Unusual 1,5-Hydride Shifts in Lewis Acid Mediated Reactions of Benzylated Sugars. Synthesis of 3-Alkylisochroman Derivatives

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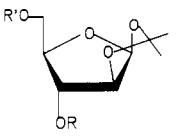
Tin(IV) chloride mediated reactions of methyl 3,5-di-*O*-(4-chlorobenzyl)-2-*O*-(3-methoxybenzyl)-D-arabino- and -D-xylofuranosides **5** and **13** afforded unexpectedly, in one step, 3-alkyl-7-methoxyisochroman derivatives **7** and **14**, respectively. These products are formed, most probably, by way of a complex process involving the intramolecular Friedel–Crafts alkylation of the activated benzyl group at O-2, leading to an internal aryl *C*-furanoside (e.g. **6**), followed by an in situ reductive opening of the tetrahydrofuranyl ring of the intermediate *C*-furanoside. An experiment with a deuterium-labeled substrate demonstrated that this reductive step occurred by way of a stereospecific, tin(IV) chloride promoted 1,5 shift of a hydride ion from the 4-chlorobenzyl substituent at O-3 to the "anomeric" position of the *C*-furanoside, with retention of configuration at the migration terminus, and formation (after aqueous processing) of 4-chlorobenzaldehyde as a byproduct. This process provides a convenient methodology for the synthesis of enantiomerically pure isochroman derivatives from readily available carbohydrate precursors.

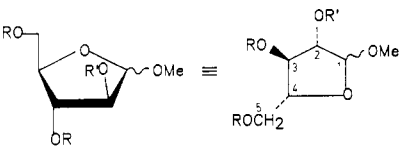
Our recent investigations[1] have shown that the *intramolecular* reactions of benzylated sugars provided a short and convenient approach to 1,2-*cis*-aryl *C*-glycosyl compounds and related systems. This type of reaction should be, therefore, particularly useful for the preparation of novel *C*-nucleoside analogues having the *arabino* configuration. Very few *arabino* *C*-nucleosides have been reported so far;[2] however, the potent antitumor and antiviral properties of the well-known *arabino* *N*-nucleosides such as ara-A or ara-C[3] have justified a growing interest into the corresponding *C*-nucleosides, and the new compounds accessible by our methodology might exhibit interesting pharmacological activity. A study of the behavior of arabinofuranosides bearing, at O-2, a group susceptible of internal C-glycosylation, and at O-3 and O-5 inert and temporary protecting groups, was thus undertaken. The *m*-methoxybenzyl group was chosen as a model substituent at O-2, and the remaining positions were protected with *p*-chlorobenzyl groups, which, according to our experience,[4] are relatively unreactive in $SnCl_4$-mediated Friedel–Crafts-type C-arylation processes. The reaction of **5**, however, took an unexpected path which revealed a novel mode of participation of benzyl groups, namely, as hydride donors. We describe in this article the remarkable conversion of glycofuranosides **5** and **13** into 3-alkyl-7-methoxyisochromans and provide evidence, based on an experiment with a labeled substrate, for the mechanism and stereochemistry of the hydride-transfer process.

Results and Discussion

1,2-*O*-Isopropylidene-β-D-arabinofuranose (**2**)[5] is the most convenient precursor of arabinofuranose derivatives



1 R=H; R'=t-BuPh$_2$Si
2 R=R'=H
3 R=R'=p-ClC$_6$H$_4$CH$_2$ (pClBn)
3-d$_4$ R=R'=p-ClC$_6$H$_4$CD$_2$ (pClBn-d$_2$)



4 R=pClBn; R'=H
4-d$_4$ R=pClBn-d$_2$; R'=H
5 R=pClBn; R'=m-MeOC$_6$H$_4$CH$_2$ (mMeOBn)
5-d$_4$ R=pClBn-d$_2$; R'=mMeOBn

having a free hydroxyl group at C-2. As described recently by Garegg and co-workers,[6] the 5-*O*-*tert*-butyldiphenylsilyl derivative **1** of **2** is readily available, in acceptable yield, from the parent sugar by selective silylation and acetonation. Fluoride ion mediated desilylation of **1**, followed by *p*-chlorobenzylation of positions 3 and 5 and methanolysis, afforded arabinofuranoside **4**, a useful starting material for the application of the intramolecular C-glycosidation methodology in the *arabino* series.

The 2-*O*-(3-methoxybenzyl) derivative of **4**, compound **5**, was treated with tin(IV) chloride, with the expectation of obtaining compound **6** by intramolecular C-arylation. However, the reaction did not give **6**, but a product much more polar than the starting material (TLC analysis) as well as a strongly UV-active byproduct, readily identified as 4-chlorobenzaldehyde after separation by column chromatography. The presence of a three-proton pattern typical of a 3,4-dialkylated methoxybenzene moiety in the low-field region of the ^{1}H NMR spectrum of the new product (**7**) clearly indicated that the intramolecular Friedel–Crafts reaction had taken place; however, the expected *C*-glycosyl compound (**6**) must have undergone subsequent transformations to account for the loss of a 4-chlorobenzyl substituent, the presence of OH groups, and the complexity of the aliphatic protons region in the NMR spectrum. Evidence for the overall structure of **7** was

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(2) (a) Acton, E. M.; Fujiwara, A. N.; Goodman, L.; Henry, D. W. *Carbohydr. Res.* **1974**, *33*, 135. (b) El Khadem, H. S.; Swartz, D. L. *Carbohydr. Res.* **1974**, *32*, C1. (c) Alenin, V. V.; Domkin, V. D. *Zhur. Obshch. Khim.* **1976**, *46*, 1911. (d) Doukhan, G.; Huynh Dinh, T.; Bisagni, E.; Chermann, J. C.; Igolen, J. *Eur. J. Med. Chem.-Chim. Ther.* **1979**, *14*, 375. (e) Chu, C. K.; Reichman, U.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem.* **1978**, *21*, 96. (f) Pankiewicz, K. W.; Kim, J.-H.; Watanabe, K. A. *J. Org. Chem.* **1985**, *50*, 3319. (g) Buchanan, J. G.; Smith, D.; Wightman, R. H. *Tetrahedron* **1984**, *40*, 119. (h) Mao, D. T.; Marquez, V. E. *Tetrahedron Lett.* **1984**, *25*, 2111. (i) Jiang, C.; Baur, R. H.; Dechter, J. J.; Baker, D. C. *Nucleosides Nucleotides* **1984**, *3*, 123.

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(5) (a) Jarrell, H. C.; Ritchie, R. G.; Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1973**, *51*, 1767. The L isomer has been fully characterized: (b) Levene, P. A.; Compton, J. *J. Biol. Chem.* **1936**, *116*, 189. (c) Morgenlie, S. *Acta Chem. Scand.* **1973**, *27*, 3609.

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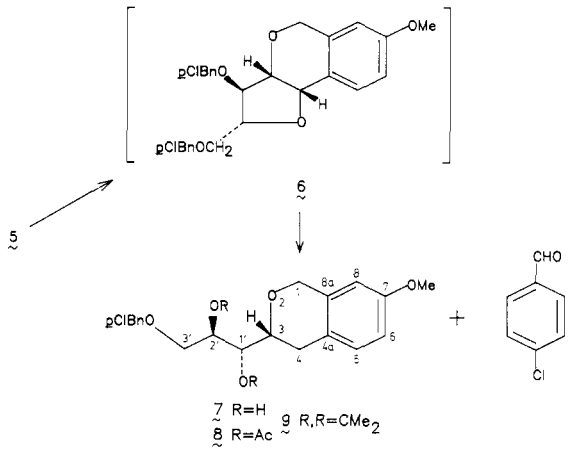
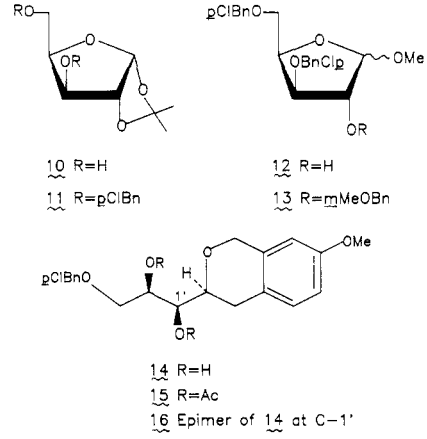
0022-3263/88/1953-3287$01.50/0

Scheme I



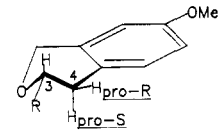
provided by the ^1H NMR spectrum of its peracetate (**8**) and of its isopropylidene derivative (**9**): thus, compound **7** contains two OH groups, at positions 3 and 4 of the starting material. While the signals of H-2 and of H-5A,5B of the starting sugar appear at "normal" chemical shifts and remain essentially unchanged on acetylation of **7**, the signal corresponding to H-1 in **5** is replaced by that of a methylene group in **7**, at a chemical shift and with coupling constants characteristic of a $PhCH_AH_BCH_X$ system. The chemical shift of the benzylic carbon ($\delta(^{13}C)$ = 29.27 ppm in **7**) is also in agreement with the presence of this fragment. These data establish unambiguously that compound **7** has the unexpected structure of a disubstituted isochroman (3,4-dihydro-1*H*-2-benzopyran) (compound **7**, Scheme I). Very similar results were obtained from D-*xylo* isomer **13**, prepared from 1,2-*O*-isopropylidene-α-D-xylo-



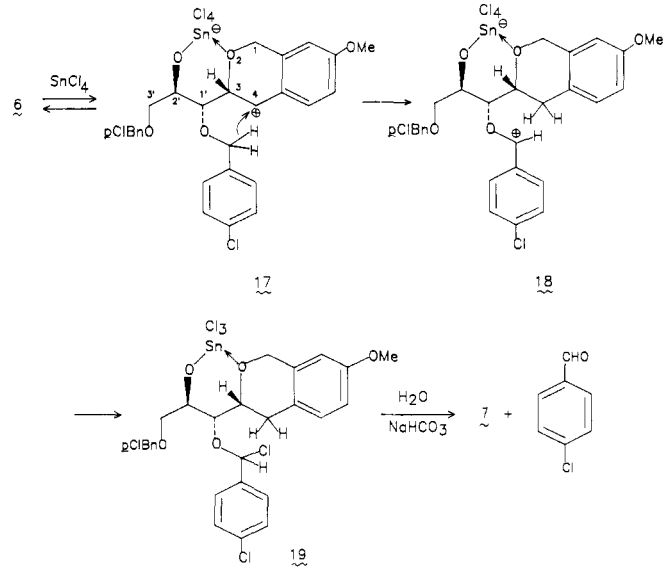
furanose (**10**) by the same sequence of reactions. Both diols **7** and **14** were obtained as readily crystallizing materials in good yields,[7] in spite of the complexity of the process involved, and the only other product that could be isolated from the reaction mixture and identified is a position isomer of **7** (see below).

The different magnitude of the coupling constants between each of the protons of the newly created methylene group and H-3 ($J_{3,4pro\text{-}R}$ = 3 Hz, $J_{3,4pro\text{-}S}$ = 11.5 Hz) indicates that the saturated portion of the bicyclic system adopts a half-chair conformation with the substituent at C-3 in equatorial position and with a trans-diaxial relationship between H-3 and H-4*pro-S* (Scheme II). Furthermore, the unusually large geminal coupling constant between H-1A and H-1B ($|J|$ > 15 Hz), as well as between H-4*pro-R*

Scheme II



Scheme III



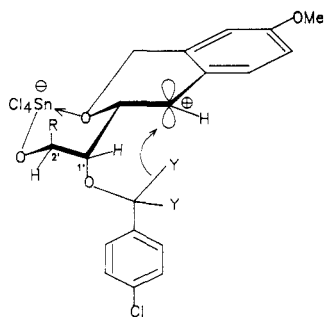
and H-4*pro-S* should be noted: as we had observed before,[1c] this feature is an indication that the benzylic methylene group is incorporated in a cyclic structure. Interestingly, this applies to both the OCH_2Ar and C-CH_2Ar fragments.

Compounds **7** and **14** arise most probably from the corresponding internal aryl *C*-glycosyl compounds (**6** in D-*arabino* series) by way of an unusual, in situ *reductive cleavage* of the C_1–O_4 bond (sugar numbering), accompanied by the loss of the 4-chlorobenzyl group at O-3. The fact that 4-chlorobenzaldehyde is obtained as a byproduct suggests the following mechanism (Scheme III): in the first step, the Lewis acid promotes the cleavage of the benzylic C_1–O_4 bond of **6**, highly reactive because of the presence of the *p*-methoxy substituent, to give a cationic intermediate such as **17**. This process was already proposed as an essential step in the $SnCl_4$-mediated reactions of tri-*O*-(3-methoxybenzyl)glycofuranose derivatives, which lead to products resulting from two consecutive intramolecular Friedel–Crafts alkylations.[1b] In the case of **17**, however, the reactivity of the benzyl group at O-3 (≡ O-1′ of **17**) is not sufficient for a second electrophilic substitution to occur; instead, in the second step, the reaction evolves by *transfer of a hydride ion* from that group to C-1 (≡ C-4 of the isochroman system); the new benzylic cation (**18**) thus formed is more stable than the starting one (**17**) owing to the presence of the oxygen atom (alkoxycarbonium ion) and the *p*-chlorophenyl substituent. That difference of stability constitutes undoubtedly one of the driving forces of the overall reaction. Trapping of a chloride ion from the reagent, to form neutral intermediate **19**, followed by hydrolytic cleavage of the substituents at O-1′ and O-2′, gives finally diol **7**, or its *xylo* analogue **14**, and 4-chlorobenzaldehyde. The lability of α-halobenzyl ethers under hydrolytic conditions is well documented[8] and this prop-

(7) Nearly quantitative yields were obtained in the *arabino* series when the reaction mixture was quenched with aqueous sodium bicarbonate and the two-phase system stirred for at least 15 min at room temperature.

(8) (a) BeMiller, J. N.; Wing, R. E.; Meyers, C. Y. *J. Org. Chem.* **1968**, *33*, 4292. (b) Horman, I.; Friedrich, S. S.; Keefer, R. M.; Andrews, L. J. *J. Org. Chem.* **1969**, *34*, 905.

Scheme IV



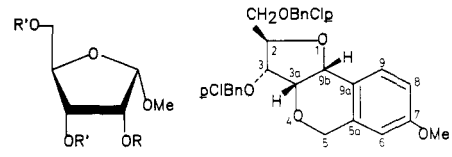
17 R=pClBnOCH$_2$ Y=H

17-d_2 R=pClBn(d_2)OCH$_2$ Y=D

erty has been recently exploited in a new and mild method of debenzylation of benzyl glycosides.[9]

The key step of the conversion of **6** into **7** is thus a remarkable intramolecular 1,5-hydride shift: although H^- shifts of this order are relatively frequent in monocyclic (transannular) and polycyclic cations,[10] 1,5-hydride shifts in acyclic systems are rare,[11] because of the large distance usually existing between the reacting sites. From a topological point of view, the ease with which the H^- transfer occurs in **17** is probably due to a particularly favorable arrangement of the migration origin and terminus: we believe indeed that the Lewis acid forms a complex[12] with both the O-2′ and the isochroman ring oxygen atoms of **17**, thereby creating a new ring which holds the alkyl chain in a rigid conformation (see details in Scheme IV); in both the *arabino* and the *xylo* isomers [which differ only by the relative orientation of the $CH_2OBnClp$ group (R in Scheme IV)], the (4-chlorobenzyl)oxy substituent at C-1′ occupies an axial position and the α-hydrogen atoms of this group are very close to the cationic center; the reaction can thus proceed via a favorable six-membered transition state. In order to test this structural requirement, the reaction was also performed in the *ribo* series: the *ribo* isomer of intermediate **17** would have, indeed, the (4-chlorobenzyl)oxy group at C-1′ in an *equatorial* position. Reaction of ribofuranoside **21** with 1.0 equiv of tin(IV) chloride led, not unexpectedly,[4] to **20** by selective cleavage of the benzyl group at O-2. However, with a smaller amount of Lewis acid (0.4 equiv), internal *C*-glycosyl compound **22** was obtained as the major product (44%, including a small amount of its 9-methoxy isomer); careful analysis of the reaction mixture led to the isolation of the *ribo* epimer of diol **7**, compound **16**, in 3% yield only. Thus, as expected, the hydride-transfer process is much less efficient in the *ribo* series because, in the key intermediate, the α-hydrogen atoms of the benzylic substituent at O-1′ would be more distant from the cationic center than in the *arabino* and *xylo* series, and the reaction stops at the stage of the internal Friedel–Crafts substitution product (**22**).

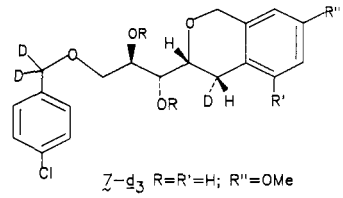
In order to probe the entire mechanism and determine the stereochemistry of the hydride-transfer process, the reaction of **5** labeled with deuterium at the benzylic position of the 4-chlorobenzyl groups was also investigated. Compound **5**-d_4 was prepared from **2** by the same sequence of reactions using α,α-dideuterio-4-chlorobenzyl chloride as the benzylating agent; as a consequence of the mode of preparation of this reagent (see Experimental Section), the degree of labeling was very high and no detectable signal could be observed for the residual benzylic protons on the ^1H NMR spectrum of **5**-d_4. The reaction of **5**-d_4 with $SnCl_4$ led to extremely interesting results:



20 R=H; R′=pClBn

21 R=mMeOBn; R′=pClBn

22



7-d_3 R=R′=H; R″=OMe

8-d_3 R=Ac; R′=H; R″=OMe

23 R=H; R′=OMe; R″=H

24 R=Ac; R′=OMe; R″=H

(1) Chromatographic separation of the clean reaction mixture afforded α-deuterio-4-chlorobenzaldehyde in nearly quantitative yield and compound 7-d_3, contaminated by a small amount of its position isomer **23**, in 89% overall yield. The presence of a 3-H pattern characteristic of a 1,2,3-trisubstituted benzene derivative in the ^1H NMR spectrum of the diacetate of **23** (compound **24**) immediately revealed the structure of this byproduct.

(2) According to their ^1H NMR and mass spectra, compounds 8-d_3 and **24** clearly contain three deuterium atoms, one at C-4 of the isochroman ring, and two in the remaining 4-chlorobenzyl substituent. Thus, the newly introduced atom at C-4 arises from the benzyl group lost during the process.

(3) Furthermore, *the pro-S hydrogen atom exclusively is replaced by deuterium at C-4*; the signal of the remaining *pro-R* hydrogen is a broad doublet exhibiting a small coupling constant with H-3 ($J_{3,4pro\text{-}R}$ = 3 Hz) and a small isotopic shift ($\Delta\delta$ = 0.02 ppm); the signal of H-3 is also simplified accordingly. Thus, the *hydride/deuteride shift is stereospecific* and, as the transferred ion is introduced in trans with respect to H-3, the reaction occurs with *retention of configuration at C-4*.

These results provide strong experimental evidence for the proposed mechanism: because of the conformational rigidity imposed to intermediate **17** by formation of a Sn(IV) complex, the migrating ion is indeed expected to be delivered stereospecifically to the *si* face of the cationic center of **17** (Scheme IV). Furthermore, the same stereochemistry had been observed for a process that involved a very similar intermediate, namely the tandem Friedel–Crafts reactions of tri-*O*-(3-methoxybenzyl)glycofuranose derivatives.[1b]

Thus, the $SnCl_4$-mediated reaction of selectively benzylated glycofuranosides **5** and **13** provides, by way of an internal Friedel–Crafts alkylation followed by an unusual hydride transfer, a short and convenient access to enantiomerically pure isochroman derivatives bearing a highly functionalized alkyl chain at C-3. As the starting sugar derivatives are readily available, the new process described

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(10) Fry, J. L.; Karabastos, G. J. *Carbonium Ions*; Olah, G. J., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1970; Vol. II, p 525 ff.

(11) (a) Atkinson, R. S.; Green, R. H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 394. (b) Djerassi, C.; Lang, R. W. *Tetrahedron Lett.* **1982**, *23*, 2063.

(12) This interpretation is supported by the strong affinity of tin(IV) chloride for oxygenated ligands and its high tendency to form hexacoordinated complexes. See: *Gmelin Handbuch der Anorganischen Chemie*, 8th ed.; Vol. 46, Pt C5, Chapter 2.10.

in this article constitutes a synthetically useful methodology for the preparation of isochroman derivatives, a heterocyclic system[13] for which few synthetic procedures are available.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage or on a Thermolyne microscope apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 243 automatic polarimeter for solutions in a 0.1-dm cell at 22 ± 3 °C. IR spectra were recorded with a Perkin-Elmer 283B spectrophotometer. Routine ^{1}H NMR spectra were recorded at 60 MHz (Varian EM360A). High-field NMR spectra (^{1}H: 250, 360 or 500 MHz) were obtained at the NIH-Resource NMR and Data Processing Laboratory of Syracuse University. Chloroform-*d* was used as the solvent with tetramethylsilane as the internal standard, unless otherwise stated. Chemical shifts and coupling constants were obtained from first-order analysis of the spectra.

Analytical TLC was performed on precoated glass plates with Merck silica gel 60 F-254 as the adsorbant (layer thickness 0.25 mm). The developed plates were air-dried and irradiated with UV light, or sprayed with a solution of ammonium phosphomolybdate[14] (or both), and heated at 120–140 °C. Column chromatography was performed on silica gel 60 (70–230 mesh) and flash chromatography[15] on silica gel 60 (230–400 mesh). Preparative liquid chromatography was performed on prepacked EM Lobar columns containing LiChroprep Silica gel 60 (40–63 μm) using a FMI Lab pump (0–46 mL/min) and an ISCO V^4 variable-wavelength UV detector. The following solvent systems were used: A, 4:1 toluene–ethyl acetate; B, ethyl acetate; C, 9:1, D, 3:1 hexane–ethyl acetate; E, 1:9 petroleum ether–ethyl acetate; F, 1:1, G, 5:2, H, 3:1 ether–hexane.

Solvents were evaporated under reduced pressure and below 40 °C. The polycyclic compounds are numbered as indicated in structures **7** and **22**.

General Benzylation Procedure. To a solution of substrate in anhydrous DMF (10 mL/mmol)[16] 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 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 product was extracted with CH_2Cl_2 (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 usually submitted to column or flash chromatography for purification.

1,2-*O*-Isopropylidene-β-D-arabinofuranose (2). To a solution of 5-*O*-(*tert*-butyldiphenylsilyl)-1,2-*O*-isopropylidene-D-arabinofuranose (**1**)[6] (7.0 g, 16.3 mmol) in anhydrous THF (200 mL) was added a 1 M solution of tetra-*n*-butylammonium fluoride in THF (33 mL, 33 mmol), and the mixture was stirred for 1 h at room temperature. The solvent was then evaporated and the residue submitted to column chromatography (solvent A; after elution of the silicon-containing byproduct, solvent B) which afforded 2.0 g (64%) of compound **2**: mp 114–115 °C [lit. mp L isomer 113–115 °C,[5c] 117–118 °C[5b]]; $[\alpha]_D$ +17.6° (*c* 1.25, MeOH) [L isomer[5c] $[\alpha]_D$ −28.9° (*c* 2, H_2O)]; R_f 0.41 (solvent B); ^{1}H NMR (360 MHz) δ 1.33 and 1.53 (2 s, 2 × 3 H, CMe_2), 2.14 (m, ~2 H, 2 OH), 3.78 (m, 2 H, H-5A,5B), 4.095 (ddd, 1 H, $J_{3,4}$ = ~1.8 Hz, $J_{4,5A(or\ B)}$ = ~4 Hz, $J_{4,5B(or\ A)}$ = ~6.6 Hz, H-4), 4.26 (br s, 1 H, H-3), 4.58 (d, 1 H, $J_{1,2}$ = 4.2 Hz, $J_{2,3}$ = ~0 Hz, H-2), 5.94 (d, 1 H, H-1).

3,5-Di-*O*-(4-chlorobenzyl)-1,2-*O*-isopropylidene-β-D-arabinofuranose (3). Benzylation of compound **2** (0.95 g, 5.0 mmol) with 4-chlorobenzyl chloride (see general procedure) afforded, after column chromatography (solvent C), 1.6 g (73%) of pure **3**: mp 53–54 °C; $[\alpha]_D$ +11.4° (*c* 0.7, $CHCl_3$); R_f 0.73 (solvent A); MS, *m/z* (relative intensity) 125 (100) and 127 (34) ($C_7H_6Cl^+$), 126 (8), 43 (7), 89 (6), 237 (5), 313 (4) and 315 (1.5) ($M^{\bullet+}$ − $C_7H_6Cl^{\bullet}$), 115 (4), 59 (4), ... 423 (1) and 425 (0.6) ($M^{\bullet+}$ − $Me^{\bullet}$).

Anal. Calcd for $C_{22}H_{24}Cl_2O_5$: C, 60.14; H, 5.51; Cl, 16.14. Found: C, 60.13; H, 5.52; Cl, 16.24.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-α- and -β-D-arabinofuranoside (4). A solution of compound **3** (1.5 g, 3.4 mmol) in 2.5% methanolic sulfuric acid (40 mL) was heated under reflux for 1 h. Water (50 mL) was then added, the organic material was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were washed with water (50 mL), dried (Na_2SO_4), and concentrated, to give 1.4 g (99%) of syrupy **4** (mixture of α and β anomers): R_f 0.20 and 0.27 (solvent A); IR (film) 3440 (OH), 2920, 2870, 1600, 1495, 1410, 1365, 1210, 1195, 1090 (br), 1050, 1015, 840, 810, and 735 cm^{-1}; MS, *m/z* (relative intensity) 125 (100) and 127 (32) ($C_7H_6Cl^+$), 126 (10), 89 (8), 75 (5), 141 (4), 90 (4), 128 (3), 99 (3), 115 (3), ... 287 (1.3) and 289 (0.4) ($M^{\bullet+}$ − $C_7H_6Cl^{\bullet}$).

Anal. Calcd for $C_{20}H_{22}Cl_2O_5$: C, 58.12; H, 5.37. Found: C, 57.93; H, 5.46.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-*O*-(3-methoxybenzyl)-α- and -β-D-arabinofuranoside (5). Benzylation of compound **4** (1.0 g, 2.4 mmol) with 3-methoxybenzyl chloride (see general procedure) afforded, after column chromatography (solvent C), 0.95 g (74%) of pure **5** (α/β ~2:1); R_f 0.56 and 0.65 (solvent A); IR (film) 2910, 2870, 2840, 1600, 1590, 1490, 1460, 1370, 1155, 1090, 1050, 1015, 805, 780, and 690 cm^{-1}; MS, *m/z* (relative intensity) 121 (100) ($C_7H_6OMe^+$), 125 (70) and 127 (23) ($C_7H_6Cl^+$), 122 (12), 317 (9), 91 (9), 245 (7), 246 (6), 126 (6), 89 (5), 77 (4), 319 (3), ... 532 (0.5) and 534 (0.3) ($M^{\bullet+}$).

A sample of the major isomer (α) was isolated by column chromatography (solvent C): ^{1}H NMR (360 MHz) δ 3.385 (s, 3 H, 1-OMe), ~3.58 and ~3.61 (ABX, 2 H, $J_{4,5A}$ = 5.3 Hz, $J_{4,5B}$ = 4.0 Hz, $J_{5A,5B}$ = 10.6 Hz, H-5A,5B), 3.79 (s, 3 H, ArOMe), 3.87 (dd, 1 H, $J_{2,3}$ = 2.7 Hz, $J_{3,4}$ = 6.2 Hz, H-3), 3.97 (br d, 1 H, $J_{1,2}$ = 1.3 Hz, H-2), 4.17 (br q, 1 H, H-4), 4.41–4.57 (3 AB, 6 H, 3 OCH_2Ar), 4.94 (s, 1 H, H-1), 6.82–6.90 (m, 3 H) and 7.14–7.29 (m, 9 H) (3 C_6H_4).

Anal. Calcd for $C_{28}H_{30}Cl_2O_6$: C, 63.04; H, 5.67. Found: C, 63.12; H, 5.72.

(3*R*)-3,4-Dihydro-3-[(1*R*,2*R*)-1,2-dihydroxy-3-[(4-chlorobenzyl)oxy]propyl]-7-methoxy-1*H*-2-benzopyran (7). To a solution of compound **5** (0.9 g, 1.7 mmol) in anhydrous CH_2Cl_2 (10 mL) was added a 1 M solution of $SnCl_4$ in CH_2Cl_2 (1.7 mL, 1.7 mmol), and the mixture was stirred for 30 min after which time TLC (solvent A) indicated the absence of starting material. Water (50 mL) was then added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with water (25 mL), dried (Na_2SO_4), and concentrated, and the residue was submitted to column chromatography (solvent A). The first, fast moving fraction was collected and identified as 4-chlorobenzaldehyde. Further elution gave the major fraction which was recrystallized from $CHCl_3$–hexane to give 420 mg (65%) of pure **7**: mp 133–134 °C; $[\alpha]_D$ +86.7° (*c* 1.2, $CHCl_3$); R_f 0.67 (solvent B); IR (KBr) 3470 (OH), 2940, 2860, 1615, 1510, 1498, 1470, 1425, 1365, 1325, 1265, 1230, 1160, 1125, 1087, 1065, 1030, 1010, 920, 852, 820, 811, 795 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.42 (dd, 1 H, $J_{3,4pro\text{-}R}$ = 2.8 Hz, $J_{4pro\text{-}R,4pro\text{-}S}$ = 15.8 Hz, H-4*pro*-*R*), 2.925 (dd, 1 H, $J_{3,4pro\text{-}S}$ = 11.9 Hz, H-4*pro*-*S*), 3.305 (dd, 1 H, $J_{3,1'}$ = 2.6 Hz, $J_{1',2'}$ = 8.4 Hz, H-1′), 3.36 (s, 2 H, 2 OH), 3.485 (dd, 1 H, $J_{2',3'A}$ = 6.8 Hz, $J_{3'A,3'B}$ = 10.0 Hz, H-3′A), 3.685 (dd, 1 H, $J_{2',3'B}$ = 2.9 Hz, H-3′B), 3.70 (s, 3 H, OMe), 3.78 (dt, 1 H, H-2′), 3.815 (td, 1 H, H-3), 4.51 (~s, 2 H, OCH_2Ar), 4.64 (d, 1 H, $J_{1A,1B}$ = 15.6 Hz, H-1A), 4.74 (d, 1 H, H-1B), 6.62 (d, 1 H, $J_{6,8}$ = 2.6 Hz, H-8), 6.735 (dd, 1 H, $J_{5,6}$ = 8.4 Hz, H-6), 7.04 (d, 1 H, H-5), 7.39 (~s, 4 H, C_6H_4); ^{13}C NMR (125.76 MHz) δ 29.27 (C-4), 55.35 (OCH_3), 68.38 (C-3′), 70.83, 71.72, 72.80, 73.87, 74.36 (C-1,3,1′,2′, OCH_2Ar), 108.99, 113.05 (C-6,8), 125.08, 133.67, 135.05, 136.42 (C-4a,8a, C-1,4 of *p*ClBn), 128.66, 129.07, 130.04 (C-5, C-2/6,3/5 of *p*ClBn), 158.03 (C-7); MS, *m/z* (relative intensity) 135 (100), 193 (41), 125 (39), and 127 (13) ($C_7H_6Cl^+$), 176 (32), 175 (28), 134 (26), 163 (22), 91 (18), 147 (18), ... 360 (1.1) and 362 (0.4) ($M^{\bullet+}$ − H_2O), 378 (1.4) and 380 (0.6) ($M^{\bullet+}$).

(13) Hepworth, J. D. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 737 ff.

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(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(16) The amount of DMF can be reduced by using a 2:1 mixture of toluene and DMF as the solvent. See, for example: Kawana, M.; Kuzuhara, H.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1492.

Anal. Calcd for $C_{20}H_{23}ClO_5$: C, 63.41; H, 6.12; Cl, 9.36. Found: C, 63.69; H, 6.13; Cl, 9.68.

Diacetate of Compound 7 (8). Compound **7** was acetylated under standard conditions (pyridine–acetic anhydride) and the diacetate **8** was purified by column chromatography (solvent C): syrup, R_f 0.53 (solvent A); ^{1}H NMR (500 MHz) δ 2.08 (s, 6 H, 2 OAc), 2.56 (dd, 1 H, $J_{3,4pro\text{-}R}$ = 3.1 Hz, $J_{4pro\text{-}R,4pro\text{-}S}$ = 15.7 Hz, H-4*pro*-*R*), 2.76 (dd, 1 H, $J_{3,4pro\text{-}S}$ = 11.5 Hz, H-4*pro*-*S*), 3.60 (dd, 1 H, $J_{2',3'A}$ = 5.2 Hz, $J_{3'A,3'B}$ = 11.0 Hz, H-3′A), ~3.76 (dd, 1 H, $J_{2',3'B}$ = 3.1 Hz, H-3′B), 3.77 (s, 3 H, OMe), 3.85 (dt, 1 H, $J_{3,1'}$ = 3.1 Hz, H-3), 4.45 and 4.52 (2 d, 2 H, J_{AB} = 12.1 Hz, OCH_2Ar), 4.67 (d, 1 H, $J_{1A,1B}$ = 15.2 Hz, H-1A), 4.83 (d, 1 H, H-1B), 5.39 (dd, 1 H, $J_{1',2'}$ = 6.8 Hz, H-1′), 5.42 (ddd, 1 H, H-2′), 6.50 (d, 1 H, $J_{6,8}$ = 2.6 Hz, H-8), 6.74 (dd, 1 H, $J_{5,6}$ = 8.4 Hz, H-6), 7.01 (d, 1 H, H-5), 7.24 and 7.30 (AA′BB′, 4 H, C_6H_4).

Isopropylidene Derivative of Compound 7 (9). Derivative **9** was prepared by treatment of compound **7** with 2,2-dimethoxypropane (neat) in the presence of Amberlite IR-120(H^+) ion-exchange resin for 4 h at room temperature, removal of the resin by filtration, evaporation of the solvent, and purification of the residue by column chromatography (solvent C): syrup, R_f 0.56 (solvent A); ^{1}H NMR (500 MHz) δ 1.41 and 1.49 (2 s, 2 × 3 H, CMe_2), 2.70 (dd, 1 H, $J_{3,4pro\text{-}R}$ = 2.7 Hz, $J_{4pro\text{-}R,4pro\text{-}S}$ = 15.5 Hz, H-4*pro*-*R*), 2.845 (dd, 1 H, $J_{3,4pro\text{-}S}$ = 11.5 Hz, H-4*pro*-*S*), 3.575 (dd, 1 H, $J_{2',3'A}$ = 5.4 Hz, $J_{3'A,3'B}$ = 10.1 Hz, H-3′A), 3.665 (dd, 1 H, $J_{2',3'B}$ = 6.8 Hz, H-3′B), 3.71 (ddd, 1 H, $J_{3,1'}$ = ~6.4 Hz, H-3), 3.79 (s, 3 H, OMe), 4.21 (m, 2 H, H-1′,2′), 4.43 and 4.53 (2 d, 2 H, J_{AB} = 11.8 Hz, OCH_2Ar), 4.69 (d, 1 H, $J_{1A,1B}$ = 15.5 Hz, H-1A), 4.855 (d, 1 H, H-1B), 6.535 (d, 1 H, $J_{6,8}$ = 2.7 Hz, H-8), 6.745 (dd, 1 H, $J_{5,6}$ = 8.1 Hz, H-6), 6.945 (d, 1 H, H-5), 7.18 and 7.22 (AA′BB′, 4 H, C_6H_4).

3,5-Di-*O*-(4-chlorobenzyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (11). Benzylation of 1,2-*O*-isopropylidene-α-D-xylofuranose (**10**)[17] (2.6 g, 13.7 mmol) with 4-chlorobenzyl chloride (see general procedure) afforded, after column chromatography (solvent D) and recrystallization from ethyl acetate–hexane, 5.6 g (93%) of pure **11**: mp 70–71 °C; $[\alpha]_D$ −48.6° (*c* 1.1, $CHCl_3$); R_f 0.38 (solvent D); MS, *m*/*z* (relative intensity) 125 (100) and 127 (33) ($C_7H_6Cl^+$), 126 (8), 313 (8) and 315 (3) ($M^{\bullet+}$ − $C_7H_6Cl^{\bullet}$), 59 (7), 43 (7), 89 (7), 115 (7), 141 (5), 90 (4), ... 438 (0.4) and 440 (0.3) ($M^{\bullet+}$).

Anal. Calcd for $C_{22}H_{24}Cl_2O_5$: C, 60.14; H, 5.51; Cl, 16.14. Found: C, 60.30; H, 5.47; Cl, 16.71.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-α- and -β-D-xylofuranoside (12). Methanolysis of **11** (3.0 g, 6.8 mmol) in methanol (50 mL) in the presence of Amberlite IR-120(H^+) ion-exchange resin (10 g) at reflux temperature for 8 h gave, after removal of the resin by filtration and evaporation of the solvent, a quantitative yield of **12** (α/β ~1:1) as a colorless syrup: $[\alpha]_D$ +46.7° (*c* 1.5, $CHCl_3$); R_f 0.18 and 0.29 (solvent A); MS, *m*/*z* (relative intensity) 125 (100) and 127 (33) ($C_7H_6Cl^+$), 126 (10), 89 (9), 255 (7), 75 (7), 87 (6), 141 (5), 90 (4), 287 (4) and 289 (1) ($M^{\bullet+}$ − $C_7H_6Cl^{\bullet}$).

Anal. Calcd for $C_{20}H_{22}Cl_2O_5$: C, 58.12; H, 5.37. Found: C, 57.64; H, 5.42.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-*O*-(3-methoxybenzyl)-α- and -β-D-xylofuranoside (13). Benzylation of compound **12** (1.15 g, 2.8 mmol) with 3-methoxybenzyl chloride (see general procedure) afforded, after column chromatography (solvent D), 1.3 g (87%) of **13** as a colorless syrup: $[\alpha]_D$ +11.2° (*c* 1.1, $CHCl_3$); R_f 0.3 (solvent D); IR (film) 3000, 2920, 2870, 2840, 1600, 1590, 1490, 1460, 1440, 1410, 1365, 1340, 1265, 1190, 1085, 1050, 1010, 805, 780, 690 cm^{-1}; ^{1}H NMR (360 MHz) δ 3.40 and 3.41 (2 s, 3 H, 1-OMe-α,β), 3.55 (dd, 0.5 H, $J_{4,5A}$ = 6.4 Hz, $J_{5A,5B}$ = 10.5 Hz, H-5Aα or -β), 3.64–3.80 (m, 1.5 H, H-5Aβ or -α, H-5B), 3.78 and 3.79 (2 s, 3 H, ArOMe-α,β), 4.01 (m, 1 H), 4.29 (dd, 0.5 H), 4.36–4.65 (m, 7.5 H) (H-2–4, 3 CH_2Ar), 4.80 (d, 0.5 H, $J_{1,2}$ = 4.1 Hz, H-1α), 4.91 (d, 0.5 H, $J_{1,2}$ = ~1.5 Hz, H-1β), 6.80–6.95 (m, 3 H) and 7.14–7.34 (m, 9 H) (3 C_6H_4); ^{13}C NMR (62.91 MHz) δ 54.18, 54.27, 54.70 (1-OCH_3, $ArOCH_3$), 68.34, 68.71 (C-5α,β), 70.35, 70.72, 70.84, 71.46, 71.64 (2 C), 74.66, 78.82, 80.45, 80.73, 82.67, 85.53 (C-2–4α,β, 3 CH_2Ar-α,β), 99.39 (C-1β), 107.06 (C-1α), 112.20, 112.30, 112.42, 112.54 (C-2,4 of *m*$MeOC_6H_4CH_2$-α,β), 118.89, 119.29 (C-6 of *m*$MeOC_6H_4CH_2$-α,β), 127.48, 127.78, 127.97, 128.43 (Ar CH's), 135.18, 135.49, 135.61, 138.11 (Ar C's), 158.71 (C-1 of *m*$MeOC_6H_4CH_2$); MS, *m*/*z* (relative intensity) 121 (100) ($C_7H_6OMe^+$), 125 (65) and 127 (21) ($C_7H_6Cl^+$), 122 (12), 317 (11), 91 (9), 245 (8), 246 (5), 126 (5), 89 (4), ... 411 (0.1) and 413 (0.1) ($M^{\bullet+}$ − $C_7H_6OMe^{\bullet}$).

(3*S*)-3,4-Dihydro-3-[(1*S*,2*R*)-1,2-dihydroxy-3-[(4-chlorobenzyl)oxy]propyl]-7-methoxy-1*H*-2-benzopyran (14). Treatment of compound **13** (1.0 g, 1.87 mmol) with $SnCl_4$ (1.07 equiv) in CH_2Cl_2 for 3 h, followed by processing of the reaction mixture with water (see preparation of **7**), isolation of the major product by column chromatography (solvent E), and recrystallization from ethyl acetate–hexane, gave compound **14** (0.32 g, 45%) as white crystals: mp 78–80 °C; $[\alpha]_D$ −47.5° (*c* 1.2, $CHCl_3$); R_f 0.69 (solvent B); ^{1}H NMR (500 MHz) δ 2.64 (dd, 1 H, $J_{3,4pro\text{-}R}$ = 2.7 Hz, $J_{4pro\text{-}R,4pro\text{-}S}$ = 15.5 Hz, H-4*pro*-*R*), 2.86 (d, 1 H, *J* = 4 Hz, OH), 2.91 (br s, 1 H, OH), 2.96 (dd, 1 H, $J_{3,4pro\text{-}S}$ = 11.5 Hz, H-4*pro*-*S*), 3.65 (d, 2 H, $J_{2',3'}$ = 5.4 Hz, 2 H-3′), 3.70 (br m, 1 H, $J_{3,1'}$ = 6.0 Hz, H-1′), 3.78 (s, 3 H, OMe), 3.85 (ddd, 1 H, H-3), 4.00 (br m, 1 H, H-2′), 4.55 (s, 2 H, OCH_2Ar), 4.79 (d, 1 H, $J_{1A,1B}$ = 14.8 Hz, H-1A), 4.86 (d, 1 H, H-1B), 6.52 (br s, 1 H, $J_{6,8}$ = 2.1 Hz, H-8), 6.75 (dd, 1 H, $J_{5,6}$ = 8.1 Hz, H-6), 7.04 (d, 1 H, H-5), 7.26–7.33 (AA′BB′, 4 H, C_6H_4); ^{13}C NMR (125.76 MHz) δ 28.97 (C-4), 55.30 (OCH_3), 68.42 (C-3′), 70.77, 71.87, 72.84, 73.02, ~77 (C-1,3,1′,2′, OCH_2Ar), 109.03, 113.10 (C-6,8), 124.53 (C-4a), 128.63 (2 C), 129.01 (2 C) (C-2,3,5,6 of $pClC_6H_4CH_2$), 130.01 (C-5), 133.61, 134.89, 136.52 (C-8a; C-1,4 of $pClC_6H_4CH_2$), 158.06 (C-7); MS, *m*/*z* (relative intensity) 135 (100), 176 (43), 125 (38) and 127 (13) ($C_7H_6Cl^+$), 193 (35), 134 (28), 175 (26), 163 (24), 147 (16), 91 (15), ... 360 (1.2) and 362 (0.4) ($M^{\bullet+}$ − H_2O), 378 (1.3) and 380 (0.5) ($M^{\bullet+}$).

Anal. Calcd for $C_{20}H_{23}ClO_5$: C, 63.41; H, 6.12. Found: C, 63.24; H, 6.28.

Diacetate of Compound 14 (15). Compound **14** was acetylated under standard conditions (pyridine–acetic anhydride) and the diacetate **15** purified by column chromatography (solvent D): syrup, $[\alpha]_D$ −38.9° (*c* 0.5, $CHCl_3$); IR (film) 2930, 2870, 1740 (C=O), 1615, 1495, 1455, 1430, 1370, 1225 (br), 1090, 1030, 950, 840, 800 cm^{-1}; ^{1}H NMR (500 MHz) δ 2.07 and 2.11 (2 s, 2 × 3 H, 2 $OCOCH_3$), 2.55 (dd, 1 H, $J_{3,4pro\text{-}R}$ = 2.7 Hz, $J_{4pro\text{-}R,4pro\text{-}S}$ = 15 Hz, H-4*pro*-*R*), 2.74 (dd, 1 H, $J_{3,4pro\text{-}S}$ = 11 Hz, H-4*pro*-*S*), 3.60 (d, 2 H, $J_{2',3'}$ = 4.1 Hz, 2 H-3′), 3.77 (s, 3 H, OMe), 3.79 (m, 1 H, $J_{3,1'}$ = ~6 Hz, H-3), 4.41 (d, 1 H, J_{AB} = 12.1 Hz) and 4.54 (d, 1 H) (OCH_2Ar), 4.55 (d, 1 H, $J_{1A,1B}$ = 15.5 Hz, H-1A), 4.79 (d, 1 H, H-1B), 5.40 (dd, 1 H, H-1′), 5.44 (m, 1 H, H-2′), 6.48 (d, 1 H, $J_{6,8}$ = 2.0 Hz, H-8), 6.73 (dd, 1 H, $J_{5,6}$ = 8.1 Hz, H-6), 7.00 (d, 1 H, H-5), 7.22–7.28 (m, 4 H, C_6H_4); ^{13}C NMR (125.76 MHz) δ 28.09, 28.71 (2 $OCOCH_3$), 54.32 (OCH_3), 67.48, 67.60, 70.29, 71.61, 71.80, 72.61 (C-1,3,1′–3′, OCH_2Ar), 108.02, 112.03 (C-6,8), 123.33 (C-4a), 127.59 (2 C), 128.16 (2 C) (C-2,3,5,6 of $pClC_6H_4CH_2$), 128.88 (C-5), ~133, 134.04, 135.0 (C-8a; C-1,4 of $pClC_6H_4CH_2$), 157.18 (C-7), 169.4 (2 C, 2 $OCOCH_3$); MS, *m*/*z* (relative intensity) 135 (100), 125 (71) and 127 (24) ($C_7H_6Cl^+$), 217 (64), 43 (64), 175 (55), 202 (52), 134 (52), 91 (29), 402 (28) and 404 (10) ($M^{\bullet+}$ − AcOH), 162 (26), 462 (16) and 464 (6) ($M^{\bullet+}$).

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-*O*-(3-methoxybenzyl)-α-D-ribofuranoside (21). Benzylation of compound **20**[4] (0.533 g, 1.29 mmol) with 3-methoxybenzyl chloride (see general procedure) afforded, after flash chromatography (solvent F), 0.52 g (87%) of pure, syrupy **21**: $[\alpha]_D$ +28.4° (*c* 1.06, $CHCl_3$); R_f 0.41 (solvent G); IR (film) 2910, 2860, 2840, 1595, 1585, 1465, 1360, 1265, 1150, 1105, 1085, 1040, 1015, 805 cm^{-1}; ^{1}H NMR (60 MHz) δ 3.53 (s and m, 5 H, OCH_3, H-5A,5B), 3.80 (s, 3 H, ArOMe), 3.8–4.5 (several m, 3 H, H-2–4), 4.63 (s, 2 H), 4.83 (br s, 4 H) (3 OCH_2Ar), 5.17 (br d, 1 H, H-1), 7.0–7.6 (m, 12 H, 3 C_6H_4).

Anal. Calcd for $C_{28}H_{30}Cl_2O_5$: C, 63.04; H, 5.67. Found: C, 62.69; H, 5.66.

Reactions of 21 with Tin(IV) Chloride. To a 0.1 M solution of **21** in dry CH_2Cl_2 was added dropwise a 10% (v/v) solution of $SnCl_4$ in CH_2Cl_2 (conditions A, 0.4 equiv; conditions B, 1.0 equiv). The solution, which turned purple after ~15 min, was stirred at room temperature until TLC analysis (solvent G) indicated the absence of starting material (24–48 h). The reaction was quenched by the addition of saturated aqueous sodium bicarbonate; the organic phase was separated and the aqueous phase extracted with $CHCl_3$; the combined organic phases were dried (Na_2SO_4) and

(17) Baker, B. R.; Schaub, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 5900.

concentrated and the residue was submitted to liquid chromatography (solvent F) which afforded the following.

Condition A: compound **22** containing a small amount (15–20%) of its 9-methoxy isomer (43.7%, R_f 0.46, solvent G) and compound **20** (3%, R_f 0.37).

Condition B: compounds **22** (8%), **20** (43%), and **16** (3.5%, R_f 0.30).

(2*R*,3*R*,3a*S*,9b*R*)-3-[(4-Chlorobenzyl)oxy]-2-[[(4-chlorobenzyl)oxy]methyl]-7-methoxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran (22). Compound **22** was separated from its position isomer by recrystallization ($CHCl_3$–diethyl ether 1:1): mp 124.4–125.6 °C; $[\alpha]_D$ +62.7° (*c* 1.13, $CHCl_3$); IR (KBr) 3030, 2995, 2950, 2880, 1620, 1510, 1500, 1460, 1385, 1355, 1325, 1282, 1218, 1110, 1090, 1065, 1035, 1015, 755, 665 cm^{-1}; ^1H NMR (250 MHz) δ 3.59 (dd, 1 H, $J_{2,2'A}$ = 2.8 Hz, $J_{2'A,2'B}$ = 10.6 Hz, H-2'A), 3.75 (dd, 1 H, $J_{2,2'B}$ = 1.0 Hz, H-2'B), 3.79 (s, 3 H, OMe), 4.16 (t, 1 H, $J_{3,3a}$ = 2.8 Hz, $J_{3a,9b}$ = 2.8 Hz, H-3a), 4.27 (narrow m, 2 H, H-2,3), 4.47 (d, 1 H, J_{AB} = 12.3 Hz) and 4.60 (d, 1 H), 4.56 (d, 1 H, J_{AB} = 12.3 Hz) and 4.74 (d, 1 H) (2 OCH_AH_BAr), 4.60 (d, 1 H, $J_{5A,5B}$ = 14.8 Hz, H-5A), 4.73 (d, 1 H, H-9b), 4.89 (d, 1 H, H-5B), 6.60 (d, 1 H, $J_{6,8}$ = 2.5 Hz, H-6), 6.84 (dd, 1 H, $J_{8,9}$ = 8.4 Hz, H-8), ~7.24 (d, 1 H, H-9), 7.24–7.41 (m, 8 H, 2 C_6H_4); MS, *m/z* (relative intensity) 125 (100) and 127 (33) ($C_7H_6Cl^+$), 161 (61), 162 (19), 135 (11), 134 (9), 163 (8), 126 (8), 91 (8), 89 (7), ... 375 (1.3) and 377 (0.4) ($M^{\bullet+}$ – $C_7H_6Cl^{\bullet}$), 500 (0.5) and 502 (0.3) ($M^{\bullet+}$).

Anal. Calcd for $C_{27}H_{26}Cl_2O_5$: C, 64.68; H, 5.23; Cl, 14.14. Found: C, 63.98; H, 5.36; Cl, 13.86.

(3*S*)-3,4-Dihydro-3-[(1*R*,2*R*)-1,2-dihydroxy-3-[(4-chlorobenzyl)oxy]propyl]-7-methoxy-1*H*-2-benzopyran (16) was obtained in traces from **21** as described above: IR (KBr) 3470, 3360 (OH), 2940, 2860, 1600, 1498, 1262, 1090, 1065, 1015, 1005, 917, 850, 802 cm^{-1}; ^1H NMR (250 MHz) δ 2.83–2.89 (m, 3 H, H-4*pro-R*, 4*pro-S*, OH), 3.78 (s, 3 H, OMe), 3.72–3.95 (m, 5 H, H-2, 1',2',3'A,3'B), 4.55 (narrow AB, 2 H, OCH_2Ar), 4.79 (narrow AB, 2 H, $J_{1A,1B}$ = ~15 Hz, H-1A, 1B), 6.52 (d, 1 H, $J_{6,8}$ = 2.5 Hz, H-8), 6.76 (dd, 1 H, $J_{5,6}$ = 8.1 Hz, H-6), 7.06 (d, 1 H, H-5), 7.24–7.35 (AA'BB', 4 H, C_6H_4); MS, *m/z* (relative intensity) 135 (100), 125 (48) and 127 (16) ($C_7H_6Cl^+$), 134 (27), 91 (21), 193 (16), 163 (14), 175 (13), 176 (13), 89 (12), ... 253 (0.3) ($M^{\bullet+}$ – $C_7H_6Cl^{\bullet}$), 378 (0.1) and 380 (0.04) ($M^{\bullet+}$).

Preparation of Labeled Substrate (5-d_4). Benzylation of **2** with α,α-dideuterio-4-chlorobenzyl chloride[18] to give **3**-d_4, methanolysis of **3**-d_4 to **4**-d_4 (α,β-mixture), and benzylation of **4**-d_4 with 3-methoxybenzyl chloride to give **5**-d_4 were performed under the conditions described above for the preparation of **3**, **4**, and **5**, respectively. Spectral characteristics of **5**-d_4 (α,β ~2:1): ^1H NMR (500 MHz) δ 3.32 and 3.39 (2 s, 3 H, 1-OMe-β and -α), 3.45–3.62 (m, 2 H, H-5A,5B), 3.78 and 3.80 (2 s, 3 H, ArOMe-β and -α), 3.85 (ddd, 0.67 H, $J_{1,3}$ = 0.67 Hz, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 6.4 Hz, H-3α), 3.96 (dd, 0.67 H, $J_{1,2}$ = 1.3 Hz, H-2α), ~4.06 (m, 1 H, H-2,3,4β), 4.165 (ddd, 0.67 H, $J_{4,5A(or\ B)}$ = 5.4 Hz, $J_{4,5B(or\ A)}$ = 4.1 Hz, H-4), 4.43 and 4.54 (2 d, 1.34 H, J_{AB} = 11.8 Hz, OCH_2Ar-α), 4.56 and 4.62 (2 d, 0.67 H, J_{AB} = 12.1 Hz, OCH_2Ar-β), 4.73 (d, 0.33 H, $J_{1,2}$ = 3.7 Hz, H-1β), 4.94 (s, 1 H, H-1α), 6.88 (m, 3 H) and 7.15–7.31 (m, 9 H) (3 C_6H_4); MS, *m/z* (relative intensity) 121 (100) ($C_7H_6OMe^+$), 101 (54), 75 (38), 45 (37), 91 (34), 105 (20), 77 (18), 41 (13), 122 (13), 78 (10).

Reaction of 5-d_4 with $SnCl_4$. To a solution of compound **5**-d_4 (26.5 mg, 0.049 mmol) in dry CH_2Cl_2 (3 mL) was added $SnCl_4$ as a 10% solution (v/v) in CH_2Cl_2 (0.085 mL, then 0.025 mL after 1 h). After 2 h at room temperature, saturated aqueous sodium bicarbonate (2 mL) was added to the cooled (0 °C), dark purple solution, and the mixture was efficiently stirred, which promoted its rapid discoloration. After 15 min, the organic phase was separated, washed with water (1 mL), dried (Na_2SO_4), and concentrated. The residue was submitted to column chromatography (ether–hexane 2:1 until the complete elution of $pClC_6H_4CDO$, then 4:1) which afforded 7 mg (~100%) of α-deuterio-4-chlorobenzaldehyde and 16.7 mg (89%) of **7**-d_3 contaminated by a small amount of position isomer **23**; samples of pure **7**-d_3 (10.4 mg) and **23** (3 mg) were obtained by column chromatography (solvent F).

7-d_3: R_f 0.35 (solvent H); MS, *m/z* (relative intensity) 136 (100), 127 (41) and 129 (14) ($C_7H_4D_2Cl$), 135 (34), 194 (29), 176 (25), 164 (21), 175 (21), 92 (14), 193 (12), ... 254 (0.6) ($M^{\bullet+}$ – $C_7H_4{}^2H_2Cl^{\bullet}$), 381 (0.3) and 383 (0.1) ($M^{\bullet+}$).

23: R_f 0.37 (solvent H); MS, *m/z* (relative intensity) 136 (100), 127 (59) and 129 (18) ($C_7H_4D_2Cl$), 164 (38), 176 (33), 106 (30), 135 (28), 175 (20), 194 (19), 177 (18), ... 254 (3) ($M^{\bullet+}$ – $C_7H_4D_2Cl^{\bullet}$).

The samples of **7**-d_3 and **23** were acetylated (pyridine–acetic anhydride) and the reaction mixtures processed under standard conditions to give, after purification of the products by column chromatography (solvent F), **8**-d_3 (8.2 mg, 65%) and **24** (2.3 mg, 62%).

Diacetate of 7-d_3 (8-d_3): ^1H NMR (500 MHz; only the signals different from those of **8** are indicated) δ 2.54 (br d, 1 H, $J_{3,4}$ = 2.4 Hz, H-4), no signal at δ 2.76, 3.84 (t, 1 H, $J_{3,1'}$ = 3.0 Hz, H-3), no AB signal at δ 4.45 and 4.52.

(3*R*,4*S*)-3,4-Dihydro-4-deuterio-3-[(1*R*,2*R*)-1,2-diacetoxy-3-[(α,α-dideuterio-4-chlorobenzyl)oxy]propyl]-5-methoxy-1*H*-2-benzopyran (24): R_f 0.65 (solvent A); ^1H NMR (500 MHz) δ 2.07 and 2.08 (2 s, 2 × 3 H, 2 OAc), 2.67 (br d, 1 H, $J_{3,4}$ = 3.0 Hz, H-4), 3.59 (dd, 1 H, $J_{2',3'A}$ = 5.6 Hz, $J_{3'A,3'B}$ = 10.9 Hz, H-3'A), 3.75 (dd, 1 H, $J_{2',3'B}$ = 3.3 Hz, H-3'B), 3.80 (s, 3 H, OMe), ~3.81 (m, 1 H, H-3), 4.66 (d, 1 H, $J_{1A,1B}$ = 15.1 Hz, H-1A), 4.83 (d, 1 H, H-1B), 5.41 (dd, 1 H, $J_{3,1'}$ = 3.3 Hz, $J_{1',2'}$ = 6.6 Hz, H-1'), 5.45 (ddd, 1 H, H-2'), 6.58 (d, 1 H, $J_{6,7}$ = $J_{7,8}$ = 7.8 Hz, H-6 or -8), 6.69 (d, 1 H, H-8 or -6), 7.13 (t, 1 H, H-7), 7.24 and 7.29 (AA'BB', 4 H, C_6H_4).

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Supplementary Material Available: Additional spectral data for compounds **3** (IR, ^1H NMR), α-**4** (^1H NMR), **11**, and **12** (IR, ^1H and ^{13}C NMR) (2 pages). Ordering information is given on any current masthead page.

(18) Prepared by reducing ethyl 4-chlorobenzoate with $LiAlD_4$ and reacting the resulting α,α-dideuterio-4-chlorobenzyl alcohol with Ph_3P/CCl_4.