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Ellagitannin Chemistry. Studies on the Stability and Reactivity of 2,4-HHDP-Containing Glucopyranose Systems

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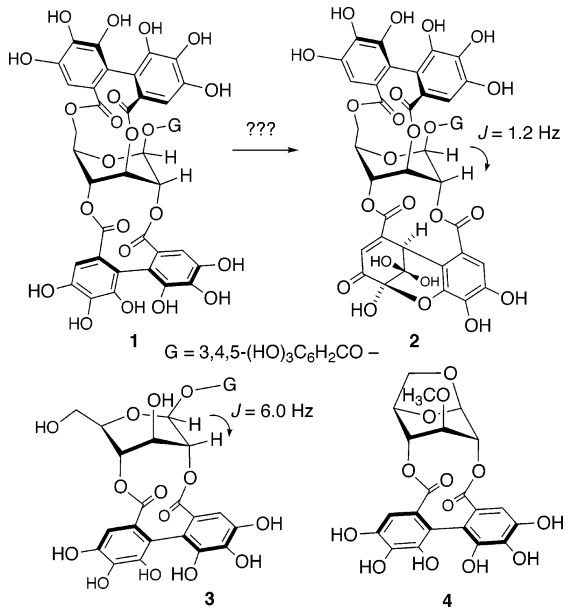
Received April 17, 2003

The synthesis of a 2,4-HHDP containing glucopyranose ellagitannin model system has been achieved. Attempts to prepare a related target bearing a 1,6 bridge led instead to the discovery of a likely strain-driven tautomerization to cyclohexadienone intermediates.

Members of the ellagitannin family of polyphenolic secondary plant metabolites feature hexahydroxydiphenoyl (HHDP) units attached at two points to a polyhydroxylated core structure, typically glucopyranose.[1] The remarkable diversity of structures within this family stems in part from the many regioisomeric HHDP connection permutations possible on the glucopyranose scaffold. Thus, among the 500+ structurally characterized members are included species with the HHDP fragment spanning positions C(1)/C(6), C(3)/C(6), C(4)/C(6), C(2)/C(3), and C(3)/C(4) on glucose. Curiously, only a single ellagitannin, phyllanemblinin B (**3**),[2] is reported to contain an HHDP unit bridging the C(2)/C(4) gap of glucose, even though there are over 15 ellagitannins which contain a modified (oxidized) version of the HHDP moiety at this position. Members of this ellagitannin subclass,[3] exemplified by the yellow crystalline species geraniin (**2**) (Scheme 1),[3a] all contain a second bridging C(3)/C(6) HHDP unit. Speculation that these geraniin-type ellagitannins arise biosynthetically from an undetected HHDP-containing intermediate **1** has been offered,[4] although no direct test of this hypothesis has been forthcoming. These observations raise questions about (1) why the 2,4-HHDP-containing ellagitannins (e.g., **1**) have not been detected in the plants that produce **2** and congeners and (2) why the singular 2,4-HHDP-containing ellagitannin phyllanemblinin B is such a privileged structure.

A long-standing interest in ellagitannin chemistry provided the impetus to probe these issues through model

SCHEME 1



system transformations.[5] The 2,4-HHDP-containing glucose derivative **4**, with its 1,6-anhydro bridge, was targeted as a relevant mimic of the rigid C(3)/C(6) HHDP-bearing unknown species **1**. In both compounds, the glucopyranose ring is frozen in the $^1C_4$ conformation. Success (or failure) in the synthesis of **4**, along with its subsequent oxidation chemistry, might then speak to the possibility that geraniin-type ellagitannin biosynthesis proceeds through an intermediate of the type **1**.

The approach to **4** commenced with the known anhydroglucose derivative **5**,[6a,b] which was processed on to an

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(2) Zhang, Y.-Jun.; Abe, T.; Tanaka, T.; Yang, C.-Ren.; Kuono, I. *J. Nat. Prod.* **2001**, *64*, 1527.

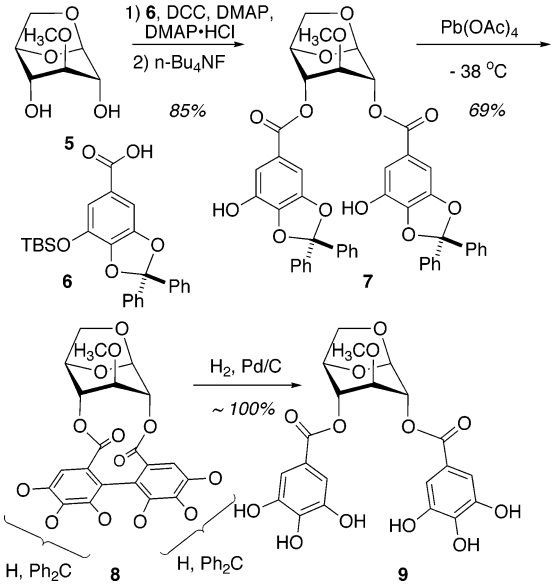
(3) See (a) Okuda, T.; Yoshida, T.; Hatano, T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 9. (b) Luger, P.; Weber, M.; Kashino, S.; Amakura, Y.; Okuda, T.; Beurskens, G.; Dauter, Z. *Acta Crystallogr.* **1998**, *B54*, 687. (c) Okuda, T.; Yoshida, T.; Hatano, T. *Heterocycles* **1990**, *30*, 1195 and references therein.

(4) Tanaka, T.; Nonaka, G. I.; Nishioka, I.; Miyahara, K.; Kawasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 369.

(5) (a) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357. (b) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742. (c) Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171. (d) Feldman, K. S.; Smith, R. S. *J. Org. Chem.* **1996**, *61*, 2606. (e) Feldman, K. S.; Sahasrabudhe, K. *J. Org. Chem.* **1999**, *64*, 209. (f) Feldman, K. S.; Lawlor, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7396. (g) Feldman, K. S.; Lawlor, M. D.; Sahasrabudhe, K. *J. Org. Chem.* **2000**, *65*, 8011. (h) Quideau, S.; Feldman, K. S. *J. Org. Chem.* **1997**, *62*, 8809. (i) Feldman, K. S.; Quideau, S.; Appel, H. M. *J. Org. Chem.* **1996**, *61*, 6656.

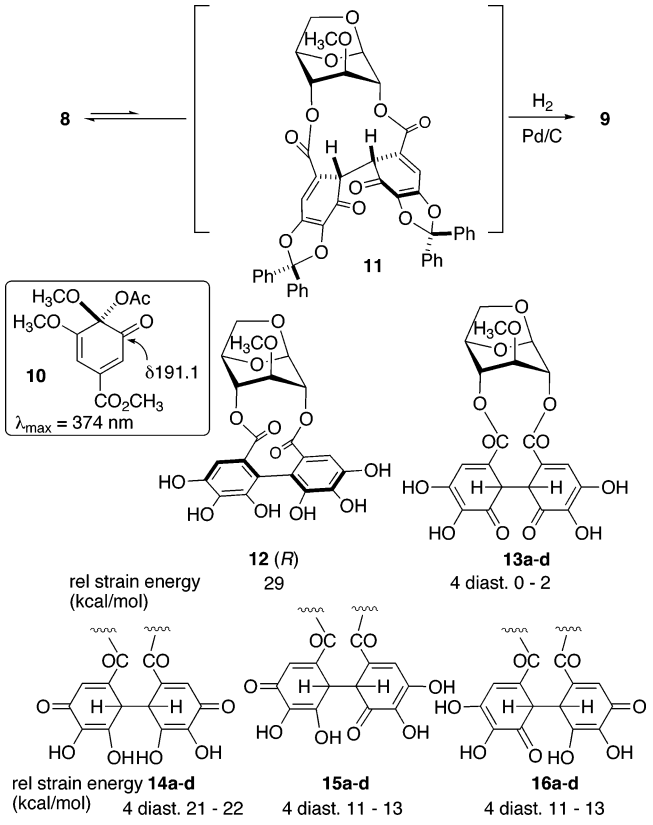
10.1021/jo034495x CCC: $25.00
Published on Web 08/23/2003

SCHEME 2



oxidative cyclization precursor **7** via bis esterification with **6**[6c] and then desilylation of the derived bis galloyl ester (Scheme 2). The choice of the bis diphenylketal galloyl phenol units as oxidative cyclization substrates was predicated upon much earlier work in the ellagitannin series,[5] wherein these particular galloyl derivatives participated in high-yielding $Pb(OAc)_4$-mediated conversion to HHDP units (Wessely oxidation). By analogy with these precedents, treatment of **7** with $Pb(OAc)_4$ at low temperature led to the expected HHDP-containing products **8** as a complex mixture of isomers. The crude oxidation product was purified by flash chromatography and then HPLC to furnish a material that appeared to be a mixture of at least six distinct isomers by ^{1}H NMR. Examination of this purified mixture by CD spectroscopy resulted in a signal with minimal elipticity at the characteristic wavelengths for HHDP analysis,[7] a result consistent with formation of **8** as a mixture of atropisomers in addition to the expected diphenyl ketal regioisomers. One key feature distinguished this HHDP-containing oxidation product from all previous galloyl-derived biaryls prepared by Wessley oxidation in the course of this research: it was bright orange ($\lambda_{max} = 386$ nm). All other HHDP derivatives prepared by Wessely oxidation were white or off-white solids, whereas the bright orange color of **8** was more reminiscent of the cyclohexadienone products (cf. **10**, Scheme 3) prepared from Wessely oxidation of simple monophenolic galloyl methyl ethers.[5a] In addition, the ^{13}C NMR spectrum presented another surprise: two signals at δ 191.5 and 190.7 along with the expected cluster of eight differentiated ester signals (four individual compounds) at δ 164−163. The suspicion that something was amiss was further fueled upon attempted hydrogenolytic deprotection of the mixture **8**. Rather than providing the expected fully phenolic HHDP group, the bis galloyl ester **9**, formally derived by hydrogenolysis of an Ar−Ar bond, was produced in high yield. This unexpected result, in conjunction with the UV/vis and ^{13}C NMR spectroscopic data acquired for **8**, prompted the mechanistic speculation shown in Scheme 3.

SCHEME 3



The supposition that the relatively high strain energy accrued upon oxidative coupling within **7** could be discharged by two tautomerizations was supported by molecular mechanics (MM) calculations[8] on model systems lacking the diphenyl ketal units **12**−**16**. On the assumption that any tautomerization process which converts **8** into a dienone is under equilibrium control, an evaluation of the calculated relative strain energies of model systems **13**−**16** for the putative bis-cyclohexadienone intermediate(s) suggests that all of the 16 isomers so examined are substantially less strained than the HHDP-containing species **12**, although caveats about the failure of MM calculations to adequately address issues of tautomerization are noted.[8] Thus, it is not unreasonable to surmise that detectable amounts of a bis cyclohexadienone, shown as **11** for illustrative purposes only, might be present in equilibrium with **8**. The intervention of such a species would provide a concise explanation for the orange color of **8**, the downfield carbonyl signals in the ^{13}C NMR (cf. **10**), and the unusual behavior upon attempted hydrogenolysis of the ketal groups. On this latter point, simple hydrogen addition

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(7) Okuda, T.; Yoshida, T.; Hatano, T.; Koga, T.; Toh, N.; Kuriyama, K. *Tetrahedron Lett.* **1982**, *23*, 3937.

(8) The directed Monte Carlo algorithm of MacroModel V 6.5 was used to identify low-energy conformers of the species reported. In each case, a 3000- to 10000-step conformational search was utilized, depending upon the number of rotatable bonds involved. All reported minima were located several times. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440

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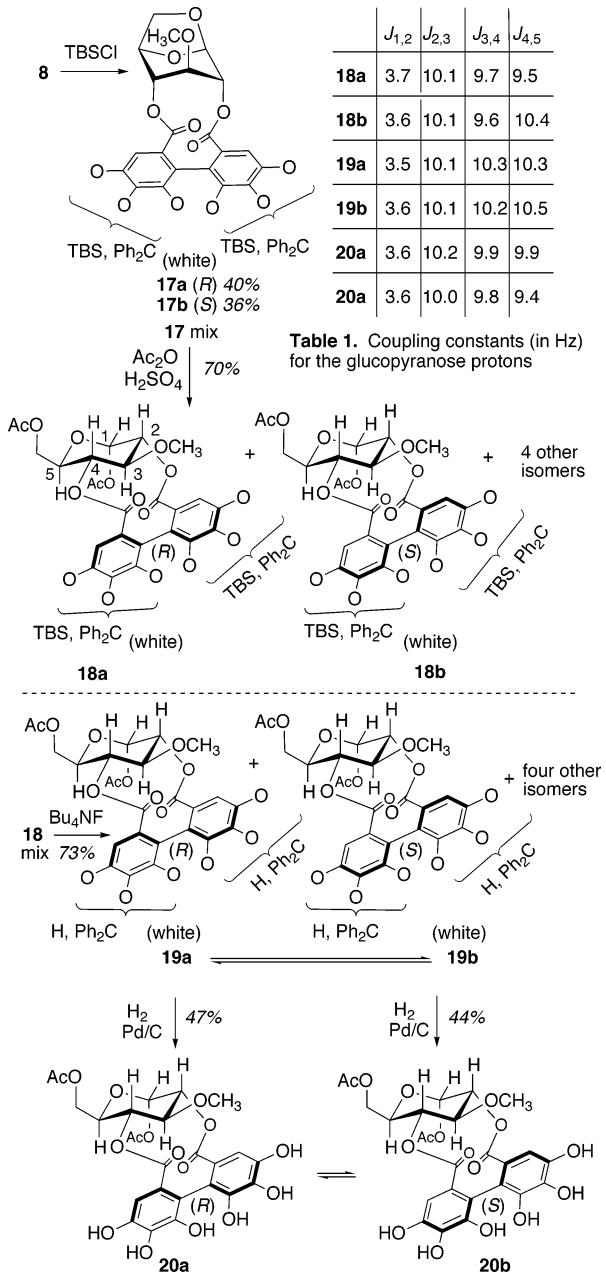
to one of the ketones of **11** could trigger a retro-Michael reaction that cleaves the two rings and furnishes **9** after tautomerization and diphenyl ketal hydrogenolytic scission. This mechanistic speculation can be extended to the geraniin series of ellagitannins, where an unobserved bis cyclohexadienone product in equilibrium with **1** might provide a platform for the subsequent oxidation/nucleophilic addition processes which characterize this family of metabolites. Although it is not realistic to use the MM-derived structure-energy data to draw any conclusions about the precise tautomers/diastereomers present, it is clear that any member of this set could serve the dual roles of (1) relieving the strain inherent in **12** and (2) preceding formation of **9**.

These preliminary results on the constrained $^1C_4$ glucopyranose framework provide a backdrop for studies on the complementary question of why phyllanemblinin B is "surprisingly" stable. Scission of the C(6)/C(1) bridge in **8** would furnish a glucopyranose species that might be flexible enough to adopt a less strained glucopyranose conformation. This structural adjustment might then permit the C(2)/C(4) HHDP unit to survive without the complications of tautomeric equilibria. Initial silylation of the free phenols within the mixture **8** led to a *white* solid **17**, a result consistent with the suppression of the equilibrium **8** ↔ **11**. Examination of the ^{1}H NMR spectrum of this mixture revealed the presence of at least four discrete isomers. Careful chromatography of this mixture led to the isolation of two major pure isomers designated as **17a** (ca. 40% of the crude mixture of isomers) and **17b** (ca. 36% of the crude mixture of isomers). The former compound displayed the characteristic CD spectrum of an (*R*)-HHDP-containing ellagitannin, whereas **17b**'s CD spectrum unmistakably indicated an (*S*)-HHDP-containing ellagitannin (**17a**: (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (−4.4), 263 (+2.2), 290 (−4.9); **17b**: (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (+1.9), 263 (−4.1), 290 (+5.8) (compare (*R*)-phyllanemblinin B (EtOH), λ_{max} ($\Delta\epsilon$) 230 (−22.8), 267 (+19.1), 295 (−16.5))). Thus, it appears that the Wessely oxidation/silylation sequence provides approximately equal amounts of (*R*)- and (*S*)-HHDP-containing products. It is unclear at present if this lack of atropselectivity results from kinetic (i.e., nonselective Pb-mediated coupling) or thermodynamic (i.e., equilibration via diones such as **11**) factors. Brief exposure of the silyl ether mixture **17** to Ac_2O/H_2SO_4 afforded a good yield of the ring-opened white diacetates **18** as a mixture of at least six compounds. Two pure isomers, designated as **18a** and **18b**, respectively, could be isolated from this mixture following careful chromatography. Isomer **18a** corresponded to the major component of the mixture (ca. 36% by ^{1}H NMR integration of the methoxy proton signals within the mixture). The CD spectrum of this species displayed the clear signature of an (*R*)-HHDP unit ((CH_3OH) λ_{max} ($\Delta\epsilon$) 237 (−8.5), 263 (+1.1), 290 (+1.0)), whereas the other pure compound **18b**, only a minor component of the overall mixture (ca. 12%), produced a characteristic CD spectrum for an (*S*)-HHDP unit ((CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (+30.7), 263 (−6.4), 290 (−12.0)). Similar reaction of pure **17a** with Ac_2O/H_2SO_4 led to formation of a 1:1 mixture of **18a** and a second isomer, whereas pure **17b** furnished a 1:1 mixture of **18b** and a new isomer. Unfortunately, not enough material could be isolated from these experiments to characterize the other isomers

SCHEME 4



	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
18a	3.7	10.1	9.7	9.5
18b	3.6	10.1	9.6	10.4
19a	3.5	10.1	10.3	10.3
19b	3.6	10.1	10.2	10.5
20a	3.6	10.2	9.9	9.9
20a	3.6	10.0	9.8	9.4

Table 1. Coupling constants (in Hz) for the glucopyranose protons

formed. The tentative assignments of anomeric stereochemistry for **18a** and **18b** rest on an analysis of the glucopyranose ring's proton−proton coupling constants (cf. Scheme 4). In particular, the large $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ values are consistent only with the near diaxial disposition of these protons in a chairlike conformation. The small $J_{1,2}$ coupling for both **18a** and **18b** (ca. 3.6 Hz) is consistent with a near 90° dihedral between these protons, a geometry best accommodated by assigning the anomeric acetate functions to the axial locations shown. Isomers **18a** and **18b** did not equilibrate at room temperature.

Desilylation of the silyl ethers within this mixture **18** resulted yet again in a complex mixture **19** of at least six isomers, from which two pure, white compounds **19a** (35%) and **19b** (27%) could be isolated by careful prep-plate chromatography. Pure silyl ether **18a** was desilylated independently to furnish two new species (55:45),

neither of which was identical to **19a** or **19b**. Similarly, pure isomer **18b** was converted to two species (70:30), the major one of which was identical to **19b**. In a notable departure from the chemistry observed with **18a**/**18b**, the isomers **19a**/**19b** equilibrated over the course of 48 h in acetone-d_6 solution. The CD spectra of both mixtures derived from **18a** and **18b**, respectively, and the **19a**/**19b** equilibrated mixture (45:55) displayed very little ellipticity at the key HHDP wavelengths. However, both **19a** and **19b** survived as discrete species long enough to acquire adequate characterization data, including CD spectra, that supported the atropisomer and anomeric stereochemistry assignments shown in Scheme 4 (see the Experimental Section and the Supporting Information). The mechanism of the HHDP isomerization remains unknown, although neither a direct Ar−Ar bond rotation nor a tautomerization-based process (cf. **8** ↔ **11**) can be ruled out.

Hydrogenolytic removal of the diphenyl ketals within the (*R*)-atropisomer **19a** delivered a single pale yellow hexaphenol isomer **20a**. Similar treatment of the pure (*S*)-atropisomer **19b** yielded a hexaphenolic product distinct from **20a**, designated as **20b**. Circular dichroism measurements for both **20a** and **20b** confirmed that the HHDP units retained their (*R*) and (*S*) absolute configurations throughout (**20a**: (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (−2.0), 263 (+1.0), 290 (−4.8); **20b**: (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (+0.9), 263 (−0.5), 290 (−0.8)). These hexaphenols, much like their ketal predecessors, underwent facile atropisomerization (**20a** ↔ **20b** equilibration) over 24 h. No evidence for any Ar−Ar cleavage products could be discerned. The complete mixture of isomers **19** from the desilylation reaction was exposed to H_2/Pd/C as described for the pure isomers, and a ca. 1:1 mixture of **20a** and **20b** resulted. Some minor and uncharacterized species were present as well (ca. 10%), but overall it appears that the acid-mediated ring opening **17** → **18** proceeded with largely inversion of stereochemistry at C(1) to furnish axial acetate-containing products. MM-based analysis of **20a**, in comparison with the bridged precursor **12**, supports the contention that cleavage of the tricyclic framework results in a substantial reduction (ca. 10 kcal/mol) in molecular strain.[8] Thus, it appears that the stability of the C(2)/C(4) HHDP unit in **20a**/**20b**, and by inference in phyllanemblinin B as well, can be attributed to the decrease in strain energy that accompanies removal of a rigidifying bridge on the β-face of the glucopyranose ring. Incorporation of such a constraint (**8** or geraniin (**2**)) leads to strain-driven rearrangement of the HHDP moiety to a reactive cyclohexadienone-containing species, which, in the natural product series, can serve as a precursor to the geraniin-based family of C(2)/C(4) HHDP-derived addition/oxidation products mentioned earlier.

Experimental Section

3-*O*-Methyl 2,4-bis((3,4-diphenylmethylene)dioxy)-5-hydroxybenzoyl)-1,6-anhydro-β-D-glucopyranoside (7). A solution of diol **5**[6a,b] (0.88 g, 5.0 mmol), acid **6**[6c] (4.48 g, 10.0 mmol), 4-(dimethylamino)pyridine (DMAP) (0.31 g, 2.5 mmol), DMAP·HCl (0.40 g, 2.5 mmol), and 1,3-dicyclohexylcarbodiimide (2.48 g, 12.0 mmol) in dry CH_2Cl_2 (100 mL) was purged with argon and stirred at room temperature for 14 h. The emulsion was then filtered through Celite, the filter cake was washed three times with 10 mL of CH_2Cl_2, and the filtrate was concentrated in vacuo. Purification of the pale yellow solid by silica gel chromatography using 30% ether in hexanes as eluent afforded 4.26 g (82%) of the diester product as frothy white solid: IR (KBr) 1714 cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz) δ 7.64−7.29 (m, 24 H), 5.59 (brs, 1H), 4.97 (s, 1H), 4.83 (brs, 2H), 4.80 (d, J = 5.0 Hz, 1H), 4.20 (d, J = 7.3 Hz, 1H), 3.77 (t, J = 7.2 Hz, 1H), 3.65 (s, 1H), 3.56 (s, 3H) 0.98 (s, 18H), 0.20 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (C_3D_6O, 90 MHz) δ 164.8, 164.7, 149.2, 149.1, 142.0, 140.1, 139.2, 129.9, 129.8, 129.7, 129.5, 128.9, 128.8, 126.5, 126.4, 124.5, 124.4, 118.9, 118.8, 118.7, 104.1, 100.0, 78.5, 74.5, 72.0, 70.9, 65.5, 58.4, 25.7, 25.4, 24.7, 18.4, −4.4, −4.7; APCIMS *m*/*z* relative intensity 1037 (MH^+, 100); HRMS (+APCI) calcd for $C_{59}H_{64}O_{13}Si_2$ 1037.3963, found 1037.3917.

A solution of this digalloylated glucose derivative (4.15 g, 4.00 mmol) in dry THF (100 mL) was cooled to 0 °C and purged with argon. A solution of tetrabutylammonium fluoride (1 M in THF, 12.00 mmol, 12 mL) was added, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction solution was then carefully diluted with ice-cold 1 M H_3PO_4, and the product was extracted into ethyl acetate. The organic extract was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated to give an off-white solid. The crude compound was purified by flash chromatography using 90% ether in hexanes as the eluent to yield 2.76 g (85%) of the bisphenol **7** as a white foam: mp 274−276 °C dec; IR (KBr) 3322, 1711 cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz) δ 9.1 (brs, 1H), 7.6−7.3 (m, 22 H), 7.22 (d, J = 1.5 Hz, 1H), 7.19 (s, J = 1.5 Hz, 1H), 5.56 (brs, 1H), 5.00 (brs, 1H), 4.83 (brs, 1H), 4.79 (d, J = 5.8 Hz, 1H), 4.22 (d, J = 7.5 Hz, 1H), 3.79 (dd, J = 7.1, 6.0, Hz, 1H), 3.54 (brs, 4H); ^{13}C NMR (C_3D_6O, 75 MHz) δ 164.8, 164.7, 150.0, 148.9, 141.2, 141.1, 140.5, 140.4, 140.3, 138.9, 129.7, 129.6, 128.7, 128.7, 126.5, 126.4, 124.5, 124.4, 118.4, 114.5, 102.6, 99.8, 78.5, 74.2, 71.9, 69.9, 65.2, 58.2; IR (KBr) 3322, 1711 cm^{-1}; APCIMS *m*/*z* relative intensity 809 (MH^+, 100); HRMS (+APCI) calcd for $C_{47}H_{36}O_{13}$ 809.2234, found 809.2229.

Lead Tetraacetate Oxidation of 3-*O*-Methyl 2,4-Bis-((3,4-diphenylmethylene)dioxy)-5-hydroxybenzoyl)-1,6-anhydro-β-D-glucopyranoside (7). A solution of $Pb(OAc)_4$ (1.58 g, 3.58 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a deoxygenated solution of bisphenol **7** (2.63 g, 3.25 mmol) in dry CH_2Cl_2 (100 mL) and pyridine (1.05 mL, 13.0 mmol) at −38 °C. The dark orange solution was stirred at −38 °C for 2 h. The solution was diluted with aqueous $NaHCO_3$ and extracted into CH_2Cl_2. The organic extract was washed with water and saturated $CuSO_4$ solution to remove traces of pyridine, dried over Na_2SO_4, and evaporated in vacuo to yield an orange-brown solid which, upon flash chromatography using 65% ether in hexanes, afforded 1.8 g (69%) of **8** as a bright orange solid: mp 222−228 °C; IR (KBr) 3410, 1714, cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz) (mixture of isomers) δ 7.8−7.2 (m, 20 H), 7.0−6.6 (2H), 5.7−5.5 (m, 1H), 5.1−4.6, (m, 3H), 4.3−4.2 (m, 1H), 3.75 (m, 1H), 3.6−3.3 (m, 4H); ^{13}C NMR (C_3D_6O, 75 MHz) δ 191.5, 190.7, 163.9, 163.8, 163.7, 163.5, 163.3, 163.1 158.5, 158.4, 158.2, 158.1, 149.1, 146.4, 144.0, 141.0, 140.7, 140.0, 139.8, 139.5, 139.4, 139.3, 137.2, 137.1, 137.0, 136.9, 129.9, 129.5, 128.9, 128.8, 128.7, 128.4, 126.7, 126.6, 126.5, 126.3, 126.2, 124.1, 124.0, 123.8, 122.9, 120.9, 120.7, 119.8, 119.5, 118.2, 107.2, 107.1, 105.4, 100.5, 99.5, 99.1, 98.9, 98.3, 96.1, 95.9, 94.1, 94.0, 77.2, 77.1, 77.0, 74.0, 73.6, 73.5, 73.4, 72.6, 70.8, 70.4, 70.2, 69.2, 69.0, 68.9, 67.9, 65.3, 65.2, 64.7, 58.0, 57.9; APCIMS *m*/*z* relative intensity 807 (MH^+, 48); HRMS (+APCI) calcd for $C_{47}H_{34}O_{13}$ 807.2077, found 807.2041

Hydrogenolysis of Compound 8. A deoxygenated solution of compound **8** (60 mg, 0.07 mmol) and 30 mg of 10% Pd on C in dry THF (10 mL) was stirred at room temperature under H_2 at 1 atm for 14 h. At that time, the flask was purged with argon, and the reaction mixture was filtered through Celite. The filtrate was concentrated in vacuo to give 35 mg (∼100%)

of **9** as a pale brown film: IR (CH_2Cl_2) 1717 cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz) δ 7.24 (s, 2 H), 7.21 (s, 2H), 5.53 (brs, 1H), 4.94 (brs, 1H), 4.81 (brs, 1H), 4.76 (d, $J = 7.2$ Hz, 1H), 4.20 (d, $J = 7.2$ Hz, 1H), 3.77 (t, $J = 7.0$ Hz, 1H), 3.54 (s, 3H); 3.52 (s, 1H); ^{13}C NMR (C_3D_6O, 75 MHz) δ 165.6, 165.4, 145.5, 138.8, 128.8, 126.6, 120.8, 120.6, 109.8, 100.1, 78.9, 74.5, 71.2, 70.2, 65.5, 58.2; APCIMS *m/z* relative intensity 481 (MH^+, 67).

3-*O*-Methyl 2,4-((3,4,3′,4′-Diphenylmethylene)dioxy)-5,5′-*tert*-butyldimethylsilyldiphenoyl)-1,6-anhydro-β-D-glucopyranoside (17). A solution of compound **8** (100 mg, 0.12 mmol) in dry CH_2Cl_2 (10 mL), imidazole (34 mg, 0.48 mmol), and TBSCl (74 mg, 0.48 mmol) was stirred at room temperature for 30 h. The reaction solution was poured into ice-cold 1 M H_3PO_4, and the product was extracted into CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated to yield a yellow solid. Purification of the crude compound by flash chromatography using 60% ether in hexanes as eluent yielded 80 mg (63%) of **17** as a white solid. Further chromatography on an SiO_2 prep-plate with 45% ethyl acetate in hexanes as the mobile phase furnished two major isomers labeled and characterized as **17a** and **17b**.

Mixed isomers **17**: IR (KBr) 1734 cm^{-1}; APCIMS *m/z* relative intensity 1035 (MH^+, 100); HRMS (+APCI) calcd for $C_{59}H_{62}O_{13}Si_2$ 1035.3807, found 1035.3891.

Isomer **17a**: ^1H NMR (C_3D_6O, 400 MHz) δ 7.6−7.4 (m, 20 H), 7.03, (s, 1H), 6.66 (s, 1H), 5.42 (s, 1H), 4.76 (brs, 1H), 4.66 (brs, 1H), 4.52 (s, 1H), 4.13 (d, $J = 7.3$ Hz, 1H), 3.70 (t, $J = 7.0$ Hz, 1H), 3.44 (s, 1H); 3.04 (s, 3H), 0.65 (s, 9H), 0.63 (s, 9H) 0.31 (s, 3H), 0.28 (s, 3H), −0.13 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (C_3D_6O, 75 MHz) δ 168.6, 164.4, 148.6, 148.1, 140.8, 140.2, 140.0, 139.9, 139.3, 138.5, 137.5, 130.0, 129.9, 129.7, 129.6, 128.9, 128.8, 128.7, 128.0, 126.6, 126.5, 126.4, 124.6, 122.6, 118.8, 118.0, 100.4, 99.6, 98.8, 74.5, 72.5, 72.2, 69.9, 65.2, 58.1, 25.1, 25.0, 18.1, 18.0, −4.1, −4.2, −5.5, −5.6; CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (−4.4), 263 (+2.2) 290 (−4.9) nm.

Isomer **17b**: ^1H NMR (C_3D_6O, 400 MHz) δ 7.6−7.4 (m, 20 H), 7.04, (s, 1H), 6.65 (s, 1H), 5.48 (s, 1H), 4.73 (brs, 1H), 4.65 (m, 1H), 4.52 (s, 1H), 4.20 (d, $J = 7.2$ Hz, 1H), 3.64 (t, $J = 7.1$ Hz, 1H), 3.44 (s, 1H); 3.05 (s, 3H), 0.65 (s, 9H), 0.62 (s, 9H) 0.31 (s, 3H), 0.27 (s, 3H), −0.13 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (C_3D_6O, 75 MHz) δ 168.5, 164.7, 148.7, 148.1, 140.8, 140.3, 140.0, 139.9, 139.7, 139.3, 138.6, 137.6, 130.0, 129.9, 129.8, 129.6, 129.0, 128.9, 128.8, 128.7, 128.0, 127.0, 126.6, 126.5, 126.4, 124.6, 122.7, 118.9, 118.1, 99.4, 98.9, 98.7, 75.5, 75.4, 72.4, 68.8, 64.2, 58.1, 25.1, 25.0, 18.1, 18.0, −4.1, −4.2, −5.5, −5.6; CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (+1.9), 263 (−4.1), 290 (+5.8) nm.

3-*O*-Methyl 1,6-Di-*O*-acetyl 2,4-((3,4,3′,4′-Diphenylmethylene)dioxy)-5,5′-*tert*-butyldimethylsilyldiphenoyl)-β-D-glucopyranoside (18). To a suspension of the mixture **17** (80 mg, 0.08 mmol) in Ac_2O (2.0 mL) was added concentrated H_2SO_4 (3 drops). After 4 min at 40 °C, the now homogeneous mixture was poured into water and stirred overnight. The mixture was extracted with CH_2Cl_2, and the organic phase was washed successively with water and saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated to give a white solid. Flash chromatography of the crude using 85% ether in hexanes afforded two isomers that were designated as **18a** and **18b** along with mixed fractions of several isomers (61 mg total, 70%).

Mixed isomers **18**: IR (KBr) 1746 cm^{-1}; APCIMS *m/z* relative intensity 1137 (MH^+, 100); HRMS (+APCI) calcd for $C_{63}H_{68}O_{16}Si_2$ 1137.4124, found 1137.4093.

Isomer **18a**: ^1H NMR (C_3D_6O, 400 MHz) δ 7.6−7.4 (m, 20 H), 7.25 (s, 1H), 7.21 (s, 1H), 6.08 (d, $J = 3.7$ Hz, 1H), 5.05 (t, $J = 9.5$ Hz, 1H), 4.84 (dd, $J = 10.1$, 3.7 Hz 1H), 4.12 (dd, $J = 11.9$, 4.2 Hz, 1H), 4.06 (m, 1H), 4.01 (dd, $J = 12.1$, 2.3 Hz, 1H), 3.90 (t, $J = 9.7$ Hz), 1H), 3.46 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (C_3D_6O, 75 MHz) δ 170.2, 169.8, 168.9, 164.5, 140.8, 140.7, 140.3, 140.0, 139.9, 137.5, 137.3, 129.8, 129.7, 129.6, 129.5, 128.9, 128.8, 128.7, 126.8, 126.5, 126.4, 118.7, 118.5, 103.9, 103.8, 88.9, 78.7, 71.1, 70.1, 69.7, 62.1, 59.9, 25.2, 20.3, 20.1, 18.1, 18.0, −4.1, −4.8, −4.9; CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (−8.5), 263 (+1.1), 290 (+1.0) nm.

Isomer **18b**: ^1H NMR (C_3D_6O, 400 MHz) δ 7.66−7.44 (m, 21 H), 7.30 (s, 1H), 6.11 (d, $J = 3.6$ Hz, 1H), 5.06 (dd, $J = 10.2$, 9.2 Hz, 1H), 4.74 (dd, $J = 10.1$, 3.6 Hz 1H), 3.84 (dd, $J = 12.2$, 4.6 Hz, 1H), 3.67 (dd, $J = 12.2$, 1.9 Hz, 1H), 3.58 (t, $J = 9.6$ Hz, 1H), 3.41 (ddd, $J = 10.4$, 4.4, 2.2 Hz, 1H), 3.29 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (C_3D_6O, 75 MHz) δ 169.9, 169.8, 168.9, 165.2, 147.6, 140.6, 140.4, 140.0 139.7, 137.5, 137.2, 137.0, 130.1, 12 9.8, 129.7, 129.6, 129.0, 128.8, 128.7, 126.7, 126.5, 126.4, 124.3, 119.0, 118.8, 103.9, 103.8, 88.9, 78.1, 71.8, 69.9, 69.4, 61.8, 60.1, 25.4, 25.0, 20.1, 20.0, 19.9, 18.2, −3.8, −4.1, −4.7; CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (+30.7), 263 (−6.4), 290 (−12.0) nm.

3-*O*-Methyl 1,6-Di-*O*-acetyl 2,4-((3,4,3′,4′-Diphenylmethylene)dioxy)-5,5′-hydroxydiphenoyl)-β-D-glucopyranoside (19). A solution of the silyl ether mixture **18** (60 mg, 0.05 mmol) in dry THF (7 mL) was cooled to 0 °C and treated with acetic acid (13 μL, 0.21 mmol). A solution of tetrabutylammonium fluoride (1 M in THF, 0.21 mmol, 0.21 mL) was added, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction solution was then carefully diluted with ice-cold 1 M H_3PO_4, and the product was extracted into ethyl acetate. The organic extract was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated to give a pale yellow solid. The crude mixture was purified on a preparative SiO_2 plate using 70% ethyl acetate in hexanes as eluent to yield a total of 35 mg (73%) of bisphenol **19** as a pale white solid. Two isomers isolated in pure form from this prep-plate were characterized as **19a** and **19b**.

Mixed isomers **19**: IR (KBr) 3310, 1746 cm^{-1}; APCIMS *m/z* relative intensity 909 (MH^+, 95); HRMS (+APCI) calcd for $C_{51}H_{40}O_{16}$ 909.2394, found 909.2431.

Isomer **19a**: ^1H NMR (C_3D_6O, 400 MHz) δ 7.70−7.43 (m, 20 H), 7.34 (s, 1H), 7.33 (s, 1H), 6.09 (d, $J = 3.5$ Hz, 1H), 5.04 (t, $J = 10.2$ Hz, 1H), 4.74 (dd, $J = 10.1$, 3.6 Hz 1H), 3.89 (dd, $J = 12.5$, 4.7 Hz, 1H), 3.85 (dd, $J = 12.3$, 2.3 Hz, 1H), 3.75 (ddd, $J = 10.3$, 4.6, 2.4 Hz, 1H), 3.26 (s, 3H), 3.20 (t, $J = 10.2$ Hz, 1H) 2.03 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (C_3D_6O, 125 MHz) δ 172.8, 172.4, 171.6, 167.6, 150.0, 149.9, 143.5, 143.4, 143.0, 141.8, 141.7, 141.3, 132.6, 132.5, 132.4, 132.2, 132.1, 131.6, 131.4, 131.3, 129.4, 129.2, 129.0, 128.9, 128.8, 120.2, 120.1, 106.6, 105.6, 91.6, 80.8, 75.5, 72.6, 72.1, 64.6, 63.1, 22.9, 22.8; CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (−5.0), 263 (+1.0), 290 (−2.0) nm.

Isomer **19b**: ^1HNMR (C_3D_6O, 400 MHz) δ 7.69−7.42 (m, 20 H), 7.40 (s, 1H), 7.25 (s, 1H), 6.14 (d, $J = 3.6$ Hz, 1H), 5.05 (t, $J = 10.2$ Hz, 1H), 4.74 (dd, $J = 10.1$, 3.6 Hz 1H), 3.82 (dd, $J = 12.6$, 4.5 Hz, 1H), 3.72 (dd, $J = 12.5$, 2.0 Hz, 1H), 3.48 (t, $J = 10.0$ Hz, 1H), 3.31 (ddd, $J = 10.5$, 4.6, 2.0 Hz, 1H), 3.28 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (C_3D_6O, 90 MHz) δ 170.1, 169.8, 169.0, 165.4, 147.4, 140.9, 140.8, 140.5, 140.1, 138.9, 138.0, 130.0, 129.8, 129.6, 128.9, 128.8, 126.8, 126.6, 126.5, 126.4, 124.0, 123.8, 118.5, 118.2, 103.6, 103.1, 89.1, 78.8, 71.8, 70.3, 69.6, 61.9, 60.3, 20.2, 20.4; CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (+16.0), 263 (−5.0), 288 (−6.0) nm.

Hexaphenol 20a. A deoxygenated solution of compound **19a** (15 mg, 0.01 mmol) and 10% Pd on carbon (10 mg) in dry THF (6 mL) was stirred at room temperature under H_2 at 1 atm for 20 h. The resultant mixture was filtered through Celite and concentrated in vacuo to give a yellow-brown film. Purification on an SiO_2 prep-plate using 1:3:1 hexane/ethyl acetate/acetic acid as the mobile phase gave 4.5 mg (47%) of **20a** as a pale-brown film: ^1H NMR (C_3D_6O, 400 MHz) δ 8.1 (s, 1H), 7.28 (d, 2H), 6.10 (d, $J = 3.6$ Hz, 1H), 4.99 (t, $J = 9.9$ Hz, 1H), 4.72 (dd, $J = 10.2$, 3.7 Hz 1H), 3.81 (m, 2H), 3.52 (m, 1H), 3.34 (s, 3H), 3.26 (t, $J = 10.2$ Hz, 1H), 2.02 (s, 3H), 1.97 (s, 3H); CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (−2.0), 263 (+1.0), 290 (−4.0) nm.

Hexaphenol 20b. A deoxygenated solution of compound **19b** (15 mg, 0.01 mmol) and 10% Pd on carbon (10 mg) in dry THF (6 mL) was stirred at room temperature under H_2 at 1

atm for 20 h. The resultant mixture was filtered through Celite and concentrated in vacuo to give a yellow-brown film. Purification on an SiO_2 prep-plate using 1:3:1 hexane/ethyl acetate/acetic acid as the mobile phase gave 4.2 mg (44%) of **20b** as a pale-brown film: ^{1}H NMR (C_3D_6O, 400 MHz) δ 8.1-(s, 1H), 7.37 (s, 1H), 7.25 (s, 1H), 6.09 (d, J = 3.5 Hz, 1H), 5.02 (t, J = 9.4 Hz, 1H), 4.71 (dd, J = 10.0, 3.6 Hz 1H), 3.92 (dd, J = 12.3, 2.2 Hz, 1H), 3.87 (dd, J = 12.5, 4.6 Hz, 1H), 3.34 (m, 1H), 3.31 (t, J = 9.8 Hz, 1H) 3.26 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H); CD (CH_3OH) λ_{max} ($\Delta\epsilon$) 238 (+0.9), 263 (−0.5), 290 (−0.8) nm.

Isomers 20a/b: IR (CH_2Cl_2) 1747 cm^{-1}; ^{13}C NMR (C_3D_6O, 75 MHz) δ 170.3, 169.9, 169.4, 167.6, 165.9, 162.5, 144.3, 144.2, 143.8, 137.9, 137.2, 128.8, 126.4 122.3, 122.0, 121.2, 120.8, 119.4, 119.1, 118.5, 111.6, 111.3, 110.7, 110.4, 89.0, 88.9, 78.3, 72.0, 71.9, 70.2, 70.1, 69.2, 69.1, 62.3, 61.9, 61.0, 60.7, 60.3, 20.5, 20.4, 20.2, 20.1; APCIMS m/z relative intensity 581 (MH^+, 100); HRMS (+APCI) calcd for $C_{25}H_{24}O_{16}$ 581.1143, found 581.1153.

Acknowledgment. Financial support from the National Institutes of Health (GM35727) is gratefully acknowledged.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for **7**−**9**, **17a**/**b**, **18a**/**b**, **19a**/**b**, and **20a**/**b** and general experimental information. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034495X