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Abnormal Beckmann fragmentation/ring closing metathesis route for preparation of 18-nor- $\Delta^{13(17)}$ -androgens and their 18-nor-13,17-epoxide derivatives

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Abstract

The synthesis of $\Delta^{13(17)}$ -androgens and the structurally related 13,17-epoxides is described. The synthetic route involves cleavage of 17-ketosteroids by an abnormal Beckmann rearrangement, modification of the D-ring cleavage product to obtain an intermediate tricyclic diene and ring closing metathesis of the diene to the $\Delta^{13(17)}$ -androgen. (3 α ,5 α)-Androst-13(17)-en-3-ol and the derivative 13 α ,17 α - and 13 β ,17 β -epoxides were prepared by this route.

Keywords

olefin metathesis; 18-nor- $\Delta^{13(17)}$ -steroids; 18-nor-13; 17-epoxysteroids; abnormal Beckmann rearrangement; neurosteroids

The modification of 3 α -hydroxysteroids has attracted considerable attention from medicinal and synthetic organic chemists because many compounds in both the androgen and pregnane series are potent modulators of ion channels in the central nervous system of animals.^{1–5} For example, spiroepoxide **1** (Figure 1) potently enhances the actions of γ -aminobutyric acid (GABA) at type-A GABA (GABA_A) receptors and is a general anesthetic in mice.⁶ However, neither the 16 α ,17 α - nor the 16 β ,17 β -epoxides **2a** and **2b**, respectively, are as potent modulators of GABA_A receptors as spiroepoxide **1**.⁶

The actions of the 13 α ,17 α - and 13 β ,17 β -epoxides (**3a** and **3b**) have not been described and, to our knowledge, synthetic routes to 13,17-epoxysteroids are not reported in the literature. To evaluate GABA_A receptor actions of these compounds, a synthetic route for their preparation that proceeds through the intermediate $\Delta^{13(17)}$ -steroid was developed. The retrosynthetic analysis shown in Scheme 1 utilizes alkene-nitrile **6**, obtained from an abnormal Beckmann rearrangement of the oxime of the corresponding 17-ketosteroid, as a precursor for the diene intermediate **5**. Ring closure *via* a ring closing metathesis reaction gives regiospecifically the

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Supplementary data

Supplementary data associated with this article includes procedures for the preparation of compounds **3a,3b,4,5,6,7,9,10** and can be found in the online version. ⁷

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$\Delta^{13(17)}$ -steroid **4**, and peracid oxidation of the double bond yields the desired epoxides **3a** and **3b**.

Thus, the commercially available (3 β ,5 α)-3-hydroxyandrostane-17-one was converted into (3 α ,5 α)-3-(benzoyloxy)androstane-17-one (**9**, 92% yield) by a Mitsunobu reaction (Scheme 2).⁷ Using a standard method, oxime **10** was obtained in 98% yield by treating steroid **9** with H₂NOH·HCl and NaOAc. The required alkene-nitrile **6** was conveniently synthesized from oxime **10** in 83% yield using a recently reported method (TFA, CH(OMe)₃, THF) that minimizes production of the lactam product of the Beckmann rearrangement.⁸ Due to the presence of TFA employed in this method, neutralization with 10% Na₂CO₃ during workup to avoid isomerization of the exocyclic double bond to the 12,13 and 13,14 positions in the secosteroid C-ring is crucial. Treatment of carbonitrile **6** with DIBALH at -78 °C yielded carboxaldehyde **7** in 85% yield.⁹ A Wittig reaction employing Ph₃P⁺MeBr⁻/KOBU^t in dry THF in the usual manner provided diene **5** in 70% yield.¹⁰ Ring closure of diene **5** was carried out using a second generation Grubbs' catalyst.^{11,12} The $\Delta^{13(17)}$ -steroid **4** was obtained in nearly quantitative yield (98%) under mild conditions and with a short reaction time.¹³ Epoxidation of steroid **4** in dry benzene using *m*CPBA at room temperature gave a mixture of 13,17-epoxides **3a** and **3b** which was easily purified by chromatography to yield the less polar 13 β ,17 β -epoxide (**3b**) and the more polar 13 α ,17 α -epoxide (**3a**) (4.8:1, 87% in total yield)^{14,15}. The overall yield for the synthesis of the epoxides was 38%.

The stereochemistry for the 13,17-epoxide products was established by single crystal X-ray diffraction analysis of steroid **3b** (Figure 2).¹⁶ Preliminary biological evaluation of epoxide **3b** indicates that the actions of this epoxide at GABA_A receptors are weak. As expected, based on previous structure–activity studies of epoxide **2a**,⁶ epoxide **3a** has little, if any, effect on GABA_A receptor function. Full pharmacological details will be included in a larger study that includes biological data for additional analogues and will be reported elsewhere.

In summary, a general and practical method for the preparation of 18-nor- $\Delta^{13(17)}$ -steroids has been developed. The sequence features the use of an abnormal Beckmann rearrangement/ring closing metathesis reaction sequence to obtain an 18-nor- $\Delta^{13(17)}$ -steroid. Isomeric 18-nor- Δ^{12} -steroids and 18-nor- Δ^{13} -steroids are not formed. The synthetic method was used to extend structure–activity studies of neurosteroid modulators of GABA_A receptors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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7. Experimental procedures are available online as supplementary data.
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9. Data for 7: oil; $[\alpha]_D^{20} = -24.58$ (c 0.86, CHCl_3); IR 3401, 3080, 2718, 1722, 1643 cm^{-1} ; ^1H NMR δ 9.71 (t, $J = 1.2$ Hz, 1H), 4.67 (s, 1H), 4.41 (s, 1H), 3.97 (m, 1H), 0.63 (s, 3H); ^{13}C NMR δ 202.74, 150.60, 104.69, 66.06, 53.17, 47.63, 42.04, 41.92, 38.25, 36.82, 36.18, 35.47, 31.95, 31.51, 28.72, 28.25, 27.14, 19.26, 10.90. Anal. Calcd for $\text{C}_{19}\text{H}_{30}\text{O}_2$: C, 78.57; H, 10.41. Found: C, 78.70; H, 10.24.
10. Data for 5: oil; $[\alpha]_D^{20} = -34.52$ (c 0.17, CHCl_3); IR 3350, 3078, 1641, 1445, 1005 cm^{-1} ; ^1H NMR δ 5.82 (m, 1H), 5.02 (m, 2H), 4.72 (s, 1H), 4.55 (s, 1H), 4.03 (m, 1H), 0.70 (s, 3H); ^{13}C NMR δ 151.35, 139.34, 113.82, 104.60, 66.36, 53.43, 47.87, 41.89, 38.46, 37.08, 36.32, 35.64, 32.07, 31.72, 30.61, 28.88, 28.47, 27.26, 26.68, 11.00. Anal. Calcd for $\text{C}_{20}\text{H}_{32}\text{O}$: C, 83.27; H, 11.18. Found: C, 83.14; H, 11.20.
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13. Data for 4: white solid; mp 118–120 °C (EtOAc/hexanes), $[\alpha]_D^{20} = -18.9$ (c 0.50, CHCl_3); IR 3435, 1635, 1444, 1014 cm^{-1} ; ^1H NMR δ 5.21 (s, 1H), 4.04 (m, 1H), 0.71 (s, 3H); ^{13}C NMR δ 146.04, 119.95, 66.67, 52.77, 52.44, 45.67, 38.86, 36.40, 36.07, 32.61, 32.47, 31.50, 29.73, 29.14, 28.65, 28.52, 25.87, 11.33. Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}$: C, 83.02; H, 10.84. Found: C, 83.07; H, 10.79.
14. Data for 3b: colorless crystals; mp 170–172 °C (from EtOAc/hexanes); $[\alpha]_D^{20} = -17.4$ (c 0.34, CHCl_3); IR 3421, 3335, 1456, 1434, 896 cm^{-1} ; ^1H NMR δ 4.05 (m, 1H), 3.41 (s, 1H), 0.78 (s, 3H); ^{13}C NMR δ 68.10, 66.29, 62.54, 52.69, 46.75, 39.47, 38.73, 36.19, 35.78, 32.25, 32.00, 28.89, 28.72, 28.18, 27.29, 23.56, 22.85, 11.14. Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_2$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.12.
15. Data for 3a: white solid; mp 144–146 °C (from EtOAc/hexanes); $[\alpha]_D^{20} = -45.7$ (c 0.54, CHCl_3); IR 3434, 1445, 1432, 731 cm^{-1} ; ^1H NMR δ 4.06 (m, 1H), 3.24 (s, 1H), 0.72 (s, 3H); ^{13}C NMR δ 68.85, 66.67, 63.72, 51.91, 46.92, 39.33, 38.86, 36.52, 36.00, 32.86, 32.41, 29.22, 28.99, 28.63, 26.64, 24.48, 23.54, 11.31. Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_2$: C, 78.21; H, 10.21. Found: C, 77.94; H, 10.00.
16. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 612073. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-330633 or email: deposit@ccdc.cam.ac.uk].

Figure 1.
Structures of known (**1,2a,2b**) neurosteroid modulators of GABA_A receptors and the previously unknown modulators (**3a,3b**) prepared herein.

Figure 2.
Crystal structure shown with 50% thermal ellipsoids of one of two unique forms of epoxide **3b**.¹⁶

Scheme 1.

Retrosynthetic analysis for the synthesis of epoxides **3a** and **3b**.

Scheme 2.

Reagents and conditions: (a) BzOH, Ph₃P, DEAD, THF, room temperature, 12 h, 92%; (b) H₂NOH·HCl, NaOAc, EtOH, reflux, 12 h, 98%; (c) TFA, CH(OMe)₃, THF, N₂, 60 °C, 2 h, 83%; (d) DIBALH, N₂, CH₂Cl₂, -78°C, 1 h, 85%; (e) Ph₃P⁺MeBr⁻, KOBu^t, THF, room temperature, 60 min, 70%; (f) Grubbs' catalyst 2nd generation, CH₂Cl₂, N₂, 45°C, 1 h, 98%; g. *m*CPBA, benzene, room temperature, 30 min, 87% (**3a**, 72%; **3b**, 15%). Total yield of the synthetic route is 38%.