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Multiple and long-range participation of benzyl groups in intramolecular *C*-arylation reactions of benzylated glycosides*

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ABSTRACT

The intrinsic reactivity of furanosides bearing activated *O*-benzyl substituents (3-methoxybenzyl), in the presence of bidentate Lewis acids such as tin(IV) chloride, was explored. These glycosides were found to exhibit extremely interesting chemical properties. Thus, with three reactive substituents (at O-2,3,5), the corresponding glycosides (**1** and **7**) underwent a novel internal bis-*C*-arylation process, which involved successive alkylations of the benzyl groups at O-2 and O-3 ("multiple participation"), leading to the formal replacement of the two C–O bonds at the anomeric center of the glycoside by two C–C bonds. The bis-*C*-arylated constitution of the resulting polycyclic compounds **4** and **8**, and the *cis* configuration of their fused ring system (a tetrahydro-[2]benzopyrano[3,4-*d*][2]benzoxepin derivative), were determined on the basis of their n.m.r.-spectral parameters.

With two 3-methoxybenzyl substituents (at O-3 and O-5, compound **6**), intramolecular alkylation of the benzyl group at O-3 or O-5 occurred when glycoside **6** was reacted with titanium(IV) chloride or tin(IV) chloride, respectively, thereby leading to novel bicyclic internal aryl *C*-glycosides (**9** and **12**) as major products ("long-range participation"). The constitution of compounds **9** and **12** was unambiguously established by the reactions of analogs of **6** bearing only *one* 3-methoxybenzyl substituent at a specific position (at O-3: **15**; at O-5: **20**). The unexpected divergent behavior of **6** in the presence of titanium(IV) and tin(IV) chloride remains to be explained.

The availability of compound **9** made it possible to independently prepare the bis-*C*-arylated derivative **8** (by way of the reverse sequence of internal *C*-arylation reactions) and thereby to definitively demonstrate its constitution. These unprecedented reactions extend the scope of the intramolecular *C*-glycosidation of substituted sugars and provide novel methodologies in synthetic carbohydrate chemistry.

INTRODUCTION

Our investigations on Lewis acid-mediated reactions of benzylated glycosides revealed a rich and yet unsuspected chemistry of sugar derivatives bearing benzyl protecting groups. A number of novel and useful synthetic processes were thus uncovered, including the following:

(*i*) *The intramolecular alkylation of the benzyl group at O-2, which leads to*

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"internal" C-glycosyl compounds[1-4]. Originally reported with benzylated glycofuranosyl acetates as substrates[2,3], the process was recently shown to be also successful in the mannopyranose series, and could be extended[4] to glycosides bearing, at O-2, an activated benz*oyl* substituent, thereby leading to the basic skeleton of a variety of natural products. The concept of stereoselective *C*-glycosidation by way of an *intramolecular* reaction was elaborated into a highly effective method for the synthesis of *C*-furanosyl compounds with stereocontrol: the Lewis acid-mediated, internal reactions of 2-*O*-organosilyl furanosides (Glyc-O-$SiMe_2R$, where R = aryl, vinyl, and allyl) were found to provide the first reliable approach to *C*-furanosides of well-defined stereochemistry[5].

(*ii*) *The selective cleavage of benzyl groups at secondary positions.* The most useful reaction of this type is the tin(IV) chloride-mediated selective debenzylation at O-2 of methyl tri-*O*-(4-chlorobenzyl)-β-D-ribofuranoside, which leads to methyl 3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside in high yield[6]. Selectively protected α-D-ribofuranosides, which constitute important building blocks in nucleoside synthesis, thus became available in only three steps from D-ribose (55% overall yield). Selective debenzylations promoted by a bidentate Lewis acid such as tin(IV) chloride were subsequently investigated in detail by Ohrui, Meguro, and coworkers[7].

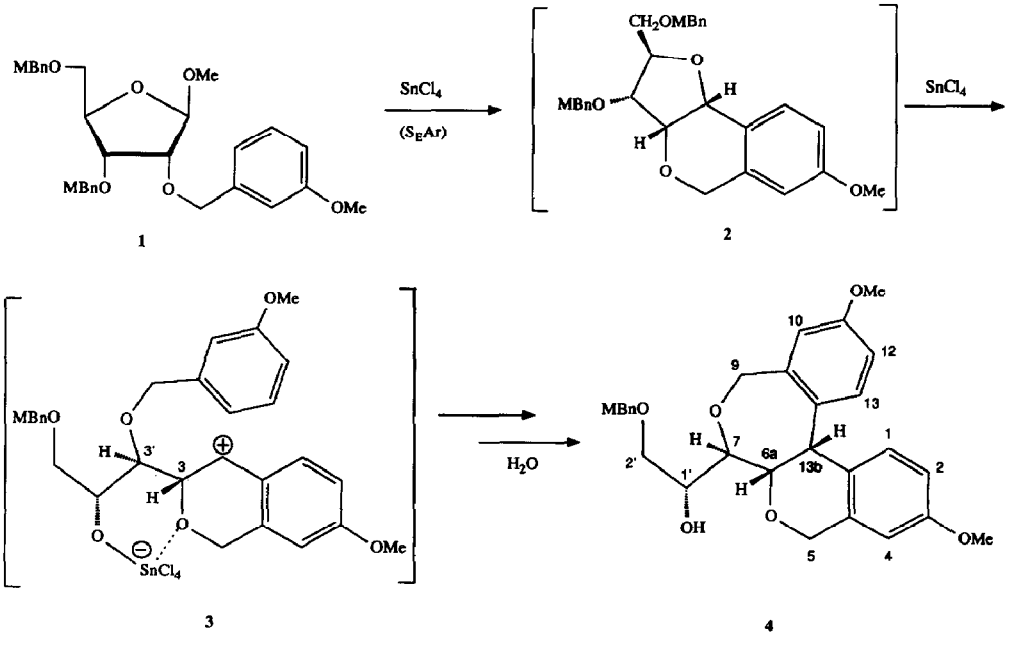
(*iii*) *Intramolecular hydride shifts. p*-Chlorobenzyl substituents were found to act as hydride donors in the course of internal *C*-arylations of benzylated furanosides[8]. The overall process results in the formal replacement of the two C–O bonds at C–1 of a glycoside by a C–C(Ar) and a C–H bond, and leads to the formation of enantiomerically pure, 3-alkylated isochroman derivatives.

(*iv*) *Multiple internal C-arylation reactions.* As shown by our early investigations on the reactivity of benzylated glycosides under Lewis acidic conditions, furanosides bearing activated benzyl groups (*e.g.*, *m*-methoxybenzyl) undergo an unusual "double *C*-glycosidation"[1] resulting from the successive intramolecular alkylations of the benzyl groups at O-2 and O-3. This remarkable process brings about the replacement, in one step, of the two C–O bonds at the anomeric center of the glycoside by C–C(Ar) bonds and is precedented only by its intermolecular version[9], namely the low-yielding reaction of a glycosyl chloride with an excess of toluene in the presence of aluminum chloride as a Friedel–Crafts catalyst.

The unique behavior of glycosides such as **1** and the complexity of the final products prompted further investigations on this latter process. We wish to report in this article definitive evidence for the constitution and configuration of the polycyclic systems resulting from the internal reactions of *m*-methoxybenzylated glycosides such as **1** and **7** with tin(IV) chloride, and the first examples of cycloalkylation reactions involving benzyl groups at remote positions (O-3 or O-5), which lead to novel, unusual bridged heteropolycyclic systems.

RESULTS AND DISCUSSION

Multiple participation of benzyl groups. — While benzylated glycofuranosyl acetates react readily with tin(IV) chloride to give the products resulting from an intramolecular Friedel–Crafts alkylation, the corresponding methyl furanosides react only very sluggishly (*i.e.*, the D-*xylo* series[4]) or lead to other products (*i.e.*, the D-*ribo* series[3]). In order to make the process feasible directly from methyl glycosides, the normal benzyl groups were replaced by more reactive *m*-methoxybenzyl groups, and such glycoside derivatives as **1** were prepared. The reaction of **1** with tin(IV) chloride proceeded rapidly and provided a crystalline compound in high yield (88%). Analysis of this product soon revealed that it was not the expected internal *C*-aryl glycoside **2** (Sheme 1), but an isomeric compound (m.s.) containing a free hydroxyl group (i.r.). Since no benzyl group had been lost during the process, this function was likely to have arisen from the cleavage of the benzylic C–O bond of the tetrahydrofuran component of **2**. The presence of the *p*-methoxy substituent indeed makes this bond particularly labile under acidic conditions (acetal-like reactivity). Tin(IV) chloride-induced cleavage of this ether linkage generates a stabilized benzylic cation (**3**) which can then participate in an electrophilic substitution and promote the alkylation of a second benzyl group. The detailed spectroscopic analysis of the final product (and of related species, see in the following reactions) demonstrated that this process actually occurs, leading to the unusual benzopyrano[3,4-*d*][2]benzoxepin system **4** by way of the successive alkylations of the benzyl groups at O-2 and at O-3. The second Friedel–Crafts reaction is ster-



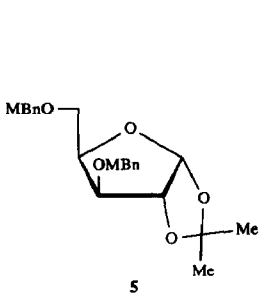
MBn = *m*-methoxybenzyl

Scheme 1.

eospecific and proceeds with retention of configuration at the former anomeric carbon to exclusively give a *cis*-fused bicyclic system.

The D-*xylo* glycosides **7** were found to undergo the same type of process, in the presence of tin(IV) chloride, to give compound **8**, the C-7 epimer of **4**, in 84% yield. The availability of two stereoisomeric products proved quite useful for the analysis of their structure.

The *constitution* of compounds **4** and **8** is supported by the following additional evidence: (*i*) ^{13}C-N.m.r. spectrum of **8**. The signal of the former anomeric carbon (now C-13b) appears at δ 44.04, a chemical shift that is consistent with the *absence* of oxygen at this carbon and with a C-*C*H(Ar$_2$) structure. The spectrum recorded in the APT-mode shows in the aromatic region the presence of 10 C–H and 8 quaternary C signals, which indicates clearly that *two* of the three *m*-methoxybenzyl substituents of the starting material have been alkylated. (*ii*) ^{1}H-N.m.r. spectrum of **4** and **8**, aromatic region. Of the three signals corresponding to a proton *meta* with respect to a methoxy group (this proton usually occurs as the lowest field signal in the spectrum of methoxybenzene derivatives), only one is a triplet (δ ~7.2), and the other two are doublets (δ



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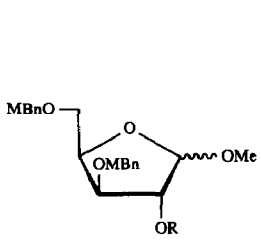
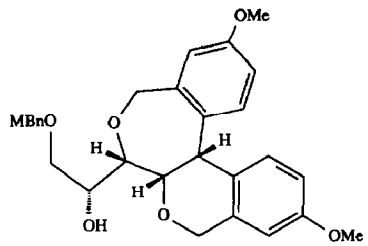


6 R = H

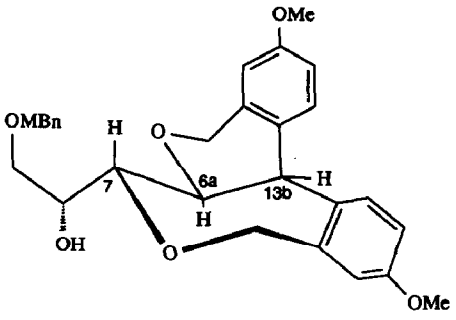
7 R = MBn



8

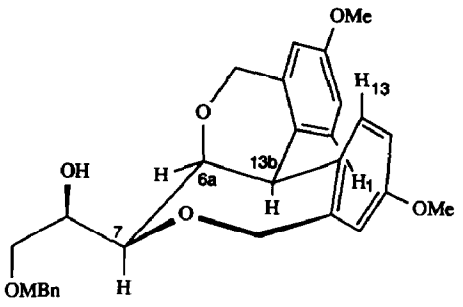
MBn = *m*-methoxybenzyl

~7.0 and ~6.3), which confirms the presence of one unchanged *m*-methoxybenzyl substituent. The fact that one of these protons appears at unusually high field is particularly interesting. The signal at δ ~6.3 is attributed to H-13, which is located in close proximity "above" the aromatic ring of the benzopyran section of the bicyclic compound in its most favorable conformation (see Scheme 2), and thereby experiences the shielding effect of the aromatic ring. The relative orientation of H-13, H-13b, and H-1 is further supported by an n.O.e. experiment on **8**. Irradiation of H-13b leads to 8% and 3% enhancements of the signals of H-1 and H-13, respectively, in agreement with the shorter distance between H-13b and H-1 (the "dihedral" angle between H-1 and H-13b is ~20°, between H-13 and H-13b ~90°). These n.m.r.-spectral features fully support the tetracyclic structure of compounds **4** and **8**. The (less likely) possibility that the second Friedel–Crafts alkylation occurred at the benzyl group at O-5 (instead of the group at O-3), however, cannot be excluded on the basis of these data. This alternative mode of reaction is ruled out by chemical evidence presented later.



4 (D-*ribo*)

$J_{6a,7} = 9.8$, $J_{6a,13b} = 3.9$ Hz



8 (D-*xylo*)

$J_{6a,7} = 1.9$, $J_{6a,13b} = 1.5$ Hz

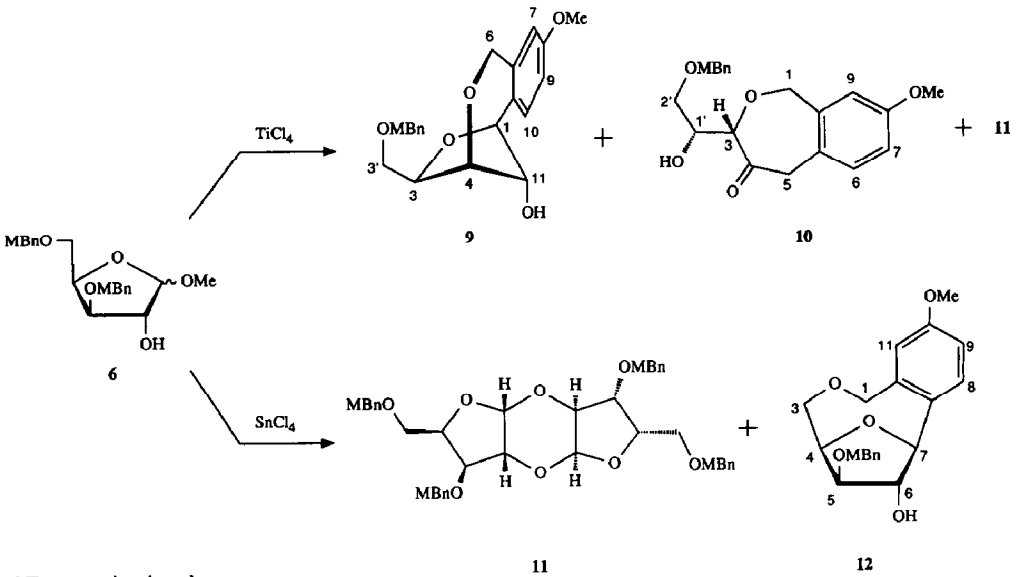
MBn = *m*-methoxybenzyl

Scheme 2.

The configuration and conformation of **4** and **8** are determined from the following ^{1}H-n.m.r. parameters. In both cases, the $^3J_{6a,13b}$ coupling constant is small (see Scheme 2), and the fusion between the two saturated heterocycles must therefore be *cis* (the *trans*-fused isomer of **4** and **8** would have H-6a and H-13b essentially antiparallel in their most favorable pseudochair conformation). Futhermore, the value of $J_{6a,7}$ in **4** (9.8 Hz) and in **8** (1.5 Hz) strongly suggests that both compounds exist in the pseudochair conformation that allows the substituent at C-7 to occupy an equatorial position (Scheme 2). This conclusion is consistent with the recent observations that the parent 2-oxabenzocycloheptane ring system[10], as well as its 1- and 3-oxa isomers[11], exclusively exist in a pseudo-chair conformation (with a barrier to inversion in the range of 10 kcal. mol^{-1}).

The unusual tandem internal *C*-arylation process is primarily driven by the availability of a reactive benzyl group at O-3. We have shown[4] indeed that, in absence of "participating" groups at O-3 and O-5 (*e.g.*, with *O*-methyl groups), the reaction stops at the stage of the internal aryl *C*-glycoside corresponding to **2**, which can be isolated in high yield. Also, the very high degree of stereoselectivity of the second internal alkylation reaction (**3**→**4**) is probably due to the formation of a six-membered tin(IV) chelate **3** which reduces the conformational flexibility about the exocyclic C-3–C-3′ bond of **3** and favors the approach of the aromatic group to the *re* face of the benzylic cation (*cis* with respect to the C-3 substituent of the isochroman system). A very similar intermediate was proposed to explain the stereospecificity of hydride transfers which we observed in related systems[8].

Participation of benzyl groups at O-3 or O-5. — The Lewis acid-mediated reactions of glycosides **1** and **7** showed, for the first time, that benzyl groups at remote positions were able to participate in internal *C*-arylation processes. The possibility of a direct reaction between a benzyl group at O-3 or O-5 and the glycosidic function was then investigated using compound **6** as the probe [activation of the furanosidic function



Scheme 3.

by a bidentate Lewis acid appears, from related studies, to be quite effective and selective when the hydroxyl group at C-2 is free (chelation effect), and the formation of dimeric species is minimal (see ref. 5 in particular)]. These investigations led to some remarkable results.

Both titanium(IV) chloride and tin(IV) chloride were examined as catalysts for the intramolecular reactions of **6**. Upon treatment with titanium(IV) chloride (1 h at room temperature), compound **6** led to the formation of a major product (**9**, 43%) and two minor products (**10**, 11%, and **11**, 9%) (Scheme 3). The aromatic region of the ^{1}H- and ^{13}C-n.m.r. spectra of the major product, the absence of anomeric carbon, and the presence of two very different benzylic geminal coupling constants ($|J_{6A,6B}|$ 14.9 Hz, $|J_{OCH_AH_{BA}r}|$ 12.2 Hz, see ref. 3) immediately revealed that one of the benzyl groups of **6** had undergone alkylation. Futhermore, the very small coupling constants between the protons of the original xylofuranose component ($J_{1,11}$ 0, $J_{4,11}$ 1.6, $J_{3,4}$ 2 Hz) indicated that compound **9** has a bicyclic structure resulting from the alkylation of the benzyl group at O-3. This rigid structure forces the "xylofuranose" component of **9** to adopt an E_2–$^3T_2$-type conformation, and the observed coupling constants are in excellent agreement with predicted values[12].

The first minor compound was identified as the intriguing tetrahydro-2-benzoxepin-4-one derivative **10**. This structure is supported in particular by the presence of a carbonyl group, of a hydroxyl group at C-1′ (C-4 of the original furanose; $\Delta\delta_{H\text{-}1'}$ = +1.22 on acetylation of **10**), and of a new methylene group [at C-5, the former anomeric carbon; $|J_{5A,5B}|$ 12.4 Hz, $\Delta\delta_{AB}$ = 1.38]. The large difference of chemical shift between H-5A and H-5B is attributable to the fact that, in the pseudochair conformation of **10**, one of the two protons is essentially coplanar with both the carbonyl group and the

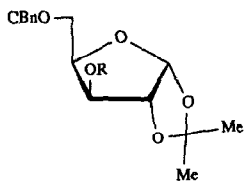
aromatic ring and is therefore shifted substantially more downfield than the other proton of the methylene group. The formation of this product can be explained simply by the Lewis acid-promoted cleavage of the benzylic C-1–O-2 bond of **9**, followed by the stabilization of the resulting benzylic cation by a formal 1,2-hydride shift. Because of competing reactions, the yield of compound **10** could not be improved by increasing the duration of the reaction of **6** with titanium(IV) chloride.

The second minor product of this reaction (**11**) exhibited spectral characteristics very similar to those of the dimeric species obtained from methyl 3,5-di-*O*-(4-chlorobenzyl)-D-xylofuranoside[5] and was therefore readily identified as the tetra-*O*-(3-methoxybenzyl) derivative of 1,2′-anhydro-2-*O*-(*α*-D-xylofuranosyl)-*α*-D-xylofuranose (**11**). That the cyclic dimer of **6** is formed only in small amount illustrates the low nucleophilicity of the hydroxyl group at O-2 in the presence of a bidentate Lewis acid such as titanium(IV) chloride.

The reaction of **6** with tin(IV) chloride gave a mixture of several products from which the two major components were isolated, compounds **11** (27%) and **12** (24%) (Scheme 3). The n.m.r.-spectral characteristics of compound **12** are also in complete agreement with a structure resulting from an internal *C*-arylation reaction; however, the parameters are quite different from those of **9**. In particular, the coupling constants of the original xylofuranose component ($J_{4,5}$ 7.2, $J_{5,6}$ 6.5, $J_{6,7}$ 6.4 Hz) are relatively large and indicate that the five-membered ring adopts a conformation of type $^2T_3$–E_3, which allows the substituents at C-5 and C-6 to occupy a *quasi*-equatorial position. Futhermore, the conversion of **6** into **12** brings about major changes in the chemical shift ($\delta_{H\text{-}3A}$ 3.56, $\delta_{H\text{-}3B}$ 4.15) and coupling constants ($J_{3A,4}$ 3.4, $J_{3B,4}$ 0, $|J_{3A,3B}|$ 12.8 Hz) of the signals corresponding to the protons at C-5 of the original glycoside. All of these features provide strong evidence that compound **12** results from the internal alkylation of the benzyl group at O-5 and possesses a bicyclic structure reminiscent of certain types of cyclonucleosides.

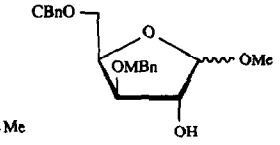
In order to confirm chemically the constitution of bicyclic *C*-glycosyl compounds **9** and **12**, substrates bearing only one reactive *m*-methoxybenzyl substituent at O-3 or O-5 were prepared and reacted under the same conditions. The selective benzylation of 1,2-*O*-isopropylidene-*α*-D-xylofuranose with one equivalent of *p*-chlorobenzyl chloride* in the presence of sodium hydride afforded the 5-*O*-and 3-*O*-(4-chlorobenzyl) derivatives **13** and **18** in a ~3:1 ratio, as well as some dibenzylated product. Compounds **13** and **18** were readily separated by flash chromatography. The site of benzylation was unambiguously established by the shifts of n.m.r.-signals promoted by the acetylation of **13** and **18** (see Experimental Section). Compounds **13** and **18** were then individually benzylated with *m*-methoxybenzyl chloride and submitted to methanolysis to obtain the required substrates, glycosides **15** and **20**. The reaction of the 3-*O*-(3-methoxybenzyl) glycoside **15** with titanium(IV) chloride (18 h, room temperature) gave a diol **16** that was immediately acetylated. The resulting diacetate **17** exhibited n.m.r.-spectral parameters

p-Chlorobenzyl groups were chosen as "unreactive" protecting groups because of their relative stability in the presence of Lewis acids such as tin(IV) chloride. See, for example, ref. 6.

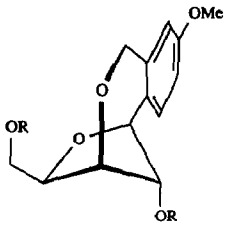


13 R = H
14 R = MBn

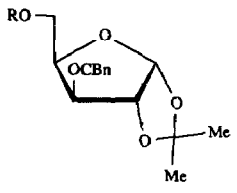
CBn = *p*-chlorobenzyl
MBn = *m*-methoxybenzyl



15

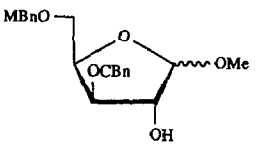


16 R = H
17 R = Ac

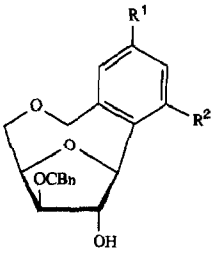


18 R = H
19 R = MBn

CBn = *p*-chlorobenzyl
MBn = *m*-methoxybenzyl



20

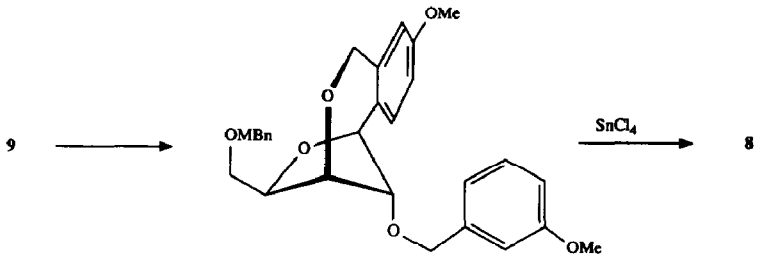


21 R^1 = OMe, R^2 = H
22 R^1 = H, R^2 = OMe

closely resembling those of **9** (magnitude of coupling constants in particular), thereby demonstrating that compound **9** arises from the internal alkylation of the benzyl group at O-3. The relatively long reaction time is probably responsible for the cleavage of the *p*-chlorobenzyl group at O-5.

5-*O*-(3-Methoxybenzyl) glycoside **20** reacted with tin(IV) chloride much more cleanly than **6**. Internal aryl C-glycoside **21** was isolated as the major product (43%) together with a small amount of its "*ortho*-alkylation" isomer **22** (9%) and of the dimer corresponding to **11** (25%). The comparison of the n.m.r. parameters of **12** and **21** also unambiguously confirmed that both possess the same constitution, namely a bicyclic structure resulting from the internal alkylation of the benzyl group at O-5.

The difference of behavior of glycoside **6** in the presence of titanium(IV) and tin(IV) chlorides is puzzling. As indicated by the rapid anomerization of the substrate (to its *α*-form only) under the conditions of the reaction, both reagents probably bind initially to O-2 and form, with O-1, a cyclic complex which activates the glycosidic function and promotes its cleavage. Major differences in the conformation of the resulting chelated intermediate could explain the divergent behavior of the tin(IV) and titanium(IV) complexes, but the details of the mechanism remain unclear.



23

MBn = *m*-methoxybenzyl

Scheme 4.

Finally, the availability of compound **9** made it possible to independently prove the constitution of bis-alkylated compound **8**. As a result of the acetal-like reactivity of its benzylic C-1–O-2 bond, compound **9** provided indeed an opportunity to achieve a synthesis of **8** by way of a reverse sequence of internal *C*-arylation processes. Thus, compound **9** was benzylated at O-11 with 3-methoxybenzyl chloride to give **23** (Scheme 4), and then it was reacted with tin(IV) chloride. The resulting product was found to be identical in all respects with compound **8**, which conclusively demonstrated that **8** arises from the internal alkylation of the benzyl groups at O-2 and O-3.

CONCLUSIONS

These investigations have shown that glycosides *O*-substituted with reactive benzyl groups possess a rich intrinsic chemistry. Not only are groups remote from the anomeric position (*e.g.*, at O-3 or O-5) susceptible of undergoing intramolecular alkylation, thereby leading to novel bicyclic systems, but also the resulting internal aryl *C*-glycosyl compounds can themselves behave as "pseudoglycosides" and undergo a further *C*-arylation at the pseudoanomeric position to give bis-*C*-arylated products. This type of reaction is particularly significant since a number of natural products of the family of the tannins[13] contain 1,1-bis-*C*-arylated hexitols as structural elements which are probably biosynthetically formed by way of a related process.

Furthermore, the internal *C*-glycosylations of benzyl groups at O-2 and O-3 (or O-5) of a xylofuranoside are stereochemically complementary. While compounds related to **2** (ref. 4) are precursors of 1,2-*cis* aryl *C*-glycosyl compounds, the cleavage of the auxiliary benzylic C–O linkage of **9** (or **12**) would lead to aryl *C*-glycosides exclusively having the 1,2-*trans* configuration.

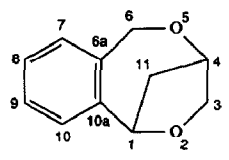
These investigations extend the scope of the intramolecular *C*-glycosidation of substituted sugars, a methodology which provides new tools for the elaboration of carbohydrates into enantiomerically pure natural products and analogues.

EXPERIMENTAL

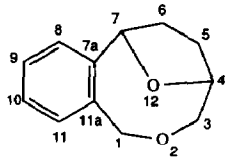
General methods. — See ref. 3. ^{1}H- and ^{13}C-n.m.r. spectra were recorded respectively at 360 MHz and at 90 MHz on a Bruker AM360 spectrometer as solutions in chloroform-*d* with tetramethylsilane as the internal standard, unless otherwise indicated. Optical rotations were determined at the indicated concentrations in chloroform.

The following solvent systems (v/v) were used for chromatography: (*A*) 2:1, (*B*) 1:1, (*C*) 1:2, (*D*) 1:4, (*E*) 1:5 ether–hexanes; (*F*) 3:7, (*G*) 1:4, (*H*) 1:9 ethyl acetate–toluene; (*I*) 1:9, and (*J*) 1:4 ethyl acetate–hexanes.

Compounds **9** and **12** and their derivatives have been named according to the *Chemical Abstracts* nomenclature for fused ring systems bearing a simple bridge. The parent compounds are named and numbered as follows:



1,3,4,6-Tetrahydro-1,4-methano-2,5-benzodioxocin



1,3,4,5,6,7-Hexahydro-4,7-epoxy-2-benzoxonin

General benzylation procedure. — To a solution of substrate in anhydrous DMF (10 mL/mmol; the amount of DMF can be reduced by using 2:1 toluene–DMF as the solvent; see for example ref. 14) was added pentane-washed sodium hydride (1.5–2.0 equiv/OH), and the suspension was stirred for 30 min at room temperature. The appropriate substituted benzyl chloride (1.25–2.0 equiv/OH) was then added, and the mixture was stirred for 2–8 h at room temperature. Excess sodium hydride was then destroyed by the careful addition of a small amount of methanol. Water (30 mL/mmol of substrate) was then added, and the benzylated products was extracted with dichloromethane (3 × 30 mL/mmol). The organic phases were combined and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was then purified by column or flash chromatography.

*Methyl 2,3,5-tri-*O*-(3-methoxybenzyl)-β-*D*-ribofuranoside* (**1**). — Methyl β-D-ribofuranoside (β:α ~10:1, ref. 15) (2.04 g, 12.4 mmol) was benzylated with 3-methoxybenzyl chloride (6.1 mL, 42 mmol) in dry methyl sulfoxide (25 mL) in the presence of powdered NaOH (2 g). After having been vigorously stirred for 2 h at room temperature, the reaction mixture was poured into ice-cold water (100 mL). The mixture was then extracted with ether (3 × 65 mL), the organic phase was dried (Na_2SO_4) and concentrated, and the residue was subjected to column chromatography (*B*). Concentration of the purest fractions and crystallization of the product from ether–hexanes afforded pure **1** (1.85 g, 28.5%. It is recommended that this benzylation be performed using the General Procedure described above for better yields): m.p. 49.5–51°; $[\alpha]_D$

+23.5° (*c* 1.0); R_F 0.48 (*A*); ^{1}H-n.m.r. data (400 MHz): δ 3.345 (s, 3 H, OCH_3), 3.54 (dd, 1 H, $J_{4,5A}$ 6.0, $J_{5A,5B}$ 10.8 Hz, H-5A), 3.65 (dd, 1 H, $J_{4,5B}$ 3.6 Hz, H-5B), 3.75, 3.78 and 3.80 (3 s, 3 × 3 H, 3 $ArOCH_3$), 3.88 (d, 1 H, $J_{2,3}$ 4.8 Hz, H-2), 4.05 (dd, 1 H, $J_{3,4}$ 7.0 Hz, H-3), 4.37 (m, 1 H, H-4), 4.46 (d, 1 H, J_{AB} 12.0 Hz) and 4.57 (d, 1 H), 4.57 (narrow AB, 2 H, J_{AB} 12.0 Hz), and 4.65 (narrow AB, 2 H, J_{AB} 12.0 Hz) (3 $ArCH_2O$), 4.95 (s, 1 H, H-1), 6.8–7.0 (several m's, 9 H), and 7.22, 7.25, and 7.26 (3 t, 3 H) (3 $CH_3OC_6H_4CH_2$).

Anal. Calc. for $C_{30}H_{36}O_8$ (524.62): C, 68.69; H, 6.92. Found: C, 68.49; H, 6.92.

(6aS, 7R, 13bS)-6a,7,9,13b-Tetrahydro-7-{(1R)-1-hydroxy-2-[(3-methoxybenzyl)oxy]-ethyl}-3,11-dimethoxy-5H-[2]benzopyrano[3,4-d][2]benzoxepin (**4**). — To a solution of glycoside **1** (497 mg, 0.95 mmol) in dry dichloromethane (5 mL) was added a 10% (v/v) solution of tin(IV) chloride in dichloroemethane (1.1 mL, 0.94 mmol), and the mixture was stirred for 2 h at room temperature. The solution gradually became deep purple. Dichloromethane (25 mL) was then added, followed by cold saturated aqueous $NaHCO_3$ (10 mL). The organic phase was separated, washed with water (10 mL), dried (Na_2SO_4), and concentrated, to afford 410 mg (88%) of crude, solid **4** (purity >90%). Pure **4** (210 mg, 45%) was obtained by recrystallization from ether–hexanes: m.p. 108–109.5°; $[\alpha]_D$ +26.3° (*c* 1.0); R_F 0.29 (*B*): ν_{max}^{KBr} 3480 (OH), 3010, 2960, 2930, 2860, 2840, 1605, 1575, 1495, 1465, 1450, 1425, 1360, 1330, 1260, 1245, 1235, 1165, 1095, 1025, 945, 935, 925, 910, 870, 860, 840, 800, 785, 765, 740, 700, 690, and 665 cm^{-1}; ^{1}H-n.m.r. data (300 MHz, assignments verified by a COSY spectrum): δ 2.85 (br s, 1 H, OH), 3.45 (dd, 1 H, $J_{6a,7}$ 9.8, $J_{7,1'}$ 4.9 Hz, H-7), 3.60 (narrow *ABX*, 2 H, $J_{1',2'A}$ 2.9, $J_{1',2'B}$ < 1, $J_{2'A,2'B}$ ~ 11 Hz, H-2'A,2'B), 3.75, 3.78 and 3.83 (3 s, 3 × 3 H, 3 $ArOCH_3$), 4.08 (br t, 1 H, H-1'), 4.10 (dd, 1 H, $J_{6a,13b}$ 3.9 Hz, H-6a), 4.40 (d, 1 H, H-13b), 4.55 (very narrow AB, 2 H), 4.80 (s, 2 H), 4.80 (d, 1 H, *J* 13.7 Hz) and 5.31 (d, 1 H) (H-5A,5B; H-9A,9B; OCH_2Ar), 6.40 (d, 1 H, *J* 7.8 Hz), 6.60–6.66 (m, 4 H), 6.82 (br d, 2 H), and 6.90 (br d, 1 H) [H-1 (or H-13), 2, 4, 10, 12; H-2,4,6 of *m*$MeOC_6H_4CH_2$], 7.02 [d, 1 H, *J* 8.8 Hz, H-13 (or H-1)], and 7.25 (t, 1 H, *J* 8.3 Hz, H-5 of *m*$MeOC_6H_4CH_2$); m.s.: *m/z* 121 (100%), 252 (48), 161 (35), 149 (35), 239 (29), 91 (27), 253 (26), 122 (24), 163 (16), 135 (16),...371 (14, $[M - CH_3OC_7H_6]^+$),...492 (5,$[M]^+$).

Anal. Calc. for $C_{29}H_{32}O_7$ (492.57): C, 70.71; H, 6.55. Found: C, 70.00; H, 6.65.

*Methyl 3,5-di-O-(3-methoxybenzyl)-α- and -β-*D*-xylofuranoside* (**6**). — Benzylation of 1,2-*O*-isopropylidene-*α*-D-xylofuranose[16] (3.0 g, 15.8 mmol) with 3-methoxybenzyl chloride in DMF–toluene (see General Procedure) afforded, after purification by column chromatography (*D*), 1,2-*O*-isopropylidene-3,5-di-*O*-(3-methoxybenzyl)-*α*-D-xylofuranose **5** (2.44 g, 36%): syrup; $[\alpha]_D$ −38° (*c* 1.0). Compound **5** (0.89 g, 2.07 mmol) was dissolved in 2.5% methanolic sulfuric acid (30 mL), and the mixture was heated under reflux for 80 min. The reaction mixture was then cooled and neutralized with methanol-washed Amberlite IRA-400 [OH^-] ion-exchange resin. The resin was removed by filtration, and the filtrate was concentrated to afford 0.74 g (88%) of a homogeneous mixture of **6***α* and **6***β* (~1:1). Analytical samples were obtained by flash chromatography (*C*). **6***α*: syrup; $[\alpha]_D$ +57.7° (*c* 1.1); R_F 0.34 (*A*); **6***β*: syrup; $[\alpha]_D$ −36.0° (*c* 1.0); R_F 0.30 (*A*); ν_{max}^{film} (*α*,*β*-mixture) 3400 (br, OH), 2920, 2820, 1590, 1580, 1485, 1460, 1450, 1260, 1150, 1090, 1040, 775, 735, and 685 cm^{-1}; ^{1}H-n.m.r. data (360 MHz,

α-anomer): δ 3.49 (s, 3 H, OCH_3), 3.655 (dd, 1 H, $J_{4,5A}$ 6.8, $J_{5A,5B}$ 10.6 Hz, H-5A), 3.73 (dd, 1 H, $J_{4,5B}$ 4.1 Hz, H-5B), 3.77 and 3.79 (2 s, 2 × 3 H, 2 $ArOCH_3$), 4.00 (dd, 1 H, $J_{2,3}$ 4.1, $J_{3,4}$ 6.0 Hz, H-3), 4.25 (br t, 1 H, H-2), 4.395 (td, 1 H, H-4), 4.51 (d, 1 H, J_{AB} 12.2 Hz) and 4.61 (d, 1 H) (OCH_2Ar), 4.53 (d, 1 H, J_{AB} 12.2 Hz) and 4.70 (d, 1 H) (OCH_2Ar), 4.99 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 6.80–6.95 (m, 6 H), and 7.23 (2 t, 2 H) (2 $CH_3OC_6H_4CH_2$); ^{13}C-n.m.r. data (90 MHz, α-anomer) δ 54.99, 55.00, 55.59 (3 OCH_3), 68.99 (C-5), 71.58, 73.17 (2 $ArCH_2O$), 76.82, 77.21, 83.41 (C-2,3,4), 101.65 (C-1), 112.71, 112.83, 113.08, 113.09, 119.54, 119.79 (C-2,4,6 of *m*MeOBn), 129.20, 129.25 (C-5 of *m*MeOBn), 139.50, 139.75 (C-1 of *m*MeOBn), 159.57, and 159.59 (C-3 of *m*MeOBn).

Anal. Calc. for $C_{22}H_{28}O_7$ (404.46): C, 65.33; H, 6.98. Found: C, 64.82; H, 6.97.

Methyl 2,3,5-tri-O-*(3-methoxybenzyl)-α-* and *-β-*D-*xylofuranoside* (**7**). — Compound **6***α,β* (479 mg, 1.19 mmol) was benzylated with 3-methoxybenzyl chloride in DMF–toluene (see General Procedure). The resulting crude mixture of anomers was purified, and the anomers were separated by column chromatography (*E*) which afforded **7***β* (222.5 mg), **7***α* (62 mg), and a mixture of **7***α* and **7***β* (215.3 mg, total yield: 80.5%). **7***β*: syrup; $[\alpha]_D$ −17.7° (*c* 1.1); R_F 0.52 (*A*); **7***α*: syrup; $[\alpha]_D$ +50.9° (*c* 1.1); R_F 0.42 (*A*); ν_{max}^{film} (α-anomer) 2960, 2920, 2830, 1595, 1580, 1490, 1455, 1430, 1260, 1150, 1100 (br), 1035 (br), 860, 780, and 690 cm^{-1}; ^{1}H-n.m.r. data (250 MHz) **7***α*: δ 3.41 (s, 3 H, OCH_3), 3.60 (dd, 1 H, $J_{4,5A}$ 6.7, $J_{5A,5B}$ 10.7 Hz, H-5A), ~3.71 (dd, 1 H, $J_{4,5B}$ 4.0 Hz, H-5B), 3.73 (s, 3 H) and 3.76 (s, 6 H) (3 $ArOCH_3$), 4.02 (dd, 1 H, $J_{1,2}$ 4.2, $J_{2,3}$ 5.6 Hz, H-2), 4.31 (t, 1 H, $J_{3,4}$ 7.2 Hz, H-3), 4.40 (td, 1 H, H-4), 4.46–4.65 (3 AB, 6 H, *J* 12 Hz, 3 OCH_2Ar), 4.82 (d, 1 H, H-1), 6.79–6.93 (m, 9 H), and 7.18–7.27 (m, 3 H) (3 $CH_3OC_6H_4CH_2$); **7***β*: 3.40 (s, 3 H, OCH_3), 3.72 (s, 3 H) and 3.77 (s, 6 H) (3 $ArOCH_3$), 3.70–3.82 (obscured ABX, 2 H, H-5A,5B), 3.97 (narrow dd, 1 H, $J_{1,2}$ 1.4, $J_{2,3}$ 2.5 Hz, H-2), 4.05 (dd, 1 H, $J_{3,4}$ 6.0 Hz, H-3), 4.46 (m, 1 H, H-4), 4.45–4.61 (3 AB, 6 H, 3 OCH_2Ar), 4.92 (d, 1 H, H-1), 6.78–6.92 (m, 9 H) and 7.18–7.27 (3 t, 3 H) (3 $CH_3OC_6H_4CH_2$).

Anal. Calc. for $C_{30}H_{36}O_8$ (524.61): C, 68.68; H, 6.92. Found: C, 68.63; H, 6.90.

*(6a*S, *7*S, *12b*S)*-6a,7,9,13b-Tetrahydro-7-{(1*R*)-1-hydroxy-2-[(3-methoxybenzyl)-oxy]ethyl}-3,11-dimethoxy-5*H*-[2]benzopyrano[3,4-*d*][2]benzoxepin* (**8**). — Glycosides **7** (150 mg, 0.29 mmol) were treated with tin(IV) chloride (1 equiv.) in dry dichloromethane as described for the preparation of **4**. Purification of the final product by column chromatography (*B*) afforded 119.9 mg (84%) of amorphous **8**: m.p. 96–98°; $[\alpha]_D$ +88.2° (*c* 1.0); R_F 0.24 (*F*); ν_{max}^{film} 3460 (OH), 3000, 2940, 2910, 2860, 2830, 1605, 1560, 1500, 1460, 1450, 1425, 1260, 1085, 1035, 900, 790, 725, and 640 cm^{-1}; ^{1}H-n.m.r. data (300 MHz, assignments verified by a COSY-spectrum): δ 3.11 (br s, 1 H, OH), 3.53 (dd, 1 H, $J_{1',2'A}$ 3.9, $J_{2'A,2'B}$ 10.1 Hz, H-2'A), 3.68 (dd, 1 H, $J_{1',2'B}$ 4.1 Hz, H-2'B), 3.72, 3.74, and 3.84 (3 s, 3 × 3 H, 3 $ArOCH_3$), 3.88 (narrow t, 1 H, $J_{6a,7}$ 1.9, $J_{6a,13b}$ ~1,5 Hz, H-6a), 4.06 (distorted dd, 1 H, $J_{7,1'}$ 6.1 Hz, H-7), 4.10 (m, 1 H, H-1'), 4.25 (~s, 1 H, H-13b), 4.46 (d, 1 H, J_{AB} 12.2 Hz), 4.61 (d, 1 H) and 4.78 (narrow AB, 2 H) (H-9A, 9B, OCH_2Ar), 4.615 (d, 1 H, $J_{5A,5B}$ 15.5 Hz, H-5A), 4.82 (d, 1 H, H-5B), 6.285 (d, 1 H, $J_{12,13}$ 8.6 Hz, H-13), 6.58 (d, 1 H, $J_{2,4}$ 2.7 Hz, H-4), 6.595 (dd, 1 H, $J_{10,12}$ 2.8 Hz, H-12), 6.74 (ddd, 1 H, *J* 1.0, 2.5 and 7.8 Hz, H-4 or 6 of *m*MeOBn), 6.77 (d, 1 H, H-10), 6.83 (dd, 1 H, $J_{1,2}$ 8.3 Hz, H-2), 6.85 (2 d, 2 H, H-2 and H-6 or 4 of *m*MeOBn), 6.98 (d, 1 H, H-1), and 7.14 (t, 1 H, *J* 7.8 Hz, H-5

of *m*MeOBn); ^{13}C-n.m.r. data [75 MHz; assignments verified by ^{1}H–^{13}C HETCOR and APT spectra; (+): positive signals (C, CH_2); (−): negative signals (CH, CH_3)]: δ 44.04 [(−), C-13b], 54.64, 54.76, 54.84 [(−), 3 OCH_3], 69.02 [(+), C-2'], 68.10, 72.84, 73.90 [(+), C-5,9, OCH_2Ar], 71.08 [(−), C-1'], 75.65 [(−), C-6a], 83.98 [(−), C-7], 109.04, 111.92 [(−), C-4,12], 112.10, 112.80, 112.85, 114.50, 119.76 [(−), C-2,10, C-2,4,6 of *m*MeOBn], 128.83 [(−), C-5 of *m*MeOBn], 129.63 [(−), C-1], 131.79 [(−), C-13], 129.45, 131.33, 134.92, 138.99, 139.04 [(+), C-4a,9a,13a,13c, C-1 of *m*MeOBn], and 157.32, 157.68, and 158.19 [(+), C-3,11, C-3 of *m*MeOBn]; m.s. data: *m/z* 252 (100%), 121 (60, $[CH_3OC_7H_6]^+$), 253 (47), 239 (40), 161 (33), 281 (31), 371 (25, $[M - CH_3OC_7H_6]^+$), 265 (19), 149 (19), 209 (14),... 492 (8, $[M]^{+\cdot}$). High-resolution m.s.: calc. for $C_{29}H_{32}O_7$: 492.2148; found: 492.2140.

Reaction of glycosides **6** *with titanium(IV) chloride.* — To a solution of **6** (α,β-mixture) (1.0 g, 2.48 mmol) in dry dichloromethane (20 mL) was added a M solution of titanium(IV) chloride in dichloromethane (2.4 mL, 2.4 mmol), and the mixture was stirred for 1 h at room temperature. Saturated aqueous $NaHCO_3$ (a quantity just sufficient to neutralize the reagent; a large excess of $NaHCO_3$ solution should be avoided as it makes the processing more difficult) was then added followed by dichloromethane (20 mL). The organic phase was separated, washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated. The resulting mixture of products was resolved by column chromatography (*G*) which afforded, in order of elution, a fast-moving compound **11** (85 mg, 9%), ketone **10** (100 mg, 11%), recovered **6***a* (150 mg, 15%), and bicyclic *C*-glycoside **9** (390 mg, 43%). The fast-moving compound [syrup; $[\alpha]_D$ −18.0° (*c* 1.0); R_F 0.68 (*F*); ^{1}H-n.m.r. data (360 MHz): δ 3.99 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 1.0 Hz, H-2), 4.12 (dd, 1 H, $J_{3,4}$ 4.2 Hz, H-3), 5.16 (d, 1 H, H-1), H-4,5A,5B hidden by OCH_3 and $ArCH_2$ signals.

Anal. Calc. for $C_{42}H_{48}O_{12}$ (744.84): C, 67.73; H, 6.50. Found: C, 67.78; H, 6.69] was identified as the tetra-*O*-(3-methoxybenzyl) derivative of 1,2'-anhydro-2-*O*-(α-D-xylofuranosyl)-α-D-xylofuranose (**11**).

(1S, 3R,4R,11S)-1,3,4,6-Tetrahydro-11-hydroxy-8-methoxy-3-[[(3-methoxybenzyl)oxy]-methyl]-1,4-methano-2,5-benzodioxocin (**9**). — M.p. 96–97° (dichloromethane–hexanes); $[\alpha]_D$ −78.1° (*c* 1.0); R_F 0.11 (*G*); ν_{max}^{Nujol} 3380 (sharp, OH), 1620, 1595, 1585, 1305, 1275, 1260, 1155, 1130, 1080, 1050, 955, 945, 930, 850, 825, 800, 775, and 735 cm^{-1}; ^{1}H-n.m.r. data (360 MHz): δ 3.77 (s, 6 H, 2 $ArOCH_3$), 3.80 (dd, 1 H, $J_{3,3'A}$ 6.5, $J_{3'A,3'B}$ 10.3 Hz, H-3'A), 3.93 (dd, 1 H, $J_{3,3'B}$ 5.0 Hz, H-3'B), 4.35 (narrow t, 1 H, $J_{3,4} \sim 2$, $J_{4,11}$ 1.6 Hz, H-4), 4.52 (d, 1 H, J_{AB} 12.2 Hz) and 4.60 (d, 1 H) (OCH_2Ar), 4.55 (d, 1 H, $J_{1,11}$ 0 Hz, H-11), 4.565 (ddd, 1 H, H-3), 4.61 (d, 1 H, $J_{6A,6B}$ 14.9 Hz, H-6A), 4.865 (d, 1 H, H-6B), 4.905 (s, 1 H, H-1), 6.59 (d, 1 H, $J_{7,9}$ 2.6 Hz, H-7), 6.75 (dd, 1 H, $J_{9,10}$ 8.3 Hz, H-9), 6.81 (ddd, 1 H, *J* 0.8, 2.5 and 8.3 Hz, H-4 or 6 of *m*MeOBn), 6.91 (m, 2 H, H-2 and 6 or 4 of *m*MeOBn), 7.19 (d, 1 H, H-10), and 7.23 (t, 1 H, H-5 of *m*MeOBn); on acetylation, the signals of H-1, H-3, H-4 and H-11 were shifted to δ 4.97 (s, 1 H), 4.45 (m, 1 H), 4.42 (br s), and 5.41 (narrow d, 1 H, $J_{4,11}$ 1.0 Hz), respectively. ^{13}C-N.m.r. data (90 MHz, assignments were verified by ^{1}H–^{13}C HETCOR): δ 55.16, 55.26 (2 $ArOCH_3$), 68.38, 68.48, 73.13 (C-3',6, OCH_2Ar), 76.97 (C-11), 81.47 (C-3), 81.88 (C-4), 87.86 (C-1), 112.11 (C-9), 112.83, 113.32 (C-2,4 of *m*MeOBn), 114.21 (C-7), 119.93 (C-6 of *m*Me-

OBn), 129.30 (C-5 of *m*MeOBn), 129.45 (C-10a), 130.39 (C-10), 139.78, 140.03 (C-6a, C-1 of *m*MeOBn), and 158.93 and 159.65 (C-8, C-3 of *m*MeOBn); m.s.: *m/z* 121 (100%), 175 (51), 91 (51), 135 (33), 163 (31), 174 (31), 149 (29), 77 (27), 147 (24), 191 (24),...251 (0.2, $[M - CH_3OC_7H_6]^+$),...372 (0.1, $[M]^+$).

Anal. Calc. for $C_{21}H_{24}O_6$ (372.42): C, 67.72; H, 6.49. Found: C, 67.51; H, 6.37.

(3S)-1,3,4,5-Tetrahydro-3-{(1R)-1-hydroxy-2-[[3-methoxybenzyl]oxy]ethyl}-8-methoxy-2-benzoxepin-4-one (**10**). — Compound **10** was obtained from **6** as described above: syrup; $[\alpha]_D$ −21.8° (*c* 1.1); R_F 0.41 (*F*); ν_{max}^{film} 3450 (OH), 2980, 2940, 2880, 1730 (br, C=O), 1500, 1475, 1270, 1210, 1090, 1020, 915, 840 (sh.), and 810 cm^{-1}; ^{1}H-n.m.r. data (360 MHz): δ 3.29 (d, 1 H, $J_{5A,5B}$ 12.4 Hz, H-5A), 3.67 (AB of ABX, 2 H, $J_{1',2'A}$ 5.5, $J_{1',2'B}$ 5.8, $J_{2'A,2'B}$ 9.6 Hz, H-2'A,2'B), 3.77 and 3.81 (2 s, 2 × 3 H, 2 $ArOCH_3$), 3.97 (d, 1 H, $J_{3,1'}$ 3.3 Hz, H-3), 4.26 (m, 1 H, H-1'), 4.55 (narrow AB, 2 H, J_{AB} 12.1 Hz, OCH_2Ar), 4.67 (d, 1 H, H-5B), 4.77 (d, 1 H, $J_{1A,1B}$ 16.0 Hz, H-1A), 5.38 (d, 1 H, H-1B), 6.51 (d, 1 H, $J_{7,9}$ 2.7 Hz, H-9), 6.74 (dd, 1 H, $J_{6,7}$ 8.4 Hz, H-7), 6.84 (dd, 1 H, *J* 2.6 and 8.2 Hz), ~6.9 (m, 2 H) (H-2,4,6 of *m*MeOBn), 7.01 (d, 1 H, H-6), and 7.27 (t, 1 H, *J* 7.7 Hz, H-5 of *m*MeOBn); upon acetylation, the signals of H-1' and H-3 were shifted to δ 5.48 (dt, 1 H, $J_{3,1'}$ 2.8) and 4.22 (d, 1 H), respectively. ^{13}C-N.m.r. data (90 MHz): δ 48.20 (C-5), 55.24, 55.29 (2 $ArOCH_3$), 70.32, 71.49, 73.30, 74.56 (C-1,1',2', OCH_2Ar), 84.02 (C-3), 110.74, 113.05, 113.32, 113.36 (C-7,9, C-2,4 of *m*MeOBn), 119.85 (C-6 of *m*MeOBn), 121.40 (C-5a), 129.48, 132.20 (C-6, C-5 of *m*MeOBn), 136.72, 139.49 (C-9a, C-1 of *m*MeOBn), 158.88, 159.80 (C-8, C-3 of *m*MeOBn), and 209.98 (C-4).

Anal. for 1'-*O*-acetyl derivative. Calc. for $C_{23}H_{26}O_7$ (414.45): C, 66.65; H, 6.32. Found: C, 66.07; H, 6.43.

(4R, 5R, 6S, 7S)-1,3,4,5,6,7-Hexahydro-6-hydroxy-5-[(3-methoxybenzyl)-oxy]-4,7-epoxy-2-benzoxonin (**12**). — To a solution of **6** (α,β-mixture) (0.50 g, 1.24 mmol) in dry dichloromethane (10 mL) was added a 1M solution of tin(IV) chloride in dichloromethane (1.2 mL, 1.2 mmol). After 1 h at room temperature, the reaction mixture was processed as described above (reaction of **6** with $TiCl_4$), to give a complex mixture of at least ten components. The major products were isolated by column chromatography (*G*): compound **11** (125 mg, 27%, eluted first), and bicyclic *C*-glycoside **12** (110 mg, 24% next compound to be eluted). Compound **12** was further purified by preparative t.l.c. (*G*): syrup; $[\alpha]_D$ −36.0° (*c* 1.0); R_F 0.40 (*F*); ν_{max}^{film} 3450 (OH), 2940, 2850, 1620, 1595, 1510, 1500, 1470, 1270, 1120, 1045, 780, and 690 cm^{-1}; ^{1}H-n.m.r. data (360 MHz): δ 3.56 (br d, 1 H, $J_{3A,4}$ ~3, $J_{3A,3B}$ 12.8 Hz, H-3A), 3.76 and 3.785 (2 s, 2 × 3 H, 2 $ArOCH_3$), 4.145 (d, 1 H, $J_{3B,4}$ 0 Hz, H-3B), 4.18–4.24 (m, 2 H, H-4,5), 4.515 (t, 1 H, $J_{5,6}$ 6.5, $J_{6,7}$ 6.5 Hz, H-6), 4.64 (narrow AB, 2 H, J_{AB} 12.2 Hz, OCH_2Ar), 4.77 (d, 1 H, H-7), 4.86 (d, 1 H, $J_{1A,1B}$ 13.7 Hz, H-1A), 4.96 (d, 1 H, H-1B), 6.64 (d, 1 H, $J_{9,11}$ 2.6 Hz, H-11), 6.71 (dd, 1 H, $J_{8,9}$ 8.3 Hz, H-9), 6.82 (dd, 1 H, *J* 2.4 and 7.8 Hz) and 6.91 (m, 2 H) (H-2,4,6 of *m*MeOBn), 7.04 (d, 1 H, H-8), and 7.245 (t, 1 H, H-5 of *m*MeOBn); after acetylation, the signals of H-3–H-7 were shifted as follows: δ 3.585 (dd, 1 H, $J_{3A,4}$ 3.4, $J_{3A,3B}$ 12.8 Hz, H-3A), 4.25 (d, 1 H, $J_{3B,4}$ 0 Hz, H-3B), 4.27 (dd, 1 H, $J_{4,5}$ 7.3 Hz, H-4), 4.37 (t, 1 H, $J_{5,6}$ 7.3 Hz, H-5), 4.86 (d, 1 H, $J_{6,7}$ 6.0 Hz, H-7), and 5.725 (dd, 1 H, H-6). ^{13}C-N.m.r. data of 6-*O*-acetyl derivative of **12** (90 MHz): δ 21.02 (CH_3CO), 55.16 (2 OCH_3), 71.00, 72.38,

78.06, 78.27, 80.73, 83.55, 85.21 (C-1,C-3–C-7, OCH_2Ar), 111.73, 113.08, 113.31, 114.79 (C-9,11, C-2,4 of *m*MeOBn), 119.82 (C-6 of *m*MeOBn), 129.40, 129.65 (C-8, C-5 of *m*MeOBn), 130.41 (C-7a), 137.54, 139.39 (C-11a, C-1 of *m*MeOBn), 159.04, 159.70 (C-10, C-3 of *m*MeOBn), and 169.58 (CH_3CO); m.s. data: *m/z* 121 (100%), 43 (77), 149 (66), 57 (63), 55 (52), 135 (47), 91 (38), 69 (38), 122 (32), 125 (30),...372 (1, $[M]^+$).

Anal. for 6-*O*-acetyl derivative. Calc. for $C_{23}H_{26}O_7$ (414.45): C, 66.65; H, 6.32. Found: C, 66.24; H, 6.34.

Selective p-*chlorobenzylation of 1,2-*O*-isopropylidene-α-*D*-xylofuranose.* — Benzylation of 1,2-*O*-isopropylidene-α-D-xylofuranose (0.95 g, 5.0 mmol) with slightly more than one molar equivalent of 4-chlorobenzyl chloride (1.0 g, 95% purity, ~5.9 mmol) in the presence of sodium hydride (15 mmol) in dry DMF (25 mL) (see General Procedure) afforded, after column chromatography (*I*, then *J*) 0.85 g (54%) of 5-*O*-(4-chlorobenzyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**13**), 0.25 g (16%) of 3-*O*-benzylated isomer **18**, and a small amount of 3,5-di-*O*-(4-chlorobenzyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (ref. 8) (0.22 g, 10%).

Physicochemical data for compound **13**. M.p. 126–127° (methanol); $[\alpha]_D$ −4.2° (*c* 1.2); R_F 0.39 (*F*); ν_{max}^{Nujol} 3460 cm^{-1}(sharp, OH); ^{1}H-n.m.r. data (360 MHz); δ 1.32 and 1.50 (2 s, 2 × 3 H, CMe_2), 3.55 (br s, 1 H, OH), 3.91 (AB of ABX, 2 H, $J_{4,5A}$ 3.7, $J_{4,5B}$ 4.1, $J_{5A,5B}$ 10.9 Hz, H-5A,5B), 4.25 (m, 2 H, H-3,4), 4.50 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 4.57 (narrow AB, J_{AB} 12.1 Hz, OCH_2Ar), 5.97 (d, 1 H, H-1), 7.33–7.47 (AA'BB', 4 H, $ClC_6H_4CH_2$); ^{13}C-n.m.r. data (90 MHz): δ 26.09, 26.68 [$C(CH_3)_2$], 68.30 (C-5), 73.22 (OCH_2Ar), 76.34, 78.06, 85.27 (C-2,3,4), 104.76 (C-1), 111.58 (CMe_2), 128.67, 129.10 (C-2,3/5,6 of *p*ClBn), and 133.75 and 135.63 (C-1,4 of *p*ClBn).

Anal. Calc. for $C_{15}H_{19}ClO_5$ (314.77): C, 57.24; H, 6.08; Cl, 11.26. Found: C, 57.05; H, 6.05; Cl, 11.33.

Physicochemical data for compound **18**: Syrup; $[\alpha]_D$ −46° (*c* 1.0); R_F 0.36 (*F*); ^{1}H-n.m.r. data (360 MHz): δ 1.33 and 1.49 (2 s, 2 × 3 H, CMe_2), 2.80 (br s, 1 H, OH), 3.835 (dd, 1 H, $J_{4,5A}$ 4.6, $J_{5A,5B}$ 11.8 Hz, H-5A), 3.93 (dd, 1 H, $J_{4,5B}$ 5.8 Hz, H-5B), 3.99 (d, 1 H, $J_{2,3}$ 0, $J_{3,4}$ 3.4 Hz, H-3), 4.30 (ddd, 1 H, H-4), 4.48 and 4.66 (2 d, AB, *J* 12.1 Hz, OCH_2Ar), 4.635 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-2), 5.97 (d, 1 H, H-1), and 7.24–7.34 (AA'BB', 4 H, $ClC_6H_4CH_2$); after acetylation, the signals of H-3, H-5A and H-5B were shifted to δ 3.92, 4.26, and 4.32, respectively. ^{13}C-N.m.r. data (90 MHz): δ 26.09, 26.56 [$C(CH_3)_2$], 60.47 (C-5), 70.92 (OCH_2Ar), 80.21, 82.20, 82.41 (C-2,3,4), 104.80 (C-1), 111.61 (CMe_2), 128.55, 128.78 (C-2,3/5,6 of *p*ClBn), and 133.62 and 135.57 (C-1,4 of *p*ClBn).

Anal. Calc. for $C_{15}H_{19}ClO_5$ (314.77): C, 57.24; H, 6.08; Cl, 11.26. Found: C, 57.13; H, 6.13; Cl, 11.35.

*Methyl 5-*O*-(4-chlorobenzyl)-3-*O*-(3-methoxybenzyl)-α- and -β-*D*-xylofuranoside* (**15**). — Benzylation of compound **13** (0.2 g, 0.64 mmol) with 3-methoxybenzyl chloride and sodium hydride (see General Procedure) afforded, after column chromatography (*H*), 255 mg (92%) of 5-*O*-(4-chlorobenzyl)-1,2-*O*-isopropylidene-3-*O*-(3-methoxybenzyl)-α-D-xylofuranose (**14**) [syrup;$[\alpha]_D$ −34° (*c* 1.0); ^{1}H-n.m.r. data (360 MHz, partial): δ 3.74 (AB of ABX, 2 H, $J_{4,5A}$ ~ $J_{4,5B}$ ~ 6.2 Hz, H-5A,5B), 3.96 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 4.39 (dt, 1 H, H-4), 4.605 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-2), and 5.95 (d, 1 H, H-1)].

Compound **14** (0.2 g, 0.46 mmol) was dissolved in 2.5% methanolic H_2SO_4 (10 mL), and the solution was heated under reflux for 0.5 h. The reaction mixture was then cooled and neutralized with solid $NaHCO_3$. Water (30 mL) was then added, and the product was extracted with dichloromethane (3 × 10 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to afford glycosides **15** ($\alpha:\beta \sim 1:1$) in essentially quantitative yield; R_F 0.31 (β) and 0.45 (α) (*F*). A sample of α-anomer **15***a* was isolated by preparative t.l.c.: syrup; ^{1}H-n.m.r. data (360 MHz): δ 3.49 (s, 3 H, OCH_3), 3.63 (dd, 1 H, $J_{4,5A}$ 6.7, $J_{5A,5B}$ 10.5 Hz, H-5A), 3.70 (dd, 1 H, $J_{4,5B}$ 4.0 Hz, H-5B), 3.77 (s, 3 H, $ArOCH_3$), 4.00 (dd, 1 H, $J_{2,3}$ 4.2, $J_{3,4}$ 6.1 Hz, H-3), 4.25 (br t, 1 H, H-2), 4.55 (dt, 1 H, H-4), 4.49 and 4.57 (2 d, AB, 2 H, *J* 12.3 Hz), and 4.52 and 4.72 (2 d, AB, 2 H, *J* 12.2 Hz) (2 OCH_2Ar), 4.98 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 6.80–6.88 (m, 3 H) and 7.21–7.31 (m, 5 H) (2 Ar).

Reaction of glycosides **15** *with titanium(IV) chloride.* — Glycosides **15** (α/β mixture) (0.10 g, 0.25 mmol) were treated with titanium(IV) chloride (0.25 mL of a M solution in dichloromethane, 0.25 mmol) in dry dichloromethane (5 mL), for 18 h at room temperature. The reaction mixture was processed as described above (reaction of **6** with $TiCl_4$). The residual syrupy material containing **16** was immediately acetylated in acetic anhydride (2 mL) in the presence of 4-dimethylaminopyridine (0.10 g). After 15 min, the reaction mixture was diluted with dichloromethane (10 mL), washed with water (2 × 2 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (*G*) afforded 25 mg (30% from **15**) of compound **17**, the 3′,11-di-*O*-acetyl derivative of compound **9**: syrup; $[\alpha]_D$ −13.6° (*c* 1.1); ^{1}H-n.m.r. data (360 MHz): δ 2.10 and 2.14 (2 s, 2 × 3 H, $2\,OCOCH_3$), 3.80 (s, 3 H, OCH_3), 4.29 (dd, 1 H, $J_{3,3'A}$ 7.2, $J_{3'A,3'B}$ 11.4 Hz, H-3′), 4.41 (ddd, 1 H, $J_{3,4}$ 2.3, $J_{3,3'B}$ 4.1 Hz, H-3), 4.46 (narrow t, 1 H, $J_{4,11}$ 1.4 Hz, H-4), 4.53 (dd, 1 H, H-3′B), 4.82 (AB, 2 H, $J_{6A,6B}$ 15.1 Hz, H-6A,6B), 5.01 (s, 1 H, H-1), 5.54 (d, 1 H, H-11), 6.625 (d, 1 H, $J_{7,9}$ 2.6 Hz, H-7), 6.78 (dd, 1 H, $J_{9,10}$ 8.3 Hz, H-9), and 7.225 (d, 1 H, H-10).

*Methyl 3-O-(4-chlorobenzyl)-5-O-(3-methoxybenzyl)-α- and -β-*D*-xylofuranoside* (**20**). — Compound **19** (0.20 g. 0.63 mmol) was benzylated with 3-methoxybenzyl chloride and sodium hydride (see General Procedure). The crude solid resulting from the processing of the reaction mixture was recrystallized from methanol to provide 240 mg (87%) of pure 3-*O*-(4-chlorobenzyl)-1,2-*O*-isopropylidene-5-*O*-(3-methoxybenzyl)-α-D-xylofuranose (**19**): m.p. 80–81°; $[\alpha]_D$ −48° (*c* 1.0); ^{1}H-n.m.r. data (360 MHz, partial): δ 3.74 (AB of ABX, 2 H, $J_{4,5A} \sim J_{4,5B} \sim 6.2$ Hz, H-5A,5B), 3.945 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 4.405 (dt, 1 H, H-4), 4.59 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-2), and 5.93 (d, 1 H, H-1). Methanolysis of compound **19** (0.2 g, 0.46 mmol), as described above for the preparation of **15**, afforded an essentially quantitative yield of glycosides **20** ($\alpha:\beta \sim 1:1$); R_F 0.30 (β) and 0.44 (α) (*F*); a sample of **20***a* was obtained by column chromatography (*G*): syrup; ^{1}H-n.m.r. data (360 MHz): δ 2.73 (br d, 1 H, $J_{2,OH}$ 7 Hz, 2-OH), 3.49 (s, 3 H, OCH_3), 3.625 (dd, 1 H, $J_{4,5A}$ 6.7, $J_{5A,5B}$ 10.5 Hz, H-5A), 3.70 (dd, 1 H, $J_{4,5B}$ 4.3 Hz, H-5B), 3.80 (s, 3 H, $ArOCH_3$), 3.98 (dd, 1 H, $J_{2,3}$ 4.2, $J_{3,4}$ 6.0 Hz, H-3), 4.25 (br m, 1 H, H-2), 4.385 (dt, 1 H, H-4), 4.50 and 4.61 (2 d, AB, 2 H, J_{AB} 12.2 Hz), 4.505 and 4.69 (2 d, AB, 2 H, J_{AB} 12.2 Hz) (2 OCH_2Ar), 4.98 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 6.82–6.92 (m, 3 H), and 7.20–7.30 (m, 5 H) (2 Ar).

Anal. Calc. for $C_{21}H_{25}ClO_6$ (408.88): C, 61.69; H, 6.16; Cl, 8.67. Found: C, 61.72; H, 6.24; Cl, 8.62.

Reaction of glycosides **20** *with tin(IV) chloride.* — A solution of glycosides **20** (α/β mixture) (0.15 g, 0.37 mmol) in dry dichloromethane (5 mL) was treated with tin(IV) chloride (as a M solution in dichloromethane, 0.4 mL, 0.4 mmol) for 19 h at room temperature. The mixture was then processed as described above (reaction of **6** with $TiCl_4$), and the final products were separated by column chromatography (*H*) which afforded, in order of elution, dimer analogue of **11** (35 mg, 25%), "ortho" isomer **22** (13 mg, 9%), and compound **21** (60 mg, 43%), the 3-*O*-(4-chlorobenzyl) analogue of **12**.

Physicochemical data for Compound **21**: Syrup; ^{1}H-n.m.r. data (360 MHz): δ 3.56 (dd, 1 H, $J_{3A,4}$ 3.4, $J_{3A,3B}$ 12.8 Hz, H-3A), 3.76 (s, 3 H, OCH_3), 4.10 (d, 1 H, $J_{3B,4}$ 0 Hz, H-3B), 4.175 (distorted t, 1 H, $J_{4,5}$ 7.2, $J_{5,6}$ 6.5 Hz, H-5), 4.22 (distorted dd, 1 H, H-4), 4.49 (dd, 1 H, $J_{6,7}$ 6.4 Hz, H-6), 4.56 and 4.65 (2 d, AB, J_{AB} 12.1 Hz, $OCH_2C_6H_4Cl$), 4.76 (d, 1 H, H-1), 4.85 and 4.95 (2 d, AB, $J_{1A,1B}$ 13.7 Hz, H-1A,1B), 6.63 (d, 1 H, $J_{9,11}$ 2.7 Hz, H-11), 6.69 (dd, 1 H, $J_{8,9}$ 8.3 Hz, H-9), 7.02 (d, 1 H, H-8), and 7.23–7.31 (AA'BB', 4 H, $OCH_2C_6H_4Cl$); after acetylation, the signals of H-5, H-6, and H-7 were shifted to δ 4.36 (t, 1 H, $J_{4,5}$ 7.5, $J_{5,6}$ 7.1 Hz), 5.72 (dd, 1 H, $J_{6,7}$ 6.0 Hz) and 4.87 (d, 1 H), respectively. ^{13}C-N.m.r. data (90 MHz; assignments were verified by ^{1}H–^{13}C HETCOR): δ 55.22 ($ArOCH_3$), 70.46 (C-3), 71.77 (OCH_2Ar), 77.64 (C-4), 78.19 (C-1), 82.91 (C-5), 83.16 (C-6), 86.90 (C-7), 111.69 (C-9), 115.32 (C-11), 128.55, 128.86, 129.01 (C-8, C-2,3/5,6 of *p*ClBn), 131.44, 133.47, 136.50, 137.25 (C-7a,11a, C-1,4 of *p*ClBn), and 158.88 (C-10).

Physicochemical data for Compound **22**: Syrup; ^{1}H-n.m.r. data (360 MHz): δ 3.60 (dd, 1 H, $J_{3A,4}$ 3.9, $J_{3A,3B}$ 12.8 Hz, H-3A), 3.86 (s, 3 H, OCH_3), 4.12 (d, 1 H, $J_{3B,4}$ 0 Hz, H-3B), 4.31 (t, 1 H, $J_{4,5}$ 7.6, $J_{5,6}$ 6.8 Hz, H-5), 4.38 (dd, 1 H, H-3), 4.53 (t, 1 H, $J_{6,7}$ 6.0 Hz, H-6), 4.60 and 4.77 (2 d, AB, J_{AB} 12.2 Hz, $OCH_2C_6H_4Cl$), 4.86 and 5.10 (2 d, AB, $J_{1A,1B}$ 13.2 Hz, H-1A,1B), 5.60 (d, 1 H, H-7), 6.74 (br d, 1 H, *J* 7.5 Hz) and 6.87 (br d, 1 H, *J* 8.2 Hz) (H-9,11), 7.16 (t, 1 H, H-10), and 7.29 (br s, 4 H, $OCH_2C_6H_4Cl$); after acetylation, the signals of H-5, H-6, and H-7 were shifted to δ 4.41 (t, 1 H, $J_{4,5}$ 7.6, $J_{5,6}$ 6.6 Hz), 5.73 (t, 1 H, $J_{6,7}$ 5.9 Hz), and 5.63 (d, 1 H), respectively.

Synthesis of **8** *from compound* **23**. — Bicyclic *C*-glycoside **9** was benzylated at O-11 with 3-methoxybenzyl chloride (see General Procedure), to give compound **23** which was purified by column chromatography: $[\alpha]_D$ −49.2° (*c* 1.2); ^{1}H-n.m.r. (360 MHz): δ 3.76, 3.77 and 3.79 (3 s, 3 × 3 H, 3 $ArOCH_3$), 3.86 (dd, 1 H, $J_{3,3'A}$ 6.4, $J_{3'A,3'B}$ 10.3 Hz, H-3'A), 3.95 (dd, 1 H, $J_{3,3'B}$ 5.0 Hz, H-3'B), 4.20 (d, 1 H, $J_{1,11}$ 0, $J_{4,11}$ 1.3 Hz, H-11), 4.465 (narrow m, 1 H, $J_{3,4}$ ~2 Hz, H-4), 4.51–4.64 (several signals, 6 H, H-3,6A, 2 OCH_2Ar), 4.93 (d, 1 H, $J_{6A,6B}$ 14.8 Hz, H-6B), 5.03 (s, 1 H, H-1), 6.59 (d, 1 H, $J_{7,9}$ 2.6 Hz, H-7), 6.74 (dd, 1 H, $J_{9,10}$ 8.3 Hz, H-9), 6.78–6.92 (several m's, 6 H, H-2,4,6 of 2 *m*MeOBn), 7.15 (d, 1 H, H-10), 7.225 and 7.245 (2 t, 2 H, H-5 of 2 *m*MeOBn).

Anal. Calc. for $C_{29}H_{32}O_7$ (492.57): C, 70.71; H, 6.55. Found: C, 70.51; H, 6.80.

Compound **23** was reacted with tin(IV) chloride (1.0 equiv) in dichloromethane (see preparation of **4**) to give an essentially quantitative yield of a product contaminated by a small amount of an isomeric by-product. The major component was isolated by preparative t.l.c. (*G*) and found to be identical to **8** {$[\alpha]_D$ +86.0° (*c* 1.0), superposable ^{1}H-

and ^{13}C-n.m.r. spectra}. The by-product was identified as the "*ortho*-alkylation" isomer of **8** (1,11-dimethoxy analog of **8**); characteristic ^{1}H-n.m.r. signals in aromatic region: δ 6.15 (d, 1 H, $J_{12,13}$ 8.7 Hz, H-13), 6.49 (dd, 1 H, $J_{10,12}$ 2.8 Hz, H-12), 6.71 (d, 1 H, H-10), 6.59 and 6.74 (2 d, 2 H, $J_{2,3} = J_{3,4} = 7.6$ Hz, H-2,4), and 7.055 (t, 1 H, H-3).

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