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2,3-Anhydrosugars in glycoside bond synthesis: application to furanosyl azides and C-glycosides

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ABSTRACT

The preparation of 2-deoxy-2-thiotolylfuranosyl azides and C-glycosides from a 2,3-anhydrosugar thioglycoside with the D-*lyxo* stereochemistry is described. The reaction is performed by treatment of the thioglycoside with a trimethylsilylated nucleophile in the presence of $BF_3{\cdot}OEt_2$. This approach provides a convenient route to the preparation of the corresponding 2-deoxy-furanosyl azides and C-glycosides. In contrast, the use of an isomeric substrate, with the 2,3-anhydro-D-*ribo* stereochemistry, gave these products in low to modest yield.

1. Introduction

Earlier work from our laboratory has reported the use of 2,3-anhydrosugar thioglycosides (**1**–**4**, Fig. 1) for the assembly of 2,3-anhydrosugar glycosides (e.g., **5**)[1] and 2-deoxy-glycosides (e.g., **6**).[2,3] With regard to the latter process, the transformation requires two steps. First, reaction with an alcohol and a Lewis acid induces the migration of the thiotolyl group from C-1 to C-2 with concomitant stereocontrolled glycosidation at C-1 thus generating a 2-deoxy-2-thiotolyl glycoside (e.g., **7**). In the products, the relationship between the groups at C-1 and C-2 is trans, while the C-3 substituent is cis to that at the anomeric carbon. In a second step, the carbon–sulfur bond is reductively cleaved to generate the 2-deoxy-glycoside. This reaction manifold is thus similar to other migration–glycosidation protocols involving thio- or selenoglycosides possessing leaving groups at C-2.[4]

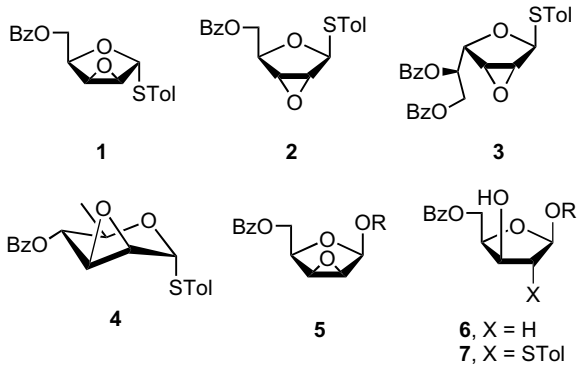

Figure 1. Structures of 2,3-anhydrosugar thioglycosides (**1**–**4**) and reaction products (**5**–**7**).

Due to the success in synthesizing 2-deoxy,[2] and 2,6-dideoxy-sugar[3] O-glycosides from **1**–**4** by reaction with a range of alcohols, we wanted to determine how other nucleophiles would perform in these reactions. We describe here studies directed towards the synthesis of 2-deoxy-2-thiotolylfuranosyl azides and C-glycosides from **1** and **2**.

Glycosyl azides are valuable carbohydrate building blocks, especially as precursors to glycosylamines.[5,6] C-Glycosides, molecules in which the anomeric oxygen is replaced by a methylene group, have been used as mimetics of O-glycosides.[7,8] These compounds, which do not contain the acetal linkages present in their O-glycoside parents, are believed to have promising applications as inhibitors of cell-surface recognition events and glycoside metabolism because of their greater chemical and enzymatic stability.[7,8] Thus, the development of new methods for the stereoselective synthesis of glycosyl azides and C-glycosides continues to be of interest.

2. Results and discussion

To explore the potential of **1** and **2** in these reactions, we initially carried out a model study in which **1** was treated with trimethylsilyl azide ($TMSN_3$) so that optimum reaction conditions could be established (Table 1). We first treated **1** with $TMSN_3$ and 10 equiv (by weight) of 4 Å molecular sieves in dichloromethane, conditions that worked well in the glycosylation of simple alcohols and activated carbohydrate alcohols.[2,3] Unfortunately, none of the desired product was detected, even after reflux for several hours. It was then determined that copper(II) triflate[2,3] could promote the reaction at room temperature, but the desired product (**8**) was obtained only in

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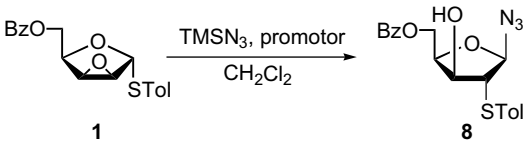
Table 1
Optimization of the synthesis of **8** from **1**[a]

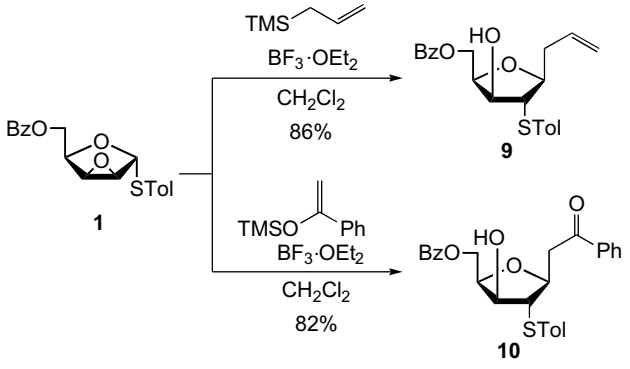


Entry	Promoter	Equiv[b]	Temperature	Yield (%)	β/α ratio[c]
1	4 Å MS	10	Reflux	0	—
2	$Cu(OTf)_2$	1.0	rt	35	100:0
3	$BF_3{\cdot}Et_2O$	1.0	−78 °C	91	100:0

[a] Conditions: thioglycoside **1** (0.29 mmol) and $TMSN_3$ (1.16 mmol) in CH_2Cl_2 (20 mL).
[b] Relative to **1**, molecular sieves are by weight.
[c] Ratio determined by ^1H NMR spectroscopy after chromatography.

low yield. Fortunately, the use of $BF_3{\cdot}Et_2O$ at −78 °C was more successful, and under these conditions the reaction provided exclusively the β-linked glycosyl azide in 91% yield. The β-stereochemistry was ascertained from the $^3J_{H1,H2}$ (1.3 Hz) of the signal for H-1, which resonated at 5.34 ppm in the ^1H NMR spectrum.[9]

Having identified a suitable promotion protocol, we next investigated the scope of this approach using nucleophiles that would produce C-glycosides (Scheme 1). For this we explored two reagents that have been widely used for the preparation of C-glycosides: allyltrimethylsilane or trimethyl(1-phenylvinyloxy)silane.[10] We were pleased to find that treatment of **1** with either of these species and $BF_3{\cdot}Et_2O$ at −78 °C gave the corresponding C-glycosides in excellent yield. Although both nucleophiles proceeded to give an excellent yield of the expected C-glycosides, when the same reaction was attempted with trimethylsilyl cyanide, only decomposition products were obtained.



Scheme 1. Synthesis of C-glycosides **9** and **10** from **1**.

Determining the sterochemistry of carbon–carbon bond formation proved initially challenging. Due to spectral overlap, ^1H–^1H coupling constants were not diagnostic and we thus turned to the measurement of Nuclear Overhauser Effects (NOEs). However, compared to six-membered rings, five-membered rings are inherently flexible and can adopt several twist and envelope conformations.[11] Therefore, we considered that the direct determination of the stereochemistry in **9** and **10** using NOEs would be problematic. To circumvent this problem, **11** and **12** (Fig. 2), derivatives of **9** and **10** that have an isopropylidene protecting group spanning O3 and O5, were synthesized (Scheme 2) to lock the five-membered ring into a more rigid conformation. Reaction of **9** with sodium methoxide followed by treatment with dimethoxypropane and *p*-toluenesulfonic acid in acetone led to the formation of **11** in 83% yield over the two steps. The synthesis of **12** was somewhat more involved. First, the ketone in **10** was reduced to an ~1:1 diastereomeric mixture of alcohols, the benzoate ester was cleaved and the product was the converted to the isopropylidene acetal **13** in 62% yield over the three steps. Next, oxidation of the alcohol with Dess–Martin periodinane gave **12** in 90% yield. The oxidation–reduction protocol was necessary because the ketone functionality interfered with the formation of the isopropylidene acetal.

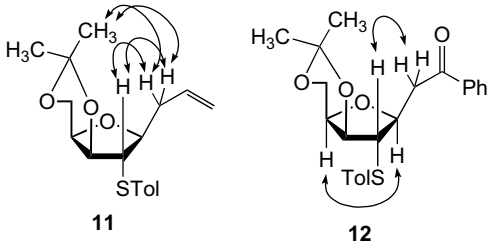
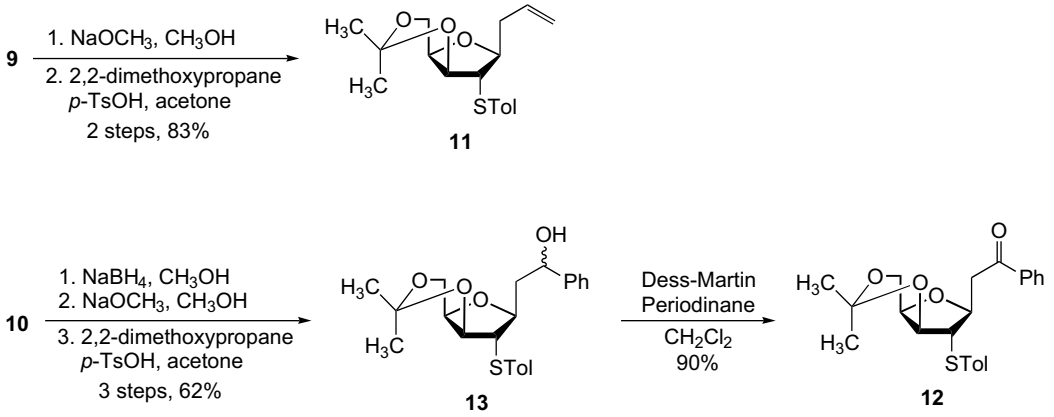


Figure 2. Key NOE interactions present in **11** and **12**.

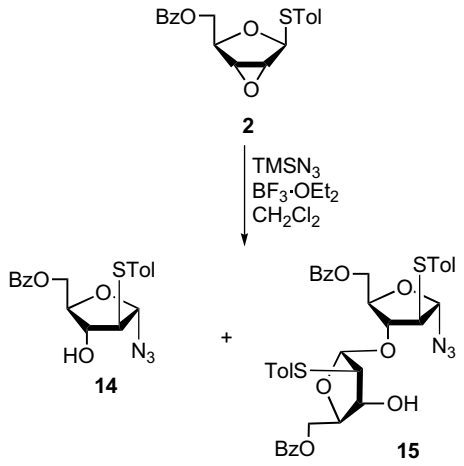
Rigid bicyclic molecules of this type are more amenable to the measurement of NOEs, and in the case of **11** and **12** the through-space interactions shown in Figure 2 were observed. These data support the structure of the products as shown, and this stereocontrol is also consistent with reactions involving oxygen nucleophiles,[2,3] in which the glycosidic bond is formed trans to the thiotolyl group.

Given the successful results with **1**, we next explored the potential for the synthesis of α-linked glycosyl azides and C-glycosides via glycosidations with thioglycoside **2**. Thus, treatment of **2** and trimethylsilyl azide and $BF_3{\cdot}Et_2O$ at −78 °C was attempted (Scheme 3). However, although this reaction gave a single product when **1** was used as the substrate, with **2** a different result was obtained. Two



Scheme 2. Synthesis of **11** and **12**.

products were isolated: the expected monosaccharide azide **14** in 49% yield, as well as disaccharide glycosyl azide **15** in 16% yield.[12] In both cases, the newly formed glycosidic linkages were found to have the α-stereochemistry, as ascertained from the $^3J_{H1,H2}$ magnitudes.

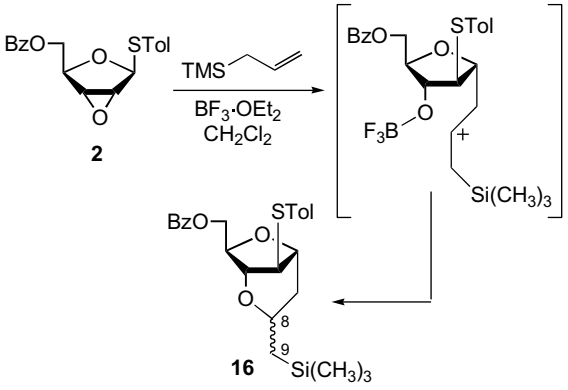


Scheme 3. Products formed from reaction of **2** and $TMSN_3$ in the presence of $BF_3 \cdot OEt_2$.

In an earlier study with **2**,[2] we reported similar oligomerization byproducts, resulting from further reaction of the hydroxyl group liberated during the initial glycosylation event. As could be done in previous cases, the formation of this byproduct could be suppressed by using the nucleophile in excess. In this particular case, 10 equiv of $TMSN_3$ were used together with 0.2 equiv of $BF_3 \cdot Et_2O$. Under these conditions, the desired product, **14**, was obtained in 86% yield.

We next investigated the reaction of **2** and allyltrimethylsilane upon activation with $BF_3 \cdot Et_2O$ at −78 °C (Scheme 4). An interesting result was obtained. From the NMR data, it was clear that the product had a trimethylsilyl group and no alkene moiety. Further analysis of the data indicated that the product was the bicyclic compound **16** produced as a 65:35 ratio of isomers. The identification of the attachment between C-9 and the silicon was ascertained by the small chemical shift values for H-9 (δ_H=1.03–0.77 ppm) and C-9 (δ_C=27.1, 25.0 ppm). The bond between O-3 and C-8 was determined by the chemical shift of H-8 (δ_H=4.16–3.88 ppm) and C-8 (δ_C=68.2, 65.6 ppm). A possible mechanism for the formation of **16** under these conditions is shown in Scheme 4.

Finally, we attempted the reaction between **2** and trimethyl(1-phenylvinyloxy)silane. However, under the conditions that had given C-glycoside **10** in good yield from **1**, with **2** the only isolated product was hydrolyzed donor.



Scheme 4. Product formed from reaction between **2** and allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$.

When the results described here for the reactions of **2** with these nucleophiles are considered together with those reported previously for alcohol nucleophiles[2] is clear that its reactivity can differ markedly from that of **1**. In particular, although **1** uniformly gives clean reactions with *O*-, *C*- and *N*-nucleophiles, under the same reaction conditions, **2** often gives multiple products or unexpected byproducts.

We are unsure as to the origin of this contrasting reactivity. The obvious structural difference in the products formed from **1** and **2** is that the oxygen at C-3 is cis, and trans, respectively, to the protected hydroxylmethyl group at C-4. It could be, therefore, that this bulky group hinders further reactions with products resulting from **1**, whereas in the case of the products arising from **2**, this group is less sterically encumbered and thus undergoes additional reactions. Such an explanation could be used to rationalize the results shown in Scheme 2, but does not readily explain the formation of **16** from **2**.

It should also be noted that we explored the possibility of synthesizing glycosyl azides and C-glycoside analogs from the analogous pyranoside systems (e.g., **4**, Fig. 1). However, in all cases the only product formed was hydrolyzed donor.

In summary, it appears that this migration–glycosidation protocol, while working well for oxygen nucleophiles is of limited scope with the carbon and nitrogen nucleophiles described here. In particular, the reactions leading to the glycosyl azides and C-glycosides proceeded in good yield with **1**, but were less successful with **2** and pyranoside analogs.

3. Experimental section

3.1. General methods

Solvents used in reactions were purified by successive passage through columns of alumina and copper under argon atmosphere before use. All reagents used in reactions were purchased from commercial sources and were used without further purification unless noted otherwise. All reactions were carried out under a positive pressure of argon atmosphere and monitored by TLC on silica gel G-25 UV_{254} (0.25 mm) unless stated otherwise. Spots were detected under UV light and/or by charring with a solution of anisaldehyde in ethanol, acetic acid and H_2SO_4. Column chromatography was performed on Silica Gel 60 (40–60 μm). The ratio between silica gel and crude product ranged from 100:1 to 20:1 (w/w). ^1H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively. ^1H NMR chemical shifts are referenced to TMS (0.0, $CDCl_3$) and ^{13}C NMR chemical shifts are referenced to $CDCl_3$ (77.23, $CDCl_3$). ^1H NMR data were obtained through first order analysis and the peak assignments were made on the basis of 2D-NMR (^1H–^1H COSY and HMQC) experiments. Optical rotations were measured at 21±2 °C at the sodium D line (589 nm) and are in unit of deg mL(dm g)$^{-1}$. ESI-MS spectra were carried out on samples suspended in THF or CH_3OH and added NaCl.

3.2. 5-*O*-Benzoyl-2-deoxy-2-*p*-thiotolyl-β-D-xylofuranosyl azide (8)

Compound **1**[1a] (100 mg, 0.29 mmol) and trimethylsilyl azide (0.16 mL, 1.22 mmol) were dissolved in CH_2Cl_2 (20 mL) and the solution was cooled to −78 °C. At this temperature $BF_3 \cdot Et_2O$ (42 μL, 0.29 mmol) was added. After stirring at this temperature for 1 h, the reaction mixture was allowed to warm to rt. Triethylamine (0.3 mL) was used to neutralize the reaction. The solution was subsequently concentrated to yield a crude oil that was purified by chromatography (4:1 hexane–EtOAc) to give **8** (103 mg, 91%) as a colorless oil: R_f 0.55 (2:1 hexane–EtOAc); $[\alpha]_D$ −68.3 (*c* 0.4, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.05 (m, 2H, Ar), 7.61–7.56 (m, 1H, Ar), 7.49–7.43 (m, 2H, Ar), 7.36–7.31 (m, 2H, Ar), 7.18–

7.13 (m, 2H, Ar), 5.34 (d, 1H, $J_{1,2}$=1.3 Hz, H-1), 4.82 (dd, 1H, $J_{5a,5b}$=11.9 Hz, $J_{4,5a}$=5.5 Hz, H-5a), 4.64–4.62 (m, 1H, H-4), 4.51 (dd, 1H, $J_{5a,5b}$=11.9 Hz, $J_{4,5b}$=6.1 Hz, H-5b), 4.28 (br d, 1H, $J_{3,4}$=3.3 Hz, H-3), 3.67 (dd, 1H, $J_{1,2}$=$J_{2,3}$=1.3 Hz, H-2), 3.10 (br, 1H, OH), 2.35 (s, 3H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.8 (C=O), 138.4 (Ar), 133.3 (Ar), 132.1 (2×Ar), 130.3 (2×Ar), 129.8 (2×Ar), 129.6 (Ar), 128.7 (Ar), 128.5 (2×Ar), 95.0 (C-1), 81.6 (C-4), 75.5 (C-3), 63.1 (C-5), 58.7 (C-2), 21.1 (tolyl CH_3). HRMS (ESI) calcd $(M+Na)^+$ $C_{19}H_{19}N_3O_4S$: 408.0989. Found: 408.0992.

3.3. 3-(5-*O*-Benzoyl-2-deoxy-2-*p*-thiotolyl-β-D-xylofuranosyl)-1-propene (9)

Compound **1**[1a] (100 mg, 0.29 mmol) and allyltrimethylsilane (0.18 mL, 1.16 mmol) were reacted with $BF_3\cdot Et_2O$ (42 μL, 0.29 mmol) in CH_2Cl_2 (20 mL) as described for the synthesis of **8**. Purification of the crude product by chromatography (4:1 hexane–EtOAc) give **9** (97 mg, 86%) as a colorless oil: R_f 0.65 (2:1 hexane–EtOAc); $[\alpha]_D$ −69.1 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.07–8.02 (m, 2H, Ar), 7.60–7.56 (m, 1H, Ar), 7.47–7.41 (m, 2H, Ar), 7.35–7.31 (m, 2H, Ar), 7.15–7.10 (m, 2H, Ar), 5.91–5.83 (m, 1H, –CH=), 5.16–5.09 (m, 2H, =CH_2), 4.76 (dd, 1H, $J_{5a,5b}$=11.7 Hz, $J_{4,5a}$=5.8 Hz, H-5a), 4.41 (dd, 1H, $J_{5a,5b}$=11.7 Hz, $J_{4,5b}$=5.0 Hz, H-5b), 4.23–4.17 (m, 2H, H-3, H-4), 3.81 (ddd, 1H, $J_{1,7a}$=11.7 Hz, $J_{1,2}$=$J_{1,7b}$=6.1 Hz, H-1), 3.36 (dd, 1H, $J_{1,2}$=6.1 Hz, $J_{2,3}$=2.2 Hz, H-2), 2.8 (br, 1H, OH), 2.56–2.41 (m, 2H, H-7a, H-7b), 2.33 (s, 3H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 167.0 (C=O), 137.3 (Ar), 133.7 (Ar), 133.3 (–CH=), 131.3 (2×Ar), 130.6 (Ar), 130.0 (2×Ar), 129.8 (2×Ar), 129.6 (Ar), 128.4 (2×Ar), 118.1 (=CH_2), 82.4 (C-1), 78.9 (C-4), 78.1 (C-3), 62.7 (C-5), 56.9 (C-2), 38.7 (C-7), 21.1 (tolyl CH_3). HRMS (ESI) calcd $(M+Na)^+$ $C_{22}H_{24}O_4S$: 407.1288. Found: 407.1286.

3.4. 2-(5-*O*-Benzoyl-2-deoxy-2-*p*-thiotolyl-β-D-xylofuranosyl)-acetophenone (10)

Compound **1**[1a] (100 mg, 0.29 mmol) and trimethyl(1-phenylvinyloxy)silane (0.25 mL, 1.22 mmol) were reacted with $BF_3\cdot Et_2O$ (42 μL, 0.29 mmol) in CH_2Cl_2 (20 mL) as described for the synthesis of **8**. Purification of the crude product by chromatography (4:1 hexane–EtOAc) gave **10** (111 mg, 82%) as a colorless oil: R_f 0.67 (2:1 hexane–EtOAc); $[\alpha]_D$ −55.8 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.07–8.02 (m, 2H, Ar), 7.96–7.92 (m, 2H, Ar), 7.60–7.54 (m, 2H, Ar), 7.48–7.40 (m, 4H, Ar), 7.36–7.32 (m, 2H, Ar), 7.14–7.09 (m, 2H, Ar), 4.78 (dd, 1H, $J_{5a,5b}$=11.8 Hz, $J_{4,5a}$=5.3 Hz, H-5a), 4.45 (dd, 1H, $J_{5a,5b}$=11.8 Hz, $J_{4,5b}$=5.5 Hz, H-5b), 4.30–4.23 (m, 3H, H-1, H-3, H-4), 4.18 (br, 1H, OH), 3.67 (dd, 1H, $J_{2,3}$=5.6 Hz, $J_{1,2}$=1.0 Hz, H-2), 3.50 (dd, 1H, $J_{7a,7b}$=17.5 Hz, $J_{1,7a}$=5.6 Hz, H-7a), 3.43 (dd, 1H, $J_{7a,7b}$=17.5 Hz, $J_{1,7b}$=5.5 Hz, H-7b), 2.32 (s, 3H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 197.9 (C=O), 166.9 (C=O), 137.3 (Ar), 136.8 (Ar), 133.5 (Ar), 133.2 (Ar), 131.1 (2×Ar), 130.6 (Ar), 130.0 (2×Ar), 129.8 (2×Ar), 129.7 (Ar), 128.6 (2×Ar), 128.4 (2×Ar), 128.2 (2×Ar), 79.6 (C-1), 79.4 (C-3), 78.3 (C-4), 63.0 (C-5), 57.0 (C-2), 41.9 (C-7), 21.1 (tolyl CH_3). HRMS (ESI) calcd $(M+Na)^+$ $C_{27}H_{26}O_5S$: 485.1393. Found: 485.1394.

3.5. 1-(3,5-*O*-Isopropylidene-2-deoxy-2-*p*-thiocresyl-α-D-xylofuranosyl)-3-propene (11)

To a solution of compound **9** (80 mg, 0.21 mmol) in 1:1, CH_2Cl_2–CH_3OH (20 mL) was added 1 M $NaOCH_3$ in CH_3OH (0.21 mL). After stirring for 2 h at rt, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The resulting oil was dissolved in acetone (10 mL) at rt. To this solution was added 2,2-dimethoxypropane (39 μL, 0.32 mmol) and *p*-TsOH (4 mg, 0.02 mmol). After stirring for 2 h at rt, the reaction mixture was neutralized with triethylamine (1 mL) and concentrated. The crude product was purified by chromatography (6:1 hexane–EtOAc) to give **11** (55 mg, 83%) as a colorless oil: R_f 0.82 (3:1 hexane–EtOAc); $[\alpha]_D$ −53.3 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.30–7.25 (m, 2H, Ar), 7.16–7.10 (m, 2H, Ar), 5.85 (dddd, 1H, $J_{2,3trans}$=17.2 Hz, $J_{2,3cis}$=10.2 Hz, $J_{1a,2}$=6.9 Hz, $J_{1b,2}$=6.9 Hz, –CH=), 5.17–5.06 (m, 2H, =CH_2), 4.22 (d, 1H, $J_{3,4}$=2.8 Hz, H-3), 4.06 (dd, 1H, $J_{5a,5b}$=13.1 Hz, $J_{4,5a}$=3.4 Hz, H-5a), 3.98 (dd, 1H, $J_{5a,5b}$=13.1 Hz, $J_{4,5b}$=2.5 Hz, H-5b), 3.89–3.81 (m, 2H, H-1, H-4), 3.39 (d, 1H, $J_{1,2}$=4.9 Hz, H-2), 2.60–2.45 (m, 2H, H-7a, H-7b), 2.33 (s, 3H, tolyl CH_3), 1.39 (s, 3H, C(CH_3)$_2$), 1.35 (s, 3H, C(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 136.9 (Ar), 134.2 (–CH=), 131.0 (Ar), 130.6 (2×Ar), 129.9 (2×Ar), 117.4 (=CH_2), 98.2 (C(CH_3)$_2$), 83.3 (C-1), 76.7 (C-3), 73.1 (C-4), 60.7 (C-5), 55.4 (C-2), 39.6 (C-7), 28.4 (C(CH_3)$_2$), 21.3 (tolyl CH_3), 19.6 (C(CH_3)$_2$). HRMS (ESI) calcd (M+Na) $C_{18}H_{24}O_3S$: 343.1338. Found: 343.1336.

3.6. 2-(3,5-*O*-Isopropylidene-2-deoxy-2-*p*-thiocresyl-β-D-xylofuranosyl)-acetophenone (12)

Compound **13** (40 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (10 mL) containing Dess–Martin periodinane (64 mg, 0.15 mmol) at rt. The reaction mixture was stirred at rt for 2 h before it was quenched by the addition satd aq $NaHCO_3$ soln and $Na_2S_2O_3$ soln. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography (6:1 hexane–EtOAc) to give **12** (36 mg, 90%) as a colorless oil: R_f 0.75 (2:1 hexane–EtOAc); $[\alpha]_D$ −9.5 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.01–7.95 (m, 2H, Ar), 7.59–7.53 (m, 1H, Ar), 7.48–7.42 (m, 2H, Ar), 7.33–7.28 (m, 2H, Ar), 7.14–7.09 (m, 2H, Ar), 4.51 (ddd, 1H, $J_{1,7a}$=7.4 Hz, $J_{1,7b}$=5.4 Hz, $J_{1,2}$=3.9 Hz, H-1), 4.26 (dd, 1H, $J_{3,4}$=2.7 Hz, $J_{2,3}$=0.9 Hz, H-3), 4.07 (dd, 1H, $J_{5a,5b}$=13.4 Hz, $J_{4,5a}$=3.4 Hz, H-5a), 4.02–3.96 (m, 2H, H-4, H-5b), 3.66 (dd, 1H, $J_{7a,7b}$=16.6 Hz, $J_{1,7a}$=7.4 Hz, H-7a), 3.53 (br d, 1H, $J_{1,2}$=3.9 Hz, H-2), 3.30 (dd, 1H, $J_{7a,7b}$=16.6 Hz, $J_{1,7b}$=5.4 Hz, H-7b), 2.32 (s, 3H, tolyl CH_3), 1.41 (s, 3H, C(CH_3)$_2$), 1.37 (s, 3H, C(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 197.7 (C=O), 137.1 (Ar), 136.9 (Ar), 133.1 (Ar), 130.9 (2×Ar), 130.7 (Ar), 129.9 (2×Ar), 128.5 (2×Ar), 128.4 (2×Ar), 98.1 (C(CH_3)$_2$), 79.9 (C-1), 76.2 (C-3), 73.1 (C-4), 60.8 (C-5), 56.7 (C-2), 45.0 (C-7), 28.9 (C(CH_3)$_2$), 21.2 (tolyl CH_3), 19.5 (C(CH_3)$_2$). HRMS (ESI) calcd $(M+Na)^+$ $C_{23}H_{26}O_4S$: 421.1444. Found: 421.1446.

3.7. 2-(3,5-*O*-Isopropylidene-2-deoxy-2-*p*-thiocresyl-β-D-xylofuranosyl)-1-(*R*/*S*)-phenyl ethanol (13)

To a solution of compound **10** (100 mg, 0.22 mmol) in CH_3OH (10 mL) was added $NaBH_4$ (33 mg, 1.08 mmol) at rt. After 30 min, the reaction was quenched by the addition of satd aq NH_4Cl soln (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. The resulting oil was dissolved in 1:1 CH_2Cl_2–CH_3OH (20 mL). To this solution was added 1 M $NaOCH_3$ in CH_3OH (0.3 mL). After stirring for 4 h at rt, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The oily residue was dissolved in acetone (10 mL) at rt. To this solution was added 2,2-dimethoxypropane (40 μL, 0.33 mmol) and *p*-TsOH (3.8 mg, 0.02 mmol). After stirring for 2 h at rt, the reaction mixture was neutralized with triethylamine (3 mL) and concentrated. The crude product was purified by chromatography (4:1 hexane–EtOAc) to give **13** (55 mg, 62%) over three steps as a colorless oil: R_f 0.56 (2:1 hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.40–7.31 (m, 4H, Ar), 7.29–7.23 (m, 3H, Ar), 7.15–7.10 (m, 2H, Ar), 5.09 (dt, 0.54H, $J_{8R,7R}$=9.2 Hz, $J_{8R,OH}$=3.3 Hz, H-2′*R*), 4.99 (dt, 0.46H, $J_{8S,7S}$=9.5 Hz, $J_{8S,OH}$=2.0 Hz, H-8*S*), 4.26 (d, 0.54H, $J_{3R,4R}$=2.7 Hz, H-3*R*), 4.24 (d, 0.46H, $J_{3S,4S}$=2.8 Hz, H-3*S*), 4.13–3.99 (m, 3H, H-1*R*, H-

1*S*, H-5*R*, H-5*S*), 3.94–3.92 (m, 0.54H, H-4*R*), 3.86–3.84 (m, 0.46H, H-4*S*), 3.64 (d, 0.54H, $J_{OH,8S}$=2.0 Hz, OH), 3.53–3.50 (m, 1H, H-2*R*, H-2*S*), 3.32 (d, 0.46H, $J_{OH,8R}$=3.3 Hz, OH), 2.35 (s, 1.62H, tolyl CH_3), 2.34 (s, 1.38H, tolyl CH_3), 2.28–2.00 (m, 2H, H-7*R*, H-7*S*), 1.42–1.38 (m, 6H, C(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 144.4 (Ar), 144.3 (Ar), 137.3 (Ar), 137.2 (Ar), 130.9 (Ar), 130.75 (Ar), 130.7 (Ar), 130.5 (Ar), 130.0 (Ar), 128.4 (Ar), 128.3 (Ar), 127.3 (Ar), 127.1 (Ar), 125.8 (Ar), 125.7 (Ar), 98.44 (*C*(CH_3)$_2$), 98.38 (*C*(CH_3)$_2$), 83.3(C-1*R*), 82.1 (C-1*S*), 76.5 (C-3*R*), 76.4 (C-3*S*), 73.5 (C-4*R*), 73.2 (C-4*S*), 72.7 (C-8*S*), 70.8 (C-8*R*), 60.6 (C-5*R*), 60.4 (C-5*S*), 56.5 (C-2*R*), 55.8 (C-2*S*), 44.3 (C-7*R*), 42.8 (C-7*S*), 28.51(C(CH_3)$_2$), 28.46 (C(*C*H_3)$_2$), 21.1 (tolyl *C*H_3), 19.5 (C(CH_3)$_2$), 19.4 (C(*C*H_3)$_2$). HRMS (ESI) calcd (M+Na)$^+$ $C_{23}H_{28}O_4S$: 423.1601. Found: 423.1601.

3.8. 5-*O*-Benzoyl-2-deoxy-2-*p*-thiotolyl-α-D-arabino-furanosyl azide (14)

Compound **2**[1a] (100 mg, 0.29 mmol) and trimethylsilyl azide (0.38 mL, 2.91 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C. At this temperature $BF_3\cdot Et_2O$ (9 μL, 0.06 mmol) was added. After stirring at this temperature for 1 h, the reaction mixture was warmed to room temperature. Triethylamine (0.3 mL) was used to neutralize the reaction and the solution was subsequently concentrated to a crude oil that was purified by chromatography (4:1 hexane–EtOAc) to give compound **14** (97 mg, 86%) as a colorless oil: R_f 0.55 (2:1 hexane–EtOAc); $[\alpha]_D$ +25.9 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08–8.05 (m, 2H, Ar), 7.62–7.57 (m, 1H, Ar), 7.48–7.44 (m, 2H, Ar), 7.36–7.40 (m, 2H, Ar), 7.14–7.11 (m, 2H, Ar), 5.42 (d, 1H, $J_{1,2}$=3.2 Hz, H-1), 4.58–4.55 (m, 2H, 2×H-5), 4.38 (ddd, 1H, $J_{3,4}$=5.9 Hz, $J_{4,5a}$=4.4 Hz, $J_{4,5b}$=4.4 Hz, H-4), 4.09 (ddd, 1H, $J_{3,OH}$=6.1 Hz, $J_{3,4}$=5.9 Hz, $J_{2,3}$=5.7 Hz, H-3), 3.43 (dd, 1H, $J_{2,3}$=5.7 Hz, $J_{1,2}$=3.2 Hz, H-2), 2.52 (d, 1H, $J_{OH,3}$=6.1 Hz, OH), 2.33 (s, 3H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.6 (C=O), 138.4 (Ar), 133.3 (Ar), 132.6 (2×Ar), 130.2 (2×Ar), 129.9 (2×Ar), 129.5 (Ar), 128.6 (Ar), 128.4 (2×Ar), 95.8 (C-1), 83.2 (C-4), 76.5 (C-3), 63.6 (C-5), 58.8 (C-2), 21.1 (tolyl CH_3). HRMS (ESI) calcd (M+Na)$^+$ $C_{19}H_{19}N_3O_4S$: 408.0989. Found: 408.0988.

3.9. 5-*O*-Benzoyl-2-deoxy-2-*p*-thiotolyl-3-*O*-(5-*O*-benzoyl-2-deoxy-2-*p*-thiotolyl-α-D-arabino-furanosyl)-α-D-arabinofuranosyl azide (15)

Compound **2**[1a] (100 mg, 0.29 mmol) and trimethylsilyl azide (0.16 mL, 1.22 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C. At this temperature $BF_3\cdot Et_2O$ (42 μL, 0.29 mmol) was added. After stirring at this temperature for 1 h, the reaction mixture was warmed to room temperature. Triethylamine (0.3 mL) was used to neutralize the reaction. The solution was subsequently concentrated to a crude oil that was purified by chromatography (6:1 hexane–EtOAc) to give **14** (55 mg, 49%) and **15** (34 mg, 16%) both as colorless oils: Data for **15**: R_f 0.53 (2:1 hexane–EtOAc); $[\alpha]_D$ +36.5 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08–8.01 (m, 4H, Ar), 7.58–7.53 (m, 2H, Ar), 7.45–7.38 (m, 4H, Ar), 7.33–7.30 (m, 2H, Ar), 7.26–7.21 (m, 2H, Ar), 7.11–7.06 (m, 4H, Ar), 5.37 (d, 1H, $J_{1,2}$=2.3 Hz, H-1), 5.10 (d, 1H, $J_{1',2'}$=2.1 Hz, H-1′), 4.66 (dd, 1H, $J_{5a,5b}$=13.9 Hz, $J_{4,5a}$=5.2 Hz, H-5a), 4.50–4.46 (m, 4H, H-4, H-5b, H-5a′, H-5b′), 4.31–4.28 (m, 1H, H-4′), 4.15 (dd, 1H, $J_{3,4}$=5.2 Hz, $J_{2,3}$=3.9 Hz, H-3), 4.01 (ddd, 1H, $J_{3',OH}$=7.2 Hz, $J_{3',4'}$=6.0 Hz, $J_{2',3'}$=4.7 Hz, H-3′), 3.60 (dd, 1H, $J_{2',3'}$=4.7 Hz, $J_{1',2'}$=2.1 Hz, H-2′), 3.42 (dd, 1H, $J_{2,3}$=3.9 Hz, $J_{1,2}$=2.3 Hz, H-2), 2.58 (d, 1H, $J_{3',OH}$=7.2 Hz, OH), 2.32 (s, 3H, tolyl CH_3), 2.30 (s, 3H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.5 (C=O), 166.2 (C=O), 138.4 (Ar), 137.7 (Ar), 133.19 (Ar), 133.16 (Ar), 132.2 (2×Ar), 131.6 (2×Ar), 130.3 (2×Ar), 130.1 (2×Ar), 129.9 (2×Ar), 129.8 (2×Ar), 129.7 (Ar), 129.6 (2×Ar), 128.9 (Ar), 128.4 (2×Ar), 128.3 (2×Ar), 107.7 (C-1), 96.0 (C-1′), 82.6 (C-4), 82.5 (C-4′), 81.7 (C-3), 76.7 (C-3′), 63.8 (C-5′), 63.3 (C-5), 58.2 (C-2′), 57.3 (C-2), 21.12 (tolyl CH_3), 21.07 (tolyl CH_3). HRMS (ESI) calcd (M+Na)$^+$ $C_{38}H_{37}N_3O_8S_2$: 750.1914. Found: 750.1918.

3.10. (1*R*,5*R*,7*R*,8*R*)-7-Benzoyloxymethyl-8-(thiotolyl)-3-(*R*/*S*)-((trimethylsilyl)methyl)-2,6-dioxabicyclo[3.2.1]octane (16)

Compound **2**[1a] (100 mg, 0.29 mmol) and allyltrimethylsilane (0.18 mL, 1.16 mmol) were dissolved in CH_2Cl_2 (20 mL) and the solution was cooled to −78 °C. At this temperature $BF_3\cdot Et_2O$ (42 μL, 0.29 mmol) was added. After stirring at this temperature for 1 h, the reaction mixture was warmed to rt. Triethylamine (0.3 mL) was used to neutralize the reaction. The solution was subsequently concentrated to yield a crude oil that was purified by chromatography (8:1 hexane–EtOAc) to give **16** (74 mg, 66%) as a 65:35 ratio of isomers as a colorless oil: R_f 0.90 (2:1 hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.07 (m, 2H, Ar), 7.59–7.54 (m, 1H, Ar), 7.46–7.42 (m, 2H, Ar), 7.38–7.34 (m, 2H, Ar), 7.16–7.12 (m, 2H, Ar), 4.88–4.57 (m, 1H, H-5a*R*, H-5a*S*), 4.74–4.64 (m, 2H, H-5b*R*, H-5b*S*, H-4*R*, H-4*S*), 4.58–4.53 (m, 1H, H-1*R*, H-1*S*), 4.40–4.33 (m, 1H, H-3*S*, H-3*R*), 4.16–4.08 (m, 0.65H, H-8*S*), 3.96–3.88 (m, 0.35H, H-8*R*), 3.86 (br s, 0.35H, H-2*R*), 3.50 (br s, 0.65H, H-2*S*), 2.34–2.25 (m, 3.35H, tolyl CH3, H-7a*R*), 2.06 (ddd, 0.65H, $J_{7aS,7bS}$=13.4 Hz, $J_{7aS,1}$=$J_{7aS,8S}$=4.6 Hz, H-7a*S*), 1.88 (ddd, 0.35H, $J_{7bR,7aR}$=14.8 Hz, $J_{7bR,1}$=$J_{7bR,8R}$=9.2 Hz, H-7b*R*), 1.48 (ddd, 0.65H, $J_{7bS,7aS}$=13.4 Hz, $J_{7bS,1}$=$J_{7bS,8S}$=10.7 Hz, H-7b*S*), 1.03 (dd, 0.35H, $J_{9aR,9bR}$=14.2 Hz, $J_{9aR,8R}$=6.5 Hz, H-9a*R*), 0.95 (dd, 0.65H, $J_{9aS,9bS}$=14.2 Hz, $J_{9aS,8S}$=6.3 Hz, H-9a*S*), 0.83–0.77 (m, 1H, H-9b*R*, H-9b*S*), 0.04–0.01 (m, 9H, Si(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.2 (C=O), 137.6 (Ar), 133.01 (Ar), 132.96 (Ar), 132.0 (Ar), 131.8 (Ar), 130.07 (Ar), 130.05 (Ar), 129.8 (Ar), 128.32 (Ar), 128.29 (Ar), 84.3 (C-1*R*), 80.12 (C-1*S*), 80.06 (C-3*S*), 79.6 (C-4*S*), 78.7 (C-3*R*), 78.3 (C-4*R*), 68.2 (C-8*S*), 66.5 (C-5*S*), 66.0 (C-5*R*), 65.6 (C-8*R*), 56.0 (C-2*S*), 50.5 (C-2*R*), 43.5 (C-7*S*), 42.7 (C-7*R*), 27.1 (C-9*R*), 25.0 (C-9*S*), 21.07 (tolyl CH_3), 21.06 (tolyl CH_3), −0.78 (Si(CH_3)$_3$), −0.82 (Si(CH_3)$_3$). HRMS (ESI) calcd (M+Na)$^+$ $C_{25}H_{32}O_4SiS$: 479.1683. Found: 479.1682.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.008.

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12. Trace amounts of a trisaccharide product could also be detected by mass spectrometry.