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TOTAL SYNTHESIS OF OPTICALLY ACTIVE (−)17β-HYDROXY-$\Delta^{9(10)}$-desA-ANDROSTEN-5-ONE[1]

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Abstract—(±)7,7a-Dihydro-1β-hydroxy-7aβ-methyl-5(6H)-indanone was resolved via the hydrogen phthalate–brucine salt. The dextrorotatory enantiomer (+)**4** was then converted in a 5-step stereospecific total synthesis to the important BCD tricyclic intermediate (−)**13**. The synthesis also adds additional proof for the absolute configuration of the bicyclic keto alcohol (+)**4** by correlation with (±)**13**, a known degradation product of natural steroids.

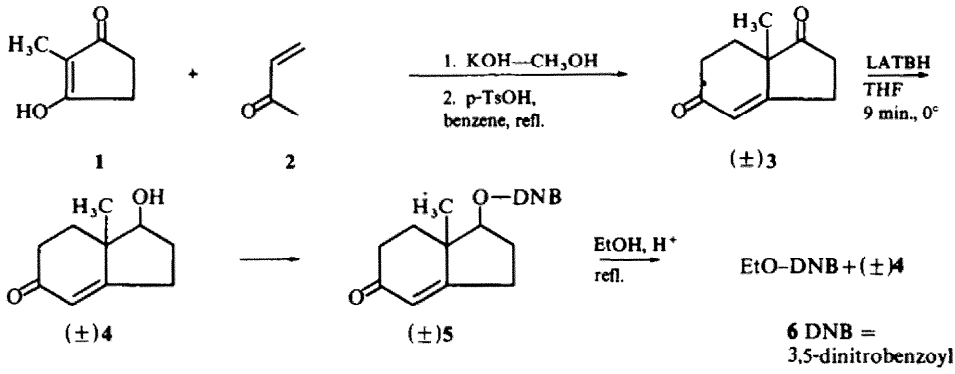
THE stereospecific total synthesis of racemic 17β-hydroxy-$\Delta^{9(10)}$-desA-androsten-5-one[2] and the successful conversion of normal steroids to retrosteroids via such BCD tricyclic intermediates[3] pointed to the importance of a new total synthesis of the desired levaorotatory enantiomer of 17β-hydroxy-$\Delta^{9(10)}$-desA-androsten-5-one, i.e. (−)**13**.

The starting material for the present scheme, 2-methylcyclopentane-1,3-dione (**1**) was prepared in a 44% overall yield[1] by modification of the original Panouse procedure[4] in which it was obtained in a 20·6% yield.

Michael addition of methyl vinyl ketone (**2**) to the dione **1** followed by dehydration, without isolation of the ketol intermediate, gave the known racemic bicyclic diketone (±)**3** in 73% yield.[5] The 1-keto group of the dione had previously been selectively and stereospecifically reduced with sodium borohydride to give the unsaturated keto alcohol (±)**4** as an oil.[6] In the present work, reduction with lithium aluminum tri-tertiary butoxy hydride gave (±)**4** as a crystalline solid, m.p. 66·5–67·5°. It was also possible to obtain crystalline (±)**4** by the original method[6] although in somewhat lower yield. The 1β-equatorial configuration of the OH group is in agreement with the product development control principle, as applied by Chinn to the reduction of the unhindered 17-keto group of steroids.[7]

The 3,5-dinitrobenzoate (±)**5** was then prepared in good yield, and had a m.p. of 149–150°. It was characterized by UV, IR and NMR spectroscopy, and by microanalysis. Boyce and Whitehurst[6] reported a m.p. of 90–91° for the compound, but gave no physical chemical or microanalytical data. Refluxing the ester with ethyl alcohol and a trace of acid resulted in transesterification; the bicyclic unsaturated keto alcohol (±)**4** and ethyl 3,5-dinitrobenzoate (**6**), m.p. 91–92°, were isolated. Since Boyce and Whitehurst used ethyl alcohol to recrystallize their compound, they most probably isolated ethyl 3,5-dinitrobenzoate (Chart I).

It was decided to do the optical resolution at the earliest possible stage of the total synthesis. The optically active bicyclic hydroxy ketone (+)**4** was therefore prepared by resolving the corresponding racemic compound (±)**4** vis the hydrogen phthalate-brucine salt; (+)**4** had previously been prepared from the racemic diketone (±)**3** by



(±)4 (±)5 (±)3

CHART I

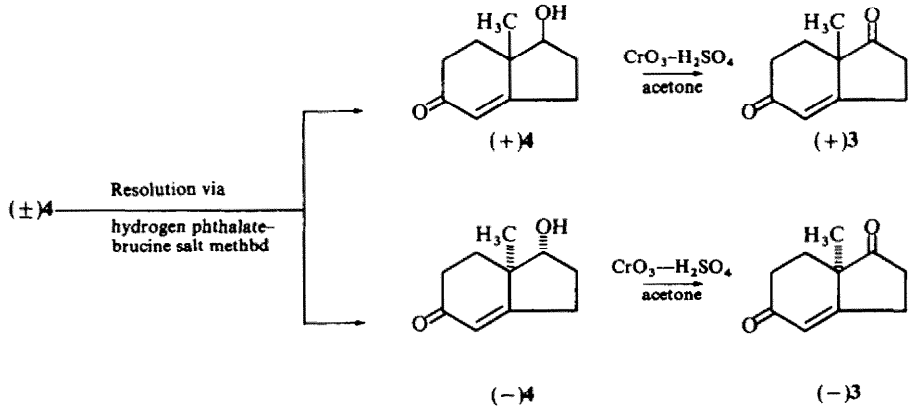
microbiological means.[8] The chemical resolution gave the desired compound in a high overall yield (75%), and did not require chromatography.

The hitherto unknown levorotatory unsaturated keto alcohol (−)4 was also obtained by this chemical resolution in 52% overall yield. The two enantiomeric alcohols had, as expected, identical m.p., UV, IR and NMR spectra, and identical but opposite rotations.

The crude unsaturated keto alcohols [(+) and (−)4] showed a slightly higher optical rotation than the pure compounds. This apparent anomaly is due to a small amount of the diketones (+)3 or (−)3, respectively, which have a very high specific rotation. The presence of this impurity could be shown by TLC.

It should be mentioned that the last step of the chemical resolution, the saponification of the optically active hydrogen phthalate, must be executed with special care, because of the sensitivity of the resulting bicyclic unsaturated keto alcohol (±)4 or (−)4 to base.

The optically active diketones (+)3 and (−)3[8] were then prepared by chromium trioxide oxidation of the corresponding alcohols (+)4 and (−)4, respectively. The results are summarized in Chart II and Table 1.



(±)4 (+)4 (+)3 (−)4 (−)3

CHART II

TABLE 1.

Compound	M.p.	λ_{max} (mμ)	ε	$[\alpha]_D^{25}$ (benzene; ~ 1%)
(+)**4**	67–68·5 (eth-peth) 84–85° (i-Pr_2O)	240	13,400	+90·4°
(+)**3**	66–66·5°	237	12,000	+362°
(−)**4**	84–85·5° (i-Pr_2O)	240	13,400	−90·4°
(−)**3**	66–66·5°	237	11,400	−363°

The dextrorotatory unsaturated keto alcohol (+)**4** was then chosen to prepare (−)17β-hydroxy-$\Delta^{9(10)}$-desA-androsten-5-one [(−)**13**], because the absolute configuration of (+)**4** which has been established,[9] corresponds to the absolute configuration of testosterone acetate at C-13 and C-17. Since (−)**13** was first obtained by the chemical degradation of testosterone acetate,[10] it was expected that (+)**4** could be converted to (−)**13** by introducing the new centers of asymmetry at C-8 and C-14 in a stereospecific total synthesis, in a fashion similar to that used[2] with racemic (±)**13**.

Chart III shows the synthesis of the desired BCD tricyclic intermediate (−)**13**. The tetrahydropyranyl ether (+)**7** of the unsaturated keto alcohol (+)**4** was prepared to protect the compound during the course of alkylation. The conjugate anion **8** was formed with sodium hydride in DMSO. This was alkylated with 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane[2] to give the crude alkylation product, which consisted of 58% C-alkylation product and 32% O-alkylation products, as indicated by VPC analysis.

The desired C-alkylation product (+)**9** and the O-alkylation product (**10**) could be separated by column chromatography, and characterized by UV and IR spectroscopy. The O-alkylation product is a di(en)ol-ether (**10**) which can be converted readily to the bicyclic unsaturated ketone (+)**7** by a short treatment (2 min at 20°) with dilute acid.

These results are similar to those obtained[2] in the alkylation of the t-butyl ether of the racemic keto alcohol (±)**4**. In the present scheme, no attempt was made to remove the cyclic ethylene ketal group selectively because of the far greater acid sensitivity of the tetrahydropyranyl protective group in comparison to the t-butyl ether group. The retention of such a bulky β-oriented protective group is important, because it favors the attack by hydrogen from the less hindered α-face of the molecule.

Catalytic hydrogenation, equilibration of the side chain, and ring closure gave the desired levorotatory BCD tricyclic intermediate (−)**13** in a 39% yield based on the C-alkylation product (+)**9**. Based on this overall yield, the catalytic hydrogenation of (+)**9** must have given a reasonable amount (at least 50%) of the C/D *trans* isomer **11**. This result is comparable to that obtained in the hydrogenation of the C-alkylation product of the racemic t-butyl ether derivative.[2]

The compound [(−)**13**] was identical in every respect with an authentic sample obtained from Roussel–Uclaf, prepared by an independent total synthesis.[11a,b]

The stereospecific total synthesis described in the present paper thus also adds additional proof for the absolute configuration[9] of the bicylic keto alcohol (+)**4** by connecting it with a known[10] degradation product of natural steroids.

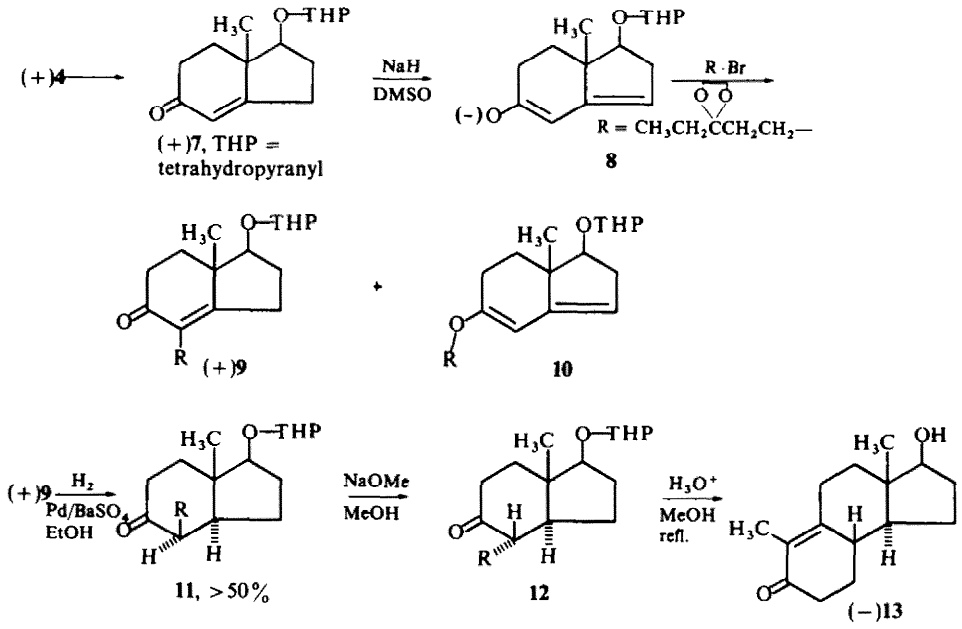


CHART III

EXPERIMENTAL*

(±)-7,7a-Dihydro-1β-hydroxy-7aβ-methyl-5(6H)-indanone (±)4

To 24·6 g of (±)-3[5] in 300 ml dry THF was added while stirring at 0° 93·75 g of lithium aluminum tri-t-butoxy hydride in 600 ml dry THF. After stirring for exactly 9 min at 0°, 50 ml acetone and 175 ml ice water were added carefully, and the resulting suspension was neutralized with 2N H_2SO_4. The solvents were evaporated under vacuum, and the residue was extracted with EtOAc and with ether. The combined extract was washed with NaCl aq, dried with $NaSO_4$, treated with Norite "A", filtered, and evaporated under vacuum to give 22·73 g (91·3%) of an oil, which crystallized after standing for 16 hr in the refrigerator. This crude, crystalline material had a m.p. of 57·5–62°. Recrystallization from ether gave 10·4 g of (±)4 (41·8%), m.p. 66·5–67·5°; λ_{max} 240 mμ (ε 13,500); ν_{max} 3620 (free OH), 3250–3500 (bonded OH), 1665 cm^{-1} (α,β-unsaturated ketone); δ 1·15 (7αβ-Me), 5·78 (vinyl proton) in $CDCl_3$. (Found: C, 72·25; H, 8·75. Calc. for $C_{10}H_{14}O_2$: C, 72·26; H, 8·49%.)

The non-crystalline residue had an UV absorption: λ_{max} 240 mμ (ε 11,570); IR and NMR spectra were compatible with (±)4; VPC indicated minor impurities in the order of 1–5%.

(±)-7,7a-Dihydro-1β-hydroxy-7aβ-methyl-5(6H)-indanone-3,5-dinitrobenzoate (±)5

To 1·66 g of (±)4 in 12·5 ml dry pyridine was added while stirring in an ice bath under N_2, 2·39 g 3,5-dinitrobenzoyl chloride. After the exothermic reaction had subsided, the reaction mixture was stirred at +20° for 16 hr, then it was heated to 95–100° for 1 hr. It was cooled to +20°, and then poured into 200 ml of ice cold 1N HCl. To the resulting stirred suspension was added 200 ml EtOAc. The water phase was separated, and re-extracted with EtOAc and with ether. The combined organic extracts were washed with water, then with $NaHCO_3$ aq, and finally with a NaCl aq. The soln was dried with Na_2SO_4, treated with Norite "A", filtered, and evaporated under vacuum to give 3·165 g (88%) of crude, crystalline (±)5, m.p. 147–148°. Recrystallization from acetone–hexane gave the analytically pure sample, m.p. 149–150°;

* All m.p. were determined in a Thomas Hoover m.p. apparatus and are corrected. All UV spectra were taken in EtOH. All NMR spectra were taken on a Varian A-60 spectrometer at 60 Mc/s and TMS as an internal standard. IR spectra were taken as ca 3% soln in $CHCl_3$ with a Beckman IR-9. VPC was obtained with a F and M model 810 instrument in the flame mode; column, 6′ × ¼″ O.D. aluminum with 1% PEG 4000 MS on 60–70 mesh Anakrom ABS; N_2 flow of 100 cc/min and programmed temp runs. All optical rotations were measured in approx 1% solns.

λ_{max} 233 mμ (ε 34,750); ν_{max}^{KBr} 1725 (CO of ester), 1675 cm^{-1} (α,β-unsaturated ketone); δ 1·36 (7aβ-Me), 5·80 (vinyl proton) in DMSO-d_6. (Found: C, 56·69; H, 4·71; N, 7·84. $C_{17}H_{16}N_2O_7$ requires: C, 56·67; H, 4·47; N, 7·78%.)

Transesterification of the 3,5-*dinitrobenzoate* (±)**5**

To 101 mg of (±)**5** was added 10 ml EtOH and 0·015 ml conc HCl, and the mixture was refluxed for 1 hr. TLC of the soln showed 3 components: the fastest was compatible with ethyl 3,5-dinitrobenzoate, the slowest corresponded to (±)**4** and the middle spot was that of the starting material (±)**5**. The mixture was cooled to room temp, and 20·1 mg of crude (±)**5** m.p. 144–145° was filtered off. The mother liquor was evaporated to dryness under vacuum. The residue was dissolved in a small amount ether, and 15·3 mg of a second crop crude (±)**5** was filtered off. The mother liquor was again evaporated to dryness under vacuum, and the residue was dissolved in acetone. A small amount of water was added, and 31·9 mg of crystalline material was filtered off, m.p. 89·5–90°. This material was identical in every respect with an authentic sample of **6**. The other product of the transesterification, (±)**4**, remained in the water and could be identified by TLC.

Racemic hydrogen phthalate of the hydroxy ketone (±)**4**

To 40 ml dry pyridine was added 19·96 g of (±)**4** and 17·76 g sublimed phthalic anhydride. The suspension was stirred under N_2 at +20° for 16 hr. The resulting soln was heated for 1 hr to 95–100° while stirring under N_2. The soln was poured into ice-water, and it was acidified to pH 2·0 at +5° with 2N HCl. The resulting crystalline ppt was filtered off, and dried to give 33·59 g (89·1%) of the crude racemic hydrogen phthalate, m.p. 179–181°. Recrystallization from acetonitrile gave analytically pure racemic hydrogen phthalate, m.p. 187–189°: λ_{max} 234 (ε 21,800), 274 (ε 1460), 281 (ε 1350); ν_{max} 3500 and 2500–2700 (OH of acid), 1725 (CO of ester), 1705 (CO of acid), 1665 (α-β-unsaturated ketone). (Found: C, 68·67; H, 6·09. $C_{18}H_{18}O_5$ requires: C, 68·78; H, 5·77%.)

Diastereoisomeric brucine salts of the (+)- *and* (−)-*hydrogen phthalates of* (+)**4** *and* (−)**4**

Brucine[12] (39·7 g) was dissolved in 640 ml dry benzene. To remove the small amount of water present, 100 ml of the benzene was distilled off.

The soln was cooled to room temp, and 28·0 g of the racemic hydrogen phthalate of (±)**4** was added in 100 ml hot benzene. Again, 100 ml benzene was distilled off and the soln was cooled to room temp. Scratching induced crystallization. After standing at +20° for 16 hr, 31·6 g of the crude brucine salt of the (+)-hydrogen phthalate was filtered off, m.p. 134·5–136° (dec), $[\alpha]_D^{25}$ −1·70° (Chf). The filtrate was used to obtain the diastereoisomeric brucine salt of the (−)-hydrogen phthalate, as described below. The crude crystalline brucine salt of the (+)-hydrogen phthalate was recrystallized from benzene to give 26·74 g of pure brucine salt, m.p. 136·5–137·5° (dec), $[\alpha]_D^{25}$ −0·293° (Chf). A second crop, 2·35 g, m.p. 133–134·5° (dec), $[\alpha]_D^{25}$ −0·182° (Chf) raised the yield to 91·8%.

The mother liquor of the crude brucine salt of the (+)-hydrogen phthalate was evaporated to dryness under vacuum. The residual oil was treated several times with ether, and the ether was evaporated under vacuum. It was then dissolved in hot acetone and a small amount of ether was added. After standing for 16 hr at +20°, 34·2 g of the crude brucine salt of the (−)-hydrogen phthalate was filtered off, m.p. 118–142° (dec), $[\alpha]_D^{25}$ −31·9° (Chf). Since the salt could not be purified readily, it was used without further purification for the preparation of the (−)-hydrogen phthalate.

(+)-*Hydrogen phthalate of* (+)**4**

To 28·83 g of the brucine salt of the (+)-hydrogen phthalate in 300 ml acetone was added while stirring at +20° 360 ml 0·16N HCl (use of 1N HCl precipitates brucine hydrochloride which can be filtered off, but in this preparation no attempt was made to recover the brucine salt). The acetone was then evaporated under vacuum and the resulting oil was extracted from the water with EtOAc and with ether. The combined extract was washed with 0·1N HCl, then with a NaCl aq, dried with Na_2SO_4, filtered, and evaporated under vacuum to give 11·51 g (100%) of the hydrogen phthalate of (±)**4**, m.p. 130–131·5, $[\alpha]_D^{25}$ +102·9° (Chf). It was crystallized from benzene to give 10·01 g, m.p. 130–130·5°, $[\alpha]_D^{25}$ +104·1° (Chf) and 1·15 g, m.p. 128·5–129°, $[\alpha]_D^{25}$ +102·9° (Chf). Both crops could be used in the next reaction step. (Found: C, 69·00; H, 5·84. $C_{18}H_{18}O_5$ requires: C, 68·78; H, 5·77%.)

(+)-(1S,7aS)-7,7a-*Dihydro*-1-*hydroxy*-7a-*methyl*-5(6H)-*indanone* (+)**4**

The (+)-hydrogen phthalate (10·86 g) was stirred under N_2 in 19 ml of 5·0N NaOH at +20° for 25 min.

The reaction mixture was then cooled in an ice bath and neutralized with 2N HCl. It was extracted with EtOAc and with ether, the combined extract was first washed with a sat $NaHCO_3$ aq then with a NaCl aq. It was dried with Na_2SO_4, filtered, and evaporated under vacuum to a solid which was crystallized from ether–pet. ether to give 5·25 g (91·5%) of crude (+)4, m.p. 67–68·5°, $[\alpha]_D^{25}$ +91·7° (Bz). TLC and IR spectroscopy showed a small amount of (+)3 to be present as an impurity; λ_{max} 240 mμ (ε 13,400). The overall yield of (+)4 is 75% based on 28·0 g of racemic hydrogen phthalate as starting material. Recrystallization from diisopropyl ether gave a second crystalline modification,[8] m.p. 84·5–85°, $[\alpha]^{25}$ +90·4° (Bz). (Found: C, 72·04; H, 8·73. Calc. for $C_{10}H_{14}O_2$: C, 72·26; H, 8·49%.)

The bicarbonate washings were then acidified with 2N HCl, it was dried with Na_2SO_4, filtered, and evaporated under vacuum to give 830 mg of the (+)-hydrogen phthalate, m.p. 129·5–130°, which could be reused in the process.

(+)-7,7a-*Dihydro*-7aβ-*methyl*-1,5(6H)-*indandione*, (+)3

To 170 mg of (+)4 in 10 ml acetone was added 0·42 ml 8·0N (O) CrO_3–H_2SO_4 while stirring under N_2 at 0° for 10 min. Water (10 ml) was added and the acetone was removed under vacuum. The resulting soln was extracted with EtOAc and with ether. The combined extract was washed free of acid with a NaCl aq, dried over Na_2SO_4, filtered, and evaporated under vacuum to give 139·7 mg of an oil. Preparative TLC on 1 mm thick silica gel plates using 1:1 mixture of benzene–EtOAc gave 98·3 mg of the (+)-diketone, m.p. 66–66·5°; λ_{max} 237 mμ (ε 12,000); ν_{max} 1746 (5-membered ring ketone), 1665 cm^{-1} (α,β-unsaturated ketone); $[\alpha]_D^{25}$ +360° (Bz).

(−)-*Hydrogen phthalate of* (−)4

To 15·86 g cf the brucine salt of the (−)-hydrogen phthalate (described under the preparation of the diastereoisomeric brucine salts) in 230 ml acetone was added while stirring at +20°, 270 ml 0·16N HCl. The acetone was then evaporated under vacuum and the resulting oil was extracted from the water with EtOAc and with ether. The combined extract was washed with 0·1N HCl, then with a Na_2SO_4, filtered, and evaporated under vacuum to give 6·82 g (96·8%) of an amorphous solid which was dissolved in 200 ml hot benzene. The soln after standing at +20° for 16 hr deposited crystals. Filtration gave 1·115 g of crude racemic hydrogen phthalate, m.p. 182·5–186°. The filtrate was evaporated to ½ its original volume and, on standing, deposited a crystalline crop which was filtered to give 3·72 g (54·5%) of the (−)-hydrogen phthalate, m.p. 130–131°; $[\alpha]_D^{25}$ −103·8° (Chf). Recrystallization from benzene gave the analytical sample with the m.p. and optical rotation unchanged. (Found: C, 68·80; H, 5·83. $C_{18}H_{18}O_5$ requires: C, 68·78; H, 5·77%)

(−)-(1R,7aR)-7,7a-*Dihydro*-1-*hydroxy*-7a-*methyl*-5(6H)-*indanone*, (−)4

A portion of the above described (−)-hydrogen phthalate (1·575 g) was stirred under N_2 in 2·8 ml 5·0N NaOH at +20° for 25 min. The reaction mixture was then worked up exactly as in the case of (+)4 to give 0·71 g (85·8%) crude (−)4, m.p. 70–79°, $[\alpha]_D^{25}$ −90·7° (Bs). TLC and IR spectroscopy showed a trace of the diketone (−)3 to be present as an impurity. The overall yield of (−)4 is 52·6% based on the racemic hydrogen phthalate starting material. Recrystallization from diisopropyl ether gave, like the enantiomeric alcohol, a second modification, m.p. 84–85·5°, $[\alpha]_D^{25}$ −90·4° (Bz); λ_{max} 240 mμ (ε 13,400). (Found: C, 72·04; H, 8·73. $C_{10}H_{14}O_2$ requires: C, 72·26; H, 8·49%.)

The basic aqueous solution was worked up as in the case of (+)4 to give 0·208 g (93% recovery) of the (−)-hydrogen phthalate, m.p. 129·5–130·5°, which can be reused in the process.

(−)-7,7a-*Dihydro*-7aα-*methyl*-1,5(6H)-*indandione*, (−)3

To 166 mg of (−)4 in 10 ml acetone was added 0·42 ml 8·0N(O) CrO_3–H_2SO_4 while stirring at −12° under N_2 for 10 min. The reaction mixture was worked up exactly as described for the preparation of (+)3 to give 133·6 mg of an oil which was purified by preparative TLC to give 85·9 mg of the (−)-diketone, m.p. 66–66·5°; λ_{max} 237 mμ (ε 11,400), $[\alpha]_D^{25}$ −363° (Bz).

(−)-17β-*Hydroxy*-$\Delta^{9(10)}$-*desA*-*androsten*-5-*one*, (−)13

(a) *Preparation of tetrahydropyranyl ether* (+)7. The alcohol (+)4 (2·5 g) was dissolved in 7 ml anhyd THF. Anhyd dihydropyran (4·5 ml) and 0·06 ml of 85% phosphoric acid were added while stirring under N_2 at +20°. The reaction mixture was refluxed for 5 hr, then cooled to approximately +10°, and added within 10 min to 25 ml of a cooled and stirred $NaHCO_3$ aq. Ether and enough water were then added to cause the separation of the organic layer. The ether layer was separated and the water layer was extracted

3 more times with ether. The combined ether extract was washed with NaCl aq, dried over Na_2SO_4, filtered, and evaporated under vacuum. The residual oil was treated with toluene and evaporated several times to give 3·70 g (98·4%) of an oil, (+)**7**. λ_{max} 238 mμ (ε 13,475); ν_{max} 1665 (α,β-unsaturated ketone), 1135, 1120, 1075, 1030 and 1020 cm^{-1} (ether bands); $[\alpha]_D^{25}$ +37·95° (Bz). The racemic (±)**7** is described in the literature.[13a,b]

(b) *Alkylation of the tetrahydropyranyl ether* (+)**7**. NaH in mineral oil (135 mg containing 53% hydride) was suspended in anhyd hexane under N_2. The hexane and mineral oil were removed and the NaH was dispersed in 4·7 ml anhyd DMSO. To this suspension was added within 10 min 743 mg of (+)**7** dissolved in 7 ml DMSO, while stirring at 18–20°. Gas evolution ceased after stirring for 1·75 hr, at which time 712 mg 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane,[2] in 4·6 ml DMSO was added within 10 min and stirring under N_2 at +20° was continued for 20 hr. The DMSO was then removed under high vacuum. The residue was treated with water and it was extracted with ether. The extract was washed with NaCl aq, extracted over Na_2SO_4, and evaporated under vacuum to give 1·115 g (93·5%) of an oil. VPC indicated 58% C-alkylation product and 32% O-alkylation product in the mixture. This crude oil was chromatographed, using a neutral aluminum oxide column (101 g of "Woelm", act. III) and benzene as the eluent. The faster moving component, 213 mg of an oil, appeared to be **10**; $\lambda_{max}^{Et_2O}$ 246 mμ (ε 15,600); ν_{max} 1639 and 1600 cm^{-1} (doublet of enol ether). The slower moving component, 631 mg of an oil, was the C-alkylation product (+)**9**; λ_{max} 249 mμ (ε 12,500); ν_{max} 1658 cm^{-1} (α,β-unsaturated ketone); $[\alpha]_D^{25}$ +19·2° (Bz). It was 89·4% pure by VPC.

(c) *Hydrogenation, equilibration and ring closure of* (+)**9**. The chromatographed alkylation product (2·84 g) was hydrogenated in two equal portions with a Parr shaking hydrogenation apparatus at 3 atm and 20°, using 150 ml of abs EtOH and 480 mg of 10% Pd–$BaSO_4$ catalyst for 1·42 g substrate. After 20 min the hydrogenation was stopped, the catalyst was filtered off and 480 mg fresh catalyst was added. After an additional 10 min the hydrogenation was finished. The soln was filtered through a pad of "Celite", and it was evaporated under vacuum to give 2·2 g of a mixture of reduction products containing at least 50% of **11**. The protective group was lost, in part, during the hydrogenation.

This mixture was then dissolved in 40 ml MeOH containing 350 mg NaOMe. The mixture was stirred under N_2 at 20° for 15 min to equilibrate. A soln of 37·0 ml 2N HCl and 65 ml distilled water was then added at once and the mixture was stirred and refluxed under N_2 for 5 hr. It was then cooled to +5° and neutralized with a 50% NaOH aq. The alcohol was evaporated under vacuum and the water soln was extracted with EtOAc and with ether. The combined extract was washed with NaCl aq, dried over Na_2SO_4 and evaporated under vacuum to give 1·39 g (85%) of an oily solid; λ_{max} 248·5 mμ (ε 11,450). It was suspended in a mixture of ether and pet. ether (b.p. 30–60°), the solvent-soluble fraction was removed and the solid residue was recrystallized from ether to give 409 mg of pure (−)**13**, m.p. 167–168·5°; λ_{max} mμ (ε 15,600); ν_{max} 3650, 3450–3550 (OH), 1665 (α,β-unsaturated ketone), 1605 cm^{-1} conj. double bond); δ 0·91 (13β-Me), 1·79 (10-Me). $[\alpha]_D^{25}$ −38·40° (Chf); $[\alpha]_D^{11}$ −41·75° (Chf); [lit.[10] $[\alpha]_D$ −42° (Chf)]. (Found: C, 76·92; H, 9·49. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%.)

An authentic sample obtained from Roussel–Uclaf, prepared by an independent total synthesis[11a,b] had m.p. 168–169·5°, identical UV, IR and NMR spectra and $[\alpha]_D^{25}$ −38·11° (Chf); $[\alpha]_D^{11}$ −41·46° (Chf).

The mother liquor of the present preparation was concentrated to a smaller volume and, on standing for 16 hr at 20°, it deposited 215 mg of a second crop of (−)**13**, m.p. 162–165°, 97·3% pure by VPC; $[\alpha]_D^{25}$ −37·45° (Chf).

2-Methylcyclopentane-1,3-dione **1**

To an ice cold soln of 23 g Na in 315 ml abs EtOH was added under N_2, with good stirring and cooling within 15 min, a cold soln of 36 g 2-butanone in 149 ml Et oxalate. It was stirred vigorously over a period of 16 hr at 20°, and then refluxed with stirring for 30 min on the steambath. It was cooled in an ice bath and acidified with 55 ml of 1 : 1 (by volume) H_2SO_4. An equal volume of acetone was added, and the Na_2SO_4 was filtered and washed with acetone.

The oily solid obtained after the evaporation of the acetone and alcohol *in vacuo* was refluxed under N_2 for 1 hr with 45 ml 2N HCl. The soln was cooled to approximately 60°. MeOH (100 ml) was added and it was stirred for 15 min at this temp (60°). The soln was cooled to 20°, and extracted thoroughly with Chf. The extract was dried over Na_2SO_4, filtered, and concentrated to an oil *in vacuo*. This oil was treated with 50 ml MeOH at about 65° for 10 min, it was cooled to 20°, and the MeOH was removed *in vacuo*. This treatment was repeated once more. The oily residue (96 g) was distilled in high *vacuo* (0·3 mm). The bath temp was slowly raised from 70° to approx 200°.

The distillate consisted of 84·6 g of a pale yellow mixture of an oil and a solid. The solid residue in the distilling flask weighed 11·4 g. The contents of the receiving flask was suspended in 100 ml acetone, 12 ml ice water added and it was allowed to stand at 20° for 15 min. The crystalline ppt was filtered off, washed twice with approximately 5 ml ice water. It was pressed well, air dried for 16 hr at 20° to give 15·84 g of colorless needles of the hydrate of 2-methylcyclopentane-1,3,4-dione, m.p. 81–82°.

Three additional crops (17·38 g) were obtained by repeated careful concentration of the mother liquors *in vacuo*, and cooling in an ice bath for approx 15 min. The crystalline crops were filtered off and washed twice with approx 2 ml ice water. These crops also had a m.p. of 81–82°.

The mother liquor was concentrated to approx half of its original volume. A yellow oil separated which was extracted with benzene. The aqueous soln was evaporated to dryness *in vacuo*. The powdery residue was taken up in Chf and the insoluble material (oxalic acid hydrate) was filtered off. The filtrate was evaporated to dryness *in vacuo*, 5 ml ice water was added and the crystalline ppt was filtered off, pressed well and air dried for 16 hr at 20°. This crop weighed 3·3 g, m.p. 80–81°.

Semicarbazide hydrochloride (26 g) was dissolved in 235 ml water. To this soln was added a soln of 35 g $NaOAc \cdot 3H_2O$ in 235 ml water. The resulting soln was added with stirring under N_2 within 30 min to a soln of the hydrate of the trione (32·6 g) in 235 ml EtOH. It was stirred for an additional 30 min, the semicarbazone was filtered through paper, and washed with a little ice water. It was pressed well, dried *in vacuo* over KOH at 60° for 16 hr to give 39·8 g of crystalline semicarbazone, m.p. 290–300° (dec).

Pellets of KOH (38·8 g) was dissolved in 388 ml ethylene glycol. The crude semicarbazone (38·8 g) was added to the soln, and the suspension was stirred and heated gradually (approx within 1 hr) to 145°. At this temp, everything went in soln. Heating and stirring was continued. At about 154°, the evolution of N_2 started. It was stirred at this temp for about 1 hr. During the next 2 hr, the temp inside of the flask was raised to 185°, and it was refluxed without stirring at this temp for 12 hr. The ethylene glycol was removed in high vacuo under N_2, until a light brown solid residue was obtained. (The complete removal of the ethylene glycol is important for the success of the following steps.) This was taken up in 200 ml ice water with external cooling, and the alkaline soln was acidified while cooling and stirring with approx 52 ml of conc HCl to pH 3. Around pH 4, the evolution of CO_2 was observed, and a light-brown ppt was formed. The suspension was stirred at ice bath temp for 1 hr, filtered through paper, washed with a little ice water, pressed well, dried *in vacuo* at 60° for 16 hr, to give 21·62 g (91·5%) of crude dione **1**, m.p. 213–214°. Recrystallization from acetone gave 17·51 g analytically pure **1**, m.p. 214–214·5°; λ_{max} 252·5 m.p. (ε 17,000). (Found: C, 64·08; H, 7·39. Calc. for $C_6H_8O_2$: C, 64·27; H, 7·19%.)

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