

Aminocyclopentanol as sugar mimics. Synthesis from unsaturated bicyclic lactones by Overman rearrangement

Marie Bøjstrup, Mette Fanefjord and Inge Lundt*

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Bicyclic cyclopentane lactones, prepared from bromodeoxyaldonolactones, were transformed into aminocyclopentanol with an Overman rearrangement as the key step. Two of the compounds prepared, **7** and **19**, were found to be good inhibitors of jack bean α -mannosidase and β -D-N-acetylglucosaminidase, respectively.

Introduction

Interest in obtaining access to polyhydroxylated aminocyclopentanes has emerged in recent years, since they have been shown to exhibit a wide range of biological activities.¹ An important feature is their ability to inhibit glycosidases, since it is assumed that they are transition state mimics of the glycosyl cation formed during the hydrolysis of glycosides.² The first synthetic aminocyclopentanol was prepared by Farr and co-workers in 1990, the so-called Merrell–Dow cyclopentylamine (MDC) **I** (Fig. 1).³ The three hydroxyl groups in MDC have configurations corresponding to those of the hydroxy groups at the 2, 3, and 4 positions in D-mannopyranose. This aminocyclopentanol can be viewed as a ring-contracted analogue of α -D-mannose where the ring oxygen is missing but having an external amino group for protonation by the glycosidase. MDC was shown to be a potent inhibitor of α -mannosidase (jack beans) with an IC_{50} value of 62 nM.³ A computational study^{3,5} showed good overlap of two of the three hydroxy groups of **I** with the 2-OH and 3-OH groups of the “flap-up” mannopyranosyl cation.^{4,5} Furthermore, the N-methyl group appeared to be located on the α -face of the ring close to C-1, suggesting that **I** could mimic the oxocarbenium ion as well as the protonated substrate.

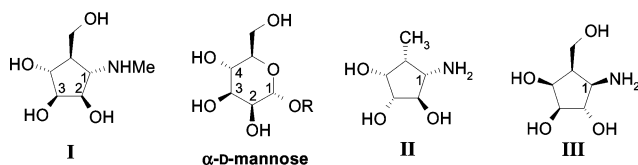
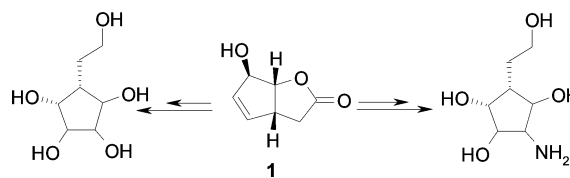


Fig. 1

Farr and co-workers never expanded the concept to other analogues of common carbohydrates. This was done years later by Reymond and co-workers in the synthesis of an aminocyclopentanol **II** (Fig. 1) in which the substitution pattern matches that of the parent carbohydrate, L-fucose. However, since the configuration of the carbon simulating C-1 in the sugar has the amino group in the “ β ”-configuration, it was shown to be only a weak inhibitor of α -L-fucosidase.⁶ Soon after, the same

group synthesized an aminocyclopentanol with a β -D-galacto substitution pattern, **III** (Fig. 1), and showed that this was selective towards β -galactosidases over α -galactosidases.⁷ Based on these findings, they suggested that aminocyclopentanol could be considered as mimics of the protonated glycosides governed by the configuration of the amino group corresponding to the anomeric configuration. Thus, it should be possible to synthesize selective inhibitors of α - or β -glycosidases by matching the stereochemistry of the aminocyclopentanol with the relevant carbohydrate. An investigation of the structure–activity relationship has just recently been published by Reymond and co-workers.⁸

Work in our group has recently been focused on the synthesis of carbohydrate mimics, especially the synthesis of carbasugars from easily available carbohydrate-based starting materials.⁹ In particular, the building block **1**, synthesized from a bromodeoxyheptonolactone derived from carbohydrates, has been shown to be well suited for the synthesis of several cyclopentanol^{10,11} (Scheme 1) and aminocyclopentanol.¹¹



Scheme 1

In the present work we further investigate the use of building block **1** and its enantiomer **ent-1** for the synthesis of aminocyclopentanol with stereochemistry mimicking common sugars in order to find new selective and potent glycosidase inhibitors.

Results and discussion

In order to obtain an amino functionality adjacent to the carbon side chain, either C-1 or C-6 of the building block **1** must be functionalized with a nitrogen. Recently we have published a method for the incorporation of nitrogen at C-1 giving access to mimics of D-sugars,¹² while introduction of nitrogen at C-6 will give access to mimics corresponding to L-sugars (Fig. 2). To pursue the latter strategy we took advantage of the allylic alcohol motif in **1** by investigation of the Overman rearrangement, which is a [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates.¹³

Department of Chemistry, Technical University of Denmark, Building 201, DK-2800, Kgs. Lyngby, Denmark. E-mail: il@kemi.dtu.dk; Fax: +45 45933968; Tel: +45 45252133

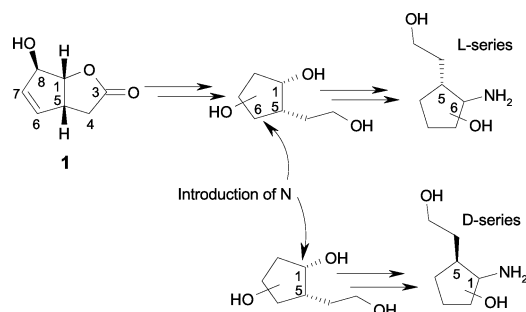
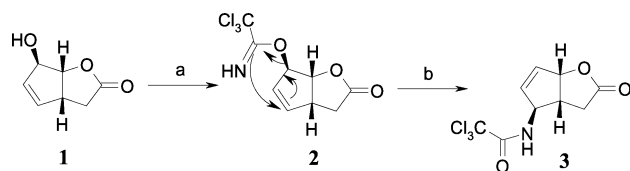


Fig. 2

This rearrangement would result in introduction of the desired amino function at C-6.

Thus, **1** was treated with NaH and trichloroacetimidate to give the crude trichloroacetimidate **2**, which was shown by NMR to be sufficiently pure to be used directly in the subsequent synthesis (Scheme 2). The imidate **2** was therefore subjected to a thermally mediated Overman rearrangement by reflux in xylene to give the allylic trichloroacetamide **3** in good yield.



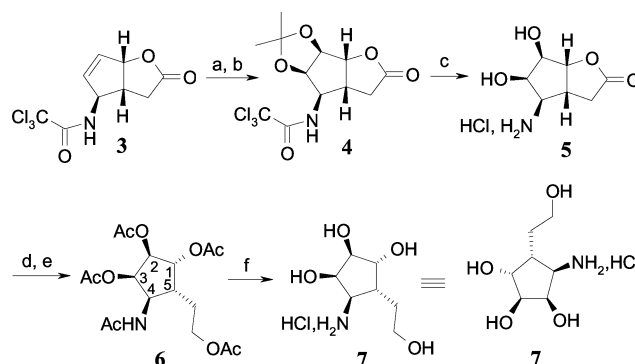
Scheme 2 Overman rearrangement. *Reagents and conditions:* a) Cl_3CCN , NaH, THF, 0°C , 1 h; b) xylene, reflux, 2 h (75%, 2 steps).

Introduction of hydroxyl groups at C-7 and C-8 might be performed by either dihydroxylation or epoxidation of the double bond in **3**, leading to mimics of different sugars.

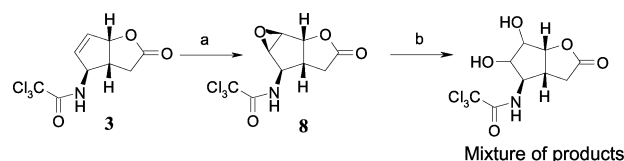
An OsO_4 -catalysed dihydroxylation was expected to be influenced with respect to the *exo-endo* selectivity by the conformation of the bicyclic system. Actually, it turned out that the allylic amide **3** gave only one product when subjected to the OsO_4 -catalysed dihydroxylation using $\text{NMO}\cdot\text{H}_2\text{O}$ as a re-oxidant. The product was directly transformed into the acetone **4** for purification. Deprotection under acidic conditions gave the amino-hydroxy-substituted lactone **5** which by reduction using $\text{Ca}(\text{BH}_4)_2$ in THF and subsequent acetylation gave **6**. Deprotection by acidic hydrolysis gave the aminocyclopentanol **7** (Scheme 3). The configurations were proven by an NOE-experiment on **6**, which showed a strong NOE from H-3 to H-4 and a medium NOE from H-2 to H-4, indicating that the *cis*-dihydroxylation had occurred from the *exo*-side of the bicyclic system.

The allylic amide **3** was also subjected to epoxidation using *m*-CPBA to give exclusively the *exo*-epoxide **8** in a good yield. The stereochemistry was confirmed by a NOESY experiment.

Not surprisingly, hydrolysis of the epoxide ring in **8** required rather harsh conditions due to the adjacent electron-withdrawing groups.¹⁴ Attempts to open the epoxide with aqueous TFA at room temperature resulted in no conversion even after several days of reaction. In contrast, heating with aqueous HCl resulted in slow opening of the epoxide together with hydrolysis of the trichloroacetamide. NMR analysis of the crude mixture showed that several products had formed, and since they were inseparable by chromatography this strategy was not pursued further (Scheme 4).

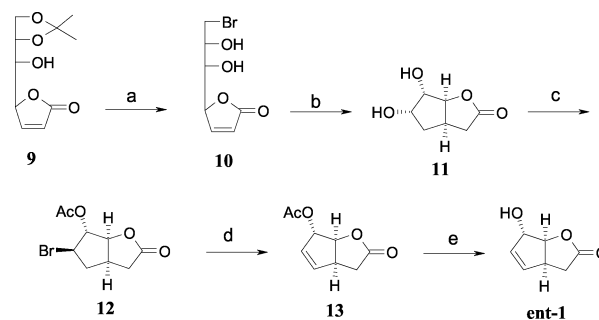


Scheme 3 Synthesis of aminocyclopentanol **7**. *Reagents and conditions:* a) OsO_4 , NMO, CH_2Cl_2 , rt, overnight; b) 2,2-dimethoxypropane, acetone, H_2SO_4 , rt, 20 min (80%); c) aq. HCl (6 M), reflux, 2.5 h (79%); d) $\text{Ca}(\text{BH}_4)_2$, ethanol, -20°C , overnight; e) Ac_2O , pyridine, rt, overnight (61%); f) aq. HCl (4 M), 60°C , 4.5 h (quant.).



Scheme 4 Epoxidation of **3**. *Reagents and conditions:* a) *m*-CPBA, CH_2Cl_2 , reflux, 4 d (98%); b) aq. HCl (4 M), 90°C , 4 h.

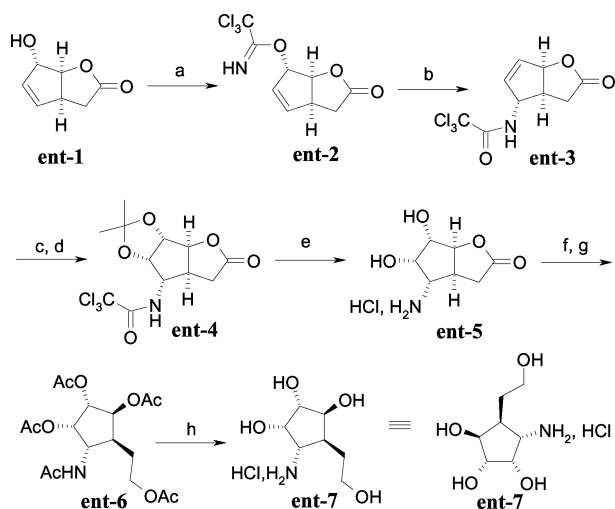
The bicyclic cyclopentane lactone **1** was prepared from a 2,3-unsaturated 6-bromo-6-deoxyheptonolactone by a radical-induced carbocyclisation.⁹ For the synthesis of **ent-1** by a similar carbocyclisation procedure, the precursor should be the 2,3-unsaturated heptonolactone **9** (Scheme 5). 2,3-Unsaturated heptonolactones are available by diastereoselective coupling of an enantiomerically pure aldehyde with 2-(trimethylsilyloxy)furan following the concept developed by Casiraghi and co-workers.¹⁵ For the synthesis of **9**, 2,3-isopropylidene-L-glyceraldehyde and 2-(trimethylsilyloxy)furan were used.^{15,16} Treatment of **9** with HBr in HOAc gave the 7-bromo-7-deoxyheptonolactone **10**, which by treatment with tributyltin hydride gave the bicyclic cyclopentane lactone **11** in quantitative yield. Treatment of the diol **11** with HBr–HOAc introduced bromine in a regio- and stereoselective reaction to **12**, which by treatment with 1,8-diazabicyclo[5.4.0]undec-5-ene (DBU) gave the unsaturated compound **13**. Finally, acidic



Scheme 5 Synthesis of **ent-1**. *Reagents and conditions:* a) HBr/AcOH, rt, 20 min, then MeOH, rt, overnight, 81%; b) Bu_3SnH , AIBN, EtOAc, rt, 4 h, quant.; c) HBr/AcOH, rt, 2 h, then Ac_2O , rt, 2 h, 88%; d) DBU, THF, reflux, overnight, 92%; e) HCl/MeOH, rt, 2 d, 94%.

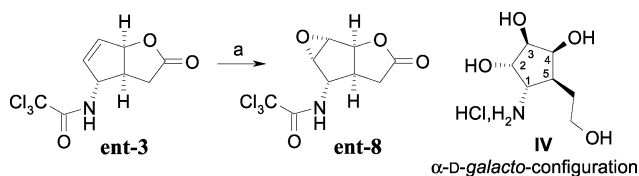
deacetylation provided the target **ent-1** in a convenient high-yielding reaction sequence from **9**.

For the synthesis of the aminocyclopentanol **ent-6**, a reaction sequence similar to the one described from **1** was performed starting with **ent-1**. The Overman rearrangement of the trichloroimidate was followed by dihydroxylation and protection to give **ent-4**, and finally reduction to give the aminocyclopentanol **ent-7** (Scheme 6).



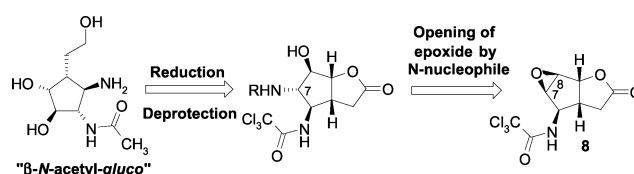
Scheme 6 Synthesis of aminocyclopentanol **ent-7**. *Reagents and conditions:* a) Cl_3CCN , NaH , THF, 0°C , 2 h; b) xylene, reflux, 3 h (43%, 2 steps); c) OsO_4 , NMO, CH_2Cl_2 , rt, overnight; d) 2,2-dimethoxypropane, acetone, conc. H_2SO_4 , rt, 2 h (72%); e) aq. HCl (6 M), reflux, 2.5 h (79%); f) $\text{Ca}(\text{BH}_4)_2$, ethanol, -20°C , overnight; g) Ac_2O , pyridine, rt, overnight (42%); h) aq. HCl (4 M), 60°C , 4.5 h (quant.).

Furthermore, **ent-3** was transformed into the epoxide **ent-8** as the only product following the procedure for preparation of **8**. The aim was to open **ent-8** regioselectively to give an aminocyclopentanol, **IV**, which would mimic a “ α -D-galacto”-configured carbocation (Scheme 7). An “ α -D-galacto”-configured cyclopentanol was considered as the missing link in a review of the configuration of the amino group as an anomer-selective mimic.¹⁷ We have now published the synthesis of **IV**¹² together with the corresponding aminocyclopentanol having a one-carbon shorter side chain directly mimicking the parent sugar.^{8,12}



Scheme 7 Epoxidation of **ent-3**. *Reagents and conditions:* a) *m*-CPBA, CH_2Cl_2 , reflux, 4 d (98%).

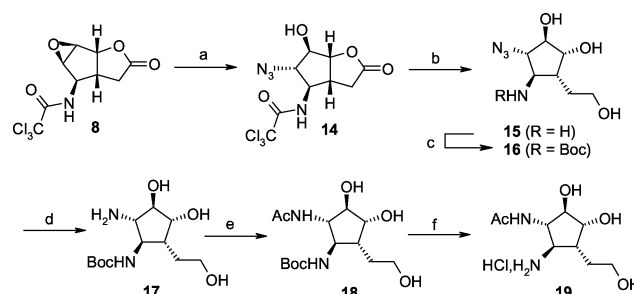
Unfortunately, **ent-8** (like **8**) was very sluggish in acid-catalysed epoxide opening. Since the epoxide **8** was readily available, the opening of the epoxide with a more efficient nucleophile than water (as described above) was explored. Furthermore, if an amino function could be introduced regioselectively, as shown in Scheme 8, a possible inhibitor for *N*-acetylglucosaminidase could be synthesized. The position and stereochemistry of the



Scheme 8 Retrosynthesis to the *N*-acetylglucosamine mimic.

groups except for the carbon side chain correspond to those of *N*-acetylglucosamine.

Following the retrosynthesis in Scheme 8, epoxide **8** was treated with NaN_3 in DMF at elevated temperatures. As was apparent from the hydrolysis of **8**, the epoxide is highly stabilised by the adjacent electron-withdrawing groups. Meanwhile, azide is a far better nucleophile compared to water, and the opening gave primarily one azide after a short reaction time at elevated temperature. The major product **14** could be isolated in a moderate yield by flash chromatography (Scheme 9). The minor isomer was not isolated, as this could not be separated from other impurities. The regioselectivity of the nucleophilic attack could not be determined at this stage, but the major product was later shown by 2D-NMR analysis of **18** to arise from nucleophilic attack at C-7.



Scheme 9 Synthesis of the potential β -D-*N*-acetylglucosaminidase inhibitor **19**. *Reagents and conditions:* a) NaN_3 , NH_4Cl , DMF, 80°C , 1.5 h (65%); b) CaCl_2 , NaBH_4 , THF, -20°C , overnight; c) Boc_2O , NaHCO_3 , acetone, H_2O , rt, overnight (40%); d) H_2 , 5% Pd/C , ethanol, rt, 2.5 h; e) H_2O -MeOH (1 : 2), Ac_2O , rt, 1 h (80%); f) aq. HCl (4 M), rt, 15 min (quant.).

Compound **14** was reduced with $\text{Ca}(\text{BH}_4)_2$ in THF, which resulted in reduction of both the lactone and the trichloroacetyl group but left the azide group untouched to give **15**. The free amine could be selectively Boc-protected under basic conditions to give **16** in a moderate yield. Reduction of the azide and selective acetylation of the free amine in **17** gave **18** in a good yield. The Boc-group was finally removed by acidic hydrolysis to give the target aminocyclopentanol **19** in a quantitative yield (Scheme 9).

Biological tests

The aminocyclopentanols **7** and **ent-7**, together with the cyclopentane lactones **5** and **ent-5**, were assayed for inhibition of a range of commercial enzymes: α -D-glucosidase (bakers' yeast), β -D-glucosidase (almonds), α -D-galactosidase (green coffee beans), β -D-galactosidase (*E. coli*), β -D-galactosidase (bovine liver), α -D-mannosidase (jack beans) and α -D-mannosidase (almonds) using the procedure described previously.¹²

The aminocyclopentanol **7** showed potent inhibition of α -D-mannosidase from jack beans ($K_i = 0.3 \mu\text{M}$). This activity is almost identical to the inhibition data obtained for the aminocyclopentanol **20** synthesized by Jäger and co-workers.¹⁸ This is an interesting result since **20** has the correct α -D-manno configuration (like DMC, **1**), while **7** has the amino group in the β -configuration and an extended side chain corresponding to an L-sugar. The non-importance of the anomeric configuration indicates that this aminocyclopentanol mimics the oxocarbenium ion rather than the protonated substrate. For DMC **1**, having the α -configuration, it was suggested that mimicking of both the “flap-up” mannopyranosyl cation as well as the protonated substrate might occur (see Introduction). Thus no anomer-selective inhibition from *manno*-configured inhibitors has been found, which also has been observed by Jäger and co-workers for the two anomers **20** and **21**¹⁸ (Fig. 3). The motif for inhibition of a mannosidase is the *cis*-relationship of the two hydroxyl groups at C-2 and C-3 (see Fig. 1) corresponding to the 2- and 3-hydroxyl groups in the substrate, as has also been found by synthesis of a range of mannostatin analogues.¹⁹

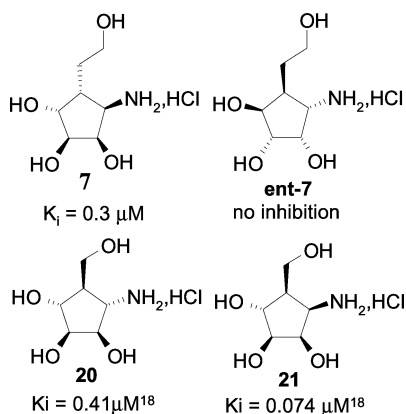


Fig. 3 K_i values for inhibition of *manno*-configured aminocyclopentanols towards α -D-mannosidase from jack beans.

The corresponding lactones **5** and **ent-5** did not show any activity towards the α -D-mannosidases or any of the other enzymes assayed.

The aminocyclopentanol **19** was tested towards β -D-N-acetylglucosaminidase from jack beans and showed inhibitory activity with K_i $8.9 \mu\text{M}$. This confirmed our expectations, as only the carbon side chain is of opposite stereochemistry to the correct β -N-acetyl-D-*gluco* configuration. The activity was about ten-fold less than for the aminocyclopentanol **22**,¹⁸ which has the correct configuration. Thus, for this enzyme the correct identity and configuration of the carbon side chain seems to be crucial for optimal activity (Fig. 4).

Conclusion

The unsaturated bicyclic lactones **1** and **ent-1** were shown to be valuable starting materials for synthesising densely functionalised aminocyclopentanols where the key step was an Overman rearrangement. The possible glycosidase inhibitors **7**, **ent-7** and **19** were synthesised. Both **7** and **19** were identified as good glycosidase inhibitors. In both compounds the configuration of the hydroxy

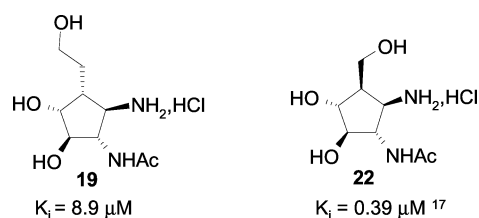


Fig. 4 K_i values for inhibition of β -D-N-acetyl-D-*gluco*-aminocyclopentanols towards β -D-N-acetylglucosaminidase from jack beans.

and amino groups were in accordance with the corresponding configurations in the respective substrates for the enzymes. The α -galactosidase could not tolerate the wrong configuration at “C-3” in **ent-7**, and the β -glucosidase was not inhibited by **7** with the wrong stereochemistry at “C-2”.

Experimental

^1H NMR spectra were recorded on a Bruker AM 500 instrument and ^{13}C NMR spectra on Varian Mercury 300 instrument. 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 the reference (CDCl_3 : $\delta = 7.26$ for ^1H , 76.93 for ^{13}C ; $\text{MeOH}-d_4$: $\delta = 3.31$ for ^1H , 49.00 for ^{13}C). When necessary, NMR data were assigned using H–H- and C–H-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 F₂₅₄ precoated silica plates, and spots were generally detected by spraying with a solution of 1.5% NH_4MoO_4 , 1% $\text{Ce}(\text{SO}_4)_2$ 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 assays

Inhibitory activities of the synthesised compounds were determined on a Labsystem iEMS reader MF following the procedure described previously.¹² The following commercial enzymes were tested: α -D-glucosidase (bakers' yeast), β -D-glucosidase (almonds), α -D-galactosidase (green coffee beans), β -D-galactosidase (*E. coli*), β -D-galactosidase (bovine liver), α -D-mannosidase (jack beans) and α -D-mannosidase (almonds).

(1S,5R,6S)-6-Trichloroacetamido-2-oxabicyclo[3.3.0]oct-7-en-3-one (**3**)

The allylic alcohol **1**¹¹ (4.02 g, 28.7 mmol) was dissolved in dry THF (45 mL) and added to NaH (1.56 g, 55–65% in mineral oil), which prior to the addition was washed with dry THF and subsequently suspended in dry THF (10 mL). The reaction mixture was stirred under nitrogen at rt for 30 min, after which the slurry was added *via* syringe to trichloroacetonitrile (4 mL, 40 mmol) over 15 min at 0°C . The mixture was stirred at this temperature for an additional 1 h, warmed to rt and filtered through a layer of MgSO_4 . The solvents were removed by

evaporation *in vacuo* to give (1*R*,5*R*,8*R*)-8-*O*-trichloroacetimido-2-oxabicyclo[3.3.0]oct-6-en-3-one (**2**) as slightly yellow crystals (quant.). The crude product was used immediately without further purification.

The imide **2** (8.16 g, 28.7 mmol) was dissolved in xylene (150 mL) and heated to reflux for 2 h. The solvent was removed by evaporation *in vacuo* to give a brown oil. The residue was dissolved in EtOAc (250 mL), treated with activated charcoal, filtered through Celite and evaporated *in vacuo* to give a yellow oil (7.47 g, 91%). Purification by flash chromatography (EtOAc–hexane, 1 : 1) gave the title compound **3** as colourless crystals (6.11 g, 75%), mp 100–102 °C. Recrystallisation of an analytical sample (EtOAc–hexane) gave mp 105–106 °C. $[a]_D^{20} + 182.9$ (*c* 1.6, CHCl₃); found; C, 38.13; H, 2.84; N, 4.80; Cl, 37.34. Calc. for C₉H₈O₃NCl₃; C, 37.99; H, 2.83; N, 4.92; Cl, 37.38; ¹H NMR (500 MHz, CDCl₃): δ_H 2.63 (1H, m, H-4'), 2.94–3.05 (2H, m, H-4, H-5), 4.76 (1H, m, H-6), 5.66 (1H, m, H-1), 6.11 (1H, ddd, *J* = 1.0, 2.2, 5.5, H-7), 6.25 (1H, ddd, *J* = 2.2, 2.2, 6.1, H-8), 6.96 (1H, d, *J* = 6.1, *NH*); ¹³C NMR (125 MHz, CDCl₃): δ_C 34.0 (C-4), 43.6 (C-5), 64.2 (C-6), 87.3 (C-1), 92.0 (C-Cl₃CO), 134.5, 135.3 (C-7, C-8), 161.8 (C-Cl₃CCO), 175.6 (C-3).

(1*R*,5*R*,6*R*,7*R*,8*S*)-6-Trichloroacetamido-7,8-isopropylidenedioxy-2-oxabicyclo[3.3.0]oct-3-one (4**)**

The allylic amide **3** (19.8 g, 69 mmol) was dissolved in CH₂Cl₂ (200 mL), and NMO·H₂O (11.4 g, 84 mmol) was added together with a catalytic amount of OsO₄(s). The mixture was stirred under N₂ at rt overnight. Na₂SO₃(s) was added and the mixture stirred for 30 min followed by evaporation *in vacuo* and co-evaporation four times with toluene. The crude residue was dissolved in acetone (200 mL), 2,2-dimethoxypropane (100 mL) and conc. H₂SO₄ (4 mL). The mixture was stirred for 20 min at rt. NaHCO₃ was then added until neutral pH, after which the mixture was filtered and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂, washed with H₂O (100 mL) and brine (100 mL), dried (MgSO₄), filtered and evaporated *in vacuo* to give colourless crystals (quant.). The compound was purified by flash chromatography (EtOAc–hexane, 1 : 3) to give the title compound as colourless crystals (19.95 g, 80%); mp 132–133 °C. An analytical sample was crystallised from EtOAc–hexane; mp 161–162 °C; $[a]_D^{20} - 12.6$ (*c* 1, CHCl₃); found; C, 39.94; H, 3.75; N, 4.20; Cl, 29.47. Calc. for C₁₂H₁₄O₅NCl₃; C, 40.19; H, 3.93; N, 3.91; Cl, 29.66; ¹H NMR (500 MHz, CDCl₃): δ_H 7.27 (1H, d, *J* = 9.0, *NH*), 4.81 (1H, d, *J* = 5.4, H-8), 4.77 (1H, dd, *J* = 5.3, 5.4, H-7), 4.66 (1H, d, *J* = 5.4, H-1), 4.20 (1H, ddd, *J* = 5.2, 8.0, 9.0, H-6), 3.00 (1H, d, *J* = 18.5, H-4), 2.94 (1H, ddd, *J* = 5.5, 8.2, 8.2, H-5), 2.77 (1H, dd, *J* = 8.2, 18.2, H-4'); 1.50 (3H, s, CH₃), 1.36 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ_C 174.6 (CO), 162.1 (COCCl₃), 112.3 ((CH₃)₂C), 86.5 (C-1), 82.1, 80.2 (C-7, C-8), 58.3 (C-6), 44.8 (C-5), 33.7 (C-4), 26.3, 24.2 (2 × CH₃).

(1*R*,5*R*,6*R*,7*R*,8*R*)-6-Amino-7,8-dihydroxy-2-oxabicyclo[3.3.0]oct-3-one hydrochloride (5**)**

Compound **4** (455 mg, 1.26 mmol) was suspended in aq. HCl (6 M, 10 mL) and heated to reflux for 2.5 h. The mixture was cooled to rt, evaporated *in vacuo* and co-evaporated 4 times with toluene to give **5** as colourless crystals (quant.). These were recrystallised

in MeOH–acetonitrile to give the title compound as colourless crystals (209 mg, 79%); mp 220–221 °C (decomposition); $[a]_D^{20} - 15.9$ (*c* 1, H₂O); Found; C, 39.81; H, 5.66; N, 6.68; Cl, 16.60. Calc. for C₇H₁₂O₄NCl; C, 40.11; H, 5.77; N, 6.68; Cl, 16.91; ¹H NMR (500 MHz, D₂O): δ_H 5.05 (1H, dd, *J* = 4.4, 9.1, H-1), 4.40 (1H, dd, *J* = 3.5, 4.5, H-7), 4.36 (1H, dd, *J* = 3.5, 4.5, H-8), 3.78 (1H, dd, *J* = 4.5, 6.5, H-6), 3.38 (1H, m, H-5), 3.14 (1H, dd, *J* = 11.1, 19, H-4), 2.76 (1H, dd, *J* = 4.1, 19.0, H-4'); ¹³C NMR (125 MHz, D₂O): δ_C 180.4 (CO), 88.6 (C-1), 77.0, 71.9 (C-7, C-8), 57.7 (C-6), 39.6, 33.6 (C-4, C-5).

(1*R*,2*S*,3*R*,4*R*,5*R*)-4-Acetamido-1,2,3-tri-*O*-acetyl-5-(2-acetoxyethyl)cyclopentane-1,2,3-triol (6**)**

CaCl₂ (551 mg, 5.0 mmol) and NaBH₄ (405 mg, 10.7 mmol) were suspended in dry ethanol (3 mL) and stirred at –20 °C for 2 h under N₂ to ensure formation of Ca(BH₄)₂. The lactone **5** (210 mg, 1.0 mmol) was dissolved in EtOH (2 mL) and added at –20 °C under N₂, and the mixture was stirred at rt overnight. The reaction was then quenched with aq. HCl (4 M, 8 mL), stirred for 30 min and evaporated *in vacuo* followed by co-evaporation with HCl/MeOH (0.1 M). The residue was dissolved in H₂O (10 mL) and loaded onto a column of ion-exchange resin (Amberlite IR-120, H⁺, 150 mL). The column was eluted with H₂O (250 mL) to neutral pH and then with 12.5% NH₃ (250 mL). The alkaline phases were concentrated to give a crude residue, which was co-evaporated three times with toluene. The residue was dissolved in dry pyridine (4 mL) and Ac₂O (1.5 mL) and stirred at rt overnight. The mixture was evaporated *in vacuo* and purified by flash chromatography (EtOAc) to give the title compound as slightly yellow crystals (267 mg, 68%). The compound was then recrystallised (EtOAc–hexane) to give the title compound as colourless crystals (235 mg, 61%); mp 110–111 °C; $[a]_D^{20} + 28.04$ (*c* 1, EtOAc); found; C, 52.48; H, 6.34; N, 3.47. Calc. for C₁₇H₂₅O₉N; C, 52.70; H, 6.50; N, 3.62; ¹H NMR (500 MHz, CDCl₃): δ_H 1.73 (1H, m, CH₂CH₂OAc), 1.86 (1H, m, CH₂CH₂OAc), 2.01, 2.03, 2.04, 2.11, 2.12 (15 H, 5 × CH₃), 2.30 (1H, m, H-5), 4.02 (1H, m, CH₂CH₂OAc), 4.12 (1H, m, CH₂CH₂OAc), 4.52 (1H, ddd, *J* = 5.1, 9.8, 10.7, H-4), 5.20 (1H, dd, *J* = 4.3, 4.7, H-2), 5.29 (1H, dd, *J* = 4.3, 8.1, H-1), 5.37 (1H, dd, *J* = 4.7, 5.1, H-3), 5.63 (1H, d, *J* = 8.9, *NH*); ¹³C NMR (75 MHz, CDCl₃): δ_C 171.0, 169.9, 169.6, 169.4, 169.1 (5 × CO), 75.9 (C-2), 74.5 (C-1), 71.9 (C-3), 62.5 (CH₂CH₂OAc), 52.4 (C-4), 41.8 (C-5), 26.1 (CH₂CH₂OAc), 23.2 (CH₃CONH), 20.9, 20.7, 20.6, 20.4 (4 × CH₃COO).

(1*R*,2*S*,3*R*,4*R*,5*R*)-4-Amino-5-(2-hydroxyethyl)-cyclopentane-1,2,3-triol hydrochloride (7**)**

Compound **6** (73 mg, 0.19 mmol) was dissolved in aq. HCl (4 M, 5 mL), the mixture was heated to 60 °C for 4.5 h, and then evaporated *in vacuo* and co-evaporated several times with toluene to give the title compound as a slightly yellow oil (40 mg, quant.); $[a]_D^{20} + 37.94$ (*c* 1, MeOH); HR-ESI-MS; C₇H₁₅O₄N·HCl, Calc. for [M – 1]; *m/z* 212.0690. Found; 212.0682; ¹H NMR (500 MHz, MeOD): δ_H 4.34 (1H, dd, *J* = 6.5, 4.5, H-3), 4.03 (1H, dd, *J* = 2.5, 6.3, H-1), 3.94 (1H, dd, *J* = 2.5, 4.5, H-2), 3.79 (1H, ddd, *J* = 5.5, 5.5, 10.5, CH₂CH₂OH), 3.63 (1H, ddd, *J* = 4.3, 10.1, 10.1, CH₂CH₂OH), 3.30 (1H, dd, *J* = 8.5, 8.5, H-4), 2.32 (1H, m, H-5), 1.89 (1H, m, CH₂CH₂OH), 1.76 (1H, m, CH₂CH₂OH);

^{13}C NMR (75 MHz, MeOD): δ_{C} 78.6 (C-2), 76.6 (C-1), 70.6 (C-3), 61.7 ($\text{CH}_2\text{CH}_2\text{OH}$), 57.5 (C-4), 45.0 (C-5), 31.4 ($\text{CH}_2\text{CH}_2\text{OH}$).

(1*R*,5*R*,6*R*,7*R*,8*S*)-6-Trichloroacetamido-7,8-epoxy-2-oxabicyclo[3.3.0]oct-3-one (8)

The allylic amide **3** (2.01 g, 7.1 mmol) was dissolved in CH_2Cl_2 (50 mL), and *m*-CPBA (50–90% in H_2O , 4.824 g, 14 mmol) was added. The mixture was heated to reflux for 4 d, after which CH_2Cl_2 (30 mL) was added and the organic phase washed with aq. Na_2SO_3 (10%, 40 mL), half-saturated aq. NaHCO_3 (2×30 mL), H_2O (25 mL) and brine (25 mL). The organic phase was dried (MgSO_4), filtered and evaporated *in vacuo* to give **8** as colourless crystals; mp 152–162 °C (520 mg, 98%). These were recrystallised from EtOAc–hexane to give the title compound as white crystals (1.45 g, 68%); mp 161–163 °C; $[\alpha]_{\text{D}}^{20} +38.74$ (*c* 1, EtOAc); found; C, 35.88; H, 2.67; N, 4.55; Cl, 35.27. Calc. for $\text{C}_9\text{H}_8\text{O}_4\text{NCl}_3$; C, 35.97; H, 2.68; N, 4.66; Cl, 35.39; ^1H NMR (500 MHz, CDCl_3): δ_{H} 2.51 (1H, m, H-5), 2.88 (1H, d, $J = 2.5$, H-4), 2.87 (1H, s, H-4'), 3.80 (1H, dd, $J = 1.7$, 2.5, H-7), 3.90 (1H, d, $J = 2.5$, H-8), 4.33 (1H, ddd, $J = 1.7$, 5.5, 7.3, H-6), 5.03 (1H, d, $J = 6.4$, H-1), 7.05 (1H, d, $J = 7.3$, *NH*); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 33.5 (C-4), 42.8 (C-5), 56.8, 59.0 (C-7, C-8), 59.3 (C-6), 81.5 (C-1), 162.4 (Cl_3CCO), 174.8 (C-3).

7-Bromo-2,3,7-trideoxy-L-arabino-hept-2-enono-1,4-lactone (10)

6,7-*O*-Isopropylidene-2,3-dideoxy-L-arabino-hept-2-enono-1,4-lactone **9** (2.90 g, 13.5 mmol) was suspended in HBr/AcOH (33.4%, 25 mL). The system was closed with a glass stopper and the reaction mixture was stirred vigorously at room temperature for 20 min, followed by addition of MeOH (50 mL), and stirring was continued at room temperature overnight. The mixture was concentrated, and then co-concentrated 5 times with MeOH, 3 times with H_2O and 3 times with toluene to give a brown syrupy residue. This was dissolved in H_2O (50 mL), extracted 3 times with CH_2Cl_2 (50 mL) which was re-extracted 3 times with H_2O . The combined aqueous phases were extracted 6 times with EtOAc (50 mL) and the combined EtOAc phases were then dried (MgSO_4) and concentrated to give yellow crystals. The combined aqueous phases from the above procedure were continuously extracted with EtOAc overnight. The organic phase was concentrated and purified by flash chromatography using EtOAc as eluent to give colourless crystals (total 2.60 g, 81%); mp 102–104 °C; $[\alpha]_{\text{D}}^{20} -83.9$ (*c* 1, MeOH); found; C, 35.83; H, 3.78; Br, 32.86. Calculated for $\text{C}_7\text{H}_9\text{O}_4\text{Br}$; C, 35.47; H, 3.83; Br, 33.71; ^1H NMR (300 MHz, D_2O) δ 7.84 (1H, dd, $J = 5.5$, 1.3, H-3), 6.36 (1H, dd, $J = 6.0$, 2.1, H-2), 5.67 (1H, dd, $J = 3.8$, 1.7, H-4), 4.08 (1H, dd, $J = 9.0$, 1.7, H-5), 4.03 (1H, ddd, $J = 8.9$, 4.7, 2.6, H-6), 3.87 (1H, dd, $J = 11.1$, 2.5, H-7), 3.80 (1H, dd, $J = 11.5$, 4.3, H-7'); ^{13}C NMR (75 MHz, D_2O) δ 176.8 (C-1), 157.4 (C-3), 121.7 (C-2), 84.2 (C-4), 70.2, 69.7 (C-5, C-6), 37.4 (C-7).

(1*S*,5*R*,7*S*,8*S*)-7,8-Dihydroxy-2-oxabicyclo[3.3.0]oct-3-one (11)

Compound **10** (2.01 g, 8.4 mmol) was dissolved in dry EtOAc (25.0 mL) and heated to reflux under N_2 . A solution of AIBN (145 mg, 0.9 mmol) and Bu_3SnH (2.5 mL, 9.4 mmol) in dry EtOAc was added slowly over 2 h. The solution was kept under reflux for an additional 2 h. Concentration left an oily residue which

was dissolved in acetonitrile (30.0 mL) and extracted five times with hexane. The acetonitrile phase was then concentrated to form a crystalline crude product, which was further purified by flash chromatography (EtOAc) to give **11** as colourless crystals (1.33 g, quant.); mp 76–77 °C; $[\alpha]_{\text{D}}^{20} +70.6$ (*c* 1.0, MeOH); found; C, 52.94; H, 6.23. Calculated for $\text{C}_7\text{H}_{10}\text{O}_4$; C, 53.16; H, 6.37; ^1H NMR (500 MHz, D_2O) δ 4.96 (1H, ddd, $J = 8.4$, 3.4, 1.8, H-1), 4.31 (1H, ddd, $J = 9.3$, 5.1, 1.4, H-7), 3.29 (1H, m, H-5), 4.23 (1H, dd, $J = 7.3$, 3.9, H-8), 3.02 (1H, ddd, $J = 19.4$, 11.0, 2.0, H-4'), 2.52 (1H, ddd, $J = 19.5$, 4.1, 1.9, H-4), 2.22 (1H, m, H-6), 1.87 (1H, ddd, $J = 14.3$, 7.4, 2.2, H-6'); ^{13}C NMR (125 MHz, D_2O) δ 182.5 (C-3), 90.4 (C-1), 77.9 (C-8), 72.9 (C-7), 37.1, 35.8 (C-4, C-6), 34.3 (C-5).

(1*S*,5*S*,7*R*,8*R*)-8-Acetoxy-7-bromo-7-deoxy-2-oxabicyclo[3.3.0]oct-3-one 12

Compound **11** (729 mg, 4.6 mmol) was suspended in HBr/AcOH (33.6%, 25.0 mL). The system was closed with a glass stopper and stirred at room temperature for 2 h, followed by addition of acetic anhydride (50.0 mL), and stirring for an additional 2 h. The reaction mixture was concentrated, and then co-concentrated with MeOH to give a syrupy residue, which was dissolved in dichloromethane (15.0 mL), washed with saturated NaCl (aq) (10.0 mL) and concentrated *in vacuo*. The crude product was purified further by flash chromatography (EtOAc–heptane, 1 : 1) giving **12** as fine yellow crystals (1.07 g, 88%); mp 71.5–73 °C; $[\alpha]_{\text{D}}^{20} +21.5$ (*c* 1.0, CHCl_3); [reported for **ent-12**:¹⁰ mp 72–73 °C; $[\alpha]_{\text{D}}^{20} -24.6$ (*c* 1.0, CHCl_3)]; ES-MS; $\text{C}_9\text{H}_{11}\text{BrO}_4\text{Na}$, Calc. for $[\text{M} + \text{Na}]$; *m/z* 283. Found; 285; ^1H NMR (300 MHz, CDCl_3) δ 5.37 (1H, dd, $J = 3.9$, 0.6, H-8), 4.76 (1H, d, $J = 8.1$, H-1), 4.10 (1H, ddd, $J = 5.1$, 4.5, 0.9, H-7), 3.02–3.18 (1H, m, H-5), 2.81 (1H, dd, $J = 18.6$, 10.8, H-4'), 2.71 (1H, ddd, $J = 14.7$, 6.3, 2.1, H-6), 2.51 (1H, dd, $J = 18.9$, 3.6, H-4), 2.09 (1H, ddd, $J = 14.7$, 5.7, 5.7, H-6), 2.05 (3H, s, CH_3); ^{13}C NMR (75.0 MHz, CDCl_3) δ 176.0 (C-3), 169.3 ($\text{CH}_3\text{--C=O}$), 87.0 (C-1), 83.5 (C-8), 46.6 (C-7), 41.0 (C-6), 36.6 (C-4), 35.5 (C-5), 20.9 (CH_3). All NMR data are identical to those reported for the enantiomer.¹⁰

(1*S*,5*S*,8*S*)-8-Acetoxy-2-oxabicyclo[3.3.0]oct-6-ene-3-one 13

Compound **12** (1.26 g, 4.8 mmol) was dissolved in dry THF (40.0 mL), and DBU (1.40 mL, 9.4 mmol) was added. The reaction mixture was heated to reflux overnight under N_2 . The reaction mixture was then cooled to room temperature, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (10.0 mL), washed with H_2O (15.0 mL) and HCl (1 M, 15.0 mL), and the combined aqueous phases were re-extracted twice with CH_2Cl_2 (15.0 mL). The combined organic phases were washed once with saturated aq. NaCl (15.0 mL), dried (MgSO_4) and concentrated to give a yellow syrup. The crude product was purified by flash chromatography (EtOAc–heptane, 1 : 2), to give the title compound as a transparent oil (0.80 g, 92%) (99%, based on recovered starting material). Crystallization from ether gave fine colourless crystals; mp 44.5–46 °C; $[\alpha]_{\text{D}}^{20} +283.3$ (*c* 1.0, CHCl_3); [reported for **ent-13**:¹¹ mp 49–50 °C; $[\alpha]_{\text{D}}^{20} -285.0$ (*c* 1.0, CHCl_3)]; ES-MS; $\text{C}_9\text{H}_{10}\text{O}_4\text{Na}$, Calc. for $[\text{M} + \text{Na}]$; *m/z* 205. Found; 205; ^1H NMR (300 MHz, CDCl_3) δ 5.97 (1H, dd, $J = 1.3$, 5.7, H-8), 5.91 (1H, dt, $J = 2.2$, 4.9 H-6), 5.62 (1H, ddd, $J = 0.6$, 1.4, 2.8, H-7),

4.90 (1H, ddd, $J = 0.6, 1.3, 5.9$, H-1), 3.70 (1H, m, H-5), 2.78 (1H, dd, $J = 10.3, 18.3$, H-4'), 2.40 (1H, dd, $J = 2.3, 18.3$, H-4), 2.04 (3H, s, CH₃); ¹³C NMR (75.0 MHz, CDCl₃) δ 175.4 (C-3), 170.1 (CH₃-C=O), 139.0 (C-6), 129.0 (C-7), 85.5 (C-1), 82.1 (C-8), 43.8 (C-4), 32.3 (C-5), 21.0 (CH₃). All NMR data are identical to those reported for the enantiomer.¹¹

(1S,5S,8S)-8-Hydroxy-2-oxabicyclo[3.3.0]oct-6-en-3-one (ent-1)

Compound **13** (280 mg, 1.5 mmol) was dissolved in a solution of dry 1% HCl/MeOH (15.0 mL), and the solution was stirred at room temperature for 2 days. The reaction mixture was concentrated, co-concentrated with toluene, and the residue was purified further by flash chromatography (EtOAc), to give the product as an oil (204 mg, 94%), which was crystallized and recrystallized from hexane–EtOAc; mp 60–66 °C; $[a]_D^{20} +169.4$ (c 1.0, CHCl₃); [reported for **1**:¹¹ mp 67–68 °C; $[a]_D^{20} +170.9$ (c 1.0, CHCl₃)]; ES-MS; C₇H₈O₃Na, Calc. for [M + Na]; m/z 163. Found; 163; ¹H NMR (300.0 MHz, CDCl₃) δ 5.93 (1H, m, H-8), 5.88 (1H, dd, $J = 1.1, 5.7$, H-6 or H-6'), 4.83 (2H, m, H-1, H-7), 3.73 (1H, m, H-5), 3.47 (1H, d, $J = 0.6$, OH), 2.78 (1H, dd, $J = 10.1, 18.2$, H-4'), 2.40 (1H, dd, $J = 1.8, 18.2$, H-4). ¹³C NMR (75.0 MHz, CDCl₃) δ 176.2 (C-3), 137.0, 132.3 (C-7, C-6), 88.4 (C-1), 80.3 (C-8), 43.6 (C-4), 32.6 (C-5). All NMR data are identical to those reported for the enantiomer.¹¹

(1R,5S,6R)-6-Trichloroacetamino-2-oxabicyclo[3.3.0]oct-7-ene-3-one (ent-3)

The allylic alcohol **ent-1** (125 mg, 0.9 mmol) was transformed to the trichloroacetamide **ent-2** and rearranged immediately to **ent-3** as described for **3** to give a crude product, which was purified by flash chromatography (EtOAc–heptane 1 : 3 → 1 : 1), giving the title compound as colourless crystals (109 mg, 43%); mp 101–103 °C; $[a]_D^{20} -166.3$ (c 1.0, CHCl₃); ES-MS; C₉H₈Cl₃NO₃Na, Calc. for [M + Na]; m/z 306. Found; 306. The ¹H and ¹³C NMR spectra were in accordance with those for **3**.

(1S,5S,6S,7S,8S)-6-Trichloroacetamido-7,8-isopropylidene-2-oxabicyclo[3.3.0]oct-3-one (ent-4)

The allylic amide **ent-3** (136 mg, 0.47 mmol) was dihydroxylated and isolated as the isopropylidene derivative as described for **4** to give the product as colourless crystals (122 mg, 72%); mp 129–130 °C. Recrystallisation from EtOAc–hexane gave mp 159–161 °C; $[a]_D^{20} +11.4$ (c 1, CHCl₃); The ¹H and ¹³C NMR spectra were identical to those described above for **4**.

(1S,5S,6S,7S,8S)-6-Trichloroacetamido-7,8-dihydroxy-2-oxabicyclo[3.3.0]oct-3-one (ent-5)

The isopropylidene derivative **ent-4** was deprotected as described above to give **ent-5** as colourless crystals; mp 218–221 °C; $[a]_D^{25} +12.1$ (c 1 in MeOH). The ¹H and ¹³C NMR spectra were identical to those described above for **5**.

(1S,2R,3S,4S,5S)-4-Acetamido-1,2,3-tri-*O*-acetyl-5-(2-acetoxyethyl)cyclopentane-1,2,3-triol (ent-6)

The bicyclic lactone **ent-5** (86 mg, 0.27 mmol) was subjected to reduction with Ca(BH₄)₂ followed by acetylation as described

above to give the product (44 mg, 42%); $[a]_D^{25} -28.0$ (c 1, EtOAc). The ¹H and ¹³C NMR spectra were identical to those described above for **6**.

(1S,2R,3S,4S,5S)-4-Amino-5-(2-hydroxyethyl)cyclopentane-1,2,3-triol hydrochloride (ent-7)

The acetylated compound **ent-6** (32.6 mg, 0.08 mmol) was dissolved in aq. HCl (4 M, 15.0 mL) heated to 60 °C for 4.5 h. Concentration *in vacuo* and co-evaporation 3 times with toluene gave the title compound as an oil (17.0 mg, quant); $[a]_D^{25} -43.3$ (c 0.5, MeOH); The ¹H and ¹³C NMR spectra were identical to those described above for **7**.

(1S,5S,6S,7S,8R)-6-Trichloroacetamino-7,8-epoxy-2-oxabicyclo[3.3.0]oct-3-one (ent-8)

The unsaturated compound **ent-3** (37 mg, 0.14 mmol) was epoxidised with *m*-CPBA (93 mg, 0.26 mmol, 50–90% in H₂O) as described above. Purification of the crude product by column chromatography (heptane–EtOAc, 1 : 1) gave **ent-8** (36 mg, 92%); $[a]_D^{22} -40.9$ (c 0.9, EtOAc); The ¹H and ¹³C NMR spectra were identical to those described above for **8**.

(1R,5R,6R,7S,8R)-6-Trichloroacetamido-7-azido-8-hydroxy-2-oxabicyclo[3.3.0]oct-3-one (14)

The epoxide **8** (297 mg, 0.99 mmol), NaN₃ (697 mg, 10.7 mmol) and NH₄Cl (650 mg, 12.2 mmol) were dissolved in dry DMF (10 mL) and heated to 80 °C for 1.5 h. The mixture was evaporated *in vacuo*, dissolved in EtOAc (50 mL) and washed with H₂O (mL). The aqueous phase was re-extracted with EtOAc (2 × 20 mL). The organic phases were combined, washed with brine (15 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a mixture of isomeric products as colourless crystals (quant.). The residue was purified by flash chromatography (EtOAc–hexane, 1 : 1) to give the title compound as colourless crystals (220 mg, 65%); mp 194–196 °C; $[a]_D^{20} -23.6$ (c 1.1, acetone); found; H, 2.64; C, 31.68; N, 16.09; Cl, 30.86. Calc. for C₉H₉O₄N₄Cl₃; H, 2.64; C, 31.46; N, 16.38; Cl, 30.96; ¹H NMR (500 MHz, acetone-*d*₆) δ 5.41 (1H, d, $J = 5.7$, NH), 4.75 (1H, dd, $J = 4.4, 9.7$, H-1), 4.20–4.09 (3H, m, H-6, H-7, H-8), 3.20 (1H, m, H-5), 2.84 (1H, dd, $J = 18.1, 10.6$, H-4), 2.62 (1H, dd, $J = 3.5, 18.2$, H-4'); ¹³C NMR (75.5 MHz, acetone-*d*₆) δ 176.3 (CO), 163.0, (COCCl₃), 86.4 (C-1), 79.8 (C-8), 68.7, 59.8 (C-6, C-7), 40.6 (C-5), 33.7 (C-4).

(1R,2R,3S,4R,5R)-4-(*N*-*tert*-Butoxycarbonyl)amino-3-azido-5-(2-hydroxyethyl)cyclopentane-1,2-diol (16)

CaCl₂ (940 mg, 8.5 mmol) and NaBH₄ (599 mg, 15.8 mmol) were suspended in dry THF (15 mL) and stirred at rt for 1.5 h. The mixture was cooled to –20 °C, **14** (362 mg, 1.05 mmol) was added, and the mixture stirred at –20 °C overnight. The reaction was quenched using aq. HCl (4 M, 8 mL) and stirred for 0.5 hour, concentrated *in vacuo* and co-evaporated twice with 1% HCl in MeOH. The residue was dissolved in water (10 mL) and loaded onto a column of ion-exchange resin (Amberlite IR-120, H⁺, 170 mL). The column was eluted with water (200 mL) to neutral pH and then with 12.5% aq. ammonia (300 mL). The alkaline

phases were concentrated *in vacuo* and then co-evaporated with aq. HCl (4 M, 10 mL) to give crude **15** (140 mg, 56%).

The above crude **15** was dissolved in acetone (3 mL) and H₂O (3 mL), and the pH was adjusted to pH 8 with NaHCO₃(s). Boc₂O (800 mg, 4.6 mmol) was added and the mixture stirred at rt overnight. The mixture was evaporated *in vacuo*, dissolved in EtOAc (10 mL) and washed with brine (10 mL). The aqueous phase was re-extracted with EtOAc (4 × 10 mL), the organic phases were combined, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography to give the title compound as colourless crystals (123 mg, 40%); mp 117–119 °C; [α]_D²⁰ +75.8 (*c* 0.7, MeOH); HR-EI-MS; C₁₂H₂₂O₅N₄, Calc. for [M + Na]; *m/z* 225.1488; found; 225.1476; ¹H NMR (500 MHz, MeOD): δ 3.85 (1H, dd, *J* = 3.2, 6.8, H-1), 3.71 (1H, dd, *J* = 9.5, 11.2, H-4), 3.67 (1H, dd, *J* = 3.1, 6.3, H-2), 3.61 (2H, m, CH₂CH₂OH), 3.38 (1H, dd, *J* = 6.7, 9.3, H-3), 2.00 (1H, m, H-5), 1.82 (1H, m, CH₂CH₂OH), 1.59 (1H, m, CH₂CH₂OH), 1.45 (3H, s, OC(CH₃)₃); ¹³C NMR (75 MHz, MeOD): δ 158.0 (CO), 82.5 (OC(CH₃)₃), 80.3 (C-2), 76.2 (C-1), 72.9 (C-3), 61.4 (CH₂CH₂OH), 59.0 (C-4), 44.4 (C-5), 30.2 (CH₂CH₂OH), 28.8 (OC(CH₃)₃). IR $\nu_{\max}$ (film)/cm⁻¹ 3316 s br (OH); 2106 s (N₃); 1690 s (C=O).

(1R,2R,3S,4R,5R)-4-(N-tert-Butoxycarbonyl)amino-3-acetamido-5-(2-hydroxyethyl)cyclopentane-1,2-diol (17)

The azide **16** (116 mg, 0.38 mmol) was dissolved in ethanol (7 mL), Pd/C (5%, 77 mg) was added and the mixture was stirred under H₂ for 2.5 h. The mixture was then filtered through Celite and evaporated *in vacuo*. The residue was dissolved in H₂O–MeOH (1 : 2, 6 mL). Ac₂O (0.4 mL) was added and the mixture was stirred at rt for 1 h. The mixture was concentrated *in vacuo* and co-evaporated three times with toluene. The residue was then purified by flash chromatography (EtOAc–hexane, 9 : 1), to give the title compound as colourless crystals (98 mg, 80%); mp 213–214 °C; [α]_D²⁰ +70.04 (*c* 1, MeOH); found; H, 8.03; C, 52.74; N, 8.54. Calc. for C₁₄H₂₆O₆N₂; H, 8.23; C, 52.82; N, 8.80; ¹H NMR (500 MHz, MeOD): δ 3.88 (1H, dd, *J* = 2.3, 6.2, H-1), 3.77 (1H, dd, *J* = 5.9, 8.7, H-3), 3.71 (1H, dd, *J* = 2.3, 5.5, H-2), 3.69 (H, dd, *J* = 8.9, 8.9, H-4), 3.63 (2H, t, *J* = 6.5, H-7, H-7'), 2.02 (1H, m, H-5), 1.95 (3H, s, CH₃CO), 1.84 (1H, m, H-6), 1.64 (1H, m, H-6'), 1.42 (9H, s, (CH₃)₃C); ¹³C NMR (75.4 MHz, MeOD): δ 173.8 (CO), 158.5 (CO), 82.9 (C-2), 80.1 (OCCH₃), 76.6 (C-1), 63.4 (C-3),

61.5 (C-7), 58.9 (C-4), 44.7 (C-5), 30.4 (C-6), 28.7 ((CH₃)₃C), 22.7 (CH₃CO).

(1R,2R,3S,4R,5R)-4-Amino-3-acetamido-5-(2-hydroxyethyl)cyclopentane-1,2-diol hydrochloride (19)

Compound **18** (44 mg, 0.14 mmol) was dissolved in aq. HCl (4 M, 5 mL) and stirred at rt for 15 min. The mixture was concentrated *in vacuo* and co-evaporated several times with toluene to give the title compound as a hygroscopic oil (36 mg, quant); [α]_D²⁰ +60.06 (*c* 1, MeOH); HR-EI-MS; C₉H₁₈O₄N₂·HCl, Calc for [M – 1] *m/z* 253.0955. Found 253.0914; ¹H NMR (500 MHz, MeOD): δ 3.97–3.95 (2H, m, H-1, H-3), 3.91 (1H, dd, *J* = 2.6, 4.5, H-2), 3.82 (1H, ddd, *J* = 4.5, 4.5, 10.3, H-7), 3.61 (1H, ddd, *J* = 3.4, 10.3, 10.3, H-7'), 3.24 (1H, dd, *J* = 8.2, 9.3, H-4), 2.31 (1H, m, H-5), 2.04 (3H, s, CH₃CO), 1.93 (1H, m, H-6), 1.77 (1H, m, H-6'); ¹³C NMR (75.4 MHz, MeOD): δ 174.9 (CO), 81.5 (C-2), 78.0 (C-1), 62.6 (C-3), 61.7 (C-4), 61.6 (C-7), 45.3 (C-5), 30.9 (C-6), 22.3 (COCH₃).

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