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Synthesis of Thiosugars as Weak Inhibitors of Glycosidases

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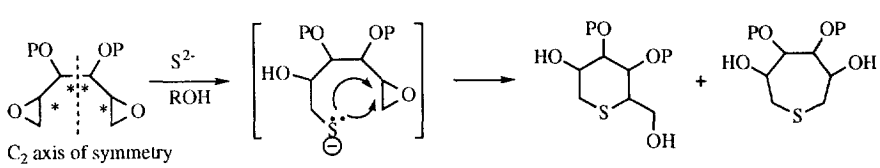
Abstract : A series of enantiomerically pure thiosugars (1,6-dideoxy-1,6-thio-D-mannitol or L-iditol, 1,5-dideoxy-1,5-thio-L-gulitol or D-glucitol and 2,5-dideoxy-2,5-thio-L-iditol or D-mannitol, and their corresponding sulfoxide or sulfone) was synthesized via thiocyclization of C_2-symmetric bis-epoxides, and subsequently followed by ring isomerization in few cases. These compounds have been evaluated as inhibitors of several glycosidases (α- and β-D-glucosidases, α-D-mannosidase and α-L-fucosidase).

Over the last several years, efforts to design and synthesize competitive inhibitors of glycosidases or glycosyl-transferases have surged, in particular because such compounds promise to be useful tools for probing the details of catalytic mechanism, and also for promising therapeutic applications (antiviral, anticancer and AIDS agents).[1] Among them are azasugars with a pyrrolidine, piperidine, azepane, indolizidine or pyrrolizidine skeleton. In connection with a programme on the development of new inhibitors of glycosidases, we have reported a facile general synthesis of azasugars.[2] We now describe the synthesis of the thio-analogues (thiosugars) and of their corresponding sulfoxide and sulfone for evaluation as inhibitors of glycosidases.
In an effort to develop new synthesis of enantiomerically pure thiosugars we have successively examined :

- opening of homochiral C_2-symmetric bis-epoxides by S^{2-} (Scheme 1). This approach, which involves a regiospecific opening of one epoxy function followed by the expected thiocyclization, would lead to the polyhydroxythiepane (7-*endo*-tet process) and/or the polyhydroxy tetrahydrothiopyrane with inversion of configuration at C_5 (6-*exo*-tet process).



C_2 axis of symmetry

P = protecting group

Scheme 1. Thiocyclization of C_2-symmetric bis-epoxides issued from D-mannitol

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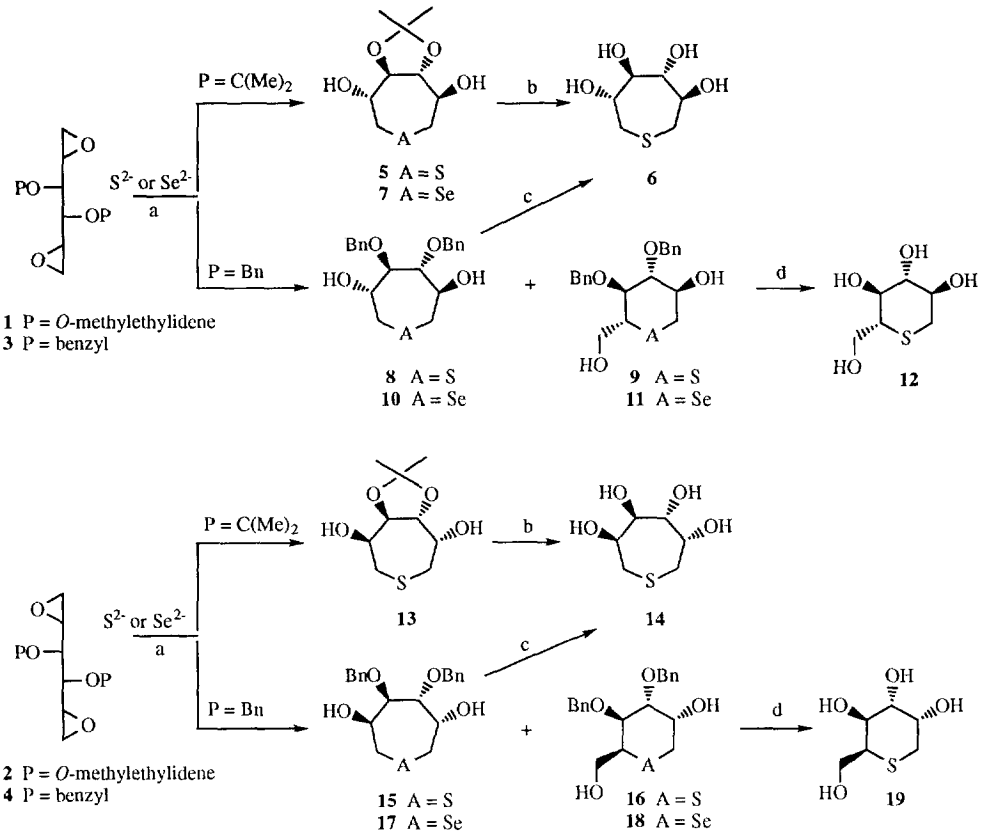


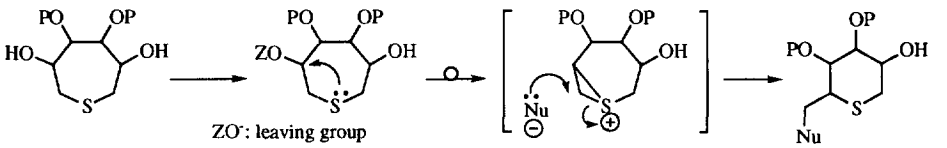
Scheme 3. (a) For reaction conditions, see Table 1. (b) CF_3CO_2H, H_2O, 20°C, 80%. (c) BBr_3 (7 eq), CH_2Cl_2, -60°C, 75%. (d) BBr_3 (7 eq), CH_2Cl_2, -60°C, 85%.

Table 1. Thio- or seleno-cyclization of D-mannitol or L-iditol bis-epoxides

Entry	bis-epoxide	Reaction conditions[a]	Compound, yield (%)[b]
1	**1**	$Na_2S.9\ H_2O$ (2 eq), EtOH, Δ	**5** (90%)
2	**1**	Na_2S-Al_2O_3, EtOH, Δ	**5** (90%)
3	**1**	[Se (2 eq), H_2O, $NaBH_4$ (4 eq)], MeOH, Δ	**7** (87%)
4	**2**	$Na_2S.9\ H_2O$ (2 eq), EtOH, Δ	**13** (50%)
5	**2**	Na_2S-Al_2O_3, EtOH, Δ	**13** (60%)
6	**2**	Ph_3SiSH (1 eq), Cs_2CO_3 (2 eq), MeOH, 20°C	**13** (50%)
7	**3**	$Na_2S.9\ H_2O$ (2 eq), EtOH, Δ	**8** (65%) - **9** (25%)
8	**3**	[Se (2 eq), H_2O, $NaBH_4$ (4 eq)], MeOH, Δ	**10** (58%) - **11** (16%)
9	**4**	$Na_2S.9\ H_2O$ (2 eq), EtOH, Δ	**15** (75%) - **16** (10%)
10	**4**	[Se (2 eq), H_2O, $NaBH_4$ (4 eq)], MeOH, Δ	**17** (75%) - **18** (10%)

[a] Equivalent of reagent for one molecule of bis-epoxide. [b] Yield of each isolated compound after flash chromatography purification.

- isomerization of these structures (Scheme 2) after activation of the free hydroxyl groups, by a S_N process via neighboring sulfur participation.



Scheme 2. Isomerization of C_2-symmetric thiepanes

- oxidation in sulfoxide or sulfone to study the influence of the oxidation state on the glycosidase inhibition, and aptitude of the partial positive charge on sulfur atom of sulfoxide or sulfone to mimic the transition-state for glycoside hydrolysis.

Preliminary results have already been disclosed,[3] we detail herein our synthetic routes, the structure of related compounds, and the results of the inhibition analysis.

Heterocyclization of C_2-symmetric bis-epoxides (Scheme 3, Table 1)

The reaction of 1,2:5,6-dianhydro-3,4-*O*-methylidene-L-iditol **1** or D-mannitol **2** with sodium sulfide is known to furnish the corresponding C_2-symmetric polyhydroxy thiepane **5** or **13** in 68 and 22% yield, respectively after acetylation for purification and subsequent deacylation by methanolysis.[4] We have simplified this procedure and obtained directly the crystalline thiepane **5** or **13** in 90 or 50% yield, after flash chromatography (entries 1, 4). The yield of **13** could be increased up to 60% by carrying out this reaction with alumina supported sodium sulfite reagent[5] (entry 5). Thus, thiocyclization of L-*ido* or D-*manno* bis-epoxide **1** or **2**, for which the 3,4-diol is protected in a *trans*-dioxolane, gave only the corresponding thiepane **5** or **13**.

With the hope to obtain the tetrahydrothiopyran skeleton by a 6-*exo* process, similar reactions were performed on the more flexible bis-epoxides **3** and **4**, for which the 3,4-diol is protected with acyclic protecting groups. These 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-L-iditol **3** and D-mannitol **4** can be prepared on a multigram scale from D-mannitol.[2] The reaction of bis-epoxide **3** with 2 eq of sodium sulfide nonahydrate in refluxing EtOH afforded a mixture of two compounds which could be easily separated by flash chromatography. The crystalline thiepane **8** and tetrahydrothiopyrane **9** were isolated in 65 and 25% yield, respectively (entry 7). Under the same experimental conditions, the diastereomeric bis-epoxide **4** gave the corresponding thiepane **15** (75%) and tetrahydrothiopyrane **16** (10%, entry 9). The C_2-symmetric thiepanes **8** and **15** were correlated to **6** and **14**, respectively after de-*O*-benzylation with a solution of boron tribromide[6] in CH_2Cl_2 at-50°C (75%). These conditions applied to **9**, or **16**, gave the polyhydroxy tetrahydrothiopyrane **12** (1-deoxythionojirimycin, the thio analogue of the glycosidase inhibitor 1-deoxynojirimycin), or **19** (1,5-anhydro-5-thio-L-gulitol), respectively.

Interestingly, this heterocyclization can also be performed with selenide ion, generated *in situ* by reduction of selenium[7] with $NaBH_4$ to afford the corresponding polyhydroxylated selepane and tetrahydroselenopyrane in similar yields, (entries 3, 8 and 10). However until now, deprotection of these seleno compounds, under similar conditions as above, gave an inextractable mixture.

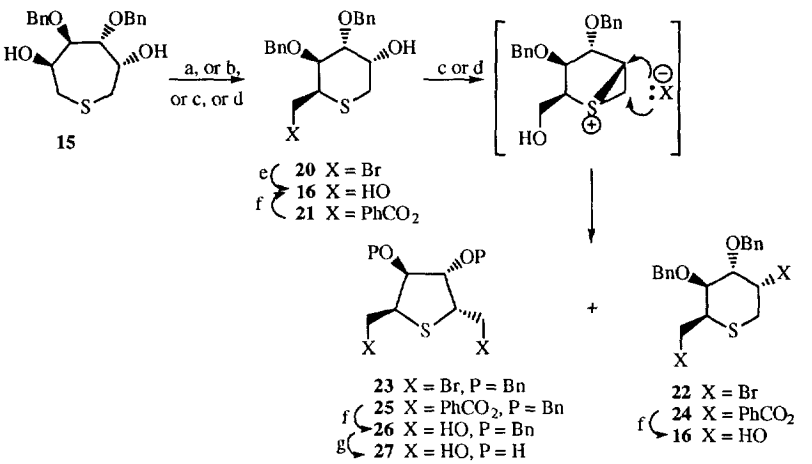
Thus, from the bis-epoxides **1**, **2**, **3** or **4** the cyclization by selenide or sulfide ion leads mainly to the seven-membered heterocycle. It is worth noting that aminocyclization of bis-epoxides **1** and **2** gives only the seven-membered aminocycle, whereas aminocyclization of bis-epoxides **3** and **4** affords a mixture of six- and seven-membered cyclic azasugars in about 55:45 to 30:70 ratio, depending on the experimental conditions.[2]

This difference of results can be explained by a more length C-S (or C-Se) bond which allows preferential opening of the second epoxide ring at the less substituted side.

In order, to obtain tetrahydrothiopyrane skeleton in a higher yield, we tried to isomerize the C_2-symmetric thiepane skeleton through an episulfonium.

Isomerization of C_2-symmetric thiepanes.

We have performed the hydroxy-activation by transformation into an alkoxyphosphonium salt by reaction with triphenylphosphine-carbon tetrahalide, or under Mitsunobu conditions[10] using benzoic acid. In the latter case methanolysis of the resulting benzoate would gave back an alcohol function.

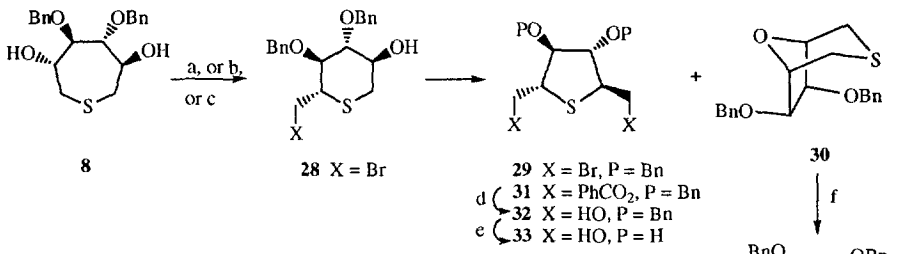


Scheme 4. (a) Ph_3P-CBr_4 (2 eq), CH_3CN, Δ, 50% of **20**. (b) Ph_3P-DEAD-$PhCO_2H$ (1.5 eq), THF, 0°C, 80% of **21**. (c) Ph_3P (13 eq), CBr_4 (7 eq), CH_3CN, 37% of **22**, 24% of **23**. (d) Ph_3P-DEAD-$PhCO_2H$ (6 eq), THF, 20°C, 45% of **24**, 35% of **25**. (e) $(Bu_3Sn)_2O$ (2.2 eq), $AgNO_3$ (2 eq), DMF, 60°C, 75%. (f) K_2CO_3(4 eq), MeOH, 20°C, 90%. (g) BBr_3 (7 eq), CH_2Cl_2, -60°C, 80%.

This rearrangement seems to be fairly general and occurs under a variety of conditions. From the results on the D-*manno*-thiepane **15** in Scheme 4, several points are noteworthy: Firstly, carrying out the reaction with a small excess of reagents leads to the L-*gulo*-tetrahydrothiopyrane. For example, with 2 eq of triphenylphosphine-carbon tetrabromide under acetonitrile reflux, the primary organic bromide **20** was isolated in 50% yield. This structure was confirmed by transformation into alcohol **16** by bis(tributyltin)oxide in presence of silver nitrate[11] in DMF at 60°C (75%). The ring contraction into the tetrahydrothiopyrane skeleton can be achieved in a higher yield by action of triphenylphosphine-diethyl azodicarboxylate (DEAD)-benzoic acid in THF at 0°C (80% of **21**). By methanolysis in presence of K_2CO_3, **21** afforded **16** (90%). These results confirm that episulfonium is formed by a stereospecific process, not by a sulfur carbonium S_N1 process, and that the ring contraction takes place towards the more stable tetrahydrothiopyrane.

Secondly, with an excess of reagents, activation of the hydroxyl group of the rearranged tetrahydrothiopyrane occurs *in situ* to give, *via* an episulfonium, a mixture of disubstituted L-*gulo*-tetrahydrothiopyrane and C_2-symmetric L-*ido*-tetrahydrothiophene. For example, treatment of **15** with an excess of Ph_3P-CBr_4 under acetonitrile reflux gave a mixture of **22** and **23** which can be easily separated by flash chromatography (37 and 24% yield, respectively). On the other hand, treatment of **15** with 6 eq of Ph_3P-

DEAD-$PhCO_2H$ in THF at 20°C gave a mixture of **24** and **25**, which after methanolysis and chromatography separation, leads to **16** and **26** (40 and 31% overall yield from **15**, respectively). Removal of the *O*-benzyl protecting groups of **26** with a solution of boron tribromide, as above, afforded the 2,5-dideoxy-2,5-thio-L-iditol **27** (80%). Thus from **15**, under Mitsunobu conditions, the L-*gulo*-tetrahydrothiopyrane **16** or the L-*ido*-tetrahydrothiophene **27** can be obtained in 72 or 25% overall yield, depending on the experimental conditions.



8 28 X = Br 29 X = Br, P = Bn

Scheme 5. (a) Ph_3P (6 eq), CBr_4 (4 eq), CH_3CN, 20°C, 30% of **28**. (b) Ph_3P-CBr_4 (10 eq), CH_3CN, Δ, 36% of **29**. (c) Ph_3P-DEAD- $PhCO_2H$ (1.5 eq), THF, 0°C, 61% of **30**, 24% of **31**. (d) K_2CO_3(8 eq), MeOH, 20°C, 90%. (e) BBr_3 (7 eq), CH_2Cl_2, -60°C, 75%. (f) Ni Raney, EtOH, 70°C, 85%.

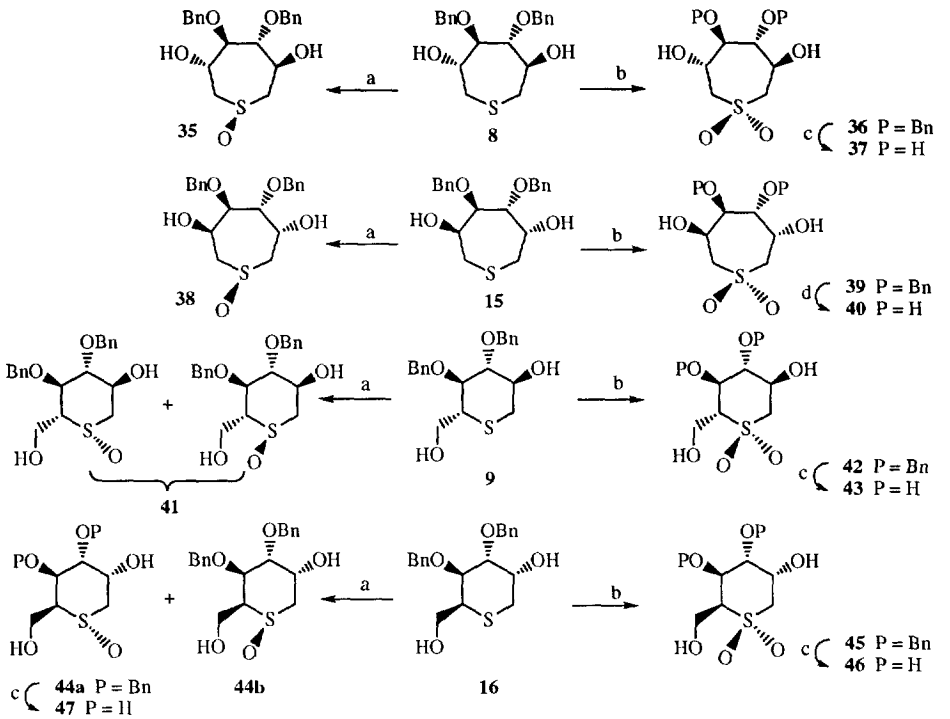
Results concerning the isomerization of the L-*ido*-thiepane **8** are reported in Scheme 5. In presence of a slight excess of Ph_3P-CBr_4, the bromomethyl-D-*gluco*-tetrahydrothiopyrane **28** was isolated in 30% yield, whereas in presence of an excess of reagents (10 eq), only the C_2-symmetric D-*manno*-tetrahydrothiophene **29** was isolated in 36% yield. Under Mitsunobu conditions [1.5 eq (Ph_3P-DEAD-$PhCO_2H$)] in THF at 10°C the bridged thioether **30** and the C_2-symmetric tetrahydrothiophene **31** were isolated in 61 and 24% yield, respectively. The latter by methanolysis (**31**--> **32**) and de-*O*-benzylation with BBr_3 gives the 2,5-dideoxy-2,5-thio-D-mannitol **33**, the thio analogue of the glycosidase inhibitor DMDP. The formation of the bridged thioether **30** can be interpreted as an intramolecular displacement of the alkoxyphosphonium intermediate by the other free hydroxyl group of the thiepane, concurrently to the evolution towards the episulfonium. The structure of **30** is assumed by ^1H NMR spectroscopy (*i.e.* experimental section), and by nickel desulfuration in ethanol to give the tetrasubstitued tetrahydrofurane **34** (85%).

Oxidation of thiosugars (Scheme 6)

The C_2-symmetric thiepane **8** (or **15**) can be oxidized[12] into the corresponding enantiopure sulfoxide **35** (or **38**) by sodium periodate (1 eq) in 84-88% yield, or into the corresponding sulfone **36** (or **39**) by *m*-chloroperbenzoic acid (2.5 eq) at room temperature (91%).

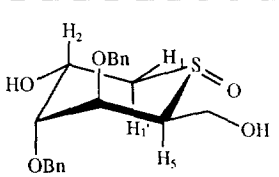
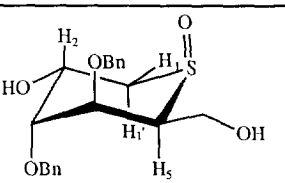
From the tetrahydrothiopyrane **9**, the $NaIO_4$ oxidation afforded a 1/1 mixture of sulfoxides diastereomers **41** which cannot be separated by flash chromatography, whereas, mild oxidation of **16** leads to a 91/9 mixture of **44a** and **44b** (82%), easily separated by flash chromatography. On the other hand, oxidation by an excess of *m*CPBA of **9** (or **16**) gave the corresponding sulfone **42** (or **45**) in 89% yield. The stereochemistry of the two sulfoxides diastereomers **44a** and **44b** was tentatively assigned by ^1H and ^{13}C NMR studies (Table 2). The small $^3J_{H3,H4}$ values for **44a** and **44b**, respectively 2.4 and 5.9 Hz indicate a chair conformation with the benzyloxy substituents in an axial position. It was found that equatorial sulfoxide **44a** was the major product, and that the axial sulfoxide **44b** the minor one. Comparison of the ^1H and ^{13}C NMR data of **44a** and **44b** reveal: -1) a deshielding effect of axial sulfoxide for the *syn*-axial proton H_2[14,15] ($\Delta\delta_{H2}$ +0.54 ppm); - 2) a

higher geminal coupling-constant in α to the axial sulfoxide[15] ($^2J_{H1,H1'}$ = -11.6 and -13.5 Hz);- 3) a shielding effect of axial sulfoxide for the α-carbon atoms[16] ($\Delta\delta_{C1}$ = -4.9 and $\Delta\delta_{C5}$ = -8.7).



Scheme 6. (a) $NaIO_4$ (1 eq), CH_3COCH_3, H_2O, 80-88% for **35**, **38**, **41** (1/1 ratio) and **44** (91/9 ratio for **44a/44b**). (b) *m*CPBA (2.5 eq), $CaCO_3$, CH_2Cl_2, 20°C, 60-92%. (c) BBr_3 (7 eq), CH_2Cl_2, -60°C, 70-85%. (d) H_2, Pd black, CH_3CO_2H, 60%.

Table 2. Selected physical data (^1H and ^{13}C NMR) of sulfoxides **44a** and **44b**.

 equatorial sulfoxide **44a**	$^3J_{H3,H4}$ (Hz): 2.4 δ_{H2} (ppm): 4.06 $^2J_{H1,H1'}$ (Hz): -11.6 δ_{H5} (ppm): 3.1 δ_{C1} (ppm): 52.1 δ_{C5} (ppm): 64.2
 axial sulfoxide **44b**	$^3J_{H3,H4}$ (Hz): 5.9 δ_{H2} (ppm): 4.60 $^2J_{H1,H1'}$ (Hz): -13.5 δ_{H5} (ppm): 2.98 δ_{C1} (ppm): 47.2 δ_{C5} (ppm): 55.5

In the particular case of sulfone **39**, de-*O*-benzylation can be performed by hydrogenolysis in presence of palladium black in acetic acid (60% of **40**). For all other sulfoxides and sulfones, deprotection can be more efficiently accomplished using, as above mentioned, a solution of boron tribromide in CH_2Cl_2 at -60°C (70-85% yield).

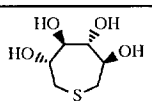
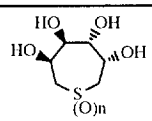
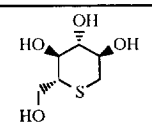
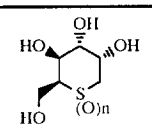
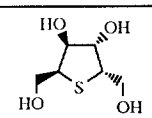
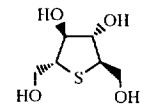
Inhibition studies[17] (Table 3)

The obtained thiosugars and their oxidative derivatives were evaluated as inhibitors of different glycosidases (α- or β-D-glucosidase, α-D-mannosidase and α-L-fucosidase).

The results of the inhibition studies show that thiosugars are weak inhibitors of glycosidases. For example, the 1-deoxythionojirimycin **12** (thio-DNJ) and the tetrahydrothiophene **33** (thio-DMDP) are less potent inhibitors of α-and β-glucosidases than the parent azasugars. The same behaviour has been reported for 1-deoxythiomannojirimycin[18] wich is a weak inhibitor of α-D-glucosidase and inactive towards β-D-glucosidase, whereas the 1-deoxymannojirimycin[2,19] is a good inhibitor of α- and β-D-glucosidases and α-D-mannosidase.

The best results are for the L-gulo-tetrahydrothiopyrane **19** which competitively inhibits the α-D-mannosidase (K_i = 700 μM), and for the L-ido-thiepane **6** which is a low inhibitor of α-D-glucosidase (K_i = 3900 μM). Comparison of inhibitory activity of **19**, **47** and **46** shows that the oxidation of the tetrahydrothiopyrane into sulfoxide and sulfone, respectively, reduce or abolish the inhibition. Like 5-thio-D-glucose[20] which is an inhibitor of α-D-glucosidase, oxidation into sulfoxide or sulfone weakened the inhibition.

Table 3. Comparison of Glycosidases inhibition

Compound		α-D-mannosidase	α-D-glucosidase	β-D-glucosidase	α-L-fucosidase
	**6**	0	40(**3900**)	28	-
	**14** (n = 0)	0	0	10	0
	40 (n = 2)	0	0	7	9
	**12** (thio-DNJ)	0	6	28	-
	**19** (n = 0)	31(**700**)	18(**2000**)	18	-
	47 (n = 1)	0	22	6	10
	46 (n = 2)	0	15	9	18
	**27**	0	18	7	10
	**33** (thio-DMDP)	0	20	0	0

For each compound, the percentage of inhibition determined at 1 mM concentration of inhibitor, and in parentheses the inhibition constant (K_i in μM, in bold) determined by the Lineweaver-Burk plot were reported.

In conclusion, the present work outlined an efficient synthetic pathway to construct various thiosugars with a tetrahydrothiophene, tetrahydrothiopyrane or thiepane framework. If these compounds exibit only moderate

inhibition against glycosidases, they can served as conformationally constrained scaffolds for the rational drug design of potent HIV inhibitors.[21] Further utilisation of this methodology in the synthesis of other thiosugars and related systems will be reported in due course.

EXPERIMENTAL SECTION

Prior to use, THF and Et_2O were distilled from sodium-benzophenone and CH_2Cl_2 from P_2O_5. CH_2Cl_2 and EtOAc were filtered on K_2CO_3 prior to use. ^1H NMR (250 MHz) and ^{13}C NMR (62,9 MHz) spectra were recorded in $CDCl_3$ (unless indicated) on a Bruker AM 250. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hertz. Mass Spectra, chemical ionization (CI), and high resolution (HRMS) were recorded in Service de Spectrométrie de Masse, Université Pierre et Marie Curie. Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) or mercury (365 nm) lamp at 20°C. All reactions were run under argon atmosphere, unless otherwise stated, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 µm) on glass. Chromatography was performed with Merck Kieselgel 60 (200-500 µm) or 60H (5-40 µm). Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

Thiocyclization of C_2-symmetric bis-epoxides.

By Na_2S: To a solution of bis-epoxide **1** (500 mg; 2.7 mmol) in ethanol (8 mL) was added sodium sulfide nonahydrate (1.29 g; 5.4 mmol). The reaction mixture was refluxed for 8 h, then concentrated *in vacuo*. To the residue was added CH_2Cl_2 (10 mL) and water (7 mL). After decantation, the organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude (CH_2Cl_2/MeOH 95/5) afforded 580 mg (90%) of the crystalline **5** (R_f 0.25).

By Na_2S/Al_2O_3: To sodium sulfide supported on alumina[5] (818 mg) was added a solution of bis-epoxide **1** (64 mg; 0.34 mmol) in ethanol (3 mL). The reaction mixture was refluxed for 2.5 h, then filtered and concentrated *in vacuo*. Flash chromatography of the crude (cyclohexane/EtOAc 1/4) afforded 68 mg (90%) of the crystalline **5** (R_f 0.27).

By Ph_3SiSH: To a solution of bis-epoxide **2** (80 mg; 0.48 mmol) in MeOH (5 mL) was added cesium carbonate (280 mg; 0.96 mmol) and triphenylsilane sulfide[22] (125 mg; 0.48 mmol). After stirring for 18 h at 20°C, the reaction mixture was concentrated *in vacuo*. To the residue were added CH_2Cl_2 (10 mL) and water (7 mL). After decantation, extraction with CH_2Cl_2 (2x7 mL), the combined organic layers were washed with brine (2x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude (cyclohexane/EtOAc 2/3) afforded 48 mg (50%) of the crystalline thiepane **13** (R_f 0.3).

1,6-Dideoxy-3,4-*O*-methylethylidene-1,6-thio-L-iditol (5): Mp 188°C, $[\alpha]_D$ +82 (c 1.01; MeOH), lit[4] mp 188°C, $[\alpha]_D$ +83 (c 1; MeOH); ^1H NMR: 3.87(m, 6H, $H_{1',2,3}$), 3.55(dd, 2H, $J_{1,1'} = -16$, $J_{1,2} = 9$, H_1), 1.43(s, 6H, CMe_2); ^{13}C NMR: 110.4(CMe_2), 80.5(C_3), 76.5(C_1), 72.3(C_2), 27.1(Me); MS (CI, NH_3) 221(M^++1), 238(M^++18); Anal. calcd for $C_9H_{16}O_4S$: C, 49.07, H, 7.33, found: C, 49.21, H, 7.81.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-thio-L-iditol (8): R_f 0.46(cyclohexane/EtOAc 3/2); mp 98°C; $[\alpha]_D$ +124 (c 0.91; CH_2Cl_2); ^1H NMR: 7.31(m, 10H, Ph), 4.56-3.98(AB, 4H, $J_{AB} = -11.2$, CH_2Ph), 3.95(m, 2H, H_2), 3.66(m, 2H, H_3), 2.90(dd, 2H, $J_{1,1'} = -15$, $J_{1',2} = 4$, $H_{1'}$), 2.70(dd, 2H, $J_{1,1'}$ -15, $J_{1,2} = 7$, H_1); ^{13}C NMR: 137.6, 128.0, 127.9(Ph), 83.7(C_3), 75.2(CH_2Ph), 72.9(C_2), 36.6(C_1); MS (CI, NH_3) 361(M^++1), 378(M^++18); Anal. calcd for $C_{20}H_{24}O_4S$, 0.3 H_2O: C, 65.66 H, 6.78, found: C, 65.69, H, 6.73.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-thio-D-glucitol (9): R_f 0.29(cyclohexane/EtOAc 3/2); $[\alpha]_D$ +76 (c 0.585; CH_2Cl_2); ^1H NMR: 7.29(m, 10H, Ph), 4.89-4.59(AB, 4H, J_{AB} = -11.7, CH_2Ph), 4.19(ddd, 1H, $J_{2,3}$ = 3.7, $J_{2,1}$ = 6.3, $J_{2,1'}$ = 7, H_2), 4.02(m, 2H, $H_{4,5}$), 3.94(d, 1H, $J_{2,3}$= 3.7, H_3), 3.73(m, 1H, $H_{6'}$), 3.6(m, 1H, H_6), 3.00(dd, 1H, $J_{1,1'}$ = -13.5, $J_{1',2}$ = 7, $H_{1'}$), 2.8(dd, 1H, $J_{1,1'}$ = -13.5, $J_{1,2}$ = 6.3, H_1); ^{13}C NMR: 137.5, 137.3, 128.4, 127.8, 127.5(Ph), 84.7(C_2), 82.5($C_{3,4}$), 81.6(C_5), 71.8, 71.6(CH_2Ph), 62.8(C_6), 30.8(C_1); MS (CI, NH_3) 361(M^++1), 378(M^++18); Anal. calcd for $C_{20}H_{24}O_4S$: C, 66.64 H, 6.71, found: C, 66.62 H, 6.73.

1,6-Dideoxy-3,4-*O*-methylethylidene-1,6-thio-D-mannitol (13): R_f 0.3(cyclohexane/EtOAc 2/3); mp 94°C, $[\alpha]_D$ -120 (c 1.21; $CHCl_3$), lit[4] mp 93-95°C, $[\alpha]_D$ -122 (c 1; $CHCl_3$); ^1H NMR: 4.33(m, 4H, $H_{2,3}$), 3.00(dd, 2H, $J_{1,1'}$ = -16, $J_{1',2}$ = 6, $H_{1'}$), 2.60(dd, 2H, $J_{1,1'}$ = -16, $J_{1,2}$ = 5, H_1), 1.43(s, 6H, CMe_2); ^{13}C NMR: 108.8(CMe_2), 75.9(C_3), 66.3(C_2), 37.5(C_1), 29.0(Me); MS (EI, %) 220(28), 205(75), 118(80), 99(45), 71(80), 59(100); Anal. calcd for $C_9H_{16}O_4S$: C, 49.07, H, 7.32, found: C, 49.18, H, 7.12.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-thio-D-mannitol (15): R_f 0.3(cyclohexane/EtOAc 7/3); mp 95°C; $[\alpha]_D$ -5 (c 0.98; CH_2Cl_2); ^1H NMR: 7.80(*br.s*, 10H, Ph), 4.70(AB, 4H, J_{AB} = -11.5, CH_2Ph), 4.25(m, 2H, H_2), 4.0(s, 2H, H_3), 2.62-2.33(AB from ABX, 4H, J_{AB} = -14.7, J_{AX} = 4.5, J_{BX} = 7, H_1); ^{13}C NMR: 138.1, 128.5, 127.9(Ph), 78.2(C_3), 74.1(CH_2Ph), 70.5(C_2), 35.5(C_1); MS (CI, NH_3) 361(M^++1), 378(M^++18); Anal. calcd for $C_{20}H_{24}O_4S$: C, 66.64 H, 6.71, found: C, 66.61, H, 6.59.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-thio-L-gulitol (16): R_f 0.18(cyclohexane/EtOAc 7/3); $[\alpha]_D$ -35 (c 1.87; CH_2Cl_2); ^1H NMR: 7.30(m, 10H, Ph), 4.64-4.52(AB, 4H, J_{AB} = -11.6, CH_2Ph), 4.15(m, 1H, H_2), 4.05(dd, 1H, $J_{4,5}$ = 3, $J_{3,4}$ = 6, H_4), 3.70(m, 3H, $H_{3,6,6'}$), 3.21(td, 1H, $J_{5,4}$ = 3, $J_{5,6}$ = 9, H_5), 2.75(dd, 1H, $J_{1,1'}$ = -13, $J_{1',2}$ = 8.5, $H_{1'}$), 2.6(dd, 1H, $J_{1,1'}$ = -13, $J_{1,2}$ = 3.5, H_1); ^{13}C NMR: 137.7, 137.5, 128.4, 128.1, 127.9, 127.7(Ph), 76.9, 75.5($C_{3,4}$), 73.1, 72.7(CH_2Ph), 67.7(C_2), 61.2(C_6), 42.6(C_5), 28.4(C_1); MS (CI, NH_3) 361(M^++1), 378(M^++18); Anal. calcd for $C_{20}H_{24}O_4S$: C, 66.64 H, 6.71, found: C, 66.60 H, 6.70.

Selenocyclization of C_2-symmetric bis-epoxides.

To a suspension of selenium (42.2 mg; 0.534 mmol) in water (500 µL) was added a solution of sodium borohydride[7] (40.6 mg; 1.068 mmol) in water (500 µL). This suspension was then added to a solution of bis-epoxide **1** (50 mg; 0.267 mmol) in methanol (300 µL). After refluxing for 4 h, then stirring at 20°C for 15 h, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. After extraction with CH_2Cl_2 (3x15 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude (cyclohexane/EtOAc 3/7) afforded 62 mg (86%) of the crystalline selenepane **7** (R_f 0.38).

1,6-Dideoxy-3,4-*O*-methylethylidene-1,6-seleno-L-iditol (7). R_f 0.38(cyclohexane/EtOAc 3/7); mp 183-185°C; $[\alpha]_D$ +44 (c 1.03, CH_2Cl_2). ^1H NMR: 3.98-3.89(m, 4H, $H_{2,3}$), 2.84(dd, 2H, $J_{1,1'}$ = -14, $J_{1',2}$ = 4.4, $H_{1'}$), 2.70(dd, 2H, $J_{1,1'}$ = -14, $J_{1,2}$ = 6, H_1), 1.42(s, 6H, CMe_2); ^{13}C NMR: 109.7(CMe_2), 83.6(C_3), 74.7(C_2), 29.8(C_1), 27.1(CMe_2).

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-seleno-L-iditol (10). R_f 0.3(cyclohexane/EtOAc 7/3); mp 86-88°C; $[\alpha]_D$ +132 (c 0.775, CH_2Cl_2). ^1H NMR: 7.80(m, 10H, Ph), 4.76(AB, 4H, J_{AB} = -11.2, CH_2Ph), 3.94(m, 2H, H_2), 3.61(m, 2H, H_3), 2.87(dd, 2H, $J_{1,1'}$ = -14, $J_{1',2}$ = 4.4, $H_{1'}$), 2.70(dd, 2H, $J_{1,1'}$ = -14, $J_{1,2}$ = 6.8, H_1); ^{13}C NMR: 137.7, 128.7, 128.1, 127.0(Ph), 84.0(C_3), 76.5(CH_2Ph), 73.2(C_2), 27.4(C_1); Anal. calcd for $C_{20}H_{24}O_4Se$: C, 58.97 H, 5.94, found: C, 58.74 H, 5.87.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-seleno-D-glucitol (11). R_f 0.18(cyclohexane/EtOAc 7/3); $[\alpha]_D$ +73 (c 0.69, CH_2Cl_2). ^1H NMR: 7.3(m, 10H, Ph), 4.58-4.38(AB, 4H, J_{AB} = -11.6, CH_2Ph), 4.25(m, 1H, $J_{1,2}$ = 6.8, $J_{1',2}$ = 7.2, $J_{2,3}$ = 3.6, H_2), 4.00(m, 2H, $H_{5,4}$), 3.95(d, 1H, $J_{3,2}$ = 3.6, H_3), 3.72(dd, 1H, $J_{6,6'}$ = -12, $J_{6',5}$ = 2.8, $H_{6'}$),

3.6(dd, 1H, $J_{6,6'}$ = -12, $J_{6,5}$ = 4, H_6), 3.0(dd, 1H, $J_{1,1'}$ = -12.8, $J_{1',2}$ = 7.2, $H_{1'}$), 2.77(dd, 1H, $J_{1,1'}$ = -12.8, $J_{1,2}$ = 6.8, H_1); ^{13}C NMR: 137.5, 137.3, 128.5, 127.9, 127.6(Ph), 84.7(C_2), 82.8, 82.6($C_{3,4}$), 82.1(C_5), 71.9, 71.6(CH_2Ph), 62.9(C_6), 22.2(C_1).

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-seleno-D-mannitol (17). R_f 0.29(cyclohexane/EtOAc 7/3); mp 88°C; $[\alpha]_{365}$ -6 (c 1.23, CH_2Cl_2). ^1H NMR: 7.81(*br.*s, 10H, Ph), 4.7(AB, 4H, J_{AB} = -11.6, CH_2Ph), 4.31(m, 2H, $J_{1,2}$ = 8.4, $J_{1',2}$ = 4.4, H_2), 3.97(*br.*s, 2H, H_3), 2.81(dd, 2H, $J_{1,1'}$ = -13.2, $J_{1',2}$ = 4.4, H_1), 2.68(dd, 2H, $J_{1,1'}$ = -13.2, $J_{1,2}$ = 8.4, H_1); ^{13}C NMR: 138.2, 128.5, 127.9(Ph), 78.7(C_3), 74.1(CH_2Ph), 70.8(C_2), 25.0(C_1); MS (CI, NH_3) 405, 406, 407, 409, 411(M^++1), 422, 423, 424, 426, 428(M^++18); Anal. calcd for $C_{20}H_{24}O_4Se$: C, 58.97 H, 5.94, found: C, 58.79 H, 6.05.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-seleno-L-gulitol (18). R_f 0.2(cyclohexane/EtOAc 7/3); $[\alpha]_D$ -30 (c 0.82, CH_2Cl_2). ^1H NMR: 7.33(m, 10H, Ph), 4.71-4.57(m, 4H, CH_2Ph), 4.24(m, 1H, H_2), 4.10(dd, 1H, $J_{4,3}$ = 6.4, $J_{4,5}$ = 3.2, H_4), 3.75(m, 2H, $H_{6,6'}$), 3.65(m, 1H, $J_{4,3}$ = 6.4, $J_{3,2}$ = 2.4, H_3), 3.43(m, 1H, H_5), 2.90(dd, 1H, $J_{1,1'}$ = -12, $J_{1',2}$ = 9.6, $H_{1'}$), 2.59(dd, 2H, $J_{1,1'}$ = -12, $J_{1,2}$ = 3.6, H_1); ^{13}C NMR: 137.9, 137.7, 128.7, 128.3, 128.2, 127.9(Ph), 77.5, 76.1($C_{3,4}$), 73.6, 72.8(CH_2Ph), 68.3(C_2), 62.5(C_6), 37.1(C_5), 20.1(C_1).

1,6-Dideoxy-1,6-thio-L-iditol (6).

By hydrolysis of the thiepane **5**: To the thiepane **5** (80 mg; 0.36 mmol) was added, at 0°C, an aqueous solution of trifluoroacetic acid 1/1 (v/v, 2 mL). After stirring 15 min at 0°C, then 15 h at room temperature, the reaction mixture was concentrated *in vacuo*. Flash chromatography of the crude (CH_2Cl_2/MeOH 85/15) afforded 52 mg(80%) of **6**.

By de-*O*-benzylation of the thiepane **8**: To the thiepane **8** (100 mg; 0.278 mmol) in CH_2Cl_2 (2 mL) was dropwise added, at -78°C, a solution of boron tribromide[6] (1 mol.L^{-1}; 1.94 mL) in CH_2Cl_2. After stirring at -60°C for 2.5 h, methanol (2 mL) then pyridine (1.54 mL) were successively added, and the temperature was raised to 20°C. The reaction mixture was then concentrated under reduce pressure. The crude was purified by flash chromatography (CH_2Cl_2/MeOH 4/1 with aqueous ammonia (1%)), and the fractions of R_f 0.4 were concentrated *in vacuo*, then solubilized in acetone to give 37.5 mg (75%) of the crystalline **6**.

Mp 111°C, $[\alpha]_D$ +85 (c 0.85, H_2O), lit[4] mp 110-112°C, $[\alpha]_D$ +89 (c 1, H_2O); ^1H NMR (D_2O): 3.83(m, 2H, $J_{1,2}$ = 6.8, H_2), 3.65(m, 2H, H_3), 2.95(dd, 2H, $J_{1,1'}$ = -15.2, $J_{1',2}$ = 4.4, $H_{1'}$), 2.77(dd, 2H, $J_{1,1'}$ = -15.2, $J_{1,2}$ = 6.8, H_1); ^{13}C NMR (CD_3OD): 76.1, 75.4($C_{2,3}$), 38.4(C_1).

1,5-Dideoxy-1,5-thio-D-glucitol (12): De-*O*-benzylation of **9** (150 mg) with a solution of boron tribromide in CH_2Cl_2 (1 mol.L^{-1}; 2.9 mL) was carried out under identical conditions described above, to give 64 mg (85%) of **12**. $[\alpha]_D$ +50 (c 1.39, H_2O); ^1H NMR (CD_3OD): 4.12(part X of ABMX, 1H, J_{XA} = 6.8, J_{XB} = 7.2, $J_{2,3}$ = 3.2, H_2), 3.96-3.88(m, 2H, $H_{4,3}$), 3.97(part X of ABMX, 1H, J_{XA} = 4.1, J_{XB} = 5.2,$J_{5,4}$ = 2.8, H_5), 3.68-3.62(AB of ABX, 2H, J_{AB} = -11.6, J_{AX} = 4.1, J_{BX} = 5.2, $H_{6,6'}$), 2.86(AB of ABX, 2H, J_{AB}= -15.4, J_{AX} = 6.8, J_{BX} = 7.2, $H_{1,1'}$); ^{13}C NMR (CD_3OD): 87.8, 82.9($C_{3,4}$), 80.2(C_2), 78.4(C_5), 63.6(C_6), 31.6(C_1); HRMS calcd for $C_5H_9O_3S$ (M^+-CH_2OH) 149.0272, found 149.0272

1,6-Dideoxy-1,6-thio-D-mannitol (14). This compound can be obtained either by hydrolysis of **13**, or either by de-*O*-benzylation of **15** according to identical conditions described above: Rf 0.3(CH2Cl2 /MeOH 85/15; mp 120°C, $[\alpha]_D$ -116 (c 0.47, H_2O), lit[4] mp 120-122°C, $[\alpha]_D$ -119 (c 1, H_2O); ^1H NMR (D_2O): 4.34(m, 2H, $J_{1,2}$ = 7.2, $J_{1',2}$ = 4.8, H_2), 4.11(*br.*s, 2H, H_3), 3.03(dd, 2H, $J_{1,1'}$ = -14.7, $J_{1',2}$ = 4.8, $H_{1'}$), 2.73(dd, 2H, $J_{1,1'}$ = -14.7, $J_{1,2}$ = 7.2, H_1); ^{13}C NMR (CD_3OD): 71.9, 76.1($C_{3,2}$), 35.8(C_1); MS (CI, NH_3) 181(M^++1), 198(M^++18).

1,5-Dideoxy-1,5-thio-L-gulitol (19): De-*O*-benzylation of **16** (100 mg) with a solution of boron tribromide in CH_2Cl_2 (1 mol.L^{-1}; 1.94 mL) was carried out under identical conditions described above, to give 42 mg (84%) of **19**. $[\alpha]_D$ -14 (c 0.65, MeOH); ^1H NMR (CD_3OD): 4.04(m, 1H, H_4), 3.78(m, H, H_3), 4.0(m, 1H, H_2), 3.68-3.56(part AB of ABX, 2H, J_{AX} = 7.2, J_{AB} = -11.2, J_{XB} = 6.7, $H_{6,6'}$), 3.27(m, 1H, H_5), 2.89(dd, 1H, $J_{1',2}$ = 11, $J_{1,1'}$ = -13, $H_{1'}$), 2.30(dd, 1H, $J_{1,2}$ = 4, $J_{1,1'}$ = -13, H_1); ^{13}C NMR (CD_3OD): 73.1, 71.7($C_{3,4}$), 68.7(C_2), 62.6(C_6), 44.1(C_5), 28.6(C_1); HRMS calcd for $C_6H_{12}O_4S$ (M^+) 180.0456, found 180.0456.

Reaction of 15 with Ph_3P/CBr_4: To a solution of dried triphenyphosphine (73 mg; 0.278 mmol) in acetonitrile (1 mL) were successively added carbon tetrabromide (115 mg; 0.325 mmol), and a solution of **15** (50 mg; 0.139 mmol) in acetonitrile (0.3 mL). After stirring at 80°C for 10 h, and addition of one equivalent of each reagents, water (3 mL) and CH_2Cl_2 (5 mL) were successively added. After decantation, the organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude (cyclohexane/EtOAc 7/3) afforded 29 mg (50%) of **20** (R_f 0.33 in cyclohexane/EtOAc 3/2). The same reaction on **15** (60 mg; 0.17 mmol) carried out with an excess of reagents [CBr_4 (387 mg; 1.2 mmol), Ph_3P (657 mg; 2.2 mmol)] for 4 h at 20°C afforded, after flash chromatography (cyclohexane/toluene/CH_2Cl_2 10/7/3), 30 mg (37%) of **22** (R_f 0.30) and 19 mg (24%) of **23** (R_f 0.37).

3,4-Di-*O*-benzyl-6-bromo-1,5,6-trideoxy-1,5-thio-L-gulitol (20): $[\alpha]_D$ -23 (c 0.80, CH_2Cl_2); ^1H NMR: 7.33(*br.s*, 10H, Ph), 4.63-4.38(m, 4H, CH_2Ph), 4.16(d 1H, $J_{3,2}$ = 4.4, H_3), 4.06(m, 1H, H_2), 3.60(m, 1H, H_4), 3.49-3.39(m, 3H, $H_{6,6',5}$), 2.90(dd, 1H, $J_{1,1'}$ = -12.8, $J_{1',2}$ = 11.2, $H_{1'}$), 2.41(dd, 2H, $J_{1,1'}$ = -12.8, $J_{1,2}$ = 4, H_1); ^{13}C NMR: 137.6, 128.7, 128.6, 128.4, 128.3, 128.1(Ph), 76.7, 73.8($C_{3,4}$), 73.4, 73.2(CH_2Ph), 67.3(C_2), 42.0(C_5), 30.5(C_6), 29.1(C_1); MS(CI, NH_3) 423, 425(M^++1), 440, 422(M^++18).

3,4-Di-*O*-benzyl-2,6-dibromo-1,2,5,6-tetradeoxy-1,5-thio-L-gulitol (22): ^1H NMR: 7.33(m, 10H, Ph), 4.75-4.49(m, 5H, CH_2Ph, H_2), 3.93(dd, 1H, $J_{4,3}$ = 4.6, $J_{4,5}$ = 1.8, H_4), 3.70(m, 1H, H_3), 3.55(m, 1H, $J_{4,5}$ = 1.8, H_5), 3.35(m, 8H, $H_{6,6',1'}$), 2.50(dd, 1H, $J_{1,1'}$ = -12.7, $J_{1,2}$ = 3.9 H_1); ^{13}C NMR: 137.7, 137.4, 128.6, 128.5, 128.2(Ph), 76.5, 75.4($C_{3,4}$), 74.7, 73.3(CH_2Ph), 57.8C_2), 41.2C_5), 30.3, 30.0($C_{1,6}$); MS(CI, NH_3) 485, 487, 489(M^++1), 502, 504, 506(M^++18).

3,4-Di-*O*-benzyl-1,6-dibromo-1,2,5,6-tetradeoxy-2,5-thio-L-iditol (23): ^1H NMR: 7.32(m, 10H, Ph), 4.55(AB, 4H, J_{AB} = 11.5, CH_2Ph), 4.09(m, 4H, $H_{2,3}$), 3.70(dd, 2H, $J_{1,1'}$ = -9.7, $J_{1',2}$ = 10.5, $H_{1'}$), 3.10(dd, 2H, $J_{1,1'}$ = -9.7, $J_{1,2}$ = 4.4, H_1); MS(CI, NH_3) 485, 487, 489(M^++1), 502, 504, 506(M^++18).

Reaction of 20 with bis(tributyltin)oxide: To a solution of **20** (70 mg; 0.65 mmol) in DMF(1.5 mL) were successively added bis(tributyltin)oxide[11] (1.85 mL; 1.43 mmol) and silver nitrate (56 mg; 1.3 mmol). After stirring at 60°C for 19 h, water (3 mL) was added, and the mixture was filtered through Celite. The filtrate was extracted with CH_2Cl_2 (2x20 mL), and the combined organic layers were washed with brine (2x20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude (cyclohexane/acetone 7/3) afforded 45 mg (75%) of the tetrahydrothiopyrane **16** (R_f 0.29). Physical data of **16** are the same that those described above.

Mitsunobu reaction[10] with 15: To a solution of triphenylphosphine (833 mg; 3.15 mmol) in THF (20 mL) at 0°C was dropwise added diethyl azodicarboxylate (DEAD) (498 µL; 3.15 mmol). After 30 min stirring, benzoic acid (386 mg; 3.15 mmol) in THF (0.5 mL) and **15** (760 mg; 2.1 mmol) in THF (1 mL) were successively added dropwise. After stirring at 0°C for 1.5 h, the reaction mixture was concentrated *in vacuo*. Flash chromatography of the crude (CH_2Cl_2/EtOAc 95/5) afforded 784 mg (80%) of **21** (R_f 0.42). The same reaction on **15** (200 mg; 0.56 mmol) carried out with an excess of reagents [Ph_3P (877 mg; 3.33 mmol), DEAD

(525 µL; 3.33 mmol), $PhCO_2H$(407 mg; 3.33 mmol)] for 18 h at room temperature afforded, after flash chromatography (cyclohexane/EtOAc 3/2, then toluene/CH_2Cl_2 15/75), 150 mg (45%) of **24** (R_f 0.26) and 120 mg (35%) of **25** (R_f 0.36).

6-*O*-Benzoyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-thio-L-gulitol (21): $[\alpha]_D$ -34 (c 0.85, CH_2Cl_2); ^1H NMR: 7.91(m, 2H, Ph), 7.56(m, 2H, Ph), 7.42(m, 1H, Ph), 7.26(m, 10H, Ph), 4.65-4.52(m, 4H, CH_2Ph), 4.42-4.32(m, 2H, $J_{6',5} = J_{6,5} = 7.3$, $H_{6,6'}$), 4.16(m, 1H, H_2), 3.94(dd, 1H, $J_{3,4} = 5.3$, $J_{4,5} = 2.5$, H_4), 3.68(dd, 1H, $J_{3,4} = 5.3$, $J_{3,2} = 2.9$, H_3), 3.52(td, 1H, $J_{5,6} = J_{5,6'} = 7.3$, $J_{4,5} = 2.5$, H_5), 2.85(dd, 1H, $J_{1,1'} = -13.2$, $J_{1',2} = 10$, $H_{1'}$), 2.58(dd, 1H, $J_{1,1'} = -13.2$, $J_{1,2} = 4$, H_1).

2,6-Di-*O*-benzoyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-thio-L-gulitol (24): $[\alpha]_D$ -16 (c 0.56, CH_2Cl_2); ^1H NMR: 7.98(m, 4H, Ph); 7.57(m, 2H, Ph); 7.43(m, 4H, Ph); 7.25(*br.*s, 10H, Ph), 5.66(ddd, 1H, $J_{2,1} = 4$, $J_{2,1'} = 11.2$, $J_{2,3} = 2.4$, H_2), 4.91-4.60(m, 4H, CH_2Ph), 4.38(m, 2H, $J_{6,5} = J_{6',5} = 7.6$, $H_{6,6'}$), 4.05(dd, 1H, $J_{3,2} = 2.4$, $J_{3,4} = 4.8$, H_3), 3.90(dd, 1H, $J_{4,5} = 2$, $J_{4,3} = 4.8$, H_4), 3.75(td, 1H, $J_{6,5} = J_{5,6'} = 7.6$, $J_{5,4} = 2$, H_5), 3.34(dd, 1H, $J_{1,1'} = -12.4$, $J_{1',2} = 11.2$, $H_{1'}$), 2.66(dd, 1H, $J_{1,1'} = -12.4$, $J_{1,2} = 4$, H_1)

1,6-Di-*O*-benzoyl-3,4-di-*O*-benzyl-2,5-dideoxy-2,5-thio-L-iditol (25): $[\alpha]_D$ -26 (c 0.79, CH_2Cl_2); ^1H NMR: 7.95(m, 4H, Ph), 7.55(m, 2H, Ph), 7.41(m, 4H, Ph), 7.26(m, 10H, Ph), 4.65(dd, 4H, $J_{1,1'} = -10.8$, $J_{1',2} = 7.2$, $H_{1'}$), 4.53(*br.*s, 4H, CH_2Ph), 4.47(dd, 2H, $J_{1,1'} = -10.8$, $J_{1,2} = 7.2$, H_1), 4.14(m, 2H, $J_{3,2} = 3.6$, H_3), 4.04(m, 2H, $J_{2,3} = 3.6$, $J_{2,1} = J_{2,1'} = 7.2$, H_2).

3,4-Di-*O*-benzyl-2,5-dideoxy-2,5-thio-L-iditol (26): A solution of **25** (120 mg; 0.21 mmol) in MeOH (3 mL) in presence of K_2CO_3 (164 mg; 1.68 mmol) was stirred at 20°C for 4 h, then concentrated *in vacuo*, and diluted with CH_2Cl_2 (5 mL) and water (5 mL). After decantation and extraction (2x10 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (cyclohexane/EtOAc 1/1) afforded 68 mg (90%) of **26** (R_f 0.17). $[\alpha]_D$ -78 (c 0.95, CH_2Cl_2); ^1H NMR: 7.31(*br.*s, 10H, Ph), 4.70-4.59(AB, 4H, $J_{AB} = -11.6$, CH_2Ph), 4.28(m, 2H, H_3), 3.78-3.67(AB of ABX, 4H, $J_{AB} = -11.6$, $J_{AX} = 7.2$, $J_{BX} = 5$, $H_{1,1'}$), 3.52(m, 2H, H_2); ^{13}C NMR: 137.5, 128.6, 128.1, 127.8(Ph), 83.6(C_3), 73.2(CH_2Ph), 63.0(C_1), 45.2(C_2)

2,5-dideoxy-2,5-thio-L-iditol (27): De-*O*-benzylation of **26** (70 mg; 0.194 mmol) with a solution of boron tribromide in CH_2Cl_2 (1 $mol.L^{-1}$; 1.36 mL) was carried out under identical condtions described above, to give 28 mg (80%) of **27**. $[\alpha]_D$ -58 (c 0.75, CH_2Cl_2); ^1H NMR: 4.21(m, 1H, $J_{3,2} = 3.2$, H_3), 3.91-3.65(AB of ABX, 2H, $J_{AB} = -10$, $J_{AX} = 6.4$, $J_{BX} = 5.4$, $H_{1,1'}$), 3.72(X of ABX, 1H, $J_{AX} = J_{BX} = 6.4$, H_2); ^{13}C NMR: 79.2(C_3), 62.6(C_1), 52.5(C_2); HRMS calcd for $C_5H_9O_3S$ (M^+-CH_2OH) 149.0272, found 149.0272

Reaction of 8 with Ph_3P/CBr_4: The reaction of **8** (80 mg; 0.22 mmol) was carried out under identical conditions [CBr_4 (295mg; 1.11 mmol), Ph_3P (350 mg; 1.39 mmol)] for 48 h at 20°C described above, to give **28** (30%; R_f 0.33, cyclohexane/EtOAc 7/3). The same reaction on **8** (50 mg; 0.139 mmol) with an excess of reagents [CBr_4 (368 mg; 1.2 mmol), Ph_3P (365 mg; 2.2 mmol)] for 5 h at 70°C afforded, after flash chromatography (cyclohexane/toluene/CH_2Cl_2 10/7/3), **29** (36%; R_f 0.46)

3,4-Di-*O*-benzyl-6-bromo-1,5,6-trideoxy-1,5-thio-D-glucitol (28): ^1H NMR: 7.34-7.29(m 10H, Ph), 4.80(m, 4H, CH_2Ph), 3.83(m, 4H, $H_{6,6',2,4}$), 3.36(t, 1H, $J_{3,4} = J_{3,2} = 7.5$, H_3), 3.0(dt, 1H, $J_{5,4} = 10.3$, $J_{5,6} = J_{5,6'} = 5.1$, H_5), 2.88(dd, 1H, $J_{1',2} = 3.6$, $J_{1',1} = -13.4$, $H_{1'}$), 2.55(dd, 1H, $J_{1,2} = 8.9$, $J_{1',1} = -13.4$, H_1); ^{13}C NMR: 137.9, 135.7, 128.7, 128.6, 128.1, 127.9, 127.8(Ph), 84.3, 79.4($C_{3,4}$), 76.5, 75.1(CH_2Ph), 70.0(C_2), 46.2(C_5), 33.2C_6), 30.4(C_1).

3,4-Di-*O*-benzyl-1,6-dibromo-1,2,5,6-tetradeoxy-2,5-thio-D-mannitol (29): ^{1}H NMR: 7.33(m, 10H, Ph), 4.55(AB, 4H, J_{AB} = -12, CH_2Ph), 4.36(*br*.s, 2H, H_3), 3.84(dd, 2H, $J_{1,1'}$ = -10, $J_{1',2}$ = 10.8, $H_{1'}$), 3.71(dd, 2H, $J_{1',2}$ = 10.8, $J_{1,2}$ = 4.4, H_2), 3.54(dd, 2H, $J_{1',1}$ = -10, $J_{1,2}$ = 4.4, H_1).

Mitsunobu reaction with 8: The reaction of **8** (250 mg; 0.694 mmol) was carried out under identical conditions [Ph_3P (350 mg; 1.39 mmol), DEAD (164 µL; 1.04 mmol), $PhCO_2H$ (127 mg; 1.04 mmol)] for 5 h at 0°C described above to give, after flash chromatography (CH_2Cl_2/toluene 75/15 to 100/0), 145 mg(61%) of **30** (R_f 0.25) and 95 mg(24%) of **31** (R_f 0.32).

[1*R*-(6-*endo*,7-*exo*]-6,7-Di-*O*-benzyl-8-oxa-3-thiabicyclo-[3.2.1]-octane-6,7-diol (30): $[\alpha]_D$ -16 (c 2.4, CH_2Cl_2); ^{1}H NMR (500 MHz): 7.33(m, 10H, Ph), 4.67(AB, 4H, J_{AB} = -11.9, C_6-CH_2Ph), 4.55(s, 2H, C_7-CH_2Ph), 4.5(m, 2H, $H_{6,7}$), 4.33(m, 1H, $H_{1,5}$), 3.16(dd, 1H, $J_{4,4'}$ = -12.8, $J_{4',5}$ = 2.5, $H_{4'ax}$), 3.08(dd, 1H, $J_{2,2'}$ = -13, $J_{2',1}$ = 3, $H_{2'ax}$), 2.29(d, 1H, $J_{2,2'}$ = -13, H_{2eq}), 2.14(d, 1H, $J_{4,4'}$ = -12.8, H_{4eq}); ^{13}C NMR: 137.8, 137.7, 128.3, 127.8(Ph), 86.6, 86.3($C_{6,7}$), 78.5, 75.9($C_{1,5}$), 72.7, 71.7(CH_2Ph), 29.0, 24.6($C_{4,2}$); Anal. calcd for $C_{20}H_{22}O_3S$: C, 70.15 H, 6.48, found: C, 70.07 H, 6.49.

1,6-Di-*O*-benzoyl-3,4-di-*O*-benzyl-2,5-dideoxy-2,5-thio-D-mannitol (31): $[\alpha]_D$ +48 (c 1.07, CH_2Cl_2); ^{1}H NMR: 7.96(m, 4H, Ph); 7.55(m, 2H, Ph); 7.41(m, 4H, Ph); 7.25(*br*.s, 10H, Ph), 4.59(*br*.s, 4H, CH_2Ph), 4.53(dd, 2H, $J_{1,1'}$ = -11.3, $J_{1',2}$ = 8.1, $H_{1'}$), 4.38(dd, 2H, $J_{1,1'}$ = -11.3, $J_{1,2}$ = 6.9, H_1), 4.23(m, 2H, H_3), 3.82(m, 2H, H_2).

3,4-Di-*O*-benzyl-2,5-dideoxy-2,5-thio-D-mannitol (32): Methanolysis of **31** (100mg; 0.278 mmol) in presence of K_2CO_3 (139 mg) was carried out under identical conditions described above, to give 57 mg (90%) of **32** (R_f 0.4 cyclohexane/acetone 3/2). $[\alpha]_D$ +46 (c 0.61, CH_2Cl_2); ^{1}H NMR: 7.31(m, 10H, Ph), 4.64(AB, 4H, J_{AB} = -11.6, CH_2Ph), 4.10(m, 2H, H_3), 3.69(m, 4H, H_1), 3.50(m, 2H, H_2); ^{13}C NMR: 137.6, 128.5, 127.9, 127.8(Ph), 85.9(C_3), 72.8(CH_2Ph), 63.3(C_1), 51.1(C_2).

2,5-dideoxy-2,5-thio-D-mannitol (33): De-*O*-benzylation of **32** (80 mg; 0.22 mmol) with a solution of boron tribromide in CH_2Cl_2 (1 mol.L^{-1}; 1.55 mL) was carried out under identical conditions described above, to give 30 mg (75%) of **33**. $[\alpha]_D$ +105 (c 0.82, CH_2Cl_2); ^{1}H NMR: 3.87(dd, 2H, $J_{1,1'}$ = -11.2, $J_{1',2}$ = 4.4, $H_{1'}$), 3.74(m, 2H, H_3), 3.58(dd, 2H, $J_{1,1'}$ = -11.2, $J_{1,2}$ = 7, H_1), 3.80(m, 2H, H_2); ^{13}C NMR: 80.1(C_3), 65.4(C_1), 50.8(C_2); HRMS calcd for $C_5H_9O_3S$ (M^+-CH_2OH) 149.0272, found 149.0272.

2,5-Anhydro-3,4-di-*O*-benzyl-1,6-dideoxy-L-gulitol (34): To a suspension of Raney nickel (104 mg; 50% in water) was added **30** (60 mg; 0.175 mmol) in ethanol (1 mL). The reaction mixture was refluxed for 16 h, then cooled to 20°C and filtered through a Celite pad. The filtrate was concentrated to about one half of its initial volume, saturated with NaCl and extracted with ethyl acetate (3x5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude (CH_2Cl_2:EtOAc 95/5) afforded 46 mg (85%) of **34**. $[\alpha]_D$ +36 (c 1.33, CH_2Cl_2); ^{1}H NMR: 7.32(m, 10H, Ph), 4.60-4.49(m, 4H, CH_2Ph), 4.06(qd, 1H, J = 6.4, J = 4, $H_{2\text{ or }5}$), 3.86(qd, 1H, J = 6.4, J = 4.4, $H_{5\text{ or }2}$), 3.77(dd, 1H, J = 1.2, J = 4, $H_{3\text{ or }4}$), 3.63(dd, 1H, J = 1.2, J = 4.4, $H_{4\text{ or }3}$), 1.33, 1.32(2d, 6H, $J_{6,5}$ = $J_{1,2}$ = 6.4, $H_{1,6}$); ^{13}C NMR: 138.2, 137.9, 128.5, 128.4, 127.8, 127.7, 127.5(Ph), 89.5, 84.6($C_{3,4}$), 79.2, 76.9($C_{2,5}$), 71.8, 71.5(CH_2Ph); 19.7, 14.2($C_{1,6}$); MS (CI, NH_3) 313(M^++1), 330(M^++18).

Oxidation by periodate: To an aqueous solution (1.3 mL) of sodium periodate (43 mg; 0.2 mmol) was added at 0°C a solution of thiosugar (0.2 mmol) in acetone (0.8 mL), then the reaction mixture was diluted by addition of water (2 mL). The reaction was monitored by t.l.c. The mixture was then filtered, and the filtrate extracted

with CH_2Cl_2 (3x15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude afforded the corresponding sulfoxide (80-88%).

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-thio-L-iditol-S-oxide (35): R_f 0.38(CH_2Cl_2/MeOH 95/5); mp 150-152°C; $[\alpha]_D$ +13 (c 1.63, CH_2Cl_2); ^1H NMR: 7.27(m, 10H, Ph), 4.77-4.48(m, 5H, $J_{5,6}$ = 2, CH_2Ph, H_5), 4.36(dt, 1H, $J_{2,3}$ = 7, $J_{2,1}$ = 7.3, $J_{2,1'}$ = 7, H_2), 3.86(dd, 1H, $J_{3,4}$ = 4.1, $J_{2,3}$ = 7, H_3), 3.71(dd, 1H, $J_{3,4}$ = 4.1, $J_{5,4}$ = 8, H_4), 3.32(m, 2H, $H_{1',6'}$), 3.15(m, 2H, $J_{5,6}$ = 2, $H_{1,6}$); ^{13}C NMR: 137.3, 137.0, 128.7, 128.3, 128.0, 127.9(Ph), 83.4, 81.7($C_{3,4}$), 73.8, 73.4(CH_2Ph), 69.4, 64.8($C_{2,5}$), 58.8, 50.7($C_{1,6}$) ; Anal. calcd for $C_{20}H_{24}O_5S$: C, 63.81 H, 6.43 found: C, 63.68 H, 6.47.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-thio-D-mannitol-S-oxide (38): R_f 0.32(CH_2Cl_2/MeOH 95/5); $[\alpha]_D$ -22 (c 1.07, CH_2Cl_2); ^1H NMR: 7.29(m, 10H, Ph), 4.72-4.50(m, 5H, CH_2Ph, H_2), 3.93(m, 1H, $J_{5,6'}$ = 4.8, H_5), 3.86(m, 1H, $J_{5,6'}$ = 4.8, $H_{6'}$), 3.68(m, 1H, H_6), 3.48(dd, 1H, $J_{1',2}$ = 9.2, $J_{1,1'}$ = -14.8, $H_{1'}$), 3.31(m, 2H, $H_{3,4}$), 2.95(d, 1H, $J_{1,1'}$ = -14.8, H_1); ^{13}C NMR: 137.7, 137.6, 128.6, 128.5, 128.1, 127.9(Ph), 80.0, 79.1($C_{3,4}$), 73.8, 73.2(CH_2Ph), 64.2, 63.5($C_{2,5}$), 53.2, 52.0($C_{1,6}$) ; MS (CI, NH_3) 377(M^++1).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-thio-D-glucitol-(*S,R*)-S-oxide (41): R_f 0.32 (EtOAc); ^1H NMR (500 MHz), mixture (1/1) of two diastereomers marked a and b: 7.34-7.26(m, 10H, Ph), 4.67(dt, 0.5H, $J_{b1,2}$ = 7.4, $J_{b1',2}$ = $J_{b3,2}$ = 4.8, H_{b2}), 4.6-4.38(m, 4.5H, $J_{a1,2}$ = 2.8, $J_{a1',2}$ = 10, $J_{a3,2}$ = 3.8, CH_2Ph, H_{a2}), 4.08(dd, 0.5H, $J_{b4,5'}$ = 4, $J_{b3,4}$ = 2.2, H_{b4}), 4.04(dd, 0.5H, $J_{b3,2}$ = 4.8, $J_{b3,4}$ = 2.2, H_{b3}), 4.02-3.98(m, 1.5H, $H_{6,6',a4}$), 3.93(m, 0.5H, $J_{a3,2}$ = 3.8, $J_{a3,4}$ = 1, H_{a3}), 3.73-3.55(2m, 2H, $H_{6,6',5}$), 3.45(dd, 0.5H, $J_{a1',2}$ = 10, $J_{a1,1'}$ = -13.5, $H_{a1'}$), 3.14(AB, 1H, J_{AB} = -14.2, $J_{b1',2}$ = 4.8, $J_{b1,2}$ = 7.4, $H_{b1,1'}$), 2.99(dd, 0.5H, $J_{a1,2}$ =2.7, $J_{a1,1'}$ = -13.5, H_{a1}); ^{13}C NMR: 137.5, 137.4, 137.1, 137.0, 128.6, 128.2, 128.0, 127.6(Ph), 85.0, 84.6, 83.7, 83.2, 82.4, 81.8($C_{2,3,4}$), 75.2, 73.7(C_5), 72.1, 72.0, 71.8, 71.6(CH_2Ph), 62.6, 62.3(C_6), 52.9, 51.3(C_1).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-thio-L-gulitol-(*S*)-S-oxide (44a): R_f 0.4(CH_2Cl_2/MeOH 95/5); $[\alpha]_D$ +48 (c 0.89, CH_2Cl_2); ^1H NMR: 7.90(m, 10H, Ph), 4.60-4.37(m, 4H, CH_2Ph), 4.20(dd, 1H, $J_{6,6'}$ = -11.6, $J_{6',5}$ = 5.6, $H_{6'}$), 4.06(m, 2H, $J_{2,1}$ = 3.5, $H_{2,4}$), 3.91(dd, 1H, $J_{6,5}$ = 6.8, $J_{6,6'}$ = -11.6, H_6), 3.73(m, 1H, H_3), 3.42(dd, 1H, $J_{1,1'}$ =-11.6, $J_{1,2}$ = 3.5, H_1), 3.10(m, 2H, $J_{5,6'}$ = 5.6, $J_{1,1'}$ = -11.6, $H_{1',5}$); ^{13}C NMR: 137.1, 136.6, 128.8, 128.7, 128.5, 128.4, 128.1(Ph), 75.0, 74.5($C_{3,4}$), 73.6, 73.2(CH_2Ph), 64.2, 62.9($C_{2,5}$), 60.1(C_6) , 52.1(C_1); Anal. calcd for $C_{20}H_{24}O_5S$: C, 63.81 H, 6.43 found: C, 63.69 H, 6.55.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-thio-L-gulitol-(*R*)-S-oxide (44b): R_f 0.27; $[\alpha]_D$ -58 (c 1.02, CH_2Cl_2); ^1H NMR: 7.31(m, 10H, Ph), 4.78-4.46(m, 5H, CH_2Ph, H_2), 4.27(dd, 1H, $J_{6,6'}$ = -11.7, $J_{6',5}$ = 5.2, $H_{6'}$), 4.00(m, 1H, $J_{4,3}$ = 5.9, $J_{4,5}$ = 3.7, H_4), 3.91(dd, 1H, $J_{6,5}$ = 5.2, $J_{6,6'}$ = -11.7, H_6), 3.80(m, 1H, $J_{4,3}$ = 5.9, $J_{3,2}$ = 2.4, H_3), 3.16(AB, 1H, J_{AB} = -13.5, $J_{1,2}$ = 3.6, $J_{1',2}$ = 8.9, $H_{1,1'}$), 2.98(m, 1H, H_5); ^{13}C NMR: 137.3, 137.2, 128.6, 128.3, 128.0, 127.9(Ph), 76.4, 75.2($C_{3,4}$), 73.6, 73.1(CH_2Ph), 62.3(C_2), 58.1(C_6) , 55.5(C_5), 47.2(C_1) .

Oxidation by peracide: To a solution of thiosugar (120 mg; 0.33 mmol) in CH_2Cl_2 (3 mL) was successively added calcium carbonate (133 mg; 1.32 mmol) and *meta*-chloroperbenzoic acid (144 mg; 0.825 mmol). The reaction was monitored by t.l.c. The reaction mixture was then filtered, and the filtrate washed with an aqueous solution of sodium bisulfite (1x10 mL), then with a saturated aqueous solution of $NaHCO_3$ (3x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude afforded the corresponding sulfone (60-92%).

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-thio-L-iditol-S,S-dioxide (36): R_f 0.34 (cyclohexane/EtOAc 2/3); $[\alpha]_D$ +28 (c 1.29, CH_2Cl_2); ^1H NMR: 7.30(m, 10H, Ph), 4.60(AB, 4H, J_{AB} = -11.7, CH_2Ph), 4.40(m, 2H, H_2), 3.78(m, 2H, H_3), 3.41(d, 4H, $J_{1,2}$ = $J_{1',2}$ = 4.9, $J_{1,1'}$ < 1, H_4); ^{13}C NMR: 137.0, 128.6, 128.3, 128.1(Ph), 81.2(C_3),

73.5(CH_2Ph), 67.4(C_2), 55.9(C_1) ; Anal. calcd for $C_{20}H_{24}O_6S$, 0.6 H_2O: C, 59.57 H, 6.30 found: C, 59.53 H, 6.23.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-thio-D-mannitol-S,S-dioxide (39): R_f 0.3 (cyclohexane/EtOAc 1/1); mp 121°C; $[\alpha]_D$ -13 (c 1.17, CH_2Cl_2); ^1H NMR: 7.80(m, 10H, Ph), 4.63(AB, 4H, J_{AB} = -12, CH_2Ph), 4.38(m, 2H, H_2), 3.85(dd, 2H, $J_{1,1'}$ = -14.4, $J_{1',2}$ = 10.8, $H_{1'}$), 3.79(*br.*s, 2H, H_3), 3.15(d, 2H, $J_{1',1}$ = -14.4, $J_{1,2}$ < 1, H_1); ^{13}C NMR: 137.5, 128.7, 128.3, 128.1(Ph), 79.4(C_3), 73.8(CH_2Ph), 64.7(C_2), 56.9(C_1); Anal. calcd for $C_{20}H_{24}O_6S$: C, 61.21 H, 6.16 found: C, 61.23 H, 6.26.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-thio-D-glucitol-S,S-dioxide (42): R_f 0.33 (cyclohexane/EtOAc 2/3); $[\alpha]_D$ +19 (c 0.89, CH_2Cl_2); ^1H NMR: 7.29(m, 10H, Ph), 4.6-4.1(m, 5H, CH_2Ph, H_2), 4.00(m, 4H, $H_{1',3,4,5}$), 3.57(m, 2H, $J_{6',5}$ = 2.6, $J_{6,5}$ = 4.3, $J_{6,6'}$ = -12.6, $H_{6,6'}$), 2.98(*br.*d, 1H, $J_{1,1'}$ = -15.6, H_1); ^{13}C NMR: 137.3, 136.7, 129.7, 128.7, 128.6, 128.3, 128.0, 127.6(Ph), 85.2, 83.1, 81.4($C_{2,3,4}$), 75.8(C_5), 72.1, 71.7(CH_2Ph), 62.0(C_6), 54.6,(C_1).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-thio-L-gulitol-S,S-dioxide (45): R_f 0.36 (cyclohexane/acetone 55/45); mp 89°C; $[\alpha]_D$ -6 (c 1.21, CH_2Cl_2); ^1H NMR: 7.80(m, 10H, Ph), 4.60-4.45(m, 4H, CH_2Ph), 4.41(m, 1H, H_2), 4.26(dd, 1H, $J_{6,6'}$ = -11.6, $J_{6',5}$ = 5.2, $H_{6'}$), 4.04(m, 1H, H_4), 3.87(dd, 1H, $J_{6,6'}$ = -11.6, $J_{6,5}$ = 6.8, H_6), 3.82(m, 1H, H_3), 3.35(m, 2H, $H_{1'}$), 3.24(dd, 1H, $J_{1,1'}$ = -13.6, $J_{1,2}$ = 4.4, H_1); ^{13}C NMR: 137.0, 136.8, 128.9, 128.8, 128.6, 128.4, 128.1(Ph), 75.7, 72.3($C_{3,4}$), 73.7, 73.4(CH_2Ph), 65.6(C_2), 60.2(C_5) , 55.9(C_6), 53.4(C_1); Anal. calcd for $C_{20}H_{24}O_6S$, 0.8 H_2O: C, 59.04 H, 6.34 found: C, 59.08 H, 6.15.

De-*O*-benzylation of sulfoxide 44a and sulfones 36, 42 and 45: This reaction, with a solution of boron tribromide in CH_2Cl_2, was carried out under identical conditions described above.

1,6-dideoxy-1,6-thio-L-iditol-S,S-dioxide (37): R_f 0.35 (CH_2Cl_2/MeOH 7/3 with ammonia 1%); ^1H NMR (CD_3OD): 4.12(m, 2H, H_2), 3.66(m, 2H, $J_{3,2}$ = 1.9, H_3), 3.39(m, 4H, $H_{1,1'}$); ^{13}C NMR: 77.3(C_3), 69.0(C_2), 58.3(C_1).

1,5-dideoxy-1,5-thio-D-glucitol-S,S-dioxide (43): R_f 0.45 (CH_2Cl_2/MeOH 3/2 with ammonia 1%); $[\alpha]_D$ +11 (c 0.925, MeOH); ^1H NMR (CD_3OD): 4.48(dt, 1H, $J_{2,1'}$ = 9.2, $J_{2,1}$ = 2.8, $J_{2,3}$ = 3.2, H_2), 3.96(m, 2H, $J_{2,3}$ = 3.2, $H_{3,4}$), 3.83(m, 1H, H_5), 3.74(dd, 1H, $J_{1',1}$ = -14.8, $J_{2,1'}$ = 9.2, H_1), 3.68(m, 2H, $H_{6,6'}$), 3.34(m, 1H, $J_{1,2}$ = 2.8, H_1); ^{13}C NMR: 88.1, 79.5, 79.4($C_{3,4,2}$), 77.3(C_5), 63.5(C_6), 55.6(C_1).

1,5-dideoxy-1,5-thio-L-gulitol-(*S*)-S-oxide (47): R_f 0.4 (CH_2Cl_2/MeOH 3/2 with ammonia 1%); $[\alpha]_D$ -19 (c 0.52, MeOH); ^1H NMR (CD_3OD): 4.08(m 1H, $J_{4,3}$ = 4.8, $J_{4,5}$ = 1.9, H_4), 4.04(m, 1H, $J_{2,3}$ = 2.6, H_2), 3.98(m, 1H, $J_{2,3}$ = 2.6, $J_{3,4}$ = 4.8, H_3), 3.70(dd, 1H, $J_{6,6'}$ = -11.0, $J_{6',5}$ = 6.9, $H_{6'}$), 3.57(dd, 1H, $J_{6,6'}$ = -11.0, $J_{6,5}$ = 6.6, H_6), 3.39(m, 1H, $J_{5,4}$ = 1.9, H_5), 2.90(dd, 1H, $J_{1,1'}$ = -12.6, $J_{1',2}$ = 10.8, $H_{1'}$), 2.33(dd, 1H, $J_{1,1'}$ = -12.6, $J_{1,2}$ = 4, H_1); ^{13}C NMR: 71.8, 71.6($C_{3,4}$), 64.7, 64.5($C_{2,5}$), 58.7(C_6), 52.1(C_1).

1,5-dideoxy-1,5-thio-L-gulitol-S,S-dioxide (46): R_f 0.3 (CH_2Cl_2/MeOH 4/1 with ammonia 1%); $[\alpha]_D$ +9 (c 0.97, MeOH); ^1H NMR (CD_3OD): 4.30(ddd, 1H, $J_{1,2}$ = 4, $J_{2,1'}$ = 11.6, $J_{2,3}$ = 2, H_2), 4.22(m, 1H, $J_{4,3}$ = 4.8, $J_{4,5}$ = 4.2, H_4), 4.15(dd, 1H, $J_{6,6'}$ = -11.6, $J_{6',5}$ = 4.8, $H_{6'}$), 3.95(m, 2H, $J_{6',6}$ = -11.6, $J_{6,5}$ = 8, $J_{3,4}$ = 4.8, $J_{3,2}$ = 2, $H_{6,3}$), 3.39(dd, 1H, $J_{1',1}$ = -13.2, $J_{2,1'}$ = 11.6, $H_{1'}$), 3.31(m, 1H, $J_{5,6}$ = 8, $J_{5,6'}$ = 4.8, H_5), 3.05(dd, 1H, $J_{1,1'}$ = -13.2, $J_{1,2}$ = 4, H_1); ^{13}C NMR: 72.3, 69.6($C_{3,4}$), 66.2(C_2), 60.7(C_5), 55.2(C_6), 54.2(C_1).

1,6-dideoxy-1,6-thio-D-mannitol-S,S-dioxide (40): Palladium black (30 mg) in acetic acid (3 mL) was completely hydrogenated prior to the addition of **39** (50 mg; 0.127 mmol) in acetic acid (0.5 mL). After stirring for 5 h, the catalyst was removed by filtration through a Celite pad and rinsed with acetic acid. Concentration *in vacuo* and flash chromatography of the crude (CH_2Cl_2/MeOH 85/15) afforded 16.8 mg (60%) of **40** (R_f 0.45).

Mp 180°C; $[\alpha]_D$ +17 (c 0.57, MeOH); ^1H NMR (CD_3OD): 4.50(*br.*d, 2H, $J_{2,1'}$ = 9.6, H_2), 4.02(*br.*s, 2H, H_3), 3.89(dd, 2H, $J_{1,1'}$ = -14.8, $J_{1',2}$ = 9.6, $H_{1'}$), 3.47(*br.*d, 2H, $J_{1',1}$ = -14.8, H_1); ^{13}C NMR: 76.0(C_3), 65.1(C_2), 57.0(C_1); MS (CI, NH_3) 312(M^+), 330(M^++18).

Inhibition analysis. α-D-Glucosidase from *Bacillus stearothermophilus*, β-D-glucose from almonds, α-D-mannosidase from jack bean and α-L-fucosidase from bovine kidney were purchased from Sigma. K_i determinations were run at 37°C using the corresponding *p*-nitrophenyl-α-(or β)-glycoside at the optimum pHs (citrate-phosphate buffer of pH 6.8, 5.0, 4.5 and 5.5 for α-D-glucosidase, β-D-glucosidase, α-D-mannosidase and α-L-fucosidase, respectively). For the inhibition studies, inhibitors were incorporated variously into each buffer to give a final concentration in the range 10^{-7}-10^{-3} mol.L^{-1}. Dissociation constants for inhibition were calculated from the slopes of plots 1/v against 1/[S] from the rates of substrate hyrolysis in the absence and presence of inhibitor (Lineweaver-Burk plots).

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