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Synthesis of C_2-Symmetric *Bis*(Cyclic Isothioureas) As Potent Inhibitors of Glycosidases

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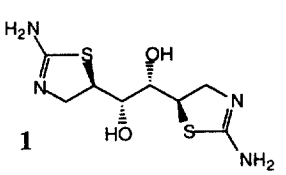
Abstract : Enantiopure C_2-symmetric *bis*(cyclic isothioureas), considered as potent inhibitors of glycosidases, have been synthesized from D-mannitol. The key step involved a mercuric-catalyzed transformation of a cyclic 1,3-thiazolidine-2-thione into a 2-*N*-*tert*-butylamino-1,3-thiazoline.

Keywords : Glycosidase, Isothiourea, Thioformamide, Thiazolidinethione, Mercuric chloride.

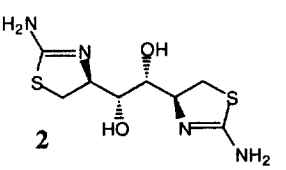
Glycosidases are involved in many biological processes, such as glycoprotein trimming, catabolism of glycoconjugates and degradation of polysaccharides. As a consequence, specific inhibitors of these enzymes are of great interest as possible therapeutic agents to treat many diseases such as diabete,[1] cancer[2] or viral infections.[3]

Most inhibitors of glycosidases described to date are mimics of the supposed transition state oxocarbenium.[4] Among sugar mimics,[5] azasugars are structures that are the most widely used. However, we focused our attention to other structures, namely isoureas[6] and isothioureas[7] which were already combined with an aminocyclitol or a sugar and revealed to be active against glycosidases. Our goal was to examine the potent inhibitory activity of such compounds in the absence of the sugar-like moiety.

As a matter of fact, we decided to synthesize some cyclized C_2-symmetric *bis*(isothioureas) from D-mannitol. We report here preliminary results concerning the syntheses of the enantiopure *bis*(2-amino-1,3-thiazolines) **1** and **2**, as potent inhibitors of glycosidases :



1



2

Three different methods for the synthesis of 2-amino-1,3-thiazoline from β-aminoalcohol are depicted in Scheme 1 : 1) reaction with thiocyanate ion, and subsequent cyclization; 2) reaction with an alkyl-, aryl- or

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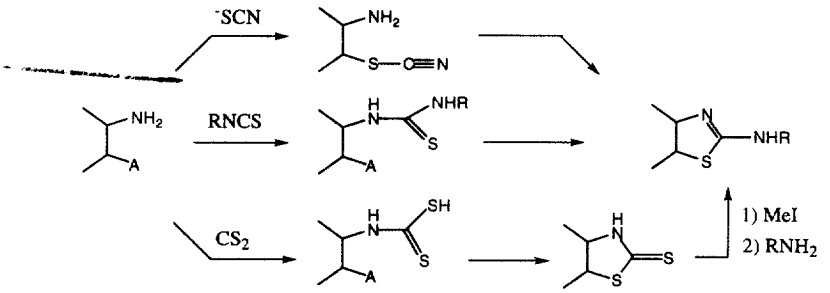
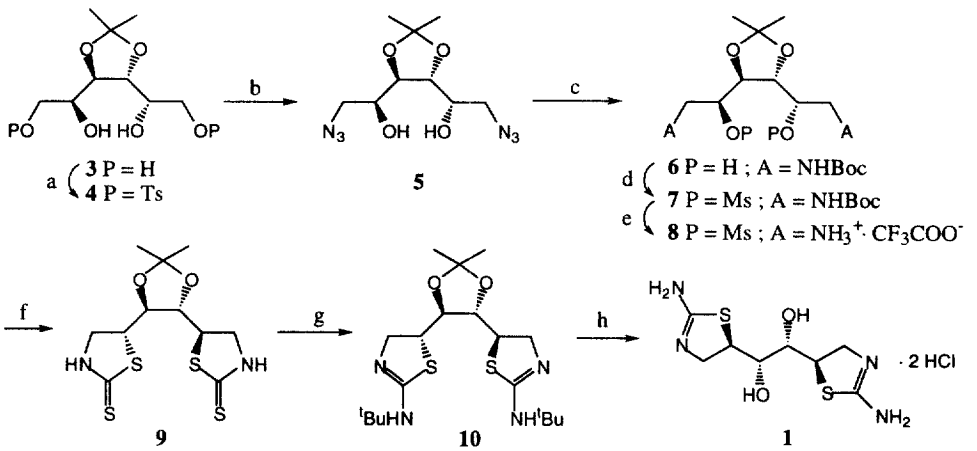
acyl-isothiocyanate, and cyclization; or 3) reaction with carbon disulfide to intermediately form a cyclic 1,3-thiazolidine-2-thione, followed by *S*-methylation and subsequent displacement of the resulting methylthio group with either ammonia or a primary amine. Among those three pathways, only a procedure derived from the last one was successful with our compounds derived from D-mannitol.



Scheme 1 : A = OH or leaving group, R = H or alkyl.

The synthesis of **1** began with the 1,6-diazido compound **5** (Scheme 2), obtained from the commercially available 3,4-*O*-methylethylidene-D-mannitol **3** by selective tosylation of primary hydroxyl groups with *p*-toluenesulfonyl chloride (86%),[8] followed by nucleophilic substitution of the resulting tosylates with sodium azide (75%). Heterogeneous catalytic reduction of **5** in the presence of di-*tert*-butyl dicarbonate[9] led to the protected 1,6-diamine **6** (83%). Mesylation of the secondary hydroxyl groups followed by deprotection of the amines with trifluoroacetic acid led to the 1,6-diammonium-2,5-dimesylate *bis*-trifluoroacetate **8** in quantitative yield.

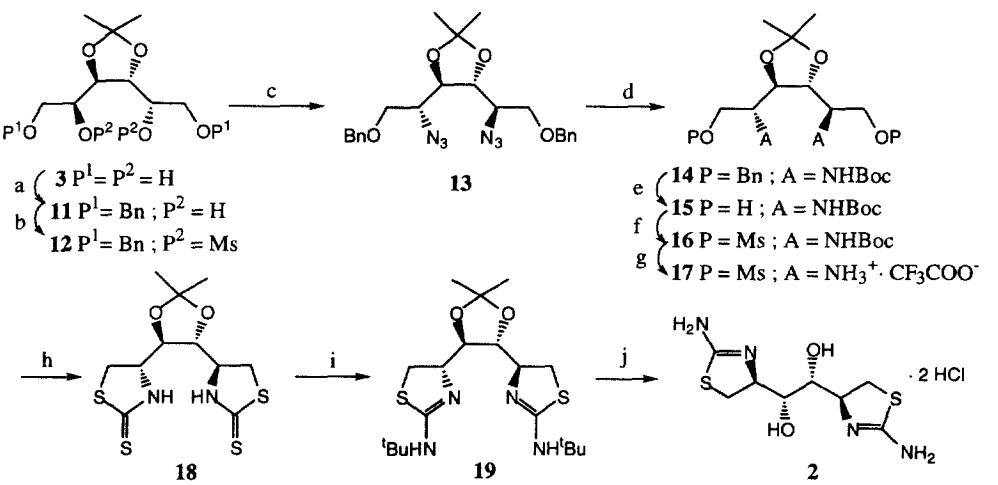


Scheme 2 : (a) TsCl, pyridine, 0°C ; (b) NaN_3, DMF, Δ ; (c) H_2, 10% Pd/C, $(Boc)_2O$, EtOAc, rt, 2h ; (d) MsCl , NEt_3, CH_2Cl_2 ; (e) TFA / CH_2Cl_2, rt, 1h ; (f) CS_2, NEt_3, CH_2Cl_2, rt, 15h ; (g) $^tBuNH_2$, NEt_3, $HgCl_2$, DMF, 80°C, 15h ; (h) concentrated HCl, reflux, 15h

Direct transformation of **8** into the *bis*(1,3-thiazolidine-2-thione) **9** with inversion of configuration at C_2 and C_5 cleanly occurred in presence of carbon disulfide and slow addition of triethylamine (90%). Under these conditions, involving the good electrophile CS_2,[10] nucleophilic addition of the primary amines and

subsequent formation of the thiazolidine rings was much faster than the intramolecular formation of aziridine rings. Although methylation at the exocyclic sulfur atoms of **9** with methyl iodide was easily achieved, all attempts to substitute the thiomethyl groups with ammonia were unsuccessful. To overcome this problem, by analogy with transformation of thiourea or thioamide into guanidine[11] or amidine,[12] respectively, direct substitution of the thioxo groups of **9** was examined. As expected, *tert*-butylamine treatment of **9** in DMF in the presence of mercuric dichloride and triethylamine led to the *bis*(2-*N*-*tert*-butylamino-1,3-thiazoline) **10** in quantitative yield. The final acetonide hydrolysis and *N*-*tert*-butyl cleavage were carried out in refluxing concentrated aqueous HCl and led to compound **1** (70%), isolated as its *bis*-chlorhydrate salt.[13]

Furthermore, from the *N*-Boc protected 2,5-diamine **15** the synthesis of **2**, which is a *N,S*-isomer of position of **1**, was efficiently carried out (Scheme 3). The diamine **15** was easily obtained from the 3,4-*O*-methylethylidene-D-mannitol **3** as follows : selective benzylation of both primary hydroxyl groups through stannylidene activation with Bu_2SnO and treatment with benzyl bromide (86%), then mesylation of the secondary hydroxyl groups and nucleophilic substitution with sodium azide (57%). Heterogeneous catalytic reduction of the diazido compound **13** in the presence of di-*tert*-butyl dicarbonate[9] led to the protected 2,5-diamine **14** (76%) which was subsequently debenzylated with sodium in liquid ammonia in quantitative yield to afford **15**. This *bis*(*N*-Boc-aminoalcohol) was successively subjected, as above, to mesylation, *N*-Boc deprotection and cyclization into *bis*(1,3-thiazolidine-2-thione) with carbone disulfide, then $HgCl_2$-catalyzed transformation into *bis*(2-*N*-*tert*-butylamino-1,3-thiazoline), prior to the final removal of all protecting groups.[14]



Scheme 3 : (a) *i*- Bu_2SnO, toluene, Δ, 15h; *ii*- BnBr, $^nBu_4NI$, toluene, 70°C, 15h ; (b) MsCl , NEt_3, CH_2Cl_2 ; (c) NaN_3, DMF, 120°C, 15h ; (d) H_2, 10% Pd/C, $(Boc)_2O$, EtOAc, rt, 2h30 ; (e) Na / NH_3 liq., 1h ; (f) MsCl, NEt_3, CH_2Cl_2 ; (g) TFA / CH_2Cl_2, rt, 1h ; (h) CS_2, NEt_3, CH_2Cl_2, rt, 15h ; (i) $^tBuNH_2$, NEt_3, $HgCl_2$, DMF, 80°C, 15h ; (j) concentrated HCl, reflux, 15h.

In summary, this study presents an efficient synthetic way to construct enantiopure C_2-symmetrical *bis*(2-amino-1,3-thiazolines) from D-mannitol. The key step involves the $HgCl_2$-catalyzed transformation of a

cyclic 1,3-thiazolidine-2-thione into a 2-*N*-*tert*-butylamino-1,3-thiazoline. The biological activity of the new compounds described here has been studied; full results will be reported in due course.

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13. Selected physical data of **1**·2 HCl: $[\alpha]^{20}_D$ +23 (c 0.9, CH_3OH) ; ^1H NMR (250 MHz, D_2O) δ: 3.86-3.99 (m, 4H, CH_2N), 4.09 (m, 2H, CHO), 4.47 (m, 2H, CHS) ; ^{13}C NMR (63 MHz, D_2O) δ: 53.4 (CH_2N), 54.8 (CHS), 73.7 (CHO), 176.0 (C=N).
14. Selected physical data of **2**·2 HCl: $[\alpha]^{20}_D$ +13 (c 1.2, CH_3OH) ; ^1H NMR (250 MHz, CD_3OD) δ: 3.54-3.60 (m, 2H, CH_2S), 3.63-3.73 (m, 2H, CH_2S), 3.82 (m, 2H, CHN), 4.46-4.57 (m, 2H, CHO) ; ^{13}C NMR (63 MHz, CD_3OD) δ: 35.2 (CH_2S), 67.6 (CHN), 74.6 (CHO), 177.3 (C=N).