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Synthesis of (17*R*)- and (17*S*)-17-hydroxy-14, 15-secoandrost-4-en-15-yn-3-one and the X-ray crystal structure of the (17*S*)-diastereomer

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(17R,S)-17-Hydroxy-14,15-secoandrost-4-en-15-yn-3-one has been shown previously to be a mechanism-based inactivator of rat liver 3α-hydroxysteroid dehydrogenase. This manuscript describes the synthesis of this diastereomeric 14,15-secosteroid from [2S-(2α,4aα,4bβ,10aβ)]-1,2,3,4a,4b,7,9,10,10a-decahydro-2,4b-dimethyl-7-oxo-2-phenanthrenecarboxylic acid methyl ester. The separation of this diastereomeric 14,15-secosteroid into (17R)- and (17S)-17-hydroxy-14,15-secoandrost-4-en-15-yn-3-one was accomplished by HPLC separation of the (S)-1-[(4-methylphenyl)sulphonyl]-2-pyrrolidinecarboxylate derivatives on a silica column. The crystal structure of (17S)-17-hydroxy-14,15-secoandrost-4-en-15-yn-3-one was then solved by X-ray diffraction analysis to establish unambiguously the absolute configuration of the diastereomeric 14,15-secosteroid. (Steroids **60**: 491–496, 1995)

Keywords: 14,15-secosteroids; hydroxysteroid dehydrogenase inhibitors; chiral resolution; X-ray structure analysis

Introduction

We previously reported the synthesis of (3*R,S*)-1,10-seco-5α-estr-1-yne-3,17β-diol as potential mechanism-based inhibitors of 3α- and 3β-hydroxysteroid dehydrogenases.[1] A recent study utilizing this compound in combination with site-directed mutagenesis to probe steroid hormone recognition by rat liver 3α-hydroxysteroid dehydrogenase has demonstrated that this compound is a mechanism-based inactivator of this enzyme.[2] As part of the same study of rat liver 3α-hydroxysteroid dehydrogenase, the ability of (17*R,S*)-17-hydroxy-14,15-secoandrost-4-en-15-yn-3-one to undergo backwards binding and also function as a mechanism-based inactivator of the enzyme also was demonstrated. In this paper we describe the synthesis of (17*R,S*)-17-hydroxy-14,15-secoandrost-4-en-15-yn-3-one, a method for the separation of the compound into its diastereomeric components, and the results of an X-ray diffraction analysis of the (17*S*)-diastereomer.

Experimental

General methods

All melting points were determined with a capillary melting point apparatus and are uncorrected. NMR spectra were recorded at ambient temperature in $CDCl_3$ (unless noted otherwise) with a 5 mm probe on either a Varian Gemini-300 operating at 300 MHz (^1H) or 75 MHz (^{13}C). For ^1H NMR and ^{13}C NMR spectra; the internal references were TMS (δ 0.00), $CDCl_3$(δ 77.00), respectively. IR spectra were recorded as films on an NaCl plate with a Perkin-Elmer 1710 FT-IR spectrophotometer. High resolution mass spectroscopic data were recorded using a VGZAB-SE double-focusing mass spectrometer. X-ray diffraction analysis was performed on a fee for service basis in the X-Ray Crystallography Facility of the Department of Chemistry, Washington University. The diffraction data was collected using a Siemens P4 diffractometer. The structure was solved by direct methods using the program Siemens SHELXTL PLUS. Elemental analyses were carried out by M-H-W Laboratories (Phoenix, AZ) or by Galbraith Laboratories (Knoxville, TN). Solvents were used either as purchased or dried and purified by standard methodology. Flash chromatog-

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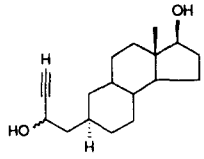

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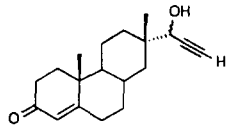


(17*R,S*)-17-Hydroxy-14,15-secoandrost-4-en-15-yn-3-one

Figure 1 Structures of mechanism-based inactivators of rat liver 3α-hydroxysteroid dehydrogenase.

raphy was performed using silica gel (32–63 microns) purchased from Scientific Adsorbants (Atlanta, GA).

[2S-(2α,4aα,4bβ,10aβ)]-1,2,3,4,4a,4b,5,6,7,9,10,10a-Dodecahydro-2,4b-dimethyl-7-oxo-2-phenanthrenecarboxylic acid methyl ester (2).

A solution of [2*S*-(2α,4aα,4bβ,10aβ)]-1,2,3,4,4a,4b,7,9,10,10a-decahydro-2,4b-dimethyl-7-oxo-2-phenanthrenecarboxylic acid methyl ester[3] (**1**, 5.0 g, 17.3 mmol) and Wilkinson's catalyst (2.4 g, 2.6 mmol) in benzene (150 mL) was shaken under an atmosphere of hydrogen (20 psi) at room temperature. After 1.5 h (monitored by TLC), the mixture was filtered and washed with benzene (3 × 50 mL). The solvent was removed to give a brown oil, which was purified by chromatography (silica gel, 40% EtOAc in hexane) to yield compound **2** (4.6 g, 92%) as a yellowish solid. The analytical sample was obtained as white crystals by a secondary chromatography (silica gel, 40% EtOAc in hexane) followed by sublimation (80–105°C/0.3 mm Hg), m.p. 67–68.5°C. IR: 1727, 1674, 1618, 1230, 1110 cm^{-1}. ^1H NMR: δ 5.75 (s, 1H, =CH), 3.68 (s, 3H, OCH_3), 1.25 (s, 3H, CH_3), 1.18 (s, 3H, CH_3). Analysis calculated for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.84; H, 9.00.

[4'aR-(4'aα,4'bβ,7'β,8'aα)]-3',4',4'a,4'b,5',6',7',8',8'a,9'-Decahydro-4'a,7'-dimethylspiro[1,3-dioxolane-2,2'(1'H)-phenanthrene]-7'-carboxylic acid methyl ester containing [4'aR-(4'aα,4'bβ,7'β,8'aα)]-4',4'a,4'b,5',6',7',8',8'a,9',10'-Decahydro-4'a,7'-dimethylspiro[1,3-dioxolane-2,2'(3'H)-phenanthrene]-7'-carboxylic acid methyl ester (3).

A mixture of compound **2** (7.1 g, 24.6 mmol), ethylene glycol (15 mL, 270 mmol) and TsOH (490 mg, 2.6 mmol) in benzene (170 mL) was refluxed for 19 h with azeotropic removal of water. After it was cooled to room temperature, K_2CO_3 (10 g) was added and the mixture was stirred for another 30 min. Then it was filtered and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed to give a yellowish sticky solid, which was purified by chromatography (neutral alumina, 10% EtOAc in hexane) to provide compound **3** (5.0 g, 74%) as white crystals, m.p. 99–102°C (from aqueous pyridine) and 1.4 g (17%) of **2** was recovered. IR: 1728, 1246, 1192, 1142, 1105, 1079, 1025, 991 cm^{-1}. ^1H NMR: δ 5.34 (dd, J = 5.0 Hz, J = 2.0 Hz, 0.75H, =CH of $\Delta^{10'}$ isomer), 5.25 (s, 0.25H, =CH of $\Delta^{1'(10'a)}$ isomer), 4.01–3.91 (m, 4H, OCH_2CH_2O), 3.67 (s, 0.75 × 3H, OCH_3 of $\Delta^{10'}$ isomer), 3.66 (s, 0.25 × 3H, OCH_3 of $\Delta^{1'(10'a)}$ isomer), 1.22 (s, 3H, CH_3), 1.01 (s, 3H, CH_3). Analysis calculated for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.81; H, 9.14.

4'aR-(4'aα,4'bβ,7'β,8'aα)]-3',4',4'a,4'b,5',6',7',8',8'a,9'-Decahydro-4'a,7'-dimethylspiro[1,3-dioxolane-2,2'(1'H)-phenanthrene]-7'-methanol containing [4'aR-(4'aα,4'bβ,7'β,8'aα)]-4',4'a,4'b,5',6',7',8',8'a,9',10'-Decahydro-4'a,7'-dimethylspiro[1,3-dioxolane-2,2'(3'H)-phenanthrene]-7'-methanol (4).

To a stirred suspension of lithium aluminum hydride (1.0 g, 26.4 mmol) in dry THF (100 mL) was added a solution of compound **3** (5.2 g, 15.6 mmol) in dry THF (50 mL) within 3 min at 0°C. After 14 h at room temperature (monitored by TLC), the reaction was quenched by addition of ethanol (10 mL) and 15% aqueous NaOH (15 mL). The mixture was stirred for 1 h and filtered. The organic layer was dried over Na_2SO_4 and the solvent was removed to give compound **4** (4.5 g, 96%) as a white solid. Crystallization of a portion of the product from aqueous pyridine gave a solid, m.p. 124–126°C. IR: 3435, 1662, 1461, 1365, 1140, 1100, 1069, 1043 cm^{-1}. ^1H NMR: δ 5.35 (d, J = 3.3 Hz, 0.75H, =CH of $\Delta^{10'}$ isomer), 5.25 (s, 0.25H, =CH of $\Delta^{1'(10'a)}$ isomer) 4.00–3.90 (m, 4H, OCH_2CH_2O), 3.27 (s, 2H, CH_2OH), 1.02 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). Exact mass calcd for $C_{19}H_{30}O_3$: 306.4492; Found: 306.2192.

[4'aR-(4'aα,4'bβ,7'β,8'aα)]-3',4',4'a,4'b,5',6',7',8',8'a,9'-Decahydro-4'a,7'-dimethylspiro[1,3-dioxolane-2,2'(1'H)-phenanthrene]-7'-carboxaldehyde (5).

To a stirred suspension of pyridinium chlorochromate (2.5 g, 11.6 mmol) and pyridine (2 mL) in dry dichloromethane (15 mL) was added a solution of compound **4** (1.2 g, 3.8 mmol) in dichloromethane (10 mL) at room temperature. After the mixture was stirred for another 2 h (monitored by TLC), it was diluted with ether (250 mL), and celite (5 g) was added. The mixture was filtered and washed with ether. The solvent was removed to provide a brown solid which was purified by chromatography (silica gel, 20% EtOAc in hexane) to given compound **5** (1.0 g, 87%) as white crystals, m.p. 115–117°C. IR: 2706, 1722, 1247, 1202, 1138, 1107, 1099, 1068, 1034, 1023, 989, 955, 946, 894, 860, 812 cm^{-1}. ^1H NMR: δ 9.41 (s, 1H, CHO), 5.36 (d, J = 5.0 Hz, 1H, =CH), 3.98–3.93 (m, 4H, OCH_2CH_2O), 1.12 (s, 3H, CH_3), 1.03 (s, 3H, CH_3). ^{13}C NMR: δ 206.17 (CHO), 139.76 (C=), 121.61 (C=), 109.21 (O-C-O), 64.35 and 64.16 (OCH_2CH_2O), 18.86 (CH_3), 16.81 (CH_3), 48.86, 45.92, 41.63, 38.30, 36.46, 35.76, 33.46, 30.85, 30.61, 26.90, 19.54. Analysis calculated for $C_{19}H_{28}O_3$: C, 74.76; H, 9.27. Found: C, 75.00; H, 9.22.

(17R,S)-17-Hydroxy-15-trimethylsilyl-14,15-secoandrost-5-en-15-yn-3-one cyclic 3-(1,2-ethanediyl acetal) (6).

To a stirred solution of (trimethylsilyl)acetylene (1.3 mL, 9.2 mmol) in dry THF was added a solution of *n*-BuLi in hexane (2.5 M, 2.5 mL, 6.3 mmol) within 5 min at −78°C under nitrogen. The temperature of the reaction was allowed to warm to 0°C for 15 min and cooled to −78°C again. Then a solution of compound **5** (1.25 g, 4.1 mmol) in dry THF (10 mL) was added dropwise over 10 min. The mixture was stirred for another 2 h at room temperature and quenched with saturated aqueous NH_4Cl (2 mL) at 0°C. Ether (150 mL) was added and the organic layer was separated and washed with brine (2 × 50 mL). After drying over Na_2SO_4, the solvent was removed to give a solid which was purified by chro-

matography (silica gel, 15% EtOAc in hexane) to yield product **6** (1.4 g, 87%) as a white solid, m.p. 166–180°C. IR: 3469, 2168, 1250, 1138, 1100, 1024, 844, 760 cm^{-1}. ^1H NMR: δ 5.36 (d, J = 4.5 Hz, 1H, =CH), 4.00–3.92 (m, 5H, *CH*OH and OCH_2CH_2O), 1.02 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.17 (s, 9H, $SiMe_3$). Analysis calculated for $C_{24}H_{38}O_3Si$: C, 71.59; H, 9.51. Found: C, 71.38; H, 9.46.

(17R,S)-17-Hydroxy-14,15-secoandrost-4-en-15-yn-3-one (7).

To a stirred solution of compound **6** (341 mg, 0.85 mmol) in MeOH (25 mL) was added a pellet of KOH (53 mg) followed by addition of THF (10 mL) at room temperature under nitrogen. After 8 h, concentrated HCl (0.1 mL) was added and the solution was concentrated on a rotary evaporator. The residue was diluted with THF (20 mL), H_2O (2 mL), and concentrated HCl (4 mL). The mixture was stirred for another 70 min (monitored by TLC) and then ether (100 mL) was added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (3 × 25 mL) and dried over $MgSO_4$. Removal of the solvent give an oil, which was purified by chromatography (silica gel, 30% EtOAc in hexane) to yield compound **7** (227 mg, 93%) as a white solid. Analysis calculated for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.66; H, 9.14.

14,15-Secoandrost-4-en-15-yne-3,17-dione (8).

To a stirred solution of compound **7** (100 mg, 0.35 mmol) in acetone (50 mL) was added Jones reagent (8N, 0.3 mL) at 5°C. After 15 min, 2-propanol (1 mL) was added to destroy any excess reagent and EtOAc (50 mL) and H_2O (50 mL) were added. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed to give a solid which was passed through a small column (silica gel, EtOAc) and then was recrystallized from Et_2O-hexane to give compound **8** (86.5 mg, 87%) as white crystals, m.p. 106–107.5°C. IR: 3235, 2932, 2087, 1671, 1616, 1464, 1381, 1273 cm^{-1}. ^1H NMR: δ 5.75 (s, 1H =CH), 3.30 (s, 1H, HC≡), 1.27 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). ^{13}C NMR: δ 199.32 (CO), 193.15 (CO), 170.51 (=C), 124.03 (=C), 80.46 (C≡), 79.42 (C≡), 52.60, 47.65, 39.85, 38.34, 35.25, 34.11, 33.72, 32.67, 32.37, 31.40, 20.11, 19.05, 17.53. Analysis calculated for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.40; H, 8.48.

1-[(4-Methylphenyl)sulfonyl]-L-proline (17R)-3-oxo-14,15-secoandrost-4-en-15-yn-17-yl ester (9) and 1-[(4-Methylphenyl)sulfonyl]-L-proline (17S)-3-oxo-14,15-secoandrost-4-en-15-yn-17-yl ester (10).

A solution of compound **7** (95 mg, 0.33 mmol), (*S*)-1-[(4-methylphenyl)sulphonyl]-2-pyrrolidinecarbonyl chloride (143 mg, 0.5 mmol) and pyridine (0.5 mL) in dichloromethane (10 mL) was stirred at room temperature for 2 h. The mixture was then diluted with dichloromethane (50 mL) and washed with 2N aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), and dried over Na_2SO_4. Removal of the solvent yielded an oil, which was purified by chromatography (silica gel, 30% EtOAc in hexane) to give 119 mg (67%) of a mixture of **9** and **10** as an oil. Separation of the mixtures was accomplished by HPLC using an Alltech Econosil silica column (250 mm × 10 mm) eluted with 30% EtOAc in hexane (3.0 mL/min).

Compound **9** (45 mg, 25%) was obtained as an oil. IR: 3276, 2931, 2120, 1754, 1667, 1616, 1599, 1347, 1159, 733, 666, 589, 548 cm^{-1}. ^1H NMR: δ 7.77 (d, J = 8.2 Hz, 2H, ArH), 7.32 (d, J = 8.1 Hz, 2H, ArH), 5.74 (s, 1H, =CH), 5.13 (s, 1H, OCH), 4.41 (t, J = 4.9 Hz, 1H, NCH), 3.45–3.43 (m, 1 diastereotopic H of NCH_2), 3.34–3.29 (m, 1 diastereotopic H of NCH_2), 2.46 (s, 1H, HC≡), 2.43 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.11 (s, 3H, CH_3). ^{13}C NMR: δ 199.32 (CO), 171.07 (COO), 170.95 (C=), 143.48 (ArC), 135.38 (ArC), 129.53 (2 × ArC), 127.40 (2 × ArC), 123.85 (C=), 78.81 (C≡), 74.85 (C≡), 73.11 (C-O), 21.43 (CH_3), 18.59 (CH_3), 17.54 (CH_3), 60.02, 52.97, 48.16, 40.41, 38.39, 37.74, 35.29, 34.31, 33.74, 32.77, 32.43, 31.59, 30.46, 24.59, 20.26.

Compound **10** (47 mg, 36%) was obtained as a solid, m.p. 138–140°C. IR: 3272, 2938, 2121, 1743, 1668, 1616, 1599, 1347, 1160, 733, 666, 589, 549 cm^{-1}. ^1H NMR: δ 7.74 (d, J = 7.7 Hz, 2H, ArH), 7.32 (d, J = 7.8 Hz, 2H, ArH), 5.74 (s, 1H, =CH), 5.09 (s, 1H, OCH), 4.29 (t, J = 4.9 Hz, 1H, NCH), 3.55–3.53 (m, 1 diastereotopic H of NCH_2), 3.26–3.24 (m, 1 diastereotopic H of NCH_2), 2.48 (s, 1H, HC≡), 2.43 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.13 (s, 3H, CH_3). ^{13}C NMR: δ 199.48 (CO), 171.13 (COO), 170.93 (C=), 143.51 (ArC), 135.02 (ArC), 129.64 (2 × ArC), 127.25 (2 × ArC), 123.87 (C=), 78.87 (C≡), 74.88 (C≡), 73.28 (C-O), 21.44 (CH_3), 18.53 (CH_3), 17.57 (CH_3), 60.75, 52.92, 48.30, 40.79, 38.40, 37.82, 35.26, 34.28, 33.76, 32.81, 32.70, 31.49, 30.91, 24.55, 20.46.

(17R)-17-Hydroxy-14,15-secoandrost-4-en-15-yn-3-one (11).

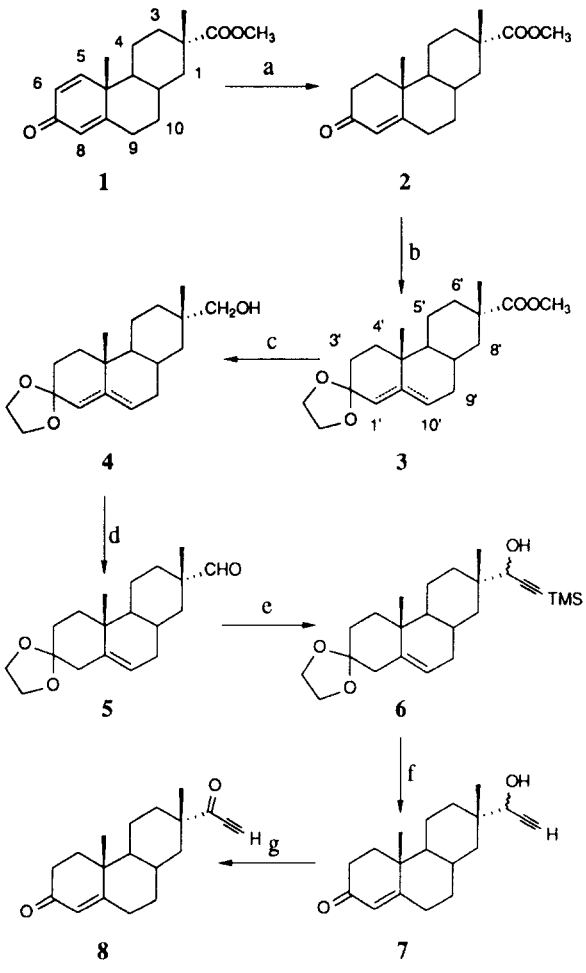
A solution of compound **9** (40 mg, 0.74 mmol) and NaOH (40 mg, 10 mmol) in MeOH (5 mL) was stirred for 3 h at room temperature under nitrogen and then was poured into a solution of 2N aqueous HCl (100 mL) at 0°C. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), and dried over Na_2SO_4. The solvent was removed to yield a solid, which was purified by chromatography (silica gel 30% EtOAc in hexane) to give compound **11** (15 mg, 70%) as white crystals, m.p. 188–189°C. IR: 3475, 3283, 2963, 2846, 2111, 1670, 1615 cm^{-1}. ^1H NMR: δ 5.75 (s, 1H, =CH), 3.97 (dd, J = 3.4 Hz, J = 2.0 Hz, 1H, OCH), 2.49 (s, 1H, HC≡), 1.18 (s, 3H, CH_3), 1.05 (s, 3H, CH_3). ^{13}C NMR: δ 199.73 (CO), 171.45 (C=), 123.83 (C=), 83.02 (C≡), 74.30 (C≡), 71.92 (C-O), 18.26 (CH_3), 17.60 (CH_3), 53.20, 40.56, 38.47, 38.27, 35.33, 34.46, 33.79, 32.90, 32.49, 31.73, 20.48. Analysis calculated for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.75; H, 9.16.

(17S)-17-Hydroxy-14,15-secoandrost-4-en-15-yn-3-one (12).

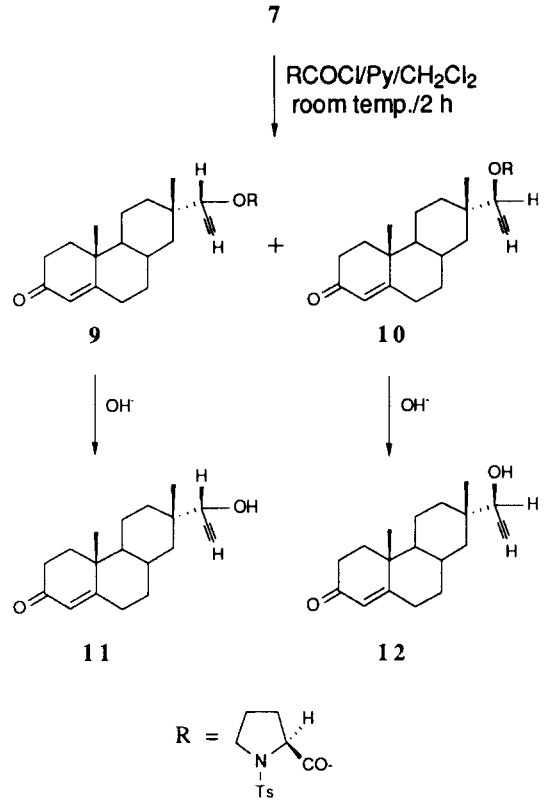
Using the procedure described immediately above, compound **10** (32 mg, 0.6 mmol) was hydrolyzed and purified by chromatography (silica gel, 50% EtOAc in hexane) to obtain compound **12** (10 mg, 59%) as white crystals, m.p. 223–224°C. IR: 3415, 3271, 2941, 2911, 2849, 2107, 1658, 1612 cm^{-1}. ^1H NMR: δ 5.75 (s, 1H, =CH), 3.97 (dd, J = 3.7 Hz, J = 2.1 Hz, 1H, OCH), 2.49 (s, 1H, HC≡), 1.18 (s, 3H, CH_3), 1.05 (s, 3H, CH_3). ^{13}C NMR: δ 199.72 (CO), 171.40 (C=), 123.88 (C=), 83.01 (C≡), 74.40 (C≡), 71.99 (C-O), 18.29 (CH_3), 17.62 (CH_3), 53.24, 40.38, 38.49, 38.31, 35.37, 34.47, 33.83, 32.92, 32.72, 31.69, 20.58. Analysis calculated for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.52; H, 8.97.

Results and discussion

Compound **1**, which was prepared by our previously published procedure,[3] was selectively hydrogenated in the presence of tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst[4] to yield enone **2** in 92% yield (Scheme 1). Compound **2** was reacted with ethylene glycol and a catalytic amount of TsOH to obtain ketal **3** in 74%



Scheme 1 (a) $H_2/(Ph_3P)_3RhCl$; (b) $HOCH_2CH_2OH/TsOH$; (c) $LiAlH_4$; (d) Pyridinium chlorochromate; (e) Lithium (trimethylsilyl)acetylide; (f) OH^- followed by H_3O^+; (g) Jones reagent.



Scheme 2

yield. Although ketal **3** appeared by thin-layer chromatography on silica gel to be a single substance, the NMR spectrum of the compound showed that it was a mixture of the $\Delta^{10'}$- and $\Delta^{1'(10'a)}$-2′-ketals. (The renumbering of the carbon atoms in the phenanthrene ring is necessitated by nomenclature rules requiring the 1,3-dioxolane ring to have priority over the phenanthrene ring). Compound **3** was then reduced to alcohol **4** with $LiAlH_4$ in 96% yield. NMR analysis showed that compound **4** was also obtained as an unresolved mixture of $\Delta^{10'}$- and $\Delta^{1'(10'a)}$-2′-ketals. Oxidation of compound **4** with pyridinium chlorochromate[5] gave aldehyde **5** (87% yield) as a single product containing only the $\Delta^{10'}$-2′-ketal group. The experimental factors responsible for the absence of the isomeric $\Delta^{1'(10')}$-2′-ketal compound in the product were not investigated. Compound **5** was reacted with lithium (trimethylsilyl)acetylide to obtain compound **6** as a mixture of diastereomers (87% yield). The trimethylsilyl group was then removed under basic conditions[6] and the ketal group was removed under acidic conditions in a one-pot reaction to yield compound **7** as a mixture of diastereomers (93% yield). Oxidation of **7** with

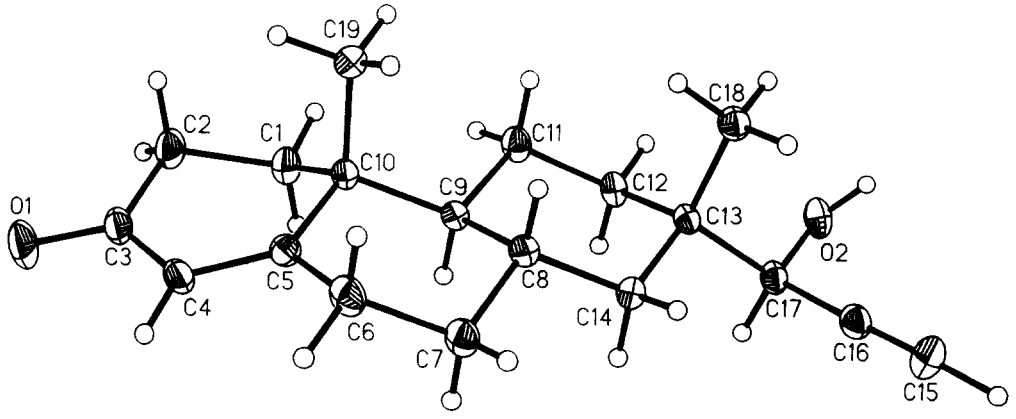


Figure 2 ORTEP drawing of (17*S*)-17-hydroxy-14,15-secoandrost-4-en-15-yn-3-one **(12)**.

Table 1 Crystal data, data collection, and refinement parameters for secosteroid **12**

Chemical formula	$C_{19}H_{26}O_2$
Color, habit	colorless plate
Formula weight	286.4
Crystal system	monoclinic
Crystal size	0.14 × 0.36 × 0.24
Space group	$P2_1$
a, Å	6.3670 (10)
b, Å	11.517 (2)
c, Å	10.942 (2)
β, deg	90.52 (3)
v, Å^3	802.3 (2)
Z	2
D_{calcd}, g/cm^3	1.185
Absorption coefficient, cm^{-1}	5.82
F (000)	312
Cu Kα radiation, λ, Å	1.54178
Monochromator	highly oriented graphite crystal
Temperature, °K	296
2θ range, deg	3.0–110.0
Scan type	2θ–θ
No. of total reflections	2125
No. of independent reflections	1903
No. of observed reflections, F > 6.0σ (F)	1618
No. of parameters refined	191
Final R	3.98%
Final wR	5.07%
GOF	1.27
Largest and mean, Δ/σ	0.006, 0.002
Largest difference peak, eÅ^{-3}	0.22
Largest difference hole, eÅ^{-3}	−0.25

Jones reagent[7] produced enantiomerically pure product **8** in 93% yield.

All attempts to separate the diastereomers of compound **7** by HPLC using different solvents and either a silica or C_{18} reverse-phase column were unsuccessful. Hence, we opted to separate the diastereomers of compound **7** after esterification (Scheme 2) with (*S*)-1-[(4-methylphenyl)sulphonyl]-2-pyrrolidinecarbonyl chloride[8] in the presence of pyridine (67% yield). The decision to prepare esters **9** and **10** (Assignment of the absolute configuration of the propargylic carbon in these structures follows from the analysis of the X-ray diffraction pattern of compound **12,** vide infra.) was based on the previously reported successful resolution of racemic alcohols as their (*S*)-1-[(4-methylphenyl)sulphonyl]-2-pyrrolidinecarboxylate derivatives by Rosini et al.[9] As anticipated, compounds **9** and **10** were readily separated by HPLC on an Alltech Econosil silica column (250 mm × 10 mm) eluted with 30% EtOAc in hexane. Basic hydrolysis of compounds **9** and **10** then gave secosteroids **11** (70% yield) and **12** (59% yield), respectively.

Table 2 Bond lengths (Å) in secosteroid **12**

O-1—C-3	1.231 (4)	O-2—C-17	1.435 (4)
C-1—C-2	1.523 (4)	C-1—C-10	1.531 (5)
C-2—C-3	1.474 (6)	C-3—C-4	1.448 (6)
C-4—C-5	1.348 (4)	C-5—C-6	1.500 (5)
C-5—C-10	1.513 (5)	C-6—C-7	1.528 (4)
C-7—C-8	1.516 (5)	C-8—C-9	1.540 (5)
C-8—C-14	1.528 (4)	C-9—C-10	1.559 (4)
C-9—C-11	1.528 (5)	C-10—C-19	1.550 (4)
C-11—C-12	1.517 (4)	C-12—C-13	1.525 (5)
C-13—C-14	1.531 (5)	C-13—C-17	1.552 (4)
C-13—C-18	1.532 (4)	C-17—C-16	1.472 (5)
C-16—C-15	1.183 (6)		

Table 3 Bond angles (°) in secosteroid **12**

C-2—C-1—C-10	113.8 (3)	C-1—C-2—C-3	111.9 (3)
O-1—C-3—C-2	120.8 (4)	O-1—C-3—C-4	121.3 (4)
C-2—C-3—C-4	117.7 (3)	C-3—C-4—C-5	123.4 (3)
C-4—C-5—C-6	120.5 (3)	C-4—C-5—C-6	122.3 (3)
C-6—C-5—C-10	117.1 (3)	C-5—C-6—C-7	112.5 (3)
C-6—C-7—C-8	111.9 (3)	C-7—C-8—C-9	109.9 (2)
C-7—C-8—C-14	111.0 (3)	C-9—C-8—C-14	111.5 (3)
C-8—C-9—C-10	114.0 (3)	C-8—C-9—C-11	110.1 (2)
C-10—C-9—C-11	113.3 (3)	C-1—C-10—C-5	109.4 (2)
C-1—C-10—C-9	108.7 (3)	C-5—C-10—C-9	109.7 (3)
C-1—C-10—C-19	110.0 (3)	C-5—C-10—C-19	107.8 (3)
C-9—C-10—C-19	111.1 (2)	C-9—C-11—C-12	111.8 (3)
C-11—C-12—C-13	113.4 (3)	C-12—C-13—C-14	108.4 (2)
C-12—C-13—C-17	107.3 (3)	C-14—C-13—C-17	108.9 (2)
C-12—C-13—C-18	111.7 (3)	C-14—C-13—C-18	111.2 (3)
C-17—C-13—C-18	109.3 (2)	C-8—C-14—C-13	114.9 (3)
O-2—C-17—C-13	111.5 (3)	O-2—C-17—C-16	110.4 (2)
C-13—C-17—C-16	113.7 (3)	C-17—C-16—C-15	175.8 (4)

The assignment of the absolute configurations of the propargylic carbons in compounds **9** through **12** follows from the solution of the X-ray diffraction pattern of a single crystal (from MeOH) of secosteroid **12** (Figure 2). Crystal data and information on data collection and refinement are given in Table 1. Data regarding bond lengths, bond angles, and atomic coordinates are given in Tables 2–4.

Now that the absolute configurations of secosteroids **9** and **10** are established and a method has been developed for their efficient separation, it becomes possible to refine further the stereochemical details of the previously observed inhibition of rat liver 3α-hydroxysteroid dehydrogenase by the mixture of these unresolved diastereomers.[2] It is anticipated that the results of such studies will be the subject of

Table 4 Atomic coordinates (× 10^4) and equivalent isotropic displacement coefficients (Å^2 × 10^3) for secosteroid **12**

	x	y	z	U (eq)
O-1	6557 (4)	9096 (3)	10416 (2)	83 (1)
O-2	447 (3)	8609	1358 (2)	53 (1)
C-1	3646 (5)	8192 (3)	7736 (3)	51 (1)
C-2	4157 (5)	8156 (4)	9098 (3)	58 (1)
C-3	5473 (5)	9147 (4)	9480 (3)	54 (1)
C-4	5309 (5)	10209 (4)	8777 (3)	49 (1)
C-5	3995 (4)	10339 (3)	7813 (3)	40 (1)
C-6	3650 (6)	11513 (3)	7252 (3)	52 (1)
C-7	3703 (5)	11481 (3)	5857 (3)	47 (1)
C-8	2213 (4)	10578 (3)	5335 (3)	37 (1)
C-9	2721 (4)	9377 (3)	5883 (2)	35 (1)
C-10	2699 (4)	9345 (3)	7308 (2)	39 (1)
C-11	1331 (5)	8449 (3)	5292 (3)	44 (1)
C-12	1513 (5)	8452 (3)	3910 (3)	43 (1)
C-13	956 (4)	9617 (3)	3331 (2)	34 (1)
C-14	2300 (5)	10559 (3)	3940 (3)	39 (1)
C-15	898 (6)	11476 (4)	688 (3)	64 (1)
C-16	1206 (5)	10638 (4)	1288 (3)	47 (1)
C-17	1534 (4)	9543 (3)	1958 (2)	42 (1)
C-18	−1389 (4)	9889 (3)	3445 (3)	44 (1)
C-19	435 (4)	9474 (4)	7798 (3)	51 (1)

a future publication. It should also be noted that secosteroids **8–10** may also be of use as inhibitors of other hydroxysteroid dehydrogenases. Given the similarity in structure between these secosteroids and testosterone and androstenedione, it would be reasonable to expect that the secosteroids would be mechanism-based inactivators of any 17β-hydroxysteroid dehydrogenase that interconverts these two androgens.

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