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INTRAMOLECULAR *C*-ARYLATION OF 2,3,5-TRI-*O*-BENZYL- AND 2,3,5-TRI-*O*-(3-METHYLBENZYL)-PENTOFURANOSE DERIVATIVES*

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ABSTRACT

Upon treatment with tin(IV) chloride, 1-*O*-acetyl-2,3,5-tri-*O*-benzyl- and 1-*O*-acetyl-2,3,5-tri-*O*-(3-methylbenzyl)pentofuranose (D-*ribo*, L-*arabino*) undergo intramolecular Friedel–Crafts alkylation of the aromatic substituent at O-2 to give unusual internal *C*-glycosyl compounds (isochroman derivatives) in high yield. The final products are also partially debenzylated at O-3 or O-5 (up to 25%) under these conditions. By contrast, the corresponding methyl glycosides are poor substrates for the intramolecular *C*-arylation reaction, as methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranoside was found to give preponderantly methyl 3,5-di-*O*-(3-methylbenzyl)-α-D-ribofuranoside (**11**) (49%), and the *C*-arylation product in 30% yield only in the presence of the same Lewis acid. The competitive formation of **11** is thought to be due to the anomerization of the substrate leading to a tin(IV) complex coordinated with O-1 and O-2, which promoted the cleavage of the benzyl group at O-2. These reactions provide a novel and efficient *C*-arylation method and suggest a new approach to selectively protected D-ribofuranose derivatives. Evidence for the uncommon *C*-arylated structure of the new products was gained from their ^{1}H- and ^{13}C(APT)-n.m.r. spectra.

INTRODUCTION

As they contain both a reactive aromatic ring and an electrophilic center, 2-*O*-benzylated glycosides and analogs constitute potential substrates for intramolecular Friedel–Crafts reactions. Surprisingly, although benzylated glycosyl carboxylates[3] and halides[4] have been frequently used in *O*- and *C*-glycosylation reactions catalyzed by hard Lewis acids, such a behavior has never been observed. In the course of our investigations on the synthesis of novel *C*-glycosyl compounds, we have recently uncovered[1] the ability of benzylated glycofuranosyl acetates to

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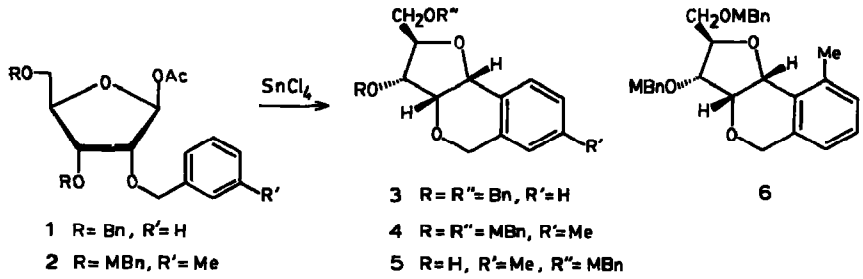
undergo readily intramolecular *C*-arylation upon reaction with a Friedel–Crafts-type catalyst. Further unexpected results were obtained[2] when D-ribofuranose derivatives bearing three 3-methoxybenzyl substituents were treated with tin(IV) chloride, as they underwent an unprecedented intramolecular double *C*-arylation resulting from the internal alkylation of the groups at O-2 and O-3.

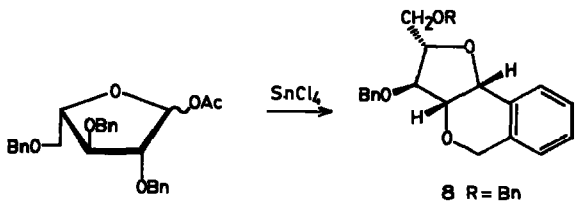
In order to determine the feasibility of the intramolecular *C*-arylation starting from the more readily accessible methyl glycosides, we examined the tin(IV) chloride-mediated reaction of a methyl glycoside containing activated benzyl groups, namely methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranoside (**10**), as well as that of the corresponding 1-*O*-acetylglycosyl compound **2**. We wish to describe, in this article, the full details of our investigations on benzylated and 3-methylbenzylated pentofuranose derivatives, provide evidence for the structure of the new compounds, and propose a mechanism accounting for our observations.



1 R= Bn, R'= H
2 R= MBn, R'= Me

3 R= R"= Bn, R'= H
4 R= R"= MBn, R'= Me
5 R= H, R'= Me, R"= MBn

6



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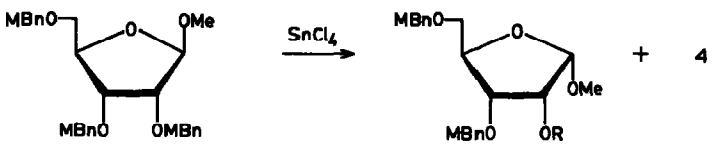
8 R= Bn
9 R= H



10

11 R= H
12 R= Ac

MBn= 3-Methylbenzyl

RESULTS AND DISCUSSION

Treatment of 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose (**1**) and -α,β-L-arabinofuranose (**7**) with tin(IV) chloride afforded, in 1–2 h at room temperature, the corresponding *C*-arylation products **3** and **8** in yields of 46 and 60%*, respectively; both reactions also gave a small amount of a more polar product (t.l.c.) that was isolated (21%) in the case of the *arabino* series and identified as the 5-*O*-debenzylated analog of **8**, compound **9**. Under the same conditions, 1-*O*-acetyl-2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranose (**2**) led preponderantly to a product resulting, as expected, from the intramolecular alkylation of the benzyl group in *para* position with respect to the activating substituent (compound **4**, 55%), as well as to a trace (7.7%) of the isomeric *ortho*-alkylation product **6**. In addition, compound **5**, which arose from the debenzylation of the final product at O-3 in this case, was isolated in a yield of 11%. The position of the free hydroxyl function in **5** and **9** was revealed by the presence of $HOCH_{(2)}$ couplings in the ^1H-n.m.r. spectrum for a solution in (^2H)chloroform.

Thus, as shown by the total yield of *C*-glycosylated products in each case, the intramolecular Friedel–Crafts reaction of benzylated 1-*O*-acetyl-glycofuranoses is a convenient process leading specifically to *cis*-substituted isochroman derivatives and, thereby, providing an efficient synthetic method for this heterocyclic system[5]. This process is much easier than the corresponding intermolecular *C*-glycosylation of aromatic or heteroaromatic compounds, which have been successful only with highly electron-rich systems, such as anisole[6], di- or tri-methoxybenzene[6–10], ferrocene[6], furane[6], and indole[11]; the Lewis acid-catalyzed *C*-glucosylation of benzene itself and toluene required drastic conditions and led to mixtures of products[12]. It is interesting to note that 2,3,5-tri-*O*-benzyl-D-ribofuranosyl bromide reacted[11] preferentially by an intermolecular process when treated with indole derivatives and silver oxide, albeit in low yield (16%).

By contrast with that of the furanoses, the reaction of benzylated 1-*O*-acetyl-hexopyranoses with the same Lewis acid gave a mixture of several partially *O*-debenzylated products, possibly including *C*-glycosyl derivatives, both in the *gluco* and in the *manno* series[13]. Further investigations are in progress to elucidate the behavior of these important substrates.

The *C*-glycosylated structure of the final products (**3**, **4**, and **8**) is supported by the absence of signals of functional groups in their i.r. spectrum and by their lack of reactivity toward potassium permanganate, which rules out the isomeric unsaturated structure resulting from elimination of acetic acid (1,4-anhydro-2,3,5-tri-*O*-benzyl-D-*erythro*-pent-1-enitol[14,15])**. Many features of their ^1H-n.m.r. spectra

*All yields are after isolation by column chromatography, or crystallization, or both.

**See comments in ref. 1. The data reported for this compound in refs. 14 and 15 are different and therefore subject to caution.

point toward their unusual constitution (a substituted *cis*-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran system): the number of aromatic protons, the chemical shift of H-1 (H-9b in polycyclic system) (δ 4.68–4.82), and the magnitude of the geminal coupling constants of the benzyl methylene groups. The protons at C-5 of the polycyclic system exhibited indeed a $|J_{gem}|$ value consistently larger (14.5–15.1 Hz) than that usually found in *O*-benzyl groups (12 Hz), a difference attributable to the change of the average position of the CH_2 group with respect to the aromatic π-system in the cyclic structure[16]. Furthermore, the substitution pattern of the tri-substituted aromatic ring in compounds **4–6** was revealed by the multiplicity of the isolated signals of H-6 (s in **4** and **5**, d in **6**) and H-9 (d in **4** and **5**, absent in **6**) (polycyclic system numbering) in the ^{1}H-n.m.r. spectra. Finally, the coupling constants for the D-ribofuranose component indicated clearly a conformation close to $^3T_2$ or ^3E for the 5-membered ring, a typical conformation for 1,2-*cis*-fused bicyclic pentofuranoid systems[17] and, thus, rule out a structure which would have resulted from the intramolecular alkylation of the benzyl group at O-5.

The most convincing evidence for the structure of the *C*-arylated products was provided by the ^{13}C-n.m.r. spectra; an APT experiment performed on compounds **3** (see Fig. 1), **4**, and **8** revealed indeed the presence of *four aromatic quater-*

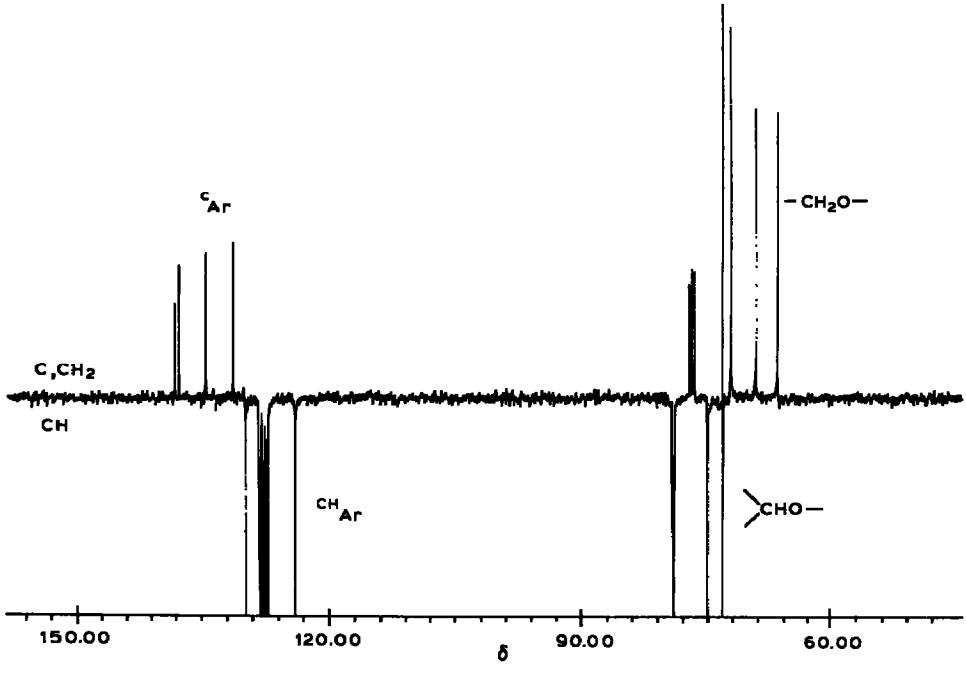
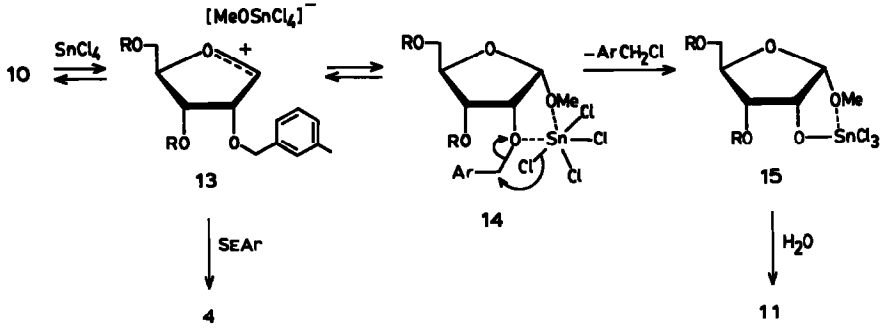


Fig. 1. ^{13}C-N.m.r. spectrum at 125.76 MHz of compound **3** (APT-experiment).

nary carbons (seven in the case of **4**), which demonstrated the existence of an additional alkylation site on one of the aromatic rings; furthermore, the signal of the former anomeric carbon (C-9b) appeared at a much higher field (δ 73–80) than in a normal furanoside (C-1, δ 100–110) and, thus, confirmed the *C*-glycosylated structure of the final products.

The behavior of methyl glycoside **10** in the presence of tin(IV) chloride was found to be remarkably different from that of the corresponding 1-*O*-acetylglycose **2**; the *C*-arylated product **4** was obtained, indeed, in a yield of 30% only, the major product being methyl 3,5-di-*O*-(3-methylbenzyl)-α-D-ribofuranoside (**11**) (49%). No trace of the β-D anomer was detected. The change of chemical shift of H-2 upon acetylation allowed an unambiguous assignment of the position of the free OH group in **11**. In order to explain the selective cleavage of the group at O-2, we suggest (see Scheme 1) that compound **10** underwent a tin(IV) chloride-mediated anomerization (see ref. 18 for examples of Lewis acid-catalyzed anomerization of methyl glycosides) to the corresponding α-D anomer which forms a favorable chelate with the reagent (**14**)*, by way of an intermediate such as **13**; this intermediate also led, competitively and irreversibly, to compound **4** by an internal SEAr reaction. The tin(IV) complex in **14** activated the 2-benzyl ether function and promoted its cleavage to 3-methylbenzyl chloride and a 2-*O*-trichlorostannyl intermediate (**15**), from which **11** was formed upon hydrolytic processing.



Scheme 1.

In light of this mechanism, the behavior of the 1-*O*-acetylglycoses (**1**, **2**, and **7**) can be justified by the facts that the acetoxy group is a stronger Lewis base than the methoxy group, and that the acetate ion acts as a *bidentate ligand* yielding a chelate-type complex with the reagent[20], thereby allowing the intermediate corresponding to **13** to undergo an SEAr reaction exclusively. It is not excluded that a

*This interpretation is supported by the strong affinity of tin(IV) chloride for oxygenated ligands and its high tendency to form hexacoordinated complexes[19].

glycosyl chloride might also be formed as an additional intermediate in this reaction.

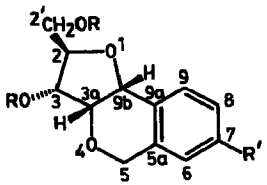
By decreasing the reactivity of the benzyl substituents towards an SEAr reaction it should be possible to achieve the 2-*O*-debenzylation of the methyl glycosides chemoselectively. Indeed, using 4-chlorobenzyl groups, we have been able to obtain exclusively the 2-*O*-debenzylated product; this very useful reaction will be described in a separate publication[21].

In conclusion, the intramolecular *C*-arylation of benzylated sugars afforded a novel method for the creation of a carbon–carbon bond between the anomeric center and an aromatic system, an unusual structural feature present in natural products such as *C*-glycosyl flavonoids and several antitumor antibiotics (nogalamycin, chromoxymycin, etc.). Because of the presence of this linkage, the synthesis of these materials is extremely difficult, and the intramolecular *C*-arylation method should provide a useful tool in this field.

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns apparatus 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°. I.r. spectra were recorded with a Perkin–Elmer 283B spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 60, 300, 360, or 400 MHz, and ^{13}C-n.m.r. spectra at 125.76 MHz, for solutions in (^{2}H)chloroform with tetramethylsilane as the internal standard; chemical shifts (δ) are given downfield from the signal of Me_4Si. Chemical shifts and coupling constants were obtained from first-order analyses of the ^{1}H-n.m.r. spectra. ^{13}C-N.m.r. spectra were recorded in the APT-mode; (+) and (−) are used to indicate positive (quaternary and methylene) and negative (methine and methyl) amplitude of the signals. Mass spectra were recorded on a g.l.c.–m.s. HP-5995 system using the direct inlet probe.

Analytical t.l.c. was performed on precoated glass-plates with Merck silica gel 60 F-254 as the adsorbent (layer thickness 0.25 mm). The developed plates were air dried and irradiated with u.v. light, or sprayed with a solution of ammonium phosphomolybdate[22] (or both), and heated at 120–140°. Column chromatography was performed on silica gel 60 (70–230 mesh) and flash chromatography[23] on silica gel 60 (230–400 mesh). The following solvent systems (v/v) were used; (*A*) 1:3, (*B*) 1:2, (*C*) 1:1, (*D*) 2:3, (*E*) 2:1, and (*F*) 3:2 ether–hexanes. Solvents were evaporated under reduced pressure and below 40°. The *C*-arylated compounds are numbered as given in Scheme 2.



Scheme 2.

*Methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-*D*-ribofuranoside* (**10**). — Pentane-washed NaH (0.5 g, 20.8 mmol) was added to dry dimethyl sulfoxide (20 mL) and the mixture stirred for 30 min at 25°. A solution of crude methyl D-ribofuranoside[24] (β:α ~10:1) (1.0 g, 6.09 mmol) in dimethyl sulfoxide (5 mL) was then carefully added, followed by 3-methylbenzyl chloride (2.8 mL, 21 mmol). After 2 h at 25°, the excess of reagent was removed by addition of methanol (1 mL), and the mixture poured into a separatory funnel containing ether (100 mL) and ice (50 g). The organic phase was separated, the aqueous phase washed with ether (50 mL), and the combined organic phases dried (Na_2SO_4) and evaporated. The syrupy residue was submitted to flash chromatography (*A*) which afforded **10** (1.64 g, 57%); an analytical sample was obtained by column chromatography (*B*); syrup, $[\alpha]_D^{20}$ +26.5° (*c* 1.2, chloroform); t.l.c. (*C*) R_F 0.53; ν_{max}^{film} 3020, 2915, 2860, 1610, 1593, 1490, 1460, 1358, 1157, 1105, 1075, 1030, 945, 775, 740, and 690 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 2.37 (s, 9 H, 3 $ArCH_3$), 3.37 (s, 3 H_2, OCH_3), 3.63 (m, 2 H, H-5A,5B), 3.90 (dd, 1 H, $J_{1,2}$ 1.0, $J_{2,3}$ 4.5 Hz, H-2), 4.08 (dd, 1 H, $J_{3,4}$ 6.8 Hz, H-3), 4.38 (m, 1 H, H-4), 4.55, 4.62 and 4.68 (3 s, 3 H_2, 3 $ArCH_2$), 5.00 (br. s, 1 H, H-1), and 7.28 (br. s, 12 H, 3 $MeC_6H_4CH_2$); m.s.: *m/z* 105 (100%), 79 (4), 77 (3), 103 (3), 135 (3), 209 (3), 91 (2), 143 (2), 281 (2), . . ., 339 (0.2, $[M - C_8H_9 - CH_3OH]^+$), and 371 (<0.1, $[M - C_8H_9]^+$).

Anal. Calc. for $C_{30}H_{36}O_5$ (476.61): C, 75.60; H, 7.61. Found: C, 75.58; H, 7.63.

*1-*O*-Acetyl-2,3,5-tri-*O*-(3-methylbenzyl)-β-*D*-ribofuranose* (**2**). — A solution of **10** (1.0 g, 2.1 mmol) in a mixture of peroxide-free 1,4-dioxane (25 mL) and M aqueous HCl (10 mL) was heated at reflux for 3 h. The mixture was cooled down and made neutral with M aqueous NaOH. The organic solvent was evaporated under reduced pressure, the remaining mixture extracted with chloroform (25 mL), the organic phase washed with saturated aqueous $NaHCO_3$ (10 mL), then with water (10 mL), dried (Na_2SO_4), and evaporated. The syrupy residue was submitted to flash chromatography (*C*) which afforded pure 2,3,5-tri-*O*-(3-methylbenzyl)-D-ribofuranose (0.74 g, 76%), t.l.c. (*C*) R_F 0.26; ν_{max}^{film} 3410 cm^{-1} (OH). Acetylation of this material with acetic anhydride (2 mL) in pyridine (6 mL) afforded, after standard processing, a quantitative yield of 1-*O*-acetyl derivative **2**. An analytical sample was obtained by column chromatography (*B*) and crystallization from ether–hexanes; m.p. 39–41.5°, $[\alpha]_D^{20}$ +51° (*c* 1.2, chloroform), t.l.c. (*C*) R_F 0.44; ν_{max}^{film} 3020, 2920, 2865, 1745 (C=O), 1610, 1593, 1490, 1460, 1230, 1100, 1040, 1010, 945, 775, 747, and 690 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 1.93 (s, 3 H, $COCH_3$), 2.35 (s, 9 H, 3 $ArCH_3$), 3.67 (m, 2 H, H-5A,5B), 3.96 (d, 1 H, $J_{1,2}$ ~0, $J_{2,3}$ 4.2 Hz, H-2), 4.16 (dd, 1 H, $J_{3,4}$ 7.5 Hz, H-3), ~4.37 (m, 1 H, H-4), 4.50 (br. s, 2 H), 4.54 (s, 2 H) and 4.69 (AB, 2 H) (3 $ArCH_2$), 6.27 (s, 1 H, H-1), and 7.23 (m and s, 12 H, 3 $MeC_6H_4CH_2$); m.s.: *m/z* 105 (100%), 43 (14), 106 (11), 79 (5), 77 (4), 143 (4), 103 (3), 119 (3), 91 (3), 121 (2), . . ., and 339 (0.4, $[M - C_8H_9 - CH_3COOH]^+$).

Anal. Calc. for $C_{31}H_{36}O_6$ (504.62): C, 73.79; H, 7.19. Found: C, 73.61; H, 7.03.

(2R,3R,3aS,9bR)-3-Benzyloxy-2-benzyloxymethyl-3,3a,5,9b-tetrahydro-2H-furo[3,2-c][2]benzopyran (**3**). — To a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose[25] (**1**) (209.5 mg, 0.45 mmol) (prepared by acetylation of 2,3,5-tri-*O*-benzyl-D-ribofuranose[24,26]) in dry dichloromethane (4 mL), was added under N_2, a 10% (v/v) solution (0.65 mL, 0.56 mmol) of $SnCl_4$ in dichloromethane, and the mixture stirred for 1.5 h at room temperature. The reagent was then removed by the addition, at 0°, of saturated aqueous $NaHCO_3$. Dichloromethane (10 mL) was added, the organic phase separated, washed with water (5 mL), dried (Na_2SO_4), and evaporated. The residue was submitted to column chromatography (*D*) which afforded crystalline **3** (84 mg, 46%). A sample was recrystallized from chloroform–ether–hexane, m.p. 111–112°, $[\alpha]_D^{20}$ +80° (*c* 0.87, chloroform); t.l.c. (*C*) R_F 0.37; ν_{max}^{KBr} 3025, 2950, 2915, 2890, 2870, 2790, 1610, 1497, 1457, 1350, 1125, 1085, 1070, 1058, 1043, 740, and 693 cm^{-1}; ^{1}H-n.m.r. (300 MHz): δ 3.54 (dd, 1 H, $J_{2,2'A}$ 3.7, $J_{2'A,2'B}$ 11.0 Hz, H-2'A), 3.70 (dd, 1 H, $J_{2,2'B}$ 2.2 Hz, H-2'B), 4.08 (dd, 1 H, $J_{3,3a}$ 3.9, $J_{3a,9b}$ 2.9 Hz, H-3a), 4.19 (ddd, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 4.27 (dd, 1 H, H-3), 4.45 (d, 1 H, *J* 12 Hz), 4.57 (d, 1 H), and 4.57 (AB, 2 H, *J* 12 Hz, 2 $OCH_2C_6H_5$), 4.68 (d, 1 H, H-9b), 4.70 (d, 1 H, $J_{5A,5B}$ 15.1 Hz, H-5A), 4.85 (d, 1 H, H-5B), 7.00 (m, 1 H), 7.15–7.35 (several m, 12 H), and 7.38 (m, 1 H) (2 $OCH_2C_6H_5$, H-6–9); ^{13}C-n.m.r.: δ 66.78, 69.41, 72.35, and 73.30 [(+), C-2', C-5, 2 $OCH_2C_6H_5$], 73.22, 75.08, 79.09, and 79.25 [(−), C-2,3,3a,9b], 124.00 [(−), C-9], 127.19–128.19 and 129.85 [(−), C-6–8, C-2–6 of 2 $OCH_2C_6H_5$], 131.36, 134.70 [(+), C-9a,5a], 137.77, and 138.30 [(+), C-1 of 2 $OCH_2C_6H_5$]; m.s.: *m/z* 91 (100%), 131 (19), 65 (9), 92 (8), 132 (7), 105 (6), 43 (5), 104 (4), 77 (4), 133 (4), . . ., 311 (2, $[M - C_7H_7]^+$), and 402 (0.1, $[M]^+$).

Anal. Calc. for $C_{26}H_{26}O_4$ (402.49): C, 77.59; H, 6.51. Found: C, 77.53; H, 6.82.

Reaction of **2** *with* $SnCl_4$. — 1-*O*-Acetylribose **2** (250 mg, 0.495 mmol) was treated with $SnCl_4$ (1 equiv.) as described for the preparation of **3**. Separation of the processed reaction mixture by column chromatography (solvent *B*, then *C* after elution of major product) afforded, in order of elution, pure **6** (17 mg, 7.7%), **4** (120 mg, 55%), and **5** (19 mg, 11.3%).

(2R,3R,3aS,9bR)-3,3a,5,9b-Tetrahydro-7-methyl-3-(3-methylbenzyloxy)-2-(3-methylbenzyloxymethyl)-2H-furo[3,2-c][2]benzopyran (**4**). — Syrup, $[\alpha]_D^{20}$ +70° (*c* 1.2, chloroform), t.l.c. (*C*) R_F 0.39; ν_{max}^{film} 3020, 2910, 2860, 1610, 1450, 1357, 1157, 1115, 1063, 780, and 692 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 2.32, 2.338 and 2.342 (3 s, 9 H, 3 $ArCH_3$), 3.61 (dd, 1 H, $J_{2,2'A}$ 3.3, $J_{2'A,2'B}$ 11.1 Hz, H-2'A), 3.77 (dd, 1 H, $J_{2,2'B}$ 2.1 Hz, H-2'B), 4.11 (t, 1 H, $J_{3,3a}$ 4.1, $J_{3a,9b}$ 2.9 Hz, H-3a), 4.26 (td, 1 H, $J_{2,3}$ 8.6 Hz, H-2), 4.31 (dd, 1 H, H-3), 4.49 (d, 1 H, *J* 11.9 Hz) and 4.60 (d, 1 H), 4.59 (d, 1 H, *J* 11.9 Hz) and 4.72 (d, 1 H) (2 AB, 2 OCH_2Ar), 4.58 (d, 1 H, $J_{5A,5B}$ 14.7 Hz, H-5A), 4.73 (d, 1 H, H-9b), 4.88 (d, 1 H, H-5B), 6.89 (s, 1 H, H-6), 7.08–7.27 (several m, 9 H, H-8, 2 $MeC_6H_4CH_2$), and 7.33 (d, 1 H, $J_{8,9}$ 7.8 Hz, H-9); ^{13}C-n.m.r.: δ 21.16, 21.29 [(−), 3 $ArCH_3$], 66.83, 69.46, 72.45 and 73.40 [(+), C-2', C-5, 2 OCH_2Ar], 73.12, 75.21, 79.15 and 79.25 [(−), C-2,3,3a,9b], 124.48, 124.64,

and 124.94 [(−), C-9, C-6 of 2 $CH_2C_6H_4Me$], 128.03–128.62 and 129.77 [(−), C-6–C-8, C-2 and C-4,5 of 2 $CH_2C_6H_4Me$], 128.49, 134.60 [(+), C-9a,5a], 137.74 (2 C), 137.82, 137.95, and 138.28 [(+), C-1 and C-3 of 2 $CH_2C_6H_4Me$]; m.s.: *m/z* 105 (100%), 145 (31), 146 (11), 106 (10), 119 (7), 79 (6), 147 (5), 187 (5), 339 (5, $[M - C_8H_9]^+$), 175 (3), . . ., and 444 (1, $[M]^+$).

Anal. Calc. for $C_{29}H_{32}O_4$ (444.57): C, 78.34; H, 7.26. Found: C, 78.40; H, 7.36.

(2R,3R,3aS,9bR)-3,3a,5,9b-Tetrahydro-3-hydroxy-7-methyl-2-(3-methylbenzyloxymethyl)-2H-furo[3,2-c][2]benzopyran (**5**). — Recrystallized from ether–hexane, m.p. 82.5–84°, $[\alpha]_D^{20}$ 0° (*c* 0.7, chloroform); t.l.c. (*C*) R_F 0.14; ν_{max}^{KBr} 3370 (OH), 3020, 2920, 2860, 1615, 1433, 1370, 1130, 1092, 1065, 990, 788, 695, and 660 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 2.33 and 2.35 (2 s, 6 H, 2 $ArCH_3$), 2.67 (br. d, 1 H, $J_{3,OH}$ ~10 Hz, HO-3), 3.69 (dd, 1 H, $J_{2,2'A}$ 4.1, $J_{2'A,2'B}$ 10.7 Hz, H-2'A), 3.78 (dd, 1 H, $J_{2,2'B}$ 2.9 Hz, H-2'B), 4.01 (ddd, 1 H, $J_{2,3}$ 8.5 Hz, H-2), 4.19 (dd, 1 H, $J_{3,3a}$ 4.5, $J_{3a,9b}$ 3.3 Hz, H-3a), 4.47 (br. td, 1 H, H-3), 4.60 (AB, 2 H, *J* 12 Hz, OCH_2Ar-2'), 4.65 (d, 1 H, $J_{5A,5B}$ 14.7 Hz, H-5A), 4.82 (d, 1 H, H-9b), 4.84 (d, 1 H, H-5B), 6.89 (s, 1 H, H-6), 7.08–7.19 (m, 4 H, $MeC_6H_4CH_2$), 7.23 (d, 1 H, $J_{8,9}$ 7.8 Hz, H-8), and 7.37 (d, 1 H, H-9); m.s.: *m/z* 105 (100%), 131 (51), 175 (47), 146 (45), 147 (40), 145 (38), 119 (34), 159 (26), 91 (26), 117 (23), . . ., 235 (7.6, $[M - C_8H_9]^+$), and 340 (2.6, $[M]^+$).

Anal. Calc. for $C_{21}H_{24}O_4$ (340.42): C, 74.09; H, 7.11. Found: C, 73.63; H, 7.06.

(2R,3R,3aS,9bR)-3,3a,5,9b-Tetrahydro-9-methyl-3-(3-methylbenzyloxy)-2-(3-methylbenzyloxymethyl)-2H-furo[3,2-c][2]benzopyran (**6**). — Syrup, $[\alpha]_D^{20}$ +54° (*c* 0.52, chloroform); t.l.c. (*C*) R_F 0.46; ν_{max}^{KBr} 3020, 2915, 2860, 1605, 1465, 1345, 1155, 1115, 1080, 1060, 920, 770, 730, and 690 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 2.35 (s, 6 H) and 2.43 (s, 3 H) (3 $ArCH_3$), 3.63 (dd, 1 H, $J_{2,2'A}$ ~3.5, $J_{2'A,2'B}$ ~10.5 Hz, H-2'A), 3.77 (dd, 1 H, $J_{2,2'B}$ ~2 Hz, H-2'B), 4.08 (dd, $J_{3,3a}$ ~3.5, $J_{3a,9b}$ ~2 Hz, H-3a), 4.30 (m, 1 H, $J_{2,3}$ ~8 Hz, H-2), 4.36 (dd, 1 H, H-3), 4.58 (AB, 2 H, *J* ~12 Hz, OCH_2Ar), 4.62 (d, 1 H, *J* ~12 Hz), and 4.75 (d, 1 H) (AB, OCH_2Ar), 4.62 (d, 1 H, H-5A), 4.80 (d, 1 H, H-9b), 4.93 (d, 1 H, $J_{5A,5B}$ ~15 Hz, H-5B), 6.90 (d, 1 H, $J_{6,7}$ 7.4 Hz, H-6), and 7.08–7.23 (several m, 10 H, H-7,8, 2 $MeC_6H_4CH_2$); m.s.: *m/z* 105 (100%), 145 (29), 106 (10), 146 (9), 119 (8), 79 (8), 77 (8), 91 (6), 103 (6), 118 (5), . . ., 339 (0.6, $[M - C_8H_9]^+$), 444 (0.1, $[M]^+$).

Anal. Calc. for $C_{29}H_{32}O_4$ (444.57): C, 78.34; H, 7.26. Found: C, 78.39; H, 7.36.

(2S,3S,3aS,9bR)-3-Benzyloxy-2-benzyloxymethyl-3,3a,5,9b-tetrahydro-2H-furo[3,2-c][2]benzopyran (**8**). — 1-*O*-Acetyl-2,3,5-tri-*O*-benzyl-L-arabinofuranose[27] (**7**) (α/β ~3:1) (300 mg, 0.65 mmol) was treated with $SnCl_4$ (1 equiv.) as described for the preparation of **3**. The processed reaction mixture was submitted to column chromatography (solvent *B*, then *C*) which afforded 157 mg (60%) of pure **8** and 43 mg (21%) of its 5-*O*-debenzylated analog (**9**). Compound **8**: syrup, $[\alpha]_D^{20}$ −5.4 ±1° (*c* 1.1, chloroform); t.l.c. (*C*) R_F 0.59; ν_{max}^{film} 3030, 2900, 2860, 1605, 1587, 1496,

1454, 1370, 1205, 1090 (br.), 740, and 693 cm^{-1}; ^{1}H-n.m.r. (400 MHz): δ 3.61 (dd, 1 H, $J_{2,2'A}$ 6.0, $J_{2'A,2'B}$ 10.0 Hz, H-2'A), 3.65 (dd, 1 H, $J_{2,2'B}$ 6.0 Hz, H-2'B), 4.00 (d, 1 H, $J_{3,3a}$ <0.5, $J_{2,3}$ 4.0 Hz, H-3), 4.21 (d overlapping br. q, 2 H, $J_{3a,9b}$ 3.0 Hz, H-3a, H-2), 4.54 (AB, 2 H, J 12.0 Hz, $OCH_2C_6H_5$), 4.64 (d, 1 H, $J_{5A,5B}$ 14.5 Hz, H-5A), 4.65 (AB, 2 H, J 12.0 Hz, $OCH_2C_6H_5$), 4.75 (d, 1 H, H-9b), 4.76 (d, 1 H, H-5B), 7.05 (m, 1 H), 7.23–7.36 (several m, 12 H), and 7.48 (m, 1 H) (H-6–9, 2 $CH_2C_6H_5$); ^{13}C-n.m.r.: δ 67.17, 70.61, 72.02, and 73.30 [(+), C-2', C-5, 2 $OCH_2C_6H_5$], 74.11, 81.34, 82.98, and 86.71 [(−), C-2,3,3a,9b], 124.08 [(−), C-9], 127.22–128.32 and 130.31 [(−), C-6–8, C-2–6 of 2 $OCH_2C_6H_5$], 130.44, 134.88 [(+), C-9a,5a], 137.68, and 138.15 [(+), C-1 of 2 $OCH_2C_6H_5$]; s.m.: *m/z* 91 (100%), 131 (17), 65 (10), 105 (10), 132 (9), 92 (9), 77 (7), 145 (6), 133 (5), 104 (5), . . ., 311 (0.4, $[M - C_7H_7]^+$), and 402 (0.3, $[M]^+$).

Anal. Calc. for $C_{26}H_{26}O_4$ (402.49): C, 77.59; H, 6.51. Found: C, 77.15; H, 6.57.

(2S,3S,3aS,9bR)-3-Benzyloxy-3,3a,5,9b-tetrahydro-2-hydroxymethyl-2H-furo[3,2-c][2]benzopyran (**9**). — Recrystallized from ether–hexane, m.p. 72–73°, $[\alpha]_D^{20}$ −51° (*c* 0.53, chloroform); t.l.c. (*C*) R_F 0.23; ν_{max}^{film} 3460 (OH), 3030, 2860, 1605, 1590, 1495, 1455, 1370, 1205, 1090, 1050 (br.), 875, 802, 740, and 695 cm^{-1}; ^{1}H-n.m.r. (400 MHz): 2.11 (br. m, 1 H, HO-2'), 3.71 (br. ddd, 1 H, $J_{2,2'A}$ 4.5, $J_{2'A,OH}$ 6.5, $J_{2'A,2'B}$ 11.5 Hz, H-2'A), 3.85 (br. dt, 1 H, $J_{2,2'B}$ 3, $J_{2'B,OH}$ 3 Hz, H-2'B), 4.10 (d, 1 H, $J_{2,3}$ 4.0, $J_{3,3a}$ <0.5 Hz, H-3), 4.16 (br. q, 1 H, H-2), 4.21 (d, 1 H, $J_{3a,9b}$ 2.8 Hz, H-3a), 4.65 (d, 1 H, J 11.8 Hz) and 4.72 (d, 1 H) (AB, $OCH_2C_6H_5$), 4.69 (d, 1 H, $J_{5A,5B}$ 15.0 Hz, H-5A), 4.78 (d, 1 H, H-9b), 4.81 (d, 1 H, H-5B), 7.08 (m, 1 H), 7.28–7.40 (several m and d, 7 H), and 7.46 (m, 1 H) (H-6–9, $CH_2C_6H_5$); m.s.: *m/z* 91 (100), 131 (74), 132 (27), 105 (18), 133 (14), 65 (11), 104 (10), 92 (9), 103 (8), 77 (8), . . ., 221 (0.2 $[M - C_7H_7]^+$), and 312 (0.1, $[M]^+$).

Anal. Calc. for $C_{19}H_{20}O_4$ (312.37): C, 73.05; H, 6.45. Found: C, 71.89 (three samples); H, 6.62.

Methyl 3,5-di-O-(3-methylbenzyl)-α-D-ribofuranoside (**11**). — Methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranoside (**10**) (300 mg, 0.63 mmol) was treated with $SnCl_4$ (1 equiv.) as described for the preparation of **3**. The processed mixture was submitted to column chromatography (solvent *B*, changed to *D*, then to *C*) which afforded, in order of elution, an unidentified impurity [6.8 mg; R_F (*C*) 0.51], compound **4** (85 mg, 30%), and compound **11** (115 mg, 49%); an analytical sample of **11** was obtained by column chromatography (*F*), syrup, $[\alpha]_D^{20}$ +108° (*c* 1.48, chloroform); t.l.c. (*C*) R_F 0.21; ν_{max}^{film} 3550 (OH), 3020, 2920, 2860, 1607, 1590, 1455, 1413, 1355, 1090, 1030, 780, 740, and 690 cm^{-1}; ^{1}H-n.m.r. (400 MHz): δ 2.32 and 2.35 (2 s, 6 H, 2 $ArCH_3$), 2.97 (br., 1 H, HO-2), 3.38 (dd, 1 H, $J_{4,5A}$ 4.5, $J_{5A,5B}$ 10.5 Hz, H-5A), 3.46 (dd, 1 H, $J_{4,5B}$ 4.0 Hz, H-5B), 3.48 (s, 3 H, OCH_3), 3.79 (dd, 1 H, $J_{2,3}$ 7.0, $J_{3,4}$ 3.1 Hz, H-3), 4.12 (br., 1 H, H-2), 4.17 (q, 1 H, H-4), 4.46 (AB, 2 H, J 12.0 Hz), 4.55 (d, 1 H, J 12.0 Hz) and 4.69 (d, 1 H) (2 OCH_2Ar), 4.89 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1), 7.09 (m, 6 H), and 7.21 (m, 2 H) (2 $CH_2C_6H_4CH_3$); m.s.: *m/z* 105 (100%), 106 (15), 77 (8), 79 (8), 103 (5), 91 (4), 121 (4), 45 (3), 131 (2), 147 (2),

. . ., and 267 (0.2, $[M - C_8H_9]^+$).

Anal. Calc. for $C_{22}H_{28}O_5$ (372.46): C, 70.95; H, 7.58. Found: C, 70.71; H, 7.55.

Methyl 2-O-acetyl-3,5-di-O-(3-methylbenzyl)-α-D-ribofuranoside (**12**). — Compound **11** was acetylated under standard conditions; the resulting product (**12**) was purified by preparative t.l.c. (solvent *C*); syrup, t.l.c. (*E*) R_F 0.54 (note: **11** has R_F 0.51 in solvent *E*); ν_{max}^{film} 3020, 2920, 2860, 1742 (C=O), 1610, 1490, 1457, 1375, 1240, 1125, 1090, 1065, 1040 (br.), 780, 743, and 695 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 2.28 (s, 3 H, $OCOCH_3$), 2.37 and 2.41 (2 s, 6 H, 2 $ArCH_3$), 3.54 (s and m, 5 H, OCH_3, H-5A,5B), 4.06 and 4.23 (2 m, 2 H, H-3,4), 4.52 (s, 2 H) and 4.58 (AB, 2 H, *J* 12 Hz) (2 OCH_2Ar), 4.95 (dd, 1 H, $J_{1,2}$ 4.5, $J_{2,3}$ 6.5 Hz, H-2), 5.16 (d, 1 H, H-1), and 7.23 (br. s, 8 H, 2 $CH_2C_6H_4Me$); m.s.: *m/z* 105 (100%), 43 (32), 106 (13), 103 (8), 79 (6), 77 (6), 191 (5), 121 (5), 135 (4), 119 (4), . . ., 309 (0.5, $[M - C_8H_9]^+$), and 382 (0.5, $[M - CH_3OH]^+$).

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