Ellagitannin Chemistry. The First Total Chemical Synthesis of an *O*(2),*O*(3)-Galloyl-Coupled Ellagitannin, Sanguiin H-5

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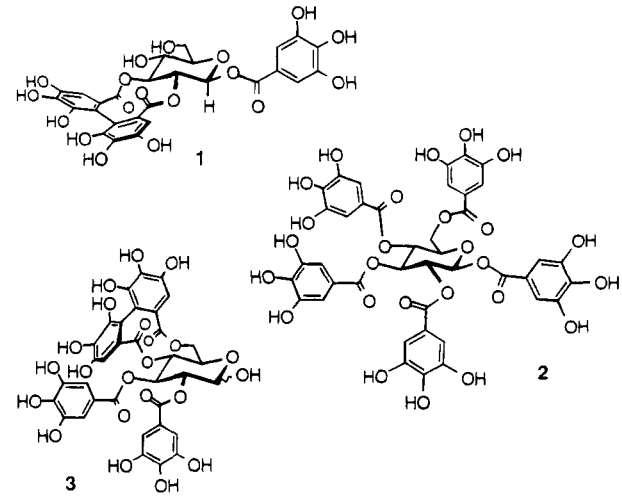
The biomimetic synthesis of sanguiin H-5 (**1**) was accomplished through the diastereoselective formation of the crucial biphenyl carbon–carbon bond between galloyl moieties at the *O*(2) and *O*(3) positions of an appropriately protected glucose-derived precursor. Furthermore, the β-anomeric galloyl linkage was established with complete stereochemical control.

Introduction

Sanguiin H-5 (**1**)[1] is a structurally simple member of the vast ellagitannin class of hydrolyzable tannins (plant polyphenols).[2] Over 500 ellagitannins have been identified thus far; however, their taxonomic distribution is not universal. The prolific occurrence of gallic acid metabolites in certain taxa of dicotyledonous plants[3] has led to their use as prominent chemotaxonomic markers. The pervasive property of astringency[4] associated with plant polyphenols is responsible for various commercial applications of many of these natural products, especially in the wine and leather tanning industries.[5] In addition, a large number of hydrolyzable tannins find use as herbal medicines.[6,9] Recent studies have revealed that some ellagitannins offer promise as potent anticancer[7] and antiviral[7e,g,8] therapeutic agents. Polyphenol–protein interactions may underlie the medicinal properties exhibited by some members of the tannin family.[9] In a related vein, some polyphenols which operate at the protein level (e.g., gallotannins) appear to be part of the chemical defense arsenal in plants.[10]



The biosynthetic pathway responsible for the genesis of ellagitannins is believed to be centered around the watershed gallotannin β-1,2,3,4,6-pentagalloyl-D-glucose (β-PGG, **2**).[11] Varied intra- (C–C) and intermolecular (C–O) oxidative coupling patterns[3a,12] of the galloyl moieties present in β-PGG (**2**) have led to the elaboration of a seemingly inexhaustible diversity of molecular frameworks, characterizing the ellagitannins as secondary metabolites. However, the mechanism of biaryl (and diaryl ether) formation from the pentagalloylated precursor remains a subject of intense speculation and debate. Various hypotheses put forth to explain the oxidative

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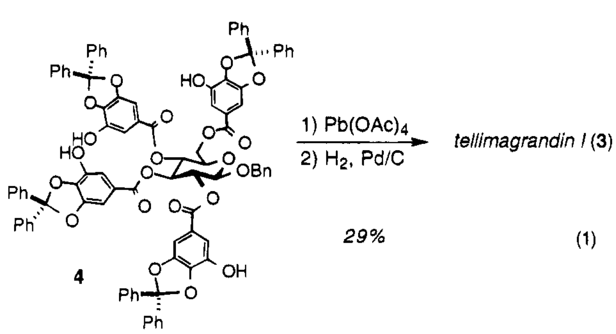
transformations of β-PGG diverge with respect to the fate of the putative aryloxy radical generated initially via one electron oxidation of a galloyl moiety in the substrate.[3a] Some pathways deemed conceivable include (1) direct C−C or C−O radical coupling to furnish biaryl moieties or diaryl ethers, respectively, or (2) further oxidation of the primary aryloxy radical to yield an electrophilic intermediate (a phenoxonium ion or an orthoquinone). This intermediate may then be subject to either intramolecular attack by appropriately positioned carbon-centered (aryl) nucleophiles or to intermolecular trapping by the phenolic hydroxyl groups of a second ellagitannin species.[3a,16e]

Schmidt,[13] and later, Haslam,[2] discerned that ellagitannins possessing hexahydroxydiphenoyl (HHDP) moieties at the 2,3- and 4,6-positions of the thermodynamically more stable $^4C_1$ glucose conformer almost invariably contain the *(S)*-atropisomer of the biaryl unit,[14] an observation that led them to postulate that *the stereochemical outcome of (C−C) oxidative biaryl coupling is governed by the conformational preferences of the galloylated polyol core.* When the glucose framework is forced to adopt the less stable $^1C_4$ (or intermediate skew-boat) conformation to allow bridging between galloyl groups at the 3,6-, 1,6-, and 2,4- positions of the carbohydrate core, the stereochemical outcome of coupling is less predictable, and instances exist where both atropisomers are formed.[14b]

A study of the applicability of the Schmidt−Haslam hypothesis to stereoselective ellagitannin synthesis has been initiated. The preparation of variously coupled ellagitannins through the biomimetic oxidative coupling of proximal galloyl moieties on a suitably protected glucopyranose ring can help delineate the scope of this biosynthetic hypothesis. During the early stages of this investigation, a number of reagents reputed to be effective phenolic oxidants were screened,[15] leading to the identification of $Pb(OAc)_4$[16] as the most efficacious mediator for the desired chemical transformation. Later efforts led to the first total chemical synthesis of the ellagitannin tellimagrandin I (**3**),[17] obtained by the regioselective and stereoselective oxidation of the diphenylketal-protected galloyl groups at the 4- and 6-positions of the tetragalloylated cyclization precursor **4**, eq 1. It is noteworthy



(1)

that the oxidation of polyfunctional substrate **4** mediated by 1 equiv of $Pb(OAc)_4$ yielded only the *O*(4),*O*(6)-galloyl coupled product, to the complete exclusion of *O*(2),*O*(3)-coupled product or even the bis-coupled product. No evidence for 2,3-HHDP-containing materials could be garnered, even upon increasing the quantity of oxidant employed in the reaction. These experiments reveal an unexpected bias toward 4,6-galloyl coupling as compared to 2,3-coupling. Thus, the need to establish the feasibility of stereoselective biaryl bond formation between galloyl esters at the 2- and 3-positions of the glucose precursor arose. In addition, the acquisition of 2,3-HHDP-containing glucose derivatives is indispensable for the elaboration of more complex (e.g., dimeric, trimeric) ellagitannin constructs in the future. In this context, the $Pb(OAc)_4$-mediated oxidation methodology developed in our laboratory was extended to include the synthesis of the first *O*(2),*O*(3)-HHDP-bearing ellagitannin, sanguiin H-5 (**1**).

Results and Discussion

Any strategy envisioned for the successful synthesis of sanguiin H-5 must address the following two critical challenges: (1) formation of only the *(S)*-atropisomer of the HHDP group via selective oxidation of the protected *O*(2)- and *O*(3)-galloyl moieties, and (2) stereochemically controlled establishment of the β-anomeric galloyl linkage. While the Schmidt−Haslam proposal provides an intuitively attractive model for predicting the stereochemical outcome of oxidative coupling between galloyl esters at the 2,3-positions of the glucose core, it does not offer a clear molecular level rationale which relates product stereochemistry to the conformational preferences of the precursor polyol. In order to investigate the structural details which might underlie stereoselectivity upon 2,3-coupling, full molecular mechanics (MM)-based conformation searches[18] of the *O*(2),*O*(3)-digalloylated model compound **5** were conducted (Scheme 1). This computational study did not reveal any conformations which differed markedly from the single "global" minimum conformer **6** within a 2 kcal/mol window. Examination of conformer **6** revealed that the *pro-S* pair of the carbon atoms (a → b, 3.99 Å) was not significantly closer than the alternative pro-*(R)* pairing (c → d, 4.11 Å). However, the difference in energy between the two stereochemically divergent coupling pathways (e.g., a → b, c → d) becomes manifest as the oxidative process proceeds through the putative diastereomeric dione species **7a** and **7b**. The *pro-S* species **7b** appears to be favored by 1.7 kcal over the *pro-R* alternative **7a**. Tautomerization of intermediates **7a** and **7b** leads unambiguously to the biphenyl-containing products **8a** and **8b**, respectively, wherein the energy difference between the *S* and *R* channels is amplified (5.3 kcal) in favor of the *(S)*-HHDP-containing product **8b**. Thus, it is plausible that the burgeoning energetic difference between

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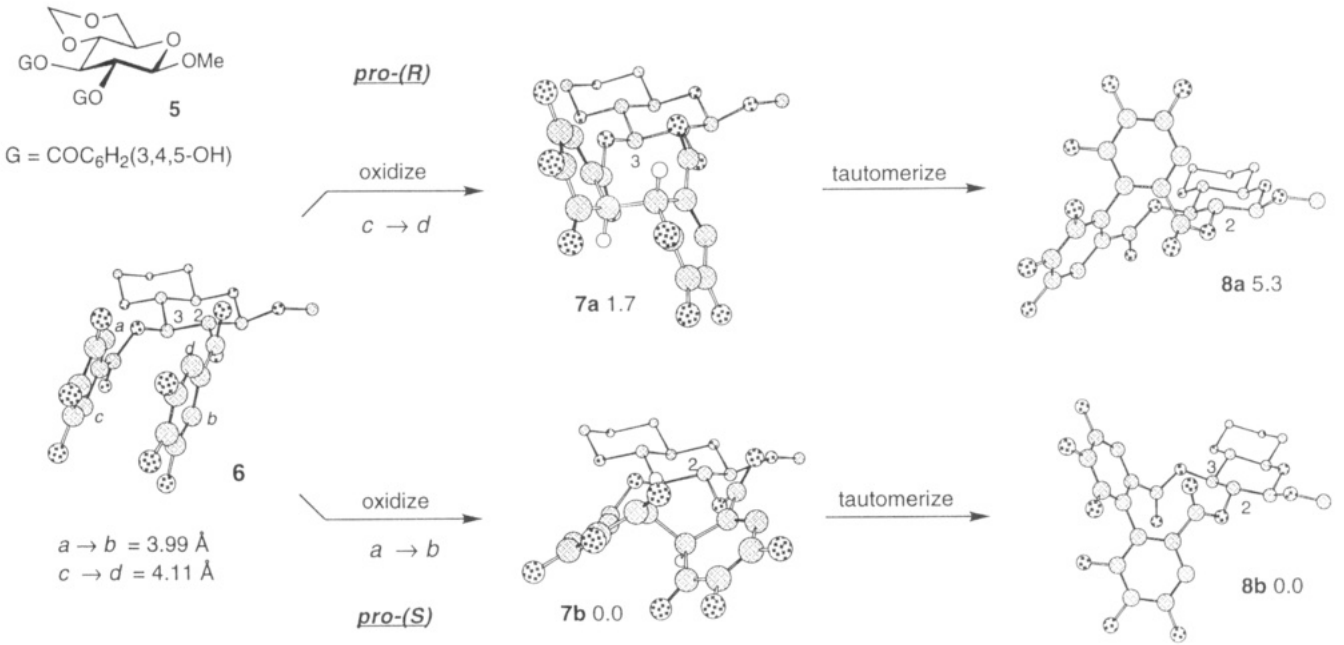
(18) Molecular mechanics calculations on all species described in Scheme 1 were performed on a Silicon Graphics PowerIndigo 2XZ computer equipped with version 4.5 of Macromodel (MM2* force field). The directed Monte Carlo conformational search subroutine was used, and all rotatable single bonds were varied. In each search, 1000 starting geometries were explored. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Scheme 1



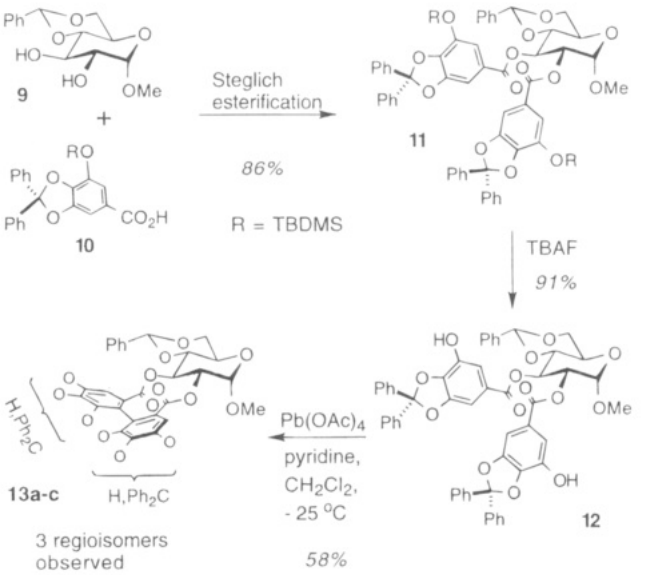
•most hydrogens omitted for clarity
•strain energy of (R) relative to (S) series shown (kcal/mol)

the two manifolds which evolves as starting material **6** proceeds to the diastereomeric products **7a** or **7b** is responsible for the stereochemical preference suggested by these calculations.

Successful synthesis of sanguiin H-5 also demands stringent stereochemical control of the disposition of the anomeric galloyl group. Toward this end, a β-selective esterification protocol has been identified which furnishes the requisite equatorial galloyl group free of isomers.[19] With the results from the MM conformational study and the anomeric functionalization experiments in hand, the synthesis of the target ellagitannin sanguiin H-5 (**1**) can be addressed.

A model system study was deemed appropriate prior to venturing toward the actual synthesis of sanguiin H-5 (**1**) (Scheme 2). Commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**9**) was esterified[20] with 3-[(*tert*-butyldimethylsilyl)oxy]-4,5-[(diphenylmethylene)-dioxy]benzoic acid (**10**)[16e] followed by desilylation of the silyl ether protecting groups in the resultant diester to yield the cyclization substrate **12**. Preliminary forays into the oxidation of compound **12** commenced with attempts at modifying the previously established 4,6-coupling conditions[16d,e,17] in order to optimize yields. More dilute solutions and lower reaction temperatures

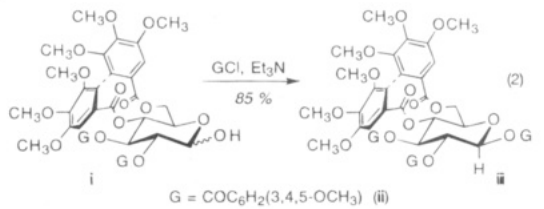
Scheme 2



compared to the 4,6-coupling case were necessary to achieve $Pb(OAc)_4$-mediated biaryl bond formation in this series, affording the three isomers **13a-c** in good yield (58%). Circular dichroism (CD)[21] measurements of all three (separated) compounds unambiguously established them as HHDP-bearing atropisomers with the *(S)*-configuration. From the standpoint of ellagitannin synthesis, this lack of regiochemical control is inconsequential; removal of the diphenyl ketal protecting groups will afford a single compound. Compounds **13a-c** represent the first examples of chemically synthesized *O*(2),*O*(3)-galloyl-coupled glucose derivatives.[14b]

Success in this model system encouraged application of the newly established oxidation conditions to a syn-

(19) Acylation of the hydroxyl functionality in a mixture of coupled and uncoupled compounds **i** with 3,4,5-trimethoxybenzoyl chloride **ii** in the presence of triethylamine afforded the mixture of compounds **iii**, containing the anomeric galloyl moiety in an exclusive β-disposition, (eq 2).



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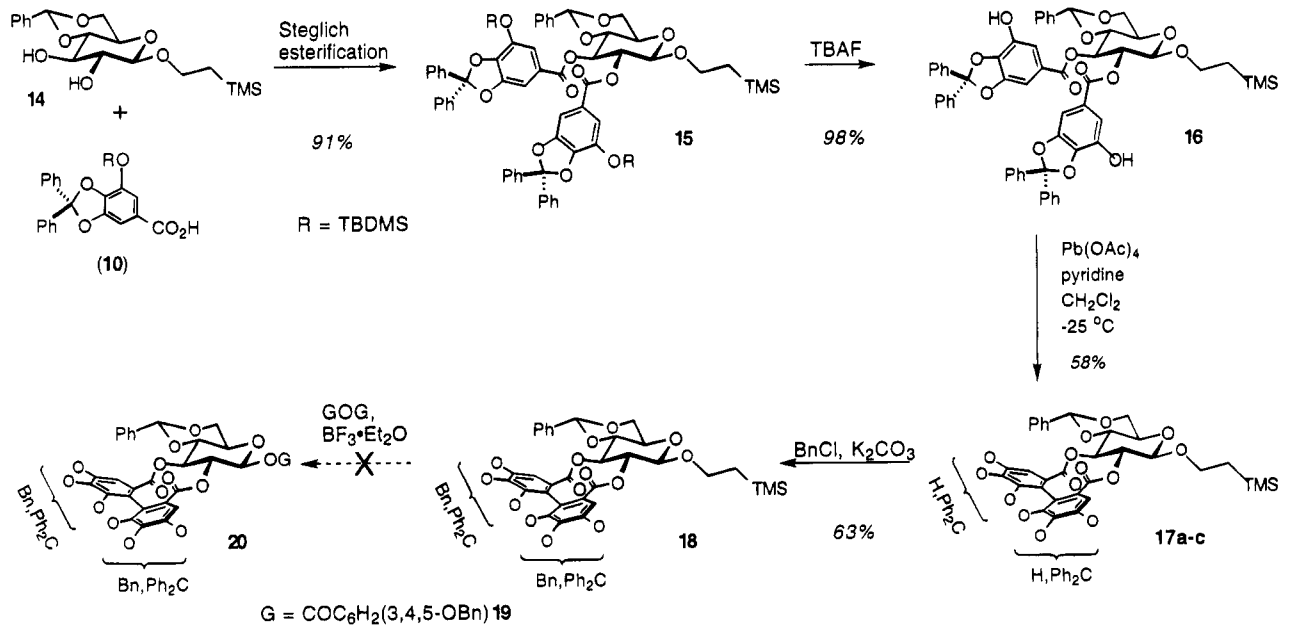
Scheme 3

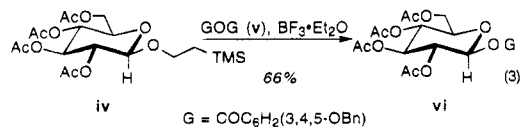


thesis of sanguiin H-5 itself. The selection of appropriate protection for the anomeric hydroxyl functionality assumed paramount importance, with a view toward preventing epimerization at this critical center by attachment of the C-1 galloyl moiety at the terminal stages of the synthesis. The (trimethylsilyl)ethyl unit seemed to be a promising candidate at this juncture.[22,23] Hence, the known compound **14**[23] was esterified with the acid **10**[16e] as previously described (Scheme 3). Desilylation of the resultant diester with TBAF provided the precursor to oxidation, **16**, which was submitted to $Pb(OAc)_4$-mediated coupling under conditions established for model compound **12.** A mixture of three isomers **17a-c** was obtained upon chromatographic purification. All three isomers shared a regioisomeric relationship but in each case maintained the *(S)*-HHDP stereochemistry (CD), thus reinforcing the highly diastereoselective outcome of the oxidative coupling reaction observed earlier. Benzylation of the mixture of regioisomers **17a-c** afforded the (new) regioisomers **18**, which were subjected to anomeric acylation using the reaction conditions advocated by Magnusson.[23] Unfortunately, exhaustive experimentation revealed that the conditions required for galloylation of the anomeric ether functionality proved to be incompatible with the structural integrity of the substrate, thus precluding the use of the (trimethylsilyl)ethyl ether as a C-1 hydroxyl protecting group in the synthetic scheme.

The quest for a hydroxyl protecting group removable under milder conditions eventually led to the selection of the photolabile *o*-nitrobenzyl moiety[24-26] for a second generation approach to sanguiin H-5 (**1**). This attempt at the target ellagitannin began with the known tetraol **21**,[26] which was further protected at the *O*(4) and *O*(6) positions by treatment with $ZnCl_2$ and benzaldehyde[27] (Scheme 4). Galloylation at the 2- and 3-positions of the glucopyranose core, followed by desilylation of the diester so obtained, led to cyclization precursor **24.** $Pb(OAc)_4$-mediated oxidation of substrate **24** furnished the expected regioisomeric mixture **25a-c**. Benzylation of the free phenols in this mixture, photolytic cleavage of the *O*(1) protecting group in the derived benzyl ether product, and β-selective galloylation with **26**[28] afforded the regioisomeric mixture **27** as a single stereoisomer at C-1. Hydrolytic removal of the benzylidene acetal and the diphenyl ketals (HOAc, H_2O) of the mixture **27** followed by hydrogenolysis to remove the benzyl protecting groups led to crude sanguiin H-5 (**1**). Purification of the crude ellagitannin was carried out using reversed-phase thin layer chromatography to afford pure material (**1**) in modest yield. All spectral data of the chemically elaborated sanguiin H-5 (**1**) coincides with that reported for the naturally occurring compound.[1]

In summary, sanguiin H-5 (**1**) represents the first *O*(2),*O*(3)-galloyl-coupled ellagitannin to be obtained via chemical synthesis.[14b] A key step in the synthesis is the formation of the biphenyl bond with complete diastereoselectivity. The formation of the *(S)*-atropisomer to the

(22) Application of Magnusson's BF_3·Et_2O-catalyzed acylation sequence to the trimethylsilylated glucose derivative **iv** yielded the desired β-anomer **vi**, eq 3.



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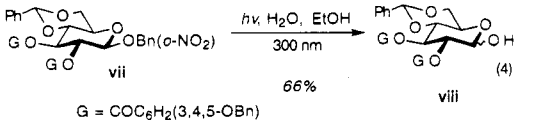
(25) Irradiation of compound **vii** at 300 nm in a Rayonet photochemical apparatus led to the anomerically deprotected derivative **viii** in good yield, eq 4.



(4)

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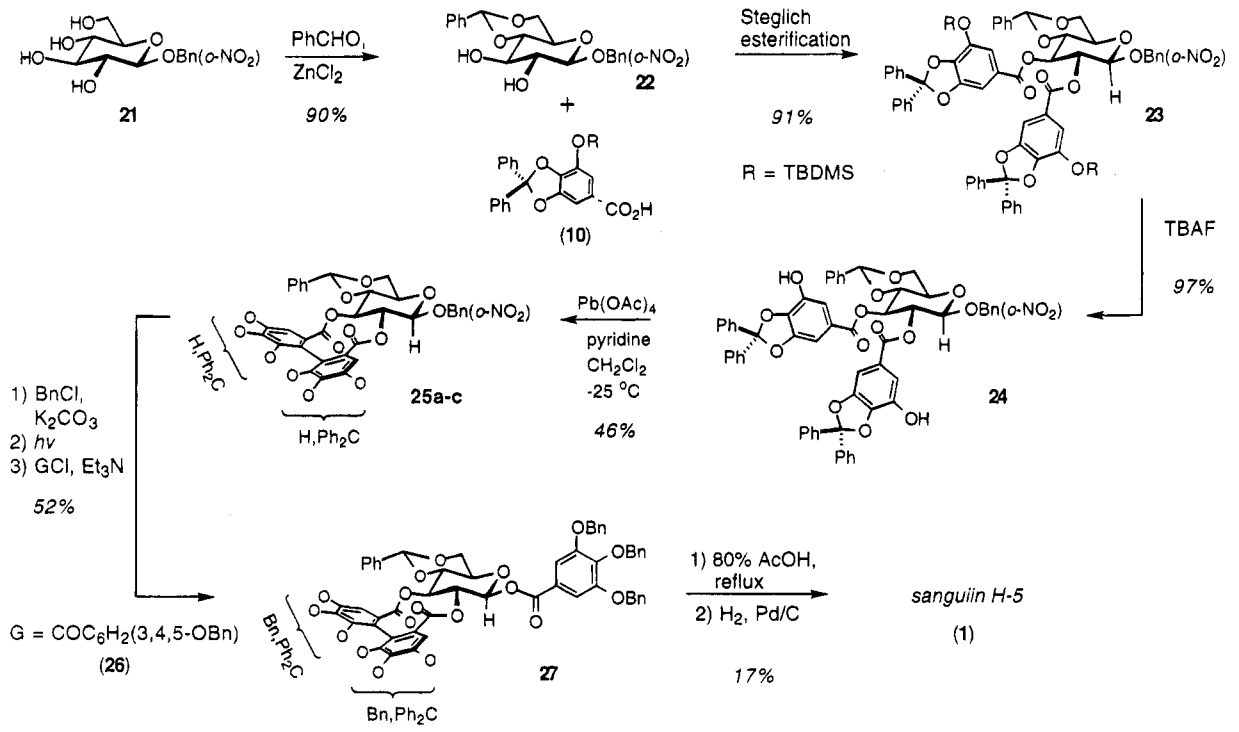
Scheme 4



exclusion its *(R)*-counterpart is in accord with the predictions of the Schmidt–Haslam proposal. Implicit in the formation of only a single atropisomer through selective oxidation of the cyclization precursor *in vitro* is that diastereoselectivity in the *in vivo* oxidative process does not necessarily require enzymic intervention. Rather, the chirality of the biphenyl C–C bond may be governed by the conformational dictates of the polyol template *in vivo* as well as *in vitro*. Also, the C-1 protecting group seems to affect the efficiency of the oxidative coupling process, possibly through an inductive effect. An electron-deficient moiety (e.g., *o*-nitrobenzyl) at this position appeared to diminish the yield of the coupled product compared to its more electron rich counterparts. The predictive value of MM conformational analyses in such systems cannot be ignored; the experimental results are in full agreement with the results from these calculations. The elaboration of sanguiin H-5 (**1**) thus demonstrates that 2,3-coupling is feasible and opens the way to more complex dimeric and trimeric ellagitannin targets.

Experimental Section

Circular dichroism (CD)[21] measurements used the wavelength range 200–300 nm, scanning at 0.5 nm intervals with an averaging time of 2.0 s at 25 °C in a 1 mm cell. The concentration of all solutions used was 1 mg per 3 mL of methanol. Liquid (flash) chromatography[29] was carried out using 32–63 μm silica gel and the indicated solvent. Preparative reversed-phase thin-layer chromatography was carried out using RP18 Prep W/UV_{254} (1 mm) plates. Tetrahydrofuran (THF) and benzene (PhH) were purified by distillation from sodium/benzophenone under argon (Ar), methylene chloride (CH_2Cl_2) was distilled from CaH_2 under Ar, while methanol (CH_3OH) was purified by distillation from Mg under Ar. Moisture-sensitive reactions were carried out in predried glassware under an inert atmosphere of Ar.

Modified Steglich Esterification[20] Reaction: General Procedure A. A solution of the appropriate polyol (1.0 equiv), acid (1.1 equiv per hydroxyl), 4-(dimethylamino)pyridine (DMAP) (0.5 equiv), DMAP·HCl (0.5 equiv), and 1,3-dicyclohexylcarbodiimide (DCC) (1.1 equiv per hydroxyl) in dry CH_2Cl_2 (0.025 M in polyol) was purged with Ar and heated at reflux under Ar for 15–20 h. The solution was returned to room temperature and filtered through Celite. The filtrate was diluted with an equal volume of CH_2Cl_2, and the reaction solution was added to ice-cold 1 M H_3PO_4. The organic fraction was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resultant crude product was purified by flash column chromatography using the solvent(s) indicated.

Silyl Ether Deprotection Reaction: General Procedure B. A deoxygenated solution of the appropriate digalloylated glucose derivative (1.0 equiv) in dry THF (0.030 M in glucose derivative) at room temperature was treated with a solution of tetrabutylammonium fluoride (1.2 equiv per silyl group) in dry THF (0.025 M final concentration of glucose derivative). The solution was stirred under Ar for 10–20 min at room temperature. At the end of the indicated time period, the reaction solution was carefully diluted with ice-cold 1 M H_3PO_4, and the product was extracted into Et_2O. The Et_2O extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography was employed to obtain the pure product from the crude residue, using the solvent(s) indicated.

Lead Tetraacetate Oxidation Reaction: General Procedure C. A solution of $Pb(OAc)_4$ (1.1 equiv) in 5 mL of dry CH_2Cl_2 was added dropwise over 20 min to a deoxygenated solution of the appropriate bis phenol (1 equiv) and pyridine (4.0 equiv) in dry CH_2Cl_2 (0.005 M final concentration of bis phenol) at −25 °C. The deep orange/yellow solution was stirred at −25 °C for the indicated time period. The reaction solution was diluted with saturated $NaHCO_3$ solution, and the products were extracted into Et_2O or EtOAc. The organic extract was washed with 1 M H_3PO_4 and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude products were purified by flash column chromatography using the solvent(s) indicated.

Methyl 4,6-*O*-Benzylidene-2,3-bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoyl)-α-D-glucopyranoside (11). By use of general procedure A, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**9**) (Aldrich) (1.0 g, 3.6 mmol) and 3-(*tert*-butyldimethylsiloxy)-4,5-((diphen-

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

ylmethylene)dioxy)benzoic acid (**10**)[16e] (3.50 g, 7.80 mmol) were coupled to afford 3.50 g (86%) of **11** as a white foam following column chromatography using 20% Et_2O in petroleum ether as the eluent: IR (CH_2Cl_2) 1720 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 7.59–7.17 (m, 29 H), 5.90 (t, J = 9.9 Hz, 1 H), 5.68 (s, 1 H), 5.22–5.17 (m, 2 H), 4.33 (dd, J = 9.5, 4.0 Hz, 1 H), 4.09 (t, J = 9.3 Hz, 1 H), 3.99 (dt, J = 9.6, 4.1 Hz, 1 H), 3.89 (t, J = 9.7 Hz, 1 H), 3.43 (s, 3 H), 0.99–0.95 (m, 18 H), 0.14–0.11 (m, 12 H); ^{13}C NMR (50 MHz, C_3D_6O) δ 165.3, 164.7, 148.5, 148.3, 141.8, 141.4, 139.8, 139.7, 138.5, 138.3, 136.9, 129.1, 128.9, 128.2, 128.1, 126.1, 123.6, 122.8, 118.9, 118.7, 118.0, 117.9, 104.2, 104.0, 101.5, 97.8, 79.4, 72.4, 69.3, 68.8, 62.4, 55.4, 25.5, 18.2, –4.6; MS (+FAB) 1143 (MH^+, 33). Anal. Calcd for $C_{66}H_{70}O_{14}Si_2$: C, 69.31; H, 6.17; Found: C, 69.30; H, 6.29.

Methyl 4,6-*O*-Benzylidene-2,3-bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-α-D-glucopyranoside (12). By use of general procedure B, **11** (3.40 g, 2.98 mmol) was desilylated in 10 min to afford 2.48 g (91%) of **12** as a white foam following flash column chromatography, eluting with 50% petroleum ether in Et_2O and then 33% petroleum ether in Et_2O: IR (CH_2Cl_2) 1722 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 9.03 (bs, 2 H), 7.59–7.08 (m, 29 H), 5.88 (t, J = 9.2 Hz, 1 H), 5.68 (s, 1 H), 5.20–5.15 (m, 2 H), 4.33 (dd, J = 9.3, 3.8 Hz, 1 H), 4.08 (t, J = 9.3 Hz, 1 H), 3.98 (dt, J = 9.5, 4.0 Hz, 1 H), 3.89 (t, J = 9.7 Hz, 1 H), 3.43 (s, 3 H); ^{13}C (50 MHz, $CDCl_3$) δ 165.8, 165.4, 148.5, 148.3, 139.5, 139.4, 139.2, 139.0, 138.7, 138.5, 136.8, 129.3, 129.0, 128.3, 128.2, 126.3, 126.2, 123.3, 122.8, 118.8, 118.7, 114.3, 103.5, 103.4, 101.7, 97.7, 79.1, 72.8, 69.9, 68.9, 62.4, 55.5; MS (+FAB) 915 (MH^+, 100). Anal. Calcd for $C_{54}H_{42}O_{14}$: C, 70.89; H, 4.63; Found: C, 70.58; H, 5.00.

Lead Tetraacetate Oxidation of Methyl 4,6-*O*-Benzylidene-2,3-bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-α-D-glucopyranoside (12). By use of general procedure C, **12** (0.50 g, 0.55 mmol) in 105 mL of dry CH_2Cl_2 at –25 °C was oxidized with a solution of $Pb(OAc)_4$ (0.27 g, 0.60 mmol) in 5 mL dry of CH_2Cl_2. The solution was allowed to stir at –25 °C for 1 h and then worked up as indicated, using Et_2O for extraction. Flash column chromatography of the crude product using 10% hexanes in CH_2Cl_2, followed by CH_2Cl_2 and 1%, 3%, and 5% Et_2O in CH_2Cl_2 as eluent, yielded 0.29 g (58%) of three regioisomers **13a-c**. The individual isolation of each isomer for characterization was accomplished by preparative TLC on precoated silica gel 60 F_{254} plates, using 3% Et_2O in CH_2Cl_2 as the solvent system.

Isomer 13a: IR (CH_2Cl_2) 1750 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 7.74–7.33 (m, 25 H), 6.68 (s, 1 H), 6.61 (s, 1 H), 5.71 (s, 1 H), 5.41 (t, J = 9.3 Hz, 1 H), 5.06 (dd, J = 9.0, 3.6 Hz, 1 H), 5.02 (d, J = 3.6 Hz, 1 H), 4.30 (d, J = 5.5Hz, 1 H), 3.99–3.87 (m, 3 H), 3.46 (s, 3 H); ^{13}C (75 MHz, C_3D_6O) δ 168.4, 168.1, 148.4, 147.9, 141.1, 141.05, 141.02, 140.9, 140.7, 140.1, 138.6, 137.0, 135.9, 130.2, 129.99, 129.97, 129.8, 129.4, 129.29, 129.28, 129.1, 129.0, 128.9, 127.6, 127.3, 127.0, 126.9, 118.9, 118.6, 117.0, 110.9, 108.4, 102.4, 100.2, 99.1, 78.7, 74.8, 74.6, 69.2, 63.9, 55.7; CD (CH_3OH) 241 nm, +40.0, 267 nm, –14.4, 288 nm, +7.5.

Isomer 13b: IR (CH_2Cl_2) 1748 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 7.67–7.13 (m, 25 H), 6.72 (s, 1 H), 6.66 (s, 1 H), 5.72 (s, 1 H), 5.45 (t, J = 9.4 Hz, 1 H), 5.12 (d, J = 3.6 Hz, 1 H), 5.06 (dd, J = 8.3, 3.6 Hz, 1 H), 4.30 (d, J = 5.4 Hz, 1 H), 4.03–3.88 (m, 3 H), 3.48, (s, 3 H); ^{13}C NMR (90 MHz, C_3D_6O) δ 168.3, 167.9, 148.2, 140.8, 140.6, 140.5, 140.4, 138.6, 136.2, 136.1, 130.1, 130.0, 129.8, 129.34, 129.30, 129.1, 129.0, 128.9, 128.5, 127.8, 127.6, 127.3, 127.1, 127.0, 126.9, 119.0, 111.8, 111.5, 107.1, 107.0, 102.4, 99.1, 78.7, 75.2, 74.6, 69.2, 69.0, 55.7; CD (CH_3OH) 237 nm, +60.0, 263 nm, –47.5, 289 nm, +11.4.

Isomer 13c: IR (CH_2Cl_2) 1753 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 7.72–7.15 (m, 25 H), 6.66 (s, 1 H), 6.62 (s, 1 H), 5.71 (s, 1 H), 5.40 (t, J = 9.2 Hz, 1 H), 5.09–5.03 (m, 2 H), 4.30 (d, J = 5.4 Hz, 1 H), 4.04–3.86 (m, 3 H), 3.47 (s, 3 H); ^{13}C NMR (C_3D_6O, 90 MHz) δ 168.5, 168.1, 148.5, 148.0, 141.2, 141.02, 141.01, 140.9, 140.7, 140.2, 138.6, 136.9, 136.0, 133.2, 130.5, 130.24, 130.20, 130.14, 130.10, 129.99, 129.97, 129.7, 129.4, 129.3, 129.2, 129.10, 129.06, 129.0, 128.89, 128.86, 127.8, 127.5, 127.3, 127.2, 127.1, 127.00, 126.99, 126.93, 126.90, 126.8, 118.8, 118.7, 117.0, 111.1, 108.4, 102.2, 100.1, 99.1, 78.7, 75.2, 74.3, 69.2, 64.0, 55.6; CD (CH_3OH) 239 nm, +46.2, 265 nm, –28.3, 288 nm, +6.2.

Isomers 13a-c: MS (+FAB) 913 (MH^+, 100); HRMS (+FAB) calcd for $C_{54}H_{40}O_{14}$ 912.2418, found 912.2433.

2-(Trimethylsilyl)ethyl 4,6-*O*-Benzylidene-2,3-bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoyl)-β-D-glucopyranoside (15). By use of general procedure A, 2-(trimethylsilyl)ethyl 4,6-*O*-benzylidene-α-D-glucopyranoside[23] (**14**) (0.39 g, 1.1 mmol) was esterified with the acid **10** (94 mg, 2.1 mmol) to yield 1.17 g (91%) of compound **15** as a white foam upon silica gel column chromatography using 20% Et_2O in petroleum ether as the eluent: IR (CH_2Cl_2) 1728 cm^{-1}; ^1H (200 MHz, C_3D_6O) δ 7.60–7.14 (m, 29 H), 5.73–5.60 (m, 2 H), 5.31 (t, J = 8.7 Hz, 1 H), 5.02 (d, J = 7.9 Hz, 1 H), 4.36 (dd, J = 9.4, 4.0 Hz, 1 H), 4.07–3.59 (m, 5 H), 0.98–0.76 (m, 20 H), 0.15–0.14 (m, 12 H), –0.077 to –0.079 (m, 9 H); ^{13}C (50 MHz, $CDCl_3$) δ 164.8, 164.3, 148.4, 141.5, 139.9, 139.8, 138.4, 136.9, 129.1, 128.9, 128.2, 128.1, 126.2, 123.3, 118.8, 118.1, 104.1, 101.4, 101.2, 78.9, 72.4, 72.0, 68.7, 67.9, 66.5, 25.5, 18.2, 18.1, –1.5, –4.6; MS (+FAB) 1229 (MH^+, 37). Anal. Calcd for $C_{70}H_{80}O_{14}Si_3$: C, 68.38; H, 6.56; Found: C, 68.28; H, 6.63.

2-(Trimethylsilyl)ethyl 4,6-*O*-Benzylidene-2,3-bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-β-D-glucopyranoside (16). Following general procedure B, **15** (1.00 g, 0.81 mmol) was desilylated in 20 min to afford 0.80 g (98%) of **16** as a white foam upon purification by flash column chromatography, eluting with 33% petroleum ether in Et_2O: IR (CH_2Cl_2) 1728 cm^{-1}; ^1H (300 MHz, C_3D_6O) δ 7.59–7.53 (m, 8 H), 7.45–7.21 (m, 19 H), 7.11–7.09 (m, 2 H), 5.67 (t, J = 9.5 Hz, 1 H), 5.66 (s, 1 H), 5.30 (dd, J = 9.4, 7.9 Hz, 1 H), 5.00 (d, J = 7.9 Hz, 1 H), 4.36 (dd, J = 10.0, 4.7 Hz, 1 H), 4.05 - 3.61 (m, 5 H), 0.91 (ddd, J = 14.0, 10.0, 6.6 Hz, 1 H), 0.79 (ddd, J = 14.0, 9.7, 5.9 Hz, 1 H), –0.08 (s, 9 H); ^{13}C (75 MHz, C_3D_6O) 165.2. 164.9, 149.1, 141.2, 140.66, 140.64, 139.2, 139.1, 138.5, 130.2, 130.1, 129.5, 129.2, 128.7, 127.0, 126.9, 124.8, 124.7, 118.8, 118.7, 115.0, 114.9, 103.0, 101.9, 101.7, 79.5, 73.3, 69.0, 67.9, 67.1, 18.5, –1.4; MS (+FAB) 1001 (MH^+, 78). Anal. Calcd for $C_{58}H_{52}O_{14}Si$: C, 69.59; H, 5.24; Found: C, 69.32; H, 5.76.

Lead Tetraacetate Oxidation of 2-(Trimethylsilyl)-ethyl 4,6-*O*-Benzylidene-2,3-bis(3,4-((diphenylmethylene)-dioxy)-5-hydroxybenzoyl)-β-D-glucopyranoside (16). By use of general procedure C, bis phenol **16** (0.37 g, 0.37 mmol) in 61 mL of dry CH_2Cl_2 at –25 °C was oxidized with $Pb(OAc)_4$ (0.18 g, 0.40 mmol) in 5 mL of dry CH_2Cl_2. This solution was stirred at –25 °C for 30 min and then worked up as indicated, using Et_2O for extraction. Purification of the crude residue by flash column chromatography using 10% hexanes in CH_2Cl_2, followed by CH_2Cl_2 and 1%, 3%, and 5% Et_2O in CH_2Cl_2 as eluent, yielded 0.21 g (58%) of the three regioisomers **17a-c**. The individual isolation of each isomer for characterization was accomplished by preparative TLC on precoated silica gel 60 F_{254} plates, using 3% Et_2O in CH_2Cl_2 as the solvent system.

Isomer 17a: IR (CH_2Cl_2) 1753 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 9.00 (s, 1H), 8.93 (s, 1H), 7.71–7.16 (m, 26 H), 6.64 (s, 1 H), 5.71 (s, 1 H), 5.26 (dd, J = 9.9, 9.2 Hz, 1 H), 4.94 (d, J = 8.1 Hz, 1 H), 4.86–4.81 (m, 1 H), 4.34 (dd, J = 10.2, 4.9 Hz, 1 H), 4.08–3.57 (m, 5 H), 1.07–0.85 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (90 MHz, C_3D_6O) δ 168.6, 167.9, 148.5, 148.0, 141.2, 141.0, 140.9, 140.7, 140.2, 138.6, 137.0, 136.0, 130.2, 130.0, 129.7, 129.6, 129.3, 129.1, 129.0, 128.8, 127.6, 127.2, 127.0, 126.9, 118.9, 118.7, 117.2, 110.9, 108.6, 102.1, 100.6, 100.1, 78.2, 77.2, 76.6, 69.1, 67.7, 67.6, 18.4, –1.1; CD (CH_3OH) 239 nm, +23.8, 266 nm, –8.3, 288 nm, +2.8.

Isomer 17b: IR (CH_2Cl_2) 1751 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 9.02 (s, 1 H), 8.94 (s, 1 H), 7.57 - 7.13 (m, 25 H), 6.69 (s, 1 H), 6.68 (s, 1 H), 5.71 (s, 1 H), 5.31 (t, J = 9.5 Hz, 1 H), 4.96 (d, J = 8.1 Hz, 1 H), 4.90–4.84 (m, 1 H), 4.33 (dd, J = 10.3, 4.8 Hz, 1 H), 4.09–3.58 (m, 5 H), 1.08–0.86 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (90 MHz, C_3D_6O) δ 168.4, 167.8, 148.2, 140.83, 140.80, 140.6, 140.5, 140.4, 138.6, 136.3, 130.2, 130.1, 129.8, 129.2, 129.1, 129.0, 128.9, 127.8, 127.7, 127.2, 127.1, 119.1, 111.5, 107.3, 107.2, 102.2, 100.5, 78.2, 77.3, 76.9, 69.1,

67.8, 67.6, 18.4, −1.1; CD (CH_3OH) 239 nm, +36.9, 264 nm, −26.2, 288 nm, +8.8.

Isomer 17c: IR (CH_2Cl_2) 1753 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 9.03 (s, 1 H), 8.85 (s, 1 H), 7.72−7.03 (m, 25 H), 6.62 (s, 1 H), 6.60 (s, 1 H), 5.71 (s, 1 H), 5.30−5.23 (m, 1 H), 4.96 (d, J = 8.2 Hz, 1 H), 4.85−4.79 (m, 1 H), 4.33 (dd, J = 10.3, 4.9 Hz, 1 H), 4.09−3.66 (m, 5 H), 1.10 - 0.89 (m, 2 H), 0.05 (s, 9 H); ^{13}C NMR (90 MHz, C_3D_6O) 168.5, 167.9, 148.5, 148.0, 141.13, 141.11, 141.0, 140.8, 140.7, 140.3, 138.6, 137.0, 136.0, 130.3, 130.2, 130.0, 129.8, 129.5, 129.3, 129.1, 129.0, 128.9, 127.6, 127.3, 127.1, 127.0, 126.9, 118.9, 118.7, 117.3, 110.9, 108.5, 102.2, 100.6, 99.8, 78.3, 76.0, 76.8, 69.1, 67.9, 67.6, 18.4, −1.1; CD (CH_3OH) 240 nm, +14.4, 266 nm, −5.6, 288 nm, +1.7.

Isomers 17a-c: MS (+FAB) 999 (MH^+, 100); HRMS (+FAB) calcd for $C_{58}H_{50}O_{14}Si$ 998.2970, found 998.2952.

Benzylation of Compounds 17a-c. K_2CO_3 (25 mg, 0.18 mmol), KI (2 mg, 0.01 mmol), and benzyl chloride (21 μL, 0.18 mmol) were added to a solution of **17a-c** (46 mg, 0.046 mmol) in 2 mL of acetone. The reaction mixture was deoxygenated and heated to reflux under Ar for 5.5 h. The cooled reaction solution was filtered through Celite, concentrated in vacuo, and purified by flash column chromatography, using 50%, 40%, 30%, 20%, and 10% hexanes in CH_2Cl_2, followed by CH_2Cl_2 as eluent, to afford 34 mg (63%) of **18** as a mixture of regioisomers: IR (CH_2Cl_2) 1753 cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz) δ 7.70−6.88 (m, 35 H), 6.86−6.77 (m, 2 H), 5.72−5.71 (m, 1 H), 5.36−4.84 (m, 7 H), 4.37−4.30 (m, 1 H), 4.08−3.67 (m, 5 H), 1.07−0.84 (m, 2 H), 0.06−0.04 (m, 9 H); MS (+FAB) 1180 (MH^+, 100).

2-Nitrobenzyl 4,6-*O*-Benzylidene-β-D-glucopyranoside (21). $ZnCl_2$ (4.97 g, 36.5 mmol) was added in an inert atmosphere to a suspension of the tetrol **20**[26] (2.17 g, 6.88 mmol) in 25 mL of benzaldehyde. The resultant suspension was allowed to stir for 16 h under Ar. The reaction solution was diluted with ice, and the crude product was extracted into EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The brown oil thus obtained was purified by flash column chromatography, eluting first with hexane and then with 50% EtOAc in hexane, to obtain 2.51 g of **21** (90%) as a white solid: IR (CH_2Cl_2) 1748 cm^{-1}; ^1H NMR (C_3D_6O, 200 MHz) δ 8.13−7.33 (m, 9 H), 5.60 (s, 1 H), 5.24 (d, J = 15.4 Hz, 1 H), 5.08 (d, J = 15.3 Hz, 1 H), 4.67−4.58 (m, 2 H), 4.24 (dd, J = 10.2, 4.4 Hz, 1 H), 3.81−3.42 (m, 4 H); ^{13}C NMR (C_3D_6O, 50 MHz) δ 139.2, 135.5, 134.6, 129.9, 129.5, 129.1, 128.7, 127.3, 125.2, 104.4, 102.1, 82.0, 75.9, 74.5, 69.2, 68.1, 67.3; MS (+FAB) 404 (MH^+, 100); HRMS (EI) calcd for $C_{20}H_{21}NO_8$ 403.1267, found 403.1230.

2-Nitrobenzyl 4,6-*O*-Benzylidene-2,3-bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoyl)-β-D-glucopyranoside (22). Following general procedure A, 2-nitrobenzyl 4,6-*O*-benzylidene-β-D-glucopyranoside **21** (0.57 g, 1.4 mmol) was galloylated with **10** (1.39 g, 3.11 mmol) to yield 1.62 g (91%) of compound **22** as a white foam upon flash column chromatography using 30% Et_2O in petroleum ether as eluent: IR (CH_2Cl_2) 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.05−7.17 (m, 33 H), 5.72 (t, J = 9.4 Hz, 1 H), 5.58−4.49 (m, 2 H), 5.32 (d, J = 15.7 Hz, 1 H), 5.06 (d, J = 15.6 Hz, 1 H), 4.89 (d, J = 7.6 Hz, 1 H), 4.46 (dd, J = 10.2, 4.2 Hz, 1 H), 3.96−3.69 (m, 3 H), 0.97 (s, 18 H), 0.13−0.12 (m, 12 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.7, 164.4, 148.4, 148.3, 146.5, 141.7, 139.8, 139.7, 139.6, 138.5, 138.4, 136.7, 134.0, 133.9, 129.2, 128.9, 128.2, 128.1, 127.8, 126.1, 124.5, 123.1, 122.9, 118.9, 118.8, 118.1, 118.0, 104.1, 101.4, 101.3, 78.9, 72.3, 71.7, 68.5, 68.0, 66.6, 25.4, 18.1, −4.5, −4.6; MS (+FAB) 1264 (MH^+, 27). Anal. Calcd for $C_{72}H_{73}NO_{16}Si_2$: C, 68.39; H, 5.82; N, 1.11; Found: C, 68.11; H, 5.98; N, 0.98.

2-Nitrobenzyl 4,6-*O*-Benzylidene-2,3-bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-β-D-glucopyranoside (23). By use of general procedure B, **22** (0.61 g, 0.49 mmol) was desilylated in 10 min to afford 0.49 g of **23** (97%) as a white foam following purification by silica gel chromatography using 33% Et_2O in petroleum ether as the eluent: IR (CH_2Cl_2) 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.91−7.05 (m, 33 H), 6.90 (bs, 1 H), 6.79 (bs, 1 H), 5.76 (t, J = 9.3 Hz, 1 H), 5.57−5.48 (m, 1 H), 5.42 (s, 1 H), 5.23 (d, J = 15.6 Hz, 1 H), 4.93 (d, J = 15.5 Hz, 1 H), 4.83 (d, J = 7.7 Hz, 1 H), 4.40−4.37 (m, 1 H), 3.95−3.72 (m, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.6, 165.1, 148.4, 148.3, 146.4, 139.4, 139.2, 139.1, 138.8, 136.6, 133.7, 133.6, 129.3, 128.3, 128.1, 127.9, 126.2, 126.1, 125.5, 123.0, 122.8, 118.7, 118.6, 114.3, 103.5, 101.4, 101.2, 78.8, 72.8, 72.2, 68.5, 68.2, 66.6; MS (+FAB) 1036 (MH^+, 100). Anal. Calcd for $C_{60}H_{45}NO_{16}$: C, 69.56; H, 4.38; N, 1.35; Found: C, 69.20; H, 4.94; N, 1.65.

Lead Tetraacetate Oxidation of 2-Nitrobenzyl 4,6-*O*-Benzylidene-2,3-bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-β-D-glucopyranoside (23). By use of general procedure C, bis phenol **23** (1.29 g, 1.25 mmol) in 244 mL of dry CH_2Cl_2 at −25 °C was oxidized with $Pb(OAc)_4$ (0.61 g, 1.4 mmol) in 5 mL of dry CH_2Cl_2. The solution was stirred at −25 °C for a further period of 1.5 h and then worked up as indicated, using EtOAc for extraction. Purification of the resultant yellow residue by silica gel chromatography using 10% hexanes in CH_2Cl_2, followed by CH_2Cl_2, 1%, 3%, and 5% Et_2O in CH_2Cl_2 as eluent, yielded 0.59 g (46%) of the regioisomeric mixture **24**. The regioisomers were characterized as their corresponding acetates **24a,b** and **24c** (separated by preparative thin-layer chromatography using 2% EtOAc in benzene as the solvent).

Isomers 24a,b: IR (CH_2Cl_2) 1778 cm^{-1}, 1756 cm^{-1}; ^1H NMR (C_3D_6O, 200 MHz) δ 8.09−7.31 (m, 29 H), 7.09−6.91 (m, 2 H), 5.75−5.72 (m, 1 H), 5.41−5.32 (m, 1 H), 5.31 - 5.10 (m, 3 H), 5.01 - 4.89 (m, 1 H), 4.40−4.36 (m, 1 H), 4.12−3.83 (m, 3 H), 2.38−2.34 (m, 6 H) (**24a**), 1.48−1.44 (m, 6 H), (**24b**).

Isomer 24c: IR (CH_2Cl_2) 1776 cm^{-1}, 1754 cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz) δ 8.15−7.10 (m, 29 H), 7.09 (s, 1 H), 6.95 (s, 1 H), 5.73 (s, 1 H), 5.39 (dd, J = 9.9, 9.1 Hz, 1 H), 5.21 (s, 1 H), 5.20 (s, 1 H), 5.14 (d, J = 8.3 Hz, 1 H), 4.99 (dd, J = 9.0, 8.2 Hz, 1 H), 4.37 (dd, J = 10.0, 4.6 Hz, 1 H), 4.08−4.01 (m, 1 H), 3.92 (t, J = 10.0 Hz, 1 H), 3.87−3.76 (m, 1 H), 2.36 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (C_3D_6O, 90 MHz) δ 168.2, 168.1, 167.8, 167.1, 149.0, 148.5, 141.0, 139.7, 139.5, 139.4, 138.5, 134.5, 133.9, 133.5, 133.4, 130.5, 130.4, 130.3, 129.84, 129.80, 129.2, 129.1, 128.9, 128.7, 127.8, 127.3, 127.2, 127.0, 125.5, 120.9, 116.9, 116.8, 111.7, 111.6, 102.2, 100.5, 77.8, 77.5, 77.3, 68.8, 67.7, 20.4; CD (CH_3OH) 216 nm, +60.0, 250 nm, −48.9, 278 nm, +17.8.

Isomers 24a-c: MS (+FAB) 1118 (MH^+, 100); HRMS(+FAB) calcd for $C_{64}H_{47}NO_{18}$ 1118.2871, found 1118.2883.

Anomeric Acylation of Compound 24. Benzyl chloride (28 μL, 0.2 mmol), K_2CO_3 (33 mg, 0.2 mmol), and KI (2 mg, 0.01 mmol) were added to a solution of **24** (0.06 g, 0.06 mmol) in 3 mL of acetone. The resultant mixture was deoxygenated and refluxed under Ar for 14 h. The cooled reaction solution was filtered through Celite and concentrated to afford a yellow oil. Trituration of the oil with hexanes afforded 65 mg of the benzylated derivative of **24** as a yellow solid. Benzylated **24** was dissolved in a mixture of 2.5 mL of THF, 2.5 mL of EtOH, and 14 μL of distilled water and irradiated at 300 nm in a Pyrex tube suspended in a Rayonet photochemical apparatus for 7 h. Removal of the solvents in vacuo afforded an oily residue, which, on trituration with hexanes, yielded 54 mg of the corresponding anomerically deprotected compound. Acylation of the mixture of C-1 anomers thus obtained in 2.5 mL of dry CH_2Cl_2 with 3,4,5-(tribenzyloxy)benzoyl chloride **25**[28] (28 mg, 0.060 mmol) and triethylamine (18 μL, 0.013 mmol) yielded 43 mg (52% over three steps) of compound **26** following chromatographic purification using 40% petroleum ether in CH_2Cl_2, 30% petroleum ether in CH_2Cl_2 and CH_2Cl_2 as eluent: IR (CH_2Cl_2) 1755 cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz) δ 7.70−7.02 (m, 52 H), 6.98−6.72 (m, 2 H), 6.39−6.28 (m, 1 H), 5.80−5.71 (m, 1 H), 5.61−5.49 (m, 1 H), 5.32−4.98 (m, 11 H), 4.43−4.32 (m, 1 H), 4.20−3.86 (m, 3 H); MS (+FAB) 1502 (M+2, 100).

Deprotection of compound 26. (a) Hydrolytic Cleavage of Diphenyl Ketals and Benzylidene Acetal. Compound **26** (68 mg, 0.040 mmol) was refluxed in 5 mL of 80% aqueous acetic acid for 7 h. Removal of solvents in vacuo and trituration of the crude residue with hexanes yielded 48 mg of a pale yellow solid. **(b) Hydrogenolysis.** A solution of this crude and 90 mg of 10% Pd on C in 5 mL of dry THF was stirred at room temperature under H_2 at 1 atm for 14 h, purged

thoroughly with Ar, filtered through Celite, and concentrated in vacuo. Purification of the resultant gray residue was accomplished by preparative thin-layer chromatography using 20% CH_3OH in water as the solvent, yielding 5 mg of sanguiin H-5 (**1**) (17% over two steps) as a pale yellow solid: ^1H NMR (C_3D_6O, 200 MHz) δ 7.14 (s, 2 H), 6.70 (s, 1 H), 6.41 (s, 1 H), 6.12 (d, J = 8.4 Hz, 1 H), 5.20 (t, J = 9.4 Hz, 1 H), 4.99 (dd, J = 9.5 Hz, 8.4 Hz, 1 H), 3.99–3.62 (m, 4 H); ^{13}C NMR (C_3D_6O, 90 MHz) δ 170.9, 168.8, 165.0, 146.3, 145.3, 139.7, 136.4, 136.2, 127.1, 126.6, 119.9, 110.2, 107.8, 107.2, 92.2, 80.4, 79.0, 75.4, 67.9, 61.8; MS (+FAB) 634 (M^+, 8); CD (CH_3OH) 237 nm, +25.6, 262 nm, −7.5, 283 nm, −1.9.

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