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PAPER

Stereoselective synthesis and biological evaluation of D-fagomine, D-3-*epi*-fagomine and D-3,4-*epi*-fagomine analogs from D-glyceraldehyde acetonide as a common building block†

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The stereoselective synthesis of D-fagomine, D-3-*epi*-fagomine, and D-3-*epi*-fagomine analogs starting from readily available D-glyceraldehyde acetonide has been achieved. The synthesis involves diastereoselective *anti*-vinylation of its homoallylimine, ring-closing metathesis, and stereoselective epoxidation followed by regioselective ring-opening or stereoselective dihydroxylation. The lack of a strong activity as glycosidase inhibitors of these compounds could be advantageous for their therapeutic use as chaperones.

Introduction

The structural analogy of polyhydroxylated piperidines to sugars confers to these compounds – known as iminosugars – remarkable biological activity derived from their ability to inhibit a number of enzymes of medicinal interest such as glycosidases[1] among others. This diverse inhibitory activity of iminosugars has been exploited for the development of a new generation of potential agents for the treatment of several diseases[2] including diabetes, lysosomal storage disorders, viral infections or cancer metastasis.

(2*R*,3*R*,4*R*)-2-Hydroxymethylpiperidine-3,4-diol, D-fagomine (Fig. 1), which was first isolated from the seeds of Japanese buckwheat *Fagopyrum esculentum Moench*[3] and later found in other plant sources,[4] has a potent antihyperglycemic effect in streptozocin-induced diabetic mice and potentiates markedly immunoreactive insulin release.[5] D-Fagomine also lowers postprandial blood glucose concentration and modulates bacterial adhesion.[6] This behavior confers to this compound a potential practical use as a dietary supplement and functional food ingredient with the ability to reduce the health risks associated with an excessive intake of fast-digestible carbohydrates or an excess of potentially pathogenic bacteria.[6] Variations in the structure of fagomine led to analogues with a different biological activity, for example 3-*epi*-fagomine (Fig. 1) was found to be a more potent inhibitor of isomaltase and β-galactosidases than fagomine whereas it does not inhibit α-galactosidase.[7]

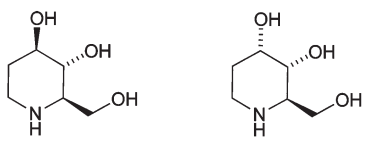

Fig. 1 Structure of D-fagomine and D-3-*epi*-fagomine.

In recent years fagomine[8] and other analogs with stereogenic[9] and substituent[10] diversity have been the subject of several syntheses with later structural modification less exploited. In this paper we report on the synthesis of new D-fagomine, D-3,4-*epi*-fagomine, and D-3-*epi*-fagomine analogs (**1**, **2** and **3**, Fig. 2) bearing a 1,2-dihydroxyethyl substituent on C_2.

Results and discussion

Ring-closing metathesis (RCM) followed by asymmetric dihydroxylation (ADH) has provided efficient synthetic protocols to gain access to a lot of polyhydroxylated piperidines and pyrrolidines.[11] This synthetic strategy can be applied to the synthesis of target compounds using dialkenyl amine **B** as a synthetic intermediate. Ring closing metathesis has been used for the construction of the piperidine ring with the desired substituent at C_2 and diastereoselective dihydroxylation was used to introduce the vicinal diol functionality in the required position. Diastereoselective *anti*-addition of vinyl organometallic reagents to imines

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† Electronic supplementary information (ESI) available: Characterisation spectra for compounds **4**–**14** and data of glycosidase inhibition assays for compounds **1**, **2** and **3**. See DOI: 10.1039/c2ob26732b

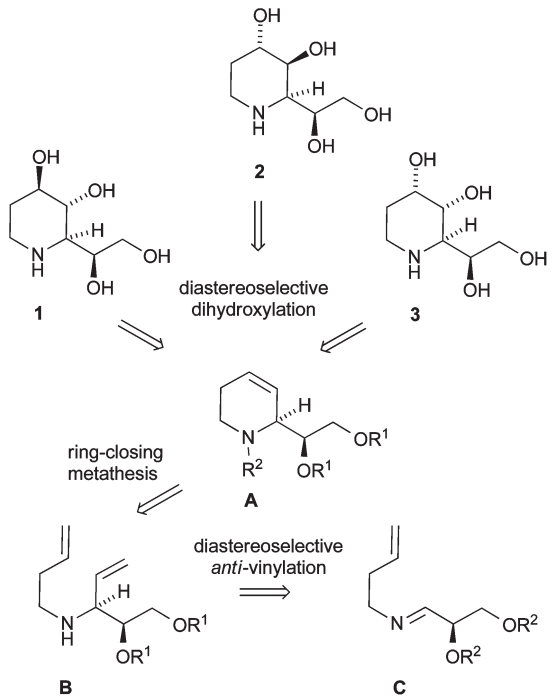
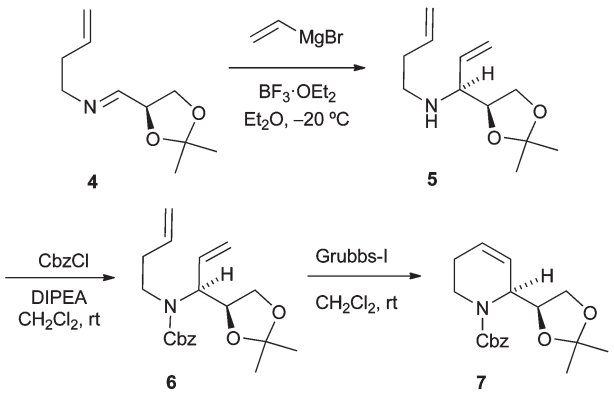


Fig. 2 Retrosynthetic approach to D-fagomine, D-*epi*-3,4-fagomine, and D-*epi*-3-fagomine analogs.



Scheme 1 Synthesis of tetrahydropyridine **7**.

derived from D-glyceraldehyde **C** gave access to the dialkenyl amine with the desired configuration (Fig. 2).

Starting *N*-homoallylimine **4** was obtained from D-glyceraldehyde acetonide, which is readily available on a gram scale from the inexpensive precursor D-mannitol according to previously described procedures.[12] Addition of vinylmagnesium bromide to the imine **4** pre-complexed with $BF_3{\cdot}OEt_2$ in diethyl ether at −20 °C proceeded with total diastereoselectivity[13] to afford dialkenyl amine **5** with *anti* configuration in 51% isolated yield (Scheme 1).

It has been previously described that addition of organometallic reagents to $BF_3{\cdot}OEt_2$ precomplexed imines derived from D-glyceraldehyde acetonide leads to the preferential formation of the corresponding *anti* diastereoisomer.[14] A Felkin–Anh-type model has been proposed to explain this selectivity.[14a] In addition it has been observed as a general trend that the vicinal

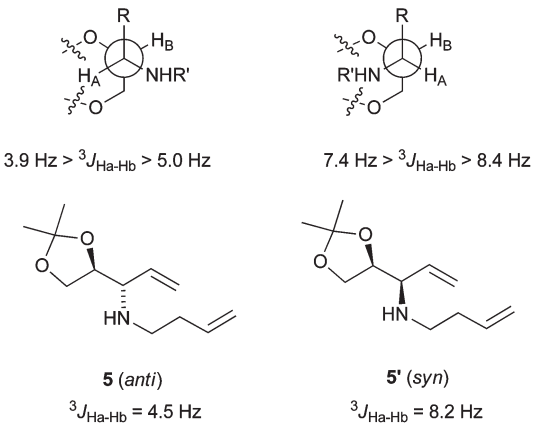


Fig. 3 $^3J_{Ha–Hb}$ values for *syn* and *anti* aminodiols obtained in the addition of organometallic reagents to imines derived from D-glyceraldehyde acetonide.

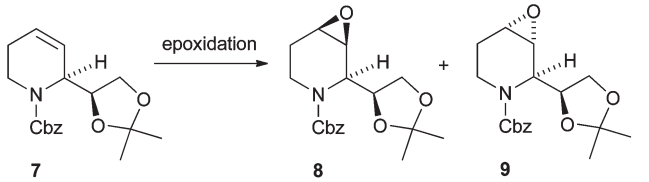
coupling constants between protons Ha and Hb for *anti* aminodiols obtained by the addition of organometallic reagents to imines derived from D-glyceraldehyde acetonide ranged from 3.9 to 5.0 Hz while for the corresponding *syn* aminodiols extended over the range 7.4 to 8.4 Hz (Fig. 3). So the stereochemistry of compound **5** has been assigned to be *anti* on the basis of the $J_{Ha–Hb}$ coupling constant value (4.5 Hz)[15] and mechanistic considerations.

Before RCM dialkenyl amine **5** was converted into the corresponding *N*-benzyloxycarbonyl derivative **6** to avoid problems derived from the presence of the free secondary amine.[16] The reaction of **5** with benzylchloroformate in diethyl ether at room temperature and in the presence of diisopropylethylamine led to the desired *N*-benzyloxycarbonyl derivative **6** which was isolated in 73% yield. Subsequent RCM in dichloromethane at room temperature using Grubbs first-generation catalyst afforded tetrahydropyridine **7** in 89% isolated yield (Scheme 1).

With diastereomerically pure **7** in hand we focused our attention on the *trans* dihydroxylation of the double bond by oxidation followed by attack with HO^-. To this end diastereoselective epoxidation with *m*CPBA was first tested. Epoxidation of **7** with *m*CPBA in dichloromethane at room temperature gave preferentially *syn* epoxide **8** (dr = 64/36). With the use of THF as a solvent *syn* diastereoselectivity was slightly increased (dr = 76/24) but the reaction rate diminished and it was necessary to increase reaction time and *m*CPBA concentration to obtain the epoxide with a good yield. The same reaction using more reactive peroxy-trifluoroacetic acid as an oxidizing agent in dichloromethane at 0 °C led to the preferential formation of *syn* epoxide **8** with the same yield and diastereoselectivity in only 0.5 h. *Syn* diastereoselectivity slightly increased with decreasing temperature. Working at −20 °C *syn* epoxide **8** with an 82/18 diastereomeric ratio was obtained in 82% yield after 0.75 h. An additional decrease of temperature did not improve diastereoselectivity and resulted in lower yield (Table 1).

Then we turned our attention to epoxidation of **7** with dioxiranes as oxidizing agents. With the use of dimethyldioxirane, generated *in situ* by oxidation of acetone with oxone®, epoxidation of compound **7** in acetonitrile–water at 0 °C was not

Table 1 Epoxidation of compound **7**



Entry	Epoxidation reagent	Solvent	T (°C)	T (h)	Yield[a] (%)	**8**/**9**[b]
1	*m*CPBA[c]	CH_2Cl_2	rt	24	80	64/36
2	*m*CPBA[c]	THF	rt	48	55	76/24
3	*m*CPBA[d]	THF	rt	48	90	76/24
4	CF_3COOOH	CH_2Cl_2	0	0.5	86	76/24
5	CF_3COOOH	CH_2Cl_2	−20	0.75	82	82/18
6	CF_3COOOH	CH_2Cl_2	−40	2	71	80/20
7	Oxone®/acetone	CH_3CN/H_2O	0	24	35	50/50
8	Oxone®/CF_3COCF_3	CH_3CN/H_2O	0	3	100	30/70
9	Oxone®/CF_3COCF_3	CH_3CN/H_2O	−20	24	60	30/70

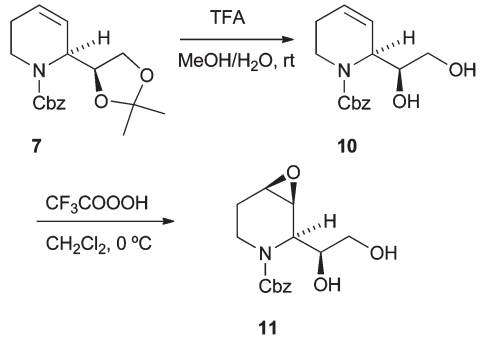
[a] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Determined by HPLC using a Waters Spherisorb column. [c] [*m*CPBA] = 0.03 mM. [d] [*m*CPBA] = 0.06 mM.

diastereoselective and an equimolecular mixture of *syn* and *anti* epoxides was obtained in 35% yield after 24 h. Nevertheless epoxidation of compound **7** under the same reaction conditions using (trifluoromethyl)methyldioxirane, generated *in situ* by oxidation of trifluoroacetone with oxone®, led to the preferential formation of *anti* epoxide **9**, and a 70/30 mixture of *anti* and *syn* epoxides was obtained in nearly quantitative yield after 3 h. The reaction at −20 °C gave essentially the same diastereomeric ratio but the reaction yield was seriously deteriorated (60% after 24 h).

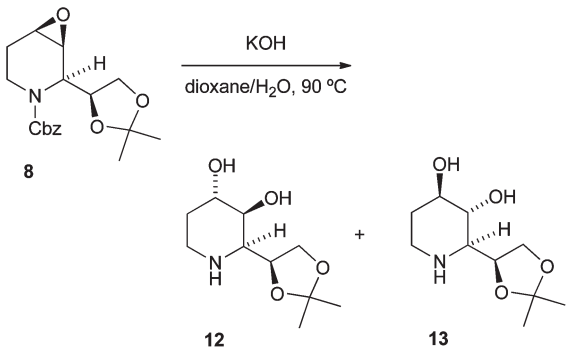
It is known that in addition to 1,3-allylic strain coordination of the peracid to a nearby group can direct the direction of epoxidation of double bonds by *m*CPBA.[17] In this case interaction of the peroxyacid with the dioxolane ring directed preferential *syn* epoxidation of compound **7**. On the other hand epoxidation of **7** with (trifluoromethyl)methyldioxirane in $CH_3CN–H_2O$ preferentially occurred from the less hindered face and compound **9**, with the epoxide ring opposite to the C_2 substituent, was obtained in excess. To potentiate the peroxyacid–substrate interaction and maximize the formation of *syn* epoxide the dioxolane ring was hydrolyzed. Epoxidation of the obtained diol **10** with peroxy-trifluoroacetic acid in dichloromethane at 0 °C proceeded exclusively *syn* to the 1,2-ethanediol substituent at C_2 to give *syn* epoxide **11** in 90% yield[18] after 0.5 h (Scheme 2). With the use of *m*CPBA in dichloromethane at room temperature diastereoselectivity was also total but an extended reaction time (24 h) was necessary to obtain epoxide **11** with a high yield (81%).[18]

Epoxide ring opening was next studied. Treatment of **8** with KOH in dioxane–water at 90 °C led to the non-regioselective opening of the epoxide with concomitant hydrolysis of the *N*-benzyloxycarbonyl group and an equimolecular mixture of *trans* diols **12** and **13** was obtained (Scheme 3).

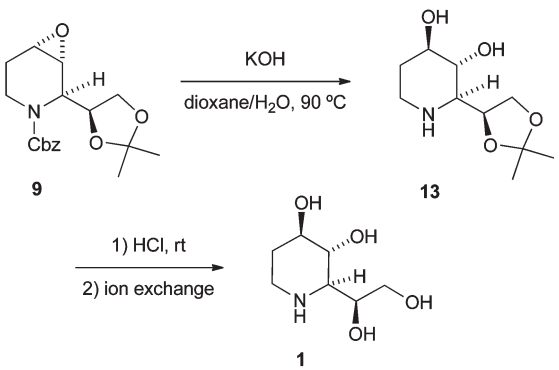
In contrast under the same reaction conditions regioselectivity of the oxirane ring opening in compound **9** was total and diol **13** was exclusively obtained. Subsequent hydrolysis of the



Scheme 2 Synthesis of *syn* epoxide **11**.



Scheme 3 Basic hydrolysis of *syn* epoxide **8**.



Scheme 4 Synthesis of D-fagomine analog **1**.

dioxolane moiety led to the desired D-fagomine analog **1** in 77% combined yield (Scheme 4).

The relative stereochemistry of compound **1** was determined from 1D gradient selective ROESY experiments and ^{1}H NMR coupling constant data. Selective irradiation at the resonance frequency of H_4 produced significant intensification of the H_2 signal and selective irradiation at the resonance frequency of H_{5a} produced significant intensification of the H_3 signal. This behavior was indicative of a 1,3-diaxial type arrangement between H_4 and H_2 and between H_{5a} and H_3. In addition the coupling constants $J_{H3–H4}$ (9.4 Hz) and $J_{H2–H3}$ (9.4 Hz) were in agreement with a *trans*-diaxial disposition of H_2, H_3 and H_4 (Fig. 4).

When epoxide **11** was treated with KOH in dioxane–water at 65 °C D-3,4-*epi*-fagomine analog **2** was obtained with a high

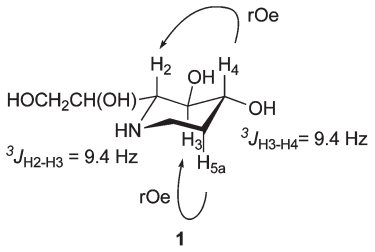
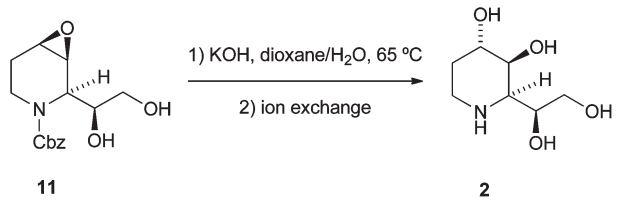
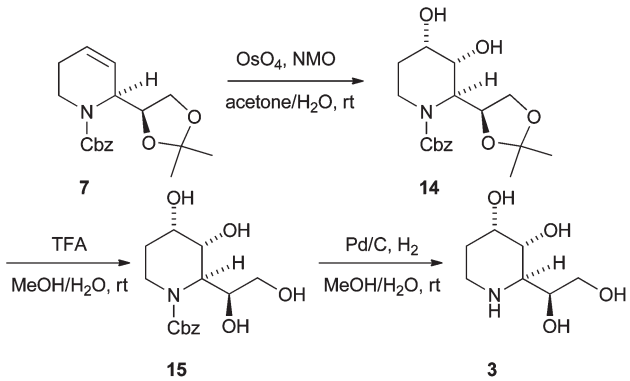


Fig. 4 Selected ^{1}H NMR data for relative stereochemistry determination of compound **1**.



Scheme 5 Synthesis of D-3,4-*epi*-fagomine analog **2**.



Scheme 6 Synthesis of D-3-*epi*-fagomine analog **3**.

regioselectivity (Scheme 5, **2**/**1** = 95/5) and isolated in 78% yield as its trifluoroacetate by column chromatography adding trifluoroacetic acid (1% v/v) to the eluent.

Using compound **7** as a substrate we then proceeded to synthesize D-3-*epi*-fagomine analog **3** (Scheme 6). Stereoselective *cis*-dihydroxylation of tetrahydropyridine **7** under Upjohn conditions[19] with a catalytic amount of OsO_4 (5 mol%) and an excess of NMO as a cooxidant in acetone–water at room temperature afforded diol **14** as a single diastereoisomer in 85% isolated yield. This remarkably high diastereoselectivity of the dihydroxylation would arise from the steric congestion at the top face of **7** which would cause the preferred approach of OsO_4 from the bottom face of the molecule. Hydrolysis of the dioxolane moiety with trifluoroacetic acid led to tetrol **15** from which compound **3** was obtained in 93% combined yield by N-debenzylation using Pd/C in methanol–water under a hydrogen atmosphere.

The relative stereochemistry of compound **3** was confirmed from ^{1}H NMR coupling constant data. The H_4 signal showed three small coupling constants (3.9, 3.1 and 3.0 Hz) indicating an equatorial disposition of the proton at C_4. As a consequence

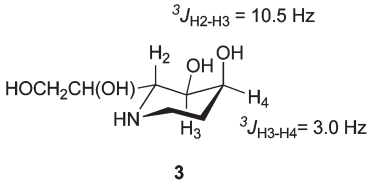


Fig. 5 Selected ^{1}H NMR coupling constant for relative stereochemistry determination of compound **3**.

the *cis* proton at C_3 should be in an axial disposition with a J_{ae} between H_3–H_4 of 3.0 Hz. The other coupling constant for this proton (10.5 Hz) fully agreed with a *trans*-diaxial disposition of H_2 and H_3 (Fig. 5).

The inhibitory activity of compounds **1**, **2** and **3** towards commercially available glycosidases[20] was assayed. The analysis of the preliminary enzyme assays by % inhibition showed that none of the compounds reached 50% inhibition of any glycosidase that was tested at a concentration of 143 μg mL^{-1} at the enzymes' optimal pH values. D-Fagomine analog **1** gave weak inhibition of *Bacillus stearothermophilus* α-glucosidase and D-3,4-*epi*-fagomine, and D-3-*epi*-fagomine analogs **2** and **3** weakly inhibited β-galactosidase. This lack of glycosidase inhibition could be advantageous for therapeutic use of such compounds as chaperones.[2b]

Summary

In summary, we have reported the synthesis of new D-fagomine, D-3,4-*epi*-fagomine, and D-3-*epi*-fagomine analogs (**1**, **2** and **3**, Fig. 2) bearing a 1,2-dihydroxyethyl substituent on C_2 from D-glyceraldehyde acetonide as a common precursor. Intermediate dialkenylamine **5** with the desired configuration was obtained by stereoselective *anti*-vinylation of $BF_3{\cdot}OEt_2$ precomplexed homoallylimine **4**. *N*-Carbobenzoxylation and subsequent ring-closing metathesis gave access to tetrahydropyridine **7** from which the D-fagomine analog was obtained using diastereoselective *anti*-epoxidation with (trifluoromethyl)methyldioxirane followed by regioselective ring-opening as key steps. In turn the D-3,4-*epi*-fagomine analog was obtained from tetrahydropyridine **10**, obtained by hydrolysis of **7**, using as key steps diastereoselective *syn*-epoxidation with peroxy-trifluoroacetic acid followed by regioselective ring-opening. The key step in the synthesis of the D-3-*epi*-fagomine analog was diastereoselective dihydroxylation of tetrahydropyridine **7** opposite to the C_2 substituent. The biological evaluation of these compounds as glycosidase inhibitors showed no significant inhibitory activity which could be advantageous for therapeutic use of such compounds as chaperones.

Experimental section

All reagents for reactions were of analytical grade and were used as obtained from commercial sources. Reactions were carried out using anhydrous solvents. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualized using UV light (254 nm), anisaldehyde, ninhydrin or ethanolic phosphomolybdic acid solution followed by heating. Column

chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh).

Melting points were determined in open capillaries using a Gallenkamp capillary melting point apparatus and are not corrected. FTIR spectra of oils were recorded as thin films on NaCl plates and FTIR spectra of solids were recorded as nujol dispersions on NaCl plates using a Thermo Nicolet Avatar 360 FT-IR spectrometer, ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a Jasco 1020 polarimeter at λ 589 nm and 25 °C in a cell with 10 cm path length, $[\alpha]_D$ values are given in 10^{-1} deg cm g^{-1} and concentrations are given in g per 100 mL. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AV-500 spectrometer, a Bruker AV-400 spectrometer or a Bruker AV-300 spectrometer operating at 500, 400 or 300 MHz for ^{1}H NMR and 125, 100 or 75 MHz for ^{13}C NMR at room temperature unless otherwise stated using a 5 mm probe. The chemical shifts (δ) are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard.[21] Coupling constants (J) are quoted in hertzs. The following abbreviations are used: s, singlet; d, doublet; m, multiplet; bs, broad singlet; bd, broad doublet, dd, doublet of doublets; ddd, doublet of doublets of doublets; bdd, broad doublet of doublets; dddd, doublet of doublet of doublets of doublets. Selective ge-1D ROESY experiments were performed with gradient pulses in the mixing time. Spectra were acquired at 300 K with optimized mixing times and 128 transients per spectrum using the Bruker standard selrogp pulse program. Special precautions such as degassing of the sample were not taken. High resolution mass spectra were recorded using a Bruker Daltonics MicroToF-Q instrument from methanolic solutions using the positive electrospray ionization mode (ESI^+). Microanalyses were performed using a Perkin-Elmer 2400 CHNS elemental analyser. Gas chromatography analyses were performed using an HP 5890 instrument equipped with a flame ionization detector using a Supelco SPB®-5 30 m × 0.25 mm × 0.25 μm capillary column. HPLC chromatography analyses were performed using a Waters 600 HPLC system equipped with a 2996 photodiode array detector using a Waters Spherisorb® 4.6 × 250 mm silica column (5 μm packing).

Glycosidase inhibition assays

Glycosidase assays were conducted as described by Watson *et al.*[22] using *p*-nitrophenyl substrates. All enzymes and *para*-nitrophenyl substrates were purchased from Sigma, with the exception of β-mannosidase which came from Megazyme. Assays were carried out in triplicate, and the values given are means of the three replicates per assay. Enzymes were assayed at 27 °C in 0.1 M citric acid–0.2 M disodium hydrogen phosphate buffers (McIlvaine) at the optimum pH for the enzyme. The incubation mixture consisted of a 10 μL enzyme solution, 10 μL of a 1 mg mL^{-1} aqueous solution of the sample and 50 μl of the appropriate 5 mM *para*-nitrophenyl substrate made up in buffer at the optimum pH for the enzyme. The reactions were stopped by addition of 70 μL 0.4 M glycine (pH 10.4) during the exponential phase of the reaction, which had been determined at the beginning using uninhibited assays in which water replaced the inhibitor. Final absorbances were read at 405 nm using a Versamax microplate reader (Molecular Devices).

(*S*,*E*)-*N*-((2,2-Dimethyl-1,3-dioxolan-4-yl)methylene)but-3-en-1-amine (4). Anhydrous $MgSO_4$ (6.26 g, 52.0 mmol) and 90% purity 3-buten-1-amine (2.17 g, 27.5 mmol) were added successively to a stirred solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (3.39 g, 26.0 mmol) in dry Et_2O (20 mL) at room temperature. After stirring at room temperature for 2 h the reaction mixture was filtered and evaporated. The resultant oil was dissolved in dry Et_2O and used in the next step without further purification. Purity of the imine was determined as 70% by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.41 (s, 3H), 2.27–2.37 (m, 2H), 3.36–3.53 (m, 2H), 3.86 (dd, J = 8.4, J = 6.4, 1H), 4.15 (dd, J = 8.4, J = 6.8, 1H), 4.52 (ddd, J = 6.8, J = 6.4, J = 5.0, 1H), 5.01 (bd, J = 10.2, 1H), 5.03 (dddd, J = 17.1, J = 1.5, J = 1.5, J = 1.5, 1H), 5.72 (dddd, J = 17.1, J = 10.2, J = 6.8, J = 6.8, 1H), 7.58 (ddd, J = 5.0, J = 1.1, J = 1.1, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3 (CH_3), 26.4 (CH_3), 34.6 (CH_2), 60.2 (CH_2), 67.4 (CH_2), 76.9 (CH), 110.1 (C), 116.3 (CH_2), 135.7 (CH), 163.4 (CH).

***N*-{(*S*)-1-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]allyl}-3-buten-1-amine (5).** $BF_3{\cdot}OEt_2$ (2.03 g, 1.8 mL, 14.3 mmol) was added dropwise to a solution of 70% purity crude imine **4** (3.74 g, 14.3 mmol) in dry Et_2O (20 mL) at −20 °C under argon. After stirring for 10 min at the same temperature a 1.0 M solution of vinylmagnesium bromide in THF (36 mL, 36.0 mmol) was added. The reaction mixture was stirred overnight at −20 °C and then quenched with water (6 mL). The mixture was vacuum filtered through a pad of Celite®, the organic layer dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford compound **5** as a single diastereoisomer as determined by GC. GC conditions: Supelco SPB®-5; T_1 = 100 °C, t_1 = 1 min, v_1 = 5 °C min^{-1}, T_2 = 150 °C, t_2 = 1 min, v_2 = 15 °C min^{-1}, T_3 = 200 °C; t_R (**5**) = 8.43.[23] Purification of the crude product by silica gel column chromatography (eluent: Et_2O–hexanes, 7 : 3) yielded compound **5** (1.53 g, 51%) as an oil. $[\alpha]_{25}^{D}$ = +14.8 (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 3325, 1641; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.41 (s, 3H), 2.20–2.28 (m, 2H), 2.30–2.50 (bs, 1H), 2.53 (ddd, J = 11.5, J = 6.8, J = 6.8, 1H), 2.74 (ddd, J = 11.5, J = 7.0, J = 7.0, 1H), 3.18 (dd, J = 8.2, J = 4.5, 1H), 3.88 (dd, J = 8.2, J = 6.9, 1H), 3.98 (dd, J = 8.2, J = 6.6, 1H), 4.14 (ddd, J = 6.9, J = 6.6, J = 4.5, 1H), 5.03 (dddd, J = 10.2, J = 2.1, J = 1.1, J = 1.1, 1H), 5.09 (dddd, J = 17.1, J = 2.1, J = 1.5, J = 1.5, 1H), 5.22 (ddd, J = 17.1, J = 1.8, J = 0.9, 1H), 5.25 (ddd, J = 10.4, J = 1.8, J = 0.6, 1H), 5.63 (ddd, J = 17.1, J = 10.4, J = 8.2, 1H), 5.77 (dddd, J = 17.1, J = 10.2, J = 6.8, J = 6.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0 (CH_3), 26.2 (CH_3), 34.0 (CH_2), 46.2 (CH_2), 62.9 (CH), 65.8 (CH_2), 77.9 (CH), 109.1 (C), 116.4 (CH_2), 118.6 (CH_2), 136.1 (CH), 136.2 (CH); HRMS (FAB^+) calcd for $C_{12}H_{22}NO_2$ (MH^+) 212.1645; found 212.1642.

***N*-Benzyloxycarbonyl-*N*-{(*S*)-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]allyl}-3-buten-1-amine (6).** DIPEA (2.58 g, 20.0 mmol) and 95% benzylchloroformate (1.79 g, 10.0 mmol) were added to a solution of compound **5** (1.41 g, 6.7 mmol) in CH_2Cl_2 (130 mL) at room temperature and stirring was continued for 2 h at the

same temperature. The reaction mixture was washed with water and the organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product by silica gel column chromatography (eluent Et_2O–hexanes, 1 : 4) yielded compound **6** (1.69 g, 73%) as an oil. $[\alpha]_{25}^{D} = -20.2$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 1701, 1641; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 1.31 (s, 3H), 1.39 (s, 3H), 2.21–2.40 (m, 2H), 3.15–3.39 (m, 2H), 3.71 (dd, *J* = 8.4, *J* = 6.3, 1H), 3.97 (dd, *J* = 8.4, *J* = 6.4, 1H), 4.23–4.44 (m, 2H), 5.00–5.08 (m, 2H), 5.11 (d, *J* = 13.1, 1H), 5.14 (d, *J* = 13.1, 1H), 5.22–5.28 (m, 2H), 5.71 (dddd, *J* = 17.1. *J* = 10.3. *J* = 6.9. *J* = 6.9, 1H), 5.99 (ddd, *J* = 17.1. *J* = 10.6. *J* = 6.4, 1H), 7.24–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 25.4 (CH_3), 26.6 (CH_3), 34.0 (CH_2), 45.9 (CH_2), 61.7 (CH), 67.2 (CH_2), 67.3 (CH_2), 76.8 (CH), 109.8 (C), 116.4 (CH_2), 118.6 (CH_2), 127.8 (CH), 128.0 (CH), 128.4 (CH), 133.5 (CH), 135.3 (CH), 136.7 (C), 156.0 (C); HRMS (FAB^+) calcd for $C_{20}H_{27}NO_4Na$ (MNa^+) 368.1832; found 368.1819.

(*S*)-1-Benzyloxycarbonyl-6-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,2,3,6-tetrahydropyridine (7). A solution of **6** (1.49 g, 4.3 mmol) in CH_2Cl_2 (80 mL) was slowly added to a solution of Grubbs first generation catalyst (350 mg, 0.43 mmol) in CH_2Cl_2 (60 mL) at room temperature. The resulting solution was vigorously stirred for 2 h at the same temperature and then evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (eluent: Et_2O–hexanes, 3 : 7) yielded compound **7** (1.21 g, 89%) as an oil. $[\alpha]_{25}^{D} = -220.9$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 1701, 1656; ^{1}H NMR (300 MHz, C_6D_6, 333 K) δ 1.28 (s, 3H), 1.40 (s, 3H), 1.50–1.62 (m, 1H), 1.89–2.11 (m, 1H), 2.80–2.95 (m, 1H), 3.75–3.88 (m, 1H), 3.88–4.04 (m, 1H), 4.04–4.20 (m, 2H), 4.52–4.77 (m, 1H), 5.09 (d, *J* = 12.4, 1H), 5.17 (d, *J* = 12.4, 1H), 5.63–5.76 (m, 1H), 5.83 (bd, *J* = 10.2, 1H), 7.02–7.31 (m, 5H); ^{13}C NMR (75 MHz, C_6D_6, 333 K) δ 24.9 (CH_3), 25.8 (CH_2), 27.0 (CH_2), 38.8 (CH_3), 54.9 (CH_2), 67.4 (CH), 67.5 (CH), 78.6 (CH_2), 109.7 (C), 125.9 (CH), 126.8 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 137.5 (C), 155.5 (C); HRMS (FAB^+) calcd for $C_{18}H_{23}NO_4Na$ (MNa^+) 340.1519; found 340.1536.

(1*S*,2*R*,6*R*)-3-Benzyloxycarbonyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-oxa-3-azabicyclo[4.1.0]heptane (8). Trifluoroacetic anhydride (609 mg, 2.90 mmol) was added dropwise to a stirred suspension of urea–hydrogen peroxide (893 mg, 9.50 mmol) and Na_2CO_3 (667 mg, 6.30 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The suspension was vigorously stirred for 10 min at 0 °C and cooled down to −20 °C prior to the addition of a solution of **7** (200 mg, 0.63 mmol) in CH_2Cl_2 (10 mL). After stirring for 45 min at −20 °C the reaction was quenched by careful addition of sat. aq. $NaHCO_3$ (50 mL) and 40% aqueous $NaHSO_3$ (20 mL) and vigorously stirred for a further 15 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford an 82/18 mixture of diastereomeric epoxides **8** and **9** as determined by HPLC. HPLC conditions: Waters Spherisorb® silica column; *n*-hexane–i-propanol, 97 : 3; flow rate 1 mL min^{-1}, UV detection at 215 nm; t_R (**8**) = 10.7 min; t_R (**9**) = 13.5 min. Purification of the diastereomeric mixture by silica gel column chromatography (eluent: Et_2O–hexanes, 1 : 1) gave diastereomerically pure compound **8** (124 mg, 59%) as an oil. Oil $[\alpha]_{25}^{D} = -93.6$ (*c* 1.01, $CHCl_3$); IR absorptions (pure) ν_{max} 1703; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 1.38 (s, 3H), 1.45 (s, 3H), 1.80–1.93 (m, 1H), 1.93–2.02 (m, 1H), 2.86 (bdd, *J* = 11.9, *J* = 11.9, 1H), 3.29–3.38 (m, 1H), 3.42 (dd, *J* = 4.2, *J* = 4.2, 1H), 3.72–3.90 (m, 1H), 3.90–4.04 (m, 2H), 4.30 (ddd, *J* = 9.2, *J* = 5.7, *J* = 5.7, 1H), 4.38–4.61 (m, 1H), 5.11 (d, *J* = 12.4, 1H), 5.15 (d, *J* = 12.4, 1H), 7.23–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 25.0 (CH_2), 25.6 (CH_3), 26.9 (CH_3), 35.1 (CH_2), 51.4 (CH), 51.9 (CH), 52.3 (CH), 67.0 (CH_2), 67.6 (CH_2), 74.2 (CH), 109.5 (C), 127.9 (CH), 128.1 (CH), 128.5 (CH), 136.5 (C), 155.4 (C); HRMS (FAB^+) calcd for $C_{18}H_{23}NO_5Na$ (MNa^+) 356.1468; found 356.1465.

(1*R*,2*R*,6*S*)-3-Benzyloxycarbonyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-oxa-3-azabicyclo[4.1.0]heptane (9). A 0.1 M solution of aqueous Na_2EDTA (0.25 mL 0.025 mmol) and 1,1,1-trifluoroacetone (1.5 g, 13.4 mmol) were added successively to a solution of **7** (400 mg, 1.26 mmol) in CH_3CN (15 mL) at 0 °C. Then a mixture of $NaHCO_3$ (730 mg, 8.80 mmol) and oxone® (3.5 g, 5.7 mmol) as a solid was added slowly over a period of 1 h at 0 °C. After being stirred for 3 h at 0 °C, the solid material was removed by filtration and the filtrate was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a 30/70 mixture of diastereomeric epoxides **8** and **9** as determined by HPLC. HPLC conditions: Waters Spherisorb® silica column; mobile phase = *n*-hexane–i-propanol, 97 : 3; flow rate 1 mL min^{-1}, UV detection at 215 nm; t_R (**8**) = 10.7 min; t_R (**9**) = 13.5 min. Purification of the diastereomeric mixture by silica gel column chromatography (eluent: Et_2O–hexanes, 1 : 1) gave diastereomerically pure compound **9** (261 mg, 63%) as an oil. $[\alpha]_{25}^{D} = -79.5$ (*c* 1.03, $CHCl_3$); IR absorptions (pure) ν_{max} 1701; ^{1}H NMR (300 MHz, $CDCl_3$, 333 K) δ 1.36 (s, 3H), 1.46 (s, 3H), 1.82–1.93 (m, 1H), 1.97–2.12 (m, 1H), 2.86–3.06 (m, 1H), 3.25–3.35 (m, 2H), 3.75–3.86 (m, 1H), 3.91 (dd, *J* = 8.6, *J* = 6.2, 1H), 4.07 (dd, *J* = 8.6, *J* = 6.6, 1H), 4.26–4.38 (ddd, *J* = 7.0, *J* = 6.6, *J* = 6.2, 1H), 4.52 (d, *J* = 7.0, 1H), 5.12 (d, *J* = 12.5, 1H), 5.17 (d, *J* = 12.5, 1H), 7.23–7.44 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6, 348 K) δ 22.1 (CH_2), 25.1 (CH_3), 26.3 (CH_3), 36.4 (CH_2), 49.7 (CH), 49.9 (CH), 54.1 (CH), 67.2 (CH_2), 67.5 (CH_2), 75.6 (CH), 109.9 (C), 128.3 (CH), 137.2 (C), 156.0 (C); HRMS (FAB^+) calcd for $C_{18}H_{23}NO_5Na$ (MNa^+) 356.147468; found 356.1485.

(*S*)-1-[(*S*)-1-Benzyloxycarbonyl-1,2,5,6-tetrahydropyridin-2-yl]-1,2-ethanediol (10). Trifluoroacetic acid (457 mg, 4.00 mmol) was added to a solution of **7** (300 mg, 0.94 mmol) in MeOH–H_2O 4 : 1 (8 mL) at room temperature. After being stirred overnight at room temperature the solvent was removed *in vacuo*. Purification of the obtained residue purified by silica gel column chromatography (eluent: Et_2O–EtOAc, 6 : 4) gave compound **10** (245 mg, 94%) as an oil. $[\alpha]_{25}^{D} = -137.9$ (*c* 0.87, $CHCl_3$); IR absorptions (pure) ν_{max} 3396, 1676, 1652; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 1.99 (ddd, *J* = 17.5, *J* = 3.4, *J* = 3.4, 1H), 2.17–2.30 (m, 1H), 2.73 (bs, 2H), 2.94 (ddd, *J* = 13.3, *J* = 12.0, *J* = 3.4, 1H), 3.56–3.67 (m, 3H), 4.17 (dd, *J* = 13.2, *J* = 5.4, 1H), 4.41 (bd, *J* = 7.2, 1H), 5.16 (d, *J* = 12.4, 1H), 5.20

(d, J = 12.4, 1H), 5.92–6.04 (m, 2H), 7.29–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 24.7 (CH_2), 38.8 (CH_2), 53.7 (CH), 63.0 (CH_2), 67.7 (CH_2), 73.9 (CH), 125.9 (CH), 126.4 (CH), 127.9 (CH), 128.3 (CH), 128.7 (CH), 136.4 (C); HRMS (FAB^+) calcd for $C_{15}H_{19}NO_4Na$ (MNa^+) 300.1206; found 300.1223.

(*S*)-1-[(1*S*,2*R*,6*R*)-3-Benzyloxycarbonyl-7-oxa-3-azabicyclo[4.1.0]-heptan-2-yl]-1,2-ethanediol (11). Trifluoroacetic anhydride (714 mg, 3.40 mmol) was added dropwise to a stirred suspension of urea–hydrogen peroxide (1.35 g, 11.00 mmol) and Na_2CO_3 (614 mg, 7.40 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The suspension was vigorously stirred for 10 min at 0 °C and a solution of **10** (200 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) was added. After stirring for 30 min at 0 °C the reaction was quenched by careful addition of sat. aq. $NaHCO_3$ (50 mL) and 40% aqueous $NaHSO_3$ (20 mL) and vigorously stirred for a further 15 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford crude epoxide **11** as a single diastereoisomer as determined by HPLC. HPLC conditions: Waters Spherisorb® silica column; mobile phase = *n*-hexane–EtOH, 9 : 1; flow rate 1 mL min^{-1}, UV detection at 215 nm; t_R (**11**) = 12.6 min. Purification of the crude product by silica gel column chromatography (eluent Et_2O–EtOAc, 3 : 7) yielded compound **11** (169 mg, 80%) as an oil. $[\alpha]_{25}^{D}$ = −86.2 (c 0.40, $CHCl_3$); IR absorptions (pure) ν_{max} 3343, 1692; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 1.91 (ddd, J = 14.6, J = 12.8, J = 4.8, 1H), 1.99 (dddd, J = 14.6, J = 3.7, J = 2.0, J = 2.0, 1H), 2.63 (bd, J = 7.5, 1H), 2.87 (ddd, J = 13.8, J = 12.3, J = 3.6, 1H), 3.30 (bs, 1H), 3.36–3.44 (m, 1H), 3.47–3.70 (m, 3H), 3.74–3.99 (m, 2H), 4.37 (ddd, J = 9.3, J = 4.5, J = 1.2, 1H), 5.08–5.18 (m, 2H), 7.27–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1 (CH_2), 35.2 (CH_2), 50.9 (CH), 51.7 (CH), 52.1 (CH), 62.3 (CH_2), 68.0 (CH_2), 70.0 (CH), 127.9 (CH), 128.4 (CH), 128.6 (CH), 136.0 (C), 156.3 (C); HRMS (FAB^+) calcd for $C_{15}H_{19}NO_5Na$ (MNa^+) 316.1155; found 316.1176.

(2*S*,3*S*,4*S*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]piperidine-3,4-diol (12) and (2*S*,3*S*,4*S*)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]piperidine-3,4-diol (13). A solution of **8** (110 mg, 0.33 mmol) in dioxane (6 mL) and 0.3 M aqueous KOH (35 mL) was heated at 90 °C for 72 h. The solvent was removed *in vacuo*, the residue dissolved in CH_2Cl_2 (2 mL) and the solvent was removed *in vacuo* again to give an equimolecular mixture of diastereomeric **12** and **13**. Purification of the diastereomeric mixture by silica gel column chromatography (eluent: EtOAc–MeOH, 1 : 1) yielded 10 mg (14%) of diastereomerically pure compound **12** as a white solid and 32 mg (44%) of diastereomerically pure compound **13** as a white solid. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.42 (s, 3H), 1.53 (dddd, J = 14.2, J = 3.3 J = 3.3 J = 3.3, 1H), 1.59 (bs, 3H), 1.94–2.01 (m, 1H), 2.83 (ddd, J = 12.5 J = 5.0, J = 3.3, 1H), 2.96 (ddd, J = 12.5, J = 12.5, J = 3.3, 1H), 3.13 (dd, J = 6.0 J = 2.0, 1H), 3.68 (dd, J = 3.8, J = 2.0, 1H), 3.88 (dd, J = 8.2, J = 7.2, 1H), 4.00 (ddd, J = 3.8, J = 3.3, J = 3.3, 1H), 4.10 (dd, J = 8.2, J = 6.2, 1H), 4.17 (ddd, J = 7.2, J = 6.2, J = 6.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (CH_3), 26.8 (CH_3), 29.4 (CH_2), 40.8 (CH_2), 56.1 (CH), 67.1 (CH_2), 68.6 (CH), 69.5 (CH), 77.0 (CH), 100.1 (C); HRMS (FAB^+) calcd for $C_{10}H_{20}NO_4$ (MH^+) 218.1387; found 218.1387. Compound **13**: M.p. = 120–122 °C; $[\alpha]_{25}^{D}$ = +17.3 (c 0.50, $CHCl_3$); IR absorptions (pure) ν_{max} 3490, 1206; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.45 (s, 3H), 1.46 (dddd, J = 12.6, J = 12.6, J = 12.6, J = 4.5, 1H), 1.96 (dddd, J = 12.6, J = 4.8, J = 2.5, J = 2.5, 1H), 2.42 (bs, 3H), 2.56 (dd, J = 9.0 J = 6.4, 1H), 2.63 (ddd, J = 12.6, J = 12.6, J = 2.5, 1H), 3.03 (ddd, J = 12.6, J = 4.5, J = 2.5, 1H), 3.23 (dd, J = 9.0, J = 9.0, 1H), 3.44–3.57 (m, 1H), 3.98 (dd, J = 8.2, J = 6.4, 1H), 4.10 (dd, J = 8.2, J = 6.4, 1H), 4.18 (ddd, J = 6.4, J = 6.4, J = 6.4, 1H); ^{13}C NMR (100 MHz, D_2O) δ 23.8 (CH_3), 25.1 (CH_3), 31.9 (CH_2), 42.8 (CH_2), 59.8 (CH), 63.7 (CH_2), 73.4 (CH), 73.9 (CH), 75.2 (CH), 109.4 (C); HRMS (FAB^+) calcd for $C_{10}H_{19}NO_4Na$ (MNa^+) 240.1206; found 240.1218.

(2*R*,3*R*,4*R*)-2-[(*S*)-1,2-Dihydroxyethyl]piperidine-3,4-diol (1). A solution of **9** (200 mg, 0.60 mmol) in dioxane (10 mL) and 0.3 M aqueous KOH (65 mL) was heated at 90 °C for 48 h. The solvent was removed *in vacuo* and the residue was dissolved in water (5 mL) and neutralized by addition of 2 M HCl. After the addition of an additional amount of 2 M HCl (3 mL) the reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*, the residue dissolved in water (15 mL) and the aqueous solution washed with CH_2Cl_2 (3 × 15 mL). Removal of the solvent left the hydrochloride salt of compound **1** which was chromatographed using Dowex 50WX8-200 resin to give the free amine **1** (82 mg, 77% yield) as an oil. $[\alpha]_{25}^{D}$ = +16.9 (c 0.68, H_2O); IR absorptions (pure) ν_{max} 3384; ^{1}H NMR (400 MHz, D_2O) δ 1.46 (dddd, J = 12.9, J = 12.9, J = 12.9, J = 4.5, 1H), 2.00 (dddd, J = 12.9, J = 4.9, J = 2.5, J = 2.5, 1H), 2.64 (ddd, J = 12.9, J = 12.9, J = 2.5, 1H), 2.73 (dd, J = 10.0 J = 3.5, 1H), 3.05 (ddd, J = 12.9, J = 4.5, J = 2.5, 1H), 3.32 (dd, J = 10.0, J = 10.0, 1H), 3.53 (ddd, J = 12.9, J = 10.0, J = 4.5, 1H), 3.69 (dd, J = 11.9, J = 7.2, 1H), 3.75 (dd, J = 11.9, J = 3.2, 1H), 4.01 (ddd, J = 7.2, J = 3.5, J = 3.2, 1H); ^{13}C NMR (100 MHz, D_2O) δ 32.0 (CH_2), 43.0 (CH_2), 62.1 (CH), 62.4 (CH_2), 72.2 (CH), 73.1 (CH), 73.3 (CH); HRMS (FAB^+) calcd for $C_7H_{15}NO_4Na$ (MNa^+) 200.0893; found 200.0889.

(2*R*,3*S*,4*R*)-2-[(*S*)-1,2-Dihydroxyethyl]piperidine-3,4-diol trifluoroacetate salt (2·TFA). A solution of **11** (130 mg, 0.44 mmol) in dioxane (10 mL) and 0.3 M aqueous KOH (40 mL) was heated at 65 °C for 20 h. The solvent was removed *in vacuo* and the residue was dissolved in water (5 mL). The aqueous solution was washed with CH_2Cl_2 (3 × 10 mL) and chromatographed using Dowex 50WX8-200 resin to give a 95/5 mixture of diastereomeric compounds **2** and **1**. Purification of the diastereomeric mixture by silica gel column chromatography (eluent: EtOAc–MeOH, 1 : 1 with 1% v/v TFA) yielded diastereomerically pure trifluoroacetate **2·TFA** (100 mg, 78%) as an oil. $[\alpha]_{25}^{D}$ = −9.4 (c 0.95, CH_3OH); IR absorptions (pure) ν_{max} 3365, 1675; ^{1}H NMR (300 MHz, D_2O) δ 1.82 (dddd, J = 14.6, J = 3.2, J = 3.2, J = 3.2, 1H), 2.14–2.33 (m, 1H), 3.24–3.36 (m, 2H), 3.58 (dd, J = 6.1, J = 1.1, 1H), 3.75–3.80 (m, 2H), 3.96–4.05 (m, 2H), 4.12–4.16 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 23.1 (CH_2), 39.4 (CH_2), 55.0 (CH), 62.2 (CH_2), 64.7 (CH), 65.4 (CH), 68.9 (CH); HRMS (FAB^+) calcd for $C_7H_{16}NO_4$ ($MH^+ - CF_3CO_2H$) 178.1074; found 178.1074.

(2*S*,3*R*,4*S*)-1-Benzyloxycarbonyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]piperidine-3,4-diol (14). NMO (222 mg, 1.90 mmol) and a solution of 2.5 wt% OsO_4–H_2O (0.36 mL, 0.03 mmol) were added successively to a solution of **7** (300 mg, 0.94 mmol) in acetone–H_2O 3 : 2 (10 mL) and the reaction mixture was stirred for 22 h at room temperature. Then an excess of Na_2SO_3 was added and stirring was continued for an additional 30 min. The solid material was removed by filtration and acetone was evaporated *in vacuo*. The obtained residue was diluted by the addition of water (50 mL) and the aqueous solution washed with Et_2O (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford crude **14** as a single diastereoisomer as determined by ^{1}H NMR. Purification of the residue by silica gel column chromatography (eluent: EtOAc–hexanes, 8 : 2) yielded diastereomerically pure compound **14** (280 mg, 85% yield) as a white solid. M.p. = 113–116 °C; $[\alpha]_{25}^{D}$ = −29.5 (*c* 1.10, $CHCl_3$); IR absorptions (pure) ν_{max} 3343, 1692; ^{1}H NMR (400 MHz, $CDCl_3$, 333K) δ 1.31 (s, 3H), 1.41 (s, 3H), 1.59–1.70 (m, 1H), 1.82 (dddd, *J* = 12.6, *J* = 12.5, *J* = 12.5, *J* = 4.8, 1H), 2.38 (bs, 2H), 2.91 (bdd, *J* = 13.2, *J* = 12.6, 1H), 3.76 (dd, *J* = 8.0, *J* = 6.8, 1H), 3.96 (dd, *J* = 8.0, *J* = 6.5, 1H), 3.96–4.05 (m, 1H), 4.05–4.17 (m, 1H), 4.13–4.26 (m, 2H), 4.38 (bd, *J* = 8.1, 1H), 5.12 (d, *J* = 13.2, 1H), 5.15 (d, *J* = 13.2, 1H), 7.22–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 25.4 (CH_3), 26.7 (CH_3), 27.9 (CH_2), 39.7 (CH_2), 60.0 (CH), 67.1 (CH), 67.6 (CH_2), 67.8 (CH_2), 67.9 (CH), 74.0 (CH), 110.2 (C), 127.8 (CH), 128.0 (CH), 128.5 (CH), 136.6 (C), 156.3 (C); HRMS (FAB^+) calcd for $C_{18}H_{25}NO_6Na$ (MNa^+) 374.1574; found 374.1576. Anal calcd for $C_{18}H_{25}NO_6$ C 61.52%, H 7.17%, N 3.99%; found C 61.40%, H 7.32%, N 3.39%.

(2*R*,3*R*,4*S*)-1-Benzyloxycarbonyl-2-[(*S*)-1,2-dihydroxyethyl]-piperidine-3,4-diol (15). Trifluoroacetic acid (292 mg, 1.60 mmol) was added to a solution of **14** (250 mg, 0.71 mmol) in MeOH–H_2O 3 : 1 (10 mL) at room temperature. After being stirred overnight at room temperature the solvent was removed *in vacuo*. The obtained residue was dissolved in water (25 mL) and the aqueous solution washed with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 214 mg of crude **15** which was used in the next step without further purification. ^{1}H NMR (300 MHz, D_2O, 333 K) δ 1.97–2.18 (m, 1H), 2.19 (dddd, *J* = 12.6, *J* = 12.2, *J* = 12.2, *J* = 5.0, 1H), 3.32 (ddd, *J* = 14.1, *J* = 12.6, *J* = 3.4, 1H), 3.80 (dd, *J* = 11.9, *J* = 6.9, 1H), 3.94 (dd, *J* = 11.9, *J* = 3.0, 1H), 4.31 (ddd, *J* = 10.0, *J* = 6.9, *J* = 3.0, 1H), 4.37–4.58 (m, 2H), 4.58–4.71 (m, 2H), 5.40–5.68 (m, 2H), 7.73–7.91 (m, 5H); ^{13}C NMR (75 MHz, D_2O, 333 K) δ 26.8 (CH_2), 39.6 (CH_2), 59.9 (CH), 63.8 (CH_2), 66.6 (CH), 67.5 (CH), 68.5 (CH_2), 69.1 (CH), 128.2 (CH), 128.8 (CH), 129.2 (CH), 136.8 (C), 157.8 (C).

(2*R*,3*R*,4*S*)-2-[(*S*)-1,2-Dihydroxyethyl]piperidine-3,4-diol (3). A solution of crude **15** (214 mg) obtained as described above in MeOH–H_2O 3 : 1 (20 mL) was hydrogenated with molecular hydrogen for 7 h at atmospheric pressure and room temperature and in the presence of 10% Pd/C (30 mg) as a catalyst. The catalyst was removed by filtration through a Celite® path and the solvent evaporated *in vacuo* to afford **3** (117 mg, 93% combined yield) as an oil. $[\alpha]_{25}^{D}$ = +24.6 (*c* 0.92, H_2O); IR absorptions (pure) ν_{max} 3385; ^{1}H NMR (400 MHz, D_2O) δ 1.67–1.80 (m, 1H), 1.85 (dddd, *J* = 14.7, *J* = 3.9, *J* = 3.1, *J* = 3.0, 1H), 2.80–2.92 (m, 2H), 3.08 (dd, *J* = 10.1, *J* = 4.1, 1H), 3.67 (dd, *J* = 10.1, *J* = 3.0, 1H), 3.70 (dd, *J* = 12.0, *J* = 6.8, 1H), 3.75 (dd, *J* = 12.0, *J* = 3.3, 1H), 3.96 (ddd, *J* = 6.8, *J* = 4.1, *J* = 3.3, 1H), 4.07 (ddd, *J* = 3.9, *J* = 3.1, *J* = 3.0, 1H); ^{13}C NMR (100 MHz, D_2O) δ 29.6 (CH_2), 38.8 (CH_2), 56.9 (CH), 62.5 (CH_2), 67.4 (CH), 68.9 (CH), 71.36 (CH); HRMS (FAB^+) calcd for $C_7H_{16}NO_4$ (MH^+) 178.1074; found 178.1076.

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