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Synthesis of Mannostatins A and B from *myo*-Inositol

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Abstract—Mannostatins A and B, along with the respective enantiomer and diastereoisomer having the (*S*)-sulfinyl function, were synthesized from *myo*-inositol. Inhibitory activity of the synthetic compounds against jack bean α-mannosidase was measured, revealing that the 4-aminocyclopentane-1,2,3-triol structure plays a major role in interaction with the enzyme.

Introduction

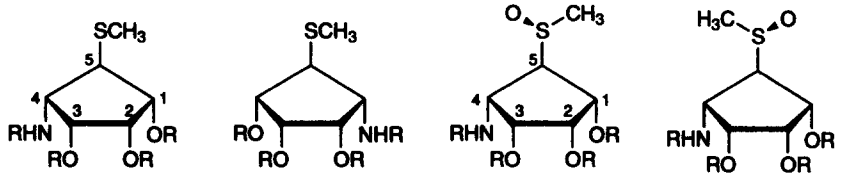
In 1989, isolation of α-mannosidase inhibitors, mannostatins A (**1**) and B (**3**) was reported by Aoyagi *et al.*[1] The absolute structures of the inhibitors were established[2] by X-ray diffraction analysis of crystalline tetra-*O*-acetyl derivative **3a** of **3**. Mannostatin B is a sulfoxide derivative of **1** and can be easily converted into **1** by treatment with glycolic acid.[2] Mannostatin A is a potent inhibitor of rat epididymis α-mannosidase (K_i = 48 μM)[2] and mannosidase II (IC_{50} = 100 nM),[3] and its simple but unique cyclopentane–polyol structure having exocyclic nitrogen and thiomethyl functions has so far stimulated much interest[4] for elucidation of enzymic action and mechanisms of glycohydrolases using **1** as a biological tool.

The synthesis of **1** has been performed almost simultaneously by five research groups[5–9] through their original synthetic sequences starting from the versatile intermediates. We here describe details of our synthesis of mannostatins A and B, and their stereoisomers from *myo*-inositol,[5] together with their inhibitory activity against jack bean α-mannosidase.

Results and Discussion

We chose the 2,3-*O*-cyclohexylidene derivative[10] **5** of (1,2,3,4,5/0)-5-acetamidocyclopentane-1,2,3,4-tetraol as the starting compound. This compound was readily available[11] from the (1,4/2,3,5)-isomer derived from *myo*-inositol according to the elegant method of Angyal *et al.*[12] Compound **5** has a *meso* structure containing two equivalent hydroxyl groups. Therefore, modification or substitution of the one hydroxyl would give rise to racemic compounds and optical resolution of the synthetic intermediates is always needed for synthesis of target chiral compounds. In the present synthesis, the racemic key compounds could be resolved by conversion into the corresponding (*S*)-*O*-acetylmandelates, which were cleanly separated by a silica gel column.

Selective sulfonylation of **5** was carried out using 1.3 molar equiv. of mesyl chloride in pyridine at 0 °C. Monitoring the progress of the reaction by TLC, the reaction was quenched after 30 min and the products were separated by a silica gel column to give the mesylate **6** (46%) and the dimesylate **7** (8.3%), together with **5** (43%) remaining unchanged. Direct substitution reaction of **6** with an excess of potassium thioacetate in *N*,*N*-dimethylformamide proceeded slowly at 120 °C, and the thioacetate **8** formed was shown by TLC to undergo decomposition to complex products on prolonged heating under these conditions. Therefore, after 1 h, the products were isolated by chromatography to afford a syrupy **8** (20%) and **6** (78%) recovered. The crude **8** was *S*-



Mannostatin A: **1**
1a

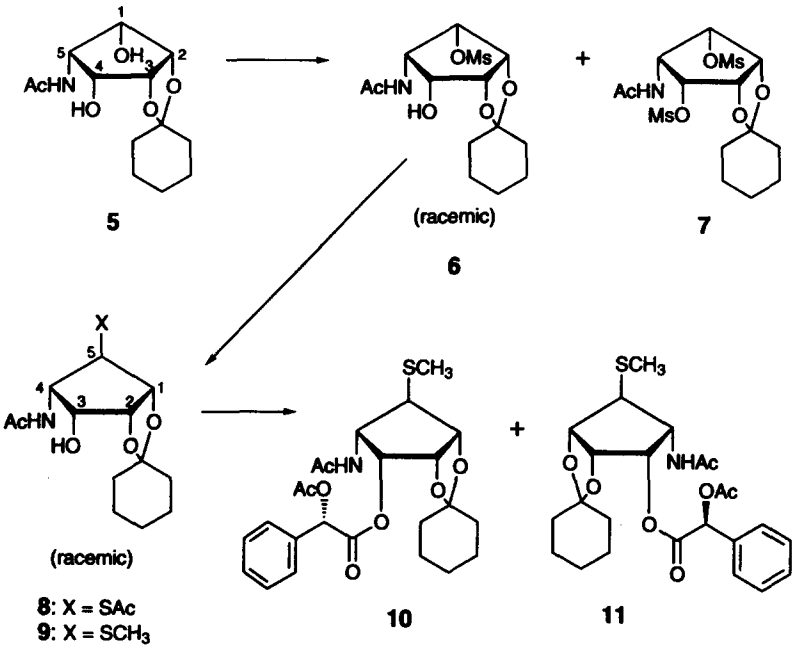
2
2a

Mannostatin B: **3**
3a

4
4a

1– **4**: R = H
1a– **4a**: R = Ac

Scheme 1.



Scheme 2.

deacetylated under Zemplén conditions and subsequently treated with methyl iodide to give the thiomethyl compound **9** quantitatively. The structures of **8** and **9** were tentatively assigned on the basis of the ^{1}H NMR spectra (270 MHz, $CDCl_3$).[13] Optical resolution was attempted at this stage by converting **9** into the (*S*)-*O*-acetylmandelyl esters. Thus, treatment of **9** with 1.2 molar equiv. of (*S*)-*O*-acetylmandelic acid in dichloromethane in the presence of 4-dimethylaminopyridine and DCC at –15 °C under Ar produced a diastereoisomeric mixture which was separated by a silica gel column with acetone:toluene as eluent, giving the esters **10** and **11** (TLC: R_f0.36 and 0.42, 1:3 acetone:toluene). In their ^{1}H NMR spectra ($CDCl_3$), a signal due to the amido proton of **10** appeared at δ 6.24 being appreciably deshielded by the proximate phenyl group, in contrast to that (δ 5.71) of **11**. These results would possibly support the assigned structures depicted in the Schemes. The absolute structures of the esters were finally determined by correlating them to known mannostatin A and its enantiomer. Thus, without further purification, **10** was treated with 1 N hydrochloric acid at 100 °C and then acetylated with acetic anhydride in pyridine to afford the crystalline tetra-*N*,*O*-acetyl derivative **1a** (13% overall yield based on **9**) of **1**. Likewise, its enantiomer **2a** was obtained from **11** in 20% overall yield. The ^{1}H NMR spectra (270 MHz, $CDCl_3$) of **1a** and **2a** were identical with each other and superimposable on that of an authentic sample[14] of **1a**. The specific rotations[15] of **1a** and **2a** were shown to be equal in number and opposite in sign.

The free bases **1** and its enantiomer **2** were purely obtained from the hydrolysate of **10** and **11**, respectively, after purification by chromatography on Amberlite IR-120 (H^+) resin with 1 N aqueous ammonia as an eluent.[16] Inhibitory activities[17] of the synthetic **1** and **2** against jack bean α-mannosidase are shown in Table 1. Distinct differences in biological activity have been observed between the enantiomeric pair of mannostatin A.

Table 1. Inhibitory activity of synthetic **1**, **2**, **3** and **4** against jack bean α-mannosidase[a]

Compound	Inhibition [IC_{50} (μg mL^{-1})]
1	0.10
2	61
3	0.033
4	0.11

[a]Jack bean α-mannosidase and *p*-nitrophenyl α-D-mannopyranoside (20 mmol) in acetate buffer (100 mmol) at pH 4.5.

Next, mannostatin B (**3**) and its diastereisomer **4** with respect to configuration of the sulfur function were synthesized from **10**. Thus, oxidation of **10** with sodium metaperiodate was carried out in methanol for 5 h at 0 °C. The crude mixture of the sulfoxides formed were hydrolyzed with 1 N hydrochloric acid, followed by conventional acetylation, giving the respective tetra-*N*,*O*-acetyl derivatives **3a** (35%) and **4a** (39%) of mannostatin B and its diastereoisomer. Compound **3a** was fully identified with an authentic sample[14] on the basis of ^{1}H NMR spectral data. The proposed structure of **4a** containing the (*S*)-sulfinyl group was supported by the ^{1}H NMR spectrum which accorded well with the consideration derived from the stereo-modeling of the molecules. Thus, in the spectra of **3a** and **4a**, the chemical shifts of the signals due to H-1 and H-4 were largely influenced by the proximity of the sulfinyl groups, the former being deshielded and the latter shielded in **4a** reversely in contrast to the corresponding signals of **3a**. Hydrolysis of **3a** and **4a** with aqueous 10% sodium hydroxide at 100 °C for 20 min afforded, after purification over resin column, mannostatin B (**3**) (90%) and its diastereoisomer **4** (89%) as a slight yellow syrup. Their

inhibitory activities[17] are listed in Table 1. Compound **4** was also shown to be a strong α-mannosidase inhibitor. These results revealed that the stereochemistry of the 4-aminocyclopentane-1,2,3-triol structure[18] would play a major role in interaction with the active site of the enzymes.

Experimental

General procedure

Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. Optical rotations were measured with Jasco DIP-370 polarimeter. Silica gel column chromatography was performed on silica gel 300 mesh (Wakogel C-300, Wako Junyaku Kogyo Co., Osaka), and analytical TLC was performed on silica gel 60 F-254 (E. Merck, Darmstadt). ^{1}H NMR spectra were recorded on a Jeol GSX-270 (270 MHz) instrument. Chemical shifts are expressed as δ values with reference to Me_4Si. IR spectra were recorded on a Jasco IR-810 or Hitachi FTS-65 spectrometer. Solutions were dried over anhydrous Na_2SO_4 and concentrated at < 45 °C under diminished pressure.

2,3-O-Cyclohexylidene derivative 5 of (1,2,3,4,5/0)-5-acetamidocyclopentane-1,2,3,4-tetraol

A mixture of the 2,3-*O*-cyclohexylidene derivative[11] (1.87 g, 4.38 mmol) of (1,4,2,3,5/0)-5-acetamido-1,4-di-*O*-mesylcyclopentane-1,2,3,4-tetraol, anhydrous sodium acetate (1.79 g, 22 mmol), and aqueous 80% 2-methoxyethanol (50 mL) was heated for 3 h at reflux temperature. The mixture was concentrated and the residue was again coevaporated with toluene. Chromatography of the residue with 1:1 acetone:chloroform as eluent gave **5** (1.15 g, 97%) as needles; mp 138–140 °C (from toluene). ^{1}H NMR ($CDCl_3$) δ 1.55–1.75 (10H, *m*, C_6H_{10}), 2.08 (3H, *s*, NAc), 2.56 (2H, *br s*, 2 OH), 4.11 (2H, *br s*, H-1,4), 4.19 (1H, *ddd*, $J_{15} = J_{45}$ = 4.4 Hz, J_{5NH} = 8.8 Hz, H-5), 4.58 (2H, *m*, H-2,3), 6.40 (1H, *d*, NH). Anal. calcd for $C_{17}H_{21}NO_9$: C, 57.55; H, 7.80; N, 5.16%; found: C, 57.70; H, 7.55; N, 5.05%.

2,3-O-Cyclohexylidene derivatives 6 and 7 of respective (1,2,3,4,5/0)-5-acetamido-1(4)-O-mesyl- and 1,4-di-O-mesylcyclopentane-1,2,3,4-tetraols

To a solution of **5** (168 mg, 0.62 mmol) in anhydrous pyridine (4 mL) was added mesyl chloride (53 mL, 0.81 mmol) at 0 °C, and it was stirred for 30 min at the same temperature. The mixture was coevaporated with toluene and the residue was chromatographed on a silica gel column with 1:3 acetone:toluene as eluent to give **7** (22 mg, 14.6% based on **5** consumed) and **6** (101 mg, 81.2%), together with **5** (72 mg) unchanged.

Compound **6**, mp 169–175 °C (from toluene). ^{1}H NMR ($CDCl_3$) δ 1.57–1.67 (10H, C_6H_{10}), 3.05 (3H, *s*, OMs), 4.16 (1H, *br dd*, J_{34} = 4.5, J_{45} = 5.0 Hz, H-4), 4.40 (1H, *dt*, J_{15} = 5.0, J_{5NH} = 8.8 Hz, H-5), 4.63–4.69 (2 H, *m*, H-2,3), 4.87 (1H, *dd*, H-1), 6.47 (1H, *d*, NH). Anal. calcd for $C_{14}H_{23}NO_7S$: C, 48.13; H, 6.64; N, 4.01%; found: C, 48.41; H, 6.42; N, 3.93%.

Compound **7**, mp 174–176 °C (from toluene). ^{1}H NMR ($CDCl_3$) δ 1.62–1.72 (10H, *m*, C_6H_{10}), 2.06 (3H, *s*, NAc), 3.12 (6H, *s*, 2 OMs), 4.71–4.76 (2H, *m*, H-2,3), 4.80 (1H, *dd*, $J_{15} = J_{45}$ = 5.1, J_{5NH} = 9.2 Hz, H-5), 4.90–4.94 (2H, *m*, H-1,4), 6.45 (1H, *d*, NH). Anal. calcd for $C_{15}H_{28}NO_9S_2$: C, 42.14; H, 5.90; N, 3.28%; found: C, 41.80; H, 5.66; N, 3.22%.

1,2-O-Cyclohexylidene derivative 8 of DL-(1,2,3,4/5)-4-acetamido-5-acetylthiocyclopentane-1,2,3-triol

To a solution of **6** (440 mg, 1.35 mmol) in DMF (20 mL) was added dropwise a solution of potassium thioacetate (1.43 g, 12.5 mmol) in DMF (10 mL) at 120 °C, and then it was stirred for 40 min at the same temperature. The mixture was coevaporated with toluene and the residue was chromatographed on silica gel with 1:6 acetone:chloroform as eluent to give **8** (114 mg) as a yellow syrup, together with **6** (345 mg) recovered. IR(neat): 3440, 2940, 1740, 1675, 1515, 1370, 1235, 1185, 1120, 945, 750, 525 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.57–1.75 (10H, *m*, C_6H_{10}), 1.98 (3H, *s*, NAc), 2.36 (3H, *s*, SAc), 2.82 (1H, *br s*, OH), 3.83 (1H, *dd*, J_{15} = 5.3, J_{45} = 10.8 Hz, H-5), 4.07 (1H, t, $J_{23} = J_{34}$ =4.2 Hz, H-3), 4.40–4.65 (3H, *m*, H-1,2,4), 6.17 (1H, *d*, J_{4NH} = 8.8 Hz, N-H).

Without further purification, compound **8** was used for the next reaction.

1,2-O-Cyclohexylidene derivative 9 of DL-(1,2,3,4/5)-4-acetamido-5-methylthiocyclopentane-1,2,3-triol

Crude **8** was dissolved in methanol (3 mL) and the solution was treated first with methanolic 1 M sodium methoxide (0.52 mL) for 15 min at 0 °C and then with methyl iodide (0.08 mL, 1.1 mmol) for 1.5 h at 0 °C. The mixture was evaporated and the residue was chromatographed on a silica gel column with 1:3 acetone:toluene as eluent to give **9** (75 mg, 92%) as a colorless syrup. IR (neat): 3440, 3320, 2940, 2860, 1660, 1540, 1450, 1380, 1280, 1110, 1040, 950, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.52–1.63 (10H, *m*, C_6H_{10}), 2.03 (3H, *s*, NAc), 2.19 (3H, *s*, OMe), 2.71 (1H, *d*, J_{3OH} = 3.4 Hz, OH), 3.75 (1H, *dd*, J_{15} = 4.2, J_{45} = 8.1 Hz, H-5), 4.13 (1H, *dd*, J_{23} = 4.2, J_{34} = 7.1 Hz, H-3), 4.35 (1H, *ddd*, J_{4NH} = 8.8 Hz, H-4), 4.51 (1H, *dd*, J_{12} = 7.1 Hz, H-1), 4.57 (1H, *dd*, H-2), 6.07 (1H, *d*, NH). Anal. calcd for $C_{14}H_{23}NO_4S$: C, 55.79; H, 7.69; N, 4.65%; found: C, 55.66; H, 7.61; N, 4.66%.

1,2-O-Cyclohexylidene derivatives 10 and 11 of the respective 1D- and 1L-(1,2,3,4/5)-4-acetamido-3-O-[(S)-O-acetylmandelyl]-5-methylthiocyclopentane-1,2,3-triols

To a mixture of **9** (53 mg, 0.18 mmol), 4-dimethylaminopyridine (4 mg, 0.04 mmol), (*S*)-*O*-acetylmandelic acid (41 mg, 0.21 mmol), and dichloromethane (2 mL) was added a solution of DCC (41 mg, 0.21 mmol) in dichloromethane (1 mL), and it was

stirred for 30 min at –15 °C. After addition of ethyl acetate (3 mL), an insoluble material was removed by filtration and the filtrate was evaporated. Chromatography of the residue on silica gel with 1:6 acetone:toluene as eluent gave **10** (35 mg) and **11** (45 mg).

Compound **10**, R_f 0.42 (1:3 acetone:toluene). ^{1}H NMR ($CDCl_3$) δ 1.35–1.84 (13H, *m*, C_6H_{10}, SMe), 2.20 (3H, *s*, OAc), 2.22 (3H, *s*, OAc), 2.98 (1H, *dd*, J_{15} = 2.7, J_{45} = 6.6 Hz, H-5), 4.41–4.49 (2H, *m*, H-1,4), 4.72 (1H, *dd*, J_{12} = 6.4, J_{23} = 5.0 Hz, H-2), 5.25 (1H, *t*, J_{34} = 5.0 Hz, H-3), 5.71 (1H, *d*, J_{4NH} = 8.8 Hz, NH), 6.04 (1H, *s*, CH), 7.36–7.56 (5H, *m*, Bz).

Compound **11**, R_f 0.36. ^{1}H NMR ($CDCl_3$) δ 1.20–1.58 (10H, *m*, C_6H_{10}), 1.92 (3H, *s*, SMe), 2.20 (3H, *s*, OAc), 2.22 (3H, *s*, Ac), 3.14 (1H, *dd*, J_{15} = 2.6, J_{45} = 5.7 Hz, H-5), 4.46 (1H, *dd*, J_{12} = 6.1 Hz, H-1), 4.54 (1H, *ddd*, J_{34} = 5.3, J_{4NH} = 8.8 Hz, H-4), 4.71 (1H, *dd*, J_{23} = 5.3 Hz, H-2), 5.26 (1H, *t*, H-3), 5.93 (1H, *s*, CH), 6.24 (1H, *d*, NH), 7.38–7.53 (5H, *m*, Bz).

*1D-(1,2,3,4/5)-5-Acetamido-1,2,3-tri-*O*-acetyl-5-methylthiocyclopentane-1,2,3-triol (tetra-*N,O*-acetylmannostatin A) (**1a**)*

A mixture of **10** (28 mg) and 1 N hydrochloric acid (1 mL) was stirred for 20 min at 100 °C and then evaporated. The residue was treated with acetic anhydride and pyridine for 1 h at room temperature and then evaporated. Chromatography on silica gel with acetone:toluene gave **1a** (10 mg, 13% based on **8**) as needles; mp 119–121 °C (from toluene), $[\alpha]_D^{28}$ +7.4° (*c* 0.45, $CHCl_3$) [Ref.[8] $[\alpha]_D$ +8.5° (*c* 0.9, $CHCl_3$)]. ^{1}H ($CDCl_3$) δ 2.05, 2.06, 2.08, 2.12, 2.17 (each 3H, 5 *s*, NAc, 3 OAc, SMe), 3.10 (1H, *dd*, J_{15} = 6.4, J_{45} = 8.6 Hz, H-5), 4.39 (1H, *ddd*, J_{34} = 5.3, J_{4NH} = 8.9 Hz, H-4), 5.17 (1 H, *t*, J_{12} = 6.2 Hz, H-1), 5.34 (1H, *dd*, J_{23} = 4.5 Hz, H-3), 5.40 (1H, *dd*, H-2), 5.81 (1H, *d*, NH). The ^{1}H NMR spectrum was superimposable on that of an authentic sample.[14] Anal. calcd for $C_{14}H_{21}NO_7S$: C, 48.40; H, 6.09; N, 4.03%; found: C, 48.12; H, 5.81; N, 3.96%.

*1L-(1,2,3,4/5)-4-Acetamido-1,2,3-tri-*O*-acetyl-5-methylthiocyclopentane-1,2,3-triol (**2a**)*

Compound **11** (46.5 mg) was similarly hydrolyzed and acetylated to give **2a** (25 mg, 19.5% based on **8**) as needles, mp 120–121 °C (from toluene); $[a]_D^{26}$ –7.4° (*c* 1.0, $CHCl_3$). The ^{1}H NMR spectrum was superimposable on that of **1a**. Anal. calcd for $C_{14}H_{21}NO_7S$: C, 48.40; H, 6.09; N, 4.03%; found: C, 48.02; H, 6.24; N, 4.12%.

*1D-(1,2,3,4/5)-4-Amino-5-methylthiocyclopentane-1,2,3-triol (mannostatin A) (**1**)*

Crude **10** (35 mg) was hydrolyzed with 1 N hydrochloride acid and the hydrochloride obtained was purified by chromatography on Amberlite IR-120 (H^+) resin with aqueous N ammonia to give **1** (3 mg, 10% based on **9**) as a syrup, R_f 0.39 (3:1:1 *n*-butanol:acetic acid:water). This compound was directly subjected to biological assay.

*1L-(1,2,3,4/5)-4-Amino-5-methylthiocyclopentane-1,2,3-triol (**2**)*

Crude **11** (45 mg) was similarly converted into the free base **2** (7 mg, 23% based on **9**) as a syrup, R_f 0.39 (3:1:1 *n*-butanol:acetic acid:water). This compound was directly subjected to biological assay.

*1D-(1,2,3,4/5)-4-Acetamido-1,2,3-tri-*O*-acetyl-5-[(R)-(**3a**) and (S)-methylsulfinyl]cyclopentane-1,2,3-triol (**4a**) (tetra-*N,O*-acetylmannostatin B and its diastereoisomer)*

To a solution of crude **9** (95 mg) in methanol (0.5 mL) was added an aqueous solution of sodium metaperiodate (42 mg in 1.5 mL), and the mixture was stirred for 5 h at 0 °C. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with aqueous sodium sulfite, dried, and evaporated. The residue was chromatographed on a silica gel with 1:1 acetone:toluene to give a crystalline sulfoxide derivative. Without further purification, it was treated with a mixture of aqueous 80% acetic acid (2 mL) containing 1 N hydrochloric acid (1.5 mL) for 2.5 h at 120 °C. The mixture was coevaporated with ethanol and the residue was chromatographed on silica gel with acetone:toluene to give crystalline **3a** (21 mg, 35% on the basis of **9**) and **4a** (24 mg, 39%).

Compound **3a**, R_f 0.32 (4:1 acetone:toluene); mp 175–178 °C (dec.) (prisms, from ethyl acetate); $[\alpha]_D^{22}$ +11.2° (*c* 0.55, $CHCl_3$). IR (KBr disc) 3280, 2700, 1740, 1660, 1540, 1375, 1250, 1220, 1040, 975, 755, 500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05, 2.07, 2.10, 2.14 (each 3H, 4 *s*, NAc, 3 OAc), 2.72 (3H, *s*, Me), 3.03 (1H, *t*, J_{15} = J_{45} = 2.9 Hz, H-5), 5.15–5.25 (2H, *m*, H-3,4), 5.44–5.51 (2H, *m*, H-1,2), 6.05 (1H, *d*, J_{4NH} = 7.7 Hz, NH). The spectrum was superimposable on that of an authentic sample.[14] Anal. calcd for $C_{14}H_{21}NO_8S$: C, 46.27; H, 5.83; N, 3.85%; found: C, 46.48; H, 5.74; N, 3.78%.

Compound **4a**, R_f 0.29 (4:1 acetone:toluene); mp 188–192 °C (needles, from ethyl acetate); $[\alpha]_D^{22}$ +16.8° (*c* 0.60, $CHCl_3$). IR (KBr disc) 3475, 3260, 2930, 1750, 1670, 1540, 1530, 1430, 1375, 1255, 1220, 1080, 1040, 1030, 955, 800, 600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90, 1.99, 2.04, 2.05 (each 3H, 4 *s*, NAc, 3 OAc), 2.53 (3H, *s*, Me), 3.08 (1H, *t*, J_{15} = J_{45} = 5.7 Hz, H-5), 4.67 (1H, *ddd*, J_{34} = 6.4 Hz, H-4), 5.18 (1H, *dd*, J_{23} = 3.9 Hz, H-3), 5.41 (1H, dd, J_{12} = 5.5 Hz, H-2), 5.72 (1H, *t*, H-1), 5.97 (1H, *d*, J_{4NH} = 7.3, NH). Anal. found: C, 46.13; H, 5.81; N, 3.82%.

*1D-(1,2,3,4/5)-4-Amino-5-[(R)-methylsulfinyl]cyclopentane-1,2,3-triol (mannostatin B) (**3**)*

A mixture of **3a** (11.2 mg) was treated with aqueous 10% sodium hydroxide (0.5 mL) for 20 min at 110 °C, and then coevaporated with ethanol. The residue was chromatographed on Amberlite IR-120 (H^+) resin with aqueous 1 N ammonia to give **3** (5 mg, 90%) as a slight yellow syrup: R_f 0.26 (3:1:1 *n*-butanol:acetic acid:water). This compound was directly subjected to biological assay.

1D-(1,2,3,4/5)-4-Amino-5-[(S)-methylsulfinyl]cyclopentane-1,2,3-triol (4) (mannostatin B diastereoisomer)

Compound **4a** (12 mg) was similarly converted into **4** (5.2 mg, 89%) as a slight yellow syrup: R_f 0.23 (3:1:1 *n*-butanol:acetic acid:water). This compound was directly subjected to biological assay.

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13. We first reported[5] the synthesis of racemic mannostatin A from compound **9**.

14. The ^{1}H NMR spectra of authentic samples have been provided by Professor T. Aoyagi (Tokyo College of Pharmacy, Hachioji) and Dr H. Morishima (Banyu Pharmaceutical Co. Ltd, Tsukuba).

15. The specific rotations of **1** and **1a** were not described in the References.[1,2]

16. The conditions used for hydrolysis of **10** and **11** and subsequent purification with acid resin column were not fully optimized here.

17. Biological assay carried out by Dr Y. Fukuda (Meiji Seika Kaisha Ltd, Yokohama).

18. The preliminary results revealed that the mannostatin A isomer DL-(1,2,3,4/5)-3-amino-5-methylthio-1,2,4-cyclopentanetriol derived from the tetra-*N,O*-acetyl derivative[5] was shown to be a very weak inhibitor (IC_{50} 860 μg mL^{-1}) of jack bean α-mannosidase.

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