Synthesis and α-Mannosidase Inhibitory Activity of Three Deoxy Derivatives of Mannostatin A

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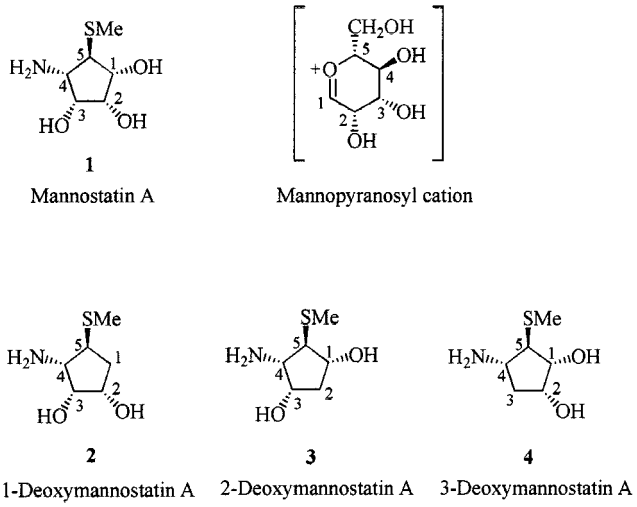
Three deoxy derivatives **2**–**4** of the α-mannosidase inhibitor mannostatin A (**1**) were synthesized, and their inhibition of Jack bean α-mannosidase was evaluated in order to elucidate the roles of each of the three hydroxyl groups of the inhibitor. The 1- and 2-deoxy derivatives **2** and **3** retained some inhibitory activity, although reduced by a factor of about 100 relative to the parent, whereas it was completely lost with the 3-deoxy derivative **4**. Structure and activity relationships are discussed in the light of these findings.

Introduction

The description of a potent and specific α-mannosidase inhibitor mannostatin A[2,3] (**1**), 1D-(1,2,3,4/5)-4-amino-5-methylthio-1,2,3-cyclopentanetriol,[4] has stimulated us to develop new glycosidase inhibitors composed of 5-amino-1,2,3,4-cyclopentanetetrols, thought to act as transition state mimics of the glycopyranosyl cations which are postulated to be formed during hydrolysis of glycosides.[1,5] Concerning conformational features of the transition state mannopyranosyl cation, it appears rather difficult to correlate the structures of known α-mannosidase inhibitors with that of the mannopyranosyl cation.[6] Recently, Winkler et al.[7] have proposed that a comparison of the structure of mannostatin A to their flap-up mannopyranosyl cation model is pertinent, suggesting the importance of good overlap of the 1- and 2-hydroxyl groups of **1** with the respective 3- and 2-hydroxyls of the mannopyranosyl cation.



Scheme 1. Three isomers of deoxymannostatin A

Results and Discussion

Although compound **1** has a simple and unique structure, very few studies of its chemical modification[3] have been carried out so far. The present paper describes the synthesis and evaluation of α-mannosidase inhibitory activity of the 1-, 2-, and 3-deoxy derivatives **2**, **3**, and **4** of mannostatin A, in an attempt to elucidate the role of each hydroxyl group of **1** in an interaction with the active site of the enzyme (Scheme 1).

The synthesis of deoxymannostatins **2** and **4** was carried out by the conventional sequence of deoxygenation/phenylthiocarbonylation of the unprotected hydroxyl groups of the 5-amino-1,2,3,4-cyclopentanetetrol derivatives, followed by treatment with tributyltinhydride in the presence of AIBN, de-*O*-acylation, conversion into triflates, direct nucleophilic substitution with a thioacetate anion, de-*S*-acetylation, *S*-methylation with iodomethane, and, finally, removal of the protecting groups by acid hydrolysis. The 2-deoxymannostatin A (**3**) was obtained by a similar deoxygenation of the protected derivative of **1**.

Reaction of the 2,3-*O*-cyclohexylidene derivative[8] **5** of (1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol with (*S*)-*O*-acetylmandelic acid in the presence of DCC and DMAP in CH_2Cl_2 gave, diastereoselectively, a 56% isolated yield of 1*S*-(*S*)-*O*-acetylmandelate[9] **6**, together with the 1*R*-ester **7** (Scheme 2). Compound **6** was converted into the phenylthiocarbonyl ester **8** (70%) by treatment in turn with DMAP (6 molar equiv.) and phenyl chlorothionocarbonate (5 molar equiv.) in MeCN at room temperature. It was found that, when the order of addition of the reagents was reversed, compound **6** was hardly esterified and migration of the cyclohexylidene group slowly occurred[10] to give, after 11 days, the 3,4-*O*-cyclohexylidene derivative **9** (56%) as the major product, together with a small amount of **8** (9%). Treatment of **8** with tributyltinhydride in the presence of AIBN gave the deoxy derivative **10** (71%). Zemplén de-

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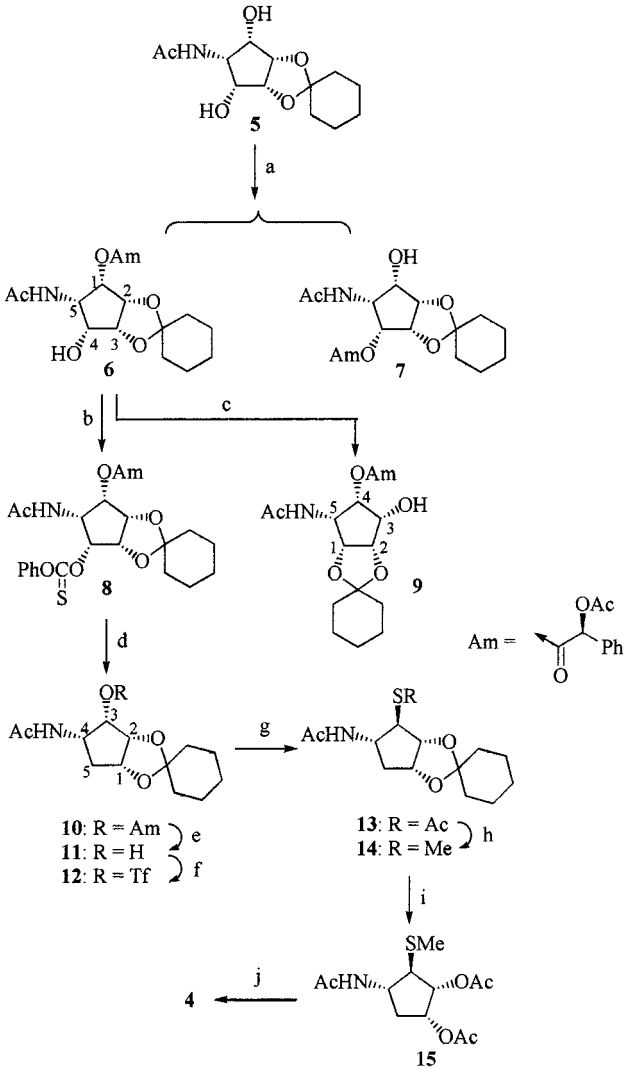
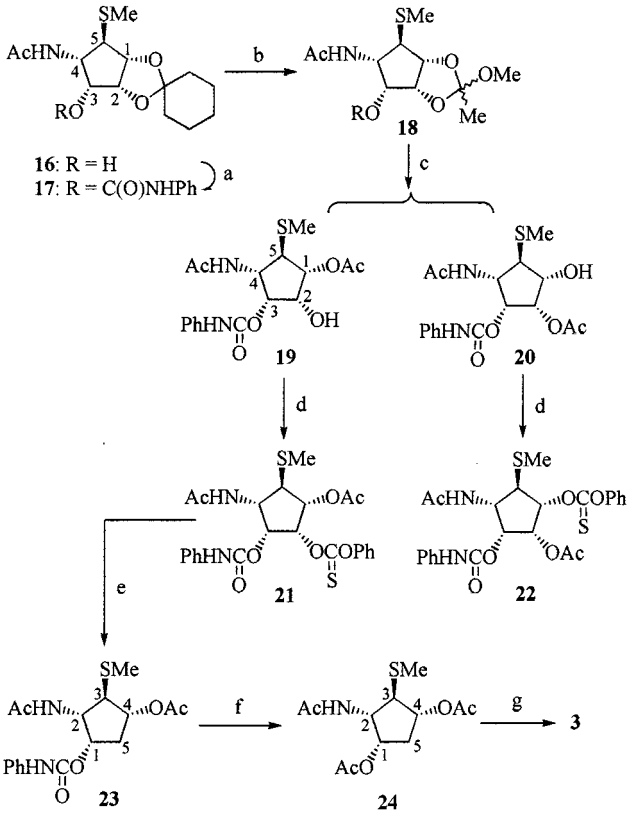


Scheme 2. Synthesis of 3-deoxymannostatin A (**4**): Reagents and conditions a) (S)-*O*-Acetylmandelic acid, DMAP, CH_2Cl_2, 0 °C; b) DMAP(6 molar equiv.), PhOC(S)Cl (5 molar equiv.), MeCN, 3 h, room temp.; c) PhOC(S)Cl (7 molar equiv.), DMAP (6 molar, equiv.), CH_3CN, 11 days, room temp.; d) nBu$_3$SnH, AIBN, toluene, 1 h, reflux; e) 1 M NaOMe/MeOH, 3 h, room temp.; f) $(CF_3CO)_2O$, pyridine, CH_2Cl_2; g) AcSK, 18-crown-6, benzene, overnight, room temp.; h) 1 M NaOMe/MeOH, room temp., MeI; i) 2 M HCl, 3 h, reflux; Ac_2O/pyridine; j) 2 M HCl, 12 h, 80 °C; Dowex 50 W × 2 (H^+) resin

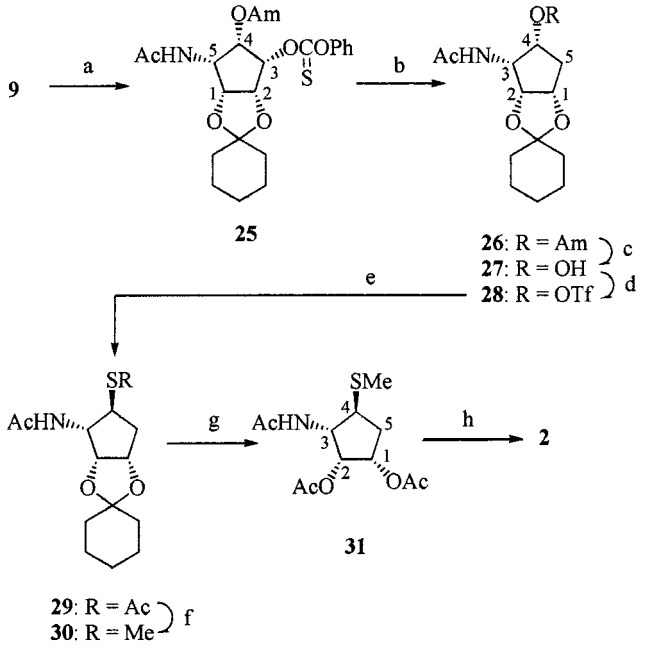
O-acylation of **10** gave the alcohol **11** (82%). Compound **11** was converted into the triflate **12**, which was directly treated with potassium thioacetate in benzene in the presence of 18-crown-6 to give the thioacetate **13** (71% overall yield). De-*S*-acetylation of **13** with methanolic sodium methoxide, and subsequent treatment with iodomethane, afforded the methylthio derivative **14** (83%) whose structure was confirmed on the basis of its ^{1}H NMR spectrum. Hydrolysis of **14** with 2 M HCl at reflux temperature, followed by treatment with acetic anhydride in pyridine, gave the tri-*N*,*O*-acetyl derivative **15** (84%). Similar hydrolysis of **15** and purification over a column of Dowex 50 W ×2 (H^+) resin with 1% aqueous ammonia gave the 3-deoxymannostatin A (**4**, ≈100%).

Preparation of the 1- and 2-deoxy derivatives **2** and **3** was attempted starting from the protected derivative **16** of mannostatin A derived from the antipode[9] of **6**. Thus, **16** was first protected as the phenylcarbamoyl derivative **17** (90%) in the usual manner (Scheme 3). Treatment of **17** with aqueous 60% acetic acid at 80 °C gave the diol, which was treated with trimethyl orthoacetate in the presence of TsOH in benzene to afford a mixture of the epimeric orthoacetates **18**. This mixture was treated with aqueous 80% acetic acid at room temperature to give an inseparable mixture (≈60%) of the 1- and 2-acetates (**19** and **20**), which were converted into the respective phenylthiocarbonates **21** (58%) and **22** (15%), respectively. 2-Deoxymannostatin A (**3**) was readily obtained by similar treatment of **21** with nBu$_3$SnH-AIBN [→**23** (70%)], and conventional deprotection and acetylation [→**24** (≈35%)]. The tri-*N*,*O*-acetyl derivative **24** gave the free base **3** (79%) by acid hydrolysis. Upon treatment with nBu$_3$SnH, compound **22** was found to give rise to a complex mixture of products, involving an elimination reaction.



Scheme 3. Synthesis of 2-deoxymannostatin A (**3**): Reagents and conditions a) PhNCO, pyridine, 6 h, room temp.; b) $(MeO)_3CMe$, TsOH, C_6H_6, room temp.; c) 60% aq AcOH, 9 h, 80 °C; d) PhOC(S)Cl, DMAP, MeCN, 0.5 h, room temp.; e) nBu$_3$SnH, AIBN, toluene, 2 h, reflux; f) 1 M NaOMe/MeOH, 2 h, reflux; Ac_2O/pyridine; g) 2 M HCl, 1.5 h, 80 °C; Dowex 50 W × 2 (H^+) resin

Synthesis of the 1-deoxymannostatin A (**2**) was therefore carried out starting from **9** (Scheme 4). Treatment of the phenylthiocarbonate **25** (91%), derived from **9**, with nBu$_3$SnH afforded the deoxy derivative **26** (77%), into which a methylthio function was incorporated as in the pre-



Scheme 4. Synthesis of 1-deoxymannostatin A (**2**): a) PhOC(S)Cl, DMAP, MeCN, 1.5 h, room temp.; b) nBu$_3$SnH, AIBN, toluene, 0.5 h, reflux; c) 1 M NaOMe/MeOH, 0.5 h, room temp.; d) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 20 min, –15 °C; e) AcSK, 18-crown-6, benzene, room temp., 2 days; f) 1 M NaOMe/MeOH, 10 min, room temp.; MeI, 2 h, room temp.; g) 2 M HCl, 2 h, reflux; Ac_2O, pyridine; h) 2 M HCl, 2 h, 80 °C; Dowex 50 W × 2 (H^+) resin

paration of **14**, giving protected 1-deoxymannostatin A **30** (13% overall yield) via the alcohol **27**, the triflate **28**, and the acetylthiolate **29**. De-*O*-cyclohexylidenation of **30**, followed by acetylation, gave the tri-*N,O*-acetyl derivative **31** (80%) whose structure was assigned from its ^{1}H NMR spectrum. The free base **2** (56%) was prepared by acid hydrolysis.

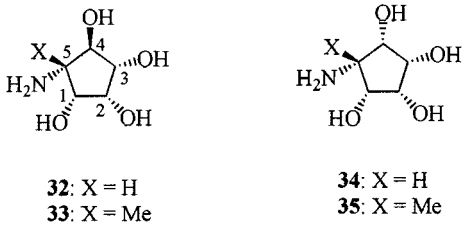
Table 1. Inhibitory activity of the compounds against Jack bean α-mannosidase (α-mannosidase, Jack bean, and nitrophenyl mannopyranoside were purchased from Sigma)

Compound	Inhibitory activity (IC_{50}, M)[a]
1[b]	2.4×10^{-7}
2	2.8×10^{-5}
3	3.1×10^{-5}
4	$>10^{-4}$
Nojirimycin B bisulfite[c]	4.2×10^{-5}

[a] 2.0 mM *p*-nitrophenyl α-D-mannopyranoside, 0.1 M acetate buffer, pH 4.5, ref.[11] – [b] Prepared following the procedure described in ref.[9] – [c] Ref.[12]

The inhibitory activities[11] of **2**, **3**, and **4** are listed in Table 1 [ref. mannostatin A (**1**) and nojirimycin B bisulfite[12]]. The 1- and 2-deoxy derivatives (**2** and **3**) retained some inhibitory potential, although about 100 times lower than the parent compound, but this activity was completely lost for the 3-deoxy derivative **4**.

We have so far demonstrated that, among twenty four stereoisomers[13] of 5-amino-1,2,3,4-cyclopentanetetrols, only the 1L-(1,2,3,5/4)- **32** and meso (1,2,3,4,5/0)-isomers **34**, and the corresponding 5-*C*-methyl derivatives[14] **33** and **35** (Scheme 5), are weak inhibitors of Jack bean α-mannosidase (IC_{50} = 1–3 × 10^{-5} M). In fact, their structures are likely to resemble that of mannostatin A, which contains four contiguous 1-, 2-, and 3-hydroxyl and 4-amino groups in *all-cis* relationships, suggesting that such a core structure is essential for the generation of inhibitory potential against α-mannosidase.



Scheme 5. Related aminocyclitols of mannostatin A

The fact that the 3-deoxy derivative **4** lost its inhibitory potential shows that the 3-hydroxyl function of **1** is essential for binding to the enzyme. This is conceivably related to the 2-hydroxyl group of the mannopyranosyl cation and the amino group located around the carbocation atom. Accordingly, in addition to Winkler's model,[7] other models may also be proposed where the 1- and 2-hydroxyl groups of **1** roughly correspond to the hydroxymethyl and the 3-hydroxyl groups of the mannopyranosyl cation, respectively.

On the other hand, it is possible that the two hydroxyl groups of the 1-deoxy derivative **2** overlap with the 3- and 2-hydroxyls of the mannosyl cation. Interestingly, generation of the 2-deoxy derivative **3** preserved moderate inhibitory potential, showing that the presence of *cis* vicinal hydroxyl groups corresponding to the 2- and 3-hydroxyls of mannopyranosyl cation is not always indispensable for mannosidase inhibitors.

Experimental Section

General: Melting points: Mel-Temp capillary melting-point apparatus, uncorrected. – Specific rotations: Jasco DIP-370 polarimeter, 1-dm cells. – IR spectra: Hitachi FT/IR-200 and BIORAD DIGITAL FT-65. ^{1}H NMR spectra: Jeol JNM EX-90 (90 MHz), Jeol GSX-270 f.t. (270 MHz), and Jeol Lambda-300 (300 MHz); solvent $CDCl_3$: internal standard tetramethylsilane (TMS); CD_3OD: external acetone; D_2O: external acetone. – Mass spectra: positive-ion electrospray ionization on a Micromass Zab Hybrid Spec Sector-TOF. – TLC: Silica Gel 60 GF (E. Merck, Darmstadt); detection by charring with concd. H_2SO_4. – Column chromatography: Wakogel C-300 (silica gel, 300 Mesh, Wako Chemical, Osaka). – Organic solutions, after drying with anhydrous Na_2SO_4, were concentrated <50 °C under reduced pressure.

All deoxymannostatin A isomers **2, 3**, and **4** were homogeneous on TLC and ^{1}H NMR spectroscopic analyses, and used directly for biological assays.

2,3-*O*-Cyclohexylidene Derivatives 6 and 7 of the Respective (1*S*,2*R*,3*R*,4*R*,5*S*)- and (1*R*,2*S*,3*S*,4*S*,5*R*)-5-Acetamido-1-*O*-[(2*S*)-2-*O*-acetylmandelyl]-1,2,3,4-cyclohexanetetrols: Following the standard procedure, diastereoselective acylation of the 2,3-*O*-cyclohexylidene derivative[9] **5** of symmetric (1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol with (2*S*)-(+)-acetylmandelic acid in the presence of DMAP gave **6** (56%) and **7** (8%).

2,3-*O*-Cyclohexylidene Derivative 8 of (1*S*,2*R*,3*S*,4*R*,5*R*)-5-Acetamido-1-*O*-[(2*S*)-2-*O*-acetylmandelyl]-4-*O*-phenoxythiocarbonyl-1,2,3,4-cyclopentanetetrol: To a solution of the acetylmandelate **6** (1.83 g, 4.09 mmol) in acetonitrile (18 mL) were added in turn DMAP (3.0 g, 6 molar equiv.) and phenyl chlorothionoformate (2.83 mL, 5.0 molar equiv.), and the mixture was stirred for 3 h at room temperature. After dilution with ethyl acetate (200 mL) the solution was washed with water, dried, and evaporated. The residue was chromatographed on a column of silica gel (240 g) with acetone/toluene (1:10) as an eluent to give **8** (1.69 g, 71%) as a colorless syrup. – $[\alpha]_D^{22}$ = +33 (*c* = 0.89, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3440 cm^{-1} (NH), 1750 (C=O), 1680 (NAc), 1520 (NH). – ^1H NMR (270 MHz, $CDCl_3$): δ = 7.59–7.12 (m, 10 H, 2 × Ph), 6.33 (d, $J_{5,NH}$ = 9.2 Hz, 1 H, NH), 6.01 [s, 1 H, PhC*H*(OAc)CO], 5.47 (dd, $J_{3,4}$ = 5.1, $J_{4,5}$ = 5.6 Hz, 1 H, 4-H), 5.01 (dd, $J_{1,2}$ = 5.1, $J_{2,3}$ = 5.5 Hz, 1 H, 2-H), 4.94 (ddd, $J_{1,5}$ = 5.8 Hz, 1 H, 5-H), 4.82 (dd, 1 H, 3-H), 4.76 (dd, 1 H, 1-H), 2.21 and 1.93 (2 s, each 3 H, 2 × Ac), 1.77–1.22 (m, 10 H, C_6H_{10}). – $C_{30}H_{33}N_2O_9S$ (583.7): calcd. C 61.74, H 5.70, N 2.40; found C 62.01, H 5.91, N 2.39. – HRMS ($C_{30}H_{33}NO_9S$): calcd. 583.1880; found 583.1876.

1,2-*O*-Cyclohexylidene Derivative 10 of (1*R*,2*R*,3*S*,4*S*)-4-Acetamido-3-*O*-[(2*S*)-2-*O*-acetylmandelyl]-1,2,3-cyclopentanetriol: To a mixture of AIBN (3.4 mg, 0.3 molar equiv.) and tributyltinhydride (55 µL, 3 molar equiv.) in toluene (0.5 mL) was added a solution of **8** (40 mg, 0.07 mmol) in toluene (3.5 mL), and the mixture was refluxed for 2 h. After cooling, it was concentrated and the residue was chromatographed on a column of silica gel (10 g) with acetone/toluene (1:4.5) as eluent to give **10** (21 mg, 71%) as a colorless syrup. – $[\alpha]_D^{22}$ = –14 (*c* = 1.2, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3440 cm^{-1} (NH), 1750 (C=O), 1660 (NAc), 1520 (NH). – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.40 (m, 5 H, Ph), 6.26 (d, $J_{4,NH}$ = 9.0 Hz, 1 H, NH), 5.99 [s, 1 H, PhC*H*(OAc)CO], 4.87 (dd, $J_{2,3}$ = 4.9, $J_{3,4}$ = 4.9 Hz, 1 H, 3-H), 4.70 (dd, $J_{1,2}$ = 6.1 Hz, 1 H, 2-H), 4.63 (ddd. $J_{1,5a}$ = 2.4, $J_{1,5b}$ = 5.4 Hz, 1 H, 1-H), 4.57 (m, 1 H, 4-H), 2.20 and 1.87 (2 s, each 3 H, 2 × Ac), 2.04–1.98 (m, 2 H, 5a-H, 5b-H), 1.52–1.25 (m, 10 H, C_6H_{10}). – HRMS ($C_{23}H_{30}NO_9$): calcd. 431.1943; found 431.1944.

1,2-*O*-Cyclohexylidene Derivative 11 of (1*R*,2*S*,3*S*,4*S*)-4-Acetamido-1,2,3-cyclopentanetriol: A solution of **10** (199 mg, 0.46 mmol) in CH_2Cl_2 (2 mL) was treated with 1 M methanolic sodium methoxide (0.23 mL, 0.5 molar equiv.) for 1.5 h at room temperature. The mixture was then diluted with ethyl acetate (25 mL), washed with water, dried, and the solvents evaporated. The residue was chromatographed on a column of silica gel (5 g) with acetone/toluene (1:1) as eluent to give **11** (199 mg, 82%) as a syrup. – $[\alpha]_D^{19}$ = –24 (*c* = 0.62, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (NH and OH), 1650 (NAc), 1540 (NH). – ^1H NMR (300 MHz, $CDCl_3$): δ = 6.18 (d, $J_{4,NH}$ = 7.2 Hz, 1 H, NH), 4.63 (ddd, $J_{1,2}$ = 6.4, $J_{1,5a}$ = 12.7, $J_{1,5b}$ = 3.2 Hz, 1 H, 1-H), 4.50 (dd, $J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 4.38 (dddd, $J_{3,4}$ = 4.6, $J_{4,5a}$ = 6.7, $J_{4,6b}$ = 4.7 Hz, 1 H, 4-H), 3.95 (dd, 1 H, 3-H), 2.12 (ddd, J_{5gem} = 6.4 Hz, 1 H, 5a-H), 2.00 (s, 3 H, Ac), 1.88 (ddd, 1 H, 5b-H), 1.78–1.39 (m, 10 H, C_6H_{10}).

1,2-*O*-Cyclohexylidene Derivative 13 of (1*R*,2*R*,3*R*,4*S*)-4-Acetamido-3-acetylthio-1,2-cyclopentanediol: To a solution of **11** (21 mg, 83 µmol) in CH_2Cl_2 (1 mL) at –15 °C were added in turn pyridine (34 µL, 5 molar equiv.) and trifluoromethanesulfonic anhydride (41 µL, 3 molar equiv.), and the mixture was stirred for 20 min at –15 °C. It was then partitioned between chloroform (10 mL) and saturated aq $NaHCO_3$ (10 mL), and the organic layer was dried and evaporated to give the crude triflate **12** as a brown syrup [R_f = 0.58, acetone/toluene (1:1)].

To a solution of the crude **12** in benzene (1 mL) were added 18-crown-6 (22 mg, 1 molar equiv.) and potassium thioacetate (94 mg, 10 molar equiv.), followed by stirring for 2 days at room temperature. After the insoluble material was removed by filtration, the filtrate was evaporated and the residue was chromatographed on a column of silica gel (8 g) with acetonitrile/toluene (1:5) as eluent to give **13** (18.5 mg, 71%) as a colorless syrup. – $[\alpha]_D^{27}$ = –26 (*c* = 0.09, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (NH), 1660 (NAc), 1540 (NH). – ^1H NMR (300 MHz, $CDCl_3$): δ = 6.39 (d, $J_{4,NH}$ = 7.0 Hz, 1 H, NH), 4.71 (ddd, 1 H, $J_{1,2}$ = 5.9, $J_{1,5a}$ = 12.4, $J_{1,5b}$ = 4.9 Hz, 1 H, 1-H), 4.49 (dd, $J_{2,3}$ = 2.2 Hz, 1 H, 2-H), 4.30 (dddd, $J_{3,4}$ = 4.8, $J_{4,5a}$ = 6.2, $J_{4,5b}$ = 3.7 Hz, 1 H, 4-H), 3.82 (dd, 1 H, 3-H), 2.35 (s, 3 H, SAc), 2.22 (m, 1 H, 5a-H), 1.95 (m, 1 H, 5b-H), 1.95 (s, 3 H, NAc), 1.75–1.34 (m, 10 H, C_6H_{10}). – HRMS ($C_{15}H_{23}NO_4S$): calcd. 313.1348; found 313.1349.

1,2-*O*-Cyclohexylidene Derivative 14 of (1*R*,2*R*,3*R*,4*S*)-4-Acetamido-3-(methylthio)-1,2-cyclopentanediol: A solution of **13** (36.5 mg, 0.12 mmol) in methanol (0.4 mL) was treated with 1 M methanolic sodium methoxide (175 µL, 1.5 molar equiv.) for 10 min at room temperature and then, after addition of iodomethane (36 µL, 5 molar equiv.), the mixture was stirred for a further 30 min at room temperature. After evaporation the residue was dissolved in chloroform (20 mL) and the solution was washed with water, dried, and evaporated. The residual product was chromatographed on a column of silica gel (3 g) with acetone/toluene (1:5) as eluent to give **14** (28 mg, 83%) as a syrup. – $[\alpha]_D^{21}$ = –26 (*c* = 0.73, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (NH), 1650 (NAc), 1540 (NH). – ^1H NMR (300 MHz, $CDCl_3$): δ = 6.42 (d, $J_{4,NH}$ = 8.3 Hz, 1 H, NH), 4.78 (m, 1 H, 1-H), 4.48 (m, 1 H, 2-H), 4.35 (m, 1 H, 4-H), 3.15 (m, 1 H, 3-H), 2.33 (m, 1 H, 5a-H), 2.26 (s, 3 H, SMe), 1.96 (m, 1 H, 5b-H), 1.94 (s, 3 H, Ac), 1.75–1.33 (m, 10 H, C_6H_{10}). – $C_{14}H_{23}NO_3S$ (285.4): calcd. C 58.92, H 8.12, N 4.91; found C 58.30, H 8.02, N 4.67.

(1*R*,2*R*,3*R*,4*S*)-4-Acetamido-1,2-di-*O*-acetyl-3-methylthio-1,2-cyclopentanediol (Tri-*N,O*-acetyl-3-deoxymannostatin A, 15): A mixture of **14** (2.5 mg, 0.01 mmol) and 2 M hydrochloric acid (0.5 mL) was heated at 100 °C for 3 h, and then evaporated to dryness. The residue was treated with acetic anhydride (0.5 mL) in pyridine (1 mL) at room temperature for 3 h, and the residual product was chromatographed on a column of silica gel (0.5 g) with acetone/toluene (1:5) as eluent to give **15** (1.9 mg, 70%) as a colorless syrup. – $[\alpha]_D^{22}$ = +3.8 (*c* = 0.01, $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$): δ = 5.69 (d, $J_{4,NH}$ = 8.6 Hz, 1 H, NH), 5.34 (ddd, $J_{1,2}$ = 4.6, $J_{1,5a}$ = 6.4, $J_{1,5b}$ = 3.9 Hz, 1 H, 1-H), 5.05 (dd, $J_{2,3}$ = 8.1 Hz, 1 H, 2-H), 4.27 (dddd, $J_{3,4}$ = 8.1, $J_{4,5a}$ = 14.9, $J_{4,5b}$ = 5.6 Hz, 1 H, 4-H), 2.97 (dd, 1 H, 4-H), 2.62 (ddd, J_{5gem} = 9.0 Hz, 1 H, 5a-H), 2.15, 2.09, 2.08, and 2.02 (4 s, each 3 H, 3 × Ac, SMe), 1.71 (ddd, 1 H, 5b-H). – $C_{12}H_{19}NO_5S$ (289.4): calcd. C 49.81, H 6.62, N 4.84; found C 49.94, H 6.81, N 4.64.

(1*R*,2*R*,3*R*,4*S*)-4-Amino-3-methylthio-1,2-cyclopentanediol (3-Deoxymannostatin A, 4): Compound **15** (4.2 mg, 0.015 mmol) was treated with 2 M hydrochloric acid (1 mL) for 20 h at 80 °C, and then the mixture was eluted from a column of Dowex 50 W × 2 (H^+) resin (1 mL) with 1% aqueous ammonia to give **4** (2.4 mg) quantitatively as a colorless syrup. – R_f = 0.37 (H_2O/AcOH/*t*BuOH 1:1:4). – $[\alpha]_D^{28}$ = +6.7 (*c* = 0.14, MeOH). – ^1H NMR (300 MHz, CD_3OD): δ = 4.01 (ddd, $J_{1,2}$ = 4.9, $J_{1,5a}$ = 7.1, $J_{1,5b}$ = 4.6 Hz, 1 H, 1-H), 3.74 (dd, $J_{2,3}$ = 7.3 Hz, 1 H, 2-H), 2.91 (m, 1 H, 4-H), 2.65 (dd, $J_{3,4}$ = 7.3 Hz, 1 H, 3-H), 2.29 (ddd, $J_{4,5a}$ = 12.9, J_{5gem} = 13.9 Hz, 1 H, 5a-H), 2.16 (s, 3 H, SMe), 1.53 (ddd, 1 H, 5b-H).

1,2-*O*-Cyclohexylidene Derivative 17 of (1*R*,2*S*,3*R*,4*S*,5*R*)-4-Acetamido-3-*O*-phenylcarbamoyl-5-methylthio-1,2,3-cyclopentanetriol:

The 1,2-*O*-cyclohexylidene derivative[9] **16** (20 mg, 0.07 mmol) of D-(1,2,3,4/5)-4-acetamido-5-(methylthio)-1,2,3-cyclopentanetriol was treated with phenylisocyanate (72 μL, 10 molar equiv.) for 6 h at room temperature. The mixture was evaporated to dryness and the residue was chromatographed on a column of silica gel (13 g) with acetone/toluene (1:12) as eluent to give **17** (25 mg, 90%) as a colorless solid. – $[\alpha]_D^{27}$ = +35 (*c* = 0.33, $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.06 (m, 5 H, Ph), 6.97 (s, 1 H, PhN*H*CO), 6.42 (d, $J_{4,NH}$ = 8.1 Hz, 1 H, NH), 5.31 (dd, $J_{2,3}$ = 5.3, $J_{3,4}$ = 5.6 Hz, 1 H, 3-H), 4.85 (dd, $J_{1,2}$ = 5.3 Hz, 1 H, 2-H), 4.56 (ddd, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 4.48 (dd, $J_{1,5}$ = 1.2 Hz, 1 H, 1-H), 3.17 (dd, 1 H, 5-H), 2.27 (s, 3 H, SMe), 1.99 (s, 3 H, OAc), 1.76–1.45 (m, 10 H, C_6H_{10}). – $C_{21}H_{28}N_2O_5S$ (420.5): calcd. C 59.98, H 6.71, N 6.66; found C 60.09, H 6.69, N 6.58.

(1*R*,2*S*,3*R*,4*S*,5*R*)-4-Acetamido-1- (19) and 2-*O*-acetyl-3-*O*-phenylcarbamoyl-1,2,3-cyclopentanetriols (20): A mixture of **17** (59 mg, 0.14 mmol) in aqueous 60% acetic acid (1 mL) was stirred for 9 h at 80 °C, and then concentrated. The residue was co-evaporated with toluene several times, then dissolved in benzene (1 mL) and treated with trimethyl orthoacetate (1 mL) for 3 h at room temperature. The reaction mixture was treated with Amberlite IRA-400 (OH^-) resin and then concentrated. The residue was treated with aqueous 80% acetic acid (2 mL) for 30 min at room temperature and the product was chromatographed on a column of silica gel (6 g) with acetone/toluene (1:3) as eluent to give an inseparable mixture (32 mg, 60%) of **19** and **20. –** R_f = 0.37 (acetone/toluene 1:1).

(1*R*,2*S*,3*R*,4*S*,5*R*)-4-Acetamido-1-*O*-acetyl-2-*O*-phenoxythiocarbonyl- (21) and (1*R*,2*R*,3*R*,4*S*,5*R*)-4-Acetamido-2-*O*-acetyl-1-*O*-phenoxythiocarbonyl-3-*O*-phenylcarbamoyl-1,2,3-cyclopentanetriols (22): A mixture (14.4 mg, 0.04 mmol) of **19** and **20** (see above) and DMAP (27.6 mg, 6 molar equiv.) was dissolved in acetonitrile (0.5 mL) and treated with phenyl chlorothionoformate (26 μL, 5 molar equiv.) for 30 min at room temperature. The mixture was processed similarly as in the preparation of **8**. The products were chromatographed on a column of silica gel (2.4 g) with acetone/toluene (1:10) as eluent to give in turn **22** (3 mg, 16%) and **21** (13 mg, 65%) as syrups.

21: $[\alpha]_D^{27}$ = –4.8 (*c* = 0.70, $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.04 (m, 5 H, Ph), 6.93 (s, 1 H, PhN*H*CO), 5.95 (dd, $J_{1,2}$ = 5.9, $J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 5.91 (d, $J_{4,NH}$ = 8.6 Hz, 1 H, NH), 5.53 (dd, $J_{3,4}$ = 5.6 Hz, 1 H, 3-H), 5.35 (dd, $J_{1,5}$ = 6.4 Hz, 1 H, 1-H), 4.56 (ddd, $J_{4,5}$ = 7.6 Hz, 1 H, 4-H), 3.19 (dd, 1 H, 5-H), 2.20 (s, 3 H, SMe), 2.09 and 2.02 (2 s, each 3 H, 2 × OAc). – $C_{24}H_{26}N_2O_7S_2$ (518.6): calcd. C 55.58, H 5.05, N 5.40; found C 56.08, H 5.48, N 5.47.

22: $[\alpha]_D^{27}$ = –13 (*c* = 0.15, $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.07 (m, 10 H, 2 × Ph), 6.87 (s, 1 H, PhN*H*CO), 5.80 (dd, $J_{1,2}$ = 6.6, $J_{1,5}$ = 5.1 Hz, 1 H, 1-H), 5.79 (d, $J_{4,NH}$ = 9.0 Hz, 1 H, NH), 5.57 (dd, $J_{2,3}$ = 4.2 Hz, 1 H, H-2), 5.44 (dd, $J_{3,4}$ = 4.9, 1 H, 3-H), 4.62 (ddd, $J_{4,5}$ = 9.0 Hz, 1 H, 4-H), 3.35 (dd, 1 H, 5-H), 2.24 (s, 3 H, SMe), 2.05 (s, 6 H, 2 × Ac).

(1*S*,2*S*,3*R*,4*R*)-2-Acetamido-4-*O*-acetyl-3-methylthio-1-*O*-phenoxythiocarbonyl-1,4-cyclopentanediol (23): To a solution of **21** (12.6 mg, 0.02 mmol) and AIBN (1.2 mg, 0.3 molar equiv.) in toluene (1.2 mL) was added tributyltinhydride (20 μL, 3 molar equiv.), and the mixture was processed as in the preparation of **10**. The product was chromatographed on a column of silica gel (1 g) with acetone/toluene (1:3) as eluent to give **23** (6.2 mg, 70%) as a syrup. – R_f = 0.43 (acetone/toluene 1:1.5). – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.13 (m, 5 H, Ph), 6.44 (s, 1 H, PhN*H*CO), 5.18 (ddd, $J_{1,2}$ = 4.9, $J_{1,5a}$ = 6.9, $J_{1,5b}$ = 1.5 Hz, 1 H, 1-H), 5.08 (dd, $J_{3,4}$ = 6.8, $J_{4,5a}$ = 8.8, $J_{4,5b}$ = 4.9 Hz, 1 H, 4-H), 4.98 (d, $J_{2,NH}$ = 9.0 Hz, 1 H, NH), 4.28 (ddd, $J_{2,3}$ = 11.0 Hz, 1 H, 2-H), 3.06 (dd, 1 H, 3-H), 2.62 (ddd, J_{5gem} = 6.1 Hz, 1 H, 5a-H), 2.15 (s, 3 H, SMe), 2.05 and 2.04 (2 s, each 3 H, 2 × Ac), 1.64 (ddd, 1 H, 5b-H).

(1*S*,2*S*,3*R*,4*R*)-2-Acetamido-1,4-di-*O*-acetyl-3-methylthio-1,4-cyclopentanediol (Tri-*N,O*-acetyl-2-deoxymannostatin A, 24): A solution of **23** (5.8 mg, 0.016 mmol) and 1 M methanolic sodium methoxide (32 μL, 2 molar equiv.) in methanol (0.5 mL) was stirred for about 12 h at 60 °C, and then evaporated to dryness. The residue was treated with acetic anhydride (0.5 mL) in pyridine (1 mL) for about 12 h at room temperature. The products were chromatographed on a silica gel column (0.7 g) with acetone/toluene (1:4) to give **24** (0.6 mg, 19%), recovered together with **23** (1.8 mg). – $[\alpha]_D^{27}$ = +13.5 (*c* = 0.27, $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$): δ = 5.63 (d, $J_{2,NH}$ = 11.3 Hz, 1 H, NH), 5.11 (ddd, $J_{1,2}$ = 5.9, $J_{1,5a}$ = 5.9, $J_{1,5b}$ = 1.5 Hz, 1 H, 1-H), 5.08 (ddd, $J_{3,4}$ = 7.1, $J_{4,5a}$ = 8.8, $J_{4,5b}$ = 4.9 Hz, 1 H, 4-H), 4.35 (ddd, $J_{2,3}$ = 11.5 Hz, 1 H, 2-H), 3.09 (dd, 1 H, 3-H), 2.61 (ddd, J_{5gem} = 6.4 Hz, 1 H, 5b-H), 2.12 (s, 3 H, SMe), 2.11, 2.08, and 2.05 (3 s, each 3 H, 3 × Ac), 1.78 (ddd, 1 H, 5a-H). – $C_{12}H_{19}NO_5S$ (289.4): calcd. C 49.81, H 6.62, N 4.84; found C 49.97, H 6.81, N 4.64.

(1*S*,2*S*,3*R*,4*R*)-2-Amino-3-methylthio-1,4-cyclopentanediol (2-Deoxymannostatin A, 3): Compound **24** (5.9 mg, 0.04 mmol) was treated with 2 M hydrochloric acid (1 mL) for 1.5 h at 80 °C, and the product was purified as in the preparation of **4** to give **3** (2.6 mg, 79%). – R_f = 0.37 (H_2O/acetic acid/*tert*-butyl alcohol 1:1:4). – $[\alpha]_D^{28}$ = +22 (*c* = 0.13, MeOH). – ^1H NMR (300 MHz, CD_3OD): δ = 4.03 (ddd, $J_{1,2}$ = 4.6, $J_{1,5a}$ = 2.7, $J_{1,5b}$ = 5.9 Hz, 1 H, 1-H), 3.98 (ddd, $J_{3,4}$ = 6.1, $J_{4,5a}$ = 4.9, $J_{4,5b}$ = 8.1 Hz, 1 H, 4-H), 2.75 (dd, $J_{1,2}$ = 4.6, $J_{2,3}$ = 9.5 Hz, 1 H, 2-H), 2.68 (dd, 1 H, 3-H), 2.34 (ddd, J_{5gem} = 14.4 Hz, 1 H, 5a-H), 2.14 (s, 3 H, SMe), 1.63 (ddd, 1 H, 5b-H).

1,2-*O*-Cyclohexylidene Derivative 9 of (1*R*,2*R*,3*R*,4*S*,5*S*)-5-Acetamido-4-*O*-[(2*S*)-2-*O*-acetylmandenyl]-1,2,3,4-cyclopentanetetrol: A solution of **6** (646 mg, 1.44 mmol) in acetonitrile (6 mL) was treated with phenylthionoformate (1.4 mL, 7 molar equiv.) and DMAP (176 mg, 6 molar equiv.) for 11 days at room temperature. The mixture was diluted with ethyl acetate (120 mL) and the solution was washed with water, dried, and evaporated. The residue was chromatographed on a column of silica gel (40 g) with acetone/toluene (1:3) as eluent to give **9** (364 mg, 56%) as a syrup. – $[\alpha]_D^{19}$ = +16.5 (*c* = 0.95, $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.31 (m, 5 H, Ph), 6.25 (d, $J_{5,NH}$ = 9.0 Hz, 1 H, NH), 5.77 [s, 1 H, PhC*H*(OAc)CO], 5.36 (dd, $J_{3,4}$ = 4.9, $J_{4,5}$ = 4.9 Hz, 1 H, 4-H), 4.60 (dd, $J_{1,2}$ = 5.4, $J_{1,5}$ = 4.9 Hz, 1 H, 1-H), 4.45 (dd, $J_{2,3}$ = 5.1 Hz, 1 H, 2-H), 4.39 (ddd, 1 H, 5-H), 3.96 (dd, 3-H), 2.22 and 1.96 (2 s, each 3 H, 2 × Ac), 1.73–1.25 (m, 10 H, C_6H_{10}). – $C_{23}H_{29}NO_8$ (447.5): calcd. C 61.73, H 6.53, N 3.13; found C 61.32, H 6.45, N 3.23. – HMRS ($C_{23}H_{29}NO_8$): calcd. 447.1893; found 447.1894.

1,2-*O*-Cyclohexylidene Derivative 25 of (1*R*,2*R*,3*R*,4*S*,5*S*)-5-Acetamido-4-*O*-[(2*S*)-2-*O*-acetylmandenyl]-3-*O*-phenoxythiocarbonyl-1,2,3,4-cyclopentanetetrol: A solution of **9** (40 mg, 0.09 mmol) in acetonitrile (0.4 mL) was treated with DMAP (65 mg, 6 molar equiv.) for 50 min at room temperature, and then phenylthionoformate (61 μL, 5 molar equiv.) was added and the mixture was stirred for 1.5 h at room temperature. The mixture was processed as in the preparation of **8** and the product was chromatographed on a column of silica gel (5 g) with acetone/toluene (1:9) as eluent to give **25** (47 mg, 91%) as a syrup. – $[\alpha]_D^{19}$ = +8.2 (*c* = 1.0, $CHCl_3$). – ^1H

NMR (300 MHz, $CDCl_3$): δ = 7.65–6.96 (m, 5 H, Ph), 6.23 (d, $J_{5,NH}$ = 9.2 Hz, 1 H, NH), 5.86 [s, 1 H, PhC*H*(OAc)CO], 5.74 (dd, $J_{3,4}$ = 5.1, $J_{4,5}$ = 4.6 Hz, 1 H, 4-H), 5.33 (dd, $J_{2,3}$ = 5.4 Hz, 1 H, 3-H), 4.95 (dd, $J_{1,2}$ = 5.4 Hz, 1 H, 2-H), 4.68 (dd, $J_{1,5}$ = 5.4 Hz, 1 H, 1-H), 4.55 (ddd, 1 H, 5-H), 2.26 and 1.91 (2 s, each 3 H, 2 × Ac), 1.73–1.43 (m, 10 H, C_6H_{10}). – $C_{30}H_{33}NO_9S$ (583.7): calcd. C 61.74, H 5.70, N 2.40; found C 61.74, H 5.76, N 2.74.

1,2-*O*-Cyclohexylidene Derivative 26 of (1*S*,2*R*,3*S*,4*R*)-3-Acetamido-4-*O*-[(2*S*)-2-*O*-acetylmandenyl]-1,2,4-cyclopentanetetrol: Compound **25** (104 mg, 0.18 mmol) was treated with tributyltinhydride (143 μL, 3 molar equiv.) as described in the preparation of **10**. The product was chromatographed on a column of silica gel (7 g) with acetone/toluene (1:6) as eluent to give **26** (59 mg, 77%) as a syrup. – $[\alpha]_D^{19}$ = +14 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.34 (m, 5 H, Ph), 6.23 (d, $J_{3,NH}$ = 9.3 Hz, 1 H, NH), 5.74 [s, 1 H, PhC*H*(OAc)CO], 5.41 (m, 1 H, 3-H), 4.69 (m, 1 H, 1-H), 4.57 (dd, $J_{1,2}$ = 5.9, $J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 4.40 (ddd, 1 H, $J_{3,4}$ = 4.9 Hz, 1 H, 3-H), 2.23 (m, 1 H, 5a-H), 2.21 and 1.89 (2 s, each 3 H, 2 × Ac), 1.82 (m, 1 H, 5b-H), 1.77–1.37 (m, 10 H, C_6H_{10}). – HRMS ($C_{23}H_{29}NO_7$): calcd. 431.1944; found 431.1942.

1,2-*O*-Cyclohexylidene Derivative 27 of (1*S*,2*R*,3*R*,4*R*)-3-Acetamido-1,2,4-cyclopentanetetrol: A solution of **26** (59 mg, 0.14 mmol) in dichloromethane (0.6 mL) was treated with 1 M methanolic sodium methoxide (70 μL) for 30 min at room temperature. The product was chromatographed on a column of silica gel (5 g) with acetone/toluene (1:1) as eluent to give **27** (23 mg, 66%) as a syrup. – $[\alpha]_D^{21}$ = +65 (*c* = 1.7, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.29 (d, $J_{3,NH}$ = 10.3 Hz, 1 H, NH), 4.75 (m, 1 H, 1-H), 4.61 (dd, $J_{1,2}$ = 5.9, $J_{2,3}$ = 5.9 Hz, 1 H, 2-H), 4.09 (m, 1 H, 3-H), 4.08 (m, 1 H, 4-H), 2.43 (d, $J_{4,OH}$ = 10.0 Hz, 1 H, OH), 2.22 (m, 1 H, 5a-H), 2.08 (s, 3 H, Ac), 1.79 (m, 1 H, 5b-H), 1.67–1.32 (m, 10 H, C_6H_{10}).

1,2-*O*-Cyclohexylidene Derivative 29 of (1*S*,2*R*,3*S*,4*S*)-3-Acetamido-4-acetylthio-1,2-cyclopentanediol: To a solution of **27** (21 mg, 83 mmol) in dichloromethane (1 mL) were added pyridine (33 μL, 5 molar equiv.) and trifluoromethanesulfonic anhydride (41 μL, 3 molar equiv.) at –15 °C, followed by stirring for 20 min at –15 °C. The mixture was diluted with chloroform and the solution was washed with saturated aqueous sodium hydrogen carbonate and water, dried, and concentrated to give the triflate **28**. – R_f = 0.58 (acetone/toluene 1:1).

Without further purification, crude **28** was dissolved in benzene (1 mL) and the solution was treated with potassium thioacetate (94 mg, 10 molar equiv.) in the presence of 18-crown-6 (22 mg) for 2 days at room temperature. The product was chromatographed on a column of silica gel (8 g) with acetonitrile/toluene (1:5) as eluent to give **29** (18.4 mg, 71% overall yield). – R_f = 0.45 (acetone/toluene 1:1). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.92 (d, $J_{3,NH}$ = 11.0 Hz, 1 H, NH), 4.63 (dd, $J_{1,2}$ = 5.4, $J_{1,5b}$ = 5.4 Hz, 1 H, 1-H), 4.51 (dd, $J_{2,3}$ = 5.1 Hz, 1 H, 2-H), 4.11 (ddd, 1 H, $J_{3,4}$ = 14.1 Hz, 1 H, 3-H), 3.80 (ddd, $J_{4,5a}$ = 5.6, $J_{4,5b}$ = 12.5 Hz, 1 H, 4-H), 2.32 and 2.00 (2 s, each 3 H, 2 × Ac), 2.17 (dd, J_{5gem} = 12.7 Hz, 1 H, 5a-H), 1.76–1.32 (m, 10 H, C_6H_{10}), 1.63 (ddd, 1 H, 5b-H).

1,2-*O*-Cyclohexylidene Derivative 30 of (1*S*,2*R*,3*S*,4*S*)-3-Acetamido-4-methylthio-1,2-cyclopentanediol: Compound **29** (4.0 mg, 0.013 mmol) was treated with 1 M methanolic sodium methoxide (19 μL, 1.5 molar equiv.) in methanol (0.2 mL) for 5 min at room temperature. Iodomethane (4 μL, 5 molar equiv.) was then added at 0 °C and the mixture was stirred for 2 h at room temperature, and then evaporated to dryness. The residual product was chromatographed on a column of silica gel (0.7 g) with acetone/toluene (1:5) to give **30** (3.6 mg, ≈100%) as a syrup. – $[\alpha]_D^{23}$ = +42 (*c* = 0.18, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.79 (d, $J_{3,NH}$ = 9.5 Hz, 1 H, NH), 4.60 (dd, $J_{1,2}$ = 5.6, $J_{1,5b}$ = 5.1 Hz, 1 H, 1-H), 4.50 (dd, $J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 4.11 (ddd, $J_{3,4}$ = 11.5 Hz, 1 H, 3-H), 2.88 (ddd, $J_{4,5a}$ = 11.5, $J_{4,5b}$ = 5.9 Hz, 1 H, 4-H), 2.14 (dd, J_{5gem} = 8.1 Hz, 1 H, 5a-H), 2.08 and 2.07 (2 s, each 3 H, Ac and SMe), 1.65 (ddd, 5b-H), 1.65–1.32 (m, 10 H, C_6H_{10}). – HRMS ($C_{14}H_{23}NO_3S$): calcd. 285.1398; found 285.1399.

(1*S*,2*R*,3*S*,4*S*)-3-Acetamido-1,2-di-*O*-acetyl-4-methylthio-1,2-cyclopentanediol (Tri-*N*,*O*-acetyl-1-deoxymannostatin A, 31): A solution of **30** (3.6 mg, 0.01 mmol) was treated with 2 M hydrochloric acid for 15 min at 100 °C, and then the product was acetylated in the usual manner. Chromatography on a column of silica gel (0.5 g) with acetone/toluene (1:3) as eluent gave **31** (3.1 mg, 80%) as a syrup. – $[\alpha]_D^{28}$ = +15 (*c* = 0.10, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.74 (d, $J_{3,NH}$ = 8.8 Hz, 1 H, NH), 5.37 (m, 1 H, 2-H), 5.35 (m, 1 H, 1-H), 4.52 (m, 1 H, 3-H), 3.15 (ddd, $J_{3,4}$ = 6.8, $J_{4,5a}$ = 6.8, $J_{4,5b}$ = 10.0 Hz, 1 H, 4-H), 2.28 (m, 1 H, 5a-H), 2.07 (m, 1 H, 5b-H), 2.18, 2.11, 2.05, and 2.02 (4 s, each 3 H, 3 × Ac and SMe). – HRMS ($C_{12}H_{19}NO_5S$): calcd. 289.0984; found 289.0984.

(1*S*,2*R*,3*S*,4*S*)-3-Amino-4-methylthio-1,2-cyclopentanediol (1-Deoxymannostatin A, 2): Compound **31** (2.0 mg, 0.01 mmol) was treated with 2 M hydrochloric acid (1 mL) for 20 h at 80 °C, and then the mixture was eluted from a column of Dowex 50 W × 2 (H^+) resin (1 mL) with 1% aqueous ammonia to give **2** (0.6 mg, 56%). – R_f = 0.49 (H_2O/AcOH/*tert*-butyl alcohol 1:1:4) – $[\alpha]_D^{19}$ = +29 (*c* = 0.04, MeOH). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.10 (m, 1 H, 1-H), 3.90 (m, 1 H, 2-H), 2.96 (m, 2 H, 3-H and 4-H), 2.15 (m, 1 H, 5a-H), 2.10 (s, 3 H, SMe), 1.86 (m, 1 H, 5b-H).

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