(17) C. W. Shoppee, F. P. Johnson, R. E. Lack, J. S. Shannon, and S. Sternhell, *Tetrahedron, Suppl. 8*, Part II, 421 (1966).
(18) All compounds reported in this paper are racemic. For convenience, only one enantiomer has been shown.
(19) All melting points were determined in a Thomas-Hoover melting point apparatus and are corrected; uv spectra were taken in ethyl alcohol with a Cary Model 14M spectrophotometer; ir spectra were taken with a Beckman IR-9 recording spectrophotometer; nmr spectra were taken in $CDCl_3$ on a Varian A-60 or HA-100 spectrometer with tetramethylsilane as an internal standard.

Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry

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Received August 20, 1973

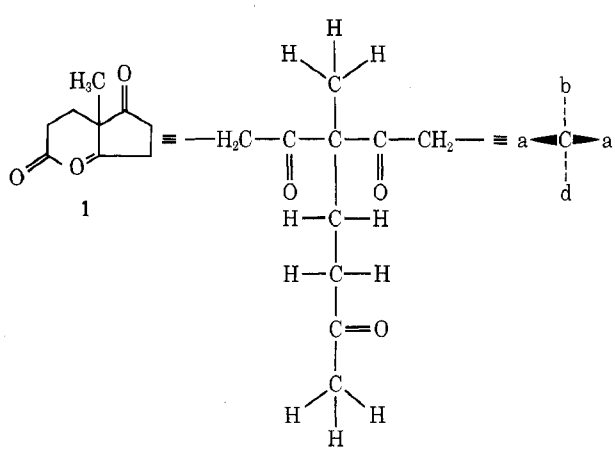
The triketone **1**, a compound of reflective symmetry, could be converted by an asymmetric aldol cyclization to the optically active bicyclic 7a-methyl ketol (+)-**2** in 100% chemical and 93.4% optical yield by the use of a catalytic amount (3% molar equiv) of (*S*)-(−)-proline. Starting with the triketone **6** the homologous 7a-ethyl bicyclic ketol (+)-**7** could be obtained in optically pure form and in 71.0% chemical yield. Dehydration of (+)-**2** gave the enone (+)-**3** of known (7a*S*) absolute configuration. The homologous enone (+)-**8** could be obtained by a similar dehydration of (+)-**7**. The CD curve of (+)-**8** was very similar to that of the lower homolog (+)-**3**. Thus, (+)-**3**, (+)-**8**, (+)-**7**, and (+)-**2** all have the same (7a*S*) absolute configuration. The CD results for (+)-**2** suggested, and a single-crystal X-ray diffraction study of racemic (±)-**2** confirmed, the cis conformation with an axial 7a-methyl and an equatorial 3a-hydroxyl group in the six-membered ring of the bicyclic system. On the other hand, similar measurements of (+)-**7** and (±)-**7** established the alternate possible cis conformation for the homologous 7a-ethyl bicyclic system. Based on the results with (*S*)-(−)-proline and also with other optically active reagents employed, two alternative reaction mechanisms have been proposed, both involving a three-point attachment of the bifunctional asymmetric reagent to the substrate molecule. The products [(+)-**2**, (+)-**7**, (+)-**8**] of this highly efficient asymmetric synthesis are important new intermediates of natural product chemistry, *e.g.*, steroid total syntheses.

One striking aspect of biological systems is the stereoselectivity associated with many of the processes. Thus, the majority of chemical substances formed and broken down in metabolic processes are optically active, and usually one particular enantiomer is formed in these processes and found in abundance in nature. As a consequence, it has been found on many occasions that the physiological activity of a particular compound resides almost exclusively in one of its optically active forms. The scientific and the practical importance of processes for the preparation of specific optical isomers is therefore quite obvious.

The classical chemical resolution procedure suffers from the disadvantage of yielding only a theoretical maximum of 50% of the desired optically active isomer based on the racemic starting material. The same disadvantage exists in an alternate procedure, in which the racemic mixture is treated with reagents of biological origin, *i.e.*, microbiological or enzymatic processes. In contrast, an asymmetric synthesis can result theoretically in a 100% yield of only one enantiomer. Its importance is evident from a recent review article,[2] a recent book written on this subject,[3] as well as the great volume of papers in the recent chemical literature describing laboratory results in this area. There appears to be some confusion in some of these papers in that reactions producing one diastereoisomeric *dl* pair of a given structure are called "asymmetric syntheses" instead of the more proper term "stereoselective syntheses," as suggested by Zimmerman and coworkers.[4]

It was our goal in the present investigation to find methods by which intermediates in natural product syntheses, *e.g.*, the optically active bicyclic diketone **3**, could be prepared in an asymmetric synthesis. We had previously prepared the compound by means of classical chemical resolution,[5] and used it in the construction of optically active tricyclic and tetracyclic systems.[5,6] We chose to use the triketone **1**, 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione, as the achiral starting material of our

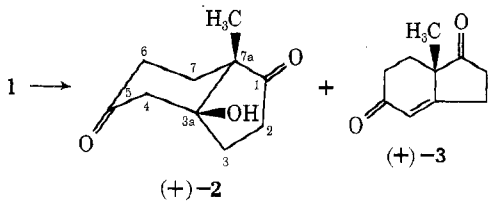
Scheme I



asymmetric synthesis owing to the special symmetry in its constitution. It has a carbon atom with four symmetrical groups, two of which are identical and two of which are dissimilar. One can bisect the molecule of **1** through the central carbon atom and the b and d groups; the two halves are mirror images, and cannot be superimposed (Scheme I). The symmetry properties resemble those of the meso form; the central carbon atom has therefore been called a "meso" carbon atom.[7] An optically active asymmetric reagent should be able to differentiate between the two identical ("enantiotopic") groups, and to convert the "meso" carbon atom, also called "prochiral center," to an asymmetric carbon atom (a center of chirality). Based on these considerations we hoped to achieve a stereoselective ring closure to the optically active bicyclic ketol **2** with the help of a properly chosen asymmetric reagent and reaction conditions.

The chemistry of the triketone **1** had been carefully studied with special attention to its cyclization reactions.[8] The problem was twofold: (a) a system had to be found

Scheme II



which would promote the cyclization of the triketone **1** to the bicyclic ketol **2** or to its dehydration product **3** in a high chemical yield; and (b) the cyclization reaction should occur with the maximum transfer of chirality, *i.e.*, with the best possible optical yield. Based on our studies concerning the cyclization reactions of the triketone **1** we knew that we must avoid basic reaction conditions, and work in an anhydrous medium in order to avoid undesired bridged ketol formation. We also recognized the advantages of a system containing pyrrolidine in the cyclization reactions of the triketone **1**. The problem at this point was to find a reagent or a combination of reagents which would contain the pyrrolidine moiety and would also contain an optically active center within the system. After a rather disappointing experiment using a combination of pyrrolidine and (+)-10-camphorsulfonic acid we chose to try (*S*)-(−)-proline for the following reasons. (a) It is an optically active pyrrolidine derivative. (b) In contrast to the pyrrolidine–(+)-camphorsulfonic acid system, the asymmetric carbon atom is in the same molecule next to the functional groups. (c) The asymmetric carbon atom is in a five-membered ring. The greater rigidity of the cyclic system usually enhances the optical rotatory power.[9] We expected a concomitant increase in the stereoselectivity of the asymmetric reagent. (d) In agreement with Ogston's hypothesis,[10] the optically active reagent should attach itself at more than one point to the symmetrical compound to be able to differentiate between the identical groups. We hoped that the two functional groups in proline would be helpful in this respect. (e) The isoelectric point of proline is at pH 6.30. We could thus hope to avoid undesired bridged ketol formation and expect to obtain the regular ketol due to the pyrrolidine nucleus in the molecule.

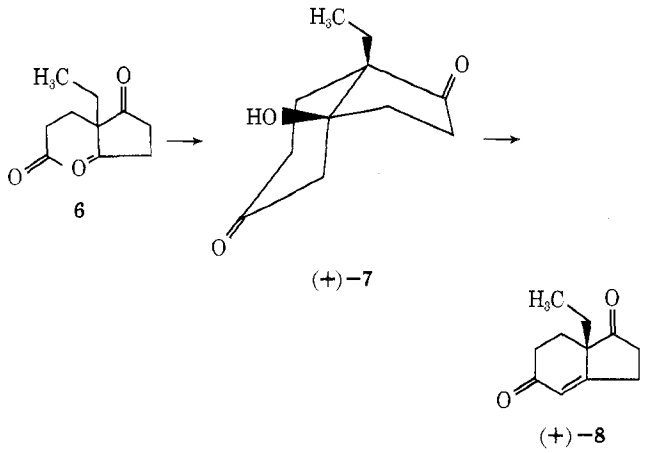
In our first experiments with (*S*)-(−)-proline we used 1 molar equiv of this reagent in various alcohols. The reactions were executed at about 20°, under a nitrogen or argon atmosphere, with magnetic stirring over a period of 3–4 days. Thin layer chromatography indicated little if any ketol **2**[8] in these experiments; the major product was the enone **3**. The optical yield of **3** was calculated as the quotient of the per cent optical purity and the per cent chemical purity, the latter by uv spectroscopy. This calculation is reasonable, owing to the high (367°)[5,11] specific rotation of the enone **3**. We found a relationship between the polarity of the alkyl group of the alcoholic solvent and the optical yield of **3**. An increase in the polarity of the alkyl group of the alcohols was accompanied by an increase in the optical yield (indicated in parentheses): ethyl alcohol (27.6%), *n*-butyl alcohol (32.2%), isopropyl alcohol (60.7%), and *tert*-butyl alcohol (83.7%). The experiment in isopropyl alcohol was also executed with a catalytic amount of (*S*)-(−)-proline (0.1 mmol/1.0 mmol of triketone **1**) under otherwise identical reaction conditions and the enone (+)-**3** was obtained in a comparable optical yield (57.2% *vs.* 60.7%). Owing to the smaller quantity of proline employed it was possible to isolate 17.4% of the intermediate bicyclic ketol (+)-**2** in this experiment in 61.3% optical purity (Scheme II). The infrared and the nmr spectra of the compound were identical with the spectra of the racemic ketol (±)-**2**.[8]

Although we had now achieved a relatively high chemical yield (75% in 2-propanol solvent) in the conversion of the triketone **1** to the optically active enone **3**, the optical yield still had to be improved. We assumed that H bonding played an important role in the asymmetric cyclization reaction and chose, therefore, to try aprotic solvents, which should interfere less with a H-bonded transition state. Since we found that increased polarity of the alcoholic solvent enhanced the optical yield, we chose to use a polar, aprotic solvent: acetonitrile. Whereas we found the enone (+)-**3** to be the major reaction product in alcoholic solvents, the use of 1 molar equiv of (*S*)-(−)-proline in acetonitrile gave the crude optically active ketol (+)-**2** in 97.3% yield. In addition, 96.5% of the asymmetric reagent could be recovered by simple filtration of the reaction mixture. The crude ketol (+)-**2** contained 3.7% (uv spectroscopy) of the enone (+)-**3**. An optically pure sample of the bicyclic ketol (+)-**2** was obtained by recrystallization from ether, and had $[\alpha]^{25}D$ +60.4° (chloroform). Dehydration of the crude ketol (+)-**2** gave the optically active enone (+)-**3** in 100% weight yield and 85.6% optical purity. Since uv spectroscopy indicated 88.2% chemical purity, the optical yield by calculation is 97.1%.[12]

In the next experiment we used *N,N*-dimethylformamide (DMF) as the polar aprotic solvent, because we had found it to be a superior solvent in the asymmetric synthesis of (+)-**7**, the ethyl homolog of (+)-**2**. Since only 3% molar equiv of (*S*)-(−)-proline was lost in the above-described conversion in acetonitrile, we also decreased the quantity of asymmetric reagent. We found that 3% molar equiv of (*S*)-(−)-proline in DMF gave excellent results, and enabled us to decrease the reaction time to 20 hr. We obtained the bicyclic ketol (+)-**2** in 100% weight yield and 93.4% optical purity. Uv spectroscopy showed no enone **3** in this sample. Dehydration of (+)-**2** gave the enone (+)-**3** in 99.4% weight yield and 87.7% optical purity. Since the chemical purity was 92.4% by uv spectroscopy, the optical yield was 94.9% by calculation. Purification without chromatography gave the enone (+)-**3** in 97% optical yield, and in 70.2% weight yield based on the triketone **1**. Chromatography of the mother liquors gave an additional 14.1% weight yield of (+)-**3** in 94.3% optical purity.

Thus we achieved both of our goals: a high chemical yield and a high optical yield. At the same time we have connected the hitherto unknown optically active ketol (+)-**2** with the dextrorotary enone (+)-**3** of known absolute configuration.[13] The extremely mild conditions of the dehydration should not have affect the 7a center, and the absolute configuration of the ketol (+)-**2** at the 7a position should, therefore, be identical with that of the enone (+)-**3**, *i.e.*, *S*. However, the relative configuration of the 3a-hydroxyl group remained to be shown. The inconclusive results of our nmr studies have been reported in connection with the racemic compound.[8] The circular dichroism (CD) measurement of the optically active ketol (+)-**2** indicated a positive Cotton effect for both the five-membered ring and the six-membered ring ketones. Based on these CD data the following three alternatives were possible: (a) the bicyclic ketol (+)-**2** was trans fused; (b) the compound was cis fused with an equatorially oriented angular methyl group in the boat form of the six-membered ring; (c) the compound was cis fused and the angular methyl group was axial in the chair form of the six-membered ring (as pictured in Scheme II). The first assumption could be excluded by consideration of possible transition states of the reaction (*vide infra*). It still remained to be seen if the bicyclic ketol (+)-**2** corresponded to assumption b or c. Therefore, we prepared the corresponding racemic ketol (±)-**2**[8] by use of racemic proline, and submitted it for a single-crystal X-ray diffraction

Scheme III



study. The results for the centrosymmetrical crystal of the unlabeled (±)-2 unequivocally indicated an axial orientation of the angular methyl group and an equatorial orientation of the hydroxyl group in the chair form of the six-membered ring.

At this point it was of scientific and of practical interest to see if we could prepare the optically active bicyclic enone 8, the ethyl homolog of (+)-3. We therefore, prepared the ethyl triketone 6 using our new method,[8] the addition of the cyclic dione 5 to methyl vinyl ketone 4 in water at 20°. It took 7 days to complete the reaction. The preparation of the lower methyl homolog 1 was faster (5 days) under otherwise identical reaction conditions. The conversion of the ethyl triketone 6 to the optically active bicyclic ketol (+)-7 was also slower than the conversion of the lower methyl homolog when (*S*)-(−)-proline and acetonitrile were used (7 days *vs.* 3 days). The slower reaction rate was accompanied by a lower optical yield (56%). In search of another aprotic highly polar solvent we chose *N,N*-dimethylformamide (DMF) and found that in this solvent the conversion of 6 to (+)-7 is nearly complete within 20 hr. To attain this fast reaction rate we found it advantageous to use 30% molar equiv of the (*S*)-(−)-proline. Purification with ether gave the optically pure ketol (+)-7 in 71.0% yield (based on the triketone 6), mp 112.0–112.5°, $[\alpha]^{25}D$ +19.0° (chloroform). The optical rotation and the melting point of the compound did not change after repeated recrystallizations from ether (Scheme III).

Dehydration of the ketol (+)-7 in refluxing benzene with a little *p*-toluenesulfonic acid gave the enone (+)-8 in 100% weight yield, mp 56–58.5°, $[\alpha]^{25}D$ +260° (benzene), corresponding to 99.5% optical purity. An optically pure sample was obtained by recrystallization from petroleum ether (bp 30–60°) and had mp 59–60°, $[\alpha]^{25}D$ +262° (benzene). The circular dichroism (CD) curve of (+)-8 resembled closely that of the enone (+)-3, the lower homolog of known 7a*S* configuration.[13] One therefore can assume the indicated 7a*S* configuration of the angular ethyl group in the enone (+)-8 and also in the ketol (+)-7 (Scheme III).

In order to determine the configuration of the 3a center and thereby the conformation of the optically active bicyclic ketol (+)-7, the circular dichroism (CD) measurement of the compound was executed. The CD curve of (+)-7 was very different from that of the lower methyl homolog (+)-2; it showed a positive Cotton effect of the five-membered ring ketone and a negative Cotton effect of the six-membered ring ketone. This is in good agreement with the structure indicated in Scheme III; *i.e.*, (+)-7 should exist as the cis conformer in which the 7a-ethyl group is equatorially oriented and the 3a-hydroxyl group axially oriented in the chair form of the six-membered ring. The reason for a preference of this conformation may be serious 1,3-diaxial interactions in the other cis conformer between the angular ethyl group and the axial hydrogens at C-4 and C-6. A similar type of interaction would also be present in the lower methyl homolog (+)-2, but it is evidently not serious since the compound has the angular methyl group in axial orientation in the chair form of the six-membered ring, as already discussed.

Table I
Crystal Data of the Racemic Ketols (±)-2 and (±)-7

Compd	(±)-2	(±)-7
Formula	$C_{10}H_{14}O_3$	$C_{11}H_{16}O_3$
Formula weight	182.22	196.25
Space group	$P2_1/c$	$Pbca$
a	10.858	6.311 Å
b	7.247	13.533 Å
c	12.360	23.906 Å
α	90	90
β	107.08	90
γ	90	90
d_{obsd}		1.29 g/cm³
d_{calcd}	1.30	1.28 g/cm³
V	929.7	2041.7 Å³
Z	4	8

In order to confirm the conclusion derived from CD measurements of the ethyl bicyclic ketol (+)-7, we prepared the corresponding racemic compound (±)-7 by treating the triketone 6 with racemic proline in DMF. The infrared and the nmr spectra of the product were in agreement with the spectra of the optically active sample. A centrosymmetrical crystal of (±)-7 without a heavy atom label was submitted for single-crystal X-ray diffraction study. The X-ray study showed that the ethyl bicyclic ketol (±)-7 existed in a cis conformation with an equatorial ethyl group and with an axial hydroxyl group in the chair form of the six-membered ring of the bicyclic system and, therefore, confirmed our earlier conclusions based on CD data for (+)-7.

Owing to the centrosymmetrical space grouping both in (±)-2 and in (±)-7 it was possible to carry out the determination by a multiple solution procedure.[14] All hydrogen atoms but the hydroxyl hydrogens have been found in both compounds. The structures have been refined by full-matrix least squares with anisotropic thermal factors for the carbon and oxygen atoms and isotropic temperature factors for the hydrogens. The discrepancy factors for the two compounds have been summarized in Table I (*cf.* Experimental Section). Stereoscopic views of these two compounds showing the molecular conformation in the solid state are shown in Figures 1 and 2.

In order to explore the mechanism of our asymmetric synthesis we investigated the effect of various asymmetric reagents on the triketone starting material 1 (for details see Experimental Section). No reaction occurred in the presence of (2*S*)-(−)-*trans*-4-hydroxyproline in acetonitrile, a solvent in which this asymmetric reagent was found to be insoluble; (*S*)-(−)-proline, on the other hand, was found to be slightly soluble in this solvent (2.6 mg/100 g). A low weight yield (12.1%) of the bicyclic ketol (+)-2 of 73.1% optical purity was obtained in isopropyl alcohol, in which this chiral reagent was found to have a small, but distinct solubility (3.5 mg/100 g).

Treatment of the triketone 1 with the *N*-methyl derivative of proline [(*S*)-(−)-hygrinic acid[15]] gave after a long reaction period only a very small amount of the bicyclic ketol 2, which was void of any optical activity. The major reaction product was a bridged ketol, (±)-4α-hydroxy-1β,4β-dimethylbicyclo[3.2.1]octane-7,8-dione, which was

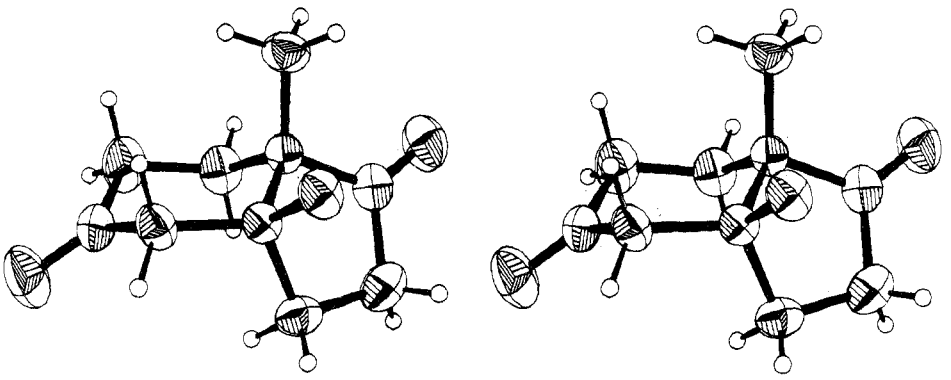


Figure 1. (±)-2.

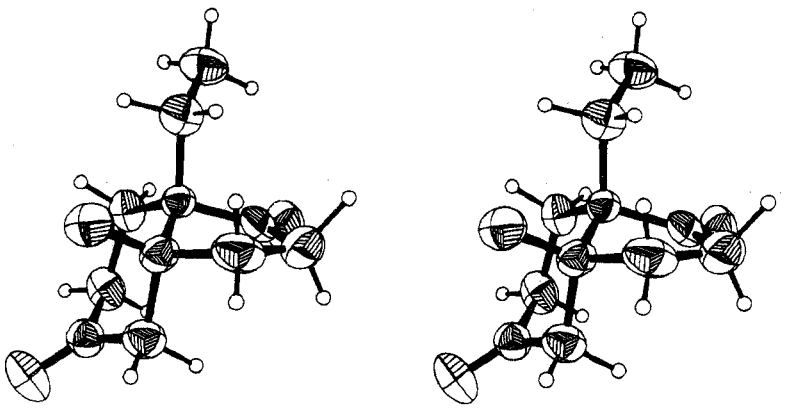


Figure 2. (±)-7.

previously obtained from the reaction of the triketone **1** with piperidinium acetate in water.[8] This then points to the importance of the secondary amino group of the asymmetric reagent, through which it may attach itself intrinsically to the triketone molecule. The naturally occurring lower homolog of (*S*)-(−)-proline, (*S*)-(−)-azetidine-2-carboxylic acid, has the same absolute configuration and also exists as a zwitterion as determined by X-ray crystallography.[16] Similarly to pyrrolidine, the parent amine (azetidine) readily forms enamines.[17] Treatment of the triketone **1** with (*S*)-(−)-azetidine-2-carboxylic acid in acetonitrile gave the desired ketol (+)-**2** in 51% weight yield and in 63.9% optical purity.

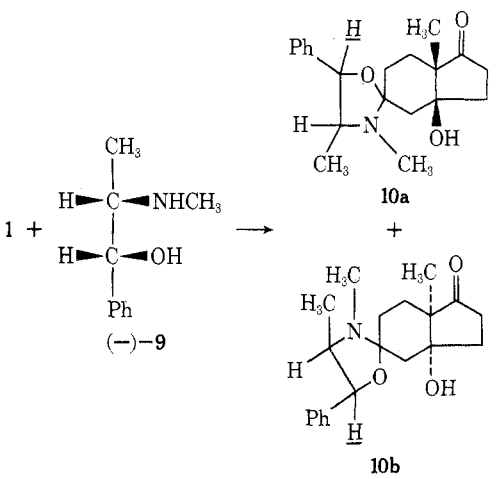
On the other hand, treatment of the triketone **1** with an equimolar amount of (±)-2-piperidinecarboxylic acid in isopropyl alcohol after 2 days at 20° gave only recovered starting material. This result cannot be related to a lack of solubility of the piperidinecarboxylic acid (103 mg/100 g), but may be explained by the lower reactivity of the parent compound (piperidine) toward ketones.[18]

Next we were interested in whether an asymmetric reagent possessing a primary amino group could be used in our asymmetric synthesis. It is known that reaction products of primary amines with carbonyl compounds (*e.g.*, imines, Schiff bases, etc.) may be at equilibrium with the corresponding enamines.[19] We chose (*S*)-(−)-phenylalanine, since it has a relatively high rotational strength ($[M]_D$ −58°), and since its isoelectric point is only slightly lower (5.48) than that of *trans*-4-hydroxyproline (5.83). Treatment of the triketone **1** with (*S*)-(−)-phenylalanine in isopropyl alcohol for 7 days gave 36.9% weight yield of the desired bicyclic ketol (+)-**2** in 19.3% optical purity.

Of special interest is an experiment in which triketone **1** was treated with an equimolar amount of (−)-ephedrine [(−)-**9**] in refluxing benzene to give a mixture of oxazolidines **10a** and **10b** (Scheme IV).

Nmr spectroscopy showed a pair of doublets centered at δ 5.23 and 5.08 ppm for the underlined benzal type of protons and corresponded respectively to **10a** and **10b** of the mixture. Thin layer chromatography indicated approximately a 60:40 mixture of two components with R_f values of 0.63 and 0.36, respectively, in 1:1 benzene–ethyl acetate. The mixture was treated with 1 *N* HCl at 20° to give a 76% weight yield of the dione **3**, $[\alpha]^{25}D$ +54.8°, corresponding to a mixture of 57.5% of the dextrorotatory and 42.5% of the levorotatory enantiomers, which was in fair agreement with the ratio for **10a** to **10b** indicated by nmr spectroscopy and by tlc.

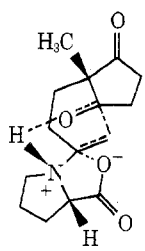
Scheme IV



Conversion of the carboxyl group of (*S*)-(−)-proline to an alkoxy carbonyl or carbinol group pointed to the importance of that C-2 substituent on the pyrrolidine nucleus. Treatment of the triketone **1** with (*S*)-(−)-proline ethyl ester gave mainly the racemic ketol (±)-**2** together with a small amount of the enone (+)-**3** of low (6%) optical purity. The reaction of the triketone **1** and (*S*)-(+)-prolinol[20] in acetonitrile gave the bicyclic ketol (+)-**2** of low (13.5%) optical purity.

Discussion

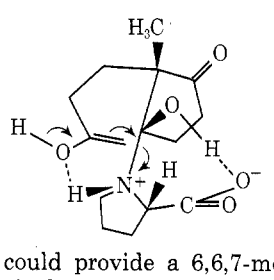
Based on the evidence accumulated so far we consider two possible mechanisms for the asymmetric synthesis with (*S*)-(−)-proline. The first would involve the formation of a protonated enamine[21a,b] and of an oxazolidone ring.



The experiment with (−)-ephedrine would seemingly lend strong support for both the enamine formation in the side chain and the oxazolidine or oxazolidone ring formation involving the second functional group of the asymmetric reagent. Preliminary results, however, in the asymmetric conversion of the triketone **1** with (*S*)-(−)-proline in the presence of ^{18}O-labeled water did not seem to confirm ^{18}O incorporation into the optically active ketol (+)-**2**, a prerequisite of the above-proposed mechanism. On the other hand, some incorporation did occur in a control experiment in which the bicyclic ketol (+)-**2** was treated with ^{18}O-labeled water in the presence of (*S*)-(−)-proline. The determination involved the mass spectrometric analysis of ^{18}O-labeled CO_2 of the respective samples.

This could indicate that the oxazolidines **10a** and **10b** of the (−)-ephedrine reaction were not necessarily formed by an enamine type of reaction involving the side-chain ketone, but rather by secondary attack on the cyclohexanone type of keto group of the primarily formed mixture of the bicyclic ketols (+)-**2** and (−)-**2**.

As an alternative, therefore, we would like to propose the following mechanism, which involves the addition of (*S*)-(−)-proline in its zwitterionic form to one of the carbonyl groups of the cyclopentanedione ring. The center of asymmetry in the asymmetric reagent would be three bonds away from the angular methyl group and only two bonds away from the 3a center, the other center of asymmetry to be formed. In the previously described mechanism the center of asymmetry of (*S*)-(−)-proline was five bonds away from the angular methyl group and four bonds away from the 3a center. The high optical yield can thus be more satisfactorily explained with the help of the structure below.



Two H bonds could provide a 6,6,7-membered conformation, and the rigidity necessary to achieve the stereoselectivity of the reaction. The vicinal hydrogens indicated in the pyrrolidine ring would again have to be on the same side of the molecule to allow the two H bonds to form. The bulky (*S*)-(−)-proline molecule would have to be opposite to the β angular methyl group, *i.e.*, on the bottom side of the molecular complex; C–C bond formation between C-3 and C-3a would have to occur from the side opposite the angular methyl group to give a cis-fused product with the concomitant regeneration of (*S*)-(−)-proline from the molecular complex.

The experimental results support this latter mechanism. Positive results have been obtained with compounds having a secondary amino group as well as another functional group capable of hydrogen bonding in the molecule. A combination of a secondary amino group with a carboxylic acid function resulted in the highest optical yields; (*S*)-(−)-proline gave 93.4%, (−)-*trans*-4-hydroxyproline gave 73.1%, and (*S*)-(−)-azetidinecarboxylic acid gave 63.9% optical yields in the asymmetric synthesis of the optically active bicyclic ketol (+)-**2** from the triketone **1**. A secondary amino group in combination with a carbinol group, on the other hand, gave a distinctly lower optical yield: 17.0% with (*S*)-(+)-prolinol and 15.4% with (−)-ephedrine. If the second function could not be involved in H bonding at all, the optical yield became extremely low; in the case of (*S*)-(−)-proline ethyl ester it was close to zero. The relatively low optical yield observed with (*S*)-(−)-phenylalanine can be explained by assuming that the course of the reaction must pass through either of the two postulated intermediates shown. Owing to the primary amino group in the molecule the tetravalent nitrogen would bear two hydrogens ready for H bonding, thereby reducing the stereoselectivity of the asymmetric reagent. The importance of an amino group capable of adding to the carbonyl function was clearly shown in the experiment using (*S*)-(−)-hygrinic acid (*N*-methylproline): no asymmetric induction occurred, and the small amount of racemic ketol **2** was most likely formed by a "push–pull" mechanism of the bifunctional catalyst.

Concerning the solvent effect it may be mentioned that the improved results obtained with polar aprotic solvents in comparison to protic ones are in good agreement with either of the two postulated reaction mechanisms in which H bonding plays an important role.

Finally, the possibility of a solid-state topochemical reaction[22] can pretty well be excluded by the findings of the present study: we have shown the importance of the solubility of the chiral reagent, especially in the case of (2*S*)-(−)-*trans*-4-hydroxyproline, and we have also demonstrated the solvent effect in general on the optical yield of this asymmetric synthesis. We believe that our results may be considered an example of a simplified model of a biological system in which (*S*)-(−)-proline plays the role of an enzyme.

Experimental Section[23]

General Procedure for the Asymmetric Synthesis. Starting material possessing a prochiral center was dissolved in the appropriate solvent (1.0 mmol of compound/1.0 ml of solvent). The asymmetric reagent was added at once, and the mixture was stirred at 20° under an inert gas atmosphere (nitrogen or argon). The amount of the reagent and the length of the reaction time have been indicated in the theoretical part or they will be given below. The asymmetric reagent was recovered by filtration, and the filtrate was evaporated *in vacuo*. The crude reaction product was purified by crystallization or by chromatography, as indicated below.

(+)-(3a*S*,7a*S*)-3a,4,7,7a-Tetrahydro-3a-hydroxy-7a-methyl-1,5(6*H*)-indandione [(+)-(2)]. **A.** The triketone **1**[8] (1.82 g, 10 mmol) and (*S*)-(−)-proline (1.15 g, 10 mmol) were stirred in acetonitrile under argon for a period of 6 days. (*S*)-(−)-Proline (1.11 g, 9.65 mmol) was recovered by filtration. The filtrate was evaporated *in vacuo*, and the residue was dissolved in ethyl acetate (30 ml). This solution was filtered without suction through 4 g of silica gel and the adsorbent was washed with an additional 70 ml of ethyl acetate. The combined filtrate, after evaporation *in vacuo*, gave 1.77 g (97.3%) of crude (+)-**2** as a crystalline solid, $[\alpha]^{25}D$ +64.0° (*c* 1.035, $CHCl_3$). Uv spectroscopy indicated 3.7% of enone (+)-**3** ($[\alpha]^{25}D$ +367.0° for pure compound). Elimination of (+)-**3** by recrystallization from ether gave analytically pure (+)-**2**: mp 119–119.5°; $[\alpha]^{25}D$ +60.4° (*c* 1.06, $CHCl_3$); ir 3600 and 3350–3508 (OH), 1742 (5-ring C=O), and 1722 cm^{-1} (6-ring C=O); nmr δ 1.26 (s, 3, 7a-CH_3), 2.63 (s, 2, -$COCH_2COH$), and 2.92 (s, 1, OH); CD (*c* 0.018, dioxane) 23° $[\theta]_{330}$ 0, $[\theta]_{296}$ + 3498, $[\theta]_{230}$ 0, *T* 40 nm.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.97; H, 7.74.

(+)-2 formed a monohydrate after standing at 20° for 6 months in a Petri dish. The physical chemical data remained essentially unchanged except for the melting point (54–56°) and microanalysis, which indicated a monohydrate.

Anal. Calcd for $C_{10}H_{14}O_3 \cdot H_2O$: C, 59.98; H, 8.05. Found: C, 60.03; H, 7.97.

B. The triketone **1** (1.82 g, 10 mmol) and (*S*)-(−)-proline (34.5 mg, 0.3 mmol) were stirred in anhydrous *N,N*-dimethylformamide (distilled from calcium hydride) under argon for 20 hr. The brown-colored reaction mixture was filtered, and the filtrate was evaporated under high vacuum at 22° (bath temperature) to give 2.4 g of an oil. This was dissolved in 10 ml of ethyl acetate and filtered through 8.0 g of silica gel. The adsorbent was eluted with 150 ml of ethyl acetate, and the solvent was evaporated *in vacuo* to give 2.0 g of an oil, which crystallized upon seeding with (+)-**2**. The crystalline mass was broken up and placed under high vacuum at 55° (bath temperature) for 1 hr to remove traces of DMF to give 1.82 g (100%) of crude (+)-**2** as a tan-colored solid, $[\alpha]^{25}D$ +56.1° (*c* 1.0, $CHCl_3$). Since uv spectroscopy indicated no enone (+)-**3** in the sample, the measured optical rotation corresponds to 93.4% optical purity. The compound was identical with the sample obtained in A by tlc and by ir and nmr spectroscopy.

C. The triketone **1** (182 mg, 1.0 mmol) and (2*S*)-(−)-*trans*-4-hydroxyproline (131 mg, 1.0 mmol) were stirred in isopropyl alcohol under nitrogen for 26 days. The mixture was filtered and 109 mg of the asymmetric reagent was recovered. The filtrate was evaporated to dryness *in vacuo*, and the oily residue was purified by preparative tlc on 1 mm thick silica gel plates with fluorescent indicator. After development with 1:1 benzene–ethyl acetate, the desired compound was contained in a weakly uv absorbent band (R_f 0.22). Elution with ethyl acetate gave 12.1% of (+)-**2**, $[\alpha]^{25}D$ +43.9° (*c* 1.0, $CHCl_3$). The compound was identical with the sample described in A by tlc and by ir and nmr spectroscopy. The strongly uv-absorbent band gave the major portion of the material (67.7%) and contained the optically active enone (+)-**3** (15.3%) together with the starting triketone **1**.

D. The triketone **1** (182 mg, 1.0 mmol) and (*S*)-(−)-azetidine-2-carboxylic acid (3 mg, 0.03 mmol) were stirred in acetonitrile under argon for 6 days. The suspension was filtered and rinsed with acetonitrile to recover the asymmetric reagent. The filtrate was passed through 0.4 g of silica gel and the adsorbent was washed with 30 ml of ethyl acetate. The solvent was evaporated *in vacuo* to give 186 mg of crude product. Preparative tlc as in C gave 93 mg (51%) of crystalline (+)-**2**, $[\alpha]^{25}D$ +38.6° (*c* 1.0, $CHCl_3$), optical purity 63.9%. The compound was identical with the sample described in A by tlc and by ir and nmr spectroscopy.

(+)-(7a*S*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indandione [(+)-3].[5,11] The dextrorotatory ketol (+)-**2** (1.79 g) obtained as described above in B was refluxed in 15.0 ml of 0.01 *N* *p*-TsOH–benzene with stirring under nitrogen for 15 min. Water was removed from the azeotrope by a Dean-Stark water separator that was filled with Linde 4A molecular sieves. After cooling to room temperature, it was stirred with 0.3 ml of 1 *N* aqueous $NaHCO_3$ for 5 min, dried with $MgSO_4$, and filtered, and the solids were rinsed with $CHCl_3$. The filtrate was evaporated *in vacuo* to give 1.6 g (99.4%) of crude (+)-**3** as an oil, which crystallized rapidly on seeding with an authentic sample,[5] $[\alpha]^{25}D$ +322° (*c* 0.94, benzene), uv 233 nm (ε 10,200). The quotient of 87.7% optical purity and 92.4% chemical purity by uv represents 94.9% optical yield.

A portion of 1.56 g of the above crude (+)-**3** was broken up in a small amount of ether on a coarse sintered glass funnel. Removal of this ether by suction gave 1.11 g of a colorless, crystalline product (70.2% yield based on the triketone **1**), mp 64–65.5°, $[\alpha]^{25}D$ +356° (*c* 0.99, benzene), uv 233 nm (ε 11,540). This represents a chemically pure sample of 97% optical purity.

Recrystallization from ether gave optically pure (+)-**3**, mp 66–66.5° (lit.[5] mp 66–66.5°), $[\alpha]^{25}D$ +367° (*c* 1.0, benzene) [lit.[5] +362° (*c* 1.0, benzene)]. The ir and nmr spectra were essentially identical with those obtained for a sample prepared *via* classical chemical resolution;[5] CD (*c* 0.0137, dioxane) 23° $[\theta]_{386}$ 0, $[\theta]_{368}$ +2649, $[\theta]_{352}$ +6261, $[\theta]_{346}$ +5659, $[\theta]_{337}$ +7585, $[\theta]_{332}$ +6620, $[\theta]_{320}$ +17,819, $[\theta]_{308}$ +26,969, $[\theta]_{303}$ +25,525, $[\theta]_{299}$ +26,488, $[\theta]_{288}$ +17,819, $[\theta]_{264}$ 0, $[\theta]_{240}$ −98,728, $[\theta]_{228}$ 0, $[\theta]_{215}$ +68,628, $[\theta]_{204}$ 0.

2-Ethyl-2-(3-oxobutyl)-1,3-cyclopentanedione (6). To a suspension of 6.3 g of 2-ethylcyclopentane-1,3-dione in 12 ml of demineralized water was added at once 8.3 ml of methyl vinyl ketone, and the mixture was stirred under nitrogen at 20° for 7 days. It was filtered to remove a small amount of debris, and extracted with benzene. The extract was washed with a little water and then with a saturated NaCl solution. It was dried with $MgSO_4$, filtered, and evaporated *in vacuo* to give 9.91 g of crude **6** as an oil.

Fractional distillation gave 8.0 g (81.5%) of pure triketone **6** as a pale yellow oil: bp 99–101° (0.035 mm); ir 1740 (C=O band, weak) and 1720 cm^{-1} (C=O band, strong); nmr δ 0.80 (t, 3, CH_3CH_2–), 1.3–2.6 (m, 6, CH_3CH_2– and $-CH_2CH_2CO$–), 2.1 (s, 3, CH_3CO–), and 2.77 (s, 4, $-COCH_2CH_2CO$–).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.30; H, 8.55.

(+)-(3a*S*,7a*S*)-7a-Ethyl-3a,4,7,7a-tetrahydro-3a-hydroxy-1,5(6*H*)-indandione [(+)-7]. The triketone **6** (4.9 g, 25 mmol) was dissolved in 25 ml of anhydrous DMF, and 0.86 g (7.5 mmol) of (*S*)-(−)-proline was added. The mixture was stirred under argon at 20–22° for 20 hr. It was filtered and the filtrate was evaporated to dryness under high vacuum. The residue was dissolved in ethyl acetate (10 ml) and filtered through 20 g of silica gel. The adsorbent was washed with 450 ml of ethyl acetate, and the filtrate was evaporated *in vacuo* to give 4.8 g (98.6%) of crude (+)-**7** as a colored, crystalline solid, $[\alpha]^{25}D$ +18.1° (*c* 1.15, $CHCl_3$). This crude material was dissolved in ethyl acetate, and again passed through 20 g of silica gel to yield 4.7 g of a nearly colorless solid. Crystallization from ether gave 3.5 g (71.0%) of optically pure ketol (+)-**7**: mp 112.0–112.5°; $[\alpha]^{25}D$ +19.0° (*c* 1.0, $CHCl_3$); ir 3620 and 3350–3550 (OH), 1745 (5-ring CO), and 1725 cm^{-1} (6-ring CO); nmr δ 0.98 (t, 3, CH_3CH_2–), 2.52 (s, 2, $-COCH_2COH$), and 2.92 (s, 1, –OH); CD (*c* 0.0976, dioxane) 23° $[\theta]_{338}$ 0; $[\theta]_{320}$ +1267, $[\theta]_{313}$ +898, $[\theta]_{308}$ +1214, $[\theta]_{301}$ +301, $[\theta]_{299}$ +330, $[\theta]_{294}$ 0, $[\theta]_{292}$ −145, $[\theta]_{289}$ −119, $[\theta]_{283}$ −304, $[\theta]_{280}$ −277, $[\theta]_{276}$ −303, $[\theta]_{242}$ −26.4, $[\theta]_{198}$ −7920.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.39; H, 8.19.

(+)-(7a*S*)-7a-Ethyl-7,7a-dihydro-1,5(6*H*)-indandione [(+)-8]. Dehydration of the optically active ketol (+)-**7** in refluxing benzene with a little *p*-toluenesulfonic acid [*cf.* method described for dehydration of (+)-**2** to (+)-**3**] gave crude (+)-**8** in 100% yield, mp 56–58.5°, $[\alpha]^{25}D$ +260° (*c* 1.0, benzene). Crystallization from petroleum ether gave optically pure (+)-**8**: mp 59–60°; $[\alpha]^{25}D$ 262° (*c* 0.95, benzene) (lit.[12] +210°); uv 241 nm (ε 10,800); ir 1755 (5-ring CO) and 1680 cm^{-1} (α,β-unsaturated CO); nmr δ 0.95 (t, 3, CH_3CH_2–), 1.73 (q, 2, CH_3CH_2–), and 5.97 (broad s, 1, $-COCH{=}CCH_2$–); CD (*c* 0.02314, dioxane) 23° $[\theta]_{385}$ 0, $[\theta]_{353}$ +8631, $[\theta]_{347}$ +8123, $[\theta]_{338}$ +10,154, $[\theta]_{334}$ +9646, $[\theta]_{323}$ +22,338, $[\theta]_{321}$ +21,831, $[\theta]_{311}$ +30,969, $[\theta]_{305}$ +28,939, $[\theta]_{301}$ +29,954, $[\theta]_{267}$ 0, $[\theta]_{242}$ −121,846, $[\theta]_{231}$ 0, $[\theta]_{215}$ +76,154.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.10; H, 7.95.

Experiment Using (*S*)-(−)-Hygrinic Acid. The triketone **1** (91 mg, 0.5 mmol) and (*S*)-(−)-hygrinic acid[15] (64 mg, 0.5 mmol) were stirred in 0.5 ml of isopropyl alcohol under argon at 20° over a period of 18 days. The solvent was then evaporated *in vacuo*, and the residue was dissolved in a small amount of benzene and applied to 1 mm thick plates of silica gel with fluorescent indicator. The plates were developed with 1:1 benzene–ethyl acetate, and gave 6.9 mg of the bicyclic ketol **2**, which was identified by ir and nmr spectroscopy and by tlc comparison with an authentic sample.[8] The sample was void of any optical activity. A faster moving component (17.8 mg) was shown to be the racemic bridged ketol (±)-**10**. It was identical by ir and nmr spectroscopy and by tlc with a previously prepared authentic sample of the compound.[8] The fastest component (54.9 mg) was unconverted triketone **1**.

Experiment with (*S*)-(−)-Proline Ethyl Ester. The triketone **1** (182 mg, 1.0 mmol) was dissolved in 0.5 ml of acetonitrile. To this was added at once a solution of 143 mg (1.0 mmol) of (*S*)-(−)-proline ethyl ester[20] in 0.5 ml of acetonitrile. The reaction mixture was stirred under argon at 20–23° for 20 hr. Preparative tlc was executed as described in the foregoing experiment. The fastest moving zone (R_f 0.8) gave 52.7 mg (28.9%) of an oil, uv 232 nm (ε 6770); ir indicated a mixture of **1** and **3**; $[\alpha]^{25}D$ +13.6° (*c* 0.99, benzene), equivalent to a 6% optical yield (61% enone **3** by uv). The second fastest zone (R_f 0.5) gave 85 mg (46.7%) of a waxy solid, mp 105–112°. This sample was identical by ir and nmr spectroscopy, by tlc, and also by mixture melting point determination with a previously prepared[8] authentic sample of (±)-**2**.

Experiment with (2*S*)-(+)-2-Hydroxymethylpyrrolidine (Prolinol). The triketone **1** (182 mg, 1.0 mmol) and (2*S*)-(+)-2-hydroxymethylpyrrolidine[20] (101 mg, 1.0 mmol) in 1.0 ml of acetonitrile were stirred under argon at 20° for 72 hr. The solvent was then evaporated *in vacuo*, and the resulting dark oil was subject-

ed to preparative tlc using the conditions described in the foregoing two experiments to give 109 mg (59%) of a solid (R_f 0.5), mp 98–102.5°. The compound was identified by ir and nmr spectroscopy to be the bicyclic ketol **2**, $[\alpha]^{25}D$ +10.4° (*c* 1.0, $CHCl_3$), optical purity 17%.

Experiment with (*S*)-(−)-Phenylalanine. To 182 mg (1.0 mmol) of triketone **1** in 1.0 ml of 2-propanol was added 165 mg (1.0 mmol) of (*S*)-(−)-phenylalanine. The mixture was stirred under argon at 20° for 7 days. It was then filtered and 152 mg of asymmetric reagent was recovered. The filtrate was evaporated *in vacuo* to give 187 mg of an oil, which was subjected to preparative tlc as described in the foregoing experiments. The slower moving zone (R_f 0.5) gave 67.2 mg (36.9%) of (+)-**2**, mp 107.5–109° (from ether), $[\alpha]^{25}D$ +11.6° (*c* 1.1, $CHCl_3$), 19.3% optical purity. Ir and nmr spectroscopy confirmed the structure. The faster moving zone (R_f 0.8) gave 93 mg (51.1%) of an oil, uv 232 nm (ε 815), 7.4% enone **3**; ir spectroscopy indicates a mixture of **1** and **3**.

Experiment with (−)-Ephedrine. To 1.0 g (5.5 mmol) of the triketone **1** in 12 ml of benzene was added 916 mg (5.55 mmol) of (−)-ephedrine. The mixture was stirred and refluxed under nitrogen for 16 hr in a Dean-Stark water separator. It was treated at ambient temperature with charcoal, filtered, and evaporated *in vacuo* to give 1.79 g (93.8%) of a mixture of oxazolidines **10a** and **10b** as a viscous oil: uv 251 nm (ε 380), 257 (ε 414), and 264 (ε 350); ir 3525 (OH) and 1740 cm^{-1} (5-ring C=O); nmr δ 0.66 (d, 3, CH_3CH–), 1.0 (s, 3, 7a-CH_3), 2.18 (s, 3, –NCH_3), 3.5 [m, 2, $CH_3NCH(CH_3)CHPh$], 5.08 and 5.23 (d, 1, PhCHO– isomers), and 7.31 (s, 5, aromatic); $[\alpha]^{23}D$ −7.67° (*c* 1.33, $CHCl_3$).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.72; H, 8.51; N, 4.02.

A portion of 0.9 g of the above mixture was dissolved in 9 ml of 1 *N* HCl. It was allowed to stand at 20° for 15 hr under nitrogen. The solution was then concentrated to a small volume *in vacuo* and extracted with ether. The ether extract was dried with Na_2SO_4, filtered, and evaporated *in vacuo* to give 341 mg (75.8%) of crude enone **3** as an oil: uv 231 nm (ε 7730); ir 1745 (5-ring C=O) and 1665 cm^{-1} (α,β-unsaturated C=O); $[\alpha]^{25}D$ +54.8° (*c* 1.0, benzene).

^{18}O-Incorporation Studies. To 182 mg (1.0 mmol) of the triketone **1** in 1.0 ml of acetonitrile containing 40 mg of $H_2{}^{18}O$ was added 3.5 mg (0.03 mmol) of (*S*)-(−)-proline and the reaction mixture was stirred at 20° under argon for 1 week. It was then worked up by preparative tlc as already described, and the area corresponding to the desired bicyclic ketol gave 40.2 mg (22%) of **2**. Mass spectral analysis for ^{18}O-labeled CO_2 of the sample indicated 7.2% ^{18}O enrichment.

In a control experiment 182 mg (1.0 mmol) of the optically active ketol (+)-**2** was dissolved in 1.0 ml of acetonitrile containing 40 mg of $H_2{}^{18}O$, and 3.5 mg (0.03 mmol) of (*S*)-(−)-proline was added. The reaction mixture was stirred at 20° under argon for 1 week. It was then evaporated to dryness *in vacuo* and dissolved in ethyl acetate. It was filtered through 0.8 g of silica gel, and the adsorbent was washed with 25 ml of ethyl acetate. The filtrate was evaporated *in vacuo* to give the ketol (+)-**2** as a colorless, crystalline solid, mp 105–109°. Mass spectral analysis for ^{18}O-labeled CO_2 of this sample showed 33.1% ^{18}O enrichment.

(±)-3a,4,7,7a-Tetrahydro-3aβ-hydroxy-7aβ-methyl-1,5(6*H*)-indandione [(±)-2]. To 1.58 g (8.68 mmol) of the triketone **1** in 90 ml of acetonitrile was added 1.0 g (8.68 mmol) of racemic proline. The reaction mixture was stirred under nitrogen at 20° for 3 days. It was filtered and the filtrate was evaporated *in vacuo* to give 1.61 g of crude (±)-**2**. This crude material was dissolved in acetonitrile and filtered through silica gel and the filtrate was evaporated *in vacuo;* final purification utilizing ether gave 895 mg of a solid, mp 122–123°. The sample was in all respects (ir and nmr spectroscopy, mixture melting point determination, and tlc) identical with an authentic sample of (±)-**2** obtained by an independent route.[8]

(±)-7aβ-Ethyl-3a,4,7,7a-tetrahydro-3aβ-hydroxy-1,5(6*H*)-indandione [(±)-7]. The triketone **6** (910 mg, 4.64 mmol) was dissolved in 5 ml of anhydrous DMF. Racemic proline (16 mg, 0.14 mmol) was added, and the mixture was stirred under argon at 20° for 24 hr. The solvent was removed under high vacuum, and the resulting dark oil was dissolved in ethyl acetate and filtered through 4.0 g of silica gel. The adsorbent was washed with 100 ml of ethyl acetate and 25 ml of $CHCl_3$, and the filtrate was evaporated *in vacuo* to give 900 mg (98.9%) of crude (±)-**7**. The sample was triturated with isopropyl ether and recrystallized from ether to give analytically pure (±)-**7**, mp 89–91°, ir and nmr spectra identical with those of the optically active (+)-**7**.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.61; H, 8.48.

Acknowledgment. The authors wish to express their thanks to Mr. Fred Bizzarro for his technical assistance in this investigation. Thanks are also due to Dr. W. Benz for the mass spectra, Dr. J. F. Blount for the X-ray, Mr. G. Raymond for the solubility studies, Dr. V. Toome, for the CD and uv, Mr. S. Traiman for the ir, Dr. T. Williams for the nmr, and Dr. F. Scheidl for the microanalytical data.

Registry No.—**1**, 25112-78-1; (+)-**2**, 33879-04-8; (±)-**2**, 51065-67-9; (+)-**3**, 17553-86-5; **6**, 34927-33-8; (+)-**7**, 35544-89-9; (±)-**7**, 51075-20-8; (+)-**8**, 33878-95-4; (−)-**9**, 321-98-2; **10a**, 35544-85-5; (*S*)-(−)-proline, 147-85-3; (*S*)-(−)-hygrinic acid, 475-11-6; (*S*)-(−)-proline ethyl ester, 5817-26-5; prolinol, 23356-96-9; (*S*)-(−)-phenylalanine, 63-91-2.

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