7-Oxanorbornane and Norbornane Mimics of a Distorted β-D-Mannopyranoside: Synthesis and Evaluation as β-Mannosidase Inhibitors

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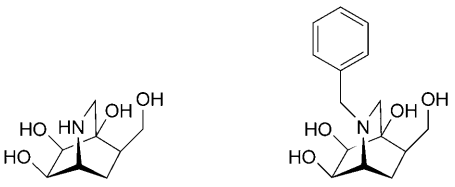
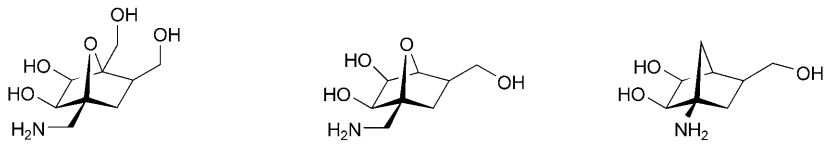
The racemic 7-oxanorbornanyl and norbornanyl aminoalcohols **3**, **4**, **42**, **45**, and **46** were synthesized and tested as snail β-mannosidase inhibitors. The amino tetraol **3** was obtained from the known sulfonyl acrylate **9** and furan **10**. Esterification provided **11** that underwent an intramolecular *Diels–Alder* reaction to the 7-oxanorbornene **12**. Reduction of **12** to **13**, desulfonylation, isopropylidenation, and *cis*-dihydroxylation gave **16**. A second isopropylidenation to **17**, followed by debenzylation and a *Mitsunobu–Gabriel* reaction provided **19** that was deprotected *via* **20** to **3**. *Diels–Alder* cycloaddition of furfuryl acetate and maleic anhydride to **21**, followed by alcoholysis of the anhydride, *cis*-dihydroxylation, isopropylidenation, and *Barton* decarboxylation gave the ester **25**. Deacetylation to **26** and a *Mitsunobu–Gabriel* reaction led to **27** that was transformed into the *N*-Boc analogue **29**, reduced to the alcohol **30**, and deprotected to **4**. The 1-aminonorbornane **5** was obtained from *Thiele*'s Acid **31**. *Diels–Alder* cycloaddition of the cyclopentadiene obtained by thermolysis of the diester **32**, methanolysis of the resulting anhydride **33**, dihydroxylation, isopropylidenation, *Barton* decarboxylation, and *Curtius* degradation led to the benzyl carbamate **39** that was reduced to the alcohol **40**, transformed into the *N*-Boc carbamate **41**, and deprotected to **5**. The alcohol **40** was also transformed into the benzylamine **42**, aniline **45**, and hydroxylamine **46**. Snail β-mannosidase was hardly inhibited by **3**, **4**, **42**, **45**, and **46**. Only the amino triol **5** proved a stronger inhibitor. The inhibition by **5** depends on the pH value (at pH 3.5: $K_i = 1900$ μM; at pH 4.5: $K_i = 340$ μM; at pH 5.5: $K_i = 110$ μM). The results illustrate the strong dependence of the inhibition by bicyclic mimics upon the precise geometry and orientation of the amino group as determined by the scaffold. It is in keeping with the hypothesis that the reactive conformation imposed by snail β-mannosidase is close to a $^{1,4}B/^{1}S_{3}$.

Introduction. – The design, synthesis, and study of glycosidase inhibitors continue to attract interest, fuelled by the potential of strong and selective glycosidase inhibitors to act as drugs (*e.g.*, against lysosomal storage disorders such as *Gaucher*'s disease [1], influenza [2], HIV [3], hepatitis B [4] and C [5], and diabetes mellitus II [6]), and their use as tools in the elucidation of the mechanism of action of glycosidases on the basis of structure–activity relations, kinetic studies, and information provided by the structure determination of enzyme–inhibitor complexes [7]. Transition-state analogues promise to be most useful. Their design is based upon existent information about the mechanism of action, and particularly about the transition state of the rate-determining step, while their study may contribute to a more detailed understanding of the mechanisms of action as summarised in several reviews [8][9]. Partial transition-state mimics may be thought of as being closer to a point of the reaction coordinate that either precedes, or follows the transition state of interest, and there are reasons to hypothesise that those preceding the rate-determining transition state of the hydrolysis by retaining β-glycosidases could be more selective. The enzymatic hydrolysis of β-D-glycosides involves a conformational change of the substrate to comply with the stereoelectronic requirement of a coplanar orientation of the scissile bond and a

doubly occupied, nonbonding orbital of the endocyclic O-atom ($n_{O(5)} - \sigma^*$) [10], and *Davies* and co-workers have postulated that all conformations (and among these $^{1,4}B$ and $^{1}S_3$ conformations) that comply with the stereoelectronic requirements are harnessed by different glycosidases [11]. We have already shown that the conformationally biased *manno*-configured isoquinuclidines **1** and **2** that mimic approximately a $^{1,4}B$ boat conformation are selective inhibitors of snail β-mannosidase [12]. While **1** is rather weak, the benzyl derivative **2** ($K_i = 1$ μM) is a strong and selective inhibitor. The *gluco*-configured analogues, however, are poor inhibitors of β-glucosidases [13], while the *N*-acetylglucosamine analogues are again strong, competitive inhibitors of bovine kidney and *Jack* bean hexosaminidases [14]. Considering the inhibition constants of *ca.* 10^{-16} μM for an ideal transition-state mimic that have been derived by *Wolfenden et al.* [15], these isoquinuclidines are still far from closely mimicking the transition state. While it may indeed not be possible to approach the transition state much more closely – on account of the lengthening of the scissile bond and the rehybridisation of the anomeric centre – it appears justified to search for inhibitors derived from scaffolds that mimic the reactive conformer more closely, particularly considering the selectivity of the inhibition displayed by the isoquinulidine-derived inhibitors.





Continuing the studies of bicyclic inhibitors[1]), we wished to modify the length of the bridge between C(1) and C(4), and to thus modulate the geometry of the boat-like shape of the inhibitor and the position of the substituents. We planned to synthesise inhibitors derived from bicyclo[2.2.1]heptanes, or their 7-oxa analogues, depending on the nature of the substituent at C(1), as 1-amino-7-oxabicyclo[2.2.1]heptanes will not be sufficiently stable. The cyclohexane ring of these inhibitors should be much closer to a $^{1,4}B$ conformation than the one of the above-mentioned isoquinuclidines.

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[1]) *Tanaka* and *Bennet* [16] synthesised 2,6-anhydro-1-deoxynojirimycin and evaluated it as glycosidase inhibitor to evidence the reactive $^{1,4}B$ conformation of the substrate. *Sinaÿ* and co-workers [17] synthesised derivatives of 1,4-anhydrogalactofuranose as inhibitors of UDP-galactose mutase to test the hypothesis of a 1,4-anhydrogalactose intermediate, and *Vogel* and co-workers [18] evaluated 7-azabicyclo[2.2.1]heptanes as inhibitors of a series of glycosidases to examine the effect of geometry and rigidity.

The *Diels–Alder* cycloadditon provides a favourable access to norbornenes and to 7-oxanorbornenes. Considering the well-known easy reversiblity of the *Diels–Alder* cycloaddition to furans, we first opted for an intramolecular *Diels–Alder* cycloaddition leading to the amino tetrol **3** (*cf. Scheme 1*). This introduces a $HOCH_2$ group corresponding to a C(4)−CH_2OH substituent of a (branched chain) mannopyranoside, with unclear consequences on the inhibition. For this reason, we planned to also prepare the amino triol **4** (*cf. Scheme 2*), a 1,4-anhydromannoheptulose derivative that is not encumbered by such a $HOCH_2$ group. Finally, considering the important and perhaps decisive position of the NH_2 substituent that is to interact with the catalytic acid of the mannosidase, we planned to also prepare the 1-aminonorbornane **5** (*cf. Scheme 3*).

Calculation of the conformation of the isoquinuclidine **2** and the norbornane **5**, and superposition[2]) of the cyclohexane moieties reveals that the cyclohexane ring of **5** adopts a boat-like shape, whilst the cyclohexane ring of the isoquinuclidine **2** adopts a conformation that is distorted towards a skew-boat (root-mean-square (rms) deviation 0.139 Å). The distance between the N-atoms amounts to 1.88 Å; the different position of the NH_2 groups is expected to affect their interaction with the catalytic acid. The secondary OH groups of the norbornane **5** corresponding to HO−C(2) and HO−C(3) of a β-D-mannopyranoside are at a slightly different position from those of the isoquinuclidine **2** (distance between the O-atoms 0.37 and 0.39 Å, resp.). The position of the C-atoms of the $HOCH_2$ groups differs by 0.42 Å.

Superposition of the cyclohexane moieties of the isoquinuclidine **2** and the 7-oxanorbornane **4** shows an even greater distance between the two NH_2 groups (atomic distance 3.15 Å), while the rms deviation remains almost unchanged (0.168 Å), in agreement with the superposition of the cyclohexane rings of **5** and **2** (rms deviation 0.035 Å).

Synthesis. – *Synthesis of the 7-Oxanorbornane* **3**. Epoxidation of allyl phenyl sulfone (**6**) by *m*-CPBA gave the oxirane **7** which was converted to the allyl alcohol **8** (*Scheme 1*). *Jones* oxidation [20] gave the sulfonylated acrylic acid **9** in an overall yield of 59%. The known benzyl ether **10** was obtained from furfuryl alcohol in three steps and in a yield of 46% according to the procedure of *Achmatowicz* and *Burzynska* [21]. Esterification of the acid **9** with the alcohol **10** under *Mukaiyama* conditions [22] afforded the ester **11** (85%), provided that Et_3N was slowly added with a syringe pump over a period of 1 h, complete immediate addition of Et_3N resulting in the formation of a black residue. The ester **11** in solution underwent an intramolecular *Diels–Alder* reaction already at room temperature, and more rapidly at 40° [23]. The solvent strongly affected the ratio of product and starting material, benzene leading to the least favourable ratio (23:77) and MeCN to the most favourable one (59:41), while in kinetically controlled *Diels–Alder* reactions the solvent has little influence on product distribution [24]. The 7-oxanorbornane **12** resulting from the cycloaddition of **11** in MeCN was separated from **11** by trituration with cyclohexane/AcOEt and isolated in a yield of 64%. Since **12** in solution was transformed within a few hours at room temperature into a mixture of product **12** and starting material **11**, it was rapidly reduced with DIBAL

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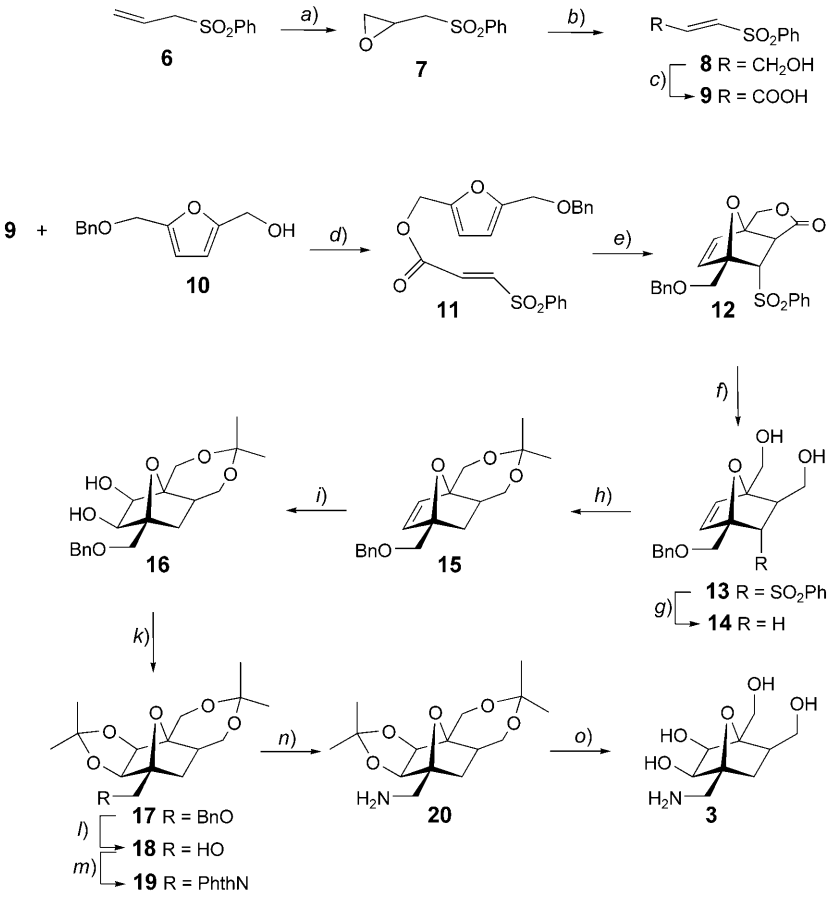
[2]) Superposition was carried out using Macromodel V. 6.0 [19]. The structures were minimized with the PRCG algorithm and using MM3* as the force field.

Scheme 1



a) *meta*-Chloroperbenzoic acid (*m*-CPBA), $ClCH_2CH_2Cl$, 85°; 88%. *b*) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), CH_2Cl_2, −10°; 89%. *c*) CrO_3, H_2SO_4, H_2O, acetone; 75%. *d*) 2-Chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2; 85%. *e*) MeCN, 40°; 64%. *f*) Diisobutylaluminum hydride (DIBAL), toluene; quant. *g*) NaHg, Na_2HPO_4, MeOH; 69%. *h*) 2,2-Dimethoxypropane, camphorsulfonic acid (CSA), acetone; 88%. *i*) OsO_4, Me_3NO, pyridine, H_2O, *t*-BuOH; 72%. *k*) 2,2-Dimethoxypropane, CSA, acetone; 97%. *l*) Pd/C, H_2 (6 bar), AcOEt; 90%. *m*) Phthalimide (PhthNH), Ph_3P, diisopropyl azodicarboxylate (DIAD), THF; 93%. *n*) $NH_2NH_2 \cdot H_2O$, EtOH; 81%. *o*) 2.5N aq. HCl, 95%.

in toluene to the diol **13** (>98%) which was desulfonylated to **14** (69%) with 2% NaHg in the presence of Na_2HPO_4 [25]. Isopropylidenation of **14** yielded 88% of the acetal **15**. Initial attempts to obtain the *cis*-diol **16** by treating **15** with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) in acetone [26] led to several side-products which were not characterized, while dihydroxylation with OsO_4 and trimethylamine *N*-oxide in *t*-BuOH/H_2O containing traces of pyridine [27] led exclusively to the *exo-cis*-diol **16** (72%) that was isopropylidenated to the tetracyclic acetal **17** (97%). Hydrogenolytic debenzylation of **17** in the presence of 10% Pd/C at 6 bar H_2 in AcOEt led to the alcohol **18** (90%). Replacement of the primary OH group by phthalimide under *Mitsunobu* con-

ditions [28] afforded **19** (93%), and hydrazinolysis provided the amine **20** (81%) which was further deprotected with 2.5N HCl to give **3** in 95% yield.

The formation of the lactone **12** is evidenced by a shift of the C=O IR band from 1782 cm^{-1} for **11** to 1731 cm^{-1} for **12**, and the replacement of four ^{1}H-NMR signals of **11** at 6.30, 6.40 ($J=3.4$), 6.84, and 7.76 ppm ($J=15.3$ Hz) by two signals at 6.65 and 6.73 ppm ($J=5.9$ Hz), evidencing the (*Z*)-configuration of the remaining alkenyl group. The *Diels–Alder* reaction is also evidenced by the *d* of the H-atom in α-position to the SO_2 group of **12** and **13**. Its chemical shift (4.25 and 3.58 ppm, resp.) shows that the corresponding H-atom is not directly bound to an alkenyl group. The assignment is supported by the spectrum of the product **14** of desulfonylation where this *d* is replaced by *dd*s at 1.60 and 1.22 ppm.

That the *cis*-dihydroxylation of **15** led to the *exo*-oriented *cis*-diol is shown by $J(10,11)=5.9$ and 6.0 Hz; the expected $J(H_{exo},H_{exo})$ of the *endo*-diol is 9–10 Hz [29].

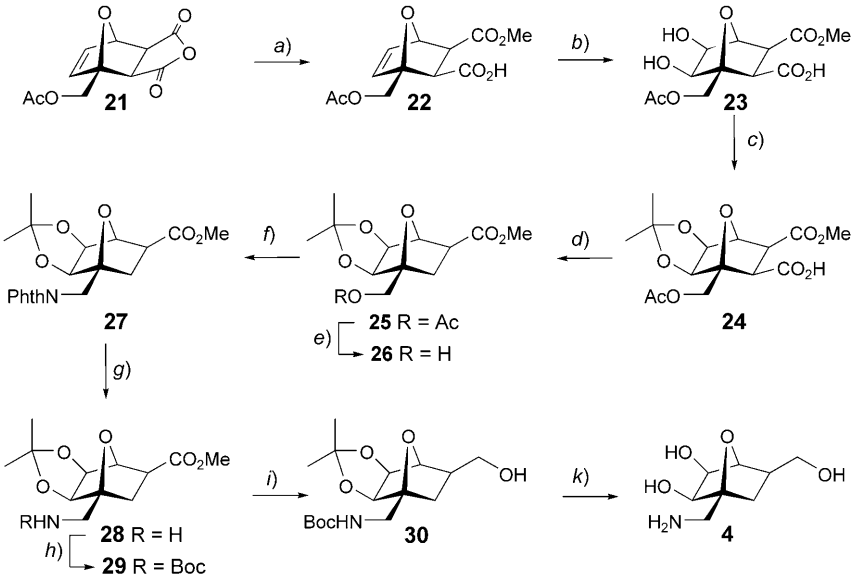
Synthesis of the 7-Oxanorbornane **4**. The known product **21** [30] of the thermodynamically controlled *Diels–Alder* cycloaddition (*e.g.*, [31]) of furfuryl acetate and maleic anhydride (34%; *Scheme 2*) was subjected to methanolysis with MeONa in MeOH. The desired mono-ester **22** was isolated from the mixture of regioisomers in a yield of 41% by crystallisation from AcOEt. It was dihydroxylated with OsO_4 and NMO [26] to provide the highly polar dihydroxy acid **23** that was isolated as a spontaneously crystallising solid by continuous extraction with AcOEt (72%). As recrystallisation of **23** led to considerable loss of material, we isopropylidenated crude **23** to **24** (75%). The corresponding acid chloride was esterified with *N*-hydroxypyridine-2-thione sodium salt (sodium omadine [32]) in THF to provide the *O*-acyl thiohydroxamate that was required for the *Barton* decarboxylation [33]. Treatment of the thiohydroxamate with Bu_3SnH and AIBN in boiling benzene proved most advantageous. However, the decarboxylation product **25** contained considerable amounts of tin residues even after purification. They were best removed after deacetylation of **25** to the alcohol **26** that was obtained in pure form in a yield of 62% from **24**. Conversion of the alcohol **26** to the phthalimide **27** (94%) [28], followed by hydrazinolysis in EtOH, led to the amine **28** (76%). It was transformed into the *N*-Boc-protected amino ester **29** (91%) and reduced with $LiBH_4$ [34] to the alcohol **30** (82%), which was fully deprotected to **4** (74%) by treatment with 2N aq. HCl.

Formation of the anhydride **21** is evidenced by a *d* at 6.47 ppm ($J=5.9$ Hz) and a *dd* at 6.63 ppm ($J=5.6$, 1.9 Hz), corresponding to the olefinically bonded H–C(8) and H–C(9). The *exo*-orientation of the anhydride moiety is supported by $J(2,6)=6.9$ Hz [29], and confirmed by the absence of a coupling between H–C(6) and H–C(7). It was only possible to establish the constitution of the product **22** of methanolysis after its decarboxylation to **25** and transformation to **26**. The decarboxylation product of the isomeric monoacid is expected to display a coupling between H_{exo}–C(8) and H–C(7); no such coupling was observed for **25**. Dihydroxylation of **22** led exclusively to the desired *exo*-oriented *cis*-diol **23**. Its configuration was deduced from the absence of a finite coupling between H–C(4) and H–C(5), and confirmed by crystal structure analysis[3]) of **26** (*Fig. 1*).

Synthesis of the 1-Aminonorbornanes **5**, **42**, **45**, *and* **46**. *Thiele*'s acid **31**, first reported in 1901 [35], appeared to be an advantageous starting material for the synthesis of the title compounds (*Scheme 3*). For its preparation, we used BuLi in Et_2O rather

[3]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-203882. 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).

Scheme 2



a) MeONa, MeOH; 41%. *b*) OsO_4, *N*-methylmorpholine *N*-oxide monohydrate (NMO), acetone/H_2O 5:1; 72%. *c*) 2,2-Dimethoxypropane, *Amberlyst 15* (H^+ form), acetone; 75%. *d*) $(COCl)_2$, DMF, CH_2Cl_2; 1-hydroxypyridine-2-thione sodium salt, THF; Bu_3SnH, 2,2′-azobis[isobutyronitrile] (AIBN), PhH. *e*) MeONa, MeOH; 62%. *f*) PhthNH, PPh_3, DIAD; 94%. *g*) $NH_2NH_2 \cdot H_2O$, EtOH; 76%. *h*) Boc_2O, CH_2Cl_2; 91%. *i*) $LiBH_4$, THF; 82%. *k*) 2N aq. HCl; 74%.

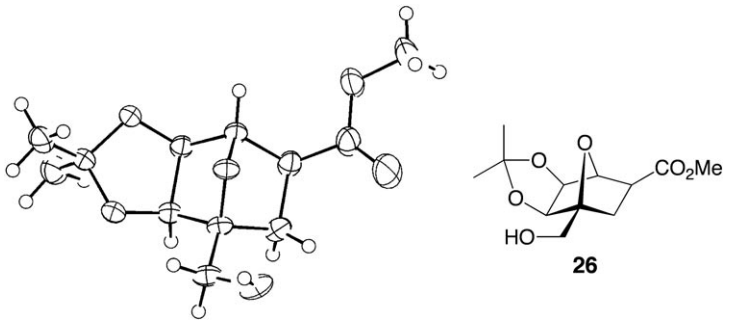


Fig. 1. *ORTEP Representation of the crystal structure of the 7-oxanorbornane* **26**

than Na in decalin [36][37]. This simplified the preparation of the diacids **31** that were obtained (crude) in 75% yield. The corresponding di(*tert*-butyl) esters **32** were obtained (88%) by treating the diacids with oxalyl chloride and then with *t*-BuOK in Et_2O. *Thiele*'s acids **31** and the diesters **32** are mixtures of isomers [37][38]. Considering that the esters **32** were thermolysed in the next step, we did not separate the isomers. The resulting cyclopentadiene was collected at $-78°$ and treated with maleic anhydride in Et_2O [39] whereupon the *endo*-anhydride **33** precipitated. Recrystallisation provided

48% of **33**. Cycloaddition of the monomer to methyl acrylate led to an inseparable mixture; presumably the cyclopentadiene isomerized prior to its reaction with methyl acrylate. The *endo*-anhydride **33** was transformed similarly to the 7-oxanorbornene derived *exo*-anhydride **21**. Methanolysis led to a 1:1 mixture of regioisomeric monoesters that could not be separated by crystallisation. Dihydroxylation of the monoesters [26] followed by isopropylidenation of the resulting *cis*-diols led to a mixture of regioisomers which were readily separated by trituration and crystallisation to give **34** in a yield of 32% from **4** besides a 4:1 mixture **35**/**34** of the regioisomeric esters (39%). Unfortunately, attempts to transform the undesired isomer **35** into the corresponding anhydride followed by methanolysis failed. Decarboxylation of **34** according to *Barton et al.* [33] using *t*-BuSH in PhMe instead of Bu_3SnH and AIBN in PhH gave the *endo*-monoester **36** (82%) that was epimerized to the *exo*-isomer **37** by treatment with MeONa in MeOH (86%). The (*tert*-butoxy)carbonyl (Boc) group was not affected. Cleavage of the *tert*-butyl ester with Me_3SiOTf and Et_3N [40] gave the carboxylic acid **38** (89%). Its *Curtius* degradation by treatment with diphenyl phosphorazidate and Et_3N in PhMe at 80–110° [41] followed by intercepting the isocyanate with benzyl alcohol (BnOH) in the presence of CuCl [42] yielded 88% of the carbamate **39**. The addition of BnOH to the isocyanate was sluggish, even in the presence of CuCl, and the addition of *t*-BnOH failed altogether, illustrating the steric hindrance of the isocyanate.

The ester **39** was reduced with $LiBH_4$ [34] to the alcohol **40** (92%). Considering that traces of Pd compounds may strongly inhibit glycosidases [43], we exchanged the *N*-benzyloxycarbonyl (Z) group against the Boc group by transfer hydrogenolysis (cyclohexa-1,4-diene in the presence of Pd/C) followed by treatment of the resulting amine with Boc_2O in EtOH [44] to provide 84% of **41**. This carbamate was fully deprotected with 2N aq. HCl to give the amino triol **5** in 85% yield.

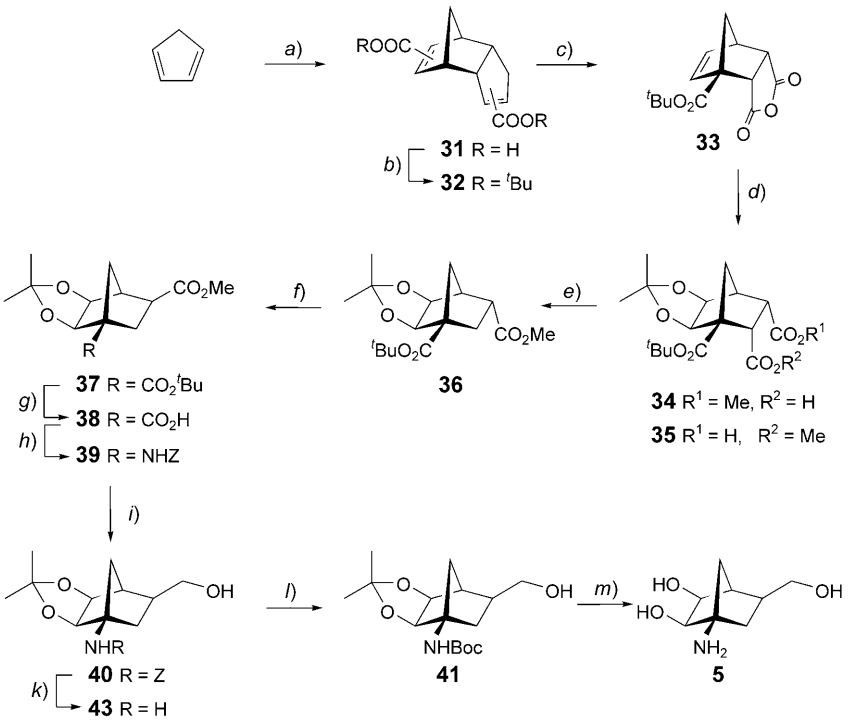
To prepare the benzylamino triol **42**, we deprotected **40** by transfer hydrogenolysis, treated the crude amine **43** with PhCHO in PhMe, and reduced the resulting imine ($NaBH_4$ in MeOH/THF) to **44** (89%; *Schemes 3* and *4*). Deprotection of **44** with 2N aq. HCl and THF gave **42** (93%) that was characterised as its hydrochloride.

In view of the essential interaction of the amino group with the catalytic acid and the role of the p*K* value of the inhibitor [9][12][45], we also prepared two less basic amines, *viz*. the aniline **45** and the hydroxylamine hydrochloride **46**.

For the preparation of the aniline, we protected the primary OH group of **40** by methoxymethylation to **47** (98%), followed by hydrogenolytic decarbamoylation. The intermediate amine was not isolated, but phenylated *in situ* with PhBr in the presence of $[Pd_2(dba)_3]$, BINAP, and *t*-BuOK [46] to yield 75% of the protected aniline **48** (75%) that was deprotected in the usual way by hydrolysis with 2N aq. HCl in MeOH to **45** (80%).

For the synthesis of **46**, we treated the crude amine **43** with anisaldehyde and oxidised the resulting imine with *m*-CPBA in $ClCH_2CH_2Cl$ at 0° to provide a *ca.* 3:1 mixture of the diastereoisomeric oxaziridines **49** [47] (78%). They were not separated, but isomerised [47][48] at 200° to the (*Z*)-nitrone **50** (63%) which was hydrolysed with 2N aq. HCl to yield 71% of **46**.

Scheme 3



a) 1.6M BuLi in hexane, Et_2O; CO_2; 75%. *b*) $(COCl)_2$, cat. DMF, CH_2Cl_2; *t*-BuOK, Et_2O; 88%. *c*) 180°; maleic anhydride, Et_2O; 48%. *d*) MeONa, MeOH; OsO_4, NMO, acetone/H_2O 5:1; 2,2-dimethoxypropane, *Amberlyst 15* (H^+ form), acetone; **34** (32%) and **35**/**34** 4:1 (39%). *e*) $(COCl)_2$, DMF, CH_2Cl_2; 1-hydroxypyridine-2-thione sodium salt, 4-(dimethylamino)pyridine (DMAP), *t*-BuSH, PhMe; 82%. *f*) MeONa, MeOH; 86%. *g*) Me_3SiOTf, Et_3N, CH_2Cl_2; 89%. *h*) Diphenylphosphoryl azide, Et_3N, BnOH, CuCl, PhMe; 88%. *i*) $LiBH_4$, THF; 92%. *k*) Pd/C, H_2, EtOH; 75%. *l*) 1. Pd/C, cyclohexa-1,4-diene; 2. Boc_2O, EtOH; 84%. *m*) 2N aq. HCl; 85%.

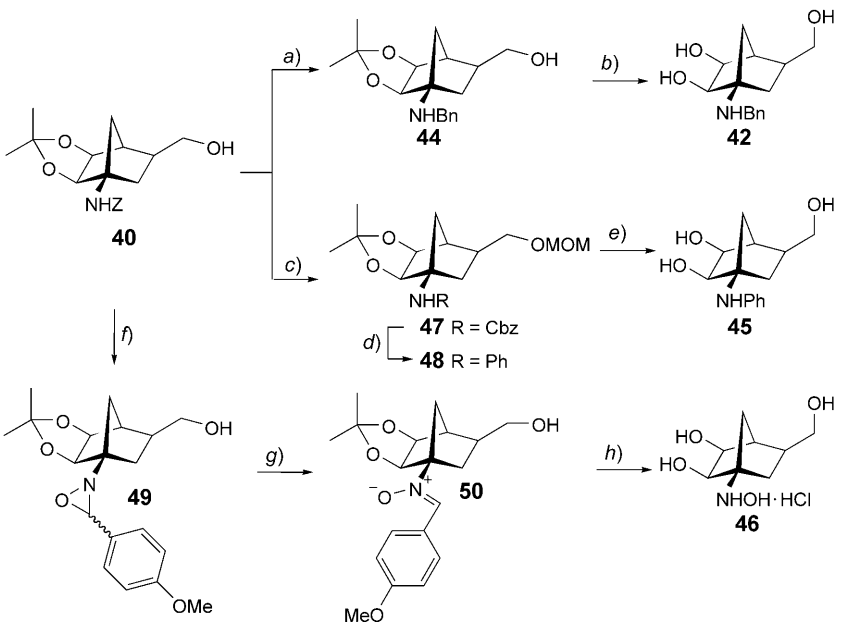
The *endo*-orientation of the anhydride moiety of **33** was evidenced by the typical $J(6,7)$ value of 4.7 Hz [29]. The regioselectivity of the anhydride opening could only be determined after the *Barton* decarboxylation. It is evidenced by $J(8,9_{exo})=11.2$, $J(8,9_{endo})=5.8$, and $J(7,8)=4.7$ Hz of the resulting monoester **36**. As expected, H–C(7) and H–C(8) of the epimerisation product **37** do not couple with each other, similarly as observed for the 7-oxanorbornane **4**. The structure of **37** was established by crystal structure analysis[4]) (*Fig. 2*). The transformation of the ester **38** to the carbamate **39** is evidenced by the $^{13}C(1)$ signals; the one of **38** resonating at 54.63 ppm, and the one of **39** at 62.50 ppm. A *s* at 155.51 ppm further evidences the carbamoyl group.

The structure of the nitrone **50** is evidenced by a new strong IR band at 1604 cm^{-1}, a ^{13}C *d* at 138.2 ppm for the C=N bond, and a corresponding ^1H *s* at 7.73 ppm.

Inhibition Studies. – The results of the inhibition study of snail β-mannosidase by the racemic 7-oxanorbornanes **3** and **4**, and the racemic norbornanes **5**, **42**, **45**, and

[4]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-203883. 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).

Scheme 4

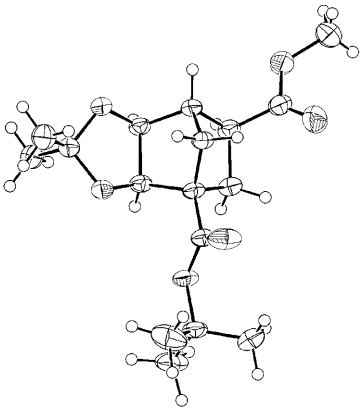


a) Pd/C, cyclohexa-1,4-diene, EtOH, 60°; PhCHO, PhMe, $-H_2O$; $NaBH_4$, MeOH/THF 1:1; 89%. *b*) 2N aq. HCl, THF; 93%. *c*) Methoxymethyl chloride (MOMCl), Et_3N, Bu_4NI, THF; 98%. *d*) Pd/C, H_2, EtOH; 15 mol-% 2,2′-bis(diphenylphosphonyl)-1,1′-binaphthalene (BINAP), 8 mol-% $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone), PhBr, PhMe, 110°; 75%. *e*) 2N aq. HCl, MeOH; 80%. *f*) Pd/C, H_2, EtOH; *p*-MeO–C_6H_4CHO, $MgSO_4$, CH_2Cl_2; *m*-CPBA, $ClCH_2CH_2Cl$; 78%. *g*) 200°; 63%. *h*) 2N aq. HCl; 71%.

46 at pH 3.5, 4.5, and 5.5 are summarised in the *Table*. At pH 4.5, the 7-oxanorbornanes **3** and **4** inhibited snail β-mannosidase very weakly (IC_{50} in the mM range). A similarly weak inhibition was displayed by the *N*-benzylnorbornane **42** ($IC_{50} > 1$ mM). No inhibition was observed for the *N*-phenylnorbornane **45** and the hydroxylamine **46** ($IC_{50} > 10$ mM). The only inhibitor with a (pH-dependent) inhibition constant in the submillimolar range is the norbornane **5**.

The poor inhibition by the 7-oxanorbornanes **3** and **4** suggests that the NH_2 group is too far removed from the catalytic acid. That **3** is a somewhat worse inhibitor than **4** suggests (weak) destabilising interactions due to the additional $HOCH_2$ group.

Similarly as observed for the isoquinuclidine-derived inhibitors [12], the inhibition strength of **5** depends considerably on the pH value. At pH 3.5, **5** inhibited snail β-mannosidase poorly ($K_i = 1900$ μM, mixed type, $\alpha = 2.7$). At pH 4.5, K_i was 340 μM (mixed type, $\alpha = 1.1$), and at pH 5.5, K_i was 110 μM (mixed type, $\alpha = 3.1$). This pH dependence suggests that only the free amine **5** binds to the active site of the enzyme. With a pK value of 8.6, **5** is mostly protonated at the pH optimum of the mannosidase, and thus not active as inhibitor. The expected K_i value of *ca.* 50 μM at pH 5.5 for the enantiomer corresponding to D-mannose [12] **5** suggests that the pK value of the amine and its proper location are the critical parameters for the inhibition by such bicyclic amines. That both location and orientation of the NH_2 group play a role is evidenced by the



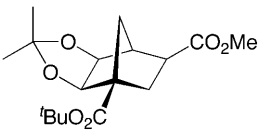


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Fig. 2. *ORTEP Representation of the crystal structure of the norbornane* **37**

Table 1. *Inhibition of β-Mannosidase from Snail* [μM] *by the 7-Oxanorbornanes* **3** *and* **4**, *and the Norbornanes* **5**, **42**, **45**, *and* **46** *at 25°*

Inhibitor (pK_{HA})	pH 3.5	pH 4.5	pH 5.5
3 (8.5)	[a])	1800[b])	[a])
4 (8.7)	[a])	1200[b])	[a])
5 (8.6)	1900[c]) ($\alpha=2.7$)	340[c]) ($\alpha=1.1$)	110[c]) ($\alpha=3.1$)
42 (8.2)	–	1400[b])	–
45 (4.7)	–	[a])	–
46 (4.9)	–	[a])	–

[a]) $IC_{50} > 10$ mM. [b]) IC_{50}. [c]) K_i.

observation that – in contradistinction to the *N*-Bn isoquinuclidine **2** – the *N*-Bn norbornane **42** is a very poor inhibitor of snail *β*-mannosidase, and this in spite of the otherwise well-established favourable effect of hydrophobic aglycon mimics on the inhibition [12][49]. The poor inhibition by the less basic aniline **45** and hydroxylamine **46** is in keeping with the hypothesis of an unfavourable location and orientation of the NH_2 group by the norbornane scaffold, considering that the loss of activity did not depend on the polar nature of the N-substituent.

Superposition of C(2)–C(5) and C(5)-*O* of the −1 unit of the octa-*N*-acetylchitooctaose in complex with the *Serratia marcescens* ChiA chitobiase mutant E315Q [50] where the −1 unit adopts a $^{1,4}B$ conformation and of C(2 to 6) of the norbornane **5** shows that the glycosidic C(1)-*O* of the −1 unit is rather remote from the NH_2 group of **5** (N···O distance 1.19 Å). However, superposition of the −1 unit (except for C(1)) in a half-chair conformation with C(2 to 6) of **5** shows that the distance between the anomeric O- and the N-atom is significantly smaller (N···O distance 0.57 Å). The poor inhibition by the oxanorbornanes and norbornanes is thus in keeping with the postulate that the reactive conformation of the snail *β*-mannosidase substrate is a boat or twist-boat ($^{1,4}B$ or $^{1}S_3$).

We thank Dr. *B. Schweizer* for the determination of the X-ray crystal structures, *M. Schneider* and *D. Manser* for the pK_{HA} determinations, Dr. *B. Bernet* for checking the *Exper. Part*, and Dr. *L. Remen* for advice during the synthesis of **3** and **6**–**12**.

Experimental Part

General. Solvents were distilled before use: THF and toluene from Na/benzophenone, and CH_2Cl_2 and MeOH from CaH_2. Reactions were run under Ar. Qual. TLC: precoated silica-gel plates (*Macherey-Nagel Alugram Sil G/UV$_{254}$*); detection by heating with 'mostain' (400 ml of 10% aq. H_2SO_4, 20 g of $(NH_4)_6Mo_7O_{24}\cdot H_2O$, 0.4 g of $Ce(SO_4)_2$). Flash chromatography (FC): silica gel *Fluka 60* (0.04–0.063 mm). FT-IR: KBr or 2% $CHCl_3$ soln. β-Mannosidase (3.2.1.25, M-9400 as a suspension in acetone, from snail), and 4-nitrophenyl β-D-mannopyranoside were purchased from *Sigma* and used without any further purification. Normal workup implies pouring the reaction mixture into a sat. aq. $NaHCO_3$ soln., extracting into the mentioned org. solvent, if necessary washing with the indicated sat. aq. soln., drying of the org. layer ($MgSO_4$), filtration, and evaporation of the volatiles.

2-[(Phenylsulfonyl)methyl]oxirane (**7**). A soln. of allyl phenyl sulfone (11.9 g, 65 mmol) in $ClCH_2CH_2Cl$ (50 ml) was treated with *m*-CPBA (25 g, 130 mmol), warmed to 85°, stirred for 150 min, cooled to 0°, treated with 0.2N $Na_2S_2O_3$ (100 ml), and vigorously stirred for 5 min. The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2 (3×50 ml). The combined org. layers were washed with sat. $NaHCO_3$ soln. (100 ml), and the aq. layer was extracted with CH_2Cl_2 (3×50 ml). The combined org. layers were dried ($MgSO_4$). Evaporation and FC (hexane/Et_2O 1:1 → 0:1) gave **7** (11.4 g, 88%). Colourless oil. R_f (hexane/Et_2O 1:1) 0.61. The spectral data of **7** are identical to those in [51][52].

3-(Phenylsulfonyl)prop-2-en-1-ol (**8**). A soln. of **7** (11 g, 82.5 mmol) in CH_2Cl_2 (100 ml) was cooled to −10°, treated with a soln. of DBU (12.55 g, 82.5 mmol) in CH_2Cl_2 (50 ml) over a period of 180 min, warmed to 0°, and treated with 2.5N HCl (150 ml). The org. layer was separated, and the aq. layer was extracted with $CHCl_3$ (5×100 ml). The combined org. layers were dried ($MgSO_4$). Evaporation gave crude **8** (9.9 g, 89%), which was used for the next reaction without further purification. White solid. R_f (hexane/AcOEt 1:4) 0.53. The spectral data of **8** are identical to those in [51].

*(*E*)-3-(Phenylsulfonyl)prop-2-enoic Acid* (**9**). At 23°, a stirred soln. of **8** (5 g, 25.5 mmol) in acetone (200 ml) was treated dropwise with a soln. of CrO_3 (3.78 g, 37.8 mmol) in H_2SO_4 (4.4 ml) and H_2O (12.8 ml) until the colour of the mixture remained orange over a period of 15 min. i-PrOH was added until the colour turned green. After filtration through a short pad of *Celite* and evaporation, the residue was crystallized from toluene (250 ml) to give **9** (4.1 g, 75%). White solid. M.p. 132°. IR ($CHCl_3$): 3700–2500*m* (br.), 1724*s*, 1448*m*, 1325*s*, 1152*s*, 1085*m*, 1038*w*, 965*w*, 822*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.83 (*d*, *J* = 15.3, H–C(3)); 7.41 (*d*, *J* = 15.3, H–C(2)); 7.50–8.00 (*m*, 5 arom. H); 8.80–9.80 (br. *s*, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): 128.70–130.00 (5 arom. CH); 134.91 (C(2)); 138.29 (1 arom. C); 145.64 (C(3)); 168.30 (C=O). EI-MS: 212 (M^+). Anal. calc. for $C_9H_8O_4S$ (212.23): C 50.94, H 3.80, O 30.16, S 15.11; found: C 51.10, H 3.92, O 30.09, S 15.25.

*{5-[(Benzyloxy)methyl]furan-2-yl}methyl (*E*)-3-(Phenylsulfonyl)prop-2-enoate* (**11**). A suspension of **9** (2.1 g, 9.4 mmol), **10** (2 g, 9.4 mmol) and 2-chloro-*N*-methylpyridinium iodide (2.88 g, 11.3 mmol) in CH_2Cl_2 (210 ml) was warmed to 40°, treated with Et_3N (2.28 g, 22.6 mmol) over a period of 60 min (syringe pump), and cooled to 23°. Normal workup (CH_2Cl_2/NH_4Cl) and FC (cyclohexane/AcOEt 4:1 → 3:1) gave **11** (3.3 g, 85%). Pale yellow oil. R_f (cyclohexane/AcOEt 2:1) 0.60. IR ($CHCl_3$): 3067*w*, 3034*m*, 2862*w*, 1782*w*, 1731*s*, 1586*w*, 1496*w*, 1448*m*, 1326*s*, 1310*m*, 1295*s*, 1165*s*, 1153*s*, 1085*s*, 1070*m*, 1024*m*, 1008*m*, 963*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.46, 4.56 (2*s*, CH_2–C(5′), PhCH_2); 5.15 (*s*, CH_2–C(2′)); 6.30, 6.40 (2*d*, *J* = 3.4, H–C(3′), H–C(4′)); 6.84 (*d*, *J* = 15.3, H–C(3)); 7.76 (*d*, *J* = 15.3, H–C(2)); 7.72–7.79 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 59.49 (CH_2–C(2′)); 64.03 (CH_2–C(5′)); 72.42 (Ph*C*H_2); 110.56, 112.60 (C(3′), C(4′)); 128.12–130.67 (10 C); 134.7 (C(2)); 137.94, 138.63 (2 arom. C); 144.08 (C(3)); 148.71, 153.39 (C(2′), C(5′)); 163.39 (C=O); Anal. calc. for $C_{22}H_{20}O_6S$ (412.46): C 64.06, H 4.89, O 23.27, S 7.77; found: C 64.13, H 5.18, O 23.20, S 7.54.

*(±)-(1*RS*,5*SR*,6*SR*,7*RS*)-7-[(Benzyloxy)methyl]-6-(phenylsulfonyl)-3,10-dioxatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one* (**12**). A soln. of **11** (5.4 g, 13.1 mmol) in MeCN (70 ml) was kept at 40° for 40 h and evaporated. The residue was triturated at 23° with cyclohexane/AcOEt 1:1, washed with cyclohexane, and filtered to yield **12** as solid (2.6 g). The filtrate and washings were evaporated. The residue was dissolved in MeCN, kept at 40° for 40 h, evaporated, triturated, and washed with cyclohexane to give further **12** (0.88 g, 64% overall). White solid. R_f (cyclohexane/AcOEt 3:1) 0.10. M.p. 132°. IR ($CHCl_3$): 3034*w*, 1782*s*, 1448*w*, 1320*s*, 1153*s*, 1085*m*, 1008*m*, 907*w*, 866*w*, 837*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.20 (*d*, *J* = 4.0, H–C(5)); 4.12 (*d*, *J* = 11.5), 4.21 (*d*, *J* = 11.8) (CH_2–C(7)); 4.25 (*d*, *J* = 3.7, H–C(6)); 4.58, 4.63 (2*d*, *J* = 11.8, 2 H–C(2)); 4.67 (*d*, *J* = 11.2), 4.76 (*d*,

J = 11.5) ($PhCH_2$); 6.65, 6.73 (2*d*, J = 5.9, H–C(8), H–C(9)); 7.25–7.85 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.99 (C(5)); 65.07 (C(6)); 67.64, 69.16 (CH_2–C(7), C(2)); 73.93 (Ph*C*H_2); 93.31, 94.02 (C(1), C(7)); 128.08–129.16, 128.75, 129.80 (9 C); 134.54, 134.81, 136.22 (3 C); 137.69, 139.85 (C(8), C(9)); 172.59 (C=O). MALDI-MS: 435 ($[M+Na]^+$). Anal. calc. for $C_{22}H_{20}O_6S$ (412.46): C 64.06, H 4.89, O 23.27, S 7.77; found: C 64.19, H 5.03, O 23.02, S 7.91.

*(±)-(1*RS*,4*RS*,5*SR*,6*RS*)-{4-[(Benzyloxy)methyl]-6-(hydroxymethyl)-5-(phenylsulfonyl)-7-oxabicyclo-[2.2.1]hept-2-en-1-yl}methanol* (**13**). Neat **13** (1 g, 2.4 mmol) was treated with 1M DIBAL in toluene (10 ml) at 0°, stirred for 15 min, warmed to 23°, stirred for 45 min, cooled to 0°, treated with sat. aq. NH_4Cl soln. (50 ml) and $CHCl_3$ (50 ml), acidified to pH 1–2 with 2.5N HCl, and stirred at 23° for 2 h. The org. layer was separated, and the aq. layer was extracted with $CHCl_3$ (5 × 50 ml). The combined org. layers were dried ($MgSO_4$). Evaporation of the solvent gave crude **13** (1 g, 99%), which was directly used for the next reaction. A small sample was purified by HPLC. White solid. R_f (AcOEt) 0.40. M.p. 113°. IR ($CHCl_3$): 3479*w* (br.), 3006*w*, 2932*w*, 2875*w*, 1585*w*, 1447*m*, 1307*m*, 1150*s*, 1086*s*, 859*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.45 (*ddd*, J = 8.7, 4.7, 4.0, H–C(6)); 3.00–3.40 (2 br. *s*, 2 OH); 3.45 (*dd*, J = 11.1, 3.9, CH–C(6); 3.50 (*dd*, J = 11.1, 8.8, CH′–C(6)); 3.58 (*d*, J = 4.9, H–C(5)); 3.88 (*d*, J = 11.4), 3.95 (*d*, J = 11.5) (CH_2–C(1)); 3.96, 4.03 (2*d*, J = 12.4, CH_2–C(4)); 4.47 (*s*, PhCH_2); 6.35, 6.57 (2*d*, J = 5.7, H–C(2), H–C(3)); 7.20–7.90 (*m*, 10 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC.GRASP spectrum): 48.32 (*d*, C(6)); 60.33 (*t*, *C*H_2–C(1); 62.04 (*t*, *C*H_2–C(6)); 66.28 (*d*, C(5)); 67.83 (*t*, *C*H_2–C(4)); 73.68 (*t*, Ph*C*H_2); 89.94, 91.15 (2*s*, C(1), C(4)); 133.89 (*d*, C(3)); 138.95 (*d*, C(2)); 127.78, 127.81, 128.19, 128.42, 129.41 (5*d*); 137.58, 139.66 (2*s*). MALDI-MS: 439 ($[M+Na]^+$).

*(±)-(1*RS*,4*RS*,6*RS*)-{4-[(Benzyloxy)methyl]-6-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-en-1-yl}methanol* (**14**). A vigorously stirred suspension of **13** (1.6 g, 3.88 mmol) and Na_2HPO_4 (4.5 g, 37 mmol) in MeOH (130 ml) was treated at 23° with NaHg 2 : 98 (15 g), stirred for 1 h, treated again with NaHg 2 : 98 (5 g), stirred for 20 min, and filtered through a short pad of *Celite*. Normal workup ($CHCl_3$/NH_4Cl) and FC (cyclohexane/AcOEt 3 : 1 → 1 : 1) gave **14** (740 mg, 69%). Colourless oil. R_f (AcOEt) 0.28. IR ($CHCl_3$): 3604*w*, 3440*w*, 1601*w*, 1453*m*, 1357*w*, 1333*w*, 1206*s*, 1095*s*, 1042*s*, 878*w*, 795*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.22 (*dd*, J = 11.4, 3.9, H_{exo}–C(5)); 1.60 (*dd*, J = 11.4, 8.2, H_{endo}–C(5)); 2.03 (*ddt*, J = 9.6, 8.1, 4.0, H–C(6)); 2.90, 3.29 (2 br. *s*, 2 OH); 3.69 (*dd*, J = 10.8, 9.6, CH–C(6)); 3.74 (*dd*, J = 10.8, 4.1, CH′–C(6)); 3.80, 3.86 (2*d*, J = 11.0, CH_2–C(1)); 4.05, 4.11 (2*d*, J = 12.2, CH_2–C(4)); 4.60, 4.70 (2*d*, J = 12.3, PhCH_2); 6.29, 6.38 (2*d*, J = 5.7, H–C(2), H–C(3)); 7.25–7.46 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC.GRASP spectrum): 32.94 (*t*, C(5)); 42.88 (*d*, C(6)); 61.20 (*t*, *C*H_2–C(1)); 63.84 (*t*, *C*H_2–C(6)); 69.58 (*t*, *C*H_2–C(4)); 73.63 (*t*, Ph*C*H_2); 88.26, 90.38 (2*s*, C(1), C(4)); 127.74 (*d*); 127.79 (2*d*); 128.43 (2*d*); 136.68, 137.31 (2*d*, C(2), C(3)); 138.00 (*s*). MALDI-MS: 299 ($[M+Na]^+$). Anal. calc. for $C_{16}H_{20}O_4$ (276.33): C 69.55, H 7.29; found: C 69.60, H 7.33.

*(±)-(1*RS*,7*RS*,9*RS*)-9-[(Benzyloxy)methyl]-4,4-dimethyl-3,5,12-trioxatricyclo[5.4.0.1^{1,9}]dodec-10-ene* (**15**). A soln. of **14** (1.8 g, 6.5 mmol), CSA (72 mg, 0.28 mmol) and 2,2-dimethoxypropane (1.3 g, 12.5 mmol) in acetone (45 ml) was stirred at 23° for 3 h. Normal workup (CH_2Cl_2/$NaHCO_3$, H_2O) and FC (cyclohexane/AcOEt 3 : 1) gave **15** (1.8 g, 88%). Colourless oil. R_f (cyclohexane/AcOEt 1 : 1) 0.75. IR ($CHCl_3$): 3000*s*, 2915*m,* 2890*w*, 1605*w*, 1503*w*, 1455*m*, 1170*m*, 1080*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.16 (*dd*, J = 11.5, 3.7, H_{exo}–C(8)); 1.37, 1.41 (2*s*, Me_2C(4)); 1.49 (*dd*, J = 11.5, 8.0, H_{endo}–C(8)); 1.89 (*dddd*, J = 11.6, 7.9, 4.8, 3.8, H–C(7)); 3.59 (*dd*, J = 11.9, 5.1, H–C(6)); 3.68 (*t*, J = 11.8, H′–C(6)); 3.85 (*d*, J = 11.7), 3.87 (*d*, J = 11.0) (2 H–C(2)); 4.07, 4.23 (2*d*, J = 13.7, CH_2–C(9)); 4.58, 4.67 (2*d*, J = 12.3, PhCH_2); 6.12, 6.37 (2*d*, J = 5.7, H–C(10), H–C(11)); 7.27–7.39 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC.GRASP spectrum): 23.92, 25.09 (2*q*, *Me*$_2$C(4)); 32.08 (*t*, C(8)); 43.71 (*d*, C(7)); 61.36 (*t*, *C*H_2–C(9)); 63.72 (*t*, C(6)); 69.97 (*t*, C(2)); 73.55 (*t*, Ph*C*H_2); 88.35, 89.93 (2*s*, C(1), C(9)); 101.64 (*s*, C(4)); 127.59 (*d*); 128.34 (2*d*); 129.29 (2*d*); 135.81, 137.69 (2*d*, C(10), C(11)); 138.21 (*s*). MALDI-MS: 339 ($[M+Na]^+$). Anal. calc. for $C_{19}H_{24}O_4$ (316.40): C 72.13, H 7.65; found: C 72.12, H 7.76.

*(±)-(1*RS*,7*RS*,9*RS*,10*SR*,11*RS*)-9-[(Benzyloxy)methyl]-4,4-dimethyl-3,5,12-trioxatricyclo[5.4.0.1^{1,9}]dodecane-10,11-diol* (**16**). A soln. of **15** (500 mg, 1.6 mmol), trimethylamine *N*-oxide (Me_3NO; 530 mg, 4.8 mmol), and pyridine (120 µl) in H_2O (0.9 ml) and *t*-BuOH (2.3 ml) was treated with OsO_4 (10 mg, 0.04 mmol), warmed to 80°, stirred for 6 h, cooled to 23°, treated with 20% aq. $NaHSO_3$ soln. (18 ml), stirred for 5 min, and treated with H_2O (30 ml). The volatiles were evaporated, and the residue was extracted with AcOEt (1 × 200 ml, 2 × 75 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. Crystallisation from MeOH (5 ml) and from EtOH (6 ml) gave **16** (406 mg, 72%). White solid. R_f (cyclohexane/AcOEt 1 : 1) 0.35. M.p. 130°. IR ($CHCl_3$): 3399*m* (br.), 2997*m*, 2937*m*, 2876*m*, 1603*w*, 1455*m*, 1385*m*, 1114*s*, 1073*s*, 1036*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.89 (*dd*, J = 12.8, 4.4, H_{exo}–C(8)); 1.35, 1.36 (2*s*, Me_2C(4)); 1.52 (*dd*, J = 12.8, 8.7, H_{endo}–C(8)); 1.86 (*ddt*, J = 11.6, 9.2, 4.6, H–C(7)); 3.27 (*dd*, J = 11.9, 5.2, H–C(6)); 3.49 (*d*, J = 6.3, HO–C(10)); 3.59 (*t*,

J = 11.8, H′–C(6)); 3.74 (t, J = 5.9, H–C(10)); 3.94, 3.97 (2d, J = 11.0, 2 H–C(2)); 4.02 (dd, J = 6.0, 3.5, H–C(11)); 4.09, 4.13 (2d, J = 14.3, 2 CH–C(9)); 4.44 (d, J = 3.9, HO–C(11)); 4.55, 4.69 (2d, J = 11.8, PhCH_2); 7.31–7.38 (m, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC.GRASP spectrum): 23.74, 25.17 (2q, Me_2C(4)); 32.25 (t, C(8)); 42.69 (d, C(7)); 60.25 (t, CH_2–C(9)); 62.56 (t, C(6)); 70.60 (t, C(2)); 74.17 (t, PhCH_2)); 75.73 (d, C(11)); 76.00 (d, C(10)); 84.23, 88.50 (2s, C(1), C(9)); 101.79 (s, C(4)); 127.95 (2d); 128.11 (d); 128.59 (2d); 137.02 (s). MALDI-MS: 373 ([M + Na]$^+$). Anal. calc. for $C_{19}H_{26}O_6$ (350.41): C 65.13, H 7.48; found: C 65.05, H 7.32.

*(±)-(1*RS*,7*RS*,9*SR*,10*SR*,14*RS*)-9-[(Benzyloxy)methyl]-4,4,12,12-tetramethyl-3,5,11,13,15-pentaoxatetracyclo[7.5.1.0^{1,7}.0^{10,14}]tetradecane* (**17**). A suspension of **16** (550 mg, 1.56 mmol), CSA (35 mg), and 2,2-dimethoxypropane (411.45 mg, 4.0 mmol) in acetone (14 ml) was stirred for 5 h at 23°, and treated with Na_2CO_3 (60 mg, 0.6 mmol). Normal workup (AcOEt/H_2O) and FC (cyclohexane/AcOEt 2 : 1) gave **17** (596 mg, 97%). Colourless oil. R_f (cyclohexane/AcOEt 1 : 1) 0.54. IR ($CHCl_3$): 3000m, 2938m, 2871m, 1710w, 1604w, 1453w, 1373m, 1266m, 1090s, 1035m, 871w. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.51 (dd, J = 13.0, 4.4, H_{exo}–C(8)); 1.28, 1.34, 1.36, 1.46 (4s, 2 Me_2C); 1.53 (dd, J = 13.0, 8.6, irrad. at 1.81 → NOE of 4.7%, H_{endo}–C(8)); 1.81 (ddt, J ≈ 11.6, 9.0, 4.5, H–C(7)); 3.34 (dd, J = 12.0, 5.3, irrad. at 1.81 → NOE of 3.8%, H–C(6)); 3.59 (t, J = 11.8, H′–C(6)); 3.74, 3.94 (2d, J = 9.9, 2 H–C(2)); 4.05 (s, CH_2–C(9)); 4.14 (d, J = 5.6, irrad. at 1.81 → NOE of 8.2%, H–C(14)); 4.31 (d, J = 5.6, H–C(10)); 6.60 (s, PhCH_2); 7.27–7.34 (m, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC.GRASP spectrum): 23.77, 24.99, 25.82, 30.43 (4q, 2 Me_2C); 30.43 (t, C(8)); 41.83 (d, C(7)); 58.51 (t, CH_2–C(9)); 59.59 (t, C(6)); 62.66 (t, C(2)); 68.03 (t, PhCH_2); 83.43 (d, C(10)); 83.78 (d, C(14)); 85.48, 87.10 (2s, C(1), C(9)); 101.76 (s, C(4)); 112.79 (s, C(12)); 127.52 (d); 127.61 (2d); 128.29 (2d); 138.41 (s). MALDI-MS: 413 ([M + Na]$^+$). Anal. calc. for $C_{22}H_{30}O_6$ (390.48): C 67.67, H 7.74; found: C 67.74, H 7.85.

*(±)-(1*RS*,7*RS*,9*SR*,10*SR*,14*RS*)-9-(Hydroxymethyl)-4,4,12,12-tetramethyl-3,5,11,13,15-pentaoxatetracyclo[7.5.1.0^{1,7}.0^{10,14}]tetradecane* (**18**). Hydrogenation of **17** (270 mg, 0.68 mmol) in AcOEt (3 ml) in the presence of 10% Pd/C (15 mg) at 6 bar for 48 h, filtration through *Celite,* evaporation, and FC (cyclohexane/AcOEt 1 : 3) gave **18** (184 mg, 90%). White solid. R_f (AcOEt) 0.63. M.p. 143°. IR ($CHCl_3$): 3507w (br.), 2999m, 2839m, 1728w, 1603w, 1456w, 1384s, 1374s, 1163m, 1108s, 1078s, 1034s, 910m, 870s. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.23 (dd, J = 12.9, 4.4, H_{exo}–C(8)); 1.27, 1.35, 1.36, 1.47 (4s, 2 Me_2C); 1.42 (dd, J = 12.9, 8.5, H_{endo}–C(8)); 1.85 (ddt, J = 11.8, 8.5, 4.8, H–C(7)); 2.13 (dd, J = 8.7, 3.8, OH); 3.36 (dd, J = 12.0, 5.3, H–C(6)); 3.60 (t, J = 11.8, H′–C(6)); 3.88 (dd, J = 12.1, 8.6, CH–C(9)); 4.06 (s, 2 H–C(2)); 4.08 (dd, J = 12.1, 3.5, CH′–C(9)); 4.18 (d, J = 5.6, H–C(14)); 4.31 (d, J = 5.6, H–C(10)). ^{13}C-NMR (100 MHz, $CDCl_3$; assignments based on a HSQC.GRASP spectrum): 23.78, 24.97, 25.56, 26.09 (4s, 2 Me_2C); 29.37 (t, C(8)); 42.04 (d, C(7)); 59.57 (t, C(2)); 61.27 (t, CH_2–C(9)); 62.43 (t, C(6)); 83.81 (d, C(10)); 84.20 (d, C(14)); 86.18, 87.22 (2s, C(1), C(9)); 101.86 (s, C(4)); 113.02 (s, C(12)). MALDI-MS: 323 ([M + Na]$^+$). Anal. calc. for $C_{15}H_{24}O_6$ (300.35): C 59.98, H 8.05; found: C 59.71, H 7.91.

*(±)-(1*RS*,7*RS*,9*SR*,10*SR*,14*RS*)-4,4,12,12-Tetramethyl-9-(phthalimidomethyl)-3,5,11,13,15-pentaoxatetracyclo[7.5.1.0^{1,7}.0^{10,14}]tetradecane* (**19**). A soln. of **18** (160 mg, 0.53 mmol), Ph_3P (275 mg, 1.0 mmol), phthalimide (155 mg, 1.05 mmol), and DIAD (150 mg, 0.8 mmol) in THF (10 ml) was heated to 65° for 4 h, and cooled to r.t. Normal workup (AcOEt/brine) and FC (cyclohexane/AcOEt 4 : 1 → 3 : 1) gave **19** (211 mg, 93%). Pale yellow solid. R_f (cyclohexane/AcOEt 1 : 1) 0.57. M.p. 146°. IR ($CHCl_3$): 3030w, 2995w, 2940w, 1777w, 1719s, 1602w, 1469w, 1433w, 1394w. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.13 (dd, J = 12.9, 4.4, H_{exo}–C(8)); 1.29, 1.33, 1.34, 1.48 (4s, 2 Me_2C); 1.41 (dd, J = 12.9, 8.5, H_{endo}–C(8)); 1.77 (ddt, J = 11.6, 8.5, 4.7, H–C(7)); 3.29 (dd, J = 12.0, 5.3, H–C(6)); 3.58 (t, J = 11.4, H′–C(6)); 4.02, 4.07 (2d, J = 14.0, CH_2–C(9)); 4.13 (d, J = 5.6, H–C(14)); 4.22 (s, 2 H–C(2)); 4.30 (d, J = 5.6, H–C(10)); 7.72–7.74, 7.85–7.87 (2m, 4 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC.GRASP spectrum): 23.74, 25.02, 26.06, 26.24 (4q, 2 Me_2C); 31.20 (t, C(8)); 37.06 (t, C(2)); 41.72 (d, C(7)); 59.66 (t, CH_2–C(9)); 62.57 (t, C(6)); 83.78 (d, C(10)); 84.32 (d, C(14)); 85.17, 87.03 (2s, C(1), C(9)); 101.81 (s, C(4)); 113.02 (s, C(12)); 123.37, 134.04 (2d, 4 arom. C); 132.04 (s, 2 arom. C); 168.21 (s, 2 C=O); MALDI-MS: 452 ([M + Na]$^+$). Anal. calc. for $C_{23}H_{27}NO_7$ (429.47): C 64.32, H 6.34, N 3.26; found: C 64.21, H 6.42, N 3.43.

*(±)-(1*RS*,7*RS*,9*SR*,10*SR*,14*RS*)-9-(Aminomethyl)-4,4,12,12-tetramethyl-3,5,11,13,15-pentaoxatetracyclo[7.5.1.0^{1,7}.0^{10,14}]tetradecane* (**20**). A soln. of **19** (150 mg, 0.377 mmol) and $NH_2NH_2 \cdot H_2O$ (72 mg, 1.4 mmol) in EtOH (15 ml) was stirred for 3 h at 80°, kept at 23° for 6 h, filtered, and the filtrate evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 100 : 5 : 1) gave **20** (92 mg, 81%). Colourless oil. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 10 : 0.5 : 0.1) 0.19. IR ($CHCl_3$): 3388w, 2944s, 2937s, 1661w, 1602w, 1456m, 1384s, 1373s, 1109s, 1076s, 1035m. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (dd, J = 12.8, 4.3, H_{exo}–C(8)); 1.28, 1.35, 1.36, 1.47 (4s, 2 Me_2C); 1.45 (dd, J = 12.8, 8.9, H_{endo}–C(8)); 1.84 (ddt, J = 11.6, 9.5, 4.5, H–C(7)); 3.07, 3.17 (2d, J = 13.4, CH_2–C(9)); 3.35 (dd, J = 12.0, 5.3, H–C(6)); 3.56 (t, J = 11.8, H′–C(6)); 4.06 (s, 2 H–C(2)); 4.15, 4.28 (2d, J = 5.7, H–C(10), H–

C(14)). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.78, 25.0, 25.69, 26.14 (4*q*, 2 *Me*$_2$C); 30.41 (*t*, C(8)); 41.92 (*t*, CH_2–C(9)); 42.19 (*d*, C(7)); 59.66 (*t*, C(2)); 62.57 (*t*, C(6)); 83.82, 86.74 (2*d*, C(10), C(14)); 86.73, 86.76 (2*s*, C(1), C(9)); 101.82 (*s*, C(4)); 112.78 (*s*, C(12)). MALDI-MS: 322 ($[M+Na]^+$). Anal. calc. for $C_{11}H_{10}O_6$ (299.37): C 60.18, H 8.42, N 4.68; found: C 60.34, H 8.50, N 4.75.

*(±)-(1*RS*,2*RS*,3*SR*,4*SR*,6*RS*)-1-(Aminomethyl)-4,5-bis(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane-2,3-diol* (**3**). A soln. of **20** (110 mg, 0.36 mmol) in CH_2Cl_2 (5 ml) was treated with 2.5N aq. HCl (15 ml) and stirred for 15 min. The org. layer was separated, and the aq. layer was washed with CH_2Cl_2 (2×5 ml). Evaporation of the aq. layer and FC (*Amberlite CG-120*, H_2O/NH_3 1:0 → 95:5) gave **3** (87 mg, 95%). Colourless solid. p*K*: 8.46. IR (KBr): 3600–2400*s* (br.), 1622*w*, 1504*w*, 1408*w*, 1094*m*, 1035*m*. ^{1}H-NMR (300 MHz, D_2O): 1.24 (*dd*, *J* = 13.1, 5.0, H_{exo}–C(6)); 1.86 (*dd*, *J* = 13.1, 8.7, H_{endo}–C(6)); 2.06–2.15 (*m*, H–C(5)); 3.39, 3.57 (2*d*, *J* = 14.0, CH_2–C(1)); 3.44 (*dd*, *J* = 10.9, 6.5, CH–C(5)); 3.73 (*dd*, *J* = 10.9, 7.2, CH′–C(5)); 3.89, 4.02 (2*d*, *J* = 11.8, CH_2–C(4)); 4.07, 4.14 (2*d*, *J* = 6.2, H–C(2), H–C(3)). ^{13}C-NMR (75 MHz, D_2O): 36.30 (*t*, C(6)); 45.77 (*t*, *C*H_2–C(1)); 47.78 (*d*, C(5)); 63.08, 68.06 (2*t*, *C*H_2–C(4), *C*H_2–C(5)); 80.34, 83.97 (2*d*, C(2), C(3)); 89.47, 94.29 (2*s*, C(1), C(4)). ESI-MS: 220 ($[M+H]^+$). Anal. calc. for $C_{11}H_{10}O_6$ (219.24): C 49.31, H 7.82, N 6.39; found: C 49.32, H 7.76, N 6.25.

*(±)-(1*RS*,2*SR*,6*RS*,7*SR*)-(3,5-Dioxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-8-en-1-yl)methyl Acetate* (**21**) [30]. A soln. of furfuryl acetate (40 g, 0.28 mol) and maleic anhydride (28 g, 0.28 mol) in Et_2O (240 ml) was kept at 25° for 7 d. Evaporation of the solvent and crystallisation from AcOEt gave **21** (23 g, 34%). White solid. R_f (cyclohexane/AcOEt 1:1) 0.26. M.p. 110° (dec.). IR ($CHCl_3$): 3038*w*, 1864*m*, 1789*s*, 1748*s*, 1435*w*, 1396*w*, 1369*w*, 1308*w*, 1154*w*, 1085*m*, 1073*m*, 1046*m*, 990*m*, 929*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.12 (*s*, AcO); 3.23, 3.34 (2*d*, *J* = 6.9, H–C(2), H–C(6)); 4.54, 4.91 (2*d*, *J* = 12.8, CH_2–C(1)); 5.45 (*d*, *J* = 1.9, H–C(7)); 6.47 (*d*, *J* = 5.9, H–C(9)); 6.63 (*dd*, *J* = 1.9, 5.6, H–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.71 (*q*, Me); 49.67, 51.37 (2*d*, C(2), C(6)); 60.69 (*t*, *C*H_2–C(1)); 82.17 (*d*, C(7)); 90.64 (*s*, C(1)); 137.27, 137.87 (2*d*, C(8), C(9)); 167.66, 169.10, 170.11 (3*s*, 3 C=O). MALDI-MS: 261 ($[M+Na]^+$). Anal. calc. for $C_{11}H_{10}O_6$ (238.2): C 55.47, H 4.23, O 40.30; found: C 55.49, H 4.41, O 40.13.

*(±)-(1*RS*,2*SR*,6*RS*,7*SR*)-1-(Acetoxymethyl)-3-(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic Acid* (**22**). A suspension of **21** (10 g, 42 mmol) in MeOH (170 ml) at 0° was treated with MeONa (2.4 g, 46 mmol), stirred for 30 min, warmed to 25°, stirred for 3 h, and evaporated. The residue was treated with sat. aq. NH_4Cl soln. (40 ml) and CH_2Cl_2 (40 ml), and acidified with 2N aq. HCl to pH 2–3. The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2 (7×15 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. Crystallisation from AcOEt (1×80 ml, 1×50 ml) gave **22** (4.73 g, 41%). White solid. R_f (CH_2Cl_2/MeOH/AcOH 10:0.2:0.2) 0.30. M.p. 115° (dec.). IR ($CHCl_3$): 3500–2500*m* (br.), 1744*s*, 1436*m*, 1368*m*, 1336*m*, 1044*m*, 996*m*, 929*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.09 (*s*, AcO); 2.93, 3.04 (2*d*, *J* = 9.0, H–C(2), H–C(3)); 3.70 (*s*, MeO); 4.50, 4.75 (2*d*, *J* = 12.2, CH_2–C(1)); 5.46 (*d*, *J* = 1.8, H–C(4)); 6.38 (*d*, *J* = 5.7, H–C(6)); 6.55 (*dd*, *J* = 5.7, 1.8, H–C(5)); 8.02 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.62 (*q*, Me); 48.34, 49.92 (2*d*, C(2), C(3)); 52.41 (*q*, MeO); 61.62 (*t*, *C*H_2–C(1)); 79.94 (*d*, C(4)); 89.43 (*s*, C(1)); 136.91, 137.79 (2*d*, C(6), C(7)); 170.69, 171.24, 175.86 (3*s*, 3 C=O). MALDI-MS: 293 ($[M+Na]^+$). Anal. calc. for $C_{12}H_{14}O_7$ (270.24): C 53.34, H 5.22, O 41.44; found: C 53.27, H 5.36, O 41.32.

*(±)-(1*RS*,2*SR*,3*RS*,4*RS*,5*RS*,6*RS*)-1-(Acetoxymethyl)-5,6-dihydroxy-3-(methoxycarbonyl)-7-oxabicyclo-[2.2.1]heptane-2-carboxylic Acid* (**23**). A soln. of **22** (2 g, 7.4 mmol), NMO (1.5 g, 11 mmol), *N*-methylmorpholine (0.75 g, 7.4 mmol), and H_2O (4 ml) in acetone (20 ml) was treated at 25° with 2.5% OsO_4 in *t*-BuOH (0.75 ml), stirred for 2 h, treated with 5% aq. $NaHSO_3$ soln. (20 ml), and acidified to pH 2–3 with 2N HCl. The mixture was continuously extracted for 6.5 h with AcOEt (500 ml) using a 200 ml *Kutscher–Steudel* apparatus. Upon standing at 25°, a precipitate was formed, which was filtered off and dried *i.v.* to give crude **23** (1.63 g, 72%). For analysis, a small sample was recrystallized in acetone. White solid. M.p. 178°. IR (KBr): 3500–2500*s* (br.), 1727*s*, 1698*s*, 1463*m*, 1441*m*, 1398*m*, 1356*m*, 1307*s*, 1275*s*, 1249*s*, 1197*s*, 1175*m*, 1093*m*, 1052*m*, 1027*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.98 (*s*, AcO); 2.97, 3.09 (2*d*, *J* = 9.7, H–C(2), H–C(3)); 3.49 (*s*, MeO); 3.77 (*dd*, *J* = 12.8, 6.5), 3.84 (*dd*, *J* = 11.2, 5.9) (H–C(5), H–C(6)); 4.18, 4.31 (2*d*, *J* = 10.6, CH_2–C(1)); 4.47 (*s*, H–C(4)); 4.72 (*d*, *J* = 7.2), 5.18 (*d*, *J* = 5.6) (2 OH); 12.00–12.20 (br. *s*, COOH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 20.38 (*q*, Me); 46.92, 49.19 (2*d*, C(2), C(3)); 51.36 (*s*, MeO); 59.72 (*t*, *C*H_2–C(1)); 71.74, 73.00 (2*d*, C(5), C(6)); 82.19 (*d*, C(4)); 87.06 (*s*, C(1)); 169.48, 170.39, 171.42 (3*s*, 3 C=O). MALDI-MS: 327 ($[M+Na]^+$). Anal. calc. for $C_{12}H_{16}O_9$ (304.25): C 47.37, H 5.30; found: C 47.26, H 5.42.

*(±)-(1*RS*,2*SR*,3*RS*,4*RS*,5*RS*,6*RS*)-1-(Acetoxymethyl)-8-(methoxycarbonyl)-4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decane-9-carboxylic Acid* (**24**). A suspension of **23** (1.3 g, 4.27 mmol), 2,2-dimethoxypropane (11.9 g, 114 mmol) and *Amberlyst 15* in acetone (200 ml) was vigorously stirred for 3 h at 23° and filtered through a short pad of *Celite*. Evaporation and FC (CH_2Cl_2/MeOH/AcOH 100:7:2) gave **24** (1.1 g, 75%). White solid. R_f

(CH_2Cl_2/MeOH/AcOH 100:5:2) 0.44. M.p. 162° (subl.). IR (KBr): 3700–2500*m* (br.), 1744*s*, 1693*s*, 1473*w*, 1437*m*, 1371*m*, 1309*w*, 1067*m*, 1048*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.21, 1.33 (2*s*, Me_2C(4)); 1.99 (*s*, AcO); 2.93, 3.00 (2*d*, *J* = 10.0, H–C(8), H–C(9)); 4.20 (*d*, *J* = 10.9), 4.27 (*d*, *J* = 10.5) (CH_2–C(1)); 4.30 (*d*, *J* = 5.9), 4.37 (*d*, *J* = 5.3) (H–C(2), H–C(6)); 4.57 (*s*, H–C(7)); 11.10–11.50 (br. *s*, COOH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 20.36 (*q*, Me); 25.25, 25.76 (2*q*, *Me*$_2$C); 46.24, 48.33 (2*d*, C(8), C(9)); 51.41 (*q*, MeO); 59.48 (*t*, *C*H_2–C(1)); 79.42, 81.20, 81.32 (3*d*, C(2), C(6), C(7)); 86.01 (*s*, C(1)); 111.13 (*s*, C(4)); 169.41, 170.27, 171.37 (3*s*, 3 C=O). MALDI-MS: 367 ([*M* + Na]$^+$). Anal. calc. for $C_{15}H_{20}O_9$ (344.32): C 52.33, H 5.85, O 41.82; found: C 52.26, H 6.03, O 41.96.

*Methyl (±)-(1*RS*,2*RS*,6*RS*,7*RS*,8*RS*)-1-(Acetoxymethyl)-4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decane-8-carboxylate* (**25**). A suspension of **24** (1.5 g, 4.4 mmol) in CH_2Cl_2 (100 ml) was treated at 23° with DMF (50 µl, 0.65 mmol) and $(COCl)_2$ (0.83 g, 6.5 mmol), and stirred until the evolution of gas ceased (1.5 h). The residue remaining after evaporation of the volatiles was dissolved in THF (100 ml). The soln. was sheltered from light, treated with 1-hydroxypyridine-2-thione sodium salt (0.98 g, 6.5 mmol) and DMAP (50 mg), stirred for 1.5 h at 23°, and evaporated at 35°. A soln. of the residue in benzene (150 ml) was treated with Bu_3SnH (3.8 g, 13 mmol) and AIBN (50 mg), heated to reflux, vigorously stirred for 45 min, treated with additional Bu_3SnH (1 g, 3.7 mmol) and AIBN (50 mg), again stirred for 3 h, cooled to 23°, and treated with sat. aq. NH_4Cl soln. (70 ml). The org. layer was separated, treated with sat. aq. NH_4Cl soln. (70 ml), vigorously stirred for 1 h, and filtered through a short pad of *Celite*. The org. layer was separated, dried ($MgSO_4$), and evaporated. FC (hexane/AcOEt 3:1 → 2:1) gave crude **25** (1 g), which was used for the next step without further purification. R_f (cyclohexane/AcOEt 1:1) 0.55.

*Methyl (±)-(1*RS*,2*RS*,6*RS*,7*RS*,8*RS*)-1-(Hydroxymethyl)-4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decane-8-carboxylate* (**26**). A soln. of crude **25** (1 g) in MeOH (30 ml) was treated with MeONa (40 mg, 0.74 mmol) and stirred for 2 h at 23°. Normal workup (CH_2Cl_2/NH_4Cl) and FC (cyclohexane/AcOEt 1:1) gave **26** (703 mg, 62% from **24**). White solid. R_f (cyclohexane/AcOEt 1:1) 0.24. M.p. 92°. IR ($CHCl_3$): 3520*w*, 2994*m*, 2954*m*, 1737*s*, 1438*m*, 1384*m*, 1374*m*, 1085*m*, 1043*m*, 990*w*, 838*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.29, 1.47 (2*s*, Me_2C(4)); 1.56 (*dd*, *J* = 13.1, 9.2, H_{endo}–C(9)); 2.16 (*dd*, *J* = 13.0, 4.7, H_{exo}–C(9)); 2.25 (br. *s*, OH); 2.54 (*dd*, *J* = 9.2, 4.7, H–C(8)); 3.72 (*s*, MeO); 3.97, 4.11 (2*d*, *J* = 12.0, CH_2–C(1)); 4.28, 4.37 (2*d*, *J* = 5.6, H–C(2), H–C(6)); 4.67 (*s*, H–C(7)). ^{13}C-NMR (100 MHz, $CDCl_3$): 25.22, 25.88 (2*q*, *Me*$_2$C(4)); 30.09 (*t*, C(9)); 43.13 (*d*, C(8)); 52.39 (*s*, MeO); 61.17 (*t*, *C*H_2–C(1)); 81.56, 82.63, 82.95 (3*d*, C(2), C(6), C(7)); 86.74 (*s*, C(1)); 112.58 (*s*, C(4)); 172.80 (*s*, C=O). MALDI-MS: 281 ([*M* + Na]$^+$). Anal. calc. for $C_{12}H_{18}O_6$ (258.27): C 55.81, H 7.02, O 37.17; found: C 55.83, H 7.06, O 36.92.

X-Ray Crystal-Structure Analysis of **26** (CCDC-203882). Crystals were obtained from Et_2O by slow evaporation at r.t. $C_{12}H_{18}O_6$ (258.27); triclinic P_1; a = 10.06310(10) Å, b = 10.3839(10) Å, c = 14.3276(2) Å; V = 1291.43(3) Å^3; $D_{calc.}$ = 1.328 Mg/m^3; Z = 4; Intensities were measured on a *Bruker Nonius KappaCCD* diffractometer (graphite monochromator, MoK_α, λ = 0.71073 Å at 202 K). Of the 13736 reflections, 7217 unique reflections were observed. R = 0.068, R_w = 0.299. The structure was solved by the direct method with SHELXL-97 [53].

*Methyl (±)-(1*RS*,2*RS*,6*RS*,7*RS*,8*RS*)-1-(Phthalimidomethyl)-4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decane-8-carboxylate* (**27**). A soln. of **26** (250 mg, 0.96 mmol), PPh_3 (510 mg, 1.9 mmol), and phthalimide (280 mg, 1.9 mmol) in THF (15 ml) was treated with DIAD (290 mg, 1.4 mmol), heated to reflux for 3 h, and cooled to 23°. Normal workup (CH_2Cl_2/NH_4Cl) and FC (cyclohexane/AcOEt 2:1 → 1:1) gave **27** (349 mg, 94%). Pale yellow foam. R_f (cyclohexane/AcOEt 1:1) 0.48. M.p. 135°. IR ($CHCl_3$): 3008*w*, 2954*w*, 1776*m*, 1718*s*, 1602*w*, 1468*w*, 1436*m*, 1429*m*, 1398*s*, 1374*m*, 1040*m*, 984*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.24, 1.38 (2*s*, Me_2C(4)); 1.53 (*dd*, *J* = 13.1, 9.0, H_{endo}–C(9)); 2.05 (*dd*, *J* = 13.4, 4.7, H_{exo}–C(9)); 2.45 (*dd*, *J* = 9.0, 4.7, H–C(8)); 3.58 (*s*, MeO); 4.12 (*d*, *J* = 14.9), 4.40 (*d*, *J* = 14.6) (CH_2–C(1)); 4.26 (*d*, *J* = 5.6), 4.39 (*d*, *J* = 5.7) (H–C(2), H–C(6)); 4.61 (*s*, H–C(7)); 7.69–7.72, 7.83–7.86 (2*m*, 4 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.67, 26.02 (2*q*, *Me*$_2$C); 30.71 (*t*, C(9)); 36.55 (*t*, CH_2–C(1)); 42.89 (*d*, C(8)); 52.32 (*q*, MeO); 81.63, 82.79, 83.11 (3*d*, C(2), C(6), C(7)); 86.09 (*s*, C(1)); 112.63 (*s*, C(4)); 123.21, 133.78 (2*d*, 4 arom. C); 131.94 (*s*, 2 arom. C); 168.07 (*s*, 2 N–C=O); 172.21 (*s*, O–C=O). MALDI-MS: 410 ([*M* + Na]$^+$). Anal. calc. for $C_{20}H_{21}NO_7$ (387.39): C 62.01, H 5.46, N 3.62; found: C 62.08, H 5.57, N 3.80.

*Methyl (±)-(1*RS*,2*RS*,6*RS*,7*RS*,8*RS*)-1-(Aminomethyl)-4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decane-8-carboxylate* (**28**). A suspension of **27** (212 mg, 0.55 mmol) and $NH_2NH_2 \cdot H_2O$ (33 mg, 0.65 mmol) in EtOH (20 ml) was stirred for 12 h at 23°, treated with $NH_2NH_2 \cdot H_2O$ (20 mg, 0.39 mmol), stirred for 3.5 h, cooled to 0°, and filtered. Evaporation and FC (CH_2Cl_2/MeOH/25% aq. NH_3 100:3:1 → 100:5:1) of the residue gave **28** (108 mg, 76%). Colourless oil. R_f (CH_2Cl_2/MeOH/25% NH_3 100:5:1) 0.25. IR ($CHCl_3$): 3389*w*, 2992*m*, 2954*m*, 1736*s*, 1621*w*, 1601*w*, 1455*w*, 1437*m*, 1383*m*, 1374*m*, 1268*m*, 1086*m*, 1042*m*, 980*w*, 869*w*. ^{1}H-NMR (300

MHz, $CDCl_3$): 1.28, 1.46 (2*s*, $Me_2C(4)$); 1.55 (*dd*, *J* = 13.1, 9.0, H_{endo}–C(9)); 1.65–1.75 (br. *s*, NH_2); 2.08 (*dd*, *J* = 2.8, 4.7, H_{exo}–C(9)); 2.53 (*dd*, *J* = 9.0, 4.7, H–C(8)); 3.12, 3.40 (2*d*, *J* = 13.4, CH_2–C(1)); 3.71 (*s*, MeO); 4.27, 4.34 (2*d*, *J* = 5.6, H–C(2), H–C(6)); 4.62 (*s*, H–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.42, 26.06 (2*q*, Me_2-C(4)); 30.64 (*t*, C(9)); 41.31 (*t*, CH_2–C(1)); 43.39 (*d*, C(8)); 52.47 (*q*, MeO); 81.32, 82.37, 82.84 (3*d*, C(2), C(6), C(7)); 87.52 (*s*, C(1)); 112.24 (*s*, C(4)); 172.84 (*s*, C=O). ESI-MS: 258 ($[M+H]^+$).

*Methyl (±)-(1*RS,*2*RS,*6*RS,*7*RS,*8*RS*)-1-({[(*tert*-*Butoxy)carbonyl]amino}methyl)-4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decane-8-carboxylate* (**29**). A soln. of **28** (62 mg, 0.25 mmol) in CH_2Cl_2 (5 ml) was treated with Boc_2O (100 mg, 0.45 mmol), stirred for 48 h at 23°, and evaporated. FC (cyclohexane/AcOEt 2 : 1 → 1 : 1) gave **29** (78 mg, 91%). White solid. R_f (cyclohexane/AcOEt 1 : 1) 0.51. M.p. 99°. IR ($CHCl_3$): 3453*m*, 3007*m*, 2936*m*, 1710*s*, 1602*m*, 1509*s*, 1455*m*, 1437*m*, 1366*s*, 1106*m*, 1089*m*, 1045*m*, 981*w*, 932*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.25 (*s*, Me–C(4)); 1.42 (*s*, Me–C(4), *t*-Bu); 1.50 (*dd*, *J* = 13.1, 9.3, H_{endo}–C(9)); 2.09 (*dd*, *J* = 13.1, 4.7, H_{exo}–C(9)); 2.49 (*dd*, *J* = 9.3, 4.7, H–C(8)); 3.55 (*dd*, *J* = 14.3, 4.7, CH–C(1)); 3.69 (*s*, MeO); 3.70 (*dd*, *J* = 14.3, 7.8, CH′–C(1)); 4.17 (*d*, *J* = 5.6), 4.32 (*d*, *J* = 5.3) (H–C(2), H–C(6)); 4.58 (*s*, H–C(7)); 4.89–4.97 (*m*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.37, 25.96 (2*q*, Me_2C(4)); 28.41 (*q*, Me_3C); 30.37 (*t*, C(9)); 39.40 (*t*, CH_2–C(1)); 43.23 (*d*, C(8)); 52.35 (*q*, MeO); 79.28 (*s*, Me_3C); 81.34, 82.51, 82.82 (3*d*, C(2), C(6), C(7)); 86.30 (*s*, C(1)); 112.31 (*s*, C(4)); 156.10 (*s*, N–C=O); 172.55 (*s*, O–C=O). MALDI-MS: 380 ($[M+Na]^+$). Anal. calc. for $C_{17}H_{27}NO_7$ (357.40): C 57.13, H 7.61, N 3.92; found: C 57.12, H 7.46, N 3.87.

tert-*Butyl (±)-(1*RS,*2*RS,*6*RS,*7*RS,*8*SR*)-{[8-(Hydroxymethyl)-4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]-dec-1-yl]methyl}carbamate* (**30**). A soln. of **29** (33 mg, 0.09 mmol) in THF (6 ml) was treated with a suspension of 0.5M $LiBH_4$ in THF (1.2 ml), stirred for 5.5 h at 23°, treated with 2% aq. NaH_2PO_4 soln., stirred for 1 h and extracted with CH_2Cl_2 (5 × 5 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (cyclohexane/AcOEt 1 : 3) gave **30** (25 mg, 82%). Colourless syrup. R_f (cyclohexane/AcOEt 1 : 3) 0.30. IR ($CHCl_3$): 3455*m*, 3019*s*, 2938*s*, 1710*s*, 1510*s*, 1455*w*, 1383*m*, 1289*m*, 1243*m*, 1164*s*, 1090*m*, 1040*w*, 971*w*, 909*w*, 857*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.18 (*dd*, *J* = 13.1, 4.4, H_{exo}–C(9)); 1.28, 1.46 (2*s*, $Me_2C(4)$); 1.39 (*dd*, *J* = 13.1, 8.1, H_{endo}–C(9)); 1.43 (*s*, *t*-Bu); 1.80–1.90 (*m*, H–C(8), OH); 3.47 (*dd*, *J* = 10.6, 8.1, CH–C(1)); 3.51 (*dd*, *J* = 10.6, 6.3, CH′–C(1)); 3.56 (*dd*, *J* = 14.3, 5.8, CH–C(8)); 3.64 (*dd*, *J* = 14.3, 7.5, CH′–C(8)); 4.17, 4.31 (2*d*, *J* = 5.6, H–C(2), H–C(6)); 4.30 (*s*, H–C(7)); 5.0 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.17, 25.91 (2*q*, $Me_2C(4)$); 28.42 (*q*, Me_3C); 30.16 (*t*, C(9)); 39.75 (*t*, CH_2–C(1)); 40.38 (*d*, C(8)); 64.20 (*t*, CH_2–C(8)); 79. 29 (*s*, Me_3C); 80.38, 82.72, 83.10 (3*d*, C(2), C(6), C(7)); 86.00 (*s*, C(1)); 111.81 (*s*, C(4)); 156.18 (*s*, C=O). MALDI-MS: 352 ($[M+Na]^+$). Anal. calc. for $C_{16}H_{27}NO_6$ (329.39): C 58.34, H 8.26, N 4.25; found: C 58.50, H 8.33, N 4.07.

*(±)-(1*RS,*2*RS,*6*RS,*7*RS,*8*SR*)-1-(Aminomethyl)-5-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane-2,3-diol* (**4**). A soln. of **30** (68 mg, 0.21 mmol) in CH_2Cl_2 (3 ml) was treated with 2N aq. HCl (15 ml) and stirred for 5 h at 23°. The aq. layer was separated and evaporated. FC (*Amberlite CG-120,* H_2O/NH_3 1 : 0 → 95 : 5) gave **4** (35 mg, 74%). Colourless oil. For analysis, **4** was transformed into its hydrochloride.

Data of **4**·HCl: pK_{HA} 8.66. IR (KBr): 3600–2400*s* (br.), 1623*m*, 1501*m*, 1407*m*, 1294*w*. ^{1}H-NMR (300 MHz, D_2O): 1.08 (*dd*, *J* = 12.8, 4.4, H_{exo}–C(6)); 1.71 (*dd*, *J* = 8.6, 12.9, H_{endo}–C(6)); 2.01–2.10 (*m*, H–C(5)); 3.38, 3.81 (2*d*, *J* = 14.0, CH_2–C(1)); 3.38–3.42 (*m*, CH_2–C(5)); 4.03, 4.06 (2*d*, *J* = 6.2, H–C(2), H–C(3)); 4.24 (*s*, H–C(4)). ^{13}C-NMR (75 MHz, D_2O): 32.42 (*t*, C(6)); 40.20 (*t*, CH_2–C(1)); 41.06 (*d*, C(5)); 63.80 (*t*, CH_2–C(5)); 74.40, 78.46 (2*d*, C(2), C(3)); 84.01 (*d*, C(4)); 84.83 (*s*, C(1)). ESI-MS: 190 ($[M+H]^+$). Anal. calc. for $C_8H_{16}ClNO_4$ (225.67): C 42.58, H 7.15, N 6.21; found: C 42.90, H 7.63, N 6.00.

*3a,4,7,7a-Tetrahydro-4,7-methano-1*H*-indene-2,5-dicarboxylic Acid* (**31**). A soln. of cyclopenta-1,3-diene (16.5 g, 250 mmol) in Et_2O (700 ml) was treated with 1.6M BuLi in hexane (190 ml, 300 mmol), heated to reflux for 2 h, cooled to 23°, stirred for 14 h, cooled to 0°, treated with gaseous CO_2 for 0.5 h, warmed to 23°, treated again with gaseous CO_2 for 1 h, and then with H_2O (500 ml). The org. layer was separated, and the aq. layer was acidified with 50% aq. H_2SO_4 soln. (30 ml) to pH 1 and stirred for 3 h. The precipitate was filtered off, triturated twice with boiling H_2O (1 × 250 ml, 1 × 200 ml), cooled to r.t., filtered, washed with H_2O (30 ml), dried azeotropically with toluene (500 ml), and filtered. Removal of the residual solvent gave **31** (20.7 g, 75%) as a mixture of isomers. For analysis, a sample was dissolved in aq. NH_3 and precipitated with H_2SO_4. Light grey solid. M.p. 210°. IR (KBr): 3600–2400*m*, 1690*s*, 1628*m*, 1602*m*, 1425*m,* 1350*m*, 1295*m*, 1243*m*. ESI-MS: 219 ($[M-H]^-$). Anal. calc. for $C_{12}H_{12}O_4$ (220.23): C 65.45, H 5.49; found: C 65.67, H 5.70.

*Di(*tert*-butyl) 3a,4,7,7a-Tetrahydro-4,7-methano-1*H*-indene-2,5-dicarboxylate* (**32**). A stirred suspension of **31** (19.5 g, 89 mmol) in CH_2Cl_2 (200 ml) was treated with DMF (0.2 ml) and $(COCl)_2$ (28.5 g, 225 mmol) until the evolution of gas ceased. The volatiles were evaporated. A soln. of the residue in Et_2O (200 ml) was added dropwise to a vigorously stirred suspension of *t*-BuOK (22 g, 195 mmol) in Et_2O (300 ml) at such a rate that a gentle reflux was maintained throughout the addition. After stirring for 90 min, the soln. was diluted with H_2O (500 ml). The org. layer was separated, washed with H_2O (400 ml), dried ($MgSO_4$), and filtered through a short

pad of silica gel. Evaporation and FC (cyclohexane/AcOEt 10:1) gave **32** (26.1 g, 88%) as a mixture of isomers. M.p. 49–51°. IR ($CHCl_3$): 2981*w*, 1698*s*, 1632*w*, 1601*w*, 1475*w*, 1456*w*, 1393*w*, 1369*m*, 1295*m*. EI-MS: 332.2 (M^+). Anal. calc. for $C_{20}H_{28}O_4$ (332.44): C 72.26, H 8.49; found: C 72.29, H 8.55.

tert-*Butyl* (±)-(*1*RS,*2*RS,*6*RS,*7*RS)-*3,5-Dioxo-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene-1-carboxylate* (**33**). The dimeric ester **32** (26 g, 77 mmol) was cracked at 180°, the monoester distilled off *i.v.* (b.p.$_{.22}$ 109°) using a *Liebig* cooler, and the distillate was collected at −78°. The distillate was dissolved in cooled (0°) Et_2O (170 ml), treated with maleic anhydride (23 g, 234 mmol), and stirred until complete dissolution of maleic anhydride. The soln. was kept at 23° overnight and filtered. Crystallisation from cyclohexane/AcOEt 1:1 (250 ml) gave **33** (19.7 g, 48%). Colourless needles. R_f (cyclohexane/AcOEt 1:1) 0.75. M.p. 155°. IR ($CHCl_3$): 3032*w*, 2984*w*, 1866*m*, 1783*s*, 1725*s*, 1477*w*, 1458*w*, 1394*w*, 1371*w*, 1324*m*, 1279*m*, 1232*m*, 1169*m*, 1137*s*, 1084*s*, 917*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.53 (*s*, *t*-Bu); 1.90 (*dt*, *J* = 8.9, 0.6, H–C(10)); 1.99 (*dd*, *J* = 8.7, 1.6, H′–C(10)); 3.53–3.57 (*m*, H–C(7)); 3.87 (*dd*, *J* = 8.4, 4.7, H–C(6)); 3.98 (*d*, *J* = 8.4, H–C(2)); 6.33 (*dd*, *J* = 5.8, 3.0, H–C(8)); 5.90 (*d*, *J* = 5.9, H–C(9)). ^{13}C-NMR (300 MHz, $CDCl_3$): 28.10 (*q*, *Me*$_3$C); 46.64, 48.49, 50.19 (3*d*, C(2), C(6), C(7)); 56.93 (*t*, C(10)); 62.76 (*s*, C(1)); 82.60 (*s*, Me$_3$*C*); 135.42, 135.35 (2*d*, C(8), C(9)); 169.04, 169.21, 170.35 (3*s*, 3 C=O). MALDI-MS: 287 ([*M* + Na]$^+$). Anal. calc. for $C_{14}H_{16}O_5$ (264.28): C 63.63, H 6.10; found: C 63.69, H 6.12.

*(±)-(1*RS,*2*SR,*6*RS,*7*RS,*8*RS,*9*RS)*-1-[(*tert*-*Butoxy)carbonyl]-8-(methoxycarbonyl)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-9-carboxylic Acid* (**34**) and *(±)-(1*RS,*2*SR,*6*RS,*7*RS,*8*RS,*9*RS)*-1-[(*tert*-*Butoxy)carbonyl]-9-(methoxycarbonyl)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-carboxylic Acid* (**35**). A soln. of **33** (5 g, 18.9 mmol) in MeOH (100 ml) was cooled to 0°, treated with MeONa (1.2 g, 22.2 mmol), stirred for 2 h, warmed to 23°, stirred for 1 h, and evaporated. The residue was treated with sat. aq. NH_4Cl soln. and CH_2Cl_2 (100 ml), and acidified to pH 3–4 with 2N HCl. The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 50 ml), dried ($MgSO_4$) and evaporated. A soln. of the residue in acetone (50 ml) was treated with NMO (3.8 g, 28.1 mmol), *N*-methylmorpholine (2.1 g, 20.9 mmol), H_2O (10 ml), and 2.5% OsO_4 in *t*-BuOH (1 ml), stirred for 24 h at 23°, poured into a soln. of 5% aq. $NaHSO_3$ soln. (150 ml), and stirred for 10 min. After removal of acetone *i.v.*, the soln. was acidified to pH 2–3 with 2N HCl and extracted with AcOEt (1 × 150 ml, 3 × 50 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in AcOEt (150 ml) and washed with 0.04N HCl (3 × 100 ml). The org. layer was dried ($MgSO_4$) and evaporated. A soln. of the residue in acetone (100 ml) was treated with 2,2-dimethoxypropane (10 ml) and *Amberlyst 15* (H^+ form; 10 mg), stirred for 10 h at 23°, and filtered. After evaporation of the filtrate, the solid was triturated with boiling hexane/AcOEt 1:1 (70 ml), and the supernatant was decanted. Recrystallization of the solid in AcOEt gave **34** (2.2 g, 32%). Evaporation of the mother liquor provided; **35**/**34** 4:1 (2.7 g, 39%).

Data of **34**. White solid. R_f (cyclohexane/AcOEt/AcOH 10:5:0.05) 0.27. M.p. 184° (dec.). IR ($CHCl_3$): 3600–2400*m* (br.), 1731*s*, 1664*w*, 1457*w*, 1437*w*, 1384*m*, 1370*m*, 1330*m*, 1265*m*, 1161*s*, 1065*m*, 1046*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.28, 1.45 (2*s*, Me$_2$C(4)); 1.41–1.50 (*m*, H–C(10)); 1.48 (*s*, *t*-Bu); 2.21 (*dd*, *J* = 10.9, 1.6, H′–C(10)); 2.58 (br. *d*, *J* = 3.7, H–C(7)); 3.08 (*dd*, *J* = 11.7, 3.9, H–C(8)); 3.38 (*d*, *J* = 11.8, H–C(9)); 3.66 (*s*, MeO); 4.57 (*d*, *J* = 5.3), 4.86 (*d*, *J* = 5.0) (H–C(2), H–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.37, 25.42 (2*q*, *Me*$_2$C(4)); 28.05 (*q*, *Me*$_3$C); 35.76 (*t*, C(10)); 42.68, 44.74, 47.04 (3*d*, C(7), C(8), C(9)); 51.77 (*q*, MeO); 59.18 (*s*, C(1)); 77.97, 78.66 (2*d*, C(2), C(6)); 82.57 (*s*, Me$_3$*C*); 109.27 (*s*, C(4)); 170.62, 170.93, 174.09 (3*s*, 3 C=O). MALDI-TOF: 393 ([*M* + Na]$^+$). Anal. calc. for $C_{18}H_{26}O_8$ (370.40): C 58.37, H 7.07; found: C 58.42, H 7.03.

Data of **35**. ^{1}H-NMR (300 MHz, $CDCl_3$, **35**/**34** 4:1): data of **35**: 1.28, 1.43 (2*s*, Me$_2$C(4)); 1.41–1.50 (*m*, H–C(10)); 1.45 (*s*, *t*-Bu); 2.16 (br. *d*, *J* = 9.6, H′–C(10)); 2.56 (br. *d*, *J* = 3.6, H–C(7)); 3.14 (*dd*, *J* = 12.4, 4.1, H–C(8)); 3.35 (*d*, *J* = 11.8, H–C(9)); 3.68 (*s*, MeO); 4.37 (*d*, *J* = 5.2), 4.78 (*d*, *J* = 5.2) (H–C(2), H–C(6)); 8.4–9.2 (br. *s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$, **35**/**34** 4:1): data of **35**: 24.12, 25.22 (2*q*, *Me*$_2$C(4)); 27.86 (*q*, *Me*$_3$C); 35.48 (*t*, C(10)); 42.64, 44.71, 47.16 (3*d*, C(7), C(8), C(9)); 51.88 (*q*, MeO); 59.24 (*s*, C(1)); 77.61, 78.23 (2*d*, C(2), C(6)); 81.32 (*s*, Me$_3$*C*); 108.91 (*s*, C(4)); 170.47, 170.71, 175.89 (3*s*, 3 C=O).

tert-*Butyl* (±)-(*1*RS,*2*SR,*6*RS,*7*RS,*8*SR)*-8-(Methoxycarbonyl)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-1-carboxylate* (**36**). A suspension of **34** (1.5 g, 4.05 mmol) in CH_2Cl_2 (25 ml) was treated with $(COCl)_2$ (770 mg, 6 mmol) and DMF (10 µl), stirred for 2 h at 23°, and evaporated. A soln. of the residue in PhMe (50 ml) was added dropwise over a period of 1 h to a boiling suspension of 1-hydroxypyridine-2-thione sodium salt (725 mg, 4.8 mmol), *t*-BuSH (2 g, 21 mmol), and DMAP (20 mg) in toluene (120 ml). The suspension was stirred for 1 h, and cooled to 23°. Normal workup (toluene/H_2O) and FC (hexane/AcOEt 10:1) gave **36** (1.09 g, 82%). White solid. R_f (cyclohexane/AcOEt 3:1) 0.55. M.p. 104°. IR ($CHCl_3$): 3011*w*, 1726*s*, 1601*w*, 1437*w*, 1369*m*, 1328*w*, 1281*m*, 1163*m*, 1104*m*, 1063*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.27, 1.43 (2*s*, Me$_2$C(4)); 1.46 (*s*, *t*-Bu); 1.48 (*ddd*, *J* = 10.7, 3.1, 1.6, H–C(10)); 1.82 (*ddd*, *J* = 13.3, 5.8, 2.3, H$_{endo}$–C(9)); 1.89 (*dd*, *J* = 13.3, 11.2, H$_{exo}$–C(9)); 2.03 (*dt*, *J* = 10.6, 2.0, H′–C(10)); 2.55–2.56 (br. *d*, *J* = 4.6, H–C(7)); 2.89 (*ddd*, *J* = 11.2, 5.8, 4.7, H–C(8)); 3.70 (*s*, MeO); 4.09 (*dd*, *J* = 5.5, 1.2, H–C(6)); 4.25 (*dd*, *J* = 5.5, 1.6, H–C(2)). ^{13}C-NMR (125 MHz,

$CDCl_3$): 24.23, 25.42 (2*q*, *Me*$_2$C(4)); 28.11 (*q*, *Me*$_3$C); 30.67 (*t*, C(9)); 34.84 (*t*, C(10)); 41.66, 43.03 (2*d*, C(7), C(8)); 51.98 (*q*, MeO); 56.59 (*s*, C(1)); 80.69, 82.55 (2*d*, C(2), C(6)); 80.69 (*s*, Me$_3$*C*); 109.38 (*s*, C(4)); 171.64, 173.47 (2*s*, 2 C=O). ESI-MS: 327 ($[M+H]^+$). Anal. calc. for $C_{17}H_{26}O_6$ (326.39): C 62.56, H 8.03; found: C 62.61, H 7.93.

tert-*Butyl* *(±)-(1*RS*,2*SR*,6*RS*,7*RS*,8*RS*)-8-(Methoxycarbonyl)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]-decane-1-carboxylate* (**37**). A soln. of **36** (930 mg, 2.85 mmol) in 0.13M MeONa in MeOH (60 ml) was stirred for 2 d at 23°. The mixture was treated with AcOH (1 ml), and evaporated. Normal workup (CH_2Cl_2/H_2O) and FC (hexane/AcOEt 11:1 → 10:1) gave **37** (619 mg) and **36** (251 mg). The recovered **36** was subjected to 0.1M MeONa in MeOH (20 ml) for 2 d. Addition of AcOH (0.3 ml), normal workup (CH_2Cl_2/H_2O) and FC (hexane/AcOEt 11:1 → 10:1) gave **37** (183 mg, 86% overall). White solid. R_f (cyclohexane/AcOEt 3:1) 0.45. M.p. 99°. IR ($CHCl_3$): 3016*w*, 2974*w*, 2929*w*, 1727*s*, 1600*w*, 1437*w*, 1369*m*, 1158*s*, 1088*m*, 1047*m*, 909*w*, 865*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.28, 1.43 (2*s*, Me$_2$C(4)); 1.46 (*s*, *t*-Bu); 1.58 (*ddd*, *J* = 10.8, 2.9, 1.4, H–C(10)); 1.61 (*ddd*, *J* ≈ 13, 9.0, 2.3, H$_{endo}$–C(9)); 1.89 (*ddd*, *J* = 11.0, 3.8, 1.5, H′–C(10)); 2.09 (*dd*, *J* = 13.1, 5.2, H$_{exo}$–C(9)); 2.25 (*ddd*, *J* = 9.0, 5.2, 1.4, H–C(8)); 2.51 (br. *s*, H–C(7)); 3.70 (*s*, MeO); 4.12 (*d*, *J* = 5.2, H–C(2)); 4.60 (*dd*, *J* = 5.5, 1.6, H–C(6)). ^{13}C-NMR (100 MHz, $CDCl_3$; assignments based on HSQC.GRASP spectrum): 24.23, 25.38 (2*q*, *Me*$_2$C(4)); 28.08 (*q*, *Me*$_3$C); 31.51 (*t*, C(10)); 32.12 (*t*, C(9)); 41.11 (*d*, C(8)); 43.84 (*d*, C(7)); 52.13 (*q*, MeO); 55.84 (*s*, C(1)); 80.69 (*s*, Me$_3$*C*); 81.58 (*d*, C(2)); 82.90 (*d*, C(6)); 110.00 (*s*, C(4)); 171.56, 174.58 (2*s*, 2 C=O). ESI-MS: 327 ($[M+H]^+$), 344 ($[M+NH_4]^+$). Anal. calc. for $C_{17}H_{26}O_6$ (326.39): C 62.56, H 8.03; found: C 62.51, H 7.98.

X-Ray Crystal-Structure Analysis of **37** (CCDC-203883). Crystals were obtained from Et_2O by slow evaporation at r.t. $C_{17}H_{26}O_6$ (326.389); triclinic P_1; $a = 6.22230(10)$ Å, $b = 10.7846(2)$ Å, $c = 13.6025(3)$ Å; $V = 886.23(3)$ Å^3; $D_{calc.} = 1.223$ Mg/m^3; $Z = 2$; Intensities were measured on an *Bruker Nonius KappaCCD* diffractometer (graphite monochromator, MoK_α, $\lambda = 0.71073$ Å at 172 K. Of the 10413 reflections, 4663 unique reflections were observed. $R = 0.0774$; $R_w = 0.1736$. The structure was refined by the direct method with SHELXL-97 [53].

*(±)-(1*RS*,2*SR*,6*RS*,7*RS*,8*RS*)-8-(Methoxycarbonyl)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-1-carboxylic Acid* (**38**). A soln. of **37** (500 mg, 1.5 mmol) and Et_3N (190 mg, 1.8 mmol) in CH_2Cl_2 (20 ml) was treated with Me_3SiOTf (750 mg, 3.4 mmol), stirred for 14 h at 23°, treated with $NaHCO_3$ (415 mg, 4.6 mmol) and H_2O (15 ml), stirred for 30 min, acidified to pH 3 with 0.2N aq. HCl, and extracted with CH_2Cl_2 (3 × 10 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (cyclohexane/AcOEt/AcOH 100:50:0.5 → 100:75:0.5) gave **38** (369 mg, 89%). White solid. R_f (cyclohexane/AcOEt/AcOH 10:5:0.05) 0.31. M.p. 153°. IR ($CHCl_3$): 3600–2400*m* (br.), 1733*s*, 1451*w*, 1437*w*, 1384*m*, 1376*m*, 1271*m*, 1176*m*, 1076*w*, 1047*m*, 946*w*, 863*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.32, 1.48 (2*s*, Me$_2$C(4)); 1.64 (*ddd*, *J* = 11.1, 4.2, 2.3, H–C(10)); 1.68–1.71 (br. *d*, *J* = 9.4, H$_{endo}$–C(9)); 1.96 (*dd*, *J* = 11.0, 1.5, H′–C(10)); 2.28 (*dd*, *J* = 9.3, 5.2, H$_{exo}$–C(9)); 2.27–2.29 (*m*, H–C(8)); 2.59 (br. *s*, H–C(7)); 3.71 (*s*, MeO); 4.19 (br. *d*, *J* = 5.1, H–C(6)); 4.28 (*dd*, *J* = 5.4, 1.6, H–C(2)). ^{13}C-NMR (100 MHz, $CDCl_3$; assignments based on HSQC.GRASP spectrum): 24.19, 25.35 (2*q*, *Me*$_2$C(4)); 32.04 (2*t*, C(9), C(10)); 40.99 (*d*, C(8)); 44.12 (*d*, C(7)); 52.26 (*q*, MeO); 54.63 (*s*, C(1)); 81.73 (*d*, C(6)); 82.30 (*d*, C(2)); 110.57 (*s*, C(4)); 174.18, 177.12 (2*s*, 2 C=O). ESI-MS: 269 ($[M-H]^-$). Anal. calc. for $C_{13}H_{18}O_6$ (270.28): C 57.77, H 6.71; found: C 57.96, H 6.84.

Methyl *(±)-(1*RS*,2*SR*,6*RS*,7*RS*,8*RS*)-1-{[(Benzyloxy)carbonyl]amino}-4,4-dimethyl-3,5-dioxatricyclo-[5.2.1.0^{2,6}]decane-8-carboxylate* (**39**). A soln. of **38** (250 mg, 0.92 mmol) and Et_3N (112 mg, 1.1 mmol) in PhMe (30 ml) was treated with diphenylphosphoryl azide (DPPA; 305 mg, 1.1 mmol), heated slowly to 110° within 3 h, treated with BnOH (1 g, 9.2 mmol) and CuCl (15 mg), stirred for 5 h, and cooled to 23°. Normal workup (toluene/H_2O), evaporation of the residual BnOH in a bulb-to-bulb apparatus at 60°/0.5 Torr, and FC (cyclohexane/AcOEt 3:1) gave **39** (307 mg, 88%). Pale yellow syrup, which solidified upon standing. R_f (cyclohexane/AcOEt 1:1) 0.60. M.p. 79°. IR ($CHCl_3$): 3442*w*, 2946*w*, 1728*s*, 1509*m*, 1272*m*, 1051*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.30, 1.45 (2*s*, Me$_2$C(4)); 1.69–1.74 (*m*, 2 H–C(10)); 1.89 (br. *s*, H–C(8)); 2.31–2.38 (*m*, 2 H–C(9)); 2.46 (br. *s*, H–C(7)); 3.69 (*s*, MeO); 4.18 (*d*, *J* = 5.5, H–C(2)); 4.22 (br. *s*, H–C(6)); 5.05, 5.13 (2*d*, *J* = 12.3, PhC*H*$_2$); 5.28 (br. *s*, HN); 7.30–7.38 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.31, 25.42 (2*q*, *Me*$_2$C(4)); 31.53, 33.24 (2*t*, C(9), C(10)); 41.53, 41.69 (2*d*, C(7), C(8)); 52.12 (*q*, MeO); 62.50 (*s*, C(1)); 66.57 (*t*, PhC*H*$_2$); 80.06, 81.28 (2*d*, C(2), C(6)); 110.31 (*s*, C(4)); 128.05, 128.06, 128.18, 128.34, 128.49 (5*d*); 136.42 (*s*); 155.51 (*s*, N–C=O); 174.55 (*s*, O–C=O). ESI-MS: 376 ($[M+H]^+$). Anal. calc. for $C_{20}H_{25}NO_6$ (375.42): C 63.99, H 6.71, N 3.73; found: C 63.98, H 6.77, N 3.64.

Benzyl *(±)-(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-[8-(Hydroxymethyl)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl]carbamate* (**40**). A soln. of **39** (250 mg, 0.67 mmol) in THF (25 ml) was treated with $LiBH_4$ (120 mg, 5.5 mmol), stirred for 48 h at 23°, treated with 10% aq. NaH_2PO_4 soln. (20 ml), stirred for 1 h, and extracted

with CH_2Cl_2 (1 × 40 ml, 3 × 10 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (cyclohexane/AcOEt 1:2) gave **40** (213 mg, 92%). Colourless foam. R_f (cyclohexane/AcOEt 1:2) 0.31. M.p. 47–49°. IR ($CHCl_3$): 3619*w*, 3434*w*, 2982*w*, 2929*w*, 1720*s*, 1510*s*, 1457*w*, 1384*w*, 1275*m*, 1164*w*, 1053*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.45, 1.53 (2*s*, Me_2C(4)); 1.55–1.73 (*m*, H–C(8), 2 H–C(9), 2 H–C(10), OH); 2.04 (br. *s*, H–C(7)); 3.54 (br. *s*, CH_2–C(8)); 4.08 (br. *d*, *J* = 5.6, H–C(6)); 4.16 (br. *d*, *J* = 5.6, H–C(2)); 5.04, 5.09 (2*d*, *J* = 12.2, PhCH_2); 5.21 (br. *s*, NH); 7.35–7.58 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; assignments based on HSQC.GRASP spectrum): 24.35, 25.49 (2*q*, *Me*$_2$C(4)); 30.76, 31.68 (2*t*, C(9), C(10)); 39.02, 39.73 (2*d*, C(7), C(8)); 62.72 (*s*, C(1)); 65.54 (*t*, Ph*C*H_2); 66.51 (*t*, *C*H_2–C(8)); 80.96, 81.84 (2*d*, C(2), C(6)); 110.19 (*s*, C(4)); 128.07 (*d*); 128.11 (2*d*); 128.53 (2*d*); 136.47 (*s*); 155.60 (*s*, C=O). ESI-MS: 348 ($[M+H]^+$). Anal. calc. for $C_{19}H_{25}NO_5$ (347.41): C 65.69, H 7.25, N 4.03; found: C 65.56, H 7.22, N 3.97.

tert-*Butyl* (±)-*(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-[8-(Hydroxymethyl)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl]carbamate* (**41**). A suspension of **40** (72 mg, 0.21 mmol), 10% Pd/C (80 mg), and cyclohexa-1,4-diene (160 mg, 2 mmol) in EtOH (1.5 ml) was heated to 70°, stirred for 2 h, cooled to 23°, treated with Boc_2O (67.8 mg, 0.31 mmol), stirred for 20 h, and evaporated. FC (cyclohexane/AcOEt 1:1) gave **41** (55 mg, 84%). Colourless foam. R_f (cyclohexane/AcOEt 1:1) 0.18. M.p. 50–52°. IR ($CHCl_3$): 3438*w*, 1709*s*, 1602*m*, 1504*s*, 1368*m*, 1274*m*, 1163*s*, 1017*w*, 861*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.30, 1.46 (2*s*, Me_2C(4)); 1.44 (*s*, *t*-Bu); 1.42–1.70 (*m*, H–C(8), 2 H–C(9), 2 H–C(10)); 1.78 (br. *s*, OH); 2.16 (br. *s*, H–C(7)); 3.50–3.55 (*m*, CH_2–C(8)); 4.03 (*dd*, *J* = 5.6, 1.3), 4.15 (br. *d*, *J* = 5.6) (H–C(2), H–C(6)); 4.93 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.33, 25.52 (2*q*, *Me*$_2$C(4)); 28.43 (*q*, *Me*$_3$*C*); 30.70, 31.47 (2*t*, C(9), C(10)); 39.06, 39.69 (2*d*, C(7), C(8)); 62.53 (*s*, C(1)); 65.63 (*t*, *C*H_2–C(8)); 79.31 (*s*, Me_3*C*); 81.27, 81.77 (2*d*, C(2), C(6)); 110.07 (*s*, C(4)); 155.25 (*s*, C=O). ESI-MS: 314 ($[M+H]^+$). Anal. calc. for $C_{16}H_{27}NO_5$ (313.39): C 61.32, H 8.68, N 4.47; found: C 61.45, H 8.65, N 4.27.

(±)-*(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-1-Amino-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-methanol* (**43**). A suspension of **40** (65 mg, 0.187 mmol) and 10% Pd/C (5 mg) in EtOH (3 ml) was hydrogenated for 2 h at 23° under H_2, and filtered. Evaporation of the filtrate and FC (CH_2Cl_2/NEt_3 10:0 → 10:1) of the residue gave **43** (30 mg, 75%). Colourless oil. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 10:1:0.1) 0.34. IR ($CHCl_3$): 3631*w*, 3373*w*, 3273*m*, 2992*s*, 1667*w*, 1590*w*, 1456*w*, 1383*s*, 1375*s*, 1318*m*, 1272*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.08–1.16 (*m*, H_{exo}–C(9), H–C(10)); 1.29, 1.44 (2*s*, Me_2C(4)); 1.32–1.35 (*m*, H_{endo}–C(9)); 1.57–1.68 (*m*, H–C(8), H′–C(10)); 2.09 (br. *s*, H–C(7)); 2.20 (br. *s*, NH_2, OH); 3.48 (*d*, *J* = 7.8, CH_2–C(8)); 3.73 (*dd*, *J* = 5.6, 1.3), 4.13 (br. *d*, *J* = 5.6) (H–C(2), H–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.20, 25.37 (2*q*, *Me*$_2$C(4)); 34.47, 34.57 (2*t*, C(9), C(10)); 39.33, 40.56 (2*d*, C(7), C(8)); 62.47 (*s*, C(1)); 65.11 (*t*, *C*H_2–C(8)); 82.38, 82.95 (2*d*, C(2), C(6)); 109.52 (*s*, C(4)). HR-ESI-MS: 214.1431 ($[M+H]^+$, $C_{11}H_{20}NO_3^+$; calc. 214.1443).

(±)-*(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-1-Amino-5-(hydroxymethyl)bicyclo[2.2.1]heptane-2,3-diol* (**5**). A soln. of **41** (55 mg, 0.18 mmol) in CH_2Cl_2 (1 ml) was treated with 2N aq. HCl (5 ml) and stirred for 36 h. The aq. layer was separated and evaporated. FC (*Amberlite CG-120,* H_2O/NH_3 1:0 → 95:5) gave **5** (25.8 mg, 85%). White solid. For anal. purpose, **5** was transformed into its HCl salt.

Data of **5**·HCl. pK_{HA} 8.60. IR (KBr): 3600–2800*s* (br.), 1623*m*, 1507*m,* 1453*w*, 1395*m*, 1307*m*, 1196*m*, 1093*s*, 1048*s*. ^{1}H-NMR (300 MHz, D_2O): 1.31 (*dd*, *J* = 12.5, 5.0, H_{exo}–C(6)); 1.57–1.89 (*m*, H–C(5), H_{endo}–C(6), 2 H–C(7)); 2.14 (br. *s*, H–C(4)); 3.45 (*d*, *J* = 7.5, CH_2–C(5)); 3.79 (*dd*, *J* = 6.1, 1.8, H–C(3)), 3.94 (br. *d*, *J* = 5.9, H–C(2)). ^{13}C-NMR (75 MHz, D_2O): 30.94, 31.50 (2*t*, C(6), C(7)); 38.25, 42.67 (2*d*, C(4), C(5)); 61.60 (*s*, C(1)); 63.81 (*d*, *C*H_2–C(5)); 72.70, 73.07 (2*d*, C(2), C(3)). ESI-MS: 174 ($[M+H]^+$). Anal. calc. for $C_8H_{16}ClNO_3$·0.5 H_2O (218.68): C 43.94, H 7.84, N 6.41; found: C 43.68, H 7.45, N 6.21.

(±)-*(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-[1-(Benzylamino)-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-yl]methanol* (**44**). A suspension of **40** (118 mg, 0.34 mmol), cyclohexa-1,4-diene (272 mg, 3.3 mmol) and 10% Pd/C (100 mg) in EtOH (10 ml) was stirred at 60° for 1 h, filtered through a short pad of *Celite,* and evaporated. A soln. of the resulting crude amine **43** in $PhCH_3$ (30 ml) was treated with PhCHO (70 mg, 0.68 mmol). The mixture was boiled under reflux for 15 h, azeotropically removing H_2O with a *Dean–Stark* condenser. After evaporation, a soln. of the residue in MeOH/THF 1:1 (20 ml) was treated with $NaBH_4$ (50 mg, 1.31 mmol) and stirred for 3 h at 23°. The mixture was diluted with Et_2O (20 ml), treated with 10% aq. NaH_2PO_4 soln. (10 ml) and stirred for 2 h. The org. layer was separated. The aq. layer was brought to pH 8 with 2N NaOH and extracted with CH_2Cl_2 (2 × 15 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. FC (AcOEt/aq. NH_3 100:1) afforded **44** (92 mg, 89%). Colourless solid. R_f (AcOEt/aq. NH_3 100:1) 0.20. M.p. 123°. IR ($CHCl_3$): 3512*w*, 3310*w*, 2991*s*, 1605*m*, 1493*w*, 1455*s*, 1317*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.23 (*dd*, *J* = 12.5, 5.2, H_{exo}–C(9)); 1.32, 1.45 (2*s*, Me_2C(4)); 1.32–1.42 (*m*, H_{endo}–C(9), H–C(10)); 1.52 (br. *d*, *J* = 10.2, H′–C(10)); 1.61–1.69 (*m*, H–C(8)); 1.76 (br. *s*, NH, OH); 2.13 (br. *s*, H–C(7)); 3.52 (*d*, *J* = 7.8, CH_2–C(8)); 3.71, 3.82 (2*d*, *J* = 12.4, PhCH_2); 4.04 (*dd*, *J* = 5.6, 1.6), 4.18 (br. *d*, *J* = 5.6) (H–C(2), H–C(6)); 7.21–7.37 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 24.31, 25.54

(2*q*, Me_2C(4)); 31.32, 32.29 (2*t*, C(9), C(10)); 39.31, 39.84 (2*d*, C(7), C(8)); 48.95 (*t*, Ph*C*H_2); 65.77 (*t*, CH_2–C(8)); 67.31 (*s*, C(1)); 80.19, 82.09 (2*d*, C(2), C(6)); 109.67 (*s*, C(4)); 126.88 (*d*); 128.10 (2*d*); 128.36 (2*d*); 140.83 (*s*). ESI-MS: 304 ($[M+H]^+$). Anal. calc. for $C_{18}H_{25}NO_3$ (303.40): C 71.26, H 8.31, N 4.62; found: C 71.54, H 8.52, N 4.61.

(±)-*(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-1-(Benzylamino)-5-(hydroxymethyl)bicyclo[2.2.1]heptane-2,3-diol* (**42**). A soln. of **44** (67 mg, 0.22 mmol) in THF (0.5 ml) and 2N HCl (5 ml) was stirred for 5 d at 23°. Evaporation and FC (*Amberlite CG-120*, H_2O/NH_3 1:0 → 95:5) gave **42** (54 mg, 93%). Colourless oil. pK_{HA} 8.2. For anal. purpose, **42** was transformed into its HCl salt.

Data of **42**·HCl. IR (KBr): 3600–2200*s* (br.), 1960*w*, 1886*w*, 1815*w*, 1668*m*, 1605*m*, 1585*m*, 1497*m*, 1453*s*, 1383*s*, 1294*s*, 1202*s*. ^{1}H-NMR (500 MHz, CD_3OD): 1.23 (*dd*, *J* = 12.4, 5.1, H_{exo}–C(6)); 1.37 (br. *d*, *J* = 10.2, H–C(7)); 1.47 (br. *t*, *J* = 12.4, H_{endo}–C(6)); 1.55 (br. *d*, *J* = 10.2, H′–C(7)); 1.68 (br. *d*, *J* = 7.7, H–C(5)); 2.01 (br. *s*, H–C(4)); 3.39 (*d*, *J* = 7.7, CH_2–C(5)); 3.66, 3.84 (2*d*, *J* = 11.9, PhCH_2); 3.70 (*dd*, *J* = 6.1, 1.7), 3.81 (*dd*, *J* = 6.1, 0.9) (H–C(2), H–C(3)); 7.23–7.48 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, CD_3OD): 32.77, 33.04 (2*t*, C(6), C(7)); 40.83, 44.24 (2*d*, C(4), C(5)); 59.96 (*t*, Ph*C*H_2); 66.06 (*t*, CH_2–C(5)); 68.40 (*s*, C(1)); 73.02, 75.09 (2*d*, C(2), C(3)); 128.35 (*d*); 129.61 (4*d*); 141.01 (*s*). HR-ESI-MS: 264.1591 ($[M+H]^+$, $C_{15}H_{22}NO_3^+$; calc. 264.160).

*Benzyl (±)-(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-{8-[(Methoxymethoxy)methyl]-4,4-dimethyl-3,5-dioxatricyclo-[5.2.1.0^{2,6}]dec-1-yl}carbamate* (**47**). A soln. of **40** (110 mg, 0.317 mmol), Bu_4NI (10 mg), and Et_3N (1.46 g, 14.4 mmol) in THF (5 ml) was treated with MOMCl (255 mg, 3.2 mmol). The mixture was stirred for 24 h at 65°, diluted with $CHCl_3$ (10 ml) and H_2O (10 ml), and brought to pH 3 with 2N HCl. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (cyclohexane/AcOEt 2:1) gave **47** (122 mg, 98%). Colourless oil. R_f (cyclohexane/AcOEt 1:1) 0.56. IR ($CHCl_3$): 3437*w*, 3010*m*, 2937*m*, 1721*s*, 1509*s*, 1454*w*, 1384*m*, 1375*m*, 1272*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.30, 1.45 (2*s*, Me_2C(4)); 1.57–1.83 (*m*, H–C(8), 2 H–C(9), 2 H–C(10)); 2.19 (br. *s*, H–C(7)); 3.35 (*s*, *Me*OCH$_2$); 3.38–3.48 (*m*, CH_2–C(8)); 4.10, 4.17 (2*d*, *J* = 5.3, H–C(2), H–C(6)); 4.59 (br. *s*, MeOCH_2); 5.04, 5.10 (2*d*, *J* = 12.1, PhCH_2); 5.19 (br. *s*, NH); 7.29–7.37 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.44, 25.59 (2*q*, Me_2C(4)); 31.21, 31.88 (2*t*, C(9), C(10)); 36.64, 40.19 (2*d*, C(7), C(8)); 55.31 (*q*, *Me*OCH$_2$); 62.74 (*s*, C(1)); 66.52 (*t*, *C*H_2–C(8)); 70.52 (*t*, Ph*C*H_2); 80.80, 81.79 (2*d*, C(2), C(6)); 96.47 (*t*, MeO*C*H_2); 110.04 (*s*, C(4)); 128.0 (3*d*); 128.43 (2*d*); 136.35 (*s*); 155.41 (*s*, C=O). ESI-MS: 414.2 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{29}NO_6$ (391.46): C 64.43, H 7.47, N 3.58; found: C 64.55, H 7.59, N 3.58.

*(±)-(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-8-[(Methoxymethoxy)methyl]-4,4-dimethyl-1-(phenylamino)-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane* (**48**). A suspension of **47** (53 mg, 0.136 mmol) and 10% Pd/C (10 mg) in EtOH (6 ml) was hydrogenated for 12 h at 23° under H_2. After filtration and evaporation, a soln. of the residue in PhMe (6 ml) was treated with *t*-BuOK (30 mg, 0.26 mmol), PhBr (45 mg, 0.28 mmol), BINAP (13 mg, 0.021 mmol), and [Pd_2(dba)$_3$] (10 mg, 0.011 mmol). The mixture was kept at reflux for 6 h and evaporated. FC (hexane/AcOEt 2:1), treatment with activated charcoal (20 mg) in CH_2Cl_2 (2 ml) for 12 h, and FC (hexane/AcOEt 3:1) gave **48** (34 mg, 75%). Colourless solid. R_f (cyclohexane/AcOEt 2:1) 0.32. M.p. 97°. IR ($CHCl_3$): 3423*w*, 3031*w*, 3010*s*, 2934*s*, 2033*w*, 1940*w*, 1922*w*, 1831*w*, 1726*w*, 1602*s*, 1498*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.32, 1.48 (2*s*, Me_2C(4)); 1.53–1.64 (*m*, 2 H–C(9)); 1.65–1.73 (*m*, 2 H–C(10)); 1.77–1.86 (*m*, H–C(8)); 2.19 (br. *s*, H–C(7)); 3.37 (*s*, *Me*OCH$_2$); 3.46 (*dd*, *J* ≈ 12, 9.6), 3.48 (*dd*, *J* = 13.6, 9.7) (CH_2–C(8)); 4.11 (*dd*, *J* = 5.6, 1.3, H–C(6)); 4.21 (*d*, *J* = 5.6, H–C(2)); 4.13 (br. *s*, NH); 4.63 (*s*, MeOCH_2); 6.74–6.79, 7.13–7.20 (5 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.42, 25.63 (2*q*, Me_2C(4)); 31.89, 32.31 (2*t*, C(9), C(10)); 37.03, 40.14 (2*d*, C(7), C(8)); 55.30 (*s*, *Me*OCH$_2$); 65.84 (*s*, C(1)); 70.61 (*t*, *C*H_2–C(8)); 81.18, 81.90 (2*d*, C(2), C(6)); 96.43 (*t*, MeO*C*H_2); 109.88 (*s*, C(4)); 116.83 (2*d*); 118.68 (*d*); 128.87 (2*d*); 146.76 (*s*). HR-ESI-MS: 334.2009 ($[M+H]^+$, $C_{19}H_{28}NO_4^+$; calc. 334.2018), 356.1829 ($[M+Na]^+$, $C_{19}H_{27}NNaO_4^+$; calc. 356.1838). Anal. calc. for $C_{19}H_{27}NO_4$ (333.43): C 68.44, H 8.16, N 4.20; found: C 68.16, H 8.06, N 4.16.

*(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-(Hydroxymethyl)-1-(phenylamino)bicyclo[2.2.1]heptane-2,3-diol* (**45**). A soln. of **48** (20 mg, 0.06 mmol) in MeOH (4 ml) was treated with 2N HCl (4 ml), stirred for 42 h, and evaporated. FC (*Amberlite CG-120,* H_2O/NH_3 1:0 → 95:5) gave **45** (12 mg, 80%). Colourless solid. pK_{HA} 4.66. IR (KBr): 3600–2400*s* (br.), 1940*w*, 1924*w*, 1901*w*, 1833*w*, 1818*w*, 1761*w*, 1600*s*, 1509*s*, 1497*s*. ^{1}H-NMR (300 MHz, D_2O): 1.25 (*dd*, *J* = 12.5, 5.0, H_{exo}–C(6)); 1.47 (*td*, *J* = 12.5, 1.9, H_{endo}–C(6)); 1.57 (br. *d*, *J* = 10.3, H–C(7)); 1.74 (br. *q*, *J* ≈ 6.5, H–C(5)); 2.03 (br. *d*, *J* = 10.3, H′–C(7)); 2.14 (br. *s*, H–C(4)); 3.31 (*d*, *J* = 7.2, CH_2–C(5)); 3.80, 3.92 (2*d*, *J* = 5.9, H–C(2), H–C(3)); 7.44–7.56 (5 arom. H). ^{13}C-NMR (75 MHz, D_2O): 33.10 (*t*, C(6), C(7)); 39.17, 41.70 (2*d*, C(4), C(5)); 64.35 (*s*, C(1)); 66.28 (*d*, *C*H_2–C(5)); 72.26, 74.22 (2*d*, (C(2), C(3)); 118.36 (2*d*); 120.19 (*d*); 129.04 (2*d*); 146.23 (*s*). HR-ESI-MS: 250.1447 ($[M+H]^+$, $C_{14}H_{20}NO_3^+$; calc. 250.1443), 272.1253 ($[M+Na]^+$, $C_{14}H_{19}NNaO_3^+$; calc. 250.1296).

*(±)-(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-{1-[3-(4-Methoxyphenyl)oxaziridin-2-yl]-4,4-dimethyl-3,5-dioxatricyclo-[5.2.1.0^{2,6}]dec-8-yl}methanol* (**49**). A suspension of **40** (120 mg, 0.346 mmol) and 10% Pd/C (10 mg) in EtOH (5 ml) was hydrogenated for 4 h at 24° under H_2. The mixture was filtered and evaporated. A soln. of the resulting crude amine **43** in CH_2Cl_2 (5 ml) and MeOH (1 ml) was treated with anisaldehyde (56 mg, 0.41 mmol) and $MgSO_4$ (400 mg), stirred for 20 h at 24°, filtered, and evaporated. A soln. of the residue in $ClCH_2CH_2Cl$ (2 ml) at 0° was treated with a previously dried ($MgSO_4$) soln. of *m*-CPBA (90 mg, 0.51 mmol) in $ClCH_2CH_2Cl$ (5 ml), stirred for 75 min, and treated with sat. aq. $NaHCO_3$ soln. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (2×10 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. FC (hexane/AcOEt 1:1 → 1:2) gave **49** (93 mg, 78%) as a diastereoisomeric mixture in a ratio of 68:32. Colourless foam.

Data of the 68:32 Mixture. R_f (cyclohexane/AcOEt 1:2) 0.32. IR ($CHCl_3$): 3612*w*, 3446*w*, 3010*m*, 2936*m*, 2840*m*, 1614*m*, 1518*s*, 1457*w*. ^{1}H-NMR (300 MHz, $CHCl_3$): 1.26 (*s*, 2.04 H), 1.32 (*s*, 0.96 H), 1.50 (*s*, 2.04 H), 1.52 (*s*, 0.96 H) (Me_2C(4)); 1.30–1.80 (*m*, H–C(8), 2 H–C(9), 2 H–C(10)); 2.24 (br. *s*, 0.32 H), 2.26 (br. *s*, 0.68 H), (H–C(7)); 3.50–3.57 (*m*, CH_2–C(8)); 3.80 (*s*, MeO); 4.16–4.22 (*m*, H–C(2), H–C(6)); 4.87 (*s*, 0.68 H), 5.01 (*s*, 0.32 H) (ArC*H*); 6.87–6.91, 7.32–7.39 (2*m*, 4 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): major and minor isomer: 24.22, 25.59 (2*q*, *Me*$_2$C(4)); 55.40 (*q*, MeO); 65.36 (*t*, *C*H_2–C(8)); 110.15 (*s*, C(4)); 127.00 (*s*); 128.57 (2*d*); 160.74 (*s*); major isomer: 25.16, 32.27 (2*t*, C(9), C(10)); 37.85, 39.81 (2*d*, C(7), C(8)); 75.69 (*s*, C(1)); 78.27 (*d*, Ar*C*H); 81.39, 82.17 (2*d*, C(2), C(6)); 113.92 (2*d*); minor isomer: 29.10, 31.82 (2*t*, C(9), C(10)); 38.84, 40.31 (2*d*, C(7), C(8)); 74.01 (*s*, C(1)); 75.34 (*d*, Ar*C*H); 81.00, 82.22 (2*d*, C(2), C(6)); 113.81 (2*d*). HR-ESI-MS: 348.1804 ([*M*+H]$^+$, $C_{19}H_{26}NO_5^+$; calc. 348.1811), 370.1621 ([*M*+Na]$^+$, $C_{19}H_{25}NNaO_5^+$; calc. 370.1630).

*(±)-(1*RS*,2*RS*,6*SR*,7*SR*,8*SR*)-8-(Hydroxymethyl)-4,4-dimethyl-1-{[(4-methoxyphenyl)methyl]imino}-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane* N-*Oxide* (**50**). Neat **49** (123 mg, 0.355 mmol) was heated in a bulb-to-bulb distillation apparatus for 4 min at 200°/0.5 Torr. FC (CH_2Cl_2/MeOH/Et_3N 100:5:2) gave **50** (77 mg, 63%). White powder. R_f (CH_2Cl_2/MeOH 10:0.8) 0.50. M.p. 224° (dec.). IR (KBr): 3369*m* (br.), 1604*s*, 1568*w*, 1510*s*, 1466*w*, 1420*m*, 1382*m*, 1326*m*, 1304*w*, 1206*s*, 1174*s*, 1050*s*. ^{1}H-NMR (300 MHz, CD_3OD): 1.32, 1.43 (2*s*, Me_2C(4)); 1.49 (*dd*, *J* = 12.8, 5.3, H_{exo}–C(9)); 1.73–1.83 (*m*, H–C(8)); 1.89 (br. *d*, *J* = 10.0, H–C(10)); 2.02 (br. *t*, *J* = 12.8, H_{endo}–C(9)); 2.14 (br. *d*, *J* ≈ 9.3, H′–C(10)); 2.31 (br. *s*, H–C(7)); 3.48–3.51 (*m*, CH_2–C(8)); 3.86 (*s*, MeO); 4.33 (*d*, *J* = 5.6, H–C(2)); 4.52 (*dd*, *J* = 5.6, 1.6, H–C(6)); 6.99–7.03, 8.30–8.33 (2*m*, 4 arom. H). ^{13}C-NMR (75 MHz, CD_3OD): 24.20, 25.37 (2*q*, *Me*$_2$C(4)); 31.79, 33.34 (2*t*, C(9), C(10)); 39.26, 41.36 (2*d*, C(7), C(8)); 55.60 (*q*, MeO); 65.03 (*t*, *C*H_2–C(8)); 81.08 (*s*, C(1)); 81.84, 82.87 (2*d*, C(2), C(6)); 111.25 (*s*, C(4)); 114.48 (2*d*); 123.53 (*s*); 132.79 (2*d*); 138.20 (*d*, C=N); 163.10 (*s*). HR-ESI-MS: 348.1801 ([*M*+H]$^+$, $C_{19}H_{26}NO_5^+$; calc. 348.1811). Anal. calc. for $C_{19}H_{25}NO_5$ (347.41): C 65.69, H 7.25, N 4.03; found: C 65.47, H 7.11, N 3.90.

*[(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-2,3-Dihydroxy-5-(hydroxymethyl)bicyclo[2.2.1]hept-1-yl](hydroxy)ammonium Chloride* (**46**). A suspension of **50** (50 mg, 0.14 mmol) in 2N HCl (2 ml) was stirred for 15 h at 20° and evaporated. FC (*RP-18*, H_2O → H_2O/MeOH 6:4) gave **46** (23 mg, 71%). Colourless powder. pK_{HA} 4.92. IR (KBr): 3650–2250*s* (br.), 1626*w*, 1453*w*, 1402*m*, 1193*w*, 1050*m*. ^{1}H-NMR (300 MHz, D_2O): 1.42 (*dd*, *J* = 11.8, 4.4, H_{exo}–C(6)); 1.64 (br. *d*, *J* = 10.6, H–C(7)); 1.71–1.88 (*m*, H–C(5), H_{endo}–C(6), H′–C(7)); 1.94 (br. *s*, H–C(4)); 3.46 (*d*, *J* = 7.5, CH_2–C(5)); 3.98 (br. *s*, H–C(2), H–C(3)). ^{13}C-NMR (75 MHz, D_2O): 28.21, 29.02 (C(6), C(7)); 37.62, 42.83 (C(4), C(5)); 63.68 (C(1)); 69.89 (*C*H_2–C(5)); 70.39, 72.74 (C(2), C(3)). HR-ESI-MS: 190.1071 ([*M*+H]$^+$, $C_8H_{16}NO_4^+$; calc. 190.1079), 379.2122 ([2*M*+H]$^+$, $C_{16}H_{31}N_2O_8^+$; calc. 379.2080).

Inhibition of Snail β-Mannosidase. Inhibition constants were determined in the same way as reported in [27] at 25° with 0.04M AcOH/AcONa buffer at the indicated pH and with 4-nitrophenyl β-D-mannopyranoside as substrate. The IC_{50} values were determined at a substrate concentration corresponding to K_M.

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