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An unexpected rearrangement giving a new thiosubstituted carbohydrate

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ABSTRACT

A new thiosubstituted 'D-arabino'-type derivative was obtained from an open carbohydrate via a cascade of four consecutive transformations in a single reaction process. Molecular orbital computations were also performed to explain the stereochemical outcome of the reaction.

1. Introduction

During our studies toward the efficient synthesis of α-*C*-(alkynyl)-galactosides,[1,2] we identified an interesting side-product, the thiosugar **3** (Scheme 1).[3] This unexpected rearrangement, which occurred during the multigram scale-up synthesis of the epoxydithio compound **2**, was solely dependent on reaction conditions and can be explained by the cascade of reactions depicted in Scheme 1.

Intrigued by this unusual transformation, we anticipated that the same kind of reaction could be applied to a formal synthesis of salacinol **4**, a highly potent α-glucosidase inhibitor.[4,5]

As described by Ghavami et al.,[6] the four-carbon sulfated side chain could be easily introduced starting from the known sulfur derivative **5**. Furthermore, anomeric reduction of the thiobenzyl moiety can be performed in two steps ($Hg(OAc)_2$/AcOH followed by Et_3SiH/TMSOTf),[7] giving the well-known sulfur derivative **6** as an interesting target.[8] The followed strategy for the synthesis of compound **6** was directly inspired from our serendipitously discovered rearrangement.[3] Compared to our earlier work, two changes were made to precursor **1**. A TBS group was used in position 5 and the terminal aldehyde was protected as a dithiobenzyl acetal (compound **7**). It was expected that the thiobenzyl group in the final anomeric position would be easier to deprotect (Scheme 2).

2. Results and discussion

The alcohol derivative **11** was easily obtained after several straightforward reactions of the known D-arabinose derivative **8**.[9] The unstable compound **7** (not shown) was then formed by mesylation of **11** in quantitative yield and was used in the next step without further purification. Although the reaction was slow, direct treatment with TBAF at 0 °C cleanly gave a product in 65% yield. It was first speculated that compound **6** had been formed as expected (Scheme 3).

However, comparison of the ^{1}H NMR data (Table 1, see Scheme 3 for numbering) clearly showed that the isolated product was different from the known compound **6**.[8,10]

Moreover, supplementary COSY and HSQC experiments unambiguously showed that the signal for C-1 in our compound appeared at 80.8 ppm. This characteristic deshielding indicated that the anomeric position possessed one oxygen and one sulfur atom. An HMBC experiment confirmed the thioether function with a correlation between H-4 and a S*CH*$_2$Ph, and consequently a pyranose form for this compound. Finally, NOESY experiments showed that spatially, H-4 was closest to H-3 (and H-1 to H-2). This implied that the configuration at C-4 is *R*, and that the anomeric configuration is β. Consequently, the structure of the isolated compound was postulated to be that of **12**.

According to the cascade mechanism which had first been envisioned, it was thought that the formation of compound **12** followed an intra-S_N1 mechanism. Indeed, the direct attack of the intermediate alkoxide on the anomeric center via an intra-S_N2 mechanism is impossible because it is governed in this case by a 5-*endo*-Tet

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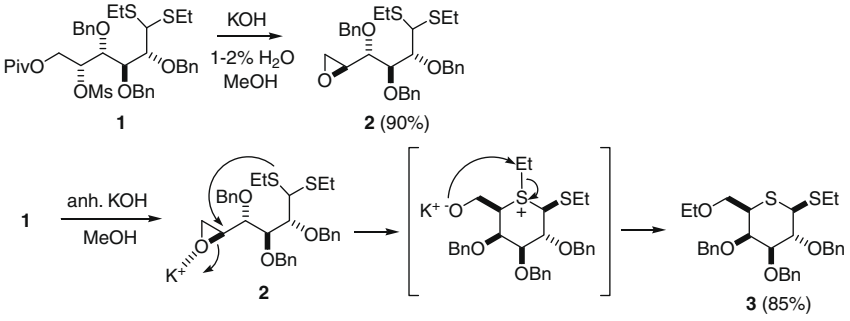
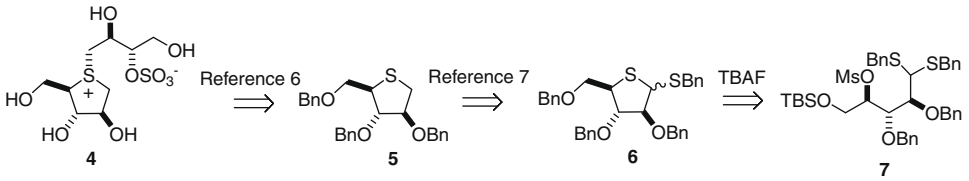
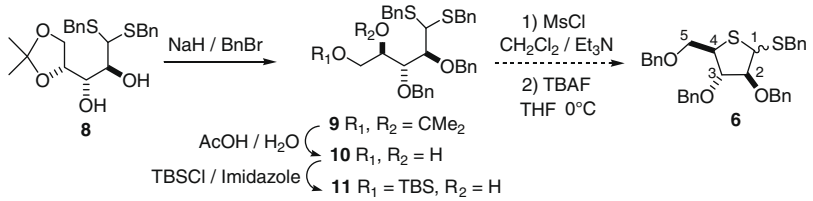


Scheme 1. Synthesis of thiosugar **3**.



Scheme 2. Salacinol **4** and target compound **6**.



Scheme 3. Synthesis of the alcohol derivative **11** and approach to salacinol.

process, forbidden by Baldwin's rules (Scheme 4).[11] The observation of an anomerically pure β-product could only result from the final ring-closure occurring on the *Re* face.

Molecular orbital computations were performed to better understand the stereochemical outcome of the reaction. Due to a prohibitive computational cost, the calculations in the present work were performed on a model system obtained by replacing all benzyl groups with methyl groups. According to the proposed mechanism for the formation of **12**, the final ring closing reaction involving the sulfonium cation **B** (Scheme 4) should lead to the two possible isomers of **12**, both adopting $^1C_4$ and $^4C_1$ chair conformations, respectively (Fig. 1).

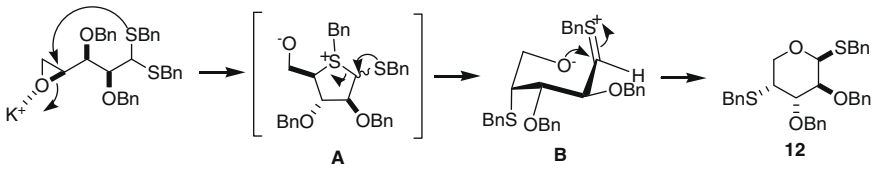
We decided to first look at the energy levels of the different conformations. When considering destabilizing effects, a maximum number of equatorial groups should favor the **12α$_{eq}$** conformation, but the stabilizing anomeric effect is a good argument in favor of both the **12α$_{ax}$** and **12β$_{ax}$** conformations. We thus decided to calculate the energies of these final structures by carefully estimating the influence of several theoretical levels on the results (Table 2).

As can be seen in Table 2, comparison of PCM values with the gas-phase results indicates that there is no significant solvent effect on the relative energies (entries 1 and 2). This is not surprising owing to the small THF dielectric constant (7.58). The different theory levels used produced consistent results, except the MP2/AUG-cc-pVDZ method (entry 5) which indicated that the **12β$_{eq}$** conformer was less stable than the **12β$_{ax}$** one. CCSD(T) studies could not be achieved due to expensive computational calculations. It was clear however that the experimental β-stereochemistry of the anomeric carbon could not be explained from the relative stability of the final product **12**. Actually, the **12α$_{ax}$** isomer was predicted to be one of the more stable isomers but it was not observed experimentally.

Therefore, in order to explain the reaction selectivity, we examined the final ring-closure mechanism leading to **12**. Only the final formation of the O–C bond was studied. For the sake of simplicity, a B3LYP/6-31G* stretching energy profile was performed for all the possible final structures **12** to characterize the dissociative reaction pathway instead of the bonding one.

Table 1
Comparison of ^{1}H and ^{13}C NMR data of known **6** and the isolated compound **12**

δ in ppm (J in hertz)	**6**	**12**		**6**	**12**
H-1	4.36 (4.6)	4.77 (1.9)	C-1	**52.0**	**80.8**
H-2	4.20 (4.6)	3.42 (1.9, 3.5)	C-2	86.6	76.0
H-3	4.20 (5.0)	3.55 (3.5, 3.1)	C-3	84.9	76.6
H-4	3.47 (5.0, 7.2, 7.3)	3.17 (3.1, 4.7, 10.4)	C-4	47.4	42.7
H-5a	3.55 (7.2, 9.3)	3.63 (10.4, 11.0)	C-5	73.6	66.5
H-5b	3.85 (7.3, 9.3)	3.85 (4.7, 11.0)	SCH_2Ph	35.7	34.7 (C-1)–36.5 (C-4)
SCH_2Ph	3.87	3.80 (C-1)–3.71 (C-4)			



Scheme 4. Proposed mechanism for the formation of **12**.

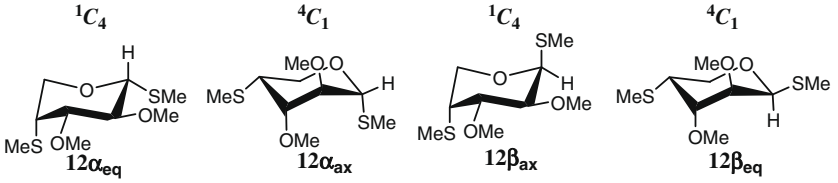


Figure 1. $^{1}C_4$ and $^{4}C_1$ chair conformations for isomers **12α** and **12β**.

Table 2
Isomer ZPE corrected relative energies (given in kcal mol^{-1})

Entry		$12\alpha_{eq}$	$12\alpha_{ax}$	$12\beta_{ax}$	$12\beta_{eq}$
1	B3LYP/6-31G*	6.4	0.1	4.6	0.0
2	B3LYP/6-31G*/PCM[a]	6.4	0.3	4.9	0.0
3	MP2/6-31G*	6.8	0.1	4.4	0.0
4	B3LYP/6-311++G**	6.3	0.0	4.8	0.1
5	MP2/AUG-cc-pVDZ[b]	4.9	0.0	2.1	3.3

[a] Fully optimized in the field of THF within the Polarized Continuum Model (PCM).
[b] Dual level: MP2/AUG-cc-pVDZ energy, Zero Point Energy (ZPE) correction obtained at the MP2/6-31G* theory level.

First, we focused on the $12\alpha_{ax}$ and $12\beta_{ax}$ isomeric forms. As expected for a dissociation reaction yielding a zwitterionic species, the energy increased when the O–C distance was scanned from its value in **12** to more than 4.0 Å. No minimum was found on the potential energy surface corresponding to the open structure preceding the cyclic system. Obviously, the reaction coordinates are not simply governed by the ultimate rupture of the C–O bond. In reality, some rotational rearrangement in the last stage of the dissociation process should be included to reach a minimum energy structure. The first steps in the reverse direction from compound **12** are very informative however, particularly for the $12\alpha_{eq}$ and $12\beta_{eq}$ isomers. Interestingly, due to the proximity of the oxygen and sulfur atoms during the potential energy scan of the C–O bond cleavage for these two species, an O–S covalent interaction is formed between these two atoms (from C–O approximately 3.2 Å), resulting in a local minimum as shown in Figure 2 within the $12\beta_{eq}$ approach.

This result is not surprising since the LUMO orbital (π^*) of the open structure is found to be delocalized over both the C and S centers. The corresponding optimized structure is a seven-membered 'tetravalent sulfur' heterocycle intermediate (Fig. 2) having an energy about 1–3 kcal/mol above the sulfonium five-membered ring **A** (Scheme 4).

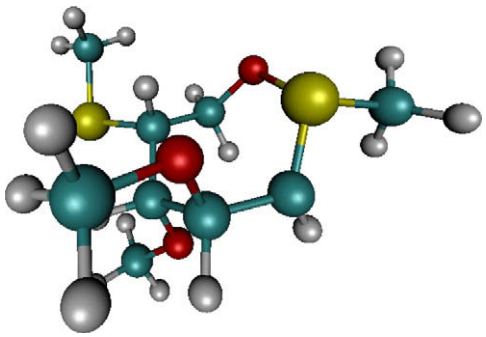


Figure 2. B3LYP/6-311++G** optimized structure of the seven-membered 'tetravalent sulfur' heterocycle.

The B3LYP/6-311++G** barrier height, computed for the transition state connecting this seven-membered heterocycle to the most stable final products $12\alpha_{eq}$ and $12\beta_{eq}$, was predicted to be 13.0 and 11.9 kcal mol^{-1}, respectively. By contrast, the final closure of precursors $12\alpha_{ax}$ and $12\beta_{ax}$ exhibited a barrier-free energy profile. Indeed, due to the above-mentioned O–S covalent interaction, the early O–S ring closure prevents the O–C ring closure when oxygen and sulfur atoms are in a face-to-face orientation (α_{eq} or β_{eq} approach) in the open structure **B** (Scheme 4) preceding cyclization. These theoretical results strongly suggest that only the α_{ax} and β_{ax} preformed geometries can favor a six-membered ring cyclization. Why then is the α_{ax} isomer not obtained experimentally?

During the simulation of the C–O breaking in $12\alpha_{ax}$ and $12\beta_{ax}$, a specific relative spatial orientation of the forming –[C=S$^+$-Me] group with respect to the neighboring methoxy group as depicted in Figure 3 was computationally observed and seems to be a key element.

Surprisingly, while a free rotation is possible around the C-1/C-2 bond, the open geometry of $12\beta_{ax}$ seems to adopt an unfavorable *syn* conformation in the early stage of the dissociation process. To complete our study, the open structures were thus examined (*syn* or *anti*) and a series of four models of increasing complexity were used as shown in Figure 4.

In the more realistic model (**F**), the anion was saturated with a hydrogen atom to form an alcohol and thus avoid ring closure during geometry optimizations. The *syn* and *anti* conformations were examined for each model structure by considering the $^{4}C_1$ or $^{1}C_4$ chair arrangement (except for the smallest model **C**). Results are summarized in Table 3.

Irrespective of the considered model or chair arrangement, the *syn* conformation is 2.6–5.0 kcal mol^{-1} more stable than the *anti* one. The OCCS torsion dihedral angle is close to 0° in all the *syn* model structures. Relative energy ΔE analysis with a series of analogue compounds of model **C** allowed us to understand this *syn* conformational preference. Our calculations emphasize a clear interaction of the antibonding σ^* (S-Me) orbital with the oxygen lone pairs.

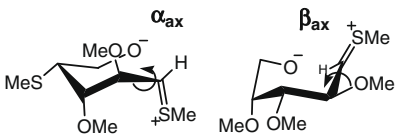


Figure 3. Specific *anti* and *syn* arrangements before closure giving **12**.

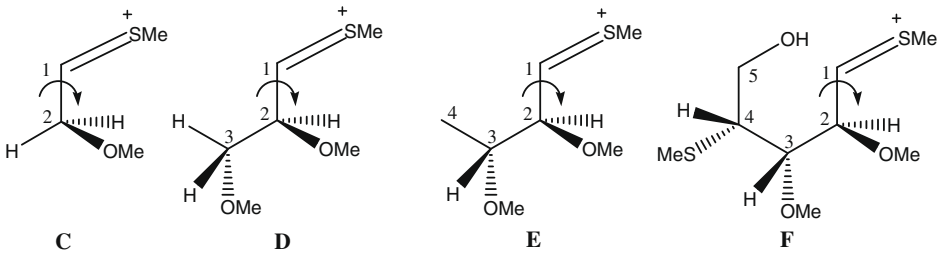


Figure 4. Internal rotation examined in open model structures.

Table 3
Relative B3LYP/6-311++G** ZPE corrected energies (kcal mol^{-1}) of *syn* and *anti* conformers for two approaches (B3LYP/6-31G* values are in brackets)

Arrangement	Conformation	Model			
		C[a]	**D**	**E**	**F**
$^1C_4$	*syn*	0.0 (0.0)	4.0 (2.2)	5.8 (4.7)	0.0 (0.0)
	anti	4.9 (5.5)	8.7 (7.3)	10.8 (10.2)	[b](4.8)
$^4C_1$	*syn*	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.2 (0.8)
	anti	4.9 (5.5)	4.8 (3.2)	4.3 (3.4)	2.8 (3.3)

[a] $^1C_4$ and $^4C_1$ arrangements can not be distinguished for this model.
[b] The molecular system goes back to the sulfonium five-membered ring during optimization.

The transition state connecting the *syn* and *anti* conformations of model **C** has been calculated. The calculated interconversional rotational barrier is 8.5 or 3.7 kcal mol^{-1} above the *syn* or *anti* structures, respectively. Thus, the equilibrium process is likely to occur under our experimental conditions (273 K). According to the energy values in Table 3, the resulting Boltzmann distribution shows that only the *syn* structure is expected to have a population for a given chair arrangement. This rules out α isomer formation (from both the $^1C_4$ and $^4C_1$ chair closure). Finally, the $^4C_1$/*syn* approach (**β_{eq}**) being prevented by the C–S closure as previously explained, only the **β_{ax}** conformer is therefore expected. The subsequent ring flipping between the two alternative chair forms could lead to both **12β_{ax}** and **12β_{eq}** anomers. These theoretical results correlate with experimental findings. According to the AUG-MP2/cc-pVDZ level of theory used (Table 2), the **12β_{ax}** conformer should be the major product, but higher levels of theory are needed to ascertain their relative energy.

3. Conclusion

We have discovered a reaction giving access to a new thiosubstituted carbohydrate, via an interesting rearrangement mechanism. Molecular orbital computations were performed in parallel with the experimental work to better explain the formation of the observed product. Based upon an electronic stabilization factor, the conformational bias for the *syn* conformation of C-1 and C-2 substituents in the open structure preceding the final cyclization promotes the β stereochemistry. As several diastereoisomers in the D-*xylo* series have already shown enzymatic activity for fungal D-xylanases,[12] an evaluation of the biological activity of derivatives of compound **12** would be of interest.

4. Experimental

4.1. General methods

All reactions were carried out under argon. Dry solvents were used in all experiments. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} plates and compounds were observed by UV or by charring the plates with an acidic anisaldehyde system. Flash column chromatography separations (silica gel, 40–63 μm) were carried out with light petroleum ether–ethyl acetate mixtures as eluent. NMR spectra were recorded on a DRX 500 Bruker spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C), using standard pulse programs, except for NOESY spectrum in which zero-quantum effects where suppressed.[13] Chemical shifts (δ) reported are referred to internal tetramethylsilane.

FT IR spectra were recorded on Nicolet Avatar 320 FT-IR as films. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Elemental analyses were performed with a Thermo Flash EA 1112 Series. Electrospray ionization mass spectrometry experiments (MS and HRMS) were obtained on a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manshester, UK) operated in positive mode (EV = 30 V, 80 °C, injection flow 5 μl/min).

5. Computational details

Full electron calculations were performed using the GAUSSIAN 03 package.[14] The structures were fully optimized at several theoretical levels. The HF-DFT (B3LYP)[15–18] level of theory was first applied using analytical gradients and the 6-31G* basis set (thus adding one set of d polarization functions on the carbon, oxygen, and sulfur atoms). The Polarized Continuum Model (PCM)[19–21] within the Self Consistent Reaction Field (SCRF) method was used in combination with method B3LYP/6-31G* to evaluate the implicit solvent effect on the energy of the modeled compounds. The minimum energy structures were fully optimized in the THF field. Additionally, the ab initio MP2 method was employed to compare with the DFT results. Finally, higher-level basis sets were used to account for more reliable relative energies. The Pople basis set 6-311++G** (a triple-zeta basis set supplemented with polarization and diffuse functions) was used in conjunction with B3LYP while the Dunning correlation consistent basis set AUG-cc-pVDZ was employed within the MP2 treatment. The restricted approach was used for all species. Vibrational frequencies were determined within the harmonic approximation, at the same theory level (vacuum and PCM), except for the MP2/AUG-cc-pVDZ level for which MP2/6-31G* frequencies were used for computational efficiency.

All transition states were characterized by one imaginary frequency (first order saddle points on the potential energy surface (PES) associated with the desired reaction pathway). In order to keep the computational CPU time to reasonable limits the B3LYP/6-31G* gas phase formalism was applied for all potential energy scans. The B3LYP/6-311++G** level of theory was found to be a suitable choice from test calculations (effective in giving satisfactory energies at a relatively small computational cost). Reported values refer to this level of theory if not otherwise noted. Thermochemical data were computed by using the KISTHEP software suite.[22]

5.1. 2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-D-arabinose dibenzyldithioacetal (9)

To a solution of diol **8** (12.9 g, 30.8 mmol) in dry DMF (76 mL) at 0 °C, were added sodium hydride (3.7 g, 60% in mineral oil), nBu$_4$N$^+$ I$^-$ (10 mg, 27 μmol) and imidazole (10 mg, 147 μmol). After stirring for 15 min, benzyl bromide (12.2 mL, 102.6 mmol) was added dropwise and the mixture was stirred for 16 h. The reaction was quenched by the addition of methanol at 0 °C and after evaporation to dryness, the residue was purified by column chromatography to give **9** (17.51 g, 94%) as a slightly yellow oil. $[\alpha]_D^{20}$ −29.7 (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.04–7.37 (m, 20H, 4Ph), 4.83 (d, 1H, *J* 12.3 Hz, CH_2Ph), 4.57 (d, 1H, *J* 12.3 Hz, CH_2Ph), 4.48 (d, 1H, *J* 11.4 Hz, CH_2Ph), 4.42 (d, 1H, *J* 11.4 Hz, CH_2Ph), 3.87–4.05 (m, 2H, H-3, H-4), 3.65–3.93 (m, 7H, H-1, H-2, 2 H-5, 2CH_2Ph), 1.33 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 138.2–138.6 (Cq Bn), 127.1–129.4 (CH Bn), 108.7 (Cq isopropylidene), 82.8 (C-2), 79.8 (C-3), 76.4 (C-4), 74.8 and 74.7 (2CH_2Ph), 66.5 (C-5), 51.2 (C-1), 36.6 (CH_2Ph from SBn), 35.5 (CH_2Ph from SBn), 26.7 (CH_3 isopropylidene), 25.4 (CH_3 isopropylidene); LRMS/HRMS (*m/z*, ESI): (M+Na) = 623.236 (calcd), 623.200 (found).

5.2. 2,3-Di-*O*-benzyl-D-arabinose dibenzyldithioacetal (10)

A solution of compound **9** (17.31 g, 28.8 mmol) in acetic acid (200 mL) and water (70 mL) was heated to reflux for 3 h. After evaporating to dryness, the residue was purified by column chromatography to give the diol **10** (14.71 g, 91%) as a slightly yellow oil. $[\alpha]_D^{20}$ +20.0 (*c* 1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.08–7.31 (m, 20H, 4Ph), 4.80 (d, 1H, *J* 12.1 Hz, CH_2Ph), 4.59 (d, 1H, *J* 12.1 Hz, CH_2Ph), 4.44 (2d, 2H, *J* 11.5 Hz, CH_2Ph), 3.90–3.62 (m, 7H, H-1, H-2, H-3, 2CH_2Ph), 3.55–3.45 (m, 3H, H-4, 2 H-5); ^{13}C NMR ($CDCl_3$): δ 137.7–138.1 (Cq Bn), 126.9–129.2 (CHBn), 81.8 (C-2), 78.5 (C-3), 74.2 and 73.9 (2CH_2Ph), 70.9 (C-4), 63.2 (C-5), 50.6 (C-1), 35.9 (CH_2Ph from SBn), 35.7 (CH_2Ph from SBn); LRMS/HRMS (*m/z*, ESI): (M+Na) = 583.205 (calcd), 583.200 (found).

5.3. 2,3-Di-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-D-arabinose dibenzyldithioacetal (11)

To a solution of **10** (2 g, 3.57 mmol) in dry CH_2Cl_2 (17 mL) were added triethylamine (620 μL, 4.44 mmol), TBDMSCl (600 mg, 3.98 mmol) and DMAP (21 mg, 172 μmol). After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water, and then with saturated NH_4Cl. The organic phase was dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was purified by column chromatography to give **11** (1.68 g, 70%) as a colorless oil. $[\alpha]_D^{20}$ −85.7 (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.12–7.35 (m, 20H, 4Ph), 4.85 (d, 1H, *J* 11.6 Hz, CH_2Ph), 4.65 (d, 1H, *J* 11.6 Hz, CH_2Ph), 4.42 (d, 1H, *J* 11.2 Hz, CH_2Ph), 4.36 (d, 1H, *J* 11.2 Hz, CH_2Ph), 3.99 (d, 1H, $J_{1,2}$ 7.0 Hz, H-1), 3.92 (dd, 1H, $J_{2,3}$ 3.4 Hz, H-2), 3.88 (d, 1H, *J* 13.0 Hz, SCH_2Ph), 3.87 (m, 1H, H-3), 3.79 (d, 1H, *J* 13.3 Hz, SCH_2Ph), 3.78 (d, 1H, *J* 13.0 Hz, SCH_2Ph), 3.75 (d, 1H, *J* 13.3 Hz, SCH_2Ph), 3.66 (m, 1H, H-4), 3.65 (dd, 1H, $J_{5a,4}$ 3.5 Hz, $J_{5a,5b}$ 9.9 Hz, H-5a), 3.55 (large dd, 1H, $J_{5b,4}$ 4.9 Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ 138.4–138.6 (Cq Bn), 127.1–129.5 (CHBn), 82.1 (C-2), 78.7 (C-3), 74.8 and 74.1 (2CH_2Ph), 71.4 (C-4), 64.0 (C-5), 51.6 (C-1), 36.7 (CH_2Ph from SBn), 35.4 (CH_2Ph from SBn); LRMS/HRMS (*m/z*, ESI): (M+Na) = 687.282 (calcd), 687.281 (found).

5.4. 2,3-Di-*O*-benzyl-4-*S*-benzyl-thio β-D-arabinopyranoside (12)

To a solution of **11** (186 mg, 275 μmol) in dry CH_2Cl_2 (8 mL) were slowly added at 0 °C triethylamine (384 μL, 2.75 mmol) and methane sulfonyl chloride (100 μL, 1.29 mmol). After stirring for 15 min, the reaction mixture was diluted with diethylether (100 mL), washed with saturated NH_4Cl (5 mL), and then with brine (5 mL). The organic phase was dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was used for the next step without further purification. The crude mixture was dissolved in dry THF (9 mL), to this solution at 0 °C was added a solution of TBAF 1 M in THF (500 μL, 500 μmol). After stirring at 0 °C for 15 h, calcium carbonate (50 mg, 0.5 mmol)), Dowex 50WX 8-400 (1.68 g) and methanol (2 mL) were added.[23] After stirring for 2 h at room temperature, the reaction mixture was filtered on Celite and washed with methanol. After evaporation to dryness, the residue was purified by column chromatography to give **12** (94 mg, 63%) as a colorless oil.

^{1}H NMR ($CDCl_3$): See main text; LRMS/HRMS (*m/z*, ESI): (M+Na) = 565.185 (calcd), 555.184 (found).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.03.024.

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