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Synthesis of aminocyclopentanols: α-D-*galacto* configured sugar mimics

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Four aminocyclopentanols, as mimics of putative intermediates in the hydrolysis of α-D-galactosides, have been synthesized through a number of stereoselective transformations using the *cis*-fused cyclopentane-1,4-lactone (1*R*, 5*S*, 7*R*, 8*R*)-7,8-dihydroxy-2-oxabicyclo[3.3.0]oct-3-one **1** as a chiral building block. The compounds were tested towards various glycosidases but showed no anomer selectivity in the inhibition of α- and β-galactosidases.

Introduction

Glycosidases are enzymes which very efficiently play a range of roles in biological systems. As a consequence of this, glycosidase inhibitors are used in the treatment and investigation of a wide range of diseases such as diabetes, viral infections and cancer.[1] The interest in the design of potent and selective glycosidase inhibitors has dramatically emerged since the first naturally occurring gylcosidase inhibitors were isolated in the late 1970s.[2] One of these was 1-deoxynojirimycin, which was shown to be a good α-glucosidase inhibitor. Since then a range of naturally occurring glycosidase inhibitors have been isolated from natural sources. The differences in structures of these inhibitors reflect the marked substrate specificity of most glycosidases and their structures have often been an inspiration for the design of synthetic analogues in order to improve their efficiency.

The mechanism of enzymatic cleavage of glycosides has been continuously under debate and the design of new inhibitors has been based on the structural similarity of putative intermediates or transition states (Fig. 1), like the oxocarbenium ion **D** or species **C**, having some carbonium ion character at C-1.[3]

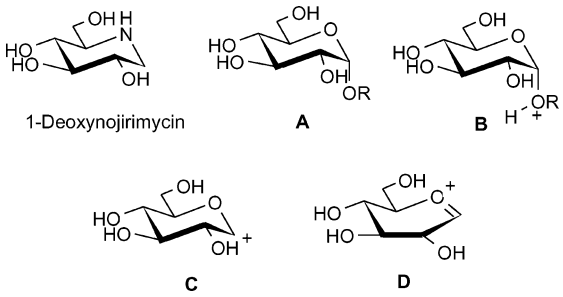

Fig. 1 1-Deoxynojirimycin and suggested intermediates or transition states of the glycosidic cleavage.

Iminodeoxy sugars of the piperidine or pyrrolidine type have been synthesized to mimic the substrate or one of the aforementioned intermediary species in the hydrolytic cleavage and have been shown to act as glycosidase inhibitors. Recently, the aminocyclopentanols have drawn considerable attention as potent glycosidase inhibitors.[4] The interest in this class of compounds began with the isolation of the potent α-mannosidase inhibitor mannostatin A (Fig. 2), an amino-(thiomethyl)cyclopentanol from the microorganism *Streptoverticillium verticillus*.[5] The overlap of the OH-groups in mannostatin with the OH-2 and OH-3 groups in the MO-optimized "flap-up"-conformation of the mannosyl cation reported by Winkler,[6] suggests mannostatin to be a mimic of this intermediary specie. The mechanism of its action is however not yet fully understood. In 1990 Farr and coworkers synthesized the potent α-mannosidase inhibitor "Merrell Dow cyclopentylamine" (MDC),[7] which can be seen as a ring-contracted analogue of α-D-mannose where the ring-oxygen is missing. The authors showed in a modelling study that this aminocyclopentanol has a conformation in which the amino group is positioned at the α-face between the ring oxygen and C-1 of the mannosyl cation, thus mimicking either the modelled "flap-up" mannosyl cation[8] or the glycoside precursor protonated at the exocyclic oxygen.

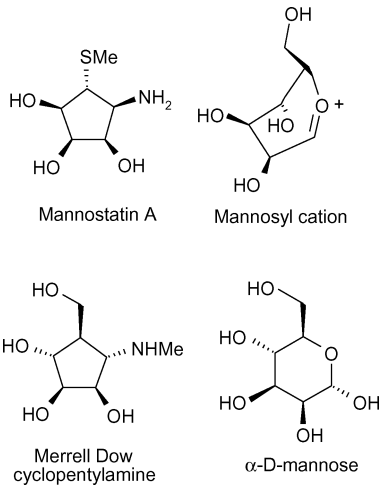

Fig. 2 Aminocyclopentanols as glycosidase inhibitors.

This concept, where an aminocyclopentanol has a substitution pattern similar to common carbohydrates, was recently expanded by Reymond[9] and Jäger[10] and their coworkers, who synthesized a selection of aminocyclopentanols with *fuco*, *manno*, *galacto* and *gluco* configurations. The configuration at the carbon, having the amino substituent mimicking either the α- or β-anomer, was especially considered. They found a close relationship between the configuration of the substitution pattern and the activity towards the relevant glycosidases, indicating that the amino group might be a mimic of the positively charged exocyclic oxygen. The available data seemed to indicate an anomer selectivity in the inhibitory activity for amino cyclopentanols with a *gluco* configuration, while the *manno* configured mimics did not show this difference.[10a] In the series of *galacto* mimics only β-configured aminocyclopentanols were available and they showed a tendency towards anomeric inhibitory selectivity.[10b]

In order to have a comparative study of both "anomers" we found a short synthesis of the α-D-*galacto* configured aminocyclopentanol based on the bicyclic *cis*-fused cyclopentane lactone chemistry, which was developed in our group.[11]

This strategy was based on the use of carbohydrate starting materials. A short and efficient method leads to bicyclic *cis*-fused

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cyclopentane lactones, like **1** (Fig. 3), by stereoselective radical induced carbocyclisations of ω-bromodeoxy-α,β-unsaturated heptonolactones. These bicyclic lactones can be converted into carbapentofuranoses functionalised at four of the five carbons in the ring[11,12] or at all five carbons[13] *via* the unsaturated bicyclic lactone **2**. For the synthesis of the aminocyclopentanols described in the present paper, we likewise took advantage of the unsaturated bicyclic lactone **2**.

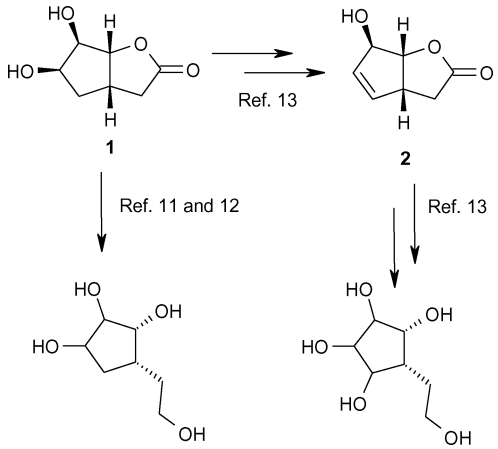


Fig. 3 Carbapentofuranoses from **1**.

Retrosynthetic analysis (Fig. 4) revealed that introduction of the amino substituent at C-6 of compound **2** would lead to mimics of L-sugars, while introduction at C-1 would lead to corresponding mimics in the D-sugar series.

Following the second strategy (Scheme 1 and Scheme 2), we describe in this paper the synthesis of four aminocyclopentanols which are mimics of α-D-galactose. Their inhibitory activity towards several glycosidases were tested in order to contribute to the elucidation of possible anomeric selectivity by this type of compounds. During the course of this study Reymond and coworkers published similar and identical compounds with an α-D-*galacto* configuration.[14]

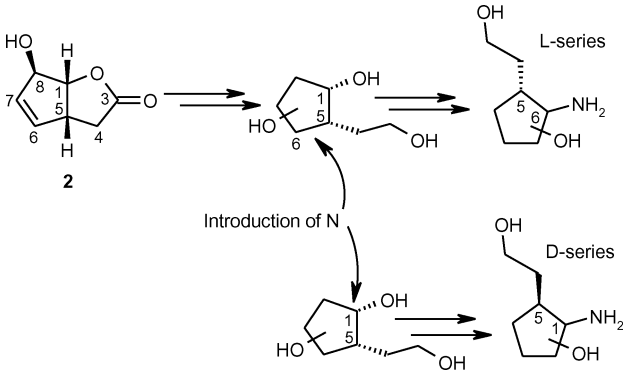
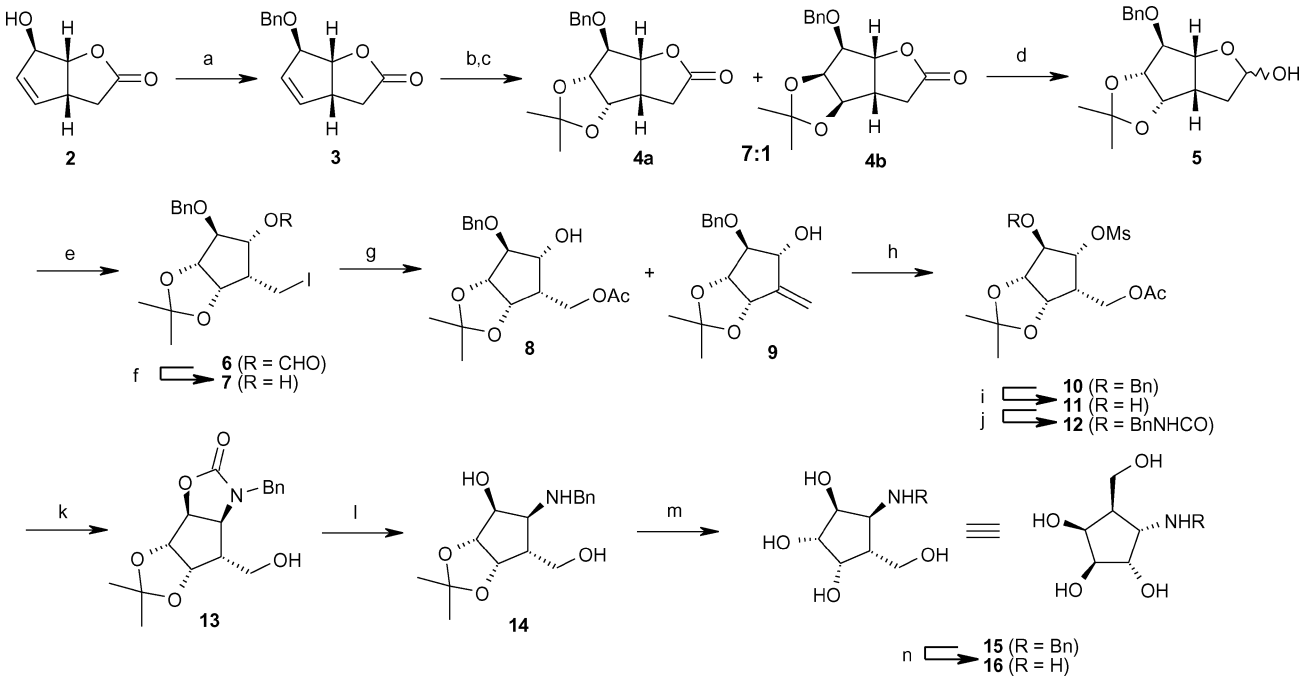


Fig. 4 Retrosynthetic analysis of aminocyclopentanols from **2**.

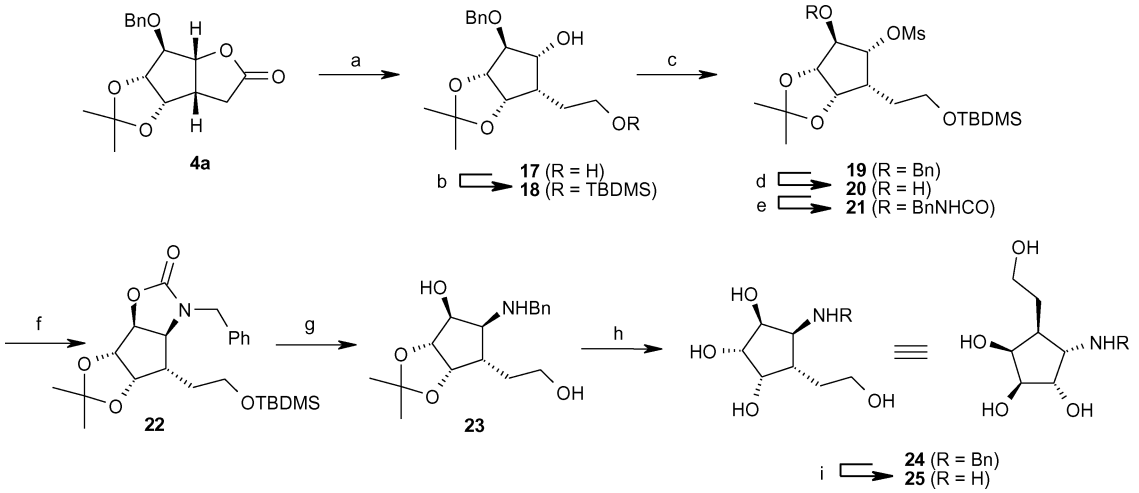
Results and discussion

By choosing the bicyclic lactone **2** as a starting compound, the side chain in the final cyclopentane will be a two-carbon chain. We have prepared the α-D-*galacto* mimics having both the two-carbon chain, as well as having the usual hydroxymethyl side chain. The cleavage of the carbon–carbon bond was performed by a Suárez fragmentation.

Dihydroxylation of the allylic alcohol **2** has been shown to proceed with a higher diastereoselectivity using the *O*-protected compound.[13] The benzyl protecting group was chosen for this protection as this showed acceptable selectivity in the dihydroxylation. Benzylation using benzyl trichloroacetimidate under acidic conditions[15] gave better yields and easier purification than benzylation under basic conditions and was therefore the method of choise for preparation of **3** in a high yield. Dihydroxylation using OsO_4 under standard Upjohn conditions followed by isopropylidene protection, gave the two stereoisomers **4a** and **4b** in a 7 : 1 relationship, where the desired compound **4a**



Scheme 1 Synthesis of aminocyclopentanols **15** and **16**. *Reagents and conditions*: a) $BnOCNCCl_3$, dioxane, triflic acid, 0 °C. 10 min (81%); b) OsO_4(s), NMO, CH_2Cl_2, 25 °C, overnight; c) acetone, 2,2-dimethoxypropane, H_2SO_4, 25 °C, 30 min (71% **4a**); d) DIBAL–H, CH_2Cl_2, −78 °C, 1.5 h (88%); e) DIB, I_2, cyclohexane, 250 W, 25 °C, 40 min; f) Na_2CO_3, MeOH, H_2O, 25 °C, 2.5 h (61%); g) CsOAc, DMF, 65 °C, overnight (61% **8**, 17% **9**); h) MsCl, DMAP, pyridine, CH_2Cl_2, 25 °C, overnight (87%); i) Pd/C (5%), MeOH, EtOAc, 25 °C, overnight (90%); j) benzylisocyanate, Et_3N, CH_2Cl_2, 25 °C, overnight (96%); k) KOtBu, THF, 25 °C, 35 min, then H_2O (72%); l) NaOH (2 M), ethanol, 65 °C, 2 h; m) HCl, H_2O, 60 °C, 5 h (65%); n) Pd/C (10%), EtOH, 25 °C, overnight (quant).



Scheme 2 Synthesis of aminocyclopentanols **24** and **25**. *Reagents and conditions*: a) $LiAlH_4$, THF, 0 °C, 5 min (84%); b) TBDMSCl, DMAP, CH_2Cl_2, 25 °C, overnight (95%); c) MsCl, DMAP, CH_2Cl_2, pyridine, 25 °C, overnight (94%); d) $Pd(OH)_2$ (10% on charcoal), EtOAc, 25 °C, 4.5 h (79%); e) benzylisocyanate, Et_3N, CH_2Cl_2, 25 °C, overnight (98%); f) KOtBu, THF, 25 °C, 15 min (87%); g) NaOH (2 M), ethanol, 65 °C, 2 h (76%); h) HCl (conc.), H_2O, 60 °C, 5 h (76%); i) Pd/C (10%), EtOH, 25 °C, overnight (quant.).

could be isolated by flash chromatography. For the C–C bond cleavage, the lactone **4a** was initially reduced with DIBAL–H to give the lactol **5**, followed by a Suárez fragmentation with diacetoxyiodobenzene (DIB) and iodide under activation by light.[16] Subsequent basic hydrolysis of the initially formed formate **6** gave the desired iodo compound **7** in a modest yield.

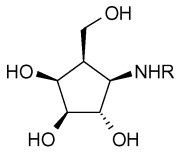
Substitution of the iodide with an oxygen nucleophile proved to be difficult, as elimination partly took place. Several acetate salts were tried, resulting in the use of CsOAc in DMF as the nucleophile to give **8** in a modest yield. Even after optimisation, a substantial amount of the elimination product **9** was formed during the reaction.

In order to obtain an analogue to a D-sugar (Fig. 4), the free secondary hydroxy group of **8** should be converted into an amino group. Thus, mesylation of **8** to **10** gave the possibility of an intermolecular substitution with a nitrogen nucleophile like N_3^-. Unfortunately, reacting **10** with NaN_3 in DMF resulted primarily in elimination and therefore an intramolecular substitution was considered. Removal of the benzyl group by catalytic hydrogenation gave **11**, which was treated with benzyl isocyanate to give the carbamate **12**. This molecule was now set up for an intramolecular substitution. Thus, treatment of **12** with KOtBu gave only the desired isoxazoline **13** with no elimination observed. Basic hydrolysis at an elevated temperature to cleave the isoxazoline and final deprotection of the isopropylidene group with aq. HCl gave the hydrochloric salt of the desired α-D-*galacto* configured aminocyclopentanol as the *N*-benzyl derivative **15**. The benzyl group could be removed by standard hydrogenation to give the unsubstituted aminocyclopentanol **16**.

In order to investigate the influence of the side chain on the inhibitory activity, we also prepared the analogues keeping the two-carbon side chain. Following a similar protocol **4a** was reduced to the corresponding hydroxy substituted cyclopentane **17** (Scheme 2). For selective introduction of an amino substituent, the primary hydroxy group was selectively protected with TBDMSCl to **18**, followed by mesylation of the free secondary hydroxy group to give **19**. Transformation of **19** into the two α-D-*galacto* configured aminocyclopentanols **24** and **25** was performed as described above for **15** and **16**.

The four aminocyclopentanols, **15**, **16**, **24** and **25**, all having an α-D-*galacto* configuration, were assayed for inhibition of a selection of glycosidases (Table 1). This revealed that only **15** and **16** showed activity towards α-galactosidase (green coffee beans). All four compounds showed activity towards β-galactosidase (bovine liver) as expected from the configuration of the side chain and hydroxy groups, but not from the configuration of the amino group. The compounds **24** and **25**, having a side chain one carbon longer than the parent carbohydrate, had a significantly lower activity for both α- and β-galactosidases than both **15** and **16**. This indicates that the hydroxymethyl group side chain is essential for optimal inhibition of these enzymes. Furthermore, it is interesting to note that the α-D-*galacto* configured inhibitors **15** and **16** are also powerful inhibitors of β-glucosidase from almonds. This cross-reactivity for inhibitors with the hydroxy groups in a *galacto* configuration is well known and is discussed in detail by Reymond and coworkers.[14]

Inhibitory activities for the β-D-*galacto* configured inhibitors **26** and **27** (Fig. 5), published by Jäger and coworkers, are shown



26: R=Bn
27: R=H

"β-D-*galacto*"

Fig. 5 β-D-*galacto* configured inhibitors from ref. 10*b*.

Table 1 K_i values (μM) obtained from inhibition data on glycosidases

Compound	α-Glucosidase (b.y.)	β-Glucosidase (a)	α-Galactosidase (g.c.b.)	β-Galactosidase (b.l.)	α-Mannosidase (a)
15	N.i.	0.53	2.26	1.01	N.i.
16	94.2	0.15	24.3	5.31	N.i.
24	N.i.	N.i.	N.i.	20.7	N.i.
25	N.i.	1.08	N.i.	31.6	N.i.
26		1.39[a]	N.i.[a]	0.006[a]	
27		2.2[a]	12.0[a]	3.3[a]	

[a] From ref. 10*b*. (B.y.): baker's yeast; (a): almonds; (g.c.b.): green coffee beans; (b.l.): bovine liver; N.i.: no inhibition.

in Table 1 for comparrison.[10b] The compounds **16** and **27**, having a primary amino group mimicking the α- and β-configuration, respectively, show very similar inhibitory activity towards both α- and β-galactosidases. The *N*-benzylated aminocylopentanol **15** has a slightly enhanced activity towards both α- and β-galactosidases, but the selectivity between these two enzymes is low. The *N*-benzylated aminocyclopentanol **26**, mimicking the β-D-*galacto* configuration, has a markedly enhanced activity towards β-galactosidases. Furthermore, the selectivity between the inhibition of α- and β-galactosidases had increased, as almost no activity was observed towards the α-galactosidase.

Conclusions

These results indicate that aminocyclopentanols with an α- or β-D-*galacto* configuration are mimics of the oxocarbenium ion intermediate of the glycosidic cleavage and therefore show similar inhibitory activity for the *N*-unsubstituted inhibitors **16** and **27**. The anomer selectivity seen for the β-D-*galacto* configured *N*-alkylated inhibitor **26** is probably due to the position of the benzyl group on the β-face of the ring, where hydrophobic interactions with the aglycon site will contribute to the binding. These hydrophobic interactions are not as important for the α-D-*galacto* configured inhibitor **15**. This was also noted by Reymond and coworkers, who drew attention to the fact that the *N*-alkyl aminocyclopentanols might not be suitable for providing α-selective inhibitors.[14]

Experimental

^{1}H NMR spectra were recorded on a Bruker AM 500 and ^{13}C NMR spectra on Varian Mercury 300 instruments. Chemical shifts were measured in δ (ppm) and coupling constants J in Hz. For NMR spectra in deuterated solvents, the solvent peak was used as reference ($CDCl_3$: $\delta = 7.26$ for ^{1}H, 76.93 for ^{13}C; MeOH-d_4: $\delta = 3.31$ for ^{1}H, 49.00 for ^{13}C). Where necessary, NMR data were assigned using HH- and CH-correlated spectra. Melting points are uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Institute of Physical Chemistry, Vienna. HR-MS was performed by BioCentrum, DTU. TLC was performed on Merck 60 F_{254} precoated silica plates and spots were generally detected by spraying with a solution of 1.5% $NH_4Mo_2O_2$, 1% Ce(IV)SO_4 and 10% H_2SO_4, followed by charring. Flash chromatography was performed with silica gel 60 (Merck, 40–63 (μm). Concentrations were performed on a rotary evaporator at a temperature below 40 °C. All solvents were distilled before use. Celite refers to Filter Aid from Celite Corporation.

Enzymatic assay

Inhibitory activities of the synthesized compounds were determined on a Labsystem iEMS reader MF. The residual hydrolytic activities of the glycosidases were measured spectrometrically of the corresponding *p*-nitrophenyl glycosides in the presence of the synthesized compounds. The following enzymes were purchased from Sigma: α-glucosidase (baker's yeast), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (bovine liver) and α-mannosidase (almonds). A typical enzymatic assay (final volume 0.3 ml) contains 0.08–0.17 units ml^{-1} of the enzyme (1 unit = 1 enzyme unit liberating 1 μmol of glycoside per minute from *p*-nitrophenyl glycoside). Each assay was performed with the 4-nitrophenyl glycoside derivatives of the appropriate sugar as substrate in a phosphate buffer (0.12 mM, pH 6.8). The assays were performed with four different concentrations of the substrates (1, 2, 3 and 4 mM in the aq. buffer solution). Enzyme and inhibitor (0.1 mM) were preincubated for 1–2 min at 25–35 °C dependent on the enzyme and the reaction was started by addition of the substrate. The *p*-nitrophenolate formed was measured by UV spectroscopy at 405 nm every 30 s.

After the initial test, the inhibitors with a $K_i < 50$ μM determined from a Lineweaver–Burk plot were assayed as described above with four different concentrations (0.03, 0.04, 0.06 and 0.12 mM) of inhibitor in order to obtain a Dixon plot for a more precise determination of the inhibition constant K_i.

K_i values were determined with a Sigma Plot program (Enzyme kinetics module 1.1) from a Lineweaver–Burke plot (initial experiments) or a Dixon plot.

(1*R*, 5*R*, 8*R*)-8-Benzyloxy-2-oxabicyclo[3.3.0]oct-6-en-3-one (3). To an ice-cooled solution of the allylic alcohol **2** (500 mg, 3.57 mmol) and benzyl trichloroacetimidate (1.18 g, 4.67 mmol) in anhydrous dioxane (10 mL) was added TfOH (10 drops). The mixture was stirred at 0 °C for 10 min, then diluted with diethyl ether (20 mL) and washed with half-saturated $NaHCO_3$ (20 mL) and water (10 mL). The organic phase was dried ($MgSO_4$), concentrated and purified by flash chromatography (EtOAc–hexane, 1 : 1) to give the title compound as colourless crystals (670 mg, 81%); mp 65–67 °C. Recrystallization from EtOAc–hexane gave mp 73–74 °C. $[\alpha]_D^{20}$ −147 (*c* 1.0 in $CHCl_3$); found: C, 72.73; H, 6.18. Calc. for $C_{14}H_{13}O_3$: C, 73.03; H, 6.13%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.36–7.30 (5H, m, Ar–H), 5.95–5.90 (2H, m, H-7, H-8), 4.94 (1H, d, $J = 6.0$, H-1), 4.69–4.60 (2H, m, PhCH_2O), 3.71 (1H, m, H-5), 2.77 (1H, dd, $J = 10.1$, 18.2, H-4), 2.38 (1H, dd, $J = 2.7$, 18.2, H-4′);^{13}C NMR (126 MHz, $CDCl_3$): δ_C 175.7 (CO), 137.5, 137.1 (C-6, C-7), 130.5, 128.5, 127.9, 127.9 (Ar–C), 87.3, 85.7 (C-1, C-8), 71.7 (Ph*C*H$_2$O), 43.6 (C-5), 32.4 (C-4).

(1*R*, 5*R*, 6*S*, 7*S*, 8*S*)-8-Benzyloxy-6,7-isopropylidenedioxy-2-oxabicyclo[3.3.0]oct-3-one (4a). Compound **3** (190 mg, 0.83 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and NMO·H_2O (167 mg, 1.23 mmol) was added together with a catalytic amount of OsO_4(s). The mixture was stirred under N_2 at rt overnight. Na_2SO_3 was added and the mixture stirred for 30 min at rt. The mixture was concentrated *in vacuo* and coevaporated three times with toluene. Dry acetone (5 mL), 2,2-dimethoxypropane (4 mL) and conc. H_2SO_4 (7 drops) were added and the mixture stirred for 30 min. The mixture was then neutralised with $NaHCO_3$(s), filtered and evaporated *in vacuo* to give the title compound and its stereoisomer in a 7 : 1 relationship. Purification by flash chromatography (EtOAc–heptane, 1 : 3) gave the title compound as colourless crystals (180 mg, 71%); mp 117–118 °C. $[\alpha]_D^{20}$ −57.9 (*c* 1.1 in EtOAc); found; C, 67.12; H, 6.74%. Calc. for $C_{17}H_{20}O_5$; C, 67.09; H, 6.62%; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.39–7.30 (5H, m, Ar–H), 4.78 (1H, d, $J = 5.8$, H-1), 4.76 (1H, dd, $J = 6.1$, 6.1, H-6), 4.73 (1H, d, $J = 5.7$, H-7), 4.65, 4.60 (2H, d, $J = 11.5$, PhCH_2O), 4.20 (1H, s, H-8), 3.10 (1H, m, H-5), 2.78 (1H, d, $J = 17.5$, H-4), 2.57 (1H, dd, $J = 9.3$, 17.5, H-4′), 1.419, 1.298 (2 × 3H, s, [(CH_3)$_2$C]);^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 176.1 (CO), 136.9, 128.5, 128.1, 127.7 (Ar–C), 111.8 [(CH$_3$)$_2$*C*], 88.6 (C-1), 86.2 (C-7), 84.6 (C-8), 80.9 (C-6), 72.1(Ph*C*H$_2$O), 42.1 (C-5), 30.1 (C-4), 25.4, 23.9 [(*C*H$_3$)$_2$C].

(1*R*, 5*S*, 6*S*, 7*S*, 8*S*)-8-Benzyloxy-6,7-isopropylidenedioxy-2-oxabicyclo[3.3.0]oct-3-ol (5). Compound **4a** (4.187 g, 13.7 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and cooled to −78 °C under an N_2 atmosphere. DIBAL–H (1 M in CH_2Cl_2, 38 mL) was added over 5 min and the mixture was stirred at −78 °C for 1.5 h. Saturated Rochelles salt (100 mL) was carefully added and the mixture was stirred for 15 min. CH_2Cl_2 (100 mL) was added and the phases separated. The water phase was re-extracted with CH_2Cl_2 (2 × 50 mL) and the organic phases were pooled and washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the a crude product (4.07 g, 96.6%). The residue was purified by flash chromatography (EtOAc–hexane, 1 : 1) to give the title compound as colourless crystals (3.69 g, 88%); mp 55–59 °C. $[\alpha]_D^{20}$ −24.4 (*c* 1.0 in EtOAc); found; C, 66.77; H, 7.30%. Calc.

for $C_{17}H_{22}O_5$; C, 66.65; H, 7.24%;^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 137.4, 128.3, 127.7, 127.6 (Ar–C), 112.2 [$C(CH_3)_2$], 100.1 (C-3), 90.5, 90.2, 88.7, 81.2 (C-1, C-6, C-7, C-8), 71.8 (PhCH_2O), 43.2 (C-5), 35.5 (C-4), 26.4, 24.6 [C(CH_3)$_2$]. 137.5, 128.3, 127.7, 127.6 (Ar–C), 111.4 [$C(CH_3)_2$], 100.8 (C-3), 88.2, 87.4, 86.3, 80.5 (C-1, C-6, C-7, C-8), 71.7 (PhCH_2O), 45.3 (C-5), 34.5 (C-4), 26.4, 24.6 [C(CH_3)$_2$].

(1*R*, 2*S*, 3*S*, 4*S*, 5*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-5-iodomethyl-cyclopentane-1,2,3,4-tetrol (7). Compound **5** (500 mg, 1.63 mmol) was suspended in dry cyclohexane (20 mL). (Diacetoxyiodo)benzene (608 mg, 1.88 mmol) and I_2 (438 mg, 1.73 mmol) were added and the mixture treated with a 250 W lamp for 40 min at rt, H_2O (10 mL) added and the phases separated. The water phase was re-extracted with diethyl ether (2 × 10 mL). The organic phases were pooled and washed with sat. $Na_2S_2O_4$ (20 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a colourless oil. This was purified by flash chromatography (EtOAc–heptane, 1 : 4) to give (1*R*, 2*S*, 3*S*, 4*S*, 5*R*)-1-formyloxy-2-benzyloxy-3,4-isopropylidene-5-iodomethyl-1,2,3,4-cyclopentane tetrol (**6**) as a colourless oil (437 mg, 62%). This oil was dissolved in MeOH–H_2O (2 : 1, 7 mL), Na_2CO_3 (600 mg) was added and the mixture stirred at rt for 2.5 h. The mixture was partly evaporated to remove MeOH. H_2O (10 mL) and CH_2Cl_2 (15 mL) were added and the phases separated. The water phase was re-extracted with CH_2Cl_2 (10 mL), the organic phases were pooled, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (EtOAc–heptane, 1 : 3) to give the title compound as a colourless syrup (400 mg, 60.7%). $[\alpha]_D^{20}$ −1.4 (*c* 1.0 in EtOAc); found; C, 47.82; H, 5.40%. Calc. for $C_{16}H_{21}O_4I$; C, 47.53; H, 5.24%; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.37–7.29 (5H, Ar–H), 4.76 (1H, dd, J = 5.2, 5.2, H-4), 4.66 (1H, dd, J = 1.5, 5.5, H-3), 4.58 (2H, s, PhCH_2O), 4.16 (1H, dd, J = 4.2, 11.0, H-1), 3.97 (1H, s, H-2), 3.45 (2H, d, J = 8.4, H-6, H-6′), 2.55 (1H, m, H-5), 2.25 (1H, d, J = 11.0, OH), 1.48, 1.33 (2 × 3H, s, [C(CH_3)$_2$]);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 137.3, 128.4, 127.9, 127.6 (Ar–C), 110.9 [$C(CH_3)_2$], 86.1 (C-2), 84.2 (C-3), 81.2 (C-4), 78.2 (C-1), 71.6(PhCH_2O), 49.3(C-5), 26.3, 22.1 [C(CH_3)$_2$], −0.9 (C-6).

(1*R*, 2*S*, 3*S*, 4*S*, 5*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-5-acetoxymethyl-1,2,3,4-cyclopentane tetrol (8) and (1*R*, 2*S*, 3*S*, 4*S*)-2-*O*-benzyl-3,4-*O*-isopropylidene-5-methylene-cyclopentane-1,2,3,4-tetrol (9). Compound **7** (881 mg, 2.18 mmol) was dissolved in dry DMF (5 mL), CsOAc (2.01 g, 11.4 mmol) was added and the mixture heated to 65 °C under N_2 overnight. After cooling to rt diethyl ether (60 mL) was added and the organic phase washed with water (3 × 30 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a mixture of two major products as a colourless oil. The residue was purified by flash chromatography (EtOAc–heptane, 1 : 4), to give the title compound as a colourless oil (450 mg, 61%); $[\alpha]_D^{20}$ −18.2 (*c* 0.5 in EtOAc); found; C, 64.48; H, 7.30%. Calc. for $C_{18}H_{24}O_6$; C, 64.27; H, 7.19%;. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.36–7.26 (5H, Ar–H), 4.77 (1H, dd, J = 5.3, 5.3, H-4), 4.62 (1H, dd, J = 1.2, 6.1, H-3), 4.59 (2H, s, PhCH_2O), 4.52 (1H, dd, J = 8.1, 11.5, CH_2OAc), 4.40 (1H, dd, J = 7.1, 11.3, CH_2OAc), 4.14 (1H, dd, J = 4.5, 10.5, H-1), 3.94 (1H, s, H-2), 2.48 (1H, m, H-5), 2.40 (1H, d, J = 10.8, OH), 2.08 (3H, s, CH_3CO), 1.47, 1.32 (2 × 3H, s, [C(CH_3)$_2$]);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 171.0 (CO), 137.4, 128.4, 127.8, 127.5 (Ar–C), 111.0 [$C(CH_3)_2$], 86.3 (C-2), 84.1 (C-3), 80.6 (C-4), 76.7 (C-1), 71.5 (PhCH_2O), 59.9 (CH_2OAc), 45.0 (C-5), 26.3, 22.9 [C(CH_3)$_2$], 20.9 (CH_3CO), followed by **9** as colourless crystals (100 mg, 17%); mp 69–72 °C; $[\alpha]_D^{20}$ −17.4 (*c* 0.4 in EtOAc); found; C, 69.33; H, 7.21%. Calc. for $C_{16}H_{20}O_4$; C, 69.54; H, 7.30%; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.36–7.29 (5H, m, Ar–H), 5.45 (2H, br s, C=CH_2), 4.92 (1H, br d, J = 6.5, H-4), 4.72 (1H, d, J = 11.9, PhCH_2O), 4.63 (1H, d, J = 11.8, PhCH_2O), 4.53 (1H, dd, J = 2.3, 6.6, H-3), 4.40 (1H, d, J = 4.7, H-1), 3.81 (1H, dd, J = 3.1, 4.9, H-2), 1.48, 1.36 (2 × 3H, s, [C(CH_3)$_2$]);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 148.4 (C-5), 137.5, 128.3, 127.7, 127.7 (Ar–C), 114,4 (= CH_2), 112.1 [$C(CH_3)_2$], 87.8 (C-2), 82.5 (C-3), 78.7 (C-4), 77.5 (C-1), 71.7 (PhCH_2O), 27.0, 24.7 [C(CH_3)$_2$].

(1*R*, 2*R*, 3*S*, 4*S*, 5*R*)-1-*O*-Mesyl-2-*O*-benzyl-3,4-*O*-isopropylidene-5-acetoxymethyl-cyclopentane-1,2,3,4-tetrol (10). Compound **8** (420 mg, 1.25 mmol) was dissolved in dry CH_2Cl_2 (6 mL) and dry pyridine (6 mL). DMAP (18 mg, cat.) was added followed by MsCl (0.5 mL, 6.4 mmol) which was added dropwise. The mixture was stirred under N_2 at rt, overnight. H_2O (20 mL) was added and the mixture stirred for 30 min. CH_2Cl_2 (20 mL) was then added and the phases separated. The organic phase was washed with aq. HCl (1 M, 2 × 20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried, filtered and evaporated *in vacuo* to give a crude residue (quant.). The residue was purified by flash chromatography (EtOAc–heptane, 1 : 2) to give the title compound as a colourless syrup (450 mg, 87%). $[\alpha]_D^{20}$ +20.9 (*c* 0.7 in EtOAc); found; C, 55.29; H, 6.37%. Calc. for $C_{19}H_{26}O_8S$; C, 55.06; H, 6.32%;^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.39–7.30 (5H, m, Ar–H), 5.03 (1H, d, J = 4.4, H-1), 4.77 (1H, dd, J = 5.8, 5.8, H-4), 4.65–4.63 (3H, m, H-3, PhCH_2O), 4.43 (1H, dd, J = 9.0, 11.7, CH_2OAc), 4.37 (1H, dd, J = 6.3, 11.4, CH_2OAc), 4.19 (1H, s, H-2), 2.98 (3H, s, CH_3SO$_2$), 2.72 (1H, m, H-5), 2.08 (3H, s, CH_3CO), 1.46, 1.29 (2 × 3H, s, [C(CH_3)$_2$]); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 170.8 (CH_3CO), 137.0, 128.5, 128.0, 127.7 (Ar–C), 111.8 [$C(CH_3)_2$], 85.0 (C-2), 84.4 (C-3), 82.2 (C-1), 79.7 (C-4), 72.0 (PhCH_2O), 59.1 (C-6), 44.6 (C-5), 38.2 (CH_3SO_2), 25.7, 23.7 [C(CH_3)$_2$], 20.9 (CH_3CO).

(1*R*, 2*R*, 3*R*, 4*S*, 5*R*)-1-*O*-Mesyl-3,4-*O*-isopropylidene-5-acetoxymethyl-cyclopentane-1,2,3,4-tetrol (11). Compound **10** (425 mg, 1.03 mmol) was suspended in MeOH–EtOAc (1 : 1, 10 mL). Pd/C (5%, 200 mg) was added and the mixture stirred in an H_2 atmosphere at rt, overnight. The mixture was then filtered through Celite and evaporated *in vacuo* to give a colourless oil (quant.). The residue was purified by flash chromatography (EtOAc–heptan, 1 : 1) to give the title compound as colourless crystals (300 mg, 90.4%); mp 98–99 °C; $[\alpha]_D^{20}$ +25.1 (*c* 1.0 in EtOAc); found; C, 44.55; H, 6.34; S, 9.78%. Calc. for $C_{12}H_{20}O_8S$; C, 44.44; H, 6.22; S, 9.88%;^{1}H NMR (500 MHz, $CDCl_3$): δ_H 4.88 (1H, d, J = 4.6 Hz, H-1), 4.78 (1H, dd, J = 5.3, 5.6 Hz, H-4), 4.54 (1H, dd, J = 1.3, 5.8, H-3), 4.46 (1H, br s, H-2), 4.43 (1H, dd, J = 8.3, 11.3, CH_2OAc), 4.36 (1H, dd, J = 6.3, 11.8, CH_2OAc), 3.03 (3H, s, CH_3SO$_2$), 2.77 (1H, m, H-5), 2.39 (1H, br s, OH), 2.08 (3H, s, CH_3CO), 1.45, 1.29 (2 × 3H, s, [C(CH_3)$_2$]);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 170.91 (CH_3CO), 111.72 [$C(CH_3)_2$], 85.92 (C-3), 84.59 (C-4), 79.76 (C-3), 78.28 (C-2), 59.13 (CH_2OAc), 44.15 (C-5) 38.18 (CH_3SO_2), 25.64, 23.71 [C(CH_3)$_2$], 20.87 (CH_3CO).

(1*R*, 2*R*, 3*S*, 4*S*, 5*R*)-1-*O*-Mesyl-2-*O*-(benzylcarbamoyl)-3,4-*O*-isopropylidene-5-acetoxymethyl-cyclopentane-1,2,3,4-tetrol (12). Compound **11** (200 mg, 0.62 mmol) was suspended in dry CH_2Cl_2 (7 mL). Et_3N (0.1 mL) and benzyl isocyanate (0.1 mL, 0.8 mmol) was added and the mixture stirred overnight at rt. Conc. aq. NH_4Cl (25 mL) and diethyl ether (25 mL) were added and the phases separated. The water phase was re-extracted twice with diethyl ether (2 × 10 mL). The organic phases were pooled, dried (Na_2SO_4), filtered and evaporated *in vacuo*. This gave a crude product, which was purified by flash chromatography (Et_2O) to give the title compound as a colourless foam (270 mg, 95.7%); $[\alpha]_D^{20}$ −9.1 (*c* 1.0 in EtOAc); found; C, 52.54; H, 6.14; S, 6.72; N, 3.10%. Calc. for $C_{20}H_{27}O_9SN$; C, 52.51; H, 5.95; S, 7.01; N, 3.06%;^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.37–7.27 (5H, m, Ar–H), 5.13 (1H, s, H-2), 4.99 (2H, br s, NH, H-1), 4.76 (1H, dd, J = 5.5, 5.5, H-4), 4.61 (1H, d, J = 5.6, H-3), 4.48–4.31 (4H, m, CH_2OAc, PhCH_2N), 3.16 (3H, s, CH_3SO$_2$), 2.61 (1H, m, H-5), 2.07 (3H, s, COCH_3), 1.49, 1.24 (2 × 3H, s, [C(CH_3)$_2$]);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 171.2 (CH_3CO),

154.6 (*C*O, carbamate), 137.8, 129.1, 128.1, 127.9 (Ar–C), 112.5 [*C*(CH$_3$)$_2$], 84.4 (C-3), 83.1 (C-1), 80.3 (C-2), 79.6 (C-4), 59.1 (*C*H$_2$OAc), 45.2 (Ph*C*H$_2$N), 44.9 (C-5), 38.4 (*C*H$_3$SO$_2$), 25.7, 23.8 [C(*C*H$_3$)$_2$], 20.9 (*C*H$_3$CO)

(1*S*, 2*S*, 3*S*, 4*S*, 5*S*)-4-*N*-Benzyl-5-acetoxymethyl-7,8-isopropylidenedioxy-2-oxa-4-azabicyclo[3.3.0]oct-3-one (13). Compound **12** (260 mg, 0.57 mmol) was suspended in dry THF (8 mL), KtOBu (197 mg, 1.8 mmol) was added in two portions, the mixture was stirred at rt for 35 min and thereafter quenched with a few drops of water. EtOAc (15 mL) and brine (15 mL) were added and the phases separated. The aqueous phase was reextracted with EtOAc (2 × 15 mL). The organic phases were pooled, dried (Na$_2$SO$_4$), filtered and evaporated *in vacuo* to give slightly yellow crystals. These were purified by flash chromatography (EtOAc–heptane, 1 : 1) to give the title compound as colourless crystals (130 mg, 71.5%); mp 112–114 °C; $[\alpha]_D^{20}$ +63.6 (*c* 0.6 in EtOAc); found; C, 64.05; H, 6.66; N, 4.33%. Calc. for C$_{17}$H$_{21}$O$_5$N; C, 63.94; H, 6.63; N, 4.39%;^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.38–7.30 (5H, m, Ar–H), 4.79 (1H, dd, *J* = 5.5, 5.5, H-1), 4.76 (1H, d, *J* = 15.3, PhC*H*$_2$N), 4.74 (1H, d, *J* = 4.9, H-2), 4.68 (1H, d, *J* = 8.1 Hz, H-3), 4.25 (1H, d, *J* = 14.7, PhC*H*$_2$N), 4.11 (1H, dd, *J* = 7.2, 7.2, H-4), 3.82 (1H, dd, *J* = 4.9, 11.8, C*H*$_2$OH), 3.72 (1H, m, C*H*$_2$OH), 2.35 (1H, m, H-5), 1.40, 1.30 (2 × 3H, s, [C(C*H*$_3$)$_2$]); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 156.9 (CO, carbamate), 135.9, 128.8, 128.0, 128.0 (Ar–C), 112.0 [*C*(CH$_3$)$_2$], 84.3 (C-2), 84.1 (C-3), 82.3 (C-1), 61.0 (*C*H$_2$OH), 60.2 (C-4), 50.4 (C-5), 46.7 (Ph*C*H$_2$N), 26.6, 24.2 [C(*C*H$_3$)$_2$].

(1*S*, 2*S*, 3*S*, 4*S*, 5*R*)-4-Benzylamino-5-hydroxymethyl-cyclopentane-1,2,3-triol (15). Compound **13** (110 mg, 0.35 mmol) was dissolved in aq. NaOH (2 M, 5 mL) and ethanol (5 mL), the mixture was heated to 65 °C for 2 h and then evaporated *in vacuo* and purified by flash chromatography (EtOAc then EtOAc–MeOH–TEA, 10 : 1 : 0.3) to give **14** as a colourless oil (65 mg, 64%). The oil was dissolved in H$_2$O (3 mL) and conc. HCl (1 mL), the mixture was heated to 60 °C for 5 h and then evaporated *in vacuo* to give the title compound as yellow crystals (64 mg, 65%); mp 140–142 °C; $[\alpha]_D^{20}$ −27.8 (*c* 0.7 in MeOH); ^{1}H NMR (500 MHz, D–MeOD): δ_H 7.53–7.45 (5H, m, Ar–H), 4.33 (1H, dd, *J* = 3.8, 8.4, H-1), 4.31 (1H, d, *J* = 13, PhC*H*$_2$N), 4.24 (1H, d, *J* = 13.2, PhC*H*$_2$N), 4.21 (1H, dd, *J* = 4.3, 6.4, H-3), 3.96 (1H, dd, *J* = 4.3, 4.3, H-2), 3.86 (1H, dd, *J* = 5.7, 10.6, C*H*$_2$OH), 3.76 (1H, dd, *J* = 7.7, 10.6 Hz, C*H*$_2$OH), 3.66 (1H, dd, *J* = 7.1, 7.3, H-4), 2.37 (1H, m, H-5);^{13}C NMR (75.5 MHz, D–MeOD): δ_C 132.8, 130.9, 130.6, 130.3 (Ar–C), 79.7 (C-2), 73.2 (C-3), 72.0 (C-1), 61.6 (C-4), 61.4 (*C*H$_2$OH), 51.3 (Ph*C*H$_2$N), 46.4 (C-5); HR-ESI–MS calculated for C$_{13}$H$_{19}$O$_4$NCl [M − 1]: 288.1003; found 288.1019.

(1*S*, 2*S*, 3*S*, 4*S*, 5*R*)-4-Amino-5-hydroxymethyl-cyclopentane-1,2,3-triol (16). Compound **15** (40 mg, 0.14 mmol) was dissolved in EtOH (10 mL), Pd/C (10%, 30 mg) was added and the mixture stirred under an H$_2$ atmosphere at rt, overnight. The mixture was filtered through celite and evaporated *in vacuo* to give the title compound as a hygroscopic oil (28 mg, quant.); $[\alpha]_D^{20}$ −8.8 (*c* 0.8 in MeOH); ^{1}H NMR (500 MHz, D–MeOD): δ_H 4.24 (1H, dd, *J* = 4.8, 4.8, H-1), 4.15 (1H, dd, *J* = 5.3, 7.4, H-3), 3.93 (1H, dd, *J* = 5.2, 5.2, H-2), 3.86 (1H, dd, *J* = 6.1, 10.9, C*H*$_2$OH), 3.78 (1H, dd, *J* = 6.9, 10.4, C*H*$_2$OH), 3.57 (1H, dd, *J* = 8.0, 8.0, H-4), 2.25 (1H, m, H-5);^{13}C NMR (75.5 MHz, D–MeOD): δ_C 79.7 (C-2), 74.4 (C-3), 72.0 (C-1), 61.2 (*C*H$_2$OH), 54.4 (C-4), 47.7 (C-5); HR-ESI–MS; calc. for C$_6$H$_{13}$O$_4$NCl [M − 1] 198.0533; found 198.0578.

(1*R*, 2*S*, 3*S*, 4*S*, 5*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-5-(2-hydroxyethyl)-cyclopentane-1,2,3,4-tetrol (17). Compound **4a** (153 mg, 0.50 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C. LiAlH$_4$ (36 mg, 0.95 mmol) was added and the mixture stirred under N$_2$ at 0 °C for 5 min. H$_2$O (4 drops), aq. NaOH (15%, 4 drops) and H$_2$O (8 drops) were then added which resulted in precipitation of salts. The mixture was filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (EtOAc–heptane, 1 : 1, then EtOAc–heptane, 2 : 1) to give the title compound as a colourless oil (130 mg, 84%); $[\alpha]_D^{20}$ +1.3 (*c* 1.25 in EtOAc); found; C, 65.92; H, 7.81%. Calc. for C$_{17}$H$_{24}$O$_5$; C, 66.21; H, 7.84%;^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.34–7.26 (5H, Ar–H), 4.72 (1H, dd, *J* = 5.0, 5.0, H-4), 4.62–4.55 (3H, m, PhC*H*$_2$O, H-3), 4.06 (1H, d, *J* = 4.2, H-1), 3.93 (1H, s, H-2), 3.81 (2H, m, CH$_2$C*H*$_2$OH), 2.34 (1H, m, H-5), 1.99 (2H, m, C*H*$_2$CH$_2$OH), 1.45, 1.33 (2 × 3H, s, [C(C*H*$_3$)$_2$]); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 137.6, 128.4, 127.8, 127.5 (Ar–C), 110.6 [*C*(CH$_3$)$_2$], 87.1 (C-2), 84.1 (C-3), 82.3 (C-4), 78.2 (C-1), 71.5 (Ph*C*H$_2$O), 61.5 (CH$_2$*C*H$_2$OH), 42.9 (C-5), 26.9 (*C*H$_2$CH$_2$OH), 26.5, 23.1 [C(*C*H$_3$)$_2$]).

(1*R*, 2*S*, 3*S*, 4*S*, 5*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-5-(2-*O*-TBDMS-hydroxyethyl)-cyclopentane-1,2,3,4-tetrol (18). Compound **17** (850 mg, 2.76 mmol) was dissolved in dry CH$_2$Cl$_2$ (20 mL), DMAP (743 mg, 6.08 mmol) and TBDMSCl (461 mg, 3.06 mmol) was added and the mixture stirred at rt under N$_2$, overnight. H$_2$O (20 mL) and CH$_2$Cl$_2$ (10 mL) were then added and the phases separated. The organic phase was washed with aq. HCl (1 M, 2 × 20 mL), aq. sat. NaHCO$_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na$_2$SO$_4$), filtered and evaporated *in vacuo* to give a crude product as a syrup. The residue was purified by flash chromatography (EtOAc–heptane, 1 : 2) to give the title compound as a colourless syrup (1.11 g, 95%); $[\alpha]_D^{20}$ +4.4 (*c* 1.0 in EtOAc); found; C, 65.52; H, 9.07%. Calc. for C$_{23}$H$_{38}$O$_5$Si; C, 65.36; H, 9.06%;. ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.36–7.26 (5H, m, Ar–H), 4.70 (1H, dd, *J* = 5.0, 5.0, H-4), 4.58–4.56 (3H, m, PhC*H*$_2$O, H-3), 4.06 (1H, dd, *J* = 4.2, 10.2, H-1), 3.92 (1H, s, H-2), 3.78 (2H, t, *J* = 6.3, CH$_2$C*H*$_2$O), 2.50 (1H, d, *J* = 10.2 Hz, O*H*), 2.37 (1H, m, H-5), 1.94 (2H, m, C*H*$_2$CH$_2$O), 1.47, 1.32 (2 × 3H, s, [C(C*H*$_3$)$_2$]), 0.90 (9H, s, [C(C*H*$_3$)$_3$]), 0.07 (6H, s, 2 × C*H*$_3$Si);^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 137.7, 128.3, 127.6, 127.4 (Ar–C), 110.5 ([*C*(CH$_3$)$_2$]), 87.4 (C-2), 84.2 (C-3), 82.6 (C-4), 77.8 (C-1), 71.4 (C-7), 54.3 (Ph*C*H$_2$O), 42.5 (C-5), 26.8 (C-6), 26.4 ([C(*C*H$_3$)$_2$]), 25.8 ([C(*C*H$_3$)$_3$]), 23.1 ([C(*C*H$_3$)$_2$]), 18.2 ([*C*(CH$_3$)$_3$]), −5.4, −5.5 (2 × *C*H$_3$Si).

(1*R*, 2*R*, 3*S*, 4*S*, 5*R*)-1-*O*-Mesyl-2-*O*-benzyl-3,4-*O*-isopropylidene-5-(2-*O*-TBDMS-hydroxyethyl)-cyclopentane-1,2,3,4-tetrol (19). Compound **18** (1.05 g, 2.48 mmol) was suspended in dry CH$_2$Cl$_2$ (10 mL) and dry pyridine (10 mL). DMAP (30 mg, 0.25 mmol) and MsCl (1 mL) were added and the mixture stirred at rt under N$_2$, overnight. H$_2$O (20 mL) was added and the phases separated. The organic phase was washed with aq. HCl (1 M, 2 × 20 mL), sat. aq. NaHCO$_3$ (20 mL) and brine (20 mL), dried (MgSO$_4$), filtered and evaporated *in vacuo* to give a yellow syrup. The residue was purified by flash chromatography (EtOAc–heptane, 1 : 3) to give the title compound as a colourless syrup (1.17 g, 94%); $[\alpha]_D^{20}$ +10.3 (*c* 1 in EtOAc); found; C, 57.99; H, 8.34; S, 6.19%. Calc. for C$_{24}$H$_{40}$O$_7$SiS; C, 57.57; H, 8.05; S, 6.40%; ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.38–7.26 (5H, m, Ar–H), 4.98 (1H, d, *J* = 4.8, H-1), 4.70 (1H, dd, *J* = 5.5, 5.5, H-4), 4.63 (2H, dd, *J* = 3.3, PhC*H*$_2$O), 4.59 (1H, d, *J* = 5.9, H-3), 4.12 (1H, s, H-2), 3.75 (2H, dd, *J* = 6.3, 5.8, CH$_2$C*H*$_2$O), 2.95 (3H, s, C*H*$_3$SO$_2$), 2.61 (1H, m, H-5), 1.94–1.83 (2H, m, C*H*$_2$CH$_2$O), 1.44, 1.29 (2 × 3H, s, [C(C*H*$_3$)$_2$]), 0.90 (9H, s, [C(C*H*$_3$)$_3$]), 0.07 (6H, s, 2 × C*H*$_3$Si);^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 137.2, 128.4, 127.9, 127.7 (Ar–C), 111.1 ([*C*(CH$_3$)$_2$]), 85.1 (C-2), 84.6 (C-1), 84.3 (C-3), 81.0 (C-4), 71.8 (CH$_2$*C*H$_2$O), 60.7 (Ph*C*H$_2$O), 41.9 (C-5), 38.5 (SO$_2$*C*H$_3$), 26.8 (*C*H$_2$CH$_2$O), 25.9 [*C*(CH$_3$)$_3$], 25.8, 23.8 (2 × [C(*C*H$_3$)$_2$]), 18.2 [C(*C*H$_3$)$_3$], −5.4 (2 × *C*H$_3$Si).

(1*R*, 2*R*, 3*R*, 4*S*, 5*R*)-1-*O*-Mesyl-3,4-*O*-isopropylidene-5-(2-*O*-TBDMS-hydroxyethyl)-cyclopentane-1,2,3,4-tetrol (20). Compound **19** (200 mg, 0.4 mmol) was suspended in EtOAc (5 mL), Pd(OH)$_2$/C (10%, 43 mg,) was added and the mixture

stirred under H_2 for 4.5 h. The mixture was filtered through celite and evaporated *in vacuo*. The residue was purified by flash chromatography (EtOAc–heptane, 1 : 1) to give the title compound as a colourless syrup (130 mg, 79%); $[a]_D^{20}$ +5.2 (*c* 1.0 in EtOAc); found; C, 49.57; H, 8.57; S, 7.35%. Calc. for $C_{17}H_{34}O_7SiS$; C, 49.72; H, 8.35; S, 7.80%;. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 4.79 (1H, d, J = 4.8, H-1), 4.71 (1H, dd, J = 5.5, 5.5, H-4), 4.49 (1H, d, J = 5.7, H-3), 4.41 (1H, s, H-2), 3.75 (2H, t, J = 6.0, CH_2CH_2O), 3.02 (3H, s, CH_3SO_2), 2.64 (1H, m, H-5), 1.92, 1.81 (2H, m, CH_2CH_2O), 1.45, 1.29 (2 × 3H, s, [$C(CH_3)_2$]), 0.90 (9H, s, [$C(CH_3)_3$]), 0.06 (6H, s, 2 × CH_3Si);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 111.0 ([$C(CH_3)_2$]), 87.3 (C-1), 85.8 (C-3), 80.9 (C-4), 78.3 (C-2), 60.8 (CH_2CH_2O), 41.4 (C-5), 38.4 (CH_3SO_2), 26.7 (CH_2CH_2O), 25.9 [$C(CH_3)_3$], 25.7, 23.8 (2 × [$C(CH_3)_2$]), 18.2 [$C(CH_3)_3$], −5.4, −5.5 (2 × CH_3Si).

(1*R*, 2*R*, 3*S*, 4*S*, 5*R*)-1-*O*-Mesyl-2-*O*-(benzylcarbamoyl)-3,4-*O*-isopropylidene-5-(2-*O*-TBDMS-hydroxyethyl)-cyclopentane-1,2,3,4-tetrol (21). Compound **20** (469 mg, 1.14 mmol) was suspended in dry CH_2Cl_2 (6 mL). Et_3N (0.2 mL) and benzylisocyanate (0.2 mL, 1.6 mmol) were added under N_2 and the mixture stirred at rt, overnight. NH_4Cl (20 mL) and CH_2Cl_2 (20 mL) were added, the phases separated and the aq. phase reextracted with CH_2Cl_2 (10 mL). The organic phases were pooled, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (EtOAc–heptane, 1 : 2) to give the title compound as a colourless syrup (610 mg, 98%); $[a]_D^{20}$ −2.4 (*c* 1.0 in EtOAc);^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.40–7.30 (5H, Ar–H), 5.07 (1H, s, H-2), 4.96 (1H, t, J = 6, $PhCH_2NH$), 4.87 (1H, d, J = 4.7, H-1), 4.70 (1H, dd, J = 5.5, 5.5, H-4), 4.57 (1H, d, J = 5.7, H-3), 4.41 (1H, dd, J = 5.8, 14.5, $PhCH_2N$), 4.33 (1H, dd, J = 5.7, 14.9, $PhCH_2N$), 3.75 (2H, t, J = 6, CH_2CH_2O), 2.49 (1H, m, H-5), 1.96–1.87 (2H, m, CH_2CH_2O), 1.48, 1.28 (2 × 3H, s, [$C(CH_3)_2$]), 0.88 (9H, s, [$C(CH_3)_3$]), 0.05 (6H, s, 2 × CH_3Si);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 154.6 (CO), 137.6, 128.7, 127.7, 127.5 (Ar–C), 111.6 ([$C(CH_3)_2$]), 85.5 (C-1), 83.9 (C-3), 80.9 (C-4), 80.6 (C-2), 60.3 (C-7), 45.1 ($PhCH_2N$), 42.1 (C-5), 38.4 (CH_3SO_2), 26.7 (C-6), 25.8 [$C(CH_3)_3$], 25.8, 23.9 (2 × [$C(CH_3)_2$]), 18.2 [$C(CH_3)_3$], −5.5 (2 × CH_3Si).

(1*S*, 2*S*, 3*S*, 4*S*, 5*S*)-4-*N*-Benzyl-6-(2-*O*-TBDMS-hydroxyethyl)-7,8-isopropylidenedioxy-2-oxa-4-azabicyclo[3.3.0]octan-3-one (22). Compound **21** (550 mg, 1.01 mmol) was suspended in dry THF (15 mL). KOtBu (200 mg, 1.8 mmol) was added and the mixtures stirred at rt under N_2 for 15 min. CH_2Cl_2 (20 mL) and brine (20 mL) were added and the phases separated. The water phase was re-extracted with CH_2Cl_2 (20 mL), the organic phases were pooled, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product as slightly yellow crystals (quant.). The residue was purified by flash chromatography (EtOAc–heptane, 1 : 3), to give the title compound as colourless crystals (390 mg, 86.5%); mp 114–116 °C; $[a]_D^{20}$ +38.9 (*c* 1.0 in EtOAc); found; C, 64.14; H, 8.32; N, 3.03%. Calc. for $C_{24}H_{37}O_5SiN$; H, 8.33; C, 64.40; N, 3.13%;^{1}H NMR (500 MHz, $CDCl_3$): δ_C 7.38–7.26 (5H, m, Ar–H), 4.87 (1H, d, J = 15.8, $PhCH_2N$), 4.69–4.65 (2H, m, H-1, H-2), 4.62 (1H, d, J = 8.2, H-3), 4.14 (1H, d, J = 15.7, $PhCH_2N$), 3.79 (1H, dd, J = 8.2, 8.2, H-4), 3.67–3.59 (2H, m, CH_2CH_2OH), 2.34 (1H, m, H-5), 1.86 (1H, m, CH_2CH_2OH), 1.70 (1H, m, CH_2CH_2OH), 1.36, 1.28 (2 × 3H, s, [$C(CH_3)_2$]), 0.91 (9H, s, [$C(CH_3)_3$]), 0.07, 0.06 (2 × 3H, s, 2 × CH_3Si);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_H 157.0 (CO), 135.7, 128.8, 127.9, 127.7 (Ar–C), 111.3 [$C(CH_3)_2$], 84.5 (C-3), 84.2, 80.9 (C-1, C-2), 63.0 (C-4), 60.8 (CH_2CH_2OH), 46.5 ($PhCH_2N$), 45.5 (C-5), 31.9 (CH_2CH_2OH), 26.9 [$C(CH_3)_2$], 25.9 [$C(CH_3)_3$], 24.6 [$C(CH_3)_2$], 18.2 [$C(CH_3)_3$], −5.4 (CH_3Si), −5.5 (CH_3Si).

(1*S*, 2*S*, 3*S*, 4*S*, 5*S*)-4-Benzylamino-5-(2-hydroxyethyl)- cyclopentane-1,2,3-triol hydrochloride (24). Compound **22** (250 mg, 0.56 mmol) was suspended in aq. NaOH (2 M, 8 mL) and ethanol (8 mL) and the mixture was heated to 70 °C for 2 h. The mixture was evaporated *in vacuo*. EtOAc (20 mL) and H_2O (10 mL) were added and the phases separated. The water phase was reextracted with EtOAc (3 × 15 mL), the organic phases were pooled, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (EtOAc then EtOAc–MEOH, 10 : 1, then EtOAc–MEOH–TEA, 10 : 1 : 0.3) to give (1*S*, 2*R*, 3*S*, 4*S*, 5*S*)-1,2-isopropylidene-4-benzylamino-5-(2-hydroxyethyl)-1,2,3-cyclopentanetriol (**23**) as a colourless oil (130 mg, 76%);^{13}C NMR (75 MHz, D–MeOD): δ_C 140.4, 129.6, 129.5, 128.3 (Ar–C), 110.8 [$C(CH_3)_2$], 85.2 (C-2), 81.3 (C-1), 72.4 (C-3), 63.7 (C-4), 62.6 (CH_2CH_2OH), 52.9 ($PhCH_2N$), 46.4 (C-5), 32.6 (CH_2CH_2OH), 26.3, 23.9 [2 × $C(CH_3)_2$]. This oil was dissolved in H_2O (6 mL) and conc. HCl (2 mL) and heated to 60 °C for 4.5 h. The mixture was then evaporated *in vacuo* and coevaporated several times with toluene to give the title compound as a colourless hygroscopic oil (130 mg, 76%); $[a]_D^{20}$ −35.9 (*c* 1.0 in MeOH); ^{1}H NMR (500 MHz, D–MeOD): δ_H 7.46 (5H, m, Ar–H), 4.35 (1H, d, J = 12.9, $PhCH_2N$), 4.29 (1H, dd, J = 4.7, 7.1, H-3), 4.13 (1H, d, J = 12.9, $PhCH_2N$), 4.06 (1H, dd, J = 4.4, 4.4, H-1), 3.97 (1H, dd, J = 4.3, 4.3, H-2), 3.84 (1H, ddd, J = 4.3, 4.3, 10.6, CH_2CH_2OH), 3.55 (1H, ddd, J = 2.3, 10.6, 10.6, CH_2CH_2OH), 3.46 (1H, dd, J = 8.7, 8.7, H-4), 2.13 (1H, m, H-5), 1.95 (1H, m, CH_2CH_2OH), 1.75 (1H, m, CH_2CH_2OH);^{13}C NMR (75 MHz, D–MeOD): δ_C 133.1, 130.8, 130.6, 130.3 (Ar–C), 81.0 (C-2), 74.0 (C-1), 73.8 (C-3), 63.8 (C-4), 62.1 (CH_2CH_2OH), 51.9 ($PhCH_2N$), 45.3 (C-5), 32.4 (CH_2CH_2OH); HR-ESI–MS; calc. for $C_{14}H_{21}O_4NCl$ [M − 1] 302.1159, found 302.1111.

(1*S*, 2*S*, 3*S*, 4*S*, 5*S*)-4-Amino-5-(2-hydroxyethyl)-cyclopentane-1,2,3-triol hydrochloride (25). Compound **24** (120 mg, 0.395 mmol) was dissolved in EtOH (20 mL). Pd/C (50 mg, 10%) was added and the mixtures stirred at rt under an H_2 atmosphere overnight. The mixture was filtered through celite and evaporated *in vacuo*. In order to ease the purification the crude product was acetylated by treatment with CH_2Cl_2 (1 mL), pyridine (1 mL) and Ac_2O (0.7 mL) and left overnight at rt. The mixture was evaporated *in vacuo* and purified by flash chromatography to give the acetylated product as an oil (70 mg, 0.18 mmol). This was suspended in aq. HCl (4 M, 5 mL) and the mixture was heated to 60 °C for 4.5 h, then evaporated *in vacuo* and coevaporated three times with toluene to give the title compound as an hygroscopic oil (39 mg, 46%); $[a]_D^{20}$ −24.6 (*c* 1.1, MeOH);^{1}H NMR (500 MHz, D–MeOD): δ_H 4.17 (1H, dd, J = 6.4, 7.7, H-3), 4.04 (1H, dd, J = 4.1, 4.1, H-1), 3.93 (1H, dd, J = 4.7, 4.7, H-2), 3.81 (1H, ddd, J = 4.9, 4.9, 10.0, CH_2CH_2OH), 3.61 (1H, ddd, J = 3.8, 10.1, 10.1, CH_2CH_2OH), 3.39 (1H, dd, J = 8.5, 8.5, H-4), 2.10 (1H, m, H-5), 1,92 (1H, m, CH_2CH_2OH), 1.79 (1H, m, CH_2CH_2OH);^{13}C NMR (75 MHz, D–MeOD): δ_C 80.5 (C-2), 74.5 (C-3), 73.1 (C-1), 61.5 (CH_2CH_2OH), 56.6 (C-4), 44.7 (C-5); HR-EI–MS; calc. for $C_7H_{15}O_4NCl$ [M − 1] 212.0690, found 212.0687.

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