Total Synthesis of (±)-17β-Hydroxy-$\Delta^{9(10)}$-des-A-androsten-5-one [(±)-2,3,3a,4,5,7,8,9,9aβ,9bα-Decahydro-3β-hydroxy-3aβ,6-dimethyl-1H-benz[e]inden-7-one]

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The title compound (**8**) is an important BCD tricyclic intermediate for the preparation of steroidal compounds. Its synthesis from (±)-7,7a-dihydro-1β-hydroxy-7aβ-methyl-5(6H)-indanone (**1**) in a five-step sequence is described. The ultraviolet, infrared (in solution), and nmr spectra of **8** are identical with those of the optically active authentic sample.

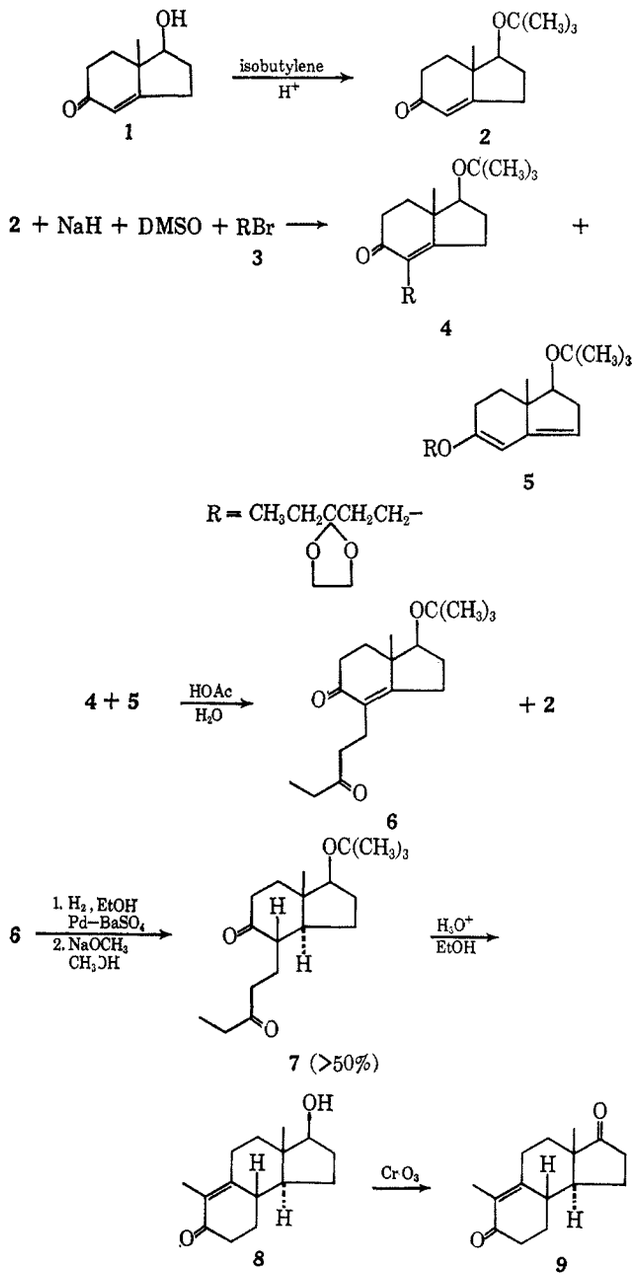
In an earlier communication,[2] Uskoković, *et al.*, described the conversion of natural steroids to retro steroids (*i.e.*, 9β,10α-steroids) through BCD tricyclic intermediates. Therefore, it became important to plan the total synthesis of a representative compound of this type, *i.e.*, 17β-hydroxy-$\Delta^{9(10)}$-des-A-androsten-5-one (**8**).

This substance was first obtained in optically active form *via* a chemical degradation of testosterone acetate.[3] The related racemic diketone (**9**) was prepared by Miescher, *et al.*,[4] in an eight-step synthesis starting with 2-methylcyclopentane-1,3-dione and 1-carbethoxy-6-chlorohexan-4-one. Velluz and co-workers[5] have considerably modified this sequence and, by resolving one of the intermediates, have obtained the desired optically active tricyclic compound (**8**) in an elegant six-step synthesis.

The synthetic scheme of the present paper is shown in Scheme I. The starting material, the crystalline bicyclic hydroxy ketone (**1**),[1] has previously been reported[6] as an oil. Since it is known[7] that such systems are sensitive to base, the bicyclic hydroxy ketone (**1**) was converted to the corresponding *t*-butyl ether (**2**). The conjugate anion of **2** was then formed in dimethyl sulfoxide with sodium hydride. This was alkylated with 1-bromo-3-pentanone cyclic ethylene ketal (**3**) to give the crude alkylation product, which consisted of 55.7% C-alkylation product (**4**) and 23.2% O-alkylation product (**5**), as indicated by vpc analysis. O-alkylation products of weakly acidic ketones have recently been reported.[8] Halo ketals (γ- and β-halo, respectively) have previously been used to alkylate cyclic α,β-unsaturated ketones[9] and a recent paper reports the preparation of a related BCD tricyclic derivative *via* alkylation with 1,3-dichloro-2-butene.[10]

The O-alkylation product (**5**) could be separated by column chromatography and characterized by ultraviolet and infrared spectroscopy. It is a di(en)ol ether,

SCHEME I



which can readily be converted into the bicyclic unsaturated ketone (**2**) by mild acid hydrolysis.

In the course of the total synthesis, it seemed advantageous to convert the mixture of C- and O-alkylation products (**4** and **5**) *via* mild acid hydrolysis of the cyclic ketal and of the enol ether groups, respec-

(1) For a preliminary report on the total synthesis of levorotatory 17β-hydroxy-$\Delta^{9(10)}$-des-A-androsten-5-one, see Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron Letters*, 6495 (1966).

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(5) (a) L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède, *Compt. Rend.*, **257**, 3086 (1963); (b) Roussel-Uclaf, Belgium Patent 629,251 (1963); (c) Roussel-Uclaf, French Patent 1,359,675 (1963).

(6) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 4547 (1960).

(7) J. D. Cocker and T. G. Halsall, *ibid.*, 3441 (1957).

(8) G. J. Heiszwolf and H. Kloosterziel, *Chem. Commun.*, **1966**, 51.

(9) (a) W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Letters*, 865 (1963); (b) G. Stork, *Pure Appl. Chem.*, **9**, 131 (1964).

(10) O. I. Fedorova, G. S. Grinenko, and V. I. Maksimov, *Dokl. Akad. Nauk SSSR*, **171**, 880 (1966).

tively, to a mixture of the desired C-alkylation product (6) and the bicyclic starting material (2). The two compounds could then be separated by column chromatography.

Catalytic hydrogenation of the enedione (6), equilibration of the side chain followed by ring closure, and removal of the *t*-butyl protective group gave the desired BCD tricyclic intermediate (8) in a 50% yield based on the enedione (6). From this yield figure, the catalytic hydrogenation must have given a reasonable amount (more than 50%) of the desired C/D *trans* isomer under the conditions described in the Experimental Section. Hydrogenation in ethyl alcohol with palladium on calcium carbonate or on carbon, as well as with palladium on barium sulfate in ethyl acetate, and the use of acidic or basic reaction media gave inferior results. It had been reported previously[6] that the bicyclic unsaturated keto alcohol (1) gave, under a variety of hydrogenation conditions, only the thermodynamically more stable C/D *cis* isomer. On the other hand, with a propionic acid side chain at C-8, a fair amount of the desired C/D *trans* isomer can be obtained.[5a,c]

The ultraviolet, infrared (in solution), and nmr spectra of the racemic BCD tricyclic compound (8) were identical with those of an optically active authentic sample obtained from Roussel-Uclaf, prepared by an independent total synthesis.[5a,c]

Oxidation of 8 with chromium trioxide gave the tricyclic diketone (9). The ultraviolet, infrared (in solution), nmr, and mass spectra were identical with those of an optically active authentic sample.

The difference between the chemical shifts of the C-13 methyls of 8 and 9 is in agreement with the difference observed with the C-13 methyl signals of 14α,17β-hydroxy and 17-keto steroids. The nmr data thus support the assigned stereochemistry.

Experimental Section[11]

1β-*t*-Butoxy-7,7a-dihydro-7aβ-methyl-5(6H)-indanone (2).—A solution of 50.0 g of crystalline bicyclic hydroxy ketone (1)[1] in 1250 ml of methylene chloride was cooled in an acetone–Dry Ice bath and treated with 12.5 ml (0.10 mole) of 45% boron fluoride etherate and 5.25 ml (0.10 mole) of 100% phosphoric acid.[12] To this was added 1880 ml of isobutylene (collected at the same temperature) and the mixture was stirred and allowed to warm to room temperature over 3 hr. More catalyst was added (0.05 mole of each) and the reaction was allowed to continue overnight at room temperature. The product was poured into 1250 ml of 2 *N* ammonium hydroxide and the aqueous phase was extracted with three 600-ml portions of methylene chloride: yield, 74 g of *t*-butoxyindanone 2 as a semisolid. This was treated with 5.0 g of Norit in 150 ml of petroleum ether (bp 30–60°), cooled overnight at −20°, and 35 g of yellow, crystalline 2 was collected: mp 41–43.5°; λ_{max} 238 mμ (ε 13,600). Concentration of the mother liquor to 75 ml afforded a second crop, 7.8 g, mp 42–43.5°, with sintering at 39°. Both crops were one-spot material by tlc (silica gel; ethyl acetate–benzene 2:1; sprayed with sulfuric acid–methanol 1:1 v/v, and heated, then sprayed with 10% phosphomolybdic acid–methanol). The analytical sample of 2 was obtained as colorless crystals, mp 43–45°, by filtration over a 20:1 column of alumina (Woelm, neutral, activity I) and elution with benzene and benzene–ethyl acetate (1–2% mixtures, followed by crystallization from petroleum ether: λ_{max} 239 mμ (ε 14,100); ν_{max} 1663 cm^{-1}; δ 1.12 (7aβ-methyl), 1.18 ppm (1β-*t*-butyl).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.81; H, 9.93.

2-(2-Bromoethyl)-2-ethyl-1,3-dioxolane (3).—To 133.5 g of anhydrous aluminum bromide was added with stirring and cooling 200 ml of methylene chloride. Hydroquinone monomethyl ether (0.1 g) was added and the suspension was cooled to −10°. Propionyl bromide (63.5 g, 41.8 ml) was added within 10 min while stirring at −10°. Most of the material dissolved. Ethylene gas was then bubbled into the solution through a calcium chloride drying tower at a rapid rate so that the temperature did not exceed 0°. After 1.5 hr, no more gas was absorbed and stirring without further addition of ethylene was continued for 30 min. The solution was transferred to a dropping funnel and added dropwise while stirring to an ice-cold solution of 125 ml of concentrated hydrochloric acid and 485 ml of ice water. The mixture was extracted with methylene chloride, washed (first with saturated sodium bicarbonate), and dried in the usual manner to afford a methylene chloride solution of 1-bromo-3-pentanone of suitable purity for the *trans*-ketalization step.

Methyl ethyl ketone cyclic ethylene ketal (235 g), *p*-toluenesulfonic acid monohydrate (0.75 g), and benzene (220 ml) were added to the above-mentioned methylene chloride solution, the mixture was stirred, and heated under nitrogen while the methylene chloride was slowly distilled through a Fenske column. As the distillation proceeded, the volume in the distilling flask was kept constant by the addition of benzene. After 6 hr, approximately 400 ml of distillate was collected and the solution was then refluxed for 16 hr longer without removal of solvent. The solution was cooled with an ice bath and a saturated sodium bicarbonate solution was added to neutralize the acid. The water layer was separated and the benzene was dried with sodium sulfate and evaporated *in vacuo*. The residual oil (3) was distilled under high vacuum: bp 41–45° (0.4 mm); 61.1 g (58%); $n^{24}D$ 1.4690. The compound should be stored in the refrigerator.

Anal. Calcd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27; Br, 38.22. Found: C, 40.45; H, 6.56; Br, 37.74.

1β-*t*-Butoxy-7,7a-dihydro-7aβ-methyl-4-(3-oxopentyl)-5(6H)-indanone Cyclic Ethylene Ketal (4) and 1β-*t*-Butoxy-2,6,7,7a-tetrahydro-7aβ-methyl-5-[3-(1,3-dioxolan-2-yl)pentoxy]-1H-indene (5).—To a 53% dispersion of sodium hydride in mineral oil (1.17 g), washed with petroleum ether and dried under nitrogen, was added 40 ml of dimethyl sulfoxide (DMSO). The mixture was stirred and heated for 1 hr at 65° under nitrogen, cooled to room temperature, a solution of 5.0 g of *t*-butoxyindanone (2) in 40 ml of DMSO was added over 3 min, and after 1.5 hr 5.40 g of 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane (3) in 20 ml of DMSO was added. The mixture was stirred at room temperature for 4 hr; 100 ml of a saturated solution of ammonium chloride was added; and extraction with four 100-ml portions of ether in the usual fashion yielded 8.5 g of a yellow oil. A 7-g portion of this oil in 15 ml of petroleum ether was chromatographed over 35 g of alumina (Woelm, neutral, activity I) and afforded as the major fraction from petroleum ether 4.7 g of 4 plus 5 as an oil: λ_{max} 249 mμ (ε 11,300); nmr analysis showed the presence of *ca.* 25% enol ether 5.

In another experiment, 554 mg of the crude alkylation product was chromatographed over 64 g of alumina (Woelm, neutral, activity III) using a 70:30 mixture of benzene and petroleum ether. It was thus possible to isolate 57.5 mg of the di(en)ol ether 5 as the faster moving and 375 mg of the desired alkylation product 4 as the slower moving components. The di(en)ol ether 5 was characterized by ultraviolet and by infrared spectroscopy: λ_{max} (ether) 245 mμ (ε 15,630); ν_{max} 1639 and 1600 cm^{-1} (doublet of enol ether). Material of this type was used for subsequent reactions. A sample of 4 obtained by preparative tlc (2-mm-plates; chloroform–ethyl acetate 19:1) analyzed as 99.4% pure by vpc: λ_{max} 250 mμ (ε 12,300); ν_{max} 1655, 1646 (inflection) cm^{-1}; δ 1.07 (7aβ-methyl), 1.18 ppm (1β-*t*-butyl).

1β-*t*-Butoxy-7,7a-dihydro-7aβ-methyl-4-(3-oxopentyl)-5(6H)-indanone (6).—A 25.0-g sample of 4 plus 5 (purified by column

(11) All melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. All ultraviolet spectra were taken in ethyl alcohol with a Cary Model 14M spectrophotometer. Nmr spectra were taken with a Varian A-60 spectrometer at 60 Mcps and tetramethylsilane as an internal standard. Infrared spectra were taken in *ca.* 3% solutions in chloroform with a Beckman IR-9 recording spectrophotometer. Vpc was performed on a F & M Model 810 in the flame mode. Columns used were 4 ft × 0.25 in. stainless steel with 3% SE 30 on 80–100 mesh Diatoport S with helium flow of 120 cc/min or 6 ft × 0.25 in. aluminum with 1% PEG 4000 MS on 60–70 mesh Anakrom ABS with nitrogen flow of 100 cc/min and programed temperature runs. Unless otherwise stated, all products were isolated by extraction with an organic solvent, washing with water and saturated sodium chloride solution, and drying over anhydrous sodium sulfate.

(12) H. C. Beyerman and G. J. Heiszwolf, *Rec. Trav. Chim.*, **84**, 203 (1965).

chromatography as described above) in 320 ml of acetic acid and 11 ml of water was stirred and warmed at 65° for 4 hr under nitrogen. The solution was cooled in an ice–water bath, neutralized to pH 9 with 10% sodium hydroxide, and the product was isolated by ether extraction (three 500-ml portions): yield, 19.5 g of **6** plus **2**: vpc analysis showed **6–3** ≅75:25; λ_{max} 249 mμ (ε 11,790). Material from combined runs totaling 25.3 g was chromatographed on Florisil (100–200 mesh, 1520 g, solvent system petroleum ether–benzene–ethyl acetate). Early fractions from 2–4% ethyl acetate–benzene contained mostly **2** (4.6 g) and mixed fractions of **2** and **6**. The major fraction from 4% ethyl acetate–benzene contained 11.1 g of enedione **6** which slowly solidified on cooling and scratching and which was crystallized from methanol–water or petroleum ether cooled to −20°. The analytical sample of **6** was obtained as colorless needles from petroleum ether and dried at room temperature *in vacuo* (0.03 mm) for 6 hr: mp 38–41°; λ_{max} 249 mμ (ε 12,500); ν_{max} 1716, 1655 cm^{-1}; δ 1.07 (7aβ-methyl), 1.18 ppm (1β-*t*-butyl).

Anal. Calcd for $C_{19}H_{30}O_3$ (306.43): C, 74.47; H, 9.87. Found: C, 74.76; H, 10.21.

(±)-17β-Hydroxy-Δ$^{9(10)}$-des-A-androsten-5-one (8).—To a prereduced suspension of 1.32 g of 10% palladium–barium sulfate in 28 ml of absolute ethyl alcohol was added 3.0 g of enedione **6** in 28 ml of ethyl alcohol and the mixture was shaken under hydrogen at room temperature and essentially atmospheric pressure. After 50 min, 120% of the theoretical amount of hydrogen had been consumed. The solvent was removed *in vacuo* and the residue (3.0 g, no ultraviolet absorption) was dissolved in 120 ml of methanol containing 12 ml of 1 *N* sodium methoxide and allowed to equilibrate under nitrogen for 15 min. The solution was neutralized with ammonium chloride and extracted with three 100-ml portions of ether. Cyclization and hydrolysis of the crude product (3.0 g) was achieved by refluxing under nitrogen for 6.5 hr in 150 ml of ethyl alcohol containing 30 ml of 3 *N* hydrochloric acid. The mixture was neutralized with 5% sodium bicarbonate, the solvent was removed *in vacuo*, and the crude product (2.0 g) was obtained by methylene chloride extraction. Crystallization from ether–petroleum ether afforded 1.16 g of the BCD tricyclic compound **8**: λ_{max} 248 mμ (ε 15,000); essentially pure by vpc. The melting range of such preparations is not an indication of purity since a typical melting point would be *ca.* 120–127° with sintering. An analytical sample of **8** was prepared by chromatography on Florisil with benzene and crystallization from ether: mp 132.5–135.5°; λ_{max} 248.5 mμ (ε 15,400); ν_{max} 3650 and 3450–3550, 1665, 1605 cm^{-1}; δ 0.91 (13-CH_3), 1.79 ppm (10-CH_3).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.02; H, 9.52.

(±)-Δ$^{9(10)}$-Des-A-androstene-5,17-dione (9).—The keto alcohol **8** (117 mg) was dissolved in 21 ml of acetone (distilled from potassium permanganate), cooled and stirred at −12°, and treated with 0.14 ml of 8 *N* chromic anhydride in sulfuric acid under nitrogen.[13] After 15 min, 10 ml of saturated sodium chloride solution was added and the mixture was extracted twice with ethyl acetate and once with ether. The organic phase was washed (1 *N* sodium bicarbonate) and worked up in the usual manner: yield, 115 mg of an oil that crystallized on scratching. Crystallization from ether–petroleum ether gave 95 mg of the tricyclic diketone **9**: mp 95–97.5°; λ_{max} 247 mμ (ε 15,900); ν_{max} 1740, 1665, 1605 cm^{-1}; δ 1.03 (13β-CH_3), 1.80 ppm (10-CH_3). Recrystallization from ether gave the pure sample of **9**, mp 98.5–100° (lit.[4] mp 98–100°).

Registry No.—**2**, 13652-01-2; **3**, 13652-02-3; **4**, 13699-65-5; **5**, 13652-03-4; **6**, 13652-04-5; **8**, 13652-05-6; **9**, 13652-06-7.

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The Synthesis of Racemic and (3*R*)-Methylcyclopentane-1,2-dicarboxylic Acids (Nepetic Acids)[1a]

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The Favorskii-type rearrangement of (+)-methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (**11a**) derived from (+)-pulegone (**8**) provides a convenient synthesis of the optically active (3*R*)-methylcyclopentane-1,2-dicarboxylic acids (**12a**, **13a**, **14a**, and **15a**). The purification of these acids was accomplished by fractional precipitation of their barium salts and preparative gas chromatography separation of their methyl esters. The correlation of the (−)-*cis,cis* acid, **15a**, derived from (+)-pulegone (**8**), with genipin (**16**) is described. The four racemic 3-methylcyclopentane-1,2-dicarboxylic acids (**12c**, **13c**, **14c**, and **15c**) were readily prepared from the racemic keto ester **11c**.

The racemic 3-methylcyclopentane-1,2-dicarboxylic acids have been synthesized, and their properties have been described.[2] Optically active acids having this carbon skeleton and the (3*S*)-methyl absolute configuration[3a,b] are known as nepetic acids. Two of these nepetic acids, the *trans,trans* isomer **4** and the *cis,trans* isomer **6**, were previously obtained as degradation products of nepetalactone (**1a**)[3c] *via* nepetonic acid (**2**) and the enol lactone **3** as shown in Chart I.[4]

A third nepetic acid, the *trans,cis* isomer **5**, was obtained from epinepetalactone **1b**.[3b] The remaining member of this series, *cis,cis*-nepetic acid (**7**), has not been described. Certain members of the enantiomeric series of 3-methylcyclopentane-1,2-dicarboxylic acids having the (3*R*)-methyl configuration were first en-

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