Synthesis and Glycosidase Inhibitory Activity of Five Stereoisomers of 5-Amino-5-*C*-methyl-1,2,3,4-cyclopentanetetrol

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In order to elucidate the essential core structure of potent α-mannosidase inhibitors, e.g. mannostatin A, 5-amino-5-*C*-methyl-1,2,3,4-cyclopentanetetrols **4–8** were designed and synthesized by a base-catalyzed nitro aldol condensation of nitroethane and the dialdehyde derived by periodate oxidation of DL-1,2-*O*-cyclohexylidene-*myo*-inositol, followed by reduction and deprotection. Biological assay of the five stereoisomers thus obtained for the six glycosidases has demonstrated the DL-(1,2/3,4,5) and (1,2,3,4,5/0) isomers to be moderate α-mannosidase inhibitors, suggesting that the *all-cis* configuration of the amino and three hydroxy groups on the cyclopentane ring plays a role in exhibiting inhibitory activity.

Discovery of the potent and specific α-mannosidase inhibitor mannostatin A[1] (**1**) has stimulated us to develop new glycosidase inhibitors composed of 5-amino-1,2,3,4-cyclopentaneterols, which are thought to act as transition state mimickings of glycopyranosyl cations postulated to form during hydrolysis of glycosides[2]. Concerning conformational feature of the transition state mannopyranosyl cation predicted in hydrolysis of mannopyranosides, it seemed rather difficult to correlate the structures of the known potent inhibitors conformationally to the postulated structure of mannopyranosyl cation[3]. Recently, Winkler and his coworkers[4] have proposed adequate correlationship by comparing the structures of some α-mannosidase inhibitors to their flap up mannopyranosyl cation model.

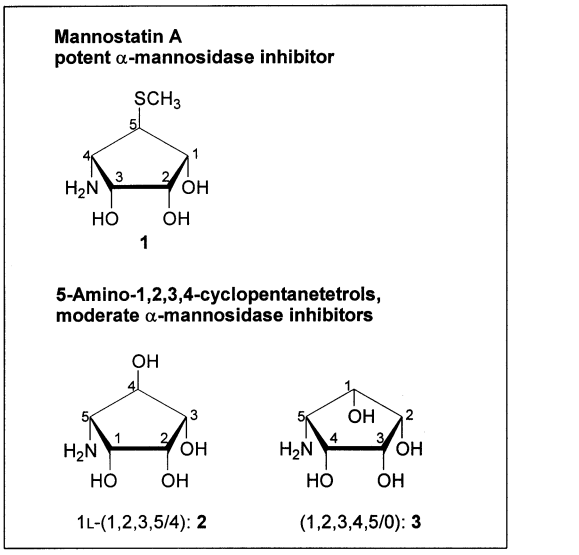
We have so far investigated synthetic studies[5] on glycosidase inhibitors containing 5-amino-1,2,3,4-cyclopentanetetrols, being initially motivated by our results[6] of the structure and inhibitory activity relationship of trehalase inhibitor trehazolin.[7] Among twenty four stereoisomers[5] of 5-amino-1,2,3,4-cyclopentanetetrols and its branched-chain derivatives, which were assayed inhibitory activity toward several glycosidases, only 1D- and 1L-(1,2,3,5/4) (**2**), and (1,2,3,4,5/0) isomers (**3**) have been shown to be weak inhibitors of Jack beans α-mannosidase ($IC_{50} = 1-10\times10^{-5}$ M). In fact, compounds **2** and **3** are likely to resemble mannostatin A in configurations the *all-cis* relationships of the amino and consecutive three hydroxy groups, suggesting that these core structures are essential for generation of inhibitory potential toward α-mannosidase, and furthermore they should conceivably be constituted the simple and close mimickings of the transition state mannopyranosyl cation. In the present paper, the five branched-chain analogs **4–8** of 5-amino-5-*C*-methyl-1,2,3,4-cyclopentanetetrol were synthesized and their enzyme inhibitory activity assayed. It seemed of interest to elucidate the influence of the *C*-methyl functions toward the inhibitory potentials, comparing the activities of **7** and **8** with those of **2** and **3**.

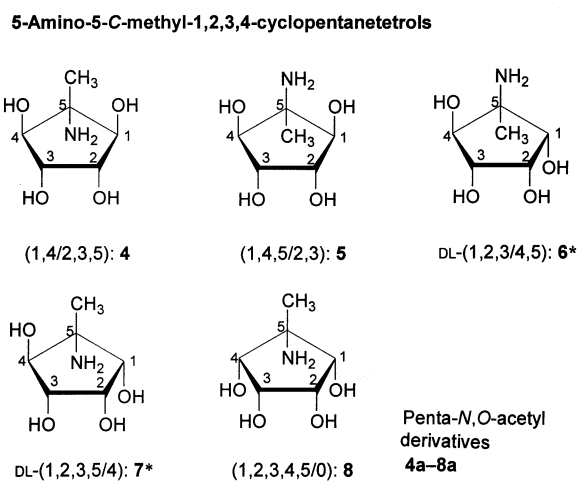
Dialdehyde/nitromethane cyclization has established itself as a generally applicable synthetic method for preparation of aminocyclitols and amino sugars.[8] Some nitroalkanes and alkanols have successfully been applied[9][10] in the reaction of glutaraldehyde, producing some unaccessible branched-chain aminocyclitols. In the present study, nitro aldol cyclization between nitroethane and a dialdehyde derived by treatment of DL-1,2-*O*-cyclohexylidene-*myo*-inositol[11] with excess of sodium metaperiodate has been carried out for synthesis of the target compounds. No cyclization product was formed when sodium methoxide, sodium hydroxide, barium hydroxide, sodium carbonate, or sodium hydrogen carbonate was used as a base catalyst. Only, under influence of DBU, the reaction occurred smoothly to give a mixture of the nitro diols, in practically acceptable yields, which was subsequently reduced in the presence of Raney nickel and acetic anhydride, followed by acetylation with acetic anhydride in pyridine, giving an inseparable mixture of the 2,3-*O*-cyclohexylidene derivatives of 5-acetamido-1,4-di-*O*-acetyl-5-*C*-methyl-1,2,3,4-cyclopentanetetrol. De-*O*-acetylation of the compounds under Zemplén conditions[12] led to a separable mixture of products, and, after silica gel chromatography, three stereoisomers of the 5-acetamido-5-*C*-methyl-1,2,3,4-cyclopentanetetrol derivatives **9**, **10**, and **11** were obtained in 16, 10, and 1% yields, respectively, based on the inositol derivative used[13]. Their structures were assigned by the ^{1}H-NMR spectra and NOE experiment, together with those of the corresponding di-*O*-acetyl derivatives **9a**, **10a**, and **11a**.

Thus, eight stereoisomers (2 chiral and 4 *meso*) are theoretically possible to be obtainable by the present preparative reaction. By analogy with the results of a similar cyclization

  1434–193X/98/0909–1929 $ 17.50+.50/0

Scheme 1. For convenience, the formulas depict only one enantiomer of the respective racemates

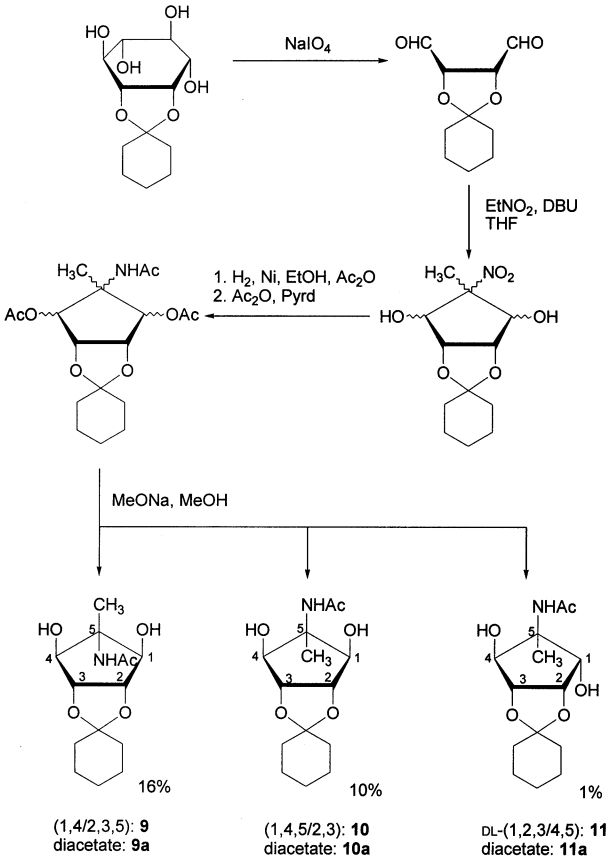




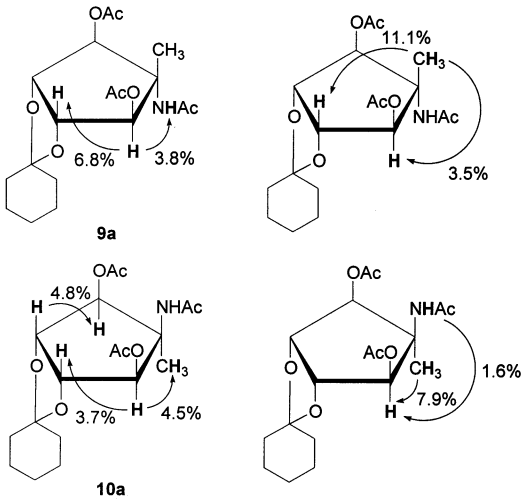
reaction with nitromethane,[14][15] the *meso* compound with a nitro group situated *cis* to the 1,3-dioxolane ring and *trans* to two vicinal hydroxy groups seemed to be formed mainly as thermodynamically stable isomer. The ^{1}H-NMR spectra (300 MHz, $CDCl_3$) of **9**, **10**, and **11** indicated that the former two were the *meso* forms and the latter the chiral, judging from the patterns of the signals due to the ring protons. The NOE experiment of the spectra of **9a** and **10a**, obtained by the conventional acetylation, clearly assigned, as expected, their structures to the (1,4/2,3,5) and (1,4,5/2,3) configurations, respectively (Scheme 3).

In order both to establish the configuration of **11** and to obtain other stereoisomers through chemical transformation, an acetate ion nucleophilic displacement reaction of the di-*O*-mesyl derivatives of **9** and **10** was carried out using potassium acetate in aqueous 2-methoxyethanol.[15][16] Only the dimesylate **12** from **9** underwent smoothly a displacement reaction, possibly through a

Scheme 2. For convenience, the formulas depict only one enantiomer of the respective racemates

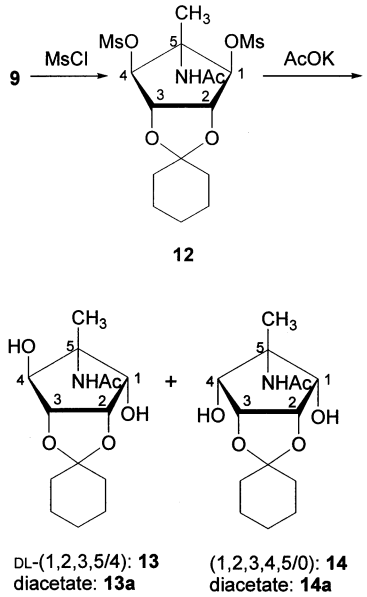


Scheme 3



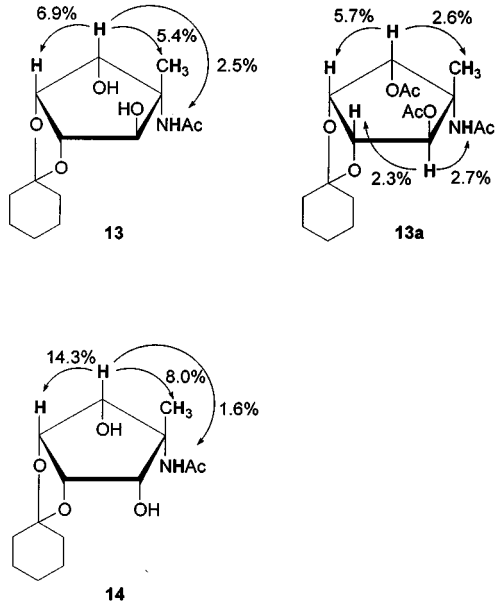
neighboring participation of the 5-acetamido group, giving the diols **13** and **14** in 55 and 5% yields, respectively. Their ^{1}H-NMR spectra showed that they were different from either **9**, **10**, or **11**, and indicated that **13** and **14** are chiral and *meso* forms, respectively. The ^{1}H-NMR spectra of the respective diacetates **13a** and **14a** also supported the above

Scheme 4



assumption. The configurations of **13** and **14** were finally established to be DL-(1,2,3,5/4) and (1,2,3,4,5/0) by the NOE experiment (Scheme 5). Consequently, compound **11** should have DL-(1,2,3/4,5) configuration.

Scheme 5



All stereoisomers **9**−**11**, **13** and **14** were deprotected by hydrolysis with 2 M hydrochloric acid for 2 h at 80°C, and the corresponding free bases **4**−**8** were isolated by chromatography on a column of Dowex 50W-X2 (H^+) resin with 4 M aqueous ammoniacal methanol as eluent and directly subjected to a biological assay[5] of inhibition toward six glycosidases: α- (Baker's yeast) and β-glucosidases (Almonds), α- (Green coffee beans) and β-galactosidases (*E. coli* and Bovin liver), and α-mannosidase (Jack beans). The free bases were further characterized by transforming them into the tetra-*N*,*O*-acetyl derivatives **4a**−**8a**.

Table 1. Inhibitory activity of compounds **4**−**8** against two glycosidases[a]

Compound	Inhibitory Activity (IC_{50}, M) β-Galactosidase (Bovin liver)	α-Mannosidase (Jack beans)
4	1.7×10^{-4}	NI
5	NI	NI
6	4.0×10^{-4}	NI
7	NI	8.3×10^{-5}
8	NI	5.6×10^{-5}

[a] NI: No inhibitory activity observed at less than 10^{-3} M.

It was demonstrated that compounds **7** and **8** possess a modest inhibitory activity against α-mannosidase, and interestingly, **4** and **6** are moderate inhibitors of bovine liver β-galactosidase (Table 1). The inhibitory potencies of the former two have good correlation with those of the parent aminocyclitols **2** and **3**, demonstrating that the *C*-methyl function itself and a possible conformational change caused by it seem not to interfere in binding between the inhibitor and the enzyme. The 4-amino-1,2,3-cyclopentanetriol core structure with *all-cis* configuration apparently plays an important role in exhibiting the inhibitory activity against α-mannosidase. The 2- and 3-OH groups in **7** and **8** overlap with two OH groups of the mannosyl cation[4]. The fact that **4** and the corresponding demethyl compound[5] do not possess any inhibitory activity against α-mannosidase may indicate that the 1-OH group assists the two hydroxy groups in binding to the enzyme and/or the amino group in employing as a cationic center.

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Experimental Section

Melting points: Mel-Temp capillary melting-point apparatus, uncorrected values. − IR: Jasco IR-810. − ^{1}H NMR: Jeol JNM GSX-270 f.t. (270 MHz) and Jeol JNM Lambda-300 (300 MHz); solvent $CDCl_3$, internal standard tetramethylsilane (TMS); D_2O, internal acetone; CD_3OD, internal acetone. − TLC: Silica Gel 60 GF (E. Merck, Darmstadt); detection by UV lamp and then by charring with concd. H_2SO_4. − Column chromatography: Silica Gel 60 KO70 (Katayama Chemical, Osaka) or Wakogel C-300 (silica gel, 300 Mesh, Wako Chemical, Osaka). − Organic solutions, after drying with anhydrous Na_2SO_4, were concentrated < 50°C at diminished pressure. The free aminocyclitols **4**−**8** were obtained as hydrochlorides, which were converted into the free bases by elution from a column of Dowex 50W X2 (H^+) resin with ammoniated methanol and directly subjected to bilogical assay, the methods of which were described in a previous paper[5].

Mixture of the 2,3-O-Cyclohexylidene Derivatives of 5-C-Methyl-5-nitro-1,2,3,4-cyclopentanetetrols: To a stirred solution of sodium metaperiodate (41.1 g, 0.192 mol) in water (200 ml) was added portionwise powdered DL-1,2-*O*-cyclohexylidene-*myo*-inositol[11]

(10.0 g, 0.038 mol) at 0−5°C, and then the mixture was stirred for 20 h at room temperature. After neutralization with sodium hydrogen carbonate, the mixture was extracted with ethyl acetate (150 ml × 3), and the extracts were dried and concentrated. The residual crude dialdehyde was dissolved in THF (80 ml) and nitroethane (5.0 ml, 0.070 mol) was added to it. To the stirred mixture was added dropwise DBU (15.7 ml, 0.10 mol) for 30 min at 0°C, and then it was stirred for 1 h at room temperature. After neutralization with acetic acid, the mixture was diluted with water (100 ml) and extracted with ethyl acetate (1 l × 3). The extracts were dried and concentrated to give a mixture of crude coupling products, which was roughly chromatographed on a column of silica gel (300 g) with acetone/toluene (1:9) to give a mixture (ca. 8.0 g) of crude nitro diols. − IR (neat): $\tilde{\nu}$ = 3300 cm^{-1} (OH), 1550 (NO_2).

Mixture of the 2,3-O-Cyclohexylidene Derivatives of 5-Acetamido-5-C-methyl-1,2,3,4-cyclopentanetetrols: The mixture (ca. 8.0 g) of the nitro diols was dissolved in ethanol (ca. 8 ml), and, after addition of acetic anhydride (4.13 ml, 1.5 equiv.), the solution was hydrogenated in the presence of Raney nickel T-4 (2 ml, suspended in ethanol) at a hydrogen pressure of 3 kg/cm^2 (Parr shaker-type apparatus) for 13 h at room temperature. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was treated with acetic anhydride (40 ml) in pyridine (80 ml) for about 12 h at room temperature. After treatment with methanol (10 ml), the mixture was concentrated. The residue was dissolved in ethyl acetate (1 l), and the solution was washed with 0.5 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The residual products were roughly eluted from a column of silica gel (500 g) with acetone/toluene (1:4) to give a mixture (ca. 5.8 g) of the tri-*N*,*O*-acetyl derivatives. − IR (neat): $\tilde{\nu}$ = 3280 cm^{-1} (NH), 1750 (ester), 1650 (amide).

2,3-O-Cyclohexylidene Derivatives **9**, **10** *and* **11** *of the Respective (1,4/2,3,5)-, (1,4,5/2,3)-, and* DL- (1,2,3/4,5)-5-Acetamido-5-C-methyl-1,2,3,4-cyclopentanetetrol: A 2.2 g portion of the above mixture was dissolved in methanol (20 ml) and the solution was treated with 1 M methanolic sodium methoxide (2 ml) for 2 h at room temperature. After neutralization with Amberlite IR 120B (H^+) resin, the mixture was concentrated and the residue was chromatographed on a column of silica gel (170 g) with acetone/toluene (1:3) to give in turn **11** (24 mg, 1% based on DL-1,2-*O*-cyclohexylidene-*myo*-inositol), **9** (652 mg, 16%), and **10** (410 mg, 10%) as crystals.

The *N*-acetyl derivatives **9**, **10**, and **11** were treated with acetic anhydride in pyridine for about 12 h at room temperature to give, after chromatography on silica gel with acetone/toluene (1:3) as eluent, the tri-*N*,*O*-acetyl derivatives **9a**, **10a**, and **11a** in 93%, 88%, and 81% yields, respectively.

9: M.p. 193−194°C (from EtOH), R_f = 0.50 (acetone/toluene, 1:1). − IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (NH and OH), 1640 (amide). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 3 H, CCH_3), 1.37−1.70 (m, 10 H, C_6H_{10}), 2.01 (s, 3 H, NAc), 4.01 (s, 2 H, 1 H, 4-H), 4.14 (br. d, 2 H, *J* = 2.9 Hz, 2 × OH), 4.40 (d, 2 H, *J* = 3.2 Hz, 2-H, 3-H), 6.18 (br. s, 1 H, NH). − $C_{14}H_{23}NO_5$ (285.4): calcd. C 58.92, H 8.12, N 4.91; found C 58.80, H 7.99, N 4.90.

9a: M.p. 196−198°C (from EtOH), R_f = 0.60 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3270 cm^{-1} (NH), 1750 (ester), 1650 (amide). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CCH_3), 1.35−1.83 (m, 10 H, C_6H_{10}), 1.88 (s, 3 H, NAc), 2.14 (s, 6 H, 2 × OAc), 4.53 (dd, 2 H, *J* = 2.6, *J* = 1.1 Hz, 2-H, 3-H), 5.54 (dd, 2 H, *J* = 2.6, *J* = 1.1 Hz, 1-H, 4-H), 6.14 (br. s, 1 H, NH). − $C_{18}H_{27}NO_7$ (369.4): calcd. C 58.52, H 7.37, N 3.79; found C 58.39, H 7.59, N 3.75.

10: M.p. 185−188°C (from EtOH), R_f = 0.44 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3320 cm^{-1} (NH, OH), 1650 (amide); − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27−1.71 (m, 10 H, C_6H_{10}), 1.47 (s, 3 H, C-CH_3), 2.05 (s, 3 H, NAc), 3.94 (br. s, 2 H, 1-H, 4-H), 4.31 (br. s, 2 H, 2 OH), 4.51 (dd, *J* = 2.2, *J* = 1.0 Hz, 2 H, 2-H, 3-H), 6.29 (br. s, 1 H, NH). − $C_{14}H_{23}NO_5$: calcd. C 58.92, H 8.12, N 4.91; found C, 58.66, H 8.07, N 4.90.

10a: M.p. 220−222°C (from EtOH), R_f = 0.60 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1} (NH), 1750 (ester), 1670 (amide); − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25−1.85 (m, 10 H, C_6H_{10}), 1.65 (s, 3 H, CCH_3), 1.96 (s, 3 H, NAc), 2.11 (s, 6 H, 2 × OAc), 4.60 (s, 2 H, 2-H, 3-H), 5.19 (s, 2 H, 1-H, 4-H), 5.68 (br. s, 1 H, NH). − $C_{18}H_{27}NO_7$: calcd. C 58.52, H 7.37, N 3.79; found C 58.71, H 7.37, N 4.04.

11: M.p. 173−175°C (from $CHCl_3$), R_f = 0.56 (acetone/toluene, 1:1). − IR (KBr): $\tilde{\nu}$ = 3440 cm^{-1} (NH), 1630 (amide); − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27−1.67 (m, 10 H, C_6H_{10}), 1.43 (s, 3 H, CCH_3), 2.01 (s, 3 H, NAc), 3.80 (br. s, 2 H, 1-H, 4-H), 4.46 (br. s, 2 H, 2-H, 3-H), 6.29 (br. s, 1 H, NH). − $C_{14}H_{23}NO_5$: calcd. C 58.92, H 8.12, N 4.91; found C 58.82, H 8.41, N 4.98.

11a: A syrup, R_f = 0.61 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3320 cm^{-1} (NH), 1750 (ester), 1650 (amide); − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23−1.89 (m, 10 H, C_6H_{10}), 1.39 (s, 3 H, CCH_3), 1.92 (s, 3 H, NAc), 2.14 (s, 6 H, 2 × OAc), 4.78 (dd, *J* = 4.4, *J* = 2.2 Hz, 2 H, 2-H, 3-H), 5.27 (br. s, 1 H, NH), 5.71 (dd, *J* = 4.4, *J* = 2.2 Hz, 2 H, 1-H, 4-H). − $C_{18}H_{27}NO_7$: calcd. C 58.52, H 7.37, N 3.79; found C 58.72, H 7.63, N 3.94.

2,3-O-Cyclohexylidene Derivative **12** *of (1,4/2,3,5)-5-Acetamido-1,4-di-O-mesyl-5-C-methyl-1,2,3,4-cyclopentanetetrol:* To a solution of **9** (0.501 g, 1.75 mmol) in pyridine (5 ml) was added methanesulfonyl chloride (815 µl, 10.5 mmol) at 0°C, and the mixture was stirred for 3 h at room temperature. The mixture was concentrated and the residue was dissolved in ethyl acetate (150 ml) and the solution was washed with water (40 ml × 2), dried, and concentrated to give a syrupy dimesylate **12**. A small portion of the product was purified by chromatography on silica gel with acetone:toluene (1:3), R_f = 0.44 (acetone/toluene, 1:2). − IR (neat): $\tilde{\nu}$ = 3390 cm^{-1} (NH), 1660 (amide), 1170 (mesyl). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 3 H, CCH_3), 1.40−1.90 (m, 10 H, C_6H_{10}), 1.99 (s, 3 H, NAc), 3.12 (s, 6 H, 2 × SO_2CH_3), 4.65 (dd, *J* = 3.2, *J* = 1.5 Hz, 2 H, 2-H, 3-H), 5.38 (br. s, 1 H, NH), 5.89 (dd, *J* = 3.2, *J* = 1.5 Hz, 2 H, 1-H, 4-H). − This compound was without further purification used in the next reaction.

2,3-O-Cyclohexylidene Derivatives **13** *and* **14** *of the Respective* DL-*(1,2,3,5/4)- and (1,2,3,4,5/0)-5-acetamido-5-C-methyl-1,2,3,4-cyclopentanetetrols:* The crude mesylate **12** (0.77 g) obtained above was dissolved in aqueous 90% 2-methoxyethanol (30 ml) and, after addition of potassium acetate (1.7 g), the mixture was heated at reflux temperature for 2 d. The mixture was concentrated and the residue was chromatographed on a silica gel column (30 g) with acetone/toluene (1:2) to give **13** (0.28 g, 56%) and **14** (24 mg, 5%).

Compound **13** and **14** were converted conventionally into the di-*O*-acetyl derivatives **13a** and **14a** in 96% and 84% yields, respectively.

13: Syrup, R_f = 0.24 (acetone/toluene, 1:2). − IR (neat): $\tilde{\nu}$ = 3420 cm^{-1} (NH, OH), 1650 (amide). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, CCH_3), 1.39−1.76 (m, 10 H, C_6H_{10}), 2.03 (s, 3 H, NAc), 3.02 (br. d, *J* ≈ 2 Hz, 1 H, 1-OH), 3.83 (d, *J* = 5.1 Hz, 1 H, 1-H), 4.31 (d, *J* = 3.9 Hz, 1 H, 4-H), 4.52 (ddd, *J* = 7.6, *J* = 3.9, *J* = 0.9 Hz, 1 H, 3-H), 4.69 (dd, *J* = 7.6, *J* = 5.1 Hz, 1 H, 2-H), 5.24 (br. s, 1 H, 4-OH), 6.63 (br. s, 1 H, NH). −

$C_{14}H_{23}NO_5$ (285.3): calcd. C, 58.92, H 8.12, N 4.91; found C 58.91, H 8.12, N 5.02.

13a: Syrup, R_f = 0.62 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1} (NH), 1750 (ester), 1680 (amide). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32−1.69 (m, 10 H, C_6H_{10}), 1.42 (s, 3 H, CCH_3), 1.94 (s, 3 H, NAc), 2.18 and 2.12 (2 s, 3 H each, 2 × OAc), 4.47 (dd, *J* = 6.7 Hz, *J* = 2.0 Hz, 1 H, 3-H), 4.80 (dd, *J* = 6.7, *J* = 5.1 Hz, 2-H), 5.13 (d, *J* = 5.1 Hz, 1 H, 1-H), 5,46 (d, *J* = 2.0 Hz, 1 H, 4-H), 6.43 (br. s, 1 H, NH). − $C_{18}H_{27}NO_7$ (369.4): calcd. C 58.52, H 7.37, N 3.79; found C 58.32, H 7.35, N 3.82.

14: M.p. 177−179°C (from ethanol), R_f = 0.15 (acetone/toluene, 1:2). − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1} (NH, OH), 1650 (amide). − ^1H (300 MHz, $CDCl_3$): δ = 1.39−1.69 (m, 10 H, C_6H_{10}), 1.44 (s, 3 H, CCH_3), 2.03 (s, 3 H, NAc), 3.76 (d, *J* = 3.7, *J* = 1.7 Hz, 2 H, 1-H, 4-H), 4.61 (d, *J* = 3.7, *J* = 1.7 Hz, 2 H, 2-H, 3-H), 6.38 (br. s, 3 H, NH). − $C_{14}H_{23}NO_5$: calcd. C 58.92, H 8.12, N 4.91; found: C 58.97, H 8.16, N 5.06.

14a: Syrup, R_f = 0.57 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (NH), 1750 (ester), 1680 (amide). − ^1H NMR (270 MHz, $CDCl_3$): δ = 1.40−1.77 (m, 10 H, C_6H_{10}), 1.65 (s, 3 H, CCH_3), 1.98 (s, 3 H, NAc), 2.17 (s, 6 H, 2 × OAc), 4.74 (br. s, 4 H, 1-H, 2-H, 3-H, 4-H), 6.19 (br. s, 1 H, NH). − $C_{18}H_{27}NO_7$: calcd. C 58.52, H 7.37, N 3.79; found C 58.39, H 7.23, N 3.85.

Preparation of 5-Amino-5-C-methyl-1,2,3,4-cyclopentanetetrols **4**−**8** *and the Penta-N,O-acetyl Derivatives* **4a**−**8a** *from* **9**−**11**, **13**, *and* **14**: Compounds **9**−**11**, **13**, and **14** were treated with 2 M hydrochloric acid at 80°C for 2 h, and then the products were chromatographed on a column of Dowex 50W-X2 (H^+) resin with 14 M aqueous ammonia and methanol (1:13) to give the free bases **4**−**8** in almost quantitatively.

Compounds **4**, **5**, **6**, **7**, and **8** were treated conventionally with acetic anhydride in pyridine for 15 h at room temp. and then the products were chromatographed on a silica gel column with acetone/toluene (1:3) to give the penta-*N*,*O*-acetyl derivatives **4a**, **5a**, **6a**, **7a**, and **8a** in 80, 90, 85, 72, and 83% yields, respectively.

(1,4/2,3,5)-5-Amino-5-C-methyl-1,2,3,4-cyclopentanetetrol (**4**): Syrup, R_f = 0.45 (acetic acid/H_2O/CH_3CN, 1:4:8). − ^1H NMR (300 MHz, D_2O): δ = 0.95 (s, 3 H, CCH_3), 3.67 (dd, *J* = 4.8, *J* = 1.6 Hz, 2 H, 2-H, 3-H), 3.85 (dd, *J* = 4.8, *J* = 1.6 Hz, 2 H, 1-H, 4-H).

Penta-N,O-acetyl Derivative **4a**: M.p. 257−259°C (from EtOH), R_f = 0.61 (acetone/toluene, 1:1). − IR (KBr): $\tilde{\nu}$ = 3440 cm^{-1} (NH), 1750 (ester), 1650 (amide). − ^1H NMR (270 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, CCH_3), 1.93 (s, 3 H, NAc), 2.07 and 2.14 (2 s, each 6 H, 4 × OAc), 5.20 (dd, *J* = 4.4, *J* = 1.5 Hz, 2 H, 1-H, 4-H or 2-H, 3-H), 5.62 (dd, *J* = 4.4, *J* = 1.5 Hz, 2 H, 2-H, 3-H or 1-H, 4-H), 6.29 (br. s, 1 H, NH). − $C_{16}H_{23}NO_9$ (373.4) calcd. C 51.47, H 6.21, N 3.75; found C 51.43, H 6.35, N 3.79.

(1,4,5/2,3)-5-Amino-5-C-methyl-1,2,3,4-cyclopentanetetrol (**5**): Syrup, R_f = 0.53 (acetic acid/H_2O/CH_3CN, 1:4:8). − ^1H NMR (300 MHz, D_2O): δ = 1.18 (s, 3 H, CCH_3), 3.61 (dd, *J* = 4.6, *J* = 1.7 Hz, 2 H, 2-H, 3-H), 3.96 (dd, *J* = 4.6, *J* = 1.7 Hz, 2 H, 1-H, 4-H).

Penta-N,O-acetyl Derivative **5a**: Syrup, R_f 0.61 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 1750 (ester), 1680 (amide). − ^1H NMR (300 MHz, $CDCl_3$) δ = 1.71 (s, 3 H, CCH_3), 2.00 (s, 3 H, NAc), 2.12 and 2.14 (2 s, each 6 H, 4 × OAc), 5.24 (d, *J* = 3.9, *J* = 1.2 Hz, 2 H, 1-H, 4-H or 2-H, 3-H), 5.32 (d, *J* = 3.9, *J* = 1.2 Hz, 2 H, 2-H, 3-H or 1-H, 4-H), 5.57 (br. s, 1 H, NH). − $C_{16}H_{23}NO_9$: calcd. C 51.47, H 6.21, N 3.75; found C 51.85, H 6.60, N 4.05.

DL-(1,2,3/4,5)-5-Amino-5-C-methyl-1,2,3,4-cyclopentanetetrol (**6**): Syrup, R_f = 0.55 (acetic acid/H_2O/CH_3CN, 1:4:8). − IR (neat): $\tilde{\nu}$ = 3420 cm^{-1} (NH_2, OH). − ^1H NMR (300 MHz, CD_3OD) δ = 1.19 (s, 3 H, CCH_3), 3.68 (d, *J* = 5.0 Hz, 1 H, 1-H or 4-H), 3.69 (d, *J* = 7.1 Hz, 1 H, 4-H or 1-H), 3.81 (dd, *J* = 5.9, *J* = 7.1 Hz, 1 H, 2-H or 3-H), 4.07 (dd, *J* = 5.5 Hz, 1 H, 3-H or 2-H).

Penta-N,O-acetyl Derivative **6a**: Syrup, R_f = 0.56 (acetone:toluene, 1:1). − IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1} (NH), 1750 (ester), 1670 (amide). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CCH_3), 1.98 (s, 3 H, NAc), 2.03, 2.08, 2.11, and 2.12 (4 s, each 3 H, 4 × OAc), 5.21 (dd, *J* = 3.5, *J* = 1.5 Hz, 1 H, 2-H or 3-H), 5.37 (br. s, 1 H, NH), 5.60 (d, *J* = 1.8 Hz, 1 H, 1-H or 4-H), 5.62 (d, *J* = 1.5 Hz, 1 H, 4-H or 1-H), 6.12 (dd, *J* = 3.5, *J* = 1.8 Hz, 1 H, 3-H or 2-H). − $C_{16}H_{23}NO_9$: calcd. C 51.47, H 6.21, N 3.75; found C 51.76, H 6.47, N 3.94.

DL-(1,2,3,5/4)-5-Amino-5-C-methyl-1,2,3,4-cyclopentanetetrol (**7**): Syrup, R_f = 0.46 (acetic acid/H_2O/CH_3CN, 1:4:8). − IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (NH_2, OH). − ^1H NMR (300 MHz, CD_3OD): δ = 1.04 (s, 3 H, CCH_3), 3.58 (d, 1 H, 1-H or 4-H), 3.70−3.76 (m, 2 H, 3-H, 4-H or 1-H, 2-H), 3.98 (dd, *J* = 4.8 Hz, 1 H, 2-H or 3-H).

Penta-N,O-acetyl Derivative **7a**: Syrup, R_f = 0.46 (acetone/toluene, 1:1). − IR (neat): $\tilde{\nu}$ = 3390 cm^{-1} (NH), 1750 (ester), 1660 (amide). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CCH_3), 1.95 (s, 3 H, NAc), 2.02, 2.07, 2.11, and 2.18 (4 s, each 3 H, 4 × OAc), 5.23 (dd, *J* = 7.2, *J* = 6.0 Hz, 1 H, 2-H or 3-H), 5.46 (d, *J* = 6.0 Hz, 1 H, 1-H or 4-H), 5.51 (dd, *J* = 7.2, *J* = 4.6 Hz, 1 H, 3-H or 2-H), 5.62 (d, *J* = 4.6 Hz, 1 H, 4-H or 1-H), 6.53 (br. s, 1 H, NH). − $C_{16}H_{23}NO_9$: calcd. C 51.47, H 6.21, N 3.75; found C 51.21, H 6.18, N 4.10.

(1,2,3,4,5/0)-5-Amino-5-C-methyl-1,2,3,4-cyclopentanetetrol (**8**): Syrup, R_f = 0.49 (acetic acid/H_2O/CH_3CN, 1:4:8). − IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (NH_2, OH). − ^1H NMR (300 MHz, CD_3OD): δ = 1.18 (s, 3 H, CCH_3), 3.56 (dd, *J* = 4.0, *J* = 2.0 Hz, 2 H, 1-H, 4-H or 2-H, 3-H), 3.97 (dd, *J* = 2.0, *J* = 4.0 Hz, 2 H, 2-H, 3-H or 1-H, 4-H).

Penta-N,O-acetyl Derivative **8a**: Syrup, R_f = 0.23 (acetone/toluene, 1:2). − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1} (NH), 1750 (ester), 1680 (amide). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.65 (s, 3 H, CCH_3), 2.01 (s, 3 H, NAc), 2.05 and 2.13 (2 s, each 6 H, 4 × OAc), 5.21 (dd, *J* = 3.9, *J* = 2.0 Hz, 2 H, 1-H, 4-H or 2-H, 3-H), 5.40 (dd, *J* = 3.9, *J* = 2.0 Hz, 2 H, 2-H, 3-H or 1-H, 4-H), 5.89 (br. s, 1 H, NH). − $C_{16}H_{23}NO_9$: calcd. C 51.47, H 6.21, N 3.75; found C 51.55, H 6.22, N 3.83.

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