A Practical and Facile Route for the Preparation of 18-Norandrostan-17-ones from Androstan-17-ones Using SmI_2-Promoted Cyclization and Dehydroxylation

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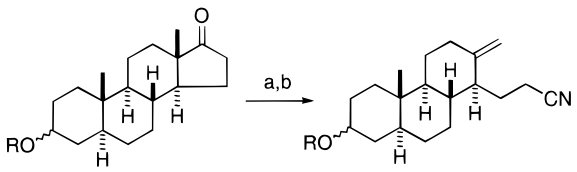
Because of their utility in biological research, significant effort has been made to develop synthetic routes to 18-norsteroids.[1] Although previous routes to 18-nor-17-ketosteroids have been published,[2] there remains a need for a more efficient and practical route for the laboratory-scale synthesis of these steroids from commercially available 17-ketosteroid precursors. Herein, we report a novel synthetic route that satisfies this need. The route has been applied to the synthesis of the C-13 epimers of (3α,5α)- and (3*β*,5α)-3-hydroxy-18-norandrostan-17-ones (**14**−**17**).

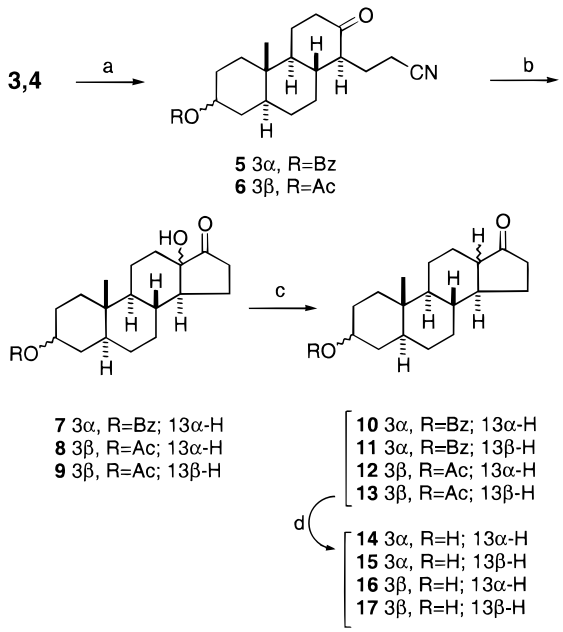
A significant drawback to the "abnormal" Beckmann rearrangement route to 18-nor-17-ketosteroids, which proceeds via alkene-nitrile rearrangement products (e.g., **3** and **4**, Scheme 1), has been the lengthy reaction sequence required for the reconstruction of the 18-norandrostan-17-one D-ring.[2h] Realizing that products **3** and **4** are readily converted into ketone-nitriles **5** and **6**, this drawback can be obviated by application of newly developed intramolecular ketone-nitrile reductive coupling reactions.[3−6] SmI_2 effects intramolecular ketone-nitrile reductive coupling reactions to give α-hydroxyketones and can also reduce these products to their corresponding ketones.[7,8] Hence, these two SmI_2-promoted reactions make possible an expeditious route from abnormal Beckmann rearrangement products to 18-nor-17-ketosteroids.

Scheme 1[a]



[a] Conditions: (a) $NH_2OH{\cdot}HCl$/NaOAc, reflux in EtOH, 2 h; (b) DCC-DMSO/CF_3CO_2H, rt, overnight.

Scheme 2[a]



[a] Conditions: (a) O_3/Me_2S, −78 °C, 91% for **5** and 86% for **6**; (b) SmI_2/BuOH-*t*, irradiation, 0−10 °C, 3 h, 79% for **7** and 66% for **8**/**9**; (c) SmI_2/MeOH, rt, 10 min, 93% for **10**/**11** and 91% for **12**/**13**; (d) NaOH(aq)/MeOH, rt, 2 h, 98% for **14**/**15** and 96% for **16**/**17**.

Accordingly, the commercially available (3α,5α)-3-(benzoyloxy)androstan-17-one 17-oxime (**1**) and (3*β*,5α)-3-(acetyloxy)androstan-17-one 17-oxime (**2**) were converted into their corresponding alkene-nitriles **3** and **4**, respectively (Scheme 1).[2e,2h] As shown in Scheme 2, ozonolysis of compounds **3** and **4** at −78 °C yielded ketone-nitriles **5** (91%) and **6** (86%), respectively. Following the general procedure of Molander,[7c] compound **5** or **6** was combined with SmI_2 in THF and irradiated with a 500-W lamp. Typically, the reductive coupling reactions finished in ∼3 h at 0−10 °C. Under these

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conditions, ketone-nitrile **5** gave only α-hydroxyketone product **7** in 79% yield. The 13*β*-hydroxy epimer of compound **7** was not found. By contrast, ketone-nitrile **6** gave a mixture (65%) of the epimeric α-hydroxyketone products **8** and **9** in a ratio of 7:1 (α:*β*).

Dehydroxylation of isolated α-hydroxyketone **7** was achieved in 93% yield using SmI_2 in THF at room temperature for 10 min. The dehydroxylation product was an epimeric mixture of the 13α-H product **10** and the 13*β*-H product **11** in a ratio of 5:4. Similarly, dehydroxylation of α-hydroxyketone **8** or **9**, or the mixture of these compounds, gave a mixture of products **12** (13α-H) and **13** (13*β*-H) in excellent yield (91%). These epimeric products are expected because the SmI_2-promoted reduction of α-hydroxyketones proceeds via an enolic intermediate.[8a] The epimeric products **10**/**11** and **12**/**13** are separated easily by chromatography.

As expected, saponification of either the pure 13α-H epimer **10** or the pure 13*β*-H epimer **11** with aqueous NaOH solution in methanol at room temperature gave, in high yield (98%), a mixture of epimerization products **14** (13α-H) and **15** (13*β*-H). Similarly, either ester **12** or ester **13** upon saponification gave a mixture of epimerization products **16** (13α-H) and **17** (13*β*-H). Whereas for characterization purposes we separated the epimeric products formed during the dehydroxylation and saponification steps, there is no practical advantage to separating the epimers formed after the dehydroxylation step. Hence, these two steps can be conveniently combined in a one-pot reaction, as described in the Experimental Section.

The stereochemistry for the C,D-ring fusion at C-13 in 18-norsteroids is generally assigned on the basis of NMR spectroscopic data. For compounds **8** and **14**, we used single crystal X-ray diffraction analysis to establish unambiguously the structures of these compounds (see Supporting Information). The structures of compounds **9**−**13** and **15**−**17** were based on the crystallographic results obtained for compounds **8** and **14**. The fact that enolization of the 18-nor-17-ketosteroids prepared herein always gave the 13α-H epimers as the major products indicates that the *cis*-C,D-ring fusion is more stable than the *trans*-C,D-ring fusion. This conclusion is in agreement with literature data on the stability of fused rings of this type.[9]

In summary, a practical method for the laboratory-scale preparation of 18-nor-17-ketosteroids from 17-ketosteroids has been developed. The reaction sequence proceeds via ozonolysis of an abnormal Beckmann rearrangement product followed by SmI_2-promoted intramolecular ketone-nitrile reductive coupling and dehydroxylation reactions. The synthetic route features accessible starting materials, a short reaction sequence, simple procedures, and high overall yields (51−62%).

Experimental Section

The ^{1}H NMR spectra were recorded on a Bruker ACF-500 spectrometer with TMS as the internal reference. The *J* values are given in hertz. The MS spectra were obtained on a ZAB-HS mass spectrometer with 70 eV. Steroids **3** and **4** were prepared according to a standard procedure for performing the abnormal Beckmann rearrangement on steroid 17-oximes.[2e]

[1*S*-(1α,4a*β*,4bα,7*β*,8a*β*,10aα)]-7-(Benzoyloxy)tetradecahydro-4b-methyl-2-oxo-1-phenanthrenepropanenitrile (5). Ozone was passed through a solution of compound **3** (11.0 g, 28.1 mmol) in methanol (180 mL) and dichloromethane (20 mL) at −78 °C until a blue color persisted. The excess ozone was removed by a stream of oxygen. After dimethyl sulfide (10.4 mL, 140.5 mmol) was added, the mixture was allowed to warm to room temperature and was stirred for 1 h. The solvent was removed to give a residue, which was purified by chromatography [silica gel, 20% EtOAc in petroleum ether (60−90 °C)] to yield 10.1 g (91%) of compound **5** as a colorless oil: IR 2230, 1705 cm^{-1}; ^{1}H NMR *δ* 8.08 (d, *J* = 7.3, 2H), 7.58 (t, *J* = 7.3, 1H), 7.48 (t, *J* = 7.3, 2H), 5.32 (d, *J* = 2.6, 1H), 0.81 (s, 3H); MS *m*/*z* (%) 393 (M$^+$, 0.2), 105 (100). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.57; H, 7.90; N, 3.62.

[1*S*-(1α,4a*β*,4bα,7α,8a*β*,10aα)]-7-(Acetyloxy)tetradecahydro-4b-methyl-2-oxo-1-phenanthrenepropanenitrile (6). Compound **6** was obtained as white crystals in 86% yield (3.47 g) from compound **4**[10] (4.0 g, 12.2 mmol) using the above-described ozonolysis procedure: mp 99.5−101 °C [from EtOAc/petroleum ether (60−90 °C)], lit.[10] mp 95 °C; IR 2280, 1731, 1700 cm^{-1}; ^{1}H NMR *δ* 4.72 (m, 1H), 2.05 (s, 3H), 0.78 (s, 3H); MS *m*/*z* (%) 331 (M$^+$, 2.1), 43 (100). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.48; H, 8.82; N, 4.23. Found: C, 72.48; H, 8.78; N, 4.29.

(3α,5α,13α)-3-(Benzoyloxy)-13-hydroxy-18-norandrostan-17-one (7). To a slurry of Sm powder (1.5 g, 10.0 mmol) was added a solution of I_2 (1.48 g, 6.0 mmol) in THF (60 mL) by syringe under Ar. The resultant slurry was stirred at room temperature for 2 h. After a dark blue SmI_2 solution was formed, the mixture was cooled to 0 °C, and a solution of compound **5** (786 mg, 2.0 mmol) and *tert*-butyl alcohol (296 mg, 4.0 mmol) in THF (20 mL) was added. The reaction mixture was irradiated with a lamp (500 W) at 0−10 °C for 3 h and monitored by TLC. The excess Sm was filtered off, and most of the solvent was removed. Then 3% aqueous HCl (100 mL) was added, and the solution was extracted with CH_2Cl_2. The combined organic layers were washed successively with 5% aqueous $NaHCO_3$ and H_2O and dried over Na_2SO_4. The solvent was removed to give a residue that was purified by chromatography [silica gel, 15% EtOAc in petroleum ether (60−90 °C)] to yield compound **7** (626 mg, 79%) as colorless crystals: mp 148.5−150 °C (Et_2O/petroleum ether); IR 3400, 1738, 1707 cm^{-1}; ^{1}H NMR *δ* 8.06 (d, *J* = 7.5, 2H), 7.57 (t, *J* = 7.5, 1H), 7.47 (t, *J* = 7.5, 2H), 5.28 (s, 1H), 2.48 (m, 1H), 0.69 (s, 3H); MS *m*/*z* (%) 396 (M$^+$, 47.9), 256 (50.4), 105 (100). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.67; H, 8.33.

(3*β*,5α,13α)-3-(Acetyloxy)-13-hydroxy-18-norandrostan-17-one (8) and (3*β*,5α,13*β*)-3-(Acetyloxy)-13-hydroxy-18-norandrostan-17-one (9). Compounds **8** and **9** as a mixture were obtained in 66% yield from compound **6** (662 mg, 2.0 mmol) using the procedure reported for the preparation of compound **7**. The products were separated by chromatography [silica gel, 15% EtOAc in petroleum ether (60−90 °C)] to give the 13α-hydroxy epimer **8** (348 mg, 57%) and the 13*β*-hydroxy epimer **9** (59 mg, 9%).

Compound **8**: mp 121−123 °C (from Et_2O/petroleum ether); IR 3315, 1724 cm^{-1}; ^{1}H NMR *δ* 4.68 (m, 1H), 2.44 (m, 1H), 2.01 (s, 3H), 0.66 (s, 3H); MS *m*/*z* (%) 334 (M$^+$, 100), 278 (48.9), 222 (42.7). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.83; H, 9.04. Found: C, 71.89; H, 9.02.

Compound **9**: mp 162−164 °C (from Et_2O/petroleum ether); IR 3455, 1718 cm^{-1}; ^{1}H NMR *δ* 4.68 (1H, m), 2.53 (dd, *J* = 8.6 and 19.4, 1H), 2.01 (s, 3H), 0.84 (s, 3H); MS *m*/*z* (%) 334 (M$^+$, 100), 278 (42.3), 274 (50.4), 256 (72.3). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.83; H, 9.04. Found: C, 72.06; H, 9.16.

(3α,5α,13α)-3-(Benzoyloxy)-18-norandrostan-17-one (10) and (3α,5α,13*β*)-3-(Benzoyloxy)-18-norandrostan-17-one (11). To a slurry of Sm powder (600 mg, 4.0 mmol) was added a solution of I_2 (762 mg, 3.0 mmol) in THF (30 mL) by syringe under Ar. The resultant slurry was stirred at room temperature for 2 h. The resultant dark blue SmI_2 solution was treated with a solution of compound **7** (393 mg, 1.0 mmol) and anhydrous MeOH (2.0 mL) in THF (10 mL). After 10 min at room temperature, the reaction solution was poured into saturated

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aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with H_2O and dried over Na_2SO_4. The solvent was removed to give a residue that was purified and separated by chromatography [silica gel, 5% Et_2O in petroleum ether (60−90 °C)] to give compounds **10** and **11** (93%) as a mixture in a ratio of 5:4.

Compound **10** (52%): mp 125−127 °C (from petroleum ether); IR 1728, 1705 cm^{-1}; ^1H NMR δ 8.06 (d, J = 7.5, 2H), 7.57 (t, J = 7.5, 1H), 7.46 (t, J = 7.5, 2H), 5.28 (s, 1H), 0.69 (s, 3H); MS m/z (%) 258 (100), 243 (31.9), 105 (36.5). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.92; H, 8.48. Found: C, 79.21; H, 8.29.

Compound **11** (41%): mp 43−46 °C (foam); IR 1732, 1701 cm^{-1}; ^1H NMR δ 8.05 (d, J = 7.5, 2H), 7.54 (t, J = 7.5, 1H), 7.46 (t, J = 7.5, 2H), 5.29 (s, 1H), 2.38 (dd, J = 8.5 and 18.6, 1H), 0.83 (s, 3H); MS m/z (%) 258 (100), 243 (39.0), 105 (93.4). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.92; H, 8.48. Found: C, 78.95; H, 8.66.

(3*β*,5α,13α)-3-(Acetyloxy)-18-norandrostan-17-one (12) and (3*β*,5α,13*β*)-3-(Acetyloxy)-18-norandrostan-17-one (13). Compounds **12** and **13** were obtained as a mixture in 91% yield from the mixture of **8** and **9** (334 mg) by the same procedure used to prepare compounds **10** and **11**. They were separated by chromatography [silica gel, 5% Et_2O in petroleum ether (60−90 °C)].

Compound **12** (56%): mp 100−103 °C (from petroleum ether), lit.[2e] mp 104−105 °C.

Compound **13** (35%): mp 145−147 °C (from petroleum ether), lit.[2e] mp 147−149 °C.

(3α,5α,13α)-3-Hydroxy-18-norandrostan-17-one (14) and (3α,5α,13*β*)-3-Hydroxy-18-norandrostan-17-one (15). A stirred solution of epimers **10** and **11** (380 mg, 1.0 mmol) in MeOH (20 mL) was treated with a solution of NaOH (500 mg) in water (1.0 mL) at room temperature for 2 h. The solution was neutralized with 2 N aqueous HCl. The product mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed to give a residue that was purified and separated by chromatography [silica gel, 25% EtOAc in petroleum ether (60−90 °C)] to give compounds **14** and **15** (270 mg, 98%).

Compound **14** (58%): mp 168−170 °C (Et_2O/petroleum ether); IR 3455, 1720 cm^{-1}; ^1H NMR δ 4.04 (d, 1H, J = 1.7), 0.63 (s, 3H); MS m/z (%) 276 (M^+, 44.0), 258 (36.5), 243 (41.6), 41 (100). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.22; H, 10.21. Found: C, 77.99; H, 10.08.

Compound **15** (40%): mp 158−160 °C (Et_2O/petroleum ether); IR 3465, 1720 cm^{-1}; ^1H NMR δ 4.05 (d, 1H, J = 2.3), 2.36 (dd, J = 8.9 and 18.9, 1H), 0.76 (s, 3H); MS m/z (%) 276 (M^+, 100), 258 (50.4), 243 (65.0). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.22; H, 10.21. Found: C, 78.35; H, 10.17.

(3*β*,5α,13α)-3-Hydroxy-18-norandrostan-17-one (16) and (3*β*,5α,13*β*)-3-Hydroxy-18-norandrostan-17-one (17). Compounds **16** and **17** (530 mg, 96.0%) were obtained from a mixture of compounds **12** and **13** (636 mg, 2.0 mmol) by the same procedure used for the preparation of compounds **14** and **15**. The products were separated by chromatography [silica gel, 25% EtOAc in petroleum ether (60−90 °C)].

Compound **16** (58%): mp 169−171 °C (Et_2O/petroleum ether); IR 1721 cm^{-1}; ^1H NMR δ 3.59 (m, 1H), 0.66 (s, 3H); MS m/z (%) 276 (M^+, 100), 258 (14.9), 243 (20.5). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.22; H, 10.21. Found: C, 78.47; H, 9.98.

Compound **17** (38%): mp 152−155 °C (Et_2O/petroleum ether); IR 3430, 1735 cm^{-1}; ^1H NMR δ 3.61 (m, 1H), 2.36 (dd, J = 8.3 and 18.5, 1H), 0.80 (s, 3H); MS m/z (%) 276 (M, 100), 258 (23.7), 243 (25.7). Anal. Calcd $C_{18}H_{28}O_2$: C, 78.22; H, 10.21. Found: C, 78.01; H, 10.25.

One-Pot Procedure for Dehydroxylation and Saponification. After the Sm-promoted dehydroxylation of **9** was complete (10 min) as described by the above procedure, a saturated aqueous solution of $NaHCO_3$ (1 mL) was added to quench the reaction, followed by MeOH (10 mL) and NaOH (1.0 g) dissolved in water (2.0 mL). The mixture was stirred for 2 h at room temperature (monitored by TLC) and neutralized with 2 N aqueous HCl. The product mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed to give crude compounds **14** and **15** as a mixture, which was separated and characterized by the previously described procedure.

Similarly, a mixture of compounds **10** and **11** was dehydroxylated and saponified in a one-pot procedure to give compounds **16** and **17**.

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Supporting Information Available: ORTEP diagrams for compounds **8** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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