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Intramolecular epoxide ring opening cyclisation reactions involving guanidines

Zainab Al Shuhaib, Marcel Arndt, Mark Dennis, Daniel M. Evans, Iestyn Jones, Patrick J. Vera Leitmann, Murphy,* Dion Roberts, Richard Rowles, Yones K. Sadaghiani, Andrew J. Thornhill
School of Chemistry, University of Wales, Bangor, Gwynedd, LL57 2UW

Robert J. Nash, Jackie Hollinshead, Barbara Bartholomew
PhytoQuest Limited, Plas Gogerddan, Aberystwyth, Ceredigion, SY23 3EB

Graham J. Tizzard and Simon J. Coles
UK National Crystallography Service, Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ

Abstract
The cyclisation of N-allyl- and N-homoallylguanidines using DMDO leading to the formation of novel 5- and 6-membered guanidine heterocycles is reported. Several of the products formed displayed weak inhibition of glycosidase enzymes.

Keywords: guanidines, epoxides, iodocyclisations, galactosidase inhibition, DMDO, epoxidation

Introduction

As part of a project directed towards the synthesis of marine natural products, we have previously reported the intramolecular cyclisation of guanidine epoxides[1] and the cyclisation of allyl and homoallyl substituted guanidines using DMDO,[1,2] I_2/K_2CO_3[1-3] and under palladium catalysed conditions.[4] We take this opportunity to report our findings on the oxidative cyclisation reactions in full.

**Epoxide ring opening using guanidines**

Very few examples of epoxide ring opening processes utilising guanidines[5] have been reported and our preliminary investigations focused on the addition of guanidine to the simple epoxide **1**. We treated **1** with guanidine in *t*-BuOH at room temperature for 24 h to effect *N*-alkylation of guanidine, which we presumed to be faster than the epoxide ring opening process. At this point, potassium *t*-butoxide was added to regenerate the free guanidine from its salt, following which the reaction was heated at 60°C for a further 48 h to affect cyclisation to give the 5-membered guanidine **2** (Scheme 1). In our previous work,[1] we had reported efforts to purify **2** by column chromatography and had succeeded in obtaining product of relatively high purity (> 95 %) though it was apparent that it was contaminated with what appeared to be polymeric material. We also tried to purify **2** by derivatisation as its *t*-butyldimethylsilyl ether **3**. However this proved difficult as the compound was prone to hydrolysis on chromatography which was thought to be promoted by the anchimeric assistance or the guanidinium group.[6] We were however able to purify **2** by HPLC and on examination of higher field NMR data, it was apparent that significant quantities of a contaminant were present. Indeed re-examination of the crude reaction product indicated a ca 9:1 ratio of **2** and what was though to be the isomeric **4**. Compound **4** gave signals at δ 3.33 (2H, dd, *J* 3.1, 12.3, 2 x CH), 3.45, (2H, dd, *J* 2.7, 12.3 Hz, 2 x CH) and 4.38 (1H, tt, *J* 2.7, 3.1 Hz, CH) ppm and this 6-*endo-tet* isomer **4** could possibly be formed by the attack of the guanidine on the CH_2 of the epoxide after alkylation or

more likely by initial epoxide opening by guanidine followed by the 6-e*xo-tet* displacement of bromine.
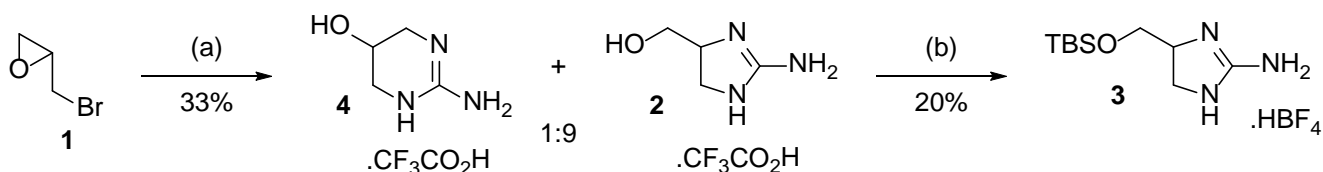
Scheme 1: (a) (i) Guanidine hydrochloride, *t*BuOK, *t*BuOH, then epoxide **1** 16 h, rt. (ii) *t*BuOK, 60°C, 24 h. (iii) CF₃CO₂H, MeOH. (c) (i) 3 equiv. TBSCl, Imid., DMF, 16-24 h. (ii) NaBF₄ (sat., aq.).

We wished to prepare **4** independently and thus reacted nitroguanidine **5** with 1,3-diaminopropan-2-ol **6** at 70°C in water to give 5-hydroxy-2-nitrimino-1,3-diazacyclohexane **7** in 27 % yield,[7] which on hydrogenation in aqueous acetic acid gave **4** as its acetate salt in 75% yield (Scheme 2). Spectroscopic data for the synthetic sample of **4** corresponded exactly to the impurity found in the previous reactions.
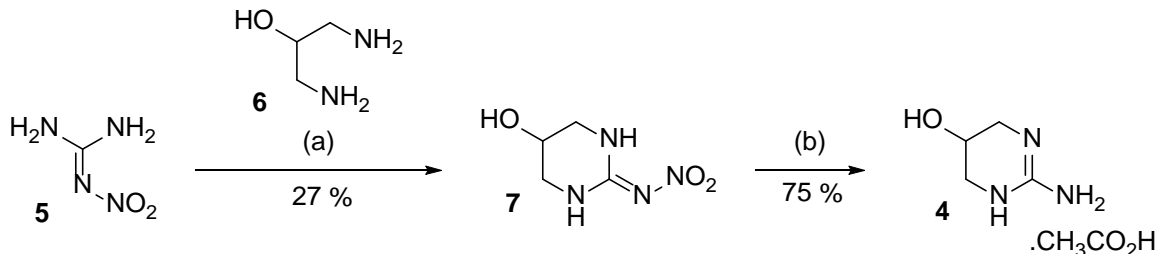
Scheme 2: (a) Water, 70 °C, 2 h (b) (a) H₂, 5 % Pd/C, 15% aqueous acetic acid 72 h.

Because of the problems with this impurity and problems associated with purification of the guanidine salts in these reaction we turned our attention to the reaction of the protected guanidines **8a**[3] and **8b**[3] and their reaction with the epoxidising agent DMDO.[8] We had previously shown[1] that the *N*-allyl-*bis*-Boc-guanidine **8a** reacts with DMDO in acetone at -20 °C to give an intermediate epoxide **9a** as evidenced by signals at δ_H 2.62 (1H, dd, *J* 2.4, 4.2 Hz, CH), 2.80 (1H, dd, *J* 4.2, 4.4 Hz, CH) and 3.14-3.22 (1H, m, CH) ppm. On continued stirring this intermediate was consumed to give, on careful work up and chromatography, a 62% yield of the cyclic product **10a** the structure of which was confirmed by X-ray analysis.[1] On attempted repeat of this reaction it was observed that a second isomeric product was always formed in the reaction and, on isolation of this, X-ray crystallography[2] confirmed the structure of the product as the rearranged product **11a** isolated in 63% yield. A similar migration of a Boc-group was reported in an *N*-Boc-protected 5-membered amide so this result is not suprising.[9] More conveniently, a complete conversion of **10a** into **11a** could be effected if a solution of the crude reaction mixture in dichloromethane was stirred with silica gel overnight or by stirring in methanol containing a small amount (ca. 5 %) of water. A similar result was observed with the Z-protected guanidine **8b** which was again treated with an excess of DMDO in acetone at -20 °C and the reaction monitored by proton NMR. Epoxidation was found to occur rapidly as evidenced by signals at δ_H 2.61 (1H, dd, *J* 2.8, 4.5 Hz, CH), 2.80 (1H, dd, *J* 4.4, 4.5 Hz, CH) and 3.16-3.22 (1H, m, CH) ppm for epoxide **9b**, but on continued stirring signals at δ_H 3.45 (1H, t, *J* 5.8 Hz, CH), 3.51 (1H,

dd, *J* 5.1, 5.7 Hz, CH), 3.87 (1H, dd, *J* 3.0, 5.5 Hz, CH), 3.92 (1H, dd, *J* 2.8, 5.8 Hz, CH), and 4.03-4.11 (1H, m, CH) ppm appeared which are evident of the structure **10b**. However, after purification on silica gel, a new product was formed in 64% yield, which had a considerably simpler spectrum with signals at δ_H 3.20 (1H, dd, *J* 10.2, 4.0 Hz, CH), 3.45-3.51 (1H, m, CH) and 3.87-3.95 (3H, m, CH, CH$_2$) ppm and the two guanidine protons at δ_H (7.50-9.60 (2H, br s, 2 x NH) which assigned the structure as **11b**. Again it was possible to effect this rearrangement by stirring the crude reaction product with silica gel in dichloromethane or by stirring in methanol containing a small amount (ca. 5 %) of water. Finally, deprotection of **1a** was accomplished by treatment with excess trifluoroacetic acid in dichloromethane for 4 h to give guanidine **2** in 98 % yield (Scheme 3).
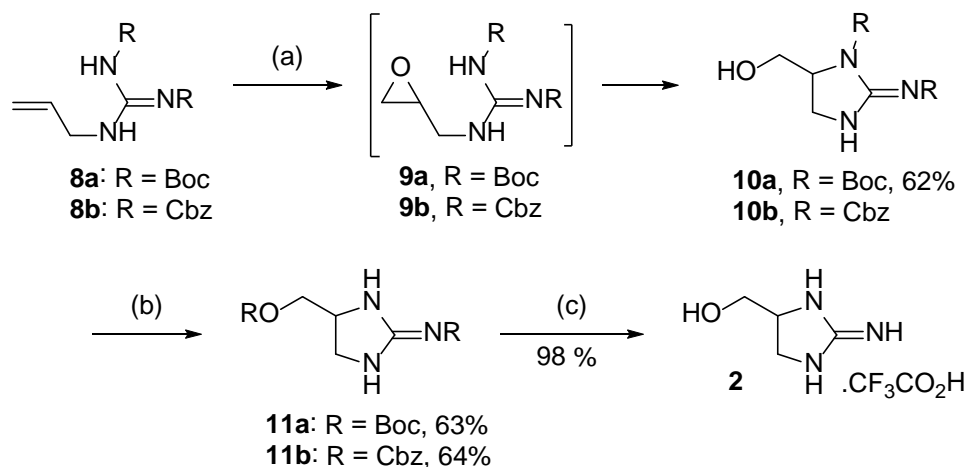
Scheme 3: (a) DMDO, acetone, -20 ˚C-rt, 3 days. (b) Silica gel, CH$_2$Cl$_2$ or MeOH/H$_2$O (95:5), 16-24 h. (c) CF$_3$CO$_2$H, CH$_2$Cl$_2$, 0 ˚C-rt, 4 h.

We were interested in the mechanism of the Boc- and Cbz-group migration and in order to investigate this a 1:1 mixture of **8a** and **8b** was treated with DMDO at -20 °C and stirred at rt for 5 days at which point the formation of a mixture of **10a** and **10b** was formed as indicated by ^{1}H NMR. This mixture was then dissolved in a mixture of methanol and water and stirred overnight at room temperature. Analysis of the product from this reaction by mass spectrometry confirmed the presence of three different ions with m/z peaks at 316.1867 and 350.1710 Daltons corresponding to the [M+H]$^+$ ions for **11a** and **11b** as well as a mass at 384.1552 which correspond closely to the [M+H]$^+$ ion for **11c/11d**. This observation suggest that the migration of the protecting groups is not exclusively intramolecular and some evidence of intermolecular rearrangement is apparent. However, this may be happening in the initial DMDO stage of the process (Scheme 4).
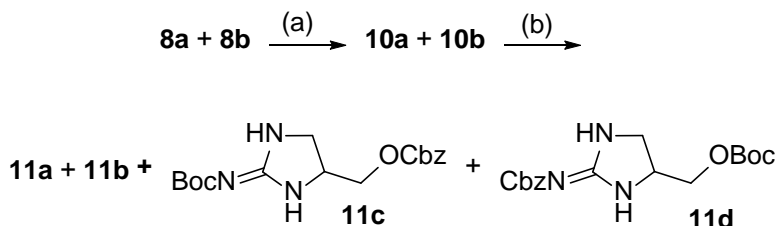
Scheme 4: (a) DMDO, acetone, -20 ˚C-rt, 5 days. (b) MeOH/H$_2$O (95:5), 16-24 h. R = Boc (**a**) or Cbz (**b**).

Following this work, we investigated the epoxidation of the dimethylallyl guanidine **8c**[3] and found that on treatment with DMDO an epoxide **12a** was formed after 16 hours which gave distinctive signals at δ$_H$ 2.95 (1H, dd, *J* 4.2, 7.4 Hz, CH), 3.24 (1H, ddd, *J* 4.4, 7.4, 14.3 Hz, CH), 3.98 (1H, ddd, *J* 4.2, 6.6, 14.3 Hz CH) ppm for the three methine protons. This epoxide slowly underwent ring opening to give some evidence for the formation of the 5-membered guanidine **13a** but this was transient and the rearranged **14a** was formed after stirring for 7 days. Attempted purification of this material was difficult as the product obtained was a gum which could not be recrystallised and was also prone to decomposition on silica gel. A similar reaction of *bis*-Z protected **8d**[3] gave as a stable product the epoxide **12b** (δ$_H$ 2.87 (1H, dd, *J* 4.1, 7.4 Hz, CH), 3.13 (1H, ddd, *J* 4.7, 7.4, 14.3 Hz, CH) and 3.88 (1H, ddd, *J* 4.1, 6.5, 14.3 Hz, CH) ppm) which on attempted recrystallisation from dichloromethane/petrol deposited a precipitate of the cyclised and rearranged 5-membered guanidine **14b**. Distinctive signals were observed at δ$_H$ 3.30 (1H, dd, *J* 10.3, 6.4 Hz, CH), 3.51 (1H, app t, *J* 10.3 Hz, CH) and 4.12 (1H, dd, *J* 10.3, 6.4 Hz, CH) ppm for the three methyne protons with 2 guanidine NH signals at δ$_H$ 8.19 (1H, br s, NH) and 8.93 (1H, br s, NH) ppm. Conclusive proof of the 5-membered system was give in the carbon spectrum with the CH-N signal at δ$_C$ 61.3 ppm, whilst the quaternary C-O appeared at δ$_C$ 84.3 ppm.¶ The slow rearrangement could be accelerated if a solution of the crude reaction mixture in dichloromethane was stirred with silica gel overnight, to give an 87 % yield of **14b**. Hydrogenation of **14b** over Pd/C gave **15** in 42 % yield after purification (Scheme 5).
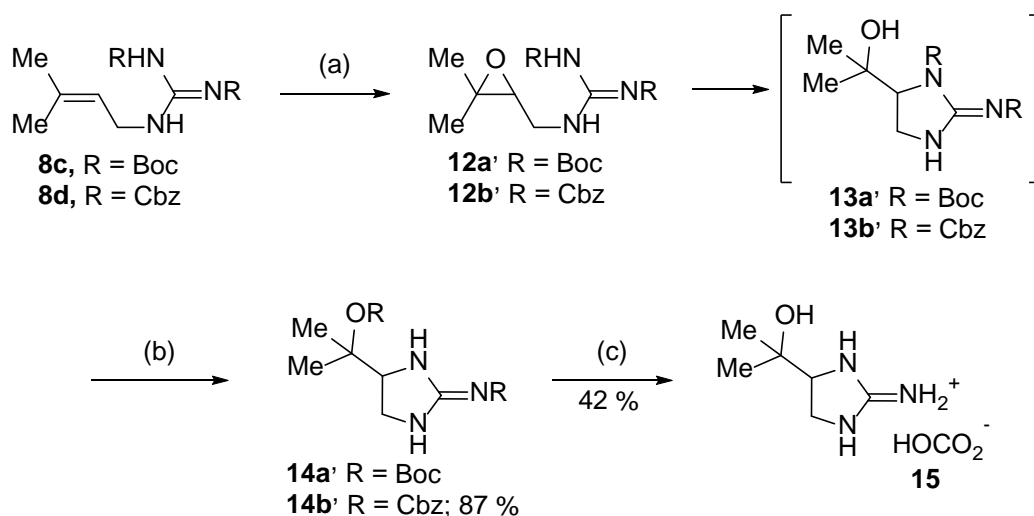
Scheme 5: (a) DMDO, acetone, -20 ˚C-rt, 5 days. (b) Silica gel, CH$_2$Cl$_2$, 16 h.
(c) i) H$_2$, 10% Pd/C, MeOH, 2 h; ii) HCl; iii) Ion exchange chromatography.

Following this the DMDO cyclisation of the homoallyl guanidine **8e**[3] was investigated and again this underwent epoxidation and cyclisation to give the 6-membered guanidine **16** which on treatement with silica gel gave **17** in 82% yield, the structure being determined by X-ray crystallography.[2] Deprotection of this compound with excess trifluoroacetic acid in chloroform for 24 h gave **18** in 66 % yield. The epoxidation reaction of the Boc-protected guanidine **8f**[3] using DMDO under identical conditions was also performed, and on completion, the crude

product **16** was dissolved in methanol/water. After stirring at rt for 4 days, purification by column chromatography gave **19a** in 72% yield. The structure of **19a** was confirmed by X-ray crystallographic analysis (Figure 1). Finally, epoxidation of the Cbz-protected guanidine **8g**[3] under identical conditions, followed by rearrangement in methanol/water gave **19b** in 79 %. This could be improved to give a 95 % yield by treatment of the crude reaction mixture from the epoxidation step with TFA in MeOH for 24 h at rt (Scheme 6).
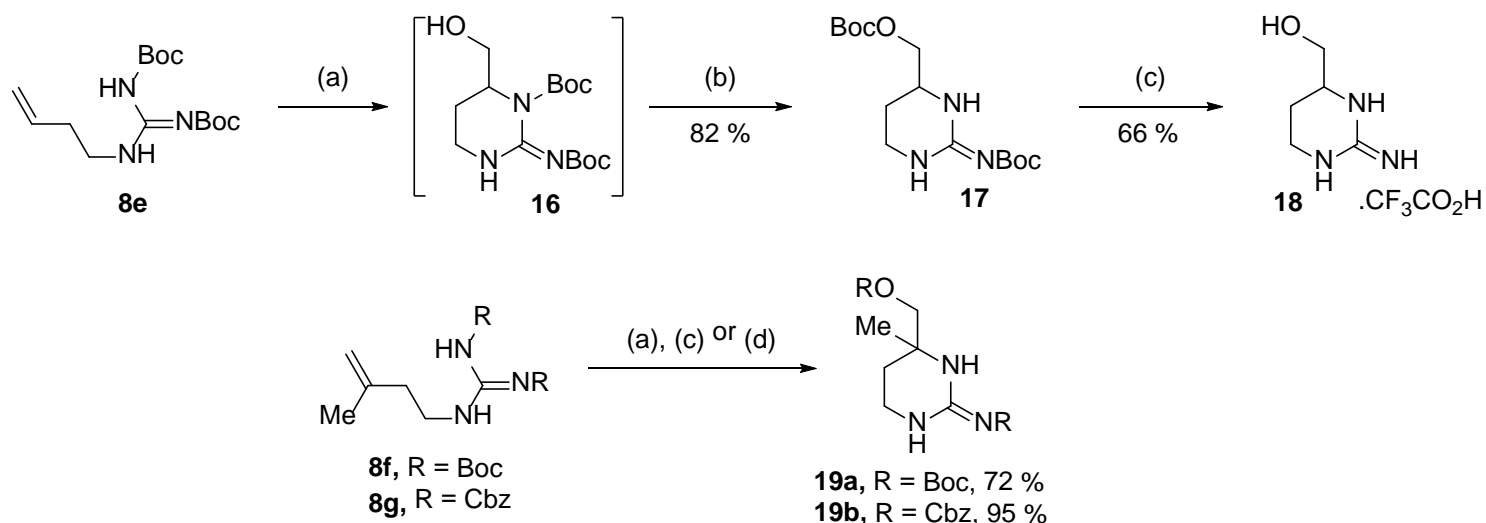
Scheme 6: (a) DMDO, acetone, -20 ˚C-rt, 24 h. (b) Silica gel, CH_2Cl_2, 24 h. (c) CF_3CO_2H, $CHCl_3$, rt, 24 h. (c) MeOH/H_2O (95:5), 4 days. (d) MeOH/CF_3CO_2H (95:5), 24 h.
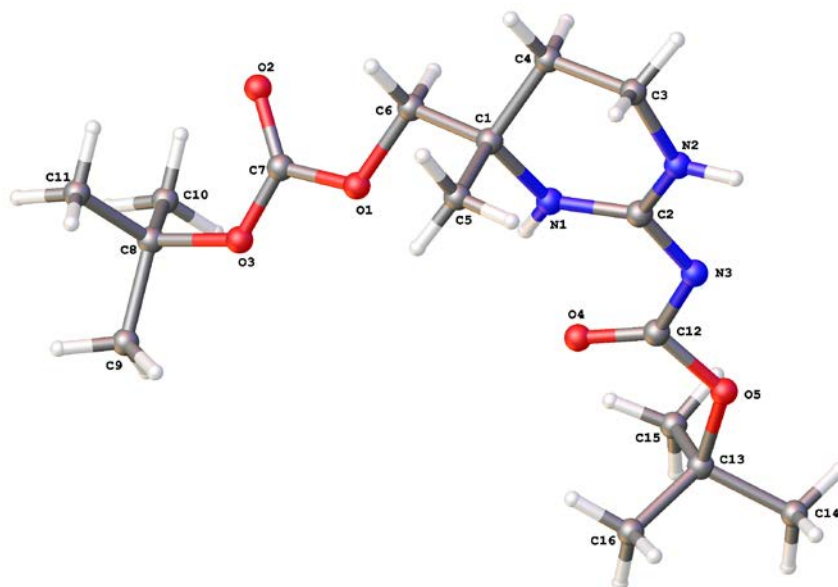

Figure 1: X-Ray structure of **19a**.

We next investigated the epoxidation of the hydroxy-substituted allyl guanidines **20**[4] and homoallyl guanidine **24**. Thus **20** was treated with an excess of DMDO at -20 °C in acetone and the mixture stirred to rt for 48

h following which the reaction mixture was evaporated and the crude product dissolved in a methanol/water mixture and the mixture stirred for 24 h. Analysis of the product **21** indicated a mixture of several isomeric compounds relating to the migration of the Boc-protecting groups and this mixture was deprotected by treatment with trifluoroacetic acid in dichloromethane for 24 h. On evaporation, the cyclised product **22** was obtained in 19% overall yield for three steps after purification by HPLC. In a similar fashion homoallyl guanidine **24** (prepared by hydrolysis of the acetate **23**[4]) was treated with DMDO to give cyclised guanidines **25**, which in turn was deprotected with trifluoroacetic acid in dichloromethane to give the guanidine **26** in 15% overall yield for three steps after purification by HPLC (Scheme 7).
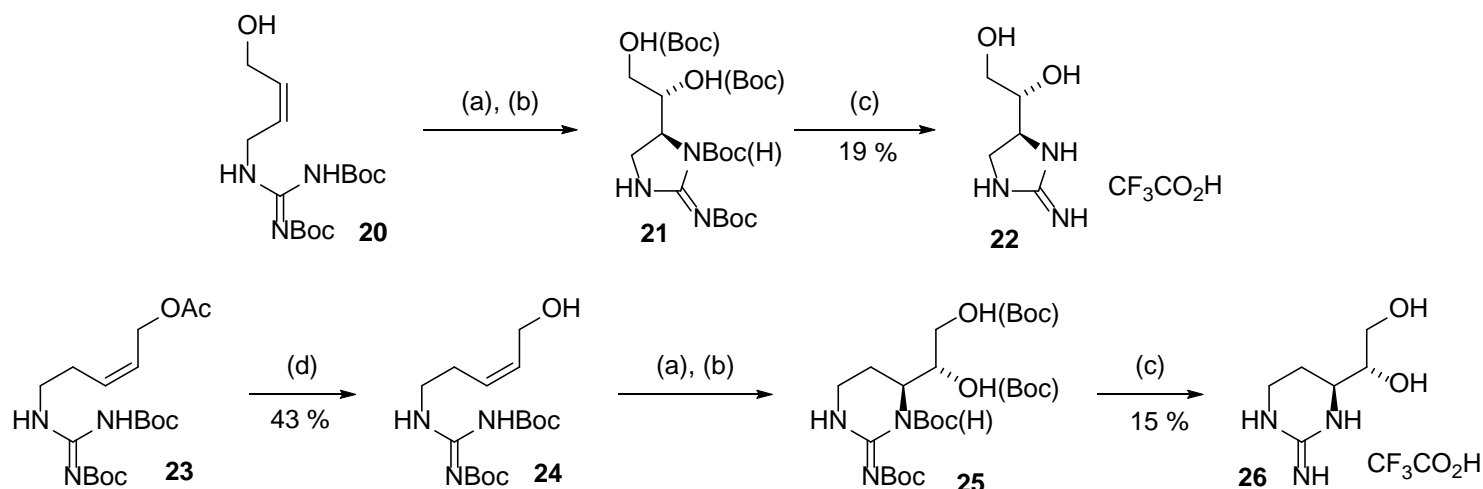
Scheme 7: (a) DMDO, acetone, -20 ˚C-rt, 24 h. (b) MeOH/H$_2$O (95:5).
(c) CF$_3$CO$_2$H, CH$_2$Cl$_2$, rt, 24 h. (d) K$_2$CO$_3$, MeOH, 4 h.

Biological activity

We have reported previously[1] that cyclic hydroxylated guanidines gave selective inhibition of b-galactosidase and glycosidases are involved in many disease states and there are many opportunities for therapeutic intervention both by inhibition and promotion of glycosidases.[10] In addition, selectivity can be more important for drug development that potency and so we here report the comparative activity of the synthesised compounds on a range of glycosidases. The guanidines **3**, **7**, **15**, **18**, **22** and **26** were investigated for activity on a panel of commercially available glycosidases from Sigma (α-glucosidases [yeast and Bacillus], β-glucosidase [almond], α-galactosidase (Green coffee bean], β-galactosidase [bovine], α-mannosidase [Jack bean], hexosaminidases [bovine kidney, Jack bean] and β-glucuronidase [bovine liver] at a top concentration of 0.14 mg/ml. 5 mM *p*-nitrophenyl-substrates were used and the pH optima for the enzymes. Compound **3** showed no significant inhibition of any of the glycosidases. Compounds **7, 15** and **18** showed some weak inhibition of the Bacillus α-glucosidase but with less than 15% inhibition at the top concentration used (0.14 mg/mL in assay) with **18** also showing weak inhibition (12%) of the β-glucosidase but more marked inhibition of the β-galactosidase (47%). Whilst **22** showed no inhibition of most enzymes tested it showed a promotion of the bovine β-*N*-acetylglucosaminidase activity (18%) which was also shown by **26** (22%) Both compounds also weakly promoted the Jack bean hexosaminidase (8.6 and

6

17% respectively). Compound **26** also showed weak but unusual promotion of the α-mannosidase (23%) but had some inhibition of the β-galactosidase (30%) Whilst this inhibition and promotion displayed by these compounds is not strong, the selectivity is of interest, e.g. **7** and **15** mainly inhibiting the bacillus α-glucosidase. The promotion of glycosidase activity, by **22** and **26** for example, of the bovine hexosaminidase, suggests improved folding or stabilization of the glycosidase due to the molecule binding to it; improved glycosidase activity is of interest to treat enzyme deficiencies (e.g. Tay Sachs disease) and improved folding and function may prevent deposition of enzymes including hexosaminidase in neurodegenerative diseases.

Conclusions

The DMDO mediated cyclisation of allyl- and homo-allyl substituted guanidines is a useful and predictable method for the synthesis of 5- and 6-membered guanidine heterocycles. We have prepared a range of these heterocycles which displayed weak inhibition of glycosidase enzymes, however two compounds showed an interesting promotion of glycosidase activity which might be of interest. We are continuing our synthetic work in this area.

Acknowledgements

Experimental

All glassware used was washed with acetone and dried with N_2 or in a vacuum oven. Reagents and starting materials were purchased from commercial suppliers and used as supplied. Diethyl ether and tetrahydrofuran were distilled from benzophenone and sodium wire, whilst dichloromethane was dried over CaH_2 and freshly distilled. DMF, chloroform and methanol were purchased as dry from Aldrich. Petrol refers to the fraction distilled between boiling range of 40-60 ℃. Column chromatography and TLC chromatography was carried out using silica and silica plates purchased from Fluorochem Ltd (particle size 35-70 μ) using HPLC grade acetic acid (AA) chloroform (CFM), dichloromethane (DCM), diethyl ether (DE), ethyl acetate (EA), hexane (HX) and methanol (ME). Compounds were visualised using UV, iodine or stained using polyphosphomolybdic acid (PMA) in EtOH or vanillin in EtOH/H_2SO_4, with heating. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR instrument as thin films, Nujol mulls, or chloroform solution on NaCl plates with absorption frequencies reported in wavenumbers (cm^{-1}). Routine NMR samples were performed on a Bruker AC250, AC400 or on a Bruker Avance-500 spectrometer. Chemical shifts for spectra are all reported in δ values (ppm) relative to the residual solvent peak in each case. Electron Ionisation (EI) and Chemical Ionisation (CI) mass spectra were recorded on an Agilent Tech. 6890N spectrometer or an XCalibur MAT900 XLT spectrometer at the EPSRC Mass Spectrometry Service (Swansea).

General conditions for epoxidation with DMDO[8]

A finely divided sample of the guanidine in a 250 mL RBF was cooled (-20 °C), whereupon a freshly prepared solution of DMDO[8] (see SI) in acetone (100-150 mL) was added. The mixture was then stirred whilst slowly warming to rt overnight and further stirred for the required time.

General condition for trifluoroacetic acid mediated Boc-deprotection.

The Boc-protected guanidine is dissolved in dichloromethane (5 mL) and cooled (0 °C) whereupon trifluoroacetic acid (5 mL) was added slowly over 5 mins and the mixture stirred to rt for the indicated time. The reaction was then evaporated and the residue repeatedly co-evaporated with chloroform to remove traces of trifluoroacetic acid.

(2-amino-4,5-dihydro-1H-imidazol-4-yl)methanol 2,2,2-trifluoroacetate 2 and 2-amino-1,4,5,6-tetrahydropyrimidin-5-ol 2,2,2-trifluoroacetate 4

Potassium *t*-butoxide (1.80 g, 16.1 mmol, 1.1 eqv.) was added to a cooled (5 °C) solution of guanidine hydrochloride (1.68 g, 17.5 mmol, 1.2 eq) in *t*-butanol (30 mL) and the mixture was stirred to rt over 1 h. 60 minutes. Epibromohydrin (1.26 ml, 14.6 mmol) was then added over 5 mins and the mixture was stirred at rt for 62 h. Further potassium *tert*-butoxide (1.80 g, 16.1 eqv.) was then added and the mixture heated (60 °C) for 24 h. The resultant white slurry was then cooled (0 °C) and TFA (5 mL) in methanol (15 mL) was added slowly over 10 mins and then mixture stirred to rt over 1 h. The reaction was evaporated onto silica gel (10 g) and purified by chromatography (gradient elution, 0-100 % ME in CFM) to give a ca. 9:1 mixture (NMR) of **2** and **4** (1.87 g) as their trifluoroacetate salts in 50% yield.

5-hydroxy-2-nitrimino-1, 3-diazacyclohexane 7[7]

A solution of nitroguanidine **5** (1.50 g, 16.6 mmol) and 1,3-diaminopropan-2-ol **6** (2.30 g, 16.6 mmol) were dissolved in water (60 mL) and the mixture heated at 70 °C for 2 h. The reaction mixture was cooled to rt and stirred for 12 h, then cooled (0 °C) and the precipitate formed collected by filtration and washed with chilled water (15 mL). The solid obtained was firstly air-dried then dried under vacuum (P_2O_5) to constant weight to give **7** (0.52 g, 27 % yield) as a white solid. **Mp** 230-233 °C (Lit[7] 233-233.5 °C); δ_H (500 MHz, D_2O) 3.45 (2H, dd, *J* 3.1, 13.0, 2 x CH), 3.57, (2H, dd, *J* 2.6, 13.0 Hz, 2 x CH), 4.38 (1H, tt, *J* 2.6, 3.1 Hz, CH); δ_C (125 MHz, D_2O) 44.3, 58.1, 153.6; **MS(CI)** 114.0 (100 %, [M+H-NO_2]$^+$) 160.0 (100%, [M+H$^+$]); **HRMS (EI)** $C_4H_8N_4O_3$ [M+H$^+$], found 160.0589, requires 160.0591.

2-amino-1,4,5,6-tetrahydropyrimidin-5-ol acetate 4

Palladium on charcoal (5 %, 0.6 g) was added to a solution of guanidine **7** (0.473 g, 2.97 mmol) in aqueous acetic acid (15 % v/v, 50 mL) and the mixture stirred under H_2 (balloon) for 72 h. The reaction was filtered through a Celite© pad and then evaporated and the crude product purified by chromatography (5-15 % ME in CFM, then 15% - 20% ME in CFM with 0.1 % acetic acid) to give **4** as a white solid (0.388 g, 75% yield). **Rf** 0.20 (15% ME in CFM with 0.1 % acetic acid); **Mp** 61-62 °C; δ_H (500 MHz, D_2O) 1.92 (3H, s, Me), 3.33 (2H, dd, *J* 3.1, 12.3, 2 x CH), 3.45, (2H, dd, *J* 2.7, 12.3 Hz, 2 x CH), 4.38 (1H, tt, *J* 2.7, 3.1 Hz, CH); ν_{max} 3340, 2981, 2865, 1579; δ_C (125 MHz, D_2O) 23.3, 43.9, 58.7, 153.6, 181.5; **MS(CI)** 116.1 (100 %, [M+H$^+$]); **HRMS(CI)** $C_4H_{10}N_3O$ ([M+H$^+$]), found 116.0817, requires 116.0818.

tert-butyl 2-((tert-butoxycarbonyl)imino)-5-(hydroxymethyl)imidazolidine-1-carboxylate 10a

Guanidine **8a**[3] (0.30 g, 1.00 mmol) was epoxidised using the standard conditions to give a crude product (0.33 g) which was purification using rapid chromatography (gradient elution: 10-100 % EA in PE, then 10 % ME in EA) to give **10a** (196.0 mg, 62 % (71% based on recovered **8a**), **11a** (40.0 mg, 13%, 14% based on recovered **8a**) and recovered **8a** (40.0 mg). Recrystallisation (EA/PE or DCM/DE) gave crystals suitable for X-ray analysis[1]); **Mp**. 130°C; δ_H (500 MHz, CDCl$_3$) 1.42 (9H, s, *t*-Bu), 1.46 (9H, s, *t*-Bu), 3.63 (1H, br d, *J* 11.3 Hz, CH), 3.69-3.78 (3H, m, 3 x CH), 4.11-4.20 (1H, m, CH), 5.87 (2H, br s, NH, OH); δ_C (62.5 MHz, CDCl$_3$) 28.1, 28.1, 48.8, 57.6, 62.3, 80.9, 83.6, 150.9, 152.9, 155.7; ν_{max} 3346, 2983, 2975, 1753, 1743, 1600, 1141; **MS(CI)** 316.1 (100%, [M+H$^+$]); **HRMS(CI)** C$_{14}$H$_{26}$N$_3$O$_5$ ([M+H]$^+$), found 316.1868, requires 316.1867.

tert-butyl-(4-((((tert-butoxycarbonyl)oxy)methyl)imidazolidin-2-ylidene)carbamate 11a.

Guanidine **10a**[3] and silica gel (ca. 1 g) in chloroform (20 mL) were stirred at rt for 72 h then filtered through a Celite© pad which was washed with chloroform and ethyl acetate. Evaporation of the solvent gave a crude compound which was recrystallised from chloroform by slow evaporation to give crystals of **11a** (70.3 mg, 64% yield) suitable for X-ray analysis.[2] **Mp.** 92-94 °C; δ_H (500 MHz, CDCl$_3$) 1.44 (9H, s, *t*-Bu), 1.48 (9H, s, *t*-Bu), 3.40 (1H, dd, *J* 6.0, 9.7 Hz, CH), 3.73 (1H, dd, *J* 9.6, 9.7 Hz, CH), 4.07 (1H, dd, *J* 6.6, 10.9 Hz, CH), 4.10 (1H, dd, *J* 5.5, 10.9 Hz, CH), 4.16 (1H, dddd, *J* 5.5, 6.0, 6.6, 9.67 Hz, CH), 6.67-8.86 (2H, br s, 2 x NH); δ_C (62.5 MHz, CDCl$_3$) 27.8, 28.4, 44.6, 52.9, 67.6, 78.8, 83.0, 153.2, 162.3, 164.4; ν_{max} 3377, 2961, 1753, 1659, 1617, 1255; **MS(CI)** 316.2 (100%, [M+H$^+$]); **HRMS(CI)** C$_{14}$H$_{26}$N$_3$O$_5$ [M+H$^+$], found 316.1871, requires 316.1867.

Benzyl (4-(((((benzyloxy)carbonyl)oxy)methyl)imidazolidin-2-ylidene)carbamate 11b

Compound **8b**[3] (0.309 g, 0.84 mmol) was epoxidised under the general conditions for 5 days to give a crude cyclised product (0.35 g) which was dissolved in dichloromethane (5 ml) and silica gel (1 g) was added and the slurry stirred overnight. Evaporation of the dichloromethane and column chromatography of the residue (0-100% EA in PE) gave **11b** (0.208 g, 0.54 mmol, 64%) as a white solid. Mp 155-157 ˚C; Rf 0.46 (EtOAc); δ_H (500 MHz, CDCl$_3$), 3.20 (1H, dd, *J* 4.0, 10.2 Hz, CH), 3.45-3.51 (1H, m, CH), 3.87-3.95 (3H, m, CH, CH$_2$), 4.94 (2H, s, CH$_2$), 5.03 (2H, s, CH$_2$), 7.10-7.30 (10H, m, 2 x Ph), 7.50-9.60 (2H, br s, 2 x NH); δ_C (125 MHz, CDCl$_3$) 44.7, 52.5, 66.6, 68.3, 70.0, 127.9, 128.0, 128.5, 128.7, 135.1, 137.3, 154.8, 163.2, 165.3; ν_{max} 3398, 3150, 3065, 3035, 2956, 1748, 1654, 1623, 1264; **MS(CI)** 384.2 (33 %, [M+H$^+$]); **HRMS(ES)** C$_{20}$H$_{22}$N$_3$O$_5$ [M+H$^+$], found 384.1558, requires 384.1554.

(2-iminoimidazolidin-4-yl)methanol 2,2,2-trifluoroacetate 2

Guanidine **11a**[3] (134 mg, 0.425 mmol) was deprotected under the standard conditions to give **2** (96.0 mg) as a gum in 98 % yield. δ_H (250 MHz, CD$_3$OD) 3.50 (1H, dd, *J* 6.1, 9.8 Hz, CH), 3.54 (1H, dd, *J* 5.2, 11.4 Hz, CH), 3.62 (1H, dd, *J* 4.5, 11.4 Hz, CH), 3.75 (1H, dd, *J* 9.8, 9.8 Hz CH), 4.07 (1H, dddd, *J* 4.5, 5.2, 6.1, 9.8 Hz, CH); δ_C (125 MHz, CD$_3$OD) 46.1, 58.1, 63.9, 161.4; ν_{max} 3352, 2943, 1552; **MS(CI)** 116 (40 % [M+H$^+$]); **HRMS(CI)** C$_4$H$_{10}$N$_3$O [M+H$^+$], found 116.0825, requires 116.0818.

tert-Butyl (Z)-(5-((tert-butoxycarbonyl)oxy)-4,4-dimethyltetrahydropyrimidin-2(1H)-ylidene)carbamate 14a

Compound **8c**[3] (0.399 g, 1.22 mmol) was epoxidised under the general conditions and after 16 hours the epoxide **12a** was formed as evidenced by proton NMR (δ_H (500 MHz, CDCl$_3$), 1.32 (3H, CH$_3$), 1.33 (3H, CH$_3$),

1.49 (9H, s, *t*Bu), 1.50 (9H, s, *t*Bu), 2.95 (1H, dd, *J* 4.2, 7.4 Hz, CH), 3.24 (1H, ddd, *J* 4.4, 7.4, 14.3 Hz, CH), 3.98 (1H, ddd, *J* 4.2, 6.6, 14.3 Hz CH), 8.57 (1H, broad s, NH), 11.47 (1H, broad s, NH) ppm), which cyclised slowly to give **14a** as a oil in quantitative yield. After work up, attempted purification by column chromatography or recrystallization led to considerable decomposition. δ_H (250 MHz, CDCl$_3$) 1.21 (3H, CH$_3$), 1.22 (3H, CH$_3$), 1.49 (9H, s, *t*Bu), 1.55 (9H, s, *t*Bu), 3.83 (1H, dd, *J* 2.5, 12.8 Hz, CH), 3.86 (1H, dd, *J* 8.9, 12.8 Hz, CH), 4.22 (1H, dd, *J* 2.7, 8.5 Hz CH), 2 x NH not observed. δ_C (62.5 MHz, CDCl$_3$) 20.9, 21.0, 27.8, 28.2, 43.3, 61.2, 79.9, 82.1, 82.8, 151.7, 160.2, 163.0; ν_{max} 3346, 1748, 1656, 1611, 1368, 1315, 1251, 1143, 998; **MS(CI)** 188.1 (100 %), 232.1 (75 %), 288.2 (25 %), 244.2 (100 %, [M+H$^+$]); **HRMS(CI)** C$_{16}$H$_{30}$N$_3$O$_5$ [M+H$^+$], found 344.2178, requires 344.2180.

Benzyl (Z)-(5-(((benzyloxy)carbonyl)oxy)-4,4-dimethyltetrahydropyrimidin-2(1H)-ylidene)carbamate 14b

Compound **8d**[3] (0.42 g, 1.13 mmol) was epoxidised under the general conditions for 5 days to give the crude epoxide **12b** (0.46 g) as a white solid. δ_H (500 MHz, CDCl$_3$) 1.21 (3H, CH$_3$), 1.22 (3H, CH$_3$), 2.87 (1H, dd, *J* 4.1, 7.4 Hz, CH), 3.13 (1H, ddd, *J* 4.7, 7.4, 14.3 Hz, CH) 3.88 (1H, ddd, *J* 4.1, 6.5, 14.3 Hz, CH), 5.04 (2H, s, CH$_2$), 5.07 (2H, s, CH$_2$), 7.16-7.31 (10H, m, 2 x Ph), 8.46 (1H, broad dd, *J* 4.7, 6.5 Hz, NH), 11.66 (1H, broad s, NH). The epoxide **12b** (0.46 g) was dissolved in a minimum amount of dichloromethane (2-3 ml) and diluted with PE (10-15 ml) and placed in a freezer. After 3 days a white amorphous precipitate of was obtained. Removal of the supernatant liquid and drying of the solid gave **14b** (100.0 mg, 23%) as a solid. The supernatant liquid was evaporated and re-dissolved in dichloromethane (10 mL), whereupon silica gel (ca. 0.3 g) was added and the mixture stirred for 48 h. After filtration and evaporation the crude product (0.36 g) was dissolved in dichloromethane (3-4 mL) and diluted with petrol (20-25 mL) and on cooling for 2-3 days a further sample of **14b** (277.0 mg, 64%) was formed giving an overall yield of 87%. δ_H (500 MHz, CDCl$_3$) 1.42 (3H, s, CH$_3$), 1.45 (3H, s, CH$_3$), 3.30 (1H, dd, *J* 10.3, 6.4 Hz, CH), 3.51 (1H, t, *J* 10.3 Hz, CH) 4.12 (1H, dd, *J* 10.3, 6.4 Hz, CH) 5.07 (1H, d, *J* 12.3 Hz, CH), 5.09 (1H, d, *J* 12.3 Hz, CH), 5.13 (2H, s, CH$_2$), 7.27-7.43 (10H, m, 2 x Ph), 8.19 (1H, br s, NH), 8.93 (1H, br s, NH); δ_C (125 MHz, CDCl$_3$) 20.7, 20.7, 42.8, 61.3, 66.5, 69.3, 84.3, 127.9, 128.0, 128.4, 128.4, 128.6, 128.7, 135.3, 137.3, 153.2, 163.4, 165.4; ν_{max} 3383, 3074, 3037, 2985, 2928, 2857, 1741, 1654, 1624, 1270, 1253, 1107; **MS (CI)** 412 (100%, [M+H$^+$]) **HRMS (CI)** C$_{22}$H$_{26}$N$_3$O$_5$ [M+H$^+$], found 412.1869, requires 412.1867.

4-(2-hydroxypropan-2-yl)imidazolidin-2-iminium hydrogen carbonate 15

Guanidine **14b** (52.6 mg, 0.128 mmol) was dissolved in methanol (3 mL), Pd/C (10 %, 120 mg) was added and the mixture stirred under hydrogen gas (balloon) for 2 h. After filtration HCl (1M ca 2-3 drops) was added and the mixture evaporated to give **15.HCl** (17.2 mg, 0.096 mmol) as a gum in 75% yield. This was dissolved in a 1:1 mixture of EtOH/H20 (0.5 ml) and applied to a column of Amberlite CG400 (2 x 1 cm, OH$^-$ form, the resin having previously been washed to neutrality with water) on eluting with water, three fractions (2 mL, 2 mL and 5 mL) gave **15** (11.0 mg) in 42% yield as the hydrogen carbonate salt. δ_H (400 MHz, D$_2$O) 1.16 (3H, s, CH$_3$), 1.21 (3H, s, CH$_3$), 3.58 (1H, dd, *J* 10.1, 6.6 Hz, CH), 3.75 (1H, dd, *J* 10.1, 10.2 Hz CH), 3.98 (1H, dd, *J* 10.2, 6.6 Hz, CH); δ_C (100 MHz, D$_2$O) 23.3, 24.4, 43.9, 63.3, 71.4, 159.7, 165.1; ν_{max} 3320, 3212, 2973, 2924, 2852, 1688, 1579, 1404, 1281, 1174, 1106, 1015, 950; **MS (CI)** 144.1 (100%, [M+H$^+$]); **HRMS (CI)** C$_{22}$H$_{26}$N$_3$O$_5$ [M+H$^+$], found 144.1127, requires 144.1131.

tert-butyl (Z)-(4-((((tert-butoxycarbonyl)oxy)methyl)tetrahydropyrimidin-2(1H)-ylidene)carbamate 17

Compound **8e**[3] (0.51 g, 1.63 mmol) was epoxidised under the general conditions for 3 days to give a crude cyclised product (0.53 g) which was dissolved in dichloromethane (5 mL) and silica gel (2 g) added and the mixture stirred for 16 h. The suspension was evaporated and compound purified by chromatography (0-10% ME in EA) and the product obtained recrystallised (EA:PE 1:2) to give **17** (0.44 g, 1.33 mmol) in 82% yield as pale yellow diamond shaped crystals. **R$_f$** 0.27 (10:90 ME:EA); **Mp** 160-161 °C; δ_H (500 MHz, CDCl$_3$) 1.45 (9H, s, ^{t}Bu), 1.47 (9H, s, ^{t}Bu), 1.79-1.85 (1H, m, CH), 1.97-2.01 (1H, m, CH), 3.37 (1H, ddd, J 4.5, 8.1, 13.1, CH), 3.42-2.46 (1H, m, CH), 3.74-3.79 (1H, m, CH), 4.06 (1H, dd, J 6.6, 11.1, CH), 4.13 (1H, dd, J 5.7, 11.1), 6.90-10.3 (2H, br s, 2 x NH); δ_C (125 MHz, CDCl$_3$) 22.4, 27.8, 28.3, 36.8, 47.9, 67.7, 80.0, 83.1, 153.1, 155.9, 159.2; ν_{max} (Nujol mull) 3152, 2724, 1747, 1632, 1594, 1454, 1376, 1156; **MS(CI)** m/z 330.3 (100 %, [M+H]$^+$); **HRMS(ES)** C$_{15}$H$_{27}$N$_3$O$_5$ [M+H$^+$], found 330.2019, requires 330.2023.

(2-Iminohexahydropyrimidin-4-yl)methanol 2,2,2-trifluoroacetate 18

Compound **17** (38.2 mg was deprotected over 14 h using the standard method to give **18** (18.5 mg, 0.076 mmol in 66 % yield as a glass after chromatography (0-10 % ME in DCM). **Rf** 0.27 (20% ME in DCM); δ_H (500 MHz, CD$_3$OD) 1.70-1.78 (1H, m, CH), 1.96-2.02 (1H, m, CH), 3.31 (1H, ddd, J 4.3, 9.3, 12.6, CH), 3.40 (1H, dt, 12.6, 5.0 Hz), 3.48-3.54 (2H, m, 2 x CH), 3.64-3.69 (1H, m, CH); δ_C (125 MHz, CD$_3$OD) 23.3, 38.0, 52.0, 65.0, 116.1 (q, $^1J_{CF}$ 285 Hz), 155.9, 159.0 (q, $^2J_{CF}$ 41 Hz); ν_{max} 3332, 3264, 3095, 2960, 2926, 2855, 1791, 1681, 1632, 1429, 1338, 1260, 1201, 1176, 1134, 1031, 835, 801, 712; **MS(CI)** 130.1 ([M+H$^+$]); **HRMS(ES)** C$_5$H$_{12}$N$_3$O [M+H$^+$], found 130.0975, requires 130.0975.

tert-Butyl(4-(((*tert*-butoxycarbonyl)oxy)methyl)-4-methyltetrahydropyrimidin-2(1*H*)-ylidene)carbamate 19a

Compound **8f**[3] (0.330 g, 1.01 mmol) was epoxidised under the general conditions for 16 hrs to give a crude cyclised product (0.35 g) on evaporation which was dissolved in dichloromethane, dried (MgSO$_4$), filtered and evaporated *in vacuo*. The resulting product was dissolved in methanol (5 mL) and water (0.1 mL) and stirred for 4 days, evaporated and purified column chromatography (20-100% EA in PE) to give **19a** (0.250 g, 0.73 mmol in 72% yield as a white solid. The solid was dissolved in dichloromethane and hexane was added to the cloud point whereupon cooling (-20 °C) gave crystals suitable for X-ray analysis (Figure 1). **Rf** 0.03 (EA); **Mp** 143-145°C; ν_{max} 3261, 2978, 2931, 1745, 1714, 1644; δ_H (500 MHz; CDCl$_3$) 1.35 (3H, s CH$_3$), 1.46 (9H, s, 3 x CH$_3$), 1.47 (9H, s, 3 x CH$_3$), 1.71 (1H, ddd, J 5.5, 7.6, 13.4, CH), 1.93-2.00 (1H, m, CH), 3.37-3.48 (2H, m, CH$_2$), 3.96 (1H, d, J 11.1 Hz, CH), 4.06 (1H, d, J 11.1 Hz, CH), 9.53 (2H, br s, 2 x NH); δ_C (125 MHz; CDCl$_3$) 24.6, 27.8, 28.0, 35.7, 52.4, 70.6, 83.6, 85.2, 152.0, 153.1, 153.4; **HRMS(ES)** C$_{16}$H$_{30}$N$_3$O$_5$ [M+H$^+$], found 344.2184, requires 344.2180.

Benzyl (4-((((benzyloxy)carbonyl)oxy)methyl)-4-methyltetrahydropyrimidin-2(1*H*)-ylidene)carbamate 19b

Compound **8f**[3] (0.50 g, 1.26 mmol) was epoxidised under the general conditions for 16 hrs to give a crude cyclised product (0.55 g) on evaporation which was dissolved in dichloromethane, dried (MgSO$_4$), filtered and evaporated *in vacuo*. The resulting product was dissolved in methanol (5 mL), cooled (0 °C) and trifluoroacetic acid (0.52 mL, 5 equiv.) was added drop wise. After warming to rt stirring was continuesd for 24 h and the mixture then evaporated and the residue purified by chromatography (50-100 % EA in PE, followed by 2-4% ME in EA) to give **19b** (0.49 g, 1.19 mmol) as a colourless gum in 95% yield. **Rf** 0.16 (60:40 EA:PE); δ_H (500 MHz, CDCl$_3$) 1.40 (3H, s, CH$_3$), 1.77 (1H, ddd, J, 5.4, 7.5, 13.9, CH), 1.97-2.05 (1H, m, CH), 3.42-3.55 (2H, m, CH$_2$), 4.08 (1H, d, J 11.2 Hz, CH), 4.19 (1H, d, J 11.2 Hz, CH), 5.17 (2H, s, CH$_2$), 5.24 (2H, s, CH$_2$), 7.32-7.42 (10H, m, 2 x Ph),

9.84 (2H, br s, NH); δ_C (125 MHz; CDCl$_3$) 24.6, 27.9, 35.7, 52.2, 68.5, 70.5, 71.7, 128.3, 128.7, 128.8, 128.8, 128.8, 129.0, 134.8, 135.0, 152.3, 154.7, 155.3; ν_{max} 3243, 3154, 3064, 3032, 2955, 2928, 2896, 1748, 1644, 1634, 1562, 1554; **HRMS(ES)** C$_{22}$H$_{26}$N$_3$O$_5$ ([M+H$^+$]), found 412.1867, requires 412.1867.

+/- (R)-1-((S)-2-iminoimidazolidin-4-yl)ethane-1,2-diol 2,2,2-trifluoroacetate 22

Compound **20**[4] (0.431 g 1.308 mmol) was epoxidised under the general conditions for 48 hrs to give crude product (490 mg) which was dissolved in MeOH (5 mL) to which water (ca. 0.2 mL) was added and the mixture stirred. After 24 h the reaction was evaporated to give crude **21** (451 mg) which was used in the next step without further purification. Compound **21** (451 mg) was then deprotected using the standard method over 24 h. Evaporation gave a gum (394 mg) which was purified by preparative HPLC (ACE 10 C18 250 x 21.8 mm column, isocratic 95:5:0.1% water:acetonitrile:TFA, 15 mL/min, elution time 4.5 mins at 210 nm) to give **22** (66.0 mg, 0.25 mmol) as a white solid in 19% yield. **Mp**. 148-49 °C; δ_H (400 MHz, CD$_3$OD) 3.54-3.64 (3H, m, 3 x CH), 3.78 (1H, dd, J 9.8, 9.8 Hz, CH), 4.13 (1H, ddd, J 4.3, 7.0, 9.8 Hz, CH); δ_C (100 MHz, CD$_3$OD) 46.5, 58.9, 64.5, 73.5, 161.5; δ_C (125 MHz, D$_2$O) 45.3, 57.0, 62.8, 72.5, 116.6 (CF$_3$, q, $^1J_{C\text{-}F}$ 329 Hz), 160.1, 163.0 (C, q, $^2J_{C\text{-}F}$ 35 Hz). ν_{max} 3332, 2976, 2921, 2855, 1738, 1638, 1614, 1361, 1277, 1253, 1158, 1102; **MS(CI)** 146.1 (100%, [M+H$^+$]); **HRMS(CI)** C$_5$H$_{12}$N$_3$O$_2$ [M+H$^+$], found 146.0920, requires 146.0924.

tert-Butyl (((*tert*-butoxycarbonyl)amino)(((Z)-5-hydroxypent-3-en-1-yl)amino)methylene)-4-azanecarboxylate 24

Acetate **23**[4] (0.650 g, 1.68 mmol) was dissolved in dry methanol (10 ml), cooled (0 ˚C) and potassium carbonate (204.0 mg, 1.48 mmol) was added and the mixture stirred for 7 h. The reaction was then filtered through a silica plug, evaporated and the residue purified by chromatography (10-75% EA in PE) to give **24** (0.250 g, 0.728 mmols) in 43% yield as a gum. Rf 0.13 (25:75 EA:PE); δ_H (400 MHz, CDCl$_3$) 1.45 (3H, s, *t*Bu), 1.46 (3H, s, *t*Bu), 2.33 (2H, app q, J 7.0 Hz, CH$_2$), 2.63 (1H, br s, OH), 3.44 (2H, app q, J 6.2 Hz, CH$_2$), 4.15 (2H, d, J 6.9 Hz, CH$_2$), 5.43-5.50 (1H, m, CH), 5.76-5.82 (1H, m, CH), 8.25 (1H, br s, NH), 11.49 (1H, br s, NH); δ_C (100 MHz, CDCl$_3$) 27.0, 28.1, 28.3, 40.4, 58.2, 79.5, 83.6, 128.2, 132.4, 153.6, 156.0, 163.5; ν_{max} 2980, 2933, 1721, 1640, 1618, 1414, 1367, 1329, 1156, 1135; **MS(ESI)** 344.2 (100 %, [M+H$^+$]); **HRMS(CI)** C$_{16}$H$_{30}$N$_3$O$_5$ [M+H$^+$], found 344.2180, requires 344.2180.

+/- (R)-1-((S)-2-Iminohexahydropyrimidin-4-yl)ethane-1,2-diol 2,2,2-trifluoroacetate 26.

Compound **24** (0.240 g, 0.700 mmol) was epoxidised under the general conditions for 48 hrs to give a crude cyclised product (246 mg) which was dissolved in MeOH (5 mL) to which water (ca. 0.2 mL) was added and the mixture stirred. After 24 h the reaction was evaporated to give crude **25** (215 mg) which was used in the next step without further purification. Compound **25** (215 mg) was dissolved in DCM (5 mL), cooled (0 ºC) and trifluoroacetic acid (5 mL) was added and the mixture stirred at rt for 48 h. Evaporation gave crude **26** (216 mg) which was purified by preparative HPLC (ACE 10 C18 250 x 21.8 mm column, isocratic 95:5:0.1 % water:acetonitrile:TFA, 15 mL/min, elution time 4.7 mins at 210 nm) to give **26** (29.0 mg, 0.106 mmol) as a gum in 15 % yield. δ_H (400 MHz, CD$_3$OD) 1.72-1.81 (1H, m, CH), 2.03-2.10 (1H, m, CH), 3.26-3.35 (1H, m, CH), 3.45 (1H, ddd, J 5.4, 5.4, 12.6 Hz, CH), 3.46-3.54 (1H, m, 2 x CH) 3.66 (1H, dd, J 4.1, 11.6 Hz, CH), 3.69 (1H, dd, J 4.0, 11.6 Hz, CH); δ_C (100 MHz, CD$_3$OD) 24.2, 38.6, 52.7, 64.6, 74.6 (trifluoroacetate signals not observed); ν_{max}

3385, 2982, 2937, 1738, 1674, 1637, 1279, 1254, 1156, 912, 732; **MS(CI)** 160.1 (100%, [M+H$^+$]); **HRMS(CI)** C$_6$H$_{14}$N$_3$O$_2$ [M+H$^+$], found 160.1078, requires 160.1081.

Glycosidase assays[11]

All enzymes and *para*-nitrophenyl substrates were purchased from Sigma β-galactosidase (bovine liver), α-glucosidase (Bakers yeast), α-mannosidase (Jack bean), β-glucosidase (almond), *α-L*-fucosidase (human placenta), *N*-acetyl-*β*-glucosaminidase (Bovine Kidney), Naringinase (*Penicillium decumbens*) and α-galactosidase (green coffee beans). Compounds were assayed at 27 °C in citric acid (0.1 M)/disodium hydrogen phosphate buffers (0.2 M) at the optimum pH for the enzyme. The incubation mixture consisted of enzyme solution (10 μl), an aqueous solution of the substrate (10 μl) appropriate *para*-nitrophenyl substrate (50 μl of a 5 mM solution in buffer). The reactions were stopped by addition of glycine (70 μl, 0.4 M at pH 10.4) during the exponential phase of the reaction. Final absorbances were read at 405 nm using a Versamax microplate reader (Molecular Devices). Assays were carried out in triplicate and the values given are means. Rat intestinal enzyme activities (Sigma rat intestine powder) were also measured using appropriate substrates as above for the enzyme activity measured, the powder (100 mg) was made up in PBS (2 mL) in ice and homogenised and then centrifuged. The supernatant was used as the glycosidase activity source as above.

¶ We had previously[2] assigned this as a 6-membered product.

References
1) Dennis. M.; Hall, L.M.; Murphy, P.J.; Thornhill, A.J.; Nash, R.; Winters, A.L.; Hursthouse, M.B.; Light, M.E. Horton, P.; *Tetrahedron Letts,* 2003, **44**, 3075-3080.
2) Albrecht, C.; Barnes, S.; Böckemeier, H.; Davies, D.; Dennis, m.; Evans, D.M.; Fletcher, M.D.; Jones, I.; Leitmann, V.; Murphy, P.J.; Rowles, R.; Nash, R.; Stephenson, R.A.; Horton, P.N.; Hursthouse, M.B.; *Tetrahedron Lett*. 2008, **49**, 185-188.
3) Al-Shuhaib, Z.; Davies, D.H.; Dennis, M.; Evans, D.H.; Fletcher, M.D.; Franken, H.; Hancock, P.; Hollinshead, J.; Jones, I.; Kähm, K.; Murphy, P.J.; Nash, R.; Potter, D.; Rowles, R.; *Tetrahedron*, 2014, **70**, 4412–4419.
4) Al-Shuhaib, Z.; Bockemeier, H.; Coghlan, L.; Dorksen, E.; Jones, I.V.; Murphy, P.J.; Nash, R.; Page, J.M., *Tetrahedron Lett*. 2013, **54**, 6716–6718.
5) (i) Chen, B.-C.; Quinlan, S. L.; Reid, J. G.; Jass, P. A.; Robinson, T. P.; Early, W. A.; Delaney, E. J.; Humora, M. J.; Madding, G. D.; Venit, J. J.; Winter, W. J. *Tetrahedron: Asymmetry* 1998, **9**, 1337-1340. (ii) Fritsche-Lang, W.; Wilharm, P.; Hadicke, E.; Fritz, H.; Prinzbach, H. *Chem. Ber*. 1985, **118**, 2044-2078. (iii) Le Merrer, Y.; Gauzy, L.; Gravier-Pelletier, C.; Depezay, J. C. *Bioorg. Med. Chem*. 2000, **8**, 307-320. (iv) Gravier-Pelletier, C.; Bourissou, D.; Le Merrer, Y.; Depezay, J. C; *Synlett* 1996, 275-277. (v) Gauzy, L.; Le Merrer Y.; Depezay, J.C. *Synlett* 1998, 402-404. (vi) Genski, T.; Macdonald, G.; Wei, X.; Lewis, N.; Taylor, R. J. K. *Synlett*, 1999, 795-797. (vii) Genski, T.; Macdonald, G.; Wei, X.; Lewis, N.; Taylor, R. J. K. *Arkivoc*, 2000, **1**, 266-273.
6) Elliott. M. C.; Long, M. S. *Tetrahedron Lett*. 2000, **43**, 9191-9194.
7) McKay, A. F.; Wright, G. F.; *J. Am. Chem. Soc*., 1948, **70**, 430-431.

8) Mikula, H.; Svatunek, D.; Lumpi, D.; Glöcklhofer, F.; Hametner, C.; Fröhlich, *Org. Process Res. Dev.* 2013, **17**, 313−316.

9) Bunch, L, Norrby, P.-O.; Frydenvang, K.; Krogsgaard-Larsen, P.; Madsen, U.; *Org lett.*, 2001, **3**, 433-435.

10) Nash, R.J.; Kato, A.; Yu, C-Y.; Fleet, G.W.J.; *Future Med. Chem.* 2011, **3** 1513-1521.

11) Watson, A.A.; Nash, R.J.; Wormald, M.R.; Harvey, D.J.; Dealler, S.; Lees, E.; Asano, N.; Kizu, H.; Kato, A.; Griffiths, R.C.; Cairns, A.J.; Fleet, G.W.J.; *Phytochemistry* 1997, **46**, 255-259.