Synthesis and Evaluation as Glycosidase Inhibitors of Isoquinuclidines Mimicking a Distorted β-Mannopyranoside

by **Matthias Böhm**, **Edwige Lorthiois**, **Muthuppalaniappan Meyyappan**, and **Andrea Vasella***

Laboratorium für Organische Chemie, ETH-Hönggerberg, Wolfgang-Pauli Strasse 10, CH-8093 Zürich

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

Racemic and enantiomerically pure *manno*-configured isoquinuclidines were synthesized and tested as glycosidase inhibitors. The racemic key isoquinuclidine intermediate was prepared in high yield by a cycloaddition (tandem *Michael* addition/aldolisation) of the 3-hydroxy-1-tosyl-pyridone **10** to methyl acrylate, and transformed to the racemic *N*-benzyl *manno*-isoquinuclidine **2** and the *N*-unsubstituted *manno*-isoquinuclidine **3** (twelve steps; *ca.* 11% from **10**). Catalysis by quinine of the analogous cycloaddition of **10** to (−)-8-phenylmenthyl acrylate provided a single diastereoisomer in high yield, which was transformed to the desired enantiomerically pure D-*manno*-isoquinuclidines (+)-**2** and (+)-**3** (twelve steps; 23% from **10**). The enantiomers (−)-**2** and (−)-**3** were prepared by using a quinidine-promoted cycloaddition of **10** to the enantiomeric (+)-8-phenylmenthyl acrylate. The *N*-benzyl D-*manno*-isoquinuclidine (+)-**2** is a selective and slow inhibitor of snail β-mannosidase. Its inhibition strength and type depends on the pH (at pH 4.5: $K_i = 1.0$ μM, mixed type, $\alpha = 1.9$; at pH 5.5: $K_i = 0.63$ μM, mixed type, $\alpha = 17$). The *N*-unsubstituted D-*manno*-isoquinuclidine (+)-**3** is a poor inhibitor. Its inhibition strength and type also depend on the pH (at pH 4.5: $K_i = 1.2 \cdot 10^3$ μM, mixed type, $\alpha = 1.1$; at pH 5.5: $K_i = 0.25 \cdot 10^3$ μM, mixed type, $\alpha = 11$). The enantiomeric *N*-benzyl L-*manno*-isoquinuclidine (−)-**2** is a good inhibitor of snail β-mannosidase, albeit noncompetitive (at pH 4.5: $K_i = 69$ μM). The *N*-unsubstituted isoquinuclidine (−)-**2** is a poor inhibitor (at pH 4.5: $IC_{50} = 7.3 \cdot 10^3$ μM). A comparison of the inhibition by the pure *manno*-isoquinuclidines (+)-**2** and (+)-**3**, (+)-**2**/(−)-**2** 1:1, and (+)-**3**/(−)-**3** 1:1 with the published data for racemic **2** and **3** led to a rectification of the published data. The inhibition of snail β-mannosidase by the isoquinuclidines **2** and **3** suggests that the hydrolysis of β-D-mannopyranosides by snail β-mannosidase proceeds *via* a distorted conformer, in agreement with the principle of stereoelectronic control.

Introduction. – The principle of stereoelectronic control requires that hydrolysis of a glycoside[1]) proceed *via* a conformer with a coplanar orientation of the scissile bond and a doubly occupied, nonbonding orbital of the endocyclic O-atom [4]. β-D-Glycosides adopting a ground-state conformation with an equatorial aglycon must undergo a conformational change, *e.g.*, from $^4C_1$ to $^{1,4}B$ or $^1S_3$, that also favours nucleophilic assistance of hydrolysis following an intermediate *S*N1/*S*N2 (DN*AN) mechanism [3]. Such a conformational change is evidenced by the crystal structure of several glycosidases in complex with substrate analogues, *viz.* four cellulases (belonging to families 5[2]) [6], 6 [7], 7 [8], and 8 [9]), three chitinases (family 18 [10] and 20 [11][12]), and a β-mannanase (family 26 [13]). These crystal structures show

[1]) For review articles on the mechanism of glycoside hydrolysis, see [1–3].

[2]) A regularly updated database with over 6300 glycosidases classified in 89 families [5] is available on the internet (http://afmb.cnrs-mrs.fr/CAZY/).

complexes of *endo*-glycosidases with ligands binding at least to subsites -2, -1, and $+1$ [14], *i.e.*, spanning the point of enzymatic cleavage[3]). The conformations adopted by the substrate analogues in subsite -1 ($^{1}S_{3}$, $^{2}S_{0}$, $^{1,4}B$, $^{2,5}B$, ^{4}E) differ from the ground-state conformation and satisfy the stereoelectronic conditions imposed on a reactive conformer. The resolution of these crystal structures, however, does not allow us to see if these conformational changes are concerted with incipient proton transfer to the glycosidic heteroatom, lengthening of the scissile bond, and rehybridisation of the anomeric center ($sp^3 \rightarrow sp^2$). Inhibitors that imitate the reactive conformation, but neither the lengthening of the scissile bond nor the rehybridisation, may mimic a structure corresponding to a point on the reaction pathway if the conformational change takes place before bond lenghthening and rehybridisation are significantly advanced. Such inhibitors may inform if the above-mentioned changes are strongly concerted, or not.

We synthesised the racemic isoquinuclidines **2** and **3** (*Fig. 1*) as mimics of the β-D-mannopyranoside $^{1,4}B$-conformer. These isoquinuclidines possess a *pseudo*-axial amino group that should allow protonation by the catalytic acid of a *syn*- or *anti*-protonating glycosidase [2]. To the best of our knowledge, only one bicyclic glycosidase inhibitor mimicking a $^{1,4}B$-conformer of the substrate has been reported [17] (**4**; *Fig. 1*). It was designed in another conceptual context and not tested against β-mannosidases; other glycosidases were only weakly inhibited. We briefly reported the synthesis of racemic **2** and **3**, and their inhibition of snail β-mannosidase [18]. Both isoquinuclidines were found to be strong, selective, and competitive inhibitors of snail β-mannosidase. To further investigate the inhibition of snail β-mannosidase by **2** and **3**, we have now synthesised and tested the individual enantiomers. We planned to obtain them by an asymmetric synthesis, proceeding *via* enantiomerically pure intermediates that should also be of interest as building blocks for other isoquinuclidines[4]). In the following, we provide details for the synthesis of racemic **2** and **3**, discuss the synthesis of the enantiomers, and report on the inhibition of snail β-mannosidase, *Jack* bean α-mannosidase, and the β-glucosidase from *Caldocellum saccharolyticum*. As detailed below, this has led to a revision of the inhibition data originally found.

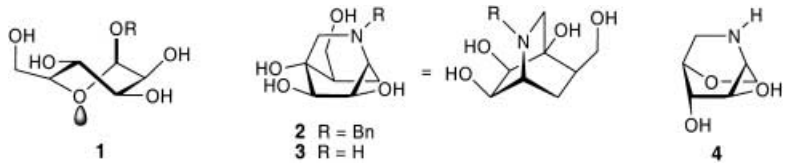


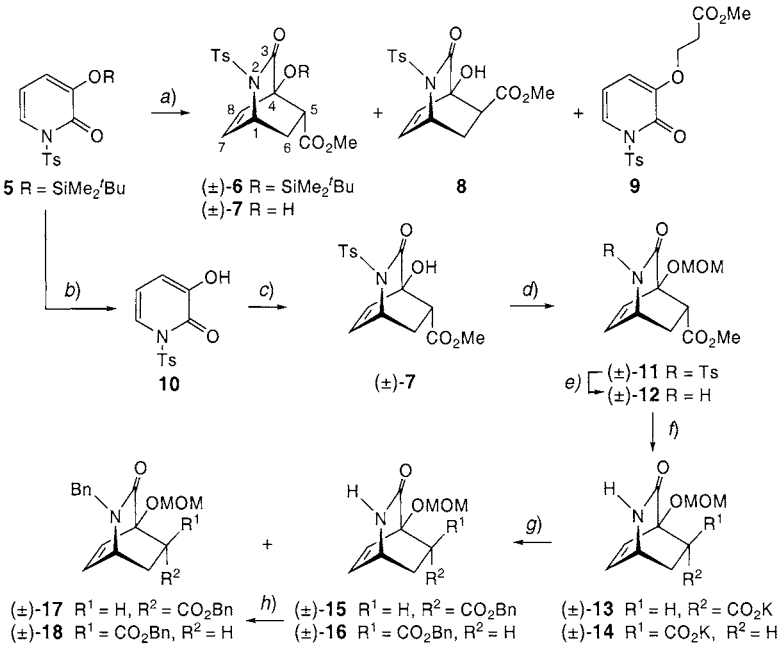
Fig. 1. $^{1}S_{3}$ *Conformation of a* β-D-*mannopyranoside* **1** *as compared to the isoquinuclidines* **2** *and* **3**, *and the bicyclic inhibitor* **4** *mimicking a* ^{1,4}B *conformation of a* β-D-*mannopyranoside*

Synthesis. – The synthesis of the racemates **2** and **3** is shown in *Schemes 1* and *2*. We planned to prepare the desired inhibitors by epimerisation, reduction, and dihydrox-

[3]) Substrate distortion was also observed for covalent glycosyl–enzyme intermediates of xylanases (family 11 [15][16]). The glycosyl–enzyme intermediate adopts a $^{2,5}B$ conformation in subsite -1.

[4]) For biologically active isoquinuclidines, see [19][20].

Scheme 1



a) Bu_4NF-SiO_2, H_2O, methyl acrylate; **7** (74%). *b*) $BF_3 \cdot Et_2O$, CH_2Cl_2; 96%. *c*) Methyl acrylate, Et_3N; (91% from **5**). *d*) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$; 88%. *e*) Na–$C_{10}H_8$, DME, −78°; 93%. *f*) K_2CO_3, MeOH. *g*) BnBr, $NaHCO_3$, DMF; **15**/**16** 20:80 (42% from **12**) and **17**/**18** 20:80 (18% from **12**). *h*) NaH, BnBr, DMF; **17** (7% from **12**) and **18** (46% from **12**).

ylation of the known alkene **6** resulting from a *Diels–Alder* addition of the pyridone **5** to methyl acrylate [21].

The *Diels–Alder* addition of **5** to methyl acrylate [21] gave the cycloadduct **6** in only 23% yield; the addition of **5** to acryloyl chloride [22], followed by esterification of the adduct, afforded **6** in a higher but still unsatisfactory yield (57%). While optimising these cycloadditions, we wondered about the influence of the bulky silyl group. Its removal should facilitate the *Diels–Alder* reaction, and also allow construction of the isoquinuclidine **7** by a tandem *Michael* addition/aldolisation. Such tandem reactions had proven useful for the construction of bicyclo[2.2.2]octanes[5]). Desilylation of **5** with Bu_4NF on silica gel, followed by addition of methyl acrylate, led indeed to the adducts **7**, **8**, and **9**. The ratio of the products depended on the solvent polarity. In H_2O, the cycloadduct **7** was the main product (74%); **8** was no longer observed. Still higher yields (91%) were obtained by desilylating **5** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 and treating the crude alcohol **10** with methyl acrylate in the presence of Et_3N.

Although a *Michael* addition/aldolisation for such transformations [24][25] is evidenced by the mild reaction conditions and the isolation of an intermediate [26], one cannot exclude an anionic *Diels–Alder* reaction [27], as proposed by *Okamura et al.*

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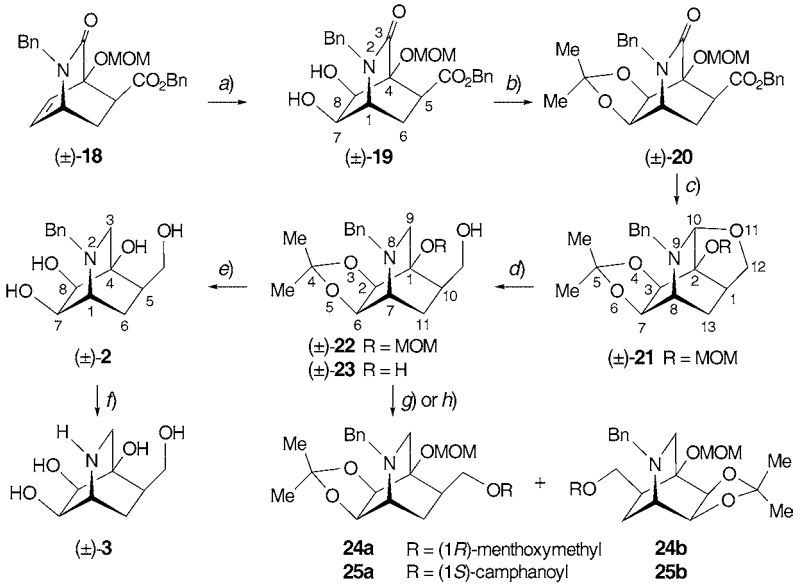
[5]) For review articles on tandem *Michael* addition/aldolisations and related tandem reactions, see [23].

Scheme 2



a) OsO_4, NMO, acetone/H_2O; 70%. *b*) $Me_2C(OMe)_2$, acetone, camphorsulfonic acid; 94%. *c*) $LiAlH_4$, THF; **21** (57%), **22** (17%), and **23** (8%). *d*) $LiAlH_4$, dioxane; 67% from **20**. *e*) CF_3CO_2H, H_2O; 87%. *f*) H_2, Pd/C, conc. HCl/MeOH/H_2O; 82%. *g*) chloromethyl (1*R*,3*S*,4*S*)-menthyl ether, $^iPr_2NEt$, CH_2Cl_2; 98%. *h*) (1*S*,4*R*)-camphanoyl chloride, $^iPr_2NEt$, DMAP, CH_2Cl_2; > 98%.

[28] for the related and independently developed cycloaddition of the pyridone **10** to dimethyl maleate and dimethyl fumarate.

To avoid a retro-*Michael* addition/aldolisation of **7**, we protected its OH group by methoxymethylation under acidic conditions to yield 88% of **11**. *N*-Detosylation of **11** with sodium naphthalenide in 1,2-dimethoxyethane (DME) at a concentration of 0.16M and at $-78°$ gave **12** in 93% yield on a 8-g scale. Higher concentrations (0.38M) resulted in lower yields (27%), and higher temperatures led to partial epimerisation. Although epimerisation is required for the synthesis of **2** and **3** (*Scheme 2*), we did not pursue this observation, since we had developed an alternative method. Treatment of **12** with 1.5 equiv. of K_2CO_3 in MeOH led to a 4 : 1 mixture of the epimeric carboxylates **13** and **14**. It is not clear to what extent the preferred formation of **14** is due to more-rapid saponification of its methyl ester, conceivably as a consequence of a selective complexation to K^+ cation. The mixture **13**/**14** was benzylated to give the benzyl esters **15**/**16** (4 : 1, 42% from **12**) and the *N*-benzylated benzyl esters **17**/**18** (4 : 1, 18% from **12**). A second benzylation converted the benzyl esters **15**/**16** to **17**/**18** (89%). The esters **17** and **18** were separated by chromatography. The *N*-benzylated benzyl ester **18** was, thus, obtained in a yield of 46% from **12**. It was dihydroxylated to **19** (OsO_4/NMO (*N*-methylmorpholine *N*-oxide monohydrate); 70%) and protected as the isopropylidene acetal **20** (94%; *Scheme 2*). $LiAlH_4$ in boiling THF reduced **20** to the N,O-acetal **21** (57%), the amine **22** (17%), and the alcohol **23** (8%). Reduction of the N,O-acetal **21**

to the amine **22** required $LiAlH_4$ in boiling dioxane. Unexpectedly, however, only small amounts of **22** were obtained by direct reduction of the lactam **20** with $LiAlH_4$ in boiling dioxane, the major product being the N,O-acetal **21** (49%), which was not reduced to **22** by further addition of $LiAlH_4$. The amine **22** was deprotected with CF_3COOH/H_2O 1:1 to provide the racemic *N*-benzylisoquinuclidine **2** (84%), which was debenzylated to the racemic *manno*-isoquinuclidine **3** by catalytic hydrogenolysis (Pd/C in MeOH/HCl; 82%). Purification of the crude product by ion-exchange chromatography afforded racemic **3**, which appeared pure on the basis of its elementary analysis, and its ^{1}H- and ^{13}C-NMR spectra. This synthesis led to racemic **3** in twelve steps and *ca.* 11% yield from the pyridone **10**.

Resolution of the isoquinuclidine **7** on a chiral phase (*Chiralpak AS-V*) provided (+)-**7** (25%, er >99:1, $[\alpha]_D^{25} = +9.0$) and (−)-**7** (32%, er 97:3, $[\alpha]_D^{25} = -8.6$) in moderate yields[6]), while attempts to obtain enantiomerically pure **3** by separation of the racemate (HPLC, *Chiralcel OD*) failed. The diastereoisomeric (1*R*)-menthoxymethyl ethers **24** [29] and (1*S*)-camphanoyl esters **25** [30] could be separated by neither HPLC nor by crystallisation.

The highest stereoselectivities in *Michael* addition/aldolisations were reported for combinations of enantiomerically pure acrylates and enantiomerically pure bases. *Cinchona* alkaloids performed particularly well [31–33], leading to an enantioselectivity in the cycloaddition of pyrones to achiral acrylates of up to 74% [34][35]. Conversely, a diastereoselectivity of up to 70% was observed for the cycloaddition of achiral Li- and TMS-dienolates to enantiomerically pure 8-phenylmenthyl acrylates [36][37].

Although enantiomerically pure isoquinuclidines had been obtained by enantioselective and diastereoselective hetero-*Diels–Alder* reactions [38], none of them possess the (substituted) 4-hydroxy and 5-carboxy substituents required for our purpose.

To prepare sufficient amounts of the enantiomerically pure isoquinuclidines, we examined the effect of enantiomerically pure bases and enantiomerically pure esters on the stereoselectivity of the cycloaddition of pyridones to acrylates (*Scheme 3*, and *Tables 1* and *2*). In a first series of experiments, we studied the effect of enantiomerically pure bases on the cycloaddition to methyl acrylate. In a second series of experiments, we investigated the combined effect of enantiomerically pure amines and acrylates on the diastereoselectivity.

Unfortunately, analytical HPLC failed to separate the enantiomeric *N*-tosylisoquinuclidines (+)-**7** and (−)-**7**, which result from the reaction of the *N*-tosylpyridone **10** with methyl acrylate in the presence of quinine. Substituting the *N*-tosyl by the larger *N*-[(naphthalen-2-yl)sulfonyl] group solved this problem; the enantiomers (+)-**27** and (−)-**27** were cleanly separated by analytical HPLC from each other, from the epimeric ester **28**, and from the *O*-alkylation product **29**. The most-significant results with enantiomerically pure amines for the cycloaddition of the *N*-[(naphthalen-2-yl)sulfonyl]-pyridone **26** to methyl acrylate are compiled in *Table 1*.

The highest ratio of enantiomers was attained in the presence of quinine or quinidine (*Entries 1–4*); these bases induce the opposite sense of chirality. The induced sense of chirality was established by converting a mixture of the isoquinuclidines (+)-

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[6]) We thank Dr. *M. Juza* and Dr. *E. Freund*, *CarboGen Laboratories AG*, Aarau, for the resolution of **7**.

Scheme 3

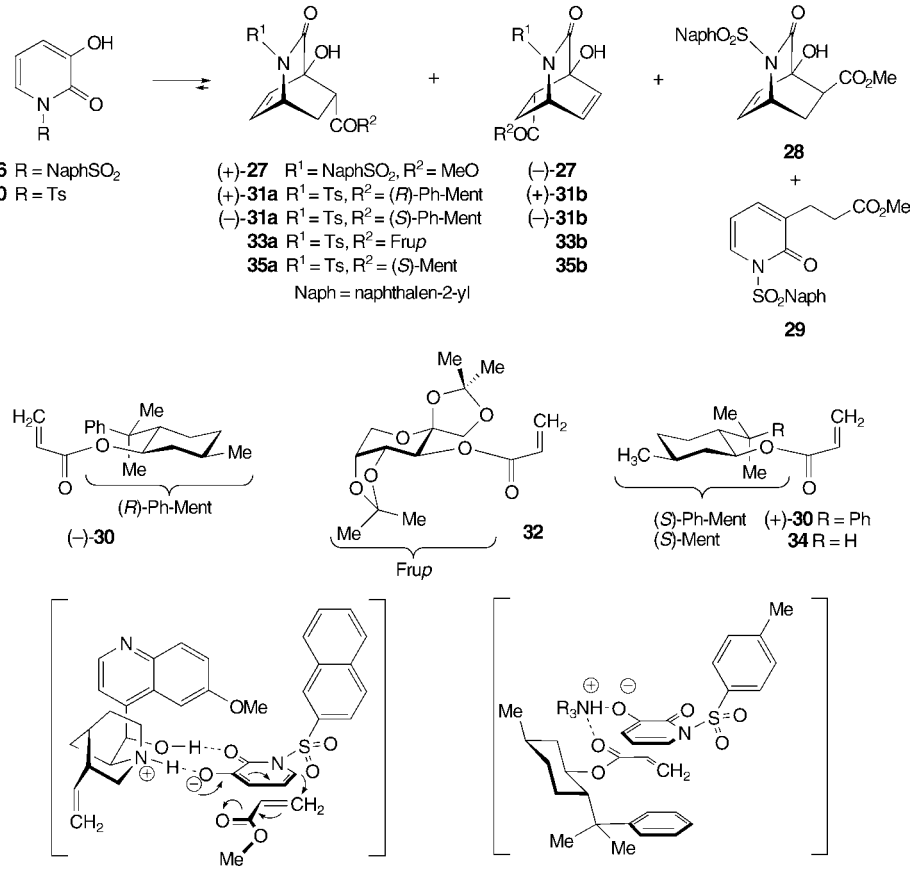


Table 1. *Ratio and Yields of (+)-***27** *and (−)-***27** *Obtained by Enantioselective Cycloaddition of the* N-*Naphthylsulfonyl-Pyridone* **26** *to Methyl Acrylate* (10 equiv.)

Entry	Base ([equiv.])	Solvent, temperature, and reaction time[a])	Yield [%]	Ratio (+)-**27**/(−)-**27**
1	Quinine (2)	Acetone, 40°, 14 h	84[a])	85 : 15[b])
2	Quinine (2)	CH_2Cl_2, 40°, 14 h	–	79 : 21[b])
3	Quinidine (2)	Acetone, 24°, 36 h	–	19 : 81[b])
4	Quinidine (2)	CH_2Cl_2, 24°, 36 h	–	19 : 81[b])
5	Cinchonidine (2)	CH_2Cl_2, 40°, 18 h	–	64 : 36[b])
6	9-Deoxy-9-aminoepiquinidine (2)	CH_2Cl_2, 40°, 6 d	–	34 : 66[b])

[a]) Obtained by crystallisation in i-PrOH/hexane 3 : 1; (+)-**27**/(−)-**27** 88 : 12. [b]) Product ratio determined by analytical HPLC of the crude product at *ca.* 90% conversion of **26**.

27/(−)-**27** (er 88 : 12) to **3** and comparing its optical rotation to that of a sample of enantiomerically pure (+)-**3**, obtained by the diastereoselective synthesis described below (*Scheme 4*). The nature of the addition products and the stereoselectivity

depend on the duration of the reaction. Initially, only the isoquinuclidines (+)-**27** and (−)-**27** were formed besides small amounts of the epimer **28**, the ratio of the products hardly changing with time. Longer reaction times, exceeding those required for 90% conversion of the pyridone **26**, led to increasing amounts of the *O*-alkylation product **29**. Changing the solvent had a small effect on the induction, acetone appearing most favourable for the cycloaddition of **26** to methyl acrylate in the presence of quinine; no induction resulted from using i-PrOH. The highest enantiomeric ratio was realized for the cycloaddition of **26** to methyl acrylate in acetone at 40° in the presence of 2 equiv. of quinine, leading to a mixture of the isoquinuclidines (+)-**27**/(−)-**27** 85:15; recrystallisation in i-PrOH/hexane gave (+)-**27**/(−)-**27** 88:12 in 84% yield (*Entry 1*). Cinchonidine or 9-deoxy-9-aminoepiquinidine [39] led to lower and opposite inductions (*Entries 5* and *6*). Low degrees of enantioselectivity (er $<60:40$) were induced by other bases, including *N*-[(anthracen-9-yl)methyl]quininium chloride/K_2CO_3 [40] and several derivatives of *N*-alkylated valinol [41][42], prolinol [43][44], (1*R*,2*S*)-diphenylethanolamine [45], and norephedrine [46]. Neither (1*R*)-*N*-(phenethyl)bornanamine [47] nor (1*R*)-*N*-(phenethyl)tritylamine [48] catalysed the *Michael* addition/aldolisation of **26** to methyl acrylate.

The stereoselectivity may be rationalised by postulating a H-bonded complex between quinine and the pyridone, the methoxyquinoline part of the catalyst shielding one face of the pyridone (*Scheme 3*). This hypothesis is in keeping with the observation that no asymmetric induction is observed in protic solvents such as i-PrOH, that lower temperatures do not lead to a higher stereoselectivity, and that the sterically less-hindered cinchonidine gave lower inductions than quinine.

The most-significant results of the diastereoselective *Michael* addition/aldolisation of the *N*-tosyl-pyridone **10** to enantiomerically pure acrylates are compiled in *Table 2*. We studied the *Michael* addition/aldolisation of **10** to the 8-phenylmenthyl acrylates (+)-**30** and (−)-**30** [49][7]), to the 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranos-3-yl acrylate **32** [51], and to the (1*S*,3*S*,4*R*)-menthyl acrylate **34** [52] in the presence of Et_3N, quinine, and quinidine.

Table 2. *Ratio and Yields of the Products Obtained by Diastereoselective Cycloaddition of the* N-*Tosyl-Pyridone* **10** *to Enantiomerically Pure Acrylates*

Entry	Acrylate ([equiv.])	Base ([equiv.]), solvent, temperature, and reaction time	Products (yields)	Ratio **a**/**b**
1	(−)-**30** (1)	Et_3N (2), CH_2Cl_2, 24°, 15 d	(+)-**31a**/(+)-**31b** (60%)	75:25[a])
2	**32** (1)	Et_3N (2), CH_2Cl_2, 24°, 1 d	**33a**/**33b** (60%)	38:62[a])
3	**34** (1)	Et_3N (2), CH_2Cl_2, 24°, 2 d	**35a**/**35b** (33%)	41:59[a])
4	(−)-**30** (5)	Quinine (2), CH_2Cl_2, 24°, 3 d	(+)-**31a**/(+)-**31b** (92%)	98:2[b])
5	(−)-**30** (1)	Quinidine (2), CH_2Cl_2, 24°, 15 d	(+)-**31a**/(+)-**31b** (65%)	70:30[a])
6	(+)-**30** (5)	Quinidine (2), CH_2Cl_2, 24°, 3 d	(−)-**31a**/(−)-**31b** (92%)	4:96[b])

[a]) Product ratio determined on the basis of the ^{1}H-NMR spectrum of the crude product. [b]) Product ratio determined by analytical HPLC of the crude product.

[7]) (−)-(1*R*,3*R*,4*S*)-8-Phenylmenthol was prepared from (+)-(1*R*)-pulegone and (+)-(1*S*,3*S*,4*R*)-phenylmenthol from (+)-(*S*)-citronellol according to *Buschmann* and *Scharf* [50]. We thank Prof. Dr. *G. Fráter*, *Givaudan AG,* Dübendorf, for a generous sample of (+)-pulegone.

The highest diastereoselectivity in the presence of Et_3N was observed for the cycloaddition to the 8-phenylmenthyl acrylate (−)-**30** (*Entries 1–3*). The absolute configuration of the 8-phenylmenthyl ester (+)-**31a** was established by X-ray crystal-structure analysis of its 4-*O*-methoxymethyl derivative (−)-**36**[8]) (*Fig. 2*). The formation of (+)-**31a** as the major diastereoisomer is rationalised by assuming a 'closed' *Michael* addition [53] to the s-*cis*, s-*trans*-conformer of (−)-**30**, followed by a (concerted?) aldolisation. This hypothesis is in keeping with the diastereoselectivity of the cycloaddition to the *β*-D-fructopyranosyl acrylate **32** leading to **33b** as the major product (*Entry 2*); the absolute configuration of **33b** was also established by X-ray crystal-structure analysis[9]) (*Fig. 2*). The diastereoisomeric ratio of the cycloaddition to the menthyl acrylate **34** was lower than the one to the 8-phenylmenthyl acrylate (−)-**30** (*Entry 3*). The configuration of the major product was not determined. On the basis of the hypothesis above, it is expected to be the diastereoisomer **35b**.

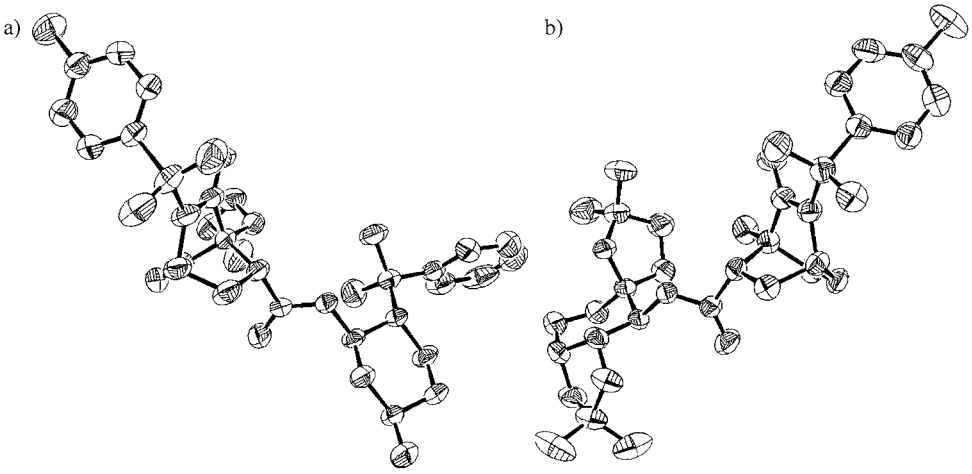


Fig. 2. *ORTEP Representation of the crystal structure* a) *of the 8-phenylmenthyl ester (−)-***36** *and* b) *of the fructopyranosyl ester* **33b**

Replacing Et_3N by quinine or quinidine had an opposite effect on the ratio of diastereoisomers (*Entries 4* and *5*). Quinine increased the ratio of the 8-phenylmenthyl esters (+)-**31a**/(+)-**31b** to 98:2, while quinidine decreased it to 70:30. A fourfold excess of the acrylate (−)-**30** was necessary to drive the cycloaddition to completion; the excess was almost quantitatively recovered (*Entry 5*). The major diastereoisomer (+)-**31a** was isolated in 84% yield by crystallisation, and its diastereoisomeric purity

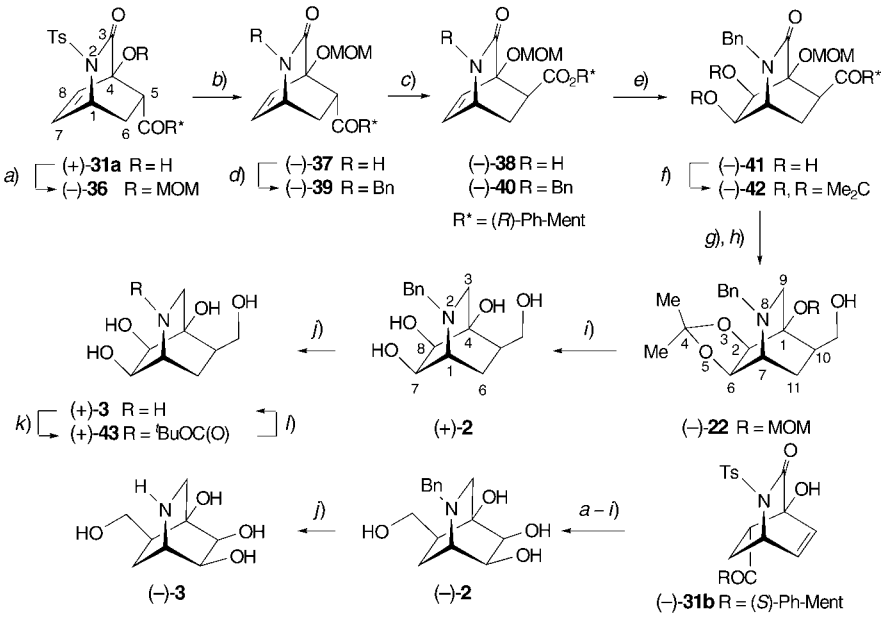
[8]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-216424. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

[9]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-216423. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

was ascertained by HPLC[10]). Its enantiomer (−)-**31b** was obtained from the addition of **10** to the 8-phenylmenthyl acrylate (+)-**30** in the presence of quinidine (*Entry 6*).

Methoxymethylation of the 8-phenylmenthyl ester (+)-**31a** and treatment of the crude product (−)-**36** with sodium naphthalenide afforded the ester (−)-**37** (81%; *Scheme 4)*. Treatment of (−)-**37** with K_2CO_3 in boiling MeOH had no effect. We speculated that chelation of a metal cation of appropriate size by the methoxymethyl substituent, and the lactam and ester C=O groups of (−)-**37** should facilitate the deprotonation of H−C(5), and stabilise the epimeric ester (−)-**38**. We compared Ba^{2+}, Mg^{2+}, K^+, and Li^+ carbonates and hydroxides for this reaction[11]). Treatment of the 8-phenylmenthyl ester (−)-**37** with 2 equiv. of $Ba(OMe)_2$ in anhydrous MeOH led to a mixture of the epimeric esters (−)-**37**/(−)-**38** 2:8. Chromatography yielded (−)-**37** (20%) and (−)-**38** (49%); the corresponding methyl esters were not observed. Higher yields were obtained by epimerisation of the *N*-benzylated ester (−)-**39** in the presence of 2 equiv. of $Ba(OMe)_2$, yielding 23% of (−)-**39** and 68% of the desired ester (−)-**40**. The *N*-benzyl lactam (−)-**40** was dihydroxylated (OsO_4/NMO), and the crude diol (−)-

Scheme 4



a) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$. *b*) Na−$C_{10}H_8$, DME, −78°; (81% from (+)-**31a**). *c*) $Ba(OMe)_2$, MeOH; (−)-**37** (20%), (−)-**38** (49%), resp. (−)-**39** (23%), (−)-**40** (68%). *d*) NaH, BnBr, DMF; 96%. *e*) OsO_4, NMO, THF/acetone/H_2O. *f*) $Me_2C(OMe)_2$, acetone, camphorsulfonic acid; (85% from (−)-**40**). *g*) $LiAlH_4$, THF and *h*) $LiAlH_4$, dioxane; 78%. *i*) CF_3CO_2H, H_2O, 100°; 83%. *j*) H_2, $Pd(OH)_2$/C, conc. HCl/MeOH/H_2O; 93%. *k*) (^{t}BuCO)$_2$O, Et_3N, MeOH; 80%. *l*) HCl, MeOH; 76%.

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10) The enantiomeric purity of (+)-**31a** is deduced from the enantiomeric purity of (+)-pulegone (er > 99.5:0.5) and the optical rotation of the 8-phenylmenthyl acrylate (+)-**30** used for the synthesis of (+)-**31a**, as detailed in the *Exper. Part*.

11) We favoured $Ba(OH)_2$ and $Ba(OMe)_2$, considering the advantageous use of $Ba(OH)_2$ in the structure determination of limonin [54].

41 was protected as the isopropylidene acetal (−)-**42** (85% from (−)-**40**). Reduction of the lactam (−)-**42** with $LiAlH_4$ in boiling THF, followed by treatment of the crude product with $LiAlH_4$ in boiling dioxane, led to the enantiomerically pure *N*-benzyl amine (−)-**22** (78%). The amine (−)-**22** was deprotected by treatment with CF_3COOH/H_2O 1:1. Chromatography of the product on an amino phase yielded 83% of the enantiomerically pure *N*-benzylamine (+)-**2**. Its hydrogenolytic debenzylation (H_2, $Pd(OH)_2/C$) gave the D-*manno*-isoquinuclidine (+)-**3** (93%). It showed a single set of signals in the ^1H- and ^{13}C-NMR spectra, identical to those of the racemate, and no sign of by-products. The L-*manno*-isoquinuclidines (−)-**2** and (−)-**3** were similarly obtained from the 8-phenylmenthyl ester (−)-**31b**. This synthesis provided the enantiomerically pure isoquinuclidine (+)-**3** in twelve steps and a yield of 23% from the pyridone **10**.

A comparison of the inhibition data of this sample of (+)-**3** with those obtained for the racemate (see below) prompted us to rigourously purify the D-*manno*-isoquinuclidine (+)-**3**. Attempts to chromatograph (+)-**3** on silica gel or on an amino phase led to decomposition. However, *N*-*tert*-butoxycarbonylation of the D-*manno*-isoquinuclidine (+)-**3**, followed by chromatography, yielded 80% of the *N*-Boc carbamate (+)-**43**, which was deprotected with HCl/MeOH to provide (+)-**3** (76%) that could not be distinguished from a sample resulting from the debenzylation of (+)-**2**.

The assignment of the configuration at C(5) of the epimeric methyl esters **7**/**8**, **27**/**28**, the epimeric benzyl esters **15**/**16** and **17**/**18**, the epimeric 8-phenylmenthyl esters (−)-**37**/(−)-**38** and (−)-**39**/(−)-**40**, and the dihydroxylated esters (±)-**19** and (−)-**41** is based on a comparison of their coupling constants $J(5,6_{endo})$ and $J(5,6_{exo})$ with each other and with those of the β-D-fructopyranosyl ester (−)-**33b**, the 8-phenylmenthyl ester (−)-**36**, and the dihydroxylated ester (−)-**41** (*cf. Tables 6* and *7* in *Exper. Part*); the structure of (−)-**33b**[8]), (−)-**36**[9]), and (−)-**41**[13]) was established by X-ray crystal structure analysis. For the (5*S*)-configured esters **7**, **15**, **17**, **27**, (−)-**33b**, (−)-**36**, (−)-**37**, and (−)-**39**, $J(5,6_{endo})$ (5.0 Hz) is smaller than $J(5,6_{exo})$ (9.8–10.3 Hz); for the (5*R*)-configured esters **8**, **16**, **18**, **19**, **28**, (−)-**38**, (−)-**40**, and (−)-**41**, $J(5,6_{endo})$ (10.1–11.2 Hz) is larger than $J(5,6_{exo})$ (5.0–5.9 Hz). The configuration of the (5*S*)-configured esters is further characterised by a $J(5,8)$ *W*-coupling (1.0–1.3 Hz) that is not observed for the (5*R*)-configured esters. For all esters, $J(1,6_{endo})$ (1.4–2.5 Hz) is smaller than $J(1,6_{exo})$ (3.4–3.9 Hz)[12]). To deduce the *endo*-orientation of H–C(7) and thereby of H–C(8) in the diols (±)-**19** and (−)-**41**, we compared the coupling of H–C(7) with the bridgehead H–C(1) ($J(1,7) = 1.5$ and < 2.5 Hz) to the coupling of H–C(1) with H_{endo}–C(6) and H_{exo}–C(6) ($J(1,6_{endo}) = 2.2$ Hz; $J(1,6_{exo}) = 3.4$ and 3.5 Hz, resp.). This evidences the *manno*-configuration of (±)-**19** and (−)-**41**, and thereby also of **2** and **3**. These deductions are corroborated by an X-ray crystal-structure analysis of the dihydroxy 8-phenylmenthyl ester (−)-**41**[13]) (*Fig. 3*), establishing the D-*manno*-configuration of (−)-**41**, (+)-**2**, and (+)-**3**.

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12) For ^1H-NMR data of related 2-aza- and 2-oxabicyclo[2.2.2]octan-3-ones, see [21][55].

13) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-216425. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

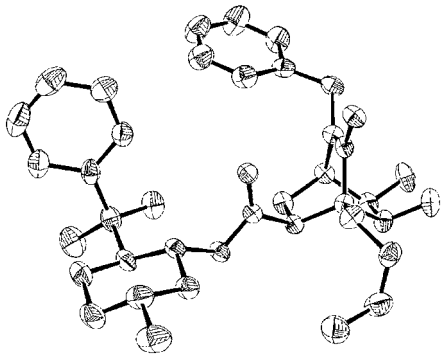

Fig. 3. *ORTEP Representation of the crystal structure of the dihydroxylated isoquinuclidine (−)-***41**

Inhibition Studies. – The results of the inhibition of snail β-mannosidase, *Jack* bean α-mannosidase, and the β-glucosidase from *Caldocellum saccharolyticum* by the enantiomerically pure *manno*-isoquinuclidines (+)-**2** and (+)-**3**, their enantiomers, and the racemate prepared by mixing the enantiomers are summarised in the *Tables 3–5*.

The *N*-benzyl-D-*manno*-isoquinuclidine (+)-**2** is a selective inhibitor of snail β-mannosidase ($K_i = 1.0$ μM, mixed type, $\alpha = 1.9$); *Jack* bean α-mannosidase and the β-glucosidase from *Caldocellum saccharolyticum* are poorly inhibited ($IC_{50} > 5 \cdot 10^3$ μM).

Table 3. *Inhibition of Snail β-Mannosidase,* Jack *Bean α-Mannosidase, and* Caldocellum saccharolyticum *β-Glucosidase by the Isoquinuclidines (+)-***2** *and (+)-***3**, *Their Enantiomers, and Their Racemates, Obtained by Mixing the Enantiomers*

Inhibitor	pK_{HA}	β-Mannosidase from snail [a])	α-Mannosidase from *Jack* bean [a])	β-Glucosidase from *Caldocellum saccharolyticum* [b])
(+)-**2**	7.5	1.0 [c]) ($\alpha = 1.9$)	$> 5 \cdot 10^3$ [d])	$> 5 \cdot 10^3$ [d])
(±)-**2** [e])		2.1 [c]) ($\alpha = 1.8$)	$> 5 \cdot 10^3$ [d])	$> 5 \cdot 10^3$ [d])
(−)-**2**		69 [c]) (noncompetitive)	n.d.	n.d.
(+)-**3**	8.4	$1.2 \cdot 10^3$ [c]) ($\alpha = 1.1$)	$2.0 \cdot 10^3$ [d])	$2.7 \cdot 10^3$ [d])
(±)-**3** [f])		$2.7 \cdot 10^3$ [d])	$3.9 \cdot 10^3$ [d])	$4.3 \cdot 10^3$ [d])
(−)-**3**		$7.3 \cdot 10^3$ [d])	n.d.	n.d.

[a]) At pH 4.5 and 25°. [b]) At pH 6.8 and 55°. [c]) K_i in μM. [d]) IC_{50} in μM. [e]) 1 : 1 Mixture of (+)-**2** and (−)-**2**). [f]) 1 : 1 mixture of (+)-**3** and (−)-**3**. n.d. = not determined.

Table 4. *Time-Dependence of the Inhibition of Snail β-Mannosidase by (+)-***2** *and (+)-***3**

Pre-incubation time [min]	IC_{50} [μM] at 25° and pH 4.5	
	(+)-**2**	(+)-**3**
0	19	$2.6 \cdot 10^3$
30	4.5	$1.9 \cdot 10^3$
60	2.0	$1.7 \cdot 10^3$
90	1.9	$1.6 \cdot 10^3$
120	1.7	$1.3 \cdot 10^3$
300	1.9	$1.5 \cdot 10^3$

Table 5. *pH-Dependence of the Inhibition of Snail β-Mannosidase by (+)-**2** and (+)-**3***

pH	K_i [μM] at 25° and 120-min pre-incubation time	
	(+)-**2**	(+)-**3**
3.5	7.9 ($\alpha = 1.2$)	–
4.5	1.0 ($\alpha = 1.9$)	$1.2 \cdot 10^3$ ($\alpha = 1.1$)
5.5	0.63 ($\alpha = 17$)	$0.25 \cdot 10^3$ ($\alpha = 11$)

Neither the inhibition constant nor the inhibition type of (+)-**2** correspond to those expected on the basis of the published data for racemic **2** ($K_i = 0.17$ μM, competitive [18]). We rechecked the inhibition of snail β-mannosidase with a sample of (+)-**2** taken from a new batch, a freshly prepared sample of (+)-**2**/(−)-**2** 1:1, the originally tested sample of racemic **2**, and the same enzyme batch. Snail β-mannosidase was inhibited *ca.* two times more strongly by (+)-**2** ($K_i = 0.98$ μM, mixed type, $\alpha = 1.7$) than by (+)-**2**/(−)-**2** 1:1 ($K_i = 2.1$ μM, mixed type, $\alpha = 1.8$) and by the original sample of racemic **2** ($K_i = 2.4$ μM, mixed type, $\alpha = 2.1$). These results are in keeping with expectation; the published values for **2** have to be corrected. The *N*-benzyl-L-*manno*-isoquinuclidin e (−)-**2** is a surprisingly good, albeit noncompetitive, inhibitor of snail β-mannosidase ($K_i = 69$ μM).

The IC_{50} value for the inhibition of snail β-mannosidase by the *N*-benzyl-D-*manno*-isoquinuclidine (+)-**2** decreases from 19 to 1.7 μM as the preincubation time is prolonged from 0 to 120 min (*Table 4*). A slow onset of the enzyme inhibition was also reported for racemic **2** [18] and for a series of strong glycosidase inhibitors [56–64]. A slow onset of the enzyme inhibition has been rationalised by postulating either a conformational change of the enzyme from a conformation that binds the substrate in its ground-state to a conformation that binds the transition state [58], or a slow desolvation of the (protonated) basic inhibitor and a slow desolvation of the catalytic site [65].

The inhibition strength and type for the *N*-benzyl-D-*manno*-isoquinuclidine (+)-**2** varies with the pH value (*Table 5*). The inhibition is *ca.* 8 times stronger at pH 4.5 than at pH 3.5, and 1.5 times stronger at pH 5.5 than at pH 4.5. The stronger inhibition of snail β-mannosidase by (+)-**2** at higher pH is in keeping with the hypothesis that the free amine (+)-**2** binds to the active site of the enzyme[14]). In agreement with this interpretation, the inhibition of snail β-mannosidase by (+)-**2** is of mixed type at pH 3.5 ($\alpha = 1.2$) and at pH 4.5 ($\alpha = 1.9$), but almost fully competitive at pH 5.5 ($\alpha = 17$).

The *N*-unsubstituted enantiomerically pure isoquinuclidine (+)-**3** is a poor and essentially noncompetitive inhibitor of snail β-mannosidase at pH 4.5 ($IC_{50} = 1.3 \cdot 10^3$ μM, $K_i = 1.2 \cdot 10^3$ μM, mixed type, $\alpha = 1.1$). The same result was obtained for samples of (+)-**3** derived by debenzylation of (+)-**2** and by Boc deprotection of (+)-**43**. As expected, snail β-mannosidase is inhibited about half as strongly by the racemate (+)-**3**/(−)-**3** 1:1 ($IC_{50} = 2.7 \cdot 10^3$ μM) as by (+)-**3**. The enantiomer (−)-**3** is also a poor inhibitor ($IC_{50} = 7.3 \cdot 10^3$ μM); the inhibition type was not determined. These inhibition

[14]) Conceivably, the partially deactivated mannosidase at pH 5.5 [66] could also be inhibited more strongly by (+)-**2**·H^+ and more weakly by (+)-**2** than the fully active enzyme at its pH optimum of 4.5.

data differ considerably from those published for *rac*-**3** ($IC_{50} = 29.4$ μM; $K_i = 20$ μM, competitive [18]). We, therefore, checked the purity of the original sample of racemic **3** and rechecked that of (+)-**3**. High-resolution MALDI mass spectrometry showed the original sample of *rac*-**3**, but not (+)-**3**, to be contaminated by the *N*-benzylated precursor **2**. A comparison of the IC_{50} value for racemic **2** (0.69 μM [18]), *rac*-**3** (29.4 μM [18]), and (+)-**3**/(−)-**3** 1:1 ($2.7 \cdot 10^3$ μM) shows that the original sample of *rac*-**3** contains 1–2% of **2**.

Although the *N*-unsubstituted D-*manno*-isoquinuclidine (+)-**3** is only a weak inhibitor of snail β-mannosidase, its inhibition strength and type show time and pH dependencies similar to those of the *N*-benzylated isoquinuclidine (+)-**2**. The IC_{50} value for the inhibition of snail β-mannosidase by (+)-**2** decreases from $2.6 \cdot 10^3$ to $1.3 \cdot 10^3$ μM as the preincubation time is prolonged from 0 to 120 min (*Table 4*). The inhibition is *ca.* 5 times stronger at pH 5.5 ($K_i = 0.25 \cdot 10^3$ μM) than at pH 4.5 ($K_i = 1.2 \cdot 10^3$ μM). The D-*manno*-isoquinuclidine (+)-**3** behaves as an almost noncompetitive inhibitor at pH 4.5 ($\alpha = 1.1$) and as an almost competitive inhibitor at pH 5.5 ($\alpha = 11$).

The dependence of the inhibition strength of (+)-**2** and (+)-**3** on the pH value and the parallel change of the inhibition type show that, in both cases, the amine binds to the active site, while the ammonium salt prefers binding to another site. We do not know whether this second site is the same as the one preferred by the L-enantiomer (−)-**2**, nor do we know about the possible effect of a pH-dependent conformational change of the enzyme.

Three main factors appear to contribute to the inhibition of snail β-mannosidase by the isoquinuclidines **2** and **3**, *viz.* the shape of the bicyclic ring, the p*K* value, and the *N*-substituent. The p*K* value of the *N*-benzylamine **2** is 7.5, and that of **3** is 8.4. At pH 4.5, therefore, only a fraction of **2** or **3** is not protonated. Assuming an increase of the inhibitory strength for **2** by a factor 8 per p*K* unit (as suggested by the 8 times stronger inhibition at pH 4.5 than at pH 3.5), one calculates a K_i value of *ca.* 2 nM for a hypothetical analogue of **2** with a pK_{HA} of 4.5. Similarly, one derives a K_i value of 2.2 μM for a hypothetical analogue of **3** with a pK_{HA} of 4.5 (as suggested by the 5 times stronger inhibition at pH 5.5 than at pH 4.5); the effect of the *N*-Bn group remains unaffected by these extrapolations. This consideration suggests that the isoquinuclidine ring is a reasonable, but certainly not optimal, mimic of the distorted, enzyme-bound substrate on the way to the transition state (*i.e.*, corresponding to a point of the reaction coordinate).

We compared the structure of the isoquinuclidine (+)-**3** to that of two enzyme-bound, distorted *gluco*-configured substrates, *viz.* to octa-*N*-acetylchitooctaose in complex with the *Serratia marcescens* ChiA chitobiase mutant E315Q (possessing a pyranoside ring distorted to a $^{1,4}B$) [12] and to 2,4-dinitrophenyl 2-deoxy-2-fluoro-β-cellobioside in complex with the *Bacillus agaradhaerans* Cel5A cellulase (possessing a pyranoside ring distorted to a $^1S_3$) [6]. The isoquinuclidine cyclohexane moiety is a significantly better mimic of the $^{1,4}B$-conformer (rms deviation 0.205 Å) than of the $^1S_3$-conformer (rms deviation 0.356 Å). The same result is obtained by comparing the position of the functional groups of (+)-**3** and of the *manno*-configured analogues of the two distorted substrates (rms deviation 0.356 Å for the $^{1,4}B$-conformer; rms deviation 0.793 Å for the $^1S_3$-conformer). The strongest deviation between the isoquinuclidine (+)-**3** and the $^1S_3$-conformer is observed for the position of the

isoquinuclidine N-atom and the anomeric O-atom of the $^1S_3$-conformer (rms deviation *ca.* 1.1 Å). Inhibitors mimicking the $^1S_3$-conformer, possessing a more suitably oriented N-atom and a lower pK_{HA} value are required to further evaluate the type of ring distortion induced by snail β-mannosidase.

The *ca.* 1000 times stronger inhibition of snail β-mannosidase by the *N*-benzylated isoquinuclidine (+)-**2** *vs.* the *N*-unsubstituted isoquinuclidine (+)-**3** corresponds to the known stronger inhibition of the β-glucosidases from sweet almonds by *N*-benzylated β-D-glucosamine *vs.* β-D-glucosamine [67]. A similar increase in inhibition strength has been reported for other inhibitors with a hydrophobic substituent mimicking the aglycon [68–71]. It is, however, not clear whether the increased inhibition strength denotes a specific binding of the hydrophobic moiety mimicking the aglycon (facilitating ring distortion?) or an unspecific binding.

We thank Dr. *B. Schweizer* for the determination of the X-ray crystal structures, *M. Schneider* and *D. Manser* for the p*K*HA determinations, Dr. *B. Bernet* for checking the experimental part, and the *Swiss National Science Foundation* for generous support.

Experimental Part

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

*3-[(*tert*-Butyl)dimethylsilyloxy]-1*H*-pyridin-2-one.* A soln. of pyridine-2,3-diol (125 g, 1.13 mol) and 1*H*-imidazole (192.0 g, 2.87 mol) in DMF (570 ml) was treated over 1.5 h at 23° with a soln. of TBDMSCl ((*t*-Bu)Me_2SiCl; 171.6 g, 1.14 mol) in DMF (700 ml) and stirred for 9 h. The mixture was divided into three portions of approximately equal volume. Each portion was poured into H_2O (200 ml), and the product was extracted with Et_2O (3 × 200 ml). The combined org. extracts were dried (Na_2SO_4), and the filtrate was concentrated until crystals started to appear. After standing overnight, the crystals were separated and washed with Et_2O. Further product was obtained by recrystallisation of the mother liquor with Et_2O to yield 3-[(*tert*-butyl)dimethylsilyloxy]-1*H*-pyridin-2-one (177.42 g, 70%) in a total of four crops. R_f (AcOEt/hexane 2:3) 0.36. M.p. 122° ([21]: 117°).

*3-[(*tert*-Butyl)dimethylsilyloxy]-1-[(4-methylphenyl)sulfonyl]-1*H*-pyridin-2-one* (**5**). A soln. of 3-[(*tert*-butyl)dimethylsilyloxy]-1*H*-pyridi n-2-one (76.9 g, 0.34 mol) in Et_2O (900 ml) was treated at 0° over 45 min with a 1.6M soln. of MeLi in Et_2O (255 ml, 0.41 mol) and stirred for 2 h. This mixture was treated over 50 min with a soln. of TsCl (78 g, 0.41 mol) in Et_2O (700 ml), stirred at 23° for 30 h, and divided into two portions. Normal workup (Et_2O/H_2O), and recrystallisation of the residue from $CHCl_3$/hexane afforded **5** (106.51 g, 82%) in a total of three crops. R_f (AcOEt/hexane 2:3) 0.72. M.p. 87–90° ([21]: 78–79°).

*Methyl (±)-(1*R*,4*S*,5*R*)-4-[(*tert*-Butyl)dimethylsilyloxy]-3-oxo-2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* (**6**). *a*) A soln. of **5** (45 mg, 0.12 mmol), methyl acrylate (0.11 ml, 1.2 mmol), and 2,6-di-(*tert*-butyl)-4-methylphenol (3 mg, 0.01 mmol) in CH_2Cl_2 (0.8 ml) was heated in a sealed tube at 110° for 230 h. Evaporation of the solvent afforded **5**/**6** 2:3. FC (hexane/AcOEt 4:1) gave **6** (13 mg, 23%) as a white solid and **5** (26 mg, 58%).

b) A soln. of **5** (45 mg, 0.123 mmol), acryloyl chloride (0.1 ml, 1.2 mmol), and 2,6-di-(*tert*-butyl)-4-methylphenol (3 mg, 0.01 mmol) in CH_2Cl_2 (0.8 ml) was heated in a sealed tube at 110° for 144 h, treated with MeOH (0.5 ml) and Et_3N (0.33 ml, 2.4 mmol) at 0°, and stirred at 23° for 20 h. Normal workup (CH_2Cl_2/H_2O, brine) and FC (cyclohexane/AcOEt 4:1) yielded **6** (32 mg, 57%) as a white solid. M.p. 118° ([21]: 118°).

*Methyl (±)-(1*R*,4*S*,5*R*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**7**), *Methyl (±)-(1*R*,4*S*,5*S*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicy-*

clo[2.2.2]oct-7-ene-5-carboxylate ((±)-**8**), *and 3-(3-Methoxy-3-oxopropyloxy)-1-[(4-methylphenyl)sulfonyl]-1H-pyridin-2-one* (**9**). *a*) By a one-pot desilylation/*Michael* addition/aldolisation reaction: a soln. of **5** (42 mg, 0.11 mmol), $Bu_4NF \cdot 3\,H_2O$ (35 mg, 0.11 mmol) and SiO_2 (0.15 g) in CH_2Cl_2 (2 ml) was stirred at 23° for 10 min, treated with methyl acrylate (60 µl, 0.06 mmol), and stirred at 23° for 24 h. Normal workup (Et_2O/H_2O, brine) gave crude (±)-**7**/(±)-**8**/**9** 93 : 4 : 3 (determined by ^{1}H-NMR). FC (cyclohexane/AcOEt 3 : 2) yielded (±)-**7** (24 mg, 63%) as a white solid.

Treatment of **5** (42 mg, 0.11 mmol) under analogous conditions as described above but in H_2O yielded crude (±)-**7**/(±)-**8** > 98 : 2 (determined by ^{1}H-NMR). FC (cyclohexane/AcOEt 3 : 2) gave (±)-**7** (28 mg, 74%) as a white solid.

b) By *Michael* addition/aldolisation: A slurry of crude **10** (38 g, 143.4 mmol) in methyl acrylate/Et_3N 1 : 1 (570 ml) was stirred at 23° for 24 h and filtered. The precipitate was washed with hexane and dried (Na_2SO_4) to yield (±)-**7** (31 g, 62%). The combined filtrate and washings were evaporated, and the residue was recrystallized from $CHCl_3$/hexane to give additional three crops of (±)-**7** (14.9 g, 29%).

*Data of (±)-***7**: R_f (AcOEt/hexane 1 : 1) 0.36. M.p. 158–160°. IR ($CHCl_3$): 3494*w* (br.), 3038*w*, 2954*w*, 1730*s*, 1597*w*, 1493*w*, 1439*m*, 1363*s*, 1261*m*, 1174*s*, 1091*s*, 1042*w*, 980*w*. ^{1}H-NMR ($CDCl_3$, 200 MHz): see *Table 6*; additionally, 7.84 (*dt*, *J* = 8.4, 1.9, 2 H); 7.32 (br. *dd*, *J* = 8.7, 0.7, 2 H); 6.42 (*dd*, *J* = 8.0, 6.1, irrad. at 5.37 → *dd*, *J* = 7.8, 1.9, H–C(7)); 6.20 (*dt*, *J* ≈ 8.1, 1.3, irrad. at 5.37 → br. *d*, *J* = 7.8, irrad. at 2.74 → *dd*, *J* ≈ 8.1, 1.9, H–C(8)); 5.37 (irrad. at 2.46 → *dt*, *J* ≈ 6.2, 1.7, irrad. at 1.88 → *ddd*, *J* = 5.3, 3.4, 1.9, H–C(1)); 3.83 (*s*, exchanges with D_2O, OH); 3.65 (*s*, MeO); 2.74 (irrad. at 1.88 → br. *d*, *J* = 9.7, irrad. at 6.20 → *dd*, *J* = 10.0, 5.0, H–C(5)); 2.46 (irrad. at 5.37 → *dd*, *J* = 13.1, 10.0, H_{exo}–C(6)); 2.43 (*s*, Me of Ts); 1.88 (irrad. at 5.37 → *dd*, *J* = 13.1, 5.0, H_{endo}–C(6)). ^{13}C-NMR ($CDCl_3$): 171.88, 171.02 (2*s*, 2 C=O); 145.67 (*s*); 134.93, 130.40 (2*d*, C(7), C(8)); 134.88 (*s*); 129.78 (2*d*); 127.96 (2*d*); 78.02 (*s*, C(4)); 52.93 (*d*, C(1)); 52.52 (*q*, MeO); 42.85 (*d*, C(5)); 33.47 (*t*, C(6)); 21.72 (*q*, Me of Ts). FAB-MS: 703 (0.9, $[2M+H]^+$), 352 (100, $[M+H]^+$), 266 (44), 155 (40), 154 (12), 91 (21). Anal. calc. for $C_{16}H_{17}NO_6S$ (351.38): C 54.69, H 4.88, N 3.99; found: C 54.73, H 5.07, N 4.04.

Table 6. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Racemic Isoquinuclidines* **7**, **8**, **15**–**19**, **27**, *and* **28**

	7	**8**	**15**	**16**	**17**	**18**	**19**	**27**	**28**
H–C(1)	5.37	5.42	4.24	4.26	4.05	4.00	3.44	5.45	5.47
H–C(5)	2.74	2.91	3.08	2.93	3.06	2.93	2.82	2.75	2.89
H_{endo}–C(6)	1.88	2.10	1.70	1.91	1.56	1.79	1.74	1.92	2.10
H_{exo}–C(6)	2.46	2.24	2.39	2.12	2.09	1.95	1.59	2.50	2.26
J(1,HN)	–	–	5.0	5.0	–	–	–	–	–
J(1,6_{endo})	1.9	2.0	1.4	1.9	1.6	2.2	2.2	1.9	2.2
J(1,6_{exo})	3.4	3.4	3.6	3.5	3.7	3.4	3.4	3.6	3.5
J(1,7)	6.1	5.8	5.6	5.5	5.9	5.6	1.5	6.0	6.0
J(1,8)	1.9	2.2	1.6	1.6	1.3	1.9	–	1.6	1.5
J(5,6_{endo})	5.0	11.2	5.0	10.5	5.0	10.6	10.1	5.0	11.2
J(5,6_{exo})	9.8	5.2	10.0	5.0	10.0	5.0	6.6	9.9	5.3
J(5,8)	1.1	–	1.2	–	1.0	–	–	1.1	–
J(6_{endo}, 6_{exo})	13.0	13.2	12.3	12.5	12.5	12.5	13.1	13.1	13.4

*Data of (+)-***7**: anal. HPLC (*Chiralcel OD* 250 × 4.6 mm, hexane/i-PrOH 4 : 1, 2 ml/min, detection at λ 245 nm): t_R 8.44 min. Prep. HPLC (200 g of *Chiralpak AS-V*, ∅ 4.9 cm, EtOH): t_R 4.3 min. M.p. 141–143° (er *ca.* 99 : 1). $[\alpha]_D^{25} = 9.0$ (er *ca.* 99 : 1; *c* = 1.0, $CHCl_3$).

*Data of (−)-***7**: anal. HPLC (*Chiralcel OD* 250 × 4.6 mm, hexane/i-PrOH 4 : 1, 2 ml/min, detection at λ 245 nm): t_R 10.4 min. Prep. HPLC (200 g of *Chiralpak AS-V*, ∅ 4.9 cm, EtOH): t_R 5.5 min. M.p. 140.5° (er *ca.* 97 : 3). $[\alpha]_D^{25} = -8.6$ (er *ca.* 97 : 3; *c* = 1.0, $CHCl_3$).

*Data of (±)-***8**: R_f (AcOEt/hexane 1 : 1) 0.26. ^{1}H-NMR ($CDCl_3$, 200 MHz): see *Table 6*; additionally, 7.92 (*d*, *J* = 8.4, 2 H); 7.35 (*d*, *J* = 8.4, 2 H); 6.48 (*dd*, *J* = 7.8, 5.8, H–C(7)); 6.31 (*dd*, *J* = 7.8, 2.2, H–C(8)); 3.97 (*s*, exchanges with D_2O, OH); 3.55 (*s*, MeO); 2.45 (*s*, Me of Ts).

Data of **9**: R_f (AcOEt/hexane 1 : 1) 0.20. IR ($CHCl_3$): 3007*w*, 1734*s*, 1666*s*, 1612*s*, 1548*w*, 1439*w*, 1178*s*, 1093*w*, 925*w*, 546*m*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.90 (*d*, *J* = 8.4, 2 H of Ts); 7.45–7.38 (*m*, H–C(4), H–C(6));

7.33 (*d*, *J* = 8.4, 2 H of Ts); 6.13 (*t*, *J* = 7.4, H–C(5)); 4.13 (*t*, *J* = 6.2, CH_2O); 3.68 (*s*, MeO); 2.70 (*t*, *J* = 6.2, CH_2CO_2); 2.45 (*s*, Me of Ts). ^{13}C-NMR ($CDCl_3$): 171.70 (*s*, CO_2); 157.11 (*s*, C(2)); 145.38, 139.12 (2*s*, C(4) of Ts, C(3)); 137.54, 131.91 (2*d*, C(4), C(6)); 132.88 (*s*, C(1) of Ts); 129.51, 128.69 (2*d*, C(2), C(3), C(5), and C(6) of Ts); 103.64 (*d*, C(5)); 51.91 (*q*, MeO); 46.64, 32.35 (2 alkyl *t*); 21.69 (*q*, Me of Ts).

*3-Hydroxy-1-[(4-methylphenyl)sulfonyl]-1*H*-pyridin-2-one* (**10**). *a*) A soln. of **5** (60 g, 0.16 mol) in CH_2Cl_2 (250 ml) was treated portionwise with $BF_3 \cdot Et_2O$ (22.1 ml, 0.17 mol) over 45 min and stirred at 23° for 24 h, when TLC showed an incomplete reaction. After treatment with an additional portion of $BF_3 \cdot Et_2O$ (5 ml, 0.04 mol), stirring was continued for 12 h. The mixture was poured into H_2O. The phases were separated, and the aq. phase was extracted with $CHCl_3$ (3 × 150 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and evaporated to give crude **10** (41.12 g, 98%).

b) Desilylation of **5** (5.00 g, 13.2 mmol) as described above and recrystallisation of the crude product from $CHCl_3$/hexane 1:1 gave pure **10** (2.24 g, 96%). R_f (AcOEt/hexane 2:3) 0.50. M.p. 165–169°. IR ($CHCl_3$): 3433*m* (br.), 3122*w*, 3022*w*, 1656*s*, 1633*s*, 1550*m*, 1433*m*, 1394*s*, 1378*s*, 1283*s*, 1172*s*, 1117*s*, 1089*m*, 1050*w*, 1017*w*, 889*w*. ^{1}H-NMR ($CDCl_3$): 8.01 (br. *d*, *J* = 8.4, 2 H of Ts); 7.67 (*dd*, *J* = 7.5, 1.6, H–C(6)); 7.37 (br. *d*, *J* = 8.4, 2 H of Ts); 6.76 (*dd*, *J* = 7.2, 1.6, H–C(4)); 6.59 (*s*, exchanges with D_2O, HO–C(3)), 6.24 (br. *t*, *J* ≈ 7.4, H–C(5)); 2.45 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 157.32 (*s*, C(2)); 147.03, 146.64 (2*s*, C(4) of Ts, C(3)); 133.04 (*s*, C(1) of Ts); 129.90, 129.65 (2*d*, C(2), C(3), C(5), and C(6) of Ts); 121.37 (*d*, C(6)); 114.50 (*d*, C(5)); 107.01 (*d*, C(4)); 21.85 (*q*, Me). EI-MS: 265 (3, M^+), 201 (46), 155 (13), 91 (100), 65 (51). Anal. calc. for $C_{12}H_{11}NO_4S$ (265.29): C 54.33, H 4.18, N 5.28, S 12.09; found: C 54.37, H 4.33, N 5.21, S 12.16.

*Methyl (±)-(1*R*,4*S*,5*R*)-4-(Methoxymethoxy)-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**11**). A well-stirred suspension of (±)-**7** (20 g, 57 mmol) and P_2O_5 (50 g, 352 mmol) in $CHCl_3$ (200 ml) was treated with dimethoxymethane (70 ml), and stirred for 1 h, when TLC showed an incomplete reaction. The suspension was treated with additional P_2O_5 (2 g, 14 mmol) and stirred for 1 h. The supernatant was decanted and washed with sat. aq. Na_2CO_3 soln. (*ca.* 50 ml). The residue was cooled in an ice bath and dissolved in sat. aq. Na_2CO_3 soln. (*ca.* 200 ml). The soln. (pH 8.0) was quickly extracted with $CHCl_3$ (2 × 200 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and evaporated. Recrystallisation of the crude product from MeOH/Et_2O afforded (±)-**11** (20.0 g, 88%). R_f (AcOEt/hexane 2:3) 0.30. M.p. 110°. IR ($CHCl_3$): 3011*w*, 2954*w*, 2829*w*, 1734*s*, 1598*w*, 1440*w*, 1361*s*, 1277*w*, 1171*s*, 1097*m*, 1068*m*, 981*m*, 957*m*, 921*w*. ^{1}H-NMR ($CDCl_3$): 7.84 (*dt*, *J* ≈ 8.4, 1.9, 2 H); 7.29 (br. *dd*, *J* = 8.7, 0.6, 2 H); 6.66 (*dt*, *J* ≈ 8.1, 1.6, irrad. at 5.34 → *dd*, *J* = 8.4, 0.9, H–C(8)); 6.51 (*dd*, *J* ≈ 8.3, 6.1, H–C(7)); 5.34 (*ddt*, *J* ≈ 6.1, 3.5, 1.9, irrad. at 6.66 → *ddd*, *J* ≈ 6.0, 3.7, 1.9, H–C(1)); 4.91 (*s*, OCH_2O); 3.67 (*s*, CO_2Me); 3.35 (*s*, *Me*OCH_2); 2.94 (*ddd*, *J* = 10.0, 5.0, 1.2, irrad. at 6.66 → *dd*, *J* = 10.0, 5.0, H–C(5)); 2.46 (*ddd*, *J* ≈ 13.1, 10.0, 3.4, irrad. at 5.34 → *dd*, *J* = 13.1, 10.3, H_{exo}–C(6)); 2.42 (*s*, Me of Ts); 1.78 (*ddd*, *J* ≈ 13.0, 5.0, 2.1, irrad. at 5.34 → *dd*, *J* = 12.8, 5.0, H_{endo}–C(6)). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.93 (*s*, *C*O_2Me); 169.53 (*s*, C(3)); 145.31, 135.12 (2*s*); 132.96, 130.87 (2*d*, C(7), C(8)); 129.63 (2*d*); 127.82 (2*d*); 94.71 (*t*, OCH_2O); 83.60 (*s*, C(4)); 55.48 (*q*, *Me*OCH_2); 51.99 (*q*, CO_2*Me*); 51.99 (*d*, C(1)); 41.26 (*d*, C(5)); 33.23 (*t*, C(6)); 21.39 (*q*, Me of Ts). CI-MS: 396 (15, $[M+H]^+$), 364 (100, $[M-CH_3OH]^+$), 198 (20), 153 (28), 45 (46, $CH_3OCH_2^+$). Anal. calc. for $C_{18}H_{21}NO_7S$ (395.43): C 54.67, H 5.35, N 3.54; found: C 54.62, H 5.37, N 3.62.

*Methyl (±)-(1*R*,4*S*,5*R*)-4-(Methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**12**). Na (3.11 g, 135.4 mg-atom) was added to a soln. of naphthalene (20.8 g, 162.5 mmol) in 1,2-dimethoxyethane (DME; 90 ml). The green mixture was stirred at 23° for 3 h and added dropwise to a cooled (−78°) soln. of (±)-**11** (8.30 g, 21 mmol) in DME (135 ml) until a pale-green colour persisted. After stirring for 5 min, the mixture was treated with sat. aq. $NaHCO_3$ soln. (45 ml), allowed to warm to 5°, and was quickly extracted with $CHCl_3$ (5 × 90 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane/MeOH 1:1:0.1) yielded (±)-**12** (4.69 g, 93%). R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.15. IR ($CHCl_3$): 3431*w*, 3207*m*, 3007*w*, 2953*w*, 1736*s*, 1685*s*, 1436*m*, 1363*m*, 1272*m*, 1172*s*, 1156*m*, 1064*m*, 1004*w*. ^{1}H-NMR ($CDCl_3$): 7.58 (br. *s*, NH); 6.72 (*dt*, *J* ≈ 8.1, 0.9, irrad. at 4.26 → br. *d*, *J* ≈ 8.1, H–C(8)); 6.49 (*dd*, *J* ≈ 8.3, 5.1, irrad. at 4.26 → *d*, *J* = 8.1, H–C(7)); 5.08, 5.00 (2*d*, *J* = 7.8, OCH_2O); 4.26 (*tdt*, *J* ≈ 5.3, 3.7, 1.9, H–C(1)); 3.68 (*s*, CO_2Me); 3.40 (*s*, *Me*OCH_2); 3.01 (*ddd*, *J* ≈ 9.6, 5.0, 1.5, H–C(5)); 2.38 (*ddd*, *J* ≈ 12.0, 10.1, 3.7, irrad. at 4.26 → *dd*, *J* ≈ 12.3, 10.1, H_{exo}–C(6)); 1.70 (*ddd*, *J* ≈ 12.0, 4.8, 1.5, irrad. at 4.26 → *dd*, *J* ≈ 12.3, 4.8, H_{endo}–C(6)). ^{13}C-NMR ($CDCl_3$): 175.44 (*s*, *C*O_2Me); 172.83 (*s*, C(3)); 132.86, 132.49 (2*d*, C(7), C(8)); 95.18 (*t*, OCH_2O); 83.56 (*s*, C(4)); 55.64 (*q*, *Me*OCH_2); 52.10 (*q*, CO_2*Me*); 47.96 (*d*, C(1)); 42.94 (*d*, C(5)); 34.74 (*t*, C(6). CI-MS: 242 (20, $[M+H]^+$), 210 (100), 198 (12), 156 (37), 124 (35), 55 (32), 45 (85). Anal. calc. for $C_{11}H_{15}NO_5$ (241.24): C 54.77, H 6.27, N 5.81; found: C 54.88, H 6.25, N 5.74.

*Benzyl (±)-(1*R*,4*S*,5*R*)-4-(Methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**15**), *Benzyl (±)-(1*R*,4*S*,5*S*)-4-(Methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**16**), *Ben-*

*zyl (±)-(1*R*,4*S*,5*R*)-2-Benzyl-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**17**), *and Benzyl (±)-(1*R*,4*S*,5*S*)-2-Benzyl-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**18**). A mixture of (±)-**12** (3.18 g, 13.2 mmol), K_2CO_3 (2.81 g, 19.8 mmol), and MeOH (40 ml) was heated to reflux for 20 h and evaporated. The residue was dissolved in DMF (60 ml), treated with $NaHCO_3$ (1.0 g, 12 mmol), dropwise with BnBr (2.4 ml, 20 mmol), and stirred for 12 h. Normal workup (AcOEt/H_2O) and FC (AcOEt/hexane/MeOH 1:1:0.1) yielded (±)-**15**/(±)-**16** 7:3 (2.36 g, 42%) and (±)-**17**/(±)-**18** 8:2 (733 mg, 18%). The mixture (±)-**15**/(±)-**16** was dissolved in DMF (35 ml), treated with NaH (355 mg, 50% in oil, 7.44 mmol) and BnBr (1.32 ml, 11.1 mmol) at 23°, stirred for 15 h, and poured in H_2O (50 ml). The product was extracted with AcOEt (3 × 100 ml), dried ($MgSO_4$), and evaporated. FC (AcOEt/hexane/MeOH 1:1:0.1) of the residue, combined with the previously isolated mixture (±)-**17**/(±)-**18**, afforded (±)-**17** (0.37 g, 7%) and (±)-**18** (2.47 g, 46%).

*Data of (±)-***15**: R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.36. ^{1}H-NMR ($CDCl_3$): see *Table 6*; additionally, 7.36–7.22 (*m*, 5 H); 7.17 (br. *d*, *J* = 4.7, irrad. at 4.24 → br. *s*, NH); 6.72 (*dt*, *J* = 8.1, 1.6, irrad. at 4.24 → *dd*, *J* = 8.4, 1.3, H–C(8)); 6.48 (*dd*, *J* = 8.1, 5.6, irrad. at 4.24 → *d*, *J* = 8.1, irrad. at 6.72 → *dd*, *J* = 5.0, 2.8, H–C(7)); 5.14, 5.08 (2*d*, *J* = 12.5, PhCH_2); 5.06. 4.97 (2*d*, *J* = 7.5, OCH_2O); 4.24 (irrad. at 6.72 → *tdd*, *J* = 5.2, 3.7, 1.6, H–C(1)); 3.26 (*s*, MeO); 3.08 (irrad. at 6.72 → *dd*, *J* = 10.0, 5.0, H–C(5)); 2.39 (irrad. at 4.24 → *dd*, *J* = 12.1, 10.0, H_{exo}–C(6)); 1.70 (irrad. at 4.24 → *dd*, *J* = 12.5, 5.0, H_{endo}–C(6)). ^{13}C-NMR ($CDCl_3$): 174.73, 171.90 (2*s*, 2 C=O); 135.80 (*s*); 132.93 (*d*), 132.19 (*d*), 128.63 (2*d*), 128.32 (*d*), 128.26 (2*d*) (5 arom. *d*, C(7), C(8)); 95.24 (*t*, OCH_2O); 83.71 (*s*, C(4)); 66.92 (*t*, PhCH_2); 55.83 (*q*, MeO); 48.25 (*d*, C(1)); 43.33 (*d*, C(5)); 35.12 (*t*, C(6)).

*Data of (±)-***16**: R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.29. ^{1}H-NMR ($CDCl_3$): see *Table 6*; additionally, 7.89 (br. *d*, *J* ≈ 5.0, irrad. at 4.26 → *s*, NH); 7.25–7.37 (*m*, 5 H); 6.74 (*dd*, *J* = 8.1, 1.6, irrad. at 4.26 → *d*, *J* = 8.1, H–C(8)); 6.46 (*dd*, *J* ≈ 8.3, 5.5, irrad. at 4.26 → *d*, *J* = 8.1, H–C(7)); 5.21, 5.10 (2*d*, *J* ≈ 12.3, PhCH_2); 5.13, 5.00 (2*d*, *J* ≈ 7.7, OCH_2O); 3.44 (*s*, MeO); 2.12 (irrad. at 4.26 → *dd*, *J* = 12.5, 5.0, H_{exo}–C(6)); 1.91 (irrad. at 4.26 → *dd*, *J* = 12.1, 10.6, H_{endo}–C(6)). ^{13}C-NMR ($CDCl_3$): 173.02, 172.52 (2*s*, 2 C=O); 135.69 (*s*); 133.94, 128.37 (2*d*), 128.02 (4*d*) (5 arom. *d*, C(7), C(8)); 94.81 (*t*, OCH_2O); 83.70 (*s*, C(4)); 66.88 (*t*, PhCH_2); 55.76 (*q*, MeO); 47.23 (*d*, C(1)); 45.42 (*d*, C(5)); 33.59 (*t*, C(6)).

*Data of (±)-***17**: R_f (AcOEt/hexane 2:3) 0.28. IR ($CHCl_3$): 3008*m*, 2952*w*, 1735*w*, 1682*s*, 1496*w*, 1450*w*, 1385*w*, 1352*m*, 1164*s*, 1057*m*, 986*m*, 919*w*. ^{1}H-NMR ($CDCl_3$): see *Table 6*; additionally, 7.39–7.20 (*m*, 9 H); 7.18 (*dd*, *J* ≈ 7.7, 1.7, 1 H); 6.74 (*dt*, *J* ≈ 8.1, 1.1, irrad. at 4.05 → *dd*, *J* = 8.1, 1.9, H–C(8)); 6.40 (*dd*, *J* = 8.1, 5.9, irrad. at 4.05 → *d*, *J* = 8.1, irrad. at 6.74 → *dd*, *J* ≈ 5.3, 1.9, H–C(7)); 5.15, 5.06 (2*d*, *J* ≈ 7.7, OCH_2O); 5.15, 5.08 (2*d*, *J* ≈ 12.3, PhCH_2O); 4.52, 4.45 (2*d*, *J* = 14.9, PhCH_2N); 4.05 (irrad. at 6.74 → *ddd*, *J* ≈ 5.3, 3.4, 1.6, H–C(1)); 3.31 (*s*, MeO); 3.06 (irrad. at 6.74 → *dd*, *J* = 10.0, 5.0, H–C(5)); 2.09 (irrad. at 4.05 → *dd*, *J* = 12.5, 10.0, H_{exo}–C(6)); 1.56 (irrad. at 4.05 → *dd*, *J* = 12.5, 5.0, H_{endo}–C(6)). ^{13}C-NMR ($CDCl_3$): 172.20, 171.52 (2*s*, C=O); 136.56, 135.96 (2*s*); 133.49 (*d*), 131.48 (*d*), 129.06 (2*d*), 128.76 (2*d*), 128.46 (*d*), 128.41 (2*d*), 128.34 (2*d*), 128.08 (*d*) (10 arom. *d*, C(7), C(8)); 95.32 (*t*, OCH_2O); 83.98 (*s*, C(4)); 66.80 (*t*, PhCH_2O); 55.69 (*q*, MeO); 52.63 (*d*, C(1)); 48.71 (*t*, PhCH_2N); 43.59 (*d*, C(5)); 33.59 (*t*, C(6)). CI-MS: 408 (32, $[M+H]^+$), 376 (22), 246 (31), 91 (100).

*Data of (±)-***18**: R_f (AcOEt/hexane 2:3) 0.19. IR ($CHCl_3$): 3008*m*, 2953*w*, 1735*s*, 1686*s*, 1606*w*, 1497*w*, 1451*m*, 1346*m*, 1166*s*, 1059*m*, 993*m*, 917*w*. ^{1}H-NMR ($CDCl_3$): see *Table 6*; additionally, 7.42–7.19 (*m*, 10 H); 6.78 (*dd*, *J* = 8.1, 1.9, irrad. at 4.00 → *d*, *J* = 8.1, H–C(8)); 6.37 (*dd*, *J* = 8.1, 5.6, irrad. at 4.00 → *d*, *J* = 8.1, H–C(7)); 5.27, 5.13 (2*d*, *J* ≈ 12.3, PhCH_2O); 5.21, 5.06 (2*d*, *J* = 7.5, OCH_2O); 4.62, 4.49 (2*d*, *J* ≈ 14.9, PhCH_2N); 3.47 (*s*, MeO); 1.95 (irrad. at 4.00 → *dd*, *J* = 12.5, 4.7, H_{exo}–C(6)); 1.79 (irrad. at 4.00 → *dd*, *J* = 12.5, 10.1, H_{endo}–C(6)). ^{13}C-NMR ($CDCl_3$): 172.74, 170.16 (2*s*, 2 C=O); 136.69, 136.08 (2*s*); 135.74 (*d*), 133.13 (*d*), 128.84 (2*d*), 128.71 (2*d*), 128.65 (2*d*), 128.60 (2*d*), 128.44 (*d*), 127.80 (*d*) (10 arom. *d*, C(7), C(8)); 95.24 (*t*, OCH_2O); 84.21 (*s*, C(4)); 67.11 (*t*, PhCH_2O); 55.83 (*q*, MeO); 51.38 (*d*, C(1)); 48.42 (*t*, PhCH_2N); 46.10 (*d*, C(5)); 32.13 (*t*, C(6)). CI-MS: 408 (46, $[M+H]^+$), 376 (53), 246 (36), 91 (100).

*Benzyl (±)-(1*R*,4*R*,5*S*,7*R*,8*R*)-2-Benzyl-7,8-dihydroxy-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]octane-5-carboxylate* ((±)-**19**). A soln. of (±)-**18** (279 mg, 0.67 mmol) and *N*-methylmorpholine *N*-oxide · H_2O (136 mg, 1.16 mmol) in acetone/H_2O 3:2 (5 ml) was treated with a cat. amount of OsO_4 (*ca.* 4 mg, 0.015 mmol) and stirred at 23° for 2 h. Normal workup (AcOEt/2M Na_2SO_3 soln.) and FC (hexane/AcOEt/MeOH 1:1:0.2) afforded (±)-**19** (210 mg, 70%). White solid. R_f (hexane/AcOEt/MeOH 1:1:0.2) 0.25. M.p. 129–131°. IR (CH_2Cl_2): 3500*s*, 3355*s* (br.), 2922*m*, 1733*s*, 1683*s*, 1450*m*, 1363*m*, 1316*w*, 1275*s*, 1155*m*, 1044*m*, 1005*m*, 908*m*. ^{1}H-NMR ($CDCl_3$): see *Table 6*; additionally, 7.32–7.15 (*m*, 10 H); 5.71, 4.69 (2*d*, *J* = 7.8, OCH_2O); 5.20, 4.04 (2*d*, *J* ≈ 14.3, PhCH_2N); 5.18 (*d*, *J* = 2.8, exchanges with CD_3OD, HO–C(8)); 5.17, 5.02 (2*d*, *J* = 12.5, PhCH_2O); 3.94 (*dd*, *J* = 8.1, 2.8, irrad. at 5.18 → *d*, *J* = 8.1, addn. of CD_3OD → *d*, *J* = 8.1, H–C(8)); 3.88 (br. *ddd*, *J* ≈ 8.1, 5.0, 1.5, irrad. at 3.68 → br. *dd*, *J* = 8.1, 1.5, addn. of CD_3OD → br. *d*, *J* ≈ 7.8, H–C(7)); 3.68 (*d*, *J* = 5.0, exchanges with CD_3OD, HO–C(7)); 3.44 (br. *s*, MeO); 1.74 (irrad. at 3.44 → *dd*, *J* = 13.5, 10.1, H_{endo}–C(6)); 1.59 (irrad. at

3.44 → *dd*, *J* = 13.7, 6.5, H_{exo}–C(6)). ^{13}C-NMR ($CDCl_3$): 172.17, 167.64 (2*s*, 2 C=O); 137.21, 136.05 (2*s*); 129.17–127.91 (several *d*); 93.71 (*t*, OCH_2O); 80.90 (*s*, C(4)); 71.0, 68.69 (2*d*, C(7), C(8)); 67.24 (*t*, Ph*C*H_2O); 56.22 (*q*, MeO); 56.17 (*d*, C(1)); 49.77 (*t*, Ph*C*H_2N); 44.32 (*d*, C(5)); 28.41 (*t*, C(6)). CI-MS: 442 (2, $[M+H]^+$), 410 (6), 363 (6), 201 (16), 106 (11), 91 (100). Anal. calc. for $C_{24}H_{27}NO_7$ (441.48): C 65.29, H 6.16, N 3.17; found C 65.31, H 6.15, N 3.24.

*Benzyl (±)-(1*R*,2*R*,6*R*,7*R*,10*S*)-8-Benzyl-1-(methoxymethoxy)-4,4-dimethyl-9-oxo-3,5-dioxa-8-azatricyclo[5.2.2.0^{2,6}]undecane-10-carboxylate* ((±)-**20**). A soln. of (±)-**19** (0.414 g, 0.938 mmol) and camphorsulfonic acid (15 mg) in acetone/2,2-dimethoxypropane 1:1 (20 ml) was stirred at 23° for 20 min. Normal workup (AcOEt/$NaHCO_3$ soln.) and FC (hexane/AcOEt 9:1) afforded (±)-**20** (0.425 g, 94%). R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.64. IR ($CHCl_3$): 3007*m*, 2938*m*, 1737*s*, 1692*s*, 1605*w*, 1490*w*, 1455*m*, 1381*m*, 1350*m*, 1314*w*, 1267*m*, 1170*s*, 1080*s*, 996*m*, 915*m*, 868*w*. ^{1}H-NMR ($CDCl_3$): 7.42–7.22 (*m*, 10 H); 5.51, 3.81 (2*d*, *J* = 14.6, PhCH_2N); 5.36, 5.13 (2*d*, *J* = 13.0, PhCH_2O); 5.28, 5.09 (2*d*, *J* = 6.5, OCH_2O); 4.50 (*d*, *J* = 7.5, H–C(2)); 4.24 (*dd*, *J* = 7.5, 2.2, irrad. at 3.54 → *d*, *J* = 7.5, H–C(6)); 3.54 (br. *q*, *J* ≈ 2.7, H–C(7)); 3.42 (*s*, MeO); 2.88 (*dd*, *J* = 9.5, 7.4, H–C(10)); 1.67–1.80 (*m*, irrad. at 2.88 → change, irrad. at 3.54 → change, 2 H–C(11)); 1.43, 1.32 (2*s*, Me_2C(4)). ^{13}C-NMR ($CDCl_3$): 172.28, 167.41 (2*s*, 2 C=O); 136.92, 135.87 (2*s*); 129.06–127.77 (several *d*); 110.86 (*s*, C(4)); 94.37 (*t*, OCH_2O); 80.36 (*s*, C(1); 79.40, 77.14 (2*d*, C(2), C(6)); 67.27 (*t*, Ph*C*H_2O); 56.16 (*q*, MeO); 52.91 (*d*, C(7)); 49.78 (*t*, Ph*C*H_2N)); 43.98 (*d*, C(10)); 27.98 (*t*, C(11)); 26.08, 24.59 (2*q*, *Me*$_2$C(4)). HR-MALDI-MS: 520.1722 (7, $[M+K]^+$, $C_{27}H_{31}KNO_7^+$; calc. 520.1738), 504.1983 ($[M+Na]^+$; calc. for $C_{27}H_{31}NaNO_7^+$: 504.1998), 460 (26), 450 (21).

*(±)-(1*R*,2*R*,3*R*,7*R*,8*R*,10*S*)-9-Benzyl-2-(methoxymethoxy)-5,5-dimethyl-4,6,11-trioxa-9-azatetracyclo[6.4.1.0^{2,10}.0^{3,7}]tridecane* ((±)-**21**), *(±)-(1*R*,2*R*,6*R*,7*R*,10*R*)-8-Benzyl-1-(methoxymethoxy)-4,4-dimethyl-3,5-dioxa-8-azatricyclo[5.2.2.0^{2,6}]undecane-10-methanol* ((±)-**22**), *and (±)-(1*R*,2*R*,6*R*,7*R*,10*R*)-8-Benzyl-1-hydroxy-4,4-dimethyl-3,5-dioxa-8-azatricyclo[5.2.2.0^{2,6}]undecane-10-methanol* ((±)-**23**). A soln. of (±)-**20** (0.164 g, 0.34 mmol) in THF (5 ml) was treated with a 1M soln. of $LiAlH_4$ in THF (1.4 ml, 1.4 mmol), stirred at 23° for 20 min, and refluxed for 20 h. The mixture was cooled to 23°, treated slowly with MeOH until effervescence ceased, and evaporated. The residue was extracted with AcOEt/Et_3N 95:5 (70 ml). The solid was filtered off and washed with AcOEt/Et_3N 95:5 (70 ml). Evaporation of the combined extracts and filtrates, and FC (AcOEt/hexane/MeOH 1:1:0.1) afforded (±)-**21** (71 mg, 57%), (±)-**22** (21 mg, 17%), and (±)-**23** (9 mg, 8%).

A soln. of (±)-**21** (540 mg, 1.50 mmol) in dioxane (60 ml) was treated with a 1M soln. of $LiAlH_4$ in THF (6.0 ml, 6 mmol), heated to reflux for 6 h, and worked up in the same way as described above. FC (AcOEt/hexane/MeOH 1:1:0.1) afforded (±)-**22** (364 mg, 67%).

*Data of (±)-***21**: R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.70. IR ($CHCl_3$): 3007*s*, 2942*m*, 2896*m*, 1730*w*, 1603*w*, 1452*m*, 1376*s*, 1147*s*, 1082*s*, 1043*s*, 1020*s*, 978*s*, 944*m*, 925*m*. ^{1}H-NMR ($CDCl_3$): 7.46 (br. *d*, *J* ≈ 7.5, 2 H); 7.44–7.18 (*m*, 3 H); 4.99, 4.92 (2*d*, *J* = 7.2, OCH_2O); 4.94 (*s*, H–C(10)); 4.66 (*d*, *J* = 8.4, H–C(3)); 4.20 (*dd*, *J* ≈ 7.8, 3.4, irrad. at 2.30 → *d*, *J* = 6.5, irrad. at 3.59 → *d*, *J* = 3.7, H_a–C(12)); 4.19, 3.78 (2*d*, *J* = 14.3, PhCH_2); 4.00 (*dd*, *J* = 8.4, 2.5, irrad. at 2.77 → *d*, *J* = 8.2, irrad. at 4.66 → *d*, *J* = 2.5, H–C(7)); 3.59 (*d*, *J* = 7.5, H_b–C(12)); 3.43 (*s*, MeO); 2.77 (br. *q*, *J* ≈ 2.7, H–C(8)); 2.35–2.26 (*m*, H–C(1)); 1.86–1.73 (*m*, 2 H–C(13)); 1.58, 1.32 (2*s*, Me_2C(5)). ^{13}C-NMR ($CDCl_3$): 139.62 (*s*); 129.12 (2*d*); 128.6 (2*d*); 126.98 (*d*); 109.85 (*s*, C(5)); 92.88 (*t*, OCH_2O); 91.04 (*d*, C(10)); 84.21 (*s*, C(2)); 77.45, 74.67 (2*d*, C(3), C(7)); 74.02 (*t*, C(12)); 56.19 (*q*, MeO); 53.78 (*t*, Ph*C*H_2); 48.54 (*d*, C(8)); 36.63 (*d*, C(1)); 31.81 (*t*, C(13)); 25.99, 25.74 (2*q*, *Me*$_2$C(5)). HR-MALDI-MS: 362.1958 ($[M+H]^+$, $C_{20}H_{28}NO_5^+$; calc. 362.1967).

*Data of (±)-***22**: R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.32. IR (CH_2Cl_2): 3527*m*, 2907*s*, 1494*w*, 1453*w*, 1376*m*, 1209*m*, 1162*m*, 1128*m*, 1044*m*. ^{1}H-NMR ($CDCl_3$): 7.31–7.22 (*m*, 5 H); 4.90, 4.85 (2*d*, *J* = 7.0, OCH_2O); 4.32, 4.28 (2 br. *d*, *J* ≈ 6.6, H–C(2), H–C(6)); 3.97, 3.86 (2*d*, *J* = 14.0, PhCH_2), 3.86, 3.79 (2 br. *d*, *J* ≈ 13.6, CH_2–C(10)); 3.37 (*s*, MeO); 3.15 (br. *d*, *J* = 9.7, H_a–C(9)); 2.89 (br. *s*, *J* = 9.0, H–C(7)); 2.81 (br. *d*, *J* = 9.6, H_b–C(9)); 2.07–1.94 (*m*, H–C(10)); 1.77 (*dt*, *J* = 13.6, 4.2, H_{exo}–C(11)); 1.54 (br. *t*, *J* ≈ 12.5, H_{endo}–C(11)); 1.67, 1.37 (2*s*, Me_2C(4)). ^{13}C-NMR ($CDCl_3$): 138.83 (*s*); 128.67 (2*d*); 128.36 (2*d*); 127.05 (*d*); 110.24 (*s*, C(4)); 92.58 (*t*, OCH_2O); 78.91, 77.43 (2*d*, C(2), C(6)); 78.10 (*s*, C(1)); 62.28 (*t*, CH_2–C(10)); 60.66 (*t*, PhCH_2); 56.11 (*q*, MeO); 50.87 (*d*, C(7)); 48.44 (*t*, C(9)); 37.24 (*d*, C(10)); 26.15, 24.20 (2*q*, *Me*$_2$C(4)); 25.75 (*t*, C(11)). FAB-MS: 364 (100, $[M+H]^+$), 272 (27). HR-MALDI-MS: 386.1944 (3, $[M+Na]^+$, $C_{20}H_{29}NNaO_5^+$; calc. 386.1944), 364.2116 (100, $[M+H]^+$, $C_{20}H_{30}NO_5^+$; calc. 364.2124), 332 (14).

*Data of (±)-***23**: R_f (AcOEt/hexane/MeOH 1:1:0.1) 0.18. IR ($CHCl_3$): 3577*m*, 3515*m*, 3007*s*, 2934*s*, 1602*w*, 1492*w*, 1452*m*, 1420*m*, 1378*s*, 1253*s*, 1159*s*, 1123*s*, 1083*s*, 1041*s*, 972*m*, 866*m*. ^{1}H-NMR ($CDCl_3$): 7.18–7.38 (*m*, 5 H); 4.32 (*dd*, *J* = 8.1, 3.1, H–C(6)); 4.06 (*dd*, *J* = 8.1, 1.9, H–C(2)); 3.97, 3.90 (2*d*, *J* = 13.4, PhCH_2); 3.96 (*dd*, *J* = 10.8, 9.1, CH_a–C(10)); 3.78 (*dd*, *J* = 10.9, 3.7, CH_b–C(10)); 2.89–2.95 (*m*, H–C(7)); 2.93 (*dd*, *J* = 9.2,

1.8, H_a–C(9)); 2.79 (*dd*, *J* = 9.3, 1.9, H_b–C(9)); 1.88 (br. *tt*, *J* ≈ 9.0, 4.1, H–C(10)); 1.67, 1.38 (2*s*, 2 Me); 1.65–1.47 (*m*, 2 H–C(11)). ^{13}C-NMR ($CDCl_3$); 139.34 (*s*); 128.42 (2*d*); 128.30 (2*d*); 126.94 (*d*); 110.53 (*s*, C(4)); 78.94, 78.32 (2*d*, C(2), C(6)); 73.55 (*s*, C(1)); 63.83 (*t*, Ph*C*H_2); 60.92 (*t*, CH_2–C(10)); 51.37 (*d*, C(7)); 49.97 (*t*, C(9)); 37.17 (*d*, C(10)); 26.43 (*t*, C(11)); 26.04, 24.26 (2*q*, *Me*$_2$C(4)). HR-MALDI-MS: 320.1860 ([*M* + H]$^+$, $C_{18}H_{26}NO_4^+$; calc. 320.1862).

*(±)-(1*R*,4*R*,5*R*,7*R*,8*R*)-2-Benzyl-5-(hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* ((±)-**2**). A soln. of (±)-**22** (18 mg, 0.05 mmol) in CF_3CO_2H/H_2O 2:1 (1.5 ml) was stirred at 100° for 3 h, and evaporated. The residue was suspended three times in toluene (10 ml) and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, NH_4^+ form, 0.1M aq. NH_3) yielded (±)-**2** (12 mg, 87%). R_f (AcOEt/MeOH 5:1) 0.40. IR (KBr): 3391*s* (br.), 3059*w*, 3028*w*, 2930*m*, 1958*w*, 1888*w*, 1815*w*, 1635*w*, 1495*w*, 1452*m*, 1411*m*, 1356*w*, 1111*s*, 1039*m*, 1010*w*, 953*w*, 910*w*, 812*w*. ^{1}H-NMR (CD_3OD): see *Table 7*; additionally, 7.40–7.13 (*m*, 5 H); 3.88 (*dd*, *J* = 10.9, 6.5, CH_a–C(5)); 3.85 (*dd*, *J* = 8.4, 2.1, irrad. at 2.66 → *d*, *J* = 8.4, H–C(7)); 3.81, 3.72 (2*d*, *J* = 13.1, PhCH_2); 3.65 (*dd*, *J* = 10.6, 6.5, CH_b–C(5)); 3.60 (*dd*, *J* = 8.4, 1.3, H–C(8)); 2.89 (*dd*, *J* ≈ 9.5, 1.8, H_a–C(3)); 2.47 (*dd*, *J* ≈ 9.6, 1.6, irrad. at 2.89 → *d*, *J* = 4.4, H_b–C(3)); 1.84–1.61 (irrad. at 2.66 → change, irrad. at 2.89 → change, H–C(5), H_{exo}–C(6)); 1.59 (irrad. at 2.66 → change, H_{endo}–C(6)). ^{13}C-NMR (CD_3OD): 140.54 (*s*); 130.22 (2*d*); 129.60 (2*d*); 128.38 (*d*); 73.56 (*s*, C(4)); 73.45, 70.33 (2*d*, C(7), C(8)); 63.81 (*t*, *C*H_2–C(5)); 61.29 (*t*, Ph*C*H_2); 56.82 (*d*, C(1)); 51.32 (*t*, C(3)); 40.14 (*d*, C(5)); 24.89 (*d*, C(6)). HR-MALDI-MS: 302.1358 (10, [*M* + Na]$^+$, $C_{15}H_{21}NNaO_4^+$; calc. 302.1368), 280.1542 (100, [*M* + H]$^+$, $C_{15}H_{22}NO_4^+$; calc. 280.1549), 199 (13). Anal. calc. for $C_{15}H_{21}NO_4 \cdot 0.5\ H_2O$ (288.34): C 62.48, H 7.69, N 4.86; found: C 62.24, H 7.47, N 4.83. pK_{HA} = 7.5.

Table 7. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Enantiomerically Pure Isoquinuclidines* **33b**, *(−)-***36** *to (−)-***41**, *and of the* manno-*Isoquinuclidines* **2** *and* **3**

	33b	(−)-**36**	(−)-**37**	(−)-**38**	(−)-**39**	(−)-**40**	(−)-**41**	**2**	**3**
H–C(1)	5.38	5.23	4.15	4.18	3.94	3.93	3.41	2.66	2.75
H–C(5)	2.79	2.28	2.61	2.09	2.52	2.06	1.88	[b])	[c])
H_{endo}–C(6)	1.94	1.35	1.43	1.62	1.21	1.47	1.47	1.59	1.52
H_{exo}–C(6)	2.49	2.18	2.22	2.00	1.87	1.85	1.61	[b])	[c])
J(1,HN)	–	–	–	6.0	–	–	–	–	–
J(1,6$_{endo}$)	2.0	2.5	2.0	1.6	1.6	2.2	2.2	2.8	2.5
J(1,6$_{exo}$)	3.8	3.4	3.4	3.9	3.5	3.4	3.5	[b])	[c])
J(1,7)	5.9	6.1	5.6	5.6	5.6	5.6	[a])	2.1	2.1
J(1,8)	1.7	1.5	1.4	1.6	1.7	1.9	[a])	1.3	1.8
J(5,6$_{endo}$)	5.0	4.6	5.0	10.3	5.0	10.3	10.3	10.6	7.8
J(5,6$_{exo}$)	9.7	10.3	10.2	4.6	10.3	4.7	6.3	[b])	[c])
J(5,8)	1.0	1.2	1.4	–	1.3	–	–	–	–
J(6$_{endo}$, 6$_{exo}$)	13.2	12.5	13.4	12.5	12.9	12.7	13.4	13.7	7.8

[a]) Broad signals; coupling constants *J*(1,7) < 2.5 Hz and *J*(1,8) < 2.5 Hz were deduced from the width of the signal at the half of their height. [b]) 2.66 (br. *q*, *J* ≈ 2.6, H–C(1)); 1.84–1.61 (*m*, H–C(5), H_{exo}–C(6)). [c]) 2.75 (br. *q*, *J* ≈ 2.4, H–C(1)); 1.95–1.76 (*m*, H–C(5), H_{exo}–C(6)).

*(±)-(1*R*,4*R*,5*R*,7*R*,8*R*)-5-(Hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* ((±)-**3**). A mixture of (±)-**2** (20 mg, 0.072 mmol) and 10% Pd/C (4 mg) in MeOH/H_2O/conc. HCl 1:1:0.1 (2.1 ml) was hydrogenated (1.5 bar) for 24 h. The mixture was filtered through *Celite*, and the filtrate was evaporated. The residue was suspended three times in toluene (10 ml) and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, NH_4^+ form, 0.1M aq. NH_3) yielded. (±)-**3** (11 mg, 82%). Colourless solid. R_f (MeOH/25% aq. NH_3 soln. 1:2) 0.45. IR (KBr): 3403*s* (br.), 3322*s*, 2921*m*, 2886*m*, 2739*m*, 2661*m*, 1632*w*, 1436*m*, 1383*m*, 1169*w*, 1110*s*, 1046*m*, 1026*m*, 995*m*, 955*m*, 898*w*. ^{1}H-NMR (D_2O): see *Table 7*; additionally, 3.99 (*dd*, *J* ≈ 8.6, 2.1, irrad. at 2.75 → *d*, *J* = 8.7, H–C(7)); 3.85 (*dd*, *J* = 10.9, 5.3, irrad. at 1.85 → *d*, *J* = 10.6, CH_a–C(5)); 3.73 (*dd*, *J* ≈ 8.6, 1.8, irrad. at 2.65 → *d*, *J* = 8.7, irrad. at 3.99 → *t*, *J* = 1.9, H–C(8)); 3.62 (*dd*, *J* ≈ 11.1, 8.0, irrad. at 1.85 → *d*, *J* = 10.6, CH_b–C(5)); 2.88 (br. *dd*, *J* ≈ 11.2, 2.0, irrad. at 1.85 → *d*, *J* = 11.2, irrad. at 2.65 → *d*, *J* ≈ 5.0, H_a–C(3)); 2.75 (irrad. at 1.52 → br. *t*, *J* ≈ 2.5, irrad. at 1.85 → *t*, *J* = 2.2, irrad. at 3.99 → change, H–C(1)); 2.65 (*dd*, *J* ≈ 11.4, 1.8, H_b–C(3)); 1.95–1.76 (irrad. at 1.52 → change, irrad. at 2.75 → change, H–C(5), H_{endo}–C(6)); 1.52 (irrad. at

1.85 → *d*, *J* = 2.5, irrad. at 2.75 → *d*, *J* = 7.8, H_{exo}–C(6)). ^{13}C-NMR (D_2O): 73.49, 70.24 (2*d*, C(7), C(8)); 73.35 (*s*, C(4)); 65.00 (*t*, CH_2–C(5)); 51.30 (*d*, C(1)); 41.58 (*t*, C(3)); 40.53 (*d*, C(5)); 29.01 (*t*, C(6)). HR-MALDI-MS: 280.1540 (22, $[M+C_7H_7]^+$, $C_{15}H_{22}NO_4^+$; calc. 280.1549), 212.0896 (10, $[M+Na]^+$, $C_8H_{15}NNaO_4^+$; calc. 212.0899), 190.1078 (100, $[M+H]^+$, $C_8H_{16}NO_4^+$; calc. 190.1079). Anal. calc. for $C_8H_{15}NO_4 \cdot 0.5\ H_2O$ (198.22): C 48.48, H 8.14, N 7.07; found: C 48.28, H 7.91, N 6.77. $pK_{HA} = 8.4$.

*(1*R*,2*R*,6*R*,7*R*,10*R*)- and (1*S*,2*S*,6*S*,7*S*,10*S*)-8-Benzyl-10-([[(1*S*,2*S*,5*R*)-(2-isopropyl-5-methylcyclohex-1-yl)oxy]methoxy]methyl)-1-(methoxymethoxy)-4,4-dimethyl-3,5-dioxa-8-azatricyclo[5.2.2.0^{2,6}]undecane* (**24a**/**24b**). A soln. of (±)-**22** (20 mg, 0.055 mmol), ^{i}Pr$_2$EtN (38 µl, 0.22 mmol) and chloromethyl (1*R*,3*S*,4*S*)-menthyl ether (35 µl, 0.163 mmol) in CH_2Cl_2 (1 ml) was stirred at 25° for 1 h and evaporated. FC (hexane/AcOEt 3:1) gave **24a**/**24b** 1:1 (27 mg, 98%). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.38. IR ($CHCl_3$): 3000*m*, 2949*m*, 2923*m*, 2871*m*, 1596*w*, 1494*w*, 1378*w*, 1263*w*, 1147*m*, 1109*m*, 1083*m*, 1039*s* (br.), 962*w*, 916*w*, 876*w*. ^{1}H-NMR ($CDCl_3$): 7.34–7.25 (*m*, 4 H); 7.20 (*tt*, *J* ≈ 6.9, 1.9, 1 H); 4.93, 4.89, 4.86, 4.85, 4.79, 4.74, 4.72, 4.72 (8*d*, *J* ≈ 7.1, 2 OCH_2O); 4.33 (br. *d*, *J* = 8.4, 0.5 H), 4.25 (*d*, *J* = 0.9, 1 H), 4.26 (*dd*, *J* = 8.4, 2.4, 0.5 H) (CH_2–C(10)); 3.99 (*dd*, *J* = 9.0, 3.4, H–C(6)); 3.96, 3.88 (2*d*, *J* = 14.0, PhCH_2); 3.73 (br. *d*, *J* = 9.3, H–C(2)); 3.40, 3.39 (*td*, *J* ≈ 10.8, 4.2, H–C(1′)); 3.36, 3.35 (2*s*, MeO); 3.06, 3.03 (2*dd*, *J* ≈ 9.4, 1.5, H_a–C(9)); 2.88 (*dt*, *J* = 3.7, 1.9, H–C(7)); 2.62, 2.58 (2 br. *d*, *J* = 9.4, H_b–C(9)); 2.27 (*sept.d*, *J* = 7.2, 2.4, Me_2CH); 2.22–1.92 (*m*), 1.72–1.46 (*m*, H–C(10), H_{endo}–C(11), H_{eq}–C(3′), H_{eq}–C(4′), H_{eq}–C(6′)); 1.92 (*dt*, *J* ≈ 14.0, 3.3, H_{exo}–C(11)); 1.66, 1.36 (2*s*, Me_2C(4)); 1.46–1.35 (*m*, H–C(5′)); 1.25 (br. *t*, *J* ≈ 11.7, H–C(2′)); 1.16–0.85 (*m*, H_{ax}–C(3′), H_{ax}–C(5′), H_{ax}–C(6′)); 0.93, 0.91, 0.91, 0.89 (4*d*, *J* ≈ 6.6, Me_2CH); 0.79 (br. *d*, *J* = 7.0, Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 141.34, 139.29 (2*s*); 128.13 (2*d*); 127.61 (4*d*); 126.10 (*d*); 109.45 (*s*, C(4)); 94.39, 94.15, 91.69, 91.69 (4*t*, 2 OCH_2O); 78.14, 77.02 (2*d*, C(2), C(6)); 77.00 (*s*, C(1)); 69.87, 69.67 (2*t*, CH_2–C(10)); 60.73 (*t*, PhCH_2); 55.55 (*q*, MeO); 55.55, 55.09 (2*d*, C(1′)); 51.07 (*d*, C(7)); 48.07 (*t*, C(9)); 48.07 (*d*, C(2′)); 41.50, 41.27 (2*t*, C(6′)); 36.20, 35.34 (2*d*, C(10)); 33.04 (*t*, C(4′)); 31.18 (*d*, C(5′)); 25.78, 23.94 (2*q*, Me_2C(4)); 25.07, 24.99 (2*d*, Me_2CH); 22.74 (*t*, C(11), C(3′)); 21.99, 20.86 (2*q*, Me_2CH); 15.56 (*q*, *Me*–C(5′)). HR-MALDI-MS: 554.3456 (10, $[M+Na]^+$, $C_{31}H_{49}NNaO_6^+$; calc. 554.3458), 532.2640 (100, $[M+H]^+$, $C_{31}H_{50}NO_6^+$; calc. 532.3638), 332 (22, $[M-\text{menthylOCH}_2\text{OCH}_2]^+$). Anal. calc. for $C_{31}H_{49}NO_6$ (531.73): C 70.02, H 9.29, N 2.63; found: C 69.84, H 9.27, N 2.75.

*(1*R*,2*R*,6*R*,7*R*,10*R*)- and (1*S*,2*S*,6*S*,7*S*,10*S*)-8-Benzyl-1-(methoxymethoxy)-4,4-dimethyl-3,5-dioxa-8-azatricyclo[5.2.2.0^{2,6}]undecane-10-methyl (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate* (**25a**/**25b**). A soln. of (±)-**22** (20 mg, 0.055 mmol), 4-(dimethylamino)pyridine (DMAP; 1.5 mg, 0.013 mmol), ^{i}Pr$_2$EtN (15 µl, 0.088 mmol) and (1*S*,4*R*)-camphanoyl chloride (134 mg, 0.062 mmol) in CH_2Cl_2 (2 ml) was stirred at 25° for 30 min and evaporated. FC (hexane/AcOEt 3:1) yielded **25a**/**25b** 1:1 (30 mg, >98%). Colourless foam. R_f (cyclohexane/AcOEt 1:1) 0.59. IR ($CHCl_3$): 2995*w*, 2931*m*, 2906*m*, 1785*s*, 1730*s* (br.), 1602*w*, 1493*w*, 1451*m*, 1398*m*, 1377*m*, 1352*m*, 1316*m*, 1264*s*, 1166*s*, 1106*s*, 1060*s*, 1044*s*, 994*m*, 910*s*, 875*m*. ^{1}H-NMR ($CDCl_3$): 7.33–7.26 (*m*, 4 H); 7.21 (*tt*, *J* ≈ 6.4, 2.2, 1 H); 4.90, 4.90, 4.83, 4.82 (4*d*, *J* = 7.2, 2 OCH_2O); 4.70, 4.68 (2*dd*, *J* = 10.3, 4.0, H–C(6)); 4.43, 4.39 (br. *d*, *J* = 10.3, H–C(2)); 4.30 (br. *d*, *J* ≈ 8.5), 4.26 (*dd*, *J* = 8.4, 2.2) (CH_2–C(10)); 3.97, 3.88 (2*d*, *J* ≈ 13.6, PhCH_2); 3.37 (*s*, MeO); 3.10, 2.63 (2 br. *d*, *J* = 9.3, H–C(9)); 2.92 (*q*, *J* ≈ 2.1, H–C(7)); 2.45 (*ddd*, *J* = 13.4, 10.5, 4.4, 1 H), 2.05 (*ddd*, *J* = 13.7, 9.4, 4.7, irrad. at 2.45 → *dd*, *J* ≈ 13.5, 4.5, 1 H), 1.93 (*ddd*, *J* ≈ 13.1, 10.9, 4.6, irrad. at 2.45 → *dd*, *J* ≈ 13.5, 9.5, 1 H), 1.70 (*ddd*, *J* = 13.4, 9.0, 4.0, irrad. at 2.45 → *dd*, *J* = 10.7, 3.8, 1 H) (2 H–C(5′), 2 H–C(6′)); 1.85, 1.83 (2*dt*, *J* ≈ 14.3, 4.2, H_{exo}–C(11)); 1.66, 1.36 (2*s*, Me_2C(4)); 1.59 (br. *dd*, *J* ≈ 13.4, 10.1, H_{endo}–C(7)); 1.12 (*s*, Me–C(6′)); 1.08, 1.06, 0.98, 0.97 (4*s*, 2 Me–C(7′)). ^{13}C-NMR ($CDCl_3$): 177.92, 167.46 (2*s*, 2 C=O); 139.42 (*s*); 128.17 (2*d*); 128.06 (2*d*); 126.61 (*d*); 109.99 (*s*, C(4)); 92.26 (*t*, OCH_2O); 91.19 (*s*, C(1′)); 78.43, 77.18 (2*d*, C(2), C(6)); 76.12 (*s*, C(1)); 67.76 (*t*, CH_2–C(10)); 60.69 (*t*, PhCH_2); 56.09 (*q*, MeO); 54.77, 54.18 (2*s*, C(4′), C(7′)); 51.50 (*d*, C(7)); 48.40 (*t*, C(9)); 35.09, 35.04 (2*d*, C(10)); 30.70, 29.00 (2*t*, C(5′), C(6′)); 27.55 (*t*, C(11)); 26.13, 24.28 (2*q*, Me_2C(4)); 16.87, 16.87, (2*q*, Me_2C(7′)); 9.82 (*q*, *Me*–C(4′)). HR-MALDI-MS: 566.2719 (4, $[M+Na]^+$, $C_{30}H_{41}NNaO_8^+$; calc. 566.2730), 544.2900 (100, $[M+H]^+$, $C_{30}H_{42}NO_8^+$; calc. 544.2910).

*3-[(*tert*-Butyl)dimethylsilyloxy]-1-[(naphthalen-2-yl)sulfonyl]-1*H*-pyridin-2-one* (6.57 g, 71%) was obtained from 3-[(*tert*-butyl)dimethylsilyloxy]-1*H*-pyridin-2-one (5.00 g, 22.2 mmol) and (naphthalen-2-yl)sulfonyl chloride (4.90 g, 23.0 mmol) in analogous way as described for the synthesis of 3-[(*tert*-butyl)dimethylsilyloxy]-1*H*-pyridin-2-one. R_f (cyclohexane/AcOEt 3:2) 0.80. M.p. 109–110°. IR ($CHCl_3$): 3122*w*, 3061*w*, 2955*m*, 2931*m*, 2859*m*, 1675*s*, 1620*s*, 1472*w*, 1464*w*, 1418*w*, 1365*s*, 1292*s*, 1177*s*, 1117*s*, 1073*m*, 954*m*, 944*m*, 838*s*. ^{1}H-NMR ($CDCl_3$): 8.78 (br. *s*, H–C(1′)); 8.04, 7.91 (2 br. *d*, *J* ≈ 8.2, H–C(5′), H–C(8′)); 7.94 (br. *d*, *J* ≈ 1.4, H–C(3′), H–C(4′)); 7.82 (*dd*, *J* = 7.5, 1.7, H–C(6)); 7.69 (*ddd*, *J* = 8.4, 6.9, 1.6), 7.63 (*ddd*, *J* = 8.4, 7.2, 1.4) (H–C(6′), H–C(7′)); 6.68 (*dd*, *J* = 7.2, 1.9, H–C(4)); 6.14 (*t*, *J* ≈ 7.3, H–C(5)); 0.86 (*s*, *t*-Bu); 0.05 (*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 157.99 (*s*, C(2)); 147.67 (*s*, C(3)); 135.77 (*s*, C(2′)); 133.49, 131.80 (2*s*, C(9′), C(10′)); 132.57 (*d*), 129.85 (2*d*), 129.08 (*d*), 127.96 (*d*), 127.75 (*d*), 123.98 (*d*), 123.33 (*d*) 122.53 (*d*), (C(4), C(6), 7 naphthalene *d*); 105.65

(*d*, C(5)); 25.43 (*q*, *Me*$_3$C); 18.27 (*s*, Me$_3$*C*); 4.88 (2, Me$_2$Si). EI-MS: 416 (1, $[M+H]^+$), 400 (5, $[M-Me]^+$), 358 (100, $[M-{}^t\text{Bu}]^+$), 191 (98, $C_{10}H_7SO_2^+$), 168 (24), 152 (33), 127 (96, $C_{10}H_7^+$), 84 (17). Anal. calc. for $C_{21}H_{25}NO_4SSi$ (415.58): C 60.69, H 6.06, N 3.37, S 7.72; found: C 60.81, H 6.27, N 3.37, S 7.66.

*1-[(Naphthalen-2-yl)sulfonyl]-1*H*-pyridin-2-one* (**26**). Compound **26** was obtained in a similar way from 3-[(*tert*-butyl)dimethylsilyloxy]-1-[(naphthalen-2-yl)sulfonyl]-1*H*-pyridin-2-one (3.00 g, 7.22 mmol) as described for the synthesis of **10** from **5**. Recrystallisation from the crude product in $CHCl_3$ afforded **26** (2.02 g, 93%) in a total of three crops. R_f (cyclohexane/AcOEt 3:2) 0.48. Anal. HPLC (*Kromasil 100 Si*-5μM, 250 × 4 mm, hexane/AcOEt 3:2, 1 ml/min; detection at λ 245 nm): t_R 4.00 min. M.p. 165–170° ($CHCl_3$). IR ($CHCl_3$): 3442*w* (br.), 3130*w*, 3038*w*, 1660*s*, 1638*s*, 1553*w*, 1436*m*, 1398*m*, 1378*m*, 1288*m*, 1178*s*, 1119*s*, 1073*m*, 857*w*. ^{1}H-NMR ($CDCl_3$): 8.80 (*d*, *J* = 1.0, H–C(1′)); 8.06 (*dd*, *J* = 9.0, 1.3), 7.94 (br. *d*, *J* ≈ 7.2) (H–C(5′), H–C(8′)); 7.98 (br. *d*, *J* ≈ 1.6, H–C(3′), H–C(4′)); 7.75 (*dd*, *J* = 7.5, 1.6, H–C(6)); 7.71 (*ddd*, *J* = 8.4, 6.5, 2.2), 7.66 (*ddd*, *J* = 8.4, 7.2, 1.5) (H–C(6′), H–C(7′)); 6.76 (*dd*, *J* = 7.2, 1.9, H–C(4)); 6.45 (*s*, OH); 6.28 (*t*, *J* ≈ 7.3, H–C(5)). ^{13}C-NMR ($CDCl_3$): 157.45 (*s*, C(2)); 147.42 (*s*, C(3)); 135.95, 132.84, 131.75 (3*s*, C(2′), C(9′), C(10′)); 132.93, 130.21, 129.23, 129.32, 128.06, 127.98, 123.29 (7 naphthalene *d*); 121.49 (*d*, C(6)); 114.48 (*d*, C(4)); 107.12 (*d*, C(5)). EI-MS: 301 (13, M^+), 237 (61, $[M-SO_2]^+$), 191 (98, $C_{10}H_7SO_2^+$), 127 (100, $C_{10}H_7^+$), 111 (14, $[M-C_{10}H_7SO_2]^+$), 84 (27). Anal. calc. for $C_{15}H_{11}NO_4S$ (301.32): C 59.79, H 3.68, N 4.65, S 10.64; found: C 59.59, H 3.81, N 4.64, S 10.56.

*Methyl (1*R*,4*S*,5*R*)- and (1*S*,4*R*,5*S*)-4-Hydroxy-2-[(naphthalen-2-yl)sulfonyl]-3-oxo-2-azabicyclo-[2.2.2]oct-7-ene-5-carboxylate* ((±)-**27**), *Methyl (1*R*,4*S*,5*S*)- and (1*S*,4*R*,5*R*)-4-Hydroxy-2-[(naphthalen-2-yl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((±)-**28**), *and 3-(3-Methoxy-3-oxopropoxy)-1-[(naphthalen-2-yl)sulfonyl]-1*H*-pyridin-2-one* (**29**). *a*) In a typical anal. experiment, a soln. of **26** (10 mg, 0.033 mmol), quinine (22 mg, 0.068 mmol), and methyl acrylate (30 μl, 0.33 mmol) in acetone (0.8 ml) was stirred at 24°. Samples (0.1 ml) were taken at regular time intervals, diluted with CH_2Cl_2 (0.5 ml), washed with a 1M aq. HCl soln. (0.5 ml), dried (Na_2SO_4), filtered through a pad of silica gel (AcOEt), and evaporated. After 36 h, anal. HPLC showed a ratio **27**/**28**/**29** of 95:4:1 and a ratio (+)-**27**/(−)-**27** of 85:15. Anal. samples of (+)-**27**/(−)-**27**, **28**, and **29** were obtained by combining the products of several experiments.

b) A mixture of **26** (500 mg, 1.66 mmol), quinine (1.08 g, 3.33 mmol), and methyl acrylate (1.5 ml, 1.57 mmol) in acetone (40 ml) was stirred at 24° for 36 h. Normal workup (CH_2Cl_2/1M HCl soln., Na_2SO_4) gave crude (+)-**27**/(−)-**27** 85:15 (678 mg, > 98%). Slightly red solid. Recrystallisation from i-PrOH/hexane 3:1 gave (+)-**27**/(−)-**27** 88:12 (538 mg, 84%). Colourless solid.

Data of **27**: R_f (cyclohexane/AcOEt 3:2) 0.28. Anal. HPLC (*Kromasil 100 Si*-5μM, 250 × 4 mm, hexane/AcOEt 3:2, 1 ml/min; detection at λ 245 nm): t_R 6.13 min. Anal. chiral HPLC (*Chiralcel OD*, 250 × 4.6 mm; hexane/i-PrOH 3:1, 2 ml/min; detection at λ 245 nm): t_R 8.44 min ((+)-**27**), 11.72 min ((−)-**27**). IR ($CHCl_3$): 3499*m*, 3034*m*, 2955*m*, 1729*s* (br.), 1626*w*, 1592*w*, 1505*w*, 1438*m*, 1361*s* (br.), 1172*s*, 1095*s*, 1074*s*, 980*m*, 949*m*, 863*m*. ^{1}H-NMR ($CDCl_3$, assignment based on a DQFCOSY spectrum): see *Table 6*; additionally, 8.61 (br. *s*, H–C(1′)); 8.02 (*dd*, *J* = 8.8, 0.9, irrad. at 7.65 → *s*), 7.92 (br. *d*, *J* = 8.1, irrad. at 7.68 → *s*) (H–C(5′), H–C(8′)); 7.96 (*d*, *J* = 8.7, H–C(4′)); 7.85 (*dd*, *J* = 8.7, 1.8, irrad. at 8.61 → *d*, *J* = 8.7, H–C(3′)); 7.68 (*td*, *J* ≈ 6.9, 1.5), 7.65 (*td*, *J* ≈ 6.8, 1.3) (H–C(6′), H–C(7′)); 6.48 (*dd*, *J* = 8.0, 6.1, H–C(7)); 6.20 (*dt*, *J* ≈ 8.1, 1.2, H–C(8)); 3.83 (br. *s*, OH); 3.69 (*s*, MeO). ^{13}C-NMR ($CDCl_3$, assignment based on a HSQC.GP spectrum): 171.96, 171.22 (2*s*, 2 C=O); 135.65 (*s*, C(2′)); 135.21 (*d*, C(8)); 134.69, 131.91 (2*s*, C(9′), C(10′)); 130.53 (*d*, C(1′)); 130.42 (*d*, C(7)); 129.81, 127.98 (2*d*, C(6′), C(7′)); 129.77, 128.06 (2*d*, C(5′), C(8′)); 129.63 (*d*, C(4′)); 111.02 (*d*, C(3′)); 77.97 (*s*, C(4)); 52.99 (*d*, C(1)); 52.44 (*q*, MeO); 42.78 (*d*, C(5)); 33.41 (*t*, C(6)). EI-MS: 388 (1, $[M+H]^+$), 302 (5, $[M-CH_2{=}CH_2CO_2Me+H]^+$), 237 (24, $[M-CH_2{=}CH_2CO_2Me-SO_2]^+$), 191 (11, $C_{10}H_7SO_2^+$), 154 (100, $[M-C_{10}H_7SO_2NCO]^+$), 127 (64, $C_{10}H_7^+$), 95 (13). Anal. calc. for $C_{19}H_{17}NO_6S$ (387.41): C 58.91, H 4.42, N 3.62, S 8.28; found: C 58.65, H 4.63, N 3.62, S 8.46.

Data of **28**: R_f (cyclohexane/AcOEt 3:2) 0.26. Anal. HPLC (*Kromasil 100 Si*-5μM, 250 × 4 mm, hexane/AcOEt 3:2, 1 ml/min; detection at λ 245 nm): t_R 6.13 min. IR ($CHCl_3$): 3493*m*, 3034*m*, 2955*m*, 1742*s* (br.), 1627*w*, 1593*w*, 1505*m*, 1437*m*, 1355*s* (br.), 1270*m*, 1172*s*, 1099*s*, 1074*s*, 1045*m*, 1020*m*, 910*m*, 860*s*. ^{1}H-NMR ($CDCl_3$): see *Table 6*; additionally, 8.66 (br. *s*, H–C(1′)); 8.02 (br. *d*, *J* = 8.8), 7.92 (*d*, *J* ≈ 8.4) (H–C(5′), H–C(8′)); 7.97 (*d*, *J* = 9.0, H–C(4′)); 7.92 (*d*, *J* ≈ 8.4, H–C(3′)); 7.68 (*ddd*, *J* ≈ 8.4, 6.6, 1.0), 7.63 (*ddd*, *J* ≈ 8.4, 6.9, 1.0) (H–C(6′), H–C(7′)); 6.48 (*dd*, *J* = 7.8, 5.9, H–C(7)); 6.28 (*dd*, *J* = 7.8, 1.5, H–C(8)); 3.93 (*s*, OH); 3.39 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 172.16, 170.65 (2*s*, 2 C=O); 137.96 (*d*, C(8)); 135.65, 131.93, 131.60 (3*s*, C(2′), C(9′), C(10′)); 131.55, 130.62, 129.79, 129.64, 129.32, 128.01, 127.82, 122.45 (8*d*, C(7), 7 naphthalene *d*); 72.86 (*s*, C(4)); 52.24 (*d*, C(1)); 52.22 (*q*, MeO); 44.92 (*d*, C(5)), 32.36 (*t*, C(6)). EI-MS: 388 (0.1, $[M+H]^+$), 301 (5, $[M-CH_2{=}CH_2CO_2Me]^+$), 237 (31, $[M-CH_2{=}CH_2CO_2Me-SO_2]^+$), 191 (14, $C_{10}H_7SO_2^+$), 154 (61, $[M-C_{10}H_7SO_2NCO]^+$), 127 (100, $C_{10}H_7^+$), 84 (100, $C{\equiv}CCO_2Me^+$), 49 (57).

Data of **29**: R_f (cyclohexane/AcOEt 3:2) 0.14. Anal. HPLC (*Kromasil 100 Si-5*μM, 250 × 4 mm; hexane/AcOEt 3:2, 1 ml/min; detection at λ 245 nm): t_R 14.84 min. IR ($CHCl_3$): 3007*m*, 2956*m*, 1732*s*, 1666*s*, 1612*s*, 1548*m*, 1505*w*, 1440*m*, 1364*s* (br.), 1326*m*, 1269*m*, 1172*s*, 1076*s*, 1008*m*, 981*m*, 949*m*, 925*m*, 861*s*. ^{1}H-NMR ($CDCl_3$): 8.54 (br. *d*, $J \approx 0.9$, H–C(1′)); 8.05 (*dd*, $J = 8.8, 1.9$, irrad. at 8.54 → *d*, $J = 8.7$, H–C(3′)); 7.99 (*d*, $J = 8.9$, H–C(4′)); 7.96 (*d*, $J = 7.2$, irrad. at 7.65 → br. *s*), 7.93 (*d*, $J = 8.4$, irrad. at 7.65 → br. *s*) (H–C(5′), H–C(8′)); 7.65 (*td*, $J \approx 7.5, 1.6$), 7.61 (*td*, $J \approx 7.5, 1.3$) (H–C(6′), H–C(7′)); 7.44 (*dd*, $J = 7.5, 1.9$, irrad. at 6.11 → *t*, $J \approx 1.2$), 7.38 (*dd*, $J = 6.8, 1.9$, irrad. at 6.11 → *t*, $J \approx 1.3$) (H–C(4), H–C(6)); 6.11 (*dd*, $J = 7.5, 6.8$, H–C(5)); 4.07, 2.62 (2*t*, $J = 6.2$, CH_2CH_2); 3.62 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 171.87 (*s*, C=O); 157.28 (*s*, C(2)); 139.32 (*s*, C(3)); 137.73 (*d*, C(6)); 135.66, 133.04, 131.92 (3*s*, C(2′), C(9′), C(10′)); 131.91 (*d*), 130.57 (*d*), 129.58 (2*d*), 129.35 (*d*), 128.11 (*d*), 127.69 (*d*), 123.38 (*d*) (C(4), 7 naphthalene *d*); 103.63 (*d*, C(5)); 51.81 (*q*, MeO); 46.55, 32.15 (2*t*, CH_2–CH_2). EI-MS: 388 (7, $[M+H]^+$), 387 (49, M^+), 356 (12, $[M-MeO]^+$), 323 (35, $[M-SO_2]^+$), 302 (5, $[M-CH_2{=}CH_2CO_2Me+H]^+$), 196 (100, $[M-C_{10}H_7SO_2]^+$), 168 (75), 127 (48), 84 (13).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Prop-2-enoate* (*(−)-8-Phenylmenthyl Acrylate*; (−)-**30**), *(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*S*,5*R*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((+)-**31a**), *and (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*S*,4*R*,5*S*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((+)-**31b**). *a*) (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol ((−)-8-phenylmenthol) was synthesised from (+)-pulegone (er > 99.3:0.7) according to a procedure from *Buschmann* and *Scharf* [50], and acetylated to (−)-**30** according to a procedure of *Whitesell et al.* [72].

b) A soln. of (−)-**30** (27.0 g, 94.3 mmol) and quinine (12.2 g, 37.6 mmol) in CH_2Cl_2 (70 ml) was treated with **10** (5.00 g, 18.9 mmol), stirred at 25° for 3 d in the absence of light. Normal workup (CH_2Cl_2/1M aq. HCl soln.) yielded a mixture of (−)-**30** and (+)-**31a**/(+)-**31b** 95.2:4.8 (determined by HPLC). The yellow residue was suspended in pentane (350 ml), stirred at 0° for 1 h, and filtered. Recrystallisation of the residue in i-PrOH yielded (+)-**31a** (6.82 g, 66%) as colourless, cotton-like fibers. FC (cyclohexane/AcOEt 20:1 → 5:1) of the filtrate afforded (−)-**30** (21.6 g, quant. recovery of the excess (−)-**30**) and (+)-**31a**/(+)-**31b** 55:45 (0.2 g, 2%). FC (cyclohexane/AcOEt 20:1 → 5:1) of the mother liquor afforded (+)-**31a**/(+)-**31b** 8:2 (1.90 g, 20%). Recrystallisation of this mixture in i-PrOH/hexane 1:1 yielded further (+)-**31a** (1.70 g, 18%) as colourless, cotton-like fibers. An anal. sample of (+)-**31b** was obtained by FC (hexane/Et_2O 2:1) of the mother liquor.

*Data of (−)-***30**. $[\alpha]_D^{25} = -17.0$ ($c = 1.0$, EtOH; [73]: −16.9, $c = 1.2$, EtOH).

*Data of (+)-***31a**: R_f (hexane/Et_2O 2:1) 0.21. Anal. HPLC (*Kromasil 100 Si-5*μM, 250 × 4 mm; hexane/AcOEt 6:1, 2 ml/min; detection at λ 245 nm): t_R 6.02 min. M.p. 171° (i-PrOH). $[\alpha]_D^{25} = 20.3$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3497*w* (br.), 3032*m*, 2959*m*, 2927*m*, 2872*m*, 1725*s* (br.), 1598*m*, 1495*m*, 1457*m*, 1367*s* (br.), 1315*m*, 1266*m*, 1173*s*, 1090*s*, 979*m*, 955*m*, 911*w*, 626*m*. ^{1}H-NMR ($CDCl_3$, assignment based on a DQFCOSY spectrum): 7.84 (*dt*, $J \approx 8.4, 1.8, 2$ H); 7.34 (br. *d*, $J = 8.1, 2$ H); 7.25 (*dd*, $J = 7.2, 1.3, 2$ H); 7.20 (*t*, $J = 7.6, 2$ H); 6.99 (*tt*, $J \approx 7.0, 1.9, 1$ H); 6.32 (*dd*, $J = 7.8, 5.6$, H–C(7)); 6.25 (*dt*, $J \approx 7.2, 1.2$, H–C(8)); 5.20 (*ddt*, $J = 5.6, 3.4, 1.9$, H–C(1)); 4.75 (*td*, $J = 10.6, 4.3$, H–C(1′)); 3.83 (*s*, OH); 2.46 (*s*, Me of Ts); 2.10 (*ddd*, $J = 13.4, 10.0, 3.1$, H_{exo}–C(6)); 2.01 (*td*, $J = 11.1, 3.6$, H–C(2′)); 1.90 (*ddd*, $J = 10.3, 5.0, 1.1$, H–C(5)); 1.78 (br. *d*, $J \approx 12.8$, H_{eq}–C(6′)); 1.74 (*dq*, $J = 13.4, 3.4$, H_{eq}–C(3′)); 1.65 (br. *d*, $J = 11.8$, H_{eq}–C(4′)); 1.48–1.37 (*m*, H–C(5′)); 1.32 (*ddd*, $J = 13.1, 5.0, 1.9$, H_{endo}–C(6)); 1.27, 1.17 (2*s*, Me_2C); 1.10 (*qd*, $J = 12.7, 2.8$, H_{ax}–C(3′)); 0.87 (*q*, $J \approx 12.2$, H_{ax}–C(6′)); 0.85 (*d*, $J = 6.5$, Me–C(5′)); 0.86 (*qd*, $J = 12.5, 2.8$, H_{ax}–C(4′)). ^{13}C-NMR ($CDCl_3$, assignment based on a HSQC.GP spectrum): 170.96, 170.65 (2*s*, 2 C=O); 151.82 (*s* of Ph); 146.61 (*s* of Ts); 136.41 (*d*, C(8)); 135.22 (*s* of Ts); 129.79 (2*d* of Ts); 129.55 (*d*, C(7)); 128.12 (2*d* of Ts); 128.01 (2*d* of Ph); 125.53 (2*d* of Ph); 125.08 (*d* of Ph); 76.58 (*s*, C(4)); 75.66 (*d*, C(1′)); 52.59 (*d*, C(1)); 50.02 (*d*, C(2′)); 42.83 (*d*, C(5)); 41.28 (*t*, C(6′)); 39.44 (*s*, Me_2C); 34.40 (*t*, C(4′)); 33.03 (*t*, C(6)); 31.14 (*d*, C(5′)); 28.47, 23.99 (*q*, Me_2C); 26.30 (*t*, C(3′)); 21.59 (*q*, Me–C(5′), Me of Ts). EI-MS: 1676 (6, $[3M+Na]^+$), 1125 (100, $[2M+Na]^+$), 847 (10), 606 (11), 574 (42, $[M+Na]^+$), 360 (8). Anal. calc. for $C_{31}H_{37}NO_6S$ (551.69): C 67.49, H 6.76, N 2.54, S 5.81; found: C 67.42, H 6.69, N 2.45, S 5.86.

*Data of (+)-***31b**: R_f (hexane/Et_2O 2:1) 0.29. Anal. HPLC (*Kromasil 100 Si-5*μM, 250 × 4 mm; hexane/AcOEt 6:1, 2 ml/min; detection at λ 245 nm): t_R 5.25 min. M.p. 167° (Et_2O/hexane). $[\alpha]_D^{25} = 14.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3511*w* (br.), 3030*w*, 2958*m*, 2928*w*, 2871*w*, 1721*s* (br.), 1598*w*, 1495*w*, 1457*w*, 1367*m* (br.), 1315*w*, 1263*w*, 1173*s*, 1089*s*, 978*w*, 949*w*, 814*w*, 625*w*. ^{1}H-NMR ($CDCl_3$): 7.84 (*dt*, $J = 8.4, 1.8, 2$ H); 7.35 (*dd*, $J = 8.7, 1.6, 2$ H); 7.21 (br. *dd*, $J \approx 8.7, 1.9, 2$ H); 7.18 (br. *t*, $J \approx 8.5, 2$ H); 6.97 (*tt*, $J \approx 6.7, 1.8, 1$ H); 6.41 (*dd*, $J = 8.1, 6.2$, irrad. at 5.27 → *d*, $J = 7.5$, H–C(7)); 6.03 (br. *d*, $J = 8.1$, irrad. at 5.27 → *d*, $J = 8.1$, H–C(8)); 5.27 (*ddt*, $J \approx 7.2, 3.4, 1.9$, H–C(1)); 4.76 (*td*, $J = 10.7, 4.4$, H–C(1′)); 3.41 (*s*, OH); 2.46 (*s*, Me of Ts); 2.07 (*td*, $J = 11.0, 3.7$, H–C(2′)); 2.04 (*ddd*, $J = 14.3, 10.6, 3.4$, irrad. at 5.27 → *dd*, $J = 14.3, 10.9$, H_{exo}–C(6)); 1.85 (br. *d*, $J \approx 13.4$, H_{eq}–C(6′)); 1.78 (*dq*, $J = 13.1, 3.1$, H_{eq}–C(3′)); 1.71 (*ddd*, $J = 10.0, 4.7, 1.9$, irrad. at 5.27 → *dd*, $J = 10.0, 5.4$, H–C(5)); 1.69–1.62 (*m*, H_{eq}–C(4′)); 1.47–1.37 (*m*, H–C(5′)); 1.33–1.24 (*m*, irrad. at 5.27 → change,

H_{endo}–C(6)); 1.24, 1.16 (2*s*, Me_2C); 1.13 (*qd*, *J* = 13.1, 3.4, H_{ax}–C(3′)); 0.98 (*q*, *J* ≈ 12.5, H_{ax}–C(6′)); 0.91 (*qd*, *J* = 12.8, 3.4, H_{ax}–C(4′)); 0.87 (*d*, *J* = 6.5, Me–C(5′)). ^{13}C-NMR ($CDCl_3$): 170.63, 170.37 (2*s*, 2 C=O); 151.62 (*s* of Ph); 145.25, 134.90 (2*s* of Ts); 133.84 (*d*, C(8)); 130.37 (*d*, C(7)); 129.51 (2*d*); 127.74 (2*d*); 127.56 (2*d*); 125.01 (2*d*); 124.71 (*d*); 78.05 (*s*, C(4)); 77.01 (*d*, C(1′)); 52.87 (*d*, C(1)); 50.05 (*d*, C(2′)); 42.20 (*d*, C(5)); 41.42 (*t*, C(6′)); 39.41 (*s*, Me_2C); 34.43, 33.14 (2*t*, C(6), C(4′)); 31.28 (*d*, C(5′)); 29.22, 23.35 (2*q*, Me_2C); 26.27 (*t*, C(3′)); 22.66, 21.77 (2*q*, Me–C(5′), Me of Ts). ESI-MS: 1125 (4, $[2M + Na]^+$), 861 (5), 574 (100, $[M + Na]^+$), 552 (30, $[M + H]^+$), 338 (64), 266 (8), 183 (16), 123 (25), 47 (13). Anal. calc. for $C_{31}H_{37}NO_6S$ (551.69): C 67.49, H 6.76, N 2.54, S 5.81; found: C 67.48, H 6.72, N 2.65, S 5.84.

*(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Prop-2-enoate* ((+)-*8-Phenylmenthyl Acrylate*; (+)-**30**) *and (1*S*,2*R*,5*S*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*S*,4*R*,5*S*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((−)-**31b**). *a*) (1*S*,2*R*,5*S*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol ((+)-8-phenylmenthol) was synthesised from (+)-citronellol (er > 98 : 2) according to a procedure of *Buschmann* and *Scharf* [50] and acetylated to (+)-**30** according to a procedure of *Whitesell et al.* [72]. A soln. of (+)-**30** (1.60 g, 5.59 mmol) and quinidine (785 mg, 2.42 mmol) in CH_2Cl_2 (4.5 ml) was treated with **10** (320 mg, 1.21 mmol) and stirred at 25° for 3 d in the absence of light. Normal workup (CH_2Cl_2/1M aq. HCl soln.) yielded a mixture of (+)-**30** and (−)-**31a**/(−)-**31b** 96 : 4 (determined by anal. HPLC). The yellow residue was suspended in pentane (22 ml), stirred at 0° for 1 h, and filtered. Recrystallisation of the residue in i-PrOH yielded (−)-**31b** (442 mg, 66%) as colourless, cotton-like fibers. FC (cyclohexane/AcOEt 20 : 1 → 5 : 1) of the filtrate afforded (+)-**30** (1.25 g, 98% of the excess (+)-**30**) and (−)-**31a**/(−)-**31b** 13 : 87 (167 mg, 25%). Recrystallisation of (−)-**31a**/(−)-**31b** in i-PrOH and FC (hexane/Et_2O 2 : 1) of the mother liquor yielded further (−)-**31b** (130 mg, 20%).

*Data of (+)-***30**: $[\alpha]_D^{25} = +16.5$ (*c* = 1.4, CH_2Cl_2; [49]: $[\alpha]_D^{23} = +16.1$ (*c* = 1.68, CH_2Cl_2)).

*Data of (−)-***31b**: $[\alpha]_D^{25} = -20.9$ (*c* = 1.0, $CHCl_3$). M.p. 168° (i-PrOH). R_f and t_R values, and ^{1}H-NMR spectrum were identical to those of (+)-**31a**.

*3-*O*-[(1*R*,4*S*,5*R*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carbonyl]-1,2 : 4,5-di-*O*-isopropylidene-β-*D*-fructopyranose* (**33a**) *and 3-*O*-[(1*S*,4*R*,5*S*)-4-Hydroxy-2-[(4-methylphenyl)-sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carbonyl]-1,2 : 4,5-di-*O*-isopropylidene-β-*D*-fructopyranose* (**33b**). A soln. of **10** (50 mg, 0.188 mmol), **32** [51] (118 mg, 0.375 mmol) and Et_3N (26 µl, 0.19 mmol) in CH_2Cl_2 (0.4 ml) was stirred at 24° for 24 h, filtered through a pad of silica gel (cyclohexane/AcOEt 2 : 1), and evaporated to yield crude **33a**/**33b** 38 : 62 (determined by ^{1}H-NMR). Prep. HPLC (*Spherisorb SW-5*µM, 20 × 200 mm; hexane/AcOEt 2 : 1, 10 ml/min) yielded **33a**/**33b** 38 : 62 (t_R 21–23 min, 104 mg, 95%) as a colourless foam. Repeated HPLC gave an anal. sample of pure **33b**.

Data of **33a** (from **33a**/**33b** 10 : 1): R_f (cyclohexane/AcOEt 3 : 2) 0.31. ^{1}H-NMR ($CDCl_3$): 7.85 (*dt*, *J* ≈ 9.4, 1.9, 2 H); 7.32 (br. *d*, *J* = 8.1, 2 H); 6.44 (*dd*, *J* = 7.8, 5.9, H–C(7′)); 6.30 (*dt*, *J* ≈ 7.8, 2.0, H–C(8′)); 5.37 (*ddt*, *J* = 5.6, 3.7, 1.9, H–C(1′)); 5.10 (*d*, *J* = 7.5, H–C(3)); 4.26 (*dd*, *J* = 7.2, 6.0, H–C(4)); 4.20 (br. *dd*, *J* ≈ 5.5, 2.2, H–C(5)); 4.11 (*dd*, *J* ≈ 13.4, 2.5, H_{eq}–C(6)); 4.05 (br. *d*, *J* = 13.4, H_{ax}–C(6)); 3.92, 3.80 (2*d*, *J* = 9.3, 2 H–C(1)); 3.88 (*s*, OH); 2.82 (*ddd*, *J* = 10.0, 5.0, 0.9, H–C(5′)); 2.52 (*ddd*, *J* = 13.4, 10.7, 3.7, H_{exo}–C(6′)); 2.04 (*s*, Me of Ts); 1.92 (*ddd*, *J* = 13.1, 5.0, 1.9, H_{endo}–C(6′)); 1.50, 1.46, 1.40, 1.33 (4*s*, 2 Me_2C). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.77, 170.67 (2*s*, 2 C=O); 145.66, 134.85 (2*s*); 135.72 (*d*, C(8′)); 129.98 (*d*, C(7′)); 129.76 (2*d*); 127.68 (2*d*); 111.86, 109.73 (2*s*, 2 Me_2C); 103.40 (*s*, C(2)); 77.70 (*s*, C(4′)); 74.42, 73.58, 71.39 (3*d*, C(3), C(4), C(5)); 71.91 (*t*, C(1)); 60.73 (*t*, C(6)); 52.72 (*d*, C(1′)); 43.46 (*d*, C(5′)); 33.48 (*t*, C(6′)); 27.70, 26.30, 26.30, 25.94, (4*q*, 2 Me_2C); 21.71 (*q*, Me of Ts).

Data of **33b**: R_f (cyclohexane/AcOEt 3 : 2) 0.33. $[\alpha]_D^{25} = -122.8$ (*c* = 0.3, $CHCl_3$). M.p. 184–185° (CH_2Cl_2/hexane). IR ($CHCl_3$): 3493*w*, 2991*m*, 2936*w*, 2889*w*, 1727*s* (br.), 1598*w*, 1456*w*, 1374*s* (br.), 1264*m*, 1173*s*, 1112*m*, 1086*s*, 1069*m*, 1013*m*, 976*m*, 886*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 7*; additionally, 7.85 (*dt*, *J* = 8.4, 1.9, 2 H); 7.37 (*dt*, *J* = 8.6, 1.9, 2 H); 6.49 (*dd*, *J* = 7.9, 6.0, H–C(7′)); 6.19 (*dt*, *J* = 7.8, 1.4, H–C(8′)); 5.10 (*d*, *J* = 8.0, H–C(3)); 4.25 (*dd*, *J* = 8.0, 5.3, H–C(4)); 4.21 (br. *dd*, *J* = 5.3, 1.9, H–C(5)); 4.11 (*dd*, *J* = 13.4, 2.5, H_{eq}–C(6)); 4.06 (br. *d*, *J* = 13.5, H_{ax}–C(6)); 3.95, 3.92 (2*d*, *J* = 8.0, 2 H–C(1)); 3.85 (*s*, OH); 2.44 (*s*, Me of Ts); 1.50, 1.48, 1.39, 1.34 (4*s*, 2 Me_2C). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.09, 170.52 (2*s*, 2 C=O); 145.40, 134.65 (2*s*); 134.51 (*d*, C(8′)); 130.48 (*d*, C(7′)); 129.58 (2*d*); 127.68 (2*d*); 112.01, 109.46 (2*s*, 2 Me_2C); 103.23 (*s*, C(2)); 77.86 (*s*, C(4′)); 74.48, 73.53, 70.85 (3*d*, C(3), C(4), C(5)); 71.10 (*t*, C(1)); 59,91 (*t*, C(6)); 52.70 (*d*, C(1′)); 42.86 (*d*, C(5′)); 33.47 (*t*, C(6′)); 27.47, 26.41, 26.07, 25.77 (4*q*, 2 Me_2C); 21.41 (*q*, Me of Ts). HR-MALDI-MS: 602.1674 (22, $[M + Na]^+$, $C_{27}H_{33}NNaO_{11}S^+$; calc. 602.1672), 413 (25), 288.0296 (100, [*M* – (1,2 : 4,5-di-*O*-isopropylidene-β-*D*-fructopyranos-3-yl acrylate) + Na]$^+$, $C_{12}H_{11}NNaO_4S^+$; calc. 288.0306). Anal. calc. for $C_{27}H_{33}NO_{11}S$ (579.62): C 55.95, H 5.74, N 2.42, S 5.53; found: C 55.79, H 5.90, N 2.41, S 5.52.

X-Ray Crystal-Structure Analysis of **33b**. The crystals were obtained by azeotropic recrystallisation from CH_2Cl_2/hexane. Monoclinic, $P2_1$; $a = 11.561(4)$ Å, $b = 6.567(5)$ Å, $c = 18.873(15)$ Å, $\beta = 96.25(5)^\circ$, $V = 1424.3(16)$ Å^3, $Z = 2$; $D_{calc} = 1.351$ Mg/m^3. From a crystal of size $0.50 \times 0.40 \times 0.15$ mm, 2867 reflections were measured on an *Enraf Nonius CAD-4* diffractometer (graphite monochromator, MoK_α radiation, $\lambda = 0.71069$ Å) at 293(2) K, by Dr. *B. Schweizer* (ETH-Zürich). $R = 0.0325$, $R_w = 0.0935$. The structure was solved by direct methods with SIR97 [74]. The non-H-atoms were refined anisotropically with SHELXL-97 [75]. The H-atoms were calculated and included in the structure factor calculation. Drawings of the molecule were made with ORTEP [76].

*(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl (1*R*,4*S*,5*R*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* (**35a**) *and (1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl (1*S*,4*R*,5*S*)-4-Hydroxy-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* (**35b**). A soln. of **10** (50 mg, 0.188 mmol), **34** [52] (79 mg, 0.376 mmol), and Et_3N (52 µl, 0.38 mmol) in CH_2Cl_2 (0.8 ml) was stirred at 24° for 24 h, filtered through a pad of silica gel (cyclohexane/AcOEt 2:1), and evaporated to yield crude **35a**/**35b** 41:59 (determined by ^{1}H-NMR). Prep. HPLC (*Spherisorb SW-5*µM, 200 × 20 mm; hexane/AcOEt 2:1, 15 ml/min) afforded **35a**/**35b** 41:59 (t_R 11 min, 29 mg, 33%). R_f (cyclohexane/AcOEt 3:2) 0.70. IR ($CHCl_3$): 3503*w* (br.), 3031*m*, 2959*s*, 2929*m*, 2872*m*, 1723*s*, 1598*w*, 1494*w*, 1456*m*, 1370*s*, 1089*s*, 1038*w*, 999*w*, 952*m*, 919*m*, 824*m*, 813*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.85 (*dt*, $J \approx 8.3$, 1.9, 2 H); 7.32 (br. *d*, $J = 8.6$, 2 H); 6.45 (*dd*, $J = 7.9$, 6.0, 0.4 H), 6.44 (*dd*, $J = 8.0$, 6.0, 0.6 H) (H−C(7)); 6.22 (*dt*, $J = 7.9$, 1.4, H−C(8)); 5.36 (*ddt*, $J = 5.6$, 3.7, 1.9, H−C(1)); 4.66 (*td*, $J = 10.9$, 4.4, H−C(1′)); 3.79 (*s*, OH); 2.70 (*ddd*, $J = 8.4$, 5.0, 1.1, 0.4 H), 2.67 (*ddd*, $J = 9.5$, 5.0, 1.1, 0.6 H) (H−C(5)); 2.48 (*ddd*, $J = 13.1$, 8.5, 3.8, 0.4 H), 2.45 (*ddd*, $J = 13.3$, 9.9, 3.8, 0.6 H) (H_{exo}−C(6)); 2.44 (*s*, Me of Ts); 1.98 (*dtd*, $J \approx 12.6$, 4.7, 1.8, 0.4 H), 1.93 (br. *d*, $J \approx 12.6$, 0.6 H) (H_{eq}−C(6′)); 1.92 (*sept.d*, $J = 6.9$, 2.6, 0.6 H), 1.79 (*sept.d*, $J \approx 7.0$, 2.8, 0.4 H) (Me_2CH); 1.86 (*ddd*, $J = 13.1$, 5.0, 2.0, 0.4 H), 1.85 (*ddd*, $J = 13.1$, 5.0, 2.0, 0.6 H) (H_{endo}−C(6)); 1.67 (br. *d*, $J \approx 12.8$, H_{eq}−C(3′), H_{eq}−C(4′)); 1.50–1.39 (*m*, H−C(5′)); 1.34 (*ddt*, $J = 12.4$, 11.0, 3.1, H−C(2′)); 1.08–0.79 (*m*, H_{ax}−C(3′), H_{ax}−C(4′)); 0.93 (*q*, $J \approx 12.6$, H_{ax}−C(6′)); 0.89, 0.81 (2*d*, $J \approx 6.8$, Me_2C); 0.72 (*d*, $J = 7.0$, Me−C(5′)). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.11, 171.08, 170.84, 170.66 (4*s*, 4 C=O); 145.60, 145.58 (2*s*); 135.44, 135.04 (2*s*); 135.44, 135.30 (2*d*, C(8)); 130.06, 129.93 (2*d*, C(7)); 129.74 (2*d*); 127.97 (4*d*); 127.74 (2*d*); 78.06, 77.97 (2*s*, C(4)); 75.80, 75.75 (2*d*, C(1′)); 52.92 (*d*, C(1)); 46.91, 46.84 (2*d*, C(2′)); 43.37, 43.22 (2*d*, C(5)); 40.69 (*t*, C(6′)); 34.16 (*t*, C(4′)); 33.56, 33.50 (2*t*, C(6)); 31.85 (*d*, C(5′)); 26.14, 25.88 (2*d*, Me_2C); 23.24, 23.16 (2*t*, C(3′)); 21.95, 21.70, 20.74 (3*q*, Me_2C, Me of Ts); 16.08, 16.00 (2*q*, Me−C(5′)). HR-MALDI-MS: 498.1920 (18, $[M + Na]^+$, $C_{25}H_{33}NNaO_6S^+$; calc. 498.1926), 288.0300 (100, [*M* − menthylacrylate + Na]$^+$, $C_{12}H_{11}NNaO_4S^+$; calc. 288.0306), 266 (26), 91 (10).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*S*,5*R*)-4-(Methoxymethoxy)-2-[(4-methylphenyl)sulfonyl]-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((−)-**36**). A soln. of (+)-**31a** (10.0 g, 18.1 mmol) and dimethoxymethane (12.7 ml, 226 mmol) in $CHCl_3$ (60 ml) was treated with P_2O_5 (16.1 g, 113 mmol) and stirred at 25° for 1 h, when TLC showed an incomplete reaction. The suspension was treated with additional dimethoxymethane (1.27 ml, 22.6 mmol) and P_2O_5 (1.61 g, 11.3 mmol), and stirred at 25° for 1 h. The supernatant was decanted to a cooled sat. aq. Na_2CO_3 soln. (100 ml), and the phases were separated. The solid residue was quickly extracted with $CHCl_3$/sat. aq. Na_2CO_3 soln. 1:1 (3 × 50 ml), and the phases were separated. The combined aq. phases were extracted with $CHCl_3$ (2 × 50 ml). The combined org. phases were dried (Na_2SO_4) and evaporated to yield crude (−)-**36** (11.0 g, >98%) as a slightly yellow solid. FC (cyclohexane/AcOEt 5:2) of a sample (110 mg) afforded (−)-**36** (97 mg, 90%). Colourless foam. R_f (cyclohexane/AcOEt 3:2) 0.61. M.p. 178° (CH_2Cl_2/i-PrOH). $[\alpha]_D^{25} = -46.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3032*m*, 2957*m*, 2927*m*, 1730*s* (br.), 1598*w*, 1495*w*, 1457*m*, 1356*s* (br.), 1273*m*, 1172*s*, 1128*m*, 1104*m*, 1090*s*, 1068*m*, 1008*m*, 982*m*, 958*m*, 917*w*. ^{1}H-NMR ($CDCl_3$): 7.84 (br. *d*, $J = 8.4$, 2 H); 7.33 (br. *d*, $J = 8.4$, 2 H); 7.29–7.15 (*m*, 4 H); 6.97 (*tt*, $J \approx 6.2$, 1.9, 1 H); 6.77 (*dt*, $J = 8.4$, 1.2, irrad. at 5.23 → *dd*, $J = 8.4$, 1.5, H−C(8)); 6.40 (*dd*, $J = 8.1$, 6.2, irrad. at 5.23 → *d*, $J = 8.4$, H−C(7)); 4.96, 4.90 (2*d*, $J = 7.8$, OCH_2O); 4.69 (*td*, $J = 10.6$, 4.0, H−C(1′)); 3.35 (*s*, MeO); 2.46 (*s*, Me of Ts); 2.18 (irrad. at 5.23 → *dd*, $J = 12.5$, 10.3, H_{exo}−C(6)); 1.95 (*td*, $J \approx 11.5$, 3.1, irrad. at 4.69 → *dd*, $J = 11.8$, 3.4, H−C(2′)); 1.82 (br. *d*, $J \approx 12.1$, irrad. at 4.69 → *ddd*, $J \approx 11.5$, 2.6, 1.3, H_{eq}−C(6′)); 1.60 (br. *d*, $J \approx 12.2$, H_{eq}−C(3′), H_{eq}−C(4′)); 1.49–1.38 (*m*, H−C(5′)); 1.35 (irrad. at 5.23 → *dd*, $J = 12.5$, 3.7, H_{endo}−C(6)); 1.29, 1.19 (2*s*, Me_2C); 1.02 (*qd*, $J \approx 13.4$, 3.4, H_{ax}−C(3′)); 0.85 (*q*, $J \approx 11.8$, irrad. at 4.69 → *m*, H_{ax}−C(6′)); 0.84 (*d*, $J = 6.5$, Me−C(5′)); 0.81 (br. *q*, $J \approx 12.3$, H_{ax}−C(4′)). ^{13}C-NMR ($CDCl_3$): 170.10, 169.40 (2*s*, 2 C=O); 151.55, 145.33, 135.51 (3*s*); 134.26 (*d*, C(8)); 130.01 (*d*, C(7)); 129.73 (2*d*); 128.10 (2*d*); 128.03 (2*d*); 125.61 (2*d*); 125.02 (*d*); 95.05 (*t*, OCH_2O); 83.79 (*s*, C(4)); 75.73 (*d*, C(1′)); 55.93 (*q*, MeO); 51.95 (*d*, C(1)); 50.36 (*d*, C(2′)); 41.79 (*d*, C(5)); 41.13 (*t*, C(6′)); 39.56 (*s*, Me_2C); 34.43, 33.31 (2*t*, C(6), C(4′)); 31.16 (*d*, C(5′)); 26.92, 25.40 (2*q*, Me_2C); 26.58 (*t*, C(3′)); 21.57 (2*q*, Me−C(5′), Me of Ts). ESI-MS: 1213 (46, [2*M* +

Na]$^+$), 913 (25), 618 (100, [M+Na]$^+$), 596 (4, [M+H]$^+$), 382 (10), 116 (21). Anal. calc. for $C_{33}H_{41}NO_7S$ (595.75): C 66.53, H 6.94, N 2.35, S 5.38; found: C 66.52, H 7.02, N 2.27, S 5.49.

*X-Ray Crystal-Structure Analysis of (−)-***36**. The crystals were obtained by azeotropic recrystallisation from CH_2Cl_2/i-PrOH. Orthorhombic. $P2_1P2_1P2_1$; $a = 11.6310(10)$ Å, $b = 11.867(2)$ Å, $c = 22.646(2)$ Å, $V = 3125.7(7)$ Å^3, $Z = 4$; $D_{calc} = 1.266$ Mg/m^3. From a crystal of size $0.35 \times 0.25 \times 0.20$ mm, 3119 reflections were measured on an *Enraf Nonius CAD-4* diffractometer (graphite monochromator, CuK_α radiation, $\lambda = 1.54184$ Å) at 293(2) K by Dr. *B. Schweizer* (ETH-Zürich). $R = 0.0420$, $R_w = 0.1287$. The structure was solved by direct methods with SIR97 [74]. The non-H-atoms were refined anisotropically with SHELXL-97 [75]. The H-atoms were calculated and included in the structure factor calculation. Drawings of the molecule were made with ORTEP [76].

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*S*,5*R*)-4-(Methoxymethoxy)-3-oxo-2-aza-bicyclo[2.2.2]oct-7-ene-5-carboxylate* ((−)-**37**). A dark-green mixture of Na (3.50 g, 152 mg-atom) and naphthalene (24.0 g, 187 mmol) in DME (100 ml) was stirred at 25° for 3 h, and added dropwise to a cooled (−78°) soln. of crude (−)-**36** (11.0 g, *ca.* 18.1 mmol) in DME (240 ml) until the green colouration persisted (*ca.* 35 ml, *ca.* 53 mmol Na−$C_{10}H_8$). The soln. was stirred at −78° for 10 min and allowed to warm to 0°. The mixture was treated with sat. aq. $NaHCO_3$ soln. (100 ml) and quickly extracted with $CHCl_3$ (3 × 50 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. FC (cyclohexane/AcOEt 2:1 → 1:1) yielded (−)-**37** (6.51 g, 81%) as a colourless oil. Crystallisation of a sample from Et_2O/pentane at −20° afforded colourless crystals. R_f (cyclohexane/AcOEt/MeOH 1:1:0.1) 0.62. M.p. 90–92° (Et_2O/pentane). $[\alpha]_D^{25} = -114.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3432*w*, 3198*w* (br.), 2956*s*, 2927*m*, 1722*s*, 1695*s*, 1600*w*, 1496*w*, 1457*m*, 1368*m*, 1347*m*, 1264*m*, 1176*s*, 1126*m*, 1064*s*, 996*m*, 956*m*, 916*w*, 847*w*. ^{1}H-NMR ($CDCl_3$): see *Table 4*; additionally, 7.38–7.19 (*m*, 4 H); 7.19–7.06 (*m*, 1 H); 6.98 (br. *s*, NH); 6.85 (br. *dd*, $J \approx 8.1, 1.4$, irrad. at 4.15 → br. *d*, $J = 8.1$, H−C(8)); 6.38 (*dd*, $J = 8.1$, 5.6, irrad. at 4.15 → *d*, $J = 8.1$, H−C(7)); 5.14, 5.00 (2*d*, $J \approx 7.7$, OCH_2O); 4.75 (*td*, $J = 10.6$, 4.4, H−C(1′)); 3.49 (*s*, MeO); 2.22 (irrad. at 4.15 → *t*, $J \approx 12.3$, irrad at 2.61 → *dd*, $J \approx 13.4$, 3.4, H_{exo}−C(6)); 1.92 (*td*, $J = 10.6$, 3.4, irrad. at 4.75 → br. *d*, $J \approx 10.6$, H−C(2′)); 1.86 (br. *d*, $J \approx 12.2$, irrad. at 4.75 → change, H_{eq}−C(6′)); 1.61–1.35 (*m*, H−C(5′)); 1.55 (br. *d*, $J = 13.7$, H_{eq}−C(3′)); 1.47 (*dt*, $J = 13.4$, 3.1, H_{eq}−C(4′)); 1.43 (irrad. at 3.61 → br. *d*, $J \approx 13.4$, H_{endo}−C(6)); 1.35, 1.23 (2*s*, Me_2C); 1.00 (*qd*, $J = 12.5$, 2.8, H_{ax}−C(3′)); 0.88 (*q*, $J \approx 11.5$, irrad. at 4.75 → *td*, $J \approx 11.5$, 3.1, H_{ax}−C(6′)); 0.82 (*d*, $J = 6.5$, Me−C(5′)); 0.78 (*qd*, $J = 12.2$, 2.8, H_{ax}−C(4′)). ^{13}C-NMR ($CDCl_3$): 175.15, 171.05 (2*s*, 2 C=O); 151.31 (*s*); 133.91, 131.18 (2*d*, C(7), C(8)); 128.04 (2*d*); 125.72 (2*d*); 125.15 (*d*); 95.22 (*t*, OCH_2O); 83.48 (*s*, C(4)); 75.51 (*d*, C(1′)); 55.80 (*q*, MeO); 50.50 (*d*, C(2′)); 47.80 (*d*, C(1)); 43.42 (*d*, C(5)); 41.29 (*t*, C(6′)); 39.86 (*s*, Me_2C); 34.66, 34.47 (2*t*, C(6), C(4′)); 31.20 (*d*, C(5′)); 27.29, 25.55 (2*q*, Me_2C); 26.85 (*t*, C(3′)); 21.16 (*q*, Me−C(5′)). EI-MS: 905 (33, [2M+Na]$^+$), 464 (100, [M+Na]$^+$), 442 (3, [M+H]$^+$), 87 (17), 55 (9). Anal. calc. for $C_{26}H_{35}NO_5$ (441.56): C 70.72, H 7.99, N 3.17; found C 70.71, H 8.07, N 3.16.

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*S*,5*S*)-4-(Methoxymethoxy)-3-oxo-2-aza-bicyclo[2.2.2]oct-7-ene-5-carboxylate* ((−)-**38**). A mixture of (−)-**37** (1.00 g, 2.26 mmol), ground molecular sieves (3 Å; 0.25 g, dried at 180° for 48 h), and $Ba(OMe)_2$ (0.50 g, 11.3 mmol) in MeOH (250 ml) was stirred at 40° for 20 h. Normal workup (CH_2Cl_2/1M aq. HCl soln.) yielded (−)-**37**/(−)-**38** 20:80 (967 mg, 97%). FC (hexane/AcOEt 1:2) afforded (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (159 mg, 30%; for data, see [49]), (−)-**37** (196 mg, 20%), and (−)-**38** (487 mg, 49%).

*Data of (−)-***38**: R_f (cyclohexane/AcOEt 3:2) 0.72. M.p. 143.5°. $[\alpha]_D^{25} = -10.9$ ($c = 0.5$, $CHCl_3$). IR ($CHCl_3$): 3434*m*, 2957*m*, 2927*m*, 1724*s*, 1702*s*, 1600*w*, 1457*w*, 1444*w*, 1367*m*, 1337*m*, 1315*w*, 1175*s*, 1160*s*, 1130*m*, 1060*s*, 1013*m*, 997*m*, 911*m*. 862*w*. ^{1}H-NMR ($CDCl_3$): see *Table 7*; additionally, 7.31–7.18 (*m*, 4 H); 7.09 (*tt*, $J \approx 7.3$, 2.8, 1 H); 6.69 (br. *d*, $J = 6.0$, irrad. at 4.18 → *s*, NH); 6.63 (*dd*, $J = 8.1$, 1.6, irrad. at 4.18 → *d*, $J = 8.4$, H−C(8)); 6.38 (*dd*, $J = 8.1$, 5.6, irrad. at 4.18 → *d*, $J = 7.8$, H−C(7)); 4.97, 4.87 (2*d*, $J \approx 7.4$, OCH_2O); 4.85 (*td*, $J \approx 10.9$, 4.4, H−C(1′)); 3.43 (*s*, MeO); 2.05 (*td*, $J \approx 11.5$, 3.0, irrad. at 4.85 → *dd*, $J = 10.2$, 4.7, H−C(2′)); 2.04–1.96 (*m*, irrad. at 4.85 → *dt*, $J = 12.1$, 3.4, H_{eq}−C(6′)); 2.00 (irrad. at 4.18 → *dd*, $J = 12.5$, 4.4, H_{exo}−C(6)); 1.72 (*dq*, $J = 13.3$, 3.4, H_{eq}−C(3′)); 1.67–1.60 (*m*, H_{eq}−C(4′)); 1.62 (irrad. at 4.18 → *dd*, $J = 12.4$, 10.3, H_{endo}−C(6)); 1.52–1.35 (*m*, H−C(5′)); 1.28, 1.18 (2*s*, Me_2C); 1.11 (*qd*, $J = 12.4$, 2.5, H_{ax}−C(3′)); 0.97 (*q*, $J \approx 12.2$, irrad. at 4.85 → *t*, $J = 10.9$, H_{ax}−C(6′)); 0.87 (*d*, $J = 6.5$, Me−C(5′)); 0.87 (*qd*, $J \approx 12.4$, 3.1, H_{ax}−C(4′)). ^{13}C-NMR ($CDCl_3$): 172.09, 171.69 (2*s*, 2 C=O); 151.82 (*s*); 134.91, 133.41 (2*d*, C(7), C(8)); 127.54 (2*d*); 125.17 (2*d*); 124.72 (*d*); 94.94 (*t*, OCH_2O); 83.99 (*s*, C(4)); 75.17 (*d*, C(1′)); 55.74 (*q*, MeO); 50.39 (*d*, C(2′)); 47.14 (*d*, C(1)); 43.32 (*d*, C(5)); 41.78 (*t*, C(6′)); 39.67 (*s*, Me_2C); 34.65, 33.51 (2*t*, C(6), C(4′)); 31.34 (*d*, C(5′)); 28.53, 24.30 (2*q*, Me_2C); 26.54 (*t*, C(3′)); 21.85 (*q*, Me−C(5′)). EI-MS: 905 (48, [2M+Na]$^+$), 682 (8), 480 (18), 464 (100, [M+Na]$^+$), 442 (8, [M+H]$^+$), 132 (12), 116 (14), 87 (5). Anal. calc. for $C_{26}H_{35}NO_5$ (441.56) C 70.72, H 7.99, N 3.17; found: C 70.80, H 8.24, N 3.23.

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*S*,5*R*)-2-Benzyl-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((−)-**39**). NaH (816 mg, *ca.* 50% in oil, *ca.* 17.0 mmol) was added to a cooled (0°) soln. of (−)-**37** (5.00 g, 11.3 mmol) in DMF (100 ml). The mixture was stirred at 0° for 5 min, treated dropwise with BnBr (2.02 ml, 17.0 mmol), and stirred at 0° for 1 h. Normal workup (AcOEt/ice-water) and FC (cyclohexane/AcOEt 5:1 → 4:1) yielded (−)-**39** (5.80 g, 96%). Colourless foam. R_f (cyclohexane/AcOEt 3:2) 0.47. M.p. 50–55°. $[\alpha]_D^{25} = -70.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3031*w*, 2956*m*, 2928*m*, 1952*w*, 1877*w*, 1807*w*, 1728*m*, 1683*s*, 1601*w*, 1496*w*, 1453*m*, 1356*m*, 1271*w*, 1175*m*, 1158*m*, 1059*m*, 993*m*, 915*w*. ^{1}H-NMR ($CDCl_3$): see *Table 7*; additionally, 7.42–7.20 (*m*, 7 H); 7.19–7.06 (*m*, 3 H); 6.84 (*dt*, $J = 8.1$, 1.6, irrad. at 3.94 → br. *d*, $J = 8.1$, H–C(8)); 6.29 (*dd*, $J = 8.1$, 5.6, irrad. at 3.94 → *d*, $J = 8.1$, H–C(7)); 5.21, 5.05 (2*d*, $J =$ 7.5, OCH_2O); 4.72 (*td*, $J = 10.6$, 4.0, H–C(1′)); 4.55, 4.37 (2*d*, $J \approx 14.8$, PhCH_2); 3.51 (*s*, MeO); 1.91 (*td*, $J \approx 9.9$, 3.1, irrad. at 4.72 → *m*, H–C(2′)); 1.87 (irrad. at 3.94 → *dd*, $J = 12.8$, 10.3, H_{exo}–C(6)); 1.82 (br. *d*, $J \approx 12.8$, irrad. at 4.72 → change, H_{eq}–C(6′)); 1.60–1.52 (*m*, H_{eq}–C(3′)); 1.48 (*dq*, $J \approx 13.4$, 3.4, H_{eq}–C(4′)); 1.46–1.35 (*m*, H–C(5′)); 1.35, 1.22 (2*s*, Me_2C); 1.21 (irrad. at 3.94 → *dd*, $J = 13.0$, 5.0, H_{endo}–C(6)); 0.98 (*qd*, $J = 12.3$, 2.8, H_{ax}–C(3′)); 0.84 (*q*, $J \approx 11.5$, irrad. at 4.72 → *m*, H_{ax}–C(6′)); 0.80 (*d*, $J = 6.5$, Me–C(5′)); 0.77 (*qd*, $J \approx 12.2$, 2.5, H_{ax}–C(4′)). ^{13}C-NMR ($CDCl_3$): 171.08, 170.70 (2*s*, 2 C=O); 151.14, 134.09 (2*s*); 136.26, 130.07 (2*d*, C(7), C(8)); 128.60 (2*d*); 127.91 (2*d*); 127.83 (2*d*); 125.33 (2*d*); 127.60 (*d*); 124.88 (*d*); 95.15 (*t*, OCH_2O); 83.73 (*s*, C(4)); 75.46 (*d*, C(1′)); 55.85 (*q*, MeO); 52.44 (*d*, C(1)); 50.53 (*d*, C(2′)); 48.55 (*t*, PhCH_2); 43.82 (*d*, C(5)); 41.30 (*t*, C(6′)); 39.88 (*s*, Me_2C); 34.57, 33.53 (2*t*, C(6), C(4′)); 31.31 (*d*, C(5′)); 26.96 (*t*, C(3′)) 26.96, 26.02 (2*q*, Me_2C); 21.79 (*q*, Me–C(5′)). ESI-MS: 1085 (16, $[2M + Na]^+$), 554 (100, $[M + Na]^+$), 510 (24), 132 (42), 116 (49), 87 (22). Anal. calc. for $C_{33}H_{41}NO_5$ (531.68): C 74.55, H 7.77, N 2.63; found: C 74.40, H 7.90, N 2.73.

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*S*,5*S*)-2-Benzyl-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-carboxylate* ((−)-**40**). A mixture of (−)-**39** (5.00 g, 9.40 mmol), ground molecular sieves (3 Å, 1.00 g, dried at 180° for 48 h) and $Ba(OMe)_2$ (3.75 g, 18.8 mmol) in MeOH (180 ml) was stirred at 40° for 12 h. The suspension was added to a mixture of AcOEt/1M aq. HCl 1:1 (500 ml). The phases were separated, and the aq. phase was extracted with AcOEt (2 × 250 ml). The combined extracts were concentrated to a volume of *ca.* 50 ml. The phases were separated, and the aq. phase was extracted with AcOEt (2 × 50 ml). The combined org. phases were washed with brine (50 ml), dried (Na_2SO_4), and evaporated. FC (hexane/AcOEt 4:1 → 1:1) afforded (−)-**39**/(−)-**40** 25:75 (4.81 g, 96%). Repeated FC (hexane/AcOEt 4:1 → 1:2) yielded (−)-**39** (1.19 g, 23%) and (−)-**40** (3.39 g, 68%) as colourless foams.

*Data of (−)-***40**: R_f (cyclohexane/AcOEt 3:2) 0.37. M.p. 49–54°. $[\alpha]_D^{25} = -7.9$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3064*w*, 3029*m*, 2957*s*, 2927*s*, 1950*w*, 1876*w*, 1810*w*, 1722*s*, 1684*s*, 1600*w*, 1496*m*, 1453*s*, 1366*s*, 1346*s*, 1160*s*, 1059*s*, 1038*s*, 996*m*, 978*m*, 911*m*, 859*w*, 820*w*. ^{1}H-NMR ($CDCl_3$): see *Table 7*; additionally, 7.38–7.15 (*m*, 9 H); 7.06 (*tt*, $J \approx 6.7$, 1.7, 1 H); 6.62 (*dd*, $J = 8.1$, 1.9, H–C(8)); 6.28 (*dd*, $J = 8.1$, 5.6, irrad. at 3.93 → *d*, $J = 8.4$, H–C(7)); 5.04, 4.92 (2*d*, $J = 7.5$, OCH_2O); 4.87 (*td*, $J = 10.6$, 4.4, H–C(1′)); 4.71, 4.43 (2*d*, $J = 15.3$, PhCH_2); 3.45 (*s*, MeO); 2.10–2.01 (*m*, irrad. at 4.87 → change, H–C(2′), H_{eq}–C(6′)); 1.85 (irrad. at 3.93 → *dd*, $J = 12.8$, 4.7, H_{exo}–C(6)); 1.73 (br. *d*, $J \approx 12.8$, H_{eq}–C(3′)); 1.47 (irrad. at 3.93 → *dd*, $J = 12.5$, 10.2, H_{endo}–C(6)); 1.46–1.27 (*m*, H_{eq}–C(4′), H–C(5′)); 1.28, 1.19 (2*s*, Me_2C); 1.12 (*qd*, $J = 13.1$, 2.8, H_{ax}–C(3′)); 0.99 (*q*, $J \approx 11.5$, irrad. at 4.87 → *t*, $J \approx 12.1$, H_{ax}–C(6′)); 0.88 (*d*, $J = 6.5$, Me–C(5′)); 0.87 (*qd*, $J \approx 12.0$, 3.4, H_{ax}–C(4′)). ^{13}C-NMR ($CDCl_3$): 172.26, 169.80 (2*s*, 2 C=O); 152.08, 136.75 (2*s*); 135.35, 132.81 (*d*, C(7), C(8)); 128.64 (2*d*); 128.48 (2*d*); 127.80 (2*d*); 127.56 (*d*); 125.40 (2*d*); 124.90 (*d*); 94.81 (*t*, OCH_2O); 84.26 (*s*, C(4)); 75.20 (*d*, C(1′)); 55.69 (*q*, MeO); 51.08 (*d*, C(1)); 50.34 (*d*, C(2′)); 48.07 (*t*, PhCH_2); 44.95 (*d*, C(5)); 41.68 (*t*, C(6′)); 39.55 (*s*, Me_2C); 34.52 (*t*, C(4′)); 31.82 (*t*, C(6)); 31.17 (*d*, C(5′)); 28.27, 24.21 (2*q*, Me_2C); 26.38 (*t*, C(3′)); 21.64 (*q*, Me–C(5′)). ESI-MS: 1085 (3, $[2M + Na]^+$), 554 (100, $[M + Na]^+$), 532 (11, $[M + H]^+$), 360 (8), 132 (25), 116 (31), 87 (22). Anal. calc. for $C_{33}H_{41}NO_5$ (531.68): C 74.55, H 7.77, N 2.63; found: C 74.40, H 7.48, N 2.81.

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*,4*R*,5*S*,7*R*,8*R*)-2-Benzyl-7,8-dihydroxy-4-(methoxymethoxy)-3-oxo-2-azabicyclo[2.2.2]octane-5-carboxylate* ((−)-**41**). A yellow soln. of (−)-**40** (250 mg, 0.47 mmol), NMO (98 mg, 0.97%, 0.70 mmol) and a 2.5% soln. of OsO_4 in *t*-BuOH (60 µl, 0.48 µmol) in THF/acetone/H_2O 1:1:2 (4 ml) was stirred at 24° for 4 h. Normal workup (AcOEt/Na_2SO_3 soln.) afforded crude (−)-**41** as a yellow foam (310 mg, > 98%). Recrystallisation of a sample in i-PrOH/hexane 3:1 afforded pure (−)-**41**. Colourless crystals. R_f (cyclohexane/AcOEt/MeOH 1:1:0.1) 0.37. M.p. 162° (i-PrOH/hexane). $[\alpha]_D^{25} = -91.9$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3494*w* (br.), 2973*m*, 2925*m*, 1728*s*, 1686*s*, 1600*w*, 1496*w*, 1455*m*, 1369*m*, 1317*m*, 1280*w*, 1177*m*, 1149*m*, 1101*m*, 1070*m*, 1004*m*, 951*w*, 908*w*, 848*m*. ^{1}H-NMR ($CDCl_3$): see *Table 7*; additionally, 7.43 (*dd*, $J = 7.8$, 1.2, 2 H); 7.38–7.17 (*m*, 7 H); 7.10 (*tt*, $J \approx 7.0$, 2.7, 1 H); 5.50, 4.58 (2*d*, $J \approx 7.3$, OCH_2O); 5.20, 4.15 (2*d*, $J \approx 14.7$, PhCH_2); 4.94 (br. *s*, exchanges with D_2O, OH); 4.78 (*td*, $J = 10.6$, 3.4, H–C(1′)); 3.84–3.78 (br. *s*, addn. of D_2O → *d*, $w_{1/2} = 2.5$, H–C(7), H–C(8)); 3.62 (*t*, $J \approx 2.5$, exchanges with D_2O, OH); 3.48 (*s*, MeO); 2.04 (*td*, $J = 11.2$, 3.4, H–C(2′)); 2.00 (br. *d*, $J \approx 12.0$, irrad. at 4.78 → *dt*, $J \approx 12.0$, 2.4, H_{eq}–C(6′)); 1.76

(*dq*, J = 13.1, 3.1, H_{eq}–C(3′)); 1.66 (br. *d*, $J \approx$ 12.5, H_{eq}–C(4′)); 1.61 (irrad. at 3.41 → *dd*, J = 13.7, 6.2, H_{exo}–C(6)); 1.69–1.42 (*m*, H–C(5′)); 1.47 (irrad. at 3.41 → *dd*, J = 13.7, 10.6, H_{endo}–C(6)); 1.23, 1.16 (2*s*, Me_2C); 1.12 (*qd*, $J \approx$ 12.8, 2.8, H_{ax}–C(3′)); 0.87 (*q*, $J \approx$ 11.7, irrad. at 4.78 → *m*, H_{ax}–C(6′)); 0.87 (*d*, J = 6.5, Me–C(5′)); 0.87 (br. *q*, $J \approx$ 12.0, H_{ax}–C(4′)). ^{13}C-NMR ($CDCl_3$): 171.19, 166.75 (2*s*, 2 C=O); 152.11, 136.56 (2*s*); 128.75 (2*d*); 128.36 (2*d*); 127.53 (2*d*); 127.39 (*d*); 125.17 (2*d*); 124.58 (*d*); 92.92 (*t*, OCH_2O); 80.94 (*s*, C(4)); 75.28 (*d*, C(1′)); 70.28, 68.26 (2*d*, C(7), C(8)); 55.92 (*q*, MeO); 55.57 (*d*, C(1)); 50.34 (*d*, C(2′)); 49.48 (*t*, Ph*C*H_2); 42.36 (*d*, C(5)); 41.51 (*t*, C(6′)); 39.57 (*s*, Me_2*C*); 34.62 (*t*, C(4′)); 31.23 (*d*, C(5′)); 28.87, 23.82 (2*q*, *Me*$_2$C); 27.97 (*t*, C(6)); 26.37 (*t*, C(3′)); 21.85 (*q*, Me–C(5′)). HR-MALDI-MS: 588.2935 (77, $[M+Na]^+$, $C_{33}H_{43}NNaO_7^+$; calc. 588.2937), 374.1270 (100, $[M-(8\text{-phenylmenthyl})+H+Na]^+$, $C_{17}H_{21}NNaO_7^+$; calc. 374.1216), 320 (52). Anal. calc. for $C_{33}H_{43}NO_7$ (565.70): C 70.07, H 7.66, N 2.48; found: C 70.04, H 7.69, N 2.48.

*X-Ray Crystal-Structure Analysis of (–)-***41**. The crystals were obtained by azeotropic recrystallisation from i-PrOH/hexane. Orthorhombic. $P2_12_12_1$; a = 6.76760(10) Å, b = 19.0481(4) Å, c = 23.3595(6) Å, V = 3011.27(11) Å^3, Z = 4; D_{calc} = 1.248 Mg/m^3. 7377 reflections were measured on a *Bruker Nonius-KappaCCD* diffractometer (graphite monochromator, MoK_α radiation, λ = 0.71073 Å) at 202 K by Dr. *B. Schweizer* (ETH-Zürich). R = 0.0672, R_w = 0.1448. All calculations were performed using maXus [77]. The non-H-atoms were refined anisotropically with SHELXL-97 [75]. Drawings of the molecule were made with ORTEP [76].

*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R,*2*R,*6*R,*7*R,*10*S)-8-Benzyl-1-(methoxymethoxy)-4,4-dimethyl-9-oxo-3,5-dioxa-8-azatricyclo[5.2.2.0^{2,6}]undecane-10-carboxylate* ((–)-**42**). A soln. of crude (–)-**41** (300 mg, *ca.* 0.47 mmol) in acetone/2,2-dimethoxypropane 1:2 (15 ml) was treated with camphorsulfonic acid (22 mg, 0.095 mmol) and stirred at 24° for 1 h. Normal workup (AcOEt/$NaHCO_3$ soln.) and FC (hexane/AcOEt 5:1) yielded (–)-**42** (241 mg, 85%). Colourless foam. R_f (cyclohexane/AcOEt 3:2) 0.37. M.p. 76–79°. $[\alpha]_D^{25} = -79.7$ (c = 1.0, $CHCl_3$). IR ($CHCl_3$): 2966*m*, 2926*m*, 1725*s*, 1690*s*, 1600*w*, 1596*w*, 1455*m*, 1384*m*, 1376*m*, 1347*w*, 1316*w*, 1178*m*, 1163*m*, 1082*m*, 986*m*, 923*w*, 872*w*, 858*w*. ^{1}H-NMR ($CDCl_3$): 7.46 (*dt*, J = 6.9, 1.6, 2 H); 7.41–7.16 (*m*, 7 H); 7.07 (*tt*, $J \approx$ 6.1, 2.9, 1 H); 5.45, 3.85 (2*d*, J = 15.0, PhCH_2); 5.15, 4.95 (2*d*, $J \approx$ 6.4, OCH_2O); 4.82 (*td*, J = 10.5, 4.4, irrad. at 2.06 → br. *d*, J = 10.3, H–C(1′)); 4.31 (*d*, J = 7.2, H–C(2)); 4.10 (*dd*, J = 7.5, 2.5, irrad. at 3.47 → *d*, J = 7.5, H–C(6)); 3.47 (*dt*, $J \approx$ 3.5, 1.9, H–C(7)); 3.44 (*s*, MeO); 2.07 (br. *d*, $J \approx$ 12.2, H_{eq}–C(6′)); 2.04 (*ddd*, J = 12.2, 10.5, 3.5, H–C(2′)); 1.93 (*dd*, J = 10.6, 5.9, H–C(10)); 1.74 (*dq*, J = 13.4, 3.5, irrad. at 2.06 → br. *d*, $J \approx$ 12.2, H_{eq}–C(3′)); 1.64 (*ddd*, J = 13.7, 5.9, 3.7, irrad. at 1.93 → *dd*, $J \approx$ 12.9, 3.1, H_{exo}–C(11)); 1.70–1.37 (*m*, H_{eq}–C(4′), H–C(5′)); 1.42 (*ddd*, J = 13.7, 10.6, 1.9, irrad. at 1.93 → *dd*, $J \approx$ 13.7, 1.9, H_{endo}–C(11)); 1.38, 1.29, 1.25, 1.17 (4*s*, Me_2C(4), *Me*$_2$PhC); 1.11 (*qd*, $J \approx$ 12.8, 3.1, irrad. at 2.07 → br. *t*, $J \approx$ 13.0, H_{ax}–C(3′)); 0.97 (*q*, $J \approx$ 12.1, irrad. at 2.06 → *t*, $J \approx$ 11.2, H_{ax}–C(6′)); 0.87 (*d*, J = 6.5, Me–C(5′)); 0.88 (*qd*, $J \approx$ 12.0, 3.4, H_{ax}–C(4′)). ^{13}C-NMR ($CDCl_3$): 171.63, 166.86 (2*s*, 2 C=O); 151.97, 136.55 (2*s*); 128.81 (2*d*); 128.41 (2*d*); 127.58 (2*d*); 127.37 (*d*); 125.22 (2*d*); 124.60 (*d*); 110.32 (*s*, C(4)); 93.99 (*t*, OCH_2O); 80.36 (*s*, C(1)); 79.30, 76.95, (2*d*, C(2), C(6)); 75.41 (*d*, C(1′)); 56.33 (*q*, MeO); 52.68 (*d*, C(7)); 50.30 (*d*, C(2′)); 49.60 (*t*, PhCH_2); 42.53 (*d*, C(10)); 41.57 (*t*, C(6′)); 39.64 (*s*, Me_2Ph*C*); 34.62 (*t*, C(4′)); 31.30 (*d*, C(5′)); 28.70, 26.07, 24.62, 24.22 (4*q*, *Me*$_2$C(4), *Me*$_2$PhC); 27.88 (*t*, C(11)); 26.49 (*t*, C(3′)); 21.81 (*q*, Me–C(5′)). HR-MALDI-MS: 628.3249 (67, $[M+Na]^+$, $C_{36}H_{47}NNaO_7^+$; calc. 628.3250), 414.1578 (100, $[M-(8\text{-phenylmenthyl})+H+Na]^+$, $C_{20}H_{25}NNaO_7^+$; calc. 414.1529), 360 (78). Anal. calc. for $C_{36}H_{47}NO_7$ (605.76): C 71.38, H 7.82, N 2.31; found: C 71.42, H 7.93, N 2.37.

*(1*R,*2*R,*6*R,*7*R,*10*R*)-8-Benzyl-1-(methoxymethoxy)-4,4-dimethyl-3,5-dioxa-2-azatricyclo[5.2.2.0^{2,6}]undecane-10-methanol* ((–)-**22**). A mixture of (–)-**42** (250 mg, 0.41 mmol), $LiAlH_4$ (32 mg, 97%, 0.82 mmol) in THF (5 ml) was heated under reflux for 1 h, when TLC showed incomplete conversion. After the addition of additional $LiAlH_4$ (32 mg, 97%, 0.82 mmol), heating was continued for 1 h. The suspension was added dropwise to a mixture of ice-water, sat. aq. NH_4Cl soln., and AcOEt (1:1:1, 30 ml) at 0°. The phases were separated, and the aq. phase was extracted with AcOEt (2 × 20 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. The residue was taken up in dioxane (5 ml), treated with $LiAlH_4$ (32 mg, 97%, 0.82 mmol), and heated to reflux for 1 h. Analogous workup as described above and FC (hexane/AcOEt 5:1 → 1:1) yielded (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (92 mg, 96%) and (–)-**22** (115 mg, 78%) as colourless oils. $[\alpha]_D^{25} = -45.8$ (c = 1, $CHCl_3$). The R_f value and ^{1}H-NMR spectrum were identical to those described above for (±)-**22**.

*(1*R,*4*R,*5*R,*7*R,*8*R*)-2-Benzyl-5-(hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* ((+)-**2**). A soln. of (–)-**22** (100 mg, 0.275 mmol) in H_2O/CF_3CO_2H 1:2 (6 ml) was stirred at 100° for 3 h, diluted with toluene (5 ml), and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, H^+ form, 0.1M aq. NH_3 soln.) and FC (*Macherey-Nagel Lichroprep*-NH_2, AcOEt/MeOH 9:1 → 6:1) yielded (+)-**2** (64 mg, 83%) as colourless cotton-like fibers. $[\alpha]_D^{25} = +15.2$ (c = 0.5, MeOH). R_f, IR, and NMR data were identical to those of (±)-**2**.

*(1*R,*4*R,*5*R,*7*R,*8*R*)-5-(Hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* ((+)-**3**) *and* tert-*Butyl (1*R,*4*R,*5*R,*7*R,*8*R*)-4,7,8-Trihydroxy-5-(hydroxymethyl)-2-azabicyclo[2.2.2]octane-2-carboxylate* ((+)-**43**). *a*) A mixture of (+)-**2** (30 mg, 0.11 mmol) and 10% $Pd(OH)_2$/C (6 mg) in MeOH/H_2O/conc. HCl 1:1:0.1 (3.3 ml) was hydrogenated (6 bar) for 24 h. The mixture was filtered through *Celite*, and the filtrate was evaporated. The residue was suspended three times in toluene (10 ml) and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, H^+ form, 0.1M aq. NH_3) yielded (+)-**3** (19 mg, 93%) as a colourless solid.

b) A soln. of (+)-**3** (22 mg, 0.12 mmol) and di-(*tert*-butyl) carbamate (51 mg, 0.23 mmol) in MeOH/Et_3N 10:1 (1.1 ml) was stirred at 27° for 3 h and evaporated. FC (AcOEt/i-PrOH/25% aq. NH_3 2:3:1) gave (+)-**43** (27 mg, 80%) as a colourless glass.

c) A soln. of (+)-**43** (20 mg, 0.069 mmol) in MeOH was treated with a 1M HCl soln. in MeOH (2 ml), stirred at 25° for 12 h, and evaporated. Ion-exchange chromatography (*Amberlite CG-120*, H^+ form, 0.1M aq. NH_3) yielded (+)-**3** (10 mg, 76%) as a colourless solid.

*Data of (+)-***43**: R_f (MeOH/25% aq. NH_3 1:1) 0.39. $[\alpha]_D^{25} = +8.3$ (c = 0.6, MeOH). IR (KBr): 3355*m* (br.), 2925*m*, 1666*s*, 1475*m*, 1417*s*, 1367*m*, 1256*m*, 1201*m*, 1159*m* (br.), 1090*m*, 1039*m*, 948*w*, 871*w*. ^{1}H-NMR (300 MHz, CD_3OD, 1:1 mixture of two rotamers): 3.93, 3.91 (2*q*, $J \approx 2.5$, H−C(1)); 3.90 (br. *d*, $J = 8.5$, H−C(8)); 3.85 (*dd*, $J = 10.9$, 5.3, CH_a−C(5)); 3.62 (*dd*, $J = 8.7$, 1.5, H−C(7)); 3.53, 3.51 (2*dd*, $J = 10.4$, 7.6, CH_b−C(5)); 3.39, 3.37 (2*dd*, $J = 10.9$, 1.2, H_a−C(3)); 3.16, 3.09 (2*dd*, $J = 10.9$, 2.8, H_b−C(3)); 1.87–1.74 (*m*, H−C(5), H_{endo}−C(6)); 1.48 (*ddd*, $J = 9.0$, 3.7, 2.2, H_{exo}−C(6)); 1.46, 1.44 (2*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, CD_3OD, 1:1 mixture of two rotamers): 157.05 (*s*, C=O); 80.95, 80.51 (2*s*, Me_3C); 72.52, 72.44 (2*s*, C(4)); 71.80, 71.73, 68.38, 68.28 (4*d*, C(7), C(8)); 63.92 (*t*, CH_2−C(5)); 51.55, 50.09 (2*d*, C(1)); 43.94, 43.17 (2*t*, C(3)); 39.54 (*d*, C(5)); 28.79, 28.74 (2*q*, Me_3C); 27.44, 27.19 (2*t*, C(6)). HR-MALDI-MS: 312.1411 ($[M + Na]^+$, $C_{13}H_{23}NNaO_6^+$; calc. 312.1423).

*Data of (+)-***3**: $[\alpha]_D^{25} = 47.0$ ($c = 0.5$, H_2O). HR-MALDI-MS: 190.1076 ($[M + H]^+$, $C_8H_{16}NO_4^+$; calc. 190.1079). Anal. calc. for $C_8H_{15}NO_4$ (189.21): C 50.78, H 7.99, N 7.40; found: C 50.69, H 7.97, N 7.24. R_f, IR and NMR spectra were identical to those of (±)-**3**.

*(1*S,*4*S,*5*S,*7*S,*8*S*)-2-Benzyl-5-(hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* ((−)-**2**) and *(1*S,*4*S,*5*S,*7*S,*8*S*)-5-(Hydroxymethyl)-2-azabicyclo[2.2.2]octane-4,7,8-triol* ((−)-**3**) were obtained from (−)-**31b** as described for the synthesis of (+)-**2** and (+)-**3** from (+)-**31a**.

*Data of (−)-***2**: $[\alpha]_D^{25} = -15.4$ ($c = 0.8$, MeOH). R_f and ^{1}H-NMR data were identical to those of (+)-**2**.

*Data of (−)-***3**: $[\alpha]_D^{25} = -49.9$ ($c = 0.7$, MeOH). R_f and ^{1}H-NMR data were identical to those of (+)-**3**.

Inhibition of Glycosidases. The IC_{50} values were determined at a substrate concentration corresponding to K_M of each enzyme. Determination of the inhibition constants (K_i) was performed at different concentrations of the inhibitor (usually six) bracketing the K_i or IC_{50} value. The measurements were started by the addition of the substrate to a pre-incubated microtiter plate containing inhibitor or H_2O, buffer, and enzyme at the indicated temp. The velocity of the substrate hydrolysis was determined by quenching the reaction after 5 min with 0.2M borate buffer (pH 9.2) and measuring the absorption at λ 405 nm, and subsequently substracting the absorption of a blank probe (H_2O, buffer, substrate). IC_{50} Values were calculated by plotting the inhibitor concentration *vs.* the rate of hydrolysis. K_i and α values were determined from the replot of the slopes and the replot of the $1/v$ axis intercepts of *Lineweaver–Burk* plots.

a) *Inhibition of Snail* β*-Mannosidase.* The inhibition studies were carried out at 25° with a 0.04M AcOH/AcONa buffer at the indicated pH and 4-nitrophenyl β-D-mannopyranoside as substrate.

b) *Inhibition of* Jack *Bean* α*-Mannosidase.* The inhibition studies were carried out at 25° with a 0.04M AcOH/AcONa buffer (pH 4.5) with 0.02M of $ZnCl_2$ and 4-nitrophenyl β-D-mannopyranoside as substrate.

c) *Inhibition of* Caldocellum saccharolyticum β*-Glucosidase.* The inhibition studies were carried out at 55° with a 0.06M KH_2PO_4/K_2HPO_4 buffer (pH 6.8) and 4-nitrophenyl β-D-glucopyranoside as substrate.

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