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Design and Synthesis of 2-Acetamido-2,3-dideoxythiodisaccharides via Diastereoselective Conjugate Addition to Sugar Enone *O*-Acetyl Oximes. Galactosidase Inhibition Studies

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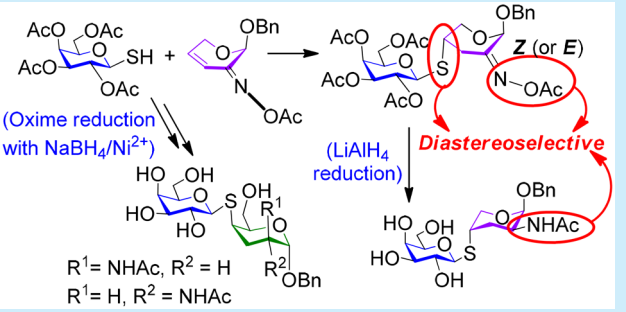
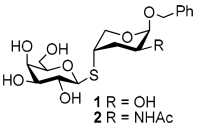
Supporting Information

ABSTRACT: The key step in a new synthesis of 2-acetamido-2,3-dideoxy-(1→4)-thiodisaccharides was the conjugate addition of a 1-thiogalactose derivative to *E* and *Z* acetyl oximes derived from sugar enones. This reaction was shown to be completely diastereoselective for both the formation of the thioglycosidic linkage and the configuration of acetyl oxime. The thiodisaccharides have been designed as inhibitors of the *β*-galactosidase from *E. coli*, and they have been shown to successfully meet such requirements.



Thiodisaccharides, a class of glycomimetics with an interglycosidic sulfur atom, are usually resistant to cleavage of the glycosidic bond by glycosidases. Therefore, there is considerable interest in these carbohydrate mimetics as useful tools in glycobiology due to their stability to enzymatic degradation and also for their potential to act as glycosidase inhibitors.[1] In addition, thiodisaccharides and their derivatives are being investigated as anticancer therapeutics.[2] Thus, molecules bearing the thio-sugar motif, mostly (1→4)-*S*-thiodisaccharides,[3] have been included within the so-called "functional CARB-pharmacophores" for the antineoplastic activity, recently proposed by Witczak and co-workers.[4]

The varied biological activities of thiodisaccharides and their use in glycobiology, mostly for the study of the carbohydrate−protein interactions,[5] has stimulated a great deal of investigations into their synthesis.[6] In this regard, in our laboratory we have developed straightforward and highly diastereoselective procedures for the synthesis of thiooligosaccharides containing furanose[7] or pyranose units.[8−10] The main key reactions for the construction of the thioglycosidic linkage have involved using 1-thioaldose derivatives as nucleophiles for the conjugate addition to sugar enones[8] and for the ring-opening of sugar epoxides[9] or sugar thiiranes.[10] A number of thiodisaccharides so obtained exhibited inhibitory activity against glycosidases. Among them, benzyl 3-deoxy-4-*S*-(*β*-D-galactopyranosyl)-4-thio-*β*-D-*threo*-pentopyranoside (**1**) showed itself to be a potent inhibitor of the *β*-galactosidase from *E. coli* (K_i = 32 *μ*M).[8c] Interestingly, a change in the configuration at C-2 in the pentose to D- led to a 25-fold decrease in the inhibition constant. The molecular basis of the inhibition has been studied by combining NMR spectroscopy and molecular modeling techniques.[11] This work provided experimental evidence that the flexibility of the dideoxypentose facilitates accommodation of the inhibitor into the active site of the enzyme. This work also showed that some amino acids at this site were involved in interactions with OH-2 and the phenyl group of **1**. Therefore, it should be expected that any modification at the C-2 stereocenter of the pentopyranose should affect the inhibitory activity of the resulting molecule.



We took into account the previous observations in the design of thiodisaccharide **2**, an analogue of **1** obtained by replacing OH-2 by a NHAc group. As a general procedure for the introduction of an amino function at C-2 and to generate the thioglycosidic linkage, we have developed the successful conjugate addition of 1-thio-*β*-D-galatopyranose derivative to an *α*,*β*-unsaturated *O*-acetyl oxime derived from a sugar enone. This reaction led to a convenient precursor of **2**. To evaluate the applicability of the procedure for the preparation of analogous thiodisaccharides having a 2-acetamido-2,3-dideoxy-4-thiohexopyranose unit at the reducing end, herein various molecules of this type have been synthesized. Studies on the kinetics of galactosidase inhibition for the unprotected thiodisaccharides have also been conducted.

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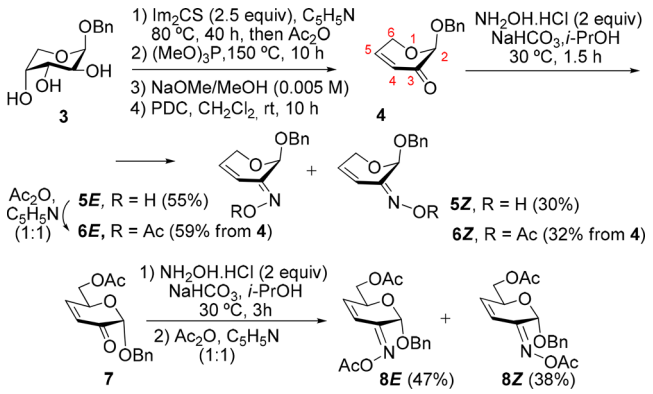
The target thiodisaccharides were synthesized starting from α,β-unsaturated ketoximes as Michael acceptors. The ketoximes were obtained by oximation of pyranones derived from pentoses or hexoses. A straightforward procedure for the preparation of such pyranones is the Lewis acid promoted glycosylation of 2-(acyloxy)glycals.[12] These compounds, when prepared from pentoses, lead to partially racemic enones. However, enantiomeric purity may be achieved by using a chiral alcohol[12] or, alternatively, a multistep procedure starting from benzyl β-D-arabinopyranoside (**3**).[13] We chose this last option since we wanted to keep the benzyloxy group, which is relevant for the interaction with the enzyme[11] (Scheme 1).

Scheme 1. Synthesis of Diastereomeric Acetyl Ketoximes from Pyranones

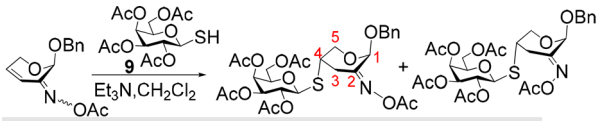


The enone **4** was treated with hydroxylamine to afford the diastereomeric mixture of oximes **5*Z*** and **5*E***, which were separated by SiO_2 column chromatography (85% overall yield, ratio **5*E*:5*Z*** ≈ 1.8:1). Acetylation of **5*E*** and **5*Z*** gave the corresponding acetyl oximes **6*E*** and **6*Z***, respectively. No isomerization was observed during the acetylation reaction. Alternatively, **6*E*** and **6*Z*** (ratio **6*E*:6*Z*** ≈ 1.8:1) were obtained in a slightly higher overall yield (91%) by direct acetylation of the crude mixture of **5*E*,*Z*** obtained from **4**. The configuration of the oximes was established by comparison of their ^{1}H and ^{13}C NMR chemical shifts in $CDCl_3$ with respect to those of the precursor enone. Thus, as already reported,[14] the proton vicinal to the oxime (H-2 or H-4) which is *syn* to the oxime hydroxyl or acetoxy group (H-2 in **5*Z*** and **6*Z***) is more strongly deshielded than the *anti* proton (H-4 in **5*Z*** and **6*Z***); therefore, the *Z* configuration was assigned to **5*Z*** and **6*Z*** (see Table S1). Similar stronger deshielding of H-4 in **5*E*** and **6*E*** suggested the *E* configuration for these compounds. In addition, in the ^{13}C NMR spectra, the signal of the carbon vicinal to the oxime (C-2 or C-4) which is *syn* to the oxime acetoxy group undergoes a stronger upfield shifting.[15] This effect was also observed for compounds **8*E*** and **8*Z***, supporting the configurational assignments based on the ^{1}H NMR spectra. Finally, the configuration of **6*E*** and **8*E*** was further confirmed by a diagnostic cross-peak in their NOESY spectra between H-4 and the methyl group of the acetyl oxime.

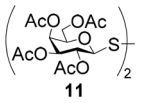
On the other hand, acetyl oxime analogues of **6*E*,*Z*** have been prepared from the pyranone **7**[16] derived from D-galactose. Thus, oximation of **7** followed by acetylation, under the reaction conditions previously employed, led to acetyl oximes **8*E*** and **8*Z*** (85% overall yield, ratio **8*E*:8*Z*** 1.2:1). The configuration of the oxime was determined according to the NMR data, as already described for **5*E*,*Z*** and **6*E*,*Z*** (Table S1).

The attempted conjugate addition of the thioaldose derivative **9** to the oximes **5*E*** and **5*Z*** was unsuccessful. In contrast, the *O*-acetyl derivatives **6*E*** and **6*Z*** showed themselves to be convenient Michael acceptors of 1-thio-D-galactopyranose derivative **9** to afford the thiodisaccharides **10*E*** and **10*Z*** (Scheme 2). The anomeric configuration of the thioaldose **9** was maintained during the conjugate addition, which took place under strict anomeric stereocontrol.

Scheme 2. Diastereoselective Synthesis of Acetyl Oxime Thiodisaccharides 10*E* and 10*Z*

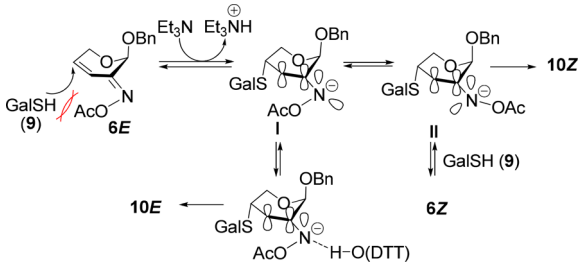


acetyl oxime	reaction conditions	**10*Z***(%)	**10*E***(%)
6*E*	−18 °C, 2.5 h	61	
6*Z*	−18 °C, 2.5 h	91	
6*E*	DTT, −18 °C, 6 h		31
6*E*	DTT, 35 °C, 3 h		70
6*Z*	DTT, 35 °C, 1.5 h		87



Thus, the thiosugar **9** approached to C-5 of the enone from the *Re* face, opposite to that containing the axially oriented (anomeric effect) benzyloxy substituent. The configuration of the sulfur-containing stereocenter (C-4) was determined from the ^{1}H NMR spectra, according to the small coupling constant values observed (2.1−5.4 Hz) between H-4 and both vicinal methylene groups (at C-3 and C-5). Interestingly, the conjugate addition of **9** to acetyl oxime **6*E***, at low temperature, afforded the thiodisaccharide **10*Z*** with a change of the oxime configuration, although in a moderate yield (61%). Longer reaction times produced increasing formation of the disulfide **11** formed by oxidation of **9**, and the yield could not be improved. Under the same reaction conditions, the conjugate addition of **9** to acetyl oxime **6*Z*** afforded an excellent yield of **10*Z*** (91%), with retention of the configuration of the oxime. The highly diastereoselective formation of the *Z*-oxime in the preparation of **10** could be explained taking into account the species formed during the conjugate addition (Scheme 3).

Scheme 3. Proposed Mechanism for the Diastereoselective Formation of 10*E* and 10*Z*



Thus, starting from **6*E*** the crowdedness generated in the initial intermediate **I** by incorporation of the bulky RSH substituent could be released by rotation of the C−N bond to give **II**, the precursor of **10*Z***. As it is expected that one of the lone electron pairs of N is involved in the conjugation of the enamine system, in both intermediates **I** and **II**, the *N*-acetoxy group should be located below the plane of the ring, opposite to that containing the benzyloxy substituent. The hindrance of the

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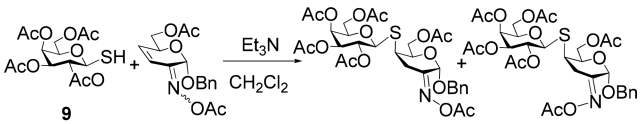
oxime acetoxy group could also be the reason for the lower yield in the formation of **10*Z*** from **6*E***, compared to that obtained from **6*Z***.

To prevent the formation of the disulfide **11**, the conjugate addition was conducted in the presence of 1,4-dithiothreitol (DTT), which is widely used to avoid the oxidation of thiols.[6,10] Starting from **6*E***, under the same reaction conditions previously employed, the yield of **10*E*** was even lower, although the *E* configuration of the acetyl oxime was maintained. Interestingly, **10*Z*** isomerizes to the *E* form in the presence of DTT. The yield of **10*E*** was low (~30%) when the reaction was conducted at −18 °C but increased to 87% by raising the temperature to 35 °C. This isomerization is difficult to rationalize, but probably the intermediate **I** could be stabilized through hydrogen bonding with the protic species DTT, locating this bulky molecule far from the thioglycosidic substituent. It is worth mentioning that all of the thioglycosylations were highly diastereoselective in the formation of one of the acetyl oximes, while the other was not appreciably detected. Unreacted starting material and the disulfide **11** were the other components of the reaction mixtures.

The previous results showed that the conjugate addition of **9** to acetyl oximes **6*E*** or **6*Z*** was completely diastereoselective for both the formation of the new stereocenter of C-4 and the configuration of the oximes. Thus, thiodisaccharides **10*E*** or **10*Z*** were obtained in yields of about 90%, under optimized conditions. The alternative procedure for the preparation of thiodisaccharide oximes, involving the oximation of the 2-keto thiodisaccharide precursor of **10**, led to less satisfactory results, as the overall yields were lower (~60%) probably due to the retro-Michael reaction promoted for the alkaline medium (oximes **6*E,Z*** were isolated from the reaction mixture). Furthermore, no diastereoselectivity in the formation of **10*E,Z*** (ratio **10*Z***:**10*E*** ~ 2:1) was observed.

The conjugate addition of 1-thio-D-galactopyranose (**9**) to the acetyl oximes **8*E*** and **8*Z*** was also conducted (Scheme 4). As for

Scheme 4. Diastereoselective Synthesis of Thiodisaccharide Acetyl Oximes 14*E* and 14*Z*



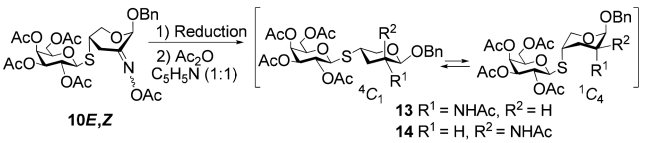
acetyl oxime	reaction conditions	**12*Z*** (%)	**12*E*** (%)
8*E*	20 °C, 24 h	73	
8*Z*	−18 °C, 2.5 h	93	
8*E*	DTT, 35 °C, 2.5 h		59
8*Z*	DTT, 35 °C, 2.5 h		87

the pentopyranones **6*E*** and **6*Z***, excellent diastereofacial selectivity was observed for the approach of the thiosugar **9** from the opposite side to the benzyloxy group. The small value of the coupling constants of H-4 with H-3ax, H-3eq and H-5 confirmed the D-*threo* configuration for the reducing end of both **12*Z*** and **12*E***. Moreover, the Michael addition of **9** to oxime **8*Z*** gave high yields of thiodisaccharide unlike that obtained from **8*E***, both in the absence or presence of DTT.

The stereochemical course of the addition of **9** to **8*E*** or **8*Z*** was identical to that shown by oximes **6*E*** and **6*Z*** in the analogous reaction. Thus, both **8*E*** or **8*Z*** reacted with **9** in the absence of DTT to give **12*Z*** diastereoselectively, while in the presence of DTT only **12*E*** was obtained. As previously explained, the configurational assignments for the oximes derivatives **12*Z*** and **12*E*** was done on the basis of characteristic chemical shifting of selected signals in the NMR spectra of the oxime compared with those of the 2-ketothiodisaccharide.[8a]

The reduction of the acetyl oxime group of **10*E,Z*** to the corresponding acetamide was attempted using several reducing agents and reaction conditions. The crude product of the reduction reaction was immediately subjected to acetylation to afford the corresponding acetamide. As shown in Scheme 5,

Scheme 5. Reduction of Thiodisaccharide Acetyl Oxime 10*E,Z*



reducing agent (equiv)	solvent	temp (°C)	yield **13** + **14**(%)	ratio **13**:**14**
$NaBH_4$ (4.6), I_2 (1.8)	THF	55	87	1.2:1.0
$NaBH_4$ (10), $NiCl_2.6H_2O$ (4)	MeOH	−18 to rt	63	1.0:4.8
BH_3 (3)	THF	−10	53	1.0:20
$LiAlH_4$ (11)	THF	−18 to 0	35	0:1.0

most of the reactions led to a diastereomeric mixture of the thiodisaccharides **13** and **14**, having opposite configuration at C-2. This mixture could not be separated by SiO_2 chromatography using varied solvent systems.

The reduction of **10*E,Z*** with $NaBH_4/I_2$ gave a very good yield (87%) when performed at 55 °C for 2 h. However, under these conditions, practically no diastereoselectivity was observed. Unfortunately, the yield dropped dramatically by lowering the reaction temperature. Other reducing agents ($NaBH_4$−$NiCl_2$ or BH_3) allowed lower temperatures to be used, but the yields were moderate, and also diastereoisomeric mixtures were obtained. Among the reducing agents explored, only $LiAlH_4$/THF (at −18 °C) led diastereoselectively to the desired thiodisaccharide **14**, although the reduction required a long time and the yield was moderate. Most of the unreacted starting **10*E,Z*** could be recovered and subjected to a second cycle of reduction, increasing the yield of **14** to about 70%. The reduction performed starting from **10*Z*** or **10*E*** gave practically the same results as those obtained from the mixture **10*E,Z*** (see Table S2).

The configuration of the C-2 stereocenter in **14** was assigned according to coupling constant values obtained from the ^1H NMR spectrum. To do this, the preferential conformation of the pentapyranoside ring was evaluated. The relatively small *J* values for the coupling of H-4 ($J \approx 4.5$ Hz) with the vicinal methylene groups were indicative of a substantial contribution of the $^1C_4$ conformation in the equilibrium. Then the relatively large *J* value for $J_{2,3a}$ (10 Hz) and small *J* values for $J_{1,2}$ and $J_{2,3b}$ (3.1 and 4 Hz, respectively) suggested an equatorial disposition for the NHAc substituent at C-2 and, hence, a *β*-D-threo configuration for the pentopyranose unit of **14**. A similar analysis performed for the diastereoisomer **13** revealed a substantial contribution of both conformers $^1C_4$ and $^4C_1$ to the equilibrium and indicated the *β*-D-*erythro* configuration for the pentopyranose ring of **13**.

The reduction of the acetyl oxime function of **12*E,Z*** was performed with $NaBH_4$ in the presence of iodine or $NiCl_2{\cdot}6H_2O$ followed by acetylation (Scheme 6). The former reagent gave a better overall yield, although no diastereoselectivity was observed. Thus, both oximes **12*E*** or **12*Z*** gave an ~1:1 ratio of the corresponding 2-acetamido-2-deoxythiodisaccharides having the *α*-D-*lyxo* (**15**) or *α*-D-*xylo* (**16**) configuration for

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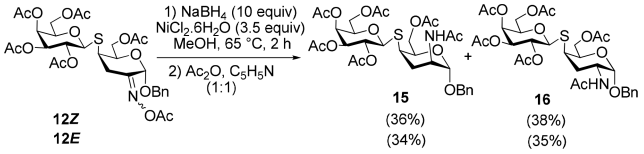
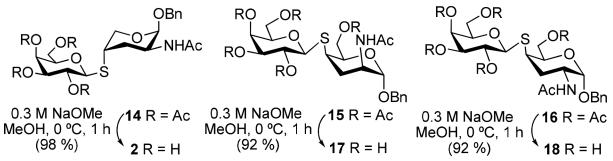
Scheme 6. Reduction of Acetyl Oxime Thiodisaccharides 12*E* and 12*Z*



the reducing end. The configuration at C-2 was established according to the relatively small coupling constant values observed for the H-2 signal ($J_{1,2}$, $J_{2,3eq}$ < 1 Hz, $J_{2,3ax}$ = 4.5 Hz) of **15**. In contrast, the ^{1}H NMR spectrum of **16** showed *J* values ($J_{1,2}$ = 3.6 Hz, $J_{2,3eq}$ = 4.8 Hz, $J_{2,3ax}$ = 12.3 Hz) in accordance with an axial disposition for H-2.

The protected thiodisaccharides **14**−**16** were *O*-deacetylated with sodium methoxide in MeOH to give the corresponding free target compounds **2**, **17**, and **18**, respectively (Scheme 7).

Scheme 7. *O*-Deacetylation of Thiodisaccharides 14−16



The thiodisaccharides **2**, **17**, and **18** were evaluated as inhibitors of the *β*-galactosidase from *E. coli*, an enzyme widely used in the field of glycobiology.[17] This enzyme is highly specific for *β*-galactopyranosyl nonreducing residues bonded to a wide variety of aglycons. In particular, thioglycosides[9,18] and (1→4)-thiodisaccharides[5c,9b] have shown inhibitory activity. Knowing the key aspects of the inhibition process at the molecular level for **1**,[11] one of the most potent inhibitors, we have designed and synthesized the analogue **2**. The 2-acetamido-2,3-dideoxy thiodisaccharides **17** and **18** formed by two hexopyranose units have also been prepared. All these compounds inhibited the enzyme (Figure S1), with **17** being the weaker inhibitor. The kinetics of the inhibition showed that **2** (K_i = 70 μM) and **18** (K_i = 0.10 mM) were, respectively, competitive and mixed inhibitors (Figures S2 and S3). Compounds **2** and **18** showed a potency of the same order as that of **1**, and both were much stronger inhibitors than methyl 4-thiolactoside[5c] and other 4-thiolactosides.[9b]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02692.

Additional tables, experimental details, characterization data, inhibition plots and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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