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Synthesis of a Potent Aminocyclitol α-Mannosidase Inhibitor, 1L-(1,2,3,5/4)-5-amino-4-*O*-methyl-1,2,3,4-cyclopentanetetrol

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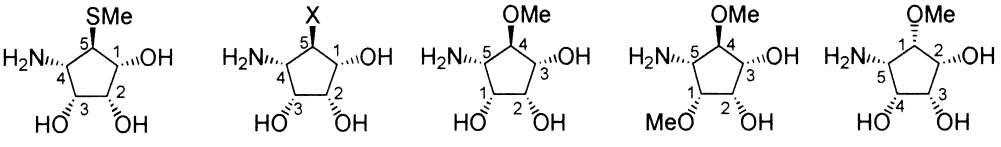
Abstract—Demethylthio-, de-*S*-methyl-, and ethylthio-derivatives of the α-mannosidase inhibitor, mannostatin A, have been synthesized and evaluated for their inhibition of Jack bean α-mannosidase in order to elucidate the roles of the methylthio group. All derivatives had lowered inhibitory potentials. However, a mannostatin A analogue with a methoxyl instead of the methylthio, exhibited about 2-fold enhancement of the activity, indicating an importance for the methyl group rather than the sulfur atom.

Identification of potent and specific α-mannosidase inhibitor mannostatin A[1,2] (**1**), 1D-(1,2,3,4/5)-4-amino-5-methylthio-1,2,3-cyclopentanetriol,[3] has stimulated us to develop new glycosidase inhibitors of 5-amino-1,2,3,4-cyclopentanetetrol type. Recently, synthesis and evaluation of α-mannosidase inhibitory activity of three deoxy derivatives of **1** have been carried out[4] to elucidate the significance of each hydroxyl groups. The 3-hydroxyl group was thereby found to be the most important, conceivably correlating with the 2-hydroxyl group of the mannopyranosyl cation[5] and the amino group located around the carbocation atom. We have shown[6] that, among twenty four stereoisomers of 5-amino-1,2,3,4-cyclopentanetetrols, only 1L-(1,2,3,5/4)- and (1,2,3,4,5/0)-isomers, and the corresponding 5-*C*-methyl derivatives[7] are moderate inhibitors of Jack bean α-mannosidase.

In the present study chemical modification concerning the methylthio function of mannostatin A **1** was carried out. Demethylthio- **2**, de-*S*-methyl- **3**, and ethylthio-derivative **4** were first synthesized. Secondly, in order to assess the roles of the sulfur atom of **1**, attempts were made to replace the methylthio group by a methoxyl group by preparation of 5-amino-4-*O*-methyl-,-1,4-di-*O*-methyl-, and-epi-4-*O*-methyl-1,2,3,4-cyclopentanetetrols (**5**, **6** and **7**).[1]

Reaction of the 2,3-*O*-cyclohexylidene derivative[8] of (1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol with (*R*)-*O*-acetylmandelic acid in the presence of DCC and DMAP in CH_2Cl_2 afforded rather diastereoselectively the 1*R*-(*R*)-*O*-acetylmandelate[9] **L-8**, (56%) an major product, together with the 1*S*-ester **D-8** (8%). Compound **L-8** was



	X
2	H
3	SH
4	SEt

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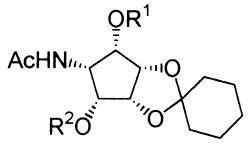
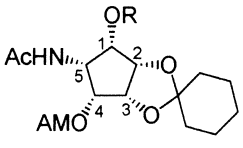
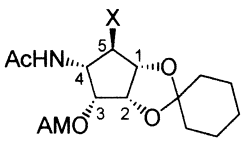


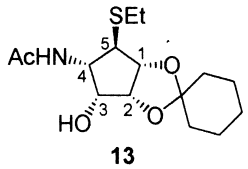
	R^1	R^2
L-8	H	AM
D-8	AM	H



	R
9	C(S)OPh
10	SO_2CF_3



	X
11	H
12	SAc



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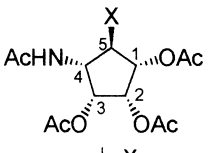
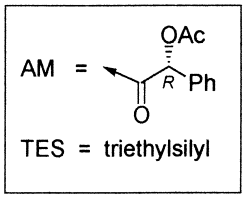


	X
2a	H
3a	SAc
4a	SEt



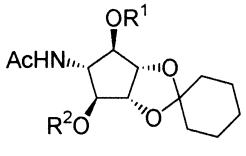
converted into the phenylthiocarbonyl ester **9** (27%) by treatment in turn with DMAP (6 molar equiv) and phenyl chlorothionocarbonate (5 molar equiv) in CH_3CN at room temperature. Reaction of **9** with tributyltinhydride in the presence of AIBN gave the deoxy derivative **11** (43%). Deprotection of **11** with 2 M HCl at 80 °C followed by conventional acetylation gave the tetra-*N,O*-acetyl derivative[10] **2a** (~100%), the structure of which was characterized on the basis of its ^{1}H NMR spectrum.

Compound **L-8** was treated with trifluoroacetic anhydride in pyridine-CH_2Cl_2 (−15 °C) and the resulting triflate **10** was then subjected to a nucleophilic substitution with potassium thioacetate-18-crown 6-ether in dry benzene to give the acetylthio derivative **12** (61%). Acid hydrolysis of **12** followed by acetylation gave the penta-*N,O,S*-acetyl derivative[11] **3a** (~100%). In addition, **12** was de-*S*-acetylated with methanolic sodium methoxide and then treated with iodoethane to give the ethylthio derivative **13** (~100%), which was converted into the tetra-*N,O*-acetyl derivative[12] **4a** (~100%).

Moderate diastereoselective acylation of the 2,3-*O*-cyclohexylidene derivative[8] **14** of (1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol with (*S*)-*O*-acetylmandelic acid (→ca. 4:1 mixture of **L-15** and **D-15**), followed by treatment with triethylsilyltriflate in CH_2Cl_2 gave a separable mixture of **L-16** (77%) and **D-16** (23%). Compound **L-16** was de-*O*-acylated under Zemplén conditions (→**17**), and subsequently treated with iodomethane-Ag_2O in MeCN to give the methyl ether **18** (~100%). Desilylation of **18** with tributylammoniumfluoride in THF (→**19**, 69%), conventional transformation into the mesylate (→**20**), and heating in 80% aq DMF at 110 °C gave through neighboring participation the 4-epimeric alcohol **21** (76%). Acid hydrolysis of **21** and successive acetylation gave the tetra-*N,O*-acetyl derivative[13] **5a** (53%).

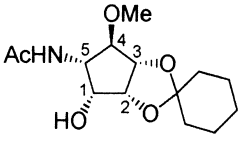
The alcohol **22** derived from **D-16** was mesylated and the sulfonate was treated with sodium acetate in aq DMF to give the 4-epimer **23** (80%). Compound **23** was methylated in the usual manner to the dimethyl ether **24** (68%), which was converted into the tri-*N,O*-acetyl derivative[14] **6a** (86%).

Compound **D-8** was silylated, deacylated (→**25**, 68%) and then methylated to give the methyl ether **26** (97%). Deprotection of **26** followed by acetylation gave the tetra-*N,O*-acetyl derivative[15] **7a** (87%).



14 – 20

	R^1	R^2
14	H	H
L-15	AM	H
D-15	H	AM
L-16	AM	TES
D-16	TES	AM
17	H	TES
18	Me	TES
19	Me	H
20	Me	Ms



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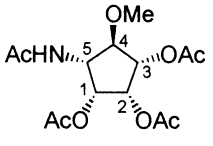
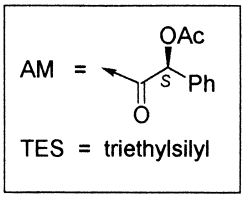


5a



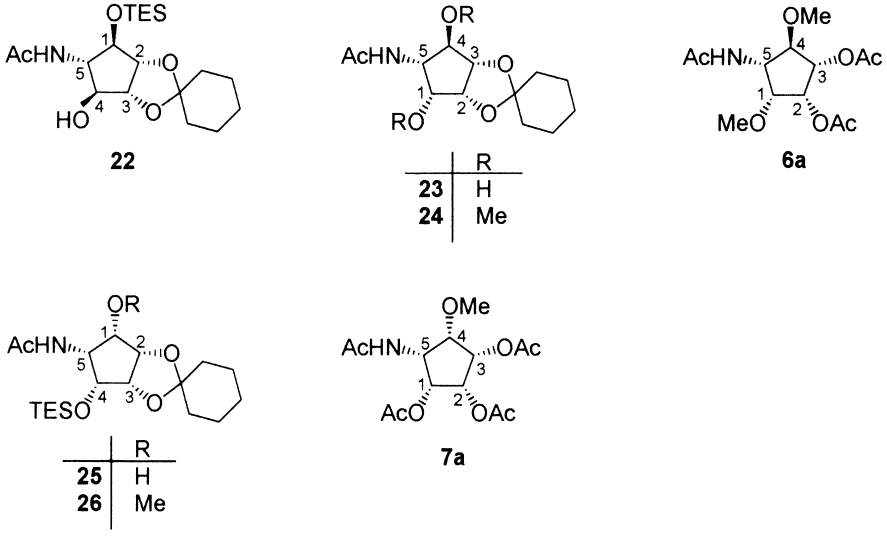


Table 1. Inhibitory activity[a] of mannostatin A **1** and six analogues **2**–**7** against α-mannosidase[b] (Jack bean)

Compound	**1**[c]	**2**	**3**	**4**	**5**	**6**	**7**
IC_{50} (μM)	0.35	11	36	5.0	0.16	NI[d]	NI

[a]2.0 mM *p*-nitrophenyl α-D-mannopyranoside, 0.1 M acetate buffer, pH 4.5.[16]
[b]α-Mannosidase and nitrophenyl mannopyranoside were purchased from SIGMA.
[c]Ref. 9.
[d]No inhibition $< 10^{-3}$ M.

Mannostain A analogues **2**–**4** were prepared by treatment of the corresponding peracetyl derivatives **2a**–**4a** with 2 M hydrochloric acid at 80 °C, and purified over a column of Dowex 50W×2 (H^+) resin with 1% aq ammonia as the eluent. The analogues **3**–**7** were obtained by hydrolysis of **3a**–**7a** with 1 M aq $Ba(OH)_2$ at 90 °C, followed by similar purification. The free bases thus obtained were directly subjected to assay of Jack bean α-mannosidase inhibition (Table 1).

Thus we finally succeeded in obtaining a compound **5** which was two times stronger than the parent **1**, which should provide a lead compound for further development of new α-mannosidase inhibitors. The configuration of the *S* or *O*-methyl function was shown to be very important. Introduction of the 1-methoxyl group at C-1 of **5** resulted in complete loss of the activity, establishing again the importance of the 1-hydroxyl group of the mannostatin family. Inhibitory activity was demonstrated to be generated by the essential core structure composed of the *O*-(or *S*-)methyl function trans to the consecutive 1- or 2-, and 3-hydroxyl and 4-amino groups in a *cis*-relationship on a cyclopentane ring.

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10. 1D-(1,2,3,4/0)-1,2,3-Tri-*O*-acetyl-4-acetamido-1,2,3-cyclopentanetriol (**2a**): $[\alpha]_d^{25}$ +16° ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.74 (1H, d, $J_{4,NH}$ 8.5 Hz, NH), 5.28–5.20 (3H, m, 1-H, 2-H, 3-H), 4.57 (1H, m, 4-H), 2.66 (1H, m, 5a-H), 2.13, 2.07, 2.05, and 2.01 (each 3 H, 4 s, 4×Ac), 1.77 (1H, m, 5b-H). -HRMS: $C_{13}H_{20}NO_7$ (MH^+, 302.1239): found 302.1229.
11. 1D-(1,2,3,4/5)-1,2,3-Tri-*O*-acetyl-4-acetamido-5-acetylthio-1,2,3-cyclopentanetriol (**3a**): $[\alpha]_d^{25}$ +26° ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.79 (1H, d, $J_{4,NH}$ 8.5 Hz, NH), 5.42 (1H, dd, $J_{2,3}$ = 3.9, $J_{3,4}$ = 4.4 Hz, 3-H), 5.40 (1H, dd, $J_{1,2}$ 7.1 Hz, 2-H), 5.26 (1H, dd, $J_{1,5}$ 6.8 Hz, 1-H), 4.52 (1H, ddd, $J_{4,5}$ 10.5 Hz, 4-H), 3.91 (1 H, dd, 5-H), 2.37, 2.15, 2.07, 2.03 and 1.99 (each 3H, 5 s, 5×Ac). -HRMS: $C_{15}H_{22}NO_8S$ (MH^+, 376.1066): found 376.1068.
12. 1D-(1,2,3,4/5)-1,2,3-Tri-*O*-acetyl-4-acetamido-5-ethylthio-1,2,3-cyclopentanetriol (**4a**): $[\alpha]_d^{25}$ +15° ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.70 (1H, d, $J_{4,NH}$ 8.8 Hz, NH), 5.42 (1H, dd, $J_{1,2}$ 5.6, $J_{2,3}$ 4.4 Hz, 2-H), 5.35 (1H, dd, $J_{3,4}$ 5.6 Hz, 3-H), 5.16 (1H, t, $J_{1,5}$ 5.6 Hz, 1-H), 4.53 (1H, ddd, $J_{4,5}$ 7.6 Hz, 4-H), 3.17 (1H, dd, 5-H), 2.73.16 (each 1 H, ABq, *J* 7.3, J_{gem} 14.9 Hz, SCH_2CH_3), 2.11, 2.08, 2.06, and 2.04 (each 3H, 4 s,

4×Ac), 1.25 (3 H, t, SCH_2CH_3). -HRMS: $C_{15}H_{24}NO_7S$ (MH^+, 362.1273): found 362.1270.

13. 1L-(1,2,3,5/4)-1,2,3-Tri-*O*-acetyl-5-acetamido-4-*O*-methyl-1,2,3,4-cyclopentanetetrol (**5a**): $[\alpha]_d^{23}$ −3° ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.82 (1H, d, $J_{5,NH}$ 9.0 Hz, NH), 5.46 (1H, dd, $J_{1,2}$ 3.9, $J_{2,3}$ 4.6 Hz, 2-H), 5.34 (1H, dd, $J_{1,5}$ 6.1 Hz, 1-H), 5.14 (1H, t, $J_{3,4}$ 4.6 Hz, 3-H), 4.57 (1H, ddd, $J_{4,5}$ 4.6 Hz, 5-H), 3.77 (1H, t, 4-H), 3.42 (3H, s, Me), 2.10, 2.08, and 2.04 (3, 6, 3 H, 3 s, 4×Ac). -HRMS: $C_{14}H_{22}NO_8$ (MH^+, 332.1345): found 332.1371.

14. 1L-(1,2,3,5/4)-2,3-Di-*O*-acetyl-5-acetamido-1,4-di-*O*-methyl-1,2,3,4-cyclopentanetetrol (**6a**): $[\alpha]_d^{22}$ −44° ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 6.05 (1H, d, $J_{5,NH}$ 8.5 Hz, NH), 5.48 (1H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 5.6 Hz, 2-H), 5.02 (1H, t, $J_{3,4}$ 5.6 Hz, 3-H), 4.44 (1H, dd, $J_{1,5}$ 6.8, $J_{4,5}$ 3.7 Hz, 5-H), 3.89 (1 H, dd, 1-H), 3.72 (1H, dd, 4-H), 3.45 and 3.37 (each 3H, 2 s, 2 Me), 2.14, 2.09, 2.08, and 2.05 (each 3H, 4 s, 4×Ac). -HRMS: $C_{13}H_{22}NO_7$ (MH^+, 304.1396): found 304.1402.

15. 1L-(1,2,3,4,5/0)-1,2,3-Tri-*O*-acetyl-5-acetamido-4-*O*-methyl-1,2,3,4-cyclopentanetetrol (**7a**): $[\alpha]_d^{22}$ +36° ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.97 (1H, d, $J_{5,NH}$ 9.0 Hz, NH), 5.29.22 (3H, m, 2-H, 3-H, 4-H), 4.74 (1H, m, 5-H), 3.86 (1H, m, 1-H), 3.40 (3H, s, Me), 2.14, 2.09, 2.08, and 2.05 (each 3H, 4 s, 4×Ac). -HRMS: $C_{14}H_{22}NO_8$ (MH^+, 332.1345): found 332.1331.

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