Ellagitannin Chemistry. Evolution of a Three-Component Coupling Strategy for the Synthesis of the Dimeric Ellagitannin Coriariin A and a Dimeric Gallotannin Analogue

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The total synthesis of the dimeric ellagitannin coriariin A is reported. The key reaction to access the dimeric framework was realized early in the synthesis pathway via a bis acylation reaction of a dehydrodigalloyl diacid with 2 equiv of a glucopyranose trichloroacetimidate. The glucose rings were subsequently functionalized, culminating in a double oxidative cyclization to form stereoselectively both (*S*)-HHDP ester units. This bis acylation strategy was also employed to prepare a gallotannin analogue of coriariin A whose earlier synthesis by orthoquinone dimerization was plagued by yield-limiting side reactions.

Dimeric ellagitannins that are C−O linked through the anomeric galloyl rings constitute a small but biologically notable subfamily of polyphenolic plant metabolites.[1] Screening for antitumor activity among these species revealed remarkable tumor remissive properties against mouse xenograft lines for several structurally similar (but not phylogenetically related) members such as coriariin A (**1**) and agrimoniin (**2**), Figure 1.[2] Furthermore, these data show that the dimeric ellagitannins are much more effective antitumor agents than their likely monomeric precursors. Subsequent studies aimed at uncovering the cellular basis for this activity suggested that coriariin A and agrimoniin did not directly kill tumor cells, but rather exerted their effect indirectly through stimulated production of tumor necrosis factor-α (TNF-α) from peripheral blood mononuclear cells (PBMCs).[2c,d,3] This cytokine displays tumor-remissive properties, although systemic toxicity has limited its use in antitumor therapies.[4]

The broad range of measured antitumor efficacy among some 45-odd monomeric, dimeric (including **1** and **2**), and trimeric ellagitannins is suggestive of a model for biological activity which requires a specific interaction between the tannin and an endogenous receptor(s), plausibly associated with the PBMCs, to initiate TNF-α release. Identifying the putative PBMC-based receptor(s) for the active ellagitannins may provide the impetus for further developing ellagitannins, or ellagitannin-inspired analogues, as biological response modifiers within the context of antitumor chemotherapies. In this vein, synthesis of the naturally occurring species, as well as rationally designed analogues, may provide appropriate probe molecules to aid in this task.

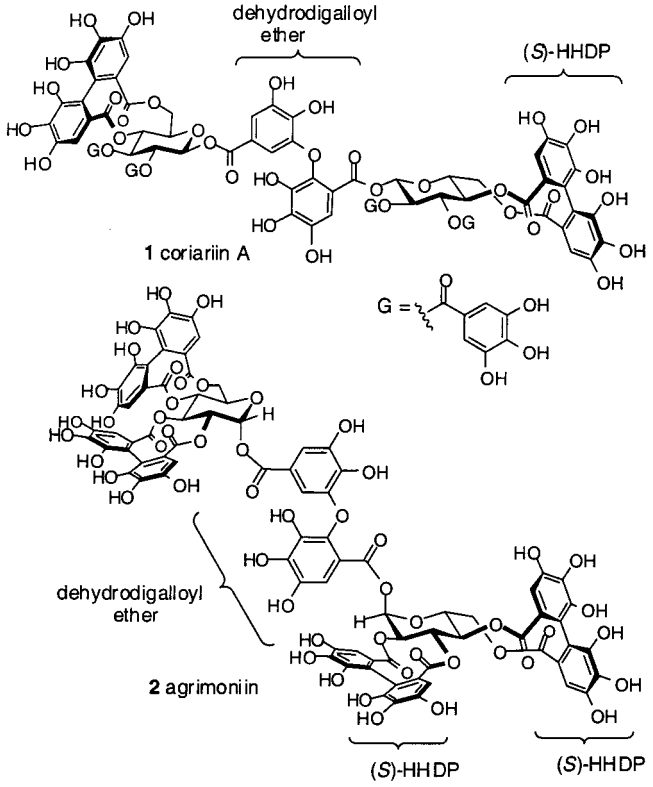

Figure 1. Representative O(1)−O(1′) linked dimeric ellagitannins.

(1) (a) Haslam, E. *Practical Polyphenolics*; Cambridge University Press: Cambridge, 1998. (b) Feldman, K. S.; Sahasrabudhe, K.; Quideau, S.; Hunter, K. L.; Lawlor, M. D. In *Plant Polyphenols 2*: *Chemistry, Biology, Pharmacology, Ecology*; Kluwer Academic/Plenum Publishers: New York, 1999. (c) Okuda, T.; Yoshida, T.; Hatano, 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; Vol. 66, p 1−117, and references therein. (d) Hatano, T.; Hattori, S.; Okuda, T. *Chem. Pharm. Bull.* **1986**, *34*, 4092. (e) Okuda, T.; Yoshida, T.; Kuwahara, M.; Memon, M. U.; Shingu, T. *Chem. Pharm. Bull.* **1984**, *32*, 2165.

(2) (a) Miyamoto, K.; Kishi, N.; Koshiura, R. *Japan J. Pharmacol.* **1987**, *43*, 187. (b) Miyamoto, K.; Kishi, N.; Koshiura, R.; Yoshida, T.; Hatano, T.; Okuda, T. *Chem. Pharm. Bull.* **1987**, *35*, 814. (c) Miyamoto, K.; Murayama, T.; Nomura, M.; Hatano, T.; Yoshida, T.; Furukawa, T.; Koshiura, R.; Okuda, T. *Anticancer Res.* **1993**, *13*, 37. (d) Murayama, T.; Kishi, N.; Koshiura, R.; Takagi, K.; Furukawa, T.; Miyamoto, K. *Anticancer Res.* **1992**, *12*, 1471. (e) Miyamoto, K.; Nomura, M.; Murayama, T.; Furukawa, T.; Hatano, T.; Yoshida, T.; Koshiura, R.; Okuda, T. *Biol. Pharm. Bull.* **1993**, *16*, 379.

(3) Feldman, K. S.; Sahasrabudhe, K.; Smith, R. S.; Scheuchenzuber, W. J. *Biorg. Med. Chem. Lett.* **1999**, *9*, 985.

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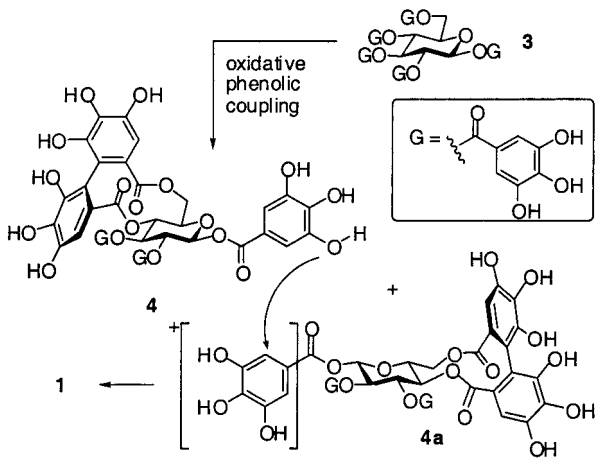
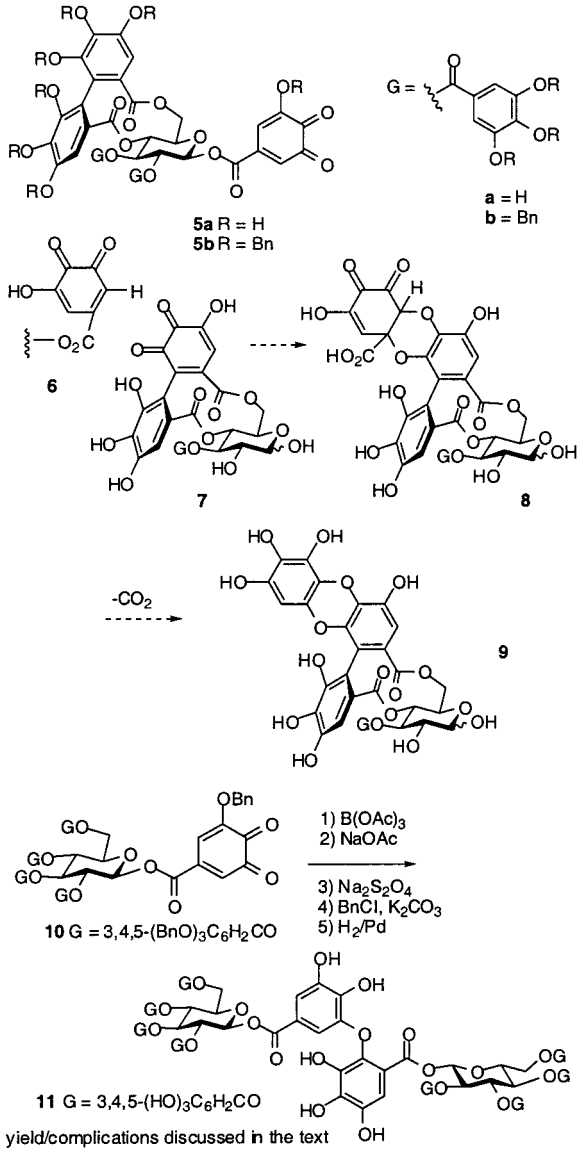
Scheme 1



Synthesis strategies in the ellagitannin area have largely fallen into two camps, depending upon whether the bis galloyl-to-HHDP (hexahydroxydiphenoyl) transformation occurs before[5a−d] or after[5e−m] attachment of the galloyl ester moieties to the glucopyranose core. In addition, the methodology for forming the key biaryl C−C bond upon HHDP synthesis has utilized both reductive (e.g., Ullmann-type)[5e,f,m] and oxidative (e.g., Wessely type)[5a−d] couplings. Several syntheses of permethyl ellagitannins have been recorded, in particular using reductive coupling methodologies, but as yet exhaustive demethylation to unveil the product polyphenol remains problematic.[5e,f,l] In contrast, HHDP synthesis by oxidative phenolic coupling has proven to be tolerant of phenolic protecting groups that are much more easily removed, and this strategy has led to the preparation of several monomeric HHDP-containing ellagitannins.[5a−d]

Application of this oxidative coupling strategy, which was patterned after much earlier biosynthesis speculation,[6] to the more complex dimeric ellagitannin target coriariin A (**1**) requires additional attention directed toward the dehydrodigalloyl ether linking unit (cf. **1**). Continuing with the biosynthesis speculation which undergirds the C−C galloyl couplings, a plausible in vivo construction of coriariin A might pass through the monomeric ellagitannin tellimagrandin II (**4**), Scheme 1. Oxidation of the anomeric galloyl unit of **4** (to **4a**) might then provide an electrophilic partner for coupling with the nucleophilic phenol at the meta position of the anomeric galloyl ester on a second molecule of tellimagrandin II. This tellimagrandin II oxidative dimerization biosynthesis speculation then can be used to formulate

Scheme 2



a synthesis plan for coriariin A which centers on an oxidative union between two appropriately functionalized derivatives of **4**.

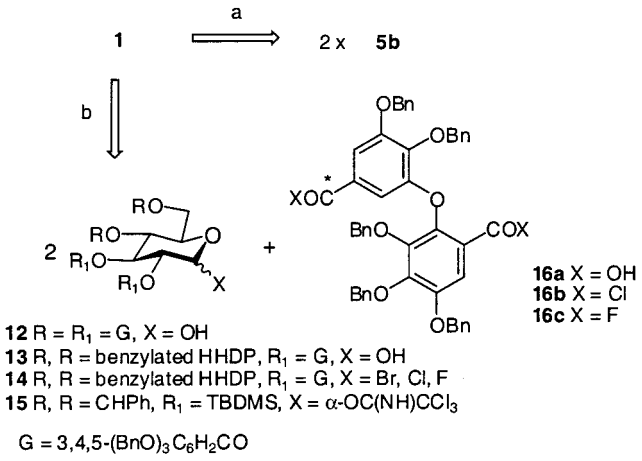
Even within the context of this biosynthesis hypothesis, the precise nature of the oxidized form of the O(1) galloyl unit of tellimagrandin II remains a matter of conjecture. Speculation can run the gamut from single-electron oxidized species (e.g., radical cation, phenoxy radical) to two-electron deficient derivatives (e.g., cyclohexadienonyl cation, orthoquinone). While each of these species could, in principle, join with the appropriate nucleophilic phenol to fashion the diaryl ether bond, some circumstantial evidence implicates the orthoquinone species **5a** as a plausible reactive intermediate, Scheme 2. Thus, the benzodioxene portion of the naturally occurring ellagitannin syzyginin B (**9**)[7] may, in fact, be biosynthesized via hetero Diels−Alder-type cycloaddition of the orthoquinones **6** and **7**. Taking a cue from this biosynthesis speculation, a Diels−Alder dimerization/reductive rearrangement sequence with the monomeric pentagalloyl-

(5) (a) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357. (b) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742. (c) Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171. (d) Feldman, K. S.; Smith, R. S. *J. Org. Chem.* **1996**, *61*, 2606. (e) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577. (f) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567. (g) Khanbabaee, K.; Lötzerich, K. *Liebigs Ann.* **1997**, 1571. (h) Khanbabaee, K.; Lötzerich, K. *J. Org. Chem.* **1998**, *63*, 8723. (i) Khanbabaee, K.; Schulz, C.; Lötzerich, K. *Tetrahedron Lett.* 1997, *38*, 1367. (j) Khanbabaee, K.; Lötzerich, K.; Borges, M.; Groβer, M. *J. Prakt. Chem.* **1999**, 341. (k) Itoh, T.; Chika, J.-i. *J. Org. Chem.* **1995**, *60*, 4968. (l) Itoh, T.; Chika, J.-i.; Shirakami, S.; Ito, H.; Yoshida, T.; Kubo, Y.; Uenishi, J.-i. *J. Org. Chem.* **1996**, *61*, 3700. (m) Dai, D.; Martin, O. R. *J. Org. Chem.* **1998**, *63*, 7628.

(6) (a) Schmidt, O. T. *Fortschr. Chem. Org. Naturstoffe* **1956**, *13*, 70. (b) Schmidt, O. T.; Mayer, W. *Angew. Chem.* **1956**, *68*, 103. (c) Gupta, R. K.; Al-Shafi, S. M. K.; Layden, K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2525. (d) Haddock, E. A.; Gupta, R. K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2535.

(7) Tanaka, T.; Orii, Y.; Nonaka, G.-i.; Nishioka, I.; Kouno, I. *Phytochemistry* **1996**, *43*, 1345.

Scheme 3



based orthoquinone **10** was explored for the synthesis of the dehydrodigalloyl ether unit in the model system **11**.[8]

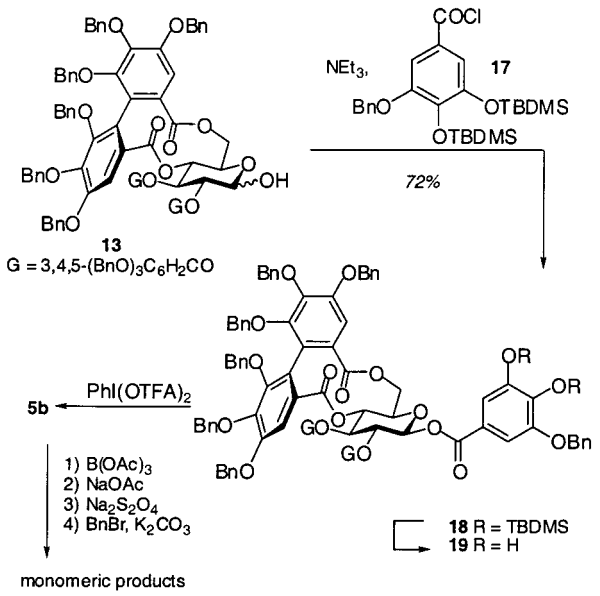
A convergent, two-component synthesis strategy for coriariin A was designed with these precedents in hand, Scheme 3. Accordingly, acquisition of tellimagrandin II-derived orthoquinone **5b** became the focal point of this first-generation synthesis. As events transpired, alternative strategies had to be developed which utilized a three-component coupling between diacyl derivatives **16** and two glucopyranose cores (e.g., **12**−**15**). Electronic tuning of the glucopyranose donors was instrumental in the successful execution of this strategy, and ultimately the target molecule was synthesized in good overall yield and with complete control of all of the stereochemical elements from **15** and **16a**.[8]

Results and Discussion

Coriariin A. Stereoselective installation of the dehydrodigalloyl ether unit linking the two glucose cores represents the primary challenge for synthesis presented by coriariin A. The initial synthesis strategy was patterned after the presumed tellimagrandin II dimerization shown in Scheme 1. Extension of the model transformation **10** → **11** to the synthesis of coriariin A required execution of the same reaction sequence on a sugar derivative containing an intact perbenzylated O(4)−O(6) HHDP unit (**5b**, Scheme 2). Toward this end, the known perbenzyl protected HHDP-containing glucopyranose derivative **13**[9a] was treated with galloyl chloride **17** in the presence of triethylamine to provide exclusively the β-esterified product **18** (Scheme 4). Subsequent desilylation of **18** gave the catechol **19**, the critical intermediate in the proposed tellimagrandin II dimerization strategy.

Oxidation of **19** to the orthoquinone Diels−Alder substrate **5b** proceeded smoothly with orthochloranil, but isolation of the product was much more difficult than in the case of the model orthoquinone **10**. Identical reaction conditions that led to precipitation of pure **10** failed to deposit **5b**. The use of lower reaction temperatures (−78 to −40 °C) and several different solvents or solvent combinations did not lead to separation of **5b** from the oxidation byproduct tetrachlorocatechol. Attempted purification by SiO_2 chromatography under a variety of

Scheme 4



conditions resulted in degradation of the orthoquinone. Exploratory Diels−Alder dimerization chemistry with impure **5b** did not afford any detectable coriariin A-like dimeric products. Examination of alternative oxidants (CAN, Ag_2O, hypervalent iodine reagents) led to the identification of $PhI(OTFA)_2$[10] (PIFA) as the most promising candidate for the oxidation of catechol **19**. Treatment of **19** with PIFA at −40 °C followed by warming to 0 °C effected complete conversion to the orthoquinone **5b**, as determined by ^1H NMR spectroscopy of the crude reaction mixture. One of the byproducts of this reaction, trifluoroacetic acid, was easily removed by concentration of the reaction solution. Attempts to completely separate the other byproduct, iodobenzene, by trituration with hexane were unsuccessful.

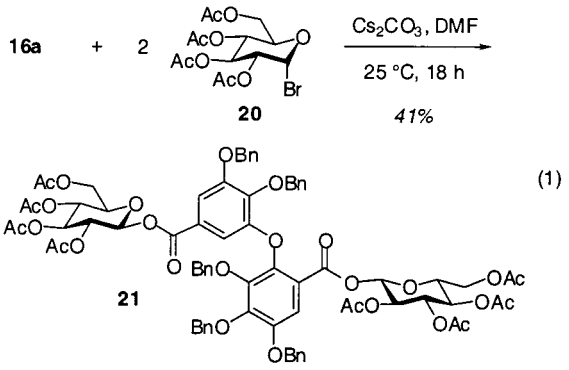
Repeated efforts to effect $B(OAc)_3$-mediated Diels−Alder dimerization of **5b** contaminated with PhI failed to furnish any detectable quantities of benzodioxene-derived products, as judged by analysis of the ^1H NMR and FABMS spectra of the reaction mixture. The signals corresponding to orthoquinone **5b** had disappeared, but eventual completion of the dehydrodigalloyl ether forming sequence led only to monomeric products (e.g., perbenzylated tellimagrandin II). Efforts to identify a more suitable Lewis acid catalyst thus far have been unsuccessful, as have purely thermal Diels Alder cycloaddition attempts. These puzzling results, in light of the presumably secure chemistry of the similar substrate **10**, prompted a reanalysis of the model system dimerization. Careful examination of several different batches of debenzylated final product "**11**" revealed that variable ratios of three difficultly separable components, in fact, were present: the expected dimer **11**, β-pentagalloylglucose (**3**), and 1-*O*-acetoxytetragalloylglucose, a species plausibly arising from interaction of $B(OAc)_3$ with an O(1)-galloylated glucopyranose derivative. Thus, in actuality the dimerization of **10** appears to provide only small and variable quantities of the dehydrodigalloyl ether-containing product **11** (best case ≤ 10% from **10**). While the dimerization results with **5b** were disappoint-

(8) Feldman, K. S.; Lawlor, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7396.
(9) (a) Feldman, K. S.; Sahasrabudhe, K. *J. Org. Chem.* **1999**, *64*, 209. (b) Sahasrabudhe, K. Ph.D. Thesis, The Pennsylvania State University, 1998.
(10) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992.

ing, at least now they are more in line with the revised picture of the model system dimerization.

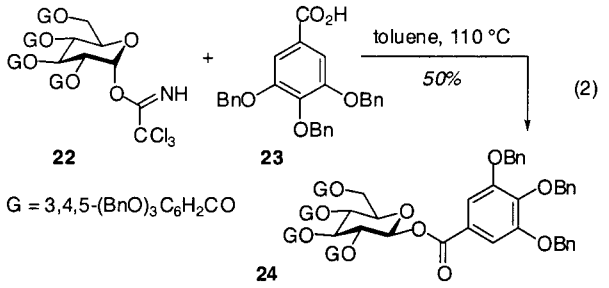
Recourse was made to an alternative three-component coupling approach for coriariin A synthesis, as the failure of the direct Diels−Alder-based tellimagrandin II dimerization strategy became apparent. While lacking a compelling biosynthetic rationale, this second-generation acylation-based assembly sequence (Scheme 3, path b, **13** + **16b**) seemed more solidly grounded on reliable precedent (i.e., **13** + tribenzylgalloyl chloride provided the anomeric acylation product in 41% yield).[9a] Toward this end, the dehydrodigalloyl chloride **16b**[9a] or fluoride **16c**,[9b] readily available from the diacid **16a**,[9a] was mixed in the presence of base with 2 equiv of either the model alcohol **12**[9a] or, independently, the HHDP-containing coriariin A precursor **13**, but no dimeric tannin species could be identified in either case. Interestingly, even monoacylated products, as might have been derived from alcohol addition to the more exposed acyl halide (* in **16b**) could not be detected. Thus, an inexplicable divergence of reaction pathways between the seemingly secure model system (Scheme 4, **13** + **17**) and the "real" system, **13** + **16b**, served to underscore marked reactivity differences between the monomeric galloyl chlorides and the bis acid chloride **16b** (or fluoride **16c**).

Strategically related companion studies that featured displacement of an anomeric leaving group within a glucopyranose core by a nucleophilic gallic acid derivative showed more promise. For example, the combination of the cesium salt of diacid **16a** with the electrophilic partner tetraacetoxybromoglucopyranose (**20**) provided dimer **21** in moderate yield (eq 1). However, application



(1)

of this transformation to the coriariin A effort was thwarted by an inability to access the requisite anomeric halides **14** from alcohol **13**. Alternatively, the trichloroacetimidate **22** was prepared in good yield from alcohol **12**, and this version of an activated glucopyranosyl donor combined smoothly with the monomeric gallic acid derivative **23** in refluxing toluene to afford the β-O(1)-acylated product **24** in acceptable yield (eq 2).[11] Disappointingly, but perhaps not surprisingly at this point, modification of this procedure to accomplish a double acylation with diacid **16a** and 2 equiv of **22** returned only unreacted starting materials. Once again, the muted reactivity of the diaryl ether diacid **16a** was not adequately anticipated by a monomeric analogue, the seemingly quite similar species **23**.



The lack of correspondence between the successful model acylations and the more complex systems required for coriariin A suggested that some fresh insights might be welcome. The arming/disarming strategies for anomeric etherification popularized by Fraser-Reid provided some guidance in this regard.[12] The Fraser-Reid work demonstrated that the electron demand at O(2) of the glucopyranose core significantly influenced the rate of substitution when reactive anomeric leaving groups (e.g., oxonium ions) were displaced by hydroxyl nucleophiles. The extrapolation of this methodology to anomeric esterification utilizing the arguably less potent leaving group trichloroacetimidate and carboxylate nucleophiles, as is required for coriariin A synthesis, did not seem unconscionable at this stage of the project. Thus, anomeric trichloroacetimidate displacement by the evidently more weakly nucleophilic diacid **16a** might benefit from incorporation of a more electron-releasing substituent at O(2) than the galloyl group of **22**. Driven by this premise, a third-generation synthesis plan for coriariin A was devised, Scheme 5. This route relied on early installation of the diaryl ether unit and later elaboration of the HHDP moieties on both glucopyranose cores. In this approach, the more electron releasing O(2) and O(3) TBDMS ethers of **15** are anticipated to enhance the prospects for 3-component coupling via double displacement of the trichloroacetimidate groups with diacid **16a**. Conversion of all of the glucose protecting groups in **26a** into the appropriately functionalized galloyl ester-bearing species **28b** then sets the stage for the second key transformation of the synthesis, the double oxidative cyclization of this octagalloylated coriariin A precursor to form the requisite HHDP units.

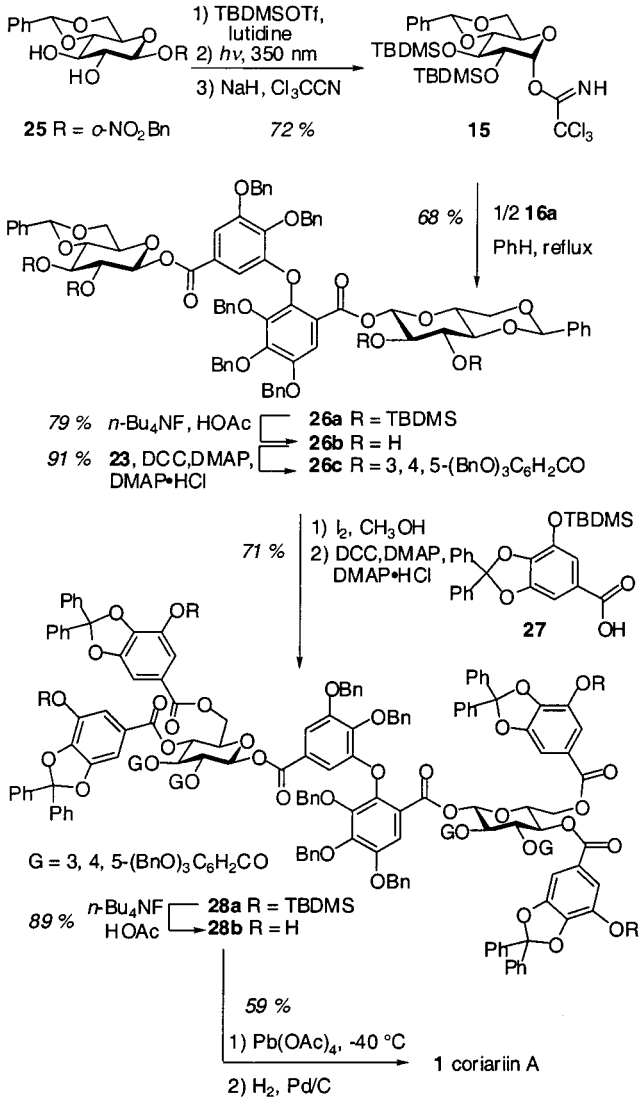
The synthesis of trichloroacetimidate **15** began with the known acetal **25**[13] (Scheme 5). Protection of the O(2) and O(3) hydroxyl groups of **25** as TBDMS ethers was followed by selective photochemical removal of the O(1)-*o*-nitrobenzyl ether. The resulting anomeric alcohol was activated for coupling by conversion to the trichloroacetimidate **15** in excellent yield, as per the earlier preparation of the galloylated glucopyranosyl trichloroacetimidate **22**. Clean three-component coupling was effected by treatment of **15** (2 equiv) with diacid **16a** in refluxing benzene to furnish the diglucopyranosyl dehydrodigalloyl diester **26a** as a single stereoisomer in reproducibly good yield. The facility of this acylation with the O(2), O(3)-

(11) (a) Schmidt, R. R.; Jung, K.-H. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed. Marcel Dekker: New York, 1997. (b) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141. (c) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731.

(12) Fraser-Reid, B.; Madsen, R. I. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997. Earlier work that describes the electronic influence of glucopyranose substituents on chemistry at the anomeric position can be found in: (b) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (c) Capon, B. *Chem. Rev.* **1969**, *69*, 407. (d) Feather, M. S.; Harris, J. F. *J. Org. Chem.* **1965**, *30*, 153.

(13) Prepared in three steps by a modification of the previously published procedure, see: (a) Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171. (b) Nicolaou, K. C.; Schreiner, E. P.; Stahl, W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 585.

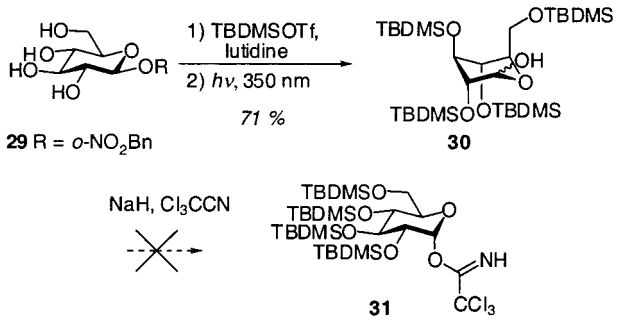
Scheme 5



disilylated glucopyranose derivative **15**, in contrast to the failures with the analogous galloylated substrates (e.g., **22**) is consistent with the O(2) electron-demand hypothesis discussed above. Thus, there may indeed be predictable O(2)-localized electronic influences for anomeric trichloroacetimidate acylation chemistry much as there are in the more familiar anomeric etherifications.

Three distinct sets of hydroxyls must be selectively and sequentially deprotected en route to the penultimate coriariin A intermediate **28b**. Deprotection of the TBDMS ethers of **26a** with acetic acid-buffered *n*-Bu_4NF furnished the tetraol **26b** in good yield.[14] The use of this reagent combination was crucial for preserving the sensitive dehydrodigalloyl ester bonds, as other common desilylation protocols (unbuffered *n*-Bu_4NF, TAS−F, HF, HF·pyridine) led to partial or complete anomeric ester hydrolysis. Galloylation at the O(2) and O(3) positions of both glucopyranose rings in **26b** with tribenzylgallic acid (**23**) (4 equiv) was accomplished using modified Steglich esterification conditions to afford the tetragalloylated substrate **26c**.[15]

Scheme 6



Construction of the requisite HHDP units commenced with deprotection of the acetal moieties in **26c** by treatment with iodine[16] to provide the corresponding tetraol which was esterified immediately with gallic acid derivative **27** (4 equiv) to afford the fully galloylated dimer **28a** in good yield. The key bis oxidative cyclization substrate **28b** was prepared by desilylation of tetrakis(TBDMS) ether **28a** with acetic acid-buffered *n*-Bu_4NF. As with the simpler substrate **26a**, the acute sensitivity of the dehydrodigalloyl ester linkages to nucleophilic attack necessitated use of the acetic acid additive. Intramolecular $Pb(OAc)_4$-mediated oxidative coupling of tetragalloylphenol **28b** under Wessely[17] oxidation conditions afforded a complex mixture of (inconsequential) regioisomeric protected bis (*S*)-HHDP containing products. This result is in accord with earlier glucopyranosyl-based digalloyl → HHDP transformations.[5a−d] Hydrogenolysis of the entire complement of protecting groups within the purified but still regioisomerically complex cyclization product mixture furnished a single product, coriariin A (**1**), in excellent yield as a light gray solid following trituration with ether and hexane. A comparison of the ^1H NMR, ^{13}C NMR, mass spectrum, and CD spectrum of the synthesized material with those reported for coriariin A,[1d] as well as a direct comparison of the ^1H NMR spectra of the synthetic and the plant-derived material (kindly provided by Professor T. Yoshida, Okayama University), verified that natural coriariin A had been synthesized.

Model Dimer 11. The newly recognized difficulties endemic in the Diels−Alder dimerization of model system **10** argued for the exploration of the alternative three-component Schmidt trichloroacetimidate acylation chemistry for the preparation of a pure sample of dimer **11**. The initial synthesis plan was designed to consolidate protecting groups since this less complex system lacked the HHDP unit of coriariin A, Scheme 6. Thus, the tetrasilylated trichloroacetimidate **31** was anticipated to serve as the glucopyranose donor in a coupling reaction with diacid **16a**. The preparation of this carbohydrate component began with the known tetraol **29**.[13] Protection of the hydroxyl groups as TBDMS ethers was followed by selective photochemical removal of the O(1)-*o*-nitrobenzyl ether. Surprisingly, the resulting alcohol **30** was found to exist in the $^1C_4$ conformation as evidenced by the small ring proton coupling constants ($J_{1,2}$ = 4.4, 3.5 Hz). This observation is precedented in pyranose systems bearing bulky O(3) and O(4) substituents in a

(14) (a) Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235. (b) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935. (c) Otera, J.; Niibo, Y.; Nozaki, H. *Tetrahedron Lett.* **1992**, *33*, 3655.

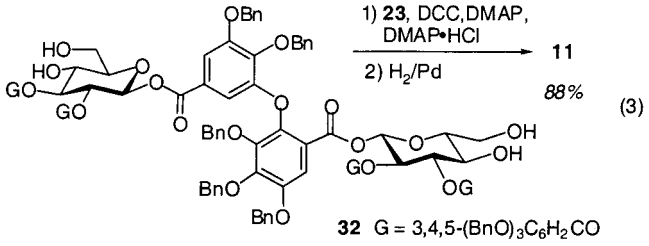
(15) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Keck, G. E.; Boden, E. P. *J. Org. Chem.* **1985**, *50*, 2394.

(16) Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827.

(17) Bubb, W. A.; Sternhell, S. *Tetrahedron Lett.* **1970**, 4499.

trans disposition.[18] The effect of this unanticipated development on the synthesis route was readily apparent as treatment of the alcohol **30** with sodium hydride and trichloroacetonitrile in benzene gave a complex mixture of products containing two anomeric trichloroacetimidates. Similar results were obtained with DBU as base in CH_2Cl_2. Attempted purification of the crude reaction mixture by silica gel chromatography resulted in decomposition of the trichloroacetimidates and recovery of alcohol **30**. Without a secure route to the desired trichloroacetimidate **31**, this route was abandoned.

The model dimer **11** was finally prepared from an advanced intermediate in the coriariin A synthesis, tetraol **32**, eq 3. Acylation of **32** with gallic acid derivative **23** furnished the fully galloylated dimer in excellent yield. Hydrogenolysis of all 29 benzyl ether protective groups within this species provided the gallotannin model dimer **11** in good yield as a light gray solid following trituration with dichloromethane and hexane. This species was formed free of monomeric contaminants, and it exhibited spectral data completely consistent with the assigned structure.



A stereoselective synthesis of the naturally occurring dimeric ellagitannin coriariin A (**1**) was accomplished in 11 steps from known diol **25**. The route features the first example of a double Schmidt-type acylation between a dehydrodigalloyl diacid and 2 equiv of a glucopyranosyl trichloroacetimidate to assemble a dimeric ellagitannin framework, a transformation made successful only after finely tuning the electronic characteristics of the glucopyranosyl donor. In addition, the double oxidative cyclization of an octagalloyl substrate establishes the utility of this Wessely oxidation-based methodology in the synthesis of dimeric ellagitannins bearing a hydrolytically sensitive dehydrodigalloyl diester linking unit. Finally, extension of this bis acylation methodology to a simple tetragalloylglucopyranose derivative afforded a coriariin A analogue featuring uncoupled O(4)/O(6) galloyl units, a compound not easily prepared in pure form through orthoquinone dimerization-based methodology.

Experimental Section

General Methods. All reactions were performed in flame-dried glassware under a positive pressure of argon with magnetic stirring. Commercial-grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, 2,6-lutidine, pyridine, and benzene were distilled from calcium hydride. THF was distilled from sodium benzophenone ketyl or dianion. Methanol was distilled from magnesium. *N*,*N*-Dimethylformamide was dried sequentially over three batches of 3 Å molecular sieves. Lead tetraacetate was recrystallized from acetic acid and stored in an inert atmosphere glovebox. Reaction product solutions and chromatography fractions were concentrated using a rotary evaporator at approximately 20 mmHg and then at ca. 0.1 mmHg (vacuum pump). Column chromatography was performed using 32−63 μm silica gel and the indicated solvent. Chemical shifts are reported in δ units using tetramethylsilane (TMS) or acetone as an internal standard for ^{1}H NMR and chloroform as the internal standard for ^{13}C NMR. Low- and high-resolution fast atom bombardment (FAB) mass spectra were run at the University of Texas at Austin. Circular dichroism (CD) measurements used the wavelength range 200−300 nm, scanning at 1.0 nm intervals with an averaging time of 8.0 s at 25 °C.

1-*O*-(3,4-*tert*-Butyldimethylsilyloxy-5-benzyloxybenzoyl)-2,3-bis(3,4,5-tribenzyloxybenzoyl)-4,6-(3,4,5,3′,4′,5′-hexabenzyloxydiphenoyl)-β-D-glucopyranoside (18). To a solution of 4,6-(3,4,5,3′,4′,5′-hexabenzyloxy)diphenoyl-2,3-bis-(3,4,5-tribenzyloxybenzoyl)-β-D-glucopyranose (**13**) (100 mg, 0.05 mmol) and 3,4-di-*tert*-butyldimethylsilyloxy-5-benzyloxybenzoyl chloride (**17**) in 2 mL of dry CH_2Cl_2 was added triethylamine (22 μL, 0.15 mmol). The reaction mixture was stirred at room temperature for 18 h and then treated with 5 mL of 1 M HCl. After extraction with 10 mL of EtOAc, the organic layer was separated and washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash column chromatography, eluting with 10%−25% EtOAc in hexanes, furnished 90 mg (72%) of anomeric ester **18** as a white solid froth: IR ($CDCl_3$) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54−6.77 (m, 73 H), 6.09 (d, J = 7.9 Hz, 1 H), 5.85−5.77 (m, 2 H), 5.52−5.26 (m, 2 H), 5.24−4.74 (m, 26 H), 4.36 (dd, J = 9.6, 5.7 Hz, 1 H), 4.12 (d, J = 13.2 Hz, 1 H), 0.98 (s, 9 H), 0.87 (s, 9 H), 0.33 (s, 6 H), 0.25 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.4, 166.8, 165.8, 164.6, 164.5, 152.58, 152.5, 152.3, 151.3, 147.9, 144.5, 143.2, 143.1, 142.4, 137.7, 137.6, 137.5, 137.41, 137.4, 136.4, 136.1, 128.6, 128.5, 128.4, 128.3, 128.23, 128.2, 128.04, 128.0, 127.92, 127.90, 127.7, 127.6, 127.5, 127.3, 127.1, 126.8, 123.8, 123.7, 123.5, 119.9, 116.1, 109.5, 109.4, 107.9, 92.9, 77.3, 77.2, 77.0, 76.6, 75.4, 75.1, 74.9, 73.4, 72.7, 71.4, 71.3, 71.2, 71.1, 70.2, 63.0, 26.1, 25.8, 18.6, 18.5. Anal. Calcd for $C_{144}H_{136}O_{26}Si_2$: C, 73.97; H, 5.82. Found: C, 74.08; H, 5.86.

1-*O*-(2-Benzyloxy-4,5-dihydroxybenzoyl)-2,3-bis(3,4,5-tribenzyloxybenzoyl)-4,6-(3,4,5,3′,4′,5′-hexabenzyloxydiphenoyl)-β-D-glucopyranoside (19). A solution of silyl ether **18** (200 mg, 0.09 mmol) in 2 mL of THF was treated with *n*-Bu_4NF (1 M in THF, 0.135 mL, 0.135 mmol) and stirred at room temperature for 45 min. The reaction mixture was diluted with Et_2O and poured over ice-cold 1 M H_3PO_4. The organic phase was separated and washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 10−50% EtOAc in hexanes, to afford 120 mg (67%) of phenol **19**: IR (CH_2Cl_2) 3538, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49−6.82 (m, 73 H), 6.15 (d, J = 8.4 Hz, 1 H), 5.96 (bs, 1 H), 5.86−5.74 (m, 2 H), 5.55 (bs, 1 H), 5.52−5.41 (m, 2 H), 5.38−4.74 (m, 26 H), 4.37 (dd, J = 6.1, 9.9 Hz, 1 H), 4.10 (d, J = 13.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.4, 166.8, 165.7, 164.8, 164.3, 152.64, 152.62, 152.60, 152.5, 152.3, 152.2, 145.7, 144.8, 144.4, 143.8, 143.1, 143.0, 138.1, 137.7, 137.6, 137.5, 137.4, 137.3, 136.4, 136.3, 135.6, 128.8, 128.7, 128.6, 128.54, 128.5, 128.45, 128.43, 128.4, 128.3, 128.23, 128.2, 128.1, 128.03, 128.0, 127.96, 127.91, 127.86, 127.84, 127.74, 127.7, 127.6, 127.54, 127.5, 127.3, 123.8, 123.7, 123.6, 123.4, 119.9, 111.9, 109.4, 109.3, 107.9, 107.8, 106.7, 92.9, 77.4, 77.2, 77.0, 76.6, 75.5, 75.4, 75.1, 75.0, 74.8, 73.3, 72.6, 71.6, 71.5, 71.2, 71.1, 70.2, 63.0. Anal. Calcd for $C_{132}H_{108}O_{26}$: C, 75.14; H, 5.12. Found: C, 74.84; H, 5.25.

Dimer 21. A solution of 3,4,5,3′,4′-pentabenzyloxydehydrodigallic acid (**16a**) (25 mg, 0.032 mmol) and Cs_2CO_3 (10 mg, 0.031 mmol) in 2 mL of MeOH was stirred for 2 h at room temperature. The solvent was removed to furnish the cesium salt as a white solid residue. A solution of tetracetoxybromo-α-D-glucose (**20**) (26 mg, 0.063 mmol) in 2 mL of DMF was

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added to the cesium salt and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was partitioned between 4 mL of Et_2O and 4 mL of water. The layers were separated and the organic layer was washed several times with water to remove the DMF, then washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification of the oily residue by flash column chromatography furnished 32 mg (41%) of the dimeric product **21** as a white solid: IR (CH_2Cl_2) 1757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53−7.07 (m, 27 H), 6.85 (d, J = 1.9 Hz, 1 H), 5.86 (d, J = 7.5 Hz, 1 H), 5.73 (d, J = 7.9 Hz, 1 H), 5.36−5.10 (m, 14 H), 4.98−4.73 (m, 2 H), 4.31−4.24 (m, 2 H), 4.11−3.91 (m, 2 H), 3.89−3.80 (m, 2 H), 2.10−1.59 (m, 24 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 170.1, 169.4, 163.9, 161.1, 152.8, 152.6, 150.0, 148.0, 146.4, 143.7, 143.6, 142.6, 136.5, 129.4, 129.2, 129.1, 129.0, 127.7, 127.3, 127.1, 123.0, 117.3, 77.4, 77.0, 76.6, 75.6, 73.5, 71.9, 71.0, 67.1, 61.4, 22.7, 21.4, 21.3, 21.2, 19.9, 19.8, 19.7, 18.4; MS (+FAB) 1449 (MH^+, 100). Anal. Calcd for $C_{77}H_{76}O_{28}$: C, 63.81; H, 5.32. Found: C, 63.79; H, 5.57.

1,2,3,4,6-Penta-*O*-(3,4,5-tri-*O*-benzyloxybenzoyl)-β-D-glucopyranose (24). A solution of trichloroacetimidate **22**[9a] (100 mg, 0.050 mmol) in 0.5 mL of toluene was treated with acid **23** (22 mg, 0.05 mmol), and the resulting reaction mixture was heated at reflux for 18 h. After cooling to room temperature, the reaction mixture was concentrated and purified by flash column chromatography, eluting with 10−40% EtOAc in hexanes, to provide 60 mg (53%) of anomeric ester **24**. The spectral data for this product matched those reported previously for this compound.[19]

1-*O*-(*o*-Nitrobenzyl)-4,6-*O*-Benzylidene-2,3-bis(*tert*-butyldimethylsilyl)-β-D-glucopyranoside. A cooled (0 °C) solution of diol **25** (1.01 g, 2.50 mmol) in 10 mL of dichloromethane was treated with 2,6-lutidine (1.15 mL, 9.87 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.70 mL, 7.40 mmol). The ice bath was removed and the pale yellow reaction mixture was stirred at room temperature for 4 h and then diluted with 50 mL of Et_2O and quenched with 20 mL of 1 M HCl. The organic layer was separated and washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 0−10% EtOAc in hexanes, to afford 1.48 g (94%) of the bis silyl ether as an oily white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.3, 1.3 Hz, 1 H), 7.92 (d, J = 7.9 Hz, 1 H), 7.65 (dt, J = 7.5, 1.2 Hz, 1 H), 7.48−7.43 (m, 3 H), 7.37−7.33 (m, 3 H), 5.42 (s, 1 H), 5.27 (d, J = 15.5 Hz, 1 H), 5.04 (d, J = 15.4 Hz, 1 H), 4.62 (d, J = 6.0 Hz, 1 H), 4.31−4.27 (m, 1 H), 3.85−3.80 (m, 1 H), 3.70 (t, J = 6.2 Hz, 1 H), 3.65−3.56 (m, 4 H), 0.88 (s, 9 H), 0.83 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.0 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 137.2, 134.7, 133.6, 129.1, 128.1, 127.9, 126.5, 124.6, 103.1, 102.2, 81.8, 77.2, 75.9, 69.1, 67.7, 65.5, 26.1, 26.1, 18.3, 18.2, −3.29, −3.43, −3.76, −3.87. MS (+APCI) 632 (MH^+, 2). Anal. Calcd for $C_{32}H_{49}NO_8Si_2$: C, 60.82; H, 7.82; N, 2.22. Found: C, 60.93; H, 7.94; N, 2.15.

4,6-*O*-Benzylidene-2,3-bis(*tert*-butyldimethylsilyl)-D-glucopyranose. A 100-mL Pyrex tube was charged with a solution of 1-*O*-(*o*-nitrobenzyl)-4,6-*O*-Benzylidene-2,3-bis(*tert*-butyldimethylsilyl)-β-D-glucopyranoside (404 mg, 0.639 mmol) in 30 mL of THF, 30 mL of absolute ethanol, and 6 mL of water. The solution was purged with argon for 10 min. The tube was sealed with a rubber septum and immersed in a Rayonet photochemical apparatus. Irradiation at 350 nm for 10 h at room temperature afforded a dark orange-red oil after concentration. Purification of the residue by flash column chromatography, eluting with 5−15% EtOAc in hexanes, provided 0.281 g (88%) of the alcohol as a sticky yellow foam (ca. 80:20 mixture of α/β anomers): IR ($CDCl_3$): 3600, 3563, 2955 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47−7.45 (m, 4 H, α,β), 7.36−7.25 (m, 6 H, α,β), 5.44 (s, 1 H, α), 5.43 (s, 1 H, β), 5.14 (dd, J = 2.0, 1.3 Hz, 1 H, α), 4.67 (t, J = 6.6 Hz, 1 H, β), 4.29 (dd, J = 10.3, 4.8 Hz, 1 H, α), 4.32−4.26 (m, 1 H, β), 4.06 (dt, J = 10.0, 5.0 Hz, 1 H, α), 3.95 (t, J = 8.7 Hz, 1 H, α), 3.80−3.74 (m, 1 H, β), 3.70−3.64 (m, 3 H, α,β), 3.54−3.45 (m, 3 H, β), 3.39 (t, J = 9.3 Hz, 1 H, α), 3.17 (s, 1 H, β), 3.16 (d, J = 1.6 Hz, α), 0.94 (s, 9 H, α), 0.92 (s, 9 H, β), 0.80 (s, 18 H, α,β), 0.15 (s, 6 H, α,β), 0.13 (s, 3 H, α), 0.12 (s, 3 H, β), 0.03 (s, 6 H, α,β), −0.03 (s, 6 H, α,β); ^{13}C NMR (90 MHz, $CDCl_3$) α anomer δ 137.2, 129.0, 128.1, 126.5, 102.4, 81.9, 74.9, 72.0, 69.1, 62.7, 26.0, 26.0, 18.2, 18.1, −3.41, −3.98, −4.17, −4.54. MS (+ESI) 497 (MH+, 15). Anal. Calcd for $C_{25}H_{44}O_6Si_2$: C, 60.44; H, 8.93. Found: C, 60.68; H, 9.14.

4,6-*O*-Benzylidene-2,3-bis(*tert*-butyldimethylsilyl)-α-D-glucopyranosyl trichloroacetimidate (15). Sodium hydride (13 mg, 0.33 mmol) was degreased by washing with hexanes, dried in vacuo, and suspended in 1 mL of benzene. A solution of 4,6-*O*-benzylidene-2,3-bis(*tert*-butyldimethylsilyl)-D-glucopyranose (132 mg, 0.266 mmol) in 4 mL of benzene was added via cannula. The reaction mixture was stirred at room temperature for 10 min, and trichloroacetonitrile (0.280 mL, 2.79 mmol) was added slowly dropwise to control vigorous bubbling. The resulting light orange reaction mixture was stirred for 4 h, diluted with 8 mL of water, and extracted with 50 mL of Et_2O. The organic phase was washed with 20 mL of brine, dried over Na_2SO_4, filtered and concentrated. The orange residue was purified by flash column chromatography, eluting with 5−20% EtOAc in hexanes, to afford 153 mg (90%) of **15** as a colorless oil: IR ($CDCl_3$) 3346, 1672 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.60 (s, 1 H), 7.50−7.45 (m, 2 H), 7.36−7.33 (m, 3 H), 6.29 (d, J = 3.4 Hz, 1 H), 5.47 (s, 1 H), 4.29 (dd, J = 10.2, 4.9 Hz, 1 H), 4.14 (t, J = 8.9 Hz, 1 H), 4.00 (td, J = 9.8, 4.9 Hz, 1 H), 3.82 (dd, J = 8.7, 3.4 Hz, 1 H), 3.70 (t, J = 10.2 Hz, 1 H), 3.50 (t, J = 9.4 Hz, 1 H), 0.88 (s, 9 H), 0.83 (s, 9 H), 0.14 (s, 3 H), 0.12 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 137.0, 129.0, 128.1, 126.4, 102.3, 96.5, 91.2, 81.9, 73.6, 71.6, 68.8, 65.3, 26.0, 26.0, 18.3, 18.0, −3.43, −4.07, −4.28, −4.51. MS (+APCI) 640 (MH^+, 0.6).

Dimer 26a. To diacid **16a**[2] (180 mg, 0.228 mmol) was added a solution of trichloroacetimidate **15** (293 mg, 0.457 mmol) in 4 mL of benzene to produce a suspension. The reaction mixture was heated at reflux for 18 h, at which time the resulting clear yellow solution was cooled to room temperature and concentrated to a yellow foam. Purification of this residue by flash column chromatography, eluting with 0−15% EtOAc in hexanes, afforded 267 mg (67%) of dimer **26a**: IR ($CDCl_3$) 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.13 (m, 37 H), 7.05 (s, 1 H), 5.90 (d, J = 6.0 Hz, 1 H), 5.85 (d, J = 6.0 Hz, 1 H), 5.43 (s, 1 H), 5.39 (s, 1 H), 5.24−4.95 (m, 10 H), 4.30 (dd, J = 10.3, 4.8 Hz, 1 H), 4.20−4.17 (m, 1 H), 3.91 (t, J = 6.8 Hz, 2 H), 3.85 (t, J = 6.0 Hz, 2 H), 3.76−3.57 (m, 5 H), 3.49−3.43 (m, 1 H), 0.85 (s, 9 H), 0.81 (s, 9 H), 0.80 (s, 18 H), 0.11 (s, 6 H), 0.08 (s, 3 H), 0.04 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 152.9, 152.8, 149.9, 147.4, 146.5, 143.1, 142.3, 137.7, 137.2, 137.1, 136.7, 136.6, 136.5, 136.2, 128.6, 128.6, 128.5, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.7, 127.7, 127.5, 126.4, 126.4, 124.3, 119.2, 111.1, 109.9, 109.5, 102.1, 101.7, 95.7, 95.4, 81.6, 81.3, 77.2, 75.8, 75.6, 75.5, 75.2, 74.9, 74.6, 71.5, 71.4, 69.0, 68.8, 65.8, 65.5, 26.0, 25.9, 25.8, 25.8, 18.2, 18.1, 17.9, −3.45, −3.50, −3.75, −3.90, −4.03, −4.16. MS (+MALDI) 1768 (MNa^+), 1784 (MK^+). Anal. Calcd for $C_{99}H_{124}O_{20}Si_4$: C, 68.09; H, 7.16. Found: C, 68.01; H, 7.43.

Tetraol 26b. A solution of dimer **26a** (263 mg, 0.151 mmol) in 4 mL of THF at room temperature was treated with acetic acid (0.052 mL, 0.908 mmol) and *n*-Bu_4NF (1 M in THF, 1.35 mL, 1.35 mmol). The resulting light yellow reaction mixture was stirred at room temperature for 7 h and then diluted with 30 mL of EtOAc and poured over 10 mL of 1 M H_3PO_4. The organic phase was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated to provide a yellow foam. Purification of the residue by flash column chromatography, eluting with 20−50% EtOAc in hexanes, gave 146 mg (75%) of tetraol **26b**: IR ($CDCl_3$) 3591, 3475 (br), 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.06 (m, 37 H), 7.01 (d, J = 1.5 Hz, 1 H), 5.79 (d, J = 8.1 Hz, 1 H), 5.62 (d, J = 8.1 Hz, 1 H), 5.48 (s, 1 H), 5.39 (s, 1 H), 5.14 (s, 5 H), 5.08−4.86 (m, 5 H), 4.33 (dd, J = 10.3, 4.5 Hz, 1 H), 4.23 (dd, J = 10.2, 4.5 Hz, 1 H), 3.85 (t, J = 9.0 Hz, 1 H), 3.73−3.66 (m, 3 H),

(19) Khanbabaee, K.; Lötzerich, K. *Tetrahedron* **1997**, *53*, 10725.

3.58−3.45 (m, 6 H), 3.32 (t, J = 9.2 Hz, 1 H), 3.09−3.06 (m, 1 H), 2.97−2.89 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 164.1, 152.8, 152.5, 150.1, 147.4, 146.5, 142.4, 142.3, 137.3, 136.9, 136.7, 136.6, 136.3, 136.1, 129.3, 129.2, 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 128.0, 127.8, 127.6, 126.4, 126.3, 123.8, 119.2, 111.0, 110.0, 109.7, 101.9, 101.7, 94.7, 94.6, 80.0, 79.8, 77.2, 76.8, 75.7, 75.6, 75.5, 73.5, 73.3, 73.0, 71.3, 68.3, 68.2, 66.9, 66.8. MS (+MALDI) 1311 (MNa^+), 1327 (MK^+). Anal. Calcd for $C_{75}H_{68}O_{20}$: C, 69.87; H, 5.32. Found: C, 69.49; H, 5.63.

Hexaester 26c. A mixture of acid 23 (183 mg, 0.415 mmol), DMAP (15 mg, 0.123 mmol), and DMAP•HCl (20 mg, 0.126 mmol) was treated with a solution of tetraol **26b** (134 mg, 0.104 mmol) in 4 mL of CH_2Cl_2. To this suspension was added DCC (107 mg, 0.519 mmol) at room temperature, and the resulting cloudy reaction mixture was stirred for 19 h. After being cooled at −18 °C for 30 min, the reaction mixture was filtered through Celite, washing with several portions of Et_2O. The filtrates were washed with 1 N HCl (15 mL), water (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to provide a yellow foam. The crude product dissolved in Et_2O was filtered again through Celite to remove residual DCU and purified by flash column chromatography, eluting with 10−30% EtOAc in hexanes, to furnish 300 mg (97%) of hexaester **26c**: IR ($CDCl_3$) 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50−6.96 (m, 98 H), 6.00 (d, J = 8.2 Hz, 1 H), 5.98 (d, J = 9.1 Hz, 1 H), 5.86 (t, J = 9.6 Hz, 1 H), 5.83 (t, J = 9.6 Hz, 1 H), 5.68 (t, J = 8.9 Hz, 2 H), 5.50 (s, 2 H), 5.17−4.89 (m, 34 H), 4.44−4.31 (m, 2 H), 3.91 (t, J = 8.9 Hz, 2 H), 3.83−3.76 (m, 4 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.2, 165.1, 163.9, 161.3, 152.7, 152.6, 152.5, 152.5, 149.9, 147.6, 146.4, 143.5, 143.1, 142.9, 142.8, 142.6, 137.7, 137.3, 136.7, 136.6, 136.5, 136.4, 136.1, 129.1, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.5, 126.2, 124.2, 123.6, 123.6, 123.1, 117.6, 110.7, 109.8, 109.6, 109.3, 109.2, 109.2, 101.6, 93.3, 92.9, 78.4, 77.2, 75.6, 75.5, 75.2, 75.1, 72.1, 72.0, 71.9, 71.8, 71.2, 71.0, 71.0, 68.3, 67.4, 67.3; MS (+MALDI) 3002 (MNa^+). Anal. Calcd for $C_{187}H_{156}O_{36}$: C, 75.39; H, 5.28. Found: C, 75.38; H, 5.30.

Tetraol 32. To a solution of the hexaester **26c** (288 mg, 0.097 mmol) in 10 mL of CH_2Cl_2/methanol (1:1) was added iodine (61 mg, 0.240 mmol). The dark brown reaction mixture was heated at reflux (sand bath 45−50 °C) for 42 h. After cooling to room temperature, the reaction mixture was diluted with 30 mL of EtOAc and washed with 10% aqueous $Na_2S_2O_3$, water, and brine (15 mL each). The organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a white oily solid. Purification of the residue by flash column chromatography, eluting with 30−50% EtOAc in hexanes and then 5:95 methanol/50% EtOAc in hexanes, provided 208 mg (77%) of tetraol **32** as a white solid: IR ($CDCl_3$) 3601, 3452 (br), 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−6.94 (m, 88 H), 5.95 (d, J = 8.2 Hz, 2 H), 5.68 (t, J = 9.0 Hz, 1 H), 5.56 (t, J = 9.0 Hz, 1 H), 5.41 (t, J = 9.4 Hz, 1 H), 5.38 (t, J = 9.6 Hz, 1 H), 5.12−4.80 (m, 34 H), 4.03−3.97 (m, 3 H), 3.85−3.72 (m, 4 H), 3.62−3.60 (m, 1 H), 3.32 (d, J = 3.5 Hz, 1 H), 3.29 (d, J = 3.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 167.0, 165.1, 164.2, 152.8, 152.6, 152.5, 152.5, 152.3, 149.8, 147.6, 146.5, 143.3, 143.2, 143.1, 143.0, 142.8, 137.7, 137.3, 136.7, 136.4, 136.4, 136.3, 136.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 128.1, 127.9, 127.7, 127.6, 127.6, 127.5, 123.6, 123.0, 117.8, 110.4, 109.5, 109.3, 109.1, 92.8, 92.2, 77.2, 75.8, 75.5, 75.1, 71.1, 71.0, 71.0, 69.1, 68.8, 61.5, 61.3; MS (−FAB) 2801 (M^+, 13). Anal. Calcd for $C_{173}H_{148}O_{36}$: C, 74.13; H, 5.32. Found: C, 73.95; H, 5.38.

Decaester 28a. A mixture of acid **27** (123 mg, 0.274 mmol), DMAP (8.5 mg, 0.070 mmol), and DMAP•HCl (11 mg, 0.069 mmol) was treated with a solution of tetraol **32** (192 mg, 0.068 mmol) in 3 mL of CH_2Cl_2. To this suspension was added DCC (71 mg, 0.344 mmol) at room temperature, and the resulting cloudy reaction mixture was stirred for 23 h. After being cooled at −18 °C for 30 min, the reaction mixture was filtered through Celite, washing with several portions of Et_2O. The filtrates were washed with 1 N HCl, water, and brine (15 mL each), dried over Na_2SO_4, filtered and concentrated to provide a yellow foam. The crude product dissolved in Et_2O was filtered again through Celite to remove residual DCU and purified by flash column chromatography, eluting with 10−30% EtOAc in hexanes, to furnish 271 mg (87%) of **28a** as a white foam: IR ($CDCl_3$) 1731 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54−6.98 (m, 128 H), 6.03 (d, J = 8.0 Hz, 1 H), 5.99 (d, J = 8.0 Hz, 1 H), 5.94−5.87 (m, 2 H), 5.82−5.71 (m, 4 H), 5.20−4.76 (m, 34 H), 4.57−4.49 (m, 2 H), 4.33−4.30 (m, 2 H), 4.17−4.10 (m, 2 H), 0.97 (s, 9 H), 0.96 (s, 18 H), 0.93 (s, 9 H), 0.18 (s, 3 H), 0.17 (s, 3 H), 0.15 (s, 3 H), 0.15 (s, 3 H), 0.12 (s, 6 H), 0.10 (s, 6 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.4, 165.3, 165.2, 165.2, 165.0, 164.1, 164.1, 163.8, 161.0, 152.6, 152.6, 152.5, 152.4, 149.7, 148.5, 148.5, 148.4, 147.5, 146.2, 143.9, 143.1, 143.0, 142.8, 142.5, 141.9, 141.9, 141.6, 139.9, 139.8, 139.6, 138.6, 138.5, 137.6, 137.4, 136.7, 136.6, 136.4, 136.3, 129.2, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 126.2, 123.9, 123.8, 123.7, 123.6, 123.5, 123.2, 122.5, 118.9, 118.9, 118.3, 118.1, 117.5, 110.6, 110.3, 109.8, 109.1, 109.1, 104.2, 104.1, 92.8, 92.5, 77.2, 75.5, 75.1, 75.0, 73.2, 71.6, 71.4, 71.2, 71.0, 70.9, 68.0, 67.8, 61.7, 61.5, 25.6, 25.5, 18.3, 18.2, 18.2, −4.50, −4.56; MS (+FAB) 4523 (MH^+). Anal. Calcd for $C_{277}H_{252}O_{52}Si_4$: C, 73.52; H, 5.61. Found: C, 73.29; H, 5.85.

Tetraphenol 28b. A solution of tetrakis(silyl ether) **28a** (251 mg, 0.055 mmol) in 4 mL of THF was treated with acetic acid (0.019 mL, 0.33 mmol) and n-Bu_4NF (1 M in THF, 0.335 mL, 0.335 mmol) at room temperature. The pale yellow reaction mixture was stirred for 1 h, diluted with 50 mL of EtOAc, and poured over 20 mL of 1 M H_3PO_4. The organic phase was washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography, eluting with 30−50% EtOAc in hexanes, provided 196 mg (87%) of **28b** as a white solid: IR ($CDCl_3$) 3574, 3416 (br), 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−6.99 (m, 128 H), 6.03 (d, J = 7.3 Hz, 1 H), 6.01 (d, J = 7.8 Hz, 1 H), 5.87 (t, J = 9.7 Hz, 1 H), 5.84 (t, J = 9.7 Hz, 1 H), 5.74−5.62 (m, 4 H), 5.28−4.86 (m, 34 H), 4.52−4.49 (m, 2 H), 4.38−4.36 (m, 1 H), 4.28−4.26 (m, 1 H), 4.19−4.11 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.8, 165.6, 165.5, 165.1, 165.0, 164.4, 164.3, 164.1, 161.5, 152.6, 152.4, 149.8, 148.4, 148.3, 147.5, 146.4, 143.5, 143.1, 143.0, 142.8, 142.4, 139.5, 139.2, 139.0, 138.7, 138.6, 138.4, 137.5, 137.4, 137.3, 136.7, 136.5, 136.4, 136.2, 129.4, 129.2, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 126.3, 126.3, 126.2, 123.7, 123.7, 123.6, 123.5, 123.3, 122.8, 122.7, 119.0, 118.9, 118.5, 118.5, 117.6, 114.3, 110.7, 109.9, 109.8, 109.7, 109.2, 109.1, 103.6, 103.5, 92.9, 92.5, 77.2, 75.7, 75.5, 75.2, 75.1, 75.0, 73.3, 73.1, 71.5, 71.2, 71.0, 70.9, 68.7, 68.6, 62.7, 62.3; MS (+FAB) 4068 (MH^+). Anal. Calcd for $C_{253}H_{196}O_{52}$: C, 74.69; H, 4.86. Found: C, 74.30; H, 5.12.

Coriariin A (1). To a cooled (−40 °C) solution of tetraphenol **28b** (177 mg, 0.044 mmol) and pyridine (0.028 mL, 0.35 mmol) in 7 mL of CH_2Cl_2 was added a solution of lead tetraacetate (42 mg, 0.095 mmol) in 2 mL of CH_2Cl_2, dropwise via syringe pump over 45 min. The resulting cloudy light orange reaction mixture was stirred at −35 °C for 75 min, and then poured into 20 mL of saturated aqueous $NaHCO_3$ and extracted with 75 mL of EtOAc. The organic phase was washed with 1 M H_3PO_4 (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to afford a light orange oil. Purification of the residue by flash column chromatography, eluting with 20−50% EtOAc in hexanes, furnished 131 mg (74%) of HHDP-containing dimeric ellagitannin as a complex mixture of regioisomers. The identity of the products was verified by inspection of the ^{1}H NMR spectrum, which contains diagnostic HHDP singlets from 6.78 to 6.70 ppm. The HHDP-containing products (122 mg, 0.03 mmol) were dissolved in 5 mL of THF and treated with 10% Pd/C (40 mg, 33 wt % of starting material). The system was purged several times with hydrogen and stirred under a balloon of hydrogen for 48 h. The reaction mixture was then purged with Ar and filtered through Celite, washing with acetone. Complete deprotection required repetition of this process two times with fresh catalyst (22 and 18 mg of Pd/C, 4 mL of THF, 24 h each). Final concentration of

the filtrates provided a gray-green oily solid which was triturated with three portions each of Et_2O and hexanes and dried to provide 45 mg (80%) of coriariin A **1** as a gray-green solid: ^{1}H NMR (400 MHz, acetone-d_6 + D_2O) δ 7.24 (d, J = 1.8 Hz, 1 H), 7.16 (s, 1 H), 7.00 (s, 2 H), 6.99 (s, 2 H), 6.95 (s, 2 H), 6.95 (s, 2 H), 6.67 (d, J = 2.0 Hz, 1 H), 6.65 (s, 1 H), 6.62 (s, 1 H), 6.46 (s, 2 H), 6.09 (d, J = 8.2 Hz, 1 H), 6.02 (d, J = 8.4 Hz, 1 H), 5.79 (t, J = 9.8 Hz, 1 H), 5.76 (t, J = 9.8 Hz, 1 H), 5.55 (dd, J = 8.4, 6.0 Hz, 1 H), 5.53 (dd, J = 8.5, 6.0 Hz, 1 H), 5.32−5.25 (m, 2 H), 5.17 (t, J = 9.0 Hz, 1 H), 5.15 (t, J = 9.1 Hz, 1 H), 4.50−4.41 (m, 2 H), 3.81 (d, J = 13.2 Hz, 1 H), 3.76 (d, J = 13.1 Hz, 1 H); ^{13}C NMR (90 MHz, acetone-d_6 + D_2O, dioxane (67.4) as internal standard) δ 168.0, 167.9, 167.5, 166.2, 165.6, 164.7, 162.0, 161.6, 147.8, 146.3, 145.7, 145.7, 145.6, 145.0, 145.0, 144.3, 143.2, 141.0, 140.7, 140.3, 139.2, 139.1, 139.1, 138.9, 136.3, 136.2, 129.5, 129.1, 129.1, 129.0, 126.6, 126.3, 125.7, 125.7, 120.3, 120.2, 120.2, 120.1, 115.6, 115.5, 112.2, 112.1, 110.1, 110.0, 109.9, 108.1, 108.0, 107.6, 93.5, 93.1, 73.1, 73.0, 72.8, 72.8, 71.5, 71.5, 70.5, 70.5, 62.9, 62.8. CD (MeOH) 231 nm, +42.7, 260 nm, −3.8, 281 nm, +10.9; HRMS (+FAB) calcd for $C_{82}H_{59}O_{52}$ (MH^+) 1875.1972, found 1875.1937.

1-*O*-(*o*-Nitrobenzyl)-2,3,4,6-tetrakis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-glucopyranoside. A suspension of tetraol **29**[13] (756 mg, 2.40 mmol) in 12 mL of CH_2Cl_2 was treated with 2,6-lutidine (2.25 mL, 19.3 mmol) and cooled at 0 °C. To the resulting pale yellow solution was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.30 mL, 14.4 mmol). The ice bath was removed, and the reaction mixture was stirred at room temperature for 3 h and then diluted with 100 mL of Et_2O and poured into 1 N HCl. The organic layer was separated and washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated to afford a light orange oil. The crude product was purified by flash column chromatography, eluting with 0−10% EtOAc in hexanes, to furnish 1.83 g (99%) of the tetrakis(silyl ether) as a pale yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.10 (d, J = 8.2 Hz, 1 H), 7.97 (d, J = 7.9 Hz, 1 H), 7.64 (t, J = 7.5 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 1 H), 5.35 (d, J = 15.7 Hz, 1 H), 4.95 (d, J = 16.1 Hz, 1 H), 4.92 (d, J = 6.5 Hz, 1 H), 3.98 (d, J = 2.6 Hz, 1 H), 3.89−3.83 (m, 1 H), 3.83 (d, J = 3.2 Hz, 1 H), 3.79−3.70 (m, 3 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.85 (s, 9 H), 0.13, 0.11, 0.09, 0.09, 0.03 (all s, 24 H total); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.7, 135.3, 133.6, 128.9, 127.5, 124.5, 101.6, 82.3, 79.0, 77.6, 70.0, 67.2, 64.0, 26.1, 25.7, 18.3, 18.3, 18.0, 17.9, −4.3, −4.3, −4.5, −4.6, −4.7, −4.8, −5.3, −5.4; MS (+APCI) 794 (MNa^+, 15).

2,3,4,6-Tetrakis-*O*-(*tert*-butyldimethylsilyl)-D-glucopyranose (30). A solution of 1-*O*-(*o*-nitrobenzyl)-2,3,4,6-tetrakis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-glucopyranoside (418 mg, 0.541 mmol) in 30 mL of THF, 30 mL of absolute ethanol, and 6 mL of water was prepared in a 100-mL Pyrex tube and purged with Ar for 10 min. The tube was sealed with a rubber septum and placed in a Rayonet photochemical apparatus. Irradiation at 350 nm for 9 h at room temperature afforded a dark orange reaction mixture which was concentrated, using several benzene washes to remove water. The resulting dark orange-red oil was purified by flash column chromatography, eluting with 0−5% EtOAc in hexanes, to provide 247 mg (72%) of alcohol **30** as a ca. 75:25 mixture of unassigned α/β anomers: IR (thin film) 3427 (br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, J = 11.8, 4.4 Hz, 1 H), 5.01 (dd, J = 9.2, 3.5 Hz, 1 H), 4.31 (d, J = 11.9 Hz, 1 H), 3.96−3.65 (m, 12 H), 3.12 (d, J = 9.2 Hz, 1 H), 0.93, 0.90, 0.89, 0.89, 0.88 (all s, 72 H total), 0.13, 0.12, 0.12, 0.11, 0.10, 0.10, 0.08, 0.06 (all s, 48 H total); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.4, 89.9, 78.4, 78.0, 77.2, 76.0, 75.9, 75.0, 72.3, 70.8, 63.6, 63.1, 26.1, 25.9, 25.9, 25.8, 25.7, 18.3, 18.0, 18.0, 17.9, 17.8, −4.2, −4.3, −4.4, −4.4, −4.5, −4.6, −4.8, −4.8, −4.9, −5.0, −5.0, −5.1, −5.3; MS (+APCI) 659 (MNa^+, 6).

Model Dimer 11. A mixture of acid **23** (35 mg, 0.079 mmol), DMAP (2.5 mg, 0.020 mmol), and DMAP·HCl (3.0 mg, 0.019 mmol) was treated with a solution of tetraol **32** (55 mg, 0.02 mmol) in 1.25 mL of CH_2Cl_2. To this suspension was added DCC (20 mg, 0.097 mmol) at room temperature, and the resulting cloudy reaction mixture was stirred for 15 h. After cooling at −18 °C for 30 min, the reaction mixture was filtered through Celite, washing with several portions of Et_2O. The filtrates were washed with 1 N HCl, water, and brine (5 mL of each), dried over Na_2SO_4, filtered and concentrated to provide a light yellow foam. The crude product dissolved in Et_2O was filtered again through Celite using cold Et_2O to remove residual DCU and purified by flash column chromatography, eluting with 10−40% EtOAc in hexanes, to provide 84 mg of the decaester, still contaminated with some DCU. Filtration through Celite using cold Et_2O furnished 78 mg (89%) of product as a white foam: IR ($CDCl_3$) 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.13 (m, 158 H), 7.05−6.97 (m, 6 H), 6.10 (t, J = 8.2 Hz, 2 H), 6.01 (t, J = 9.8 Hz, 1 H), 5.99 (t, J = 9.7 Hz, 1 H), 5.82−5.73 (m, 4 H), 5.14−4.83 (m, 58 H), 4.75−4.69 (m, 2 H), 4.34−4.27 (m, 4 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.6, 165.4, 165.4, 165.1, 164.9, 164.9, 163.9, 161.2, 152.7, 152.6, 152.6, 152.5, 152.3, 149.7, 147.6, 146.3, 143.9, 143.2, 143.1, 143.0, 142.7, 142.6, 142.5, 137.6, 137.5, 137.5, 137.4, 137.3, 137.3, 136.6, 136.6, 136.5, 136.4, 136.3, 136.3, 136.3, 136.2, 128.7, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 127.5, 124.5, 124.5, 123.7, 123.6, 123.1, 110.6, 110.3, 109.8, 109.2, 109.2, 92.9, 92.6, 77.2, 75.5, 75.1, 75.0, 73.3, 73.3, 72.7, 72.6, 71.4, 71.3, 71.2, 71.1, 71.0, 70.9, 69.8, 69.7, 63.0, 62.9; MS (+FAB) 4493 (MH^+, 10). Anal. Calcd for $C_{235}H_{236}O_{52}$: C, 76.19; H, 5.29. Found: C, 76.04; H, 5.30.

A solution of the perbenzylated model dimer (39 mg, 0.009 mmol) in 2 mL of THF was treated with 10% Pd/C (10 mg, 25 wt % of starting material). The system was purged several times with hydrogen and stirred under a balloon of hydrogen for 36 h. The reaction mixture was then purged with Ar and filtered through Celite, washing with acetone. Concentration of the filtrates provided a gray oily solid which was triturated with two portions each of dichloromethane and hexanes and dried to afford 17 mg (99%) of gallotannin dimer **11** as a light gray solid: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.22 (d, J = 2.0 Hz, 1 H), 7.17 (s, 2 H), 7.13 (s, 2 H), 7.10 (s, 1 H), 7.03 (s, 2 H), 7.01 (s, 2 H), 7.00 (s, 2 H), 7.00 (s, 2 H), 6.95 (s, 2 H), 6.93 (s, 2 H), 6.73 (d, J = 1.9 Hz, 1 H), 6.21 (d, J = 8.3 Hz, 1 H), 6.13 (d, J = 8.3 Hz, 1 H), 5.97 (t, J = 9.5 Hz, 1 H), 5.92 (t, J = 9.6 Hz, 1 H), 5.62 (t, J = 9.7 Hz, 1 H), 5.60 (t, J = 9.7 Hz, 1 H), 5.54 (t, J = 9.1 Hz, 2 H), 4.50−4.43 (m, 4 H), 4.39−4.35 (m, 2 H); ^{13}C NMR (90 MHz, acetone-d_6) δ 166.8, 166.8, 166.2, 166.2, 166.0, 166.0, 165.9, 165.2, 162.6, 148.3, 146.8, 146.3, 146.3, 146.2, 143.8, 141.5, 141.5, 140.9, 139.7, 139.7, 139.6, 139.6, 139.5, 139.4, 139.4, 138.1, 121.8, 121.7, 121.0, 120.9, 120.9, 120.8, 119.7, 113.5, 112.7, 110.6, 110.6, 110.5, 110.2, 108.5, 93.7, 93.4, 74.3, 74.1, 73.8, 73.7, 73.7, 73.6, 72.0, 71.9, 69.6, 69.4, 63.3, 62.9; HRMS (+FAB) calcd for $C_{82}H_{63}O_{52}$ (MH^+) 1879.2285, found 1879.2308.

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