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Synthesis and Biological Evaluation of Potent Glycosidase Inhibitors: *N*-Phenyl Cyclic Isourea Derivatives of 5-Amino- and 5-Amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols

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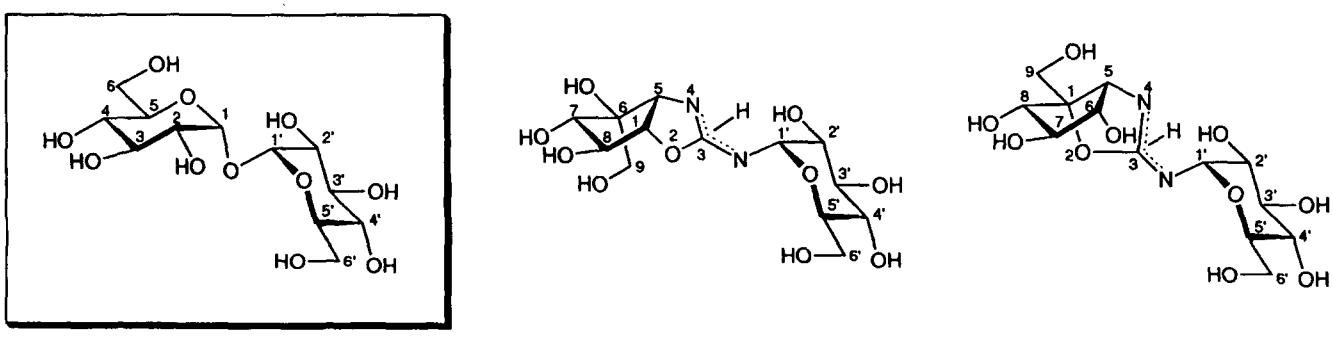
Abstract—Twenty-four stereoisomers of 5-amino- and 5-amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols and twenty-six of the corresponding *N*-phenyl cyclic isourea derivatives were assayed for inhibitory activity against six glycosidases. Among them, as has been expected for structure mimics of putative transition state glucopyranosyl cation for glycoside hydrolysis, 1L-(1,2,4,5/3)-5-amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraol **L-4** and its *N*-phenyl cyclic isourea derivative ***S*-19** were shown to have strong inhibitory activity, IC_{50} 4×10^{-7} and 7.6×10^{-9} M, respectively, against baker's yeast α-glucosidase. It has been analogously explained that compounds ***R,S*-22** and ***R,S*-26** possessed high inhibitory potency against *Escherichia coli* and bovine liver β-galactosidases, respectively. © 1997 Elsevier Science Ltd.

Introduction

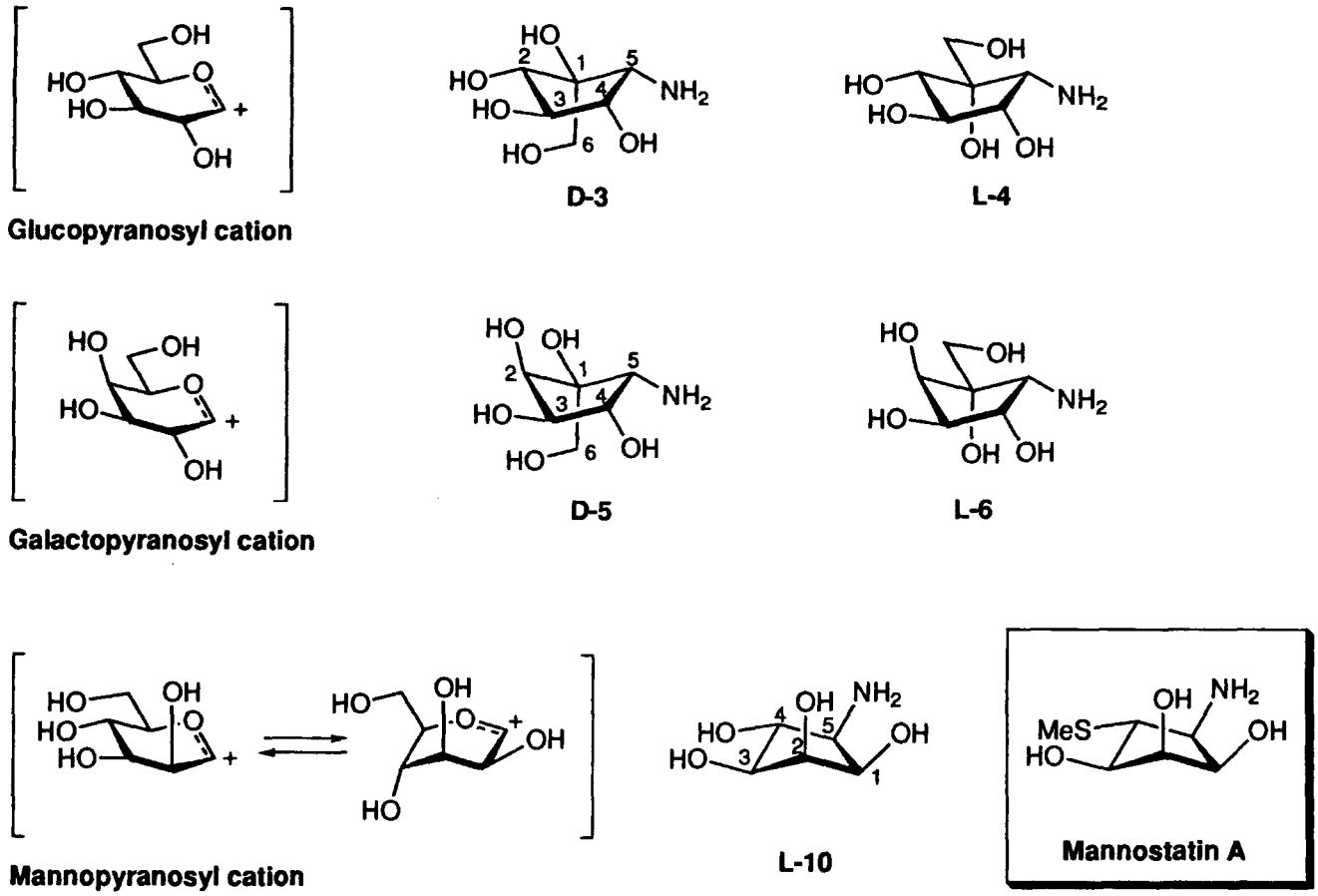
We preliminarily reported[1] that studies[2–5] on structure and inhibitory activity relationships of trehalase inhibitor trehazolin[6] **1** led to the finding of a new type of potent glycosidase inhibitors, *N*-phenyl cyclic-isourea derivatives of 5-amino- and 5-amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols.[7] On the basis of the structural feature of **1**, the aminocyclitol moiety combined with cyclic isourea function was considered to correspond with one of the two α-D-glucopyranose residues as a mimic of substrate α,α-trehalose (Scheme 1). In fact, the topology of the hydroxyl and hydroxymethyl groups of the cyclitol moiety has been shown[2,3,5] to play an important role for exhibiting the inhibitory activity. Furthermore, the cyclic isourea part would constitute the charge distribution part for binding the active site of the enzyme. These considerations stimulated the development of new glycosidase inhibitors composed of modified aminocyclopentanepolyols. Inhibitory potency of 5-amino and 5-amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols have therefore been explained by their structural features, mimicking the postulated glycosyl cations formed during hydrolysis of glycosides (Scheme 2).[8]

In this paper, a total of 24 stereoisomers (**3–16** (10 enantiomeric pairs and four *meso*)) of 5-amino-1,2,3,4-cyclopentanetetraol and its *C*-(hydroxymethyl) derivatives (Scheme 3), and 26 (**17–30** (12 enantiomeric pairs and two racemic)) of their *N*-phenyl cyclic isourea derivatives (Scheme 4) were subjected to biological assay using six glycosidases (Tables 1 and 2). It has been demonstrated that very strong inhibitory activity against α-glucosidase (baker's yeast), observed for some stereoisomers, e.g. 1L-(1,2,4,5/3) **L-4** and its enantiomer,[5] could be well understood by attributing to their



α,α-Trehalose **Trehazolin: 1** **Epitrehazolin: 2**

Scheme 1. α,α-Trehalose and trehalase inhibitors trehazolin **1** and epitrehazolin **2**.



Scheme 2. Comparison of some 5-amino- and 5-amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentantetraols, and putative glycosyl cations in glycoside hydrolysis.

close mimicking of the glucopyranosyl cation (Scheme 2). The structure of compound **D-5** that showed moderate potency against β-galactosidases also seemed to bear a striking resemblance to galactopyranosyl cation structure. However, concerning inhibitory potency against α-mannosidase, structural correlation between inhibitors **L-10** and mannostatin A,[9] and flexible mannopyranosyl cation seemed to be not so rational as have been observed for those of α-glucosidase and β-galactosidase.

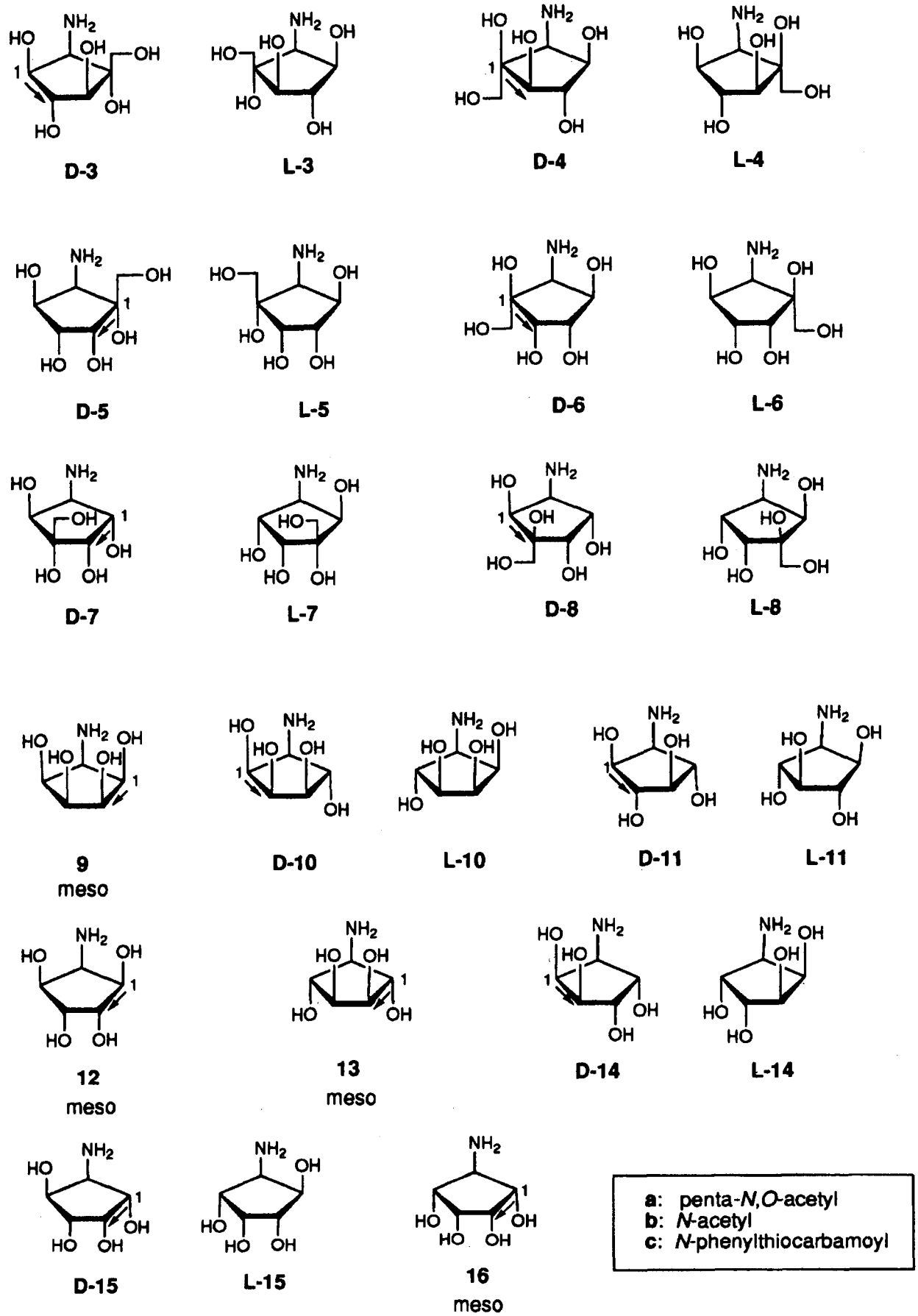
Results and Discussion

Synthesis of new 5-amino-1,2,3,4-cyclopentanetetraols

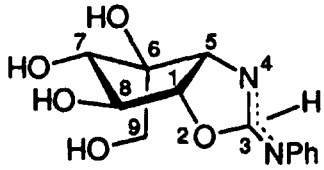
Seven new 5-amino-1,2,3,4-cyclopentanetetraol isomers (three pairs of chiral and one *meso* isomers) were prepared and characterized (Scheme 5). The *meso* isomer was needed to verify the structures of new chiral compounds obtained here.

Thus, the 2,3-*O*-cyclohexylidene derivative[10,11] **D-31** of 5-acetamido-1-*O*-(β-D-glucopyranosyl)-1,2,3,4-cyclopentanetetraol was converted into the mesylate **D-32** (91%), which was substituted with an acetate ion through S_N2 reaction by treatment with excess sodium acetate in aq DMF at 100 °C, followed by acetylation with acetic anhydride in pyridine, giving the acetate **D-33** (96%). Hydrolysis of **D-33** with 4 M hydrochloric acid at 90 °C for two days and purification by a column of Dowex 50W-X2 (H^+) resin with 1 M aq ammonia with an eluent gave 1D-(1,2,3,5/4)-5-amino-1,2,3,4-cyclopentanetetraol **D-10** (92%) as a syrup. The free base was converted into the penta-*N*,*O*-acetyl derivative **D-10a**, the structure of which was verified by comparing with an authentic sample[12] of its racemate. Similarly, the enantiomer **L-10** was prepared from **L-31** in good yield via the mesylate **L-32** and the acetate **L-33**.

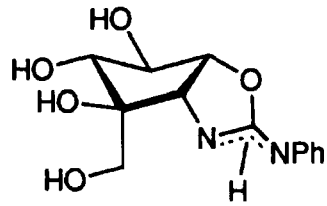
Optically resolved *O*-cyclohexylidene-*N*,*O*-isopropylidene derivative[2] **D-34** of 1D-(1,2,3/4,5)-5-acetamido-1,2,3,4-cyclopentanetetraol was deprotected with aq acetic acid and the resulting *N*-acetyl derivative **D-15b** was treated with 2,2-dimethoxypropane in DMF in the presence of *p*-toluenesulfonic acid (PTSA) for two days at 70 °C to give two diisopropylidene derivatives **D-35** (22%) and **D-36** (34%). Their structures were determined by inversion of the configurations of the 3-hydroxyl groups through the triflates. Thus, **D-35** was converted into the triflate **D-37**, which without purification was treated with potassium acetate in benzene in the presence of 18-crown-6 ether to afford through S_N2 reaction the acetate **D-38**. Treatment of **D-38** with 2 M



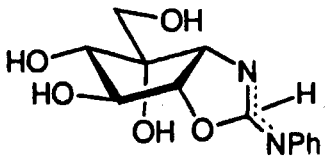
Scheme 3. Structural formulae and numbering system of 5-amino-1,2,3,4-cyclopentanetetraols and derivatives employed in the present study.



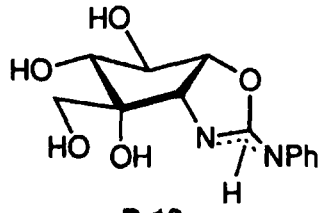
S-17



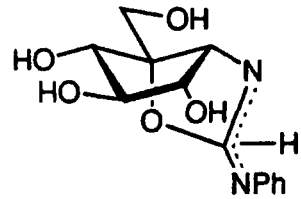
R-17



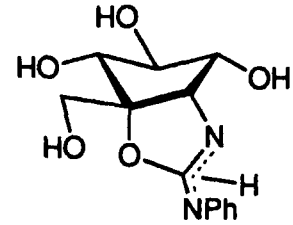
S-18



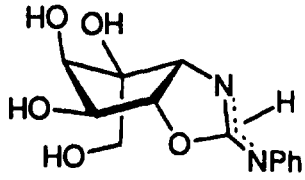
D-18



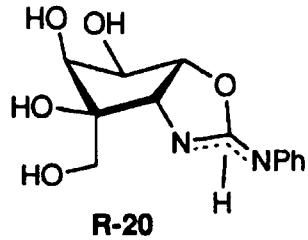
S-19



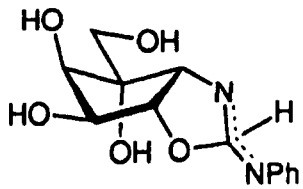
R-19



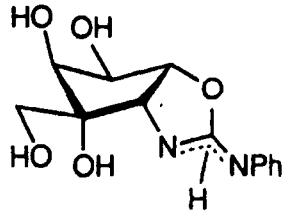
S-20



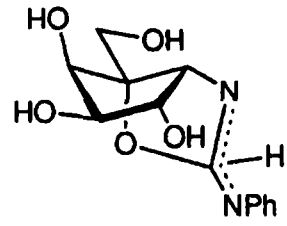
R-20



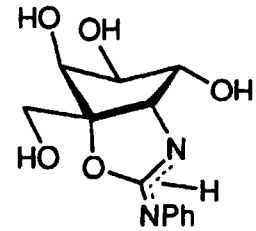
S-21



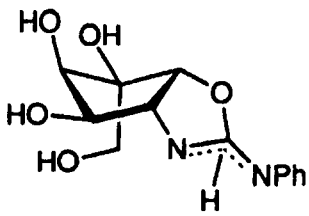
R-21



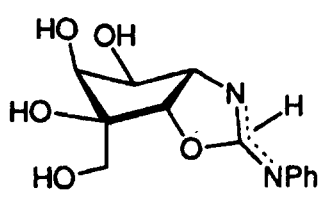
S-22



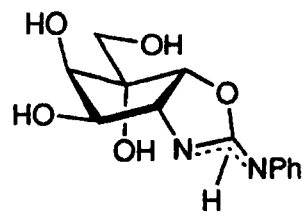
R-22



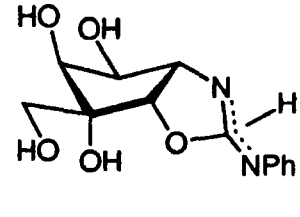
R-23



S-23

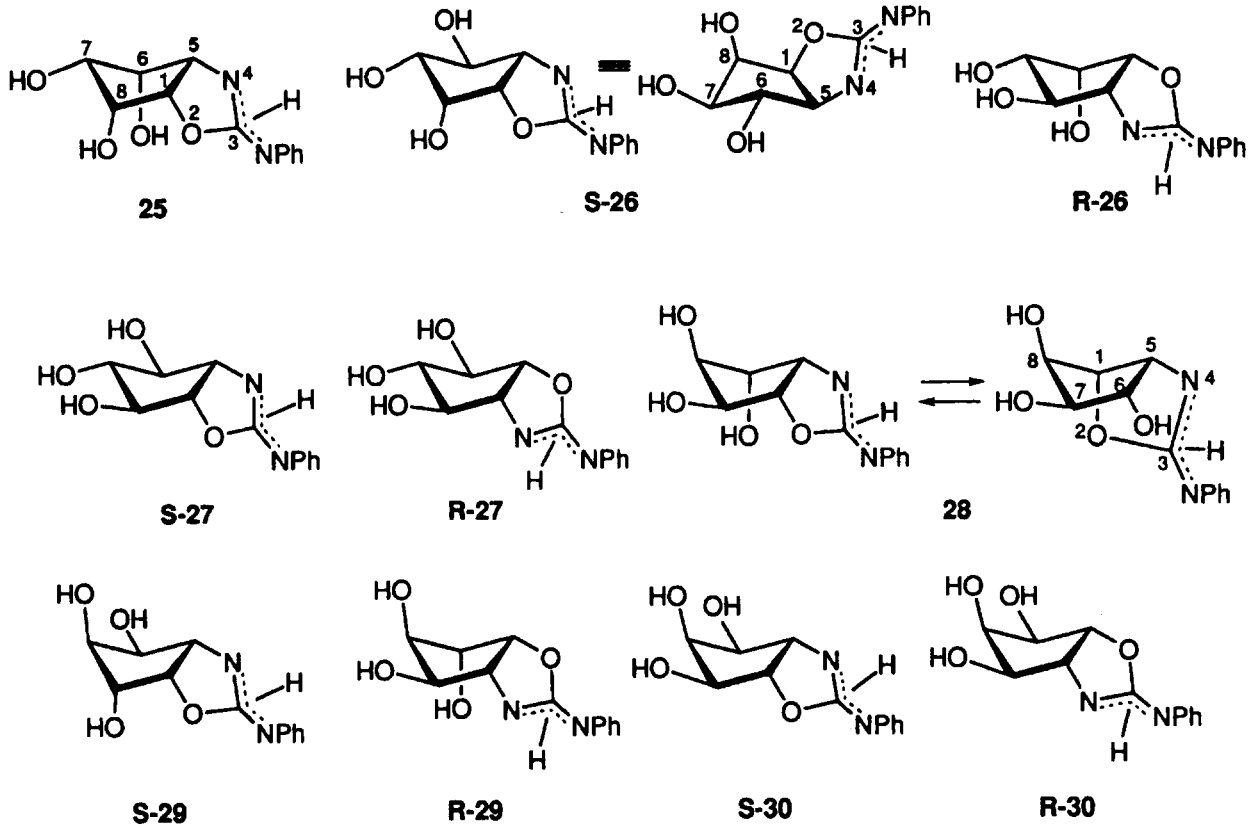


R-24



S-24

Scheme 4. Structural formulae and numbering system of the *N*-phenyl cyclic isourea derivatives employed in the present study.



Scheme 4. continued.

hydrochloric acid followed by acetylation gave a chiral penta-*N*,*O*-acetyl derivative **D-14a** quantitatively. Similar acid hydrolysis of **D-14a** and subsequent purification by a resin column gave the free base **D-14** quantitatively. On the other hand, **D-36** was converted into known *meso* isomer[12] **12a** quantitatively through sulfonylation (→the triflate **D-39**), direct substitution by an acetate ion (→the acetate **L-40** (66%)), and deprotection followed by acetylation. Therefore, on the basis of these transformations, the structures of **12a** and **D-14a**, combined with those of **D-35** and **D-36**, were clearly verified.

Similarly, starting from enantiomeric **L-34**, compound **L-14** was synthesized.

1D- **D-15** and 1L-(1,2,3/4,5)-5-amino-1,2,3,4-cyclopentanetetraols **L-15** were prepared by hydrolysis of the respective acetylmandelyl esters[2] **D-41** and **L-41** with hydrochloric acid, followed by purification by a column of acidic resin. The structures of **D-**, **L-15** were established by transforming them into the penta-*N*,*O*-acetyl derivatives, which were compared with the known racemate[12] **DL-15a**.

Synthesis of 5-amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols

Two pairs of new chiral 5-amino-2-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols were synthesized (Scheme 6).

Oxidation of compound **D-35** with PCC in dichloromethane at 0 °C gave the ketone, which was directly treated with salt-free $Ph_3P{=}CH_2$ in THF at −15 °C for 3 h to produce the *exo*-methylene derivative **L-42** (70%). Removal of the protecting groups with aq acetic acid, followed by conventional acetylation, afforded tetra-*N*,*O*-acetyl derivative **L-43** (96%). Hydroxylation of **L-43** with osmium tetraoxide in acetone in the presence of NMO followed by conventional acetylation afforded two penta-*N*,*O*-acetyl derivatives **D-7a** (36%) and **D-8a** (55%). Hydrolysis of **D-7a** and **D-8a** with 2 M hydrochloric acid at 80 °C and purification by a column of acidic resin gave the respective free bases **D-7** and **D-8** in good yields. Their structures were finally established on the basis of ^{1}H NMR spectra, especially, by NOE experiment as shown in Scheme 7. Similarly, the respective enantiomers **L-7** and **L-8** were prepared starting from compound **L-35**.

Alternatively, osmium oxidation of **L-42** afforded two diols which, without separation, were treated with hydrochloric acid followed by acetylation to give **D-7a** (84%) and **D-8a** (12%). Interestingly, selectivity of osmium oxidation has been shown to be rather controlled by the adjacent *O*-protecting groups.

Preparation of *N*-phenyl cyclic isoureas

Preparation of the *N*-phenyl cyclic isoureas[13] (**17–30**) was conventionally carried out[2] by treatment of the thioureas (**3c–12c**, **14c**, **15c**), obtained from 5-amino-

Table 1. Inhibitory activity of 5-amino- and 5-amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols against six glycosidases

	IC_{50} (M)					
Compound	**α-glucosidase[a] (baker's yeast)**	**β-glucosidase[b] (almonds)**	**α-mannosidase[c] (Jack beans)**	**α-galactosidase[d] (*E. coli*)**	**β-galactosidase[e] (*E. coli*)**	**β-galactosidase[e] (Bovin liver)**
D-3	2.6×10^{-4}	2.1×10^{-5}	—[f]	—	—	4.2×10^{-4}
L-3	—	—	—	—	—	—
D-4	1.6×10^{-5}	—	—	—	—	—
L-4	4.0×10^{-7}	2.9×10^{-5}	—	—	—	3.6×10^{-4}
D-5	—	1.0×10^{-5}	—	—	—	3.6×10^{-5}
L-5	—	2.1×10^{-4}	—	—	—	—
D-6	—	—	—	—	—	—
L-6	—	5.6×10^{-4}	—	—	—	—
D-7	—	—	—	—	—	—
L-7	—	—	5.6×10^{-4}	—	—	—
D-8	—	—	—	—	—	—
L-8	—	—	—	—	—	—
9	—	—	2.9×10^{-5}	—	—	—
D-10	—	8.4×10^{-5}	1.1×10^{-4}	—	7.8×10^{-6}	4.7×10^{-5}
L-10	—	—	1.0×10^{-5}	—	1.3×10^{-4}	—
D-11	—	1.7×10^{-4}	—	—	—	6.1×10^{-4}
L-11	—	—	—	—	—	—
12	—	1.2×10^{-5}	—	—	—	2.4×10^{-4}
13	—	6.7×10^{-4}	—	—	—	3.4×10^{-4}
D-14	—	5.0×10^{-5}	—	—	—	—
L-14	—	—	2.5×10^{-4}	—	—	—
D-15	6.7×10^{-4}	1.3×10^{-4}	—	—	2.7×10^{-4}	1.8×10^{-4}
L-15	—	—	—	—	—	—
16	—	—	—	—	—	—

(a) 0.66 mM *p*-nitrophenyl α-D-glucopyranoside, 0.1 M potassium phosphate buffer pH 6.8.[16] (b) 0.33 mM *p*-nitrophenyl β-D-glucopyranoside, 0.1 M acetate buffer, pH 5.0.[17] (c) 2.0 mM *p*-nitrophenyl α-D-mannopyranoside, 0.1 M acetate buffer, pH 4.5.[18] (d) 9.9 mM *p*-nitrophenyl α-D-galactopyranoside, 0.1 M potassium phosphate buffer, pH 6.5.[19] (e) 2.0 mM *o*-nitrophenyl β-D-galactopyranoside, 0.1 M 2-mercaptoethanol, 50 mM potassium phosphate buffer including 1.3 mM $MgCl_2$, pH 7.3.[20] (f) No inhibitory activity observed at less than 6.7×10^{-4} M. (g) No inhibitory activity observed at less than 4.0×10^{-4} M.

and 5-amino-*C*-(hydroxymethyl)-1,2,3,4-cylopentanetetraols and phenylisothiocyanate in the usual manner, with yellow mercuric(II) oxide (3 molar equiv) in acetone:ethanol (2:1) at room temperature, and the products were isolated and purified by a column of Dowex 50W-X2 (H^+) resin with ammoniacal methanol as eluate (Scheme 8). The structures of the isoureas were confirmed on the basis of the IR and ^1H NMR spectra. In the cases of cyclization of **D, L-4c** and **D, L-6c**, where two positional isomers of the cyclic isoureas were possibly formed, the products were separated by a silica gel chromatography with ethanol:toluene as an eluent. The resulting free bases were directly subjected to bioassay. The isourea rings composed of the tertiary hydroxyls are more stable than those of the secondary, and the less stable isomers tend to be interconvertible to the stable isomers on standing. Similar phenomena have been observed for trehazolin analogues.[2,3,5]

Biological assay against six glycosidases

Comparison of the structures of aminocyclitol[2,14] **D-3** derived from trehazolin **1** and its 1-epimer **L-4** with a flattened half-chair pyranose-structure postulated for glucopyranosyl cation suggested that the latter seemed to be more matching as a structure mimic. As has been expected, concerning inhibitory activity against α-glucosidase (baker's yeast), compounds **D-3** and **L-4** showed IC_{50} 2.6×10^{-4} M and 4×10^{-7} M, respectively (Table 1). It is interesting of note that the enantiomer **D-4** still possessed weak activity IC_{50} 1.6×10^{-5} M. However, in contrast, epitrehazolin[5] **2**, the aminocyclopentane part of which was composed of **L-4**, decreased its inhibitory activity against silkworm trehalase by about sixfold compared to **1**, demonstrating conceivably that the binding site and shape for glucose residue might be somewhat unalike for the cases of baker's yeast α-glucosidase and trehalase. Although the 1-de(hydroxymethyl) derivatives **D, L-11** of **D, L-3** seemed to resemble a glucopyranosyl cation, adopting the envelop conformation with three OH groups in pseudo-equatorial positions, they were demonstrated to lack the activity completely.

Incorporation of *N*-phenyl cyclic isourea function into the aminocyclitols, in order to change the positive charge distribution part of inhibitors, resulted generally in great improvement of their inhibitory potency (Table 2), showing that the cyclic isourea parts, conceivably, in addition to the stacking effect of the phenyl group, play a very important role in binding the active site of enzymes. Especially, the *N*-phenyl cyclic isourea derivatives ***S*-18** and ***S*-19**,[15] a pair of the positional isomers obtained from **L-4** , have been demonstrated to possess very strong potency against baker's yeast α-glucosidase.

Table 2. Inhibitory activity of *N*-phenyl cyclic isourea derivatives against six glycosidases

Compound	IC_{50} (M)					
	α-glucosidase[a] (baker's yeast)	β-glucosidase[b] (almonds)	α-mannosidase[c] (Jack beans)	α-galactosidase[d] (*E. coli*)	β-galactosidase[e] (*E. coli*)	β-galactosidase[e] (Bovin liver)
***S*-17**	1.3×10^{-6}	—[g]	1.9×10^{-4}	—	—	—
***R*-17**	1.8×10^{-4}	—	7.9×10^{-5}	—	—	3.6×10^{-4}
***S*-18**	2.9×10^{-8}	—	—	—	—	1.5×10^{-4}
***R*-18**	2.3×10^{-6}	1.1×10^{-5}	—	—	—	5.2×10^{-5}
***S*-19**	7.6×10^{-9}	—	—	—	—	3.0×10^{-6}
***R*-19**	1.0×10^{-6}	4.8×10^{-5}	—	—	—	1.9×10^{-6}
***S*-20**	—	5.0×10^{-5}	—	—	—	5.8×10^{-5}
***R*-20**	—	7.2×10^{-5}	—	—	—	8.6×10^{-6}
***S*-21**	—	2.6×10^{-4}	—	3.6×10^{-4}	—	3.6×10^{-5}
***R*-21**	—	4.8×10^{-5}	—	1.2×10^{-4}	—	2.4×10^{-5}
***S*-22**	—	2.1×10^{-4}	—	—	—	2.9×10^{-6}
***R*-22**	—	4.9×10^{-6}	—	—	—	5.7×10^{-7}
***S*-23**	—	—	—	—	—	—
***R*-23**	—	—	—	—	—	—
***S*-24**	—	—	—	4.6×10^{-5}	—	—
***R*-24**	—	—	—	—	—	—
25	1.7×10^{-4}	3.0×10^{-4}	—	—	4.2×10^{-5}	—
***S*-26**	—	2.2×10^{-6}	—	—	2.0×10^{-7}	6.0×10^{-5}
***R*-26**	8.2×10^{-5}	6.4×10^{-6}	—	4.0×10^{-4}	9.4×10^{-7}	2.5×10^{-4}
***S*-27**	—	1.7×10^{-5}	—	—	—	—
***R*-27**	—	2.4×10^{-4}	—	—	—	—
28	—	2.4×10^{-4}	7.8×10^{-5}	—	—	2.4×10^{-7}
***S*-29**	2.0×10^{-5}	—	—	—	—	2.1×10^{-5}
***R*-29**	2.5×10^{-4}	—	—	—	—	6.1×10^{-5}
***S*-30**	—	—	3.4×10^{-4}	—	—	6.9×10^{-5}
***R*-30**	—	2.8×10^{-4}	2.3×10^{-4}	—	—	3.7×10^{-5}

(a) 0.66 mM *p*-nitrophenyl α-D-glucopyranoside, 0.1 M potassium phosphate buffer pH 6.8.[16] (b) 0.33 mM *p*-nitrophenyl β-D-glucopyranoside, 0.1 M acetate buffer, pH 5.0.[17] (c) 2.0 mM *p*-nitrophenyl α-D-mannopyranoside, 0.1 M acetate buffer, pH 4.5.[18] (d) 9.9 mM *p*-nitrophenyl α-D-galactopyranoside, 0.1 M potassium phosphate buffer, pH 6.5.[19] (e) 2.0 mM *o*-nitrophenyl β-D-galactopyranoside, 0.1 M 2-mercaptoethanol, 50 mM potassium phosphate buffer including 1.3 mM $MgCl_2$, pH 7.3.[20] (f) No inhibitory activity observed at less than 6.7×10^{-4} M. (g) No inhibitory activity observed at less than 4.0×10^{-4} M.

Compound ***S*-17**[4] also increased its activity 100-fold compared to the parent free base **D-3**.

Compounds **D-5**, **D-10**, and **12** possess a mild inhibitory activity against both β-galactosidase and β-glucosidase. The topological relationship between three hydroxyl groups of galactopyranosyl cation and those of the above compounds may explain the potency. In fact, addition of *N*-phenyl cyclic isourea function (**D-10**, **12** → ***S*-26**, **28**) increased their activity. Surprisingly, the free base **L-6** expected to be a galactosidase inhibitor (Scheme 2) by analogy to **L-4** has been shown to lack the potency at all. However, the *N*-phenyl cyclic isourea derivative ***R*-22** derived from its enantiomer **D-6** possessed considerable potency against both two enzymes. In contrast to the case of ***R*, *S*-19**, the enantiomer ***S*-22** was a weaker inhibitor.

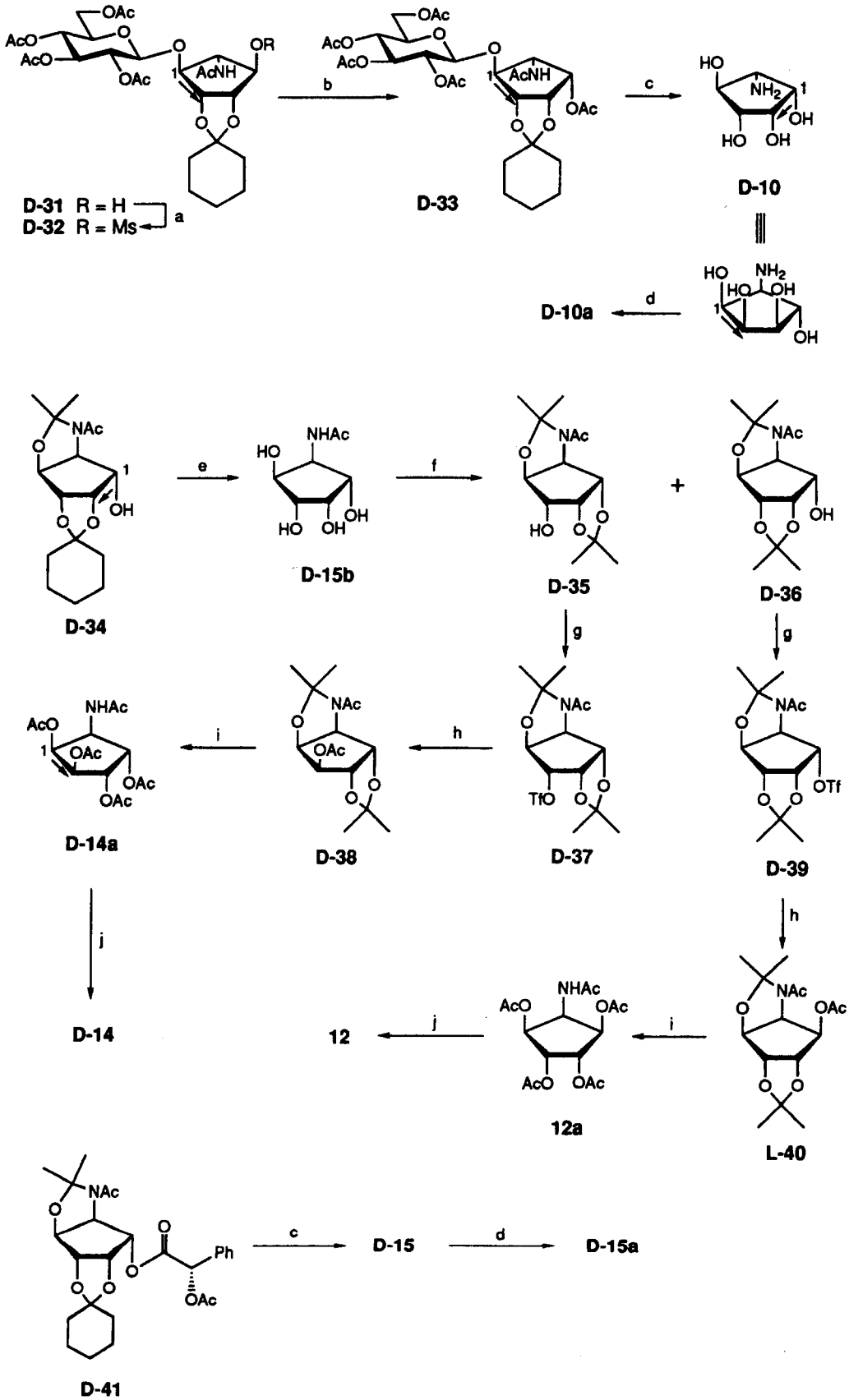
On the other hand, strong activity of compounds ***R*, *S*-26** and **28** may be deduced from the *trans–cis* configurational relationship of their three hydroxyl groups at C-6, 7, and 8 to those at C-2, 3, and 4 of galactopyranosyl cation (Scheme 4). Very interestingly, they show specific inhibitory potency against β-galactosidases from *E. coli* and bovine liver, respectively. Concerning α-mannosidase inhibitors, it is noteworthy that only aminocyclitols **9** and **L-10** structurally related to mannostatin A[9] (Scheme 2) possessed a mild potency; however, similar modification (**L-10** → ***R*-26**) of the part of positive charge developing completely deprived it of the activity. Interestingly, ***R*-26** possesses a moderate inhibitory activity against almond β-glucosidase.

In summary, the present molecular modeling studies of all aminocyclitols and their cyclic isourea derivatives seem to be helpful for understanding the structure and inhibitory activity relationship of strong α-glucosidase inhibitors **L-4**, ***S*-18** and ***S*-19**, and of β-galactosidase inhibitors ***R*, *S*-22**. Apparently, the hydroxyl group topology on cyclopentane ring may be a very important factor for the design of new glycosidase inhibitors of this kind.

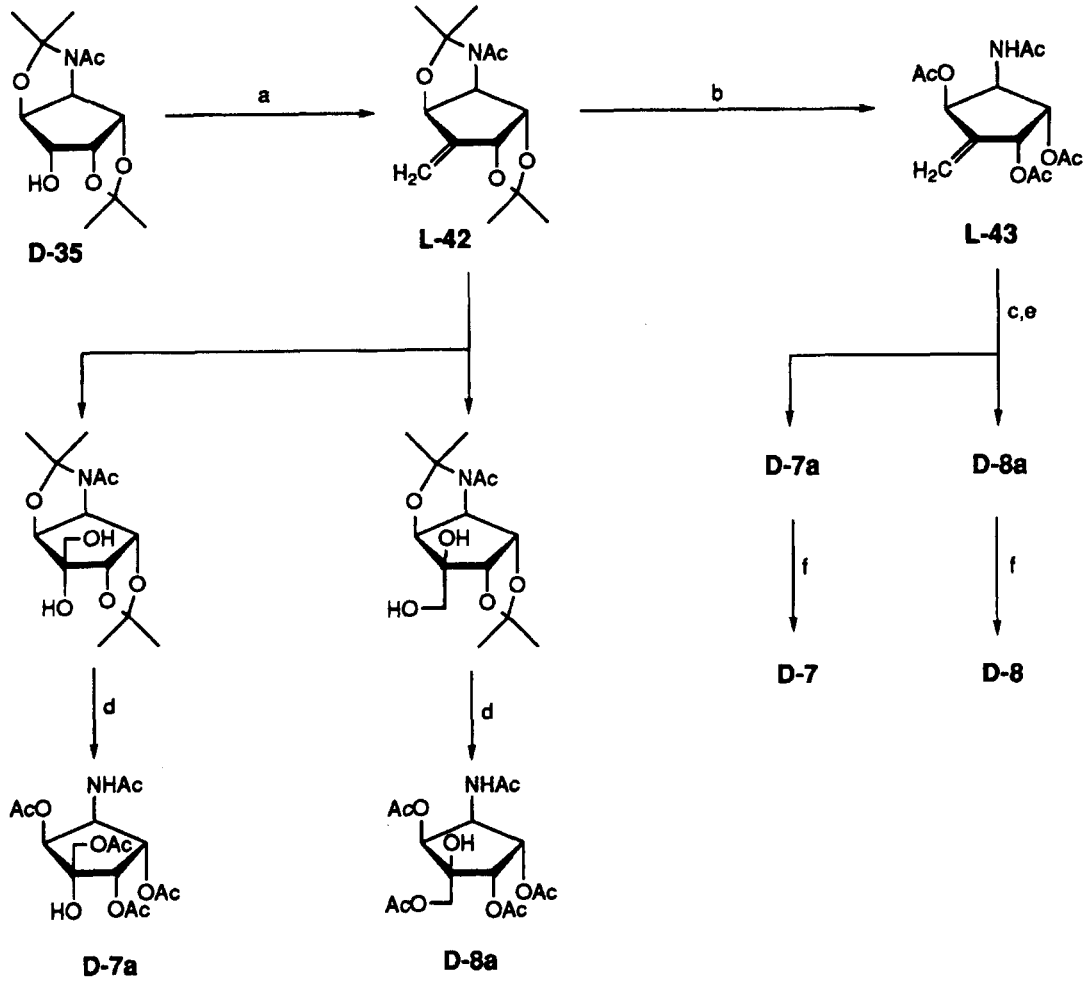
Experimental

General methods

Melting points were determined on a MEL-TEMP capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg

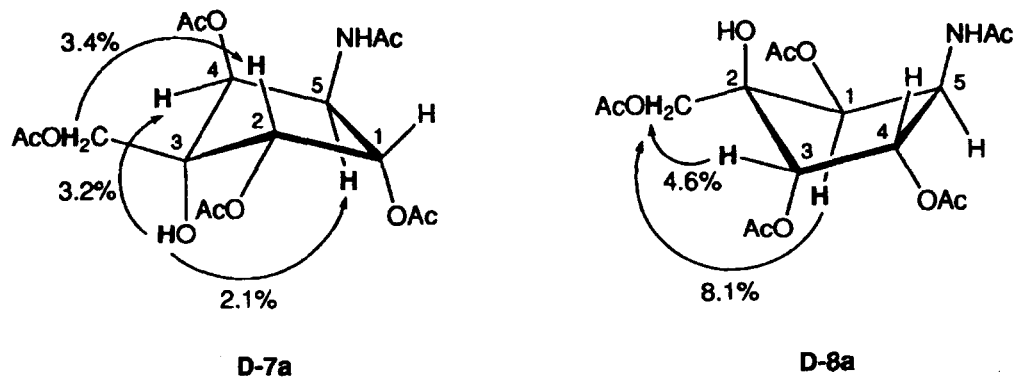


Scheme 5. Synthesis of 5-amino-1,2,3,4-cyclopentanetetraols **D-10**, **D-14**, and **D-15**. Reaction conditions: (a) MsCl, pyridine; (b) NaOAc, 80% aq DMF, 100 °C; (c) 4 M HCl, 90 °C, then chromatography on Dowex 50W-X2 (H^+) with 4 M aq ammonia; (d) Ac_2O, pyridine; (e) 70% aq AcOH, 80 °C; (f) $Me_2C(OMe)_2$, TsOH, DMF, 70 °C; (g) Tf_2O, pyridine, CH_2Cl_2, −15 °C; (h) KOAc, 18-crown-6 ether, benzene, 25 °C; (i) 2 M HCl, 80 °C, then Ac_2O, pyridine; (j) 2 M HCl, 80 °C, then acidic resin column with 4 M aq ammonia.

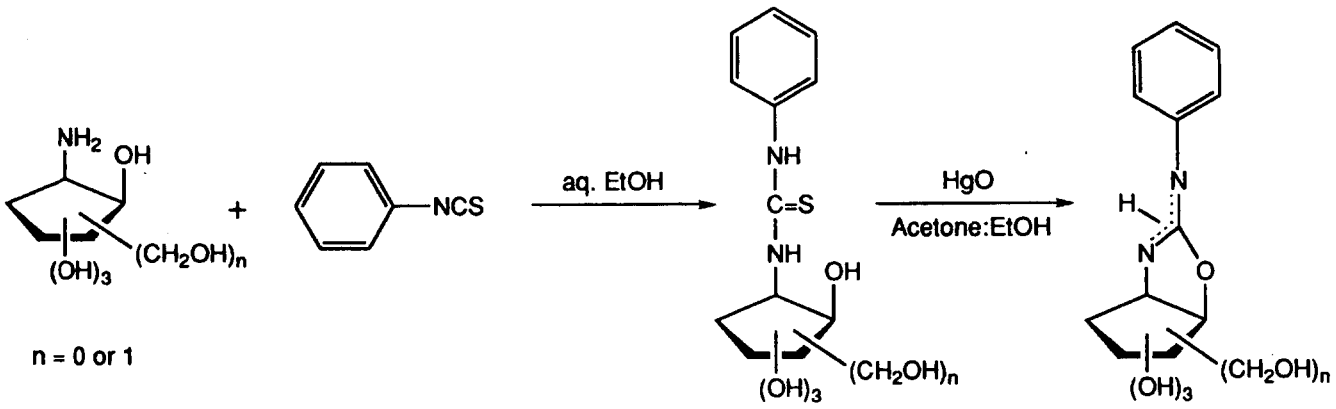


Scheme 6. Synthesis of 5-amino-2-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols **D-7** and **D-8**. Reaction conditions: (a) PCC, molecular sieves 4 Å, CH_2Cl_2, 25 °C, then $Ph_3P{=}CH_2$ (salt free)/THF, −15 to 25 °C; (b) 80% aq AcOH, 80 °C, then Ac_2O, pyridine; (c) OsO_4/*t*-BuOH, NMO, 80% aq acetone, 50 °C; (d) 2 M HCl, then Ac_2O, pyridine; (e) Ac_2O, pyridine; (f) 2 M HCl, 80 °C, then chromatography on Dowex 50W-X2 (H^+) with 4 M aq. ammonia.

$cm^2\ g^{-1}$. ^1H NMR spectra were recorded for solutions in deuteriochloroform with internal tetramethylsilane (TMS) as a reference, hexadeuteriodimethylsulfoxide with internal TMS as a reference, or dideuterium oxide with internal acetone (δ 2.08) or internal *t*-butanol (δ 1.22) as a reference with a JEOL JNM-GX 270 FT (270 MHz) instrument. IR spectra were measured with a JASCO IR-810 (neat) or Hitachi BIO-RAD DEGILAB FTS-65 (KBr disk) spectrometer. TLC was performed on silica gel 60 F-254 (E. Merck, Darmstadt). The silica gel used for column chromatography was Wakogel C-300 (Wako Junyaku Kogyo Co., Osaka, Japan; 300 mesh), or silica gel 60 KO70 (Katayama Kagaku Kogyo Co., Osaka, Japan; 70–230 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at <45 °C under diminished pressure.



Scheme 7. NOE data of the *N,O*-acetyl derivatives **D-7a** and **D-8a**.



Scheme 8.

Each enantiomeric pair of compounds was fully characterized by comparison of their ^{1}H NMR and IR spectra, and TLC data. One set of these respective data is reported here.

In this paper, nomenclature of cyclitols follows IUPAC–IUB 1973 recommendations for cyclitols.[7] D,L- and *R,S*-notations in numbering the chiral compounds denote the absolute configurations at the C-1.

Bioassay

Glycosidases and nitrophenyl glycosides were purchased from SIGMA. A 96-well microplate was used for bioassay, and the absorbance of nitrophenol produced by the enzyme reaction was measured with 405 nm at several concentrations of the samples to calculate IC_{50} values.

2,3-*O*-Cyclohexylidene derivative D-32 of 1L-(1,4/2,3,5)-5-acetamido-1-*O*-methanesulfonyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,4-cyclopentanetetraol. To a solution of the 2,3-*O*-cyclohexylidene derivative[11] **D-31** (166 mg, 0.276 mmol) of 1L-(1,4/2,3,5)-5-acetamido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,4-cyclopentanetetraol in pyridine (1.5 mL) was added dropwise methanesulfonyl chloride (43 μL, 0.552 mmol, 2 equiv) at 0 °C. The mixture was stirred for 1 h at room temperature and then evaporated. The residue was dissolved in water (15 mL) and extracted with $CHCl_3$ (20 mL × 3), and the extracts were washed with water and dried. Removal of a solvent gave a syrupy residue, which was chromatographed on a column of silica gel (8 g) with acetone:toluene (1:4, v/v) as eluent to afford the mesylate **D-32** (170 mg, 90.5%) as a syrup; R_f 0.68 (acetone:toluene, 1:1), $[\alpha]_D^{23}$ −14.3 (*c* 0.97; $CHCl_3$), IR (neat) ν 3400 (NH), 1750 (OAc), 1670 (NAc), and 1520 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.01 (1 H, d, $J_{5,NH}$ = 7.7 Hz, NH), 5.21 (1 H, dd, $J_{2',3'}$ = 9.2, $J_{3',4'}$ = 9.5 Hz, 3′-H), 5.12 (1 H, dd, *J* = 2.9 and 12.8 Hz, 1-H), 5.07 (1 H, dd, $J_{3',4'}$ = 9.5, $J_{4',5'}$ = 9.9 Hz, 4′-H), 4.99 (1 H, dd, $J_{1',2'}$ = 8.1, $J_{2',3'}$ = 9.2 Hz, 2′-H), 4.70–4.64 (1 H, m, 2-H), 4.69 (1 H, d, $J_{1',2'}$ = 8.1 Hz, 1′-H), 4.50 (1 H, m, 3-H), 4.38 (1 H, m, 4-H), 4.25–4.15 (3 H, m, 5- and 2 × 6-H), 3.78–3.70 (1 H, m, 5′-H), 3.13 (3 H, s, Ms), 2.10, 2.07, 2.03, and 2.01 (3, 3, 3, and 6 H, 4 s, 5 Ac), 1.75–1.26 (10 H, m, C_6H_{10}). Anal. calcd for $C_{28}H_{41}NO_{16}S$: C, 49.48; H, 6.08; N, 2.06%. Found: C, 49.36; H, 6.30; N, 2.11%.

2,3-*O*-Cyclohexylidene derivative D-33 of 1D-(1,2,3,5/4)-5-acetamido-1-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,4-cyclopentanetetraol. The mesylate **D-32** (148 mg, 0.218 mmol) was treated with NaOAc (179 mg, 2.18 mmol, 10 equiv) in 80% aq DMF (5 mL) for 12 h at 100 °C. The reaction mixture was evaporated and the residue was acetylated with acetic anhydride (1 mL) in pyridine (2 mL) for 3 h at room temperature. After concentration, column chromatography of the residue on silica gel (4 g) with acetone:toluene (1:3, v/v) gave the compound **D-33** (135 mg, 96.1%) as a syrup, R_f 0.55 (acetone:toluene, 1:1), $[\alpha]_D^{23}$ −20.7 (*c* 0.94; $CHCl_3$), IR (neat) ν 3200 (NH), 1780 (OAc), 1680 (NAc), and 1590 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.18 (1 H, d, $J_{5,NH}$ = 7.3 Hz, NH), 5.21 (1 H, t, $J_{2',3'}$ = $J_{3',4'}$ = 9.4 Hz, 3′-H), 5.20–5.15 (1 H, m, 1-H), 5.09 (1 H, dd, $J_{3',4'}$ = 9.4, $J_{4',5'}$ = 9.9 Hz, 4′-H), 4.96 (1 H, dd, $J_{1',2'}$ = 8.1, $J_{2',3'}$ = 9.4 Hz, 2′-H), 4.83–4.76 (1 H, m, 4-H), 4.76 (1 H, d, $J_{1',2'}$ = 8.1 Hz, 1′-H), 4.72–4.64 (1 H, m, 5-H), 4.38 (1 H, dd, $J_{2,3}$ = 1.5, $J_{3,4}$ = 5.9 Hz, 3-H), 4.31 (1 H, dd, $J_{5',6'a}$ = 4.6, J_{gem} = 12.5 Hz, 6′a-H), 4.20 (1 H, dd, $J_{5',6'b}$ = 1.9, J_{gem} = 12.5 Hz, 6′b-H), 4.02 (1 H, d, $J_{2,3}$ = 1.5 Hz, 2-H), 3.81 (1 H, ddd, $J_{4',5'}$ = 9.9, $J_{5',6'a}$ = 4.6, $J_{5',6'b}$ = 1.9 Hz, 5′-H), 2.14, 2.07, 2.06, 2.02, 2.00 and 1.98 (each 3 H, 6 s, 6 Ac), 1.75–1.20 (10 H, m, C_6H_{10}). Anal. calcd for $C_{29}H_{41}NO_{15}$: C, 54.12; H, 6.42; N, 2.18%. Found: C, 53.82; H, 6.63; N, 2.17%.

1D-(1,2,3,5/4)-5-amino-1,2,3,4-cyclopentanetetraol (D-10). Compound **D-33** (130 mg, 0.202 mmol) was treated with 4 M HCl (3 mL) for two days at 90 °C. The mixture was evaporated to give a crude amine hydrochloride, which was purified by a column of Dowex 50W-X2 (H^+) resin (3 mL) with 1 M aq NH_4OH as eluent to afford the free base **D-10** (27.8 mg, 92.4%) as a syrup, R_f 0.35 (AcOH:water:acetonitrile, 1:10:40), $[\alpha]_D^{20}$ +8.2 (*c* 0.50; water), IR (neat) ν 3250 (OH and NH_2) cm^{-1}; ^{1}H NMR (D_2O, ref *t*-BuOH) δ 4.10–4.02 (2 H, m, 2- and 3-H), 3.90–3.81 (2 H, m, 1- and 4-H), 3.02–2.90 (1 H, m, 5-H).

1D-(1,2,3,5/4)-5-Acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetraol (D-10a). The amino alcohol **D-10** (10.0 mg, 0.0670 mmol) was acetylated with acetic anhydride (0.5 mL) in pyridine (1 mL) for 2 h at room temperature. After evaporation, column chromatography of silica gel (1 g) with acetone:toluene (1:2, v/v) as eluent gave the penta-*N,O*-acetyl derivative **D-10a** (24.1 mg, ~100%) as a syrup; R_f 0.56 (acetone:toluene, 1:1), $[\alpha]_D^{23}$ −15.4 (*c* 1.22; $CHCl_3$), IR (neat) ν 3300 (NH), 1750 (OAc), 1660 (NAc), and 1540 (NH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.86 (1 H, d, $J_{5,NH}$ = 8.4 Hz, NH), 5.46–5.22 (4 H, m, 1-, 2-, 3-, and 4-H), 4.54 (1 H, m, 5-H). Anal. calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90%. Found: C, 49.79; H, 6.09; N, 3.93%.

2,3-*O*-Cyclohexylidene derivative L-32 of 1D-(1,4/2,3,5)-5-acetamido-4-O-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-*O*-methanesulfonyl-1,2,3,4-cyclopentanetetraol. The 2,3-*O*-cyclohexylidene derivative[11] **L-31** (64.0 mg, 0.106 mmol) of 1D-(1,4/2,3,5)-5-acetamido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,4-cyclopentanetetraol was mesylated, as in the preparation of the diastereomer **D-32**, to give the mesylate **L-32** (72.3 mg, ~100%) as a syrup; R_f 0.73 (acetone:toluene, 1:1), $[\alpha]_D^{23}$ −3.9 (*c* 0.63; $CHCl_3$) and +4.5 (*c* 0.53; acetone), IR (neat) ν 3250 (NH), 1780 (OAc), 1690 (NAc), and 1560 (NH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.96 (1 H, d, $J_{5,NH}$ = 7.7 Hz, NH), 5.22 (1 H, dd, $J_{2',3'}$ = 9.2, $J_{3',4'}$ 9.5 Hz, 3'-H), 5.10 (1 H, t, $J_{3',4'} = J_{4',5'}$ 9.5 Hz, 4'-H), 4.98 (1 H, dd, $J_{1',2'}$ = 7.7, $J_{2',3'}$ = 9.2 Hz, 2'-H), 4.94 (1 H, br d, $J_{1,5}$ = 4.4 Hz, 1-H), 4.73–4.68 (2 H, m, 2- and 3-H), 4.70 (1 H, d, $J_{1',2'}$ = 7.7 Hz, 1'-H), 4.30 (1 H, br d, $J_{4,5}$ = 4.4 Hz, 4-H), 4.29 (1 H, dd, $J_{5',6'a}$ = 4.4, J_{gem} = 12.5 Hz, 6'a-H), 4.21 (1 H, ddd, $J_{1,5} = J_{4,5}$ = 4.4, $J_{5,NH}$ = 7.7 Hz, 5-H), 4.15 (1 H, dd, $J_{5',6'b}$ = 2.4, J_{gem} = 12.5 Hz, 6'b-H), 3.74 (1 H, dd, $J_{4',5'}$ = 9.5, $J_{5',6'a}$ = 4.4, $J_{5',6'b}$ = 2.4 Hz, 5'-H), 3.14 (3 H, s, Ms), 2.10, 2.07, 2.03, 2.00, and 1.99 (each 3 H, 5 s, 5 Ac), 1.71–1.30 (10 H, m, C_6H_{10}). Anal. calcd for $C_{28}H_{41}NO_{16}S$: C, 49.48; H, 6.08; N, 2.06%. Found: C, 49.92; H, 6.48; N, 2.22%.

2,3-*O*-Cyclohexylidene derivative L-33 of 1L-(1,2,3,5/4)-5-acetamido-1-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,4-cyclopentanetetraol. The mesylate **L-32** (82.9 mg, 0.122 mmol) was treated, as in the preparation of **D-33**, to afford the hexa-*N,O*-acetyl derivative **L-33** (78.5 mg, ~100%) as a syrup; R_f 0.61 (acetone:toluene, 1:1), $[\alpha]_D^{21}$ +4.0 (*c* 0.87; $CHCl_3$) and +6.9 (*c* 0.87; acetone), IR (neat) ν 3200 (NH), 1780 (OAc), 1680 (NAc), and 1590 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.25 (1 H, d, $J_{5,NH}$ = 7.7 Hz, NH), 5.22 (1 H, dd, $J_{2',3'}$ = 9.2, $J_{3',4'}$ = 9.5 Hz, 3'-H), 5.11 (1 H, t, $J_{3',4'} = J_{4',5'}$ = 9.5 Hz, 4'-H), 4.95 (1 H, dd, $J_{1',2'}$ = 8.4, $J_{2',3'}$ = 9.2 Hz, 2'-H), 4.85 (1 H, d, $J_{1',2'}$ = 8.4 Hz, 1'-H), 4.77 (1 H, dd, $J_{1,2}$ = 4.8, $J_{2,3}$ = 5.5 Hz, 2-H), 4.56 (1 H, d, $J_{2,3}$ = 5.5 Hz, 3-H), 4.36–4.30 (1 H, m, 5-H), 4.33 (1 H, dd, $J_{5',6'a}$ = 4.0, J_{gem} 12.5 Hz, 6'a-H), 4.11 (1 H, dd, $J_{5',6'b}$ = 2.2, J_{gem} = 12.5 Hz, 6'b-H), 4.08 (1 H, s, 4-H), 3.77 (1 H, ddd, $J_{4',5'}$ = 9.5, $J_{5',6'a}$ = 4.0, $J_{5',6'b}$ = 2.2 Hz, 5'-H), 2.15, 2.10, 2.02, and 1.99 (3, 6, 3, and 6 H, 4 s, 6 Ac), 1.80–1.25 (10 H, m, C_6H_{10}). Anal. calcd for $C_{29}H_{41}NO_{15}$: C, 54.12; H, 6.42; N, 2.18%. Found: C, 53.81; H, 6.49; N, 2.23%.

1L-(1,2,3,5/4)-5-Amino-1,2,3,4-cyclopentanetetraol (L-10). Compound **L-33** (77.4 mg, 0.120 mmol) was treated, as in the preparation of **D-10**, to give the free base **L-10** (17.9 mg, ~100%) as a syrup, $[\alpha]_D^{23}$ −7.3 (*c* 0.55; water).

1L-(1,2,3,5/4)-5-Acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetraol (L-10a). The free base **L-10** (17.9 mg, 0.120 mmol) was acetylated, as in the preparation of **D-10a**, to give the hexa-*N,O*-acetyl derivative **L-10a** (43.2 mg, ~100%) as a syrup; $[\alpha]_D^{23}$ +14.5 (*c* 1.22, $CHCl_3$). Anal. calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90%. Found: C, 50.04; H, 6.13; N, 3.92%.

1,2-*O*-:4,5-*N,O*-Diisopropylidene D-35 and 2,3-:4,5-*N,O*-diisopropylidene derivatives D-36 of 1D-(1,2,3/4,5)-5-acetamido-1,2,3,4-cyclopentanetetraol. A mixture of 1D-(1,2,3/4,5)-5-acetamido-2,3-*O*-cyclohexylidene-4,5-*N,O*-isopropylidene-1,2,3,4-cyclopentanetetraol[2] **D-34** (495 mg, 1.59 mmol) and 70% aq AcOH (10 mL) was heated for 12 h at 80 °C, and evaporated. The tetraol obtained was then treated with 2,2-dimethoxypropane (2.0 mL, 15.9 mmol, 10 equiv) and *p*-toluenesulfonic acid monohydrate (30.3 mg, 0.159 mmol, 0.1 equiv) in DMF (8.5 mL) for two days at 70 °C. After neutralization with triethylamine, the reaction mixture was evaporated and the residue was chromatographed on a column of silica gel (18 g) with acetone:toluene (1:8, v/v) as eluent to afford, first, the 1,2-*O*-isopropylidene derivative **D-35** (95.2 mg, 22.1%) as crystals; mp 96–97 °C (from toluene), R_f 0.33 (acetone:toluene, 1:4), $[\alpha]_D^{29}$ +10.3 (*c* 0.82; $CHCl_3$), IR (neat) ν 3450 (OH) and 1660 (NAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.90 (1 H, dd, *J* 4.8, *J* 6.6 Hz, 2- or 4-H), 4.63 (1 H, dd, *J* = 0.8, *J* = 4.8 Hz, 2- or 4-H), 4.52 (1 H, dd, *J* = 1.5, *J* = 6.6 Hz, 1- or 5-H), 4.31 (1 H, dd, *J* = 1.5, *J* = 4.8 Hz, 1- or 5-H), 4.16 (1 H, ddd, *J* = 0.7, *J* = 0.8, *J* = 4.8 Hz, 3-H), 2.63 (1 H, d, $J_{3,OH}$ = 0.7 Hz, OH), 2.15 (3 H, s, Ac), 1.60, 1.56, 1.51, and 1.38 (each 3 H, 4 s, 2 × CMe_2). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16%. Found: C, 57.39; H, 8.22; N, 5.18%.

The second fractions gave the 2,3-*O*-isopropylidene derivative **D-36** (147 mg, 34.1%) as crystals, mp 146–147 °C (from EtOAc), R_f 0.18 (acetone:toluene, 1:4), $[\alpha]_D^{29}$ −29.2 (*c* 0.98; $CHCl_3$), IR (neat) ν 3400 (OH) and 1630 (NAc) cm^{-1}, ^1H NMR (DMSO-d_6) δ 5.47 (1 H, d, $J_{1,OH}$ = 7.0 Hz, OH), 4.56 (1 H, dd, *J* = 4.2, *J* = 5.1 Hz, 2- or 5-H), 4.36 (1 H, d, *J* = 5.1 Hz, 3- or 4-H), 4.29 (1 H, dd, *J* = 5.3, *J* = 8.1 Hz, 2- or 5-H), 4.18 (1 H, d, *J* = 5.5 Hz, 3- or 4-H), 3.94 (1 H, ddd, *J* = 4.2, *J* = 7.0, $J_{1,OH}$ = 7.0 Hz, 1-H), 2.12 (3 H, s, Ac), 1.54, 1.42, 1.41, and 1.25 (each 3 H, 4 s, 2 × CMe_2). Anal. found: C, 57.59; H, 8.28; N, 5.24%.

3,4-*O*-:1,5-*N,O*-Diisopropylidene derivative D-38 of 1D-(1,2,5/3,4)-5-acetamido-2-*O*-acetyl-1,2,3,4-cyclopentanetetraol. To a stirred solution of the alcohol **D-35** (67.3 mg, 0.248 mmol) in CH_2Cl_2 (2 mL) were added pyridine (100 μL, 1.24 mmol, 5 equiv) and trifluoromethanesulfonic anhydride (84 μL, 0.496 mmol, 2 equiv) at −15 °C. After stirring for 30 min at the same temparature, satd aq $NaHCO_3$ (10 mL) was added to the mixture, and it

was extracted with $CHCl_3$ (20 mL × 3). The extracts were conventionally processed to give the triflate **D-37**. The crude compound was dissolved in benzene (3 mL), 18-crown-6 ether (131 mg, 0.496 mmol, 2 equiv) and KOAc (122 mg, 1.24 mmol, 5 equiv) were added, and the reaction mixture was stirred for 14 h at room temperature. Evaporation of the mixture gave a syrupy residue, which was chromatographed on a column of silica gel (2.5 g) with acetone:toluene (1:10, v/v) as eluent to afford the acetate **D-38** (56.4 mg, 72.6%) as a syrup; R_f 0.50 (acetone:toluene, 1:3), $[\alpha]_D^{27}$ +92.5 (*c* 0.53; $CHCl_3$), IR (neat) ν 1740 (OAc) and 1680 (NAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.01 (1 H, dd, J = 3.7, J = 6.6 Hz), 4.90 (1 H, t, J = 6.6 Hz), 4.79 (1 H, dd, J = 3.7, J = 4.4 Hz), 4.42 (1 H, dd, J = 1.1, J = 6.6 Hz), 4.19 (1 H, dd, J = 1.1, J = 4.4 Hz), 2.17 and 2.16 (each 3 H, 2 s, 2 Ac), 1.65, 1.53, 1.49, and 1.33 (each 3 H, 4 s, 2 × CMe_2). Anal. calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47%. Found: C, 57.38; H, 7.61; N, 4.48%.

1D-(1,2,5/3,4)-5-Acetamido-1,2,3,4-tetra-O-acetyl-1,2,3,4-cyclopentanetetraol (D-14a). Compound **D-38** (53.4 mg, 0.170 mmol) was treated with 2 M HCl (2 mL) for 3 h at 80 °C. After evaporation, the residual amine hydrochloride was acetylated conventionally. Silica gel column chromatography (2 g) with acetone:toluene (1:3, v/v) gave the penta-*N*,*O*-acetyl derivative **D-14a** (61.2 mg, ~100%) as a syrup; R_f 0.24 (acetone:toluene, 1:2), $[\alpha]_D^{25}$ −15.5 (*c* 0.87; acetone), IR (neat) ν 3300 (NH), 1750 (OAc), 1660 (NAc), and 1540 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.10 (1 H, d, $J_{5,NH}$ = 8.4 Hz, NH), 5.48 (1 H, dd, J = 4.0, J = 5.1 Hz, 1- and 4-H), 5.35 (1 H, dd, J = 7.3, J = 8.4 Hz, 1- and 4-H), 5.33 (1 H, dd, $J_{2,3}$ = 5.9, J = 4.0 Hz, 2- and 3-H), 5.28 (1 H, dd, $J_{2,3}$ = 5.9, J = 7.3 Hz, 2- and 3-H), 4.69 (1 H, ddd, $J_{5,NH}$ = 8.4, J = 5.1, J = 8.4 Hz, 5-H), 2.14, 2.09, 2.06, 2.03, and 1.98 (each 3 H, 5 s, 5 Ac). Anal. calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90%. Found: C, 49.89; H, 6.15; N, 3.92%.

1D-(1,2,5/3,4)-5-Amino-1,2,3,4-cyclopentanetetraol (D-14). Compound **D-14a** (56.2 mg, 0.156 mmol) was treated with 2 M HCl (2 mL) for 1 h at 90 °C. The mixture was concentrated and the residual amine hydrochloride was purified by a column of Dowex 50W-X2 (H^+) resin (2.5 mL) with 2 M aq NH_4OH as eluent to afford the free base **D-14** (23.3 mg, ~100%) as a syrup; R_f 0.60 (AcOH:water:acetonitrile, 1:4:8), $[\alpha]_D^{27}$ −8.6 (*c* 0.67; water), IR (neat) ν 3350 (OH and NH_2) cm^{-1}; ^1H NMR (D_2O, ref *t*-BuOH) δ 4.04–3.97 (2 H, m), 3.93 (1 H, dd, J = 4.8, J = 9.9 Hz, 1- or 4-H), 3.90 (1 H, dd, J = 6.8, J = 7.3 Hz, 1- and 4-H), 3.07 (1 H, dd, J = 4.8, J = 6.8 Hz, 5-H).

2,3-*O*-:4,5-*N*,*O*-Diisopropylidene derivative L-40 of 1L-(1,4,5/2,3)-5-acetamido-1-*O*-acetyl-1,2,3,4-cyclopentanetetraol. The alcohol **D-36** (132 mg, 0.487 mmol) was treated, as in the preparation of **D-38**, to give the acetate **L-40** (100 mg, 65.6%) as crystals; mp 147–148 °C (from EtOAc), R_f 0.45 (acetone:toluene, 1:3), $[\alpha]_D^{29}$ +24.0 (*c* 0.76; $CHCl_3$), IR (neat) ν 1740 (OAc), and 1650 (NAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42 (1 H, dd, J = 1.1, J = 5.5 Hz, 1-H), 4.69 (1 H, d, J = 5.5 Hz, 3- or 4-H), 4.67 (1 H, d, J = 7.3 Hz, 3- or 4-H), 4.55 (1 H, t, J = 5.5 Hz, 2- or 5-H), 4.52 (1 H, dd, J = 1.1, J = 7.3 Hz, 2- or 5-H), 2.10, and 2.07 (each 3 H, 2 s, 2 Ac), 1.67, 1.53, 1.46, and 1.30 (each 3 H, 4 s, 2 × CMe_2). Anal. calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47%. Found: C, 57.56; H, 7.72; N, 4.46%.

(1,4,5/2,3)-5-Acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,-4-cyclopentanetetraol (12a). Compound **L-40** (91.9 mg, 0.291 mmol) was treated with 2 M HCl (3 mL) for 3 h at 80 °C and then acetylated conventionally. Column chromatography on silica gel gave the penta-*N*,*O*-acetyl derivative **12a** (103 mg, 98.3%). The spectral data were identical with those of an authentic sample.[12]

1,2-*O*-:4,5-*N*,*O*-Diisopropylidene derivative L-35 and 2,3-*O*-:4,5-*N*,*O*-diisopropylidene derivative L-36 of 1L-(1,2,3/4,5)-5-acetamido-1,2,3,4-cyclopentanetetraol. The cyclohexylidene derivative[2] **L-34** (431 mg, 1.38 mmol) was treated, as in the preparation of the enantiomers, to give, first, the 1,2-*O*-isopropylidene derivative **L-35** (87.6 mg, 23.3%) as crystals, mp 91–93 °C (from toluene), $[\alpha]_D^{29}$ −9.6 (c 0.82; $CHCl_3$). Anal. found: C, 57.34; H, 8.19; N, 5.12%. ^1H NMR, IR, and R_f were identical with those of the enantiomer.

The second fractions gave the 2,3-*O*-isopropylidene derivative **L-36** (117 mg, 31.3%) as crystals, mp 146–147 °C (from EtOAc), $[\alpha]_D^{29}$ +31.9 (*c* 0.97; $CHCl_3$). Anal. found: C, 57.30; H, 8.21; N, 5.25%.

3,4-*O*-:1,5-*N*,*O*-Diisopropylidene derivative L-38 of 1L-(1,2,5/3,4)-5-acetamido-2-*O*-acetyl-1,2,3,4-cyclopentanetetraol. The alcohol **L-35** (71.6 mg, 0.264 mmol) was treated, as in the preparation of **D-38**, to give the acetate **L-38** (77.6 mg, 93.8%) as a syrup, $[\alpha]_D^{27}$ −98.8 (*c* 1.12; $CHCl_3$). Anal. found: C, 57.32; H, 7.70; N, 4.44%.

1L-(1,2,5/3,4)-5-Acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetraol (L-14a). Compound **L-38** (61.6 mg, 0.197 mmol) was treated, as in the preparation of **D-14a**, to afford the penta-*N*,*O*-acetyl derivative **L-14a** (70.6 mg, ~100%) as a syrup; $[\alpha]_D^{25}$ +14.3 (*c* 0.95; acetone). Anal. found: C, 49.88; H, 6.11; N, 3.81%.

1L-(1,2,5/3,4)-5-Amino-1,2,3,4-cyclopentanetetraol (L-14). The acetate **L-14a** (69.6 mg, 0.194 mmol) was converted, as in the preparation of the enantiomer, into the free base **L-14** (28.9 mg, ~100%) as a syrup, $[\alpha]_D^{27}$ +8.3 (*c* 1.45; water).

2,3-*O*-:4,5-*N*,*O*-Diisopropylidene derivative D-40 of 1D-(1,4,5/2,3)-5-acetamido-1-*O*-acetyl-1,2,3,4-cyclopentanetetraol. The alcohol **L-36** (97.0 mg, 0.358 mmol) was treated, as in the preparation of **L-40**, to afford the acetate **D-40** (71.6 mg, 63.9%) as crystals, mp 147–148 °C (from EtOAc), $[\alpha]_D^{29}$ −23.1 (*c* 0.60; $CHCl_3$). Anal. found: C, 57.24; H, 7.64; N, 4.47%.

(1,4,5/2,3)-5-Acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetraol (12a). The acetate **D-40** (60.8 mg, 0.194 mmol) was treated, as in the preparation of **12a**,

to give crystalline **12a** (69.7 mg, ~100%), which was identical with an authentic sample[12] in all respects.

1D-(1,2,3/4,5)-5-Amino-1,2,3,4-cyclopentanetetraol (D-15). The 2,3-*O*-cyclohexylidene-4,5-*N*,*O*-isopropylidene derivative[2] **L-41** (175 mg, 0.359 mmol) of 1D-(1,2,3/4,5)-*N*-acetyl-1-*O*-[(2′*S*)-2′-*O*-acetylmandelyl]-1,2,3,4-cyclopentanetetraol was treated with 2 M HCl (4 mL) for 4 h at 80 °C. The reaction mixture was evaporated and the crude amine hydrochloride was purified by a column of Dowex 50W-X2 (H^+) resin (2 mL) with 1 M aq NH_4OH as eluent to give the free base **D-15** (51.3 mg, 95.7%) as crystals, mp 125–126 °C (from MeOH), R_f 0.33 (water:acetonitrile, 1:4), $[\alpha]_D^{21}$ −14.6 (*c* 2.11; water), IR (KBr disk) ν 3420 (OH and NH_2) cm^{-1}; ^1H NMR (D_2O, ref *t*-BuOH) δ 4.03–3.99 (2 H, m), 3.89 (1 H, t, *J* = 5.1 Hz), 3.78 (1 H, dd, *J* = 4.4, *J* = 8.1 Hz), 3.21 (1 H, t, *J* = 8.1 Hz, 5-H).

1D-(1,2,3/4,5)-5-Acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetraol (D-15a). Compound **D-15** (51.3 mg, 0.344 mmol) was acetylated conventionally. Silica gel column chromatography (5 g) with acetone:toluene (1:2, v/v) gave the penta-*N*,*O*-acetyl derivative **D-15a** (121 mg, 97.8%) as crystals; mp 127–129 °C (from toluene), $[\alpha]_D^{13}$ −14.7 (*c* 1.07; acetone). Anal. calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90%. Found: C, 50.08; H, 6.18; N, 3.92%. The ^1H NMR spectrum was identical with that of the racemate.[12]

1L-(1,2,3/4,5)-5-Amino-1,2,3,4-cyclopentanetetraol (L-15). The 2,3-*O*-cyclohexylidene-4,5-*N*,*O*-isopropylidene derivative[2] **D-41** (185 mg, 0.379 mmol) of 1L-(1,2,3/4,5)-*N*-acetyl-1-*O*-[(2′*S*)-2′-*O*-acetylmandelyl]-1,2,3,4-cyclopentanetetraol was hydrolyzed, as in the preparation of **D-15**, to give the free base **L-15** (56.0 mg, 98.9%) as crystals, mp 120–121 °C (from MeOH), $[\alpha]_D^{23}$ +12.1 (*c* 2.19; water).

1L-(1,2,3/4,5)-5-Acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetraol (L-15a). Compound **L-15** (56.0 mg, 0.376 mmol) was acetylated conventionally to give the penta-*N*,*O*-acetyl derivative **L-15a** (135 mg, ~100%) as crystals; mp 125–128 °C (from toluene), $[\alpha]_D^{13}$ +14.3 (*c* 2.68; acetone). Anal. found: C, 49.98; H, 6.18; N, 3.79%.

1,2-*O*-:3,4-*N*,*O*-Isopropylidene derivative L-42 of 1L-(1,2/3,4)-3-acetamido-5-methylene-1,2,4-cyclopentanetriol. To a stirred solution of the alcohol **D-35** (117 mg, 0.430 mmol) in dichloromethane (8 mL) were added molecular sieves 4 Å (350 mg) and PCC (557 mg, 2.58 mmol, 6 equiv) at 0 °C, and then the mixture was stirred for 12 h at room temperature. Celite was added to the reaction mixture and the slurry was charged on a column of silica gel (20 g), and it was eluted with diethyl ether, giving the ketone (110 mg) as a syrup. The ketone was treated with $Ph_3P{=}CH_2$ (salt free), prepared from Ph_3PCH_3Br and $NaNH_2$ in THF, in THF (1 mL) for 3 h at −15 °C and for 1 h at room temperature. After addition of satd aq NH_4Cl (5 mL), the mixture was stirred for 30 min at room temperature, diluted with satd NH_4Cl (5 mL), and extracted with $CHCl_3$ (20 mL × 3). The extracts were washed with water, dried, and evaporated to give a syrupy residue, which was chromatographed on a column of silica gel (7 g) with EtOAc:hexane (1:3, v/v) as eluent to afford the olefin **L-42** (80.8 mg, 70.2%) as a syrup, R_f 0.60 (acetone:toluene, 1:2), $[\alpha]_D^{23}$ +120 (*c* 0.92; $CHCl_3$), IR (neat) ν 1640 (NAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.58 (1 H, d, *J* = 2.2 Hz, 6-H), 5.54 (1 H, d, *J* = 1.8 Hz, 6-H), 5.16 (1 H, ddd, *J* = 1.8, 2.2, and 6.2 Hz, 1- or 4-H), 4.91 (1 H, d, *J* = 5.1 Hz, 1- or 4-H), 4.50 (1 H, dd, *J* = 1.8 and 6.2 Hz, 2- or 3-H), 4.14 (1 H, dd, *J* = 1.8 and 5.1 Hz, 2- or 3-H), 2.19 (3 H, s, Ac), 1.63, 1.54, 1.45 and 1.36 (each 3 H, 4 s, 2 × CMe_2). Anal. calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24%. Found: C, 62.80; H, 8.35; N, 5.36%.

1,2-*O*-:3,4-*N*,*O*-Isopropylidene derivative D-42 of 1D-(1,2/3,4)-3-acetamido-5-methylene-1,2,4-cyclopentanetriol. The alcohol **L-35** (50.0 mg, 0.184 mmol) was treated, as in the preparation of **L-42**, to give the olefin **D-42** (34.8 mg, 70.7%) as a syrup; $[\alpha]_D^{23}$ −125 (*c* 0.97; $CHCl_3$). Anal. found: C, 62.83; H, 8.24; N, 5.34%.

1L-(1,2/3,4)-3-Acetamido-1,2,4-tri-*O*-acetyl-5-methylene-1,2,4-cyclopentanetriol (L-43). Compound **L-42** (70.3 mg, 0.263 mmol) was treated with 80% aq acetic acid (2 mL) for 6 h at 80 °C, and the mixture was evaporated. The triol obtained was acetylated with acetic anhydride (0.5 mL) in pyridine (1.5 mL) for 2 h at room temperature. After evaporation, the product was chromatographed on a column of silica gel (2 g) with acetone:toluene (1:3, v/v) as eluent to give the tetra-*N*,*O*-acetyl derivative **L-43** (79.1 mg, 96.0%) as a syrup; R_f 0.28 (acetone:toluene, 1:2), $[\alpha]_D^{24}$ −93.0 (*c* 0.95; $CHCl_3$), IR (neat) ν 1740 (OAc) and 1660 (NAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90 (1 H, d, $J_{4,NH}$ = 8.8 Hz, NH), 5.76–5.62 (4 H, m, 2-, 5-, and 2 × 6-H), 5.29 (1 H, dd, $J_{2,3}$ = 11.0, $J_{3,4}$ = 5.9 Hz, 3-H), 4.76 (1 H, ddd, $J_{3,4}$ = 5.9, $J_{4,5}$ = 10.3, $J_{4,NH}$ = 8.8 Hz, 4-H), 2.09, 2.06, and 1.99 (3, 6, and 3 H, 3 s, 4 Ac). Anal. calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47%. Found: C, 53.75; H, 6.34; N, 4.45%.

1D-(1,2/3,4)-3-Acetamido-1,2,4-tri-*O*-acetyl-5-methylene-1,2,4-cyclopentanetriol (D-43). Compound **D-42** (34.8 mg, 0.130 mmol) was treated, as in the preparation of **L-43**, to give the olefin **D-43** (40.8 mg, ~100%) as a syrup, $[\alpha]_D^{24}$ +93.4 (*c* 0.98; $CHCl_3$). Anal. found: C, 53.53; H, 6.27; N, 4.53%.

1D-(1,2,3/4,5)-5-Acetamido-3-acetoxymethyl-1,2,4-(D-7a) and 1D-(1,4,5/2,3)-5-acetamido-2-acetoxymethyl-1,3,4-tri-*O*-acetyl-1,2,3,4-cyclopentanetetraol (D-8a). (A) To a solution of compound **L-43** (79.1 mg, 0.252 mmol) in 80% aq acetone (3 mL) were added *N*-methylmorpholine-*N*-oxide (NMO) (171 mg, 1.26 mmol, 5 equiv) and 0.05 M *t*-butanol solution (1.0 mL, 0.0505 mmol, 0.2 equiv) of osmium tetraoxide at room temperature. The mixture was stirred for 12 h at 50 °C in the dark. After the reaction mixture was cooled to room temperature, $NaHSO_3$ (210 mg, 2.02 mmol, 8 equiv) and Na_2SO_4 (400 mg) were added to it, and the mixture was stirred for 2 h at room temperature and then filtered through a bed of Celite, which was washed with acetone. The filtrate and

washings were combined and evaporated to give a syrupy residue, which was acetylated with acetic anhydride (0.5 mL) in pyridine (1.5 mL) conventionally. Column chromatography on silica gel (2 g) with acetonitrile:toluene (7:10, v/v) gave, first, the penta-*N,O*-acetyl derivative **D-8a** (54.5 mg, 55.4%) as a syrup; R_f 0.28 (acetone:toluene, 1:1), $[\alpha]_D^{21}$ −18.3 (*c* 0.92; acetone), IR (neat) ν 3350 (OH and NH), 1750 (OAc) and 1660 (NAc) cm^{-1}, ^1H NMR ($CDCl_3$) δ 6.12 (1 H, d, $J_{5,NH}$ = 8.8 Hz, NH), 5.55 (1 H, dd, $J_{1,2}$ = 5.4, $J_{1,5}$= 6.8 Hz, 1-H), 5.31 (1 H, d, $J_{1,2}$ = 5.4 Hz, 2-H), 5.27 (1 H, d, $J_{4,5}$ = 9.1 Hz, 4-H), 4.62 (1 H, ddd, $J_{1,5}$ = 6.8, $J_{4,5}$ = 9.1, $J_{5,NH}$ = 8.8 Hz, 5-H), 4.27 and 4.21 (each 1 H, ABq, J_{gem} = 12.2 Hz, 2 × 6-H), 2.14, 2.11, 2.08, 2.03 and 2.01 (each 3 H, 5 s, 5 Ac). Anal. calcd for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60%. Found: C, 49.26; H, 6.28; N, 3.77%.

The second fractions gave the penta-*N,O*-acetyl derivative **D-7a** (35.4 mg, 36.0%) as a syrup; R_f 0.26 (acetone:toluene, 1:1), $[\alpha]_D^{21}$ −34.0 (*c* 1.02; acetone), IR (neat) ν 3300 (OH and NH), 1750 (OAc) and 1660 (NAc) cm^{-1}, ^1H NMR (270 MHz, $CDCl_3$) δ 5.85 (1 H, d, $J_{5,NH}$ = 8.3 Hz, NH), 5.39 (1 H, d, $J_{1,5}$ = 5.4 Hz, 1-H), 5.28 (1 H, dd, $J_{3,4}$ = 7.8, $J_{4,5}$ = 7.3 Hz, 4-H), 5.21 (1 H, d, $J_{3,4}$ = 7.8 Hz, 3-H), 4.98 (1 H, ddd, $J_{1,5}$ = 5.4, $J_{4,5}$= 7.3, $J_{5,NH}$ = 8.3 Hz, 5-H), 4.21 and 4.13 (each 1 H, ABq, J_{gem} = 12.0 Hz, 2 × 6-H), 2.14, 2.11, 2.08, 2.07, and 1.96 (each 3 H, 5 s, 5 Ac). Anal. found: C, 49.45; H, 6.26; N, 3.75%.

(B) To a solution of the *exo*-olefin **L-42** (34.6 mg, 0.129 mmol) in 80% acetone aq (1 mL) were added NMO (75.8 mg, 0.645 mmol, 5 equiv) and 0.05 M OsO_4 in *t*-BuOH (0.52 ml, 0.0259 mmol, 0.2 equiv) at room temperature. The mixture was stirred for 24 h at 50 °C in the dark and then $NaHSO_3$ (108 mg, 1.03 mmol, 8 equiv) and Na_2SO_4 (200 mg) was added to the mixture at 0 °C. After 2 h, the mixture was filtered through a bed of Celite and the bed was washed with acetone thoroughly. The filtrate and washings were combined and evaporated to give a crude diol. This residue was treated with 2 M HCl (2 mL) for 1.5 h at 80 °C, followed by acetylation with acetic anhydride (1.5 mL) in pyridine (1.5 mL) for 2 h at room temperature. After evaporation, silica gel column chromatography (5 g) with acetonitrile:toluene (4:5, v/v) gave, first, the acetate **D-8a** (6.2 mg, 12.3%) as a syrup. The second fractions gave the acetate **D-7a** (42.3 mg, 83.9%) as a syrup. The spectroscopic data of these compounds were identical with those of the compounds obtained by the method A.

1L-(1,2,3/4,5)-5-Acetamido-3-acetoxymethyl-1,2,4-(L-7a) and 1L-(1,2,5/3,4)-5-acetamido-2-acetoxymethyl-1,3,4-tri-*O*-acetyl-1,2,3,4-cyclopentanetetrael (L-8a). The olefin **D-43** (40.8 mg, 0.130 mmol) was treated, as in the preparation of **D-7a** and **D-8a**, to give, first, compound **L-8a** (24.9 mg, 55.1%) as a syrup; $[\alpha]_D^{23}$ +18.6 (*c* 0.90; acetone) Anal. found: C, 49.45; H, 6.29; N, 3.75%.

The second fractions gave the compound **L-7a** (17.0 mg, 37.6%) as a syrup; $[\alpha]_D^{22}$ +32.1 (*c* 1.50; acetone). Anal. found: C, 49.26; H, 6.26; N, 3.74%.

1D-(1,2,3/4,5)-5-Amino-3-hydroxymethyl-1,2,3,4-cyclopentanetetraol (D-7). Compound **D-7a** (19.7 mg, 0.0506 mmol) was treated with 2 M HCl (2 mL) for 3 h at 80 °C. The reaction mixture was evaporated to give the amine hydrochloride, which was purified by a column of Dowex 50W-X2 (H^+) resin (1 mL) with 4 M aq NH_4OH as eluent to afford the free base **D-7** (11.5 mg, 93.7%) as a syrup; R_f 0.50 (AcOH:water:acetonitrile, 1:10:20), $[\alpha]_D^{20}$ +11.6 (*c* 0.56; pyridine), IR (neat) ν 3350 (OH and NH_2) cm^{-1}; ^1H NMR (D_2O, ref *t*-BuOH at 70 °C) δ 4.01–3.88 (3 H, m, 1-, 2-, and 4-H), 3.77 and 3.63 (each 3 H, ABq, J_{gem} = 11.9 Hz, 2 × 6-H), 3.42–3.33 (1 H, m, 5-H).

1L-(1,2,3/4,5)-5-Amino-3-hydroxymethyl-1,2,3,4-cyclopentanetetraol (L-7). Compound **L-7a** (37.1 mg, 0.0953 mmol) was treated, as in the preparation of **D-7**, to give the free base **L-7** (17.1 mg, ~100%) as a syrup; $[\alpha]_D^{21}$ −8.8 (*c* 0.86; pyridine).

1D-(1,2,5/3,4)-5-Amino-2-hydroxymethyl-1,2,3,4-cyclopentanetetraol (D-8). Compound **D-8a** (30.0 mg, 0.0770 mmol) was treated with 2 M HCl (2 mL) for 3 h at 80 °C. The reaction mixture was evaporated to give the amine hydrochloride, which was purified by a column of Dowex 50W-X2 (H^+) resin (1 mL) with 4 M aq NH_4OH as eluent to afford the free base **D-8** (16.7 mg, 98.2%) as a syrup; R_f 0.50 (AcOH:water:acetonitrile, 1:10:20), $[\alpha]_D^{20}$ −7.2 (*c* 0.52; water), IR (neat) ν 3400 (OH and NH_2) cm^{-1}; ^1H NMR (D_2O, ref *t*-BuOH at 70 °C) δ 4.15–3.92 (3 H, m, 1-, 3-, and 4-H), 3.78 and 3.61 (each 1 H, ABq, J_{gem} = 12.3 Hz, 2 × 6-H), 3.34–3.24 (1 H, m, 5-H).

1L-(1,2,5/3,4)-5-Amino-2-hydroxymethyl-1,2,3,4-cyclopentanetetraol (L-8). Compound **L-8a** (18.0 mg, 0.0462 mmol) was treated, as in the preparation of **D-8**, to give the free base **L-8** (8.4 mg, ~100%) as a syrup, $[\alpha]_D^{21}$ +7.0 (*c* 0.39; water).

General synthetic procedure for thioureas

Known 5-amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols **D, L-3**, **D, L-4**, **D, L-5**, and **D, L-6** used in this paper were prepared following previously reported procedures.[2] Similarly, 5-amino-1,2,3,4-cyclopentanetetraol[3] **D, L-11** and its three *meso* isomers[12] **9**, **13**, and **16** were synthesized following the standard procedures.

To a solution of an amino alcohol in 80% aq ethanol was added phenylisothiocyanate (1.5–2.0 equiv) purchased from TCI (Tokyo Chemical Industry Co., Ltd.) at room temperature. The reaction mixture was stirred for 2–24 h at room temperature, and then evaporated to give a crude thiourea, which was purified by chromatography on silica gel with ethanol:toluene (1:2, v/v) as eluent to afford a thiourea (72–100%).

***N*-[(1*S*)-(1,3,5/2,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (L-3).** $[\alpha]_D^{25}$ −20.6 (*c* 1.45; MeOH). Anal. calcd for $C_{13}H_{18}N_2O_5S$:

C, 49.67; H, 5.77; N, 8.91%. Found, 49.65; H, 5.94; N, 8.70%. The ^{1}H NMR and IR spectra, and R_f value were identical with those of the enantiomer.[4]

***N*-[(1*R*)-(1,2,3,5/4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (L-4c).** R_f 0.41 (EtOH:toluene, 1:2), $[\alpha]_D^{22}$ +43.9 (*c* 1.18; acetone), IR (KBr disk) ν 3280 (OH and NH) and 1540 (NH) cm^{-1}; ^{1}H NMR (D_2O, ref acetone) δ 7.38–7.17 (5 H, m, Ph), 4.66 (1 H, m, 1-H), 3.97 (1 H, dd, $J_{1,5}$ = 8.1, $J_{4,5}$ = 4.6 Hz, 5-H), 3.87 (1 H, dd, $J_{3,4}$ = 8.4, $J_{4,5}$ = 4.6 Hz, 4-H), 3.67 (1 H, d, $J_{3,4}$ = 8.4 Hz, 3-H), 3.38 and 3.33 (each 1 H, ABq, J_{gem} = 12.1 Hz, 2 × 6-H). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.93; H, 6.17; N, 8.59%.

***N*-[(1*S*)-(1,2,3,5/4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (D-4c).** $[\alpha]_D^{24}$ −44.9 (*c* 1.07; acetone). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.74; H, 6.12; N, 8.66%.

***N*-[(1*R*)-(1,5/2,3,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-N'-phenylthiourea (D-5c).** R_f 0.64 (water:acetonitrile, 1:8), $[\alpha]_D^{31}$ +21.2 (*c* 0.55; MeOH), IR (KBr disk) ν 3400 (OH and NH) and 1530 (NH) cm^{-1}; ^{1}H NMR (D_2O, ref acetone) δ 7.40–7.14 (5 H, m, Ph), 4.83 (1 H, d, $J_{1,5}$ = 6.6 Hz, 1-H), 4.12 (1 H, dd, $J_{1,5}$ = 6.6, $J_{4,5}$ = 3.3 Hz, 5-H), 3.94–3.77 (2 H, m, 3- and 4-H), 3.43 and 3.32 (each 1 H, ABq, J_{gem} = 11.7 Hz, 2 × 6-H). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.86; H, 6.11; N, 8.61%.

***N*-[(1*S*)-(1,5/2,3,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (L-5c).** $[\alpha]_D^{29}$ −20.5 (*c* 0.39; MeOH). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.41; H, 6.25; N, 8.42%.

***N*-[(1*R*)-(1,2,5/3,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (L-6c).** R_f 0.65 (water:acetonitrile, 1:8), $[\alpha]_D^{30}$ +12.5 (*c* 0.43; MeOH), IR (KBr disk) ν 3400 (OH and NH) and 1530 (NH) cm^{-1}; ^{1}H NMR (D_2O, ref acetone) δ 7.42–7.18 (5 H, m, Ph), 4.70–4.50 (1 H, m, 1-H), 4.11 (1 H, dd, $J_{1,5}$ = 8.1, $J_{4,5}$ = 5.0 Hz, 5-H), 4.04 (1 H, dd, $J_{3,4}$ = 4.6, $J_{4,5}$ = 5.0 Hz, 4-H), 3.87 (1 H, d, $J_{3,4}$ = 4.6 Hz, 3-H), 3.71 and 3.48 (each 1 H, ABq, J_{gem} = 12.1 Hz, 2 × 6-H). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.74; H, 6.20; N, 8.61%.

***N*-[(1*S*)-(1,2,5/3,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (D-6c).** $[\alpha]_D^{29}$ −11.6 (*c* 0.24; MeOH). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.36; H, 6.22; N, 8.35%.

***N*-[(1*S*)-(1,2/3,4,5)-2,3,4,5-Tetrahydroxy-3-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (D-7c).** R_f 0.62 (water:acetonitrile, 1:8), $[\alpha]_D^{22}$ +14.6 (*c* 0.50; MeOH), IR (KBr disk) ν 3410 (OH and NH) and 1540 (NH) cm^{-1}; ^{1}H NMR (D_2O) δ 7.45–7.15 (5 H, m, Ph), 4.85–4.65 (1 H, m, 1-H), 4.07 (1 H, d, $J_{1,2}$ 5.5 Hz, 2-H), 4.05–3.94 (1 H, m, 5-H), 3.79 (1 H, br d, $J_{4,5}$ 7.3 Hz, 4-H), 3.59 and 3.47 (each 1 H, ABq, J_{gem} 11.7 Hz, 2 × 6-H). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.81; H, 6.11; N, 9.28%.

***N*-[(1*R*)-(1,2/3,4,5)-2,3,4,5-Tetrahydroxy-3-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (L-7c).** $[\alpha]_D^{19}$ −15.7 (*c* 0.99; MeOH). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.67; H, 6.09; N, 9.40%.

***N*-[(1*S*)-(1,2,3/4,5)-2,3,4,5-Tetrahydroxy-3-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (D-8c).** R_f 0.71 (water:acetonitrile, 1:8), $[\alpha]_D^{22}$ +35.3 (*c* 1.09; MeOH), IR (KBr disk) ν 3430 (OH and NH) and 1540 (NH) cm^{-1}; ^{1}H NMR (D_2O, ref acetone) δ 7.43–7.15 (5 H, m, Ph), 4.85–4.50 (1 H, m, 1-H), 4.15–4.03 (2 H, m, 2- and 5-H), 3.82 (1 H, d, $J_{4,5}$ = 5.1 Hz, 4-H), 3.68 and 3.50 (each 1 H, ABq, J_{gem} = 11.9 Hz, 2 × 6-H). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.95; H, 5.93; N, 9.25%.

***N*-[(1*R*)-(1,2,3/4,5)-2,3,4,5-Tetrahydroxy-3-(hydroxymethyl)cyclopentyl]-*N'*-phenylthiourea (L-8c).** $[\alpha]_D^{19}$ −38.7 (*c* 0.43; MeOH). Anal. calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91%. Found: C, 49.86; H, 6.16; N, 9.21%.

***N*-[(1,2,3,4,5/0)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (9c).** R_f 0.37 (EtOH:toluene, 1:2), IR (KBr disk) ν 3400 (OH and NH) and 1530 (NH) cm^{-1}; ^{1}H NMR (D_2O; ref acetone) δ 7.40–7.16 (5 H, m, Ph), 4.64–4.50 (1 H, m, 5-H), 4.13–4.06 (2 H, m, 1- and 4-H), 3.92–3.87 (2 H, m, 2- and 3-H). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 50.82; H, 5.86; N, 9.84%.

***N*-[(1S)-(1,2,3,4/5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (D-10c).** R_f 0.30 (EtOH:toluene, 1:4), $[\alpha]_D^{22}$ +11.8 (*c* 1.03; MeOH), ν (KBr disk) 3250 (OH and NH) and 1580 (NH) cm^{-1}; ^{1}H NMR (D_2O, ref acetone) δ 7.30–7.15 (5 H, m, Ph), 4.51–4.40 (1 H, m, 1-H), 4.22–3.74 (4 H, m, 2-, 3-, 4-, and 5-H). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 50.64; H, 5.92; N, 9.77%.

***N*-[(1*R*)-(1,2,3,4/5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (L-10c).** $[\alpha]_D^{19}$ −8.7 (*c* 0.75; MeOH). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 50.60; H, 5.75; N, 9.64%.

***N*-[(1*S*)-(1,2,4/3,5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (D-11c).** R_f 0.79 (water:acetonitrile, 1:4), $[\alpha]_D^{24}$ +22.1 (*c* 1.02; acetone), IR (KBr disk) ν 3400 (OH and NH) and 1550 (NH) cm^{-1}; ^{1}H NMR (D_2O, ref acetone) δ 7.40–7.15 (5 H, m, Ph), 4.60–4.45 (1 H, m, 1-H), 4.03–3.96 (1 H, m, 2-H), 3.79–3.67 (1 H, m, 5-H), 3.62–3.55 (2 H, m, 3- and 4-H). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 50.44; H, 5.81; N, 9.64%.

***N*-[(1*R*)-(1,2,4/3,5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (L-11c).** $[\alpha]_D^{27}$ −22.2 (*c* 0.47; acetone). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 50.88; H, 5.70; N, 9.56%.

***N*-[(1,2,5/3,4)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (12c).** R_f 0.44 (EtOH:toluene, 1:2), mp 156–158 °C (from EtOH:toluene, 1:2), IR (KBr disk) ν 3430, 3290, and 3160 (OH and NH) and 1570 and 1510 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.38–7.17 (5 H, m, Ph), 4.71 (1 H, m, 1-H), 4.09 (2 H, dd, J = 2.4 and 7.0 Hz, 2- and 5-H), 3.90 (2 H, d, J = 2.4 Hz, 3- and 4-H). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 50.58; H, 5.92; N, 9.89%.

***N*-[(1*S*)-(1,2,3/4,5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (D-14c).** R_f 0.46 (EtOH:toluene, 1:2), $[\alpha]_D^{26}$ +20.7 (*c* 0.91; EtOH), IR (KBr disk) ν 3420 (OH and NH), and 1540 and 1500 (NH) cm $^{-1}$; ^1H NMR (D_2O, ref acetone) δ 7.40–7.15 (5 H, m, Ph), 4.57–4.44 (1 H, m, 1-H), 4.13 (1 H, dd, J = 3.7 and 4.4 Hz, 2- or 5-H), 4.04–3.82 (3 H, m, 2- or 5-, 3-, and 4-H). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 51.01; H, 5.93; N, 9.71%.

***N*-[(1*R*)-(1,2,3/4,5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (L-14c).** $[\alpha]_D^{26}$ −20.3 (*c* 0.53; EtOH). Anal. calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85%. Found: C, 50.81; H, 5.93; N, 9.87%.

***N*-[(1*S*)-(1,2/3,4,5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (D-15c).** R_f 0.31 (EtOH:toluene, 1:2), $[\alpha]_D^{23}$ +62.7 (*c* 1.89; acetone), IR (KBr disk) ν 3320 (OH and NH), and 1530 and 1500 (NH) cm^{-1}, ^1H NMR (D_2O, ref acetone) δ 7.20–7.00 (5 H, m, Ph), 4.70–4.60 (1 H, m, 1-H), 4.11 (1 H, dd, J = 6.2 and 8.1 Hz, 2- or 5-H), 3.90–3.81 (2 H, m, 2- or 5- and 3- or 4-H), 3.72 (1 H, br s, 3- or 4-H). Anal. calcd for $C_{12}H_{16}N_2O_4S{\cdot}0.5H_2O$: C, 49.13; H, 5.84; N, 9.55%. Found: C, 48.83; H, 5.80; N, 9.39%.

***N*-[(1*R*)-(1,2/3,4,5)-2,3,4,5-Tetrahydroxycyclopentyl]-*N'*-phenylthiourea (L-14c).** $[\alpha]_D^{23}$ −61.5 (*c* 2.44; acetone). Anal. calcd for $C_{12}H_{16}N_2O_4S{\cdot}0.25H_2O$: C, 49.90; H, 5.76; N, 9.70%. Found: C, 49.79; H, 5.96; N, 9.61%.

General synthetic procedure for isoureas

Each thioureas were treated with yellow HgO (3 equiv), freshly prepared from NaOH and $HgCl_2$ and dried thoroughly, in ethanol:acetone (1:2, v/v) for 3–24 h at room temperature.[2] The reaction mixture was filtered through a bed of Celite and the bed was washed with ethanol. The filtrate and washings were combined and evaporated to give crude isoureas, which were chromatographed on a column of Dowex 50W-X2 (H^+) resin with 14 M aq NH_4OH:methanol (1:13, v/v) as eluent to afford isoureas (87–100%) as a very hygroscopic white solid.

In this preparative reaction, the thioureas having two *cis*-hydroxyl groups adjacent to the nitrogen function on cyclopentane ring produced a mixture of two positionally isomeric cyclo-isoureas. Therefore, two isoureas were separated by preparative TLC (developed by ethanol:toluene or methanol:chloroform) and further purified by a column of Dowex 50W-X2 (H^+) resin with 14 M aq NH_4OH:methanol (1:13, v/v) as eluate. The free isoureas thus obtained were subjected to biological assay immediately. The products ratio originally depends on stereochemical requirements and later on the work up conditions. Under basic conditions, a pair of isoureas can be interconvertible with each other and finally move to the more stable isoureas, the cyclic isourea rings of which are composed of tertiary hydroxyl groups.

(1*R*,5*S*,6*S*,7*R*,8*S*)-6-Hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*R*-17). $[\alpha]_D^{26}$ −86.4 (*c* 0.91; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5{\cdot}0.25H_2O$: C, 54.83; H, 5.84; N, 9.84%. Found: C, 54.83; H, 5.66; N, 9.84%.

^1H NMR and IR data, and R_f value were identical with those of the enantiomer reported.[4]

(1*S*,5*R*,6*S*,7*S*,8*R*)-6-Hydroxymethyl-(*S*-18) and (1*S*,5*R*,6*S*,7*R*,8*S*)-1-hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*S*-19). Compound ***S*-18** (51%): R_f 0.22 (EtOH:toluene, 1:2), $[\alpha]_D^{28}$ +50.1 (*c* 0.15; MeOH), IR (KBr disk) ν 3430 (OH and NH), 1660 (C=N), and 1580 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.26–6.97 (5 H, m, Ph), 4.56 (1 H, dd, $J_{1,5}$ = 9.5, $J_{1,8}$ = 4.2 Hz, 1-H), 4.25 (1 H, d, $J_{1,5}$ = 9.5 Hz, 5-H), 4.13 (1 H, dd, $J_{1,8}$ = 4.2, $J_{7,8}$ = 9.5 Hz, 8-H), 3.67 (1 H, d, $J_{7,8}$ = 9.5 Hz, 7-H), 3.46 (2 H, s, 2 × 9-H). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99%. Found: C, 55.30; H, 5.81; N, 9.84%.

Compound ***S*-19** (44%): R_f 0.17 (EtOH:toluene, 1:2), $[\alpha]_D^{28}$ −27.5 (*c* 0.26; MeOH), IR (KBr disk) ν 3420 (OH and NH), 1670 (C=N), and 1560 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.29–6.97 (5 H, m, Ph), 4.06 (1 H, d, $J_{5,6}$ = 5.9 Hz, 5-H), 3.76 and 3.56 (each 1 H, ABq, J_{gem} = 12.5 Hz, 2 × 9-H), 3.72–3.61 (3 H, m, 6-, 7-, and 8-H). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99% . Found: C, 55.25; H, 5.75; N, 10.01.

(1*R*,5*S*,6*R*,7*R*,8*S*)-6-Hydroxymethyl-(*R*-18) and (1*R*,5*S*,6*R*,7*S*,8*R*)-1-hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*R*-19). Compound ***R*-18** (62%): $[\alpha]_D^{28}$ −57.9 (*c* 0.24; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99%. Found: C, 55.16; H, 5.80; N, 9.75%.

Compound ***R*-19** (35%): $[\alpha]_D^{28}$ +24.7 (*c* 0.33; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99%. Found: C, 55.26; H, 5.76; N, 9.80%.

(1*S*,5*R*,6*R*,7*R*,8*R*)-6-Hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*S*-20). R_f 0.41 (water:acetonitrile, 1:10), $[\alpha]_D^{30}$ +64.9 (*c* 0.29; MeOH),

IR (KBr disk) ν 3430 (OH and NH), 1650 (C=N), and 1580 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.30–6.95 (5 H, m, Ph), 4.87 (1 H, dd, $J_{1,5}$ = 8.4, $J_{1,8}$ = 1.5 Hz, 1-H), 4.27 (1 H, d, $J_{1,5}$ = 8.4 Hz, 5-H), 4.09 (1 H, dd, $J_{1,8}$ = 1.5, $J_{7,8}$ = 5.1 Hz, 8-H), 3.87 (1 H, d, $J_{7,8}$ = 5.1 Hz, 7-H), 3.66 and 3.56 (each 1 H, ABq, J_{gem} = 12.1 Hz, 2 × 9-H). Anal. calcd for $C_{13}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 53.97; H, 5.92; N, 9.68%. Found: C, 54.07; H, 5.74; N, 9.78.

(1*R*,5*S*,6*S*,7*S*,8*S*)-6-Hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*R*-20). $[\alpha]_D^{30}$ −69.4 (*c* 0.34; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99%. Found: C, 55.45; H, 5.96; N, 10.08%.

(1*S*,5*R*,6*S*,7*R*,8*R*)-6-Hydroxymethyl-(*S*-21) and (1S,5*R*,6S,7*R*,8R)-1-hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*S*-22). Compound ***S*-21** (51%): R_f 0.48 (AcOH:MeOH:$CHCl_3$, 1:10:40), $[\alpha]_D^{27}$ +56.8 (*c* 0.38; MeOH), IR (KBr disk) ν 3400 (OH and NH), 1660 (C=N), and 1580 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.30–6.95 (5 H, m, Ph), 4.77 (1 H, dd, $J_{1,5}$ = 9.2, $J_{1,8}$ = 4.4 Hz, 1-H), 4.29 (1 H, dd, $J_{1,8}$ = 4.4, $J_{7,8}$ = 4.0 Hz, 8-H), 4.19 (1 H, d, $J_{1,5}$ = 9.2 Hz, 5-H), 3.91 (1 H, d, $J_{7,8}$ = 4.0 Hz, 7-H), 3.73 and 3.55 (each 1 H, ABq, J_{gem} = 12.1 Hz, 2 × 9-H). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99%. Found: C, 55.20; H, 5.90; N, 9.68%.

Compound ***S*-22** (39%): R_f 0.38 (AcOH:MeOH:$CHCl_3$, 1:10:40), $[\alpha]_D^{27}$ −32.6 (*c* 0.13; MeOH), IR (KBr disk) ν 3400 (OH and NH), 1650 (C=N), and 1560 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.35–7.05 (5 H, m, Ph), 4.10 (each 1 H, 2 d, J = 4.4 and 5.9 Hz, 5 and 8-H), 4.04 (1 H, dd, $J_{6,7}$ = 8.1, J = 5.9 Hz, 6- or 7-H), 3.91 (1 H, dd, J = 4.4, $J_{6,7}$ = 8.1 Hz, 6- or 7-H), 3.87 and 3.73 (each 1 H, ABq, J_{gem} = 13.2 Hz, 2 × 9-H). Anal. calcd for $C_{13}H_{16}N_2O_5 \cdot 0.25H_2O$: C, 54.83; H, 5.84; N, 9.84%. Found: C, 54.43; H, 5.94; N, 9.81%.

(1*R*,5*S*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-(*R*-21) and (1*R*,5S,6*R*,7*S*,8*S*)-1-hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*R*-22). Compound ***R*-21** (31%): $[\alpha]_D^{25}$ −53.6 (*c* 0.43; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 53.97; H, 5.92; N, 9.68%. Found: C, 54.02; H, 5.78; N, 9.74.

Compound ***R*-22** (62%): $[\alpha]_D^{25}$ +35.2 (*c* 0.29; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 53.97; H, 5.92; N, 9.68% . Found: C, 53.62; H, 5.99; N, 9.53.

(1*S*,5*S*,6*S*,7*S*,8*S*)-8-Hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*S*-23). R_f 0.39 (water:acetonitrile, 1:8), $[\alpha]_D^{22}$ +13.4 (*c* 0.40; MeOH), IR (KBr disk) ν 3440 (OH and NH), 1660 (C=N), and 1600 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.30–6.95 (5 H, m, Ph), 4.80 (1 H, d, $J_{1,5}$ = 8.1 Hz, 1-H), 4.30 (1 H, br d, J = 8.1 Hz, 5-H), 3.89 (1 H, br d, J = 5.1 Hz, 6-H), 3.77 (1 H, d, $J_{6,7}$ = 4.7 Hz, 7-H), 3.67 and 3.59 (each 1 H, ABq, J_{gem} = 12.1 Hz, 2 × 9-H). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99%. Found: C, 55.31; H, 5.76; N, 9.90%.

(1*R*,5*R*,6*R*,7*R*,8*R*)-8-Hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*R*-23). $[\alpha]_D^{22}$ −12.8 (*c* 0.78; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99%. Found: C, 55.52; H, 5.84; N, 9.98%.

(1*S*,5*S*,6*S*,7*S*,8*R*)-8-Hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*S*-24). R_f 0.43 (water:acetonitrile, 1:8), $[\alpha]_D^{22}$ +111 (*c* 0.32; MeOH), IR (KBr disk) ν 3420 (OH and NH), 1660 (C=N), and 1600 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.35–6.95 (5 H, m, Ph), 4.75 (1 H, d, $J_{1,5}$ = 9.0 Hz, 1-H), 4.15 (1 H, dd, $J_{1,5}$ = 9.0, $J_{5,6}$ = 3.9 Hz, 5-H), 4.03 (1 H, dd, $J_{5,6}$ = 3.9, $J_{6,7}$ = 4.2 Hz, 6-H), 3.92 (1 H, d, $J_{6,7}$ = 4.2 Hz, 7-H), 3.73 and 3.66 (each 1 H, ABq, J_{gem} = 12.3 Hz, 2 × 9-H). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; N, 5.75; N, 9.99%. Found: C, 55.58; H, 5.82; N, 10.13%.

(1*R*,5*R*,6*R*,7*R*,8*S*)-8-Hydroxymethyl-3-phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (*R*-24). $[\alpha]_D^{22}$ −108 (*c* 0.35; MeOH). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; N, 5.75; N, 9.99%. Found: C, 55.56; H, 6.03; N, 10.19%.

(1*SR*,5*SR*,6*RS*,7*RS*,8*SR*)-3-Phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (25). R_f 0.59 (EtOH:$CHCl_3$, 1:1), IR (KBr disk) ν 3400 (OH and NH) and 1650 (C=N) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.28–6.95 (5 H, m, Ph), 4.86 (1 H, dd, $J_{1,5}$ = 7.3, $J_{1,8}$ = 5.3 Hz, 1-H), 4.28 (1 H, dd, $J_{1,5}$ = 7.3, $J_{5,6}$ = 7.0 Hz, 5-H), 3.96 (1 H, dd, $J_{1,8}$ = 5.3, $J_{7,8}$ = 4.4 Hz, 8-H), 3.93–3.85 (2 H, m, 6- and 7-H). Anal. calcd for $C_{12}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 56.58; H, 5.74; N, 11.00%. Found: C, 56.40; H, 5.75; N, 10.90%.

(1*S*,5*S*,6*S*,7*R*,8*S*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*S*-26). R_f 0.34 (water:acetonitrile, 1:8), $[\alpha]_D^{21}$ +72.2 (*c* 0.22; MeOH), IR (KBr disk) ν 3450 (OH and NH) and 1650 (C=N) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.30–7.00 (5 H, m, Ph), 4.96 (1 H, dd, $J_{1,5}$ = 5.0, $J_{1,8}$ = 7.7 Hz, 1-H), 4.19 (1 H, dd, $J_{1,5}$ = 5.0, $J_{5,6}$ = 4.2 Hz, 5-H), 4.04 (1 H, dd, $J_{1,8}$ = 7.7, $J_{7,8}$ = 1.5 Hz, 8-H), 3.92 (1 H, dd, $J_{6,7}$ = 3.7, $J_{7,8}$ =1.5 Hz, 7-H), 3.85 (1 H, dd, $J_{5,6}$ = 4.2, $J_{6,7}$ = 3.7 Hz, 6-H). Anal. calcd for $C_{12}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 56.58; H, 5.74; N, 11.00%. Found: C, 56.74; H, 6.02; N, 10.76.

(1*R*,5*R*,6*R*,7*S*,8*R*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*R*-26). $[\alpha]_D^{23}$ −68.0 (*c* 0.22; MeOH). Anal. calcd for $C_{12}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 56.58; H, 5.74; N, 11.00%. Found: C, 56.60; H, 5.68; N, 10.97%.

(1*S*,5*S*,6*S*,7*R*,8*R*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*S*-27). R_f 0.39 (EtOH:toluene, 1:20), $[\alpha]_D^{22}$ +37.8 (*c* 0.61; acetone), IR (KBr disk) ν 3400 (OH and NH) and 1650 (C=N) cm^{-1}, ^1H NMR (D_2O, ref acetone) δ 7.30–7.07 (5 H, m, Ph), 4.70–4.60 (1 H, m, 1-H), 4.01 (1 H, dd, $J_{1,5}$ = 9.5, $J_{5,6}$ = 4.8 Hz, 5-H), 3.87 (1 H, dd, $J_{1,8}$ = 5.1, $J_{7,8}$ = 7.3 Hz, 8-H), 3.66 (1 H, dd, $J_{5,6}$ = 4.8, $J_{6,7}$ = 8.1 Hz, 6-H), 3.61 (1 H, dd, $J_{6,7}$ = 8.1, $J_{7,8}$ = 7.3 Hz, 7-H). Anal. calcd for

$C_{12}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 56.58; H, 5.74; N, 11.00%. Found: C, 56.62; H, 5.72; N, 11.05%.

(1*R*,5*R*,6*R*,7*S*,8*S*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*R*-27). $[\alpha]_D^{25}$ −35.1 (*c* 1.18; acetone). Anal. calcd for $C_{12}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 56.58; H, 5.74; N, 11.00%. Found: C, 56.69; H, 5.76; N, 10.85%.

(1*SR*,5*SR*,6*RS*,7*SR*,8*RS*)-3-Phenylamino-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (28). R_f 0.28 (AcOH:EtOH:toluene, 1:2:4), IR (KBr disk) ν 3310 and 3060 (OH and NH), 1670 (C=N), and 1595 (NH) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.26–6.96 (5 H, m, Ph), 4.69 (1 H, dd, $J_{1,5}$ = 7.9, $J_{1,8}$ = 1.1 Hz, 1-H), 4.30 (1 H, dd, $J_{1,5}$ = 7.9, $J_{5,6}$ = 6.3 Hz, 5-H), 4.00 (1 H, dd, $J_{5,6}$ = 6.3, $J_{6,7}$ = 8.0 Hz, 6-H), 3.99 (1 H, dd, $J_{1,8}$ = 1.1, $J_{7,8}$ = 4.3 Hz, 8-H), 3.83 (1 H, dd, $J_{6,7}$ = 8.0, $J_{7,8}$ = 4.3 Hz, 7-H). Anal. calcd for $C_{12}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 56.58; H, 5.74; N, 11.00%. Found: C, 56.93; H, 5.78; N, 11.05%.

(1*S*,5*S*,6*S*,7S,8*S*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*S*-29). R_f 0.42 (EtOH:toluene, 1:2), $[\alpha]_D^{29}$ +126 (*c* 0.84; MeOH), IR (KBr disk) ν 3420 (OH and NH), and 1650 (C=N) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.30–6.95 (5 H, m, Ph), 4.83 (1 H, dd, $J_{1,5}$ = 7.7, $J_{1,8}$ = 5.5 Hz, 1-H), 4.12 (1 H, dd, $J_{1,5}$ = 7.7, $J_{5,6}$ = 7.0 Hz, 5-H), 4.10 (1 H, dd, $J_{1,8}$ = 5.5, $J_{7,8}$ = 5.1 Hz, 8-H), 3.84 (1 H, dd, $J_{6,7}$ = 4.4, $J_{7,8}$ = 5.1 Hz, 7-H), 3.78 (1 H, dd, $J_{5,6}$ = 7.0, $J_{6,7}$ = 4.4 Hz, 6-H). Anal. calcd for $C_{12}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 56.58; H, 5.74; N, 11.00%. Found: C, 56.38; H, 5.65; N, 10.99%.

(1*R*,5*R*,6*R*,7*R*,8*R*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*R*-29). $[\alpha]_D^{29}$ −132 (*c* 1.18; MeOH). Anal. calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19%. Found: C, 57.30; H, 5.80; N, 11.21%.

(1*S*,5*S*,6*S*,7*S*,8*R*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*S*-30). R_f 0.27 (AcOH:EtOH:toluene, 1:2:4), $[\alpha]_D^{23}$ +64.7 (*c* 1.67; MeOH), IR (KBr disk) ν 3390 (OH and NH), and 1660 and 1600 (C=N) cm^{-1}; ^1H NMR (D_2O, ref acetone) δ 7.25–6.94 (5 H, m, Ph), 4.78 (1 H, dd, $J_{1,5}$ = 9.2, $J_{1,8}$ = 3.9 Hz, 1-H), 4.18 (1 H, dd, $J_{1,5}$ = 9.2, $J_{5,6}$ = 3.8 Hz, 5-H), 3.99 (1 H, dd, $J_{1,8}$ = 3.9, $J_{7,8}$ = 4.0 Hz, 8-H), 3.92 (1 H, dd, $J_{6,7}$ = 4.0, $J_{7,8}$ = 4.0 Hz, 7-H), 3.81 (1 H, dd, $J_{5,6}$ = 3.8, $J_{6,7}$ = 4.0 Hz, 6-H). Anal. calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19%. Found: C, 57.59; H, 5.83; N, 11.34%.

(1*R*,5*R*,6*R*,7*R*,8*S*)-3-Phenylamino-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol (*R*-30): $[\alpha]_D^{23}$ −58.4 (*c* 1.89; MeOH). Anal. calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19%. Found: C, 57.55; H, 5.77; N, 11.03%.

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