A Facile Synthesis of (−)-(*R*)-5-Methyl-2-cyclohexen-1-one and Related 2-Substituted Enones from (+)-Pulegone[1]

Drury Caine,* Katherine Procter, and Roger A. Cassell

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332, and Department of Chemistry, University of Alabama, University (Tuscaloosa), Alabama 35486

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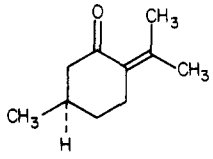
Monoterpenes of known absolute configuration are particularly attractive chiral starting materials for the synthesis of more complex natural products.[2] The readily available (+)-pulegone (1) is a useful compound in this respect.[3] Among other possible transformations, it can be converted into (+)-(*R*)-3-methylcyclohexanone (2) by an acid-catalyzed retroaldol reaction.[4] Enones related to 2 are useful intermediates for the synthesis of lycopodium-type alkaloids. For example, (−)-(*R*)-5-methyl-2-cyclohexenone (**3a**) has been converted into (+)-luciduline[5] and racemic 2-allyl-5-methyl-2-cyclohexenone (cf. **3b**) has been used in the synthesis of (±)-fawcettimine and (±)-8-deoxyserratinone.[6]



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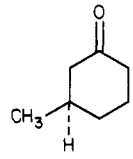

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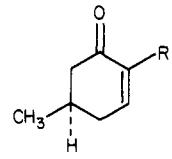
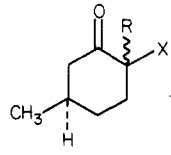
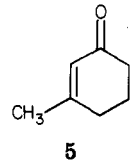


3a, R = H
b, R = $CH_2CH{=}CH_2$
c, R = CH_3

The conversion of the saturated ketone 2 into the enone **3a** has been accomplished (1) by preparation of bromo ketone **4a** by reaction of 2 with bromine in water followed by dehydrobromination via the ethylene ketal or with semicarbazide followed by hydrolysis[4c] or (2) by treatment of 2 with lithium diisopropylamide (LDA), trapping of the lithium enolate mixture thus generated with diphenyl disulfide to obtain the 2-phenylsulfenyl ketone **4b**, oxidation of the sulfide to the sulfoxide, and thermal elimination of phenylsulfenic acid.[5]





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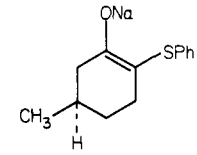
4a, R = H, X = Br
b, R = H, X = SPh
c, R = $CH_2CH{=}CH_2$, X = SPh
d, R = CH_3, X = SPh

The first of the above methods suffers from the fact that the bromo ketone **4a** is formed in very poor yield and the yields of enone **3a** in either of the dehydrohalogenation methods are also low. The second method has the drawback that the deprotonation step is not highly regioselective and consequently some of the undesired regioisomer of **4b** is produced in the phenylsulfenylation step. In an experiment conducted under similar conditions to those reported by Oppolzer and Petrzilka,[5] we found that when the crude mixture of phenylsulfenyl ketones was oxidized and phenylsulfenic acid thermally eliminated enone **3a** and its isomer, 3-methyl-2-cyclohexenone (5), were produced in a ca. 85:15 ratio.[7]

We wish to report that (+)-pulegone can be converted directly into the 2-phenylsulfenyl sodium enolate **6** by a procedure that does not involve the intermediacy of ketone 2. This enolate can be protonated to give ketone **4b** or alkylated[8] to produce the corresponding 2-alkyl-2-phenylsulfenyl ketones such as **4c** and **4d**. The method involves the conversion of (+)-pulegone into the known diastereomeric mixture of epoxides **7** by reaction with



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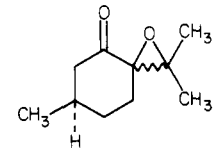

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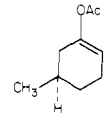
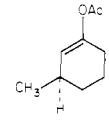
hydrogen peroxide in aqueous sodium hydroxide[9] and then reaction of the epoxide mixture with sodium thiophenoxide in THF at reflux for 24 h. A possible pathway for the reaction involves nucleophilic attack of the thiophenoxide anion at the 2-position of the epoxide to open the ring and generate the anion of a β-hydroxy-α-phenylsulfenyl ketone that undergoes retroaldol reaction[10] to produce enolate **6** and acetone. Addition of water to the reaction mixture gave **4b** that upon oxidation and thermal elimination gave enone **3a**, free of contamination with its regioisomer **5**. The enolate **6** was apparently not protonated by the acetone



i



ii

consistent with those of Antony and Maloney,[7b] who found that kinetic deprotonation of 2 with tritylllithium in dimethoxyethane and quenching of the enolate mixture with acetic anhydride also gave a ca. 4:1 mixture of i and ii. They are also consistent with the recently reported studies of Schlecht[7c] in which it was observed that kinetic deprotonation of various 3-alkylcyclohexanones with LDA in THF at −78 °C gave enolate mixtures containing the distal and proximal isomers in 2–3:1 ratios. (b) Antony, A.; Maloney, T. *J. Org. Chem.* **1972**, *37*, 1055. (c) Schlecht, M. F. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, Washington, Mar 1983; American Chemical Society: Washington, DC, 1983; Paper No. 191. We thank Professor Schlecht for sharing his experimental results with us prior to publication.

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(10) (a) We recently reported[10b] that α,β-epoxycyclohexanone derivatives undergo reaction with thiophenol in the presence of amines to produce β-hydroxy-α-phenylsulfenyl ketones. Upon base treatment these compounds were observed to undergo retroaldol cleavage to produce aldehydo or keto enolates that could be trapped with electrophilic and/or nucleophilic reagents. However, no reaction was observed when the diastereomeric mixture of pulegone epoxides was refluxed with thiophenol and triethylamine in acetonitrile solution for several hours. (b) Caine, D.; Crews, E.; Salvino, J. M. *Tetrahedron Lett.* **1983**, 2083.

(1) We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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(5) Oppolzer, W.; Petrzilka, M. *Helv. Chem. Acta* **1978**, *61*, 2755.

(6) Harayama, T.; Takatani, M.; Inubushi, Y. *Tetrahedron Lett.* **1979**, 4307.

(7) (a) Also, addition of enone 2 to excess LDA in THF at −78 °C and quenching of the enolate mixture with acetic anhydride gave a ca. 3–4:1 mixture of the enol acetates i and ii in good yield. These results are

* To whom correspondence should be addressed at the University of Alabama.

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generated in the retroaldol reaction since addition of allyl bromide or methyl iodide gave the corresponding 2-allyl and 2-methyl ketones **4c** and **4d**, respectively, in reasonably good yields. Oxidation of these compounds and thermal elimination of phenylsulfenic acid gave the optically active forms of the known enones **3b**[11] and **3c**[12] in 53% and 50% yields, respectively. In neither case could any of the isomeric β-methyl-substituted enones be detected.

Further studies on the generation of specific α-phenylsulfenyl enolates by reaction of epoxides of α-methylene and α-alkylidene carbonyl compounds with alkali-metal thiophenoxides are in progress.

Experimental Section

General Data. Unless otherwise indicated, all materials employed were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. All reactions were conducted under a dry nitrogen atmosphere. Boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 1420 ratio recording spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM360 spectrometer. Chemical shifts are expressed in parts per million downfield with respect to tetramethylsilane (Me_4Si) as an internal standard. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6M mass spectrometer at 70 eV. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard Model 5790 gas chromatograph equipped with a 12.5-m fused silica (cross-linked dimethylsilicone) column and a flame ionization detector. High-pressure liquid chromatography was performed on a system constructed from Laboratory Data Control parts using a refractive index detector and a 4.6 mm × 25 cm stainless-steel column containing 5 μm of silica. Ultraviolet spectra were recorded on a Varian Model DMS-100 spectrophotometer using 95% ethanol as the solvent. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter.

General Procedure for Preparation of the Sodium Enolate 6. To a mixture of 0.143 g (5.95 mmol) of sodium hydride (obtained by washing of a 60% oil dispersion with hexane) in 10 mL of anhydrous THF was added a solution of 0.66 g (5.95 mmol) of thiophenol in 25 mL of anhydrous THF. After the evolution of hydrogen had ceased, the mixture was stirred at room temperature for 0.5 h and 0.50 g (2.98 mmol) of a diastereomeric mixture of pulegone epoxides (**7**), prepared according to the published procedure,[9] in 20 mL of anhydrous THF was added. The resulting mixture was then refluxed for 24 h, cooled to room temperature, and transferred via a cannula to a solution of the appropriate enolate trapping agent (see A–C below).

A. Formation of (−)-(*R*)-5-Methylcyclohex-2-enone (3a). After generation of the solution of the 2-phenylsulfenyl enolate **6** in THF as described above, it was transferred with stirring to ~200 mL of a saturated solution of NH_4Cl via a cannula. The resulting mixture was stirred at room temperature for 1 h and extracted with three 50-mL portions of ether. The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 0.75 g of the crude 2-phenylsulfenyl ketone **4b** as a mixture of stereoisomers. The crude material was dissolved in 250 mL of dry CH_2Cl_2 (distilled from P_2O_5) and cooled to −78 °C. To the cold solution was added slowly with stirring a mixture of 0.60 g (~3.5 mmol) of ~85% *m*-chloroperbenzoic acid (MCPBA) in 125 mL of dry CH_2Cl_2. The reaction mixture was stirred at −78 °C for 3 h, and then 175 mL of a 10% aqueous solution of $NaHSO_3$ was added with stirring. The reaction mixture was warmed to room temperature, and the organic layer was separated and washed with three 100-mL portions of saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to give 0.80 g of the crude sulfoxide corresponding to **4b** as a yellow oil. This material was dissolved in 500 mL of dry CCl_4 containing a few milligrams of solid $CaCO_3$, and the mixture was refluxed for 24 h. Filtration of the mixture through Celite and removal of the solvent under reduced pressure gave 0.50 g of crude enone **3a**. Chromatography of the crude material on silica gel and elution with 10% ether–hexane gave 0.16 g (~49% yield from epoxide mixture **7**) of enone **3a**, bp 85–87 °C (20–22 torr) (lit.[5] bp, 60–70 °C (12 torr)), that exhibited the same optical rotation and spectral properties as those reported previously.[5]

B. Formation of (−)-(*R*)-5-Methyl-2-allyl-2-cyclohexenone (3b). A solution of the enolate **6** prepared as described above was added via a cannula to a stirred solution of 1.21 g (10 mmol) of allyl bromide in 25 mL of THF at room temperature, and the solution was stirred for 3 h. After the usual workup, a crude mixture of the 2-allyl-2-(phenylsulfenyl)cyclohexenone derivative **4c** and allylphenyl thioether was obtained. The ether was readily separated from the ketone by chromatography of the mixture on silica gel using 10% ether–hexane as the elution solvent. Compound **4c** (0.81 g) was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) 1.15 (d, J = 3.4 Hz, 3 H), 1.7–2.8 (br absorption, 7 H), 3.5 (d, J = 6 Hz, 2 H), 4.8–5.4 (m, 2 H), 5.6–6.3 (m, 1 H), 7.1–7.6 ppm (br absorption, 5 H).

Subsequent oxidation of **4c** to the corresponding sulfoxide and thermal elimination of phenylsulfenic acid as described in part A gave 0.24 g (~53% yield from epoxide mixture **7**) of enone **3b**: bp 105–110 °C (15–16 torr) (lit.[11] bp 116–122 °C (35 torr)); $[\alpha]^{21}_D$ −49.3° [*c* 1.0 (95% ethanol)]. The UV, IR, and ^{1}H NMR spectral properties of **3b** were identical with those previously reported[11] for the racemic compound.

C. Preparation of (−)-(*R*)-2,5-Dimethyl-2-cyclohexenone (3c). The same quantity of a THF solution of the enolate **6** as was used in parts A and B was transferred via a cannula to a solution of 1.52 g (10 mmol) of methyl iodide in 25 mL of THF with stirring at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h, and 100 mL of a saturated aqueous solution of NH_4Cl was added. The mixture was extracted with three 50-mL portions of ether, and the combined ethereal extracts were dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave ~1.0 g of a yellow oil that according to ^{1}H NMR analysis contained a mixture of the desired 2-phenylsulfenyl ketone **4d** and thioanisole. Chromatography of the mixture on silica gel and elution with 10% ether–hexane gave 0.60 g of **4d**: ^{1}H NMR ($CDCl_3$) 1.15 (d, J = 3 Hz, 3 H), 1.35 (s, 3 H), 1.7–2.6 (br absorption, 7 H), 7.1–7.6 ppm (br absorption, 5 H). Subsequent oxidation of **4c** to the corresponding sulfoxide and thermal elimination of phenylsulfenic acid as described above gave 0.19 g (~51% from epoxide mixture **7**) of enone **3c**: bp 94–96 °C (18 torr) (lit.[12] bp 189–190 °C (760 torr)); $[\alpha]^{21}_D$ −46.5° [*c* 1.0 (95% ethanol)]; mass spectrum, *m/e* (70 eV) 124 (60, M^+), 82 (100); 69 (40), 55 (48); IR (liquid film) 1670, 1030, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.15 (d, J = 3 Hz, 3 H), 1.8 (s, 3 H), 1.9–2.7 (br absorption, 5 H), 6.7–6.9 ppm (m, 1 H).

Registry No. **3a**, 54307-74-3; **3b**, 90528-94-2; **3c**, 90528-95-3; *cis*-**4b**, 69743-82-4; *trans*-**4b**, 69661-34-3; *cis*-**4c**, 90461-80-6; *trans*-**4c**, 90528-96-4; *cis*-**4d**, 90461-81-7; *trans*-**4d**, 90528-97-5; **6**, 90461-82-8; **7** (α-epoxide), 7599-91-9; **7** (β-epoxide), 7599-90-8; PhSH, 108-98-5; $BrCH_2CH{=}CH_2$, 106-95-6; CH_3I, 74-88-4.

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Dehydrobromination of 1,2-Dibromocyclohexane and Related Compounds by Lithium Chloride in Hexamethylphosphoric Triamide. An Improved Synthesis of 1,3-Cyclohexadiene and Some Deuterium-Labeled Analogues

Adrian Weisz and Asher Mandelbaum*

Department of Chemistry, Technion—Israel Institute of Technology, Haifa, Israel

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Several synthetic routes have been described for the preparation of 1,3-cyclohexadiene (**1**), which is an important intermediate in many organic and organometallic syntheses.[1] The recommended method is the base-cata-

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