A Novel 1,3 O → C Silyl Shift and Deacylation Reaction Mediated by Tetra-*n*-butylammonium Fluoride in an Aromatic System

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A novel 1,3 O → C migration of a silyl group accompanied by a deacylation reaction was discovered during the conversion of 2-acetyl-3,17-bis(*tert*-butyldimethylsilyl)-β-estradiol (**4**) and 3,17-bis(*tert*-butyldimethylsilyl)-2-propionyl-β-estradiol (**5**) to 2,17-bis(*tert*-butyldimethylsilyl)-β-estradiol (**6**) in the presence of tetra-*n*-butylammonium fluoride. A crossover experiment indicated that the transformation is intramolecular.

The migratory aptitude of the silyl group is well known. Documented examples include radical 1,2 C → O,[1,2] C → N,[1] Si → O,[3] and 1,3 C → O[4] migrations; anionic 1,3 C → O,[5,6] O → C,[4,7-17] 1,4 O → C,[14,18-22] C → O,[23] C → C,[24] and 1,5 O → O[25] migrations; photochemical 1,3 Si → C[26] migrations; thermal 1,3 C → O,[27-31] O → C,[32] and 1,5 C → O[33] migrations; high pressure 1,3 O → C migrations;[34] catalyzed 1,3 O → C[35,36] and C → C migrations;[37] and neutral 1,4 C → O migrations.[38] We now wish to report an unprecedented 1,3 O → C shift of a silyl group in an aromatic system in which the migrating silyl group displaces an acyl group. Specifically, the transformation was discovered in the unexpected, fluoride-mediated conversion of intermediates **4** and **5** to product **6** as depicted in Scheme 1.

2-Iodoestradiol (**2**) was obtained by treating estradiol (**1**) with iodine in the presence of mercuric acetate.[39] Reaction of intermediate **2** with *tert*-butyldimethylsilyl chloride afforded the bis-silyl ether **3**. Halogen lithium exchange on the iodide **3**, followed by reaction of the intermediate lithiated species with acetyl chloride or propionyl chloride at low temperature in THF, gave the acylated derivatives **4** and **5**.

In an attempt to desilylate the bis-silyl ethers **4** and **5**, both of these compounds were treated with tetra-*n*-butylammonium fluoride in THF at room temperature. However, instead of the expected desilylated products, both **4** and **5** yielded the same, unanticipated product. The chemical ionization mass spectrum of the product displayed a base peak at MH^+ at m/z 501, consistent with the molecular formula $C_{30}H_{52}O_2Si_2$. This indicated the retention of both of the *tert*-butyldimethylsilyl groups in the product. The IR spectrum of the product showed the disappearance of the absorptions at 1764 and 1761 cm^{-1} present in the starting materials **4** and **5**. In addition, the ^1H NMR spectrum of the product had singlets at δ 7.25 and 6.41, indicating the presence of substituents at C-2 and C-3 on the aromatic ring. On the basis of this spectral data, structure **6** was tentatively assigned to the product. The structural assignment of **6**

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(1) Harris, J. M.; MacInnes, I.; Walton, J. C.; Maillard, B. *J. Organomet. Chem.* **1991**, *403*, C25-C28.
(2) Reetz, M. T.; Greif, N.; Kliment, M. *Chem. Ber.* **1978**, *111*, 1095–1107.
(3) Ballestri, M.; Chatgilialoglu, C.; Lucarini, M.; Pedulli, G. F. *J. Org. Chem.* **1992**, *57*, 948–952.
(4) Alberti, A.; Chatgilialoglu, C.; Pedulli, G. F.; Zanirato, P. *J. Am. Chem. Soc.* **1986**, *108*, 4993–4998.
(5) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951–1954.
(6) Damrauer, R.; Eaborn, C.; Happer, D. A. R.; Mansour, A. *J. Chem. Soc., Chem. Commun.* **1983**, 348.
(7) Gornowicz, G. A.; West, R. *J. Am. Chem. Soc.* **1968**, *90*, 4478–4479.
(8) West, R.; Gornowicz, G. A. *J. Organomet. Chem.* **1971**, *28*, 25–35.
(9) Simchen, G.; Pfetschinger, J. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 428–429.
(10) Kuwajima, I.; Takeda, R. *Tetrahedron Lett.* **1981**, 2381–2384.
(11) Billediau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 4515–4518.
(12) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4345–4348.
(13) Sampson, P.; Wiemer, D. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1746–1747.
(14) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Kusakabe, M.; Sato, F. *Heterocycles* **1987**, *25*, 549–561.
(15) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312.
(16) Al-Mansour, A. I.; Al-Gurashi, M. A. M. R.; Eaborn, C.; Fattah, F. A.; Lickiss, P. D. *J. Organomet. Chem.* **1990**, *393*, 27–32.
(17) Duhamel, L.; Gralak, J.; Ngono, B. *J. Organomet. Chem.* **1994**, *464*, C11-C13.
(18) Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4349–4352.
(19) Mora, J.; Costa, A. *Tetrahedron Lett.* **1984**, *25*, 3493–3496.
(20) Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1987**, *28*, 5965–5968.
(21) Lautens, M.; DeLanghe, P. H. H. *J. Org. Chem.* **1992**, *57*, 3270–3272.
(22) Maruloto, S.; Kuwajima, I. *J. Am. Chem. Soc.* **1993**, *115*, 9021–9024.
(23) Evans, D. A.; Takacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371–378.
(24) Daney, M.; Lapouyade, R.; Bouas-Laurent, H. *J. Org. Chem.* **1983**, *48*, 5055–5062.
(25) Torisawa, Y.; Shibasaki, M.; Idegami, S. *Chem. Pharm. Bull.* **1983**, *31*, 2607–2615.
(26) Leigh, W. J.; Sluggett, G. W. *Organometallics* **1994**, *13*, 269–281.
(27) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84.
(28) Larson, G. L.; Fernandez, Y. V. *J. Organometal. Chem.* **1975**, *86*, 193–196.
(29) Brook, A. G.; MacRae, D. M.; Bassindale, A. R. *J. Organomet. Chem.* **1975**, *86*, 185–192.
(30) Kwart, H.; Barnette, W. E. *J. Am. Chem Soc.* **1977**, *99*, 614–616.
(31) Kwart, H. *Phosphorus Sulfur* **1983**, *15*, 293–310.
(32) Raucher, S.; Schindele, D. C. *Synth. Commun.* **1987**, *17*, 637–646.
(33) Anderson, G.; Cameron, D. W.; Feutrill, G. I.; Read, R. W. *Tetrahedron Lett.* **1981**, *222*, 4347–4348.
(34) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *Organometallics* **1984**, *3*, 1583–1585.
(35) Lutsenko, I. F.; Baukov, Y. I.; Burlachenko, G. S.; Khasapov, B. N. *J. Organometal. Chem.* **1966**, *5*, 20–28.
(36) Makioka, Y.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1994**, 645–648.
(37) Hosomi, A.; Shirahata, A.; Sakurai, H. *Chem. Lett.* **1978**, 901–904.
(38) Coe, P. L.; Jones, A. S.; Kumar, A.; Walker, R. T. *Tetrahedron Lett.* **1988**, *29*, 835–836.
(39) Tsukamoto, T.; Yada, Y. *Agric. Biol. Chem.* **1987**, *51*, 2025–2027.

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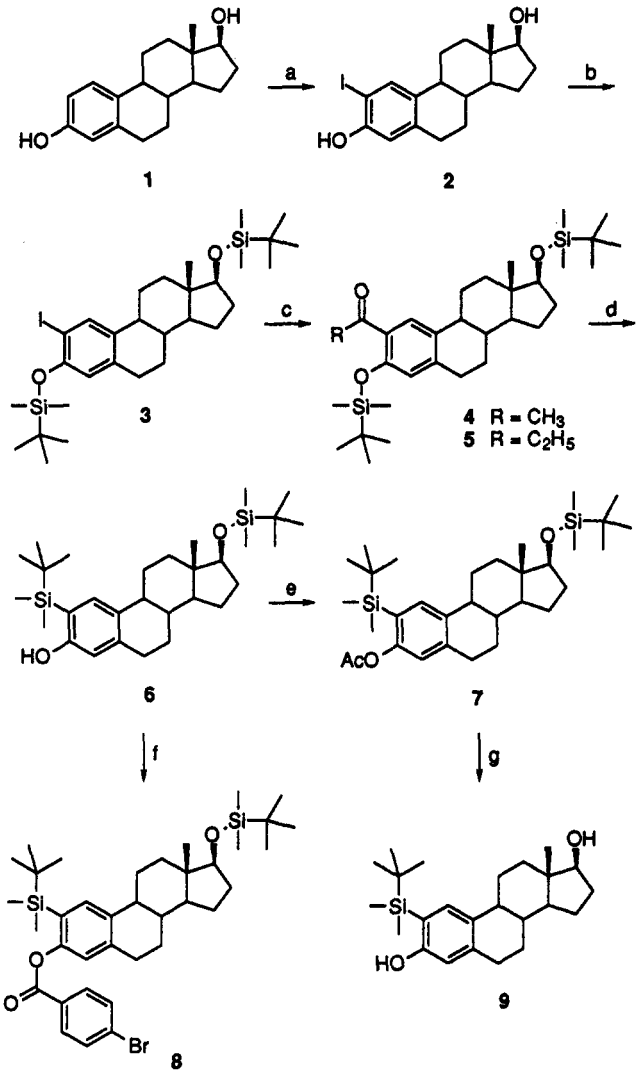
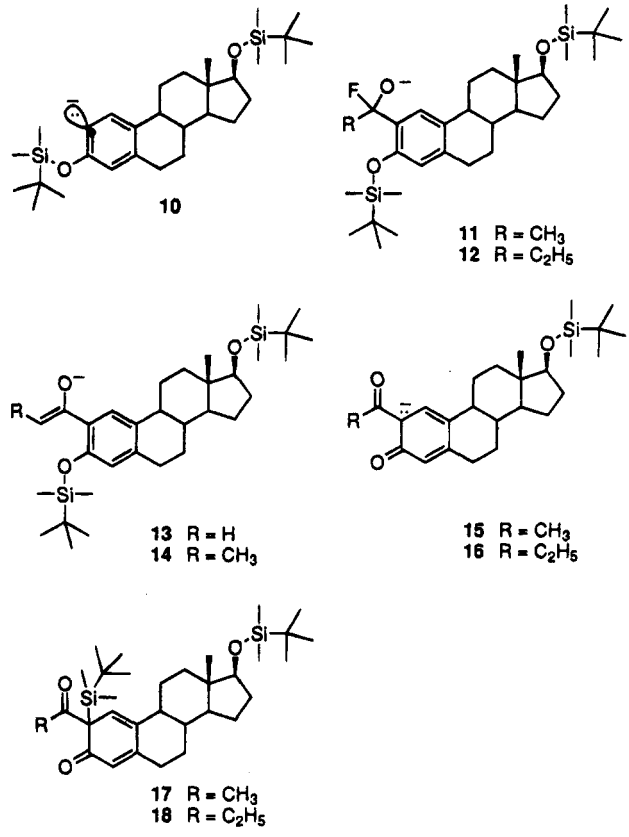
Scheme 1[a]



[a] Reagents and conditions: (a) (1) $Hg(OAc)_2$, HOAc, 50 °C (10 min); (2) I_2, HOAc, 23 °C (2 h); (b) TBDMSCl, DMF, THF, imidazole, 23 °C (17 h); (c) (1) *n*-BuLi, THF, −78 °C (30 min); (2) RCOCl, −78 °C (1 h); (d) *n*-Bu_4NF, THF, 23 °C (48 h); (e) Ac_2O, Py, 23 °C (12 h); (f) 4-bromobenzoyl chloride, Py, reflux (1.5 h); (g) *n*-Bu_4NF, THF, reflux (9 h).

was confirmed by X-ray analysis of the crystalline *p*-bromobenzoate **8**.[40] Compound **6** was also acetylated to afford the acetate **7**, which was then converted to 2-*tert*-butyldimethylsilyl-β-estradiol **(9)** on treatment with tetra-*n*-butylammonium fluoride in refluxing THF.

The 1,3 O → C silyl shift accompanied by deacylation in the conversion of **4** and **5** to **6** is quite remarkable, and several mechanistic scenarios may be considered to account for this transformation. Anionic 1,3 O → C silyl migrations in (trialkylsiloxy)benzenes closely related to the anion **10** have been documented,[9] and this type of rearrangement has also been reported to occur in similar systems.[4,7-17] Indeed, during an attempt to prepare the 2-allyl derivative, it was found that treatment of the iodide **3** with *n*-butyllithium in THF at −78 °C followed by allyl bromide in fact afforded the rearranged product **6**, presumably *via* the 2-lithiated species. However, the formation of the anion **10** from **4** or **5** by tetra-*n*-butylammonium fluoride is questionable. The generation of the anion **10** through elimination of an acyl fluoride from **11** or **12** may be considered, but seems improbable from the standpoint of the stabilities of the anions concerned. The formation of **10** through elimination of ketene from the anions **13** or **14**, generated through utilization of fluoride as a base,[41] also appears unlikely from the standpoint of the relative stabilities of the anions involved.



An alternative mechanism would involve the cleavage of the O–Si bonds of the phenolic silyl ethers of **4** and **5** to afford the corresponding fluorosilane and the resonance-stabilized anions **15** and **16**. Reaction of these anions with *tert*-butyldimethylsilyl fluoride would then afford intermediates **17** and **18**, which would yield **6** through elimination of the corresponding acylium ions, followed by protonation during the workup of the reaction mixture. Alternatively, the acyl groups of **17** and **18** could be eliminated through anionic species related to **11** and **12** or **13** and **14**. The proposed fluoride-mediated 1,3 shift of the *tert*-butyldimethylsilyl group in **4** and **5** to form **17** and **18** is similar to the reported fluoride-catalyzed 1,3 C → C shift of the trimethylsilyl group in allylsilanes,[37] and the 1,3 O → C rearrangement of *O*-alkyl-*O*-silylketene acetals to α-silyl esters in the presence of mercuric iodide[35] or lanthanoid trifluoromethanesulfonates.[36] The mechanism also bears some resemblance to the fluoride-catalyzed addition of silylacetylenes[42] and silyl enol ethers[43] to carbonyl compounds.

Crossover experiments were considered in order to gain further insight into the mechanism. It can be expected

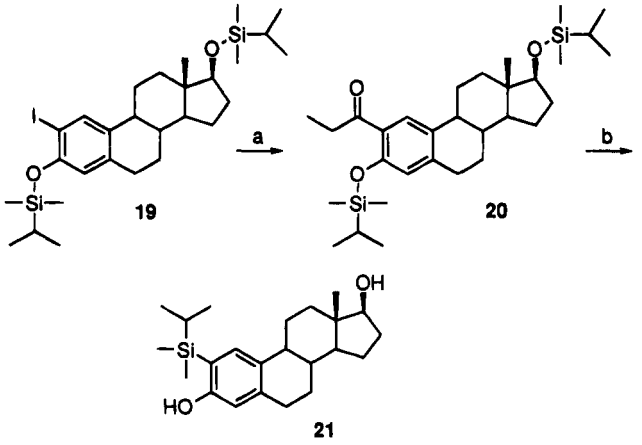
(40) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(41) Pless, J. *J. Org. Chem.* **1974**, *39*, 2644–2646.

(42) Nakamura, E.; Kuwajima, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 498–499.

(43) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932–945.

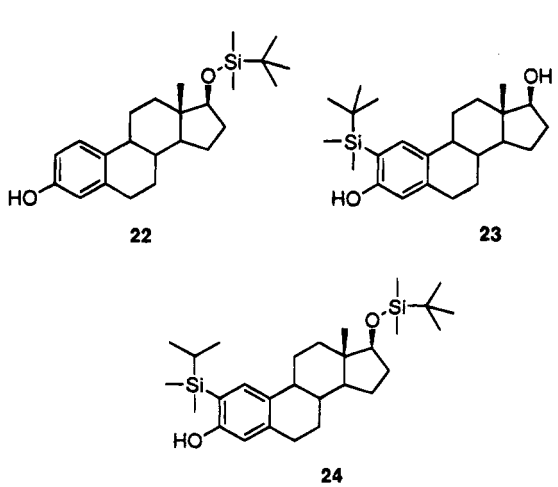
Scheme 2[a]



[a] Reagents and conditions: (a) (1) *n*-BuLi, THF, −78 °C (30 min); (2) EtCOCl, −78 °C (1 h); (b) *n*-BuNF, THF, 23 °C (17 h).

that an anionic 1,3 O → C silyl shift involving the anion **10** would be an intramolecular process.[9] On the other hand, cleavage of the O−Si bond by fluoride followed by reaction of the resulting *tert*-butyldimethylsilyl fluoride with the anions **15** or **16** would be expected to be an intermolecular process. In order to obtain a partner for the reactant **5** to be used in crossover experiments, the bis(isopropyldimethylsilyl) compound **20** was prepared as outlined in Scheme 2. The starting material **19** was obtained by silylation of **2** with isopropyldimethylsilyl chloride in DMF in the presence of imidazole. Iodine−lithium exchange of **19** and reaction of the intermediate aryl lithium species with propionyl chloride afforded **20**. Compound **20** was converted to **21** on treatment with tetra-*n*-butylammonium fluoride in THF at room temperature. In contrast to **4** and **5**, the 17β O−Si bond of **20** was cleaved by fluoride under these reaction conditions.

To perform the crossover experiment, an equimolar mixture of **5** and **20** was treated with *tetra*-butylammonium fluoride in THF at room temperature. The major products of the reaction were **6** and **21**, accompanied by a minor product **22**. None of the crossover products **23** and **24** were detected, indicating that the reaction is an intramolecular process. These results indicate that an anionic species such as **10** may in fact be involved in the presently reported silyl migration-deacylation reaction.



The scope of the presently reported 1,3 O → C silyl shift and deacylation reaction remains unexplored. However, the reaction is noteworthy because of the widespread use of tetra-*n*-butylammonium fluoride to remove silyl protecting groups in organic synthesis.[44]

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz using $CDCl_3$ as the solvent, except where noted otherwise. Low resolution chemical ionization mass spectra (CIMS) were determined using 2-methylpropane as the reagent gas. Microanalyses were performed by the Purdue Microanalytical Laboratory.

2-Iodoestradiol (2).[41] A solution of $Hg(OAc)_2$ (2.34 g, 7.6 mmol) in AcOH (200 mL) was added to a solution of estradiol **(1)** (4.0 g, 14.7 mmol) in AcOH (100 mL) at 50 °C. After stirring for 10 min, a solution of iodine (3.82 g, 30.1 mmol) in AcOH (100 mL) was added dropwise to the reaction mixture at 50 °C. The resulting yellow solution was stirred at room temperature for 2 h. The orange solution was diluted with saturated aqueous NaCl solution (100 mL), and the products were extracted twice with ether (200 and 50 mL). The combined ether layer was washed twice with saturated aqueous NaCl solution (30 and 20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the filtrate gave the crude product as a yellow solid. Flash chromatography (silica gel 230−400 mesh, ether:hexane 2:1 by volume) and recrystallization from ether-hexane gave 2-iodoestradiol (2.63 g, 45%) as a white solid: mp 154−155 °C (lit.[41] mp 146−153 °C). The ^{1}H NMR spectrum was identical to that previously reported.[41] Anal. Calcd for $C_{18}H_{23}IO_2$: C, 54.28; H, 5.82; I, 31.86. Found: C, 54.23; H, 5.94; I, 31.75.

3,17-Bis(*tert*-butyldimethylsilyl)-2-iodoestradiol (3). A solution of 2-iodoestradiol **(2)** (769 mg, 1.93 mmol) in anhydrous DMF (20 mL) and anhydrous THF (20 mL) containing *tert*-butyldimethylsilyl chloride (872 mg, 5.97 mmol) and imidazole (767 mg, 11.6 mmol) was stirred at room temperature for 17 h. The reaction mixture was diluted with saturated aqueous NaCl solution (10 mL) and extracted twice with ether (30 and 20 mL). The combined ether layer was washed with saturated aqueous NaCl solution (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product as a white solid, which was subjected to flash chromatography (silica gel 230−400 mesh, ether:hexane 1:60 by volume) to give compound **3** (1.05 g, 87.0%) as a pale yellow, amorphous solid: mp 153−156 °C; ^{1}H NMR δ 7.61 (s, 1 H), 6.51 (s, 1 H), 3.63 (t, J = 8.1 Hz, 1 H), 2.72 (m, 2 H), 2.18 (m, 2 H), 1.86 (m, 3 H), 1.34 (m, 8 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.73 (s, 3 H), 0.26 (s, 6 H), 0.04 (s, 3 H), 0.02 (s, 3 H); FABMS (NBA) m/z (relative intensity) 625 (MH^+, 21), 569 (MH^+ − *t*-Bu, 100).

2-Acetyl-3,17-bis(*tert*-butyldimethylsilyl)estradiol (4). *n*-Butyllithium (1.6 M in hexane, 4.8 mmol) was added to a solution of **3** (1.50 g, 2.4 mmol) in anhydrous THF (47 mL) at −78 °C with stirring. The resulting yellow solution was stirred at this temperature for 0.5 h under argon. Acetyl chloride (0.35 mL, 4.8 mmol) was added dropwise. The yellow solution was stirred at −78 °C for 1 h. The reaction mixture was treated with saturated aqueous NaCl solution (47 mL) and extracted with ether (94 mL). The ether layer was washed with saturated aqueous NaCl solution (47 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product as a yellow solid. Flash chromatography (silica gel 230−400 mesh, ether:hexane 1:40 to 1:30 by volume) gave **4** as a colorless oil (570 mg, 43.9%): IR (neat) 2927, 1764, 1366, 1248, 1195, 836, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.36 (s, 1 H), 6.75 (s, 1 H), 3.62 (t, J = 8.0 Hz, 1 H), 2.82 (m, 2 H), 2.35−1.0 (m, 13 H), 2.25 (s, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.72 (s, 3 H), 0.24 (s, 3 H), 0.23 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H); CIMS m/z (isobutane) 543 (MH^+, 100).

3,17-Bis(*tert*-butyldimethylsilyl)-2-propionylestradiol (5). This compound was prepared using the same

(44) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

procedure as described above for compound **4**. From **3** (320 mg, 0.51 mmol) and propionyl chloride (0.1 mL, 1.1 mmol), compound **5** was obtained as a pale yellow, amorphous solid (140 mg, 49.3%): mp 80–84 °C. IR (neat) 2928, 1761, 1360, 1255, 1142, 1097, 936, 773 cm^{-1}; ^1H NMR δ 7.37 (s, 1 H), 6.76 (s, 1 H), 3.65 (t, J = 6.1 Hz, 1 H), 2.83 (m, 2 H), 2.56 (q, J = 7.5 Hz, 2 H), 2.32 (m, 2 H), 1.89 (m, 3 H), 1.38 (m, 11 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.75 (s, 3 H), 0.25 (s, 3 H), 0.24 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); CIMS m/z (relative intensity) 557 (MH^+, 100).

2,17β-Bis(*tert*-butyldimethylsilyl)estradiol (6). (a) Preparation from 5. A solution of the silyl ether **5** (1.18 g, 2.12 mmol) in THF (20 mL) containing tetra-*n*-butylammonium fluoride (3.2 mL of a 1 M solution in THF, 1.5 equiv) was stirred at room temperature under argon for 48 h. The reaction mixture was diluted with saturated NaCl solution (20 mL), and the product was extracted twice with ether (30 and 20 mL). The combined ether layer was dried over anhydrous Na_2SO_4. Evaporation of the filtrate gave the crude product as an oil. This oil was subjected to flash chromatography purification (silica gel 230–400 mesh, ether:hexane 1:20 by volume) to afford **6** as a pale yellow, amorphous solid (810 mg, 76.4%): mp 85–89 °C; IR (neat) 2927, 1471, 1389, 1249, 1140, 1096, 836, 772 cm^{-1}; ^1H NMR δ 7.25 (s, 1 H), 6.41 (s, 1 H), 4.60 (s, 1 H, exchangeable with D_2O), 3.63 (t, J = 8.5 Hz, 1 H), 2.77 (m, 2 H), 2.40 (m, 1 H), 2.15 (m, 1 H), 1.85 (m, 3 H), 1.35 (m, 8 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.73 (s, 3 H), 0.29 (s, 6 H), 0.02 (s, 3 H), 0.01 (s, 3 H); CIMS m/z (relative intensity) 501 (MH^+, 100).

(b) Preparation from 4. From **4** (0.29 g, 0.53 mmol) in THF (10 mL), treatment with tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.1 mL, 2 equiv) using the same procedure as above gave the product **6** (170 mg, 64.2%) as a solid.

(c) Preparation from 3. *n*-Butyllithium in hexane (1.6 M, 7.1 mL, 11.4 mmol) was added to a solution of the silyl ether **3** (3.57 g, 5.7 mmol) in anhydrous THF (60 mL) at −78 °C under argon. The resulting reaction mixture was stirred at that temperature for 0.5 h. Allyl bromide (0.99 mL, 11.4 mmol, 2 equiv) was added dropwise, and the resulting reaction mixture was stirred at - 78 °C for 1.5 h. The reaction mixture was diluted with saturated NaCl solution (20 mL), and the products were extracted with ether (2 × 30 mL). The combined ether layer was dried over anhydrous Na_2SO_4. Evaporation of the filtrate at 30 °C gave the crude product as an oil. Flash chromatography (silica gel 230–400 mesh, ether:hexane 1:30 by volume) gave product **6** as a pale yellow solid (1.56 g, 54.7%).

3-Acetyl-2,17β-bis(*tert*-butyldimethylsilyl)estradiol (7). A solution of compound **6** (250 mg, 0.5 mmol) in acetic anhydride (10 mL) and pyridine (3 mL) was stirred at room temperature under argon for 12 h. The product was extracted with ether (30 mL) in the presence of saturated NaCl solution (20 mL). An emulsion developed and was filtered under suction through a Celite pad to give separate water and organic phases. The ether layer was dried over anhydrous Na_2SO_4. Evaporation of the filtered ether solution gave the crude product as a white solid. Flash chromatography (silica gel 230–400 mesh, ether:hexane 1:1 by volume) of this crude material gave the product **7** (200 mg, 73.8%) as a white, amorphous glass: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (s, 1 H), 6.77 (s, 1 H), 3.65 (t, J = 8.2 Hz, 1 H), 2.84 (m, 2 H), 2.27 (s, 3 H), 2.22 (m, 2 H), 1.90 (m, 3 H), 1.40 (m, 8 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.74 (s, 3 H), 0.26 (s, 3 H), 0.25 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); CIMS m/z (relative intensity) 543 (MH^+, 34).

3-(*p*-Bromobenzoyl)-2,17β-bis(*tert*-butyldimethylsilyl)-estradiol (8). A solution of the phenolic silyl ether **6** (0.81 g, 1.62 mmol) in pyridine (10 mL) containing *p*-bromobenzoyl chloride (533 mg, 2.43 mmol, 1.5 equiv) was stirred at reflux under argon for 1.5 h. The reaction mixture was diluted with saturated aqueous NaCl solution (10 mL) and extracted with ether (20 mL). The ether layer was dried over anhydrous Na_2SO_4. Evaporation of the filtered ether solution gave the crude product as a pale yellow solid. Flash chromatography (silica gel 230–400 mesh, ether:hexane 1:10 by volume) gave product **8** (440 mg, 39.8%) as a white solid. Recrystallization from ether and hexane afforded small white crystals, mp 175–176 °C. Repeated recrystallization of these small white crystals from ether and hexane in a tightly sealed flask for one week standing at room temperature gave one big, single crystal of **8** (7 mg) for X-ray crystal structure determination: IR (neat) 3660, 1710, 1692, 1565, 1502, 1345, 1186, 1163, 1122, 1026, 871, 784, 561, 530, 500 cm^{-1}; ^1H NMR δ 8.06 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H), 7.43 (s, 1 H), 6.80 (s, 1 H), 3.66 (t, J = 8.1 Hz, 1 H), 2.86 (m, 2 H), 2.30 (m, 2 H), 1.90 (m, 3 H), 1.80–1.00 (m, 11 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.76 (s, 3 H), 0.19 (s, 6 H), 0.04 (s, 3 H), 0.03 (s, 3 H); CIMS m/z (relative intensity) 683 (MH^+, 99), 685 (MH + 2, 100). Anal. Calcd for $C_{37}H_{55}BrO_3Si_2$: C, 64.98; H, 8.11; Br, 11.68; Si, 8.21. Found: C, 65.07; H, 8.29; Br, 11.87; Si, 7.91.

2-(*tert*-Butyldimethylsilyl)estradiol (9). A solution of compound **7** (200 mg, 0.37 mmol) in THF (20 mL) containing tetra-*n*-butylammonium fluoride (2 mL of a 1 M solution in THF, 2 mmol) was heated at reflux under argon for 9 h. A brown solution developed. The reaction mixture was diluted with saturated NaCl solution (10 mL) and extracted with ether (2 × 10 mL). The combined ether layer was dried over anhydrous Na_2SO_4. Evaporation of the filtered ether solution gave the crude product as an oil. This oil was purified by flash chromatography (silica gel 230–400 mesh, ether:hexane 2:1 by volume) to give product **9** as a solid (469.4 mg, 76%) which was recrystallized from ether and hexane: mp 208–209 °C; IR 3752, 3040, 2943, 2890, 1233, 830, 816, 674, 658 cm^{-1}; ^1H NMR δ 7.25 (s, 1 H), 6.42 (s, 1), 5.30 (brs, 1 H, exchangeable with D_2O), 3.74 (t, J = 8.2 Hz, 1 H), 2.79 (m, 2 H), 2.50–1.10 (m, 14 H), 0.91 (s, 9 H), 0.78 (s, 3 H), 0.30 (s, 6 H). CIMS m/z (relative intensity) 387 (MH^+, 100). Anal. Calcd. for $C_{24}H_{38}O_2Si$: C, 74.55; H, 9.91; Si, 7.26. Found: C, 74.78; H, 10.13; Si, 6.91.

2-Iodo-3,17β-bis(isopropyldimethylsilyl)estradiol (19). A solution of the diol **2** (2.53g, 5.75 mmol) in anhydrous DMF (30 mL) containing imidazole (1.56 g, 23.0 mmol) was stirred at room temperature under argon for 0.5 h. Isopropyldimethylsilyl chloride (2.36 g, 17.2 mmol) was added dropwise. The resulting reaction mixture was stirred at room temperature for 18 h. A turbid suspension developed. The suspension was diluted with saturated NaCl solution (20 mL) at 0–5 °C and extracted twice with ether (30 and 20 mL). The combined ether layer was washed with saturated NaCl solution (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product as an oil, which was subjected to flash chromatography (silica gel 230–400 mesh, ether:hexane 1:30 by volume) to give compound **19** as an oil (2.83 g, 82.3%): ^1H NMR δ 7.61 (s, 1 H), 6.52 (s, 1 H), 3.63 (t, J = 8.0 Hz, 1 H), 2.75 (m, 2 H), 2.17 (m, 3 H), 1.87 (m, 3 H), 1.75–1.10 (m, 5 H), 1.08 (s, 6 H), 0.99 (d, J = 1.6 Hz, 3 H), 0.96 (d, J = 1.6 Hz, 3 H), 0.80 (m, 1 H), 0.74 (s, 3 H), 0.26 (s, 6 H), 0.05 (s, 3 H), 0.04 (s, 3 H); CIMS m/z (relative intensity) 599 (MH^+, 100).

3,17β-Bis(isopropyldimethylsilyl)-2-propionylestradiol (20). *n*-BuLi (1.6 M in hexane, 2.1 mL, 3.34 mmol) was added to a solution of the iodide **19** (1.0 g, 1.67 mmol) in anhydrous THF (20 mL) at −78 °C with stirring under argon. The resulting yellow solution was stirred at this temperature for 0.5 h under argon. Propionyl chloride (0.29 mL, 309.1 mg, 3.34 mmol) was added dropwise. The resulting yellow solution was stirred at −78 °C under argon for 1 h. The reaction mixture was treated with saturated with NaCl solution (20 mL) and extracted with ether (2 × 30 mL). The combined ether layer was washed with saturated NaCl solution (2 × 30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product as an oil. Flash chromatography of this oil (silica gel 230–400 mesh, ether:hexane 1:30 by volume) gave compound **20** as a colorless oil (150 mg, 17.0%): IR (neat): 1761 cm^{-1}; ^1H NMR δ 7.37 (s, 1 H), 6.76 (s, 1 H), 3.64 (t, J = 8.5 Hz, 1 H), 2.83 (m, 2 H), 2.59 (q, J = 7.6 Hz, 2 H), 2.25 (m, 3 H), 1.88 (m, 3 H), 1.70–0.79 (m, 24 H), 0.75 (s, 3 H), 0.20 (s, 6 H), 0.04 (s, 3 H), 0.03 (s, 3 H); CIMS m/z (relative intensity) 529 (MH^+, 100).

2-(Isopropyldimethylsilyl)estradiol (21). A solution of tetra-*n*-butylammonium fluoride in THF (1 M, 0.5 mL, 0.5 mmol) was added to a solution of the silyl ether **20** (30 mg, 0.057 mmol) in THF (5 mL) at room temperature. After

stirring at room temperature under argon for 17 h, the reaction mixture was diluted with saturated NaCl solution (10 mL) and extracted with ether (2 × 10 mL). The combined ether layer was washed with saturated NaCl solution (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the filtrate gave the crude product as an oil. Preparative TLC (silica gel 1000 microns, ether:hexane 2:3 by volume) gave product **21** as an oil (10.5 mg, 50.0%): ^{1}H NMR (acetone-d_6) δ 8.01 (s, 1 H, exchangeable with D_2O), 7.22 (s, 1 H), 6.48 (s, 1 H), 3.67 (t, J = 8.1 Hz, 1 H), 3.58 (d, J = 5.1 Hz, 1 H, exchangeable with D_2O), 3.04 (m, 2 H), 2.69 (m, 2 H), 2.25 (m, 1 H), 2.15–0.80 (m, 17 H), 0.75 (s, 3 H), 0.18 (s, 6 H); CIMS m/z (relative intensity) 373 (MH^+, 100); HRCIMS calcd for $C_{23}H_{36}O_2Si$: 373.2563. Found: 373.2559.

Crossover Experiment. Treatment of a Mixture of 5 and 20 with Tetra-*n*-butylammonium Fluoride in THF. Tetra-*n*-butylammonium fluoride in THF (1.0 M, 15.1 mL, 8.8 equiv) was added to a solution of **20** (456 mg, 0.86 mmol) and **5** (480 mg, 0.86 mmol) in THF (20 mL) at room temperature. After stirring at room temperature under argon for 24 h, the reaction mixture was diluted with saturated NaCl solution (30 mL) and the products were extracted with ether (2 × 50 mL). The combined ether layer was washed with saturated NaCl solution (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the filtrate gave the crude product as an oil. Flash chromatography (silica gel 230–400 mesh, ether:hexane 2:3 by volume) gave product **21** as an thick oil (290 mg, 90.7%) and compound **6** as an oil (163 mg, 37.9%). Compound **22**[45] was also isolated from the above flash chromatography as a pale yellow solid (85 mg, 22%): mp 155–157 °C; IR (neat) 3810, 3042, 2882, 1482, 1414, 1310, 1275, 1191, 903, 875, 853, 804, 593, 562, 531 cm^{-1}; ^{1}H NMR δ 7.14 (d, J = 8.0 Hz, 1 H), 6.62 (dd, J = 8.2 and 2.8 Hz, 1 H), 6.54 (d, J = 3.2 Hz, 1 H), 4.46 (brs, 1 H), 3.63 (t, J = 7.8 Hz, 1 H), 2.79 (m, 2 H), 2.30–1.00 (m, 11 H), 0.88 (s, 9 H), 0.73 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H); LRCIMS m/z (relative intensity) 387 (MH^+, 100).

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Supporting Information Available: An HPLC profile of compound **21**, ^{1}H NMR spectra of compounds **3**–**7**, **19**, **20**, and an ORTEP drawing and X-ray data acquisition parameters for compound **8** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(45) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.