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.

(11) Harayama, T.; Takatani, M.; Inubushi, Y. *Chem. Pharm. Bull.* **1979**, *27*, 726.
(12) Harayama, T.; Cho, H.; Inubushi, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2273.

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

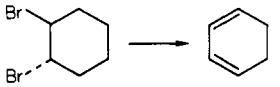
Received November 9, 1983

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-

0022-3263/84/1949-2648$01.50/0

lyzed dehydrobromination of 1,2-dibromocyclohexane (2).[1]

In the course of a study on the fragmentation of Diels–Alder adducts under electron impact,[2] we were in need of various deuterium-labeled analogues of 1,3-cyclohexadiene. Several attempts of dehydrobromination of 2 either by sodium isopropoxide[1] or by sodium hydroxide in ethylene glycol[1b] on a small scale showed that these methods were not practical for the syntheses of labeled 1. The yields are not high in the large-scale preparations (35–55%[1]). In the small-scale experiments it was difficult to isolate any cyclohexadiene. We developed a convenient method which is useful in the preparation of small quantities of labeled analogues of 1 and can be recommended for a laboratory synthesis of 1,3-cyclohexadiene itself. The synthesis is based on the dehydrobromination of 2 by lithium chloride in hexamethylphosphoric triamide (HMPTA).[3]

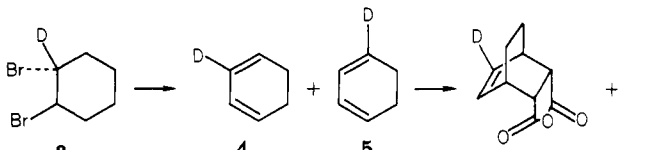


2 1

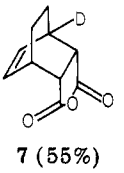
The procedure is as follows: Lithium carbonate and lithium chloride in HMPTA are heated to 160 °C in a two-necked flask equipped with an additional funnel and a condenser set for distillation. 1,2-Dibromocyclohexane is added slowly to the heated mixture, resulting in an immediate distillation of 1,3-cyclohexadiene. The diene may be used for Diels–Alder and for organometallic syntheses without further purification. NMR spectra show it is at least 95% pure. The yields are 75–90% in relatively large-scale preparation (≥10 g). In smaller scale preparations the yield is lower, ~65%, but still greater than in the previous procedures.

The simplicity of the procedure and the high yields suggest it as a method of choice for the laboratory preparation of 1,3-cyclohexadiene. An even better yield (~90%) was obtained in the dehydrobromination of 3-bromocyclohexene under the same conditions. This synthesis has been also successfully applied in the preparation of 1,3-cycloheptadiene (from 3-bromocycloheptene) and 4-methyl-1,3-cyclohexadiene (from 3,4-dibromo-1-methylcyclohexane).

The synthesis of deuterium-labeled cyclohexadienes throws light on the mechanism of the dehydrobromination of 2. 1-Deuterio-1,2-dibromocyclohexane (3) gives rise to



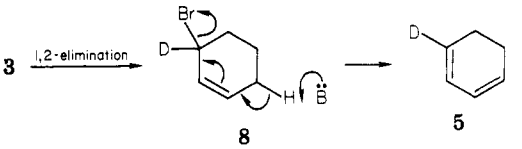
3 4 5 6 (45%)



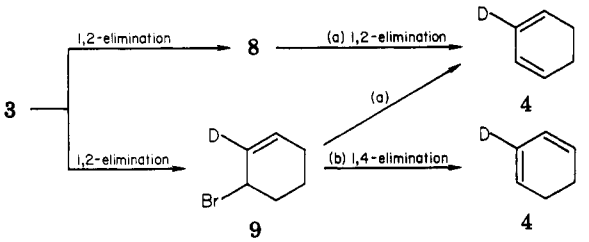
7 (55%)

a 45:55 mixture of 2-deuterio- and 1-deuterio-1,3 cyclohexadiene (4 and 5, respectively). The structures and concentration ratio of 4 and 5 were deduced from the NMR spectrum of their Diels–Alder adducts 6 and 7.

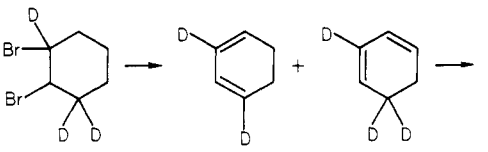
The formation of 5 can be understood as a result of 1,2-dehydrobromination leading to 8 followed by a 1,4-



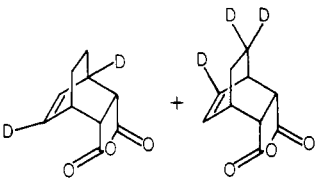
elimination step involving a proton from position 4. The isomer 4 may be formed by two processes: (a) two successive 1,2-elimination steps (two possible sequences) and (b) 1,2-dehydrobromination to 9 followed by a 1,4-elimination.



A similar result was obtained for the dehydrobromination of 1,3,3-trideuterio-1,2-dibromocyclohexane (10). This



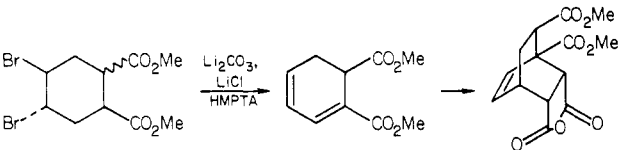
10 11 12



13 14
50% 50%

reaction gave rise to a 1:1 mixture of di- and trideuteriocyclohexadienes 11 and 12. The concentration ratio was obtained from both mass and NMR spectra of the Diels–Alder adducts 13 and 14.

It is noteworthy that the lithium chloride HMPTA dehydrobromination of the methyl esters of both 4,5-dibromo-*cis*- and -*trans*-hexahydrophthalic acids 15 gives rise



15-*cis* 15-*trans* 16 17

to the 2,3-dihydrophthalic ester 16 by the 1,4-elimination in the second step. It should be noted that only 1,2-elimination has been reported in the case of *trans*-1,2-dihydroxy- and -1,2-diacetoxy-4,5-dibromocyclohexanes.[4,5]

Experimental Section

Laboratory-Scale Preparation of 1,3-Cyclohexadiene. A mixture of lithium carbonate (27 g) and lithium chloride (17 g) in hexamethylphosphoric triamide (HMPTA, Merck, 80 mL) was

(1) (a) Schaeffer, J. P.; Endres, L. "Organic Syntheses", Wiley: New York, 1973; Collect. Vol. 5, p 285 and references cited therein. (b) Hine, J.; Brown, J. A.; Zalkow, L. H.; Gardner, W. E.; Hine, M. *J. Am. Chem. Soc.* **1955**, *77*, 594.

(2) Mandelbaum, A.; Weisz, A.; Karpati, A. *Int. J. Mass Spectrom. Ion Phys.* **1983**, *47*, 415.

(3) King, P. F.; Paquette, L. A. *Synthesis* **1977**, 279.

(4) Demuth, M. R.; Garrett, P. E.; White, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 634.

(5) Platt, K. L.; Oesch, F. *Synthesis* **1977**, 449.

heated in an oil bath at 160 °C in a 150-mL two-necked flask equipped with an addition funnel and a short condenser set for distillation. After 0.5 h 1,2-dibromocyclohexane (157 g) was added dropwise, which resulted in an immediate distillation of 1,3-cyclohexadiene. After all the dibromocyclohexane had been added (~1 h), a gentle stream of nitrogen was passed through the system which resulted in an additional small amount of distillate. The resulting 1,3-cyclohexadiene (42.6 g, 82%) was used for Diels–Alder additions and for a reaction with iron tricarbonyl without further purification. In some experiments at higher temperatures small amounts (<5%) of HMPTA could be detected by NMR spectroscopy.

1,3-Cyclohexadiene-*1,3-d*$_2$ (11) and 1,3-Cyclohexadiene-*2,6,6-d*$_3$ (12). A solution of bromine (9.63 g) in CCl_4 (6 mL) was added to cyclohexene-*1,3,3-d*$_3$ (5.07 g) in CCl_4 (12 mL) and absolute alcohol (0.6 mL) at −5 °C.[6] The solvent was evaporated off on a steam bath, and the resulting crude dibromide (12.46 g) was dehydrobrominated by the above procedure with lithium carbonate (9.5 g) and lithium chloride (6 g) in HMPTA (30 mL). The distillate was a 1:1 mixture of 1,3-cyclohexadiene-*1,3-d*$_2$ and 1,3-cyclohexadiene-*2,6,6-d*$_3$ (by mass spectrometry of the adduct with maleic anhydride, 3.15 g, 75%).

1,6-Dihydrophthalic Acid, Dimethyl Ester (16). Dehydrobromination of 4,5-dibromo-*trans*-cyclohexane-1,2-dicarboxylic acid, dimethyl ester[7] (**15**-*trans*, 17.1 g) by the procedure reported for 5,6-diacetoxy-1,3-cyclohexadiene[5] gave rise to **16** (bp 126–130 °C/(5–10 torr), 3.5 g). This compound was also obtained by the same procedure from 4,5-dibromo-*cis*-cyclohexane-1,2-dicarboxylic acid, dimethyl ester (**15**-*cis*). NMR: δ 2.38–3.25 (m, 3 H), 4.7 (s, 3 H), 4.8 (s, 3 H), 5.8–6.3 (m, 2 H), 7.1–7.3 (m, 1 H).

1,7-Bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydride (17). A mixture of **16** (3 g), maleic anhydride (4.52 g), and 4-*tert*-butylcatechol (0.05 g) in 1,2-dichlorobenzene (25 ml) was refluxed (oil bath at 175 °C) for 4.5 h. After removal of the solvent (74 °C (30 torr)), the residue crystallized on the addition of ether: white crystals, 2.75 g; mp 114–116 °C. Recrystallization from petroleum ether (100–120 °C) raised the mp to 128–129 °C; NMR δ 1.9–2.2 (m, 2 H), 3.1–3.6 (m, 3 H), 3.7 (s, 3 H), 3.95 (s, 3 H), 6.3–6.8 (m, 2 H); mass spectrum, *m/z* (relative intensity) 294 ($M^{+\cdot}$, 44), 263 ($[M - CH_3O]^+$, 18), 262 ($[M - CH_3OH]^{+\cdot}$, 2), 208 (4), 190 (4), 181 (3), 180 (4), 163 (21), 137 (27), 136 (45), 131 (9), 105 (100), 103 (16), 91 (12), 78 (12), 77 (43), 59 (21), 55 (20); M_r found (high-resolution mass spectrometry) 294.0741, calculated for $C_{14}H_{14}O_7$ 294.0740. Anal. C, 57.24; H, 4.92. Calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80.

Acknowledgment. This study was supported by the Fund for the Promotion of Research at the Technion and by the Wolf Foundation.

Registry No. 1, 592-57-4; 2, 7429-37-0; 3, 89780-18-7; 4, 83992-79-4; 5, 90295-59-3; 6, 85015-25-4; 7, 85015-24-3; 10, 89831-48-1; 11, 17647-16-4; 12, 90295-60-6; 13, 85015-26-5; 14, 85015-27-6; 15-*cis*, 26595-97-1; 15-*trans*, 90409-98-6; 16, 90295-61-7; 17, 90295-62-8; lithium carbonate, 554-13-2; lithium chloride, 7447-41-8; hexamethylphosphoric triamide, 680-31-9; cyclohexene-*1,3,3-d*$_3$, 27926-35-8; maleic anhydride, 108-31-6.

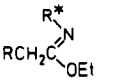
(6) Snyder, H. R.; Brooks, L. A. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, p 171.
(7) Klein, J.; Dunkelblum, E. *J. Org. Chem.* **1971**, *36*, 145.

Communications

Asymmetric Electrophilic Syntheses Using Chiral Acyclic Imidate Ester Enolates. Highly Enantioselective Syntheses of Carboxylic Acid Esters

Summary: Chiral imidate esters ($RCH_2C(OEt)=NR^*$; R = Me, Et; R* = (*S*)-$CH(CH_2Ph)CH_2OCH_3$, (*R*)-$CH(Ph)CH_2OCH_3$, (*S*)-$CH(i\text{-}Pr)CH_2OCH_3$) were prepared and deprotonated with various bases to give the corresponding lithio anion derivatives. Alkylations of the lithio derivatives proceeded in high synthetic yield and with good to excellent asymmetric induction to give α,α-disubstituted carboxylic acid derivatives. The structures of the imidate esters and their lithio derivatives are discussed.

Sir: Asymmetric synthesis is an area of synthetic methodology which has recently seen significant advances[2] including new methods for asymmetric carbon–carbon bond formation employing chiral nucleophiles which proceed with an efficiency and predictability such that they are now routinely useful in multistep natural product syntheses.[3] In this report, we describe a new class of chiral nucleophiles, acyclic imidate ester enolates.



(*S*)-**1**, R = CH_3; R* = $CH(CH_2Ph)CH_2OCH_3$
(*S*)-**2**, R = C_2H_5; R* = $CH(CH_2Ph)CH_2OCH_3$
(*R*)-**3**, R = CH_3; R* = $CH(Ph)CH_2OCH_3$
(*R*)-**4**, R = C_2H_5; R* = $CH(Ph)CH_2OCH_3$
(*S*)-**5**, R = CH_3; R* = $CH(i\text{-}Pr)CH_2OCH_3$
(*R*)-**6**, R = CH_3; R* = $CH(Ph)CH_3$

Chiral acyclic imidate esters **1**–**6** were readily prepared in 70–90% yield by modifications of literature procedures[4] either by treatment of an ortho ester with an amine or by alkylation of an amide with Et_3OBF_4. The chiral β-methoxy amines were available from amino acids.[5] The C=N stereochemistry of **1**–**6** was shown to be *E* (as drawn) by correlation of the ^1H and ^{13}C NMR spectra of **1**–**6** with spectra reported for other imidate esters, imines, and oxazolines. Of particular importance was the observation that $^{1,5}J_{H\text{-}H}$ across the C=N bond in both **1**–**6** and their alkylated products were <0.5 Hz, indicating $E_{C=N}$ stereochemistry.[6]

Chiral imidate ester enolates were generated at low temperatures by deprotonation of **1**–**6** using bases such as *n*-BuLi, *t*-BuLi, or lithium diethylamide (LDEA) and were

(1) Camille and Henry Dreyfus Teacher–Scholar, 1980–1985.
(2) Mosher, H. S.; Morrison, J. D. *Science (Washington, D.C.)* **1983**, *221*, 1013–1019; Bergbreiter, D. E.; Newcomb, M. in "Asymmetric Synthesis": Morrison, J. D., Ed.; Academic Press; New York, 1983; Vol 2, Part A, Chapter 9.
(3) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32. Masamune, S.; Choy, W. *Ibid.* **1982**, *15*, 47–63.
(4) Neilson, D. G. In "The Chemistry of Amidines and Imidates": Patai, S., Ed.; Wiley: London, 1975; Chapter 9. Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179–211.
(5) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892–898.
(6) Meese, C. O.; Walter, W.; Berger, M. *J. Am. Chem. Soc.* **1974**, *96*, 2259–2260.

0022-3263/84/1949-2650$01.50/0