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H_{ax} vs. H_{eq} Migrations in Tetrahydropyranylidenes Generated by Bamford-Stevens Reactions. Temperature Dependence and Non-stereoselective Activation by Ring Oxygen.

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Respectfully dedicated to the memory of Derek H.R. Barton

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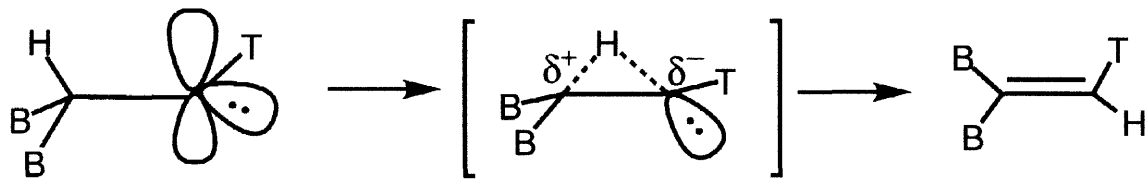
Abstract: For 1,2-shifts in singlet carbenes, a tetrahydropyranyl oxygen strongly activates its adjacent H's. To determine whether this activation is stereoselective for H_{ax} or H_{eq}, we studied d-labeled analogs of 17a-oxa-D-homosteroidal C-16 ketones (**6a**). A putative carbene center was generated at C-16 by thermal and photic Bamford-Stevens reactions, and the relative proportions of H and D shift from C-17 were assayed. After correction for primary H/D isotope effects, the H_{ax}/H_{eq} migration ratios in thermolysis were 2.2 at 170 °C, 3.3 at 120 °C, and 4.1 at 95 °C; and in photolysis it was 4.4 at -70 °C. The ratio at 170 °C is virtually the same as for ordinary cyclohexylidenes under comparable thermal conditions, so the ring oxygen activates H_{ax} and H_{eq} non-stereoselectively. Graphical analysis of the temperature dependence in thermolysis gave ΔE_a (or $\Delta(\Delta H^{\ddagger})$) = 2.7 k cal/mol (in favor of H_{ax}) and $\Delta(\Delta S^{\ddagger})$ 4.5 e.u. (in favor of H_{eq}). Extrapolation indicates the H_{ax}/H_{eq} ratio would be *ca.* 10 at room temperature, corresponding to $\Delta(\Delta G^{\ddagger})$ = *ca.* 1.35 kcal/mol.

Introduction

Singlet carbenes generated in various ways frequently undergo 1,2-migration of H (or, less often, other groups) to produce alkenes.[1] Early research[2] established that non-migrating (*i.e.* bystander) substituents markedly assist the H shifts; and more recently the magnitudes of assistance by several different bystanders (B) were estimated for carbenes of type B-CH_2-$\ddot{C}$-CH_3 generated by thermal Bamford-Stevens (B-S) reactions.[1] It is widely accepted that during H shift the origin carbon becomes electron deficient (see Scheme **1**, T = group attached to terminus carbon); and this view is supported by experimental findings[2] that bystanders capable of electron release (*e.g.* R, OR, Ar) facilitate the 1,2-shift and by various theoretical computations.[3,4,5] Alkyl substituents can donate electrons through hyperconjugation;[4] and OR (a strong activator)[6] presumably does so by lone pair delocalization and an aryl[7] through π involvement when its ring can adopt the proper orientation.

Scheme 1



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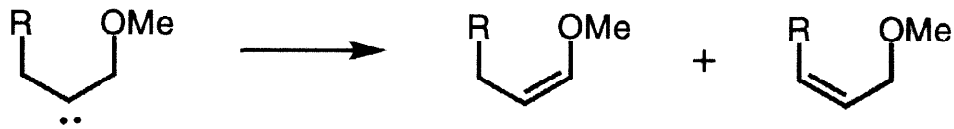
For acyclic carbenes the magnitude of H acceleration by a given bystander differs according to whether the transition state leads to a Z or E alkene.[1-4] The superior activating power of alkoxyl relative to alkyl is evident from product ratios in carbenes of type **1**. In thermal B-S reactions at 160 °C, alkenes **Z-2** are favored over **Z-3** by factors of 12.2 (R = CH_3)[2b,8] and 25.8 (R = Et).[8,9]

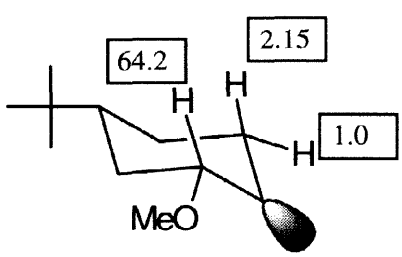


1 **Z-2** **Z-3**

a) R = CH_3 ⟶ 12.2 : 1

b) R = CH_2CH_3 ⟶ 25.8 : 1

In cyclic carbenes, various stereochemical features can also influence H shifts. For example, in chair-shaped cyclohexylidenes generated by B-S reactions migration of a 2° H_{ax} is preferred over a 2° H_{eq} by a factor of *ca.* 2.15[10] in thermolysis at 160-170 °C, and by a factor of 1.40[11] in photolysis at 25 °C. And how much a bystander α-substituent (such as OR, R, Ar) affects these rate ratios depends on whether that substituent is itself axial or equatorial.[1,10] Specifically, for a bystander OMe the approximate relative migration rates for α-H shifts in the epimers **4** and **5** according to a published analysis[1,10b] are displayed in the rectangular boxes. Note that equatorial OMe (**4**) increases kH_{ax} by a factor of 64.2/2.15 = 29.9, whereas axial OMe (**5**) increases kH_{eq} by only a factor of 1.6. Clearly, the ability to lower the E_a for H shift depends markedly on the initial stereochemistry of the OMe; equatorial OMe is a more powerful activator than axial OMe by a factor of *ca.* 19 (*i.e.* 29.9/1.6).



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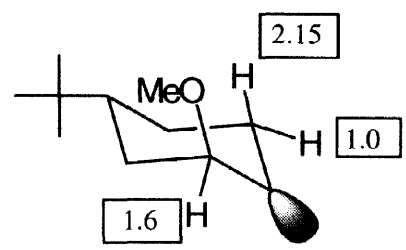
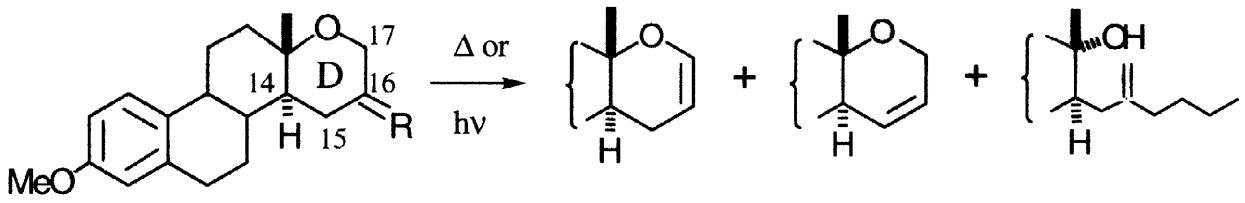


5

To learn whether this stereochemical dependence is somehow related to conformational positioning around the C–OMe bond, which in turn could influence lone pair locations, we reported[12] on B-S reactions of the steroidal ketone **6a** having an oxygen in a trans-locked, decalin-type ring. The corresponding tosylhydrazone Li salt **6c** (prepared from **6b** with BuLi) gave alkenes **7** and **8** in the ratio 21:1 on thermolysis at 170 °C, and in the ratio 14:1 on photolysis at -70 °C. In both cases, ring-opened product **9** was also produced (by a non-carbenic side reaction).[13a] The 21:1 regioselectivity in the thermal case demonstrates that ring oxygen activates its adjacent C-17 H's more effectively than ring alkyl C-14 activates its adjacent C-15 H's; and the 21:1 preference is comparable to the selectivities noted above for acyclic analogs **1a** and **1b**.



6 **7** **8** **9**

a) R = O
b) R = NNHTs
c) R = NN(Li)Ts

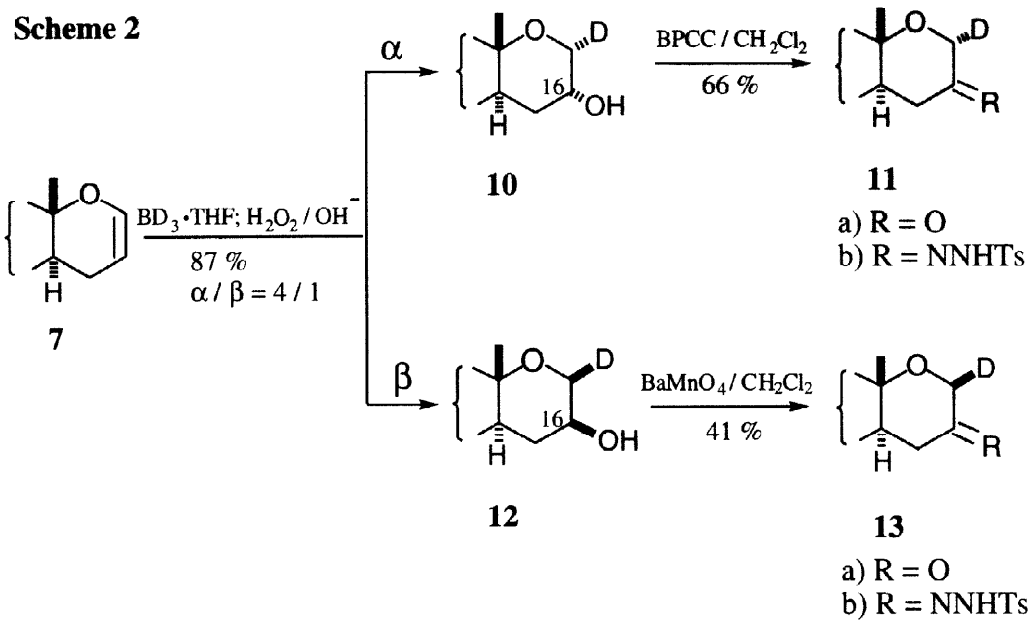
Δ (170 °C) ⟶ **7/8** = 21/1
hν (-70 °C) ⟶ **7/8** = 14/1

In the heterocyclic ring of **6** the axial and equatorial bonds at C-17 initially have different spatial relationships with respect to the lone pairs on ring oxygen. Therefore, as H begins to migrate, any quantum mechanical mixing of lone pair orbitals and the antibonding orbitals of these C–H bonds could differ for H_{ax} and H_{eq}. (Compare various anomeric effects in neutral molecules, and in cationic, anionic, and radical reactions of α-substituted tetrahydropyranyl systems.)[14,15] An additional feature in our heterocyclic carbene is the possibility of 1,3-delocalization of an oxygen lone pair into the vacant p orbital of the (singlet) carbene. Such 1,3-interaction might alter the stability of the starting carbene as well as of a transition state during rearrangement. Therefore, it was important to learn whether the strong activation by ring oxygen in **6** selectively favors one of its α-hydrogens over the other, *i.e.* whether the H_{ax}/H_{eq} shift ratio at C-17 differs significantly from the normal[10] ratio of *ca.* 2.15.

Synthesis and B-S Reactions

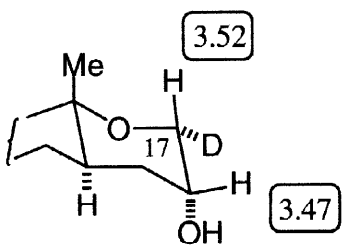
Our approach required deuterium labeled analogs, whose syntheses are summarized in Scheme **2**. Deuteroboration of known[12] enol ether **7** gave the d-labeled counterparts (**10** and **12**) of known 16 α- and 16β-alcohols,[12] with D necessarily cis to OH in each case. After separation, the alcohols were individually oxidized to their respective ketones (**11a** and **13a**) under selective conditions that minimized loss and epimerization of deuterium. Each ketone was converted to its corresponding p-tosylhydrazone (**11b** and **13b**). Scheme **3** summarizes mass spectral D assays as well as relevant ^1H NMR chemical shifts, which agreed with expectations based on the known non-labeled series.[12] For additional confirmation, we also reduced ketones **11a** and **13a** (as well as the natural abundance analog)[12] with $NaBD_4$. The major product was C-16 α-alcohol (*i.e.* OH_{ax}, D_{eq}), and the ^1H NMR chemical shifts and J couplings in each of these three reference compounds were likewise consistent with our D assignments at C-17.

Scheme 2



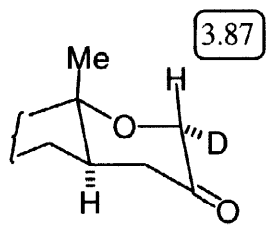
Scheme 3

D-Assays and ^{1}H NMR Chemical Shifts (▢ = C_6D_6 ; ▢ = acetone-d_6)



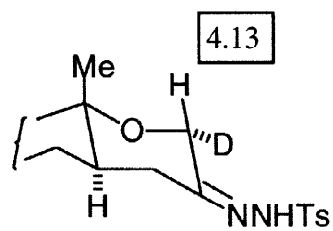
10

d_0 = 8.8 %
d_1 = 81.3 %
d_2 = 9.9 %

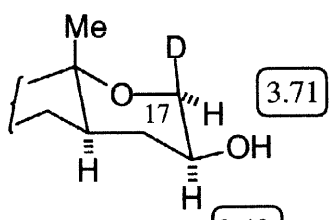


11a

d_0 = 7.7 %
d_1 = 92.3 %
d_2 = 0.0 %
87.4 % eq
4.9 % ax

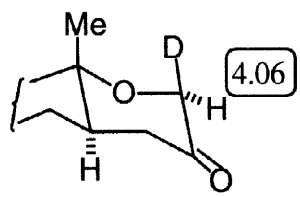


11b



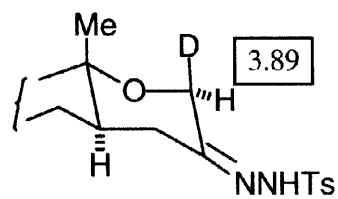
12

d_0 = 10.5 %
d_1 = 85.6 %
d_2 = 3.9 %



13a

d_0 = 10.4 %
d_1 = 85.2 %
d_2 = 3.0 %
d_3 = 1.4 %
79.0 % eq
6.2 % ax

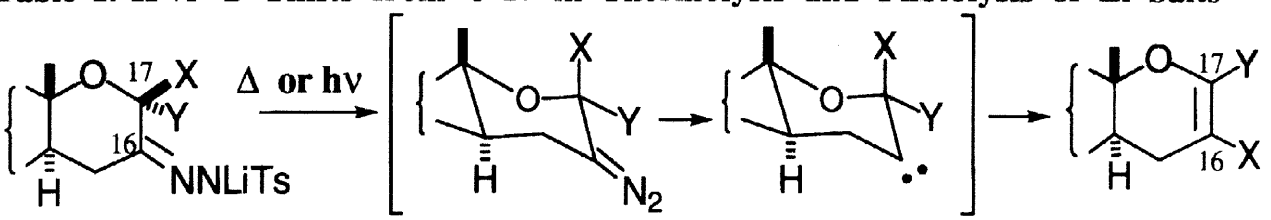


13b

Labeled tosylhydrazones **11b** and **13b** were converted with BuLi to salts **14a** and **14b**, respectively, which were thoroughly dried and thermolyzed (neat) at three different temperatures (170 °C, 120 °C, and 95 °C). Also, a pentane suspension of each salt was photolyzed at -70 °C. Under aprotic conditions such B-S reactions are known to proceed via labile diazo intermediates, which initially generate singlet carbenes on loss of N_2 (see **14** → **15** → **16** → **17** in Table 1).[16,17]

The major alkene (**17**) from each run was separated from the product mixture and purified, and the relative proportions of positional isotopomers **17a** and **17b** were determined by integration of the two vinyl H signals and correction for d_0 contributions (Table 1). These data provided the individual k_H/k_D isotope effects (termed I_{ax} and I_{eq}) for shift of H_{ax} and H_{eq} and, ultimately, the desired H_{ax}/H_{eq} migration ratios. Table 1 summarizes all the relevant data.

Table 1. H *vs* D Shifts from C-17 in Thermolysis and Photolysis of Li Salts



14 **15** **16** **17**

a) X = H, Y = D
b) X = D, Y = H

a) X = H, Y = D
b) X = D, Y = H

Substrate	Conditions	Alkene **17** Mass Spec.(Rel.%)			Corrected Ratio[a]	H/D Isotope Effect[b]		Migration Ratio
		d_0	d_1	d_2	**17a /17b**	I_{ax}	I_{eq}	H_{ax}/H_{eq}
14a	Δ, 170 °C (<1mmHg)	12.3	85.6	2.1	2.9	–	–	2.2[d]
14b[c]		–	–	–	–			
14a	Δ, 120 °C (<1mmHg)	16.7	76.6	6.7	4.3[e]	2.0	1.3	3.3
14b		12.0	86.1	1.9	0.59			
14a	Δ, 95 °C (<1mmHg)	11.9	83.1	5.0	5.4	2.0	1.3	4.1
14b		12.7	87.3	0.0	0.50			
14a	hν, pentane -70 °C	11.6	87.5	0.9	5.4[e]	1.8	1.2	4.4
14b		11.2	85.3	3.5	0.41[e]			

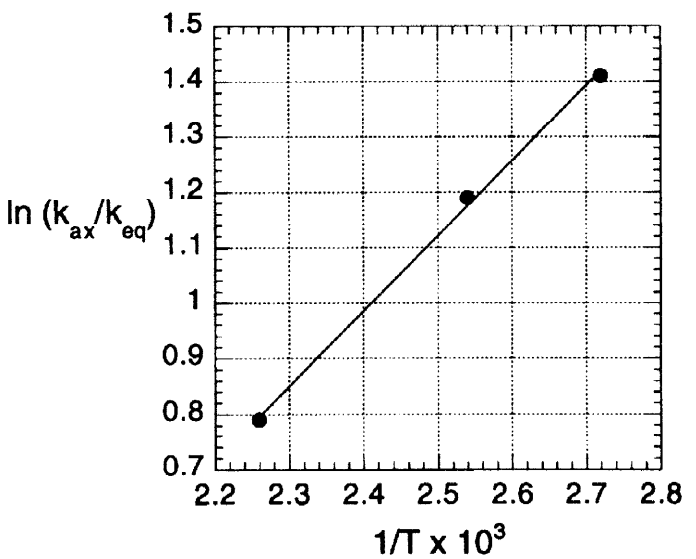
[a]Determined by ^1H NMR (400 MHZ) and corrected for the natural abundance component (which contributes equally to each of the vinylic H signals) by use of the mass spectral d_0 and d_1 values. We did not further refine these corrected ratios for the small amount of stereochemical inhomogeneity of the d_1 species. Such refinement would not alter the numbers perceptibly because of the high configurational purity of each monolabeled ketone precursor (normalized D_{eq}/D_{ax} = 94.7/5.3 in **11a**; and $D_{ax}D_{eq}$ = 92.7/7.3 in **13a**. [b]From our presnet data along with earlier findings (ref. 10b) that I_{ax} = 1.53 I_{eq} for thermal B-S and I_{ax} = 1.44 I_{eq} for photic B-S. [c]This D epimer was not studied at 170 °C; therefore I_{ax} and I_{eq} at this temperature cannot be evaluated directly. [d]Derived from the data on **14a** along with the assumption that I_{ax} = 2.0 and I_{eq} = 1.3, *i.e.* the same values as found at 120 °C and 95 °C. [e]Average from two runs. Uncorrected ^1H NMR ratios were measured for each run, but mass spectral assay of alkene **17** was done only in the first run; and these same d_0 and d_1 values were also used to correct the NMR data from the second run.

Discussion

The H_{ax}/H_{eq} ratio at C-17 for *thermal* B-S of our heterocycle at 170 °C (*i.e.* 2.2) is virtually the same as the normal ratio for cyclohexylidenes at comparable temperature.[10] Therefore, although ring oxygen powerfully activates both C-17 H's for migration, it does not favor one H over the other. Evidently, the *initial* spatial differences of oxygen lon pairs and C–H bonds are not related to degree of activation. This conclusion does not imply that spatial relationships are unimportant but only that H_{ax} and H_{eq} shift in our heterocycle benefit about equally in terms of net $\Delta G^{\ddagger}$.[13b]

Note that the H_{ax}/H_{eq} selectivity went up as the temperature was lowered, viz. 3.3 at 120 °C and 4.1 at 95 °C. This trend when displayed graphically (Fig. 1) as a linear Arrhenius-type plot related to Eq. 1 (or to its nearly equivalent thermodynamic expression Eq. 2)[18] provides a slope and intercept corresponding to Eq. 3. Therefore, although the E_a (or $\Delta H^{\ddagger}$) for H_{ax} shift is lower than for H_{eq} shift (by *ca.* 2.7 kcal/mol), the frequency (*i.e.* entropic) component favors H_{eq} shift (by *ca.* 4.5 e.u.). Graphical extrapolation indicates that the H_{ax}/H_{eq} selectivity would climb to 9.8 at 25 °C and would fall to unity around 325 °C; and above 325 °C, H_{eq} shift would prevail because of dominance of the $\Delta(\Delta S^{\ddagger})$ component. We are mindful of the potential experimental errors inherent in B-S methodology and in a graphical plot involving just three data points and a limited temperature range; consequently these numbers should be viewed only as quasi-quantitative. Nevertheless, they do reveal for heterocycle **6** (and perhaps for other cyclohexylidenes) the importance of temperature in competitive H migrations, especially when enthalpic and entropic factors favor different outcomes.[19]

In the B-S *photolyses* conducted at -70 °C, the observed H_{ax}/H_{eq} selectivity was 4.4, a value seemingly fairly similar to those from the thermal runs. However, an appreciation of the contrast between thermal and photic B-S processes becomes striking if we realize that the graphical plot in Fig. 1 predicts for *thermolysis* at -70 °C an H_{ax}/H_{eq} ratio of 82! Therefore, when researchers compare behavior of carbenes generated thermally vs. photically, not only must they consider whether some of the products arise directly from excited states of nitrogenous precursors[17] but also whether temperature differences play a significant role. Similar caveats apply to comparisons between theoretical calculations and experimental data.[4]



$$\ln\left(\frac{k_{ax}}{k_{eq}}\right) = \frac{-\Delta E_a}{R}\left(\frac{1}{T}\right) + \ln\left(\frac{A_{ax}}{A_{eq}}\right) \quad \text{Eq. 1}$$

$$\ln\left(\frac{k_{ax}}{k_{eq}}\right) = \frac{-\Delta(\Delta H^{\ddagger})}{R}\left(\frac{1}{T}\right) + \frac{\Delta(\Delta S^{\ddagger})}{R} \quad \text{Eq. 2}$$

$$\ln\left(\frac{k_{ax}}{k_{eq}}\right) = 1355\left(\frac{1}{T}\right) - 2.266 \quad \text{Eq. 3}$$

Fig. 1

Experimental Section

General. Unless stated otherwise, all experimental features involving deuterated compounds are the same as reported earlier for the natural abundance analogs.[12]

Deuteroboration of Enol Ether 7. Deuteriodiborane was generated by very slow addition of BF_3 etherate (3.5 mL, 28.5 mmol) to a stirred solution of $NaBD_4$ (Aldrich, 99.9% D, 1.0 g, 24 mmol) in dry diglyme (20 mL). Throughout addition a slow stream of Ar carried the evolved $(BD_3)_2$ gas through a second solution of $NaBD_4$ in diglyme (1 M, 10 mL) and then into a solution of enol ether **7**[12] (4.27 g, 15 mmol) in dry THF (50 mL) maintained at 0 °C. After BF_3 etherate addition was complete (*ca.* 1h), the generator solution was stirred 30 min longer at room temperature then was heated at *ca.* 80 °C for 1 h. The reaction vessel was disconnected and treated with 2N NaOH (15 mL) followed by dropwise addition of 30% H_2O_2 (12 mL). The mixture was stirred 1 h at room temperature. Workup, separation, and purification as reported[12] gave the 17α-deuterio-16α-ol **10** (2.54 g, 56%, mp 132-133.5 °C) and 17β-deuterio-16β-ol **12** (0.60 g, 13%, 148-150.5 °C). High Resolution MS data appear in Scheme 3.

Oxidation of 17α-Deuterio-3-methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-16α-ol (10) with 2.2'-Bipyridinium Chlorochromate.[20] A solution of 17α-D-16α-ol **10** (130 mg, 0.43 mmol) and 2.2'-bipyridinium chlorochromate (BPCC, Aldrich, 500 mg, 1.72 mmol, 4 equiv.) in dry CH_2Cl_2 (15 mL) was stirred 4 h at room temperature under Ar, during which time dark brown granular solid appeared. It was collected in a Hirsch funnel packed 2 cm deep with Celite, which was then washed with ether (30 mL). Evaporation left crude product (125 mg), which contained *ca.* 20% of starting alcohol. Column chromatography (silica; 1/1 hexane/ether) gave starting alcohol (20 mg) and ketone **11a** (86 mg, 66%). ^1H NMR (400 MHz) before and after chromatography showed virtually the same ratio (90:5) of 17αD/17βD in ketone **11a**. High Resolution MS data appear in Scheme 3.

Oxidation of 17β-Deuterio-3-methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-16β-ol (12) with Barium Manganate.[21] A mixture of 17β-D-16β-ol **12** (27 mg, 0.089 mmol) and $BaMnO_4$ (Aldrich, 70 mg, 0.271 mmol) in dry CH_2Cl_2 (30 mL) was stirred at room temperature under Ar. After *ca.* 70% completion (80 h) the reaction was stopped, and the black suspension was filtered through a short column of silica, which was then washed twice (50 mL) with CH_2Cl_2. Column chromatography on silica (1/1 hexane/ether) gave pure ketone **13a** (11 mg, 41%). NMR analysis before and after chromatography showed virtually the same proportions (82.4/6.5) of 17βD/17αD in ketone **13a**. High Resolution MS data appear in Scheme 3.

Reduction of Ketones with $NaBD_4$. (a) Natural Abundance Ketone 6a.[12] A solution of $NaBD_4$ (Aldrich, 99.9% D, 3 mg, 0.072 mmol) in water (0.5 mL) and methanol (2 mL) was added to a stirred solution of ketone **6a** (20 mg, 0.067 mmol) in methanol (5 mL). The mixture was warmed to 40 °C for 20 min and stirred at room temperature for an additional 20 min. Normal workup by ether extraction gave 19 mg (94%) of crude alcohol mixture, from which pure axial alcohol (15 mg, 74%) was isolated by preparative TLC (silica/ether); mp 131-133 °C (lit[12] 132.5-133 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (d, 1H, J_{gem} = 11 Hz, C-17βH), 3.92 (dd, 1H, J_{gem} = 11, J_w = 1.5 Hz, C-17αH). In C_6D_6 δ 3.35 (d, 1H, J_{gem} = 11 Hz, C-17βH), 3.74 (dd, 1H, J_{gem} = 11 Hz, J_w = 1.5 Hz, C-17αH). The mp and NMR are consistent for a 16α-OH, 16β-D stereochemistry.

(b) 17α-D-Ketone 11a. Reduction of **11a** and workup similar to that in procedure **a** gave 59% of doubly labeled 16α-alcohol (16β-D, 17α-D), mp 131.5-133.5 °C. In C_6D_6 the 17β-H appeared as a broad singlet at δ 3.32.

(c) 17β-D-Ketone 13a. Reduction of **13a** as in procedure **a** gave 70% of doubly labeled 16α–alcohol (16β-D, 17β-D), mp 131-133 °C. In C_6D_6 the 17α-H appeared as a broad singlet at δ 3.72.

Preparation of Tosylhydrazones. (a) From Ketone 11a. A mixture of 17α-D-ketone **11a** (31 mg, 0.066 mmol) and p-toluenesulfonylhydrazide (12 mg, 0.064 mmol) in absolute ethanol (20 mL) was stirred at room temperature for 20 min, during which time solid **11b** precipitated. It was collected and recrystallized from ethanol; 23 mg, 75%, mp 157.5-159.5 °C (dec) (lit[12] 161-162 °C, dec). ^{1}H NMR (400 MHz, acetone-d_6) δ 4.13 (bs, 1H, C-17βH). A weak double doublet at δ 3.91 (< 0.1H) was visible and corresponded to the small proportion of d_0 species.[12] Owing to extensive fragmentation, **11b** did not show a molecular ion in a high resolution mass spectrum.

(b) From Ketone 13a. This ketone was converted to 17β-deuteriotosylhydrazone **13b** (70%) mp 157.5-159 °C (dec) by the procedure used in part **a**. ^{1}H NMR (acetone-d_6) δ 3.89 (bs, 1H, C-17α–H). A weak (< 0.1H) double doublet at δ 4.15 corresponded to the small proportion of d_0 species.[12]

Preparation of Li Salts. (a) From 17α-Deuteriotosylhydrazone 11b. A stirred suspension of **11b** (44 mg, 0.094 mmol) in dry benzene (5 mL) in an oven-dried flask was treated with *n*-butyllithium (0.3 M in hexane, 0.3 mL, 0.090 mmol) at -70 °C under Ar. After 1 h, the solvent was evaporated, and the white salt **14a** (43 mg) was dried at room temperature for 10-15 h at 1-3 mm Hg.

(b) From 17β-Deuteriotosylhydrazone 13b. By a procedure as in part **a**, **13b** (27 mg) was converted to its Li salt **14b**, which was dried as described.

Control Reaction. Regeneration of Tosylhydrazone 11b from Li Salt 14a. To test for possible configurational change of D during salf formation we added H_2O to Li salt **14a**. The pink aqueous solution was washed with ether, and the aqueous layer was acidified at 5 °C to pH 6-7 by dropwise addition of 0.1 N H_2SO_4 to precipitate tosylhydrazone **11b** (total recovery 73%, mp 161-163 °C, dec). In the ^{1}H NMR (400 MHz) of **11b**, the ratios of 17α-D : 17β-D : natural abundance species were 86.5:1.0:12.5 before conversion to Li salt and 83.5:1.5:15.0 after regeneration from the Li salt, confirming that D stereochemistry had been largely preserved.

Thermolyses of Li Salts.[12] (a) Li Salt 14a. The dry salt was heated at 170 °C under vacuum (0.5-1.0 mm Hg) for 2 h. Column chromatography (silica/hexane) of the white solid distillate gave pure alkene **17** (58%) and a mixture (*ca.* 1:3 by NMR) of the d-labeled counterparts of alkenes **8** and **9** (*ca.* 8.3%). The relative proportions of **17a:17b** in the major alkene were determined by ^{1}H NMR integration of known vinyl H signals,[12] and deuterium content was assayed by High Resolution MS. Salt **14a** was similarly thermolyzed at 120 °C (duplicate runs) and also at 95 °C. All analytical data are displayed in Table 1.

(b) Li Salt 14b. The dry salt was thermolyzed at 120 °C and also at 95 °C under vacuum (0.025-0.50 mm Hg) for 4 h. NMR and mass analyses are given in Table 1.

Photolyses of Li Salts.[12] (a) Li Salt 14 a. In duplicate runs dry salt suspended in dry pentane under Ar was stirred and irradiated at -70 °C for 3 h with a medium-pressure Hg lamp and worked up as reported.[12] Direct analysis of the alkene product mixture by ^{1}H NMR (400 MHz) provided the **17a:17b** ratio,

and GC-Low Resolution MS gave the deuterium content of component **17** (Table 1). The minor alkenes (<10%) consisted of the d-counterparts of **8** and **9**.

(b) Li Salt 14 b. In duplicate runs, dry salt **14b** was photolyzed for 2 h at -70 °C as in procedure **a**. See data in Table 1.

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