recrystallization from ethyl acetate (lit. mp 226-226.5 °C dec,[2] 223.5-224 °C dec[1]).

The 8.56 g of undistilled residue was dissolved in 3:7 ether-hexane and filtered through a short column of silica gel. The eluent was evaporated and the residue was distilled (short path) to afford 0.85 g (5%) of slightly yellow **1**, bp 75-85 °C (0.15 mm).

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Registry No. **1**, 24037-79-4; **2**, 18631-96-4; **4**, 16686-11-6; **5**, 930-68-7; **6**, 75506-74-0; **7**, 75506-75-1.

Acid-Catalyzed Annelation of α-Alkyl Aldehydes and α,β-Unsaturated Ketones. A One-Pot Synthesis of 4,4-Dimethyl-2-cyclohexen-1-one

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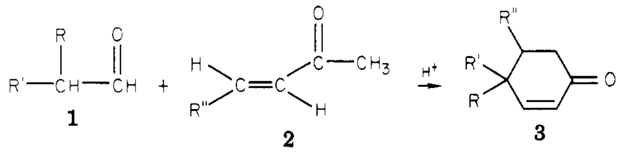
Annelations involving α-alkyl aldehydes, especially the condensation of methyl vinyl ketone and isobutyraldehyde, have been widely used. Base catalysis has customarily been utilized to effect this condensation. The yields under these conditions are not particularly good and byproducts are numerous. A thorough study of the base-catalyzed condensation of methyl vinyl ketone and isobutyraldehyde was recently reported by Krabbenhoft.[1] An alternative to base catalysis is to convert the aldehyde to an enamine, condense it with methyl vinyl ketone, hydrolyze the resulting Diels-Alder adduct, and finally cyclize under acidic conditions. This approach, which is described in *Organic Syntheses*,[2] is somewhat involved but gives a good overall yield. Spiroannelations have been accomplished by Martin and by Kane using the same principle.[3]

A publication by Heathcock et al. reporting the successful acid-catalyzed annelation of cyclic ketones[4] inspired us to consider applying similar conditions to the condensation of methyl vinyl ketone and isobutyraldehyde. Since isobutyraldehyde has only one α-hydrogen, an acid-promoted dimerization would produce an aldol that cannot dehydrate readily. Aldol formation should, therefore, be a particularly facile equilibrium wherein steric factors favor the monomeric aldehyde. As expected, addition of a small amount of acid to a mixture of methyl vinyl ketone and isobutyraldehyde caused a very smooth and moderately exothermic condensation to the desired 2,2-dimethyl-5-oxohexanal. This intermediate can be isolated in high yield, but it is more convenient to carry out the cyclization directly using an azeotropic distillation to remove the water.

The reluctance of isobutyraldehyde to participate in acid-catalyzed aldol condensations is further evidenced by the fact that a subsequent reaction of this aldehyde with the cyclized product (a major side reaction in the case of base catalysis[1]) does not appear to be significant in the presence of acid. For this reason it is possible to use excess isobutyraldehyde as the solvent for the azeotropic distillation. The net result is an extremely simple, one-pot synthesis of 4,4-dimethyl-2-cyclohexen-1-one in which the starting materials are mixed in a 2:3 (ketone-aldehyde) ratio, treated with acid, cooled initially, then refluxed through a Dean-Stark trap, and finally distilled.

Table I. Results of Several Annelations



R	R'	R''	solvent[a]	% yield[b]	bp, °C (mmHg)	lit. bp, °C (mmHg)
Me	Me	H	IBA	71	56-61 (5)	73-74 (14)[2]
Me	Me	H	Ben	70	73-76 (14)	
Me	Et	H	Ben	65	73-78 (7)	91 (14)[5]
Et	Et	H	Ben	75	92-96 (5)	80-90 (4)[6]
Me	Ph	H	Ben	74	127-130 (1)	93-94 (0.25)[7]
$-(CH_2)_5-$		H	Ben	56	122-126 (5)	83 (0.2)[8]
Me	Me	Me	IBA	36[c]	66-84 (5)	86-87 (14)[9]

[a] IBA = isobutyraldehyde, Ben = benzene. [b] Except for the last entry, yields given are for distilled, analytically and spectrally pure product. [c] NMR revealed minor impurities.

The acid-catalyzed annelation has been applied to other α-alkyl aldehydes and methyl vinyl ketone with comparable success. With other aldehydes a 1:1 ratio of substrates was used and cyclization was carried out by using a benzene/water azeotrope. Table I lists the results from a number of cases. Isobutyraldehyde and 3-penten-2-one have also been condensed to afford 4,4,5-trimethyl-2-cyclohexen-1-one. The yield in this case, although adequate, was substantially lower than that in the case of methyl vinyl ketone.

Experimental Section

General. Aldehydes used were reagent grade except for the 2-phenylbutanal, which was techical (90%). The unsaturated ketones were usually distilled before use, but yields were not noticeably changed with undistilled material. Boiling ranges are uncorrected. The NMR spectrum was determined by using a Varian Associates T-60 spectrometer with Me_4Si as an internal standard.

4,4-Dimethyl-2-cyclohexen-1-one. A mixture of 272 mL (3 mol) of isobutyraldehyde and 162 mL (2 mol) of methyl vinyl ketone was treated at room temperature with 2.0 mL of concentrated H_2SO_4. The solution was warmed cautiously to 45-50 °C and maintained at that temperature by means of occasional cooling with a cold-water bath. (**Caution**: A violent reaction may ensue if the temperature is allowed to exceed 65 °C.) The exothermic reaction subsided within about 1 h. The solution was then refluxed through a Dean-Stark trap until water removal ceased (ca. 3 h). Distillation of the mixture at 6 mm of pressure gave a forerun of isobutyraldehyde followed by the product. High temperatures were needed to drive the last of the product from the viscous residue in the pot. As a result, the boiling range was sometimes broadened due to superheating. The collected product was nonetheless quite pure. Redistillation produced a sharper boiling range with negligible loss.

General Procedure for Condensation in Benzene. A solution of 0.5 mol each of the aldehyde and methyl vinyl ketone

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in 200 mL of benzene was treated with 0.5 mL of concentrated H_2SO_4 at room temperature. Over a 1-h period the temperature of the solution was gradually raised to reflux. Refluxing was maintained until water, collected in a Dean–Stark trap, ceased to separate (ca. 3 h). The cooled solution was washed with $NaHCO_3$ solution. The aqueous wash was extracted once with ether. The combined organic solutions were dried (Na_2SO_4), concentrated under reduced pressure, and then distilled.

4,4,5-Trimethyl-2-cyclohexen-1-one. A mixture of 61 mL (0.75 mol) of isobutyraldehyde and 47 mL (0.48 mol) of 3-penten-2-one was treated with 0.5 mL of concentrated H_2SO_4 and then warmed slowly to reflux. Unlike the condensation with methyl vinyl ketone, no initial exotherm was noted. In fact, NMR spectra revealed that the starting materials were consumed gradually throughout the course of the reaction. Removal of water via reflux through a Dean–Stark trap required 16 h. Considerably more than the theoretical amount of water was collected. Distillation of the mixture at reduced pressure followed by redistillation of the product gave 24 g (36% yield) of material with a slightly broad boiling range but which appeared by NMR to be relatively clean: NMR ($CDCl_3$) δ 1.0 (br m, 5-H), 1.0 (s, 3 H, 4-CH_3), 1.1 (d, J = 7 Hz, 3 H, 5-CH_3), 1.2 (s, 3 H, 4-CH_3), 2.3 (br m, 6-H's), 5.8 (d, J = 10 Hz, 1 H, 3-H), 6.7 (d, J = 10 Hz, 1 H, 2-H).

Registry No. **1** (R = Me; R′ = Me), 78-84-2; **1** (R = Me; R′ = Et), 96-17-3; **1** (R = Et; R′ = Et), 97-96-1; **1** (R = Me; R′ = Ph), 93-53-8; **1** (R,R′ = $-(CH_2)_5-$), 2043-61-0; **2** (R″ = H), 78-94-4; **2** (R″ = Me), 3102-33-8; **3** (R = Me; R′ = Me; R″ = H), 1073-13-8; **3** (R = Me; R′ = Et; R″ = H), 17429-32-2; **3** (R = Et; R′ = Et; R″ = H), 35161-14-9; **3** (R,R′ = $-(CH_2)_5-$; R″ = H), 30834-42-5; **3** (R = Me; R′ = Me; R″ = Me), 17429-29-7; **3** (R = Me; R′ = Ph; R″ = H), 17429-36-6.

Optically Active (C_3)-Cyclotriveratrylene-d_9. Energy Barrier for the "Crown to Crown" Conformational Interconversion of Its Nine-Membered-Ring System

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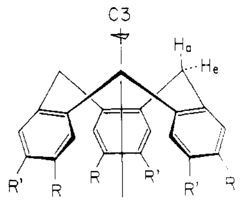
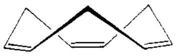
It has been widely accepted[1-5] that cyclotriveratrylene[6] (CTV) 1 exists as a single rigid "crown" conformer having C_{3v} symmetry.[7-10] The invariance of the ^{1}H NMR spectrum of 1 over a temperature range up to 200 °C[2] and the resolution of several of its derivatives into enantiomers which are optically stable at room temperature[11,12] indicate that the inversion barrier is greater than 23 kcal·mol^{-1}. However, evidence that ring inversion may occur on heating has recently been reported.[12] In this paper, we describe the synthesis of optically active (C_3)-cyclotriveratrylene-d_9, 2, and the determination of its thermal optical stability. We conclude that the activation energy for the conformational "crown to crown" interconversion process (which leads to racemization) is 26.5 kcal·mol^{-1}.

Reaction of optically pure triphenols (+)- and (−)-**3**, previously described,[12] with excess 99.6% deuterated methyl-d_3 iodide and 25% aqueous sodium hydroxide in HMPA at room temperature[13] afforded the desired (+)- and (−)-**2**, respectively. Although the methylation appeared complete within a few minutes (as indicated by TLC), all preparative runs were carried out by using longer times (3 to 16 h) so as to ensure that the last traces of phenolic material were consumed. Conventional workup (see Experimental Section) followed by thin-layer or column chromatography on silica gel afforded samples of (+)- and (−)-**2** having optical rotations in the range of $[\alpha]^{25}_{D}$ 3.0 to 3.4 ± 0.2° (in chloroform). In order to ascertain that contamination with a trace of **3** (i.e., 1.3%) or of incompletely methylated phenolic products was not responsible for these rotations, a sample having $[\alpha]^{25}_{D}$ +3.1 ± 0.2° was chromatographed over basic alumina; 91% was recovered, with $[\alpha]^{25}_{D}$ +3.0 ± 0.2°. A control experiment showed that CTV 1, contaminated with 1.3% (+)-**3**, was completely cleaned of this impurity by passage through basic alumina. Additionally, the latter sample of (+)-**2** was recrystallized from benzene to give a clathrate[7] [(+)-**2**, 0.5 C_6H_6, ca. 2 H_2O]; once desolvated this product again exhibited $[\alpha]^{25}_{D}$ +3.0 ± 0.2°.



1 R = R' = OCH_3
2 R = OCH_3 R' = OCD_3
3 R = OCH_3 R' = OH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Optical rotations of (+)- and (−)-**2** in the visible region are among the highest values previously reported for chirality due to isotopic substitution.[14,15] Compound (+)-**2** shows a comparatively[15] strong circular dichroism consisting of an exciton couplet (276 nm, $\Delta\epsilon$ −0.23; 297 nm, $\Delta\epsilon$ +0.26) which remained unchanged at each step of the purification process described above. A detailed discussion

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