THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 19

SEPTEMBER 21, 1973

Steroid Total Synthesis. X.[1] Optically Active Estrone Precursors and Racemic Equilenin Methyl Ether[2]

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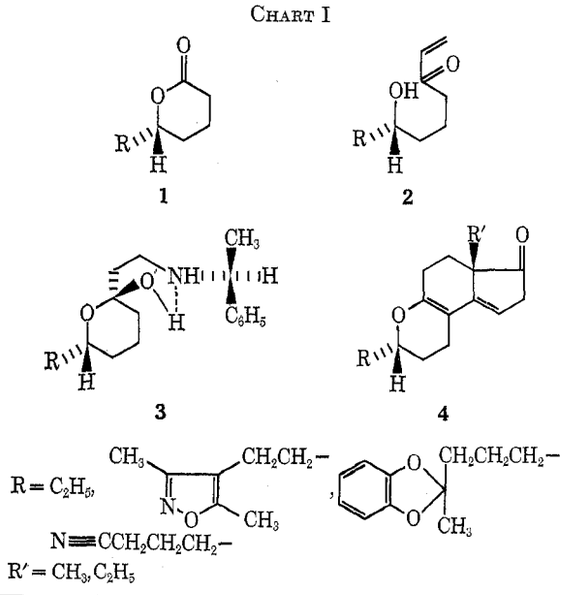
Received April 11, 1973

A total synthesis of (+)-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one (**27b**, a known precursor of estrone) is described. The key step involves condensation of the optically active Mannich base mixture **14b** with 2-methyl-1,3-cyclopentanedione giving predominantly the desired epimer (1*R*)-(+)-2-(5,6,7,7a-tetrahydro-7a*S*-methyl-1,5-dioxo-4-indanyl)-1-(3-methoxyphenyl)ethanol (**18b**). The latter substance was converted into **27b** *via* the corresponding *p*-bromobenzoate derivative **22b** and the intermediates (*S*)-(+)-7,7a-dihydro-4-(*m*-methoxystyryl)-7a-methyl-1,5(6*H*)-indandione (**24b**) and (*S*)-(+)-7,7a-dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione (**25b**). The Mannich base **14b** was prepared in nine stages starting from *m*-methoxyacetophenone *via* (*R*)-(+)-4-hydroxy-4-(3-methoxyphenyl)butyric acid γ-lactone (**5b**). Configurational assignments were made with the aid of an X-ray analysis of the racemic diketo ester **22a**. In the racemic series, (±)-equilenin 3-methyl ether (**33a**) was obtained in five stages starting from the ketol **18a**.

Previous publications from our laboratories have described several practical approaches to the total synthesis of optically active 19-nor steroids[1,3,4] and related compounds.[5,6] The basic scheme (Chart I) utilizes, initially, the reaction of vinylmagnesium chloride with an appropriately substituted δ-lactone **1** at −50° giving a vinyl ketone **2**. In order to introduce optical activity, the starting lactone may be optically active[5] or, alternatively,[1,3,4,6] the racemic vinyl ketone **2** may be treated with an optically active amine (*e.g.*, α-methylbenzylamine) giving a diastereomeric mixture of Mannich bases. In the latter procedure, the resulting base mixture can be resolved, usually as the oxalic acid salt, giving the desired diasteromer **3** (predominantly the hemiketal form shown). Of crucial importance is the observation[1,3-6] that condensation of a 2-alkylcyclopentane-1,3-dione with the optically active intermediates **2** or **3** (or related 4-hydroxyalkyl vinyl ketone derivatives) occurs with substantial asymmetric induction furnishing predominantly the desired dienol ether **4**, possessing the natural C_{13} configuration. The latter substances can then be transformed efficiently into optically active 19-nor steroids or related B,C,D-tricyclic materials.

CHART I



One logical extension of this synthetic scheme would be its application to the total synthesis of the aromatic steroidal hormones estrone and equilenin in optically active form.[7] The modifications required to achieve this end are delineated in Scheme I.[8] We envisioned

(1) Part IX: N. Cohen, B. Banner, R. Mueller, R. Yang, M. Rosenberger, and G. Saucy, *J. Org. Chem.*, **37**, 3385 (1972).

(2) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstract No. ORGN 6.

(3) Part VI: J. W. Scott, R. Borer, and G. Saucy, *J. Org. Chem.*, **37**, 1659 (1972).

(4) Part VIII: M. Rosenberger, A. J. Duggan, R. Borer, R. Müller, and G. Saucy, *Helv. Chim. Acta*, **55**, 2663 (1972).

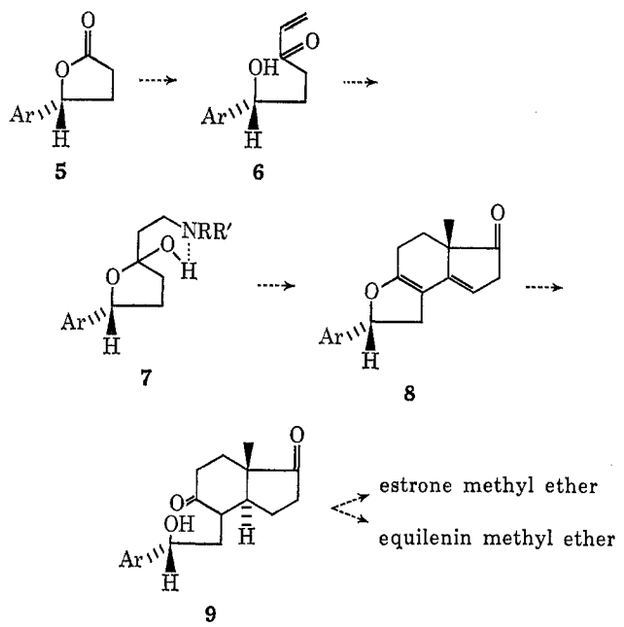
(5) Part II: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2121 (1971).

(6) Part III: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2517 (1971).

(7) For other asymmetric total syntheses of estrone or estrone intermediates see (a) R. Bucourt, L. Nédélec, J.-C. Gasc, and J. Weill-Raynal, *Bull. Soc. Chim. Fr.*, 561 (1967); (b) C. Rufer, E. Schröder, and H. Gibian, *Justus Liebigs Ann. Chem.*, **701**, 206 (1967); (c) R. Bucourt, M. Vignau, and J. Weill-Raynal, *C. R. Acad. Sci., Ser. C*, **265**, 834 (1967); (d) U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem.*, **83**, 492 (1971).

(8) Throughout this paper Ar = *m*-methoxyphenyl. Although absolute configurations are shown, racemic modifications are often referred to and are denoted as the **a** series. The **b** and **c** series refer to optically active compounds of the absolute configurations shown.

SCHEME I



5 6 7 8 9

the reaction of γ-lactone **5** with vinylmagnesium chloride, giving the vinyl ketone **6**, which either directly or *via* Mannich base **7** hopefully would afford the dienol ether **8** upon condensation with 2-methylcyclopentane-1,3-dione. We considered diene **8** a highly desirable intermediate not only because its formation should proceed with a high degree of asymmetric induction, but also since its catalytic hydrogenation should give mainly the desired 14α stereochemistry by analogy with the course of hydrogenation of the homologous dienol ethers **4** from the previous work.[1,3-6] After hydration of the hydrogenation product (an enol ether), the ketol **9** would be produced, which hopefully could be converted to either estrone methyl ether or equilenin methyl ether by acid-catalyzed cyclization with appropriate manipulation of the benzylic hydroxyl function.

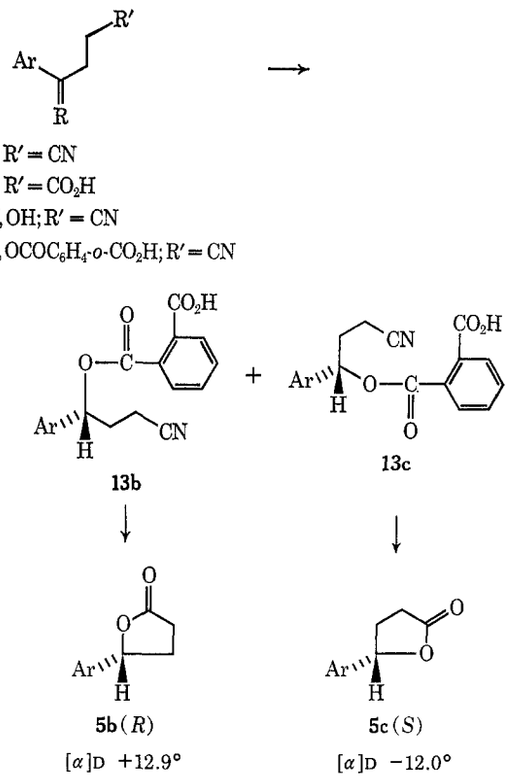
Results and Discussion

The synthesis of the required starting lactone **5** is shown in Scheme II. Commercially available *m*-methoxyacetophenone was converted by standard procedures into the known substances nitrile **10**[9] and acid **11**.[10] Reduction of **11** with sodium borohydride followed by acidification gave the racemic lactone **5a** in 90% yield.

In order to produce optically active materials, we chose the scheme in which an optically active lactone is used as a starting point[5] rather than that involving resolution of a suitable Mannich base.[1,3,4,6] This decision was based primarily on the ready availability of the hydroxy nitrile **12a**, an intermediate which seemed ideally suited for optical resolution at an early stage in the synthesis. This material was prepared in 94% yield by sodium borohydride reduction of **10**.

Resolution of **12a** *via* the acid phthalate derivative **13a** was accomplished readily using (*R*)-(+)-α-methylbenzylamine, which afforded the half ester **13b** in 40% yield. By the use of (*S*)-(−)-α-methylbenzylamine, the enantiometric half ester **13c** was obtained. Basic hydrolysis of these phthalates followed by acidification furnished the (*R*)-(+)-lactone **5b** (89% yield) and (*S*)-(−)-lactone **5c** (84% yield), respectively. It should be noted that, at this point, the absolute configurations of these materials were unknown. Fortuitously, we chose the positively rotating lactone for further transformations which ultimately led to products having the desired natural configuration (see below).

SCHEME II



10, R = O; R′ = CN
11, R = O; R′ = CO_2H
12a, R = H, OH; R′ = CN
13a, R = H, $OCOC_6H_4$-*o*-CO_2H; R′ = CN

13b **13c**

5b (*R*) **5c** (*S*)
$[\alpha]_D$ +12.9° $[\alpha]_D$ −12.0°

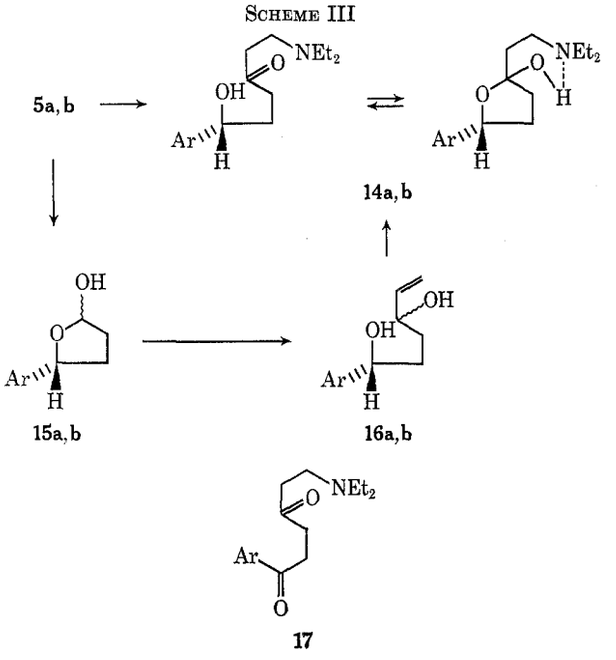
Having the required γ-lactones in hand, we next turned our attention to their conversion into the vinyl ketones **6**. In model studies, the racemic lactone **5a** was treated with vinylmagnesium chloride in tetrahydrofuran at −50°[5] and the resultant crude product was treated directly with diethylamine. This produced the desired Mannich base **14a** (Scheme III) (mixture of keto and hemiketal forms), but in only 11% yield (in striking contrast to the usual 80% yield of the bases derived by the same sequence from δ-lactones[1,3-6]). The neutral fraction isolated from this reaction appeared to consist mainly of divinyl diol resulting from further reaction of the initially formed vinyl ketone with the Grignard reagent.[11]

A possible explanation for the differing behavior of γ- and δ-lactones toward vinylmagnesium chloride involves the nature of the initial products formed in the reaction. The vinyl ketone formed in the δ-lactone case apparently exists under the reaction conditions predominantly in the cyclic form ii, protected from further attack by Grignard reagent. On the other

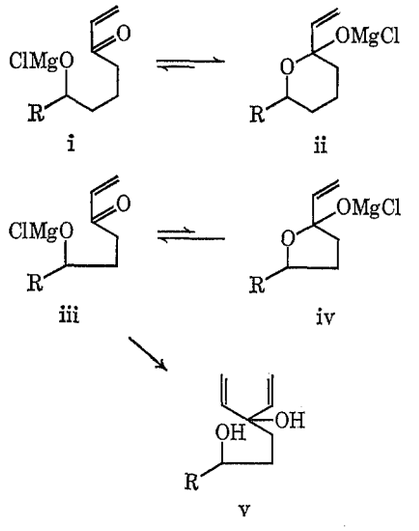
(9) E. B. Knott, *J. Chem. Soc.*, 1190 (1947).
(10) H. W. Thompson, *J. Chem. Soc.*, 2310 (1932).

(11) The reaction of γ-butyrolactone with alkyl Grignard reagents at −70° has previously been reported to give mainly 1,4-diols.[12] On the other hand, the preparation of α,β-ethynyl ketones by reaction of γ-butyrolactones with phenylethynyllithium at −70° has been described recently.[13]
(12) V. N. Belov and Y. I. Tarnopol'skii, *Zh. Org. Khim.*, **1**, 634 (1965), and references cited therein.
(13) H. Ogura, H. Takahashi, and T. Itoh, *J. Org. Chem.*, **37**, 72 (1972).

SCHEME III



hand, the corresponding vinyl ketone derived from the γ-lactone must exist to a great extent in the open form iii, rendering it susceptible to further attack by Grignard reagent and giving rise to the useless divinyl diol v.

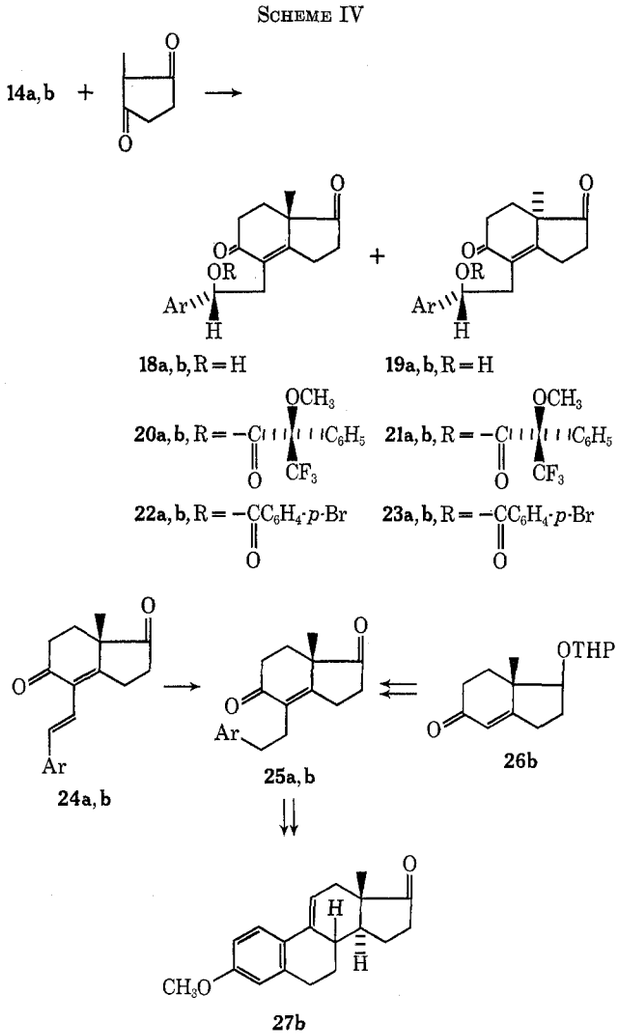


In order to circumvent the difficulty inherent in treating lactone **5** directly with vinylmagnesium chloride, an alternative sequence[5] was employed. Reduction of **5a** with diisobutylaluminum hydride, in toluene, at −70° gave the crystalline lactol **15a** in quantitative yield. Treatment of the latter compound with vinylmagnesium chloride in tetrahydrofuran furnished diol **16a** again in quantitative yield. Oxidation of **16a** with activated manganese dioxide,[14a,b] in benzene, in the presence of diethylamine[5] afforded a mixture of amines in 60% yield, consisting mainly of the desired Mannich base **14a**. By control of the reaction conditions, it was possible to keep the amount of undesired acetophenone **17** formed at trace levels. Using the same sequence of reactions, the (+)-lactone **5b** was converted into the optically active base mixture **14b** in yields comparable to those observed in the racemic series.

The ability to selectively oxidize an allylic alcohol in the presence of a benzylic alcohol with manganese dioxide is, to our knowledge, unprecedented and may find further application in synthesis. Our results are in agreement with those of Gritter and Wallace,[14b] who reported that allyl alcohol is more readily oxidized than benzyl alcohol and suggested a steric effect to be responsible for the rate difference. Similarly, in the case of diol **16**, steric factors are most likely responsible for the difference in rate of oxidation of the two hydroxyl functions.

Condensation of the racemic Mannich base **14a** with 2-methyl-1,3-cyclopentanedione (Scheme IV) in

SCHEME IV



refluxing toluene–acetic acid[15] for 1 hr unexpectedly produced none of the desired dienol ether **8a**. Instead, a mixture of ketols was produced from which the major

(14) (a) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, pp 637–643; Vol. II, 1969, pp 257–263; Vol. III, 1972, pp 191–194; and references cited therein. (b) R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, **24**, 1051 (1959). These authors point out that the rate and specificity of manganese dioxide oxidations is dependent on several factors, one of which is the manner in which the oxidizing agent is prepared. A description of the preparation of the manganese dioxide used for the oxidation of **16** to **14** is included in the Experimental Section.[37]

(15) G. Saucy, R. Borer, and A. Fürst, *Helv. Chim. Acta*, **54**, 2034 (1971).

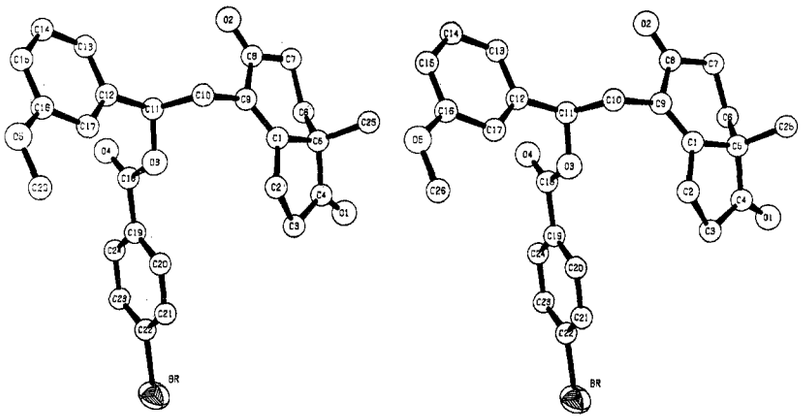


Figure 1.—Stereoview of **22a**.

epimer **18a** was isolated in 50% yield by crystallization. The relative configuration of this material was determined by an X-ray analysis of the corresponding *p*-bromobenzoate derivative **22a** (Figure 1).

Several unsuccessful experiments were carried out in an effort to cyclize **18a** to **8**. Heating in the presence of *p*-toluenesulfonic acid gave the diene **24a**. Treatment of **18a** with acetic anhydride led only to acetylation while exposure to dicyclohexylcarbodiimide in pyridine[16] led to recovered starting material.

The failure to isolate dienol ether **8** is probably due to strain inherent in this tricyclic fused dihydrofuran system (relative to the homologous dihydropyrans **4** isolated previously), making the hydroxy enedione form preferred by virtue of the relative product stabilities. Although we were unable to overcome this second deviation from our original plan, we nonetheless were encouraged by the observation that reaction of **14a** with 2-methyl-1,3-cyclopentanedione appeared to be quite stereoselective (substantially one ketol isomer produced). We felt that the optically active Mannich base **14b** when treated similarly should result in ketol **18b** with substantial asymmetric induction and hopefully (if the stereochemistry at the benzylic center had been properly chosen), affording the required 13β stereochemistry (steroid numbering).[17]

Condensation of the optically active base **14b** with 2-methyl-1,3-cyclopentanedione in refluxing toluene–acetic acid[15] for 1 hr gave a mixture of epimeric ketols **18b** and **19b** in 50–60% yield which, although noncrystalline, could be easily freed of other impurities by column chromatography. This mixture, without separation, was then dehydrated with *p*-toluenesulfonic acid and the disubstituted double bond in the intermediate diene **24** was selectively hydrogenated over palladium on carbon. The resultant enedione **25**,[7d,18] although optically impure, showed a specific rotation in the region of +150°. This result was encouraging, since it indicated that substantial asymmetric induction had taken place in the condensation of the optically active Mannich base **14b** with methylcyclopentanedione. Furthermore, the positive direction of the rotation signified that the preponderant epimer formed in this reaction was the desired **18b** having the natural, *S* configuration at the newly formed ring fusion center.[19,20] It should be noted that the dehydration–hydrogenation sequence was employed since efforts to convert the racemic ketol **18a** directly to tetracyclic materials were unrewarding.

It was of interest to determine the enantiomeric purity of the benzylic center in our intermediates, since we had no assurance that our original optical resolution had been successful or, assuming complete resolution, that racemization of this center had been avoided in the sequence leading from **5b** to **18b** and **19b**. To this end, we employed the nmr method of Mosher and coworkers.[21] Thus, when the mixture of **18b** and **19b** was treated with the acid chloride derived from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), an ester mixture (**20b**, **21b**) was produced which showed essentially a single resonance in the ^{19}F nmr spectrum (δ 7.38, downfield from TFA as an external standard) indicating that the benzylic center was enantiomerically pure. On the other hand, when the racemic ketol **18a** was esterified with this reagent, the ester produced exhibited two resonance peaks of approximately equal intensity (δ 7.38, 7.00) in the ^{19}F spectrum.[22]

Examination of the ^{1}H spectra of the esters **20a** and **20b**, **21b** yielded information regarding not only the enantiomeric purity but also the absolute configuration of the benzylic center. Thus, the resonance due to the aromatic methoxyl group in the ester derived from the racemic ketol occurred as two approximately equal peaks at δ 3.78 and 3.74, whereas the spectra of the optically active ester showed only the δ 3.78

(16) This reagent has been used for the dehydration of hydroxy acids to strained lactones; *cf.* R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958); W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. M. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961); J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965).

(17) The mechanism of the key asymmetric annelation producing mainly the dienol ethers **4** has been discussed previously.[6] We feel that a similar mechanism is operable in the reaction between **14** and 2-methyl-1,3-cyclopentanedione leading to a preponderance of ketol **18** over the epimer **19**.

(18) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).

(19) W. Acklin, V. Prelog, and A. P. Prieto, *Helv. Chim. Acta*, **41**, 1416 (1958).

(20) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron*, **24**, 2039 (1968).

(21) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

(22) It should be noted that the MTPA ester produced in the optically active series is epimeric at C_{13} (steroid numbering). This factor should have no effect on the analysis of enantiomeric purity at C_8, however, because of the distance separating the two asymmetric centers.

resonance peak. On the basis of the configurational correlation model proposed recently for MTPA derivatives,[23] it would be predicted that our optically active ketols **18b** and **19b**, the MTPA ester mixture derived from which exhibited the relatively lower field aromatic methoxy resonance, have the *R* configuration at the benzylic center. This assignment was confirmed by the ensuing transformations (see below).

Our next problem involved the synthesis of enedione **25b** in optically pure form. To accomplish this it was necessary to free the required ketol **18b** from its isomer **19b**. In contrast to the behavior in the racemic series, this mixture could not be induced to crystallize. When the mixture was converted to the *p*-bromobenzoate derivative, however, a crystalline product was obtained, recrystallization of which led, in 46% yield, to the desired major isomer **22b** in pure form. This material was spectrally and chromatographically identical with the racemic modification on which the X-ray analysis had been carried out. The minor ester **23b** was never isolated in pure form.

Since both the absolute configuration at C_{13} (steroid numbering) and the relative configuration of the two asymmetric centers in ester **22b** are known, it follows that the absolute configuration of the benzylic center must be *R* as predicted above. Thus, the absolute configuration of the positively rotating lactone **5b** from which **22b** is derived must be *R* also.

Treatment of **22b** with *p*-toluenesulfonic acid in refluxing toluene gave the crystalline diene **24b** (81% yield) which on selective hydrogenation over palladium on carbon furnished optically pure enedione **25b**, now showing $[\alpha]_D$ +195°, in 98% yield. From this value and the rotation obtained for **25b** when no separation of ketols **18b** and **19b** was carried out (+153°), it was possible to estimate that the ratio of **18b** to **19b** in the original mixture was approximately 8:1.

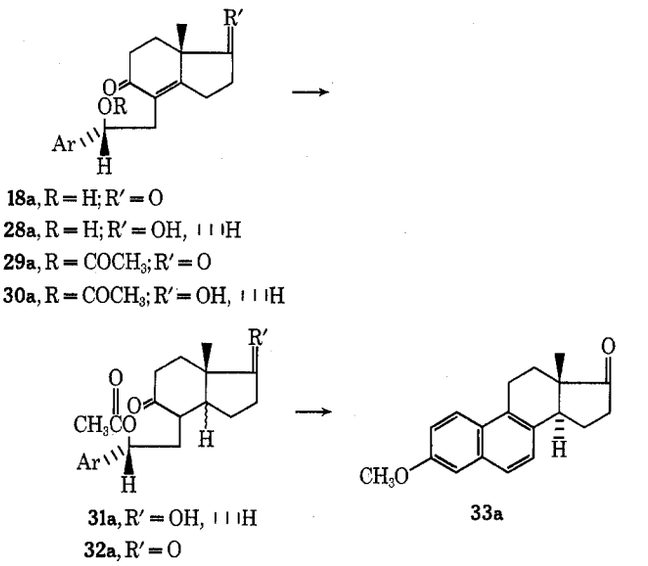
In order to verify the optical purity of enedione **25b** this material was synthesized by an alternative route starting from a substance of known optical purity. Thus, the (+)-tetrahydropyranyl ether **26b**[20] was alkylated with *m*-methoxyphenethyl tosylate using the procedure of Whitehurst and coworkers.[24] Acid hydrolysis of the product followed by oxidation with Jones reagent[25] gave **25b**. The optical rotations for the enedione samples produced by the two routes were in excellent agreement. While this work was in progress, an alternative asymmetric synthesis of **25b** was disclosed.[7d]

Enedione **25b** (produced from **22b**) was converted to (+)-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one (**27b**) using known procedures.[18] The properties of **27b** obtained in this way were in excellent agreement with those reported.[26,27] The final steps leading to estrone have been described previously.[18]

(23) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **95**, 512 (1973).
(24) D. J. Crispin, A. E. Vanstone, and J. S. Whitehurst, *J. Chem. Soc. C*, 10 (1970).
(25) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(26) K. Tsuda, S. Nozoe, and Y. Okada, *Chem. Pharm. Bull.*, **11**, 1271 (1963).
(27) K. Tsuda, E. Ohki, and S. Nazoe, *J. Org. Chem.*, **28**, 786 (1963).

A synthesis of racemic equilenin methyl ether starting from the ketol **18a** is shown in Scheme V. In

SCHEME V



order to carry out this transformation, a procedure was required which would allow selective catalytic hydrogenation of the enone double bond whicle preserving the benzylic hydroxyl function. Our initial studies were performed on the diol **28a**,[28] derived from **18a** by selective borohydride reduction.[29] Unfortunately, when **28a** was hydrogenated over palladium catalysts, both double-bond reduction and benzylic alcohol hydrogenolysis were found to occur simultaneously. In addition, substantial amounts of materials in which the carbonyl group had been lost by hydrogenolysis were obtained.

A somewhat more successful approach involves prior acetylation of the hydroxyl group giving the diketo acetate **29a**. Selective reduction[29] with sodium borohydride then afforded the corresponding 17β-ol **30a**[28] in essentially quantitative overall yield from **18a**. After many failures with other catalysts, it was found that hydrogenation of **30a** over palladium on barium sulfate yielded the desired keto acetate **31a** (mixture of isomers) in 25% yield. Oxidation[25] of the latter material followed by cyclization–aromatization of the resulting diketo acetate **32a** by treatment first with methanolic hydrochloric acid[18] and then with *p*-toluenesulfonic acid in refluxing benzene gave racemic equilenin methyl ether (**33a**)[18,30-32] in 42% yield. The material thus produced was spectrally and chromatographically identical with the ether obtained by methylation of natural equilenin.[33]

(28) Hydrogenation of **18a** or **29a** was not attempted since it is known that, in such systems, the 17 ketone gives rise to more of the undesired cis-fused hydrindanone than the corresponding 17β-hydroxy compound.[18]
(29) J. N. Gardner, B. A. Anderson, and E. P. Oliveto, *J. Org. Chem.*, **34**, 107 (1969).
(30) A. Horeau, E. Lorthioy, and J. P. Guetté, *C. R. Acad. Sci., Ser. C*, **269**, 558 (1969).
(31) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *J. Amer. Chem. Soc.*, **69**, 2942 (1947).
(32) R. P. Stein, G. C. Buzby, Jr., and H. Smith, *Tetrahedron*, **26**, 1917 (1970).
(33) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Amer. Chem. Soc.*, **62**, 824 (1940).

Experimental Section[34]

3-(3-Methoxybenzoyl)propionitrile (10).—3-Dimethylamino-*m*-methoxypropiophenone hydrochloride was prepared in 80% yield from *m*-methoxyacetophenone using the procedure of Nobles and Burckhalter.[35] White solid, mp 166–168°, was obtained (lit.[35] mp 168°). This material was converted into keto nitrile **10** in 58% yield by the method described by Knott.[9] Pale yellow solid, mp 52–53.5°, was obtained after recrystallization from methanol (lit.[9] mp 54°).

3-(3-Methoxybenzoyl)propionic Acid (11). A.—A 37.5-g (0.78 mol) sample of 50% sodium hydride–mineral oil dispersion was washed several times with hexane in a stream of nitrogen. A 610-ml portion of redistilled dimethyl carbonate was then added and the mixture was stirred in an oil bath at 90° while 111 g (0.74 mol) of *m*-methoxyacetophenone was added dropwise. As soon as the reaction began, the oil bath was removed and the addition of the ketone was continued over 40 min. The resulting brown solution was heated at reflux for 1 hr, then cooled in an ice bath and neutralized with 70 ml of glacial acetic acid. The resulting mixture was treated with 500 ml of ice water and worked up with ether (the organic extracts were additionally washed with aqueous sodium bicarbonate solution). Removal of ether and excess dimethyl carbonate left 163 g of orange, oily methyl *m*-methoxybenzoylacetate which was sufficiently pure for further use. A sample was distilled, bp 103–108° (0.2 mm) [lit.[36] bp 140–148° (0.8–1.4 mm)].

A 35.6-g (0.74 mol) sample of 50% sodium hydride–mineral oil dispersion was washed several times with hexane and then suspended in 450 ml of dry tetrahydrofuran. The resulting mixture was stirred while 160 g (0.74 mol) of crude methyl *m*-methoxybenzoylacetate was added dropwise. After heating at reflux for 1 hr, the reaction mixture was cooled in an ice bath and 113.5 g (0.74 mol) of methyl bromoacetate in 40 ml of dry tetrahydrofuran was added dropwise. After the addition was complete, the reaction mixture was stirred and heated at reflux for 1 hr, then cooled and the precipitated sodium bromide was filtered with suction. The filtrate was concentrated at reduced pressure and the residue was treated with 300 ml of ether and 8 ml of glacial acetic acid. Work-up with ether gave 206 g of crude product from which some mineral oil was decanted. Distillation afforded 163.5 g (79%) of dimethyl *m*-methoxybenzoylsuccinate as a viscous yellow oil, bp 152–156° (0.1 mm) [lit.[36] bp 161–162° (0.35 mm)].

A mixture of 163.5 g (0.586 mol) of this keto diester and 670 ml of concentrated hydrochloric acid was stirred at reflux for 20 hr. The mixture was cooled, diluted with 300 ml of water, and extracted with methylene chloride. The methylene chloride layer was in turn extracted with 1 l. of 10% aqueous sodium hydroxide and discarded. The alkaline solution was then chilled in an ice bath and acidified with concentrated hydrochloric acid. The precipitated product was filtered with suction, washed with water, and dried. Recrystallization from a mixture of 400 ml of benzene and 50 ml of hexane gave 59.4 g of first crop as tan solid, mp 104–107°, and 19.1 g of second crop, mp 105–107° (lit.[10] mp 108°). The total yield of **11** was 69.5%.

B.—A mixture of 39.9 g (0.211 mol) of keto nitrile **10** and 250 ml of 10% aqueous sodium hydroxide was stirred at reflux for 4 hr. The resulting red solution was cooled and extracted twice with ether and the ether extracts were discarded. The aqueous alkaline solution was acidified with 50 ml of concentrated HCl and worked up with methylene chloride. The solid residue was recrystallized from benzene, giving 33.5 g (76.2%) of off-white solid, mp 108–109°.

(±)-4-Hydroxy-4-(3-methoxyphenyl)butyric Acid γ-Lactone (5a).—A solution of 33.5 g (0.161 mol) of keto acid **11** in 400 ml of 10% aqueous sodium hydroxide was stirred while a solution of 12.1 g (0.32 mol) of sodium borohydride in 60 ml of water was added dropwise. The resulting solution was stirred at room temperature for 4 hr, then cooled in an ice bath and cautiously treated dropwise with 240 ml of concentrated hydrochloric acid. After stirring at 40–50° for 45 min the reaction mixture was cooled and worked up with ether (the ether extracts were additionally washed with two portions of saturated aqueous sodium bicarbonate), giving 30 g of viscous oily lactone. Distillation afforded 27.85 g (90%) of colorless oil, bp 133–140° (0.2 mm). A sample was evaporatively redistilled giving an analytical specimen, ir ($CHCl_3$) 1780 cm^{-1} (lactone C=O).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.78; H, 6.31. Found: C, 69.00; H, 6.34.

(±)-4-Hydroxy-4-(3-methoxyphenyl)butyronitrile (12a).—A slurry of 14.9 g (0.079 mol) of the keto nitrile **10** in 120 ml of absolute ethanol was stirred in an ice–salt bath at −5 to 0° while a solution of 1.5 g (0.04 mol) of sodium borohydride in 100 ml of absolute ethanol was added dropwise over a 30-min period. The reaction mixture was gradually allowed to warm to room temperature as it was stirred for 1.25 hr, then neutralized with 1 *N* aqueous HCl and worked up with ether. There was obtained 14.2 g (94.3%) of the crude hydroxy nitrile **12a** as a colorless liquid which was sufficiently pure for further use.

A sample from a similar run was chromatographed on silica gel (50 parts, eluted with 9:1 benzene–ether) and evaporatively distilled to give the analytical sample as a pale yellow liquid, bp 130–175° (bath temperature) (0.07 mm). This material showed a single spot on tlc analysis; ir ($CHCl_3$) 3475, 3600 (OH), 2250 (C≡N), 1590, 1600 cm^{-1} (anisole); mass spectrum *m/e* 191 (M^+).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.83; H, 6.80; N, 7.16.

(±)-[3-Cyano-1-(3-methoxyphenyl)]-1-propyl Hemiphthalate (13a).—A solution of 56.1 g (0.294 mol) of crude hydroxy nitrile **12a**, 44.4 g (0.3 mol) of phthalic anhydride, and 160 ml of anhydrous pyridine was heated at 100° for 5 hr. The reaction mixture was cooled and poured into a mixture of ice and 3 *N* aqueous hydrochloric acid and the resulting acidic aqueous solution was extracted three times with ether. The ether extracts were combined and extracted with 10% aqueous sodium carbonate solution, then discarded. The alkaline extracts were combined, washed with ether (discarded), then carefully acidified with 10% aqueous HCl and extracted with chloroform. There was obtained 93.6 g (93.8%) of hemiphthalate **13a** as a brown oil which was used without purification. A sample from a similar experiment showed the following spectral data: ir ($CHCl_3$) 3400–3050 (broad H-bonded OH), 2250 (C≡N), 1740 (ester C=O), 1710 (acid C=O), 1605, 1595 cm^{-1} (anisole); mass spectrum *m/e* 339 (M^+).

(*R*)-(−)-3-Cyano-1-(3-methoxyphenyl)-1-propyl Hemiphthalate (13b) (*R*)-(+)-α-Methylbenzylamine Salt.—To a solution of 93.6 g (0.276 mol) of crude hemiphthalate **13a** in 200 ml of acetonitrile was added 35 g (0.29 mol) of (*R*)-(+)-α-methylbenzylamine in 20 ml of acetonitrile. The mixture was heated on the steam bath for 5 min, and then allowed to stand for 2 days at room temperature. The white solid obtained was recrystallized twice from acetonitrile, giving 25.3 g (39.8%) of pure salt as a colorless solid, mp 124.5–126°, $[\alpha]^{25}D$ −51.08° (*c* 1, EtOH).

The analytical specimen showed mp 122–123.5°; $[\alpha]^{25}D$ −51.57° (*c* 1, EtOH); nmr ($CDCl_3$) δ 8.37 (m, 3, NH_3^+), 7.23 (m, 13, aromatic), 5.85 (m, 1, HCO), 4.16 (m, 1, PhCH), 3.72 (s, 3, OCH_3), 2.19 (m, 4, CH_2CH_2CN), 1.38 ppm (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{19}H_{17}NO_5 \cdot C_8H_{11}N$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.22; H, 5.96; N, 5.86.

(*S*)-(+)-[3-Cyano-1-(3-methoxyphenyl)]-1-propyl Hemiphthalate (13c) (*S*)-(−)-α-Methylbenzylamine Salt.—A resolution of 187.6 g (0.556 mol) of acid phthalate **13a** was carried out with (*R*)-(+)-α-methylbenzylamine as described in the preceding

(34) Unless otherwise noted, reaction products were isolated by addition of brine and extraction with the specified solvent. Organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under water aspirator pressure at 40–50° on a rotary evaporator. The crude reaction products were then dried under high vacuum to constant weight. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an atmosphere of nitrogen. Column chromatography was performed using Merck (Darmstadt) silica gel, 0.05–0.2 mm. Thin layer chromatography was performed using Brinkmann silica gel G plates with uv indicator. Unless otherwise noted plates were developed with 1:1 benzene–ethyl acetate. Spots were detected with uv light, iodine vapor, or *p*-toluenesulfonic acid spray followed by heating. Varian A-60 and HA-100 or Jeolco C-60H spectrometers were used to obtain the pmr spectra. Chemical shifts are reported relative to TMS. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14 M spectrophotometer. Low-resolution mass spectra were obtained on CEC 21-110 or JMS-01SG instruments. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Tetrahydrofuran and pyridine were slurried over Woelm grade I neutral alumina just prior to use.

(35) W. L. Nobles and J. H. Burckhalter, *J. Amer. Pharm. Ass. Sci. Ed.*, **47**, 77 (1958).

(36) J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward, *J. Amer. Chem. Soc.*, **90**, 439 (1968).

experiment. The mother liquor and washes after removal of the first crop of *R,R* salt were combined and concentrated *in vacuo*, giving a brown, oily residue. This material was treated with aqueous 3 *N* HCl and extracted with ether, affording 114 g (0.337 mol) of hemiphthalate as a brown oil. After dissolution in 200 ml of acetonitrile this material was treated with a solution of 41 g (0.338 mol) of (*S*)-(−)-α-methylbenzylamine in 50 ml of acetonitrile. The mixture was heated on the steam bath for 15 min and then allowed to stand for 2 days at room temperature. The white solid obtained was recrystallized twice from acetonitrile, giving 36.3 g (28.4%) of the pure *S,S* salt as a white solid, mp 132–133°, $[\alpha]^{25}D$ +55.75° (*c* 1, EtOH). The nmr spectrum was essentially identical with that of the *R,R* salt.

Anal. Calcd for $C_{19}H_{17}NO_5 \cdot C_8H_{11}N$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.64; H, 6.27; N, 6.08.

(*S*)-(−)-4-Hydroxy-4-(3-methoxyphenyl)butyric Acid γ-Lactone (5c).—A 10-g (0.022 mol) sample of the *S,S* salt from the preceding experiment was treated with 3 *N* aqueous HCl and the resultant acid was isolated by ether extraction, giving the hemiphthalate **13c** as a colorless oil, $[\alpha]^{25}D$ +21.77° (*c* 1, EtOH). This material was treated with 160 ml of 10% aqueous NaOH and heated at reflux with stirring for 5 hr. The reaction mixture was cooled, washed once with ether, acidified with 3 *N* aqueous HCl, and stirred for 1.75 hr at room temperature. The reaction mixture was then saturated with sodium chloride and the product was isolated with ether. (The combined organic extracts were additionally washed with saturated aqueous sodium bicarbonate solution.). The residual colorless oil was evaporatively distilled, giving 3.5 g (83.8%) of the lactone **5c** as a colorless liquid, bp 170–185° (bath temperature) (0.1 mm), $[\alpha]^{25}D$ −12.05° (*c* 1, EtOH). Tlc analysis showed a single spot, R_f 0.4; ir ($CHCl_3$) 1780 (γ-lactone C=O), 1605, 1590 cm^{-1} (anisole); mass spectrum *m/e* 192 (M^+). The spectra were essentially identical with those of the racemic form **5a** and the *R* isomer **5b**.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.45; H, 6.34.

(*R*)-(+)-4-Hydroxy-4-(3-methoxyphenyl)butyric Acid γ-Lactone (5b).—A 36.7-g (0.08 mol) sample of the (*R*)-(+)-α-methylbenzylamine salt of the *R* hemiphthalate **13b** was converted into the acid as described in the previous experiment, giving **13b** as a colorless oil. A sample from a similar experiment showed $[\alpha]^{25}D$ −22.02° (*c* 1, EtOH). This material was hydrolyzed and lactonized as described in the previous experiment, giving 13.6 g (88.8%) of lactone **5b** as a colorless liquid. A sample was evaporatively distilled, giving a colorless liquid, bp 170–180° (bath temperature) (0.1 mm), $[\alpha]^{25}D$ +12.93° (*c* 1, EtOH). The ir, nmr, and mass spectra and the tlc mobility were identical with those of the *S* and *R,S* modifications.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.44; H, 6.18.

(±)-Mannich Base Mixture 14a. A. From Lactone 5a.—The procedure of Saucy and Borer[5] was employed. A solution of 19.2 g (0.1 mol) of lactone **5a** in 64 ml of dry tetrahydrofuran was cooled to −65° and stirred while 80 ml (0.16 mol) of 2 *M* vinylmagnesium chloride in tetrahydrofuran was added dropwise over 40 min keeping the internal temperature at −50 to −60°. The mixture was stirred for 10 min more at this temperature, decomposed with 10 ml of methanol keeping the temperature near −50°, and poured onto a mixture of 80 g of ice, 6 ml of glacial acetic acid, and 16 g of ammonium chloride. The resulting mixture was extracted three times with ether and the combined extracts were treated with 50 ml of diethylamine and dried over anhydrous magnesium sulfate for 1 hr at room temperature. After filtration, the ether solution was concentrated at reduced pressure, giving 25.2 g of a yellow oil. This material was redissolved in ether and washed three times with 50-ml portions of 1 *N* aqueous hydrochloric acid. The combined acid extracts were washed once with ether and the combined ether solutions were dried over magnesium sulfate and set aside.

The combined acid washes were chilled in an ice bath and made alkaline with 50 ml of 10% aqueous sodium hydroxide. The mixture was worked up with ether, giving 3.22 g (11%) of yellow oily, Mannich base mixture **14a**: ir (film), 3330 (OH), 3180 (broad H-bonded OH), 1710 (ketone C=O, m), 1600 cm^{-1} (anisole); uv max (95% EtOH) 215 nm (ε 8780), 272 (2070), 279 (1900); nmr ($CDCl_3$) δ 7.00 (m, aromatic), 5.19 (t, *J* = 7 Hz, HCO of major component), 4.95 (m, HCO of minor component, approximately 0.33 of major component), 3.76 (s, OCH_3), 1.05 ppm (2 t, $-CH_2CH_3$ of each component); mass spectrum *m/e* 293 (M^+). Tlc analysis (9:1 C_6H_6–Et_3N) showed a single spot, R_f 0.3.

The ether solution containing neutral material which had been set aside was filtered and concentrated at reduced pressure. The residual yellow oil was stirred for 17 hr at room temperature in 100 ml of 2.8 *M* methanolic sodium hydroxide. This solution was concentrated at reduced pressure and worked up with ether, giving 15.4 g of the oily divinyl diol **v** (R = *m*-methoxyphenyl), ir (film) 3450 (OH), 3125 (HC=), 1640 (C=C), 1615 (anisole), 995, 885 cm^{-1} (vinyl).

B. From Diol 16a.—The method of Saucy[5] was employed. A slurry of 660 ml of benzene and 284 g of activated manganese dioxide[37] was stirred with ice-bath cooling while 42 ml of diethylamine was added followed by 28.2 g (0.127 mol) of crude diol **16a**. The ice bath was removed and the reaction mixture was stirred at room temperature for 4.5 hr. The manganese dioxide was filtered with suction and the filter cake was washed thoroughly with methylene chloride. The combined filtrate and washes were concentrated at reduced pressure. The red oily residue was dissolved in ether and the ether solution was extracted three times with 1 *N* aqueous HCl and set aside. The combined acidic, aqueous solutions were basified with 10% potassium hydroxide and worked up with ether, giving 22.4 g (60.3%) of red, oily Mannich base mixture **14a**. The material produced in this manner typically showed the following spectral properties: uv max (95% EtOH) 214 nm (ε 9990), 253 (1210), 271 (1860), 278 (1720), 303 (360); ir (film) 3000–3600 (H-bonded OH), 1710 (C=O), 1680 (shoulder, acetophenone impurity C=O), 1590, 1600 cm^{-1} (anisole). Tlc analysis (9:1 C_6H_6:Et_3N) showed a main spot, R_f 0.3, with a more mobile, minor impurity (acetophenone **17**). The major spot was identical with that of the Mannich base produced in part A.

The ether extracts containing neutral products which had been set aside afforded 6.7 g of oily material which appeared by tlc and spectral analysis to be a mixture of three components, one of which was the starting diol. It was found that longer exposure to MnO_2 led to increased amounts of acetophenone **17** in the product.

Optically Active Mannich Base Mixture 14b.—A 1.98-g (0.0084 mol) sample of crude, optically active diol **16b** was oxidized with 18 g of activated manganese dioxide[37] in 60 ml of benzene and 3 ml of diethylamine using the procedure described for the racemic modification in part B of the preceding experiment. There was obtained 1.7 g (68.8%) of Mannich base **14b** as a red oil which was used without further purification. The ir spectrum and tlc mobility were identical with those of the racemic modification.

(±)-5-(3-Methoxyphenyl)tetrahydrofuran-2-ol (15a).—A solution of 8.82 g (0.046 mol) of lactone **5a** in 60 ml of dry toluene was stirred at −70° while 50 ml of a 25% solution of diisobutylaluminum hydride in toluene (Texas Alkyls Co.) was added dropwise over 10 min. The resulting mixture was stirred at −70° for 1 hr, then cautiously poured into a mixture of 70 g of ice and 18 ml of glacial acetic acid. The toluene layer was separated and work-up with ether was carried out in the usual manner (the organic solution was additionally washed with aqueous sodium bicarbonate solution). This gave 9 g of colorless oil which crystallized on standing. Recrystallization from benzene–hexane gave 6.87 g (77.2%) of white solid, mp 76–78°. An analytical sample was obtained by further recrystallization from benzene–hexane as a colorless solid: mp 76.5–78°; ir ($CHCl_3$) 3450, 3625 (OH), 1600 cm^{-1} (anisole).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.01; H, 7.28. Found: C, 67.74; H, 7.16.

(5*R*)-5-(3-Methoxyphenyl)tetrahydrofuran-2-ol (15b).—A 1.87-g (0.01 mol) sample of (*R*)-(+)-lactone **5b** was reduced proportionately, with diisobutylaluminum hydride using the procedure described in the previous experiment. There was obtained 1.8 g of crude lactol **15b** as a colorless oil. The ir spectrum and tlc mobility were identical with those of the racemic modification. This material was used without purification.

(37) The activated manganese dioxide used in this work was prepared by Dr. D. Andrews of the Technical Development Division, Hoffmann-La Roche Inc., Nutley, N. J. The following procedure is typical. Pyrolusite (10 kg) was added in portions to a solution of 5 l. of concentrated HNO_3 in 20 l. of hot water and the entire mixture was heated at reflux for 30 min. After cooling, the acid solution was siphoned off and the residual manganese dioxide was washed in turn with hot water (3 × 25 l.), 1% aqueous sodium bicarbonate (25 l.), and water (2 × 25 l.) and then dried to constant weight at 100–120° in a circulating air oven. The recovery of MnO_2 was 79%.

(±)-1-(3-Methoxyphenyl)-5-hexene-1,4-diol (16a).—The procedure of Saucy and Borer[5] was employed. A solution of 24.9 g (0.128 mol) of crude lactol **15a** in 135 ml of dry tetrahydrofuran was added dropwise to 210 ml of stirred, 2 *M* vinylmagnesium chloride in tetrahydrofuran with occasional cooling to moderate the exothermic reaction. After the addition was complete, the solution was stirred at room temperature for 3 hr and then poured into 600 ml of ice-cold aqueous ammonium chloride solution and worked up with ether. The residual, pale-yellow, oily diol (28.3 g; 99%) was sufficiently pure for further use. A sample from another identical run was chromatographed on silica gel. The materials from the fractions eluted with 3:2 benzene–ether to pure ether were combined and evaporatively distilled, giving the analytical sample as a viscous, colorless oil, bp 155–163° (bath temperature) (0.2 mm). Tlc analysis showed a single spot, R_f 0.25; ir ($CHCl_3$) 3400, 3600 (OH), 1600 (anisole), 990 cm^{-1} (vinyl).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.18. Found: C, 70.02; H, 8.32.

(1*R*)-1-(3-Methoxyphenyl)-5-hexene-1,4-diol (16b).—This material was prepared from lactol **15b** in quantitative yield using the procedure described in the preceding experiment for the racemic modification. The crude diol was a viscous, pale-yellow oil which was spectrally and chromatographically identical with the racemic modification and was used without further purification.

(1*R*,*S*)-2-[5,6,7,7a-Tetrahydro-(7a*S*,*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethanol (18a).—The procedure of Saucy, *et al.*,[15] was employed. A mixture of 4 g (0.0137 mol) of crude racemic Mannich base mixture **14a** prepared as described above (MnO_2 method), 1.62 g (0.0145 mol) of 2-methyl-1,3-cyclopentanedione, 15 ml of acetic acid, and 55 ml of toluene was stirred and heated at reflux for 1 hr. After cooling, the resulting solution was diluted with ether and washed three times with water and twice with saturated aqueous sodium bicarbonate. Completion of the usual work-up gave 4.097 g of the mixture of **18a** and **19a** as a red gum. This material was recrystallized from hexane–benzene, giving 2.172 g (50.4%) of tan solid, mp 110–112° (tlc, R_f 0.33). Further recrystallization of a sample gave the analytical specimen of **18a**: mp 113–114°; uv max (95% EtOH) 217 nm (ε 10,800), 251 (9320), 279 (2600); ir ($CHCl_3$) 3500, 3625 (OH), 1750 (cyclopentanone C=O), 1660 (conjugated ketone C=O), 1600 cm^{-1} (anisole); mass spectrum *m/e* 314 (M^+); nmr ($CDCl_3$) δ 1.17 (s, 3, C_{7a} CH_3), 3.76 (s, 3, OCH_3), 4.82 ppm (m, 1, HCO).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.58; H, 7.07. Found: C, 72.37; H, 6.81.

The minor epimer **19a** exhibits the same tlc mobility as **18a** and was never isolated in pure form. In another run, the crude product (1.09 g) was chromatographed on 50 g of silica gel. Elution with 49:1 to 4:1 benzene–ether gave fractions containing 0.176 g of impurities which were less polar than the ketols **18a** and **19a**. Spectroscopic investigation of these materials failed to reveal the presence of the diene **8a**. Elution with 1:1 benzene–ether gave 0.801 g (69.7%) of the crystalline mixture of ketols **18a** and **19a**.

Attempted Conversion of Ketol 18a to the Diene 8a.—A solution of 31.4 mg (0.1 mmol) of ketol **18a** and 22 mg (0.106 mmol) of *N*,*N*′-dicyclohexylcarbodiimide[16] in 1 ml of dry pyridine was stirred at room temperature. After 3.25 hr tlc analysis indicated that only the starting materials were present. The solution was then heated at 105–110° for 19 hr. After cooling, work-up with ether gave a quantitative recovery of starting materials (tlc).

Treatment of **18a** with *p*-toluenesulfonic acid in refluxing benzene or with acetic anhydride gave the diene **24a** or the diketo ester **29a**, respectively. These reactions are described in detail below. Again, no trace of the diene **8a** was detected.

(1*R*)-(+)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethanol (18b) and (1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*R*)-methyl-1,5-dioxo-4-indanyl]-1(3-methoxyphenyl)ethanol (19b).—A mixture of 8.3 g (0.028 mol) of the crude optically active Mannich base **14b**, 3.36 g (0.03 mol) of 2-methyl-1,3-cyclopentanedione, 30 ml of glacial acetic acid, and 100 ml of toluene was stirred and heated at reflux for 1 hr. The reaction mixture was cooled and worked up with ether as described for the racemic series above, giving 8.2 g of crude, red, oily product. This material was chromatographed on 400 g of silica gel. The fractions eluted with 1:1 benzene–ether and ether afforded 5.5 g (62%) of the mixture of ketols **18b** and **19b** with the former predominating, as an orange oil: $[\alpha]^{25}D$ +117.59° (*c* 1, EtOH); this material was essentially homogeneous on tlc analysis; uv max (95% EtOH) 219 nm (ε 10,410), 252 (8675), 279 (2820); ir ($CHCl_3$) 3450, 3600 (OH), 1750 (cyclopentanone C=O), 1655 (conjugated ketone C=O), 1590, 1600 cm^{-1} (anisole); mass spectrum *m/e* 314 (M^+); nmr ($CDCl_3$) δ 4.82 (m, 1, HCO), 3.72 (s, 3, OCH_3), 1.13 ppm (s, 3, C_{7a} CH_3).

(1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (20b) and (1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (21b).—The procedure of Mosher *et al.*,[21] was employed. A mixture of 105.6 mg (0.336 mmol) of the optically active hydroxy enedione mixture **18b** and **19b**, 92.3 mg (0.365 mmol) of the acid chloride[21] derived from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (Aldrich), 50 drops of carbon tetrachloride, and 25 drops of dry pyridine was allowed to stand at room temperature in a stoppered flask overnight. The reaction mixture was treated with water and extracted with ether. The ether extract was washed with 1 *N* aqueous HCl, saturated aqueous sodium bicarbonate solution, water, and brine and then dried. Solvent removal gave 0.176 g of crude ester as a brown oil. This material was chromatographed on 15 g of silica gel. Elution with 4:1 and 1:1 benzene–ether afforded 0.154 g (86.4%) of the ester mixture **20b** and **21b** as a brown oil (tlc, R_f 0.45): ir (film) 1750 (cyclopentanone C=O and ester C=O), 1670 (α,β-unsaturated ketone C=O), 1590, 1600 cm^{-1} (anisole); uv max (95% EtOH) 250 nm (ε 9180); pmr ($CDCl_3$) δ 7.30 (m, 6, aromatic), 6.89 (m, 3, aromatic), 6.01 (d of d, 1, J = 6, 8.5 Hz, HCO), 3.78 (s, 3, aromatic OCH_3), 3.46 (m, 3, aliphatic OCH_3), 1.11 ppm (s, 3, C_{7a} CH_3). The ^{19}F spectrum was obtained on a Varian XL-100 instrument at 94.1 MHz in $CDCl_3$ solution using CF_3CO_2H as an external standard. The spectrum showed essentially a single resonance band at 7.38 ppm downfield from TFA. The amount of 1*S* isomer present was <1%.

(1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate and (1*S*)-2-[5,6,7,7a-Tetrahydro-(7a*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (20a).—The racemic ketol **18a** was esterified with the acid chloride derived from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid as described in the previous experiment. The product, after chromatographic purification, was a pale-yellow oil: tlc, R_f 0.43; ir (film) 1750 (cyclopentanone and ester C=O), 1670 (α,β-unsaturated ketone C=O), 1590, 1600 cm^{-1} (anisole); pmr ($CDCl_3$) δ 7.30 (m, 6, aromatic), 6.85 (m, 3, aromatic), 6.00 (m, 1, HCO), 3.78 (s, ~1.5, aromatic OCH_3 of 1*R* diastereomer), 3.74 (s, ~1.5, aromatic OCH_3 of 1*S* diastereomer), 3.47 (m, 3, aliphatic OCH_3), 1.12 ppm (s, 3, C_{7a} CH_3). The ^{19}F spectrum (same conditions as the previous experiment) showed two resonance bands of approximately equal intensity at δ 7.38 and 7.00 ppm downfield from external TFA. The δ 7.00 band was essentially absent in the spectrum of the mixture **20b** and **21b** (previous experiment).

(1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl 4-Bromobenzoate (22b).—A mixture of 2.6 g (8.3 mmol) of the optically active hydroxy enedione mixture **18b** and **19b**, 3.65 g (16.6 mmol) of 4-bromobenzoyl chloride, and 75 ml of dry pyridine was stirred at room temperature for 20 hr. The reaction mixture was then treated with 25 ml of water, allowed to stir for 15 min at room temperature before acidification with 3 *N* aqueous HCl, and then extracted with methylene chloride. The organic extracts were combined, washed once with water, twice with aqueous saturated sodium bicarbonate solution, and once with brine, then dried. Solvent removal gave a yellow solid residue which was chromatographed on 250 g of silica gel. The fractions eluted with 9:1 and 4:1 benzene–ether afforded 3.39 g (82.3%) of yellow solid (mixture of esters **22b** and **23b**).

This material was recrystallized four times from ethanol, giving 1.9 g (46.3%) of pure ester **22b** as colorless crystals: mp 126–127° (homogeneous on tlc analysis, R_f 0.47); $[\alpha]^{25}D$ + 143.85° (*c* 0.5, C_6H_6); uv max (95% EtOH) 247 nm (ε 29,450); ir ($CHCl_3$) 1745 (cyclopentanone C=O), 1725 (ester C=O), 1670 (conjugated ketone C=O), 1590 cm^{-1} (anisole); mass spectrum *m/e* 496 (M^+); nmr ($CDCl_3$) δ 7.71 (A_2B_2 m, 4, *p*-BrC_6H_4C=O), 7.05 (m, 4, *m*-$CH_3OC_6H_4$), 6.08 (t, 1, J = 7 Hz, HCO), 3.78 (s, 3, OCH_3), 1.13 ppm (s, 3, C_{7a} CH_3). The spectra and tlc mobility were identical with those of the racemic ester **22a**.

Anal. Calcd for $C_{26}H_{25}BrO_5$: C, 62.78; H, 5.07; Br, 16.06. Found: C, 63.08; H, 5.01; Br, 15.97.

(1*R*,*S*)-2-[5,6,7,7a-Tetrahydro-(7a*S*,*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl 4-Bromobenzoate (22a).—This material was prepared starting from the racemic ketol **18a** using the procedure described in the previous experiment. The pure ester was obtained in 82% yield as a pale-yellow solid, mp 139–140°. Crystals suitable for X-ray analysis were grown by slow crystallization from an ethanol–methylene chloride mixture. The ir, uv, nmr, and mass spectra as well as the tlc mobility were identical with those of the (+) form **22b**.

Anal. Calcd for $C_{26}H_{25}BrO_5$: C, 62.78; H, 5.07; Br, 16.06. Found: C, 63.04; H, 5.19; Br, 16.08.

(*S*)-(+)-7,7a-Dihydro-4-(*m*-methoxystyryl)-7a-methyl-1,5(6*H*)-indandione (24b).—A solution of 1.84 g (3.71 mmol) of the pure diketo ester **22b** and 0.3 g of *p*-toluenesulfonic acid monohydrate in 50 ml of toluene was stirred at reflux for 1.5 hr. The reaction mixture was cooled, diluted with ether, washed with aqueous saturated sodium bicarbonate solution and brine, and dried. Solvent removal gave an orange-yellow solid which was chromatographed on silica gel (60 g), yielding 0.9 g (81%) of an orange-yellow solid (eluted with 4:1 and 9:1 benzene–ether). Recrystallization from ethanol afforded 0.732 g (66.5%) of the diene **24b** as yellow needles, mp 111.5–112.5°. This material was homogeneous on tlc analysis, R_f 0.48. An analytical specimen was obtained as yellow needles, mp 112–112.5°, by further recrystallization of a sample from ethanol: $[\alpha]^{25}D$ + 164.35° (*c* 0.5, C_6H_6); uv max (95% EtOH) 219 nm (ϵ 23,520), 279(16,200), sh 315 (12,800); ir ($CHCl_3$) 1750 (cyclopentanone C=O), 1670 (α,β-unsaturated ketone), 1640 (C=C, w), 1600, 1585 cm^{-1} (anisole); nmr ($CDCl_3$) δ 6.95 (m, 6, aromatic and vinyl), 3.78 (s, 3, OCH_3), 1.34 ppm (s, 3, C_{7a} CH_3).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.07; H, 6.98.

(*R*,*S*)-7,7a-Dihydro-4-(*m*-methoxystyryl)-7a-methyl-1,5(6*H*)-indandione (24a).—This material was prepared starting from the racemic diketo ester **22a** using the procedure described in the preceding experiment. The analytical specimen was obtained by recrystallization from ether–ethanol as a yellow solid, mp 93–94°. The ir, uv, and nmr spectra as well as the tlc mobility were essentially identical with those of the (+) form **24b**.

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.80; H, 6.69.

(*S*)-(+)-7,7a-Dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione (25b). A. From Diene 24b.—The pure diene **24b** (0.407 g, 1.38 mmol) was hydrogenated in 25 ml of dry toluene in the presence of 0.2 g of 5% palladium on carbon.[38] After 25 min, 37.5 ml of hydrogen had been absorbed (34.4 ml theory) and the hydrogenation was stopped. The catalyst was filtered and washed with ether and the combined filtrate and washings were concentrated at reduced pressure. The residual, colorless oil was chromatographed on silica gel (20 g) to give 0.401 g (97.8%) of the enedione (eluted with 9:1 and 4:1 benzene–ether). A sample from a similar run was rechromatographed on silica gel and evaporatively distilled to give an analytical specimen of optically pure **25b** as a pale yellow oil, bp 170–185° (bath temperature) (0.05 mm), which was homogeneous on tlc analysis (R_f 0.45): $[\alpha]^{25}D$ + 195.05° (*c* 0.5, C_6H_6); uv max (95% EtOH) 220 nm (ϵ 11,470), 250 (9380), 278 (2630); ORD (*c* 0.5975, dioxane, 23°) $[\phi]_{700}$ +349.1°, $[\phi]_{589}$ +528.1°, $[\phi]_{371}$ +7099.6°, $[\phi]_{366}$ +6905.1°, $[\phi]_{357}$ +8655.7°, $[\phi]_{348}$ +6321.6°, $[\phi]_{341}$ +7391.4°, $[\phi]_{335}$ +6127.1°, $[\phi]_{325}$ +11969.8°, $[\phi]_{316}$ +4638.3°, $[\phi]_{313}$ +4787.9°, $[\phi]_{310}$ 0°, $[\phi]_{282}$ −43889.5°, $[\phi]_{260}$ −73415.2°, $[\phi]_{245}$ 0°, $[\phi]_{231}$ +74200.8°, and $[\phi]_{210}$ (last) 0°; ir ($CHCl_3$) 1750 (cyclopentanone C=O), 1665 (α,β-unsaturated ketone C=O), 1600, 1585 cm^{-1} (anisole); nmr ($CDCl_3$) δ 7.16 (m, 1, aromatic), 6.68 (m, 3, aromatic), 3.75 (s, 3, OCH_3), 1.18 ppm (s, 3, C_{7a} CH_3).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.21; H, 7.47.

B. From Enone 26b.—A 2-g (8 mmol) sample of the enone **26b**[20] (94.5% optically pure) was alkylated with *m*-methoxyphenethyl tosylate[24] (2.42 g, 7.96 mmol) using the procedure of Whitehurst, *et al.*[24] The crude alkylate was hydrolyzed[24] and the resulting red, oily product (2.3 g) was chromatographed on 125 g of silica gel. Elution with 1:1 benzene–ether gave 0.758 g (31.6%) of oily (1*S*,7a*S*)-1-hydroxy-7,7a-dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-5(6*H*)-indanone: tlc R_f 0.24; ir (film) 3425 (OH), 1650 (α,β-unsaturated ketone C=O), 1600, 1585 cm^{-1} (anisole).

A solution of this material in 25 ml of acetone was stirred with ice-bath cooling while 0.8 ml of Jones reagent[25] was added dropwise from a syringe over a 5-min period. The resulting mixture was stirred at 0–5° for 5 min, then decomposed with aqueous sodium bisulfite solution and worked up with ether, giving 0.754 g of brown oil. This material was chromatographed on 37.5 g of silica gel. The fractions eluted with 19:1 benzene–ether afforded 0.6 g of yellow, oily enedione which was homogeneous on tlc analysis, R_f 0.44. Evaporative distillation gave 0.532 g (70.5%) of viscous, pale-yellow, oily **25b**: bp 195–200° (bath temperature) (0.1 mm); $[\alpha]^{25}D$ +185° (*c* 0.5, C_6H_6); uv max (95% EtOH) 220 nm (ϵ 11,160), 250 (9580), 278 (2460); mass spectrum *m/e* 298 (M^+); ORD (*c* 0.4200, dioxane, 23°) $[\phi]_{700}$ +312.2°, $[\phi]_{589}$ +489.6°, $[\phi]_{370}$ +6754.7°, $[\phi]_{365}$ +6655.3°, $[\phi]_{356}$ +8244.7°, $[\phi]_{348}$ +5860.7°, $[\phi]_{340}$ +6953.3°, $[\phi]_{334}$ +5662.0°, $[\phi]_{325}$ +11068.6°, $[\phi]_{316}$ +4044.3°, $[\phi]_{313}$ +4257.1°, $[\phi]_{310}$ 0°, $[\phi]_{280}$ −37803.4°, $[\phi]_{260}$ −57471.4°, $[\phi]_{246}$ 0°, $[\phi]_{231}$ +66411.4°, and $[\phi]_{210}$ (last) 0°. The ir and nmr spectra were essentially identical with those of the material produced in part A above. The $[\alpha]D$ when corrected for the optical purity of the starting material corresponds to a value of +195.9° for optically pure material (lit.[7d] $[\alpha]^{25}D$ +181°).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.41; H, 7.32.

C. From the Mixture of Ketols 18b and 19b.—A solution of 0.493 g (1.57 mmol) of the hydroxy enedione mixture **18b** and **19b** and 50 mg of *p*-toluenesulfonic acid monohydrate in 15 ml of toluene was stirred and heated at reflux for 20 min. The reaction mixture was cooled, diluted with ether, washed with saturated aqueous sodium bicarbonate solution and brine, then dried and filtered. Solvent removal gave the crude diene (mixture of **24a** and **24b**) as a red oil which was hydrogenated in 30 ml of toluene in the presence of 0.15 g of 5% palladium on carbon.[38] After 15 min, 39.2 ml of hydrogen had been absorbed (39.3 ml theory) and the hydrogenation was stopped. The catalyst was filtered and washed with ether and the combined filtrate and washings were concentrated at reduced pressure to give 0.46 g of the crude enedione as a red oil. This material was chromatographed on silica gel (50 g) to give 0.352 g of an orange oil (eluted with 9:1 benzene–ether). Evaporative distillation gave 0.335 g (71.6%) of a yellow oil: bp 145–175° (bath temperature) (0.01 mm); $[\alpha]^{25}D$ +149.68° (*c* 0.5, C_6H_6); uv max (95% EtOH) 249 nm (ϵ 8940). Preparative gas chromatographic purification of a sample prepared in this way was carried out using an F & M Model 320 instrument on an 8 ft × 0.5 in. o.d. stainless steel column packed with 10% SE-30 silicone on 70–80 mesh Chromosorb W AW-DMCS at 280° with a helium carrier gas flow rate of 2–2.5 ml/sec. The major peak (94%, retention time 8.8 min) was collected and evaporative distillation of this material gave a mixture of the *S* isomer (**25b**) and racemic enedione (**25a**) as a pale yellow oil: bp 150–180° (bath temperature) (0.03 mm); $[\alpha]^{25}D$ +153.60° (*c* 0.5, C_6H_6); uv max (95% EtOH) 219 nm (ϵ 11,115), 250 (8770), 279 (2470); ORD (*c* 0.3178, dioxane, 23°) $[\phi]_{700}$ +254.8°, $[\phi]_{589}$ +396.4°, $[\phi]_{370}$ +5346.3°, $[\phi]_{366}$ +5281.1°, $[\phi]_{355}$ +6519.8°, $[\phi]_{349}$ +4824.7°, $[\phi]_{342}$ +5607.4°, $[\phi]_{335}$ +4694.3°, $[\phi]_{324}$ +8662.1°, $[\phi]_{313}$ +2980.5°, $[\phi]_{309}$ 0°, $[\phi]_{271}$ −30736.3°, $[\phi]_{255}$ −43030.8°, $[\phi]_{244}$ 0°, $[\phi]_{230}$ +45173°, and $[\phi]_{208}$ (last) +2528.5°. The ir and nmr spectra as well as the tlc mobility of this material were identical with those of the products from part A and B and with those of the racemic modification **25a**[18] described in the following experiment. The observed rotation corresponds to an optical purity of 78.5%.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.21; H, 7.56.

(*R*,*S*)-7,7a-Dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione (25a).—A 1-g (3.184 mmol) sample of ketol **18a** was dehydrated and the resulting diene was hydrogenated as described in part C of the preceding experiment. After purification by chromatography and evaporative distillation there was obtained 0.675 g (71.3%) of racemic enedione **25a** as a yellow oil, bp 180–220° (bath temperature) (0.1 mm), which was homogeneous on tlc analysis: ir (film) 1740 (cyclopentanone C=O), 1660 (α,β-unsaturated ketone C=O), 1600 (anisole), 780, 690 cm^{-1}; uv max (95% EtOH) 220 nm (ϵ 10,400), 250 (8300) [lit.[18] bp 160–190° (bath temperature) (0.05 mm); uv max 249 nm (ϵ 9000); ir 1740, 1660, 1600, 780, and 690 cm^{-1}]. The

(38) A 5% palladium-on-carbon catalyst prepared at F. Hoffmann-La Roche and Co., AG, Basle, Switzerland, and designated AK-4 was employed for this hydrogenation.

physical spectra and tlc mobility of this material were essentially identical with those of the optically active form described in the preceding experiment.

(+)-3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one (27b).—The sequence of Smith, *et al.*,[18] was employed. A solution of 0.87 g (2.92 mmol) of the optically pure enedione **25b** (prepared from diene **24b**) in 15 ml of ethanol was stirred and cooled in an ice–salt bath to −8° while a solution of 30 mg (0.793 mmol) of sodium borohydride in 25 ml of ethanol was added dropwise over a 15-min period keeping the temperature below 0°.[29] The reaction mixture was then stirred for 15 min at *ca.* −3°. The pH was adjusted to 6–7 with 3 *N* aqueous HCl and after diluting with brine, the reaction mixture was worked up with ether, giving a colorless oil. This material was chromatographed on silica gel (100 g), affording 770.3 mg (88.0%) of (1*S*,7a*S*)-1-hydroxy-7,-7a-dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-5(6*H*)-indanone as a pale yellow oil (eluted with 1:1 and 1:3 benzene–ether). The ir spectrum and tlc mobility of this material were identical with those of the sample prepared from enone **26b** as described above.

This hydroxy ketone was hydrogenated in 30 ml of absolute ethanol in the presence of 0.2 g of 5% palladium on carbon.[38] After 2.25 hr, 66 ml of hydrogen had been absorbed (64 ml theory) and the hydrogenation appeared to have stopped. The catalyst was filtered and washed well with ethanol and the combined filtrate and washings were concentrated at reduced pressure to give a colorless oil. Chromatography on 75 g of silica gel afforded 464 mg (60.1%) of the major component as a colorless oil (eluted with 1:2 and 1:4 benzene–ether): ir (film) 3430 (OH), 1710 (cyclohexanone C=O), 1600, 1585 cm^{-1} (anisole); tlc R_f 0.29.

A solution of this material in 15 ml of acetone was stirred with ice-bath cooling at 0° while 1.25 ml of Jones reagent[25] was added dropwise from a syringe. The reaction mixture was stirred for 5 min at 0–5°, then the excess oxidant was decomposed with 2-propanol. The reaction mixture was worked up with ether, giving a pale-yellow oil. Chromatography on silica gel (50 g) afforded 434 mg (93.8%) of diketone as a pale-yellow oil (eluted with 4:1 and 1:1 benzene–ether) (tlc R_f 0.46): ir (film) 1740 (cyclopentanone C=O), 1715 (cyclohexanone C=O), 1600, 1585 cm^{-1} (anisole).

A solution of this diketone in 10 ml of methanol was stirred at room temperature while 2 ml of 10 *N* aqueous HCl was added. The reaction mixture became warm and after 10 min, a white precipitate was present. After 4 hr of stirring at room temperature, the reaction mixture was chilled at 0° for 1.5 hr. The white precipitate was filtered, washed with cold methanol, and dried under vacuum to give 247.9 mg of white solid, mp 130–133°. Recrystallization from methanol gave 156.8 mg (38.5%) of the pure ketone **27b** as colorless needles: mp 142.5–144°; homogeneous on tlc analysis, R_f 0.50; $[\alpha]^{25}D$ +290.92° (*c* 0.5, $CHCl_3$); ir ($CHCl_3$) 1735 (cyclopentanone C=O), 1605 cm^{-1} (anisole); uv max (95% EtOH) 263 nm (ϵ 19,300), 297 (3400), infl 310 (2220); nmr ($CDCl_3$) δ 7.52 (d, 1, aromatic), 6.68 (m, 2, aromatic), 6.13 (m, 1, C_{11} H), 3.76 (s, 3, OCH_3), 0.92 ppm (s, 3, C_{13} CH_3); ORD (*c* 0.3034, dioxane, 23°) $[\phi]_{700}$ +650.6°, $[\phi]_{589}$ +948.1°, $[\phi]_{321}$ +18812.4°, $[\phi]_{250}$ 0°, $[\phi]_{243}$ −1858.9°, $[\phi]_{240}$ 0°, $[\phi]_{226}$ +11153.6°, $[\phi]_{220/224}$ +8365.2°, $[\phi]_{216}$ 0°, and $[\phi]_{210}$ (last) −9294.7° [lit.[26] mp 142–144°; $[\alpha]^{25}D$ +289° ($CHCl_3$); uv max (EtOH) 263 nm (ϵ 17,300)].

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.53; H, 7.78.

(1*R*,*S*)-2-[(1*S*,*R*)-Hydroxy-5,6,7,7a-tetrahydro-(7a*S*,*R*)-methyl-5-oxo-4-indanyl]-1-(3-methoxyphenyl)ethanol (28a).—The procedure of Oliveto, *et al.*[29] was employed. A mixture of 2.76 g (8.8 mmol) of ketol **18a** and 28 ml of ethanol was stirred at −10° while 9.2 ml (2.67 mmol) of 0.29 *M* ethanolic sodium borohydride was added dropwise over a 10-min period. After stirring at −5 to 5° for 50 min, the reaction mixture was decomposed with 3 *N* aqueous HCl and worked up with ether, giving 2.91 g of diol **28a** as a tan foam (tlc 0.15): ir (film) 3450 (OH), 1640 cm^{-1} (α,β-unsaturated ketone C=O).

Hydrogenation of this material over 5% palladium on carbon[38] in ethanol was not selective. When it was allowed to proceed to completion, about 2 molar equiv of hydrogen was absorbed. The crude product was reoxidized[25] and the resulting ketone mixture was chromatographed on silica gel. The early fractions eluted with 19:1 benzene–ether gave a yellow oil which appeared to be a mixture of compounds lacking both the benzylic hydroxyl and cyclohexanone functions: ir (film) 1740 (cyclopentanone C=O), 1600 cm^{-1} (anisole); uv max (95% EtOH) 215 nm (ϵ 6375), 271 (1360), 278 (1360); mass spectrum *m/e* 284 (M^+), 286 (M^+). The later fractions eluted with 19:1 benzene–ether and 9:1 benzene–ether afforded a pale-yellow oil which was a mixture of isomers of (±)-3a,4,7,7a-tetrahydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione: ir (film) 1750 (cyclopentanone C=O), 1710 (cyclohexanone C=O), 1600 cm^{-1} (anisole); uv max (95% EtOH) 215 nm (ϵ 7400), 271 (1760), 278 (1680); mass spectrum *m/e* 300 (M^+). The ratio of these products varied considerably from run to run.

(1*R*,*S*)-2-[5,6,7,7a-Tetrahydro-(7a*S*,*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl Acetate (29a).—A 0.5-g (1.59 mmol) sample of ketol **18a** was allowed to stand at room temperature in a solution of 5 ml of pyridine and 2.5 ml of acetic anhydride for 27 hr. The solvents were partially removed at reduced pressure and the residue was poured into saturated aqueous sodium bicarbonate and worked up with ether (the ether extracts were additionally washed twice with 1 *N* HCl), giving 0.573 g (100 + %) of the oily acetate **29a**. This material showed a single spot on tlc analysis, R_f 0.4. After drying thoroughly, it still contained some ether and showed the following spectral properties: uv max (95% EtOH) 220 nm (ϵ 11,010), 249 (9190), 275 (3040), 281 (2620); ir ($CHCl_3$) 1750 (cyclopentanone, ester C=O), 1670 (α,β-unsaturated ketone C=O), 1600 cm^{-1} (anisole); mass spectrum *m/e* 356 (M^+); nmr ($CDCl_3$) δ 5.80 (t, 1, *J* = 7 Hz, HCO), 3.78 (s, 3, OCH_3), 2.02 (s, 3, CH_3C=O), 1.15 ppm (s, 3, C_{7a} CH_3). This material was used without further purification.

(1*R*,*S*)-2-[(1*S*,*R*)-Hydroxy-5,6,7,7a-tetrahydro-(7a*S*,*R*)-methyl-5-oxo-4-indanyl]-1-(3-methoxyphenyl)ethyl Acetate (30a).—The procedure of Oliveto, *et al.*,[29] was employed. A 0.526-g (1.48 mmol) sample of the crude acetate **29a** from the preceding experiment was dissolved in 4.6 ml of ethanol and the solution was stirred at −10° while 1.56 ml of a 0.291 *M* ethanolic sodium borohydride solution was added dropwise from a syringe. The resulting mixture was stirred in the cold for 40 min and then decomposed with 1 *N* aqueous HCl. Work-up with ether gave 0.545 g of a yellow gum which was homogeneous on tlc analysis (R_f 0.26): ir (film) 3400 (OH), 1730 (ester C=O), 1650 (α,β-unsaturated ketone C=O), 1600 (anisole), 1230 cm^{-1} (acetate); uv max (95% EtOH) 219 nm (ϵ 9210), 248 (9300); nmr ($CDCl_3$) δ 7.10 (m, 4, aromatic), 5.84 (t, 1, *J* = 8 Hz, HCO), 3.82 (s, 3, OCH_3), 2.04 (s, CH_3C=O), 1.02 ppm (s, 3, C_{7a} CH_3); mass spectrum *m/e* 358 (M^+). This material was used without further purification.

(±)-3-Methoxyestra-1,3,5(10),6,8-pentaen-17-one [(±)-Equilenin 3-Methyl Ether] (33a).—A 0.742-g (2.08 mmol)sa mple of hydroxy keto ester **30a** was hydrogenated in 30 ml of ethanol over 0.2 g of 5% palladium on barium sulfate at 1 atm and room temperature. After 5.67 hr, 53 ml of hydrogen had been consumed (theory for 1 molar equiv, 52 ml). The catalyst was filtered and washed with fresh ethanol. The combined filtrate and washes were concentrated at reduced pressure, giving 0.736 g of a cloudy glass, uv max (95% EtOH) 244 nm (ϵ 4760). Tlc analysis showed six spots. This material was chromatographed on 37.5 g of silica gel. Elution with 9:1 benzene–ether–4:1 benzene–ether gave various materials derived from hydrogenolysis of the benzylic acetate and enone functions as evidenced by lack of ester or cyclohexanone absorptions in the ir spectra. Elution with 1:1 benzene–ether gave 109 mg of an oil which was a mixture of isomers of ketol ester **31a** (tlc, R_f 0.29): ir (film) 3450 (OH), 1730 (ester C=O), 1700 (cyclohexanone C=O), 1590 cm^{-1} (anisole) (no conjugated ketone present). The later fractions eluted with 1:1 benzene–ether and ether gave 0.163 g of starting acetate **30a** (tlc, R_f 0.25). The mixture fractions (0.204 g) which contained the desired material were rechromatographed on 10 g of silica gel affording an additional 0.082 g of **31a** and 0.052 g of starting material. In this way, a total of 0.191 g (25.5%; 36% based on recovered starting material) of **31a** and 0.215 g (29%) of recovered **30a** was obtained.

When this hydrogenation was carried out with palladium on carbon, palladium on calcium carbonate, or platinum or rhodium on alumina, only trace amounts of **31a** were produced.

The above ketol ester **31a** (0.191 g, 0.53 mmol) was dissolved in 5 ml of acetone. The resulting solution was stirred and cooled to 0–5° while 0.19 ml of Jones reagent[25] was added from a syringe. The resulting red mixture was stirred for several minutes, then decomposed with 2-propanol. Work-up with ether gave 0.171 g of the oily diketo ester mixture **32a** which was homogeneous on tlc analysis (R_f 0.5): ir (film) 1735 (ester and

cyclopentanone C=O), 1700 (cyclohexanone C=O), 1590 cm^{-1} (anisole). Material from a similar run showed the following spectral properties: uv max (95% EtOH) 215 nm (ϵ 6960), 272 (2030), 279 (1840); nmr ($CDCl_3$) δ 6.85 (m, 4, aromatic), 5.90 (t, 1, J = 8 Hz, HCO), 3.87 (s, 3, OCH_3), 2.02 (s, CH_3C=O), 1.26 (s, C_{7a} CH_3, minor isomer), 1.02 ppm (s, C_{7a} CH_3, major isomer); mass spectrum m/e 358 (M^+).

An ice-cold solution of this diketo ester (0.171 g, 0.475 mmol) in 3 ml of methanol was stirred while 0.625 ml of 10 N aqueous HCl was added. The resulting solution was stirred at 0–5° for 10 min and then at room temperature for 3.5 hr. Work-up with ether gave 0.162 g of oily product. This material was stirred and heated at reflux in 5 ml of benzene containing 25 mg of *p*-toluenesulfonic acid monohydrate. After cooling the solution was diluted with ether, washed once with aqueous sodium bicarbonate solution, dried, and concentrated at reduced pressure, giving 138 mg of semicrystalline residue. Chromatography on 7.5 g of silica gel gave 63 mg (42.5% based on **31a**) of pure, racemic equilenin 3-methyl ether (**33a**) (eluted with 49:1 benzene–ether; tlc, one spot, R_f 0.57). Recrystallization from ethanol gave colorless plates, mp 183–186° (lit.[30] mp 186°; lit.[31,33] mp 185–186°; lit.[32] mp 188–190°). The ir, uv, and nmr spectra and tlc mobility of this racemic material were identical with those of *d*-equilenin methyl ether, mp 195–196°, prepared by methylation of (+)-equilenin (Searle) as described by Wilds, *et al.*[33]

Crystallography.—Crystals of **22a** were obtained from an ethanol–methylene chloride mixture as well-formed prisms. The crystal data are a = 14.67 (1), b = 7.09 (1), c = 24.81 (3) Å, β = 116.90 (5)°, d_{obsd} (aqueous KI) = 1.42, d_{calcd} = 1.435 g cm^{-3} for Z = 4, space group $P2_1/c$.

The intensities of 4571 independent X-ray diffraction maxima with $2\theta < 140°$ were measured on a Hilger-Watts Model Y290 four-circle diffractometer using Ni-filtered Cu Kα radiation. A rapid, stationary crystal–stationary detector technique was used to collect the data and an empirical correction was applied to convert the peak top data to integrated scan data. A total of 3531 reflections were significantly greater than background and these data were used for the structure analysis. The dimensions of the data crystal were 0.35 × 0.35 × 0.45 mm. The data were corrected for absorption (μ = 29.8 cm^{-1}).

The structure was solved by the heavy atom method. Refinement of the structure was carried out by full matrix least squares. All atoms had isotropic temperature factors except the bromine, which was assigned anisotropic thermal parameters; hydrogen atoms were not included. At the conclusion of the refinement, R = 0.132. A difference Fourier calculated at this point had no features greater than 1.0 electron/Å^3 in magnitude.[39]

Acknowledgments.—We wish to express our gratitude to the personnel of the Physical Chemistry Department of Hoffmann-La Roche Inc., Nutley, N. J., for carrying out many of the spectral and microanalytical determinations required in this work and to the members of the Kilo Laboratory who assisted in the preparation of certain of the starting materials.

Registry No.—**5a,** 40901-47-1; **5b,** 38102-79-3; **5c,** 38102-77-1; **10,** 38102-72-6; **11,** 38102-67-9; **12a,** 38171-50-5; **13a,** 38171-49-2; **13b,** 40901-54-0; **13b** (*R*)-(+)-α-methylbenzylamine salt, 38102-75-9; **13c,** 40903-49-9; **13c** (*S*)-(−)-α-methylbenzylamine salt, 38171-48-1; **14a,** 38102-69-1; **14b,** 40901-59-5; **15,** 38102-70-4; **16,** 38102-71-5; **18a,** 40901-62-0; **18b,** 38680-53-4; **19b,** 38680-54-5; **20a,** 40903-58-0; **20b,** 40901-66-4; **21b,** 40903-60-4; **22a,** 40901-68-6; **22b,** 38680-56-7; **24a,** 38680-42-1; **24b,** 38680-57-8; **25a,** 18300-15-7; **25b,** 15375-09-4; **26b,** 17780-12-0; **27b,** 1670-49-1; **28a,** 40901-76-6; **29a,** 40903-70-6; **30a,** 40901-78-8; **31a,** 38680-49-8; **32a,** 38680-50-1; **33a,** 4820-56-8; (*R*)-(+)-α-methylbenzylamine, 3886-69-9; 2-methyl-1,3-cyclopentanedione, 765-69-5; (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid, 20445-31-2; *p*-toluenesulfonic acid, 104-15-4.

Supplementary Material Available.—Listings of structure factors and atomic parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3229.

(39) See paragraph at end of paper regarding supplementary material.

The Stereocontrolled Synthesis of *trans*-Hydrindan Steroidal Intermediates

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Received February 15, 1973

Catalytic hydrogenation of simple $\Delta^{3a(4)}$-indan derivatives (*e.g.*, **1a**) gave mainly (88.5%) the thermodynamically favored cis-fused bicyclic products. In the presence of a β-oriented bulky C-1 substituent ~30% of trans-fused derivatives and with an additional bulky substituent at C-4 ~50% of trans-fused hydrogenation products could be obtained. With a carboxylic acid or a carboxylic ester substituent at C-4 practically full stereocontrol has been achieved to yield the desired trans-fused bicyclic compounds (**8** and **13**). A theoretical explanation of the stereochemical results has been included.

During the course of an investigation of a new total synthesis of steroidal compounds the problem of the stereocontrolled preparation of *trans*-hydrindan derivatives became of prime importance. These bicyclic compounds correspond to the CD portion of the steroidal skeleton, and if properly functionalized they may become suitable building blocks of a new totally synthetic scheme to obtain steroidal compounds.

It has been previously reported[2a] that indan derivatives, *e.g.*, the bicyclic unsaturated keto alcohol **1a**, gave, under a variety of hydrogenation conditions, only the thermodynamically more stable C/D cis keto alcohol **2**. We found 88.5% of cis compound **2** in the reaction mixture by vpc, which is in fair agreement with a more recent publication reporting ~80% of **2** as estimated by nmr spectroscopy.[2b]

It was of interest to discover whether the desired C/D trans stereoisomer could be obtained by the catalytic hydrogenation of a properly modified and substituted bicyclic system. The *tert*-butyl ether **1b** has therefore been subjected to catalytic hydrogenation under a variety of reaction conditions. It was hoped that preferential α-side attack would occur owing to the β-oriented bulky substituent at the C-1 position of the molecule. The *tert*-butyl ether group was removed by hydrolysis of the reduction products, and the resulting mixture of **2** and **3** was subjected to fractionation by

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