Synthesis of 2-Azabicyclo[3.2.2]nonane-Derived Monosaccharide Mimics and Their Evaluation as Glycosidase Inhibitors

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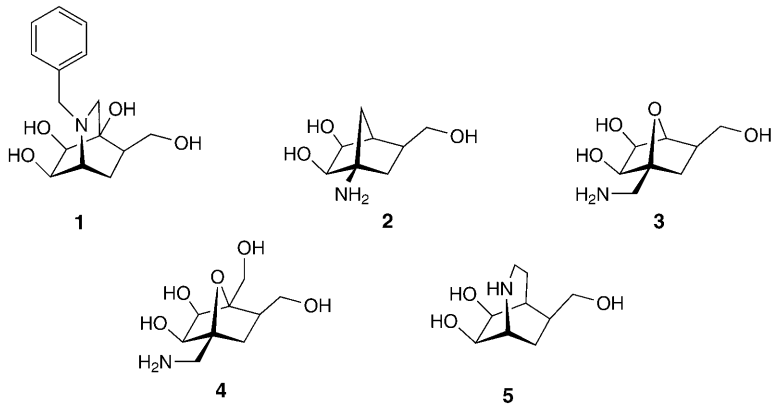
The racemic 2-azabicyclo[3.2.2]nonanes **5** and **18** were synthesized and tested as β-glycosidase inhibitors. The intramolecular *Diels–Alder* reaction of the masked *o*-benzoquinone generated from 2-(allyloxy)phenol (**6**) gave the α-keto acetal **7** which was reduced with SmI_2 to the hydroxy ketone **8**. Dihydroxylation, isopropylidenation ($\rightarrow$ **12**), and *Beckmann* rearrangement provided lactam **15**. *N*-Benzylation of this lactam, reduction to the amine **17**, and deprotection provided the amino triol **19** which was debenzylated to the secondary amine **5**. Both **5** and **19** proved weak inhibitors of snail β-mannosidase ($IC_{50} > 10$ mM), *Caldocellum saccharolyticum* β-glucosidase ($IC_{50} > 10$ mM), sweet almond β-glucosidase ($IC_{50} > 10$ mM), yeast α-glucosidase (**5**: $IC_{50} > 10$ mM; **19**: $IC_{50} = 1.2$ mM), and *Jack* bean α-mannosidase (no inhibition detected).

Introduction. – Together with the crystal-structure analysis of glycosidase-inhibitor complexes [1] and the use of isotopically labelled compounds [2], the synthesis and evaluation of inhibitors contribute to elucidating the mechanism of action of the enzymatic hydrolysis of glycosides, as summarized in several reviews [3]. For example, the determination and interpretation of inhibition constants and kinetics of conformationally biased (more or less close) mimics of the transition state are a valuable source of information about the stereoelectronically required [4] conformational change of the substrate imposed by β-glycosidases [5]. Thus, the isoquinuclidine **1** [6], mimicking the $^{1,4}B$ conformation of a D-mannopyranoside, inhibits snail β-mannosidase strongly ($K_i = 1$ μM) and selectively, while the corresponding *gluco*-configured diastereoisomer is inactive against β-glucosidases, evidencing a different conformational itinerary. The norbornane **2** and its 7-oxa analogues **3** and **4** [7], possessing a shorter bridge between the centers corresponding to C(1) and C(4), and mimicking a $^{1,4}B$ conformation more closely than the isoquinuclidine **1** differ considerably in the location and orientation of the N-atom, and are rather weak inhibitors of snail β-mannosidase. In this context, 2-azabicyclo[3.2.2]nonanes ('homoisoquinuclidines') such as **5** appeared of interest, as they possess a longer bridge ensuring a boat-like conformation of the cyclohexane ring mimicking the pyranosyl (glycon) moiety. We anticipated differences to **1** in the orientation of the C–N bond and in the location of the basic N-atom ('the glycosidic heteroatom') that is to interact with the catalytic acid. An evaluation of the inhibition of β-glycosidases by such amines may allow to more precisely assess the optimal pre-transition state conformation of this type of glycosidase inhibitors.



However, superposition[1]) of the cyclohexane moiety of **5** with that of **1** (root-mean-square deviation (rms) 0.462 Å) shows that the position of the N-atom of **5** and of the OH group mimicking C(2)–OH of the parent sugar remais almost unchanged, while there is a distance of 0.899 Å between the OH group of **1** and **5** mimicking C(3)–OH. The additional CH_2 group of the bridge distinguishing **5** from **1** leads to bending of the bridge so that the atomic distance between the bridgehead C-atoms in **5** (d=2.738 Å) does not strongly differ from the one in **1** (d=2.577 Å). One expects a slightly lower inhibition constant for **5** than for **1**, considering that the C(4)–OH group of a mannoside is not mimicked by **5**, provided that the additional CH_2 group of **5** will not lead to destabilising interactions. In several cases, homologation of rigid aza sugars was reported to weaken the inhibition. The homologue of castanospermine [9] is a 170-fold weaker inhibitor of the sweet almond β-glucosidases, and the homologue of swainsonine [10] proved an extremely poor inhibitor. These observations were rationalized by assuming an unfavourable entropy of binding due to the lowered rigidity [11].

The preparation of 2-azabicyclo[3.2.2]nonanes was first described 1960 by *Hall* [12] who obtained 2-azabicyclo[3.2.2]nonan-3-one from bicyclo[2.2.2]octanone by a *Beckmann* rearrangement. *Liao* and co-workers. [13] prepared functionalized bicyclo[2.2.2]octanones by an intramolecular *Diels–Alder* reaction of 'masked *o*-benzoquinones', which were generated by oxidation of 2-methoxyphenols with iodobenzene diacetate. We decided to apply this method to the synthesis of the desired 2-azabicyclo[3.2.2]nonanes.

Synthesis. – We modified the known synthesis of the keto acetal **7** based on the oxidation of 2-methoxyphenol in the presence of allyl alcohol [13] by oxidising 2-(allyloxy)phenol (**6**) [14] with iodobenzene diacetate in MeOH (*Scheme*). The intramolecular *Diels–Alder* reaction of the intermediate cyclohexadienone diminished the fraction of the dimeric by-product, and increased the yield from 30 to 41% of crystallized,

[1]) Calculation and superposition was carried out using Macromodel v 6.0 [8]. The structures were minimized with the PRCG algorithm and using the MM3* force field.

analytically pure **7**[2]). Reduction of **7** with 0.1M SmI_2 in the presence of MeOH [15] gave smoothly the keto alcohol **8** (97%). Silylation [16] with ^{t}BuPh$_2$SiCl provided **9** in an almost quantitative yield. Dihydroxylation [17] of **9** gave a 78:22 mixture of the two diastereoisomeric *cis*-diols **10** and **11**. This mixture was not readily separated. It was isopropylidenated by treatment with 2,2-dimethoxypropane/acetone in the presence of camphorsulfonic acid (CSA) to yield a mixture including some side-products. Substituting acetone by CH_2Cl_2 and CSA by pyridinium *p*-toluenesulfonate (PPTS) [18] led to a clean conversion of **10**/**11** into the acetals **12** and **13** that were separated by chromatography, and isolated in 75 and 24% yields, respectively. Treatment of **12** with $NH_2OH \cdot HCl$ led initially to a mixture of diastereoisomeric oximes, as evidenced by TLC (R_f (cyclohexane/AcOEt 2:1) 0.34 and 0.52). The mixture progressively converged to a single oxime **14**, as indicated by a single spot on TLC (R_f 0.34) and evidenced by the ^{1}H-NMR spectrum of the crude. Treatment of **14** with diphenylphosphinated polystyrene[3]) ('Ph_3P on resin') in CCl_4 [19] proved sufficient to induce the *Beckmann* rearrangement of **14** to the lactam **15** (75% from **12**). Several attempts to reduce **15** to the corresponding amine proceeded sluggishly or failed. The lactam **15** was, therefore, *N*-benzylated (BnBr, ^{t}BuOK) to **16** (91%) that was readily reduced with $BH_3 \cdot SMe_2$ [20] to the amine **17** (79%). The reduction led first to a stable borane–amine complex[4]). Treatment of the crude with $N(CH_2CH_2OH)_3$, followed by aqueous workup, provided the amine **17** (R_f 0.69). Desilylation of **17** with NH_4F [22] gave the amino alcohol **18** (96%) that was deisopropylidenated to yield 90% of the triol **19**. Hydrogenolysis of **19** in the presence of Pd/C in MeOH/6N HCl 1:1 provided the ammonium salt **5** (89% after recrystallisation).

The configuration of the diastereoisomers **12** and **13** was unambiguously assigned on the basis of NOEs. H–C(6) and H′–C(11) of **12** showed a NOE of 3.3%, H–C(2) and H–C(10) one of 7.0%. This is in keeping with the NMR spectrum of **13** which showed only a NOE (2.3%) between H–C(2), respectively H–C(6) and H–C(9). The bridgehead *H*–*C*(1) of lactam **15** couples with N*H* ($J = 7.3$), as established by deuterium exchange and a DQF-COSY spectrum. This evidences the location of the N-atom in the ring that is in keeping with the (*Z*)-configuration of the oximino group, as evidenced by a downfield shift of 0.18 ppm for H–C(9) of **14** as compared to **12**. The interpretation of the NMR spectra was confirmed by an X-ray crystal-structure determination[5]) of **15** and the ammonium salt **5** (*Fig.*).

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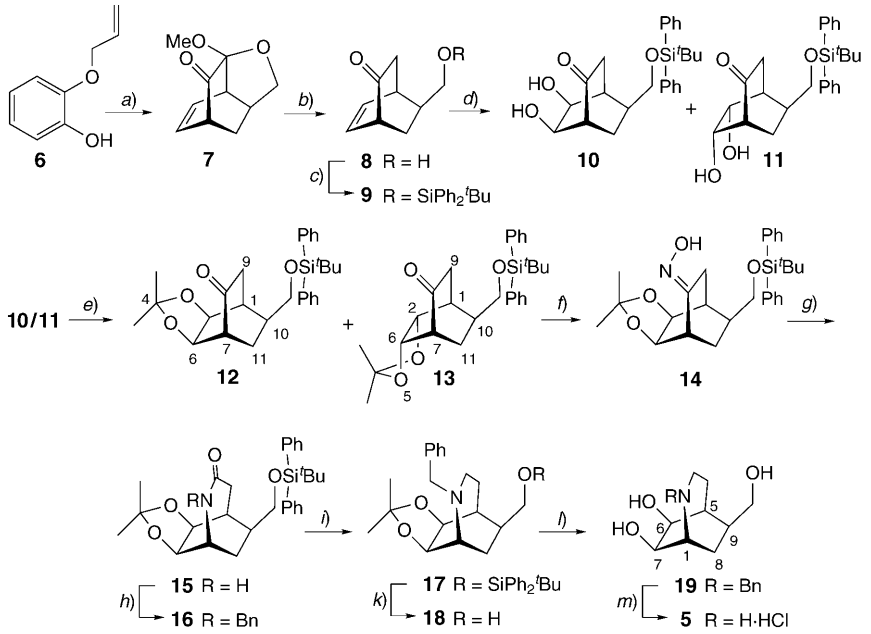
[2]) We thank Dr. *Jean-François Poisson,* postdoctoral fellow (2000–2001) and *Sophia Gallo* for exploratory work on the preparation of **7** and **8**.

[3]) This was used because of difficulties to separate **14** from Ph_3PO by chromatography or crystallisation. Substituting Ph_3P by DPPE (1,2-bis(diphenylphosphino)ethane) did not lead to the product.

[4]) The crude resulting from aqueous workup with 20% aq. NaH_2PO_4 solution showed IR bands at 1333 and 2399 cm^{-1}, evidencing B–N and B–H bonds; TLC (cyclohexane/AcOEt 2:1) showed a single spot (R_f 0.73). For the formation and characterization of a similar borane-amine complex, see [21].

[5]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-256199 (**15**) and CCDC-263629 (**5**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Scheme

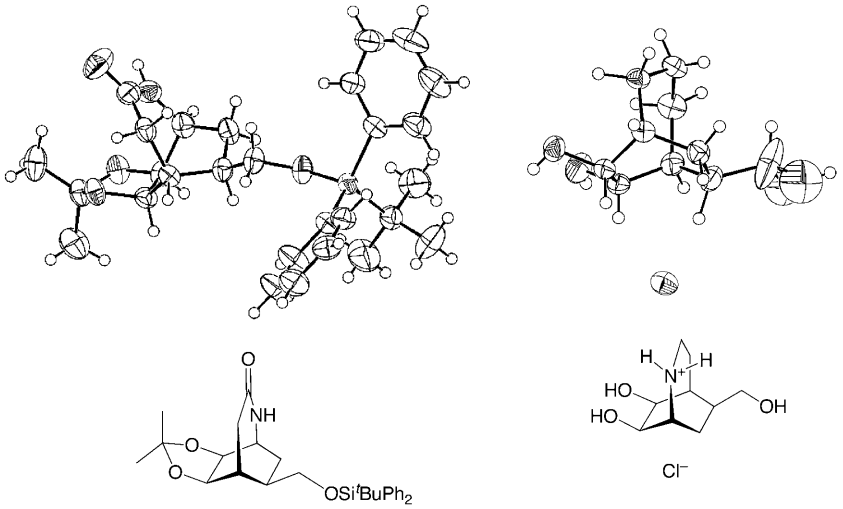


a) (Diacetoxyiodo)benzene (DAIB), MeOH, 50°; 41%. *b*) SmI_2, THF, MeOH; 97%. *c*) ^{t}BuPh$_2$SiCl, 1*H*-imidazole, DMF; quant. *d*) *N*-Methylmorpholine *N*-oxide monohydrate (NMO), cat. OsO_4, acetone/H_2O; **10**/**11** 78:22 (86%). *e*) 2,2-Dimethoxypropane, pyridinium *p*-toluenesulfonate, CH_2Cl_2; **12** (75%), **13** (24%). *f*) $NH_2OH \cdot HCl$, pyridine, EtOH. *g*) Diphenylphosphinylated polystyrene, CCl_4; 75% from **12**. *h*) BnBr, ^{t}BuOK, THF; 91%. *i*) $BH_3 \cdot SMe_2$, THF, 65°; 79%. *k*) NH_4F, MeOH, 50°; 96%. *l*) 2N HCl, MeOH; 90%. *m*) Pd/C, 6 bar H_2, 6N HCl, MeOH; 89%.

Glycosidase Inhibition. – The results of the inhibition of snail β-mannosidase, *Caldocellum saccharolyticum* β-glucosidase, sweet almond β-glucosidases, yeast α-glucosidase, and *Jack* bean α-mannosidase by the 2-azabicyclo[3.2.2]nonanes **5** and **18** are summarized in the *Table*. Neither **5** nor **18** are inhibitors, as shown by the lowest IC_{50} value of 1.2 mM (inhibition of the α-glucosidase from yeast by **18**). By comparison, the inhibition by the isoquinuclidine **1** of snail β-mannosidase is characterised by a K_i of 1.0 μM [23].

The crystal structure of **5** (*Fig.*) reveals that the preferred conformation of the cyclohexane moiety of **5** in the crystal is close to a boat ($^{1,4}B$), as shown by a ring-puckering analysis according to *Cremer* and *Pople* [24]. The general puckering amplitude Q[6]) (0.76 Å) is in the same range as the Q value of an unsubstituted cyclohexane ring (0.63 Å). The puckering parameters of **5** ($\Theta = 93.2°$; $\Phi = 11.8°$) indicate a distorted $^{1,4}B$ conformation, the values differing slightly from those expected for an ideal cyclohexane $^{1,4}B$ conformer ($\Theta = 90°$; $\Phi = 0°$). An ideal $^{1,4}B$-cyclohexane ring of **5** would be characterised by dihedral angles H–C(6)–C(7)–H and H–C(8)–C(9)–H of 0°; the

[6]) Q is the total puckering amplitude and a measure for the difference of the bond lengths compared to those of a cyclohexane ring. Θ and Φ give the magnitude of distortion.



15 **5**

Figure. *ORTEP Representation of the crystal structure of the lactam* **15** *and of the trihydroxy ammonium chloride* **5** (disorder of the $HOCH_2$ group)

Table. *Inhibition of Glycosidases by the Homoisoquinuclidines* **5** *and* **19** *at the Indicated pH.*

	Conditions	**5**	**19**
β-Mannosidase (*Helix pomatia*)	pH 4.5; 25° Acetate buffer *p*-Nitrophenyl β-D-mannopyranoside[a])	$IC_{50} > 10$ mM	$IC_{50} > 10$ mM
β-Glucosidase (*Caldocellum saccharolyticum*)	pH 6.8; 55° Phosphate buffer *p*-Nitrophenyl β-D-glucopyranoside[a])	$IC_{50} > 10$ mM	$IC_{50} > 10$ mM
β-Glucosidase (Sweet Almonds)	pH 6.8; 37° Phosphate buffer *p*-Nitrophenyl β-D-glucopyranoside[a])	$IC_{50} > 10$ mM	$IC_{50} \approx 6$ mM
α-Glucosidase (Yeast)	pH 6.8; 37° Phosphate buffer *p*-Nitrophenyl α-D-glucopyranoside[a])	$IC_{50} > 10$ mM	$IC_{50} = 1.2$ mM
α-Mannosidase (*Jack* Beans)	pH 4.5; 37° Acetate buffer *p*-Nitrophenyl α-D-mannopyranoside[a])	[b])	[b])

[a]) Substrate used in the assay. [b]) No inhibition detected.

experimental values are 8.6° and 29.4°, respectively, in accordance with the above considerations.

Namchuk and *Withers* [25] showed that the interaction of the substrate C(4)–OH with the *Agrobacterium faecalis* β-glucosidase contributes *ca.* 2.5 kJ mol^{-1} to binding.

A difference of 2.5 kJ/mol in binding energy would only lower the inhibition constant by a factor of 2–3. Conceivably, C(4)–OH interacts significantly more strongly with snail β-mannosidase than the C(4)–OH group of a glucoside with the β-glucosidase of *A. faecalis*. Alternatively, or in concert, unfavourable steric interactions with the larger bridge may impair the binding of **5** or **18**.

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Experimental Part

General. Solvents were distilled before use: THF from Na/benzophenone, CH_2Cl_2, CCl_4, DMF, and MeOH from CaH_2. Reactions were run under Ar. Qual. TLC: precoated silica-gel plates (*Macherey-Nagel Alugram Sil G/UV$_{254}$*); detection by heating with 'mostain' (400 ml of 10% aq. H_2SO_4, 20 g of $(NH_4)_6Mo_7O_{24}\cdot H_2O$, 0.4 g of $Ce(SO_4)_2$). Flash chromatography (FC): silica gel *Fluka 60* (0.04–0.063 mm). FT-IR: KBr or 2% $CHCl_3$ soln. The glycosidases and the pyranosides for the enzymatic assays were purchased from *Sigma* and used without any further purification.

2-(Prop-2-enyloxy)phenol (**6**) [14]. A suspension of catechol (25 g, 0.23 mol), allyl bromide (28 g, 0.23 mol), and K_2CO_3 (31.4 g, 23 mmol) in acetone (300 ml) was stirred for 5.5 h at 60°, evaporated, treated with H_2O (200 ml) and Et_2O (150 ml), and acidified to pH 3 with 50% aq. H_2SO_4. After separation of layers, the aq. layer was extracted with Et_2O (2 × 150 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. Distillation (80°/0.5 Torr) of the residue gave **6** (26.6 g, 79%). Yellowish, malodorous oil. R_f (cyclohexane/AcOEt 3:1) 0.29. B.p.$_{0.5}$ 70–75°. IR ($CHCl_3$): 3540*m*, 3061*w*, 1649*w*, 1598*w*, 1500*s*, 1466*w*, 1424*w*, 1358*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.61 (*dt*, *J* = 5.6, 1.2, CH_2=CH–CH_2O); 5.32 (*dq*, *J* = 10.6, 1.3, (*E*) CH*H*=CH); 5.41 (*dq*, *J* = 17.4, 1.6, (*Z*) CH*H*=CH); 5.69 (br. *s*, OH); 6.07 (*ddt*, *J* = 16.8, 10.6, 5.6, CH_2=C*H*); 6.80–6.94 (*m*, 4 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 69.88 (*t*, CH_2=CH–*C*H$_2$O); 112.28, 114.79 (2*d*, C(3), C(6)); 118.31 (*t*, *C*H$_2$=CH); 120.12, 121.73 (2*d*, C(4), C(5)); 132.83 (*d*, CH_2=*C*H); 145.48, 145.75 (2*s*, C(1), C(2)). EI-MS: 150.0677 (51, M^+). Anal. calc. for $C_9H_{10}O_2$ (150.18): C 71.98, H 6.71; found: C 71.70, H 6.62.

(1RS,3SR,6SR,7RS)-3-Methoxy-4-oxatricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (**7**). A soln. of DAIB (8.1 g, 25 mmol) in MeOH (25 ml) was treated dropwise with a soln. of **6** (2.5 g, 16.8 mmol) in MeOH (10 ml) at 50° over a period of 3.5 h, stirred for 1.5 h, and evaporated. FC (hexane/AcOEt/NEt_3 5:1:0.02) gave crude **7** (1.6 g), which was suspended in boiling hexane/AcOEt 5:1 (7 ml) and treated dropwise with AcOEt until a clear soln. resulted. The soln. was cooled to 23° and inoculated with a seed crystal to give **7** (1.25 g, 41%). Colourless solid. R_f (cyclohexane/AcOEt 2:1) 0.28. M.p. 67°. IR ($CHCl_3$): 3011*w*, 1746*s*, 1603*w*, 1447*w*, 1361*w*, 1326*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.72–1.88 (*m*, irrad. at 2.47 → 1.79, br. *d*, *J* ≈ 13.5 and 1.86, *dd*, *J* = 13.4, 2.8, 2 H–C(10)); 2.43–2.50 (*m*, irrad. at 1.79 → br. *t*, *J* = 3.9, irrad. at 3.30 → *dt*, *J* = 9.0, 3.0, H–C(6)); 3.12–3.15 (*m*, irrad. at 1.79 → *dd*, *J* = 6.5, 1.2, H–C(1)); 3.30 (br. *t*, *J* = 6.2, H–C(7)); 3.46 (*s*, MeO); 3.74 (*d*, *J* = 8.1, H–C(5)); 4.08 (*dd*, *J* = 7.8, 3.1, irrad. at 2.47 → *d*, *J* = 8.1, H′–C(5)); 6.17 (br. *t*, *J* = 6.3, irrad. at 3.14 → *dd*, *J* = 8.0, 5.3, irrad. at 3.30 → br. *d*, *J* = 7.5, H–C(8)); 6.29 (br. *t*, *J* = 6.5, irrad. at 3.14 → *dd*, *J* = 8.1, 1.3, irrad. at 3.30 → *dd*, *J* = 7.8, 5.2, H–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 31.05 (*t*, C(10)); 35.54 (*d*, C(7)); 42.84, 45.76 (2*d*, C(1), C(6)); 51.18 (*q*, MeO); 73.84 (*t*, C(5)); 100.45 (*s*, C(3)); 129.53, 130.84 (2*d*, C(8), C(9)); 201.48 (*s*, C(2)). HR-ESI-MS: 203.0683 ([*M* + Na]$^+$, $C_{10}H_{12}NaO_3^+$; calc. 203.0684), 383.1469 ([2 *M* + Na]$^+$, $C_{20}H_{24}NaO_6^+$; calc. 383.1471). Anal. calc. for $C_{10}H_{12}O_3$ (180.20): C 66.65, H 6.71; found: C 66.72, H 6.82.

(1RS,4RS,8SR)-8-(Hydroxymethyl)bicyclo[2.2.2]oct-5-en-2-one (**8**). A soln. of **7** (1 g, 5.6 mmol) in THF (20 ml) and MeOH (10 ml) was treated in portions with 0.1M SmI_2 in THF (250 ml, 25 mmol) at 21° until the green-blue colour remained, stirred for 15 h, and evaporated. The residue was treated with H_2O (30 ml) and $CHCl_3$ (30 ml), and acidified with 2N HCl until a clear emulsion resulted (pH 2–3). After separation of the layers, the aq. layer was extracted with CH_2Cl_2 (7 × 15 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (hexane/AcOEt 1:2) gave **8** (817 mg, 97%). Colour-

less oil. R_f (cyclohexane/AcOEt 1:3) 0.36. IR ($CHCl_3$): 3442*w*, 3010*w*, 1721*s*, 1610*w*, 1408*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.26 (*ddd*, *J* = 13.4, 5.6, 1.9, H–C(7)); 1.57–1.64 (*m*, exchange with D_2O, OH); 1.84 (*dt*, *J* = 13.7, 3.4, H′–C(7)); 1.94–2.02 (*m*, H–C(3), H–C(8)); 2.27 (*dd*, *J* = 19.0, 2.2, H′–C(3)); 3.03–3.12 (*m*, H–C(1), H–C(4)); 3.49–3.57 (*m*, addn. of D_2O → *dd*, *J* = 10.3, 8.7), 3.71–3.78 (*m*, addn. of D_2O → *dd*, *J* = 10.9, 5.9) (CH_2–C(8)); 6.20 (*tt*, *J* = 7.4, 0.8), 6.44 (*td*, *J* = 7.8, 1.3) (H–C(5), H–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.27 (*t*, C(7)); 33.26 (*d*, C(8)); 34.81 (*t*, C(3)); 37.82 (*d*, C(4)); 48.52 (*d*, C(1)); 64.29 (*t*, *C*H_2–C(8)); 128.06, 138.72 (2*d*, C(5), C(6)); 212.81 (*s*, C(2)). HR-ESI-MS: 327.1562 ($[2M+Na]^+$, $C_{18}H_{24}NNaO_4^+$; calc. 327.1572).

*(1*RS*,4*RS*,8*SR*)-8-{[(*tert*-Butyl)diphenylsilyloxy]methyl}bicyclo[2.2.2]oct-5-en-2-one* (**9**). A soln. of **8** (545 mg, 3.6 mmol) and 1*H*-imidazole (370 mg, 5.4 mmol) in DMF (20 ml) at 0° was treated with ^{t}BuPh$_2$SiCl (985 µl, 3.79 mmol), warmed to 23°, stirred for 48 h, diluted with H_2O (40 ml), and extracted with Et_2O (1 × 30 ml, 2 × 20 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. FC (hexane/AcOEt) 5:1) gave **9** (1.4 g, quant.). Colourless oil. R_f (cyclohexane/AcOEt 5:1) 0.56. IR ($CHCl_3$): 3011*w*, 1964*w*, 1896*w*, 1823*w*, 1720*s*, 1602*m*, 1472*w*, 1428*m*, 1113*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.06 (*s*, *t*-Bu); 1.16 (*ddd*, *J* = 13.7, 7.6, 1.7, H–C(7)); 1.74 (*ddd*, *J* = 13.7, 10.9, 3.8, H′–C(7)); 1.89 (*ddd*, *J* = 18.7, 3.3, 1.7, H–C(3)); 1.96–2.06 (*m*, H–C(8)); 2.14 (*dd*, *J* = 18.7, 1.9, H′–C(3)); 3.02–3.06 (*m*, irrad. at 1.16 → br. *dd*, *J* = 6.3, 3.9, H–C(1)); 3.11–3.13 (*m*, irrad. at 2.01 → *d*, *J* = 6.2, H–C(4)); 3.46 (*t*, *J* ≈ 10.2, irrad. at 2.01 → *d*, *J* = 11.5), 3.74 (*dd*, *J* = 10.2, 5.8, irrad. at 2.01 → *d*, *J* = 10.0) (CH_2–C(8)); 6.17 (br. *t*, *J* = 7.9, irrad. at 3.04 → *d*, *J* = 8.1, irrad. at 3.12 → *dd*, *J* = 8.1, 5.0, H–C(6)); 6.62 (br. *t*, *J* = 7.7, irrad. at 3.04 → *dd*, *J* = 8.1, 5.4, irrad. at 3.12, *d*, *J* = 8.1, H–C(5)); 7.35–7.74 (*m*, 10 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 19.45 (*s*, Me_3C); 25.90 (*t*, C(7)); 27.12 (*q*, *Me*$_3$C); 33.57 (*d*, C(8)); 34.78 (*t*, C(3)); 38.01 (*d*, C(4)); 48.77 (*d*, C(1)); 65.34 (*t*, *C*H_2–C(8)); 127.65 (2*d*); 127.69 (2*d*); 128.09 (*d*); 129.07 (*d*); 129.73 (*d*); 133.41 (2*s*); 134.70 (*d*); 135.44 (3*d*); 138.84 (*d*); 212.87 (*s*, C(2)). HR-ESI-MS: 413.1910 ($[M+Na]^+$, $C_{25}H_{30}NaO_2Si^+$; calc. 413.1913). Anal. calc. for $C_{25}H_{30}O_2Si$ (390.60): C 76.88, H 7.74; found: C 76.69, H 7.65.

*(1*RS*,4*SR*,5*SR*,6*RS*,8*SR*)- and (1*RS*,4*SR*,5*RS*,6*SR*,8*SR*)-8-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-5,6-dihydroxybicyclo[2.2.2]octan-2-one* (**10** and **11**, resp.). A soln. of **9** (1.4 g, 3.6 mmol), NMO (590 mg, 4.3 mmol), H_2O (4 ml), and MeCN (4 ml) in acetone (20 ml) was treated with 2.5% OsO_4 in *t*-BuOH (0.1 ml), stirred for 22 h at 22°, poured into a 20% aq. $NaHSO_3$ soln. (50 ml) at 0°, and stirred for 10 min. After evaporation of acetone, the residual soln. was extracted with Et_2O (1 × 100 ml, 3 × 30 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (hexane/AcOEt 1:1) yielded **10**/**11** 78:22 (1.33 g, 86%). Colourless glass.

Data of **10**/**11** *78:22*. R_f (cyclohexane/AcOEt 1:2) 0.59. IR ($CHCl_3$): 3603*w*, 3062*w*, 2932*m*, 1968*w*, 1897*w*, 1829*w*, 1728*s*, 1605*w*, 1472*w*, 1427*w*, 1100*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.04 (*s*, *t*-Bu); 1.00–1.12 (*m*, 0.22 H), 1.20 (*ddd*, *J* = 14.3, 5.6, 2.8, 0.78 H) (H–C(7)); 1.84 (*td*, *J* = 14.0, 3.1, 0.78 H), 1.94–2.05 (*m*, 0.22 H) (H′–C(7)); 1.94–2.05 (*m*, H–C(8)); 2.16 (*dd*, *J* = 19.9, 2.2, 0.78 H), 2.26 (*ddd*, *J* = 17.7, 10.2, 4.1, 0.22 H) (H–C(3)); 2.38–2.59 (*m*, H–C(1), H′–C(3), H–C(4)); 2.88 (br. *s*, 0.44 H), 3.09 (br. *s*, 1.56 H) (2 OH); 3.43–3.65 (*m*, CH_2–C(8)); 3.93 (br. *ddd*, *J* = 7.8, 5.0, 2.5, 0.22 H) 4.03–4.06 (*m*, 1 H), 4.20 (br. *td*, *J* = 8.1, 4.0, 0.78 H) (H–C(5), H–C(6)); 7.36–7.65 (10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): major and minor isomer: 23.62 (*t*, C(7)); 26.97 (*s*, *Me*$_3$C); 33.73 (*t*, C(3)); 67.93, 69.52 (2*d*, C(5), C(6)); 127.70 (4*d*); 129.74 (2*d*); 133.24 (2*s*); 135.43 (4*d*); major isomer: 19.35 (*s*, Me_3C); 34.51 (*d*, C(8)); 36.51 (*d*, C(4)); 50.83 (*d*, C(1)); 65.01 (*t*, *C*H_2–C(8)); 214.91 (*s*, C(2)); minor isomer: 19.97 (*s*, Me_3C); 36.60 (*d*, C(8)); 38.15 (*d*, C(4)); 50.59 (*d*, C(1)); 65.63 (*t*, CH_2–C(8)); 214.10 (*s*, C(2)). HR-ESI-MS: 447.1957 ($[M+Na]^+$, $C_{25}H_{32}NaO_4Si^+$; calc. 447.1968). Anal. calc. for $C_{25}H_{32}O_4Si$ (424.61): C 70.72, H 7.60; found: C 70.55, H 7.67.

*(1*RS*,2*SR*,6*RS*,7*RS*,10*SR*)- and (1*RS*,2*RS*,6*SR*,7*RS*,10*RS*)-10-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-4,4-dimethyl-3,5-dioxatricyclo[5.2.2.0^{2,6}]undecan-8-one* (**12** and **13**, resp.). A soln. of **10**/**11** 78:22 (1.29 g, 3.04 mmol), pyridinium *p*-toluenesulfonate (5 mg), and 2,2-dimethoxypropane (1.7 g, 16.3 mmol) in CH_2Cl_2 (15 ml) was stirred for 16 h at 20° and evaporated. FC (hexane/AcOEt 10:1) gave **12** (1.06 g, 75%) and **13** (332 mg, 24%).

Data of **12**. Colourless glass. R_f (cyclohexane/AcOEt 3:1) 0.47. IR ($CHCl_3$): 2933*m*, 1961*w*, 1894*w*, 1823*w*, 1729*s*, 1602*w*, 1472*w*, 1428*m*, 1089*s*. ^{1}H-NMR (500 MHz, $CDCl_3$; assignment based on a DQF-COSY and a HSQC spectrum): 1.04 (*s*, *t*-Bu); 1.20 (*ddd*, *J* = 14.6, 6.1, 2.8, H–C(11); 1.35, 1.42 (2*s*, Me_2-

C(4)); 1.77 (*td*, *J* = 14.3, 3.3, irrad. at 4.40 → NOE of 3.3%, H′–C(11)); 1.88–1.96 (*m*, irrad. at 4.29 → NOE of 7.0%, H–C(10)); 2.09 (*dd*, *J* = 19.4, 1.7, H–C(9)); 2.42 (*ddd*, *J* = 19.5, 2.8, 1.2, H′–C(9)); 2.59 (br. *q*, *J* ≈ 3.2, H–C(7)); 2.60–2.61 (*m*, irrad. at 4.29 → NOE of 5.1%, irrad. at 4.40 → NOE of 5.0%, H–C(1)); 3.56 (*dd*, *J* = 10.3, 9.2), 3.64 (*dd*, *J* = 10.3, 6.0) (CH_2–C(10)); 4.29 (*ddd*, *J* = 7.8, 3.7, 1.3, irrad. at 1.35 → NOE of 1.7%, H–C(2)); 4.40 (*dd*, *J* = 7.7, 3.8, irrad. at 1.35 → NOE of 1.6%, H–C(6)); 7.30–7.78 (*m*, 10 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignment based on a HSQC spectrum): 19.23 (*s*, Me_3C); 22.62 (*t*, C(11)); 23.96, 25.64 (2*q*, Me_2C(4)); 26.86 (*q*, Me_3C); 33.18 (*d*, C(1)); 33.57 (*t*, C(9)); 34.08 (*d*, C(10)); 48.06 (*d*, C(7)); 65.00 (*t*, CH_2–C(10)); 75.64 (*d*, C(2)); 76.90 (*d*, C(6)); 108.68 (*s*, C(4)); 127.80 (4*d*); 129.86 (4*d*); 133.32 (2*s*); 135.53 (4*d*); 212.06 (*s*, C(8)). HR-ESI-MS: 487.2267 ($[M+Na]^+$, $C_{28}H_{36}NaO_4Si^+$; calc. 487.2281). Anal. calc. for $C_{28}H_{36}O_4Si$ (464.68): C 72.37, H 7.81; found: C 72.12, H 8.11.

Data of **13**. Colourless solid. M.p. 102°. R_f (cyclohexane/AcOEt 3 : 1) 0.52. IR ($CHCl_3$): 2933*m*, 1962*w*, 1894*w*, 1829*w*, 1729*s*, 1602*w*, 1472*m*, 1428*m*, 1384*m*, 1110*s*. ^{1}H-NMR (500 MHz, $CDCl_3$; assignment based on a DQF-COSY and a HSQC spectrum): 1.04 (*s*, *t*-Bu); 1.03–1.06 (*m*, H–C(11)); 1.38 (*s*, irrad. at 4.29 → NOE of 2.9%, Me–C(4)); 1.55 (*s*, Me–C(4)); 1.88 (br. *dt*, *J* = 19.6, 1.6, irrad. at 4.29 → NOE of 2.3%, H–C(9)); 2.20 (br. *ddd*, *J* = 14.1, 10.8, 3.4, H′–C(11)); 2.45 (*dd*, *J* = 19.6, 3.3, H′–C(9)); 2.48–2.51 (*m*, irrad. at 4.29 → NOE of 3.1%, H–C(1), H–C(10)); 2.62 (br. *q*, *J* ≈ 3.4, irrad. at 4.29 → NOE of 3.1%, H–C(7)); 3.48 (*dd*, *J* = 10.4, 8.6), 3.59 (*dd*, *J* = 10.4, 5.7) (CH_2–C(10)); 4.27 (*dd*, *J* = 8.2, 3.5, H–C(2)); 4.30 (*dd*, *J* = 8.0, 3.1, H–C(6)); 7.35–7.79 (*m*, 10 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignment based on a HSQC and a HMBC spectrum): 19.25 (*s*, Me_3C); 20.01 (*t*, C(11)); 24.17, 25.64 (2*q*, Me_2C(4)); 26.90 (*q*, Me_3C); 28.54 (*d*, C(10)); 33.75 (*d*, C(1)); 36.25 (*t*, C(9)); 48.04 (*d*, C(7)); 65.66 (*t*, CH_2–C(10)); 71.69 (*d*, C(2)); 75.76 (*d*, C(6)); 110.31 (*s*, C(4)); 127.73 (2*d*); 127.76 (2*d*); 129.74 (2*d*); 133.48, 133.52 (2*s*); 135.59 (2*d*); 135.60 (2*d*); 213.08 (*s*, C(8)). HR-ESI-MS: 487.2266 ($[M+Na]^+$, $C_{28}H_{36}NaO_4Si^+$; calc. 487.2281). Anal. calc. for $C_{28}H_{36}O_4Si$ (464.68): C 72.37, H 7.81; found: C 72.19, H 7.89.

*(1*RS*,2*SR*,6*RS*,7*RS*,11*RS*)-11-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-4,4-dimethyl-3,5-dioxa-8-aza-tricyclo[5.3.2.0^{2,6}]dodecan-9-one* (**15**). A soln. of **12** (1 g, 2.2 mmol), $NH_2OH \cdot HCl$ (225 mg, 3.2 mmol) and pyridine (10 ml) in EtOH (32 ml) was stirred at 65° for 72 h and evaporated. The residue was dissolved in CH_2Cl_2 (30 ml) and H_2O (20 ml). The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined org. layers were dried (Na_2SO_4), evaporated, and co-evaporated with toluene to afford the crude oxime **14** (1.44 g). White foam. R_f (cyclohexane/AcOEt 2 : 1) 0.34. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.04 (*s*, *t*-Bu); 1.12 (*ddd*, *J* = 14.0, 5.9, 3.1, H–C(11)); 1.35, 1.43 (2*s*, Me_2C(4)); 1.68 (*td*, *J* = 14.0, 3.1, H′–C(11)); 1.80–1.91 (*m*, H–C(10)); 2.27 (*dd*, *J* = 19.6, 1.9, H–C(9)); 2.53 (br. *d*, *J* = 18.1, H′–C(9)); 2.56 (br. *s*, OH); 2.60–2.64 (*m*, H–C(7), H–C(1)); 3.56 (*t*, *J* = 9.8), 3.64 (*dd*, *J* = 10.3, 6.2) (CH_2–C(10)); 4.20–4.28 (*m*, H–C(2), H–C(6)); 7.13–7.65 (*m*, 10 arom. H).

A suspension of the crude oxime (1.44 g) and 'polymer bound Ph_3P' (2.6 g, corresp. to 4.3 mmol Ph_3P) in CCl_4 (200 ml) was stirred vigorously for 3.5 h at 85°, cooled to 20°, and concentrated *i.v.* to 100 ml. The residue was treated with sat. aq. $NaHCO_3$ soln. (20 ml) and CH_2Cl_2 (50 ml), stirred vigorously for 30 min, and filtered through a small pad of *Celite*. After separating the layers, the aq. layer was extracted with CH_2Cl_2 (4 × 20 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. FC (AcOEt/MeOH 100 : 0 → 100 : 1 yielded **15** (776 mg, 75%). Colourless solid. M.p. 167°. R_f (AcOEt) 0.36. IR ($CHCl_3$): 3411*w*, 2933*m*, 1962*w*, 1894*w*, 1829*w*, 1657*w*, 1471*m*, 1428*w*, 1384*w*, 1211*m*, 1112*s*. ^{1}H-NMR (400 MHz, $CDCl_3$; assignment based on a DQF-COSY spectrum): 1.04 (*s*, *t*-Bu); 1.40, 1.49 (2*s*, Me_2C(4)); 1.60 (br. *ddd*, *J* ≈ 12, 6.0, 1.3, H–C(12)); 1.87–1.98 (*m*, H–C(11), H′–C(12)); 2.47 (br. *d*, *J* ≈ 20, H–C(10)); 2.62–2.70 (*m*, H–C(1), H′–C(10)); 3.25–3.29 (*m*, addn. of CD_3OD → br. *t*, *J* ≈ 4.8, H–C(7)); 3.61 (*dd*, *J* = 10.3, 8.7), 3.68 (*dd*, *J* = 10.6, 5.7) (CH_2–C(11)); 4.11 (*dd*, *J* = 8.0, 4.2, H–C(6)); 4.43 (br. *t*, *J* = 7.6, H–C(2)); 5.90 (br. *d*, *J* = 7.3, exchange with CD_3OD, NH); 7.36–7.70 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.24 (*s*, Me_3C); 24.83, 26.86 (2*q*, Me_2C(4)); 26.86 (*q*, Me_3C); 29.20 (*t*, C(12)); 30.75 (*d*, C(11)); 31.20 (*t*, C(10)); 35.41 (*d*, C(1)); 48.50 (*d*, C(7)); 65.09 (*t*, CH_2–C(11)); 75.70, 75.83 (2*d*, C(2), C(6)); 109.94 (*s*, C(4)); 127.89 (2*d*); 127.86 (2*d*); 128.44, 128.56 (2*d*); 132.08, 132.17 (2*s*); 135.49 (2*d*); 135.52 (2*d*); 174.37 (*s*, C(9)). HR-ESI-MS: 502.2392 ($[M+Na]^+$, $C_{28}H_{37}NNaO_4Si^+$; calc. 502.2390). Anal. calc. for $C_{28}H_{37}NO_4Si$ (479.69): C 70.11, H 7.77, N 2.92; found: C 69.95, H 7.60, N 2.92.

X-Ray Crystal Structure Analysis of **15** (CCDC-256199). Crystals were obtained from Et_2O by slow evaporation at r.t. $C_{28}H_{37}NO_4Si$ (479.69); monoclinic; $a=7.7838(3)$ Å, $b=36.4362(2)$ Å, $c=9.6051(9)$ Å; $\beta=104.096(2)^\circ$; $V=2642(3)$ Å^3; $D_{calc.}=1.206$ Mg/m^3; $Z=4$. Intensities were measured on a *Bruker Nonius Kappa CCD* diffractometer (graphite monochromator, MoK_α, $\lambda=0.71073$ Å at 298 K. Of the 9223 reflections, 4907 unique reflections were observed. $R=0.0704$; $R_w=0.1520$. The structure was refined by the direct method with SHELXL-97 [26].

*(1*RS*,2*SR*,6*RS*,7*RS*,11*SR*)-8-Benzyl-11-{[(*tert*-butyl)diphenylsilyloxy]methyl}-4,4-dimethyl-3,5-dioxa-8-azatricyclo[5.3.2.0^{2,6}]dodecan-9-one* (**16**). A soln. of **15** (420 mg, 0.88 mmol) in THF (42 ml) was treated with ^{t}BuOK (125 mg, 1.1 mmol), stirred until ^{t}BuOK had dissolved, treated with BnBr (3 g, 17 mmol), stirred for 22 h at 21°, treated with sat. aq. NH_4Cl soln. (30 ml), and extracted with $CHCl_3$ (1×30 ml) and CH_2Cl_2 (4×10 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (hexane/AcOEt 2:1) gave **16** (452 mg, 91%). Colourless foam. R_f (cyclohexane/AcOEt 2:1) 0.47. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.03 (*s*, *t*-Bu); 1.22–1.28 (*m*, H–C(12)); 1.40, 1.48 (2*s*, Me_2C(4)); 1.73–1.84 (H–C(11)), H′–C(12)); 2.60 (*dd*, $J=18.4$, 1.8, H–C(10)); 2.61–2.67 (*m*, H–C(1)); 2.84 (br. *dd*, $J=18.4$, 5.5, H′–C(10)); 3.45 (br. *q*, $J\approx4.4$, H–C(7)); 3.58 (*d*, $J=6.3$, CH_2–C(11)); 3.68 (*d*, $J=15.1$), 5.60 (*d*, $J=14.8$) (PhCH_2); 4.15 (*dd*, $J=8.0$, 4.7), 4.40 (*t*, $J=7.5$) (H–C(2), H–C(6)); 7.17–7.67 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.46 (*s*, Me_3C); 25.07, 26.31 (*q*, Me_2C(4)); 27.08 (*q*, Me_3C); 29.10 (*t*, C(12)); 31.77 (*d*, C(11)); 32.33 (*t*, C(10)); 35.31 (*d*, C(1)); 53.37 (*d*, C(7)); 65.11 (*t*, CH_2–C(11)); 75.97, 76.20 (2*d*, C(2), C(6)); 76.89 (*t*, PhCH_2); 110.28 (*s*, C(4)); 127.42 (*d*); 128.01 (2*d*); 128.10 (2*d*); 128.47 (2*d*); 128.71 (2*d*); 130.06, 130.14 (2*d*); 133.41, 133.59 (2*s*); 135.74 (2*d*); 135.72 (2*d*); 137.98 (*s*); 171.89 (*s*, C(9)). HR-ESI-MS: 570.3025 ([$M+H$]$^+$, $C_{35}H_{44}NO_4Si^+$; calc. 570.3040). Anal. calc. for $C_{35}H_{43}NO_4Si$ (569.81): C 73.78, H 7.61, N 2.46; found: C 73.65, H 7.50, N 2.52.

*(1*RS*,2*SR*,6*RS*,7*RS*,11*SR*)-8-Benzyl-11-{[(*tert*-butyl)diphenylsilyloxy]methyl}-4,4-dimethyl-3,5-dioxa-8-azatricyclo[5.3.2.0^{2,6}]dodecane* (**17**). A soln. of **16** (150 mg, 0.26 mmol) in THF (4.5 ml) was treated with a 2M $BH_3\cdot SMe_2$ soln. in THF (1.3 ml, 2.6 mmol), stirred at 65° for 5 h, cooled to 0°, treated dropwise with $N(CH_2CH_2OH)_3$ (0.45 g, 3 mmol), stirred vigorously at 65° for 70 min, cooled to 23°, and treated with H_2O (5 ml) and 1N NaOH soln. (2 ml). The mixture was extracted with Et_2O (1×10 ml, 2×5 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. FC (hexane/AcOEt/Et_3N 5:1:0.01) yielded **17** (116 mg, 79%). Colourless thick oil. R_f (cyclohexane/AcOEt 2:1) 0.69. IR ($CHCl_3$): 3011*s*, 1962*w*, 1894*w*, 1825*w*, 1732*w*, 1603*w*, 1588*w*, 1472*w*, 1428*m*, 1372*m*, 1112*s*. ^{1}H-NMR (400 MHz, $CDCl_3$, assignment based on a DQF-COSY and a HSQC spectrum): 1.05 (*s*, *t*-Bu); 1.36 (*ddd*, $J=14.5$, 10.1, 4.8, H–C(10)); 1.38–1.42 (*m*, H–C(12)); 1.39, 1.65 (2*s*, Me_2C(4)); 1.52 (*ddd*, $J=15.7$, 10.6, 5.4, H′–C(12)); 1.75–1.82 (*m*, H–C(11)); 1.96–2.04 (*m*, H′–C(10)); 2.27 (*ddd*, $J=12.1$, 9.9, 4.8, H–C(9)); 2.45 (*tdd*, $J=8.7$, 5.8, 2.9, H–C(1)); 2.63 (br. *td*, $J=11.8$, 5.5, H′–C(9)); 3.14 (br. *t*, $J\approx4.5$, H–C(7)); 3.66 (*s*, PhCH_2); 3.69 (*d*, $J=7.7$, CH_2–C(11)); 3.97 (*dd*, $J=8.6$, 4.8, H–C(6)); 4.18 (*dd*, $J=8.5$, 6.2, H–C(2)); 7.16–7.67 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; assignment based on a HSQC and a HMBC spectrum): 19.28 (*s*, Me_3C); 22.48 (*t*, C(10)); 23.77 (*t*, C(12)); 24.68, 26.14 (2*q*, Me_2C(4)); 26.89 (*q*, Me_3C); 33.56 (*d*, C(1)); 36.44 (*d*, C(11)); 46.79 (*t*, C(9)); 57.91 (*d*, C(7)); 63.49 (*t*, PhCH_2); 65.50 (*t*, CH_2–C(11)); 77.05 (*d*, C(2)); 77.28 (*d*, C(6)); 108.42 (*s*, C(4)); 126.58 (*d*); 127.68 (4*d*); 127.94 (2*d*); 128.74 (2*d*); 129.64, 129.66 (2*d*); 133.80, 133.89 (2*s*); 135.60 (4*d*); 140.47 (*s*). HR-ESI-MS: 556.3230 ([$M+H$]$^+$, $C_{35}H_{46}NO_3Si^+$; calc. 556.3247). Anal. calc. for $C_{35}H_{45}NO_3Si$ (555.83): C 75.63, H 8.16, N 2.52; found: C 75.55, H 8.25, N 2.48.

*(1*RS*,2*SR*,6*RS*,7*RS*,11*SR*)-8-Benzyl-4,4-dimethyl-3,5-dioxa-8-azatricyclo[5.3.2.0^{2,6}]dodecane-11-methanol* (**18**). A suspension of **17** (485 mg, 0.27 mmol) and NH_4F (800 mg, 21.5 mmol) in MeOH (20 ml) was warmed to 50° for 16 h and evaporated. A suspension of the residue in CH_2Cl_2 (10 ml) was filtered through cotton, and the solid was washed with CH_2Cl_2 (2×5 ml). Evaporation of the filtrate and FC (hexane/AcOEt/NEt_3 1:2:0.1 → 1:2:0.2) gave **18** (265 mg, 96%). Colourless glass. R_f (cyclohexane/AcOEt/NEt_3 1:2:0.1) 0.37. IR ($CHCl_3$): 3618*w*, 2934*s*, 1953*w*, 1890*w*, 1820*w*, 1606*w*, 1494*w*, 1453*w*, 1371*m*, 1207*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.39, 1.66 (2*s*, Me_2C(4)); 1.43–1.58 (*m*, H–C(10), 2 H–C(12)); 1.70–1.82 (*m*, H–C(11)); 2.06 (*dddd*, $J=17.7$, 9.0, 5.9, 3.1, H′–C(10)); 2.24 (br. *s*, exchange with D_2O, OH); 2.38 (*ddd*, $J=9.0$, 5.9, 3.1, H–C(1)); 2.43 (*ddd*, $J=12.5$, 9.0, 5.0, H–C(9)); 2.79 (br. *dt*, $J=12.1$, 5.6, H′–C(9)); 3.02 (br. *td*, $J\approx4.7$, 2.2, H–C(7)); 3.69 (*d*, $J=7.2$, CH_2–C(11)); 3.74 (*s*, PhCH_2); 3.99 (*dd*, $J=8.4$, 4.7, H–C(2)); 4.18 (*dd*, $J=8.4$, 5.9, H–C(6)); 7.18–7.38 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz,

$CDCl_3$): 22.79 (*t*, C(10)); 24.53 (*t*, C(12)); 24.66, 26.23 (2*q*, Me_2C(4)); 34.17 (*d*, C(1)); 36.38 (*d*, C(11)); 46.83 (*t*, C(9)); 57.60 (*d*, C(7)); 63.67 (*t*, PhCH_2); 64.83 (*t*, CH_2–C(11)); 76.73 (*d*, C(2)); 77.16 (*d*, C(6)); 104.47 (*s*, C(4)); 126.66 (*d*); 127.96 (2*d*); 128.75 (2*d*); 140.00 (*s*). HR-ESI-MS: 318.2069 ($[M+H]^+$, $C_{19}H_{28}NO_3^+$; calc. 318.2069). Anal. calc. for $C_{19}H_{27}NO_3$ (317.43): C 71.89, H 8.57, N 4.41; found: C 71.97, H 8.56, N 4.41.

*(1*RS*,5*RS*,6*SR*,7*RS*,9*SR*)-2-Benzyl-9-(hydroxymethyl)-2-azabicyclo[3.2.2]nonane-6,7-diol* (**19**). A soln. of **18** (259 mg, 0.816 mmol) in MeOH (4 ml) was treated with 2N HCl (11 ml) and stirred for 36 h at 21°. After evaporation of the solvent, a soln. of the residue in H_2O (2 ml) was brought to pH 8 with 2N NaOH. Evaporation and FC (CH_2Cl_2/MeOH/25% aq. NH_3 10 : 0.75 : 0.2) gave **19** (203 mg, 90%). Colourless oil. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 10 : 0.75 : 0.2) 0.37. pK_a 9.92. IR (KBr): 3412*s* (br.), 2921*s*, 1954*w*, 1881*w*, 1814*w*, 1747*w*, 1638*w*, 1451*s*, 1070*s*. ^{1}H-NMR (300 MHz, CD_3OD): 1.39–1.48 (*m*, H–C(4)); 1.58 (*ddd*, *J* = 15.6, 7.2, 2.2, H_{endo}–C(8)); 1.65 (*ddd*, *J* = 15.6, 10.6, 5.0, H_{exo}–C(8)); 1.80–1.90 (*m*, H–C(9)); 1.95–2.03 (*m*, H′–C(4), H–C(5)); 2.49 (*td*, *J* = 12.5, 4.4, H–C(3)); 2.65 (br. *dd*, *J* = 12.5, 4.7, H′–C(3)); 3.14 (br. *t*, *J* ≈ 5.3, H–C(1)); 3.54–3.67 (*m*, H–C(6), H–C(7), CH_2–C(9)); 7.20–7.34 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz, CD_3OD): 21.36 (*t*, C(4)); 22.20 (*t*, C(8)); 38.19 (*d*, C(9)); 38.39 (*d*, C(5)); 48.67 (*t*, C(3)); 60.00 (*d*, C(1)); 62.91 (*t*, PhCH_2); 64.81 (*t*, CH_2–C(9)); 66.82 (*d*, C(6)); 71.94 (*d*, C(7)); 128.02 (*d*); 129.06 (2*d*); 129.94 (2*d*); 139.38 (*d*). HR-ESI-MS: 278.1747 ($[M+H]^+$, $C_{16}H_{24}NO_3^+$; calc. 278.1756). Anal. calc. for $C_{16}H_{23}NO_3$ (277.36): C 69.29, H 8.36, N 5.05; found: C 69.01, H 8.36, N 5.05.

*(1*RS*,5*RS*,6*SR*,7*RS*,9*SR*)-2-Azonia-6,7-dihydroxy-9-(hydroxymethyl)bicyclo[3.2.2]nonane Chloride* (**5**). A suspension of **19** (184 mg, 0.66 mmol) and 10% Pd/C (150 mg) in MeOH (7.5 ml) and 6N HCl (7.5 ml) was hydrogenated for 20 h at 21° under 6 bar of H_2, filtered through a pad of *Celite* (washing with 10 ml of H_2O/MeOH 1 : 1), and taken to dryness. A soln. of the residue in H_2O (5 ml) was filtered through a PTFE syringe filter. The solvent was evaporated. Crystallisation of the residue from MeOH (5 ml) gave **5** (94 mg). Concentration of the mother liquor to 50% of its volume and cooling (0°) gave a second crop of **5** (38 mg, 89% overall). White plates. M.p. 235°. IR (KBr): 3600–2000*s* (br.), 1586*s*, 1484*s*, 1458*s*, 1440*s*, 1382*s*, 1264*s*, 1091*s*. ^{1}H-NMR (400 MHz, D_2O; assignment based on a DQF-COSY spectrum): 1.59 (*ddd*, *J* = 16.4, 8.0, 1.2, H_{endo}–C(8)); 1.80 (*ddd*, *J* = 16.0, 10.8, 5.4, H–C(4)); 1.90–1.98 (*m*, H–C(9)); 2.07–2.16 (*m*, H_{exo}–C(8)), H′–C(4)); 2.33 (br. *td*, *J* = 8.6, 4.8, H–C(5)); 3.12 (*ddd*, *J* = 14.5, 9.4, 5.3, H–C(3)); 3.22 (*td*, *J* ≈ 13.7, 5.9, H′–C(3)); 3.59 (*d*, *J* = 7.6, CH_2–C(9)); 3.77 (br. *td*, *J* = 5.8, 1.2, H–C(1)); 4.09 (*dd*, *J* = 8.9, 5.5, H–C(6)); 4.18 (*dd*, *J* = 8.8, 4.6, H–C(7)). ^{13}C-NMR (75 MHz, D_2O): 19.31 (C(4)); 23.40 (C(8)); 34.94, 35.70 (C(5), C(9)); 39.35 (C(3)); 55.36 (C(1)); 63.04 (CH_2–C(9)); 64.70, 67.76 (C(6), C(7)). ESI-MS: 188.2 (100, $[M+H]^+$). Anal. calc. for $C_9H_{18}ClNO_3$ (223.70): C 48.32, H 8.11, N 6.26; found: C 48.13, H 7.93, N 6.12.

X-Ray Crystal-Structure Analysis of **5** (CCDC-263629). Crystals were obtained from hot MeOH by slow cooling to r.t. $C_9H_{18}ClNO_3$ (223.70); triclinic P_1; *a* = 6.6733(2) Å, *b* = 7.1437(2) Å, *c* = 11.2070(3) Å; α = 87.8978(11)°, β = 80.3466(11)°, γ = 87.5959(11)°; *V* = 525.99(3) Å^3; $D_{calc.}$ = 1.412 Mg/m^3; *Z* = 2. Intensities were measured on a *Bruker Nonius Kappa CCD* diffractometer (graphite monochromator, MoK_α, λ = 0.71073 Å at 298 K. Of the 4987 reflections, 2552 unique reflections were observed. *R* = 0.0917; R_w = 0.2628. The structure was refined by the direct method with SHELXL-97 [26].

Determination of the Inhibition Constants. Inhibition constants were determined in the same way as reported in [23] (snail β-mannosidase, β-glucosidase from *C. saccharolyticum*, and *Jack* bean α-mannosidase), [27] (sweet almonds β-glucosidases) and [28] (yeast α-glucosidase).

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