under reduced pressure. Preparative thin layer chromatography of the residue (silica gel eluted with 4:1 benzene–ethyl acetate) resulted in the isolation of 25 mg of the major component. When quickly recrystallized from methanol, fine crystalline material was obtained, mp 180–193° slow decomposition, then rapid gas evolution: uv max 229 nm (ϵ 1.1 × 10^4) and shoulder 260 nm (ϵ 5 × 10^3); ir 5.51, 5.69, 5.81, 6.00, and 6.15 μm; PMR (T-60) τ 4.16 (narrow m, 6-CH), 7.93 (s, CH_3CO), 7.97 (s, CH_3CO), 9.18 (s, 19-CH_3), and 9.42 (s, 18-CH_3); *m/e* 418, 376, 356 (base), 328, 164, 162, and 133; metastable peaks at *m/e* 335 and 302 confirmed the fragmentation sequence, *m/e* 376 → 356 → 328.

Anal. Calcd for $C_{24}H_{31}O_5F$: C, 68.87; H, 7.47; F, 4.54. Found: C, 68.64; H, 7.72; F, 4.96.

In an attempt to repeat the above experiment with 0.5 g of **2a**, the same conditions were used except heat (bath temperature ~50°) was used when concentrating the filtrate after removal of the catalyst. In this case, the major product isolated, **9b** (250 mg, preparative TLC), was different from that described above in that it had mp 155–160°; *m/e* 430 (M^+), 388, 356 (base), 328, 164, 162, and 133; uv max 230 nm (ϵ 1.8 × 10^4); ir 5.62 and 5.73 μm; PMR (T-60) τ 4.55 (m, 6-CH), 6.29 (s, OCH_3), 7.90 (s, O_2CCH_3), 7.99 (s, O_2CCH_3), 8.99 (s, 19-CH_3) and 9.20 (s, 18-CH_3).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 68.95; H, 8.03.

A solution of 200 mg of this material (**9b**) in a mixture of 10 ml of methanol, five drops of water, and 200 mg of potassium acetate was heated at reflux for 16 hr under nitrogen. The mixture was concentrated and then the residue was extracted with ethyl acetate. After drying and concentration, the residue was eluted on a thick layer (1000 μ) silica gel-coated plate. The major component **11** was extracted and crystallized from methanol, 70 mg: mp 147–149°; *m/e* 388 (M^+), 356 (base), 332, and 328; uv max 244 (ϵ 1.08 × 10^4) and 287.5 nm (ϵ 1.72 × 10^3); ir 5.77, 5.97, and 6.19 μm; PMR τ 6.21 (s, OCH_3), 7.98 (s, O_2CCH_3), 8.77 (s, 19-CH_3), and 9.17 (s, 18-CH_3).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 68.56; H, 8.25. Found: C, 68.16; H, 8.27.

Stability of the Trifluoromethyl Steroids 2b and 3b to Methanolic Sodium Acetate. A solution of 20 mg of each of the steroids **2b** and **3b** was dissolved with 200 mg of sodium acetate in 5 ml of methanol. These solutions were heated at reflux for 30 min, then cooled and concentrated. The ethyl acetate extracts of the respective residues were concentrated to a crystalline material which, after recrystallization, were identified by mixture melting point, ir spectra, and TLC mobilities with their corresponding starting materials.

Acknowledgment. The authors wish to thank Dr. Byron Arison and Mr. Jack L. Smith for their assistance in interpreting the NMR and mass spectra discussed in this paper.

Registry No.—**1a**, 2352-19-4; **1b**, 425-51-4; **1c**, 6693-79-4; **1d**, 566-93-8; **2a**, 53821-28-6; **2b**, 53821-29-7; **2c**, 53821-30-0; **2d**, 53821-31-1; **3a**, 53821-32-2; **3b**, 53821-33-3; **4**, 13583-12-5; **5**, 53821-34-4; **6a**, 53821-35-5; **9a**, 53821-36-6; **9b**, 53821-37-7; **11**, 53821-38-8; **13**, 53835-06-6; trifluoromethyl iodide, 2314-97-8.

References and Notes

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(9) Melting points were determined on a Kofler hot-stage and are uncorrected. Infrared spectra were determined with a Perkin-Elmer spectrometer, Model 137, as chloroform solutions and are in accord with the assigned structures. PMR spectra were obtained from deuteriochloroform solutions with a Varian Model A-60A spectrometer unless otherwise noted. Mass spectra were obtained on either a CEC Model 21-110 or an LKB Type 9000 spectrometer by the direct probe technique. Rotational data were obtained from 1% chloroform solutions. Irradiations were carried out in a Rayonet photochemical reactor, Type RS, using lamps with peak intensity at 3500 Å. All isolated products were analyzed by thin-layer chromatography on silica gel-coated glass plates eluted with an appropriate benzene–ethyl acetate system.

Total Syntheses of Optically Active 19-Norsteroids. (+)-Estr-4-ene-3,17-dione and (+)-13β-Ethylgon-4-ene-3,17-dione

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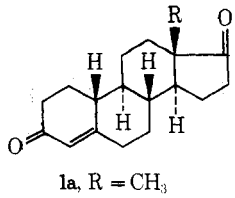
Highly efficient total syntheses of the title 19-norsteroids are described in which the chirality is introduced early in the synthetic scheme *via* an asymmetric synthesis of the bicyclic intermediates **4a** and **4b**. These substances are then converted in five stages into the key α-methylene ketones **9a** and **9b**. Michael addition of the β-keto ester **17** (prepared starting from diketene and formaldehyde) to the enones **9** followed by cyclization, saponification, and decarboxylation then affords the tricyclic compounds **20a** and **20b** which are readily transformed into the title diones in three additional stages. The efficiency of this approach is demonstrated by the production of **1a** and **1b** in overall yields of 27 and 18%, respectively, based on the starting 2-alkyl-1,3-cyclopentanediones.

In a previous publication,[2] two of us described a convergent, stereo-controlled total synthesis of racemic 19-norsteroids in which the synthetic strategy involved initial construction of a bicyclic C,D-ring synthon followed by elaboration of ring B and finally ring A. We now wish to present the results of a team effort directed toward the application of this scheme to the production of optically active 19-norsteroids of biological and commercial significance.[3] In particular, we wish to describe highly efficient and practical syntheses of diones (+)-**1a**[3,4] and (+)-**1b**[5] in which all carbon atoms of the final steroid molecule are derived from readily available building blocks. Furthermore, the crucial problem of introduction of chirality is solved *via*



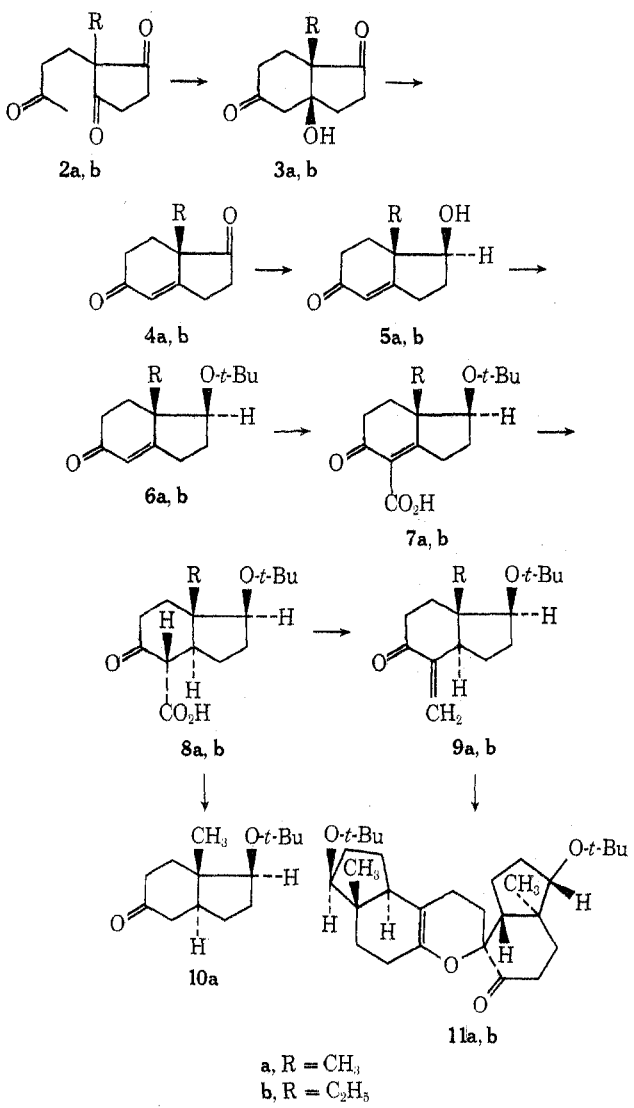
1a, R = CH_3
b, R = C_2H_5

an asymmetric synthesis[6] of the aforementioned C,D-bicyclic intermediates carried out at the earliest possible stage of the synthetic pathway. In order to avoid unnecessary repetition of the previously described work, we will not discuss each transformation in detail. Instead, we have chosen to concentrate on those areas in which substantial modifications of previous procedures were required and to emphasize pertinent experimental data which demonstrate the potential of this approach.

Results

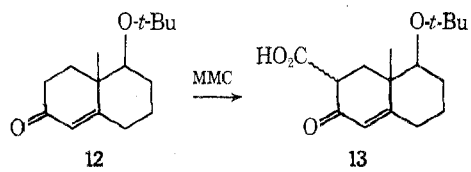
A. Synthesis of the α-Methylene Ketones 9a and 9b. The starting materials, triketones **2a** and **2b** (Scheme I), were prepared and cyclized with *S*-proline in *N,N*-dimethylformamide (DMF) on a 50–250-g scale, essentially as described previously.[6,7] In the angular methyl series, the crude ketol **3a** was directly dehydrated with *p*-toluenesulfonic acid giving enedione **4a** in 90–94% overall yield. This material was used as such without further purification. In the homologous series, the ketol **3b** was purified by recrystallization prior to dehydration which procedure allowed isolation of pure enedione **4b** in 65% yield. Selective reduction of these enediones with sodium borohydride[8] followed by treatment of the resulting ketols **5**[9] with isobutylene–phosphoric acid–boron trifluoride etherate[10,11] gave the keto ethers **6** in essentially quantitative yield.

Scheme I



The efficient preparation of the unsaturated keto acids **7a** and **7b** proved to be one of the major challenges encountered in this work. The original method involving carbonation of the sodio enolate of **6a** with CO_2[12] gave low direct yields (25–45%) of the desired acid **7a** thus requiring extensive recycling of the recovered enone. Subsequently, it was found that direct carbonation of **6a** with magnesium methyl carbonate (MMC) in DMF[13] afforded the desired keto acid **7a** in 64% yield, whereas similar carbonation of the homologous enone **6b** produced **7b** in 41% yield.[14] Pyrolysis of the mother liquor residues obtained after purification of the keto acids **7** caused decarboxylation of any regioisomeric 6-ξ-indancarboxylic acids present. Distillation then allowed recovery of the starting enones **6** which could be recycled (on a much smaller scale than required with the NaH–CO_2 procedure) thus raising the overall yields of the desired keto acids to 74% (**7a**) and 53% (**7b**).

The success of the MMC reaction is most likely due to the enhanced stability of the resultant magnesium chelates produced (relative to the analogous sodium derivatives formed using the NaH–CO_2 procedure) thus reducing the reversibility of the carbonation process. The regioselectivity observed in both carbonation procedures is apparently due to the preferance for heteroannular dienolate formation in indanones such as **6.** In this regard, it should be noted that the decalone derivative **12** afforded keto acid **13**



as the major carbonation product upon treatment with MMC under the conditions employed for the indanone cases. Similar results have been reported by Julia and Huynh.[15]

The high stereospecificity observed[12] in the hydrogenation of acid **7a** eliminated the need for a great deal of investigation at this stage. However, during the course of the hydrogenation and work-up, some decarboxylation of the unstable, saturated keto acids **8** was found to occur. In order to minimize this side reaction, the hydrogenations were carried out at 0° in methanol, a solvent which can then be readily removed also at low temperature (*ca.* 10°).

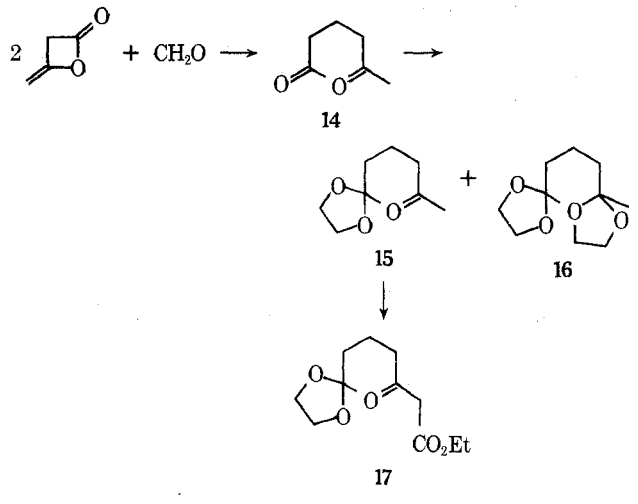
Two major side reactions were found to plague the decarboxylative Mannich reaction by which the keto acid **8a** is converted into the key α-methylene ketone **9a**,[2,16] namely decarboxylation of the starting material to the indanone **10a** and dimerization of the product giving rise to **11a.** Both of these side reactions were minimized by reducing the reaction time and by operating at low temperatures. The degree of dimerization was further controlled by simplifying the work-up procedure so that the product could be isolated more rapidly. From a study of the catalyst system, it was determined that the conversion of **8a** to **9a** was greatly accelerated by base catalysis which enabled large scale reactions to be completed in 1 day. For example, the following results were obtained upon reaction of **8a** in DMSO with formaldehyde: (a) no catalyst (24 hr, 20°), uv 60–65% **9a;** (b) 0.1–1.0 equiv of piperidine hydrochloride (3 hr, 20°),[2] 80–85% **9a;** (c) 0.1 equiv of piperidine or pyrrolidine (15 min, 20°), 95% **9a.** In the case of both **9a** and its homolog **9b,** the crude methylene ketone preparations were used without further purification.

The structure of the dimer **11a** rests mainly on spectral data and on analogy to the work of Eschenmoser and coworkers[17] in the onocerol series. Of the possible stereoiso-

mers, the endo-trans-trans, as indicated, seems most probable.

B. Synthesis of the Annulating Agent 17. The original procedure[2] for the preparation of the annulating agent, β-keto ester **17**, although attractive for small scale operation, was not readily adaptable to large scale preparations. Thus, a more practical synthesis of this substance was developed as shown in Scheme II. On warming an aqueous solution of

Scheme II

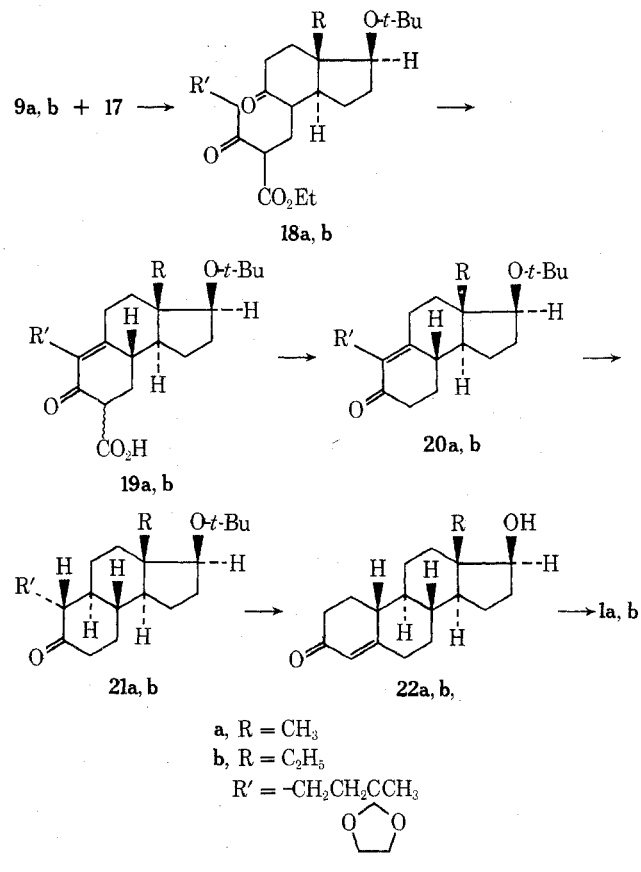


diketene (2 mol) and formaldehyde (1 mole) to 40°, copious amounts of CO_2 were evolved and 2,6-heptanedione (**14**)[18] could be isolated in 40% yield. We assumed that diketene was being hydrolyzed to acetoacetic acid which could then react *via* decarboxylative alkylation with formaldehyde to give 4-hydroxy-2-butanone. We further suspected that the latter material would suffer dehydration to yield methyl vinyl ketone. However, when acetoacetic acid was allowed to react with methyl vinyl ketone, only a 3.5% yield of **14** was obtained suggesting that methyl vinyl ketone is not, in fact, a preferred intermediate under our experimental conditions.

As anticipated, monoketalization of the symmetrical diketone **14** posed some problems. Under all conditions employed we obtained an equilibrium mixture of starting diketone, monoketal **15**,[2] and diketal **16**. However, by working in a two-phase system, with an excess of ethylene glycol at 0°, we were able to direct the ketalization toward the formation of the desired monoketal as the major product. Separation of the reaction mixture efficiently into its three primary components was accomplished by means of a chemical separation since fractional distillation was unsuccessful in achieving this end. The monoketal and the small amount of unreacted diketone formed sodium bisulfite addition compounds from which the diketal could be separated by ether extraction. Selective liberation of the desired monoketal was achieved by careful pH control. The recovered diketal could be partially hydrolyzed to an equilibrium mixture resembling the original ketalization product and was therefore recycled into the sodium bisulfite separation of a subsequent batch. In this fashion a 64% yield of the monoketal **15** could be isolated. Carbethoxylation of **15** with sodium hydride and diethyl carbonate gave the β-keto ester **17** in 83% yield.

C. Synthesis of 19-Norsteroids. The series of reactions[2] consisting of a Michael condensation between the methylene ketones **9a** and **9b** and the annulating agent **17** (→**18**), *in situ* alkaline cyclization–saponification (**18** → **19**) to form the steroid B ring and finally decarboxylation proceeded smoothly affording **20a** and **20b** in high overall yields. The formation of by-products was found to be minimized when a solution of the methylene ketone was slowly added (*ca.* 3 hr) to the annulating agent in methanolic sodium methoxide. Inverse or rapid addition of the annulating agent are detrimental and the impurities formed under these conditions are to a great extent carried through the subsequent reactions and can interfere with the purification of the end product.

Scheme III



a, R = CH_3
b, R = C_2H_5
R′ = $-CH_2CH_2CCH_3$ (O,O)

Hydrogenation of the tricyclic enones **20** was carried out essentially as described previously[2] although the use of triethylamine was not essential for producing high yields of the desired trans-anti-trans compounds **21**. The crude hydrogenation products were then treated with hydrochloric acid under conditions which caused ketal hydrolysis, cyclodehydration, and *tert*-butyl ether cleavage and led to 19-nortestosterone (**22a**)[19] and its 18-methyl homolog **22b**[20] in excellent yields. Oxidation[21] then afforded the target diones **1** which were readily purified by recrystallization.

In summary, we have described a highly efficient and stereoselective route to optically and chemically pure 19-norsteroids which requires a minimum amount of intermediate purification (although the intermediates can, in most instances, be readily isolated if desired). Utilizing this synthetic sequence, the diones (+)-**1a** and (+)-**1b** can be produced in overall yields of 27 and 18%, respectively, based on starting 2-alkyl-1,3-cyclopentanedione. This represents an average yield per chemical reaction of 93.4% in the **a** series and 91.4% in series **b**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Thin-layer chromatography was

carried out for the **a** series on silica gel plates prepared as follows: H_2O (68 ml) was added to 35 g of Mallinckrodt silica gel (Silic AR^R TLC-7GF-5, pH7, gypsum fluorescence, 5% $CaSO_4$). The mixture was shaken well for 1 min, and then spread 250 μ thick on glass plates. These were air dried and then heated at 100° for 1 hr. E. Merck, Darmstadt, Silica Gel 60F-254 tlc plates were utilized for the **b** series. Both types of plates were developed by spraying with H_2SO_4–MeOH 1:1 (v/v) and heating. Tlc solvent system A, EtOAc–C_6H_6 4:1 (v/v); B, C_6H_6–EtOAc 1:1; C, C_6H_6–EtOAc 4:1; D, C_6H_6–EtOAc 8:2; E, CH_2Cl_2–EtOAc 8:1; F, CH_2Cl_2–EtOAc–HOAc 16:1.0:0.25; G, C_6H_6–EtOAc 95:5; H, C_6H_6–EtOAc 1:2; I, C_6H_6–EtOAc 9:1. Most reactions (except hydrogenations) were carried out under an atmosphere of nitrogen. Unless otherwise stated, organic extracts were washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. Rotary evaporators were used for solvent removal at the temperatures indicated, generally with a water pump (*ca.* 20 mm) or with the aid of a high vacuum pump (*ca.* 0.5 mm). Ultraviolet spectra were measured in 95% EtOH solution on a Cary Model 14M spectrophotometer. Unless otherwise noted, nmr spectra were measured on a Varian A-60 instrument in $CDCl_3$ solution. Chemical shifts are reported relative to TMS as an internal standard. Infrared spectra were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Low resolution mass spectra were obtained on CEC21-110 or JMS-01SG instruments. Solvent abbreviations: PE = petroleum ether (bp 30–60°), ligroin = petroleum ether (bp 60–70°).

(+)-(7a*S*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indandione (4a). Trione **2a** (250 g, 1.375 mol) (prepared from 2-methyl-1,3-cyclopentanedione in 88% yield, on a 200-g scale, as decribed previously[7]) was dissolved in 1.375 l. of DMF (H_2O 0.05%) and 2.5 g of finely ground *S*-proline was added. The mixture was stirred at 23–26° for 22.5 hr. The solvent was removed (60°, high vacuum) and 261 g of a dark green oil was obtained. Tlc analysis (system B) showed the ketol **3a** as the main spot. This material was dehydrated in 800 ml of C_6H_6 containing 7.5 g of *p*-toluenesulfonic acid monohydrate, at reflux. After *ca.* 1.5 hr, 25 ml of H_2O was collected in a Dean-Stark apparatus. The cooled solution was washed (saturated $NaHCO_3$, and saturated NaCl solutions), the aqueous phases were extracted with C_6H_6, and the combined organic layers were evaporated to give 235 g of a dark green-brown oil. Flash distillation through a 5-cm Vigreux column (107–123° (0.07–0.08 mm)) afforded 211.8 g (94%) of **4a,** as a light yellow oil which crystallized upon cooling at *ca.* +3°, $[\alpha]^{25}D$ +319.21° (*c* 0.5, C_6H_6) {lit.[6] $[\alpha]^{25}D$ +367° (*c* 1, C_6H_6)}. Such material was used without further purification.

(+)-(3a*S*,7a*S*)-7a-ethyl-3a,4,7,7a-tetrahydro-3a-hydroxy-1,5(6*H*)-indandione (3b). A solution of 58.88 g (0.3 mol) of trione **2b** (prepared in 90% yield from 2-ethyl-1,3-cyclopentanedione, as described previously[6]) in 300 ml of DMF was stirred with 10.34 g (0.09 mol) of *S*-(−)-proline at 23° for 20 hr. The residual proline was collected by filtration, washed with Et_2O, and air dried (8.14 g, 78.6%, recovered). The solvents were removed (35° bath, 0.45–0.5 mm), and the over-weight (77.24 g), viscous residue was taken up in 250 ml of EtOAc and filtered through 480 g of silica gel (E. Merck AG, 0.05–0.2 mm). The column was eluted with 4.5 l. of the same solvent. By evaporation of the eluate *in vacuo,* a tan paste was obtained which was dried (55° (0.05 mm) for 0.5 hr) giving 54.79 g (93.2%) of crude β-hydroxy ketone (**3b**): $[\alpha]^{25}D$ +28.65° (*c* 1.745, $CHCl_3$); Uv analysis indicated *ca* 5% enedione **4b** was present.

This crude material was crystallized from 3.5 l. of Et_2O (with Norit treatment) and concentrated to 1.4 l. from which 28.0 g of **3b** was obtained after cooling overnight at room temperature. Concentration to 200 ml and 50 ml successively produced crops of 9.48 g and 1.31 g for a total of 38.80 g (66%) of **3b:** mp range 113–114.5°; $[\alpha]^{25}D$ +18.90° to 19.90° (*c* 1.0, $CHCl_3$) [lit.[6] mp 112–112.5°; $[\alpha]^{25}D$ +19.0° (*c* 1.0, $CHCl_3$)]. Tlc analysis (system B) showed only a single component for each crop.

(+)-(7a*S*)-7,7a-Dihydro-7a-ethyl-1,5(6*H*)-indandione (4b). Dehydration of 30.01 g (0.153 mol) of the ketol **3b** in 225 ml of C_6H_6 with 0.431 g of *p*-toluenesulfonic acid at reflux was complete in 45 min (2.4 ml of H_2O was collected). Work-up as described above for **4a,** and removal of the solvent *in vacuo,* gave an oil that crystallized upon cooling. There was obtained 27.03 g (99.2%) of **4b** as a cream colored powder: mp 57.5–59°; $[\alpha]^{25}D$ +263.19° (*c* 1.035, C_6H_6); uv max 241 nm (ϵ 10,960); tlc (system B) showed one component {lit.[6] mp 59–60°; $[\alpha]^{25}D$ +262° (*c* 0.95, C_6H_6)}. This material was used without further purification.

(+)-(1*S*,7a*S*)-7a-Methyl-7,7a-dihydro-1-hydroxy-5(6*H*)-indanone (5a). To a chilled (−10°) solution of indandione **4a** {120 g, 0.732 mol; $[\alpha]^{25}D$ +354° (*c,* 0.5, C_6H_6)} in 600 ml of absolute EtOH was added 7.5 g (0.19 mol) of $NaBH_4$ in 720 ml of the same solvent. The rate of addition was adjusted so as to maintain the internal temperature between −5 and −10° (*ca.* 0.5 hr). The reaction mixture was allowed to warm to +5° over a 50-min interval, and then cooled again to −10° at which point the pH was adjusted to between 5 and 7 with 2 *N* HCl. The solvent was removed *in vacuo* (45°), the aqueous residue was worked up by extraction with EtOAc giving a semisolid product which was dried at 45° (high vacuum). This afforded 117 g (96%) of indanone **5a.** Such material was used without purification. A similar preparation had $[\alpha]^{25}D$ +90° (*c* 1.0, C_6H_6). Recrystallization of such material from ether–PE afforded indanone exhibiting $[\alpha]^{25}D$ +97.7° (*c* 1.0, C_6H_6) {lit.[9] $[\alpha]^{25}D$ +90.4° (*c* 1.0, C_6H_6)}.

(+)-(1*S*,7a*S*)-7a-Ethyl-7,7a-dihydro-1-hydroxy-5(6*H*)-indanone (5b). Treatment of 26.88 g (0.151 mol) of indandione **4b** with 1.615 g (0.045 mol) of $NaBH_4$, as described for the **a** series, gave the indanone **5b,** 26.98 g (99%), as an oil: $[\alpha]^{25}D$ +70.3° (*c* 1.28, C_6H_6). The analytical specimen was obained by preparative tlc (solvent system B): $[\alpha]^{25}D$ +71.59° (*c* 0.95, C_6H_6); uv max 240 nm (ϵ 11800); mass spectrum *m/e* 180 (M^+).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.84.

(+)-(1*S*,7a*S*)-1-*tert*-Butoxy-7a-methyl-7,7a-dihydro-5(6*H*)-indanone (6a). A CH_2Cl_2 solution (795 ml) of indanone **5a** (79.4 g, 0.477 mol) was stirred and cooled to −75°. To this was added 8.3 ml of H_3PO_4 (prepared by dissolving 4.0 g of P_2O_5 in 11.0 ml of 85% H_3PO_4), 19.8 ml of 47% boron trifluoride etherate and 400 ml of liquid isobutylene. The mixture was stirred for 1.5 hr at −75° and then overnight at room temperature. The reaction mixture was then poured into 795 ml of 2 *N* NH_4OH solution and the product was extracted with CH_2Cl_2. Solvent removal (45°) gave 102.54 g (97%) of the *tert*-butyl ether **6a,** which was used without further purifcation (tlc analysis with solvent system C). A sample of **6a** crystallized from PE as white needles: mp 62–65°; $[\alpha]^{25}D$ +55° (*c* 1.0, $CHCl_3$); uv max 238 nm (ϵ 13800).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.80; H, 10.13.

(+)-(1*S*,7a*S*)-1-*tert*-Butoxy-7a-ethyl-7,7a-dihydro-5(6*H*)-indanone (6b). The indanone **5b** (26.64 g, 0.148 mol) was converted into the correspondng *tert*-butyl ether, as described for the preparation of **6a.** There was obtained 34.19 g (98.3%) of **6b,** as a dark yellow oil, suitable for further conversions without purification: uv max 243 nm (ϵ 11,230); $[\alpha]^{25}D$ +58.71° (*c* 1.62, $CHCl_3$). A sample from a separate preparation was purified by chromatography on silica gel followed by vacuum distillation [bp 95–99° (0.025 mm)]. The colorless oil so obtained (homogeneous by tlc, solvent system D) had the following properties: $[\alpha]^{25}D$ +56.17° (*c* 0.99, $CHCl_3$); uv max 242 nm (ϵ 11,280); mass spectrum *m/e* 236 (M^+).

(+)-(1*S*,7a*S*)-5,6,7,7a-Tetrahydro-1-*tert*-butoxy-7a-methyl-5-oxo-4-indancarboxylic Acid (7a). To 50.0 g (0.225 mol) of compound **6a** {$[\alpha]^{25}D$ +54.2° (*c* 1.0, $CHCl_3$)} was added 335 ml of magnesium methylcarbonate[13] (MMC) (3.5 equiv, 2.3 *M*) in DMF. The reaction vessel was placed in an oil bath (preheated to 125°), the mixture was stirred, and N_2 was bubbled through the solution. The internal temperature (115°) was maintained for 2 hr (reaction progress monitored by tlc analysis, solvent system E). The solution was chilled and poured into a mixture of ice and concentrated HCl. The aqueous phase (pH 3) was extracted with C_6H_6, and the organic phase was then extracted with 15% Na_2CO_3 solution. Acidification of the basic phase followed by extraction with C_6H_6 gave, after removal of the solvent *in vacuo* (45°), 57.9 g of yellow-brown solid. This material was purified with Et_2O–PE. There was obtained 38.41 g (64.3%) of **7a** as a yellow solid, mp 100–103°, and sintering: $[\alpha]^{25}D$ +35.2° (*c* 1.0, $CHCl_3$). A sample of the acid, obtained from a different experiment, crystallized from Et_2O–PE as yellow plates: mp 103–109°; $[\alpha]^{25}D$ +36.9° (*c* 1.0, $CHCl_3$); uv max 247 nm (ϵ 9670).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.40; H, 8.30.

The mother liquor residue (14 g) from the above purification was stirred and heated in a 160° oil bath for 30 min. The residual material was then distilled at 0.5 mm, through a 15 cm Claisen head with the heating bath at 165–195°. There was obtained 5.11 g (10.2%) of pure, recovered keto ether **6a** which could be recycled.

(+)-(1*S*,7a*S*)-5,6,7,7a-Tetrahydro-1-*tert*-butoxy-7a-ethyl-5-oxo-4-indancarboxylic Acid (7b). Following the procedure of the preceding experiment, 33.99 g (0.144 mol) of **6b** was treated with 214 ml (3.5 equiv, 2.18 *M*) of MMC in DMF. However, the

crude carboxylic acid was not extracted with Na_2CO_3 from the C_6H_6 phase as above. Rather, the solvent was removed and the resulting oil was dried to constant weight (0.2 mm, 23°) giving 39.31 g of a brownish-orange, partially crystalline mass. Trituration with pentane afforded 14.31 g (35.5%) of **7b** as a pale yellow solid: mp 86–86.5°; $[\alpha]^{25}D$ +24.35° (*c* 1.08, $CHCl_3$). A second crop was obtained from the mother liquors, by recrystallization from pentane, as a yellow solid (2.25 g, 5.6%): mp 82–83.5°, $[\alpha]^{25}D$ +30.33° (*c* 1.055, $CHCl_3$). This material contained a trace of starting compound **6b** (tlc analysis, solvent system D) but was satisfactory for further conversions. An analytical sample of **7b** was obtained by recrystallization from pentane with Norit treatment giving large colorless needles: mp 88.5–90°; $[\alpha]^{25}D$ +20.66° (*c* 0.93, $CHCl_3$); uv max 242 nm (ε 8,550).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.85; H, 8.75.

Decarboxylation of the mother liquor residues from the above trituration by heating in toluene at reflux, followed by distillation, allowed recovery of the starting enone **6b**. By this process the total yield of **7b** was raised to 53% based on recovered starting material.

***rac*-4,4a,5,6,7,8-Hexahydro-5β-*tert*-butoxy-4aβ-methylnaphthalen-2(3*H*)-one (12).** The preparation of **12** from the corresponding alcohol[22] was performed essentially as described for the *tert*-butyl ether **6a**. The enone **12**, analyzed and used as obtained, had the following properties: mp 63–68°; uv max 243 nm (ε 13950).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.16; H, 10.24.

***rac*-1,2,3,5,6,7,8,8a-Octahydro-8β-*tert*-butoxy-8aβ-methyl-3-oxo-2ξ-naphthoic Acid (13).** Reaction of 1.4 g (5.94 mmol) of **12** with MMC, as described for **7a**, afforded after one crystallization from Et_2O, 0.57 g of racemic 2ξ-naphthoic acid (**13**), mp 101.5–103° dec (tlc analysis with solvent system E). Further recrystallization gave the analytical sample as colorless crystals: mp 106–108° dec; uv max 242 nm (ε 13100).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.85; H, 8.61.

(+)-(1*S*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-7a-methyl-3a,4,5,6,7,7a-hexahydro-5-oxo-4-indancarboxylic Acid (8a). A solution of the unsaturated acid **7a** [100 g, 0.376 mol; $[\alpha]^{25}D$ +34.0° (*c* 1.0, $CHCl_3$)] in MeOH (800 ml) was added to 10 g of 10% Pd on $BaSO_4$. The mixture was chilled in an ice bath to *ca.* 0° and hydrogenated at essentially atmospheric pressure until uptake ceased (*ca.* 35 min). The solvent was removed *in vacuo* (high vacuum pump) in a 10° water bath, to give 111.65 g of crude, oily saturated acid suitable for subsequent conversions (tlc analysis with solvent system F). This substance is relatively unstable and should be treated accordingly. The analytical sample of **8a** was obtained from another experiment as a semisolid foam: $[\alpha]^{25}D$ +36.3° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.73; H, 9.17.

(+)-(1*S*,3a*S*,7a*S*)-1-*tert*-Butoxy-3a,4,7,7a-tetrahydro-7a-methyl-5(6*H*)-indanone (10a). A 1.3-g sample of saturated keto acid **8a** was heated *in vacuo* at 90° for 30 min (monitored by tlc, solvent system C or F) and yielded 1.1 g of the indanone. One crystallization from MeOH–H_2O gave 0.72 g of **10a**: mp 39.5–40.5°; $[\alpha]^{25}D$ +82.2° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.35; H, 11.14.

(+)-(1*S*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-7a-ethyl-3a,4,5,6,7,7a-hexahydro-5-oxo-4-indancarboxylic Acid (8b). Hydrogenation of 17.21 g (0.061 mol) of **7b** in 172 ml of MeOH with 1.72 g of 10% Pd on $BaSO_4$ catalyst was carried out at 23° (*ca.* 3.25 hr). Evaporation of the solvent *in vacuo* (23°, high vacuum) gave 19.05 g (over-weight) of a semisolid product (tlc solvent system D): $[\alpha]^{25}D$ +16.9° (*c* 1.0, $CHCl_3$). Such material was used preferably the same day, for conversion to the methylene ketone (below). A separate sample of **8b**, prepared for analysis by crystallization from 1:1 MeOH–H_2O followed by trituration with cold pentane, had: mp 76–78° dec; $[\alpha]^{25}D$ +13.10° (*c* 0.95, $CHCl_3$); mass spectrum *m/e* 282 (M^+).

(+)-(1*S*,3a*R*,7a*S*)-1-*tert*-Butoxy-7a-methyl-3a,6,7,7a-tetrahydro-4-methyleneindan-5(4*H*)-one (9a). To 111.65 g (assumed to be 0.376 mol) of crude saturated keto acid **8a** (described above) was added a solution consisting of 240 ml of DMSO, 186 ml of approximately 37% aqueous HCHO (*ca.* 5 equiv), and 3.74 ml of piperidine (*ca.* 0.1 equiv) (exothermic on mixing, precooled before addition to the keto acid). The reaction mixture was stirred for 25 min, and then poured into 600 ml of a mixture of ice water and saturated NaCl solution (1:1). The product was isolated by extraction with Et_2O, then the organic extracts were washed with 5% $NaHCO_3$ and afforded, after solvent removal (water pump, 25°), 93.96 g of crude, orange-red, oily methylene ketone (tlc analysis system F). A sample dried *in vacuo* at room temperature exhibited uv max 232 nm (ε 4260). A sample of **9a** from another batch crystallized from MeOH–H_2O giving white crystals: mp 56–60.5°; $[\alpha]^{25}D$ +35.6° (*c* 1.0, $CHCl_3$); uv max 232 nm (ε 4760); nmr δ 5.94 (m, 1, CH=), 5.00 ppm (m, 1, CH=); ir ($CHCl_3$) 1690 (C=O), 1625 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.23; H, 10.38.

(+)-(1*S*,3a*R*,7a*S*)-1-*tert*-Butoxy-7a-ethyl-3a,6,7,7a-tetrahydro-4-methyleneindan-5(4*H*)-one (9b). The crude, saturated keto acid **8b** (19.05 g; containing some solvent—assumed to be 0.061 mol), prepared above, was converted into the corresponding methylene ketone **9b**, as described for the preparation of **9a**. There was obtained 15.17 g of a yellow semisolid: $[\alpha]^{25}D$ +15.27° (*c* 1.92, $CHCl_3$); uv max 232 nm (ε 4000) (tlc analysis with solvent system G). This material was used without purification.

Another sample was prepared for analysis by first crystallization from MeOH–H_2O, followed by chromatography (silica gel 50:1, eluted with C_6H_6–EtOAc 97.5:2.5), and finally preparative tlc (solvent system G). Removal of the solvent left a colorless crystalline residue: mp 57–60.5°; uv max 232 nm (ε 4,800); $[\alpha]^{25}D$ +5.56° (*c* 1.11, $CHCl_3$); nmr δ 5.93 (m, 1, CH=), 4.97 ppm (m, 1, CH=).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.68; H, 10.59.

(−)-1′,3-Di-*tert*-Butoxy-1,2,3,3a,4,5,6′,7′,7′a,8,9,9bα-dodecahydro-3aβ,7′aα-dimethyl-5′*H*-spiro[cyclopenta[*f*][2*H*]benzopyran[2,4′(3′a*H*)]indan]-5′-one (11a). Dimer **11a** was isolated from crude semisolid methylene ketone **9a** by trituration with cold (−20°) MeOH. The white, insoluble material was removed by filtration and recrystallized from warm MeOH giving white needles: mp 148–154°; $[\alpha]^{25}D$ −10.3° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 1720 (C=O), 1685 cm^{-1} (C=C-O); mass spectrum *m/e* 472 (M^+).

Anal. Calcd for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.42; H, 10.16.

2,6-Heptanedione (14). A mixture of 1 l. of H_2O, 204 g (2.5 mol) of 37% CH_2O solution, and 420 g (5.0 mol) of diketene was stirred and carefully warmed to 40° (CO_2 evolution!). The exothermic reaction was maintained at 40° for 24 hr (for the first 6–8 hr water cooling was necessary, then slight warming was required), cooled, and saturated with NaCl. The oil which precipitated was extracted with C_6H_6, which in turn was washed with $NaHCO_3$ solution. The residue (196.4 g), after removal of the solvent (40° bath), was distilled through a 10-cm Vigreux column. The main fraction [**14**: 129.5 g (40%); bp 83–99° (7–10 mm)] was a colorless oil which crystallized upon standing (mp 32–34°) (lit.[18] mp 34°) and was used without further purification. It may be crystallized from Et_2O–hexane.

6-(1,3-Dioxolan-2-yl)-2-heptanone (15).[2] A heterogeneous mixture of 2,6-heptanedione (**14**) (100 g, 0.795 mol), ethylene glycol (200 g, 3.23 mol), and toluene (500 ml) was stirred for 20 min in an ice bath. Concentrated H_2SO_4 (36 g, 20 ml, 0.367 mol) was added and vigorous stirring was maintained at ice bath temperature for 35 min. The colorless, lower ethylene glycol layer was separated and washed twice with toluene. To the original toluene layer was added *at once* a slurry of 100 g of $NaHCO_3$ in 50 ml of H_2O. This basic phase was used in turn to wash the two toluene extracts. The three toluene extracts were then washed, in turn, with two portions of saturated NaCl solution. The combined organic layers were evaporated (water pump) and *ca.* 145 g of a colorless oil was obtained. Gc analysis[23] showed a mixture of **14**:**15**:**16** = 11:61:28.

The crude oil in 250 ml of Et_2O was extracted four times with 200-ml portions of *cold* 20% (w/v) $NaHSO_3$ solution. The organic phase consisted of mainly (86%) diketal **16** (47.2 g), which could be recycled (see below).

Isolation of the desired monoketal (**15**) was carried out as follows. The $NaHSO_3$ layers were added slowly (*foaming!*) to a stirred slurry of 150 g of $NaHCO_3$ in 250 ml of toluene. The pH of the aqueous layer was adjusted to 7.5[24] (*glass electrode*) by the addition of *ca.* 20–50 g of $Na_2CO_3 \cdot H_2O$ and stirred for 30 min. Extraction of the H_2O layer with toluene, followed by removal of the solvent from the combined organic extracts (water pump vacuum, then 100° bath at 14 mm), gave 63.9 g (47%) of **15** as a colorless oil, used without further purification [bp of **15**: 112–116° (10 mm)]. This material was *ca.* 95% pure by gc analysis.[23]

The diketal **16** was recycled in the following manner. The 47.2 g of isolated diketal residue described above was dissolved in 100 ml

of toluene and 2.5 ml of 0.1 *N* HCl was added. After refluxing for 15 min and immediately cooling in an ice bath, 3 ml of saturated $NaHCO_3$ solution was added, followed by 25 ml of saturated NaCl. The organic phase was separated, and the solvent was removed. The residue (40.8 g), which contained *ca.* 50–55% monoketal (**15**) by gc analysis,[23] can be added to the next batch prior to the $NaHSO_3$ extraction.

7-(1,3-Dioxolan-2-yl)-3-oxooctanoic Acid Ethyl Ester (17).[2] To 97.0 g (2.26 mol) of NaH (56% dispersion in oil), which had been rinsed with hexane in the usual manner, was added 236 g (2.0 mol) of freshly distilled diethyl carbonate, followed by 250 ml of anhydrous Et_2O. The slurry was stirred and heated at gentle reflux, and 172 g (1 mol) of monoketal **15** was added slowly. A constant H_2 evolution was usually observed after *ca.* 25 g of **15** had been added. This induction period may take up to 90 min. Only after this point has been reached, is the remainder (*ca.* 150 ml) of **15** added over a period of 3–4 hr. After the addition was complete, the mixture was heated for another 90 min, and then stirred overnight at room temperature. The reaction mixture was chilled in an ice bath, 40 ml of EtOH in 400 ml of toluene was added (over 15 min), and stirring was continued for 45 min. Decantation into 170 ml of glacial HOAc and 500 g of ice, saturation of the aqueous phase with NaCl, and extraction with toluene (which was subsequently washed with $NaHCO_3$) gave 256.7 g of a yellow oily product *ca.* 77% pure.[25] The main fraction from distillation through a 10-cm Vigreux column [125–144° (0.2 mm)] weighed 202.6 g (83%), assayed 89% pure,[25] and was suitable for use in the annulation reactions.

(−)-3β-*tert*-Butoxy-3aβ-methyl-1,2,3,3a,4,5,8,9,9aβ,9bα-decahydro-6-{2-(2-methyl-1,3-dioxolan-2-yl)ethyl}-7*H*-benz[*e*]inden-7-one (20a). To a mixture of 125.0 g (10% excess; 81% pure[25]) of β-keto ester **17** in 750 ml of 0.1 *N* NaOMe in MeOH, was added dropwise, over 3 hr, a solution of 93.96 g (assumed to be 0.376 mol) of crude methylene ketone **9a** in 380 ml of MeOH (the α-methylene ketone solution was kept chilled during the addition to reduce dimer formation). The reaction mixture was allowed to remain overnight (*ca.* 16 hr) at room temperature then the intermediate diketo ester **18a** which had formed was saponified and cyclized by the addition of 180 ml of 5 *N* NaOH solution followed by stirring for 1 hr at room temperature. Most of the MeOH was then removed at 25° (water pump), H_2O was added, and the solution was extracted with C_6H_6. The aqueous phase was chilled and acidified to pH 3 (6 *N* HCl). The product was extracted with EtOAc, and the solvent was removed *in vacuo* (water pump, 55°). The crude product at this point is mainly a mixture of the acid **19a** and the corresponding decarboxylated product **20a** (tlc, solvent system C). Complete decarboxylation of the above mixture was brought about by heating the material *in vacuo* (high vacuum pump), in an 80° bath, to constant weight (*ca.* 3.0 hr) giving 146.88 g of an orange-red oil: uv max 250 nm (ε 12750). This material was used without purification in the following step.

The analytical sample of **20a** was prepared from a different batch by chromatography (silica gel), followed by crystallization from MeOH–H_2O giving colorless solid: mp 75–76.5°; $[\alpha]^{25}D$ −19.6° (*c* 0.5, $CHCl_3$); uv max 249 nm (ε 14800).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.60; H, 9.74.

(−)-3β-*tert*-Butoxy-3aβ-ethyl-1,2,3,3a,4,5,8,9,9aβ,9bα-decahydro-6-{2-(2-methyl-1,3-dioxolan-2-yl)ethyl}-7*H*-benz[*e*]inden-7-one (20b). The crude methylene ketone **9b** (15.16 g) was allowed to react with 20.2 g (0.067 mol) of annulating agent **17** exactly as described for the formation of **18a**, above. The resulting methanol solution of **18b** was treated with 29.1 ml of 5 *N* aqueous NaOH solution and stirred for 1.25 hr, then the MeOH was removed *in vacuo*, water was added, and neutral impurities were removed by ether extraction. After acidification (6 *N* HCl) of the aqueous alkaline solution and extraction (EtOAc), as for the **a** series, 27.2 g of a yellow, oily mixture of **19b** and **20b** was obtained: uv max 251 nm (ε 11,375).

A 22.0-g portion of this crude material in 200 ml of toluene was refluxed for 30 min (tlc analysis with solvent system D). Removal of the solvent and trituration with ligroin gave 19.08 g of a semisolid. Partial purification of a 9.23-g portion was realized by removal of low boilers by distillation [130° bath (0.1 mm)]. The solid residue (7.46 g; mp 109.5–115°; $[\alpha]^{25}D$ −23.83° (*c* 1.15, $CHCl_3$); uv max 250 nm (ε 13,850); (*ca.* 91% pure) was used for the subsequent conversion. A similar preparation was filtered over silica gel (in Et_2O), crystallized from PE (with Norit treatment), and afforded the analytical sample of **20b** as colorless needles: mp 121.5–122°; $[\alpha]^{25}D$ −35.27° (*c* 1.16, $CHCl_3$); uv max 249 nm (ε 15,200).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97. Found: C, 74.29; H, 9.85.

(+)-17β-Hydroxyestr-4-en-3-one (19-Nortestosterone) (22a). Crude **20a** (146.8 g, 0.376 mol) in 1.47 l. of 95% EtOH was added to 14.7 g of 5% palladium on carbon (Engelhard Industries) and hydrogenated at essentially atmospheric pressure at 65°. To the resulting ethanolic solution of **21a** (after filtration to remove the catalyst) was added 345 ml of 6 *N* HCl. The mixture was refluxed for 2.5 hr (monitored by tlc analysis, solvent system H). The solution was chilled and adjusted to pH 5, most of the EtOH was removed, and the aqueous residue was extracted with C_6H_6. The crude product (106.1 g) was obtained as a greenish-yellow oil. A sample, dried *in vacuo* (90°), exhibited $[\alpha]^{25}D$ +41.6° (*c* 1.0, $CHCl_3$); uv max 240 nm (ε 14400).

From an earlier run, a pure sample of **22a** was obtained by filtration over silica gel (in $CHCl_3$), followed by recrystallization (CH_2Cl_2–Et_2O): mp and mmp (with authentic **22a**) 117–118°; $[\alpha]^{25}D$ +58.7° (*c* 1.0, $CHCl_3$); uv max 240 nm (ε 16850). This preparation was identical by spectral and tlc comparison with authentic material (from Searle Chemicals, Inc.).

(+)-13β-Ethyl-17β-hydroxygon-4-en-3-one (22b). Compound **20b** (3.63 g, 8 mmol, *ca.* 91% purity by uv analysis) in 181.5 ml of a 0.5% solution of triethylamine in absolute EtOH was hydrogenated, as above, with 1.09 g of 5% palladium on carbon. The solvent was removed, and the crude oily product (4.07 g) which still contained some solvent was used directly.

The analytical sample of **21b** was obtained by hydrogenation of a pure sample of **20b,** as above. The crude product was recrystallized from pentane, and then from PE (−20°). Chromatography on silica gel (C_6H_6–EtOAc 75:25) and finally treatment with PE gave pure **21b:** mp 81.5–83°; $[\alpha]^{25}D$ −1.97°, $[\alpha]^{25}_{365}$ −133.77° (*c* 1.01, $CHCl_3$).

Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.54; H, 10.49.

The crude **21b** above (4.07 g) was dissolved in 43.5 ml of MeOH and 43.5 ml of 2 *N* HCl and heated at reflux for 4 hr (monitored by tlc, solvent system B). Work-up as for **22a** and trituration of the crude product with PE afforded 2.36 g of **22b,** as a crystalline solid: mp 146–151°; $[\alpha]^{25}D$ +40.73° (*c* 1.10, $CHCl_3$); uv max 240 nm (ε 15,900). This material was used directly.

A pure sample of **22b** was obtained from another experiment (as above). Crude cyclized product was triturated (PE), crystallized (EtOAc), and chromatographed on silica gel (30:1, C_6H_6–EtOAc). A final recrystallization from Et_2O gave **22b** as needles: mp 159–160°; $[\alpha]^{25}D$ +51.09° (*c* 1.01, $CHCl_3$); uv max 241 nm (ε 17,200) {lit.[20] mp 154–157°; $[\alpha]^{25}D$ +52.4° ($CHCl_3$)}.

(+)-Estr-4-ene-3,17-dione {(+)-19-Norandrost-4-ene-3,17-dione} (1a). A solution of 106.1 g of crude 19-nortestosterone (**22a**), described above, in 720 ml of acetone, was chilled to −5°. Jones reagent[21] (80 ml, 2.7 *M*) was added dropwise so that the temperature remained between −5 and 0° (*ca.* 1 hr) (monitored by tlc–solvent system H). Most of the acetone was then removed *in vacuo* (50°). The dark-green residue was diluted with ice water and extracted with C_6H_6. Removal of the solvent gave 92.76 g of crude dione. A small sample dried at 90° (0.005 mm) had the following properties: $[\alpha]^{25}D$ +114° (*c* 1.0, $CHCl_3$); uv max 240 nm (ε 14230). Recrystallization from CH_2Cl_2–Et_2O afforded 49.58 g of white, crystalline **1a:** mp 163–169.5°; $[\alpha]^{25}D$ +140° (*c* 1.0, $CHCl_3$). A second crop (1.43 g) was obtained: mp 155–163°; $[\alpha]^{25}D$ +134° (*c* 1.0, $CHCl_3$). Both crops were blended to afford the final product. Yield: 51.01 g (50%, based on the 100 g batch of crystalline acid **7a** used above); mp 163–169.5° (167.4–169.9° corrected); $[\alpha]^{25}D$ +139.4° (*c* 1.184, $CHCl_3$); uv max 238 nm (ε 16600) {lit.[4] mp 170–171°, $[\alpha]^{25}D$ +147°}.

(+)-13β-Ethylgon-4-ene-3,17-dione (1b). Oxidation (as described in the preceding experiment) of the 2.3 g of **22b** (described above) in 70 ml of acetone, with 2.8 ml of Jones reagent[21] (monitored by tlc–solvent system B), produced 2.2 g of crude dione **1b:** mp 148–166°; $[\alpha]^{25}D$ +81.4° (*c* 1.20, $CHCl_3$); uv max 240 nm (ε 16000). Recrystallization from acetone gave 1.0 g of colorless prisms, mp 174.5–175.5°, $[\alpha]^{25}D$ +97.80° (*c* 1.23, $CHCl_3$); uv max 239 nm (ε 17200). A second crop (0.415 g) was obtained, mp 172–174°, $[\alpha]^{25}D$ +97.77° (*c* 1.165, $CHCl_3$) {lit.[5] mp 175–176°; $[\alpha]^{23}D$ +92.9° (*c* 1.0, $CHCl_3$)}.

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Registry No.—**1a,** 734-32-7; **1b,** 21800-83-9; **2a,** 25112-78-1; **2b,** 34927-33-8; **3b,** 35544-89-9; **4a,** 17553-86-5; **4b,** 33878-95-4; **5a,** 16271-49-1; **5b,** 53016-43-6; **6a,** 41878-38-0; **6b,** 53078-16-3; **7a,** 31944-51-1; **7b,** 53702-05-9; **8a,** 53702-06-0; **8b,** 53662-91-2; **9a,** 53702-07-1; **9b,** 53052-91-8; **10a,** 53662-92-3; **11a,** 53662-93-4; **12,** 53662-94-5; **12** corresponding alcohol, 50302-16-4; **13,** 53662-95-6; **14,** 13505-34-5; **15,** 15580-05-9; **17,** 27428-41-7; **20a,** 24157-07-1; **20b,** 53662-96-7; **21b,** 53662-97-8; **22a,** 434-22-0; **22b,** 793-55-5; diketene, 674-82-8; formaldehyde, 50-00-0.

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(24) If the pH is greater than 7.5, dione **14** starts to be liberated.
(25) Assayed by uv analysis: analytically pure **17** shows uv max (0.1 *N* $NaOCH_3$) 273 nm (ε 12500).

Novel Total Syntheses of (+)-Estrone 3-Methyl Ether, (+)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one, and (+)-Equilenin 3-Methyl Ether

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Conjugate addition of *m*-methoxybenzylmagnesium chloride to the optically active enones **1a** and **1b** in the presence of cuprous salts gives the key tricyclic ketones **2a** and **2b,** respectively, in good yields. Cyclization of the latter materials produces the 9,11-dehydro compounds **4a** and **4b** which can be converted into the target steroids **7a** and **7b** efficiently *via* the intermediates **5a,b** and **6a,b.** Treatment of **4a** with trifluoroacetic acid leads to disproportionation as well as *tert*-butyl ether cleavage and the formation of estrapentaene **8a** oxidation of which yields (+)-equilenin 3-methyl ether (**10a**). In contrast, exposure of **4a** to *p*-toluenesulfonic acid gives the mixture of estratetraenols **11a** and **12a.**

The homologous, optically active α-methylene ketones **1a** and **1b** are readily available intermediates of great utility in the total synthesis of 19-norsteroids[1] and androstanes.[2] In the previous work,[1,2] β-keto ester intermediates containing the carbon atoms destined to become rings A and B of the steroid nucleus were added in a Michael reaction to the enones **1.** It occurred to us that these unsaturated ketones should also be valuable for the production of estrone and related compounds[3] *via* a short and potentially efficient scheme involving, as the key transformation, conjugate addition of *m*-methoxybenzyl Grignard reagents or derived organocopper species[4] to the enone system producing the tricyclic ketones **2.** We have investigated this approach and report the results herein.

Results

The reaction of *m*-methoxybenzylmagnesium chloride with enone **1a** was found to be regioselective, in the desired mode, when carried out in the presence of cuprous ion. Under these conditions, it was possible to obtain the 1,4 adduct **2a** in 80–90% yield after chromatographic purification, the 1,2 adduct **3a** being formed in only minor amounts. In