Unusual Cyclization Products Derived from Photolysis of Breslow's Steroidal Benzophenone Esters

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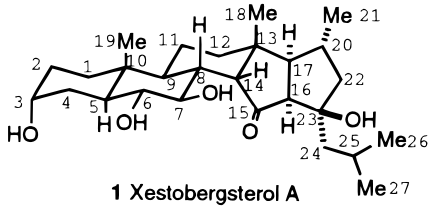
In 1973, Breslow and co-workers developed a method for "remote functionalization" of steroids,[2] namely, functionalization of C9, C14, and C17 by photolysis of benzophenone esters α-linked to the steroid backbone at C3. They observed selective abstraction of tertiary hydrogens by the diradical of the benzophenone carbonyl and, by choosing tethers of appropriate length, were able to achieve good regioselectivity of hydrogen atom abstraction, e.g., selectivity for abstraction of C9, C14, or C17.

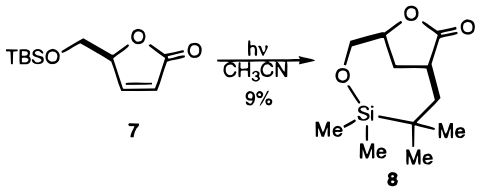
Recently, our efforts have been directed at expanding the Breslow concept to natural product synthesis.[3] In a projected total synthesis of xestobergsterol A (**1**), a potent



1 Xestobergsterol A

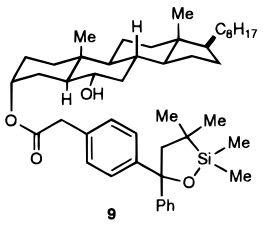
inhibitor of histamine release from rat mast cells,[4] we investigated the possibility of using Breslow's remote functionalization as a means of producing the required 14*β* 15-ketone present in this molecule. Before using the substrate functionalized on the side chain, we first carried out model studies using the benzophenone ester **4b** derived from cholesterol, e.g., with an unfunctionalized side chain. The diol **2** was prepared by hydroboration−oxidation of the commercially available cholesteryl acetate. A regioselective Mitsunobu reaction[5] with the known carboxylic acid **3**[6] provided the ester **4a** in good yield. Inversion proceeded much faster at C3 than at C6 due to severe steric hindrance encountered in the inversion of the 6α alcohol, e.g., the 1,3-diaxial interaction of the carboxylate with the C-18 methyl group. Finally, protection of the free alcohol at C6 as its *tert*-butyldimethylsilyl ether provided the desired substrate **4b**.

Photolysis of the benzophenone ester **4b** gave the desired olefin **5** in modest yield but also afforded two diastereomeric lactones, **6a** and **6b**. Presumably, the lactones are formed by the mechanism shown in Scheme 1. Photolysis generates the diradical **I**, which abstracts a hydrogen atom from the *tert*-butyl group, generating the primary radical **II** stabilized by the *β*-silicon atom.[7−9] Subsequent coupling of the benzhydryl radical and the primary radical produces an equal mixture of the 16-membered macrocyclic lactones **6a** and **6b**. We have not determined the structures of the individual diastereoisomers. Although we can find no examples in the literature of this novel cyclization to generate large ring lactones, there is a report of a similar photocyclization involving the primary radical from a *tert*-butyldimethylsilyl ether, namely, the photocyclization of the butenolide silyl ether **7** to form the strained eight-membered ring **8** which has been reported by Mann and co-



7 **8**

workers.[10] As far as we can tell, these are the only two photocyclizations involving the primary radical formed from the *tert*-butyldimethylsilyl group. Both lactones **6a,b** exhibit slow rotation of the *para*-disubstituted benzene ring, and therefore each has six resonances for the six aromatic carbons in the ^{13}C NMR (e.g., the symmetry due to rotation is lost). In addition it is noteworthy that one of the two lactones (stereochemistry undetermined) underwent transannular silicon transfer on storage at 25 °C for 1 year to produce the five-membered ring **9**. The other lactone was stable on storage. We can offer no good rationalization for this difference in behavior.



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In our successful synthesis of 7-deoxyxestobergsterol A[3] and recently xestobergsterol A[11] itself, we were able

(1) Saul Winstein Fellow, UCLA, 1998−9; Dissertation Award Fellow, UCLA, 1998−9.

(2) (a) Breslow, R. *Chemtracts* **1988**, *1*, 333. (b) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251. (c) Breslow, R.; Wife, R. L. *Tetrahedron Lett.* **1976**, 517.

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(4) (a) Shoji, N.; Umeyama, A.; Shin, K.; Takeda, K.; Arihara, S.; Kobayashi, J.; Takei, M. *J. Org. Chem.* **1992**, *57*, 2996. (b) Kobayashi, J.; Shinonaga, H.; Shigemori, H.; Umeyama, A.; Shoji, N.; Arihara, S. *J. Nat. Prod.* **1995**, *58*, 312.

(5) Mitsunobu, O. *Synthesis* **1981**, 1.

(6) Zderic, J. A.; Kubitschek, M. J.; Bonner, W. A. *J. Org. Chem.* **1961**, *26*, 1635.

(7) Although there is some evidence that a primary radical *β* to a silicon atom is somewhat stabilized,[8] there are also theoretical calculations that indicate that α-silyl stabilization of alkyl radicals is greater than *β*-silyl stabilization.[9] We have no good argument for why the primary radical *β* to silicon (e.g., abstraction of a hydrogen atom from the *tert*-butyl group) **II** is formed rather than the corresponding primary radical α to the silicon atom (e.g., abstraction of a hydrogen atom from the methyl group). One possible explanation is that the transition state for abstraction of the hydrogen atom from the methyl group α to silicon suffers from larger steric interactions than the corresponding transition state for abstraction of the hydrogen atom *β* to the silicon.

(8) (a) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281. (b) Jackson, R. A.; Ingold, K. U.; Griller, D.; Nazran, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 208.

(9) Ibrahim, M. R.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 819.

(10) Brown, D.; Cardin, C. J.; Mann, J. *J. Chem. Soc., Chem. Commun.* **1995**, 825.

(11) Jung, M. E.; Johnson, T. W. Submitted for publication.

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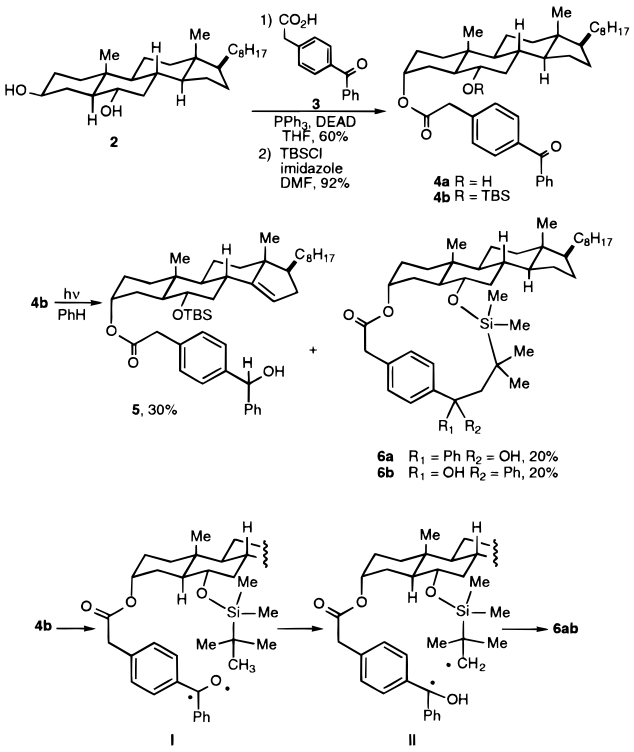
Scheme 1



to avoid these undesired cyclization products by protecting the C6 alcohol as the acetate and observed no unusual products from that substrate. However, the formation of these lactones represents an unusual photocyclization reaction involving the participation of a *tert*-butyldimethylsilyl protecting group and therefore implies that this normally extremely stable protecting group has unrecognized photochemical reactivity. We have also shown that regioselective Mitsunobu reactions can be carried out on steroidal diols with excellent regioselectivity and good yield. Further work in this area is in progress.[11]

Experimental Section

General Methods. All reactions were carried out under argon with the exclusion of moisture. Reagents were purchased from commercial sources and used without further purification unless otherwise specified. The following solvents and reagents were distilled from the indicated agent under argon: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl; dichloromethane, benzene, and toluene from calcium hydride; and triethylamine from calcium hydride. Flash column chromatography was carried out in the indicated solvent system on 230−400 mesh silica gel. The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz, and the carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz. Spectra were taken in the indicated solvent at ambient temperature, and the chemical shifts are reported in parts per million relative to the solvent used. The infrared (IR) spectra were recorded on a Fourier transform IR spectrometer.

3α-((4-Benzoyl)phenylacetyloxy)-6α-hydroxy-5α-cholestane (4a). To a stirring solution of the diol **2** (300 mg, 0.741 mmol) in THF (10 mL) at 25 °C were added triphenylphosphine (389 mg, 1.482 mmol) and the carboxylic acid **3** (196 mg, 1.482 mmol), followed by the dropwise addition of diethylazodicarboxylate (233 μL, 1.482 mmol). The reaction was stirred for 0.5 h and then quenched with water. The mixture was extracted with ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 3:1 hexanes/ethyl acetate) provided the ester **4a** (280 mg, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90−7.30 (9H, m), 5.11 (1H, m), 3.68 (2H, s), 3.29 (1H, ddd, J = 10.6, 10.6, 4.3 Hz), 2.20−0.50 (30H, m), 0.88 (3H, d, J = 6.5 Hz), 0.857 (3H, d, J = 6.6 Hz), 0.855 (3H, d, J = 6.6 Hz), 0.74 (3H, s), 0.62 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.02, 170.00, 139.28, 137.45, 136.09, 132.26, 130.29, 129.88, 129.26, 128.16, 70.17, 69.31, 56.06, 56.01, 53.65, 46.80, 42.40, 41.82, 41.58, 39.65, 39.39, 36.28, 36.02, 35.63, 34.04, 32.92, 28.05, 27.90, 27.00, 25.56, 24.01, 23.70, 22.74, 22.48, 20.55, 18.55, 12.37, 11.92. FTIR (thin film): 3497, 2944, 1732, 1659, 1607, 1468, 1447 cm^{-1}. High-resolution MS (EI, m/z): 626.4323, calcd for $C_{42}H_{58}O_4$ 626.4335.

3α-((4-Benzoyl)phenylacetyloxy)-6α-[((1,1-dimethyl)ethyl)dimethylsilyloxy]-5α-cholestane (4b). To a stirring solution of the alcohol **4a** (143 mg, 0.228 mmol) in dry DMF (5 mL) at 25 °C was added imidazole (31 mg, 0.456 mmol) followed by *tert*-butyldimethylsilyl chloride (38 mg, 0.251 mmol), and the reaction was stirred for 4 h. Water was added and the mixture extracted with ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 8:1 hexanes/ether) provided the ether **4b** (155 mg, 92%) as a clear glass. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90−7.70 (4H, m), 7.65−7.30 (5H, m), 5.09 (1H, m), 3.69 (2H, s), 3.29 (1H, ddd, J = 10.6, 10.6, 4.4 Hz), 1.90−0.60 (29H, m), 0.88 (3H, d, J = 6.7 Hz), 0.856 (3H, d, J = 6.6 Hz), 0.852 (3H, d, J = 6.6 Hz), 0.82 (9H, s), 0.75 (3H, s), 0.63 (3H, s), −0.01 (3H, s), −0.02 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.75, 169.86, 139.43, 137.70, 136.04, 132.20, 130.45, 129.94, 129.32, 128.22, 70.49, 70.21, 56.14, 53.73, 46.83, 42.52, 42.03, 41.86, 39.81, 39.55, 36.37, 36.19, 35.80, 34.13, 33.25, 28.15, 28.03, 27.52, 25.93, 25.81, 24.13, 23.88, 22.91, 22.68, 22.63, 20.70, 18.71, 18.03, 12.54, 12.09, −3.85, −4.72. FTIR (thin film): 2936, 1732, 1661, 1609, 1472, 1447 cm^{-1}. High-resolution MS (CI, m/z): 741.5276, calcd for $C_{48}H_{73}O_4Si$ $(M + H)^+$ 741.5278.

Lactone 6a and Lactone 6b. Ester **4b** (604 mg, 0.815 mmol) was photolyzed (450 W mercury arc lamp, Pyrex filter) in degassed benzene (815 mL) for 10 h at room temperature. The solvent was evacuated in vacuo and the residue subjected to flash column chromatography (silica gel, 4:1 hexanes/ethyl acetate) to provide olefin **5** (181 mg, 30%), lactone **6a** (120 mg, 20%), and lactone **6b** (120 mg, 20%).

Data for Lactone 6a. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80−7.00 (9H, m), 5.10 (1H, s), 4.99 (1H, m), 3.63 (1H, d, J = 13.1 Hz), 3.49 (1H, d, J = 13.1 Hz), 3.28 (1H, ddd, J = 10.6, 10.6, 4.4 Hz), 2.43 (1H, d, J = 14.9 Hz), 2.20 (1H, d, J = 14.9 Hz), 2.10−0.60 (29H, m), 0.91 (3H, d, J = 5.3 Hz), 0.886 (3H, d, J = 6.2 Hz), 0.881 (3H, d, J = 6.5 Hz), 0.878 (3H, s), 0.73 (3H, s), 0.70 (3H, s), 0.67 (3H, s), 0.27 (3H, s), −0.07 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.74, 149.16, 145.08, 133.29, 131.28, 128.79, 127.99, 126.95, 126.28, 125.96, 125.31, 78.09, 71.82, 69.04, 57.17, 56.27, 55.98, 53.76, 46.55, 42.94, 42.55, 41.82, 39.76, 39.52, 36.66, 36.18, 35.90, 34.60, 33.30, 31.61, 28.77, 28.16, 28.10, 28.03, 27.72, 25.79, 24.15, 23.93, 22.93, 22.85, 22.68, 22.59, 20.70, 18.70, 14.15, 12.26, 12.08, −2.03, −4.29. FTIR (thin film): 3409, 2946, 1732, 1468 cm^{-1}. High-resolution MS (EI, m/z): 741.5262, calcd for $C_{48}H_{73}O_4Si$ $(M+H)^+$ 741.5278.

Data for Lactone 6b. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80−7.00 (9H, m), 5.04 (1H, m), 3.64 (1H, d, J = 12.7 Hz), 3.42 (1H, d, J = 12.7 Hz), 3.23 (1H, ddd, J = 10.3, 10.3, 4.5 Hz), 2.95 (1H, d, J = 14.6 Hz), 2.20−0.70 (30H, m), 2.07 (1H, d, J = 14.6 Hz), 1.08 (3H, s), 0.92 (3H, d, J = 6.5 Hz), 0.874 (3H, d, J = 6.6 Hz), 0.870 (3H, d, J = 6.6 Hz), 0.75 (3H, s), 0.67 (3H, s), 0.44 (3H, s), 0.03 (3H, s), −0.19 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.73, 150.25, 145.53, 132.39, 129.87, 128.77, 128.30, 127.45, 126.96, 125.91, 125.63, 80.58, 69.97, 69.32, 56.31, 56.26, 53.95, 47.50, 46.32, 42.81, 42.56, 42.44, 39.90, 39.53, 36.47, 36.18, 35.86, 34.06, 33.50, 28.19, 28.03, 27.67, 27.40, 26.01, 24.18, 23.88, 22.83, 22.57, 21.22, 20.71, 20.65, 18.68, 12.43, 12.06, −2.87, −6.27. FTIR (thin film): 3505, 2944, 1732, 1466 cm^{-1}. High-resolution MS (EI, m/z): 739.5114, calcd for $C_{48}H_{71}O_4Si$ $(M - H)^+$ 739.5122.

3α-(4-(2,2,3,3-Tetramethyl-5-phenyl-1,2-oxasilalane-5-yl)-phenylacetyloxy)-5α-cholestan-6α-ol (9). Lactone **6a** (20 mg, 0.027 mmol) was stored (neat) in a sample vial for approximately 1 year. Ester **9** was formed cleanly as a clear glass (20 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60−7.35 (4H, m), 7.35−7.05 (5H, m), 5.09 (1H, m), 3.54 (2H, s), 3.30 (1H, ddd, J = 10.7, 10.7,

4.5 Hz), 2.54 (1H, d, J = 13.6 Hz), 2.49 (1H, d, J = 13.6 Hz), 1.85−0.50 (30H, m), 0.92 (3H, d, J = 6.5 Hz), 0.877 (3H, d, J = 6.6 Hz), 0.876 (3H, s), 0.872 (3H, d, J = 6.6 Hz), 0.825 (3H), 0.763 (3H, s), 0.654 (3H, s), 0.22 (3H, s), 0.21 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.02, 148.82, 147.94, 132.34, 128.85, 127.90, 126.23, 125.48, 125.35, 84.51, 69.69 (2 carbons), 56.25 (2 carbons), 55.41, 53.73, 47.17, 42.58, 41.88, 41.48, 39.85, 39.53, 36.50, 36.17, 35.78, 34.24, 33.01, 28.20, 28.04, 27.18, 25.65, 25.46, 25.27, 24.19, 23.82, 23.04, 22.84, 22.59, 20.68, 18.70, 12.48, 12.06, −2.03, −2.19. FTIR (thin film): 3443, 2938, 1732, 1466, 1447 cm^{-1}.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds, e.g., compounds **4a**, **4b**, **6a**, **6b**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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