A Unified Strategy for the Synthesis of Highly Substituted Dihydrobenzofurans and Dihydrobenzopyrans

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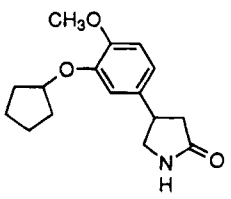
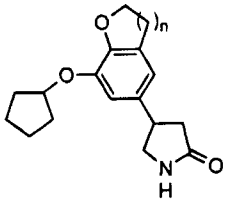
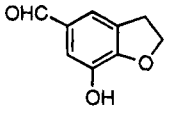
Rolipram (**1**, (±)-4-(3-cyclopentoxy-4-methoxyphenyl)-2-pyrrolidinone) is a selective inhibitor of cyclic nucleotide phosphodiesterase type IV (PDE IV), which was developed by Schering AG as an antidepressant.[1] With an aim at improving the PDE IV inhibitory activity of rolipram, we initiated the synthesis of rolipram analogs with modifications to its aromatic nucleus. The apparently simple modification that we envisioned involved tethering the labile 4-methoxy group back to the aromatic ring in the form of a cyclic ether, which, while preserving similar electronic and steric profiles as the parent rolipram, might also possess better pharmacokinetic properties.[2] In this regard we designed both the dihydrobenzofuran **2** (n = 1) and the dihydrobenzopyran **3** (n = 2) as our targets. Our immediate goal became the synthesis of the previously unreported dihydrobenzofuran **4** and dihydrobenzopyran **5**, which can then be transformed to **2** and **3** by previously established synthetic routes.[3] In this paper we report our efforts that have led to the successful syntheses of both **4** and **5**. The synthesis of the densely and diversely substituted aromatic nuclei of **4** and **5** required selective chemistry that should find application toward the synthesis of other substituted dihydrobenzofurans and dihydrobenzopyrans.



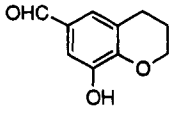
Rolipram (1)



2: n = 1
3: n = 2



4



5

The synthesis of **4** began by protection of the catechol unit of commercially available 3-bromo-4,5-dihydroxybenzaldehyde (**6**) (CH_3OCH_2Cl, K_2CO_3, DMF) to afford the corresponding catechol bis(methoxymethyl) ether **7**. Stille coupling[4] of **7** using tributylvinyltin and $Pd(PPh_3)_4$ (toluene, 100 °C) afforded styrene **8** in 87% yield. Treatment of **8** with BH_3·THF, followed by oxidation of the intermediate organoborane with $NaBO_3·4H_2O$,[5] provided diol **9** in 68% yield. We were unable to prevent borane-mediated reduction of the aldehyde carbonyl in **8** during the hydroboration procedure.[6] However, by virtue of its benzylic nature, we were able to selectively reoxidize the hydroxyl group with MnO_2 to give aldehyde **10**. With the 2-ethanol side chain in place, we were prepared to complete the synthesis of the dihydrobenzofuran **4**. To this end, the methoxymethyl protecting groups were removed (2 N acetic acid, 80 °C)[7] to give intermediate triol **11**. Initial attempts were made to cyclize **11** by standard methods. Mitsunobu-type closure of **11** (PPh_3, DEAD, THF) failed to deliver **4**.[8,9] Similarly, after sequential treatment of **11** with TsCl and triethylamine, we were able to detect **4** in only very low yield. Very recently, a new method for hydroxyl activation was reported for the synthesis of the parent, unsubstituted 2,3-dihydrobenzofuran.[10] Following this lead, when hydroxy catechol **11** was treated with the Vilsmeier reagent, $[ClCH{=}N(CH_3)_2]^+Cl^-$, and subsequently triethylamine (TEA), we were pleased to observe clean formation of the cyclodehydration reaction product **4**.[11] The present application of this new method for hydroxyl activation within the context of dihydrobenzofuran synthesis represents a considerable extension of the scope of this procedure.

The synthesis of dihydrobenzopyran **5** followed along the same strategic lines as the synthesis of **4**. Also beginning from the bis(methoxymethyl) ether **7**, we now needed to install a 3-propanol side chain and therefore looked for an appropriate coupling partner to meet this requirement. Stille coupling between 3-(*tert*-butyldi-

(1) Schwabe, U.; Miyake, M.; Ohga, Y.; Daly, J. W. *Mol. Pharmacol.* **1976**, 900.

(2) Drug metabolism studies on rolipram have shown that demethylation of the 4-methoxy group is a significant metabolic pathway in the clearance of rolipram. Krause, W.; Kuhne, G.; Jakobs, U.; Hoyer, G.-A. *Drug Met. Disp.* **1993**, *21*, 682.

(3) Marivet, M. C.; Bourguignon, J.-J.; Lugnier, C.; Mann, A.; Stoclet, J.-C.; Wermuth, C.-G. *J. Med. Chem.* **1989**, *32*, 1450.

(4) (a) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422 and references cited therein. (b) For a recent review see: Mitchell, T. N. *Synthesis* **1992**, 803.

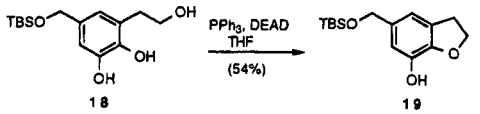
(5) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

(6) By careful titration of **8** with BH_3·THF we were able to isolate in 94% yield the product stemming from only carbonyl reduction. Clearly, in the case of **8**, in which the aldehyde carbonyl and the double bond are nearly equally disposed, hydride reduction is considerably faster than hydroboration.

(7) Rahman, M. A. A.; Elliott, H. W.; Binks, R.; Küng, W.; Rapoport, H. *J. Med. Chem.* **1966**, *9*, 1.

(8) Synthesis of dihydrobenzofurans and dihydrobenzopyrans by intramolecular Mitsunobu cyclization was first reported by Aristoff and co-workers: Aristoff, P. A.; Harrison, A. W.; Huber, A. M. *Tetrahedron Lett.* **1984**, *25*, 3955. For other applications of this method, see: (a) Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* **1985**, *26*, 123. (b) Sugihara, H.; Mabuchi, H.; Hirata, M.; Imamoto, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1930. (c) Shih, T. L.; Wyvratt, M. J.; Mrozik, H. *J. Org. Chem.* **1987**, *52*, 2029.

(9) Our inability to cyclize aldehyde **11** by this procedure was certainly unexpected. One might predict that the presence of the aldehyde carbonyl in **11**, by lowering the pK_a of the *p*-hydroxyl proton, would facilitate the Mitsunobu cyclization. We did find during the course of this work that Mitsunobu cyclization of silyl ether **18** provided dihydrobenzofuran **19** in 54% yield. To the best of our knowledge, this represents the only reported Mitsunobu cyclization of an unprotected *catechol*. For a recent, comprehensive review of the Mitsunobu reaction, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335. The ^1H NMR spectra of **18** and **19**, as well as a brief description of the synthesis of **18**, are provided in the supplementary material.



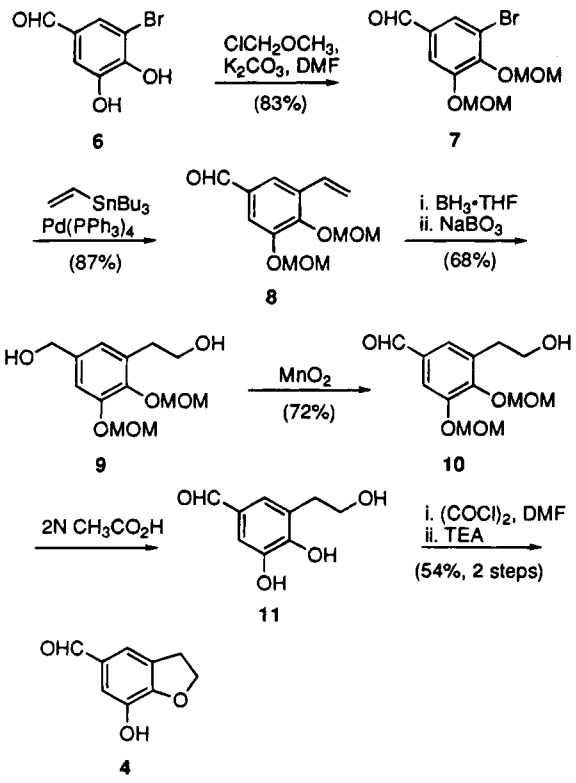
18 **19**

(10) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *Tetrahedron Lett.* **1993**, *34*, 7483.

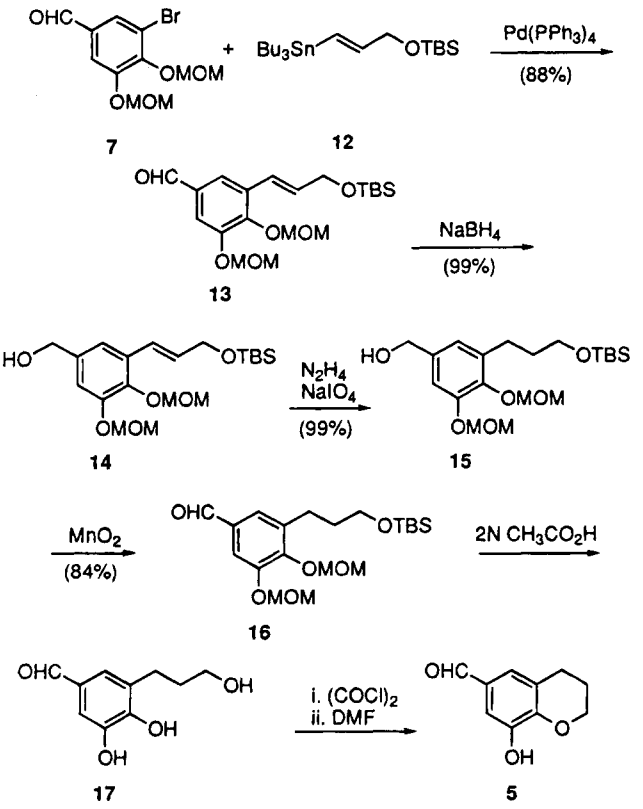
(11) The overall yield for this two-step process is not optimized. Due to its physical properties, we found it more convenient to use triol **11** without purification.

0022-3263/94/1959-4346$04.50/0

Scheme 1



Scheme 2



methylsiloxy)-1-(tributylstannyl)-(*E*)-propene[12] (**12**) and aryl bromide **7** ($Pd(PPh_3)_4$, toluene) cleanly delivered the three carbons, providing styrene **13** in 88% yield.[13] As reflected by the isomer ratio of the starting vinyltin reagent **12**, styrene **13** was isolated as a 6:1 inseparable mixture (for clarity, only the *E* isomer is shown). We were unsuccessful in our attempts to selectively hydrogenate the double bond in **13**,[14] so we pursued an alternative strategy for reduction. The following three-step procedure was developed. Reduction of the aldehyde carbonyl with $NaBH_4$ in methanol provided unsaturated alcohol **14**, which was reduced with diimide (generated from periodate oxidation of hydrazine)[15] to give saturated alcohol **15**. Reoxidation of the benzylic hydroxyl with MnO_2 provided us with aldehyde **16**. Albeit three steps were required in order to achieve an apparently straightforward transformation (**13** → **16**), the 82% overall yield for the sequence is respectable, and no chromatographic purification of the intermediates was necessary. With **16** in hand, we carried out the same deprotection/cyclization chemistry that we used successfully in the synthesis of dihydrobenzofuran **4**. Thus, treatment of **16** with acetic acid effected removal of the *tert*-butyldimethylsilyl group as well as both MOM ethers, giving an intermediate triol **17**, which was subjected to the cyclodehydration conditions as before, affording dihydrobenzopyran **5**.[16]

In summary, we have described the syntheses of the densely and diversely substituted dihydrobenzofuran **4** and dihydrobenzopyran **5**. Both syntheses involved a palladium-mediated Stille coupling onto a protected catechol to install the requisite side chains, and both involved a new cyclodehydration reaction of an unprotected hydroxy catechol to form the final heterocyclic targets. With the general availability of 2-bromophenols and the wide scope that the Stille coupling offers in substituted aromatic synthesis, we believe that the present strategy can be widely applied to the synthesis of other dihydrobenzofurans and -pyrans.[17] Biological activity of rolipram derivatives **2** and **3** will be published elsewhere.

Experimental Section[18]

3-Bromo-4,5-bis(methoxymethoxy)benzaldehyde (7). To a solution of 3-bromo-4,5-dihydroxybenzaldehyde (10.1 g, 46.5 mmol) in DMF (100 mL) was added K_2CO_3 (25 g). The stirring

(12) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634. Consistent with these authors' preparation of **12** we too observed an inseparable mixture of *E* and *Z* isomers in a ratio of approximately 6:1. The ^1H NMR spectrum (300 MHz, $CDCl_3$) of our material differed slightly to that reported: (*E* isomer only) δ 0.07 (s, 6), 0.89 (t, 9, J = 7.1 Hz), 0.92 (s, 9), 1.28–1.55 (m, 12), 4.21 (dd, 2, J = 1.4, 3.9 Hz), 6.06 (dt, 1, J = 3.9, 19.1 Hz), 6.19 (dd, 1, J = 1.2, 19.0 Hz).

(13) We had occasion to investigate other reagents related to **12**. In our hands, we found **12** to be both the most convenient to prepare and the highest yielding coupling partner. Specifically, the analogous THF-protected propenol (Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265) coupled with **7** in 63% yield, while the free alcohol (prepared by nBu_4NF-induced desilylation of **12**; see also: Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851) coupled with **7** in only 30% yield.

(14) The following conditions were examined: (a) H_2/PtO_2 in each of ethanol, ethyl acetate, and THF; (b) $H_2/Pd(OH)_2$ in ethyl acetate; (c) H_2/10% Pd/C in ethyl acetate. In all cases, and with varying reaction times, product mixtures containing the reduced aldehyde, as well as products of hydrogenolysis, were observed.

(15) Hoffman, J. M.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1245.

(16) The yields for this two-step transformation were variable, ranging from 20–54%. We have found that, in general, higher yields (50–54%) are obtained when beginning this sequence from the hydroxybenzaldehyde derivative in which the TBS protecting group is not present. The ^1H NMR spectra of crude **17** (obtained from the deprotection of **16**) and **5** are provided in the supplementary material.

(17) Recently, Larock and co-workers described a direct synthesis of 2-substituted 2,3-dihydrobenzopyrans by palladium-catalyzed annulation of 1,4-dienes with 2-iodophenols: Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509.

mixture was cooled to 0 °C, and chloromethyl ether (13.1 g, 163 mmol) was added. The resulting mixture was stirred for 15 h at rt and diluted with H_2O. The mixture was extracted with ether:hexanes (1:1, 5 × 60 mL), and the combined extracts were washed with 0.5 N NaOH, H_2O (2 × 100 mL), and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford an orange oil. This oil was passed through a short pad of silica gel (1:1 hexanes:ethyl acetate) to afford the bis-MOM ether **7** as a yellow oil (11.7 g, 83%): IR (neat) 2840, 1700, 1275 cm^{-1}; ^1H NMR δ 3.51 (s, 3), 3.66 (s, 3), 5.27 (s, 2), 5.31 (s, 2), 7.62 (d, 1, J = 1.7), 7.75 (d, 1, J = 1.9), 9.84 (s, 1); ^{13}C NMR δ 56.52, 58.08, 95.17, 98.89, 115.26, 118.43, 128.85, 133.19, 149.29, 151.26, 189.76. Anal. Calcd for $C_{11}H_{13}BrO_5$: C, 43.30; H, 4.29. Found: C, 43.3; H, 4.31.

3,4-Bis(methoxymethoxy)-5-ethenylbenzaldehyde (8). To a solution of **7** (4.58 g, 15.0 mmol) and vinyltributyltin (5.0 g, 15.7 mmol) in toluene (75 mL) was added tetrakis(triphenylphosphine)palladium (346 mg, 0.3 mmol). The solution was heated at 100 °C for 8 h, cooled to rt, and diluted with ether (50 mL). The solution was washed with 5% NH_4OH (2 × 30 mL), H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford an orange oil. Silica gel chromatography (5:2 hexanes:ethyl acetate) provided **8** as a colorless oil (3.3 g, 87%): IR (neat) 2840, 1700, 1580 cm^{-1}; ^1H NMR δ 3.52 (s, 3), 3.58 (s, 3), 5.24 (s, 2), 5.27 (s, 2), 5.43 (d, 1, J = 11.3), 5.86 (d, 1, J = 17.6), 7.12 (dd, 1, J = 11.0, 17.8), 7.58 (d, 1, J = 1.9), 7.73 (d, 1, J = 2.0), 9.92 (s, 1); ^{13}C NMR δ 56.37, 57.76, 95.02, 99.04, 114.70, 116.81, 122.49, 130.63, 132.58, 132.94, 149.28, 150.53, 191.18. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.68; H, 6.43.

3,4-Bis(methoxymethoxy)-5-(2-hydroxyethyl)benzyl Alcohol (9). To a solution of **8** (1.63 g, 6.46 mmol) in THF (10 mL) at 0 °C was added dropwise BH_3·THF (13.3 mL of 1 M THF solution). The solution was stirred for 3 h at 0 °C, and H_2O (13 mL) was added *slowly*. To this mixture was added $NaBO_3$·$4H_2O$ (5.8 g), and the mixture was stirred vigorously at rt for 15 h. The mixture was partitioned between ether and H_2O, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an oil. Silica gel chromatography (7:3 ether:CH_2Cl_2) yielded **9** as a colorless oil, which solidified on standing (1.20 g, 68%): IR (neat) 3360, 1160 cm^{-1}; ^1H NMR δ 1.74 (t, 1, J = 6), 1.97 (t, 1, J = 5.6), 2.97 (t, 2, J = 6.4), 3.50 (s, 3), 3.60 (s, 3), 3.88 (dt, 2, J = 6.1, 6.1), 4.61 (d, 2, J = 5.8) 5.13 (s, 2), 5.21 (s, 2), 6.90 (d, 1, J = 1.7), 7.06 (d, 1, J = 1.7). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.36; H, 7.42.

3,4-Bis(methoxymethoxy)-5-(2-hydroxyethyl)benzaldehyde (10). To a solution of **9** (1.17 g, 4.3 mmol) in $CHCl_3$ (12 mL) was added MnO_2 (1.87 g, 5 equiv). The mixture was heated at 80 °C for 2 h and cooled to rt. The mixture was further diluted with $CHCl_3$ and filtered through Celite. Concentration of the solution under reduced pressure provided an oil, which was chromatographed on silica gel (1:1 hexanes:ethyl acetate) to afford **10** as a colorless oil, which solidified on standing (840 mg, 72%): IR (neat) 3450, 1695 cm^{-1}; ^1H NMR δ 2.05 (t, J = 5.4), 3.03 (t, 2, J = 6.3), 3.51 (s, 3), 3.59 (s, 3), 3.91 (dt, 2, J = 5.6, 6.3), 5.24 (s, 2), 5.25 (s, 2), 7.45 (d, 1, J = 2.0), 7.55 (d, 1, J = 2.0), 9.87 (s, 1); ^{13}C NMR δ 33.30, 56.35, 57.54, 62.44, 94.92, 99.08, 114.25, 126.62, 132.46, 133.81, 150.02, 150.81, 191.23. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.98; H, 6.77.

5-Formyl-7-hydroxy-2,3-dihydrobenzofuran (4). A solution of hydroxybenzaldehyde **10** (399 mg, 1.47 mmol) was stirred in 2 N acetic acid (6 mL) at 80 °C for 20 h. Upon being cooled to rt the mixture was diluted with H_2O and extracted with ethyl acetate (5 × 15 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude intermediate triol as a brownish-orange oil: ^1H NMR (DMSO) δ 2.72 (t, 2, J = 7.0), 3.57 (t, 2, J = 7.0), 7.12 (d, 1, J = 1.7), 7.19 (d, 1, J = 1.7), 9.67 (s, 1). The ^1H NMR spectrum of this material is provided in the supplementary material.

To a solution of oxalyl chloride (197 mg, 1.55 mmol) in CH_2Cl_2 (6 mL) cooled to 0 °C was added dropwise dimethylformamide (DMF, 539 mg, 7.39 mmol). The resulting solution was maintained at 0 °C for 20 min, and a solution of the crude triol prepared above, dissolved in a minimum volume of DMF, was added dropwise. The solution was stirred for 30 min at 0 °C, the cooling bath was removed, and triethylamine (1.48 g, 14.7 mmol) was added dropwise. The resulting mixture was stirred at rt for 20 h and poured into 2 N HCl. The mixture was extracted with CH_2Cl_2, and the combined extracts were washed with H_2O and brine. The solution was dried ($MgSO_4$), filtered, concentrated under reduced pressure to afford an orange oil. Silica gel chromatography (1:1 hexanes:ethyl acetate) provided **4** as a pale yellow oil, which solidified on standing (130 mg, 54%): ^1H NMR δ 3.32 (t, 2, J = 8.3), 4.76 (t, 2, J = 8.7), 5.81 (bs, 1), 7.33 (s, 1), 7.36 (s, 1), 9.78 (s, 1); ^{13}C NMR δ 190.82, 152.75, 140.74, 131.39, 128.68, 119.56, 117.09, 73.22, 29.66; FAB HRMS calcd for $C_9H_9O_3$ 165.0552 (M + H^+), found 165.0552. We were unable to obtain satisfactory microanalytical data for **4**. The ^1H NMR spectrum of this material is provided in the supplementary material.

3,4-Bis(methoxymethoxy)-5-[3-(*tert*-butyldimethylsiloxy)-1(*E*)-propenyl]benzaldehyde (13). To a solution of **7** (3.85 g, 12.6 mmol) and 3-[(*tert*-butyldimethylsiloxy)-1(*E*)-propenyl]-tributyltin (**12**) (6.13 g, 13.3 mmol) in toluene (38 mL) was added tetrakis(triphenylphosphine)palladium (292 mg, 0.25 mmol). The solution was heated at 100 °C for 2 h, cooled to rt, and diluted with ether (50 mL). The solution was washed with 5% NH_4OH (2 × 30 mL), H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. Silica gel chromatography (4:1 hexanes:ethyl acetate) provided **13** as a colorless oil (4.4 g, 88%): IR (neat) 1695, 1470, 1395, 1160 cm^{-1}; ^1H NMR δ 0.12 (s, 6), 0.95 (s, 9), 3.52 (s, 3), 3.58 (s, 3), 4.31 (dd, 2, J = 1.4, 4.4), 5.23 (s, 2), 5.26 (s, 2), 6.41 (dt, 1, J = 4.6, 16.1), 7.02 (d, 1, J = 16.1), 7.55 (d, 1, J = 1.4), 7.69 (d, 1, J = 1.5), 9.91 (s, 1). Anal. Calcd for $C_{20}H_{32}O_6Si$: C, 60.58.; H, 8.13. Found: C, 60.38; H, 8.11.

3,4-Bis(methoxymethoxy)-5-[3-(*tert*-butyldimethylsiloxy)-1-(*E*)-propenyl]benzyl Alcohol (14). To a solution of **13** (2.28 g, 5.76 mmol) in methanol (17.5 mL) at 0 °C was added in portions $NaBH_4$ (435 mg, 11.5 mmol). The resulting dark mixture was stirred for 10 min and quenched slowly with H_2O. The mixture was extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to obtain **14** as a slightly brown oil (2.28 g, 99%): IR (neat) 3430, 1590, 1470, 1250, 1159, 840 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.94 (s, 9), 3.50 (s, 3), 3.58 (s, 3), 4.36 (dd, 2, J = 1.8, 4.8), 4.61 (s, 2), 5.10 (s, 2), 5.20 (s, 2), 6.30 (dt, 1, J = 4.9, 15.9), 6.96 (d, 1, J = 16.1), 7.05 (d, 1, J = 1.7), 7.15 (d, 1, J = 1.7); ^{13}C NMR δ −5.34, 18.30, 25.84, 56.14, 56.17, 63.89, 64.88, 94.99, 99.02, 113.78, 118.08, 123.72, 130.83, 131.81, 137.12, 143.32, 150.12. Anal. Calcd for $C_{20}H_{34}O_6Si$: C, 60.27; H, 8.59. Found: C, 60.37; H, 8.67.

3,4-Bis(methoxymethoxy)-5-[3-(*tert*-butyldimethylsiloxy)propyl]benzyl Alcohol (15). To a stirring mixture of **14** (2.10 g, 5.27 mmol) and hydrazine (6.6 mL, 0.21 mol) in 95% ethanol:THF (50 mL:15 mL) at 0 °C was added slowly a solution of $NaIO_4$ (11.27 g, 52.7 mmol) in H_2O (20 mL). The resulting slurry was heated with stirring at 75 °C for 2 h (with reflux condenser left open to atmosphere), over which time the mixture turned to a pale yellow, homogeneous solution. The solution was cooled to rt, diluted with CH_2Cl_2, and washed with 1 N NaOH, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afforded **15** as a slightly yellow oil (2.11 g, 99%): IR (neat) 3435, 1260, 840 cm^{-1};

(18) All starting materials were obtained from commercial suppliers and used without further purification. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. All reactions and chromatography fractions were analyzed by thin-layer chromatography on 2.5- × 7.5-cm silica gel plates (250-μm SiO_2 thickness), visualized with UV light and I_2 stain. Flash column chromatography was carried out using Merck silica gel 60 (230−400 mesh). Evaporation of solvents was accomplished with a rotary evaporator. IR spectra were measured as thin films on KCl plates unless otherwise indicated. ^1H-NMR spectra were measured in $CDCl_3$ using either a Varian VXZ-300 or a Varian Unity-300 instrument unless otherwise indicated. J values are reported in Hz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Apparent multiplicities are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. All mass spectra were taken in the positive ion mode by fast-atom bombardment (FAB). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

^{1}H NMR δ 0.06 (s, 6), 0.91 (s, 9), 1.85 (m, 2), 2.74 (t, 2, J = 7.8), 3.50 (s, 3), 3.60 (s, 3), 3.67 (t, 2, J = 6.3), 4.60 (s, 2), 5.10 (s, 2), 5.20 (s, 2), 6.87 (d, 1, J = 1.7), 7.01 (d, 1, J = 1.7); ^{13}C NMR δ −5.34, 18.30, 25.91, 26.73, 33.44, 56.18, 57.34, 62.81, 65.03, 94.98, 98.99, 112.71, 121.81, 136.63, 136.87, 144.30, 149.70. Anal. Calcd for $C_{20}H_{36}O_6Si$: C, 59.97; H, 9.06. Found: C, 59.78; H, 9.09.

3,4-Bis(methoxymethoxy)-5-[3-(*tert*-butyldimethylsiloxy)propyl]benzaldehyde (16). To a solution of **15** (2.00 g, 5.00 mmol) in $CHCl_3$ (15 mL) was added MnO_2 (4.35 g, 50 mmol). The mixture was heated at 50 °C for 1 h and cooled to rt. The mixture was further diluted with $CHCl_3$ and filtered through Celite. Concentration under reduced pressure provided an oil, which was chromatographed on silica gel (8:1 hexanes:ethyl acetate) to afford **16** as an oil (1.67 g, 84%): IR (neat) 1700, 1595, 1295, 1160 cm^{-1}; ^{1}H NMR δ 0.06 (s, 6), 0.91 (s, 9), 1.87 (m, 2), 2.82 (t, 2, J = 7.8), 3.51 (s, 3), 3.59 (s, 3), 3.68 (t, 2, J = 6.1), 5.22 (s, 2), 5.25 (s, 2), 7.42 (d, 1, J = 1.3), 7.52 (d, 1, J = 1.3), 9.87 (s, 1); ^{13}C NMR δ −5.40, 18.24, 25.87, 26.69, 32.98, 56.31, 57.50, 62.46, 94.94, 98.89, 113.75, 126.16, 132.30, 137.10, 149.96, 150.43, 191.08. Anal. Calcd for $C_{20}H_{34}O_6Si$: C, 60.27; H, 8.59. Found: C, 60.35; H, 8.63.

6-Formyl-8-hydroxy-2,3-dihydrobenzopyran (5). Dihydrobenzopyran **5** was prepared from **16** using the procedure described for the synthesis of **4** (*vide supra*);[16] ^{1}H NMR δ 2.07 (m, 2), 2.85 (t, 2, J = 6.4), 4.35 (t, 2, J = 5.2), 5.77 (s, 1), 7.19 (s, 1), 7.28 (d, 1, J = 1.7), 9.79 (s, 1); ^{13}C NMR δ 21.78, 24.08, 67.55, 112.42, 122.60, 124.55, 129.35, 145.40, 147.57, 191.41. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.25; H, 5.67.

Supplementary Material Available: ^{1}H NMR spectra of compounds **4**, **5**, **11**, **17**, **18**, and **19** and a description of the synthesis of **18**, including ^{1}H NMR data of the synthetic intermediates (8 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.