Thiosugars: reactivity, methodology and applications

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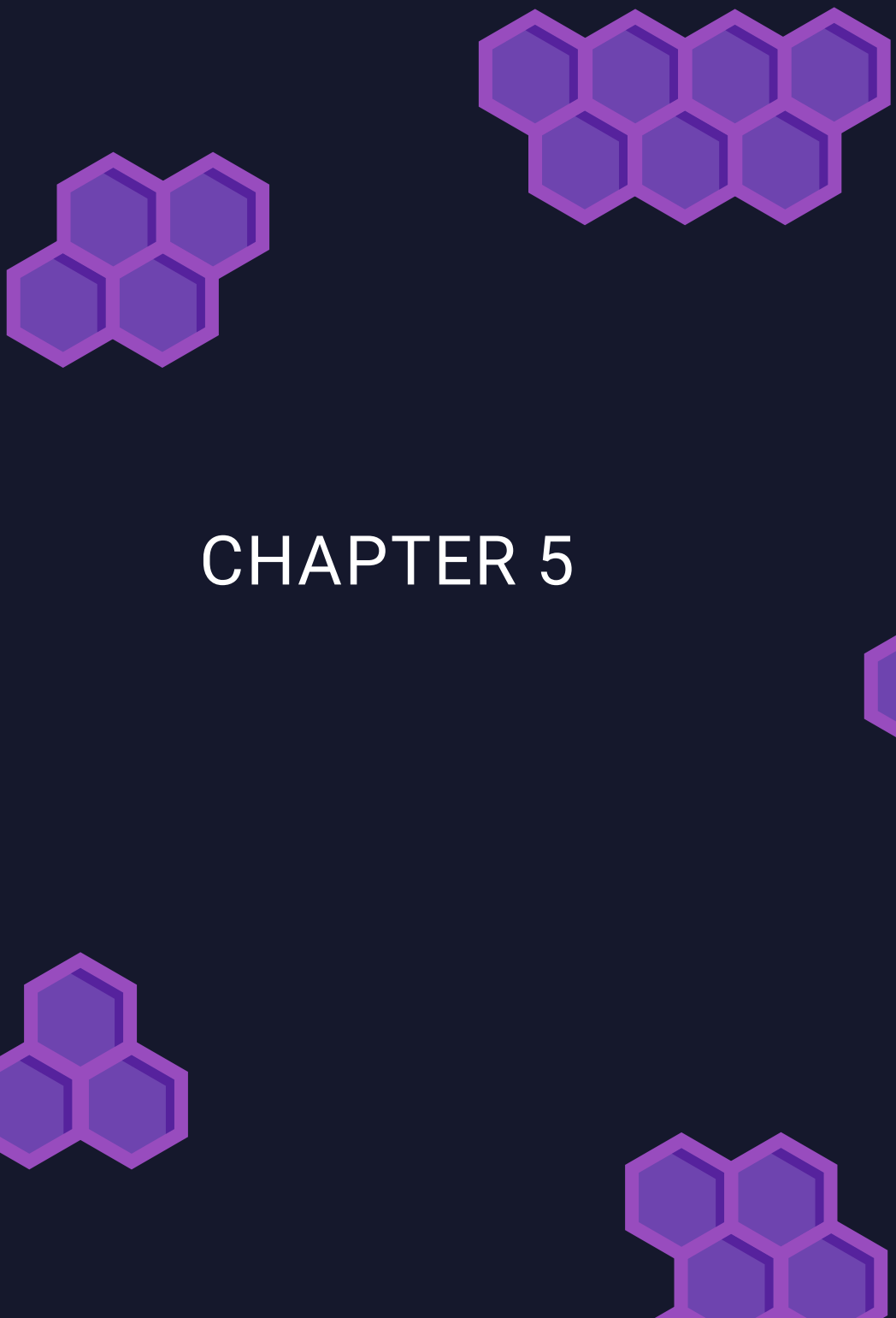
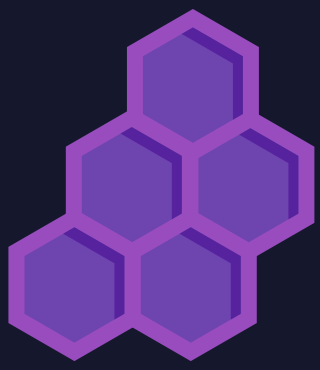
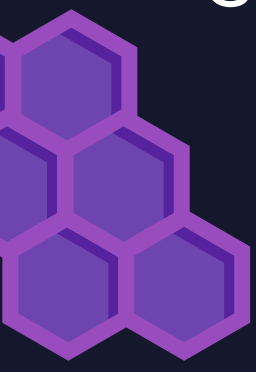


CHAPTER 5



SYNTHESIS, REACTIVITY AND STEREOSELECTIVITY OF 5-THIO PYRANOSIDES



5.1 Introduction

Up to here, this thesis has dealt with the synthesis, the glycosylating properties and application of 4-thiopentafuranosides. The present chapter is devoted to the corresponding 5-thiopyranosides. These carbohydrates are very rare in nature and only 5-thio-D-mannose (Figure 1, A) has been discovered by isolation from the marine sponge *Clathria pyramida*.[1] Remarkably, its biosynthesis is still covered in mystery. In contrast, a variety of 5-thiopyranosides have been synthesized as mimics of the parent glycosides, to perturb biological processes. For instance, 5-thio-L-fucose (Figure 1, B) was recently successfully used for modulating the fucosylation profile of therapeutic proteins.[2] In comparison with 5-O-glycosides the glycosidic bonds of the corresponding 5-thiopyranosides are hydrolytically and enzymatically more stable and implementation of 5-thiopyranosides is expected to increase metabolic stability of oligosaccharide-based drugs.[3]

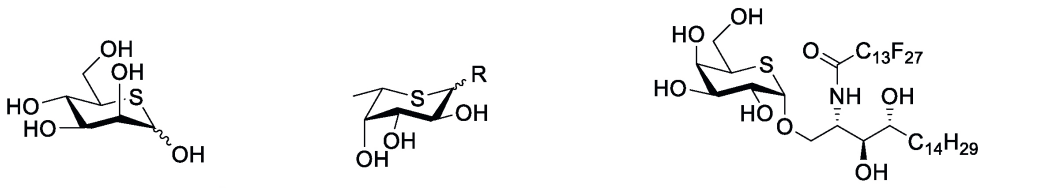
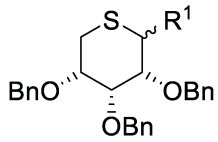
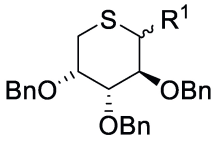


Figure 1. Examples of 5-thiopyranose derivatives.

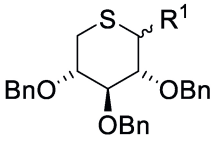
Based on these properties, 5-thiopyranoside analogues are explored in the development of inhibitors of glycan processing enzymes.[4–6] An example of another application is represented by the 5-thio analogue of α-GalCer (Figure 1, C) that has been shown to be capable of selectively enhancing TH1 cytokine production.[7] To effectively generate 5-thiopyranosyl containing oligosaccharides and glycoconjugates, it is of importance to investigate the glycosylating properties in terms of reactivity and stereoselectivity of relevant 5-thiopyranoside donors. This chapter describes the synthesis of all four diastereoisomers of the 5-thio-pentopyranosides (thio-ribopyranoside, thio-arabinopyranoside, thio-xylopyranoside and thio-lyxopyranoside, Figure 2) to map structure-stereoselectivity relationships of the associated thiopyranosyl donors in Lewis acid-mediated S_N1-type glycosylations. The putative ribosyl, arabinosyl, xylosyl, and lyxosyl thiocarbenium ion intermediates were investigated computationally following a method that has been applied for 4-thio furanosyl thiocarbenium ions, as outlined in Chapter 2.



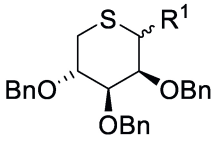
D-ribosyl donor
R1. R^1=OAc
R2. R^1=C(NPh)CF_3



D-arabinosyl donor
A1. R^1=OAc
A2. R^1=C(NPh)CF_3



D-xylosyl donor
X1. R^1=OAc
X2. R^1=C(NPh)CF_3



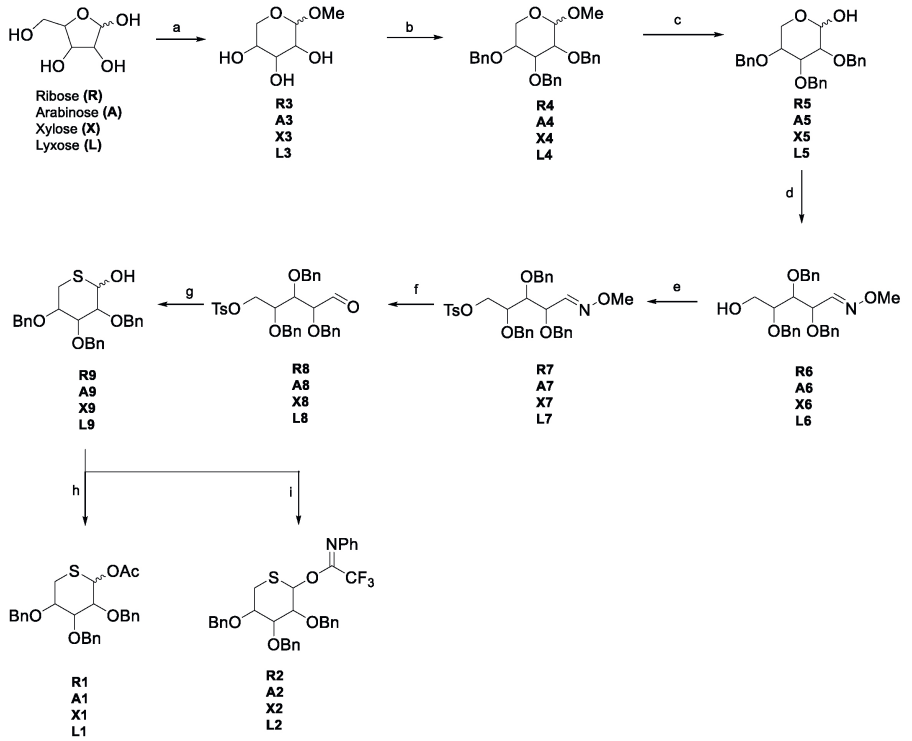
D-lyxosyl donor
L1. R^1=OAc
L2. R^1=C(NPh)CF_3

Figure 2. The studied 5-thiopyranosyl donors.

5.2 Synthesis of donors

All 5-thiopyranosyl acetate and imidate donors (ribose **R1** and **R2**, arabinose **A1** and **A2**, xylose **X1** and **X2**, lyxose **L1** and **L2**, respectively) were obtained by the same sequence of reactions (Scheme 1). Fischer glycosylation of each commercially available pentose sugar (D-ribose, D-arabinose, D-xylose, D-lyxose) with methanol under thermodynamic conditions resulted in the formation of an anomeric mixture of the respective pentoses in their 1-O-methyl pyranose form (*i.e.* **3** in Scheme 1). All free hydroxyl functionalities were then benzylated using benzyl bromide and sodium hydride yielding per-benzylated **4**. Next, deprotection of the anomeric center by hydrolysis using formic acid in water, yielded hemiacetal **5**. Addition of O-methylhydroxylamine hydrochloride to a solution of 5 in pyridine followed by stirring of the mixture for two hours at 50 °C, resulted in the opening of the pyranose ring and the formation of a E/Z-mixture of **6**. The free primary hydroxyl in oxime **6** was sulfonylated using tosyl chloride and *N*-methylimidazole yielding **7**. At this stage the aldehyde was reconstituted by dissolving oxime 7 in a mixture of acetone, formalin and hydrochloric acid affording linear aldehyde 8. The S_N2 substitution of the tosylate was effected with an aqueous solution of sodium hydrosulfide in DMF at 0 °C to give, after ring closure, hemithioacetal **9**. Finally, **9** was either transformed in acetate donor

1, using acetic anhydride in pyridine, or into imidate **2**, using 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride and cesium carbonate in acetone.



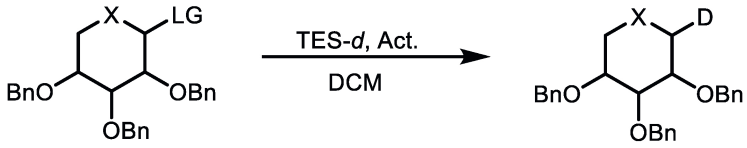
Scheme 1. Conditions and reagents: a) MeOH, AcCl, 70°C; b) DMF, NaH, BnBr; c) HCOOH (80% in H_2O), 60 °C; d) Pyridine, CH_3ONH_2·HCl, 50 °C; (**R6**: 93%, **A6**: 94%, **X6**: 93%, **L6**: 82% over 4 steps); e) CH_3CN, p-TsCl, N-methylimidazole, HCl (**R7**: 88%, **A7**: 99%, **X7**: 80%, **L7**: quant.); f) acetone, Formalin, HCl (**R8**: 72%, **A8**: 83%, **X8**: 78%, **L8**: 94%); g) DMF, NaSH (**R9**: 61%, **A9**: 79%, **X9**: 69%, **L9**: 57%); h) pyridine, Ac_2O, 0 °C; (**R1**: 60%, **A1**: 21%, **X1**: 73%, **L1**: 95%); i) acetone, H_2O, 2,2,2-trifluoro-N-phenylacetimidoyl chloride, Cs_2CO_3 (**R2**: 54%, **A2**: 58%, **X2**: 53%, **L2**: 97%)

5.3 Glycosylations and CEL maps

With all the 5-thio pyranosyl donors (R-, A-, X- and L- **1** and **2**) available, the glycosylation reactions could be examined. The same conditions as used for glycosylations of the 4-thiofuranosides, described in Chapter 2, were initially applied. Unfortunately, activation of acetate donors **1** with 1.3 equivalents of TMSOTf at -78 °C, in the presence of 2 equivalents of TES-*d* proceeded sluggishly and led to a complex mixture of inseparable compounds. Similar results were obtained when *C*-nucleophiles, such as allyltrimethylsilane and

methallyltrimethylsilane were used. Guided by the reduced reactivity of pyranose donors in comparison to furanose donors, it was decided to explore the more reactive imidate donors **2** instead. The results of these glycosylation reactions are summarized in Table 1, alongside the results previously obtained for the 5-*O*-pyranoside derived thioglycosyl donors,[8] which were activated with the diphenyl sulfoxide/triflic anhydride mixture.

Table 1. Results of the substitution reaction of TES-*d* with the 5-oxo and 5-thiopyranosides.



X=O, LG=SPh
X=S, LG=OIm.

Act = Ph_2SO/Tf_2O
Act = TMSOTf

	X = O			X = S		
	α:β ratio (comp.)	α:β ratio (exp.)[a,b]	Yield	α:β ratio (comp.)	α:β ratio (exp.)[c,b]	Yield
Riboside	>98:2	>98:2	69%	>98:2	>98:2	73%
Arabinoside	<2:98	<2:98	79%	20:80	18:82	65%
Xyloside	>98:2	>98:2	86%	<2:98	>98:2	55%
Lyxoside	<2:98	<2:98	81%	<2:98	<2:98	60%

[a]Reagents and conditions: 2 eq. TES-*d*, 1.3 eq. Ph_2SO, 1.3 eq. Tf_2O, -78 °C, 3 days. [b]The α:β-ratio was established by NMR spectroscopy. [c]Reagents and conditions: 5 eq. TES-*d*, 0.5 eq. TMSOTf, -30 °C, 3 days.

While probing the conditions for the 5-thio donors it was found that the imidate donors also showed a low reactivity and a large excess (5 eq.) of TES-*d* along with a relatively large amount (0.5 eq.) of TMSOTf were required to consistently generate glycosylated product. Upon reaction of the 5-thioribosyl imidate donor (**R2**) with triethylsilane-*d* the 1,2-*cis* addition product was formed selectively (1,2-cis:1,2-trans = >98:2). Next, the other three donors underwent the same glycosylation to deliver the results depicted in Table 1 and from these it becomes clear that the stereoselectivities of the reactions of the 5-thiopyranosyl donors are similar to those obtained with the *O*-pyranosides. In all cases, the 1,2-*cis* products are formed selectively and only the 5-thioarabinosyl donor **A2** provides a significant amount of the trans product (α/β = 18:82). Of note, when performing the reaction on the ribosyl (**R2**) and lyxosyl (**L2**) donors, a significant amount of the 1,2-alkene side product, generated by the competing elimination reaction, was observed.

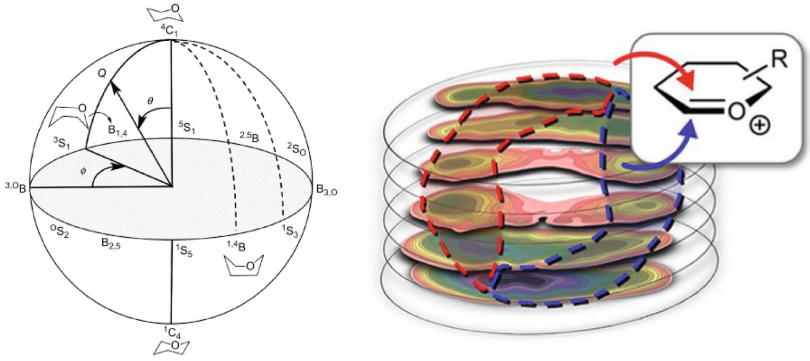
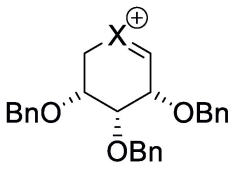
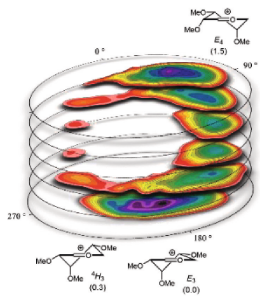
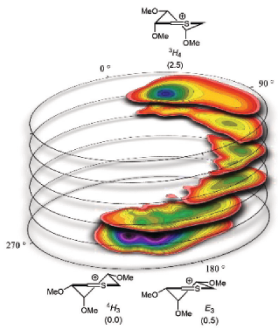
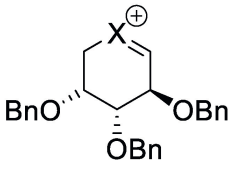
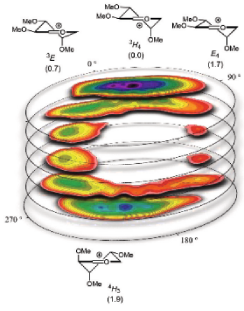
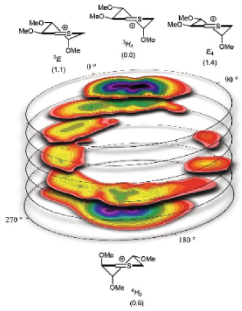
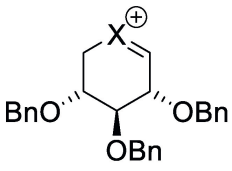
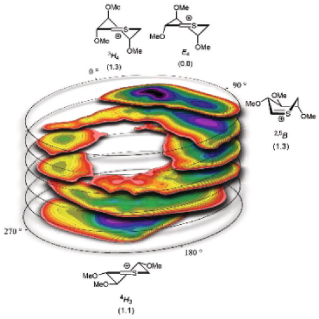
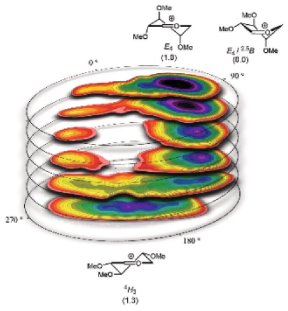
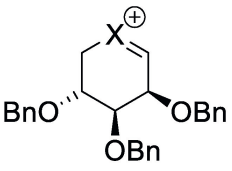
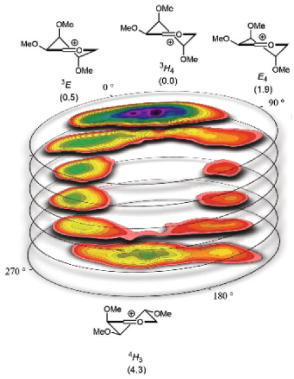
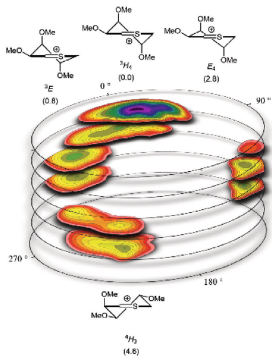
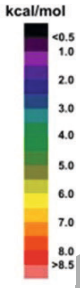


Figure 3. (A) Cremer-Pople sphere, including some relevant conformers. (B) Computed conformers and their associated energy are visualized in a CEL (Conformational Energy Landscape). The family of the top face-selective (^{3}E, $^{3}H_{4}$, E_{4}, and $B_{2,5}$)-like structures is found in the area contoured with the red-dashed line, while the bottom face-selective family of (^{4}E, $^{4}H_{3}$, E_{3}, and ^{2,5}B)-like conformers is found on the opposite side of the sphere, grouped within the blue-dashed line. Reprint from ref.[8]

To understand the observed *cis*-selectivity in the substitution reactions, the thiocarbenium ions were computationally investigated. To this end, the complete conformational space that the pyranosyl thiocarbenium ions can adopt, was mapped using the computational approach previously described by Hansen *et al. (Figure 3)*.[8,9] The conformational energy landscapes (CEL), plotted on the Cremer-Pople sphere (a spherical representation describing all possible conformations a six-membered ring can adopt) were generated by computing the energy of a suite of conformations, by scanning the three dihedral angles (C1-C2-C3-C4, C3-C4-C5-O5, and C5-O5-C1-C2) from −75° to 75° in 15° increments (11^{3} = 1331), thereby filling the complete conformation space. Using Gaussian 09, employing the B3LYP hybrid functional and the 6-311G(d,p) basis set, the structures of these conformers were optimized and their relative energies computed. The energies obtained from the DFT calculations were corrected for solvation in DCM using a polarized continuum model (PCM) and subsequently a Gibbs free energy correction was applied at the temperature of the experimental glycosylation reactions. The energy landscapes were then generated by visualizing the relative energy in contour plots on "slices" of the conformational sphere. Table 2 shows the CEL maps for the diastereoisomeric sets of both the pyranosyl thiocarbenium ions and oxocarbenium ions. The CEL maps show that the thiocarbenium ions adopt structures similar to their oxocarbenium ion counterparts and the minimal energy conformers can be found generally around $^{3}H_{4}$ and $^{4}H_{3}$ poles. The presence of the 4-*S* ring atom does influence the puckering of the six-membered ring going from an approximate puckering of 45° for the oxocarbenium ions to approximately 55° for the thiocarbenium ions, as a result of the longer C–S bonds.

Table 2. The conformational energy landscapes of the pyranosyl 5-oxo-carbenium ions and 5-thio thiocarbenium ions.

	X = O	X = S
 **Ribosyl**		
 **Arabinosyl**		
 **Xylosyl**		
 **Lyxosyl**		



Analyzing the individual stereoisomers, the CEL map of the ribopyranosyl thiocarbenium shows a clear minimum for the $^{4}H_{3}$ half-chair. This conformer places the substituents at the C2- and C3-position in a position that allows for stabilization of the thiocarbenium ion. As empirically established by Woerpel and co-workers[10–12] and supported by previous computational studies,[8] an oxocarbenium ion is best stabilized by an equatorial OMe substituent at the C2-position to allow for electron density donation by the axial C2–H2 bond. In contrast, the electron density of the ether groups at the C3-position and C4-position is nearest and most stabilizing to the electron-depleted anomeric center when placed axially. The CEL maps reveal that the stereoelectronic "stability guidelines" that play a decisive role in determining the stability and reactivity of pyranosyl oxocarbenium ions equally apply to thiocarbenium ions. A minor population of the ribosyl thiocarbenium ion adopting a $^{3}H_{4}$ conformation (ΔG_{DCM} = 2.5 kcal/mol) can be found. Assuming that the $^{4}H_{3}$ thiocarbenium ion is preferentially attacked on the α-face and the $^{3}H_{4}$ structure on the opposite β-side, the Boltzmann-weighed population of both families of conformers predicts a >98:2 α/β selectivity, which matches the ratio obtained in the experiment. The CEL maps of the arabinosyl thiocarbenium ion show a moderate preference for the $^{3}H_{4}$ conformer, while the $^{4}H_{3}$ is only 0.6 kcal/mol higher in energy. Nucleophilic attack on the population of conformers leads to a moderate α-selectivity of 80:20, corresponding well with the experimental findings. For the xylopyranosyl thiocarbenium ion, the canonical half-chair conformations are relatively high in energy, in line with the xylopyranosyl oxocarbenium ion. For the xylosyl thiocarbenum ion an E_{4} conformation is found to be most favorable. The xylosyl oxocarbenium ion was shown to preferentially take up a structure in between the E_{4} and $^{2,5}B$ conformations. It was proposed that this $E_{4}/^{2,5}B$ oxocarbenium ion is preferentially attacked from the bottom face providing the 1,2-*cis* product. Although attack on the E_{4} conformer of the xylosyl thiocarbenium ion seems to be most favorable from the top face, as this is most accessible and leads to a chair like product, the addition product was formed with >98:2 α/β selectivity. No clear explanation for this discrepancy is available. It may be reasoned however that, given the similar stereochemical outcome of the 5-O and 5-S-xylopyranosyl donors and the similarity in the CEL maps that similar stereoelectronic effects develop in the transition states leading to the products from the oxocarbenium and thiocarbenium ions. More detailed transition state calculations are required to shed light on the reactivity of the (non-canonical) conformers and the interactions that develop in the transition states originating from these. The lyxosyl $^{3}H_{4}$ conformer is stereoselectively attacked to provide the β-product. In line with the pyranosyl oxocarbenium ion series, the lyxose configured thiocarbenium shows the strongest preference for a single conformer, since it puts all substituents in their favored position, which translates into the highest stereoselectivity in the substitution reactions. Overall,

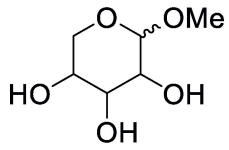
there is good agreement between the stereoselectivity that is theoretically predicted based on the CEL maps, in combination with Woerpel's inside attack model and the stereoselectivity obtained experimentally for three out of four pyranosyl thiocarbenium ions.

5.4 Conclusion

In conclusion, this chapter deals with the stability/reactivity of pyranosyl thiocarbenium ions, by probing all four diastereoisomeric C5-S-pentopyranosides experimentally and computationally revealing that all pyranosyl thiocarbenium ions react in a 1,2-*cis*-selective manner. A parallel can be drawn between the stereoselectivity observed for the thiocarbenium ions and the corresponding oxocarbenium ions, revealing similar stereoelectronic effects to be decisive for the relative stability of the ions. Activation of the C5-thiopyranosyl donors proved to be relatively difficult, indicating that the formation of the thiocarbenium ions is slower than the generation of their oxocarbenium ion counterparts. The C5-S-arabinose donor showed poorest stereoselectivity, which can be accounted for by the fact that the difference in stability between the $^{4}H_{3}$ and the $^{3}H_{4}$ conformers is relatively small. The CEL mapping method revealed the E_{4} conformation to be most favorable for the xylosyl thiocarbenium. This envelope is likely most readily attacked from the top face. Thus, for this structure there is poor agreement between the computed stereoselectivity and the selectivity obtained experimentally. For the corresponding xylosyl oxocarbenium ion a bottom-face selective E_{4} / $^{2,5}B$ conformation was previously found and it was reasoned that this structure is preferentially attacked from the bottom face. In the region of the conformational sphere, where the E_{4} and E_{4} / $^{2,5}B$ conformations are found, small structural differences may have a decisive effect on the selection from the two different diastereotopic addition pathways. The observed discrepancy encountered for the xylose donor, could indicate the need for a closer mesh of data points for this part of the conformational energy landscape. It would also be worthwhile to computationally probe the transition states of the reactions taking place on either diastereotopic face of the different conformers. Nonetheless, the parallels between the structures of the oxocarbenium and thiocarbenium ions and the fact that the thiocarbenium ions are formed less readily underpin the use of C-5-thioglycosides as stabilized mimetics to probe and interfere with naturally occurring glycosylation pathways.

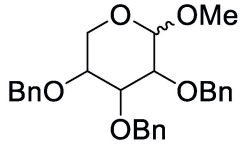
5.5 Experimental

Standard procedure for 2-methoxytetrahydro-2H-pyran-3,4,5-triol (3)



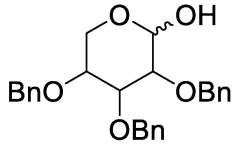
Pentose was dissolved in MeOH (0.4 M) at 70 °C. Acetyl chloride (0.8 eq.) was added and the solution was refluxed for 1 night. Na_2CO_3 was added to quench the reaction and neutralize the solution to pH 7. The solution was filtered and the filtrate was concentrated in vacuo and used in the next step without purification.

Standard procedure for 3,4,5-tris(benzyloxy)-2-methoxytetrahydro-2H-pyran (4)



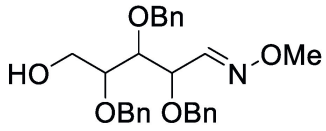
NaH (3.2 eq.) as a 60% suspension in mineral oil was added to a cooled (0 °C) solution of crude **3** in DMF (0.1M). Benzyl bromide (3.2 eq.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by the addition of ice. The aqueous layer was extracted with ethyl acetate and the organic layer was washed several times with water and brine, dried using $MgSO_4$ and concentrated in vacuo.

Standard procedure for 3,4,5-tris(benzyloxy)tetrahydro-2H-pyran-2-ol (5)



Crude **4** was dissolved (0.1M) in 80% (v/v) formic acid aqueous solution, and stirred at 60 °C for 24 h. The reaction mixture was allowed to cool at room temperature and extracted with CH_2Cl_2, neutralized with sat. aqueous solution of NaHCO3, dried using Na_2SO_4 and concentrated in vacuo.

Standard procedure for 2,3,4-tris(benzyloxy)-5-hydroxypentanal O-methyl oxime (6)



CH_3ONH_2·HCl was added to a solution of crude **5** in pyridine. The mixture was stirred for 2 hours at 50 °C. The reaction mixture was diluted with ethyl acetate and washed three times with H_2O. The product was isolated using column chromatography (eluent: ethyl acetate/petroleum ether=10/90 – 25/75) yielding **6**.

(2S,3S,4R,E)-2,3,4-tris(benzyloxy)-5-hydroxypentanal O-methyl oxime (R6)

Standard procedure for **6**, using: **R5** (8.1 g, 19.3 mmol), CH_3ONH_2·HCl (3.34 g, 40 mmol) and pyridine (40 ml). Yield: 8.12 g, 18.1 mmol, 93%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.44 (dd, J = 8.1, 5.8 Hz, 5H; Ar), 7.27 (d, J = 4.7 Hz, 5H; Ar), 7.27 – 7.19 (m, 5H; Ar), 6.90 (d, J = 6.3 Hz, 1H; H1 min), 6.81 (d, J = 6.3 Hz, 1H; ?H1 maj), 5.05 (dd, J = 6.3, 2.3 Hz, 1H; H1 maj), 5.02 (dd, J = 6.4, 2.4 Hz, 1H; H1 min), 4.83 – 4.63 (m, 6H; CH_2Bn), 4.31 – 4.29 (m, 1H; H2), 3.96 – 3.95 (m, 1H; H3), 3.88 (s, 3H; -OMe), 3.62 – 3.57 (m, 1H; H4), 2.75 (d, J = 5.7 Hz, 1H; H5), 2.69 (d, J = 5.1 Hz, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (C1 min), 148.6 (C1 maj), 138.0 (C_q-Ar), 137.9 (C_q-Ar), 137.8 (C_q-Ar), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.1 (CH-Ar), 128.1 (CH-Ar), 127.9 (CH-Ar), 127.9 (CH-Ar), 127.8 (CH-Ar), 80.1 (C3), 78.5 (C4), 77.2 (C2), 74.3 (CH_2Bn), 72.4 (CH_2Bn), 71.2 (CH_2Bn), 61.9 (-OMe), 61.0 (C5). IR (thin film, cm^{-1}): 3031, 2869, 1598 (C=N),1497, 1454, 1208, 1093, 1040,735, 696. HRMS: [M+H] calcd for $C_{27}H_{32}NO_5$ 450.2280, found 450.2275

(2R,3S,4R,E)-2,3,4-tris(benzyloxy)-5-hydroxypentanal O-methyl oxime (A6)

Standard procedure for **6**, using: **A5** (4.7 g, 11.2 mmol), CH_3ONH_2·HCl (1.7 g, 22.4 mmol) and pyridine (23.3 ml). Yield: 4.7 g, 10.5 mmol, 94%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.30 – 7.20 (m, 15H; Ar), 6.88 (d, J = 6.2 Hz, 1H; H1), 4.90 (dd, J = 6.3, 3.3 Hz, 1H; H2), 4.47 – 4.32 (m, 6H; x3 CH_2Bn), 4.22 (dd, J = 8.2, 4.3 Hz, 1H; H4), 3.91 (dd, J = 7.5, 3.3 Hz, 1H; H3), 3.88 (s, 3H; -OMe), 3.84 – 3.82 (m, 1H; H5), 3.80 – 3.79 (m, 1H; H5), 2.09 (s, 1H; -OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (C1), 128.6 (CH-Ar), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.5 (CH-Ar), 128.4 (CH-Ar), 128.4 (CH-Ar), 128.1 (CH-Ar), 128.0 (CH-Ar), 127.98 (CH-Ar), 127.97 (CH-Ar), 127.9 (CH-Ar), 80.1 (C4), 78.7 (C3), 77.3 (C2), 75.2 (CH_2Bn), 72.3 (CH_2Bn), 71.8 (CH_2Bn) 71.2 (C5), 61.9 (-OMe). IR (thin film, cm^{-1}): 3434 (O-H) 2901, 1723 (C=N), 1496,

1453, 1040, 1027, 875, 733, 695. HRMS: [M+H] calcd for $C_{27}H_{32}NO_5$ 450.2280, found 450.2275.

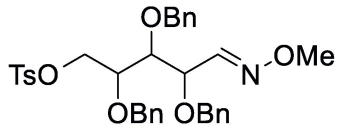
(2S,3R,4R,E)-2,3,4-tris(benzyloxy)-5-hydroxypentanal O-methyl oxime (X6)

Standard procedure for **6**, using: **X5** (11.5 g, 27.3 mmol), CH_3ONH_2·HCl (4.6 g, 54.6 mmol) and pyridine (57 ml). Yield: 11.4 g, 25.4 mmol, 93%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.41 (d, J = 7.8 Hz, 1H; H1 maj), 7.33 (d, J = 2.6 Hz, 9H; CH-Ar), 7.31 – 7.29 (m, 6H; CH-Ar), 6.89 (d, J = 6.2 Hz, 1H; H1 min), 4.86 (dd, J = 6.2, 3.4 Hz, 1H; H2 min), 4.69 – 4.55 (m, 5H; CH_2Bn), 4.42 (dd, J = 11.7, 9.0 Hz, 1H; CH_2Bn), 4.25 (dd, J = 7.8, 4.6 Hz, 1H; H2 maj), 3.91 – 3.89 (m, 1H; H3 min), 3.88 (s, 3H; -OMe maj), 3.85 (s, 1H; -OMe min), 3.77 – 3.73 (m, 2H; H3-H4), 3.68 (d, J = 12.2 Hz, 2H; H5 min- H5 maj), 3.51 (d, J = 8.3 Hz, 2H; H5 min- H5 maj). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (C1 min), 148.3 (C1 maj), 138.3 (C_q-Ar), 137.9 (C_q-Ar), 137.5 (C_q-Ar), 128.62 (CH-Ar), 128.55 (CH-Ar), 128.5 (CH-Ar), 128.4 (CH-Ar), 128.10 (CH-Ar), 128.06 (CH-Ar), 128.04 (CH-Ar), 127.96 (CH-Ar), 127.9 (CH-Ar), 80.2 (C3 maj), 79.7 (C3 min), 79.2 (C4 maj), 78.9 (C4 min), 76.3 (C2 maj) 74.8 (CH_2Bn min), 74.7 (CH_2Bn maj), 73.2 (CH_2Bn min), 73.1 (CH_2Bn maj), 72.3 (CH_2Bn min), 71.3 (CH_2Bn maj), 71.2 (C2 min), 62.2 (-OMe min), 62.0 (-OMe maj), 61.7 (C5 min), 61.5 (C5 maj). IR (thin film, cm^{-1}):3031, 2869, 1727 (C=N), 1497 ,1454, 1208, 1027, 1037, 878, 734. HRMS: [M+H] calcd for $C_{27}H_{32}NO_5$ 450.2280, found 450.2275.

(2R,3R,4R,E)-2,3,4-tris(benzyloxy)-5-hydroxypentanal O-methyl oxime (L6)

Standard procedure for **6**, using: **L5** (49.4.3 mmol), CH_3ONH_2·HCl (8.24 g, 98.7 mmol) and pyridine (100 ml). Yield: 12.78 g, 40.3 mmol, 82%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.45 (d, J = 8.1 Hz, 1H; H1 maj), 7.34 – 7.28 (m, 15H; Ar), 6.88 (d, J = 6.8 Hz, 1H; H1 min) 4.71 – 4.40 (m, 6H; x3 CH_2-Bn), 4.22 (dd, J = 8.2, 4.8 Hz, 1H; H2), 3.89 (s, 3H; -OMe), 3.88-3.87 (m, 1H; H3), 3.76 – 3.71 (m, 1H; H5), 3.68 – 3.65 (m, 1H; H5), 3.65 – 3.62 (m, 1H; H4).^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4(C1), 138.3(C_q-Bn), 138.1 (C-Ar), 137.7 (C_q-Bn), 128.6(CH-Ar), 128.51 (CH-Ar), 128.48 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.1 (CH-Ar) , 128.1 (CH-Ar), 128.0 (CH-Ar), 127.9 (CH-Ar), 80.5 (C3), 79.6 (C4), 76.8 (C2), 74.4 (CH_2Bn), 73.3 (CH_2Bn), 71.0 (CH_2Bn), 62.0 (-OMe), 61.8 (C5). IR (thin film, cm^{-1}): 3435, 2936, 2873, 1726 (C=N), 1497, 1454, 1089, 1040, 1027, 733. HRMS: [M+H] calcd for $C_{27}H_{32}NO_5$ 450.2280, found 450.2275.

Standard procedure for 2,3,4-tris(benzyloxy)-5-(methoxyimino)pentyl 4-methylbenzenesulfonate (7)



4-methylbenzenesulfonyl chloride was added to a solution of **6** in acetonitrile. N-methylimidazole was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 2 h. Ethyl acetate and hydrochloric acid (1M aq. solution) were added to the reaction mixture and the aqueous layer was removed. The organic layer was washed with sat. aqueous solution of $NaHCO_3$, brine and then dried with $MgSO_4$. The solvent was removed under reduced pressure. The product **7** was isolated using column chromatography (eluent: ethyl acetate/pentane= 5/95 – 10/90).

(2R,3S,4S,E)-2,3,4-tris(benzyloxy)-5-(methoxyimino)pentyl 4-methylbenzenesulfonate (R7)

Standard procedure for **7**, using: **R6** (10.9 g, 24.6 mmol), 4-methylbenzenesulfonyl chloride (6.9 g, 36.3 mmol), acetonitrile (108 ml) and *N*-methylimidazole (5 ml). Yield: 12.92 g, 21.4 mmol, 88%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.79 – 7.67 (m, 2H; Ar), 7.31 (d, J = 8.0 Hz, 1H; 1H), 7.31 – 7.26 (m, 11H; Ar), 7.26 – 7.08 (m, 6H; Ar), 6.69 (d, J = 6.2 Hz, 1H; H1 min), 5.02 – 4.94 (m, 1H; H2 min), 4.84 – 4.60 (m, 2H; CH_2Bn), 4.61 – 4.44 (m, 3H; CH_2Bn), 4.46 – 4.28 (m, 1H; CH_2Bn), 4.28 – 4.23 (m, 1H; H5), 4.26 – 4.25 (m, 1H;H2), 4.17 – 4.10 (m, 1H; H5), 4.02 – 3.97 (m, 1H; H3 min), 3.87 (s, 3H; -OMe), 3.85 – 3.80 (m, 1H; H4), 3.80 (dd, J = 8.6, 2.8 Hz, 1H; H3), 2.38 (s, 3H; Me(Ts)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1 (C1 min), 144.8 (C1 maj), 137.8 (C_q-Ts), 137.7 (C_q-Ar), 137.6 (C_q-Ar), 132.9 (C_q-Ar), 129.9 (C_q-Ts), 129.6 (CH-Ar), 128.53 (CH-Ar), 128.46 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.1 (CH-Ar), 128.1 (CH-Ar), 127.9 (CH-Ar), 127.7 (CH-Ar), 81.1 (C2 min), 79.2 (C3), 76.4 (C2), 74.1 (CH_2Bn), 72.9 (CH_2Bn), 71.3 (CH_2Bn), 69.4 (C5), 62.1 (C4), 62.0 (-OMe), 21.8 (Me(Ts)). IR (thin film, cm^{-1}): 2938, 2871, 1598 (C=N), 1497 , 1455, 1362, 1189, 1096, 1041 , 736, 697, 668. HRMS: [M+H] calcd for $C_{34}H_{38}NO_7S$ 604.2639, found 604.2632

(2R,3S,4R,E)-2,3,4-tris(benzyloxy)-5-(methoxyimino)pentyl 4-methylbenzenesulfonate (A7)

Standard procedure for **7**, using: **A6** (4.7 g, 10.5 mmol), 4-methylbenzenesulfonyl chloride (3.0 g, 15.7 mmol), acetonitrile (47 ml) and *N*-methylimidazole (2 ml). Yield: 6.3 g, 10.5 mmol, quantitative. ^{1}H NMR (400 MHz, chloroform-d) **δ** 7.74 (dd, J = 8.2, 1.7 Hz, 3H; Ar), 7.33 (d, J = 8.0 Hz, 1H; H1 maj), 7.30 – 7.27 (m, 8H; Ar), 7.26 – 7.17 (m, 6H; Ar), 7.16 – 7.10 (m, 3H; Ar), 6.83 (d, J = 6.1 Hz, 1H; H1 min), 4.82

(dd, J = 6.1, 2.8 Hz, 1H; H2 min), 4.57 (m, 1H; CH_2Bn), 4.43 – 4.38 (m, 2H; CH_2Bn), 4.37 (d, J = 2.2 Hz, 1H; H5), 4.32 (d, J = 11.7 Hz, 1H; CH_2Bn), 4.22 (d, J = 11.3 Hz, 1H; H5), 4.19 – 4.17 (m, 1H; H2 maj), 4.17 – 4.15 (m, 1H; CH_2Bn), 3.87 (s, 1H; -OMe min), 3.85 (s, 3H; -OMe maj), 3.83 – 3.80 (m, 1H; H4), 3.71 (dd, J = 7.0, 4.0 Hz, 1H; H3), 2.39 (s, 3H; Me(Ts)). ^{13}C NMR (101 MHz, $CDCl_3$) **δ** 151.2 (C1 min), 148.6 (C1 maj), 144.9 (C_q-Ts), 137.6 (C_q-Ar), 137.52 (C_q-Ar, 137.47 (C_q-Ar), 132.9 (C_q-Ts), 129.9 (CH-Ar), 128.53 (CH-Ar), 128.45 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.1 (CH-Ar), 128.0 (CH-Ar), 127.9 (CH-Ar), 127.8 (CH-Ar), 127.8 (CH-Ar), 79.7 (C3), 76.8 (C2 trans), 76.7 (C4), 75.0 (CH_2Bn), 72.4 (CH_2Bn), 72.2 (C2 cis), 71.2 (CH_2Bn), 69.1 (C5), 62.4 (-OMe cis), 61.9 (-OMe trans), 21.8 (Me(Ts)). IR (thin film, cm^{-1}): 3031, 2866, 1598 (C=N), 1497, 1363, 1176, 1040, 1029 (S=O), 743, 698. HRMS: [M+H] calcd for $C_{34}H_{38}NO_7S$ 604.2639, found 604.2632.

(2R,3R,4S,E)-2,3,4-tris(benzyloxy)-5-(methoxyimino)pentyl 4-methylbenzenesulfonate (X7)

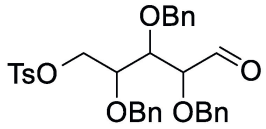
Standard procedure for **7**, using: **X6** (11.4 g, 25.4 mmol), 4-methylbenzenesulfonyl chloride (7.3 g, 18.4 mmol), acetonitrile (113 ml) and *N*-methylimidazole (5 ml). Yield: 12.22 g, 20.2 mmol, 80%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.40 – 7.19 (m, 20H; Ar – H1 maj), 6.85 (d, J = 6.0 Hz, 1H; H1 min), 4.89 (dd, J = 6.1, 3.1 Hz, 1H; H2 min), 4.66 – 4.51 (m, 7H; CH_2Bn), 4.40 (d, J = 11.4 Hz, 1H; CH_2Bn), 4.31 – 4.22 (m, 2H, H2 maj - H5), 4.13 (dd, J = 10.7, 6.5 Hz, 1H; H5), 3.94 – 3.90 (m, 1H; H4), 3.89 (s, 3H; -OMe maj), 3.86 (s, 1H; -OMe min), 3.67 (t, J = 4.8 Hz, 1H; H3), 2.45 (s, 3H; Me(Ts)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (C1 min), 148.0 (C1 maj), 144.8 (C_q-Ts), 137.7 (C_q-Ar), 137.4 (C_q-Ar), 137.3 (C_q-Ar), 132.7 (C_q-Ts), 129.9 (CH-Ar), 129.8 (CH-Ar), 128.5 (CH-Ar), 128.40 (CH-Ar), 128.36 (CH-Ar), 128.2 (CH-Ar), 128.1 (CH-Ar), 128.0 (CH-Ar), 127.9 (CH-Ar), 127.82 (CH-Ar), 127.76 (CH-Ar), 78.9 (C3), 76.4(C2), 75.8 (C4), 74.2 (CH_2Bn), 73.40 (CH_2Bn), 71.34 (CH_2Bn), 70.4 (C5) 61.9 (-OMe), 21.7 (Me(Ts)). IR (thin film, cm^{-1}):3031, 2868, 1678 (C=N), 1497, 1123, 1009, 815, 736, 682. HRMS: [M+H] calcd for $C_{34}H_{38}NO_7S$ 604.2639, found 604.2632.

(2R,3R,4R,E)-2,3,4-tris(benzyloxy)-5-(methoxyimino)pentyl 4-methylbenzenesulfonate (L7)

Standard procedure for **7**, using: **L6** (16.9 g, 37.5 mmol), 4-methylbenzenesulfonyl chloride, acetonitrile (170 ml) and *N*-methylimidazole (8 ml). Yield: 37.5 mmol, quantitative. ^{1}H NMR (400 MHz, chloroform-d) δ 7.69 (t, J = 8.0 Hz, 2H; Ar), 7.37 – 7.32 (m, 1H; H1 maj), 7.33 – 7.25 (m, 16H; Ar), 7.21 – 7.16 (m, 2H; Ar),), 6.78 (d, J = 6.4 Hz, 1H; H1 min), 4.87 (dd, J = 6.6, 3.4 Hz, 1H; H2 min), 4.59 (d, J = 11.3 Hz, 2H; CH_2Bn), 4.57 – 4.49 (m, 1H; H5), 4.49 – 4.41 (m, 3H; CH_2Bn), 4.27 (d, J = 11.7 Hz, 1H; H5), 4.19 (dd, J = 8.2, 5.6 Hz, 1H; H2 maj), 4.15 – 4.06 (m, 1H; CH_2Bn), 3.90 – 3.86 (m, 1H; H4), 3.85 (s, 3H; -OMe), 3.80 (d, J = 3.6 Hz, 1H; H3 min) 3.74 (dd, J = 5.5, 3.9 Hz, 1H; H3), 2.41 (s, 3H; Me(Ts)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5

(C_q-Ts), 150.2 (C1 min), 148.3(C1 maj), 145.0(C_q-Ar), 137.8 (C_q-Ar), 137.7 (C_q-Ar), 132.8 (C_q-Ts), 130.0 (CH-Ar), 129.9 (CH-Ar), 128.54 (CH-Ar), 128.46 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.12 (CH-Ar), 128.06 (CH-Ar), 127.9 (CH-Ar), 79.1 (C3 maj), 78.0 (C3 min), 76.8 (C4 min), 76.3 (C2 maj), 74.1 (CH_2Bn), 73.7 (CH_2Bn), 71.9 (C2 min), 71.0 (C5), 69.7 (CH_2Bn), 63.0 (-OMe), 21.8 (Me(Ts)). IR (thin film, cm^{-1}): 3030, 2924, 1600 (C=N), 1496, 1453, 1033 (S=O), 1121, 697, 683. HRMS: [M+H] calcd for $C_{34}H_{38}NO_7S$ 604.2639, found 604.2632.

Standard procedure for 2,3,4-tris(benzyloxy)-5-oxopentyl 4-methylbenzenesulfonate (8)



30% (w/w) formalin aqueous solution and hydrochloric acid (2M aq. solution) were added to a solution of **7** dissolved in acetone. The resultant was stirred for 13h at room temperature. Ethyl acetate and sat. aqueous solution of $NaHCO_3$ were added to the reaction mixture and the aqueous layer was removed. The organic layer was then washed with sat. aqueous solution of $NaHCO_3$, H_2O, brine, dried with Na_2SO_4 and the solvent was removed under reduced pressure. The product was isolated using column chromatography (eluent: ethyl acetate/ pentane= 10/90-15/85).

(2R,3R,4R)-2,3,4-tris(benzyloxy)-5-oxopentyl 4-methylbenzenesulfonate (R8)

Standard procedure for **8**, using: **R7** (12.92 g, 21.40 mmol), 30% formalin aqueous solution (126 ml), 2M aq. HCl solution (5 ml) and acetone (212 ml). Yield: 8.87 g, 15.43 mmol, 72%. ^{1}H NMR (400 MHz, chloroform-d) **δ** 9.45 (d, J = 1.5 Hz, 1H; H1 min), 9.40 (d, J = 0.8 Hz, 1H; H1 maj), 7.74 – 7.70 (m, 3H; CH-Ar), 7.31 (q, J = 3.9, 3.2 Hz, 12H; CH-Ar), 7.24 – 7.14 (m, 5H; CH-Ar), 4.72 – 4.66 (m, 1H; CH_2Bn), 4.57 – 4.46 (m, 4H; CH_2Bn), 4.46 – 4.39 (m, 1H; CH_2Bn), 4.26 (dd, J = 10.7, 1.9 Hz, 1H; H5), 4.18 – 4.12 (m, 1H; H5), 4.05 – 4.04 (m, 1H; H2), 3.95 – 3.92 (m, 1H; H3), 3.91 (dd, J = 3.8, 2.1 Hz, 1H; H4), 2.39 (s, 3H; ME (Ts)). ^{13}C NMR (101 MHz, $CDCl_3$) **δ** 201.0 (C1), 144.9 (C_q-Ts), 137.24 (C_q-Ar), 137.17 (C_q-Ar), 137.1 (C_q-Ar), 132.8 (C_q-Ts), 129.9 (C2), 129.7 (CH-Ar), 128.7 (CH-Ar), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.4 (CH-Ar), 128.22 (CH-Ar), 128.17 (CH-Ar), 127.9 (CH-Ar), 127.8 (CH-Ar), 81.8 (C2), 79.7 (C4), 75.0 (C3), 73.4 (CH_2Bn), 72.9 (CH_2Bn), 72.8 (CH_2Bn), 68.8 (C5), 21.8 (Me(Ts)). IR (thin film, cm^{-1}): 3031, 1719 (C=O), 1496, 1364, 1176, 1096, 1026, 737, 697. HRMS: $[M + Na]^+$: calcd for $C_{33}H_{34}O_7SNa$ 597.1923, found 597.1917

(2R,3R,4S)-2,3,4-tris(benzyloxy)-5-oxopentyl 4-methylbenzenesulfonate (A8)

Standard procedure for **8**, using: **A7** (9.91 g, 16.42 mmol), 30% formalin aqueous solution (97 ml), 2M aq. HCl solution (5 ml) and acetone (162 ml). Yield: 7.86 g, 13.68 mmol, 83%. ^{1}H NMR (400 MHz, chloroform-d) **δ** 7.73 (d, J = 8.3 Hz, 1H; H1), 7.34 – 7.22 (m, 16H; Ar), 7.22 – 7.08 (m, 3H; Ar), 4.67 – 4.60 (m, 1H; CH_2Bn), 4.49 – 4.40 (m, 3H; CH_2Bn), 4.43 – 4.40 (m, 1H; H5), 4.24 – 4.19 (m, 2H; CH_2Bn), 4.18 (d, J = 4.4 Hz, 1H; H5), 4.01 – 3.96 (m, 2H; H2 – H3), 3.85 – 3.80 (m, 1H; H4), 2.38 (s, 3H; CH_3-Ts). ^{13}C NMR (101 MHz, $CDCl_3$) **δ** 202.0 (CH-aldehyde), 144.9 (C_q-Ts), 137.2 (C_q-Bn), 137.0 (C_q-Bn), 136.9 (C_q-Bn), 132.8 (C_q-Ts), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.42 (CH-Ar), 128.35 (CH-Ar), 128.3 (CH-Ar), 128.2 (CH-Ar), 128.1 (CH-Ar), 128.0 (CH-Ar), 127.91 (CH-Ar), 127.89 (CH-Ar), 83.5 (C2), 77.9 (C3), 76.1 (C4), 74.2 (CH_2Bn), 73.4 (CH_2Bn), 72.2 (CH_2Bn), 68.2 (C5), 21.7 (CH_3-Ts). IR (thin film, cm^{-1}): 3064, 2937, 1724 (C=O), 1454, 1362, 1176, 1095, 815, 736, 697. HRMS: [M + Na] calcd for $C_{33}H_{34}O_7SNa$ 597.1923, found 597.1917

(2R,3S,4R)-2,3,4-tris(benzyloxy)-5-oxopentyl 4-methylbenzenesulfonate (X8)

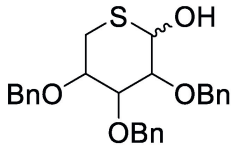
Standard procedure for **8**, using: **X7** (12.22 g, 20.24 mmol), 30% formalin aqueous solution (120 ml), 2M aq. HCl solution (4.3 ml) and acetone (200 ml). Yield: 9.12 g, 15.87 mmol, 78%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.80 (d, J = 8.3 Hz, 1H; H1 min), 7.67 (dd, J = 8.3, 1.9 Hz, 1H; H1 maj), 7.40 – 7.25 (m, 19H; CH-Ar), 4.64 – 4.44 (m, 6H; CH_2Bn), 4.24 – 4.21 (m, 1H; H4), 4.22 – 4.16 (m, 1H; H5), 4.07 (dd, J = 10.7, 6.6 Hz, 1H; H5), 3.88 (d, J = 2.6 Hz, 1H; H3), 3.62 (t, J = 4.8 Hz, 1H; H2), 2.40 (s, 3H; Me(Ts)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1 (C1), 145.2 (C_q-Ar), 144.9 (C_q-Ar), 144.7 (C_q-Ar), 130.0 (CH-Ar), 129.2 (CH-Ar), 128.8 (CH-Ar), 128.7 (CH-Ar), 128.5 (CH-Ar), 128.5 (CH-Ar), 128.3 (CH-Ar), 128.1 (CH-Ar), 127.9 (CH-Ar), 127.1 (CH-Ar), 79.0 (C2), 76.6 (C3), 75.9 (C4), 74.3 (CH_2Bn), 73.5 (CH_2Bn), 72.0 (CH_2Bn), 71.4 (C5), 21.7 (CH_3-Ts). IR (thin film, cm^{-1}): 3064, 2937, 1724 (C=O), 1454, 1362, 1176, 1095, 815, 736, 697. HRMS: [M + Na] calcd for $C_{33}H_{34}O_7SNa$ 597,1923, found 597.1917

(2R,3S,4S)-2,3,4-tris(benzyloxy)-5-oxopentyl 4-methylbenzenesulfonate (L8)

Standard procedure for **8**, using: **L7** (23.08 g, 38.5 mmol), 30% formalin aqueous solution (205 ml), 2M aq. HCl solution (10 ml) and acetone (385 ml). Yield: 20.94 g, 36.44 mmol, 94%. ^{1}H NMR (400 MHz, chloroform-d) δ 9.63 (d, J = 1.0 Hz, 1H; H1 aldehyde min), 9.54 (d, J = 1.4 Hz, 1H; H1 aldehyde maj), 7.75 – 7.64 (m, 4H; Ar), 7.40 – 7.24 (m, 11H; Ar), 7.24 – 7.15 (m, 5H; Ar), 4.62 (d, J = 11.8 Hz, 1H; CH_2Bn), 4.54 – 4.42 (m, 3H; CH_2Bn), 4.43 (d, J = 2.9 Hz, 1H; H5), 4.44 – 4.37 (m, 2H; CH_2Bn), 4.38 – 4.36 (m, 1H; H5), 3.97 (dd, J = 2.8, 1.4 Hz, 1H; H2 maj), 3.92 (dd, J = 5.4, 2.8 Hz, 1H; H4), 3.90 – 3.86 (m, 1H; H3), 2.41 (s, 3H; Me(Ts)). ^{13}C NMR

(101 MHz, $CDCl_3$) δ 201.56 (C1), 144.84 (C_q -Ts), 137.23 (C_q-Ar), 137.15 (C_q-Ar), 137.08(C_q-Ar), 132.96 (C_q-Ts), 129.94 (CH-Ar), 128.70 (CH-Ar), 128.65 (CH-Ar), 128.53 (CH-Ar), 128.30 (CH-Ar), 128.27 (CH-Ar), 128.20 (CH-Ar), 128.11 (CH-Ar), 128.10 (CH-Ar), 127.97 (CH-Ar), 83.46 (C2), 79.37 (C4), 77.24 (C3), 73.56 (CH_2Bn), 73.22 (CH_2Bn), 72.95 (CH_2Bn), 71.23 (C5), 21.83 (Me(Ts)).IR (thin film, cm^{-1}):3031, 1719 (C=O), 1496, 1364, 1176, 1096, 1026, 737, 697. HRMS: [M + Na] calcd for $C_{33}H_{34}O_7SNa$ 597,1923, found 597.1917

Standard procedure for 3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-ol (9)



A 15% (w/v) sodium hydrogen sulfide aqueous solution was added dropwise to a solution of **8** in DMF at 0 °C and the reaction mixture was stirred at room temperature for 1.5 h. Ethyl acetate and brine were added to the reaction mixture and the aqueous layer was removed. The organic layer was washed three times with $NaHCO_3$ aqueous solution, brine and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: ethyl acetate/pentane= 10/90 – 20/80) yielding **9**.

(3R,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-ol (R9)

Standard procedure for **9**, using: **R8** (8.9 g, 15.4 mmol), 15% sodium hydrogen sulfide solution (5.35 ml), DMF (165 ml). Yield: 4.13 g, 9.46 mmol, 61%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.34 (d, J = 17.6 Hz, 15H; CH-Ar), 5.39 (d, J = 3.9 Hz, 1H; H1), 4.87 (d, J = 12.1 Hz, 2H; CH_2Bn), 4.82 – 4.71 (m, 2H; CH_2Bn), 4.60 – 4.52 (m, 2H; CH_2Bn), 4.38 (d, J = 2.9 Hz, 1H; H3), 3.97 – 3.89 (m, 1H; H4), 3.87 (dd, J = 4.3, 2.8 Hz, 1H; H2), 3.65 – 3.59 (m, 1H; H5), 3.58 – 3.51 (m, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.14 (C_q-Ar), 137.91 (C_q-Ar), 137.75 (C_q-Ar), 128.72 (CH-Ar), 128.65 (CH-Ar), 128.59 (CH-Ar), 128.50 (CH-Ar), 128.37 (CH-Ar), 128.28 (CH-Ar), 127.98 (CH-Ar), 127.52 (CH-Ar), 127.13 (CH-Ar), 83.54 (C2), 81.54 (C3), 79.11 (C1), 78.70 (C4), 76.09 (CH_2Bn), 75.20 (CH_2Bn), 70.99 (CH_2Bn), 69.80 (C5). IR (thin film, cm^{-1}): 3030, 2965 (O-H), 1728, 1454, 1091, 1069, 734, 695. HRMS: [M + Na] calcd for $C_{26}H_{28}O_4SNa$ 459.1606, found 459.1601; $[M + NH_4]^+$: calcd for $C_{26}H_{32}O_4SN$ 454.2052, found 454.2046

(3S,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-ol (A9)

Standard procedure for **9**, using: **A8** (7.14 g, 12.4 mmol), 15% sodium hydrogen sulfide solution (4.3 ml), DMF (132 ml). Yield: 4.3 g, 9.9 mmol, 79%. ^{1}H NMR

(400 MHz, chloroform-d) δ 7.36 – 7.16 (m, 15H; Ar), 4.76 (d, J = 11.7 Hz, 1H; CH_2Bn), 4.61 – 4.58 (m, 1H; H1), 4.57 – 4.55 (m, 2H; CH_2Bn), 4.51 – 4.34 (m, 3H; CH_2Bn), 4.06 – 4.01 (m, 1H; H4), 3.93 – 3.89 (m, 1H; H3), 3.88 (d, J = 3.7 Hz, 1H; H2), 3.25 – 3.18 (m, 1H; H5), 2.48 (dd, J = 13.0, 3.8 Hz, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.36 (C_q-Ar), 137.57 (C_q-Ar),137.33 (C_q-Ar), 128.69 (CH-Ar), 128.66 (CH-Ar), 128.59 (CH-Ar), 128.57 (CH-Ar), 128.26 (CH-Ar), 127.92 (CH-Ar), 127.88 (CH-Ar), 127.66 (CH-Ar), 127.57(CH-Ar) , 77.26 (C1), 77.15(C2), 75.15(C4), 74.57(CH_2Bn), 74.31(C3) , 72.31 (CH_2Bn), 71.17 (CH_2Bn), 21.77(C5). IR (thin film, cm^{-1}): 3030, 2965 (O-H), 1728, 1454, 1091, 1069, 734, 695. HRMS: [M + Na] calcd for $C_{26}H_{28}O_4SNa$ 459.1606, found 459.1601; $[M + NH_4]^+$: calcd for $C_{26}H_{32}O_4SN$ 454.2052, found 454.2046

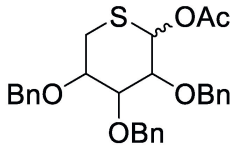
(3R,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-ol (X9)

Standard procedure for **9**, using: **X8**, 15% sodium hydrogen sulfide solution (5.51 ml), DMF (170 ml). Yield: 4.79g, 10.97 mmol, 69%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.38 – 7.26 (m, 15H; Ar), 4.86 (d, J = 4.0 Hz, 1H; H1), 4.85 – 4.81 (m, 1H; CH_2Bn), 4.78 – 4.73 (m, 1H; CH_2Bn), 4.71 – 4.66 (m, 3H; CH_2Bn), 4.50 – 4.47 (m, 1H; CH_2Bn), 3.82 – 3.77 (m, 1H; H3), 3.74 – 3.69 (m, 2H; H2-H4), 2.97 (dd, J = 13.2, 11.0 Hz, 1H; H5), 2.61 – 2.55 (m, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.90 (C_q-Ar), 138.39 (C_q-Ar), 138.01 (C_q-Ar), 128.71 (CH-Ar), 128.63 (CH-Ar), 128.56 (CH-Ar), 128.44 (CH-Ar), 128.21 (CH-Ar), 128.10 (CH-Ar), 127.91 (CH-Ar), 127.86 (CH-Ar), 127.69 (CH-Ar), 85.07 (C3 min), 84.36 (C3 maj), 84.01 (C2 min), 82.10 (C2 maj), 82.07 (C4 maj), 81.47 (C4 min), 76.54 (CH_2Bn), 73.29 (CH_2Bn), 72.94 (CH_2Bn), 71.71 (C1), 25.72 (C5). IR (thin film, cm^{-1}): 3030, 2965 (O-H), 1728, 1454, 1091, 1069, 734, 695. HRMS: [M + Na] calcd for $C_{26}H_{28}O_4SNa$ 459.1606, found 459.1601; [M + NH_4] calcd for $C_{26}H_{32}O_4SN$ 454.2052, found 454.2046

(3S,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-ol (L9)

Standard procedure for **9**, using: **L8** (20.94 g, 36.44 mmol), 15% sodium hydrogen sulfide solution (12.8 ml), DMF (392 ml). Yield: 8.9 g, 29.61 mmol, 57%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.36 – 7.28 (m, 15H; Ar), 4.87 (d, J = 2.5 Hz, 1H; H1), 4.88 – 4.78 (m, 2H; CH_2Bn), 4.77 – 4.68 (m, 4H; CH_2Bn), 3.82 – 3.75 (m, 1H; H3), 3.73 (d, J = 3.0 Hz, 1H; H2), 3.71 (m, 1H; H4), 2.98 (dd, J = 13.0, 10.9 Hz, 1H; H5), 2.59 (dd, J = 14.0, 3.8 Hz, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.90 (C_q-Ar), 138.79 (C_q-Ar), 138.00 (C_q-Ar), 128.68 (CH-Ar), 128.60 (CH-Ar),128.49 (CH-Ar), 128.25 (CH-Ar), 128.13 (CH-Ar), 127.95 (CH-Ar), 127.91 (CH-Ar), 127.83 (CH-Ar), 127.75 (CH-Ar), 84.36 (C2), 82.09 (C4-C3), 76.60 (C1), 73.37 (CH_2Bn), 72.99 (CH_2Bn), 71.75 (CH_2Bn), 25.76 (C5). IR (thin film, cm^{-1}): 3499 (O-H), 3030, 2870, 1727, 1496, 1453, 1360, 1069, 1027, 735, 697. HRMS: [M + Na] calcd for $C_{26}H_{28}O_4SNa$ 459.1606, found 459.1601; [M + NH_4] calcd for $C_{26}H_{32}O_4SN$ 454.2052, found 454.2046

Standard procedure for 3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl acetate (1)



9 was dissolved in pyridine at 0 °C. Acetic anhydride was added and the reaction was stirred for 1h. Ethyl acetate and H_2O were added to the reaction mixture and the aqueous layer was removed. The organic layer was washed three times with H_2O, brine and dried with Na_2SO_4. The solvent was removed under reduced pressure and the product was isolated using column chromatography (eluent: ethyl acetate/pentane= 1/99 – 10/90) yielding **1**.

(3R,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl acetate (R1)

Standard procedure for **1**, using: **R9** (4.13 g, 9.46 mmol), pyridine (28.3 ml) and acetic anhydride (18.9 ml). Yield: 2.3 g, 4.82 mmol, 60%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.39 – 7.25 (m, 15H; Ar), 6.27 (d, J = 4.8 Hz, 1H; H1 min), 6.01 (d, J = 3.7 Hz, 1H; H1 maj), 4.91 – 4.74 (m, 2H; CH_2Bn), 4.57 – 4.48 (m, 4H; CH_2Bn), 4.25 – 4.23 (m, 1H; H3), 4.10 (t, J = 3.5 Hz, 1H; H2), 4.02 – 3.95 (m, 1H; H4), 3.99 – 3.92 (m, 1H; H5), 3.71 – 3.68 (m, 1H; H5), 2.09 (s, 1H; -OMe min), 2.05 (s, 3H; -OMe maj). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93 (C_q-OAc), 138.29 (C_q-Ar), 138.10 (C_q-Ar), 137.92 (C_q-Ar), 128.67 (CH-Ar), 128.64 (CH-Ar), 128.55 (CH-Ar), 128.51 (CH-Ar), 128.37 (CH-Ar), 127.89 (CH-Ar), 127.79 (CH-Ar), 127.71 (CH-Ar), 127.53 (CH-Ar), 84.56 (C2 maj), 84.23 (C2 min), 80.69 (C1 maj), 79.51 (C3), 78.72 (C4), 76.10 (CH_2Bn), 73.46 (CH_2Bn), 72.72 (CH_2Bn), 71.20 (C5), 21.53 (CH_3-OAc min), 21.18 53 (CH_3-OAc maj). IR (thin film, cm^{-1}): 3064, 2922, 1724 (C=O), 1400, 1455, 1175, 1096, 738, 698. HRMS: [M + Na] calcd for $C_{28}H_{30}O_5SNa$ 501.1712, found 501.1706; [M + NH_4] calcd for $C_{28}H_{34}O_5SN$ 496.2158, found 496.2152

(3S,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl acetate (A1)

Standard procedure for **1**, using: **A9** (4.3 g, 9.87 mmol), pyridine (29.4 ml) and acetic anhydride (19.6 ml). Yield: 1.0 g, 2.0 mmol, 21%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.38 – 7.22 (m, 15H; Ar), 5.72 (d, J = 3.6 Hz, 1H; H1), 4.68 – 4.47 (m, 6H; CH_2Bn), 4.06 (dd, J = 3.4, 2.4 Hz, 1H; H2), 4.03 (td, J = 4.7, 4.1, 3.0 Hz, 1H; H4), 3.70 (dd, J = 4.6, 2.4 Hz, 1H; H3), 3.29 (dd, J = 12.9, 10.4 Hz, 1H; H5), 2.43 (dd, J = 12.9, 3.4 Hz, 1H; H5), 1.98 (s, 3H; CH_3- OAc). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.99(C_q-OAc), 138.63 (C_q-Ar), 138.46 (C_q-Ar), 137.69 (C_q-Ar), 128.57 (CH-Ar), 128.49(CH-Ar), 128.32 (CH-Ar), 128.04 (CH-Ar), 127.88 (CH-Ar), 127.74 (CH-Ar), 127.64 (CH-Ar), 127.58 (CH-Ar), 127.49 (CH-Ar), 76.59 (C3) , 76.46 (C4), 74.74(C2),

73.04 (CH_2Bn) , 72.92 (CH_2Bn), 72.31 (C1), 71.02 (CH_2Bn), 23.34(C5), 21.22 (CH_3-OAc). IR (thin film, cm^{-1}): 3030, 2896, 1734 (C=O), 1453, 1223, 1087, 1073, 1016, 733, 695. HRMS: [M + Na] calcd for $C_{28}H_{30}O_5SNa$ 501.1712, found 501.1706; [M + NH_4]$^+$: calcd for $C_{28}H_{34}O_5SN$ 496.2158, found 496.2152

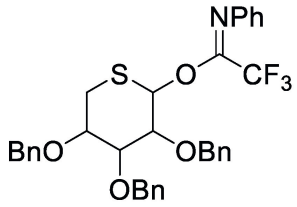
(3R,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl acetate (X1)

Standard procedure for **1**, using: **X9** (4.79 g, 10.97 mmol), pyridine (33.0 ml) and acetic anhydride (22.0 ml). Yield: 2.2 g, 4.6 mmol, 60%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.36 – 7.25 (m, 15H; CH-Ar), 6.10 – 6.07 (m, 1H; H1 maj), 5.80 (d, J = 8.7 Hz, 1H; H1 min), 4.80 – 4.66 (m, 4H; CH_2Bn), 4.60 (d, J = 11.3 Hz, 2H; CH_2Bn), 3.83 – 3.71 (m, 3H; H2 - H3 - H4), 2.95 – 2.85 (m, 1H; H5), 2.69 – 2.62 (m, 1H; H5), 2.15 (s, 3H; -OMe maj), 1.98 (s, 1H; -OMe min). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.71 (C_q- OAc), 138.87 (C_q-Ar), 138.24 (C_q-Ar), 137.78 (C_q-Ar), 128.62 (CH-Ar), 128.56 (CH-Ar), 128.44 (CH-Ar), 128.26 (CH-Ar), 128.18 (CH-Ar), 128.00 (CH-Ar), 127.98 (CH-Ar), 127.72 (CH-Ar), 85.01 (C2 min), 84.21(C3 min) , 83.08 (C2 maj), 82.39 (C3 maj), 81.73 (C4 maj), 81.42 (C4 min), 76.58 (CH_2Bn), 74.01 (C1 min), 73.32 (CH_2Bn), 73.01 CH_2Bn), 71.03 (C1 maj), 28.26 (C5 min), 26.90 (C5 maj), 21.28 (CH_3-OAc maj), 20.94 (CH_3-OAc min). IR (thin film, cm^{-1}): 3031, 2870, 1764 (C=O), 1497, 1454, 1369, 1214, 1066, 1027, 735, 696. HRMS: [M + Na] calcd for $C_{28}H_{30}O_5SNa$ 501.1712, found 501.1706; [M + NH_4] calcd for $C_{28}H_{34}O_5SN$ 496.2158, found 496.2152

(3S,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl acetate (L1)

Standard procedure for **1**, using: **L9** (4.03 g, 9.24 mmol), pyridine (27.7 ml) and acetic anhydride (18.5 ml). Yield: 9.5 g, 19.95 mmol, 95%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.38 – 7.27 (m, 15H; Ar), 6.11 – 6.06 (m, 1H; H1), 4.85 (s, 2H; CH_2Bn), 4.79 – 4.57 (m, 4H; CH_3Bn), 3.83 – 3.70 (m, 3H; H2-H3-H4), 2.94 – 2.87 (m, 1H; H5), 2.68 – 2.62 (m, 1H; H5), 2.16 (s, 3H; CH_3-OAc). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.76 (C_q-OAc), 138.89 (C_q-Ar), 138.26 (C_q-Ar), 137.81 (C_q-Ar), 128.65 (CH_2Bn), 128.59 (CH_2Bn), 128.48 (CH_2Bn), 128.29 (CH-Ar), 128.22 (CH-Ar), 128.18 (CH-Ar), 128.03 (CH-Ar), 128.01 (CH-Ar), 127.75 (CH-Ar), 83.11 (C2), 82.42 (C3), 81.76 (C4), 76.62 (CH_2Bn), 73.37 (CH_2Bn), 73.04 (CH_2Bn), 71.06 (C1), 26.93 (C5), 21.32 (CH_3-OAc). IR (thin film, cm^{-1}): 3031, 2868, 1745 (C=O), 1454, 1369, 1214, 1068, 912, 736, 697. HRMS: [M + Na] calcd for $C_{28}H_{30}O_5SNa$ 501.1712, found 501.1706; [M + NH_4]$^+$: calcd for $C_{28}H_{34}O_5SN$ 496.2158, found 496.2152

Standard procedure for 3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl (E)-2,2,2-trifluoro-*N*-phenylacetimidate (2)



9 and cesium carbonate were dissolved in acetone. 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride was added and the reaction was stirred at room temperature for 16 hours. The reaction mixture was filtered over a pad of celite and concentrated in vacuo. The product was isolated using column chromatography after neutralizing the silica with triethylamine solution (pentane: triethylamine =90/10) (eluent: ethyl acetate/pentane= 1/99-10/90) yielding **2**.

(3R,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl (E)-2,2,2-trifluoro-*N*-phenylacetimidate (R2)

Standard procedure for **2**, using: **R9** (0.57 g, 1.03 mmol). Cesium carbonate (0.5 g, 1.55 mmol, 1.5 eq.). Acetone (6.6 ml). 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (0.25 ml, 1.55 mmol, 1.5 eq.). Yield: 0.33 g, 0.56 mmol, 54%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.57 – 7.51 (m, 2H; CH-Ar), 7.47 – 7.25 (m, 13H; CH-Ar), 7.30 – 7.12 (m, 3H; CH-Ar), 7.11 – 7.05 (m, 1H; CH-Ar), 6.83 – 6.74 (m, 1H; CH-Ar), 6.10 (d, J = 4.3 Hz, 1H; H1), 4.79 – 4.70 (m, 2H; CH_2Bn), 4.70 – 4.64 (m, 2H; CH_2Bn), 4.50 – 4.47 (m, 2H; CH_2Bn), 4.32 – 4.25 (m, 2H; H2-H4), 3.93 (dd, J = 9.2, 6.0 Hz, 1H; H5), 3.78 (ddd, J = 7.7, 6.0, 4.9 Hz, 1H; H3), 3.66 (dd, J = 9.2, 7.6 Hz, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.64 (C_q-imid.), 138.10 (C_q-Ar-imid.), 138.05 (C_q-Ar-imid.), 137.65 (C_q-Ar-imid.), 135.18 (C_q-Ar-imid.), 129.45 (CH-Ar), 128.78 (CH-Ar), 128.58 (CH-Ar), 128.50 (CH-Ar), 127.93 (CH-Ar), 127.80 (CH-Ar), 127.72 (CH-Ar), 126.48 (CH-Ar), 124.32 (CH-Ar), 120.66 (CH-Ar), 119.56 (CH-Ar), 85.03 (C1), 84.72 (C4), 79.21 (C2), 73.71 (CH_2Bn), 73.45 (CH_2Bn), 72.90 (CH_2Bn), 70.63 (C5), 46.41 (C3) IR (thin film, cm^{-1}): 3030,1716 (C=N),1600, 1497,1453, 1153,1072, 910, 733, 697. HRMS: [M + Na] calcd for $C_{34}H_{32}F_3NO_4SNa$: 630.192, found 630.1896

(3S,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl (E)-2,2,2-trifluoro-*N*-phenylacetimidate (A2)

Standard procedure for **2**, using: **A9** (0.30 g, 0.72 mmol). Cesium carbonate (0.35 g, 1.08 mmol, 1.5 eq.). Acetone (4.6 ml). 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (0.18 ml, 1.08 mmol, 1.5 eq.). Yield: 0.25 g, 0.42 mmol, 58%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.55 (d, J = 8.1 Hz, 1H; H1 min), 7.43 – 7.25 (m, 19H; Ar), 7.14 – 6.98 (m, 1H; Ar), 6.74 – 6.72 (m, 1H; H1 maj), 4.82 – 4.61 (m, 6H; CH_2Bn),

4.33 (d, J = 9.5 Hz, 1H; H3), 4.17 – 4.06 (m, 1H; H2), 3.84 (dd, J = 9.7, 2.9 Hz, 1H; H4), 2.93 (d, J = 14.2 Hz, 1H; H5), 2.64 (dd, J = 14.4, 4.6 Hz, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.90 (C_q-imid.), 143.21 (C_q-Ar-imid.), 138.74 (C_q-Ar), 138.44 (C_q-Ar), 138.29 (C_q-Ar), 130.46 (C_q-F_3), 129.52 (CH-Ar), 128.85 (CH-Ar), 128.52 (CH-Ar), 128.45 (CH-Ar), 128.02 (CH-Ar), 127.96 (CH-Ar), 127.84 (CH-Ar), 127.75 (CH-Ar), 127.71 (CH-Ar), 127.60 (CH-Ar), 126.52 (CH-Ar), 120.58 (C1 min), 119.57 (C1 maj), 78.86 (C2), 78.09 (C3), 74.70 (C4), 73.90 (CH_2Bn), 73.02 (CH_2Bn), 71.97 (CH_2Bn), 28.34 (C5). IR (thin film, cm^{-1}): 3030,1716 (C=N),1600, 1497,1453, 1153,1072, 910, 733,697. HRMS: $[M + Na]^+$: calcd for $C_{34}H_{32}F_3NO_4SNa$: 630.192, found 630.1896

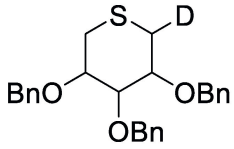
(3R,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl (E)-2,2,2-trifluoro-*N*-phenylacetimidate (X2)

Standard procedure for **2**, using: **X9** (0.30 g, 0.66 mmol). Cesium carbonate (0.32 g, 0.99 mmol, 1.5 eq.). Acetone (4.2 ml). 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (0.32 ml, 2.03 mmol, 1.5 eq.). Yield: 0.21 g, 0.35 mmol, 53%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.40 – 7.22 (m, 20H; Ar), 6.28 – 6.20 (m, 1H; H1 maj), 6.03 – 5.96 (m, 1H; H1 min), 4.89 – 4.66 (m, 6H; CH_2Bn), 3.92 – 3.82 (m, 2H; H2-H3), 3.76 (ddd, J = 11.1, 8.5, 4.4 Hz, 1H; H4), 2.94 (dd, J = 13.4, 11.2 Hz, 1H; H5), 2.66 (ddd, J = 13.3, 4.4, 1.4 Hz, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.78 (C_q-imid.), 143.78 (C_q-Ar-imid.), 138.83 (C_q-Ar), 138.22 (C_q-Ar), 138.05 (C_q-Ar), 135.18 (C_q-F_3) , 129.44 (CH-Ar), 128.86 (CH-Ar), 128.61 (CH-Ar), 128.56 (CH-Ar), 128.44 (CH-Ar), 128.24 (CH-Ar), 128.02 (CH-Ar), 127.99 (CH-Ar), 127.91 (CH-Ar),127.68 (CH-Ar), 126.49 (CH-Ar), 120.68 (C1), 83.31 (C2), 82.27 (C3), 81.59 (C4), 76.64 (CH_2Bn), 73.36 (CH_2Bn), 73.08 (CH_2Bn), 26.93 (C5). IR (thin film, cm^{-1}): 3030,1716 (C=N),1600, 1497,1453, 1153,1072, 910, 733,697. HRMS: [M + Na] calcd for $C_{34}H_{32}F_3NO_4SNa$ 630.192, found 630.1896.

(3S,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-yl (E)-2,2,2-trifluoro-*N*-phenylacetimidate (L2)

Standard procedure for **2**, using: **L9** (0.59 g, 1.35 mmol). Cesium carbonate (0.66 g, 2.03 mmol, 1.5 eq.). Acetone (8.6 ml). 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (0.32 ml, 2.03 mmol, 1.5 eq.). Yield: 0.8 g, 1.32 mmol, 97%. 1H NMR (400 MHz, chloroform-d) δ 7.51 – 7.04 (m, 20H; Ar), 5.91 – 5.84 (m, 1H; H1), 4.86 – 4.61 (m, 6H; CH2Bn), 4.18 – 4.09 (m, 1H; H2), 4.04 – 3.97 (m, 1H; H3), 3.72 (d, J = 9.1 Hz, 1H; H4), 2.84 (d, J = 10.6 Hz, 1H; H5), 2.79 – 2.72 (m, 1H; H5). 13C NMR (101 MHz, CDCl3) δ 182.12(Cq-imid.), 138.55(Cq-Ar-imid.), 138.24 (Cq-Ar), 138.08 (Cq- Ar), 137.98 (Cq-Ar), 137.86 (Cq-F3), 129.55 (CH-Ar), 129.30 (CH-Ar), 128.89 (CH-Ar), 128.87 (CH-Ar), 128.30 (CH-Ar), 128.20 (CH-Ar), 128.00 (CH-Ar), 127.88(CH-Ar), 127.72 (CH-Ar), 120.77(CH-Ar), 119.46 (C1), 83.33 (C2), 82.30 (C3), 81.62 (C4), 74.15 (CH2Bn), 73.41 (CH2Bn), 73.12 (CH2Bn), 28.01 (C5). IR (thin film, cm-1): 3030,1716 (C=N),1600, 1497,1453, 1153,1072, 910, 733,697. HRMS: [M + Na] calcd for $C_{34}H_{32}F_3NO_4SNa$ 630.192, found 630.1896.

Standard procedure for 3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-d (10)



The donor (1eq.) was co-evaporated in dry toluene for three times, dissolved in dry DCM and stirred with freshly activated molecular sieves (4Å) at room temperature for 1 hour under nitrogen atmosphere. The solution was then cooled The acceptor (5 eq.) was added. The activator TMSOTf (0.5 eq.) was added and the reaction mixture was stirred till product formation. The reaction was quenched upon addition of triethylamine. The reaction mixture was filtered through a pad of celite and concentrated in vacuo.The product was isolated using column chromatography (eluent: ethylacetate / pentane= 1/99 – 5/95).

(3R,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-d (R10)

Standard procedure for **10**, using **R2** (0.08 g; 0.13 mmol), the acceptor triethyl(silane-d) (0.08 g; 0.65 mmol), TMSOTf (0.1 ml; 0.05 mmol) and DCM (5 ml) was started at -78 °C and performed in 3 days at -30 °C. Column chromatography (eluent: ethyl acetate/pentane= 1/99 – 5/95) yielded the title compound (0.040 g, 0.095 mmol, 73%, α:β = 98 : 2 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.27 (m, 15H), 4.93 – 4.80 (m, 2H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.65 – 4.51 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 3.78 (d, *J* = 1.6 Hz, 1H), 3.56 (ddt, *J* = 9.7, 4.0, 1.9 Hz, 1H), 3.03 (dd, *J* = 12.7, 11.2 Hz, 1H), 2.44 (d, *J* = 4.0 Hz, 1H), 2.41 (d, *J* = 3.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.59, 138.86, 138.43, 138.13, 136.75, 135.18, 129.46, 128.62, 128.58, 128.55, 128.26, 128.22, 128.09, 127.90, 127.87, 127.77, 127.68, 127.63, 127.54, 127.50, 127.36, 126.50, 120.68, 114.40, 80.35, 80.29, 76.69, 74.23, 73.79, 71.01, 70.86, 69.82, 29.82, 25.53. IR (neat): 2902, 2895, 2256,1494, 1430, 1317, 12, 1026, 1016, 912 cm^{-1}. HRMS $[M + Na]^+$: calcd for $C_{26}H_{27}DO_3SNa$: 444.1720, found 444.1721.

(3S,4R,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-d (A10)

Standard procedure for **10**, using **A2** (0.07 g; 0.11 mmol), the acceptor triethyl(silane-d) (0.06 g; 0.5 mmol), TMSOTf (0.1 ml; 0.05 mmol) and DCM (5 ml) was started at -78 °C and performed in 3 days at -30 °C. Column chromatography (eluent: ethyl acetate/pentane= 1/99 – 5/95) yielded the title compound (0.03 g, 0.07 mmol, 65%, α:β = 18 : 82). ^{1}H NMR (400 MHz, Chloroform-d) **δ** 7.37 – 7.24 (m, 15H; Ar), 4.78 – 4.46 (m, 6H; CH_2Bn), 4.04 (ddd, J = 9.8, 3.4, 2.3 Hz, 1H; H4), 3.90 (dd, J = 5.7, 2.5 Hz, 1H; H2), 3.67 (dd, J = 5.8, 2.2 Hz, 1H; H3), 3.07 – 2.96 (m, 2H; H1- $H5_{ax}$), 2.49 (dd, J = 12.8, 3.2 Hz, 1H; $H5_{eq}$), 2.41 (d, J = 4.9 Hz, H1 trans). ^{13}C NMR (101 MHz, $CDCl_3$) **δ** 138.87 (C_q-Ar), 138.69 (C_q-Ar), 138.32 (C_q-

Ar), 128.56 (CH-Ar), 128.51 (CH-Ar), 128.44 (CH-Ar), 127.86 (CH-Ar), 127.84 (CH-Ar), 127.81 (CH-Ar), 127.71 (CH-Ar), 127.69 (CH-Ar), 77.09 (C3), 75.95 (C4), 75.69 (C2), 73.43 (CH_2Bn), 71.44 (CH_2Bn), 71.19 (CH_2Bn), 26.87 (C5). IR (neat): 2902, 2895, 2256,1494, 1430, 1317, 12, 1026, 1016, 912 cm^{-1}. HRMS $[M + Na]^+$: calcd for $C_{26}H_{27}DO_3SNa$: 444.1720, found 444.1714.

(3R,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-d (X10)

Standard procedure for **10**, using **X2** (0.08 g; 0.13 mmol), the acceptor triethyl(silane-d) (0.08 g; 0.65 mmol), TMSOTf (0.1 ml; 0.07 mmol) and DCM (6.5 ml) was started at -78 °C and performed in 2 days at -30 °C. Column chromatography (eluent: ethyl acetate/pentane= 1/99 – 5/95) yielded the title compound (0.03 g, 0.071 mmol, 55%, α:β = 98 : 2). ^{1}H NMR (400 MHz, Chloroform-d) **δ** 6.87 – 6.71 (m, 15H; Ar), 4.27 – 4.13 (m, 6H; CH_2Bn), 3.16 (ddd, J = 11.0, 9.0, 4.4 Hz, 2H; H2-H4), 2.84 (t, J = 9.0 Hz, 1H; H3), 2.27 – 2.21 (m, 2H; H1-$H5_{eq}$), 2.00 (dd, J = 13.7, 11.0 Hz, 1H; $H5_{ax}$). ^{13}C NMR (101 MHz, $CDCl_3$, major anomer - Cis) **δ** 138.99 (C_q-Ar), 138.46 (C_q-Ar), 128.57 (CH-Ar), 128.44 (CH-Ar), 128.21 (CH-Ar), 127.96 (CH-Ar), 127.87 (CH-Ar), 127.67 (CH-Ar), 86.85 (C3), 82.29 (C2), 82.29 (C4), 73.16 (CH_2Bn), 73.16 (C5), 31.25 (C1). IR (neat): 2902, 2895, 2256, 1494, 1430, 1317, 1298, 1026, 1016, 912 cm^{-1}. HRMS $[M + Na]^+$: calcd for $C_{26}H_{27}DO_3SNa$: 444.1720, found 444.1714.

(3S,4S,5S)-3,4,5-tris(benzyloxy)tetrahydro-2H-thiopyran-2-d (L10)

Standard procedure for **10**, using **L2** (0.06 g; 0.13 mmol), the acceptor triethyl(silane-d) (0.07 g; 0.7 mmol), TMSOTf (0.1 ml; 0.07 mmol) and DCM (6.5 ml) was started at -78 °C and performed in 2 days at -30 °C. Column chromatography (eluent: ethyl acetate/pentane= 1/99 – 5/95) yielded the title compound (0.06 g, 0.1 mmol, 60%, α:β = 2 : 98). ^{1}H NMR (400 MHz, Chloroform-d) **δ** 7.36 – 7.25 (m, 15H; Ar), 4.78 – 4.45 (m, 6H; CH_2Bn), 3.92 – 3.88 (m, 1H; H2 – H4 trans), 3.66 (tt, J = 8.8, 3.9 Hz, 2H; H2 – H 4 cis), 3.33 (t, J = 8.9 Hz, 1H; H3), 2.77 – 2.70 (m, 2H; H1 – H5), 2.50 (dd, J = 13.4, 11.1 Hz, 1H; H5). ^{13}C NMR (101 MHz, $CDCl_3$) **δ** 138.98 (C_q-Ar), 138.45 (C_q-Ar), 135.20 (C_q-Ar), 129.47 (CH-Ar), 128.56 (CH-Ar), 128.49 (CH-Ar), 128.43 (CH-Ar), 128.19 (CH-Ar), 127.95 (CH-Ar), 127.86 (CH-Ar), 127.66 (CH-Ar), 126.50 (CH-Ar), 86.83 (C3), 82.34 (C4), 82.28 (C2), 76.46 (CH_2Bn), 73.14 (CH_2Bn), 31.54 (C5), 31.23 (C1). IR (neat):, 2902, 2896, 2256, 1494, 1430, 1317, 1298, 1026, 1016, 912 cm^{-1}. HRMS $[M + Na]^+$: calcd for $C_{26}H_{27}DO_3SNa$: 444.1720, found 444.1714.

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