Articles

Ellagitannin Chemistry. First Total Synthesis of the 2,3- and 4,6-Coupled Ellagitannin Pedunculagin

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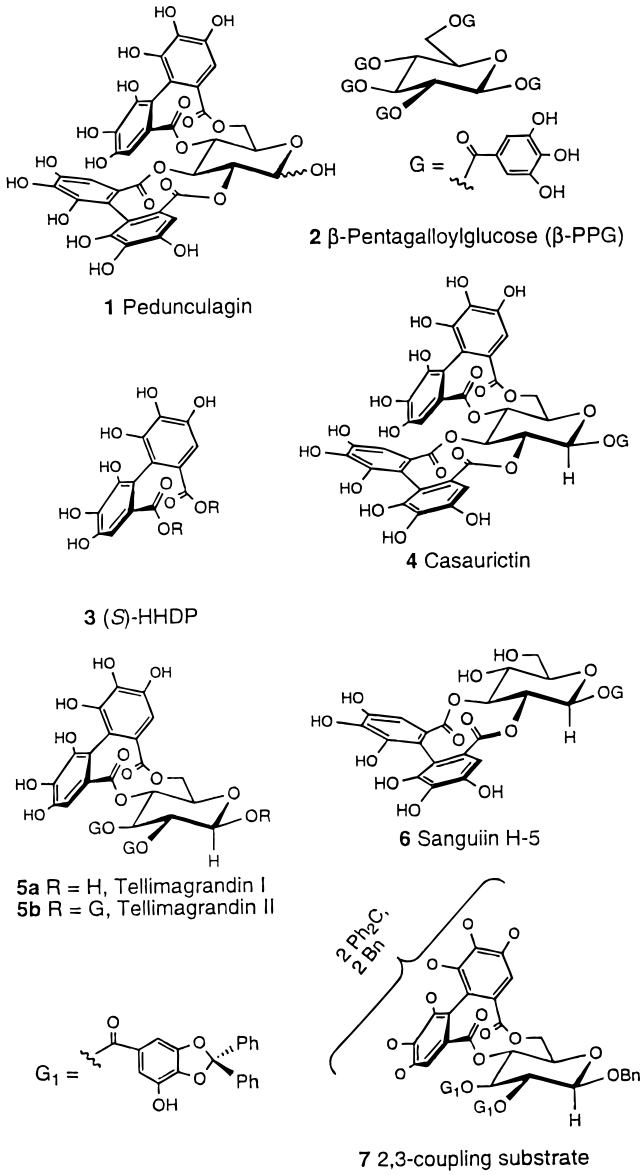
The biomimetic synthesis of pedunculagin (**1**) was accomplished through the sequential diastereoselective formation of two biphenyl C−C bonds. The synthesis strategy employed is predicated on extensive conformational modeling and involves initial oxidative coupling of the galloyl moieties at the O(2) and O(3) positions of an appropriately protected glucose-derived core, followed by installation and oxidative coupling of galloyl esters at the O(4) and O(6) positions.

Introduction

Pedunculagin[1] (**1**) is a member of the broad class (Chart 1) of hydrolyzable polyphenol vegetable extracts know as ellagitannins.[2] These compounds are secondary metabolites of dicotyledonous species of Angiospermae and are thought to be derived from the watershed gallotannin β-1,2,3,4,6-pentagalloyl-D-glucose (β-PGG, **2**).[2a,3] The defining structural feature of monomeric ellagitannins that distinguishes them from the related gallotannins is the 6,6′-dicarbonyl-2,2′,3,3′,4,4′-hexahydroxybiphenyl moiety which is commonly designated by the trivial name hexahydroxydiphenoyl (HHDP, **3**). Over 500 ellagitannins have been identified thus far. This structural diversity is a consequence of the almost inexhaustible number of combinations and permutations involving intra-(C−C) and inter-(C−O) molecular oxidative coupling available to the putative gallotannin precursor **2**. Historically, plant polyphenols have found commercial use predominantly in the leather tanning and wine industries.[2a] Recently, however, these compounds have been identified as the principle curative and palliative agents in a variety of traditional herbal medicines.[4] Although these applications appear superficially disparate, in fact they both may stem from a pervasive attribute of polyphenols, astringency (protein recognition and binding).[5]

Ellagitannins exhibit a wide variety of therapeutically interesting anticancer[4f,6] and antiviral[6eg,7] activities at the μM−nM level. Pedunculagin itself has been shown to inhibit the promising anticancer target enzyme DNA topoisomerase II[8] *in vivo*, with an IC_{100} of 500 nM.[9] This activity is 100 times greater than the clinically useful topoisomerase II poison etoposide (VP-16).[8b] Significantly, pedunculagin's mode of topoisomerase inhibition

Chart 1



⊗ Abstract published in *Advance ACS Abstracts,* April 1, 1996.

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is distinct from that of VP-16. While VP-16 stabilizes the topoisomerase−DNA cleavage intermediate and leads to formation of protein-linked DNA breaks (PLDBs),[8b,9] pedunculagin does not induce PLDBs and, in fact, inhibits formation of PLDBs by VP-16 in some cases. Thus, this tannin may interfere with initial topoisomerase II−DNA binding prior to formation of the protein−DNA intermediate.

Pedunculagin displays intriguing activity in several other biological assays as well. It inhibits protein kinase C with an IC_{50} of 4 μM.[10,11] It may provide a new avenue for treatment of conditions such as liver injury and arteriosclerosis, as it almost completely inhibits the formation of tissue-damaging lipid peroxides at a dose of 5 μg/mL (IC_{50} = 1.5 μM).[12] Finally, pedunculagin also exhibits antiviral activity by inhibiting reverse transcriptase in mouse leukemia virus-infected cells with an IC_{50} of 0.1 μg/mL (130 nM).[13] With a LD_{50} of >100 mg/kg p.o. in mice and rats,[13] pedunculagin's minimal toxicity is striking for such a medicinally active compound.

Results and Discussion

Pedunculagin presents several challenging problems related to the efficient installation of the HHDP moieties on the glucose core. Both regiochemical and stereochemical issues must be addressed in designing a strategy of biaryl synthesis with this target. A paradigm for predicting the stereochemical outcome of oxidative coupling with certain glucose-bound galloyl groups has been developed by earlier workers in this field.[14,15] Schmidt[1b,16] and later Haslam[2a,17] have observed that ellagitannins featuring HHDP moieties at the 2,3- and 4,6-positions of the thermodynamically more stable $^4C_1$ glucose core predominantly possess the (*S*)-atropisomer. This observation has led them to postulate that the stereochemical outcome of biaryl formation in gallotannin systems is dictated by the conformational preferences of the galloylated glucose core. Experimental support for this hypothesis is found in the $Pb(OAc)_4$-mediated oxidative cyclizations used in the tellimagrandin I (**5a**) (*S*)-4,6-coupling[14b] and the sanguin H-5 (**6**) (*S*)-2,3-coupling.[15] However, while the Schmidt−Haslam postulate offers a simple empirical basis for predicting the stereochemical outcome of oxidative coupling between galloyl esters, it offers no clear molecular rationale that relates product stereochemistry to the conformational preferences enforced by the glucopyranoside framework.

Any synthesis strategy for a 2,3- and 4,6-coupled ellagitannin target must initially confront the question of which HHDP unit to install first. Prior studies with tellimagrandin I[14] (**5a**) and sanguin H-5[15] (**6**) indicate that for either choice a sound basis for anticipating the desired (*S*) stereochemistry exists. However, subsequent studies in the tellimagrandin series revealed that a 2,3-galloyl coupling substrate **7** which already bears an HHDP unit at O(4)/O(6) could not be induced to form the second O(2)/O(3) HHDP moiety under standard ($Pb(OAc)_4$) oxidative cyclization conditions.[18] The other possible sequence, O(2)/O(3) galloyl coupling first followed by O(4)/O(6) coupling, appears by default to be the only option available for pedunculagin. To its credit, this strategy does offer the twin economies of (1) relatively fewer protecting group manipulations and (2) placing a lower yielding step (2,3-coupling) earlier in the synthesis route while reserving the normally more efficient 4,6-coupling for the later stages when material is more precious.

This route raises an unexplored stereochemical issue: will the added rigidification of the glucose core which necessarily attends HHDP formation at O(2)/O(3) adversely affect the O(4)/O(6) galloyl coupling transforma-

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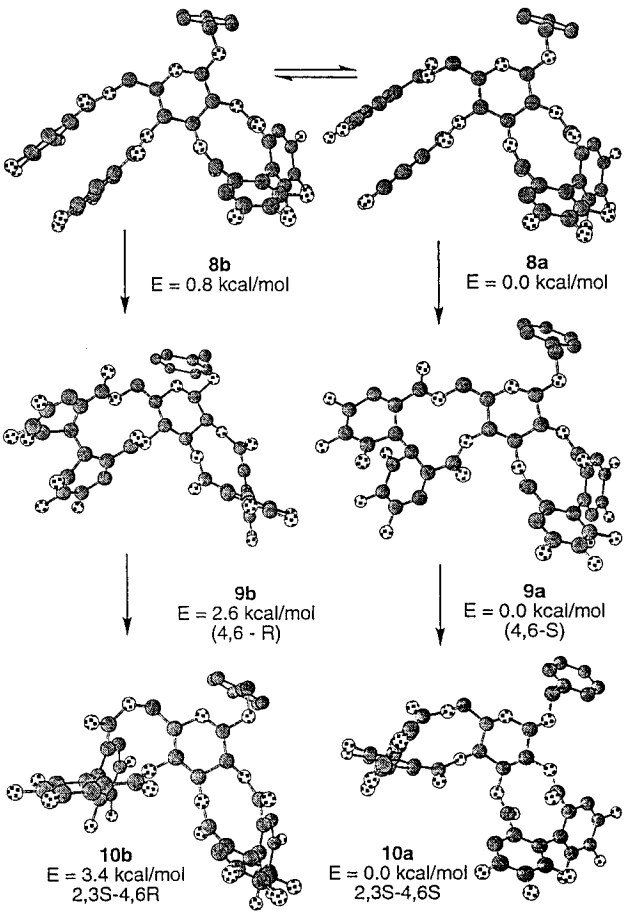
Scheme 1



•hydrogens omitted for clarity
•relative strain energy of (*R*) vs. (*S*) series shown

tion? The conformational preferences of O(4) and O(6) galloyl groups on such a substrate were revealed by molecular mechanics (MM)-based analysis of the model compound **8a**/**8b** (Scheme 1).[19] In the absence of hard conformational data on the coupling precursors (e.g., X-ray-derived structures), MM-based analyses offer the next best means to access this information. Upon comparison of the relative strain energies of closely related structures, systematic errors introduced by the approximations and constraints inherent in MM-based analyses are anticipated to largely cancel out. The results from this computational study parallel those of the simpler 2,3-unfunctionalized system explored in conjunction with the tellimagrandin I synthesis effort.[14] Both pro-(*R*) **8b** and pro-(*S*) **8a** conformations of the starting material **8a**/**8b** can be identified. These conformers differ by the rotational orientation of the O(6) galloyl esters in each species and align different and diastereotopic inter-ring aromatic carbons as nearest neighbors for coupling. Carbon−carbon bond formation can proceed from either species to afford the presumed dione intermediates **9a** (from **8a**) and **9b** (from **8b**). These calculations suggest that the modest 0.8 kcal/mol preference for the pro-(*S*) conformer **8a** is amplified upon coupling up to a 2.6 kcal/mol difference favoring the (*S*) intermediate **9a**. Tautomerization of these putative dione intermediates **9a** and **9b** then unambiguously furnish the (*S*) and (*R*) atropisomeric products **10a** and **10b**, respectively. Once again, the energy difference between the (*S*) and (*R*) reaction manifolds is magnified and the "natural" (*S*) isomer **10a** is favored by over 3 kcal/mol. To the extent that the greater energetic penalty associated with the (*R*) dione **9b** is at least partially expressed in the transition state leading to its formation, the product of the lower energy (*S*) manifold (**10a**) is expected to predominate. This transition state energy-based conclusion rests on the untested assumption that coupling stereochemistry is under kinetic control. Fortunately, thermodynamics run parallel to kinetics in this series. Alternative inter-ring carbon pairings (not shown) invariably lead to dione intermediates calculated to be 5−10 kcal/mol higher in strain energy than that of the diones **9a**/**9b** shown.

The synthesis of pedunculagin (**1**) is thus predicated upon construction of the more demanding 2,3-HHDP unit prior to installation of the more accommodating 4,6-HHDP moiety, based upon these computational studies and experimental precedent. To this end, the known[20] diol **11** was esterified with the gallic acid derivative **12**[14c] under standard Steglich esterification conditions (Scheme 2).[21] TBAF-mediated desilylation of **13** afforded the requisite cyclization substrate **14** in moderate yield. As suggested by the previous studies associated with the synthesis of sanguin H-5 (**6b**), higher dilution and lower temperatures as compared to those of the 4,6-coupling reaction are required to maximize the yield of 2,3-couplings.[15] Upon $Pb(OAc)_4$-mediated biaryl bond formation, three regioisomers were formed in modest overall yield (45%). The regioisomers of **15** were not separated, as the biphenyl ketals were destined for eventual removal. Instead, the free phenols were benzylated and the O(4)/O(6) benzylidene acetal was hydrolytically cleaved with iodine to yield the diol **17**. The tentative stereochemical assignment of the 2,3-HHDP unit in **15** is based on the well-characterized cyclization results in the closely related sanguin H-5 work.[15]

Incorporation of the 4,6-HHDP group follows essentially the same protocol described for the 2,3-HHDP moiety (Scheme 3). Esterification of **17** with gallic acid derivative **12** followed by desilylation afforded **18b** as a mixture of three regioisomers. With $Pb(OAc)_4$-mediated oxidative coupling of the O(4) and O(6) galloyl derivatives, the protected pedunculagin precursor **19** was obtained as a mixture of at least nine regioisomers in excellent yield. As expected, the 2,3-coupling proved to be more difficult than the 4,6-coupling, and the decision to initiate the synthesis scheme with assembly of the 2,3-HHDP moiety appears justified. Removal of the benzyl ethers and biphenyl ketals was achieved in one step from

(19) (a) Molecular mechanics calculations on all species described herein were performed on a Silicon Graphics Power Indigo 2XZ computer equipped with MacroModel v4.5 (MM3* force field). Multiconformational searches were preformed utilizing a Monte Carlo algorithm with 1000 steps and PRCG initial minimization (derivative convergence at 0.01 kJ/(Å mol)). The structure set thereby obtained was further minimized via the FMNR method (derivative convergence at 0.01 kJ/(Å mol)), and identical structures were eliminated via structural comparison. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. S. *J. Comput. Chem.* **1990**, *11*, 440. (b) The perhydroxylated substrates were modeled instead of the diphenyl ketal cyclization precursors both as a concession to computational economy and to avoid the regiochemical ambiguities inherent in modeling the latter species. This approximation is supported by the results obtained from modeling one regioisomer of the diphenyl ketal-containing substrate **14**, as the global minimum energy conformation of **14** only differed from the global minimum energy conformation of the analogous free hydroxyl substrate by an RMS deviation in the core pyranose/galloyl region of 0.06 Å (see supporting information).

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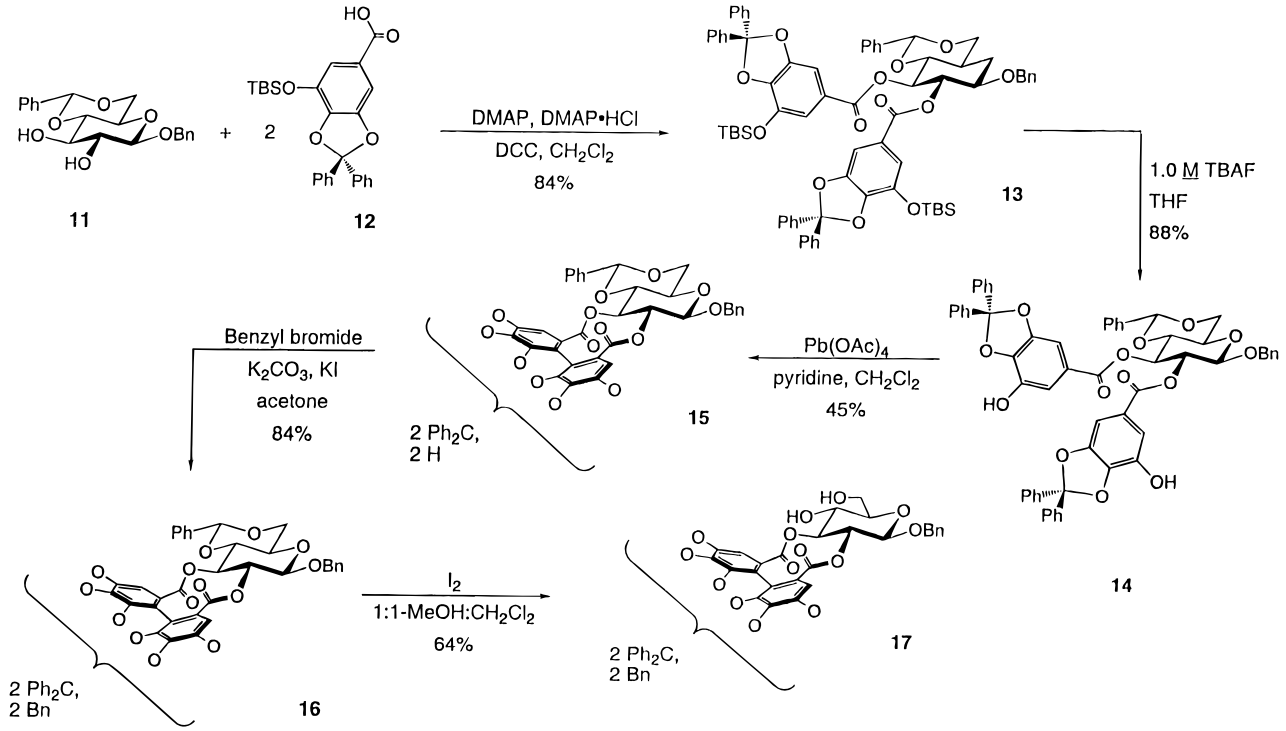
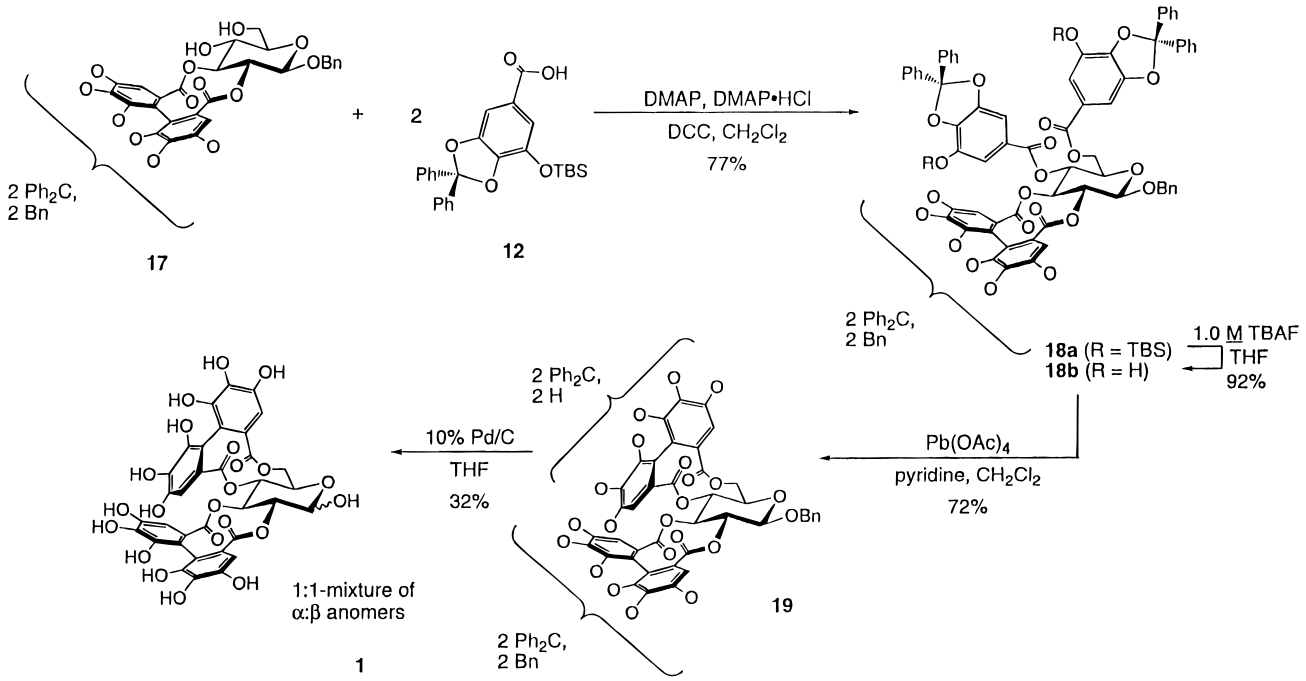
Scheme 2



Scheme 3



the mixture of regioisomers **19** via hydrogenolysis over Pd/C to furnish pedunculagin (**1**) following chromatographic purification. Circular dichroism (CD)[22] of the hydrogenolysis product unambiguously established that both HHDP atropisomers bore the (*S*)-configuration. Moreover, all spectral data of the chemically elaborated pedunculagin (**1**) coincides with that reported for the naturally occurring compound.[1d]

The biosynthetic sequencing of the 2,3- and 4,6-galloyl couplings that precedes *in vivo* assembly of casuarictin (**4**) (a logical precursor to pedunculagin via hydrolysis of the anomeric galloyl group) is currently unknown. Neither the modeling nor the synthesis studies reported herein lend insight into this fascinating question. However, MM-based analyses of the presumed biosynthetic precursor(s) to casuarictin, β-1,2,3,4,6-pentagalloyl-D-glucose (**2**) and tellimagrandin II (**5b**), do present an intriguing perspective. The "global" minimum energy structure for **2** (depicted in Scheme 4 as **2′**) features galloyl esters at the O(4) and O(6) positions that adopt

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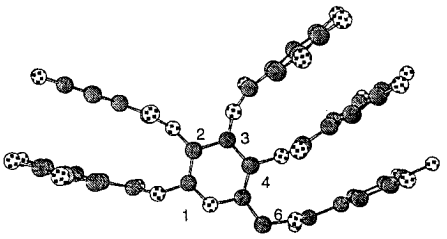
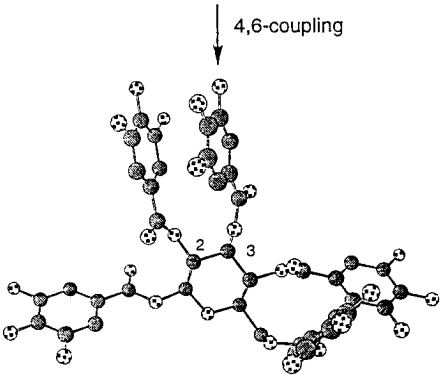
Scheme 4



2'
"global minimum" conformation
of β-pentagalloylglucose.
Hydrogens omitted for clarity.



5b'
"global minimum" conformation
of tellimagrandin II.
Hydrogens omitted for clarity.

an appropriate alignment for cyclization. On the other hand, the O(2) and O(3) galloyl esters are separated by a considerable distance and a low-energy cyclization pathway from this conformation is difficult to envision. In fact, not a single conformational isomer among the 20 discrete minima located within 2.5 kcal/mol of **2** juxtaposes the O(2) and O(3) galloyl groups in a conformation conductive for cyclization. However, upon oxidative phenolic coupling of the O(4)/O(6) galloyl groups, a conformation of the product tellimagrandin II (depicted in Scheme 4 as **5b′**) wherein the O(2)/O(3) galloyl esters achieve proper alignment for coupling is observed to be isoenergetic with an O(1)/O(2) pairing alternative. Therefore, these calculations support an interpretation of the biosynthesis of casuarictin in which the precursor **2′** is not readily disposed to undergo initial formation of a 2,3-HHDP moiety. Only after O(4)/O(6) galloyl coupling has occurred can the product **5b′** adopt a conformation predisposed for O(2)/O(3) cyclization. Of course, the role (if any) that plant enzymes might play in modifying these conformational preferences is unknown at present.

In summary, pedunculagin (**1**) is the first O(2)/O(3)- and O(4)/O(6)-galloyl coupled ellagitannin to be obtained via chemical synthesis. Moreover, it represents an important step toward the chemical synthesis of the more complex dimeric ellagitannins such as agrimoniin. The formation of the HHDP (*S*)-atropisomers in both the 2,3- and 4,6-positions, to the exclusion of the (*R*)-atropisomer, is in accord with the predictions of the Haslam−Schmidt proposal. The regiochemical and stereochemical predictive power of MM conformational analyses cannot be ignored, but should be used with caution. With a strong dependence of conformational preference on peripheral substituents, utilization of the correct model system is essential. Further studies are underway to refine understanding of the molecular basis of the Haslam−Schmidt postulate and to probe its relevance to the stereochemical outcome of oxidative phenolic cyclization.

Experimental Section

Liquid (flash) chromatography was carried out using 32−63 μm silica gel and the indicated solvent. Analytical thin-layer chromatography was performed using precoated (0.25 mm thickness) silica gel (60 F_{254}) plates. Preparative reverse-phase thin layer chromatography was performed using precoated (1.0 mm thickness) silica gel C_{18} (SIL RP-18W/UV_{254}) plates. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were purified by distillation from sodium/benzophenone under nitrogen, while methylene chloride (CH_2Cl_2) was distilled from CaH_2 under nitrogen. Moisture-sensitive reactions were carried out in predried glassware under an inert atmosphere of Ar.

Benzyl 4,6-*O*-Benzylidene-2,3-bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoyl)-α-D-glucopyranoside (13). A solution of 3.67 g (10.2 mmol) of benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**11**), 9.65 g of (21.5 mmol, 2.1 equiv) 3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoic acid (**12**), 0.63 g (5.1 mmol, 0.5 equiv) of DMAP, 0.81 g (5.1 mmol, 0.5 equiv) of DMAP·HCl, and 6.34 g (30.7 mmol, 3.0 equiv) of DCC in 100 mL of CH_2Cl_2 (0.1 M in diol) was purged under Ar and then heated at reflux for 24 h. The reaction was monitored by TLC (10% Et_2O in CH_2Cl_2). Upon complete consumption of **11**, the reaction mixture was cooled to rt and filtered through a plug of silica gel. The solvent was removed, and a white foam was isolated. The crude isolate was purified via column chromatography in 2:1 CH_2Cl_2:hexanes as eluent to afford 10.5 g of white solid **13** (84% yield): R_f 0.92 (5% Et_2O in CH_2Cl_2); IR (KBr) 1731, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.21−7.73 (m, 34H), 5.51−5.82 (m, 3H), 5.01 (d, J = 3.8 Hz, 1H), 4.87 (d, J = 2.3 Hz, 1H), 4.79 (d, J = 3.8 Hz, 1H), 4.50−4.63 (m, 1H), 4.03 (t, J = 2.5 Hz, 2H), 3.17−3.30 (m, 1H), 1.09 (s, 18H), 0.25 (s, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.8, 164.3, 148.3, 141.6, 141.5, 139.9, 139.8, 138.4, 136.8, 136.5, 129.2, 128.3, 128.20, 128.16, 128.1, 127.8, 127.6, 126.2, 126.1, 126.1, 123.3, 123.2, 118.8, 118.0, 104.1, 101.4, 78.9, 72.2, 70.8, 55.7, 34.9, 25.5, 25.4, 24.6, 18.2, −4.5, −4.6; MS (FAB$^+$) *m*/*e* 1219.0 (MH^+). Anal. Calcd for $C_{72}H_{74}O_{14}Si_2$: C, 70.91; H, 6.12. Found: C, 71.14; H, 6.27.

Benzyl 4,6-*O*-Benzylidene-2,3-bis(4,5-((diphenylmethylene)dioxy)-3-hydroxybenzoyl)-α-D-glucopyranoside ((Diphenylmethylene)dioxy)benzoyl)-α-D-glucopyranoside (14). Benzyl 4,6-*O*-benzylidene-2,3-bis(3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)benzoyl)-α-D-glucopyranoside (**13**) (8.07 g, 6.62 mmol) was dissolved in 250 mL of THF. Then 13.9 mL (13.9 mmol, 2.1 equiv) of 1.0 M TBAF in THF was added to this solution. The reaction turned yellow instantly upon addition of the TBAF solution, and TLC (5% Et_2O in CH_2Cl_2) indicated that the reaction was complete in less than 5 min. The reaction mixture was diluted with 200 mL of Et_2O and was washed with 3 × 150 mL of 1 M H_3PO_4, 3 × 200 mL of water, and 2 × 150 mL of a saturated NaCl solution. The organic layer was dried over Na_2SO_4, and 10.2 g of clear oil was isolated following filtration and solvent removal in vacuo. The crude oil was purified by column chromatography, eluting with CH_2Cl_2 and then 5% Et_2O in CH_2Cl_2, to afford 5.80 g **14** as a white foam (88% yield): R_f 0.27 (5% Et_2O in CH_2Cl_2); IR (KBr) 1725, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02−7.65 (m, 34H), 6.00−6.50 (br s, 2H), 5.62 (t, J = 3.5 Hz, 1H), 5.47 (s, 1H), 5.46 (t, J = 3.5 Hz, 1H), 4.81 (d, J = 6.7 Hz, 1H), 4.72 (d, J = 4 Hz, 1H), 4.52 (d, J = 6.7 Hz, 1H), 4.48 (dd, J = 2.5, 4 Hz, 1H), 3.77−3.91 (m, 2H), 3.59−3.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 165.3, 164.9, 148.5, 148.4, 148.3, 139.59, 139.55, 139.49, 139.4, 139.1, 139.1, 138.8, 138.6, 138.5, 136.6, 136.5, 136.4, 134.5, 129.8, 129.3, 129.2, 129.1, 129.0, 128.3, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 126.3, 126.3, 126.2, 126.0, 123.1, 123.0, 122.8, 122.7, 118.7, 118.6, 114.4, 114.2, 103.6, 103.5, 101.5, 100.0, 78.7, 72.5, 72.2, 71.6, 70.9, 70.8, 68.5, 66.5, 60.9; MS (FAB$^+$) *m*/*e* 991.5 (MH^+). Anal. Calcd for $C_{60}H_{46}O_{14}$: C, 72.72; H, 4.68. Found: C, 72.50; H, 5.12.

Lead Tetraacetate Oxidative 2,3-Coupling Product 15. A solution of 245 mg (0.55 mmol, 1.1 equiv) of $Pb(OAc)_4$ in 5 mL of dry CH_2Cl_2 was added dropwise over 40 min to a deoxygenated solution of 500 mg (0.5 mmol) of benzyl 4,6-*O*-benzylidene-2,3-bis(3,4-((diphenylmethylene)dioxy)-5-hydroxybenzoyl)-α-D-glucopyranoside (**14**) and 162 μL (2.0 mmol, 4.0 equiv) of pyridine 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 an additional 1 h. The reaction solution was diluted with saturated aqueous $NaHCO_3$ and poured into 250 mL of Et_2O. The organic extract was washed with 3 × 300 mL of 1 M H_3PO_4, 3 × 300 mL of saturated $NaHCO_3$, 3 × 400 mL of water, and 1 × 300 mL of saturated NaCl and then dried over Na_2SO_4. The organic layer was filtered and concentrated in vacuo to afford 0.53 g of a yellow powder. The crude products were purified by flash column chromatography, eluting first with CH_2Cl_2 and then with 5% Et_2O in CH_2Cl_2, to afford 222 mg of the desired coupling product **15** as a mixture of three regioisomers (45% yield). ^{1}H- and ^{13}C-NMR spectra are reported for the lowest R_f (pure) regioisomer only: R_f 0.64 (5% Et_2O in CH_2Cl_2); IR (KBr) 1752, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04−7.62 (m, 30H), 6.71 (s, 1H), 6.60 (s, 1H), 5.52 (d, J = 7 Hz, 1H), 5.29−5.36 (m, 1H), 5.28 (s, 1H), 5.20 (br s, 1H), 5.06−5.13 (m, 1H), 4.92 (d, J = 14 Hz, 1H), 4.77 (d, J = 12 Hz, 1H), 4.67 (d, J = 14 Hz, 1H), 4.37−4.40 (m, 1H), 3.82−3.91 (m, 2H), 3.43−3.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 167.0, 147.3, 139.0, 138.8, 138.7, 138.7, 138.4, 137.8, 136.6, 135.4, 129.6, 129.33, 129.25, 129.0, 128.6, 128.5, 128.29, 128.26, 128.2, 128.03, 127.98, 127.84, 127.81, 127.7, 127.2, 127.1, 126.6, 126.5, 126.4, 126.31, 126.29, 126.2, 110.8, 110.5, 101.6, 101.1, 99.1, 76.2, 76.0, 75.7, 75.5, 71.1, 71.0, 68.8, 66.9; MS (FAB$^+$) m/e 989.8 (MH$^+$).

2,3-Coupling Benzylation Product 16. Benzyl bromide (47 μL, 0.39 mmol, 2.1 equiv) was added to a solution of 185 mg (0.19 mmol) of the 2,3-coupling product **15** (as a mixture of three regioisomers), 57 mg (0.41 mmol, 2.2 equiv) of K_2CO_3, and 6 mg (0.037 mmol, 0.2 equiv) of KI in 15 mL of acetone. The reaction was purged with Ar and brought to reflux under an Ar atmosphere. TLC (CH_2Cl_2) showed complete consumption of starting material after 12 h. The reaction mixture was filtered through a Celite pad, and the solvent was removed in vacuo to provide 201 mg of an orange/brown solid. The crude products were purified by flash column chromatography, eluting with 3:1 CH_2Cl_2:hexanes, to afford 184 mg of the desired benzylation product **16** as a mixture of three regioisomers (84% yield): R_f 0.83 (CH_2Cl_2); IR (KBr) 1757, 1701, 1686 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.89−7.54 (m, 40H), 6.75 (s, 1H), 6.60 (s, 1H), 5.45 (s, 1H), 5.01−5.32 (m, 5H), 4.79−4.93 (m, 2H), 4.54−4.77 (m, 2H), 4.34 (dd, J = 6.4, 2.8 Hz, 1H), 3.70−3.88 (m, 2H), 3.38−3.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.4, 130.0, 130.24, 130.16, 130.1, 130.03, 129.99, 129.7, 129.6, 129.3, 129.22, 129.15, 129.10, 129.07, 129.02, 128.97, 128.94, 128.86, 128.78, 128.70, 128.65, 128.59, 128.56, 128.4, 128.3, 128.2, 127.7, 127.6, 127.4, 127.23, 127.16, 127.05, 126.96, 126.8, 126.74, 126.71, 110.3, 102.7, 102.09, 102.06, 102.0, 100.0, 78.0, 77.1, 77.0, 76.6, 74.9, 72.5, 72.5, 71.6, 68.9, 67.6; MS (FAB$^+$) m/e 1169.8 (MH$^+$). Anal. Calcd for $C_{74}H_{56}O_{14}$: C, 76.02; H, 4.83. Found: C, 75.84; H, 5.05.

Removal of the Benzylidene Acetal To Form Diol 17. The benzylated 2,3-coupling product **16** (as a mixture of three regioisomers) (184 mg, 0.16 mmol) was dissolved in 20 mL of 1:1 MeOH:CH_2Cl_2. The solution was purged with Ar, and 40 mg (0.16 mmol) of I_2 was added. The reaction was shielded from light, brought to reflux under Ar, and held there for 1 h. It was then cooled to rt and allowed to stand for another 18 h under Ar. TLC (CH_2Cl_2 or 5% Et_2O in CH_2Cl_2) showed that most of the starting material had been consumed at this time. The reaction was diluted with 40 mL of Et_2O and washed with 4 × 50 mL of saturated $Na_2S_2O_4$. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo to provide 254 mg of a red/brown solid, **17**. The crude product was purified via column chromatography, eluting first with CH_2Cl_2, followed by 5% Et_2O in CH_2Cl_2, to afford 105 mg of a pinkish/white solid (64% yield) as a mixture of three regioisomers: IR (KBr) 1752 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.88−7.52 (m, 35H), 6.75 (s, 1H), 6.58 (s, 1H), 4.72−5.22 (m, 7H), 4.56−4.70 (m, 2H), 3.68−3.92 (m, 3H), 3.27−3.39 (m, 1H), 1.95−2.35 (br s, 2H); MS (FAB$^+$) m/e 1081.3 (MH$^+$).

Steglich Esterification of the 2,3-Coupled Diol 18 To Form 18a. A solution of 208 mg (0.19 mmol) of 4,6-dihydroxyglucopyranoside **17**, 190 mg (0.42 mmol, 2.1 equiv) of 3-(*tert*-butyldimethylsiloxy)-4,5-((diphenylmethylene)dioxy)-benzoic acid **12**, 12 mg (0.096 mmol, 0.5 equiv) of DMAP, 15 mg (0.096 mmol, 0.5 equiv) of DMAP·HCl, and 119 mg (0.58 mmol, 3.0 equiv) of DCC in 20 mL of CH_2Cl_2 (0.01 M in diol) was purged under Ar and then heated at reflux for 48 h. The reaction was monitored by TLC (CH_2Cl_2). Upon complete consumption of starting diol, the reaction mixture was cooled to rt and filtered through a plug of silica gel. The solvent was removed in vacuo, and 0.62 g of a yellow/white foam was isolated. The crude isolate was purified via column chromatography, in sequence eluting with 1:2 CH_2Cl_2:hexanes, 1:1 CH_2Cl_2:hexanes, 2:1 CH_2Cl_2:hexanes, and finally 100% CH_2Cl_2 to afford 288 mg of a white solid (77% yield): R_f 0.75 (CH_2Cl_2); IR (KBr) 1758, 1726 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05−7.66 (m, 59H), 6.76 (s, 1H), 6.62 (s, 1H), 5.63 (t, J = 9.7 Hz, 1H), 5.33−5.44 (m, 1H), 5.28 (d, J = 5.8 Hz, 2H), 5.01−5.13 (m, 4H), 4.91 (d, J = 12.5 Hz, 1H), 4.75 (d, J = 12.5 Hz, 1H), 4.67 (d, J = 11 Hz, 1H), 4.30−4.42 (m, 2H), 1.00 (s, 9H), 0.99 (s, 9H), 0.23 (s, 6H), 0.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 164.9, 149.5, 142.8, 141.8, 139.5, 137.7, 130.3, 129.3, 129.0, 128.3, 127.5, 126.9, 125.1, 124.4, 119.3, 109.8, 104.8, 102.6, 99.2, 77.9, 76.4, 75.0, 73.2, 72.6, 71.2, 68.9, 63.4, 25.9, −4.3; MS (FAB$^+$) m/e 1941.5 (MH$^+$). Anal. Calcd for $C_{119}H_{104}O_{22}Si_2$: C, 73.59; H, 5.40. Found: C, 73.44; H, 5.59.

Synthesis of Pedunculagin (1). Glucopyranoside **18a** (288 mg, 0.15 mmol) was dissolved in 10 mL of THF. A solution of 1.0 M TBAF in THF (311 μL, 0.31 mmol, 2.1 equiv) was added to this solution. The reaction turned yellow instantly upon addition of the TBAF solution, and TLC (5% Et_2O in CH_2Cl_2) indicated that the reaction was complete in less than 5 min. The reaction mixture was diluted with 25 mL of Et_2O and was washed with 3 × 40 mL of 1 M H_3PO_4, 3 × 40 mL of water, and 2 × 40 mL of saturated NaCl solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo, leading to 426 mg of an oily solid. The crude bis phenol **18b** was purified by column chromatography, eluting with CH_2Cl_2 and then 5% Et_2O in CH_2Cl_2, to afford 233 mg of white solid **18b** (92% yield) as a mixture of three regioisomers: R_f 0.62 (5% Et_2O in CH_2Cl_2); IR (KBr) 1757, 1734, 1718, 1701, 1686, 1676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02−7.65 (m, 59H), 6.72 (s, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 6.59 (s, 1H), 6.55 (s, 1H), 6.53 (s, 1H), 6.10 (br s, 1H), 6.01 (br s, 1H), 5.92 (br s, 1H), 5.54 (t, J = 5.5 Hz, 1H), 4.89−5.38 (m, 16H), 4.61−4.79 (m, 2H), 4.52−4.60 (m, 2H), 4.21−4.34 (m, 2H); MS (FAB$^+$) m/e 1714.5 (MH$^+$). These deprotected bis phenols were taken directly on and submitted to lead tetraacetate oxidative coupling conditions. A solution of 24 mg (0.05 mmol, 1.1 equiv) of $Pb(OAc)_4$ in 2 mL of dry CH_2Cl_2 was added dropwise over 40 min to a deoxygenated solution of 85 mg (0.05 mmol) of the TBAF deprotection product **18b** and 16 μL (0.20 mmol, 4.0 equiv) of pyridine 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 an additional 1 h. The reaction solution was diluted with a saturated $NaHCO_3$ solution, and the products were extracted into 12 mL of Et_2O. The organic extract was washed with 3 × 20 mL of 1 M H_3PO_4, 3 × 20 mL of saturated $NaHCO_3$, 3 × 20 mL of water, and 2 × 20 mL of saturated NaCl and then dried over Na_2SO_4. The organic layer was filtered and concentrated in vacuo to afford 85 mg of a yellow powder. The crude products were purified by flash column chromatography, eluting first with CH_2Cl_2 and then with 2% Et_2O in CH_2Cl_2, to afford the desired coupling product **19** as a mixture of at least nine different regioisomers (72% combined yield): R_f 0.64, 0.56, 0.47 (3% Et_2O in CH_2Cl_2). The ^{1}H NMR is reported for a mixture that contains two major and one minor regioisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02−7.65 (m, 57H), 6.82 (s, 1H), 6.81 (s, 1H), 6.78 (s, 1H), 6.77 (s, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 6.58 (s, 1H), 6.54 (s, 1H), 6.52 (s, 1H), 6.38 (s, 1H), 5.38−5.54 (m, 3H), 5.03−5.29 (m, 12H), 4.73−4.99 (m, 4H), 4.56−4.71 (m, 4H), 3.80−4.04 (m, 3H); MS (FAB$^+$) m/e 1712.8 (MH$^+$). These products from

the lead tetraacetate oxidative coupling reaction were taken directly on through hydrogenolysis without attempting to further separate regioisomers. A solution of 83 mg (0.05 mmol) of the 4,6-coupling product **19** and 63 mg of 10% Pd/C in 2 mL of THF was purged 3× with H_2. The reaction solution was stirred under 1 atm of H_2 for 24 h. TLC (reverse phase, 10% MeOH in water) showed a high R_f (0.67) spot which was consistent with the natural product. The reaction was filtered through Celite, and 67 mg of a brown material was isolated. Preparative reverse-phase TLC (10% MeOH in water, 0.02% AcOH) followed by extraction of acetone-soluble constituents from the partially purified chromatography product resulted in isolation of 25 mg of pedunculagin as a floculent brown solid. This material readily dissolve in 2 mL of acetone-d_6 with 50 μL of 20% DCl in D_2O, leaving behind 13 mg of a floculent white solid. Peduculagin **1** (12 mg) was thus isolated in 21%overall yield from **18a** (1:1 mixture of α:β anomers). This material coeluted with an authentic sample of natural pedunculagin (C_{18} reverse phase, 10% CH_3OH in H_2O; R_f = 0.67): ^{1}H NMR (300 MHz, acetone-d_6) δ 6.65 (s, 1H), 6.64 (s, 1H), 6.59 (s, 1H), 6.58 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 6.32 (s, 1H), 6.31 (s, 1H), 5.56 (s, 4H), 5.45 (t, J = 6.4 Hz, 1H), 5.43 (s, 1H), 5.23−5.31 (m, 2H), 5.19 (t, J = 7.3 Hz, 1H), 5.02−5.12 (m, 4H), 4.84 (d, J = 5.4 Hz, 1H), 4.82 (d, J = 6.1 Hz, 1H), 4.53−4.62 (m, 1H), 4.18−4.24 (m, 1H), 3.71−3.88 (m, 4H), 3.03−3.12 (m, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.4, 168.9, 168.1, 167.9, 145.2, 145.0, 144.4, 136.2, 126.7, 126.1, 115.8, 114.0, 108.4, 107.7, 107.6, 107.5, 107.3, 95.3, 91.7, 78.3, 77.5, 75.7, 75.5, 72.4, 69.9, 69.6, 67.4, 63.5; CD (MeOH) 238 nm, +41.9, 263 nm, −14.7, 284 nm, +6.5; MS (FAB$^-$) m/e 785.3 (MD$^+$).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR and CD spectra of synthetic pedunculagin, the ^{1}H NMR spectrum of natural pedunculagin, and the global minimum energy conformations derived from **14** and its des ketal analog (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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