

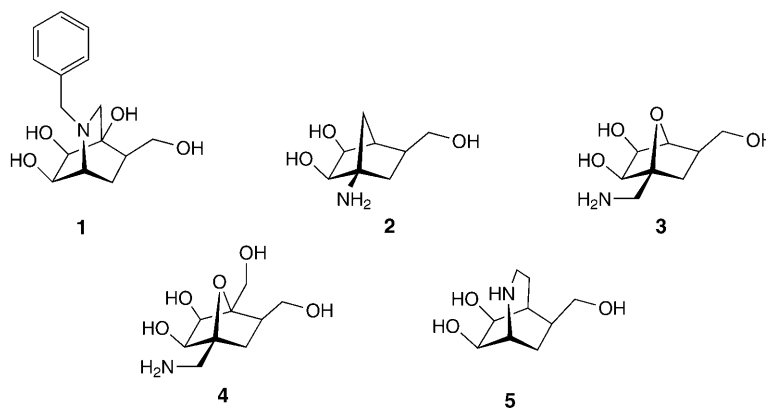
Synthesis of 2-Azabicyclo[3.2.2]nonane-Derived Monosaccharide Mimics and Their Evaluation as Glycosidase Inhibitors

by **Stephan Buser** and **Andrea Vasella***

Laboratorium für Organische Chemie, Departement Chemie und Angewandte Biowissenschaften, ETH Zürich, Hönggerberg, HCI, CH-8093 Zürich

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*-Benzoylation 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 ('homoisquinuclidines') 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, superposition¹⁾ 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 remains 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 CH₂ 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 CH₂ 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 SmI₂ in the presence of MeOH [15] gave smoothly the keto alcohol **8** (97%). Silylation [16] with ^tBuPh₂SiCl 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 CH₂Cl₂ 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 NH₂OH·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 ¹H-NMR spectrum of the crude. Treatment of **14** with diphenylphosphinated polystyrene³ ('Ph₃P on resin') in CCl₄ [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, ^tBuOK) to **16** (91%) that was readily reduced with BH₃·SMe₂ [20] to the amine **17** (79%). The reduction led first to a stable borane-amine complex⁴). Treatment of the crude with N(CH₂CH₂OH)₃, followed by aqueous workup, provided the amine **17** (*R*_f 0.69). Desilylation of **17** with NH₄F [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/6*N* 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 NH (*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 determination⁵) of **15** and the ammonium salt **5** (*Fig.*).

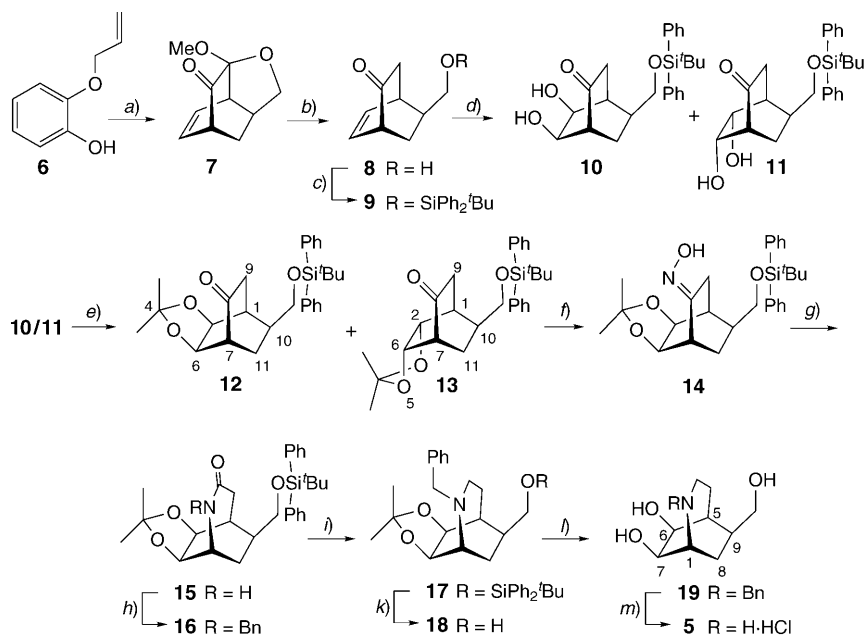
²) We thank Dr. *Jean-François Poisson*, postdoctoral fellow (2000–2001) and *Sophia Gallo* for exploratory work on the preparation of **7** and **8**.

³) This was used because of difficulties to separate **14** from Ph₃PO by chromatography or crystallisation. Substituting Ph₃P by DPPE (1,2-bis(diphenylphosphino)ethane) did not lead to the product.

⁴) The crude resulting from aqueous workup with 20% aq. NaH₂PO₄ 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) $^t\text{BuPh}_2\text{SiCl}$, 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) $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, EtOH. g) Diphenylphosphinylated polystyrene, CCl_4 ; 75% from **12**. h) BnBr , $^t\text{BuOK}$, THF; 91%. i) $\text{BH}_3\cdot\text{SMe}_2$, THF, 65°; 79%. k) NH_4F , MeOH, 50°; 96%. l) 2*N* HCl, MeOH; 90%. m) Pd/C, 6 bar H_2 , 6*N* 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** ($\Theta = 93.2^\circ$; $\Phi = 11.8^\circ$) indicate a distorted $^{1,4}B$ conformation, the values differing slightly from those expected for an ideal cyclohexane $^{1,4}B$ conformer ($\Theta = 90^\circ$; $\Phi = 0^\circ$). An ideal $^{1,4}B$ -cyclohexane ring of **5** would be characterised by dihedral angles $\text{H-C}(6)\text{--C}(7)\text{--H}$ and $\text{H-C}(8)\text{--C}(9)\text{--H}$ 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.

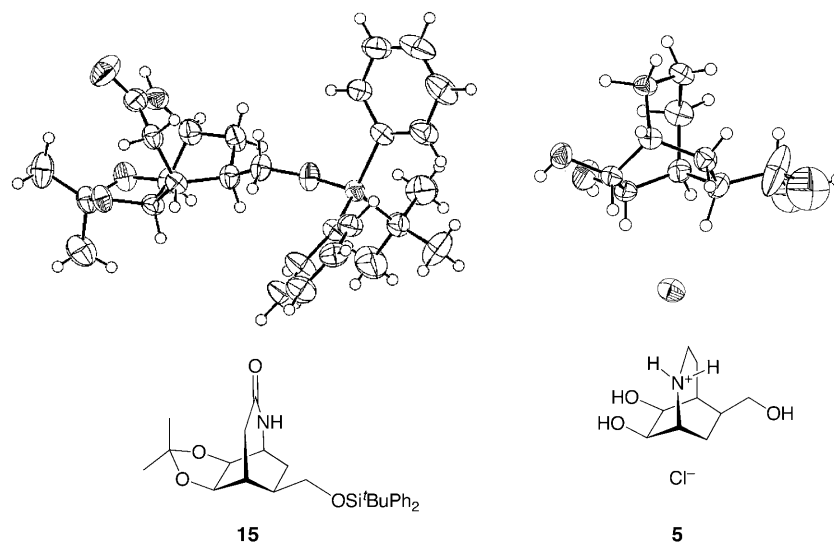


Figure. ORTEP Representation of the crystal structure of the lactam **15** and of the trihydroxy ammonium chloride **5** (disorder of the HOCH₂ group)

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

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

We thank *F. Hoffmann La Roche AG*, Basel, and the *Swiss National Science Foundation* for generous support, *Dr. B. Schweizer* for the X-ray crystal-structure determination, *M. Schneider* and *P. Kälin* for the pK_{HA} determination, and *Dr. B. Bernet* for checking the experimental part.

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/UV₂₅₄*); detection by heating with 'mostain' (400 ml of 10% aq. H_2SO_4 , 20 g of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot \text{H}_2\text{O}$, 0.4 g of $\text{Ce}(\text{SO}_4)_2$). 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): 3540m, 3061w, 1649w, 1598w, 1500s, 1466w, 1424w, 1358w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 4.61 (dt, $J=5.6, 1.2$, $\text{CH}_2=\text{CH}-\text{CH}_2\text{O}$); 5.32 (dq, $J=10.6, 1.3$, (E) $\text{CHH}=\text{CH}$); 5.41 (dq, $J=17.4, 1.6$, (Z) $\text{CHH}=\text{CH}$); 5.69 (br. s, OH); 6.07 (ddt, $J=16.8, 10.6, 5.6$, $\text{CH}_2=\text{CH}$); 6.80–6.94 (m, 4 arom. H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 69.88 (t, $\text{CH}_2=\text{CH}-\text{CH}_2\text{O}$); 112.28, 114.79 (2d, C(3), C(6)); 118.31 (t, $\text{CH}_2=\text{CH}$); 120.12, 121.73 (2d, C(4), C(5)); 132.83 (d, $\text{CH}_2=\text{CH}$); 145.48, 145.75 (2s, C(1), C(2)). EI-MS: 150.0677 (51, M^+). Anal. calc. for $\text{C}_9\text{H}_{10}\text{O}_2$ (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): 3011w, 1746s, 1603w, 1447w, 1361w, 1326w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.72–1.88 (m, irradi. at 2.47 → 1.79, br. d, $J \approx 13.5$ and 1.86, dd, $J=13.4, 2.8$, 2 H–C(10)); 2.43–2.50 (m, irradi. at 1.79 → br. t, $J=3.9$, irradi. at 3.30 → dt, $J=9.0, 3.0$, H–C(6)); 3.12–3.15 (m, irradi. 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, $J=7.8, 3.1$, irradi. at 2.47 → d, $J=8.1$, H'–C(5)); 6.17 (br. t, $J=6.3$, irradi. at 3.14 → dd, $J=8.0, 5.3$, irradi. at 3.30 → br. d, $J=7.5$, H–C(8)); 6.29 (br. t, $J=6.5$, irradi. at 3.14 → dd, $J=8.1, 1.3$, irradi. at 3.30 → dd, $J=7.8, 5.2$, H–C(9)). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 31.05 (t, C(10)); 35.54 (d, C(7)); 42.84, 45.76 (2d, C(1), C(6)); 51.18 (q, MeO); 73.84 (t, C(5)); 100.45 (s, C(3)); 129.53, 130.84 (2d, C(8), C(9)); 201.48 (s, C(2)). HR-ESI-MS: 203.0683 ($[\text{M}+\text{Na}]^+$, $\text{C}_{10}\text{H}_{12}\text{NaO}_3^+$; calc. 203.0684), 383.1469 ($[2\text{M}+\text{Na}]^+$, $\text{C}_{20}\text{H}_{24}\text{NaO}_6^+$; calc. 383.1471). Anal. calc. for $\text{C}_{10}\text{H}_{12}\text{O}_3$ (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 (CHCl₃): 3442w, 3010w, 1721s, 1610w, 1408w. ¹H-NMR (300 MHz, CDCl₃): 1.26 (ddd, J = 13.4, 5.6, 1.9, H–C(7)); 1.57–1.64 (*m*, exchange with D₂O, 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 D₂O → *dd*, J = 10.3, 8.7), 3.71–3.78 (*m*, addn. of D₂O → *dd*, J = 10.9, 5.9) (CH₂–C(8)); 6.20 (*tt*, J = 7.4, 0.8), 6.44 (*td*, J = 7.8, 1.3) (H–C(5), H–C(6)). ¹³C-NMR (75 MHz, CDCl₃): 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*, CH₂–C(8)); 128.06, 138.72 (*2d*, C(5), C(6)); 212.81 (*s*, C(2)). HR-ESI-MS: 327.1562 ([2*M* + Na]⁺, C₁₈H₂₄NNaO₄⁺; calc. 327.1572).

(*IRS,4RS,8SR*)-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 ^tBuPh₂SiCl (985 μl, 3.79 mmol), warmed to 23°, stirred for 48 h, diluted with H₂O (40 ml), and extracted with Et₂O (1 × 30 ml, 2 × 20 ml). The combined org. layers were dried (Na₂SO₄) and evaporated. FC (hexane/AcOEt) 5:1 gave **9** (1.4 g, quant.). Colourless oil. R_f (cyclohexane/AcOEt 5:1) 0.56. IR (CHCl₃): 3011w, 1964w, 1896w, 1823w, 1720s, 1602m, 1472w, 1428m, 1113s. ¹H-NMR (300 MHz, CDCl₃): 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*, irradi. at 1.16 → *br. dd*, J = 6.3, 3.9, H–C(1)); 3.11–3.13 (*m*, irradi. at 2.01 → *d*, J = 6.2, H–C(4)); 3.46 (*t*, J ≈ 10.2, irradi. at 2.01 → *d*, J = 11.5), 3.74 (*dd*, J = 10.2, 5.8, irradi. at 2.01 → *d*, J = 10.0) (CH₂–C(8)); 6.17 (*br. t*, J = 7.9, irradi. at 3.04 → *d*, J = 8.1, irradi. at 3.12 → *dd*, J = 8.1, 5.0, H–C(6)); 6.62 (*br. t*, J = 7.7, irradi. at 3.04 → *dd*, J = 8.1, 5.4, irradi. at 3.12, *d*, J = 8.1, H–C(5)); 7.35–7.74 (*m*, 10 arom. H). ¹³C-NMR (300 MHz, CDCl₃): 19.45 (*s*, Me₃C); 25.90 (*t*, C(7)); 27.12 (*q*, Me₃C); 33.57 (*d*, C(8)); 34.78 (*t*, C(3)); 38.01 (*d*, C(4)); 48.77 (*d*, C(1)); 65.34 (*t*, CH₂–C(8)); 127.65 (*2d*); 127.69 (*2d*); 128.09 (*d*); 129.07 (*d*); 129.73 (*d*); 133.41 (*2s*); 134.70 (*d*); 135.44 (*3d*); 138.84 (*d*); 212.87 (*s*, C(2)). HR-ESI-MS: 413.1910 ([*M* + Na]⁺, C₂₅H₃₀NaO₂Si⁺; calc. 413.1913). Anal. calc. for C₂₅H₃₀O₂Si (390.60): C 76.88, H 7.74; found: C 76.69, H 7.65.

(*IRS,4SR,5SR,6RS,8SR*)- and (*IRS,4SR,5SR,6SR,8SR*)-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), H₂O (4 ml), and MeCN (4 ml) in acetone (20 ml) was treated with 2.5% OsO₄ in *t*-BuOH (0.1 ml), stirred for 22 h at 22°, poured into a 20% aq. NaHSO₃ soln. (50 ml) at 0°, and stirred for 10 min. After evaporation of acetone, the residual soln. was extracted with Et₂O (1 × 100 ml, 3 × 30 ml). The combined org. layers were dried (MgSO₄) 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 (CHCl₃): 3603w, 3062w, 2932m, 1968w, 1897w, 1829w, 1728s, 1605w, 1472w, 1427w, 1100s. ¹H-NMR (300 MHz, CDCl₃): 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*, CH₂–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). ¹³C-NMR (75 MHz, CDCl₃): major and minor isomer: 23.62 (*t*, C(7)); 26.97 (*s*, Me₃C); 33.73 (*t*, C(3)); 67.93, 69.52 (*2d*, C(5), C(6)); 127.70 (*4d*); 129.74 (*2d*); 133.24 (*2s*); 135.43 (*4d*); major isomer: 19.35 (*s*, Me₃C); 34.51 (*d*, C(8)); 36.51 (*d*, C(4)); 50.83 (*d*, C(1)); 65.01 (*t*, CH₂–C(8)); 214.91 (*s*, C(2)); minor isomer: 19.97 (*s*, Me₃C); 36.60 (*d*, C(8)); 38.15 (*d*, C(4)); 50.59 (*d*, C(1)); 65.63 (*t*, CH₂–C(8)); 214.10 (*s*, C(2)). HR-ESI-MS: 447.1957 ([*M* + Na]⁺, C₂₅H₃₂NaO₄Si⁺; calc. 447.1968). Anal. calc. for C₂₅H₃₂O₄Si (424.61): C 70.72, H 7.60; found: C 70.55, H 7.67.

(*IRS,2SR,6RS,7RS,10SR*)- and (*IRS,2RS,6SR,7RS,10RS*)-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 CH₂Cl₂ (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 (CHCl₃): 2933m, 1961w, 1894w, 1823w, 1729s, 1602w, 1472w, 1428m, 1089s. ¹H-NMR (500 MHz, CDCl₃; 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 (*2s*, Me₂–

C(4)); 1.77 (*td*, $J=14.3, 3.3$, irradi. at 4.40 → NOE of 3.3%, H'–C(11)); 1.88–1.96 (*m*, irradi. 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*, $J\approx 3.2$, H–C(7)); 2.60–2.61 (*m*, irradi. at 4.29 → NOE of 5.1%, irradi. at 4.40 → NOE of 5.0%, H–C(1)); 3.56 (*dd*, $J=10.3, 9.2$), 3.64 (*dd*, $J=10.3, 6.0$) (CH₂–C(10)); 4.29 (*ddd*, $J=7.8, 3.7, 1.3$, irradi. at 1.35 → NOE of 1.7%, H–C(2)); 4.40 (*dd*, $J=7.7, 3.8$, irradi. at 1.35 → NOE of 1.6%, H–C(6)); 7.30–7.78 (*m*, 10 arom. H). ¹³C-NMR (125 MHz, CDCl₃; assignment based on a HSQC spectrum): 19.23 (*s*, Me₃C); 22.62 (*t*, C(11)); 23.96, 25.64 (2*q*, Me₂C(4)); 26.86 (*q*, Me₃C); 33.18 (*d*, C(1)); 33.57 (*t*, C(9)); 34.08 (*d*, C(10)); 48.06 (*d*, C(7)); 65.00 (*t*, CH₂–C(10)); 75.64 (*d*, C(2)); 76.90 (*d*, C(6)); 108.68 (*s*, C(4)); 127.80 (*4d*); 129.86 (*4d*); 133.32 (2*s*); 135.53 (*4d*); 212.06 (*s*, C(8)). HR-ESI-MS: 487.2267 ([*M*+Na]⁺, C₂₈H₃₆NaO₄Si⁺; calc. 487.2281). Anal. calc. for C₂₈H₃₆O₄Si (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 (CHCl₃): 2933*m*, 1962*w*, 1894*w*, 1829*w*, 1729*s*, 1602*w*, 1472*m*, 1428*m*, 1384*m*, 1110*s*. ¹H-NMR (500 MHz, CDCl₃; 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*, irradi. at 4.29 → NOE of 2.9%, Me–C(4)); 1.55 (*s*, Me–C(4)); 1.88 (br. *dt*, $J=19.6, 1.6$, irradi. 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*, irradi. at 4.29 → NOE of 3.1%, H–C(1), H–C(10)); 2.62 (br. *q*, $J\approx 3.4$, irradi. at 4.29 → NOE of 3.1%, H–C(7)); 3.48 (*dd*, $J=10.4, 8.6$), 3.59 (*dd*, $J=10.4, 5.7$) (CH₂–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). ¹³C-NMR (125 MHz, CDCl₃; assignment based on a HSQC and a HMBC spectrum): 19.25 (*s*, Me₃C); 20.01 (*t*, C(11)); 24.17, 25.64 (2*q*, Me₂C(4)); 26.90 (*q*, Me₃C); 28.54 (*d*, C(10)); 33.75 (*d*, C(1)); 36.25 (*t*, C(9)); 48.04 (*d*, C(7)); 65.66 (*t*, CH₂–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]⁺, C₂₈H₃₆NaO₄Si⁺; calc. 487.2281). Anal. calc. for C₂₈H₃₆O₄Si (464.68): C 72.37, H 7.81; found: C 72.19, H 7.89.

(*IRS*, 2*SR*, 6*RS*, 7*RS*, 1*IRS*)-11-[[*tert*-Butyl]diphenylsilyloxy]methyl]-4,4-dimethyl-3,5-dioxo-8-azatricyclo[5.3.2.0^{2,6}]dodecan-9-one (**15**). A soln. of **12** (1 g, 2.2 mmol), NH₂OH·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 CH₂Cl₂ (30 ml) and H₂O (20 ml). The aq. layer was extracted with CH₂Cl₂ (3 × 20 ml). The combined org. layers were dried (Na₂SO₄), 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. ¹H-NMR (300 MHz, CDCl₃): 1.04 (*s*, *t*-Bu); 1.12 (*ddd*, $J=14.0, 5.9, 3.1$, H–C(11)); 1.35, 1.43 (2*s*, Me₂C(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*, $J=10.3, 6.2$) (CH₂–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 Ph₃P' (2.6 g, corresp. to 4.3 mmol Ph₃P) in CCl₄ (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. NaHCO₃ soln. (20 ml) and CH₂Cl₂ (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 CH₂Cl₂ (4 × 20 ml). The combined org. layers were dried (Na₂SO₄) 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 (CHCl₃): 3411*w*, 2933*m*, 1962*w*, 1894*w*, 1829*w*, 1657*w*, 1471*m*, 1428*w*, 1384*w*, 1211*m*, 1112*s*. ¹H-NMR (400 MHz, CDCl₃; assignment based on a DQF-COSY spectrum): 1.04 (*s*, *t*-Bu); 1.40, 1.49 (2*s*, Me₂C(4)); 1.60 (br. *ddd*, $J\approx 12, 6.0, 1.3$, H–C(12)); 1.87–1.98 (*m*, H–C(11), H'–C(12)); 2.47 (br. *d*, $J\approx 20$, H–C(10)); 2.62–2.70 (*m*, H–C(1), H'–C(10)); 3.25–3.29 (*m*, addn. of CD₃OD → br. *t*, $J\approx 4.8$, H–C(7)); 3.61 (*dd*, $J=10.3, 8.7$), 3.68 (*dd*, $J=10.6, 5.7$) (CH₂–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 CD₃OD, NH); 7.36–7.70 (*m*, 10 arom. H). ¹³C-NMR (100 MHz, CDCl₃): 19.24 (*s*, Me₃C); 24.83, 26.86 (2*q*, Me₂C(4)); 26.86 (*q*, Me₃C); 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*, CH₂–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]⁺, C₂₈H₃₇NNaO₄Si⁺; calc. 502.2390). Anal. calc. for C₂₈H₃₇NO₄Si (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 Et₂O by slow evaporation at r.t. C₂₈H₃₇NO₄Si (479.69); monoclinic; $a = 7.7838(3)$ Å, $b = 36.4362(2)$ Å, $c = 9.6051(9)$ Å; $\beta = 104.096(2)^\circ$; $V = 2642(3)$ Å³; $D_{\text{calc}} = 1.206$ Mg/m³; $Z = 4$. 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].

(*IRS,2SR,6RS,7RS,1ISR*)-8-Benzyl-11-[[*(tert-butyl)diphenylsilyloxy*]methyl]-4,4-dimethyl-3,5-dioxo-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 'BuOK (125 mg, 1.1 mmol), stirred until 'BuOK had dissolved, treated with BnBr (3 g, 17 mmol), stirred for 22 h at 21°, treated with sat. aq. NH₄Cl soln. (30 ml), and extracted with CHCl₃ (1 × 30 ml) and CH₂Cl₂ (4 × 10 ml). The combined org. layers were dried (MgSO₄) and evaporated. FC (hexane/AcOEt 2:1) gave **16** (452 mg, 91%). Colourless foam. R_f (cyclohexane/AcOEt 2:1) 0.47. ¹H-NMR (300 MHz, CDCl₃): 1.03 (s, *t*-Bu); 1.22–1.28 (*m*, H–C(12)); 1.40, 1.48 (2s, Me₂C(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*, $J \approx 4.4$, H–C(7)); 3.58 (*d*, $J = 6.3$, CH₂–C(11)); 3.68 (*d*, $J = 15.1$, 5.60 (*d*, $J = 14.8$) (PhCH₂); 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). ¹³C-NMR (75 MHz, CDCl₃): 19.46 (s, Me₃C); 25.07, 26.31 (*q*, Me₂C(4)); 27.08 (*q*, Me₂C); 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*, CH₂–C(11)); 75.97, 76.20 (*2d*, C(2), C(6)); 76.89 (*t*, PhCH₂); 110.28 (s, C(4)); 127.42 (*d*); 128.01 (*2d*); 128.10 (*2d*); 128.47 (*2d*); 128.71 (*2d*); 130.06, 130.14 (*2d*); 133.41, 133.59 (2s); 135.74 (*2d*); 135.72 (*2d*); 137.98 (s); 171.89 (s, C(9)). HR-ESI-MS: 570.3025 ($[M+H]^+$, C₃₅H₄₄NO₄Si⁺; calc. 570.3040). Anal. calc. for C₃₅H₄₃NO₄Si (569.81): C 73.78, H 7.61, N 2.46; found: C 73.65, H 7.50, N 2.52.

(*IRS,2SR,6RS,7RS,1ISR*)-8-Benzyl-11-[[*(tert-butyl)diphenylsilyloxy*]methyl]-4,4-dimethyl-3,5-dioxo-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 BH₃·SMe₂ soln. in THF (1.3 ml, 2.6 mmol), stirred at 65° for 5 h, cooled to 0°, treated dropwise with N(CH₂CH₂OH)₃ (0.45 g, 3 mmol), stirred vigorously at 65° for 70 min, cooled to 23°, and treated with H₂O (5 ml) and 1N NaOH soln. (2 ml). The mixture was extracted with Et₂O (1 × 10 ml, 2 × 5 ml). The combined org. layers were dried (Na₂SO₄) and evaporated. FC (hexane/AcOEt/Et₃N 5:1:0.01) yielded **17** (116 mg, 79%). Colourless thick oil. R_f (cyclohexane/AcOEt 2:1) 0.69. IR (CHCl₃): 3011s, 1962w, 1894w, 1825w, 1732w, 1603w, 1588w, 1472w, 1428m, 1372m, 1112s. ¹H-NMR (400 MHz, CDCl₃, 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 (2s, Me₂C(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 (*ddd*, $J = 8.7, 5.8, 2.9$, H–C(1)); 2.63 (*br. td*, $J = 11.8, 5.5$, H'–C(9)); 3.14 (*br. t*, $J \approx 4.5$, H–C(7)); 3.66 (s, PhCH₂); 3.69 (*d*, $J = 7.7$, CH₂–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). ¹³C-NMR (100 MHz, CDCl₃; assignment based on a HSQC and a HMBC spectrum): 19.28 (s, Me₃C); 22.48 (*t*, C(10)); 23.77 (*t*, C(12)); 24.68, 26.14 (2*q*, Me₂C(4)); 26.89 (*q*, Me₂C); 33.56 (*d*, C(1)); 36.44 (*d*, C(11)); 46.79 (*t*, C(9)); 57.91 (*d*, C(7)); 63.49 (*t*, PhCH₂); 65.50 (*t*, CH₂–C(11)); 77.05 (*d*, C(2)); 77.28 (*d*, C(6)); 108.42 (s, C(4)); 126.58 (*d*); 127.68 (*4d*); 127.94 (*2d*); 128.74 (*2d*); 129.64, 129.66 (*2d*); 133.80, 133.89 (2s); 135.60 (*4d*); 140.47 (s). HR-ESI-MS: 556.3230 ($[M+H]^+$, C₃₅H₄₆NO₃Si⁺; calc. 556.3247). Anal. calc. for C₃₅H₄₅NO₃Si (555.83): C 75.63, H 8.16, N 2.52; found: C 75.55, H 8.25, N 2.48.

(*IRS,2SR,6RS,7RS,1ISR*)-8-Benzyl-4,4-dimethyl-3,5-dioxo-8-azatricyclo[5.3.2.0^{2,6}]dodecane-11-methanol (**18**). A suspension of **17** (485 mg, 0.27 mmol) and NH₄F (800 mg, 21.5 mmol) in MeOH (20 ml) was warmed to 50° for 16 h and evaporated. A suspension of the residue in CH₂Cl₂ (10 ml) was filtered through cotton, and the solid was washed with CH₂Cl₂ (2 × 5 ml). Evaporation of the filtrate and FC (hexane/AcOEt/NEt₃ 1:2:0.1 → 1:2:0.2) gave **18** (265 mg, 96%). Colourless glass. R_f (cyclohexane/AcOEt/NEt₃ 1:2:0.1) 0.37. IR (CHCl₃): 3618w, 2934s, 1953w, 1890w, 1820w, 1606w, 1494w, 1453w, 1371m, 1207s. ¹H-NMR (300 MHz, CDCl₃): 1.39, 1.66 (2s, Me₂C(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 D₂O, 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*, $J \approx 4.7, 2.2$, H–C(7)); 3.69 (*d*, $J = 7.2$, CH₂–C(11)); 3.74 (s, PhCH₂); 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). ¹³C-NMR (75 MHz,

CDCl₃): 22.79 (*t*, C(10)); 24.53 (*t*, C(12)); 24.66, 26.23 (*2q*, Me₂C(4)); 34.17 (*d*, C(1)); 36.38 (*d*, C(11)); 46.83 (*t*, C(9)); 57.60 (*d*, C(7)); 63.67 (*t*, PhCH₂); 64.83 (*t*, CH₂–C(11)); 76.73 (*d*, C(2)); 77.16 (*d*, C(6)); 104.47 (*s*, C(4)); 126.66 (*d*); 127.96 (*2d*); 128.75 (*2d*); 140.00 (*s*). HR-ESI-MS: 318.2069 ([*M*+H]⁺, C₁₉H₂₈NO₃⁺; calc. 318.2069). Anal. calc. for C₁₉H₂₇NO₃ (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 2*N* HCl (11 ml) and stirred for 36 h at 21°. After evaporation of the solvent, a soln. of the residue in H₂O (2 ml) was brought to pH 8 with 2*N* NaOH. Evaporation and FC (CH₂Cl₂/MeOH/25% aq. NH₃ 10:0.75:0.2) gave **19** (203 mg, 90%). Colourless oil. *R*_f (CH₂Cl₂/MeOH/25% aq. NH₃ 10:0.75:0.2) 0.37. p*K*_a 9.92. IR (KBr): 3412*s* (br.), 2921*s*, 1954*w*, 1881*w*, 1814*w*, 1747*w*, 1638*w*, 1451*s*, 1070*s*. ¹H-NMR (300 MHz, CD₃OD): 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), CH₂–C(9)); 7.20–7.34 (*m*, 5 arom. H). ¹³C-NMR (75 MHz, CD₃OD): 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*, PhCH₂); 64.81 (*t*, CH₂–C(9)); 66.82 (*d*, C(6)); 71.94 (*d*, C(7)); 128.02 (*d*); 129.06 (*2d*); 129.94 (*2d*); 139.38 (*d*). HR-ESI-MS: 278.1747 ([*M*+H]⁺, C₁₆H₂₄NO₃⁺; calc. 278.1756). Anal. calc. for C₁₆H₂₃NO₃ (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-Azonio-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 6*N* HCl (7.5 ml) was hydrogenated for 20 h at 21° under 6 bar of H₂, filtered through a pad of Celite (washing with 10 ml of H₂O/MeOH 1:1), and taken to dryness. A soln. of the residue in H₂O (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*. ¹H-NMR (400 MHz, D₂O; 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, CH₂–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)). ¹³C-NMR (75 MHz, D₂O): 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 (CH₂–C(9)); 64.70, 67.76 (C(6), C(7)). ESI-MS: 188.2 (100, [*M*+H]⁺). Anal. calc. for C₉H₁₈ClNO₃ (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. C₉H₁₈ClNO₃ (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) Å³; *D*_{calc.} = 1.412 Mg/m³; *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).

REFERENCES

- [1] I. Tews, A. Perrakis, A. Oppenheim, Z. Dauter, K. S. Wilson, C. E. Vorgias, *Nat. Struct. Biol.* **1996**, *3*, 638; G. Sulzenbacher, H. Driguez, B. Henrissat, M. Schülein, G. J. Davies, *Biochemistry* **1996**, *35*, 15280; G. J. Davies, M. Dauter, A. M. Brzozowski, M. E. Bjørnvaad, K. V. Andersen, M. Schülein, *Biochemistry* **1998**, *37*, 1926; D. M. F. van Aalten, D. Komander, B. Synstad, S. Gaseidnes, M. G. Peter, V. G. H. Eijssink, *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 8979; S. Fort, A. Varrot, M. Schülein, S. Cottaz, H. Driguez, G. J. Davies, *ChemBioChem* **2001**, *2*, 319.
- [2] L. Hosie, M. L. Sinnott, *Biochem. J.* **1985**, *226*, 437; A. J. Bennet, M. L. Sinnott, *J. Am. Chem. Soc.* **1986**, *108*, 7287; Y. L. Zhang, J. Bommuswamy, M. L. Sinnott, *J. Am. Chem. Soc.* **1994**, *116*, 7557.

- [3] G. Legler, *Adv. Carbohydr. Chem. Biochem.* **1990**, 48, 319; J. D. McCarter, S. G. Withers, *Curr. Opin. Struct. Biol.* **1994**, 4, 885; T. D. Heightman, A. T. Vasella, *Angew. Chem., Int. Ed.* **1999**, 38, 750; C. S. Rye, S. G. Withers, *Curr. Opin. Chem. Biol.* **2000**, 4, 573; V. H. Lillielund, H. H. Jensen, X. F. Liang, M. Bols, *Chem. Rev.* **2002**, 102, 515; A. Vasella, G. J. Davies, M. Böhm, *Curr. Opin. Chem. Biol.* **2002**, 6, 619; H. Yuasa, C. Saotome, O. Kanie, *Trends Glycosci. Glycotechnol.* **2002**, 14, 231; V. L. Schramm, *Acc. Chem. Res.* **2003**, 36, 588.
- [4] P. Deslongchamps, *Pure Appl. Chem.* **1975**, 43, 351; A. J. Kirby, R. J. Martin, *J. Chem. Soc., Chem. Commun.* **1978**, 803; A. J. Kirby, R. J. Martin, *J. Chem. Soc., Chem. Commun.* **1979**, 1079; P. Deslongchamps, 'Stereo-electronic Effects in Organic Chemistry', Pergamon Press, Oxford, 1983; S. G. Li, A. J. Kirby, P. Deslongchamps, *Tetrahedron Lett.* **1993**, 34, 7757.
- [5] F. Vincent, T. M. Gloster, J. Macdonald, C. Morland, R. V. Stick, F. M. V. Dias, J. A. M. Prates, C. Fontes, H. J. Gilbert, G. J. Davies, *ChemBioChem* **2004**, 5, 1596.
- [6] M. Böhm, A. Vasella, *Helv. Chim. Acta* **2004**, 87, 2566.
- [7] S. Buser, A. Vasella, *Helv. Chim. Acta* **2005**, 88, 3151.
- [8] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, 11, 440.
- [9] G. Grädnig, A. Berger, V. Grassberger, A. E. Stütz, G. Legler, *Tetrahedron Lett.* **1991**, 32, 4889.
- [10] W. H. Pearson, E. J. Hembre, *J. Org. Chem.* **1996**, 61, 5537.
- [11] G. Legler, in 'Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond', Ed. A. E. Stütz, Wiley-VCH, Weinheim, 1999.
- [12] H. K. Hall, *J. Am. Chem. Soc.* **1960**, 82, 1209.
- [13] C.-S. Chu, T.-H. Lee, P. D. Rao, L.-D. Song, C.-C. Liao, *J. Org. Chem.* **1999**, 64, 4111.
- [14] C. Hurd, H. Greengard, F. Pilgrim, *J. Am. Chem. Soc.* **1930**, 52, 1700; K. Hollmann, M. Ecker, *Z. Chem.* **1989**, 29, 63; G. Foulard, T. Brigaud, C. Portella, *Tetrahedron* **1996**, 52, 6187; G. C. R. Ellis-Davies, *Tetrahedron Lett.* **1998**, 39, 953; R. Mamouni, M. Soukri, S. Lazar, M. Akssira, G. Guillaumet, *Tetrahedron Lett.* **2004**, 45, 2631.
- [15] T.-H. Lee, C.-C. Liao, *Tetrahedron Lett.* **1996**, 37, 6869.
- [16] S. Hanessian, P. Lavallée, *Can. J. Chem.* **1975**, 53, 2975.
- [17] V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, 23, 1973.
- [18] P. A. Grieco, *J. Org. Chem.* **1977**, 42, 3772.
- [19] R. M. Waters, N. Wakabayashi, E. S. Fields, *Org. Prep. Proced. Int.* **1974**, 6, 53.
- [20] H. C. Brown, Y. M. Choi, S. Narasimhan, *J. Org. Chem.* **1982**, 47, 3153.
- [21] L. Czollner, J. Kuszmann, A. Vasella, *Helv. Chim. Acta* **1990**, 73, 1338.
- [22] W. J. Zhang, M. J. Robins, *Tetrahedron Lett.* **1992**, 33, 1177.
- [23] M. Böhm, E. Lorthiois, M. Meyyappan, A. Vasella, *Helv. Chim. Acta* **2003**, 86, 3787.
- [24] D. Cremer, J. A. Pople, *J. Am. Chem. Soc.* **1975**, 97, 1354.
- [25] M. N. Namchuk, S. G. Withers, *Biochemistry* **1995**, 34, 16194.
- [26] G. M. Sheldrick, 'SHELXL-97, Program for the Refinement of Crystal Structures', Universität Göttingen, Germany, 1997.
- [27] M. Böhm, E. Lorthiois, M. Meyyappan, A. Vasella, *Helv. Chim. Acta* **2003**, 86, 3818.
- [28] M. Terinek, A. Vasella, *Helv. Chim. Acta* **2004**, 87, 3035.

Received October 19, 2005