A Versatile Approach to the Synthesis of (+)-Mannostatin A Analogues

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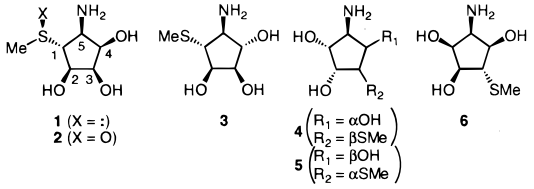
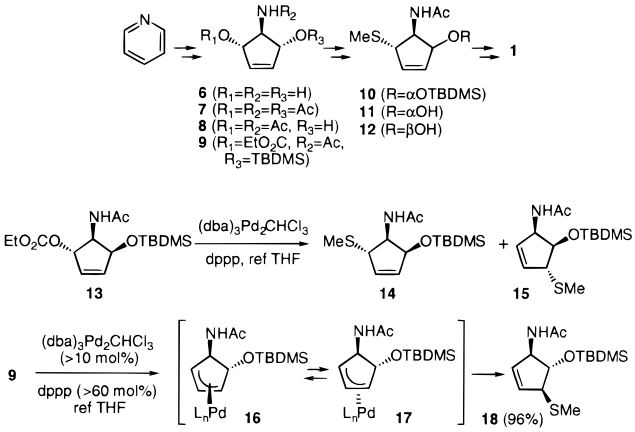
Members of the aminocyclopentitol family of natural products are known to be potent inhibitors of a variety of glycosidases,[1] enzymes that are responsible for post-translational processing of ribosome-synthesized glycopeptides.[2] As a result of this property, these substances play potentially important roles in studies of polysaccharide biosynthesis and in the development of new treatments for viral infections.[3] Mannostatins A (**1**) and B (**2**), recently isolated[4] members of this group, are tight-binding inhibitors of mannosidases. The structural simplicity of **1** and **2** along with their interesting biological properties has stimulated several recent studies focusing on the synthesis of the natural products and their N-substituted stereoisomeric and regioisomeric analogues.[5]



Earlier, we described the results of investigations which demonstrate how a pyridinium salt photoelectrocyclization/aziridine ring cleavage sequence can be used to quickly assemble functionally and stereochemically rich aminocylopentenes.[6] This chemistry is the basis for our recently disclosed[7] synthesis of (+)-mannostatin A

Scheme 1



which utilizes (1) transformation of pyridine to the aminodiol **6**, (2) enzymatic desymmetrization (**7** → **8**), (3) Pd°-promoted thioether formation (**9** → **10**), and (4) hydroxyl inversion (**11** → **12**) (Scheme 1). An important aspect of this strategy is its versatility, which makes it potentially applicable to the synthesis of a number of regioisomeric and stereoisomeric aminocyclopentitols. In this publication, we describe how this chemistry can be applied to the preparation of the previously unreported mannostatin analogues, (+)-4-epimannostatin (**3**) and (+)-mannostatin A regioisomers **4**−**6**.

Regiochemical diversity can be introduced into the mannostatin A synthetic sequence by the choice of substrate and conditions used for the Pd°-catalyzed methylthiolation process. We have reported that unlike carbonate **9**, reaction of the *cis*-*trans*-isomer **13** with TMSSMe[8] in the presence of $(dba)_3Pd_2CHCl_3$ and dppp yields a regioisomeric mixture of thioethers **14** and **15** (2:1) as a consequence of an expected lack of steric control in nucleophilic ring opening of the Pd-π-allyl intermediate.[9] Also, we have observed that the regiochemical course of Trost[8] methylthiolation of **9** can be altered by changing the quantities of catalyst and ligand used. As originally reported, treatment of **9** with TMSSMe (5 equiv), $(dba)_3Pd_2CHCl_3$ (5 mol %), and dppp (30 mol %) in refluxing THF leads to exclusive formation of the *trans*,*trans*-adduct **10** (91% at 60% conversion). In an attempt to drive this process to completion, higher mole ratios of the Pd catalyst (> 10 mol %) and dppp (> 60 mol %) were used. Under these conditions, **9** is converted to the regioisomeric thioether **18** exclusively (86% yield at 94% conversion). This regiochemical reversal is likely due to the intervention of a previously described[10] Pd°-dependent isomerization of the initially formed π-allyl intermediate (**16** → **17**) which competes with addition of $TMSSCH_3$.

The amidocyclopentenyl thioethers **10**, **15**, and **18** are convenient starting points for syntheses of the mannostatin analogues **3**−**6**. For example, contrary to what

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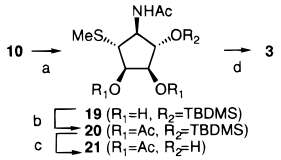
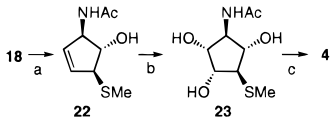
Scheme 2[a]



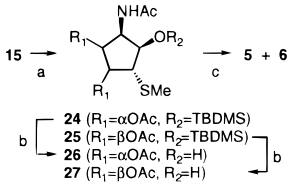
[a] (a) OsO_4, pyr (81%); (b) Ac_2O, pyr, DMAP (95%); (c) TBAF, THF (91%); (d) 6 N HCl (82%).

Scheme 3[a]



[a] (a) HF (89%); (b) OsO_4, TMEDA, CH_2Cl_2 (71%); (c) 6 N HCl (82%).

Scheme 4[a]



[a] (a) OsO_4, pyr; Ac_2O, pyr (82%, 1:1, silica gel); HF (88%, 87%); (c) 6 N HCl (100%).

seemed to be reliable precedents,[5a,11] OsO_4 dihydroxylation of **10** occurs exclusively from the β-face to produce diol **19**, whose stereochemistry is assigned based on X-ray crystallographic analysis of the diacetate derivative **20** (Scheme 2). Thus, in contrast to closely related systems,[11] dihydroxylation of **10** occurs anti (rather than syn) to the bulky methylthio and siloxy substituents at the allylic centers. Desilylation of **20** (→ **21**) followed by acid hydrolysis furnishes the HCl salt of (+)-4-epimannostatin A (**3**, $[\alpha]^{25}_D$ +26° (*c* 1.4, CH_3OH)).

A combination of effects control the stereochemistry of OsO_4 dihydroxylation of the alcohol **22**, derived by TBAF treatment of silyl ether **18**. Accordingly, under the hydroxyl-directing conditions suggested by Donohoe,[12] osmylation of **22** yields the triol **23** (ca. 6:1 preference as judged by ^{13}C NMR analysis, see Supporting Information) (Scheme 3). In this case, both hydroxyl guidance and steric effects direct glycol formation from the α-face of **22**. Subsequent amide hydrolysis in **23** affords the HCl salt of mannostatin regioisomer **4** ($[\alpha]^{25}_D$ +10° (*c* 1.0, MeOH).

The major regioisomer **14** obtained by methylthiolation of the allylic carbonate **13** serves as an intermediate in one of the approaches we have reported[7] for synthesis of mannostatin A. The minor thioether **15** of this process can be used to prepare the mannostatin analogues **5** and **6**. Accordingly, unselective dihydroxylation of **15** followed by acetylation yields a 1:1 mixture of separable diacetates **24** and **25** (stereochemistry assigned by NOE) (Scheme 4). Silyl ether deprotection (→ **26** and **27**, respectively) followed by amide and ester hydrolysis affords the respective HCl salts of **5** ($[\alpha]^{25}_D$ +20° (*c* 1.0, MeOH)) and **6** ($[\alpha]^{25}_D$ +7° (*c* 1.0, MeOH)).

Table 1. K_I Values of Analogues 3−6 in the Jack Bean α-Mannosidase-Catalyzed Hydrolysis of *p*-Nitrophenyl-α-D-mannopyranoside at pH 8.0 (25 °C)

analog	K_I	analog	K_I
1	0.37 ± 0.06 μM	**5**	0.10 ± 0.01 mM
3	0.7 ± 0.3 mM	**6**	0.14 ± 0.01 mM
4[15]	17 ± 3 μM		

Although having potentially significant biomedical properties, only a few analogues of mannostatin have been prepared and evaluated as mannosidase inhibitors thus far.[5b,13] The synthetic methods described above, arising from a pyridinium salt photochemistry platform, have allowed us to access a number of previously unreported members this amniocyclopentitol family. A preliminary evaluation of the analogues **3**−**6** as inhibitors of jack bean α-mannosidase[14] (Table 1) has shown that one of these substances, **4**,[15] is a modestly strong inhibitor of this enzyme (K_I = 17 μM vs 0.4 μM for synthetic (+)-mannostatin A).

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions, and chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.24 ppm for ^1H and δ 77.0 ppm for ^{13}C). ^{13}C NMR resonance assignments were aided by the use of the DEPT-135 technique to determine numbers of attached hydrogens. IR spectral vibrational frequencies are expressed in cm^{-1}. Optical rotations [α] were measured at 589 nm (sodium D line). Column chromatography was performed with either type 60 (230−400 mesh) silica gel, Alcoa type F-20 alumina (neutral, 80−200 mesh), or Fluorisil (100−200 mesh). Preparative TLC was performed on 20 × 20 cm plates coated with type 60 GF-254 silica gel. Mass spectra were recorded by using electron impact ionization unless specified as chemical ionization by CI. All reactions were run under a dry N_2 atmosphere unless otherwise noted. Organic extracts obtained following workup of reaction mixtures were dried over anhydrous Na_2SO_4 or $MgSO_4$. All compounds prepared in this study were oils unless otherwise noted and were judged to be >95% pure by use of NMR spectroscopic methods unless otherwise noted.

(1*R*,2*R*,3*S*,4*S*,5*S*)-1-Methylthio-4-*tert*-butyldimethylsilyloxy-5-acetamidocyclopentane-2,3-diol (19). A solution of silyl ether **10** (0.30 g, 1.0 mmol) in 9 mL of pyridine containing osmium tetraoxide (0.40 g, 1.6 mmol) was stirred at 25 °C for 48 h. The solvent was removed in vacuo, giving a residue which dissolved in THF (30 mL), water (1.5 mL) and sodium metabisulfite (5.0 g). The mixture was stirred at 65 °C for 5 h and filtered. The filtrate was dried and concentrated in vacuo to give a residue which was subjected to column chromotography (silica gel, 1:1 acetone:hexanes) yielding 0.30 g (89%) of **19**: $[\alpha]^{25}_D$ +16.0° (*c* 1.4, $CHCl_3$). ^1H NMR 6.56 (d, J = 8.5 Hz, 1H, NH), 4.02−3.97 (m, 2H, H_1 and H_2), 3.82 (t, J = 3.6 Hz, 1H, H_3), 3.58 (dt, J = 8.5, 4.3 Hz, 1H, H_4), 3.48 (brs, 2H, OH), 2.93 (t, J = 7.1 Hz, 1H, H_5), 2.12 (s, 3H, SCH_3), 1.98 (s, 3H, $COCH_3$), 0.84 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR 170.4 (C=O), 78.0, 77.5, 75.6 (C_1, C_2, and C_3), 61.9, 53.1 (C_4 and C_5), 25.6 ($C(CH_3)_3$), 23.3 ($COCH_3$), 17.9 ($C(CH_3)_3$), 13.6 (SCH_3), −4.7, −4.9 ($Si(CH_3)_2$); IR (neat) 3290, 2954, 2916, 1652, 1558, 1472, 1253, 1092; MS

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(15) It should be noted that, despite repeated purification attempts, **4** is obtained in only ca. 85% purity (see Supporting Information). The likely contaminant in this sample is the 1*S*,2*S*-diastereomer of **4**.

m/*z* (rel intensity) 335 (0.4), 278 (100), 260 (47); HRMS calcd *m*/*z* for $C_{14}H_{29}O_4NSiS$ 335.1587, found 335.1560.

(1*R*,2*R*,3*S*,4*S*,5*S*)-1-Methylthio-2,3-diacetoxy-4-*tert*-butyldimethylsilyloxy-5-acetamidocyclopentane (20). A solution of diol **19** (0.28 g, 0.84 mmol), 4-DMAP (30 mg, 0.24 mmol), and acetic anhydride (0.55 mL, 5.82 mmol) in 6 mL of pyridine was stirred at 25 °C for 12 h, quenched with water, and extracted with $CHCl_3$. The organic extracts were dried and concentrated in vacuo to give a residue which was subjected to column chromotography (silica gel, 3:1 hexanes:acetone) to afford the diacetate **20** (0.33 g, 95%): $[\alpha]^{25}_D$ +15.5° (c 1.0, $CHCl_3$); ^{1}H NMR 5.68 (d, J = 8.6 Hz, 1H, NH), 5.24 (t, J = 5.6 Hz, 1H, H_1), 5.01 (t, J = 5.3 Hz, 1H, H_2), 4.17 (t, J = 5.6 Hz, 1H, H_3), 3.83 (m, 1H, H_4), 3.02 (dd, J = 8.3, 6.6 Hz, 1H, H_5), 2.10 (s, 3H, SCH_3), 2.04 (s, 6H, $COCH_3$), 1.99 (s, 3H, $NCOCH_3$), 0.84 (s, 9H, $C(CH_3)_3$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR 169.6, 169.5, 169.4 (C═O), 77.5, 76.0, 72.9 (C_1, C_2, and C_3), 58.5, 50.4 (C_4 and C_5), 25.5 ($C(CH_3)_3$), 23.4 ($NCOCH_3$), 20.7, 20.6 ($OCOCH_3$), 17.8 ($C(CH_3)_3$), 13.0 (SCH_3), −4.9 ($Si(CH_3)_2$); IR (neat) 2924, 2852 1751, 1655, 1246, 1088; CIMS *m*/*z* (rel intensity) 420 (M + 1, 6), 362 (100); HRMS calcd *m*/*z* for $C_{18}H_{34}O_6NSiS$ 420.1876 (M + 1), found 420.1877.

(1*R*,2*R*,3*R*,4*S*,5*S*)-1-Methylthio-2,3-diacetoxy-5-acetamidocyclopentan-4-ol (21). A solution of silyl ether **20** (0.30 g, 0.72 mmol) containing 1 mL of a THF solution of tetrabutylammonium fluoride (1 M) in THF (5 mL) was stirred at 25 °C for 2.5 h, diluted with water, and extracted with $CHCl_3$. The organic extracts were dried and concentrated in vacuo to give a residue which was subjected to column chromatography (silica gel, 1:1 hexanes:acetone) to provide 0,2 g (91%) of monoalcohol **21**: $[\alpha]^{25}_D$ +17.5° (*c* 1.6, $CHCl_3$). ^{1}H NMR 5.96 (brs, 1H, NH), 5.27 (dd, J = 7.9, 6.2 Hz, 1H, H_3), 5.12 (dd, J = 6.0, 4.6 Hz, 1H, H_2), 4.91 (brs, 1H, OH), 4.07 (t, J = 6.2 Hz, 1H, H_1), 3.53 (m, 1H, H_5), 3.78 (dd, J = 10.2, 7.9 Hz, 1H, H_4), 2.09 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.04 (s, 3H, CH_3); ^{13}C NMR 172.8, 169.8, 169.4 (C═O), 79.7, 75.5, 71.4 (C_1, C_2, C_3), 58.3 (C_5), 49.6 (C_4), 23.0, 20.6, 20.6 (OCH_3), 11.9 (SCH_3); IR (neat) 3300, 2906, 2833, 1742, 1653, 1544, 1249, 1052; FABMS *m*/*z* (rel intensity) 306 (M + 1, 100), 246 (40), 242 (39); HRMS calcd *m*/*z* for $C_{12}H_{20}O_6NS$ 306.1011 (M + 1), found 306.1024.

(1*R*,2*R*,3*R*,4*S*,5*S*)-1-Methylthio-5-aminocyclopentane-2,3,4-triol Hydrochloride 3·HCl). A stirred solution of monoalcohol **21** (0.19 g, 0.62 mmol) in aqueous HCl (6 M, 4 mL) solution was heated at 100 °C for 12 h. The solvent was removed in vacuo and remaining oil was washed with ether and $CHCl_3$. The residue was dried in vacuo to afford (+)-**3**·HCl (0.11 g, 82%): $[\alpha]^{25}_D$ +25.7° (*c* 1.4, CH_3OH). ^{1}H NMR (D_2O) 3.97 (quintet, J = 5.8 Hz, 2H, H_1 and H_3), 3.85 (t, J = 5.6 Hz, 1H, H_2), 3.11 (dd, J = 8.8, 6.8 Hz, 1H, H_4), 2.85 (dd, J = 8.8, 6.4 Hz, 1H, H_5), 2.05 (s, 3H, SCH_3); ^{13}C NMR (D_2O, $CDCl_3$ external reference) 79.3, 77.3, 75.2 (C_1, C_2, and C_3), 59.5 (C_4), 52.5 (C_5), 14.3 (SCH_3); IR (neat) 3310, 2895, 2833, 1508, 1124, 1062; FABMS *m*/*z* (rel intensity) 180 (M + 1, 100); HRMS calcd *m*/*z* for $C_6H_{14}O_3NS$ 180.0694 (M + 1), found 180.0687.

(3*S*,4*S*,5*R*)-3-Methylthio-4-*tert*-butyldimethylsilyloxy-5-acetamidocyclopent-1-ene (18). A solution of allyl carbonate **9** (0.252 g, 0.73 mmol) and methylthiotrimethylsilane (0.516 mL, 3.65 mmol) in 8 mL of dry THF under N_2 was prepared. In a separate flask, tris(dibenzylideneacetone)dipalladium(0)−chloroform adduct ($(dba)_3Pd_2CHCl_3$) (0.076 g, 0.072 mmol) and 1,3-bis(diphenylphosphino)propane (dppp) (0.180 g, 0.44 mmol) were dissolved in 4.0 mL of dry THF under N_2. When the latter solution sustained a yellow color (ca.10 min), half of it was added via syringe to the allyl carbonate solution, and the mixture was stirred at 65 °C for 4 h at which time the other half of Pd solution was added. The mixture was stirred at 65 °C for 20 h and concentrated in vacuo to give a residue which was subjected to column chromatography (silica gel, 2:1 ether:hexanes) to yield 15 mg of recoved **9** and 0.19 g (86%) of **18**: $[\alpha]^{25}_D$ +49.2° (*c* 0.6, $CHCl_3$). ^{1}H NMR 5.85−5.82 (m, 1H, vinyl), 5.72−5.69 (m, 1H, vinyl), 5.62 (d, J = 8.9 Hz, 1H, NH), 4.75−4.70 (m, 1H, H_3), 3.96 (t, J = 2.2 Hz, 1H, H_4), 3.38 (m, 1H, H_5), 2.09 (s, 3H, SCH_3), 1.92 (s, 3H, $COCH_3$), 0.83 (s, 9H, $C(CH_3)_3$), 0.09 (s, 3H, $Si(CH_3)$), 0.08 (s, 3H, $Si(CH_3)$); ^{13}C NMR 169.0 (C═O), 133.2, 131.6 (CH═CH), 83.1 (C_4), 62.4, 57.6 (C_3 and C_5), 25.6 ($C(CH_3)_3$), 23.4 ($COCH_3$), 17.9 ($C(CH_3)_3$), 14.7 (SCH_3), −4.7, −4.9 ($Si(CH_3)_2$); IR (neat) 3064, 1641, 1547, 1128; MS *m*/*z* (rel intensity) 301 (0.6), 254 (48), 244 (90); HRMS calcd *m*/*z* for $C_{14}H_{27}O_2NSSi$ 301.1532, found 301.1555.

(3*S*,4*S*,5*R*)-3-Methylthio-5-acetamidocyclopent-1-en-4-ol (22). A solution of silyl ether **18** (0.30 g, 1.0 mmol) and 0.5 mL of aqueous HF (48%) in CH_3CN (10 mL) was stirred at 25 °C for 3 h, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The organic extracts were dried and concentrated in vacuo to give 0.17 g (89%) of **22**: $[\alpha]^{25}_D$ +23.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR 6.67 (d, J = 6.0 Hz, 1H, NH), 5.80 (dt, J = 5.9, 1.9 Hz, 1H, vinyl), 5.65 (dt, J = 5.9, 1.8 Hz, 1H, vinyl), 5.06 (brs, 1H, OH), 4.62 (m, 1H, H_2), 4.07 (t, J = 4.3 Hz, 1H, H_1), 3.56 (m, 1H, H_5), 2.09 (s, 3H, SCH_3), 2.00 (s, 3H, $COCH_3$); ^{13}C NMR 172.1 (C═O), 134.4, 129.3 (CH═CH), 85.1 (C_1), 64.3, 55.8 (C_2 and C_5), 22.6 ($COCH_3$), 13.6 (SCH_3); IR (neat) 3287, 2916, 1641, 1555; FABMS *m*/*z* (rel intensity) 188 (100), 140 (77); HRMS calcd *m*/*z* for $C_8H_{14}O_2NS$ 188.0745 (M + 1), found 188.0750.

(1*R*,2*R*,3*R*,4*S*,5*R*)-3-Methylthio-5-acetamidocyclopentane-1,2,4-triol (23). A solution of **22** (0.15 g, 0.80 mmol), TMEDA (0.15 mL, 0.99 mmol), and osmium tetraoxide (0.25 g, 0.98 mmol) in CH_2Cl_2 (52 mL) was stirred at −78 °C for 3 h, warmed to 25 °C, and concentrated in vacuo, giving a residue which dissolved in THF (25 mL), water (1.5 mL), and sodium metabisulfite (6.2 g). The mixture was heated at 70 °C for 5 h, filtered, dried, and concentrated in vacuo to give a residue which was subjected to column chromotography (silica gel, 1:1 acetone:hexanes, and then acetone) yielding 0.09 g (50%, ca. 85% purity as judged by ^{13}C NMR analysis, see Supporting Information) **23**: $[\alpha]^{25}_D$ +16.0° (*c* 1.2, CH_3OH). ^{1}H NMR (D_2O) 4.19 (t, J = 4.3 Hz, 1H, H_4), 4.10 (dd, J = 6.3, 4.5 Hz, 1H, H_3), 3.90 (quintet, J = 6.0 Hz, 2H, H_1 and H_2), 2.88 (dd, J = 8.3, 5.9 Hz, 1H, H_5), 2.05 (s, 3H, SCH_3), 1.92 (s, 3H, $COCH_3$); ^{13}C NMR (D_2O, $CDCl_3$ external reference) 167.9 (C═O), 82.4, 73.6, 72.4 (C_1, C_2, and C_4), 59.7, 56.1 (C_3 and C_5), 24.3 ($COCH_3$), 16.8 (SCH_3); IR (neat) 3341, 2885, 1648, 1539; FABMS *m*/*z* (rel intensity) 222 (M + 1, 100), 180 (18); HRMS calcd *m*/*z* for $C_8H_{16}O_4NS$ 222.0800, found 222.0798.

(1*R*,2*R*,3*R*,4*S*,5*R*)-3-Methylthio-5-acetamidocyclopentane-1,2,4-triol Hydrochloride (4·HCl). A solution of triol **23** (0.30 g, 1.4 mmol) and HCl (6 M, 3 mL) was stirred at 100 °C for 12 h and concentrated in vacuo. The residue was washed with ether and $CHCl_3$. and dried in vacuo to afford (+)-**4**·HCl (0.24 g, 82%, ca. 85% purity as judged by ^{13}C NMR analysis, see Supporting Information): $[\alpha]^{25}_D$ +17.6° (*c* 1.0, CH_3OH). ^{1}H NMR (D_2O) 4.28 (dd, J = 7.2, 7.2 Hz, 1H, H_2), 4.20 (t, J = 4.7 Hz, 1H, H_4), 4.05 (dd, J = 9.1, 6.0 Hz, 1H, H_1), 3.42 (t, J = 6.7 Hz, 1H, H_3), 2.89 (q, J = 5.0 Hz, 1H, H_5), 2.08 (s, 3H, SCH_3); ^{13}C NMR (D_2O, $CDCl_3$ external reference) 80.6, 74.1, 70.6 (C_1, C_2, and C_4), 60.1 (C_3), 56.4 (C_5), 16.8 (SCH_3); IR (neat) 3269, 2906, 2833, 1503, 1062; FABMS *m*/*z* (rel intensity) 180 (M + 1, 100); HRMS calcd *m*/*z* for $C_6H_{14}O_3NS$ 180.0694 (M + 1), found 180.0698.

(1*R*,2*R*,3*R*,4*R*,5*R*) and (1*S*,2*S*,3*R*,4*R*,5*R*)-1,2-Diacetoxy-3-methylthio-4-*tert*-butyldimethylsilyloxy-5-acetamidocyclopentane (24 and 25). A solution of silyl ether **15** (0.178 g, 0.59 mmol) and osmium tetraoxide (0.225 g, 0.89 mmol) in pyridine (6.5 mL) was stirred at 25 °C for 24 h and concentrated in vacuo, giving a residue which dissolved in THF (25 mL), water (1.5 mL), and sodium metabisulfite (6.0 g). The mixture was stirred at 65 °C for 5 h and filtered, dried, and concentrated in vacuo to give a residue**.** A solution of the residue, 4-DMAP (17 mg, 0.14 mmol), and acetic anhydride (0.362 mL, 3.84 mmol) in 5 mL of pyridine was stirred at 25 °C for 12 h, quenched with water, and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to give a residue which was subjected to column chromotography (silica gel, 4:1 hexanes:acetone) to afford the **24** (0.106 g, 43% yield) and **25** (0.096 g, 39% yield).

24: $[\alpha]^{25}_D$ −4.6° (*c* 1.7, $CHCl_3$); ^{1}H NMR 5.84 (d, J = 8.7 Hz, 1H, NH), 5.24 (t, J = 6.3 Hz, 1H, H_2), 5.09 (q, J = 4.7 Hz, 1H, H_1), 4.65 (m, 1H, H_5), 4.03 (dd, J = 7.4, 4.9 Hz, 1H, H_4), 2.97 (t, J = 5.0 Hz, 1H, H_3), 2.10 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 0.88 (s, 9H, $C(CH_3)_3$), 0.13 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR 170.8, 170.0, 169.7 (C═O), 75.3, 73.5, 70.1 (C_1, C_2, and C_4), 55.8, 53.2 (C_3 and C_5), 25.7 ($C(CH_3)_3$), 23.4 ($NCOCH_3$), 20.7, 20.7 ($OCOCH_3$), 17.9 ($C(CH_3)_3$), 15.9 (SCH_3), −4.6, −5.0 ($Si(CH_3)_2$); IR (neat) 2926, 2845, 1752, 1639, 1373, 1238; FABMS *m*/*z* (rel intensity) 420 (M + 1, 34), 362 (19); HRMS calcd *m*/*z* for $C_{18}H_{34}O_6NSiS$ 420.1876 (M + 1), found 420.1887.

25: $[\alpha]^{25}_D$ −11.7° (*c* 1.2, $CHCl_3$); ^1H NMR 5.86 (d, *J* = 8.5 Hz, 1H, NH), 5.34 (t, *J* = 4.2 Hz, 1H, H_1), 5.06 (q, *J* = 4.0 Hz, 1H, H_2), 4.43 (m, 1H, H_5), 4.02 (q, *J* = 2.9 Hz, 1H, H_4), 3.02 (dd, *J* = 8.6, 3,9 Hz, 1H, H_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 0.92 (s, 9H, $C(CH_3)_3$), 0.16 (s, 3H, $Si(CH_3)_2$), 0.07 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR 169.7, 169.6, 169.1 (C═O), 74.7, 74.4, 72.8 (C_1, C_2, and C_4), 54.9, 50.4 (C_3 and C_5), 25.8 ($C(CH_3)_3$), 23.4 ($NCOCH_3$), 20.7, 20.7 ($OCOCH_3$), 17.9 ($C(CH_3)_3$), 13.4 (SCH_3), −4.4, −5.2 ($Si(CH_3)_2$); IR (neat) 2924, 2852, 1747, 1648, 1243; FABMS *m*/*z* (rel intensity) 420 (M + 1, 19), 362 (15); HRMS calcd *m*/*z* for $C_{18}H_{34}O_6NSiS$ 420.1876 (M + 1), found 420.1856.

(1*R*,2*R*,3*R*,4*S*,5*R*)-1,2-Diacetoxy-3-methylthio-5-acetamidocyclopentan-4-ol (26). A solution of silyl ether **24** (0.061 g, 0.14 mmol) and 0.1 mL of aqueous HF (48%) in CH_3CN (3 mL) was stirred at 25 °C for 3 h, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to give a residue which was subjected to column chromatogrophy (silica gel, 1:1 hexanes:acetone) to provide 39 mg of **26** (88%) as a clear oil: $[\alpha]^{25}_D$ +0.5° (*c* 0.8, $CHCl_3$). ^1H NMR 6.15 (d, *J* = 6.1 Hz, 1H, NH), 5.47 (t, *J* = 4.5 Hz, 1H, H_3), 5.17 (q, *J* = 4.3 Hz, 1H, H_4), 4.38 (q, *J* = 7.6 Hz, 1H, H_2), 4.24 (t, *J* = 6.5 Hz, 1H, H_1), 3.06 (t, *J* = 4.8 Hz, 1H, H_5), 2.14 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.02 (s, 3H, CH_3); ^{13}C NMR 171.4, 171.0, 169.9 (C═O), 74.9, 73.0, 70.7 (C_1, C_3, C_4), 55.1, 54.4 (C_2, C_5), 29.6 ($NCOCH_3$), 20.7, 20.6 ($COCH_3$), 15.6 (SCH_3); IR (neat) 3362, 2957, 2926, 1752, 1648, 1540, 1238, 1083; FABMS *m*/*z* (rel intensity) 306 (M + 1, 13), 246 (10); HRMS calcd *m*/*z* for $C_{12}H_{20}O_6NS$ 306.1011 (M + 1), found 306.1004.

(1*S*,2*S*,3*R*,4*S*,5*R*)-1,2-Diacetoxy-3-methylthio-5-acetamidocyclopentan-4-ol (27). A solution of silyl ether **25** (0.042 g, 0.10 mmol) and 0.1 mL of aqueous HF (48%) in CH_3CN (3 mL) was stirred at 25 °C for 2.5 h, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to give a residue which was subjected to column chromatogrophy (silica gel, 1:1 hexanes:acetone) to provide 26 mg of **27** (87%) as a clear oil: $[\alpha]^{25}_D$ +1.9° (*c* 1.1, $CHCl_3$). ^1H NMR 6.06 (d, *J* = 7.7 Hz, 1H, NH), 5.40 (t, *J* = 4.3 Hz, 1H, H_4), 5.03 (q, *J* = 3.6 Hz, 1H, H_3), 4.45 (m, 1H, H_2), 4.13 (m, 1H, H_1), 3.11 (q, *J* = 4.5 Hz, 1H, H_5), 2.16 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.02 (s, 3H, CH_3); ^{13}C NMR 170.4, 169.6, 169.5 (C═O), 75.3, 74.3, 72.7 (C_1, C_3, C_4), 54.7, 50.9 (C_2, C_5), 23.1 ($NCOCH_3$), 20.8, 20.6 ($COCH_3$), 14.2 (SCH_3); IR (neat) 3360, 2966, 2926, 1750, 1644, 1542, 1233, 1083; FABMS *m*/*z* (rel intensity) 306 (M + 1, 100), 246 (61); HRMS calcd *m*/*z* for $C_{12}H_{20}O_6NS$ 306.1011 (M + 1), found 306.0999.

(1*R*,2*R*,3*S*,4*R*,5*R*)-3-Methylthio-5-acetamidocyclopentane-1,2,4-triol Hydrochloride (5·HCl). A solution of triol **26** (12 mg, 0.04 mmol) in HCl (6 M, 1 mL) was stirred at 100 °C for 12 h and concentrated in vacuo, giving a residue which was washed with ether and $CHCl_3$ and dried in vacuo to afford (+)-**5**·HCl (9 mg, 100%): $[\alpha]^{25}_D$ +19.5° (*c* 1.1, CH_3OH). ^1H NMR (D_2O) 4.17−4.06 (m, 3 H, H_1, H_2, and H_4), 3.51 (t, *J* = 8.4 Hz, 1H, H_3), 2.99−2.95 (m, 1H, H_5), 2.07 (s, 3H, SCH_3); ^{13}C NMR (D_2O, $CDCl_3$ external reference) 76.6, 74.1, 72.9 (C_1, C_2, and C_4), 58.3, 57.8 (C_4 and C_5), 16.3 (SCH_3); IR (neat) 3331, 2895, 2833, 1503, 1114; FABMS *m*/*z* (rel intensity) 180 (M + 1, 100); HRMS calcd *m*/*z* for $C_6H_{14}O_3NS$ 180.0690 (M + 1), found 180.0681.

(1*S*,2*S*,3*S*,4*R*,5*R*)-3-Methylthio-5-acetamidocyclopentane-1,2,4-triol Hydrochloride (6·HCl). A solution of triol **27** (15 mg, 0.05 mmol) in HCl (6 M, 1 mL) was stirred at 100 °C for 12 h and concentrated in vacuo, giving a residue which was washed with ether and $CHCl_3$ and dried in vacuo to afford (+)-**6**·HCl (10 mg, 100%): $[\alpha]^{25}_D$ +7.2° (*c* 1.0, CH_3OH). ^1H NMR (D_2O) 4.09 (m, 2H, H_1 and H_2), 3.73 (dd, *J* = 9.3, 3.9 Hz, 1H, H_4), 3.60 (m, 1H, H_3), 2.89 (dd, *J* = 9.3, 5.7 Hz, 1H, H_5), 2.06 (s, 3H, SCH_3); ^{13}C NMR (D_2O, $CDCl_3$ external reference) 76.0, 74.7, 72.7 (C_1, C_2, and C_4), 58.2, 54.1 (C_3 and C_5), 15.0 (SCH_3); IR (neat) 3268, 2895, 2833, 1503, 1114, 1057; FABMS *m*/*z* (rel intensity) 180 (M + 1, 100); HRMS calcd *m*/*z* for $C_6H_{14}O_3NS$ 180.0694 (M + 1), found 180.0698.

α-Mannosidase K_I Values. The K_I value for **3**−**6** were measured by using a minor modification of the earlier reported method.[14] Enzymatic activities of jack bean α-mannosidase (Sigma, EC 3.2.1.24) were determined by using 0.1 M NaTRICINE solutions of the substrate, *p*-nitrophenyl-α-D-mannopyranoside (2 mM, 1 mM, 0.667 mM, 0.500 mM, 0.400 mM) at pH 8.0 (25 °C) and fixed concentrations of the inhibitors. Production of *p*-nitrophenolate was monitored by a continuous spectrophotometric assay (410 nm, $\epsilon = 16200\ M^{-1}\ cm^{-1}$).[16] The enzymatic reactions were initiated by adding 25 μg of jack bean α-mannosidase, and the K_I values were calculated by using the FORTRAN program COMPL.[17]

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds prepared in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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