Ellagitannin Chemistry. The First Synthesis of Dehydrohexahydroxydiphenoate Esters from Oxidative Coupling of Unetherified Methyl Gallate

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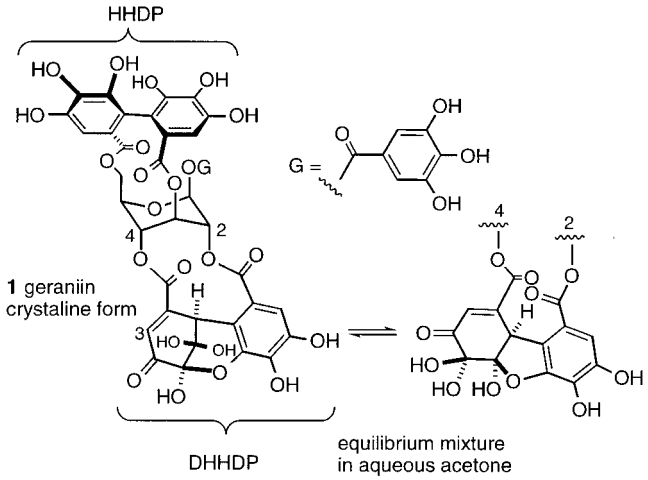
A simple *o*-chloranil-mediated oxidative dimerization of methyl gallate in anhydrous ether furnishes a dimethyl dehydrohexahydroxydiphenoate (DHHDP) product as a pale yellow precipitate in good yield. This methyl gallate dehydrodimer rapidly rearranges in acetone to give a mixture of two additional DHHDP regioisomers. One of these species corresponds to the isomer of the dehydrohexahydroxydiphenoyl group commonly observed in dehydroellagitannin natural products. Sodium dithionite-mediated reduction of the initially formed dimethyl dehydrohexahydroxydiphenoate and/or its derived regioisomers efficiently furnishes dimethyl hexahydroxydiphenoate (HHDP). Addition of *N*-(carbobenzyloxy)-L-cysteine benzyl ester to dimethyl dehydrohexahydroxydiphenoate(s) in THF solution produces two diastereomeric 3-*S*-cysteinyl derivatives of dimethyl hexahydroxydiphenoate.

Progress in the synthesis of bioactive ellagitannin plant secondary metabolites depends upon the development of reliable methodologies for the facile preparation of their characteristic galloyl-derived biaryl and diaryl ether acyl groups.[1,2] Novel approaches for synthesizing hexahydroxydiphenoyl (HHDP) and dehydrodigalloyl units have recently been developed[1,3] and successfully applied to the total synthesis of several naturally occurring ellagitannins.[4] Access to *dehydro*hexahydroxydiphenoyl (DHHDP) units and DHHDP-containing ellagitannins, exemplified by the $^4C_1$-glucopyranosyl-containing geraniin (**1**),[5] remains a challenge. Current art is defined by Schmidt's 30-year-old report on the preparation of a DHHDP phenazine derivative via a multistep procedure from ellagic acid.[6]

The chemical details of the biogenesis of ellagitannin HHDP and DHHDP esters are still under active investigation.[1a,2] Although these two units differ only by their oxidation level, it is not clear if the former precedes the latter during biosynthesis. Thus, oxidation of a glucose-bound HHDP unit could afford a DHHDP product, but it is also possible that the DHHDP functionality can emerge directly from the oxidative dimerization of glucose-bound galloyl rings (vide infra). In aqueous acetone solution, the DHHDP unit of geraniin-type ellagitannins exists as a mixture of the two possible five- and six-membered ring hemiketals,[1,5,7] whereas only the six-membered ring is observed for other DHHDP-containing ellagitannins.[8] A requirement for glucose-free DHHDP and HHDP units in our ongoing chemical studies of ellagitannin natural products led us to revisit the oxidation of methyl gallate (**2**) for preparing unprotected versions of these compounds in a concise and efficient manner. The results obtained bear on strategies for dehydroellagitannin chemical synthesis and also on hypotheses advanced for their biosynthesis.



Results and Discussion

The value of *o*-chloranil in the clean oxidation of galloyl *monoethers* has been the subject of previous reports from this laboratory.[3,9] In the current study, this mild and selective oxidant is equally successful in furnishing good yields of characterizable oxidative dimerization products from *unetherified* methyl gallate (**2**). This observation

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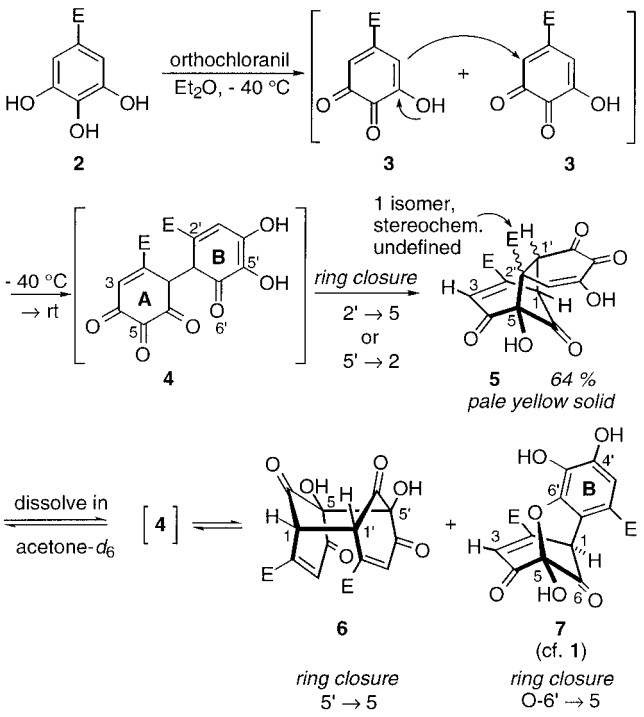
Scheme 1[a]

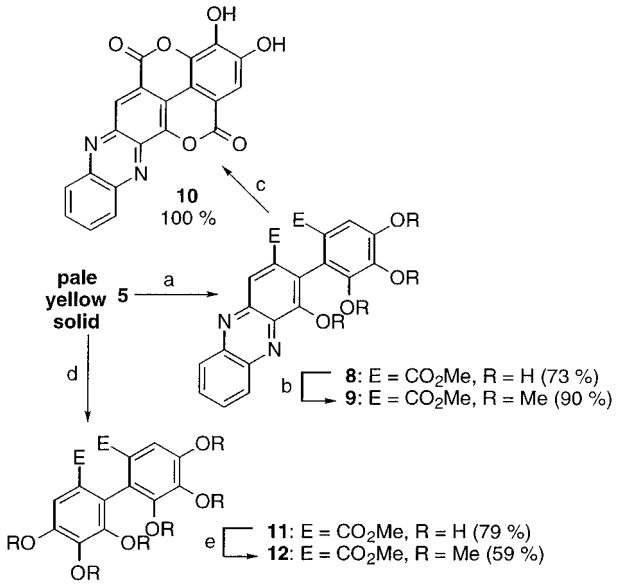


[a] E = CO_2CH_3.

stands in stark contrast to the many previous attempts at gallate ester (or acid) oxidation with a host of chemical and biochemical oxidants. These oxidation attempts invariably delivered ellagic acid and/or purpurogallin derivatives with only occasional HHDP ester formation in modest yield.[10] Thus, treatment of an equimolar amount of *o*-chloranil in Et_2O at −40 °C with **2**, and allowing the reddish solution to warm slowly to rt, furnished a pale yellow precipitate in a reproducible 64% yield. Mass spectrometric, combustion, and rapid NMR analyses indicated that this solid was a dimer of the hydroxyorthoquinone **3**, but a combination of derivatizations and careful NMR study was necessary to unveil its structure (Scheme 1).

The pale yellow solid compound was first converted to its phenazine derivative **8** in order to verify its quinonoid nature (Scheme 2).[5f,11] The phenazine **8** was further transformed into a known permethylated derivative **9**[5d,6] and bislactonized to form **10**[5d,f,11a] in order to determine unambiguously the regiochemistry of phenazine formation. Most importantly, the pale yellow solid was reduced

Scheme 2[a]



[a] Reaction conditions: (a) *o*-phenylenediamine, AcOH−CH_3CN; (b) CH_2N_2, Et_2O; (c) H_2O−MeOH, reflux; (d) $Na_2S_2O_4$, H_2−THF, 0 °C; (e) MeI, NaH, DMF.

to afford a known compound, dimethyl hexahydroxydiphenoate (**11**). Several reducing agents (H_2, Pd/C;[5f] Zn−Cu; $Na_2S_2O_4$)[8c] were tried under various experimental conditions. The sodium dithionite ($Na_2S_2O_4$)-mediated reduction was found to be superior in providing **11** in high yield and with relatively good purity. Ellagic acid was not detected; it was readily obtained, however, as an off-white precipitate upon trituration of **11** with aqueous acetone at rt. The only byproduct, methyl gallate (**2**), which presumably resulted from reductive cleavage of transient intermediate **4**, was typically detected in 5−15% yield by ^1H NMR analysis. The propensity of hydroxyorthoquinone-derived dimers to undergo ready dissociation into their quinonoid monomeric form is documented.[12b] Permethylation of **11** furnished **12** in good yield. This two-step procedure for the synthesis of **11** from commercially available methyl gallate compares favorably with previously reported routes to HHDP derivatives.[10j,q,13]

The structural elucidation of the first-formed precipitate **5** and its rearrangement products **6** and **7** commenced with ^1H and ^{13}C NMR analyses that, in the case of **5**, had to be performed immediately after preparation of the sample at a concentration ≥0.3 M to record

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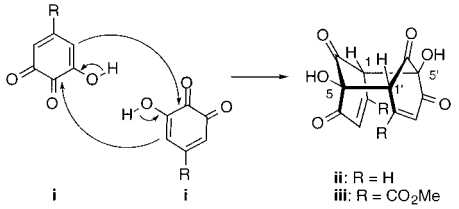


Table 1: HMBC Data for Compounds 5−7[a]

	proton	HMBC
5	H-1	C-2, C-3, C-5, C-6, C-7, C-1′(?), C-2′
	H-1′	C-1, C-2, C-2′(?), C-6′, C-7′
	H-3	C-1, C-5, C-7
	H-3′	C-5 (w), C-1′, C-4′, C-5′, C-7′(w)
	OH-4′	C-3′, C-4′, C-5′
	OH-5	C-4, C-5, C-6, C-2′
6	H-1/1′	C-1/1′, C-2/2′, C-3/3′, C-5/5′, C-6/6′, C-7/7′
	H-3/3′	C-1/1′, C-2/2′, C-5/5′, C-7/7′
	OH-5/5′	C-4/4′, C-5/5′, C-6/6′
7	H-1	C-2, C-3, C-5, C-6, C-7, C-1′, C-2′, C-6′
	H-3	C-1, C-2 (w), C-5, C-7
	H-3′	C-1′, C-2′ (w), C-7′, C-4′, C-5′
	OH-4′	C-3′, C-4′, C-5′
	OH-5	C-4, C-5, C-6
	OH-5′	C-4′, C-5′, C-6′

[a] Chemical shift assignments are given in the Experimental Section; ? = ambiguous, w = weak intensity.

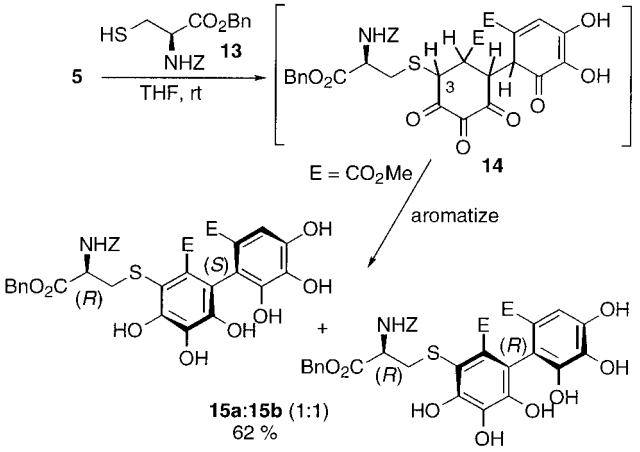
relatively clean spectra. The detection and assignment of the nonoxygenated aliphatic quaternary carbon (C-2′ at 53.0 ppm) by ^{13}C and DEPT NMR analyses was key to the elucidation of this structure. A delayed $^{1}H-^{1}H$ COSY experiment[14] was run to confirm the assigment of the pair of allylic coupled protons H-1/H-3 ($^{4}J \approx 1.0$ Hz). H-1′ is vicinally coupled with H-1, but no correlation was observed with H-3′. These observations and HMQC/HMBC data (Table 1) are all in agreement with structure **5**. This dimer plausibly arises from an intramolecular direct (2′ → 5) or conjugate (5′ → 2) addition of a ring B enol to the cyclohexenetrione unit of **4** (Scheme 1).

Dimer **5** in acetone-d_6 was rapidly converted into the symmetrical dimer **6**, which slowly (ca. 7 days) equilibrated to a ca. 1:1 mixture of **6** and **7** upon storage at −10 °C. This equilibration is much more rapid at rt and gives rise to 1:2 to 1:4 mixtures of **6** and **7** after ca. 24 h. Although extensive degradation to unidentified products accompanies this isomerization, **6**:**7** mixtures are typically stable long enough to permit complete NMR characterization.

The symmetrical nature of structure **6** was apparent from the number of signals in both the ^{1}H and ^{13}C spectra. The presence of tertiary alcoholic carbons α to two ketone carbonyls (C-5/5′) was indicated by a resonance at 96.0 ppm. This compound likely results from a direct enol/carbonyl coupling within **4** to form the C-5/C-5′ bond of the tricyclic core (Scheme 1). Similar compounds have been observed as products of the oxidative dimerization of various pyrogallols.[12]

The assignment of structure **7** depended upon the observation of two phenolic hydroxyl protons (OH-4′ and OH-5′) resonating at 8.47 and 8.70 ppm, respectively, as well as the observation of one hemiketal hydroxyl proton OH-5 resonating at 7.36 ppm. The allylic proton H-1 (5.90 ppm) exhibits diagnostic HMBC responses with the vinylic carbon C-3 (130.4 ppm), the hemiketal carbon C-5 (98.2 ppm), the carbonyl carbon C-6 (195.3 ppm), and, more importantly, three aromatic carbons (ring B) resonating at 113.7 ppm (C-1′), 121.8 ppm (C-2′), and 143.4 ppm (oxygenated C-6′). Compound **7** is the third DHHDP species observed in acetone-d_6 solution, and its formation can be rationalized via (1) initial aromatization of ring B in **4** followed by (2) intramolecular addition of the resulting phenol (OH-6′) to the central carbonyl carbon C-5 (Scheme 1). The regiochemistry of hemiketalization (phenol addition to C-5 vs C-6) is determined unambiguously from observation of three-bond HMBC responses between H-3 and C-5 and between OH-5 and C-4/C-6. Compound **7** corresponds to the nonhydrated form of the six-membered ring hemiketal DHHDP ester group contained in ellagitannin natural products (e.g., **1**). HMBC data for compounds **5**−**7** are given in Table 1.

Scheme 3



Alternative mechanisms to the simple two-step conversion of putative intermediate orthoquinone **3** to dimer **5** can be envisioned. For example, it is possible that dimer **5** is formed via a direct one-step Diels−Alder-type cycloaddition of one molecule of (protonated?) **3** acting as a dipolar (cationic?) five-carbon 4π component with the alkene (2π) of a second molecule of **3**. In addition, nascent orthoquinone **3** may be trapped by nucleophilic phenol **2** to furnish intermediate dimethyl HHDP **11** after aromatization. This species could undergo subsequent *o*-chloranil-mediated oxidation to deliver **5** via an unobserved orthoquinone derivative of **11**, a process in accord with earlier speculation by Schmidt.[6] At present, no basis to distinguish between these three hypotheses exists.

The electrophilicity of the DHHDP unit of ellagitannin natural products may be relevant to their expression of biological activity. Tanaka et al. have shown that thiol nucleophiles such as cysteine methyl ester and glutathione add to the DHHDP ester groups of **1** to give dihydro-1,4-thiazine derivatives and various rearranged sulfide derivatives, respectively.[15] In every case, initial thiol addition occurs at the C-3 carbon (cf. **1**) of the DHHDP unit. The yellow solid **5** was combined with *N*-(carbobenzyloxy)-L-cysteine benzyl ester (**13**)[3] in THF solution to afford, probably via an intermediate of type **14**, a 1:1 diastereomeric mixture of the rearomatized adducts **15a:15b** in good yield (Scheme 3). This type of C-3 sulfur-bearing HHDP unit has not been reported by Tanaka et al.,[15] but it might be relevant to dehydroellagitannin-mediated covalent modification of proteins in vivo.

In summary, methyl gallate (**2**) can be oxidized by *o*-chloranil to furnish dehydroellagitannin-related dimethyl dehydrohexahydroxydiphenoates. Their clean

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reduction by sodium dithionite offers a convenient and reproducible two-step synthesis of dimethyl hexahydroxydiphenoate, a C−C-coupled biaryl acyl unit requisite for ellagitannin synthesis. This study provides support for a dehydroellagitannin biosynthesis hypothesis featuring galloyl-derived orthoquinones, as opposed to phenoxy radicals and even perhaps phenoxonium ions,[16] in galloyl oxidative coupling. In addition, DHHDP esters are masked quinonoid electrophiles that can be efficiently trapped by a cysteinyl nucleophile to furnish 3-*S*-cysteinyl-HHDP units. This thiol addition reaction may be involved in the covalent modification of proteins by dehydroellagitannins, thus mediating the biological activity of these DHHDP-containing natural products.

Experimental Section

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium/benzophenone under Ar immediately before use. Moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under Ar. Solvents for chromatography (Et_2O, EtOAc, CH_2Cl_2, hexane) were distilled from CaH_2 prior to use. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 32−63 μm silica gel and the indicated solvents. Melting points are uncorrected. One- and two-dimensional NMR spectra of samples in the indicated solvent were run at either 300 or 500 MHz (^{1}H). Carbon multiplicities were determined by DEPT90 and DEPT135 experiments.[17] Correlation information was obtained with inverse-detected short-range (one bond) ^{1}H−^{13}C HMQC[18] and long-range (two and three bonds) ^{1}H−^{13}C HMBC[19] correlative experiments and with delayed ^{1}H−^{1}H correlative experiments[14] using a fixed delay of 200 ms. Chemical impact mass spectra (CIMS) were obtained with isobutane as the reagent gas, and electron impact mass spectra (EIMS) were obtained at 50−70 eV. FAB high-resolution mass spectra were obtained from the mass spectrometry laboratory at the University of Texas at Austin. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN. ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information to establish purity for those compounds that were not subject to combustion analyses.

Dimethyl Dehydrohexahydroxydiphenoates 5−7. A solution of methyl gallate (**2**) (2.08 g, 11.3 mmol) in Et_2O (250 mL) was added dropwise under Ar to a stirred −40 °C cooled solution of *o*-chloranil (3.05 g, 12.4 mmol) in Et_2O (50 mL). After completion of the addition, the reaction mixture was allowed to warm slowly to rt over 2 h. A yellowish solid precipitated out of the mixture. Stirring was continued for 1 h, after which time the solid was collected by filtration and washed extensively with cold Et_2O to give **5** (1.32 gm, 64%) as a pale yellow solid: mp 210 °C dec; IR (KBr) 3345, 1782, 1728, 1682 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 3.73 (s, MeO-7′), 3.87 (s, MeO-7), 4.61 (dd, J = 7.8, 0.9 Hz, H-1), 4.68 (d, J = 7.8 Hz, H-1′), 6.32 (s, OH-5), 6.43 (s, H-3′), 6.88 (d, J = 1.1 Hz, H-3), 8.50 (s, OH-4′); ^{13}C NMR (CD_3COCD_3) δ 196.9 (C-6), 195.3 (C-4), 191.4 (C-6′), 176.7 (C-5′), 171.0 (C-7′), 164.4 (C-7), 153.7 (C-2), 151.0 (C-4′), 132.3 (C-3), 119.4 (C-3′), 96.8 (C-5), 53.9 (MeO-7), 53.6 (MeO-7′), 53.4 (C-1′), 53.0 (C-2′), 50.2 (C-1); CIMS m/z (relative intensity) 367 ([MH + 2]$^+$, 2), 365 (MH$^+$, 3). Anal. Calcd for $C_{16}H_{12}O_{10}$: C, 52.76; H, 3.32. Found: C, 52.50; H, 3.48.

6: ^{1}H NMR (CD_3COCD_3) δ 3.95 (s, MeO-7/7′), 4.36 (s, H-1/1′), 5.86 (s, OH-5/5′), 7.02 (s, H-3/3′); ^{13}C NMR (CD_3COCD_3) δ 196.2 (C-6/6′), 190.3 (C-4/4′), 164.3 (C-7/7′), 146.6 (c-2/2′), 133.4 (C-3/3′), 96.0 (C-5/5′), 54.0 (MeO-7/7′), 53.2 (C-1/1′).

7: ^{1}H NMR (CD_3COCD_3) δ 3.77 (s, MeO-7), 3.91 (s, MeO-7′), 5.90 (s, H-1), 6.96 (s, H-3), 7.14 (s, H-3′), 7.36 (s, OH-5), 8.47 (s, OH-4′), 8.70 (s, OH-5′); ^{13}C NMR (CD_3COCD_3) δ 195.3 (C-6), 189.3 (C-4), 167.3 (C-7′), 164.8 (C-7), 147.8 (C-2), 146.8 (C-4′) 143.4 (C-6′), 137.8 (C-5′), 130.4 (C-3), 121.8 (C-2′), 114.2 (C-3′), 113.7 (C-1′), 98.2 (C-5), 53.5 (MeO-7), 52.4 (MeO-7′), 46.8 (C-1).

Methyl 4-Hydroxy-3-[4,5,6-trihydroxy-2-(methoxycarbonyl)phenyl]phenazine-2-carboxylate (8). Solid dimethyl dehydrohexahydroxydiphenoate **5** (107 mg, 0.29 mmol) was dissolved in CH_3CN (4 mL) and treated with a solution of *o*-phenylenediamine (48 mg, 0.44 mmol) in glacial AcOH (2 mL) for 15 h at rt.[5f] The resulting orangeish precipitate was collected by filtration, triturated with water, recollected by filtration, and extensively washed with Et_2O to give **8** (94 mg, 73%) as a yellow solid: mp 402 °C dec; IR (KBr) 3400−3000, 1729, 1617 cm^{-1}; ^{1}H NMR (CD_3COCD_3 + 2 drops CD_3SOCD_3) δ 3.43 (s, 3 H), 3.67 (s, 3 H), 7.21 (s, 1 H), 7.96−7.99 (m, 2 H), 8.24 (s, 1 H), 8.27−8.31 (m, 2 H); ^{13}C NMR (CD_3COCD_3) δ 167.43, 167.37, 151.0, 145.2, 144.9, 144.5, 143.3, 142.8, 137.8, 137.6, 136.5, 132.3, 131.9, 130.7, 130.1, 122.1, 121.8, 119.2, 118.5, 110.7, 52.3, 51.4; EIMS m/z (relative intensity) 436 (M$^+$, 46); HRMS (EI) calcd for $C_{22}H_{16}O_8N_2$ 436.0907, found 436.0921.

Methyl 4-Methoxy-3-[4,5,6-trimethoxy-2-(methoxycarbonyl)phenyl]phenazine-2-carboxylate (9). Phenolic phenazine **8** (28 mg, 0.06 mmol) in MeOH (1 mL) was treated with an excess of ethereal diazomethane for 12 h, after which time the resulting yellow solution was evaporated to dryness. The residue was purified by preparative TLC, eluting with CH_2Cl_2−MeOH (20:1), to afford **9**[5d,6] (28 mg, 90%) as a yellow oil, which was crystallized from MeOH−H_2O to furnish small yellow needles: mp 156−158 °C (lit.[6] mp 158−159 °C); IR (KBr) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 3 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 3.98 (s, 3 H), 4.00 (s, 6 H), 7.48 (s, 1 H), 7.85−7.91 (m, 2 H), 8.25−8.36 (m, 2 H), 8.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.7, 166.5, 152.54, 152.46, 151.2, 145.6, 143.8, 143.4, 142.9, 139.7, 133.9, 131.2, 130.9, 130.2, 129.7, 129.6, 127.8, 125.9, 124.4, 109.0, 62.3, 60.8, 60.7, 56.0, 52.4, 51.8; EIMS m/z (relative intensity) 492 (M$^+$, 61); HRMS (FAB) calcd for $C_{26}H_{24}O_8N_2$ 493.1611, found 493.1617.

Phenazine Bis-lactone 10. Phenolic phenazine **8** (37 mg, 0.09 mmol) in 1:1 MeOH−H_2O (3 mL) was refluxed for 12 h, after which time the resulting reddish brown precipitate was collected by filtration, washed with H_2O and then Et_2O to furnish 32 mg of **10**[5d,f,11a] as a brick red solid in quantitative yield: mp >400 °C (lit.[5d] mp >360 °C); IR (KBr) 3422, 1762, 1734 cm^{-1}; ^{1}H NMR (CF_3COOD) δ 8.10 (s, 1 H), 8.45 (t, J = 7.5 Hz, 1 H), 8.64 (t, J = 7.5 Hz, 1 H), 8.73 (d, J = 8.7 Hz, 1 H), 8.82 (d, J = 8.7 Hz, 1 H), 9.63 (s, 1 H); ^{13}C NMR (CF_3COOD) δ 163.0, 161.7, 153.4, 147.3, 144.7, 144.1, 142.0, 139.5, 138.7, 137.6, 136.2, 132.8, 132.7, 125.8, 124.4, 123.3, 121.8, 116.0, 113.5; FABMS m/z (relative intensity) 373 (MH$^+$, 61); HRMS (FAB) calcd for $C_{20}H_8O_6N_2$ 373.0461, found 373.0461.

Dimethyl 4,4′,5,5′,6,6′-Hexahydroxy-2,2′-diphenoate (11). Solid dimethyl dehydrohexahydroxydiphenoate (**5**) (280 mg, 0.77 mmol) was dissolved in THF (12 mL). The resulting solution was cooled to 0 °C (ice−water bath), and sodium dithionite (268 mg, 1.54 mmol) was added. The reaction mixture was stirred for 30 min, after which time it was poured over ice-cold water (20 mL), extracted with EtOAc (2 × 20 mL), washed with brine, dried over Na_2SO_4, filtered, and evaporated at rt to furnish crude **11** (262 mg) as a beige solid. ^{1}H NMR analysis indicated the presence of about 15% of methyl gallate (**2**); 5−15% of **2** was typically observed in repeated runs. Further purification by silica gel column chromatography, eluting with EtOAc:AcOH (100:1), afforded **11**[10j,13b] (223 mg, 79%) as an off-white solid: mp 258 °C (lit.[10j] mp 210 °C dec); IR (Nujol) 1727 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 3.46 (s, 6 H), 7.12 (s, 2 H), 7.66 (bs, 6 H); ^{13}C NMR (CD_3COCD_3) δ 167.4, 144.6, 144.5, 137.6, 122.6, 118.7, 110.7, 51.3; CIMS m/z (relative intensity) 367 (MH$^+$, 3).

Dimethyl 4,4′,5,5′,6,6′-Hexamethoxy-2,2′-diphenoate (12). Compound **11** (50 mg) was permethylated according to Itoh's

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procedure to furnish **12**[13c,20] as a yellowish beige syrup in 59% yield: IR (CCl_4) 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 12 H), 3.94 (s, 6 H), 3.95 (s, 6 H), 7.37 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 166.9, 152.0, 151.1, 145.3, 126.5, 124.9, 108.8, 60.7, 60.5, 55.9, 51.8; CIMS *m*/*z* (relative intensity) 450 (M^+, 42); HRMS (FAB) calcd for $C_{22}H_{26}O_{10}$ 450.1526, found 450.1525.

Dimethyl 3-*N*-(Carbobenzyloxy)-*S*-cysteinyl-4,4′,5,5′,6,6′-hexahydroxy-2,2′-diphenoate Benzyl Esters (15a/b). Solid dimethyl dehydrohexahydroxydiphenoate (**5**) (179 mg, 0.49 mmol) was dissolved in THF (10 mL) and added dropwise at rt over 1 h to a solution of *N*-(carbobenzyloxy)-L-cysteine benzyl ester **13** (170 mg, 0.49 mmol).[3] Evaporation of the solvent afforded a dark yellow oil, which was purified by column chromatography, eluting with light petroleum−EtOAc−AcOH (1:2:0.02), to give **15a**:**15b** (215 mg, 62%) in a 1:1 ratio as an amorphous pale yellow solid: IR (KBr) 3394, 1708 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 3.07−3.40 (m, 4 H), 3.37 (s, 3 H), 3.38 (s, 3 H), 3.43 (s, 3 H), 3.45 (s, 3 H), 4.38−4.49 (m, 2 H), 5.00−5.19 (m, 8 H), 6.92 (d, J = 7.8 Hz, 2 H), 7.074 (s, 1 H), 7.077 (s, 1 H), 7.27−7.36 (m, 20 H), 7.7−8.3 (bs, 12 H); ^{13}C NMR (CD_3COCD_3) δ 171.5/171.3, 169.1/168.9, 167.3/167.2, 157.2/156.9, 147.3, 146.4/146.3, 145.4, 145.3, 145.1, 137.9, 137.54/137.46, 136.8/136.7, 134.4/134.3, 133.7/133.6, 129.3, 129.2, 128.9, 128.8, 128.6, 123.4/123.3, 115.8/115.6, 115.4/115.2, 110.8 (2), 106.0/105.8, 67.5/67.4, 67.0/66.9, 54.9/54.8, 51.8/51.7, 51.6 (2), 38.7/37.7; FABMS *m*/*z* (relative intensity) 710 (MH^+, 100); HRMS (FAB) calcd for $C_{34}H_{31}O_{14}NS$ 710.1543, found 710.1554.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **6**−**8**, **11**, **12**, and **15a**/**b** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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