Galloyl-Derived Orthoquinones as Reactive Partners in Nucleophilic Additions and Diels−Alder Dimerizations: A Novel Route to the Dehydrodigalloyl Linker Unit of Agrimoniin-Type Ellagitannins

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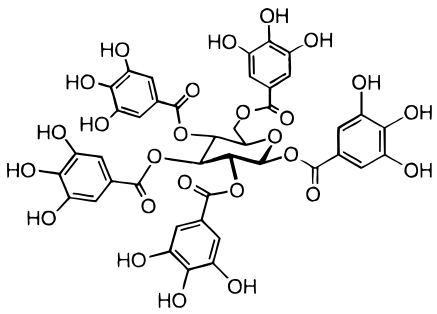
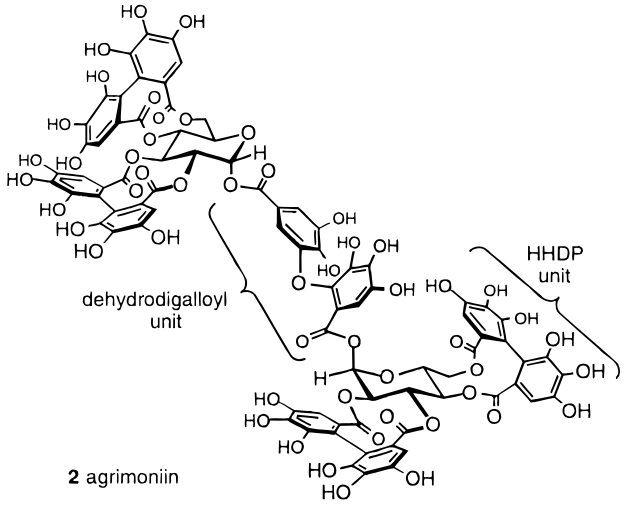
Orthochloranil-mediated oxidation of galloyl monoethers furnishes the derived orthoquinones in excellent yield. These reactive electrophiles participate in a variety of nucleophilic addition reactions with heteroatomic and carbanionic partners. In addition, Lewis acid-mediated dimerization of the orthoquinones provides an efficient route to dehydrodigalloyl-type diaryl ether units characteristic of several ellagitannin natural products. The implications for ellagitannin biosynthesis and gallotannin−protein covalent attachment are discussed.

The structural diversity and pharmaceutical potential embodied by the extensive gallotannin and ellagitannin[1] families of secondary plant metabolites has stimulated several recent studies in both organic synthesis[2] and drug discovery.[3] The relative simplicity of the gallotannin structural motif, as exemplified by the naturally occurring β-pentagalloylglucose (**1,** β-PGG), gives way to a myriad of skeletal possibilities for the ellagitannins as galloyl rings are joined through oxidative couplings, cf. agrimoniin (**2**).[4] While no direct evidence yet implicates β-PGG as the biosynthetic precursor of ellagitannins, this presumption underscores numerous biosynthetic hypotheses and synthetic strategies. A survey of the more than 500 structurally characterized ellagitannins reveals that C−C biaryl bond formation is almost exclusively the province of *intra*molecular coupling,[5] while C−O linkages between galloyls invariably span either two different galloylated glucose cores or act as attachment points for a third galloyl ring to a hexahydroxydiphenyl (HHDP) unit. Plausible reactive intermediates which have been postulated to precede galloyl coupling include phenoxonium ions (two-electron oxidation) and/or phenoxy radicals (one-electron oxidation).[2a,b,6] The electrophilicity of phenoxonium ions might also be moderated by deprotonation to furnish related orthoquinone intermediates.



1 β-pentagalloyl glucose



2 agrimoniin

Catechol-derived orthoquinones have long been identified as occupying a central position in the chemistry of such diverse biological operations as insect cuticle sclerotization,[7a,b] melanization,[7c−g] food browning and wine ageing,[7h−k] arene hepatotoxicity,[7l] brain catecholamine aberrant metabolism,[7m,n] estrogen-mediated carcinogenesis,[7o,p] and poison oak/ivy contact dermatitis in humans.[7q,r] In these systems, the electrophilic orthoquinone typically scavenges endogenous protein or peptidic nucleophiles leading to a covalent link between the arene ring and the nucleophilic heteroatom. However, the role that *galloyl*-derived orthoquinones might play in either (1) the expression of biological activity for select members of the tannin family, or (2) the biosynthesis of oligomeric ellagitannins has received scant attention. The reactive and electrophilic character of these orthoquinones can indeed provide a unifying theme to these otherwise disparate avenues of tannin chemistry. One particular biological system where galloyl-derived orthoquinones may occupy a pivotal position involves gallotannins, LdNPV (*Lymantria dispar* nuclear polyhedrosis virus), and gypsy moth (GM) caterpillars.[8] The gallotannin-mediated attenuation of infectivity for naturally occurring LdNPV has ominous implications for manage-

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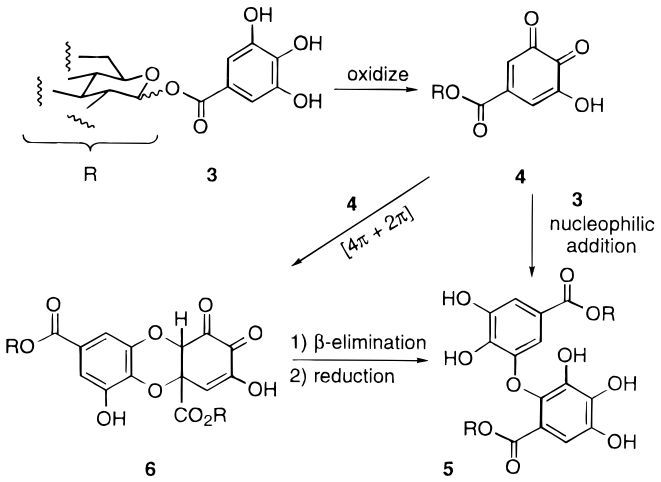
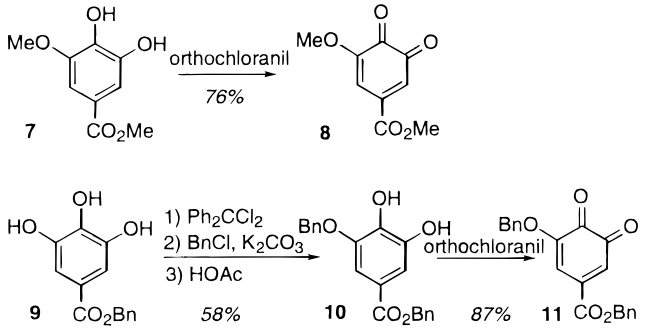
ment of outbreaks of this significant forest defoliator. The highly alkaline (pH = 8−11) and oxidizing (E_h = +200−250 mV) GM caterpillar midgut provides a favorable milieu for ingested polyphenol (e.g., galloyl) oxidation.[8] Thus, conversion of galloyl units to orthoquinonoid electrophiles, followed by covalent trapping of nucleophilic sites on a LdNPV surface envelope protein, might constitute a plausible molecular hypothesis for tannin-mediated suppression of infectivity. Chemical precedence for this sequence of events can be gleaned from the work of Nonaka, who observed that the naturally occurring (masked) orthoquinone-containing ellagitannin geraniin combines with the nucleophilic amino acid methyl cysteine to furnish a covalent conjugate addition product.[9]

The biosynthetic construction of the C−O linked dehydrodigalloyl moiety (cf. **2**) may also proceed through an electrophilic orthoquinone intermediate **4** and utilize either a phenolic galloyl nucleophile **3** (e.g., **4** + **3** → **5**) or a second orthoquinone partner via Diels−Alder chemistry, **4** + **4** → **6** → **5**, Scheme 1. The addition of phenolic

Scheme 1



Scheme 2



nucleophiles to orthoquinones has been documented,[10] while the Diels−Alder route is much more speculative. Interestingly, Abdul-Hajj et al. have reported the spontaneous dimerization of a steroidal orthoquinone to provide a diaryl ether product and its oxidized monoorthoquinone derivative upon standing at rt for 2 h.[7o,11] The mechanistic basis for this transformation is open to interpretation but might involve chemistry analogous to that presented in Scheme 1.

In this report we detail and expand upon our initial studies on the nucleophilic capture of galloyl-derived orthoquinones.[12] Furthermore, we describe the Diels−Alder dimerization of these species to afford protected versions of the dehydrodigalloyl linker unit which bridges the monomer modules in agrimoniin-type ellagitannins. These studies address the legitimacy of invoking galloyl orthoquinones as central intermediates in the aforementioned in vivo chemistry.

Results and Discussion

The preparation of monoether versions of galloyl orthoquinones (Scheme 2) followed from the seminal work of Horner et al., who described the clean orthochloranil-mediated oxidative conversion of various catechol derivatives to orthoquinones.[13] The galloyl derivative **7** was explored in Horner's original study, but isolation of a pure, monomeric orthoquinone product was not described. However, careful control of the reaction conditions permitted acquisition of pure samples of the orthoquinones **8** and **11** in excellent yield (see Experimental Section). The bright yellow powdery solid **8** and the burgundy solid **11** were obtained as analytically pure compounds by this procedure. Both solid compounds were stable indefinitely at room temperature but gradually decomposed to unidentified materials in solution.

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(5) For an exception, see Jiang, Z.-H.; Tanaka, T.; Kouno, I. *J. Chem. Soc., Chem. Commun.* **1995**, 1467.

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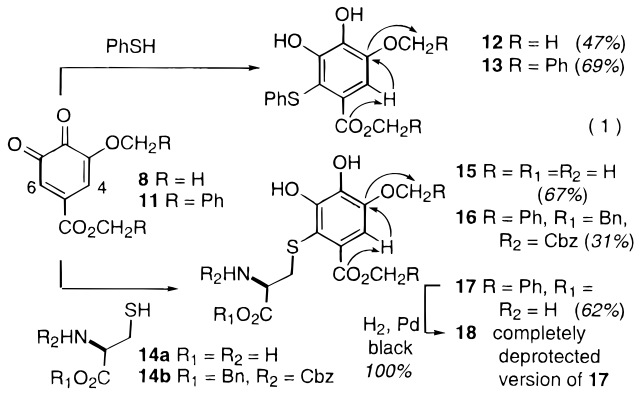
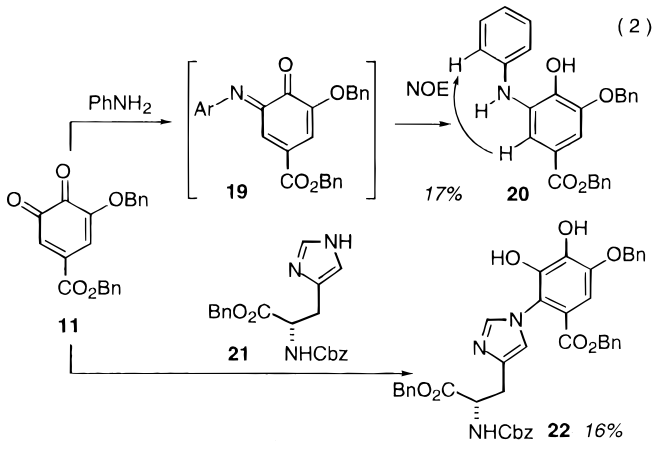
The potent orthoquinone electrophiles **8** and **11** were allowed to react with a range of sulfur, nitrogen, phenoxide, and carbon-based nucleophiles in an effort to define the scope and limitations of the addition process. The thiol nucleophiles PhSH and cysteines **14a** and **14b** all afforded conjugate addition products with the orthoquinones **8** and **11** (eq 1). In each pairing, titration of the thiol in THF or THF:H_2O with the orthoquinone in THF led to immediate discharge of the quinone solution's characteristic color and furnished the rearomatized monoadduct in good yield. This sequence of addition minimized the opportunity for subsequent oxidation of the electron-rich products **12**, **13**, **15**−**17** by the orthoquinones themselves. Hydrogenolysis of the benzyl protecting groups in **17** liberated the parent-derivatized amino acid **18**. The 1,6-regiochemistry of addition was assigned by HMBC NMR experiments. Relevant correlations are shown on the structures **13** and **17**. This regiochemical outcome is in complete accord with much precedent in related orthoquinone/sulfur nucleophile couplings.[7a,d,e,h,k,r] One simple rationalization for the observed regiochemistry of attack might cite the additional electrophilic activation of C(6) by the ester moiety which is absent from C(4) in **8**/**11**.



(1)

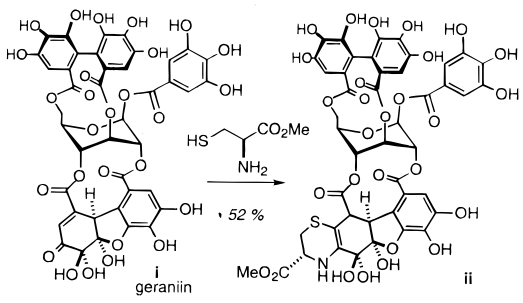
The addition of nitrogen-based nucleophiles (aniline, lysine, histidine) to the orthoquinone **11** did not proceed as smoothly as did the addition of the sulfur species. Reaction with aniline did not afford any evidence for conjugate addition, but rather delivered the direct carbonyl addition product **20** in modest yield, (eq 2). An orthoquinone monoimine intermediate **19** presumably precedes **20** although the reductant of **19** has not been identified. The regiochemistry of diarylamine **20** was secured through the NOESY-based correlation shown. In contrast, the histidine derivative **21** did combine with orthoquinone **11** at C(6) to furnish small quantities of the rearomatized conjugate adduct **22**. N^{α}-(carbobenzyloxy)lysine did not participate in conjugate addition with **11** to any detectable degree (THF−1 M NaOH), and only a complex and intractable product mixture resulted. These disappointing intermolecular amine additions can be contrasted to the well-known intramolecular cyclization of dopamine quinones to various indole derivatives.[7c,m,n]



(2)

Matters deteriorated further upon attempted addition of phenol itself or galloyl-based phenols to either orthoquinone **8** or **11**. No anionic or Lewis acidic experimental conditions could be devised which permitted isolation of any characterizable adducts. Rapid decolorization of the orthoquinone solution was generally observed, and orthoquinone precursors **7**/**10** were isolated in varying amounts. Enforced intramolecularity was of no avail, as the phenolic orthoquinone **23** failed to cyclize. Finally, the presumably more electrophilic bromo orthoquinone **24** provided no advantage in these diaryl ether synthesis attempts.

The addition of carbanionic nucleophiles to orthoquinones can proceed to furnish either C−C- or C−O-coupled products. Enolates favor conjugate addition, as exemplified by the addition of a β-keto ester enolate to a putative



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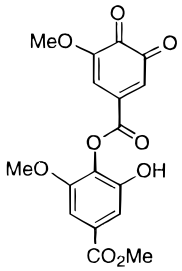

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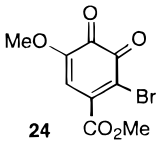
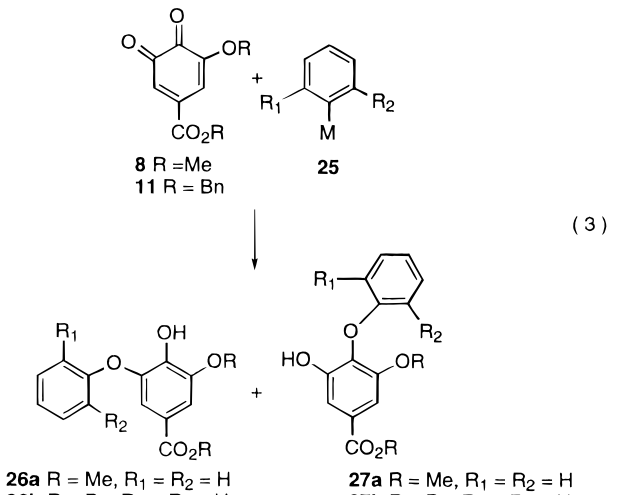


24

orthoquinone derived from methyl gallate under the influence of $K_3Fe(CN)_6$.[14] Grignard reagents, however, combine with orthoquinones to provide aryl ethers, presumably through an indirect mechanistic pathway featuring electron transfer and radical coupling.[15] This latter process might be exploited in the development of a diaryl ether synthesis from galloyl-derived orthoquinone electrophiles and aryl organometallics, (eq 3) and Table 1.

A survey of phenyl−metal species (PhLi, PhMgBr, PhMgBr/CuI, PhMgBr/$CeCl_3$) in combination with orthoquinones **8**/**11** revealed that the best yields of diaryl ether products **26**/**27** attended the Grignard reagent with either Cu or Ce additives. The assignment of regiochemistry was based on ^{1}H NMR analysis of the derived permethyl ethers (see Experimental Section). Moderate regioselectivity with the phenyl organometallics was observed for the "meta" isomer **26** over the "para" alternative **27** as might be desired for possible application to dehyrodigalloyl construction. Curiously, the presumably more hindered 2,6-dimethoxyphenyl nucleophile (entry *h*) furnished only the more crowded diaryl ether **27d**, albeit in very low yield. The regiochemical outcome of these additions might be related to both the stabilities[16] of the putative precursor radical anions **28a** and **28b** and the steric demands of bond formation, although the basis for the unexpected "para" isomer selectivity in entry h remains obscure. All attempts to add galloyl-derived organometallics to orthoquinone **8** failed, thus eliminating this process from consideration as a dehydrodigalloyl synthesis strategy.



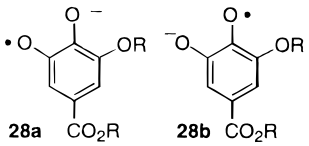
8 R =Me
11 R = Bn

25

(3)

26a R = Me, $R_1 = R_2$ = H
26b R = Bn, $R_1 = R_2$ = H
26c R = Me, R_1 = H, R_2 = OMe
26d R = Me, $R_1 = R_2$ = OMe

27a R = Me, $R_1 = R_2$ = H
27b R = Bn, $R_1 = R_2$ = H
27c R =Me, R_1 = H, R_2 = OMe
27d R =Me, $R_1 = R_2$ = OMe

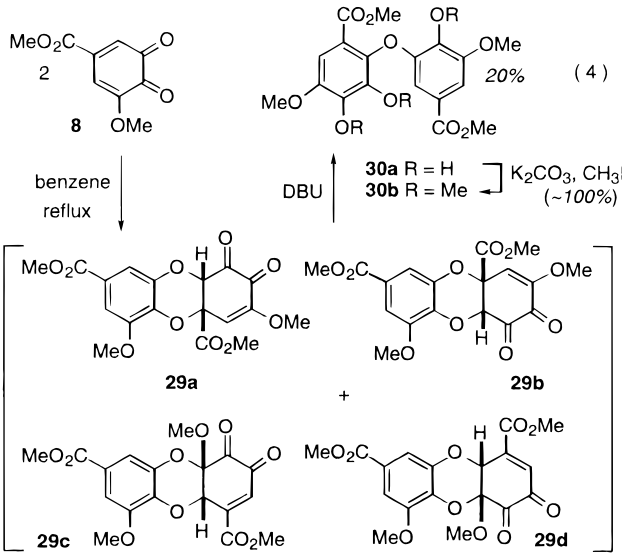


28a **28b**

Table 1. Diary Ethers via Oxophilic Aryl Carbanion Addition to Orthoquinones 8 and 11, Eq 3

entry	R	R_1	R_2	M, *T* (°C)	**26**:**27**	yield (%)
a	Bn	H	H	MgBr, rt	2:1	23
b	Bn	H	H	MgBr, −78	3:1	55
c	Me	H	H	MgBr, −78	1.8:1	50
d	Me	H	H	MgBr/CuI, −90	5.5:1	60
e	Me	H	H	MgBr/$CeCl_3$, −90	5.2:1	75
f	Me	OMe	H	MgBr/CuI, −90	1:1	37
g	Me	OMe	H	MgBr/$CeCl_3$, −90	1:1	47
h	Me	OMe	OMe	MgBr/CuI, −90	0:1	9

The last and most successful attempt to synthesize the dehydrodigalloyl linker unit characteristic of the agrimoniin-type dimeric ellagitannins from galloyl-derived orthoquinone precursors utilized hetero-Diels−Alder dimerization to form the key C−O bond connection. Simply warming orthoquinone **8** in refluxing benzene afforded a complex mixture of three (out of a possible four, **29a**−**d**) benzodioxene adducts (^{1}H NMR) which could be further processed by DBU treatment to furnish the dehydrodigalloyl unit **30a** in modest yield after acidic workup (eq 4). No external reductant was added, and the endogenous reducing agent has yet to be identified. Unfortunately, compound sensitivity precluded isolation and characterization of any pure species between **8** and **30a**.



8

20%

(4)

benzene reflux

DBU

30a R = H
30b R = Me

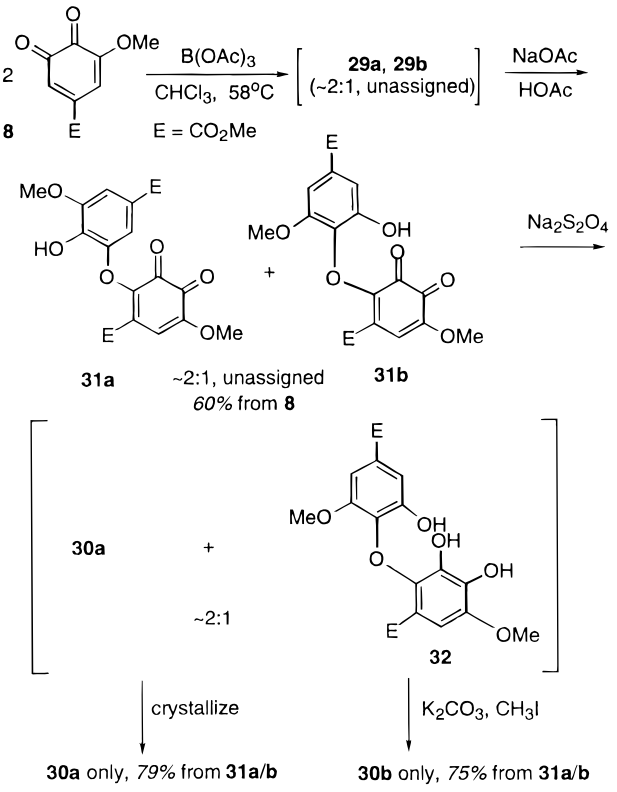
K_2CO_3, CH_3I (*~100%*)

29a **29b** **29c** **29d**

Subsequent optimization studies led to significant improvements in overall yield and revealed the likely intervention of a Smiles rearrangement[17] to favorably adjust regiochemistry of the catechol product, Scheme 3. A survey of Lewis acids/solvents/temperatures converged on the use of $B(OAc)_3$[18] in $CHCl_3$ at 58 °C for optimum yield of benzodioxene via $[4\pi + 2\pi]$ dimerization of **8**. The intermediates derived from this procedure could be detected by ^{1}H NMR (~2:1 of **29a** and **29b**, unassigned) but could not be isolated as discrete compounds. Elimination of the β-phenoxide moieties in **29a**/**b** with NaOAc/HOAc furnished the isolable orthoquinones **31a**/**31b** as

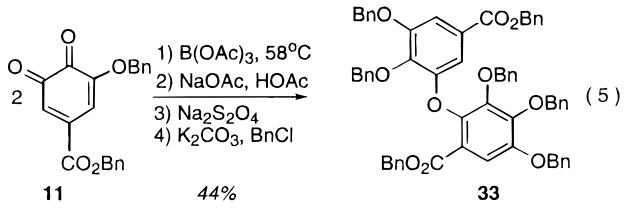
(14) Wanzlick, H.-W. *Chem. Ber.* **1959**, *92*, 3006.
(15) (a) Blomberg, C. *Bull. Soc. Chim. Fr.* **1972**, 2143. (b) Blomberg, C.; Grootveld, H. H.; Gerner, T. H.; Bickelhaupt, F. *J. Organometal. Chem.* **1970**, *24*, 549−553. (c) Beak, P.; Yamamoto, J.; Upton, C. J. *J. Org. Chem.* **1975**, 40, 3052. (d) Wege, D. *Aust. J. Chem.* **1971**, *24*, 1531.
(16) Methyl gallate: $pK_a(1) = 7.85$, $pK_a(2) = 10.0$. Ackermann, G.; Hesse, D.; Volland, P. *Z. Anorg. Allg. Chem.* **1970**, *377*, 92.
(17) (a) Yoshida, T.; Ahmed, A. H. F.; Memon, M. U.; Okuda, T. *Phytochemistry* **1993**, *33*, 197. (b) Yoshida, T.; Maruyama, T.; Nitta, A.; Okuda, T. *Chem. Pharm. Bull.* **1992**, *40*, 1750.

Scheme 3



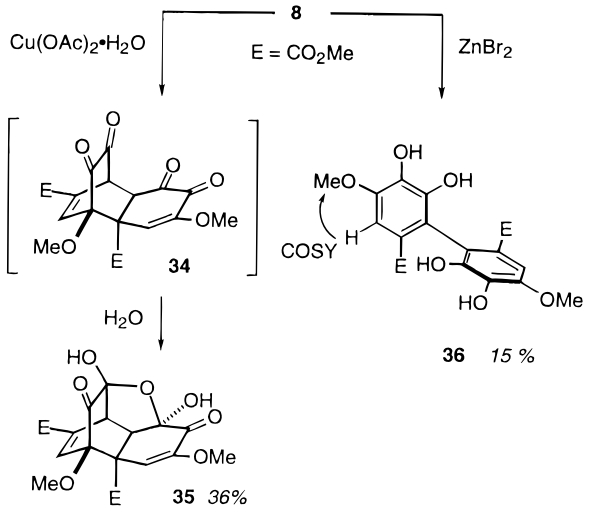
a 2:1 mixture (unassigned) in moderate overall yield from **8**. Finally, reduction of this mixture with hydrosulfite furnished the desired dehydrodigalloyl products **30a**/**32** as a 2:1 mixture of regioisomers, from which only a single "meta" isomer **30a** was deposited upon crystallization from wet CH_2Cl_2 (see Experimental Section). Apparently, Smiles rearrangement-mediated equilibration of the catechol products during crystallization leads to an enrichment in isomer **30a** over the alternative **32**. The mother liquor, which was enriched in "para" isomer **32** (^{1}H NMR), was evaporated and treated with K_2CO_3 in acetone for 10 h at rt to furnish exclusively **30a**. Neither isolation of the intermediate orthoquinones **31a**/**b** nor eventual crystallization to obtain **30a** is necessary, as washing of the crude elimination products **31a**/**b** with hydrosulfite solution furnishes the dehydrodigalloyl products **30a**/**32** directly, while treatment of the ~2:1 mixture **30a**/**32** with K_2CO_3/CH_3I in acetone provides only the single regioisomeric permethylated dehydrodigalloyl unit **30b** in good yield.

The benzyl-protected orthoquinone **11** behaved similarly with the important exception that the regioisomeric benzylated diaryl ethers analogous to **30a**/**32** could not be crystallized. However, benzylation of this crude diaryl ether product mixture was accompanied again by complete equilibration favoring the desired "meta" isomer **33** (eq 5). This regioisomeric preference may be related to the greater stability of the para alkoxide over the meta alternative (cf. **28a** and **28b**, with an aryl group instead of an oxygen radical). The overall chemical yield of this four-step sequence (44% from **11** to **33**) and the complete control of regiochemistry compares favorably with current art (i.e., Ullmann coupling, ~18%)[19] for assembly of the dehydrodigalloyl linker in usefully protected form.



(5)

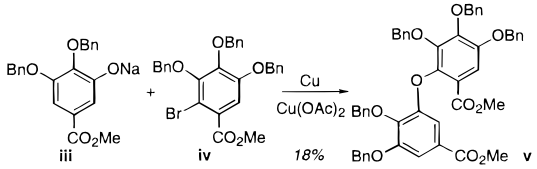
Exposure of the orthoquinone **8** to either $Cu(OAc)_2 \cdot H_2O$ or $ZnBr_2$ produced an entirely different suite of dimeric adducts (eq 6). Stoichiometric copper acetate mediation afforded a moderate yield of the all-carbon Diels–Alder adduct **34** isolated as its hydrate **35**. The structural and exo stereochemical assignment of **35** rests upon the observation of two hemiketal carbons in the ^{13}C NMR spectrum (δ 96.9, 97.8) and a mass of 2 × **13** + 18, along with all the other expected signals. Interestingly, stirring a solution of orthoquinone **8** with $B(OAc)_3$ at rt furnished this same Diels–Alder adduct **35** admixed with the hetero-[$4\pi + 2\pi$]-derived species **29a**/**b**. Warming this mixture to 58 °C promoted conversion of **35** into **29a**/**b**, suggesting that the all-carbon dimer might be kinetically preferred, but the benzodioxene products are thermodynamic minima. Treatment of **8** with $ZnBr_2$ did not lead to isolation of any [$4\pi + 2\pi$] addition products, but rather the HHDP unit **36** was formed in small amounts. The regiochemistry of **36** was assigned by a delayed ^{1}H–^{1}H COSY experiment which revealed the diagnostic five-bond coupling response shown. The mechanistic subtleties of this transformation, which include the mode of C–C bond formation (nucleophilic coupling or [$4\pi + 2\pi$] cycloaddition followed by fragmentation) and source of reductant for any first-formed mono orthoquinone adduct, remain obscure. Resubmission experiments showed that tricycle **35** was not vulnerable to $ZnBr_2$-mediated fragmentation.



(6)

(18) The structure of the actual catalytic species in this heterogeneous mixture is unknown. Successful Diels–Alder dimerizations accompanied use of either freshly prepared[18a] $B(OAc)_3$ (mp 119 °C → dec, lit. 120 °C) or boron pyroacetate, $((AcO)_2B)_2O$,[18b] mp 141–146 °C (lit. 145–147 °C). (a) Kelly, T. R.; Montury, M. *Tetrahedon Lett.* **1978**, 4311. (b) Lalancette, J. M.; Bessette, F.; Cliche, J. M. *Can. J. Chem.* **1966**, *44*, 1577.

(19) Unpublished results, K. Sahasrabude, Pennsylvania State University.



In summary, these studies show that galloyl-derived orthoquinones are accessible and tractable intermediates in several biologically relevant bond-forming processes. These reactive but selective electrophiles function as expected in nucleophile capture experiments to furnish good yields of conjugate addition products with thiols, but are not effective traps for amines. This model work has implications for the in vivo chemistry hypothesized to underlie the antiviral activity of tannins against LdNPV. Specifically, cysteinyl residues on the LdNPV envelope proteins[20] rather than lysyl or histidyl alternatives are the likely loci for covalent modification by galloyl-derived orthoquinoid electrophiles in the GM midgut. Experiments to test this premise are ongoing. The successful demonstration of dehydrodigalloyl preparation through orthoquinone dimerization bears on both synthesis and biosynthesis issues. This Diels–Alder-based strategy provides the most reliable and efficient assembly of this important ellagitannin linker unit to date and attests to the feasibility of an operational in vivo orthoquinone dimerization route for galloyl oxidative coupling in ellagitannin genesis.

Experimental Section

Melting points are uncorrected. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Further elimination of organic solvents, as well as drying of residues, was accomplished under high vacuum. Column chromatography was carried out with 32–63 μm silica gel, and preparative thin layer chromatography was performed on silica gel 60 F-254 precoated plates (E. Merck). Solvents for chromatography (Et_2O, EtOAc, CH_2Cl_2, hexane) were distilled from CaH_2 prior to use. Light petroleum refers to the fraction boiling in the 40–60 °C range. Tetrahydrofuran (THF) was purified by distillation from sodium/benzophenone under N_2 immediately before use. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under Ar. One- and two-dimensional NMR spectra of samples in the indicated solvent were run at 300 or 500 MHz (^{1}H). Diagnostic correlation information was obtained with inverse-detected long-range ^{1}H–^{13}C correlative HMBC experiments[21a] and delayed ^{1}H–^{1}H correlative experiments[21b] using a fixed delay of 250 ms. NOE information was obtained with a Hahn-echo NOESY experiment,[22] using a mixing time of 1s and a relaxation delay of 4 s. Low and high resolution mass spectra (EIMS, HRMS) were obtained at 50–70 eV by electron impact. Chemical impact mass spectra (CIMS) were obtained with isobutane as the reagent gas, and positive fast atom bombardment mass spectra (FABMS) were obtained in a 2-nitrophenyl octyl ether matrix. Combustion analyses were performed by Midwest Microlab, Indianapolis, IN, or Galbraith Laboratories, Knoxville, TN. ^{13}C NMR spectra are provided in the supporting information to establish purity for those compounds which were not subject to combustion analyses.

Methyl 3-Methoxy-1,2-dioxocyclohexa-3,5-diene-5-carboxylate (8). Methyl 3-*O*-methylgallate (**7**) (1.96 g, 9.9 mmol), prepared from methyl gallate according to the method of Scheline,[23] was dissolved in dry Et_2O (100 mL) and added dropwise over 4 h via a dropping funnel to a stirring solution of orthochloranil (2.68 g, 10.9 mmol, recrystallized from benzene) in dry Et_2O (50 mL) at −30 °C. The reaction mixture was kept stirring at −30 °C for 2 h and then stored at −20 °C for 10 h. The orange precipitate was collected by filtration and extensively washed with cold Et_2O to afford **8** (1.48g, 76%) as a bright yellow powdery solid, mp 122–124 °C (from Et_2O-CH_2Cl_2). IR ($CHCl_3$) 1727, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3 H), 3.94 (s, 3 H), 6.49 (d, J = 1.5 Hz, 1 H), 6.75 (d, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 179.9, 174.1, 164.8, 153.2, 141.3, 124.2, 106.3, 56.3, 53.4; EIMS m/z (relative intensity) 196 (M^+, 27). Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 54.71; H, 4.05.

Benzyl Gallate (9). Benzyl alcohol (2.91 mL, 28.1 mmol), Et_3N (4.28 mL, 30.7 mmol), and DMAP (626 mg, 5.12 mmol) were successively added to an ice-cold stirring solution of 3,4,5-triacetoxybenzoyl chloride[24] (8.04 g, 25.6 mmol) in dry CH_2Cl_2 (50 mL). The solution was maintained at 0 °C for 30 min and then allowed to warm up to rt. Stirring was continued for 4 h, after which time the reaction mixture was poured over ice-cold H_2O, extracted with CH_2Cl_2, washed several times with 3% HCl and H_2O, dried over Na_2SO_4, filtered, and evaporated to give benzyl 3,4,5-triacetoxybenzoate (8.66 g, 88%) as a white solid, mp 106–107 °C (from CH_2Cl_2–light petroleum). IR ($CHCl_3$) 1769, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6 H), 2.29 (s, 3 H), 5.34 (s, 2 H), 7.32–7.42 (m, 5 H), 7.82 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 167.6, 166.3, 164.2, 143.4, 138.7, 135.4, 128.5, 128.4, 128.3, 128.2, 122.3, 67.3, 20.5, 20.1; CIMS m/z (relative intensity) 387 (MH^+, 2), 91 (100). Anal. Calcd for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70. Found: C, 61.88; H, 4.67.

Deacetylation was performed by treating a solution of benzyl 3,4,5-triacetoxybenzoate (5.42 g, 14.0 mmol) in MeOH-H_2O-CH_2Cl_2 (5:1:1, 140 mL) with powdered K_2CO_3 (19.00 g, 137.5 mmol) at 0 °C with vigorous stirring. After formation of a beige creamy precipitate, the reaction mixture was allowed to warm up to rt. Stirring was continued for 1 h, after which time the reaction mixture was cautiously acidified with concd HCl (20 mL), diluted with EtOAc (100 mL), washed with brine, dried over Na_2SO_4, filtered, and evaporated. The resulting oily residue was purified by column chromatography, eluting with EtOAc–light petroleum (1:1), to give benzyl gallate (**9**) (3.05 g, 84%) as a beige solid, which was crystallized from Et_2O–light petroleum to furnish small off-white needles, mp 148 °C. IR (KBr) 1693 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 5.27 (s, 2 H), 7.15 (s, 2 H), 7.30–7.47 (m, 5 H), 8.15 (bs, 3 H); ^{13}C NMR (CD_3COCD_3) δ 166.5, 146.0, 138.9, 137.7, 129.3, 128.8, 121.6, 109.9, 66.6; CIMS m/z (relative intensity) 261 (MH^+, 36), 91 (100). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.55; H, 4.76.

Benzyl 3-*O*-Benzylgallate (10). Powdered K_2CO_3 (10.15 g, 73.5 mmol) and dichlorodiphenylmethane (7.05 mL, 36.7 mmol) were successively added to a solution of benzyl gallate (8.69 g, 33.4 mmol) in CH_3CN (20 mL). This mixture was stirred at room temperature for 10 h, after which time it was cautiously poured over ice-cold 3% HCl, extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated to furnish an amber oil. This crude residue was submitted to column chromatography, eluting with hexane–Et_2O (3:1), to give 12.11 g of a golden foam. This material (3.99 g, 9.41 mmol) was treated with benzyl chloride (1.35 mL, 11.7 mmol), powdered K_2CO_3 (1.95 g, 14.1 mmol), and KI (312 mg, 1.88 mmol) in refluxing acetone for 10 h. After cooling to rt, the reaction mixture was filtered and evaporated to an oily residue. This residue was dissolved in Et_2O, washed sequentially with H_2O, saturated aqueous $NaHCO_3$ and then brine, dried over Na_2SO_4, filtered, and evaporated. The resulting crude product was purified by column chromatography, eluting with light petroleum–Et_2O (2:1), to give the diphenyl ketal of benzyl 3-*O*-benzyl gallate (4.01 g, 83%) as a yellow oil which solidified upon standing, mp 107–109 °C. IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.22 (s, 2 H), 5.28 (s, 2 H), 7.30–7.41 (m, 18 H), 7.54–7.57 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 165.6, 148.4, 142.0, 139.8, 139.5, 136.5, 136.1, 129.3, 128.5, 128.3, 128.14, 128.10, 128.0, 127.6, 126.3, 124.2, 118.5, 112.9, 104.2, 71.7, 66.6; CIMS m/z (relative intensity) 515 (MH^+, 10), 91 (100); HRMS calcd for $C_{34}H_{26}O_5$ 514.1780, found 514.1780.

This ketal (3.95 g, 7.7 mmol) was suspended in 80% aqueous AcOH (100 mL) and heated to reflux for 6 h, after which time the reaction mixture was cooled down to rt, and then parti-

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(23) (a) Scheline, R. R. *Acta Chem. Scand.* **1966**, *20*, 1182. (b) Jurd, L. *J. Am. Chem. Soc.* **1959**, *81*, 4606.

(24) Eisenhauer, H. R.; Link, K. P. *J. Am. Chem. Soc.* **1953**, *75*, 2046.

tioned between EtOAc and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The resulting brownish oil was purified by column chromatography, eluting with light petroleum−EtOAc (3:1), to give **10** (2.49 g, 93%) as amber crystals, mp 92−94 °C (from Et_2O−light petroleum). IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.11 (s, 2 H), 5.31 (s, 2 H), 5.44 (bs, 1 H), 5.91 (bs, 1 H), 7.33−7.43 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 166.2, 145.7, 143.6, 137.3, 136.1, 135.8, 128.7, 128.5, 128.1, 128.0, 121.7, 111.3, 106.4, 71.5, 66.7; CIMS *m/z* (relative intensity) 351 (MH^+, 18), 91 (100). Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.55; H, 5.18.

Benzyl 3-(Benzyloxy)-1,2-dioxocyclohexa-3,5-diene-5-carboxylate (11). Prepared from **10** (1.8−3.2 mmolar scale) in 81−87% as described for **8**, burgundy red solid, mp 136−137 °C. IR ($CHCl_3$) 1724, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.06 (s, 2 H), 5.31 (s, 2 H), 6.56 (d, J = 1.5 Hz, 1 H), 6.76 (d, J = 1.5 Hz, 1 H), 7.36−7.41 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 179.9, 174.2, 164.1, 152.1, 141.4, 134.5, 134.3, 128.9, 128.82, 128.78, 128.7, 128.4, 127.7, 124.4, 107.8, 71.1, 68.3; EIMS *m/z* (relative intensity) 350 ($[M + 2]^+$, 90), 271 (15), 91 (100). Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.41; H, 4.63. Found: C, 72.06; H, 4.61.

Methyl 3,4-Dihydroxy-5-methoxy-2-(phenylthio)benzoate (12). The orthoquinone **8** (50 mg, 0.26 mmol) was dissolved in dry THF (3 mL) and added via a syringe pump at rt over 4 h to a stirring solution of thiophenol (28 μL, 0.27 mmol) in dry THF (2 mL). The dark red color of the orthoquinone solution immediately discharged upon addition. The reaction mixture was kept stirring at rt for 2 h and then poured over saturated aqueous $Na_2S_2O_3$, extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated. The resulting oil was purified by column chromatography, eluting with CH_2Cl_2, to give **12** (36 mg, 47%) as a pale yellow amorphous solid. IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3 H), 3.98 (s, 3 H), 6.97 (s, 1 H), 7.06−7.26 (m, 5 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.7, 148.0, 145.6, 136.2, 135.9, 129.1, 127.5, 126.8, 126.1, 109.9, 106.8, 56.4, 52.2; EIMS *m/z* (relative intensity) 306 (M^+, 100). Anal. Calcd for $C_{15}H_{14}O_5S$: C, 58.81; H, 4.61; S, 10.47. Found: C, 58.69; H, 4.69; S, 10.54.

Benzyl 5-(Benzyloxy)-3,4-dihydroxy-2-(phenylthio)-benzoate (13). Prepared from **11** (50 mg, 0.14 mmol) in 69% as described for **12**, yellow amorphous solid. IR ($CHCl_3$) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (s, 2 H), 5.22 (s, 2 H), 7.00−7.42 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 147.1, 145.8, 136.6, 135.8, 135.6, 135.5, 129.0, 128.8, 128.6, 128.4, 128.2, 128.1, 127.9, 127.4, 126.5, 125.9, 109.9, 108.4, 71.4, 67.1; CIMS *m/z* (relative intensity) 459 (MH^+, 15), 91 (100). Anal. Calcd for $C_{27}H_{22}O_5S$: C, 70.72; H, 4.84; S, 7.00. Found: C, 70.59; H, 5.10; S, 6.93.

Methyl 2-(*S*-Cysteinyl)-3,4-dihydroxy-5-methoxybenzoate (15). The orthoquinone **8** (100 mg, 0.51 mmol) was dissolved in dry THF (10 mL) and added via a syringe pump at rt over 4 h to a stirring solution of cysteine (60 mg, 0.50 mmol, 0.98 equiv) in H_2O−THF (2:1, 5 mL). The solution was then diluted in $CHCl_3$ (10 mL) and extracted twice with H_2O (3 mL). Lyophilization of the aqueous layer afforded crude **15** as a pink solid which was purified by trituration with acetone:H_2O (9:1) to give **15** (105 mg, 67%) as a white solid, mp 194−196 °C. IR (KBr) 1684 cm^{-1}; ^1H NMR [CD_3COCD_3−2 M DCl, (9:1)] δ 3.41 (dd, J = 14.6, 8.7 Hz, 1 H), 3.64 (dd, J = 14.6, 4.2 Hz, 1 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.11 (dd, J = 8.7, 4.2 Hz, 1 H), 6.96 (s, 1 H); ^{13}C NMR [CD_3COCD_3−2 M DCl, (9:1)] δ 169.4, 169.3, 149.4, 148.6, 137.9, 128.2, 109.5, 106.7, 56.5, 52.94, 52.86, 35.45; FABMS *m/z* (relative intensity) 318 (MH^+, 100), 286 (20). Anal. Calcd for $C_{12}H_{15}O_7NS$: C, 45.42; H, 4.77; N, 4.41; S, 10.10. Found: C, 45.02; H, 4.83; N, 4.53; S, 10.09.

***N*-(Carbobenzyloxy)cysteine Benzyl Ester (14b).** Benzyl alcohol (533 mg, 4.93 mmol) was added to a suspension of *N*,*N*′-bis(carbobenzyloxy)cystine (1.00 g, 1.97 mmol, prepared in 87% yield from cystine according to the method of Du Vigneau and Miller)[25] in CH_2Cl_2 (40 mL). Dicyclohexylcarbodiimide (854 mg, 4.14 mmol) and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol)[26] were then added to this suspension at 0 °C. This reaction mixture was allowed to warm up to rt and gently stirred overnight. After filtration through Celite, the filtrate was successively washed with 1 M H_3PO_4 and water, dried over Na_2SO_4, filtered, and evaporated. The residue was submitted to column chromatography, eluting with light petroleum−EtOAc (2:1), to furnish crude *N*,*N*′-bis(carbobenzyloxy)cystine dibenzyl ester which was crystallized from EtOH as white spherulites (1.18 g, 87%), mp 78 °C (lit.[27] mp 79 °C). IR ($CHCl_3$) 3429, 1720, 1506, 1339 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (m, 4 H), 4.60−4.70 (m, 2 H) 5.08 (s, 4 H), 5.14 (s, 4), 5.73 (d, J = 7.7 Hz, 2 H), 7.28−7.36 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 155.6, 136.0, 134.8, 128.6, 128.51, 128.45, 128.4, 128.2, 128.1, 67.6, 67.1, 53.4, 40.9; EIMS *m/z* (relative intensity) 688 (MH^+, 0.1), 91 (100).

The reduction of *N*,*N*′-bis(carbobenzyloxy)cystine dibenzyl ester to white crystalline *N*-(carbobenzyloxy)cysteine was accomplished at rt with Zn dust in 80% aqueous AcOH[28] (97%), mp 66 °C. IR ($CHCl_3$) 3428, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 1 H), 2.97 (m, 1 H), 4.67−4.72 (m, 1 H), 5.10 (s, 2 H), 5.13−5.24 (AB quartet, 2 H), 5.77 (bd, J = 7.3 Hz, 1 H), 7.29−7.34 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 155.6, 135.9, 134.9, 128.58, 128.55, 128.5, 128.4, 128.2, 128.0, 67.5, 67.1, 55.2, 27.1; EIMS *m/z* (relative intensity) 345 (MH^+, 0.5), 91 (100); HRMS calcd for $C_{18}H_{19}O_4NS$ 345.1035, found 345.1061.

5-(Benzyloxy)-2-(*N*-carbobenzyloxy-*S*-cysteinyl)-3,4-dihydroxybenzoic Acid Dibenzyl Ester (16). The orthoquinone **11** (83 mg, 0.24 mmol) was dissolved in dry THF (4 mL) and added via syringe pump at rt over 4 h to a stirring solution of the cysteine derivative **14b** (165 mg, 0.48 mmol) in dry THF (4 mL). Discharge of the dark red color of the orthoquinone solution was observed. Evaporation of the solvent afforded a pale yellow residue. Purification of this residue by column chromatography, eluting with light petroleum−EtOAc (2:1), furnished **16** (52 mg, 31%) as an oil. IR ($CHCl_3$) 3693, 3534, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (dd, J = 14.0, 6.6 Hz, 1 H), 3.28 (dd, J = 14.0, 4.1 Hz, 1 H), 4.54 (m, 1 H), 4.94−5.14 (m, 6 H), 5.28 (s, 2 H), 5.94 (bd, J = 7.6 Hz, 1 H), 7.15 (s, 1 H), 7.25−7.40 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 166.0, 156.1, 146.4, 146.2, 136.9, 136.0, 135.8, 135.7, 134.8, 128.7, 128.55, 128.48, 128.45, 128.4, 128.32, 128.28, 128.1, 128.0, 127.7, 126.4, 112.0, 108.8, 71.3, 67.6, 67.12, 67.09, 54.2, 39.6; EIMS *m/z* (relative intensity) 693 (MH^+, 0.8), 91 (100); HRMS (FAB) calcd for $C_{39}H_{35}O_9NS$ 694.2111, found 694.2106.

Benzyl 5-(Benzyloxy)-2-(*S*-cysteinyl)-3,4-dihydroxybenzoate (17). The orthoquinone **11** (64 mg, 0.18 mmol) was dissolved in dry THF (3 mL) and added via syringe pump at rt over 4 h to a stirring solution of cysteine (21 mg, 0.17 mmol) in H_2O−THF (2:1, 2 mL). Discharge of the dark red color of the orthoquinone solution was observed. After 1 h, the reaction mixture was pale yellow and a white precipitate started to form. After completion of addition, the precipitate was collected by filtration and washed with EtOAc to give 43 mg of **17**. The filtrate and washings were extracted with H_2O, and the aqueous layer was lyophilized to give an additional 8.5 mg of **17** (62%) as a white solid, mp 184−186 °C. IR (KBr) 1723 cm^{-1}; ^1H NMR [CD_3COCD_3−2 M DCl, (9:1)] δ 3.30 (dd, J = 14.7, 9.0 Hz, 1 H), 3.56 (dd, J = 14.7, 4.1 Hz, 1 H), 4.06 (dd, J = 9.0, 4.1 Hz, 1 H), 5.15 (s, 2 H), 5.27 (s, 2 H), 7.01 (bs, 1 H), 7.24−7.42 (m, 10 H); ^{13}C NMR [CD_3COCD_3−2 M DCl, (9:1)] δ 169.3, 168.2, 148.9, 148.00, 138.3, 137.2, 136.5, 129.2, 129.1, 128.9, 128.8, 128.6, 128.3, 127.8, 109.8, 108.5, 71.1, 67.6, 52.8, 35.7; FABMS *m/z* (relative intensity) 470 (MH^+, 100); HRMS (FAB) calcd for $C_{24}H_{23}O_7NS$ 470.1273, found 470.1268.

2-(*S*-Cysteinyl)-3,4,5-trihydroxybenzoic Acid (18). Debenzylation of **17** (70 mg, 0.15 mmol) in THF−H_2O (1:1, 4 mL) was accomplished by using Pd black (20 mg) under H_2 (balloon). A catalytic amount of AcOH was added, and the mixture was stirred for 4 h at rt. The Pd black was filtered off, and THF was removed by evaporation at rt. Lyophilization

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of the aqueous residue afforded 42 mg of **18** (quantitative yield), mp 164−166 °C dec. IR (KBr) 1654 cm^{-1}; ^1H NMR [CD_3COCD_3−2 M DCl, (9:1)] δ 3.26 (dd, J = 14.7, 9.3 Hz, 1 H), 3.59 (dd, J = 14.7, 4.0 Hz, 1 H), 4.00 (dd, J = 9.3, 4.0 Hz, 1 H), 6.93 (s, 1 H); ^{13}C NMR [CD_3COCD_3−2 M DCl, (9:1)] δ 170.7, 169.6, 149.1, 147.0, 136.8, 128.4, 110.8, 106.9, 52.6, 35.2; FABMS m/z (relative intensity) 290 (MH^+, 20), 245 (100); HRMS (FAB) calcd for $C_{10}H_{11}O_7NS$ 290.0334, found 290.0333.

Benzyl 5-Anilino-3-(benzyloxy)-4-hydroxybenzoate (20). The orthoquinone **11** (60 mg, 0.14 mmol) was dissolved in dry THF (3 mL) and added via syringe pump at rt over 3 h to an ice-cold stirring solution of aniline (20 μL, 0.22 mmol, 1.57 equiv) in dry THF (2 mL). No color discharge was observed. Stirring was continued for 3 h, after which time the mixture was evaporated at rt to give a brownish oil. Purification of this residue was performed by preparative TLC, eluting with hexane−Et_2O (2:1), to give **20** (12.4 mg, 17%) as a brown solid, mp 130−132 °C (from $CHCl_3$). IR ($CHCl_3$) 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (s, 2 H), 5.32 (s, 2 H), 5.96 (bs, 1 H), 6.02 (bs, 1 H), 6.97 (bt, J = 7.3 Hz, 1 H), 7.13 (bd, J = 8.7Hz, 1 H), 7.27−7.45 (m, 13 H), 7.77 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.3, 145.4, 142.3, 139.0, 136.3, 136.0, 131.0, 129.4, 128.8, 128.6, 128.5, 128.09, 128.06, 127.9, 121.6, 118.5, 111.6, 106.1, 71.6, 66.4; EIMS m/z (relative intensity) 425 (M^+, 33), 334 (40), 91 (100); HRMS calcd for $C_{27}H_{23}O_4N$ 425.1627, found 425.1613.

***N*$^{\alpha}$-(Carbobenzyloxy)histidine Benzyl Ester (21).** *N*$^{\alpha}$-(Carbobenzyloxy)histidine (735 mg, 2.54 mmol, Aldrich) was converted to its benzyl ester derivative as described for *N*,*N*′-bis(carbobenzyloxy)cystine dibenzyl ester. After filtration through Celite, the filtrate was washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated. The residue was submitted to column chromatography, eluting with CH_2Cl_2−MeOH (20:1), to furnish **21**[29] as a white foam (604 mg, 63%). IR ($CHCl_3$) 3463, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (m, 2 H), 4.65 (m, 1 H), 5.03−5.19 (m, 2 H), 5.10 (s, 2 H), 6.26 (bd J = 6.6 Hz, 1 H), 6.56 (s, 1 H), 7.26−7.43 (m, 10 H), 7.48 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.6, 156.2, 136.2, 135.3, 135.2, 133.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 115.8, 66.9, 66.8, 54.1, 29.3; EIMS m/z (relative intensity) 379 (M^+, 10.9), 91 (100); HRMS calcd for $C_{21}H_{21}O_4N_3$ 379.1532, found 379.1540.

***N*$^{\tau}$-[4-(Benzyloxy)-6-(carbobenzyloxy)-2,3-dihydroxyphenyl]-*N*$^{\alpha}$-(carbobenzyloxy)histidine Benzyl Ester (22).** Orthoquinone **8** (100 mg, 0.29 mmol) was dissolved in dry THF (5 mL) and added via syringe pump at rt over 20 h to a stirring solution of the histidine derivative **21** (272 mg, 0.72 mmol) in dry THF (10 mL). Evaporation of the solvent afforded a reddish residue which was dissolved in CH_2Cl_2 (3 mL). A precipitate of unidentified material formed upon standing overnight at rt. Filtration and purification of the mother liquor by preparative TLC, eluting three times with CH_2Cl_2−MeOH (20:1), furnished **22** (33 mg, 16%) as an oil. IR ($CHCl_3$) 3385, 1718 cm^{-1}; ^1H NMR [CD_3COCD_3−CD_3SOCD_3, (9:1)] δ 2.96−3.11 (m, signal overlapping with water signal), 4.53−4.59 (m, 1 H), 4.94-5.20 (m, 6 H), 5.25 (s, 2 H), 6.71 (s, 1 H), 7.18 (s, 1 H), 7.21−7.40 (m, 22 H), 7.52 (s, 1 H), 7.54 (s, 1 H); ^{13}C NMR [CD_3COCD_3−CD_3SOCD_3, (9:1)] δ 172.3, 165.6, 156.8, 147.2, 143.9, 140.3, 138.0, 137.7, 137.1, 136.9, 129.14, 129.07, 129.02, 129.00, 128.9, 128.8, 128.61, 128.58, 128.5, 120.4, 120.2, 119.4, 107.6, 71.4, 67.0, 66.9, 66.6, 55.1, ? ; FABMS m/z (relative intensity) 728 (MH^+, 100); HRMS (FAB) calcd for $C_{42}H_{21}O_9N_3$ 728.2608, found 728.2607.

Diaryl Ethers via Oxophilic Addition to Quinonoid Carbonyls: Procedure A. A solution of PhMgBr (3.0 M in Et_2O, 2.0 equiv) was added dropwise to a stirring solution of orthoquinone **8** or **11** (0.03−0.05 M in THF, 1.0 equiv) at the indicated temperature. The burgundy color of the quinone solution became light brown upon addition of the Grignard reagent. The reaction mixture was maintained at the indicated temperature and then allowed to warm up to 0 °C over *ca.* 2 h (for the low temperature runs), after which time it was poured over ice−cold saturated NH_4Cl, extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated to give the crude diaryl ethers as oily residues.

Procedure B. CuI (5 mg) was added to a solution of **8** or **11** (0.03−0.05 M in THF, 1.0 equiv) cooled at −78 °C or −90 °C. The mixture was stirred for 30 min, and the Grignard reagent solution (PhMgBr, 3.0 M in Et_2O, 2.0 equiv, or 2-MeOPhMgBr, 0.2 M in THF, 2.0 equiv) was added dropwise. The mixture was then allowed to react and worked-up as described in procedure A.

Procedure C. Anhydrous $CeCl_3$ (2.0 equiv) was suspended in dry THF (2.5 mL). The suspension was vigorously stirred overnight at rt and then cooled down to −78 °C or −90 °C. A solution of the *o*-quinone **11** (0.05 M in THF, 1.0 equiv) was then added, and the mixture was stirred for 30 min, after which time the Grignard reagent solution (PhMgBr, 3.0 M in Et_2O, 2.0 equiv, or 2-MeOPhMgBr, 0.2 M in THF, 2.0 equiv) was added dropwise. The mixture was then allowed to react and worked-up as described in procedure A.

Diaryl Ethers 26a and 27a. By following general procedures A, B, or C, orthoquinone **8** and PhMgBr were combined to afford an oily brown residue. Purification of this crude product by column chromatography, eluting with light petroleum−Et_2O (3:1), led to **26a** and **27a** as white solids.

26a: mp 83−85 °C; IR ($CHCl_3$) 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 3 H), 3.97 (s, 3 H), 6.05 (bs, 1 H), 7.00 (bd, J = 8.6 Hz, 2 H), 7.09 (bt, J = 7.6 Hz, 1 H), 7.32 (bt, J = 8.0 Hz, 2 H), 7.35 (d, J = 1.7 Hz, 1 H), 7.42 (d, J = 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 156.9, 147.6, 142.8, 141.8, 129.7, 123.3, 121.5, 117.6, 115.1, 108.2, 56.4, 52.1; CIMS m/z (relative intensity) 275 (MH^+, 100). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.66; H, 5.29.

27a: mp 150−152 °C; IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H), 3.91 (s, 3 H), 5.75 (bs, 1 H), 6.89 (bd, J = 7.9 Hz, 2 H), 7.05 (bt, J = 7.3 Hz, 1 H), 7.26 (d, J = 1.8 Hz, 1 H), 7.28 (bt, J = 7.6 Hz, 2 H), 7.41 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 157.1, 152.4, 149.6, 134.1, 129.6, 127.6, 122.8, 115.0, 110.6, 105.7, 56.2, 52.3; CIMS m/z (relative intensity) 275 (MH^+, 100). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.94; H, 5.38.

Diaryl Ethers 26b and 27b. By following general procedure A, orthoquinone **11** and PhMgBr were combined to afford an oily brown residue. Purification of this crude product by preparative TLC, eluting with CH_2Cl_2, led to **26b** and **27b** as amorphous solids. The regiochemistry of addition was determined by comparison of the ^{13}C NMR spectra of **26b** and **27b** with those of **26a** and **27a**.

26b: IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (s, 2 H), 5.27 (s, 2 H), 6.02 (s, 1 H), 6.97 (dt, J = 7.7, 1.6 Hz, 2 H), 7.08 (bt, J = 7.4 Hz, 1 H), 7.28−7.45 (m, 13 H), 7.54 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 165.6, 157.0, 146.7, 142.9, 142.5, 136.0, 135.7, 129.7, 128.7, 128.5, 128.2, 128.0, 127.9, 123.2, 121.5, 117.3, 115.9, 110.0, 71.7, 66.6; EIMS m/z (relative intensity) 426 (M^+, 3.7). Anal. Calcd for $C_{27}H_{22}O_5$: C, 76.04; H, 5.20. Found: C, 76.09; H, 5.38.

27b: IR ($CHCl_3$) 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.00 (s, 2 H), 5.35 (s, 2 H), 5.70 (s, 1 H), 6.92−7.45 (m, 16 H), 7.47 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 165.7, 157.3, 151.0, 149.7, 136.0, 135.9, 134.9, 129.6, 128.6, 128.3, 128.2, 127.8, 127.3, 126.9, 123.0, 115.9, 110.8, 107.3, 70.5, 66.9; EIMS m/z (relative intensity) 426 (M^+, 34). Anal. Calcd for $C_{27}H_{22}O_5$: C, 76.04; H, 5.20. Found: C, 75.76; H, 5.59.

Diaryl Ethers 26c and 27c. By following general procedures B or C, orthoquinone **8** and 2-MeOPhMgBr were combined to afford an oily brown residue. Purification of this crude product by preparative TLC, eluting with light petroleum−Et_2O (3:1), led to **26c** and **27c** as yellow oils.

26c: IR ($CHCl_3$) 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3 H), 3.86 (s, 3 H), 3.97 (s, 3 H), 6.45 (bs, 1 H), 6.89−7.17 (m, 4 H), 7.28 (d, J = 1.8 Hz, 1 H), 7.39 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 150.7, 147.5, 145.2, 144.5, 141.2, 125.1, 121.2, 120.4, 113.4, 112.7, 108.1, 56.4, 55.9, 52.0; CIMS m/z (relative intensity) 305 (MH^+, 100), 273 (38); HRMS calcd for $C_{16}H_{16}O_6$ 304.0947, found 304.0925.

27c: IR ($CHCl_3$) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 6.81−7.08 (m, 4 H), 7.23 (d, J = 1.9 Hz, 1 H), 7.35 (d, J = 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 152.6, 150.0, 149.3, 146.7, 136.4, 127.4, 124.1, 121.3, 117.7, 112.4, 110.8, 105.4, 56.2, 56.1, 52.2; CIMS m/z (relative

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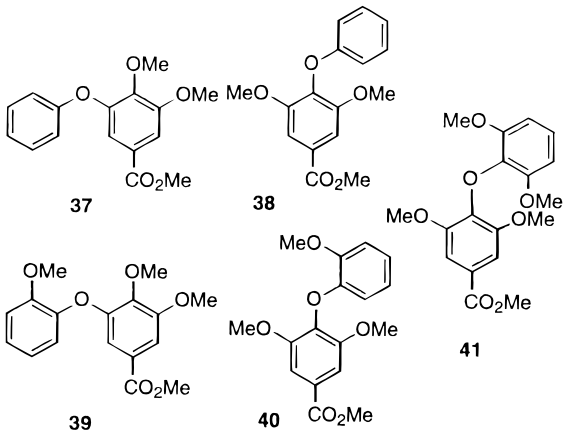
intensity) 305 (MH^+, 100), 273 (8); HRMS calcd for $C_{16}H_{16}O_6$ 304.0947, found 304.0949.

Diaryl Ether 27d. 2,6-Dimethoxybromobenzene (166 mg, 0.76 mmol) and Mg turnings (46 mg, 1.89 mmol) were suspended in dry THF (5 mL) and heated to reflux. A solution of 1,2-dibromoethane (98 μL, 1.1 mmol) in dry THF (2 mL) was added dropwise over 2 h to the refluxing reaction mixture. After cooling down to rt, the resulting pale yellow Grignard solution was added over 15 min to a −90 °C solution of the orthoquinone **8** (100 mg, 0.51 mmol) in dry THF (10 mL) containing 15 mg of CuI. The reaction mixture was maintained at −90 °C for 1 h and then allowed to warm up to rt over 3 h. At that time it was worked-up as described in procedure A. The resulting oily residue was purified by preparative TLC, eluting with light petroleum−Et_2O (3:1), to afford **27d** (15 mg, 9%) as the sole regioisomer. IR ($CHCl_3$) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 3.80 (s, 6 H), 3.88 (s, 3 H), 6.39 (s, 1 H), 6.60 (d, J = 8.4 Hz, 2 H), 7.05 (t, J = 8.4 Hz, 1 H), 7.14 (d, J = 2.0 Hz, 1 H), 7.32 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.8, 152.3, 151.5, 149.0, 139.0, 135.7, 125.6, 124.4, 110.5, 106.0, 105.4, 56.5, 56.4, 52.1; CIMS m/z (relative intensity) 335 (MH^+, 100), 303 (15); HRMS calcd for $C_{17}H_{18}O_7$ 334.1052, found 334.1028.

Methylations of the diaryl ethers **26a**/**c**, **27a**/**c**/**d** were performed on a 0.04−0.08 mmol scale using powdered K_2CO_3 (2 equiv) and CH_3I (2 equiv) in acetone (5 mL) for the purpose of securing the regiochemistry of addition. After refluxing overnight, the mixture was cooled to rt, diluted in CH_2Cl_2, washed with cold 3% HCl and then H_2O, dried over Na_2SO_4, filtered, and evaporated to give **37**−**41**, respectively, as yellow oils which were directly analyzed by ^1H NMR.



37: ^1H NMR ($CDCl_3$) δ 3.86 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 6.97 (bd, J = 7.6 Hz, 2 H), 7.08 (bt, J = 7.4 Hz, 1 H), 7.29−7.35 (m, 2 H), 7.32 (d, J = 1.9 Hz, 1 H), 7.43 (d, J = 1.9 Hz, 1 H).

38: ^1H NMR ($CDCl_3$) δ 3.83 (s, 6 H), 3.94 (s, 3 H), 6.85 (bd, J = 8.6 Hz, 2 H), 7.00 (bt, J = 7.4 Hz, 1 H), 7.22−7.28 (m, 2 H), 7.38 (s, 2 H).

39: ^1H NMR ($CDCl_3$) δ 3.83 (s, 2 × 3 H), 3.94 (s, 3 H), 3.97 (s, 3 H), 6.90−7.15 (m, 4 H), 7.13 (d, J = 1.9 Hz, 1 H), 7.36 (d, J = 1.9 Hz, 1 H).

40: ^1H NMR ($CDCl_3$) δ 3.81 (s, 6 H), 3.93 (s, 3 H), 3.95 (s, 3 H), 6.42−6.45 (m, 1 H), 6.71−6.77 (m, 1 H), 6.91−6.98 (m, 2 H), 7.36 (s, 2 H).

41: ^1H NMR ($CDCl_3$) δ 3.71 (s, 6 H), 3.75 (s, 6 H), 3.90 (s, 3 H), 6.56 (d, J = 8.4 Hz, 2 H), 6.95 (t, J = 8.4 Hz, 1 H), 7.29 (s, 2 H).

Dehydrodigallates via Hetero-Diels−Alder Dimerizations: Procedure D. The orthoquinone **8** (50 mg, 0.26 mmol) was dissolved in benzene-d_6 (1 mL). This solution was refluxed for 8 h, after which time ^1H NMR analysis indicated complete conversion of **8** into a mixture of three out of the four possible regioisomeric 1,4-dioxene products **29a**−**d** in a 3:2:1 ratio. Degradation of these products upon solvent evaporation and silica gel chromatograhy prevented their separation for complete characterization. Their identification by ^1H NMR analysis (benzene-d_6) is based on the observation of three sets of two aromatic doublets (J = 2.0 Hz) resonating at 7.87/7.37 ppm, 7.74/7.40 ppm and 7.80/7.31 ppm, and three sets of two singlets resonating at 5.60/4.87 ppm, 5.57/5.00 ppm, and 6.97/5.23 ppm. The reaction mixture was then cooled to rt and directly treated with DBU (60 μL, 0.40 mmol) for 1 h, after which time it was poured over ice-cold 3% HCl, extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered, and evaporated. The resulting yellow oil was submitted to column chromatography, eluting with CH_2Cl_2−MeOH (20:1), to furnish **30a** (10 mg, 20%) as the sole regioisomer. Methylation of **30a** with CH_3I/K_2CO_3 in acetone afforded **30b** in quantitative yield.

Procedure E. The orthoquinone **8** (85 mg, 0.43 mmol) was dissolved in $CDCl_3$ (4 mL). $B(OAc)_3$ (81 mg, 0.43 mmol) was added, and the resulting heterogeneous mixture was heated at 58 °C (oil bath temperature) for 20 h, after which time ^1H NMR analysis indicated complete conversion of **8** into a 2:1 mixture of tentatively assigned 1,4-dioxenes **29a**/**b**. Diagnostic ^1H NMR ($CDCl_3$) signals included two sets of two singlets resonating at 5.60/6.23 ppm and 5.70/6.16 ppm. The reaction mixture was then filtered, and the boron-containing pellet was washed with CH_2Cl_2. The filtrate and washings were evaporated at rt to give a reddish residue, which was directly treated with NaOAc (36 mg, 0.44 mmol) in AcOH (2 mL) for 2 h at rt. This reaction mixture was then partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The resulting light brown residue was submitted to column chromatography at −78 °C, eluting with hexane−EtOAc (1:1), to afford the 2:1 regioisomeric mixture **31a**/**b** (51 mg, 60%) as a bright yellow solid.

This mixture was then treated with $Na_2S_2O_4$ (113 mg, 0.65 mmol) in THF:H_2O (10 mL). This reductive treatment was performed in a separatory funnel. Discharge of the reaction mixture's yellow color was observed upon shaking the reaction mixture for ca. 2 min. The mixture was then diluted with EtOAc (20 mL), washed with brine, dried over Na_2SO_4, filtered, and evaporated to afford quantitatively an unseparable 2:1 regioisomeric mixture **30a**/**32** (51 mg) as a crude pale yellow oil. Four successive crystallizations of this oily mixture (40 mg) from CH_2Cl_2-H_2O furnished 31.7 mg of **30a** only (79%) from **31a**/**b**. Alternatively, direct methylation of the mixture **30a**/**32** (53 mg from another run) with CH_3I/K_2CO_3 in acetone afforded 44 mg of **30b** only (75%).

Dehydrodigallate 30a: white solid, mp 207 °C (from CH_2Cl_2-H_2O); IR ($CHCl_3$) 3530, 1716 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 3.61 (s, 3 H), 3.71 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 6.84 (d, J = 1.8 Hz, 1 H), 7.10 (s, 1 H), 7.27 (d, J = 1.8 Hz, 1 H), 8.31 (bs, 2 H), 8.61 (bs, 1 H); ^{13}C NMR (CD_3COCD_3) δ 166.9, 165.8, 148.9, 147.7, 145.8, 141.7, 140.8, 140.3, 138.5, 120.7, 115.1, 109.4, 108.1, 105.6, 56.7, 56.6, 52.0, 51.9; CIMS m/z (relative intensity) 395 (MH^+, 25), 199 (100); HRMS calcd for $C_{18}H_{18}O_{10}$ 394.0900, found 394.0937.

Dehydrodigallate 30b: off-white solid, mp 113 °C (lit.[30] mp 112−113 °C); IR ($CHCl_3$) 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 3.96 (s, 3 H), 4.05 (s, 3 H), 6.80 (d, J = 1.8 Hz, 1 H), 7.301 (d, J = 1.8 Hz, 1 H), 7.304 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 166.40. 165.2, 153.2, 152.2, 150.3, 147.2, 146.9, 142.1, 141.8, 124.9, 119.3, 108.8, 108.7, 107.1, 61.3, 61.2, 61.1, 56.2 (2), 52.2, 52.1; CIMS m/z (relative intensity) 436 (M^+, 40), 405 (100); HRMS calcd for $C_{21}H_{24}O_{10}$ 436.1369, found 436.1388.

Orthoquinones 31a/b: amorphous yellow solid; IR ($CHCl_3$) 3455, 1718, 1633 cm^{-1}; **31a**: ^1H NMR ($CDCl_3$) δ 3.697 (s, 3 H), 3.801 (s, 3 H), 3.909 (s, 3 H), 4.01 (s, 3 H), 5.90 (s, 1 H), 7.40 (d, J = 1.8 Hz, 1 H), 7.56 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.47 (2), 166.8, 165.9, 151.6, 149.0, 140.8, 136.7, 134.0, 132.5, 124.5, 111.5, 108.3, 105.3, 56.8, 56.2, 54.3, 52.4; **31b**: ^1H NMR ($CDCl_3$) δ 3.685 (s, 3 H), 3.812 (s, 3 H), 3.913 (s, 3 H), 3.97 (s, 3 H), 5.77 (s, 1 H), 7.33 (d, J = 1.8 Hz, 1 H), 7.48 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.50 (2), 167.0, 166.0, 151.6, 148.5, 140.5, 136.7, 134.2, 132.8, 125.5, 112.1, 107.2, 105.4, 56.4, 56.1, 54.2, 53.7; CIMS m/z (relative intensity) 393 (MH^+, 5), 199 (35); HRMS calcd for $C_{18}H_{16}O_{10}$ 392.0743, found 392.0742.

Dehydrodigallate 33. The orthoquinone **11** (200 mg, 0.57 mmol) was dissolved in $CDCl_3$ (4 mL) and converted to a 2:1 regioisomeric mixture of the benzylated analogs of **31a**/**31b**

(156 mg, 78%) as described in procedure E. Diagnostic ^{1}H NMR ($CDCl_3$) signals of the benzylated analogs of the 1,4-dioxene intermediates **29a**/**b** included two sets of two singlets resonating at 5.58/6.27 ppm and 5.67/6.18 ppm. The benzylated analogs of **31a**/**31b** each exhibited a diagnostic ^{1}H NMR ($CDCl_3$) singlet at 5.90 ppm and 5.76 ppm. Reduction of the benzylated analogs of **31a**/**31b** (54 mg) with $Na_2S_2O_4$ as described in procedure E, followed by benzylation with benzyl chloride (4 equiv), K_2CO_3 (5 equiv), and KI (0.6 equiv) in refluxing acetone for 10 h furnished, after standard workup, crude **33** as the sole diaryl ether regioisomer. Purification by preparative TLC, eluting with light petroleum−Et_2O (3:2), afforded 43 mg of pure **33** as an oil (57%). IR ($CHCl_3$) 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.92 (s, 2 H), 4.95 (s, 2 H), 5.07 (s, 2 H), 5.09 (s, 2 H), 5.12 (s, 2H), 5.16 (s, 2 H), 5.25 (s, 2 H), 6.94 (d, J = 1.9 Hz, 1 H), 7.06−7.46 (m, 37 H); ^{13}C NMR ($CDCl_3$) δ 165.7, 164.8, 152.7, 152.6, 150.0, 147.0, 146.5, 142.5, 141.9, 137.9, 136.8, 136.7, 136.3, 136.1, 135.4, 128.6, 128.5, 128.4, 128.3, 128.17, 128.15, 128.11, 128.08, 128.05, 127.97, 127.94, 127.87, 127.7, 127.6, 127.5, 124.8, 120.0, 111.0, 109.5, 109.2, 75.61, 75.56, 74.9, 71.4, 71.3, 67.1, 66.5; FABMS m/z (relative intensity) 969 (MH^+, 100), 878 (40); HRMS (FAB) calcd for $C_{63}H_{52}O_{10}$ 968.3560, found 968.3564. Anal. Calcd for $C_{63}H_{52}O_{10}$: C, 78.08; H, 5.41. Found: C, 77.46; H, 5.70.

Diels−Alder Adduct 35. $Cu(OAc)_2.H_2O$ (86 mg, 0.43 mmol) was added to a solution of the orthoquinone **8** (84 mg, 0.43 mmol) in $CDCl_3$ (4 mL). The reaction mixture was stirred at rt for 24 h, after which time it was filtered. The filtrate was evaporated, and the residue was submitted to column chromatography at −78 °C, eluting with hexane−EtOAc (1:1), to afford **35** (32 mg, 36%) as a white solid, mp 174 °C (from CH_2Cl_2). IR ($CHCl_3$) 3508, 3453, 3356, 3156, 1794, 1763, 1725, 1701 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 3.29 (d, J = 4.7 Hz, 1 H), 3.63 (s, 3 H), 3.67 (s, 3 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 4.43 (dd, J = 4.7, 2.2 Hz, 1 H), 6.07 (s, 1 H), 6.51 (s, 1 H), 6.93 (s, 1 H), 7.57 (d, J = 2.2 Hz, 1 H); ^{13}C NMR (CD_3COCD_3) δ 197.4, 185.9, 170.6, 164.1, 149.2, 137.1, 132.2, 112.8, 97.8, 96.9, 90.5, 56.1, 55.8, 54.3, 53.6, 52.6, 51.3, 45.2; EIMS m/z (relative intensity) 410 (M^+, 3.9), 392 ($M^+ - H_2O$, 2.6); HRMS calcd for $C_{18}H_{16}O_{10}$ 392.0743, found 392.0747.

Dimethyl 2,2′,3,3′-Tetrahydroxy-4,4′-dimethoxybiphenyl-6,6′-dicarboxylate (36). Anhydrous $ZnBr_2$ (118 mg, 0.52 mmol) was added to a solution of the orthoquinone **8** (103 mg, 0.52 mmol) in $CDCl_3$ (4 mL). The reaction mixture was stirred at rt. Monitoring of the reaction by ^{1}H NMR analysis indicated complete disappearance of the starting quinone **8** after ca. 20 h. The resulting mixture was filtered, and the filtrate was submitted to preparative TLC, eluting with CH_2Cl_2−MeOH (20:1), to afford **36** (16 mg, 15%) as a beige solid, mp 280 °C dec (from CH_2Cl_2). IR (KBr) 3539, 3386, 1778, 1695 cm^{-1}; ^{1}H NMR [CD_3COCD_3−CD_3SOCD_3, (9:1)] δ 3.48 (s, 6 H), 3.88 (s, 6 H), 7.15 (s, 2 H); ^{13}C NMR [CD_3COCD_3−CD_3SOCD_3, (9:1)] δ 167.5, 146.9, 144.4, 138.4, 121.8, 121.6, 106.0, 56.3, 51.3; EIMS m/z (relative intensity) 394 (M^+, 18.2), 363 (4.9), 332 (4.8), 288 (2.1); HRMS calcd for $C_{18}H_{18}O_{10}$ 394.0900, found 394.0913.

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Supporting Information Available: Copies of ^{13}C NMR spectra for **14b**, **16**, **18**, **20**-**22**, **26c**, **27c**, **27d**, **30a**/**b**, **31a**/**b**, **35**, and **36** (14 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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