(10) P. v. R. Schleyer, *J. Am. Chem. Soc.*, **79**, 3292 (1957).
(11) **Note Added in Proof:** A procedure similar to that reported here has appeared since submission of this work (D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, **100**, 3636 (1978)).

Branching Strategy in Organic Synthesis. A Versatile Ketone to Enone Homologation

Douglass F. Taber* and Bruce P. Gunn

Department of Pharmacology, School of Medicine, Vanderbilt University, Nashville, Tennessee 37232

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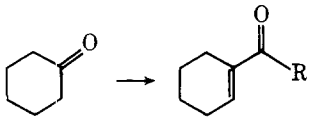
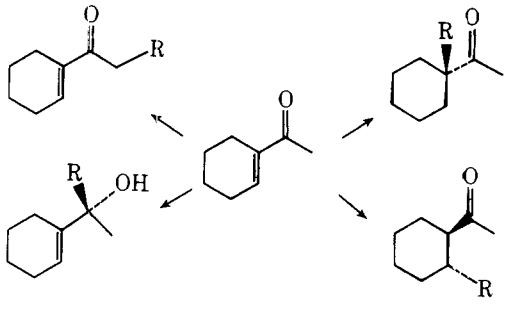
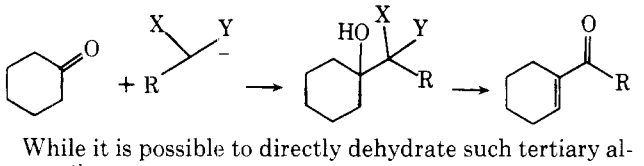
The delineation of new strategies for the construction of carbon–carbon bonds is fundamental to the development of synthetic organic chemistry. We report such a strategy, a simple procedure for the conversion of a ketone to the homologated enone.[1]



We chose ketones to be the starting functionality because of their central role in organic construction. Enones were chosen for the targets because they are activated for branching at four contiguous centers.



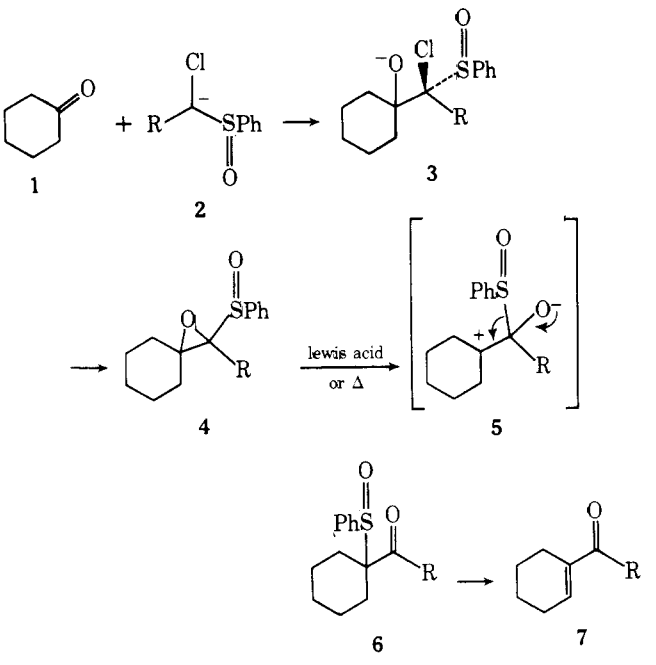
In developing this method, we sought a nucleophilic reagent the condensation of which with a ketone would lead to an adduct that could be readily carried on to the enone. There are two subproblems in the conversion of the adduct to the enone: unmasking of the carbonyl and elimination to introduce the olefin.



While it is possible to directly dehydrate such tertiary alcohols,[1b] we thought it preferable to introduce a group which could undergo elimination under very mild conditions. The phenylsulfinyl group seemed an ideal candidate.[2] The problem then was to exchange phenylsulfinyl for hydroxyl in the course of unmasking the carbonyl. The mechanism we envisioned is outlined in Scheme I.[3]

A search of the literature indicated that chlorosulfoxides are readily available from the corresponding sulfides[4] and that they can be deprotonated[5] and condensed with ketones to give epoxides.[6] There was a report[7] that **4** (R = H) smoothly thermolyzed to **7** (R = H). While this work was in progress an extensive study of this aldehyde synthesis was published.[8]

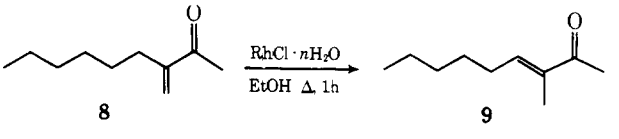
Scheme I



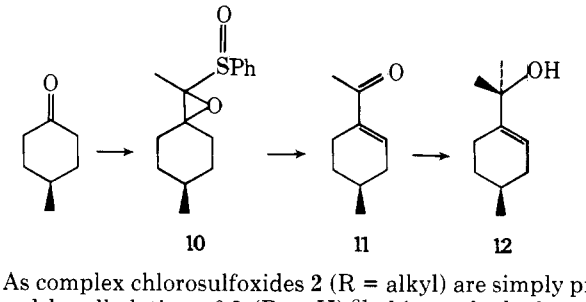
Results and Discussion

We have prepared representative chlorosulfoxides **2** (R = H, Me, Et) and investigated their condensation with typical ketones[9] and the thermolysis of the resultant sulfoxides. The results are summarized in Table I.

Entries 7 and 8 suggest an important consideration. Where two regioisomeric enones could be formed, it would be desirable to cleanly make one or the other. This has been found to be possible. Thus, reluctance to eliminate a methine proton[2] appears to be sufficient to ensure the formation of a single regioisomer (entry 7). Even more significantly, we have found that when a mixture of regioisomers is formed (entry 8), the mixture is cleanly converted to the more substituted isomer by refluxing with a catalytic amount of $RhCl_3 \cdot nH_2O$[17] in 95% ethanol for an hour.[18] Neither the disubstituted enone **8** nor the *Z* isomer of **9** could be detected in the product by NMR.



The synthetic utility of this procedure is illustrated by the preparation of 8-hydroxy-*p*-menth-3-ene (**12**), a component of the essential oil of *Mentha gentilis*.[19] Thus, condensation of **2** (R = Me) with 4-methylcyclohexanone gave the corresponding epoxysulfoxide **10**. Thermolysis of **10** led to the known[20] enone **11**, which on addition of methyllithium gave **12**.



As complex chlorosulfoxides **2** (R = alkyl) are simply prepared by alkylation of **2** (R = H),[21] this method of enone construction should be widely applicable in organic synthesis.

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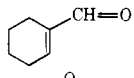
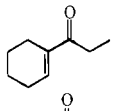
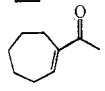
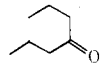
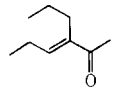
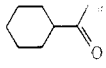
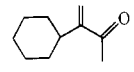
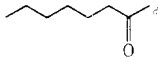
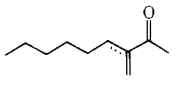
Table I

entry	carbonyl compd	registry no.		yield of epoxide[a]	registry no.	product enone	registry no.	yield of enone[b]	DNP mp,[c] °C	DNP lit. mp, °C
1		108-94-1	H	81	21849-30-9		192-88-7	87	218–219	219–220[i]
2			Me	97	68318-05-8		932-66-1	71	203–204	202–203[j]
3			Et	82	68318-06-9		1655-03-4	63	206–207	206–207[k]
4		120-92-3	Me	97	68318-07-0		16112-10-0	83	204–205	210–202[l]
5		502-42-1	Me	98	68318-08-1		14377-11-8	72	177–178	178[m]
6		123-19-3	Me	74	68318-09-2		68318-12-7	71[e]	135–136[h]	*n*
7		823-76-7	Me	96	68318-10-5		34970-11-1	65[f]	122–123	*o*
8		111-13-7	Me	88	68318-11-6			57[g]		

[a] Yield of chromatographed material, homogeneous by TLC and pure by NMR. [b] The sulfoxide was pyrolyzed, and the crude pyrolysate was purified by short column chromatography[23] to remove traces of thiophenol-derived material. For most applications it would not be necessary to chromatograph the enone before carrying it on. [c] Recrystallized from ethyl acetate. [d] The carbonyl compound was warmed with a slight molar excess of anydrous LiBr[10] in THF, and the resultant complex was allowed to cool before addition to the chlorosulfoxide anion. [e] ≥95% *E* by NMR. [f] ≥95% disubstituted enone by NMR. [g] ~65% disubstituted enone by NMR. [h] Semicarbazone; registry no., 68318-13-8. [i] Reference 11. [j] Reference 12. [k] Reference 13. [l] Reference 14. [m] Reference 15. [n] Calcd for $C_{10}H_{19}NO_3$: C, 60.91; H, 9.64; N, 21.32. Found: C, 61.03; H, 9.91, N, 20.98. [o] NMR spectrum was identical with the published[16] spectrum.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. ^1H NMR spectra were determined on a JEOLCO MH-100 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference, tetramethylsilane. Coupling (J) is in hertz (Hz). Organic chemicals were purchased from Aldrich Chemical Co. unless otherwise indicated. Organometallics were purchased from Alfa Inorganics and were titrated prior to use. Solvent mixtures (e.g., 5% ethyl acetate/hexane) are v/v. R_f values indicated refer to thin-layer chromatography on microscope slides coated with EM silica gel 60 PF-254. Column chromatography was carried out using the short column technique,[23] modified by running the columns under air pressure (5–20 psig). Bulb-to-bulb distillation was carried out using an Aldrich Kugelrohr. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Isomerization of 8 to 9. To 150 mg of a mixture of **8** and **9**, prepared by the general procedure outlined below, was added a small portion of methyl stearate. The NMR spectrum of the mixture showed a 1:1 ratio of **8**/**9** and a total vinyl proton/ester ratio of 3:1 (on a mole basis). The solvent was evaporated and the mixture taken up in 10 mL of 95% ethanol. Rhodium trichloride hydrate[17] (15 mg, 10 wt %) was added, and the mixture was refluxed under a nitrogen atmosphere for 80 min.[18] The mixture was diluted with water, extracted with CH_2Cl_2, dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. An NMR spectrum of the residual oil showed only **9** present. The vinyl proton/ester ratio of 3:1 was maintained.

Preparation of Enone 11. Chlorosulfoxide **2** (R = Me) (377 mg, 2.00 mmol, in 0.5 mL of THF) was added over 1 min to a magnetically stirred solution of 2.95 mmol of lithium diisopropylamide in 10 mL of THF under N_2 in a −78 °C cooling bath to give a clear pale yellow solution. A THF solution of 4-methylcyclohexanone[22] (560 mg, 5.0 mmol, in 1 mL of THF) was added over 30 s to give a clear colorless solution. The cooling bath was removed, and the reaction mixture was stirred and allowed to warm for 15 min. Sodium hydroxide (50% aqueous solution, 2 mL) was added and the reaction mixture stirred rapidly at room temperature for 1 h. The mixture was diluted with 5% aqueous HCl, extracted with CH_2Cl_2, dried over K_2CO_3, evaporated, and chromatographed on TLC silica gel[23] to give **10** as a colorless oil: 477 mg, 1.83 mmol, 90%; R_f (30% EtOAc/hexane) 0.29; NMR δ 0.09 (d, J = 5 Hz, 3 H), 1.25 (s, 3 H), 1.0–2.4 (m, 9 H), 7.04–7.46 (m, 5 H).

A solution of **10** (477 mg, 1.83 mmol) in 5 mL of CH_2Cl_2 was evaporated onto 0.5 g of $CaCO_3$,[2] and the mixture was distilled bulb-to-bulb (30 mm, oven temperature 150–170 °C for 15 min) to give 310 mg of crude distillate. This was chromatographed on TLC silica gel[23] to give **11** as a colorless oil: 150 mg, 1.1 mmol, 60% based on **10**; R_f (10% EtOAc/hexane) 0.43; NMR δ 0.98 (d, J = 6 Hz, 3 H), 0.9–2.6 (m, 7 H), 2.26 (s, 3 H), 6.78 (brs, 1 H). 2,4-Dinitrophenylhydrazone, mp 216–217 °C (EtOAc) (lit.[20] mp 206–207 °C for optically active enone).

Preparation of Alcohol 12. To enone **11** (56 mg, 0.41 mmol) in 10 mL of Et_2O at room temperature was added MeLi (1.0 mL of 1.07 M solution in Et_2O) over 1 min. The mixture was diluted with 5% aqueous HCl, extracted with Et_2O, dried over K_2CO_3, concentrated in vacuo, and chromatographed on TLC silica gel[23] to give **12** as a pale yellow oil: 45 mg, 0.29 mmol, 72%; R_f (30% EtOAc/hexane) 0.52; NMR δ 0.90 (d, J = 6 Hz, 3 H), 1.26 (s, 6 H), 1.0–2.2 (m, 8 H), 5.50 (brs, 1 H); IR (thin film) superimposable on published spectrum.[24]

Acknowledgments. We are grateful to Professor Durst for sharing some of his procedures with us. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the NIH (GM 15431) for partial support of this work.

Registry No.—**2** (R = H), 68318-14-9; **2** (R = Me), 68318-15-0; **2** (R = Et), 68318-16-1; **8**, 68318-17-2; **9**, 18402-87-4; **10**, 68318-18-3; **11**, 22273-97-8; **12**, 18479-65-7; 4-methylcyclohexanone, 589-92-4.

References and Notes

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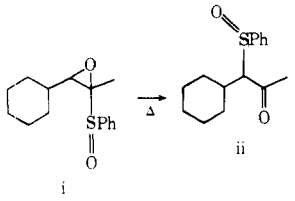
(3) Durst[7] suggests a rather different mechanism. The intermediacy of the phenylsulfinyl ketone is supported by the isolation of sulfoxide ii (which has no low-energy elimination pathway available) on thermolysis of i.



i ii

(4) (a) M. Hojo, R. Masuda, T. Saeki, and S. Uyeda, *Synthesis*, 697 (1976). (b) The crude chlorosulfoxides show a main spot on TLC (30% v/v EtOAc/hexane) at R_f ~0.2. They were purified by filtration through silica gel (CH_2Cl_2/EtOAc) followed by bulb-to-bulb distillation ($bp_{0.3}$ = 120–130 °C (bath temperature)). Chlorosulfoxides so purified were colorless oils indefinitely stable in the freezer. Development of dark yellow or brown color on addition to LDA/THF at −78 °C is an indication of insufficiently purified chlorosulfoxide.
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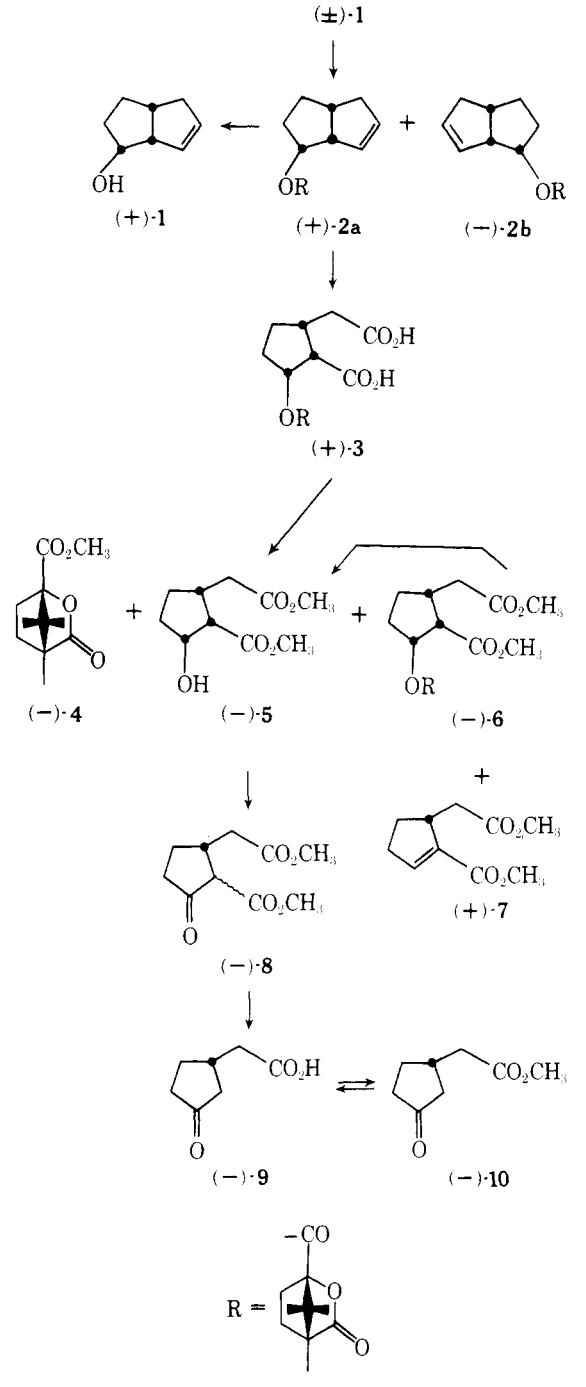

Absolute Configuration of *endo-cis*-Bicyclo[3.3.0]oct-7-en-2-ol and Specific Rotation of 3-Oxocyclopentaneacetic Acid

Hiroko Kuritani, Yoshiko Takaoka, and Keiji Shingu*

Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka, 560 Japan

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The *cis*-bicyclo[3.3.0]octane skeleton has often been found in natural products and proved to be a useful precursor for the synthesis of some monoterpenes,[1] yet the absolute configuration of its simplest asymmetric derivatives has not been established.[2]

In connection with our studies on optical activity of simple chromophores,[3] we report here the chemical correlation of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-ol (**1**) to 3-oxocyclopentaneacetic acid (**9**). The specific rotation of the latter has also been determined.

(±)-*endo-cis*-Bicyclo[3.3.0]oct-7-en-2-ol (**1**)[4] was treated with (−)-camphanyl chloride[5] in pyridine. The resulting diastereomeric mixture of camphanates was separated by fractional recrystallization, or by column chromatography on silica gel, to give **2a**, $[\alpha]_{589}$ +129.0° (ethanol), and **2b**, $[\alpha]_{589}$ −139.8° (ethanol), each in pure form.[6] Hydrolysis of (+)-**2a** gave optically pure (+)-**1**, $[\alpha]_{589}$ +210.6° (methanol).

Oxidation of (+)-**2a** with sodium metaperiodate in the presence of ruthenium dioxide gave the diacid **3**, $[\alpha]_{589}$ +3.2° (ethanol). Solvolysis of **3** with sulfuric acid in methanol proceeded only partially, affording the desired alcohol **5**, $[\alpha]_{589}$ −11.8° (ethanol), and methyl camphanate (**4**), $[\alpha]_{589}$ −124.4° (ethanol), as well as the esterification product **6**, $[\alpha]_{589}$ −4.87° (ethanol), and a small amount of the olefinic product **7**, $[\alpha]_{589}$ +54.1° (carbon tetrachloride). Methanolysis of **6** with hydrogen chloride gave (−)-**4** and (−)-**5** in 80% yield. (−)-**5** was oxidized with Jones' reagent to yield the ketone **8**, $[\alpha]_{589}$ −66.8° (methanol). Hydrolytic decarboxylation of (−)-**8** with concentrated hydrochloric acid gave the acid **9**, which was purified via the methyl ester **10**, $[\alpha]_{589}$ −121.0° (chloroform). The optical rotation of the regenerated acid **9**, $[\alpha]_{589}$ −115.5°

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