Neurosteroid Analogues. 7. A Synthetic Route for the Conversion of 5*β*-Methyl-3-ketosteroids into 7(*S*)-Methyl-Substituted Analogues of Neuroactive Benz[*e*]indenes

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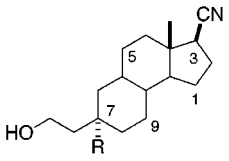
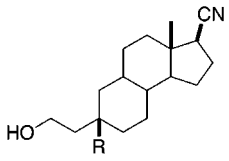
We previously reported that benz[*e*]indenes **1** and **2** enhance the actions of the inhibitory neurotransmitter *γ*-aminobutyric acid (GABA) at $GABA_A$ receptors.[1−7] Because of this pharmacological action, the compounds are of interest as lead compounds for identifying new drug candidates with anticonvulsant, sedative-hypnotic, and anesthetic activities. Conceptually, compounds **1** and **2** are accessible from 19-norsteroids by breaking the A-ring between C-2 and C-3 and then removing C-1 and C-2. Indeed, we have prepared benz[*e*]indene **1** from (5α,17*β*)-17-hydroxyestran-3-one by this route (ozonolysis of a Δ^2-enol derivative followed by removal of C-1 and C-2).[3,8]



1: R = H
3: R = Me



2: R = H
4: R = Me

Benz[*e*]indene **2** could not be similarly prepared from (5*β*,17*β*)-17-hydroxyestran-3-one by this method because the preferred direction of enolization of the 3-keto group is toward C-4.[9] Instead, this compound was prepared by total synthesis.[4] However, this route is not optimal since a tedious separation of C-7 epimers (benz[*e*]indene numbering system[10]) is required at a late stage of the synthesis.

Continuation of our pharmacological studies has required us to prepare benz[*e*]indene **4** by a route that does not require separation from the diastereomeric benz[*e*]-indene **3**. We report here a new route from a 5*β*-methyl-19-norsteroid precursor that accomplishes this goal. The route (Scheme 1) utilizes commercially available 19-nortestosterone (**5**) as a starting material and gives the desired product in 12 steps with an overall yield of 7.6%.

Results and Discussion

The 1,4-addition of CH_3MgX to Δ^4-3-ketosteroids in the presence of copper salts is known to yield exclusively 5*β*-methyl-3-ketosteroids in high yield.[11,12] Accordingly, CH_3-MgI was reacted in the presence of $Cu(OAc)_2$ with 19-nortestosterone (**5**) to yield steroid **6** in 81% yield. Bromination of compound **6** with Br_2 followed by dehydrobromination using $CaCO_3$ in refluxing dimethylacetamide gave the Δ^1-3-ketosteroid **8** as the major product. A minor product assigned as structure **7** on the basis of it's ^{1}H NMR spectrum [*δ* 7.06 (1H, dd, J = 10.2, 6.0 Hz), 6.09 (1H, d, J = 10.2 Hz), 5.17 (1H, s)] was converted into steroid **8** when reduced with Zn dust in AcOH. The overall yield for the conversion of steroid **6** into product **8** was 84%. Oxidation of steroid **8** with PDC gave product **9** in 97% yield.

The cleavage of the A-ring of steroid **9** into a compound that was readily converted into benz[*e*]indene **11** in high yield was unexpectedly difficult. A variety of methods were investigated for this purpose. These methods included the following: (1) epoxidation of the double bond followed by ring opening using the Tanabe-Eschenmoser rearrangement;[13,14] (2) OsO_4−$Ba(ClO_3)_2$ oxidation;[15] and (3) ozonolysis. While it was possible to cleave the A-ring using any of these methods, only the ozonolysis method gave a product, which could be expeditiously converted into benz[*e*]indene **11**. Ozonolysis of steroid **9** in CH_2Cl_2 containing AcOH, followed by reduction of the initial ozonolysis products with Zn dust in AcOH gave a complex mixture of carboxylic acid products. Treatment of these products with CH_2N_2 gave a mixture of methyl esters that was separated by flash column chromatography. The components of this mixture that were isolated included the expected aldehyde **10a** (28%), the diester **10b** [14%, characterized only by ^{1}H NMR *δ* 3.67 (3H, s), 3.65 (3H,s)], and benz[*e*]indene **11** (4%). The formation of compound **11** was unexpected, and the structure of the oxidized intermediate that gives rise to this minor product was not determined. Aldehyde **10a** is an unstable oil that readily rearranges to multiple products. For this reason, it was characterized spectroscopically and then immediately decarbonylated using Wilkinson's catalyst in

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(10) In addition to the different numbering system for steroids and benz[*e*]indenes, the nomenclature used for the assignment of the α and *β* stereodescriptors for benz[*e*]indenes and steroids is also different. For benz[*e*]indenes, the α-side of the reference plane is that side on which the preferred substituent lies at the lowest-numbered stereogenic position. See *Chemical Abstracts Index Guide-Appendix IV*; American Chemical Society: Washington, DC, 1994; ¶203, pp 195I−196I.
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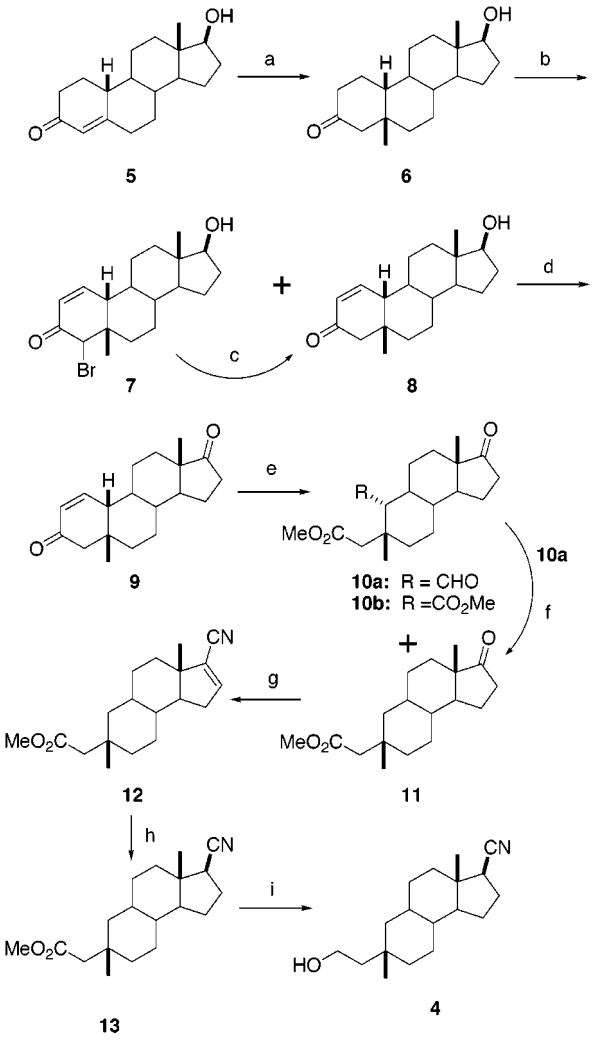
Scheme 1[a]



[a] Reagents (a) CH_3MgI, $Cu(OAc)_2{\cdot}H_2O$; (b) (1) Br_2, $CHCl_3$; (2) $CaCO_3$, dimethylacetamide, reflux; (c) Zn, AcOH; (d) PDC, CH_2Cl_2; (e) (1) O_3, CH_2Cl_2, AcOH, −40 to −45 °C; (2) Zn, AcOH; (3) CH_2N_2; (f) $[(Ph)_3P]_3RhCl$, benzonitrile, reflux; (g) (1) KCN, AcOH; (2) $POCl_3$, pyridine; (h) 10% Pd/C, EtOAc; (i) $LiBH_4$, THF, 50 °C.

refluxing benzonitrile to obtain benz[*e*]indene **11** (84% yield). The total yield of compound **11** obtained from steroid **9** by this ozonolysis-decarbonylation sequence was 27%.

The remaining steps in the conversion of compound **11** into benz[*e*]indene **4** are straightforward. Compound **11** was first converted into an α-cyanohydrin using KCN in AcOH and the product was immediately dehydrated to the α,β-unsaturated nitrile **12** (overall yield 49%). Catalytic hydrogenation (10% Pd/C) of compound **12** followed by selective reduction of the methyl ester group with $LiBH_4$ in THF gave the required benz[*e*]indene **4** (87% yield for the two steps combined). Preliminary experiments have shown that benz[*e*]indene **4** potentiates $GABA_A$ receptors and causes anesthesia in mice when injected intravenously through the tail vein. Details of the pharmacological profile of benz[*e*]indene **4** will be published elsewhere.

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were recorded at ambient temperature at 300 MHz (^{1}H) or 75 MHz (^{13}C). IR spectra were recorded as films for liquids or KBr disks for solids. Elemental analyses were carried out by M−H−W Laboratories, Phoenix, AZ. Solvents were used either as purchased or dried and purified by standard methodology. Organic extracts were dried over anhydrous Na_2SO_4. Column chromatography was performed using silica gel (32−63 microns) purchased from Scientific Adsorbents, Atlanta, GA. The 19-nortestosterone was purchased from Steraloids, Inc., Newport, RI.

(5β,17β)-17-Hydroxy-5-methylestran-3-one (6). CH_3MgI (34.0 mL, 3.0 M solution in EtOEt, 102.0 mmol) was added to a stirred THF (400 mL) solution containing 19-nortestosterone (**5**, 11.05 g, 40.2 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (812 mg, 4.07 mmol) at 0 °C for 1.5 h under N_2. After addition, the ice bath was removed, and the resulting mixture was stirred at room temperature overnight. Saturated aqueous NH_4Cl (200 mL) was added to quench the reaction at 0 °C. The reaction mixture was extracted with EtOAc, which was washed with water, brine and dried. After solvent removal, the crude product was purified by column chromatography (silica gel eluted with 20% EtOAc in hexanes) to give product **6** (9.47 g, 81%) as a colorless solid: mp 158−160 °C (lit.[16] mp 157.5−159.5 °C; lit.[12] mp 160−162 °C); IR (KBr) 3406, 2949, 2914, 2840, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.68 (1H, t, J = 8.4 Hz), 2.71 (1H, d, J = 14.4 Hz), 0.95 (3H, s), 0.77 (3H, s); ^{13}C NMR ($CDCl_3$) δ 213.48, 81.89, 50.15, 48.12, 45.48, 42.82, 41.35, 39.88, 39.56, 38.94, 36.63, 36.21, 30.44, 29.23, 26.49, 25.81, 23.03, 22.73, 10.91. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.68, H, 10.23.

(5β,17β)-17-Hydroxy-5-methylestr-1-en-3-one (8). Br_2 (0.8 M in $CHCl_3$, 8.85 mL, 7.08 mmol) was added dropwise during 1.5 h at room temperature to a solution of ketone **6** (2.06 g, 7.08 mmol) in $CHCl_3$ (70 mL). The solution was stirred further for 12 h and then diluted with EtOAc (400 mL), washed successively with saturated aqueous $NaHCO_3$, water, and brine, and dried. After solvent removal, the residue was dissolved in dimethylacetamide (10 mL), added during 20 min to boiling dimethylacetamide (50 mL) containing $CaCO_3$ (2.15 g, 21.5 mmol), and refluxed for 0.5 h. Following filtration and solvent removal, the residue was extracted with EtOAc. The extract was washed successively with water and brine and dried. After solvent removal, the residue was purified by column chromatography (silica gel eluted with 20% EtOAc in hexanes) to give pure enone **8** (1.07 g) and a mixture of products **7** and **8** (794 mg).

The mixture of products **7** and **8** (794 mg) was stirred with Zn dust (410 mg, 6.27 mmol) in AcOH (9 mL) at room temperature for 2 h and then poured into 100 mL saturated aqueous $NaHCO_3$ (100 mL). After extraction with EtOAc, washing of the extract with water and brine, and drying, the EtOAc was removed and the residue purified by column chromatography (silica gel eluted with 15% acetone in hexanes) to give enone **8** (638 mg).

The total amount of product **8** obtained as a colorless solid was 1.71 g (84%): mp 140−142 °C; IR (KBr) 3529, 2956, 2915, 2853, 1664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.07 (1H, dd, J = 10.2, 6.0 Hz), 5.98 (1H, d, J = 10.2 Hz), 3.65 (1H, t, J = 8.4 Hz), 2.76 (1H, d, J = 17.1 Hz), 0.99 (3H, s), 0.79 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.53, 153.76, 127.90, 81.80, 49.46, 48.92, 46.69, 45.01, 42.99, 40.84, 38.89, 36.42, 36.12, 30.18, 28.70, 26.45, 26.21, 23.02, 10.95. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.30, H, 9.59.

(5β)-5-Methylestr-1-ene-3,17-dione (9). Enone **8** (961 mg, 3.33 mmol) was oxidized by mixing with PDC (2.43 g, 6.46 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 16 h and diluted with EtOEt (500 mL). The organic layer was washed with water (5 × 70 mL) and brine and dried. After solvent removal, the residue was purified by column chromatography (silica gel eluted with 15% EtOAc in hexanes) to give compound **9** (926 mg, 97%) as a white solid: mp 155−156 °C; IR (KBr) 2922, 1738, 1670, 1449, 1249, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.08 (1H, dd, J = 10.2, 6.3 Hz), 5.99 (1H, d, J = 10.2 Hz), 2.77 (1H, d, J = 17.1 Hz), 2.46 (1H, dd, J = 18.6, 8.7 Hz), 1.02 (3H, s), 0.92 (3H, s); ^{13}C NMR ($CDCl_3$) δ 220.63, 199.90, 152.94, 127.90, 49.62, 48.50, 47.44, 46.38, 44.74, 40.02, 38.51, 35.92, 35.31, 31.09, 28.45, 25.83, 25.28, 21.26, 13.47. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.77, H, 9.21.

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[3a*S*-(3aα,5a*β*,6*β*,7*β*,9aα,9b*β*)]-6-Formyl-3a,7-dimethyldodecahydro-3-oxo-1*H*- benz[*e*]indene-7-acetic Acid Methyl Ester (10a). Ozone was bubbled into a solution of enone **9** (241 mg, 0.84 mmol) in CH_2Cl_2 (60 mL) and AcOH (0.3 mL) at −40 to −45 °C until TLC showed that the enone **9** was no longer present. The excess ozone was discharged with a stream of oxygen. After solvent removal at room temperature, the residue was dissolved in AcOH (6 mL) and mixed with zinc dust (200 mg, 3.06 mmol). The mixture was stirred at room temperature for 9 h and then extracted with EtOAc. The EtOAc was washed with water and brine and dried. After solvent removal, the residue was dissolved in EtOAc and methylated using an EtOEt solution of CH_2N_2. The products were purified by column chromatography (silica gel eluted with 10−20% EtOAc in hexanes) to give in order of elution: compound **11** (10 mg, 4%), compound **10b** (41 mg, 14%), and aldehyde **10a** (75 mg, 28%) as an unstable oil: ^{1}H NMR ($CDCl_3$) δ 9.68 (1H, d, J = 4.8 Hz), 3.66 (3H, s), 2.79 (1H, d, J = 13.5 Hz), 2.46 (1H, dd, J = 18.6, 7.8 Hz), 2.27 (1H, d, J = 13.5 Hz), 1.17 (3H), 0.88 (3H, s); ^{13}C NMR ($CDCl_3$) δ 220.52, 205.53, 171.93, 64.72, 51.32, 49.90, 47.82, 39.85, 38.82, 37.85, 37.12, 36.77, 35.36, 31.14, 27.65, 26.18, 24.75, 21.21, 13.66.

[3a*S*-(3aα,5a*β*,7*β*,9aα,9b*β*)]-3a,7-Dimethyldodecahydro-3-oxo-1*H*-benz[*e*]indene-7-acetic Acid Methyl Ester (11). The aldehyde **10a** (17 mg, 0.05 mmol) was decarbonylated by refluxing with $[(Ph)_3P]_3RhCl$ (77 mg, 0.08 mmol) in benzonitrile (3 mL) for 5 h. The precipitate was removed by filtration and the solvent was removed in vacuo. The residue was extracted with EtOAc and the extract was washed with water, brine and dried. After solvent removal, the residue was purified by column chromatography (silica gel eluted with 15% EtOAc in hexanes) to give product **11** (13 mg, 84%) as an oil: IR (film) 2922, 1732, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.65 (3H, s), 2.45 (1H, dd, J = 18.9, 8.4 Hz), 2.32 (2H, s), 1.03 (3H, s), 0.89 (3H, s); ^{13}C NMR ($CDCl_3$) δ 221.23, 172.97, 50.96, 50.11, 48.30, 44.43, 41.17, 40.70, 39.11, 37.39, 35.60, 33.72, 31.32, 29.68, 28.73, 25.45, 21.21, 13.69. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.74, H, 9.44.

[3a*S*-(3aα,5a*β*,7*β*,9aα,9b*β*)]-3-Cyano-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-3a,7-dimethyl-1H-benz[*e*]indene-7-acetic Acid Methyl Ester (12). Compound **11** (491 mg, 1.68 mmol) in EtOH (60 mL) was mixed with KCN (2.99 g, 45.9 mmol), and the flask was sealed with a rubber septa. AcOH (4 mL) was added via a syringe, and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with EtOEt (500 mL) and the EtOEt was washed with water, brine and dried. After solvent removal, the residue was mixed with pyridine (20 mL) and $POCl_3$ (0.8 mL, 8.58 mmol) and refluxed for 6 h under N_2. The reaction mixture was poured into 5 N HCl (80 mL) at 0 °C. The aqueous solution was extracted with EtOEt (4 × 150 mL), and the combined extracts were washed with water and brine and dried. After solvent removal, the residue was purified by column chromatography (silica gel eluted with 10−15% EtOAc in hexanes) to give recovered starting material **11** (76 mg) and product **12** (211 mg, 49%) as an oil: IR (film) 2915, 2212, 1732, 1589, 1456, 957 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.55 (1H, m), 3.57 (3H, s), 2.25 (2H, s), 0.95 (3H, s), 0.85 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.84, 147.20, 127.43, 115.73, 54.75, 50.90, 48.68, 44.31, 41.14, 39.61, 39.33, 37.30, 33.67, 32.17, 29.61, 28.86, 26.27, 16.19; HRMS FAB (*m/e*) calcd for $C_{19}H_{27}NO_2Li$ $(M + Li)^+$ 308.2202, found 308.2201.

[3*S*-(3α,3aα,5a*β*,7*β*,9aα,9b*β*)]-3a,7-Dimethyldodecahydro-7-(2-hydroxyethyl)-1*H*-benz[*e*]indene-3-carbonitrile (4). Compound **12** (259 mg, 0.86 mmol) was hydrogenated using 10% Pd/C (101 mg) catalyst in EtOAc (40 mL) containing AcOH (1.5 mL). The catalyst was removed by filtration, and the filtrate was diluted with EtOEt (300 mL). The EtOEt was washed with water and brine and dried. After solvent removal, crude product **13** (262 mg) was obtained. Compound **13** had: ^{1}H NMR ($CDCl_3$) δ 3.58 (3H, s), 2.24 (2H, s), 2.23 (1H, t, J = 9.6 Hz), 0.94 (3H, s), 0.86 (3H, s); ^{13}C NMR ($CDCl_3$) δ 173.09, 121.34, 53.05, 51.06, 44.99, 44.31, 41.58, 41.26, 40.12, 38.76, 37.59, 36.89, 33.72, 29.73, 29.11, 26.59, 26.37, 23.90, 14.28.

Product **13** (262 mg), without further purification, was reduced with $LiBH_4$ (2M solution in THF, 3.6 mL, 7.2 mmol) in THF (90 mL) at 50 °C for 40 h under N_2. The reaction mixture was quenched by addition of 10% HCl (12 mL) at 0 °C. Most of the THF was removed on a rotary evaporator, and the remaining aqueous residue was extracted with EtOEt. The EtOEt was washed with water and brine and dried. After solvent removal, the residue was purified by column chromatography (silica gel eluted with 20% EtOAc in hexanes) to give benz[*e*]indene **4** (207 mg, 87%): mp 113−115 °C; IR (KBr) 3501, 2915, 2246, 1450, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.64 (2H, t, J = 7.8 Hz), 2.30 (1H, t, J = 9.6 Hz), 0.92 (3H, s), 0.90 (3H, s); ^{13}C NMR ($CDCl_3$) δ 121.41, 59.34, 53.14, 45.01, 44.43, 41.67, 40.11, 38.86, 38.57, 37.89, 36.94, 32.47, 29.85, 29.23, 26.48, 26.36, 23.90, 14.28; Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.53; H, 10.49; N, 5.22.

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