ClPhCO_3H$, 18 h, room temperature; (ii) 0.5 M H_2SO_4/MeOH, 1 h, 0°C; (iii) Ac_2O/pyridine, 18 h, room temperature; (iv) EtMgI, benzene, 18 h, room temperature.

Table 2. ^{1}H NMR data for 17-noralkyl-16,17-dihydroxysteroids

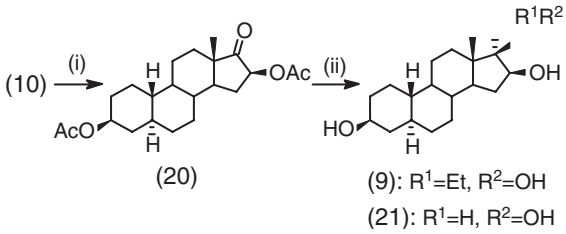
Steroid[A]	H16[B]	H17[B]	H18[B]
5α-androstane-16α,17α-diol	4.42, m	3.62, d (*J* 5)	0.69, s
5α-androstane-16α,17β-diol	4.16, unclear	3.53, d (*J* 6)	0.75, s
(19)	4.03, ddd (*J* 2, 6, 9)	3.42, d (*J* 6)	0.79, s
5α-androstane-16β,17α-diol	4.11, unclear	3.60, s	0.90, s
5α-androstane-16β,17β-diol	4.15, ddd (*J* 5, 8, 8)	3.37, d (*J* 8)	0.79, s
(22)	4.11, ddd (*J* 5, 8, 8)	3.33, d (*J* 8)	0.85, s

[A] 5α-androstane-16,17-diol data from Combe et al.[14]
[B] s = singlet, d = doublet, m = multiplet.

Acetylation of (16) gave the diacetate (17), which was then treated with ethylmagnesium iodide to provide a mixture of three products. These were identified as the required 17α-alkyl addition product (8), its 17-epimer (18) and a 17-noralkyl reduction product (19). The two alkylation products arise from the competing directing powers of the 18β-methyl and 16α-acetoxy groups and were differentiated by two-dimensional nuclear Overhauser enhancement spectroscopy (2D-NOESY) experiments, with (18) exhibiting a significantly stronger correlation between the protons at C18 and C20 than (8). The stereochemistry of the reduction product was also assigned on the basis of ^{1}H NMR data. 2D-NOESY experiments showed a minor correlation between the protons at C18 and C16, but negligible correlation between those at C18 and C17, and suggested an α orientation for the proton at C17. In addition, when compared with data obtained by Combe et al.[14] in a study of the ^{1}H NMR characteristics of 5α-androstane-16,17-diols, the data obtained for (19) here gave a significantly better match for 5α-androstane-16α,17β-diol than for 5α-androstane-16α,17α-diol (Table 2). On the basis of this evidence the 17-hydroxyl of (19) was assigned a β orientation.

The formation of a reduction product during the Grignard reaction must be attributed to the extremely hindered nature of the ketone, and while a variety of remedies were tried to minimize the effect, little improvement could be achieved. Best results were obtained by substitution of benzene for ether as primary solvent[15] and by reaction at ambient temperature rather than at reflux.[16] Under these conditions the 17α-alkyl, 17β-alkyl, and 17-noralkyl products were formed in roughly equal amounts.

The preparation of the 16β-epimer started with treatment of the enol acetate (10) with lead(IV) acetate as described by Johnson,[10] and this provided the 16β-acetoxy-17-ketone (20) (Scheme 5). Reaction of this ketone with ethylmagnesium iodide gave a mixture of two products. This time the 18β-methyl and 16β-acetoxy groups were directing in concert, so only the 17α-alkyl addition product (9) and 17-noralkyl reduction product (21) were produced. The stereochemistry of the addition product was assigned based on prediction (steric grounds) and precedent set by analogous Grignard reactions using methylmagnesium halides.[18] The stereochemistry of the reduction product was assigned based on



Scheme 5. Reagents and conditions: (i) $Pb(OAc)_4$, HOAc, Ac_2O, 18 h, room temperature; (ii) EtMgI, benzene, 18 h, room temperature.

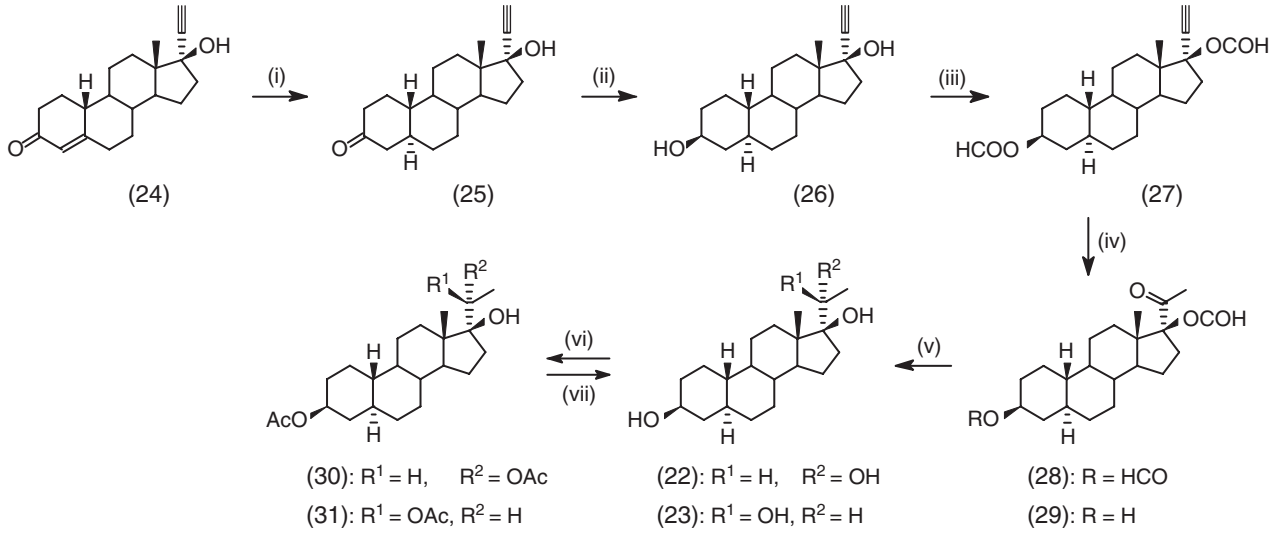
prediction and comparison with Combe's data[14] (Table 2). In each case the 17-hydroxyl was assigned a β orientation, and under the conditions described previously the ratio of addition to reduction products was 1.8 : 1.

Following this, the three synthesized 3,16,17-triols were analyzed by gas chromatography–mass spectrometry as their tris(trimethylsilyl ether) derivatives and compared with post-administration urine samples. The derivatives of compounds (8) and (9) were found to match the two most intense urinary 16-hydroxylated metabolites with regard to both mass spectra and retention times, the elution order being (8) followed by (9) (Table 1). From this it may be inferred that the 3β,5α A-ring configuration observed for the 19-nor-17α-pregnane-3,17-diol metabolite in the horse extends to the reduced 16-hydroxylated metabolites, and also that the equine metabolic 16-hydroxylation of (1) gives rise to both α and β configurations. Interestingly the trimethylsilylated derivative of (18), the 17-epimer of (8), was also found to give a retention time match to a minor urinary 16-hydroxylated metabolite which, due to its weak signal to noise ratio, had not previously had an absolute structure assigned. Unfortunately an unequivocal mass spectroscopic match was not possible as the spectra of these compounds are dominated by intense D-ring fragments with little or no characteristic fine structure. However the presence of 17-epimerized 17α-alkyl anabolic steroid metabolites is not without precedent.

17-Epimers are generally believed to derive from the spontaneous hydrolysis of 17-sulfate conjugates in the urine by a tertiary carbonium ion intermediate.[18] In the present case it is also conceivable that the inversion could occur in a similar manner during the deconjugation step of the analytical process. Hence the 17-epimers would be artefacts rather than true metabolites, but given that their formation in urine can be rapid, they are important nonetheless. Phase II metabolic studies of the metabolite corresponding to (8) did reveal the presence of sulfate conjugation, and so this proposed mechanism for 17-epimerization is certainly plausible here.

19-Nor-17α-pregnane-3,17,20-triols

Assuming the 3β,5α-configuration for the A-ring, the target 20-hydroxy metabolites selected were (20*R*)-19-nor-5α, 17α-pregnane-3β,17β,20-triol (22) and (20*S*)-19-nor-5α, 17α-pregnane-3β,17β,20-triol (23). The preparation of 17α-pregnane-17,20-diol analogues has not been extensively researched, although an obvious approach is by the corresponding 20-ketone. Salamon and Reichstein[19] developed a general entry to these compounds based on the treatment



Scheme 6. Reagents and conditions: (i) Li/NH_3; (ii) $NaBH_4$; 1 h, room temperature; (iii) *p*-toluenesulfonic acid, HCOOH, 2 d, 5°C; (iv) *N*-bromoacetamide, NaOAc, HOAc, 45 min, room temperature, and then Zn powder, 20 min, reflux; (v) $NaBH_4$, MeOH, 1 h, room temperature; (vi) Ac_2O, pyridine, 18 h, room temperature; (vii) KOH, MeOH, 2 h, reflux.

of 17β-acetoxy-17α-pregn-20-ynes with hypobromous acid followed by zinc debromination. Schor et al.[20] later refined the procedure by substituting a formate protecting group for the acetate, which they found unduly difficult to remove in the presence of the 20-ketone without inducing an irreversible D-ring rearrangement. The latter variation was also used here in the interests of retaining flexibility with regard to the final reduction step.

Following the above approach, the synthetic progestogen norethindrone (24) was chosen as a readily available and relatively inexpensive starting material. Reduction of the A-ring of (24) to give the required 3β,5α stereochemistry was performed in two stages (anhydrous lithium–ammonia reduction with an ammonium chloride and then acid quench[7]) to give the saturated 3-ketone (25) (Scheme 6). This reaction is particularly sensitive to any trace of water or alcohol, either of which leads to simultaneous reduction of the alkyne function. Treatment of (25) with sodium borohydride then completes the reduction to the diol (26).

The next step was the protection of the 17β-hydroxy function, which was achieved using cold formic acid with 4-toluenesulfonic acid as catalyst. Being quite strongly acidic, this reaction has a tendency to induce D-ring rearrangement. However, by reducing the temperature of the solution to just above its freezing point, the diformate (27) was able to be produced in high yield with minimal by-product formation. Oxidation of (27) with hypobromous acid followed by debromination with zinc metal gave the diprotected 20-ketone (28) as well as a small amount of its 3-deformylated analogue (29). Sodium borohydride reduction of either (28) or (29) then gave a mixture of the required triols (22) and (23). At room temperature the two products were formed in approximately a 1 : 1 ratio, with higher temperatures appearing to favour the (20*S*)-epimer.

Poor solubility and chromatographic resolution made separation of the triols difficult, although acetylation of the crude product mixture afforded the much more easily separated diacetates (30) and (31). Stereochemistry was also assigned at this point by X-ray crystallographic analysis of (31) (Fig. 1). Finally, alkaline hydrolysis of (30) and (31) returned the triols (22) and (23), respectively.

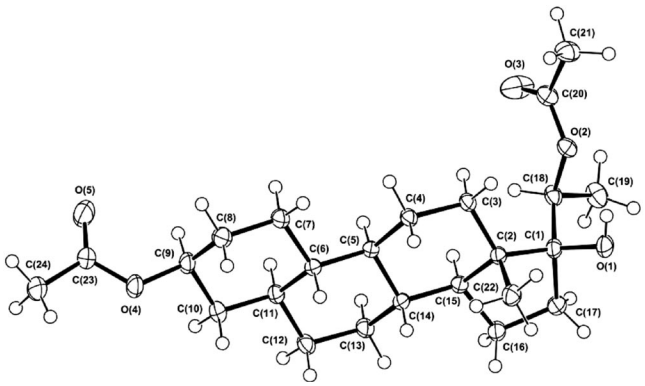


Fig. 1. 50% Displacement ellipsoid plot derived from single crystal X-ray analysis of compound (31).

Gas chromatographic–mass spectrometric analysis of the tris(trimethylsilyl ether) derivatives of the synthesized 3,17,20-triols was again successful, with mass spectroscopic and retention time matches to the two major side-chain hydroxylated metabolites observed in the post-administration urine samples. The order of elution was (23) followed by (22) (Table 1). This once again confirms the 3β,5α stereochemistry already observed for the 3,17-diol and 3,16,17-triol metabolites, as well as establishing non-stereospecific 20-hydroxylation as a significant metabolic pathway for (1) in the horse.

Experimental

Norethandrolone, norethindrone, and 17α-methyl-5α-androstane-3β, 17β-diol were purchased from Steraloids (Newport, RI, USA). 19-Nortestosterone was purchased from Sigma (Castle Hill, Australia). Potassium tri(*s*-butyl)borohydride in tetrahydrofuran (THF) solution (K-Selectride, 1 M) was purchased from Aldrich (Castle Hill, Australia).

All solvents were distilled prior to use. Ether and benzene were dried by storing over sodium wire, pyridine by storing over potassium hydroxide pellets, and *N*,*N*-dimethylformamide (DMF) by storing over type A4 molecular sieves. Tetrahydrofuran and 1,4-dioxan were dried by distillation from sodium benzophenone ketyl immediately prior to use. Liquid ammonia was dried by stirring with small portions of sodium metal until a constant blue colour was obtained, and then quenched with a minimum of solid ammonium chloride.

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, New Zealand. Infrared spectra were acquired on a Perkin Elmer 1600 series spectrometer as chloroform solutions between sodium chloride plates. ^{1}H and ^{13}C NMR spectra were acquired on Bruker AC-200F (^{1}H 200 MHz) or AMX-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometers with samples dissolved in deuterated solvents as described and referenced to solvent residuals.

Crystal structure analysis was conducted by the Crystal Structure Analysis Facility, University of Sydney. Details appear below.

Gas chromatographic–mass spectrometric analyses were performed on a Shimadzu QP-5000 instrument equipped with a J&W Scientific DB-5 MS capillary column (12 m × 0.2 mm ID) and using helium as carrier gas. Chemical derivatization procedures and instrument parameters were as described in a previous publication.[1]

19-Nor-5α,17α-pregnane-3β,17β-diol (2)

A solution of norethandrolone (1) (1.00 g) in 1,4-dioxan (25 mL) was added to a vigorously stirred solution of lithium (500 mg) in liquid ammonia (100 mL). After 5 min the reaction was quenched by the dropwise addition of methanol until the blue colour was discharged, after which ammonium chloride (5 g) was added. The ammonia was then allowed to evaporate. Water (100 mL) was added to the residue and the mixture was extracted with ethyl acetate (100 mL). The organic fraction was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/dichloromethane (10% v/v) and recrystallized from acetone/light petroleum to give (2) (688 mg, 68%) as a white crystalline solid, mp 186–187°C (lit.[7] 181–183°C). δ_H (20,0 MHz, $CDCl_3$) 0.87 (3 H, s, H18), 0.97 (3 H, t, *J* 7.3, H21), 3.48–3.68 (1 H, m, H3).

17β-Hydroxy-19-nor-5α,17α-pregnan-3-one (3)

A solution of (2) (100 mg) and chromium(VI) oxide (33 mg) in acetic acid (98% v/v, 5 mL) was stirred for 30 min at room temperature. Excess oxidant was decomposed by the addition of isopropyl alcohol (1 mL), after which the solution was basified with potassium hydroxide solution (2 M, 50 mL) and extracted with ethyl acetate (50 mL). The organic fraction was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was recrystallized from acetone/light petroleum to give (3) (94 mg, 95%) as a white crystalline solid, mp 216–218°C (lit.[7] 212–213°C). δ_H (200 MHz, $CDCl_3$) 0.90 (3 H, s, H18), 0.97 (3 H, t, *J* 7.2, H21).

19-Nor-5α,17α-pregnane-3α,17β-diol (4)

A solution of potassium tri(*s*-butyl)borohydride in tetrahydrofuran (1 M, 800 μL) was added to a solution of (3) (50 mg) in anhydrous tetrahydrofuran (10 mL) and stirred for 1 h at room temperature under nitrogen. The reaction was quenched by the addition of water (50 mL) and the mixture was extracted with ethyl acetate (50 mL). The organic fraction was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by chromatography on silica using ethyl acetate/light petroleum (40% v/v) and recrystallized from acetone/light petroleum to give (4) (38 mg, 76%) as a white crystalline solid, mp 189–190°C (lit.[21] 186–186.5°C). δ_H (200 MHz, $CDCl_3$) 0.88 (3 H, s, H18), 0.97 (3 H, t, *J* 7.3, H21), 4.03–4.13 (1 H, m, H3). A quantity of the 3β-epimer (2) (5 mg, 10%) was also recovered.

17β-Hydroxy-19-nor-5β,17α-pregnan-3-one (5)

A solution of norethandrolone (1) (150 mg) in methanol (9 mL) and potassium hydroxide solution (5 M, 1 mL) was hydrogenated for 2 h at 3 atm over palladium on charcoal (10%, 10 mg). The catalyst was removed by filtration, and the filtrate was diluted with water (50 mL) and extracted with ethyl acetate (50 mL). The organic fraction was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by chromatography on silica using ethyl acetate/light petroleum (20% v/v) and recrystallized from acetone/light petroleum to give (5) (123 mg, 81%) as a white crystalline solid, mp 150–152°C (lit.[22] 155–157°C). δ_H (200 MHz, $CDCl_3$) 0.91 (3 H, s, H18). A small quantity of the 5α-epimer (3) (8 mg, 5%) was also recovered.

19-Nor-5β,17α-pregnane-3α,17β-diol (6)

A solution of (5) (50 mg) and lithium aluminium hydride (24 mg) in anhydrous ether (10 mL) was stirred for 1 h at room temperature under nitrogen. The reaction was quenched by the addition of ethyl acetate (1 mL) followed by dilute hydrochloric acid (0.5 M, 50 mL). The mixture was then extracted with ethyl acetate (50 mL). The organic fraction was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by chromatography on silica using ethyl acetate/light petroleum (40% v/v) and recrystallized from acetone/light petroleum to give (6) (40 mg, 79%) as a white crystalline solid, mp 179–181°C (Found: C 78.0, H 11.1%. $C_{20}H_{34}O_2$ requires C 78.4, H 11.2%). ν_{max} ($CHCl_3$)/cm^{-1} 3604, 3446 (broad). δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, s, H18), 0.98 (1 H, t, *J* 7.3, H21), 3.58–3.68 (1 H, m, H3). δ_C (100 MHz, $CDCl_3$) 8.5, 15.2, 24.2, 26.0, 26.7, 29.5, 30.4, 32.2, 32.3, 34.4, 36.4, 37.1, 39.2, 40.6, 43.4, 47.3, 50.3, 72.5, 84.3 (one signal obscured or overlapping). A quantity of the 3β-epimer (7) (4 mg, 8%) was also recovered.

19-Nor-5β,17α-pregnane-3β,17β-diol (7)

A solution of potassium tri(*s*-butyl)borohydride in tetrahydrofuran (1 M, 800 μL) was added to a solution of (5) (50 mg) in anhydrous tetrahydrofuran (10 mL) and stirred for 1 h at room temperature under nitrogen. The reaction was quenched by the addition of water (50 mL) and the mixture was extracted with ethyl acetate (50 mL). The organic fraction was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by chromatography on silica using ethyl acetate/light petroleum (40% v/v) and recrystallized from acetone/light petroleum to give (7) (42 mg, 83%) as a white crystalline solid, mp 162–164°C (Found: C 78.4, H 11.5%. $C_{20}H_{34}O_2$ requires C 78.4, H 11.2%). ν_{max} ($CHCl_3$)/cm^{-1} 3614, 3447 (broad). δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, s, H18), 0.98 (1 H, t, *J* 7.3, H21), 4.10–4.15 (1 H, m, H3). δ_C (100 MHz, $CDCl_3$) 8.5, 15.2, 22.1, 24.2, 26.4, 26.6, 27.6, 29.5, 30.7, 32.1, 32.3, 34.1, 34.4, 38.5, 41.5, 43.3, 47.3, 50.4, 67.9, 84.3. A small quantity of the 3α-epimer (6) (2 mg, 4%) was also recovered.

17β-(t-Butyldimethylsilyl)oxy-5α-estr-4-en-3-one (12)

A solution of (11) (2.00 g), *t*-butylchlorodimethylsilane (1.32 g), and imidazole (1.19 g) in anhydrous *N*,*N*-dimethylformamide (25 mL) was stirred for 12 h at room temperature. The reaction was quenched by the addition of hydrochloric acid (0.5 M, 250 mL) and the resulting mixture was extracted with ethyl acetate (250 mL). The organic fraction was washed with sodium carbonate solution (0.5 M, 250 mL), water (250 mL) and brine (250 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/light petroleum (10% v/v) and recrystallized from ether/methanol to give (12) (2.63 g, 93%) as a white crystalline solid, mp 137–139°C (lit.[11] 137–138°C). δ_H (200 MHz, $CDCl_3$) 0.00, (6 H, 2 × s incompletely resolved, $OSi(CH_3)_2$), 0.76 (3 H, s, H18), 0.86 (9 H, s, $OSiC(CH_3)_3$), 3.52–3.62 (1 H, m, H17), 5.82 (1 H, s, H4).

17β-(t-Butyldimethylsilyl)oxy-5α-estran-3β-ol (13)

A solution of (12) (2.50 g) in ether (50 mL) was added to a vigorously stirred solution of lithium (1.25 g) in liquid ammonia (250 mL).

The reaction was immediately quenched by the dropwise addition of methanol until the blue colour was discharged after which ammonium chloride (10 g) was added. The ammonia was then allowed to evaporate. Water (250 mL) was added to the residue and the mixture was extracted with ethyl acetate (250 mL). The organic fraction was washed with water (250 mL) and brine (250 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/dichloromethane (5% v/v) and recrystallized from ether/light petroleum to give (13) (1.65 g, 65%) as a white crystalline solid, mp 140–141°C (lit.[23] 135–138°C). δ_H (200 MHz, $CDCl_3$) 0.01, (6 H, 2 × s incompletely resolved, $OSi(CH_3)_2$), 0.69 (3 H, s, H18), 0.87 (9 H, s, $OSiC(CH_3)_3$), 3.47–3.67 (2 H, m, H3 and H17).

*17β-(*t*-Butyldimethylsilyl)oxy-5α-estran-3β-yl Acetate (14)*

A solution of (13) (1.60 g) in acetic anhydride (50 mL) and anhydrous pyridine (50 mL) was allowed to stand for 18 h at room temperature. The solvent was then removed by evaporation at reduced pressure. The residue was reconstituted in ethyl acetate (250 mL) and washed with hydrochloric acid (0.5 M, 250 mL), sodium carbonate solution (0.5 M, 250 mL), water (250 mL) and brine (250 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/light petroleum (5% v/v) and recrystallized from ether/methanol to give (14) (1.59 g, 90%) as a white crystalline solid, mp 140–141°C (Found: C 72.1, H 10.9%. $C_{26}H_{46}O_3Si$ requires C 71.8, H 10.7%). ν_{max} ($CHCl_3$)/cm^{-1} 1717. δ_H (400 MHz, $CDCl_3$) 0.00, (6 H, 2 × s incompletely resolved, $OSi(CH_3)_2$), 0.70 (3 H, s, H18), 0.87 (9 H, s, $OSiC(CH_3)_3$), 2.02 (3 H, s, $OCOCH_3$), 3.49–3.59 (1 H, m, H17), 4.18–4.28 (1 H, m, H3). δ_C (100 MHz, $CDCl_3$) −4.1, −3.8, 12.0, 18.8, 22.2, 24.1, 26.3, 26.5, 28.9, 31.2, 31.6, 32.6, 34.1, 37.8, 40.0, 41.8, 42.0, 44.1, 46.9, 48.8, 50.4, 73.8, 82.6, 171.4 (two signals obscured or overlapping).

19-Norepiandrosterone Acetate (15)

A solution of chromium(VI) oxide (690 mg) in sulfuric acid (4 M, 2.5 mL) was added with stirring and cooling to a solution of (14) (1.50 g) and potassium fluoride (400 mg) in acetone (50 mL). After stirring for 30 min at 0°C followed by 1 h at room temperature, the solution was diluted with water (500 mL) and the resulting mixture was extracted with ethyl acetate (500 mL). The organic fraction was washed with water (500 mL) and brine (500 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/dichloromethane (5% v/v) and recrystallized from ether/light petroleum to give (15) (1.02 g, 93%) as a white crystalline solid, mp 185–186°C (lit.[24] 182.5°C). δ_H (200 MHz, $CDCl_3$) 0.86 (3 H, s, H18), 2.01 (3 H, s, $OCOCH_3$), 4.57–4.77 (1 H, m, H3).

5α-Estr-16-ene-3β,17-diyl Diacetate (10)

A solution of (15) (970 mg) in isopropenyl acetate (25 mL) and sulfuric acid (18 M, 2 drops) was boiled gently so as to reduce its volume by half over about 1 h. The solution was restored to its original volume by the addition of more isopropenyl acetate (approx. 12.5 mL) and the boiling was continued to again reduce its volume by half over about 1 h. The dilution–concentration sequence was repeated twice more, after which the solution was cooled and the reaction quenched by the addition of sodium carbonate solution (0.5 M, 100 mL). The resulting mixture was extracted with ethyl acetate (100 mL). The organic fraction was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on neutral alumina using dichloromethane, and recrystallized from ether/light petroleum to give (10) (898 mg, 82%) as a white crystalline solid, mp 104–106°C (Found: C 73.4, H 8.8%. $C_{22}H_{32}O_4$ requires C 73.3, H 8.9%). ν_{max} ($CHCl_3$)/cm^{-1} 1749, 1724. δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, s, H18), 2.01 (3 H, s, $OCOCH_3$ at C3), 2.14 (3 H, s, $OCOCH_3$ at C17), 4.54–4.64 (1 H, m, H3), 5.45 (1 H, s, H16). δ_C (100 MHz, $CDCl_3$) 16.3, 21.8, 22.1, 26.2, 28.7, 29.4, 30.7, 32.5, 33.9, 34.1, 40.0, 40.0, 41.8, 45.6, 47.0, 49.2, 54.1, 73.7, 111.8, 160.5, 169.6, 171.4.

16α-Hydroxy-17-oxo-5α-estran-3β-yl Acetate (16)

A solution of (10) (420 mg) and 3-chloroperbenzoic acid (302 mg) in chloroform (25 mL) was allowed to stand for 18 h at room temperature. The reaction was quenched by thoroughly washing with sodium thiosulfate solution (5% w/v, 50 mL). The organic fraction was further washed with sodium carbonate solution (0.5 M, 50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was reconstituted in methanol (25 mL) and cooled in an ice bath. Sulfuric acid (0.5 M, 2.5 mL) was added and the solution was stirred for 1 h at 0°C. The reaction was quenched by the addition of sodium carbonate solution (0.5 M, 250 mL), and the resulting mixture was extracted with ethyl acetate (250 mL). The organic fraction was washed with water (250 mL) and brine (250 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/dichloromethane (5% v/v) and recrystallized from ether/light petroleum to give (16) (304 mg, 78%) as a white crystalline solid, mp 145–147°C (Found: C 72.0, H 9.1%. $C_{20}H_{30}O_4$ requires C 71.8, H 9.0%). ν_{max} ($CHCl_3$)/cm^{-1} 3559 (broad), 1745, 1723. δ_H (400 MHz, $CDCl_3$) 0.96 (3 H, s, H18), 2.01 (3 H, s, $OCOCH_3$), 4.35 (1 H, d, *J* 7.3, H16), 4.63–4.73 (1 H, m, H3). δ_C (100 MHz, $CDCl_3$) 14.8, 22.1, 25.4, 28.8, 30.0, 31.1, 32.0, 32.5, 33.8, 39.9, 41.3, 41.6, 46.8, 48.1, 48.4, 48.6, 72.0, 73.5, 171.3, 220.1.

17-Oxo-5α-estran-3β,16α-diyl Diacetate (17)

A solution of (16) (250 mg) in acetic anhydride (25 mL) and anhydrous pyridine (25 mL) was allowed to stand for 18 h at room temperature. The solvent was then removed by evaporation at reduced pressure. The residue was reconstituted in ethyl acetate (50 mL) and washed with hydrochloric acid (0.5 M, 50 mL), sodium carbonate solution (0.5 M, 50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/light petroleum (5% v/v) and recrystallized from ether/light petroleum to give (17) (276 mg, 98%) as a white crystalline solid, mp 157–158°C (Found: C 70.0, H 8.6%. $C_{22}H_{32}O_5$ requires C 70.2, H 8.6%). ν_{max} ($CHCl_3$) 1753, 1728. δ_H (400 MHz, $CDCl_3$) 0.95 (3 H, s, H18), 2.01 (3 H, s, $OCOCH_3$ at C3), 2.10 (3 H, s, $OCOCH_3$ at C16), 4.62–4.72 (1 H, m, H3), 5.39 (1 H, d, *J* 8.7, H16). δ_C (100 MHz, $CDCl_3$) 14.9, 21.5, 22.1, 25.5, 28.8, 30.1, 30.1, 32.0, 32.5, 33.7, 39.9, 41.2, 41.6, 46.8, 48.5, 48.6, 73.1, 73.5, 171.0, 171.3, 214.8 (one signal obscured or overlapping).

19-Nor-5α,17α-pregnane-3β,16α,17β-triol (8)

Magnesium turnings (142 mg) were stirred with ethyl iodide (914 mg) and anhydrous ether (478 mg) in anhydrous benzene (20 mL) with gentle heating until all the metal was dissolved. The solution was then cooled, and a solution of (17) (220 mg) in anhydrous benzene (5 mL) was added and stirred for 18 h at room temperature. The reaction was quenched by the careful addition of cold ethyl acetate (50 mL) and the resulting mixture was washed with hydrochloric acid (0.5 M, 50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was resolved into three products by chromatography on silica using ethyl acetate/dichloromethane (50% v/v). The least polar product was recrystallized from acetone to give *19-nor-5α,17β-pregnane-3β,16α,17α-triol* (18) (45 mg, 24%) as a white crystalline solid, mp 199–200°C (Found: C 74.3, H 10.5%. $C_{20}H_{34}O_3$ requires C 74.5, H 10.6%). δ_H (400 MHz, CD_3OD) 0.78 (3 H, s, H18), 0.99 (3 H, t, *J* 7.5, H21), 1.60 (2 H, q, *J* 7.5, H20), 3.49–3.59 (1 H, m, H3), 4.05 (1 H, dd, *J* 2.0, 8.8, H16). δ_C (100 MHz, CD_3OD) 8.9, 16.3, 26.7, 29.1, 29.8, 32.8, 33.0, 35.2, 36.6, 36.8, 42.9, 42.9, 44.5, 48.1, 48.8, 49.6, 71.4, 77.5, 83.2 (one signal obscured or overlapping). The intermediate product was recrystallized from acetone/ether to give (8) (51 mg, 27%) as a white glassy solid, mp 168–172°C (Found: C 74.4, H 10.5%. $C_{20}H_{34}O_3$ requires C 74.5, H 10.6%). δ_H (400 MHz, CD_3OD) 0.92 (3 H, s, H18), 1.08 (3 H, t, *J* 7.3, H21), 1.62 (2 H, q, *J* 7.3, H20),

3.50–3.60 (1 H, m, H3), 4.25 (1 H, dd, *J* 3.2, 10.0, H16). δ_C (100 MHz, CD_3OD) 10.3, 15.8, 24.3, 26.9, 29.8, 32.3, 34.4, 35.1, 35.4, 36.8, 42.9, 43.4, 44.5, 48.1, 71.4, 82.2, 86.2 (three signals obscured or overlapping). The most polar product was recrystallized from acetone to give *5α-estrane-3β,16α,17β-triol* (19) (46 mg, 27%) as a white crystalline solid, mp 231–233°C (Found: C 73.7, H 10.6%. $C_{18}H_{30}O_3$ requires C 73.4, H 10.3%). δ_H (400 MHz, CD_3OD) 0.79 (3 H, s, H18), 3.42 (1 H, d, *J* 5.8, H17), 3.49–3.59 (1 H, m, H3), 4.03 (1 H, ddd, *J* 1.9, 5.8, and 8.5, H16). δ_C (100 MHz, CD_3OD) 13.1, 26.7, 29.8, 32.0, 35.0, 35.3, 36.8, 38.3, 42.5, 42.9, 44.5, 45.2, 48.1, 49.6, 49.9, 71.4, 79.0, 91.0.

17-Oxo-5α-estran-3β,16β-diyl diacetate (20)

A solution of (10) (420 mg) and lead(IV) acetate (568 mg) in acetic acid (glacial, 20 mL) and acetic anhydride (500 μL) was stirred for 18 h at room temperature. The solvent was then removed by evaporation at reduced pressure. The residue was reconstituted in dry ether (25 mL), and water-saturated ether (25 mL) was added to decompose the lead complex. After stirring for about 5 min the mixture was filtered and the filtrate was washed with sodium carbonate solution (0.5 M, 50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by chromatography on silica using ethyl acetate/dichloromethane (5% v/v) and recrystallized from ether/light petroleum to give (20) (320 mg, 73%) as a white crystalline solid, mp 191–193°C (Found: C 70.0, H 8.3%. $C_{22}H_{32}O_5$ requires C 70.2, H 8.6%). ν_{max} ($CHCl_3$)/cm^{-1} 1737. δ_H (400 MHz, $CDCl_3$) 0.95 (3 H, s, H18), 2.00 (3 H, s, $OCOCH_3$ at C3), 2.09 (3 H, s, $OCOCH_3$ at C16), 4.62–4.72 (1 H, m, H3), 4.97 (1 H, dd, *J* 8.6 and 8.6, H16). δ_C (100 MHz, $CDCl_3$) 15.2, 21.4, 22.1, 25.6, 28.8, 29.8, 30.5, 32.4, 32.4, 33.7, 39.8, 40.4, 41.6, 45.7, 46.8, 47.9, 48.8, 73.5, 75.4, 170.9, 171.3, 215.4.

19-Nor-5α,17α-pregnane-3β,16β,17β-triol (9)

Magnesium turnings (142 mg) were stirred with ethyl iodide (914 mg) and anhydrous ether (478 mg) in anhydrous benzene (20 mL) with gentle heating until all the metal was dissolved. The solution was then cooled, and a solution of (20) (220 mg) in anhydrous benzene (5 mL) was added and stirred for 18 h at room temperature. The reaction was quenched by the careful addition of cold ethyl acetate (50 mL) and the resulting mixture was washed with hydrochloric acid (0.5 M, 50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was resolved into two products by chromatography on silica using ethyl acetate/dichloromethane (40% v/v). The less-polar product was recrystallized from acetone to give (9) (92 mg, 49%) as a white crystalline solid, mp 239–240°C (Found: C 74.9, H 10.9%. $C_{20}H_{34}O_3$ requires C 74.5, H 10.6%). δ_H (400 MHz, CD_3OD) 0.88 (3 H, s, H18), 0.95 (3 H, t, *J* 7.2, H21), 1.63 (2 H, q, *J* 7.2, H20), 3.49–3.59 (1 H, m, H3), 3.83 (1 H, dd, *J* 6.2 and 8.1, H16). δ_C (100 MHz, CD_3OD) 7.8, 15.3, 27.0, 28.5, 29.9, 32.5, 34.0, 36.4, 36.8, 42.9, 43.2, 44.5, 47.4, 47.5, 48.3, 49.8, 71.4, 73.7, 81.6. The more-polar product was recrystallized from acetone to give *5α-estrane-3β,16β,17β-triol* (21) (46 mg, 27%) as a white crystalline solid, mp 253–255°C (Found: C 73.1, H 10.3%. $C_{18}H_{30}O_3$ requires C 73.4, H 10.3%). δ_H (400 MHz, CD_3OD) 0.85 (3 H, s, H18), 3.33 (1 H, d, *J* 7.7, H17), 3.49–3.59 (1 H, m, H3), 4.11 (1 H, ddd, *J* 5.0, 7.7, and 7.7, H16). δ_C (100 MHz, CD_3OD) 12.9, 26.8, 29.9, 32.2, 35.1, 36.1, 36.8, 39.0, 42.4, 42.9, 44.1, 44.5, 48.2, 48.3, 49.9, 71.1, 71.4, 82.5.

17β-Hydroxy-19-nor-5α,17α-pregn-20-yn-3-one (25)

A solution of (24) (2.00 g) in anhydrous 1,4-dioxan (40 mL) was added to a vigorously stirred solution of lithium (1.00 g) in anhydrous liquid ammonia (200 mL). The reaction was immediately quenched by the addition of ammonium chloride (10 g), after which the ammonia was allowed to evaporate. Water (250 mL) was added to the residue and the mixture was extracted with ethyl acetate (250 mL). The organic fraction was washed with water (250 mL) and brine (250 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/dichloromethane (10% v/v) and recrystallized from acetone/light petroleum to give (25) (1.27 g, 63%) as a white crystalline solid, mp 220–223°C (lit.[7] 222–223°C). δ_H (200 MHz, $CDCl_3$) 0.87 (3 H, s, H18), 2.57 (1 H, s, H21).

19-Nor-5α,17α-pregn-20-yne-3β,17β-diol (26)

Sodium borohydride (756 mg) was added to a solution of (25) (1.20 g) in 1,4-dioxan (95 mL) and water (5 mL) in small portions with stirring and cooling so as to maintain the solution at around 20–25°C. After stirring for 1 h at room temperature the solvent was removed by evaporation at reduced pressure. Water (250 mL) was added to the residue and the mixture was extracted with ethyl acetate (250 mL). The organic fraction was washed with water (2 × 250 mL) and brine (250 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/dichloromethane (20% v/v) and recrystallized from acetone/light petroleum to give (26) (1.09 g, 90%) as a white crystalline solid, mp 191–193°C (lit.[7] 192–193°C). δ_H (200 MHz, CD_3OD) 0.87 (3 H, s, H18), 2.89 (1 H, s, H21), 3.45–3.65 (1 H, m, H3).

19-Nor-5α,17α-pregn-20-yne-3β,17β-diyl Diformate (27)

Diol (26) (930 mg) was added to ice-cold formic acid (130 mL) and stirred in an ice bath until dissolution was complete. Toluenesulfonic acid monohydrate (50 mg) was added and the stirring continued until this also dissolved. The solution was then allowed to stand for 2 days at 5°C. After diluting with cold ether (500 mL), the acid was neutralized by stirring in an ice bath with successive portions of ice-cold sodium carbonate solution (1 M, 1 L) until the aqueous fraction remained basic. The organic fraction was then washed with water (500 mL) and brine (500 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was purified by chromatography on silica using ethyl acetate/dichloromethane (10% v/v) and recrystallized from ether/light petroleum to give (27) (1.00 g, 91%) as a white crystalline solid, mp 84–86°C (Found: C 73.8, H, 8.3%. $C_{22}H_{30}O_4$ requires C 73.7, H, 8.4%). ν_{max} ($CHCl_3$)/cm^{-1} 3304, 2118, 1724. δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, s, H18), 2.69 (1 H, s, H21), 4.77–4.87 (1 H, m, H3), 8.02 (1 H, s, OCOH at C3), 8.16 (1 H, s, OCOH at C17). δ_C (100 MHz, $CDCl_3$) 14.1, 24.0, 26.1, 28.8, 31.1, 32.5, 33.7, 33.9, 38.3, 39.8, 41.6, 42.1, 46.7, 48.0, 48.5, 48.9, 73.6, 77.2, 83.4, 86.0, 160.9, 161.4.

20-Oxo-19-nor-5α,17α-pregnan-3β,17β-diyl Diformate (28)

A solution of (27) (850 mg), *N*-bromoacetamide (1.31 g), and sodium acetate (4.00 g) in acetic acid (200 mL) and water (20 mL) was stirred for 45 min at room temperature. Zinc powder (1.24 g) was added and the mixture was heated at reflux until colourless (20 min). The mixture was then cooled and filtered, and the solvent was removed by evaporation at reduced pressure. Sodium carbonate solution (0.5 M, 100 mL) was added to the residue and the mixture was extracted with ethyl acetate (100 mL). The organic fraction was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was resolved into two products by chromatography on silica using ethyl acetate/light petroleum (20% v/v). The less polar product was recrystallized from ether/light petroleum to give (28) (509 mg, 57%) as a white crystalline solid, mp 138–140°C (Found: C 70.2, H 8.7%. $C_{22}H_{32}O_5$ requires C 70.2, H, 8.6%). ν_{max} ($CHCl_3$)/cm^{-1} 1720. δ_H (400 MHz, $CDCl_3$) 1.01 (3 H, s, H18), 2.07 (3 H, s, H21), 4.74–4.84 (1 H, m, H3), 8.00 (1 H, s, OCOH at C3), 8.09 (1 H, s, OCOH at C17). δ_C (100 MHz, $CDCl_3$) 15.6, 25.1, 26.1, 27.9, 28.8, 31.1, 32.5, 33.6, 33.9, 34.5, 39.8, 41.6, 41.9, 46.6, 47.3, 47.8, 48.2, 73.6, 97.6, 161.4, 161.7, 208.1. The more polar product was recrystallized from ether/light petroleum to give *3β-hydroxy-20-oxo-19-nor-5α,17α-pregnan-17β-yl formate* (29) (125 mg, 15%) as a white crystalline solid, mp 200–201°C (Found: C 72.4, H 9.0%. $C_{21}H_{32}O_4$ requires C 72.4, H, 9.3%). ν_{max} ($CHCl_3$)/cm^{-1} 3460 (broad), 1721. δ_H (400 MHz, $CDCl_3$) 1.01 (3 H, s, H18), 2.07 (3 H, s, H21), 3.51–3.61 (1 H, m, H3), 8.09 (1 H, s, OCOH at C17). δ_C (100 MHz, $CDCl_3$) 15.6, 25.1, 26.2, 27.9, 29.0, 31.2, 33.6, 34.1, 34.6, 36.4, 41.7, 42.0, 44.0, 46.7, 47.3, 47.9, 48.3, 71.1, 97.7, 161.7, 208.2.

(20R)-17β-Hydroxy-19-nor-5α,17α-pregnane-3β,20-diyl Diacetate (30)
and (20S)-17β-Hydroxy-19-nor-5α,17α-pregnane-3β,20-diyl Diacetate (31)

Sodium borohydride (1.00 g) was added to a solution of (28) (400 mg) in methanol (25 mL) in small portions with stirring and cooling so as to maintain the solution at around 20–25°C. After stirring for 1 h at room temperature, the solvent was removed by evaporation at reduced pressure. Water (100 mL) was added to the residue and the mixture was extracted with ethyl acetate (100 mL). The organic fraction was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was reconstituted in acetic anhydride (25 mL) and anhydrous pyridine (25 mL), and allowed to stand for 18 h at room temperature. The solvent was then removed by evaporation at reduced pressure. The residue was reconstituted in ethyl acetate (50 mL) and washed with hydrochloric acid (0.5 M, 50 mL), sodium carbonate solution (0.5 M, 50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was resolved into two products by chromatography on silica using ethyl acetate/dichloromethane (5% v/v). The less-polar product was recrystallized from ether/light petroleum to give (31) (203 mg, 47%) as a white crystalline solid, mp 202–204°C (Found: C 70.8, H 9.4%. $C_{24}H_{38}O_5$ requires C 70.9, H 9.4%). ν_{max} ($CHCl_3$)/cm^{-1} 3586, 1724. δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, s, H18), 1.28 (3 H, d, *J* 6.2, H21), 2.00 (3 H, s, $OCOCH_3$ at C3), 2.03 (3 H, s, $OCOCH_3$ at C20), 4.61–4.71 (1 H, m, H3), 4.94 (1 H, q, *J* 6.2, H20). δ_C (100 MHz, $CDCl_3$) 15.6, 16.2, 22.1, 22.2, 24.0, 26.6, 28.8, 31.3, 32.5, 34.0, 34.0, 34.1, 39.9, 41.6, 42.7, 46.8, 47.9, 48.0, 51.5, 73.7, 73.9, 85.4, 170.5, 171.3. The more-polar product was recrystallized from ether/light petroleum to give (30) (194 mg, 45%) as a white crystalline solid, mp 170–171°C (Found: C 71.0, H 9.4%. $C_{24}H_{38}O_5$ requires C 70.9, H 9.4%). ν_{max} ($CHCl_3$)/cm^{-1} 3586, 1725. δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, s, H18), 1.29 (3 H, d, *J* 6.2, H21), 2.01 (3 H, s, $OCOCH_3$ at C3), 2.06 (3 H, s, $OCOCH_3$ at C20), 4.61–4.71 (1 H, m, H3), 4.97 (1 H, q, *J* 6.2, H20). δ_C (100 MHz, $CDCl_3$) 15.5, 17.1, 22.1, 22.2, 24.6, 26.4, 28.9, 31.5, 32.5, 34.1, 34.2, 35.0, 40.0, 41.7, 42.7, 46.8, 47.6, 48.4, 51.2, 73.7, 74.8, 85.3, 171.0, 171.3.

(20R)-19-Nor-5α,17α-pregnane-3β,20,17β-triol (22)

A solution of (30) (140 mg) and potassium hydroxide (500 mg) in methanol (25 mL) was heated at reflux for 2 h. The reaction was then cooled and the solvent was removed by evaporation at reduced pressure. Water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The organic fraction was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The extracted residue was recrystallized from acetone to give (22) (109 mg, 98%) as a white glassy solid, mp 180–182°C (Found: C 74.4, H 10.5%. $C_{20}H_{34}O_3$ requires C 74.5, H 10.6%). δ_H (400 MHz, CD_3OD) 0.93 (3 H, s, H18), 1.25 (3 H, d, *J* 6.3, H21), 3.48–3.58 (1 H, m, H3), 3.88 (1 H, q, *J* 6.3, H20). δ_C (100 MHz, CD_3OD) 15.6, 19.6, 24.6, 27.1, 29.7, 32.1, 33.3, 34.8, 34.9, 36.6, 42.6, 43.5, 44.2, 47.8, 48.1, 49.3, 51.8, 70.4, 71.1, 86.4.

(20S)-19-Nor-5α,17α-pregnane-3β,20,17β-triol (23)

Diacetate (31) (150 mg) was hydrolyzed as described previously. Recrystallization of the product from acetone gave (23) (113 mg, 95%) as a white crystalline solid, mp 231–233°C (Found: C 74.4, H 10.6%. $C_{20}H_{34}O_3$ requires C 74.5, H 10.6%). δ_H (400 MHz, CD_3OD) 0.90 (3 H, s, H18), 1.24 (3 H, d, *J* 6.3, H21), 3.49–3.59 (1 H, m, H3), 3.85 (1 H, q, *J* 6.3, H20). δ_C (100 MHz, CD_3OD) 15.9, 19.8, 25.3, 27.1, 29.7, 31.6, 32.2, 33.1, 35.0, 36.6, 42.7, 43.5, 44.3, 47.9, 48.3, 51.2, 51.3, 71.2, 71.4, 85.9.

Crystal Data

Compound (31). The structure has been deposited with the Cambridge Crystallographic Data Centre and has the deposition number CCDC 206513. Formula $C_{24}H_{38}O_4$, *M* 406.54, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* 9.1060(15), *b* 26.745(5), *c* 9.1030(15) Å, *V* 2216.9(6) $Å^3$, D_c 1.218 g cm^{-3}, *Z* 4, crystal size 0.601 × 0.248 × 0.070 mm, colourless, habit blade, *T* 150(2) K, $\lambda(Mo_{K\alpha})$ 0.71069 Å, $\mu(Mo_{K\alpha})$ 0.083 mm^{-1}, $2\theta_{max}$ 66.00, $-13 \le h \le 13$, $-40 \le k \le 40$, $-13 \le l \le 13$, *N* 32667, N_{ind} 4633 (R_{merge} 0.0512), N_{obs} 3580 ($I > 2\sigma(I)$), N_{var} 269, residuals* *R*1(*F*) 0.0395, *wR*2(F^2) 0.0881, GoF(all) 1.362, $\Delta\rho_{min,max}$ −0.183, 0.304 e^- $Å^{-3}$.

Structure Determination

A colourless blade-like crystal was attached with Exxon Paratone N to a short length of fibre supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A Bruker SMART 1000 CCD diffractometer employing graphite monochromated $Mo_{K\alpha}$ radiation generated from a sealed tube was used for the data collection. Cell constants were obtained from a least squares refinement against 994 reflections located between 4.73 and 59.70° 2θ. Data were collected at 150(2) K with ω-scans to 66.00° 2θ. The data integration and reduction were undertaken with SAINT and XPREP,[25] and subsequent computations were carried out with teXsan,[26] WinGX,[27] and Xtal[28] graphical user interfaces. The intensities of 168 standard reflections recollected at the end of the experiment did not change significantly during the data collection.

The structure was solved in the space group $P2_12_12_1$ by direct methods with SIR97,[29] and extended and refined with SHELXL-97.[30] The non-hydrogen atoms were modelled with anisotropic displacement parameters, and in general a riding atom model was used for the hydrogen atoms. The hydroxyl hydrogen site was located and modelled with an isotropic displacement parameter. The absolute structure could not be determined.

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* $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2 - F_c^2)^2/\Sigma (wF_c^2)^2)^{1/2}$ all reflections $w = 1/[\sigma^2(F_o^2) + (0.03P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$.

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