Syntheses via Isoxazolines, Part 25[+]

Amino(hydroxymethyl)cyclopentanetriols, an Emerging Class of Potent Glycosidase Inhibitors—Part I: Synthesis and Evaluation of β-D-Pyranoside Analogues in the *manno*, *gluco*, *galacto*, and GlcNAc Series

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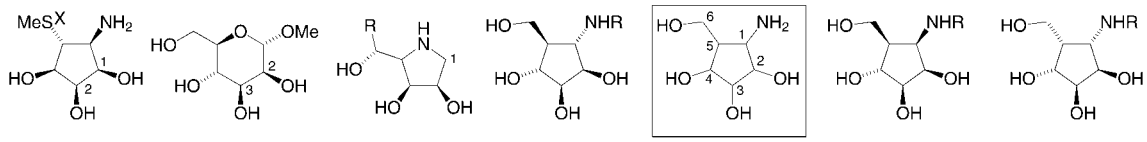
The wide-ranging relevance of glycoside-processing enzymes has stimulated many efforts to identify appropriate inhibitors,[1] by way of screening and isolation of natural products as well as by reasoning, design, and synthesis.[2–7] Parallel to these approaches, debates as to the mechanism of glycoside hydrolysis and glycosidase inhibition have abounded.[1–4] "Traditional" inhibitors represent six-membered carbocycles and *N*-heterocycles or five-membered iminopolyols, with close relationship to the respective monosaccharide.[1, 2] A noteworthy exception from this was reported with the discovery of mannostatin A (**1a**) in 1986, an amino(methylthio)cyclopentanetriol, and its (*R*)-sulfoxide, mannostatin B (**1b**).[8] Both were shown to be potent, selective, and competitive inhibitors of α-D-mannosidase from rat epididymis ($K_i = 48$ nM) and two other enzymes, one of which is the glycoprotein-processing mannosidase II (from mung beans; $K_i = 10 - 15$ nM).[8]

N-Acetylation of **1a** abolished its inhibitory activity. In the course of syntheses of **1a**,[3, 9] several derivatives were prepared that also displayed very good inhibition of α-mannosidase from jack beans [(*S*)-sulfoxide, sulfone, *N*-benzyl compound of **1a**; $K_i \approx 70$, 126, 380 nM, respectively].[9] The enantiomer of **1a** (having the "α-L-*allo* configuration"), with a supposedly better fit to the mannopyranosyl cation intermediate,[2] proved inactive, but the 2,3-bis-epimer of **1a** again showed some inhibitory activity ($K_i = 13$ μM).[9]

On trying to rationalize the high activity of the mannostatins **1**, with their unexceptional structures and seemingly nonfitting configuration, a comparison with the natural α-D-mannoside substrates **2** and the 1,4-iminoglycitol inhibitors **3** was made. We concluded that the methylthio appendix in **1a** might be either nonessential or an equivalent of a hydroxymethyl group as present in **2** or in active 1,4-iminoglycitols such as **3**, and further, that the "essential" (see below) hydroxy groups at C1 and C2 in **1a** corresponded to 2-OH and 3-OH, respectively, in **2** and **3**. The latter point is in agreement with the results of an analysis of alkaloidal inhibitor structures.[2] Actually, a compound of this type, the *N*-methyl compound **4b** with "α-D-*manno*" configuration—a precise ring-contracted match of α-**2**—had been designed as an α-mannosidase inhibitor (although no reference to **1**[8] was made) and, indeed, had proven highly active[10] (Table 1). Finally, a more advanced hypothesis arose: that the amino(hydroxymethyl)cyclopentane skeleton might serve as a general framework to generate a new family of glycosidase inhibitors **5** (according to IUPAC nomenclature **5** would be named 4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol), with specific activities as indicated by the absolute configuration of the two or three hydroxy groups at the ring. Herein we present detailed syntheses and inhibition results of the *manno* series, along with activities of the *gluco*, GlcNAc, and *galacto* compounds[11] mostly obtained by the nitrone route.[12] The syntheses and further details for the *gluco*,[11b,c,d] *galacto*,[11d] and *N*-GlcNAc[11e] series will be reported separately (see Part II for the *galacto* series).[11a]



For the synthesis of **4b**, Farr et al.[10] had adopted Vasella's scheme of converting aldohexoses into cyclopentane derivatives, that is, by an intramolecular 1,3-dipolar cycloaddition of nitrones derived from tri-*O*-benzyl-5-hexenoses.[12] In order to obtain specific relatives of **1a**/**5** with a primary amino group, notably the diastereomers **6** and **7**, the isoxazoline route involving nitrile oxide cycloaddition for the carbocycle-forming step[13] was chosen. The known, unstable D-*lyxo*-5-hexenose **9**[12] was prepared from the mannoside **2** via the bromide **8** and

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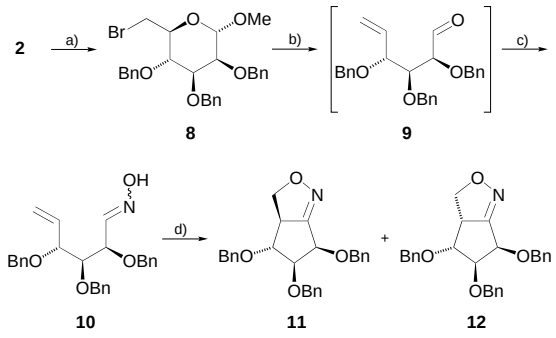
Table 1. Inhibitory activities of newly synthesized and known compounds toward two α-D-mannosidases.

Inhibitor	R	Enzyme source: jack beans IC_{50} [μM]	jack beans K_i [μM]	almonds IC_{50} [μM]	almonds K_i [μM]
1a		0.02[8c] 0.07[3]	n.d.	n.d.	n.d.
3a	H	n.d.	14[1c]	n.d.	n.d.
3b	CH_3	n.d.	0.5[1a]	n.d.	n.d.
4a·HBr	H	0.39	0.41	0.23	0.61
4b	CH_3	0.062[10]	n.d.	n.d.	n.d.
4c	Bn	0.9	1.0	0.5	0.5
6a·HBr	H	0.17	0.074	0.13	0.12
6b·HBr	CH_3	1.3	1.3	0.42	0.15
6c·HBr	Bn	13	0.50	13	2.2
7a·HBr	H	5.8	4.6	6.2	5.3
7b	CH_3	42	21	66	45
7c	Bn	[24]	3.4	4.0	3.1
swainsonine		0.2[1a]	0.001[1a]	0.4[17]	> 1000[1a]
manno-nojirimycin		n.d.	1.2[1a]	n.d.	21[1a]

n.d. = not determined.

directly transformed into the oxime **10** (Scheme 1). This was treated with sodium hypochlorite[14] to undergo chlorination, loss of HCl, and cycloaddition of the transiently formed nitrile oxide. The resulting mixture of the bicyclic diastereomers **11** and



Scheme 1. *Synthesis of intermediate isoxazolines **11** and **12**. a) Five steps, ref. [12a] 53%; see refs. [3b, 10]; overall yield 50–60% from **2**, as reported; b) Zn, $CeCl_3 \cdot 7H_2O$, MeOH, reflux, 8 h; see ref. [3b]; c) $HONH_3Cl$, pyridine, 25 °C, 2 h; yield of **10** (E/Z mixture, 75:25) 53% (13% of **8** recovered, corrected yield 61%); d) NaOCl, Bu_4NHSO_4, CH_2Cl_2, ultrasound, 15 °C, 5 d; MPLC separation (petrol ether/EtOAc, 3:1); **11**: 32%, m.p. 87 °C, $[\alpha]_D^{20} = -171$ (c = 1.11, $CHCl_3$); **12**: 18%, oil, $[\alpha]_D^{20} = -51$ (c = 1.24, $CHCl_3$).*

12 (62:38) was separated chromatographically (Scheme 1). To the major isomer, **11** (32%), was assigned the "D-*manno*" configuration (5-H/5a-H *trans*) on the basis of ^1H and ^{13}C NMR data, for example from a long-range coupling, $^4J_{3,5a} = 0.8$ Hz, not observed with **12**. This was confirmed by comparison with the data of a tri-*O*-benzoyl derivative of **11** whose structure had been established independently by crystal structure analysis.[15]

Both **11** and **12** were reduced with lithium aluminum hydride in diethyl ether[16] and gave the respective amino alcohols in high yield as a single diastereomer each, as expected ($LiAlH_4$, Et_2O, 25 °C, 1 d, 98 and 67%, respectively).[16] The hydrobromides of **6a** and **7a** were obtained in the form of analytically pure, colorless salts after hydrogenolytic debenzylation in methanol/hydrobromic acid (H_2, 4 bar, Pd/C, MeOH/HBr, 25 °C, 20 h, 83% of **6a**·HBr, m.p. 68–72 °C, $[\alpha]_D^{20} = 3.7$ (c = 0.81, H_2O); and 93% of **7a**·HBr, m.p. 172 °C, $[\alpha]_D^{20} = 27$ (c = 0.83, H_2O)). The *manno* parent compound **6a** was transformed into the derivatives **6b** and **6c** by reductive amination procedures.[11b] For the synthesis of **4a**, **4c**, **7b**, and **7c**, we adopted the known routes of 1,3-dipolar cycloaddition of nitrones with *N*-methyl or *N*-benzyl substituents (see above).[10–12]

The new candidates **4a**, **4c**, **6a–c**, and **7a–c** were used in inhibition tests with 24 commercially available glycosidases under standard conditions.[17] The cases with IC_{50} values below 1 mM are listed in Table 1 and compared to results obtained with the known, strong α-mannosidase inhibitors **1a**, **3a**, **3b**, **4b**, swainsonine, and *manno*-nojirimycin. The data show that **4a**, **4c**, **6a–6c**, and **7a–7c** indeed constitute strong, competitive inhibitors of the two α-mannosidases available for testing, with **6a–c** (having "β-D-*manno*" configuration) being more active than the "β-L-*gulo*"-type **7a–c**. The former (**6a–c**) also weakly inhibited β-mannosidase (from *Helix pomatia*). Further, comparison of the results obtained with **4** and **6**—corresponding to α/β anomers—shows that there is no clear-cut effect in favor of the former, which has the "α-D-*manno*" configuration.

The high selectivity and the strong effects of the aminocyclopentanetriols shown in Table 1 raise a number of questions with regard to the mechanism of the inhibition and to the structure of active species or purported intermediates in α-mannosidase catalysis (there is no similarly strong effect of **4a**, **4c**, **6a–c**, and **7a–c** on the β-mannosidase tested). With **1a** and **5–7**, structural features are similar; the only stereochemical prerequisite for α-mannosidase inhibition apparently is the proper orientation of the two hydroxy groups corresponding to 2-OH and 3-OH of the α-mannoside.

The more general hypothesis put forward at the outset of this project was then pursued. To this purpose, amino(hydroxymethyl)cyclopentanetriols of the other configurations, that is, the β-D-*gluco* parent **14** and *N*-cyclohexyl derivative **15**, and the β-D-*galacto* and β-D-GlcNAc compounds **16** and **17**, respectively, were secured, again following the route of intramolecular 1,3-dipolar nitrone cycloadditions.[10–12] In order to complement this, the α-D-*gluco* compound **13** was prepared by using an intramolecular version of the $[4^+ + 2]$ polar cycloaddition[18] of an *N*-acyliminium derivative of the respective enose (compare **9**).[11f]

The most interesting results of inhibition tests with these compounds, along with those in which miglitol was used as a standard, are listed in Table 2 (altogether, since 1994 about 100 of such aminocyclopentanepolyol compounds have been prepared and submitted to comprehensive tests with 24 to 29 different, commercially available glycosidases).[11, 19]

The first, and very rewarding assessment of these results is that the ring-contracted pyranoside analogues indeed mimic the respective natural substrates well, each of them showing strong or excellent inhibition with one or more of the pertinent enzymes. Proper selectivity, however, is only observed for the GlcNAc case, in which the structural relationship apparently is decisive. Concerning "*gluco*" inhibitors, both the analogue of the

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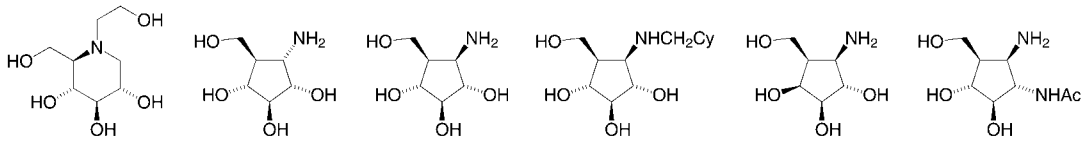

miglitol | **13** | **14** | **15** | **16** | **17**

D-*gluco* | "α-D-*gluco*" | "β-D-*gluco*" | "β-D-*gluco*" | "β-D-*galacto*" | "β-D-GlcNAc"

α-anomer (**13**) and of the β-anomer (**14**) act on α- as well as on β-glucosidases, but not with the same strength in all cases. *N*-Substitution, as shown with the *N*-cyclohexylmethyl derivative **15**, is answered in rather different ways (see entries 9 – 11 for **14** and **15** in Table 2). The β-D-glucosidase from *Caldocellum saccharolyticum* has the same response to this change, whereas the almond enzyme exhibits a very low K_i value (smaller by a factor of 275), and a similar effect is seen with the β-xylosidase (entry 11, Table 2). A preliminary conclusion may be that the active sites of the glucosidase from almonds and of the xylosidase are very similar, whereas that of the β-glucosidase from *Caldocellum* is different. This example—and many others not detailed here[11]—again shows that indirect mapping of active sites, with eventual differentiation of enzymes of the same stereochemical family, by various *N*-substituted derivatives of such inhibitors may become a valuable tool, in particular with regard to classification of the enzyme into the proper family.[20]

Another brief comment on the data shown in Table 2 concerns the *gluco*/*galacto* relationship: Miglitol, the "α-D-*gluco*" compound **13** and the two "β-D-*gluco*" representatives all inhibit most of the α- and the β-glucosidases tested, and one of the four β-D-galactosidases assayed (the one from bovine liver). The "β-D-*galacto*" isomer **1b**, on the other hand, interacts strongly with all enzymes of its own stereochemical group (entries 1 – 4, Table 2) and with both β-glucosidases; however, no activity is seen with the α-*gluco*-specific enzymes. Thus, the configuration of the 4-hydroxy group seems to be unimportant for the β-glucosidases, but not for three (nonmammalian) of the four β-galactosidases.

In summary, amino(hydroxymethyl)cyclopentanetriols in all series studied so far constitute strong inhibitors of some or all of the stereochemically corresponding glycohydrolases. Access to the parent structures, which can be regarded as ring-contracted 1,5-deoxapyranosyl amines, is straightforward, as well as to derivatives with widely varying *N*-substituents. It is easy to predict that this family of inhibitor structures will become a valuable tool for "insight" studies of glycosidases, concerning informations on active sites, differentiation and classification, three-dimensional structure elucidations, and—hopefully—therapeutic applications. Optimization of inhibitor activity and selectivity could be achieved by probing *N*-substituents, which so far has been carried out for β-D-*gluco* compounds (to be detailed separately) and for the β-D-*galacto* series (which is described in the following Short Communication[11a]).

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*Table 2. Inhibitory activities of miglitol and compounds **13** – **17** toward different enzymes.*[a]

Entry	Enzyme (source)[b]	miglitol (D-gluco)	**13** ("α-D-gluco")	**14** ("β-D-gluco")	**15** ("β-D-gluco")	**16** ("β-D-galacto")	**17** ("β-D-GlcNAc")
1	β-D-Gal (E.c.)	n.i.	n.i.	n.i.	n.i.	4.5	n.i.
2	β-D-Gal (b.l.)	48	21	2.6	0.18	3.3	n.i.
3	β-D-Gal (A.o.)	[720]	n.i.	n.i.	n.i.	0.6	n.i.
4	β-D-Gal (j.b.)	n.i.	n.i.	n.i.	[1000]	0.15	n.i.
5	α-D-Glc (y.m.)	n.i.	1.6	6.2	67	n.i.	n.i.
6	α-D-Glc (r.m.)	0.54	85	n.i.	n.i.	n.i.	n.i.
7	α-D-Glc (b.y.)	n.i.	0.6	0.7	100	n.i.	n.i.
8	α-D-Glc (R.m.)	19	n.i.	30	5.1	n.i.	n.i.
9	β-D-Glc (a)	1.8	6.5	6.6	0.024	2.2	n.i.
10	β-D-Glc (C.s.)	84	1.5	2.6	2.7	0.17	n.i.
11	β-D-Xyl (A.n.)	n.i.	300	1.7	0.032	n.i.	n.i.
12	β-D-GlcNAc (j.b.)	n.i.	n.i.	n.i.	342	n.i.	0.39
13	β-D-GlcNAc (b.e.)	n.i.	n.i.	n.i.	n.i.	n.i.	0.65

[a] K_i and [IC_{50}] values are given in μM; n.i. = inhibition < 50% at 1 mM. All inhibitions were of the competitive kind. [b] Enzymes and enzyme sources: β-D-Gal = β-D-galactosidase, α-D-Glc = α-D-glucosidase, β-D-Glc = β-D-glucosidase, β-D-Xyl = β-D-xylosidase, β-D-GlcNAc = β-D-*N*-acetylglucosaminidase; E.c. = *Escherichia coli*, b.l. = bovine liver, A.o. = *Aspergillus oryzae*, j.b. = jack beans, y.m. = yeast maltase, r.m. = rice maltase, b.y. = baker's yeast isomaltase, R.m. = *Rhizopus* mold, a. = almonds, C.s. = *Caldocellum saccharolyticum*, A.n. = *Aspergillus niger*, b.e. = bovine epididymis A.

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Amino(hydroxymethyl)cyclopentanetetriols, an Emerging Class of Potent Glycosidase Inhibitors—Part II: Synthesis, Evaluation, and Optimization of β-D-Galactopyranoside Analogues

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carbohydrate mimics · cycloaddition · glycosidases · hydrolases · inhibitors

From efforts to rationalize the strong activity of mannostatins, the related structures of amino(hydroxymethyl)cyclopentanetriols were derived and shown to be highly active glycosidase inhibitors, first in the α-D-*manno* and then in other series (see Part I[1] and ref. [2]). Concerning the β-D-*galacto* series,[2] to be detailed here, the parent compound **13** and the *N*-methyl derivative **14** (prepared and assayed first) showed remarkable inhibitory effects as well as distinct changes in activity and selectivity when substituting NH_2 for $NHCH_3$.[2a] Thus, some 20 related structures were chosen and prepared for optimization.[2, 3] This led to several compounds with K_i values near or below the nanomolar range, which is reported herein.

The starting material for the cycloadditions was the protected L-*arabino*-5-hexenose **1**, obtained in three steps from D-galactose.[2–4] The hexenose **1** was converted into the corresponding isoxazolidines (**2** – **7**) on treatment with *N*-substituted hydroxylamines via intermediate nitrones,[2–4] following a route proposed earlier by Vasella et al.[5] (Scheme 1). Here, the diastereomeric ratio (d.r.) of the *syn*-/*anti*-cyclopentanoisoxazolidines (**2**:**5**, **3**:**6**, **4**:**7**) varied strongly, depending on the solvent used for the cycloaddition.[2, 3] In polar solvents the *syn*-tricycle was preferred, independent of R. For the cycloaddition with PhNHOH in methanol, d.r. values up to 87:13 (*syn*/*anti*) were observed (Scheme 1).[2b] In contrast, when the reaction was performed with BnNHOH in a nonpolar solvent like chloroform, a d.r. value of $<$ 5:95 in favor of the *anti* isomer resulted.[2b]

The free amino(hydroxymethyl)cyclopentanetriols **13** – **17** were obtained in the form of their hydrobromide salts from

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