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Hydrogen Migrations in a Constrained Cyclohexylidene. H_{ax}/H_{eq} Shift Ratios in Thermal and Photic Bamford-Stevens Reactions.

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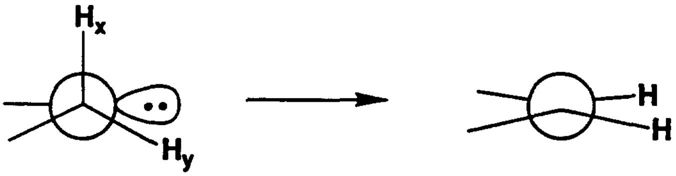
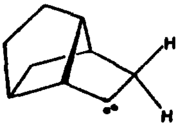
Abstract: Homobrexan-2-one was synthesized labeled in the α-position with ^{13}C and also with an axial or equatorial D. Their p-tosylhydrazone Li salts were thermolyzed and photolyzed (Bamford-Stevens reaction) to generate putative singlet carbenes, which undergo competitive 1,3-insertion to a tetracycle and 1,2-H (or D) shift to an alkene. After correction for isotope effects, the Hax/Heq shift ratios were *ca.* 1.7 and *ca.* 1.2 for the thermal and photic processes, respectively. These ratios are free of chair-boat and epimerization ambiguities.

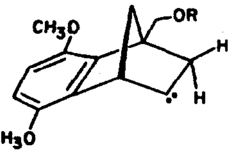
Respectfully dedicated to Sir Derek H. R. Barton on the occasion of his 75th birthday.

Interest in the stereochemistry of 1,2-H shifts in singlet carbenes has been ongoing for over three decades.[1] A central question has been whether a hydrogen initially perpendicular to the carbene plane (H_x) migrates at a different rate than one oriented approximately in the plane (H_y). Acyclic systems have not lent themselves to experimental study because of their conformational mobility. Bridged polycycles have been studied, in which the C—H bonds adjacent to the carbene are rigidly oriented (for some examples see adjoining structures). These carbenes were generated by thermolysis of diazo precursors (prepared *in situ*), and the H_{exo}/H_{endo} shift ratios were determined through deuterium labeling (and correction for isotope effects). The exo/endo ratios ranged from 138 to *ca.* 7.[2] Various interpretations for these ratios have been suggested, but some researchers believe that these norbornyl-type systems can exhibit special electronic or steric features not necessarily typical of other molecules.[2c,3]

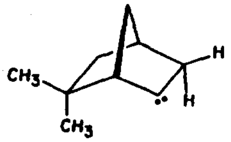




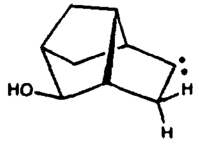
k_{exo}/k_{endo} = 138 (ref. 2a)



13 (ref. 2b)



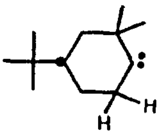
16 (ref. 2c)



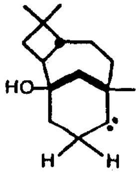
ca. 7 (ref. 2d)

Carbenes in 6-membered rings have also been examined, and they hold extra significance because axial and equatorial H's vicinal to a carbene carbon possess the two geometric alignments typified by H_x and H_y. Powell and Whiting[4a] and Seghers and Shechter[4b] examined substituted cyclohexylidenes that involved competitive migration of tertiary H *vs* secondary H and reported a preference for H_{ax} over H_{eq} shift. But the magnitude of this preference could not be reliably quantified because it was not known how the geminal bystander substituent influenced the shift of the tertiary H.

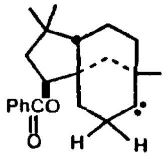
Three cyclohexyl systems (shown below) have been investigated in which the competing axial and equatorial H's were both secondary; and by D labeling these substrates displayed low H_{ax}/H_{eq} selectivity: (0.7 - 1.5).[4c,d] However, those studies also retain ambiguity because of uncertainty about the possible role of boat-like conformations. (Chair $\rightleftharpoons$ twist boat interconversion markedly alters the alignment between C—H bonds and adjacent carbenic orbitals.) The availability of an H_{ax}/H_{eq} ratio that is free of ambiguity would be useful not only as a calibration for theoretical calculations but also to analyze and interpret the behavior of more-complicated cyclohexylidenes.[1b]



k_{ax}/k_{eq} = 1.5 (ref. 4c)

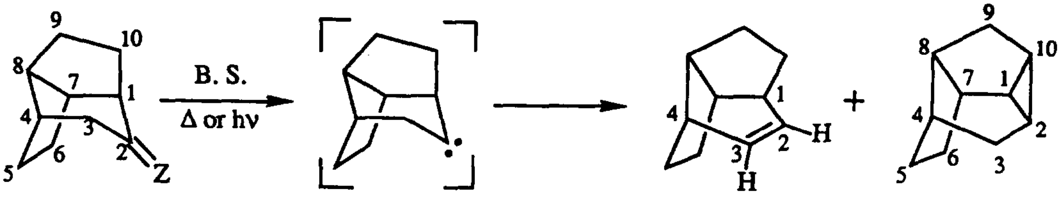


ca. 1 (ref. 4d)



ca. 0.7 (ref. 4d)

A cyclohexylidene that avoids this difficulty is obtainable from homobrexan-2-one (*1*), in which the 6-membered ring cannot reasonably distort to a twist boat because of constraint by the two ethano bridges. Earlier we reported efficient synthetic routes to this ketone and to related compounds.[5] We now present details of a study that used double isotopically labeled ketones as carbene precursors to obtain the H_{ax}/H_{eq} migration ratio.[1a]



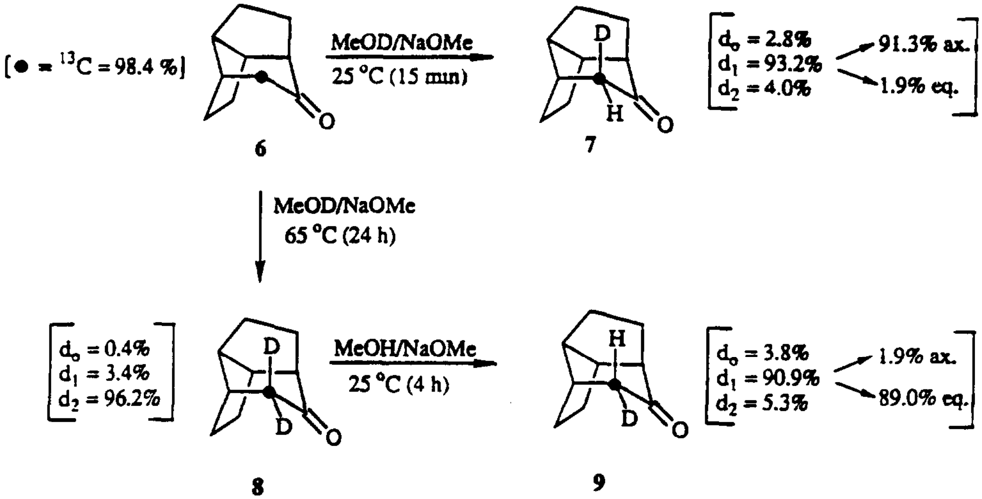
1 Z = O
2 Z = NNHTs
3
4
5

An established way to convert a ketone to a diazo unit involves thermolysis (or photolysis) of a salt of the corresponding p-tosylhydrazone (Bamford-Stevens reaction).[6] Diazo compounds are thermally (and photically) labile and *in situ* evolve N_2 to generate putative singlet carbenes. Applied to the Li salt of the tosylhydrazone **2**, thermolysis afforded a separable mixture (*ca.* 1:3 repectively) of known alkene **4** (via 1,2-H shift) and tetracyclic hydrocarbon **5** (via 1,3-insertion).[7] The structure of **5** is based on exact mass, NMR (^{1}H and ^{13}C), and IR spectral analyses. For example, C—H stretch at 3010 cm^{-1} and ^{1}H NMR absorption around δ 0.55 are indicative of cyclopropyl C—H. All other possible intramolecular insertions would be 1,4-type and would produce cyclobutyl rings, whose IR and ^{1}H NMR spectral peaks are characteristically different than those observed.[8] In alkene **4** (C_2 symmetry) the vinyl H's are equivalent. Therefore to probe the stereochemistry of H shift in the **3** → **4** rearrangement we had to distinguish not only the two α-H's in **3** but also the two vinyl carbons in **4** (to sort out migration origin from migration terminus). We accomplished our goal by labeling C-3 with ^{13}C as well as with a deuterium.

Synthesis of Doubly-Labeled Precursors. Ketone fully labeled in the α-carbon with ^{13}C (**6**) was prepared from brexan-2-one by our published homologation route[5] except that $Me_3Si^{13}CN$ was used in place of the natural abundance reagent.[9] Analog **6**[10] was stereoselectively converted to axial *d*-ketone **7** by mild exchange in MeOD/NaOMe. More vigorous treatment gave the d_2-ketone **8**, from which the equatorial *d*-ketone **9** was obtained by selective washout of the axial deuterium. As expected, no exchanges took place at the C-1 bridgehead site.

The adjoining scheme shows typical data from these exchanges, which were readily monitored by observance of lanthanide-induced shifts (LIS) of the C-3 hydrogens[11a] in conjunction with mass spectral assays of *d*-content. Our configurational D assignments were secured by $LiAlH_4$ reduction of each ketone (actually done on ketones lacking the ^{13}C) to the axial and equatorial alcohols, whose vicinal coupling constants for carbinyl H were consistent with expectations from the known, non-labeled analogs.[5b,12]

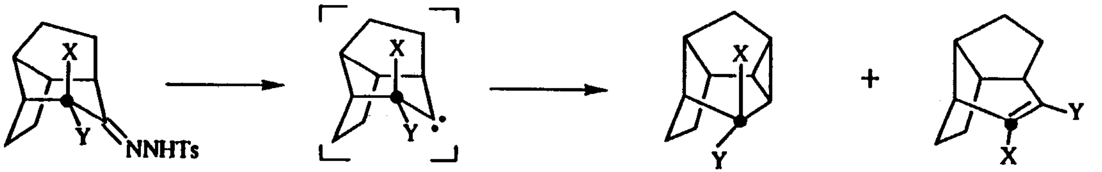
The unusually high axial preference in these "mild" alkaline ketonizations was unexpected based on exchanges reported for other cyclohexanones, where lower ax/eq selectivity was found.[13] Common explanations (other than steric hindrance considerations) for low ax/eq selectivity in ketonization include a transition state that is "early" (i.e. enolate-like) or one that leads to a twist boat shape for equatorial approach (in order to maintain good stereoelectronic overlap with the developing carbonyl). Perhaps the inaccessibility of a twist boat in our substrate prevents the "equatorial" ketonization from attaining a stereoelectronically assisted path and therefore from effective competition with the "axial" path.



We found that conversion of **7** to its tosylhydrazone **10b** in MeOH at 25°C resulted in some D loss. Conducting the reaction in MeOD overcame the problem, since any D removed initially by enolization was reinstated stereoselectively as axial D, accompanied by some additional d_2 species. The equatorial *d*-ketone **9** gave tosylhydrazone **10c** conventionally in MeOH. The tosylhydrazones were not readily amenable to mass spectral analyses, but LIS ^{1}H NMR proved satisfactory for assay of D stereochemistry[11b] and agreed well (± 3-4%) with the ^{2}H NMR assays obtained on the derived tetracycles **12**.

Bamford-Stevens Reactions. Each tosylhydrazone was converted with t-BuLi to its Li salt, which was thoroughly dried, and pyrolyzed (neat, *ca.* 120-160° C). The distillate (**12** + **13**) was rid of minor impurities by column chromatography, and ^{1}H NMR of the vinyl H region was used to quantify the ratio of **13(a+b)/13(a+c)**. (A ^{12}C—H multiplet centered near δ 5.47 is easily distinguished from the pair of ^{13}C—H multiplets (J_{CH} = 157 Hz).) Analysis of the same product mixture by GC/MS provided the d_0, d_1, and d_2 isotopic composition of **12** and of **13**. Then the tetracycle component **12** was isolated, purified, and analyzed by ^{2}H NMR to quantify the **12(b+d)/12(c+d)** ratio . The chemical shift for the deuterium in **12** (doublet, J_{CD} = 20 Hz) depends on its configuration. Thus **12b** (from **10b**) showed a strong doublet at δ 1.98 and a weak doublet at 1.43; whereas **12c** (from **10c**) showed the same doublets, but with reversed intensities (weak at 1.98, strong at 1.43). Importantly, in each case the relative intensity of the weak doublet corresponded virtually quantitatively to the amount of d_2 species plus the small proportion of epimeric d_1 species present in the precursor tosylhydrazone. These NMR assays establish that D has not altered its initial stereochemical integrity at any stage of the Bamford-Stevens sequence, either by enolization or by any sort of internal H or D transfers at the Li salt stage.[14] With configurational integrity intact in carbene **11** we are now assured that the relative proportions of alkenes **13b** and **13c** (Table) reveal the stereoselectivity in the **11**→**13** rearrangement. These proportions embody not only ax/eq competition but also H/D isotope effects. By making the usual

	X	Y
a	H	H
b	D	H
c	H	D
d	D	D



10 11 12 13

Thermolysis and Photolysis of Homobrexan-2-one p-Tosylhydrazone Li Salts[a]

Substrate (as Li salt)	Conditions[b]	Tetracycle 12 Rel. %				Rel % 12b/12c	Alkene 13 Rel. %				Corrected Ratio[c]	Isotope Effect[d]	Migration Ratio
		12a	12b	12c	12d		13a	13b	13c	13d	13b/13c	k_H/k_D	H_{ax}/H_{eq}
10b	Δ, neat 120-160°C	4.6	72.3	1.3	21.8	98.2 / 1.8	7.2	43.9	32.5	16.4	1.32	2.30	1.73
10c		13.8	8.4	76.6	1.2	9.9 / 90.1	17.2	63.6	18.6	0.6	4.00		
10b	hv, pentane 25°C	4.2	72.7	0.9	22.3	98.8 / 1.2	6.0	40.1	35.2	18.8	1.14	1.34	1.17
10c		14.0	8.3	76.4	1.4	9.8 / 90.2	15.3	50.6	33.3	0.9	1.58		

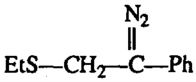
[a] Relative % of isotopic species were derived from combination of GC/MS and NMR and are averages of triplicate experiments. Standard deviations were <1%. [b] Typical yields of product (12 + 13): 63±8% (thermal); 81±5% (photic). [c] Corrected for the presence of the small proportion of the other epimer and therefore represents the outcome for a stereochemically homogeneous precursor. See ref. 12 for all raw data and calculations. [d] Based on the presumption that isotope effects are the same for H_{ax} and H_{eq} shift.

presumption[2, 3a, 15] that k_H/k_D is the same for axial and equatorial shift, we evaluated, and corrected for, the isotope effect and arrived at the H_{ax}/H_{eq} migration ratio of *ca.* 1.7 (Table).

As no H_{ax}/H_{eq} shift ratios have been reported for carbenes generated by irradiation, we conducted parallel photochemical studies on the same Li salts (in pentane, 25°C). The **12**/**13** product ratio was *ca.* 1.2/1 and, as before, the D stereochemistry in each tetracycle (and therefore in the "photic" carbene **11**) corresponded quantitatively to that in its related tosylhydrazone precursor. Notwithstanding the lower temperature used in the photolyses, the **12**/**13** product ratio (*ca.* 1.3/1) and the H_{ax}/H_{eq} migration ratio (*ca.* 1.2, see Table) indicate lower selectivity than in the thermolysis runs. Such less-discriminate behavior for photic carbenes is not uncommon[6b] and could indicate involvement of higher energy states (vibrational or electronic)[16] or perhaps some rearrangement from non-carbenic intermediates.

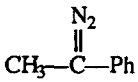
Our thermal and photic H_{ax}/H_{eq} migration ratios are free of chair-boat ambiguity at any stage of the Bamford-Stevens reaction (tosylhydrazone salt, diazohydrocarbon, carbene) and free of uncertainties about possible D epimerizations via internal H or D transfers at the Li salt stage.[14] The findings have recently been used to interpret results from more-substituted cyclohexylidenes.[1b]

We wish to emphasize that our stereochemical findings are presented in terms of the traditional view that hydrogen migration takes place *after* loss of nitrogen from a diazo intermediate (i.e., from a discrete carbene) rather than in concert with rupture of a carbon-nitrogen bond. The issue of timing in "carbene" rearrangements was adumbrated in an early paper by Robson and Shechter, who thermolyzed diazo compounds **14** and **15** and concluded from kinetic and product studies that EtS migration in **14** (the major rearrangement pathway) does not accelerate the first-order decomposition rate of **14** (relative to that of **15**). Accordingly, they envisioned bond breaking involving N_2 expulsion as a principal feature of the rate-determining step followed by migration of EtS in the derived carbene (or something that has extensive carbenic character).[17]



$\mathrm{EtS{-}CH_2{-}\overset{N_2}{\overset{\|}{C}}{-}Ph}$

14



$\mathrm{CH_3{-}\overset{N_2}{\overset{\|}{C}}{-}Ph}$

15

More recently, kinetic studies of various diazirines have indicated that photo-induced 1,2 shifts in these substrates can occur not only from the derived carbene but also competitively from a second transient, presumably an activated nitrogen-containing species.[18] Those findings with diazirines raise the possibility that non-carbenic and carbenic paths might compete in ***thermal*** as well as in ***photo-induced*** rearrangements of diazirines and, perhaps, of other substrates such as diazo compounds[18d] and N-aziridinylimines.[19]

Probing the timing of events in carbene rearrangements can be far from simple, because the competition among pathways could depend on numerous factors, including: (a) Method of excitation. (It is well known that product mixtures can differ appreciably for carbenes generated thermally vs photochemically.) (b) Physical state of the medium (gas, solution, cold matrix, solid). (c) Intrinsic migratory aptitude of a substituent, and assistance to migration provided by bystander groups.[1b] (d) Inherent stability of the putative carbene. Furthermore, Carpenter has recently pointed out that for some reactions, the common perceptions of "concertedness" and "non-concertedness" may require modification.[20] Among other things, he analyzed the energetics for N_2 loss in 2,3-diazabicyclo [2.2.1]-hept-2-ene, and some of his conclusions about transition states and short-lived intermediates might well apply to N_2 loss from activated diazirines, diazo compounds, or other related carbene precursors.

Interestingly, in connection with theoretical computation of activation energies for carbene rearrangements Frenking and Schmidt suggest, on the basis of various considerations, that even if isomerization is concerted with N_2 loss in a diazo precursor the relative activation barriers for competing migrations should parallel those for free carbenes.[22] This consideration would imply that our observed H_{ax}/H_{eq} migration selectivity (at least for the *thermal* Bamford-Stevens process) remains valid regardless of the extent of contribution by a concerted process. We note also that MINDO/3 and MNDO computations of hydrogen migration in cyclohexylidene by Kyba[21] and ab initio computations by Evanseck and Houk[3c] indicated little or no H_{ax}/H_{eq} preference. Experimental studies of the four diversely structured cyclohexyl systems investigated to date have likewise revealed little ax/eq stereoselectivity (range, including present study, *ca.* 0.7 -1.7).[1] This agreement between theory and experiment tends to suggest that cyclohexyl diazo compounds derived by thermal Bamford-Stevens routes give carbenes, which rearrange; and if concerted rearrangements compete they either show similar H_{ax}/H_{eq} selectivity (cf. Frenking and Schmidt[22]) or their involvement.is minor.

Finally, we stress that in our study, as well as in all earlier stereochemical studies involving axial-equatorial or exo-endo deuterium labeling and reliance on product ratios,[2, 3a, 4c,d 15] the presumption was made that k_H/k_D isotope effects are essentially equal for axial and equatorial trajectories. If that presumption should prove to be inaccurate,[1b, 23] the derived numbers would need adjustment.

Experimental Section

General — All temperatures are in °C and are uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 400 MHz at 400 MHz and 100 MHz, respectively, unless specified otherwise. Chemical shifts were referenced to internal TMS or to the residual H in perdeuterated solvents (δ 7.26 for $CDCl_3$, 7.15 for C_6D_6). GC/MS were obtained on spectrometers equipped with SE-54, DG-5, or OV-17 capillary columns. IR spectra ($CHCl_3$ or CCl_4) were run on on a Perkin-Elmer model 599B instrument, with polystyrene film as an external calibration. Analytical and preparative GC, purification of solvents, etc. were conducted as described elsewhere;[5b] additional details are available in ref. 12. For some IR and NMR spectra we list only peaks relevant for assay, but more complete assignments are available.[12] In NMR assignments, subscripts **x**, **n**, and **a** signify exo, endo, and anti.

LIS ^1H NMR of 1.[5b] (C_6D_6, Eu(fod)$_3$, 0.15 eq) δ 4.26 (br s, 1 H, H_1), 3.81 (d, 1 H, J_{gem} = 15.5 Hz, H_{3ax}), 3.71 (d, 1 H, J_{gem} = 15.5 Hz, H_{3eq}), 2.62 (m, 1 H, H_7), 2.52 (m, 1 H, H_8), 2.39 (m, 1 H, H_4), 2.25 (m, 2 H), 2.02 (m, 5 H), 1.83 (m, 1 H), 1.05 (s, t-Bu).

LIS ^1H NMR of 2.[5b] (C_6H_6, Eu(fod)$_3$, 0.50 eq) δ 13.10 (br s, 1 H, NH), 10.41 (m, 2 H, $H_{2',6'}$), 7.30 (m, 2 H, $H_{3',5'}$), 5.44 (br s, 1 H, H_1), 4.70 (d, 1 H, J_{gem} = 15 Hz, H_{3eq}), 3.71 (d, 1 H, J_{gem} = 15 Hz, H_{3ax}), 2.45 (m, 3 H), 2.15 (m, 7 H), 1.85 (m, 4 H), 1.43 (s, t-Bu).

Thermal Bamford-Stevens Reaction on Tosylhydrazone 2. Isolation of Tetracycle 5. This tosylhydrazone[5b] (0.160 mmol) in THF (0.5 mL) at 0° under Ar was converted to its Li salt by treatment with t-BuLi (0.165 mmol) in pentane (0.1 mL). After 15 min the stirred mixture was evaporated *in vacuo*, and the white solid was dried under vacuum (0.1mm Hg) for 24 h. It was thermolyzed (1.5 - 2 h) under vacuum. Product distillation began *ca.* 120° and ceased *ca.* 160° The solid that collected in the cold trap (-150°) was chromatographed (neutral alumina, Brockman activity III, pentane). The colorless semi-solid (typical yield ca. 60%) consisted (via GC) of known alkene 4 and tetracycle 5 (average ratio *ca.* 1/3.3) along with a trace (<1%) of an unidentified hydrocarbon, eluted first, which was not the known 2-methylene brexane.[5b] Alkene 4 and tetracycle 5 were separated and individually purified by preparative GC. Analytically pure 5 was a colorless, waxy solid, mp 42-47°, with a terpene-like odor. IR ($CDCl_3$) 3010 (w), 2925 (s), 2845 (m) cm^{-1}. ^1H NMR δ 2.30 (pseudo q, 1 H, $J_{7,6x}$ = 6 Hz, $J_{7,8}$ = 6 Hz, $J_{7,1}$ = 4 Hz, H_7), 2.05 (ddd, 1 H, J_{gem} = 13.2 Hz, $J_{3x,4}$ = 8.4 Hz, $J_{3x,5x}$ = 2 Hz, H_{3x}), 1.90-1.62 (m, 6 H), 1.57-1.44 (m, 3 H), 1.28 (m, 1 H, $J_{1,2}$ = 6 Hz, $J_{1,10}$ = 6 Hz, $J_{1,7}$ = 4 Hz, H_1), 1.17 (m, 1 H, $J_{10,1}$ = 6 Hz, $J_{10,2}$ = 6 Hz, $J_{10,9a}$ = 8 Hz, H_{10}), 0.58 (m, 1 H, $J_{2,1}$ = 6 Hz, $J_{2,10}$ = 6 Hz, $J_{2,3n}$ = 5 Hz, H_2). ^{13}C NMR (broad band decoupled) δ 43.3 (C_7), 41.6 (C_3), 37.1, 35.8, 27.7, 26.5, 26.0, 25.3 (C_1), 16.5 (C_{10}), 11.02 (C_2). High resolution MS calcd for $C_{10}H_{14}$ 134.1096, found 134.1090.

In a control experiment, vacuum thermolysis (200°, 2 h) of a mixture of 4 and 5 in the presence of one equivalent of Li p-toluenesulfinate did not alter the 4/5 ratio.

Photic Bamford-Stevens Reaction on Tosylhydrazone 2. The dry Li Salt (prepared from 0.16 mmol of 2 and 0.16 mmol t-BuLi) suspended in stirred, degassed pentane (6 mL) in a quartz tube was irradiated (2 h, 25°) with a Pyrex filtered, water cooled, medium pressure Hg lamp (Hanovia, 450 W). Column chromatography gave a semi-solid mixture consisting of 4 and 5 (average ratio 1/1.2, respectively) along with 1% of an unidentified product. A separate control irradiation (2 h, 25°) of a 4+5 mixture in the presence of one equivalent of LiTs did not alter the 4/5 ratio.

Preparation of ^{13}C Labeled Trimethylsilyl Cyanide (TMS—^{13}CN). We explored several published routes[9] to TMSCN (and various modifications) before preparation of the labeled reagent. The following procedure proved superior, reproducible, and gave the best yield and purity. A rigorously flame dried flask under N_2 was charged with $K^{13}CN$ (1.85 g, 27.9 mmol, Cambridge Isotope Laboratories, 99% ^{13}C) which had been previously dried at 60° in high vacuum for several days. (WARNING: KCN CAN REACT WITH MOISTURE TO LIBERATE HCN.) The flask and $K^{13}CN$ granules under N_2 were gently flame dried again (60-70°) and, when cool, we added via syringe 14.8 mL of 1,3-dimethyl-2-imidazolidinone (DMI, also known as N,N-dimethyl ethylene urea (DMEU); Aldrich), which had been purified earlier by vacuum distillation from calcium hydride and storage (24 h) over freshly activated molecular sieves 4Å. To this well-stirred suspension we slowly added (5 min) trimethylsilyl trifluoromethanesulfonate (Aldrich, 99% pure, 6.27 g, 1.0 eq) via syringe. The stirred mixture was heated at 65° for 2.5 h in an oil bath. The oil bath was heated gradually to *ca.* 245° over 2 h, during which period under N_2 flow the product distilled over (distillate temperature *ca.* 85-105°); 2.49 g (89%) colorless liquid. By ^1H NMR analysis the product consisted of (in relative mol %): $TMS^{13}CN$ (91.2%), DMI (2.2%), $TMSN^{13}C$ (1.2%), and $(TMS)_2O$ (6.5%). The $TMS^{13}CN$ content was 2.16 g (77%). This ^{13}C labeled trimethylsilyl cyanide was used directly for preparation of 6.

3-^{13}C-Homobrexan-2-one (6). We prepared **6** (mp 141-144°) from brexan-2-one as reported[5b] except that TMS ^{13}CN was used. IR ($CHCl_3$) 2930 (s), 2880 (sh, m) 1705 (s) cm^{-1}. ^{1}H NMR (C_6D_6) Eu(fod)$_3$ 0.15 eq) δ 3.78 (br s, 1 H, H_1), 3.42 (dd, 1 H, $J_{C,Hax}$ = 44 Hz, J_{gem} = 16 Hz, H_{3ax}), 3.10 (dd, 1 H, J_{CHeq} = 57 Hz, J_{gem} = 16 Hz, H_{3eq}), 2.30 (m, 3 H, $H_{7,8,4}$), 2.14 (m, 1 H), 1.85 (m, 7 H), 0.85 (s, t-Bu). MS ^{13}C = 98.4%.

Tosylhydrazone of 6. (mp 160.5-164°, dec):[5b] IR ($CHCl_3$) 3575 (w), 3285 (w), 1645-1625 (w), 1601 (w), 1390-1300 (m), 1125 (s) cm^{-1}. LIS ^{1}H NMR (C_6D_6, Eu(fod)$_3$ 0.5 eq) δ 9.60 (br s, 2 H, $H_{2',6'}$), 7.15 (m, 2 H, $H_{3',5'}$), 4.37 (br s, 1 H, H_1), 3.57 (br d, 1 H, J_{CHeq} = 130 Hz, H_{3eq}), 3.21 (br d, 1 H, J_{CHax} = 130 Hz, H_{3ax}), 2.12 (m, 3 H), 2.00 (s, 3 H, CH_3), 1.74 (m, 9 H), 1.20 (s, t-Bu).

Thermal Bamford-Stevens Reaction on Tosylhydrazone of 6. Conducted as described above for **2** this reaction provided the ^{13}C labeled material **12a** + **13a** that served as NMR and GC/MS reference standards. The ^{13}C content was 97.9% for **12** and 98.0% for **13**.

Introduction of Deuterium. All deuterations to be described were conducted first on non-labeled ketone **1** to obtain reference standards for NMR and MS. Furthermore, these mono-deuterated ketones were individually reduced ($LiAlH_4$) to the known axial and equatorial alcohols, whose vicinal coupling constants for the carbinyl H's are reported.[5b] The H,H couplings in the epimeric D alcohols were completely consistent with our stereochemical assignments. (For example, for equatorial alcohol the large diaxial J_{HH} is absent when D is axial and is present when D is equatorial).

Axial-3-D-3-^{13}C-homobrexan-2-one (7). A solution of **6** (3.31 mmol) in CH_3OD (20.2 mL, 99.5% D) was added to a stirred solution of NaH (3.31 mmol, 60% dispersion in mineral oil) in CH_3OD (20.2 mL). After 15 min at 25°, D_2O (135 mL, 99.8% D) was added, and after ether extraction and a brine wash the extract was dried (Na_2SO_4) and evaporated. More pentane (200 mL) was added, dried, and evaporated *in vacuo* to give **7** (mp 119-131°). IR 2475-2385 (w), 1705 (s) cm^{-1}. LIS ^{1}H NMR (C_6D_6, Eu(fod)$_3$ 0.15 eq) δ 4.25 (br s, 1.00 H, H_1), 3.26 (br d, 0.98 H, J_{CHeq} = 134 Hz, H_{3eq}), 2.78 - 1.75 (11 H). The NMR assay corresponds to 2% ($d_1eq + d_o$) and 98% ($d_1ax + d_2$). Mass spectral analysis (2.8% d_o, 93.2% d_1, 4.0% d_2) in conjunction with the NMR assay led to the isotopic deuterium distribution shown alongside **7**.[12]

3,3-Dideuterio-3-^{13}C-homobrexane-2-one (8). A stirred mixture of **6** (3.30 mmol), CH_3OD (25 mL), NaH (3.30 mmol, 60% dispersion in mineral oil) was heated 24 h at 65° under Ar. Dilution with D_2O (100 mL) and normal workup gave **8** (mp 112-128°). IR 2475-2385 (w), 2195 (w), 1700 (s) cm^{-1}. LIS ^{1}H NMR (C_6D_6, Eu(fod)$_3$ 0.15 eq) δ 3.70 (br s, 1.000 H, H_1), 3.07 (br d, 0.018 H, J_{CHeq} = 60 Hz, H_{3eq}), 2.44-1.60 (11 H). The NMR assay corresponds to 98% ($d_1ax + d_2$) and 2% ($d_1eq + d_o$). Mass spectral analysis gave 0.4% d_o, 3.4% d_1, 96.2% d_2 (see **8**).[12]

Equatorial-3-D-3-^{13}C-homobrexan-2-one (9). Ketone **8** (3.14 mmol) in CH_3OH (24 mL) containing NaH (3.14 mmol, 60% dispersion in mineral oil) was stirred 4 h at 25° under Ar. Dilution with H_2O (128 mL) and workup gave **9** (mp 110-120°). IR 2490-2420 (w), 1705 (s) cm^{-1}. LIS ^{1}H NMR (C_6D_6, Eu(fod)$_3$ 0.15 eq) δ 4.00 (br s, 1.00 H, H_1), 3.55 (br d, 0.98 H, J_{CHax} = 120 Hz, H_{3ax}), 2.52-1.67 (11 H). The NMR assay corresponds to 98% ($d_1eq + d_2$) and 2% ($d_1ax + d_o$). Mass spectral analysis (3.8% d_o, 90.9% d_1, 5.3% d_2) in conjunction with the NMR assay led to the deuterium distribution shown alongside **9**.[12]

Tosylhydrazone 10b and Its Li Salt. Ketone **7** (403 mg) was converted to the N-deutero analog of **10b** by treatment with $TsNHNH_2$ (447mg) in anhydrous CH_3OD (20 mL, 99.5% D) at 25° for 24 h. After evaporation of solvent *in vacuo* the residue was dried 12 h under vacuum and was recrystallized from minimum CH_3OD/pentane (1:1) (78%, mp 160-165°, dec). LIS ^1H NMR (C_6D_6, $Eu(fod)_3$ 0.5 eq) δ 2.71 (br d, 0.83 H, J_{CH} = 130 Hz, H_{3eq}). The NMR assay of **10b** corresponds to 83% ($d_1ax + d_2$) and 17% ($d_1eq + d_o$). It was converted to its Li salt (t-BuLi, 1.05 eq), which was thoroughly dried in vacuum.

Tosylhydrazone 10c and Its Li Salt. Ketone **9** gave **10c** by the same procedure except that the solvent was CH_3OH; mp 161-164° (dec), from minimum MeOH/pentane (1:1). LIS ^1H NMR (C_6D_6, $Eu(fod)_3$ 0.5 eq) δ 3.05 (br d, 0.13 H, J_{CH} = 126 Hz, H_{3eq}), 2.45 (br d, 1.00 H, J_{CH} = 126 Hz, H_{3ax}). The NMR assay of **10c** corresponds to 87% ($d_1eq + d_2$) and 13% ($d_1ax + d_o$). The Li salt of **10c** was prepared (t-BuLi, 1.05 eq) and dried.

Thermolysis of Li Salt of 10b. Thermolysis under vacuum (0.1 mm) was done in triplicate, and the assays given are averaged values. The product mixture began to distill *ca* 120° and continued up to *ca.* 160°. The solid in the cold trap was chromatographed on neutral alumina to give 63 ± 8% of colorless semisolid, consisting of **12/13** in the ratio 4.9 ± 0.3. The known[5b] vinyl ^1H NMR signals in natural abundance **13** allowed us to assay the H content at the ^{13}C site. ^1H NMR δ 5.47 (ddd, 0.074 H, J_{CH} = 157 Hz, $J_{3,4}$ = 5 Hz, $J_{3,1}$ = 2 Hz, H_3), δ 5.45 (dd, 0.095 H, $J_{2,1}$ = 5 Hz, H_2). GC/MS (10 scans averaged) provided the d_o, d_1, and d_2 composition of **12** and also of **13**. The triplicate samples were combined, and tetracycle **12** was isolated and purified. ^2H NMR assay gave the ratio **12(b+d)/12(c+d)** as 80.3/19.7. These data in conjunction with the GC/MS values provided the isotopic compositions shown in the Table.

Thermolysis of Li Salt of 10c. Thermolysis in triplicate gave 67 ± 1% of semi-solid containing **12/13** in the ratio 3.6 ± 0.2. ^1H NMR indicated 0.097 H for H_3 and 0.217 H for H_2. GC/MS (10 scans) revealed the isotopic composition for **12** and for **13**; and ^2H NMR on purified **12** gave **12(b+d)/12(c+d)** as 11.0/89.0. See Table for derived data.

Photolysis of Li Salt of 10b. Photolysis in triplicate gave the **12/13** mixture (81 ± 5%) in the ratio 1.33 ± 0.02. ^1H NMR revealed 0.266 H for H_3 and 0.297 H for H_2. GC/MS (10 scans) and then ^2H NMR on purified **12** gave **12(b+d)/12(c+d)** = 80.4/19.6 and led to the data in the Table.

Photolysis of Li Salt of 10c. Photolysis in triplicate gave the **12/13** mixture (72 ± 7%) in the ratio 1.20 ± 0.03. ^1H NMR indicated 0.423 H for H_3 and 0.572 H for H_2. GC/MS (10 scans) and ^2H NMR on purified **12** gave **12(b+d)/12(c+d)** = 11.1/88.9 and led to the data in the Table.

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References and Footnotes

1. References to relevant theoretical and experimental work and to earlier reviews are given in: (a) Nickon, A.; Stern, A. G.; Ilao, M. C. *Tetrahedron Lett.* **1993**, *34*, 1391-1394. b) Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84-89.
2. (a) Nickon, A.; Huang, F.-C.; Weglein, R.; Matsuo, K.; Yagi, H.; *J. Am. Chem. Soc.* **1974**, *96*, 5264-5265. (b) Kyba, E. P.; Hudson, C. W. *J. Am. Chem. Soc.* **1976**, *98*, 5696-5697. (c) Freeman, P. K.; Hardy, T. A.; Balyeat, J. R.; Westcott, L. D. Jr. *J. Org. Chem.* **1977**, *42*, 3356-3359. (d) Nickon, A.; Huang, F.-C. unpublished.
3. (a) Kyba, E. P.; Hudson, C. W. *J. Org. Chem.* **1977**, *42*, 1935-1939. (b) Nickon, A.; Weglein, R. C. **1986**, *27*, 2675-2678. (c) Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 9148-9156.
4. (a) Powell, J. C.; Whiting, M. C. *Tetrahedron* **1961**, *12*, 168-172. (b) Seghers, L.; Shechter, H. *Tetrahedron Lett.* *1976*, 1943-1946; Press, L. S.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *100*, 1872-1875. (c) Kyba, E. P.; John, A. M. *J. Am. Chem. Soc.* **1977**, *99*, 8329-8330. (d) Nickon, A.; Edamura, F.; Huang, F.-C.; Matsuo, K.; Morgan, J; Yagi, H. unpublished.
5. (a) Nickon, A.; Stern, A. G. *Tetrahedron Lett.* **1985**, *26*, 5915-5918. (b) Stern, A. G.; Nickon A. *J. Org. Chem.* **1992**, *57*, 5342-5352.
6. (a) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1959**, *81*, 5512-5513. (b) Nickon, A.; Zurer, P. S-J. *J. Org. Chem.* *1981*, *46*, 4685-4694.
7. The known[5] ring-contracted alkene, 2-methylenebrexane, from shift of C-3 was not produced (detectability limit 0.01%) in this reaction. Controls established that the product ratio is stable to the reaction conditions.
8. (a) Liebman, S. A.; Gudzinowicz, B. J. *Anal. Chem.* **1961**, *33*, 931-934. (b) Roberts, J. D.; Mazur, R. H. *J. Am. Chem. Soc.* **1951**, *73*, 2509-2520. (c) Srinivasan, R. *J. Am. Chem. Soc.* **1961**, *83*, 4923-4927.
9. (a) Kantlehner, W.; Haug, E.; Mergen, W. W. *Synthesis* **1980**, 460-461. (b) Livinghouse, T. *Org. Syn.* **1981**, *60*, 126-132. (c) For additional details on various less-successful procedures see Ilao, M. C. Ph.D. Dissertation, The Johns Hopkins University, 1991.
10. This ^{13}C-labeled ketone was carried through the Bamford Stevens sequence to obtain ^{13}C-labeled samples of alkene and tetracycle that served as mass spectral reference standards.
11. (a) The ^{1}H chemical shifts and couplings were sensitive to Eu(fod)$_3$ concentration, etc. However, under a given set of conditions the doublet (J_{CH} = 120-134 Hz) from H_{ax} always appeared at larger δ than the doublet from H_{eq}. (b) Behavior that was sensitive to LIS concentration was also observed for the α-H doublet in the tosylhydrazones, except that Heq always showed a larger δ than H_{ax}.
12. For full details see Stern, A. G. Ph.D. Dissertation, **1987**, The Johns Hopkins University.
13. (a) House, H.O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935-942. (b) Fraser, R. R.; Champagne, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 657-658. (c) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758-764. (d) Trimitsis, G. B.; Van Dam, E. M. *J. Chem. Soc. Chem. Commun.* **1974** 610-611. (e) Metzger, P.; Casadevall, E. *Tetrahedron Lett.* **1973**, 3341-3344. For reviews of

stereoelectronic and steric arguments see: (f) Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1-77. (g) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263-268.

14. For examples of proton transfers in tosylhydrazones and related see: (a) Kaufman, G.; Cook, F.; Shechter, H.; Bayless, J.; Friedman, L. *J. Am. Chem. Soc.* **1967**, *89*, 5736-5737. (b) Dauben, W. G.; Rivers, G. T.; Zimmerman, W. T. *J. Am. Chem. Soc.* **1977**, *99*, 3414-3420. (c) Vedejs, E.; Lee, N. *J. Am. Chem. Soc. **1991**, 113*, 5483-5485.
15. (a) Nickon, A.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3917-3918. (b) Nickon, A.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1972**, *94*, 7081-7086.
16. Chang, K.-T.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 5082-5084.
17. Robson, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1967**, *89*, 7112-7114.
18. (a) Modarelli, D. A.; Platz, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 470-475. (b) Modarelli, D. A.; Morgan, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7034-7041. (c) White, W. R.; Platz, M. S. *J. Org. Chem.* **1992**, *57*, 2841-2846. (d) Seburg, R. A.; McMahon, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 7183-7189. (e) Chen, N.; Jones, M. Jr.; White, W. R.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 4981-4992. (f) LaVilla, J. A.; Goodman, J. L. *Tetrahedron Lett.* **1990**, *31*, 5109-5112. (g) Liu, M. T. H.; Soundararajan, N.; Paike, N.; Subramanian, R. *J. Org. Chem.* **1987**, *52*, 4223-4227. (h) Moss, R. A.; Ho, G-J. *J. Phys. Org. Chem.* **1993**, *6* 126-131. (i) Fox, J. M.; Scacheri, J. E. G.; Jones K. G. L.; Jones, M. Jr; Shevlin, P. B.; Armstrong, B.; Sztyrbicka, R. *Tetrahedron Lett.* **1992**, *33*, 5021-5024.
19. Felix, D.; Muller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 1276-1319.
20. Carpenter, B. K. *Acc. Chem. Res.* **1992**, *25*, 520-528.
21. Kyba, E. P. *J. Am. Chem. Soc.* **1977**, *99*, 8330-8332.
22. Frenking, G.; Schmidt, J. *Tetrahedron* **1984**, *40*, 2123-2132.
23. (a) Nickon, A.; Ilao, M. C.; Stern, A. G.; Summers, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 9230-9232. (b) For examples of unusually high k_H/k_D isotope effects in rearrangements of carbenes generated by photolysis of diazirines see: Moss, R. A.; Ho, G-J.; Liu, W.; Sierakowski, C. *Tetrahedron Lett.* **1993**, *34*, 927-930, and references cited there.