Chemical Modification of the α-Mannosidase Inhibitor Mannostain A: Synthesis of a Potent Inhibitor 1L-(1,2,3,5/4)-5-Amino-4-*O*-methyl-1,2,3,4-cyclopentanetetrol[‡]

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Demethylthio-, *S*-demethyl-, and *S*-ethyl derivatives of the α-mannosidase inhibitor, mannostasin A, were synthesized and evaluated for their inhibition of Jack bean α-mannosidase with the prime objective of elucidating the role of the methylthio group. All methylthio derivatives had significantly lowered inhibitory potentials. However, one mannostatin A analogue with a methoxyl instead of the methylthio group exhibited about twofold enhancement of the activity. The structure and inhibitory activity relationships of mannostatin A and related compounds are discussed in light of our results. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2005)

Introduction

Identification of a potent and specific α-mannosidase inhibitor, mannostatin A[2–10] [**1**, 1D-(1,2,3,4/5)-4-amino-5-methylthio-1,2,3-cyclopentanetriol],[11] has stimulated us to develop new glycosidase inhibitors of the aminocyclopentitol type. These inhibitors are thought to act as transition state mimics of the glycopyranosyl cations that are postulated to be formed during hydrolysis of glycosides.[12,13] It appears rather difficult to correlate clearly the structures of known α-mannosidase inhibitors[14] with the conformational features of the transition state of mannopyranosyl cations. Recently, Winkler and Holan[15,16] proposed two conformational models (flap-up and -down) for mannopyranosyl cations, and suggested that comparison of the structure of mannostatin A to the former is pertinent, having a good overlap of the 1- and 2-hydroxy groups in **1** with the respective 3- and 2-hydroxy groups of the flap-up model (Figure 1).

Identification of the potent and specific inhibition of α-mannosidase by mannostatin A (**1**) has led us to investigate novel glycosidase inhibitors of the 5-amino-1,2,3,4-cyclopentanetetrol type, with elucidation of their structure–inhibitory activity relationships. In a preceding paper, the synthesis and evaluation of the α-mannosidase inhibitory activity of three deoxy derivatives, **2**–**4**, of **1** were described,[17,18] pointing to the clear significance of each hydroxy group (Figure 2). The 3-hydroxy groups of **1** and related compounds were found to be essential, conceivably

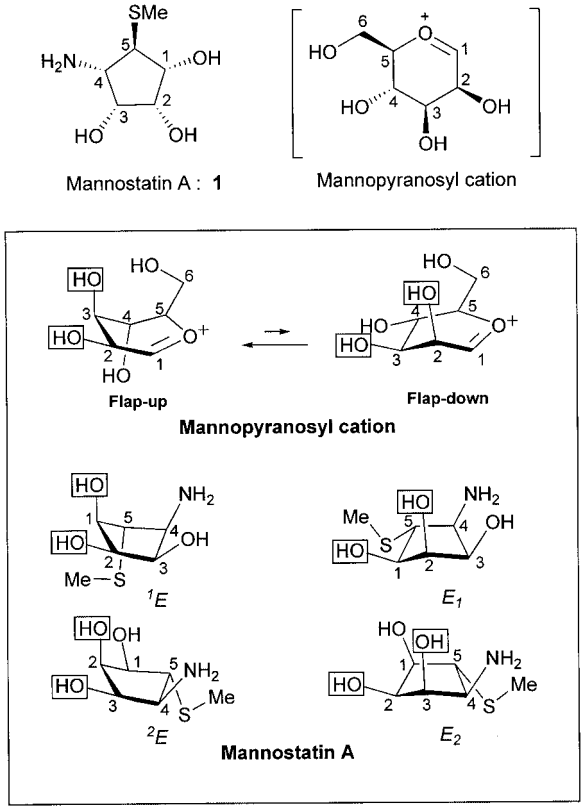

Figure 1. Mannostatin A (**1**) and mannopyranosyl cation. Comparison of preferred conformations (flap-up and -down) of the postulated transition-state mannopyranosyl cation with those of mannostatin A.

corresponding to the 2-hydroxy group of the mannopyranosyl cation. The amino groups located on the β-faces between the ring oxygen atoms and anomeric carbon atoms

[‡] Part of this work was previously reported: Ref.[1]

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of these derivatives were also found to be essential. Thus, among the 24 known stereoisomers[19] of 5-amino-1,2,3,4-cyclopentanetetrol, only **L-5** and **7**, and the corresponding 5-*C*-methyl derivatives,[20] **DL-6** and **8**, were found to possess moderate inhibitory activity against Jack bean α-mannosidase (Table 1). Comparison of the activities of **L-5** and **L-9** suggests the role of the 3-hydroxy groups. All compounds containing *cis*-1,2-dihydroxy groups are likely to be matched with the 2- and 3-hydroxy groups of the mannopyranosyl cation. This consideration is in line with the findings that only mannostatin A isomer[21] **D-10** and the 2,3-diepimer[22] are moderate α-mannosidase inhibitors, and no other isomers[21,23] lacking vicinal *cis*-hydroxy groups show inhibitory activity.

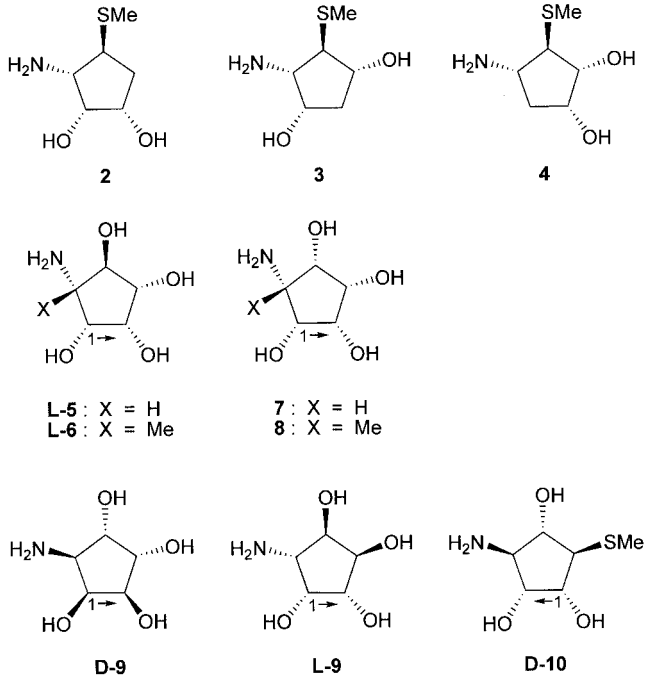


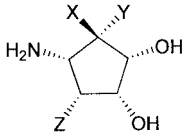
Figure 2. Three deoxy derivatives of mannostatin A and analogous aminocyclopentitol α-mannosidase inhibitors.

Table 1. Inhibitory activity (IC_{50}, μM) against α-mannosidase (Jack beans); NI: no inhibition $< 10^{-3}$ M.

Compound[a]	Inhibitory activity
1	0.35
2	28
3	31
4	NI
D-5	110
L-5	10
L-6	83
7	29
8	56
D-9	NI
L-9	250
D-10	17[b]
11	11
12	36
13	5
14	0.16
15	NI
16	NI

[a] Only inhibitory activity against α-mannosidase is listed. [b] The K_i value was shown.[21]

In this paper we describe the details of chemical modification[1] of the methylthio functionality of mannostatin A (**1**), with the focus on the synthesis and evaluation of the inhibitory activity of demethylthio (**11**), de-*S*-methyl (**12**), and ethylthio (**13**) derivatives (Figure 3). Furthermore, in order to assess the role of the sulfur atom of **1**, attempts were made to replace the methylthio group with a methoxy group, preparing 4-*O*-methyl-, 1,4-di-*O*-methyl-, and epi-4-*O*-methylaminocyclopentanetetrols (**14**, **15** and **16**), which led to finding a very strong α-mannosidase inhibitor, **14**, comparable to the parent **1**.



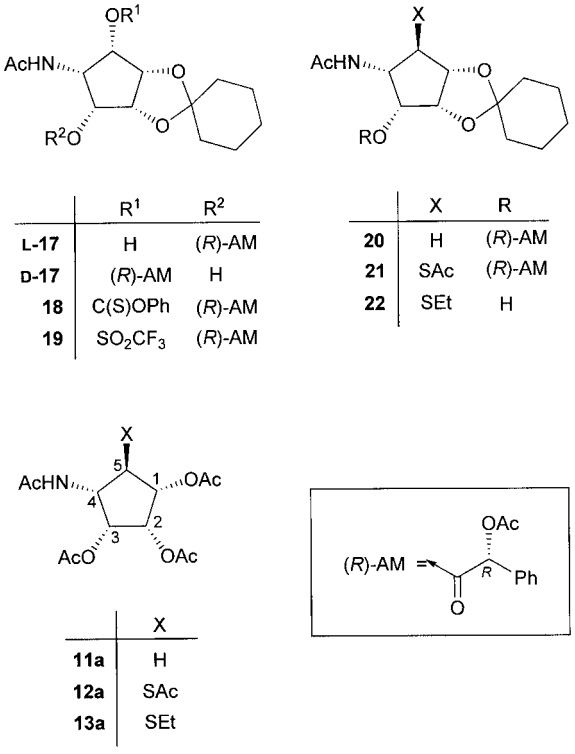
	X	Y	Z
11	H	H	OH
12	SH	H	OH
13	SEt	H	OH
14	OMe	H	OH
15	OMe	H	OMe
16	H	OMe	OH

Figure 3. Chemical modification of the methylthio functionality of mannostatin A.

Results and Discussion

Reaction of the 2,3-*O*-cyclohexylidene derivative[24,25] of (1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol with (2*R*)-*O*-acetylmandelic acid in the presence of DCC and DMAP in CH_2Cl_2 diastereoselectively afforded 1*R*(2*R*)-*O*-acetylmandelate[26] **L-17** (56%) together with the (1*S*) ester **D-17** (8%) (Figure 4). Compound **L-17** was converted into the phenylthiocarbonyl ester **18** (71%) by treatment with DMAP (6 equiv.) and phenyl chlorothionocarbonate (5 equiv.) in CH_3CN at room temperature. Reaction of **18** with tributyltin hydride in the presence of AIBN gave the deoxy derivative **20** (71%). Deprotection of **20** with 2 M HCl at 80 °C, followed by conventional acetylation, gave the tetra-*N*,*O*-acetyl derivative **11a** (ca. 100%), the structure of which was characterized on the basis of its ^1H NMR spectrum.

Compound **L-17** was treated with triflic anhydride in pyridine/CH_2Cl_2 at –15 °C, and the resulting triflate **19** was then subjected to nucleophilic substitution with potassium thioacetate/18-crown-6 ether in dry benzene to give the acetylthio derivative **21** (61%). Acid hydrolysis of **21** followed by acetylation gave the penta-*N*,*O*,*S*-acetyl derivative **12a** (ca. 100%). In addition, **21** was de-*S*-acetylated with methanolic sodium methoxide and the resulting crude thiol was treated with iodoethane to give the ethylthio derivative **22**

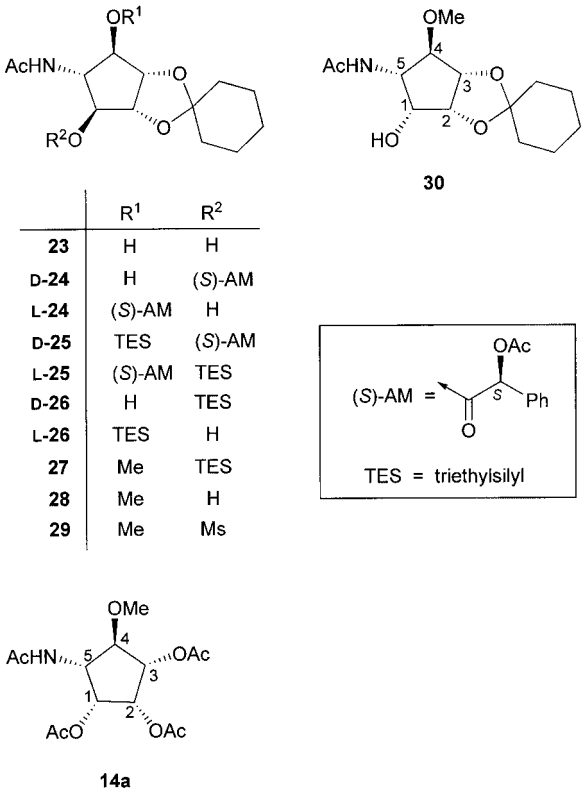


	R^1	R^2
L-17	H	(*R*)-AM
D-17	(*R*)-AM	H
18	C(S)OPh	(*R*)-AM
19	SO_2CF_3	(*R*)-AM

	X	R
20	H	(*R*)-AM
21	SAc	(*R*)-AM
22	SEt	H

	X
11a	H
12a	SAc
13a	SEt

Figure 4. Synthesis of demethylthio, *S*-demethyl, and *S*-ethyl derivatives of mannostatin A.



	R^1	R^2
23	H	H
D-24	H	(*S*)-AM
L-24	(*S*)-AM	H
D-25	TES	(*S*)-AM
L-25	(*S*)-AM	TES
D-26	H	TES
L-26	TES	H
27	Me	TES
28	Me	H
29	Me	Ms

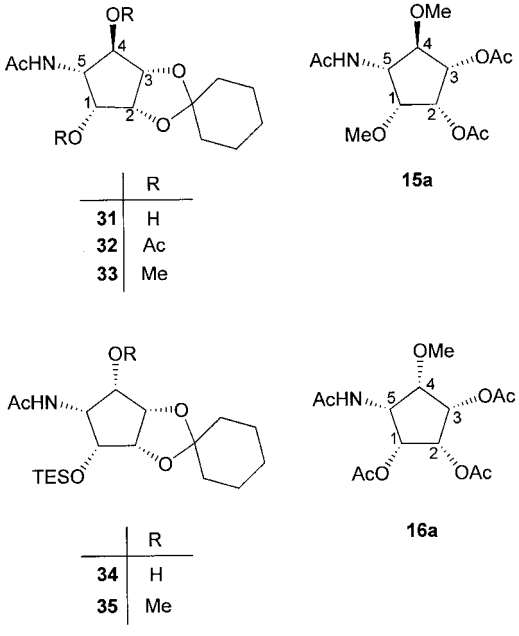
Figure 5. Synthesis of 1L-(1,2,3,5/4)-5-amino-4-*O*-methyl-1,2,3,4-cyclopentanetetrol (**14**).

(ca. 100%), which was purified by conversion into the tetra-*N*,*O*-acetyl derivative **13a** (ca. 100%).

Diastereoselective acylation of the 2,3-*O*-cyclohexylidene derivative[26] of (1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**23**) with (2*S*)-*O*-acetylmandelic acid afforded a mixture (ca. 4:1) of the esters **L-24** and **D-24**, which was directly treated with triethylsilyl triflate in CH_2Cl_2 to give a separable mixture of the triethylsilylates **L-25** (77%) and **D-25** (23%) (Figure 5). Compound **L-25** was de-*O*-acylated under Zemplén conditions to give **26**, which was subsequently treated with iodomethane/Ag_2O in acetonitrile to give the methyl ether **27** (ca. 100%). Desilylation of **27** with tetrabutylammonium fluoride in THF to give **28** (69%), was followed by conventional transformation into the mesylate **29**. Crude mesylate **29** was hydrolyzed by heating in 80% aq. DMF at 110 °C to give, through neighboring-group participation, the 4-epimeric alcohol **30** (76% overall yield). Acid hydrolysis of **30** and successive acetylation gave the tetra-*N*,*O*-acetyl derivative **14a** (53%).

The alcohol **L-26** derived from **D-25** was mesylated and the resulting crude sulfonate was treated with sodium acetate in aqueous DMF to give the 4(1)-epimer **31** (80%) of **23** (Figure 6). The structure of **31** was confirmed by the ^1H NMR spectrum of its di-*O*-acetyl derivative **32**. Compound **31** was then methylated in a conventional manner to give the dimethyl ether **33** (68%), which was converted conventionally into the tri-*N*,*O*-acetyl derivative **15a** (86%).

Compound **D-17** was silylated and deacylated to give **34** (68%), and then methylated to give the methyl ether **35**



	R
31	H
32	Ac
33	Me

	R
34	H
35	Me

Figure 6. Synthesis of the 1-*O*-methyl derivative **15a** and 4-epimer **16a** of **14a**.

(97%). Conventional deprotection of **35** followed by acetylation gave the tetra-*N*,*O*-acetyl derivative **16a** (87%).

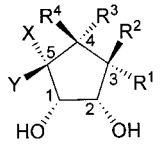
Mannostatin A analogues **11**–**13** were prepared by treatment of the corresponding peracetyl derivatives **11a**–**13a** with 2 M hydrochloric acid at 80 °C, and purified on a col-

umn of Dowex-50 W×2 (H^+) resin with 1% aqueous ammonia as the eluent. The analogues **14**–**16** were also obtained by hydrolysis of **14a**–**16a** with 1 M aqueous $Ba(OH)_2$ at 90 °C, followed by a similar purification. The free bases thus obtained were directly subjected to assays of α-mannosidase inhibition.

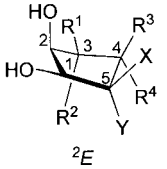
Biological Assay

Listed in Table 1 are the Jack bean α-mannosidase inhibitory activities[27] for newly prepared compounds **11**–**16**, together with those of deoxy- (**2**–**4**), *C*-methyl- (**6** and **8**), and hydroxymethyl (**9** and **10**) aminocyclopentitol derivatives (Table 1). The moderate inhibitor 4-amino-1,2,3-cyclopentanetriol (**11**) appeared to have the minimum core structure for exhibiting inhibitory activity against α-mannosidase, suggesting that possible enhancement of activity could be achieved by chemical modification, for example, through *N*-substitution with alkyl or phenylalkyl functionalities.[28] Incorporation of the appropriate functionalities at the 5-carbon atom of **11** with methylthio and methoxy groups, as shown in compounds **1** and **14**, increased the activity dramatically. In contrast, derivatives having hydrophilic substituents at C-5, such as **L-5** and **7**, exhibited decreased activity, indicating that the presence of a hydrophobic region of space around C-5 is essential. Furthermore, the fact that the 4-epimer (**16**) of **14** completely lacked activity suggests that substituents located on the β-face at C-5 are important. It became apparent that the more the structures resembled mannostatin A (**1**), the greater their inhibitory potential. Farr[29] reported the synthesis of a strong mannosidase inhibitor, amino(hydroxymethyl)cyclopentanetriol **36**, with a 1L-(1,2,4/3,5*N*) configuration, and demonstrated good overlap between **36** and the mannopyranosyl cation by molecular modeling (Figure 1 and Table 2).[16] Recently, Jäger[30] described the synthesis of two stereoisomers, **37** and **38**, having 1L-(1,2,4,5*N*/3) and 1 L-(1,2/3,4,5*N*) configurations, respectively. From a structural viewpoint, the *cis*-vicinal hydroxy groups adjacent to the amino group should match with the 2- and 3-hydroxy groups of the cation adopting the flap-up conformation, as roughly depicted in Figure 1. Although studies[31] on a moderate α-mannosidase inhibitor, deoxymannonojirimycin, demonstrated that 5-hydroxymethyl branching is not indispensable for inhibitory action, we found the strong inhibitory activity of compounds **36** and **37** to depend on the presence of 4-hydroxymethyl groups, matching the 5-hydroxymethyl group of the mannopyranosyl cation. In the cases of compounds **1** and **14**, the methylthio and methoxy groups seem to act as hydroxymethyl equivalents to provide a certain hydrophobic region of space, increasing their potency.

Table 2. Present data for inhibitory activity (IC_{50} [μM]) of mannostatin A (**1**) and **14**, and those reported for isomeric amino(hydroxymethyl)cyclopentanetriols **36**–**38** against α-mannosidase (Jack beans) (reference compound **1**: IC_{50} = 0.02; 0.07 μM].



14, 36 – 38



^2E

Compd.	R^1	R^2	R^3	R^4	X	Y	IC_{50} [μM]
1	OH	H	H	SMe	NH_2	H	0.32
14	OH	H	H	OMe	NH_2	H	0.16
36	H	OH	CH_2OH	H	H	NH_3Br	0.39
37	H	OH	CH_2OH	H	NH_3Br	H	0.17
38	H	OH	H	CH_2OH	H	NH_3Br	5.8

Conclusions

We obtained a strong α-mannosidase inhibitor amino-*O*-methylcyclopentanetriol **14**, the activity of which was comparable to that of the parent **1**, providing a lead compound for further development. The configuration of the hydrophobic *S*- or *O*-methyl functionality was shown to be very important, and the significance of a free 1-hydroxy group adjacent to the amino group was again verified by comparing the activities of the pairs **14** and **16**, and **14** and **15**, respectively. Strong inhibitory activity was demonstrated to be generated by an essential core structure composed of the 5-*O*-(or *S*-)methyl functionality and consecutive 1-, 2-, and 3-hydroxy, and 4-amino groups on the cyclopentane ring. Vicinal 2- and 3-hydroxy groups in a *cis* relationship match the 3- and 2-hydroxy groups of the postulated mannopyranosyl cation, and the amino functionality locates on the α- or β-face between pyranoid oxygen atom and anomeric carbon atoms. *N*-Substitution with normal or modified alkyl and phenylalkyl groups might improve inhibitory potential, as suggested by previous results.[28,30]

Experimental Section

General: Melting points: Mel-Temp capillary melting-point apparatus, uncorrected values. Specific rotations: Jasco DIP-370 polarimeter, 1-dm cells. IR spectra: Hitachi FT/IR-200 and BIORAD DIGITAL FT-65 spectrometers. ^1H NMR spectra: Jeol JNM EX-90 (90 MHz); Jeol GSX-270 f.t. (270 MHz), and Jeol Lambda-300 (300 MHz) spectrometers; solvent $CDCl_3$: internal tetramethylsilane (TMS) standard. CD_3OD: external acetone standard; D_2O: external acetone standard. Mass spectra: positive-ion electrospray ionization with a Micromass Zab Hybrid Spec Sector-TOF mass spectrometer. TLC: Silica Gel 60 GF (E. Merck Darmstadt); detection by charring with concentrated 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 at <50 °C under reduced pressure.

2,3-*O*-Cyclohexylidene Derivative of (1*R*,2*S*,3*R*,4*S*,5*S*)-5-Acetamido-1-*O*-[(2*R*)-2-*O*-acetylmandelyl]-4-*O*-phenoxythiocarbonyl-1,2,3,4-cyclopentanetetrol (18): To a solution of **L-17**[26] (1.83 g, 4.1 mmol) in acetonitrile (18 mL) were added DMAP (3.0 g, 24.5 mmol, 6 equiv.) and phenyl chlorothioformate (2.83 mL, 20.5 mmol, 5 equiv.), and the reaction mixture was stirred at room temperature

for 3 h. The mixture was diluted with ethyl acetate (200 mL), the solution was washed with water, dried, and the solvents were evaporated. The residual product was purified by chromatography on a silica gel column (240 g, acetone/toluene, 1:10) to give **18** (1.69 g, 71%) as a syrup. TLC (acetone/toluene, 1:3): R_f = 0.43. $[\alpha]_D^{18}$ = –30 (c = 0.64, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.22–1.77 (m, 10 H, C_6H_{10}), 1.93, 2.21 (2 s, each 3 H, 2×Ac), 4.76 (dd, $J_{1,2}$ = 5.1, $J_{1,5}$ = 5.8 Hz, 1 H, 1-H), 4.82 (dd, $J_{3,4}$ = 5.1, $J_{2,3}$ = 5.5 Hz, 1 H, 3-H), 4.94 (ddd, $J_{4,5}$ = 5.6, $J_{1,5}$ = 5.8, $J_{5,NH}$ = 9.2 Hz, 1 H, 5-H), 5.01 (dd, $J_{1,2}$ = 5.1, $J_{2,3}$ = 5.5 Hz, 1 H, 2-H), 5.47 (dd, $J_{3,4}$ = 5.1, $J_{4,5}$ = 5.6 Hz, 1 H, 4-H), 6.01 [s, 1 H, PhC*H*(OAc)CO], 6.33 (d, $J_{5,NH}$ = 9.2 Hz, 1 H, NH), 7.12–7.59 (m, 10 H, 2×Ph) ppm. HRMS: calcd. for $C_{30}H_{33}NO_9S$ 583.1876; found 583.1871 [M^+].

1,2-*O*-Cyclohexylidene Derivative of (1*S*,2*S*,3*R*,4*R*)-4-Acetamido-3-*O*-[(2*R*)-2-*O*-acetylmandelyl]-1,2,3-cyclopentanetetrol (20): To a solution of AIBN (3.4 mg, 0.021 mmol, 0.3 equiv.) in toluene (0.5 mL) was added tributyltin hydride (55.4 μL, 0.21 mmol, 3 equiv.) dropwise, followed by a mixture of **18** (40 mg, 0.07 mmol) and toluene (3.5 mL). The reaction mixture was heated at reflux for 2 h, then concentrated to dryness, and the product was purified by chromatography on a silica gel column (10 g, acetone/toluene, 1:4.5) to give **20** (21 mg, 71%) as a syrup. TLC (acetone/toluene, 1:3): R_f = 0.18. $[\alpha]_D^{22}$ = +21 (c = 0.54, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.52 (m, 10 H, C_6H_{10}), 1.98–2.04 (m, 2 H, 5a-H, 5b-H), 1.87, 2.20 (2 s, each 3 H, 2×Ac), 4.57 (m, 1 H, 4-H), 4.63 (ddd, $J_{1,5a}$ = 2.4, $J_{1,5b}$ = 5.4, $J_{1,2}$ = 6.1 Hz, 1 H, 1-H), 4.70 (dd, $J_{2,3}$ = 4.9, $J_{1,2}$ = 6.1 Hz, 1 H, 2-H), 4.87 (dd, $J_{2,3}$ = $J_{3,4}$ = 4.9 Hz, 1 H, 3-H), 5.99 [s, 1 H, PhC*H*(OAc)CO], 6.26 (d, $J_{4,NH}$ = 9.0 Hz, 1 H, NH), 7.40–7.52 (m, 5 H, Ph) ppm. HRMS: calcd. for $C_{23}H_{30}NO_9$ 431.1944; found 431.1949 [M^+].

Tetra-*N*,*O*-acetyl-(1*S*,2*S*,3*R*,4*R*)-4-amino-1,2,3-cyclopentanetriol (11a): A mixture of **20** (8.2 mg, 19 μmol) and 2 M hydrochloric acid (1.0 mL) was heated at 80 °C for 1 h, and then concentrated to dryness. The residue was treated with acetic anhydride (0.5 mL) and pyridine (1 mL) at room temperature overnight. The reaction mixture was coconcentrated with toluene, and the residue was purified by chromatography on a column of silica gel (0.7 g, acetone/toluene, 1:2) to give **11a** (5.7 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.39. $[\alpha]_D^{25}$ = +16 (c = 0.42, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (m, 1 H, 5a-H), 2.01, 2.05, 2.07, 2.13 (4 s, each 3 H, 4×Ac), 2.66 (m, 1 H, 5b-H), 4.57 (m, 1 H, 4-H), 5.20–5.28 (m, 3 H, 1-H, 2-H, 3-H), 5.74 (d, $J_{4,NH}$ = 8.5 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{13}H_{20}NO_7$ 302.1239; found 302.1229 [M^+].

Penta-*N*,*O*,*S*-acetyl-(1*R*,2*R*,3*R*,4*S*,5*S*)-4-amino-5-thio-1,2,3-cyclopentanetriol (12a): A mixture of **21**[26] (12.0 mg, 24 μmol) and 2 M hydrochloric acid (1.0 mL) was stirred at 80 °C for 1 h, and then coconcentrated with EtOH. The residue was acetylated in the usual manner and the product was purified by chromatography on a column of silica gel (0.7 g, acetone/toluene, 1:4) to give **12a** (8.9 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.48. $[\alpha]_D^{25}$ = +26 (c = 0.37, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99, 2.03, 2.07, 2.15, 2.37 (5 s, each 3 H, 5×Ac), 3.91 (dd, $J_{1,5}$ = 6.8, $J_{4,5}$ = 10.5 Hz, 1 H, 5-H), 4.52 (ddd, $J_{3,4}$ = 4.4, $J_{4,NH}$ = 8.5, $J_{4,5}$ = 10.5 Hz, 1 H, 4-H), 5.26 (dd, $J_{1,5}$ = 6.8, $J_{1,2}$ = 7.1 Hz, 1 H, 1-H), 5.40 (dd, $J_{2,3}$ = 3.9, $J_{1,2}$ = 7.1 Hz, 1 H, 2-H), 5.42 (dd, $J_{2,3}$ = 3.9, $J_{3,4}$ = 4.4 Hz, 1 H, 3-H), 5.79 (d, $J_{4,NH}$ = 8.5 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{15}H_{24}NO_7S$ 376.1066; found 376.1068 [M^+].

1,2-*O*-Cyclohexylidene Derivative of (1*R*,2*S*,3*R*,4*S*,5*R*)-4-Acetamido-5-ethylthio-1,2,3-cyclopentanetriol (22): A solution of **21** (5.7 mg, 11 μmol) in MeOH (0.2 mL) was treated with 1 M methanolic sodium methoxide (17 μL) at room temperature for 10 min, and then iodoethane (9 μL, 1.1 mmol) was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated and the residue was purified by chromatography on a column of silica gel (0.5 g, acetone/toluene, 1:3) to give **22** (3.6 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:2): R_f = 0.27. $[\alpha]_D^{22}$ = +1.7 (c = 0.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.38–1.77 (m, 10 H, C_6H_{10}), 2.03 (s, 3 H, Ac), 2.70 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 3.17 (dd, $J_{3,4}$ = 3.9, $J_{4,5}$ = 8.8 Hz, 1 H, 4-H), 4.16 (dd, $J_{1,5}$ = 4.4, $J_{1,2}$ = 4.9 Hz, 1 H, 1-H), 4.34 (ddd, $J_{1,5}$ = 4.4, $J_{4,5}$ = 8.8, $J_{5,NH}$ = 9.0 Hz, 1 H, 5-H), 4.51 (dd, $J_{3,4}$ = 3.9, $J_{2,3}$ = 7.1 Hz, 1 H, 3-H), 4.58 (dd, $J_{1,2}$ = 4.9, $J_{2,3}$ = 7.1 Hz, 1 H, 2-H), 6.08 (d, $J_{5,NH}$ = 9.0 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{15}H_{25}NO_4S$ 315.1504; found 315.1506 [M^+].

Tetra-*N*,*O*-acetyl-(1*R*,2*R*,3*R*,4*S*,5*S*)-4-amino-5-ethylthio-1,2,3-cyclopentanetriol (13a): Compound **22** (6.0 mg, 19 μmol) was hydrolyzed as in the preparation of **11**, and the product was acetylated in the usual manner. The product was purified by a column of silica gel (0.7 g, acetone/toluene, 1:2) to give **13a** (6.9 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.40. $[\alpha]_D^{25}$ = +15 (c = 0.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.04, 2.06, 2.08, 2.11 (4 s, each 3 H, 4×Ac), 2.45 (br. q, J = 7.3 Hz, 2 H, CH_2CH_3), 3.17 (dd, $J_{1,5}$ = 5.6, $J_{4,5}$ = 7.6 Hz, 1 H, 5-H), 4.53 (ddd, $J_{3,4}$ = 5.6, $J_{4,5}$ = 7.6, $J_{4,NH}$ = 8.8 Hz, 1 H, 4-H), 5.16 (t, $J_{1,2}$ = $J_{1,5}$ = 5.6 Hz, 1 H, 1-H), 5.35 (dd, $J_{2,3}$ = 4.4, $J_{3,4}$ = 5.6 Hz, 1 H, 3-H), 5.42 (dd, $J_{2,3}$ = 4.4, $J_{1,2}$ = 5.6 Hz, 1 H, 2-H), 5.70 (d, $J_{4,NH}$ = 8.8 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{15}H_{24}NO_7S$ 362.1273; found 362.1270 [M^+].

2,3-*O*-Cyclohexylidene Derivatives of (1*S*,2*S*,3*R*,4*R*,5*R*)- and (1*R*,2*R*,3*S*,4*S*,5*S*)-5-Acetamido-1-*O*-[(2*S*)-2-*O*-acetylmandelyl]-4-*O*-triethylsilyl-1,2,3,4-cyclopentanetetrol (D-25 and L-25): A mixture of 1D- and 1L-(1,4/2,3,5)-5-acetamido-1-*O*-[(2*S*)-2-*O*-acetylmandelyl]-1,2,3,4-cyclopentanetetrol (**D-24** and **L-24**, 336 mg, 0.752 mmol) derived[26] from the diol **23**, triethylsilyl triflate (255 μL, 1.13 mmol, 1.5 equiv.), and 2,6-lutidine (262 μL, 2.25 mmol, 3 equiv.) in dichloromethane (3.5 mL) was stirred under argon at 0 °C for 90 min. To the reaction mixture was then added saturated aqueous $NaHCO_3$ (60 mL), and the aqueous layer was thoroughly extracted with chloroform (3×20 mL). The extracts were dried, and the solvents were evaporated. The residue was purified by chromatography on a silica gel column (40 g, ethyl acetate/toluene, 1:7) to give **L-25** (326 mg, 77%) and **D-25** (94 mg, 23%), each as a syrup.

L-25: TLC (acetone/toluene, 1:4): R_f = 0.48. $[\alpha]_D^{25}$ = +37 (c = 1.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.59 [dd, J = 7.8, J_{gem} = 16.1 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.93 [t, J = 7.8 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.39–1.70 (m, 10 H, C_6H_{10}), 1.85, 2.18 (2 s, each 3 H, 2×Ac), 4.02 (dd, $J_{1,2}$ = 2.2, $J_{1,5}$ = 4.4 Hz, 1 H, 1-H), 4.12 (ddd, $J_{1,5}$ = 4.4, $J_{4,5}$ = 4.6, $J_{5,NH}$ = 9.0 Hz, 1 H, 5-H), 4.41 (dd, $J_{1,2}$ = 2.2, $J_{2,3}$ = 6.6 Hz, 1 H, 2-H), 4.57 (dd, $J_{3,4}$ = 2.2, $J_{2,3}$ = 6.6 Hz, 1 H, 3-H), 5.04 (dd, $J_{3,4}$ = 2.2, $J_{4,5}$ = 4.6 Hz, 1 H, 4-H), 5.63 (br. d, $J_{5,NH}$ = 9.0 Hz, 1 H, NH), 5.87 [s, 1 H, PhC*H*(OAc)CO], 7.36–7.46 (m, 5 H, Ph) ppm. HRMS: calcd. for $C_{27}H_{38}NO_8Si$ 532.2367; found 532.2367 [M^+].

D-25: TLC (acetone/toluene, 1:4): R_f = 0.44. $[\alpha]_D^{25}$ = +28 (c = 1.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.63 [dd, J = 8.1, J_{gem} = 15.4 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.96 [t, J = 8.1 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.37–1.71 (m, 10 H, C_6H_{10}), 1.92, 2.17 (2 s, each 3 H, 2×Ac), 4.07 (m, 1 H, 1-H), 4.26 (m, 1 H, 5-H), 4.33 (m, 2 H, 2-H, 3-H), 5.10 (m, 1 H, 4-H), 5.72 (br. d, $J_{5,NH}$ = 9.0 Hz, 1 H, NH), 5.90 [s, 1 H, PhC*H*(OAc)CO], 7.37–7.48 (m, 5 H, Ph) ppm. HRMS: calcd. for $C_{27}H_{38}NO_8Si$ 532.2367; found 532.2388 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*R*,2*S*,3*S*,4*S*,5*R*)-5-Acetamido-1-*O*-triethylsilyl-1,2,3,4-cyclopentanetetrol (D-26): A solution

of the *S*-acetylmandelate **L-25** (159 mg, 0.28 mmol) in CH_2Cl_2 (1.6 mL) was treated with 1 M methanolic sodium methoxide (57 μL, 57 μM) at 0 °C for 3 h. The product was purified by chromatography on a column of silica gel (10 g, acetone/toluene, 1:2) to give the alcohol **D-26** (109 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:2): R_f = 0.41. $[a]_D^{25}$ = +10 (*c* = 1.65, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.69 [dd, *J* = 8.1, J_{gem} = 15.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.99 [t, *J* = 8.1 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.36–1.77 (m, 10 H, C_6H_{10}), 1.97 (s, 3 H, Ac), 3.79 (d, $J_{4,OH}$ = 8.1 Hz, 1 H, OH), 4.00–4.07 (m, 3 H, 1-H, 4-H, 5-H), 4.50 (m, 1 H, 2-H), 5.64 (m, 1 H, 3-H), 5.90 (m, 1 H, NH) ppm. HRMS: calcd. $C_{19}H_{35}NO_5Si$ 385.2285; found 385.2303 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*S*,2*R*,3*R*,4*R*,5*S*)-5-Acetamido-1-*O*-triethylsilyl-1,2,3,4-cyclopentanetetrol (L-26): D-25 (149 mg, 0.26 mmol) was deacylated as in the preparation of **D-26** to give **L-26** (167 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:2): R_f = 0.41. $[a]_D^{25}$ = –7.4 (*c* = 1.0, $CHCl_3$). HRMS: calcd. for $C_{19}H_{36}NO_5Si$ 386.2363; found 386.2354 [M^+]. The ^1H NMR spectrum was found to be superimposable on that of **D-26**.

2,3-*O*-Cyclohexylidene Derivative of (1*S*,2*S*,3*S*,4*S*,5*R*)-5-Acetamido-1-*O*-methyl-4-*O*-triethylsilyl-1,2,3,4-cyclopentanetetrol (27): To a solution of **D-26** (12.3 mg, 2 mmol) in acetonitrile (0.5 mL) were added silver oxide (11.4 mg, 48 μM) and iodomethane (0.2 mL, 3.19 mmol), and the mixture was refluxed for 6 h. An insoluble material was removed by filtration, and the filtrate was concentrated to dryness. The residue was purified by chromatography on a silica gel column (0.7 g, acetone/toluene, 1:7) to give the methyl ether **27** (12.7 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.71. $[a]_D^{25}$ = –0.1 (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.63 [dd, *J* = 8.1, J_{gem} = 14.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.96 [t, *J* = 8.1 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.32–1.70 (m, 10 H, C_6H_{10}), 1.97 (s, 3 H, Ac), 3.42 (s, 3 H, Me), 3.71 (m, 1 H, 4-H), 4.06–4.11 (m, 2 H, 1-H, 5-H), 4.41 (m, 1 H, 2-H), 4.52 (dd, $J_{2,3}$ = 2.2, $J_{3,4}$ = 6.6 Hz, 1 H, 3-H), 5.73 (br. d, $J_{5,NH}$ = 7.6 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{20}H_{37}NO_5Si$ 399.2441; found 399.2441 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*R*,2*S*,3*R*,4*S*,5*S*)-5-Acetamido-1-*O*-methyl-1,2,3,4-cyclopentanetetrol (28): A solution of **27** (83 mg, 0.21 mmol) in THF (1.6 mL) was treated with TBAF (59 μL, 0.25 mmol) at room temperature for 1.5 h, and then the reaction mixture was concentrated to dryness. The residue was dissolved in ethyl acetate (15 mL), and the solution was washed with 1 M hydrochloric acid, saturated aqueous $NaHCO_3$, and water, dried, and the solvents were evaporated. The residual product was purified by chromatography on a silica gel column (5 g, acetone/toluene, 1:1) to give **28** (40.5 mg, 69%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.34. $[a]_D^{27}$ = +12 (*c* = 0.82, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.75 (m, 10 H, C_6H_{10}), 2.01 (s, 3 H, Ac), 3.48 (s, 3 H, Me), 3,62 (m, 1 H, 1-H), 4.03 (m, 2 H, 4-H, 5-H), 4.29 (m, 1 H, OH), 4.56 (br. s, 2 H, 2-H, 3-H), 5.99 (br. s, 1 H, NH) ppm. HRMS: calcd. for $C_{14}H_{23}NO_5$ 285.1576; found 285.1589 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*R*,2*R*,3*S*,4*R*,5*S*)-5-*O*-Acetamido-4-*O*-methyl-1,2,3,4-cyclopentanetetrol (30): To a solution of **28** (16.5 mg, 58 μmol) in pyridine (0.4 mL) was added mesyl chloride (22.4 μL, 0.29 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and then coconcentrated with toluene. The residue was diluted with $CHCl_3$ (15 mL), and the solution was washed thoroughly with water, dried, and the solvents were evaporated. The resulting crude mesylate **29** was dissolved in aqueous DMF (80%, 3.0 mL) and, after addition of sodium acetate (18 mg, 2.2 mmol), the mixture was stirred at 110 °C overnight. The reaction mixture was then coconcentrated with ethanol and toluene, and the residue was purified by chromatography on a silica gel column (1.5 g, acetone/toluene, 1:3) to give the alcohol **30** (12.6 mg, 76%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.42. $[a]_D^{25}$ = –29 (*c* = 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.76 (m, 10 H, C_6H_{10}), 2.03 (s, 3 H, Ac), 3.23 (d, $J_{4,OH}$ = 3.7 Hz, 1 H, OH), 3.43 (s, 3 H, Me), 3.68 (dd, $J_{1,2}$ = 2.7, $J_{1,5}$ = 6.6 Hz, 3 H, 1-H), 4.11 (ddd, $J_{4,OH}$ = 3.7, $J_{4,5}$ = 4.6, $J_{3,4}$ = 4.9 Hz, 1 H, 4-H), 4.41 (ddd, $J_{4,5}$ = 4.6, $J_{1,5}$ = 6.6, $J_{5,NH}$ = 8.5 Hz, 1 H, 5-H), 4.45 (dd, $J_{1,2}$ = 2.7, $J_{2,3}$ = 7.1 Hz, 1 H, 2-H), 4.58 (dd, $J_{3,4}$ = 4.9, $J_{2,3}$ = 7.1 Hz, 1 H, 3-H), 6.12 (br. d, $J_{5,NH}$ = 8.5 Hz, 1 H, NH) ppm. HRMS: *m*/*z* = 285.1575 [M^+]. $C_{14}H_{23}NO_5$ (285.1576).

(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Acetamido-1,2,3-*O*-acetyl-4-*O*-methyl-1,2,3,4-cyclopentanetetrol (14a): A mixture of **30** (31.4 mg, 0.11 mmol) and aqueous acetic acid (60%, 1.0 mL) was stirred at 60 °C for 5.5 h and then concentrated to dryness. The residual product was acetylated in the usual manner, and the product was purified by chromatography on a silica gel column (3 g, acetone/toluene, 1:3) to give the acetyl derivative **14a** (19.2 mg, 53%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.32. $[a]_D^{23}$ = –3.1 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04, 2.08, 2.10 (3 s, 3 H, 6 H, 3 H, 4 × OAc), 3.42 (s, 3 H, Me), 3.77 (t, $J_{3,4}$ = $J_{4,5}$ = 4.6 Hz, 1 H, 4-H), 4.57 (ddd, $J_{4,5}$ = 4.6, $J_{1,5}$ = 6.1, $J_{5,NH}$ = 9.0 Hz, 1 H, 5-H), 5.14 (t, $J_{2,3}$ = $J_{3,4}$ = 4.6 Hz, 1 H, 3-H), 5.34 (dd, $J_{1,2}$ = 3.9, $J_{1,5}$ = 6.1 Hz, 1 H, 1-H), 5.46 (dd, $J_{1,2}$ = 3.9, $J_{2,3}$ = 4.6 Hz, 1 H, 2-H), 5.82 (br. d, $J_{5,NH}$ = 9.0 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{14}H_{22}NO_8$ 332.1345; found 332.1371 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*S*,2*R*,3*S*,4*R*)-5-Acetamido-1,2,3,4-cyclopentanetetrol (31): Alcohol **L-26** (167 mg, 0.433 mmol) was mesylated as in the preparation of **29**. During the above processing, when the reaction mixture was concentrated and coconcentrated with toluene, a partial removal of the triethylsilyl group was observed. The resulting crude mesylate was treated with sodium acetate (178 mg, 2.16 mmol) in aqueous 80% DMF (2.0 mL) at 110 °C overnight, and then the mixture was concentrated and coconcentrated with ethanol and toluene. The residue was purified by chromatography on a column of silica gel (10 g, acetone/toluene, 1:1) to give the diol **31** (94 mg, 80%) as a syrup. TLC (acetone/toluene, 2:1): R_f = 0.28. $[a]_D^{21}$ = –28 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.76 (m, 10 H, C_6H_{10}), 2.03 (s, 3 H, Ac), 4.13–4.21 (m, 3 H, 3-H, 4-H, 5-H), 4.49 (d, $J_{1,2}$ = 7.1 Hz, 1 H, 1-H), 4.65 (dd, $J_{2,3}$ = 4.9, $J_{1,2}$ = 7.1 Hz, 1 H, 2-H), 6.52 (br. s, 1 H, NH) ppm. HRMS: calcd. for $C_{13}H_{21}NO_5$ 271.1420; found 271.1413 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*S*,2*S*,3*R*,4*R*)-5-Acetamido-1,4-di-*O*-acetyl-1,2,3,4-cyclopentanetetrol (32): Diol **31** (91 mg, 0.34 mmol) was acetylated with acetic anhydride in pyridine in the usual manner, and the product was purified by chromatography on a column of silica gel (10 g, acetone/toluene, 1:4) to give the di-*O*-acetyl derivative **32** (119 mg, ca. 100%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.50. $[a]_D^{23}$ = +38 (*c* = 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.82 (m, 10 H, C_6H_{10}), 1.99, 2.08, 2.16 (3 s, each 3 H, 3 × Ac), 4.48 (dd, $J_{3,4}$ = 1.7, $J_{2,3}$ = 6.3 Hz, 1 H, 3-H), 4.54 (ddd, $J_{4,5}$ = 4.6, $J_{1,5}$ = 5.1, $J_{5,NH}$ = 8.5 Hz, 1 H, 5-H), 4.77 (dd, $J_{1,2}$ = 5.1, $J_{2,3}$ = 6.3 Hz, 1 H, 2-H), 5.11 (dd, $J_{3,4}$ = 1.7, $J_{4,5}$ = 4.6 Hz, 1 H, 4-H), 5.18 (t, $J_{1,2}$ = $J_{1,5}$ = 5.1 Hz, 1 H, 1-H), 6.17 (d, $J_{5,NH}$ = 8.5 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{17}H_{25}NO_7$ 355.1631; found 355.1612 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*S*,2*R*,3*S*,4*R*)-5-Acetamido-1,4-di-*O*-methyl-1,2,3,4-cyclopentanetetrol (33): Diol **31** (76 mg, 0.28 mmol) was methylated with silver oxide (194 mg, 0.837 mmol) and iodomethane (1.74 mL, 27.9 mmol) in acetonitrile (1.0 mL) at 80 °C for 5 h. The product was purified by chromatography on a

column of silica gel (3 g, acetone/toluene, 1:5) to give ether **33** (57 mg, 68%) as a syrup. TLC (acetone/toluene, 2:1): R_f = 0.62. $[a]_D^{22}$ = –31 (c = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.81 (m, 10 H, C_6H_{10}), 3.44, 3.44 (2 s, each 3 H, 2×Me), 3.62 (s, 1 H, 4-H), 3.88 (t, $J_{1,2}$ = $J_{1,5}$ = 4.9 Hz, 1 H, 1-H), 4.41 (d, $J_{2,3}$ = 4.9 Hz, 1 H, 3-H), 4.44 (dd, $J_{1,5}$ = 4.9, $J_{5,NH}$ = 7.1 Hz, 1 H, 5-H), 4,73 (t, $J_{1,2}$ = $J_{2,3}$ = 4.9 Hz, 1 H, 2-H), 6.34 (d, $J_{5,NH}$ = 7.1 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{15}H_{26}NO_5$ 300.1811; found 300.1816 [M^+].

(1*S*,2*R*,3*S*,4*R*)-5-Acetamido-2,3-di-*O*-acetyl-1,4-di-*O*-methyl-1,2,3,4-cyclopentanetetrol (15a): Compound **33** (54 mg, 0.18 mmol) was hydrolysed with 60% aqueous acetic acid at 80 °C for 2 h. The product was acetylated in the usual manner, and the acetyl derivative was purified by chromatography on a column of silica gel (3 g, acetone/toluene, 1:3) to give the di-*O*-acetyl derivative **15a** (46.5 mg, 86%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.39. $[a]_D^{22}$ = –44 (c = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.06, 2.06, 2.14 (3 s, each 3 H, 3×Ac), 3.37, 3.45 (2 s, each 3 H, 2×Me), 3.72 (dd, $J_{4,5}$ = 3.7, $J_{3,4}$ = 5.6 Hz, 1 H, 4-H), 3.89 (dd, $J_{1,2}$ = 3.6, $J_{1,5}$ = 6.8 Hz, 1 H, 1-H), 4.44 (ddd, $J_{4,5}$ = 3.7, $J_{1,5}$ = 6.8, $J_{5,NH}$ = 8.5 Hz, 1 H, 5-H), 5.02 (t, $J_{2,3}$ = $J_{3,4}$ = 5.6 Hz, 1 H, 3-H), 5.48 (dd, $J_{1,2}$ = 3.6, $J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 6.05 (d, $J_{5,NH}$ = 8.5 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{13}H_{22}NO_7$ 304.1396; found 304.1402 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*R*,2*S*,3*S*,4*S*,5*R*)-5-Acetamido-1-*O*-triethylsilyl-1,2,3,4-cyclopentanetetrol (34): To a solution of **D-17**[24] (114 mg, 0.254 mmol) in CH_2Cl_2 (1.5 mL) were added 2,6-lutidine (89 μL, 0.763 mmol) and triethylsilyl triflate (86 μL, 0.38 mmol) at 0 °C under argon, and the mixture was stirred at 0 °C for 30 min. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was extracted with chloroform (3×10 mL). The extracts were washed with water, dried, and the solvents were evaporated. The residual product was treated with 1 M methanolic sodium methoxide (50 μL) in CH_2Cl_2 (1.0 mL) at 0 °C for 30 min. After neutralization with aqueous acetic acid, an insoluble material was removed by filtration and washed with acetone. The filtrate and washings were combined and the solvents were evaporated to dryness. The residue was purified by chromatography on a column of silica gel (10 g, acetone/toluene, 1:4) to give the alcohol **34** (66 mg, 68%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.48. $[a]_D^{21}$ = +25 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.63 [dd, J = 8.1, J_{gem} = 15.1 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.97 [t, J = 8.1 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.36–1.83 (m, 10 H, C_6H_{10}), 2.04 (s, 3 H, Ac), 3.06 (d, $J_{4,OH}$ = 10.0 Hz, 1 H, OH), 4.00 (ddd, $J_{3,4}$ = $J_{4,5}$ = 6.6, $J_{4,OH}$ = 10.0 Hz, 1 H, 4-H), 4.08 (t, $J_{1,2}$ = $J_{1,5}$ = 4.4 Hz, 1 H, 1-H), 4.15 (ddd, $J_{1,5}$ = 4.4, $J_{4,5}$ = 6.6, $J_{5,NH}$ = 7.8 Hz, 1 H, 5-H), 4.44 (dd, $J_{1,2}$ = 4.4, $J_{2,3}$ = 6.6 Hz, 1 H, 2-H), 4.53 (t, $J_{2,3}$ = $J_{3,4}$ = 6.6 Hz, 1 H, 3-H), 6.37 (d, $J_{5,NH}$ = 7.8 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{19}H_{35}NO_5Si$ 385.2285; found 385.2284 [M^+].

2,3-*O*-Cyclohexylidene Derivative of (1*R*,2*S*,3*S*,4*S*,5*R*)-5-Acetamido-1-*O*-methyl-4-*O*-triethylsilyl-1,2,3,4-cyclopentanetetrol (35): To a solution of **34** (57 mg, 0.15 mmol) in acetonitrile (1.0 mL) were added silver oxide (51 mg, 0.22 mmol) and a large excess of iodomethane (0.9 mL, 14.7 mmol), and the suspension was refluxed at 80 °C overnight. After cooling, an insoluble material was removed by filtration, and the filtrate was concentrated. The residue was purified by chromatography on a column of silica gel (3 g, acetone/toluene, 1:6) to give the methyl ether **35** (57 mg, 97%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.56. $[a]_D^{21}$ = +8.3 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.63 [dd, J = 8.1, J_{gem} = 15.6 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.97 [t, J = 8.1 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.32–1.84 (m, 10 H, C_6H_{10}), 2.00 (s, 3 H, Ac), 3.44 (t, $J_{3,4}$ = $J_{4,5}$ = 5.4 Hz, 1 H, 4-H), 3.46 (s, 3 H, Me), 3.92 (t, $J_{1,2}$ = $J_{1,5}$ = 5.4 Hz, 1 H, 1-H), 4.44 (t, $J_{1,2}$ = $J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 4.60 (t, $J_{2,3}$ = $J_{3,4}$ = 5.4 Hz, 1 H, 3-H), 4.62 (ddd, $J_{1,5}$ = $J_{4,5}$ = 5.4, $J_{5,NH}$ = 9.8 Hz, 1 H, 5-H), 6.27 (d, $J_{5,NH}$ = 9.8 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{20}H_{37}NO_5Si$ 399.2441; found 399.2427 [M^+].

(1*R*,2*R*,3*S*,4*S*,5*R*)-5-Acetamido-1,2,3-tri-*O*-acetyl-4-*O*-methyl-1,2,3,4-cyclopentanetetrol (16a): A mixture of **35** (10 mg, 25 μmol) and aqueous acetic acid (60%, 2.0 mL) was stirred at 80 °C for 9 h, and then coconcentrated with ethanol and toluene. The residue was treated with acetic anhydride (0.5 mL) and pyridine (1.0 mL) at room temperature overnight. The reaction mixture was concentrated, and the residue was purified by chromatography on a column of silica gel (0.7 g, acetone/toluene, 1:3) to give the acetyl derivative **16a** (7.3 mg, 87%) as a syrup. TLC (acetone/toluene, 1:1): R_f = 0.41. $[a]_D^{22}$ = +36 (c = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05, 2.08, 2.09, 2.14 (4 s, each 3 H, 4×Ac), 3.40 (s, 3 H, Me), 3.86 (m, 1 H, 4-H), 4,74 (m, 1 H, 5-H), 5.22–5.29 (m, 3 H, 1-H, 2-H, 3-H), 5.97 (d, $J_{5,NH}$ = 9.0 Hz, 1 H, NH) ppm. HRMS: calcd. for $C_{14}H_{22}NO_8$ 332.1345; found 332.1331 [M^+].

(1*S*,2*S*,3*R*,4*R*)-4-Amino-1,2,3-cyclopentanetriol (11): A mixture of **11a** (8.3 mg, 28 μmol) and 2 M hydrochloric acid (1 mL) was stirred at 80 °C for 1 h, and the solvents were evaporated to dryness. The residual product was purified by chromatography on a column of Dowex-50 W×2 (H^+) resin (1 mL, 1 M aqueous ammonia) to give the free base **11** (3.7 mg, ca. 100%). TLC (H_2O/AcOH/*t*BuOH, 1:1:4): R_f = 0.33. $[a]_D^{24}$ = +46 (c = 0.4, MeOH). ^1H NMR (300 MHz, D_2O): δ = 1.46 (ddd, $J_{1,5a}$ = 6.1, $J_{4,5a}$ = 6.8, J_{gem} = 14.6 Hz, 1 H, 5a-H), 2.35 (ddd, $J_{1,5b}$ = 7.6, $J_{4,5b}$ = 8.5, J_{gem} = 14.6 Hz, 1 H, 5b-H), 3.24 (ddd, $J_{3,4}$ = 5.6, $J_{4,5a}$ = 6.8, $J_{4,5b}$ = 8.5 Hz, 1 H, 4-H), 3.80 (t, $J_{1,2}$ = $J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 3.87 (dd, $J_{2,3}$ = 4.4, $J_{3,4}$ = 5.6 Hz, 1 H, 3-H), 3.97 (ddd, $J_{1,2}$ = 4.4, $J_{1,5a}$ = 6.1, $J_{1,5b}$ = 7.6 Hz, 1 H, 1-H) ppm. HRMS: calcd. for $C_5H_{12}NO_3$ 134.0817; found 134.0798 [M^+].

(1*R*,2*R*,3*R*,4*S*,5*R*)-4-Amino-5-thio-1,2,3-cyclopentanetriol (12): Compound **12a** (8.9 mg) was hydrolyzed as in the preparation of **11**, and the product was purified on a column of Dowex-50 W×2 (H^+) resin (1 mL, 1 M aqueous ammonia) to give **12** (2.9 mg, 74%) as a syrup. TLC (H_2O/AcOH/*t*BuOH, 1:1:2): R_f = 0.24. $[a]_D^{24}$ = +66 (c = 0.1, MeOH). ^1H NMR (300 MHz, D_2O): δ = 3.12 (dd, $J_{1,5}$ = 5.6, $J_{4,5}$ = 7.8 Hz, 1 H, 5-H), 3.88–3.98 (m, 3 H, 1-H, 2-H, 3-H), 3.95 (m, 1 H, 4-H) ppm. HRMS: calcd. for $C_5H_{13}NO_3S$ 167.0616; found 167.0633 [M^+].

(1*R*,2*R*,3*R*,4*S*,5*R*)-4-Amino-5-ethylthio-1,2,3-cyclopentanetriol (13): Compound **13a** (5.9 mg, 16 μmol) was hydrolyzed as in the preparation of **11**, and the product was purified by a column of Dowex-50 W×2 (H^+) resin (1 mL, 1 M aqueous ammonia) to give **13** (2.9 mg, ca. 100%) as a syrup. TLC (MeOH/chloroform, 1:2): R_f = 0.23. $[a]_D^{24}$ = –54 (c = 0.15, MeOH). ^1H NMR (300 MHz, D_2O): δ = 1.11 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.54 (br. q, J = 7.3 Hz, 2 H, CH_2CH_3), 2.84 (dd, $J_{3,4}$ = 6.3, $J_{4,5}$ = 7.8 Hz, 1 H, 4-H), 3.00 (dd, $J_{1,5}$ = 5.6, $J_{4,5}$ = 7.8 Hz, 1 H, 5-H), 3.82 (dd, $J_{2,3}$ = 5.4, $J_{3,4}$ = 6.3 Hz, 1 H, 3-H), 3.90 (t, $J_{1,2}$ = $J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 3.96 (dd, $J_{1,2}$ = 5.4, $J_{1,5}$ = 5.6 Hz, 1 H, 1-H) ppm. HRMS: calcd. for $C_7H_{15}NO_3S$ 193.0773; found 193.0781 [M^+].

(1*R*,2*R*,3*R*,4*R*,5*S*)-5-Amino-4-*O*-methyl-1,2,3,4-cyclopentanetetrol (14): Compound **14a** (9.2 mg, 28 μmol) was treated with 2 M aqueous barium hydroxide (1 mL) at 90 °C for 5 h. After neutralization with carbon dioxide, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to dryness. The product was purified on a column of Dowex-50 W×2 (H^+) resin (1 mL, 1% aqueous ammonia) to give the free base **14** (1.9 mg, 42%) as a syrup. TLC (H_2O/AcOH/BuOH, 1:1:2): R_f = 0.46. $[a]_D^{20}$ = +53

(c = 0.1, MeOH). ^{1}H NMR (300 MHz, D_2O): δ = 2.92 (m, 1 H, 5-H), 3.32 (s, 3 H, Me), 3.48 (m, 1 H, 4-H), 3.81 (m, 1 H, 3-H), 3.89 (m, 2 H, 1-H, 2-H) ppm. HRMS: calcd. for $C_6H_{14}NO_4$ 164.0923; found 164.0922 [M^+].

(1*R*,2*S*,3*R*,4*R*)-5-Amino-1,4-di-*O*-methyl-1,2,3,4-cyclopentanetetrol (15): Compound **15a** (7.4 mg, 24 μmol) was treated with 1 M aqueous barium hydroxide (1 mL) at 90 °C overnight. After neutralization with CO_2, an insoluble material was removed by filtration through a Celite pad, and the filtrate was concentrated to dryness. The residue was purified by chromatography on a column of Dowex-50 W × 2 (H^+) resin (1 mL, 1 M aqueous ammonia) to give the di-*O*-methyl ether **15** (4.3 mg, ca. 100%) as a syrup. TLC (H_2O/AcOH/BuOH, 1:1:2): R_f = 0.41. $[\alpha]_D^{22}$ = +23 (c = 0.3, MeOH). ^{1}H NMR (300 MHz, D_2O): δ = 3.13 (dd, $J_{4,5}$ = 5.4, $J_{1,5}$ = 6.3 Hz, 1 H, 5-H), 3.31, 3.32 (2 s, each 3 H, 2 × Me), 3.50 (t, $J_{3,4}$ = $J_{4,5}$ = 5.4 Hz, 1 H, 4-H), 3.58 (dd, $J_{1,2}$ = 3.7, $J_{1,5}$ = 6.3 Hz, 1 H, 1-H), 3.77 (t, $J_{2,3}$ = $J_{3,4}$ = 5.4 Hz, 1 H, 3-H), 4.03 (dd, $J_{1,2}$ = 3.7, $J_{2,3}$ = 5.4 Hz, 1 H, 2-H) ppm. HRMS: calcd. for $C_7H_{16}NO_4$ 178.1079; found 178.1087 [M^+].

(1*S*,2*R*,3*R*,4*R*,5*S*)-5-Amino-1-*O*-methyl-1,2,3,4-cyclopentanetetrol (16): Compound **16a** (57 mg, 17 μmol) was treated with 1 M aqueous barium hydroxide (1 mL) at 90 °C overnight. After neutralization with carbon dioxide, the mixture was filtered through a pad of Celite which was washed with water thoroughly. The filtrate and washings were concentrated and the residue was purified by chromatography on a column of Dowex-50 W × 2 (H^+) resin (1 mL, 1 M aqueous ammonia) to give the amine **16** (2.8 mg, ca. 100%) as a syrup. TLC (H_2O/AcOH/BuOH, 1:1:3): R_f = 0.19. $[\alpha]_D^{20}$ = –16 (c = 0.14, MeOH). ^{1}H NMR (300 MHz, D_2O): δ = 3.32 (m, 4 H, 5-H, Me), 3.60 (dd, $J_{1,2}$ = 4.9, $J_{1,5}$ = ≈ 5 Hz, 1 H, 1-H), 3.81 (t, $J_{2,3}$ = $J_{3,4}$ = 5.1 Hz, 1 H, 3-H), 3.92 (t, $J_{3,4}$ = $J_{4,5}$ = 5.1 Hz, 1 H, 4-H), 3.99 (dd, $J_{1,2}$ = 4.9, $J_{2,3}$ = 5.1 Hz, 1 H, 2-H) ppm. HRMS: calcd. for $C_{14}H_{22}NO_8$ 164.0923; found 164.0915 [M^+].

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