Synthesis of 5-Azacastanospermine, a Conformationally Restricted Azafagomine Analogue

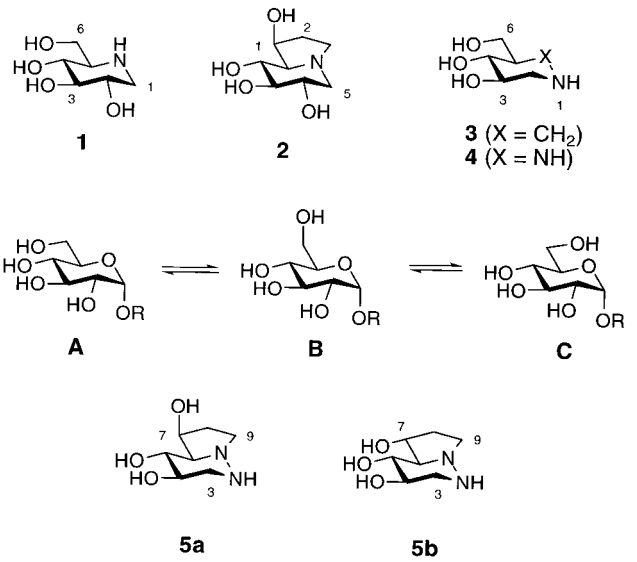
Kåre Søndergaard, Xifu Liang, and Mikael Bols*[a]

Abstract: The 5-aza-6-deoxy analogue of castanospermine (±)-**5a** and its 1-epimer (±)-**5b** was synthesized. The synthesis started from the known compound 5-benzyloxy-7-hydroxyhepta-1,3-diene, which was protected and subjected to Diels–Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione to give two epimeric adducts. One of these was transformed through epoxidation, acetolysis, a series of side-chain transformations that converted it into a terminally protected aldehyde, deprotection, and hydrogenolysis/reductive amination into **5a**. By a similar set of reactions the other adduct epimer was converted into **5b**. The castanospermine analogue **5a** was a weaker inhibitor of almond β-glucosidase and rice α-glucosidase than castanospermine (**2**) or 1-azafagomine (**4**), but was considerably more potent than its epimer **5b**. This suggests that these enzymes have a strong preference for binding substrates or azasugars with the 6-OH in an axial conformation.

Keywords: azasugars · enzymes · glycosidases · indolizidine · inhibitors

Introduction

Glycosidases and related enzymes are crucial in many biological processes. Potent and selective inhibitors of these enzymes are important, because they can be used to interfere with such processes.[1] Azasugar inhibitors, in particular, are subject to intense current interest.[2] The classical type of azasugar, the natural product 1-deoxynojirimycin (**1**),[3] is a glucose analogue in which the ring oxygen is replaced by a nitrogen atom. Another natural product, castanospermine (**2**),[3a] is an analogue of **1** in which the incorporation of a second ring has forced the 6-hydroxyl group to be locked in an axial conformation. That 6-hydroxyl group has been found to be important for binding. The 6-deoxy analogues of **1**[3b] and **2**[3c] are much weaker inhibitors of α- and β-glucosidase than **1** and **2** themselves, and the 6-deoxy-6-fluoro analogue is also a poor inhibitor; this suggests that the 6-OH acts as a hydrogen bond donor.[3d–e] Castanospermine (**2**) appears almost as a result of rational drug design; **2** is a more potent inhibitor than **1** of almond β-glucosidase but is inactive against yeast α-glucosidase, which **1** inhibits.[3a] This may presumably be caused by differences between the various glycosidases as to which 6-OH conformer of the substrate they bind (Scheme 1). It may be envisaged that different glycosidases may accept the substrate in either conformer **A**, **B**, or **C**. While **1** should in principle be able to inhibit a glycosidase regardless of which conformer it binds, **2** would be expected only to bind to enzymes that prefer conformer **B** but perhaps more tightly. The limited structural information available from X-ray crystallography of enzyme inhibitor complexes have so far only shown binding in mode **B**.[2]



Scheme 1. Structure of glycosidase inhibitors **1**–**3** and **5**, the three conformers **A**–**C**, and the targets **5a** and **5b**.

Recently it was found that a subtle change in the classical structure of an azasugar, by moving the nitrogen atom to the

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anomeric position, led to a new group of very potent glycosidase inhibitors.[4] Members of this group are isofagomine (**3**),[4a] its stereoisomers,[4b–d] and 1-azafagomine (**4**, Scheme 1).[4e, f]

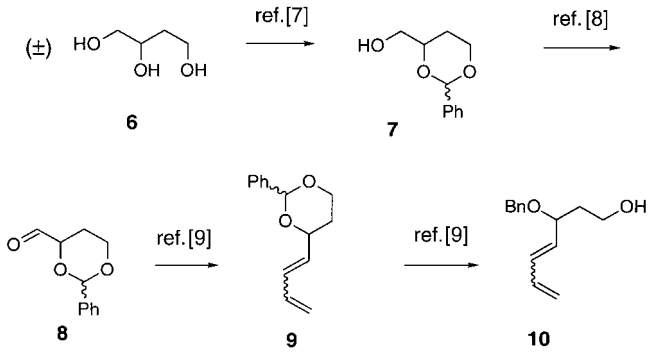
Since **3** and **4** have a very different inhibitory profile than **1** (which includes inhibition of transferases[4i] and phosphorylases[4e]), the effect of locking the conformation of the 6-OH was not obvious. Presumably a castanospermine analogue of **3** or **4** would only bind to glycosidases prefering the substrate in a certain conformation. The purpose of the present work was to address this problem by synthesizing castanospermine analogues having nitrogen in the anomeric position. It was decided that the azafagomine analogue **5a** would have the greatest geometrical resemblance to **2** because it retains a nitrogen atom at the bridgehead. It was also of interest to study the epimer **5b** as this compound should bind to enzymes that prefer substrate conformer **A**. The epimer of **2** has been synthesized several times,[5] but no enzyme inhibition data has been reported.

In the present paper we report the synthesis of **5a** and **5b** and report that **5a** is by far the better inhibitor of the two epimers towards a series of enzymes inhibited by **4**.

Results and Discussion

Castanospermine (**2**) has been synthesized numerous times,[5a–c, e, 6] but most of those approaches were not applicable to the synthesis of **5a**. The synthesis that could most readily be adapted to the synthesis of hydrazine **5a** was that of Ganem et al.,[6i] in which a protected derivative of **1** was converted to a 6-aldehyde followed by chain extension in the 6-position and cyclization through nucleophilic substitution on a terminal mesylate. A similar procedure starting from a derivative of **4** is conceivable. However, it was judged more efficient to build the 1-azafagomine ring with the desired side-chain in an intermolecular Diels–Alder reaction.

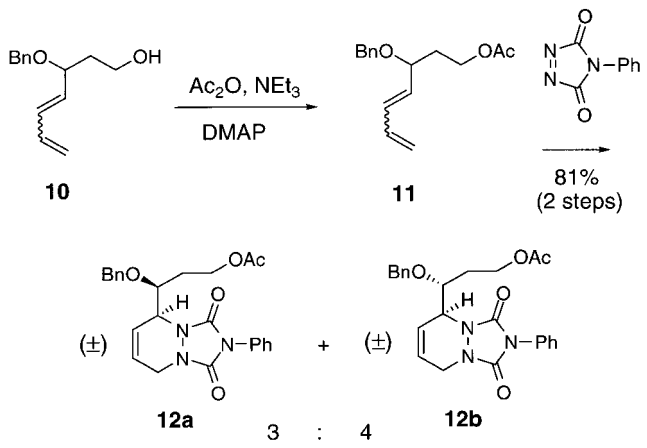
The synthesis started from the racemic triol **6**, which was converted through a known series of reactions into the diene **10** (Scheme 2). The sequence consisted of diprotection with



Scheme 2. Synthesis of **10** to give principally the *Z* diene.

PhCHO/TsOH to furnish benzylidene derivative **7**,[7] subjection to Swern oxidation to give aldehyde **8**,[8] reaction with $Ph_3P^+CH_2CH{=}CH_2$/BuLi to yield diene **9**, and finally opening of the benzylidene with DIBAL to give **10**.[9] This compound was mainly the *Z* isomer (*E*/*Z* 1:1.75). The *E*/*Z* ratio was determined from the integrals of H-4 in ^{1}H NMR. For the *E* isomer H-4 caused a dd at $\delta = 5.58$, while the *Z* isomer H-4 gave a t at $\delta = 5.36$.

As the free terminal hydroxyl group was found to cause problems both in the Diels–Alder reaction and in later stages of the synthesis, it was protected as an acetate by treatment of **10** with Ac_2O, Et_3N, and DMAP to give **11** (Scheme 3). This



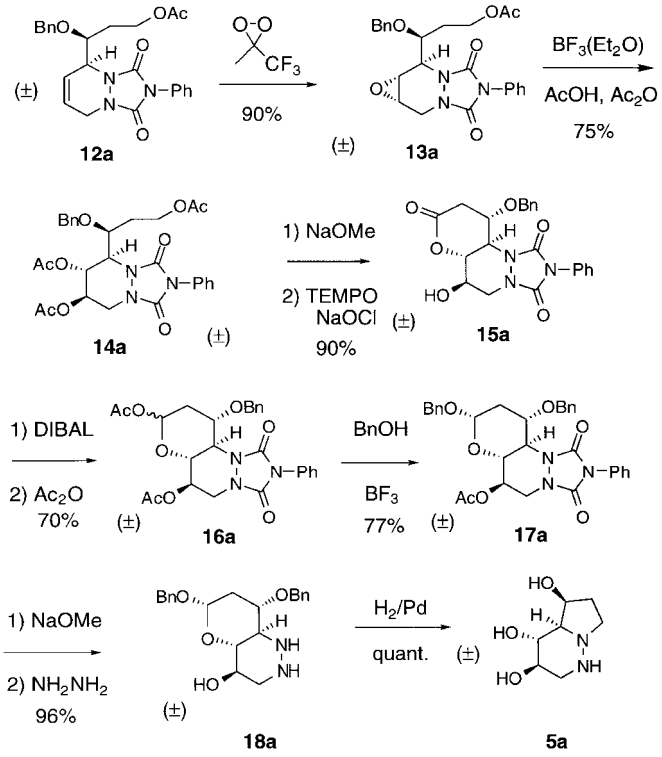
Scheme 3. Diels–Alder reaction to form the 1-azafagomine ring with the desired side-chain.

was treated with 4-phenyl-1,2,4-triazoline-3,5-dione[10] in EtOAc at 75 °C to give two diastereomeric Diels–Alder adducts, **12a** and **12b**, in 35% and 46% yield, respectively. The relatively slow rate of reaction of **11** may be due to the large content of *Z* diene, as *E* dienes add to this dienophile with ease.[10b]

The fact that two stereoisomers are formed suggests that the chiral center (C-3) in the diene had limited effect on the face of addition of the dienophile. This contrasts with a study in which Diels–Alder reactions were performed with a rather similar *E* diene.[10b] However, it was possible to obtain stereochemically pure *E* diene by photoisomerization[9] of the *E*/*Z* mixture in the presence of iodine, and with that diene the Diels–Alder reaction indeed had a high selectivity towards **12b**, which accords with the above-mentioned study.[10b] Thus it appears that the *trans* diene gives only one product in the Diels–Alder reaction, while the *cis* diene gives a mixture. Unfortunately, **12b** is the isomer that leads to the epi-castanospermine analogue **5b**.

The adduct **12a** was subjected to epoxidation with CF_3MeCO/oxone in aqueous MeCN,[11] which gave the *anti* epoxide **13a** stereochemically pure in 90% yield (Scheme 4). The stereoselectivity in this case is much higher than that of epoxidation of the corresponding 2-hydroxymethyl analogue, in which case a 25% *syn* epoxide is obtained.[4e] The higher selectivity is probably caused by more steric hindrance on the *syn* face being caused by the more bulky 2-substituent; X-ray structures of similar compounds show that the 2-substituent is almost axial[4e] and therefore close to the *syn* face of the alkene.

Aqueous hydrolysis using dilute $HClO_4$ did not give the desired *trans* diol owing to hydrolysis of the acetate and



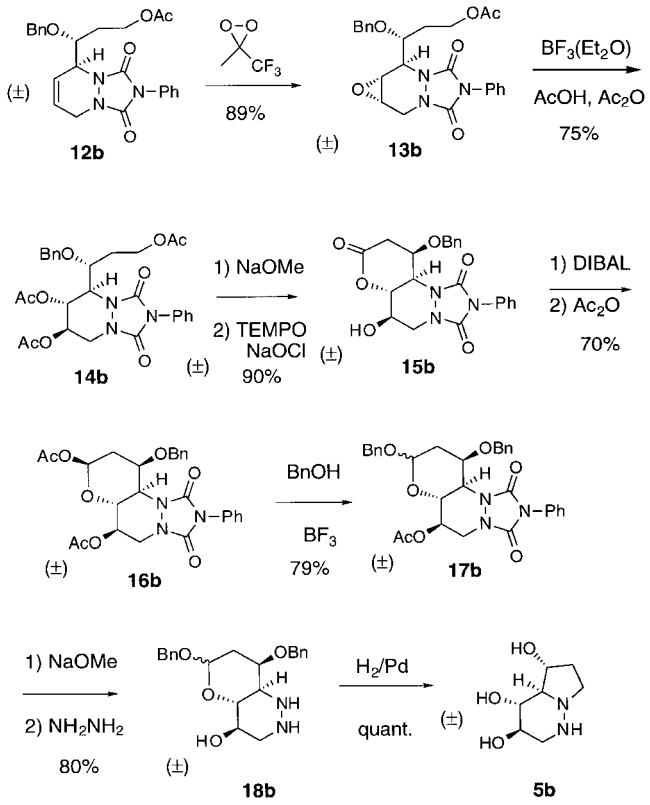
Scheme 4. Synthesis of castanospermine analogue **5a**.

intramolecular attack of the thus formed terminal alcohol on the epoxide to form a pyran. Therefore the epoxide was subjected to acetolysis conditions as this kept the acetate protecting group in place during the transformation. Treatment of **13a** with $BF_3 \cdot Et_2O$ and Ac_2O in AcOH gave the desired *trans* triacetate **14a** in 75% yield as the only stereoisomer.

At this stage of the synthesis many attempts were made to obtain **5a** by cyclization of a deprotected derivative of **14a** (such as **19a** or **20a** in Scheme 7 below) with a Mitsunobu-type dehydration process using CBr_4/PPh_3 and similar reagents, which has been so successfully applied in several indolizidine syntheses.[9, 12] However, none of these attempts led to cyclized products, but rather to oxidation/decomposition of the hydrazine. It was evident that the unprotected hydrazine was too sensitive for many cyclization procedures, and that a reductive amination reaction was necessary to close the pyrrolidine ring. This would require that an aldehyde or ester fuctionality was installed in the side-chain, but these functionalities were found to be reduced by the NH_2NH_2 at 100 °C, the temperature necessary to remove the phenylurazol protection group. Consequently such an aldehyde would have to be masked in a way that it would be released during the hydrogenolysis reaction. This could be conveniently done as a benzyl glycoside.

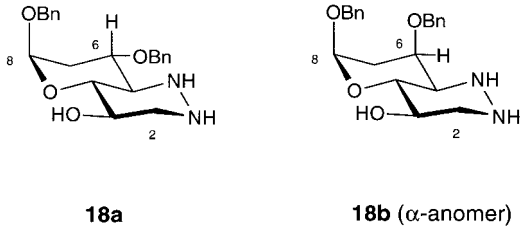
Deacetylation with NaOMe/MeOH followed by TEMPO-catalysed oxidation with NaOCl as oxidant gave the δ-lactone **15a** in 90% yield. DIBAL reduction of the lactone gave a hemiacetal, which was isolated as the diacetate **16a** in 70% yield after acetylation with Ac_2O/NEt_3/DMAP. This was converted to a benzyl acetal by a glycosidation-type protocol: The hemiacetal acetate was treated with BnOH and $BF_3 \cdot Et_2O$ to give an anomeric mixture of benzyl acetals **17a**. Finally deacetylation with NaOMe/MeOH and hydrazinolysis in neat NH_2NH_2/H_2O at 100 °C led to the hydrazine **18a** in 96% yield, which upon hydrogenolysis with Pd/C catalyst at 1 atm in MeOH gave the target **5a** in quantitative yield (Scheme 4).

Similarly the other diastereomeric product from the Diels–Alder reaction **12b** was subjected to an identical sequence of reactions (Scheme 5). Its behavior and the yields were virtually identical to those of its isomer. It is notable that the stereoselectivity of the epoxidation was equally high for **12b**.



Scheme 5. Synthesis of the epimer **5b**.

The configurational assignment of the two series of compounds was carried by analysis of the spectrum of **18a** (Scheme 6). The 6-proton is axial, which can be seen from the



Scheme 6. Conformations of hydrazine **18a**.

large values of J_{67ax} (11.2 Hz) and J_{56} (9.1 Hz). Similarly, in the spectrum of the α-anomer of **18b** it can be seen that the couplings to H-6 are all small, being 2.9, 2.9 and 2.4 Hz. This

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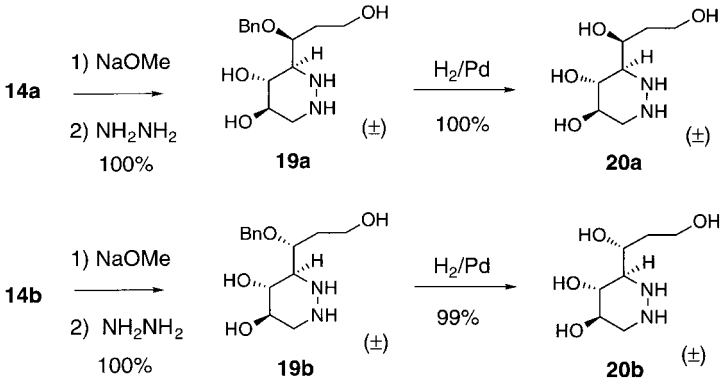
clearly shows that H-6 in that case is equatorial. Furthermore the spectrum of **5a** closely resembles that of **2**: H-7 of **5a** is a ddd at $\delta = 4.45$ with $J = 0.9$, 3.3, and 7.1 Hz, while H-1 of **2**, the equivalent of H-7 in **5a**, is a ddd at $\delta = 4.24$ with $J = 1.7$, 2.9, 6.9 Hz.

The two monocyclic analogues of **5a** and **5b** were also made (Scheme 7, **20a** and **20b**). Each of the triacetates **14a** and **14b** was subjected to deacetylation with NaOMe/MeOH, hydrazinolysis (NH_2NH_2/H_2O, 100 °C) and hydrogenolysis (H_2, Pd/C, 1 atm) in the presence of HCl to give **20a** and **20b**, respectively, in essentially quantitative yield. A small $J_{33'} = 3.2$ Hz in **20b** revealed that this compound was in conformation **B** and/or **C** with regard to the side-chain. The side-chain conformation of **20a** could not be elucidated. For comparison, compound **4** has $J_{33'} = 3$ Hz and $J_{33'} = 6$ Hz, a fact that reveals that conformation **B** is present to a significant extent. So it is possible that the extention of the side-chain of **4** to form **20** has not changed the conformation much.



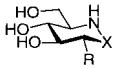
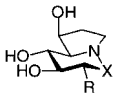
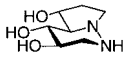
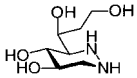
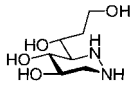
Scheme 7. Synthesis of open-chain analogues of compound **5**, **20a** and **20b**.

The new compounds (±)-**5a**, (±)-**5b**, (±)-**20a**, and (±)-**20b** were tested for inhibition of α-glucosidase from yeast and rice, isomaltase from yeast, and β-glucosidase from sweet almonds (Table 1). These enzymes was chosen because either **2** or **4** has been found to inhibit them strongly. Where inhibition was found it was competitive. The data were compared with data for **1**, **2**, and **4** taken from the literature or by test (Table 1). It should be noted that since the enantiomer of **4** has been found to be an extremely poor inhibitor,[4f] it is unlikely that the enantiomers resembling L-glucose of the racemates **5** and **20** play any role in significant inhibition of these enzymes.

It is remarkable that for all the enzymes investigated **5a** is a weaker inhibitor than **4**; only the inhibition of rice α-glucosidase is essentially identical for the two substances (when taking into account that **5a** is racemic). It is also remarkable that, even then, **5a** is a much more potent inhibitor than **5b** of all enzymes except yeast α-glucosidase.

The weak inhibition of yeast α-glucosidase by **5a** can, however, readily be explained, because **2** is a much weaker inhibitor of that enzyme than **1**. This suggests that **2** (or **5a**) cannot fit properly into the active site, presumably because of steric hindrance from the ethylene bridge or unfavorable nonpolar interactions. This is supported by the facts that there is no difference in the K_i value of epimers **5a** and **5b**, and that the unconstrained analogues **20a** and **20b** are slightly more potent. Since none of these compounds can fit into the active site and bind in a mode similar to the substrate, there is no particular reason why one of the epimers of **5** should be more potent than the other, and the more flexible analogues **20** may be expected to be better at adopting an alternative mode of binding.

Table 1. Inhibition of various enzymes by synthesized compounds. Inhibition was competitive; values shown are K_i in μM. Unless noted otherwise the temperature was 25 °C and the pH 6.8.

	α-Glucosidase (yeast)	α-Glucosidase (rice)	Isomaltase (yeast)	β-Glucosidase (almond)
				
1 X = CH_2, R = OH	25[a]	0.01[b]	11[a]	47[a]
4 X = NH, R = H	2.0[c]	6	0.27[c]	0.33[c]
				
2 X = CH_2, R = OH	> 1500[a]	0.015[b]	–	1.5[d]
5a X = NH, R = H	600	15	79	10
				
5b	570	> 1000	550	690
				
20a	275	250	> 1000	660
				
20b	380	150	> 1000	820

[a] Ref. [2c]. [b] pH not given, Ref. [2c]. [c] Ref. [13]. [d] pH 5.0, Ref. [2c].

The same arguments imply that **5a** binds to the active site of rice α-glucosidase, isomaltase, and β-glucosidase in a mode similar to the substrate, because binding is so much stronger than that of **5b**. It also shows that those three enzymes prefer the substrate in conformer **B** (Scheme 1).

The virtually identical inhibition of rice α-glucosidase by **4** and **5a** is understandable when they are compared with **1** and **2**, which also have identical, albeit much greater, inhibition effects on the enzyme. It must be concluded that locking the conformation of the 6-OH group into the preferred conformation simply does not increase binding much.

The most puzzling results are the inhibition data for β-glucosidase. Though **5a** clearly binds to the active site aligned in a similar way as the other inhibitors, it is fifteen times weaker than **4**. Yet **2** is thirty times more potent than **1**, a fact that suggests that locking the 6-OH into conformation **B** can increase binding to β-glucosidase considerably. Perhaps these inconsistencies are unrelated to the conformation of the 6-OH, but rather are caused by subtle differences in basicity of the nitrogen atoms.

In summary it must be concluded that the gain in binding that may be obtained by restricting the conformation of the 6-OH in an azasugar inhibitor appears to be limited and easily overpowered by other effects. While **5a** was found to be an

equal or weaker inhibitor than **4**, **2** is similarly in many cases equal or weaker than **1**. It is likely, however, that more selective inhibitors will be obtained by such geometrical restriction.

Experimental Section

General: All reactions were carried out under an inert atmosphere in preheated glass equipment. Solvents were distilled under anhydrous conditions. Thus THF was distilled from sodium/benzophenone and used directly. All reagents were used as purchased without further purification. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates (Merck, 60, F_{254}) were visualized by spraying with cerium sulfate (1%) and molybdic acid (1.5%) in 10% H_2SO_4 and heating till colored spots appeared. All enzymes and substrates for the enzyme assays were purchased from Sigma.

(2*SR*,1′*SR*)- and (2*SR*,1′*RS*)-(3-Acetoxy-1-benzyloxypropyl)-8-phenyl-1,6,8-triazabicyclo[4.3.0]non-3-ene-7,9-dione (12a and 12b): Triethylamine (17 g, 169 mmol, 12.5 equiv) and 4-dimethylaminopyridine (86 mg, 0.71 mmol, 0.05 equiv) were added to a solution of dienol **10** (2.956 g, 13.5 mmol) in $CHCl_3$ (50 mL) under stirring at room temperature. Acetic anhydride (8.64 g, 85 mmol, 6 equiv) was added dropwise and the reaction mixture was stirred for 5 minutes. The reaction was monitored by TLC with EtOAc/pentane (1:6) as eluent; R_f (**11**) 0.76. After concentration, $CHCl_3$ (100 mL) was added and the organic phase was washed with a 10% $NaHCO_3$ solution (30 mL), and subsequently dried ($MgSO_4$) and concentrated to give the crude acetate **11** (3.692 g) in a 1.75:1 ratio in favor of the *Z* isomer as a yellow oil, which was used without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 7.36-7.20$ (m, 5H, Ar), 6.64–6.14 (m, 2H), 5.68–5.08 (m, 3H, ratio: 1.75:1), 4.62–3.84 (m, 5H), 1.98 (s, 3H, -OCOCH_3), 2.09–1.69 (m, 2H, -CH_2CH$_2$OCOCH$_3$); HRMS (ES): 283.1317, calcd for $C_{16}H_{20}O_3$+Na: 283.1317.

A solution of 271 mg of the crude *E*/*Z* diene **11** (≈1 mmol) in EtOAc (1 mL) was added to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione[10] (317 mg, 1.81 mmol, 1.7 equiv) in EtOAc (3 mL) at 0 °C under stirring and thereafter the reaction mixture was refluxed for 25 minutes. Concentration and column chromatography (EtOAc/pentane 40:60) gave **12a** ($R_f = 0.26$, 152 mg, 35%) and **12b** ($R_f = 0.14$, 200 mg, 46%). **Diastereomer 12a**: ^{13}C NMR ($CDCl_3$): $\delta = 170.3$ (-*O*COCH$_3$), 151.5, 150.4 (C-7, C-9), 137.0, 130.4, 128.6, 127.9, 127.5, 127.4 (Ar), 124.9, 121.2 (C-3, C-4), 73.8, 72.4 (C-2′, Ph*C*H$_2$O-), 60.2 (-*C*H$_2$OCOCH$_3$), 53.9 (C-2), 42.6 (C-5), 29.0 (-*C*H$_2$CH$_2$O-COCH$_3$), 20.3 (-OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.48-7.16$ (m, 10H, Ar), 6.02 (br s, 2H, H-3, H-4), 4.70 (m, 1H, H-2), 4.65/4.54 (d, 2H, PhCH_2O-, $J =$ 11.4 Hz), 4.25 (ddd, 1H, H-2′, $J = 3.3$ Hz, 9.2 Hz), 4.17–3.88 (m, 4H, H-5eq, H-5ax, CH_2OCOCH$_3$), 1.90 (s, 3H, -OCOCH_3), 1.62 (m, 2H, CH_2CH$_2$OCOCH$_3$); HRMS(ES): *m*/*z*: 458.1695, calcd for $C_{24}H_{25}O_5N_3$+Na: 458.1692. **Diastereomer 12b**: ^{13}C NMR ($CDCl_3$): $\delta = 170.3$ (-*O*COCH$_3$), 151.4, 149.8 (C-7, C-9), 136.9, 130.6, 128.5, 127.9, 127.5, 127.4, 127.1, 125.0 (Ar), 122.0, 120.2 (C-3, C-4), 75.1, 72.9 (C-2′, Ph*C*H$_2$O-), 60.2 (-*C*H$_2$OCOCH$_3$), 55.4 (C-2), 42.7 (C-5), 30.4 (-*C*H$_2$CH$_2$OCOCH$_3$), 20.3 (-OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.48-7.12$ (m, 10H, Ar), 6.04 (ddd, 1H, H-4, J 1.5 Hz, 10.6 Hz), 5.95 (ddd, 1H, H-3; $J = 1.8$ Hz, 4.0 Hz, 10.6 Hz), 4.62 (dddd, 1H, H-2, $J = 1.7$ Hz, 3.0 Hz), 4.51/4.43 (d, 2H, PhCH_2O-, J_{gem} 11.4 Hz), 3.96–4.28 (m, 5H, H-2′, H-5eq, H-5ax, CH_2OCOCH$_3$), 1.94 (s, 3H, -OCOCH_3), 1.86 (m, 2H, CH_2CH$_2$OCOCH$_3$); HRMS(ES): *m*/*z*: 458.1693, calcd for $C_{24}H_{25}O_5N_3$+Na: 458.1692.

(2*RS*,3*RS*,4*SR*,1′*SR*)-3,4-Epoxy-(1-acetoxy-3-benzyloxypropyl)-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (13a): Alkene **12a** (386 mg, 0.89 mmol) was dissolved in CH_3CN (10 mL) and water (8 mL) in a flask fitted with a dry ice/acetone condenser. The solution was cooled to 0 °C, and $NaHCO_3$ (620 mg) and 1,1,1-trifluoroacetone (1 mL) was added, followed by oxone (3 g) in small portions over a period of 5 min under stirring. The cooling was discontinued and the reaction mixture was stirred for 105 min; subsequently another charge of $NaHCO_3$ (310 mg), 1,1,1-trifluoroacetone (0.5 mL), and oxone (1.5 g) was added. After 55 min the reaction was worked up by the addition of water (50 mL), extracted with $CHCl_3$ (3 × 50 mL), dried ($MgSO_4$), and concentrated to give **13a** (362 mg, 90%) as a yellow oil. ^{13}C NMR ($CDCl_3$): $\delta = 137.2$, 131.3, 129.3, 128.8, 128.5, 125.7 (Ar), 74.3 (C2′), 73.2 (-O*C*H$_2$Ph), 60.9 (-*C*H$_2$OCOCH$_3$), 53.9 (C2), 49.6, 48.4 (C3, C4), 40.9 (C5), 30.2 (-*C*H$_2$CH$_2$OCOCH$_3$), 21.1 (-OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.44-7.24$ (m, 10H, Ar), 4.64 (m, 1H, H2), 4.61 (d, 1H, -OCH_2Ph, $J_{gem} = 11.4$ Hz), 4.58 (d, 1H, -OCH_2Ph), 4.33 (dd, 1H, H5eq, $J_{5eq,5ax} = 14.0$ Hz, $J_{5eq,4} = 2.3$ Hz), 4.20 (m, 1H, H2′), 4.06 (m, 2H, -CH$_2$CH_2OCOCH$_3$), 3.72 (dd, 1H, H5ax, $J_{5ax,4} = 1$ Hz), 3.46 (m, 1H, H-3), 3.40 (m, 1H, H4), 1.90 (s, 3H, -OCOCH_3), 1.85 (m, 2H, -CH_2CH$_2$OCOCH$_3$); HRMS(ES): *m*/*z*: 474.1638, calcd for $C_{24}H_{25}O_6N_3$+Na: 474.1641.

(2*RS*,3*RS*,4*SR*,1′*RS*)-3,4-Epoxy-(1-acetoxy-3-benzyloxypropyl)-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (13b): Epoxide **13b** was prepared in the same way from **12b** in a yield of 89% as a yellow oil. ^{13}C NMR ($CDCl_3$): $\delta = 170.3$ (-*O*COCH$_3$), 150.1 (C-7, C-9), 136.6, 130.5, 128.5, 128.0, 127.7, 127.5, 124.8 (Ar), 75.5 (C-2′), 73.4 (Ph*C*H$_2$O-), 60.0 (-*C*H$_2$OCOCH$_3$), 54.7 (C-2), 48.2, 47.5 (C-3, C-4), 40.1 (C-5), 30.4 (-*C*H$_2$CH$_2$OCOCH$_3$), 20.4 (-OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.44-7.18$ (m, 10H, Ar), 4.53 (m, 1H, H-2), 4.61 (d, 1H, PhCH_2O-, $J = 11.4$ Hz), 4.46 (d, 1H, PhCH_2O-), 4.30 (m, 1H, H2′), 4.06–4.28 (m, 3H, H-5eq, -CH_2OCOCH$_3$), 3.62 (m, 1H, H-5ax, $J_{5ax,5eq} = 13.9$ Hz), 3.51 (m, 1H, H-3, $J_{3,4} = 2.9$ Hz), 3.42 (m, 1H, H-4), 2.02 (m, 2H, -CH_2CH$_2$OCOCH$_3$), 2.00 (s, 3H, OCOCH_3); HRMS(ES): *m*/*z*: 474.1646, calcd for $C_{24}H_{25}O_6N_3$+Na: 474.1641.

(2*RS*,3*RS*,4*RS*,1′*SR*)-3,4-Diacetoxy-2-(1-acetoxy-3-benzyloxypropyl)-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (14a): Epoxide **13a** (37 mg, 0.082 mmol) was dissolved in acetic acid (1 mL) and acetic anhydride (0.2 mL) under nitrogen. Freshly distilled boron trifluoride etherate (3 μL, 0.024 mmol, 0.29 equiv) was added carefully under stirring at room temperature, and the reaction mixture was stirred for 2 h. The reaction was quenched by the addition of a saturated $NaHCO_3$ solution (2 mL) followed by extraction (EtOAc, 3 × 5 mL). The combined organic phases were washed consecutively with a saturated $NaHCO_3$ solution and brine. After drying (Na_2SO_4), concentration, and column chromatography (EtOAc/pentane (40:60), R_f 0.43), triacetate **14a** (34 mg, 75%) was obtained as a yellow oil. ^{13}C NMR ($CDCl_3$): $\delta = 170.9$, 169.4, 168.9 (-*O*COCH$_3$), 155.0, 152.4 (C-7, C-9), 137.2, 131.1, 129.5, 129.1, 128.7, 128.3, 128.1, 128.0, 125.7 (Ar), 73.1, 72.8 (-O*C*H$_2$Ph, C2′), 66.5, 65.8 (C3, C4), 60.5, 59.7 (-*C*H$_2$ OCOCH$_3$, C2), 46.3 (C5), 31.1 (-*C*H$_2$CH$_2$OCOCH$_3$), 21.1 (-OCOCH$_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.46-7.04$ (m, 10H, Ar), 5.04 (m, 2H, H-3, H-4), 4.53 (d, 1H, -OCH_2Ph, $J_{gem} = 11.2$ Hz), 4.44 (d, 1H, -OCH_2Ph), 4.34 (m, 1H, H-2, $J = 9,8$ Hz), 4.25–4.12 (m, 3H, -CH_2OCOCH$_3$, H-2′), 4.07 (dd, 1H, H-5eq, $J_{5eq,5ax} = 13.3$ Hz, $J_{5eq,4} = 1.4$ Hz), 3.50 (dd, 1H, H-5ax, $J_{5ax,4} = 2.8$ Hz), 2.09 (s, 3H, -OCOCH_3), 2.08 (s, 3H, -OCOCH_3), 1.94 (s, 3H, -OCOCH_3), 2.10–1.90 (m, 2H, -CH_2CH$_2$OCOCH$_3$); HRMS(ES): 576.1956, calcd for $C_{28}H_{31}O_9N_3$+Na: 576.1958.

(2*RS*,3*RS*,4*RS*,1′*RS*)-3,4-Diacetoxy-2-(1-acetoxy-3-benzyloxypropyl)-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (14b): Compound **14b** was prepared in a similar way from epoxide **13b** (R_f 0.45 in EtOAc/pentane 1:1) as a yellow oil in a yield of 75%. ^{13}C NMR ($CDCl_3$): $\delta = 170.2$, 168.4 (-*O*COCH$_3$), 154.2, 150.2 (C7, C9), 136.6, 130.2, 128.7, 128.0, 127.9, 127.4, 127.0, 124.9 (Ar), 73.2, 70.6 (Ph*C*H$_2$O-, C-2′), 65.3, 64.5 (C-3, C-4), 59.9, 57.2 (C-2, -*C*H$_2$OCOCH$_3$), 45.6 (C-5), 29.3 (-*C*H$_2$CH$_2$OCOCH$_3$), 20.3 (-OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.40-7.05$ (m, 10H, Ar), 5.43 (m, 1H, H-3), 4.98 (m, 1H, H4, $J = 2.4$ Hz), 4.54 (d, 1H, PhCH_2O-, $J_{gem} =$ 12.1 Hz), 4.42 (d, 1H, PhCH_2O-), 4.33 (dd, 1H, H2, $J = 1.2$ Hz, $J = 9.7$ Hz), 4.26–4.05 (m, 3H, -CH_2OCOCH$_3$, H-2′), 3.96 (dd, 1H, H-5eq, $J_{5eq,4} =$ 2.2 Hz, $J_{5eq,5ax} = 13.3$ Hz), 3.44 (dd, 1H, H-5ax, $J_{5ax,4} = 2.4$ Hz), 2.00 (s, 3H, -OCOCH$_3$), 1.91 (s, 3H, -OCOCH$_3$), 1.85 (s, 3H, -OCOCH$_3$), 2.00–1.70 (m, 2H, -CH_2CH$_2$OCOCH$_3$); HRMS(ES): 576.1955, calcd for $C_{28}H_{31}O_9N_3$+Na: 576.1958.

Lactone 15a: Triacetate **14a** (380 mg, 6.86×10^{-4} mol) was dissolved in MeOH (10 mL) and a small piece of sodium was added. After 55 min of stirring at room temperature the solvent was evaporated in vacuo. The resultant syrup was dissolved in $CHCl_3$ (15 mL) and water (3 mL) followed by adjustment to pH 9 by addition of $NaHCO_3$. Potassium bromide (8 mg, 6.86×10^{-5} mol, 0.10 equiv) and TEMPO (5 mg, 3.43×10^{-5} mol, 0.05 equiv) were added, followed by careful addition of aqueous NaOCl buffered with $NaHCO_3$. The reaction was monitored by TLC (R_f (triol) 0.09, R_f (**15a**) 0.66 in EtOAc). The organic layer was separated, and the water phase was extracted with chloroform. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to give **15a** (260 mg, 90% in 2 steps) as a white powder. M.p.: decomp; ^{1}H NMR ($CDCl_3$): $\delta = 7.60-7.05$ (m, 10H, Ar), 5.20 (m, 1H, H-6), 4.65 (d, 1H, -OCH$_2$Ph, $J_{gem} = 13.0$ Hz), 4.55 (d, 1H, -OCH$_2$Ph), 4.35 (dd, 1H, H-2eq,

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$J_{2eq,3}=4.7$ Hz, $J_{2eq,2ax}=12.5$ Hz), 4.05–3.7 (m, 2H, H-3, H-4), 3.60 (dd, 1H, H-5, $J_{5,6}=3.9$ Hz, $J_{5,4}=10.4$ Hz), 3.15–2.90 (m, 2H, H-2ax, H-7eq), 2.75 (dd, 1H, H-7ax, $J_{7ax,6}=5.7$ Hz, $J_{7ax,7eq}=15.6$ Hz); ^{13}C NMR ([D$_6$]DMSO): $\delta=170.1$ (C-8), 152.0, 150.6 (C=O's), 138.1, 131.2, 129.0, 128.3, 128.1, 127.7, 127.5, 126.4 (Ar), 77.6 (C-4), 71.6, 70.2, 66.1 (C-3, C-5, -OCH_2Ph), 62.1 (C-6), 46.2 (C-2), 34.1 (C-7); HRMS(ES): m/z: 446.1348, calcd for $C_{22}H_{21}O_6N_3$+Na: 446.1328.

Lactone 15b: Performed as for preparation of **15a** except that triacetate **14b** was used as starting material. R_f 0.69 in EtOAc. Mp: decomp; ^{1}H NMR ($CDCl_3$): $\delta=7.20-7.50$ (m, 10H, Ar), 5.20 (m, 1H, H-6), 4.70 (s, 1H, -OCH_2Ph), 4.68 (s, 1H, -OCH_2Ph), 4.35 (dd, 1H, H-2eq, $J_{2eq,3}=4.9$ Hz, $J_{2eq,2ax}=12.4$ Hz), 4.05 (m, 2H, H-3, H-4), 3.50 (dd, 1H, H-5, $J_{5,6}=4.9$ Hz, $J_{5,4}=9.9$ Hz), 3.05 (dd, 1H, H-2ax, $J_{2ax,3}=10.1$ Hz), 2.90 (dd, 1H, H-7eq, $J_{7eq,6}=1.9$ Hz, $J_{7eq,7ax}=18.5$ Hz), 2.60 (dd, 1H, H-7ax, $J_{7az,6}=3.7$ Hz); ^{13}C NMR ([D$_6$]DMSO): $\delta=167.7$ (C-8), 152.2, 150.6 (C=O's), 138.3, 131.3, 129.0, 128.3, 127.6, 126.5 (Ar), 76.6 (C-4), 70.8, 69.0, 66.8 (C-3, C-5, -OCH_2Ph), 57.5 (C-6), 46.2 (C-2), 35.1 (C-7); HRMS(ES): m/z 446.1328, calcd for $C_{22}H_{21}O_6N_3$+Na: 446.1328.

Diacetate 16a: Lactone **15a** (31 mg, 7.32×10^{-5} mol) was dissolved in dry THF (3 mL) and cooled to $-78\,^\circ$C under nitrogen. DIBALH (0.25 mL, 1.5 M solution in toluene, 3.75×10^{-4} mol, 4.8 equiv) was added carefully, and the reaction mixture was stirred for 4 h. The cooling was removed and the reaction was quenched immediately by the addition of water (5 mL) followed by extraction with EtOAc. The combined organic phase was washed consecutively with 2 M HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was dissolved in $CHCl_3$ (4 mL) and NEt_3 (118 μL, 8.46×10^{-4} mol, 12 equiv), DMAP (1 mg, 8.19×10^{-6} mol, 0.11 equiv) and acetic anhydride (40 μL, 4.23×10^{-4} mol, 6 equiv) was added. The reaction mixture was stirred at room temperature for 20 min followed by the addition of saturated $NaHCO_3$ (aq). The water phase was extracted ($CHCl_3$), washed (brine), dried ($MgSO_4$), and concentrated, followed by flash chromatography to give **16a** (R_f 0.23 in EtOAc/pentane 40:60) as a mixture (1:1) of anomers (26 mg, 70% in 2 steps). ^{1}H NMR ($CDCl_3$): $\delta=7.10-7.50$ (m, 20H, Ar), 6.19 (dd, 1H, H-8a, $J_{8a,7eq}=1.2$ Hz, $J_{8a,7ax}=3.7$ Hz), 5.75 (dd, 1H, H-8b, $J_{8b,7eq}=2.4$ Hz, $J_{8b,7ax}=9.2$ Hz), 5.10 (m, 2H), 4.70 (t, 2H, $J=10.2$ Hz), 4.53 (dt, 1H, $J=5.4$ Hz, $J=10.2$ Hz), 4.45 (dd, 2H, $J=4.1$ Hz, $J=10.2$ Hz), 4.31 (dt, 2H, $J=5.6$ Hz, $J=11.8$ Hz), 3.87 (t, 1H, $J=9.6$ Hz), 3.42–3.60 (m, 3H), 3.02 (t, 1H, $J=10.8$ Hz), 2.98 (t, 1H, $J=10.8$ Hz), 2.39–2.48 (m, 2H), 3.46–3.60 (m, 4H), 2.08 (s, 3H, -$OCOCH_3$), 2.04 (s, 3H, -$OCOCH_3$), 2.03 (s, 3H, -$OCOCH_3$), 2.01 (s, 3H, -$OCOCH_3$), 1.80–1.93 (m, 2H); ^{13}C NMR ($CDCl_3$): 168.7 (2C, -$OCOCH_3$), 168.0 (2C, -$OCOCH_3$), 152.6, 152.3, 149.1, 148.8 (C=O's), 136.8, 136.7, 129.9, 128.2, 127.5 (2C), 127.3 (2C), 126.9, 124.9 (2C, Ar), 90.9, 90.2 (C-8), 73.1, 70.6, 70.2, 69.8, 67.8, 67.6 (2C, C-3, C-4, C-6, -OCH_2Ph), 61.1, 60.8 (C-5), 46.4, 45.8 (C-2), 32.7 (2C, C-7), 20.0, 19.8 (-$OCOCH_3$); HRMS(ES): m/z: 532.1656, calcd for $C_{26}H_{27}O_8N_3$+Na: 532.1696.

Diacetate 16b. Performed as for preparation of **16a** except that lactone **15b** was used as starting material. The yield was 70% of β-anomer exclusively. ^{1}H NMR ($CDCl_3$): $\delta=7.20-7.60$ (m, 10H, Ar), 6.05 (dd, 1H, H-8, $J_{8,7eq}=2.3$ Hz, $J_{8,7ax}=9.8$ Hz), 5.16 (m, 1H, H-6), 5.07 (dt, 1H, H-3, $J_{3,2eq}=5.5$ Hz, $J_{3,2ax}$, $J_{3,4}=9.8$ Hz), 4.77 (d, 1H, -OCH_2Ph, $J_{gem}=11.3$ Hz), 4.65 (d, 1H, -OCH_2Ph), 4.43 (dd, 1H, H-2eq, $J_{2eq,2ax}=11.8$ Hz), 4.30 (t, 1H, H-4, $J_{4,5}=9.8$ Hz), 3.48 (dd, 1H, H-5, $J_{5,6}=2.7$ Hz), 3.06 (dd, 1H, H-2ax), 2.22 (ddd, 1H, H-7eq, $J_{7eq,6}=3.7$ Hz, $J_{7eq,7ax}=14.1$ Hz), 2.10 (s, 6H, -$OCOCH_3$), 1.74 (ddd, 1H, H-7ax, $J_{7ax,6}=2.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=169.9$, 168.8 (-$OCOCH_3$), 152.3, 150.8 (C=O's), 138.0, 130.8, 129.3, 128.5, 128.4, 127.8, 125.7 (Ar), 91.0 (C-8), 72.1, 71.8, 70.8, 68 (C-3, C-4, C-6, -OCH_2Ph), 60.2 (C-5), 43.8 (C-2), 33.1 (C-7), 21.1, 20.8 (-$OCOCH_3$); HRMS(ES): m/z: 532.1692, calcd for $C_{26}H_{27}O_8N_3$+Na: 532.1696.

Glycoside 17a: Diacetate **16a** (44 mg, 8.63×10^{-5} mol) was dissolved in $CHCl_3$ (2 mL) and BnOH (53 μL, 5.18×10^{-4} mol, 6 equiv) was added under nitrogen at room temperature. BF_3/Et_2O (90 μL, 7.17×10^{-4} mol, 8.3 equiv) was carefully added. After 1 h the reaction mixture was worked up by the addition of $CHCl_3$ (3 mL) and subsequently washed with saturated solution of $NaHCO_3$. The water phase was extracted with $CHCl_3$ (3×10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated followed by column chromatography in EtOAc/pentane (20:80) to give **17a** exclusively as the α-anomer (37 mg, 77%, R_f 0.15). ^{1}H NMR ($CDCl_3$): $\delta=7.00-7.60$ (m, 15H, Ar), 5.18 (dt, 1H, H-3, $J_{3,2eq}=5.9$ Hz, $J_{3,4}$, $J_{3,2ax}=9.9$ Hz), 5.00 (dd, 1H, H-8, $J_{8,7ax}=3.5$ Hz, $J_{8,7eq}=1.0$ Hz), 4.25–4.80 (m, 6H, -OCH_2Ph, H-6, H-2eq, $J_{2eq,2ax}=10.8$ Hz), 3.90 (t, 1H, H-4, $J_{4,5}=9.9$ Hz), 3.44 (t, 1H, H-5), 3.02 (t, 1H, H-2ax), 2.47 (ddd, 1H, H-7eq, $J_{7eq,7ax}=13.8$ Hz), 2.10 (s, 3H, -$OCOCH_3$), 1.71 (ddd, 1H, H-7ax); ^{13}C NMR ($CDCl_3$): 169.9 (-$OCOCH_3$), 154.0, 149.9 (C=O's), 138.4, 137.0, 131.4, 129.4, 128.8, 128.7, 128.5, 128.3, 127.9, 126.2 (Ar), 96.4 (C-8), 70.9, 69.8, 69.6, 69.2 (2C, -OCH_2Ph, C-3, C-4, C-6), 62.7 (C-5), 47.8 (C-2), 35.0 (C-7), 21.1 (-$OCOCH_3$); HRMS(ES): m/z: 580.2057, calcd for $C_{31}H_{31}O_7N_3$+Na: 580.2060.

Glycoside 17b: Performed as for preparation of **17a** except that diacetate **16b** was used as starting material. Two anomers were isolated in 42% and 37% yield for β- and α-anomer, respectively. ***β*-Anomer**: ^{1}H NMR ($CDCl_3$): $\delta=7.20-7.50$ (m, 15H, Ar), 5.15 (dt, 1H, H-3, $J_{3,2eq}=5.5$ Hz, $J_{3,4}$, $J_{3,2ax}=9.8$ Hz), 5.10 (m, 1H, H-6), 5.02 (dd, 1H, H-8, $J_{8,7eq}=2.1$ Hz, $J_{8,7ax}=9.7$ Hz), 4.86 (d, 1H, H-OCH_2Ph, $J_{gem}=11.8$ Hz), 4.77 (d, 1H, H-OCH_2Ph, $J_{gem}=11.3$ Hz), 4.65 (d, 1H, H-OCH_2Ph), 4.59 (d, 1H, H-OCH_2Ph), 4.46 (dd, 1H, H-2eq, $J_{2eq,2ax}=11.8$ Hz), 4.19 (t, 1H, H-4, $J_{4,5}=9.8$ Hz), 3.49 (dd, 1H, H-5, $J_{5,6}=2.9$ Hz), 3.04 (dd, 1H, H-2ax), 2.23 (ddd, 1H, H-7eq, $J_{7eq,6}=3.6$ Hz, $J_{7eq,7ax}=14.2$ Hz), 2.13 (s, 3H, -$OCOCH_3$), 1.71 (ddd, 1H, H-7ax, $J_{7ax,6}=2.4$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=169.9$ (-$OCOCH_3$), 152.4, 151.1 (C=O's), 138.5, 137.3, 131.0, 129.4, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 125.9 (Ar), 97.7 (C-8), 72.1, 71.4, 71.2, 70.9, 68.7 (C-3, C-4, C-6, -OCH_2Ph), 60.8 (C-5), 44.1 (C-2), 34.5 (C-7), 21.0 (-$OCOCH_3$); HRMS(ES): m/z: 580.2098, calcd for $C_{31}H_{31}O_7N_3$+Na: 580.2060. ***α*-Anomer**: ^{1}H NMR ($CDCl_3$): $\delta=7.60-7.10$ (m, 15H, Ar), 5.14 (ddd, 1H, H-3, $J_{3,2eq}=5.5$ Hz, $J_{3,4}=9.8$ Hz, $J_{3,2ax}=11.7$ Hz), 5.05 (m, 2H, H-6, H-8), 4.83 (d, 1H, -OCH_2Ph, $J_{gem}=11.5$ Hz), 4.73 (d, 1H, -OCH_2Ph, $J_{gem}=11.1$ Hz), 4.64 (t, 1H, H-4, $J_{4,5}=9.8$ Hz), 4.62 (d, 1H, -OCH_2Ph), 4.45 (d, 1H, -OCH_2Ph), 4.43 (dd, 1H, H-2eq, $J_{2eq,2ax}=11.5$ Hz), 3.60 (dd, 1H, H-5, $J_{5,6}=2.9$ Hz), 3.14 (dd, 1H, H-2ax), 2.40 (dd, 1H, H-7eq, $J_{7eq,6}=1.8$ Hz, $J_{7eq,7ax}=15.4$ Hz), 2.13 (s, 3H, -$OCOCH_3$), 1.86 (ddd, 1H, H-7ax, $J_{7ax,6}=3.3$ Hz, $J_{7ax,8}=4.6$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=169.8$ (-$OCOCH_3$), 151.9, 151.1 (C=O's), 138.4, 137.5, 130.9, 129.2, 128.4, 128.1, 128.0, 127.7, 127.4, 125.7 (Ar), 95.6 (C-8), 71.0, 69.2, 69.0, 68.4, 64.7 (C-3, C-4, C-6, -OCH_2Ph), 60.4 (C-5), 44.0 (C-2), 30.8 (C-7), 20.9 (-$OCOCH_3$); HRMS(ES): m/z: 580.2061, calcd for $C_{31}H_{31}O_7N_3$+Na: 580.2060.

Hydrazine 18a: Glycoside **17a** (14 mg, 2.54×10^{-5} mol) was dissolved in MeOH (4 mL) and a small piece of sodium was added. After 20 min of stirring the solvent was evaporated. Hydrazine hydrate (5 mL) was added, and subsequently the reaction mixture was heated to 100 °C for 16 h. Excess hydrazine hydrate was evaporated and the remaining syrup was exposed to column chromatography in MeOH/EtOAc (1:5) to give **18a** (9 mg, 96%, R_f 0.13). ^{1}H NMR (CD_3OD): $\delta=7.20-7.40$ (m, 10H, Ar), 5.05 (d, 1H, H-8, $J_{8,7ax}=2.4$ Hz), 4.76 (d, 1H, -OCH_2Ph, $J_{gem}=12.2$ Hz), 4.58 (d, 1H, -OCH_2Ph, $J_{gem}=10.9$ Hz), 4.45 (2d, 2H, -OCH_2Ph), 3.78 (ddd, 1H, H-6, $J_{6,7eq}=5.0$ Hz, $J_{6,5}=9.1$ Hz, $J_{6,7ax}=11.2$ Hz), 3.60 (ddd, 1H, H-3, $J_{3,2eq}=5.1$ Hz, $J_{3,4}=9.1$ Hz, $J_{3,2ax}=10.4$ Hz), 3.52 (t, 1H, H-4, $J_{4,5}=9.1$ Hz), 3.14 (dd, 1H, H-2eq, $J_{2eq,2ax}=13.2$ Hz), 2.66 (dd, 1H, H-2ax), 2.58 (t, 1H, H-5), 2.34 (ddd, 1H, H-7eq, $J_{7eq,8}=0.9$ Hz, $J_{7eq,7ax}=13.0$ Hz), 1.64 (ddd, 1H, H-7ax); ^{13}C NMR (CD_3OD): $\delta=139.7$, 139.2, 129.4, 129.3, 129.1, 128.9, 128.7, 128.6 (Ar), 97.8 (C-8), 75.0, 74.0 (-OCH_2Ph), 71.9, 70.6, 69.5 (C-3, C-4, C-6), 65.8 (C-5), 53.3 (C-2), 36.3 (C-7); HRMS(ES): m/z: 393.1788, calcd for $C_{21}H_{26}O_4N_2$+Na: 393.1790.

Hydrazine 18b: Performed as for preparation of **18a** except that diacetate **17b** was used as starting material. Yield: 80% as a colorless oil. ***β*-Anomer**: R_f 0.24 in MeOH/EtOAc 1:4; ^{1}H NMR ($CDCl_3$): $\delta=7.40-7.20$ (m, 10H, Ar), 4.93 (d, 1H, -OCH_2Ph, $J_{gem}=11.9$ Hz), 4.89 (dd, 1H, H-8, $J_{8,7eq}$ 1.9 Hz, $J_{8,7ax}=9.8$ Hz), 4.65 (d, 1H, -OCH_2Ph), 4.60 (d, 1H, -OCH_2Ph, $J_{gem}=11.6$ Hz), 4.44 (d, 1H, -OCH_2Ph), 3.93 (q, 1H, H-6, $J_{6,5}$, $J_{6,7eq}$, $J_{6,7ax}=2.6$ Hz), 3.70 (ddd, 1H, H-3, $J_{3,2eq}=5.1$ Hz, $J_{3,4}=9.2$ Hz, $J_{3,2ax}=10.2$ Hz), 3.52 (t, 1H, H-4, $J_{4,5}=9.2$ Hz), 3.11 (dd, 1H, H-2eq, $J_{2eq,2ax}=13.1$ Hz), 2.58 (dd, 1H, H-5), 2.53 (dd, 1H, H-2ax), 2.25 (ddd, 1H, H-7eq, $J_{7eq,7ax}=14.0$ Hz), 1.58 (ddd, 1H, H-7ax); ^{13}C NMR ($CDCl_3$): $\delta=139.6$, 139.2, 129.4, 129.3, 129.1, 129.0, 128.8 (Ar), 98.5 (C-8), 77.2, 74.8, 72.3, 71.4, 70.6 (C-3, C-4, C-6, -OCH_2Ph), 61.7 (C-5), 54.6 (C-2), 36.0 (C7); HRMS(ES): m/z: 393.1793, calcd for $C_{21}H_{26}O_4N_2$+Na: 393.1790. ***α*-Anomer**: R_f 0.19 in MeOH/EtOAc 1:4; ^{1}H NMR (CD_3OD): $\delta=7.40-7.10$ (m, 10H, Ar), 5.05 (dd, 1H, H-8, $J_{8,7eq}=1.0$ Hz, $J_{8,7ax}=4.0$ Hz), 4.90 (d, 1H, -OCH_2Ph, $J_{gem}=11.6$ Hz) 4.74 (d, 1H, -OCH_2Ph, $J_{gem}=10.8$ Hz), 4.43 (d, 1H, -OCH_2Ph), 4.29 (d, 1H, -OCH_2Ph), 3.97 (t, 1H, H-4, $J_{4,3}$, $J_{4,5}=9.3$ Hz), 3.88 (m, 1H, H-6), 3.68 (ddd, 1H, H-3, $J_{3,2eq}=4.9$ Hz, $J_{3,2ax}=10.8$ Hz), 3.12 (dd, 1H, H-2eq, $J_{2eq,2ax}=12.7$ Hz), 2.70 (dd, 1H, H-5, $J_{5,6}=2.9$ Hz), 2.58 (dd, 1H, H-2ax), 2.40 (ddd, 1H, H-7eq, $J_{7eq,6}=2.4$ Hz, $J_{7eq,7ax}=15.0$ Hz), 1.82 (ddd,

1H, H-7ax, $J_{7ax,6} = 2.9$ Hz); ^{13}C NMR (CD_3OD): $\delta = 138.0$ (2C), 129.2 (2C), 129.1, 129.1, 128.4, 128.3 (Ar), 97.0 (C-8), 70.3, 69.6, 69.5, 68.6, 68.2 (C-3, C-4, C-6, -OCH_2Ph), 61.1 (C-5), 54.9 (C-2), 32.5 (C-7); HRMS(ES): m/z: 393.1786, calcd for $C_{21}H_{26}O_4N_2$+Na: 393.1790.

(4*RS*,5*RS*,6*RS*,7*SR*)-1,2-Diaza-4,5,7-trihydroxy-[4.3.0]-bicyclononane (5a): To a solution of **18a** (14 mg, 3.78×10^{-5} mol) in MeOH (3 mL) was added Pd/C (20 mg, 10%) and 3 drops of concentrated HCl. Hydrogenationen at 1 atm was performed for 4 h followed by filtration of the catalyst through a pad of Celite. Evaporation of the solvent gave **5a** (8 mg, quant.) as the hydrochloride. R_f 0.31 in EtOH/NH_4OH (25%) 9:1; ^{1}H NMR ($CDCl_3$): $\delta = 4.45$ (ddd, 1H, H-7, $J_{7,8b} = 0.9$ Hz, $J_{6,7} = 3.3$ Hz, $J_{7,8a} = 7.1$ Hz), 3.75 (m, 2H, H-4, H-5), 3.51 (dt, 1H, H-9b, $J_{9b,8a} = 3.4$ Hz, $J_{9a,9b}$, $J_{9b,8b} = 9.4$ Hz), 3.49 (dd, 1H, H-3eq, $J_{3eq,4} = 3.8$ Hz, $J_{3ax,3eq} = 13.2$ Hz), 2.95 (m, 1H, H-3ax), 2.87 (dt, 1H, H-9ax, $J_{9ax,8ax} = 8.3$ Hz), 2.79 (dd, 1H, H-6, $J_{5,6} = 8.9$ Hz), 2.44 (dddd, 1H, H-8b, $J = 3.0$ Hz, $J_{8eq,8ax} = 11.3$ Hz), 1.84 (dquint, 1H, H-8a); ^{13}C NMR ($CDCl_3$): $\delta = 70.3$, 68.5, 68.3, 66.4 (C-4, C-5, C-6, C-7), 50.7, 48.4 (C-3, C-9), 30.7 (C-8); HRMS(ES): m/z: 175.1076, calcd for $C_7H_{14}O_3N_2$+H: 175.1083.

(4*RS*,5*RS*,6*RS*,7*RS*)-1,2-Diaza-4,5,7-trihydroxy-[4.3.0]-bicyclononane (5b): Prepared as for **5a** except that hydrazine **18b** was used as starting material. ^{1}H NMR (D_2O): $\delta = 4.44$ (ddd, 1H, H-7, $J_{7,8b} = 3.2$ Hz, $J_{6,7} = 4.9$ Hz, $J_{7,8a} = 8.1$ Hz), 3.77 (ddd, 1H, H-4, $J_{4,3eq} = 5.5$ Hz, $J_{4,5} = 8.4$ Hz, $J_{4,3ax} = 9.2$ Hz), 3.58 (t, 1H, H-5, $J_{5,6} = 9.2$ Hz), 3.45 (dd, 1H, H-3eq, $J_{3eq,3ax} = 13.0$ Hz), 3.24–3.45 (m, 2H, H-9b, H-9a), 3.04 (dd, 1H, H-3ax), 3.00 (dd, 1H, H-6), 2.45 (ddd, 1H, H-8b, $J_{8eq,8ax} = 17.0$ Hz, $J = 8.2$ Hz, $J = 14.6$ Hz), 1.86 (ddt, 1H, H-8a, $J = 3.2$ Hz, $J = 7.3$ Hz); ^{13}C NMR (D_2O): $\delta = 70.9$, 70.2, 69.7, 67.4 (C-4, C-5, C-6, C-7), 49.5 (C-3), 45.9 (C-9), 29.7 (C-8); HRMS(ES): m/z: 175.1085, calcd for $C_7H_{14}O_3N_2$+H^+: 175.1083.

(3*RS*,4*RS*,5*RS*,1′*SR*)-4,5-Dihydroxy-3-(1-acetoxy-3-benzyloxypropyl)-hexahydropyridazine (19a): Triacetate **14a** (221 mg, 3.99×10^{-4} mol) was suspended in MeOH (5 mL). A small lump of sodium was added at room temperature and the mixture was stirred for 5 min. The reaction was monitored by TLC (R_f (triol) 0.09 in EtOAc). The reaction mixture was concentrated and hydrazine hydrate (10 mL) was added, and then the mixture was heated to 100 °C for 20 h. The reaction was monitored by TLC (R_f (**19a**) 0.52 in MeOH/$CHCl_3$ 1:1). Concentration gave a syrup which was dissolved in water and put on an ion-exchange column (Amberlyst 15, H^+), washed with water, and eluted with 2.5% NH_4OH. Concentration gave hydrazine **19a** (120 mg, 100%) as a brown oil. ^{13}C NMR (D_2O): $\delta = 137.2$, 128.4, 128.3, 128.1 (Ar), 73.4, 72.7, 71.9, 71.2 (C-4, C-5, OCH_2Ph, C-3′), 63.5 (-CH_2CH_2OH), 57.7 (C-3), 51.8 (C-6), 33.6 (-CH_2CH_2OH); ^{1}H NMR (D_2O): $\delta = 7.40$ (m, 5H, Ar), 4.65 (d, 1H, -OCH_2Ph, $J_{gem} = 10.6$ Hz), 4.58 (d, 1H, -OCH_2Ph), 4.10 (t, 1H, H-3′, $J_{3',\text{-}CH2CH2OH} = 6.8$ Hz), 3.35–3.75 (m, 4H, H-4, H-5, -CH_2CH_2OH), 3.15 (dd, 1H, H-6eq, $J_{6eq,5} = 4.4$ Hz, $J_{6eq,6ax} = 12.6$ Hz), 2.60 (dd, 1H, H-3, $J_{3,3'} = 1.4$ Hz, $J_{3,4}$ 9,6 Hz), 2.49 (dd, 1H, H-6ax, $J_{6ax,6eq} = 12.4$ Hz), 1.85 (m, 2H, -CH_2CH_2OH). HRMS(ES): m/z: 305.1468, calcd for $C_{14}H_{22}O_4N_2$+Na: 305.1477.

(3*RS*,4*RS*,5*RS*,1′*RS*)-4,5-Dihydroxy-3-(1-acetoxy-3-benzyloxypropyl)-hexahydropyridazine (19b): Prepared as for **19a** except that triacetate **14b** was used as starting material. ^{1}H NMR (D_2O): $\delta = 7.00$–7.30 (m, 5H, Ar), 4.41 (d, 1H, -OCH_2Ph, $J_{gem} = 11.4$ Hz), 4.27 (d, 1H, -OCH_2Ph), 3.74 (ddd, 1H, H-3′, J(3′,-CH_2CH_2OH) = 10.3 Hz, $J_{3',3} = 2.9$ Hz), 3.20–3.50 (m, 3H, -CH_2OH, H-5), 3.06 (dd, 1H, H-4, $J_{4,5} = 9.9$ Hz), 2.90 (dd, 1H, H-6eq, $J_{6eq,5} = 5.1$ Hz, $J_{6eq,6ax} = 12.8$ Hz), 2.75 (dd, 1H, H-3, $J_{3,4} = 10.3$ Hz, 2.28 (dd, 1H, H-6ax, $J_{6ax,5} = 10.6$ Hz), 1.65–1.25 (m, 2H, -CH_2CH_2OH); ^{13}C NMR (D_2O): $\delta = 136.1$, 127.6, 127.5, 127.2 (Ar), 72.9, 70.8 (2C), 70.4 (C-4, C-5, OCH_2Ph, C-3′), 61.6 (-CH_2CH_2OH), 57.1 (C-3), 49.9 (C-6), 30.0 (-CH_2CH_2OH); HRMS (ES): m/z: 305.1478, calcd for $C_{14}H_{22}O_4N_2$+Na: 305.1477.

(3*RS*,4*RS*,5*RS*,1′*SR*)-4,5-Dihydroxy-3-(1,3-dihydroxypropyl)-hexahydropyridazine (20a): Benzylhydrazine **19a** (42 mg, 0.149 mmol) was dissolved in MeOH (10 mL); Pd on carbon (30 mg, 10%) and 4 drops of concentrated HCl were added. Hydrogenation under 1 atm was carried out for 25 min followed by filtration through a pad of Celite and concentration to give pure **20a** (R_f 0.29 in MeOH/EtOAc (1:1), 40 mg, quant.). ^{13}C NMR (D_2O): $\delta = 69.2$, 67.6, 63.2, 62.3 (C-4, C-5, C-3′, -CH_2CH_2OH), 57.9 (C-3), 48.4 (C-6), 35.2 (-CH_2CH_2OH); ^{1}H NMR (D_2O): $\delta = 4.23$ (m, 1H, H-3′, $J =$ 5 Hz, $J = 6$ Hz), 3.49–3.86 (m, 5H, H4, H5, H6eq, -OCH_2CH_2OH), 2.90 (m, 2H, H-3, H6ax), 1.60–1.90 (m, 2H, -CH_2CH_2OH); HRMS(ES): m/z: 193.1171, calcd for $C_7H_{16}O_4N_2$+H: 193.1188.

(3*RS*,4*RS*,5*RS*,1′*RS*)-4,5-Dihydroxy-3-(1,3-dihydroxypropyl)-hexahydropyridazine (20b): Prepared as for **20a** except that triacetate **19b** was used as starting material. Yield: 99%. R_f 0.25 in MeOH/EtOAc 1:1; ^{1}H NMR (D_2O): $\delta = 4.15$ (ddd, 1H, H-3′, $J_{3',3} = 3.2$ Hz, $J_{3',\text{-}CH2CH2OH} = 10.0$ Hz), 3.40–3.90 (m, 5H, H-4, H-5, H6eq, -CH_2CH_2OH), 3.12 (dd, 1H, H-3, $J_{3,4} =$ 10.2 Hz), 2.95 (dd, 1H, H-6ax, $J_{6ax,5} = 11.0$ Hz, $J_{6ax,6eq} = 12.6$ Hz), 1.55–1.95 (m, 2H, -CH_2CH_2OH); ^{13}C NMR (D_2O): $\delta = 69.4$, 68.0, 65.6, 63.0 (C-4, C-5, C-3′, -CH_2CH_2OH), 58.0 (C3), 48.1 (C6), 32.8 (-CH_2CH_2OH); HRMS(ES): m/z: 193.1173, calcd for $C_7H_{16}O_4N_2$+H: 193.1188.

Measurements of glycosidase inhibition: Each glycosidase assay was performed by preparing 2 mL samples in cuvettes consisting of 1 mL sodium phosphate buffer (0.1M) of pH 6.8, 0.2 to 0.8 mL of a 1.0 or 10 mM solution of either 4-nitrophenyl α-D-glucopyranoside or 4-nitrophenyl β-D-glucopyranoside, 0.1 mL of a solution of either the potential inhibitor or water, and distilled water to a total volume of 1.9 mL. Eight of the samples contained the potential inhibitor at fixed concentration, but with varying nitrophenyl glycoside concentration. Another eight samples contained no inhibitor, but also varying nitrophenyl glycoside concentration. Finally the reaction was started by adding 0.1 mL of a diluted solution of either α-glucosidase from bakers yeast (EC 3.2.1.20, Sigma G-5003), α-glucosidase from rice, isomaltase from yeast, or β-glucosidase from almonds (EC 3.2.1.21, Sigma G-0395), and the formation of 4-nitrophenol was followed for 2 min (20 min for rice α-glucosidase) at 25 °C by measuring absorbance at 400 nm. Initial velocities were calculated from the slopes for each of the eight reactions and used to construct two Hanes plots, one with and without inhibitor. From the two Michaelis–Menten constants (K_m) thus obtained, the inhibition constant (K_i) was calculated.

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