Electrocyclic Ring Opening of a β-Lithiocyclopropyloxirane. Generation and Trapping of (2Z,4E)-Cyclohepta-2,4-dienol

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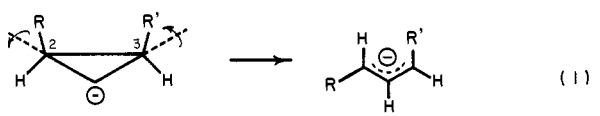
Abstract: A novel concerted electrocyclic ring opening of a β-lithiocyclopropyloxirane is described. Metalation of *exo*-7-bromobicyclo[4.1.0]hept-2-ene *anti*-oxide (**3**) with *n*-butyllithium at 0 °C afforded *exo*-bicyclo[3.2.0]hept-6-en-2-ol (**4**). A mechanism involving conrotatory ring opening of the metalated cyclopropane (**6**) to (*Z*,*E*)-cycloheptadiene oxide **7** followed by conrotatory ring closure is proposed to explain the formation of **4**. Evidence for the intermediacy of (*Z*,*E*)-diene **7** was obtained by trapping with 1,3-diphenylisobenzofuran (**8**) to afford the four stereoisomeric trans-fused Diels–Alder adducts **9a–d**. The structure and ring juncture stereochemistry of adducts **9** were established by conversion to the known *trans*-cycloheptene adduct **13**. When metalation of bromocyclopropyl epoxide **3** was carried out at −70 °C, the major products were 2,5-di-*n*-butylcyclohept-3-en-1-ol (**14**) and 4,5-di-*n*-butylcyclohept-2-en-1-ol (**15**). These compounds are evidently formed by addition of *n*-butyllithium to the trans double bond of **7** giving allylic carbanion **16**, which undergoes alkylation with *n*-butyl bromide at the termini of the allyl anion.

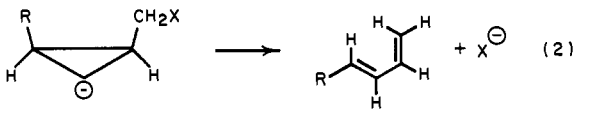
The electrocyclic ring opening of cyclopropyl carbanions to allyl anions (eq 1) has been a topic of considerable interest.[1] Although



(1)

thermodynamically favored and orbital-symmetry allowed in a conrotatory mode,[2] this transformation evidently has a relatively high activation energy. Thus, cyclopropyllithium, cyclopropylmagnesium halides, and their alkyl derivatives are quite stable at room temperature.[3] Only when aryl or electron-withdrawing groups are situated at both the 2- and 3-positions to stabilize the incipient negative charge does ring opening occur readily.[1b,d-k] For example, the cyclopropyllithium reagent formed by metalation of 2,3-diphenylcyclopropanecarbonitrile with lithium diisopropylamide is stable at −78 °C but isomerizes to the allyl anion at −25 °C.[1j]

In the course of our investigations on the cyclization of lithiated cyclopropyl epoxides,[4] we have discovered a novel rearrangement which is initiated by a facile, concerted ring opening of a β-metalated cyclopropylcarbinyl derivative (eq 2). Evidently the



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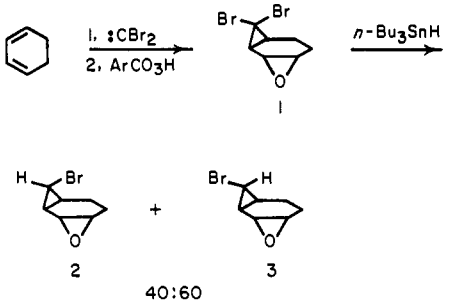
activation barrier to this electrocyclic reaction can be lowered substantially by simultaneous departure of a leaving group to form a 1,3-diene. The driving force of the reaction under the orbital symmetry constraint of conrotation generates in the present case a highly strained (2*Z*,4*E*)-cycloheptadiene derivative as a transient intermediate.

Results and Discussion

Cyclopropanation of 1,3-cyclohexadiene with 1 equiv of dibromocarbene[5] followed by epoxidation with *m*-chloroperoxybenzoic acid afforded exclusively the *anti*-dibromocyclopropyl epoxide **1**. Selective reduction of one bromo substituent with tri-*n*-butyltin hydride in benzene[6] gave rise to a 40:60 mixture of endo and exo isomers (**2** and **3**) (eq 3) in 47% overall yield from



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1,3-cyclohexadiene. The exo isomer was readily obtained in suitably pure form by crystallization at −25 °C.

exo-Bromocyclopropyl epoxide **3** was treated with *n*-butyllithium in tetrahydrofuran (THF) at 0 °C with the expectation[4] that the resulting cyclopropyllithium reagent might undergo cyclization with inversion of configuration to give either (or both) tricyclo[4.1.0.0^{6,7}]heptan-3-ol or (and) *endo*-tricyclo[2.2.1.0^{3,7}]-heptan-2-ol. Instead a rearrangement occurred which afforded the known[7] *exo*-bicyclo[3.2.0]hept-6-en-2-ol (**4**) in 24–36% yield.

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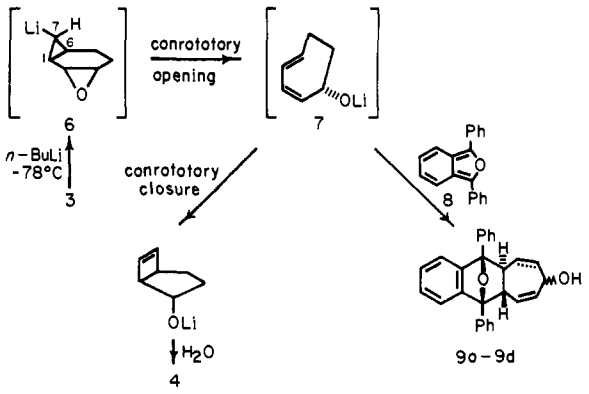
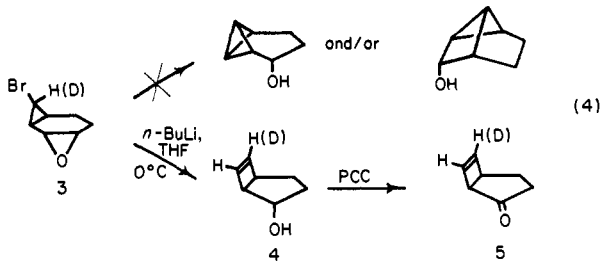
Scheme I



The identity of the product was first revealed by correspondence of ^{1}H NMR data[8] and was confirmed by pyridinium chlorochromate (PCC) oxidation[9] to ketone **5**, an authentic sample of which was available in our laboratory (eq 4).[10]



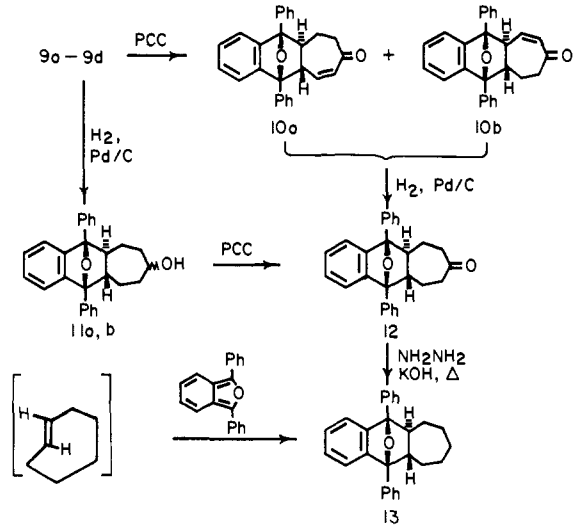
(4)

A deuterium labeling experiment was carried out to determine the location of the carbon derived from C-7 of **3** and whether a symmetrical intermediate might have been formed in the rearrangement. 7-Deuteriobromocyclopropyl epoxide **3-*d*** was prepared by reduction of **1** with tri-*n*-butyltin deuteride. Lithiation of **3-*d*** with *n*-butyllithium gave rise to **4-*d***, which was oxidized to **5-*d***. The ^{1}H NMR spectrum of the latter showed clearly that the deuterium label resided in only one of two nonequivalent vinyl positions. The placement of the label at C-6 is based upon the mechanism proposed below. When the lithiation of **3** was followed by addition of D_2O, no deuterium was incorporated into the resulting rearrangement product.

The rearrangement of **3** to **4** under the influence of *n*-butyllithium is unprecedented, the closest apparent analogy being the ring expansion of cyclopropylcarbenes to cyclobutenes.[11] However, the complete retention of deuterium in the lithiation–rearrangement of **3-*d*** and the absence of deuterium incorporation in the D_2O quench seems to exclude various conceivable carbene rearrangement or insertion mechanisms.

It is very likely that the initial step in the mechanism is rapid bromine–lithium exchange with retention of configuration to form *exo*-cyclopropyllithium **6**.[4,12] A mechanism for the rearrangement consistent with the labeling experiments involves conrotatory ring opening of the cyclopropyllithium with concomitant epoxide cleavage to form a (*Z,E*)- or (*E,Z*)-cyclohepta-2,4-dienyl oxide, which then undergoes rapid conrotatory cyclization to *exo*-bicyclo[3.2.0]hept-6-ene 2-oxide (see Scheme I). The strain energy associated with the *E* double bond in a seven-membered ring would presumably provide sufficient driving force to form the cyclobutene ring. (*E,Z*)-1,3-Cycloheptadiene has in fact been postulated as an intermediate in the thermal rearrangement of tricyclo[3.1.0.0^{6,7}]heptane to bicyclo[3.2.0]hept-6-ene[13] and in the thermal ring opening of the latter.[14] The strained (*E,Z*)-diene has recently been detected in the photochemical cyclization of 1,3-cycloheptadiene in a matrix at 20 K.[15] Two conrotatory ring-opening pathways are possible leading to (*Z,E*)-cyclohepta-2,4-diene oxide (**7**) or its *E,Z* isomer.

Scheme II



Direct evidence for the ring-opening mechanism was obtained by interception of the proposed (*Z,E*)-diene intermediate. Reaction of **3** with *n*-butyllithium at −70 °C in the presence of diphenylisobenzofuran **8** afforded trans fused Diels–Alder adducts **9** (36%). Evidently all four possible modes of addition to the *E* double bond occur to form an inseparable mixture of four isomers differing in the position of the double bond and the stereochemistry of the hydroxyl group.

The structure and stereochemistry of the adducts **9** were established by the reactions and correlation illustrated in Scheme II. Oxidation of **9** with pyridinium chlorochromate afforded a 65:35 mixture of two α,β-enones (**10a + 10b**). The conjugated nature of these enones showed conclusively that the Diels–Alder reaction with **8** had occurred at the 4,5-double bond of the 2,4-cycloheptadiene oxide intermediate **7**. A mixture of two epimeric alcohols (**11a,b**) was obtained by catalytic hydrogenation of **9**. Catalytic hydrogenation of **10a,b** and pyridinium chlorochromate oxidation of **11a,b** gave the same saturated ketone **12** as a single, sharp-melting isomer.

Conversion of **12** to the known[16a] diphenylisobenzofuran adduct (**13**) of (*E*)-cycloheptene was accomplished by Wolff–Kishner reduction. The identification of the product as the trans fused isomer **13** is based upon the agreement of melting points (147–149 °C; lit.[16a] 148–150 °C) and direct comparison of IR and ^{1}H NMR spectra.[17] The known cis (endo,endo) isomer of **13** has a distinctly different melting point (189–192 °C).[18] The appearance of three one-proton absorptions in the 360-MHz ^{1}H NMR spectrum of **13** is further evidence against either of the symmetrical cis isomers.

A deuterium labeling experiment provided further support for the intermediacy of (*Z,E*)-diene oxide **7**. Lithiation of **3-*d*** in the

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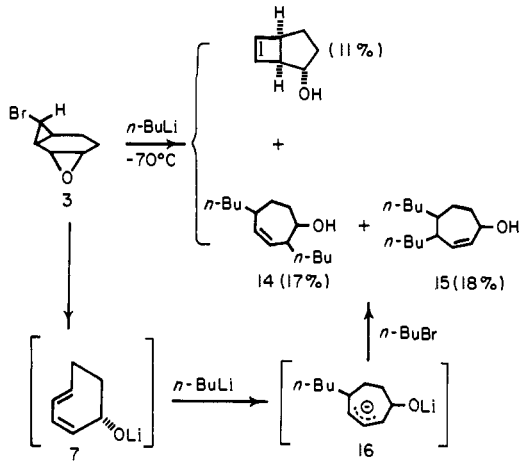
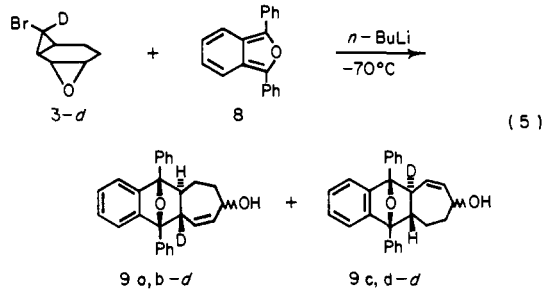
Scheme III



presence of diphenylisobenzofuran afforded labeled adducts **9a–d-d** (eq 5).[19] The absence of the absorption (δ 2.6) attributable to



(5)

the allylic hydrogen in the ^{1}H NMR spectrum of the product indicates the position of the deuterium atom at the trans ring fusion in the adduct and at C-4 on the *E* double bond of its precursor.

When the metalation of **3** with *n*-butyllithium was conducted at −70 °C in the absence of **8**, the isolated yield of bicyclic alcohol **4** was reduced considerably (11%). The main products under these conditions were 2,5-di-*n*-butylcyclohept-3-en-1-ol (**14**) and 4,5-di-*n*-butylcyclohept-2-en-1-ol (**15**). Small amounts (10–15%) of **14** and **15** were subsequently detected along with bicyclic alcohol **4** in the product mixture from lithiations carried out at 0 °C and accompanying adducts **9** from reactions performed in the presence of **8** at −70 °C.

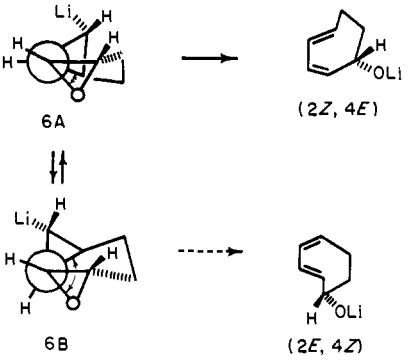
Each of the two regioisomeric dibutyl cycloheptenols was obtained as a single stereoisomer. The gross structures of the compounds are apparent from their molecular weights (MS, M^+ 224) and ^{1}H NMR spectra (two *n*-butyl groups and two vinyl protons). The assignments were confirmed by oxidation of **14** to a β,γ-enone and **15** to an α,β-enone. No evidence is available to allow the assignment of the relative stereochemistry of the three substituents.

A reasonable mechanism to explain the formation of the dibutyl cycloheptenols is shown in Scheme III. Addition of unreacted *n*-butyllithium to the highly strained *E* double bond of **7** would give rise to allylic carbanion **16** (or corresponding isomeric allyllithium reagents). Alkylation of **16** with *n*-butyl bromide generated in the initial bromine–lithium exchange at the termini of the allylic carbanion leads to **14** and **15**. Although the apparent facility of the reaction of **16** with *n*-butyl bromide (15 min at −70 °C) seems surprising at first sight, the mechanism of this coupling reaction need not occur via a traditional S_N2 transition state. A pathway involving electron transfer from **16** to butyl bromide, bromide dissociation, and radical coupling would appear to be a reasonable alternative.

A series of reactions of **3** with varying amounts and concentrations of *n*-butyllithium and in the presence of added *n*-butyl bromide was carried out to determine the effect on the yield of **14** and **15**. The isolated yields of these dibutylated products (17–19% of **14** and 18–19% of **15**) did not change appreciably in three reactions with 1.2 equiv (0.07 M), 8 equiv (1.2 M), and 34 equiv (1.3 M) of *n*-butyllithium in THF at −78 °C. Lithiation of **3** with 5 equiv of *n*-butyllithium in the presence of 3 and 10 equiv of *n*-butyl bromide resulted in a slight increase in the yields of **14** and **15** (22% each). Although the lack of an appreciable change in the yields of **14** and **15** in these experiments is somewhat surprising, the kinetics of the various competing reactions may be complex and there seems to be no reason to doubt the validity of the mechanism proposed in Scheme III.[20]

The double ring opening of a β-lithiocyclopropyloxirane such as **6** to an unstrained lithium dienyl alkoxide must be a highly exothermic process. For example, we estimate that the enthalpy change attending cyclopropyl anion → dienyl alkoxide anion isomerization is ca. 61 kcal/mol on the basis of strain energies, bond energies, and relative anion stability.[21] Although this estimate should represent an upper limit, ignoring as it does the effects of bonding to lithium, it appears that sufficient driving force is available to create the strained *E* double bond of **7**.

Two different conrotatory ring opening pathways are potentially available to **6**, one leading to (2*Z*,4*E*)-dienyl alkoxide **7** and the other to its 2*E*,4*Z* isomer (eq 6). The apparently exclusive



(6)

generation of **7** may be attributed to stereoelectronic control. Two conformations (**6A** and **6B**) of **6** differing in the dihedral angle (ϕ) between the internal cyclopropane ring bond (C-1/C-6) and the adjacent C–O bond of the epoxide are possible. The more favorable alignment of these bonds in **6A** ($\phi \sim 45°$) compared to **6B** ($\phi \sim 90°$) evidently directs the conrotatory ring opening to **7**, albeit via a syn elimination of the C–O bond.

The facility (complete in 5 min at −95 °C) of this cyclopropyl "carbanion" ring opening is remarkable and contrasts sharply with the stability of alkyl-substituted cyclopropyllithium reagents.[3c-f] It is therefore clear that the ring opening is concerted; i.e., the transition-state energy is lowered by interaction with the C–O bond of the epoxide. This reaction may be regarded as a forerunner of a general class of β-metallocyclopropylcarbinyl → 1,3-butadiene fragmentation reactions. Other combinations of electrocyclic transformations with Grob-type heterolytic fragmentations can be readily conceived.

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are not corrected. All boiling points are uncorrected. ^{1}H NMR spectra were obtained with either a

(19) We thank Neris Pupius, who carried out this reaction under the supervision of L.A.L.

(20) The total recovery of characterizable products was generally 40–50% in all of the lithiation reactions of **3**. Most of the remaining material was evidently a complex mixture of polar byproducts which were difficult to elute from the silica gel column used to isolate the major products. Self-Diels–Alder reactions and/or anionic oligomerization of **7** may well compete with the formation of **4**, **9**, **14**, and **15** and give rise to a host of polar byproducts.

(21) Average bond energies, the strain energy of cyclopropane, and pK_a data were obtained from: Streitwieser, A., Jr.; Heathcock, C. H. "Introduction to Organic Chemistry", 2nd ed.; Macmillian: New York, 1981; pp 83, 669, 1195. The strain energy of oxirane was assumed to be the same as cyclopropane (i.e., 27 kcal/mol). The enthalpy change associated with the reaction cyclopropyl oxirane → 2,4-pentadien-1-ol is −23 kcal/mol. Assuming entropy changes are negligible, we estimate the enthalpy difference between the phenyl anion (a stand-in for the cyclopropyl anion) and a suitable alkoxide to be ca. −38 kcal/mol (1.4 ΔpK_a). Hence, the overall enthalpy change should be about −61 kcal/mol.

Varian EM-390 (90 MHz) or a Nicolet NT-360 (360 MHz) spectrometer. The frequency was 90 MHz unless specified otherwise. Infrared (IR) spectra were obtained with a Perkin-Elmer 137 sodium chloride spectrophotometer. Mass spectra were obtained on a Varian CH-5 mass spectrometer. Microanalyses were performed by J. Nemeth and associates in the University of Illinois Microanalytical Laboratory. Analytical gas chromatography (GC) was performed on a Varian Model 3700 gas chromatograph by using the following column: 1.8 m × 6.4 mm, 3% OV-17 on 100/120-mesh Chromosorb Q.

All reagents and solvents were reagent grade and used without further purification unless otherwise specified. Technical grade hexane and ethyl acetate used for flash chromatography were distilled prior to use. Tetrahydrofuran (THF) was distilled from the sodium ketyl of benzophenone. *n*-Butyllithium was obtained as a commercially prepared solution in hexane and was titrated prior to use.[22]

7,7-Dibromobicyclo[4.1.0]hept-2-ene. The method of Winstein and Sonnenberg[5] was used with some modification. A mixture of 41.5 g (0.520 mol) of 1,3-cyclohexadiene[23] and 100 g (0.89 mol) of potassium *tert*-butoxide in 500 mL of pentane was stirred and cooled at 0 °C as 131 g (0.520 mol) of bromoform was added over 1 h under nitrogen. After an additional 3 h at 0 °C, the mixture was poured into water. The organic product was extracted with three portions of pentane. The solution was washed with three portions of water, dried ($MgSO_4$), and evaporated under reduced pressure. Distillation of the residual liquid through a 15-cm Vigreux column gave 88.8 g (68%) of 7,7-dibromobicyclo[4.1.0]hept-2-ene as a light yellow liquid: bp 46–48 °C (0.25 mm) (lit.[24] bp 68–70 °C (0.8 mm)). The IR and ^1H NMR spectral data of the product correspond to those reported by Banwell and Halton.[25]

7,7-Dibromobicyclo[4.1.0]hept-2-ene *anti*-Oxide (1). The procedure described by Paquette and co-workers[26] was used. A mixture of 23.1 g (91.7 mmol) of 7,7-dibromobicyclo[4.1.0]hept-2-ene and 14.3 g (0.18 mol) of sodium bicarbonate in 350 mL of dichloromethane was stirred and cooled at 0 °C as a solution of 28 g (ca. 0.14 mol) of 80–90% *m*-chloroperoxybenzoic acid in 400 mL of dichloromethane was added over a 50-min period. After an additional 3 h at 0 °C and then overnight at room temperature, the mixture was washed with two portions of water, three portions each of saturated sodium metabisulfite solution, saturated sodium bicarbonate solution, and two portions of brine. The organic solution was dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallization of the residual solid from pentane gave 19.5 g (79%) of dibromocyclopropyl epoxide **1** as colorless crystals: mp 56–58 °C; IR (Nujol) ν_{max} 2880, 1350, 1265, 1205, 1065, 1030, 945, 920, 860, 810, 790, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.3 (m, 6 H), 3.16 (br s, 1 H, epoxide H), 3.32 (br s, 1 H, epoxide H).

Anal. Calcd for $C_7H_8Br_2O$: C, 31.38; H, 3.01; Br, 59.64. Found: C, 31.33; H, 2.99; Br, 59.82.

***endo*- and *exo*-7-Bromobicyclo[4.1.0]hept-2-ene *anti*-Oxide (2 and 3).** The procedure described by Seyferth and co-workers[6] was used with some modification. A solution of 40.2 g (0.150 mol) of dibromocyclopropyl epoxide **1** in 250 mL of benzene was stirred at room temperature as 43.7 g (0.150 mol) of tri-*n*-butyltin hydride was added dropwise under a nitrogen atmosphere. Stirring was continued at room temperature overnight, after which the solvent was evaporated under reduced pressure. Distillation of the residual liquid through a 15-cm Vigreux column gave 24.6 g (87%) of bromocyclopropyl epoxides **2** and **3** as a colorless liquid, bp 52–55 °C (0.05 mm), which solidified upon cold storage. Analysis by GC (100 °C, 40 mL/min, t_R = 3.3 and 3.8 min) indicated that the product was a 60:40 mixture of exo and endo isomers, respectively. Recrystallization from pentane gave *exo*-bromocyclopropyl epoxide **3** as colorless crystals, mp 46–48 °C. The spectral data for the endo isomer **2** are as follows: IR (film) ν_{max} 2950, 2900, 2850, 1460, 1430, 1370, 1270, 1220, 1120, 1040, 970, 930, 880, 840, 815, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.4 (m, 2 H, 2 bridgehead H), 1.8–2.2 (m, 4 H, 2 CH_2), 3.22 (br s, 2 H, 2 epoxide H), 3.28 (t, 1 H, J = 7 Hz, CHBr). The spectral data for the exo isomer **3** are as follows: IR (Nujol) ν_{max} 2900, 2850, 1460, 1375, 1265, 1250, 1225, 1190, 1020, 955, 915, 865, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–1.6 (m, 2 H, 2 bridgehead H), 1.7–2.1 (m, 4 H, 2 CH_2), 3.00 (6-line m, 2 H, 2 epoxide H), 3.38 (t, 1 H, J = 3.5 Hz, CHBr).

Anal. Calcd for C_7H_9BrO: C, 44.47; H, 4.80; Br, 42.47. Found: C, 44.53; H, 4.64; Br, 42.33.

Similar reduction of dibromocyclopropane **1** with tri-*n*-butyltin deuteride[27] gave a 40:60 mixture of labeled bromocyclopropanes **2**-*d* and **3**-*d*, respectively (0.92 g, 68%). The spectral data of the product are identical with those described for unlabeled **2** and **3**, with the exception of the disappearance of the triplets at δ 3.28 and 3.38 in the ^1H NMR spectrum.

***exo*-Bicyclo[3.2.0]hept-6-en-2-ol (4).** The previously described procedure[4b] was used with some modification. A solution of 1.00 g (5.29 mmol) of *exo*-bromocyclopropyl epoxide **3** in 25 mL of THF was stirred and cooled at 0 °C as a 17.6-mL portion (42.3 mmol) of 2.46 M *n*-butyllithium in hexane was added slowly under a nitrogen atmosphere. After 1.5 h at 0 °C, the solution was hydrolyzed by slow addition of water. The organic product was extracted with four portions of ether, the solution was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 1.08 g of a bright yellow liquid. Flash chromatography (120 g of silica gel, elution with 30% ethyl acetate–hexane) followed by distillation in a Kugelrohr oven at 100 °C (0.1 mm) gave 161 mg (28%) of the known bicyclic alcohol **4** as a colorless liquid; IR (film) ν_{max} 3300, 2900, 1460, 1320, 1270, 1160, 1065, 990, 940, 840, 740, 710 cm^{-1}. The ^1H NMR spectrum of the product corresponds to that reported by Svensson.[8]

Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.60; H, 9.12.

Small amounts (ca. 6% each) of dibutylcycloheptenols **14** and **15** were also isolated in other runs. The characterization of **14** and **15** will be described later. Similar reaction of **3**-*d* with *n*-butyllithium gave labeled **4**-*d* (82 mg, 25%). The spectral data of the product are similar to those reported for unlabeled **4**, with the major exception that the signal due to the vinyl protons (δ 5.95) has become a sharp singlet and been reduced to a single proton. Similar lithiation of **3** with *n*-butyllithium followed by quenching with D_2O gave unlabeled **4** (129 mg, 28%), whose spectral properties have been previously reported.

Bicyclo[3.2.0]hept-6-en-2-one (5). The method of Corey and Suggs[9] was used with some modification. A solution of 150 mg (0.70 mmol) of pyridinium chlorochromate in 1.2 mL of dichloromethane was stirred at room temperature as a solution of 51 mg (0.46 mmol) of bicyclic alcohol **4** in 0.5 mL of dichloromethane was added slowly under a nitrogen atmosphere. After 2 h at room temperature, the reaction mixture was poured into ether. The black, gummy precipitate was removed by filtration through a short (5 × 80 mm) column of silica gel. Evaporation of the solvent under reduced pressure gave 26 mg (52%) of bicyclic ketone **5**[10,28] as a colorless liquid; IR ($CHCl_3$) ν_{max} 3000, 1723 (C=O), 1525, 1430, 1210, 1040, 930 cm^{-1}. The ^1H NMR spectral data of the product correspond to those reported by Svensson.[8] The identity of the product was confirmed by direct comparison of IR and ^1H NMR spectra with those of an authentic sample.[10] Similar oxidation of deuterated alcohol 4-*d* gave labeled ketone **5**-*d* (45 mg, 74%). The ^1H NMR spectral data of the product correspond to those previously reported, with the exception that the signals due to the vinyl protons of **5** (doublets at δ 6.32 and 6.10) have simplified (singlet at δ 6.11) and decreased in area to a single proton in **5**-*d*.

(8*R*)- and (8*S*)-(5α,5aβ,10aα,11α)-5,11-Epoxy-5a,6,7,8,10a,11-hexahydro-5,11-diphenyl-5*H*-cyclohepta[*b*]naphthalen-8-ol (9a,b) and (8*R*)- and (8*S*)-(5α,5aα,10aβ,11α)-5,11-Epoxy-5a,6,7,8,10a,11-hexahydro-5,11-diphenyl-5*H*-cyclohepta[*b*]naphthalen-8-ol (9c,d). A solution of 2.25 g (11.9 mmol) of *exo*-bromocyclopropyl epoxide **3** and 3.22 g (11.9 mmol) of 1,3-diphenylisobenzofuran (**8**) in 100 mL of THF was stirred and cooled at −78 °C as a 5.6-mL portion (14 mmol) of 2.5 M *n*-butyllithium in hexane was added over a 25-min period under nitrogen. After an additional 30 min at ≤−70 °C, the reaction mixture was quenched by rapid addition of 4 mL of methanol, allowed to warm to room temperature, and poured into water. The organic product was extracted with three portions of ether, and the solution was dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave 5.2 g of a bright yellow wet solid. Flash chromatography (300 g of silica gel, elution with 30% ethyl acetate–hexane) followed by recrystallization from ethanol gave 1.64 g (36%) of allylic alcohols **9a-d** as white crystals: mp 148–161 °C; IR (Nujol) ν_{max} 3300, 2880, 2830, 1610, 1455, 1350, 1310, 1120, 1040, 1025, 995, 970, 820, 785, 765, 750, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.0 (m, 4 H, 2 CH_2), 1.80 (s, 1 H, OH), 2.3 (m, 1 H, bridgehead H), 2.6 (m, 1 H, bridgehead H), 4.34 (m, 0.65 H, C*H*OH of **9a,b**), 4.58 (m, 0.35 H, C*H*OH of **9c,d**), 5.3–5.8 (m, 2 H, 2 vinyl H), 6.9–7.2 (m, 4 H, benzo H), 7.3–7.7 (m, 10 H, phenyl H).

Anal. Calcd for $C_{27}H_{24}O_2$; C, 85.23; H, 6.36. Found: C, 84.91; H, 6.62.

Small amounts (ca. 6% each) of dibutylcycloheptenols **14** and **15** were also isolated in other runs. These compounds are described in detail

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below. Similar reaction of **3-*d*** with *n*-butyllithium in the presence of 1,3-diphenylisobenzofuran (**8**) gave labeled **9a–d-*d*** (210 mg, 34%), mp 147–159 °C. The spectral data of the product are similar to those reported for **9a–d**, with the exception of the disappearance of the signal from the allylic bridgehead proton (δ 2.6).

In a later run, excess maleic anhydride was added after the methanol quench but before warming to scavenge the unreacted diphenylisobenzofuran. Although this facilitated the purification of the adducts **9** by flash chromatography, it did not affect the isolated yield of product.

(5α,5aβ,10aα,11α)-5,11-Epoxy-5a,6,10a,11-tetrahydro-5,11-diphenyl-5*H*-cyclohepta[*b*]naphthalen-8-ol (10a) and (5α,5aα,10aβ,11α)-5,11-Epoxy-5a,6,10a,11-tetrahydro-5,11-diphenyl-5*H*-cyclohepta[*b*]naphthalen-8-ol (10b). A solution of 270 mg (1.25 mmol) of pyridinium chlorochromate in 16 mL of dichloromethane was stirred at room temperature as a solution of 298 mg (0.783 mmol) of allylic alcohols **9a–d** in 13 mL of dichloromethane was slowly added over a 15-min period under a nitrogen atmosphere. After an additional 1 h at room temperature, the reaction mixture was poured into ether. The dark, gummy precipitate was removed by filtration through a short (8 × 100 mm) silica gel column. Evaporation of the solvent under reduced pressure gave 300 mg of a fluffy white solid. Flash chromatography (35 g of silica gel, elution with 30% ethyl acetate–hexane) followed by recrystallization from ethanol gave 264 mg (89%) of α,β-enones **10a,b** as white crystals, mp 162–204 °C. Analysis by HPLC (3% THF–isooctane, 2.2 mL/min, t_R = 9.3 and 11.5 min) indicated the product was a 35:65 mixture of isomers, respectively: IR (Nujol) ν_{max} 2880, 2820, 1660, 1450, 1375, 1320, 1260, 1200, 1020, 1005, 990, 945, 810, 755, 715, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–2.8 (m, 5 H), 3.0 (5-line m, 0.65 H, allylic H of **10a**), 3.6 (m, 0.35 H, allylic H of **10b**), 5.95 (dt, 1 H, J = 12, 3 Hz, vinyl H_α), 6.72 (dd, 1 H, J = 12, 3 Hz, vinyl H_β), 7.0–7.2 (m, 4 H, benzo H), 7.3–7.7 (m, 10 H, phenyl H).

Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86. Found: C, 85.60; H, 5.91.

(8*R*)- and (8*S*)-(5α,5aα,10aβ,11α)-5,11-Epoxy-5a,6,7,8,9,10,10a,11-octahydro-5,11-diphenyl-5*H*-cyclohepta[*b*]naphthalen-8-ol (11a,b). A solution of 280 mg (0.74 mmol) of allylic alcohols **9a–d** in 30 mL of absolute ethanol was added to 30 mg of 5% palladium on carbon in one portion under a nitrogen atmosphere. The nitrogen was replaced by a hydrogen sweep and after stirring at room temperature for 2 h, the catalyst was removed by filtration through a short pad of celite. Evaporation of the solvent under reduced pressure gave 0.30 g of a white solid. Recrystallization from ethanol gave 247 mg (88%) of epimeric alcohols **11a,b** as white crystals: mp 145–158 °C; IR (Nujol) ν_{max} 3400, 2880, 1690, 1455, 1375, 1345, 1315, 1010, 990, 752, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–2.7 (m, 10 H), 1.30 (s, 1 H, OH), 3.82 (apparent quintet, 1 H, J_{app} = 9 Hz, C*H*OH), 7.13 (s, 4 H, benzo H), 7.3–7.8 (m, 10 H, phenyl H).

Anal. Calcd for $C_{27}H_{26}O_2$: C, 84.78, H, 6.85. Found: C, 84.88; H, 6.83.

(5α,5aα,10aβ,11α)-5,11-Epoxy-5a,6,7,10,10a,11-hexahydro-5,11-diphenyl-5*H*-cyclohepta[*b*]naphthalen-8-ol (12). (A) By Reduction of 10a,b. Catalytic hydrogenation of 208 mg (0.550 mmol) of enones **10a,b** according to the preceding procedure for the preparation of **11a,b** afforded 0.20 g of a white solid. Flash chromatography (30 g of silica gel, elution with 25% ethyl acetate–hexane) followed by recrystallization from ethanol gave 174 mg (83%) of ketone **12** as white crystals: mp 193–195 °C; IR (Nujol) ν_{max} 2870, 2800, 1700, 1455, 1370, 1315, 1140, 1020, 990, 940, 765, 750, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8–2.1 (m, 6 H), 2.3–2.7 (m, 4 H, $(CH_2)_2C{=}O$), 7.15 (br s, 4 H, benzo H), 7.3–7.8 (m, 10 H, phenyl H).

Anal. Calcd for $C_{27}H_{24}O_2$: C, 85.23; H, 6.36. Found: C, 84.97; H, 6.57.

(B) By Oxidation of 11a,b. Pyridinium chlorochromate oxidation of 50 mg (0.13 mmol) of alcohols **11a,b** according to the procedure described for the preparation of enones **10a,b** afforded 48 mg of a yellow oil. Flash chromatography (8 g of silica gel, elution with 25% ethyl acetate–hexane) followed by recrystallization from absolute ethanol gave 41 mg (83%) of previously described ketone **12**.

(5α,5aα,10aβ,11α)-5,11-Epoxy-5a,6,7,8,9,10,10a,11-octahydro-5,11-diphenyl-5*H*-cyclohepta[*b*]naphthalene (13). A solution of 56.5 mg (0.148 mmol) of ketone **12** and 94 mg (1.4 mmol) of 85% potassium hydroxide in 2.0 mL of diethylene glycol and 0.50 mL (8.5 mmol) of 85% hydrazine hydrate was stirred and heated at 120 °C for 3 h and then at 210 °C for 7 h. The reaction mixture was cooled and poured into water. The organic product was extracted with four portions of ether, and the solution was dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave 96 mg of a yellow oil. Flash chromatography (9 g of silica gel, elution with 3% ethyl acetate–hexane) followed by recrystallization from ethanol gave 40 mg (74%) of *trans*-cycloheptene adduct **13** as white crystals: mp 147–149 °C (lit.[16a] mp 148–150 °C); IR (Nujol) ν_{max} 2980, 2860, 1600, 1490, 1440, 1340, 1310, 1260, 1090, 1015, 970, 915, 805, 770, 740, 705 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.0–1.7 (m, 9 H), 1.89 (m, 1 H), 1.97 (m, 1 H), 2.44 (m, 1 H), 7.09 (s, 4 H, benzo H), 7.2–7.7 (15-line m, 10 H, phenyl H). The identity of the product was confirmed by direct comparison of IR and ^{1}H NMR (90 MHz) spectra of an authentic sample.[16b,17]

Anal. Calcd for $C_{27}H_{26}O$: C, 88.48; H, 7.15. Found: C, 88.24; H, 7.41.

2,5-Di-*n*-butylcyclohept-3-en-1-ol (14) and 4,5-Di-*n*-butylcyclohept-2-en-1-ol (15). A solution of 1.63 g (8.62 mmol) of *exo*-bromocyclopropyl epoxide **3** in 25 mL of THF was stirred and cooled at −78 °C as a 30-mL portion (66 mmol) of 2.2 M *n*-butyllithium in hexane was added over a 15-min period under a nitrogen atmosphere. After an additional 5 min at ≤−60 °C, the reaction mixture was quenched with methanol, allowed to warm to room temperature, and poured into water. The organic product was extracted with four portions of ether. The solution was washed with two portions of water and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave 1.55 g of a yellow liquid. Flash chromatography (120 g of silica gel, elution with 30% ethyl acetate–hexane) followed by Kugelrohr distillation at 150 °C (0.1 mm) gave 324 mg (17%) of homoallylic alcohol **14** (R_f = 0.44) and 337 mg (18%) of allylic alcohol **15** (R_f = 0.37) as colorless oils, along with 100 mg (11%) of bicyclic alcohol **4** (R_f = 0.33). For **14**: IR (film) ν_{max} 3300, 2880, 2820, 1640 (C=C), 1460, 1370, 1135, 1010, 815, 730 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (br s, 6 H, 2 CH_3), 1.1–1.8 (m, 4 H, two CH_2), 1.32 (br s, 12 H, 6 CH_2), 1.52 (s, 1 H, OH), 1.9–2.4 (m, 2 H, 2 allylic H), 3.27 (apparent dt, 1 H, J_{app} = 9, 3 Hz, C*H*OH), 5.2–5.7 (16-line m, 2 H, 2 vinyl H); mass spectrum, m/e (relative intensity) 224 (M^+, 12), 206 (100), 167 (41), 163 (34), 149 (76), 138 (83), 109 (100), 83 (92), 82 (52).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.06; H, 12.46.

For **15**: IR (film) ν_{max} 3300, 2880, 2820, 1660 (C=C), 1460, 1375, 1270, 1035, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6 H, J = 6 Hz, 2 CH_3), 1.1–1.9 (m, 5 H), 1.3 (br s, 12 H, 6 CH_2), 1.98 (s, 1 H, OH), 2.3 (br s, 1 H, allylic H), 4.32 (m, 1 H, C*H*OH), 5.65 (d, 2 H, J = 4 Hz, 2 vinyl H); mass spectrum, m/e (relative intensity) 224 (M^+, 4), 206 (29), 167 (79), 149 (56), 83 (88), 71 (49), 70 (100), 57 (59), 43 (54).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.56; H, 12.60.

2,5-Di-*n*-butylcyclohept-3-en-1-one was prepared by oxidation of 101 mg (0.451 mmol) of homoallylic alcohol **14** according to the procedure described for the preparation of bicyclic ketone **5**: yield, 80 mg (80%) as a colorless oil; IR (film) ν_{max} 2880, 2820, 1705 (C=O), 1460, 1375, 1345, 1225, 1180, 960, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6 H, J = 6 H, 2 CH_3), 1.3 (br s, 12 H, 6 CH_2), 1.4–2.7 (m, 5 H), 3.4 (m, 1 H, CH=CHC*H*RCO), 5.1–5.7 (16-line m, 2 H, 2 vinyl H).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.09; H, 11.53.

4,5-Di-*n*-butylcyclohept-2-en-1-one was prepared by oxidation of 106 mg (0.473 mmol) of allylic alcohol **15** according to the procedure described for the preparation of bicyclic ketone **5**: yield, 70 mg (67%) as a colorless oil; IR (film) ν_{max} 2880, 2820, 1665 (C=O), 1465, 1375, 1255, 1170, 1120, 945, 825, 785, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.7–1.1 (m, 6 H, 2 CH_3), 1.2–1.6 (m, 12 H, 6 CH_2), 1.7–2.2 (m, 3 H), 2.4–2.7 (m, 3 H, $COCH_2$ and allylic H), 5.95 (d, 1 H, J = 12 Hz, CH=C*H*CO), 6.30 (dd, 1 H, J = 12, 6 Hz, C*H*=CHCO).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.13; H, 11.51.

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Registry No. 1, 87598-29-6; **2**, 87598-30-9; **2-*d***, 87598-31-0; **3**, 87678-08-8; **3-*d***, 87678-09-9; **4**, 52759-75-8; **4-*d***, 87598-32-1; **5**, 1072-77-1; **5-*d***, 87598-33-2; **8**, 5471-63-6; **9a**, 87598-34-3; **9a-*d***, 87598-35-4; **9b**, 87678-10-2; **9b-*d***, 87679-00-3; **9c**, 87678-11-3; **9c-*d***, 87678-13-5; **9d**, 87678-12-4; **9d-*d***, 87678-14-6; **10a**, 87598-36-5; **10b**, 87678-15-7; **11a**, 87598-37-6; **11b**, 87678-16-8; **12**, 87598-38-7; **13**, 1173-00-8; **14**, 87598-39-8; **15**, 87598-40-1; 7,7-dibromobicyclo[4.1.0]hept-2-ene, 3135-31-7; 1,3-cyclohexadiene, 592-57-4; bromoform, 75-25-2; 2,5-di-*n*-butylcyclohept-3-en-1-one, 87598-41-2; 4,5-di-*n*-butylcyclohept-2-en-1-one, 87598-42-3.