Studies Relevant to Ellagitannin Chemistry: Highly Diastereoselective Intramolecular Biaryl Coupling in Bis(iodotrimethoxybenzoyl) Hexopyranose Derivatives

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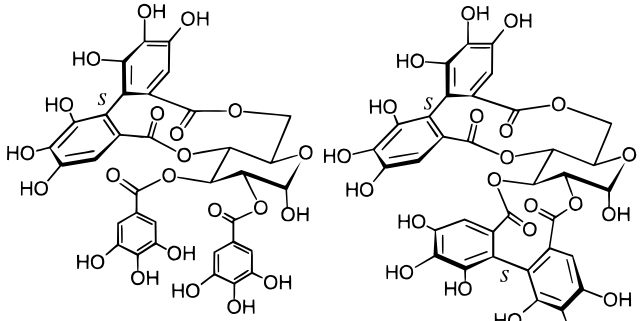
Received September 16, 1997

Internal biaryl coupling reactions of carbohydrate derivatives carrying two 2-iodo-3,4,5-trimethoxybenzoyl groups under Ullmann conditions were investigated. With substituents at positions 2,3 or 4,6 of a D-glucopyranoside, 2,3 of a D-mannopyranoside, and 3,4 of a D-galactopyranoside, the coupling was found to proceed with a very high degree of stereoselectivity, leading exclusively to the (*S*)-epimer of the resulting hexamethoxydiphenoyl residue from the D-*gluco* and D-*galacto* substrates, and to the (*R*)-epimer from the D-*manno* substrate. With substituents at positions 2,4 of D-glucopyranose derivatives in the $^1C_4$ conformation and at positions 5,6 of a D-glucofuranose derivative, the coupling proceeded efficiently but with modest stereoselectivity. Some deiodinated starting material was formed as a byproduct in all reactions. These results are relevant to ellagitannin chemistry in that they provide further understanding of the structural requirements for highly diastereoselective biaryl coupling within carbohydrate units. In addition, the efficient, complementary reactions of the D-*manno* and D-*galacto* substrates provide a method for the enantioselective synthesis of hexamethoxydiphenoic acid derivatives

Introduction

Ellagitannins[1] are gallic acid metabolites characterized by the presence of one or more axially chiral hexahydroxydiphenoyl residues connected, in most cases, to a glucopyranose scaffold by ester functions. Tellimagrandin I (**1**) and pedunculagin (**2**) are two examples of monomeric ellagitannins. According to Schmidt[1a] and Haslam,[1b,2] all ellagitannins arise from penta-*O*-galloyl-*β*-D-glucopyranose, the ultimate biosynthetic precursor of both gallotannins and ellagitannins; the



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diphenoyl units are thought to be generated by oxidative C−C couplings between adjacent galloyl esters, the diastereoselectivity of the coupling being dictated by conformational constraints within the polysubstituted glucopyranose substrate ("Schmidt−Haslam hypothesis," see ref 1d). While a biomimetic strategy would provide a straightforward approach for the chemical synthesis of ellagitannins, the implementation of such a strategy has eluded the efforts of synthetic chemists until very recently: Feldman and co-workers have now developed an efficient methodology[3] for internal oxidative couplings of glucose galloates and have reported the first syntheses of a number of free, monomeric ellagitannins, including tellimagrandin I and pedunculagin.[4] Previous syntheses of ellagitannin derivatives (per-*O*-methyl tellimagrandins) were achieved by esterification of glucose diols with preformed (*S*)-hexamethoxydiphenoic acid.[5]

Intrigued by the dearth of precedent on the synthesis of ellagitannins from carbohydrate substrates, we have also carried out studies on hexopyranoses carrying substituted benzoyl groups, with the goal of examining both the feasibility and the stereochemistry of the internal aryl−aryl bond formation process. Unsuccessful attempts of linking adjacent 3,4,5-trimethoxybenzoyl substituents in D-glucopyranosides under oxidative conditions using reagents such as VOF_3[6,7] prompted us to

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(1) (a) Schmidt, O. T. *Fortschr. Chem. Org. Naturst.* **1956**, *13*, 70−136. (b) Haslam, E.; Cai, Y. *Nat. Prod. Rep.* **1994**, 41−66. (c) Okuda, T.; Yoshida, T.; Hatano, T. *Prog Chem. Org. Nat. Prod.* **1995**, *66*, 1−117. (d) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475−503, and ref. cited.

(2) Gupta, R. K.; Al-Shafi, S. M. K.; Layden, K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2525−2534.

(3) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357−3366.

(4) (a) Tellimagrandin I: Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742−1745. (b) Sanguiin H-5: Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171−8178. (c) Pedunculagin: Feldman, K. S.; Smith, R. S. *J. Org. Chem.* **1996**, *61*, 2606−2612.

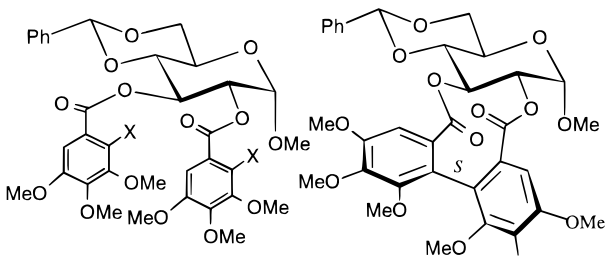
(5) (a) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577−2580. (b) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567−5570. Examples of synthesis of ellagitannins by way of the diastereoselective esterification of glucose diols with racemic hexaalkoxydiphenoic acid derivatives have been very recently reported: (c) Itoh, T.; Chika, J.-I.; Shirakami, S.; Ito, H.; Yoshida, T.; Kubo, Y.; Uenishi, J.-I. *J. Org. Chem.* **1996**, *61*, 3700−3705. (d) Khanbabaee, K.; Schulz, C.; Lötzerich, K. *Tetrahedron Lett.* **1997**, *38*, 1367−1368.

10.1021/jo971722k CCC: $15.00
Published on Web 10/08/1998

consider performing the biaryl coupling reaction[8] under reductive, Ullmann-type conditions. We wish to report, in this article, the results of our investigations on sugar derivatives carrying 2-iodo-3,4,5-trimethoxybenzoyl substituents; the finding of substrates that lead to (*R*) or (*S*)-atropisomers with a very high degree of stereoselectivity is particularly noteworthy.

Results and Discussion

A series of methyl D-hexopyranosides carrying two 2-iodo-3,4,5-trimethoxybenzoyl substituents at positions 2,3 (**3**, **9**), 3,4 (**12**), or 4,6 (**6a**, **6b**) were prepared from the corresponding diols by esterification with 2-iodo-3,4,5-trimethoxybenzoic acid[9] in the presence of DCC and DMAP.[10] Since the treatment of some of these substrates with zerovalent nickel reagents [$Ni(Ph_3P)_2Cl_2-Ph_3P-Zn$ in DMF,[11] $NiI_2-Zn-KI$ in HMPA,[12] $NiCl_2-Ph_3P-Zn$ in DMF[13]] promoted exclusively the deiodination of the starting material, subsequent studies were conducted using classical Ullmann conditions.[14,15] The reaction of these substrates with pretreated copper powder[15] under the conditions described by Miyano[16] (DMF, reflux temperature or below[17]) led to the results that follow.



2,3-Disubstituted D-glucopyranoside **3** gave the corresponding 2,3-diphenoyl derivative **5** as a *single* stereoisomer together with a relatively large amount of deiodinated starting material (**4**) (ratio of **4** and **5**: ~1.2:1). A sample of **5** could be isolated by preparative TLC, and its configuration was determined to be *S* on the basis of its CD-spectrum[1c,18] and by comparison with the data reported by Itoh et al.[5c] for both epimers of the same glucopyranose derivative. The ratio between coupling and reduction products was slightly improved when the substituents were at position 4,6 of the D-glucopyranose carrier (Table 1). The reaction of **6a** with Cu(0) afforded a mixture of three unseparable products in a ratio of ~2:1:1.[19] The NMR spectral data of the major product were found to match exactly those of per-*O*-methyl tellimagrandin I,[5a] thus establishing its structure as **7a** and the configuration of the diphenoyl unit as *S*. The first minor product was identified, by comparison with an authentic sample, as deiodinated starting material **8a**; the structure of the second minor product remained uncertain. With benzyl groups at positions 2 and 3 instead of trimethoxybenzoyl groups (substrate **6b**), the reaction gave a homogeneous mixture of only two products in a ~1:1 ratio, namely the 4,6-diphenoyl derivative **7b** and reduction product **8b**. The configuration of the single atropisomer **7b** was assigned to be *S* on the basis of its CD-spectrum (Table 2). The most interesting and useful results were obtained from substrates carrying the substituents in vicinal axial−equatorial position and having the nonnatural D-*manno* and D-*galacto* configuration: the reaction of 2,3-*cis*-disubstituted D-mannopyranoside **9** and of 3,4-*cis*-disubstituted D-galactopyranoside **12** gave the desired diphenoyl derivatives **10** and **13** in very good yields and readily separable from a minor amount of deiodinated starting material (**11** and **14**). Both reactions generated the biaryl unit as a *single atropisomer*. As expected from the nearly enantiomeric relationship between the 2,3-positions in the D-*manno* series and the 4,3-positions in the D-*galacto* series, these substrates gave products of opposite configuration: the CD-spectra of **10** and **13** established unambiguously[1c,18] that the diphenoyl groups in **10** and **13** have the (*R*)- and (*S*)-configuration, respectively (Table 2).

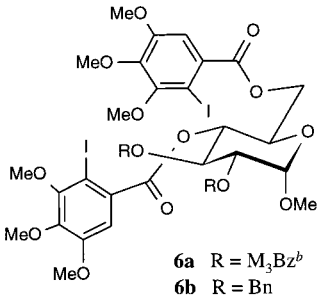
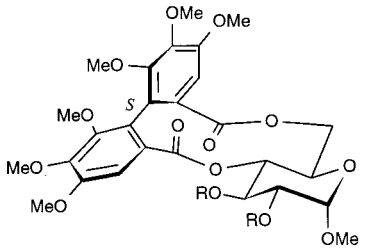
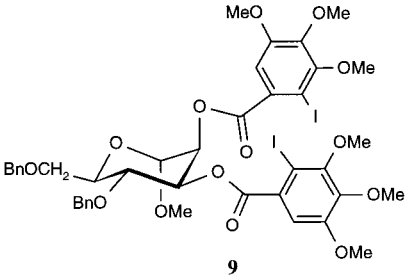
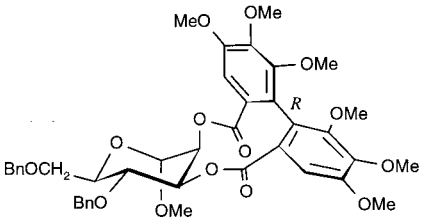
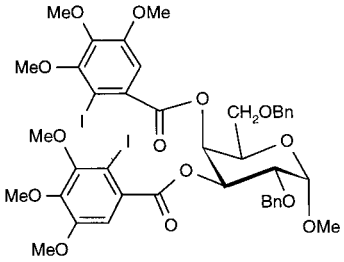
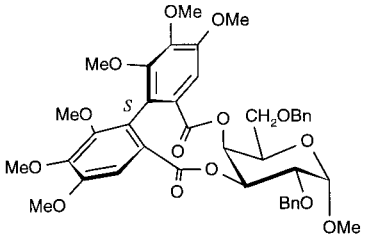
Considering that the diphenoyl residue can be readily removed from the hexopyranoside under basic conditions,[5b,c] the D-*manno* and D-*galacto* diols thus constitute convenient templates for the asymmetric synthesis of hexamethoxydiphenoic acid derivatives with a high degree of enantiomeric purity. The method is complementary to that reported by Lipshutz (chiral template: (*S*,*S*)-stilbene diol).[5b]

To further probe the stereochemistry of the biaryl coupling in carbohydrate substrates, we also investigated the Ullmann reactions of the following systems; in all cases, the reaction gave a nonseparable mixture of two epimeric diphenoyl derivatives and some reduction product (see results in Table 3).

1,3-Diaxially disubstituted hexopyranoses: a number of ellagitannins or their biosynthetic precursors contain a diphenoyl group between positions 2 and 4 of a glucopyranose unit in the $^1C_4$ conformation (chebulinic acid, geraniin, etc.[1c]). The reactions of substrates **15** and **16** could therefore serve as models for the synthesis of such natural products. The coupling between the groups at O-2 and O-4 in **15** proceeded, however, with essentially no stereoselectivity, a result that can be attributed to the near symmetry of the substrate. With a 3,6-anhydro

(6) Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3772.
(7) Feldman (ref 4a) reported the successful coupling of the trimethoxybenzoyl groups at O-4 and O-6 of methyl tetrakis-*O*-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside using VOF_3.
(8) General review on biaryl coupling: Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327−3359.
(9) Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortès, L.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 4933−4938.
(10) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475−4478. See also ref 5a.
(11) (a) Kende, A. S.; Liebeskind, L. S.; Braitsch, D. M. *Tetrahedron Lett.* **1975**, 3375−3378. (b) Zembayashi, M.; Tamao, K.; Yoshida, J.-I.; Kumada, M. *Tetrahedron Lett.* **1977**, 4089−4092.
(12) Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* **1979**, 917−918.
(13) Colon, I.; Kelsey, D. R. *J. Org. Chem.* **1986**, *51*, 2627−2637.
(14) Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139−196. *Chem. Rev.* **1964**, *64*, 613−632. *Synthesis* **1974**, 9−21.
(15) Fuson, R. C.; Cleveland, E. A. *Organic Syntheses*; Wiley: New York, 1955; Coll. Vol. III, pp 339−340.
(16) Miyano, S.; Handa, S.; Shimizu, K.; Tagami, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1942−1947.
(17) Despite the high temperature used, the reactions were clean, and the conversion was essentially quantitative.
(18) Okuda, T.; Yoshida, T.; Hatano, T.; Koga, T.; Toh, N.; Kuriyama, K. *Tetrahedron Lett.* **1982**, *23*, 3937−3940; 3941−3944. For comparative results, see Table 2. A negative Cotton effect at about 250 nm followed by a positive Cotton effect at about 225 nm was taken as evidence for the (*S*)-configuation of the hexamethoxydiphenoyl unit.
(19) The ratio of products was improved to 4:1:1 when the reaction was performed at lower temperature (105 °C, 5 d).

Table 1. Intramolecular Biaryl Couplings

Starting Material	Coupling Product	Reduction Product[a]
 **6a** R = M_3Bz[b] **6b** R = Bn	 **7a** R = M_3Bz (50%)[c] **7b** R = Bn (50%)[c]	**8a** (25%)[c] **8b** (50%)[c]
 **9**	 **10** (77%)	**11** (21%)
 **12**	 **13** (69%)	**14** (29%)

[a] I → H in starting material. [b] M_3Bz = 3,4,5-trimethoxybenzoyl. [c] Ratios estimated by NMR.

Table 2. CD Spectral Data for 5, 7b, 10, and 13[a]

compd no.	molar ellipticities $[\theta] \times 10^{-4}$ (λ, nm)			
5	−1.3 (302)	+1.9 (272)	−4.2 (245)	?
7b	−1.4 (301)	+3.2 (266)	−3.7 (246)	+9.8 (222)
10		−2.1 (278)	+1.2 (257)	−3.2 (230)
13	−0.2 (308)	+0.47 (278)	−0.49 (254)	~0.8 (225)

[a] Spectra recorded in MeOH.

bridge and the configuration at C-1 inverted (compound **16**), the coupling was more efficient and its stereoselectivity was improved (3:1), but remained modest.

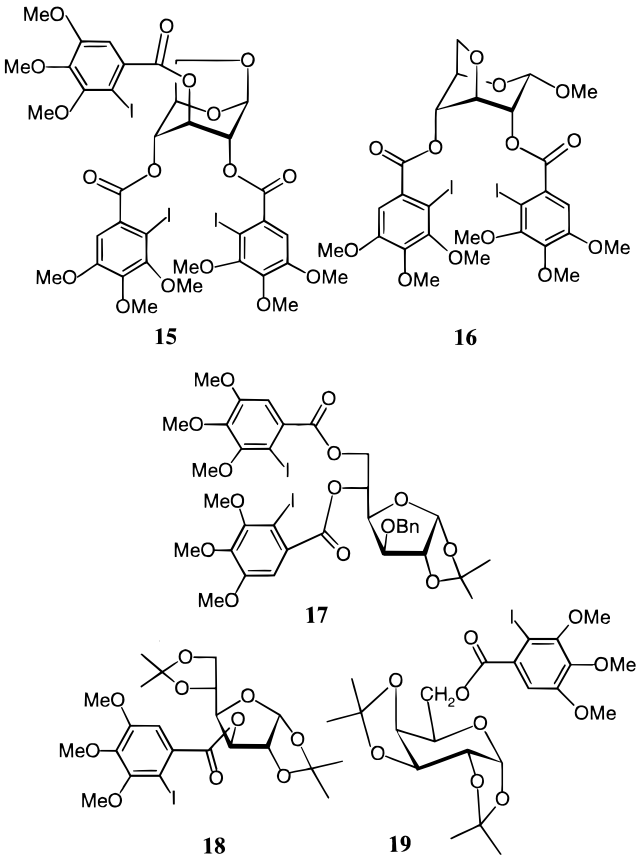
Vicinally disubstituted acyclic system: as shown by the reaction of substrate **17** with Cu(0), the coupling was efficient in this system, but the sugar carrier provided very little control of its stereoselectivity.

Monosubstituted carbohydrate derivatives (intermolecular reactions): the reactions of substrates **18** and **19** were each examined for comparison with the intramolecular processes. The coupling was found to occur with low efficiency and with no stereoselectivity. The carbohydrate residues in this system appear, therefore, to be too remote from the reaction site for controlling its diastereoselectivity, in contrast with Myers's tighter molecular system which makes use of a chiral oxazoline as a carboxyl surrogate.[5a]

The results reported herein illustrate the strong dependence of the stereochemistry of the internal coupling process on the relative position of the two substituted benzoyl groups within the carbohydrate framework. The very high diastereoselectivity observed in the reactions of substrates **3**, **9**, and **12** implies that a considerable degree of preorganization already exists in the starting hexopyranosides. The recently published X-ray crystal structure of compound **5**, prepared by Itoh and coworkers[5c] by the esterification of the corresponding glucose diol with racemic hexamethoxydiphenoic acid, is particularly revealing in that respect: the diphenoyl ester linkages adopt in **5** a near-(*Z*)-*syn* conformation, i.e., a conformation strongly reminiscent of that of the starting benzoates. It is indeed well-established, from numerous crystal structure determinations,[20] that benzoyl groups at secondary positions in hexopyranosides adopt preferentially a (*Z*)-*syn* conformation[21] (see Figure 1) whether the group is in equatorial or axial disposition. This interpretation is consistent with the results of Feldman's molecular mechanics calculations[1d] on model 2,3-di-O-galloyl glucopyranosides and coupling products: while a

(20) Jeffrey, G. A.; Sundaralingam, M. *Adv. Carbohydr. Chem. Biochem.* **1985**, *43*, 203−421 and ref. cited.

(21) Fowler, P.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 269−287.



small energy difference was found between starting conformers leading to either atropisomers,[22] this difference increases along the reaction path, and the final epimers are more than 5 kcal/mol apart in energy in their most favorable conformation, namely the more stable *S*-epimer with the two ester linkages in a near (*Z*)-*syn* conformation and the *R*-epimer with one of the linkages in a near (*E*)-*syn* conformation. That the conformation of the starting benzoates in hexopyranosides is conserved in the final product is of considerable predictive usefulness: thus, the reactions of the D-*manno* and D-*galacto* substrates having both participating benzoyloxy groups in a (*Z*)-*syn* conformation were expected to lead to the (*R*) and (*S*)-atropisomer, respectively, as has been observed. Quite remarkably, the same degree of stereocontrol appears to be effective in internal couplings under such different mechanistic conditions as reductive and oxidative[3,4] C−C bond formation.

A similar preorganization appears to be operative when the groups are in position 4 and 6 of the glucopyranose system. In the other systems (**15**−**17**), the control of the stereoselectivity by the substrate is less efficient most probably as a result of a greater conformational flexibility around the C−O−C(O) bonds of the ester linkage.

Although the couplings are performed under conditions far remote from those of the biosynthetic process, our results provide further understanding of the structural requirements for highly diastereoselective coupling within carbohydrate units; they clearly illustrate the importance of conformational effects in the substrate, thus lending further experimental support for the "Schmidt−Haslam hypothesis" for ellagitannin biosynthesis.

(22) The (*R*)-atropisomer is generated in this system if one of the benzoyl groups is in the (*E*)-*syn* conformation.

Table 3. Ullmann Reactions of 15−19: Results[a]

substrate	coupling products, % yield (diast. ratio)	reduction product,[b] % yield
15	42 (53:47)[c]	58
16	90 (73:27)	10
17	89 (59:41)	11
18	56 (50:50)	44
19	40 (50:50)	60

[a] Product ratio determined by ^{1}H NMR. [b] I → H in starting material. [c] 2,4-Coupling and deiodination of gem at O-3.

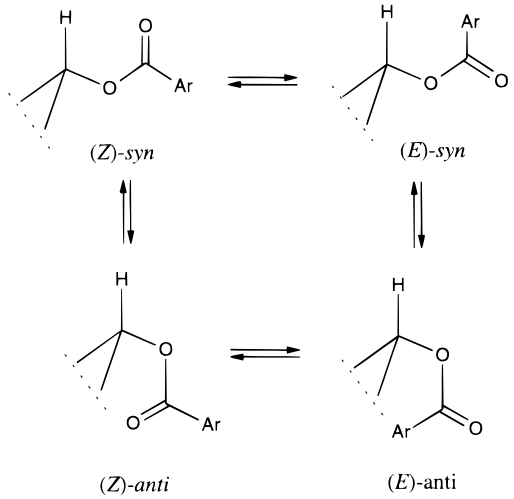


Figure 1. Conformations of benzoates about the H−C−O−C and C−O−C=O bonds.

Experimental Section

General procedures and methods of characterization have been described previously.[23] CD spectra were recorded on a Jasco J-20 ORD/UV-5 spectropolarimeter with a Sproul Scientific SS 15−2 CD modification or on a JASCO J-710 spectropolarimeter (University of Rochester).

Esterification Procedure. A mixture of diol (1 mmol), 2-iodo-3,4,5-trimethoxybenzoic acid[9] (2.05 mmol), DCC (2.1 mmol), and DMAP (0.3 mmol) in CH_2Cl_2 (10 mL) was stirred overnight at room temperature. The resulting solids were removed by filtration, and the solvent was evaporated in vacuo. Ether (20 mL) was added to the residue, the additional precipitate of DCU was removed by filtration, and the filtrate was concentrated. The product was purified by flash column chromatography (FCC).

Methyl 4,6-*O*-Benzylidene-2,3-bis-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (3). Prepared from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and purified by FCC (hexane−ethyl acetate 1.6:1); yield: 93%. $[\alpha]^{20}_D$ − 18.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.47, 3.71, 3.815, 3.82, 3.845, 3.86, 3.90 (7s, 7 × 3H, 7 OCH_3), 3.8−3.92 (m occluded by 5s, 2H, H-4, 6A), 4.06 (td, 1H, $J_{4,5} = J_{5,6A} = 9.8$, $J_{5,6B} = 4.8$ Hz, H-5), 4.37 (dd, 1H, $J_{6A,6B} = 10.3$ Hz, H-6B), 5.19 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 5.33 (dd, 1H, $J_{2,3} = 9.8$ Hz, H-2), 5.56 (s, 1H, PhCH), 6.00 (t, 1H, $J_{3,4} = 9.8$ Hz, H-3), 6.99 (s, 1H) and 7.37 (s, 1H) (2 ArH), 7.32−7.34 (m, 3H) and 7.47−7.50 (m, 2H) (Ph); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.2, 56.4, 60.9, 61.0, 62.5, 68.9, 70.8, 72.6, 79.1, 83.4, 84.9, 97.8, 101.6, 110.6, 111.9, 126.3, 128.2, 128.4, 129.1, 131.2, 136.9, 144.9, 145.7, 153.4, 153.5, 153.9, 154.0, 165.0, 166.0. Anal. Calcd for $C_{34}H_{36}I_2O_{14}$: C, 44.27; H, 3.93; I, 27.51. Found: C, 44.53; H, 4.37; I, 26.70.

Methyl 4,6-Bis-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-2,3-bis-*O*-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (6a). Prepared from methyl 2,3-bis-*O*-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside[5a] and purified by FCC (hexane−ethyl ac-

(23) Saavedra, O. M.; Martin, O. R. *J. Org. Chem.* **1996**, *61*, 6987−6993.

etate 3:2); yield: 96%. $[\alpha]^{20}_D$ +71.5 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.50 (s, 3H), 3.75 (s, 3H), 3.81−3.89 (several s, 27H), 3.93 (s, 3H), 3.96 (s, 3H) (13 OCH_3), 4.41 (ddd, 1H, $J_{4,5}$ = 9.9, $J_{5,6A}$ = 4.5, $J_{5,6B}$ = 1.9 Hz, H-5), 4.53 (dd, 1H, $J_{6A,6B}$ = 12.3 Hz, H-6A), 4.75 (dd, 1H, H-6B), 5.18 (dd, 1H, $J_{1,2}$ = 3.5, $J_{2,3}$ = 9.9 Hz, H-2), 5.30 (d, 1H, H-1), 5.78 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, H-4), 6.10 (t, 1H, H-3), 6.92 (s, 1H) and 7.44 (s, 1H) (2 ArH), 7.19 (s, 2H) and 7.27 (s, 2H) (2 ArH_2); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.2, 56.5, 60.4, 60.9, 61.0, 61.1, 63.6, 67.3, 69.4, 71.0, 72.5, 83.5, 84.1, 97.2, 107.2, 107.4, 110.2, 111.1, 123.9, 124.0, 130.4, 130.5, 142.8, 142.9, 145.1, 145.2, 153.0, 153.5, 153.9, 154.0, 165.5, 165.6, 166.0; HR−FABMS calcd for $C_{47}H_{52}I_2O_{22}$ *m/z* 1222.1039, found 1222.1063.

Methyl 2,3-Di-*O*-benzyl-4,6-bis-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (6b). Prepared from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[24] and purified by FCC (hexane−ethyl acetate 1:1); yield: 86.7%. $[\alpha]^{20}_D$ +3.6 (*c* 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.43, 3.65, 3.845, 3.855, 3.89, 3.90, 3.92 (7s, 7 × 3H, 7 OCH_3), 3.66 (occluded dd, 1H, H-2), 4.10 (t, 1H, $J_{2,3} \cong J_{3,4}$ = 9.8 Hz, H-3), 4.18 (ddd, 1H, $J_{4,5}$ = 10.2, $J_{5,6A}$ = 4.8, $J_{5,6B}$ = 2.3 Hz, H-5), 4.39 (dd, 1H, $J_{6A,6B}$ = 12.3 Hz, H-6A), 4.62 (dd, 1H, H-6B), ∼4.64 (d, 1H, *J* = 12.1 Hz) and 4.79 (d, 1H) (OCH_AH_BPh), 4.65 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.71 (d, 1H, *J* = 11.6 Hz) and 4.95 (d, 1H) (OCH_AH_BPh), 5.41 (t, 1H, H-4), 6.99 (s, 1H) and 7.38 (s, 1H) (2 ArH), 7.15−7.35 (m, 10H, 2 Ph); ^{13}C NMR ($CDCl_3$) δ 55.8, 56.2, 56.6, 60.8, 61.0, 63.9, 67.3, 71.2, 73.5, 75.3, 79.1, 79.8, 83.9, 84.0, 98.3, 110.5, 111.2, 127.3, 127.4, 128.0, 128.1, 128.2, 128.5, 130.5, 130.5, 137.9, 138.3, 145.0, 145.1, 153.4, 153.5, 153.8, 153.9, 165.2, 166.1. Anal. Calcd for $C_{41}H_{44}I_2O_{14}$: C, 48.54; H, 4.37; I, 25.02. Found: C, 48.65; H, 4.43; I, 25.12.

Methyl 4,6-Di-*O*-benzyl-2,3-bis-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-α-D-mannopyranoside (9). Prepared from methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside[25] and purified by FCC (hexane−ethyl acetate 2:1); yield: 93%. $[\alpha]^{20}_D$ −16.2 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.45, 3.49, 3.67, 3.82, 3.84, 3.85, 3.91 (7s, 7 × 3H, 7 OCH_3), 3.76−3.92 (m, 2H, H-6A, 6B), 3.99 (br d, 1H, $J_{4,5}$ = 9.9 Hz, H-5), 4.37 (t, 1H, $J_{3,4}$ = 9.8 Hz, H-4), 4.52 and 4.67 (2d, AB, 2H, *J* = 12.0 Hz, OCH_AH_BPh), 4.56 and 4.71 (2d, AB, 2H, *J* = 11.3 Hz, OCH_AH_BPh), 4.95 (s, 1H, H-1), 5.67 (narrow m, 1H, H-2), 5.81 (dd, 1H, $J_{2,3}$ = 3.2 Hz, H-3), 6.92 (s, 1H, 1 ArH), 7.16−7.19 (m, 5H, 4 PhH, 1 ArH), 7.26−7.33 (m, 6H, 6 PhH); ^{13}C NMR ($CDCl_3$) δ 54.9, 55.7, 60.5, 60.6, 60.7, 68.5, 71.1, 71.3, 72.8, 72.9, 73.4, 74.2, 83.3, 84.2, 98.1, 110.1, 111.3, 127.2, 127.3, 127.4, 127.6, 128.0, 128.1, 129.5, 130.9, 137.6, 137.7, 144.5, 145.2, 152.9, 153.0, 153.5, 153.7, 164.9, 165.2. Anal. Calcd for $C_{41}H_{44}I_2O_{14}$: C, 48.54; H, 4.37; I, 25.02. Found: C, 48.80; H, 4.53; I, 25.23.

Methyl 2,6-Di-*O*-benzyl-3,4-bis-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-α-D-galactopyranoside (12). Prepared from methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[26] and purified by FCC (hexane−ethyl acetate 3:1); yield 70%. $[\alpha]^{20}_D$ +34.9 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.47, 3.59, 3.65, 3.84, 3.85, 3.87, 3.91 (7s, 7 × 3H, 7 OCH_3), ∼3.62 (m, 2H, H-6A, 6B), 4.18 (dd, 1H, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.5 Hz, H-2), 4.33 (t, 1H, $J_{4,5} \cong 0$, $J_{5,6A} \cong J_{5,6B} \cong$ 6.1 Hz, H-5), 4.51 (AB, 2H, *J* = 11.9 Hz, OCH_AH_BPh), 4.65 (d, 1H, *J* = 12.5 Hz) and 4.75 (d, 1H) (AB, OCH_AH_BPh), 4.84 (narrow d, 1H, H-1), 5.76 (dd, 1H, $J_{3,4}$ = 3.3 Hz, H-3), 5.94 (narrow m, 1H, H-4), 7.04 (s, 1H) and 7.08 (s, 1H) (2 ArH), 7.23−7.31 (m, 10H, 2 Ph); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.1, 56.2, 60.8, 61.0, 61.1, 67.8, 68.7, 71.0, 71.2, 73.0, 73.6, 74.1, 83.6, 83.9, 98.6, 110.8, 111.2, 127.6, 127.7, 127.8, 127.9, 128.4, 128.5, 130.6, 131.3, 137.8, 138.0, 144.8, 145.2, 153.3, 153.8, 154.0, 165.5, 165.6. Anal. Calcd for $C_{41}H_{44}I_2O_{14}$: C, 48.54; H, 4.37; I, 25.02. Found: C, 48.63; H, 4.41; I, 25.51.

1,6-Anhydro-2,3,4-tris-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-α-D-glucopyranose (15). A suspension of 1,6-anhydro-β-D-glucopyranose (0.162 g, 1.0 mmol) in CH_2Cl_2 (12 mL) containing 2-iodo-3,4,5-trimethoxybenzoic acid (0.69 g, 2.05 mmol), DCC (0.452 g, 2.2 mmol), and DMAP (0.037 g) was stirred at room temperature for 24 h. The solids were then removed by filtration, and the solvent was evaporated. Ether (10 mL) was added, the insoluble fraction was removed by filtration, and the filtrate was concentrated. The residue was submitted twice to flash chromatography (hexane−ethyl acetate 2:1) which afforded pure **15** (0.62 g, 97% based on the benzoic acid): $[\alpha]^{20}_D$ −19.3 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.71, 3.72, 3.86, 3.86, 3.87, 3.90, 3.91, 3.92, 3.93 (9s, 9 × 3H, 9 OCH_3), ∼3.9 (occluded m, 1H, H-6A), 4.34 (d, 1H, $J_{6A,6B}$ = 7.9 Hz, H-6B), 4.89 (br d, 1H, $J_{5,6A}$ = 5.5 Hz, H-5), 5.10 (d, 1H), 5.17 (d, 1H) (H-2,4), 5.70 (t, 1H, $J_{2,3} \cong J_{3,4}$ = 3.6 Hz, H-3), 5.72 (s, 1H, H-1), 7.23, 7.24, 7.30 (3s, 3H, 3 ArH); ^{13}C NMR ($CDCl_3$) δ 56.3, 56.4, 60.8, 60.9, 61.0, 61.1, 66.5, 70.7, 72.1, 72.9, 74.8, 84.1, 84.3, 84.7, 100.0, 111.0, 111.2, 111.5, 129.1, 129.7, 129.8, 145.5, 145.6, 153.4, 153.6, 154.0, 165.0, 165.3, 165.4. HR−FABMS calcd for $C_{36}H_{37}I_3O_{17}$ *m/z* 1121.9164, found 1121.9114.

Methyl 3,6-Anhydro-2,4-bis-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (16). Prepared from methyl 3,6-anhydro-α-D-glucopyranoside[27] and purified by FCC (hexane−ethyl acetate 1:1); yield: 26%. $[\alpha]^{20}_D$ +34.2 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.48, 3.51, 3.56, 3.80, 3.82, 3.83, 3.84 (7s, 7 × 3H, 7 OCH_3), 4.11 (dd, 1H, $J_{5,6A}$ = 3.2, $J_{6A,6B}$ = 10.8 Hz, H-6A), 4.31 (d, 1H, $J_{5,6B}$ = 0, H-6B), 4.69 (t, 1H, $J_{4,5}$ = 2.9 Hz, H-5), 4.89 (t, 1H, $J_{2,3}$ = 4.0, $J_{3,4}$ = 5.3 Hz, H-3), 5.02 (dd, 1H, H-4), 5.19 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 5.42 (t, 1H, H-2), 6.72 (s, 1H), 7.21 (s, 1H) (2 ArH); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.1, 57.6, 60.7, 60.9, 68.7, 68.9, 70.5, 71.8, 73.3, 83.2, 84.1, 96.3, 110.3, 112.4, 128.9, 130.7, 144.6, 145.3, 152.8, 152.9, 153.7, 165.8, 166.1. HR−FABMS calcd for $C_{27}H_{30}I_2O_{13}$ *m/z* 815.9775, found 815.9772.

3-*O*-Benzyl-5,6-bis-*O*-(2-iodo-3,4,5-trimethoxybenzoyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (17). Prepared from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose and purified by FCC (hexane−ethyl acetate 3:1); yield: 93%. $[\alpha]^{20}_D$ −51.3 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32, 1.48 (2s, 2 × 3H, CMe_2), 3.74 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.89 (s, 6H) (6 OCH_3), 4.14 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-3), 4.58−4.66 (m, 4H, H-2,4, OCH_2Ph), 4.68 (dd, 1H, $J_{5,6A}$ = 6.4, $J_{6A,6B}$ = 12.4 Hz, H-6A), 4.95 (dd, 1H, $J_{5,6B}$ = 2.1 Hz, H-6B), 5.86 (m, 1H, H-5), 5.96 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 7.1 (s, 1H, ArH), 7.21−7.36 (m, 6H, Ph, ArH); ^{13}C NMR ($CDCl_3$) δ 26.3, 27.0, 56.4, 60.8, 61.0, 64.7, 70.1, 72.4, 78.6, 81.6, 81.9, 84.0, 84.1, 105.4, 111.2, 111.3, 112.1, 127.9, 128.0, 128.5, 130.5, 130.6, 137.1, 145.1, 145.2, 153.4, 153.4, 153.9, 153.9, 165.1, 165.9. HR−FABMS calcd for $C_{36}H_{40}I_2O_{14}$ *m/z* 950.0507, found: 950.0470.

3-*O*-(2-Iodo-3,4,5-trimethoxybenzoyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (18). Prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.39 g, 1.5 mmol), 2-iodo-3,4,5-trimethoxybenzoic acid (0.53 g, 1.58 mmol), DCC (0.37 g, 1.8 mmol), and DMAP (0.056 g) according to the general procedure; crude **18** was purified twice by flash chromatography (hexane−ethyl acetate 5:1). Yield: 0.848 g (97%). $[\alpha]^{20}_D$ −36.5 (*c* 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30, 1.35, 1.43, 1.56 (4s, 4 × 3H, 2 CMe_2), 3.88 (s, 6H), 3.92 (s, 3H) (3 OCH_3), 4.05−4.15 and 4.30−4.37 (2m, 4H, H-4,5,6A,6B), 4.75 (d, 1H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 0, H-2), 5.46 (d, 1H, $J_{3,4}$ = 2.3 Hz, H-3), 5.97 (d, 1H, H-1), 7.17 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 25.4, 26.3, 26.8, 26.9, 56.3, 60.9, 61.1, 67.5, 72.8, 77.7, 80.0, 83.3, 83.8, 105.3, 109.4, 110.8, 112.5, 130.7, 145.3, 153.5, 154.0, 165.4. HR−FABMS calcd for $C_{22}H_{29}IO_{10}$ *m/z* 580.0805, found 580.0780.

6-*O*-(2-Iodo-3,4,5-trimethoxybenzoyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (19). Prepared from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose as described for the preparation of **18** and purified by FCC (hexane−ethyl acetate 5:1); yield: 97%. $[\alpha]^{20}_D$ −32 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32, 1.35, 1.48, 1.51 (4s, 4 × 3H, 2CMe_2), 3.87, 3.88, 3.91 (3s, 3 × 3H, 3 OCH_3), 4.20 (ddd, 1H, $J_{4,5}$ = 1.8, $J_{5,6A}$ =

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7.9, $J_{5,6B}$ = 4.2 Hz, H-5), 4.34 (m, 2H, H-2,4), 4.43 (dd, 1H, $J_{6A,6B}$ = 11.6 Hz, H-6A), 4.55 (dd, 1H, H-6B), 4.65 (dd, 1H, $J_{2,3}$ = 7.9, $J_{3,4}$ = 2.4 Hz, H-3), 5.56 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 7.24, (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.0, 26.0, 26.2, 56.3, 60.8, 61.0, 64.7, 66.2, 70.6, 70.9, 71.2, 83.8, 96.4, 108.8, 109.8, 111.0, 131.2, 145.0, 153.4, 153.9, 166.4. Anal. Calcd for $C_{22}H_{29}IO_{10}$: C, 45.53; H, 5.04; I, 21.87. Found: C, 45.78; H, 5.14; I, 21.63.

Ullmann Reactions. General Procedure. A solution of acylated glycoside (0.5 mmol) in DMF (6 mL) was slowly added (syringe-pump) to refluxing DMF (6 mL) containing pretreated Cu[15] (4 mmol) over a period of 4−5 h. The reaction mixture was kept at reflux temperature for an additional period of 2 h. The solids were then removed by filtration through a pad of Celite, the solvent was evaporated in vacuo, and the residue was submitted to flash chromatography (hexane−ethyl acetate).

Methyl 4,6-*O*-Benzylidene-2,3-*O*-[(*S*)-4,4′,5,5′,6,6′-hexamethoxy-2,2′-diphenoyl]-α-D-glucopyranoside (5). Treatment of **3** with Cu as described in the general procedure (duration of addition: 1 h) gave compound **4**[28] and **5** in a 1.2:1 ratio (NMR). Separation of the components of the mixture by preparative TLC (ethyl acetate−hexane 1:2, multiple developments) afforded pure **5** in 40% yield. $[\alpha]^{20}_D$ +3.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.49, 3.61, 3.67, 3.89, 3.925, 3.93, 3.94 (7s, 7 × 3H, 7 OCH_3), 3.84, 3.87 (2t, 2H, $J \sim$ 10 Hz, H-4,6A), 3.99 (td, 1H, $J_{5,6A}$ = 4.6, $J_{4,5} \cong J_{5,6B} \cong$ 9.8 Hz, H-5), 4.33 (dd, 1H, $J_{5,6A}$ = 4.6, $J_{6A,6B}$ = 10.2 Hz, H-6B), 4.97 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.20 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 5.58 (s, 1H, PhCH), 6.64 (t, 1H, H-3), 6.77 (s, 2H, 2 ArH), 7.38−7.41 (m, 3H) and 7.50−7.53 (m, 2H) (Ph). HR−FABMS calcd for $C_{34}H_{36}O_{14}$ *m/z* 668.2103, found 668.2085.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-[(*S*)-4,4′,5,5′,6,6′-hexamethoxy-2,2′-diphenoyl]-α-D-glucopyranoside (7b). Treatment of **6b** with Cu as described in the general procedure afforded compound **7b** and **8b** in a 1:1 ratio (NMR). Separation of the components of the mixture by preparative TLC (ethyl acetate−hexane 1:3, multiple developments) afforded a sample of pure **7b**: $[\alpha]^{20}_D$ −44 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.38, 3.69, 3.76, 3.85, 3.87, 3.947, 3.955 (7s, 7 × 3H, 7 OCH_3), 3.62 (dd, 1H, $J_{1,2}$ = 3.8, $J_{2,3}$ = 9.2 Hz, H-2), 3.82 (br d, 1H, $J_{5,6A}$ < 1, $J_{6A,6B}$ = 12.9 Hz, H-6A), 3.97 (t, 1H, J = 9.5 Hz, H-3), 4.13 (br dd, 1H, $J_{4,5} \cong$ 10, $J_{5,6B}$ = 6.1 Hz, H-5), 4.51 (d, 1H, H-1), 4.63 (d, 1H, J_{AB} = 12.1 Hz) and 4.81 (d, 1H), 4.76 (d, 1H, J_{AB} = 11.9 Hz) and 4.89 (d, 1H) (2 OCH_AH_BPh), 4.92 (t, 1H, $J_{3,4} \cong J_{4,5} \cong$ 10 Hz, H-4), 5.04 (dd, 1H, H-6B), 6.54 (s, 1H) and 6.72 (s, 1H) (2 ArH), 7.21−7.35 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.0, 56.1, 60.8, 61.0, 61.1, 63.8, 67.0, 72.3, 73.8, 74.8, 79.2, 80.0, 99.0, 105.6, 105.7, 122.5, 123.3, 127.5, 128.0, 128.1, 128.3, 128.5, 128.6, 137.9, 138.6, 144.2, 144.7, 152.3, 152.4, 153.0 (2C), 166.9, 168.0. HR−FABMS calcd for $C_{41}H_{45}O_{14}$ ($[M + H]^+$) *m/z* 761.2809, found 761.2805.

Methyl 4,6-Di-*O*-benzyl-2,3-*O*-[(*R*)-4,4′,5,5′,6,6′-hexamethoxy-2,2′-diphenoyl]-α-D-mannopyranoside (10). Treatment of **9** with Cu as described in the general procedure and separation of the products by flash chromatography (ethyl acetate−hexanes 2:9) gave compounds **10** and **11** in 77% and 21% yield, respectively. Compound **10**: $[\alpha]^{20}_D$ −79.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.41, 3.51, 3.56, 3.83, 3.89, 3.95, 3.99 (7s, 7 × 3H, 7 OCH_3), 3.65 (ABX, 2H, H-6A,6B), 3.7−3.8 (m, 2H, H-4,5), 4.00 (d, 1H, J_{AB} = 11.0 Hz) and 4.19 (d, 1H) (OCH_AH_BPh), 4.47 (d, 1H, J_{AB} = 12.2 Hz) and 4.61 (d, 1H) (OCH_AH_BPh), 4.97 (narrow d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 5.12 (dd, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 5.32 (dd, 1H, $J_{3,4}$ = 8.5 Hz, H-3), 7.06 (s, 1H) and 7.57 (s, 1H) (2 ArH), 6.93 (m, 2H), 7.19 (m, 3H) and 7.28−7.35 (m, 5H) (2 Ph); ^{13}C NMR ($CDCl_3$) δ 55.0, 56.0, 56.2, 60.9, 61.0, 68.6, 69.3, 70.7, 72.7, 73.6, 74.6, 77.6, 77.9, 98.6, 105.4, 107.2, 111.0, 122.7, 123.9, 125.0, 127.6, 127.7, 127.8, 127.9, 128.3, 128.5, 129.4, 137.7, 138.1, 144.3, 146.6, 152.1, 152.4, 152.8, 165.6, 170.3. Anal. Calcd for $C_{41}H_{44}O_{14}$: C, 64.73; H, 5.83. Found: C, 64.68; H, 5.90.

Methyl 2,6-Di-*O*-benzyl-3,4-*O*-[(*S*)-4,4′,5,5′,6,6′-hexamethoxy-2,2′-diphenoyl]-α-D-galactopyranoside (13). Treatment of **12** with Cu as described in the general procedure and separation of the products by flash chromatography (ethyl acetate−hexanes 1:4) gave compounds **13** and **14** in 69% and 29% yield, respectively. Compound **13**: $[\alpha]^{20}_D$ +105.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.38, 3.56, 3.57, 3.92, 3.934, 3.95, 3.99 (7s, 7 × 3H, 7 OCH_3), 3.67 (d, 2H, $J_{5,6}$ = 6.3 Hz, H-6's), 3.76 (dd, 1H, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.3 Hz, H-2), 3.98 (d, 1H, J_{AB} = 12.1 Hz, OCH_AH_BPh), 4.20 (br t, 1H, H-5), 4.47 (d, 1H, H-1), 4.52 (d, 1H, OCH_AH_BPh), 4.56 (AB, 2H, J_{AB} = 12.0 Hz, OCH_2-Ph), 5.31 (narrow dd, 1H, $J_{3,4}$ = 3.0, $J_{4,5}$ = 1.4 Hz, H-4), 5.41 (dd, 1H, H-3), 6.87 (s, 1H) and 7.55 (s, 1H) (2 ArH), 7.07 (m, 2H) and 7.24−7.32 (m, 8H) (2 Ph); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.1, 56.3, 60.9, 61.1, 67.1, 68.6, 73.3, 73.6, 73.8, 75.5, 77.5, 99.2, 104.9, 110.8, 123.3, 123.7, 124.5, 127.7, 127.7, 128.0, 128.1, 128.4, 129.4, 137.8, 137.9, 144.2, 146.4, 152.3, 152.4, 152.7, 152.8, 165.9, 170.7. Anal. Calcd for $C_{41}H_{44}O_{14}$: C, 64.73; H, 5.83. Found: C, 64.83; H, 6.37.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research in its initial stage.

Supporting Information Available: Spectral data for compounds **4**, **8b**, **11**, and **14** (8 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.

JO971722K

(28) Data for the reduced products, **4**, **8b**, **11**, and **14**, are provided in Supporting Information.