Ellagitannin Chemistry. The First Total Chemical Synthesis of an Ellagitannin Natural Product, Tellimagrandin I

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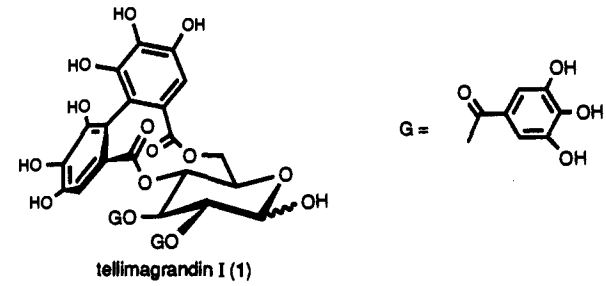
Abstract: Tellimagrandin I was synthesized by two different biogenetically patterned routes. One route featured diastereoselective galloyl ester coupling between the O(4) and O(6) galloyl moieties in a glucose-derived substrate bearing additional protected galloyl groups on O(2) and O(3). The second route relied on a completely diastereoselective and regioselective $Pb(OAc)_4$-based oxidative coupling exclusively between the O(4) and O(6) galloyl esters in a glucose-derived substrate featuring oxidation sensitive galloyl groups on O(2)–O(6). Molecular mechanics-based conformational analysis provides a rationale for the observed selectivity.

The ellagitannin family of secondary plant metabolites, exemplified by tellimagrandin I (**1**),[1] is believed to originate from β-pentagalloylglucose via oxidative coupling between some subset (either 2 or 4) of the galloyl esters radiating out from the central pyranose core.[2] The mechanistic details underlying this appealing proposal have been subject to much conjecture, as a paucity of experimental evidence has limited critical evaluation of various hypotheses.[2] Interest in these compounds has burgeoned recently as a consequence of their promising anticancer and antiviral properties (**1** inhibits herpes simplex virus absorption by cultured cells at nanomolar levels[3]).[3a] However, access to homogeneous samples of natural products and their analogs is hampered by both (sometimes) inadequate purification techniques[4] and a lack of progress toward their synthesis.[5] We have initiated a program in total synthesis of ellagitannins (and analogs) to provide materials for biological evaluation, and our efforts have led to the recent disclosure of the first example of diastereoselective oxidative coupling of model galloyl esters to yield the heretofore elusive[5] (*S*)-hexahydroxydiphenyl (HHDP) moiety crucial to successful ellagitannin synthesis.[6] We now report the extension of this promising development to the first total synthesis of a naturally occurring ellagitannin, tellimagrandin I (**1**). Particularly noteworthy features of this study are (1) the completely diastereoselective and high yielding coupling of O(4),O(6)-bound galloyl esters in a functionally complex glucose-derived substrate and (2) the entirely regioselective O(4),O(6) galloyl coupling in 2,3,4,6-tetragalloylated glucose substrates. Taken together, these



tellimagrandin I (1)

results provide tangible evidence that bears on prevailing speculation concerning the stereo- and regiochemical control elements operating during ellagitannin biosynthesis.[2,7]

Two related but distinct strategies for the synthesis of tellimagrandin I were envisioned: a conservative approach in which the challenge of regioselective oxidation of a 2,3,4,6-tetragalloylated substrate is met by appropriate choice of protecting groups and a more faithfully biogenetic plan where the question of oxidation selectivity in a pergalloylated substrate remains open. The former approach is detailed in Scheme 1 and relies upon standard carbohydrate manipulation chemistry to assemble the key cyclization precursor **5**. Companion studies had revealed that perbenzylated galloyl units, as attached to O(2) and O(3) in **5**, were unreactive to Pb(IV)-based oxidants. Hence, treatment of bis(phenol) **5** with $Pb(OAc)_4$ afforded the HHDP-containing cyclization product **6** in good yield and with strictly *S* stereochemistry in the biaryl unit, but as a (inconsequential) mixture of regioisomeric diphenyl ketal isomers. Simple hydrogenation of the mixture of **6** liberated all of the hydroxyl moieties and furnished natural tellimagrandin I completely free of contaminants. The synthetic material exhibited spectral data coincident with that published for the natural product.[1]

While this synthesis was adequate for delivering the pure target molecule **1** in eight steps from D-glucose, it became increasingly clear that the length of this route could be halved if regioselective O(4),O(6) galloyl coupling could be realized in a substrate bearing the key diphenyl ketal protected galloyl esters at all four glucose oxygens. The cyclization precursor **8** was prepared in three routine steps from D-glucose to explore this possibility and subjected to $Pb(OAc)_4$-mediated oxidative cyclization using various Pb(IV):**8** ratios, eq 1. We were gratified to observe that, upon treatment with 1.1 equiv of $Pb(OAc)_4$, substrate **8** furnished the O(4),O(6)

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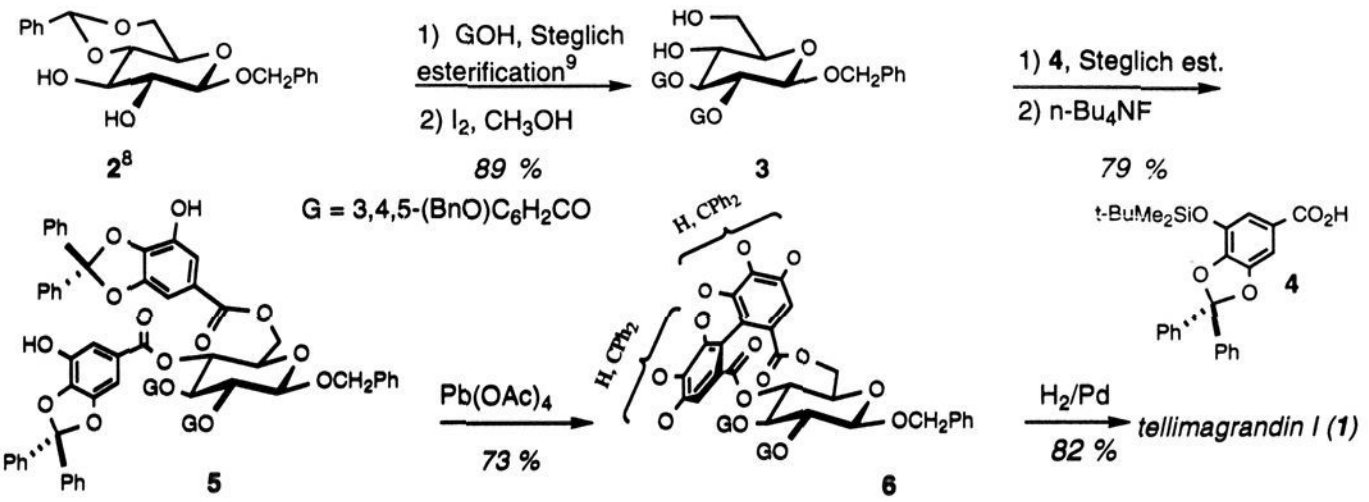
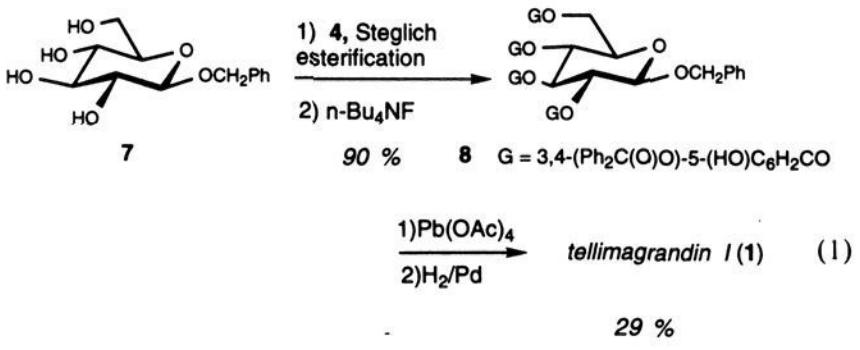
Scheme 1

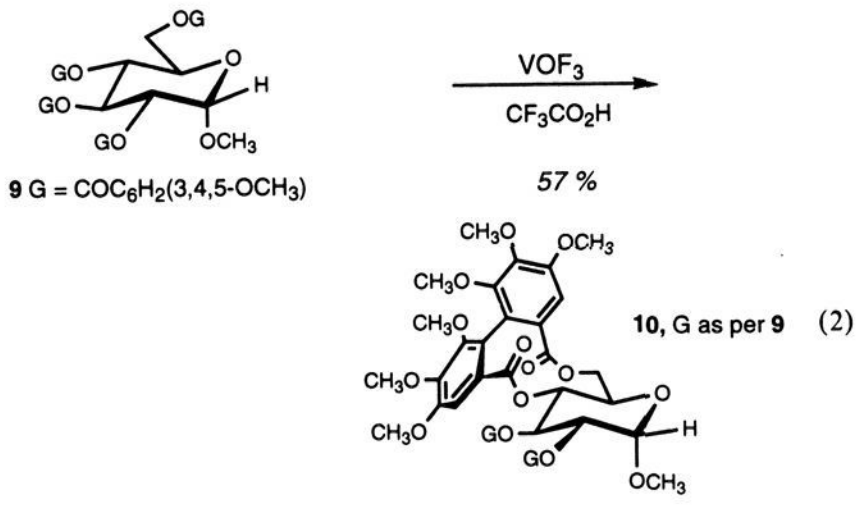




(1)

galloyl coupled product as the only cyclized material! Hydrogenation of the crude reaction mixture afforded natural tellimagrandin I (**1**) in 29% yield along with 29% of 2,3,4,6-tetragalloylglucose derived from uncyclized material. The structural basis for this unprecedented[10] regioselectivity remains under investigation (vide infra), but one hypothesis governing ellagitannin biosynthesis which invokes initial oxidation at an O(1)-bound galloyl group (not present in **8**) followed by charge relay to the O(6) galloyl ester cannot be operating here.[7]

In a parallel series of studies, we have documented the utility of a VOF_3-based protocol[11] for diastereoselective and regioselective oxidative cyclization of glucose-bound per-*O*-methylgalloyl esters, eq 2. As in the $Pb(OAc)_4$-mediated oxidative coupling of phenolic

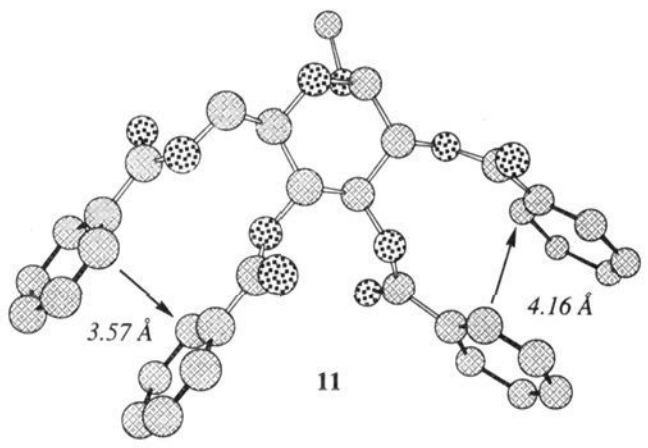


(2)

galloyl units, strict stereochemical control of atropisomer formation was observed, and no evidence for alternative coupling modes was detected.[12] Thus, the facile synthesis of per-*O*-methyltellimagrandin I (**10**) via the vanadium chemistry presents an attractive alternative to the lead chemistry when methylated derivatives of the natural product are desired.

In summary, the first total chemical synthesis of the ellagitannin secondary plant metabolite tellimagrandin I has been recorded.

Two biogenetically patterned routes described herein rely on the natural conformational preferences of the glucose-bound galloyl esters to induce *S* stereochemistry upon HHDP formation and, hence, lend support to earlier speculation by Haslam[2b] and Schmidt[2a] concerning the structural basis for stereochemical control in this transformation during biosynthesis—clearly, enzymic intervention is not an absolute requirement for (*S*)-HHDP formation. The origins of the regioselectivity seen in the cyclizations reported in eqs 1 and 2 remain a pressing unanswered question, although a molecular mechanics-based conformational study[13] of a model tetrabenzoyl analog of **9** furnishes evidence which supports a simple proximity-based argument. Thus, "global" [13] energy minimum conformation **11** juxtaposes both



the O(4),O(6) and O(2),O(3) (but not the O(3),O(4)) benzoyl units within reasonable bonding distance, but the slightly shorter C–C gap between the O(4),O(6) rings is consistent with preferential reaction at this site.

Experimental Section

Infrared (IR) spectra were recorded on Perkin-Elmer 281B and 1600 FT infrared spectrophotometers. Magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded on either Bruker ACE-200, WP-200, AM-300, or WM-360 spectrophotometers. Chemical shifts are reported in δ using tetramethylsilane (TMS) as an internal standard for ^{1}H NMR and chloroform or acetone as the internal standard for ^{13}C NMR. Low- and high-resolution mass spectra (MS, HRMS) were obtained on either a Kratos MS9/50 or MS25 hexapole focusing mass spectrometer, while fast atom bombardment mass spectra (FABMS, HRFABMS) were obtained on a Kratos MS50 hexapole focusing mass spectrometer. Liquid (flash) chromatography was carried out using 32–63-μm silica gel (Woelm-Pharma) and the indicated solvent. Analytical thin-layer chromatography was performed using precoated silica gel (60 F_{254}) plates (E. Merck). Ether (Et_2O), tetrahydrofuran (THF), and benzene (PhH) were purified by distillation from sodium/benzophenone under nitrogen, while methylene chloride (CH_2Cl_2) was distilled from CaH_2 under nitrogen. Moisture

(10) Preliminary scouting experiments indicated that diphenyl ketal protected galloyl esters attached to O(2) and O(3) of a glucose derivative did afford satisfactory yields of the 2,3-HHDP-containing product upon treatment with $Pb(OAc)_4$. Thus, coupling between the O(2) and O(3) galloyl esters of **8** could plausibly compete with the observed O(4),O(6) galloyl coupling.

(11) For example, see: Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3772.

(12) Resubmission of the purified product **10** to further VOF_3-mediated oxidation did not provide any new compounds.

(13) Molecular mechanics calculations were performed using Macromodel3.1x on a Silicon Graphics 4D25G computer. A directed Monte Carlo search algorithm with 2000 initial steps was used to explore conformational space about all exocyclic rotatable bonds. Approximately 50 unique conformations were found within 1.5 kcal/mol of **11**, which itself was identified in 12 out of the 2000 minimizations. The lowest energy structure which appeared aligned to give an *R* rather than an *S* biphenyl atropisomer was approximately 0.5 kcal/mol more strained than **11**.

sensitive reactions were carried out in predried glassware under an inert atmosphere of Ar.

Modified Steglich[9] Esterification Reaction: General Procedure A. A solution of the appropriate polyol (1.0 equiv), acid (1.1 equiv per hydroxyl), 4-(dimethylamino)pyridine (DMAP) (0.50 equiv per polyol), DMAP·HCl (0.50 equiv per polyol), and 1,3-dicyclohexylcarbodiimide (DCC) (1.1 equiv per hydroxyl) in dry CH_2Cl_2 (0.10 M in polyol) was purged with Ar and heated at reflux under Ar for 16–20 h. The solution was allowed to cool to room temperature, diluted with an equal volume of Et_2O, filtered through a plug of silica gel, and concentrated in vacuo. The residue was purified by flash column chromatography with the indicated eluent to furnish the desired esters.

Silyl Ether Deprotection Reaction: General Procedure B. A solution of the appropriate *tert*-butyldimethylsilyl-protected glucose derivative (1.0 equiv) in dry THF (0.080 M) was added to a cooled (0 °C) solution of tetrabutylammonium fluoride (1.2 equiv per silyl group) in dry THF (0.040 M final concentration of glucose derivative). The solution was stirred under Ar for 20 min at 0 °C and 3–4 h at room temperature. The solution was partitioned between 1 M H_3PO_4 and EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography using the indicated eluent to furnish the desired phenols.

Benzyl 4,6-*O*-Benzylidene-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside. By use of general procedure A, benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside[8] (**2**) (2.1 g, 5.9 mmol) and 3,4,5-*tris*(benzyloxy)benzoic acid (5.9 g, 13 mmol, 2.3 equiv) were coupled to afford 6.3 g (89%) of benzyl 4,6-*O*-benzylidene-2,3-bis(3,4,5-*tris*(benzyloxy)benzoyl)-β-D-glucopyranoside as a light yellow solid foam following flash column chromatography using 33% hexane in CH_2Cl_2, and then CH_2Cl_2, as the eluent: IR (CCl_4) 1733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.17 (m, 44 H), 5.69 (t, J = 9.3 Hz, 1 H), 5.55 (s, 1 H), 5.52 (t, J = 9.3 Hz, 1 H), 5.08 (s, 2 H), 5.06 (s, 4 H), 5.03 (s, 6 H), 4.91 (d, J = 12.5 Hz, 1 H), 4.81 (d, J = 7.6 Hz, 1 H), 4.65 (d, J = 12.4 Hz, 1 H), 4.47 (dd, J = 10.6, 4.6 Hz, 1 H), 3.97–3.87 (m, 2 H), 3.70 (dd, J = 9.4, 4.4 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.2, 164.8, 152.4, 142.6, 137.3, 136.7, 136.5, 136.4, 129.0, 128.40, 128.37, 128.32, 128.12, 128.07, 128.05, 127.91, 127.87, 127.82, 127.76, 127.71, 127.5, 126.1, 124.4, 124.2, 109.2, 101.4, 100.0, 78.7, 75.0, 72.6, 72.3, 71.1, 70.8, 68.6, 66.6; MS (+FAB) 1203 (MH^+, 50).

Benzyl 2,3-Bis(3,4,5-*tris*(benzyloxy)benzoyl)-β-D-glucopyranoside (3). A solution of benzyl 4,6-*O*-benzylidene-2,3-bis(3,4,5-tris(benzyloxy)-benzoyl)-β-D-glucopyranoside (2.0 g, 1.7 mmol) and iodine (0.42 g, 1.7 mmol, 1.0 equiv) in 17 mL of dry CH_3OH and 17 mL of dry CH_2Cl_2 was heated at reflux under Ar for 40 h. The solution was cooled, diluted with 50 mL of EtOAc, washed with saturated $Na_2S_2O_3$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo to yield 1.9 g (100%) of benzyl 2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**3**) as a white solid foam: IR ($CHCl_3$) 3608–3380, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.15 (m, 39 H), 5.48 (t, J = 8.9 Hz, 1 H), 5.21 (t, J = 9.4 Hz, 1 H), 5.07 (s, 2 H), 5.05 (s, 6 H), 5.00–4.84 (m, 3 H), 4.93 (d, J = 8.8 Hz, 2 H), 4.86 (d, J = 12.5 Hz, 1 H), 4.73 (d, J = 8.0 Hz, 1 H), 4.66 (d, J = 12.7 Hz, 1 H), 4.03–3.86 (m, 2 H), 3.66 (bs, 1 H), 3.57–3.52 (m, 1 H), 2.23 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 164.9, 152.5, 142.9, 142.8, 137.3, 136.8, 136.4, 128.5, 128.43, 128.35, 128.1, 128.01, 127.97, 127.88, 127.79, 127.55, 127.49, 124.2, 123.6, 109.2, 99.3, 78.3, 75.9, 75.1, 71.5, 71.1, 71.0, 70.9, 70.1, 62.3; MS (+FAB) 1115.5 (MH^+, 53); HRFABMS calcd for $C_{69}H_{63}O_{14}$ (MH^+) 1115.4218, found 1115.3968.

Benzyl 4,6-Bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)-dioxy)benzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside. By use of general procedure A, benzyl 2,3-bis(3,4,5-tris(benzyloxy)-benzoyl)-β-D-glucopyranoside (**3**) (1.8 g, 1.6 mmol) and 3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoic acid[6] (**4**) (1.6 g, 3.6 mmol, 2.2 equiv) were coupled to afford 3.1 g (98%) of benzyl 4,6-bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)-benzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside as a white solid foam following flash column chromatography using 10% hexane in CH_2Cl_2 as the eluent: IR ($CDCl_3$) 1729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–7.09 (m, 63 H), 5.74 (t, J = 9.6 Hz, 1 H), 5.55 (t, J = 9.7 Hz, 1 H), 5.54 (t, J = 8.8 Hz, 1 H), 5.07 (s, 2 H), 5.04 (s, 2 H), 5.03 (s, 2 H), 4.98 (s, 4 H), 4.96 (s, 2 H), 4.89 (d, J = 12.4 Hz, 1 H), 4.77 (d, J = 7.9 Hz, 1 H), 4.66 (d, J = 12.5 Hz, 1 H), 4.62 (d, J = 11.0 Hz, 1 H), 4.36 (dd, J = 12.1, 6.2 Hz, 1 H), 4.04 (m, 1 H), 0.99 (s, 9 H), 0.96 (s, 9 H), 0.19 (s, 6 H), 0.12 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.8, 164.5, 152.5, 152.4, 148.6, 142.7, 142.6, 142.0, 141.7, 139.8, 139.6, 138.6, 138.5, 137.5, 137.4, 136.5, 136.4, 129.2, 128.5, 128.4, 128.3, 128.15, 128.08, 128.05, 127.98, 127.9, 127.8, 127.65, 127.57, 126.2, 124.4, 124.0, 123.6, 122.5, 119.0, 118.8, 109.3, 109.1, 104.11, 104.05, 98.9, 75.1, 75.0, 73.3, 72.6, 72.2, 71.2, 71.1, 70.3, 69.3, 63.0, 25.5, 18.3, 18.2, –4.5, –4.6; MS (+FAB) 1976.5 (MH^+, 10).

Benzyl 4,6-Bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-2,3-bis(3,4,5-*tris*(benzyloxy)benzoyl)-β-D-glucopyranoside (5). By use of general procedure B, benzyl 4,6-bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoyl)-2,3-bis(3,4,5-tris(benzyloxy)-benzoyl)-β-D-glucopyranoside (1.3 g, 0.70 mmol) was desilylated to afford 0.99 g (81%) of benzyl 4,6-bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-2,3-bis(3,4,5-(*tris*(benzyloxy)benzoyl)-β-D-glucopyranoside (**5**) as a white solid foam following flash column chromatography using 4% Et_2O in CH_2Cl_2 as the eluent: IR ($CHCl_3$) 3575, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.08 (m, 63 H), 5.88 (bs, 1 H), 5.80 (bs, 1 H), 5.74 (t, J = 9.2 Hz, 1 H), 5.57 (m, 2 H), 5.07 (s, 2 H), 5.00 (s, 4 H), 4.96 (s, 6 H), 4.86 (d, J = 12.7 Hz, 1 H), 4.78 (d, J = 7.8 Hz, 1 H), 4.64 (d, J = 12.7 Hz, 1 H), 4.59 (d, J = 15.5 Hz, 1 H), 4.38 (dd, J = 12.1, 5.1 Hz, 1 H), 4.00 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 164.8, 164.6, 152.4, 152.3, 148.31, 148.27, 142.7, 142.6, 139.4, 139.2, 139.1, 138.7, 138.5, 137.3, 137.2, 136.4, 129.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.54, 127.48, 126.2, 126.1, 124.2, 123.7, 123.4, 122.6, 118.7, 114.4, 114.3, 109.2, 109.1, 103.4, 99.1, 75.02, 74.98, 73.4, 72.2, 72.1, 71.0, 70.9, 70.4, 69.5, 63.0; MS (+FAB) 1747 (MH^+, 14).

Tellimagrandin I (1). A solution of lead tetraacetate (84 mg, 0.19 mmol, 1.1 equiv) in 4 mL of dry CH_2Cl_2 was added dropwise over 20 min to a cooled (0 °C) solution of benzyl 4,6-bis(3,4-((diphenylmethylene)-dioxy)-5-hydroxybenzoyl)-2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside (**5**) (300 mg, 0.17 mmol) and pyridine (55 μL, 0.68 mmol, 4.0 equiv) in 20 mL of dry CH_2Cl_2. The orange solution was stirred at 0 °C for 30 min, quenched by the addition of 30 mL of saturated $NaHCO_3$ solution, and extracted with 50 mL of Et_2O. The organic layer was washed with 1 M H_3PO_4 and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue on silica gel using 2% Et_2O in CH_2Cl_2, followed by 4% Et_2O in CH_2Cl_2, as the eluent afforded 215 mg (73%) of a mixture of four isomers of the 4,6 oxidatively coupled glucose derivative **6** as a yellow solid. A solution of this mixture of isomers **6** (215 mg, 0.12 mmol) and 10% Pd/C (120 mg) in 10 mL of dry THF was purged six times with H_2. The mixture was stirred at room temperature under 1 atm of H_2 for 48 h, purged thoroughly with Ar, filtered through Celite, and concentrated in vacuo. ^1H NMR analysis revealed only partial deprotection so the crude residue was resubmitted to reaction conditions as described above for an additional 20 h. The resultant solid was washed thoroughly with hexane and Et_2O to extract diphenylmethane and dried in vacuo to yield 77 mg (82%) of tellimagrandin I[1] (**1**) (2.4:1 mixture of α:β anomers) as a tan/gray solid: IR (KBr) 3650–3000, 1705, 1702 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 8.00–7.40 (bs, 6 H), 7.06 (s, 2 H), 7.05 (s, 2 H), 6.98 (s, 2 H), 6.94 (s, 2 H), 6.65 (s, 1 H), 6.64 (s, 1 H), 6.45 (s, 1 H), 6.43 (s, 1 H), 5.89 (t, J = 10.0 Hz, 1 H), 5.62 (t, J = 9.8 Hz, 1 H), 5.57 (d, J = 3.6 Hz, 1 H), 5.35–5.21 (m, 3 H), 5.15–5.07 (m, 4 H), 4.67 (dd, J = 9.8, 6.1 Hz, 1 H), 4.27 (dd, J = 9.6, 6.1 Hz, 1 H), 3.85 (d, J = 12.7 Hz, 1 H), 3.77 (d, J = 13.0 Hz, 1 H); ^{13}C NMR (75 MHz, C_3D_6O) δ 168.2, 167.6, 166.4, 166.3, 166.1, 165.5, 146.0, 145.7, 145.2, 145.1, 144.64, 144.59, 139.2, 139.0, 138.9, 136.5, 126.6, 126.1, 121.2, 120.9, 120.8, 115.8, 115.5, 110.1, 108.1, 107.7, 96.8, 91.3, 74.2, 73.5, 73.0, 72.1, 71.12, 71.06, 67.3, 63.5, 55.4; MS (+FAB) 787.3 (MH^+, 100); HRFABMS calcd for $C_{34}H_{76}O_{22}$ 786.0916, found 786.1161; CD (CH_3OH) 239 nm, +29.5, 262 nm, –29.5, 287 nm, +20.0.

Benzyl 2,3,4,6-Tetrakis(3-(*tert*-butyldimethylsiloxy-4,5-((diphenyl-methylene)dioxy)benzoyl)-β-D-glucopyranoside. By use of general procedure A, benzyl β-D-glucopyranoside (**7**) (0.17 g, 0.63 mmol) and 3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoic acid (**4**) (1.2 g, 2.8 mmol, 4.4 equiv) were coupled to afford 1.2 g (96%) of benzyl 2,3,4,6-tetrakis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)-dioxy)benzoyl)-β-D-glucopyranoside as a white solid foam following flash column chromatography using 25% Et_2O in hexane as the eluent: IR ($CHCl_3$) 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.01 (m, 53 H), 5.69 (t, J = 9.7 Hz, 1 H), 5.47 (t, J = 9.7 Hz, 1 H), 5.46 (t, J = 8.8 Hz, 1 H), 4.85 (d, J = 12.2 Hz, 1 H), 4.69 (d, J = 7.9 Hz, 1 H), 4.63 (d, J = 12.6 Hz, 1 H), 4.57 (d, J = 12.1 Hz, 1 H), 4.31 (dd, J = 12.2, 6.4 Hz, 1 H), 3.97 (m, 1 H), 1.00 (s, 9 H), 0.98 (s, 9 H), 0.96 (s, 9 H), 0.92 (s, 9 H), 0.20 (s, 6 H), 0.13 (s, 6 H), 0.10 (s, 6 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 164.9, 164.4, 164.3, 148.54, 148.45, 148.33, 148.29, 141.9, 141.61, 141.58, 139.90, 139.86, 139.83, 139.76, 139.71, 139.68, 138.6, 138.44, 138.39, 138.3, 136.4, 129.2, 129.0, 128.3, 128.24, 128.21, 128.17, 127.9, 127.8, 126.2, 126.1, 123.7, 123.2,

122.7, 122.5, 119.0, 118.9, 118.82, 118.76, 118.10, 117.99, 117.91, 104.22, 104.16, 104.10, 104.0, 98.9, 72.6, 71.7, 70.2, 69.3, 63.0, 25.5, 18.3, 18.22, 18.19, 18.16, –4.5, –4.56, –4.63, –4.7; MS (+FAB) 1992.3 (MH^+, 10).

Benzyl 2,3,4,6-Tetrakis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-β-D-glucopyranoside (8). By use of general procedure B, benzyl 2,3,4,6-tetrakis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)-dioxy)benzoyl)-β-D-glucopyranoside (1.4 g, 0.70 mmol) was desilylated to afford 1.0 g (94%) of benzyl 2,3,4,6-tetrakis(3,4-((diphenylmethylene)-dioxy)-5-hydroxybenzoyl)-β-D-glucopyranoside (**8**) as a white solid foam following flash column chromatography using 50% hexane in EtOAc as the eluent: IR ($CHCl_3$) 3575–3100, 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.56–6.94 (m, 53 H), 6.55 (bs, 1 H), 6.38 (bs, 2 H), 5.63–5.41 (m, 3 H), 4.79–4.62 (m, 2 H), 4.57–4.47 (m, 2 H), 4.38–4.26 (m, 1 H), 3.96–3.90 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 165.9, 165.1, 164.9, 148.4, 139.4, 139.3, 139.0, 138.9, 138.8, 138.63, 138.58, 136.2, 129.2, 128.2, 127.7, 126.2, 123.3, 122.9, 122.2, 122.1, 118.73, 118.67, 118.62, 118.57, 114.2, 103.5, 99.1, 73.2, 72.0, 71.9, 70.6, 69.7, 63.2; MS (+FAB) 1535.3 (MH^+, 100).

Methyl 2,3,4,6-Tetrakis(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside[14] (9). By use of general procedure A, methyl α-D-glucopyranoside (0.50 g, 2.6 mmol) and 3,4,5-trimethoxybenzoic acid (2.4 g, 11 mmol, 4.4 equiv) were coupled to afford 1.9 g (77%) of methyl 2,3,4,6-tetrakis-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (**9**) as a white solid foam following flash column chromatography using Et_2O as the eluent: IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 2 H), 7.27 (s, 2 H), 7.16 (s, 2 H), 7.11 (s, 2 H), 6.11 (t, J = 9.9 Hz, 1 H), 5.66 (t, J = 9.8 Hz, 1 H), 5.31 (d, J = 3.5 Hz, 1 H), 5.19 (dd, J = 10.2, 3.5 Hz, 1 H), 4.74 (d, J = 9.5 Hz, 1 H), 4.44–4.41 (m, 2 H), 3.914 (s, 3 H), 3.912 (s, 3 H), 3.90 (s, 6 H), 3.88 (s, 6 H), 3.870 (s, 3 H), 3.867 (s, 3 H), 3.863 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 6 H), 3.51 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.4, 165.3, 165.2, 164.9, 152.63, 152.55, 142.4, 142.3, 142.2, 142.1, 124.3, 123.7, 123.6, 123.5, 106.9, 106.7, 106.6, 96.8, 72.1, 70.6, 69.6, 67.3, 63.1, 60.6, 55.84, 55.76, 55.3; MS (+FAB) 970.3 (M^+, 100); HRFABMS calcd for $C_{47}H_{54}O_{22}$ 970.3106, found 970.3163.

(14) Britton, G.; Crabtree, P. W.; Haslam, E.; Stangroom, J. E. *J. Chem. Soc. C* **1966**, 783.

Per-*O*-methyltellimagrandin I (10). A solution of methyl 2,3,4,6-tetrakis(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (**9**) (0.20 g, 0.21 mmol) in 4 mL of dry CH_2Cl_2 was added dropwise over 30 min to a cooled (0 °C) solution of vanadium oxytrifluoride (0.21 g, 1.7 mmol, 8.0 equiv) in 38 mL of dry CH_2Cl_2 and 4.2 mL of trifluoroacetic acid. The solution was stirred at 0 °C under Ar for 3 h, quenched slowly by the addition of saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered through Celite, and concentrated in vacuo. Purification of the residue by flash column chromatography using 10% Et_2O in CH_2Cl_2 as the eluent afforded 116 mg (57%) of per-*O*-methyltellimagrandin I (**10**) as a white solid foam: IR ($CDCl_3$) 1816, 1794, 1749, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 2 H), 7.19 (s, 2 H), 6.81 (s, 1 H), 6.66 (s, 1 H), 5.93 (t, J = 10.0 Hz, 1 H), 5.33–5.25 (m, 3 H), 5.10 (dd, J = 9.9, 3.8 Hz, 1 H), 4.44 (dd, J = 9.9, 6.3 Hz, 1 H), 3.93 (s, 6 H), 3.92 (s, 3 H), 3.89 (s, 6 H), 3.86 (s, 6 H), 3.81 (s, 3 H), 3,76 (s, 6 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.44 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 167.0, 165.8, 165.5, 153.1, 152.9, 152.8, 152.3, 144.6, 144.1, 142.5, 142.4, 128.4, 127.7, 124.0, 123.9, 122.6, 122.2, 107.14, 107.06, 105.7, 105.5, 97.5, 72.9, 71.1, 70.2, 66.7, 63.3, 61.0, 60.9, 60.8, 60.7, 56.1, 56.0, 55.9, 55.8; MS (+FAB) 968.3 (M^+, 100); CD (CH_3OH) 229 nm, +24.3, 247 nm, –9.0, 276 nm, +14.5; HRFABMS calcd for $C_{47}H_{52}O_{22}$ 968.2950, found 968.3076.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **1**, **3**, **5**, **8**, **9**, and **10** (12 pages). This material is contained in many 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.