Synthesis of Ring-C Aromatic Steroids

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A practical multistep synthetic route to ring-C aromatic testosterone analogue **8b** from 1,7-dihydroxynaphthalene (**1a**) is described. The key intermediate in this sequence is the diketone **7**. The synthesis of **8b** from **7** was achieved by reduction with sodium borohydride under carefully controlled conditions followed by separation using high-pressure liquid chromatography. Studies with europium shift reagent were used for assigning the β stereochemistry for the 17-hydroxy group of **8b**.

The preparation and biological evaluation of ring-C aromatic steroids is an area that has received relatively little attention. An examination of Drieding models of these compounds shows a similarity of the molecular topology to natural steroids. The spatial relationship of the C-3 and C-17 substituents to each other and the plane of the molecule differ only slightly from those found in the natural steroids.

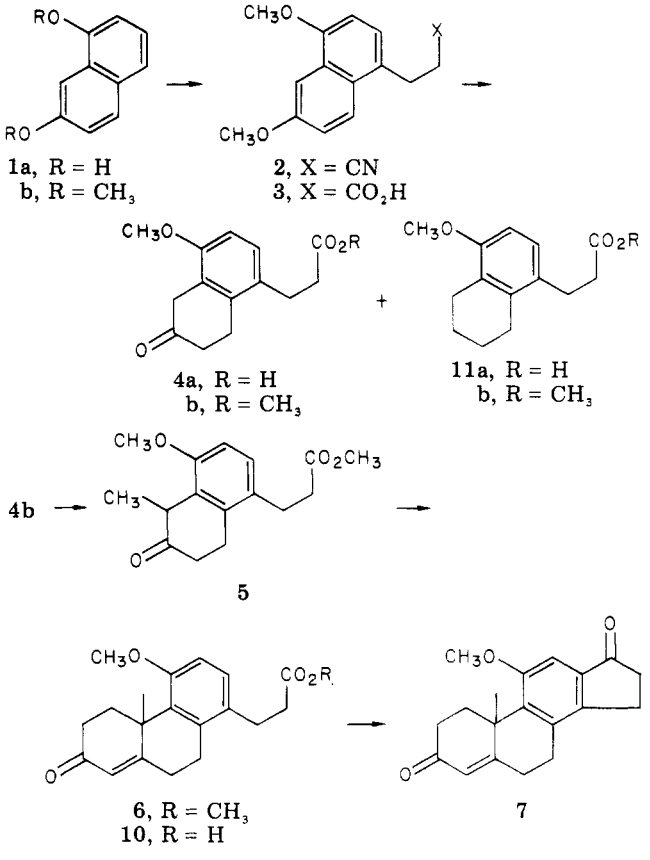
The ring-C aromatic steroids thus have potential as a new class of agents useful in the antifertility field. In order to explore this view we developed a practical synthetic route to ring-C aromatic testosterone analogue **8**, the details of which are presented in this paper.

Prior to the present work, only a few ring-C aromatic steroids were known and of these very little biological information was available. Viridin, an antifungal metabolite of *Gliocladium virens*, is a naturally occurring compound with a ring-C aromatic steroid nucleus.[1] A few ring-C aromatic steroids have been prepared chemically. For example, ergosterol [2-4] and cholic acid[5,6] have been converted to 12-methyl ring-C aromatic steroids by molecular rearrangement. More recently Hewett and coworkers[7] have utilized the Wagener–Meerwein shift of the 13β-methyl group to the 17β position to prepare several 11-hydroxy ring-C aromatic steroids, but this procedure has a limited value as it does not allow the introduction of functionalities in the 17 position. In addition, total syntheses of ring-C aromatic steroids have been reported.[8-12]

The above synthetic routes do not appear to provide a practical method for the preparation of ring-C aromatic steroid hormone analogues. They either do not provide useful A- and D-ring functionalities or suffer from synthetic difficulties that limit their practicality.

Therefore, as a first objective we set out to prepare the diketone **7** in gram quantities. The synthetic route used to prepare this key ring-C aromatic steroid system is outlined in Scheme I. This route is based on an earlier synthesis of keto acid **10**.[10,12] A number of significant improvements in the early steps of this synthesis have made the route practical.

Scheme I



The sequence begins with 1,7-dihydroxynaphthalene (**1a**) which is methylated with dimethyl sulfate to give 1,7-dimethoxynaphthalene (**1b**) in 90% yield. The cyanoethylation of this compound to give nitrile **2** was not successful initially. Study of this reaction showed that the order and timing of the addition of anhydrous aluminum chloride and hydrogen chloride are critical. Under the conditions developed, nitrile **2** is obtained in yields of 85–95%. Hydrolysis of nitrile **2** with potassium hydroxide in ethanol gives acid **3** in 85–95% yield.

The reduction of acid **3** to keto acid **4a** was a doubtful step in the synthesis at the outset. It has been reported[10,13] that conditions for this reaction are critical with slight

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(13) Private communication by B. G. Hazra. He stated that the reaction was undependable and had not been run successfully on quantities greater than 0.5 g.

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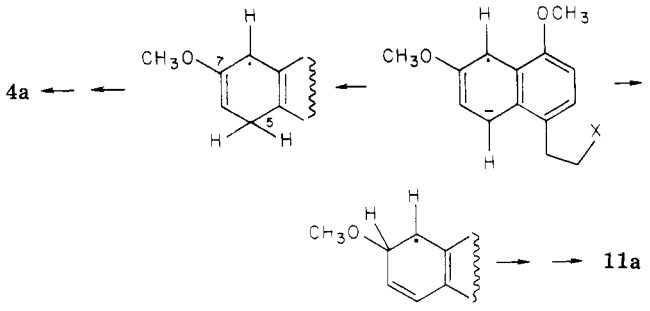
changes giving tetralin acid **11a** as the major product.

We have found that the use of *tert*-butyl alcohol as the alcohol in the reaction medium improved this situation considerably. Under these conditions, the reaction has been run quite reproducibly on 65 g of acid **3** with hydrogenolysis product **11a** being formed to an extent of less



than 20%. We reasoned that the formulation of the reduced product **11a** can be accounted for by the protonation of an intermediate anion at C-7 rather than at C-5. Thus the use of a hindered alcohol like *tert*-butyl alcohol, as a proton source, should favor the formation of the described product **4a** and suppress the formation of **11a**.

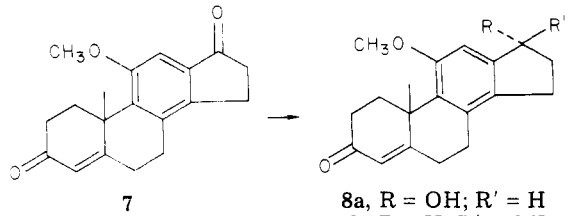
The crude keto acid **4a** is esterified with diazomethane and keto ester **4b** purified as a bisulfite addition compound. Decomposition of the addition compound gives pure (GLC) keto ester **4b** in 40–50% yield from acid **3**.

The methylation of keto ester **4b** by preparing the pyrrolidine enamine and treating it with methyl iodide gives a 76% yield of compound **5** after chromatography on Florisil.

The Robinson annelation has been carried out by using the procedure of Howell and Taylor.[14] Under these conditions the ester group is also hydrolyzed and acid **10** is isolated. The crude acid was usually used in the next step without purification. The pure acid was prepared by converting a sample of the crude acid to methyl ester **6** with diazomethane. The methyl ester was then purified by chromatography and hydrolyzed to give acid **10**; mp 72–74 °C.

The final ring closure of keto acid **10** to give diketone **7** has been effected by using polyphosphoric acid as the dehydrating agent. Chromatography on Florisil (15% ethyl acetate/benzene eluent) followed by recrystallization from ether/ethyl acetate or from ethanol afforded the pure diketone **7**. Extensive drying (40 h at 140 °C) is required to obtain a solvent-free analytical sample; mp 206.5–207.5 °C.

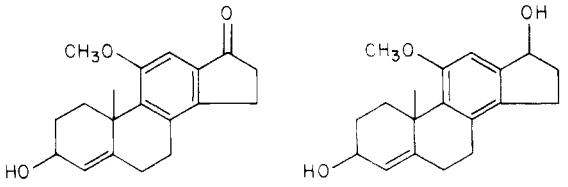
The reduction of diketone **7** to give testosterone analogue **8b** is complicated by competitive reduction of the



7 **8a**, R = OH; R' = H
b, R = H; R' = OH

3-keto group. Several 3-ketone-protected derivatives and various reducing agents were examined (see below) for this reduction, but the best method found for producing **8b** was reduction of diketone **7** with sodium borohydride in ethanol under carefully controlled conditions. Chakravarti et al.[11] have reported the preparation of **8** (undetermined stereochemistry at C-17) by following a different sequence.

The reduction of diketone **7a** was carried out at 0 °C with a limited amount of sodium borohydride, and the progress of the reaction was monitored by high-pressure liquid chromatography (LC) (μ-Porasil, 1:3 ether/methylene chloride). Additional sodium borohydride was added in batches until most of the diketone **7** had been consumed. Under these conditions the crude reaction mixture consists of 7% diketone **7**, 6% 3-ol **12**, 48% 17α-ol **8a**, 37% 17β-ol **8b** and 1% each of two isomers of diol **13** as analyzed by LC.



12 **13**

These components were separated by chromatography on a Waters System 500 preparative chromatograph to give about a 20% yield of each of the 17-epimers **8a** (mp 193–196 °C) and **8b** (mp 172–174 °C) greater than 95% pure (LC) as well as smaller amounts of the other components.

The assignment of the β stereochemistry for the 17-hydroxy group of **8b** has been made on the basis of a comparison of the difference in the NMR shift of the angular methyl group in the two isomers induced by a europium shift reagent. Tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium (III) (Eu(fod)$_3$) was used as the shift reagent with weighed amounts added to mixtures of 2:1 and 1:2 **8a** and **8b** in $CDCl_3$, and the proton NMR spectra were recorded. The results are shown for the 2:1 mixture in Table I. When 0.5 equiv or more of shift reagent had been added, the peak due to the C_{10}-CH_3 began to resolve into two peaks with a greater shift observed for the **8b** isomer. The **8b** isomer also showed the larger shift when Eu(fod)$_3$ was added to the 1:2 mixture of **8a** and **8b**.

An examination of Drieding models shows that the C-17 oxygen to C_{10}-CH_3 hydrogen distance is shorter in the 17 β-hydroxy (**8b**) (6.1–6.2 Å) than in the 17α-hydroxy isomer (**8a**) (6.6–6.7 Å). Since the change in chemical shift induced by lanthanide shift reagents decreases with increasing distance from the complexing site[15-18] and since the hydroxy group should be the primary complexing site in **8**, the larger chemical shift observed for the methyl group in **8b** suggests the 17β-hydroxy assignment for this isomer. The ketone group in **8** probably also complexes with the europium reagent, but this should lead to virtually identical shifts in both isomers.

A number of other reducing agents have been examined for the conversion of diketone **7** to alcohol **8**, but the results have been less satisfactory than the above sodium borohydride conditions. The use of sodium cyanoborohydride resulted in almost exclusive reduction of the 3-ketone to give compound **12**. Diisobutylaluminum hydride also gave mostly **12** and small amounts of **8** isomers. Lithium aluminum hydride formed mostly two isomers of diol **13**

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Table I. NMR-Induced Chemical Shift Data for Isomers of 8, Using Eu(fod)$_3$ Shift Reagent

molar ratio of Eu(fod)$_3$	δ (8a), mp 193-196 °C				δ (8b), mp 172-174 °C			
	C_{10}-CH_3	aromatic	vinylic	OCH_3	C_{10}-CH_3	aromatic	vinylic	OCH_3
0	1.68	6.90	5.83	3.87	1.70	6.93	5.87	3.87
0.2	1.83	8.23	6.50	3.95	1.83	8.23	6.50	3.95
0.3	2.22	9.12	6.95	3.98	2.22	9.12	6.95	3.98
0.4	2.55	10.17	7.80	4.10	2.58	10.17	7.80	4.10
0.6	3.00	11.38	8.95	4.17	3.03	11.42	8.95	4.20
0.8	3.55	12.80	10.63	4.27	3.63	12.87	10.68	4.32
1.0	4.10	13.83	12.33	4.40	4.22	13.95	12.43	4.47

with some **12** and **8** isomers. Treatment with Red-Al in toluene gave similar results. Since reduction of the 3-ketone function is a competing reaction in the conversion of **7a** to **8**, the use of 3-ketone-protecting derivatives such as the enol ether and the enamine followed by lithium aluminum hydride reduction were tried but proved unsatisfactory. Similarly the $NaBH_4$ reduction of 3-enol acetate gave only traces of the desired epimers of **8**. The 3-ethylene thioketal was also explored as an intermediate for the synthesis of **8**. However, considerable difficulty was experienced in the complete formation of the thioketal using conventional means and this approach was therefore not examined further.

The difficulty encountered in the reduction of the 17-ketone in the ring-C aromatic steroid is apparently due to the fact that the C/D rings form an indanone system. This gives less selectivity between reaction at the 17-ketone and the 3-ketone as compared to the case for natural steroids.

Preliminary biological test results[19] have shown that both **8a** and **8b** show a high degree of androgen binding in an in vitro binding test, thus lending support to the hypothesis that ring-C aromatic steroids are very similar to natural steroids.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 spectrometer in deuteriochloroform (unless otherwise stated), using tetramethylsilane as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 700 spectrometer. Mass spectral analyses were carried out on Hitachi Perkin-Elmer RMU6L and CEC 110 spectrometers. Precoated TLC plates (silica gel 60F254, EM Reagents) were used for thin-layer chromatographic analysis. Microanalyses were performed by Spang Microanalytical Laboratories and Atlantic Microlab Inc.

High-pressure liquid chromatographic (LC) separations were performed on Waters Associates liquid chromatograph A202 and Prep LC/System 500. A Varian Aerograph Model 1400 gas chromatograph (3% OV-17) was used in GLC analysis.

β-(4,6-Dimethoxy-1-naphthalene)propionitrile (2).[12] Into a flame-dried 1-L, three-necked, round-bottom flask, fitted with a reflux condenser protected by a $CaSO_4$ drying tube, a gas inlet tube, a magnetic stirrer, and a 250-mL Erlenmeyer flask containing 90 g (0.68 mol) of $AlCl_3$ connected by a Gooch tube, were added 125 g (0.665 mol) of 1,7-dimethoxynaphthalene, 110 g (2.0 mol) of acrylonitrile, and 200 mL of *sym*-tetrachloroethane (distilled and stored over molecular sieves). The mixture was cooled to 0–5 °C with an ice bath. Approximately 0.3 g of $AlCl_3$ was introduced into the reaction flask. Dry HCl was then bubbled through the reaction mixture for 10 min. The rest of the $AlCl_3$ was added in three portions at 10-min intervals with continuous passage of HCl. The temperature of the mixture was maintained at 0–5 °C for an additional 1.5 h and then allowed to warm to room temperature (20 °C). The reaction was quenched after 2 h of stirring at 20 °C at which point the starting material had disappeared (R_f 0.42). The reaction mixture was poured into 500 mL of H_2O and extracted with ether. The ether extracts were washed with 10% NaOH and then with water until the washings were neutral. The dried ($MgSO_4$) ether–$CHCl_2CHCl_2$ layer was evaporated under reduced pressure to give 155 g of crude **2**; mp 95–96 °C (lit.[12] 104–105 °C); IR ($CHCl_3$) 2250 cm^{-1} (C≡N); NMR δ 6.7–8.0 (m, 5 H), 4.07 (s, 3 H), 4.0 (s, 3 H), 3.25 (t, 2 H), 2.70 (t, 2 H).

β-(4,6-Dimethoxy-1-naphthalene)propionic Acid (3). A solution of 80 g (0.33 mol) of β-(4,6-dimethoxy-1-naphthalene)propionitrile and 69 g (1.23 mol) of KOH in 800 mL of 80% ethanol was heated under reflux for 48 h. The ethanol was removed under reduced pressure and diluted with 1 L of water. The aqueous solution was extracted with ether and acidified to pH 2 with 6 N HCl. The precipitated solid was collected by filtration and washed with water until the washings were neutral. The air-dried material, 75 g (87%), had the following: mp 184–185 °C (lit.[12] 186–188 °C); IR (KBr) 1710 cm^{-1}; NMR (pyridine-d_5) δ 8.15–6.65 (5 H, m), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.50 (t, 2 H), 2.90 (t, 2 H).

Methyl β-(4-Methoxy-6-oxo-5,6,7,8-tetrahydro-1-naphthalene)propionate (4b). Into a 3-L, three-neck, round-bottom flask, fitted with a gas inlet tube, a dry-ice condenser protected by a KOH drying tube, and a mechanical stirrer, was distilled 1 L of NH_3 (from Na). A 65-g (0.25-mol) sample of solid β-(4,6-dimethoxy-1-naphthalene)propionic acid was added rapidly to the NH_3. The gas inlet tube was replaced with a dropping funnel through which was added 250 mL of *tert*-butyl alcohol (distilled from CaH_2) and 350 mL of THF (distilled from $LiAlH_4$). Sodium (26.3 g, 1.1 mol) was added to the mixture with stirring over a period of 45 min. The mixture (which had become dark blue) was stirred until the blue color disappeared and then 120 mL of CH_3OH was added to the reaction mixture. The NH_3 was allowed to evaporate overnight. Water was added to the pasty residue and the mixture acidified with 6 N HCl. The solution was heated under reflux for 10 min. Tetrahydrofuran and *tert*-butyl alcohol were removed from the cooled reaction mixture under reduced pressure. The aqueous residue was extracted with ether, and the ether was washed with water until the washings were neutral. Evaporation of the dried (Na_2SO_4) extract gave 70 g of crude keto acid.

Treatment of crude keto acid **4a** with ethereal diazomethane gave 57 g of crude **4b**. Analysis by GLC ($^1/_8$ in. 2% OV-17, 260 °C, He 30 mL/min) showed two major fractions with retention times of 1.6 (19%) and 3.5 min (81%). It was purified by treatment with sodium bisulfite,[20] as described below.

Crude ester **4b** was dissolved in 1400 mL of absolute ethanol, and to it was added a solution of $NaHSO_3$ (130 g of $NaHSO_3$ in 226 mL of H_2O and 63 mL of absolute ethanol). The white precipitate that formed on standing overnight was filtered and then washed with ether. The solid was suspended in water and brought to pH 10 with solid $Na_2CO_3 \cdot H_2O$. The suspension was extracted with ether, and the ether extract was washed with water until the washings were neutral. The dried (Na_2SO_4) ether layer gave 30 g (43%) of pure **4b**: mp 78–80 °C (lit.[10] 78–80 °C); IR (KBr) 1718, 1740 cm^{-1}; NMR δ 6.7, 7.11 (AB q, J = 9 Hz), 3.80 (s, 3 H), 3.70 (s, 3 H), 3.58 (s, 2 H), 3.0 (m, 4 H).

Methyl β-(4-Methoxy-5-methyl-6-oxo-5,6,7,8-tetrahydro-1-naphthalene)propionate (5). A 24-g (0.0916-mol) sample of **4b**, 20 mL of pyrrolidine, 500 mL of benzene, and 10 mg of *p*-toluenesulfonic acid were heated under reflux under nitrogen

(19) The biological test results were provided by the Contraceptive Development Branch, National Institute of Child Health and Development, National Institutes of Health.

(20) M. D. Soffer, M. P. Bellis, H. E. Gellerson, and R. A. Stewart, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 903.

for 3 h. The benzene and excess pyrrolidine were removed at reduced pressure to leave a brown residue which solidified upon removal of the last traces of solvent at the vacuum pump. The solid was dissolved in 500 mL of CH_3OH and 10 mL of CH_3I, and the mixture was heated under reflux for 4 h. The excess CH_3I was removed under reduced pressure. A solution of 25 g of CH_3COONa in 250 mL of H_2O and 25 mL of CH_3COOH was added to the methanol solution, and the mixture was heated under reflux for 2 h. Methanol was removed under reduced pressure and the residue dissolved in ether and 1 N HCl. The ether layer was washed with a saturated solution of $NaHCO_3$ and water. Evaporation of the dried ($MgSO_4$) ether layer gave 25 g of a brown oily residue. The oil was purified by column chromatography on Florisil (40:1) and eluted with 30% ether/petroleum ether to give 19.3 g (76%) of an oil which was assigned structure **5**:[10] IR (film) 1718 (C=O), 1740 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.7, 7.1 (AB, J = 9 Hz), 3.8 (s, 3 H), 3.65 (s, 3 H), 1.3 (d, J = 8 Hz, 3 H). This material was used in the subsequent step without further purification.

Methyl β-(4-Methoxy-4b,5,6,7,9,10-hexahydro-4b-methyl-7-oxo-1-phenanthrene)propionate (6). The general procedure of Howell and Taylor[14] was followed. (*N,N*-Diethylamino)-3-butanone[21] (14.3 g, 0.1 mol) in 50 mL of dry ether and 0.1 mL of benzyl alcohol was placed in a 500-mL, three-neck, round-bottom flask fitted with a condenser, N_2 inlet, dropping funnel, and magnetic stirrer. The solution was cooled to 0–5 °C with an ice bath, and to it was added dropwise 14.3 mL (28.6 g, 0.2 mol) of CH_3I in 50 mL of ether. A white precipitate forms as the addition proceeds. The mixture was allowed to stir for another hour at 0 °C, and then the excess CH_3I and ether were removed under reduced pressure.

The white paste which remained was cooled to 0 °C and ketone **5** (13.8 g, 0.05 mol) was added in 100 mL of benzene (dried over sieves). Then a solution of $NaOCH_3$ (from 4.69 g of Na, 0.2 g-atom) in 50 mL of CH_3OH (distilled from Mg) was added to the mixture over a period of 5 min. The mixture was allowed to stir at 0-5 °C for an additional 2 h, followed by heating under reflux for 10 min.

The dark red solution was acidified with 1 N HCl and extracted with ether. The ether was washed with water and dried (Na_2SO_4). Evaporation gave 15 g of a crude red foam shown to be acid **10**. A sample of the red foam was esterified with ethereal CH_2N_2 to give an oil which was purified by column chromatography on Florisil (40:1). Elution with ether/petroleum ether (1:1) gave the α,β-unsaturated keto ester **6**: IR (film) 1660 (C=O), 1720 cm^{-1} (C=O); NMR (CCl_4) δ 1.66 (s, 3 H), 2.8 (m, 12 H), 3.63 (s, 3 H), 3.83 (s, 3 H), 6.71, 6.98 (AB q, J_{AB} = 8 Hz). This sample of ester was then hydrolyzed to acid **10** by the procedure described below.

In most cases crude keto acid **10** was cyclized directly to diketone **7**.

β-(4-Methoxy-5,4b,6,7,9,10-hexahydro-4b-methyl-7-oxo-1-phenanthrene)propionic Acid (10). An 850-mg sample of ester **6** (2.6 mmol) was dissolved in 27 mL of CH_3OH. To it was added 0.48 g of KOH in 2 mL of H_2O. The mixture was heated under reflux under N_2 for 2 h. The methanol was removed under reduced pressure and the residue taken up in 20 mL of H_2O. The water was extracted with ether, and the ether extracts were discarded. The aqueous layer was acidified with 1 N HCl and extracted with ether. The ether layer was washed with water until the washings were neutral and dried (Na_2SO_4). Evaporation gave 680 mg (85%) of the acid as a fluffy yellow solid: mp 72–74 °C; IR ($CHCl_3$) 1660 (C=O), 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.70 (s, 3 H), 2.6 (m, 12 H), 3.66 (s, 3 H), 5.06 (s, 1 H), 6.8, 7.06 (AB q, J = 8 Hz), 10.6 (s, 1 H).

Preparation of 11-Methoxy-18-norandrosta-4,8(9),11,13(14)-tetraene-3,17-dione (7). To 15 g of crude keto acid **10** was added 150 mL (~300 g) of polyphosphoric acid in a 500-mL round-bottom flask fitted with a mechanical stirrer and a $CaSO_4$ drying tube. This mixture was heated with stirring at 100 °C in an oil bath for 2 h.

The mechanical stirrer was removed and placed in a 2-L beaker containing 1 L of ice water. The warm polyphosphoric acid mixture was poured into the stirring ice water. The water was extracted first with ether (200 mL) and then with CH_2Cl_2 (two 200-mL portions). The combined organic layers were washed with 5% $NaHCO_3$ solution and then with water. Evaporation of the dried (Na_2SO_4) layer gave 13 g of a residue which was chromatographed on 400 g of Florisil and eluted with 15% ethyl acetate/benzene to give 3.8 g (mp 191–195 °C) of diketone **7a** (overall yield 25% from **5**). Recrystallization from ethanol followed by drying in refluxing xylene vapors gave pure **7**: mp 206.5–207.5 °C; IR (CCl_4) 1670 (C=O), 1705 cm^{-1} (C=O); NMR (CCl_4) δ 1.7 (s, 3 H), 2.8 (m, 2 H), 3.9 (s, 3 H), 5.8 (s, 1 H), 7.1 (s, 1 H). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.80. Found: C, 76.96; H, 6.81.

17-Hydroxy-11-methoxy-18-norandrosta-4,8(9),11,13(14)-tetraen-3-one (8). Diketone **7a** (2.2 g, 7.5 mmol) was dissolved in 450 mL of C_2H_5OH in a 1-L Erlenmeyer flask and cooled to 0–5 °C in an ice bath, and sodium borohydride (110 mg, 2.9 mmol, 11.6 mequiv of H) was added and the mixture stirred at 0 °C. The reaction was monitored by high-pressure liquid chromatography (LC) with (1:3) ether/methylene chloride; k' values for diketone **7**, 3-alcohol **12**, 17-alcohols **8a** and **8b**, and diol **13** were 0.94, 2.17, 2.81, and 4.0, respectively. Aliquots (0.5 mL) were withdrawn at intervals and quenched with a drop of acetic acid. After evaporation to dryness, they were taken up in CH_2Cl_2 (0.5 mL) and examined by LC. As the reaction progressed, more $NaBH_4$ was added in batches of 20 mg until most of the ketone was reduced and traces of diols were observed (total time 9 days). Excess $NaBH_4$ was decomposed by addition of 4.0 mL of glacial acetic acid (no further effervescence of H_2), and then ethanol and acetic acid were removed under reduced pressure. A light yellow foam (2.7 g) was obtained. This was separated into four main fractions by LC on a Waters System 500 instrument, using two silica columns and eluting with (1:3) ether/methylene chloride at flow rate of 250 mL/min: fraction i corresponded to starting diketone (0.125 g); fraction ii contained the faster moving 17-alcohol (**8a**) contaminated with **12** (740 mg); fraction iii contained the later eluting 17-alcohol (**8b**) along with the diols **13** (870 mg); fraction iv corresponded to the diols **13** (150 mg).

Individual isomers **8a** and **8b** and **12** were purified by repeated chromatography on the Waters instrument, using the CH_3CN/CH_2Cl_2 system.

3-Hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-17-one (12) was isolated as a colorless solid: mp 191–192 °C; NMR δ 7.12 (s, 1 H), 5.53 (s br 1 H), 4.20 (d, 1 H, J = 9 Hz), 3.86 (s, 3 H), 2.76, 2.42, 2.07 (m, 12 H), 1.58 (s, 3 H); IR (CH_2Cl_2) 3600 (OH), 1700 cm^{-1} (>C=O); UV λ_{max} (EtOH) 320 (ε 15 000), 262 (35 000), 219 nm (48 300); mass spectrum m/e 298 (M^+), 283, 280, 265, 241, 224, 223 (100%). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.38; H, 7.47.

17α-Hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-3-one (8a) was obtained as a very light buff colored powder: mp 193–196 °C; IR ($CHCl_3$) 3600, 2950, 1660, 1080 cm^{-1}; NMR δ 6.97 (s, 1 H), 5.87 (s, 1 H), 4.27 (br t, J = 5 Hz, 1 H), 3.88 (s, 3 H), 2.67 (m, 13 H), 1.70 (s, 3 H); UV λ_{max} (EtOH) 285 (ε 3710), 245 nm (ε 8340); mass spectrum m/e 298 (M^+), 283 (100%), 280, 265. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.27; H, 7.51.

17β-Hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-3-one (8b) was isolated as a colorless powder: mp 172–174 °C; IR ($CHCl_3$) 3650, 2940, 1660, 1090 cm^{-1}; NMR δ 7.00 (s, 1 H), 5.94 (s, 1 H), 5.27 (br t, J = 5 Hz, 1 H), 3.90 (s, 3 H), 2.75 (m, 13 H), 1.68 (s, 3 H); UV λ_{max} (EtOH) 283 (ε 3810), 245 nm (7080); mass spectrum m/e 298 (M^+), 283 (100%), 265. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.34; H, 7.47.

3,17-Dihydroxy-18-norandrosta-4,8,11,13-tetraene (13) was isolated as a light buff colored solid: mp 94–96 °C; IR ($CHCl_3$) 3600 (OH), 1060, 1120 cm^{-1}; NMR δ 6.90 (s, 1 H), 5.47 (br s, 1 H), 5.20 (v br s, 1 H), 4.25 (br t, J = 8 Hz, 1 H), 3.83 (s, 3 H), 2.87 (m, 12 H), 1.57 (s, 3 H); mass spectrum m/e 300 (M^+), 285, 282, 264, 249 (100%), 223. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 74.98; H, 8.37.

3-Acetoxy-11-methoxy-18-norandrosta-3,5,8,11,13-pentaen-17-one. In a 25-mL round-bottom flask were placed diketone **7** (30 mg, 0.1 mmol), acetic anhydride (0.2 mL), benzene (5 mL), and *p*-toluenesulfonic acid, and the mixture was heated at reflux for 8 h. The benzene and excess acetic anhydride were removed under reduced pressure, and the residue was taken up in CH_2Cl_2

(21) A. L. Wilds, R. M. Nowak, and K. T. McCaleb, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 291.

and filtered through a short column of silica gel (2 g). Upon evaporation of the solvent, a yellow residue (25 mg) of 3-acetoxy-11-methoxy-18-norandrosta-3,5,8,11,13-pentaen-17-one was obtained: NMR δ 1.47 (s, 3 H), 2.17 (s, 3 H), 2.83 (m, 8 H), 3.43 (d, J = 4 Hz, 2 H), 3.92 (s, 3 H), 5.7 (t, J = 4 Hz, 1 H), 5.93 (br s, 1 H), 7.2 (s, 1 H); IR 1740, 1692, 1600 cm^{-1}; mass spectroscopic molecular weight 338.15163 (calcd for $C_{21}H_{22}O_4$ 338.15181).

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Registry No. **1b**, 5309-18-2; **2**, 22442-51-9; **3**, 22442-52-0; **4a**, 27230-52-0; **4b**, 27230-53-1; **5**, 70179-52-1; **6**, 27266-10-0; **7**, 70179-53-2; **8a**, 70179-54-3; **8b**, 70179-55-4; **10**, 70179-56-5; **11a**, 70179-57-6; **12**, 70179-58-7; **13**, 70179-59-8; acrylonitrile, 107-13-1; *N,N*-(diethylamino)-3-butanone, 3299-38-5; 3-acetoxy-11-methoxy-18-norandrosta-3,5,8,11,13-pentaen-17-one, 70179-60-1.

Stereoselective Synthesis of the Proposed American Coneflower Juvenile Hormone Mimic. Some Observations on the Cyclopropylcarbinyl Rearrangement in Substituted Systems

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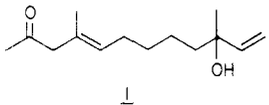
A stereoselective synthesis of the proposed structure (1) of echinolone, the potent juvenile hormone mimic from the American coneflower, is reported. Oxygen and trisubstituted olefin functionality were introduced through a cyclopropylcarbinyl rearrangement of carbinol **25**. The complexity of related rearrangements in model systems has been found to be a function of the presence or absence of remote unsaturation. Synthetic racemic 1 has been found to be devoid of JH activity in a standard assay, and these results are discussed with regard to the structure of the natural product.

Jacobson and co-workers have reported the isolation of a compound from the roots of *Echinacea angustifolia* D.C., the American coneflower, said to be a highly active juvenile hormone mimic.[1] The highly publicized mimic, dubbed "echinolone", reportedly produces marked juvenilizing effects in the standard *Tenebrio molitor* assay at levels below 1 μg. On the basis of spectral data,[2] microozonolysis, and carbon skeleton chromatography, the only structure for echinolone said to be consistent with these data is that of (+)-10-hydroxy-4,10-dimethyl-(*E*)-4,11-dodecadien-2-one (1). A nonstereoselective synthesis of 1 has recently been

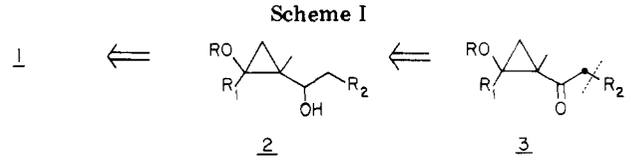


1

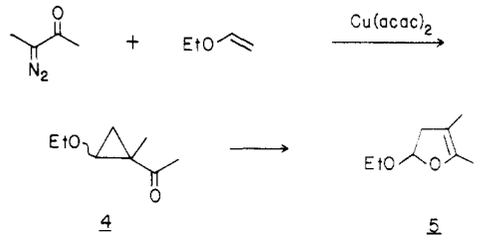
reported.[3] We report a stereoselective synthesis of racemic 1 resulting from our efforts to provide synthetic proof for the suggested structure of echinolone as well as some observations on the cyclopropylcarbinyl rearrangement used in its construction.

The key structural features in 1 which were considered in planning a synthesis were the presence of the β,γ-unsaturated carbonyl group at C-2, the proximal trisubstituted olefinic unit with its potential for isomerization, and the presence of the tertiary allylic alcohol containing the lone chiral center at C-10. We initially chose to attempt a synthesis of 1 through the use of a cyclopropylcarbinyl rearrangement of **2** (Scheme I) such that both the olefinic unit of correct stereochemistry and the proximal oxygen function could be introduced simultaneously at a late stage in the synthesis.

Scheme I



Scheme II



While the cyclopropylcarbinyl rearrangement[4] has found considerable use in the stereoselective synthesis of trisubstituted olefins,[5] more highly substituted systems

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(2) Only infrared spectral data has been published;[1a] mass and ^1H NMR spectral data are said to be consistent with the proposed structure, but no data has been disclosed. In addition microozonolysis is said to support structure 1 through formation of formaldehyde, 2,4-pentanedione, and 2-hydroxy-2-methylheptanal. Formation of the last product is clearly inconsistent with structure 1, however, though this may be the result of a typographical or transcriptional error.

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