Stereocontrolled Total Synthesis of 19-Nor Steroids

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Received February 15, 1973

The C/D trans bicyclic β-keto ester **1** (electron donor) and ethyl vinyl ketone **2** (electron acceptor) model system gave the BCD-tricyclic **6** with the undesired stereochemistry at the steroidal C-8 position. Converting **1** to the electron acceptor β-keto mesylate **11** and attacking this with the anion of the β-keto ester **12** gave the desired BCD intermediate, (±)-**16**. The new synthetic scheme lends itself to the direct preparation of C-6-substituted derivatives (*e.g.*, **15**). Alternatively, the C/D trans bicyclic β-keto acid **17** could be converted to the α-methylene ketone **19**. An attack on this electron acceptor with the anion of **12** gave (±)-17β-hydroxy-$\Delta^{9(10)}$-de-*A*-androsten-5-one, (±)-**7**, in a two-step synthesis. Attacking **19** with the anion of a long-chain β-keto ester **20** gave (±)-19-nortestosterone, (±)-**21**, in a five-step stereocontrolled synthesis involving a single annulation reaction.

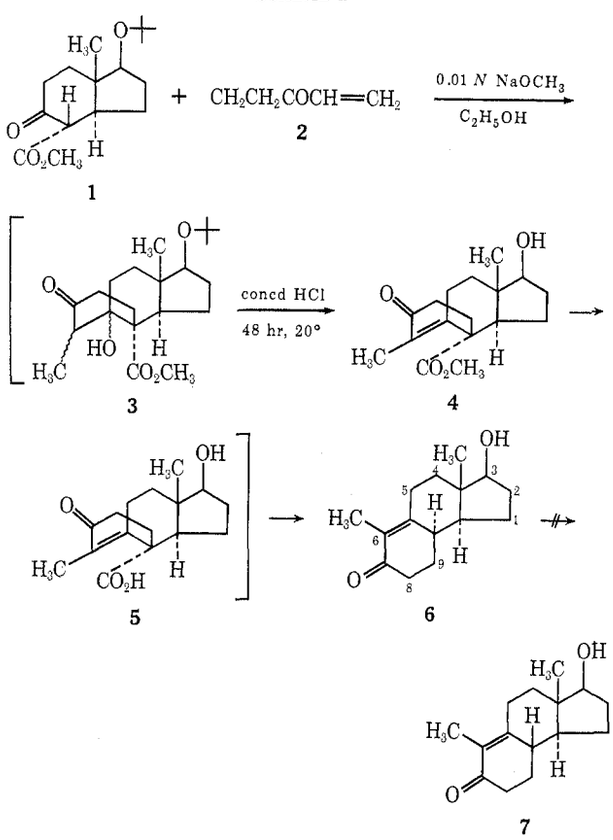
The total synthesis of steroids in general and of 19-nor steroids in particular has been quite extensively explored during the past approximately 35 years.[2]

In planning a new scheme of the total synthesis of 19-nor steroids it was contemplated to construct a properly functionalized bicyclic intermediate with the desired C/D trans stereochemistry, and then elaborate and attach ring B or rings A and B in a stereocontrolled single annulation reaction. The first problem has been the topic of the preceding communication;[3] the second part of the problem constitutes the subject matter of the present discussion.

In the first synthetic approach it was planned to use the C/D trans bicyclic β-keto ester **1**[3] as an electron donor and an α,β-unsaturated ketone such as ethyl vinyl ketone (**2**) as an electron acceptor in a model reaction. It was most important to find out if the desired stereochemistry could be obtained at C-8 and maintained at C-14 (steroidal numbering) during the course of the synthetic operation. The BCD-tricyclic intermediate (±)-**7** with the proper stereochemistry has been available to us for comparison by two independent syntheses in these laboratories.[4]

Since we have shown that the sodium enolate of the β-keto ester **1** can be formed with 0.01 *N* sodium methoxide in methanol,[3] the addition reaction to ethyl vinyl ketone **2** has been carried out in the presence of a catalytic amount of this base in methanol. Attempts to decarboxylate the reaction product **3** (Scheme I) under conditions normally used for β-keto esters were unsuccessful, suggesting the indicated ketol ester type of structure. Only after the elimination of water from **3** with concentrated hydrochloric acid could the vinylogous β-keto ester **4** be converted into a BCD tricyclic ketone **6** *via* hydrolysis to **5** followed by decarboxylation. The compound **6** proved to be different from the desired tricyclic racemic compound (±)-**7** by uv and ir spectroscopy and also by vpc analysis.

SCHEME I[a]



[a] All compounds reported in this paper are racemic; for convenience, only one enantiomer is shown.

The tricyclic derivative **6** is most likely a 9a-α isomer, formed by an sp^3-hybridized transition state in the decarboxylation reaction.[5] It could not be equilibrated to the desired (±)-**7**. There is presumably strong preference to involve the C-5 rather than the C-9a position in the conjugate anion formation, because of the C/D trans ring junction.[6]

There are probably two reasons for obtaining the wrong isomer: (a) the alkylation reaction proceeds in agreement with the *axial* alkylation principle[6,7] and (b) the initially formed alkylation product closes to the ketol ester intermediate **3**, thereby fixing the undesired stereochemistry of the B/C ring junction.

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(2) (a) For leading references up to 1966 see L. Velluz, J. Mathieu, and G. Nomine, *Tetrahedron, Suppl. 8, Part II*, 495 (1966). (b) P. Crabbe in "Terpenoids and Steroids," Vol. 2, K. H. Overton, Senior Reporter, The Chemical Society, London, 1972, p 329. (c) P. J. May in "Terpenoids and Steroids," Vol. 1, K. H. Overton, Senior Reporter, The Chemical Society, London, 1971, p 468. (d) S. E. Danishefsky and S. Danishefsky in "Progress in Total Synthesis," Vol. 1, Appleton-Century-Crofts, New York, N. Y., 1971, p 242. (e) A. A. Akhrem and Y. A. Titov, "Total Steroid Synthesis," Plenum Press, New York, N. Y., 1970.

(3) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **38**, 3239 (1973).

(4) (a) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967); (b) G. Saucy, R. Borer, and A. Fürst, *Helv. Chim. Acta*, **54**, 2034 (1971).

(5) J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, **88**, 3522 (1966).

(6) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem.*, **77**, 185 (1965).

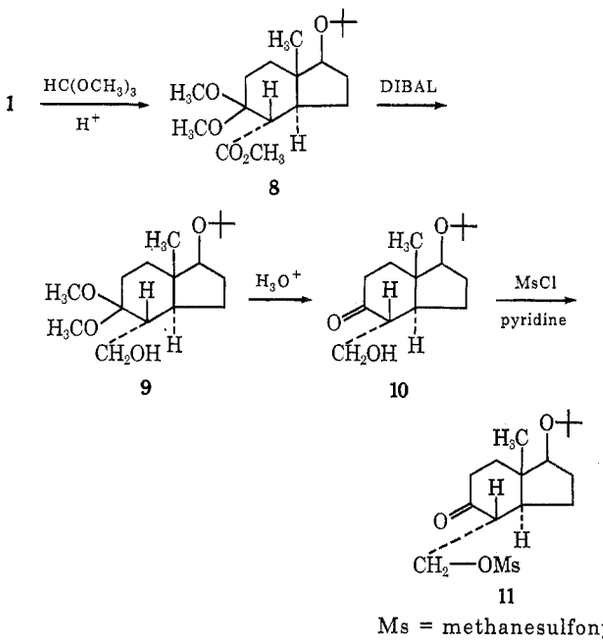
(7) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

On the other hand, the total synthesis of (±)-8β-methoxycarbonylestrone 3-methyl ether from 4α-methoxycarbonyl-7aβ-methyl-3aα-perhydroindene-1,5-dione and vinylcyclohexenone has been recently reported.[8] Structural differences of this Michael acceptor in comparison with ethyl vinyl ketone may well explain the different steric course of this synthesis.

In view of the results with ethyl vinyl ketone we decided to try to use the CD bicyclic compound as an electron acceptor rather than electron donor moiety in a synthesis which would allow the introduction of the proper stereochemistry at C-8 (steroidal numbering). Based on this idea we have indeed worked out two synthetic routes, one *via* the β-keto mesylate **11** and another *via* the α-methylene ketone **19**, leading to compounds possessing the desired stereochemistry.

The C/D trans bicyclic β-keto ester **1** was converted in a four-step sequence involving ketalization, reduction, hydrolysis, and mesylation to the β-keto mesylate **11** in an 87% overall yield (Scheme II). This β-keto

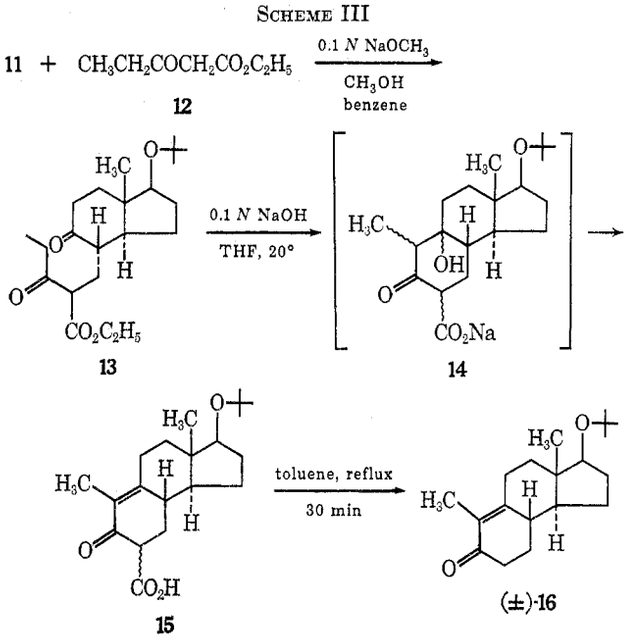
SCHEME II



mesylate was then allowed to react with the anion of ethyl propionyl acetate (**12**) to give the diketo ester **13**. The side chain of **13** assumed the thermodynamically favorable α equatorial orientation. This was due to the presence of an enolizable proton at the C-8 position (steroidal numbering). No ring closure occurred at this stage, because of the preferred enolization of the side-chain keto group toward the carboxylic ester function. Saponification of the ester group of **13** allowed ring closure to a nonisolated ketol (**14**) which was dehydrated to the α,β-unsaturated β-keto acid **15** by careful acidification of the reaction mixture. Decarboxylation in refluxing toluene gave the crude BCD tricyclic intermediate (±)-**16** (Scheme III). The structure was confirmed and the purity of the sample was established by comparing the uv, ir, tlc, and vpc data of the sample with those of an optically active sample

(8) K. Sakai and S. Amemiya, *Chem. Pharm. Bull.*, **18**, 641 (1970).

SCHEME III



of **16**.[9] This then constitutes chemical evidence of the stereochemistry of the bicyclic intermediate by connecting it with a BCD tricyclic derivative of known steric arrangement.

It should be pointed out that the carboxylic acid group in **15** is at the steroidal C-6 position. The metabolic role of a substituent at C-6 is well known.[2a] The new synthetic scheme thus lends itself to the preparation of such C-6 substituted derivatives.

Next we considered means of simplifying and improving the above-described synthesis. It was hoped that the trans bicyclic β-keto acid **17** could be converted to a β-amino ketone **18** in a Mannich reaction. The β-amino ketone in turn could be used in place of the β-keto mesylate **11** in the modified scheme. The β-keto acid **17**, however, suffered extensive decarboxylation in the presence of aqueous formaldehyde and piperidine hydrochloride. The desired reaction product could therefore not be obtained. It should be mentioned that these were essentially the conditions used by Mannich[10] to prepare β-amino ketones from β-keto acids, and by Robinson[11] and Schöpf[12] in their tropinone syntheses.

It occurred to us that decarboxylation of the β-keto acid **17** might lead to an intermediate $\Delta^{8(9)}$-enol (steroidal numbering), which could immediately be quenched by the formaldehyde–piperidine system, if the proper solvent was used. We chose to try dimethyl sulfoxide, because it was known to promote the decarboxylation of vinylogous β-keto acids.[13] The β-keto acid **17** was therefore dissolved in dimethyl sulfoxide, and the solution was allowed to stand at room temperature. Considerable decarboxylation occurred after a period of 2 hr, as indicated by thin layer chromatography. The β-keto acid **17** was then allowed to react with aqueous formaldehyde and piperidine hydrochloride in dimethyl sulfoxide at room temperature, giving

(9) Obtained through the courtesy of Dr. R. A. Micheli of these laboratories.

(10) C. Mannich and M. Bauroth, *Chem. Ber.*, **57**, 1108 (1924).

(11) R. Robinson, *J. Chem. Soc.*, **111**, 766 (1917).

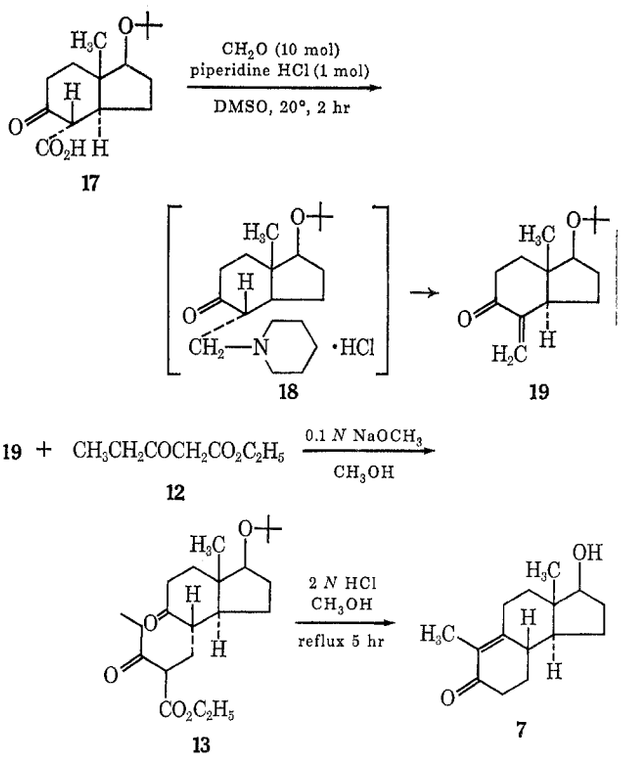
(12) C. Schöpf and G. Lehmann, *Justus Liebigs Ann. Chem.*, **518**, 1 (1935).

(13) K. Tanabe, R. Takasaki, R. Hayashi, and Y. Morisawa, Excerpta Medica No. 111, Second International Congress on Hormonal Steroids, 1966, p 191.

the α-methylene ketone **19** in excellent yield. The expected intermediate **18** was most likely formed, but it lost piperidine hydrochloride in the highly polar reaction medium. Although the crude, unpurified α-methylene ketone **19** can be used in the total synthesis, a sample of it was purified by preparative thin layer chromatography, and its structure was verified by uv, ir, nmr, and low-resolution mass spectrometry.

Michael addition of the anion of ethyl propionyl acetate (**12**) to **19** gave the diketo ester **13** (Scheme IV).

SCHEME IV

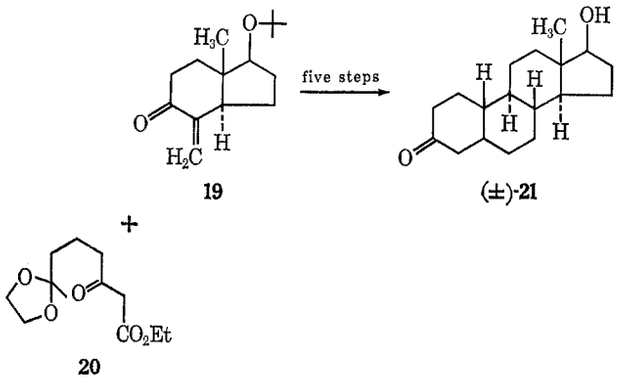


17 18 19 12 13 7

The compound was identical by ir spectroscopy and tlc with the sample obtained from the β-keto mesylate **11** (Scheme III). The addition most likely involved formation of the $\Delta^{8(9)}$-enol, followed by ketonization. Protonation at C-8 (steroidal numbering) must have occurred from the preferred axial direction,[6] thereby placing the side chain of **13** in the stereochemically desired equatorial configuration. No ring closure occurred at this stage for reasons already explained during the discussion of Scheme III. Hydrolysis of the *tert*-butyl ether and of the β-keto ester groups with refluxing hydrochloric acid in methanol, on the other hand, was accompanied by ring closure, dehydration, and decarboxylation to give the desired racemic BCD tricyclic intermediate (±)-**7**. The compound was in all respects identical with a sample obtained by an independent route.[4a] It may also be mentioned that the corresponding optically active derivative (−)-**7** has also been described in the literature.[14,15]

After having realized the above-described results we were ready to adapt our scheme to the preparation of 19-nor steroids. The strategy of the synthesis involved the addition of an A–B (fragment) building block, the β-keto ester **20**, to a B (fragment)–CD building block, the bicyclic trans α methylene ketone **19**, to give in a five-step stereocontrolled synthesis racemic 19-nortestostereone (±)-**21** or the optically active 19-nor steroid, if optically active **19** were used in the synthesis. Rings A and B are thus constructed in a single annulation reaction (Scheme V).

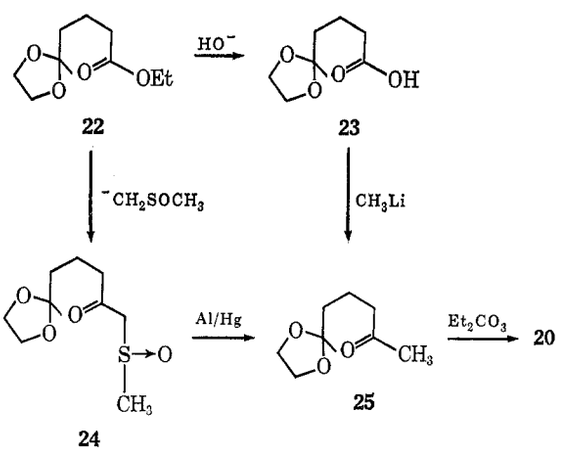
SCHEME V



19 (±)-21 20

The β-keto ester **20** was prepared by two routes (Scheme VI) starting with the known[16] ketal ester **22**.

SCHEME VI



22 23 24 25 20

This compound (**22**) was allowed to react with methylsulfinyl carbanion[17] to give the β-keto sulfoxide **24**. Reduction with aluminum amalgam gave the ketal ketone **25**. This compound has been previously obtained by an independent synthesis.[18] Alternatively, the ketal ester **22** could be saponified to the known[19] ketal acid **23** and the latter converted to the ketal ketone **25** with methyllithium. Carbethoxylation at the terminal carbon atom[20] of the anion of **25** gave the desired β-keto ester **20**, the A–B (fragment) building block.

Michael addition of this compound (**20**) to the crude α-methylene ketone **19** gave the diketo ester **26**. This

(14) Roussel-Uclaf, French Patent 1,359,657 (1963); L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède, *C. R. Acad. Sci.*, **257**, 3086 (1963).

(15) (a) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron*, **24**, 2039 (1968); (b) G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2121 (1971).

(16) R. I. Meltzer, A. D. Lewis, J. Volpe, and D. M. Lustgarten, *J. Org. Chem.*, **25**, 712 (1960).

(17) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964).

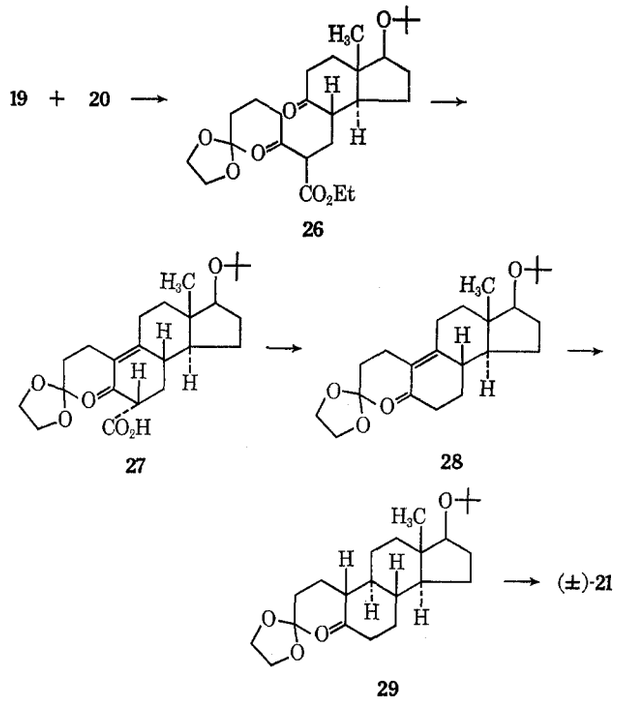
(18) C. Feugeas, *Bull. Soc. Chim. Fr.*, 2568 (1963).

(19) R. A. LeMahieu, *J. Org. Chem.*, **32**, 4149 (1967).

(20) S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, **69**, 2677 (1947).

was then converted to the unsaturated keto acid **27** *via* saponification of the ester group followed by ring closure and dehydration (Scheme VII). Nmr spectros-

SCHEME VII



copy of **27** indicated an equatorial carboxyl group (quartet centered at δ 3.33, C-6 hydrogen; $J_{6H,7eH}$ = 4.5, $J_{6H,7aH}$ = 14.5 Hz).

Decarboxylation of the crude β-keto acid **27** in refluxing toluene gave the enone **28**.[21] It should be mentioned that under carefully controlled reaction conditions it is possible to maintain the carboxylic acid or the carboxylic ester group to the very end of the total synthesis, and thus obtain C-6 substituted 19-nor steroids.[22] Catalytic hydrogenation of the $\Delta^{9(10)}$ double bond of **28** gave intermediate **29** with the desired 9α,10β configuration. It should be mentioned that intermediates **27**, **28**, and **29** could be purified by trituration and crystallization. During the course of the total synthesis, however, this was not necessary, and only the final product was purified by the appropriate method.

Hydrolysis of the *tert*-butyl ether group and of the protective cyclic ethylene ketal group as well as ring closure and dehydration could be achieved by refluxing crude **29** with hydrochloric acid in methanol to give racemic 19-nortestosterone [(±)-**21**], which could be purified by crystallization or by chromatography. The uv, ir, nmr, and tlc data of (±)-**21** obtained by this synthesis were in agreement with those of an optically active authentic sample [(+)-**21**].[23]

It may be mentioned that the desired bicyclic optically active enantiomer (+)-(1*S*,7a*S*)-7,7a-dihydro-1-hydroxy-7a-methyl-5(6*H*)-indanone is available both through conventional chemical resolution[15a] and also through asymmetric synthesis.[24] With this starting material the synthesis of the desired optical isomer of the α-methylene ketone **19** as well as of 19-nortestosterone **21** and of other optically active 19-nor steroids can now be realized.

(21) C. A. Henrick, E. Böhme, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **90**, 5926 (1968), report the presence of optically active **28** in a reaction mixture obtained by an independent route, but the pure compound has not been described in the paper.

(22) Z. G. Hajos, U. S. Patent 3,692,803 (Sept 19, 1972).

(23) This sample was obtained from Organon, Inc., West Orange, N. J.

Experimental Section[25]

Alkylation of the β-Keto Ester 1[3] with Ethyl Vinyl Ketone.—The β-keto ester **1** (54.0 mg) was dissolved in 1.8 ml of absolute ethyl alcohol, and 0.05 ml of 1 *N* sodium ethoxide in ethanol was added. The solution was stirred for 10 min at 20° under nitrogen, and 0.33 ml of a solution of ethyl vinyl ketone (1 ml) in ethyl alcohol (10 ml) was added after which the solution was allowed to stand at 20° for 72 hr. The resulting mixture showed no starting material by tlc; it showed a major reaction product with an R_f of 0.53 (silica gel, 80% benzene, 20% ethyl acetate) which had no absorption in the uv. Concentrated HCl (0.8 ml) was added to one half of the preparation, and it was allowed to stand at 20° for 48 hr. The reaction mixture was extracted with ether. The extract was washed with saturated $NaHCO_3$ and NaCl solutions, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 6.5 mg of **6** as an oil: uv 243 nm (ϵ 8950); ir 3620 (unassociated OH), 3200–3560 (associated OH), 1715 (saturated keto impurity), and 1655 cm^{-1} (α,β-unsaturated ketone). Thin layer chromatography showed a major uv-absorbent and a minor uv-nonabsorbent component. The uv-absorbent spot was slightly slower than that of (±)-**7**. Vpc showed one major component (73.8%) with a retention time of 19.9 min. Retention time for (±)-**7** was 17.4 min.

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-5,5-dimethoxy-7aβ-methyl-4α-indancarboxylic Acid Methyl Ester (8).—The β-keto ester **1** (141 mg) was dissolved in a mixture of 1.25 ml of methanol and 0.55 ml of trimethyl orthoformate. The solution was cooled in an ice bath to 0°, and 0.26 ml of 2 *N* methylsulfuric acid was added with stirring under nitrogen. After 5 min at 0° the mixture was allowed to stand at 20° for 16 hr. It was cooled with an ice bath and neutralized with 1 *N* $NaOCH_3$. The solvent was evaporated *in vacuo*, and the residue was extracted with ether. The extract was washed with aqueous $NaHCO_3$ and NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 160 mg (97.5%) of **8** as an oil, ir 1728 cm^{-1} (ester carbonyl).

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-5,5-dimethoxy-7aβ-methyl-4-indanmethanol (9).—The ketal ester **8** (160 mg) was dissolved in 3.5 ml of dry toluene. The solution was cooled to 0°, and 4.5 ml of a 20% solution of diisobutylaluminum hydride in toluene was added within 5 min with stirring under nitrogen. After an additional 30 min at 0° the mixture was allowed to stand at 20° for 16 hr. It was then cooled with an ice bath, and 3.0 ml of methanol was added carefully with stirring. After 10 min at 0° it was stirred at 20° for 1 hr. The crystalline precipitate was filtered through a pad of Celite, and it was washed and extracted thoroughly with ethyl acetate. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 131.6 mg (90%) of **9** as an oil, ir 3575 cm^{-1} (unassociated OH).

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-oxo-4-indanmethanol (10).—The ketal alcohol **9** (31.6 mg) was dissolved in 1.8 ml of acetone. The solution was cooled to 5°, and 0.2 ml of distilled water and 0.03 ml of 2 *N* HCl were added with stirring. After 20 min the solution was neutralized with 0.065 ml of saturated $NaHCO_3$ solution. Acetone was evaporated *in vacuo*, and the residue was extracted with ether. The extract was washed with a saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 30.2 mg (99.2%) of **10** as an oil, ir 3580 (unassociated OH) and 1695 cm^{-1} (keto carbonyl).

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-

(24) Z. G. Hajos and D. R. Parrish, forthcoming publication.

(25) All melting points were determined in a Thomas-Hoover melting point apparatus and are corrected; unless otherwise noted all uv spectra were taken in ethyl alcohol; ir spectra were taken in chloroform; nmr spectra were taken in $CDCl_3$ on Varian A-60 or HA-100 spectrometers with tetramethylsilane as an internal standard; analytical vpc was performed on a F & M Model 810 in the flame mode using a 6 ft × 0.25 in. aluminum column with 1% PEG 4000MS on 60–70 mesh Anakrom ABS with nitrogen flow of 100 ml/min and programmed temperature.

oxo-4-indanmethanol Methanesulfonate (11).—The β-keto alcohol **10** (17.4 mg), dissolved in 0.25 ml of dry pyridine, was cooled to 0°. Methanesulfonyl chloride (8.0 mg) in 0.56 ml of dry pyridine was added while stirring. The reaction mixture was then allowed to stand at 20° for 1.5 hr. It was evaporated to dryness *in vacuo*, and the residue was dissolved in chloroform and washed with water and a saturated NaCl solution. It was dried ($NaSO_4$), filtered, and evaporated *in vacuo* to give 24.1 mg of **11** as an oil, ir 1705 (keto carbonyl), 1353, and 1175 cm^{-1} (sulfonate).

(±)-2-(1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-oxo-4-indanylmethyl)-3-oxovaleric Acid Ethyl Ester (13).—The β-keto mesylate **11** (22.9 mg) was dissolved in a mixture of 0.3 ml of methanol and 0.3 ml of anhydrous benzene. Ethyl propionyl acetate **12** (59.5 mg) and 1.0 *N* $NaOCH_3$ (0.07 ml) were added and the mixture was stirred at 0° under nitrogen for 2 hr and at 20° for 16 hr. The reaction mixture was neutralized with 0.1 *N* HCl and evaporated to dryness *in vacuo*. It was treated two times with toluene, dissolved in toluene, filtered, and taken to dryness under high vacuum to give 23.8 mg (90.9%) of the diketo ester **13** as an oil, ir 1735 (ester carbonyl) and 1710 cm^{-1} (keto carbonyls).

(±)-3β-*tert*-Butoxy-2,3,3a,4,5,7,8,9,9aβ,9bα-decahydro-3aβ,6-dimethyl-7-oxo-1*H*-benz[*e*]indene-8α-carboxylic Acid (15).—The crude diketo ester **13** (23.8 mg) was dissolved in 0.5 ml of tetrahydrofuran, and 0.5 ml of 0.2 *N* NaOH was added with stirring at 20° under nitrogen. The reaction mixture was allowed to stand at room temperature for 16 hr. The solvent was then evaporated *in vacuo*, and the residue was dissolved in water and extracted with chloroform to remove neutral material. The aqueous solution was carefully acidified with 2 *N* HCl and extracted with chloroform. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo* to give 12.7 mg (60.8%) of the crude β-keto acid **15**: uv (CH_2Cl_2) 248 nm (ε 6650); ir 1740 (carboxyl carbonyl), 1710 (saturated keto impurity), 1655 (α,β-unsaturated ketone), and 1601 cm^{-1} (conjugated double bond).

(±)-3β-*tert*-Butoxy-2,3,3a,4,5,7,8,9,9aβ,9bα-decahydro-3aβ,6-dimethyl-1*H*-benz[*e*]inden-7-one [(±)-16].—The unsaturated β-keto acid **15** (10.6 mg) was dissolved in 3 ml of toluene, and the solution was heated at reflux for 1 hr under nitrogen. The solvent was removed *in vacuo* to give 10.1 mg of crude **16** as an oil: uv 246.5 nm (ε 7340); ir 1710 (saturated keto impurity), 1655 (α,β-unsaturated ketone), and 1605 cm^{-1} (conjugated double bond). Vpc indicated 57.3% of **16** by comparison with an optically active authentic sample[9] of **16**.

(±)-1β-*tert*-Butoxy-3aα,6,7,7a-tetrahydro-7aβ-methyl-4-methyleneindan-5(4*H*)-one (19).—The β-keto acid **10** (2.95 g)[8] was dissolved in a mixture of 22 ml of DMSO and 12.2 ml of 36–38% aqueous formaldehyde solution. Piperidine hydrochloride (1.35 g) was added, and the mixture was stirred under nitrogen for 3 hr. A solution of 935 mg of sodium bicarbonate in water (100 ml) was added, and the solution was extracted three times with benzene. The extract was washed with water and with saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 2.67 g of crude **19** as an oil, uv 227 nm (ε 4050).

A sample of **19** (236 mg) was purified by preparative thin layer chromatography on silica gel with fluorescent indicator. The sample was applied at the rate of 30 mg per plate measuring 8 in. × 8 in. × 1 mm thick. The development was carried out with a mixture of 92.5% benzene and 7.5% ethyl acetate. The area corresponding to the major component gave 153 mg (65%) of pure methylene ketone **19** as an oil which crystallized upon standing in a Dry Ice box: mp 42.5–44°; uv 231 nm (ε 4260); ir 1690 (keto carbonyl) and 1625 cm^{-1} (exocyclic conjugated double bond); nmr δ 0.78 (s, 3, 7aβ-methyl), 1.15 [s, 9, C $(CH_3)_3$], 3.60 (t, 1, C-1 proton), and 4.98 and 5.92 ppm (m, 2, $C{=}CH_2$); mass spectrum *m/e* 180 ($C_{11}H_{16}O_2$), 57 (C_4H_9).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.32; H, 10.25.

(±)-2,3,3a,4,5,7,8,9,9aβ,9bα-Decahydro-3β-hydroxy-3aβ,6-dimethyl-1*H*-benz[*e*]inden-7-one [(±)-7].—To the crude methylene ketone **19** (115.2 mg) was added 410 mg of freshly distilled ethyl propionyl acetate (purchased from K & K Laboratories). The mixture was cooled to 0°, and 0.87 ml of 0.1 *N* $NaOCH_3$ was added with stirring under nitrogen. The reaction mixture was allowed to stand for 18 hr at 0° and 20° for 4 hr. It was then cooled with an ice bath and neutralized with 0.87 ml of 0.1 *N* HCl. The solvent was removed *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was washed with water and a saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 220 mg of the crude diketo ester **13** as an oil, ir 1735 (ester carbonyl) and 1710 cm^{-1} (keto carbonyls).

The compound **13** was identical with the sample obtained from the β-keto mesylate **11** as described above.

The β-diketo ester **13** (220 mg) was dissolved in 4 ml of methanol, and 4.0 ml of 2 *N* HCl was added. The reaction mixture was stirred and refluxed under nitrogen for 6 hr. It was then cooled with an ice bath, and neutalized with 0.4 ml of 19.5 *N* NaOH and then with 0.4 ml of 1.0 *N* NaOH. The solvent was evaporated *in vacuo*, and the residue was extracted two times with ethyl acetate and once with ether. The combined extract was washed once with water and two times with saturated NaCl solution. It was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 114 mg (100%) of crude (±)-**7** as an oil that crystallized upon seeding with an authentic sample:[4a] uv 247.5 nm (ε 10,100); ir 3620 (unassociated OH), 3250–3580 (associated OH), 1728 (ester impurity), 1655 (α,β-unsaturated ketone), and 1605 cm^{-1} (conjugated double bond).

A sample of the crude BCD tricyclic compound (±)-**7** (109 mg) was purified by preparative thin layer chromatography on silica gel with fluorescent indicator. The sample was applied at the rate of 27 mg per plate measuring 8 in. × 8 in. × 1 mm thick. The development was carried out with a mixture of 50% benzene–ethyl acetate. The area corresponding to the major component gave 72.5 mg (66.5%) of an oil that crystallized upon seeding with an authentic sample, uv 248 nm (ε 13,320). Trituration with a 2:1 mixture of ether–petroleum ether (bp 30–60°) gave 50.6 mg (45.4% overall yield, based on the β-keto acid **17**) of pure (±)-**7**: mp 131–133°; uv 247.5 nm (ε 14,920); ir 3620 (unassociated OH), 3300–3550 (associated OH), 1660 (α,β-unsaturated ketone), and 1605 cm^{-1} (conjugated double bond); nmr δ 0.92 (s, 3, 3aβ-methyl), 1.80 (s, 3, C-6 methyl), 3.72 (t, 1, C-3 proton).

1-Methylsulfinyl-6-(1,3-dioxolan-2-yl)-2-heptanone (24).—To a 53% dispersion of sodium hydride in mineral oil (29.2 g), which had been washed with anhydrous hexane and dried under nitrogen, was added 378 ml of dimethyl sulfoxide (distilled from calcium hydride). The mixture was stirred under nitrogen, and it was heated slowly to 68–71°. After 1.5 hr, the evolution of hydrogen ceased, and a turbid gray solution of the sodium salt of the methylsulfinyl carbanion[17] had formed. The solution was cooled to 18°, and the ketal ester **22** (60.6 g) was added within 40 min to the stirred solution at a rate not to exceed an exothermic reaction temperature of 18–20°. It was then stirred at 25° for 1 hr. The solution was poured onto ice, neutralized with ice-cold 1 *N* HCl, and extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 104 g of an oil. Volatile impurities were removed under high vacuum (bath temperature 80°) to give 52.5 g (75%) of the β-keto sulfoxide **24**: uv 282 nm (ε 127); uv (0.01 *N* potassium methoxide) 252 nm (ε 5420); ir 1712 (keto carbonyl) and 1045 cm^{-1} (sulfoxide); nmr δ 1.30 (s, 3, $CH_3C{<}$), 1.68 (s, 4, $-CH_2CH_2-$), 2.68 [s, 5, CH_3SO- and $(-CH_2CO)_3$], 3.74 (s, 2, $-COCH_2SO-$), 3.93 (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74; S, 13.68. Found: C, 50.96; H, 7.55; S, 13.81.

6-(1,3-Dioxolan-2-yl)-2-heptanone (25). A. From the β-Keto Sulfoxide 24.—The β-keto sulfoxide **24** (40.0 g) was dissolved in a mixture of 2160 ml of tetrahydrofuran, 240 ml of H_2O, and 34 ml of 1 *N* NaOH. The solution was added at once to aluminum amalgam prepared from 46.2 g of aluminum foil, and it was shaken for 2 hr under a fast stream of nitrogen to entrain the methyl mercaptan formed. It was filtered through a pad of Celite on a sintered glass funnel; the gelatinous precipitate was washed thoroughly with ether. The filtrate was concentrated *in vacuo* to a small volume (approximately 50 ml) and extracted with ether. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), treated with Norit A, filtered, and evaporated *in vacuo* to give 26.31 g (89.5%) of the ketal ketone **25** as an oil: ir 1708 cm^{-1} (keto carbonyl); nmr δ 1.32 (s, 3, $CH_3C{<}$), 1.65 (s, 4, $-CH_2CH_2-$), 2.13 (s, 3, CH_3CO), 2.45 (m, 2, $-CH_2CO-$) 3.93 (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 63.09; H, 9.42.

B. From the Ketal Acid 23.—The ketal acid **23** (348 mg)[19] was dissolved in 5 ml of anhydrous tetrahydrofuran. The solution was cooled to 0°, and 1.25 ml of a 1.6 *M* solution of methyllithium in diethyl ether was added dropwise within 1 hr, with stirring under nitrogen. The solution was allowed to come to 20°, and 2.5 ml of methyllithium reagent was added at this temperature

within 2 hr. The reaction mixture was added to crushed ice, and the organic solvents were removed *in vacuo*. The residue was extracted with ether, and the extract was washed with a saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 308 mg (89.5%) of crude **25**. The compound was identical by ir with a sample obtained from **24** by method A.

7-(1,3-Dioxolan-2-yl)-3-oxooctanoic Acid Ethyl Ester (20).—To a 53% dispersion of sodium hydride in mineral oil (4.55 g, 0.1 mol) which was washed with anhydrous hexane and dried under nitrogen was added 11.8 g (0.1 mol) of diethyl carbonate in 12.5 ml of anhydrous ether. This mixture was stirred under nitrogen, and 8.6 g (0.05 mol) of the ketal ketone **25** was added dropwise over a period of 2 hr. A gentle reflux was maintained throughout the addition, and refluxing was continued for an additional 1.5 hr. The mixture was then cooled with an ice bath, 20 ml of anhydrous ether and 2 ml of absolute ethyl alcohol were added, and it was stirred for 45 min to destroy any unreacted NaH. The suspension was diluted with an equal volume of ether, and the ice-cold suspension was added to a rapidly stirred cold mixture of 6 ml of glacial acetic acid and 200 ml of ice water. It was then immediately neutralized with 2 ml of a saturated $NaHCO_3$ solution. The ethereal layer was separated, and the aqueous layer was extracted two more times with ether. The extract was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 12.1 g (99.3%) of the crude β-keto ester **20**. Fractional distillation gave 7.38 g (61.8%) of the pure β-keto ester **20**: bp 110–112° (0.02 mm); uv 244 nm (ε 1050); ir 1740 (ester carbonyl) and 1718 cm^{-1} (keto carbonyl); nmr δ 1.27 (t, 3, CH_3CH_2–), 1.30 [s, 3, $CH_3C(O)O$], 1.68 (s, 4, $-CH_2CH_2-$), 2.49 (m, 4, $-CH_2-CH_2CO-$), 3.34 (s, 2, $COCH_2CO-$), 3.93 (s, 4, $-OCH_2CH_2O-$), 4.20 (q, 2, CH_3CH_2-).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.51; H, 8.15.

(±)-3β-*tert*-Butoxy-2,3,3a,4,5,7,8,9,9aβ,9bα-decahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3aβ-methyl-7-oxo-1*H*-benz[*e*]inden-8α-carboxylic Acid (27).—A mixture of 2.36 g (0.01 mmol) of freshly prepared, crude methylene ketone **19** and 2.68 g (0.011 mol) of β-keto ester **20** was cooled in an ice bath. A 0.1 *N* $NaOCH_3$ solution in methanol (20 ml) was added, and the solution was allowed to stand at 0° for 64 hr and at 20° for 4 hr. The pH of the solution was then adjusted in the cold to 7.5 with 0.5 *N* HCl and the methanol was evaporated *in vacuo*. The oily residue was dissolved in 77.5 ml of tetrahydrofuran, 77.5 ml of 0.2 *N* aqueous NaOH was added, and the mixture was stirred at 20° under nitrogen for 6 hr. The tetrahydrofuran was evaporated *in vacuo*, and the basic solution was extracted with ether. The ether extract was washed with water and saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 1.42 g of a neutral impurity: uv 244 nm (ε 3000); ir 1710 (s) and 1670 cm^{-1} (w).

An aliquot (42.5 ml) of the aqueous basic solution (250 ml) was carefully acidified at 0° with 5.1 ml of 0.5 *N* HCl to pH 3.5. The mixture was immediately extracted with ethyl acetate and with ether. The combined extract was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 523.8 mg (71%) of crude, unsaturated β-keto acid **27** as an amorphous solid: uv 247 nm (ε 12,550); ir 1750 (carboxyl carbonyl), 1710 (ketone impurity), 1660 and 1630 (α,β-unsaturated ketone), and 1601 cm^{-1} (conjugated double bond).

A few drops of ether were added to 742 mg of the crude solid **27**, and it was kept at −10° for 72 hr. A rather large crystalline crop was formed, which could be purified by trituration at room temperature with petroleum ether. Recrystallization from ether gave analytically pure **27**: mp 129° dec; uv 249 nm (ε 14,400); ir 1755 (carboxyl carbonyl), 1665 and 1625 (α,β-unsaturated ketone), and 1598 cm^{-1} (conjugated double bond); nmr δ 0.90 (s, 3, methyl), 1.15 [s, 9, $OC(CH_3)_3$], 1.35 [s, 3, $CH_3C(O)O$], 3.33 (q, 1, C-6 proton, $J_{6H,7eH}$ = 4.5, $J_{6H,7aH}$ = 14.5 Hz).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.84; H, 8.70.

(±)-3β-*tert*-Butoxy-1,2,3,3a,4,5,8,9,9aβ,9bα-decahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3aβ-methyl-7*H*-benz[*e*]inden-7-one (28).—Crude unsaturated β-keto acid **27** (523.8 mg) was dissolved in 50 ml of toluene. The solution was stirred and heated at reflux under nitrogen for 30 min. It was cooled to room temperature and extracted with a 0.5 *N* $NaHCO_3$ solution and with saturated NaCl solution. The toluene solution was dried (Na_2SO_4) and evaporated *in vacuo* to give 414.7 mg (88.1%) of unsaturated keto compound **28** as an oil: uv 247 nm (ε 10,780); ir 1665 (α,β-unsaturated keto carbonyl) and 1601 cm^{-1} (C=C).

Similar treatment of the pure β-keto acid **27** (50 mg) gave 44.9 mg of analytically pure **28**: mp 85.5–86.5° (petroleum ether); uv 248 nm (ε 16,400); ir 1663 (α,β-unsaturated keto carbonyl) and 1605 cm^{-1} (C=C).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.77; H, 10.13.

(±)-3β-*tert*-Butoxy-1,2,3,3a,4,5,5aα,6,8,9,9aβ,9bα-dodecahydro-6α-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3aβ-methyl-7*H*-benz[*e*]inden-7-one (29).—Crude unsaturated keto compound **28** (414.7 mg) was dissolved in 20.75 ml of absolute ethyl alcohol containing 0.5% (by volume) of triethylamine. The compound was hydrogenated in the presence of 124.5 mg of Pd on carbon catalyst at 20° and atmospheric pressure to give 407.2 mg (98%) of the saturated keto compound **29** as an oil, ir 1710 cm^{-1} (keto carbonyl).

Catalytic hydrogenation of a pure, crystalline sample of the unsaturated keto compound **28** (234 mg) under identical reaction conditions gave analytically pure **29**: mp 94.5–96° (petroleum ether); ir 1710 cm^{-1} (keto carbonyl); nmr δ 0.79 (s, 3, 3aβ-methyl), 1.13 [s, 9, $OC(CH_3)_2$], 1.33 [s, 3, $CH_3C(O)O$], 3.94 (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.35; H, 10.52.

(±)-19-Nortestosterone [(±)-21].—Crude seco compound **29** (407.2 mg) was dissolved in 15 ml of methanol. To the stirred solution was added 15 ml of 2 *N* HCl, and it was heated at reflux under nitrogen for 5 hr. It was neutralized with 3 *N* NaOH and evaporated to a small volume *in vacuo*. The residue was extracted with ethyl acetate. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), treated with Norit A, filtered, and evaporated *in vacuo* to give 222.7 mg of crude (±)-**21** as an amorphous solid, uv 239 nm (ε 13,710). Purification by trituration with petroleum ether and a small amount of ether gave 158.4 mg (34.2% overall yield based on the α-methylene ketone **19**) of (±)-**21**, mp 106–115°, uv 239 nm (ε 14,950). Alternatively the crude mixture may be purified by preparative tlc to give pure (±)-19-nortestosterone [(±)-**21**] in 39.7% overall yield based on **19**: mp 118–122° (lit.[26] mp 121–122°); uv nm (ε 16,500) [lit.[27] 240.5 nm (ε 17,000)]; ir 2635 (OH), 1663 (α,β-unsaturated CO), and 1620 cm^{-1} (C=C); nmr δ 0.81 (s, 3, C_{18} methyl), 3.68 (t, 1, C-17 H), 5.82 (s, 1, C-4 vinyl H). An analytical sample was prepared by trituration of the above sample with ether, mp 123–124.5°.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.00; H, 9.87.

Acknowledgment.—The authors wish to express their thanks to Mr. Fred Bizzarro for his technical assistance in part of this investigation. Thanks are due to Dr. T. Williams for the nmr, to Dr. V. Toome for the uv, to Mr. S. Traiman for the ir spectroscopic data, to Dr. F. Vane for the mass spectra determinations, to Mr. H. Jenny for the vpc results, and to Dr. F. Scheidl for the microanalyses.

Registry No.—**1**, 27504-58-1; **2**, 1629-58-9; **6**, 40762-81-0; **7**, 13652-05-6; **8**, 27504-59-2; **9**, 27504-60-5; **10**, 27504-61-6; **11**, 27504-62-7; **12**, 4949-44-4; **13**, 40762-87-6; **15**, 27510-09-4; **16**, 40762-89-8; **19**, 27504-55-8; **20**, 27428-41-7; **21**, 5972-58-7; **22**, 40745-29-7; **23**, 5694-89-3; **24**, 29310-40-5; **25**, 15580-05-9; **27**, 27510-05-0; **28**, 27601-48-5; **29**, 27510-06-1; trimethyl orthoformate, 149-73-5; methanesulfonyl chloride, 124-63-0.

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