

## 1,2-Hydrogen Shifts in Thermal and Photic Bamford-Stevens Reactions of Cyclohexanones. Activation by an Endocyclic Oxygen.

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**Abstract:** Alkoxy substituents are known to activate  $\alpha$  H's for rearrangement to carbenic centers. In acyclic systems, the degree of transition state stabilization depends on whether the alkoxy group positions itself *syn* or *anti* to the moiety connected to the other side of the carbenic carbon; and in cyclohexylidenes, it depends on whether the alkoxy substituent is initially axial or equatorial on the ring. To assess the relative activating power of a tetrahydropyranyl ring oxygen we synthesized and studied a 17a-oxa-D-homo steroidal C-16 ketone (**11a**). The carbonyl group was converted to a putative singlet carbene center by thermal and photic Bamford-Stevens (B-S) reactions, and the relative amounts of H migration from C-17 *vs.* C-15 were determined. The ring oxygen proved to be a more powerful activator than ring alkyl by a factor of 21:1 in thermolysis at 170 °C and *ca.* 14:1 in photolysis at -70 °C.

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### Introduction

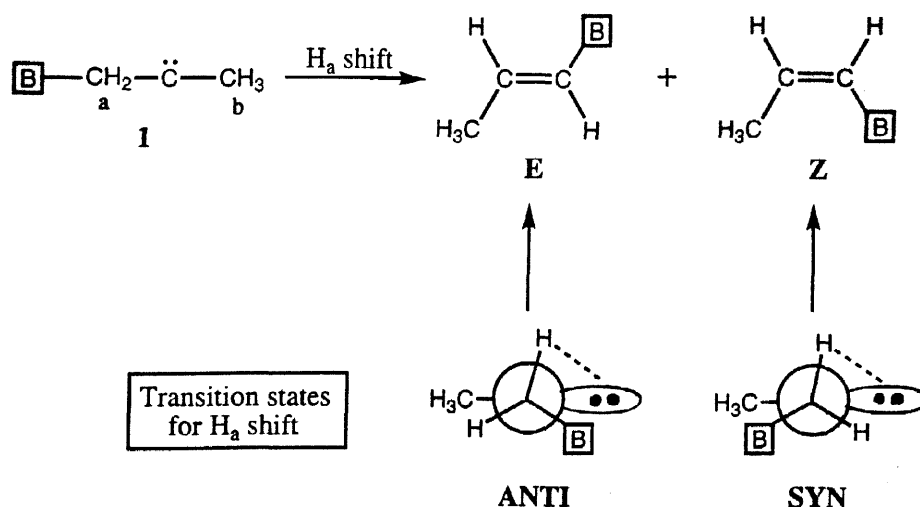
Thermolyses (or direct photolyses) of arylsulfonylhydrazone metal salts (Bamford-Stevens reactions; B-S) under aprotic conditions produce diazohydrocarbons, which readily lose N<sub>2</sub> to generate, initially, singlet carbenes.<sup>1,2</sup> A common fate of such carbenes is 1,2-shift of a substituent (usually H, but also other groups such as aryl, alkyl, OR, SR, etc) to produce alkenes.<sup>3,4</sup> The ease of rearrangement is influenced – often strongly – by nonmigrating (*i.e.* bystander) substituents, so when two or more migrators compete, the outcome can be dictated by factors other than their intrinsic migratory aptitudes.<sup>3</sup>

Published data on H shifts in open chain carbenes such as **1** (Scheme 1) reveal that common bystander groups (B) promote rearrangement of H<sub>a</sub> (relative to H<sub>b</sub>) and that the overall activating power of different B groups is: OMe > alkyl > Ph.<sup>3</sup> Shift of H<sub>a</sub> can produce E and Z alkene isomers *via* transition states<sup>5</sup> in which B is ANTI or SYN, respectively, to CH<sub>3</sub> (the group attached to the migration terminus). Product ratios reveal that when B = alkyl or Ph, the anti transition state is favored over syn; but for B = OMe, syn is preferred over anti. In terms of simple steric interaction between B and terminus CH<sub>3</sub>, syn geometries should be less favorable than anti, so the B = OMe case must have additional overriding features. Such features might include: (a) destabilization of anti from repulsion between oxygen lone pairs and the nonbonded carbene electrons; (b) stabilization of syn through donation of the carbene lone pair into the antibonding ( $\sigma^*$ ) orbital of the (nearly) antiplanar C–O bond; (c) stabilization of syn through nuclear-electron attraction between H's on the terminus CH<sub>3</sub> and lone pairs on OMe.

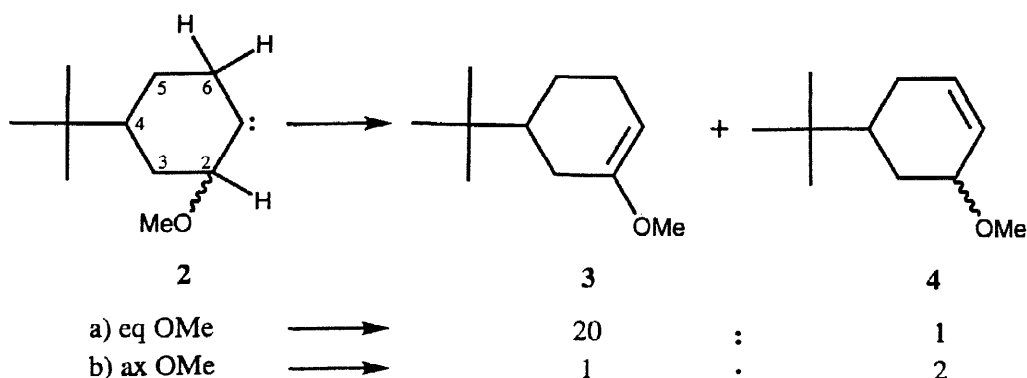
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## Scheme 1



In ring compounds, carbenes can be subject to various additional features that influence the ease of H shifts. For example, in cyclohexylidenes (generated by thermal and photolytic B-S reactions on chair-shaped cyclohexanones) the inherent  $H_{ax}/H_{eq}$  migration ratio for  $2^\circ$  hydrogens is known to be relatively low (2.15 thermolysis<sup>6</sup> at *ca.* 160 °C; 1.40 photolysis<sup>7</sup> at *ca.* 25 °C) despite the distinctly different initial alignment of the axial and equatorial C–H bonds with respect to the adjacent carbene orbitals.<sup>5a,b</sup> Interestingly, when an  $\alpha$ -bystander substituent is on the ring, its influence on the migrating  $3^\circ$  H depends on the initial stereochemistry of that substituent.<sup>3,6</sup> For example, Press and Shechter observed that the  $OMe_{eq}$  and  $OMe_{ax}$  epimers **2a** and **2b** (generated by thermal B-S reactions) produce alkenes **3** and **4** in markedly different proportions, as shown.<sup>8</sup> Detailed analysis<sup>6a</sup> of the relative rearrangement rates of all the competing H's (two H's at C-6 and one at C-2) revealed that the alkoxy substituent in epimer **2a** strongly activates its geminal H (by a factor of 29.8), whereas the alkoxy group in epimer **2b** provides very little activation (factor of 1.56).<sup>9</sup>



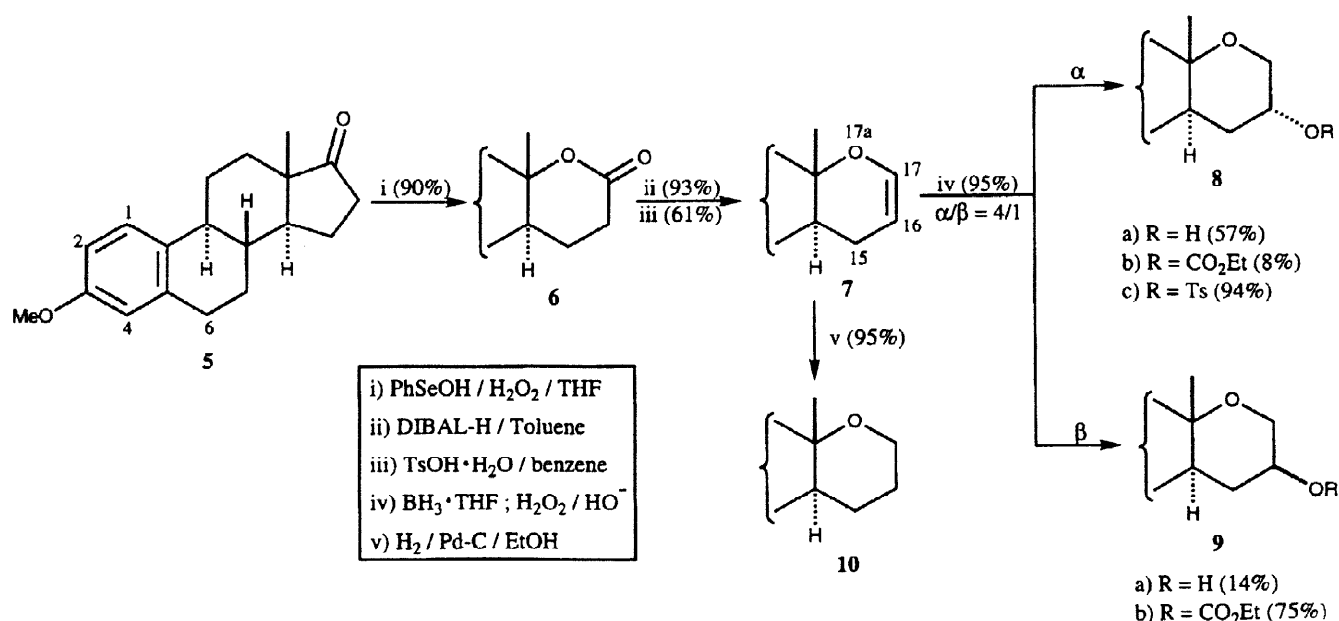
In view that the activating power of OMe on a 6-membered ring depends so much on the OMe stereochemistry, (and in view that OMe in open chain analog **1** favors a syn rather than anti transition state structure) it became important to test how H shifts would be affected by an oxygen incorporated within the carbenic ring. We now report the first investigation of regioselectivity in such a heterocyclic system.

### Synthesis

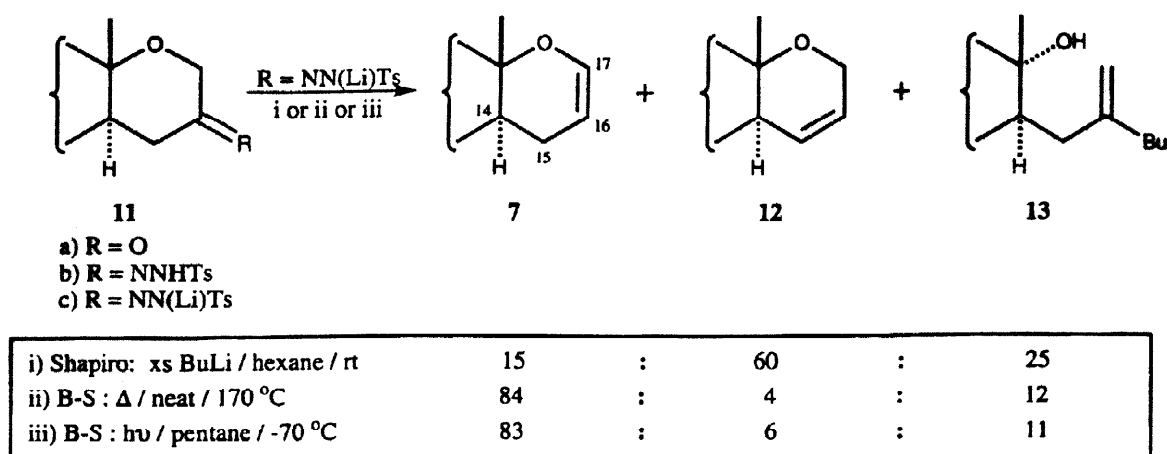
Our study utilized steroidal molecules; and Schemes 2 and 3 outline the syntheses and transformations involved. Estrone methyl ether (**5**) was converted (via known lactone **6**) to the new enol ether **7**, which was fully characterized. It showed vinyl H signals at  $\delta$  4.71 and 6.26 ( $J_{16,17} = 10$  Hz); and catalytic hydrogenation converted it to the known saturated analog **10**. Conventional hydroboration/oxidation converted enol ether **7** to a 4:1 mixture of the  $16\alpha$ -alcohol **8a** and  $16\beta$ -alcohol **9a**, which were separated and individually characterized. The  $^1\text{H}$  NMR chemical shifts and coupling constants for the carbinyl H at C-16 and for the  $\alpha$ - and  $\beta$ -hydrogens at C-17 in each epimer agree with expectations based on their assigned axial and equatorial geometries. We further confirmed these assignments for **8a** and **9a** by treatment with ethyl chloroformate to produce "cathylate" derivatives. It is known that this reagent readily esterifies equatorial alcohols at room temperature, but axial alcohols react sluggishly or not at all.<sup>10</sup> As expected, cathylate **8b** was obtained in low yield (8%) even after prolonged (20 h) treatment, whereas we isolated cathylate **9b** in 75% yield after 1h. We also converted **8a** to its tosylate (**8c**) for later use.

Ketone **11a** (Scheme 3) needed for our B-S study, was conveniently prepared by oxidation of the **8a** + **9a** alcohol mixture from hydroboration. This ketone was fully characterized, and its C-17 hydrogens ( $\delta$  4.13  $H_{ax}$ , 4.20  $H_{eq}$ ,  $J_{gem}$  18 Hz) were easily identified by NMR. The corresponding tosylhydrazone derivative (**11b**) was prepared conventionally, and a notable feature in its  $^1\text{H}$  NMR spectrum is that  $H_{eq}$  at C-17 appears at

Scheme 2



## Scheme 3

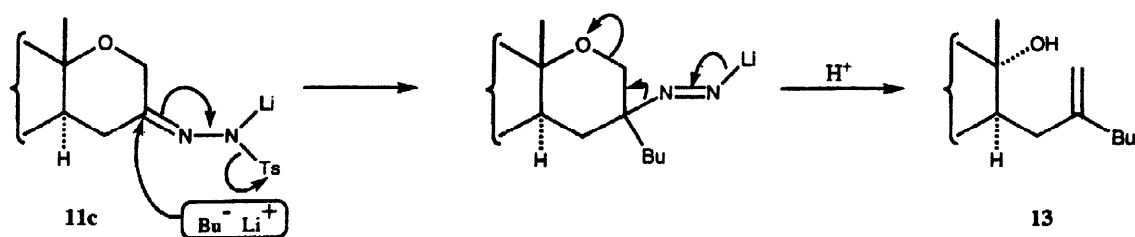


higher field ( $\delta$  3.91) than the corresponding  $H_{ax}$  ( $\delta$  4.15).<sup>11</sup> The 3.91 absorption shows a "W" coupling of 1.5 Hz (as well as the  $J_{gem} = 18$  Hz) in confirmation of its assignment as  $H_{eq}$ .

To facilitate our B-S product studies we needed to prepare and characterize alkene **12**, which we obtained by a Shapiro reaction<sup>12</sup> on tosylhydrazone **11b** and also by 1,2-elimination on tosylate **8c**. The Shapiro reaction (2.5 equiv BuLi, room temperature) gave the two expected alkenes, **7** and **12**, as well as an unexpected product (identified as **13**) in the ratio 15:60:25. The desired major alkene **12** was separated and fully characterized. Its  $^1H$  NMR showed the C-17 and C-14 allylic H's at  $\delta$  4.13 and 2.22, respectively, and the C-16 and C-15 vinylic H's at 5.46 and 5.79, respectively, with  $J_{15,16} = 10$  Hz and  $J_{15,14} = 2$  Hz.

The unexpected product (assigned structure **13**) was isolated as an oil, whose high-resolution mass spectrum (exact for  $C_{23}H_{34}O_2$ ) indicated a butyl group had been introduced, and whose  $^1H$  NMR showed narrow vinylic singlets characteristic of a  $R_2C = CH_2$  unit. One reasonable pathway to ring-opened **13** is shown (Scheme 4), although several variants can be written. Related types of alkylations of tosylhydrazones have been reported for other alkyllithium reagents.<sup>13</sup>

## Scheme 4



In a second (less effective) approach to alkene **12** we treated tosylate **8c** with the bulky base DBU<sup>14</sup> to effect E-2 elimination. The major product was alkene **7** (63%) and the minor product was alkene **12** (19%).

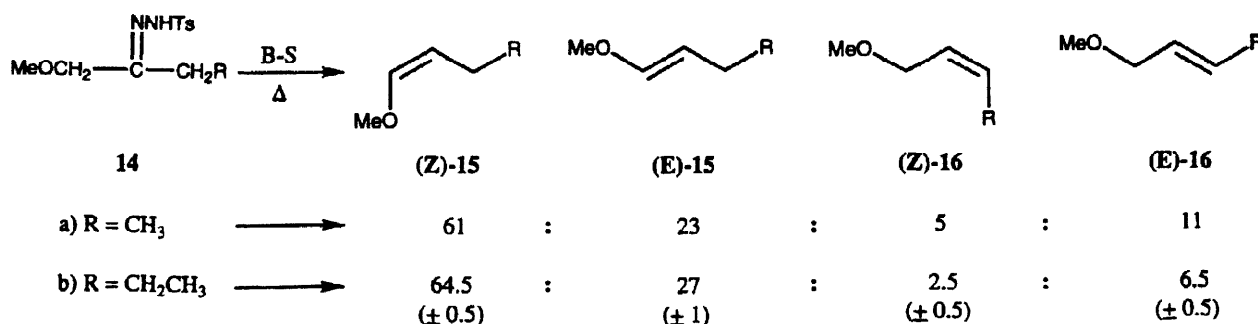
### Bamford-Stevens Reactions

Tosylhydrazone **11b** was converted (1 equiv BuLi) to its Li salt **11c**, which was isolated, thoroughly dried, and subjected to thermolysis (neat,  $170 \pm 5$  °C) and also to photolysis (pentane suspension, -70 °C). From thermolysis the isolated product (54% yield) consisted of expected alkenes **7** and **12**, along with ring-opened byproduct **13** in the ratio 84:4:12. Photolysis of **11c** gave the same three products (62% yield) and in similar proportions (83:6:11). By separate control reactions on known mixtures of **7** and **12** we established that each alkene was stable to the thermal and photic B-S conditions, and that no interconversions or selective losses on workup occur that might alter the ratio of these two alkenes.

### Discussion

**Thermal B-S.** The large preference for H rearrangement from C-17 over C-15 (84:4 = 21:1) in thermolysis at 170 °C establishes that oxygen in a six-membered heterocycle strongly activates adjacent H's. Note that in this tetrahydropyranyl ring system, migration of H's from C-15 should be assisted by bystander alkyl residue C-14 which, based on acyclic analogs,<sup>3</sup> is expected to exert its own appreciable activation. Therefore, the observed 21:1 regioselectivity favoring migration from C-17 means that **ring oxygen** activates H's 21 times more effectively than does the C-14 **ring alkyl**.

Among acyclic tosylhydrazones that have been studied under comparable B-S conditions, the closest analogs to our heterocycle **11** are **14a**<sup>15,16</sup> and **14b**.<sup>16</sup> For any comparison of cyclic *vs.* acyclic systems, we should first realize that the transition states for 2° H shifts in 6-membered rings must necessarily be of the "syn" type (see Scheme 1), because the bystander ring atoms are tethered to each other. Consequently, for acyclic analogs we need to focus on alkene proportions that arise likewise from "syn" transition states; and in **14** at 160 °C these syn transition states produce Z-alkenes, *i.e.* (Z)-**15** and (Z)-**16**, in the ratios shown. The (Z)-**15** : (Z)-**16** proportions from **14a** and also from **14b** indicate that for syn transition geometries, open chain alkoxy (OMe) activates more effectively than open chain alkyls (Me or Et) by factors of about 12.2–25.8.<sup>6b</sup> Therefore, the 21:1 regioselectivity we observed in our rigid steroidal heterocycle **11c** is of the same order as those for acyclic counterparts, notwithstanding the multitude of conformational isomers that populate the mobile open-chain series.



**Photic B-S.** Products from carbenes generated photolytically often contain higher proportions of the minor components than products from thermally generated carbenes,<sup>1</sup> perhaps because species generated by irradiation can react from higher energy levels. For our system **11c**, the ratios of **7:12** from photolysis and thermolysis are similar (83:6 vs. 84:4).<sup>6b</sup> This outcome is likely a coincidence, given that our photolysis (–70 °C) was conducted at a temperature *ca.* 240° lower than the thermolysis (170 °C). Furthermore, there is growing evidence that products derived from photolysis of certain nitrogen-containing precursors can sometimes arise in part directly from excited species in which the departing nitrogen plays some role.<sup>17</sup> For thermal B-S reactions in open chain systems Robson and Shechter have reported kinetic evidence that N<sub>2</sub> loss precedes H shift,<sup>18</sup> but further research will be needed to learn whether some thermally-induced B-S rearrangements can also proceed directly from activated nitrogen-containing species, in competition with generation of discrete carbenes. If so, the influence of bystander groups on rearrangements of those species would require study. And of special interest for the case of H acceleration by a tetrahydropyranyl ring oxygen is whether the heteroatom activates its adjacent H<sub>ax</sub> and H<sub>eq</sub> by different amounts, in view that the axial C–H bond is positioned favorably with respect to the more polarizable lone pair on oxygen and might be subject to "anomeric" type effects.<sup>19</sup>

### Experimental Section

**General.** All temperatures are in degrees Celsius (°C) and are uncorrected. IR spectra were recorded in CHCl<sub>3</sub>. <sup>1</sup>H NMR were taken on Varian Model T-60, CFT-20, or XL-400 spectrometers. Chemical shifts are referenced to the residual H signal in deuterated solvents or to internal tetramethylsilane. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Low resolution GC-MS was conducted in the Department of Chemistry, Stanford University, through the courtesy of Mr. H.Y. Lee, on a Hewlett-Packard Model 5970 GC connected to an H-P Model 5890 mass spectrometer. High resolution MS was performed by Mass Spectrometry Service Laboratory at the University of Minnesota on an AET Model MS-30. Elemental analyses were provided by MicAnal Organic Microanalysis, Tucson, AZ.

Analytical TLC was performed on plates coated with silica gel GF (250 μ thick). Visualization involved a spray with 5% ethanolic phosphomolybdic acid (Aldrich) followed by heat to above 100 °C (for steroids). Preparative TLC was done on silica gel GF plates (1000 or 2000 μ thick) or on UNIPLATE-T Taper Plates (silica GF). Column chromatography involved silica gel-60 (25–40 mesh); flash column chromatography followed published techniques<sup>20</sup> with Ar gas to enhance hydrostatic pressure.

Photochemical reactions were conducted with a water-cooled, medium pressure mercury lamp (Hanovia, 450 watt) surrounded by a quartz filter and immersed in the solution being irradiated. "Dry" glassware indicates it was heated overnight in an oven above 120 °C then cooled under argon. "Dry" ether and tetrahydrofuran (THF) refer to commercial reagents refluxed over sodium-benzophenone ketyl and then freshly distilled just prior to use. All other solvents were obtained "dry" by reflux over CaH<sub>2</sub> and distillation under inert atmosphere. "Anhydrous" and "absolute" refer to the commercially available reagents. The *n*-butyllithium was purchased (Aldrich) as a solution in hexane and was assayed by titration with 3,4,5-trimethoxybenzyl alcohol as indicator.<sup>21</sup> All solvents were removed on a rotary evaporator at reduced pressure.

**3-Methoxy-estra-1,3,5(10)-trien-17-one (**5**; estrone-3-methyl ether).** Estrone (Sigma) was treated with dimethyl sulfate and benzyl-*n*-butylammonium hydroxide phase transfer catalyst.<sup>22</sup> The derived ether **5**

was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/MeOH; mp 171.5–172.5 (lit.<sup>23</sup> 167.5–169). Characteristic reference peaks: IR 1715 (C=O), 1608, 1500 cm<sup>-1</sup>; <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>) δ 0.91 (s, 3H, angular CH<sub>3</sub>), 2.80–2.90 (m, 2H, C6-H benzylic), 3.77 (s, 3H, OCH<sub>3</sub>), 6.63 (d, 1H, J<sub>2,4</sub> = 3 Hz, C4-H), 6.75 (dd, 1H, J<sub>1,2</sub> = 8.5 Hz, J<sub>2,4</sub> = 3 Hz, C2-H), 7.18 (d, 1H, J<sub>1,2</sub> = 8.5 Hz, C1-H).

**3-Methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-17-one (6).** This known lactone<sup>24</sup> was obtained by adaptation of Grieco's procedure<sup>25</sup> for Baeyer-Villiger type oxidations. Benzene peroxyseleminic acid was prepared *in situ* by addition of 30% H<sub>2</sub>O<sub>2</sub> (21.5 mL, ca. 20 mmol) to a stirred solution of benzeneseleninic acid (Aldrich, 437 mg, 2.31 mmol, 1.05 equiv) in THF (10 mL) at room temperature. After 30 min **5** (625 mg, 2.2 mmol) dissolved in THF (10 mL) was added slowly to the stirred oxidation solution. After 24 h, aqueous NaHCO<sub>3</sub> was added, and the organic layer was washed with aqueous NaHSO<sub>3</sub> and brine and then dried (MgSO<sub>4</sub>). The derived **6** (645 mg, 90%, mp 168–172) was recrystallized from EtOH; white needles, mp 171–171.5 (lit.<sup>24</sup> 172.4–174). IR 1715 (C=O); <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>) δ 1.35 (s, 3H, angular CH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), aromatic region same as for **5**.

**3-Methoxy-17a-oxa-D-homoestra-1,3,5(10),16-tetraene (7) via the Corresponding 17 α-ol Hemiacetal.** Lactone **6** (188 mg, 0.63 mmol) stirred in dry toluene (50 mL) under Ar at ca. -70° was treated dropwise with diisobutylaluminum hydride solution (Aldrich, 1 M in toluene, 0.8 mL, 0.8 mmol) during 1 h. After an additional 1 h at low temperature the mixture was poured into a batch of ice, glacial acetic acid, and water, all of which was stirred 30 min. The organic layer was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and then washed successively with water, aqueous NaHCO<sub>3</sub>, and brine, and was dried (MgSO<sub>4</sub>). Evaporation and recrystallization of the solid from methanol left 174 mg (93%) of white hemiacetal, mp 165–168 (lit.<sup>26</sup> mp 182–188, from acetone). IR 3600, 3400, 1608, 1500, 1260, 1240 cm<sup>-1</sup>; <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>) δ 1.21 (s, 3H, angular CH<sub>3</sub>), 2.80–2.89 (m, 2H, C6-H benzylic), 3.77 (s, 3H, OCH<sub>3</sub>), 5.10 (bs, 1H, C17-βH), aromatic region same as for **5**.

The hemiacetal (160 mg, probably largely the 17 α-ol epimer) in benzene (20 mL) was treated with *p*-toluenesulfonic acid monohydrate (Baker 99%, 10 mg) at room temperature. After 13 h the stirred mixture was diluted with ether (20 mL), washed with aqueous NaHCO<sub>3</sub> and brine, and dried (MgSO<sub>4</sub>). Evaporation left 119 mg (74%); mp 110–117. TLC showed no starting material and a major product (R<sub>f</sub> ca. 0.7) along with four unresolved minor components (R<sub>f</sub> 0.3–0.5). The major product (**7**) was isolated by column chromatography on silica (4:1 hexane-ether); 98 mg (61%), mp 120–125. The analytical sample (mp 122–123.5, from ethanol) showed: IR 1650, 1603, 1500 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.89–1.15 (m, 1H), 1.18 (s, 3H, angular CH<sub>3</sub>), 1.30–1.50 (m, 3H), 1.55–1.81 (m, 3H), 1.98–2.08 (m, 2H), 2.12–2.26 (m, 1H), 2.34–2.51 (m, 2H), 2.80–2.94 (m, 2H, C6-H benzylic), 3.77 (m, 3H, OCH<sub>3</sub>), 4.71 (dd, 1H, J<sub>16,17</sub> = 10 Hz, J<sub>15,16</sub> = 2.5 Hz, C16-H vinylic), 6.26 (d, 1H, J<sub>16,17</sub> = 10 Hz, C17-H vinylic), aromatic region same as for **5**; [α]<sub>D</sub><sup>30</sup> + 21°. **Analysis.** Calc'd for C<sub>19</sub>H<sub>24</sub>O<sub>2</sub> (284.40); C, 80.24; H, 8.51. Found: C, 80.48; H, 8.60. High-resolution MS, 284.1775. C<sub>19</sub>H<sub>24</sub>O<sub>2</sub> requires 284.1776.

The four minor components were not identified, but GC-low resolution MS indicated that each has a molecular ion at 284, and <sup>1</sup>H NMR data were recorded for each component (isolated by preparative TLC).<sup>27</sup>

**3-Methoxy-17a-oxa-D-homoestra-1,3,5(10)-triene (10).** Enol ether **7** (50 mg) in absolute ethanol (20 mL) was hydrogenated with 5% Pd/C (10 mg, Aldrich) in a Parr hydrogenator (20 psi) for 15 h at room

temperature. Workup and recrystallization from aqueous methanol gave 48 mg (95%) of **10**; mp 147.8–148 (lit<sup>25</sup> 150–151). A double resonance NMR experiment at 400 MHz (C<sub>6</sub>D<sub>6</sub>) made it possible to distinguish the 17  $\beta$ H (axial) from the 17  $\alpha$ H (equatorial):  $\delta$  3.60 (m, 1H,  $J_{\text{gem}} = 11.5$  Hz,  $J_{16\alpha, 17\beta} = 12$  Hz,  $J_{16\beta, 17\beta} = 2$  Hz, C17- $\beta$ H), 3.66 (m, 1H,  $J_{\text{gem}} = 11.5$  Hz,  $J_{16\alpha, 17\alpha} = 5$  Hz, C17- $\alpha$ H).

**3-Methoxy-17 $\alpha$ -oxa-D-homoestra-1,3,5(10)-trien-16 $\alpha$ -ol (8a) and -16 $\beta$ -ol (9a) by Hydroboration of Enol Ether 7.** A solution of BH<sub>3</sub> • THF (Aldrich, 1M, 0.7 mL, 1.9 equiv) was added to a stirred solution of enol ether **7** (104 mg, 0.37 mmol) in THF (20 mL) at room temperature under Ar. After 2h, 2N NaOH (3 mL) was added slowly, followed by dropwise addition of 30% H<sub>2</sub>O<sub>2</sub> (3 mL) and continued stirring for 1h. Ether (20 mL) and brine (20 mL) were added, and the aqueous layer was again extracted with ether. The combined ether extract was washed with NaHSO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), and evaporated. The white solid (95 mg, 95%) showed a major and one minor component (by TLC), which were separated by flash column chromatography (silica/ether) followed by preparative TLC (silica/ether). The major alcohol (**8a**, 62 mg, 57%, mp 131.5–133.5) gave the analytical sample (mp 132.5–133 dec) after recrystallizations from ethanol. IR 3595, 3400, 3000, 2940, 1608, 1500, 1045 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.10–1.17 (m, 2H), 1.19 (s, 3H, angular CH<sub>3</sub>), 1.22–2.51 (m, 9H), 2.78–2.90 (m, 2H, C6-H benzylic), 3.68 (d, 1H,  $J_{\text{gem}} = 11$  Hz, C17 -  $\beta$ H), 3.77 (s, 3H, OCH<sub>3</sub>), 3.87 (bs, 1H, C16- $\beta$ H), 3.92 (dd, 1H,  $J_{\text{gem}} = 11$  Hz,  $J_{\text{vic}}$  or  $J_{\text{w}} = 2$  Hz, C17 -  $\alpha$ H), aromatic region same as for **5**; 400 MHz (C<sub>6</sub>D<sub>6</sub>)  $\delta$  3.40 (s, 3H, OCH<sub>3</sub>), 3.47 (bs, 1H, C16- $\beta$ H), 3.54 (bs, 2H, C17 -  $\alpha$  and  $\beta$ H overlapped);  $[\alpha]_{\text{D}}^{27} + 90^\circ$ . **Analysis.** Calc'd for C<sub>19</sub>H<sub>26</sub>O<sub>3</sub> (302.40; C, 75.46; H, 8.67. Found: C, 75.17; H, 8.47. High-Resolution MS, 302.1881. C<sub>19</sub>H<sub>26</sub>O<sub>3</sub> requires 302.1882.

The minor alcohol (**9a**, 15 mg, 14%, mp 149–150.5) was recrystallized twice from aqueous ethanol; mp 150–151.5. IR 3580, 3415, 3000, 2740, 1608, 1500, 1040. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.15–1.70 (m, 6H), 1.19 (s, 3H, angular CH<sub>3</sub>), 1.83–2.50 (m, 5H), 2.78–2.90 (m, 2H, C6-H benzylic), 3.44 (m, 1H, C17 -  $\beta$ H), 3.77 (s, 3H, OCH<sub>3</sub>), 3.75–3.83 (m, 2H, C16- $\beta$ H and C-17- $\alpha$ H), aromatic region same as for **5**; 400 MHz (C<sub>6</sub>D<sub>6</sub>)  $\delta$  3.34 (dd or pseudo t, 1H,  $J_{\text{gem}} = 10$  Hz,  $J_{16,17} = 10$  Hz, C17 -  $\beta$ H) 3.40 (s, 3H, OCH<sub>3</sub>), 3.48 (m, 1 H, C16 -  $\alpha$ H), 3.73 (ddd, 1H,  $J_{16,17} = 5$  Hz,  $J_{\text{gem}} = 10$  Hz,  $J_{\text{w}} = 1.5$  Hz, C17 -  $\alpha$ H);  $[\alpha]_{\text{D}}^{32} + 107^\circ$ . High Resolution MS, 302.1882. C<sub>19</sub>H<sub>26</sub>O<sub>3</sub> requires 302.1882.<sup>28</sup>

**Carboethoxylation ("Cathylation") of 16 $\alpha$ -Alcohol 8a.**<sup>10</sup> A solution of **8a** (31 mg) in anhydrous dioxane (2 mL) and anhydrous pyridine (2 mL) was treated dropwise with ethyl chloroformate (Aldrich, 1.5 mL, 15 equiv), and the mixture was stirred 20 h at room temperature. Workup followed by preparative TLC (silica/1:1 hexane-ether) gave starting alcohol **8a** (25 mg, 81%) and a small yield (3 mg, 8%, mp 128–129) of its cathylate **8b**. The analytical sample (from absolute methanol) had mp 128.5–129. IR 2930, 1735, (C=O), 1608, 1500, 1378, 1260 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  0.78–0.85 (m, 1H), 0.88 (s, 3H, angular CH<sub>3</sub>), 0.97 (t, 3H,  $J_{\text{vic}} = 7.5$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 0.98–1.98 (m, 8H), 2.07–2.15 (m, 2H), 2.57–2.63 (m, 2H, C6-H benzylic), 3.40 (s, 3H, OCH<sub>3</sub>), 3.54 (dd, 1H,  $J_{\text{gem}} = 13.5$  Hz,  $J_{16\beta, 17\beta} = 1.5$  Hz, C17 -  $\beta$ H), 3.80–4.00 (m, 3H, C17- $\alpha$ H and OCH<sub>2</sub>CH<sub>3</sub>), 4.67 (bs, 1H, C16- $\beta$ H), aromatic region same as for **5**;  $[\alpha]_{\text{D}}^{27} + 110^\circ$ . **Analysis.** Calc'd for C<sub>22</sub>H<sub>30</sub>O<sub>5</sub> (374.46): C, 70.56; H, 8.08. Found: C, 70.74; H, 8.06.

**Cathylation of 16 $\beta$ -Alcohol 9a.**<sup>10</sup> Ethyl chloroformate (0.2 mL, 5 equiv) was added dropwise to **9a** (14 mg) in anhydrous dioxane (1 mL) and anhydrous pyridine (2 mL). After 1 h, workup gave 16 mg of a white, semi-solid; TLC (silica/ether) indicated one major component, two minor components with lower R<sub>f</sub>, and

no starting alcohol. The cathylate (mp 99–101) was isolated by short column chromatography and for analysis was recrystallized from absolute methanol; mp 100–100.5. IR 3000, 2940, 1732 (C=O), 1608, 1500, 1467, 1380, 1260  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  0.80–0.90 (m, 1H), 0.91 (s, 3H, angular  $\text{CH}_3$ ), 0.96 (t, 3H,  $J_{\text{vic}} = 7.5$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.10–1.41 (m, 5H), 1.55–1.63 (m, 2H), 1.78–1.85 (m, 1H), 2.03–2.17 (m, 3H), 2.50–2.67 (m, 2H, C6-H benzylic), 3.40 (s, 3H,  $\text{OCH}_3$ ), 3.52 (m, 1H, C17- $\beta\text{H}$ ), 3.90–4.01 (m, 3H, C17- $\alpha\text{H}$  and  $\text{OCH}_2\text{CH}_3$ ), 4.81–4.89 (m, 1H, C16- $\alpha\text{H}$ ), aromatic region same as for **5**.  $[\alpha]_{\text{D}}^{27} + 127^\circ$ . **Analysis.** Calc'd for  $\text{C}_{22}\text{H}_{30}\text{O}_5$  (374.46): C, 70.56; H, 8.08. Found: C, 70.45; H, 8.02.

**Tosylation of Alcohol 8a.** A mixture of **8a** (100 mg, 0.33 mmol), *p*-toluenesulfonyl chloride (Aldrich, 70 mg, 1.1 equiv), THF (20 mL) and pyridine (10 mL) was stirred at room temperature for 20 h. Sulfuric acid (2N, 15 mL) was added, and the organic layer was washed with brine and dried ( $\text{MgSO}_4$ ). Evaporation and crystallization from  $\text{CH}_2\text{Cl}_2$ /ether gave 137 mg (94%) of the 16 $\alpha$ -tosylate **8c**, mp 147–148 (dec). Two more recrystallizations gave mp 147.5–148 (dec). IR 3040, 3000, 2940, 1605, 1500, 1360, 1190, 1172  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.01–1.10 (m, 1H), 1.12 (s, 3H, angular  $\text{CH}_3$ ), 1.12–1.22 (m, 1H), 1.38–1.53 (m, 2H), 1.68–1.86 (m, 1H), 2.35–2.49 (m, 1H), 2.45 (s, 3H, *p*- $\text{CH}_3$ ), 2.78–2.89 (m, 2H, C6-H benzylic), 3.70 (dm, 1H,  $J_{\text{gem}} = 13.7$  Hz, C17- $\beta\text{H}$ ), 3.77 (s, 3H,  $\text{OCH}_3$ ), 3.78 (dd, 1H,  $J_{\text{gem}} = 13.7$  Hz,  $J_{\text{w}} = 2$  Hz, C17- $\alpha\text{H}$ ), 4.69 (s, 1H, C16- $\beta\text{H}$ ), 6.63 (d, 1H,  $J_{2,4} = 3$  Hz, C4-H), 6.75 (dd, 1H,  $J_{1,2} = 8.5$  Hz,  $J_{2,4} = 3$  Hz, C2-H), 7.18 (d, 1H,  $J_{1,2} = 8.5$  Hz, Cl-H), 7.34 (d, 2H,  $J = 8$  Hz, ortho H), 7.83 (d, 2H,  $J = 8$  Hz, meta H);  $[\alpha]_{\text{D}}^{27} + 52^\circ$ . **Analysis.** Calc'd for  $\text{C}_{26}\text{H}_{32}\text{O}_5\text{S}$  (456.58): C, 68.39; H, 7.06. Found: C, 68.63; H, 7.18.

**3-Methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-16-one (11a).** A mixture (92 mg, 0.33 mmol) of alcohols **8a** and **9a** (from hydroboration of **7**) and pyridinium dichromate<sup>29</sup> (Aldrich, 98%, 198 mg, 0.57 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was stirred under Ar at room temperature for 22 h. Anhydrous ether (10 mL) was added, the mixture was filtered through  $\text{MgSO}_4$ , which was washed with more ether (30 mL). Evaporation left 82 mg (84%) of white solid, mp 148–152. Two recrystallizations from aqueous methanol followed by vacuum sublimation afforded analytically pure ketone **11a**, mp 150.5–151. IR 3000, 2840, 2775, 1718 (C = O), 1608, 1500  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.18–1.25 (m, 1H), 1.28 (s, 3H, angular  $\text{CH}_3$ ), 1.30–1.77 (m, 2H), 1.88–1.96 (m, 1H), 1.99–2.04 (m, 2H), 2.12–2.21 (m, 2H), 2.37–2.44 (m, 1H), 2.48–2.53 (m, 1H, C15- $\beta\text{H}$ ?), 2.73 (dd, 1H,  $J_{\text{gem}} = 18$  Hz,  $J_{14\alpha,15\alpha} = 5$  Hz, C15- $\alpha\text{H}$ ), 2.70–2.92 (m, 2H, C6-H benzylic), 3.77 (s, 3H,  $\text{OCH}_3$ ), 4.13 (d, 1H,  $J_{\text{gem}} = 18$  Hz, C17- $\beta\text{H}$ ), 4.20 (d, 1H,  $J_{\text{gem}} = 18$  Hz, C17- $\alpha\text{H}$ );  $[\alpha]_{\text{D}}^{31} + 39^\circ$ . **Analysis.** Calc'd for  $\text{C}_{19}\text{H}_{24}\text{O}_3$  (300.38): C, 75.97; H, 8.05. Found: C, 75.87; H, 8.32. High Resolution MS, 300.1725.  $\text{C}_{19}\text{H}_{24}\text{O}_3$  requires 300.1725.

**Conversion of Ketone 11a to its *p*-Toluenesulfonylhydrazone (11b).** Ketone **11a** (54 mg, 0.12 mmol) and *p*-toluenesulfonylhydrazide (Aldrich, 21 mg, 0.11 mmol, 0.95 equiv) in absolute ethanol (25 mL) was stirred at room temperature for 30 min, during which time the product precipitated. Evaporation of solvent and recrystallization of the solid from ethanol gave 45 mg (80%), mp 159–161 (dec). Three recrystallizations gave a constant mp 161–162 (dec). IR 3112, 3000, 2940, 2860, 1605, 1500, 1360, 1187, 1170  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, acetone- $d_6$ )  $\delta$  1.21 (s, angular  $\text{CH}_3$ ), 1.20–2.45 (m, 9H), 2.41 (s, 3H, *p*- $\text{CH}_3$ ), 2.78–2.90 (m, 2H, C6-H benzylic), 3.04 (dd, 1H,  $J_{\text{gem}} = 18$  Hz,  $J_{14,15\alpha} = 4$  Hz, C15- $\alpha\text{H}$ ), 3.73 (s, 3H,  $\text{OCH}_3$ ), 3.91 (dd, 1H,  $J_{\text{gem}} = 18$  Hz,  $J_{\text{w}} = 1.5$  Hz, C17- $\alpha\text{H}$ ), 4.15 (d, 1H,  $J_{\text{gem}} = 18$  Hz, C17- $\beta\text{H}$ ), 6.61 (d, 1H,  $J_{2,4} =$

3 Hz, C4-H), 6.68 (d, 1H,  $J_{1,2} = 8.5$  Hz,  $J_{2,4} = 3$  Hz, C2-H), 7.18 (d, 1H,  $J_{1,2} = 8.5$  Hz, C1-H), 7.38 (d, 2H,  $J = 8$  Hz, ortho-H), 7.78 (d, 2H,  $J = 8$  Hz, meta H);  $[\alpha]_D^{30} + 64^\circ$ . **Analysis.** Calc'd for  $C_{26}H_{32}O_4N_2S$  (468.60): C, 66.64; H, 6.88. Found: C, 66.42; H, 6.91.

**3-Methoxy-17a-oxa-D-homoestra-1,3,5(10),15 tetraene (12) and Ring-opened Alkenol 13.** (a) **By a Shapiro Reaction.** *n*-Butyllithium (1M, 1.5 mL, 2.5 equiv) was added dropwise under Ar to a stirred suspension of tosylhydrazone **11b** (286 mg, 0.61 mmol) in dry hexane (30 mL) at room temperature. After 30 min water (10 mL) was added, and the organic layer was washed with brine, dried ( $MgSO_4$ ), and evaporated to leave 107 mg. TLC (silica/1:1 hexane-ether) showed three components, enol ether **7** ( $R_f = 0.7$ ), alkene **12** ( $R_f = 0.6$ , and ring-opened alkenol **13** ( $R_f = 0.5$ ); their ratio was 15:60:25 respectively, as determined by integration of olefinic H in a  $^1H$  NMR spectrum. Separation of the three products by column chromatography (silica/hexane) gave **12** (54 mg, mp 101–103.5). For analysis **12** was recrystallized repeatedly from aqueous ethanol; mp 103–104;  $[\alpha]_D^{35} + 36^\circ$ . IR 3040, 2940, 1610, 1500, 1350, 1280, 1100  $cm^{-1}$ .  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.17 (s, 3H, angular  $CH_3$ ), 1.20–1.72 (m, 7H), 1.87–2.93 (m, 1H), 2.08–2.16 (m, 1H), 2.22 (m, 1H, C14-H), 2.37–2.52 (m, 2H), 3.77 (s, 3H,  $OCH_3$ ), 4.13 (m, 2H, C17-H allylic), 5.46 (dm, 1H,  $J_{15,16} = 10$  Hz, C16-H vinylic), 5.79 (dd, 1H,  $J_{14,15} = 2$  Hz,  $J_{15,16} = 10$  Hz, C15-H vinylic), aromatic region same as in **5**. **Analysis.** Calc'd for  $C_{19}H_{24}O_2$  (284.40): C, 80.24; H, 8.51. Found: C, 79.84; H, 8.24.

The oily alkenol **13** was purified by column chromatography and by bulb-to-bulb vacuum distillation (110°/0.5 mm Hg). IR 3600–3500, 3000, 2935, 2860, 1610, 1501, 1042  $cm^{-1}$ .  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.92 (t, 3H,  $J_{vic} = 9$  Hz,  $CH_2CH_3$ ), 1.18 (s, 3H, angular  $CH_3$ ), 1.20–1.74 (m, 9H), 1.84–1.92 (m, 1H), 2.05–2.24 (m, 5H), 2.28–2.44 (m, 3H), 2.78–2.90 (m, 2H, C6-H benzylic), 3.77 (s, 3H,  $OCH_3$ ), 4.82 (s, 1H, vinylic), 4.90 (s, 1H, vinylic), aromatic region same as in **5**. High-Resolution MS, 342.2557.  $C_{23}H_{34}O_2$  requires 342.2559. We had insufficient sample for optical rotation or for combustion analysis.

(b) **Tetraene 12 by 1,2-Elimination on Tosylate 8c.** A solution of **8c** (50 mg, 0.11 mmol) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU; Aldrich, 20  $\mu$ L, 0.14 mmol) in benzene (10 mL) was stirred at room temperature for 15 h. The mixture left on evaporation of solvent was separated by short column chromatography to give 20 mg (63%) of **7** and 6 mg (19%) of **12** (mp 101–103 after one recrystallization), both of which were identified spectroscopically.

**Bamford-Stevens Reactions.**<sup>27</sup> **Preparation of Li Salt 11c.** A stirred suspension of dry tosylhydrazone **11b** (26 mg, 0.056 mmol) in freshly distilled benzene (5 mL) in an oven-dried flask was treated with *n*-butyllithium (1.2 M in hexane, 0.046 mL, 0.055 mmol, 0.98 equiv) at 0° under Ar. With every drop added, a shade of yellow appeared, which quickly faded to white. After 1 h, the solvent was evaporated to leave white Li salt **11c** (27 mg). Prior to use, this salt was dried 20 h under vacuum (0.05–1.0 mm Hg) at 25°.

(i) **Thermolysis.** Dry salt **11c** (27 mg) was heated at 170 ( $\pm 5^\circ$ ) for 2 h under vacuum (0.05–1.0 mm Hg) in a Kugelrohr apparatus.<sup>27</sup> The distillate deposited as a white solid (8.5 mg, 54%) in the cooled receiver and was transferred with  $CH_2Cl_2$ , which was evaporated.  $^1H$  NMR (400 MHz,  $C_6D_6$ ) showed alkenes **7**:**12**:**13** in the ratio 84:4:12.

(ii) **Photolysis.** Dry salt **11c** (from 37 mg **11b** and 0.94 equiv *n*-BuLi) was suspended in pentane (160 mL) under Ar and was cooled to  $-76^\circ$ . The stirred mixture was irradiated 2 h, while the temperature was maintained below  $-70^\circ$ .<sup>27</sup> The solvent was evaporated, water (2 mL) and ether (5 mL) were added, and the

water layer was extracted with more ether, which was then washed with brine and dried (MgSO<sub>4</sub>). Evaporation left white solid (14 mg, 62%), comprised of **7**:**12**:**13** in the ratio 83:6:11 (via 400 MHz <sup>1</sup>H NMR).

**Control Experiments: Stability of Alkenes 7 and 12 to Thermolysis and Photolysis.** An 88:12 mixture of **7** (22 mg) and **12** (3 mg) plus *p*-toluenesulfonic acid sodium salt hydrate (Aldrich 0.088 mmol) was subjected to the thermolysis conditions (170°, 0.03–0.05 mm Hg). The distillate (23.7 mg, 95% recovery) contained **7** and **12** in the ratio 87:13. A similar control on an initial 1:1 mixture, likewise did not effect the ratio.

A mixture (20 mg) of **7** and **12** (ratio 87:13) plus *p*-toluenesulfonic acid sodium salt hydrate (0.088 mmol) was subjected to the photolysis conditions and workup. The ratio of recovered alkenes (17 mg, 85%) was 88:12.

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28. Carbon analysis on this sample was  $\alpha$ . 4% low and after one sublimation was  $\alpha$ . 1% low, presumably from tenacious residual solvent(s) of recrystallization. Possible contamination by enol ether **7** (or its hemiacetal precursor) or by epimer **8a** would not account for low carbon analyses.
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