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SYNTHESIS OF *C*-GLYCOSYLARENES BY WAY OF INTERNAL REACTIONS OF BENZYLATED AND BENZOYLATED CARBOHYDRATE DERIVATIVES*

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ABSTRACT

"Internal" *C*-glycosylarenes [*e.g.*, (2*R*,3*S*,3a*S*,9b*R*)-3,3a,5,9b-tetrahydro-3-methoxy- and -3,7-dimethoxy-2-methoxymethyl-2*H*-furo[3,2-*c*][2]benzopyran] were prepared by intramolecular reactions of 2-*O*-benzyl derivatives of methyl 3,5-di-*O*-methyl-D-xylofuranoside (**2**) and their conversion into authentic *C*-glycosylated aromatic systems was investigated. The auxiliary benzylic linkage could not be cleaved by hydrogenolysis; isochroman derivatives {*e.g.*, (3*S*)-3,4-dihydro-3-[(1*R*,2*R*)-2-hydroxy-1,3-dimethoxypropyl]-5-methoxy-1*H*-2-benzopyran} were obtained under these conditions. However, oxidation of the primary benzylic position with ruthenium tetraoxide gave the corresponding lactone {a dihydroisocoumarin derivative, *e.g.*, (2*R*,3*S*,3a*S*,9b*R*)-2,3,3a,9b-tetrahydro-3,7-dimethoxy-2-methoxymethyl-5*H*-furo[3,2-*c*][2]benzopyran-5-one} which could be opened by saponification, thereby leading to a stereochemically unique *C*-glycosylbenzoic acid derivative. The same type of lactone was obtained directly from a derivative of **2** bearing a sufficiently reactive benzoyl group at O-2 (3,5-dimethoxybenzoyl); this process provides a useful approach to a heterocyclic system present in a variety of natural products. In related studies, the 2-*O*-phenyl substituent was found to be much less reactive than the 2-*O*-benzyl group in intramolecular Friedel–Crafts reactions of 2-*O*-substituted glycofuranosides. The first examples of successful internal *C*-arylation in the pyranoid series were achieved from 2-*O*-(3-methoxybenzyl)-D-mannopyranosides; the resulting "internal *C*-glycosides" {(2*R*,3*S*,4*S*,4a*S*,10b*S*)-2,3,4,4a,6,10b-hexahydro-3,4,8-trimethoxy-2-methoxymethylpyrano[3,2-c][2]benzopyran and 3,4-bis(benzyloxy)-2-benzyloxymethyl-8-methoxy analog} contain a heterocyclic skeleton closely related to that of the natural product bergenin.

INTRODUCTION

C-Glycosylarenes[1] form a broad class of natural products derived from plants

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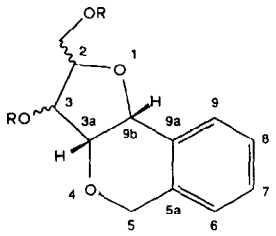
(*e.g.*, *C*-glycosylflavonoids) or microorganisms (*e.g.*, the gilvocarcins) that are characterized by the existence of a carbon–carbon linkage between the anomeric center of a carbohydrate unit and an aromatic component. Because of the difficulty of creating such a linkage, a great deal of effort has been dedicated to the stereoselective *C*-glycosylation of simple aromatic systems as models. Most of the methods reported so far are based on the reaction of a glycosyl halide or equivalent with an activated aromatic compound (Friedel–Crafts process)[2–10], or with an aromatic organometallic reagent[11–19], or more recently, on the palladium-mediated coupling of glycals with aromatic reagents[20,21]. Although usually acceptable in the glucopyranose series, the stereoselectivity of these processes is generally poor in the furanoid series, or the configuration of the major pseudoanomer cannot be easily predicted (see, for example, refs. 6 and 9). Our recent findings[22,23] on the behavior of benzylated sugars in the presence of a Lewis acid suggested a different approach to the stereoselective *C*-glycosylation of aromatic systems, namely by way of *intramolecular* reactions*. The internal *C*-arylation of benzylated pentofuranoses leads, for example, to a polycyclic system (**1**) in which the two heterocyclic components are necessarily *cis*-fused. The cleavage of the benzylic C-5–O-4 bond of this system would release a *C*-furanosylarene in which the aglycon group is exclusively in position *cis* with respect to O-2. The proposed method would ensure the complete control of the anomeric configuration of the final *C*-glycosyl compound.

We describe herein investigations on the reactivity of such ring systems as **1** under reductive and oxidative cleavage conditions, and on the internal alkylation of other electron-rich aromatic systems linked to O-2 of a furanoside, and we report the first successful internal *C*-arylations of benzylated hexopyranosides.

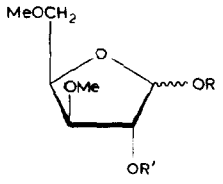
RESULTS AND DISCUSSION

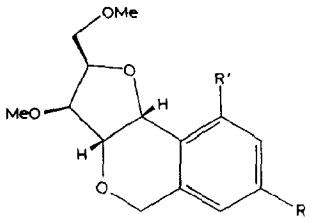
Furanoid series. — The xylofuranose system is particularly favorable for the study of internal *C*-glycosylations and related processes since derivatives selectively substituted at O-2 are readily available. Thus, methyl 3,5-di-*O*-methyl-D-xylofuranoside[25] (**2**) was used as the starting material for all the reactions of furanosides described in this article. The feasibility of the intramolecular Friedel–Crafts process in the D-xylofuranose series was tested on the 2-*O*-benzyl derivative of **2**, compound **3**. This derivative was found to be quite inert in the presence of tin(IV) chloride, as the starting material was recovered essentially unchanged after four days at room temperature. However, the corresponding glycosyl acetate **5** underwent rapidly internal *C*-arylation, leading to the tricyclic system **14** in 67% yield after 30 min under the same conditions (and to 13% of xylofuranose **4**), a behavior that is consistent with our earlier observations on the higher reactivity of glycosyl acetates in related reactions[23,26]. By contrast, the Lewis acid-catalyzed, cycli-

*We recently disclosed a novel and highly successful application of this concept to 2-*O*-arylsilylpentofuranosides (see ref. 24).



1 3, 3a, 5, 9b-Tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran ring system



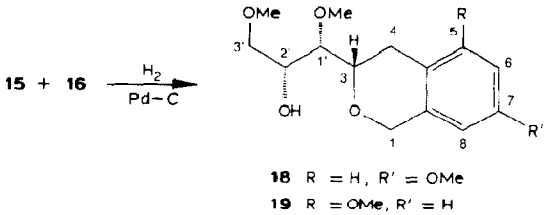


2 R = Me, R' = H
3 R = Me, R' = Bn
4 R = H, R' = Bn
5 R = Ac, R' = Bn
6 R = Me, R' = $CH_2C_6H_4(OMe\text{-}3)$
7 R = Me, R' = $CH_2C_6H_3(OMe_2\text{-}3,5)$
8 R = Me, R' = $COC_6H_4(OMe\text{-}3)$
9 R = Me, R' = $CH_2C_4H_3O(2)$
10 R = Me, R' = Ph
11 R = H, R' = Ph
12 R = Ac, R' = Ph
13 R = Me, R' = $COC_6H_3(OMe_2\text{-}3,5)$

14 R = R' = H
15 R = OMe, R' = H
16 R = H, R' = OMe
17 R = R' = OMe

alkylation takes place very effectively from the methyl glycoside when the substituent at O-2 is a more reactive 3-methoxybenzyl group. Thus, treatment of **6** with tin(IV) chloride rapidly gave the 7-methoxy analog of **14**, compound **15**, and a small proportion (~9%) of its 9-methoxy regioisomer **16**, in 85–90% overall yield. A further increase of the reactivity of the benzyl group is detrimental to the process; reaction of the 2-*O*-(3,5-dimethoxybenzyl)-D-xylofuranoside **7** with tin(IV) chloride led to an intractable mixture, probably resulting from the decomposition of the acid-sensitive *C*-glycosyl compound **17**. Evidence that the internal *C*-arylation actually takes place in this case was provided by the observation that methyl 2-*O*-(3,5-dimethoxybenzyl)-3,5-di-*O*-(3-methoxybenzyl)-D-xylofuranoside effectively undergoes tandem Friedel–Crafts reactions involving the groups at O-2 and O-3 and leading to tetracyclic systems (see ref. 26).

The signals, in the ^{1}H-n.m.r. spectrum, of the three aromatic protons of **15** and **16** form a pattern characteristic of 1,2,4- and 1,2,3-trisubstituted aromatic systems, respectively. In the spectrum of **14**, the signals of H-6 and H-9 ("ortho" protons; δ 7.04 and 7.51) are well differentiated from those of H-7 and H-8 (δ ~7.28). Furthermore, the spectra of **14–16** unequivocally established that a large

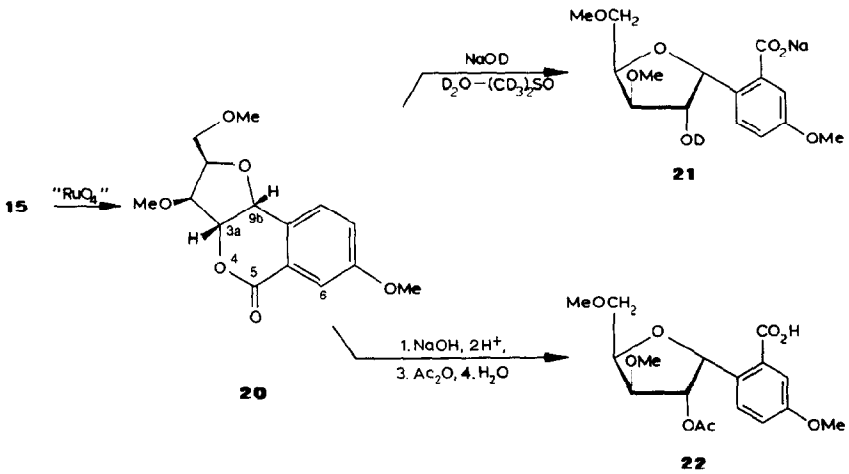


18 R = H, R' = OMe
19 R = OMe, R' = H

(absolute) value for the geminal coupling constant of the benzylic methylene group ($J_{5A,5B}$ 14.6–15.0 Hz for **14–16** *vs.* ~12 Hz for normal *O*-benzyl groups) is characteristic of the incorporation of this group in a cyclic system.

As the benzylic ether linkage of isochromans is known[27] to be much more resistant to reductive cleavage than acyclic benzyl ethers, the selective hydrogenolysis of the C-5–O-4 bond of **14** and **15**, in the presence of a secondary benzylic C–O bond (C-9b–O-1), was expected to be difficult; indeed, while no reaction occurred under conditions of catalytic-transfer hydrogenation (ammonium formate[28] or cyclohexadiene[29]; 10% Pd–C), 3-substituted isochroman derivatives such as **18** were obtained from **15** and related systems under standard hydrogenolysis conditions. The constitution of **18** was readily identified by comparing the n.m.r. spectra with those of closely related isochroman derivatives resulting from hydride-transfer reactions[30].

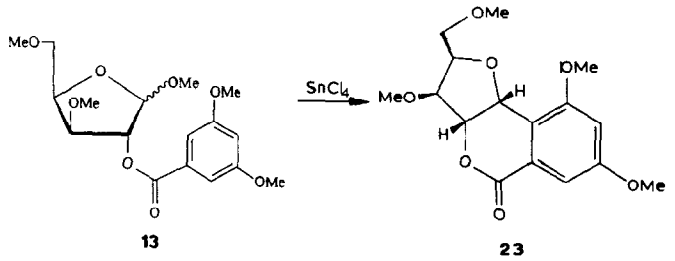
The cleavage of the auxiliary C–O linkage by way of an oxidative process was then investigated. Primary benzyl ethers can be converted into the corresponding esters with ruthenium(VIII) oxide[31,32], a procedure that has been applied occasionally to carbohydrate derivatives[33,34]. Although it proceeded slowly and required a larger excess of cooxidant, the oxidation of **15** with ruthenium(VIII) oxide afforded successfully lactone **20** in 40–55% yield. Interestingly, better yields were obtained in this case when the oxidation was performed in the absence of acetonitrile (see ref. 32). The selectivity of this oxidant for the primary benzylic position is quite remarkable, and products which might result from an oxidation at C-9b were formed only in traces. Compound **20**, a crystalline material exhibiting all of the expected spectral properties including shifted n.m.r.-signals for H-3a and H-6 ($\Delta\delta$ +0.76 and +1.08 p.p.m., respectively, with respect to the corresponding signals in the spectrum of **15**), is an obvious precursor of *C*-glycosylarenes. The lactone ring resisted attempts of cleavage by methanolysis but could be readily opened by saponification; treatment of **20** with sodium deuteroxide in a mixture of deuterium oxide and deuterated dimethylsulfoxide led rapidly to its complete conversion into the corresponding hydroxycarboxylate **21**, as indicated by ^{1}H-n.m.r. analysis. The cleavage of the acyl bond at O-2 (O-4–C-5 in **20**) and the radical change of conformation about the "*C*-glycosyl" linkage (which brings the carboxylate group in close proximity to H-1) were clearly demonstrated by the upfield shift of the signal for H-2 ($\Delta\delta$ −0.99 p.p.m.) and the downfield shift of that for H-1 ($\Delta\delta$ +0.30 p.p.m.), with respect to the corresponding signals for **20** (H-3a and H-9b) in the same solvent. As a result of the strong tendency of the free *C*-glycosylbenzoic acid to



relactonize and of its relatively high solubility in aqueous solution, its isolation was difficult; a sample of the 2-*O*-acetyl derivative **22** was obtained in 16% yield (containing ~21% of **20**) after saponification of **20** in 1,4-dioxane–aqueous sodium hydroxide, neutralization, extraction, and immediate acetylation of the resulting product. Compound **22** also regenerated slowly lactone **20** and could not be purified by chromatography. These results demonstrated, nevertheless, that *C*-glycosylarenes of well-defined anomeric configuration can be prepared by way of intramolecular Friedel–Crafts reactions of benzylated sugars.

As a result of the 1,2-*cis* configuration of the *C*-glycosylarene **22**, the ^{1}H-n.m.r. signal of its 2-*O*-acetyl group appeared at an unusually high field (δ 1.73); this chemical shift is characteristic of the *cis*-configuration and constitutes a particularly useful probe of the anomeric configuration of *C*-furanosylarenes which is usually difficult to determine by other means (see refs. 10 and 17).

Lactones such as **20** might be obtained directly from 2-*O*-benzoyl derivatives of the starting furanoside. To investigate this possibility, both the 2-*O*-(3-methoxybenzoyl) and the 2-*O*-(3,5-dimethoxybenzoyl) derivatives of **2** (compounds **8** and **13**) were prepared and treated with tin(IV) chloride. As expected, the 3-methoxybenzoyl substituent was not sufficiently reactive to undergo internal *C*-glycosylation under these conditions. The reaction of **13**, however, afforded successfully the corresponding dihydroisocoumarin derivative **23** (46% yield of

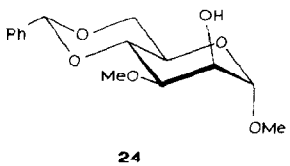


isolated product); although the cyclialkylation of **13** proceeded more slowly than that of benzyl derivatives, the process is particularly useful since it provides, in one step, a heterocyclic system present in a variety of natural products.

Two other types of electron-rich aromatic substituents at O-2 of a furanose derivative were examined, namely, the 2-furanmethyl and the phenyl groups. The 2-*O*-(2-furanmethyl) derivative of **2**, compound **9**, was prepared by alkylating **2** with the extremely reactive 2-furanmethyl chloride. The acid-sensitive substituent, however, did not survive the conditions of the internal *C*-glycosylation; treatment of **9** with tin(IV) chloride afforded rapidly the α-D anomer of **2** as the only product.

The phenyl substituent was readily introduced at O-2 of **2** by treating the oxyanion of **2** with diphenyliodonium chloride, an efficient reagent for the phenylation of inorganic and organic bases[35]. As no internal *C*-glycosyl compound was obtained from the reactions of the 2-*O*-phenyl glycoside **10** with a variety of Lewis acids [$SnCl_4$, $BF_3 \cdot Et_2O$, $Zn(OSO_2CF_3)_2$], compound **10** was converted into the corresponding glycosyl acetate **12**. However, both the acetate **12** (in the presence of $SnCl_4$) and the glycosyl bromide derived from **12** (in the presence of $ZnBr_2$) failed to give the expected tricyclic product. All reactions were performed under relatively mild conditions (room temperature, no large excess of Lewis acid) to avoid the conversion of the substrate into a benzofuran, a well-known reaction of β-phenoxyacetals in the presence of a Lewis acid[36]. Thus, in spite of the apparent higher reactivity of the *O*-phenyl group, the internal *C*-glycosylation of this group is more difficult than that of the 2-*O*-benzyl group. We suggest that this behavior is due not only to a more strained transition state of the internal electrophilic substitution, but also to an inefficient overlap of the nonbonding orbitals of the oxygen atom with the aromatic π-electrons system, in the reacting conformation, which results in a net deactivation of the aromatic component.

Pyranoid series. — As most naturally occurring *C*-glycosylarenes contain a pyranoid sugar, it was of particular interest to extend the scope of the internal *C*-arylation process to substituted hexopyranose derivatives. In the D-*gluco* series, derivatives of 1,6-anhydro-D-glucopyranose were considered to have a more appropriate structure than normal glucopyranosides for the internal reaction to take place; however, no tricyclic products were obtained from 1,6-anhydro-2,3,4-tri-*O*-benzyl-D-glucopyranose, nor from the apparently very favorably constituted tri-*O*-(3-methoxybenzyl) analog. We turned our attention to D-mannopyranose derivatives, from which a *C*-β-D-glycosyl linkage should be formed exclusively.



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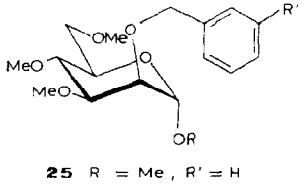
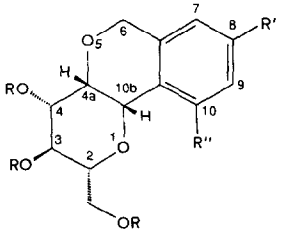
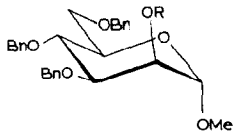


25 R = Me, R' = H
26 R = Ac, R' = H
27 R = Me, R = OMe





28 R = Me, R' = OMe, R'' = H
29 R = Bn, R' = OMe, R'' = H
30 R = Bn, R' = H, R'' = OMe

31 R = H
32 R = $CH_2C_6H_4(OMe-3)$

Model substrates **25–27** were prepared from a common precursor, compound **24**, which was obtained by regioselective methylation of the stannylidene derivative of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[37]. Neither glycosyl acetate **26** nor the corresponding tetra-*O*-benzyl derivative underwent internal alkylation of the benzyl group at O-2 under a variety of conditions [$SnCl_4$, $Me_3SiOSO_2CF_3$, $Zn(OSO_2CF_3)_2$]; other products were isolated such as, for example, the deacetylated starting material or the corresponding trehalose-type dimer. The lower reactivity of the pyranoid substrates was further demonstrated by the absence of reaction between the 2-*O*-(3-methoxybenzyl) mannopyranoside **27** and tin(IV) chloride, conditions which readily promoted the internal *C*-arylation of the xylofuranoside **6**. However, the cyclization took place on attempted hydrolysis of the glycosidic function of **27** under the (drastic) conditions described by Koto *et al.*[38] for the hydrolysis of related mannopyranosides (acetic acid–3M sulfuric acid, heat), leading to compound **28**, the first example of an internal *C*-glycosylarene in the pyranoid series, in 50% yield (isolated compound). The spectral characteristics of **28**, in particular the signals in the aromatic region of its ^{1}H-n.m.r. spectrum and the large geminal coupling constant of the benzylic methylene group ($J_{6A,6B}$ 15.1 Hz), unambiguously established its tricyclic structure.

In order to be able to further elaborate the final product, for example, into analogs of the natural product bergenin[39], the same process was applied to the tri-*O*-benzyl analog of **27**, compound **32**. The versatile precursor of **32**, compound **31**, was obtained by regioselective benzylation of the corresponding 4,6-di-*O*-benzyl derivative in the presence of a Cu(II) salt, as described recently by Eby *et al.*[40]. The internal Friedel–Crafts reaction of **32** proceeded efficiently, leading to both para and ortho substitution products **29** and **30** (9:2 ratio) in 75–80% overall yield. The behavior of these mannopyranose derivatives thus demonstrate that the internal *C*-arylation process is very effective also in the pyranose series, provided that the aromatic component is sufficiently reactive.

In conclusion, the intramolecular *C*-arylation of 2-*O*-benzylated and -benzoylated sugars leads to polycyclic systems which constitute precursors of several types of natural products. Furthermore, as a consequence of the internal process, the polycyclic systems are stereochemically unique and their cleavage leads to *C*-

glycosylarenes having exclusively the 1,2-*cis*-configuration. This sequence provides a useful method for the stereocontrolled synthesis of *C*-furanosylarenes.

EXPERIMENTAL

General methods. — See ref. 23. Optical rotations were measured with a Perkin–Elmer 243 automatic polarimeter for solutions in a 0.1-dm cell at 22 ±3°. The following solvent systems were used for chromatography: (*A*) hexanes; (*B*) 3:1, (*C*) 2:1, (*D*) 1:1, (*E*) 2:3, (*F*) 1:2, (*G*) 1:3, and (*H*) 1:5 hexanes–ether; (*J*) 20:1, (*K*) 7:3, and (*L*) 1:1 hexanes–ethyl acetate.

*Methyl 3,5-di-*O*-methyl-α- and -β-*D*-xylofuranoside* (**2**). — To a stirred solution of 1,2-*O*-isopropylidene-α-D-xylofuranose[41] (2.0 g, 10.53 mmol) in a mixture of dry toluene (18 mL) and dry *N,N*-dimethylformamide (6 mL) was added hexane-washed NaH (1.62 g, 67.5 mmol) and, after 8 min, methyl iodide (2.6 mL, 41.7 mmol). The mixture was stirred for 1 h at room temperature. Methanol (4 mL) was then carefully added, followed by toluene (15 mL), and the mixture was extracted with water (2 × 25 mL), dried ($MgSO_4$), and concentrated to give essentially pure 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-α-D-xylofuranose[42] (1.93 g, 84%), syrup, $[\alpha]_D^{22}$ −46.4° (*c* 1.25, water); n_D 1.4421; lit.[42] $[\alpha]_D$ −46.9° (*c* 2.1, water); n_D 1.4432.

Methanolysis of 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-α-D-xylofuranose (2.8 g, 12.8 mmol) in 2.5% methanolic H_2SO_4 (30 mL) for 1 h at reflux temperature gave, after neutralization of the solution with methanol-washed Amberlite IR-400 (OH^-) ion-exchange resin, removal of the resin by filtration, and evaporation of the filtrate, compound **2** (ref. 25; 2.23 g, 91%) as a mixture of anomers. This material was used without further purification or separation in subsequent experiments.

*Methyl 2-*O*-benzyl-3,5-di-*O*-methyl-α- and -β-*D*-xylofuranoside* (**3**). — To a stirred solution of **2** (1.0 g, 5.2 mmol) in a mixture of dry toluene (12 mL) and dry *N,N*-dimethylformamide (4 mL) was added hexane-washed NaH (0.483 g, 20.1 mmol) and, after 10 min, benzyl chloride (1.73 mL, 14.9 mmol). The mixture was stirred for 24 h at room temperature. Methanol (4 mL) was then added, followed by toluene (10 mL), and the mixture was extracted with water (2 × 20 mL), dried ($MgSO_4$), and concentrated. The residue was submitted to column chromatography (*B*) which afforded pure fractions of α-**3** and β-**3**, as well as a mixture of the two anomers (total yield 1.15 g, 78%). β Anomer: syrup, $[\alpha]_D^{22}$ −42° (*c* 0.98, chloroform), t.l.c. (*F*) R_F 0.41; α anomer: syrup, $[\alpha]_D^{22}$ +88° (*c* 1.2, chloroform); t.l.c. (*B*) R_F 0.33; mixture of anomers: ν_{max}^{film} 2920, 2830, 1450, 1195, 1105, 1055, 735, and 695 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 3.48 (s, 9 H, 3 OCH_3), 3.5–4.6 (several m, 5 H, H-2–5), 4.70 (s, 2 H, OCH_2Ph), 4.88 (d, 0.5 H, $J_{1,2}$ 4 Hz, H-1α), 5.00 (d, 0.5 H, $J_{1,2}$ ~1 Hz, H-1β), and 7.47 (s, 5 H, C_6H_5).

Anal. Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.58; H, 7.68.

*1-*O*-Acetyl-2-*O*-benzyl-3,5-di-*O*-methyl-α- and -β-*D*-xylofuranose* (**5**). — Hydrolysis of **3** (1:1, v/v, 1,4-dioxane–0.5M aqueous HCl, reflux, 3 h) and acetyla-

tion of the resulting syrupy 2-*O*-benzyl-3,5-di-*O*-methyl-D-xylofuranose (**4**) [R_F (*F*) 0.38] under standard conditions afforded **5** as a mixture of anomers, syrup, $[\alpha]_D^{22}$ +13.8° (*c* 0.8, chloroform), t.l.c. (*F*) R_F 0.37 and 0.40; ν_{max}^{film} 2920, 1735 (C=O), 1450, 1365, 1230, 1090, 1005, 735, and 690 cm^{-1}; ^{1}H-n.m.r. (60 MHz, ~85% β anomer): δ 2.11 (s, 3 H, $COCH_3$), 3.38 and 3.45 (2 s, 2 × 3 H, 2 OCH_3), 3.5–4.7 (several m, 5 H, H-2–5), 4.75 (s, 2 H, OCH_2Ph), 6.29 (s, 1 H, H-1), and 7.48 (s, 5 H, C_6H_5); m.s.: *m/z* 91 (100%), 205 (22), 163 (14), 43 (14), 45 (12), 101 (10), 71 (9), 92 (8), 144 (8), 143 (8), . . . 219 (2 [M − C_7H_7]$^+$).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.78; H, 7.27.

(2R,3S,3aS,9bR)-3,3a,5,9b-Tetrahydro-3-methoxy-2-methoxymethyl-2H-furo[3,2-c][2]benzopyran (**14**). — To a solution of **5** (118 mg, 0.38 mmol) in anhydrous dichloromethane (4 mL) was added a M solution of $SnCl_4$ in dichloromethane (0.07 mL, 0.07 mmol). After 30 min at room temperature, dichloromethane (10 mL) was added, followed by saturated aqueous $NaHCO_3$ (30 mL). The organic phase was separated, washed with water (10 mL), dried ($MgSO_4$), and concentrated. The residue was submitted to column chromatography (*C*) which afforded **14** (63.6 mg, 67%), as well as a small amount (13 mg, 13%) of xylofuranose **4**. Compound **14**: syrup, $[\alpha]_D^{22}$ −51° (*c* 1.0, chloroform), t.l.c. (*F*) R_F 0.51; ν_{max}^{film} 2900, 1445, 1370, 1195, 1100, 1065, 975, 940, 920, 870, 800, and 740 cm^{-1}; ^{1}H-n.m.r. (250 MHz): δ 3.39 and 3.49 (2 s, 2 × 3 H, 2 OCH_3), 3.61 and 3.68 (ABX, 2 H, $J_{2,2'A}$ 5.8, $J_{2,2'B}$ 6.8, $J_{2'A,2'B}$ 10.2 Hz, H-2'A,2'B), 3.93 (d, 1 H, $J_{2,3}$ 4.1, $J_{3,3a}$ ~0 Hz, H-3), 4.28 (d, 1 H, $J_{3a,9b}$ 3.4 Hz, H-3a), 4.39 (br. q, 1 H, H-2), 4.64 and 4.77 (AB, 2 H, $J_{5A,5B}$ 14.6 Hz, H-5A,5B), 4.86 (d, 1 H, H-9b), 7.04 (m, 1 H, H-6), 7.28 (m, 2 H, H-7,8), and 7.51 (m,1 H, H-9); m.s.: *m/z* 45 (100%), 117 (55), 131 (40), 118 (31), 173 (31), 103 (29), 116 (27), 71 (27), 132 (25), 145 (25), . . . 250 (1, [M]$^+$).

Anal. Calc. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.24. Found: C, 66.94; H, 7.42.

Methyl 2-O-(3-methoxybenzyl)-3,5-di-O-methyl-α- and -β-D-xylofuranoside (**6**). — Compound **2** (454 mg, 2.36 mmol) was treated with 3-methoxybenzyl chloride (1.9 mol. equiv.) in a mixture of toluene (20 mL) and *N,N*-dimethylformamide (10 mL) in the presence of NaH (3.3 mol. equiv.) for 30 min at 75–80°. Processing as described for the preparation of **3** afforded, after column chromatography (*D*), 548 mg (74%) of compound **6** (mixture of anomers), syrup, t.l.c. (*E*) R_F 0.55 and 0.62; ν_{max}^{film} 2920, 2830, 1600, 1585, 1490, 1455, 1265, 1190, 1110, 1050, 780, and 690 cm^{-1}; ^{1}H-n.m.r. (360 MHz, α/β ~1:1): δ 3.36 (s, 1.5 H), 3.39 (s, 1.5 H), 3.405 (s, 1.5 H), 3.41 (s, 3 H) and 3.42 (s, 1.5 H) (3 OCH_3), 3.46 (dd, 0.5 H, $J_{4,5A}$ 7.9, $J_{5A,5B}$ 10.8 Hz, H-5Aα), 3.56 (dd, 0.5 H, $J_{4,5B}$ 3.3 Hz, H-5Bα), 3.57 (dd, 0.5 H, $J_{4,5A}$ 7.5, $J_{5A,5B}$ 10.5 Hz, H-5Aβ), 3.65 (dd, 0.5 H, $J_{4,5B}$ 4.2 Hz, H-5Bβ), 3.810 and 3.812 (2 s, 3 H, $ArOCH_3$), 3.835 (dd, 0.5 H, $J_{2,3}$ 2.1, $J_{3,4}$ 5.9 Hz, H-3β), 3.91 (dd, 0.5 H, $J_{1,2}$ 4.2, $J_{2,3}$ 5.9 Hz, H-2α), 3.94 (br., 0.5 H, $J_{1,2}$ 1.3, $J_{2,3}$ 2.1 Hz, H-2β), 4.08 (dd, 0.5 H, $J_{3,4}$ 7.5 Hz, H-3α), 4.36 (td, 0.5 H, H-4α), 4.43 (ddd, 0.5 H, H-4β), 4.55–4.65 (2 AB, 2 H, 2 OCH_2Ar), 4.79 (d, 0.5 H, H-1α), 4.93 (d, 0.5 H, H-1β), 6.84 (dd, 1 H), 6.91 (m, 2 H), and 7.265 (dt, 1 H) ($MeOC_6H_4CH_2$); m.s.: *m/z* 121 (100%, [$MeOC_7H_6$]$^+$), 207 (73), 248 (69), 45 (60), 75 (54), 267 (36), 233 (31), 71 (26), 91 (22), 101 (21), . . . 281 (2 [M − MeO]$^+$).

Anal. Calc. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 62.11; H, 7.86.

(2R,3S,3aS,9bR)-3,3a,5,9b-Tetrahydro-3,7- (**15**) *and -3,-9-dimethoxy-2-methoxymethyl-2H-furo[3,2-c][2]benzopyran* (**16**). — Compound **6** (1.0 g, 3.2 mmol) was treated with $SnCl_4$ (1.06 mol. equiv.) in dichloromethane (50 mL) for 2 h at room temperature under N_2, and the mixture processed as described for the preparation of **14**. Column chromatography (*D*) of the crude product afforded **15** contaminated by a small amount (9%) of its position isomer **16**. Samples of pure **15** (466 mg, 52%) and **16** (44 mg, 5%) were obtained by low-pressure liquid chromatography (*F*). Compound **15**: syrup, $[\alpha]_D^{22}$ −12° (*c* 1.1, chloroform); t.l.c. (*G*) R_F 0.60; ν_{max}^{film} 2900, 2830, 1610, 1500, 1455, 1320, 1275, 1250, 1195, 1100, 1070, 1035, 980, 925, 855, 835, 805, and 595 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 3.39 and 3.48 (2 s, 2 × 3 H, 2 OCH_3), 3.60 and 3.66 (ABX, 2 H, $J_{2,2'A}$ 6.7, $J_{2,2'B}$ 5.9, $J_{2'A,2'B}$ 10.0 Hz, H-2'A,2'B), 3.78 (s, 3 H, $ArOCH_3$), 3.92 (d, 1 H, $J_{2,3}$ 3.75, $J_{3,3a}$ ~0 Hz, H-3), 4.23 (br. d, 1 H, $J_{3a,9b}$ 2.9 Hz, H-3a), 4.39 (br. q, 1 H, H-2), 4.61 and 4.73 (AB, 2 H, $J_{5A,5B}$ 14.6 Hz, H-5A,5B), 4.82 (d, 1 H, H-9b), 6.56 (d, 1 H, $J_{6,8}$ 2.5 Hz, H-6), 6.83 (dd, 1 H, $J_{8,9}$ 8.4 Hz, H-8), and 7.41 (d, 1 H, H-9); ^{13}C-n.m.r. (90 MHz): δ 55.23 ($ArOCH_3$), 58.35, 59.12 (2 OCH_3), 66.90, 70.61 (C-2',5), 72.70, 78.91, 79.00, 85.80 (C-2,3,3a,9b), 108.81, 113.42 (C-6,8), 123.36 (C-9a), 131.75 (C-9), 135.67 (C-5a), and 159.24 (C-7); m.s.: *m/z* 162 (100%), 45 (90), 203 (59), 175 (54), 147 (52), 134 (43), 148 (36), 178 (34), 91 (32), 161 (31), . . . 280 (17, $[M]^+$).

Anal. Calc. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.68; H, 7.29.

Compound **16**. — Syrup, $[\alpha]_D^{22}$ −11° (*c* 1.0, chloroform); t.l.c. (*G*) R_F 0.54; ^{1}H-n.m.r. (360 MHz): δ 3.39 and 3.48 (2 s, 2 × 3 H, 2 OCH_3), 3.63 (dd, 1 H, $J_{2,2'A}$ 5.85, $J_{2'A,2'B}$ 10.0 Hz, H-2'A), 3.73 (dd, 1 H, $J_{2,2'B}$ 6.7 Hz, H-2'B), 3.86 (s, 3 H, $ArOCH_3$), 3.92 (d, 1 H, $J_{2,3}$ 4.2, $J_{3,3a}$ ~0 Hz, H-3), 4.18 (br. d, 1 H, $J_{3a,9b}$ 2.5 Hz, H-3a), 4.42 (dt, 1 H, H-2), 4.63 (d, 1 H, $J_{5A,5B}$ 15.0 Hz, H-5A), 4.78 (d, 1 H, H-5B), 5.01 (d, 1 H, H-9b), 6.63 (d, 1 H, *J* 7.5 Hz), and 6.77 (d, 1 H, *J* 8.4 Hz) (H-6,8), and 7.23 (t, 1 H, H-7); ^{13}C-n.m.r. (90 MHz): δ 55.61 ($ArOCH_3$). 58.39, 59.12 (2 OCH_3), 66.50 (C-2'), 69.01, 70.36, 78.81, 78.84, 85.07 (C-2,3,3a,5,9b), 109.06, 115.96 (C-6,8), 119.63 (C-9a), 129.18 (C-7), 135.94 (C-5a), and 158.97 (C-9).

Methyl 2-O-(3,5-dimethoxybenzyl)-3,5-di-O-methyl-α- and -β-D-xylofuranoside (**7**). — Compound **2** (210 mg, 1.1 mmol) was treated with 3,5-dimethoxybenzyl chloride[43] as described for the preparation of **6**. Column chromatography (*B*) of crude **7** afforded pure fractions of α-**7** and β-**7**, as well as a mixture of anomers (total yield 220 mg, 59%). β Anomer: syrup, $[\alpha]_D^{22}$ −22.9° (*c* 0.7, chloroform); t.l.c. (*F*) R_F 0.26. α Anomer: syrup, $[\alpha]_D^{22}$ +74° (*c* 0.9, chloroform); t.l.c. (*F*) R_F 0.20. Mixture of anomers: ν_{max}^{film} 2920, 2830, 1590, 1460, 1365, 1290, 1200, 1150, 1100, 1055, 1020, 840, 828, and 818 cm^{-1}; ^{1}H-n.m.r. (500 MHz, α/β 2:3): δ 3.36, 3.39, 3.405, 3.41, 3.42 (5 s, 9 H, 3 OCH_3), 3.46 (dd, 0.6 H, $J_{4,5A}$ 7.4, $J_{5A,5B}$ 10.8 Hz, H-5Aα), 3.55 (dd, 0.6 H, $J_{4,5B}$ 3.4 Hz, H-5Bα), 3.57 (dd, 0.4 H, $J_{4,5A}$ 7.4, $J_{5A,5B}$ 10.1 Hz, H-5Aβ), 3.645 (dd, 0.4 H, $J_{4,5B}$ ~4.5 Hz, H-5Bβ), 3.79 (s, 6 H, 2 $ArOCH_3$), 3.83 (dd, 0.4 H, $J_{2,3}$ 2.0, $J_{3,4}$ 5.4 Hz, H-3β), 3.91 (dd, 0.6 H, $J_{1,2}$ 4.7, $J_{2,3}$ 5.4 Hz, H-2α), 3.94 (br. s, 0.4 H, $J_{1,2}$ <0.8 Hz, H-2β), 4.08 (t, 0.6 H, $J_{3,4}$ 7.4 Hz,

H-3α), 4.36 (td, 0.6 H, H-4α), 4.42 (m, 0.4 H, H-4β), 4.55 and 4.75 (2 AB, 2 H, *J* 12.1 Hz, OCH_2Ar α,β), 4.79 (d, 0.6 H, H-1α), 4.92 (s, 0.4 H, H-1β), 6.39, 6.50, and 6.53 (3 narrow d, 3 H, *J* 2 Hz, Ar).

Anal. Calc. for $C_{17}H_{26}O_7$: C, 59.63; H, 7.65. Found: C, 59.46; H, 7.49.

(3S)-3,4-Dihydro-3-[(1R,2R)-2-hydroxy-1,3-dimethoxypropyl]-7- (**18**) *and -5-methoxy-1H-2-benzopyran* (**19**). — The mixture of regioisomers (**15** and **16**) resulting from the reaction of **6** with $SnCl_4$ was dissolved in ethanol and hydrogenolyzed with H_2 in the presence of 10% Pd–C for 1 h at room temperature and under atmospheric pressure. The catalyst was removed by filtration, the filtrate concentrated, and the residue separated by preparative t.l.c. to afford the 7-methoxyisochroman derivative **18** and its 5-methoxy regioisomer **19** in 54% overall yield. Compound **18**: syrup, t.l.c. (*G*) R_F 0.22; ν_{max}^{film} 3450 (OH), 2930, 2840, 1617, 1505, 1455, 1270, 1085 (br.), 1032, 960, 920, 850, 800, and 725 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 2.58 (dd, 1 H, $J_{3,4pro\text{-}R}$ 2.9, $J_{4pro\text{-}R,4pro\text{-}S}$ 15.6 Hz, H-4*pro-R*), 2.88 (dd, 1 H, $J_{3,4pro\text{-}S}$ 11.3 Hz, H-4*pro-S*), 3.28 (t, 1 H, $J_{3,1'}$ 4.7, $J_{1',2'}$ 3.6 Hz, H-1'), 3.34 (s, 3 H, OCH_3), 3.455 (AB of ABX, 2 H, $J_{2',3'A} \approx J_{2',3'B} \approx 6$ Hz, H-3'A,3'B), 3.545 (s, 3 H, OCH_3), 3.70 (s, 3 H, $ArOCH_3$), 3.83 (ddd, 1 H, H-3), 3.96 (td, 1 H, H-2'), 4.74 (AB, 2 H, $J_{1A,1B}$ 15.0 Hz, H-1A,1B), 6.45 (d, 1 H, $J_{6,8}$ 2.4 Hz, H-8), 6.67 (dd, 1 H, $J_{5,6}$ 8.4 Hz, H-6), and 6.965 (d, 1 H, H-5); ^{13}C-n.m.r. (90 MHz; assignment by ^{1}H–^{13}C correlations): δ 29.22 (C-4), 55.26 ($ArOCH_3$), 59.11 and 61.22 (2 OCH_3), 68.50 (C-1), 70.26 (C-2'), 73.73 (C-3'), 76.33 (C-3), 82.28 (C-1'), 108.82 (C-8), 112.83 (C-6), 124.92 (C-4a), 129.92 (C-5), 135.32 (C-8a), and 157.89 (C-7); m.s.: *m/z* 45 (100%), 135 (63), 134 (30), 207 (18), 91 (16), 43 (13), 190 (10), 162 (9), 136 (7), 147 (7), . . . 282 (0.1 $[M]^+$).

Compound **19**: t.l.c. (*G*) R_F 0.27; ^{1}H-n.m.r. (360 MHz): δ 2.69 (AB of ABX, 2 H, $J_{3,4pro\text{-}R}$ ~4, $J_{3,4pro\text{-}S}$ ~11, $J_{4pro\text{-}R,4pro\text{-}S}$ ~16 Hz, H-4*pro-R*,4*pro-S*), 3.30 (t, 1 H, $J_{3,1'}$ 4.3, $J_{1',2'}$ ~4 Hz, H-1'), 3.34 (s, 3 H, OCH_3), 3.47 (AB of ABX, 2 H, $J_{2',3'A} \approx J_{2',3'B} \approx 6$ Hz, H-3'A,3'B), 3.56 (s, 3 H, OCH_3), 3.76 (s, 3 H, $ArOCH_3$), 3.82 (td, 1 H, H-3), 4.02 (dt, 1 H, H-2'), 4.75 (AB, 2 H, $J_{1A,1B}$ 14.9 Hz, H-1A,1B), 6.54 (d, 1 H, *J* 7.6 Hz) and 6.63 (d, 1 H, *J* 8.1 Hz), (H-6,8), and 7.07 (t, 1 H, H-7).

(2R,3S,3aS,9bR)-2,3,3a,9b-Tetrahydro-3,7-dimethoxy-2-methoxymethyl-5H-furo[3,2-c][2]benzopyran-5-one (**20**). — To a solution of crude **15** (3.0 g, containing ~30% of chromatographically undistinguishable **6**) in carbon tetrachloride (200 mL) was added ruthenium(IV) oxide hydrate (732 mg, 5.5 mmol) and then a solution of $NaIO_4$ (9.88 g) in water (100 mL), and the mixture was stirred efficiently at room temperature. Additional $NaIO_4$ (9.88 g) in water (50 mL) was added after 24 h, and again after 48 h. After 72 h, the mixture was filtered twice through a Celite pad. 2-Propanol was then added to the filtrate until its color changed from purple to orange. The aqueous phase was separated, the organic phase extracted with 5% aqueous Na_2SO_3 (50 mL), dried ($MgSO_4$), and concentrated. The residue was submitted to liquid chromatography (*C* then *D*) which afforded **20** (1.21 g; 38%, 55% with respect to **15** only), m.p. 103–104° (ether–hexanes), $[\alpha]_D^{22}$ −33.6° (*c* 0.51, chloroform; 1-dm cell), t.l.c. (*G*) R_F 0.35; ν_{max}^{KBr} 2940, 1740 (C=O), 1620, 1595,

1510, 1465, 1370, 1330, 1280, 1210, 1130, 1100, 1080, 1030, 850, and 775 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 3.39 and 3.50 (2 s, 2 × 3 H, 2 OCH_3), 3.62 (m, 2 H, H-2′A,2′B), 3.87 (s, 3 H, $ArOCH_3$), 4.18 (d, 1 H, $J_{2,3}$ 4.1, $J_{3,3a}$ <0.8 Hz, H-3), 4.50 (~q, 1 H, $J_{2,2'A} \approx J_{2,2'B} \approx 6$ Hz, H-2), 4.99 (d, 1 H, $J_{3a,9b}$ 3.0 Hz, H-3a), 5.03 (d, 1 H, H-9b), 7.18 (dd, 1 H, $J_{6,8}$ 2.8, $J_{8,9}$ 8.4 Hz, H-8), 7.43 (d, 1 H, H-9), and 7.64 (d, 1 H, H-6); ^{13}C-n.m.r. (90 MHz; assignments by ^{1}H–^{13}C correlations): δ 55.64 ($ArOCH_3$), 58.83 and 59.18 (2 OCH_3), 70.75 (C-2′), 71.40 (C-9b), 80.18 (C-2), 81.64 (C-3a), 85.12 (C-3), 113.04 (C-6), 121.82 (C-8), 125.01, 127.52 (C-5a, 9b), 130.95 (C-9), 160.75 (C-7), and 162.98 (C-5); m.s.: *m/z* 45 (100%), 71 (46), 191 (36), 73 (31), 161 (19), 148 (15), 192 (14), 193 (12), 176 (11), 120 (10), 217 (10), . . . 294 (1, $[M]^+$).

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found; C, 61.36; H, 6.15.

*Sodium 2-[3,5-di-*O*-methyl-α-*D*-(2-*O*-^{2}H)-xylofuranosyl]-5-methoxybenzoate* (**21**). — Lactone **20** (35 mg) was dissolved in di($^2H_3$)methyl sulfoxide (0.75 mL)–deuterium oxide (0.5 mL), and the ^{1}H-n.m.r. spectrum of **20** in this solvent system was recorded [360 MHz; reference $(C^2H_3)_2SO$ signal, δ 2.50]: δ 3.22 and 3.40 (2 s, 2 × 3 H, 2 OCH_3), ~3.41 (dd, 1 H, $J_{2,2'A}$ 7.5, $J_{2'A,2'B}$ 10.6 Hz, H-2′A), 3.53 (dd, 1 H, $J_{2,2'B}$ 4.1 Hz, H-2′B), 3.81 (s, 3 H, $ArOCH_3$), 4.15 (d, 1 H, $J_{3,3a}$ <0.5, $J_{2,3}$ 4.4 Hz, H-3), 4.24 (ddd, 1 H, H-2), 4.95 (d, 1 H, $J_{3a,9b}$ 2.8 Hz, H-9b), 5.23 (~d, 1 H, H-3a), 7.30 (dd, 1 H, $J_{8,9}$ 8.4, $J_{6,8}$ 2.6 Hz, H-4′), 7.45 (d, 1 H, H-6), and 7.55 (d, 1 H, H-9).

A 10% solution of sodium deuteroxide in deuterium oxide (0.1 mL) was then added to the solution of **20**. After 1 h at room temperature, all of the lactone **20** had been converted into the corresponding *C*-glycosylated benzoate **21**; ^{1}H-n.m.r. (same conditions as above): δ 3.23 and 3.29 (2 s, 2 × 3 H, 2 OCH_3), 3.39 (dd, 1 H, $J_{4,5A}$ 7.4, $J_{5A,5B}$ 10.3 Hz, H-5A), 3.52 (dd, 1 H, $J_{4,5B}$ 4.1 Hz, H-5B), 3.67 (s, 3 H, $ArOCH_3$), 3.71 (d, 1 H, $J_{3,4}$ ~3.5 Hz, H-3), 4.24 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-2), 4.36 (ddd, 1 H, H-4), 5.25 (d, 1 H, H-1), 6.79 (dd, 1 H, $J_{3',4'}$ 8.5, $J_{4',6'}$ ~2.7 Hz, H-4′), 6.84 (d, 1 H, H-6′), and 7.22 (d, 1 H, H-3′). Acidification of the solution with deuterium chloride in deuterium oxide rapidly promoted the relactonization of **21** into **20**.

*2-(2-*O*-Acetyl-3,5-di-*O*-methyl-α-*D*-xylofuranosyl)-5-methoxybenzoic acid* (**22**). — Compound **20** (171 mg, 0.58 mmol) was saponified in a homogeneous mixture of 1,4-dioxane (5 mL) and 5% aqueous NaOH (1 mL) for 1.5 h at room temperature. Dichloromethane (10 mL) and water (2 mL) were then added and the mixture was carefully acidified to pH 4–5 (indicator) with 0.1M aqueous HCl. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The organic phases were combined and dried (Na_2SO_4). Acetic anhydride (1 mL) and 4-*N*,*N*-dimethylaminopyridine (70 mg) were then added and the mixture was stirred for 1 h at room temperature. The solution was then extracted rapidly with cold 0.1M aqueous HCl, washed with water, dried and concentrated to afford 36 mg (16%) of a compound (containing ~20% of lactone **20**) tentatively identified as the mixed anhydride of **22** and acetic acid. On exposure to moist air, this com-

pound was completely converted into **22** (containing ~21% of lactone **20**). Compound **22**: ν_{max}^{film} 2800–3400 (OH) and 1730 cm^{-1} (C=O); ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 1.73 (s, 3 H, $OCOCH_3$), 3.44 and 3.53 (2 s, 2 × 3 H, 2 OCH_3), 3.68 (AB of ABX, $\Delta\delta_{AB}$ very small, 2 H, H-5A,5B), 3.84 (s, 3 H, $ArOCH_3$), 3.89 (d, 1 H, $J_{2,3}$ ~0, $J_{3,4}$ 4.1 Hz, H-3), 4.53 (ddd, 1 H, H-4), 5.79 and 6.06 (2 d, $J_{1,2}$ 3.4 Hz, H-1,2), 7.07 (dd, 1 H, $J_{3',4'}$ 8.7, $J_{4',6'}$ 2.8 Hz, H-4'), 7.55 (d, 1 H, H-6'), and 7.72 (d, 1 H, H-3'); m.s.: *m/z* 45 (100, $[CH_2OCH_3]^+$), 43 (80, $[CH_3CO]^+$), 163 (43), 231 (34), 87 (18), 71 (17), 179 (16), 41 (13), 263 (13, $[M - CH_3OH - CH_3CO_2]^+$), 101 (10), . . . 309 (0.1, $[M - CH_2OCH_3]^+$, 355 (0.05, $[M + H]^+$). Because of its tendency to lactonize, compound **22** could not be purified by chromatographic methods.

*Methyl 2-*O*-(3-methoxybenzoyl)-3,5-di-*O*-methyl-α- and -β-*D*-xylofuranoside* (**8**). — To a solution of **2** (101 mg, 0.53 mmol) in pyridine (6 mL) was added 3-methoxybenzoyl chloride (0.18 mL, 1.3 mmol) and 4-*N*,*N*-dimethylaminopyridine (13.4 mg, 0.11 mmol). The mixture was stirred for 2 h at room temperature. Chloroform (10 mL) was then added, the mixture extracted with M aqueous HCl, washed with saturated aqueous $NaHCO_3$ (5 mL), and then with water (5 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue submitted to column chromatography (*A*) which afforded **8** (49.5 mg, 29%), syrup, $[\alpha]_D^{22}$ +95° (*c* 1.1, chloroform, α anomer mostly), t.l.c. (*F*) R_F 0.70; ν_{max}^{film} 2960, 2850, 1735, 1610, 1595, 1495, 1470, 1460, 1435, 1290, 1265, 1230, 1100, 1045, 1025, and 755 cm^{-1}.

Anal. Calc. for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 58.93; H, 6.92.

*Methyl 2-*O*-(3,5-dimethoxybenzoyl)-3,5-di-*O*-methyl-α- and -β-*D*-xylofuranoside* (**13**). — Compound **2** (5 mmol) was treated with 3,5-dimethoxybenzoyl chloride (5 mmol) in dichloromethane (10 mL) in the presence of 4-*N*,*N*-dimethylaminopyridine (5 mmol) (1 h). Processing of the mixture as described for the preparation of **8** afforded a nearly quantitative yield of **13** (α/β 1:1), syrup, t.l.c. (*B*) R_F 0.41; ν_{max}^{film} 2940, 2850, 1735 (C=O), 1605, 1465, 1435, 1360, 1335, 1310, 1235, 1210, 1160, 1110, 1065 (br.), and 765 cm^{-1}; ^{1}H-n.m.r. (360 MHz, α/β 29:21) (α anomer): δ 3.37, 3.44, 3.48 (3 s, 3 × 3 H, 3 OCH_3), 3.57 (dd, 1 H, $J_{4,5A}$ 7.1, $J_{5A,5B}$ 10.6 Hz, H-5A), 3.64 (dd, 1 H, $J_{4,5B}$ 3.6 Hz, H-5B), 3.84 (s, 6 H, 2 $ArOCH_3$), 4.30 (dd, 1 H, $J_{2,3}$ 5.4, $J_{3,4}$ 6.9 Hz, H-3), 4.435 (td, 1 H, H-4), 5.09 (dd, 1 H, $J_{1,2}$ 4.5 Hz, H-2), 5.27 (d, 1 H, H-1), 6.67 (t, 1 H, *J* 2.3 Hz), and 7.21 (d, 2 H) (3 ArH); (β anomer): δ 3.44, 3.47, 3.52 (3 s, 3 × 3 H, 3 OCH_3), 3.645 (dd, 1 H, $J_{4,5A}$ 7.5, $J_{5A,5B}$ 10.4 Hz, H-5A), 3.71 (dd, 1 H, $J_{4,5B}$ 4.5 Hz, H-5B), 3.83 (s, 6 H, 2 $ArOCH_3$), 3.90 (~d, 1 H, $J_{2,3}$ <1, $J_{3,4}$ 5.4 Hz, H-3), 4.50 (ddd, 1 H, H-4), 5.06 (~s, 1 H, $J_{1,2}$ <1 Hz, H-2), 5.34 (~s, 1 H, H-1), 6.675 (t, 1 H, *J* 2.3 Hz), and 7.16 (d, 2 H) (3 ArH); m.s. *m/z* 45 (100), 165 (85), 75 (37), 101 (35), 137 (22), 122 (17), 41 (13), 166 (11), 107 (9), 71 (9), . . . 356 (0.1, $[M]^+$).

(2R,3S,3aS,9bR)-2,3,3a,9b-Tetrahydro-3,7,9-trimethoxy-2-methoxymethyl-5H-furo[3,2-c][2]benzopyran-5-one (**23**). — Compound **13** (100 mg, 0.28 mmol) was treated with $SnCl_4$ (0.3 mL of a M solution in dichloromethane, 0.3 mmol) in

anhydrous dichloromethane (2 mL) for 15 h at room temperature, and the mixture processed as described for the preparation of **14**. The final products were separated by preparative t.l.c. (1:4 ethyl acetate–toluene) which afforded 35 mg (35%) of recovered starting material and 27 mg (46% with respect to starting material consumed) of **23**, m.p. 84–85°, $[\alpha]_D^{22}$ −18.3° (*c* 0.6, chloroform), t.l.c. (*L*) R_F 0.36; ν_{max}^{KBr} 2940, 2870, 1740 (C=O), 1620, 1470, 1335, 1240, 1210, 1145, 1095, 1065, 1045, 1015, 945, 850, and 775 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 3.39 and 3.50 (2 s, 2 × 3 H, 2 OCH_3), 3.64 (AB of ABX, 2 H, $J_{2,2'A}$ 6.7, $J_{2,2'B}$ 5.6, $J_{2'A,2'B}$ 10.1 Hz, H-2'A,2'B), 3.86 (s, 6 H, $ArOCH_3$), 4.16 (dd, 1 H, $J_{2,3}$ 4.0, $J_{3,3a}$ 1.1 Hz, H-3), 4.47 (ddd, 1 H, H-2), 4.95 (dd, 1 H, $J_{3a,9b}$ 3.1 Hz, H-3a), 5.31 (d, 1 H, H-9b), 6.69 (d, 1 H, $J_{6,8}$ 2.4 Hz, H-8), and 7.22 (d, 1 H, H-6); ^{13}C-n.m.r. (90 MHz): δ 55.76, 55.98 ($ArOCH_3$), 58.81, 59.19 (OCH_3), 66.34 (C-9b), 70.59 (C-2'), 79.94 (C-2), 81.73 (C-3a), 84.88 (C-3), 103.78, 104.75 (C-6,8), 117.25 (C-9a), 125.77 (C-5a), 158.65, 161.59 (C-7,9), and 163.18 (C-5).

Anal. Calc. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.34; H, 6.86.

*Methyl 2-O-(2-furanmethyl)-3,5-di-O-methyl-α- and -β-*D*-xylofuranoside* (**9**). — Unstable 2-furanmethyl chloride was prepared according to Lukes and Dienstbierova[44] (caution: may decompose explosively[44]) and used immediately for the preparation of **9**. Reaction of **2** (522 mg, 2.72 mmol) with NaH (98 mg, 4.1 mmol) and then with 2-furanmethyl chloride (629 mg, 5.4 mmol) for 30 min at room temperature in a mixture of dry toluene (30 mL) and dry *N,N*-dimethylformamide (15 mL) afforded, after processing (see preparation of **6**) and flash chromatography (*F*), compound **9** (339 mg, 46%; mixture of anomers), syrup, t.l.c. (*H*) R_F 0.56 and 0.64; ν_{max}^{film} 2950, 2880, 1470, 1380, 1225, 1185, 1140, 1090, 945, and 780 cm^{-1}.

Anal. Calc. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 56.95; H, 7.20.

*Methyl 3,5-di-O-methyl-2-O-phenyl-α- and -β-*D*-xylofuranoside* (**10**). — To a solution of **2** (679 mg, 3.5 mmol) in dry toluene (9 mL)–dry *N,N*-dimethylformamide (3 mL) was added pentane-washed NaH (280 mg, 11.7 mmol), and the mixture was stirred for 5 min at room temperature. Diphenyliodonium chloride (Aldrich) (1.10 g, 3.5 mmol) was then added and the mixture heated at 62° for 18 h. Excess NaH was then destroyed by the addition of methanol (5 mL) to the cooled mixture. Toluene (10 mL) was added, the mixture extracted with water (2 × 25 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (*C*) which afforded pure fractions of α-**10** and β-**10**, and a mixture of anomers (total: 661 mg, 70%). β Anomer: syrup, $[\alpha]_D^{22}$ −32° (*c* 1.1, chloroform), t.l.c. (*F*) R_F 0.53. α Anomer: syrup, $[\alpha]_D^{22}$ +117° (*c* 0.9, chloroform), t.l.c. (*F*) R_F 0.41. Mixture of anomers: ν_{max}^{film} 2920, 2820, 1595, 1585, 1490, 1230, 1190, 1100 (br.), 1050 (br.), 750, and 690 cm^{-1}; ^{1}H-n.m.r. (360 MHz, α/β ~1:3): δ 3.39, 3.42, 3.43, and 3.45 (4 s, 9 H, 3 OCH_3), 3.56 (dd, 0.25 H, $J_{4,5A}$ 7.0, $J_{5A,5B}$ 10.7 Hz, H-5Aα), 3.63 (dd, 0.25 H, $J_{4,5B}$ 3.6 Hz, H-5Bα), 3.64 (dd, 0.75 H, $J_{4,5A}$ 7.4, $J_{5A,5B}$ 10.2 Hz, H-5Aβ), 3.71 (dd, 0.75 H, $J_{4,5B}$ 4.9 Hz, H-5Bβ), 3.98 (dd, 0.75 H, $J_{2,3}$ 1.6, $J_{3,4}$ 5.7 Hz, H-3β), 4.28 (dd, 0.25 H, $J_{2,3}$ 5.7, $J_{3,4}$ 7.0 Hz, H-3α), 4.45 (dt, 0.25 H, H-4α),

4.52 (td, 0.75 H, H-4β), 4.64 (dd, 0.25 H, $J_{1,2}$ 4.5 Hz, H-2α), 4.67 (br. s, 0.75 H, H-2β), 4.95 (s, 0.75 H, H-1β), 5.13 (d, 0.25 H, H-1α), 6.97 (m, 3 H), and 7.30 (m, 2 H), (OC_6H_5); m.s.: *m/z* 163 (100%), 131 (68), 75 (63), 45 (52), 223 (43), 115 (16), 77 (16), 101 (15), 164 (11), 85 (11), . . . 268 (4, $[M]^+$).

Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.46; H, 7.45.

1-O-Acetyl-3,5-di-O-methyl-2-O-phenyl-α- and -β-D-xylofuranose (**12**). — A solution of **10** (500 mg, 1.86 mmol) in 1,4-dioxane (10 mL)–0.5M aqueous HCl (10 mL) was heated under reflux for 5 h. Dichloromethane (30 mL) was then added, the organic phase separated, washed with water (2 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was submitted to column chromatography (*G*) which afforded syrupy 3,5-di-*O*-methyl-2-*O*-phenyl-D-xylofuranose (**11**) (357 mg, 75%), $[\alpha]_D^{22}$ +9.8° (*c* 0.82, chloroform), t.l.c. (*F*) R_F 0.28. Compound **11** (217 mg, 0.85 mmol) was acetylated under standard conditions (acetic anhydride–pyridine). Column chromatography (*D*) of the crude acetate afforded syrupy **12** (222 mg, 87%) as a mixture of anomer, t.l.c. (*F*) R_F 0.33 and 0.37; ^{1}H-n.m.r. (60 MHz; mostly β anomer): δ 2.13 (s, 3 H, $OCOCH_3$), 3.46 and 3.52 (2 s, 6 H, 2 OCH_3), 3.73 (~d, 2 H, 2 H-5), ~4.06 (d, 1 H, $J_{2,3}$ ~1, $J_{3,4}$ ~5 Hz, H-3), ~4.6 (m, 1 H, H-4), 4.90 (br. s, 1 H, H-2), 6.33 (s, 1 H, H-1), and 6.95–7.65 (m, 5 H, OC_6H_5); m.s.: *m/z* 43 (100%), 45 (66), 149 (39), 191 (25), 131 (25), 94 (23), 87 (20), 163 (17), 77 (17), 101 (11), . . . 296 (7, $[M]^+$).

Anal. Calc. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.81. Found: C, 60.73; H, 6.83.

1-O-Acetyl-2-O-benzyl-3,4,6-tri-O-methyl-α-D-mannopyranoside (**26**). — Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside[37] (**24**) (2.96 g, 10 mmol) was benzylated under standard conditions (see preparation of **3**) to afford methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside (2.24 g, 58%). Methanolysis of this compound (2.23 g, 5.8 mmol) in methanolic HCl under reflux (see ref. 37) afforded methyl 2-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside (1.97 g, 83%). This compound (1.17 g, 3.9 mmol) was methylated (NaH–methyl iodide in *N,N*-dimethylformamide) to give methyl 2-*O*-benzyl-3,4,6-tri-*O*-methyl-α-D-mannopyranoside (**25**) [0.58 g, 45%, after purification by column chromatography (*B*); $[\alpha]_D^{22}$ +15.6° (*c* 1.0, chloroform)]. Hydrolysis of **25** (213 mg, 0.65 mmol) under the conditions described by Koto *et al.*[38] and acetylation of the resulting 2-*O*-benzyl-3,4,6-tri-*O*-methyl-D-mannopyranose (acetic anhydride–pyridine) gave compound **26** [89.8 mg, 39% from **25**, after purification by flash chromatography (*D*)], syrup, $[\alpha]_D^{22}$ +28.5° (*c* 1.3, chloroform), t.l.c. (*G*) R_F 0.67; ν_{max}^{film} 2920, 2830, 1755 (C=O), 1455, 1375, 1230, 1155, 1110, 1015, 960, 790, 740, and 695 cm^{-1}; ^{1}H-n.m.r. (500 MHz): δ 2.055 (s, 3 H, $OCOCH_3$), 3.34, 3.395 and 3.54 (3 s, 3 × 3 H, 3 OCH_3), 3.46 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 9.4 Hz, H-3), 3.58 (t, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 3.60 (d, 2 H, $J_{5,6}$ 3.7 Hz, 2 H-6), 3.695 (dt, 1 H, H-5), 3.73 (dd, 1 H, $J_{1,2}$ 2.0 Hz, H-2), 4.69 and 4.76 (AB, 2 H, *J* 12.5 Hz, OCH_2Ph), 6.185 (d, 1 H, H-1), and 7.25–7.42 (m, 5 H, C_6H_5); m.s.: *m/z* 91 (100%), 101 (94), 102 (25), 43 (21), 177 (19), 45 (14), 71 (12), 87 (12), 115 (9), 135 (8), . . . 263 (0.4, $[M - C_7H_7]^+$), and 295 (0.2, $[M - CH_3CO_2]^+$).

Methyl 2-O-(3-methoxybenzyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside (**27**). — Compound **27** was prepared from **24** by way of the same sequence of reactions as that described above for the preparation of **26**, with the substitution of 3-methoxybenzyl chloride for benzyl chloride. Compound **27** was purified by column chromatography (*J*), syrup, $[\alpha]_D^{22}$ +16.7° (*c* 0.7, chloroform), t.l.c. (*F*) R_F 0.40; ν_{max}^{film} 2920, 2830, 1600, 1585, 1490, 1460, 1380, 1265, 1120, 1090 (br.), 1055, 970, 780, 745, and 695 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 3.28 (s, 3 H), 3.40 (s, 6 H), and 3.50 (s, 3 H) (4 OCH_3), 3.75 (s, 3 H, $ArOCH_3$), 3.43–4.5 (several m, 6 H, H-2–6), 4.63 (br. s, 3 H, H-1, OCH_2Ar), and 6.6–7.3 (m, 4 H, Ar).

(2R,3S,4S,4aS,10bS)-2,3,4,4a,6,10b-Hexahydro-3,4,8-trimethoxy-2-methoxymethylpyrano[3,2-c][2]benzopyran (**28**). — A solution of **27** (156 mg, 0.44 mmol) in acetic acid (3 mL)–3M aqueous H_2SO_4 (3 mL) was heated at 90° for 3 h. The mixture was then cooled to room temperature. Water (20 mL) was added, the mixture extracted with dichloromethane (3 × 20 mL), the organic phases were combined and washed with aqueous $NaHCO_3$ (3 × 20 mL), then with water (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (*L*) which afforded **28** (70.7 mg, 50%), m.p. 131.4–131.6°, $[\alpha]_D^{22}$ −26.5° (*c* 0.4, chloroform), t.l.c. (*F*) R_F 0.33; ν_{max}^{KBr} 2980, 2940, 2900, 2830, 1615, 1510, 1465, 1325, 1270, 1117, 1098, 1087, 1022, 988, 855, 840, 825, 810, 798, and 790 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 3.36 (s, 3 H), 3.57 (s, 6 H) and 3.77 (s, 3 H) (4 OCH_3), 3.45–3.70 (several m, 5 H, H-2–4, H_2-2′), 3.99 (br. d, 1 H, $J_{4a,10b}$ ~0, $J_{4,4a}$ ~2 Hz, H-4a), 4.20 (s, 1 H, H-10b), 4.75 (d, 1 H, $J_{6A,6B}$ 15.1 Hz, H-6A), 5.00 (d, 1 H, H-6B), 6.54 (d, 1 H, $J_{7,9}$ 2.3 Hz, H-7), 6.79 (dd, 1 H, $J_{9,10}$ 8.3 Hz, H-9), and 7.30 (d, 1 H, H-10); m.s: *m/z* 205 (100%), 89 (77), 162 (73), 45 (69), 161 (50), 134 (44), 206 (26), 91 (25), 135 (22), 74 (22), . . . 324 (4, $[M]^+$).

Anal. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.61; H, 7.15.

Methyl 3,4,6-tri-O-benzyl-2-O-(3-methoxybenzyl)-α-D-mannopyranoside (**32**). — Compound **31** (600 mg, 1.29 mmol), prepared by selective benzylation of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside in the presence of $CuCl_2$ as described by Eby *et al.*[40] was treated with 3-methoxybenzyl chloride (253 mg, 1.6 mmol) in the presence of NaH (31 mg) in *N,N*-dimethylformamide (50 mL) for 24 h at room temperature. Processing of the mixture (see preparation of **3**) afforded, after column chromatography (*K*), **32** (669 mg, 89%), syrup, $[\alpha]_D^{22}$ +27° (*c* 1.0, chloroform), t.l.c. (*K*) R_F 0.56; ν_{max}^{film} 3070, 3040, 2910, 1605, 1590, 1492, 1458, 1365, 1265, 1100 (br.), 1055 (br.), 965, 780, 735, and 690 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 3.32 (s, 3 H, OCH_3), 3.73 (s, 3 H, $ArOCH_3$), 3.70–3.77 (m, 3 H, H-5,6), 3.79 (dd, 1 H, $J_{1,2}$ 1.9, $J_{2,3}$ 3.0 Hz, H-2), 3.88 (dd, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.97 (t, 1 H, $J_{4,5}$ ~9 Hz, H-4), 4.50 (d, 1 H, *J* 10.8 Hz) and 4.88 (d, 1 H), 4.55 (d, 1 H, *J* 12.1 Hz) and 4.66 (d, 1 H), 4.61 (s, 2 H), and 4.71 (s, 2 H) (4 OCH_2Ph), 4.78 (br. s, 1 H, H-1), 6.82 (m, 1 H), 6.95 (m, 2 H), and 7.15–7.36 (several m, 16 H) (3 C_6H_5, $MeOC_6H_4CH_2$); ^{13}C-n.m.r. (90 MHz): δ 54.52, 54.91 (2 OCH_3), 69.09 (C-6), 71.44, 71.88, 72.33, 73.15, 74.31, 74.72, 74.85, 80.02 (C-2–6, 4 OCH_2Ar), 98.78 (C-1), 112.88, 113.13, 119.87, 129.09 (Ar–CH of BnOMe-3), 127.25–128.12 (Ar–CH of Bn), 138.16,

138.26, 138.29, 139.76 (Ar–C), and 159.47 (*ipso*-C of BnOMe-3): m.s.: *m/z* 121 (100%), 91 (91), 45 (23), 122 (21), 89 (20), 137 (15), 65 (13), 107 (12), 77 (10), 195 (10), . . . 584 (0.1, $[M]^+$).

Anal. Calc. for $C_{36}H_{40}O_7$: C, 73.95; H, 6.90. Found: C, 73.72; H, 7.20.

(2R,3S,4S,4aS,10bS)-3,4-Bis(benzyloxy)-2-benzyloxymethyl-2,3,4,4a,6,10b-hexahydro-8-methoxypyrano[3,2-c][2]benzopyran (**29**). — Compound **32** (350 mg, 0.60 mmol) was added to acetic acid (50 mL)–3M aqueous H_2SO_4 (6 mL), and the mixture stirred at 80° for 1 h and at room temperature for 24 h. The acid was then neutralized with saturated aqueous $NaHCO_3$ and the mixture extracted with dichloromethane (4 × 40 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated, and the residue purified by flash chromatography (*K*) which afforded **29** (258 mg, 78%) containing ~18% of its unseparable "ortho" isomer **30**, syrup, $[\alpha]_D^{22}$ 0° (*c* 1.0, chloroform); t.l.c. (*K*) R_F 0.43; ν_{max}^{film} 3075, 3045, 2940, 2860, 1620, 1600, 1505, 1460, 1370, 1270, 1240, 1100, 1080, 1030, 735, and 695 cm^{-1}; ^1H-n.m.r. (360 MHz): δ 3.77 (s, 3 H, OCH_3), 3.60–3.85 (several m, 5 H, H-2,2'A,2'B,4,4a), 3.88 (t, 1 H, $J_{3,4} \approx J_{4,5} \approx 9.2$ Hz, H-3), 4.15 (s, 1 H, H-10b), 4.53 (s, 2 H), 4.78 (s, 2 H), 4.57 (d, 1 H, *J* 10.7 Hz), and 4.95 (d, 1 H) (3 OCH_2Ph), 4.69 (d, 1 H, $J_{6A,6B}$ 15.3 Hz, H-6A), 5.02 (d, 1 H, H-6B), 6.54 (d, 1 H, $J_{7,9}$ 2.5 Hz, H-7), 6.79 (dd, 1 H, $J_{9,10}$ 8.4 Hz, H-9), 7.22–7.34 (m, 14 H), and 7.41 (m, 2 H) (H-10, 3 C_6H_5); detectable signals of 10-methoxy isomer **30**: δ 4.31 (s, 1 H, H-10b), 5.05 (d, 1 H, $J_{6A,6B}$ 15.3 Hz, H-6B), 6.63 (d, 1 H, $J_{7,8}$ ~8 Hz), and 6.74 (d, 1 H) (H-7,9); ^{13}C-n.m.r. (90 MHz): δ 55.29 (OCH_3), 68.46, 69.84, 71.11, 71.81, 73.39, 73.63, 75.00, 75.32, 79.26, 81.85 (C-2–4a,2',6,10b, 3 OCH_2Ph), 108.51, 113.24 (C-7,9), 124.42 (C-10a), 127.25–128.41 (Ar–CH of Bn), 131.81 (C-10), 136.60, 138.22, 138.39 (Ar–C of Bn, C-6a), and 159.77 (C-8); m.s.: *m/z* 91 (100%), 162 (16), 175 (9), 92 (8), 149 (8), 161 (8), 134 (8), 135 (7), 163 (6), 65 (6), . . . 552 (0.6, $[M]^+$), 461 (0.5 $[M - C_7H_7]^+$).

Anal. Calc. for $C_{35}H_{36}O_6$: C, 76.06; H, 6.57. Found: C, 76.26; H, 6.48.

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