were stirred at 1000 rpm and heated at 180 °C for 10 h. The reactor was then cooled and the following product recovery apparatus was attached to the shut-off valve on the reactor head. A short length of heated, flexible stainless steel tubing was connected to a 24/40 joint attached to a 100 mL, 3-neck flask fitted with a condenser. The flask was cooled in an ice bath. The shut-off valve was opened and the stirred reactor heated as the crude 1-butene **2** was distilled into the flask. Heating was continued until the temperature of the reactor contents reached 120 °C. This synthesis was performed three times. The combined products comprised 143 g of clear, colorless liquid. This was distilled on a spinning band column, bp 37 °C, giving 81.2 g of **2** of purity >95%, including a 35.6-g fraction >99.6%. The combined yield of **2** from all fractions was 99.7 g (0.804 mol), 54%. The 1-butene **2** has a very high vapor pressure and is easily lost. Care must be taken to keep it cold and in a tight container. ^{1}H NMR ($CDCl_3$): δ 1.85 (s, 3), 2.80 (q, 2, J = 11 Hz), 5.01 (s, 1), 5.12 (s, 1). Mass spectrum (electron impact): m/e 124.

It is unclear why the analytical-scale experiment gives essentially a quantitative yield of the 1-butene **2** while the preparative-scale synthesis gives a 54% isolated yield. One important difference between the two is that the preparative runs are about three times more concentrated in MgO for the purpose of increasing reactor productivity. This much higher concentration of MgO causes the reaction medium to be much more viscous and difficult to stir. This could cause local overheating at the reactor walls and possibly inhibit the generation of fresh MgO surface during the reaction.

4,4,4-Trifluoro-2-methyl-2-butene (3). A 3-neck, 25-mL flask was fitted with a condenser, gas bubbler, septum, argon inlet, thermometer, and a magnetic stir bar. The flask was charged with 0.28 g (7.18 mmol) of potassium metal and 15 mL of 3-ethyl-3-pentanol under argon. The mixture was stirred at 30 °C until all of the potassium had been consumed, and 1.51 g (9.41 mmol) of **1** was injected. A rapid exotherm to 40 °C occurred as the solution became turbid with the precipitation of KCl. Stirring was continued for 1.5 h from the time **1** was added. Argon flow was stopped, and 200 μL of benzene was injected. Quantitative GC was performed as noted (Table I). The reaction product was recovered by distillation ^{1}H NMR ($CDCl_3$): δ 1.90 (br s, 6) and 5.45 (q, 1, J = 8 Hz). Mass spectrum (electron impact): m/e 124.

Dehydrochlorination of 2-Chloro-2-methylbutane (5). These experiments were performed as described for **1**. Authentic samples of **6** and **7** were used for characterization and calibration. The dehydrochlorination of **5** is much faster than **1**, and shorter reaction times are required.

Acknowledgment. I am pleased to acknowledge the skillful experimental assistance provided by Mr. Thomas Barker. My thanks also to Drs. Robert Kinsey, George Benedikt, and James Chen for NMR spectra and to Dr. Robert Lattimer for mass spectrometric analyses.

Registry No. **1**, 352-46-5; **2**, 138835-37-7; **3**, 352-42-1; **4**, 406-49-5; **5**, 594-36-5; **6**, 513-35-9; **7**, 563-46-2; MgO, 1309-48-4; CaO, 1305-78-8; $KOC(C_2H_5)_3$, 20484-37-1; 2,6-diMePyr, 108-48-5; 2-*t*-BuPyr, 5944-41-2; 3,4-diMePyr, 583-58-4.

Evidence for the Formation of Heterocyclic Arene Oxides and a γ-Keto Enal by Reaction of Menthofuran with Dimethyldioxirane

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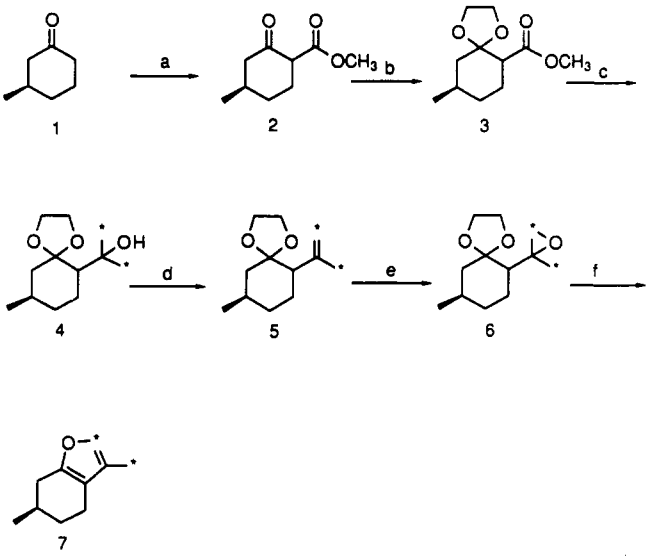
Epoxides have been proposed as reactive intermediates in the metabolism of furans,[1] but there is little evidence for the formation of such heterocyclic arene oxides. An epoxide of the *dihydro*furan, aflatoxin B_1, has been prepared and characterized,[2] and NMR data has been presented for a 4,5-epoxyfuran intermediate in the oxidation of a tetrasubstituted fungicidal furan, methfuroxam (2,4,5-trimethyl-*N*-phenyl-3-carboxamide), by *m*-chloroperoxybenzoic acid (*m*-CPBA).[3] In the case of less substituted furans, as well as methfuroxam, *m*-CPBA oxidation primarily yields ene diones and ene lactones.[3,4] More recently, an epoxide was characterized by NMR as a likely mutagenic product of the oxidation of 2,3-dimethylbenzo[*b*]furan by dimethyldioxirane.[5]

Scheme I[a]



[a] (a) NaH, THF, dimethyl carbonate; (b) ethylene glycol, *p*-TSOH, benzene; (c) $^{13}CH_3I$, Et_2O, Mg; (d) *p*-TSOH, benzene, Δ; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (f) 2 N HCl, pentane.

We now report that the oxidizing agent, dimethyldioxirane,[6] converts the terpenoid furan, menthofuran (4,5,6,7-tetrahydro-3,6-dimethylbenzofuran), to both a γ-keto enal and diastereomeric furan epoxides at low temperatures (−40 °C to −20 °C), which then form stable ene lactones at higher temperatures (0–20 °C). Menthofuran is of interest as a potentially toxic terpene in mint oils and as a proximate toxic mammalian metabolite of the monoterpene, (*R*)-(+)-pulegone.[7] The ultimate toxic species is unknown, although indirect evidence suggests that a γ-keto enal is formed that irreversibly binds to target tissue proteins.[8]

(1) For a review, see: Burka, L. T.; Boyd, M. R. *Bioactivation of Foreign Compounds*; Academic Press: New York, 1985; p 243.

(2) Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929.

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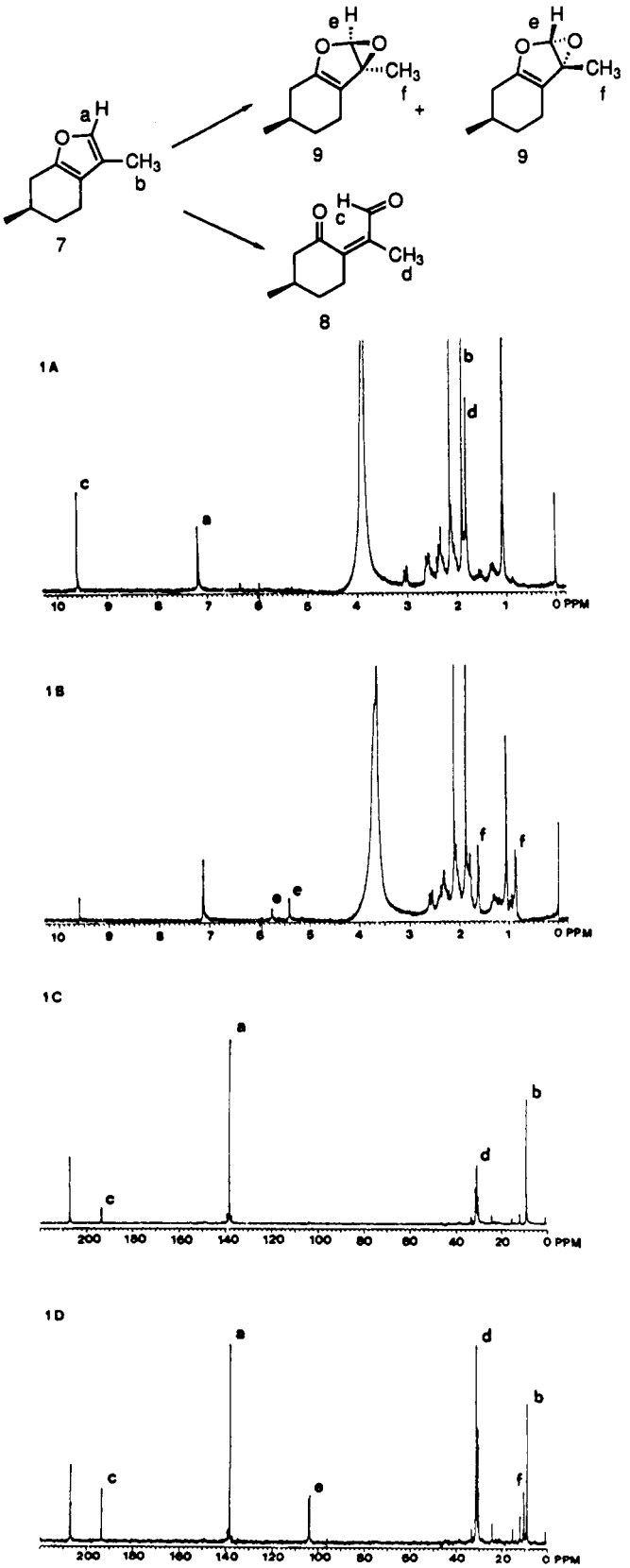


Figure 1. The scheme at the top shows the structures of the reactant and major products. Lower case letters shown on the structures correspond to positions that are noted on the NMR spectra. (A) ^1H NMR spectrum taken immediately after mixing 0.35 equiv of dimethyldioxirane with menthofuran, and the sample maintained at −40 °C. (B) ^1H NMR spectrum of the same sample taken at −20 °C. (C) ^{13}C NMR spectrum taken immediately after mixing 0.35 equiv of dimethyldioxirane with [2,8-$^{13}C_2$]menthofuran, and the sample maintained at −40 °C. (D) ^{13}C NMR spectrum of the same sample taken at −20 °C.

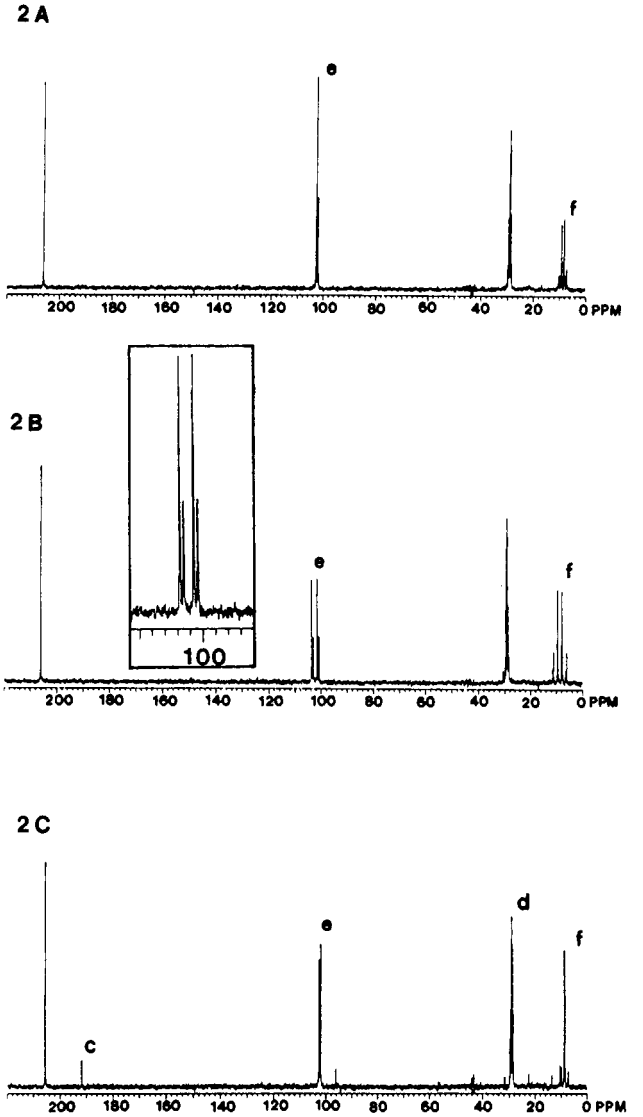


Figure 2. (A) ^{13}C NMR spectrum taken immediately after mixing 1.0 equiv of dimethyldioxirane with [2,8-$^{13}C_2$]menthofuran, and the sample maintained at −20 °C. (B) The same sample proton-coupled. (C) The same sample (decoupled) at −10 °C.

Results and Discussion

In order to determine sites of oxidation, menthofuran (7) was synthesized that contained ^{13}C at C-2 and C-8 as shown in Scheme I. The synthesis was based on a sequence described by Jennings et al.,[9] with incorporation of ^{13}C from [^{13}C]methyl iodide in the Grignard addition step (see the Experimental Section). Based on EIMS with selected ion monitoring (SIM) of the parent ions of the final product, menthofuran, the mole fraction (expressed as percent) of molecules that contained two, one, and zero atoms of ^{13}C above natural abundance was 96.3%, 2.8%, and 0.9%, respectively.

Reactions of menthofuran with dimethyldioxirane in acetone-d_6 were followed by both ^1H and ^{13}C NMR. The ^1H NMR spectrum taken immediately after mixing 0.35 equiv dimethyldioxirane with menthofuran at −40 °C (Figure 1A) showed new singlets at 1.8 and 9.60 ppm for the γ-keto enal, 2(*Z*)-(2′-keto-4′-methylcyclohexylidene)-

(8) McClanahan, R. H.; Thomassen, D.; Slattery, J. T.; Nelson, S. D. *Chemical Res. Toxicol.* **1989**, *2*, 349. Madyastha, K. M.; Raj, C. P. *Biochem. Biophys. Res. Commun.* **1990**, *173*, 1086.

(9) Jennings, P. W.; Campbell, W. H.; Gingerich, S. B. *J. Labeled Comp. Radiopharm.* **1980**, *18*, 1605.

propanal (8). These same signals are observed in the ^1H NMR spectra of the γ-keto enal prepared by another route (refer to the Experimental Section). Upon warming from −40 °C to −20 °C (Figure 1B), two new singlets appeared at 5.41 and 5.77 ppm. These chemical shift values are similar to the hemiacetal proton of the 8,9-epoxide of aflatoxin B_1 (H8: 5.48 ppm)[2] and are likely the hemiacetal protons in diastereomeric epoxides (9) formed from menthofuran. Two new doublets appear at 0.86 and 1.62 ppm and are interpreted to represent the chemical shifts for hydrogens on methyl groups attached to the epoxide ring diastereomers.

Results of ^{13}C NMR studies with [2,8-$^{13}C_2$]menthofuran helped substantiate results of the ^1H NMR studies. Immediately after mixing dimethyldioxirane with menthofuran at −40 °C, a new resonance signal at 193 ppm appeared (Figure 1C), for the ^{13}C signal of the carbonyl carbon of an α,β-unsaturated aldehyde.[10] Resonance absorption for the ^{13}C-labeled methyl group occurs at approximately 31.4 ppm, near to the resonance signals of the acetone (solvent) methyl groups. Upon warming from −40 °C to −20 °C, new peaks appeared at 103.6 and 104.2 ppm for epoxide ^{13}C hemiacetal carbon atoms (one signal for each possible diastereomer), and peaks appeared at 10.4 and 11.9 ppm for their ^{13}C labeled methyl groups (Figure 1D).

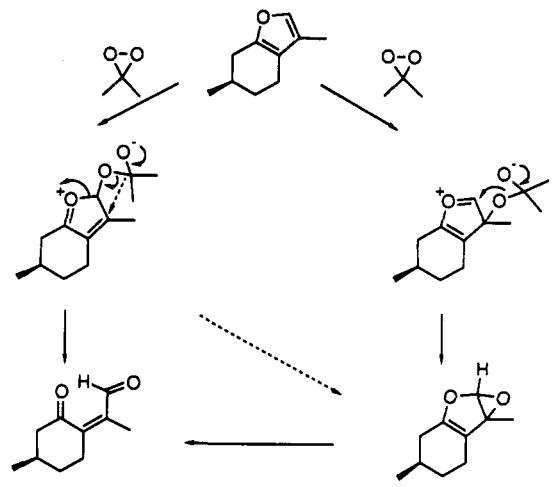
In a separate experiment, an equimolar amount of dimethyldioxirane was used in an attempt to increase the concentration of the products so that ^{13}C–^1H decoupling experiments could be carried out to correlate epoxide protons and carbon atoms. Interestingly, at −20 °C only resonance signals for the epoxide were observed (Figure 2A). The corresponding fully proton-coupled spectrum (Figure 2B) confirms that the epoxide hemiacetal carbon of each diastereomer is coupled to the hemiacetal hydrogen (two singlets become two doublets, $J_{^{13}C}$ = 167 Hz). When this sample was warmed to −10 °C, resonance signals for the γ-keto enal appeared (Figure 2C), which indicated that the furan epoxide rearranged to the γ-keto enal.

Additional evidence for the formation of the epoxide was obtained by FAB MS of a reaction of 1.1 equiv of dimethyldioxirane with menthofuran in acetone. The reaction temperature was maintained at −78 °C while it was added to 3-nitrobenzyl alcohol on the probe immediately before insertion into the ion source. The major ions observed in the spectrum occurred at m/z 167 (relative abundance = 100%) and m/z 149 (relative abundance = 96%). All other ions had a relative abundance of 20% or less. The ion at m/z 167 could represent protonated molecular ions of menthofuran epoxide and/or the isomeric γ-keto enal. However, the protonated γ-keto enal does not lose water under these conditions, whereas the protonated epoxide could dehydrate to generate the ion at m/z 149. Support for this possibility is the apparent generation of small amounts of a diepoxide of menthofuran (MH^+ = m/z 183) under the reaction conditions, that dehydrates to yield an ion at m/z 165.

Around 20 °C the γ-keto enal and/or the epoxides rearranged to form mint lactones that were further oxidized either in air or by excess dimethyldioxirane to hydroxy mint lactones (data not shown). These compounds have been observed previously as products of both the chemical[4,11] and metabolic[7,12] oxidation of menthofuran.

(10) Kalinowski, H.-O. *Carbon-13 NMR Spectroscopy*; John Wiley and Sons, Ltd.: New York, 1988; p 195.
(11) Hirsch, J. A.; Eastman, R. H. *J. Org. Chem.* **1967**, *32*, 2915. Foote, C. S.; Wuestoff, M. T.; Burstain, I. G. *Tetrahedron* **1967**, *23*, 2601.
(12) Thomassen, D.; Knebel, N.; Slattery, J. T.; McClanahan, R. H.; Nelson, S. D. *Chem. Res. Toxicol.* **1992**, *5*, 123.

Scheme II



Mechanisms for the oxidation of menthofuran by dimethyldioxirane to the γ-keto enal and a furan epoxide are shown in Scheme II. Because of the polarized double bonds in furans, we have invoked ionic intermediates that may arise from a transition state less symmetrical than the "butterfly" transition state suggested previously.[6] We do not know why the formation of the γ-keto enal predominates at low temperatures (−80 °C to −40 °C) whereas epoxide formation with subsequent sigmatropic ring opening to the γ-keto enal predominates at higher temperatures (−20 °C to +20 °C). Electronically, the favored reaction may be epoxide formation, but proper overlap of the interacting orbitals for epoxide formation may require more thermal energy. Alternatively, as suggested by a reviewer, less stable regioisomeric epoxides at the tetrasubstituted double bond may be formed preferentially at lower temperatures that yield the γ-keto enal. Since ^{13}C was not incorporated into the bridgehead positions, we would not have detected the presence of these epoxides.

Experimental Section

General. Gas chromatography was performed on a fused silica capillary column (60-m × 0.32-mm i.d.) coated with DB-5 (J and W Scientific, Folsom, CA). Helium was used as a carrier gas (head pressure 15 psi), and the injector and detector blocks were maintained at 250 °C. The oven was held at 60 °C for 3 min following splitless injection, after which a linear ramp of 10 °C/min was initiated until a temperature of 150 °C was reached. All flash column chromatography separations were performed on silica gel (230–400 mesh, 60 Å) (Aldrich) with an exception for purification of menthofuran in which Florisil (60–100 mesh) (Aldrich) was used. Menthofuran was purchaded from Eastman Kodak Co. (Rochester, NY). (*R*)-(+)-3-Methylcyclohexanone (1) was obtained from Aldrich Chemical Co. Inc. (Milwaukee, WI) and was optically pure, $[\alpha]^{25}$ = 13.5° (neat). Iodomethane-^{13}C (99 atom % ^{13}C) was obtained from Aldrich. All other chemicals were obtained from J. T. Baker Chemical Co. (Phillipsburg, NJ) or Aldrich. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$. Methylene chloride was distilled from phosphorus pentoxide after drying over calcium chloride.

Low-Temperature NMR. Acetone-d_6 was used as a solvent for the low-temperature ^1H and ^{13}C NMR studies. Menthofuran (22 mg, 0.147 mmol) was dissolved in 100 μL of acetone-d_6 in an NMR tube and cooled to −78 °C in dry ice/acetone. To this was added 800 μL of dimethyldioxirane-d_6 solution (previously cooled to −78 °C). The air in the tube was replaced with nitrogen gas and the sample was kept at −78 °C in dry ice/acetone. ^1H NMR spectra were recorded at temperatures ranging from −78 °C to +20 °C with a 5-min equilibrium period following every 20 °C increment. Little reaction occurred until the sample reached approximately −40 °C. For ^{13}C NMR the sample was prepared in the same way except that [2,8-$^{13}C_2$]-(*R*)-menthofuran was used.

FAB MS. FAB mass spectra were obtained using a VG70SEQ Tandem Hybrid mass spectrometer. A neutral xenon beam was used at 8 keV energy, and the accelerating potential of the ions was 8 kV. Magnetic field scanning from m/z 50 to 1200 was repeated at 10-s intervals. A 1-μL sample of approximately 80 mM solution of menthofuran and dimethyldioxirane in acetone was kept at −78 °C and was mixed with 2 μL of 3-nitrobenzyl alcohol as the matrix on the stainless steel target of the FAB probe. The probe was immediately inserted into the ion source of the mass spectrometer.

GS/MS. GC conditions were the same as described for GC analysis except an analytical DB-5 (30-m × 0.32-mm) column was used. (*R*)-(+)-3-Methylcyclohexanone was used as the internal standard. Mass spectrometer conditions were ion source temperature, 200 °C; emission current, 200 μA; accelerating voltage, 8 kV. Spectra were recorded at a nominal resolution of $M/\Delta M$ = 1000 (10% valley). High-resolution mass spectra were obtained at a resolution of 20 000 over a range of 50–250 amu with perfluorokerosene as a standard.

Methyl 4(*R*)-methyl-2-oxocyclohexanecarboxylate (2): ^{1}H NMR δ 12.10 (s, 1 H, exchanges with D_2O, enol OH), 3.75 (s, 3 H, $COCH_3$), 1.70–2.36 (m, 7 H, cyclohexyl hydrogens), 1.03 (d, 3 H, J = 6.0 Hz, $CHCH_3$).

Ethylene ketal of methyl 4(*R*)-methyl-2-oxocyclohexanecarboxylate (3): ^{1}H NMR δ 3.90–3.96 (m, 4 H, $-OCH_2CH_2O-$), 3.68, 3.67 (2 s, 3 H, diastereomeric CO_2CH_3), 2.55–2.72 (m, 1 H, $CHCO_2CH_3$), 1.20–1.94 (m, 7 H, cyclohexyl hydrogens), 0.94, 0.90 (2 d, 3 H, J = 6.5 Hz, diastereomeric ring methyl hydrogens); ^{13}C NMR δ 172.68 ($^{13}COCH_3$), 109.03 (ketal carbon), 65.10, 64.74 ($-O^{13}CH_2{}^{13}CH_2O-$).

Ethylene ketal of 1(*R*/*S*)-[2-([1,3-$^{13}C_2$]-2-hydroxylpropyl)]-4(*R*)-methyl-2-oxocyclohexane (4): ^{1}H NMR δ 4.78, 4.47 (2 d, 1 H, exchange with D_2O, diastereomeric OH), 3.85–4.09 (m, 4 H, $-OCH_2CH_2O-$), 1.37–1.57 (4 partially overlapping d, 6 H, $C(OH)(13CH_3)_2$), 0.86, 0.95 (2 d, 3 H, diastereomeric ring methyl hydrogens); ^{13}C NMR δ 31.0, 28.5 (two diastereomeric methyl carbons); IR 3495.5 cm^{-1} (OH).

Ethylene ketal of 1(*R*/*S*)-[2-([1,3-$^{13}C_2$]-1-propenyl)]-4-(*R*)-methyl-2-oxocyclohexane (5): ^{1}H NMR δ 4.84 (m, 2 H, $J_{^{13}C,H}$ = 153.89 Hz, vinylic protons), 3.82–3.94 (m, 4 H, $-OCH_2CH_2O-$), 2.20 (m, 1 H, $CHC(CH_3)=CH_2$), 2.81 (dd, 3 H, $J_{^{13}C,H}$ = 122.79 Hz, $J_{C(CH_3),CH_2}$ = 6.00 Hz, $C(CH_3)=CH_2$), 0.91 (d, 3 H, J = 6.2 Hz, ring methyl hydrogens); ^{13}C NMR δ 113.21 ($C(CH_3)=^{13}CH_2$), 23.46 ($^{13}C(CH_3)=CH_2$); IR 3083.5 (=CH), 1644.0 cm^{-1} (C=C).

Ethylene ketal of epoxide 6: ^{1}H NMR δ 3.82–4.05 (m, 4 H, $-OCH_2CH_2O-$), 2.17–3.15 (m, 2 H, $(CH_3)COCH_2$), 1.05–1.61 (3 dd, 3 H, $(CH_3)CO$), 0.90 (d, J = 6.4 Hz, ring methyl hydrogens); ^{13}C NMR δ 55.78, 53.49, 52.30 ($CO^{13}CH_2$), 22.24, 20.45, 18.99 ($(^{13}CH_3)COCH_2$); IR 948.7, 936.7, 846.0, 818.8, 803.1 cm^{-1} (epoxide).

[2,8-$^{13}C_2$]-(*R*)-Menthofuran (7): ^{1}H NMR δ 7.04 (d, 1 H, J = 198.22 Hz, furan proton), 2.93 (ddd, 3 H, J = 126.78, 7.38, 1.31 Hz), 1.09 (d, 3 H, J = 6.67 Hz, ring methyl hydrogens); ^{13}C NMR δ 136.64 (2^{13}C), 8.22 (8^{13}C); GC, the retention time was the same as a standard sample; GC/MS m/z 152 $[M]^{\cdot+}$, 137 $[M - CH_3]^+$, 110 $[M - C_2H_2O]^+$ (base peak). Selected ion monitoring (SIM) revealed that the incorporation of two ^{13}C atoms was 96.34%. HRMS: required 152.1229 ($C_8{}^{13}C_2H_{14}O$), found 152.1256.

2(*Z*)-(2′-Keto-4′-methylcyclohexylidene)propanal. The γ-keto enal was prepared according to Manfredi et al.[4] A solution of 1.1 g (6.7 mmol) of menthofuran and 1.3 g (7.4 mmol) of *m*-CPBA in 50 mL of CH_2Cl_2 was stirred at 25 °C for 15 min. The reaction was washed successively with 10% $Na_2S_2O_3$, 10% $NaHCO_3$, and brine and dried over anhydrous K_2CO_3. The excess of *m*-CPBA was removed by passing the organic layer rapidly through a column containing activated alumina. Evaporation of the solvent at reduced pressure yielded 0.86 g of a crude product as a pale yellow oil: ^{1}H NMR δ 9.65 (s, 1 H), 1.82 (s, 3 H), 1.03 (d, 3 H); ^{13}C NMR δ 200.1, 185.0, 151.3, 144.5, 41.2, 31.7, 29.6, 21.7, 20.8, 8.4.

Registry No. 1, 13368-65-5; 2, 13368-66-6; 3 (isomer 1), 139238-79-2; 3 (isomer 2), 139238-81-6; 4 (isomer 1), 139131-57-0; 4 (isomer 2), 139238-82-7; 5 (isomer 1), 139131-58-1; 5 (isomer 2), 139238-83-8; 6, 139131-59-2; 7, 139131-60-5; 8, 132183-58-5; 9 (isomer 1), 139131-61-6; 9 (isomer 2), 139238-80-5.

Chiral Base-Induced [2,3] Wittig Rearrangement of Acyclic α-(Propargyloxy)acetic Acids and Amides

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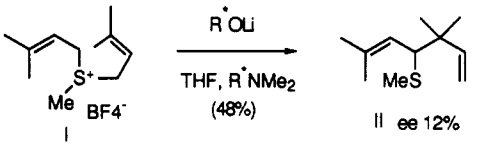
Received November 13, 1991

Base-initiated [2,3] sigmatropic rearrangements have only recently been employed to effect stereoselective transformations in acyclic systems.[1] Rearrangements of allylic ethers ([2,3] Wittig)[2] and sulfonium salts are especially important as they effect carbon chain homologation, often with high diastereoselectivity. Nonracemic allylic ethers and sulfonium salts rearrange with essentially complete 1,3-stereocenter transfer.[2,3] In some cases chiral auxiliaries have been employed to effect enantioselective rearrangements of otherwise achiral allylic ethers.[4] In principle, such rearrangements might be effected with a chiral base. However, to date only a few examples of this approach have been recorded.

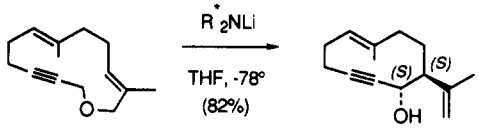
Trost was the first to examine chiral base initiated [2,3] rearrangement of a sulfonium salt.[5] He found that treatment of the bis-allylic system I with the Li alkoxide of (*S*)-1-phenyl-2,2,2-trifluoroethanol in the presence of a chiral amino ether cosolvent afforded the rearranged sulfide II of undetermined absolute configuration with an ee of 12% (eq 1). Some years later we effected a [2,3]



I II ee 12% (1)

R*OLi = (S)-PhCH(CF$_3$)OLi, R*NMe$_2$ = (S,S)-[Me$_2$NCH$_2$CH(OMe)]$_2$

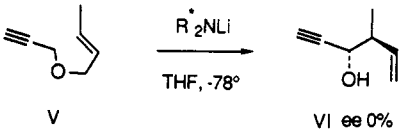
Wittig rearrangement of the 13-membered allylic ether III with lithiated bis[(*S*,*S*)-1-phenylethylamine] affording the ring-contracted propargylic alcohol IV of 70% ee (eq 2).[6]



III IV ee 70% (2)

R*$_2$NLi = (S,S)-[PhCH(CH$_3$)]$_2$NLi

However, a 17-membered homologue of III gave the corresponding 14-membered propargylic alcohol of only 30% ee, and the acyclic ether V rearranged to the racemic alcohol VI (eq 3). We also found that the acyclic α-(al-



V VI ee 0% (3)

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