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Synthesis of phenyl 3,4-di-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-1-thio-α,β-L-*xylo*-hexopyranoside. A glycosyl donor for axenose

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Abstract

A new synthesis of the methyl-branched sugar axenose is described. Axenose is found in the antibiotics axenomycin, dutomycin, and polyketomycin. The synthesis is based on additions of organometallic reagents to pentodialdo-1,4-furanosides and allows the preparation of derivatives of methyl α-L-axenoside which are protected at the tertiary C-3 hydroxyl group. Conversion to thioglycoside derivatives for use in oligosaccharide synthesis was carried out directly from the methyl glycoside by treatment with phenylthiotrimethylsilane and trimethylsilyl trifluoromethanesulfonate.

1. Introduction

The methyl-branched sugar L-axenose occurs in disaccharides found in the antibiotics axenomycin,[1] dutomycin,[2] and polyketomycin.[3] In axenomycin, axenose is glycosylated at the 4-position with the trideoxy sugar amicetose, while in both dutomycin and polyketomycin, axenose is attached to amicetose via an α-1,4 glycosidic linkage, giving the disaccharide shown in Fig. 1. The synthesis of disaccharides of axenose is a challenging problem owing to the presence of the 2-deoxy glycosidic linkage and because of the multiple steps required to obtain suitably protected monosaccharide derivatives. There have been no syntheses of axenose-containing disaccharides described in the literature. We decided to investigate this problem in the context of our studies of the synthesis of carbohydrate components of antibiotics. In this paper, we describe a new synthesis of axenose and its thioglycoside derivatives for use in coupling reactions.

The structure of axenose was reported by Arcamone and co-workers as 2,6-dideoxy-3-*C*-methyl-L-*xylo*-pyranose in 1973.[1] Three syntheses of axenose have been reported, the first, a racemic synthesis, leading to D,L-axenose before the identification of the L-enantiomer as a natural product,[4] and the second by Garegg and Norberg, from L-fucose, based on the addition of methylmagnesium iodide to a keto

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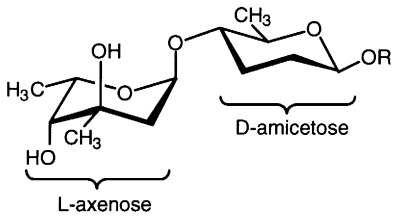
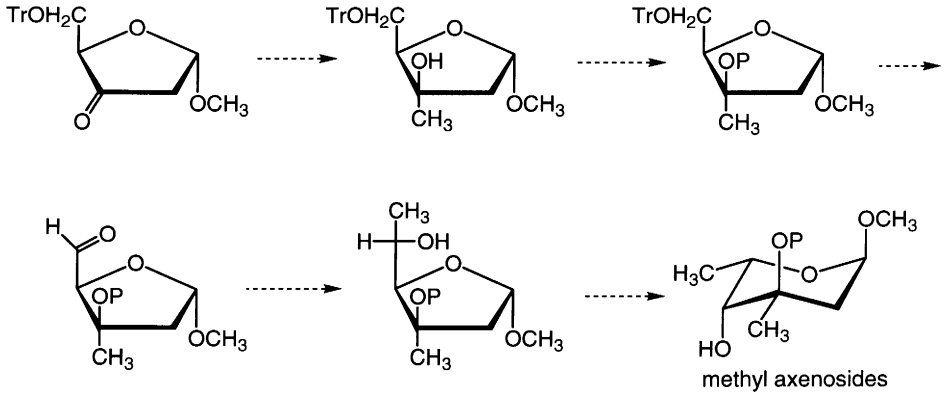


Fig. 1. Disaccharide found in dutomycin and polyketomycin (R=aglycone)

sugar in its pyranose form.[5] The third synthesis was reported by our laboratory in 1995.[6] Our approach was developed in the context of the study of stereoselectivity of addition of organometallic reagents to pentodialdo-1,4-furanoses and led to the synthesis of L-axenose and D-evermicose from a common intermediate. Our finding that the configuration of the anomeric center in the starting furanoside had a large effect on the stereochemical outcome of the chain extension reaction at C-5 prompted us to investigate an alternative synthesis of axenose, in which the branching methyl group at C-3 is introduced *prior* to the extension at C-5. This reordering of steps affords an intermediate with additional steric bulk on the β-face (at C-3), so that chain extension reactions at C-5 would be expected to favor the product of chelation control and give the L-*xylo* stereochemistry that is required for L-axenose. This route is shorter and also allows for protection of the C-3 hydroxyl at an early stage in the synthesis, a step that is necessary in order for glycosylation at the C-4 hydroxyl group to be carried out selectively. In this paper, we describe the synthesis of derivatives of L-axenose based on this approach, key steps of which are summarized in Scheme 1.

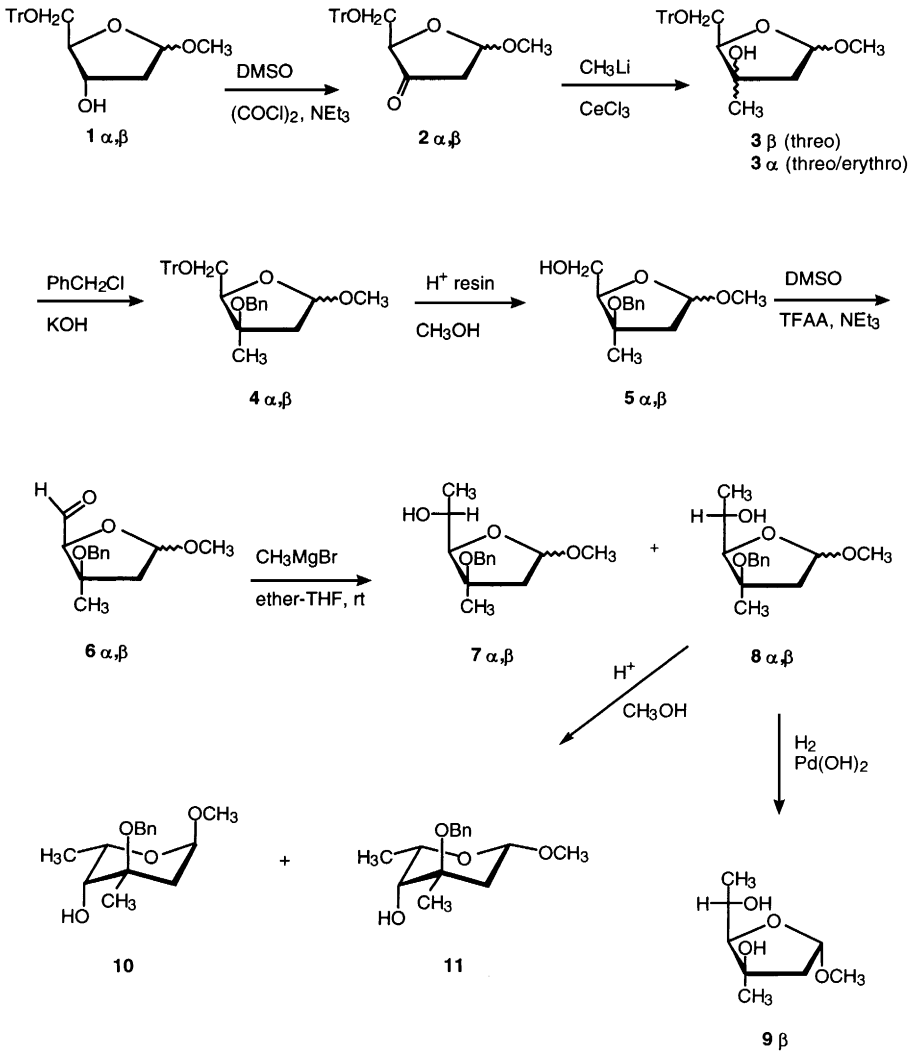


Scheme 1. Proposed synthesis of L-axenose

2. Results and discussion

Tritylation of a 1:1 mixture of anomers of methyl 2-deoxy-D-*ribo*-hexofuranoside[7] by the method of Leonard[8] gave a 66% yield of trityl ethers **1α,β** that were separable by flash chromatography on silica gel. The acid sensitivity of 2-deoxy furanosides required careful handling in the purification and in subsequent steps. Each anomer was carried through the sequence outlined in Scheme 2 independently, so that the effects of anomeric configuration on the stereoselectivity of addition reactions could be determined. A question that seemed important to address was whether the product of a chelation controlled addition to C-5 would be favored with the additional oxygen on the β-face. If so, this would allow for a shorter, more efficient synthesis of L-axenose. Oxidation of the C-3 hydroxyl group of **1α,β** was carried out with

methyl sulfoxide and oxalyl chloride or trifluoroacetic anhydride to provide the corresponding 3-uloses **2α**,**β**. Both anomers of the ulose were susceptible to elimination of methanol, consistent with earlier work of Villani[6] on related compounds. Because of this, the branching C-3 methyl group could not be introduced by treatment with methyllithium, which gave unsaturated products. However, the addition of methylcerium[9] occurred smoothly to give a 5:1 ratio of *threo* to *erythro* products in the case of the α-anomer, and the *threo* product exclusively in the case of the β-anomer. Attempted benzylation of the C-3 hydroxyl group in either anomer of the *threo* product proved difficult; however, treatment of **3β** or **3α** (*threo*) with powdered KOH in neat benzyl chloride, according to the procedure of Allerton and Fletcher,[10] gave benzyl ethers **4α** and **4β** in 70 and 87% yields, respectively. Protection of the tertiary alcohol at this point in the synthesis enables the 4-hydroxyl group to be uniquely unmasked by furanoside–pyranoside isomerization at a later stage. This protection would be necessary in disaccharide syntheses in which axenose serves as the acceptor, as would be the case for axenomycin.



Scheme 2. Synthesis of L-axenose derivatives

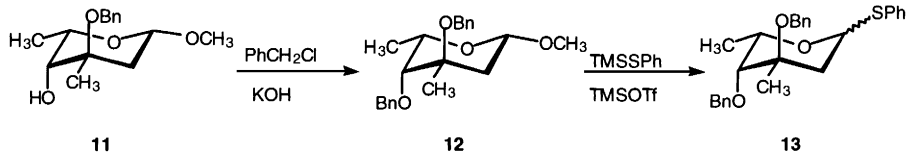
Several attempts for detritylation of **4** under acidic conditions or by hydrogenolysis gave unsatisfactory results. Partial debenzylation occurred when hydrogenolysis was attempted, and ring isomerization/anomerization occurred under acidic conditions. After many experiments, it was found that treatment of either **4α** or **4β** with Amberlyst-15 (H^+) resin[11] resulted in anomerization to mixtures of approximately 7:1 and 4:1, respectively, of detritylated products **5α**,**β**. In early attempts of this deprotection with older resin, yields of less than 60% of products were obtained and the reaction time varied from 8 to 10 h. However, with freshly generated resin, the deprotection proceeded in less than 3 h in 85% yield on a multigram scale. We tried to substitute a TBDMS protecting group for the trityl ether in this sequence, but found that the group was not stable to the strongly basic conditions required for the benzylation.

The next step required oxidation of the C-5 hydroxyl group to the aldehyde to allow for chain extension and completion of the synthesis. The use of trifluoroacetic anhydride in the place of oxalyl chloride in the Swern procedure[12] gave the respective dialdoses **6α**,**β** which were used immediately owing to their instability. Conditions for the chain extension reaction at C-5 of **6** were selected based on the systematic study of Villani on the stereoselectivity of additions of organometallic reagents to pentodialdo-1,4-furanosides.[6] Consistent with predictions based on our studies, a greater proportion (1.4:1) of the addition product **8β**, resulting from chelation control, was obtained using methylmagnesium bromide in ether. Due to solubility problems, it was necessary to include THF as a cosolvent in the addition to **6α**. It is interesting to note that the addition to **6β** occurred with opposite stereoselectivity, giving a 1.3:1 ratio of products **7β** and **8α** favoring the D-arabino isomer **7β**. In our previous study, we discovered that additions to pentodialdo-1,4-furanosides **14α** and **14β**, which lack the C-3 substituent on the β-face, also exhibited a dependence on anomeric configuration, with the L-*lyxo* product (chelation-controlled) being favored for **14α**, but not for **14β**, which gives the product (D-*ribo*), consistent with a Felkin–Anh transition state.[13] In the chelation-control model for dialdoses, it is the ring oxygen and the aldehyde oxygen that are thought to participate in chelation with the metal ion. Our previous study and the results described herein indicate that the model is insufficient to account for the observed selectivity, which depends on additional factors such as the anomeric substituent. Although selectivity for the L-*xylo* isomers **8α**,**β** was not high, the facile separation of **8β** from the product mixture by flash chromatography afforded sufficient quantities of axenose precursor for further studies.

The structure of **8β** was confirmed by a comparison of NMR data of the reduction product methyl 2,6-dideoxy-3-*C*-methyl-β-L-*xylo*-hexofuranoside **9β** with spectra obtained for material synthesized by Villani.[6b]

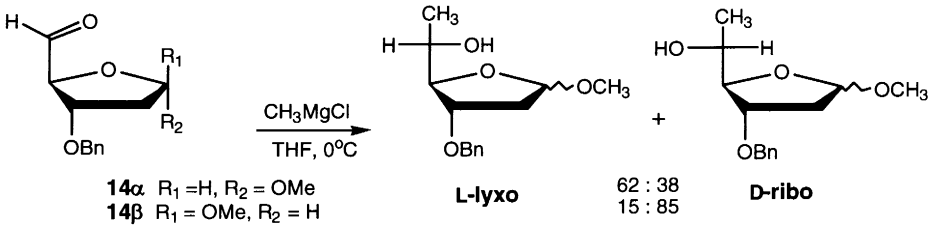
Equilibration of **8β** in methanolic hydrogen chloride gave α- and β-pyranosides **10** and **11**, with the β-pyranoside comprising about 35% of the total of 66% pyranoside, as measured by ^{1}H NMR. The higher amount of furanosides in this equilibration relative to those of unbranched monosaccharides is ascribed to the unfavorable steric interactions of the axial C-3 substituent. Similar behavior was noted by Angyal for methyl-branched sugars in their reducing form.[14] Reequilibration of the product to give higher yields of **11**, while not attempted in this study, could be carried out as described in the synthesis of the methyl-branched sugar L-nogalose developed in this laboratory.[15] The β-anomer of **11** was the one most easily separated from the furanosides present in the equilibration, so it was chosen to pursue the synthesis of glycosyl donors for axenose (Scheme 3).

In dutomycin and polyketomycin, axenose is attached by an α-1,4-linkage to the C-4 hydroxyl group of amicetose, so donors for the axenose residue are required for the synthesis of the dissacharide portion of



Scheme 3. Synthesis of phenyl thioglycosides

these two antibiotics.† The versatility of thioglycosides as donors is well documented in oligosaccharide synthesis.[16] They can be activated by several methods and converted to glycosyl sulfoxides, glycosyl halides, or to glycals. Protection of the C-4 hydroxyl group of **11** as its benzyl ether using benzyl chloride and potassium hydroxide gave dibenzyl ether derivative **12** in 92% yield. Treatment of **12** with phenylthiotrimethylsilane and trimethylsilyl trifluoromethanesulfonate[17] smoothly afforded the phenylthioglycoside **13** as a 3:1 mixture of α:β anomers in 82% yield. In our recent synthesis of the cororubicin trisaccharide,[18] we observed no difference in the outcome of coupling reactions of separate α- and β-anomers of phenylthioglycosides. Studies of the glycosylations of amicetose with **13** and its derivatives are in progress.



3. Experimental

3.1. General methods

^{1}H NMR spectra were recorded on a Varian XL 300 MHz spectrometer at 300 MHz with TMS as an internal reference in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were recorded on a Varian XL 300 MHz spectrometer at 75 MHz and referenced with $CDCl_3$. Melting points were determined in an open capillary tube with a Thomas Hoover apparatus and are uncorrected. TLC analyses were conducted on silica gel Kieselgel 60 F254 (Merck) glass plates and visualized by UV254 nm or with ammonium molybdate–ceric sulfate reagent. Flash chromatography[19] was carried out with 'Baker' silica gel. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter as $[\alpha]_D$ values at 23°C. Elemental analyses were carried out at Merck Research Laboratories. High resolution mass spectra were measured at Merck Research Laboratories using ES-FT/ICR/MS with propylene glycol as internal standard on a Bruker ES-FT mass spectrometer.

† The situation in axenomycin is opposite, as noted above, in which amicetose is attached to the C-4 hydroxyl group of axenose.

3.2. *Methyl 2-deoxy-5-*O*-trityl-α-*D*-glycero-pentofuranosid-3-ulose and methyl 2-deoxy-5-*O*-trityl-β-*D*-glycero-pentofuranosid-3-ulose* **2α,β**

To a stirring solution of oxalyl chloride (2.73 g, 21.5 mmol, 1.9 mL) in dichloromethane (45 mL) at −78°C was added a solution of methyl sulfoxide (3.36 g, 43 mmol, 3.05 mL) in dichloromethane (15 mL). After 15 min, a solution of methyl 2-deoxy-5-*O*-trityl-α-D-*erythro*-pentofuranoside **1α** (7.0 g, 17.9 mmol) in dichloromethane (25 mL) was added and the reaction mixture was stirred for an additional 30 min. Triethylamine (9.1 g, 90 mmol, 12.5 mL) was added and the reaction mixture was allowed to warm to 0°C for 1 h. Saturated aqueous sodium hydrogen carbonate (75 mL) was added and the whole was extracted with ethyl acetate (2×75 mL). The organic layers were combined, washed with saturated aqueous sodium chloride (50 mL), and the organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting syrup was purified by flash column chromatography over silica gel (10 in×6 cm) with hexanes:ethyl acetate (4:1) to give (4.5 g, 65%) of **2α**: $[\alpha]_D$=+188 (*c* 1.09, $CHCl_3$); R_f=0.53 in 4:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.48–7.21 (m, 15H, Ar), 5.47 (d, $J_{1,2}$=5.1 Hz, 1H, H-1), 4.04 (bt, $J_{4,5}$, $J_{4,5'}$=2.5, 3.5 Hz, 1H, H-4), 3.46 (s, 3H, OCH_3), 3.44 (dd, $J_{5,5'}$=10.2 Hz, 1H, H-5), 3.32 (dd, 1H, H-5′), 2.81 (dd, $J_{2,2'}$=18.1 Hz, 1H, H-2), 2.46 (d, 1H, H-2′); ^{13}C NMR (75 MHz) δ 212.02 (C=O), 143.45 (*ipso*), 128.59, 127.91, 126.96 (Ar), 101.41 (C-1), 86.63 (Ph_3C), 77.29 (C-4), 62.87 (C-5), 54.88 (OCH_3), 44.02 (C-2).

Compound **2β** was obtained as a syrup in 60% yield using the same method. From 6.1 g (15.6 mmol) of **1β**, 3.6 g of **2β** was obtained. In a scale-up preparation of **2β**, oxidation by the following procedure gave improved results. To a stirring solution of methyl sulfoxide (4.92 g, 63 mmol, 4.47 mL) in dichloromethane (120 mL) at −78°C under nitrogen was added a solution of trifluoroacetic anhydride (10.1 g, 48 mmol, 6.8 mL) in dichloromethane (20 mL). After 10 min, a solution of **1β** (11.7 g, 30.0 mmol) in dichloromethane (120 mL) was added and the reaction mixture was stirred for an additional 15 min. Triethylamine (9.4 g, 93 mmol, 13.0 mL) was added and the reaction mixture was allowed to warm to 0°C for 1 h. The reaction mixture was treated as described above to yield **2β** as an amber oil (9.1 g, 78% yield): $[\alpha]_D$=−28.5 (*c* 1.20, $CHCl_3$); R_f=0.37 in 4:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.58–7.19 (m, 15H, Ar), 5.34 (dd, $J_{1,2}$, $J_{1,2'}$=1.5, 5.7 Hz, 1H, H-1), 4.21 (ddd, $J_{4,5}$, $J_{4,5'}$, $J_{2,4}$=2.9, 6.6, 0.9 Hz, 1H, H-4), 3.42 (dd, $J_{5,5'}$=10.1 Hz, 1H, H-5), 3.33 (s, 3H, OCH_3), 3.25 (dd, 1H, H-5′), 2.75 (dd, $J_{2.2'}$=18.2 Hz, 1H, H-2), 2.46 (dd, 1H, H-2′); ^{13}C NMR (75 MHz) δ 211.91 (C=O), 143.55 (*ipso*), 128.65, 127.66, 126.90 (Ar), 102.17 (C-1), 86.61 (Ph_3C), 79.54 (C-4), 64.73 (C-5), 54.88 (OCH_3), 43.48 (C-2).

3.3. *Methyl 2-deoxy-3-*C*-methyl-5-*O*-triphenylmethyl-α-*D*-threo-pentofuranoside and methyl 2-deoxy-3-*C*-methyl-5-*O*-triphenylmethyl-β-*D*-threo-pentofuranoside* **3α,β**

To a flask charged with dried cerium trichloride (4.88 g, 19.8 mmol, 130–140°C under vacuum for 24 h) under nitrogen was added dry tetrahydrofuran (60 mL) and the resulting suspension was stirred for 18 h. The suspension was cooled to −78°C and a solution of methyllithium in diethyl ether (12.9 mL, 1.4 M, 18.1 mmol) was added. The resulting brownish suspension was stirred for an additional hour after which a solution of **2α** (3.2 g, 8.2 mmol) in tetrahydrofuran (18 mL) was added. The resulting suspension was stirred at −78°C for 15 min and allowed to warm to 0°C. After 2 h, water (10 mL) was added and the resulting slurry was stirred vigorously for 15 min. The organic layer was decanted off and the semi-solid residue was washed with ethyl acetate (2×35 mL). The organic layers were combined and washed with saturated aqueous sodium chloride (40 mL), and the organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting oil was purified by flash

column chromatography over silica gel (6.5 in×6 cm) with hexanes:ethyl acetate (88:12 to 75:25) to yield the *threo* product (2.6 g, 78%, R_f=0.52 in 4:1 toluene:ethyl acetate) and its C-3 epimer, the *erythro* product (0.52 g, 16%, R_f=0.64 in 4:1 toluene:ethyl acetate). Data for the **3α** *threo* isomer: $[\alpha]_D$=+56.5 (*c* 1.26; $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.50–7.19 (m, 15H, Ar), 5.14 (dd, $J_{1,2}$, $J_{1,2'}$=3.3, 5.7 Hz, 1H, H-1), 3.91 (app t, $J_{4,5}$=4.8 Hz, 2H, H-5), 3.41 (d, 1H, H-4), 3.39 (s, 3H, OCH_3), 2.65 (s, 1H, OH), 2.31 (dd, $J_{2,2'}$=14.0 Hz, 1H, H-2), 1.92 (dd, 1H, H-2′), 1.38 (s, 3H, 3-CH_3); ^{13}C NMR (75 MHz) δ 143.45 (*ipso*), 128.45, 127.85, 127.06 (Ar), 103.94 (C-1), 82.27 (C-4), 78.54 (C-3), 62.19 (C-5), 55.19 (OCH_3), 48.86 (C-2), 25.68 (3-CH_3). HRMS: calcd for $C_{26}H_{28}O_4$ (M+Na): 427.1872. Found: 427.1880.

The addition of methylcerium to **2β** afforded *threo* product **3β** as a single isomer. From 3.4 g (8.8 mmol) of **2β**, 2.2 g (68%) of syrupy **3β** was obtained: $[\alpha]_D$=−34.5 (*c* 1.36; $CHCl_3$); R_f=0.63 in 4:1 toluene:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.56–7.19 (m, 15H, Ar), 5.05 (dd, $J_{1,2}$, $J_{1,2'}$=1.7, 3.3 Hz, 1H, H-1), 3.96 (dd, $J_{4,5}$, $J_{5,5'}$=6.4, 4.2 Hz, 2H, H-5), 3.37 (d, 1H, H-4), 3.35 (s, 3H, OCH_3), 3.27 (s, 1H, OH), 2.04 (dd, 2H, H-2), 1.26 (s, 3H, 3-CH_3); ^{13}C NMR (75 MHz) δ 143.94 (*ipso*), 128.70, 127.64, 126.79 (Ar), 104.42 (C-1), 87.20 (C-4), 77.41 (C-3), 64.31 (C-5), 54.75 (OCH_3), 46.93 (C-2), 23.01 (3-CH_3). Anal. calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.32; H, 7.15.

*3.4. Methyl 3-*O*-benzyl-2-deoxy-3-*C*-methyl-5-*O*-triphenylmethyl-α-*D*-threo-pentofuranoside and methyl 3-*O*-benzyl-2-deoxy-3-*C*-methyl-5-*O*-triphenylmethyl-β-*D*-threo-pentofuranoside **4α,β***

To a solution of **3α** (200 mg, 0.49 mmol) in benzyl chloride (neat, 1.5 mL) was added powdered potassium hydroxide (1.0 g) and the resulting slurry was heated to 130–140°C for 2 h, after which time no starting material was observed by TLC. The reaction mixture was allowed to cool to ambient temperature and was then transferred to a separation funnel with water and ethyl acetate. The layers were separated, the organic layer was washed with saturated aqueous sodium chloride and dried with anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting syrup was purified by flash column chromatography over silica gel with hexanes:ethyl acetate (90:10 to 75:25) to give **4α** as a syrup (155 mg, 70% yield): $[\alpha]_D$=+14.6 (*c* 1.39; $CHCl_3$); R_f=0.66 in 3:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.55–7.03 (m, 20H, Ar), 5.08 (dd, $J_{1,2}$, $J_{1,2'}$=3.5, 5.8 Hz, 1H, H-1), 4.37 (ABq, J=12.1 Hz, 2H, Bn), 4.09 (t, $J_{4,5}$=3.7 Hz, 2H, H-5), 3.45 (d, 1H, H-4), 3.41 (s, 3H, OCH_3), 2.54 (dd, $J_{2,2'}$=14.2 Hz, 1H, H-2), 1.79 (dd, 1H, H-2′), 1.43 (s, 3H, 3-CH_3); ^{13}C NMR (75 MHz) δ 144.07 (*ipso*), 139.18 (*ipso*), 128.70, 127.58, 126.73 (Ar), 127.99, 126.80, 126.39 (Ar), 103.94 (C-1), 84.75 (C-4), 82.85 (C-3), 64.51 (Bn), 62.49 (C-5), 55.18 (OCH_3), 43.76 (C-2), 21.51 (3-CH_3). HRMS: calcd for $C_{33}H_{34}O_4$ (M+Na): 517.2349. Found: 517.2366. The β-anomer **4β** was also prepared by the same method. From 6.5 g (16.1 mmol) of **3β**, 6.9 g (87%) of syrupy **4β** was obtained, which was purified by flash column chromatography over silica gel with hexanes:ethyl acetate (9:1 to 3:1): $[\alpha]_D$=–42.7 (*c* 1.41; $CHCl_3$); R_f=0.53 in 3:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.55–7.06 (m, 20H, Ar), 5.06 (dd, $J_{1,2}$, $J_{1,2'}$=2.5, 5.9 Hz, 1H, H-1), 4.37 (ABq, J=11.8 Hz, 2H, Bn), 4.03 (dd, $J_{4,5}$, $J_{5,5'}$=6.7, 4.8 Hz, 2H, H-5), 3.46 (d, 1H, H-4), 3.39 (s, 3H, OCH_3), 2.31 (dd, $J_{2,2'}$=13.9 Hz, 1H, H-2), 1.99 (dd, 1H, H-2′), 1.37 (s, 3H, 3-CH_3); ^{13}C NMR (75 MHz) δ 144.19 (*ipso*), 139.20 (*ipso*), 128.75, 127.88, 126.66 (Ar), 128.61, 127.52, 126.51 (Ar), 104.45 (C-1), 87.02 (C-4), 81.44 (C-3), 65.00 (Bn), 63.98 (C-5), 55.20 (OCH_3), 42.29 (C-2), 22.49 (3-CH_3). Anal. calcd for $C_{33}H_{34}O_4$: C, 80.13; H, 6.93. Found: C, 79.71; H, 6.95.

*3.5. Methyl 3-*O*-benzyl-2-deoxy-3-*C*-methyl-α-*D*-threo-pentofuranoside and methyl 3-*O*-benzyl-2-deoxy-3-*C*-methyl-β-*D*-threo-pentofuranoside **5α,β***

To a stirring solution of trityl ether **4α** (0.88 g, 1.78 mmol) in methanol (20 mL) was added Amberlyst-15 macroreticular resin (strongly acidic; 500 mg) and the reaction mixture was allowed to stir for 8 h at

room temperature, filtered through Celite, neutralized with triethylamine, and concentrated at reduced pressure. Careful purification by flash column chromatography over silica gel with hexanes:ethyl acetate (85:15 to 50:50) yielded a syrup (283 mg, 63%) containing a 7:1 mixture of α- and β-anomers with nearly identical R_f values. Column fractions highly enriched in β-anomer were pooled for NMR analysis and subsequent oxidation when the detritylation was carried out on a larger scale (see below). The α-anomer eluted first. Compound **5α**: R_f=0.5 in 1:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.36–7.24 (m, 5H, Ar), 5.16 (dd, $J_{1,2}$, $J_{1,2'}$=2.5, 5.8 Hz, 1H, H-1), 4.46 (ABq, J=11.4 Hz, 2H, Bn), 3.99–3.83 (m, 2H, H-4, H-5), 3.39 (s, 3H, OCH_3), 2.77 (dd, $J_{5,OH}$, $J_{5',OH}$=3.9, 8.1, 1H, OH), 2.56 (dd, $J_{2,2'}$=13.9 Hz, 1H, H-2), 1.89 (dd, 1H, H-2′), 1.52 (s, 3H, 3-CH_3); ^{13}C NMR (75 MHz) δ 138.29 (*ipso*), 128.28, 127.43, 126.77 (Ar), 103.86 (C-1), 84.91 (C-4), 84.78 (C-3), 65.24 (Bn), 60.97 (C-5), 55. 13 (OCH_3), 43.74 (C-2), 22.41 (3-CH_3). HRMS: calcd for $C_{14}H_{20}O_4Na$ (M+Na): 275.1254. Found: 275.1258. Compound **5β**: R_f=0.5 in 1:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.36–7.24 (m, 5H, Ar), 5.04 (dd, $J_{1,2}$, $J_{1,2'}$=3.3, 5.9 Hz, 1H, H-1), 4.49 (ABq, J=11.0 Hz, 2H, Bn), 3.99-3.83 (m, 3H, H-4, H-5), 3.40 (s, 3H, OCH_3), 2.71 (d, $J_{5,OH}$=6.2 Hz, 1H, OH), 2.37 (dd, $J_{2,2'}$=13.8 Hz, 1H, H-2), 2.11 (dd, 1H, H-2′), 1.49 (s, 3H, 3-CH_3); ^{13}C NMR (75 MHz) δ 138.3 (Ar *ipso*), 128.36, 127.51, 127.03 (Ar), 104.7 (C-1), 86.4 (C-4), 84.80 (C-3), 66.08 (Bn), 62.3 (C-5), 55.13 (OCH_3), 42.24 (C-2), 23.88 (3-CH_3). HRMS: calcd for $C_{14}H_{21}O_4$ (M+H): 253.1434. Found: 253.1429.

A larger scale detritylation of **4β** (2.4 g, 4.85 mmol) under these conditions gave 700 mg (57%) of a 4:1 mixture of **5α** and **5β**.

*3.6. Methyl 2-deoxy-3-*C*-methyl-α-*D*-*threo*-pentodialdo-1,4-furanoside* **6α,β**

To a stirring solution of methyl sulfoxide (0.91 g, 12 mmol, 0.83 mL) in dichloromethane (15 mL) at −78°C under nitrogen was added a solution of trifluoroacetic anhydride (1.9 g, 8.9 mmol, 1.3 mL). After 10 min, a solution of alcohol **5α** (1.4 g, 5.6 mol) in dichloromethane (15 mL) was added and the reaction mixture was stirred for an additional 15 min. Triethylamine (1.7 g, 17 mmol, 2.4 mL) was added and the reaction mixture was allowed to warm to room temperature for 1 h. Saturated aqueous ammonium chloride (40 mL) was added and the mixture was extracted with ethyl acetate (2×50 mL). The organic layers were combined, washed with saturated aqueous sodium chloride (30 mL) and the organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated at reduced pressure to give 1.2 g of crude, unstable dialdose **6α** which was used promptly: R_f=0.63 in 3:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 9.7 d, J=3.7 Hz, CHO); ^{13}C NMR (75 MHz) δ 201.14 (CHO). Oxidation of **5β** (0.68 g, 2.7 mmol) using the same method gave 0.6 g of dialdofuranoside **6β** (R_f=0.66 in 3:1 hexanes:ethyl acetate).

*3.7. Methyl 3-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-α-*D*-*arabino*-hexofuranoside* **7α** *and methyl 3-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-β-*L*-*xylo*-hexofuranoside* **8β**

To a stirring solution of pentodialdo-1,4-furanoside **6α** (1.2 g, 4.8 mmol) in diethyl ether (anhydrous, 20 mL) under nitrogen at room temperature was added a solution of methylmagnesium chloride in tetrahydrofuran (3.2 mL of a 3.0 M solution). The resulting mixture was stirred for 1 h, after which saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted with diethyl ether (2×30 mL). The organic layers were combined, washed with saturated aqueous sodium chloride (10 mL) dried with anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting oil was purified by flash column chromatography over silica gel with hexanes:ethyl acetate (4:1 to 7:3) to yield 345 mg (27%) of β-L-*xylo* isomer **8β** and 260 mg (20%) of the α-D-*arabino* isomer **7α**. Compound **7α**: R_f=0.79 in 1:1 hexanes:ethyl acetate; $[\alpha]_D$=+60.4 (*c* 0.81; $CHCl_3$); ^{1}H NMR (300 MHz)

δ 7.38–7.23 (m, 5H, Ar), 5.05 (dd, $J_{1,2}$, $J_{1,2'}$=1.4, 5.6 Hz, 1H, H-1), 4.51 (ABq, J=11.5 Hz, 2H, Bn), 4.05 (ddq, $J_{4,5}$, $J_{5,OH}$, $J_{5,6}$=8.0, 4.0, 6.4 Hz, 1H, H-5), 3.57 (d, 1H, H-4), 3.34 (s, 3H, OCH_3), 3.21 (d, 1H, OH), 2.45 (dd, $J_{2,2'}$=13.5 Hz, 1H, H-2), 1.98 (dd, 1H, H-2′), 1.63 (s, 3H, 3-CH_3), 1.30 (d, 3H, H-6); ^{13}C NMR (75 MHz) δ 138.28 (*ipso*), 128.43, 127.50, 126.88 (Ar), 103.49 (C-1), 88.83 (C-4), 84.47 (C-3), 67.43 (C-5), 65.52 (Bn), 54.64 (OCH_3), 44.59 (C-2), 25.17 (3-CH3), 20.10 (C-6). HRMS calcd for $C_{15}H_{23}O_4$ (M+H): 267.1591. Found: 267.1592.

Compound **8β**: R_f=0.60 in 1:1 hexanes:ethyl acetate; $[\alpha]_D$=+58 (*c* 0.98; $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.36–7.24 (m, 5H, Ar), 5.19 (dd, $J_{1,2}$, $J_{1,2'}$=2.8, 5.7 Hz, 1H, H-1), 4.47 (ABq, J=11.4 Hz, 2H, Bn), 4.23–4.18 (m, 1H, H-5), 3.61 (brd, $J_{4,5}$=2.2 Hz, 1H, H-4), 3.39 (s, 3H, OCH_3), 3.38 (d, 1H, OH), 2.60 (dd, $J_{2,2'}$=14.0 Hz, 1H, H-2), 1.84 (dd, 1H, H-2′), 1.50 (s, 3H, 3-CH_3), 1.32 (d, $J_{5,6}$=6.6 Hz, 3H, H-6); ^{13}C NMR (75 MHz) δ 138.29 (Ar *ipso*), 128.48, 127.543, 126.89 (Ar), 103.38 (C-1), 87.43 (C-4), 85.15 (C-3), 65.11 (Bn), 60.97 (C-5), 55.06 (OCH_3), 43.88 (C-2), 21.90 (3-CH_3), 19.85 (C-6). HRMS calcd for $C_{15}H_{23}O_4$ (M+H): 267.1591. Found: 267.1593.

3.8. *Methyl 3*-O-*benzyl-2,6-dideoxy-3*-C-*methyl-β*-D-arabino-*hexofuranoside* **7β** *and methyl 3*-O-*benzyl-2,6-dideoxy-3*-C-*methyl-α*-L-xylo-*hexofuranoside* **8α**

To a stirring solution of pentodialdo-1,4-furanoside **6β** (600 mg, 2.7 mmol) in diethyl ether (anhydrous, 10 mL) under nitrogen at room temperature was added a solution of methylmagnesium chloride in tetrahydrofuran (1.8 mL of a 3.0 M solution). The resulting mixture was stirred for 1 h, after which saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted with diethyl ether (2×20 mL). The organic layers were combined, washed with saturated aqueous sodium chloride (10 mL), dried with anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting oil was purified by flash column chromatography over silica gel with hexanes:ethyl acetate (4:1 to 7:3) to yield 148 mg (23%) of β-D-*arabino* isomer **7β** and 107 mg (17%) of α-L-*xylo* isomer **8α**.
Compound **7β**: R_f=0.74 in 1:1 hexanes:ethyl acetate; $[\alpha]_D$=−61 (*c* 1.31; $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.38–7.23 (m, 5H, Ar), 4.96 (dd, $J_{1,2}$, $J_{1,2'}$=3.8, 5.8 Hz, 1H, H-1), 4.52 (ABq, J=10.9 Hz, 2H, Bn), 4.12 (dq, $J_{4,5}$, $J_{5,6}$=9.1, 6.3 Hz, 1H, H-5), 3.44 (d, 1H, H-4), 3.38 (s, 3H, OCH_3), 2.31 (dd, $J_{2,2'}$=13.5 Hz, 1H, H-2), 2.18 (dd, 1H, H-2′), 1.54 (s, 3H, 3-CH_3), 1.25 (d, 3H, H-6); ^{13}C NMR (75 MHz) δ 137.89 (*ipso*), 128.45, 127.67, 127.22 (Ar), 104.69 (C-1), 89.76 (C-4), 84.34(C-3), 67.77 (C-5), 66.61(Bn), 55.37 (OCH_3), 42.27 (C-2), 25.32 (3-CH_3), 19.46 (C-6).

Compound **8α**: R_f=0.57 in 1:1 hexanes:ethyl acetate; $[\alpha]_D$=−41 (*c* 1.22; $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.36–7.24 (m, 5H, Ar), 5.07 (dd, $J_{1,2}$, $J_{1,2'}$=2.2, 5.7 Hz, 1H, H-1), 4.49 (ABq, J_{ab}=11.0 Hz, 2H, Bn), 4.12 (dq, $J_{4,5}$, $J_{5,6}$=2.8, 6.5 Hz, 1H, H-5), 3.59 (d, 1H, H-4), 3.44 (s, 3H, OCH_3), 2.49 (dd, $J_{2,2'}$=13.9 Hz, 1H, H-2), 2.00 (dd, 1H, H-2′), 1.44 (s, 3H, 3-CH_3), 1.27 (d, 3H, H-6); ^{13}C NMR (75 MHz) δ 138.29 (Ar *ipso*), 128.24, 127.53, 127.07 (Ar), 104.11 (C-1), 90.533 (C-4), 82.93 (C-3), 65.65, 65.21 (Bn, C-5), 55.08 (OCH_3), 41.77 (C-2), 23.10 (3-CH_3), 20.17 (C-6).

3.9. *Methyl 2,6-dideoxy-3*-C-*methyl-β*-L-xylo-*hexofuranoside* **9β**

A sample of 25 mg of **8β** was treated with hydrogen and palladium hydroxide (20 mg) in ethanol (5 mL) to give debenzylated product **9β**, the ^{1}H and ^{13}C NMR spectrum of which matched reports by Villani.[6b]

3.10. *Methyl 3*-O-*benzyl-2,6-dideoxy-3*-C-*methyl*-α-L-xylo-*hexopyranoside* ***10*** *and methyl 3*-O-*benzyl-2,6-dideoxy-3*-C-*methyl*-β-L-xylo-*hexopyranoside* ***11***

To a stirring solution of **8β** (320 mg, 1.2 mmol) in methanol (anhydrous, 20 mL) was added hydrogen chloride (1.32 mL of a 1.0 M solution in diethyl ether) and the resulting solution was heated at 50°C for 3 h. The reaction mixture was allowed to cool to room temperature after which silver carbonate (530 mg, 1.9 mmol) was added and the mixture was stirred for 0.5 h. The suspension was filtered through Celite and concentrated at reduced pressure. The resulting oil was purified by flash column chromatography over silica gel with hexanes:ethyl acetate (4:1 to 7:3) to yield 130 mg (41%) of β-anomer **11** and 62 mg (19%) of α-anomer **10**.

Compound **11**: $[\alpha]_D$=+13.1 (*c* 1.1; $CHCl_3$); R_f=0.63 in 1:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.38–7.22 (m, 5H, Ar), 4.58 (dd, $J_{1,2}$, $J_{1,2'}$=2.4, 9.8 Hz, 1H, H-1), 4.51 (ABq, J=10.2 Hz, 2H, Bn), 4.19 (dq, $J_{4,5}$, $J_{5,6}$=0.9, 6.6 Hz, 1H, H-5), 3.49 (s, 3H, OCH_3), 3.19 (dd, $J_{4,OH}$=10.1 Hz, 1H, H-4), 2.08–1.95 (m, 2H, H-2, OH), 1.53 (dd, $J_{2,2'}$=14.2 Hz, 1H, H-2′), 1.40 (s, 3H, 3-CH_3), 1.27 (d, 3H, H-6); ^{13}C NMR (75 MHz) δ 138.69 (*ipso*), 128.31, 127.36, 127.11 (Ar), 100.01 (C-1), 77.12 (C-3), 72.51 (C-4), 68.83 (C-5), 63.45 (Bn), 56.33 (OCH_3), 35.30 (C-2), 21.38 (3-CH_3), 16.54 (C-6). HRMS calcd for $C_{15}H_{23}O_4$ (M+H): 267.1591. Found: 267.1592.

Compound **10**: R_f=0.58 in 1:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.38–7.22 (m, 5H, Ar), 4.71 (d, $J_{1,2}$=4.8 Hz, 1H, H-1), 4.50 (ABq, J=10.2 Hz, 2H, Bn), 4.53 (q, $J_{5,6}$=6.6 Hz, 1H, H-5), 3.36 (s, 3H, OCH_3), 3.18 (d, $J_{4,OH}$=9.3 Hz, 1H, H-4), 2.11 (dd, $J_{2,2'}$=15.6 Hz, 1H, H-2), 1.92 (d, 1H, OH), 1.69 (dd, 1H, H-2′), 1.34 (s, 3H, 3-CH_3), 1.21 (d, 3H, H-6); ^{13}C NMR (75 MHz) δ 139.33 (*ipso*), 128.46, 127.64, 127.11 (Ar), 97.95 (C-1), 74.23 (C-3), 73.56 (C-4), 63.76 (C-5), 62.32 (Bn), 54.82 (OCH_3), 30.99 (C-2), 22.30 (3-CH_3), 16.66 (C-6).

3.11. *Methyl 3,4-di*-O-*benzyl-2,6-dideoxy-3*-C-*methyl*-β-L-xylo-*hexopyranoside* ***12***

To a stirring solution of β-anomer **11** (430 mg, 1.61 mmol) in benzyl chloride (neat, 3.1 mL) was added powdered potassium hydroxide (2.1 g) and the resulting slurry was heated to 120–130°C for 1.5 h, after which time no starting material was observed by TLC. The reaction mixture was allowed to cool and was then transferred to a separation funnel with water and ethyl acetate. The layers were separated, the organic layer was washed with saturated aqueous sodium chloride and was dried with anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting syrup was purified by flash column chromatography over silica gel with hexanes:ethyl acetate (9:1) to give the product as a syrup (530 mg, 92% yield): $[\alpha]_D$=−22.6 (*c* 1.29; $CHCl_3$); R_f=0.66 in 3:1 hexanes:ethyl acetate; ^{1}H NMR (300 MHz) δ 7.47–7.22 (m, 10H, Ar), 4.70 (ABq, J=11.7 Hz, 2H, 4-OBn), 4.61 (dd $J_{1,2}$, $J_{1,2'}$=2.1, 9.9 Hz, 1H, H-1), 4.49 (ABq, J=11.1 Hz, 2H, 3-OBn), 4.15 (dq, $J_{4,5}$, $J_{5,6}$=1.2, 6.6 Hz, 1H, H-5), 3.50 (s, 3H, OCH_3), 3.10 (d, 1H, H-4), 2.00 (dd, $J_{2,2'}$=13.8 Hz, 1H, H-2), 1.73 (dd, 1H, H-2′), 1.37 (s, 3H, 3-CH_3), 1.29 (d, 3H, H-6); ^{13}C NMR (75 MHz) δ 138.65, 137.94 (*ipso*), 128.28, 128.07, 127.85, 127.46, 127.31, 127.09 (Ar), 99.43 (C-1), 80.07 (4-OBn), 77.53 (C-3), 75.78 (C-4), 69.10 (C-5), 63.16 (Bn), 56.13 (OCH_3), 35.86 (C-2), 21.43 (3-CH_3), 16.89 (C-6). HRMS calcd for $C_{22}H_{29}O_4$ (M+H): 357.2060. Found: 357.2061.

3.12. *Phenyl 3,4-di*-O-*benzyl-2,6-dideoxy-3*-C-*methyl-1-thio*-α,β-L-xylo-*hexopyranoside* ***13***

To a stirring solution of dibenzyl ether **12** (750 mg, 2.1 mmol) in dichloromethane (dry, 8 mL) under nitrogen at 0°C was added phenylthiotrimethylsilane (2.0 mL, 10.5 mmol), then trimethylsilyl

trifluoromethanesulfonate (457 mL, 2.52 mmol). The reaction mixture was allowed to warm to ambient temperature for 3 h. The reaction mixture was then poured into water and extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium chloride and was dried with anhydrous sodium sulfate, filtered and concentrated at reduced pressure to give a syrup that was purified by flash column chromatography over silica gel with hexanes:ethyl acetate (94:6). The product was obtained as a syrup containing a 3:1 mixture of β- and α-anomers (748 mg, 82% yield): R_f=0.57 in 5:1 hexanes:ethyl acetate; β-anomer: ^{1}H NMR (300 MHz) δ 7.58–7.17 (m, 15H, Ar), 5.07 (dd, $J_{1,2}$, $J_{1,2'}$=5.4, 9.0 Hz, 1H, H-1), 4.68 (ABq, J=11.7 Hz, 2H, 4-OBn), 4.45 (ABq, J=11.6 Hz, 2H, 3-OBn), 4.20 (dq, $J_{4,5}$, $J_{5,6}$=0.9, 6.5 Hz, 1H, H-5), 3.10 (brs, 1H, H-4), 2.29–2.02 (m, 2H, H-2), 1.33 (s, 3H, 3-CH_3), 1.29 (d, 3H, H-6); ^{13}C NMR (75 MHz) δ 138.52, 138.09 (*ipso*), 134.77 (SAr *ipso*), 130.68–126.56 (Ar), 80.02 (4-OBn), 79.90 (C-1), 76.82 (C-3), 75.64 (C-4), 71.95 (C-5), 63.26 (3-OBn), 35.69 (C-2), 21.39 (3-CH_3), 17.37 (C-6). HRMS: calcd for $C_{27}H_{30}O_3SNa$ (M+Na): 457.1808. Found: 457.1816.

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