Steroids 76 (2011) 1098–1102

Contents lists available at ScienceDirect

Steroids

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

Efficient syntheses of 17-β-amino steroids

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ARTICLE INFO

Article history:
Received 8 March 2011
Received in revised form 20 April 2011
Accepted 21 April 2011
Available online 4 May 2011

Keywords:
17-β-Amino steroids
Reductive amination
Sodium triacetoxyborohydride
Catalytic hydrogenolysis

ABSTRACT

17β-Amino steroids such as 17β-amino-1,3,5(10)-estratrien-3-ol (**1**), 17β-amino-5α-androstan-3β-ol (**2**) and, 17β-amino-3β-hydroxyandrost-5-ene (**3**) have been widely used as a key intermediates in the synthesis of a variety of biologically active steroid derivatives though concise, high yielding syntheses of these compounds has yet to be reported. 17β-Amino-1,3,5(10)-estratrien-3-ol (**1**) and 17β-amino-5α-androstan-3β-ol (**2**) were prepared in high yield by reductive amination of estrone and epiandrosterone using benzylamine and sodium triacetoxyborohydride followed by catalytic hydrogenolysis of the resulting 17β-benzylamino derivatives. Attempts to prepare 17β-amino-3β-hydroxyandrost-5-ene (**3**) from dehydroepiandosterone using a similar approach resulted in partial reduction of the double bond. 17β-Amino-3β-hydroxyandrost-5-ene (**3**) was ultimately obtained in high yield by reductive amination of dehydroepiandosterone using allylamine and sodium triacetoxyborohydride followed by removal of the allyl group from the resulting 17β-allylamino derivative with dimethylbarbituric acid and $Pd(PPh_3)_4$ as catalyst.

1. Introduction

17β-Amino steroids such as 17β-amino-1,3,5(10)-estratrien-3-ol, 17β-amino-5α-androstan-3β-ol and, 17β-amino-3β-hydroxyandrost-5-ene (**1–3**, Fig. 1) are non-natural steroids that have been widely used as a key intermediates in the synthesis of a variety of biologically active steroid derivatives [1–8]. During the course of our studies on steroid-based anticancer agents it became necessary to prepare compounds **1–3** which are not commercially available. Compound **1** has been synthesized by reduction of the 17-hydrazone of estrone (E1) using Ra–Ni [9] and by reduction of 17-oxime of E1 using Na/*n*-propanol [5,10–13]. Although the hydrazone/Ra–Ni procedure produces **1** in good overall yield it has not found widespread use possibly because a considerable excess of Ra–Ni is required and the hydrazone is poorly soluble in many organic solvents and so the reduction must be carried out under conditions of high dilution. The oxime-sodium approach appears to be the method of choice for the synthesis of **1**. However, as noted by Lemini et al., this procedure, even after an initial recrystallization, yields product that consists of a 4:1 mixture of **1** and its alpha epimer [10]. Multiple recrystallizations in MeOH are required to remove the α-epimer which results in low to moderate yields [10]. Compound **2** has been prepared by reduction of the 17-oxime of epiandrosterone (EA) using Na/*n*-propanol [8,14]. This reaction again produces an α,β mixture though after several recrystallizations compound **2** yields as high as 62% have been reported [8]. Compound **2** has also been prepared in an unspecified yield from the 3β-acetate ester of EA via a Leukart–Wallach amination [15] and in a 50% yield by reductive amination of epiandrosterone with hydrazine hydrate, aluminum and mercuric chloride in aq. ethanol [16]. Compound **3** has been prepared in high yield by reduction of the 17-oxime of the 3β-acetate of dehydroepiandrosterone (DHEA) using Na/*n*-BuOH yields with only small amounts (approximately 5%) of the α-isomer being formed [3]. In this report we describe an efficient synthesis of compounds **1–3** using a reductive amination approach.

2. Experimental

2.1. General remarks

Tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone under argon. Reagent grade 1,2-dichloroethane was used without further purification. CH_2Cl_2 was distilled from calcium hydride under nitrogen. Degassed CH_2Cl_2 was obtained by freezing dry CH_2Cl_2 in liquid nitrogen followed by pumping under high vacuum then thawing. This process was repeated three times. Hydrogenolysis reactions were carried out in HPLC grade ethanol. Benzylamine and allyl alcohol (Aldrich,

Abbreviations: E1, estrone; EA, epiandrosterone; DHEA, dehydroepiandrosterone; STAB-H, sodium triacetoxyborohydride.

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doi:10.1016/j.steroids.2011.04.013

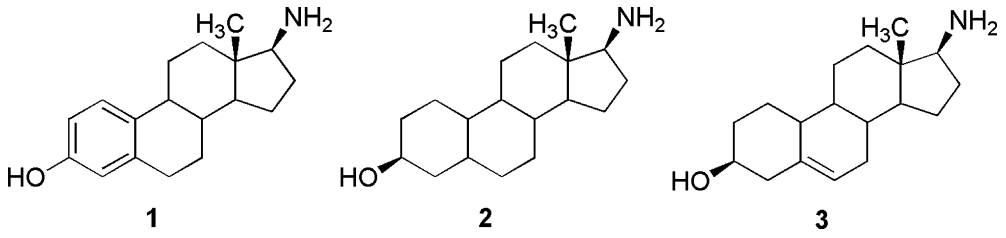


Fig. 1. Structures of 17β-amino-1,3,5(10)-estratrien-3-ol (**1**), 17β-amino-5α-androstan-3β-ol (**2**) and, 17β-amino-3β-hydroxyandrost-5-ene (**3**).

Milwaukee, Wisconsin, USA) were distilled before use. Sodium triacetoxyborohydride (Aldrich, Milwaukee, Wisconsin, USA) was used as is. Flash chromatography was performed using silica gel 60 Å (234–400 mesh) (Silicycle, Quebec, Canada). TLC was performed using silica coated TLC plates (Silicycle, Quebec, Canada). All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer. Chemical shifts (δ) for ^{1}H NMR spectra recorded in $CDCl_3$ are reported in parts per million (ppm) relative to Me_4Si (0.0 ppm) while those recorded in DMSO-d_6 or DMSO-d_6-benzene-d_6 (1:1) are reported in parts per million (ppm) relative to the solvent residual peak (2.49 ppm) and are reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened), coupling constant in Hz, integration. Chemical shifts (δ) for ^{13}C spectra are reported in ppm relative to $CDCl_3$ (δ 77.0, central peak) or DMSO-d_6 (δ 39.5, central peak).

2.2. General procedure for the reductive amination of E1, EA and DHEA

The steroid was dissolved in dry THF (approximately 0.1 mmol steroid/mL THF) and then an equivalent volume of 1,2-dichloroethane was added. To this was added 4 eq. of benzylamine or allylamine, 4 eq. glacial acetic acid and 2.5 eq. STAB-H. The mixture was stirred for 24–48 h. An equivalent volume of aq. saturated Na_2CO_3 was added and the mixture stirred for 10 min. Two volumes of EtOAc were added and the organic layer was obtained. The organic layer was washed with aq. saturated Na_2CO_3 (3×), water (10×) and then brine (1×). The organic layer was dried (Na_2SO_4), filtered and concentrated leaving a white solid. In the case of allylamine **7**, the crude product is >98% pure by ^{1}H and ^{13}C and no further purification was necessary for further manipulations. However, if highly pure **7** is desired, it can be subjected to silica gel flash chromatography using (5% MeOH/0.5% aq. NH_4OH/94.5% CH_2Cl_2 as eluent) (R_f = 0.25). In the case of benzylamines **4–6**, an impurity was often present which was identified by ^{1}H NMR as *N*-benzylacetamide. Careful silica gel chromatography (run by gravity, 40% EtOAc–60% benzene then 65% EtOAc–35% benzene) is required to remove this impurity (see Schemes 1 and 2 for the yields of **4**–**7**). *N*-benzylacetamide is slightly soluble in water and can also be removed by dissolving the crude material in EtOAc and washing extensively with water. Alternatively, the *N*-benzylacetamide impurity can be carried through the hydrogenolysis reaction as we found that it did not affect the hydrogenolysis and could be very easily removed by chromatography after the hydrogenolysis reaction.

2.3. 17β-Benzylamino-1,3,5(10)-estratrien-3-ol (*4*)

Prepared using the general procedure described above. White amorphous solid; R_f = 0.30 (5% MeOH/0.5% aq. NH_4OH/94.5% CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 0.81 (s, 3H), 1.17–1.58 (m, 7H), 1.65–1.76 (m, 1H), 1.79–1.90 (m, 1H), 2.01–2.30 (m, 4 H), 2.65–2.85 (m, 3H), 3.88 (AB system, overlapping dd, J = 14.0 Hz, 2H), 4.49 (bs, 2H), 6.49 (s, 1H), 6.57 (d, J = 8.3 Hz, 1H), 7.0 (d, J = 8.4 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR 154.0, 140.1, 138.0, 132.0, 128.5, 128.3, 127.1, 126.3, 115.6, 113.0, 68.1, 52.5, 52.3, 44.0, 43.2, 38.8, 38.1, 29.7, 29.4, 27.4, 26.5, 23.5, 12.0; LREIMS (70 eV, m/z): 361 (M^+, 100%), 270 (15%), 146 (94%), 91 (48%), HREIMS calcd. for $C_{25}H_{31}NO$ (M^+) 361.2406, found 361.2408.

2.4. 17β-Benzylamino-5α-androstan-3β-ol (*5*)

Prepared using the general procedure described above. White amorphous solid; R_f = 0.30 (5% MeOH/0.5% aq. NH_4OH/94.5% CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 0.65–2.05 (m, 24H), 0.71 (s, 3H), 0.79 (s, 3H), 2.54 (t, J = 8.2 Hz, 1H), 3.55 (m, 1H), 3.78 (AB system, overlapping dd, J = 14.0 Hz, 2H), 7.12–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 141.0, 128.3, 128.0, 126.8, 70.9, 68.2, 54.6, 53.3, 52.7, 45.0, 42.9, 38.2, 37.1, 35.6, 35.5, 31.9, 31.5, 29.6, 28.7, 23.8, 21.1, 12.4, 12.1; LREIMS (70 eV, m/z): 381 (M^+, 47%), 290 (12%), 146 (100%), 91 (20%); HREIMS calcd. for $C_{26}H_{39}NO$ (M^+), 381.3032, found 381.3039.

2.5. 17β-Benzylamino-3β-hydroxyandrost-5-ene (*6*)

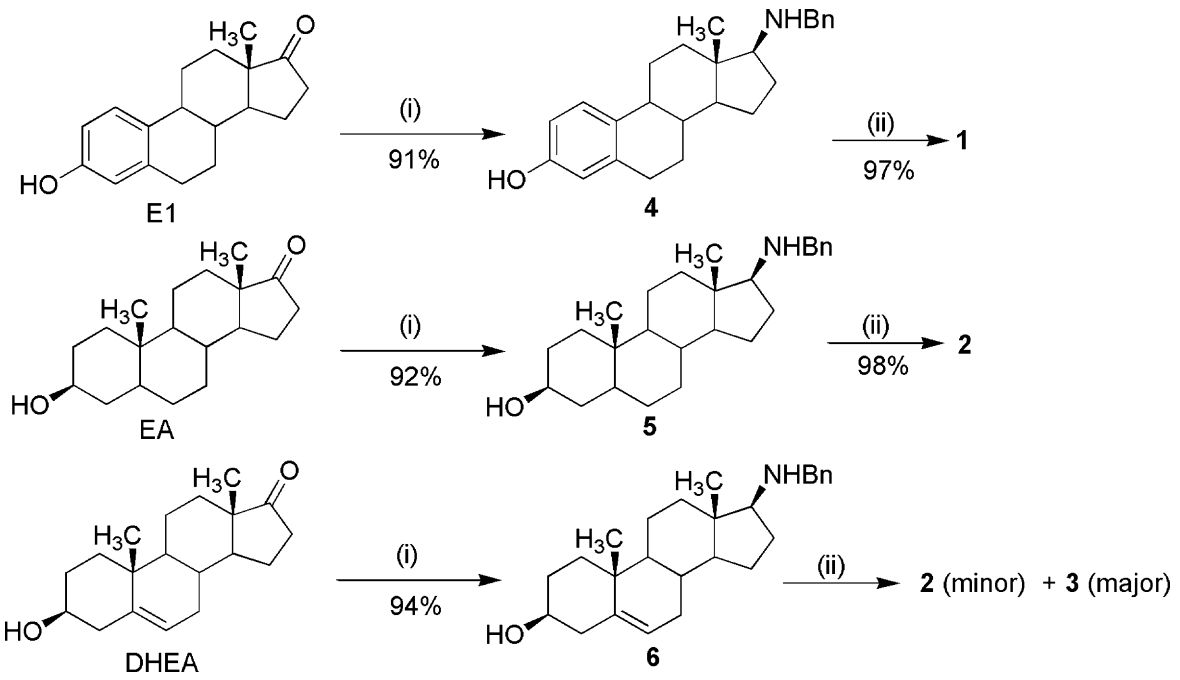
Prepared using the general procedure described above. White amorphous solid; R_f = 0.30 (5% MeOH/0.5% aq. NH_4OH/94.5% CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 0.74 (s, 3H), 1.00 (s, 3H), 0.65–1.63 (m, 13H), m (1.74–2.06 (m, 5H), 2.56 (t, J = 8.5 Hz, 1H), 3.41–3.52 (m, 1H), 3.79 (AB dd, J = 13.8 Hz, 2H)), 5.32 (d, J = 3.2 Hz, 1H), 7.15–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) 141.1, 140.8, 128.3, 128.0, 126.7, 121.5, 71.7, 68.1, 53.6, 52.7, 50.4, 42.6, 42.3, 38.0, 37.3, 36.6, 31.9, 31.7, 29.6, 23.9, 20.8, 19.4, 11.8; LR + ESIMS: 380.3 (M+H); HR + ESIMS calcd. for $C_{26}H_{38}NO$ (M+H), 380.2961, found 380.2953.

2.6. 17β-Allylamino-3β-hydroxyandrost-5-ene (*7*)

Prepared using the general procedure described above. White amorphous solid; R_f = 0.25 (5% MeOH/0.5% aq. NH_4OH/94.5% CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 0.67 (s, 3H), 0.96 (s, 3H), 0.7–1.60 (m, 12H), 1.71–2.01 (m, 6 H), 2.51 (t, J = 8.0 Hz, 1H), 3.21 (d, J = 5.6 Hz, 1H), 3.43 (m, 1H), 5.01 (d, J = 10.2 Hz, 1H), 5.10 (d, J = 17.1 Hz, 1H), 5.76–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$) 140.9, 137.3, 121.3, 115.6, 71.4, 68.2, 53.5, 51.4, 50.3, 42.5, 42.3, 37.9, 37.3, 36.5, 31.8, 31.6, 29.5, 23.8, 20.8, 19.4, 11.7; LREIMS (70 eV, m/z): 329 (M^+, 15%), 314 (100%), 96.1 (30%); HREIMS calcd. for $C_{22}H_{35}NO$ (M^+), 329.2719, found 329.2716.

2.7. General procedure for the hydrogenolysis of *4* and *5*

Compound **4** or **5** was added to absolute ethanol (approximately 15 mg **4** or **5** per mL of solvent) and heated gently with a heat gun until the steroid completely dissolved. The mixture was allowed to cool and then 10% Pd/C (13 wt%) was added and the flask fitted with a balloon filled with H_2 and the mixture was stirred for 24 h. The mixture was filtered through Celite and the filtrate concentrated to give a white solid. If any *N*-benzylacetamide was present



Scheme 1. *Reaction conditions*: (i) benzylamine, acetic acid, sodium triacetoxyborohydride, THF–$ClCH_2CH_2Cl$, rt, 24–48 h; (ii) H_2, cat. Pd/C, ethanol.

from the reductive amination it can be easily removed by subjecting the crude material to flash chromatography (10% MeOH/1.0% aq. NH_4OH/89.5% CH_2Cl_2 as eluent).

2.8. 17β-Amino-1,3,5(10)-estratrien-3-ol (*1*)

Prepared using the general procedure described above. White amorphous solid; R_f = 0.20 (10% MeOH/1.0% aq. NH_4OH/89.5% CH_2Cl_2); ^1H NMR (C_6D_6-DMSO-d_6, 1:1) 0.58 (s, 3H), 1.0-1.45 (m, 9H), 1.51–1.60 (m, 1H), 1.68–2.0 (m, 3H), 2.08 (bt, 1H), 2.20 (bd, 1H), 2.61 (t, *J* = 9.1 Hz, 1H), 2.65–2.90 (bs, 2H), 6.71 (s, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 9.23 (bs, 1H); ^{13}C NMR (C_6D_6-DMSO-d_6, 1:1) 155.3, 137.0, 130.4, 125.8, 115.1, 112.8, 62.5, 51.4, 43.6, 42.5, 38.9, 36.4, 30.9, 29.3,27.1, 26.1, 22.9, 10.7; LREIMS (70 eV, *m*/*z*): 271 (M^+, 100%), 254 (50%), 213 (42%); HR + ESIMS calcd. for $C_{18}H_{26}NO$ (M+H), 272.2012, found 272.2014.

2.9. 17β-Amino-5α-androstan-3β-ol (*2*)

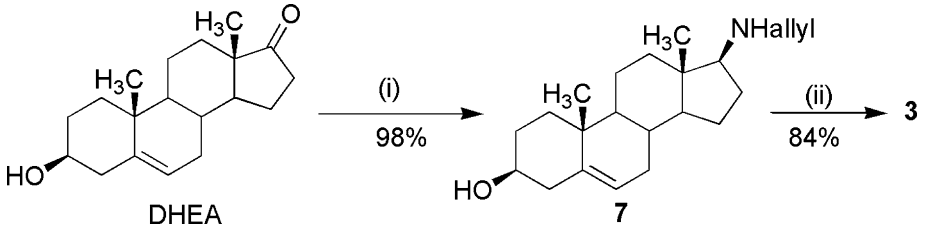
Prepared using the general procedure described above. White amorphous solid; R_f = 0.25 (10% MeOH/1.0% aq. NH_4OH/89.5% CH_2Cl_2); ^1H NMR ($CDCl_3$) 0.60 (s, 3H), 0.80 (s, 3H), 0.75–1.79 (m, 20H), 1.9–2.05 (m, 1H), 2.62 (d, *J* = 8.7 Hz, 1H), 3.50–3.62 (m, 1H); ^{13}C NMR ($CDCl_3$) 70.7, 62.8, 54.5, 53.0, 44.9, 42.6, 38.2, 37.0, 36.7, 35.7, 35.5, 31.8, 31.4, 31.2, 28.6, 23.5, 20.8, 12.3, 11.1; LREIMS (70 eV, *m*/*z*): 291 (M^+, 100%), 259 (20%); HREIMS calcd. for $C_{19}H_{33}NO$ (M^+) 291.2562, found 291.2567

2.10. 7β-Amino-3β-hydroxyandrost-5-ene (*3*)

A solution of compound **7** (180 mg, 0.54 mmol) in dry, degassed CH_2Cl_2 (2 mL) was added to a solution of dimethylbarbituric acid (254 mg, 1.64 mmol) and $Pd(Ph_3)_4$ (12 mg, 0.011 mmol) in dry, degassed CH_2Cl_2 (2 mL). The mixture was stirred for 3 h at 35 °C under Ar then CH_2Cl_2 (20 mL) was added and the mixture was washed with sat. Na_2CO_3, water and brine. The organic layer was dried (Na_2SO_4) and concentrated and the residue purified by flash chromatography (10% MeOH/1.0% aq. NH_4OH/89.5% CH_2Cl_2). White amorphous solid; R_f = 0.25 (10% MeOH/1.0% aq. NH_4OH/89.5% CH_2Cl_2); ^1H NMR ($CDCl_3$) 0.62 (s, 3H), 0.99 (s, 3H), 0.85–1.85 (m, 19H), 1.85–2.04 (m, 1H), 2.12–2.30 (m, 2H), 2.63 (t, *J* = 8.0 Hz, 1H), 3.40–3.54 (m, 1H), 5.3 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 140.9, 121.4, 71.5, 62.8, 53.3, 42.4, 42.3, 37.3, 36.6, 32.2, 31.6, 31.3, 23.6, 20.7, 19.4, 11.0; LREIMS (70 eV, *m*/*z*): 289 (M^+, 5%), 274 (100%), 239 (33%); HREIMS calcd. for $C_{19}H_{31}NO$ (M^+) 289.2406, found 289.2408.

3. Results and discussion

Our initial approach to compounds **1–3** was to perform a reductive amination of E1, EA or DHEA using $NaCNBH_3$ and ammonium acetate. Li et al. reported that 3-methoxy-17-β-amino-1,3,5(10)-estratrien could be obtained in high yield by reacting 3-methoxyestrone with 1.9 eq. $NaCNBH_3$ and 10 eq. ammonium acetate in THF–MeOH for 4 days [4]. However, the compound was never characterized or purified and the crude product was used for



Scheme 2. *Reaction conditions*: (i) allylamine, acetic acid, sodium triacetoxyborohydride, THF–$ClCH_2CH_2Cl$, rt, 24–48 h; (ii) 2,3-dimethylbarbituric acid, $Pd(PPh_3)_4$, CH_2Cl_2.

subsequent transformations. Nevertheless, we attempted to prepare compounds **1–3** using the same procedure with E1, EA and DHEA as substrates. Attempts using 100–200 mg of substrate gave compounds **1–3** as 17-α,β mixtures as determined by ^{1}H NMR and the reaction was very slow. Moreover, upon scale-up (2 g), other impurities appeared as determined by ^{1}H NMR especially with E1 as substrate.

Szendi et al. have reported the synthesis of the 17-acetamido derivatives of compounds **2** and **3** and the 17-acetamido derivative of the 3-methoxy analog of **1** via a reductive amination route [14]. In their procedure the 17-benzylimines of 3-methoxyestrone, EA and DHEA were first prepared by boiling 3-methoxyestrone, EA or DHEA in an excess of benzylamine (bp = 184 °C) for 6 h followed by removal of the excess benzylamine by distillation and drying of the resulting residue under high vacuum for several hours. The crude imines were reduced using 5 eq. $NaBH_4$ and then the resulting crude amines debenzylated by catalytic hydrogenation using H_2 and Pd/C to give **1–3**. Compounds **1–3** were not purified and no yield or characterization data was reported. Instead, the crude material was acetylated at N17 using Ac_2O/pyridine and the conclusion that the reduction of the imines to the amines gave exclusively the β-isomer appears to have been based on ^{1}H NMR analysis of the crude acetylated product. On the basis of these results we decided to prepare compounds **1–3** using a similar approach. However, we wished to avoid the prior preparation and isolation of the benzylimines and perform a one-pot reductive amination using benzylamine and a hydride source (Scheme 1). Although $NaCNBH_3$ has been widely used in reductive aminations, we elected to use sodium triacetoxyborohydride (STAB-H) as this has been shown to be a particularly effective reagent for performing reductive aminations [17]. Reductive aminations using STAB-H proceed best in 1,2-dichloroethane (DCE) though other solvents such as THF and to a lesser extent, DMF and acetonitrile, have been used [17]. We found E1, EA and DHEA to be almost completely insoluble in DCE. Consequently, we first attempted the reactions in THF, in which they are readily soluble, using 4.0 eq. benzylamine and 2.5 eq. STAB-H. Unfortunately, the reactions were slow and after 4 days unreacted starting material was still present. However, when the reactions were performed in a 1:1 mixture of THF–DCE they were complete within 24–48 h. After aq. workup and chromatography the pure 17β-benzylamines **4–6** were isolated in a 91–94% yield. Compounds **4**–**6** were subjected to hydrogenolysis using 15 wt% of 10% Pd/C under an atmosphere of H_2 (balloon) for 16 h. This gave crude **1** and **2** in yields of 97–98%. Although Szendi et al. report the preparation of **3** by hydrogenolysis of **6** using H_2–Pd/C we found that these conditions resulted in some reduction of the double bond and we were unable to develop conditions that gave pure **3** from **6** [14]. Therefore, allylamine **7** was prepared in 98% yield using the reductive amination approach and the allyl group was then removed in good yield using dimethylbarbituric acid and cat. $Pd(PPh_3)_4$ (Scheme 2).

Lemini et al. have performed a detailed analysis of the ^{1}H NMR spectra of **1** and its α-epimer [10]. They have shown that in a 1:1 mixture of C_6D_6:DMSO-d_6 the 17-α proton of **1** appears as a triplet at approximately 2.6 ppm, whereas the 17-β-proton of the α-epimer of **1** appears as a doublet at 3.05 ppm. The ^{1}H NMR spectrum of crude **1** from 2.4 to 3.1 ppm in a 1:1 mixture of C_6D_6:DMSO-d_6 is shown in Fig. 2. The triplet for the 17-α proton of **1** at 2.6 is clearly evident as are the benzylic protons attached to C-6 which appear as a broad singlet from 2.7 to 2.8 ppm. No doublet corresponding to the 17-β-proton of the α-epimer of **1** is evident indicating that **1** was obtained as its β-epimer and that the reductive amination of E1 using benzylamine and STAB-H gave exclusively the β-epimer of **4**. The ^{1}H and ^{13}C NMR's of **2–7** are also consistent with exclusive formation of the β-isomer (see supplementary data).

In summary, a facile and efficient approach to the synthesis of 17β-amino-1,3,5(10)-estratrien-3-ol (**1**), 17β-amino-5α-androstan-3β-ol (**2**) and, 17β-amino-3β-hydroxyandrost-5-ene (**3**) was developed using a reductive amination approach. We anticipate that this approach will be very useful in the synthesis of 17-amino steroid derivatives.

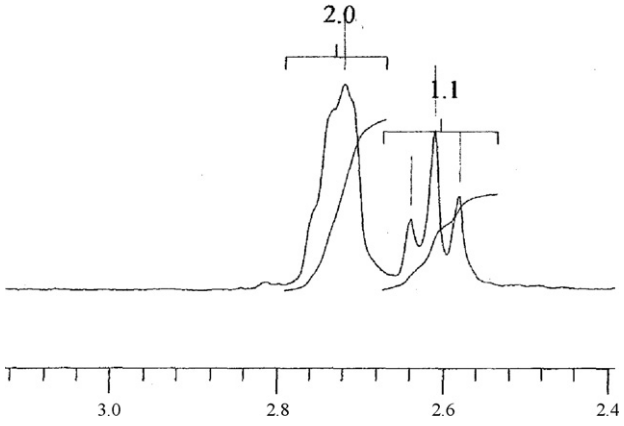


Fig. 2. ^{1}H NMR of crude **1** from 2.4 to 3.2 ppm in a 1:1 mixture of C_6D_6:DMSO-d_6.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for support of this work through a Discovery Grant to SDT.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.steroids.2011.04.013.

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