Ellagitannin Chemistry. Syntheses of Tellimagrandin II and a Dehydrodigalloyl Ether-Containing Dimeric Gallotannin Analogue of Coriariin A

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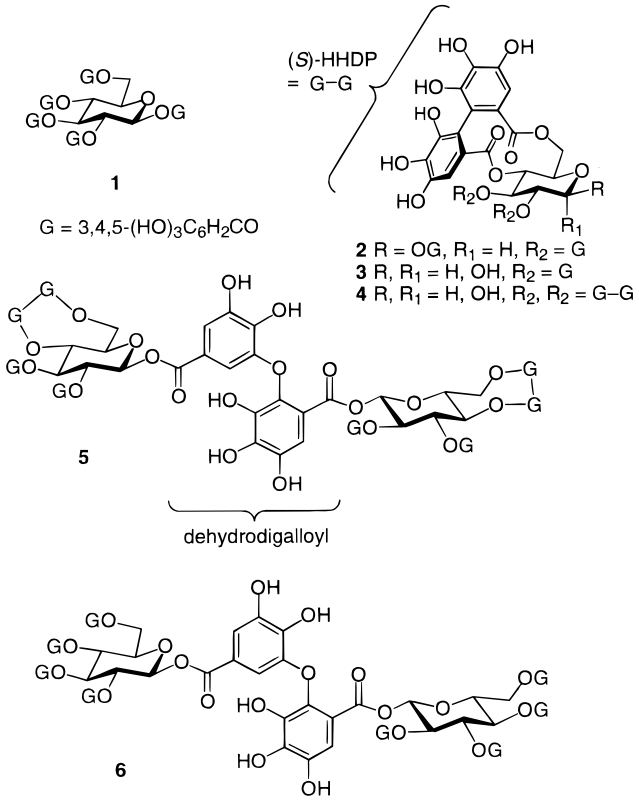
The first chemical synthesis of the naturally occurring ellagitannin tellimagrandin II is reported. Key steps of the synthesis include the atropselective oxidative coupling of suitably protected galloyl rings at the O(4) and O(6) positions of a glucopyranose core, and the stereoselective acylation of the derived anomeric alcohol with a galloyl chloride. In addition, the synthesis of a novel gallotannin−ellagitannin hybrid is described. This dimeric construct relied on a hetero Diels−Alder cycloaddition/reductive rearrangement sequence to deliver the intact skeleton from a monomeric pentagalloylglucose-based orthoquinone.

The ellagitannin subfamily of the hydrolyzable tannins spans over 500 structurally characterized members.[1−4] An increasing interest in the role played by these secondary plant metabolites in polyphenol-rich folk medicines from China and Japan has led to the identification of several ellagitannins which hold promise as potent antiviral and anticancer therapeutic agents.[1,5,6] The challenge of selective C−C and C−O bond formation within these complex structures has stimulated many recent synthesis studies.[7−13] The defining structural feature of the ellagitannins is a **h**exa**h**ydroxy**di**p**h**enoyl (HHDP) moiety bridging two oxygens of a carbohydrate core, typically glucose. Current hypotheses for the biosynthetic origin of ellagitannins suggest that the variations in ellagitannin skeletal architecture emerge from the myriad C−C and C−O modes of oxidative galloyl coupling available to a pivotal intermediate, the naturally occurring gallotannin β-D-pentagalloylglucose (β-D-PGG, **1**). Thus, the monomeric ellagitannin tellimagrandin II (**2**) may arise from the intramolecular C−C oxidative coupling of the O(4) and O(6) galloyl moieties of β-D-PGG, whereas the dimeric ellagitannin coriariin A (**5**) may presumably arise from intermolecular C−O oxidative coupling of the anomeric galloyl groups of two tellimagrandin II units.



A number of oligomeric ellagitannins, including coriariin A (**5**) and the structurally related species agrimoniin and gemin A (not shown), induce tumor regression in mice infected with sarcoma-180 tumors (1−3 regressors out of 6, 100%−238% increase in life span).[14,15] The

(1) Berlinck, R. G. S.; Hatano, T.; Okuda, T.; Yoshida, T. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1995; p 1.

(2) Haslam, E. *Plant Polyphenols-Vegetable Tannins Revisited*; Cambridge University Press: Cambridge, 1989.

(3) Haslam, E.; Cai, Y. *Nat. Prod. Rep.* **1994**, 41.

(4) Quideau, S.; Feldman, K. *Chem. Rev.* **1996**, *96*, 475.

(5) Okuda, T.; Yoshida, T.; Hatano, T. In *Economic and medicinal plant research, Vol. 5, plants and traditional medicines*; Wagner, H. S., Farnsworth, N. R., Eds.; Academic Press: London, 1991; p 129.

(6) Okuda, T.; Yoshida, T.; Hatano, T. In *Phenolic Compounds in Food and their Effects on Health, II*; Huang, M.-T., Ho, C.-T., Lee, C. Y., Eds.; American Chemical Society: Washington, DC, 1992; p 160.

(7) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 1162.

(8) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742.

(9) (a) Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171. (b) Zehari, U.; Amit, B.; Patchornik, A. *J. Org. Chem.* **1972**, *37*, 2281.

(10) Feldman, K. S.; Quideau, S.; Appel, H. M. *J. Org. Chem.* **1996**, *61*, 6656.

(11) (a) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577. (b) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567

(12) (a) Khanbabaee, K.; Lötzerich, K. *Tetrahedron* **1997**, *53*, 10725. (b) Khanbabaee, K.; Lötzerich, K. *Liebigs Ann. Chem.* **1997**, 1571.

(13) (a) Itoh, T.; Chika, J.-i. *J. Org. Chem.* **1995**, *60*, 4968. (b) Itoh, T.; Chika, J.-i.; Shirakami, S.; Ito, H.; Yoshida, T.; Kubo, Y.; Uenishi, J.-i. *J. Org. Chem.* **1996**, *61*, 3700.

(14) Miyamoto, K.-I.; Kishi, N.; Koshiura, R.; Yoshida, T.; Hatano, T.; Okuda, T. *Chem. Pharm. Bull.* **1987**, *35*, 814.

(15) Miyamoto, K.-I.; Murayama, T.; Nomura, M.; Hatano, T.; Yoshida, T.; Furukawa, T.; Koshiura, R.; Okuda, T. *Anticancer Res.* **1993**, *13*, 37.

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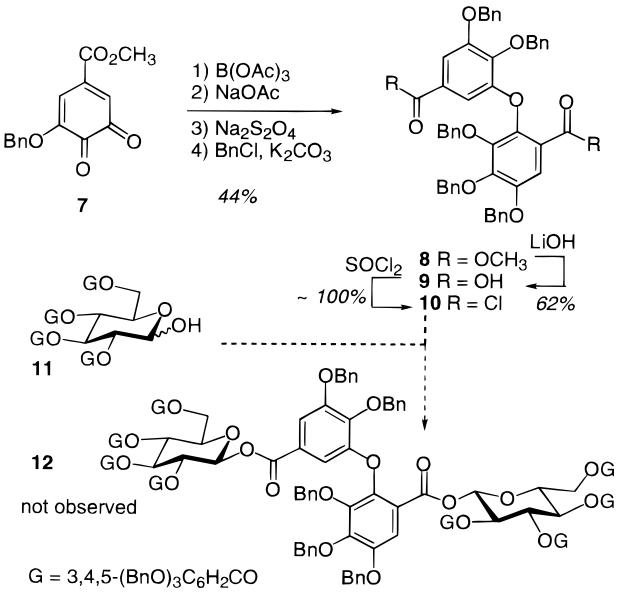
monomeric tannins tellimagrandin I (**3**), tellimagrandin II (**2**), β-D-PGG (**1**), and pedunculagin (**4**) are much less effective antitumor agents (no regressors, 27%−82% increase in life span). Some structural requirements for antitumor activity among these ellagitannins are immediately evident from these data. Among the monomeric species, the presence of HHDP units is not critical for biological activity, but the presence of an anomeric galloyl group leads to improved potency. Within the dimeric species, the anomeric stereochemistry does not affect antitumor efficacy. Could a simple *dimeric gallotannin* that meets these structural requirements exhibit biological activity? To test this premise, the dimeric gallotannin **6** has been synthesized. Compound **6** is a gallotannin analogue of the naturally occurring dimeric ellagitannin coriariin A (**5**) and is identical to the parent compound except that it lacks the O(4)/O(6) coupled HHDP units of coriariin A. The synthesis of this compound also serves to model a synthesis plan for coriariin A. In addition, the biomimetic synthesis of the monomeric precursor to coriariin A, tellimagrandin II (**2**), is reported.

Results and Discussion

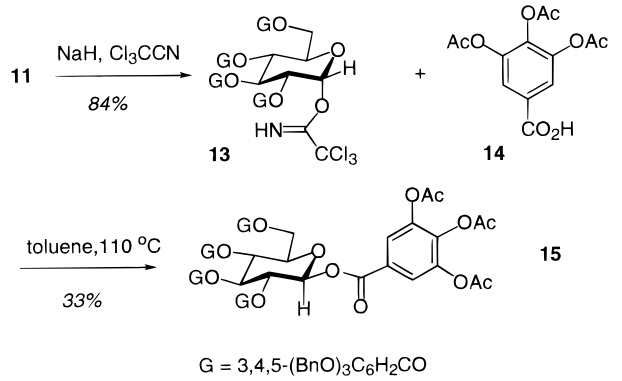
Any strategy directed toward the synthesis of **6** must address two key issues: (1) formation of the dehydrodigalloyl ether linking unit and (2) establishment of the β-anomeric galloyl linkage with stereochemical control. The former goal might be approached by application of methodology developed in-house for the synthesis of simple dehydrodigalloyl ethers.[10] The latter point will be explored initially within the context of a tellimagrandin II synthesis effort. In addition to anomeric ester stereochemistry, the tellimagrandin II synthesis requires (1) stereoselective formation of the (*S*)-atropisomer of the HHDP moiety and (2) selective manipulation of the anomeric center in a manner which is compatible with other functional groups present in the molecule. Chemical precedents that bear on these issues can be gleaned from earlier work on the syntheses of tellimagrandin I and sanguin H-5.[8,9] Thus, $Pb(OAc)_4$-mediated oxidative galloyl coupling has proved to be a robust strategy for the preparation of stereochemically secure (*S*)-HHDP units.[7,8] In addition, the photolabile O(1)-*o*-nitrobenzyl moiety has mediated selective protection/deprotection chemistry at the anomeric center in similar polygalloylated glucose systems.[9] Finally, the β-anomeric galloyl linkages in both **6** and tellimagrandin II (**2**) might be secured by coupling the anomeric hydroxyl group of an appropriately protected intermediate with a galloyl chloride in the presence of a suitable base.[9,16]

An initial attempt toward the construction of the dimeric gallotannin **6** followed a strategy wherein the alcohol **11**, obtained by the selective ammonolysis of perbenzyl β-D-PGG, would be coupled with the diacid chloride **10**, Scheme 1. To this end, the dehydrodigallic acid **9** was synthesized from the methyl gallate-derived orthoquinone **7** in five steps.[10] The diacid chloride **10** proved to be extremely susceptible to hydrolysis, and all efforts to isolate **10** failed to furnish acceptable amounts of the pure compound. To circumvent this unanticipated lability, the diacid **9** was treated with thionyl chloride, the thionyl chloride was removed in vacuo, and the resultant crude oil was used directly in the attempted bis acylation. However, all efforts to effect this coupling failed to furnish the fully acylated dimeric compound **12**.

Scheme 1



Scheme 2



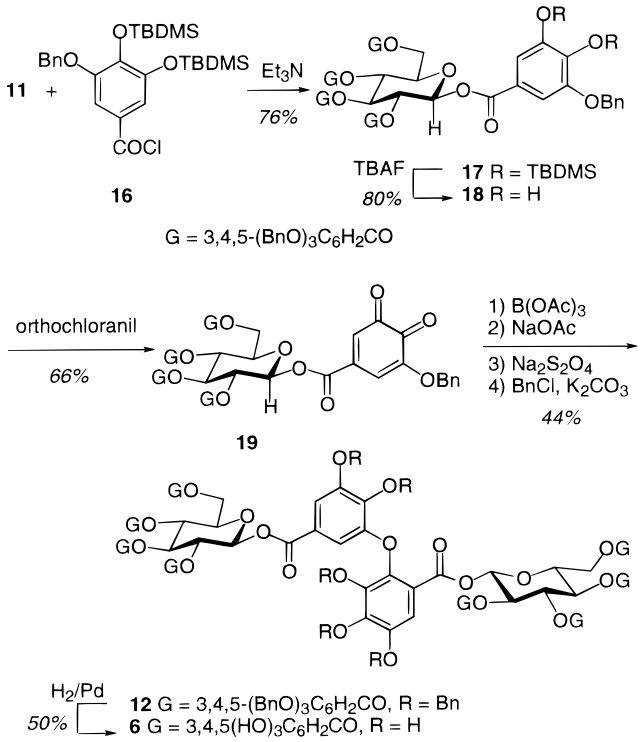
Other unsuccessful trials to achieve this coupling included the reaction of the alcohol **11** directly with the diacid **9** (or with activated derivatives) under various esterification protocols and the reaction of the diacid **9** with the trichloroacetimidate **13** derived from the alcohol **11** (Scheme 2).[17,18] The reaction of the trichloroacetimidate **13** with the acid **14** afforded the O(1)-esterified product **15** in 33% yield but failed to furnish any desired product **12** upon reaction with the diacid **9**.

These failures forced a reevaluation of the synthesis strategy, and eventually a possibly more biomimetic approach via dimerization of two activated β-D-PGG units was pursued. In this route, acylation of **11** with the galloyl chloride **16** in the presence of triethylamine provided the pentaester **17** featuring strictly β-stereochemistry at the anomeric position (Scheme 3). Desilylation of compound **17** furnished the catechol **18** which was oxidized to the orthoquinone **19** with orthochloranil.[10] The orthoquinone **19** precipitated cleanly from the reaction mixture, obviating the need for further purification of this sensitive compound. The $B(OAc)_3$-

(16) Bols, M.; Hansen, H. C. *Acta Chem. Scand.* **1993**, *47*, 818.

(17) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141.
(18) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731.

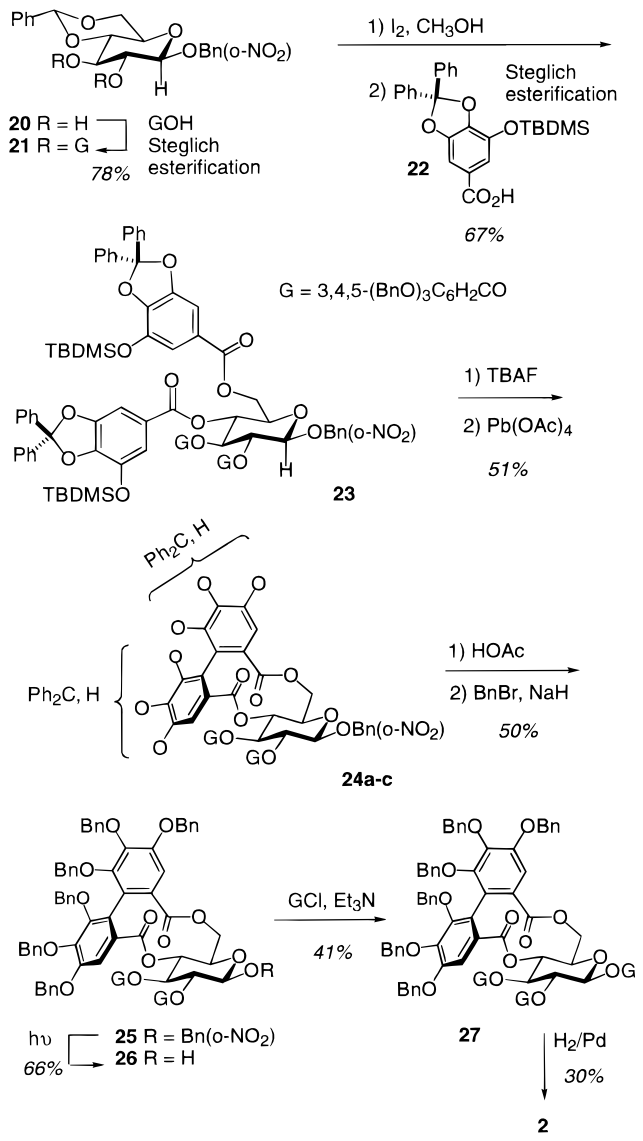
Scheme 3



mediated Diels−Alder dimerization of the orthoquinone **19** followed by a three-step reduction/rearrangement sequence[10] furnished the perbenzylated gallotannin dimer **12** in 44% yield starting from the orthoquinone **19**, in analogy with the preparation of the simple dehydrodigalloyl ether **8** from orthoquinone **7**. In the final step, hydrogenolysis of the benzyl ethers in **12** furnished the dimeric gallotannin **6** in 50% yield.

The synthesis of tellimagrandin II (**2**) began with the known acetal **20** (Scheme 4).[9] Galloylation at the 2 and 3 positions of the carbohydrate core furnished the diester **21** in 78% yield. Deprotection of the O(4), O(6) benzylidene acetal in **21** provided an 84% yield of an intermediate diol which was immediately esterified at both the O(4) and O(6) positions with excess **22** to provide the tetragalloyl compound **23**. Desilylation of bis silyl ether **23** provided the oxidative cyclization precursor. Intramolecular $Pb(OAc)_4$-mediated oxidative coupling of the galloyl groups at the O(4) and O(6) positions in this bis phenol furnished the 4,6-(*S*)-HHDP-bearing compounds **24a**−**c** in 67% yield as a mixture of three regioisomers. Hydrogenolysis of the diphenylmethylene ketals in **24a**−**c** proved to be a capricious reaction, and hence a two-step deprotection/protection strategy was adopted. The diphenylmethylene ketals of **24a**−**c** were cleaved with 80% HOAc, and the resulting hexaphenolic compound was directly benzylated to provide **25**, now as a single isomer, in 50% yield over two steps. The presence of benzyl ethers at all of the phenolic positions proved to be advantageous in the final stages of the tellimagrandin II synthesis because they imparted favorable chromatographic and spectroscopic properties to late intermediates while preserving the means to deliver pure polyphenolic product in the final step. Selective photochemical cleavage of the O(1)-nitrobenzyl ether of **25** furnished a 66% yield of the perbenzylated tellimagrandin I derivative **26** featuring a free anomeric hydroxyl group. Esterification of 3,4,5-tribenzyloxybenzoyl chloride with this alcohol in

Scheme 4



the presence of triethylamine provided **27** as the exclusively *β*-esterified product in 41% yield. In the final step, hydrogenolysis of the benzyl ethers in **27** furnished crude tellimagrandin II, which was purified by repeated filtration and trituration with hexanes and diethyl ether to yield **2** in 30% yield as a gray solid. All spectral data for the chemically synthesized tellimagrandin II (**2**) correlated with the published data for the naturally occurring compound.[19,20] The presence of the (*S*)-HHDP atropisomer was further confirmed by CD measurement.

In summary, the first total synthesis of a dehydrodigalloyl ether-containing dimeric gallotannin **6**, an analogue of coriariin A, from a gallotannin orthoquinone intermediate has been achieved. This synthesis demonstrates the value of the $B(OAc)_3$-mediated Diels−Alder dimerization of orthoquinones in accessing this class of compounds. Additionally, the synthesis of tellimagrandin II (**2**), a possible biosynthetic precursor to coriariin A, has been completed. The application of the methodology developed for the synthesis of these two compounds

(19) Gupta, R. K.; Al-Shafi, S. M. K.; Layden, K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2525.
(20) Nonaka, G.-I.; Harada, M.; Nishioka, I. *Chem. Pharm. Bull.* **1980**, *28*, 687.

toward the synthesis of the more complex target coriariin A is currently in progress.

Experimental Section

Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded on either 200, 300, or 360 MHz (^{1}H) spectrometers. Low-resolution fast atom bombardment mass spectra (FABMS) were obtained in a 2-nitrophenyl octyl ether (NPOE) matrix or in a nitrobenzyl alcohol (NBA) matrix. High-resolution fast atom bombardment mass spectra were run at the University of Texas at Austin. Circular dichroism (CD)[21,22] measurements used the wavelength range 200−350 nm, scanning at 0.5 nm intervals with an averaging time of 10.0 s at 25 °C in a 1 mm cell. The concentration of the solution(s) used was 1 mg/ mL. Liquid (flash) column chromatography[23] was carried out using 32−63 μm silica gel and the indicated solvent. Combustion analyses were performed by Midwest Microlab, Indianapolis, IN or Galbraith Laboratories, Knoxville, TN. Ether (Et_2O) and tetrahydrofuran (THF) were purified by distillation from sodium/benzophenone under nitrogen. Benzene, methylene chloride (CH_2Cl_2), methanol, and toluene were distilled from CaH_2 under nitrogen. Moisture-sensitive reactions were carried out in predried glassware under an inert atmosphere of Ar. Copies of ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information to establish purity for those compounds that were not subjected to combustion analyses.

Modified Steglich Esterification[24,25] Reaction: General Procedure A. A solution of the appropriate polyol (1.0 equiv), acid (1 equiv per hydroxyl), 4-(dimethylamino)pyridine (DMAP) (0.5 equiv), DMAP·HCl (0.5 equiv), and 1,3-dicyclohexylcarbodiimide (DCC) (1.25 equiv per hydroxyl) in dry CH_2Cl_2 (0.1 M in acid) was purged with Ar and heated under Ar at reflux for 15−20 h. The solution was cooled to room temperature, diluted with an equal volume of Et_2O, and filtered through Celite; the filtrate was poured into ice-cold 1 M H_3PO_4. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography using the solvents indicated.

Modified Steglich Esterification Reaction: General Procedure B. A solution of the appropriate polyol (1.0 equiv), acid (1 equiv per hydroxyl), 4-(dimethylamino)pyridine (DMAP) (0.5 equiv), DMAP·HCl (0.5 equiv), and 1,3-dicyclohexylcarbodiimide (DCC) (1.5 equiv per hydroxyl) in dry CH_2Cl_2 (0.1 M in acid) was purged with Ar and heated under Ar at reflux for 15−20 h. The solution was cooled to room temperature and filtered through Celite. The filtrate was diluted with an equal volume of EtOAc and poured into ice-cold 1 M H_3PO_4. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography with the indicated eluent to furnish the desired esters.

Silyl Ether Deprotection Reaction: General Procedure C. To a solution of the appropriate *tert*-butyldimethylsilyl (TBDMS)-protected glucose derivative (1.0 equiv) in dry THF (0.01−0.05 M in TBDMS-protected glucose derivative) was added a solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (1.0 M solution in THF) (1.5 equiv per TBDMS group). The reaction was stirred at room temperature and followed by TLC (10−45 min). At the end of the indicated time period, the reaction solution was carefully treated with ice-cold 1 M H_3PO_4, and the product was extracted with Et_2O. The Et_2O layer was separated, washed with water and then brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude residue using the indicated solvents provided the pure product.

2,3,4,6-Tetrakis(3,4,5-tris(benzyloxy)benzoyl)-α-D-glucopyranose (11). 1,2,3,4,6-Pentakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside[26] (7.0 g, 3.1 mmol) was dissolved in a mixture of 200 mL of dry THF and 100 mL of dry MeOH and cooled to 0 °C. Ammonia gas was bubbled through the solution for 10 min. The reaction was stirred at 0 °C for 30 min, allowed to warm to room temperature, and stirred for a further period of 2.5 h. Removal of the solvents followed by flash column chromatography eluting with 10%, 25%, and then 50%, EtOAc in hexanes furnished 4.16 g (73%) of 2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-D-glucopyranose (**11**) as a white solid froth (mixture of α and β anomers). A portion of this product (30 mg) was further purified by preparative TLC using 10% EtOAc in benzene to provide 22 mg of **11**: IR (CH_2Cl_2) 3483, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−6.64 (m, 68 H), 6.23, (t, J = 9.9 Hz, 1 H), 5.79 (d, J = 3.7 Hz, 1 H), 5.70 (t, J = 9.9 Hz, 1 H), 5.75−4.65 (m, 27 H), 4.29 (dd, J = 4.3 Hz, 12.1 Hz, 1 H), 3.40 (bs, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 166.7, 165.7, 165.4, 165.1, 152.54, 152.50, 152.4, 143.1, 142.9, 142.8, 142.7, 142.6, 137.4, 137.35, 137.3, 136.6, 136.45, 136.4, 136.33, 136.3, 128.5, 128.4, 128.33, 128.2, 128.1, 128.07, 128.05, 128.0, 127.94, 127.9, 127.86, 127.8, 127.78, 127.56, 127,51, 127.4, 127.3, 124.6, 124.1, 123.9, 109.4, 109.3, 109.1, 90.4, 75.1, 75.0, 72.8, 71.2, 71.1, 70.9, 70.0, 67.6, 63.1; MS (+FAB) 1869 (MH^+, 0.5). Anal. Calcd for $C_{118}H_{100}O_{22}$: C, 75.80; H, 5.35. Found: C, 76.13; H, 5.45.

Methyl 3-Benzyloxy-1,2-dioxocyclohexa-3,5-diene-5-benzoate (7). To a solution of orthochloranil (1.97 g, 8.02 mmol) in 5 mL of Et_2O cooled to −30 °C was added dropwise via an addition funnel over 6 h a solution of methyl 3-benzyloxy-4,5-dihydroxybenzoate (2.0 g, 7.3 mmol) in 115 mL of Et_2O. The reaction was stirred for a further 0.5 h at −30 °C and then stored at −20 °C for 20 h. The precipitated red solid was collected by filtration, washed with cold Et_2O, and dried on a vacuum pump to afford 1.11 g (55%) of the orthoquinone **7**: IR ($CDCl_3$) 1727, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.26 (m, 5 H), 6.74 (s, 1 H), 6.73 (s, 1 H), 6.56 (s, 2 H), 3.92 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.9, 174.2, 164.7, 152.1, 141.3, 134.3, 128.8, 128.7, 127.7, 124.4, 107.7, 71.1, 53.4; MS (−FAB) 272 (M−, 12). Anal. Calc for $C_{15}H_{12}O_5$: C, 66.18; H, 4.41; Found: C, 65.75; H, 4.45.

Diaryl Ether 8. The orthoquinone **7** (200 mg, 0.72 mmol) was dissolved in 5 mL of $CDCl_3$. $B(OAc)_3$ (136 mg, 0.72 mmol) was added, and the heterogeneous mixture was heated at 62−65 °C (oil bath temperature) for 15 h, at which time ^{1}H NMR analysis indicated the absence of the orthoquinone. The reaction mixture was cooled and filtered. The $B(OAc)_3$ pellet was washed with cold CH_2Cl_2, and the filtrate and washings were evaporated to give a brown oil which was immediately stirred with NaOAc (60 mg, 0.76 mmol) in 5 mL of HOAc for 2 h. This reaction mixture was partitioned between EtOAc and water, and the organic layer was washed with brine and dried (Na_2SO_4). Concentration of the organic layer in vacuo furnished a yellow oil which was purified by flash column chromatography (−78 °C, under argon) to yield 150 mg of a regioisomeric mixture of dehydrodigalloyl quinones as a yellow solid. The mixture of quinones was immediately stirred with $Na_2S_2O_4$ (180 mg, 1.08 mmol) in 8 mL of THF/ 2 mL of water at 0 °C for 10 min. The dark yellow reaction mixture decolorized to a pale yellow solution over this time. The reaction mixture was partitioned between EtOAc and water, and the organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to furnish 150 mg of a white solid (regioisomeric mixture of dehydrodigalloyl ethers). The crude white solid (150 mg, 0.27 mmol) was benzylated with BnCl (126 μL, 1.10 mmol), K_2CO_3 (190 mg, 1.37 mmol), and KI (27 mg, 0.16 mmol) in 30 mL of refluxing acetone for 24 h. The reaction mixture was cooled and filtered through Celite, and the filtrate was concentrated in vacuo to an oil which was purified by flash column chromatography using 1:1 Et_2O/ hexanes to furnish 98 mg of **8** (44%, starting from **7**): IR (CH_2-

(21) Okuda, T.; Yoshida, T.; Hatano, T.; Koga, T.; Toh, N.; Kuriyama, K. *Tetrahedron Lett.* **1982**, *23*, 3937.
(22) Okuda, T.; Yoshida, T.; Hatano, T. *J. Nat. Prod.* **1989**, *52*, 1.
(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(24) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(25) Keck, G. E.; Boden, E. P. *J. Org. Chem.* **1985**, *50*, 2394.
(26) Armitage, R.; Bayliss, G. S.; Gramshaw, J. W.; Haslam, E.; Haworth, R. D.; Jones, K.; Rogers, H. J.; Searle, T. *J. Chem. Soc.* **1961**, 1842.

Cl_2) 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.13 (m, 27 H), 6.90 (d, J = 1.8 Hz, 1 H), 5.14 (s, 4 H), 5.12 (s, 4 H), 4.97 (s, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 166.4, 165.2, 152.6, 149.9, 146.8, 146.5, 142.5, 141.7, 137.9, 136.8, 136.7, 136.6, 136.3, 128.61, 128.6, 128.5, 128.34, 128.3, 129.2, 128.1, 127.96, 127.9, 127.7, 127.5, 125.0, 119.8, 110.8, 109.14, 109.12, 75.6, 75.3, 75.1, 71.4, 71.2, 52.3, 52.1; MS (+FAB) 816.5 (M^+, 100); HRFABMS calcd for $C_{51}H_{44}O_{10}$ 816.2934, found 816.2933.

3,4,5,3′,4′-Pentabenzyloxydehydrodigallic Acid (9). The diaryl ether **8** (0.30 g, 0.37 mmol) and lithium hydroxide hydrate (0.15 g, 3.7 mmol) in 16 mL of a 3:1 MeOH/water mixture were brought to reflux and held there with TLC monitoring for 3.5 h. The reaction mixture was cooled, and the solvents were removed in vacuo. Flash column chromatography on the residue using 50% EtOAc in hexanes and then 1% HOAc in EtOAc as eluents furnished 0.18 g (62%) of the diacid **9** as a white solid: IR (KBr pellet) 2629, 1688 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 7.57−7.17 (m, 27 H), 6.96 (d, J = 1.7 Hz, 1 H), 5.26 (s, 2 H), 5.22 (s, 2 H), 5.20 (s, 2 H), 5.15 (s, 2 H), 5.01 (s, 2 H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 167.2, 165.9, 153.8, 150.9, 150.5, 149.0, 147.5, 147.2, 143.1, 142.5, 139.1, 138.0, 137.9, 137.7, 137.6, 129.4, 129.3, 129.2, 129.1, 128.97, 128.92, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 126.3, 121.3, 111.7, 109.8, 76.1, 75.9, 75.6, 71.9, 71.7, 52.2, 52.0; MS (+FAB) 788.5 (M+, 100); HRFABMS calcd for $C_{49}H_{40}O_{10}$ 788.2621, found 788.2614.

1-*O*-2,3,4,6-Tetrakis(3,4,5-tris(benzyloxy)benzoyl)-α-D-glucopyranosyl Trichloroacetimidate (13). A solution of 2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-D-glucopyranose (**11**) (1.0 g, 0.54 mmol) in 10 mL of dry benzene was added to degreased sodium hydride (0.014 g, 0.58 mmol), followed by addition of trichloroacetonitrile (536 μL, 5.20 mmol), and the resultant solution was stirred at room temperature for 18 h. The reaction was diluted with water, and the product was extracted into 25 mL of EtOAc. The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solution was concentrated in vacuo and purified by flash column chromatography using 10% and then 20% EtOAc in hexanes as eluent to afford 0.90 g (84%) of 1-*O* −2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-α-D-glucopyranosyl trichloroacetimidate (**13**) as a white solid: IR (CH_2Cl_2) 3342, 1728, 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.65 (S, 1 H), 7.41−7.15 (m, 68 H), 6.88 (d, J = 3.6 Hz, 1 H), 6.21 (t, J = 10.1 Hz, 1 H), 5.73 (t, J = 10.1 Hz, 1 H), 5.54 (dd, J = 3.7 Hz, 10.2 Hz, 1 H), 5.13−4.88 (m, 24 H), 4.82−4.65 (m, 2 H), 4.32 (dd, J = 5.0 Hz, 12.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 165.54, 165.50, 165.1, 165.0, 160.5, 152.60, 152.57, 152.51, 152.50, 143.3, 143.1, 142.8, 137.4, 137.3, 136.6, 136.5, 136.4, 136.3, 128.52, 128.50, 128.43, 128.40, 128.34, 128.30, 128.24, 128.20, 128.13, 128.11, 128.10, 128.0, 127.96, 127.9, 127.82, 127.8, 127.6, 127.52, 127.50, 124.6, 123.9, 123.5, 109.6, 109.4, 109.2, 109.1, 93.2, 90.8, 75.1, 71.3, 71.21, 71.20, 71.11, 71.1, 70.8, 69.2, 62.8; MS (+FAB) 2012 (MH^+, 78). Anal. Calcd for $C_{120}H_{100}Cl_3NO_{22}$: C, 71.61; H, 4.97; Cl, 5.22; N, 0.70. Found: C, 71.61; H, 5.07; Cl, 5.42; N, 0.72.

1-*O*-3,4,5-Triacetoxybenzoyl-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (15). A solution of 1-*O*-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-α-D-glucopyranosyl trichloroacetimidate (**13**) (170 mg, 0.08 mmol) and 3,4,5-triacetoxybenzoic acid (**14**) (25 mg, 0.08 mmol) in 0.8 mL of dry toluene was brought to reflux and held there for 18 h. The reaction was cooled, the solvent was removed in vacuo, and the residue was purified by silica gel flash column chromatography using 20%, 40%, and then 60% EtOAc in hexanes as eluent to yield 60 mg (33%) of 1-*O*-3,4,5-triacetoxybenzoyl-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**15**) as a white solid: IR (CH_2Cl_2) 1738, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81(s, 1 H), 7.46−7.16 (m, 69 H), 6.27 (d, J = 8.2 Hz, 1 H), 6.05 (t, J = 9.7 Hz, 1 H), 5.81 (t, J = 9.1 Hz, 1 H), 5.69 (t, J = 9.6 Hz, 1 H), 5.15−4.88 (m, 24 H), 4.75 (d, J = 10.1 Hz, 1 H), 4.42−4.32 (m, 2 H), 2.27 (s, 3 H), 2.25 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.6, 166.4, 165.8, 165.2, 165.1, 162.9, 152.8, 152.73, 152.7, 143.8, 143.3, 142.7, 139.7, 137.7, 137.6, 137.5, 136.9, 136.7, 136.6, 136.5, 128.7, 128.6, 128.53, 128.50, 128.4, 128.3, 128.21, 128.20, 128.1, 128.0, 127.8, 127.79, 127.75, 126.8, 124.7, 123.8, 123.7, 123.1, 109.6, 109.5, 109.3, 109.2, 93.3, 75.33, 75.3, 73.53, 73.5, 71.4, 71.3, 71.2, 69.9, 63.4, 20.8, 20.3; MS (+FAB) 2147 (MH^+, 25). Anal. Calcd for $C_{131}H_{110}O_{29}$: C, 73.25; H, 5.13. Found: C, 72.84; H, 5.34.

3,4-Di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoic Acid. A solution of 3-benzyloxy-4,5-dihydroxybenzoic acid (3.00 g, 11.5 mmol) and *tert*-butyldimethylsilyl chloride (4.34 g, 28.8 mmol) in 13 mL of DMF (minimum volume required to dissolve the reactants) was treated with *N*,*N*′-diisopropylethylamine (6.0 mL, 35 mmol). The turbid brown solution was stirred at room temperature for 18 h, at which time TLC indicated complete absence of starting material and the presence of 3,4-di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoic acid along with 3,4-di-*tert*-butyldimethylsilyl (3,4-di-*tert*-butyldimethylsiloxy-5-benzyloxy)benzoate. The reaction mixture was treated with 20 mL of 1 M H_3PO_4 and extracted with 200 mL of Et_2O. The organic layer was separated and washed with water (10 × 50 mL) and then brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10%, and then 25%, EtOAc in hexanes, to yield 1.53 g of the title compound as a white solid along with 3.61 g of 3,4-di-*tert*-butyldimethylsilyl (3,4-di-*tert*-butyldimethylsiloxy-5-benzyloxy)benzoate as a yellow oil. The silyl ester product was stirred in 60 mL of a 1:6:2 solution of HOAc/THF/water at room temperature for 2.5 h, at which time TLC showed the presence of only the title compound. The reaction solution was treated with a saturated aqueous solution of sodium bicarbonate and extracted into EtOAc. The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). Removal of the solvent in vacuo followed by trituration of the residue with hexanes afforded a further 2.52 g of 3,4-di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoic acid (4.05 g over two steps, 71%): IR (CH_2Cl_2) 3504, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.33 (m, 7 H), 5.05 (s, 2 H), 0.99 (s, 9 H), 0.90 (s, 9 H), 0.24 (s, 6 H), 0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 151.2, 147.7, 136.2, 128.6, 128.4, 128.2, 116.3, 107.8, 70.9, 26.1, 25.8, 19.0, 18.6, −3.8, −4.1; MS (+FAB) 488 (MH^+, 52). Anal. Calcd for $C_{26}H_{40}O_5Si_2$: C, 63.93; H, 8.19. Found: C, 64.17, H, 8.00.

3,4-Di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoyl Chloride (16). A solution of 3,4-di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoic acid (1.50 g, 3.07 mmol) in 30 mL of CH_2Cl_2 was treated with oxalyl chloride (295 μL, 3.38 mmol) and then a catalytic amount of DMF. The reaction was stirred at room temperature with monitoring by TLC. After 2 h, consumption of starting material was indicated, and removal of solvents in vacuo and drying under high vacuum provided 1.55 g (100%) of **16**: IR (CH_2Cl_2) 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44−7.34 (m, 7 H), 5.05 (s, 2 H), 0.99 (s, 9 H), 0.90 (s, 9 H), 0.26 (s, 6 H), 0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 151.3, 147.9, 143.9, 135.7, 128.8, 128.5, 128.4, 124.6, 118.2, 108.9, 71.2, 26.0, 25.7, 18.7, 18.6, −4.0, −4.1; MS (+FAB) (MH+, 24); HRFABMS calcd for $C_{26}H_{39}O_4Si_2Cl$ 507.2154, found 507.2126.

1-*O*-(3,4-Di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoyl)-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (17). Triethylamine (116 μL, 1.62 mmol) was added to a solution of 2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-D-glucopyranose (**11**) (1.00 g, 0.54 mmol) and 3,4-di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoyl chloride (**16**) (0.33 g, 0.65 mmol) in 12 mL of dry CH_2Cl_2 (0.05 M in alcohol), and the solution was stirred at room temperature for 18 h. The reaction was treated with 10 mL of 1 M HCl and extracted with 25 mL of EtOAc. The organic layer was separated and washed with water and then brine, dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the crude mixture using 10% and then 25% EtOAc in hexanes as eluents afforded 0.96 g (76%) of 1-*O*-(3,4-*tert*-butyldimethylsiloxy-5-benzyloxybenzoyl)-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**17**) as a white solid froth: IR (CH_2Cl_2) 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.13 (m, 75 H), 6.28 (d, J = 8.2 Hz, 1 H), 6.08 (t, J = 9.7 Hz, 1 H), 5.88 (dd, J = 9.9 Hz, 8.3 Hz, 1 H), 5.78 (t, J = 9.6 Hz, 1 H),

5.17−4.79 (m, 27 H), 4.43−4.38 (m, 2 H), 0.98 (s, 9 H), 0.87 (s, 9 H), 0.25 (s, 3 H), 0.20 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 165.5, 164.9, 164.7, 164.4, 152.5, 152.4, 152.3, 151.1, 147.7, 143.1, 143.0, 142.9, 142.5, 142.2, 137.4, 137.3, 137.2, 136.7, 136.3, 135.9, 128.7, 128.5, 128.4, 128.35, 128.32, 128.24, 128.21, 128.1, 128.06, 128.03, 127.96, 127.90, 127.81, 127.7, 127.5, 127.4, 124.5, 123.8, 123.7, 123.66, 123.6, 120.0, 116.1, 109.3, 109.1, 107.8, 92.7, 75.1, 75.0, 73.5, 73.1, 71.1, 71.0, 70.9, 70.8, 69.8, 63.2, 26.0, 25.7, 18.5, 18.4, −3.4, −3.5. Anal. Calcd for $C_{144}H_{138}O_{26}Si$: C, 73.90; H, 5.90. Found: C, 73.91; H, 5.94.

1-*O*-(2-Benzyloxy-4,5-dihydroxybenzoyl)-2,3,4,6-tetrakis-(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (18). By use of general procedure C, 1-*O*-(3,4-di-*tert*-butyldimethylsiloxy-5-benzyloxybenzoyl)-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**17**) (1.10 g, 0.47 mmol) (0.02 M solution in THF) was desilylated in 45 min to provide 0.80 g (80%) of 1-*O*-(3-benzyloxy-4,5-dihydroxybenzoyl)-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**18**) after flash column chromatography using 10%, 25%, and then 50% EtOAc in hexanes as eluents: IR ($CDCl_3$) 3534, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.16 (m, 75 H), 6.24 (d, J = 8.1 Hz, 1 H), 6.04 (t, J = 9.6 Hz, 1 H), 5.96 (bs, 1 H), 5.83 (dd, J = 9.7, 8.1 Hz, 1 H), 5.73 (t, J = 0.6 Hz, 1 H), 5.50 (bs, 1 H), 5.14−4.76 (m,27 H), 4.43−4.34 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 165.5, 165.0, 164.9, 164.3, 152.59, 152.57, 152.47, 145.7, 143.7, 143.3, 143.2, 143.1, 142.6, 138.1, 137.5, 137.3, 136.4, 136.3, 135.6, 128.7, 128.6, 128.5, 128.45, 128.40, 128.3, 128.2, 128.1, 128.09, 128.06, 127.9, 127.8, 127.5, 124.6, 123.8, 123.7, 123.6, 119.9, 111.9, 109.4, 109.3, 109.2, 106.7, 92.9, 75.1, 75.08, 73.4, 73.37, 73.3, 71.4, 71.34, 71.3, 71.22, 71.2, 71.1, 69.9, 63.2. Anal. Calcd for $C_{132}H_{110}O_{26}$: C, 75.07; H, 5.21. Found: C, 74.88; H, 5.22.

1-*O*-(3-Benzyloxy-1,2-dioxocyclohexa-3,5-diene-5-benzoyl)-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (19). To a solution of orthochloranil (100 mg, 0.38 mmol) in 4 mL of dry Et_2O (0.1 M in orthochloranil), cooled to −30 °C, was added dropwise via an addition funnel over 1.5 h a solution of 1-*O*-(2-benzyloxy-4,5-dihydroxybenzoyl)-2,3,4,6-tetrakis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**18**) (0.80 g, 0.38 mmol) in 12 mL of dry Et_2O (0.03 M in diphenol). After the addition was completed, the resulting deep red solution was stirred at −30 °C for a further 3 h, and then it was stored in a freezer at − 20 °C for 18 h. The precipitated red solid was collected by filtration, washed with cold Et_2O, and dried on a vacuum pump to afford 0.53 g (66%) of **19** as a red amorphous powder: IR ($CDCl_3$) 1730, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.17 (m, 73 H), 6.79 (d, J = 1.4 Hz, 1 H), 6.47 (s, 1 H), 6.13 (d, J = 7.9 Hz, 1 H), 6.03 (t, J = 9.6 Hz, 1 H), 5.74 (t, J = 9.2 Hz, 2 H), 5.15−4.85 (m, 26 H), 4.79 (d, J = 9.5 Hz, 1 H), 4.41−4.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 179.6, 173.8, 165.6, 165.5, 164.9, 164.8, 162.8, 152.6, 152.5, 152.4, 143.3, 143.2, 140.1, 137.4, 137.3, 136.6, 136.3, 136.2, 134.2, 128.8, 128.6, 128.5, 128.49, 128.42, 128.3, 128.2, 128.14, 128.10, 127.99, 127.92, 127.88, 127.85, 127.83, 127.76, 127.5, 125.6, 124.4, 123.4, 123.3, 109.4, 109.3, 109.2, 106.8, 93.8, 75.1, 73.5, 72.9, 71.2, 71.18, 71.12, 71.0, 69.3, 62.8; MS (+FAB) 2109 (MH$^+$, 21). Anal. Calcd for $C_{132}H_{108}O_{26}$: C, 75.14; H, 5.12. Found: C, 74.75; H, 5.29.

Benzylated Dimer 12. The orthoquinone **19** (100 mg, 0.047 mmol) was dissolved in 1.5 mL of $CDCl_3$. $B(OAc)_3$ (10 mg, 0.052 mmol) was added, and the heterogeneous mixture was heated at 62−65 °C (oil bath temperature) for 24 h, at which time ^{1}H NMR analysis indicated absence of the orthoquinone. The reaction mixture was cooled and filtered. The residue was washed with CH_2Cl_2, and the filtrate and washings were evaporated to give a reddish brown solid which was immediately treated with NaOAc (4 mg, 0.052 mmol) in HOAc (2 mL)/THF (0.5 mL) for 2 h. This reaction mixture was partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield a yellow residue. Flash column chromatography at −78 °C using 10% and then 50% EtOAc in hexanes as eluents provided 78 mg of a yellow solid which was immediately treated with $Na_2S_2O_4$ (2 mg, 0.071 mmol) in 10 mL of 8:2 THF/water for 10 min at 0 °C. The dark yellow reaction mixture decolorized to a pale yellow solution over this time. The reaction mixture was partitioned between EtOAc and water, and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a white solid which was dried under high vacuum. The crude white solid (78 mg, 0.018 mmol) was benzylated with benzyl chloride (9 μL, 0.07 mmol), K_2CO_3 (13 mg, 0.09 mmol), and KI (92 mg, 0.01 mmol) in 5 mL of refluxing acetone for 24 h. The reaction mixture was cooled and filtered through Celite, and the filtrate was concentrated in vacuo to an oil which was purified by flash column chromatography using 10% and then 20% EtOAc in hexanes as eluents to furnish 46 mg (44%, over four steps) of the perbenzylated dimeric gallotannin **12**: IR (CH_2Cl_2) 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64−7.05 (m, 163 H), 7.04 (s, 1 H), 6.23 (d, J = 8.1 Hz, 1 H), 6.08 (m, 2 H), 5.94 (t, J = 9.8 Hz, 1 H), 5.84 (t, J = 9.0 Hz, 1 H), 5.74 (t, J = 9.7 Hz, 1 H), 5.70−5.62 (m, 2 H), 5.15−4.70 (m, 59 H), 4.58−4.31 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.0, 165.62, 165.6, 165.0, 164.9, 164.7, 164.2, 152.6, 152.54, 152.5, 143.3, 143.21, 143.2, 143.1, 142.7, 137.5, 137.4, 136.7, 136.5, 136.4, 136.3, 128.51, 128.5, 128.42, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.61, 127.6, 127.5, 124.6, 123.7, 123.6, 123.3, 19.5, 109.41, 109.4, 109.2, 93.0, 92.2, 75.1, 73.5, 73.3, 73.2, 71.4, 71.3, 71.2, 71.1, 71.0, 69.8, 69.7, 63.1; MS (+FAB) 4493 (MH$^+$, 35). Anal. Calcd for $C_{285}H_{236}O_{52}$: C, 76.20; H, 5.26. Found: C, 76.07; H, 5.52.

Phenolic Dimer 6. A solution of the dimer **12** (32 mg, 0.007 mmol) and 10% Pd on C (6 mg, 20 wt % of **12**) in 2.5 mL of dry THF was stirred at room temperature under a balloon of H_2 at 1 atm for 20 h, purged several times with argon, filtered twice through Celite, and concentrated under reduced pressure. The resultant brown-gray residue was triturated with Et_2O, hexanes, and then benzene to yield 6 mg (50%) of the debenzylated dimeric gallotannin **6** as a pale gray solid: ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.42−6.93 (m, 18 H), 6.78 (s, 1 H), 6.32 (d, J = 8.3 Hz, 1 H), 6.18 (d, J = 8.3 Hz, 1 H), 6.09−5.87 (m, 2 H), 5.69−5.39 (m, 4 H), 4.56−4.25 (m, 6 H); ^{13}C NMR (acetone-d_6, 90 MHz) δ 169.4, 166.4, 165.9, 165.8, 165.6, 165.5, 164.9, 146.0, 145.8, 139.3, 139.1, 129.3, 129.2, 128.5, 121.5, 120.7, 120.6, 120.0, 110.4, 110.3, 110.1, 93.4, 92.9, 74.0,73.3, 71.8, 69.3, 69.2, 66.9, 62.8; MS (+FAB) 1879 (MH$^+$, 22), 1901 (M + Na$^+$, 36); HRFABMS calcd for $C_{82}H_{62}O_{52}$ 1878.2207, found 1878.2190; calcd for $C_{82}H_{62}O_{52}Na$ 1901.2105, found 1901.2085.

2-Nitrobenzyl 4,6-*O*-Benzylidene-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (21). By use of general procedure A, 2-nitrobenzyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**20**)[9] (5.20 g, 12.9 mmol) and 3,4,5-tribenzyloxybenzoic acid (11.4 g, 25.8 mmol) were coupled to afford 12.6 g (78%) of 2-nitrobenzyl 4,6-*O*-benzylidene-2,3-bis(3,4,5-tris(benzyloxy)-benzoyl)-β-D-glucopyranoside (**21**) as a white solid foam following flash column chromatography using 10% and then 20% EtOAc in hexanes as eluent: IR ($CDCl_3$) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06−8.03 (m, 1 H), 7.67−7.64 (m, 1 H), 7.44−7.17 (m, 41 H), 5.78 (t, J = 9.5 Hz, 1 H), 5.60−5.55 (m, 2 H), 5.33 (d, J = 15.4 Hz, 1 H), 5.12−4.99 (m, 13 H), 4.94 (d, J = 7.8 Hz, 1 H), 4.49 (dd, J = 10.3 Hz, 4.6 Hz, 1 H), 3.99−3.87 (m, 2 H), 3.77 (dd, J = 9.4 Hz, 4.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 164.9, 152.5, 152.4, 146.6, 142.8, 142.7, 137.3, 136.6, 136.5, 136.4, 133.8, 133.7,129.1, 128.4, 128.3, 128.2, 128.1, 128.06, 128.0, 127.9, 127.8, 127.5, 127.4, 126.1, 124.6, 124.3, 124.0, 109.3, 109.2, 101.5, 101.3, 78.7, 75.1, 72.1, 72.2, 71.2, 68.5, 68.1, 66.8; MS (+FAB) 1248 (MH$^+$, 22). Anal. Calcd for $C_{76}H_{65}NO_{16}$: C, 73.13; H, 5.21; N, 1.12. Found: C, 73.11; H, 5.17; N, 0.92.

2-Nitrobenzyl 2,3-Bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside. A solution of 2-nitrobenzyl 4,6-*O*-benzylidene-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**21**) (1.4 g, 1.1 mmol) and iodine (0.28 g, 1.1 mmol) in 17 mL of dry CH_3OH and 17 mL of dry CH_2Cl_2 was heated at reflux under Ar for 48 h. The solution was cooled to room temperature, treated with a saturated aqueous solution of $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was separated, washed with water and then brine, dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography

using 30% and then 50% EtOAc in benzene provided 1.10 g (84%) of 2-nitrobenzyl 2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside as a white solid froth: IR (CH_2Cl_2) 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04−8.01 (m, 1 H), 7.64−7.60 (m, 1 H), 7.43−7.17 (m, 36 H), 5.53 (dd, *J* = 9.7 Hz, 8.0 Hz, 1 H), 5.33−5.27 (m, 2 H), 5.13−4.83 (m, 13 H), 4.96 (d, *J* = 8.0 Hz, 1 H), 4.91−4.84 (m, 1 H), 4.04−3.93 (m, 3 H), 3.64−3.60 (m, 1 H), 3.56 (bs, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 165.1, 152.6, 146.8, 137.3, 136.4, 133.8, 133.7, 128.52, 128.5, 128.44, 128.4, 128.14, 128.1, 127.99, 127.91, 127.6, 127.53, 127.5, 124.7, 124.0, 123.5, 109.3, 109.2, 100.7, 78.1, 75.1, 71.6, 71.2, 71.1, 71.0, 69.9, 68.1, 62.1; MS (+FAB) 1159 (M^+, 18). Anal. Calcd for $C_{69}H_{61}NO_{16}$: C, 71.44; H, 5.26; N, 1.21. Found: C, 71.30; H, 5.45; N, 1.18

2-Nitrobenzyl 4,6-Bis(3-*tert*-butyldimethylsiloxy-4,5-diphenylmethyl-enedioxybenzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (23). By use of general procedure B, 2-nitrobenzyl 2,3-bis(3,4,5-tris(benzyloxy)-benzoyl)-β-D-glucopyranoside (2.10 g, 1.81 mmol) was coupled with 3-*tert*-butyldimethylsiloxy-4,5-diphenylmethylenedioxybenzoic acid (**22**) (1.62 g, 3.62 mmol) to afford 2.99 g (80%) of 2-nitrobenzyl 4,6-bis(3-*tert*-butyldimethylsiloxy-4,5-diphenylmethylenedioxybenzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**23**) as a white solid foam following flash column chromatography using 10% and then 20% EtOAc in hexanes as eluent: IR (CH_2Cl_2) 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 75 MHz) δ 8.05(d, *J* = 1.3 Hz, 1 H), 7.98 (d, *J* = 4 Hz, 1 H), 7.70−7.15 (m, 60 H), 5.84 (t, *J* = 9.7 Hz, 1 H), 5.67−5.56 (m, 2 H), 5.31 (d, *J* = 15.2 Hz, 2 H), 5.13−4.89 (m, 14 H), 4.64, (d, *J* = 10.6 Hz, 1 H), 4.38−4.32 (m, 1 H), 4.15−4.12 (m, 1 H), 0.99 (s, 9 H), 0.96 (s, 9 H), 0.19 (s, 6 H), 0.18 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 165.3, 164.9, 164.4, 152.5, 148.6, 146.8, 142.8, 142.0, 141.7, 139.9, 139.6, 138.6, 137.4, 136.5, 133.7, 129.2, 128.9, 128.4, 128.3, 128.1, 128.0, 127.6, 127.5, 126.2, 124.6, 124.2, 124.0, 123.5, 122.5, 119.1, 118.8, 118.2, 109.3, 109.1, 104.1, 100.1, 75.1, 75.0, 73.3, 72.8, 72.3, 71.2, 71.1, 68.9, 68.3, 62.5, 26.05, 26.04, 18.3, 18.2, −4.0; MS (+FAB) 2020 (MH^+, 23). Anal. Calcd for $C_{121}H_{113}NO_{24}Si_2$: C, 71.92; H, 5.59; N, 0.69. Found: C, 72.16; H, 5.80; N, 0.58.

2-Nitrobenzyl 4,6-Bis(3,4-diphenylmethylenedioxy-5-hydroxybenzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside. By use of general procedure C, 2-nitrobenzyl 4,6-bis(3-*tert*-butyldimethylsiloxy-4,5-diphenylmethylenedioxybenzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**23**) (2.64 g, 1.31 mmol) (0.05 M solution in THF) was desilylated in 35 min to afford 1.80 g (77%) of 2-nitrobenzyl 4,6-bis(3,4-diphenylmethylenedioxy-5-hydroxybenzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside following flash column chromatography using 10% and then 40% EtOAc in hexanes as eluent: IR (CH_2Cl_2) 3554, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05−8.02 (m, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.68−7.08 (m, 60 H), 6.26 (bs, 1 H), 5.83 (t, *J* = 9.6 Hz, 1 H), 5.63−5.52 (m, 2 H), 5.42 (d, *J* = 15.8 Hz, 1 H), 5.14−4.87 (m, 14 H), 4.62 (d, *J* = 12.1 Hz, 1 H), 4.31−4.25 (m, 1 H), 4.11−4.06 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 165.4, 164.9, 164.5, 152.5, 148.5, 148.3, 146.3, 142.8, 139.6, 139.2, 138., 138.7, 138.6, 137.4, 137.3, 135.5, 134.4, 134.2, 129.4, 129.3, 128.5, 128.4, 128.35, 128.31, 128.3, 128.2, 128.1, 127.99, 127.90, 127.8, 127.6, 127.5, 126.3, 126.2, 124.8, 124.1, 123.7, 123.6, 122.7, 118.9, 118.7, 114.4, 113.6, 109.3, 109.2, 103.6, 100.7, 75.1, 73.2, 72.7, 72.3, 71.2, 71.1, 69.5, 67.7, 63.2; MS (+FAB) 1792 (MH^+,40). Anal. Calcd for $C_{109}H_{85}NO_{24}$: C, 73.03; H, 4.75; N, 0,78. Found: C, 73.23; H, 4.88; N, 0.55.

Regioisomeric Mixture of 2-Nitrobenzyl 4,6-(3,4-Diphenylmethylenedioxy-5-hydroxy-3′,4′-diphenylmethylenedioxy-5′hydroxy)diphenoyl-2,3-bis(3,4,5-tris(benzyloxy)-benzoyl)-β-D-glucopyranoside (24a−c). A solution of $Pb(OAc)_4$ (0.49 g, 1.10 mmol) in 5 mL of dry CH_2Cl_2 was added dropwise to a cooled (−30 °C) deoxygenated solution of 2-nitrobenzyl 4,6-bis(3,4-diphenylmethylenedioxy-5-hydroxybenzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (1.80 g, 1.0 mmol) and pyridine (326 μL, 4.0 mmol) in 180 mL of dry CH_2Cl_2 (0.005 M in bis phenol) over 30 min. The deep orange solution was stirred at −30 °C for a further 1 h, treated with 100 mL of a saturated aqueous solution of $NaHCO_3$, and extracted with 250 mL of EtOAc. The organic layer was washed with 75 mL of 1 M H_3PO_4 and then brine and dried (Na_2SO_4). Concentration in vacuo, followed by purification of the resultant yellow residue by silica gel chromatography using 10%, 20%, and then 35% EtOAc in hexanes furnished 1.21 g (67%) of a mixture of three regioisomers **24a−c** as a yellow solid: IR (CH_2Cl_2) 1747, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05−8.02 (m, 1 H), 7.98−7.00 (m, 57 H), 6.79−6.71 (m, 2 H), 5.66−5.56 (m, 2 H), 5.48−5.29 (m, 2 H), 5.18−4.79 (m, 15 H), 4.14−3.90 (m, 2 H); MS (+FAB) 1790 (MH^+, 80). Anal. Calcd for $C_{109}H_{83}NO_{24}$: C, 73.11; H, 4.64; N, 0.78. Found: C, 72.89; H, 4.88; N, 0.67.

2-Nitrobenzyl 4,6-(3,4,5,3′,4′,5′-Hexabenzyloxy)diphenoyl-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (25). 2-Nitrobenzyl 4,6-(3,4-diphenylmethylenedioxy-5-hydroxy-3′,4′-diphenylmethylenedioxy-5′-hydroxy)diphenoyl-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**24a−c**) (1.30 g, 0.73 mmol) was brought to reflux in 75 mL of 80% HOAc and held there for 16 h. The solvent was removed to yield an oil which was triturated with hexanes to afford 1.10 g of crude 2-nitrobenzyl 4,6-(3,4,5,3′,4′,5′-hexahydroxy)diphenoyl-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside as a yellow solid. The crude hexahydroxy compound (1.10 g, 0.75 mmol) and sodium hydride (0.22 g, 9.03 mmol) (60% suspension in oil) were stirred in 10 mL of dry THF at 0 °C for 10 min. After addition of benzyl bromide (0.81 mL, 6.8 mmol) and then tetra-*n*-butylammonium iodide (TBAI) (0.25 g, 0.68 mmol), the resulting turbid brown suspension was allowed to warm to room temperature over 30 min and was stirred for a further 18 h at room temperature. The reaction was diluted with water and extracted with Et_2O. The organic layer was separated, washed with water and then brine, dried (Na_2SO_4), and concentrated to a yellow oil. Purification of this residue by flash column chromatography using 10%, 20%, and then 30% EtOAc in hexanes as eluents yielded 0.75 g (50%) of 2-nitrobenzyl 4,6-(3,4,5,3′,4′,5′-hexabenzyloxy)diphenoyl-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**25**) as a white solid froth: IR (CH_2Cl_2) 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08−8.05 (m, 1 H), 7.70−7.67, (m, 1 H), 7.49−6.85 (m, 68 H), 5.73−5.61 (m, 2 H), 5.47−5.34 (m, 2 H), 5.23−4.73 (m, 27 H), 4.22−4.17 (m, 1 H), 4.11 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.4, 166.7, 165.9, 164.9, 152.7, 152.6, 152.5, 152.3, 152.2, 146.8, 144.7, 144.5, 143.1, 137.7, 137.6, 137.5, 137.4, 16.5, 136.4, 133.9, 133.7, 128.7, 128., 128.5, 128.46, 128.39, 128.36, 128.33, 128.26, 128.22, 128.1, 128.02, 128.01, 127.9, 127.87, 127.84, 127.7, 127.6, 127.56, 127.50, 127.4, 127.3, 127.2, 126.7, 124.6, 124.1, 123.9, 123.6, 123.4, 109.5, 108.0, 107.9, 101.3, 75.4, 75.1, 75.0, 74.9, 73.4, 72.4, 71.9, 71.3, 71.2, 71.1, 70.3, 68.1, 67.9, 63.1; MS (+FAB) 2002 (MH^+, 56). Anal. Calcd for $C_{125}H_{103}NO_{24}$: C, 74.96; H, 5.15; N, 0.69. Found: C, 74.73; H, 5.17; N, 0.64.

4,6-(3,4,5,3′,4′,5′-Hexabenzyloxy)diphenoyl-2,3-bis(3,4,5-tris(benzyl-oxy)benzoyl)-α-D-glucopyranose (26). 2-Nitrobenzyl 4,6-(3,4,5,3′,4′,5′-hexabenzyloxy)diphenoyl-2,3-bis-(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**25**) (100 mg, 0.05 mmol) was dissolved in a mixture of 6 mL of THF, 6 mL of EtOH, and 1 mL of distilled water and irradiated in a Pyrex tube suspended in a Rayonet photochemical apparatus at 350 nm for 7.5 h. Removal of solvents in vacuo yielded an oil which upon flash column chromatography using 10% and then 20% EtOAc in hexanes as eluents provided 62 mg (66%) of 4,6-(3,4,5,3′,4′,5′-hexabenzyloxy)diphenoyl-2,3-bis(3,4,5-tris-(benzyloxy)benzoyl)-D-glucopyranose as a white solid (mixture of α and β anomers). A sample (25 mg) of this product was further purified by preparative thin-layer chromatography using 5% EtOAc in benzene as eluent to provide 15 mg of (**26**): IR (CH_2Cl_2) 3512, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47−6.83 (m, 66 H), 6.05 (t, *J* = 10.1 Hz, 1 H), 5.72 (d, *J* = 3.7 Hz, 1 H), 5.40−4.69 (m, 28 H), 3.94 (d, *J* = 12.9 Hz, 1 H), 3.37 (bs, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.7, 167.0, 165.9, 165.3, 152.64, 152.6, 152.54, 152.52, 152.3, 152.2, 144.7, 144.3, 142.9, 142.8, 137.7, 137.6, 137.5, 137.4, 137.3, 136.5, 136.42, 136.4, 136.31, 136.3, 128.8, 128.5, 128.4, 128.4, 128.32, 128.3, 128.2, 128.1, 128.0, 127.97, 127.91, 127.88, 127.83, 127.7, 127.6, 127.56, 127.53, 127.3, 127.6, 127.56, 127.53, 127.3,

124.1, 123.9, 123.7, 123.4, 109.3, 108.0, 107.8, 90.7, 75.5, 75.4, 75.1, 75.0, 74.8, 73.1, 71.2, 71.1, 71.0, 70.9, 70.4, 67.0, 63.5; MS (+FAB) 1867 (MH^+, 16); HRMS calcd for $C_{118}H_{98}O_{22}$ 1866.6549, found 1866.6528.

4,6-(3,4,5,3′,4′,5′-Hexabenzyloxy)diphenoyl-1,2,3-tris-(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (27). A solution of 4,6-(3,4,5,3′,4′,5′-hexabenzyloxy)diphenoyl-2,3-bis(3,4,5-tribenzyloxybenzoyl)-D-glucopyranose (**26**) (100 mg, 0.05 mmol) in 5 mL of benzene was added to a flask containing a solution of the 3,4,5-tribenzyloxybenzoyl chloride (30 mg, 0.06 mmol) and triethylamine (22 μL, 0.15 mmol) in 2 mL of benzene. The reaction mixture was stirred at room temperature for 18 h. The solution was then treated with 5 mL of ice-cold 1 M HCl and extracted with 15 mL of EtOAc. The organic layer was washed with water and then brine and dried (Na_2SO_4). Removal of solvents in vacuo furnished a white solid which was purified by flash column chromatography using 10% and then 25% EtOAc in hexanes as eluents to provide 50 mg (41%) of 4,6-(3,4,5,3′,4′,5′-hexabenzyloxy)diphenoyl-1,2,3-tris-(3,4,5-tribenzyloxy)benzoyl-β-D-glucopyranoside (**27**) as a white solid: IR ($CDCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50−6.84 (m, 83 H), 6.10 (d, J = 7.6 Hz, 1 H), 5.82 (m, 2 H), 5.51 (t, J = 9.7 Hz, 1 H), 5.42 (dd, J = 6.4 Hz, 13.3 Hz), 5.21−4.72 (m, 30 H), 4.38 (dd, J = 6.0 Hz, 9.9 Hz, 1 H), 4.10 (d, J = 12.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.4, 166.8, 165.7, 164.8, 164.2, 152.7, 152.61, 152.6, 152.5, 152.3, 152.2, 144.8, 144.4, 143.3, 143.2, 143.1, 137.64, 137.6, 137.5, 137.34, 137.31, 137.3, 136.44, 136.4, 136.3, 128.6, 128.42, 128.4, 128.38, 128.3, 128.22, 128.2, 128.03, 128.0, 127.97, 127.91, 127.9, 127.7, 127.6, 127.5, 127.3, 123.8, 123.6, 123.4, 123.2, 109.5, 109.4, 109.3, 107.91, 107.9, 93.1, 75.5, 75.4, 75.1, 75.0, 74.8, 73.1, 72.7, 71.6, 71.2, 70.1, 63.0; MS (+FAB) 2288 (M^+, 20). Anal. Calcd for $C_{146}H_{120}O_{26}$: C, 76.57; H, 5.24. Found: C, 76.38, H, 5.40.

Tellimagrandin II (2). A solution of 4,6-(3,4,5,3′,4′,5′-hexabenzyloxy)diphenoyl-1,2,3-tris(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**27**) (26 mg, 0.01 mmol) and 10% Pd/C (5 mg, 20 wt % of starting material) in 1.5 mL of THF was purged with hydrogen six times and stirred at room temperature under a balloon of hydrogen for 18 h. The reaction mixture was then purged with argon twice and filtered twice through Celite. The filtrate was concentrated to a dark brown solid which was triturated several times with hexanes and diethyl ether and dried to furnish 3 mg (30%) of tellimagrandin II (**2**) as a gray solid: ^1H NMR (acetone-d_6, 200 MHz) δ 7.11 (s, 2 H), 6.99 (s, 2 H), 6.96 (s, 2 H), 6.65 (s, 1 H), 6.45 (s, 1 H), 6.20 (d, J = 8.3 Hz, 1 H), 5.84 (t, J = 9.7 Hz, 1 H), 5.59 (t, J = 8.9 Hz, 1 H), 5.37 (dd, J = 6.4 Hz, 13.4 Hz, 1 H), 5.21(t, J = 10 Hz, 1 H), 4.54 (dd, J = 5.9 Hz, 9.9 Hz, 1 H), 3.88 (d, J = 14 Hz, 1 H); ^{13}C NMR (acetone-d_6, 90 MHz) δ 168.0, 167.6, 166.2, 165.4, 165.0, 146.1, 145.9, 145.8, 145.3, 144.5, 139.8, 139.3, 139.1, 136.6, 126.6, 126.0, 120.6, 120.5, 119.9, 115.5, 110.4, 110.2, 110.1, 108.3, 107.9, 93.7, 73.2, 73.1, 71.7, 70.7, 63.1; MS (+FAB) 938 (M^+, 56), 937 (M − 1, 95); CD (MeOH) 235 nm, +31.7, 261 nm, −7.5, 281.5 nm, +7.7; HRMS calcd for $C_{41}H_{29}O_{26}$ 937.0947, found 937.0943.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **2**, **6**, **8**, **9**, **16**, and **26**. (12 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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