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THIOSUGARS FROM *D*-MANNITOL

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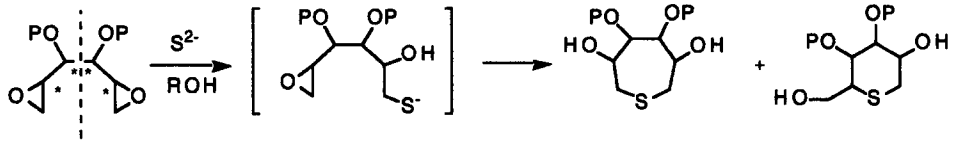
Abstract : Enantiomerically pure thiosugars, with a thiepan, tetrahydrothiopyran or tetrahydrothiophene backbone, have been synthesized by thio-heterocyclization of enantiopure C_2-symmetric bis-epoxides and possibly ring contraction.

Sugars including intracyclic sulfur atom (thiosugars) are of considerable interest at present. For example, 5-thio-*D*-glucose inhibits the release of insuline,[1] 5-thio-α-*L*-fucose is a specific inhibitor of bovine α-*L*-fucosidase,[2] 5-thio-*D*-mannose has been isolated from a marine sponge,[3] 1-deoxythiomannojirimycin is a weak competitive inhibitor of yeast α-D-glucosidase.[4] Morever, an iminothiosugar has recently been proposed as a potential transition-state analogue of a glycosidase.[5]

In an effort to develop new syntheses of enantiomerically pure thiosugars to study their glycosidase inibitor activity, we have examined the opening of homochiral C_2-symmetric bis-epoxides by the sulfide ion :



C_2 axis of symmetry, P = protecting group

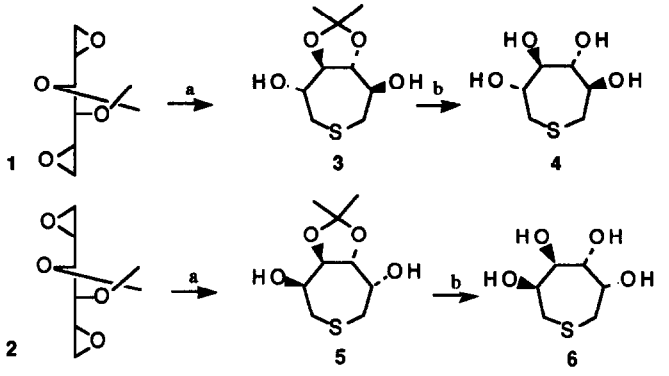
This approach, which involves a regiospecific opening of one epoxy function by S^{2-} followed by the expected thioheterocyclization, relied on the higher nucleophilicity of the thiolate group than that of the liberated hydroxyl group resulting from the opening of the first epoxide.

Thioheterocyclization of 1,2:5,6-dianhydro-3,4-di-*O*-isopropylidene-*L*-iditol **1** and *D*-mannitol **2** has previously been reported.[6] In that case, where the 3,4-diol is protected in a *trans*-dioxolane, the thiepanes **3** and **5** were, respectively, the only products obtained (Scheme I).[7]

We anticipated that the nucleophilic ring opening of the flexible bis-epoxides **7** and **8** (Scheme II) where the 3,4-diol is protected as a dibenzyl ether, would enable the synthesis of tetrahydrothiopyran by the 6-exo-tet process.[8] 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-*L*-iditol **7** and *D*-mannitol **8** can be prepared on a multigram scale from *D*-mannitol.[9] The reaction of bis-epoxide **7** 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 **9** and tetrahydrothiopyran **10** were isolated in 65% and 23% yield, respectively.

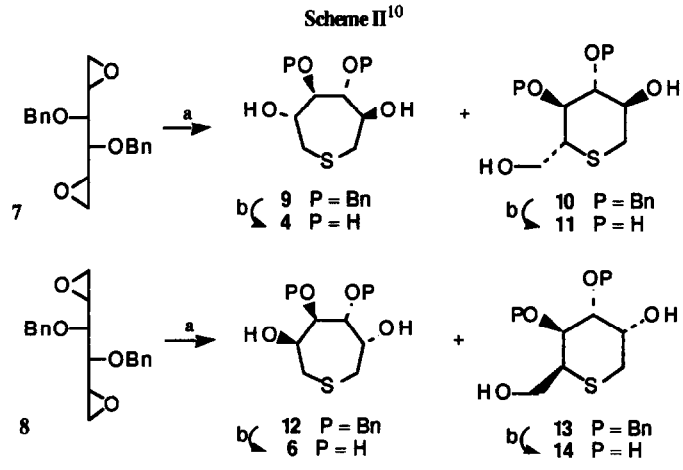
Scheme I[6,7]



a) $Na_2S.9\ H_2O$, EtOH, reflux, 90% from 1; 60% from 2 with Al_2O_3;[7] b) CF_3CO_2H, H_2O, 20°C, 75%

Under the same conditions, the diastereomeric bis-epoxide **8** gave the corresponding thiepane **12** (75%) and tetrahydrothiopyran **13** (≤ 10% yield).

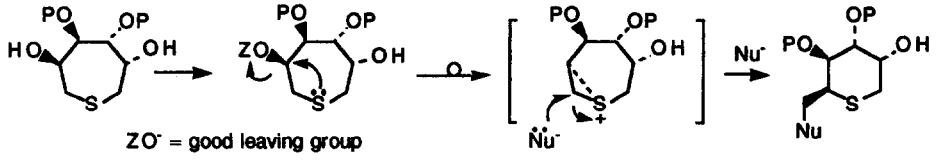
Scheme II[10]



a) $Na_2S.9\ H_2O$, EtOH, reflux; b) BBr_3, CH_2Cl_2, -50°C, 85%

The C_2 symmetric thiepanes **9** and **12** were correlated to **4** and **6**, respectively, after de-*O*-benzylation with a solution of boron tribromide in CH_2Cl_2 at -50°C (85% yield).[11] These conditions applied to **10** or **13** gave the new polyhydroxytetrahydrothiopyran **11** (1-deoxythionojirimycin, the thio analogue of the glycosidase inhibitor 1-deoxynojirimycin[12]) or **14** (1,5-anhydro-5-thio-*D*-glucitol), respectively.

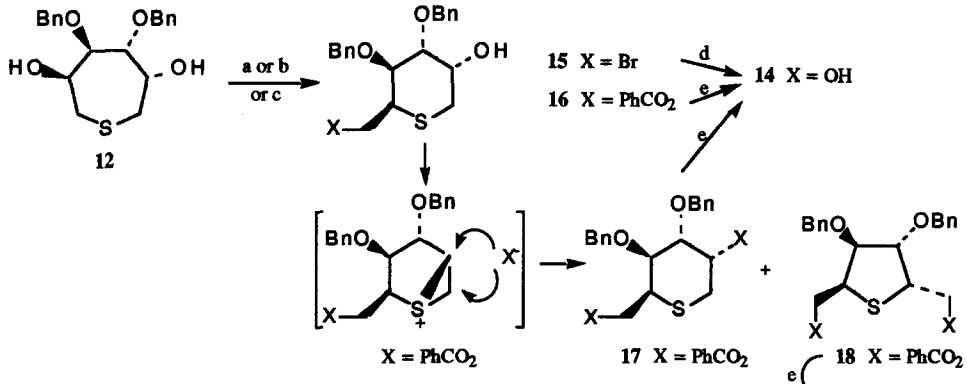
In order to obtain tetrahydrothiopyran in a higher yield, we tried to isomerize the C_2 symmetric thiepane skeleton[13] through an episulfonium :



ZO^- = good leaving group

After many experiments, we found that the treatment of **12** with 2.5 eq of triphenylphosphine-CBr_4 under acetonitrile reflux gave the bromotetrahydrothiopyran **15** in 45% yield (Scheme III). To confirm this structure, the primary organic bromide **15** was transformed into the corresponding alcohol **14** by bis(tributyltin)oxide in presence of silver nitrate in DMF at 60°C (74% yield).[14] Interestingly, we observed that the ring contraction can be achieved in a higher yield under the Mitsunobu conditions.[15] Thus, the action of 1.5 eq of triphenylphosphine-diethylazodicarboxylate-benzoic acid on **12** in THF at 0°C afforded the benzoate **16** (80% yield), which lead to the alcohol **14** by methanolysis (90% yield). It should be noted that these results confirm, firstly that episulfonium is formed by a stereospecific process, not by a sulfur carbonium SN_1 process, and secondly, that the ring contraction takes place towards the more stable tetrahydrothiopyran. We also observed that the treatment of **12** with 4 eq of Ph_3P-$PhCO_2H$-DEAD at 20°C led to a mixture of compounds, from which the tetrahydrothiopyran **17** and the C_2 symmetric tetrahydrothiophene **18** were isolated in 43% and 33% yield, respectively. By methanolysis, **17** gave the alcohol **14**, and **18** the C_2 symmetric tetrahydrothiophene **19**.

Scheme III[10]

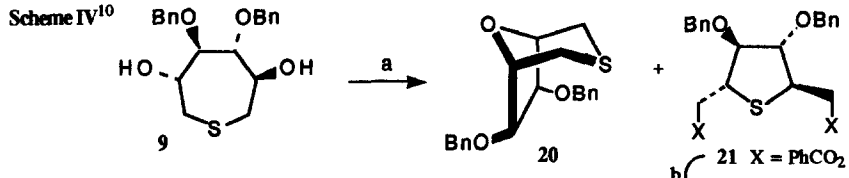


a) 2.5 eq Ph_3P, CBr_4, CH_3CN, reflux, 45% of **15**; b) 1.5 eq Ph_3P-DEAD-$PhCO_2H$, THF,0°C, 80% of **16**; c) 4 eq Ph_3P-DEAD-$PhCO_2H$, THF, 20°C, 43% and 33% of **17** and **18**, respect.; d) $(Bu_3Sn)_2O$, $AgNO_3$, DMF, 60°C, 74%; e) MeOH, K_2CO_3, 90%.

This result shows that in presence of an excess of reagents, the thiepane **12** affords the thiopyran **16**, and the latter undergoes, *in situ*, a transformation to an episulfonium intermediate, the nucleophilic opening of which giving rise to the formation of the two isomers.

These Mitsunobu conditions applied to the diastereomeric thiepane **9** (Scheme IV) gave a mixture of the bridged thioether **20** and of the C_2 symmetric tetrahydrothiophene **21**, respectively isolated in 61% and 24% yield. The latter, by methanolysis, gave 3,4-di-*O*-benzyl-2,5-dideoxy-2,5-thio-*D*-mannitol **22**, the thio analogue

Scheme IV[10]



a) 4 eq Ph_3P-DEAD-$PhCO_2H$, THF, 20°C, 61% and 24% of **20** and **21**, respect.; b) MeOH, K_2CO_3, 90%.

of the glycosidase inhibitor DMDP.[12] The formation of the bridged thioether **20** 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.

In conclusion, starting from homochiral C_2 symmetric bis-epoxides, prepared from *D*-mannitol, the synthesis of enantiomerically pure polyhydroxytetrahydrothiopyran (1-deoxythionojirimycin and its *L*-gulito analogue), and of polyhydroxytetrahydrothiophene (2,5-dideoxy-2,5-thio-*L*-iditol and *D*-mannitol)[16] has been achieved by sulfide heterocylization and subsequent ring contractions. Further utilization of this methodology in the synthesis of polyhydroxylated thioheterocycles and related systems, as well as relevant biological data of these new compounds with several glycosidases, will be reported in due course.

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7. We have simplified and improved the synthesis of **3** and **5** by the following procedure : reaction of **1** (or **2**) with 2 equiv of $Na_2S.9\ H_2O$ under EtOH reflux afforded directly, after flash chromatography, the crystalline thiepane **3** (or **5**) in 90% (or 50%) yield. The yield of **5** could be increased up to 60% by carrying out this reaction with alumina supported sodium sulfide reagent (Czech, B., Quici, S.; Regen, S.L. *Synthesis* **1980**, 113; Lay Choo Tan; Pagni, R.M.; Kabalka, G.W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* **1992**, *33*, 7709-7712).
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16. Selected physical data of thiosugars **11**, **14**, **19** and **22** :

    11 : $[\alpha]_D$ +50 (c 1.39, MeOH); ^1H NMR (250 MHz, CD_3OD) 4.12(X from ABMX, 1H, J_{XA} 6.8, J_{XB} 7.2, $J_{2,3}$ 3.2, H_2), 3.96-3.88(m, 2H, $H_{4,3}$), 3.79(X from ABMX, 1H, J_{XA} 4.1, J_{XB} 5.2, $J_{5,4}$ 2.8, H_5), 3.68, 3.62(AB from ABX, 2H, J_{AB} 11.6, J_{AX} 4.1, J_{BX} 5.2, $H_{6,6'}$), 2.81, 2.86(AB from ABX, 2H, J_{AB} 15.4, J_{AX} 6.8, J_{BX} 7.2, $H_{1,1'}$); ^{13}C NMR (CD_3OD) 87.8, 84.7, 80.2, 78.4(C_{2-5}), 63.6(C_6), 31.6(C_1).

    14 : $[\alpha]_D$ -14 (c 0.65, MeOH); ^1H NMR (250 MHz, CD_3OD) 4.04(m, 1H, H_4), 4.0(m, 1H, H_2), 3.78(m, 1H, H_3), 3.68-3.56(AB from ABX, 2H, J_{AX} 7.2, J_{AB} 11.2, J_{BX} 6.7, $H_{6,6'}$), 3.27(m, 1H, H_5), 2.89(q, 1H, $J_{1',2}$ 11, $J_{1,1'}$ 13, $H_{1'}$), 2.30(q, 1H, $J_{1,2}$ 4, $J_{1,1'}$ 13, H_1); ^{13}C NMR (CD_3OD) 73.1, 71.7, 68.7, 44.1(C_{2-5}), 62.6(C_6), 28.6(C_1).

    19 : $[\alpha]_D$ -78 (c 0.95, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) 7.31(large s, 10H, Ph), 4.73, 4.57(AB, 4H, CH_2Ph), 4.28(m, 2H, H_3), 3.78, 3.67(AB from ABX, 4H, J_{AB} 11.6, J_{AX} 7.2, J_{BX} 5, H_1), 3.52(m, 2H, H_2); ^{13}C NMR ($CDCl_3$) 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).

    22 : $[\alpha]_D$ +46 (c 0.61, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) 7.31(m, 10H, Ph), 4.70, 4.59(AB, 4H, CH_2Ph), 4.10(m, 2H, H_3), 3.69(m, 4H, H_1), 3.50(m, 2H, H_2); ^{13}C NMR ($CDCl_3$) 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).

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