Electrophilic Bromination of *N*-Acylated Cyclohex-3-en-1-amines: Synthesis of 7-Azanorbornanes

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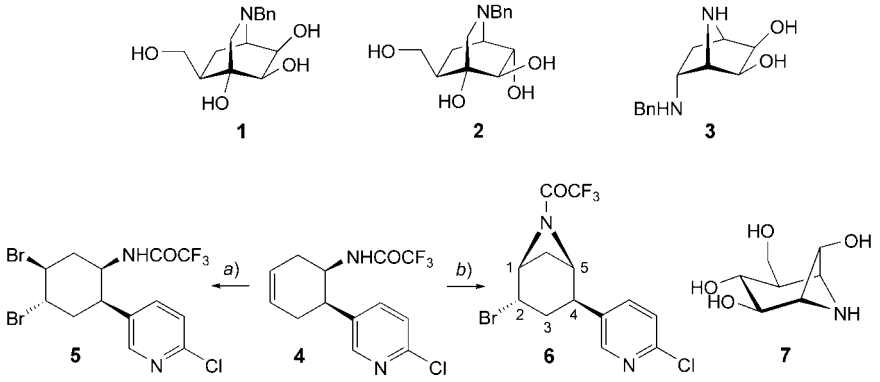
The intramolecular bromo-amidation and the dibromination-cyclisation of the *N*-acylcyclohex-3-en-1-amines **4**, **8**, **9**, **11**, **13**, **14**, and **16** was studied in view of the synthesis of bicyclic amines that are of interest as building blocks and potential glycosidase inhibitors. The trifluoroacetamides **4**, **9**, and **14** reacted with *N*-bromosuccinimide (NBS) in AcOH to give dihydro-1,3-oxazines in good yields. The stereoselectivity of the dibromination of the alkenes **8** and **9** depends on the nature of the protecting group, the reagent, and the reaction conditions. Br_2 in CH_2Cl_2 transformed the alkenes **8** and **9** predominantly into diaxial *trans*,*trans*-dibromides. Bromination of **9** with $PhMe_3NBr_3$ or with Br_2 in the presence of Et_4NBr gave predominantly the diequatorial *trans*,*cis*-**27** besides some *trans*,*trans*-**28**. A similar bromination of the *C(5)*-substituted *N*-acyl-4-aminocyclohexenes **11**, **13**, **14**, and **16** with $PhMe_3NBr_3$ was accompanied by intramolecular side reactions that were suppressed by the addition of excess Et_4NBr. Under these conditions, **11** gave diastereoselectively *trans*-dibromides, while its reaction with Br_2 gave *trans*-dibromides along with the dihydrooxazinone **31**. Also the carbamate **13** reacted with $PhMe_3NBr_3/Et_4NBr$ selectively to the *trans*-dibromide **32** and with Br_2 to the *trans*-dibromides **32** and **33**, the dihydrooxazinone **34**, and the bicyclic ether **35**. Similarly, the trifluoroacetamide **14** provided the dibromide **36** (89%), while its reaction with Br_2 led to the dihydrooxazine **22**, and the dibromides **36** and **37**. The *N*-benzyl-*N*-Boc derivative **16** did not yield any dibromide; it reacted with $PhMe_3NBr_3/Et_4NBr$ to the dihydrooxazinone **38**, and with Br_2 to the oxazinone **38** and the bicyclic ether **39**. The high stereoselectivity of the bromination with $PhMe_3NBr_3/Et_4NBr$ suggests an anchimeric assistance of the NHR substituent. Deprotection, cyclisation, and carbamoylation transformed the dibromides **27**, **29**, and **32** into the 7-azanorbornanes **42**, **49**, and **53**. The diols **45** and **57** were obtained from **42** and **53** *via* HBr elimination and stereoselective dihydroxylation; they proved weak inhibitors of several glycosidases. In no case could the formation of a bicyclic azetidine (6-azabicyclo[3.1.1]heptane) from the dibromides **26** and **30** be observed.

Introduction. – According to the principle of stereoelectronic control, hydrolysis of glycopyranosides with an equatorial aglycon requires an *anti*- or *syn*-periplanar arrangement of a C(5)O lone pair and the scissile bond and, thus, a distortion of the ground-state chair conformation [1][2]. Substrates or inhibitors adopting such a conformation have been observed in the crystal structure of their complexes with several β-glycosidases (see [3] and refs. cit. therein), and *Varrot et al.* have postulated that all conformations satisfying this stereoelectronic requirement are harnessed by one or the other glycosidase [4]. Mimics of the corresponding conformers are of interest as potential glycosidase inhibitors. The calystegines, hydroxylated 8-azabicyclo[3.2.1]octanes isolated from *Calystegia sepium* and other species, are competitive inhibitors of several α- and β-glycosidases (K_i values ranging from 0.8 to 200 μM [5]). The binding mode of the calystegines has not yet been determined. They may bind as mimics of isofagomine that adopts a $^4C_1$ conformation, but they may as well adopt a distorted chair conformation. The isoquinuclidine **1**, a 2-azabicyclo[2.2.2]octane (*Scheme 1*), mimicking a slightly distorted $^{1,4}B$ conformer of a β-D-mannopyranoside inhibits selectively snail β-mannosidase ($K_i = 1.0$ μM at pH 4.5, mixed type inhibition) [3],

while the analogous mimic **2** of a β-D-glucopyranoside is a very poor inhibitor of several β-glucosidases [6][1]); these observations have been taken as evidence that the enzymatic hydrolysis of β-D-glucopyranosides and β-D-mannopyranosides proceed *via* different reactive conformations [3][6]. The high inhibitory selectivity of the isoquinuclidines **1** and **2** shows that bicyclic hydroxylated amines mimicking reactive conformations of β-D-glycopyranosides are attractive as potential glycosidase inhibitors.

Scheme 1



a) Br_2, Et_4NBr, CH_2Cl_2; 89% [11]. *b*) NBS, AcOH; 85% [11].

In the context of a synthesis of epibatidine [10], a 7-azabicyclo[2.2.1]heptane, *Corey et al.* reported the formation of a bicyclic azetidine **6**, a 6-azabicyclo[3.1.1]heptane in a yield of 85% upon treatment of the trifluoroacetamide **4** with NBS in AcOH [11] (*Scheme 1*). This transformation attracted our interest, since azetidines such as **7** are of interest as potential glycosidase inhibitors. The postulated transformation of **4** to **6** is remarkable. It postulates an *N*- rather than an *O*-alkylation of an amide by a *bona fide* epibromonium ion, and an *N*-alkylation leading to a four- rather than to a five-membered ring, *i.e.*, to a 6-azabicyclo[3.1.1]heptane rather than to a 7-azabicyclo[2.2.1]heptane[2]). 6-Azabicyclo[3.1.1]heptanes and 7-azanorbornanes (=7-azabicyclo[2.2.1]heptanes) are both of interest as potential glycosidase inhibitors.

6-Azabicyclo[3.1.1]heptane was prepared in low yield by cyclisation of *trans*-3-bromocyclohexylamine in $NaOH/H_2O$ [14]. 6-Azabicyclo[3.1.1]heptanes were also prepared by intramolecular nucleophilic substitution of a *trans*-3-bromocyclohexyl-

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[1]) An attempt to mimic the axial orientation of the glycosidic bond in a distorted β-D-glucopyranoside by an iminosugar in the $^1C_4$ conformation resulted in a weak ($K_i = 200$ μM) inhibitor of the Cel7B endocellulase from *Humicola insolens* (family 7) [7], and 2,6-anhydro-1-deoxynojirimycin mimicking the $^{2,5}B$ conformation involved in the enzymatic hydrolysis of α-D-glucopyranosides [8] is a very weak inhibitor of several α- and β-glycosidases [9].

[2]) As a rule, electrophilic cyclisations of *N*-alkenylated amides involve the carbonyl O-atom and lead to oxazolines and dihydrooxazines [12]. In keeping with this rule, *N*-cyclohex-3-enylbenzamide cyclised to a bicyclic dihydro-1,3-oxazine upon treatment with NBS in AcOH [13]. The formation of cyclic amides by *N*-alkylation is preferred if *O*-alkylation would lead to a strained product, or if the NH group is deprotonated [12].

amine (83% yield) [15], a *trans*-3-[(methylsulfonyl)oxy]cyclohexylamine (22%) [16], and a *trans*-3-azidocyclohexanol (24%) [17]. 7-Azanorbornanes and 7-azanorbornenes were synthesised by *Diels–Alder* and 1,3-dipolar cycloadditions, by cyclisation of cyclohexylamines and pyrrolidines, and by ring contraction of tropinone derivatives [18–22]. The cycloadditions gave 7-azanorbornanes in a single step, but required high pressure [23][24] or particularly reactive dienophiles and dienes [25–32] to ensure sufficiently high yields; intramolecular substitution of cyclohexylamines remains a competitive route to 7-azanorbornanes [33–51]. Of particular interest for our purpose was the highly stereoselective bromination of the aminocyclohexene **4** to the dibromide **5** and its base-catalysed cyclisation [11]. Similarly, 2-*exo*-chloro-*N*-methyl-7-azanorbornane was synthesised by chlorination of *N*-methylcyclohex-3-enylamine, yielding a 1:1 mixture of the epimeric 3,4-*trans*-dichlorocyclohexylamines, followed by cyclisation of the 1,4-*trans*-isomer [52]. The only 7-azanorbornanes known to act as glycosidase inhibitors are both enantiomers of the amino diol **3**. They were prepared by *Vogel et al.* as rigid analogues of 2-(aminomethyl)pyrrolidines, known glycosidase inhibitors [25], but proved weaker inhibitors than the conformationally flexible 2-(aminomethyl)pyrrolidines.

The potential of bicyclic amines to act as glycosidase inhibitors prompted us to examine the bromocyclisation and dibromination-cyclisation of the *N*-acylcyclohex-3-en-1-amines **8**, **9**, **11**, **13**, **14**, and **16** (*Scheme 2*) and the effect on the cyclisation of the nature of the *N*-acyl group, of a substituent at C(5), and of the brominating agent.

Results and Discussion. – The cyclohexenes **8** [53][54] and **9** [55] were prepared by *Curtius* rearrangement of commercial cyclohex-3-enecarboxylic acid and treatment of the resulting isocyanate with *t*-BuOH and CuCl [56] or with CF_3COOH [55]. This one-pot procedure yielded 92% of **8** and 84% of **9**[3]) (*Scheme 2*).

The racemic *C(5)*-substituted *N*-acylcyclohex-3-en-1-amines **11**, **13**, **14**, and **16** were prepared from the monoester **10** [57] (*Scheme 2*). *Curtius* rearrangement of the monoacid **10** and treatment of the resulting isocyanate with *t*-BuOH and CuCl [56] gave the *β*-amino-acid derivative **11** (90%), which was reduced to the alcohol **12** (74%). Treating the dianion of **12** with 1.0 equiv. of BnBr (*cf.* [58–60]) yielded 95% of the benzyl ether **13** besides 5% of the dihydro-1,3-oxazin-2-one **15**; the dianion was generated by adding **12** to a suspension of 2.0 equiv. of NaH in DMF. Inverse addition of 1.2 equiv. of NaH to **12** in DMF, followed by treatment with 1.5 equiv. of BnBr, gave **13** (55%), **15** (33%), and the *N*,*O*-dibenzyl derivative **16** (12%). The trifluoroacetamide **14** was obtained in a yield of 84% by deprotection of the carbamate **13** with CF_3COOH, followed by acylation.

We first examined the transformation of the unsaturated trifluoroacetamides **9**, **14**, and **4** with *N*-bromosuccinimide (NBS) in AcOH, *i.e.*, under the conditions described by *Corey et al.* [11], but at 10° rather than 0° to avoid freezing of AcOH (*Scheme 2*). Under these conditions, the trifluoroacetamide **9** reacted to give the dihydro-1,3-

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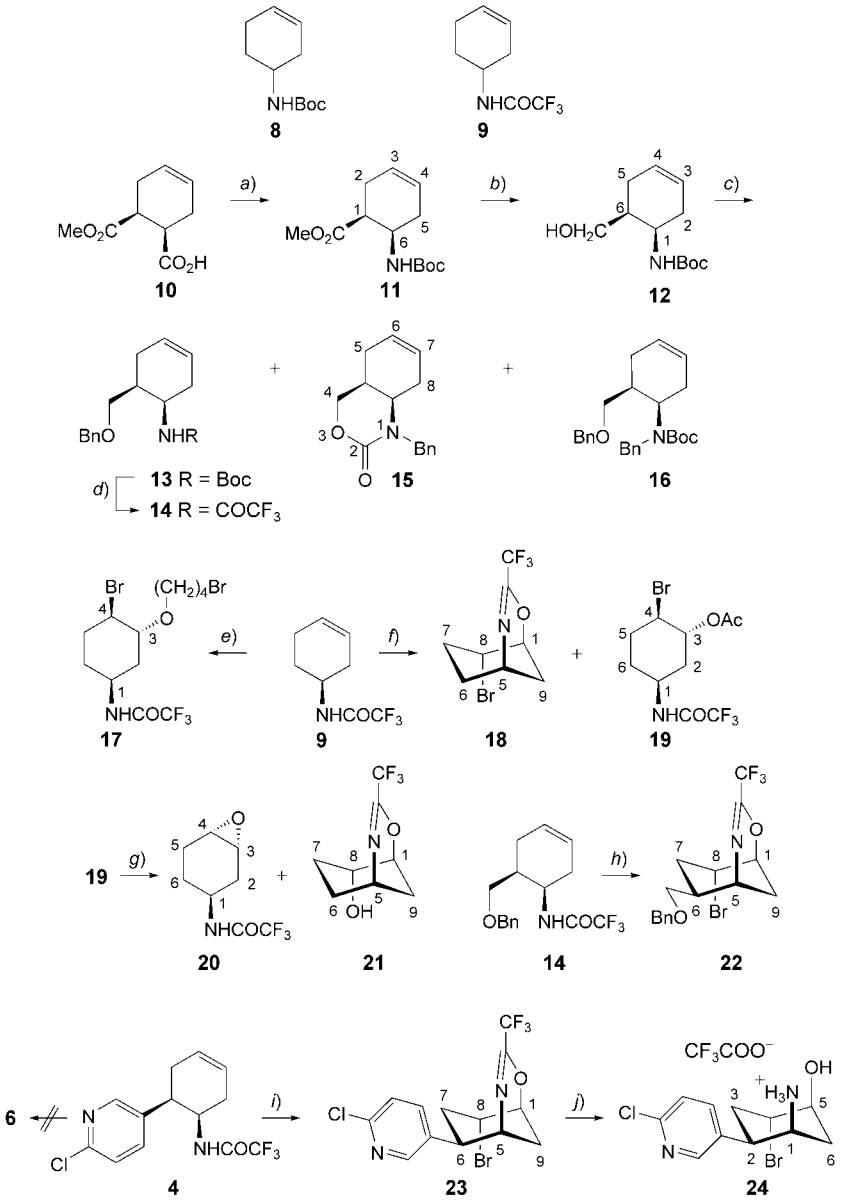
[3]) The synthesis of **9** from cyclohex-3-enecarbonyl chloride required isolation of the reactive acyl azide and proceeded in a yield of 86% [55].

Scheme 2



a) Diphenylphosphoryl azide (DPPA), Et_3N, toluene, then *t*-BuOH, CuCl; 90%. *b*) $LiBH_4$, THF; 74%. *c*) Addition of **12** to NaH in DMF, then BnBr; 95% of **13**, 5% of **15** *or* **12** in DMF, then NaH and BnBr; 12% of **16**, 55% of **13**, 33% of **15**. *d*) CF_3COOH, CH_2Cl_2; $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; 84%. *e*) *N*-Bromosuccinimide (NBS), THF; 31%. *f*) NBS, AcOH; 31% of **18**, 24% of **19**. *g*) **19**, NaH, THF; 28% of **20**, 33% of **21** *or* **19**, K_2CO_3, MeOH, H_2O; 89% of **21**. *h*) NBS, AcOH; 79%. *i*) NBS, AcOH; 81%. *j*) CF_3COOH, THF, H_2O; quant.

oxazine **18** (31%) and the bromo acetate **19** (24%)[4]). Treatment of **19** with NaH in THF gave the epoxide **20** (28%) and the dihydro-1,3-oxazine **21** (34%), which was obtained in higher yields (89%) by treatment of **19** with K_2CO_3 in $MeOH/H_2O$. Similarly, treatment of the trifluoroacetamide **14** with NBS in AcOH led to a dihydro-1,3-oxazine **22** that was readily isolated in a yield of 79%. Also the conformationally biased trifluoroacetamide **4** yielded 81% of the dihydro-1,3-oxazine **23** as a single product. Its ^{13}C-NMR data could not be distinguished from those reported by *Corey et al.* for their main product to which they assigned the structure **6**. Also the chemical-shift values for the ^{1}H-NMR signals of **23** (at 300 MHz) were indistinguishable from those reported by *Corey et al.* (NMR spectrum registered at 500 MHz). Coupling constants could not be compared as the resolution of the reported spectrum and the one registered by us appear to differ. To substantiate the contention that the cyclisation product possesses structure **23** rather than **6**, we hydrolysed the cyclisation product with aqueous CF_3COOH in THF and obtained the trifluoroacetate **24**$\cdot CF_3COOH$ in a nearly quantitative yield.

The coupling constants for the H–C(1) *td* of the carbamate **11** ($J(1,2) = J(1,2') = 6.2$ Hz, $J(1,6) = 3.1$ Hz) evidence an equilibrium between the $^1H_6$, $^6H_1$, $^{2,5}B$, and $B_{2,5}$ conformers[5]). The complexity of the NMR spectrum precluded a straightforward conformational analysis for **12**–**16**. $CH_2(4)$ of the dihydrooxazin-2-one **15** resonates as a *t* at 4.27 ppm ($J = 11.4$ Hz) and as a *ddd* at 4.13 ppm ($J = 10.6$, 4.7, 1.9 Hz) with the smallest coupling constant resulting from a *W* coupling with H–C(8a). Modelling shows that this is consistent only with a $^{4a}H_{8a}$ conformation of the carbocycle. The MS of the bromo ether **17** shows the presence of two Br substituents. The C(3) *d* resonates at 78.01 ppm, the C(1) and C(4) *d*s resonate at 49.38 and 44.74 ppm, resp. The 4-bromobutoxy substituent is evidenced by the C(1′) and C(4′) *t* at 68.81 and 33.69 ppm, resp., and by two additional *t* in the region between 30.68 and 26.54 ppm. The small coupling constants for the H–C(3) *q* (3.2 Hz) and the H–C(4) *q* (3.1 Hz) indicate the preferred axial orientation of the C(3) and C(4) substituents. In keeping with the relative configuration, the large width ($W_{1/2}$) of *ca.* 21 Hz for H–C(1) evidences that $NHCOCF_3$ is equatorial. The C(3) *d* of the bromo acetate **19** resonates at 71.96 ppm, and the C(1) and C(4) *d*s resonate at 47.53 and 44.75 ppm, resp. The coupling constants for the H–C(3) and H–C(4) *q* (both 3.4 Hz) and the $W_{1/2}$ of the H–C(1) *m* of *ca.* 20 Hz, very similar to those of **17**, evidence the same relative configuration of **17** and **19**. The chemical-shift values for the H–C(3) *m* (3.26–3.23 ppm) and the H–C(4) *td* (3.18 ppm), and the C(3) and C(4) *d*s (51.98 and 50.80 ppm) of **20** are typical of epoxides. The configuration of **20** is not strictly established, but derived from its mode of formation. The MS of the dihydro-1,3-oxazines **18**, **22**, and **23** show the presence of only one Br substituent. The IR C=N bands of **18**, **21**, **22**, and **23** at 1686, 1689, 1688, and 1688 cm^{-1}, resp., are in agreement with the dihydro-1,3-oxazine structure (see [62][63] for the IR spectra of related dihydro-1,3-oxazines). Only **21** shows an OH band, and none of the dihydro-1,3-oxazines give rise to an NH band. The chemical shift for the C(1) *d* of **18**, **21**, **22**, and **23** (73.8–74.5 ppm) evidences the dihydrooxazine and not the azetidine structure. These δ values are similar to those for C(6) of 2-(trifluoromethyl)- (78.6 and 75.7 ppm [64]), 2-methyl- (72.26 ppm [62]), and 2-phenyl-4,5-dihydro-6*H*-[1,3]oxazines (74.2 ppm [65]). The chemical-shift values for the C(5) and C(8) *d*s of the bromo-1,3-oxazines **18**, **22**, and **23** are similar to each other (46.7–51.3 ppm) and were not assigned separately. The C(5) and C(8) *d*s of the hydroxy-1,3-oxazine **21** resonate at 46.94 and 67.39 ppm, resp. For the azetidine **6**, one expects similar chemical-shift values for C(1) and C(5). ^{13}C-NMR Chemical-shift values for similar azetidine trifluoroacetamides have not been reported. The *C*–N *d* of a tricyclic *N*-acetylazetidine resonate at 62.8 and 60.6 ppm [66]. Similarly, the *C*–N *d* of *N*-acetyl-5-azabicyclo[2.1.1]hexane resonates at 63.0 ppm [67]. The identical $J(1,9) = J(5,9)$ values derived for the axial H–C(9) *dt* of **18**, **21**, **22**, and **23** (1.5–1.6 Hz) are in keeping with the bicyclic structure. A *W* coupling between H–C(8) and the equatorial

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[4]) NBS in THF transformed **9** mostly into the dibromo ether **17** (31%), resulting from solvent capture of the *bona fide* epibromonium ion.

[5]) Calculated coupling constants (Macromodel version 6.0, MM3* force field [61]) for $^1H_6$: $J(1,2) = 5.2$, $J(1,2') = 1.7$, $J(1,6) = 2.6$; for $^6H_1$: $J(1,2) = 4.7$, $J(1,2') = 11.9$, $J(1,6) = 2.1$; for $^{2,5}B$: $J(1,2) = 3.9$, $J(1,2') = 12.0$ Hz, $J(1,6) = 9.2$ Hz); for $B_{2,5}$: $J(1,2) = 4.2$, $J(1,2') = 2.2$, $J(1,6) = 9.0$ Hz.

H–C(9) (1.6–1.9 Hz) evidences that the Br substituent of **18**, **22**, and **23** is axial. For **21**, the small J(7ax,8) of 3.4 Hz evidences the axial orientation of HO–C(8). The large J(6,7ax) values for **22** and **23** (12.1 and 10.3 Hz, resp.) evidence that the $BnOCH_2$ and the pyridyl groups are equatorial. C(1) of **24** · F_3COOH resonates as a *d* at 68.14 ppm. The δ values for the C(3) and C(6) *d*s are similar to each other (51.09 and 50.29 ppm) and were not assigned separately. The small vicinal couplings for H–C(1) (*q*, 3.4 Hz) and H–C(6) (*qd*, 3.4 Hz) evidence the axial orientation of the Br and OH substituents. The identical coupling constants $J(1,2) = J(2,3) = 3.4$ Hz evidence the *cis*-configuration at C(1) and C(3). The large J(4,5ax) value of 12.1 Hz confirms the equatorial orientation of the pyridyl residue. The $^1C_4$ conformation of the cyclohexane is corroborated by the vicinal coupling constants.

Not unexpectedly, bromination of the (trifluoroacetamido)cyclohexenes **9** and **14** under conditions favouring anchimeric assistance provided neither azetidines nor 7-azanorbornanes. We, therefore, examined the dibromination of the *N*-acylcyclohex-3-en-1-amines **8**, **9**, **11**, **13**, **14**, and **16**, followed by intramolecular substitution of one of the Br substituents (*Scheme 3*). For this, we compared three reaction conditions: bromination with 2 equiv. of Br_2 in the presence of 10 equiv. of Et_4NBr (*cf.* [11]), bromination with 2 equiv. of $PhMe_3NBr_3$, and bromination with excess Br_2. The crude products were analysed by ^{1}H-NMR spectroscopy; pure products were only isolated in a few cases.

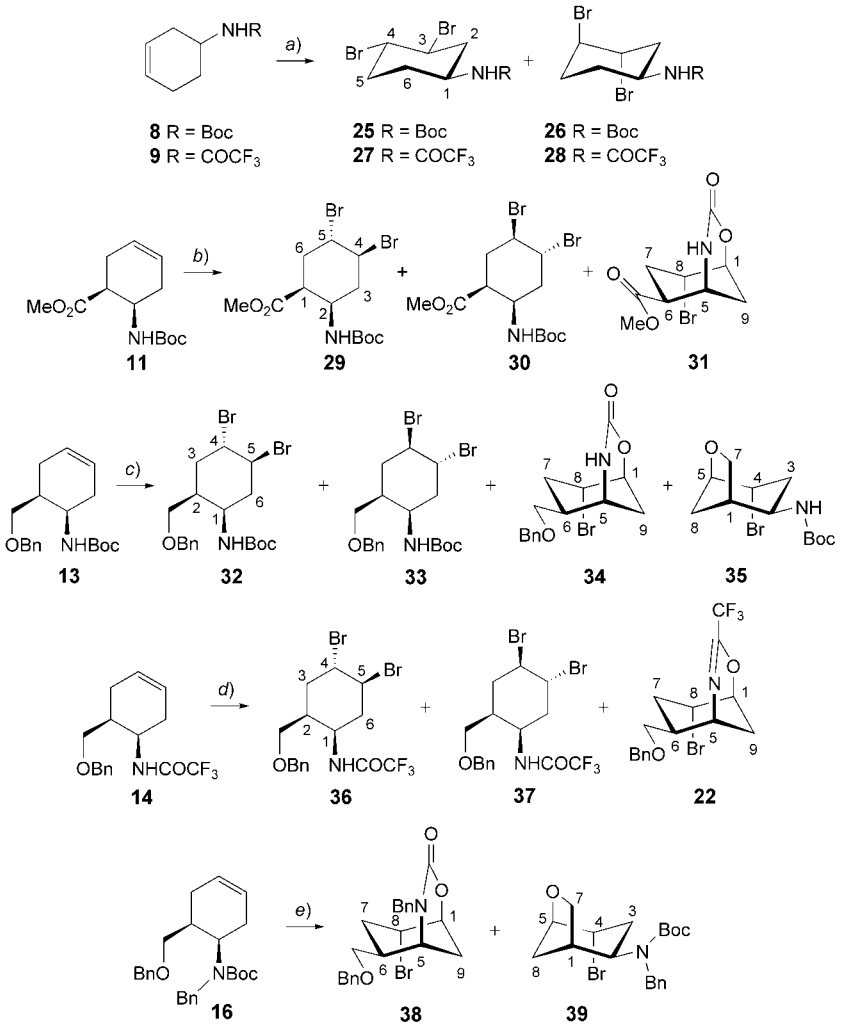
Bromination of **8** and **9** led to a mixture of the epimeric 3,4-*trans*-dibromocarbamates **25**/**26** and dibromoamides **27**/**28**, respectively. The stereoselectivity of the bromination depended on the nature of the *N*-protecting group and on the reaction conditions (*Table 1*). Bromination of the trifluoroacetamide **9** showed a greater tendency to provide the 1,4-*trans*-isomer than bromination of the carbamate **8**, as seen by comparing *Entries 11* to *1*, *12* to *2*, *13* to *5*, and *14* to *10*. The highest 1,4-*trans/cis* ratios (86:14 and 85:15) resulted from treating **9** with $PhMe_3NBr_3$ in CH_2Cl_2 at 0° (*Entry 13*) or with Et_4NBr and Br_2 in CH_2Cl_2 at −78° (*Entry 11*). The highest proportion of the 1,4-*trans*-isomer derived from **8** also resulted from bromination under these conditions (*Entries 1* and *5*). Conversely, the lowest 1,4-*trans/cis*-ratio (<1:9,

Table 1. *Stereoselectivity of the Dibromination of the Alkenes* **8** *and* **9**[a])

Entry	Starting material	Reagents	Solvent	Temp.	**25**/**26** or **27**/**28**
1	**8**	Et_4NBr, Br_2	CH_2Cl_2	−78°	57:43
2	**8**	Br_2	CH_2Cl_2	−78°	17:83
3	**8**	Br_2	Et_2O	−78°	<10:90
4	**8**	Br_2	Et_2O	0°	14:86
5	**8**	$PhMe_3NBr_3$	CH_2Cl_2	0°	43:57
6	**8**	$PhMe_3NBr_3$	$CHCl_3$	0°	37:73
7	**8**	$PhMe_3NBr_3$	Et_2O	0°	14:86
8	**8**	$PhMe_3NBr_3$	cyclohexane	r.t.	17:83
9	**8**	$PhMe_3NBr_3$	toluene	r.t.	25:75
10	**8**	$PhMe_3NBr_3$	MeCN	0°	*ca.* 40:60
11	**9**	Et_4NBr, Br_2	CH_2Cl_2	−78°	85:15
12	**9**	Br_2	CH_2Cl_2	−78°	23:77
13	**9**	$PhMe_3NBr_3$	CH_2Cl_2	0°	86:14
14	**9**	$PhMe_3NBr_3$	MeCN	0°	78:22

[a]) Conditions: 2 equiv. of Br_2. For Et_4NBr and Br_2, see the *Exper. Part* (*a*). For $PhMe_3NBr_3$, see the *Exper. Part* (*b*).

Scheme 3



a) See *Table 1*. *b*) Et_4NBr, Me_3PhNBr_3; 84% of **29**, 6% of **30** *or* Br_2, CH_2Cl_2; 28% of **29**, 30% of **30**, 36% of **31**. *c*) $PhMe_3NBr_3$, CH_2Cl_2; 46% of **32**, 49% of **34** *or* Br_2, CH_2Cl_2; 18% of **32**. 6% of **33**, 32% of **35**, 43% of **34** *or* Et_4NBr, $PhMe_3NBr_3$, CH_2Cl_2; 82% of **32**. *d*) Et_4NBr, $PhMe_3NBr_3$, CH_2Cl_2; 89% of **36** *or* Br_2, CH_2Cl_2; 19% of **22**, 42% of **36**, 32% of **37**. *e*) Br_2, CH_2Cl_2; 26% of **39**, 32% of **38**.

Entry 3) resulted from treating **8** with Br_2 in Et_2O at 0°. Among the conditions that were used for the dibromination of both **8** and **9**, Br_2 in CH_2Cl_2 led to the highest proportion of the 1,4-*cis*-isomer (*Entries 2* and *12*; 17:83 and 23:77, resp.). On a preparative scale (10 g), bromination of **9** with $PhMe_3NBr_3$ in CH_2Cl_2, followed by chromatography, led to 79% of **27** and 15% of **28**.

Bromination of the protected β-acylamino ester **11** in CH_2Cl_2 with 2 equiv. of $PhMe_3NBr_3$ in the presence of 10 equiv. of Et_4NBr gave the *trans*-dibromides **29** (84%)

and **30** (6%). Br_2 in CH_2Cl_2 led to lower yields of **29** (28%) and **30** (30%), and also yielded 36% of the dihydrooxazin-2-one **31**, presumably resulting from interception of the epibromonium ion[6]).

Bromination of the benzyloxylated carbamate **13** with 2 equiv. of $PhMe_3NBr_3$ in CH_2Cl_2 gave the dibromide **32** (46%) and the dihydrooxazin-2-one **34** (49%). A yield of 82% of **32** resulted upon treating a more highly concentrated solution of **13** with 2 equiv. of $PhMe_3NBr_3$ in the presence of 10 equiv. of Et_4NBr. Bromination with Br_2 in CH_2Cl_2 yielded the *trans*-dibromides **32** (18%) and **33** (6%), the dihydrooxazin-2-one **34** (43%), and the bicyclic ether **35** (32%). No conditions were found to produce predominantly the dibromide **33**.

Bromination of the analogous trifluoroacetamide **14** with 2 equiv. of $PhMe_3NBr_3$ and 10 equiv. of Et_4NBr in CH_2Cl_2 gave the *trans*-dibromide **36** as the only product in a yield of 89%, while bromination with Br_2 in CH_2Cl_2 led to the *trans*-dibromides **36** (42%) and **37** (32%) and to the dihydro-1,3-oxazine **22** (19%).

Finally, bromination of the *N*-benzylated carbamate **16** with Br_2 in CH_2Cl_2 gave the dihydrooxazin-2-one **38** (32%) and the bicyclic ether **39** (26%). According to TLC, bromination of **16** with 2 equiv. of $PhMe_3NBr_3$ and 10 equiv. of Et_4NBr in CH_2Cl_2 gave **38** as the main product; **39** was not detected.

The results of the bromination of the cyclohex-3-en-1-amines[7]) **8**, **9**, **11**, **13**, **14**, and **16** depend on the structure of the starting material and on the reaction conditions. Similarly as observed in the bromination of **8** and **9**, the *C(6)*-substituted trifluoroacetamide **14** led to a higher proportion of the 1,4-*trans*-configured product than the *C(6)*-substituted carbamate **13**, particularly with $PhMe_3NBr_3/Et_4NBr$ as brominating agent. Replacing the $BnOCH_2$ by the MeOCO group, as in **11**, also favoured the 1,4-*trans*-isomer with a 1,3-*cis*-relation between the *N*-substituent and Br. A dihydrooxazinone was obtained from **11** only upon bromination with Br_2 in CH_2Cl_2, while **13** led to the dihydrooxazinone **34** also upon bromination with $PhMe_3NBr_3$. The *N*-benzylated carbamate **16**, lacking a N–H bond, did not form a dibromo compound; main products resulting from the action of Br_2 in CH_2Cl_2 were the dihydrooxazinone **38** and the oxolane **39**[8]). The related oxolane **35** resulted from **13** under similar reaction conditions.

These observations suggest a different reaction mechanism for the bromination by $PhMe_3NBr_3$ and Et_4NBr and by Br_2 in CH_2Cl_2, as it is known from kinetic studies of brominations with Br_2 and Br_3^- (see [68–71] and refs. cit. therein). With Br_2, the rate-limiting ionisation of a 2:1 π-complex between Br_2 and the alkene leads to an epibromonium tribromide ion pair, which rapidly collapses to the dibromide and Br_2. Bromination with tribromides[9]) is characterised by a rate-limiting nucleophilic attack of Br^- on a 1:1 π-complex between Br_2 and the alkene, leading to the dibromide and Br^- without proceeding through an intermediate. The formation of the oxolanes **35** and

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[6]) For a related bromo-carbamoylation, see [53].

[7]) For a report on the dependence of the stereoselectivity of the dibromination and bromohydroxylation of 3a,4,5,7a-tetrahydro-3*H*-benzoxazol-2-one (allylic C,O bond) upon the *N*-protecting group and the reaction conditions, see [51].

[8]) A similar formation of bicylic products in the bromination of **8** and **9** cannot be excluded.

[9]) Br_3^- predominates in the equilibrium between Br_2 and Br^-: $K = 2 \times 10^7$ l/mol (1,2-dichloroethane); $K = 1.2 \times 10^5$ l/mol ($CHCl_3$) (see [69] and refs. cit. therein).

39 and of the dihydro-1,3-oxazine **22** upon bromination by Br_2, but not by Br_3^-, correlates with the higher reactivity of an epibromonium ion as compared to a Br_2–alkene π-complex [72]. Preparatively significant is the addition of excess Br^- in the $PhMe_3NBr_3$ bromination, leading to higher yields of the 1,4-*trans*-products (84% of **29** from **11**, 82% of **32** from **13**, and 89% of **36** from **14**).

The 1,4-*cis*-dibromides **26** and **28** are almost certainly formed by diaxial bromination of the pseudoequatorial conformer of **8** and **9**, and the 1,4-*trans*-configured **25** and **27** must result from the diaxial bromination of the pseudoaxial conformer[10]) of **8** and **9**, suggesting an anchimeric assistance of the NHR group. The increased yield of **25** and the selective formation of **27** resulting from the bromination with Br_3^- suggest that the NHBoc and $NHCOCF_3$ substituents act as H-bond donor to Br^- acting as nucleophile [74] or as leaving group [68][70][75–77], or to Br_3^- [78][79]. The higher proportion of the isomers with a 1,3-*cis*-relation between the *N*-substituent and proximal Br resulting from bromination of the trifluoroacetamides indeed correlates with the better H-bond-donating properties of the more highly acidic CF_3CONH group. This explanation suggests that particularly favourable H-bonds are formed between the pseudoaxial *N*-substituents of **8**, **9**, **11**, **13**, and **14** and $PhMe_3NBr_3$, a complexation that is perhaps assisted by a simultaneous interaction with the MeOCO group in the case of **11**. The N–H ⋯ Br_3^- H-bond is expected to promote the liberation of Br_2 and lead to a pseudointramolecular bromination, in keeping with the observation that bromination of **16**, lacking an N–H bond, does not lead to dibromides. It is also conceivable that the formation of **25** and **27** is favoured by intramolecular delivery of H-bonded Br^- to the π-complex resulting from attack of Br_2 on the cyclohexene from the side opposite to the *N*-substituent.

We next studied the transformation of the 1,3-*cis*-substituted dibromides **25**, **27**, **29**, and **32** into 7-azabicyclo[2.2.1]heptanes, and the transformation of the 1,3-*trans*-substituted dibromides **26**, **30**, and **37** into 6-azabicyclo[3.1.1]heptanes, *i.e.*, the corresponding azetidines. Elimination of HBr from the cyclised monobromo compounds, followed by dihydroxylation, should lead to potential glycosidase inhibitors.

Deacylation of the carbamates **25** and **26** with CF_3CO_2H, followed by base treatment, gave the crude amines **40** and **46**, respectively, in very high yield (*Scheme 4*). Prolonged heating of **40** in $CHCl_3$ in the presence of K_2CO_3 gave the crude azanorbornane **41**, which was carbamoylated to **42** (83% from **25**); **42** was similarly prepared on a 10-g scale from **27** by hydrolysis (K_2CO_3, $MeOH/H_2O$), cyclisation, and carbamoylation (93%). Base-catalysed elimination of HBr (*t*-BuOK in THF) transformed **42** into the known azanorbornene **43** [80] (87%). Dihydroxylation (OsO_4, *N*-methylmorpholine *N*-oxide monohydrate (NMO); *cf.* [81]) of **43** provided the diol **44** that was isolated in 82% yield after chromatography and in 56% by crystallisation. Deprotection of the dihydroxycarbamate **44** yielded 97% of the ammonium salt **45** · HCl.

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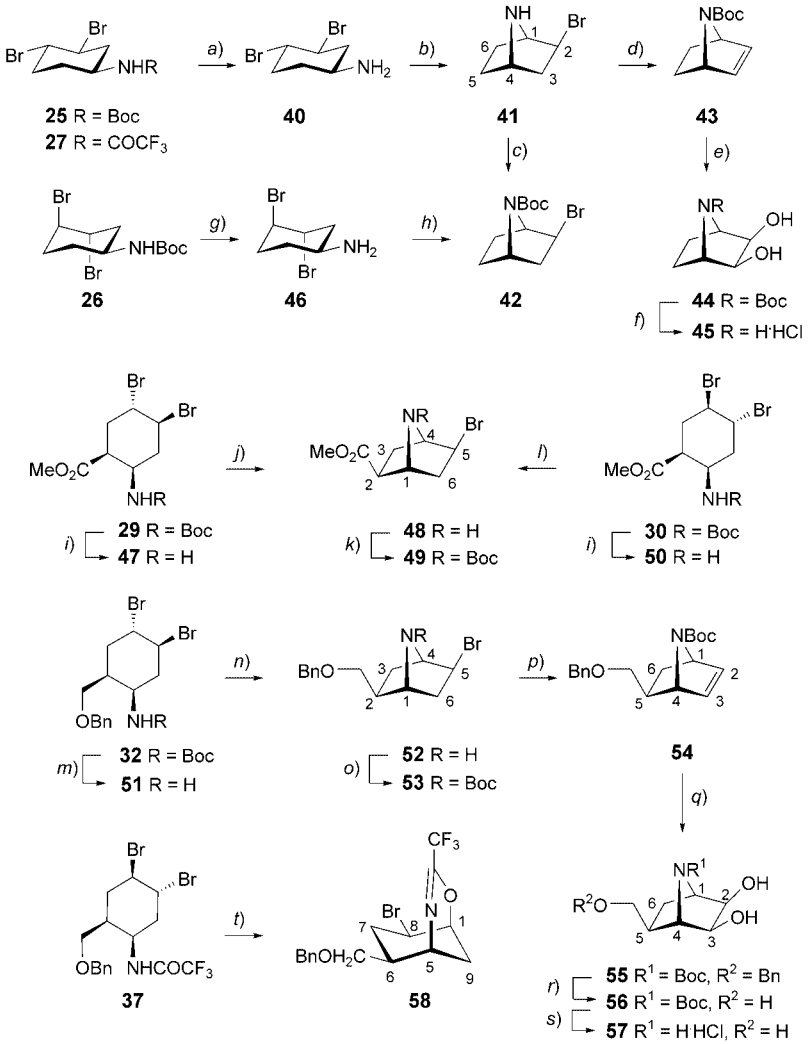
[10]) Similarly, the *syn*-selectivity of the *cis*-dihydroxylation of (trifluoroacetamido)cyclohexenes was rationalised by a neighbouring group participation in the conformer with a pseudoaxial $NHCOCF_3$ substituent [73].

Scheme 4



a) From **25**: CF_3COOH, CH_2Cl_2, then K_2CO_3; quant.; from **27**: K_2CO_3, MeOH, H_2O; 99%. *b*) K_2CO_3, $CHCl_3$; quant. *c*) Boc_2O, K_2CO_3, $CHCl_3$; 83% from **25**, 93% from **27**. *d*) *t*-BuOK, THF; 87%. *e*) OsO_4, *N*-methylmorpholine *N*-oxide monohydrate (NMO), acetone, H_2O; 56%. *f*) 0.1N HCl; quant. *g*) CF_3COOH, CH_2Cl_2, then K_2CO_3; 100%. *h*) K_2CO_3, 1,3-dichlorobenzene, then Boc_2O, 1,3-dichlorobenzene; 62%. *i*) CF_3COOH, CH_2Cl_2, then K_2CO_3; quant. *j*) K_2CO_3, $CHCl_3$. *k*) Boc_2O, K_2CO_3, $CHCl_3$; 62% from **29**. *l*) K_2CO_3, 1,3-dichlorobenzene, then Boc_2O, K_2CO_3; 21%. *m*) CF_3COOH, CH_2Cl_2, then K_2CO_3; quant. *n*) K_2CO_3, $CHCl_3$; quant. *o*) Boc_2O, K_2CO_3, $CHCl_3$; 84% from **32**. *p*) *t*-BuOK, THF; 92%. *q*) OsO_4, NMO, acetone, H_2O; 81%. *r*) H_2-Pd/C, MeOH; 60%. *s*) 0.1N HCl; 100%. *t*) K_2CO_3, MeOH, H_2O; quant.

The amine **46** did not cyclise to a 6-azabicyclo[3.1.1]heptane, *i.e.*, an azetidine. It did not react with K_2CO_3 in boiling $CHCl_3$ or in 1,3-dichlorobenzene up to 120°[11]); at 130°, a product formed, which, upon carbamoylation, gave **42** (62%). Presumably, at this temperature, the diaxial dibromide **46** rearranged to the diequatorial **40** (*cf.* [82][83]), which cyclised to the azanorbornane **41**.

Hydrolysis of the carbamates **29** and **30** with CF_3COOH in CH_2Cl_2, followed by treatment with base, gave the amines **47** and **50**, respectively. Treating **47** with K_2CO_3 in boiling $CHCl_3$ gave the azanorbornane **48**, which was *N*-butoxycarbonylated to **49** (62% from **47**). We had hoped that the amine **50**, adopting a conformation with an axial *N*-substituent and equatorial Br (*vide infra*), would be more prone to cyclise to an azetidine than the amine **46**. However, K_2CO_3 in boiling $CHCl_3$ did not affect **50**, nor was any reaction observed upon heating **50** in the presence of K_2CO_3 in 1,3-dichlorobenzene up to 100°. At 120°, a slow conversion to a product was observed by TLC; carbamoylation of the product afforded the 7-azanorbornane **49** (21%); *i.e.*, **50** behaved similarly to **46**.

Elimination of the Boc group of **32** gave the amine **51**. According to the ^{1}H-NMR spectrum, it partially cyclised to the azanorbornane **52** during isolation. The cyclisation was completed by boiling a solution of the mixture **51**/**52** in $CHCl_3$ in the presence of K_2CO_3. The resulting 6-azabicyclo[2.2.1]heptane **52** was carbamoylated to **53** (84% from **32**). Elimination of HBr with *t*-BuOK in THF transformed **53** into the azanorbornene **54** (92%), which was dihydroxylated (OsO_4, NMO [81]) to the diol **55** (81%). Hydrogenolytic debenzylation of **55**, followed by acidolytic deacylation, gave the azanorbornane **57** · HCl in *ca.* 60% yield.

Attempted hydrolysis (K_2CO_3, MeOH/H_2O) of the amide **37** led to the dihydro-1,3-oxazine **58**. A similar formation of a dihydro-1,3-oxazine upon treatment of '*N*-(3-*trans*-4-*cis*-dibromocyclohexyl)benzamide' with AgOAc in AcOH was reported by *Della* and *Jefferies* [13].

The MS of the dihydrooxazin-2-ones **31**, **34**, and **38** show the presence of only one Br substituent. Strong IR bands at 1715, 1715, and 1687 cm^{-1}, resp., evidence the NHCOO group. Signals for a *t*-Bu group were missing from the NMR spectra. The chemical-shift values for the C(1) *d* of **34** (75.49 ppm) and **38** (76.03 ppm; no ^{13}C-NMR spectrum for **31**) evidence that C(1) is bound to O. $J(1,9_{ax}) = 1.6$ Hz and $J(5,9_{ax}) = 2.2$ Hz are in agreement with the bicyclic structure. A *W* coupling (1.6 Hz) is observed between NH and the axial H–C(9) of **31** and **34**. A *W* coupling between H–C(8) and the equatorial H–C(9) (1.6 Hz for **31**, **34**, and **38**) evidences an axial Br substituent. The large *J*(6,7ax) value (10.9 Hz for **31**, 12.1 Hz for **38**; not determined for **34** due to the complexity of the spectrum) evidences the equatorial MeOCO and $BnOCH_2$ groups.

The MS of the bicyclic oxolanes **35** and **39** show the presence of only one Br substituent. According to the NMR spectra, **35** and **39** are devoid of *O*-Bn groups. The chemical-shift values for the C(5) *d* of **35** (77.11 ppm) and **39** (77.23 ppm), and *J*(7a,7b) = 8.7 Hz evidence the oxolane moiety. *J*(2,3eq) (5.5 and 4.8 Hz, resp.), *J*(2,3ax) (12.1 and 13.2 Hz, resp.), *J*(3eq,4) (0 Hz), and *J*(3ax,4) (5.3 and 5.1 Hz, resp.) values evidence an equatorial *C(2)*-carbamoyl and an axial Br–C(4) moiety, and a chair conformation of the cyclohexane ring. A *W* coupling between H–C(4) and the equatorial H–C(8) (1.2 and 1.6 Hz, resp.) corroborates the axial orientation of the Br substituent. The bridgehead H–C(1) couples with H_{exo}–C(7) (4.0 and 4.1 Hz, resp.) but not with H_{endo}–C(7), similarly to levoglucosans. The bridgehead H–C(1) and H–C(5) do not couple with the axial H–C(8), but with the equatorial H–C(8) (5.6 Hz).

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[11]) Similarly, heating *t*-3,*c*-4-dichloro-*N*-methylcyclohexylamine in DMF at temperatures up to 100° did not lead to cyclisation, and harsher conditions led to elimination [52].

The configuration and conformation of the dibromides **25**–**28**, **40**, and **46** were deduced from their ^{1}H-NMR spectra. In these bromides, the *N*-substituent is equatorial, as evidenced by the large J(1,2ax) and J(1,6ax) values of **26**–**28**, **40**, and **46**, and by the large $W_{1/2}$ value of *ca.* 20 Hz for the H–C(1) *m* of **25**. The small $W_{1/2}$ values for the H–C(3) and H–C(4) *m* of the dibromides **26**, **28**, and **46** evidence an axial orientation of the Br-atoms. This is corroborated by a small J(4,5ax) value (3.1–3.4 Hz). The large $W_{1/2}$ value of the H–C(3) and H–C(4) *m* of the dibromide **27** and the large J(3,4) values of **25** and **40** (9.3 and 10.6 Hz, resp.) evidence the equatorial orientation of the Br-atoms. The large J(2,3ax) = J(3ax,4) = 9.0 Hz, and J(5,6ax) = 9.3 Hz for **29** evidence an equatorial orientation of BocNH–C(2), Br–C(4), and Br–C(5). The small vicinal coupling J(1,6) = 4.7 Hz evidences the axial orientation of the MeOCO group. The ring adopts a $^1C_4$ conformation. The similar coupling pattern for H–C(6) and H′–C(6) of the amine **47** resonating as *ddd* at 2.77 (J = 14.8, 7.6, 3.7 Hz) and 2.13 ppm (J = 14.8, 8.8, 4.4 Hz), and the values of the coupling constants evidence an equilibrium of the two chair conformers. The identical J(1,6) = J(5,6) = 4.4 Hz and J(1,6′) = J(5,6′) = 7.1–7.3 Hz of the dibromides **32** and **36** evidence the 1,5-*cis*-configuration. The identical coupling pattern for the H–C(3) and H′–C(3) *ddd* resonating at 2.34 (J = 14.6, 7.6, 3.6 Hz) and 2.08 ppm (J = 14.6, 7.6, 4.0 Hz) (for **32**), and at 2.46 (J = 14.3, 8.3, 3.6 Hz) and 2.06 ppm (J = 13.7, 7.8, 2.8 Hz) (for **36**), and the coupling constants evidence the 2,4-*trans*-configuration and an equilibrium of the two chair conformers. The complexity of the ^{1}H-NMR spectrum of **30** precluded a straightforward conformational analysis. The large J(3ax,4) = 11.2 Hz and J(4,5) = 9.8 Hz, and the small J(2,3ax) = 3.1 Hz of the amine **50** evidence the equatorial orientation of Br–C(4) and Br–C(5), the axial orientation of H_2N–C(2), and a $^4C_1$ conformation. Similarly, J(2,3ax) = J(3ax,4) = 9.7 Hz and J(5,6ax) = 10 Hz of **37** evidence an equatorial orientation of $BnOCH_2$–C(2), Br–C(4), and Br–C(5), and a $^1C_4$ conformation. The small J(1,6ax) = 3.6 Hz evidences an axial $NHCOCF_3$. The structure of a diastereoisomer of **32** was tentatively assigned to **33**, assuming that only *trans*-dibromides are obtained.

The *exo*-orientation of Br–C(2) of the azanorbornanes **41** and **42** is evidenced by the absence of a coupling between H–C(2) and H–C(1) [84]. Similarly, H–C(2) and H–C(3) of the *meso*-diols **44** and **45** · HCl do not couple with H–C(1) and H–C(4), resp. The *exo*-orientation of the substituents at C(2) and C(5) of the azanorbornanes **48**, **49**, **52**, and **53**, and of the substituents at C(2), C(3), and C(5) of **56** and **57** · HCl is similarly evidenced. H–C(2) and H–C(3) of the azanorbornene **54** resonate as a br. *d* at 6.29 ppm. The H–C(5) *m* at 1.90–1.79 ppm precluded a straightforward assignment of the configuration at C(5); also the ^{1}H-NMR spectrum of the diol **55** was too complex. The triol **56** formed a gel in $CDCl_3$; the NMR spectra were recorded of solutions in CD_3OD.

The C=N band in the IR spectrum (in $CHCl_3$) of the dihydro-1,3-oxazine **58** (1689 cm^{-1}) and the chemical-shift values for C(1), C(5), and C(8) (74.99, 50.15, and 46.50 ppm, resp.) are similar to the corresponding values for the dihydro-1,3-oxazines **18**, **22**, and **23**. H–C(8) of **58** resonates as a *ddd* at 4.16 ppm. The large coupling constant J(7ax,8) = J(6,7ax) = 12.5 Hz evidences the equatorial Br–C(8) and $BnOCH_2$–C(6). H_{ax}–C(9) of the dihydro-1,3-oxazines **18**, **22**, and **23** is shifted downfield (2.26–2.74 ppm) due to the axial Br–C(8) as compared to H_{ax}–C(9) of the equatorially brominated **58** (δ = 1.86 ppm). The geminal J(7eq,7ax) of the axially brominated dihydro-1,3-oxazine **22** is larger (15.9 Hz) than J(7eq,7ax) for the equatorially brominated **58** (14.0 Hz), where the *gauche*-relation of Br–C(6) and both H–(7) lead to a decreased ^2J value (*cf.* [85][86]).

Inhibition Studies. The azanorbornanes **45** · HCl and **57** · HCl were tested against snail β-mannosidase, the α-mannosidase from *Jack* beans (family 38) (both at pH 4.5), the β-glucosidases from sweet almonds (family 1), the β-glucosidase from *Caldocellum saccharolyticum* (family 1), and the α-glucosidase from brewer's yeast (family 13) (all three at pH 6.8; *Table 2*), and proved at best weak inhibitors of these glycosidases. The weak selectivity is surprising; considering the weak inhibition, an interpretation may not be meaningful.

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Table 2. *Inhibition of Glycosidases by the Azanorbornanes* **45** · *HCl and* **57** · *HCl* (IC_{50} values in mM)

	45 · HCl	**57** · HCl
β-Mannosidase (snail)	no inh. at 2 mM	*ca.* 25% inh. at 2.5 mM
α-Mannosidase (*Jack* beans)	no inh. at 2 mM	0.55
β-Glucosidases (almonds)	1.74	2.05
β-Glucosidase (*C. saccharolyticum*)	2.2	1.95
α-Glucosidase (brewer's yeast)	*ca.* 10% inh. at 1.6 mM	no inh. at 2 mM

Experimental Part

General. Solvents were freshly distilled from CaH_2 (CH_2Cl_2, MeOH, Et_3N) and Na/benzophenone (THF, toluene). For large-scale operations, toluene was dried by standing over molecular sieves (4 Å), and $CHCl_3$ was dried by filtration through Al_2O_3. All reactions were carried out under Ar, unless stated otherwise. Anal. TLC: *Merck* precoated silica-gel *60 F-254* plates; detection by treatment with a 1% soln. of $KMnO_4$ in a 6% aq. K_2CO_3 soln.; NH_4OH = 25% aq. NH_3 soln. Flash chromatography (FC): silica gel *60* (40–63 μm). M.p.: uncorrected. FT-IR Spectra: absorption in cm^{-1}. NMR Spectra: chemical shifts in ppm relative to TMS; coupling constants in Hz. FAB-MS: in 3-nitrobenzyl alcohol (NOBA) matrix. HR-MALDI-MS: in 2,5-dihydroxybenzoic acid (DHB) matrix.

tert-*Butyl* N-*(Cyclohex-3-enyl)carbamate* (**8**) [53][54]. At r.t., a soln. of cyclohex-3-enecarboxylic acid (2 g, 1.85 ml, 15.85 mmol) in toluene (50 ml) was treated with Et_3N (2.43 ml, 17.44 mmol) and diphenylphosphoryl azide (DPPA; 3.59 ml, 16.65 mmol), stirred for 30 min, slowly warmed to 80°, and stirred under reflux for 3 h (IR control). After cooling to r.t., the mixture was treated with *t*-BuOH (7.44 ml, 79.3 mmol) and CuCl (50 mg, 0.51 mmol), and stirred at 100° for 2 h. The mixture was cooled, diluted with sat. aq. $NaHCO_3$ soln. (100 ml), and extracted with Et_2O (3 × 100 ml). The org. phases were dried (Na_2SO_4) and evaporated. FC (50 g of silica gel; cyclohexane/AcOEt 12:1) gave **8** (2.88 g, 92%). Colourless crystals. R_f (cyclohexane/AcOEt 3:1) 0.71. M.p. 52–54°. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.71–5.63, 5.63–5.55 (2*m*, H–C(3), H–C(4)); 4.59–4.49 (*m*, NH); 3.84–3.70 (*m*, H–C(1)); 2.43–2.32 (*m*, 1 H); 2.17–2.08 (*m*, 2 H); 1.92–1.79 (*m*, 2 H); 1.57–1.49 (*m*, 1 H); 1.45 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 127.21, 124.75 (2*d*, C(3), C(4)); 79.21 (*s*, Me_3C); 45.77 (*d*, C(1)); 32.15 (*t*); 28.49 (*q*, Me_3C); 23.67 (*t*, 2 C).

N-*(Cyclohex-3-enyl)-2,2,2-trifluoroacetamide* (**9**) [55]. At r.t., a soln. of cyclohex-3-enecarboxylic acid (10 g, 9.3 ml, 79.3 mmol) in toluene (250 ml) was treated with Et_3N (13 ml, 95 mmol) and DPPA (17.9 ml, 83.2 mmol), stirred for 30 min, slowly heated to 80°, and stirred under reflux for 5 h (IR control). After cooling to r.t., the mixture was treated with CF_3COOH (15.2 ml, 119 mmol) and stirred at 80° for 16 h. After cooling to r.t., the soln. was washed with sat. aq. $NaHCO_3$ soln. (2 × 400 ml), dried (Na_2SO_4), and evaporated. FC (60 g of silica gel; cyclohexane/AcOEt 12:1) gave **9** (12.91 g, 84%). Colourless crystals. R_f (cyclohexane/AcOEt 3:1) 0.70. M.p. 59–60° ([55]: 62–63°). FT-IR (1.5%, $CHCl_3$): 3428*m* (NH), 3008*w*, 2926*w*, 2845*w*, 1723*s* (C=O), 1532*m*, 1439*w*, 1372*w*, 1337*w*, 1290*m*, 1171*s*, 1045*w*, 940*w*, 865*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.28–6.14 (*m*, NH, exch. with D_2O); 5.79–5.71, 5.67–5.59 (2*m*, H–C(3), H–C(4)); 4.25–4.13 (*m*, H–C(1)); 2.52–2.40 (br. *d*, $J \approx$ 17.7, 1 H); 2.27–2.07 (*m*, 2 H); 2.04–1.86 (*m*, 2 H); 1.77–1.64 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 127.49, 123.73 (2*d*, C(3), C(4)); 45.55 (*d*, C(1)); 30.95, 27.17, 22.93 (3*t*, C(2), C(5), C(6)). ^{19}F-NMR (282 MHz, $CDCl_3$): −75.75 (*s*).

Methyl cis-6-[[(tert-*Butoxy)carbonyl]amino}-cyclohex-3-enecarboxylate* (**11**). A soln. of **10** (25 g, 136 mmol) in toluene (450 ml) was treated with Et_3N (22.7 ml, 163 mmol) and DPPA (30.7 ml, 143 mmol), heated slowly to 80°, kept at this temp. until N_2 evolution ceased, and refluxed for 200 min. After cooling to r.t., the mixture was treated with *t*-BuOH (64 ml, 678 mmol) and CuCl (500 mg, 5.1 mmol), and stirred at 100° for 15 h. The mixture was cooled and washed with sat. aq. $NaHCO_3$ soln. (2 × 400 ml). The aq. phases were extracted with Et_2O (2 × 400 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (230 g of silica gel; cyclohexane/AcOEt 9:1) gave **11** (31.4 g, 90%) as a slightly yellow oil, which crystallised upon standing at −20°. R_f (cyclohexane/AcOEt 3:1) 0.52. M.p. 51.8–55.5°. FT-IR (1%, $CHCl_3$): 3442*w* (NH), 3019*m*, 2982*w*, 1708*s* (C=O), 1501*s*, 1438*m*, 1393*w*, 1368*m*, 1305*m*, 1066*w*, 850*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.67 (*dtd*, J = 10.3, 3.1, 1.6), 5.60 (*dtd*, J = 10.3, 3.1, 1.6) (H–C(3), H–C(4)); 5.14 (br. *d*, J = 9.0, NH); 4.23–4.14 (*m*, H–C(6)); 3.69 (*s*, MeO); 2.80 (*td*, J = 6.2, 3.1, H–C(1)); 2.57–2.46 (br. *d*, $J \approx$ 18, H–C(2)); 2.42–2.25

(*m*, H′–C(2), H–C(5)); 2.22–2.10 (br. *d*, $J \approx 18$, H′–C(5)); 1.43 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.78 (*s*, MeO*C*O); 155.17 (*s*, *t*-BuO*C*O); 124.85, 124.68 (2*d*, C(3), C(4)); 79.30 (*s*, Me_3C); 51.92 (*q*, MeO); 46.21 (*d*, C(1)); 42.18 (*d*, C(6)); 30.81 (*t*); 28.46 (*q*, *Me*$_3$C); 25.45 (*t*). EI-MS: 255 (1, M^+), 201 (7, $[M - C_4H_6]^+$), 199 (9, $[M - C_4H_8]^+$), 182 (13), 168 (14), 155 (18, $[M - C_4H_8 - CO_2]^+$), 150 (16), 145 (14, $[M - C_4H_8 - C_4H_6]^+$), 142 (8), 138 (61), 101 (87, $[M - C_4H_8 - C_4H_6 - CO_2]^+$). Anal. calc. for $C_{13}H_{21}NO_4$ (255.31): C 61.16, H 8.29, N 5.49; found: C 61.06, H 8.20, N 5.41.

tert-*Butyl* N-*{*cis-*6-(Hydroxymethyl)cyclohex-3-enyl}carbamate* (**12**). A cold (0°) soln. of **11** (27.6 g, 108 mmol) in THF (350 ml) was treated with $LiBH_4$ (3.5 g, 162 mmol) and stirred at r.t. for 19 h. After cooling to 0°, the mixture was treated with sat. aq. NH_4Cl soln. (40 ml) and diluted with AcOEt (400 ml). The org. phase was separated, washed with sat. aq. $NaHCO_3$ soln. (2 × 400 ml), dried (Na_2SO_4), and evaporated. FC (125 g of silica gel; cyclohexane/AcOEt 3:1) gave **12** (18.3 g, 74%). Colourless crystals. R_f (cyclohexane/AcOEt 3:1) 0.26. M.p. 105.0–105.9°. FT-IR (0.5%, $CHCl_3$): 3611*w*, 3435*w*, 2983*w*, 1684*m* (C=O), 1502*s*, 1368*m*, 1062*w*, 921*w*, 843*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.70 (br. *d*, $J \approx 10.0$), 5.60 (br. *d*, $J \approx 10.0$) (H–C(3), H–C(4)); 4.74 (*d*, J = 8.4, NH); 4.22–4.15 (*m*, H–C(1)); 4.15–3.85 (br. *s*, OH); 3.48 (*dd*, J = 12.1, 4.7), 3.22 (*t*, J = 11.2) (C*H*$_2$OH); 2.44 (br. *d*, $J \approx 18.0$, H–C(2)); 2.09 (br. *d*, $J \approx 18$, H′–C(2)); 2.05–1.88 (*m*, H–C(5), H–C(6)); 1.66–1.51 (*m*, H′–C(5)); 1.44 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.26 (*s*, C=O); 126.45, 123.49 (2*d*, C(3), C(4)); 79.89 (*s*, Me_3C); 63.57 (*t*, CH_2OH); 43.26 (*d*, C(1)); 38.90 (*d*, (C(6)); 31.16 (*t*, C(5)); 28.39 (*q*, *Me*$_3$C); 23.40 (*t*, C(2)). EI-MS: 227 (0.1, M^+), 197 (1, $[M - H_2C{=}O]^+$), 173 (20, $[M - C_4H_6]^+$), 171 (20, $[M - C_4H_8]^+$), 154 (16), 153 (13, $[M - C_4H_8 - H_2O]^+$), 141 (6), 127 (7, $[M - C_4H_8 - CO_2]^+$), 117 (56, $[M - C_4H_8 - C_4H_6]^+$), 110 (26), 99 (27, $[M - C_4H_8 - C_4H_6 - H_2O]^+$), 93 (25), 92 (75), 73 (68, $[M - C_4H_8 - C_4H_6 - CO_2]^+$). Anal. calc. for $C_{12}H_{21}NO_3$ (227.30): C 63.41, H 9.31, N 6.16; found: C 63.60, H 9.16, N 6.11.

tert-*Butyl* N-*{*cis-*6-[(Benzyloxy)methyl]cyclohex-3-enyl}carbamate* (**13**), cis-*1-Benzyl-1,4,4a,5,8,8a-hexahydrobenzo*[d]*[1.3]oxazin-2-one* (**15**), *and* tert-*Butyl* N-*benzyl*-N-*{*cis-*6-[(benzyloxy)methyl]cyclohex-3-enyl}carbamate* (**16**). *a*) A cold (–30°) suspension of NaH (6.19 g of a 60% suspension in oil, 155 mmol) in DMF (225 ml) was treated dropwise with a soln. of **12** (17.6 g, 77.4 mmol) in DMF (50 ml), warmed to –20°, treated dropwise with BnBr (9.19 ml, 77.4 mmol), and stirred for 45 min. After treatment with MeOH (9 ml), the mixture was stirred at –30° for 30 min. and diluted with AcOEt (1000 ml). The org. phase was washed with H_2O (2 × 500 ml), dried (Na_2SO_4), and evaporated. FC (27.3 g of silica gel; cyclohexane/AcOEt 9:1 → 3:2) gave **13** (23.5 g, 95%) as a colourless oil, which crystallized upon standing, and **15** (980 mg, 5%) as a yellow oil, which crystallized upon standing.

b) A cold (0°) soln. of **12** (380 mg, 1.67 mmol) in DMF (5 ml) was treated with NaH (88 mg of a 55% suspension in oil, 2.00 mmol), stirred for 30 min at 0°, treated dropwise with BnBr (0.30 ml, 2.51 mmol), stirred for 5 min, allowed to warm to r.t., and stirred for 19 h. The mixture was cooled to 0°, treated with MeOH (0.15 ml), stirred at 0° for 30 min, diluted with AcOEt (50 ml), and washed with H_2O (2 × 30 ml). The org. phase was dried (Na_2SO_4) and evaporated. FC (60 g of silica gel; cyclohexane/AcOEt 10:1) gave **16** (85 mg, 12%, colourless oil) and **13** (293 mg, 55%, colourless oil, which crystallised upon standing). Elution of the column with MeOH gave **15** (134 mg, 33%, yellow oil).

Data of **13**: R_f (cyclohexane/AcOEt 3:1) 0.66. M.p. 62.8–65.8°. FT-IR (3%, $CHCl_3$): 3438*m* (NH), 3090*w*, 3067*w*, 3020*m*, 2981*m*, 2922*m*, 2866*m*, 1706*s* (C=O), 1501*s*, 1455*m*, 1392*m*, 1367*s*, 1337*w*, 1303*w*, 1118*m*, 1075*m*, 1029*w*, 1001*w*, 968*w*, 941*w*, 909*w*, 875*w*, 844*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.25 (5 arom. H); 5.67–5.54 (*m*, H–C(3), H–C(4)); 5.20 (*d*, J = 8.4, NH); 4.54, 4.48 (2*d*, J = 11.8, PhC*H*$_2$); 4.10–4.01 (*m*, H–C(1)); 3.58 (*t*, $J \approx 8.7$, CH–C(6)); 3.36 (*dd*, J = 9.3, 5.6, CH′–C(6)); 2.43–2.19 (*m*, 3 H); 2.08–1.98 (*m*, 1 H); 1.85–1.75 (*m*, 1 H); 1.44 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.56 (*s*, C=O); 138.23 (*s*); 128.28 (*d*, 2 C); 127.52 (*d*, 2 C); 127.47 (*d*); 125.55, 124.59 (2*d*, C(3), C(4)); 78.84 (*s*, Me_3C); 73.36, 72.05 (2*t*, PhC*H*$_2$, *C*H$_2$–C(6)); 46.41 (*d*, C(1)); 36.48 (*d*, C(6)); 30.97 (*t*, C(5)); 28.55 (*q*, *Me*$_3$C); 26.33 (*t*, C(2)). ESI-MS: 657 (14, $[2M + Na]^+$), 377 (6), 356 (4, $[M + K]^+$), 340 (36, $[M + Na]^+$), 318 (60, $[M + 1]^+$), 262 (13, $[M + 1 - C_4H_8]^+$), 218 (4, $[M + 1 - C_4H_8 - CO_2]^+$). Anal. calc. for $C_{19}H_{27}NO_3$ (317.43): C 71.89, H 8.57, N 4.41; found: C 71.78, H 8.54, N 4.37.

Data of **15**: Colourless, amorphous. R_f (cyclohexane/AcOEt 3:1) 0.12. M.p. 79.8–81.6°. FT-IR (1.5%, $CDCl_3$): 3028*w*, 3015*m*, 2912*w*, 2851*w*, 1682*s* (C=O), 1604*w*, 1486*w*, 1451*m*, 1361*w*, 1129*m*, 1075*w*, 1035*w*, 963*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.24 (5 arom. H); 5.60–5.49 (*m*, H–C(6), H–C(7)); 5.03 (*d*, J = 15.3, PhC*H*); 4.27 (*t*, J = 11.4, H–C(4)); 4.19 (*d*, J = 15.3, PhC*H*′); 4.13 (*ddd*, J = 10.6, 4.7, 1.9, H′–C(4)); 3.43–3.35 (*m*, H–C(8a)); 2.50–2.31 (*m*, H–C(4a), H–C(5), H–C(8)); 2.15–2.03 (*m*, H′–C(8)); 1.89 (br. *d*, $J \approx 18$, H′–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.12 (*s*, C=O); 137.14 (*s*); 128.55 (*d*, 2 C); 127.82 (*d*, 2 C); 127.49 (*d*); 123.99, 122.20 (2*d*, C(6), C(7)); 67.77 (*t*, C(4)); 50.87 (*t*, PhC*H*$_2$); 50.80 (*d*, C(8a)); 29.90 (*d*, C(4a)); 27.31, 25.46 (2*t*, C(5), C(8)). EI-MS: 243 (23, M^+), 189 (17, $[M - C_4H_6]^+$), 150 (4), 144 (20), 128 (9), 91 (100, Bn^+).

Data of **16**: Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.74. FT-IR (3%, $CHCl_3$): 3089*w*, 3067*w*, 3030*m*, 3013*s*, 2980*m*, 2931*m*, 2862*m*, 1681*s*, 1496*m*, 1477*m*, 1454*s*, 1405*m*, 1392*m*, 1367*s*, 1351*m*, 1339*m*, 1272*m*, 1123*m*, 1076*m*, 1028*w*, 1012*w*, 971*w*, 904*w*, 884*w*, 857*w*, 853*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.42–7.13 (10 arom. H); 5.64 (br. *d*, *J* = 10.3), 5.56 (br. *d*, *J* = 10.0) (H–(3), H–C(4)); 4.65 (br. *d*, *J* ≈ 17, PhC*H*N); 4.54–4.45 (*m*, H–C(1)); 4.51, 4.45 (2*d*, *J* = 11.8, PhCH_2O); 4.29 (*d*, *J* = 16.8, PhC*H*′N); 3.64 (*dd*, *J* = 9.2, 4.8, CH–C(6)); 3.43 (*t*, *J* ≈ 8.9, CH′–C(6)); 2.47–2.29 (*m*, 2 H); 2.23–2.07 (*m*, 3 H); 1.38 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.90 (*s*, C=O); 140.53, 138.42 (2*s*); 128.87–125.90 (several *d*); 125.77, 125.11 (2*d*, C(3), C(4)); 79.67 (*s*, Me_3C); 73.07, 70.26 (2*t*, PhCH_2O, CH_2–C(6)); 52.54 (*d*, C(1)); 48.22 (*t*, PhCH_2N); 37.77 (*d*, C(6)); 28.35 (*q*, *Me*$_3$C); 27.55, 27.26 (2*t*, C(2), C(5)). ESI-MS: 837 (9, $[2M+Na]^+$), 467 (25), 446 (7, $[M+K]^+$), 430 (46, $[M+Na]^+$), 408 (16, $[M+1]^+$), 318 (26), 308 (14, $[M+1-C_4H_8-CO_2]^+$).

N-*{*cis-*6-[(Benzyloxy)methyl]cyclohex-3-enyl}-2,2,2-trifluoroacetamide* (**14**). A soln. of **13** (1 g, 3.15 mmol) in CH_2Cl_2 (25 ml) was treated with CF_3CO_2H (4 ml, 52 mmol), stirred at r.t. for 1.5 h, and evaporated. The soln. of the residue (milky oil) in CH_2Cl_2 (10 ml) was treated with Et_3N (4 ml, 28.7 mmol) and $(CF_3CO)_2O$ (1.7 ml, 12.2 mmol), stirred at r.t. for 19 h, and evaporated. FC (cyclohexane/AcOEt 9:1) of the residue (orange oil) gave **14** (848 mg, 84%). Yellow oil. R_f (cyclohexane/AcOEt 3:1) 0.66. FT-IR (1%, $CHCl_3$): 3363*w* (NH), 3033*w*, 2920*w*, 2868*w*, 2848*w*, 1718*s* (C=O), 1583*m*, 1455*w*, 1440*w*, 1373*w*, 1290*w*, 1093*w*, 1074*w*, 1004*w*, 911*w*, 849*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.92–7.82 (br. *s*, NH); 7.40–7.28 (5 arom. H); 5.61 (br. *d*, *J* = 11.8, H–C(4)); 5.57 (br. *d*, *J* = 11.5, H–C(3)); 4.52, 4.48 (2*d*, *J* = 11.5, PhCH_2); 4.33 (*tdd*, *J* = 8.4, 5.6, 2.8, H–C(1)); 3.72 (*t*, *J* = 9.8, CH–C(6)); 3.48 (*dd*, *J* = 9.7, 4.4, CH′–C(6)); 2.50–2.32 (*m*, H–C(2), H–C(5), H–C(6)); 2.02 (br. *dd*, *J* ≈ 17, 9, H′–C(2)); 1.82 (br. *d*, *J* ≈ 18, H′–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.10 (*s*); 128.41 (*d*, 2 C); 127.94 (*d*); 127.73 (*d*, 2 C); 124.91, 123.98 (2*d*, C(3), C(4)); 73.85, 71.51 (2*t*, PhCH_2, CH_2–C(6)); 47.76 (*d*, C(1)); 34.94 (*d*, C(6)); 28.16, 27.37 (2*t*, C(2), C(5)); signals for $COCF_3$ hidden by noise. ^{19}F-NMR (282 MHz, $CDCl_3$): −76.14 (*s*). ESI-MS: 368 (7, $[M+Na+MeOH]^+$), 352 (18, $[M+K]^+$), 336 (100, $[M+Na]^+$), 314 (60, $[M+1]^+$).

N-*[*c-*4-Bromo*-t-*3-(4-bromobutoxy)cyclohex*-r-*1-yl]-2,2,2-trifluoroacetamide* (**17**). A cold (0°) soln. of **9** (59 mg, 0.33 mmol) in THF (2 ml) was treated with *N*-bromosuccinimide (NBS) (29 mg, 0.16 mmol) and stirred for 25 h while allowed to warm to r.t. The mixture was diluted with Et_2O (10 ml), washed with sat. aq. $Na_2S_2O_5$ soln. (3 × 10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated. FC (2 g of silica gel; cyclohexane/AcOEt 12:1) of the residue (31 mg, colourless oil) gave **17** (14.7 mg, 31%) as a colourless oil and an unidentified by-product (3.2 mg). R_f (toluene/AcOEt 10:1) 0.58. FT-IR (1.5%, $CHCl_3$): 3428*w* (NH), 2953*w*, 1725*s* (C=O), 1536*m*, 1435*w*, 1384*w*, 1357*w*, 1097*m*, 968*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.14–6.07 (br. *s*, NH); 4.32 (*q*, *J* = 3.2, H–C(3)); 4.22–4.08 (*m*, H–C(1)); 3.76 (*q*, *J* = 3.1, H–C(4)); 3.59–3.49 (*m*, 2 H), 3.45 (*t*, *J* = 6.5, 2 H) (2 H–C(1′), 2 H–C(4′)); 2.30 (*ddt*, *J* = 15.4, 12.1, 3.5, H–C(5)); 2.10–1.65 (*m*, 2 H–C(2), H′–C(5), 2 H–C(6), 2 H–C(2′), 2 H–C (3′)). ^{13}C-NMR (75 MHz, $CDCl_3$): 78.01 (*d*, C(3)); 68.81 (*t*, C(1′)); 49.38, 44.74 (2*d*, C(1), C(4)); 33.69 (*t*, C(4′)); 30.68, 29.58, 28.59, 28.14, 26.54 (5*t*, C(2), C(5), C(6), C(2′), C(3′)). ^{19}F-NMR (282 MHz, $CDCl_3$): −75.74 (*s*). ESI-MS: 482 (7), 480 (13), 478 (7, $[M+Na+MeOH]^+$); 466 (20), 464 (37), 462 (18, $[M+K]^+$); 450 (50), 448 (100), 446 (51, $[M+Na]^+$).

*(1*RS*,5*RS*,8*RS*)-8-Bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene* (**18**) *and* N-*(*t-*3-acetoxy*-c-*4-bromocyclohex*-r-*1-yl)-2,2,2-trifluoroacetamide* (**19**). *a*) A soln. of **9** (210 mg, 1.09 mmol) in AcOH (10 ml) was treated with NBS (580 mg, 3.26 mmol), stirred at r.t. for 85 min, and evaporated. The residue, suspended in AcOEt (25 ml), was washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (20 ml). The aq. phases were extracted with AcOEt (25 ml), and the combined org. phases were dried (Na_2SO_4) and evaporated. FC (15 g of silica gel; cyclohexane/AcOEt 9:1) of the residue (520 mg) gave **18** (91.5 mg, 31%) and **19** (86.3 mg, 24%) as red oils.

b) A soln. of **9** (31 mg, 0.16 mmol) in AcOH (1.6 ml) was treated at 5° with NBS (88.5 mg, 0.50 mmol), stirred at r.t. for 1.5 h, and evaporated. A suspension of the residue in AcOEt (25 ml) was washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated. Two FC (2 g of silica gel; cyclohexane/AcOEt 9:1) of the residue (72 mg, yellow, amorphous) gave **19** (9.3 mg, 17%) as a colourless oil.

Data of **18**: R_f (cyclohexane/AcOEt 3:1) 0.68. FT-IR (1.5%, $CHCl_3$): 2953*w*, 1788*w*, 1686*m*, 1443*w*, 1391*w*, 1369*w*, 1349*m*, 1332*w*, 1288*m*, 1159*s*, 1124*s*, 1114*m*, 1090*w*, 1051*m*, 1021*m*, 981*w*, 903*w*, 851*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.75–4.70 (*m*, H–C(1)); 4.50–4.45 (*m*, H–C(8)); 3.93–3.88 (*m*, H–C(5)); 2.59 (*dt*, *J* = 14.0, 1.6, H_{ax}–C(9)); 2.18–2.01 (*m*, H–C(6)); 1.99–1.83 (*m*, H′–C(6), CH_2(7)); 1.77 (*dtd*, *J* = 14.0, 3.7, 1.9, H_{eq}–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 74.47 (*d*, C(1)); 48.17, 46.73 (2*d*, C(5), C(8)); 25.02, 24.90, 22.85 (3*t*, C(6), C(7), C(9)); *q* for CF_3CO hidden by noise. ESI-MS: 196 (10), 194 (10, $[M-CCF_3+4H]^+$); 87 (100).

Data of **19**: R_f (cyclohexane/AcOEt 3:1) 0.49. FT-IR (1.5%, $CHCl_3$): 3426*w* (NH), 3034*w*, 3008*w*, 2959*w*, 1727*s* (C=O), 1537*m*, 1457*w*, 1436*w*, 1374*m*, 1260*m*, 1095*w*, 1063*w*, 1036*m*, 1018*m*, 983*w*, 909*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.25–6.16 (br. *s*, NH); 5.21 (*q*, *J* = 3.4, H–C(3)); 4.27 (*q*, *J* = 3.4, H–C(4)); 4.24–4.11

(*m*, H–C(1)); 2.32–1.73 (*m*, 6 H); 2.11 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.89 (*s*, Me*C*=O); 156.85 (*q*, *J* = 37.6, F_3CC=O); 115.91 (*q*, *J* = 289.3, CF_3); 71.96 (*d*, C(3)); 47.53, 44.75 (2*d*, C(1), C(4)); 30.81, 28.43, 26.55 (3*t*, C(2), C(5), C(6)); 21.07 (*q*, Me). ^{19}F-NMR (282 MHz, $CDCl_3$): −75.70 (*s*). ESI-MS: 388 (35), 386 (34, $[M + Na + MeOH]^+$); 356 (97), 354 (100, $[M + Na]^+$).

N-*(*trans-*3,4-Epoxycyclohexyl)-2,2,2-trifluoroacetamide* (**20**) *and (1*RS,*5*RS,*8*RS*)-3-(Trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-en-8-ol* (**21**). *a*) A cold (0°) soln. of **19** (17 mg, 51 μmol) in THF (1.5 ml) was treated with NaH (3.7 mg of a 50% suspension in oil, 77 μmol), stirred at 0° for 1 h, stirred for 20 h while warming to r.t., and poured into H_2O (10 ml). The mixture was extracted with CH_2Cl_2 (4 × 15 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (2 g of silica gel; cyclohexane/AcOEt 2:1) of the residue (11.9 mg, colourless oil) gave **20** (3.0 mg, 28%) and **21** (3.6 mg, 33%), both as colourless volatile oils.

b) **21** (16.7 mg, 89%) was obtained by hydrolysis of **19** (30 mg, 90 μmol) in MeOH (1 ml) and H_2O (0.2 ml) with K_2CO_3 (30 mg, 217 μmol).

Data of **20**: R_f (cyclohexane/AcOEt 1:1) 0.59. FT-IR (0.2%, $CHCl_3$): 3410*w* (NH), 2950*w*, 1727*s* (C=O), 1528*w*, 1262*s*, 1171*s*, 1093*m*, 1020*m*, 974*w*, 928*w*, 822*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.13–5.99 (br. *s*, NH); 4.08–3.96 (*m*, H–C(1)); 3.26–3.23 (*m*, *J* = 2.2, 1.9, irr. at 2.46 → *dd*, *J* = 3.7, 2.2, H–C(3)); 3.18 (*td*, *J* = 3.7, 1.6, H–C(4)); 2.46 (*ddt*, *J* = 14.6, 5.3, 1.5, H–C(2)); 2.10–2.03 (*m*, 2 H–C(5)); 1.81–1.70 (*m*, H–C(6)); 1.75 (*ddd*, *J* = 14.6, 8.6, 2.7, H′–C(2)); 1.38 (*dtd*, *J* = 12.7, 10.0, 7.2, H′–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.98, 50.80 (C(3), C(4)); 43.68 (C(1)); 30.84, 25.65, 21.99 (C(2), C(5), C(6)); signals for CF_3CO hidden by noise. ^{19}F-NMR (282 MHz, $CDCl_3$): −75.72. ESI-MS (neg. mode): 254 (65, $[M + HCOO]^-$), 208 (60, $[M - 1]^-$), 91 (68), 45 (100).

Data of **21**: R_f (cyclohexane/AcOEt 1:1) 0.47. FT-IR (0.5%, $CHCl_3$): 3618*w* (OH), 2998*w*, 2948*w*, 1689*m*, 1446*w*, 1393*w*, 1322*w*, 1290*m*, 1262*w*, 1153*s*, 1100*s*, 1080*m*, 1023*m*, 1004*m*, 970*w*, 936*w*, 851*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.59–4.55 (*m*, H–C(1)); 4.18–4.13 (*m*, H–C(8)); 3.90–3.84 (*m*, H–C(5)); 2.26 (*dt*, *J* = 14.0, 1.5, H_{ax}–C(9)); 2.02 (*tdd*, *J* = 13.6, 4.7, 3.1, H–C(6)); 1.88–1.78 (*m*, H′–C(6)); 1.73–1.62 (*m*, H_{eq}–C(7), H_{eq}–C(9)); 1.53 (*dddd*, *J* = 15.3, 13.4, 5.3, 3.4, H_{ax}–C(7)); OH hidden between 1.73 and 1.47. ^{13}C-NMR (75 MHz, $CDCl_3$): 74.26 (*d*, C(1)); 67.39 (*d*, C(8)); 46.94 (*d*, C(5)); 25.02, 23.92, 22.46 (3*t*, C(6), C(7), C(9)). ^{19}F-NMR (282 MHz, $CDCl_3$): −73.43 (*s*). EI-MS: 209 (24, M^+); 153 (99, $[M - 56]^+$).

*(1*RS,*5*SR,*6*RS,*8*RS*)-6-[(Benzyloxy)methyl]-8-bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene* (**22**). A soln. of **14** (36 mg, 115 μmol) in AcOH (3 ml) was treated at 10° with NBS (61 mg, 345 μmol), stirred for 90 min at r.t., and evaporated. The residue was suspended in AcOEt (20 ml), and washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (20 ml). The aq. phases were extracted with AcOEt (20 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (2 g of silica gel; hexane/AcOEt 8:1) of the residue (85 mg, yellow oil) gave **22** (36 mg, 79%). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.68. FT-IR (0.5%, $CHCl_3$): 3008*w*, 2927*m*, 2857*w*, 1728*w*, 1688*m*, 1602*w*, 1454*w*, 1442*w*, 1390*w*, 1362*w*, 1166*s*, 1130*s*, 1110*m*, 1076*m*, 1040*w*, 914*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.26 (5 arom. H); 4.74–4.69 (*m*, H–C(1)); 4.57 (*d*, *J* = 11.8, PhC*H*); 4.51–4.47 (*m*, H–C(8)); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.04–3.99 (*m*, H–C(5)); 3.56 (*dd*, *J* = 9.0, 7.5, CH–C(6)); 3.29 (*dd*, *J* = 9.0, 6.5, CH′–C(6)); 2.65–2.54 (*m*, H–C(6)); 2.54 (*dt*, *J* = 14.3, 1.6, H_{ax}–C(9)); 2.12 (br. *dd*, *J* = 15.9, 2.5, H_{eq}–C(7)); 1.83 (*dtd*, *J* = 14.3, 3.9, 1.6, H_{eq}–C(9)); 1.57 (*ddd*, *J* = 15.9, 12.1, 4.0, H_{ax}–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 147.62 (*q*, *J* = 38.4, O–C=N); 138.05 (*s*); 128.30 (*d*, 2 C); 127.56 (*d*, 3 C); 116.26 (*q*, *J* = 275.9, CF_3); 74.33 (*d*, C(1)); 73.28 (*t*, Ph*C*H$_2$); 71.34 (*t*, *C*H$_2$–C(6)); 47.80, 47.68 (2*d*, C(5), C(8)); 38.04 (*d*, C(6)); 28.88 (*t*, C(7); 23.32 (*t*, C(9)). ^{19}F-NMR (282 MHz, $CDCl_3$): −73.10 (*s*). HR-MS (MALDI): 412 (86), 410.0578 (100, $C_{16}H_{20}BrF_3NO_3^+$, $[M + H_3O]^+$; calc. 410.0579); 394 (1); 392.0475 (1, $C_{16}H_{18}BrF_3NO_2^+$, $[M + 1]^+$; calc. 392.0473); 316 (16), 314 (16, $[M + 4 - CF_3C]^+$); 312 (14), 310 (14); 298 (6), 296 (6, $[M + 2 - COCF_3]^+$).

*(1*RS,*5*SR,*6*SR,*8*RS*)-8-Bromo-6-(6-chloropyridin-3-yl)-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene* (**23**). A soln. of **4** (50 mg, 167 μmol) in AcOH (3 ml) was treated at 10° with NBS (89 mg, 501 μmol), stirred for 90 min at r.t., and evaporated. A suspension of the residue in AcOEt (20 ml) was washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated. FC (2 g of silica gel; hexane/AcOEt 6:1) of the residue (99 mg, yellow, amorphous) gave **23** (52 mg, 81%). Colourless oil. R_f (toluene/AcOEt 10:1) 0.42. FT-IR (1%, $CHCl_3$): 3003*w*, 2945*w*, 1688*m*, 1586*w*, 1565*w*, 1461*m*, 1441*w*, 1387*w*, 1363*w*, 1335*w*, 1161*s*, 1128*s*, 1106*m*, 1087*w*, 1053*w*, 1025*w*, 1001*w*, 967*w*, 929*w*, 915*w*, 875*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.33 (*d*, *J* = 2.5, 1 arom. H); 7.62 (*dd*, *J* = 8.4, 2.8, 1 arom. H); 7.28 (*d*, *J* = 8.4, 1 arom. H); 4.79 (*tt*, *J* = 3.5, 1.7, irr. at 4.02–3.97 → *td*, *J* = 3.5, 1.6, irr. at 2.74 → *td*, *J* = 3.6, 2.2, H–C(1)); 4.62–4.57 (*m*, H–C(8)); 4.02–3.97 (*m*, H–C(5)); 3.52 (*ddd*, *J* = 10.3, 6.5, 2.2, H–C(6)); 2.74 (*dt*, *J* = 14.3, 1.6, H_{ax}–C(9)); 2.21–2.08 (*m*, 2 H–C(7)); 1.95 (*dtd*, *J* = 14.3, 4.0, 1.6, H_{eq}–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 150.54 (*s*); 149.54 (*d*); 138.42 (*d*); 135.87 (*s*);

124.35 (*d*); 73.82 (*d*, C(1)); 51.26, 47.62 (2*d*, C(5), C(8)); 40.45 (*d*, C(6)); 32.12, 24.18 (2*t*, C(7), C(9)); 2*q* for CF_3CO hidden by noise. ^{19}F-NMR (282 MHz, $CDCl_3$): −73.54 (*s*).

*[*t*-4-Bromo-*c*-2-(6-chloropyridin-3-yl)-5-hydroxycyclohex-*r*-1-yl]ammonium Trifluoroacetate* (**24**·CF_3COOH). A soln. of **23** (5.6 mg, 14.6 μmol) in THF (1 ml) and H_2O (0.33 ml) was treated with CF_3COOH (1 drop), stirred at r.t. for 50 min, and evaporated. The residue was co-evaporated with MeOH to yield crude **24**·CF_3COOH (7.8 mg, quant.). Colourless oil. R_f (CH_2Cl_2/MeOH 9:1) 0.40. ^{1}H-NMR (300 MHz, D_2O): 8.33 (*d*, *J* = 2.5, 1 arom. H); 7.83 (*dd*, *J* = 8.4, 2.5, 1 arom. H); 7.52 (*d*, *J* = 8.4, 1 arom. H); 4.61–4.56 (*qd*, *J* = 3.4, 2, irr. at 2.09 → *q*, *J* = 3.4, H−C(4)); 4.25 (*q*, *J* = 3.4, irr. at 2.64 → *t*, *J* = 3.4, H−C(5)); 3.86–3.78 (*m*, H−C(1), H−C(2)); 2.90 (*ddd*, *J* = 15.6, 12.1, 3.4, H_{ax}−C(3)); 2.64 (*dt*, *J* = 15.6, 3.4, H_{ax}−C(6)); 2.23 (br. *dt*, *J* = 15.6, 3.1, H_{eq}−C(3)); 2.09 (br. *d*, *J* = 15.5, H_{eq}−C(6)). ^{13}C-NMR (75 MHz, D_2O): 149.64; 148.35; 139.65; 133.89; 124.86; 68.14 (C(5)); 51.09, 50.29 (C(1), C(4); 43.02 C(2)); 35.34, 30.20 (C(6), C(3)). ^{19}F-NMR (282 MHz, D_2O): −76.08 (*s*). HR-MS (MALDI): 425 (24), 423 (23); 402 (22); 380 (28); 307 (38), 305.0044 (33, $C_{11}H_{15}BrClN_2O^+$, $[M+1]^+$; calc. 305.0056).

tert-*Butyl* N-*(*c*-3,*t*-4-dibromocyclohex-*r*-1-yl)carbamate* (**25**) *and* tert-*Butyl* N-*(*t*-3,*c*-4-dibromocyclohex-*r*-1-yl)carbamate* (**26**). A soln. of **8** (849 mg, 4.3 mmol) in CH_2Cl_2 (50 ml) was treated with Et_4NBr (9.0 g, 43 mmol) at r.t., cooled to −78°, treated with Br_2 (0.44 ml, 1.38 g, 8.6 mmol) over a period of 10 min, stirred at −78° for 2 h, and poured into sat. aq. $Na_2S_2O_5$ soln. (50 ml). The mixture was extracted with AcOEt (4 × 50 ml), and the combined org. phases were dried (Na_2SO_4) and evaporated. FC (60 g of silica gel; cyclohexane/AcOEt 12:1) gave **26** (590 mg, 38%) and **25** (775 mg, 50%).

Data of **25**: Colourless crystals. R_f (cyclohexane/AcOEt 3:1) 0.60. M.p. 128–129°. FT-IR (1.5%, $CHCl_3$): 3441*w* (NH), 3008*m*, 2980*m*, 1708*s* (C=O), 1501*s*, 1449*w*, 1392*w*, 1368*m*, 1337*w*, 1313*m*, 1274*m*, 1164*s*, 1076*w*, 1045*m*, 1012*w*, 949*w*, 917*w*, 860*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.67–4.57 (br. *s*, NH); 4.10 (*td*, *J* = 9.3, 4.1), 4.02 (*td*, *J* = 9.3, 4.1) (H−C(3), H−C(4)); 3.66–3.53 (br. *s*, $W_{1/2} \approx 20$, H−C(1)); 2.79–2.69 (br. *d*, *J* = 13.4, 1 H); 2.52–2.43 (*m*, 1 H); 2.06–1.97 (*m*, 1 H); 1.95–1.73 (*m*, 2 H); 1.42 (br. *s*, *t*-Bu); 1.38–1.21 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.13 (*s*, C=O); 79.91 (*s*, Me_3C); 55.33, 53.44 (2*d*, C(3), C(4)); 48.18 (*d*, C(1)); 42.99 (*t*, C(2)); 34.33, 32.12 (2*t*, C(5), C(6)); 28.43 (*q*, Me_3C). ESI-MS: 414 (53), 412 (100), 410 (56, $[M+Na+MeOH]^+$); 336 (37), 334 (78), 332 (36). Anal. calc. for $C_{11}H_{19}Br_2NO_2$ (357.08): C 37.00, H 5.36, N 3.92; found: C 37.25, H 5.31, N 3.85.

Data of **26**: Colourless crystals. R_f (cyclohexane/AcOEt 3:1) 0.67. M.p. 105–106°. FT-IR (1.5%, $CHCl_3$): 3442*m* (NH), 3008*m*, 2980*m*, 1709*s* (C=O), 1503*s*, 1454*w*, 1435*w*, 1392*w*, 1368*m*, 1323*w*, 1310*w*, 1280*w*, 1166*s*, 1045*m*, 1031*w*, 1018*m*, 958*w*, 906*w*, 867*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.64–4.60, 4.60–4.55 (2*m*, H−C(3), H−C(4)); 4.53–4.43 (br. *s*, NH); 4.07–3.92 (br. *s*, H−C(1)); 2.55 (*ddt*, *J* = 15.6, 12.1, 3.4, H−C(5)); 2.33–2.18 (*m*, 2 H); 2.04–1.94 (br. *d*, *J* ≈ 15.3, 1 H); 1.93–1.83 (br. *d*, *J* ≈ 12.8, 1 H); 1.71 (*qd*, *J* = 12.3, 3.4, H_{ax}−C(6)); 1.44 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.30 (*s*, C=O); 79.66 (*s*, Me_3C); 52.36, 51.79 (2*d*, C(3), C(4)); 44.95 (*d*, C(1)); 35.24 (*t*, C(2)); 28.45 (*q*, Me_3C); 28.38, 27.59 (2*t*, C(5), C(6)). ESI-MS: 414 (48), 412 (100), 410 (50, $[M+Na+MeOH]^+$); 398 (17), 396 (32), 394 (14, $[M+K]^+$); 382 (26), 380 (53), 378 (27, $[M+Na]^+$).

N-*(*c*-3,*t*-4-Dibromocyclohex-*r*-1-yl)-2,2,2-trifluoroacetamide* (**27**) *and* N-*(*t*-3,*c*-4-Dibromocyclohex-*r*-1-yl)-2,2,2-trifluoroacetamide* (**28**). *a*) Conversion of **9** (102 mg, 0.53 mmol) according to the preparation of **25**/**26** gave **28** (51 mg, 27%) and **27** (120 mg, 64%).

b) At 0°, a soln. of **9** (11.61 g, 60.1 mmol) in CH_2Cl_2 (250 ml) was treated with Me_3PhNBr_3 (45.2 g, 120.2 mmol), stirred for 2.5 h, and poured into ice-cold sat. aq. $Na_2S_2O_5$ soln. (600 ml). The aq. phase was extracted with AcOEt (2 × 500 ml), and the combined org. phases were dried (Na_2SO_4) and evaporated. FC (200 g of silica gel; cyclohexane/AcOEt 12:1) gave **28** (3.27 g, 15%) and **27** (16.79 g, 79%).

Data of **27**: Amorphous solid. R_f (cyclohexane/AcOEt 3:1) 0.48. M.p. 99–100°. FT-IR (1.5%, $CHCl_3$): 3426*w* (NH), 3400*w*, 3008*w*, 2957*w*, 2862*w*, 1727*s* (C=O), 1535*m*, 1448*w*, 1438*w*, 1424*w*, 1381*w*, 1344*w*, 1293*w*, 1263*m*, 1170*s*, 1082*w*, 997*w*, 950*w*, 928*w*, 878*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.13–7.00 (*m*, NH); 4.33–4.19 (*m*, H−C(3), H−C(4)); 4.08 (*qt*, *J* = 8.1, 4.0, H−C(1)); 2.80 (*dtd*, *J* = 14.0, 4.1, 1.6, H−C(2)); 2.51 (*ddt*, *J* = 14.6, 7.2, 3.4, H−C(5)); 2.16–1.91 (*m*, H−C(6), H′−C(2), H′−C(5)); 1.65–1.53 (*m*, H′−C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.77 (*q*, *J* = 37, C=O); 115.89 (*q*, *J* = 288, CF_3); 53.54, 51.66 (2*d*, C(3), C(4)); 46.61 (*d*, C(1)); 38.20 (*t*, C(2)), 30.84, 28.85 (2*t*, C(5), C(6)). ESI-MS (neg. mode): 390 (37), 388 (53), 386 (23, $[M+Cl]^-$); 354 (46), 352 (100), 350 (47, $[M-H]^+$). Anal. calc. for $C_8H_{10}Br_2F_3NO$ (352.98): C 27.22, H 2.86, N 3.97; found: C 27.34, H 2.50, N 3.91.

Data of **28**: Amorphous solid. R_f (cyclohexane/AcOEt 3:1) 0.59. M.p. 114–115°. FT-IR (1.5%, $CHCl_3$): 3426*m* (NH), 3011*w*, 2957*w*, 1728*s* (C=O), 1536*m*, 1454*w*, 1436*w*, 1385*w*, 1339*w*, 1298*w*, 1278*w*, 1259*m*, 1171*s*, 1027*w*, 962*w*, 899*w*, 849*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.41–6.29 (*m*, NH); 4.69–4.64 (*m*, H−C(3)); 4.64–4.59 (*m*, H−C(4)); 4.40 (*tdt*, *J* = 11.8, 8.1, 4.1, H−C(1)); 2.61 (*dddd*, *J* = 15.6, 12.5, 4.1, 3.1, H_{ax}−C(5)); 2.46

(*ddd*, $J = 14.2$, 11.7, 3.4, $H_{ax}-C(2)$); 2.25 (br. *d*, $J \approx 14.3$, $H_{eq}-C(2)$); 2.05 (br. *d*, $J \approx 14.9$, $H_{eq}-C(5)$); 1.98 (br. *d*, $J \approx 13.3$, $H_{eq}-C(6)$); 1.86 (*qd*, $J = 12.1$, 3.7, $H_{ax}-C(6)$). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.30, 50.58 (2*d*, C(3), C(4)); 44.83 (*d*, C(1)); 33.82 (*t*, C(2)); 27.81, 26.49 (2*t*, C(5), C(6)). ESI-MS (neg. mode): 390 (36), 388 (50), 386 (23, $[M + Cl]^-$); 354 (47), 352 (100), 350 (49, $[M - H]^-$). Anal. calc. for $C_8H_{10}Br_2F_3NO$ (352.98): C 27.22, H 2.86, N 3.97; found: C 27.33, H 2.96, N 3.84.

Methyl c-*4*,t-*5*-*Dibromo*-c-*2*-*{[(*tert-*butoxy)carbonyl]amino}cyclohexane*-r-*1*-*carboxylate* (**29**), *Methyl* t-*4*,c-*5*-*Dibromo*-c-*2*-*{[(*tert-*butoxy)carbonyl]amino}cyclohexane*-r-*1*-*carboxylate* (**30**), *and Methyl (1*RS,*5*SR,*6*RS,*8*RS*)*-8*-*Bromo*-*3*-*oxo*-*2*-*oxa*-*4*-*azabicyclo[3.3.1]nonane*-*6*-*carboxylate* (**31**). *a*) At 0°, a suspension of **11** (110 mg, 0.43 mmol) and Et_4NBr (905 mg, 4.3 mmol) in CH_2Cl_2 (1 ml) was treated with $PhMe_3NBr_3$ (323 mg, 0.86 mmol), stirred for 2 h, treated with sat. aq. $Na_2S_2O_5$ soln. (10 ml), and extracted with Et_2O (2 × 10 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (12 g of silica gel; cyclohexane/AcOEt 9:1) gave **29** (151 mg, 84%) and **30** (11 mg, 6%).

b) At −78°, a soln. of **11** (210 mg, 0.795 mmol) in CH_2Cl_2 (2 ml) was treated with Br_2 (0.2 ml, 3.9 mmol), stirred for 75 min, treated with sat. aq. $Na_2S_2O_5$ soln. (10 ml), and warmed to 0°. Workup as described in *a* and FC (50 g of silica gel; cyclohexane/AcOEt 9:1) of the residue (293 mg; colourless, amorphous) gave **29** (92 mg, 28%) and **30** (99.5 mg, 30%). Elution of the column with MeOH gave **31** (81 mg, 36%).

Data of **29**: Colourless crystals. R_f (toluene/AcOEt 10:1) 0.47. M.p.: 148.8–150.0°. FT-IR (0.5%, $CHCl_3$): 3437*w* (NH), 3019*s*, 2980*w*, 2952*w*, 1728*s* (C=O), 1709*s* (C=O), 1602*w*, 1499*s*, 1446*w*, 1367*m*, 1309*m*, 1065*w*, 1012*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.50 (br. *d*, $J = 9.3$, NH); 4.34–4.10 (br. *s*, 2 H), 4.10–3.94 (br. *s*, 1 H) (H−C(2), H−C(4), H−C(5)); 3.72 (*s*, MeO); 3.01 (br. *dt*, $J \approx 5.0, 4.4$, H−C(1)); 2.78 (br. *ddd*, $J = 14.6, 5.6, 3.4$, $H_{eq}-C(6)$); 2.58 (br. *d*, $J = 14.0$, $H_{eq}-C(3)$); 2.28 (*dt*, $J = 14.0$, 9.0, $H_{ax}-C(3)$); 2.09 (*ddd*, $J = 14.3$, 9.3, 4.7, $H_{ax}-C(6)$); 1.40 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.30 (*s*, *C*O_2Me); 154.70 (*s*, *C*O_2CMe_3); 79.77 (*s*, Me_3C); 52.27 (*q*, MeO); 52.02 (*d*, C(2)); 47.84, 43.37 (2*d*, C(4), C(5)); 38 (br. *d*, C(1)); 28.39 (*q*, *Me*$_3$C); the C(3) and C(6) *t* are hidden, presumably under the *Me*$_3$C *q*. ESI-MS: 418 (45), 416 (100), 414 (52, $[M + 1]^+$); 362 (14), 360 (32), 358 (15, $[M + 1 - C_4H_8]^+$).

Data of **30**: Colourless crystals. R_f (toluene/AcOEt 10:1) 0.43. M.p. 101.5–109.0°. FT-IR (0.5%, $CHCl_3$): 3440*w* (NH), 3030*m*, 2981*w*, 2955*w*, 1725*s* (C=O), 1709*s* (C=O), 1602*w*, 1500*s*, 1439*m*, 1367*m*, 1280*m*, 1096*w*, 1053*w*, 1007*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.62–5.45 (*m*, NH); 4.63–4.53 (*m*, 1 H), 4.40–4.28 (*m*, 2 H) (H−C(2), H−C(4), H−C(5)); 3.71 (*s*, MeO); 2.87–2.75 (*m*, 3 H); 2.61–2.50 (*m*, 1 H); 2.04 (*dt*, $J = 14.6$, 4.7, 1 H); 1.44 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.20 (*C*O_2CMe_3) (one signal hidden by noise); 79.94 (Me_3C); 52.46 (MeO); 52.13, 50.39, 45.49 (C(2), C(4), C(5)); 42.20 (C(1)); 31.95, 27.08 (C(3), C(6)); 28.54 (*Me*$_3$C). ESI-MS: 472 (11), 470 (21), 468 (9, $[M + Na + MeOH]^+$); 456 (10), 454 (21), 452 (10, $[M + K]^+$); 440 (52), 438 (100), 436 (58, $[M + Na]^+$); 418 (7), 416 (17), 414 (8, $[M + 1]^+$); 362 (13), 360 (28), 358 (12, $[M + 1 - C_4H_8]^+$); 318 (5), 316 (9), 314 (5, $[M + 1 - C_4H_8 - CO_2]^+$).

Data of **31**: Yellowish, amorphous. R_f (cyclohexane/AcOEt 3:1) 0.0. M.p. 190–197° (dec.). FT-IR (1.5%, $CHCl_3$): 3438*w* (NH), 3025*w*, 3011*w*, 2952*w*, 1715*s* (C=O), 1502*w*, 1438*m*, 1407*w*, 1367*w*, 1347*w*, 1326*w*, 1154*w*, 1101*m*, 1062*w*, 1040*w*, 1005*w*, 978*w*, 953*w*, 891*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.76–5.68 (br. *s*, NH); 4.67–4.63 (*m*), 4.56–4.51 (*m*) (H−C(1), H−C(8)); 4.06–4.01 (*m*, H−C(5)); 3.73 (*s*, MeO); 3.00 (*ddd*, $J = 10.9$, 5.9, 1.6, H−C(6)); 2.56 (*ddt*, $J = 14.0$, 2.2, 1.6, irr. at 5.72 → *dt*, $J = 14.0$, 1.6, $H_{ax}-C(9)$); 2.43–2.37 (*m*, $CH_2(7)$); 2.10 (*dtd*, $J = 14.3$, 4.1, 1.6, $H_{eq}-C(9)$). ESI-MS: 329 (33), 327 (34, $[M + MeOH + NH_4]^+$); 312 (19), 310 (18, $[M + MeOH + 1]^+$); 280 (100), 278 (80, $[M + 1]^+$).

tert-*Butyl* N-*{*c-*2*-*[(Benzyloxy)methyl]*-t-*4*,c-*5*-*dibromocyclohex*-r-*1*-*yl}carbamate* (**32**), tert-*Butyl* N-*{*c-*2*-*[(Benzyloxy)methyl]*-c-*4*,t-*5*-*dibromocyclohex*-r-*1*-*yl}carbamate* (**33**), *(1*RS,*5*SR,*6*RS,*8*RS*)*-6*-*[(Benzyloxy)methyl]*-8*-*bromo*-*2*-*oxa*-*4*-*azabicyclo[3.3.1]nonan*-*3*-*one* (**34**), *and (1*RS,*2*SR,*4*SR,*5*SR*)*-4*-*Bromo*-*2*-*[[(*tert-*butoxy)carbonyl]amino]*-*6*-*oxabicyclo[3.2.1]octane* (**35**). *a*) At 0°, a soln. of **13** (130 mg, 0.41 mmol) in CH_2Cl_2 (10 ml) was treated with $PhMe_3NBr_3$ (310 mg, 0.82 mmol), stirred for 160 min, treated with sat. aq. $Na_2S_2O_5$ soln. (20 ml), and extracted with Et_2O (2 × 20 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (15 g of silica gel; cyclohexane/AcOEt 10:1) gave **32** (91 mg, 46%). Elution of the column with MeOH gave **34** (69 mg, 49%).

b) At −78°, a soln. of **13** (140 mg, 0.44 mmol) in CH_2Cl_2 (10 ml) was treated with Br_2 (0.07 ml, 1.32 mmol), stirred for 160 min, and worked up as described in *a*. FC (15 g of silica gel; cyclohexane/AcOEt 10:1) gave **32** (37.5 mg, 18%), **33** (14 mg, 6%), and **35** (43.4 mg, 32%). Elution of the column with MeOH gave **34** (58 mg, 43%).

c) At −78°, a suspension of **13** (2.0 g, 6.5 mmol) and Et_4NBr (13.2 g, 63 mmol) in CH_2Cl_2 (20 ml) was treated with $PhMe_3NBr_3$ (4.79 g, 12.6 mmol) and allowed to warm to r.t. within 20 h. Workup as described in *a* and FC (100 g of silica gel; cyclohexane/AcOEt 10:1) gave **32** (2.48 g, 82%) as colourless crystals.

Data of **32**: Colourless crystals. R_f (toluene/AcOEt 10:1) 0.58. M.p. 117° (dec.). FT-IR (2%, $CHCl_3$): 3433*w* (NH), 3020*m*, 2981*m*, 2932*w*, 2868*w*, 1707*s* (C=O), 1502*s*, 1455*m*, 1393*m*, 1377*m*, 1323*w*, 1280*w*, 1090*m*, 1040*w*, 1028*w*, 981*w*, 857*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39–7.26 (5 arom. H); 5.60 (br. *d*, *J* = 8.1, NH); 4.54, 4.46 (2*d*, *J* = 11.8, PhC*H*$_2$); 4.50–4.41 (*m*, H–C(4)); 4.37–4.29 (*m*, H–C(5)); 4.03–3.93 (*m*, H–C(1)); 3.67 (*dd*, *J* = 9.7, 7.2, CH–C(2)); 3.47 (*dd*, *J* = 9.7, 5.3, CH′–C(2)); 2.66 (*dt*, *J* = 14.6, 4.4, H–C(6)); 2.49–2.40 (*m*, H–C(2)); 2.34 (*ddd*, *J* = 14.6, 7.6, 3.6, H–C(3)); 2.22 (*dt*, *J* = 14.6, 7.3, H′–C(6)); 2.08 (*ddd*, *J* = 14.6, 7.6, 4.0, H′–C(3)); 1.43 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.07 (*s*, C=O); 137.65 (*s*); 128.41 (*d*, 2 C); 127.34 (*d*); 127.58 (*d*, 2 C); 79.35 (*s*, Me$_3$*C*); 73.46 (*t*, Ph*C*H$_2$); 70.69 (*t*, *C*H$_2$–C(2)); 53.06, 52.06, 48.33 (3*d*, C(1), C(4), C(5)); 36.43 (*d*, C(2)); 28.54 (*q*, *Me*$_3$C); 2*t* hidden (probably at 28.54). ESI-MS: 518 (14), 516 (29), 514 (15, $[M+K]^+$); 502 (49), 500 (100), 498 (57, $[M+Na]^+$); 446 (19), 444 (19), 442 (7, $[M+Na-C_4H_8]^+$); 380 (5), 378 (10), 376 (7, $[M+1-C_4H_8-CO_2]^+$). Anal. calc. for $C_{19}H_{27}Br_2NO_3$ (477.24): C 47.82, H 5.70, N 2.93; found: C 47.94, H 5.76, N 2.86.

Data of **33**: Colourless oil. R_f (toluene/AcOEt 10:1) 0.56. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.12 (5 arom. H); 5.21 (br. *s*, NH); 4.49 (*d*, *J* = 12.1), 4.44 (*d*, *J* = 11.8) (PhC*H*$_2$); 4.26–4.05 (*m*, 2 H); 4.00–3.94 (*m*, 1 H); 3.54 (br. *dd*, *J* = 9.5, 5.1, CH–C(2)); 3.41 (br. *dd*, *J* = 9.0, 4.4, CH′–C(2)); 2.79 (br. *d*, *J* = 14.0, 1 H); 2.58–2.39 (*m*, 2 H); 2.09–1.96 (*m*, 2 H); 1.46 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.32 (C=O); 137.48; 128.35 (2 C); 127.73; 127.61 (2 C); 80.35 (Me$_3$*C*); 73.59 (Ph*C*H$_2$); 71.56 (*C*H$_2$–C(2)); 52.78, 49.67, 48.54 (C(1), C(4), C(5)); 40.62 (C(2)); 35.86; 28.47 (*Me*$_3$C); 1 signal hidden by other signal. ESI-MS: 518 (16), 516 (35), 514 (21, $[M+K]^+$); 502 (43), 500 (100), 498 (44, $[M+Na]^+$).

Data of **34**: Yellow, amorphous. R_f (toluene/AcOEt 10:1) 0.02. M.p. 136–141°. FT-IR (1%, $CHCl_3$): 3443*w* (NH), 3033*w*, 3010*m*, 2867*w*, 1715*s* (C=O), 1604*w*, 1436*m*, 1409*w*, 1369*w*, 1294*w*, 1102*m*, 1038*w*, 904*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41–7.29 (5 arom. H); 5.33–5.28 (*m*, NH); 4.68–4.64 (*m*, H–C(1)); 4.54 (*d*, *J* = 12.1, PhC*H*); 4.50–4.46 (*m*, H–C(8)); 4.45 (*d*, *J* = 12.1, PhC*H*); 3.78–3.73 (*m*, H–C(5)); 3.37 (*dd*, *J* = 9.5, 5.1, CH–C(6)); 3.31 (*t*, *J* = 9.2, CH′–C(6)); 2.53 (*ddt*, *J* = 14.0, 2.2, 1.6, H$_{ax}$–C(9)); 2.41–2.30 (*m*, H–C(6)); 2.04 (*dtd*, *J* = 14.0, 4.0, 1.6, irr. at 4.48 → *dt*, H$_{eq}$–C(9)); 1.97–1.90 (*m*, 2 H–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.72 (*s*, C=O); 137.80 (*s*); 128.45 (*d*, 2 C); 127.82 (*d*); 127.34 (*d*, 2 C); 75.49 (*d*, C(1)); 73.30 (*t*, Ph*C*H$_2$); 70.35 (*t*, *C*H$_2$–C(6)); 47.68, 46.00 (2*d*, C(5), C(8)); 36.92 (*d*, C(6)); 28.19, 24.30 (2*t*, C(7), C(9)). ESI-MS: 705 (31), 703 (23), 701 (16, $[2M+Na]^+$); 364 (19), 362 (23, $[M+Na]^+$); 342 (15), 340 (15, $[M+1]^+$); 298 (75), 296 (100, $[M+1-CO_2]^+$).

Data of **35**: Colourless, amorphous. R_f (toluene/AcOEt 10:1) 0.25. M.p. 153.3–155.0°. FT-IR (1%, $CHCl_3$): 3445*w* (NH), 3031*w*, 3011*m*, 2981*m*, 2885*w*, 1711*s* (C=O), 1501*s*, 1454*w*, 1393*w*, 1368*m*, 1326*w*, 1278*m*, 1087*w*, 1053*m*, 1030*m*, 1000*w*, 971*w*, 945*w*, 923*w*, 883*w*, 859*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.51 (br. *d*, *J* = 6.9, NH); 4.29 (*dd*, *J* = 5.6, 4.4, H–C(5)); 4.14 (*t*, *J* = 4.7, H–C(4)); 4.05–3.93 (*m*, $W_{1/2} \approx 20$, H–C(2)); 3.86 (*d*, *J* = 8.7, H$_{endo}$–C(7)); 3.79 (*dd*, *J* = 8.7, 4.0, H$_{exo}$–C(7)); 2.59–2.54 (*m*, H–C(1)); 2.52 (*d*, *J* = 12.8, H$_{ax}$–C(8)); 2.20 (*dd*, *J* = 15.1, 5.5, irr. at 3.99 → *d*, *J* = 15.1, H$_{eq}$–C(3)); 1.97 (*ddd*, *J* = 14.9, 12.1, 5.3, irr. at 3.99 → *dd*, *J* = 14.9, 5.3, H$_{ax}$–C(3)); 1.87 (*dtd*, *J* = 12.5, 5.6, 1.2, H$_{eq}$–C(8)); 1.43 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.70 (*s*, C=O); 79.71 (*s*, Me$_3$*C*); 77.11 (*d*, C(5)); 68.52 (*t*, C(7)); 47.80, 47.47 (2*d*, C(2), C(4)); 40.37 (*d*, C(1)); 34.54, 31.94 (2*t*, C(3), C(8)); 28.43 (*q*, *Me*$_3$C). ESI-MS: 346 (12), 344 (12, $[M+K]^+$); 330 (37), 328 (29, $[M+Na]^+$).

N-*{*c-*2-[(Benzyloxy)methyl]*-t-*4,*c-*5-dibromocyclohex*-r-*1-yl}-2,2,2-trifluoroacetamide* (**36**) *and* N-*{*c-*2-[(Benzyloxy)methyl]*-c-*4,*t-*5-dibromocyclohex*-r-*1-yl}-2,2,2-trifluoroacetamide* (**37**). *a*) A cold (0°) soln. of **14** (31 mg, 98.9 μmol) in CH_2Cl_2 (1 ml) was treated with Et_4NBr (208 mg, 989 μmol) and $PhMe_3NBr_3$ (75 mg, 198 μmol), stirred for 1 h, and treated with sat. aq. $Na_2S_2O_5$ soln. (2 ml). The mixture was extracted with Et_2O (2 × 20 ml), and the combined org. phases were dried (Na_2SO_4), and evaporated. FC (2 g of silica gel; cyclohexane/AcOEt 10:1) of the residue (62 mg, colourless oil) gave **36** (42 mg, 89%). Colourless oil.

b) At −78°, a soln. of **14** (52.5 mg, 167 μmol) in CH_2Cl_2 (2 ml) was treated with Br_2 (25 μl, 502 μmol), stirred for 1 h, and treated with sat. aq. $Na_2S_2O_5$ soln. (15 ml). The mixture was extracted with Et_2O (2 × 20 ml), and the combined org. phases were dried (Na_2SO_4), and evaporated. FC (12 g of silica gel; hexane/AcOEt 10:1) of the residue (91 mg, yellow oil) gave **22** (12.6 mg, 19%), **36** (33.2 mg, 42%), and **37** (25 mg, 32%) as colourless oils.

Data of **36**: R_f (toluene/AcOEt 10:1) 0.62. FT-IR (0.5%, $CHCl_3$): 3389*w* (NH), 3339*w* (NH), 2928*w*, 2857*w*, 1722*s*, 1603*w*, 1541*m*, 1452*w*, 1427*w*, 1369*w*, 1292*w*, 1278*w*, 1102*w*, 1091*w*, 1027*w*, 987*w*, 929*w*, 906*w*, 856*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01–7.91 (br. *s*, NH); 7.41–7.27 (5 arom. H); 4.52 (*d*, *J* = 12.4), 4.48 (*d*, *J* = 12.1) (PhC*H*$_2$); 4.48–4.41, 4.41–4.33, 4.33–4.24 (3*m*, H–C(1), H–C(4), H–C(5)); 3.73 (*t*, *J* ≈ 8.6, CH–C(2)); 3.54 (*dd*, *J* = 9.7, 3.6, CH′–C(2)); 2.74 (*dt*, *J* = 14.9, 4.4, H–C(6)); 2.53 (*tt*, *J* ≈ 8.1, 4.0, H–C(2)); 2.46 (*ddd*, *J* = 14.3, 8.3, 3.6, H–C(3)); 2.30 (*dt*, *J* = 14.9, 7.1, H′–C(6)); 2.06 (*ddd*, *J* = 13.7, 7.8, 2.8, H′–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.85 (*q*, *J* = 36.6, C=O); 137.07; 128.83 (2 C); 128.43; 128.16 (2 C); CF_3 hidden by noise; 74.10

(Ph*C*H$_2$); 70.88 (*C*H$_2$–C(2)); 52.18 (C(1)); 50.71, 48.55 (C(4), C(5)); 35.58 (C(2)); 27.13 (C(3), C(6)). ^{19}F-NMR (282 MHz, CDCl$_3$): −76.68. ESI-MS: 530 (4), 528 (9), 526 (6, $[M+\mathrm{Na}+\mathrm{MeOH}]^+$); 514 (24), 512 (40), 510 (18, $[M+\mathrm{K}]^+$); 498 (54), 496 (100), 494 (53, $[M+\mathrm{Na}]^+$).

Data of **37**: R_f (cyclohexane/AcOEt 3:1) 0.51. FT-IR (1%, CHCl$_3$): 3331*w* (NH), 3033*w*, 3013*w*, 2868*w*, 1725*s* (C=O), 1539*m*, 1455*w*, 1366*w*, 1283*w*, 1102*m*, 1072*w*, 1028*w*, 895*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 7.90–7.81 (br. *s*, NH); 7.40–7.24 (5 arom. H); 4.52, 4.48 (2*d*, *J* = 11.8, PhC*H*$_2$); 4.27–4.16 (*m*, H–C(1), H–C(4), H–C(5)); 3.83 (*dd*, *J* = 9.3, 6.2, CH–C(2)); 3.58 (*dd*, *J* = 9.8, 2.3, CH′–C(2)); 2.91 (br. *ddd*, *J* ≈ 15, 5, 4, H$_{eq}$–C(6)); 2.57 (br. *dt*, *J* = 14.6, 3.9, H$_{eq}$–C(3)); 2.27 (*dt*, *J* = 14.4, 9.7, H$_{ax}$–C(3)); 2.21–2.11 (*m*, H–C(2)); 2.14 (*ddd*, *J* = 14.6, 10.0, 3.6, H$_{ax}$–C(6)). ^{13}C-NMR (75 MHz, CDCl$_3$): 136.39; 128.54 (2 C); 128.23; 127.95 (2 C); 74.02 (Ph*C*H$_2$); 71.86 (*C*H$_2$–C(2)); 53.00 (br., CBr); 51.30 (C(1)); 50.65 (br., CBr); 38.61 (C(2)); 34.76 (C(3)); 27.02 (C(6)); COCF$_3$ signals hidden by noise. ^{19}F-NMR (282 MHz, CDCl$_3$): −75.80 (*s*). ESI-MS: 514 (70), 512 (100), 510 (37, $[M+\mathrm{K}]^+$); 498 (40), 496 (84), 494 (40, $[M+\mathrm{Na}]^+$).

*(1*RS*,5*SR*,6*RS*,8*RS*)-4-Benzyl-6-[(benzyloxy)methyl]-8-bromo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one* (**38**) *and (1*RS*,2*SR*,4*SR*,5*SR*)-2-{(Benzyl)[(*tert*-Butoxy)carbonyl]amino}-4-bromo-6-oxabicyclo[3.2.1]octane* (**39**). At −78°, a soln. of **16** (30 mg, 73 μmol) in CH_2Cl_2 (3 ml) was treated with Br_2 (7.5 μl, 146 μmol), stirred for 3 h, and treated with sat. aq. $Na_2S_2O_5$ soln. The mixture was extracted with Et_2O (2 × 20 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (2 g of silica gel; cyclohexane/AcOEt 6:1) of the residue (36 mg, orange oil) gave **39** (7.6 mg, 26%) as a colourless oil and **38** (10.2 mg, 32%) as a colourless oil, which became a glass upon standing.

Data of **38**: R_f (cyclohexane/AcOEt 3:1) 0.21. FT-IR (0.5%, CHCl$_3$): 3014*w*, 2952*w*, 2862*w*, 1687*s* (C=O), 1604*w*, 1496*w*, 1450*m*, 1362*w*, 1309*w*, 1123*m*, 1106*m*, 1074*w*, 1046*w*, 1001*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 7.42–7.19 (10 arom. H); 5.27 (*d*, *J* = 14.9, PhC*H*N); 4.64 (br. *t*, *J* = 3.4, H–C(1)); 4.67 (*s*, PhC*H*$_2$O); 4.51–4.47 (*m*, H–C(8)); 3.80–3.76 (*m*, H–C(5)); 3.76 (*d*, *J* = 14.9, PhC*H*N); 3.42–3.37 (*m*, CH$_2$–C(6)); 2.50–2.42 (*m*, H–C(6)); 2.43 (*ddd*, *J* = 14.0, 2.2, 1.6 H$_{ax}$–C(9)); 1.98 (*ddd*, *J* = 15.6, 12.1, 4.0, H$_{ax}$–C(7)); 1.88 (br. *d*, *J* = 15.9, H$_{eq}$–C(7)); 1.74 (*dtd*, *J* = 14.0, 4.0, 1.6, H$_{eq}$–C(9)). ^{13}C-NMR (75 MHz, CDCl$_3$): 137.61, 137.24 (2*s*); 128.84, 128.40, 128.30, 128.22, 127.94 (5*d*); 76.03 (*d*, C(1)); 73.61 (*t*, Ph*C*H$_2$O); 70.49 (*t*, *C*H$_2$–C(6)); 52.92 (*t*, Ph*C*H$_2$N); 49.26, 47.73 (2*d*, C(5), C(8)); 37.19 (*d*, C(6)); 28.39, 25.73 (2*t*, C(7), C(9)). ESI-MS: 901 (4), 899 (8), 897 (3, $[2M+\mathrm{K}]^+$); 885 (59), 883 (100), 881 (49, $[2M+\mathrm{Na}]^+$); 486 (10), 484 (9, $[M+\mathrm{Na}+\mathrm{MeOH}]^+$); 470 (27), 468 (23, $[M+\mathrm{K}]^+$); 454 (92), 452 (95, $[M+\mathrm{Na}]^+$); 432 (7), 430 (6, $[M+1]^+$).

Data of **39**: R_f (cyclohexane/AcOEt 3:1) 0.49. FT-IR (1.5%, CHCl$_3$): 3027*w*, 3013*m*, 2979*m*, 2887*w*, 1683*s* (C=O), 1604*w*, 1496*w*, 1478*w*, 1454*m*, 1392*m*, 1381*m*, 1367*m*, 1353*m*, 1330*w*, 1313*w*, 1120*w*, 1082*w*, 1055*m*, 1035*m*, 1019*w*, 974*w*, 955*w*, 929*w*, 882*w*, 864*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 7.34–7.11 (5 arom. H); 4.57 (*d*, *J* = 17.1, PhC*H*); 4.57–4.49 (*m*, H–C(2)); 4.49 (*d*, *J* = 16.8, PhC*H*); 4.24 (*t*, *J* = 5.0, H–C(5)); 4.16–4.12 (*m*, H–C(4)); 3.86 (*d*, *J* = 8.7, H$_{endo}$–C(7)); 3.64 (*dd*, *J* = 9.0, 4.1, H$_{exo}$–C(7)); 2.55 (*d*, *J* = 12.5, H$_{ax}$–C(8)); 2.54–2.48 (*m*, H–C(1)); 2.43 (br. *td*, *J* = 13.2, 5.1, H$_{ax}$–C(3)); 1.99 (br. *dd*, *J* = 14.5, 4.8, H$_{eq}$–C(3)); 1.84 (*dtd*, *J* = 12.5, 5.4, 1.6, H$_{eq}$–C(8)); 1.45 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, CDCl$_3$): 155.66 (*s*, C=O); 139.58 (*s*); 128.45 (*d*, 2 C); 126.76 (*d*, 1 C); 126.08 (*d*, 2 C); 80.38 (*s*, Me$_3$*C*); 77.23 (*d*, C(5)); 69.61 (*t*, C(7)); 53.04 (*d*, C(2); 48.58 (*d*, C(4)); 47.12 (*t*, Ph*C*H$_2$); 40.63 (*d*, C(1)); 34.00, 32.66 (2*t*, C(3), C(8)); 28.46 (*q*, *Me*$_3$C). ESI-MS: 817 (10), 815 (15), 813 (9, $[2M+\mathrm{Na}]^+$); 452 (26), 450 (25, $[M+\mathrm{Na}+\mathrm{MeOH}]^+$); 436 (39), 434 (34, $[M+\mathrm{K}]^+$); 420 (100), 418 (98, $[M+\mathrm{Na}]^+$); 398 (6), 396 (5, $[M+1]^+$); 342 (15), 340 (13, $[M+1-\mathrm{C_4H_8}]^+$).

c-*3*,t-*4-Dibromocyclohexan*-r-*1-amine* (**40**). At r.t., a soln. of **25** (350 mg, 0.98 mmol) in CH_2Cl_2 (20 ml) was treated with CF_3COOH (1.5 ml, 19.3 mmol), stirred for 3.5 h, and evaporated. The residual oil, dissolved in sat. aq. K_2CO_3 soln. (15 ml), was extracted with $CHCl_3$ (4 × 40 ml), and the combined org. phases were dried (K_2CO_3), and evaporated to yield crude **40** (266 mg, 100%). Colourless oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.49. ^{1}H-NMR (300 MHz, CDCl$_3$): 4.06, 3.98 (2*td*, *J* = 10.6, 4.4, H–C(3), H–C(4)); 2.84 (*tt*, *J* = 11.2, 3.7, H–C(1)); 2.59 (*ddd*, *J* = 13.1, 6.5, 4.1, 1 H); 2.47 (*ddd*, *J* = 14.0, 7.8, 3.4, 1 H); 1.98–1.72 (*m*, 3 H); 1.32–1.18 (*m*, 1 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 56.29, 54.57 (2*d*, C(3), C(4)); 50.03 (*d*, C(1)); 47.75 (*t*, C(2)); 35.97, 35.89 (2*t*, C(5), C(6)). ESI-MS: 260 (46), 258 (100), 256 (51, $[M+1]^+$); 178 (50), 176 (53, $[M-\mathrm{Br}]^+$).

*(1*RS*,2*SR*,4*SR*)-2-Bromo-7-azabicyclo[2.2.1]heptane* (**41**). A soln. of **40** (266 mg, 0.98 mmol) in $CHCl_3$ (20 ml) was treated with K_2CO_3 (140 mg, 0.98 mmol), stirred under reflux for 12 d, cooled to r.t., and treated with 10% aq. K_2CO_3 soln. (10 ml). The org. phase was separated, and the aq. phase was extracted with $CHCl_3$ (4 × 20 ml). The combined org. phases were dried (K_2CO_3) and evaporated to give crude **41** (200 mg, 100%). Brown oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.56. ^{1}H-NMR (300 MHz, CDCl$_3$): 4.08 (*dd*, *J* = 7.2, 2.8, H–C(2)); 3.73–3.67, 3.64–3.56 (2*m*, H–C(1), H–C(4)); 2.18 (*dd*, *J* = 14.3, 6.9, H$_{endo}$–C(3)); 2.00 (*ddt*, *J* = 14.3, 5.3, 2.5, H$_{exo}$–C(3)); 1.73 (*tdd*, *J* = 11.8, 5.3, 3.7, 1 H); 1.64–1.52 (*m*, 1 H); 1.28–1.09 (*m*, 2 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 64.97 (*d*, C(1)); 56.74 (*d*, C(4)); 53.84 (*d*, C(2)); 44.83 (*t*, C(3)); 28.56, 27.04 (2*t*).

*(1*RS,*2*SR,*4*SR*)-2-Bromo-7-[(*tert-*butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane* (**42**). At r.t., a soln. of **41** (200 mg, 0.98 mmol) in $CHCl_3$ (10 ml) was treated with K_2CO_3 (140 mg, 0.98 mmol) and Boc_2O (855 mg, 3.92 mmol), and stirred for 19 h. The mixture was washed with H_2O, and the aq. phase was extracted with $CHCl_3$ (2×25 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 12:1) gave **42** (224 mg, 83% from **25**). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.61. FT-IR (0.7%, $CHCl_3$): 3008*m*, 2980*m*, 2879*w*, 1694*s* (C=O), 1477*w*, 1454*w*, 1392*s*, 1368*s*, 1321*m*, 1177*m*, 1153*s*, 1134*m*, 1101*m*, 1048*w*, 983*w*, 907*m*, 886*w*, 872*w*, 849*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.41–4.36, 4.34–4.27 (2*m*, H–C(1), H–C(4)); 3.99 (*dd*, $J = 7.2$, 3.4, H–C(2)); 2.33–2.23 (br. *d*, $J \approx 14$, H_{exo}–C(3)); 2.17 (*dd*, $J = 13.7$, 7.5, H_{endo}–C(3)); 1.94–1.82 (*m*, H–C(6)); 1.78–1.63 (*m*, H–C(5)); 1.46 (*s*, *t*-Bu); 1.43–1.25 (*m*, H′–C(6), H′–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$); 155.00 (*s*, C=O); 79.93 (*s*, Me_3C); 63.89 (*d*, C(1)); 55.61 (br. *d*, C(4)); 49.71 (br. *d*, C(2)); 43.61 (*t*, C(3)); 28.52, 28.00 (2*t*, C(5), C(6)); 28.27 (*q*, Me_3C). ESI-MS: 332 (97), 330 (100, $[M + Na + MeOH]^+$); 316 (50), 314 (45, $[M + K]^+$); 300 (45), 298 (46, $[M + Na]^+$). Anal. calc. for $C_{11}H_{18}BrNO_2$ (276.17): C 47.84, H 6.57, N 5.07; found: C 47.78, H 6.47, N 5.16.

Transformation of **27** *into* **42**. At r.t., a soln. of **27** (15.28 g, 43.3 mmol) in MeOH (500 ml) and H_2O (200 ml) was treated with K_2CO_3 (29.9 g, 216 mmol) and stirred for 13.5 h. MeOH was removed *in vacuo* below 40°. The residue was treated with sat. aq. K_2CO_3 soln. (100 ml) and extracted with $CHCl_3$ (5×300 ml). The combined org. phases were dried (K_2CO_3) and evaporated. The residue (crude **40**; 11.1 g, 43.2 mmol) was dissolved in $CHCl_3$ (1 l), treated with K_2CO_3 (5.97 g, 43.2 mmol), heated under reflux for 13 d, cooled to r.t. treated with Boc_2O (60 ml, 0.26 mol) and K_2CO_3 (5.97 g, 43.2 mmol), and stirred at r.t. for 3 d. The mixture was washed with H_2O (500 ml), and the aq. phase was extracted with $CHCl_3$ (500 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (300 g of silica gel; toluene/AcOEt 40:1) gave **42** (11.27 g, 93% from **27**).

*7-[(*tert-*Butoxy)carbonyl]-7-azabicyclo[2.2.1]hept-2-ene* (**43**) [80]. A soln. of **42** (1.058 g, 3.83 mmol) in THF (50 ml) was treated with *t*-BuOK (473 mg, 4.21 mmol), heated under reflux for 3 h, cooled, and poured into brine (50 ml). The resulting mixture was extracted with Et_2O (3×100 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (35 g of silica gel; cyclohexane/AcOEt 12:1) gave **43** (652 mg, 87%). Colourless oil. Data: see [80].

*(1*RS,*2*RS,*3*SR,*4*SR*)-7-[(*tert-*Butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2,3-diol* (**44**). A soln. of **43** (98 mg, 0.50 mmol) in acetone (23 ml) and H_2O (2.5 ml) was treated with *N*-methylmorpholine *N*-oxide monohydrate (NMO; 102 mg, 0.75 mmol) and 2.5% OsO_4 in *t*-BuOH (0.5 ml, 40 μmol), stirred at r.t. for 22 h, diluted with sat. aq. $Na_2S_2O_5$ soln. (50 ml), and extracted with $CHCl_3$ (4×100 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (30 g of silica gel; cyclohexane/AcOEt 1:1) gave **44** (93.5 mg, 82%) as a yellow oil. Crystallisation from hexane/CH_2Cl_2 gave colourless needles of **44** (64 mg, 56%). R_f (cyclohexane/AcOEt 1:1) 0.19. M.p. 82°. FT-IR (0.5%, $CHCl_3$): 3502*w* (OH), 3004*m*, 2988*m*, 2884*w*, 1697*s* (C=O), 1466*m*, 1368*s*, 1318*m*, 1170*s*, 1141*s*, 1111*m*, 1056*s*, 1010*w*, 972*w*, 931*w*, 803*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.11 (br. *s*, H–C(1), H–C(4)); 3.79 (br. *s*, H–C(2), H–C(3)); 3.28–3.08 (br. *s*, 2 OH); 1.73–1.65 (*m*, H–C(5), H–C(6)); 1.45 (*s*, *t*-Bu); 1.81 (*d*, $J = 8.1$, H′–C(5), H′–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.22 (*s*, C=O); 80.25 (*s*, Me_3C); 74.24 (*d*, C(2), C(3)); 62.26 (*d*, C(1), C(4)); 28.26 (*q*, Me_3C); 24.27 (*t*, C(5), C(6)). ESI-MS: 498 (4, $[2M + K]^+$), 481 (45, $[2M + Na]^+$), 476 (8, $[2M + NH_4]^+$), 459 (3, $[2M + 1]^+$), 262 (13, $[M + MeOH + 1]^+$), 247 (95, $[M + NH_4]^+$), 230 (96, $[M + 1]^+$), 206 (2), 174 (7). Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.63, H 8.35, N 6.11; found C 57.78, H 8.25, N 6.10.

*(1*RS,*2*RS,*3*SR,*4*SR*)-2,3-Dihydroxy-7-azoniabicyclo[2.2.1]heptane Chloride* (**45**·HCl). A soln. of **44** (19.9 mg, 86 μmol) in 0.1N HCl (5 ml, 500 μmol) was stirred at 30° for 20 h and lyophilised to give colourless amorphous **45**·HCl (14.0 mg, 97%). R_f (PrOH/AcOH/H_2O 4:1:1) 0.25. M.p. 205–215° (dec.). ^{1}H-NMR (300 MHz, D_2O): 4.80 (*d*, $J = 1.2$, OH, NH); 4.16 (*d*, $J = 1.2$, H–C(2), H–C(3)); 4.06 (*ddd*, $J = 3.7$, 2.3, 1.5, H–C(1), H–C(4)); 1.95–1.88 (*m*, H–C(5), H–C(6)); 1.69 (br. *d*, $J = 8.1$, H′–C(5), H′–C(6)). ^{13}C-NMR (75 MHz, D_2O): 71.47 (*d*, C(2), C(3)); 64.32 (*d*, C(1), C(4)); 21.18 (*t*, C(5), C(6)), ESI-MS: 152 (7, $[M + Na]^+$), 130 (100, $[M + 1]^+$), 87 (24). HR-ESI-MS: 130.08620 (100, $C_6H_{12}NO_2^+$, $[M + 1]^+$; calc. 130.08626).

t-*3*,c-*4*-*Dibromocyclohexan*-r-*1*-*amine* (**46**). According to the preparation of **40**, **26** (295 mg, 0.826 mmol) yielded **46** (226 mg, quant.) as a colourless oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.47. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.70–4.65 (*m*, H–C(3)); 4.60–4.56 (*m*, H–C(4)); 3.33 (*tt*, $J = 10.6$, 4.4, H–C(1)); 2.51 (*dddd*, $J = 15.3$, 12.1, 4.4, 3.1, H_{ax}–C(5)); 2.33 (*ddd*, $J = 14.3$, 10.9, 3.4, H_{ax}–C(2)); 2.17 (br. *d*, $J = 14.3$, H_{eq}–C(2)); 2.04 (br. *d*, $J = 15.3$, H_{eq}–C(5)); 1.88–1.69 (*m*, 2 H–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 52.78, 52.71 (2*d*, C(3), C(4)); 45.33 (*d*, C(1)); 38.65 (*t*, C(2)); 30.98, 28.48 (2*t*, C(5), C(6)). ESI-MS: 355 (28), 353 (58), 351 (29); 292 (8), 290 (17), 288 (8, $[M + MeOH + 1]^+$); 260 (48), 258 (100), 256 (51, $[M + 1]^+$).

Cyclisation of **46**. A soln. of **46** (49 mg, 0.19 mmol) in 1,3-dichlorobenzene (10 ml) was treated with K_2CO_3 (26 mg, 0.19 mmol) and heated slowly to 120°. TLC indicated no change. Then, the mixture was heated at 130° for 2 d, when TLC indicated the formation of a new compound (R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.56). The mixture was cooled to r.t., treated with Boc_2O (0.21 ml, 0.95 mmol), stirred for 3 d, and washed with sat. aq. K_2CO_3 soln. (25 ml). The aq. phase was extracted with $CHCl_3$ (3 × 25 ml), and the combined org. phases were dried (Na_2SO_4) and evaporated. FC (15 g of silica gel; cyclohexane/AcOEt 12:1) gave **42** (32.5 mg, 62%). Colourless oil.

Methyl c-*2-Amino*-c-*4*,t-*5-dibromocyclohexane*-r-*1-carboxylate* (**47**). A soln. of **29** (147 mg, 0.356 mmol) in CH_2Cl_2 (7.5 ml) was treated with CF_3CO_2H (0.5 ml), stirred at r.t. for 13 h, and evaporated. The residue was suspended in sat. aq. K_2CO_3 soln. (15 ml) and extracted with $CHCl_3$ (3 × 20 ml). The combined org. phases were dried (K_2CO_3) and evaporated to give **47** (140 mg, quant.). Slightly yellow oil. R_f (CH_2Cl_2/MeOH 9:1) 0.72. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.61–4.52 (*m*, 1 H), 4.35–4.26 (*m*, 1 H) (H–C(4), H–C(5)); 3.74 (*s*, MeO); 3.42–3.31 (*m*, H–C(2)); 3.02–2.98 (*m*, H–C(1)); 2.77 (*ddd*, *J* = 14.8, 7.6, 3.7, H–C(6)); 2.62 (br. *d*, *J* = 13.7, H–C(3)); 2.34 (*dt*, *J* = 14.6, 7.4, H′–C(3)); 2.13 (*ddd*, *J* = 14.8, 8.0, 4.4, H′–C(6)). ESI-MS: 318 (49), 316 (100), 314 (46, $[M+1]^+$); 236 (49), 234 (48, $[M-Br]^+$).

*Methyl (1*RS,*2*SR,*4*RS,*5*SR*)-5-Bromo-7-azabicyclo[2.2.1]heptane-2-carboxylate* (**48**). A soln. of **47** (133 mg, ca. 0.35 mmol) in $CHCl_3$ (10 ml) was treated with K_2CO_3 (0.35 mmol), heated under reflux for 30 d, allowed to cool to r.t., and washed with sat. aq. K_2CO_3 soln. (15 ml). The aq. phase was extracted with $CHCl_3$ (2 × 25 ml). The combined org. phases were dried (K_2CO_3) and evaporated to give crude **48** (122 mg). Yellow oil. R_f (CH_2Cl_2/MeOH 9:1) 0.74. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.00 (*dd*, *J* = 8.9, 3.4, H–C(5)); 3.92 (*d*, *J* = 4.7, H–C(1)); 3.80 (*d*, *J* = 5.3, H–C(4)); 3.66 (*s*, MeO); 2.36 (*dd*, *J* = 8.7, 4.4, H–C(2)); 2.17 (*dd*, *J* = 14.3, 6.9, H_{endo}–C(6)); 2.12–2.01 (*m*, H_{exo}–C(6)); 2.05 (*dt*, *J* = 13.0, 4.9, H_{exo}–C(3)); 1.58 (*dd*, *J* = 13.2, 8.9, H_{endo}–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 174.49 (*s*, C=O); 64.63, 60.53 (2*d*, C(1), C(4)); 52.18 (*q*, MeO); 50.95 (*d*, C(5)); 45.95 (*d*, C(2)); 43.53, 32.45 (2*t*, C(3), C(6)).

*Methyl (1*RS,*2*SR,*4*RS,*5*SR*)-5-Bromo-7-[(*tert-*butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2-carboxylate* (**49**). A soln. of **48** (122 mg, *ca.* 0.35 mmol) in $CHCl_3$ (15 ml) was treated with K_2CO_3 (48 mg, 0.35 mmol) and Boc_2O (0.32 ml, 1.4 mmol), stirred at r.t. for 16 d, and washed with H_2O (20 ml). The aq. phase was extracted with $CHCl_3$ (2 × 20 ml). The combined org. phases were dried (K_2CO_3) and evaporated. FC (15 g of silica gel; cyclohexane/AcOEt 6:1) gave colourless crystalline **49** (74 mg, 62% from **29**). R_f (cyclohexane/AcOEt 3:1) 0.35. M.p. 56.7–58.6°. FT-IR (1.5%, $CHCl_3$): 3027*w*, 3012*w*, 2982*w*, 2954*w*, 1737*s* (COOMe), 1697*s* (COO*t*Bu), 1477*w*, 1437*m*, 1392*m*, 1368*s*, 1323*m*, 1303*w*, 1145*s*, 1104*w*, 1039*w*, 979*w*, 916*w*, 883*w*. ^{1}H-NMR (300 MHz, C_6D_6, 50°): 4.60–4.43 (br. *s*, H–C(1)); 4.38–4.25 (br. *s*, H–C(4)); 3.34 (*s*, MeO); 3.29 (*dd*, *J* = 7.5, 3.5, H–C(5)); 2.24 (*dt*, *J* = 13.1, 5.1, H_{exo}–C(3)); 2.01 (*ddd*, *J* = 13.9, 5.0, 3.6, H_{exo}–C(6)); 1.82 (*dd*, *J* = 8.7, 4.7, H–C(2)); 1.46 (*dd*, *J* = 14.0, 7.5, H_{endo}–C(6)); 1.42 (*s*, *t*-Bu); 0.87 (*dd*, *J* = 13.1, 8.7, H_{endo}–C(3)). ^{13}C-NMR (75 MHz, C_6D_6, 50°): 172.23 (*s*, *C*O_2Me); 153.99 (*s*, *C*O_2*t*Bu); 79.83 (*s*, Me_3C); 64.18, 59.51 (2*d*, C(1), C(4)); 51.63 (*q*, MeO); 48.36, 46.15 (2*d*, C(2), C(5)); 43.25, 31.67 (2*t*, C(3), C(6)); 28.29 (*q*, Me_3C). ESI-MS: 693 (35), 691 (65), 689 (32, $[2M+Na]^+$); 390 (14), 388 (14, $[M+Na+MeOH]^+$); 374 (22), 372 (20, $[M+K]^+$); 358 (100), 356 (96, $[M+Na]^+$); 336 (18), 334 (22, $[M+1]^+$); 280 (22), 278 (20, $[M+1-C_4H_8]^+$); 236 (16), 234 (18, $[M+1-C_4H_8-CO_2]^+$).

Methyl c-*2-Amino*-t-*4*,c-*5-dibromocyclohexane*-r-*1-carboxylate* (**50**). According to the preparation of **47**, **30** (84 mg, 0.20 mmol) was transformed into **50** (93 mg, quant.). Slightly yellow oil. R_f (CH_2Cl_2/MeOH 9:1) 0.62. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.50 (*ddd*, *J* = 11.1, 9.8, 4.4, H–C(4)); 4.12–4.03 (*m*, H–C(5)); 3.70 (*s*, MeO); 2.68–2.56 (*m*, 4 H); 2.52 (*dt*, *J* = 14.3, 4.4, H_{eq}–C(3)); 2.08 (*ddd*, *J* = 14.3, 11.2, 3.1, H_{ax}–C(3)).

Cyclisation of **50**. A soln. of **50** (93 mg, *ca.* 0.20 mmol) in 1,3-dichlorobenzene (15 ml) was treated with K_2CO_3 (27.6 mg, 0.20 mmol), stirred for 28 d at 120°, allowed to cool to r.t., treated with K_2CO_3 (27.6 mg, 0.20 mmol) and Boc_2O (0.3 ml, 1.3 mmol), stirred at r.t. for 10 d, and washed with H_2O (30 ml). The aq. phase was extracted with $CHCl_3$ (2 × 20 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (12 g of silica gel; hexane/AcOEt 4:1) of the oily residue gave **49** (14 mg, 21%) as a yellow oil.

c-*2-[(Benzyloxy)methyl]*-t-*4*,c-*5-dibromocyclohexan*-r-*1-amine (***51**). A soln. of **32** (290 mg, 0.607 mmol) in CH_2Cl_2 (15 ml) was treated with CF_3CO_2H (0.93 ml, 12.1 mmol), stirred at r.t. for 3 h, and evaporated. The residue was taken up in sat. aq. K_2CO_3 soln. (20 ml) and extracted with $CHCl_3$ (3 × 25 ml). The combined org. phases were dried (K_2CO_3) and evaporated to give crude **51** as a colourless oil (250 mg, quant.). R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.61. ESI-MS: 380 (1), 378 (2), 376 (1, $[M+1]^+$); 298 (96), 296 (100, $[M-Br]^+$).

*(1*RS,*2*SR,*4*RS,*5*SR*)-2-[(Benzyloxy)methyl]-5-bromo-7-azabicyclo[2.2.1]heptane* (**52**). A soln. of crude **51** (250 mg) in $CHCl_3$ (20 ml) was treated with K_2CO_3 (83 mg, 0.607 mmol), heated under reflux for 40 h, cooled to r.t., treated with K_2CO_3 (*ca.* 100 mg), and filtered. Evaporation of the filtrate gave crude **52** (268 mg, quant.).

Slightly yellow oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.88. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.25 (5 arom. H); 4.54 (*d*, *J* = 12.1), 4.48 (*d*, *J* = 11.8) (PhC*H*$_2$); 4.20–3.90 (br. *s*, NH); 4.07 (*dd*, *J* = 6.1, 4.5, H–C(5)); 3.88 (*d*, *J* = 5.0), 3.84 (*d*, *J* = 3.4) (H–C(1), H–C(4)); 3.46 (*t*, *J* ≈ 8.9, CH–C(2)); 3.31 (*dd*, *J* = 9.3, 5.3, CH′–C(2)); 2.31–2.17 (*m*, 2 H–C(6)); 1.84 (*tt*, *J* = 8.4, 5.1, H–C(2)); 1.55 (*dd*, *J* = 13.1, 8.4, H_{endo}–C(3)); 1.45 (*dt*, *J* = 13.1, 5.0, H_{exo}–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.00 (*s*); 128.35 (*d*, 2 C); 127.72 (*d*, 2 C); 127.63 (*d*); 73.29 (*t*, PhCH_2); 72.45 (*t*, CH_2–C(2)); 65.26, 59.42 (2*d*, C(1), C(4)); 50.68 (*d*, C(5)); 43.87 (*t*); 40.95 (*d*, C(2)); 31.30 (*t*). ESI-MS: 298 (10), 296 (6, $[M+1]^+$); 97 (100).

*(1*RS*,2*SR*,4*RS*,5*SR*)-2-[(Benzyloxy)methyl]-7-[(*tert*-butoxy)carbonyl]-5-bromo-7-azabicyclo[2.2.1]heptane* (**53**). A soln. of **52** (268 mg) in $CHCl_3$ (25 ml) was treated with K_2CO_3 (84 mg, 0.607 mmol), and Boc_2O (0.55 ml, 2.4 mmol) and stirred at r.t. for 6 d. The mixture was washed with H_2O (25 ml), and the aq. phase was extracted with $CHCl_3$. The combined org. phases were dried (Na_2SO_4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 10:1) gave colourless crystalline **53** (194 mg, 84% from **32**). R_f (cyclohexane/AcOEt 3:1) 0.59. M.p. 112.2–113.6°. FT-IR (1%, $CHCl_3$): 3027*w*, 3015*m*, 2977*w*, 2932*w*, 2864*w*, 1693*s* (C=O), 1477*w*, 1455*w*, 1393*m*, 1368*m*, 1322*m*, 1111*m*, 910*w*. ^{1}H-NMR (300 MHz, $CDCl_3$; *ca.* 2:1 mixture of diastereoisomers): signals for the major diastereoisomer: 7.38–7.24 (5 arom. H); 4.54 (*d*, *J* = 12.1, PhC*H*); 4.50 (br. *s*, H–C(4)); 4.45 (*d*, *J* = 11.8, PhC*H*′); 4.37 (*d*, *J* = 5.3, H–C(1)); 4.00 (*dd*, *J* = 7.2, 3.7, H–C(5)); 3.30 (*t*, *J* = 8.9, CH–C(2)); 3.17 (*dd*, *J* = 9.2, 6.4, CH′–C(2)); 2.31 (br. *dt*, *J* = 14.0, 4.4, H_{exo}–C(6)); 2.21 (*dd*, *J* = 13.9, 7.3, H_{endo}–C(6)); 1.98–1.85 (*m*, H–C(2)); 1.55 (*dd*, *J* = 12.9, 8.3, H_{endo}–C(3)); 1.48 (*s*, *t*-Bu); 1.47–1.35 (*m*, H_{exo}–C(3)); signals for the minor diastereoisomer: 4.48 (br. *s*, H–C(4)); 4.31 (*d*, *J* = 4.7, H–C(1)); the other signals are hidden by the signals of the major diastereoisomer. ^{13}C-NMR (75 MHz, $CDCl_3$; *ca.* 2:1 mixture of diastereoisomers): signals of the major diastereoisomer: 138.01 (*s*); 128.35, 128.27, 127.61, 127.49 (4*d*); 80.05 (*d*, Me_3C); 73.25 (*t*, PhCH_2); 72.42 (*t*, CH_2–C(2)); 63.79, 57.18 (2*d*, C(1), C(4)); 49.73 (*d*, C(5)); 42.99 (*t*); 41.91 (*d*, C(2)); 32.79 (*t*); 28.39 (*q*, Me_3C); signals for the minor diastereoisomer: 138.01 (*s*); 128.35, 128.27, 127.61, 127.49 (4*d*); 79.92 (*d*, Me_3C); 73.34 (*t*, PhCH_2); 72.30 (*t*, CH_2–C(2)); 62.91, 57.65 (2*d*, C(1), C(4)); 48.88 (*d*, C(5)); 43.61 (*t*); 42.71 (*d*, C(2)); 31.66 (*t*); 28.46 (*q*, Me_3C). ESI-MS: 420 (100), 418 (94, $[M+Na]^+$); 364 (72), 362 (67, $[M+Na-C_4H_8]^+$); 298 (8), 296 (8). Anal. calc. for $C_{19}H_{26}BrNO_3$ (396.32): C 57.58, H 6.61, N 3.53; found: C 57.88, H 6.51, N 3.61.

*(1*RS*,4*RS*,5*SR*)-5-[(Benzyloxy)methyl]-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]hept-2-ene* (**54**). A soln. of **53** (167 mg, 0.42 mmol) in THF (12 ml) was treated with *t*-BuOK (71 mg, 0.63 mmol), heated under reflux for 25 h, cooled to 0°, diluted with Et_2O (20 ml), and washed with brine (25 ml). The aq. phase was extracted with Et_2O (25 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (15 g of silica gel; cyclohexane/AcOEt 10:1) gave **54** (123 mg, 92%). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.58. FT-IR (1.5%, $CHCl_3$): 3028*w*, 3012*m*, 2981*m*, 2939*w*, 2864*w*, 1694*s* (C=O), 1496*w*, 1477*w*, 1455*w*, 1393*m*, 1368*s*, 1298*m*, 1110*m*, 1029*w*, 949*w*, 912*w*, 876*w*, 861*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.25 (5 arom. H); 6.29 (br. *d*, *J* = 10.0, H–C(2), H–C(3)); 4.70–4.51 (*m*, PhCH_2, H–C(1), H–C(4)); 3.51 (*dd*, *J* = 9.2, 6.1, CH–C(5)); 3.51–3.37 (*m*, CH′–C(5)); 1.90–1.79 (*m*, H–C(5)); 1.42 (*s*, *t*-Bu); 1.38–1.28 (*m*, 2 H–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$; *ca.* 6:5 mixture of diastereoisomers): 138.25 (*s*); 136.55 (*d*, 0.55 C), 136.26 (*d*, 0.45 C), 135.12 (*d*, 0.45 C), 134.70 (*d*, 0.55 C) (C(2), C(3)); 128.28 (*d*, 2 C); 127.56 (*d*, 2 C); 127.47 (*d*); 79.69 (*s*, Me_3C); 72.23 (*t*, PhCH_2, CH_2–C(5)); 61.56 (*d*), 60.12 (*d*, 0.45 C), 59.08 (*d*, 0.55 C) (C(1), C(4)); 39.62 (*d*, 0.55 C), 38.79 (*d*, 0.45 C) (C(5)); 29.63 (*t*, C(6)); 28.36 (*q*, Me_3C). ESI-MS: 370 (3, $[M+Na+MeOH]^+$), 354 (22, $[M+K]^+$), 338 (100, $[M+Na]^+$), 316 (8, $[M+1]^+$), 260 (33, $[M+1-C_4H_8]^+$), 216 (8, $[M+1-C_4H_8-CO_2]^+$). Anal. calc. for $C_{19}H_{25}NO_3$ (315.41): C 72.35, H 7.99, N 4.44; found: C 72.41, H 8.02, N 4.52.

*(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-[(Benzyloxy)methyl)-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2,3-diol* (**55**). A soln. of **54** (114 mg, 0.36 mmol) in acetone (23 ml) and H_2O (2.5 ml) was treated with NMO (73 mg, 0.54 mmol) and 2.5% OsO_4 in *t*-BuOH (0.5 ml), stirred at r.t. for 13 h, diluted with sat. aq. $Na_2S_2O_5$ soln. (50 ml), and extracted with $CHCl_3$ (2 × 100 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (12 g of silica gel; cyclohexane/AcOEt 1:1) gave **55** (102 mg, 81%). Yellow oil. R_f (cyclohexane/AcOEt 1:1) 0.19. FT-IR (1%, $CHCl_3$): 3488*w* (br., OH), 3028*w*, 3013*m*, 2981*m*, 2932*w*, 2864*w*, 1727*w*, 1692*s*, 1670*s*, 1500*w*, 1478*w*, 1455*m*, 1386*s*, 1368*s*, 1318*m*, 1112*m*, 1091*m*, 1051*m*, 909*w*, 870*w*. ^{1}H-NMR (300 MHz, C_6D_6, 50°): 7.24–7.02 (5 arom. H); 4.26 (*d*, *J* = 12.1, PhC*H*); 4.20 (*d*, *J* = 11.2, PhC*H*′); 4.21–4.17, 4.02–3.97 (2*m*, H–C(1), H–C(4)); 3.46–3.41, 3.39–3.33 (2*m*, H–C(2), H–C(3)); 3.16–2.95 (*m*, 2 OH); 3.08 (*t*, *J* = 9.0, CH–C(5)); 2.91 (*dd*, *J* = 9.0, 6.5, CH′–C(5)); 1.46 (br. *quint.*, *J* ≈ 7.0, H–C(5)); 1.37 (*s*, *t*-Bu); 0.83–0.76 (*m*, CH_2(6)). ^{13}C-NMR (75 MHz, $CDCl_3$; *ca.* 1:1 mixture of diastereoisomers, most signals isochronic for both diastereoisomers): 155.76 (*s*, C=O); 137.91 (*s*); 128.31, 127.58 (2*d*) (1*d* hidden by noise or other signal); 80.30 (*s*, Me_3C); 74.62, 74.01 (2*d*, C(2), C(3)); 73.25 (*t*, PhCH_2); 72.17 (*t*, CH_2–C(5)); 64.64 (*d*, *ca.* 0.47 C), 62.99 (*d*), 60.89 (*d*, *ca.* 0.53 C) (C(1), C(4)); 38.44 (*d*, C(5)); 28.77 (*t*, C(6)); 28.34 (*q*, Me_3C). HR-MALDI-MS (DHB):

372.1783 (80, $C_{19}H_{27}NNaO_5^+$, $[M+Na]^+$; calc. 372.1787), 316 (66, $[M+Na-C_4H_8]^+$), 272 (28, $[M+Na-C_4H_8-CO_2]^+$), 250 (100, $[M+1-C_4H_8-CO_2]^+$).

*(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-7-[(*tert*-Butoxy)carbonyl]-5-(hydroxymethyl)-7-azabicyclo[2.2.1]heptane-2,3-diol* (**56**). A suspension of 10% Pd/C (30 mg) in MeOH (5 ml) was treated with a soln. of **55** (91 mg, 0.26 mmol) in MeOH (5 ml), put under a H_2 atmosphere (balloon), and stirred at r.t. for 19 h. Filtration through a membrane filter and evaporation gave crude **56** as a yellow oil (61 mg, 90%). Repeated FC (12 g of silica gel; CH_2Cl_2/MeOH 12:1) gave **56**. (41 mg, 60%). Colourless oil. R_f (CH_2Cl_2/MeOH 9:1) 0.46. FT-IR (1%, $CHCl_3$): 3693*w*, 3623*w*, 3489*w* (br., OH), 3028*w*, 3011*m*, 2972*s*, 2875*w*, 1674*s* (C=O), 1603*w*, 1475*m*, 1456*m*, 1393*s*, 1369*s*, 1318*m*, 1115*m*, 1050*m*, 911*w*, 872*w*. ^{1}H-NMR (300 MHz, CD_3OD; *ca.* 1:1 mixture of diastereoisomers): 4.02 (br. *s*, H–C(4)); 3.99 (br. *d*, $J=5.3$, H–C(1)); 3.80 (br. *d*, $J\approx6.2$), 3.77 (*d*, $J=6.2$) (H–C(2), H–C(3)); 3.32–3.24 (*m*, CH_2–C(5)); 1.82 (*dtd*, $J=8.1, 7.9, 4.7$, H–C(5)); 1.48 (*dd*, $J=12.8, 8.4$, H_{endo}–C(6)); 1.45 (*s*, *t*-Bu); 1.10, 1.09 (2*dt*, $J=12.5, 5.3$, H_{exo}–C(6)). ^{13}C-NMR (75 MHz, CD_3OD; *ca.* 1:1 mixture of diastereoisomers): 156.61 (C=O); 79.92, 79.80 (Me_3C); 73.67, 73.46, 73.37 73.16 (C(2), C(3)); 63.97 (2 C), 63.83, 62.95, 62.41, 61.22 (C(1), C(4), CH_2–C(5)); 40.99 (2 C, C(5)); 28.25, 27.94 (C(6); 27.43 (Me_3C). HR-MALDI-MS (DHB): 314.1745 (49, $C_{13}H_{25}NNaO_6^+$, $[M+Na+MeOH]^+$; calc. 314.1580), 224 (11).

*(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-2,3-Dihydroxy-5-(hydroxymethyl)-7-azoniabicyclo[2.2.1]heptane Chloride* (**57**·HCl). A soln. of **56** (40 mg, 0.154 mmol) in 0.1N HCl (5 ml) was stirred at r.t. for 43 h and lyophilised to give colourless amorphous **57**·HCl·H_2O (33.2 mg, 100%). R_f (PrOH/AcOH/H_2O 4:1:1) 0.52. ^{1}H-NMR (300 MHz, CD_3OD): 4.10–4.06 (*m*, H–C(2), H–C(3)); 3.93 (*d*, $J=5.0$, H–C(1)); 3.91 (br. *s*, H–C(4)); 3.65 (*dd*, $J=10.7, 4.5$, CH–C(5)); 3.48 (*dd*, $J=10.6, 5.9$, CH′–C(5)); 2.09 (*sext.*, $J=4.9$, H–C(5)); 1.86 (*dd*, $J=13.5, 9.2$, H_{endo}–C(6)); 1.67 (*dt*, $J=13.5, 5.1$, H_{exo}–C(6)). ^{13}C-NMR (75 MHz, CD_3OD): 72.11 (C(2), C(3)); 68.48 (CH_2–C(5)); 66.03 (C(4)); 63.21 (C(1)); 37.46 (C(5)); 26.74 (C(6)). HR-ESI-MS: 160.09655 ($C_7H_{14}NO_3^+$, $[M+1]^+$; calc. 160.09682).

*(1*RS*,5*SR*,6*RS*,8*SR*)-6-[(Benzyloxy)methyl]-8-bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene* (**58**). A soln. of **37** (9.3 mg, 19.7 μmol) in MeOH (1.5 ml) and H_2O (0.6 ml) was treated with K_2CO_3 (13.5 mg, 98 μmol), stirred at r.t. for 26 h, and evaporated. The residue was suspended in sat. aq. K_2CO_3 soln. (10 ml), and extracted with $CHCl_3$ (3 × 10 ml). The combined org. phases were dried (K_2CO_3) and evaporated to yield crude **58** (1.6 mg, quant.). Colourless oil. R_f (toluene/AcOEt 10:1) 0.36. FT-IR (1%, $CHCl_3$): 3008*m*, 2871*m*, 1689*m*, 1455*w*, 1393*w*, 1373*w*, 1319*w*, 1300*w*, 1128*s*, 1107*s*, 1090*s*, 909*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.27 (5 arom. H); 4.79–4.75 (*m*, H–C(1)); 4.54, 4.48 (2*d*, $J=11.8$, PhCH_2); 4.16 (*ddd*, $J=12.5, 5.3, 2.2$, H–C(8)); 4.06–4.02 (*m*, H–C(5)); 3.55 (*dd*, $J=9.0, 7.2$, CH–C(6)); 3.27 (*dd*, $J=9.0, 6.9$, CH′–C(6)); 2.36 (*dt*, $J=13.9, 4.7$, H_{eq}–C(7)); 2.28–2.16 (*m*, H–C(6)); 2.11 (*dt*, $J=14.0, 4.1$, H_{eq}–C(9)); 1.86 (*dt*, $J=14.0, 1.6$, H_{ax}–C(9)); 1.52 (*dt*, $J=14.0, 12.5$, H_{ax}–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$); 137.88 (*s*); 128.33, 127.60 (2*d*); 75.65 (*d*, C(1)); 73.41 (*t*, PhCH_2)); 71.38 (*t*, CH_2–C(6)); 50.15, 46.50 (2*d*, C(5), C(8)); 44.27 (*d*, C(6)); 31.65 (*t*, C(9)); 28.82 (*t*, C(7)). ^{19}F-NMR (282 MHz, $CDCl_3$): −73.69 (*s*). ESI-MS: 448 (1), 446 (1, $[M+Na+MeOH]^+$); 432 (16), 430 (15, $[M+K]^+$); 416 (97), 414 (100, $[M+Na]^+$); 394 (23), 392 (22, $[M+1]^+$); 380 (42), 378 (81), 376 (40, $[M-CF_3CN+HBr]^+$); 298 (11), 296 (16, $[M-CF_3CN]^+$).

Inhibition Studies. Determination of the IC_{50} values was performed with a range of inhibitor concentrations (typically 4–8 concentrations), which bracket the IC_{50} value, using $[S]\approx K_M$. β-Glucosidase from almonds (pH 6.8, 37°), β-glucosidase from *Caldocellum saccharolyticum* (pH 6.8, 55°), and α-glucosidase from brewer's yeast (pH 6.8, 37°) as described in [87]. For β-mannosidase from snail acetone powder (pH 4.5, 27°), 4-nitrophenyl β-D-mannopyranoside was used as substrate [3], and for α-mannosidase from *Jack* beans (pH 4.5, 25°) 4-nitrophenyl α-D-mannopyranoside [3].

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