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Synthesis and Conversion of 2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione to the Isomeric Racemic Ketols of the [3.2.1]Bicyclooctane and of the Perhydroindan Series

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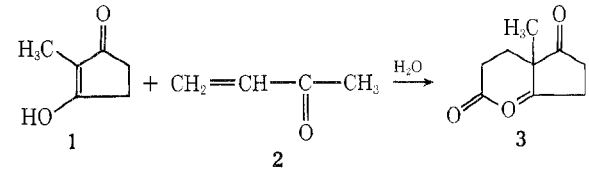
Michael addition of 2-methylcyclopentane-1,3-dione to methyl vinyl ketone in water gives 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (**3**), an important intermediate of natural product chemistry. Neutral piperidinium acetate in water cyclizes **3** to the bridged ketol **4** of the [3.2.1]bicyclooctane series. Additional piperidine epimerizes the C-4 center of **4** to give the more stable bridged ketol **5**. The C-8 keto group of **5** can be reduced to give the dihydroxy ketone **6**. The structure and the stereochemistry of **4**, **5**, and **6** have been proven by ir and nmr spectroscopy and by chemical correlation. A skeletal isomer, the bicyclic ketol **7** of the perhydroindan series, could be obtained by cyclizing **3** with pyrrolidinium acetate in anhydrous ether. A discussion of the reaction mechanism for each of the three selective cyclization reactions is presented.

In connection with the stereocontrolled total synthesis of 19-norsteroids[2] it became necessary to prepare certain CD-bicyclic steroidal intermediates. The triketone **3** [2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione] was considered the key intermediate of the synthesis provided that it could be prepared in reasonably good yield and be selectively cyclized to the desired CD-bicyclic ketol (**7**) of the perhydroindan series. The possibility of an asymmetric conversion of the triketone **3** had also been considered at the outset of our studies; this problem, however, shall be discussed in the accompanying publication.[3] This communication deals with the problem of an improved synthesis of the triketone **3**, and with its selective conversions to the isomeric racemic ketols **4**, **5**, and **7** *via* directed aldol cyclization reactions.

The preparation of the triketone **3** from 2-methylcyclopentane-1,3-dione (**1**) and methyl vinyl ketone (**2**) in refluxing methanol and a catalytic amount of potassium hydroxide had been reported in the literature.[4] The compound **3** had been described as a crystalline solid, mp 117–118°. Upon repeating the literature procedure we found the triketone **3** to be an oil, and confirmed its structure by ir and nmr spectroscopy.[5] We could also isolate a very small amount of a crystalline by-product from the reaction mixture, mp 121–122°. It was different from the triketone **3** by thin layer chromatography, and corresponded to the bridged ketol **4**, whose synthesis shall be described below. We have also found that the best way to prepare the triketone **3** is to allow the dione **1** and methyl vinyl ketone (**2**) to react in water.[6] The previously reported[5] yield of 54% was thus increased to 87.6% of pure triketone **3**. The reaction may be considered a Michael addition under slightly acidic reaction conditions due to the enolic nature of the dione **1** (Scheme I).

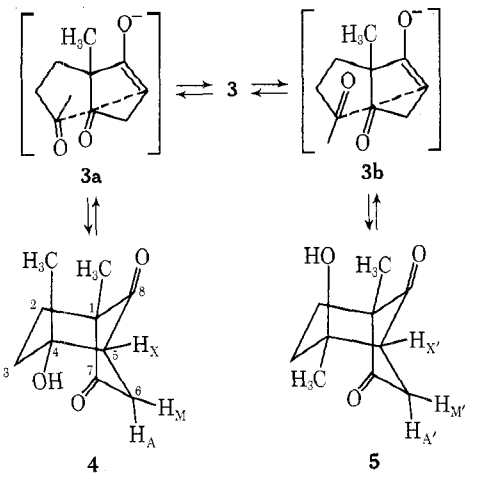
Next we investigated the chemical properties of the triketone **3** under a variety of reaction conditions. We, therefore, dissolved the compound **3** in water, added a neutral solution of piperidinium acetate in water, and stirred the solution at 20° for 3 days. The reaction mixture was then worked up to give a crystalline product **4**, mp 114–116.5°, in 51% yield. Microanalysis indicated an empirical formula of $C_{10}H_{14}O_3$. Infrared spectroscopy in chloroform showed a hydroxyl band at 3600 cm^{-1}, a five-membered ring ketone at 1762 cm^{-1} and a six-membered ring ketone at 1720 cm^{-1}. Its nmr spectrum in $CDCl_3$ indicated the bridged ketol structure **4**: δ 1.07 (s, 3, 1-CH_3), 1.45 (s, 3, 4-CH_3), 1.78 (m, 4, -CH_2CH_2-), 2.18 (s, 1, -OH), 3.10, 2.55, 2.85 (AMX, 3, J_{AM} = 18, J_{AX} = 0, J_{MX} = 7 Hz, -$CHCH_2CO$-). The stereochemical assignment at C-4 is the result of a comparison of the nmr spectra of **4** with that of the isomeric bridged ketol **5**, as will be discussed below. The infrared spectrum of **4** in Nujol was identical with the spectrum published for the compound of mp 118.5–120.5°, to which the triketone structure **3** had been erroneously assigned, despite a strong band at 3.1 μ in the infrared.[7]

Scheme I

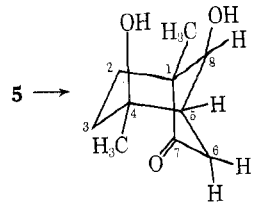


The bridged ketol structure **4** was thus proven to be the correct formula for the previously reported mp 118.5–120.5° "triketone" of the literature. It remained to be seen, however, if our bridged ketol **4** could be converted to the higher melting substance (mp 157–159°) under the reaction conditions described by the same group of investigators.[7] Therefore, we dissolved the compound **4** in water, added 1 molar equiv of piperidine, and then added enough glacial acetic acid to neutralize the system. The solution was then allowed to stand for 3.5 days at 20°. It should be noted that in the course of the preparation of the bridged ketol **4** we added neutral piperidinium acetate to the triketone **3**, whereas here we first added basic piperidine to the aqueous solution of the compound **4** to be isomerized. Work-up of the reaction mixture gave a product **5**, mp 154–158°, in 57% yield. Microanalysis agreed with an empirical formula of $C_{10}H_{14}O_3$, and indicated that compound **5** was an isomer of the bridged ketol **4**. The nmr spectrum of **5** in $CDCl_3$ showed the following peaks: δ 1.07 (s, 3, 1-CH_3), 1.43 (s, 3, 4-CH_3), 1.60–2.30 (m, 4, -CH_2CH_2-), 2.63, 2.85 (A′M′X′ = A_2X, 3, J_{AX} = 4.5 Hz, -$CHCH_2CO$-). This spectrum clearly indicated

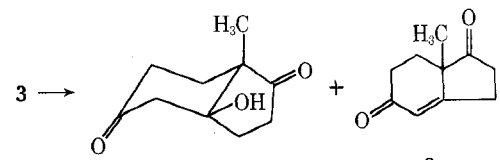
Scheme II



Scheme III



Scheme IV



that the compound had the bridged ketol structure **5**, and is thus an isomer of the above-described bridged ketol **4**.

Comparison of the nmr spectra of **4** and of **5** showed that one of the methylene protons at C-6 in compound **4** is significantly deshielded by the hydroxyl group at C-4 (H_A at δ 3.1 in compound **4** and H_A at δ 2.63 in compound **5**). The difference (0.47 ppm) is in good agreement with the known syn axial effect of a hydroxyl group of approximately 0.4–0.5 ppm and confirms the C-4 equatorial configuration of the hydroxyl group of the bridged ketol **4**. A C-4 equatorial methyl group would have shown a much smaller effect of approximately 0.18 ppm.[8]

It should be mentioned that the infrared spectrum of the bridged ketol **5** in Nujol was identical with that of the mp 157–159° substance of the literature to which the perhydroindane structure **7** had been erroneously assigned.[7] The compound **5** had been prepared by independent methods in two research groups, and the correct bridged ketol skeleton was elucidated by nmr spectroscopy; however, no stereochemical assignments could be made.[5,9]

The formation of the bridged ketol **4** from the triketone **3** is the result of enolization of the five-membered ring ketone in the aqueous medium and bond formation *via* nucleophilic attack of the enolate on the keto group in the side chain. Preferential enolization of cyclic over aliphatic type monoketones is well known from the literature.[10] The reaction may be considered to proceed *via* **3a** (Scheme II). This favorable molecular arrangement allows maximum π-orbital overlap by an almost parallel alignment of the enolic double bond of the five-membered ring and the carbonyl group in the butanone side chain. The six-membered ring may thus be considered the result of an almost perpendicular attack on the side-chain keto group, placing the newly formed hydroxyl group in an equatorial arrangement. Bond formation and bond breaking can thus occur readily, and it was therefore expected that the reverse reaction, *i.e.*, the retro-aldol type of ring opening of **4** to the triketone **3**, should occur just as readily *via* the same molecular arrangement (**3a**) in agreement with the principle of microscopic reversibility.[11]

We could also conclude that the previously described conversion[7] of the lower melting substance to the higher melting compound should correctly be formulated as the isomerization of the lower melting bridged ketol **4** to its higher melting isomer **5** with resulting epimerization of the C-4 center. The retro-aldol type of ring opening of **4** proceeds *via* **3a** to give the triketone **3**, which in turn cyclizes to the bridged ketol **5** *via* **3b**, as shown in Scheme II. This molecular arrangement of the enolic intermediate should therefore be less favorable than **3a**, since it allows less π-orbital overlap. Nucleophilic attack of the enolate on the side-chain keto group places the newly formed hydroxyl group into an axial configuration in **5**. Again, by the principle of microscopic reversibility,[11] the bridged ketol **5** should be more stable, since its formation as well as its possible opening to the triketone **3** would have to proceed through the same unfavorable, energy-rich conformation (**3b**) of the enolic intermediate.

We also attempted the triethylamine-catalyzed Michael addition of methyl vinyl ketone (**2**) to 2-methyl-1,3-cyclopentanedione (**1**), to obtain the desired triketone **3** in analogy to the previously reported conversion[12] of the homologous diketone, 2-methyl-1,3-cyclohexanedione. The reaction indeed gave some triketone **3**, but also the higher melting bridged ketol **5** through the same unfavorable conformation (**3b**) of the enolic intermediate.

Further evidence for the stereochemistry of the bridged ketol **5** was obtained upon its reduction with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran. The reduction gave the dihydroxy ketone **6** in 78% yield. Infrared spectroscopy indicated a five-membered ring ketone at 1742 cm^{-1}. A doublet at δ 3.96 in the nmr spectrum of the compound confirmed that the cyclohexanone type of carbonyl group at C-8 had been reduced (Scheme III).

High-dilution techniques were employed in further investigation of the infrared spectrum of **6** and indicated strong intramolecular H bonding, thereby establishing the C-8 axial configuration of the hydroxyl group in the six-membered ring, and the C-8 equatorial configuration of the same hydroxyl in the five-membered ring. Since the C-8 carbonyl group may be considered sterically hindered by the C-4 axially oriented hydroxyl group in the six-membered ring, and nonhindered in the five-membered ring, the stereochemistry of the reduction is in agreement with theoretical expectations.[13]

Next we turned to the preparation of the bicyclic ketol **7** of the perhydroindan series starting with the triketone **3**. To avoid bridged ketol formation conditions had to be found which allowed the enolization of the keto group in the side chain and nucleophilic attack thereof on the five-membered ring. We, therefore, prepared a neutral solution of pyrrolidinium acetate in anhydrous ether and added to it at 0° an ethereal solution of the triketone **3** (Scheme IV). Somewhat similar reaction conditions were used to prepare the homologous ketol, *cis*-9-hydroxy-10-methyldecalin-2,5-dione, from 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione.[14]

Work-up of our reaction mixture and separation by preparative thin layer chromatography gave the desired ketol **7** in 21% yield and the bicyclic enone **8** in 22% yield. The formation of the ketol **7** in the presence of pyrrolidinium

acetate in anhydrous ether can be explained by a nucleophilic attack on the five-membered ring system by an enol or an enamine derivative of the side-chain keto group of **3**. Piperidinium acetate in water, on the other hand, led to the conversion of the triketone **3** to the bridged ketol **4**, because an enol or an enamine derivative of the keto group in the aliphatic side chain was either never formed, or else it was immediately quenched or reversed by the water. It should also be noted that in comparison to pyrrolidine, piperidine is known to show a decreased reactivity toward ketones.[15] This effect should be more pronounced with the less reactive aliphatic type of ketones.

The structure of the bicyclic ketol **7** was confirmed by infrared and nmr spectroscopy. The stereochemical assignment was based on the preference of the formation of cis-fused derivatives in aldol cyclization reactions.[14] A study of the additivity of the chemical shift of the angular methyl group was then executed; we used the data of the previously prepared[16] racemic *cis*- and *trans*-perhydroindan-1,5-diones for comparison. The nmr peak width at half height of the angular methyl group was measured and compared with that of the tetramethylsilane signal ($\Delta W_{h/2}$). We found a small value of 0.2 Hz, which would support the cis fusion of the bicyclic system.[17] This result, however, had to be substantiated by other means, since the trans-fused isomer of the bicyclic ketol **7** would have to show the same kind of long-range coupling as **7**, which is one of the two possible cis conformers. Its conformation has been proven in connection with our studies of the corresponding optically active derivative, and it is the subject of the accompanying publication.[3]

Experimental Section[18,19]

2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (3). To a suspension of 65 g of 2-methylcyclopentane-1,3-dione in 136 ml of demineralized water was added at once 96 ml of methyl vinyl ketone, and the mixture was stirred under nitrogen at 20° for 5 days. It was then extracted with benzene and treated with Na_2SO_4, charcoal, and $MgSO_4$. After filtration, the solids were extracted with 100 ml of boiling benzene. Evaporation *in vacuo* of the combined benzene extract gave 100.9 g of crude **3**. Fractional distillation gave 92.5 g (87.6%) of pure triketone **3** as a pale yellow oil; bp 100–109° (0.08–0.1 mm); ir 1770 (C=O, m) and 1725 cm^{-1} (C=O, s); nmr δ 1.12 (s, 3, 2-CH_3), 2.22 (s, 3, CH_3CO–), 2.82 (m, 4, -$COCH_2CH_2CO$–).[5]

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.88; H, 8.01.

(±)-4α-Hydroxy-1β,4β-dimethylbicyclo[3.2.1]octane-7,8-dione (4). To 15 ml of water was added 0.39 ml of piperidine. The pH of the solution was adjusted to 7.0 with 0.23 ml of glacial acetic acid. The resulting solution was added to a solution of 546 mg of triketone **3** in 5 ml of water at 20° within 5 min. The reaction mixture was stirred at this temperature for 3 days under nitrogen and then saturated with NaCl and extracted with ether. It was dried with Na_2SO_4 and $MgSO_4$, filtered, and evaporated *in vacuo* to give 454 mg of a solid, mp 97–110°. Treatment with ether gave the analytical sample: mp 114–116.5°; ir (Nujol) 3450 and 3245–3255 (OH), 1760 (7-C=O), and 1720 cm^{-1} (8-C=O); ir ($CHCl_3$) 3600 (OH), 1766 (7-C=O), and 1723 cm^{-1} (8-C=O); nmr, *cf.* discussion.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.79; H, 7.82.

(±)-4β-Hydroxy-1β,4α-dimethylbicyclo[3.2.1]octane-7,8-dione (5). To a solution of 50 mg of **4** in 2 ml of water was added 0.04 ml of piperidine. After 5 min at 20° the basic solution was neutralized with approximately 0.02 ml of glacial acetic acid and stirred under N_2 at 20° for 3.5 days. It was then saturated with NaCl and extracted with ether. The extract was dried with Na_2SO_4 and $MgSO_4$, filtered, and evaporated *in vacuo* to give 28.5 mg (57%) of crude **5** as a waxy solid which could be purified with ether and petroleum ether (bp 30–60°) to give mp 154–158° (lit. mp 157–159[7] and 164–166°[5]). An analytically pure sample of **5** was obtained after several recrystallizations from ether: mp 173–174°; ir (Nujol) 3500 (OH), 1760 (7-C=O), and 1720 cm^{-1} (8-C=O); ir ($CHCl_3$) 3600 and 3350–3510 (OH), 1775 (7-C=O), and 1730 cm^{-1} (8-C=O); nmr, *cf.* discussion.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.88; H, 7.74.

(±)-4β,8β-Dihydroxy-1β,4α-dimethylbicyclo[3.2.1]octan-7-one (6). The bridged ketol **5** (364 mg) was dissolved in 8 ml of dry tetrahydrofuran. It was cooled to 0° and 1.072 g of lithium tri-*tert*-butoxyaluminum hydride was added at once while stirring under nitrogen. After 10 min the reaction mixture was allowed to come to room temperature and stirring was continued for 16 hr. It was then cooled in an ice bath, a few pieces of ice and 4.0 ml of 2 *N* H_2SO_4 were added, and the resulting mixture was evaporated to dryness on a rotary evaporator at 20°. The solid residue was taken up in ethyl acetate, $MgSO_4$ was added, and the residue was filtered after 5 min. Evaporation *in vacuo* gave 288 mg (78.3%) of crude **6** as a crystalline product, which was purified with ether to give **6**: mp 135–140°; ir ($CHCl_3$) 3610 and 3480 (OH), 1742 cm^{-1} (5-ring C=O); nmr δ 1.02 (s, 3, 1-CH_3), 1.23 (s, 3, 4-CH_3), 3.97 [d, 1, -CH(OH)CH–], and 4.73 (broad, 2, 4-OH and 8-OH).

(±)-3a,4,7,7a-Tetrahydro-3aβ-hydroxy-7aβ-methyl-1,5(6*H*)-indandione (7). Pyrrolidine (0.08 ml) was added to 1.5 ml of dry ether under N_2, the resulting solution was cooled to 0°, and 0.07 ml of glacial acetic acid was added to adjust the pH to 6.8. To this stirred solution was added 182 mg of the triketone **3** dissolved in 1.5 ml of dry ether within 5 min. After stirring for 1.5 hr at 0° an oily product separated. The ether was evaporated *in vacuo* at 0° and replaced with methylene chloride, which dissolved the product. Preparative tlc was done on four 20 × 20 cm, 1 mm thick plates of silica gel with fluorescent indicator. The methylene chloride solution was applied, and plates were developed with 1:1 benzene–ethyl acetate. The uv-absorbent band (R_f 0.5) gave 33.7 mg of the racemic bicyclic diketone **8**: mp 69–72° (lit.[4] mp 72–73°); uv 238 nm (ϵ 8130); ir ($CHCl_3$) 1740 (5 ring C=O) and 1652 cm^{-1} (conjugated C=O). The desired compound **7** was contained in a weakly uv-absorbent band (R_f 0.2). Elution with ethyl acetate gave 21.6 mg of crude racemic ketol **7**, mp 107–110°. Recrystallization from ether gave analytically pure **7**: mp 124–125°; ir ($CHCl_3$) 3600 and 3350–3510 (OH), 1740 (5-ring C=O), and 1720 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).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.89; H, 7.66.

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Registry No.—**1**, 765-69-5; **2**, 78-94-4; **3**, 25112-78-1; **4**, 51153-51-6; **5**, 51153-52-7; **6**, 51065-66-8; **7**, 51065-67-9.

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(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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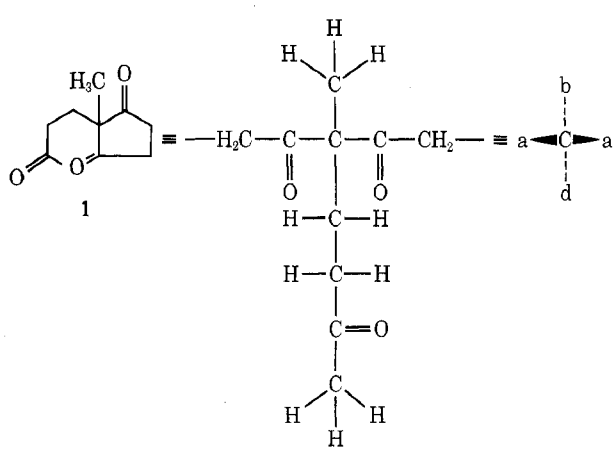
The triketone **1**, a compound of reflective symmetry, could be converted by an asymmetric aldol cyclization to the optically active bicyclic 7a-methyl ketol (+)-**2** in 100% chemical and 93.4% optical yield by the use of a catalytic amount (3% molar equiv) of (*S*)-(−)-proline. Starting with the triketone **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