Isoquinuclidine Mimics of β-D-Glucopyranosides: Differences and Similarities in the Mechanism of Action of some β-D-Glucosidases and a β-D-Mannosidase

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Duilio Arigoni, in dankbarer und freundschaftlicher Verbundenheit, zum 75. herzlich zugeeignet

The D-*gluco*-isoquinuclidines **3** and **4** were prepared and tested as inhibitors of the β-glucosidases from *Caldocellum saccharolyticum* and from sweet almonds; the results are compared to the inhibition of snail β-mannosidase by the D-*manno*-isoquinuclidines **1** and **2**. Exploratory experiments in the racemic series showed that treatment of the ester epoxide **6** with benzyl alcoholates leads only to epimerisation, transesterification, and formation of the cyclopropane **9**. Ring opening of the reduced epoxide **13** by NaN_3 proceeded regioselectively to provide **14**. Treatment of the C(6)–O-triflate **16** with AcOCs induced a rearrangement; the reaction with NaN_3 gave the *C*(5)-azido derivative **14**. The acetoxy triflate **18**, however, reacted with AcOCs to provide the desired *gluco*-isoquinuclidine **19**. Similarly, the enantiomerically pure acetoxy triflate **22** provided the D-*gluco*-isoquinuclidine **24**, which was reduced and deprotected to provide **3** and **4**. The deoxy analogues **30** and **31** were obtained by reductive deiodination of the iodide **27**, derived from **22**. The D-*gluco*-isoquinuclidines **3**, **4**, **30**, and **31** are much weaker inhibitors of β-glucosidases than the D-*manno*-analogues **1** and **2** of snail β-mannosidase. The *N*-benzyl derivative **3** is a weaker inhibitor than the *N*-unsubstituted analogue in the *gluco*-series, while it is a much stronger inhibitor in the *manno*-series. A consideration of the pK_{HA} values of the isoquinuclidines **1**–**4** and the pH value of the enzyme assays suggests that the D-*gluco*-isoquinuclidines are poor mimics of the shape of a reactive, enzyme-bound *gluco*-conformer, while the D-*manno*-analogues are reasonably good mimics of a reactive, enzyme-bound *manno*-conformer. The inhibition results may also suggest that the glycosidase induced lengthening of the scissile bond and rehybridisation of the anomeric centre are more strongly correlated with the change of the ground-state conformation during hydrolysis of β-D-glucopyranosides than of β-D-mannopyranosides.

Introduction. – Stereoelectronic control of glycoside hydrolysis requires a coplanar arrangement of the scissile bond and a doubly occupied, nonbonding orbital of the ring O-atom, *i.e.*, a pseudoaxial orientation of the scissile bond [1]. β-D-Glycopyranosides possessing an equatorial glycosidic bond must, therefore, change conformation to undergo hydrolysis. This aspect and the cationic character of the transition state are expected to be common to all β-D-glycopyranosidases[1]). One must, however, expect differences for β-D-glycosidases belonging to different families[2]) and hydrolyzing different substrates. Glycosidase inhibitors[3]) may contribute to an analysis of similarities and differences of the mechanism of action of individual β-glycosidases. Recently, we became interested in the difference between the mechanism of action of

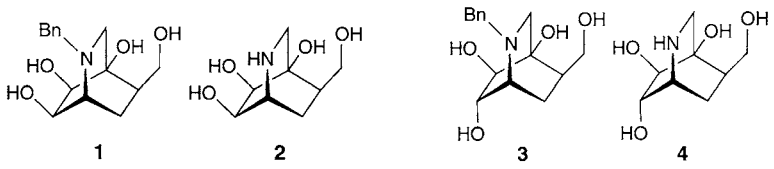
[1]) For review articles on the mechanism of glycoside hydrolysis, see [2–4].

[2]) A regularly updated database with over 6000 glycosidases classified in 89 families [5] is available on the internet (http://afmb.cnrs-mrs.fr/CAZY/).

[3]) For review articles on glycosidase inhibitors, see [4][6].

β-D-glucosidases and snail β-D-mannosidase. The catalytic nucleophile of retaining β-D-glucosidases of family 1 [7] and 3 [8] strongly interacts with the C(2)OH group of the substrate, an interaction that is geometrically not feasible for β-D-mannosidases. We speculated about the effect of this interaction [2], concluding that the mechanism of action of β-D-glucosidases and β-D-mannosidases should differ at the beginning of the reaction, but lead to similar cationic intermediates. Not too surprisingly then, a comparison of the inhibition by *gluco*- and *manno*-configured tetrahydroimidazopyridine-type inhibitors did not point to differences between the mechanism of action of the β-glucosidases from *Caldocellum saccharolyticum* (family 1) and from sweet almonds [9], and the β-D-mannosidase from snail [10]. These inhibitors mimic shape and charge of an oxycarbenium cation, but also the cooperative interaction of the substrate with the catalytic acid and nucleophile [11] that is typical for an early stage of the hydrolysis. Inhibitors mimicking the shape of an early stage of the reaction may, however, evidence differences in the mechanism of action of these glycosidases not visible for inhibitors with a trigonal anomeric centre.

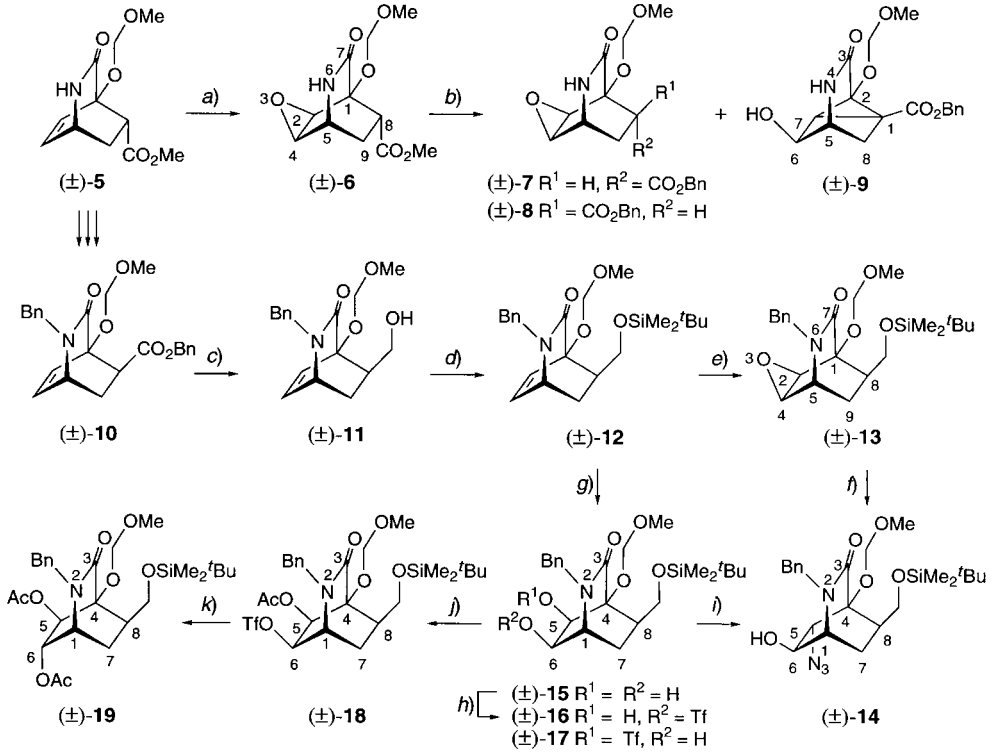
We found that the *manno*-configured isoquinuclidines **1** and **2** [12] mimicking the $^{1,4}B$ conformer of a β-D-mannopyranoside are selective inhibitors of snail β-mannosidase (at pH 4.5: $K_i = 0.001$ mM, $\alpha = 1.9$ for **1**; $K_i = 1.2$ mM, $\alpha = 1.1$ for **2**), the strength and type of inhibition depending on the pH value[4]). An evaluation of the main factors contributing to the inhibition (shape, pK_{HA} value, and *N*-substituent) suggested that the inhibition results agree with the hypothesis of a conformational change of the substrate, as discussed above. We wondered if the analogous D-*gluco*-isoquinuclidines **3** and **4** would similarly inhibit β-glucosidases, or if this inhibition would differ from the one of snail β-mannosidase by the D-*manno*-isoquinuclidines **1** and **2**. In the following, we describe the synthesis and inhibitory effect of the D-*gluco*-isoquinuclidines **3** and **4** on several glucosidases and on snail β-mannosidase, and compare the inhibition of glucosidases by the D-*gluco*-isoquinuclidines **3** and **4** to the inhibition of snail β-mannosidase by the D-*manno*-isoquinuclidines **1** and **2**.



Synthesis. – We have recently described an efficient synthesis of the D-*manno*-configured isoquinuclidines **1** and **2** *via* the alkene **20** (*cf. Scheme 2*). We planned to synthesise the D-*gluco*-configured isoquinuclidines **3** and **4** by a regioselective ring opening of an epoxide derived from **20**, or by an inverting substitution of the *cis*-diol **21**. Exploratory experiments were performed with the racemic alkene **5** [12][14] (*Scheme 1*). Epoxidation of **5** with *meta*-chloroperbenzoic acid (*m*CPBA) in the presence of 4,4′-thiobis[6-(*tert*-butyl)-3-methylphenol] [15] yielded 85% of the epoxide

[4]) A $B_{2,5}$ conformer has been postulated by *Davies* and co-workers [13] as reactive conformation of the substrate of the *Pseudomonas cellulosa* mannanase Man26A.

Scheme 1



a) *m*CPBA, 4,4′-thiobis[6-(*tert*-butyl)-3-methylphenol], $ClCH_2CH_2Cl$, Δ; 85%. *b*) CsF, BnOH, DMF, Δ; ((±)-**7**/(±)-**8** 7:3 (33%) and (±)-**9** (10%). *c*) $LiBH_4$, THF, Δ; 78%. *d*) 1. MeLi, THF, 0°; 2. ^{t}BuMe$_2$SiCl, THF, 0°; 87%. *e*) Dimethyldioxirane, acetone, 0°; 71%. *f*) NaN_3, DMF, Δ; (±)-**13** (44%) and (±)-**14** (20%). *g*) *N*-Methylmorpholine *N*-oxide monohydrate (NMO · H_2O), OsO_4, acetone/H_2O; 81%. *h*) $(CF_3SO_2)_2O$ (Tf_2O), pyridine, −10°; (±)-**16** (81%). *i*) NaN_3, DMF, Δ; 78%. *j*) 1. Tf_2O, pyridine; 2. Ac_2O, pyridine; 66%. *k*) AcOCs, DMF, Δ; 84%.

6[5]). Its structure was established by X-ray crystal-structure analysis[6]) (*Fig.*). Treatment of **6** with BnOH in the presence of CsF gave the epimeric benzyl esters **7**/**8** 7:3 (33%) and the cyclopropane **9** (10%). No benzyl ether was observed. BnOLi and BnONa led only to transesterification and epimerisation. We, therefore, transformed the ester **5** into the silyl ether **12** before epoxidation or dihydroxylation. Dealkylative epimerisation of the ester **5**, followed by benzylation, provided the benzyl ester **10** (46% [12]). Its reduction with $LiBH_4$ in boiling THF yielded 78% of the alcohol **11**. Silylation gave the silyl ether **12** (87%). Its oxidation with dimethyldioxirane led to the epoxide **13** (71%). All attempts to substitute **13** with AcOCs failed to provide the

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[5]) For a similar diastereoselective epoxidation of an isoquinuclidine lactam, see [16].

[6]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-217684. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

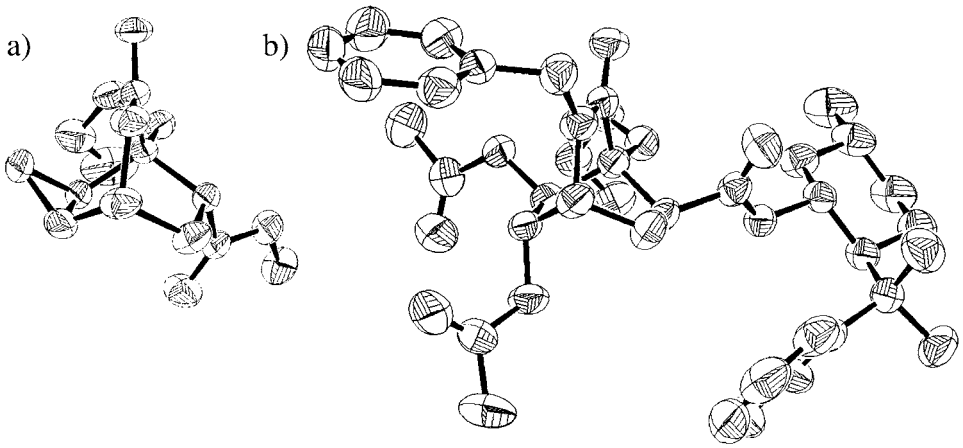

Figure. *ORTEP Representation of the Crystal Structure* a) *of the Epoxide (±)-***6** *and* b) *of the Diacetoxy 8-Phenylmenthyl Ester* **24**.

desired *trans*-acetoxy alcohol, and treatment of **13** with NaN_3 gave only the azido alcohol **14** (20%). The regioselectivity of the ring opening shows that the effect of the electronegative C(5)–*N*-substituent is more important than the combined effects of the (unfavourably oriented) *C*(1)-alkoxy group and of the steric hindrance of C(2).

Dihydroxylation of the alkene **12** led diastereoselectively to the diol **15** (81%). It was *O*-sulfonylated with trifluoromethanesulfonic acid anhydride (Tf_2O) in pyridine at $-10°$ to give regioselectively the triflate **16** (81%). Treatment of **16** with AcOCs in DMF at 120° did not lead to substitution; IR and ^{1}H-NMR analysis of the crude product suggested formation of a deoxy ketone (*cf.* [17]). Surprisingly, treatment of **16** with NaN_3 in DMF at 85° led to substitution at C(5), providing the azido alcohol **14** (78%). This result suggests a migration of the Tf group from *O*–C(6) to *O*–C(5) and a more facile substitution of the resulting triflate **17**. Acetylation of *O*–C(5) should prevent this migration and allow substitution at C(6). The acetoxy triflate **18** was prepared by treating the diol **15** with Tf_2O in pyridine and then with Ac_2O (66%). Substitution of **18** with AcOCs in DMF at 60° gave indeed 84% of the desired *gluco*-configured diacetate **19**.

The configurations of the epoxides **6** and **13** were deduced from the coupling between H–C(4) and the bridgehead H–C(5) ($J(4,5) = 4.4$ and 4.5 Hz, resp.) and from the *W*-coupling between H–C(4) and H_{endo}–C(9) ($J(4,6_{endo}) = 1.3$ and < 2.2 Hz, resp.; *Table 2* in *Exper. Part*). This interpretation is in keeping with the crystal structure of **6**[6]). The structure of the cyclopropane **9** agrees with the multiplicity and chemical shifts of the signals for C(1) (*s* at 32.01 ppm), C(2) (*s* at 68.18 ppm), and C(7) (*d* at 37.54 ppm). The constitution of the azido alcohol **14** was assigned on the basis of a decoupling experiment; irradiation of the H–C(6) signal affected the signals for H–C(1) ($J(1,6) = 2.1$), H–C(5) ($J(5,6) = 0.8$), and OH ($J(6,OH) = 6.2$ Hz). The configuration of **14** was deduced from the small coupling between H–C(5) and H–C(6) ($J(5,6) = 0.8$ Hz) and by comparing the coupling of H–C(6) with the bridgehead H–C(1) ($J(1,6) = 2.1$ Hz) to the coupling of H–C(1) with H_{endo}–C(7) and

$H_{exo}-C(7)$ ($J(1,7_{endo}) = 2.5$, $J(1,7_{exo}) = 4.4$ Hz). This deduction was corroborated by NOE experiments confirming that H–C(6), $H_{endo}-C(7)$, and H–C(8) are on the same, and H–C(5) and $H_{endo}-C(7)$ on opposite sides of the cyclohexane ring of **14**.

The configuration of the diol **15** was deduced by comparing the coupling of H–C(6) with the bridgehead H–C(1) ($J(1,6) = 1.9$ Hz) to the coupling of H–C(1) with $H_{endo}-C(7)$ and $H_{exo}-C(7)$ ($J(1,6_{endo}) = 2.2$; $J(1,6_{exo}) = 3.7$ Hz). This deduction was corroborated by NOE experiments confirming that H–C(6), $H_{endo}-C(7)$, and H–C(8) are on the same side of the cyclohexane ring of **15**. The constitution of the triflate **16** was assigned on the basis of decoupling experiments confirming the coupling between OH and H–C(5) ($J(5,OH) = 3.7$ Hz), H–C(5) and H–C(6) ($J(5,6) =$ 7.9 Hz), and H–C(6) and H–C(1) ($J(1,6) = 1.7$ Hz). The configuration of the *gluco*-configured diacetate **19** was deduced by comparing the coupling of H–C(6) with the bridgehead H–C(1) ($J(1,6) = 4.4$ Hz) to the coupling of H–C(1) with $H_{endo}-C(7)$ and $H_{exo}-C(7)$ ($J(1,7_{endo}) = 2.2$, $J(1,7_{exo}) = 3.0$ Hz); as expected, the coupling between H–C(5) and H–C(6) is small ($J(5,6) = 1.6$ Hz). Also this deduction was corroborated by NOE experiments, confirming that H–C(5) and H–C(8) are on the same, and H–C(6) and H–C(8) on opposite sides of the cyclohexane ring of **19**.

On the basis of these results, we treated the enantiomerically pure diol **21** with Tf_2O and then with Ac_2O in pyridine to yield the acetoxy triflate **22** (81%) and the bis-triflate **23** (11%; *Scheme 2*). The crystalline diol **21** was obtained in 77% yield by dihydroxylation of the alkene **20** [12]. Substitution of **22** with AcOCs yielded 94% of the D-*gluco*-configured diacetate **24**. Reduction of **24** ($LiAlH_4$) and acetylation of the crude product gave the *O*-acetylated *N*-benzyl amine **25** (88%). It was deprotected by cleaving the methoxymethyl acetal with Me_3SiBr, followed by deacetylation, to yield 87% of the *N*-benzyl-D-*gluco*-isoquinuclidine **3**. Catalytic hydrogenolysis of **3** under acidic conditions led to the *N*-unsubstituted D-*gluco*-isoquinuclidine **4** (95%). This synthesis provided the enantiomerically pure *N*-unsubstituted D-*gluco*-isoquinuclidine **4** in eight steps and 55% yield from the diol **21**.

The X-ray crystal-structure analysis of the enantiomerically pure diacetoxy 8-phenylmenthyl ester **24**[7]) (*Fig.*) established the D-*gluco*-configuration of **24** and thereby also of **3** and **4**. Selected chemical shifts and coupling constants of the isoquinuclidines **3**, **4**, and **22**–**25** are given in *Table 3* (*Exper. Part*).

To study the interaction of glucosidases with the isoquinuclidine OH group mimicking C(2)OH of the substrate, we also synthesised the 2-deoxy-D-*gluco*-isoquinuclidines **30** and **31**[8]). Treatment of the acetoxy triflate **22** with Bu_4NI gave the iodide **27** (95%) that was deiodinated with Bu_3SnH in toluene at 43° to provide the lactam **28** in 90% yield. Selected chemical shifts and coupling constants of **27** and **28** are given in *Table 3* (*Exper. Part*). Reduction of **28** with $LiAlH_4$, followed by acetylation of the crude product, gave the *O*-acetylated *N*-benzyl amine **29** (91%) that was deprotected by treatment with ethanolic HCl to yield 89% of the *N*-benzyl-2-deoxy-

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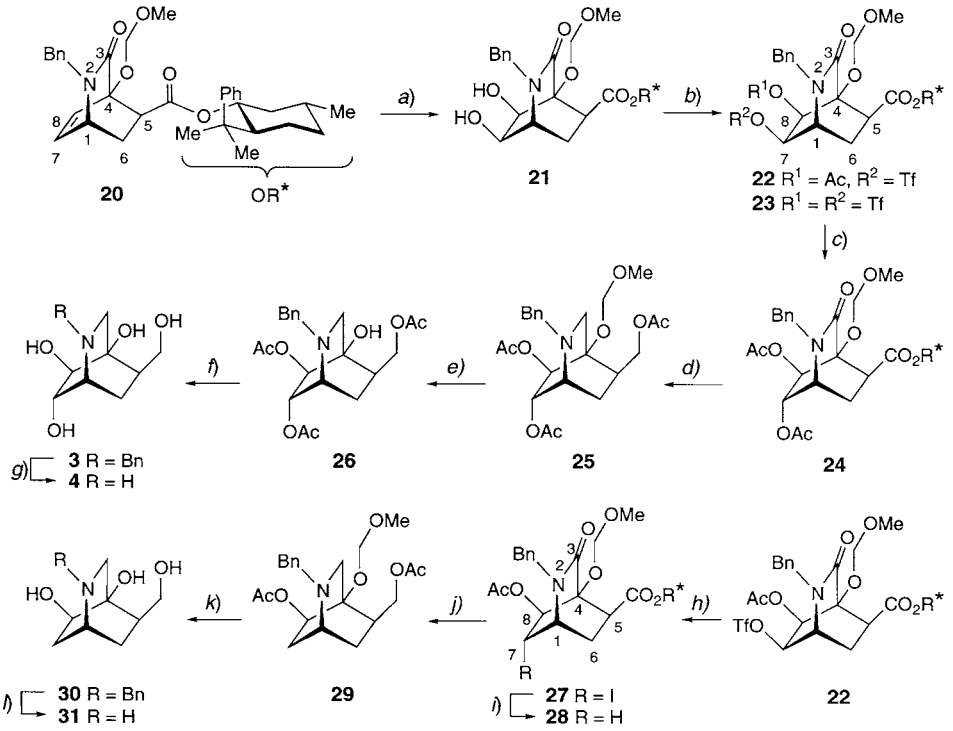
[7]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-217685. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

[8]) The isoquinuclidines **30** and **31** were prepared by *Corinne Baumgartner* as part of her undergraduate training.

Scheme 2



a) NMO · H_2O, OsO_4, THF/acetone/H_2O; 77%. *b*) 1. Tf_2O, pyridine; 2. Ac_2O, pyridine; **22** (81%) and **23** (11%). *c*) CsOAc, DMF, Δ; 94%. *d*) 1. $LiAlH_4$, THF, Δ; 2. 4-(Dimethylamino)pyridine (DMAP), Ac_2O, pyridine; 88%. *e*) Me_3SiBr, molecular sieves (4 Å), CH_2Cl_2, Δ; 88%. *f*) NH_3/MeOH; 99%. *g*) H_2, $Pd(OH)_2$–C, MeOH/H_2O/HCl; 95%. *h*) Bu_4NI, DMF, Δ; 95%. *i*) 2,2′-Azobis(isobutyronitrile) (AIBN), Bu_3SnH, toluene, Δ; 90%. *j*) 1. $LiAlH_4$, THF, Δ; 2. DMAP, Ac_2O, pyridine; 91%. *k*) EtOH/H_2O/HCl; 89%. *l*) H_2, $Pd(OH)_2$/C, MeOH/H_2O/HCl; 92%.

D-*gluco*-isoquinuclidine **30**. Catalytic hydrogenolysis of **30** under acidic conditions led to the *N*-unsubstituted 2-deoxy-D-*gluco*-isoquinuclidine **31** (92%). This synthesis provided **31** in eight steps and 52% yield from the diol **21**.

Inhibition studies. – The D-*gluco*-isoquinuclidines **3** and **4** are both weak inhibitors of the β-glucosidases from *C. saccharolyticum* and from sweet almonds, and of the cellulase Cel7A from *Trichoderma reesei*[9]); the *N*-unsubstituted D-*gluco*-isoquinuclidine **4** is a weak inhibitor of the β-D-glucan glucohydrolase from barley, whereas the *N*-benzyl D-*gluco*-isoquinuclidine **3** did not inhibit this enzyme[10]) (*Table 1*). The D-*gluco*-

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[9]) We thank Prof. Dr. *Jerry Ståhlberg*, Swedish University of Agricultural Sciences, Uppsala, for a generous sample of *T. reesei* Cel7A.

[10]) Compound **3** did not inhibit barley β-D-glucan glucohydrolase up to a concentration of 4 mM, when it started to precipitate. We thank Dr. *M. Hrmova*, University of Adelaide, for testing **3** and **4** as barley β-D-glucan glucohydrolase inhibitors.

isoquinuclidines **3** and **4** do neither inhibit the *endo*-1,3-glucanase from soybean[11]) nor the endoglucanase NtEg1 from *Nasutitermes takasagoensis*[12]). Surprisingly, the *N*-benzyl-D-*gluco*-isoquinuclidine **3** is a stronger inhibitor of snail β-mannosidase than of the glucosidases from *C. saccharolyticum* and sweet almonds. The 2-deoxy-D-*gluco*-isoquinuclidines **30** and **31** are weak inhibitors of the glucosidase from *C. saccharolyticum*; the β-glucosidases from sweet almonds are neither inhibited by **30** nor by **31** (*Table 1*).

Table 1. K_M *and* IC_{50} *Values* [mM] *for the Inhibition of* C. saccharolyticum *and Sweet Almond* β*-Glucosidases, Barley* β*-*D*-Glucan Glucohydrolase,* T. reesei *Cellulase Cel7A, and Snail* β*-Mannosidase by the Isoquinuclidines* **3**, **4**, **30**, *and* **31** *at the Given Temperature and pH Value*

Enzyme	Temp.	pH	K_M	IC_{50} Values			
				3	**4**	**30**	**31**
C. saccharolyticum β-glucosidase	55°	6.80	0.80	2.1[a])	1.9[b])	9.4	4.8
Sweet almond β-glucosidases	37°	6.80	3.4	3.3	2.7	n.i.[e])	n.i.[e])
Barley β-D-glucan glucohydrolase	37°	5.25	1.7	n.i.[c])	2.2[d])	–	–
T. reesei Cel7A	30°	5.72	0.39	6.0	12.6	–	–
Snail β-mannosidase	25°	4.50	0.58	0.15	2.0	–	–

[a]) $K_i = 1.5$ mM ($\alpha = 5.7$). [b]) $K_i = 1.3$ mM ($\alpha = 9.0$). [c]) n.i. = no inhibition up to a concentration of [**3**] = 4 mM. [d]) $K_i \cdot 2$. [e]) n.i. = no inhibition up to a concentration of [**30**] = [**31**] = 4 mM.

To compare the inhibition of the *C. saccharolyticum* and sweet almond β-glucosidases at pH 6.8 by the D-*gluco*-isoquinuclidines **3** ($pK_{HA} = 6.6$) and **4** ($pK_{HA} = 7.8$) with the inhibition of snail β-mannosidase at pH 4.5 by the D-*manno*-isoquinuclidines **1** ($pK_{HA} = 7.5$) and **2** ($pK_{HA} = 8.4$) [12], we considered the difference between the pK_{HA} value of the isoquinuclidines **3** and **4**, and the pH value of the enzyme assays, as we did for **1** and **2** [12]. On the basis of the pH dependence of the inhibition of snail β-mannosidase by the D-*manno*-isoquinuclidines **1** and **2**, we concluded that the amines rather than the ammonium salts act as inhibitors. An extrapolation of the pH-dependent inhibition constants (at pH 4.5: $K_i = 1.0$ μM, $\alpha = 1.9$ for **1** and $K_i = 1.2$ mM, $\alpha = 1.1$ for **2**) suggested that D-*manno*-isoquinuclidines corresponding to **1** and **2**, but with a (hypothetical) pK_{HA} value equivalent to the pH optimum of the β-mannosidase (pH *ca.* 4.5) would show an inhibition constant of *ca.* 2 nM and *ca.* 2 μM, respectively. The assumption of a similar dependence on the pH of the inhibition constants for the β-glucosidase from *C. saccharolyticum* by the D-*gluco*-isoquinuclidines **3** and **4** suggests that D-*gluco*-isoquinuclidines with a (hypothetical) pK_{HA} value equivalent to the pH optimum of the β-glucosidase (pH *ca.* 6.8) would show inhibition constants of *ca.* 2 mM and *ca.* 0.3 mM, respectively, *i.e.*, larger or similar to the *Michaelis–Menten* constant ($K_M = 0.60$ mM). The same assumption suggests IC_{50} values of *ca.* 5 mM and *ca.* 0.5 mM for the inhibition of the β-glucosidases from sweet almonds by D-*gluco*-isoquinuclidines

11) We thank Prof. Dr. *J. Ebel*, Ludwig-Maximilian-Universität, München, for testing **3** and **4** as inhibitors of the β-D-glucanase from soybean.

12) We thank Prof. *E. Meyer*, Texas A&M University, for a generous sample of the endoglucanase NtEg1 from the termite *N. takasagoensis.*

corresponding to **3** and **4**, but with a (hypothetical) pK_{HA} value equivalent to the pH optimum of the β-glucosidase (pH *ca.* 6.8).

These considerations confirm that isoquinuclidines are much stronger inhibitors of snail β-mannosidase than of the β-glucosidases from *C. saccharolyticum* and from sweet almonds. They evidence that shape, and not charge, is at the origin of this difference[13]). The enzymatic hydrolysis of β-D-mannopyranosides may proceed *via* a conformer that is mimicked (more or less well, as indicated by the mixed-type inhibition) by the D-*manno*-isoquinuclidines **1** and **2**, while the enzymatic hydrolysis of the β-D-glucopyranosides proceeds *via* a significantly different conformer. The weakening effect of the *N*-Bn substituent on the inhibition by the *gluco*-isoquinuclidines **3** and **4** is significant, since the β-glucosidases from sweet almonds show a strong affinity for hydrophobic aglyca [9][19][20]. The destabilising interaction with the *N*-Bn group contrasts with its effect on the inhibition of the β-mannosidase. This may reflect a location of the *N*-Bn group of **3**, as imposed by the inappropriate structure of the D-*gluco*-isoquinuclidine, that significantly deviates from the location of the aglycon part of the substrate on the way to the transition state. One also has to consider the possibility that the change of the ground-state conformation precedes lengthening of the scissile bond and rehybridisation of the anomeric centre during hydrolysis of β-D-mannopyranosides, but not of β-D-glucopyranosides; an incipient conformational change that is strongly correlated with bond breaking would also lead to structures not mimicked by an isoquinuclidine. This, too, would constitute a significant difference to the mechanism of action of snail β-mannosidase.

We thank Dr. *B. Schweizer* for the determination of the X-ray crystal structures, *D. Manser* and *M. Schneider* for the pK_{HA} determinations, Dr. *B. Bernet* for checking the *Exper. Part*, and the *Swiss National Science Foundation* and *Oxford Glycosciences Ltd.*, Abingdon, UK, for generous support.

Experimental Part

General. Solvents were distilled before use. If not specified otherwise, all reactions were carried out under a N_2 atmosphere. Normal workup implies pouring the reaction mixture into the indicated sat. aq. soln., extracting into the mentioned org. solvent, if necessary washing with the indicated sat. aq. soln., drying of the org. layer (Na_2SO_4 or $MgSO_4$), filtration, and evaporation of the volatiles. TLC: *Merck* silica-gel *60F-254* plates; detection with I_2, by heating with *Mostain* (400 ml of 10% H_2SO_4 soln., 20 g of $(NH_4)_6Mo_7O_{24}\cdot 6\,H_2O$, 0.4 g of $Ce(SO_4)_2$) or with $KMnO_4$ soln. (3 g of $KMnO_4$, 20 g of K_2CO_3, 0.25 ml of AcOH in 300 ml of H_2O). Flash chromatography (FC): silica gel *Fluka 60* (0.04–0.063 mm) if not indicated otherwise. IR Spectra: 0.5% KBr suspension, 3% $CHCl_3$ or CH_2Cl_2 soln. ^{1}H- (300 MHz, if not indicated otherwise) and ^{13}C-NMR (75 MHz, if not indicated otherwise): δ in ppm and J in Hz.

Methyl rac-*(1*R,*2*R,*4*R,*5*R,*8*R*)-1-(Methoxymethoxy)-7-oxo-3-oxa-6-azatricyclo[3.2.2.0^{2,4}]octane-8-carboxylate* ((±)-**6**). A soln. of (±)-**5** (1.60 g, 6.63 mmol), *m*CPBA (2.86 g, 16.6 mmol), and 4,4′-thiobis[6-(*tert*-butyl)-3-methylphenol] (42 mg, 0.117 mmol) in $ClCH_2CH_2Cl$ (50 ml) was heated to reflux for 4.5 h. Normal workup (CH_2Cl_2/Na_2SO_3 soln., $MgSO_4$) and FC (cyclohexane/AcOEt/MeOH 1:1:0.1) gave (±)-**6** (1.46 g, 85%). White solid. R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.29. M.p. 122° (CH_2Cl_2/Et_2O). IR ($CHCl_3$): 3424*w*, 3223*m*, 3007*m*, 2901*w*, 1706*s*, 1437*m*, 1364*m*, 1271*m*, 1175*m*, 1152*m*, 1096*w*, 1060*m*, 984*m*, 908*w*. ^{1}H-NMR ($CDCl_3$): see *Table 2*; additionally, 5.86 (br. *d*, $J\approx 0.9$, HN); 5.16, 4.94 (2*d*, $J = 7.5$, OCH_2O); 3.72 (*s*, CO_2Me); 3.39 (*s*, *Me*OCH_2); 2.94 (*dd*, $J = 10.3$, 5.8, H–C(8)); 2.33 (*ddd*, $J = 13.2$, 10.3, 4.1, H_{exo}–C(9)); 1.87 (*ddt*, $J = 13.2$, 5.8, 1.3, H_{endo}–C(9)). ^{13}C-NMR ($CDCl_3$): 173.18, 171.06 (2*s*, 2 C=O); 95.05 (*t*, OCH_2O); 81.76 (*s*, C(1)); 56.95 (*q*, *Me*OCH_2); 52.58

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[13]) We consider the possibility of an unfavourable interaction of CH_2(3) of the D-*gluco*-isoquinuclidines **3** and **4** (corresponding to an axial *C*(4)-substituent in a β-D-glucoside) with the β-glucosidase from *C. saccharolyticum* as improbable, since this enzyme cleaves both β-D-glucosides and β-D-galactosides [18].

Table 2. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Racemic Isoquinuclidines (±)-***6** to *(±)-***9**, *(±)-***13** to *(±)-***16**, *(±)-***18**, *and (±)-***19**. For an easier comparison, all isoquinuclidines are numbered in the same way as (±)-**14** to (±)-**19**.

	(±)-**6**	(±)-**7**	(±)-**8**	(±)-**9**	(±)-**13**	(±)-**14**	(±)-**15**	(±)-**16**	(±)-**18**	(±)-**19**
H–C(1)	3.90	3.90	3.90	3.54	3.66	2.80	3.46	3.63	3.71	3.62
H–C(5)	4.06	4.09	3.78	2.88	3.69	3.82	3.97	4.08	5.34	5.05
H–C(6)	3.60	3.61	3.50	4.27	3.40	3.28	3.95	4.98	4.98	4.52
J(1,5)	0.6	0.9	[a])	–	0.8	–	–	–	–	–
J(1,6)	4.4	4.3	4.1	3.0	3.4	2.1	1.9	1.7	1.6	4.4
J(1,7$_{endo}$)	1.3	[b])	2.1	1.2	[c])	2.5	2.2	2.2	2.2	2.2
J(1,7$_{exo}$)	4.1	4.3	3.1	3.7	[c])	4.4	3.7	4.0	4.1	3.0
J(5,6)	4.4	4.3	4.1	–	4.5	0.8	8.4	7.9	7.8	1.6
J(5,OH)	–	–	–	–	–	–	2.5	3.7	–	–
J(6,7$_{endo}$)	1.3	–	–	–	[c])	–	–	–	–	–
J(6,7$_{exo}$)	–	–	–	–	–	–	–	–	–	1.6
J(6,OH)	–	–	–	–	–	6.2	8.4	–	–	–

[a]) Broad signal; J(1,5) <1.5 Hz is deduced from the width of the signal at the half of the height. [b]) Broad signal; J(1,7$_{endo}$) <2.5 Hz is deduced from the width of the signal at the half of the height. [c]) Broad signals; $J(1,7_{endo}) \approx J(1,7_{exo}) \approx 2.9$ Hz, J(6,7$_{endo}$) <2.2 Hz are deduced from the width of the signal at the half of the height.

(*q*, CO_2Me); 50.06 (*d*, C(5)); 48.91 (*d*, C(8)); 45.58, 44.15 (2*d*, C(2), C(4)); 31.34 (*t*, C(9)). CI-MS: 258 (57, $[M+H]^+$), 226 (95), 214 (14), 197 (29), 153 (19), 45 (100). Anal. calc. for $C_{11}H_{15}NO_6$ (257.24): C 51.36, H 5.88, N 5.44; found C 51.37, H 5.83, N 5.48.

*X-Ray Crystal-Structure Analysis of (±)-***6**. The crystals were obtained by recrystallisation from CH_2Cl_2/Et_2O. Triclinic, *P*1, $a = 6.9317(12)$ Å, $b = 9.5462(13)$ Å, $c = 9.625(2)$ Å, $\alpha = 105.880(12)^\circ$, $\beta = 91.401(13)^\circ$, $\gamma = 104.468(12)^\circ$, $V = 590.2(2)$ Å^3, $Z = 1$, $D_{calc.} = 1.447$ Mg/m^3. From a crystal of size $0.40 \times 0.40 \times 0.20$ mm, 1988 reflexions were measured on an *Enraf Nonius* CAD-4 diffractometer (graphite monochromator, CuK_α radiation, $\lambda = 1.54184$ Å) at 293(2) K, by Dr. *B. Schweizer* (ETH-Zürich). $R = 0.0610$, $R_w = 0.2324$. The structure was solved by direct methods with SHELXS-96 [21]. The non-H-atoms were refined anisotropically with SHELXL-97 [22]. The H-atoms were calculated and included in the structure factor calculation. Drawings of the molecule were made with ORTEP [23].

Benzyl rac-*(1*R,*2*R,*4*R,*5*R,*8*R*)- and* rac-*(1*R,*2*R,*4*R,*5*R,*8*S*)-1-(Methoxymethoxy)-7-oxo-3-oxa-6-azatricyclo[3.2.2.0^{2,4}]octane-8-carboxylate* ((±)-**7** and (±)-**8**, resp.), *and Benzyl* rac-*(1*R,*2*S,*5*R,*6*S,*7*S*)-6-Hydroxy-2-(methoxymethoxy)-3-oxo-4-azatricyclo[3.2.1.0^{2,7}]octane-1-carboxylate* ((±)-**9**). A soln. of (±)-**6** (30 mg, 0.12 mmol) and dry CsF (90 mg, 0.58 mmol) in DMF (1 ml) was treated with BnOH (0.06 ml, 0.58 mmol) at 23° and stirred at 100° for 72 h. Normal workup (Et_2O/ice-water; $MgSO_4$) and FC (cyclohexane/AcOEt/MeOH 1:1:0.1) gave (±)-**7**/(±)-**8** 7:3 (13 mg, 33%) and (±)-**9** (4 mg, 10%).

*Data for (±)-***7**/*(±)-***8** *7:3:* R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.33. ^{1}H-NMR ($CDCl_3$): see *Table 2*; additionally, 7.38–7.28 (*m*, 5 H); 6.38 (br. *d*, $J = 5.6$, 0.7 H), 6.00 (br. *s*, 0.3 H) (HN); 5.29, 4.98 (2*d*, $J = 7.5$, 0.6 H), 5.19, 4.93 (2*d*, $J = 7.5$, 1.4 H) (OCH_2O); 5.21, 5.14 (2*d*, $J = 12.1$, 1.4 H), 5.21, 5.10 (2*d*, $J = 12.5$, 0.6 H) (PhCH_2); 3.48 (*s*, 0.9 H), 3.28 (*s*, 2.1 H) (MeO); 3.09 (*dd*, $J = 9.8$, 4.8, 0.3 H), 3.01 (*dd*, $J = 10.4$, 5.9, 0.7 H) (H–C(8)); 2.36 (*ddd*, $J = 13.2$, 10.4, 4.3, 0.7 H), 2.18 (*ddd*, $J = 13.4$, 4.8, 3.1, 0.3 H) (H$_{exo}$–C(9)); 2.09 (*ddd*, $J = 13.4$, 9.8, 2.1, 0.3 H), 1.88 (br. *dd*, $J = 13.2$, 5.9, $w_{1/2} = 2.5$, 0.7 H) (H$_{endo}$–C(9)).

*Data for (±)-***9**: R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.11. IR ($CHCl_3$): 3426*s*, 2957*s*, 2927*s*, 2871*s*, 2858*s*, 1731*s*, 1685*s*, 1458*s*, 1379*m*, 1359*m*, 1270*m*, 1177*m*, 1167*m*, 1109*w*, 1089*w*, 998*w*, 978*w*. ^{1}H-NMR ($CDCl_3$): see *Table 2*; additionally, 7.36–7.30 (*m*, 5 arom. H, HN); 5.20, 5.12 (2*d*, $J = 12.5$, PhCH_2); 4.99, 4.77 (2*d*, $J = 6.9$, OCH_2O); 4.41–4.07 (*m*, exchange with D_2O, HO); 4.27 (addn. of $D_2O \rightarrow d$, $J = 3.0$, H–C(6)); 3.33 (*s*, MeO); 2.12 (*dd*, $J = 12.8$, 3.7, H$_{exo}$–C(8)); 2.00 (*dd*, $J = 12.8$, 1.2, H$_{endo}$–C(8)). ^{13}C-NMR ($CDCl_3$): 169.66, 167.43 (2*s*, 2 C=O); 135.78 (*s*); 128.92 (2*d*); 128.71 (2*d*); 128.58 (*d*); 97.66 (*t*, OCH_2O); 70.04 (*d*, C(6)); 67.55 (*t*, PhCH_2); 68.18 (*s*, C(2)); 57.10 (*q*, MeO); 51.21 (*d*, C(5)); 37.54 (*d*, C(7)); 33.24 (*t*, C(8)); 32.01 (*s*, C(1)). CI-MS: 334 (65, $[M+H]^+$), 302 (48), 184 (10), 91 (100), 45 (30).

rac-*(1*R,*4*S,*8*R*)-2-Benzyl-8-(hydroxymethyl)-4-(methoxymethoxy)-2-azabicyclo[2.2.2]oct-5-ene-3-one* ((±)-**11**). A boiling soln. of $LiBH_4$ (207 mg, 9.42 mmol) in THF (4.8 ml) was treated dropwise with a soln. of (±)-**10** (640 mg, 1.57 mmol) in THF (4.8 ml), heated to reflux for 90 min, cooled to 23°, treated dropwise with MeOH (5 ml), and stirred at 23° for 1 h. Normal workup (AcOEt/H_2O; Na_2SO_4) and FC (AcOEt/hexane/MeOH 1:1:0.1) gave (±)-**11** (374 mg, 78%). Colourless oil. R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.27. IR (CH_2Cl_2): 3453*m*, 3068*w*, 2932*m*, 1679*s*, 1452*m*, 1421*m*, 1226*w*, 1162*m*, 1057*m*, 993*m*, 919*w*. ^{1}H-NMR ($CDCl_3$): 7.34–7.15 (*m*, 5 H); 6.75 (*dd*, *J* = 8.1, 1.9, irrad. at 3.95 → *d*, *J* = 8.1, H–C(5)); 6.29 (*dd*, *J* = 8.1, 5.9, irrad. at 3.95 → *d*, *J* = 8.1, H–C(6)); 5.16, 5.05 (2*d*, *J* = 7.5, OCH_2O); 4.59, 4.40 (2*d*, *J* = 14.8, PhCH_2); 3.95 (*ddt*, *J* = 5.3, 3.5, 1.9, H–C(1)); 3.70–3.56 (*m*, CH_2–C(8)); 3.49 (*s*, MeO); 2.92 (br. *s*, exchange with D_2O, HO); 2.18 (*ddt*, *J* = 10.0, 7.2, 5.0, H–C(8)); 1.70 (*ddd*, *J* = 12.5, 10.3, 2.2, irrad. at 3.95 → br. *dd*, *J* = 12.5, 10.6, H_{endo}–C(7)); 1.27 (*ddd*, *J* = 12.8, 5.0, 3.4, irrad. at 3.95 → *dd*, *J* = 12.1, 4.7, H_{exo}–C(7)). ^{13}C-NMR ($CDCl_3$): 171.64 (*s*, C(3)); 136.84 (*s*); 135.75, 131.92 (2*d*, C(5), C(6)); 129.14 (2*d*); 128.69 (2*d*); 128.15 (*d*); 96.0 (*t*, OCH_2O), 86.98 (*s*, C(4)); 64.95 (*t*, CH_2–C(8)); 56.13 (*q*, MeO), 52.41 (*d*, C(1)); 48.64 (*d*, C(8)); 42.38 (*t*, PhCH_2); 31.27 (*t*, C(7)). CI-MS: 304 (3, $[M+H]^+$), 272 (10), 138 (100), 91 (42), 45 (51). Anal. calc. for $C_{17}H_{21}NO_4$ (303.96): C 67.31, H 6.98, N 4.62; found: C 67.26, H 7.21, N 4.63.

rac-*(1*R,*4*S,*8*R*)-2-Benzyl-8-[[(*tert*-*butyl)dimethylsilyloxy]methyl]-4-(methoxymethoxy)-2-azabicyclo[2.2.2]-oct-5-en-3-one* ((±)-**12**). A cooled (0°) soln. of (±)-**11** (285 mg, 0.94 mmol) in THF (5 ml) was treated with a 1.5M soln. of MeLi in Et_2O (0.72 ml, 1.15 mmol), stirred for 15 min, treated with a soln. of ^{t}BuMe$_2$SiCl (174 mg, 1.15 mmol) in THF (3 ml), and stirred at 0° for 1 h. Normal workup (AcOEt/NH_4Cl soln.; Na_2SO_4) and FC (hexane/AcOEt 3:7) gave (±)-**12** (341 mg, 87%). Colourless oil. R_f (AcOEt/hexane 7:3) 0.60. ^{1}H-NMR ($CDCl_3$): 7.32–7.16 (*m*, 5 H); 6.70 (*dd*, *J* = 8.1, 1.9, irrad. at 3.94 → *d*, *J* = 8.1, H–C(5)); 6.28 (*dd*, *J* = 8.1, 5.6, irrad. at 3.94 → *d*, *J* = 8.4, H–C(6)); 5.13, 5.01 (2*d*, *J* = 7.2, OCH_2O); 4.57, 4.37 (2*d*, *J* = 14.9, PhCH_2); 4.02 (*dd*, *J* = 9.7, 4.9, irrad. at 2.12 → *d*, *J* = 10.0, CH_a–C(8)); 3.94 (*ddt*, *J* = 5.0, 3.0, 1.9, H–C(1)); 3.47 (*s*, MeO); 3.30 (*t*, *J* = 9.7, irrad. at 2.12 → *dd*, *J* = 9.3, 2.0, CH_b–C(8)); 2.12 (*tt*, *J* ≈ 9.5, 4.3, H–C(8)); 1.70 (*ddd*, *J* = 13.1, 4.7, 3.1, irrad. at 3.94 → *dd*, *J* = 12.8, 4.7, irrad. at 2.12 → change, H_{exo}–C(7)); 1.62 (*ddd*, *J* = 12.5, 10.3, 1.9, irrad. at 3.94 → *dd*, *J* = 12.8, 9.6, irrad. at 2.12 → change, H_{endo}–C(7)); 0.84 (*s*, *t*-Bu); 0.02, 0.00 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 171.04 (*s*, C(3)); 136.71 (*s*); 135.43, 131.87 (2*d*, C(5), C(6)); 128.65 (2*d*); 128.20 (2*d*); 127.57 (*d*); 95.17 (*t*, OCH_2O); 84.05 (*s*, C(4)); 63.73 (*t*, CH_2–C(8)); 55.56 (*q*, MeO); 52.44 (*t*, PhCH_2); 48.25 (*d*, C(1)); 42.46 (*d*, C(8)); 31.39 (*t*, C(7)); 25.91 (*q*, *Me*$_3$CSi); 18.26 (*s*, Me$_3$*C*Si); −5.34, −5.41 (2*q*, Me_2Si). CI-MS: 418 (7, $[M+H]^+$), 386 (27), 360 (41), 258 (33), 145 (35), 115 (100), 91 (90), 45 (57). Anal. calc. for $C_{23}H_{35}NO_4Si$ (417.62): C 66.15, H 8.45, N 3.35; found: C 65.14, H 8.45, N 3.42.

rac-*(1*R,*2*R,*4*R,*5*R,*8*R*)-6-Benzyl-8-[[(*tert*-*butyl)dimethylsilyloxy]methyl]-1-(methoxymethoxy)-3-oxa-6-azatricyclo[3.2.2.0^{2,4}]octan-7-one* ((±)-**13**). A cooled (0°) soln. of (±)-**12** (44 mg, 0.10 mmol) in CH_2Cl_2 (2 ml) was treated with a freshly prepared *ca.* 0.1M soln. of dimethyldioxirane in acetone [24] (2.1 ml, *ca.* 0.21 mmol) and stirred at 0° for 3 h, when TLC showed an incomplete reaction. The mixture was treated with a *ca.* 0.1M soln. of dimethyldioxirane in acetone (1.0 ml, *ca.* 0.10 mmol) and stirred at 0° for 20 min. Normal workup (CH_2Cl_2, $Na_2S_2O_3$ soln.; Na_2SO_4) and FC (cyclohexane/EtOAc 4:1) gave (±)-**13** (32 mg, 71%). R_f (cyclohexane/AcOEt 4:1) 0.22. IR (CH_2Cl_2): 2955*s*, 2930*s*, 2857*m*, 1687*s*, 1495*m*, 1463*m*, 1350*w*, 1160*s*, 1106*s*, 1059*s*, 996*s*, 920*w*, 839*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 7.38–7.26 (*m*, 5 H); 5.25, 5.02 (2*d*, *J* = 7.0, OCH_2O); 4.83, 4.23 (2*d*, *J* = 15.0, PhCH_2); 3.92 (*dd*, *J* = 9.6, 3.6, CH_a–C(8)); 3.48 (*s*, MeO); 3.33 (*t*, *J* ≈ 9.6, CH_b–C(8)); 2.29 (*tdd*, *J* ≈ 8.5, 5.0, 3.7, H–C(8)); 1.81 (*dd*, *J* ≈ 13.8, 10.4, $w_{1/2}$ = 2.9, H_{endo}–C(9)); 1.75 (br. *dd*, *J* ≈ 13.7, 5.8, $w_{1/2}$ = 2.9, H_{exo}–C(9)); 0.86 (*s*, *t*-Bu); 0.04, 0.02 (2*s*, Me_2Si). CI-MS: 434 (41, $[M+H]^+$), 402 (52), 376 (59), 316 (100), 202 (26), 91 (84), 45 (44).

rac-*(1*R,*4*R,*5*S,*6*R,*8*R*)-5-Azido-2-benzyl-8-[[(*tert*-*butyl)dimethylsilyloxy]methyl]-6-hydroxy-4-(methoxy-methoxy)-2-azabicyclo[2.2.2]octan-3-one* ((±)-**14**). A soln. of (±)-**13** (32 mg, 0.073 mmol) and NaN_3 (12 mg, 0.18 mmol) in DMF (3 ml) was stirred at 120° for 20 h. Normal workup (AcOEt/H_2O; Na_2SO_4) and FC (cyclohexane/AcOEt 7:3) gave (±)-**13** (14 mg, 44%) and (±)-**14** (7 mg, 20%).

Data of (±)-**14**: R_f (cyclohexane/AcOEt 13:7) 0.46. IR (CH_2Cl_2): 3595*w*, 2955*s*, 2950*s*, 2856*m*, 2114*s*, 1683*s*, 1462*m*, 1156*m*, 1096*m*, 1044*m*, 994*m*, 840*s*. ^{1}H-NMR (200 MHz, C_6D_6): see *Table 2*; additionally, 7.22–7.10 (*m*, 5 H); 5.70 (*d*, *J* = 8.0, irrad. at 3.82 → NOE of 3.1%), 5.00 (*d*, *J* = 8.0) (OCH_2O); 4.84, 4.10 (2*d*, *J* = 14.5, PhCH_2); 4.01 (*dd*, *J* = 9.5, 4.2, CH_a–C(8)); 3.82 (irrad. at 3.28 → NOE of 1.9%, H–C(5)); 3.56 (*t*, *J* ≈ 9.5, CH_b–C(8)); 3.37 (*s*, MeO); 3.28 (irrad. at 3.82 → *dd*, *J* ≈ 4.6, 0.8, irrad. at 2.80 → br. *d*, *J* ≈ 4.6, irrad. at 3.82 → NOE of 2.0%, H–C(6)); 2.80 (irrad. at 3.28 → NOE of 5.7%, H–C(1)); 2.59 (*tt*, *J* ≈ 9.4, 4.4, H–C(8)); 1.54 (*dt*, *J* = 14.1, 4.5, irrad. at 2.80 → *dd*, *J* ≈ 14.1, 4.4, H_{exo}–C(7)); 1.26 (*ddd*, *J* = 14.1, 10.4, 2.5, irrad. at 2.80 → br. *dd*, *J* ≈ 14.1, 10.4, irrad. at 3.28 → NOE of 2.6%, H_{endo}–C(7)); 1.12 (*d*, *J* = 6.2, HO–C(6)); 0.95 (*s*, *t*-Bu); 0.06, 0.04 (2*s*, Me_2Si). ^{13}C-NMR (125 MHz, C_6D_6): 168.89 (*s*, C(3)); 137.71 (*s*); 137–125 (several *d*); 94.74

(*t*, OCH_2O); 81.16 (*s*, C(4)); 76.56 (*d*, C(6)); 69.74 (*d*, C(5)); 63.83 (*t*, *C*H_2−C(8)); 56.18 (*d*, C(1)); 56.02 (*q*, MeO); 49.75 (*t*, Ph*C*H_2); 36.64 (*d*, C(8)); 26.76 (*t*, C(7)); 26.17 (*q*, *Me*$_3$CSi); 18.58 (*s*, Me$_3$*C*Si); −5.28, −5.40 (2*q*, Me_2Si). CI-MS: 477 (6, $[M+H]^+$), 449 (25), 417 (38), 391 (61), 359 (86), 202 (34), 91 (100), 75 (28), 45 (19).

rac-*(1*R*,4*R*,5*R*,6*R*,8*R*)-2-Benzyl-8-{[(*tert*-butyl)dimethylsilyloxy]methyl}-5,6-dihydroxy-4-(methoxymethoxy)-2-azabicyclo[2.2.2]octan-3-one* ((±)-**15**). A soln. of (±)-**12** (640 mg, 1.53 mmol) and *N*-methylmorpholine *N*-oxide · H_2O (NMO · H_2O; 310 mg, 2.29 mmol) in acetone/H_2O 3:2 (20 ml) was treated with OsO_4 (*ca.* 20 mg, *ca.* 0.08 mmol) and stirred at 25° for 2 h. Normal workup (AcOEt/Na_2SO_3 soln.; Na_2SO_4) and FC (hexane/AcOEt 1:1) gave (±)-**15** (565 mg, 81%). R_f (hexane/AcOEt 1:1) 0.51. IR (CH_2Cl_2): 3500*s*, 3366*s*, 2933*m*, 2855*m*, 1678*s*, 1461*m*, 1094*s*, 1011*m*, 839*s*. ^{1}H-NMR ($CDCl_3$): see *Table 2*; additionally, 7.35–7.27 (*m*, 5 H); 5.77, 4.78 (2*d*, *J* = 7.8, OCH_2O); 5.35 (*d*, *J* = 2.5, HO−C(5)); 5.12, 4.13 (2*d*, *J* = 14.6, Ph*C*H_2); 3.97 (irrad. at 1.66 → NOE of *ca.* 2%, H−C(5)); 3.95 (irrad. at 3.46 → *t*, *J* ≈ 8.4, irrad. at 1.66 → NOE of *ca.* 2%, H−C(6)); 3.87 (*dd*, *J* = 9.7, 4.0, CH_a−C(8)); 3.73 (br. *d*, *J* ≈ 5.5, HO−C(6)); 3.52 (*s*, MeO); 3.46 (irrad. at 1.66 → NOE of 4.9%, H−C(1)); 3.27 (*t*, *J* = 9.5, CH_b−C(8)); 2.06 (*tdd*, *J* = 9.7, 5.6, 4.0, irrad. at 1.66 → NOE of 7.6%, H−C(8)); 1.66 (*ddd*, *J* = 14.0, 10.0, 2.2, irrad. at 3.46 → *dd*, *J* = 14.0, 10.0, H_{endo}−C(7)); 1.39 (*ddd*, *J* = 14.0, 5.9, 3.7, irrad. at 3.46 → *dd*, *J* = 14.0, 5.6, irrad. at 1.66 → NOE of 24.6%, H_{exo}−C(7)); 0.84 (*s*, *t*-Bu); −0.02, −0.03 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 168.79 (*s*, C(3)); 137.53 (*s*); 128.91 (2*d*); 128.86 (2*d*); 127.84 (*d*); 93.58 (*t*, OCH_2O); 81.27 (*s*, C(4)); 71.43, 68.84 (2*d*, C(5), C(6)); 63.89 (*t*, *C*H_2−C(8)); 57.10 (*d*, C(1)); 55.88 (*q*, MeO), 49.70 (*t*, Ph*C*H_2); 39.58 (*d*, C(8)); 28.09 (*t*, C(7)); 25.92 (*q*, *Me*$_3$CSi); 18.29 (*s*, Me$_3$*C*Si); −5.51, (*q*, Me_2Si). CI-MS: 452 (6, $[M+H]^+$), 420 (39), 362 (66), 334 (40), 91 (100), 75 (77), 49 (57). Anal. calc. for $C_{23}H_{37}NO_6Si$ (451.63): C 61.17, H 8.26, N 3.10; found: C 61.17, H 8.06, N 3.14.

rac-*(1*R*,4*R*,5*R*,6*R*,8*R*)-2-Benzyl-8-{[(*tert*-butyl)dimethylsilyloxy]methyl}-5-hydroxy-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-6-yl Trifluoromethanesulfonate* ((±)-**16**) *and Its Transformation to* (±)-**14**. A cooled (−10°) soln. of (±)-**15** (1.01 g, 2.24 mmol) in pyridine (13 ml) was treated with Tf_2O (0.48 ml, 2.92 mmol) and stirred for 30 min. Normal workup (AcOEt/$NaHCO_3$ soln.; Na_2SO_4) and FC (cyclohexane/AcOEt 7:3) gave (±)-**16** (1.05 g, 81%). Pale white foam. R_f (hexane/AcOEt 7:3) 0.35. ^{1}H-NMR ($CDCl_3$): see *Table 2*; additionally, 7.33–7.29 (*m*, 5 H); 5.78, 4.75 (2*d*, *J* = 8.0, OCH_2O); 5.21 (*d*, *J* = 3.7, HO−C(5)); 4.95, 4.25 (2*d*, *J* = 14.7, Ph*C*H_2); 4.90 (irrad. at 3.63 → *d*, *J* = 7.9, H−C(6)); 4.08 (irrad. at 5.21 → *d*, *J* = 7.9, H−C(5)); 3.82 (*dd*, *J* = 9.8, 3.9, CH_a−C(8)); 3.55 (*s*, MeO); 3.40 (*dd*, *J* = 9.7, 8.4, CH_b−C(8)); 2.06–1.98 (*m*, H−C(8)); 1.72 (*ddd*, *J* = 14.3, 9.6, 2.2, irrad. at 3.63 → *dd*, *J* ≈ 14.3, 9.6, H_{endo}−C(7)); 1.64 (*ddd*, *J* = 14.3, 6.5, 4.0, irrad. at 3.63 → *dd*, *J* ≈ 14.3, 6.5, H_{exo}−C(7)); 0.85 (*s*, *t*-Bu); 0.03, 0.01 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 168.05 (*s*, C(3)); 136.25 (*s*); 129.0 (2*d*); 128.96 (2*d*); 128.15 (*d*); 118.20 (*q*, *J*(C,F) ≈ 320, CF_3); 93.87 (*t*, OCH_2O); 82.88 (*d*, C(6)); 80.82 (*s*, C(4)); 72.19 (*d*, C(5)); 63.13 (*t*, *C*H_2−C(8)); 56.15 (*q*, MeO); 54.33 (*d*, C(1)); 49.17 (*t*, Ph*C*H_2); 39.42 (*d*, C(8)); 27.66 (*t*, C(7)); 26.08 (*q*, *Me*$_3$CSi); 18.51 (*s*, Me$_3$*C*Si); −5.26, −5.38 (2*q*, Me_2Si).

A soln. of (±)-**16** (21 mg, 0.035 mmol) and NaN_3 (35 mg, 0.53 mmol) in DMF (1 ml) was stirred at 85° for 4 h. Normal workup (AcOEt/H_2O; Na_2SO_4) and FC (cyclohexane/AcOEt 8:2) gave (±)-**14** (13 mg, 78%).

rac-*(1*R*,4*R*,5*R*,6*R*,8*R*)-2-Benzyl-8-{[(*tert*-butyl)dimethylsilyloxy]methyl}-4-(methoxymethoxy)-3-oxo-6-[(trifluoromethyl)sulfonyloxy]-2-azabicyclo[2.2.2]oct-5-yl Acetate* ((±)-**18**). A cooled (0°) soln. of (±)-**15** (210 mg, 0.47 mmol) in pyridine (3 ml) was treated with Tf_2O (0.17 ml, 0.61 mmol), stirred at 25° for 7 h, treated with Ac_2O (0.3 ml, 1.7 mmol), and stirred at 25° for 12 h. Normal workup (AcOEt/H_2O; Na_2SO_4) and FC (hexane/AcOEt 17:3) gave (±)-**18** (180 mg, 66%). R_f (hexane/AcOEt 7:3) 0.85. IR ($CHCl_3$): 3004*m*, 2968*m*, 1727*s*, 1687*s*, 1473*m*, 1418*s*, 1120*s*, 1009*m*. ^{1}H-NMR ($CDCl_3$): see *Table 2*; additionally, 7.36–7.26 (*m*, 5 H); 5.39, 4.81 (2*d*, *J* = 7.5, OCH_2O); 5.34 (irrad. at 4.98 → *s*, H−C(5)); 5.03, 4.23 (2*d*, *J* = 14.8, Ph*C*H_2); 4.98 (irrad. at 3.71 → *d*, *J* = 8.1, H−C(6)); 3.83 (*dd*, *J* = 10.0, 3.7, CH_a−C(8)); 3.71 (irrad. at 4.98 → br. *s*, H−C(1)); 3.42 (*dd*, *J* = 10.0, 8.1, CH_b−C(8)); 3.36 (*s*, MeO); 2.26–2.14 (*m*, H−C(8)); 2.11 (*s*, Ac); 1.76 (*ddd*, *J* = 12.3, 10.0, 2.2, irrad. at 3.71 → *dd*, *J* = 12.1, 10.0, H_{endo}−C(7)); 1.65 (*ddd*, *J* = 10.3, 6.2, 4.1, irrad. at 3.71 → *dd*, *J* = 10.3, 6.2, H_{exo}−C(7)); 0.85 (*s*, *t*-Bu); 0.03, 0.00 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 170.13, 167.88 (2*s*, 2 C=O); 136.16 (*s*); 129.07 (2*d*); 128.94 (2*d*); 128.33 (*d*); 118.45 (*q*, *J*(C,F) = 321, CF_3); 93.90 (*t*, OCH_2O); 80.76 (*s*, C(4)); 77.74, 71.37 (2*d*, C(5), C(6)); 62.92 (*t*, *C*H_2−C(8)); 55.98 (*q*, MeO); 54.86 (*d*, C(1)); 49.21 (*t*, Ph*C*H_2); 38.88 (*d*, C(8)); 27.49 (*t*, C(7)); 25.89 (*q*, *Me*$_3$CSi); 20.32 (*s*, Me$_3$*C*Si); 18.32 (*q*, *Me*C=O); −5.51, −5.61 (2*q*, Me_2Si). ^{19}F-NMR (282 MHz, $CDCl_3$): −74.77 (*s*). HR-MALDI-MS: 648.1883 (100, $[M+Na]^+$, $[C_{26}H_{38}F_3NNaO_9SSi]^+$; calc. 648.1886), 594.1796 (94, $[M-MeO]^+$, $[C_{25}H_{35}F_3NO_8SSi]^+$; calc. 594.1805).

rac-*(1*R*,4*R*,5*R*,6*S*,8*R*)-2-Benzyl-8-{[(*tert*-butyl)dimethylsilyloxy]methyl}-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]octane-5,6-diyl Diacetate* ((±)-**19**). A soln. of (±)-**18** (20 mg, 0.032 mmol) in DMF (0.5 ml) was treated with AcOCs (9 mg, 0.048 mmol) and stirred at 60° for 6 h. Normal workup (AcOEt/H_2O; Na_2SO_4) and FC (hexane/AcOEt 1:4) gave (±)-**19** (15 mg, 84%). Colourless solid. R_f (hexane/AcOEt 17:3) 0.33. M.p.

82–83°. ^{1}H-NMR ($CDCl_3$): see *Table 2*; additionally, 7.34–7.25 (*m*, 5 H); 5.19 (*d*, *J* = 7.4), 4.83 (*d*, *J* = 7.4, irrad. at 5.05 → NOE of 0.6%) (OCH_2O); 5.05 (irrad. at 4.52 → *s*, H–C(5)); 4.62, 4.56 (2*d*, *J* = 14.6, PhCH_2); 4.52 (irrad. at 3.62 → br. *s*, irrad. at 5.05 → NOE of 4.5%, H–C(6)); 3.86 (*dd*, *J* = 10.0, 4.0, irrad. at 2.34 → *d*, *J* = 10.0, CH_a–C(8)); 3.62 (irrad. at 4.52 → br. *s*, irrad. at 4.52 → NOE of 6.8%, H–C(1)); 3.41 (*t*, *J* = 10.0, irrad. at 2.34 → *d*, *J* = 9.8, CH_b–C(8)); 3.38 (*s*, MeO); 2.39–2.29 (*m*, irrad. at 5.05 → NOE of 7.3%, H–C(8)); 2.05 (*s*, irrad. at 4.52 → NOE of 1.3%, 2 Ac); 2.00 (*ddd*, *J* ≈ 14.0, 10.0, 2.2, irrad. at 2.34 → br. *d*, *J* ≈ 12.5, irrad. at 3.62 → *dd*, *J* = 14.0, 10.3, H_{endo}–C(7)); 1.60–1.49 (*m*, irrad. at 2.34 → br. *d*, *J* ≈ 14.0, irrad. at 3.62 → br. *dd*, *J* ≈ 14.0, 5.6, irrad. at 4.52 → *ddd*, *J* ≈ 14.0, 6.0, 3.0, H_{exo}–C(7)); 0.86 (*s*, *t*-Bu); 0.03, 0.01 (2*s*, Me_2Si). HR-MALDI-MS: 558.2490 (94, $[M + Na]^+$, $[C_{27}H_{41}NNaO_8Si]^+$; calc. 558.2499), 504.2408 (100, $[M - MeO]^+$, $[C_{26}H_{38}NO_7Si]^+$; calc. 504.2418), 416.1887 (27).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*R*,5*S*,7*R*,8*R*)-2-Benzyl-7,8-dihydroxy-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]octane-5-carboxylate* (**21** [12]). A yellow soln. of **20** (3.00 g, 5.64 mmol) and $NMO \cdot H_2O$ (1.18 g, 8.46 mmol) in THF/acetone/H_2O 3:1:2 (60 ml) was treated with a 2.5% soln. of OsO_4 in *t*-BuOH (0.71 ml, 0.056 mmol) and stirred at 24° for 6 h. Normal workup (AcOEt/Na_2SO_3 soln.; brine; Na_2SO_4) and recrystallisation of the crude product from i-PrOH/hexane gave **21** (2.44 g, 77%). Colourless crystals. M.p. 162° (Et_2O/hexane; [12]: 162°).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*R*,5*S*,7*R*,8*R*)-8-Acetoxy-2-benzyl-4-(methoxymethoxy)-3-oxo-7-[(trifluoromethyl)sulfonyloxy]-2-azabicyclo[2.2.2]octane-5-carboxylate* (**22**) *and (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*R*,5*S*,7*R*,8*R*)-2-Benzyl-4-(methoxymethoxy)-3-oxo-7,8-bis[(trifluoromethyl)sulfonyloxy]-2-azabicyclo[2.2.2]octane-5-carboxylate* (**23**). A soln. of **21** [12] (3.00 g, 5.30 mmol) in CH_2Cl_2/pyridine 1:1 (60 ml) was treated dropwise with Tf_2O (0.96 ml, 5.82 mmol) at 24°, stirred for 12 h, treated with Ac_2O (1.0 ml, 10.6 mmol), and stirred at 25° for 4 h. Normal workup (AcOEt/$NaHCO_3$ soln.; Na_2SO_4) and FC (cyclohexane/AcOEt 6:1) gave **23** (0.45 g, 11%) and **22** (3.16 g, 81%) as colourless foams.

Data of **22**: R_f (cyclohexane/AcOEt 3:2) 0.64. M.p. 86–90° (Et_2O/hexane). $[\alpha]_D^{25} = -59.3$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 2966*m*, 2928*m*, 2852*w*, 1766*m*, 1728*s*, 1701*s*, 1600*w*, 1496*w*, 1454*w*, 1422*m*, 1371*m*, 1322*m*, 1143*s*, 1079*m*, 999*m*, 961*m*, 897*m*, 842*w*. ^{1}H-NMR ($CDCl_3$): see *Table 3*; additionally, 7.43–7.16 (*m*, 9 H); 7.15–7.08 (*m*, 1 H); 5.20, 4.13 (2*d*, *J* ≈ 14.8, PhCH_2); 5.07, 4.64 (2*d*, *J* = 7.4, OCH_2O); 4.81 (*td*, *J* = 10.8, 4.4, H–C(1′)); 4.80 (irrad. at 3.62 → *d*, *J* = 7.5, H–C(7)); 3.30 (*s*, MeO); 2.08 (*td*, *J* ≈ 12.5, 3.7, irrad. at 4.81 → *m*, H–C(2′)); 2.08 (*s*, Ac); 1.96 (br. *d*, *J* ≈ 10.9, irrad. at 4.81 → *d*, *J* = 10.6, H_{eq}–C(6′)); 1.91 (*dd*, *J* = 10.3, 5.9, H–C(5)); 1.86 (*dq*, *J* ≈ 13.4, 3.7, H_{eq}–C(3′)); 1.72 (*ddd*, *J* = 14.0, 5.9, 3.7, irrad. at 3.62 → *dd*, *J* = 14.3, 5.9, H_{exo}–C(6)); 1.72–1.63 (*m*, H_{eq}–C(4′)); 1.46 (*ddd*, *J* = 14.0, 10.3, 2.2, irrad. at 3.62 → *dd*, *J* = 14.0, 10.0, H_{endo}–C(6)); 1.52–1.38 (*m*, H–C(5′)); 1.24, 1.16 (2*s*, *Me*$_2$PhC); 1.17 (*qd*, *J* ≈ 12.6, 3.4, H_{ax}–C(3′)); 0.91 (*qd*, *J* ≈ 11.6, 3.6, H_{ax}–C(4′)); 0.90 (*q*, *J* ≈ 12.2, irrad. at 4.81 → *m*, H_{ax}–C(6′)); 0.88 (*d*, *J* = 6.5, Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 170.31, 169.54, 165.77 (3*s*, 3 C=O); 152.16, 135.15 (2*s*); 128.90 (2*d*); 128.63 (2*d*); 127.94 (*d*); 127.60 (2*d*); 125.08 (2*d*); 124.74 (*d*); 116.97 (*q*, *J*(C,F) = 316, CF_3); 93.38 (*t*, OCH_2O); 79.90 (*d*, C(8)); 77.87 (*s*, C(4)); 75.68 (*d*, C(1′)); 70.39 (*d*, C(7)); 56.05 (*q*, MeO); 53.40 (*d*, C(1)); 50.27 (*d*, C(2′)); 49.09 (*t*, PhCH_2); 41.55 (*t*, C(6′)); 41.39 (*d*, C(5)); 39.44 (*s*, Me_2PhC); 34.55 (*t*, C(4′)); 31.26 (*d*, C(5′)); 29.78, 22.75 (2*q*, *Me*$_2$PhC); 27.60 (*t*, C(6)); 26.22 (*t*, C(3′)); 21.83 (*q*, *Me*–C(5′)); 20.29 (*q*, *Me*C=O). ^{19}F-NMR (282 MHz, $CDCl_3$): −74.80 (*s*). HR-MALDI-MS: 762.2536 (52, $[M + Na]^+$, $[C_{36}H_{44}F_3NNaO_{10}S]^+$; calc. 762.2536), 548.0892 (100, $[M - (8\text{-phenylmenthyl}) + H + Na]^+$, $[C_{20}H_{22}F_3NNaO_{10}S]^+$; calc. 548.0814), 494.0814 (80, $[M - (8\text{-phenylmenthyl}) - MeO + H]^+$, $[C_{19}H_{19}F_3NO_9S]^+$; calc. 494.0733). Anal. calc. for $C_{36}H_{44}F_3NO_{10}S$ (739.80): C 58.45, H 5.99, N 1.89, S 4.33; found: C 58.50, H 6.10, N 1.90, S 4.33.

Data of **23**: R_f (cyclohexane/AcOEt 3:2) 0.76. M.p. 86–90°. $[\alpha]_D^{25} = 10.0$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 2960*w*, 2928*w*, 1731*s*, 1709*m*, 1600*w*, 1496*w*, 1455*m*, 1428*s*, 1369*w*, 1324*m*, 1139*s*, 1092*m*, 1000*m*, 948*m*, 923*m*, 888*m*, 859*m*. ^{1}H-NMR ($CDCl_3$): see *Table 3*; additionally, 7.42–7.28 (*m*, 5 H); 7.24–7.16 (*m*, 4 H); 7.12 (*ddt*, *J* ≈ 8.1, 5.9, 2.6, 1 H); 5.42, 4.98 (2*d*, *J* = 14.8, PhCH_2); 5.41, 4.86 (2*d*, *J* ≈ 7.6, OCH_2O); 4.80 (*td*, *J* = 10.6, 4.4, H–C(1′)); 3.37 (*s*, MeO); 2.32 (*dd*, *J* = 10.6, 5.3, H–C(5)); 2.18 (br. *d*, *J* ≈ 11.5, H_{eq}–C(6′)); 2.06 (*td*, *J* = 10.6, 3.5, H–C(2′)); 1.67–1.50 (*m*, H_{eq}–C(3′), H_{eq}–C(4′)); 1.58 (*ddd*, *J* = 14.3, 10.7, 1.9, H_{endo}–C(6)); 1.50–1.31 (*m*, H–C(5′)); 1.33 (*dt*, *J* ≈ 14.3, 5.0, H_{exo}–C(6)); 1.19, 1.12 (2*s*, *Me*$_2$PhC); 1.05 (*qd*, *J* ≈ 12.5, 2.5, H_{ax}–C(3′)); 0.95 (*q*, *J* ≈ 11.2, H_{ax}–C(6′)); 0.87 (*d*, *J* = 6.5, Me–C(5′)); 0.85 (*qd*, *J* ≈ 11.6, 3.6, H_{ax}–C(4′)). ^{13}C-NMR ($CDCl_3$): 169.91, 164.44 (2*s*, 2 C=O); 150.81, 135.15 (2*s*); 128.49 (2*d*); 128.45 (2*d*); 127.81 (*d*); 127.48 (2*d*); 124.94 (2*d*); 124.74 (*d*); 118.10, 117.94 (2*q*, *J*(C,F) ≈ 312, 2 CF_3); 93.51 (*t*, OCH_2O); 80.48, 77.79, 76.91 (3*d*, C(7), C(8), C(1′)); 76.31 (*s*, C(4)); 55.59 (*q*, MeO); 52.52 (*d*, C(1)); 49.32 (*d*, C(2′)); 48.70 (*t*, PhCH_2); 42.12 (*d*, C(5)); 40.63 (*t*, C(6′)); 39.59 (*s*, Me_2PhC); 34.15 (*t*, C(4′)); 31.02 (*d*, C(5′)); 27.67 (*t*, C(6)); 26.75 (*t*, C(3′)); 26.64, 26.56 (2*q*, *Me*$_2$PhC); 21.50 (*q*, *Me*–C(5′)). ^{19}F-NMR (282 MHz, $CDCl_3$): −73.97, −73.49 (2*s*). HR-MALDI-MS:

Table 3. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Enantiomerically Pure Isoquinuclidines* **3**, **4**, *and* **22**–**28**.

	3	**4**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
H–C(1)	4.02	3.78	3.62	3.74	3.63	2.82	2.78	3.51	3.41
H_{endo}–C(7)	–	–	4.80	4.87	4.47	–	–	3.45	1.99
H_{exo}–C(7)	2.71	2.69	–	–	–	5.02	5.09	–	1.41
C(8)	3.48	3.39	5.20	4.99	4.83	4.96	4.80	5.13	5.00
$J(1,6_{endo})$	1.9	2.8	2.2	1.9	2.5	2.5	2.6	2.5	2.2
$J(1,6_{exo})$	[a])	3.1	3.7	4.4	4.0	2.8	3.1	4.0	[b])
$J(1,7_{endo})$	–	–	1.7	1.9	–	–	–	–	1.8
$J(1,7_{exo})$	[a])	3.6	–	–	4.4	4.0	3.9	2.1	3.8
$J(3,8)$	[a])	1.3	–	–	–	–	1.6	–	–
$J(6_{exo},7_{exo})$	[a])	1.2	–	–	1.9	2.5	1.9	2.2	2.2
$J(7_{endo},7_{exo})$	–	–	–	–	–	–	–	–	15.6
$J(7_{endo},8)$	–	–	7.8	7.8	–	–	–	–	8.1
$J(7_{exo},8)$	[a])	1.5	–	–	0.6	1.9	2.2	2.2	1.2

[a]) Broad signals; $J(1,6_{exo}) < 3.5$, $J(1,7_{exo}) \approx 3.5$, $J(3,8) \approx J(6_{exo},7_{exo}) \approx J(7,8) < 2.5$ Hz deduced from the width of the signals at the half of their height. [b]) 3.41 (br. *s*, H–C(1)); 1.83–1.76 (*m*, H_{exo}–C(6)).

852.1914 (88, $[M+Na]^+$, $[C_{35}H_{41}F_6NNaO_{11}S_2]^+$; calc. 852.1923), 638.0170 (100, [*M* – (8-phenylmenthyl) + H + Na]$^+$, $[C_{19}H_{19}F_6NNaO_{11}S_2]^+$; calc. 638.0201), 584.0105 (94, [*M* – (8-phenylmenthyl) – MeO + H]$^+$, $[C_{18}H_{16}F_6NO_{10}S_2]^+$; calc. 584.0120).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*R*,5*S*,7*S*,8*R*)-7,8-Diacetoxy-2-benzyl-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]octane-5-carboxylate* (**24**). A soln. of **22** (2.50 g, 3.38 mmol) and AcOCs (973 mg, 5.07 mmol) in DMF (50 ml) was stirred at 80° for 2.5 h. Normal workup (AcOEt/H_2O; Na_2SO_4) and FC (cyclohexane/AcOEt 3:1) gave **24** (2.05 g, > 98%) as a colourless solid. Recrystallisation from CH_2Cl_2/hexane (1:3) gave **24** (1.92 g, 94%). Colourless needles. R_f (cyclohexane/AcOEt 3:2) 0.39. M.p. 174.5° (CH_2Cl_2/hexane). $[\alpha]_D^{25} = 19.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 2957*m*, 2927*m*, 1741*s* (br.), 1697*s*, 1600*w*, 1496*m*, 1454*m*, 1373*s*, 1330*m*, 1299*m*, 1159*s*, 1129*m*, 1090*m*, 1056*s*, 1038*s*, 978*m*, 959*m*, 916*m*, 850*w*. ^{1}H-NMR ($CDCl_3$): see *Table 3*; additionally, 7.40–7.18 (*m*, 9 H); 7.14–7.04 (*m*, 1 H); 4.99, 4.65 (2*d*, $J = 7.5$, OCH_2O); 4.83 (irrad. at 3.63 → *d*, $J = 0.6$, H–C(8)); 4.78 (*td*, $J = 10.6$, 4.3, H–C(1′)); 4.67, 4.55 (2*d*, $J = 14.6$, PhCH_2); 4.47 (irrad. at 3.63 → br. *s*, H–C(7)); 3.29 (*s*, MeO); 2.10, 2.09 (2*s*, 2 Ac); 2.06 (*dd*, $J \approx 10.0$, 6.5, H–C(5)); 2.14–2.04 (*m*, irrad. at 4.78 → change, H_{eq}–C(6′)); 2.00 (br. *d*, $J \approx 13.7$, irrad. at 4.81 → br. *s*, H–C(2′)); 1.84–1.73 (*m*, H_{eq}–C(3′)); 1.78 (*ddd*, $J = 13.7$, 10.0, 2.5, H_{endo}–C(6)); 1.70–1.59 (*m*, H_{eq}–C(4′)); 1.66 (*m*, irrad. at 3.63 → *ddd*, $J \approx 13.4$, 6.7, 1.9, H_{exo}–C(6)); 1.53–1.35 (*m*, H–C(5′)); 1.24, 1.16 (2*s*, *Me*$_2$PhC); 1.12 (*qd*, $J \approx 12.8$, 3.1, H_{ax}–C(3′)); 0.98–0.80 (*m*, H_{ax}–C(4′)); 0.89 (*q*, $J \approx 11.7$, irrad. at 4.78 → *m*, H_{ax}–C(6′)); 0.87 (*d*, $J = 6.5$, Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 170.96, 169.35, 168.84, 166.62 (4*s*, 4 C=O); 152.25, 135.97 (2*s*); 128.63 (2*d*); 128.52 (2*d*); 127.78 (*d*); 127.56 (2*d*); 125.10 (2*d*); 124.55 (*d*); 93.10 (*t*, OCH_2O); 78.17, 75.41, 74.99 (3*d*, C(7), C(8), C(1′)); 77.00 (*s*, C(4)); 55.92 (*q*, MeO); 51.06 (*d*, C(1)); 50.30 (*d*, C(2′)); 48.42 (*t*, PhCH_2); 42.45 (*d*, C(5)); 41.51 (*t*, C(6′)); 39.48 (*s*, Me$_2$Ph*C*); 34.61 (*t*, C(4′)); 31.26 (*d*, C(5′)); 29.44, 23.13 (2*q*, *Me*$_2$PhC); 26.67 (*t*, C(6)); 26.29 (*t*, C(3′)); 21.83 (*q*, *Me*–C(5′)); 20.90, 20.84 (2*q*, 2 *Me*C=O). ESI-MS: 1321 (8, $[2M+Na]^+$), 672 (100, $[M+Na]^+$), 650 (6, $[M+H]^+$). Anal. calc. for $C_{37}H_{47}NO_9$ (649.77): C 68.39, H 7.29, N 2.16; found: C 68.24, H 7.30, N 2.30.

X-Ray Crystal-Structure Analysis of **24**. The crystals were obtained by azeotropic recrystallisation in CH_2Cl_2/hexane. Orthorhombic, $P2_1P2_1P2_1$, $a = 9.575(2)$ Å, $b = 13.034(2)$ Å, $c = 28.313(3)$ Å, $V = 3533.5(10)$ Å^3, $Z = 4$, $D_{calc.} = 1.221$ Mg/m^3. From a crystal of size 0.40 × 0.30 × 0.30 mm, 3644 reflexions were measured on an *Enraf Nonius CAD-4* diffractometer (graphite monochromator, CuK_α radiation, $\lambda = 1.54184$ Å) at 293(2) K, by Dr. *B. Schweizer* (ETH-Zürich). $R = 0.0355$, $R_w = 0.1094$. The structure was solved by direct methods with SIR97 [25]. The non-H-atoms were refined anisotropically with SHELXL-97 [22]. The H-atoms were calculated and included in the structure factor calculation. Drawings of the molecule were done with ORTEP [23].

*(1*R*,4*R*,5*R*,7*S*,8*R*)-7,8-Diacetoxy-2-benzyl-4-(methoxymethoxy)-2-azabicyclo[2.2.2]octane-5-methyl Acetate* (**25**) *and (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acetate.* A mixture of **24** (250 mg,

0.385 mmol) and $LiAlH_4$ (160 mg, 3.85 mmol) in THF (12.5 ml) was heated to reflux for 5 h, cooled to 0°, treated dropwise with MeOH (3 ml), and evaporated. The residue was suspended in pyridine/Ac_2O 2:1 (4.5 ml), treated with DMAP (5 mg, 0.04 mmol), and stirred at 24° for 12 h. The mixture was filtered through *Celite*, and the residue was washed with AcOEt (3 × 5 ml). Normal workup (CH_2Cl_2/$NaHCO_3$ soln.; brine; Na_2SO_4) and FC (cyclohexane/AcOEt 5:1 → 3:1) gave (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl acetate (97 mg, 92%) as a colourless oil and **25** (152 mg, 88%) as a colourless solid.

Data of **25**: R_f (cyclohexane/AcOEt 3:2) 0.41. $[\alpha]_D^{25} = 21.5$ ($c = 1.2$, $CHCl_3$). IR ($CHCl_3$): 2958*w*, 2826*w*, 1736*s*, 1494*w*, 1453*w*, 1370*m*, 1151*w*, 1121*w*, 1080*w*, 1030*m*, 921*w*. ^{1}H-NMR ($CDCl_3$): see *Table 3*; additionally, 7.34–7.21 (*m*, 5 H); 4.70, 4.60 (2*d*, $J = 7.2$, OCH_2O); 4.38 (*dd*, $J = 10.9$, 4.5, CH_a–C(5)); 4.17 (*dd*, $J = 10.9$, 9.0, CH_b–C(5)); 3.80, 3.75 (2*d*, $J = 13.6$, PhCH_2); 3.30 (*s*, MeO); 2.94 (*dd*, $J = 10.0$, 1.6, H_a–C(3)); 2.65 (*dd*, $J = 10.0$, 1.2, H_b–C(3)); 2.36–2.20 (*m*, H–C(5)); 2.13, 2.08, 2.05 (3*s*, 3 Ac); 1.94 (*ddd*, $J = 13.7$, 10.3, 2.5, H_{endo}–C(6)); 1.67 (*dddd*, $J = 14.0$, 5.6, 2.8, 2.5, H_{exo}–C(6)). ^{13}C-NMR ($CDCl_3$): 170.79, 169.65, 169.38 (3*s*, 3 C=O); 138.11 (*s*); 128.11 (2*d*); 128.05 (2*d*); 126.91 (*d*); 91.24 (*t*, OCH_2O); 76.27, 75.16 (2*d*, C(7), C(8)); 75.54 (*s*, C(4)); 64.97 (*t*, CH_2–C(5)); 59.13 (*t*, PhCH_2); 55.87 (*q*, MeO); 51.35 (*d*, C(1)); 48.58 (*d*, C(3)); 34.91 (*d*, C(5)); 24.34 (*t*, C(6)); 21.04, 21.01, 20.97 (3*q*, 3 *Me*C=O). HR-MALDI-MS: 450.2118 (83, $[M+H]^+$, $[C_{23}H_{32}NO_8]^+$; calc. 450.2128), 448.1970 (26, $[M-H]^+$, $[C_{23}H_{30}NO_8]^+$; calc. 448.1971), 390.1914 (100, $[M-OAc]^+$, $[C_{21}H_{28}NO_6]^+$; calc. 390.1917). Anal. calc. for $C_{23}H_{31}NO_8$ (449.50): C 61.46, H 6.95, N 3.12; found: C 61.47, H 7.03, N 2.95.

*Data of (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acetate:* see [26].

*(1*R*,4*R*,5*R*,7*S*,8*R*)-7,8-Diacetoxy-2-benzyl-4-hydroxy-2-azabicyclo[2.2.2]octane-5-methyl Acetate* (**26**). A cooled (0°) mixture of **25** (1.20 g, 2.67 mmol) and molecular sieves (4 Å; 0.60 g) in CH_2Cl_2 (60 ml) was treated dropwise with Me_3SiBr (0.71 ml, 5.38 mmol) and heated to reflux for 2 h. Normal workup (AcOEt/$NaHCO_3$ soln.; brine; Na_2SO_4) and FC (cyclohexane/AcOEt 2:1 → 1:1) gave **26** (955 mg, 88%). Colourless oil. R_f (cyclohexane/AcOEt 1:2) 0.60. $[\alpha]_D^{25} = 19.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3577*w*, 2961*w*, 2837*w*, 1735*s*, 1494*w*, 1453*w*, 1369*m*, 1125*w*, 1079*w*, 1031*m*, 977*w*, 914*w*. ^{1}H-NMR ($CDCl_3$): see *Table 3*; additionally, 7.33–7.21 (*m*, 5 H); 4.41 (*dd*, $J = 11.2$, 6.2, CH_a–C(5)); 4.23 (*dd*, $J = 11.2$, 7.4, CH_b–C(5)); 3.81, 3.74 (2*d*, $J = 13.4$, PhCH_2); 2.74 (*dd*, $J = 10.0$, 1.6, H_a–C(3)); 2.65 (*dd*, $J = 10.0$, 1.6, H_b–C(3)); 2.31 (*s*, HO–C(4)); 2.15, 2.06, 2.04 (3*s*, 3 Ac); 2.15–2.06 (*m*, H–C(5)); 1.95 (*ddd*, $J = 13.4$, 10.6, 2.6, H_{endo}–C(6)); 1.58 (*dddd*, $J = 13.6$, 5.3, 3.1, 1.9, H_{exo}–C(6)). ^{13}C-NMR ($CDCl_3$): 171.37, 170.77, 169.40 (3*s*, 3 C=O); 138.22 (*s*); 128.23 (4*d*); 127.05 (*d*); 79.18, 74.34 (2*d*, C(7), C(8)); 71.75 (*t*, CH_2–C(5)); 65.08 (*s*, C(4)); 59.13 (*t*, PhCH_2); 51.40 (*d*, C(1)); 50.11 (*t*, C(3)); 37.49 (*d*, C(5)); 24.45 (*t*, C(6)); 21.13 (*q*, 3 *Me*CO). HR-MALDI-MS: 406.1856 (73, $[M+H]^+$, $[C_{21}H_{28}NO_7]^+$; calc. 406.1866), 404.1701 (26, $[M-H]^+$, $[C_{21}H_{26}NO_7]^+$; calc. 404.1709), 346.1651 (100, $[M-OAc]^+$, $[C_{19}H_{24}NO_5]^+$; calc. 346.1654). Anal. calc. for $C_{21}H_{27}NO_7$ (405.45): C 62.21, H 6.71, N 3.45; found: C 61.94, H 6.91, N 3.23.

*(1*R*,4*R*,5*R*,7*S*,8*R*)-2-Benzyl-5-(hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* (**3**). A cooled (0°) soln. of **26** (50 mg, 0.123 mmol) in MeOH (20 ml) was saturated with NH_3 and stirred at 24° for 12 h. Ion-exchange chromatography (*Amberlite CG-120*, H^+ form, 0.1M aq. NH_3) gave **3** (34 mg, 99%). Colourless solid. R_f (AcOEt/MeOH 10:1) 0.30. $[\alpha]_D^{25} = 8.0$ ($c = 0.5$, EtOH). IR (0.5% in KBr): 3374*s* (br.), 2899*m* (br.), 1495*w*, 1452*m*, 1380*m*, 1150*m*, 1111*m*, 1038*s*, 975*m*, 926*w*, 803*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 3*; additionally, 7.44–7.33 (*m*, 5 H); 3.89 (*dd*, $J = 10.6$, 5.6, CH_a–C(5)); 3.83, 3.79 (2*d*, $J \approx 13.3$, PhCH_2); 3.70 (*dd*, $J = 10.9$, 7.8, CH_b–C(5)); 2.73 (br. *d*, $J = 10.3$, H_a–C(3)); 2.60 (br. *d*, $J = 10.6$, H_b–C(3)); 2.00 (*ddd*, $J = 13.1$, 11.2, 1.9 H_{endo}–C(6)); 1.87 (br. *tt*, $J = 10.9$, 6.0, H–C(5)); 1.63 (br. *d*, $J \approx 13.0$, $w_{1/2} = 12$, H_{exo}–C(6)). ^{13}C-NMR (75 MHz, D_2O): 139.73 (*s*); 131.87 (2*d*); 131.11 (2*d*); 130.14 (*d*); 82.21, 76.54 (2*d*, C(7), C(8)); 74.91 (*s*, C(4)); 64.41 (*t*, CH_2–C(5)); 60.96 (*t*, PhCH_2); 55.50 (*d*, C(1)); 50.77 (*t*, C(3)); 40.52 (*d*, C(5)); 25.11 (*t*, C(6)). HR-MALDI-MS: 302.1360 (3, $[M+Na]^+$, $[C_{15}H_{21}NNaO_4]^+$; calc. 302.1368), 280.1541 (100, $[M+H]^+$, $[C_{15}H_{22}NO_4]^+$; calc. 280.1549). Anal. calc. for $C_{15}H_{21}NO_4 \cdot \frac{1}{2} H_2O$ (288.34): C 62.48, H 7.69, N 4.86; found: C 62.56, H 7.60, N 4.89. $pK_{HA} = 6.6$.

*(1*R*,4*R*,5*R*,7*S*,8*R*)-5-(Hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* (**4**). A mixture of **3** (31 mg, 0.11 mmol), 20% Pd(OH)–C (6 mg), MeOH (3 ml), and conc. aq. HCl (0.15 ml) was stirred at 24° for 12 h under H_2 (6 bar). The mixture was filtered through *Celite*, and the residue was washed with MeOH (3 × 5 ml). The filtrate was diluted with toluene (5 ml) and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, H^+ form, 0.1M aq. NH_3) gave **4** (21 mg, 95%). Colourless solid. R_f (MeOH/25% aq. NH_3 5:2) 0.49. $[\alpha]_D^{25} = +61.1$ ($c = 0.4$, H_2O). IR (0.5% in KBr): 3391*s* (br.), 2935*m*, 2890*m*, 1636*w*, 1530*m*, 1423*m*, 1384*m*, 1258*w*, 1172*w*, 1112*m*, 1045*m*, 1008*m*, 926*w*, 808*w*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 3*; additionally, 3.90 (*dd*, $J = 10.6$, 7.2, CH_a–C(5); 3.62 (*dd*, $J = 10.9$, 7.2, CH_b–C(5)); 2.89 (*dd*, $J = 10.9$, 1.3, H_a–C(3)); 2.70 (*dd*, $J \approx 10.9$, 1.2, H_b–C(3)); 2.16 (*ddd*, $J = 14.0$, 11.2, 2.8, H_{endo}–C(6)); 1.84 (*dqd*, $J \approx 11.2$, 5.9, 1.3, H–C(5)); 1.38 (*dddd*, $J = 14.0$, 4.7, 3.1, 1.2, H_{exo}–C(6)). ^{13}C-NMR (75 MHz, CD_3OD): 81.59, 72.98 (2*d*, C(7), C(8)); 78.41 (*s*, C(4)); 63.84

(*t*, *C*H$_2$–C(5)); 50.29 (*t*, C(3)); 40.65, 39.95 (2*d*, C(1), C(5)); 26.19 (*t*, C(6)). ESI-MS: 401 (18, $[2M+Na]^+$), 360 (43, $[2M-H_2O]^+$), 250 (18), 212 (30, $[M+Na]^+$), 190 (38, $[M+H]^+$), 181 (43), 149 (100). Anal. calc. for $C_8H_{15}NO_4\cdot\frac{3}{4}H_2O$ (202.72): C 47.40, H 8.20, N 6.91; found: C 47.26, H 8.36, N 6.75. pK_{HA} = 7.80.

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*R*,5*R*,7*S*,8*S*)-8-Acetoxy-2-benzyl-4-(methoxymethoxy)-7-iodo-3-oxo-2-azabicyclo[2.2.2]octane-5-carboxylate* (**27**). A soln. of **22** (348 mg, 0.47 mmol) and Bu_4NI (1.74 g, 4.70 mmol) in DMF (5 ml) was stirred at 80° for 6 h. Normal workup (Et_2O/10% aq. $Na_2S_2O_3$ soln.; Na_2SO_4) and FC (cyclohexane/AcOEt 4:1) gave **27** (322 mg, 95%). Colourless foam. R_f (cyclohexane/AcOEt 2:3) 0.48. M.p. 56–60°. $[\alpha]_D^{25}$ = 35.8 (*c* = 0.7, $CHCl_3$). IR ($CHCl_3$): 3011*m*, 2959*s*, 2928*s*, 1750*s*, 1728*s*, 1697*s*, 1610*w*, 1496*m*, 1453*m*, 1371*s*, 1324*m*, 1133*m*, 1077*m*, 1045*s*, 992*m*, 926*w*, 849*w*. ^{1}H-NMR ($CDCl_3$): see *Table 3*; additionally, 7.37–7.17 (*m*, 10 H); 5.13 (irrad. at 3.51 → *s*, H–C(8)); 5.01, 4.59 (2*d*, *J* = 7.8, OCH_2O); 4.78 (*td*, *J* = 10.6, 4.4, H–C(1′)); 4.72, 4.48 (2*d*, *J* = 14.9, PhC*H*$_2$); 3.45 (irrad. at 3.51 → br. *s*, H–C(7)); 3.28 (*s*, MeO); 2.47 (*ddd*, *J* = 13.4, 10.0, 2.5, H_{endo}–C(6)); 2.10 (*td*, *J* ≈ 11.5, 3.4, irrad. at 4.78 → *m*, H–C(2′)); 2.09 (*dd*, *J* = 10.6, 7.5, H–C(5)); 2.04 (*s*, Ac); 2.04–1.92 (*m*, irrad. at 3.51 → change, irrad. at 4.78 → change, H_{exo}–C(6), H_{eq}–C(6′)); 1.89 (*dq*, *J* ≈ 12.8, 3.3, H_{eq}–C(3′)); 1.70 (br. *d*, *J* ≈ 12.5, H_{eq}–C(4′)); 1.50–1.37 (*m*, H–C(5′)); 1.25, 1.18 (2*s*, *Me*$_2$PhC); 1.17 (*qd*, *J* ≈ 12.8, 3.4, H_{ax}–C(3′)); 0.93 (*qd*, *J* ≈ 12.5, 3.4, H_{ax}–C(4′)); 0.89 (*q*, *J* ≈ 12.0, irrad. at 4.78 → *t*, *J* ≈ 12.8, H_{ax}–C(6′)); 0.88 (*d*, *J* = 6.5, Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 170.89, 169.26, 166.15 (3*s*, 3 C=O); 152.15, 135.95 (2*s*); 128.63 (2*d*); 128.49 (2*d*); 127.93 (*d*); 127.73 (2*d*); 125.17 (2*d*); 124.98 (*d*); 93.18 (*t*, OCH_2O); 81.50 (*d*, C(8)); 77.91 (*s*, C(4)); 75.48 (*d*, C(1′)); 55.93 (*q*, MeO); 55.92 (*d*, C(1)); 50.39 (*d*, C(2′)); 48.08 (*t*, PhC*H*$_2$); 41.50 (*d*, C(5)); 41.50 (*t*, C(6′)); 39.37 (*s*, Me_2PhC); 34.64 (*t*, C(4′)); 31.28 (*d*, C(5′)); 29.95, 22.44, 21.85; 20.62 (4*q*, *Me*$_2$PhC, *Me*–C(5′), *Me*C=O); 29.63 (*t*, C(6)); 26.22 (*t*, C(3′)); 24.10 (*d*, C(7)). HR-MALDI-MS: 740.2059 (69, $[M+Na]^+$, $[C_{35}H_{44}INNaO_7]^+$; calc. 740.2060), 526.0340 (100, [*M* – 8-phenylmenthyl + H + Na]$^+$, $[C_{19}H_{22}INNaO_7]^+$; calc. 526.0339). Anal. calc. for $C_{35}H_{44}INO_7$ (717.64): C 58.58, H 6.18, N 1.95; found: C 58.63, H 6.37, N 1.88.

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*R*,5*S*,8*S*)-8-Acetoxy-2-benzyl-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]octane-5-carboxylate* (**28**). A soln. of **27** (250 mg, 0.35 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN; 0.62 mg, 0.004 mmol) in toluene (1 ml) was treated with Bu_3SnH (0.19 ml, 0.70 mmol), stirred at 43° for 2 h, and evaporated. FC (cyclohexane/AcOEt 3:1) gave **28** (185 mg, 90%). Colourless foam. R_f (cyclohexane/AcOEt 2:3) 0.32. M.p. 59–65°. $[\alpha]_D^{25}$ = 9.2 (*c* = 0.8, $CHCl_3$). IR ($CHCl_3$): 3013*m*, 2959*m*, 2928*m*, 1728*s*, 1690*s*, 1601*w*, 1496*w*, 1456*m*, 1180*m*, 1159*m*, 1092*m*, 1051*m*, 1017*m*, 977*m*, 960*m*, 924*w*, 847*w*. ^{1}H-NMR ($CDCl_3$): see *Table 3*; additionally, 7.36–7.20 (*m*, 9 H); 7.11 (*dddd*, *J* = 9.0, 7.8, 4.3, 3.5, 1 H); 5.08, 4.68 (2*d*, *J* = 7.5, OCH_2O); 4.86, 4.42 (2*d*, *J* = 14.9, PhCH_2); 4.81 (*td*, *J* = 10.8, 4.4, H–C(1′)); 3.32 (*s*, MeO); 2.11–1.98 (*m*, H_{eq}–C(6′)); 2.07 (*td*, *J* ≈ 10.6, 3.5, irrad. at 1.79 → *t*, *J* ≈ 10.6, H–C(2′)); 2.05 (br. *dd*, *J* = 10.0, 6.2, H–C(5)); 2.02 (*s*, Ac); 1.99 (irrad. at 5.00 → br. *d*, *J* ≈ 15.6, irrad. at 3.41 → *dd*, *J* = 15.6, 8.7, H_{endo}–C(7)); 1.83–1.76 (*m*, irrad. at 3.41 → change, H_{exo}–C(6)); 1.79 (*dq*, *J* ≈ 12.8, 3.2, H_{eq}–C(3′)); 1.67 (br. *ddd*, *J* ≈ 12.8, 3.4, 2.8, H_{eq}–C(4′)); 1.52 (*ddd*, *J* = 12.8, 10.3, 2.2, irrad. at 3.41 → *dd*, *J* = 13.1, 10.4, irrad. at 2.05 → *dd*, 10.3, 2.2, H_{endo}–C(6)); 1.48–1.35 (*m*, H–C(5′)); 1.41 (irrad. at 5.00 → *dt*, *J* ≈ 15.6, 4.3, irrad. at 3.41 → *dt*, *J* ≈ 14.6, 2.2, irrad. at 2.05 → br. *dd*, *J* ≈ 15.6, 3.8, H_{exo}–C(7)); 1.25, 1.17 (2*s*, *Me*$_2$PhC); 1.14 (*q*, *J* ≈ 12.7, irrad. at 1.79 → *td*, *J* ≈ 12.1, 2.2, H_{ax}–C(3′)); 0.91 (*q*, *J* ≈ 12.1, H_{ax}–C(6′)); 0.90 (*qd*, *J* ≈ 12.8, 3.4, irrad. at 1.79 → *q*, *J* ≈ 12.6, H_{ax}–C(4′)); 0.88 (*d*, *J* = 7.8, Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 171.30, 169.84, 166.88 (3*s*, 3 C=O)); 152.07, 136.56 (2*s*); 128.42 (2*d*); 128.33 (2*d*); 127.54 (*d*); 127.48 (2*d*); 125.06 (2*d*); 124.64 (*d*); 93.11 (*t*, OCH_2O); 78.61 (*s*, C(4)); 75.24 (*d*, C(1′)); 72.96 (*d*, C(8)); 55.78 (*q*, MeO); 50.25 (*d*, C(2′)); 48.95 (*d*, C(1)); 48.01 (*t*, PhCH_2); 42.53 (*d*, C(5)); 41.53 (*t*, C(6′)); 39.47 (*s*, Me_2PhC); 36.72 (*t*, C(7)); 34.57 (*t*, C(4′)); 32.20 (*t*, C(6)); 31.23 (*d*, C(5′)); 26.30 (*t*, C(3′)); 29.18, 23.36, 21.80; 21.07 (4*q*, *Me*$_2$PhC, Me–C(5′), *Me*C=O). HR-MALDI-MS: 614.3082 (100, $[M+Na]^+$, $[C_{35}H_{45}NNaO_7]^+$; calc. 614.3094), 400.1360 (98, [*M* – 8-phenylmenthyl + H + Na]$^+$, $[C_{19}H_{23}NNaO_7]^+$; calc. 400.1372), 346.1286 (55). Anal. calc. for $C_{35}H_{45}NO_7$ (591.73): C 71.04, H 7.66, N 2.37; found: C 71.11, H 7.74, N 2.25.

*(1*R*,4*R*,5*R*,8*R*)-8-Acetoxy-2-benzyl-4-(methoxymethoxy)-2-azabicyclo[2.2.2]octane-5-methyl Acetate* (**29**) *and (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acetate.* A mixture of **28** (150 mg, 0.25 mmol) and $LiAlH_4$ (85 mg, 2.23 mmol) in THF (10 ml) was heated to reflux for 90 min, cooled to 0°, treated dropwise with MeOH (20 ml), and evaporated. The residue was suspended in pyridine/Ac_2O 2:1 (30 ml), treated with DMAP (2 mg, 0.03 mmol), and stirred at 25° for 12 h. The mixture was filtered through *Celite*, and the residue was washed with AcOEt (3 × 5 ml). Normal workup (CH_2Cl_2/$NaHCO_3$ soln.; brine; Na_2SO_4) and FC (cyclohexane/AcOEt 3:1 → 1:1) gave (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl acetate (70 mg, > 98%) and **29** (90 mg, 91%) as colourless oils.

Data of **29**: R_f (cyclohexane/AcOEt/MeOH 1:1:0.1) 0.30. $[\alpha]_D^{25}$ = 13.2 (*c* = 0.9, $CHCl_3$). IR ($CHCl_3$): 2951*m*, 2925*w*, 1731*s*, 1602*w*, 1494*w*, 1453*m*, 1369*s*, 1149*s*, 1126*m*, 1045*s*, 922*m*, 830*w*. ^{1}H-NMR ($CDCl_3$): 7.34–

7.20 (*m*, 5 H); 5.02 (*ddd*, *J* = 9.3, 3.1, 1.8, H–C(8)); 4.75, 4.61 (2*d*, *J* = 7.5, OCH_2O); 4.42 (*dd*, *J* ≈ 10.7, 4.6, CH_a–C(5)); 4.21 (*dd*, *J* = 10.6, 9.4, CH_b–C(5)); 3.69 (*s*, PhCH_2); 3.32 (*s*, MeO); 2.98 (*dd*, *J* = 9.9, 1.6, H_a–C(3)); 2.73 (*dd*, *J* = 10.0, 1.9, H_b–C(3)); 2.65 (*quint.*, *J* ≈ 2.5, H–C(1)); 2.22 (br. *tt*, *J* ≈ 9.7, 4.3, H–C(5)); 2.13 (*ddd*, *J* ≈ 14.9, 9.7, 2.0, H_{endo}–C(7)); 2.12, 2.08 (2*s*, 2 Ac); 1.89 (*dq*, *J* ≈ 14.3, 3.0, H_{exo}–C(7)); 1.81 (*ddd*, *J* ≈ 13.4, 4.8, 2.8, H_{exo}–C(6)); 1.71 (*ddd*, *J* ≈ 13.4, 10.6, 2.5, H_{endo}–C(6)). ^{13}C-NMR ($CDCl_3$): 171.01, 170.21 (2*s*, 2 C=O); 138.84 (*s*); 128.19 (2*d*); 128.13 (2*d*); 126.81 (*d*); 91.21 (*t*, OCH_2O); 75.14 (*s*, C(4)); 71.67 (*d*, C(8)); 65.57 (*t*, CH_2–C(5)); 59.49 (*t*, C(3)); 55.92 (*q*, MeO); 49.70 (*t*, PhCH_2); 48.46 (*d*, C(1)); 35.11 (*d*, C(5)); 33.48 (*t*, C(7)); 29.80 (*t*, C(6)); 21.39, 21.09 (2*q*, 2 *Me*C=O). HR-MALDI-MS: 414.1883 ($[M+Na]^+$, $[C_{21}H_{30}NNaO_6]^+$; calc. 414.1893), 392.2064 ($[M+H]^+$, $[C_{21}H_{30}NO_6]^+$; calc. 392.2073).

*Data of (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acetate:* see [26].

*(1*R*,4*R*,5*R*,8*R*)-2-Benzyl-5-(hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,8-diol* (**30**). A soln. of **29** (38 mg, 0.10 mmol) and 37% aq. HCl (0.4 ml) in EtOH (4 ml) was stirred at 25° for 24 h and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, 0.1M aq. NH_3) and FC (*Macherey-Nagel Lichoprep*-NH_2, AcOEt/MeOH 10:1) gave **30** (23 mg, 89%). Colourless solid. R_f (*Macherey-Nagel Nanosil*-NH_2; AcOEt/MeOH 6:1) 0.39. $[\alpha]_D^{25} = -14.6$ (*c* = 0.6, MeOH). IR (0.5% in KBr): 3400*m*, 3083*w*, 3028*w*, 2937*m*, 2892*m*, 2866*m*, 1956*w*, 1883*w*, 1810*w*, 1740*w*, 1602*w*, 1494*w*, 1453*w*, 1384*w*, 1351*w*, 1119*m*, 1031*m*, 990*w*, 956*w*, 916*w*, 817*w*. ^{1}H-NMR (CD_3OD): 7.35–7.26 (*m*, 4 H); 7.21 (*tt*, *J* ≈ 6.9, 1.9, 1 H); 3.90 (*dd*, *J* ≈ 10.5, 6.5, CH_a–C(5)); 3.73 (*dd*, *J* ≈ 10.5, 5.9, CH_b–C(5)); 3.71, 3.67 (2*d*, *J* ≈ 13.4, PhCH_2); 3.72–3.67 (*m*, H–C(8)); 2.78 (*dd*, *J* = 10.0, 1.5, H_a–C(3)); 2.61 (*dd*, *J* = 10.3, 2.2, H_b–C(3)); 2.62–2.58 (*m*, H–C(1)); 2.00 (*ddd*, *J* = 14.0, 9.3, 2.8, H_{endo}–C(7)); 1.92 (br. *d*, *J* ≈ 13.7, H_{exo}–C(7)); 1.78 (*dqd*, *J* ≈ 13.7, 6.9, 1.0, H–C(5)); 1.70–1.66 (*m*, 2 H–C(6)). ^{13}C-NMR (CD_3OD): 139.80 (*s*); 129.76 (2*d*); 129.15 (2*d*); 127.95 (*d*); 73.32 (*s*, C(4)); 72.70 (*d*, C(8)); 63.93 (*t*, CH_2–C(5)); 60.52 (*t*, C(3)); 51.33 (*t*, PhCH_2); 50.55 (*d*, C(1)); 40.78 (*d*, C(5)); 34.08 (*t*, C(7)); 30.33 (*t*, C(6)). HR-MALDI-MS: 264.1596 ($[M+H]^+$, $[C_{15}H_{22}NO_3]^+$; calc. 264.1600). Anal. calc. for $C_{15}H_{21}NO_3 \cdot ½\ H_2O$ (272.16): C 68.15, H 8.39, N 5.30; found: C 67.92, H 8.46, N 5.26.

*(1*R*,4*R*,5*R*,8*R*)-5-(Hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,8-diol* (**31**). A mixture of **30** (23 mg, 0.09 mmol), 20% Pd(OH)–C (6 mg), MeOH (1 ml), and 37% aq. HCl (0.15 ml) was stirred at 24° for 16 h under H_2 (6 bar). The mixture was filtered through *Celite*, and the residue was washed with MeOH (3 × 5 ml). The filtrate was diluted with toluene (5 ml) and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, 0.1M aq. NH_3) gave **31** (14 mg, 92%). Colourless solid. R_f (MeOH/25% aq. NH_3 soln. 3:1) 0.25. $[\alpha]_D^{25} = +25.3$ (*c* = 0.8, H_2O). IR (0.5% in KBr): 3293*m*, 3221*m*, 3045*m*, 2910*m*, 2776*m*, 2482*w*, 2138*w*, 1610*m*, 1480*w*, 1410*m*, 1337*m*, 1262*w*, 1155*m*, 1111*m*, 993*m*, 958*w*, 901*w*, 846*w*. ^{1}H-NMR (CD_3OD): 3.85 (*dd*, *J* = 10.9, 4.7, CH_a–C(5)); 3.79 (br. *d*, *J* = 9.7, H–C(8)); 3.76 (*dd*, *J* = 10.9, 5.0, CH_b–C(5)); 3.45 (*quint.*, *J* ≈ 2.8, H–C(1)); 3.31 (*dd*, *J* ≈ 11.5, 1.5, H_a–C(3)); 3.23 (*dd*, *J* = 11.5, 1.6, H_b–C(3)); 2.36 (*ddd*, *J* = 14.9, 9.7, 1.9, H_{endo}–C(7)); 1.99 (br. *d*, *J* ≈ 15.5, H_{exo}–C(7)); 1.95–1.85 (*m*, H–C(5), 2 H–C(6)). ^{13}C-NMR (CD_3OD): 70.20 (*s*, C(4)); 70.05 (*d*, C(8)); 61.41 (*t*, CH_2–C(5)); 46.82 (*d*, C(1)); 39.82 (*t*, C(3)); 38.72 (*d*, C(5)); 35.20 (*t*, C(7)); 27.87 (*t*, C(6)). ESI-MS: 174 (45, $[M+H]^+$), 163 (54), 153 (26), 145 (35), 103 (100), 97 (54).

Inhibition of Glycosidases. The IC_{50} values were determined at a substrate concentration corresponding to the K_M of each enzyme. IC_{50} Values were calculated by plotting the inhibitor concentration *vs.* the rate of hydrolysis. Determination of the inhibition constants K_i was performed at five different concentrations of the inhibitor bracketing the IC_{50} value. K_i Values and α values were determined from the replot of the slopes and the replot of the $1/v$ axis intercepts of *Lineweaver–Burk* plots [27].

a) *Inhibition of* C. saccharolyticum *β-Glucosidase.* $K_M = 0.80$ mM ([28]: $K_M = 0.50–0.78$ mM; [18]: $K_M = 0.51$ mM). The inhibition studies were carried out at pH 6.8 (KH_2PO_4/K_2HPO_4 buffer, 0.06M) and 55°. The reaction was started by the addition of 4-nitrophenyl β-D-glucopyranoside after pre-incubating the enzyme in the presence of the inhibitor for 30 min at 55°. After 15 min, the enzyme reaction was quenched by the addition of borate buffer (pH 9.2, 0.2M). The rate of hydrolysis was determined by measuring the absorption at λ = 405 nm and subsequently substracting the absorption of a blank probe (H_2O, buffer, substrate).

b) *Inhibition of Sweet Almonds β-Glucosidases.* $K_M = 3.4$ mM ([28]: $K_M = 2.9–3.1$ mM). The inhibition studies were carried out at pH 6.8 (KH_2PO_4/K_2HPO_4 buffer, 0.06M) and 37°. The reaction was started by the addition of 4-nitrophenyl β-D-glucopyranoside after pre-incubating the enzyme in the presence of the inhibitor for 30 min at 37°. The velocity of the substrate hydrolysis was determined by measuring the increase of absorption per min at $\lambda = 405$ nm during 10 min.

c) *Inhibition of* T. reesei *Cellulase Cel7A.* $K_M = 0.39$ mM ([29]: $K_M = 0.406$ mM). The inhibition studies were carried out at pH 5.7 (KH_2PO_4/Na_2HPO_4 buffer, 0.05M) and 30°. The reaction was started by the addition of 4-nitrophenyl β-lactopyranoside after pre-incubating the enzyme in the presence of the inhibitor for 30 min at 30°.

After 10 min, the enzyme reaction was quenched by the addition of borate buffer (pH 9.2, 0.2M). The rate of hydrolysis was determind by measuring the absorption at $\lambda = 405$ nm and subsequently substracting the absorption of a blank probe (H_2O, buffer, substrate).

d) *Inhibition of* N. takasagoensis *Endoglucanase NtEg1*. $K_M = 8.7$ mg/ml (corresponding to *ca.* 0.032 mM of 'sodium carboxymethyl cellulose'). According to a personal communication from Prof. *E. Meyer*, Texas A&M University, the inhibition studies were carried out at pH 5.6 (AcONa buffer, 0.04M containing $CaCl_2$, 0.8 mM) and 37°. The reaction was started by the addition of a 2.3 (*w*/*w*) 'sodium carboxymethyl cellulose' soln. (average molecular weight *ca.* 250000 Da, degree of carboxymethyl substitution 0.7 (*w*/*v*)) after pre-incubating the enzyme in the presence of the inhibitor for 30 min at 37°. After 30 min, the mixture was added to a soln. of tetrazolium blue reagent soln. [30] and heated to 100° for 3 min. After cooling to 25°, the rate of hydrolysis was determined by measuring the absorption at $\lambda = 660$ nm and subsequently substracting the absorption of a blank probe (H_2O, buffer, substrate).

e) *Inhibition of Snail β-Mannosidase.* $K_M = 0.58$ mM ([10]: $K_M = 0.42 - 0.80$ mM). The inhibition studies were carried out at pH 4.5 (AcONa buffer, 0.04M) and 25°. The reaction was started by the addition of 4-nitrophenyl β-D-mannopyranoside after pre-incubating the enzyme in the presence of the inhibitor for 120 min at 25°. After 5 min, the enzyme reaction was quenched by the addition of borate buffer (pH 9.2, 0.2M). The rate of hydrolysis was determined by measuring the absorption at $\lambda = 405$ nm and subsequently substracting the absorption of a blank probe (H_2O, buffer, substrate).

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