cis-3,5-Bis(4-chlorophenyl)-1,2-dioxolane (**3c**): ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.60 (dt, 1 H, J = 7 and 12 Hz), 3.47 (dt, 1 H), 5.41 (t, 2 H, J = 7 Hz), 7.16 (s, 8 H); ^{13}C NMR δ 51.5, 82.6, 127.9, 129.0, 134.2, 137.2. **3c** including small amounts of **4c**: IR (KBr) 1690, 1600, 1500, 1100, 1020, 840 cm^{-1}; MS (20 eV) m/z 298, 300 (M^+). Anal. Calcd for $C_{15}H_{12}O_2Cl_2$: C, 61.03; H, 4.09. Found: C, 60.97; H, 4.18.

trans-3,5-Bis(4-chlorophenyl)-1,2-dioxolane (**4c**): ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.00 (t, 2 H, J = 7 Hz), 5.41 (t, 2 H), 7.27 (s, 8 H); ^{13}C NMR δ 51.1, 81.9, 127.9, 129.0, 134.3, 137.2.

Typical Procedure for DCA-Sensitized Photolysis of 1,2-Dioxolane. An acetonitrile solution (4 mL) containing a 6:4 mixture of **3c** and **4c** (4×10^{-2} mmol) and DCA (2.2×10^{-3} mmol) in the presence of biphenyl or $Mg(ClO_4)_2$ (4×10^{-2} mmol) were irradiated under argon or O_2 atmosphere through an aqueous NH_3–$CuSO_4$ filter solution using a merry-go-round apparatus for 40 min. The reaction mixture was analyzed by ^{1}H NMR. The product ratio was determined by integration of the signals. The results are shown in Table II.

DCA-Sensitized Photolysis of 3d and 4d for Preparative Runs. A 7:3 mixture of **3d** and **4d** (0.2 mmol) and DCA (0.01 mmol) in acetonitrile (8 mL) was irradiated for 3 h under argon atmosphere, and the solvent was removed. ^{1}H NMR analysis of the reaction mixture showed the formation of **5d**, **6d**, and **7d** in a 57:29:14 ratio. Formation of **6d** and **7d** was confirmed by the comparison of the spectra with an authentic sample. The reaction mixture was chromatographed on silica gel. Elution with EtOAc–benzene (2:8) gave 1,3-bis(4-methoxyphenyl)-1-hydroxypropan-3-one (**5d**, 23 mg, 40%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.23 (d, 2 H, J = 6 Hz), 3.72 (s, 3 H), 3.77 (s, 3 H), 5.18 (t, 1 H, J = 6 Hz), 7.00 (ABq, 4 H, $\Delta\nu$ = 26 Hz, J = 8 Hz), 7.29 (ABq, 4 H, $\Delta\nu$ = 60 Hz, J = 8 Hz); ^{13}C NMR δ 46.8, 69.8, 55.5, 55.3, 113.8, 113.9, 127.0, 129.7, 130.5, 135.3, 159.1, 163.9, 198.8; IR (neat) 1660, 1600, 1510, 1250, 1170, 1030, 830 cm^{-1}; MS (70 eV) m/z 268 (M^+).

Thermolysis of 1,2-Dioxolane. A solution of a 6:4 mixture of **3c** and **4c** (4×10^{-2} mmol) in benzene was refluxed for 8 h under N_2. ^{1}H NMR analysis of the reaction mixture showed the formation of **6d** and **7d** in a 1:1 ratio.[6] Similar solution in acetonitrile was stirred for 2 h at 50 °C, and the 1,2-dioxolanes were recovered quantitatively.

Triplet-Sensitized Photolysis of 1,2-Dioxolanes. A benzene solution (4 mL) containing a 6:4 mixture of **3d** and **4d** (4×10^{-2} mmol) in the presence of benzophenone (0.1 mmol) was irradiated under argon atmosphere through a Toshiba UV-35 glass filter (>320 nm) for 100 min. ^{1}H NMR analysis showed the formation of **5d**, **6d**, and **7d** in a 27:52:21 ratio (conv: 69%). Similar irradiation in the presence of fluorenone through an aqueous $NaNO_2$ filter solution (>400 nm) for 35 min gave **5d**, **6d**, and **7d** in a 33:50:17 ratio (conv: 95%). Irradiation without triplet sensitizer under the same conditions gave **3d** and **4d** quantitatively.

DCA-Sensitized Photolysis of a Keto Alcohol. An acetonitrile solution (16 mL) containing **5a** (0.15 mmol) and DCA (0.035 mmol) in the presence of $Mg(ClO_4)_2$ (0.8 mmol) was irradiated with O_2 bubbling for 4 h, and the solvent was removed. The reaction mixture was chromatographed on silica gel to give benzoic acid (12 mg, 66%). An acetonitrile solution (4 mL) containing **5a** (4×10^{-2} mmol) and DCA (2.2×10^{-3} mmol) in the presence of $Mg(ClO_4)_2$ (0.2 mmol) was irradiated under O_2 atmosphere using a merry-go-round apparatus for 180 min. ^{1}H NMR analysis showed the formation of benzoic acid (conv: 74%). In the absence of $Mg(ClO_4)_2$, a complex mixture which contains only small amount of benzoic acid and large quantities of polymeric material was formed (conv: 40%).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for **3a–4a**, **3b–4b**, **3c–4c**, and **5d** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of Brexan-2-one and Ring-Expanded Congeners

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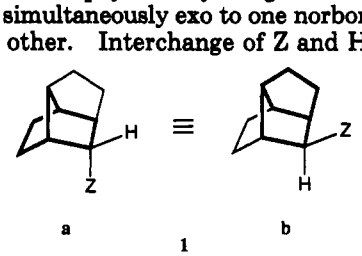
We report an efficient eight-step synthesis (26% overall yield) of brexan-2-one (tricyclo[4.3.0.0^{3,7}]nonan-2-one, **12**). This ketone then served as a convenient precursor to the mechanistically useful molecules, homobrexan-2-one (tricyclo[5.3.0.0^{4,8}]decan-2-one, **14**) and homobrexene (tricyclo[5.3.0.0^{4,8}]dec-2-ene, **20**). Several homologation sequences for the preparation of **14** were developed and can be easily adapted to allow selective introduction of ^{13}C and ^{2}H labels in **14** and **20** for various mechanistic studies.

Introduction

The tricyclic brexane skeleton **1** is comprised of two partially superposed norbornyl units (see bold lines in **1a** and **1b**),[1] and its C_2 symmetry relegates a substituent Z at C-2 to be simultaneously exo to one norbornyl unit and endo to the other. Interchange of Z and H at that site



1

produces neither an enantiomer nor a diastereomer but a structure superposable upon the original (i.e., **1a** ≡ **1b**). This unique situation, along with the skeletal rigidity, has led researchers to use brexyl systems for a variety of mechanistic and synthetic studies.

For example, mechanistic studies of brexyl 2-brosylate (**1**, Z = OBs) and related compounds have provided new data[2] relevant to the long-standing, but currently quiescent, debates[3] about solvolysis behavior of *exo*- and

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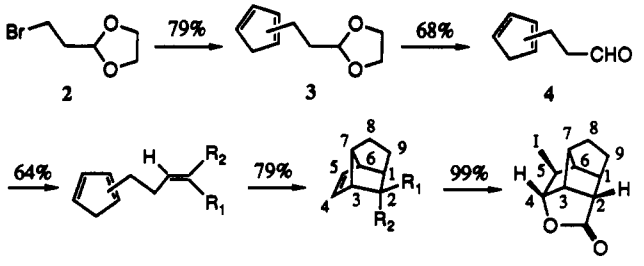
Scheme I



5a, $R_1 = H$; $R_2 = CO_2CH_3$
5b, $R_1 = CO_2CH_3$; $R_2 = H$

6a, $R_1 = H$; $R_2 = CO_2CH_3$
6b, $R_1 = CO_2CH_3$; $R_2 = H$
7a, $R_1 = H$; $R_2 = CO_2H$
7b, $R_1 = CO_2H$; $R_2 = H$

8

endo-norbornyl substrates. Also, the parent hydrocarbon (Z = H) and several of its monofunctional derivatives have served in studies involving carbocations,[4] carbenes,[5] homoenolate ions,[6] and chiroptical behavior.[7] And a trisubstituted brexane played a key role in the total synthesis of the sesquiterpene, sativene.[8]

Further, the homologated ketone 14 (trivially named homobrexan-2-one), which is obtainable from brexan-2-one, permits easy access to tricyclo[5.3.0.$0^{4,8}$]decanes. This latter ring system possesses the C_{10} skeleton found in lumibullvalene;[9] and the parent hydrocarbon, homobrexane, is believed to be a major conduit in the Lewis acid isomerization of [3.3.2]propellanes to adamantane.[10]

Suitable synthetic routes to brexanes functionalized in the ethano bridges are currently available,[11] but efficient entries to derivatives monofunctionalized in the methano bridge (i.e., at C-2) were unveiled only recently by us and by Stille and Grubbs.[12] Previously reported syntheses[7,11c] of the crucial ketone brexan-2-one have been daunting (e.g., 12 sequential steps, overall yield <1%) and have involved some laborious and costly procedures. Likewise, a previous synthesis of the homolog homobrexan-2-one by Tobe et al.,[10] via a multistage route, suffers from a low overall yield (1%) and lack of versatility; for example, it would not allow for site-selective introduction of ^{13}C into the six-membered ring. We now report full experimental details of convergent preparations of brexan-2-one and homobrexan-2-one in 25.5% and 24% overall yields, respectively; some of the findings were announced in a preliminary report.[12b]

Discussion

Our synthesis of brexan-2-one (12) starts from commercially available 2-(2-bromoethyl)-1,3-dioxolane (2) and leads to an epimeric mixture of unsaturated tricycles **6a** and **6b**, as summarized in Scheme I.

Nucleophilic displacement of bromide by cyclopentadienyl sodium provided the expected[13] isomeric dioxolanes **3**. Acidic hydrolysis of the acetals afforded a mixture of propanals **4**. A modified Wittig reaction[14] of **4** with triphenylphosphoranylidene acetate gave a five-component mixture of *E*/*Z* trienoic esters **5** (two *E* isomers, **5a**, 92–98%) and three *Z* isomers (**5b**, 2–8%). Heating this mixture as a dilute solution in benzene effected intramolecular Diels–Alder cycloaddition.[8,15] The product consisted largely of *endo*-2-(carboxymethyl)-4-brexene (**6a**), along with some of its exo epimer **6b**. Numerous repetitions of the thermolysis and the appropriate control experiments indicated that the proportion of **6a** ranged from 96 to 99.5% depending upon the cis–trans composition of the acrylic double bond in **5**. An analytically pure sample of the minor component (exo ester, **6b**) was obtained by repeated column chromatography, followed by distillation. To get a rigorously pure sample of the major component (endo ester **6a**), as well as to establish its endo configuration, we used a general iodolactonization method that was developed by Berson and Ben-Efraim[16] for the separation of epimeric norbornenyl esters. Accordingly, our mixture of esters (**6a**/**6b** = 20/1) was saponified[16b] and was then treated with I_2 in $NaHCO_3$ to give iodo lactone **8** and the sodium salt of exo acid **7b**. The IR and ^1H NMR spectral characteristics of **8** were consistent with those reported for the iodo lactone from *endo*-5-norbornene-2-carboxylic acid.[16,17] Treatment of our iodo lactone **8** with zinc in acetic acid generated endo acid **7a**, which was esterified to **6a** with diazomethane.

^1H NMR chemical shifts and coupling constants of endo ester **6a** and exo ester **6b** closely paralleled those reported for correspondingly substituted norbornenes.[18] The spectral data, in conjunction with the iodolactone separation technique, firmly establishes our stereochemical assignments for these two Diels–Alder products. However, the **6a**/**6b** proportion is of no consequence to our synthetic objective because catalytic hydrogenation of the mixture affords 2-carbomethoxybrexane (**9a**) uniquely.

We attempted unsuccessfully to convert ester **9a** to brexan-2-one (**12**) through direct oxidative decarboxylation[19] of 2-carboxybrexane (**9b**) and ultimately turned to a general method developed by Trost et al.[20] This three-step procedure (Scheme II) entailed the following: (i) conversion of **9a** to its enolate with lithium cyclohexylisopropylamide followed by quenching with dimethyl

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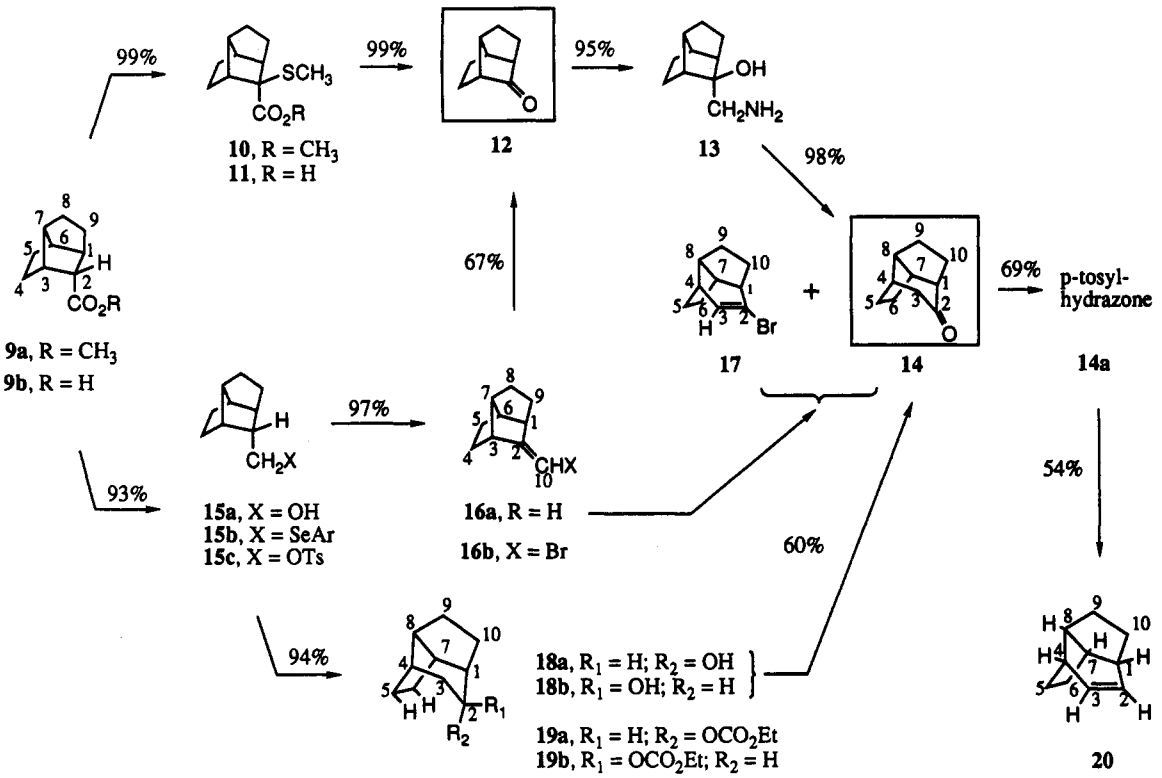
Scheme II



disulfide to give **10**; (ii) saponification to the corresponding acid **11**; and (iii) oxidative decarboxylation of the sodium salt with *N*-chlorosuccinimide to provide brexan-2-one (**12**). This volatile, liquid ketone (26% overall yield from the initial bromodioxolane) was identical in all respects to an authentic sample.[11c]

To affirm the flexibility of our synthesis, we developed three branch routes to the important ring-expanded homolog homobrexan-2-one (**14**) as shown in Scheme II. The homobrexane skeleton is an appealing target because its central six-membered ring is constrained by the two ethano bridges to adopt a chair conformation and cannot flip to a boatlike form. Consequently, this ring system will be useful in studies that address boat–chair ambiguities. One synthetic route involved conversion of **12** to amino alcohol **13** by sequential action of trimethylsilyl cyanide[21] (TMSCN) and $LiAlH_4$, followed by Tiffeneau–Demjanov rearrangement[22] of semipinacol **13** with nitrous acid to give ketone **14**. (The ^{13}C NMR spectrum of **14** was superimposable on that of an authentic sample.[10,23]) Our overall yield of **14** was 24%, reckoned from the original bromodioxolane. Further, this synthesis offers an economical way to label the homobrexane skeleton with ^{13}C for mechanistic studies because the TMSCN reagent can be conveniently prepared from ^{13}C-enriched KCN.[24]

Our second route to **14** involved $LiAlH_4$ reduction of ester **9a** to alcohol **15a**. Conversion of **15a** to seleno ether **15b** with *o*-nitrophenyl selenocyanate,[25] followed by oxidation of **15b** and concomitant in situ syn elimination[8,26] of the intermediate selenoxide, provided 2-methylenebrexane (**16a**). Reaction of alkene **16a** with cyanogen azide (generated from NaN_3 and BrCN in CH_3CN),[27-29] and hydrolytic workup gave ketone **14** (46%). Also isolated from the reaction was an unexpected (35%) byproduct, bromo olefin **16b**, as well as a small amount (7%) of an isomeric bromoalkene, which may be 2-bromohomobrex-2-ene (**17**) based on GC/MS data. The formation of bromoalkenes had not previously been observed by investigators who developed this method of ring expansion, but such byproducts evidently arise from bromide in the milieu.

Interestingly, treatment of alkene **16a** with *m*-chloroperoxybenzoic acid effects exocyclic methylene cleavage and gave us brexan-2-one (**12**) in 67% yield. This type of transformation is not without precedent. A similar outcome was observed by Naffa and Ourisson[30a] and was further elaborated upon by Nayak and Dev[30b] when lon-

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(23) We thank Professor Yoshito Tobe for a copy of his ^{13}C NMR spectrum. Curiously, our **14** has mp 143–144 °C, whereas his mp is 47–49 °C. Professor Tobe wrote to suggest that his solid and ours may differ in crystal form. Interestingly, the saturated hydrocarbon has mp 122–124 °C (Wiseman, J. R.; Vanderbilt, J. J.; Butler, W. M. *J. Org. Chem.* **1980**, *45*, 667–671.)

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gifolene was treated with peroxybenzoic acid to produce longicamphenilone.

Our third branch route to **14** entailed conversion of alcohol **15a** to tosylate **15c**. Acid-catalyzed rearrangement,[31] followed by hydrolytic workup, gave a 1/6.9 mixture of axial and equatorial 2-homobrexanols, (**18a** and **18b**, respectively). Chromic oxidation[32] of this mixture provided **14**.

To obtain analytically pure samples of the individual axial (**18a**) and equatorial alcohols (**18b**), we reduced ketone **14** under different conditions. $LiAlH_4$ gave a 2.25/1 mixture of **18a** and **18b**, respectively. Predominance of the axial isomer is reasonably explained by "steric approach control"[33] (i.e., attack on the carbonyl from the less hindered equatorial direction.)

The ^1H NMR spectrum of the alcohol mixture showed a multiplet at δ 3.94–3.85, attributed to the C-2 axial H in epimer **18b** ($J_{2ax,3ax}$ = 10.4 Hz; $J_{2ax,3eq}$ = 6.5 Hz; $J_{2ax,1}$ = 4.0 Hz), and a multiplet at δ 3.78–3.66 for the C-2 equatorial H in epimer **18a** ($J_{2eq,3ax}$ = 3.2 Hz; $J_{2eq,3eq}$ = 2.5 Hz; $J_{2eq,1}$ = 1.8 Hz). These vicinal couplings are the basis for our axial–equatorial assignments and are in line with those of other cyclohexanols[34a] and cyclohexanol-containing ring systems[33] and were important for (and consistent with) stereochemical assignments in connection with some of our other projects involving deuterium labeling.[24]

An unusual feature in the ^1H NMR spectrum of **18** was that the C-2 equatorial H in axial alcohol **18a** (δ 3.78–3.66) is at higher frequency than the C-2 axial H in equatorial alcohol **18b** (δ 3.94–3.85). Generally, equatorial carbinyl H's appear at lower frequency relative to axial ones in cyclohexanol systems,[35] an outcome that has been attributed to the spatial position of H with respect to the diamagnetic anisotropy zones of the carbon–carbon bonds.[36] However, transannular van der Waals compression between H's has been suggested[37] to be responsible for enhanced deshielding of carbinyl hydrogens in several polycyclic alkanols. On this basis we presume that the C-2 axial carbinyl H in **18b** appears at lower frequency because of its steric compression with the syn H's at C-5 and C-6.

We were unable to separate alcohols **18a** and **18b** by column chromatography or by fractional crystallizations from several solvent systems, so we resorted to selective carboxyethylation ("cathylation"), a separation procedure developed by Fieser et al.[38] Treatment of our mixture (**18a**/**18b** = 2.25) with an excess of ethyl chlorocarbonate in dry pyridine converted all the equatorial OH to the cathylate, but left about half of the axial alcohol unchanged. Column chromatography effectively provided analytically pure crystals of axial alcohol **18a**, but did not separate the cathylates.

Eventually, we obtained a pure sample of equatorial[33,39] alcohol by K/NH_3 reduction[40] of **14**. The crude product consisted of equatorial alcohol **18b** (70.2%), axial alcohol **18a** (3.9%), an unidentified impurity (3.7%), and some starting ketone **14** (22.2%), which we believe was protected from reduction in the form of the enolate anion generated from amide or from traces of H_2O. Preparative GC provided pure crystalline **18b** for spectral characterization and elemental analysis.

With acceptable syntheses of target ketone **14** in hand (the TMSCN route preferred), we then focused on its conversion to homobrex-2-ene (**20**), a pivotal alkene for various ongoing mechanistic and photochemical studies involving carbenes.[24] To this end, ketone **14** was readily converted[41] to its tosylhydrazone (**14a**), which was subjected to a Shapiro reaction[42] to give homobrex-2-ene (**20**) in 54% yield.

This alkene has C_2 symmetry and was fully characterized by elemental and spectroscopic analyses. The broad-band decoupled ^{13}C NMR spectrum of **20** showed, as expected, five signals. The olefinic carbons[43] appeared at δ 128.82, and the four different aliphatic carbons fell between δ 45.51 and 24.05. The fully coupled ^{13}C NMR spectrum showed the olefinic carbon at δ 128.82 as a doublet ($J_{C\text{-}13,H}$ = 158.2 Hz), a bridgehad carbon as a doublet at δ 45.51 ($J_{C\text{-}13,H}$ = 134.9 Hz), and the other bridgehead carbon at δ 44.38 ($J_{C\text{-}13,H}$ = 134.9 Hz). The two different methylene carbons appeared as a triplet at δ 33.51 ($J_{C\text{-}13,H}$ = 125.1 Hz) and a triplet at δ 24.05 ($J_{C\text{-}13,H}$ = 125.8 Hz). Its ^1H NMR spectrum showed a pseudo (ABX)[18,44] triplet (J = 2.9 Hz) centered at δ 5.46 for the equivalent vinylic H's; a multiplet between δ 2.23 and 2.17 for the equivalent tertiary H's at C-7 and C-8; a multiplet between δ 2.17 and 2.07 for the equivalent H's at C-1 and C-4; and the correct area integration for the remaining (eight) methylene H's. These assignments were verified be decoupling experiments in which irradiation of the allylic multiplet at δ 2.17–2.07 drastically changed the appearance of the vinyl H's at δ 5.46.

We wanted to determine the magnitude of the coupling[18,45] between the two alkene H's in **20** as a possible probe of conformation[45] and particularly to seek physical evidence for any twist[46] that might be imparted to the double bond. Because these H's are equivalent, the J's cannot be obtained from conventional ^1H NMR spectra. Accordingly, we used the ^{13}C satellite method of Laszlo and

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Schleyer[47] and found $J_{2,3}$ = 9.3 Hz, $J_{2,1}$ = 5.4 Hz, and $J_{2,4}$ = 1.5 Hz. These J's are in line with corresponding couplings for norbornenyl,[18] bicyclo[3.2.1]octenyl,[48] and cyclohexenyl[45b] systems. However, the relative chemical shifts of the allylic (C-1, C-4) vs the homoallylic (C-7, C-8) bridgehead H's in **20** are unusual and prompted us to search the literature for analogies. Although we found several examples[9,49] of allylic H's appearing at higher frequency than homoallylic H's, no explanations have been put forward.

Several factors could play roles in the "reversal" of relative chemical shifts for allylic and bridgehead homoallylic H's in alkenes. In the case of **20**, one factor could be the spatial location of these H's with respect to diamagnetic anisotropy zones of the double bond.[18] Another factor might be the substantial s character of the bridgehead and olefinic carbons.[49b] However, since both bridgehead carbons in **20** have virtually identical ^{13}C–H couplings (ca. J = 135 Hz) and since information about the hybrid character of carbon is often revealed by the magnitude of such couplings (e.g., J = 125 Hz for sp^3 and J = 250 for sp),[50] it seems likely that the anisotropy factor is mainly responsible for the chemical shift reversal in **20**.

Furthermore, examination of molecular models of **20** suggests that a skeletally-induced twist of the double bond could accentuate anisotropy effects. And, although the C=C stretching frequency[46c] (namely 1600 cm^{-1}, $CHCl_3$) did not suggest any unusual double-bond geometry in **20**, the ultraviolet spectrum in pentane showed λ 196 nm, which is slightly "red shifted" from cyclohexene's λ 183 nm[51] (in 3-methylpentane) and λ 190 nm[52] (in cyclohexane). This bathochromic shift observed for **20** could arise from double-bond strain.

In summary, we have developed convergent, efficient syntheses of brexan-2-one (**12**, eight steps, 26% overall yield) and homobrexan-2-one (**14**, 10 steps, 24% overall yield). The route involved an intramolecular Diels–Alder reaction as a key step. The homologation of **12** to **14** can easily be adapted for regioselective introduction of a ^{13}C label at C-2 in homobrexane, in homobrexan-2-one, and in homobrex-2-ene by use of TMSCN prepared from ^{13}C-enriched KCN. Such labeled analogs are potentially useful for mechanistic studies of carbene rearrangements and of "adamantaneland"[10,23,58] rearrangements.

Experimental Section

General. Melting points and boiling points are uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 400 and 100 MHz, respectively, unless specified otherwise. Chemical shifts were referenced to TMS or to the residual H in perdeuterated solvents (δ 7.26 for $CDCl_3$, δ 7.15 for C_6D_6, δ 3.30 for CD_3OD). Low-resolution mass spectra were obtained on spectrometers equipped with SE-54, DG-5, or OV-17 capillary columns.

Analytical GC was performed on a FFAP Golay (100 ft, i.d. = 0.02 in.) column (He pressure = 14 psi, column temperature = 150 °C unless otherwise specified). An SE-52 capillary column (25 m, i.d. = 0.33 mm) was also used as specified. Preparative GC was performed on an instrument equipped with a 15% SE-30 on Chromosorb W column (20 ft, i.d. = $^3/_8$ in). TLC was conducted on preparative silica GF plates (2000, 1000, or 500 μm thickness) or on analytical plates coated with silica GF or neutral alumina GF (250 μm). Column chromatography was carried out on silica gel, 70–230 mesh, or on neutral alumina, activity III.

Anhydrous solvents were obtained by distillation under Ar from a specified substance and by storage over activated molecular sieves. 18-Crown-6 KCN complex[21b] was prepared by addition of KCN (123 mg, 1.89 mmol) to 18-crown-6 (500 mg, 1.89 mmol) in anhydrous MeOH (5 mL) under Ar at rt. When dissolution was complete, the solvent was evaporated in vacuo, and the residue was dried under high vacuum for 24 h. The white residue was ground into a powder and used directly.

2-(Cyclopentadienylethyl)-1,3-dioxolanes (3). NaH (64.8 g, 1.62 mol, 60% mineral oil dispersion), under Ar, was washed with dry pentane to remove mineral oil, and the supernatant was decanted. Anhydrous THF (500 mL) was added, and the mixture was cooled to 0 °C. Freshly cracked cyclopentadiene[53] was added dropwise over 1 h to the stirred mixture. After the NaH was consumed (ca. 45 min), the dark rosy solution was cooled to −70 °C over 15 min and dioxolane **2** (100 g, 0.49 mol, Aldrich, purity = 88%) was added dropwise over 15 min. The mixture was allowed to warm to 25 °C over 2 h and was poured into pentane (300 mL), followed by the slow addition of H_2O (300 mL). The aqueous phase was extracted with ether.

The combined organic extract was worked up conventionally by washing with H_2O and then with brine, drying over Na_2SO_4, and evaporation in vacuo. Column chromatography (silica gel, pentane:ether = 6:1) of the resultant amber oil (134.7 g) in four batches gave a mixture of acetals (total 71.7 g, 79%) as a faint yellow oil: GC purity = 89.6% **3** + 11.4% solvent; TLC (silica gel, pentane:ether = 6:1) one spot. An analytical sample of **3** was obtained by bulb to bulb distillation (bp 88 °C (1.5 mm)): GC purity = 99.9%; HPLC (heptane:ether = 19:1) t_R = 7.0 min (43.7%) and t_R = 7.4 min (56.3%); IR (neat) 3080 (w), 1600 (w), 1445 (m), 1035 (s) cm^{-1}; ^1H NMR (80 MHz) δ 6.44–6.03 (m, 3 H, vinyl), 4.90–4.84 (t, J = 4.7 Hz, 1 H, methine), 4.01–3.82 (m, 4 H, OCH_2CH_2O), 2.96–2.87 (m, 2 H, endocyclic allylic), 2.55–2.41 (m, 2 H, exocyclic allylic), 2.03–1.83 (m, 2 H, homoallylic); UV λ (MeOH) 246 nm (ε = 4188). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.38; H, 8.61.

3-Cyclopentadienylpropanals (4). A solution of dioxolanes **3** (33.3 g, 0.18 mol, purity = 89.6% + 10% solvent) in THF (628 mL) was added to a rapidly stirred solution of acetic acid (433 g, 7.22 mol) and H_2O (650 mL). The mixture was heated at reflux for 4 h under Ar and was slowly poured into a mixture of $NaHCO_3$ (758 g, 9.03 mol) and H_2O–ice (ca. 1.5 L). The mixture was stirred until the effervescence ceased (pH ca. 8). Conventional workup gave an amber oil (66 g), which can be assayed by GC and used directly in the next reaction with very little reduction in yield of the trienoic esters. Column chromatography of the crude aldehydes (silica gel, CH_2Cl_2:pentane = 1:1) afforded a mixture of cyclopentadienyl propanals (15.9 g, 68%) as a slightly yellow oil: GC purity 93.7% + 6.3% solvent; TLC (silica gel, CH_2Cl_2:pentane = 1:1) one spot. Because of the volatility of this material a small amount of solvent was allowed to remain in the eluted sample to minimize loss. The mixed aldehydes are unstable and polymerize even under Ar in the freezer and therefore should be used immediately in the next reaction. A colorless analytical sample of the aldehyde mixture, **4**, was obtained by bulb to bulb distillation (bp 60 °C (2 mm)): GC purity = 97%; HPLC (heptane:ether = 19:1) t_R = 5.8 min (16%) and t_R = 9.4 min (84%); IR (neat) 3050 (w), 2720 (m), 1715 (s), 1600 (w), 1360 (w), 900 (s), cm^{-1}; ^1H NMR (80 MHz) δ 9.82 (s, 1 H, CHO), 6.46–6.03 (m, 3 H, vinyl), 2.97–2.90 (m, 2 H, endocyclic allylic), 2.71 (s, 4 H, CH_2CH_2); UV λ (MeOH) 244.5 nm (ε = 2838). Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.37; H, 8.33.

Methyl (*E*)-2-(4-Cyclopentadienyl)pentenoates (5a) and Methyl (*Z*)-2-(4-Cyclopentadienyl)pentenoates (5b). Following a modified procedure of Roush,[14] we added methyl triphenylphosphoranylideneacetate (46.9 g, 0.138 mol, Aldrich, 98%) to a rapidly stirred, 25 °C solution of aldehydes **4** (13.23 g, 0.102

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mol, purity = 93.7%) in CH_2Cl_2 (200 mL) under Ar. After an initial temperature rise to 43 °C, the mixture was stirred for 20 h at 25 °C. The solvent was then evaporated in vacuo, and the dark pink residue was triturated with a 6:1 solution of pentane–ether (5 × 200 mL). The combined washings were filtered through silica gel (ca. 20 g), and the filter cake was rinsed with additional solvent (ca. 200 mL). Evaporation of the combined filtrate at 25 °C afforded a yellow oil (20.1 g), which was subjected to column chromatography (silica gel, pentane:ether = 6:1) to afford a mixture of **5a** and **5b** (12.0 g, 64%). GC analysis was not possible due to decomposition of the *E*-esters. ^{1}H NMR (80 MHz) indicated 97% purity of the mixture (**5a**/**5b** = 12.1). In about 10 trials the relative proportions of **5a** (*E*-ester) ranged between 92 and 98% and **5b** (*Z*-ester) ranged between 2 and 8%. Repeated column chromatography (silica gel, pentane:ether = 6:1) of a mixture of **5a** and **5b** effected their separation. Bulb to bulb distillation of each compound provided analytical samples. The *Z*-esters **5b** were stable to distillation (110 °C (0.15 mm)). However, only a small amount of the pure *E*-esters **5a** distilled over; most had decomposed extensively in the flask.

Data for **5a** (*E*-esters): TLC (silica gel, pentane:ether = 6:1) one spot; R_f = 0.65; HPLC (heptane:ether = 19:1) t_R = 5.5 min (68.1%) and 5.9 min (31.3%) for **5a**; t_R = 4.3 min (0.8%) for **5b**; IR (neat) 3060 (w), 1720 (s), 1655 (m), 1435 (m), 1320 (m), 1275 (m) cm^{-1}; ^{1}H NMR (80 MHz) δ 7.15–6.70 (m, 1 H, CH=CCO$_2$), 6.44–6.02 (m, 3 H, vinyl), 5.82 (d, 1 H, *J* = 17.1 Hz, C=CHCO$_2$), 3.72 (s, 3 H, OCH$_3$), 2.96–2.86 (m, 2 H, endocyclic allylic), 2.57–2.42 (m, 4 H, CH$_2$CH$_2$); UV λ (MeOH) 235 nm (ε = 5759), λ 203 nm (ε = 24 537). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found C, 73.92; H, 8.03.

Data for **5b** (*Z*-esters): TLC one spot; R_f = 0.84; HPLC t_R = 4.3 min (26.5%), 4.4 min (28.6%), and 4.5 min (39.2%) for **5b**; t_R = 5.94 min (5.6%) for **5a**; IR (neat) 3060–3005 (w), 2990 (w), 1720 (s), 1655 (m), 1435 (m), 1320 (m), 1275 (m) cm^{-1}; ^{1}H NMR (80 MHz) δ 6.45–5.90 (m, 4 H, vinyl and CH=CCO$_2$), 5.70 (d, 1 H, *J* = 10.3 Hz, C=CHCO$_2$), 3.71 (s, 3 H, OCH$_3$), 2.96–2.70 (m, 4 H, endocyclic allylic and CH$_2$C=CCO$_2$), 2.60–2.30 (m, 2 H, CH$_2$); UV λ (MeOH) 326 nm (ε = 5769), λ 205 nm (ε = 22 065). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found C, 73.98; H, 7.88.

Methyl *endo*- and *exo*-Brex-4-ene-2-carboxylates (6a and 6b). A mixture of esters **5a** and **5b** (13.9 g, 0.074 mol, purity = 95%, **5a**/**5b** = 12/1) was diluted with benzene (1.5 L) to make a ca. 1% solution (wt/wt). The solution was heated in sealed tubes under Ar at 115 °C for 215 h. The solvent was evaporated at ca. 10 °C, and the residual, dark amber oil (23.6 g) was chromatographed (silica gel, pentane:ether = 6:1) to give a mixture of endo and exo esters **6a** and **6b** (11.76 g, 79%) as a faint yellow oil. GC purity = 88% + 12% solvent, t_R = 3.1 min for **6b** and 3.8 min for **6a**; **6a**/**6b** = 24.1. We found, in ca. 10 runs, that the endo ester **6a** ranged between 96 and 99.5% and exo ester **6b** ranged between 0.5 and 4.0%. An analytical sample of exo ester **6b** was obtained directly from the mixture by column chromatography (silica gel–20% $AgNO_3$, pentane:ether = 6:1, R_f = 0.27 for **6b** and 0.57 for **6a**) followed by bulb to bulb distillation (75 °C (0.10 mm) of the purest fractions.

Exo ester **6b**: GC purity = 95% + 5% **6a**; TLC (silica gel, pentane:ether = 6:1) one spot; R_f = 0.65; IR (neat) 3060 (m), 1735 (s), 1240 (s), 1220 (s), 1180 (s) cm^{-1}; ^{1}H NMR δ 6.21 (dd, 1 H, $J_{4,5}$ = 5.6, $J_{4,3}$ = 2.4 Hz, H$_4$), 5.89 (dd, 1 H, $J_{5,4}$ = 5.6, $J_{5,6}$ = 2.8 Hz, H$_5$), 3.70 (s, 3 H, OCH$_3$), 2.87–2.86 (br s, 1 H, H$_3$), 2.75–2.72 (br s, 1 H, H$_6$), 2.28–2.26 (m, 1 H, H$_2$), 2.14–2.12 (m, 1 H, H$_1$), 2.04 (d, 1 H, *J* = 6.7 Hz, H$_7$), 1.74–1.63 (m, 2 H, CH$_2$), 1.48–1.38 (m, 2 H, CH$_2$). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.11; H, 7.94.

The analytical sample of endo ester **6a** was obtained by a modified separation method developed by Berson and Ben-Efraim.[16a] Saponification of our mixture of **6a** and **6b**, followed by treatment of the acids with iodine in aqueous $NaHCO_3$, produced an iodo lactone **8** from the endo acid and left the exo acid as a sodium salt. Treatment of **8** with Zn/HOAc regenerated the endo acid, which was reconverted to the endo ester **6a** with diazomethane. For experimental details see sections dealing with iodo lactone **8**, endo acid **7a**, and the conversion of endo acid **7a** to endo ester **6a**.

Endo ester **6a**: GC purity = 99.5%; TLC (silica gel, pentane:ether = 6:1) one spot, R_f = 0.58; IR (neat) 3060 (w), 1736 (s), 1620 (w), 1200 (s) cm^{-1}; ^{1}H NMR δ 6.06 (dd, 1 H, $J_{4,5}$ = 5.6, $J_{4,3}$ = 2.4 Hz, H$_4$), 5.84 (dd, 1 H, $J_{5,4}$ = 5.6, $J_{5,6}$ = 2.8 Hz, H$_5$), 3.58 (s, 3 H, OCH$_3$), 2.95–2.80 (br s, 1 H, H$_3$), 2.65–2.52 (br s, 1 H, H$_6$), 2.46 (d, 1 H, $J_{2,3}$ = 4.9 Hz, H$_2$), 2.25–2.15 (br s, 2 H, H$_1$ + H$_7$), 1.87–1.50 (m, 2 H, CH$_2$), 1.49–1.00 (m, 2 H, CH$_2$). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 4.92. Found: C, 73.96; H, 8.13.

***exo*-6-Iodo-4-oxa-3-oxotetracyclo[5.3.1.0.0^{2,11}]undecane (8).** We added a solution of KOH (189 mg, 3.36 mmol) in H_2O (1.5 mL) and MeOH (3.0 mL) to a mixture of **6a** and **6b** (309 mg, 1.68 mmol, purity = 97%, **6a**/**6b** = 20/1) under Ar. The mixture was heated to 75 °C and then refluxed 3 h. TLC was used to monitor the progress. The MeOH was evaporated in vacuo, and the aqueous solution was extracted with ether. The aqueous solution was acidified (pH ca. 3–5) with 2 N H_2SO_4 and was extracted with ether. Conventional workup and drying gave yellow crystals (270 mg).

A batch of the crude mixture of acids (243 mg, ca. 1.48 mmol) was dissolved in a solution of $NaHCO_3$ (433 mg, 5.15 mmol) in H_2O (6.9 mL). This rapidly stirred solution was treated dropwise over 15 min with 4.5 mL of a stock solution of I_2 (12.6 g, 0.050 mol) and KI (26.0 g, 0.157 mol) in H_2O (149 mL). Note: 4.5 mL of this solution corresponds to 378 mg (1.49 mmol) of I_2.) The mixture was stirred at 25 °C under Ar for 50 min, after which a precipitated brown oil was extracted with ether. The combined ether extract was washed with 10% aqueous thiosulfate solution, and conventional workup gave a yellow wax (396 mg). Repeated recrystallization from pentane–ether (20:1) provided analytically pure iodo lactone **8**, as white crystals, mp 89–90 °C: IR (CCl_4) 2965 (s), 2915 (w); 2880 (m), 1785 (s), 1170 (s) cm^{-1}; ^{1}H NMR (80 MHz) δ 5.20 (d, 1 H, $J_{4,3}$ = 4.6 Hz, H$_4$), 4.08 (s, 1 H, H$_5$), 3.25–2.80 (dm, 2 H, *J* = 4.8 Hz, H$_1$ + H$_3$), 2.65–2.45 (dm, 2 H, *J* = 5.0 Hz, H$_6$ + H$_7$), 2.03 (d, 1 H, $J_{2,3}$ = 5.3 Hz, H$_2$), 1.95–1.35 (m, 4 H, CH$_2$). Anal. Calcd for $C_{10}H_{11}IO_2$: C, 41.40; H, 3.82. Found: C, 41.62; H, 3.86.

***endo*-Brex-4-ene-2-carboxylic Acid (7a).** A solution of iodo lactone **8** (1.81 g, 6.24 mmol, mp 89–90 °C) in acetic acid (2.6 mL) under Ar was stirred rapidly and was cooled to 15 °C as zinc dust (0.816 g, 12.48 mmol) was slowly added over 10 min, followed by more acetic acid (2.0 mL). The mixture was stirred for 1.5 h at 15 °C and an additional 4.0 h at 25 °C. The mixture was filtered, and the insoluble residue was washed with acetic acid (ca. 2 mL) and H_2O (ca. 5 mL). The combined washings and filtrate were diluted with H_2O (dilution precipitated a white material). Aqueous saturated $NaHCO_3$ was then added until effervescence ceased (pH ca. 8). The basic solution was extracted with ether which afforded crude starting iodo lactone (127 mg) after workup.

The basic aqueous layer was acidified with 4 N H_2SO_4 until pH ca. 3. The acidic solution was extracted with ether, which was worked up conventionally. The derived yellow oil was triturated with H_2O, and the resultant solid was collected, rinsed with H_2O, and then dissolved in ether. Workup left crude endo acid **7a** (831 mg). Repeated recrystallization from pentane–ether (19:1) provided pure **7a** as white crystals, mp 94.5–96 °C; IR (CCl_4) 3520 (w), 3400–2400 (s), 1750 (w), 1710–1690 (s), 1285–1275 (s), 1255–1240 (m), 920 (w) cm^{-1}; ^{1}H NMR (80 MHz CCl_4; external lock $CDCl_3$) δ 11.95 (s, 1 H, CO$_2$H), 5.94–5.85 (m, 2 H, H$_4$ + H$_5$), 2.86–2.78 (m, 1 H, H$_3$), 2.52–2.51 (br s, 1 H, H$_6$), 2.35 (d, 1 H, *J* = 4.9 Hz, H$_2$), 2.30–2.00 (br s, 2 H, H$_1$ + H$_7$) 1.95–0.85 (m, 4 H, CH$_2$). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.43; H, 7.49.

Methyl *endo*-Brex-4-ene-2-carboxylate (6a). A diazomethane–ester[54] solution (16 mL, 8.75 mmol by titration with ethereal benzoic acid) was carefully added to solid endo acid **7a** (718 mg, 4.4 mmol, mp 94–96 °C) until the resultant solution became permanently yellow. The excess of diazomethane was removed under water aspiration. The solvent was evaporated in vacuo to leave a milky white residue, which was dissolved in ether and was washed with saturated Na_2SO_4 solution. The organic layer was worked up to give endo ester **6a** as a colorless oil (750 mg, 96%): TLC (silica gel, pentane:ether = 6:1) one spot, R_f = 0.58. A pure sample of **6a** was obtained by bulb to bulb distillation (bp 80 °C (0.1 mm)). The analytical data were given earlier.

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Intramolecular Diels–Alder Reaction of Enriched Methyl (*E*)-2-(4-Cyclopentadienyl)pentenoates (5a). A sample (2.2 g, 0.012 mol), which consisted of *E*-esters **5a** (96%) and *Z*-esters **5b** (4%) in benzene (250 mL), was heated in a sealed tube under Ar at 115 °C for 94 h. The solvent was evaporated in vacuo, and the residue (3.9 g) was subjected to flash column chromatography (silica gel, pentane:ether = 6:1) to afford a yellow oil (1.9 g, 80%). GC (purity = 92% + 8% solvent) gave the following ratios and retention times: exo ester **6b** (1.0%, t_R = 3.1 min); endo ester **6a** (98.6%, t_R = 3.4 min); starting *E*-esters **5a** (0.4%, t_R = 7.28 min).

Intramolecular Diels–Alder Reaction of Enriched Methyl (*Z*)-2-(4-Cyclopentadienyl)pentenoates (5b). A sample (20 mg, 0.11 mmol) that consisted of *Z*-esters **5b** (82%) and *E*-esters **5a** (18%) in benzene (0.23 mL) was heated in a sealed tube under Ar at 115 °C for 120 h. GC showed exo ester **6b** (50.9%); endo ester **6a** (19.3%); *Z*-esters **5b** (6.1%, t_R = 4.1 min); and *E*-esters **5a** (23.8%).

Epimerization of Methyl *endo*-Brex-4-ene-2-carboxylate (6a). Modifying a procedure of Roberts et al.,[55] we heated (78 °C) a solution of endo ester **6a** (611 mg, 3.43 mmol, purity = 99.5%) and NaOMe (371 mg, 6.86 mmol) in MeOH (4.2 mL) under Ar for 144 h (pH was ca. 10 during this period). Aliquots were worked up at 24, 48, 76, and 144 h. GC indicated that after 24 h the ratio of esters remained at an equilibrium value of 92% endo ester **6a** and 8% exo ester **6b**.

Stability of Endo and Exo Esters 6a and 6b to the Reaction Conditions. A mixture of **6a** and **6b** (49/1) in benzene (to make ca. 1% solution, wt/wt) was heated in a sealed tube under Ar for 210 h at 115 °C. GC indicated the **6a**/**6b** ratio had not changed.

Methyl Brexane-2-carboxylate (9a). We hydrogenated[11a] a 76/1 mixture of **6a** and **6b** (1.75 g, purity = 98% + 2% original trienoic esters **5a** and **5b**) in ether (141 mL) with 10% Pd/C (1.75 g) for 20 h at rt. The mixture was passed through Celite, the filter cake was rinsed with ether, and the filtrate was evaporated in vacuo to give a colorless oil (1.81 g). Column chromatography (silica gel, pentane:ether = 6:1) gave the saturated ester **9a** (1.79 g, 99%): TLC (silica gel, pentane:ether = 6:1) one spot, R_f = 0.45. GC purity = 98% **9a** (t_R = 2.8 min) + 2% methyl 5-cyclopentylpentanoate (t_R = 2.4 min) based on peak enhancement with material characterized by ^{1}H NMR. The analytical sample, obtained by bulb to bulb distillation (bp 118 °C (0.1 mm)), had GC purity = 98.1% + 1.9% methyl (5-cyclopentyl)pentanoate: IR (neat) 1735 (s), 1200 (s), 1100 (s) cm^{-1}; ^{1}H NMR (400 MHz) δ 3.66 (s, 3 H, OCH_3), 2.33–2.31 (br s, 1 H, H_1), 2.30–2.28 (m, 1 H, H_3), 2.20–2.16 (m, 1 H, H_7), 2.01–1.99 (m, 1 H, J = 4.7 Hz, H_2), 1.94–1.91 (br s, 1 H, H_6), 1.67–1.40 (m, 6 H, CH_2), 1.27–1.12 (m, 2 H, CH_2). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.31; H, 8.85.

Brexane-2-carboxylic Acid (9b). A solution of ester **9a** (750 mg, 4.16 mmol) in MeOH (7.16 mL) was added to a solution of KOH (467 mg, 8.32 mmol) in H_2O (3.7 mL). The mixture was allowed to reflux (at 85 °C) under Ar for 5 h. The MeOH was evaporated in vacuo, and the aqueous alkaline solution was extracted with ether to remove starting ester. The aqueous layer was acidified with 2 N H_2SO_4 to a pH ca. 3–5 and was extracted with ether, which was worked up to give off-white crystals (648 mg, 94%, mp 89–91 °C). Repeated crystallization from pentane provided **9b** as white crystals, mp 91–92 °C: IR (CCl_4) 3615 (w) 3400–3000 (m), 1750 (w), 1703 (s), 1270 (m, 1245 (m), 1230 (m), 1215 (w) cm^{-1}; ^{1}H NMR (80 MHz, CCl_4; external lock $CDCl_3$) δ 13.75 (s, 1 H, CO_2H), 2.25 (br s, 2 H), 2.15–2.05 (m, 1 H), 2.05–1.75 (m, 2 H), 1.75–1.05 (m, 8 H, CH_2). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.43; H, 8.54.

2-Carbomethoxy-2-(methylthio)brexane (10). Following a general method of Trost and Tamaru,[20] we added *n*-butyllithium (18.6 mL, 48.4 mmol, 2.6 M solution in hexanes, Aldrich) dropwise to a solution of dry cyclohexylisopropylamine (9.64 mL, 58.0 mmol, Aldrich) in anhydrous THF (63 mL) at −78 °C under Ar. [Note: An excess of amine relative to *n*-butyllithium (i.e., 1.2/1) is needed to prevent *n*-butyllithium acylation of ester **9a** and ultimate formation of tertiary alcohol]. The cloudy mixture was stirred at −78 °C for 30 min, and a solution of **9a** (3.76 g, 16.7 mmol, 80% **9a**, + 13% methyl (5-cyclopentyl)pentanoate + 6% solvent) in anhydrous THF (21.0 mL) and dry HMPA (10.5 mL) was added dropwise (followed by a 4.2-mL THF rinse to ensure complete transfer of **9a**) to the rapidly stirred mixture at −78 °C. The resultant solution was allowed to warm to −25 °C and was stirred at that temperature under Ar for 2 h. Dimethyl disulfide (6.0 mL, 65.8 mmol, 99%) was added in one portion, and the mixture was stirred 15 min at −25 °C and 35 min at 0 °C. The mixture was poured into H_2O (ca. 250 mL) and was extracted with CH_2Cl_2. Conventional workup gave a yellow liquid, which was added to 1 M HCl (11 mL) and was extracted with ether. The ether was washed with 1 M HCl until pH ca. 3–5. The combined aqueous washings were back-extracted with ether (ca. 50 mL), and the ether was washed with saturated aqueous $NaHCO_3$ (ca. 10 mL) and worked up to give a yellow oil (6.4 g). Column chromatography (silica gel, pentane:ether = 6:1) afforded a clear, viscous oil (4.10 g, 99%): GC 91.5% **10** (t_R = 17.1 min) + 8.5% solvent; TLC (silica gel, pentane:ether = 6:1) one spot, R_f = 0.78. The analytical sample of ester **10** was obtained as a viscous, colorless liquid by bulb to bulb distillation (105 °C (0.05 mm)): GC purity = 99.5%; IR (neat) 1718 (s), 1455 (m), 1435 (m), 1260–1205 (s) cm^{-1}; ^{1}H NMR (400 MHz) δ 3.75 (s, 3 H, OCH_3), 2.79 (br s, 1 H, H_1), 2.18–2.16 (m, 1 H, H_3), 2.07–2.04 (m, 1 H, H_7), 2.02–2.00 (br s, 1 H, H_6), 1.94 (s, 3 H, SCH_3), 1.89–1.72 (m, 2 H, CH_2), 1.65–1.35 (m, 6 H, CH_2). Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 63.51; H, 8.01.

2-Carboxy-2-(methylthio)brexane (11). A solution of **10** (3.92 g, 14.9 mmol, purity = 86%) in ethylene glycol (119 mL) was added to a mixture of KOH (8.36 g, 149 mmol) and ethylene glycol (59 mL). The rapidly stirred mixture was allowed to reflux under Ar for 2 h in an oil bath at 200 °C. The solution was allowed to cool to rt and was transferred to a mixture of ice and H_2O, which was extracted with ether to remove starting material, and the aqueous layer was acidified to pH ca. 3–5 with 1 M HCl. Extraction with ether and workup gave a yellow oil (4.08 g) which solidified in a minimum quantity of pentane and was dried under high vacuum to leave a white solid (3.07 g, 97%, mp 79–83 °C). Repeated recrystallization from pentane gave mp 82–84 °C: IR (CCl_4) 3675 (w), 3620 (w), 3060 (sh), 1760 (w), 1730 (m), 1730 (m), 1685 (s), 1275 (s) cm^{-1}; ^{1}H NMR (400 MHz, CCl_4; external lock $CDCl_3$) δ 11.58 (s, 1 H, CO_2H), 2.92 (br s, 1 H, H_1), 2.36–2.33 (m, 1 H, H_3), 2.30–2.22 (m, 1 H, H_7), 2.21–2.20 (br s, 1 H, H_6), 2.19 (s, 3 H, SCH_3), 2.10–1.93 (m, 4 H, CH_2), 1.83–1.63 (m, 4 H, CH_2). Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60. Found: C, 62.25; H, 7.75.

Oxidative Decarboxylation of 11 to Brexan-2-one (Tricyclo[4.3.0.0^{3,7}]nonan-2-one) (12). Solid $NaHCO_3$ (2.28 g, 26.9 mmol) was added in one portion to a rapidly stirred solution of **11** (2.0 g, 9.4 mmol, mp 76–81 °C) in MeOH (124 mL) under Ar. The mixture was stirred at rt for 10 min, and solid *N*-chlorosuccinimide (2.95 g, 21.7 mmol, 98%) was added in four portions over 15 min. The mixture was stirred 3 h under Ar at rt, and saturated aqueous Na_2SO_3 (40 mL) was added, followed by 1 M HCl (131 mL) until pH ca. 4.0. After an additional 2 h to ensure complete hydrolysis of the intermediate dimethyl ketal, the stirred mixture was diluted with H_2O (ca. 245 mL) and was extracted with pentane (3 × 250 mL). The combined pentane extract was worked up (without heat) to afford a colorless, volatile liquid (1.38 g, 99%). GC showed 93% brexan-2-one (**12**), t_R = 11.38 min + 6% solvent: TLC (neutral alumina, Brockmann activity III, pentane:ether = 69:1) one spot, R_f = 0.34. A small portion (ca. 20 mg) subjected to bulb to bulb distillation (bp 100 °C (1.0 mm)) gave a clear liquid ketone whose IR and NMR spectra were identical to those of an authentic sample:[56] IR (neat) 3466 (w), 1841 (w), 1746 (s), 1069 (s) 765 (s), cm^{-1}; ^{1}H NMR (400 MHz) δ 2.41–2.36 (m, 2 H, H_1 + H_3), 2.35–2.30 (m, 2 H, H_6 + H_7), 1.97–1.78

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(m, 4 H, CH_2), 1.68–1.57 (m, 4 H, CH_2).

2-(Aminomethyl)-2-hydroxybrexane (13). Modifying a general procedure of Evans et al.[21] we added a solution of brexan-2-one (**12**, 426 mg, 2.97 mmol, 95% **12** + 5% solvent) in $CHCl_3$ (5 mL) in one portion to a rapidly stirred mixture of trimethylsilyl cyanide (1.01 mL, 7.43 mmol, Aldrich, 98%) and 18-crown-6 KCN complex (51 mg, 0.15 mmol, see General). The stirred mixture under Ar was heated at 95 °C and allowed to reflux for 6 h. (The progress was followed by GC (10 psi, T_i = 100 °C, T_f = 150 °C, program rate = 5 °C/min) which showed **12** at t_R = 13.5 min and (trimethylsilyl)cyanohydrin at t_R = 23.4 min.) Most of the $CHCl_3$ was evaporated in vacuo, and the bright red residual oil was dissolved in anhydrous ether (4.5 mL). The ether solution was added dropwise to a rapidly stirred suspension of $LiAlH_4$ (356 mg, 8.91 mmol, 95%) and anhydrous ether (4.0 mL) under Ar. The stirred mixture was maintained at reflux for 1 h. The mixture was allowed to cool to rt under positive Ar flow, additional ether (50 mL) added, and H_2O (9 mL) was cautiously added dropwise to the rapidly stirred mixture, followed by aqueous 20% NaOH (9 mL) and additional H_2O (9 mL). The mixture was stirred 30 min and was poured into H_2O (ca. 10 mL). The alkaline mixture was extracted with ether, which was worked up to give a yellow oil. The oil was dissolved in 6 M HCl (5 mL) and was extracted with ether to remove organic impurities. The aqueous layer was made basic (pH ca. 8–9) with aqueous 20% NaOH (ca. 25 mL) and was extracted with ether. Conventional workup gave a white solid (472 mg, 95%, 72–85 °C), which rapidly turned light tan on exposure to air. The analytical sample of 2-(aminomethyl)-2-hydroxybrexane (**13**) was obtained by repeated recrystallization from ether to give off-white crystals, mp 92–93 °C: IR (CCl_4) 3565 (w), 3400 (m), 2460–2380 (w), 1640–1560 (m) cm^{-1}; ^1H NMR (400 MHz) δ 2.76 (d, 1 H, J = 12.5 Hz, CH_2N), 2.64 (d, 1 H, J = 12.5 Hz, CH_2N), 2.40–1.96 (m, 2 H, $H_1 + H_3$), 1.95–1.88 (m, 1 H, H_7), 1.79–1.70 (m, 4 H), 1.65–1.56 (m, 3 H), 1.47–1.30 (m, 5 H). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25. Found: C, 71.69; H, 10.42.

Ring Expansion of 13 to Tricyclo[5.3.0.0^{4,8}]decan-2-one (Homobrexan-2-one) (14). Modifying a general procedure of McKinney and Patel,[22] we added a solution of glacial HOAc (30 μL, 0.53 mmol) and H_2O (490 μL) to amino alcohol **13** (50 mg, 0.30 mmol, mp 92–93 °C) under Ar. The rapidly stirred solution was cooled to 0 °C, and a solution of $NaNO_2$ (32 mg, 0.45 mmol, 97%) in H_2O (490 μL) was added dropwise over 5 min. The mixture was stirred for 1 h at 0 °C (under Ar) and was heated to reflux over 1 h. The acidic mixture was allowed to cool to rt and was made slightly basic (pH ca. 7–8) with saturated $NaHCO_3$ (ca. 10 mL). The mixture was extracted with ether (5 × 10 mL), and the combined ether extract was washed with additional $NaHCO_3$ (5 mL). Conventional workup left a white solid (48.6 mg, mp 90–120 °C), which was chromatographed (neutral alumina, Brockmann activity III, pentane:ether = 9:1) to give homobrexan-2-one (**14**) as white crystals (44 mg, 98%, mp 143–144 °C undepressed in a mixture with authentic sample): TLC (neutral alumina, Brockmann activity III, pentane:ether = 9:1) one spot, R_f = 0.27. GC of a pentane solution of **14** showed one peak at t_R = 3.7 min. The 400-MHz ^1H NMR ($CDCl_3$ and CD_3OD) spectra, the 100-MHz ^{13}C broad band decoupled NMR ($CDCl_3$) spectrum, the IR (CCl_4) spectrum, and the low-resolution mass spectrum were all identical to those of an analytically pure sample of **14** prepared by cyanogen azide homologation of 2-methylenebrexane (**16a**).

Direct Conversion of Brexan-2-one (12) to Homobrexan-2-one (14). A mixture of trimethylsilyl cyanide (1.34 mL, 9.18 mmol, 97%), brexan-2-one (**12**, 1.10 g, 7.34 mmol, purity = 91% **12** + 9% solvent), 18-crown-6 KCN complex (121 mg, 0.37 mmol, see General), and dry $CHCl_3$ (2 mL) was stirred 5 h under Ar in an oil bath at 95 °C. The dark brown mixture was allowed to cool to rt, and anhydrous ether (10 mL) was added. The resultant solution was transferred via a cannula, dropwise over 15 min, to a rapidly stirred suspension of $LiAlH_4$ (880 mg, 22.0 mmol, 95%) and anhydrous ether (15 mL). The mixture was maintained at reflux for an additional 1 h, was allowed to cool to rt, and was transferred to a flask containing ether (70 mL). Water (30 mL) was added dropwise to the rapidly stirred suspension, followed by aqueous 20% NaOH (30 mL) and then additional H_2O (30 mL). The basic mixture was stirred for 15 min and was extracted with ether (3 × 250 mL). Conventional workup gave a yellow solid (2.06 g), which was dissolved in a solution of acetic acid (735 μL, 12.9 mmol) and H_2O (12 mL) cooled to 0 °C (under Ar). A solution of $NaNO_2$ (783 mg, 11.0 mmol, 97%) and distilled H_2O (12 mL) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and was heated at reflux for 1 h. The acidic mixture was allowed to cool to rt, was made slightly basic (pH ca. 7–8) with saturated $NaHCO_3$ (65 mL), and was extracted with ether (5 × 100 mL). The combined ether extract was washed with saturated aqueous $NaHCO_3$ (25 mL) and worked up to give a yellow solid (1.54 g). Column chromatography (neutral alumina, Brockmann activity III, pentane:ether = 9:1) gave hombrexan-2-one (**14**, 971 mg, mp 143–144 °C, 88% from brexan-2-one) as white crystals. The material was homogeneous by TLC and GC and was identical to analytically pure ketone **14**.

2-(Hydroxymethyl)brexane (15a). A solution of ester **9a** (642 mg, 3.49 mmol, purity = 98%) in dry THF (3 mL) was added dropwise to a rapidly stirred suspension of $LiAlH_4$ (154 mg, 3.84 mmol, 95%) and THF (3 mL) under Ar at 0 °C. After addition, the mixture was refluxed for 6 h and was allowed to cool to rt. The THF was evaporated in vacuo, H_2O (1.5 mL) was added dropwise, followed by aqueous 20% NaOH (1.0 mL) and then more H_2O (1.5 mL). The mixture was stirred 30 min at rt and was extracted with ether (3 × 25 mL). Workup left a viscous, colorless oil (516 mg). Column chromatography (silica gel, pentane:ether = 5:2) gave a colorless liquid (505 mg, 93%). GC of a pentane solution showed on peak at t_R = 6.6 min (purity = 98%). TLC (silica gel, pentane:ether = 5:2, one spot, R_f = 0.23). The analytically pure alcohol **15a** was obtained by distillation (bp 118 °C, (0.25 mm)) to give a viscous, colorless liquid. At −20 °C the liquid formed crystals that melted at room temperature: GC purity = 98%; IR (neat) 3320 (br, m), 1045 (m), 995 (m) cm^{-1}; ^1H NMR (80 MHz) δ 3.53 (d, 2 H, J = 7.9 Hz, CH_2O), 2.15–1.70 (m, 3 H, bridgehead), 1.70–0.85 (m, 11 H; 1 H exchanges with D_2O). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.66; H, 10.74.

2-[[(2′-Nitrophenyl)seleno]methyl]brexane (15b). In adaptation of a general procedure of Grieco et al.[25] we added tri-*n*-butylphosphine (7.20 mL, 27.47 mmol, Aldrich, 95%) dropwise to a rapidly stirred solution of 2-nitrophenyl selenocyanate (5.92 g, 25.28 mmol, Fluka, 97%) in anhydrous THF (49 mL) under Ar at rt. The dark brown mixture was stirred 5 min until a golden solid (suspected *n*-$Bu_3P^+SerArCN^-$) precipitated. A solution of alcohol **15a** (2.59 g, 14.98 mmol, purity = 88% + 12% solvent) and dry pyridine (0.675 mL, 8.43 mmol) was added in one portion. The resultant dark red solution and was stirred under Ar (at rt) for 2.5 h, during which time a yellow solid (suspected *n*-$Bu_3P{=}O$) precipitated from the light amber solution. Evaporation (in vacuo) gave an amber oil (23 g). Column chromatography (silica gel, pentane:ether = 9:1), followed by recrystallization from pentane, gave three crops (4.01 g, mp 82–84 °C; 0.78 g, mp 80–82.5 °C; 0.06 g, mp 84–86 °C) of bright yellow crystals (total 4.85 g, 96%): TLC (silica gel, pentane:ether = 9:1) one spot, R_f = 0.46. Several additional recrystallizations gave analytical pure seleno ether **15b** as bright yellow crystals (mp 85–86 °C): IR (CCl_4) 3060 (w), 1590 (s), 1510 (s), 1335 (s), 1305 (s), 1040 (s) 855 (s) cm^{-1}; ^1H NMR (80 MHz) δ 8.30–8.10 (dm, 1 H, $J_{3',4'}$ = 7.5 Hz, $ArH_{3'}$), 7.55–7.10 (m, 3 H, ArH), 3.05–2.65 (dd, 2 H, J = 8.2, 2.3 Hz, CH_2Se), 2.15–1.72 (m, 3 H, bridgehead), 1.71–1.10 (m, 10 H); UV λ (pentane) 394 (ϵ = 3791), 254 (ϵ = 13 766), 204 (ϵ = 11 851) nm. Anal. Calcd for $C_{16}H_{19}NO_2Se$: C, 57.15; H, 5.70. Found: C, 57.05; H, 5.72.

2-Methylenebrexane (16a). We added[26b] aqueous 30% H_2O_2 (2.0 mL, 19.40 mmol) dropwise, over 30 min, to a stirred solution of selenoether **15b** (2.61 g, 7.76 mmol, mp 82–85 °C) in THF (44 mL) cooled to −10 °C. After 30 min, the solution was allowed to warm to rt over 1.75 h, was poured into H_2O (325 mL), and was extracted with pentane (3 × 100 mL). The pentane was washed with 10% Na_2CO_3 (2 × 25 mL) and with 20% NaOH (3 × 50 mL) until the purple color of the alkaline extracts disappeared. The pentane was washed with brine (2 × 25 mL), dried over Na_2SO_4, and was evaporated in vacuo (the distillation and receiving flasks were cooled with ice–H_2O baths). Column chromatography (neutral alumina, Brockmann activity I, pentane) of the extremely volatile, light yellow liquid (1.62 g) gave a colorless liquid (1.32 g, 97%): GC (100 °C, 12 psi) purity = 76.4% **16a**

(t_R = 1.56 min) + 23.6% solvent). *Note:* Previous attempts to concentrate the extremely volatile olefin on the rotary evaporator resulted in substantial product loss. TLC (neutral alumina, pentane) one spot, R_f = 0.76. Bulb to bulb distillation (bp 80 °C (760 mm)) gave an analytical sample of alkene **16a** as a colorless liquid: GC purity = 98%; IR (neat) 3060 (w), 2940 (s), 2900 (shoulder), 2860 (m), 1665 (m), 875 (m) cm^{-1}; ^1H NMR (400 MHz) δ 4.70 (s, 2 H, exo $=CH_2$), 2.42 (s, 2 H, $H_1 + H_3$), 2.00–1.99 (s, 2 H, $H_6 + H_7$), 1.73–1.59 (m, 4 H, CH_2), 1.51–1.42 (m, 2 H, CH_2), 1.32 (t, J = 8.5 Hz, CH_2); UV (hexane) λ 197.5 nm (ϵ = 12 227); low-resolution MS m/e 134.1 (M^+ 47), 91.1 (100). Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.68; H, 10.53.

Conversion of Alkene 16a to Homobrexan-2-one (14), 10-(Bromomethylene)tricyclo[4.3.0.0^{3,7}]nonane (16b), and Suspected 2-Bromo-2-homobrexane (17) with Cyanogen Azide. We adapated a general procedure of McMurry and Coppolino.[27a] Solid NaN_3 (4.23 g, 65.0 mmol) was added to a stirred solution (0 °C) of cyanogen bromide (6.89 g, 65.0 mmol) in acetonitrile (16.3 mL), and the mixture was stirred 4 h at 0 °C. An aliquot (15.4 mL, ca. 61.7 mmol) of the supernatant was removed, was added to a stirred mixture of alkene **16a** (1.42 g, 7.7 mmol, purity = 73% **16a** + 27% pentane), $LiClO_4$ (828 mg, 7.8 mmol), and MeOH (10.4 mL), and the (vented) mixture was stirred 12 days at rt. The mixture was treated with 6 N HCl (6 mL), was warmed to 35 °C, was stirred for 3 h, was diluted with H_2O (100 mL), and was extracted with ether (3 × 150 mL). The ether was washed with brine (25 mL), dried over $MgSO_4$, filtered through basic alumina (13 g) topped with a layer of Celite (13 g), and was evaporated in vacuo to afford a yellow oil. Column chromatography (neutral alumina, Brockmann activity III, pentane:ether = 9:1) gave pure fractions of homobrexan-2-one (**14**, 551 mg, 46%, mp 14–143 °C). GC of a pentane solution showed one peak at t_R = 5.63 min, purity = 95%: TLC (neutral alumina, pentane:ether = 9:1) one spot, R_f = 0.27. The remaining fractions contained a two-component mixture (792 mg, 42%) of a major bromo compound **16b** and a minor isomer thought to be 2-bromo-2-homobrexene (**17**): GC (purity = 73% **16b** (t_R = 14.0 min) + 14% **17** (t_R = 15.2 min) + 13% solvent); TLC (neutral alumina, pentane:ether = 9:1) one spot, R_f = 1.0. Column chromatography (silica gel, pentane) of the olefinic mixture gave a clear liquid (334 mg): GC (purity = 94.5% **16b** + 2.7% **17** + 2.8% solvent). Flash column chromatography (20% $AgNO_3$ impregnated silica gel, pentane) of the two-component mixture did not improve the purity of **16b**. Bulb to bulb distillation (95 °C (0.4 mm)) gave 2-(bromomethylene)brexane (**16b**) as a colorless liquid: GC purity = 97.1% **16b** + 2.9% **17**; IR (neat) 3035 (w) 1650 (w), 1240 (s), 755 (s), 715 (s), 670 (s) cm^{-1}; ^1H NMR (400 MHz) δ 5.78 (s, 1 H, $=CHBr$), 2.78–2.74 (br s, 1 H, H_1), 2.57–2.53 (br s, 1 H, H_3), 2.18–2.14 (m, 1 H, H_6), 2.10–2.06 (m, 1 H, H_7), 1.75–1.61 (m, 4 H, CH_2), 1.55–1.34 (m, 4 H, CH_2); broad band decoupled ^{13}C NMR (100 MHz) δ 154.21 (C_2), 94.04 ($=CHBr$), 51.91, 50.62, 49.72, 48.61, 31.46, 28.93, 22.90, 22.69; coupled ^{13}C NMR (100 MHz) δ 154.21 (s), 94.04 (d, J = 198.0 Hz), 51.91 (d, J = 138.9 Hz), 50.62 (d, J = 132.2 Hz), 49.72 (d, J = 141.5 Hz), 48.61 (d, J = 138.8 Hz), 31.46 (t, J = 131.9 Hz), 28.93 (t, J = 130.6 Hz), 22.90 (t, J = 131.7 Hz), 22.69 (t, J = 129.2 Hz); low-resolution GC (SE-54)/MS m/e 214 (M + 2, 10), 212 (M^+, 10), 91 (100) for **16b**; and 214 (M + 2, 14), 212 (M^+, 13), 91 (100) for the minor constituent thought to be 2-bromo-homobrexene (**17**). For **16b**: high-resolution MS m/e calcd for $C_{10}H_{13}Br$ 212.0201, found 212.0200; UV λ (MeOH) 206 nm (ϵ = 14 752). Anal. Calcd for $C_{10}H_{13}Br$: C, 56.36; H, 6.15. Found: C, 56.55; H, 6.34.

The analytical sample of homobrexan-2-one (**14**) was obtained, as white crystals, after four recrystallizations from minimum quantities of pentane; mp 143–144 °C (contrast lit.[10,23] mp 47–49 °C). GC of a pentane solution showed one peak at t_R = 5.1 min (purity = 99.2%): TLC one spot, R_f = 0.27; IR (CCl_4) 1715 (s), 1470–1420 (m), 1350 (m) cm^{-1}. ^1H NMR (400 MHz) δ 2.62–2.55 (br t, 1 H, J = 5.2 Hz, H_1), 2.52–2.47 (m, 1 H, H_{3ax}), 2.47–2.43 (m, 1 H, H_7), 2.43–2.38 (m, 1 H, H_8), 2.31–2.25 (m, 1 H, H_4), 2.08–1.71 (m, 6 H), 1.68–1.58 (m, 3 H); ^1H NMR (400 MHz, CD_3OD) δ 2.68–2.61 (ddd, 1 H, $J_{3ax,3eq}$ = 14.4 Hz, $J_{3ax,4}$ = 5.2 Hz, $J_{3ax,5exo}$ = 1.9 Hz, H_{3ax}), 2.61–2.55 (m, 2 H, $H_1 + H_7$), 2.55–2.48 (m, 1 H, H_8), 2.39–2.32 (m, 1 H, H_4), 2.18–1.98 (m, 4 H, CH_2 and H_{3eq}), 1.98–1.80 (m, 2 H, CH_2), 1.79–1.56 (m, 3 H, CH_2); ^1H NMR (400 MHz, C_6D_6) δ 2.56–2.49 (t, 1 H, J = 2.9 Hz, H_1), 2.18–2.06 (dd, 1 H, $J_{3ax,3eq}$ = 8.3 Hz, $J_{3ax,4}$ = 3.0 Hz, H_{3ax}) 2.01–1.94 (m, 1 H, H_7), 1.94–1.86 (m, 2 H, H_8 and H_{3eq}), 1.82–1.73 (m, 1 H, H4), 1.62–1.94 (m, 8 H, CH_2); broad band decoupled ^{13}C NMR (100 MHz) δ 215.32 (C=O), 58.64 (C_1), 47.89 (C_7), 46.49 (C_8), 43.57 (C_3), 41.24 (C_4), 43.57, 41.24, 32.21, 29.55, 24.13, 23.75; coupled ^{13}C NMR (100 MHz). 215.32 (s, C=O), 58.64 (d, J = 139.4 Hz, C_1), 48.89 (d, J = 140.3 Hz, C_7), 46.49 (d, J = 135.7 Hz, C_8), 43.57 (t, J = 127.0 Hz, C_3), 41.24 (d, J = 137.1 Hz, C_4), 32.21 (t, J = 132.4 Hz), 29.55 (t, J = 133.4 Hz), 24.13 (t, J = 128.9 Hz), 23.75 (t, J = 131.7 Hz); low-resolution MS m/e 150 (M^+, 60), 106 (100); high-resolution mass spectrum m/e calcd for $C_{10}H_{14}O$ 150.1045, found 150.1042. Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.68; H, 9.22.

Cleavage of 2-Methylenebrexane (16a) to Brexan-2-one (12) with *m*-Chloroperoxybenzoic Acid. We added a solution of **16a** (275 mg, 1.50 mmol, purity = 73% **16a** + 17% solvent) in $CHCl_3$ at 0 °C, in one portion, to solid *m*-chloroperoxybenzoic acid (1.32 g, 6.11 mmol, mp 92–95 °C, Alfa, 80%). The resultant solution was stirred for 2.5 h and was neutralized with saturated Na_2CO_3 (2 × 20 mL) until the effervesence ceased and the pH was ca. 8. The mixture was extracted with $CHCl_3$ (2 × 20 mL) and worked up conventionally to afford a yellow liquid (301 mg). Column chromatography (neutral alumina, Brockmann activity III, pentane:ether = 9:1) gave a colorless liquid (171 mg, 71%): GC (100 °C, 10 psi) purity = 85.2% **12**, t_R = 15.2 min + 7.3% solvent + 2.2% starting alkene **16a**, t_R = 2.0 min + 5.3% unknown, t_R = 16.6 min); TLC (neutral alumina, pentane:ether = 9:1) one spot, R_f = 0.35. Repeated column chromatography followed by bulb to bulb distillation (100 °C (1.0 mm)) gave brexan-2-one (**12**), as a colorless liquid: GC (purity = 98% 1 + 2% solvent). Its IR and ^1H NMR spectra were identical in all essential respects to those of a pure sample of **12**.[11c,56]

2-(Hydroxymethyl)brexane *p*-Toluenesulfonate (15c). Modifying a procedure of Nedenskov, Heide, and Clauson-Kass,[31] we added a solution of alcohol **15a** (261 mg, 1.38 mmol, purity = 80.6% + 13.4% 5-cyclopentylpentanol + 6% ether) in dry pyridine (0.23 mL), in one portion, to a stirred solution of *p*-toluenesulfonyl chloride (354 mg, 1.84 mmol, 99%) in pyridine (0.41 mL) under Ar. The mixture was stirred 24 h at rt, was diluted with ether (21 mL), and was poured over cracked ice (21 mL). Acidification with 6 M HCl (ca. 2 mL) to pH ca. 3, extraction with ether (3 × 45 mL), followed by conventional workup gave a yellow oil (459 mg). Column chromatography (silica gel, pentane:ether = 9:1) gave tosylate **15c** as a colorless, viscous liquid (364 mg, 86%): TLC (silica gel, pentane:ether = 9:1) one spot, R_f = 0.32): IR (neat) 2960 (s), 2890 (m), 1600 (m), 1500–1450 (w), 1365 (s), 1175 (s), 1100 (m), 1000–900 (s) cm^{-1}; ^1H NMR (400 MHz) δ 7.84–7.78 (dm, 2 H, J = 8.1 Hz, $H_{6'} + H_{2'}$), 7.39–7.34 (dm, 2 H, J = 8.1 Hz, $H_{5'} + H_{3'}$), 4.05–3.99 (m, 1 H, OCH_2), 3.95–3.89 (t, 1 H, J = 9.2 Hz, OCH_2), 2.50–2.40 (s, 3 H, CH_3), 2.05–2.00 (br s, 1 H), 1.99–1.94 (m, 1 H), 1.87–1.82 (m, 1 H), 1.62–1.53 (m, 4 H), 1.51–1.33 (m, 3 H), 1.33–1.26 (m, 3 H). Anal. Calcd for $C_{17}H_{22}O_3S$: C, 66.64; H, 7.24. Found: C, 66.45; H, 7.37.

Rearrangement of Tosyl Ester 15c to Axial Tricyclo[5.3.0.0^{4,8}]decan-2-ol (18a) and Equatorial Tricyclo[5.3.0.0^{4,8}]decan-2-ol (18b). We heated a stirred mixture of tosylate **15c** (261.0 mg, 0.85 mmol), glacial HOAc (0.24 mL, 4.21 mmol), *p*-toluenesulfonic acid monohydrate (2.3 mg, 0.01 mmol), and H_2O (1.26 mL) at 120 °C under Ar for 24 h. The mixture was allowed to cool to rt, and a solution of NaOH (243 mg, 6.07 mmol) in H_2O (365 mL) was added to saponify acetate esters. The alkaline mixture (under Ar) was heated at reflux for 3 h, was allowed to cool, and was extracted with ether (3 × 50 mL). Workup gave a light yellow solid (140 mg): GC of a pentane–ether (6:1) solution showed three peaks: t_R = 4.14 min (6.3%, unknown), t_R = 5.86 min (9.4%, axial alcohol **18a**), and t_R = 6.50 min (84.3% equatorial alcohol **18b**). The alcohols were identified by peak enhancement with authentic samples prepared by reduction of homobrexan-2-one (**14**). Column chromatography (silica gel, pentane:ether = 6:1) gave white crystals (121 mg, 94%, mp 134–140 °C). GC of a pentane–ether (6:1) solution showed two peaks, t_R = 5.74 min (12.6%, axial alcohol **18a**) and t_R = 6.68 min (87.4%, equatorial alcohol **18b**). TLC (silica gel, pentane:ether = 6:1) one spot, R_f = 0.33. ^1H NMR (400 MHz) of the epimeric mixture showed signals for the 2-carbinyl H of equatorial alcohol **18b** at δ 3.94–3.85 (m, $J_{2,3ax}$ = 10.4 Hz, $J_{2,3eq}$ = 6.5, $J_{2,1}$ = 4.0 Hz)

and for the 2-carbinyl H of axial alcohol **18a** at δ 3.78–3.66 (m, $J_{2,3ax}$ = 3.6 Hz, $J_{2,3eq}$ = 2.6 Hz, $J_{2,1}$ = 1.8 Hz); ratio **18b**/**18a** = 6.7. Attempts to separate the epimers by chromatography and fractional recrystallization were unsuccessful, so the mixture was oxidized to homobrexan-2-one as described text.

Oxidation of Epimeric Mixture of 18a and 18b to Homobrexan-2-one (14). We employed a modified procedure of Walborsky.[32] A solution of CrO_3 (116 mg, 1.16 mmol) in HOAc (1.76 mL) and H_2O (0.10 mL) was added dropwise (over 30 min) to a stirred mixture of alcohols **18a** and **18b** (101 mg, 0.66 mmol, mp 134–140 °C, **18b**/**18a** = 6.7) in HOAc (1.75 mL) and THF (1.0 mL) at 0 °C. The addition rate was controlled so as not to let the temperature exceed 25 °C, and progress was followed by GC. After 2 h at rt, the mixture was made basic with $NaHCO_3$ (20 mL) and was extracted with ether (3 × 50 mL). Conventional workup gave a white solid. GC of a pentane solution showed six peaks: ketone **14** (t_R = 6.75 min, 69.0%); starting alcohols **18a** (t_R = 7.27 min, 1.3%) and **18b** (t_R = 7.40 min, 9.8%); and three unknowns (t_R = 6.49–7.04 min, 19.9%). Column chromatography (silica gel, pentane:ether = 6:1) gave **14** as white crystals (64 mg, 60%, mp 142.5–144 °C). GC (SE-52, 150 °C, 14 psi) of a pentane solution showed one major peak at t_R = 6.60 min (92%). The IR and ^1H NMR spectra of this sample were identical in all essential respects to those of an analytical sample of homobrexan-2-one (**14**).

$LiAlH_4$ Reduction of Homobrexan-2-one (14). We added $LiAlH_4$ (182 mg, 4.53 mmol, 95%) to a stirred solution of ketone **14** (100 mg, 0.67 mmol, purity = 99.4%) in ether (8 mL) under Ar. The suspension was stirred 20 h at room temperature, H_2O (4 mL) was added dropwise over 5 min, stirring was continued for 15 min, and 20% NaOH (4 mL) was added. This mixture was stirred 15 min and was extracted with ether (3 × 50 mL). Conventional workup afforded white crystals (112 mg, mp 156–167 °C): GC 63% **18a**, 28% **18b**, 9% BHT (ether stabilizer); TLC (silica gel, pentane:ether = 9:1) one spot, R_f = 0.19. ^1H NMR (400 MHz) showed the C-2 carbinyl hydrogen at δ 3.78–3.66 (m, 0.69 H, $J_{2,3ax}$ = 3.2 Hz, $J_{2,3eq}$ = 2.5 Hz, $J_{2,1}$ = 1.8 Hz), for **18a** and at δ 3.94–3.85 (m, 0.31 H, $J_{2,3ax}$ = 10.4 Hz, $J_{2,3eq}$ = 6.5 Hz, $J_{2,1}$ = 4.0 Hz) for **18b**; ratio **18a**/**18b** = 2.25.

Unsuccessful attempts to separate the alcohols by chromatography and by fractional recrystallization led us to explore a carboethoxylation ("cathylation") procedure as follows.

Action of Ethyl Chlorocarbonate on a Mixture of Alcohols 18a and 18b. Isolation of Axial Alcohol 18a. We applied the general, stereoselective carboethoxylation procedure of Fieser et al.[38] Ethyl chlorocarbonate (0.78 mL, 7.92 mmol, 97%) was added dropwise to a stirred solution of a mixture of **18a** and **18b** (150 mg, 0.99 mmol, mp 156–167 °C **18a**/**18b** = 2.25) and dry pyridine (0.61 mL, 7.52 mmol) in anhydrous dioxane (7 mL) under Ar. The mixture was stirred at rt for 30 min, and H_2O (5 mL) was added followed by 36% HCl (0.38 mL). The mixture was stirred overnight, H_2O (25 mL) was added, and the mixture was extracted with ether (3 × 25 mL). Workup gave a clear oil (1118 mg). TLC (silica gel, pentane:ether = 6:1) showed seven spots. GC showed three major peaks (excluding solvent) at t_R = 6.04 min (**18a**, 37.3%), t_R = 10.9 min (suspected axial carbonate **19a**, 41.3%), and t_R = 12.5 min (suspected equatorial carbonate **19b**, 21.4%). Column chromatography (silica gel, pentane:ether = 6:1) gave fractions containing starting alcohol **18a** (60.2 mg, 40%, mp 166–178 °C) as white crystals. The remaining fractions contained a two-component carbonate mixture (121 mg, 56%) of **19a** and **19b**: GC purity = 54% **19a** (t_R = 6.85 min) + 29% **19b** (t_R = 7.78 min) + 17% unknowns. TLC (silica gel, pentane: ether = 6:1) three spots. The carbonate mixture was again subjected to column chromatography, which only removed most of the unknowns but did not separate **19a** and **19b**: GC purity = 64% **19a** + 31% **19b** + 5% unknown; TLC (silica gel, pentane:ether = 9:1) one spot, R_f = 0.49; IR (neat) 1740 (s), 1370 (m), 1265 (s) cm^{-1}. ^1H NMR (400 MHz) showed for the C-2 carbinyl H of equatorial carbonate **19b** δ 4.84–4.78 (m, 0.35 H, $J_{2,3ax}$ = 10.6 Hz, $J_{2,3eq}$ = 5.0 Hz, $J_{2,1}$ = 3.7 Hz) and for the C-2 carbinyl H of the axial carbonate **19a** δ 4.54–4.48 (m, 0.65 H, $J_{2,3ax}$ = 3.5 Hz, $J_{2,3eq}$ = 2.6 Hz, $J_{2,1}$ = 2.3 Hz). The analytical sample of axial alcohol **18a** was obtained after several recrystallizations from pentane; mp 190–191 °C; IR (KBr) 3500–3020 (br, s), 1025 (axial CO, s), cm^{-1}; IR (CCl_4) 3610 (w), 1025 (axial CO, s) cm^{-1}; ^1H NMR (400 MHz) δ 3.78–3.66 (m, 1 H, $J_{2,3ax}$ = 3.2 Hz, $J_{2,3eq}$ = 2.5 Hz, $J_{2,1}$ = 1.8 Hz, $W_{1/2}$ = 10.0 Hz, H_2), 2.45–2.34 (m, 1 H, H_7), 2.19–2.02 (m, 3 H, H_8 + H_4 + H_1), 2.01–1.90 (m, 2 H), 1.90–1.61 (m, 6 H), 1.54–1.30 (m, 3 H). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.28; H, 10.44.

K/NH_3 Reduction of Homobrexan-2-one (14). Isolation of Equatorial Homobrexan-2-ol (18b). We were guided by a general procedure of Murphy and Sullivan.[40c] A solution of ketone **14** (200 mg, 1.33 mmol, mp 143–144 °C, purity = 99.4%) in anhydrous ether (1 mL) was added to a stirred mixture of dry liquid ammonia (26 mL), under Ar at −78 °C, containing enough potassium metal (ca. 50 mg) to maintain a blue color. More metal (131 mg, 3.35 mmol) was added, and the mixture was allowed to reflux for 30 min. Ammonium chloride (350 mg, 6.5 mmol) was added, and the ammonia was allowed to evaporate at rt. The residue was mixed with ether (25 mL) and H_2O (25 mL), and the mixture was extracted with ether (4 × 50 mL). The ether was dried over Na_2SO_4 and was evaporated in vacuo to afford a white solid (244 mg). GC of an ether solution showed four peaks: t_R = 2.83 min (**14**, 22.2%), t_R = 3.88 min (**18a**, 3.9%), t_R = 4.41 min (**18b**, 70.2%), and t_R = 5.39 min (unidentified, 3.7%); ratio **18b**/**18a** = 18/1. Preparative TLC (silica gel, pentane:ether = 5:1) gave pure fractions containing starting ketone **14** (22.7 mg, 11.3%, mp 142–143 °C). GC of a pentane solution of the remaining fractions (141 mg, 64%) showed three peaks at t_R = 3.05 min (BHT ether stabilizer, 8.5%), t_R = 4.56 min (**18a**, 1.2%), and t_R = 4.81 min (**18b**, 90.3%), ratio **18b**/**18a** = 75.3). Preparative GC (SE-30, 210 °C, flow rate 100 mL/min) provided analytically pure equatorial homobrexan-2-ol (**18b**) as white crystals (mp 157.5–158.5 °C). GC of an ether solution showed peaks at t_R = 3.95 min **18a**, 1.0%) and t_R = 4.62 min (**18b**, 99.0%): IR (KBr) 3540–3080 (br, s), 1065 (s) and 1035 (s) (equatorial CO): ^1H NMR (400 MHz) δ 3.94–3.85 (m, $J_{2,3ax}$ = 10.4 Hz, $J_{2,3eq}$ = 6.5 Hz, $J_{2,1}$ = 4.0 Hz, $W_{1/2}$ = 23 Hz, H_2), 2.25–2.17 (pseudo q, 1 H, $J_{7,6ex}$ = 6 Hz, $J_{7,8}$ = 5 Hz, $J_{7,1}$ = 3 Hz, H_7), 2.12–2.03 (pseudo q, 1 H, $J_{8,9anti}$ = 6 Hz, $J_{8,7}$ = 5 Hz, $J_{8,4}$ = 5 Hz, H_8), 2.03–1.89 (m, 2 H, H_1 + H_4), 1.85–1.42 (m, 10 H), 1.34–1.23 (m, 1 H, $J_{3ax,3eq}$ = 14 Hz, $J_{3ax,2}$ = 11 Hz, $J_{3ax,4}$ = 5 Hz, $J_{3ax,6exo}$ = 2 Hz, H_{3ax}), 1.21–1.15 (br s, 1 H, OH). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.97; H, 10.77.

Tricyclo[5.3.0.$0^{4,8}$]decan-2-one *p*-Toluenesulfonylhydrazone (14a). Modifying a general procedure of Swartz,[41] we added *p*-toluenesulfonylhydrazine (656 mg, 3.52 mmol) to a solution of **14** (278 mg, 1.76 mmol, purity = 95%, mp 140–143 °C) in MeOH (18 mL). The solution was stirred at 65 °C for 1.5, and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and was extracted with 1 M HCl (2 × 50 mL). The CH_2Cl_2 solution was washed with brine (25 mL) and dried over Na_2SO_4, and the solvent was evaporated in vacuo. Repeated recrystallization (ether:MeOH = 19:1) of the residue (650 mg) gave an analytical sample of **14a** as white crystals (mp 162–163 °C dec; average yield after one crystallization 69%, mp 161–164 °C): IR (KBr) 3200 (s), 1630 (w), 1600 (m), 1335 (s), 1160 (s) cm^{-1}; ^1H NMR (400 MHz) δ 7.82 (d, 2 H, J = 8.6 Hz, $H_{2'}$ + $H_{6'}$), 7.32 (d, 2 H, J = 8.6 Hz, $H_{3'}$ + $H_{5'}$), 2.78–2.65 (br s, 1 H, H_1), 2.45–2.38 (s, 3 H, CH_3), 2.35–2.20 (m, 3 H), 2.19–2.09 (m, 1 H), 2.08–1.98 (m, 1 H), 1.97–1.80 (m, 2 H), 1.78–1.58 (m, 3 H), 1.54–1.45 (m, 2 H), 1.43–1.20 (m, 2 H); ^1H NMR (400 MHz, C_6D_6) δ 7.98–8.80 (d, 2 H, 8.0 Hz, $H_{2'}$ + $H_{6'}$), 6.77 (d, 2 H, J = 8.0 Hz, $H_{3'}$ + $H_{5'}$), 2.59 (t, 1 H, J = 3.2 Hz, H_1), 1.86–1.73 (s, 3 H, CH_3; and m, 2 H, J = 3.2 Hz, H_7 + H), 1.56–1.38 (m, 4 H), 1.37–1.12 (m, 5 H), 1.04–0.96 (m, 1 H), 0.58–0.36 (br s, 2 H); low-resolution MS m/e 318.1 (M^+, 1.25), 163.1 (100). Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96. Found: C, 63.98; H, 6.92.

Tricyclo[5.3.0.$0^{4,8}$]dec-2-ene (Homobrex-2-ene) (20) by a Shapiro Reaction. We used the general method of Shapiro and Duncan.[42c] A solution of methyllithium (3.37 mL, 4.71 mmol, Aldrich, 1.4 M in ether) was added dropwise over 35 min to a stirred mixture of **14a** (500 mg, 1.57 mmol, mp 160–163 °C dec) in anhydrous ether (3.3 mL) cooled to 20 °C under Ar. The deep yellow mixture was stirred for 12 h at room temperature, H_2O (5 mL) was added, and the mixture was extracted with pentane (3 × 50 mL). Conventional workup gave a yellow oil (332 mg). Column chromatography (neutral alumina, Brockmann activity I, pentane) gave pure fractions of homobrex-2-ene (**20**) as a clear liquid (128 mg, 54%): GC (75 °C, 10 psi) purity = 88% **20** + 12% pentane; TLC (neutral alumina, pentane) one spot, R_f = 0.95. The analytical sample of **20** was obtained as a colorless liquid by bulb

to bulb distillation (bp 126 °C (760 mm)): GC purity = 99.9%; IR (neat) 3020 (m), cm^{-1}; IR ($CHCl_3$) 3060 (br, w), 1600 (m), 1460–1400 (m) cm^{-1}; ^1H NMR (400 MHz) 5.49–5.42 (pseudo ABX[43] t, J = 2.9 Hz, 2 H, vinyl). The first order coupling constants for the magnetically equivalent vinyl H's (elucidated by the ^{13}C method of Laszlo and Schleyer[47]) were as follows: $J_{2,3}$ = 9.25 Hz,[45] $J_{2,1}$ = 5.4 Hz, $J_{2,4}$ = 1.5 Hz. Other assignments are as follows: δ 2.23–2.17 (m, 2 H, bridgehead homoallylic[9]), 2.17–2.07 (m, 2 H, allylic), 1.82–1.73 (m, 4 H), 1.65–1.56 (m, 6 H), 1.55 (s, H_2O in $CDCl_3$); broad band decoupled ^{13}C NMR (100 MHz) δ 128.82 (vinyl), 45.51, 44.38, 33.51, 24.05; coupled ^{13}C NMR (100 MHz) δ 128.82 (d, J = 158.2 Hz), 45.51 (d, J = 134.9 Hz), 44.38 (d, J = 134.9 Hz), 33.51 (t, J = 125.1 Hz), 24.05 (t, J = 125.8 Hz); low-resolution GC (SE-54)/MS (70 eV) m/e (relative intensity) 135.1 (M + 1, 9.2), 134.1 (M^+, 47.5), 133.1 (M − 1, 8.57), 91.1 (100); UV λ (pentane) 196 nm. Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.66; H, 10.77.

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Photochemically and Thermally Induced Free-Radical Reactions of α,β-Epoxy Ketones with Tributyltin Hydride: Selective C_α–O Bond Cleavage of Oxiranylmethyl Radicals Derived from α,β-Epoxy Ketones

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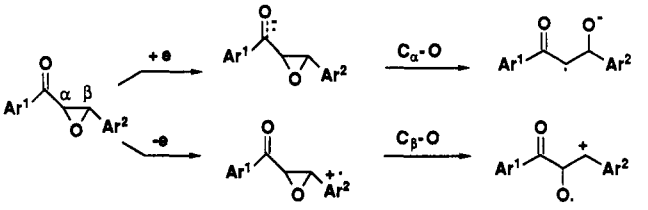
Free-radical reactions of α,β-epoxy ketones with tributyltin hydride have been studied. These substances were selectively converted to β-hydroxy ketones under both photochemical and thermal conditions. The photoreaction is initiated by hydrogen abstraction of an epoxy ketone triplet from tributyltin hydride, while azoisobutyronitrile is used as an initiator for the thermal reaction. In general, the photoreaction conditions are particularly useful for aroyl-substituted epoxy ketones while the thermal conditions are applicable to a variety of epoxy ketones. It was also found that the epoxy esters and epoxy alcohols did not undergo the ring-opening reaction under the similar conditions. Tributyltin radical attack on the carbonyl of epoxy ketones is a key process for both the photoreaction and the thermal reaction. Regioselective ring opening of the resulting oxiranylmethyl radical finally produces β-hydroxy ketones. In order to capture the free-radical intermediates, the reaction of epoxy ketones with allyltributyltin was conducted. The isolation of α-allylated β-hydroxy ketones is interpreted by the involvement of a novel 1,5-tributyltin transfer.

Introduction

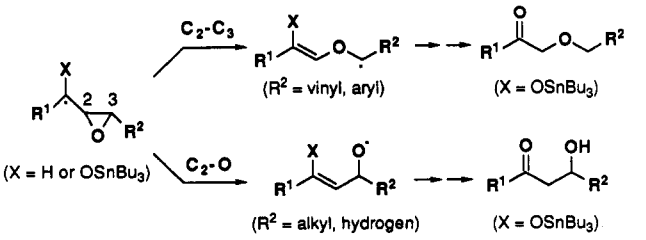
Free radicals play important roles in many chemical and biological processes.[1] Intensive studies on organic free radicals conducted in the area of physical organic chemistry have provided substantial information about fundamental properties of these species.[2] Such efforts have also stimulated synthetic organic chemists to apply free-radical processes to organic synthesis.[3]

Our program on *selective organic reactions induced by ion radicals or free radicals* has started by studying the ring-opening reactions of epoxy carbonyl compounds.[4] We expected that anion radical generation from α,β-epoxy carbonyl compounds would cause selective C_α–O bond cleavage while cation radicals from these substances would undergo selective C_β–O bond cleavage. These expectations

Scheme I



Scheme II



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