Aminocyclopentitol Inhibitors of α-L-Fucosidases

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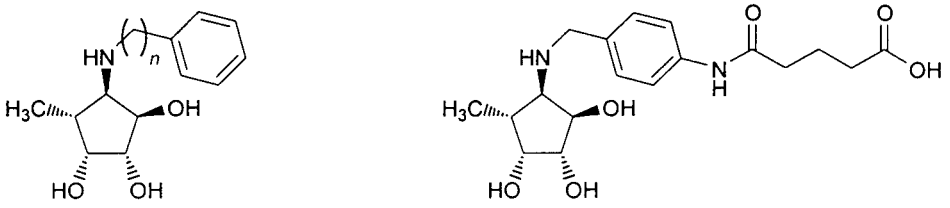
Aminocyclopentitol analogs of α-L-fucose were synthesized stereoselectively from D-ribose. Alkyl substituents were attached at the NH_2 group to mimic the glycosidic leaving group. The resulting (alkylamino)cyclopentitols inhibited α-L-fucosidases selectively with inhibition constants in the range of $K_i = 10^{-7}$ M. Comparisons with stereoisomers and acyclic analogs showed that this inhibition only occurs with *N*-alkyl substitution and proper configuration at the cyclopentane, as expected for transition-state-analog-type inhibition. These observations were supported by molecular-modeling comparisons between inhibitor and transition state.

Introduction. – Glycosidase inhibitors can be used for treating diabetes, cancer, viral (HIV, influenza) and bacterial infections, and as insecticides [1]. In conjunction with our interest in raising glycosidase catalytic antibodies [2], we have been interested in designing glycosidase inhibitors that are also transition-state analogs of the glycosidic bond hydrolysis reaction. In particular, we have investigated the preparation of α-L-fucosidase inhibitors [3]. Such inhibitors might be used as haptens to prepare α-L-fucosidase catalytic antibodies [4], which could be useful to hydrolyze fucosylated cell-surface glycoconjugates [5] such as Sialyl *Lewis* x *in vivo*, and thus serve as a novel therapeutic agent for treating inflammation and cancer. Herein we report the synthesis and properties of α-L-fucosidase inhibitors **1**–**4** based on an aminocyclopentitol core (*Fig. 1*). Inhibitor **4** can be conjugated to carrier proteins and used as a hapten for immunizations.



1 $n = 1$
2 $n = 2$
3 $n = 3$

4

Fig. 1. *Aminocyclopentitol inhibitors of α-L-fucosidases*

Results. – *Design.* Glycosidase inhibitors were first isolated from natural sources, mostly plants, where they apparently act either as antifeedants or as insecticides [6]. A

large number of inhibitors have also been synthesized. All of these structures are generally either considered to be or designed as stable mimics of the oxocarbonium cation which occurs as an intermediate both in the acid-catalyzed and in the enzyme-catalyzed glycosidic bond-cleavage reaction. These inhibitors include one or more of the following structural features: *a*) a carbo- or heterocycle featuring the substituents of the glycosidic substrate in the correct relative configuration; *b*) an sp^2 center at the position corresponding to C(1) of the glycoside substrate, which induces a half-chair conformation resembling that of the oxocarbonium cation; *c*) a basic functional group in a position either corresponding to or in proximity of one or both of the glycosidic O-atoms. A nonbonding electron pair in this basic functional group, typically at a N-atom, usually forms a H-bond or a salt bridge with one of the catalytic carboxy groups within the enzyme's active site. Typical examples include deoxy-nojirimycin **5**, isofagomine **6**, and imidazole **7** (*Fig. 2*) [1c].

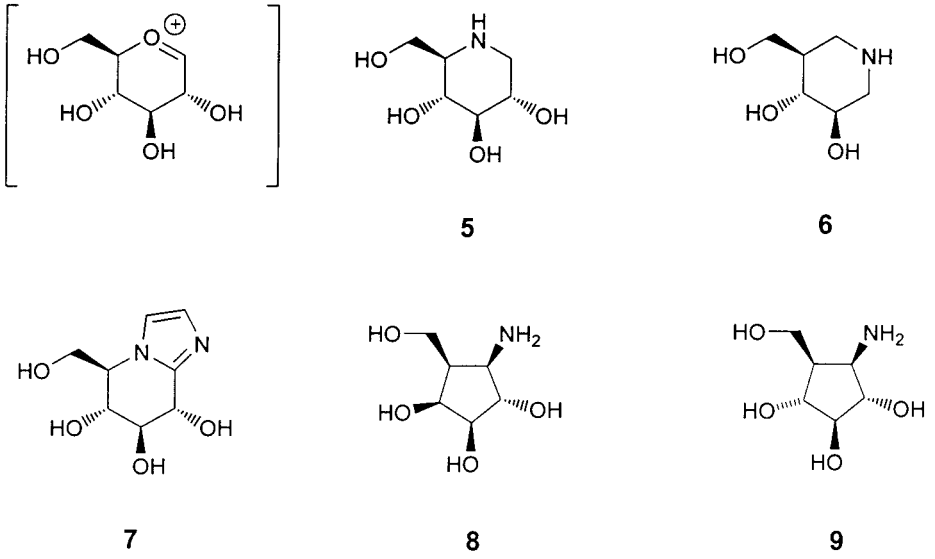


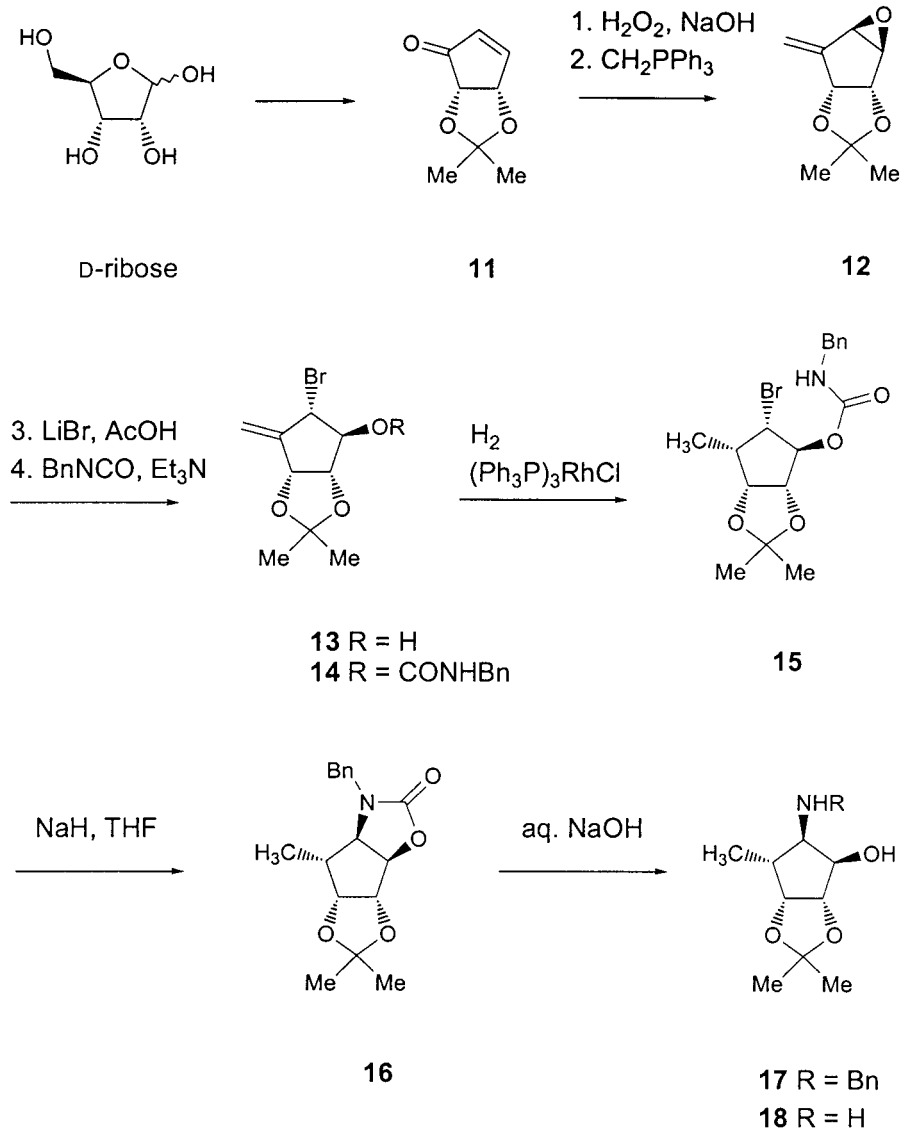
Fig. 2. *Structure of oxocarbonium-cation intermediate for hydrolysis of* D*-glucosides and some glycosidase inhibitors*

Recently, we have shown that aminocyclopentitols, which may be considered as analogs of protonated glycosides, such as '*β-galacto*'-aminocyclopentitol **8** or '*β-gluco*'-aminocyclopentitol **9**, are good and selective inhibitors of *β*-galactosidases and *β*-glucosidases, with competitive inhibition constants in the range of $K_i = 10^{-7}$ M [7]. In addition to displaying the substitution pattern of the glycoside substrate that other inhibitors do, the aminocyclopentitols incorporate an additional stereogenic unit at the NH_2-substituted C-atom, whose relative configuration renders the *α*- or *β*-anomeric configuration at the glycosidic bond. This suggests that one should be able to add an alkyl substituent at that N-atom as a leaving-group mimic with specification of the anomeric configuration. The resulting inhibitor would mimic the transition state of the glycosidic bond-cleavage reaction, and not simply the oxocarbonium ion intermediate.

We decided to test this hypothesis with the example of simple *N*-alkyl derivatives of an '*α*-L-*fuco*'-configurated aminocyclopentitol, for which we had developed an efficient synthesis [8].

Synthesis. The core '*α*-L-*fuco*'-aminocyclopentitol **10** (see below, *Fig. 3*) was prepared from enone **11** according to a synthetic scheme similar to that used previously for the *β*-configured analog and with the allylic epoxide **12** as key intermediate (*Scheme 1*). Opening of the allylic epoxide **12** with LiBr in AcOH gave bromohydrin **13**

Scheme 1. *Stereoselective Synthesis of* '*α*-L-fuco'-*Aminocyclopentitols*



in good yield. This particular reagent combination was found after trying unsuccessfully a series of published procedures for opening epoxides with bromide. It should be noted that the acetonide protecting group of the diol moiety is stable towards AcOH, which serves as a mild acid to activate the epoxide and as the solvent for the reaction. The OH group in **13** was then converted to urethane **14** by reaction with benzyl isocyanate. The C=C bond was reduced stereoselectively from the sterically less-hindered α-face using H_2 and *Wilkinson*'s catalyst. This catalyst was mild enough not to reduce the bromo and *N*-benzyl functions. Reaction of the resulting intermediate **15** with NaH in THF then gave tricyclic compound **16**, now featuring the target 'α-L-*fuco*'-aminocyclopentitol in protected form. The carbamate was then saponified to give amine **17**. Hydrogenation of the benzyl group then gave **18**.

Amine **17** was hydrolyzed in acid to give **1**. Boc-protection of the amine **18** and subsequent acidic hydrolysis gave the free 'α-L-*fuco*'-aminocyclopentitol **10** (*Fig. 3*). Reductive amination of benzeneacetaldehyde and benzenepropanal with amine **18** and hydrolysis with acid gave the *N*-(2-phenylethyl) and *N*-(3-phenylpropyl)-substituted 'α-L-*fuco*'-aminocyclopentitols **2** and **3**. Alternatively, reductive amination of the functionalized aldehyde **21**, prepared in two steps from 4-aminobenzyl alcohol, gave, after hydrolysis, derivative **4**, suitable for conjugation to a protein such as BSA or KLH. *N*-Benzyl-substituted 'β-L-*fuco*'-aminocyclopentitol **20** was also prepared by reductive amination of **19** [3] for comparison purposes. Furthermore, we included (*R*)- and (*S*)-2-aminobutanol (*R*)- and (*S*)-**22**, which we had discovered in a broad screen for inhibition with commerically available compounds, and which represent truncated acyclic analogs of **10** and **19**, respectively, as well as the corresponding *N*-benzyl analogs (*R*)- and (*S*)-**23** as acyclic analogs of **1** and **20**, respectively.

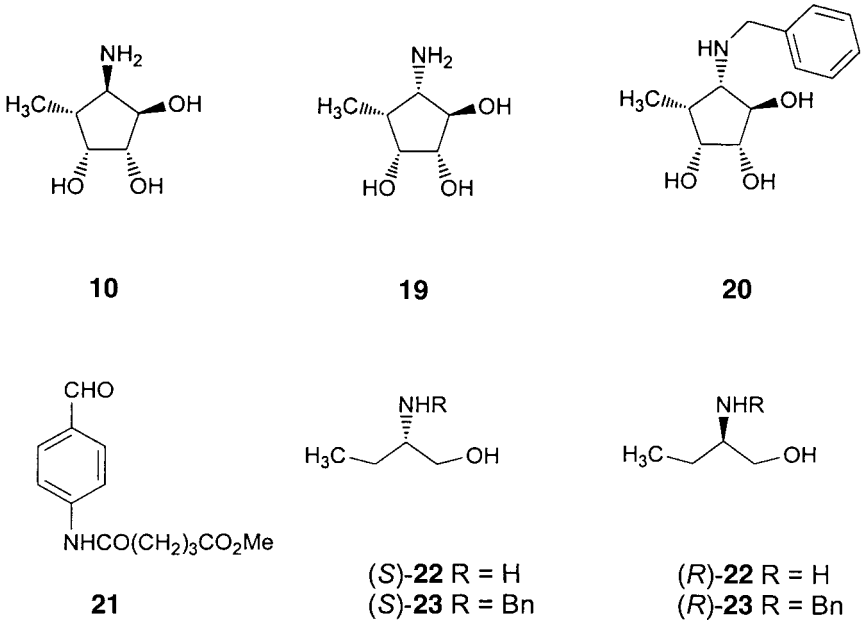


Fig. 3. *Structures of aminocyclopentitols and related structures*

Enzyme Inhibition. All deprotected aminocyclopentitols were tested for inhibition of four different α-L-fucosidases, three of mammalian origin and one of microbial origin. Assays were conducted in aqueous HEPES buffer at pH 6.8 by means of the hydrolysis of 4-nitrophenyl α-L-fucoside as a test reaction, under which conditions all enzymes showed satisfactory activity. Competitive inhibition constants were determined by measuring the *Michaelis-Menten* parameter V_{max} (in arbitrary absorbancy units at 405 nm) and K_M of each enzyme for the 4-nitrophenyl-α-L-fucoside substrate at a series of inhibitor concentrations [I]. The K_i value was then obtained as the value of the x intercept on the $-[I]$ axis when reploting K_M/V_{max} as a function of inhibitor concentration (*Dixon* replot, *Fig. 4*). The results are shown in the *Table.*

The free aminocyclopentitols **10** and **19** showed comparable inhibition potencies with all enzymes. Their inhibition potency was approximately 10-fold stronger than that of their acyclic analogs **22**. The picture looked different with the *N*-alkylated compounds. There, the properly configured *N*-benzyl-substituted '*α*-L-*fuco*'-aminocyclopentitol **1** showed a quite strong inhibition, with K_i as low as $3 \cdot 10^{-7}$ M. By contrast, its β-configured stereoisomer **20** was equally weak or weaker than **19** for all enzymes, while the acyclic analogs did not inhibit the enzymes at all.

Variation of the spacer between the phenyl group and the aminocyclopentitol in the α-series allowed further optimization of inhibition potency. The optimum was reached with the *N*-(2-phenylethyl) derivative **2**, which showed comparably strong potency on all four enzymes, including the *Fucosarium oxysporum 377* α-L-fucosidase, which tended to be only weakly inhibited by the other derivatives in the series. Derivative **4**, suitable for conjugation to a protein, was also a potent inhibitor of all enzymes.

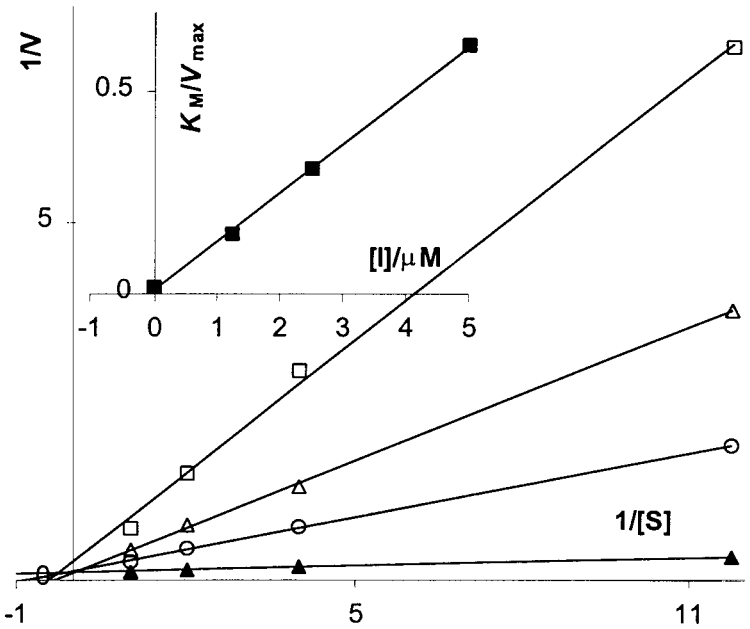


Fig. 4. Lineweaver-Burk *plot and* Dixon *replot for inhibition of human-placenta* α-L-*fucosidase by inhibitor* **2**

Table 1. *Inhibition Data on α-L-Fucosidases*[a])

	K_i [μM]			
	bovine kidney	bovine epididymis	human placenta	*Fucosarium oxysporum 377*
1	0.7	0.6	0.3	6
2	0.4	0.3	0.09	0.3
3	0.4	0.3	0.14	3
4	0.4	0.7	0.19	50
10	15	12	14	125
19	28	18	22	60
20	110	28	18	180
(*R*)-**22**	400	350	200	1100
(*S*)-**22**	200	125	100	1300
(*R*)-**23**	(13%)	(9%)	(6%)	(15%)
(*S*)-**23**	(26%)	(24%)	(26%)	(22%)

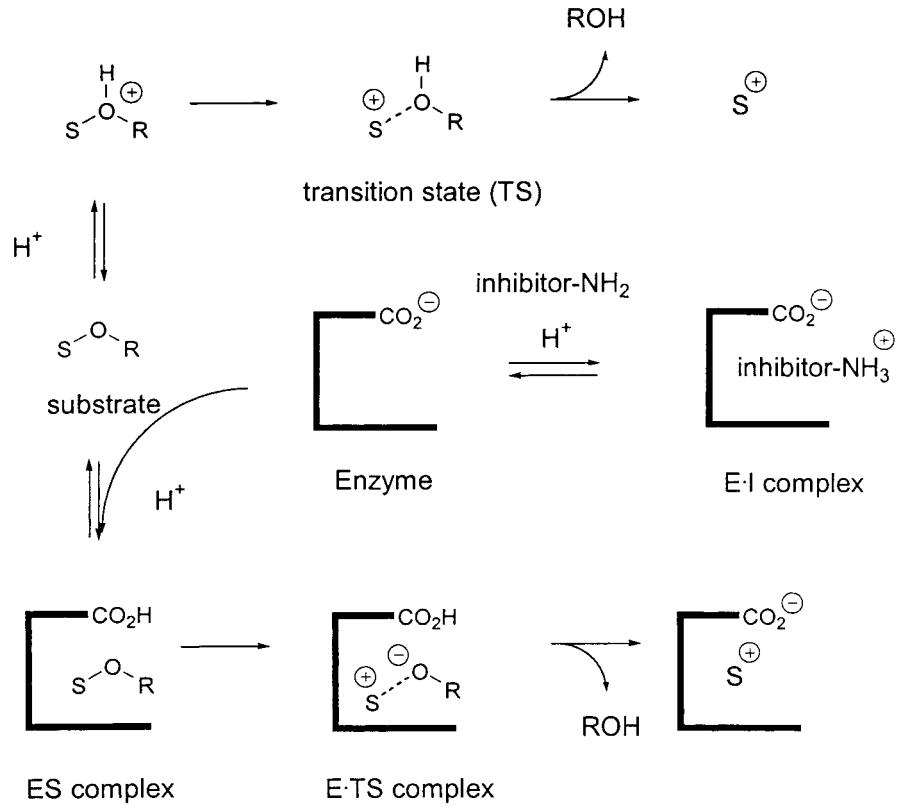
[a]) Measured in 0.1M HEPES buffer at pH 6.8, 25°, with 4-nitrophenyl α-L-fucoside as substrate. Competitive inhibition constant K_i as determined by *Dixon* replot (*Fig. 4*). For weak inhibitors **23**, the number in bracket is the percent inhibition as measured with 1 mM of the inhibitor and 1 mM substrate.

Discussion. – The occurrence of a 100-fold selectivity in inhibition of α-L-fucosidases in the α-configured, *N*-substituted aminocyclopentitols **1** over its β-configured stereoisomer **20** is striking. The reinforcing effect of the *N*-benzyl substituent on inhibition indeed only occurs with the α-configured cyclopentitol, while it diminishes the inhibition effect with the β-analog as well as with the closely related 2-aminobutanols. These results suggest that **1**, and perhaps only **1** (and its derivatives **2**–**4**), occupies the enzyme's active site as an analog of the transition state, with the benzyl group binding in a pocket normally occupied by the glycosidic leaving group.

Binding of the inhibitors to the fucosidase enzyme can be compared with transition-state binding by means of *Pauling*'s analysis of enzymatic catalysis [9]. The general chemical mechanism for glycosidic-bond cleavage involves pre-equilibrium protonation of the leaving-group O-atom in a glycosidic substrate SOR (*Scheme 2*), followed by heterolytic bond cleavage to generate the oxocarbonium cation S^+, *via* a cationic transition state (TS) [10]. The corresponding enzyme-catalyzed process starts with the catalytic carboxy group as carboxylate, which is the predominant form at physiological pH, and binds H^+ and the substrate. Glycosidic-bond cleavage follows, with the bond scission preceeding leaving-group protonation, so that the transition state features a partial negative charge on the leaving-group O-atom, with the catalytic carboxy group still in protonated form next to it [11]. Transition-state binding by the enzyme is formulated starting with the positively charged chemical transition state and the enzyme with its catalytic carboxy group as carboxylate, accompanied by a proton transfer between the leaving group's O-atom and this carboxylate. Inhibitor binding should be similar to the transition-state binding event, the only difference being that the bound inhibitor probably remains as an ion pair with protonated amino group and negatively charged catalytic carboxy group, without proton transfer.

This formulation of transition-state binding is reasonable for glycosidases because the overall molecular geometry of the transition state, in particular the transition-state

Scheme 2. *Mechanisms of Acid-Catalyzed* (upper row) *and Enzyme-Catalyzed* (lower row) *Cleavage of Glycoside S–O–R to the Oxocarbonium-Cation Intermediate S^+ and Aglycone ROH, and Inhibitor Binding*



bond length and angles, do not change significantly between the chemical and the enzymatic mechanism. In that situation it is interesting to compare the inhibitors with the calculated transition state **24** for the acid-catalyzed hydrolysis of phenyl α-L-fucoside, a model substrate with a leaving group matching the aromatic group chosen for the inhibitors. A model transition-state can be generated by enforcing an elongated glycosidic bond in the protonated glycoside. We chose a transition-state bond length of 1.9 Å, as suggested by the calculation of *Bürgi* and *Dubler-Steudle* [12]. To allow structural comparisons, we searched for the most stable conformations in both transition state **24** and the inhibitors by allowing free rotations of the bonds joining the phenyl group to the carbohydrate part of the molecules. The most stable conformations of protonated **1**, **2**, and **20** and of **24** are shown in *Fig. 5*, where the molecules are displayed with their molecular surfaces colored according to the electrostatic potential. While the weak inhibitor **20** · H^+ clearly differs from **24**, the potent inhibitors **1** · H^+, **2** · H^+, and the transition state **24** present good similarities in terms of structure and charge distribution. A good overlap between inhibitor and transition state, as demonstrated here, does not often occur with glycosidase inhibitors, in particular since most inhibitors do not incorporate a leaving-group mimic in conjunction with a glycosidic analog

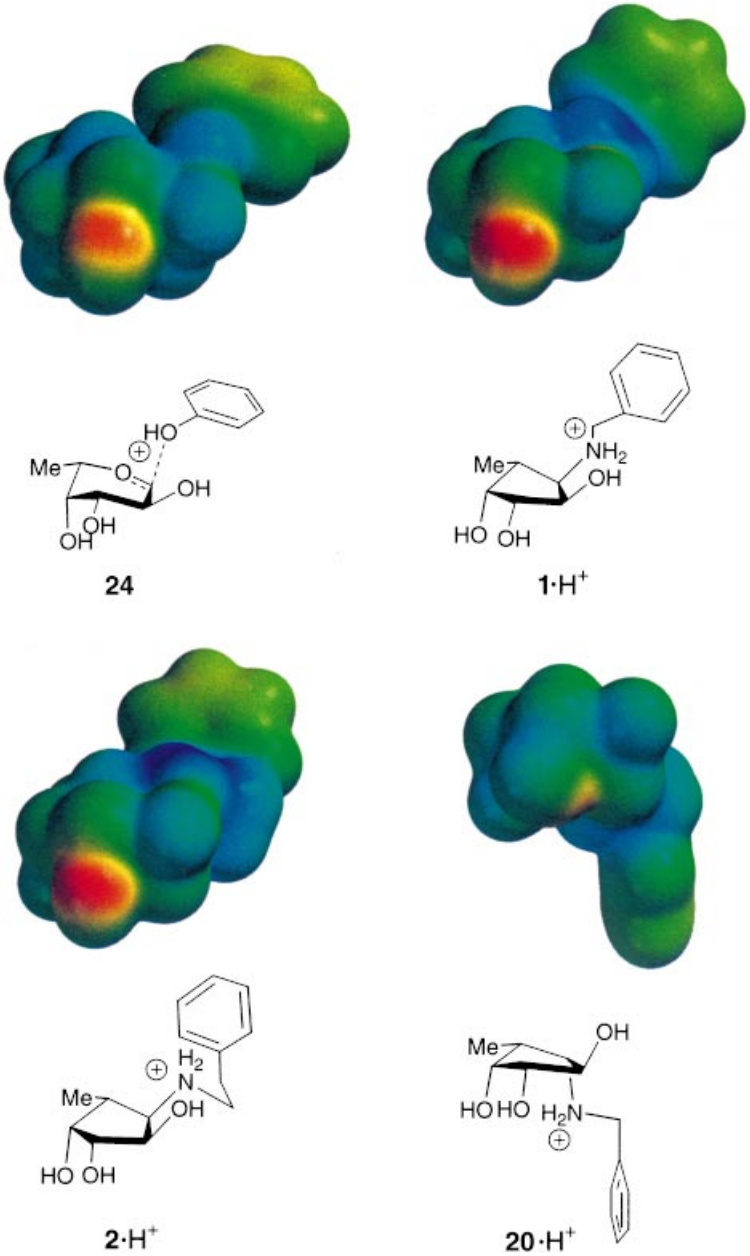


Fig. 5. *Lowest-energy conformations for simulated transition state* **24** *and the protonated forms of inhibitors* **1**, **2**, *and* **20**, *as calculated with Spartan 5.1 (see Exper. Part*). Electronic-density surfaces are colored according to electrostatic potential ranging from +12 kcal/mol (red) to +140 kcal/mol (blue).

allowing for an sp^3 substitution at the position corresponding to C(1), with specification of the anomeric configuration[1]).

Conclusion. – The experiments above demonstrate a series of α-L-fucosidase inhibitors based on an aminocyclopentitol framework and incorporating a leaving-group mimic as an *N*-alkyl substituent. The structural analogies to the transition state for α-L-fucoside cleavage, together with the finding that enzyme inhibition occurs selectively only with the correct configurational pattern, and across four different fucosidases, provides good qualitative support for the idea that these inhibitors are transition-state analogs. It must be mentioned that the inhibition constants $K_i = 10^{-7}$ M measured are not the best values available in the literature, where several inhibitors have been reported with $K_i = 10^{-8}$ M for inhibition of α-L-fucosidases [14]. Derivatives suitable for conjugation to a protein such as **4** might function as haptens to generate catalytic antibodies with α-L-fucosidase activity. Immunization experiments are in progress, and their results will be reported separately.

We would like to thank Prof. Dr. *Vladimír Křen* of the Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic, for a sample of *Fusarium oxysporum 377* α-L-fucosidase. This work was supported by the University of Bern, the *Swiss National Science Foundation*, the *Wander Stiftung*, the European COST program D13, and the Swiss 'Office Fédéral de l'Education et de la Science'.

Experimental Part

1. *Syntheses. (1*S*,2*S*,3*S*,4*R*)-1-Bromo-3,4-*O*-isopropylidene-5-methylidenecyclopentane-2,3,4-triol* (= *(3a*S*,4*S*,5*S*,6a*R*)-5-Bromotetrahydro-2,2-dimethyl-6-methylidene-4*H*-cyclopenta-1,3-dioxol-4-ol*; **13**). Allylic epoxide **12** (220 mg, 1.31 mmol) and LiBr (568 mg, 6.54 mmol) were dissolved in AcOH (4 ml) and stirred for 4.5 h at r.t. FC (hexane/AcOEt 2:1; R_f 0.45) and co-evaporation with toluene (3×) yielded **13** (276 mg, 85%). Colorless oil. $[\alpha]_D^{20} = -54.7$ ($c = 0.51$, $CHCl_3$). IR (Film): 3418*s* (br.), 3012*s*, 2990*s*, 2936*s*, 1728*w*, 1456*m*, 1383*s*, 1374*s*, 1344*w*, 1311*w*, 1274*m*, 1243*m*, 1206*s*, 1156*s*, 1073*s*, 1047*s*, 997*w*, 967*m*, 940*w*, 909*m*, 865*s*, 853*m*. ^{1}H-NMR (500 MHz, $CDCl_3$)[2]): 5.63 (*dd*, $^4J(CH_2{=}C(5),1) = 1.6$, $^4J(CH_2{=}C(5),4) = 1.4$, 1 H, $CH_2{=}C(5)$); 5.62 (*dd*, $^4J(CH_2{=}C(5),1) = 1.6$, $^4J(CH_2{=}C(5),4) = 1.4$, 1 H, $CH_2{=}C(5)$); 5.00 (*dt*, $^3J(4,3) = 6.4$, $^4J(4, CH_2{=}C(5) =$ 1.4, H–C(4)); 4.52–4.47 (*m*, H–C(3), H–C(1)); 4.38 (*dd*, $^3J(2,1) = 4.5$, $^3J(2,3) = 2.5$, H–C(2)); 1.56 (*s*, 3 H, Me_2C); 1.35 (*s*, 3 H, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$)[2]): 146.94 (*s*, C(5)); 118.91 (*t*, $CH_2{=}C(5)$); 112.96 (*s*, Me_2C); 84.83 (*d*, C(3)); 82.57 (*d*, C(2)); 79.70 (*d*, C(4)); 52.22 (*d*, C(1)); 26.52 (*q*, Me_2C); 24.87 (*q*, Me_2C). NMR Signals assigned by C,H correlation and homo-decoupling experiments. HR-EI-MS: 232.9813 ($C_8H_{10}BrO_3^+$, $[M - Me]^+$; calc. 232.9813).

*(1*S*,2*S*,3*R*,4*R*)-2-*O*-(Benzylcarbamoyl)-1-bromo-3,4-*O*-isopropylidene-5-methylidenecyclopentane-2,3,4-triol* (= *(3a*R*,4*S*,5*S*,6a*R*)-5-Bromotetrahydro-2,2-dimethyl-6-methylidene-4*H*-cyclopenta-1,3-dioxol-4-yl Benzylcarbamate*; **14**). A soln. of **13** (54 mg, 0.22 mmol) in abs. CH_2Cl_2 (1.4 ml) was cooled in an ice bath to 0°. After adding Et_3N (12 µl, 0.087 mmol) and benzyl isocyanate (31 µl, 0.36 mmol), the mixture was stirred at 0° for 5 h, then diluted in Et_2O (50 ml), and washed with H_2O. The aq. phase was extracted (Et_2O) and the combined org. layer washed (brine) and evaporated. FC (hexane/AcOEt 2:1; R_f 0.46) yielded **14** (85 mg, quant.). Yellow oil. $[\alpha]_D^{20} = -13.5$ ($c = 0.46$, $CHCl_3$). IR (Film): 3381*s* (br.), 2989*s*, 2934*s*, 2360*w*, 1806*w*, 1727*s*, 1513*s*, 1455*m*, 1432*w*, 1379*s*, 1336*m*, 1286*m*, 1252*s*, 1232*s*, 1205*s*, 1162*m*, 1123*m*, 1085*s*, 1070*s*, 1035*s*, 1017*s*, 994*m*, 932*m*, 864*m*. ^{1}H-NMR (300 MHz, $CDCl_3$)[2]): 7.4–7.2 (*m*, $PhCH_2$); 5.61 (*d*, $^2J = 4.1$, $CH_2{=}C(5)$); 5.31 (*m*, H–C(2)); 4.99 (br. *d*, $J = 6.24$, H–C(3), NH); 4.60 (*m*, H–C(4), H–C(1)); 4.39 (*d*, $^2J = 5.9$, $PhCH_2$); 1.61 (*s*, 3 H, Me_2C); 1.34 (*s*, 3 H, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$)[2]): 154.58 (*s*, C=O); 147.99 (*s*, C(5)); 137.91 (*s*, arom. C); 128.75 (*d*, arom. C); 127.71

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[1]) *Vasella* and co-workers find increased potency for inhibitors such as **7** by attaching aglycone mimics at the imidazole ring. This leads to strong inhibitors of β-glycosidases. This design is not transition-state-analogy-based and cannot be used to obtain α-selective inhibitors.

[2]) Arbitrary numbering; systematic names are given in parentheses after the nonsystematic names.

(*d*, arom. C); 127.65 (*d*, arom. C); 119.44 (*t*, *C*H$_2$=C(5)); 112.80 (*s*, Me$_2$*C*); 83.99 (*d*, (2)); 83.44 (*d*, C(3)); 80.73 (*d*, C(4)); 48.11 (*d*, C(1)); 45.27 (*t*, PhCH$_2$); 26.14 (*q*, *Me*$_2$C); 24.52 (*q*, *Me*$_2$C). HR-LSI-MS/MS: 382.0656 ($C_{17}H_{21}BrNO_4^+$; calc.: 382.0654). Anal. calc. for $C_{17}H_{20}BrNO_4$: C 53.42, H 5.27; found: C 53.26, H 5.31.

*(1*S*,2*S*,3*R*,4*R*,5*S*)-2-*O*-(Benzylcarbamoyl)-1-bromo-3,4-*O*-isopropylidene-5-methylcyclopentane-2,3,4-triol* (=*(3a*R*,4*S*,5*S*,6*S*,6a*R*)-5-Bromotetrahydro-2,2,6-trimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl Benzylcarbamate*; **15**). To a soln. of **14** (46 mg, 0.12 mmol) in benzene (10 ml), a spatula of *Wilkinson*'s catalyst (cat. amount) was added. The flask was evacuated and filled with H_2 (3×). After stirring overnight, the mixture was evaporated. FC (hexane/AcOEt 2:1; R_f 0.4) yielded **15** (34 mg, 74%). White solid. M.p. 112–114°. $[\alpha]_D^{20}$ = +28.0 (*c* = 0.44, $CHCl_3$). IR (KBr): 3331*s* (br.), 2977*w*, 2933*s*, 1726*m*, 1698*s*, 1540*m*, 1456*m*, 1380*m*, 1372*m*, 1310*w*, 1269*m*, 1206*m*, 1147*m*, 1077*m*, 1064*m*, 1046*w*, 1012*m*, 996*m*, 864*m*. ^{1}H-NMR (300 MHz, $CDCl_3$)^2): 7.4–7.2 (*m*, *Ph*CH$_2$); 5.37 (*s*, NH); 4.97 (br. *m*, H–C(4)); 4.63 (*dd*, ^3J(2,3) = 5.9, ^3J(2,1) = 5.5, H–C(2)); 4.54 (*d*, ^3J(3,2) = 5.9, H–C(3)); 4.38 (*d*, ^2J = 5.9, PhC*H*$_2$); 4.19 (*d*, ^3J(1,2) = 5.5, H–C(1)); 2.37 (*m*, H–C(5)); 1.59 (*s*, 3 H, *Me*$_2$C); 1.29 (*s*, 3 H, Me$_2$C); 1.25 (*d*, ^3J(3,5) = 6.6, Me–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$)^2): 154.68 (*s*, C=O); 138.04 (*s*, arom. C); 128.56 (*d*, arom. C); 127.48 (*d*, arom. C); 127.19 (*d*, arom. C); 111.64 (*s*, Me$_2$*C*); 84.64 (*d*, C(2)); 83.84 (*d*, C(3)); 82.27 (*d*, C(4)); 55.32 (*d*, C(1)); 45.04 (*t*, Ph*C*H$_2$); 40.09 (*d*, C(5)); 25.27 (*q*, *Me*$_2$C); 23.54 (*q*, *Me*$_2$C); 12.41 (*q*, *Me*–C(5)). HR-LSI-MS/MS: 384.0812 ($C_{17}H_{23}BrNO_4^+$; calc.: 384.0810). Anal. calc. for $C_{17}H_{22}BrNO_4$: C 53.14, H 5.77; found: C 53.19, H 5.78.

*(1*R*,2*R*,3*R*,4*R*,5*R*)-4-(Benzylamino)-3-*O*-4-*N*-(oxomethylidene)-1,2-*O*-isopropylidene-5-methylcyclopentane-1,2,3-triol* (=*(3a*R*,3b*R*,6a*R*,7*R*,7a*R*)-6-Benzylhexahydro-2,2,7-trimethyl-5*H*-1,3-dioxolo[4,5:3,4]cyclopent[1,2-*d*]oxazol-5-one*; **16**). To a soln. of **15** (140 mg, 0.37 mmol) in THF (15 ml), NaH (90 mg, 3.5 mmol) was added. The mixture was stirred for 3 h, poured into H_2O (15 ml) and extracted (Et_2O, 3×). The combined org. layer was washed (brine) and evaporated. FC (hexane/AcOEt 2:1; R_f 0.4) yielded **16** (88 mg, 80%). Yellowish solid. M.p. 111–113°. $[\alpha]_D^{20}$ = –42.0 (*c* = 0.35, $CHCl_3$). IR (KBr): 3434br, 2988*w*, 2931*w*, 2908*w*, 2360*w*, 1728*s*, 1444*m*, 1424*m*, 1369*m*, 1246*m*, 1222*m*, 1202*w*, 1163*w*, 1096*m*, 1035*m*, 1003*w*, 978*w*, 864*m*. ^{1}H-NMR (400 MHz, $CDCl_3$)^2): 7.4–7.2 (*m*, *Ph*CH$_2$); 4.84 (*d*, ^2J = 15.2, 1 H, PhC*H*$_2$); 4.68 (*d*, ^3J(2,1) = 5.1, H–C(2)); 4.63 (*d*, ^3J(3,4) = 7.8, H–C(3)); 4.56 (*dd*, ^3J(1,2) = 5.1, ^3J(1,5) = 4.7, H–C(1)); 4.16 (*d*, ^2J = 15.2, 1 H, PhC*H*$_2$); 3.74 (*dd*, ^3J(4,3) = 7.8, ^3J(4,5) = 7.5, H–C(4)); 2.21 (*m*, H–C(5)); 1.38 (*s*, 3 H, *Me*$_2$C); 1.30 (*s*, 3 H, *Me*$_2$C); 1.16 (*d*, ^3J(3,5) = 7.0, Me–C(5)). NOE: H–C(4)/H–C(3), H–C(2)/H–C(1), H–C(1)/H–C(5). ^{13}C-NMR (75 MHz, $CDCl_3$)^2): 156.90 (*s*, C=O); 135.76 (*s*, arom. C); 128.74 (*d*, arom. C); 127.86 (*d*, arom. C); 127.77 (*d*, arom. C); 111.31 (*s*, Me$_2$*C*); 84.93 (*d*, C(1)); 83.82 (*d*, C(3)); 83.22 (*d*, C(2)); 64.19 (*d*, C(4)); 46.79 (*t*, Ph*C*H$_2$); 43.33 (*d*, C(5)); 26.79 (*q*, *Me*$_2$C); 24.47 (*q*, *Me*$_2$C); 13.63 (*q*, *Me*–C(5)). HR-EI-MS: 303.1471 ($C_{17}H_{21}NO_4^+$; calc.: 303.1471). Anal. calc. for $C_{17}H_{21}NO_4$: C 67.31, H 6.98, N 4.62; found: C 67.29, H 6.93, N 4.55.

*(1*R*,2*S*,3*R*,4*R*,5*R*)-4-(Benzylamino)-1,2-*O*-isopropylidene-5-methylcyclopentane-1,2,3-triol* (=*(3a*S*,4*R*,5*R*, 6*R*,6a*R*)-5-(Benzylamino)tetrahydro-2,2,6-trimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol*; **17**). A soln. of **16** (77 mg, 0.25 mmol) in EtOH (12 ml) and 2M NaOH (12 ml) was heated for 3.5 h at 60° and evaporated. FC (hexane/AcOEt 2:1; R_f 0.15) yielded **17** (64 mg, 91%). White solid. M.p. 81–83°. $[\alpha]_D^{20}$ = +55.0 (*c* = 0.28, $CHCl_3$). IR (KBr): 3434 (br.), 3316*s*, 3284*s*, 2976*s*, 2938*s*, 2862*m*, 2360*m*, 1729*w*, 1498*w*, 1452*s*, 1377*s*, 1264*s*, 1205*s*, 1164*m*, 1134*m*, 1047*s*, 1033*m*, 999*s*, 883*w*, 864*m*. ^{1}H-NMR (300 MHz, $CDCl_3$)^2): 7.4–7.2 (*m*, *Ph*CH$_2$); 4.55–4.49 (*m*, H–C(1), H–C(2)); 3.87 (*m*, H–C(3)); 3.83 (*d*, ^2J = 12.9, 1 H, PhC*H*$_2$); 3.74 (*d*, ^2J = 12.9, 1 H, PhC*H*$_2$); 2.93 (*dd*, ^3J(4,5) = 11.1, ^3J(4,3) = 4.1, H–C(4)); 1.96 (*m*, H–C(5)); 1.41 (*s*, 3 H, Me$_2$C); 1.30 (*s*, 3 H, Me$_2$C); 1.16 (*d*, ^3J(Me–C(5),5) = 7.0, Me–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$)^2): 139.52 (*s*, arom. C); 128.48 (*d*, arom. C); 128.02 (*d*, arom. C); 127.29 (*d*, arom. C); 109.55 (*s*, Me$_2$*C*); 83.23 (*d*, C(1)); 81.01 (*d*, C(2)); 72.74 (*d*, C(3)); 64.51 (*d*, C(4)); 52.70 (*t*, Ph*C*H$_2$); 39.45 (*d*, C(5)); 25.94 (*q*, *Me*$_2$C); 23.66 (*q*, *Me*$_2$C); 11.19 (*q*, *Me*–C(5)). HR-EI-MS: 277.1673 ($C_{16}H_{23}NO_3^+$; calc.: 277.1678). Anal. calc. for $C_{16}H_{23}NO_3$: C 69.29, H 8.36, N 5.05; found: C 69.15, H 8.26, N 5.01.

*(1*R*,2*S*,3*R*,4*R*,5*R*)-4-Amino-1,2-*O*-isopropylidene-5-methylcyclopentane-1,2,3-triol* (=*(3a*S*,4*R*,5*R*,6*R*, 6a*R*)-5-Aminotetrahydro-2,2,6-trimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol*; **18**). To a soln. of **17** (50 mg, 0.18 mmol) in EtOH (15 ml), 10% Pd/C (5 mg) was added. The flask was evacuated and filled with H_2 (3×). After stirring overnight the mixture was filtered over *Celite*® and evaporated. FC (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1; R_f 0.25) yielded **18** (26 mg, 78%). White solid. M.p. 101–103°. $[\alpha]_D^{20}$ = +47.1 (*c* = 0.34, $CHCl_3$). IR (KBr): 3350*s*, 3286*m*, 2979*s*, 2940*s*, 2359*w*, 1592*m*, 1463*m*, 1384*s*, 1372*s*, 1263*s*, 1210*s*, 1166*s*, 1127*m*, 1094*m*, 1058*s*, 1043*m*, 1000*s*, 977*m*, 958*m*, 876*m*, 816*w*. ^{1}H-NMR (300 MHz, $CDCl_3$)^2): 4.52 (*dd*, ^3J(1,2) = 5.9, ^3J(1,5) = 5.5, H–C(1)); 4.32 (br. *d*, ^3J(2,1) = 5.9, H–C(2)); 3.79 (br. *d*, ^3J(3,4) = 4.1, H–C(3)); 2.81 (*dd*, ^3J(4,5) = 11.4, ^3J(4,3) = 4.1, H–C(4)); 2.40 (*m*, OH, NH$_2$); 1.81 (*m*, H–C(5)); 1.36 (*s*, 3 H, *Me*$_2$C); 1.27 (*s*, 3 H, *Me*$_2$C); 1.06 (*d*, ^3J(Me–C(5),5) = 7.0, Me–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$)^2): 110.83 (*s*, Me$_2$*C*);

85.12 (*d*, C(1)); 82.01 (*d*, C(2)); 77.13 (*d*, C(3)); 58.71 (*d*, C(4)); 42.13 (*d*, C(5)); 26.27 (*q*, *Me*$_2$C); 23.92 (*q*, *Me*$_2$C); 11.28 (*q*, *Me*−C(5)). Anal. calc. for $C_9H_{17}NO_3$: C 57.73, H 9.15, N 7.48; found: C 57.68, H 9.06, N 7.39.

*(1*R*,2*R*,3*R*,4*R*,5*R*)-4-(Benzylamino)-5-methylcyclopentane-1,2,3-triol* (**1**). To a soln. of **17** (7 mg, 25 μmol) in H_2O (3 ml), 37% HCl soln. (1 ml) was added. The soln. was stirred for 5 h at 60°. Lyophilization yielded **1**·HCl (7 mg, quant.). $[\alpha]_D^{20} = +20.3$ ($c = 0.335$, MeOH). IR (KBr): 3385 (br.), 2933*s*, 2363*w*, 1718*m*, 1559*m*, 1499*w*, 1457*s*, 1210*m*, 1129*m*, 1050*m*, 1027*m*, 997*w*, 890*w*. ^{1}H-NMR (300 MHz, CD_3OD): 7.55–7.4 (*m*, *Ph*CH$_2$); 4.31 (*d*, $^2J = 13.2$, 1 H, PhC*H*$_2$); 4.22 (*dd*, $^3J(3,4) = 7.0$, $^3J(3,2) = 4.4$, H−C(3)); 4.16 (*d*, $^2J = 13.2$, 1 H, PhC*H*$_2$); 4.05 (*dd*, $^3J(1,5) = 5.2$, $^3J(1,2) = 4.1$, H−C(1)); 3.96 (*dd*, $^3J(2,3) = 4.4$, $^3J(2,1) = 4.1$, H−C(2)); 3.34 (*m*, H−C(4)); 2.20 (*m*, H−C(5)); 1.15 (*d*, $^3J(6,5) = 7.0$, Me). ^{13}C-NMR (75 MHz, CD_3OD): 132.74 (*s*, arom. C); 131.02 (*d*, arom. C); 130.63 (*d*, arom. C); 130.22 (*d*, arom. C); 80.36 (*d*, C(1)); 73.63 (*d*, C(3)); 73.50 (*d*, C(2)); 64.84 (*d*, C(4)); 51.77 (*t*, Ph*C*H$_2$); 39.34 (*d*, C(5)); 13.34 (*q*, Me). EI-MS: 237 ([*M* − HCl]$^+$), 220, 208, 202, 190, 162, 106.

*(1*R*,2*R*,3*R*,4*R*,5*R*)-4-Amino-5-methylcyclopentane-1,2,3-triol* (**10**). To a mixture of impure **18** (22 mg, 0.12 mmol), $(Boc)_2O$ (61 mg, 0.28 mmol), and $NaHCO_3$ (39 mg, 0.46 mmol), AcOEt (0.5 ml) and H_2O (0.5 ml) were added, and the mixture was stirred overnight at r.t. After adding more solvent (5 ml each), the aq. phase was extracted with AcOEt (3 × 8 ml) and evaporated. FC (hexane/AcOEt 2:1; R_f 0.25) yielded *N*-[(*tert*-butoxy)carbonyl]-protected **10** (13 mg, 40%). Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.82 (*d*, ^3J(NH, 4) = 8.8, NH); 4.52 (*dd*, $^3J(1,2) = 5.9$, $^3J(1,5) = 5.5$, H−C(1)); 4.36 (br. *d*, $^3J(2,1) = 5.9$, H−C(2)); 4.00 (br. *m*, H−C(3)); 3.79 (br. *m*, H−C(4)); 2.04 (*m*, H−C(5)); 1.46 (*s*, t_{Bu}); 1.44 (*s*, 3 H, Me$_2$C); 1.29 (*s*, 3 H, Me$_2$C); 1.09 (*d*, ^3J(Me, 5) = 7.0, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.89 (*s*, C=O); 110.06 (*s*, Me$_2$*C*); 86.12 (*d*, C(1)); 83.66 (*d*, C(2)); 79.64 (*d*, C(3)); 79.10 (*s*, Boc); 60.48 (*d*, C(4)); 39.45 (*d*, C(5)); 28.34 (*q*, Boc); 25.95 (*q*, Me$_2$C); 23.76 (*q*, Me$_2$C); 10.75 (*q*, Me).

To a soln. of *N*-Boc-protected **10** (13 mg, 45 μmol) in H_2O (3 ml), 37% HCl soln. (1 ml) was added. The soln. was stirred for 5.5 h at 60° and evaporated. Lyophilization of the H_2O-containing residue yielded free **10**·HCl (8 mg, quant.). $[\alpha]_D^{20} = +14.6$ ($c = 0.335$, MeOH). IR (KBr): 3425 (br.), 3028*m*, 2927*s*, 2361*m*, 2341*m*, 1587*w*, 1506*m*, 1145*m*, 1120*m*, 1077*m*, 1048*w*, 983*w*, 945*w*. ^{1}H-NMR (400 MHz, CD_3OD): 4.11 (*dd*, $^3J(3,4) = 7.3$, $^3J(3,2) = 5.1$, H−C(3)); 3.94 (*dd*, $^3J(1,2) = 4.5$, $^3J(1,5) = 4.3$, H−C(1)); 3.89 (*dd*, $^3J(2,3) = 5.1$, $^3J(2,1) = 4.5$, H−C(2)); 3.24 (*dd*, $^3J(4,5) = 9.3$, $^3J(4,3) = 7.3$, H−C(4)); 2.05 (*m*, H−C(5)); 1.16 (*d*, ^3J(Me, H) = 7.0, Me). ^{13}C-NMR (75 MHz, CD_3OD): 80.64 (*d*, C(3)); 74.80 (*d*, C(1)); 73.72 (*d*, C(2)); 57.77 (*d*, C(4)); 40.77 (*d*, C(5)); 12.80 (*q*, Me). HR-EI-MS: 148.0962 ($C_6H_{14}NO_3^+$; calc.: 148.0974).

*(1*R*,2*R*,3*R*,4*R*,5*R*)-5-Methyl-4-[(2-phenylethyl)amino]cyclopentane-1,2,3-triol* (**2**). To a mixture of **18** (10 mg, 53 μmol) and benzeneacetaldehyde (15 mg, 125 μmol) in MeOH (ROMIL; 1 ml), $NaCNBH_3$ (10.2 mg, 160 μmol) was added. The mixture was stirred for 24 h, then 1M HCl (0.5 ml) was added. After stirring overnight, the crude was purified by prep. HPLC (*RP-C18*): **2**·CF_3COOH (4.9 mg, 37%). $[\alpha]_D^{20} = +13.3$ ($c = 0.21$, MeOH). IR (KBr): 3422 (br.), 2360*w*, 2343*m*, 1677*s*, 1558*w*, 1456*m*, 1436*w*, 1384*w*, 1205*s*, 1137*s*, 840*w*, 801*w*. ^{1}H-NMR (300 MHz, D_2O): 7.4–7.25 (*m*, *Ph*CH$_2$); 4.20 (*dd*, $^3J(3,4) = 7.7$, $^3J(3,2) = 6.6$, H−C(3)); 3.98 (*dd*, $^3J(1,5) = 5.2$, $^3J(1,2) = 4.4$, H−C(1)); 3.92 (*dd*, $^3J(2,3) = 6.6$, $^3J(2,1) = 4.4$, H−C(2)); 3.31–3.24 (*m*, H−C(4), CH$_2$N); 2.98 (*m*, PhC*H*$_2$); 2.16 (*m*, H−C(5)); 1.07 (*d*, ^3J(Me, 5) = 7.0, Me). ^{13}C-NMR (75 MHz, CD_3OD): 137.79 (*s*, arom. C); 129.99 (*d*, arom. C); 129.70 (*d*, arom. C); 128.27 (*d*, arom. C); 80.21 (*d*, C(3)); 73.74 (*d*, C(2)); 73.53 (*d*, C(1)); 65.24 (*d*, C(4)); 49.17 (*t*, CH$_2$N); 39.64 (*d*, C(5)); 33.44 (*t*, Ph*C*H$_2$); 13.83 (*q*, Me). HR-LSI-MS: 252.1600 ($C_{14}H_{22}NO_3^+$; calc.: 252.1600).

*(1*R*,2*R*,3*R*,4*R*,5*R*)-5-Methyl-4-[(3-phenylpropyl)amino]cyclopentane-1,2,3-triol* (**3**). As described for **2**, with **18** (10.3 mg, 55 μmol), benzenepropanal (16 mg, 120 μmol), MeOH (1 ml), $NaCNBH_3$ (24 mg, 380 μmol), and 1M HCl (0.5 ml): **3**·CF_3COOH (2.8 mg, 20%). $[\alpha]_D^{20} = +16.2$ ($c = 0.105$, MeOH). IR (KBr): 3440 (br.), 2925*m*, 2359*w*, 1682*s*, 1614*s*, 1558*w*, 1456*w*, 1204*s*, 1133*s*, 1061*w*, 840*w*, 801*w*. ^{1}H-NMR (300 MHz, D_2O): 7.4–7.25 (*m*, *Ph*CH$_2$); 4.18 (*dd*, $^3J(3,4) = 7.7$, $^3J(3,2) = 6.6$, H−C(3)); 3.98 (*dd*, $^3J(1,5) = 5.2$, $^3J(1,2) = 4.1$, H−C(1)); 3.92 (*dd*, $^3J(2,3) = 6.6$, $^3J(2,1) = 4.1$, H−C(2)); 3.22 (*dd*, $^3J(4,5) = 8.5$, $^3J(4,3) = 7.7$, H−C(4)); 3.00 (*m*, PhC*H*$_2$CH$_2$CH$_2$); 2.68 (*t*, ^3J(CH$_2$,CH$_2$) = 7.7, PhCH$_2$CH$_2$*C*H$_2$); 2.14 (*m*, H−C(5)); 1.97 (*quint.*, ^3J(CH$_2$,CH$_2$) = ^3J(CH$_2$,CH$_2$) = 7.7, PhCH$_2$C*h*$_2$CH$_2$); 1.05 (*d*, ^3J(Me, 5) = 7.0, Me). ^{13}C-NMR (75 MHz, CD_3OD): 138.36 (*s*, arom. C); 129.69 (*d*, arom. C); 129.37 (*d*, arom. C); 127.46 (*d*, arom. C); 80.15 (*d*, C(3)); 73.73 (*d*, C(2)); 73.47 (*d*, C(1)); 65.28 (*d*, C(4)); 47.67 (*t*, PhCH$_2$CH$_2$*C*H$_2$); 39.63 (*d*, C(5)); 33.63 (*t*, Ph*C*H$_2$CH$_2$CH$_2$); 29.07 (*t*, PhCH$_2$*C*H$_2$CH$_2$); 13.77 (*q*, Me). HR-LSI-MS: 266.1756 ($C_{15}H_{24}NO_3^+$; calc.: 266.1756).

Methyl 5-[(4-Formylphenyl)amino]-5-oxopentanoate (**21**). To a soln. of Et_3N (930 μl, 6.65 mmol) In CH_2Cl_2 (25 ml), 4-aminobenzyl alcohol (810 mg, 6.58 mmol) and methyl 5-chloro-5-oxopentanoate (1 ml, 7.24 mmol) were added. After stirring for 2.5 h at r.t., CH_2Cl_2 (50 ml) was added, and the org. phase washed with 1M HCl (2 × 30 ml). Extraction of the aq. phase with CH_2Cl_2 (2 × 30 ml), evaporation, and FC (hexane/AcOEt 1.4; R_f

0.36) yielded *methyl 5-{[4-(hydroxymethyl)phenyl]amino}-5-oxopentanoate* (1.37 g, 83%). White solid. M.p. 77–79°. IR (KBr): 3301 (br.), 2950*m*, 1727*s*, 1655*s*, 1599*m*, 1538*s*, 1460*m*, 1412*m*, 1388*w*, 1317*m*, 1265*m*, 1206*m*, 1175*m*, 1076*w*, 1022*m*, 1012*m*, 994*m*, 893*w*, 820*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.50 (*d*, ^3J = 8.1, 2 H); 7.31 (*d*, ^3J = 8.1, 2 H); 4.65 (*s*, 2 H); 3.70 (*s*, 3 H); 2.45 (*m*, 4 H); 2.05 (*quint.* $^3J = {}^3J$ = 7.0, 2 H). ^{13}C-NMR (75 MHz, CD_3OD): 173.9; 171.0, 137.2; 136.8; 127.7; 120.0; 64.8; 51.7; 36.27; 32.92; 20.72. EI-MS: 251 (M^+), 235, 220, 218, 149, 132, 129, 123, 107, 101, 94.

To cooled (0°) pyridine (18.2 ml), cromium(VI) trioxide (1.55 g, 15.5 mmol) was added in portions. The above 4-(hydroxymethyl)phenyl derivative (1.30 g, 5.2 mmol) was dissolved in pyridine (10 ml) and added dropwise to the chromium(VI) soln. After stirring for 1.5 h at r.t., the mixture was poured into H_2O (120 ml), extracted with AcOEt (3 × 120 ml), washed with brine (200 ml), and evaporated. FC (hexane/AcOEt 1:1; R_f 0.25) yielded **21** (698 mg,54%). White solid. M.p. 118–119°. IR (KBr): 3341*s*, 2954*w*, 1729*s*, 1701*s*, 1674*m*, 1598*m*, 1523*s*, 1435*w*, 1420*w*, 1388*w*, 1323*m*, 1299*m*, 1278*m*, 1248*w*, 1216*m*, 1160*s*, 1065*w*, 986*w*, 852*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.92 (*s*, CH=O)); 7.86 (br. *d*, ^3J = 8.1, 2 arom. H); 7.72 (br. *d*, ^3J = 8.1, 2 arom. H); 3.72 (*s*, MeO); 2.49 (*m*, CH_2(2), CH_2(4)); 2.08 (*quint*, $^3J = {}^3J$ = 7.0, CH_2(3)). ^{13}C-NMR (75 MHz, CD_3OD): 191.06 (*d*, CHO); 173.80 (*s*, C(1)); 171.00 (*s*, C(5)); 143.63 (*s*, arom. C); 132.13 (*s*, arom. C); 131.12 (*d*, arom. C); 119.20 (*d*, arom. C); 51.71 (*q*, MeO); 36.43 (*t*, CH_2(4)); 32.83 (*t*, CH_2(2)); 20.22 (*t*, CH_2(3)). EI-MS: 249 (M^+), 218, 129, 121, 101.

*5-Oxo-5-{[4-{[[(1*R*,2*R*,3*R*,4*R*,5*R*)-2,3,4-trihydroxy-5-methylcyclopentyl]amino}methyl]phenyl}amino}-pentanoic Acid* (**4**). To a mixture of **18** (21 mg, 112 μmol) and **21** (57 mg, 229 μmol) in MeOH (2 ml), $NaCNBH_3$ (18.2 mg, 290 μmol) was added. The mixture was stirred for 18 h at r.t. To the crude ester, 1M NaOH (1 ml) was added and stirred for 5 h at r.t. After evaporation, 1M HCl (2 ml) was added and stirred overnight. The crude was purified by prep. HPLC (*RP-C18*): **4** · CF_3COOH (23.8 mg, 46%). $[\alpha]_D^{20} = +9.4$ (c = 0.16, MeOH). IR (KBr): 3422 (br.), 2926*m*, 2360*w*, 2343*m*, 1674*s*, 1612*s*, 1526*m*, 1413*m*, 1350*w*, 1310*w*, 1232*w*, 1204*s*, 1134*s*, 840*w*, 801*w*. ^{1}H-NMR (300 MHz, CD_3OD): 7.66 (*d*, ^3J = 8.6, 2 H); 7.45 (*d*, ^3J = 8.6, 2 H); 4.26 (*d*, ^2J = 12.9, 1 H); 4.21 (*dd*, ^3J(1′,2′) = 7.3, ^3J(2′,3′) = 4.4, 1 H, H–C(2′)); 4.12 (*d*, ^2J = 12.9, 1 H); 4.06 (*dd*, ^3J(4′,5′) = 5.9, ^3J(3′,4′) = 4.0, 1 H, H–C(4′)); 3.96 (*dd*, ^3J(2′,3′) = 4.4, ^3J(3′,4′) = 4.0, 1 H, H–C(3′)); 3.37 (*dd*, ^3J(1′,5′) = 8.6, ^3J(1′,2′) = 7.3, 1 H, H–C(1′)); 2.45 (*t*, ^3J(4,3) = 7.4, CH_2(4)); 2.39 (*t*, ^3J(2,3) = 7.4, CH_2(2)); 2.20 (*m*, H–C(5′)); 1.97 (*quint.*, $^3J = {}^3J$ = 7.4, CH_2(3)); 1.15 (*d*, ^3J(Me, 5′) = 7.0, Me). NOE: H–C(2′)/H–C(3′), H–C(2′)/H–C(1′). ^{13}C-NMR (75 MHz, CD_3OD): 176.88 (*s*); 173.97 (*s*); 141.17 (*s*); 131.69 (*d*); 127.97 (*s*); 121.36 (*d*); 80.40 (*d*, C(3′)); 73.66 (*d*, C(2′)); 73.55 (*d*, C(4′)); 64.67 (*d*, C(1′)); 51.21 (*t*, ArCH_2); 39.65 (*d*, C(5′)); 36.89 (*t*, C(4)); 34.10 (*t*, C(2)); 22.00 (*t*, C(3)); 13.57 (*q*, Me). HR-LSI-MS: 367.1872 ($C_{18}H_{27}N_2O_6^+$; calc.: 367.1869).

*(1*R*,2*R*,3*R*,4*S*,5*R*)-4-(Benzylamino)-5-methylcyclopentane-1,2,3-triol* (**20**). Free *trans*-amino alcohol **19** (6.3 mg, 34 μmol) was treated with benzaldehyde (4 μl, 39 μmol) and titanium(IV) isopropoxide (15 μl, 50 μmol) and stirred for 90 min. After addition of EtOH (40 μl) and $NaCNBH_3$ (2 mg, 30 μmol), the soln. was stirred over one weekend. Evaporation and prep. HPLC (*RP-C18*) yielded **20** · CF_3COOH (3.2 mg, 27%). $[\alpha]_D^{20} = -6.2$ (c = 0.13, MeOH). IR (KBr): 3426 (br.), 2924*w*, 2360*w*, 2343*m*, 1684*s*, 1653*m*, 1558*m*, 1540*w*, 1506*w*, 1456*m*, 1207*s*, 1136*s*, 841*w*, 800*m*. ^{1}H-NMR (300 MHz, CD_3OD): 7.55–7.4 (*m*, 5 H); 4.44 (*d*, ^2J = 13.2, 1 H, PhCH_2); 4.26 (*dd*, ^3J(3,2) = 6.6, ^3J(3,4) = 5.2, H–C(3)); 4.22 (*d*, ^2J = 13.2, 1 H, PhCH_2); 3.88 (*dd*, ^3J(1,2) = 4.4, ^3J(1,5) = 4.1, H–C(1)); 3.82 (*dd*, ^3J(2,3) = 6.6, ^3J(2,1) = 4.4, H–C(2)); 3.35 (*dd*, ^3J(4,5) = 8.2, ^3J(4,3) = 5.2, H–C(1)); 2.48 (*m*, H–C(5)); 1.12 (*d*, ^3J(Me, 5) = 7.4, Me). ^{13}C-NMR (50 MHz, CD_3OD): 132.74 (*s*, arom. C); 131.02 (*d*, arom. C); 130.63 (*d*, arom. C); 130.22 (*d*, arom. C); 80.89 (*d*, C(3)); 80.00 (*d*, C(1)); 75.15 (*d*, C(2)); 65.37 (*d*, C(4)); 51.37 (*t*, PhCH_2); 37.34 (*d*, C(5)); 9.23 (*q*, Me). HR-EI-MS: 237.1354 ($C_{13}H_{19}NO_3^+$; calc.: 237.1365).

2. *Enzyme Measurements.* The following glycosidases were assayed: α-L-fucosidase (EC 3.2.51) from bovine kidney (*Sigma*), α-L-fucosidase from bovine epididymis (*Sigma*), α-L-fucosidase from human placenta (*Sigma*), α-L-fucosidase from *Fucosarium Oxysporum 377* (provided by Dr. *V. Křen*). All buffers and solns. were prepared with *MilliQ*-deionized H_2O. Enzymes were diluted with 0.1M HEPES buffer, pH 6.8. Substrate and inhibitors were used as 10 mM stock solns. in buffer.

Reactions were initiated by addition of substrate to a soln. containing enzyme and inhibitor in 0.1M HEPES buffer pH 6.8, 25°. The assays (100 μl) were followed in individual wells of flat-bottom 96-well half-area polystyrene cell culture plates (*Costar*) by means of a UV *Spectramax 250* instrument from *Molecular Devices*. The release of 4-nitrophenol was followed at 405 nm over 15 min. The concentration of each enzyme in the assays was adjusted such as to give *ca.* 0.2 to 0.5 *OD* increase as given by the instrument. The initial rate of reaction of the first 10 min was linear and was used to calculate the rate. Rates were expressed in relative units as m$OD \cdot min^{-1}$. The competitive inhibition constants K_i [μM] were determined from *Dixon* replots of inhibition data.

3. *Molecular Modelling*. Conformers of all stable transition-state analogs and of the model **24** were calculated with the Monte Carlo method on a *DEC-DPW500au* workstation with Spartan 5.1. All conformers were geometry-optimized by mechanics protocol MMFF 94 and further optimized with semi-empirical model PM3. The electronic potentials were calculated on these optimized geometries and superimposed onto a surface of constant electron density (0.002 e/au3) (blue = positive, red = negative). Only the minimum energy conformer is shown.

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