Ellagitannin Chemistry. Preparative and Mechanistic Studies of the Biomimetic Oxidative Coupling of Galloyl Esters

Ken S. Feldman* and Susan M. Ensel

Contribution from the Chemistry Department, The Pennsylvania State University, University Park, Pennsylvania 16802

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Abstract: The construction of strictly the (*S*)-hexahydroxydiphenyl (HHDP) unit via biomimetic cyclization of suitably protected glucose-derived digalloyl esters has been achieved in good yield. Studies on substrates of increasing complexity utilizing a range of oxidants ($Pb(OAc)_4$, VOF_3, Tl_2O_3) have helped define the scope and limitations of this approach to ellagitannin synthesis. Computer modeling of key cyclization precursors helped elucidate the molecular-level structural details which undergird the Haslam/Schmidt biosynthesis model for this class of naturally occurring secondary plant metabolites.

Introduction

The hydrolyzable tannin family of secondary plant metabolites (gallotannins and ellagitannins) constitutes a vast array of polyphenolic natural products which are in evidence in approximately 41% of all orders of dicotyledonous plants.[1] Despite this widespread occurrence and a long history of study, their role in the plant's life processes remains a matter of speculation. Current dogma favors an interpretation wherein the gallotannins (and possibly the ellagitannins) are, at the very least, prominent members of the plant's chemical arsenal against predation by both herbivores and pathogens.[1b,2] The molecular basis for this ecological activity remains undefined by experiment, although many lines of circumstantial evidence converge on a model featuring initial protein-(gallo)tannin complexation (possibly followed by precipitation and/or covalent bond formation) which can result in predator feeding deterrence (astringency), reduced nutritional uptake, or interference with pathogen infection, as conditions warrant.[1b,2] Study of these issues is further clouded by adaptive responses among some herbivores which confer a distinct survival *advantage* upon tannin ingestion, perhaps portending a coevolutionary "arms race" in this area between plant and predator.[2]

Over 150 structurally characterized ellagitannins have been identified, primarily through the efforts of Schmidt,[1a] Haslam,[1b] Okuda,[1c] and Nishioka.[1d] This unparalleled diversity is also a reminder of the biosynthetic resourcefulness of plants under evolutionary pressure, as the genesis of each of these ellagitannins can, in principle, be traced to a single watershed gallotannin intermediate, β-pentagalloyl-D-glucose (β-PPG, **5**), eq 1. Oxidative phenolic coupling both within one β-PPG module and between different β-PPG units in almost every conceivable combination and permutation then affords the monomeric, dimeric, etc., naturally occurring ellagitannin products. There is, however, one crucial identifying structural characteristic of ellagitannins in each case: a stereochemically homogenous hexahydroxydiphenyl (HHDP) moiety (or oxidized derivative thereof) spanning two of the glucose core's oxygens. Representative examples (shown in Chart 1) include the simple monomers tellimagrandin I (**1a**) and II (**1b**),[3] the linear dimer agrimoniin (**2**),[4] and the highly oxidized complex monomer chebulagic acid (**3**).[5] It is noteworthy that all O(4)–O(6) and O(2)–O(3) galloyl coupled species bear (*S*)-HHDP units, while the O(3)–O(6) coupled congeners display (*R*)-HHDP stereochemistry.

Recent ethnobiologically directed discovery of extremely promising chemotherapeutic activity among the ellagitannin subfamily of hydrolyzable tannins has broadened the challenge of developing models for tannin–protein interaction. Thus, while available data is consistent with gallotannin but not ellagitannin participation in nonspecific multidentate association with biological macromolecules,[1b] a few select ellagitannins display striking biological activity at the submicromolar level. For example, tellimagrandin I (**1a**) exhibits effective in vitro antiherpetic activity (EC_{50} = 45 nM) by blocking virus adsorption to cultured cells,[3b,c] while chebulagic acid (**3**) is the most potent DNA topoisomerase I inhibitor yet reported, with an IC_{50} (50 nM) surpassing that of camptothecin by 50-fold.[5d] Perhaps most intriguing of all is the host-mediated antitumor activity of agrimoniin (**2**), which presumably underlies its reputed use in anticancer therapy in China.[4b] This ellagitannin apparently does not manifest its tumor remissive properties by a mechanism based on differential cytotoxicity, but rather elicits an immune response involving, at the very least, stimulated secretion of interleukin-1β by peripheral blood mononuclear cells.[4c] It is plausible that at least some of these phenomena ultimately will be traced to very specific recognition/binding of key proteins (receptors?) which mediate the observed biological response. In this vein, speculation about the basis for the contrasting properties of gallotannins and

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(1) Leading references to the chemistry of the hydrolyzable tannins can be found in the following reviews: (a) Schmidt, O. T. *Fortschr. Chem. Org. Naturst.* **1956**, *13*, 70. (b) Haslam, E. *Plant Polyphenols*; Cambridge University Press: Cambridge, 1989. (c) Okuda, T.; Yoshida, T.; Hatano, T. *Phytochemistry* **1993**, 32, 507. (d) Kashiwada, Y.; Nonaka, G.-i.; Nishioka, I.; Chang, J.-J.; Lee, K.-H. *J. Nat. Prod.* **1992**, *55*, 1033. (e) Gross, G. G. In *Plant Polyphenols*; Hemingway, R. W., Laks, P. D., Eds.; Plenum Press: New York, 1992.

(2) (a) Rhoades, D. F.; Cates, R. G. *Recent Adv. Phytochem.* **1976**, *10*, 168. (b) Schultz, J.C. In *Chemistry and Significance of Condensed Tannins*; Hemingway, R. W., Karchesy, J. J., Eds.; Plenum Press: New York, 1989. (c) Schultz, J. C.; Hunter, M. D.; Appel, H. M. In *Plant Polyphenols*; Hemingway, R. W., Laks, P. D., Eds.; Plenum Press: New York, 1992. (d) Zucker, W. V. *Am. Nat.* **1983**, *121*, 335. (e) Apple, H. M. *J. Chem. Ecol.* **1993**, *19*, 1521.

(3) (a) Wilkens, C. K.; Bohm, B. A. *Phytochemistry* **1976**, *15*, 211. (b) Okuda, T.; Yoshida, T.; Hatano, T. Polyphenols from Asian Plants. Structural Diversity and Antitumor and Antiviral Activities. In *Phenolic Compounds in Food and their Effects on Health, II*; Huang, M.-T., Ho, C.-T., Lee, C. Y., Eds.; ACS Symposium Series 507; American Chemical Society: Washington, DC, 1992. (c) Fukuchi, K.; Sakagami, H.; Okuda, T.; Hatano, T.; Tanuma, S.; Kitajima, K.; Inoue, Y.; Inoue, S.; Ichikawa, S.; Nonoyama, M.; Konno, K. *Antiviral Res.* **1989**, *11*, 285.

(4) (a) Miyamoto, K.; Koshiura, R.; Ikeya, Y.; Taguchi, H. *Chem. Pharm. Bull.* **1985**, *33*, 3977. (b) Sugi, M. In *Cancer Therapy in China Today*; Kondo, K., Ed.; Shizensha: Tokyo, 1977; p 93. (c) Murayama, T.; Kishi, N.; Koshiura, R.; Takagi, K.; Furukawa, T.; Miyamoto, K.-J. *Anticancer Res.* **1992**, *12*, 1471.

(5) (a) Yoshida, T.; Fuji, R.; Okuda, T. *Chem. Pharm. Bull.* **1980**, *28*, 3713. (b) Yoshida, T.; Okuda, T.; Koga, T.; Toh, N. *Chem. Pharm. Bull.* **1982**, *30*, 2655. (c) Hatano, T.; Yoshida, T.; Shingu, T.; Okuda, T. *Chem. Pharm. Bull.* **1988**, *36*, 3849. (d) Barry, D. E.; MacKenzie, L.; Shultis, E. A.; Chan, J. A.; Hecht, S. M. *J. Org. Chem.* **1992**, *57*, 420.

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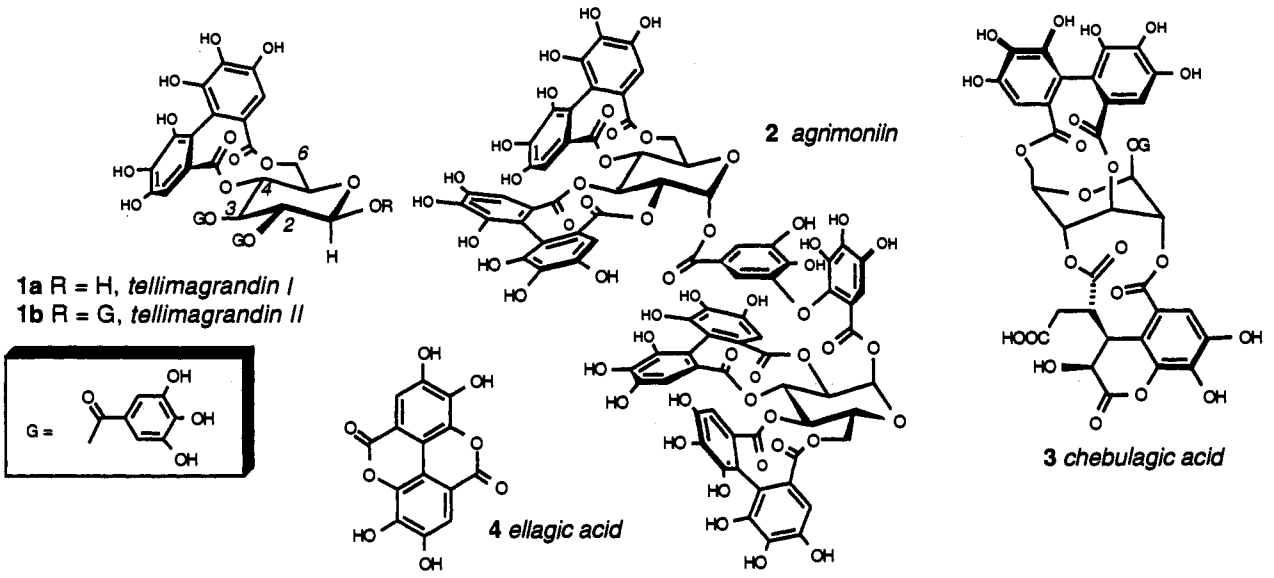
Chart 1

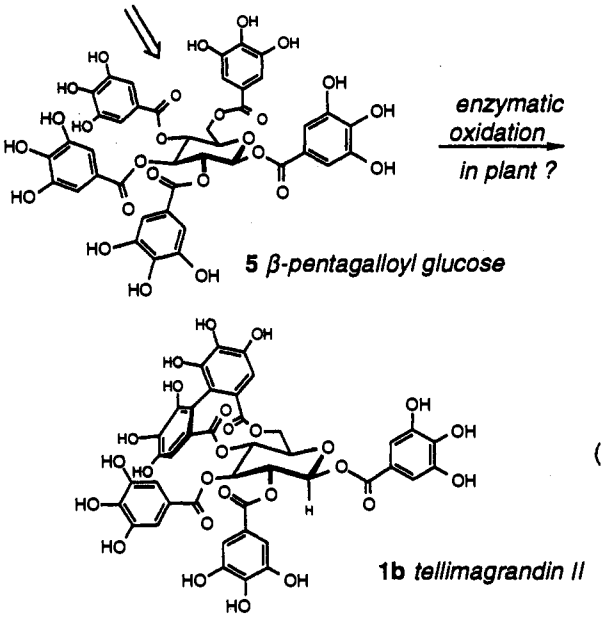


ellagitannins with respect to protein interactions has focused on the increased conformational flexibility of the former when compared with the much more rigid (preorganized) framework of the latter.

Efforts to correlate gallotannin and ellagitannin structure with protein binding ability underlie attempts to develop meaningful hypotheses for the presumed evolutionary benefit that these species impart to the plant and the role that they may play in mediating the biological responses noted above. The most informative studies are those of Haslam, who showed that, among a limited set of naturally occurring ellagitannins and gallotannins, those species that were both conformationally flexible and featured a galloyl "rich" core had the greatest affinity for the test case protein bovine serum albumin.[6] In addition, ^{1}H NMR studies with select tannins and model peptides (or caffeine) revealed that association appears to be localized at the unencumbered O(1) and O(6) galloyl residues of the tannin species.[1b] However, these studies have not been extended either to physiochemical conditions resembling the herbivore gut or to proteins physiologically relevant to the plant/herbivore interaction.[2e] In addition, tannin *analogs* whose structures are designed to probe specific binding hypotheses have not heretofore been available, as efforts directed toward the chemical synthesis of these plant metabolites have lagged far behind the isolation and biomolecule-binding studies.

We have initiated a program of organic synthesis designed to provide naturally occurring gallotannins and ellagitannins and rationally designed structural analogs to address the structure/function issues which contribute to the protein recognition capability of this class of molecules. A full accounting of our preliminary studies focusing on (*S*)-HHDP preparation, prerequisite to progress in ellagitannin synthesis, is reported herein.[7]

The early recognition that galloylated glucose substrates were likely to be biosynthetic precursors to the HHDP-containing ellagitannin products (eq 1) spurred much effort at developing oxidative coupling protocols which effected this transformation in vitro. Numerous studies from 1916 to the present detailed the consequences of exposing various galloyl esters, including glucose-borne ones, to a host of oxidizing conditions.[8] In those cases where products could be identified, biaryl bond formation was detected in low to modest yields (5–40%). Unfortunately, overreaction plagued these transformations, leading to formation of purpurgallin-type structures or, more commonly, ellagic acid (**4**) via bis lactonization. *Reductive* coupling of suitably activated



(1)

galloyl synthons via Ullmann (or related) procedures has been successfully employed to deliver derivatives of the HHDP unit characteristic of the ellagitannins, although in protected forms (per-*O*-methyl ethers) not likely to be useful ultimately in natural product synthesis.[9] Nevertheless, at the start of our work, a biomimetic oxidative cyclization procedure for HHDP (ellagitannin) synthesis had not yet been realized, despite the simplicity and intuitive appeal of this approach.

The foundations for such an approach have been laid by Schmidt,[1a] and later refined by Haslam,[1b] who postulated that the inherent conformational preferences of the precursor galloylated glucose will translate directly into the naturally occurring HHDP stereochemistry upon oxidative bond formation. However, the molecular level details that define the mechanism by which

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(7) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 1162.

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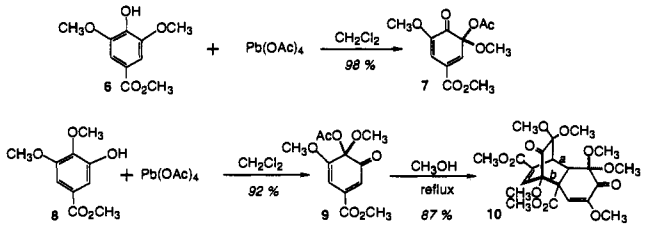
Scheme 1



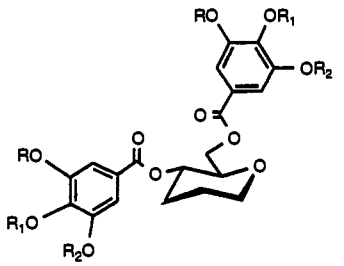
this conformational information is parlayed into product stereochemistry remained unresolved. The biomimetic oxidative cyclization chemistry described below, in conjuction with computer-modeling studies of cyclization precursors and intermediates, is designed to directly test the feasibility of the Haslam/Schmidt proposal and, in addition, perhaps clarify and refine the nature of the interactions which control diastereoselectivity upon biaryl bond formation.

Results and Discussion

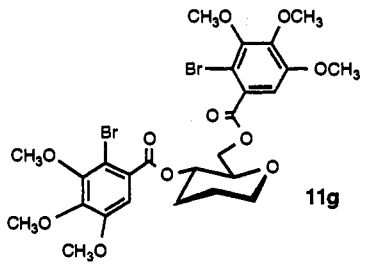
The long history of failure to observe HHDP formation upon oxidative coupling of galloyl esters tempered our enthusiasm for immediate study of ellagitannin-type systems, and so we initially focused our efforts on achieving selective and controlled oxidation of simple methyl gallate derivatives. Since many of the problems which thwarted the oxidative coupling studies mentioned earlier can conceivably be traced to the polyhydroxylic nature of the product (over oxidation, lactonization), it seemed plausible that prospecting among various partially etherified methyl gallate derivatives for a suitable candidate for controlled oxidation might prove rewarding. In this circumstance, biaryl bond formation would have to be followed in a subsequent chemical operation by nondestructive ether deprotection to liberate the target HHDP unit. In any event, the products of carbon–carbon bond formation were never detected upon screening most differently O-methylated methyl gallate derivatives (substitution patterns analogous to those of **11a–f**) with a range of oxidants. However, two particular combinations of substrate and oxidant, diethers **6** and **8** with $Pb(OAc)_4$,[10] furnished excellent yields of the monooxidation product quinone ketals **7** and **9**, respectively (Scheme 1). Ketal **9** could be dimerized to provide a single Diels–Alder product **10** in high yield. This dimer (regiochemical assignment based on mechanistic considerations) possesses, in fact, the key biaryl bond (**10**, bond *a*) required for HHDP synthesis. Unfortunately, all attempts (SmI_2, Zn/Ac_2O) to cleave selectively the other newly formed bond, bond *b*, and thus liberate the HHDP unit were not successful. Nevertheless, these examples were noteworthy in that they suggested the possibility of selective and controlled oxidation of a suitably methylated galloyl ester substrate, in distinct contrast to the earlier unsuccessful oxidation studies on the free phenols.

One favorable interpretation of the selective reaction of **6** and **8** with $Pb(OAc)_4$ would involve initial oxidation of the monophenol to furnish a reactive electrophilic intermediate followed by quenching of this species by available nucleophiles (^-OAc) in solution. In this scenario, the intermolecular competition between acetate to yield **7** or **9** and an unoxidized gallate ester (**6** or **8**) to deliver a biaryl product is won by the former nucleophile. It seemed reasonable then, to pursue this inquiry further in a substrate bearing two galloyl esters in close proximity. In this case, internal delivery of the aromatic nucleophile may confer a distinct advantage over acetate in the competition for the intermediate reactive electrophile provided that untoward energetic (conformational) barriers are not engendered. If, however, we design our substrate along the lines of the Haslam/Schmidt biosynthetic hypothesis, this latter complication seems increasingly remote.

With these thoughts in mind, various permutations of O-methylated bis galloyl esters **11a–f** of the glucose-derived diol 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (**21**)[11] were prepared and subjected to oxidation with a range of reagents $(Pb(OAc)_4$, VOF_3, Tl_2O_3, $Tl(NO_3)_3$, $Mn(acac)_3$, Cu(II)·amine, $K_2S_2O_8/CuSO_4$, $NaIO_4$, $PhI(OAc)_2$, $(NH_4)_2Ce(NO_3)_6$, RuO_2, and $Fe(ClO_4)_3)$. This Edisonian approach led eventually to the discovery



11a R = H, $R_1 = R_2 = CH_3$
11b R = R_1 = H, $R_2 = CH_3$
11c R = $R_1 = R_2$ = H
11d R_1 = H, R = $R_2 = CH_3$
11e R = R_2 = H, $R_1 = CH_3$
11f R = $R_1 = R_2 = CH_3$



11g

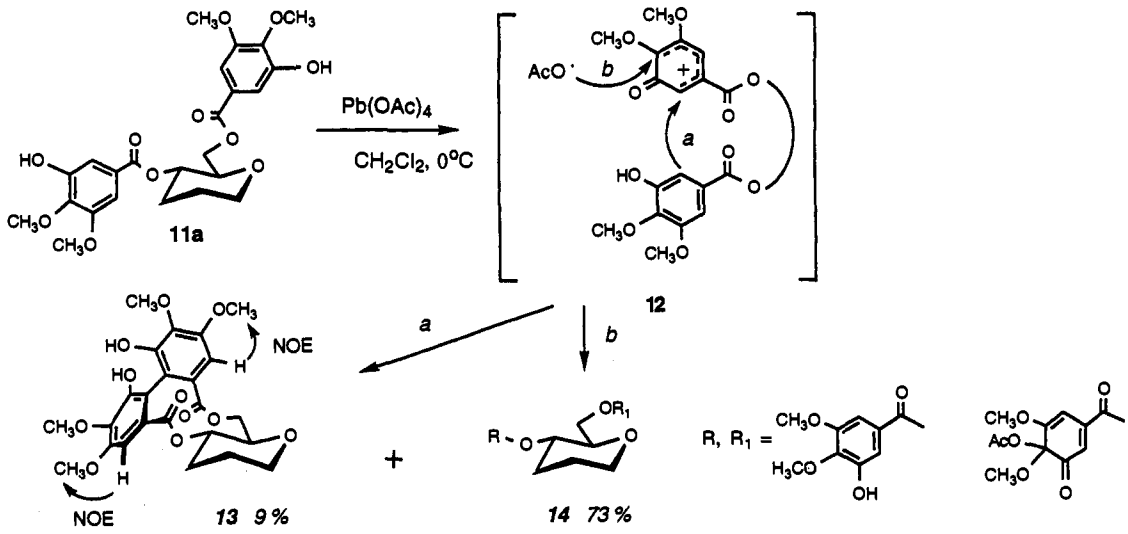
that the unsymmetrically dimethylated bis galloyl species **11a**, upon exposure to $Pb(OAc)_4$, afforded the products of controlled oxidation, **13** and **14** (Scheme 2). In addition, other successful substrate/reagent combinations were identified (**11f**/VOF_3 and **11f**/Tl_2O_3) and are discussed below. Reductive Ullmann-type cyclization of the dibromide **11g** was explored briefly, but only uncyclized, debrominated products resulted.

The major product(s) of the Pb-based oxidation of **11a** was the expected quinone ketal mixture **14** in analogy with the related oxidation of the simple methyl ester **8**. However, the real triumph in this transformation lies in formation of the biaryl containing product **13**, albeit in modest yield. Furthermore, this methylated version of an HHDP unit was produced as a single regioisomer (assignment via DNOE measurements) and a single stereoisomer of (*S*) absolute configuration (CD).[12] This latter point is of some consequence, as it provides evidence in support of the Haslam/Schmidt biosynthetic postulate underlying our strategy. While securing results consistent with a hypothesis does not guarantee the validity of that hypothesis, it seemed plausible that we could continue to exploit our working model (vide supra) for galloyl oxidation/nucleophilic trapping, which is predicated on the Haslam/Schmidt argument, in order to maximize the production of **13** over **14**. Thus, as noted earlier for the simple methyl gallate oxidations (Scheme 1), we speculated that initial Pb(IV)-mediated oxidation of **11a** results in the formation of a species whose reactivity resembles that of the cyclohexadienonyl cation **12**. Subsequent (irreversible?) partitioning of this intermediate down pathways *a* and *b* (Scheme 2) then furnishes the observed products **13** and **14**, respectively. A discussion of cyclization stereoselectivity will accompany the computer/conformational modeling results (vide infra).

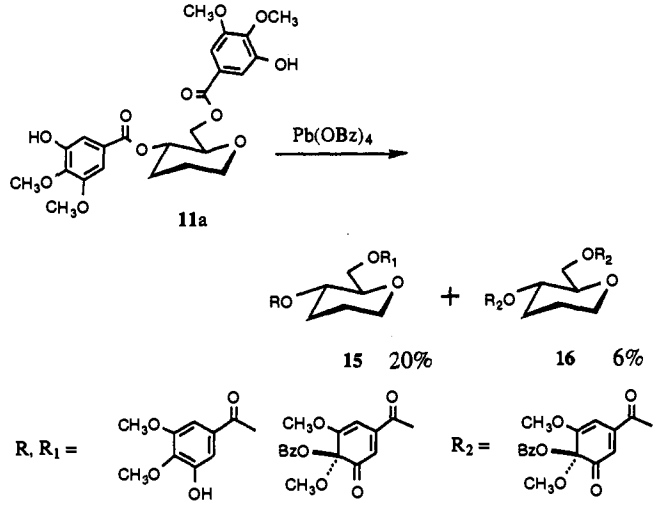
Two distinct approaches for favoring pathway *a* (**13** synthesis) over pathway *b* (**14** synthesis) emerge upon consideration of this mechanistic model. Each approach is designed to retard the rate of pathway *b* and thus allow the (presumed) slower alternative pathway *a* to "catch up." The first approach relies on replacing acetate with a less nucleophilic counterion in the Pb(IV) reagent.

(10) (a) Aylward, J. B. *J. Chem. Soc. B* **1967**, 1268. (b) Norman, R. O. C.; Thomas, C. B.; Willson, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 325. (c) Bubb, W. A.; Sternhell, S. *Tetrahedron Lett.* **1970**, *51*, 4499. (d) Hoshino, O.; Hara, H.; Ogawa, M.; Umezawa, B. *J. Chem. Soc., Chem. Commun.* **1975**, 306. (e) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1990**, *55*, 5669.
(11) Lemieux, R. U.; Brewer, J. T. *Adv. Chem. Ser.* **1973**, *117*, 121.
(12) Okuda, T.; Yoshida, T.; Hatano, T. *J. Nat. Prod.* **1989**, *52*, 1.

Scheme 2



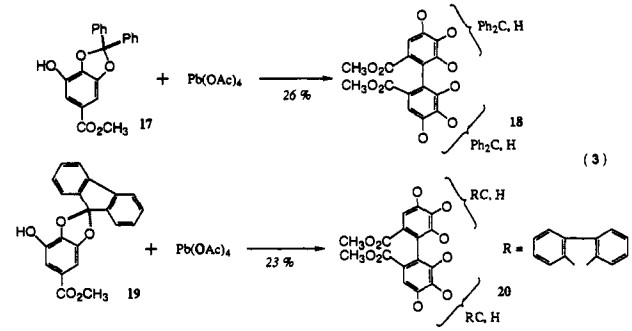
Surveying the literature for Pb(IV) oxidants revealed that only tetrakis(trifluoroacetate)[13] and tetrakis(benzoate)[14] were known compounds. The former reagent is likely to be too vigorous an oxidant for the phenolic substrate of interest, and so the latter Pb reagent was examined for the oxidation of **11a**, eq 2. While



(2)

benzoate is a slightly *better* nucleophile than acetate (~1.6× with the test electrophile CH_3I),[15] it was hoped that recourse could be made eventually to appropriate electron deficient analogs (e.g., *p*-nitrobenzoate). The lack of biaryl-containing product upon oxidation of **11a** with $Pb(OBz)_4$ is consistent with this analysis, although not particularly encouraging. This approach was abandoned, however, as favorable results from the second strategy for suppressing the pathway *b* reaction materialized.

The second attempt to alter the partitioning ratio of putative intermediate **12** focused on magnifying the differential *steric* environment about each of the distinct carbons in this species which suffer nucleophilic capture. Thus, replacement of the methyl ethers in **11a** with groups that more effectively block the adjacent ring carbon may increase intramolecular nucleophilic attack along pathway *a* at the expense of the acetate addition pathway. At present, we have no explanation for the observation that acetate does not add along pathway *a* to furnish a tetrahydroxylated galloyl ester. In any event, the bulky methyl gallate-derived diphenyl and fluorenyl ketals **17** and **19**, respectively, were prepared to test this premise. Oxidation of **17** and **19** with $Pb(OAc)_4$ (eq 3) followed a different course than that



(3)

ascribed to the related bis methyl ether **8**. No quinone ketal-type products were detected in contrast to the simpler system **8**; rather, modest yields of the biaryl diesters **18** and **20** were isolated uncontaminated by lactonic (e.g., ellagic acid derived) impurities. The coupled products were formed in each case as inseparable 1:1 mixtures of regioisomeric biaryls. These observations are consistent with the model's predictions that pathway *a* can be favored over pathway *b* as a consequence of differential steric bulk, and thus provided encouragement to pursue this tactic in a system relevant to ellagitannin synthesis.

The glucose diol-derived diphenyl ketal and fluorenyl ketal galloyl esters **23a** and **23b**, respectively, were prepared uneventfully as indicated in Scheme 3 and treated with $Pb(OAc)_4$ as per the standard protocol. After much optimization of reaction parameters (concentration, time, additive(s)), maximum yields of the desired (protected) HHDP-containing coupled products **24a,b** could be obtained to the near exclusion of quinone ketal-containing species. It is also worth noting that not only do these bulky ketal groups afford synthetically useful yields of coupled products but they offer the possibility for mild and selective liberation of the HHDP unit requisite for natural products synthesis via simple hydrogenolysis.

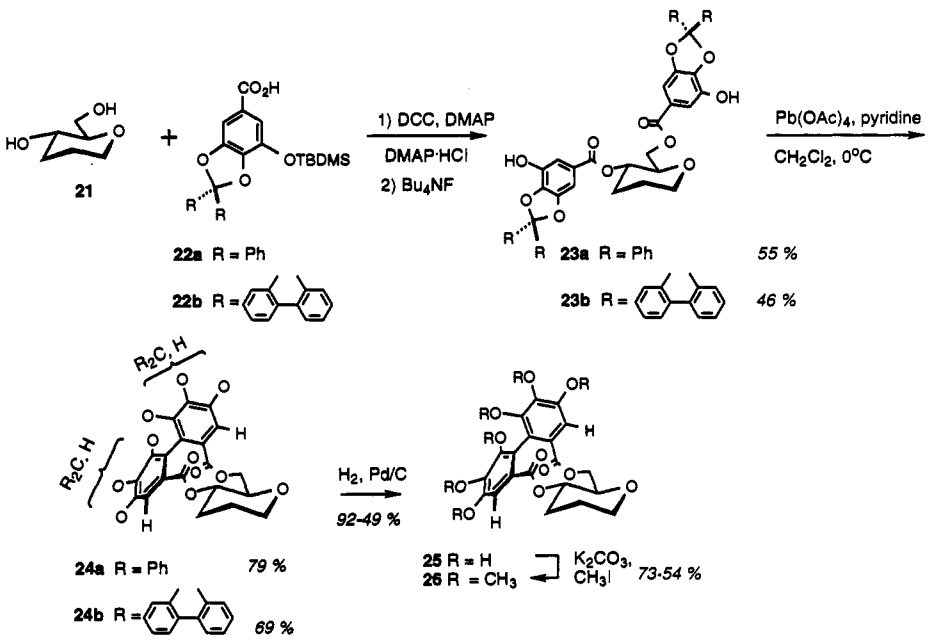
The coupling products **24a** were isolated as a chromatographically separable mixture of four isomers, while oxidative cyclization of **23b** furnished **24b** as three separable isomers, in contrast to the single isomer produced from **11a**. Each isomer in each series was independently deprotected through hydrogenolysis to afford the identical hexahydroxy product **25**. In addition, each independently secured polyol was per-*O*-methylated to deliver

(13) (a) Partch, R. E. *J. Am. Chem. Soc.* **1967**, *89*, 3662. (b) Campbell, J. R.; Kalman, J. R.; Pinhey, J. T.; Sternhell, S. *Tetrahedron Lett.* **1972**, 1763. (c) Kalman, J. R.; Pinhey, J. T.; Sternhell, S. *Tetrahedron Lett.* **1972**, 5369.

(14) (a) Hurd, C. D.; Austin, P. R. *J. Am. Chem. Soc.* **1931**, *53*, 1543. (b) Hey, D. H.; Stirling, C. J. M.; Williams, G. H. *J. Chem. Soc.* **1954**, 2747. (c) McClelland, R. A.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 570.

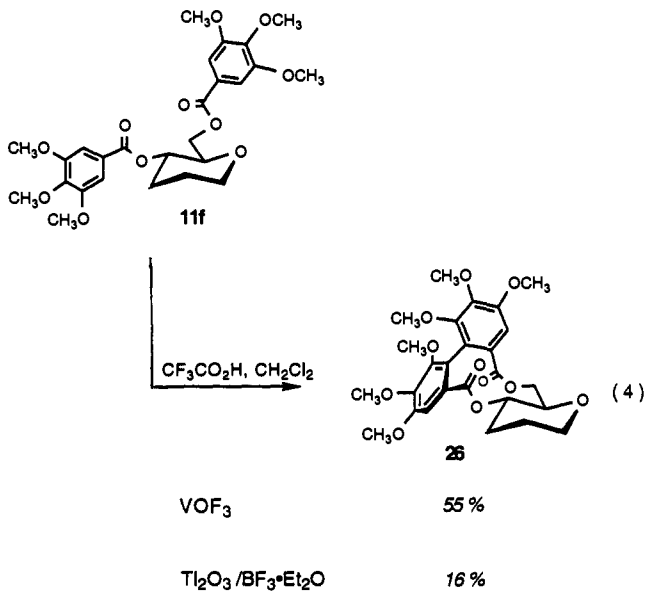
(15) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

Scheme 3



the identical hexamethoxybiaryl **26**. The biphenyl stereochemistry of each intermediate along the way was unambiguously established as (*S*) via CD measurements. Thus, the exquisite stereochemical control suggested in Scheme 2 was maintained in these more complex systems. The oxidation products within each series must therefore all be regioisomers of one another, and their ratios (2.0:1.6:1.5:1.0 for **24a**, 1.6:1.3:1.0 for **24b**) indicate that biaryl bond formation occurred without any noticeable regioselectivity. This lack of regioselectivity bears no consequence for ellagitannin synthesis, however, as each isomer can be smoothly reduced to the desired hexahydroxy target (e.g., **25**).

Diastereoselective oxidative galloyl coupling was also achieved with the per-O-methylated bis galloyl substrate **11f** and VOF_3 or Tl_2O_3 as oxidants (eq 4). Optimization of the VOF_3 system



(4)

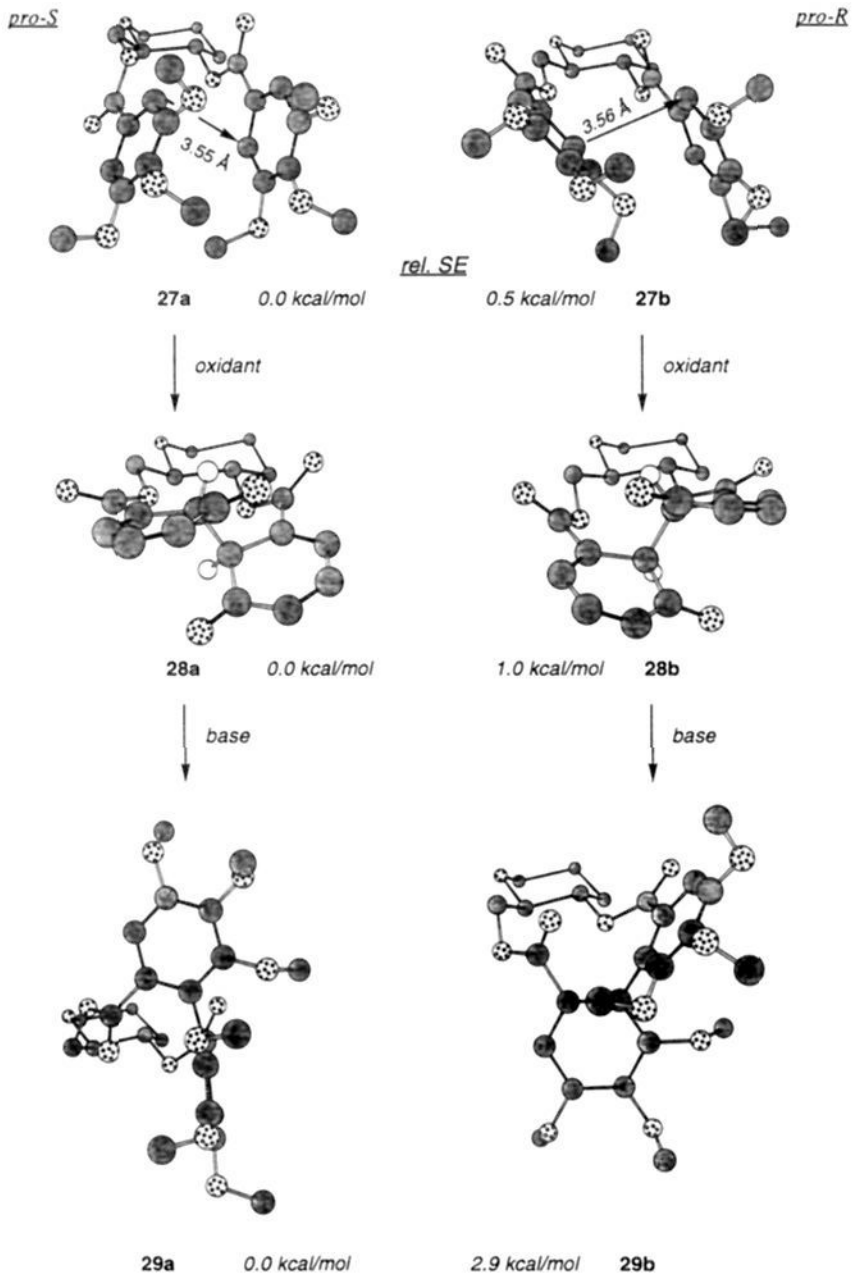
eventually led to production of protected HHDP-containing product **26** with strictly (*S*) stereochemistry in the biaryl moiety in good yield upon exposure of hexaether **11f** to 3.5 equiv of VOF_3 in dilute CH_2Cl_2 (5 mM) admixed with 9% CF_3CO_2H. Attempts to substitute the methyl ethers of **11f** with alternative, more readily removable protecting groups (benzyl, allyl, acetate) did not lead to useful results—no biaryl-containing products were identified upon VOF_3/CF_3CO_2H oxidation. In addition, neither $VOCl_3$ nor $VO(OEt)Cl_2$ were suitable oxidants for hexaether **11f**. In a scouting experiment, thallium-based oxidation (Tl_2O_3) of hexaether **11f** furnished a modest and unoptimized yield of the (*S*)-hexa-*O*-methyl-HHDP-containing product **26**. As neither of these galloyl ether/metal-based oxidative coupling procedures offered the advantages of the Pb(IV) system described earlier with respect to either mildness of conditions or flexibility in ellagitannin synthesis, they were not further pursued.

The stereochemcial outcome of the cyclization reactions described above is consistent with the predictions of the Haslam/Schmidt biosynthetic hypothesis for ellagitannin formation, but these reactions do not, in and of themselves, provide any insight into the intimate molecular interactions which underlie this postulate. We have therefore utilized a molecular mechanics-based conformational analysis to probe these structural details.[16] Full conformational searches of the hexamethoxyl digalloyl substrate **11f**, the desmethoxy model diketones **28a/28b** resembling the putative intermediate of oxidative cyclization, and the (*S*) and (*R*) biaryl containing products **29a** and **29b**, respectively, about all rotatable bonds afforded discrete families of low-energy conformations for each compound which typically differed significantly only by the disposition of the methoxy units. The "global" minima are represented in Scheme 4, along with their relative strain energies.

The hexamethoxy substrate **11f** affords two types of low-energy conformers—those with a clockwise galloyl "tilt" (relative to the plane of the pyran ring) which precede the (*S*) biaryl product (e.g., **27a**) and those with an alternative counterclockwise "tilting", as shown in conformer **27b**, which ultimately furnishes (*R*) biaryl product **29b**. The distances between the two closest trans-ring carbon atoms are shown in each case, and it is bond formation between these most proximate carbons that ultimately dictates which product atropisomer is formed. The calculated energy difference between these conformers is too small (0.5 kcal/mol) to fully account for the observed stereoselectivity. However, this energy difference is amplified upon transversing the reaction coordinate from starting material to product, where an almost

(16) Molecular mechanics calculations on **11a**, **28**, and **29** were performed on a Silicon Graphics 4D25G computer equipped with version 3.1× of Macromodel (MM2* force field). The directed Monte Carlo conformational search subroutine was used, and all rotatable single bonds were varied. In each search, 1000 starting geometries were explored. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Scheme 4



3 kcal/mol difference in strain energy separates the (*S*) from the (*R*) atropisomer. We speculate that, even though these model compounds differ from the "real" system in significant structural ways (e.g., **11f** vs **23a**), they provide a reliable indication of the *relative* energetics of the *pro-S* and *pro-R* reaction channels as the digalloyl precursor is converted to the protected HHDP product. Thus, the *pro-S* manifold is increasingly favored throughout, with the cyclization reaction commencing down the biosynthetically "correct" path as a consequence of the subtle conformational shifts ("tilts") of the substrate digalloyl units.

Experimental Section

Infrared (IR) spectra were recorded on Perkin-Elmer 281B and 1600 FT infrared spectrophotometers. Magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded on either a Bruker ACE-200, WP-200, AM-300, or WM-360 spectrophotometer. Chemical shifts are reported in δ units using tetramethylsilane (TMS) as an internal standard for ^{1}H NMR and chloroform or acetone as the internal standard for ^{13}C NMR. Difference NOE NMR experiments were performed using the Bruker software program NOEDIFF.AUR. Low- and high-resolution mass spectra (MS, HRMS) were obtained on either a Kratos MS9/50 or MS25 hexapole focusing mass spectrometer, while fast atom bombardment mass spectra (FABMS) were obtained on a Kratos MS50 hexapole focusing mass spectrometer. Liquid (flash) chromatography[17] was carried out using 32–63-μm silica gel column (Woelm-Pharma) and the indicated solvent. Ether (Et_2O), tetrahydrofuran (THF), and benzene (PhH) 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.

Modified Steglich[18] Esterification Reaction: General Procedure A. A solution of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (**21**)[11] (1.0 equiv), the appropriate acid (2.0 equiv), 4-(dimethylamino)pyridine (DMAP) (0.50 equiv), DMAP·HCl (0.50 equiv), and 1,3-dicyclohexylcarbodiimide (DCC) (3.0 equiv) in dry CH_2Cl_2 (0.10 M in acid) was purged with Ar and heated at reflux under Ar for 10–20 h. The solution was allowed to cool to room temperature, a few drops of CH_3OH and CH_3CO_2H were added to deactivate the excess DCC, and stirring was continued for 30 min. The solution was diluted with an equal volume of Et_2O, filtered through a plug of silica gel, washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography with the indicated eluent to furnish the desired diester.

Benzyl Ether Deprotection Reaction: General Procedure B. A solution of the benzyl ether protected diester (1.0 equiv) and the indicated amount of 10% Pd/C in 95% EtOH (0.10–0.050 M) was purged six times with H_2, stirred at room temperature for 12–20 h under 1 atm of H_2, and then purged thoroughly with Ar. The mixture was filtered through Celite and concentrated in vacuo to furnish the desired phenol.

Silyl Ether Deprotection Reaction: General Procedure C. A solution of the appropriate *tert*-butyldimethylsilyl-protected glucose derivative (1.0 equiv) in dry THF (0.080 M) was added to a cooled (0 °C) solution of tetrabutylammonium fluoride (1.2 equiv per silyl group) in dry THF (0.040 M final concentration of glucose derivative). The solution was stirred under Ar for 20 min at 0 °C and 3–4 h at room temperature. The solution was partitioned between 1 M H_3PO_4 and EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographically purified using the indicated eluent to furnish the desired phenols.

Lead Tetraacetate Oxidation Reaction: General Procedure D. A solution of lead tetraacetate (1.1 equiv) in 2–4 mL of dry CH_2Cl_2 was added dropwise over 20 min to a cooled (0 °C) solution of the appropriate bisphenol (1.0 equiv) and pyridine (4.0 equiv) in dry CH_2Cl_2 (5–33 mM final concentration of bisphenol). The orange/yellow solution was stirred at 0 °C for 30 min, quenched by the addition of saturated $NaHCO_3$ solution, and extracted with Et_2O. The organic layer was washed with 1 M H_3PO_4 and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographically purified using the indicated eluent to furnish the desired biphenyl.

Diphenylmethylene and 9,9-Fluorenyl Ketal Deprotection Reactions: General Procedure E. A solution of the dihydroxybiphenyl diester (1.0 equiv) and the indicated amount of 10% Pd/C in dry THF (10–40 mM) was purged six times with H_2. The mixture was stirred at room temperature under 1 atm of H_2 for 3–16 h, purged thoroughly with Ar, filtered through Celite, and concentrated in vacuo. The solid was washed thoroughly with hexane to extract diphenylmethane/fluorene and dried in vacuo to furnish the desired hexahydroxybiphenyl diester.

Methyl Ether Formation Reaction: General Procedure F. A solution of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexahydroxybiphenyl-6,6′-dicarboxylate (**25**) (1.0 equiv) in acetone (15–27 μM) was added to an Ar-filled flask containing potassium carbonate (8.0 equiv). Iodomethane (8.0 equiv) was added, and the solution was heated at reflux for 4–8 h. Additional iodomethane (8.0 equiv) was added, and reflux was continued another 4–8 h. The solution was cooled and concentrated in vacuo, and the residue was purified by flash column chromatography using 33% hexane in Et_2O as the eluent to furnish 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexamethoxybiphenyl-6,6′-dicarboxylate (**26**) as a white solid foam.

Oxidation of Methyl 3,5-Dimethoxy-4-hydroxybenzoate (6). By a modification of general procedure D (no pyridine), methyl 3,5-dimethoxy-4-hydroxybenzoate (**6**) (50 mg, 0.24 mmol) in 5 mL of dry CH_2Cl_2 was oxidized to afford 64 mg (98%) of quinone ketal **7** as a bright yellow oil: IR (CCl_4) 1740 (C=O), 1716 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.88 (d, J = 1.6 Hz, 1 H), 6.50 (d, J = 1.7 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.54 (s, 3 H), 2.15 (s, 3 H); ^{13}C NMR (90 MHz, C_3D_6O) δ 186.4, 170.4, 165.3, 151.8, 133.3, 129.5, 106.6, 94.8, 56.1, 52.9, 52.1, 20.2; MS *m/z* (relative intensity) 270 (M^+, 0.02), 228(55); HRMS calcd for $C_{12}H_{14}O_7$ 270.0739, found 270.0762.

Oxidation of Methyl 3,4-Dimethoxy-5-hydroxybenzoate (8). By a modification of general procedure D (no pyridine), methyl 3,4-dimethoxy-5-hydroxybenzoate (**8**) (0.50 g, 2.4 mmol) in 12 mL of dry CH_2Cl_2 was oxidized to afford 0.59 g (92%) of quinone ketal **9** as a bright yellow oil: IR ($CDCl_3$) 1733 (C=O), 1693 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.57 (d, J = 1.2 Hz, 1 H), 5.87 (d, J = 1.0 Hz, 1 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.46 (s, 3 H), 2.15 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.1, 169.4, 165.4, 161.8, 142.1, 120.3, 93.7, 93.2, 56.4, 52.8, 52.2, 20.1; MS *m/z* (relative intensity) 270 (M^+, 12), 228 (MH^+ – Ac, 100); HRMS calcd for $C_{12}H_{14}O_7$ 270.0739, found 270.0735.

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(18) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

Dimerization of Quinone Ketal 9. A solution of quinone ketal **9** (50 mg, 0.19 mmol) in 2 mL of CH_3OH was heated at reflux for 18 h. The solution was cooled, concentrated in vacuo, and purified by flash column chromatography using 25% hexane in Et_2O as the eluent to afford 39 mg (87%) of quinone ketal dimer **10** as a white solid, mp 136 °C (dec): IR (CCl_4) 1761 (C=O), 1726 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.00 (d, J = 1.7 Hz, 1 H), 5.73 (s, 1 H), 3.86 (s, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 1 H), 3.66 (s, 3 H), 3.59 (s, 3 H), 3.58 (s, 3 H), 3.39 (s, 3 H), 3.26 (s, 3 H), 3.06 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.9, 187.9, 172.2, 162.8, 151.2, 138.1, 134.4, 109.8, 97.8, 92.9, 92.0, 58.3, 55.9, 55.6, 53.3, 52.5, 51.3, 50.5, 49.1, 48.7, 44.8, 38.9; MS *m/z* (relative intensity) 484 (M^+, 1).

1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis(3,4-dimethoxy-5-hydroxybenzoate) (11a). By use of general procedure A, 3-(benzyloxy)-4,5-dimethoxybenzoic acid[19] (2.4 g, 8.3 mmol, 2 equiv) was esterified with diol **21** (0.55 g, 4.2 mmol) to afford 2.2 g (78%) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3-(benzyloxy)-4,5-dimethoxybenzoate) as a white solid foam following flash column chromatography using 33% hexane in Et_2O as the eluent: IR ($CHCl_3$) 1725 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45–7.23 (m, 14 H), 5.10 (s, 2 H), 5.08 (s, 2 H), 5.18–4.94 (m, 1 H), 4.73 (d, J = 11.3 Hz, 1 H), 4.28 (dd, J = 11.7, 5.1 Hz, 1 H), 4.00–3.88 (m, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.90–3.70 (m, 1 H), 3.43 (t, J = 9.7 Hz, 1 H), 2.40–2.30 (m, 1 H), 1.85–1.50 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.3, 164.5, 152.6, 152.5, 151.5, 151.4, 142.6, 142.4, 136.2, 128.0, 127.5, 127.4, 126.9, 124.3, 124.27, 108.5, 108.4, 106.7, 70.6, 70.4, 69.0, 67.3, 64.1, 60.2, 55.6, 55.5, 28.9, 24.5; MS (+FAB) 672.3 (M^+, 78); HRMS calcd for $C_{38}H_{40}O_{11}$ 672.2570, found 672.2533.

By use of general procedure B, 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3-(benzyloxy)-4,5-dimethoxybenzoate) (2.3 g, 3.4 mmol) was debenzylated using 0.35 g of 10% Pd/C to afford 1.7 g (100%) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4-dimethoxy-5-hydroxybenzoate) (**11a**) as a white solid foam: IR ($CDCl_3$) 3520 (OH), 1725 (C=O), 1715 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 1 H), 7.30 (s, 1 H), 7.17 (s, 2 H), 5.03 (dt, J = 9.9, 4.5 Hz, 1 H), 4.60 (d, J = 11.9 Hz, 1 H), 4.35 (dd, J = 11.9, 5.5 Hz, 1 H), 4.03 (d, J = 9.4 Hz, 1 H), 3.90 (s, 6 H), 3.87 (s, 6 H), 3.82–3.78 (m, 1 H), 3.49 (t, J = 10.3 Hz, 1 H), 2.37 (d, J = 8.2 Hz, 1 H), 1.95–1.50 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 165.0, 152.0, 151.9, 149.1, 149.0, 139.9, 139.7, 124.9, 124.8, 110.3, 110.2, 105.3, 69.2, 69.0, 67.6, 64.2, 60.6, 60.5, 55.7, 55.6, 29.0, 24.6; MS *m/z* (relative intensity) 492 (M^+, 19); HRMS calcd for $C_{24}H_{28}O_{11}$ 492.1631, found 492.1619.

1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis(3,4,5-trimethoxybenzoate) (11f). By use of general procedure A, 3,4,5-trimethoxybenzoic acid (1.6 g, 7.5 mmol, 2.0 equiv) was esterified with diol **21** (0.50 g, 3.8 mmol) to afford 1.7 g (87%) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4,5-trimethoxybenzoate) (**11f**) as a white solid following flash column chromatography using 5% Et_2O in CH_2Cl_2 as the eluent: IR ($CHCl_3$) 1730 (C=O), 1705 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29 (s, 4 H), 5.07 (dt, J = 9.8, 4.6 Hz, 1 H), 4.69 (dd, J = 11.9, 2.3 Hz, 1 H), 4.32 (dd, J = 11.9, 5.5 Hz, 1 H), 4.04 (d, J = 12.4 Hz, 1 H), 3.90 (s, 18 H), 3.87–3.75 (m, 1 H), 3.49 (t, J = 8.9 Hz, 1 H), 2.39 (d, J = 8.3 Hz, 1 H), 1.95–1.58 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.7, 164.8, 152.7, 152.6, 142.2, 142.0, 124.7, 124.6, 106.7, 69.2, 67.6, 64.4, 60.6, 55.9, 29.2, 24.8; MS *m/z* (relative intensity) 520 (M^+, 3); HRMS calcd for $C_{26}H_{32}O_{11}$ 520.1944, found 520.1958.

(*S*)-1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′-dihydroxy-3,3′,4,4′-tetramethoxybiphenyl-6,6′-dicarboxylate (13). By a modification of general procedure D (no pyridine), 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4-dimethoxy-5-hydroxybenzoate) (**11a**) (50 mg, 0.10 mmol) in 3 mL of dry CH_2Cl_2 was oxidatively coupled to afford 4.5 mg (9%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′-dihydroxy-3,3′,4,4′-tetramethoxybiphenyl-6,6′-dicarboxylate (**13**) (light yellow solid) and 40 mg (73%) of a mixture of monoquinone ketal compounds **14** (yellow solid) following flash column chromatography using 50% hexane/EtOAc as the eluent.

13: IR ($CHCl_3$) 3535–3140 (OH), 1745 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.72 (s, 1 H), 6.55 (s, 1 H), 6.20–6.00 (bs, 2 H), 5.38 (dd, J = 13.0, 6.1 Hz, 1 H), 4.78 (dt, J = 10.5, 4.2 Hz, 1 H), 4.20–3.90 (m, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 3.899 (s, 3 H), 3.896 (s, 3 H), 3.83 (d, J = 13.0 Hz, 1 H), 3.65 (dd, J = 9.6, 5.6 Hz, 1 H), 3.42 (dt, J = 11.9, 2.4 Hz, 1 H), 2.30 (d, J = 8.9 Hz, 1 H), 1.92–1.60 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.9, 167.4, 151.60, 151.55, 147.8, 137.5, 137.1, 129.9, 129.0, 114.7, 114.1, 103.7, 102.3, 78.4, 70.9, 68.7, 64.7, 61.1, 55.9, 29.9, 25.4; MS *m/z* (relative intensity) 490 (M^+, 100); HRMS calcd for $C_{24}H_{26}O_{11}$ 490.1475, found 490.1482; CD (CH_3OH, nm) +36 (230), −10 (250), +14 (268).

14: IR ($CHCl_3$) 3526 (OH), 1726 (C=O), 1687 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.32–7.17 (m, 2 H), 6.63–6.55 (m, 1 H), 5.99–5.84 (m, 2 H), 5.03–4.85 (m, 1 H), 4.57–4.51 (m, 1 H), 4.35–4.22 (m, 1 H), 4.02–3.99 (m, 1 H), 3.96–3.82 (m, 9 H), 3.73–3.63 (m, 1 H), 3.58–3.43 (m, 1 H), 3.47–3.46 (m, 3 H), 2.40–2.36 (m, 1 H), 2.16 (s, 3 H), 1.84–1.73 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 169.7, 169.6, 165.9, 164.9, 164.0, 162.1, 162.0, 161.7, 152.0, 151.8, 149.0, 148.9, 142.2, 142.1, 139.7, 139.6, 139.5, 125.3, 125.25, 125.1, 120.7, 120.5, 120.4, 110.1, 109.9, 105.7, 94.0, 93.8, 93.4, 70.3, 69.9, 69.2, 68.8, 67.8, 65.3, 64.8, 64.5, 60.9, 56.6, 56.0, 52.4, 29.3, 29.0, 24.8, 24.7, 20.3; MS *m/z* (relative intensity) 550 (M^+, 1.2), 490 (M^+ − HOAc, 17).

Lead Tetrabenzoate Oxidation of 1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis(3,4-dimethoxy-5-hydroxybenzoate) (11a). By two modifications of general procedure D (no pyridine and substitution of *lead tetrabenzoate* for lead tetraacetate), 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4-dimethoxy-5-hydroxybenzoate) (**11a**) (50 mg, 0.10 mmol) in 2 mL of dry CH_2Cl_2 was oxidized to afford 12 mg (20%) of monoquinone ketal **15** as a yellow oil and 4 mg (6%) of bisquinone ketal **16** as a yellow oil following flash column chromatography using 33% hexane in Et_2O as the eluent.

15: ^1H NMR (360 MHz, $CDCl_3$) δ 8.07–8.05 (m, 2 H), 7.64–7.44 (m, 3 H), 7.35–7.20 (m, 2 H), 6.72–6.63 (m, 1 H), 5.96–5.86 (m, 2 H), 5.02–4.90 (m, 1 H), 4.60–4.52 (m, 1 H), 4.34–4.26 (m, 1 H), 4.04–4.00 (m, 1 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 3.75–3.70 (m, 1 H), 3.62 (s, 3 H), 3.51–3.42 (m, 1 H), 2.40–2.31 (m, 1 H), 1.89–1.54 (m, 3 H); MS *m/z* (relative intensity) 612 (M^+, 4); HRMS calcd for $C_{31}H_{32}O_{13}$ 612.1843, found 612.1859.

16: ^1H NMR (200 MHz, $CDCl_3$) δ 8.08–8.02 (m, 4 H), 7.66–7.43 (m, 6 H), 6.74–6.63 (m, 2 H), 6.01–5.90 (m, 2 H), 4.93 (dt, J = 10.1, 4.7 Hz, 1 H), 4.55 (d, J = 12.1 Hz, 1 H), 4.27 (dd, J = 12.3, 4.9 Hz, 1 H), 4.02 (d, J = 11.0 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.71–3.59 (m, 1 H), 3.62 (s, 3 H), 3.61 (s, 3 H), 3.57–3.41 (m, 1 H), 2.38–2.32 (m, 1 H), 1.90–1.46 (m, 3 H); MS *m/z* (relative intensity) 732 (M^+, 4); HRMS calcd for $C_{38}H_{36}O_{15}$ 732.2054, found 732.2089.

3-(*tert*-Butyldimethylsiloxy)-4,5-(diphenylmethylenedioxy)benzoic Acid (22a). Lithium hydroxide (0.60 g, 14 mmol, 5.0 equiv) and 7 mL of H_2O were added to a solution of methyl 3,4-(diphenylmethylenedioxy)-5-hydroxybenzoate[20] (1.0 g, 2.9 mmol) in 21 mL of CH_3OH, and the mixture was heated at reflux for 1 h. The solution was cooled, diluted with 50 mL of EtOAc, washed with ice-cold 1 M H_3PO_4 and brine, dried (Na_2SO_4), and concentrated in vacuo to yield 0.82 g (85%) of 3,4-(diphenylmethylenedioxy)-5-hydroxybenzoic acid as a white solid, mp 174–176 °C: IR ($CDCl_3$) 3600–3460 (OH), 3270–2630 (CO_2H), 1735 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.26 (m, 12 H); ^{13}C NMR (50 MHz, C_3D_6O) δ 167.1, 149.2, 141.3, 140.8, 138.9, 130.1, 129.2, 126.9, 125.7, 118.7, 115.0, 103.1; MS *m/z* (relative intensity) 334 (M^+, 63).

3,4-(Diphenylmethylenedioxy)-5-hydroxybenzoic acid (4.5 g, 14 mmol) was dissolved in 130 mL of DMF and added to an Ar-filled Schlenk flask. After cooling to 0 °C, diisopropylethylamine (5.6 mL, 32 mmol, 2.4 equiv) and *tert*-butyldimethylsilyl chloride (6.1 g, 41 mmol, 3.0 equiv) were added. The solution was warmed to room temperature and stirred for 14 h. The mixture was quenched by the addition of 100 mL of ice-cold 1 M H_3PO_4 and extracted with 150 mL of Et_2O. The organic phase was washed with H_2O (2×) and brine, dried (Na_2SO_4), and concentrated in vacuo to afford 7.6 g of *tert*-butyldimethylsilyl 3-(*tert*-butyldimethylsilyl)-4,5-(diphenylmethylenedioxy)benzoate as a white solid: IR ($CDCl_3$) 1695 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.24 (m, 12 H), 0.98 (s, 18 H), 0.32 (s, 6 H), 0.16 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 148.4, 141.5, 139.7, 138.5, 129.1, 128.2, 126.1, 125.5, 119.0, 118.1, 104.3, 25.64, 25.56, 25.49, 18.2, 17.7, -4.6, -4.9.

The crude residue of *tert*-butyldimethylsilyl 3-(*tert*-butyldimethylsiloxy)-4,5-(diphenylmethylenedioxy)benzoate (7.6 g, 14 mmol) was dissolved in 120 mL of a 3:1:1 mixture of acetic acid:THF:H_2O, and the solution was stirred at room temperature for 4 h. The solution was quenched with 30 g of $NaHCO_3$, diluted with 50 mL of H_2O, and extracted with 150 mL of EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield 5.6 g (88% over two steps) of 3-(*tert*-butyldimethylsiloxy)-4,5-(diphenylmethylenedioxy)benzoic acid (**22a**) as a white solid, mp 202–204 °C: IR ($CDCl_3$) 3100–2630 (CO_2H),

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1690 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.29 (m, 12 H), 1.00 (s, 9 H), 0.19 (s, 6 H); ^{13}C (90 MHz, $CDCl_3$) δ 171.7, 148.6, 142.2, 139.7, 138.6, 129.3, 128.3, 126.2, 123.1, 119.3, 118.3, 104.4, 25.5, 18.3, –2.9; MS *m/z* (relative intensity) 448 (M^+, 22); HRMS calcd for $C_{26}H_{28}O_5Si$ 448.1706, found 448.1717.

3-(*tert*-Butyldimethylsiloxy)-4,5-(fluoren-9-ylidenedioxy)benzoic Acid (22b). Methyl gallate (2.5 g, 14 mmol) and 9,9-dichlorofluorene[21] (3.5 g, 15 mmol, 1.1 equiv) were heated (210 °C) under Ar for 1 h. Purification of the black residue by flash column chromatography using 20% EtOAc in hexane and then 33% EtOAc in hexane as the eluent afforded 2.8 g (60%) of methyl 3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoate as a white solid, mp 230–231 °C: IR ($CHCl_3$) 3574 (OH), 1716 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.62–7.26 (m, 10 H), 5.21 (s, 1 H), 3.90 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.6, 149.6, 140.3, 139.5, 139.0, 131.9, 128.8, 124.1, 120.4, 113.8, 103.4, 52.2; MS *m/z* (relative intensity) 346 (M^+, 100).

Lithium hydroxide (2.4 g, 57 mmol, 5.0 equiv) and 30 mL of H_2O were added to a solution of methyl 3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoate (3.9 g, 11 mmol) in 90 mL of CH_3OH and heated at reflux for 6 h. The solution was cooled, diluted with 150 mL of EtOAc, washed with ice-cold 1 M H_3PO_4 and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography using 20% hexane in Et_2O as the eluent afforded 3.7 g (99%) of 3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoic acid as a white solid, mp 208–210 °C: IR ($CHCl_3$) 3500–3250 (OH), 3200–2890 (CO_2H), 1677 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, C_3D_6O) δ 7.81–7.18 (m, 10 H); ^{13}C NMR (90 MHz, C_3D_6O) δ 167.0, 150.6, 141.6, 141.3, 140.3, 140.1, 132.8, 129.8, 125.5, 124.9, 121.5, 120.3, 114.9, 103.0; MS *m/z* (relative intensity) 332 (M^+, 52).

DMF (110 mL) was added to an Ar filled flask containing 3,4-fluoren-9-ylidenedioxy)-5-hydroxybenzoic acid (3.7 g, 11 mmol). After cooling to 0 °C, diisopropylethylamine (4.6 mL, 27 mmol, 2.4 equiv) and *tert*-butyldimethylsilyl chloride (5.0 g, 33 mmol, 3.0 equiv) were added. The solution was warmed to room temperature and stirred for 16 h. The solution was quenched by the addition of 100 mL of ice-cold 1 M H_3PO_4 and extracted with 150 mL of Et_2O. The organic layer was washed with H_2O (2×) and brine, dried (Na_2SO_4), and concentrated in vacuo to furnish 6.2 g of *tert*-butyldimethylsilyl 3-(*tert*-butyldimethylsiloxy)-4,5-(fluoren-9-ylidenedioxy)benzoate as a white solid, mp 130–134 °C: IR ($CHCl_3$) 1696 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.25 (m, 10 H), 1.07 (s, 9 H), 0.99 (s, 9 H), 0.43 (s, 6 H), 0.23 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9, 149.6, 142.9, 140.7, 139.5, 138.5, 131.6, 128.7, 125.3, 124.1, 120.3, 119.6, 119.0, 104.4, 25.61, 25.59, 18.3, 17.8, –4.5, –4.8; MS *m/z* (relative intensity) 560 (M^+, 9).

The crude residue of *tert*-butyldimethylsilyl 3-(*tert*-butyldimethylsiloxy)-4,5-(fluoren-9-ylidenedioxy)benzoate (6.2 g, 11 mmol) was dissolved in 120 mL of a 3:1:1 mixture of acetic acid:THF:H_2O and stirred at room temperature for 2 h. The solution was quenched with 30 g of $NaHCO_3$, diluted with 50 mL of H_2O, and extracted with 150 mL of EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield 4.4 g (89% over two steps) of 3-(*tert*-butyldimethylsiloxy)-4,5-(fluoren-9-ylidenedioxy)benzoic acid (**22b**) as a white solid, mp 220–222 °C. IR ($CDCl_3$) 3220–2400 (CO_2H), 1700 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.26 (m, 10 H), 0.95 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 149.8, 140.6, 139.6, 138.6, 131.7, 128.7, 124.2, 122.8, 120.3, 119.4, 104.4, 25.6, 18.3, –4.5; MS *m/z* (relative intensity) 446 (M^+, 10); HRMS calcd for $C_{26}H_{26}O_5Si$ 446.1549, found 446.1579.

Oxidation of Methyl 3,4-(Diphenylmethylenedioxy)-5-hydroxybenzoate (17). By a modification of general procedure D (no pyridine), methyl 3,4-(diphenylmethylenedioxy)-5-hydroxybenzoate (**17**) (200 mg, 0.57 mmol) in 6 mL of dry CH_2Cl_2 was oxidatively coupled to afford 52 mg (26%) of the biphenyl diester mixture **18** as a light yellow solid foam following flash column chromatography using 40% hexane in Et_2O as the eluent: ^{1}H NMR (200 MHz, C_3D_6O) δ 8.81 (s, 1 H), 8.44 (s, 1 H), 7.68–7.33 (m, 20 H), 7.30 (s, 1 H), 7.17 (s, 1 H), 3.38 (s, 3 H), 3.31 (s, 3 H); ^{13}C NMR (75 MHz, C_3D_6O) δ 167.0, 166.8, 148.0, 147.8, 141.2, 141.1, 141.0, 140.9, 140.0, 139.6, 138.3, 137.6, 130.2, 130.1, 130.01, 129.96, 129.3, 129.0, 127.1, 127.04, 126.98, 126.91, 125.6, 125.2, 122.9, 118.7, 118.4, 115.3, 113.1, 103.3, 51.64, 51.57; MS *m/z* (relative intensity) 694 (M^+, 24); HRMS calcd for $C_{42}H_{30}O_{10}$ 694.1839, found 694.1816.

Oxidation of Methyl 3,4-(Fluoren-9-ylidenedioxy)-5-hydroxybenzoate (19). By a modification of general procedure D (no pyridine), methyl 3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoate (**19**) (80 mg, 0.23 mmol) in 3 mL of dry CH_2Cl_2 was oxidatively coupled to afford 18 mg (23%) of the biphenyl diester mixture **20** as a light yellow solid foam following flash column chromatography using 50% hexane in Et_2O as the eluent: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.15 (m, 18 H), 5.71 (s, 1 H), 3.89 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.2, 164.4, 150.1, 146.5, 141.6, 140.9, 140.2, 140.1, 139.63, 139.56, 139.4, 139.3, 134.1, 131.8, 128.7, 124.28, 124.26, 124.1, 121.0, 120.7, 120.31, 120.29, 116.5, 112.2, 105.1, 102.8, 52.3, 52.1; MS *m/z* (relative intensity) 690 (M^+, 77); HRMS calcd for $C_{42}H_{26}O_{10}$ 690.1526, found 690.1536.

1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis(3,4-(diphenylmethylenedioxy)-5-hydroxybenzoate) (23a). By use of general procedure A, 3-(*tert*-butyldimethylsiloxy)-4,5-(diphenylmethylenedioxy)benzoic acid (**22a**) (5.3 g, 12 mmol, 2.0 equiv) was esterified with diol **21** (0.78 g, 5.9 mmol) to afford 3.9 g (66%) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3-(*tert*-butyldimethylsiloxy)-4,5-(diphenylmethylenedioxy)benzoate) as a white solid foam following flash column chromatography using CH_2Cl_2 as the eluent: IR ($CHCl_3$) 1714 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.64–7.31 (m, 24 H), 5.02 (dt, J = 10.3, 4.7 Hz, 1 H), 4.62 (d, J = 10.7 Hz, 1 H), 4.32 (dd, J = 12.0, 5.9 Hz, 1 H), 4.05 (d, J = 7.6 Hz, 1 H), 3.81–3.77 (m, 1 H), 3.49 (t, J = 11.2 Hz, 1 H), 2.42 (d, J = 8.3 Hz, 1 H), 1.92–1.60 (m, 3 H), 1.07 (s, 18 H), 0.25 (s, 12 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.7, 164.6, 148.5, 148.4, 141.6, 141.4, 139.8, 139.76, 139.7, 139.6, 138.6, 138.5, 129.2, 129.1, 128.2, 126.1, 123.9, 123.7, 118.7, 118.66, 118.1, 118.0, 104.0, 103.8, 77.8, 68.7, 67.8, 64.0, 29.3, 25.5, 24.9, 18.2, 1.12; MS *m/z* (relative intensity) 992 (M^+, 8).

By use of general procedure C, 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3-(*tert*-butyldimethylsiloxy)-4,5-(diphenylmethylenedioxy)-benzoate) (3.8 g, 3.8 mmol) was desilylated to afford 2.4 g (83%) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4-(diphenylmethylenedioxy)-5-hydroxybenzoate) (**23a**) as a white solid foam following flash column chromatography using 10% Et_2O in CH_2Cl_2 as the eluent: IR ($CHCl_3$) 3500–3100 (OH), 1720 (C=O), 1695 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.14 (m, 22 H), 7.136 (s, 1 H), 7.131 (s, 1 H), 4.88 (dt, J = 9.8, 4.8 Hz, 1H), 4.58 (d, J = 10.7 Hz, 1 H), 4.15 (dd, J = 12.0, 5.6 Hz, 1 H), 3.88 (d, J = 8.5 Hz, 1 H), 3.64–3.59 (m, 1 H), 3.31 (t, J = 10.7 Hz, 1 H), 2.24–2.21 (m, 1 H), 1.80–1.35 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 165.3, 148.4, 148.3, 139.5, 139.4, 139.3, 138.7, 138.5, 129.2, 129.15, 128.2, 126.2, 123.4, 118.6, 118.4, 114.1, 103.2, 103.1, 77.6, 69.3, 67.7, 64.1, 29.0, 24.5; MS *m/z* (relative intensity) 764 (M^+, 21); HRMS calcd for $C_{46}H_{36}O_{11}$ 764.2257, found 764.2283.

1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis(3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoate) (23b). By use of general procedure A, 3-(*tert*-butyldimethylsiloxy)-4,5-(fluoren-9-ylidenedioxy)benzoic acid (**22b**) (4.3 g, 9.6 mmol, 2.0 equiv) was esterified with diol **21** (0.64 g, 4.8 mmol) to afford 2.4 g (51%) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis-(3-(*tert*-butyldimethylsiloxy)-4,5-(fluoren-9-ylidenedioxy)benzoate) as a white solid foam following flash column chromatography using CH_2Cl_2 as the eluent: IR ($CHCl_3$) 1713 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62–7.21 (m, 20 H), 5.04 (dt, J = 9.9, 4.4 Hz, 1 H), 4.62 (dd, J = 11.9, 1.9 Hz, 1 H), 4.35 (dd, J = 12.0, 5.9 Hz, 1 H), 4.06 (d, J = 10.1 Hz, 1 H), 3.84–3.78 (m, 1 H), 3.50 (t, J = 9.9 Hz, 1 H), 2.42 (d, J = 8.9 Hz, 1 H), 1.95–1.50 (m, 3 H), 0.96 (s, 18 H), 0.19 (s, 12 H); MS *m/z* (relative intensity) 988 (M^+, 1).

By use of general procedure C, 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3-(*tert*-butyldimethylsiloxy)-4,5-(fluoren-9-ylidenedioxy)benzoate) (2.4 g, 2.4 mmol) was desilylated to afford 1.6 g (88%) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoate) (**23b**) as a white solid foam following flash column chromatography using 10% Et_2O in CH_2Cl_2 as the eluent: IR ($CHCl_3$) 3600–3080 (OH), 1740 (C=O), 1730 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.10 (m, 20 H), 4.93 (dt, J = 9.7, 4.7 Hz, 1 H), 4.52 (d, J = 11.4 Hz, 1 H), 4.27 (dd, J = 12.0, 4.9 Hz, 1 H), 3.92 (d, J = 9.0 Hz, 1 H), 3.70–3.62 (m, 1 H), 3.35 (t, J = 10.6 Hz, 1 H), 2.30–2.20 (m, 1 H), 1.84–1.40 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 165.4, 149.6, 149.5, 140.24, 140.21, 140.19, 140.1, 139.7, 139.6, 139.5, 139.4, 139.3, 131.6, 128.6, 124.13, 124.06, 124.0, 123.3, 120.1, 120.0, 119.8, 103.0, 102.9, 77.6, 68.9, 67.7, 64.0, 29.0, 24.5; MS *m/z* (relative intensity) 760 (M^+, 26); HRMS calcd for $C_{46}H_{32}O_{11}$ 760.1944, found 760.1996.

Oxidative Coupling of 1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis-(3,4-(diphenylmethylenedioxy)-5-hydroxybenzoate) (23a). By use of general procedure D, 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4-(diphenylmethylenedioxy)-5-hydroxybenzoate) (**23a**) (50 mg, 65 μmol)

(21) Martin, C. W.; Gill, H. S.; Landgrebe, J. A. *J. Org. Chem.* **1983**, *48*, 1898.

in 13 mL of dry CH_2Cl_2 was oxidatively coupled to afford 39 mg (79%) of four isomers (A–D) of the bis(diphenylmethylenedioxy)biphenyl diester **24a** as light yellow solids following flash column chromatography using 2% Et_2O in CH_2Cl_2, and then 5% Et_2O in CH_2Cl_2, as the eluent.

Isomer A: IR ($CHCl_3$) 3650–3360 (OH), 1690 (C=O), 1670 (C=O) cm^{-1}; ^1H NMR (200 MHz, C_3D_6O) δ 7.65–7.40 (m, 20 H), 6.70 (s, 1 H), 6.58 (s, 1 H), 5.15 (dd, J = 12.9, 6.1 Hz, 1 H), 4.53 (dt, J = 10.3, 4.0 Hz, 1 H), 3.88 (d, J = 10.0 Hz, 1 H), 3.63 (d, J = 12.9 Hz, 1 H), 3.57 (dd, J = 9.4, 5.7 Hz, 1 H), 3.38 (dt, J = 11.4, 5.3 Hz, 1 H), 1.73–1.60 (m, 3 H); ^{13}C NMR (50 MHz, C_3D_6O) δ 168.2, 167.7, 148.1, 141.5, 141.3, 140.5, 130.1, 129.2, 126.8, 119.1, 100.8, 99.9, 79.1, 71.5, 68.9, 65.3, 26.1; MS (+FAB) 763.3 (M^+ + 1); HRMS calcd for $C_{46}H_{34}O_{11}$ 762.2101, found 762.2104.

Isomer B: IR ($CHCl_3$) 3540–3050 (OH), 1730 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.68–7.26 (m, 20 H), 6.80 (s, 1 H), 6.63 (s, 1 H), 5.36 (dd, J = 12.9, 6.1 Hz, 1 H), 4.74 (dt, J = 10.2, 3.6 Hz, 1 H), 3.96 (d, J = 7.7 Hz, 1 H), 3.79 (d, J = 12.9 Hz, 1 H), 3.58 (dd, J = 8.8, 5.8 Hz, 1 H), 3.37 (t, J = 11.0 Hz, 1 H), 2.23–2.15 (m, 1 H), 1.90–1.50 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 147.7, 146.5, 140.0, 139.6, 139.0, 138.9, 138.8, 137.8, 136.9, 135.1, 129.5, 129.4, 129.2, 128.5, 128.3, 128.2, 127.5, 126.7, 126.5, 126.31, 126.29, 119.1, 118.9, 116.7, 111.2, 107.6, 102.0, 78.3, 70.9, 68.5, 64.7, 29.8, 25.3; MS *m/z* (relative intensity) 762 (M^+, 67); HRMS calcd for $C_{46}H_{34}O_{11}$ 762.2101, found 762.2151.

Isomer C: IR ($CHCl_3$) 3535–2735 (OH), 1745 (C=O), 1720 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69–7.25 (m, 20 H), 6.75 (s, 1 H), 6.65 (s, 1 H), 5.31 (dd, J = 13.0, 6.1 Hz, 1 H), 4.81 (dt, J = 9.9, 3.8 Hz , 1 H), 3.96 (d, J = 11.9 Hz, 1 H), 3.87 (d, J = 13.1 Hz, 1 H), 3.61 (dd, J = 9.5, 5.9 Hz, 1 H), 3.36 (t, J = 7.8 Hz, 1 H), 2.21 (d, J = 8.4 Hz, 1 H), 1.68–1.54 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.1, 167.0, 147.7, 146.8, 140.0, 139.7, 139.3, 138.8, 137.9, 136.6, 135.8, 129.4, 129.2, 128.4, 128.3, 128.2, 128.1, 126.9, 126.5, 126.3, 119.0, 118.8, 116.2, 112.9, 107.6, 100.8, 78.4, 70.8, 68.5, 64.7, 29.8, 25.3; MS *m/z* (relative intensity) 762 (M^+, 100); HRMS calcd for $C_{46}H_{34}O_{11}$ 762.2101, found 762.2130.

Isomer D: IR ($CHCl_3$) 3630–2870 (OH), 1740 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51–7.06 (m, 20 H), 6.67 (s, 1 H), 6.61 (s, 1 H), 5.90 (bs, 1 H), 5.51 (bs, 1 H), 5.34 (dd, J = 13.1, 6.2 Hz, 1 H), 4.81 (dt, J = 10.3, 3.5 Hz, 1 H), 3.97 (d, J = 10.0 Hz, 1 H), 3.83 (d, J = 13.0 Hz, 1 H), 3.60 (dd, J = 9.9, 5.8 Hz, 1 H), 3.36 (t, J = 8.9 Hz, 1 H), 2.19 (d, J = 8.8 Hz, 1 H), 1.75–1.53 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.7, 167.2, 147.4, 147.2, 139.4, 139.3, 139.0, 138.7, 135.9, 135.4, 129.3, 129.1, 128.6, 128.1, 128.0, 127.9, 127.4, 127.2, 127.0, 126.8, 126.7, 119.1, 119.0, 112.1, 110.6, 108.0, 107.9, 78.5, 70.7, 68.6, 64.6, 29.8, 25.3; MS *m/z* (relative intensity) 762 (M^+, 100); HRMS calcd for $C_{46}H_{34}O_{11}$ 762.2101, found 762.2131.

Oxidative Coupling of 1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis-(3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoate) (23b). By use of general procedure D, 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4-(fluoren-9-ylidenedioxy)-5-hydroxybenzoate) (**23b**) (100 mg, 0.13 mmol) in 5 mL of dry CH_2Cl_2 was oxidatively coupled to afford 68 mg (69%) of three isomers (A–C) of the bis(fluoren-9-ylidenedioxy)biphenyl diester **24b** as light yellow solids following flash column chromatography using 2% Et_2O in CH_2Cl_2, and then 5% Et_2O in CH_2Cl_2, as the eluent.

Isomer A: IR ($CHCl_3$) 3545–3025 (OH), 1745 (C=O), 1725 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.57–7.15 (m, 16 H), 6.75 (s, 1 H), 6.54 (s, 1 H), 6.43 (bs, 1 H), 6.32 (bs, 1 H), 5.35 (dd, J = 13.0, 6.1 Hz, 1 H), 4.77 (dt, J = 10.3, 3.7 Hz, 1 H)), 3.96 (d, J = 7.5 Hz, 1 H), 3.72 (d, J = 12.9 Hz, 1 H), 3.57 (dd, J = 9.2, 6.2 Hz, 1 H), 3.35 (t, J = 11.4 Hz, 1 H), 2.12 (d, J = 9.6 Hz, 1 H), 1.88–1.47 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.0, 167.4, 149.1, 149.0, 140.4, 140.37, 140.2, 140.1, 139.7, 139.6, 139.3, 139.2, 138.4, 137.8, 137.7, 131.8, 131.6, 129.0, 128.9, 128.8, 127.9, 124.5, 124.4, 124.39, 120.3, 120.2, 120.1, 118.4, 117.5, 102.8, 101.4, 78.4, 70.9, 68.6, 64.7, 29.7, 25.3; MS *m/z* (relative intensity) 758 (M^+, 58); HRMS calcd for $C_{46}H_{30}O_{11}$ 758.1788, found 758.1769.

Isomer B: IR ($CHCl_3$) 3625–3415 (OH), 1735(C=O) cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 8.85 (bs, 1 H), 8.60 (bs, 1 H), 7.83–7.16 (m, 16 H), 6.76 (s, 1 H), 6.75 (s, 1 H), 5.38 (dd, J = 12.8, 6.1 Hz, 1 H), 4.79 (dt, J = 9.9, 4.1 Hz, 1 H), 3.94 (d, J = 10.2 Hz, 1 H), 3.78 (d, J = 13.0 Hz, 1 H), 3.72 (dd, J = 9.7, 6.0 Hz, 1 H), 3.44 (t, J = 9.9 Hz, 1 H), 2.30–2.19 (m, 1 H), 1.85–1.70 (m, 3 H); ^{13}C NMR (75 MHz, C_3D_6O) δ 168.2, 168.0, 149.9, 149.5, 142.0, 141.6, 141.5, 141.4, 140.8, 140.5, 140.2, 140.1, 139.9, 138.1, 136.9, 132.7, 132.6, 129.8, 129.7, 129.67, 129.6, 128.9, 125.9, 125.0, 124.9, 121.4, 121.3, 121.25, 121.2, 120.2, 120.0, 118.5, 111.0, 109.5, 100.7, 79.1, 71.6, 68.9, 65.4, 26.2; MS *m/z* (relative intensity) 758 (M^+, 40); HRMS calcd for $C_{46}H_{30}O_{11}$ 758.1788, found 758.1752.

Isomer C: IR ($CHCl_3$) 3280–3040 (OH), 1735 (C=O), 1720 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.13 (m, 16 H), 6.90 (s, 1 H), 6.65 (s, 1 H), 6.52 (bs, 1 H), 5.56 (bs, 1 H), 5.49 (dd, J = 13.0, 6.2 Hz, 1 H), 4.95 (dt, J = 10.4, 3.7 Hz, 1 H), 4.02 (d, J = 10.0 Hz, 1 H), 3.96 (d, J = 13.0 Hz, 1 H), 3.71 (dd, J = 9.6, 5.9 Hz, 1 H), 3.43 (t, J = 11.1 Hz, 1 H), 2.29 (d, J = 9.2 Hz, 1 H), 1.87–1.61 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.2, 167.3, 148.8, 148.0, 140.5, 140.4, 140.3, 140.0, 139.5, 139.4, 139.2, 138.0, 137.9, 136.7, 131.7, 131.69, 131.6, 131.58, 128.9, 128.8, 128.78, 128.6, 128.0, 127.7, 125.0, 124.6, 124.4, 124.0, 120.3, 120.2, 120.1, 120.0, 116.7, 112.5, 108.9, 100.9, 78.4, 70.8, 68.6, 64.8, 29.8, 25.4; MS *m/z* (relative intensity) 758 (M^+, 9); HRMS calcd for $C_{46}H_{30}O_{11}$ 758.1788, found 758.1738.

(*S*)-1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-Hexahydroxybiphenyl-6,6'-dicarboxylate (25). By use of general procedure E, isomer A of **24a** (56 mg, 73 μmol) was deprotected using 50 mg of 10% Pd/C to afford 31 mg (96%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexahydroxybiphenyl-6,6'-dicarboxylate (**25**) as a light yellow solid foam: IR ($CHCl_3$) 3500–3180 (OH), 1715 (C=O), 1705 (C=O) cm^{-1}; ^1H NMR (200 MHz, C_3D_6O) δ 6.63 (s, 1 H), 6.49 (s, 1 H), 6.40–5.50 (b, 6 H), 5.23 (dd, J = 12.9, 6.2 Hz, 1 H), 4.62 (dt, J = 10.1, 4.0 Hz, 1 H), 3.89 (d, J = 10.8 Hz, 1 H), 3.67–3.56 (m, 2 H), 3.45–3.32 (m, 1 H), 1.76–1.56 (m, 3 H); ^{13}C NMR (75 MHz, C_3D_6O) δ 168.7, 168.1, 145.1, 145.08, 144.7, 144.5, 136.3, 135.8, 127.4, 126.5, 115.9, 115.2, 108.1, 107.1, 79.3, 71.1, 68.9, 64.9, 26.2; MS *m/z* (relative intensity) 434 (M^+, 2); HRMS calcd for $C_{20}H_{18}O_{11}$ 434.0849, found 434.0812.

By use of general procedure E, isomer B of **24a** (50 mg, 66 μmol) was deprotected using 22 mg of 10% Pd/C to afford 14 mg (49%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexahydroxybiphenyl-6,6'-dicarboxylate (**25**) as a light yellow solid foam.

By use of general procedure E, isomer C of **24a** (30 mg, 39 μmol) was deprotected using 12 mg of 10% Pd/C to afford 15 mg (89%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexahydroxybiphenyl-6,6'-dicarboxylate (**25**) as a light yellow solid foam.

By use of general procedure E, isomer D of **24a** (15 mg, 20 μmol) was deprotected using 10 mg of 10% Pd/C to afford 5 mg (58%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexahydroxybiphenyl-6,6'-dicarboxylate (**25**) as a light yellow solid foam.

(*S*)-1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-Hexamethoxybiphenyl-6,6'-dicarboxylate (26). By use of general procedure F, the hexahydroxybiphenyl compound generated from isomer A of **24a** (31 mg, 71 μmol) was methylated to afford 15 mg (41%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexamethoxybiphenyl-6,6'-dicarboxylate (**26**) as a white solid foam: IR ($CHCl_3$) 1715 (C=O), 1700 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.85 (s, 1 H), 6.68 (s, 1H), 5.34 (dd, J = 12.9, 6.0 Hz, 1 H), 4.75 (dt, J = 10.3, 3.9 Hz, 1 H), 4.05–3.97 (m, 1 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.90 (s, 6 H), 3.79 (d, J = 13.0 Hz, 1 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.63 (dd, J = 9.6, 5.7 Hz, 1 H), 3.42 (dt, J = 12.0, 3.0 Hz, 1 H), 2.31 (d, J = 8.3 Hz, 1 H), 1.91–1.55 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 167.6, 152.92, 152.9, 152.3, 152.1, 144.3, 143.8, 129.0, 128.1, 122.8, 121.9, 106.1, 104.6, 78.4, 71.0, 68.6, 64.7, 61.0, 60.7, 60.6, 59.9, 29.9, 25.3; MS *m/z* (relative intensity) 518 (M^+, 100); HRMS calcd for $C_{26}H_{30}O_{11}$ 518.1788, found 518.1742; CD (CH_3OH, nm) +25 (228), –26 (245), +29 (263).

By use of general procedure F, the hexahydroxybiphenyl compound generated from isomer B of **24a** (14 mg, 32 μmol) was methylated to afford 9 mg (54%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexamethoxybiphenyl-6,6'-dicarboxylate (**26**) as a white solid foam.

By use of general procedure F, the hexahydroxydiphenyl compound generated from isomer C of **24a** (14 mg, 32 μmol) was methylated to afford 11 mg (66%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexamethoxybiphenyl-6,6'-dicarboxylate (**26**) as a white solid foam.

By use of general procedure F, the hexahydroxydiphenyl compound generated from isomer D of **24a** (5 mg, 12 μmol) was methylated to afford 4 mg (64%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-hexamethoxybiphenyl-6,6'-dicarboxylate (**26**) as a white solid foam.

(*S*)-1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2',3,3',4,4'-Hexahydroxybiphenyl-6,6'-dicarboxylate (25). By use of general procedure E, isomer A of **24b** (30 mg, 40 μmol) was deprotected using 7 mg of 10% Pd/C to afford 16 mg (92%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-

hexitol 2,2′,3,3′,4,4′-hexahydroxybiphenyl-6,6′-dicarboxylate (**25**) as a light yellow solid foam.

By use of general procedure E, isomer B of **24b** (56 mg, 74 μmol) was deprotected using 20 mg of 10% Pd/C to afford 27 mg (84%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexahydroxybiphenyl-6,6′-dicarboxylate (**25**) as a light yellow solid foam.

By use of general procedure E, isomer C of **24b** (11 mg, 15 μmol) was deprotected using 7 mg of 10% Pd/C to afford 6 mg (92%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexahydroxybiphenyl-6,6′-dicarboxylate (**25**) as a light yellow solid foam.

(*S*)-1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-Hexamethoxybiphenyl-6,6′-dicarboxylate (26). By use of general procedure F, the hexahydroxybiphenyl compound generated from isomer A of **24b** (16 mg, 37 μmol) was methylated to afford 12 mg (63%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexamethoxybiphenyl-6,6′-dicarboxylate (**26**) as a white solid foam.

By use of general procedure F, the hexahydroxybiphenyl compound generated from isomer B of **24b** (23 mg, 53 μmol) was methylated to afford 20 mg (73%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexamethoxybiphenyl-6,6′-dicarboxylate (**26**) as a white solid foam.

By use of general procedure F, the hexahydroxydiphenyl compound generated from isomer C of **24b** (7 mg, 16 μmol) was methylated to afford 5 mg (60%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexamethoxybiphenyl-6,6′-dicarboxylate (**26**) as a white solid foam.

VOF_3-Mediated Oxidation of 1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis(3,4,5-trimethoxybenzoate) (11f). A solution of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4,5-trimethoxybenzoate) (**11f**) (50 mg, 96 μmol) in 1 mL of dry CH_2Cl_2 was added dropwise over 10 min to a cooled (0 °C) solution of vanadium trifluoride oxide (42 mg, 0.34 mmol, 3.5 equiv) in 19 mL of dry CH_2Cl_2 and 2 mL of trifluoroacetic acid. The solution was stirred at 0 °C under Ar for 3 h, quenched slowly by the addition of saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered through Celite, and concentrated in vacuo. Purification of the residue by flash column chromatography using 5% Et_2O in CH_2Cl_2 as the eluent afforded 27 mg (55%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexamethoxybiphenyl-6,6′-dicarboxylate (**26**) as a white solid foam. All of the spectral data (including CD) for this biphenyl diester were coincident with that reported earlier for this compound.

Tl_2O_3-Mediated Oxidation of 1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol Bis(3,4,5-trimethoxybenzoate) (11f). A solution of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol bis(3,4,5-trimethoxybenzoate) (**11f**) (104 mg, 0.20 mmol) in 1 mL of CH_2Cl_2 was added to a stirred solution of thallium(III) oxide (50 mg, 0.11 mmol, 0.54 equiv) in 3 mL of dry CH_2Cl_2 and 0.40 mL of trifluoroacetic acid. Boron trifluoride etherate (47 μL, 0.38 mmol, 1.9 equiv) was then added, and the solution was stirred at room temperature under Ar for 8 h. The reaction mixture was carefully quenched by the addition of saturated $NaHCO_3$ solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered through Celite, and concentrated in vacuo. Purification of the residue by flash column chromatography using 33% hexane in Et_2O as the eluent afforded 17 mg (16%) of (*S*)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol 2,2′,3,3′,4,4′-hexamethoxybiphenyl-6,6′-dicarboxylate (**26**) as a white solid foam. All of the spectral data for this biphenyl diester were coincident with that reported earlier for this compound.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **7**, **9**, **10**, **11a,f**, **13**, **14**, **15** (^1H), **16** (^1H), **18**, **20**, **22a,b**, **23a,b**, **25**, and **26**. (32 pages). This material is contained in many 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.