Asymmetric synthesis of 3-amino-4-hydroxy-2-(hydroxymethyl)pyrrolidines as potential glycosidase inhibitors†

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Three diastereoisomers of 3-amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine have been synthesised by a divergent route starting from *trans*-4-hydroxy-L-proline. Regio- and stereoselective introduction of the 3-amino and 4-hydroxyl functional groups was achieved using either a tethered aminohydroxylation reaction or by employing intra- and intermolecular epoxide-opening strategies. Preliminary biological data indicate that two of these novel amino pyrrolidines are moderate inhibitors of β-galactosidase.

Introduction

Glycosidase enzymes have considerable biological importance as they are involved in a wide range of vital natural processes such as intestinal digestion, post-translational processing of glycoproteins and the lysosomal catabolism of glycoconjugates. Consequently, there has been substantial interest in recent years in designing, synthesising and testing glycosidase inhibitors, both to gain a greater insight into the active site structures and mechanisms of these enzymes, and to also generate new therapeutics.[1] Strong selective inhibitors of glycosidic cleaving enzymes have many potential applications and certain sugar mimics have aroused increasing interest as potential anti-viral, anti-cancer and anti-diabetic agents as well as agrochemicals.[2] Much of the effort toward the synthesis of glycosidase inhibitors has focused on the iminosugar family, which are sugar analogues in which the ring oxygen has been replaced by an imino group.[3] The biological activity of these compounds is thought to be due to their ability to mimic the oxocarbenium-ion like transition state involved in glycoside hydrolysis.

Structurally, some of the most simple iminosugars are those based on polyhydroxylated pyrrolidines (Fig. 1). Thus, the triol **1** is a strong competitive inhibitor of α-galactosidase[4] whilst the diastereoisomeric compounds **2a** and **3a** show only weak activity against this enzyme but are inhibitors of α-glucosidase.[4,5] Many other polyhydroxylated pyrrolidines have also been studied and shown to exhibit glycosidase inhibition.[6] In relative contrast, amino pyrrolidines have only received limited attention in this area despite the fact that replacement of a hydroxyl group with an amino substituent has been shown to significantly alter the biological activity of the molecule. For example, the 2-aminomethyl pyrrolidine **2b** is a more potent inhibitor of α-mannosidase than the corresponding triol **2a**.[5] In addition, the presence of the primary amine in **2b** has been used to functionalise the molecule at this position, in a combinatorial-based approach to inhibitor discovery which has generated compounds displaying anti-cancer activity.[7] Related 2-aminomethyl pyrrolidines have also found use as ligands in analogues of the anti-cancer agent cisplatin.[8]

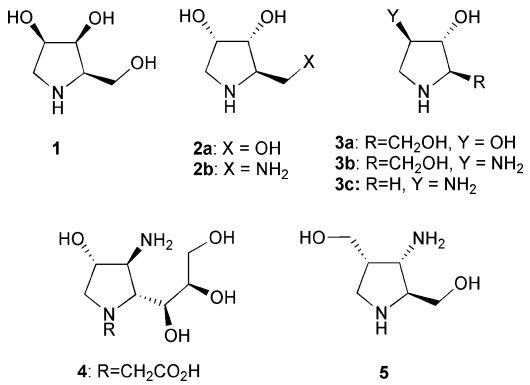

Fig. 1 Polyhydroxylated and amino pyrrolidine glycosidase inhibitors.

The introduction of amine substituents directly on the pyrrolidine ring at either the C-3 or C-4 positions has also led to the discovery of novel inhibitors. Thus, the syntheses of the 4-amino pyrrolidines **3b**[9] and **3c**[10] have been reported and the latter shown to inhibit α-mannosidase with a K_i (40 μM) comparable to that for 1-deoxymannojirimycin. Additionally, the 3-amino pyrrolidines **4** and **5** have been shown to inhibit sialidase and α-glucosidase respectively.[11,12] Related 3-amino pyrrolidines have also been synthesised although biological testing was not reported.[13,14]

The potential biological activity associated with 3-amino-4-hydroxy pyrrolidines makes them attractive synthetic targets, especially since further derivatisation through the two amine groups is also possible. Previously we have communicated the first synthesis of the 3-amino analogue of **1**.[15] In this paper we report full details of our original synthesis, together with an extension to our strategy thereby allowing access to a further two diastereoisomers of the 3-amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine moiety. In addition we also present preliminary data on the glycosidase activity of these novel compounds.

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† Electronic supplementary information (ESI) available: Synthetic and characterisation data for compounds **11–19** and **25**, X-ray structure for **25** and protocol for inhibition studies. See DOI: 10.1039/b711994a

Results and discussion

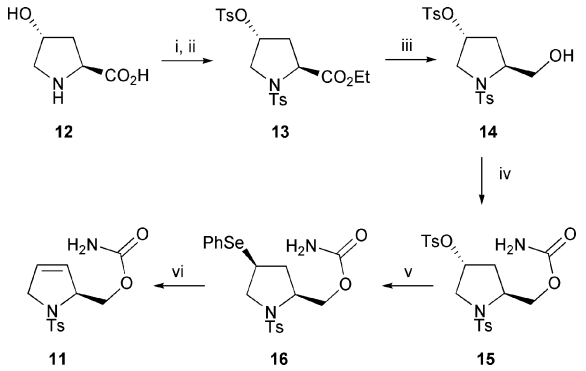
Synthesis of (2*S*,3*S*,4*R*)-3-amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine (6)

Our synthetic strategy to the target amino pyrrolidines **6–8** is outlined in Scheme 1. We envisaged that all three stereoisomers could be produced from the key intermediate **9**, a suitably protected 2,5-dihydro-pyrrole. Thus, the all *syn*-isomer **6** could be accessed using a homoallylic version of the tethered aminohydroxylation (TA) reaction developed by Donohoe and co-workers.[16] The two *anti*-amino alcohols **7** and **8** could potentially be produced *via* ring-opening of an epoxide such as **10**, in which the key elements would be control of both the facial selectivity of the epoxidation step and the regioselectivity of epoxide ring-opening.

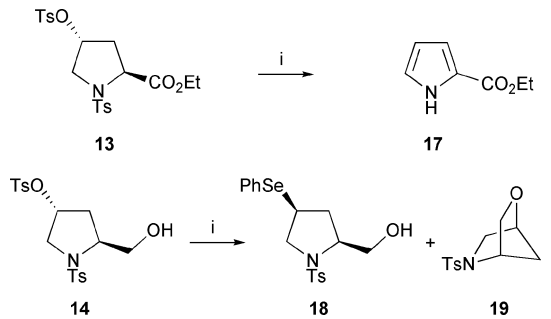
The key 2,5-dihydro-pyrrole intermediate, in the form of homoallylic carbamate **11**, was synthesised from *trans*-4-hydroxy-L-proline **12** using a modification of the route reported by Schofield and co-workers[14] (Scheme 2).

Initial conversion of **12** to the corresponding ethyl ester was followed by reaction with excess *p*-toluenesulfonyl chloride to protect the amine and activate the 4-hydroxyl group giving **13** in excellent yield.[17] Reduction of the ethyl ester using $LiBH_4$ (generated *in situ* from $NaBH_4$–LiCl)[18] produced the alcohol **14**, which was converted to the carbamate **15** by reaction with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate.[16a] Nucleophilic displacement of the *p*-toluenesulfonate ester by phenylselenide anion (generated from $(PhSe)_2$ and $NaBH_4$) proceeded smoothly to give the selenide **16** in excellent yield. Finally, oxidation of **16** resulted in spontaneous elimination of the product selenoxide to furnish the carbamate **11** in six steps from **12** and in 38% overall yield. It should be noted that attempts to introduce the phenylselanyl group at earlier stages of the synthesis were unsuccessful (Scheme 3). Thus, reaction of **13** with phenylselenide anion gave a mixture of products from which only the known pyrrole **17**[19] (formation of which is facilitated by the acidity of the C-2 proton) could be isolated in low yield. Reaction of **14** under the same conditions did generate the corresponding selenide **18**, but the major product was the bicyclic ether **19**.

With the key intermediate **11** in hand, we next turned our attention to the TA reaction to install the *syn*-amino alcohol functionality required for pyrrolidine **6** (Scheme 4). Pleasingly, reaction of **11** under the conditions reported by Donohoe and co-workers[16] led to the formation of the expected bicyclic carbamate **20** (21–40%) together with variable amounts of the isomeric 2-oxazolidinone **21** (10–28%) resulting from migration of the carbamate group—similar migrations in the TA reaction have been

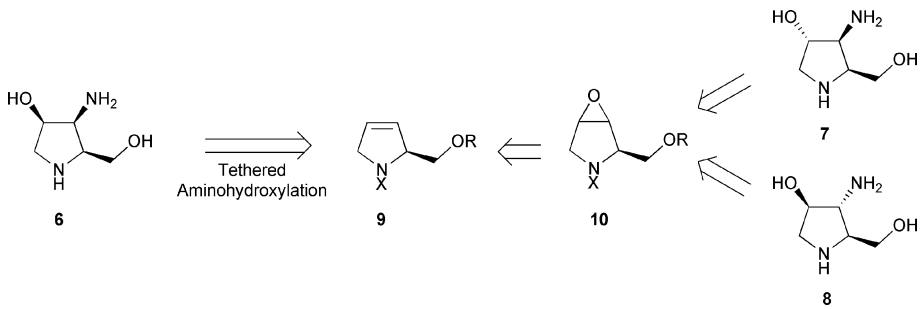


Scheme 2 *Reagents and conditions*: i, $SOCl_2$, EtOH, reflux, 98%; ii, NEt_3, TsCl, DMAP, CH_2Cl_2, rt, 96%; iii, $NaBH_4$, LiCl, THF–EtOH, 0 °C, 91%; iv, $Cl_3CCONCO$, CH_2Cl_2, 0 °C; K_2CO_3, MeOH, 0 °C, 91%; v, $(PhSe)_2$, $NaBH_4$, THF–EtOH, reflux, 94%; vi, H_2O_2, pyridine, CH_2Cl_2, 0 °C, 52%.

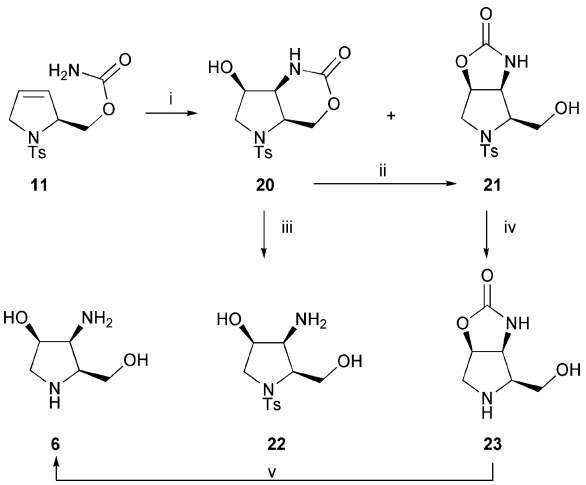


Scheme 3 *Reagents and conditions*: i, $(PhSe)_2$, $NaBH_4$, THF–EtOH, reflux, **17**: 10%, **18**: 25%, **19**: 42%.

noted elsewhere.[20] The two products were readily separable by flash column chromatography and their stereostructures confirmed by X-ray crystallographic analysis. For reactions carried out on a relatively large scale (*i.e.* > 0.5 mmol) the combined yield of **20** + **21** was consistently in the region of 50%, with recovery of *ca.* 40% of the starting material **11**; these yields are comparable with TA reactions for other homoallylic substrates carried out under Donohoe and co-workers' original conditions.[16b,c,21,22] However, smaller scale reactions (*i.e.* < 0.1 mmol) were found to be much more capricious, with overall yields for **20** + **21** varying from 4–40% suggesting incomplete turnover of the osmium catalyst and/or decomposition of the *N*-chlorocarbamate intermediate formed during the reaction.[22] Whilst we did not fully explore the equilibration between **20** and **21**, preliminary evidence suggests that the migrated product **21** is thermodynamically favoured. Thus, longer reaction times for the TA reaction resulted in greater



Scheme 1



Scheme 4 *Reagents and conditions*: i, NaOH, ^{t}BuOCl, $^{i}Pr_2NEt$ (5 mol%), $K_2Os(OH)_4O_2$ (4 mol%), ^{n}PrOH–H_2O (1 : 1), rt, **20**: 21–40%, **21**: 10–28%, recovered **11**: 38–40%; ii, $LiAlH_4$, Et_2O, reflux, 100%; iii, LiOH, H_2O–MeOH, reflux, 57%; iv, Na–NH_3, −78 °C to rt, 95%; v, LiOH, H_2O–MeOH, reflux, 35%.

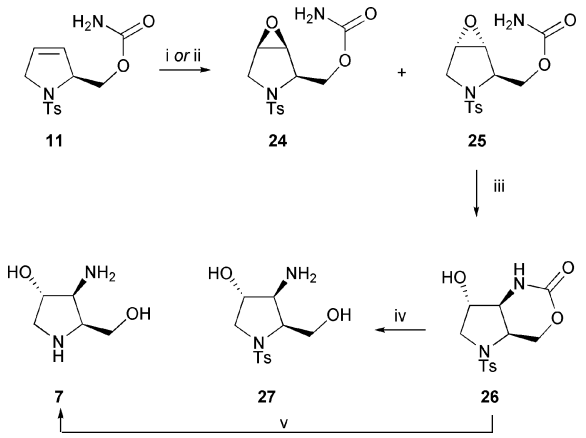
proportions of **21** (relative to **20**) being isolated and **21** was also isolated from the attempted reduction of **20** (*vide infra*). In addition, on standing in MeOH-d_4, nmr samples of **20** slowly converted to **21** whilst the reverse transformation was not observed under similar conditions.

Attempted reduction of the carbamate group in **20** using $LiAlH_4$ in refluxing ether led only to quantitative conversion to **21**, which proved surprisingly resistant to reduction under these conditions. Removal of the carbamate from **20** could be achieved by heating with LiOH in aqueous methanol[23] to give **22** (this reaction could also be carried out on a mixture of **20** and **21** to give **22** in 68% yield). Disappointingly, all efforts to remove the *N*-tosyl protecting group from **22** were unsuccessful, resulting only in decomposition. Reversal of the deprotection steps finally allowed access to the target pyrrolidine **6**. Thus, treatment of **21** with sodium in ammonia gave **23** in excellent yield and subsequent hydrolysis of the carbamate produced **6**, which was characterised and stored as its hydrochloride salt.

Synthesis of (2*S*,3*S*,4*S*)-3-amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine (7)

Having successfully secured the all *syn*-pyrrolidine **6** we turned our attention to the synthesis of the diastereoisomer **7**, epimeric at the C-4 position. We hoped to access the *anti*-amino alcohol functionality present in **7** by means of an intramolecular epoxide ring-opening strategy using the C-2 carbamate group to supply the nitrogen nucleophile. The synthetic route is shown in Scheme 5.

Initial attempts at the epoxidation of **11** with *m*CPBA gave a 1 : 3 mixture of **24**–**25** in low yield together with significant quantities (*ca.* 50%) of recovered starting material. The electron poor alkene proved more amenable to epoxidation with the dioxirane generated *in situ* from trifluoroacetone–oxone®, giving the same mixture of epoxides in an excellent 98% yield. Although the epoxides proved to be inseparable, they were assigned the relative stereochemistries shown on the basis of their H2–H3 coupling constants (**24**: $J_{2,3}$ =1.8 Hz; **25**: $J_{2,3}$ = 0 Hz) and comparison to literature



Scheme 5 *Reagents and conditions*: i, *m*CPBA, CH_2Cl_2, reflux, 31% (**24**–**25**; 1 : 3); ii, Na_2EDTA, CF_3COCH_3, oxone®, $NaHCO_3$, CH_3CN, 0 °C, 98% (**24**–**25**; 1 : 3); iii, NaOH (or ^{t}BuOK), ^{n}PrOH, ^{t}BuOCl, rt, 43–50%; iv, LiOH, H_2O–MeOH, reflux, 67%; v, Na–NH_3, −78 °C to rt, 41%.

values for similar systems.[24] This assignment was confirmed by the unambiguous synthesis of **25** *via* an alternative route (see ESI†) and X-ray analysis of **26** (*vide infra*). Working with this mixture of compounds we next investigated the intramolecular epoxide-opening of the major isomer **25** to give **26**.[25] Whilst analogous reactions (with *N*-substituted carbamates) have been successfully carried out under either basic or Lewis acidic conditions,[26] we found that treatment of **25** with a variety of reagents (*e.g.* NaH or ^{t}BuOK in refluxing THF or Me_3Al in CH_2Cl_2) gave only recovered starting material. In an effort to increase the acidity of the NH proton we prepared the corresponding *N*-benzoyl analogue of **25** (as a 4 : 1 mixture of epoxide isomers) but this derivative also resisted all attempts to carry out the key cyclisation reaction.

Our previous success with the TA reaction of **11** (Scheme 4), which involves initial deprotonation of the carbamate, prompted us to investigate this set of basic conditions next. However, prolonged heating of **25** with NaOH in ^{n}PrOH again gave only recovered starting material. Despite this failure, we repeated the reaction but this time included ^{t}BuOCl in the basic mixture in the hope that isolation of the *N*-chloro carbamate salt of **25** would provide evidence for the formation of the carbamate anion. No *N*-chloro products were isolated from this reaction, but much to our surprise the target ring-opened product **26** was produced in moderate yield. Subsequent optimisation of the reaction increased the yield to 43% when carried out with the mixture of **24** and **25** (based on the 1 : 3 ratio) although none of the minor epoxide isomer **24** could be re-isolated from the reaction. Working with the pure epoxide **25** (synthesised by an alternative route—see ESI†) increased the yield further to 50%. The predicted stereochemistry of **26** was confirmed by X-ray crystallographic analysis as shown (Fig. 2).‡ The reaction could also be carried out in comparable yields using ^{t}BuOK as the base.

The vital role played by the ^{t}BuOCl in the formation of **26** is unclear. We speculated that the reaction may involve formation of a *N*-chlorocarbamate salt as has been proposed in the mechanism

‡ For the X-ray diffraction analysis of compound **26** there are two unique molecules in the unit cell. One of the molecules is not stable to anisotropic refinement (not shown in Fig. 2) and some atoms (C7A, O1A, N1A, C1A, C2A, O3A, C3A, O4A) have been refined as isotropic.

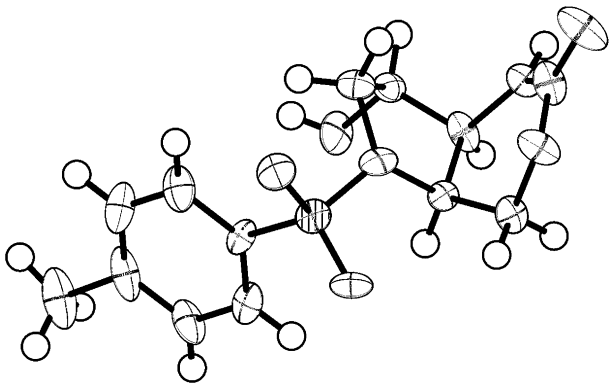


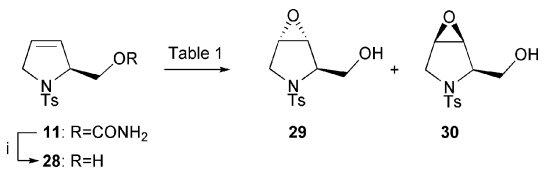
Fig. 2 X-Ray structure for **26** (ellipsoids are shown at 50% probability). There are two unique molecules in the asymmetric unit of which only one is shown.‡

for the tethered aminohydroxylation reaction.[16] However, all attempts[27] to produce and isolate the *N*-chloro analogue of **25** were unsuccessful and thus the exact nature of the hypochlorite involvement remains to be shown.

Deprotection of **26** was carried out as for the all *syn*-isomer. Thus, hydrolysis of the carbamate group was achieved by heating with LiOH in MeOH–H_2O to give **27**, but all efforts to subsequently remove the *N*-tosyl protecting group were unsuccessful. Pleasingly, treatment of **26** with excess sodium in ammonia resulted in clean removal of both tosyl and carbamate functional groups to give the novel amino pyrrolidine **7**, which was again characterised and stored as its hydrochloride salt.

Synthesis of (2*S*,3*R*,4*R*)-3-amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine (8)

In order to synthesise the amino pyrrolidine **8** we required access to a *syn*-epoxide such as the minor isomer **24** from the epoxidation reaction discussed above. We initially explored the possibility of



Scheme 6 *Reagents and conditions*: i, NaOH, ^{n}PrOH, H_2O, reflux, 87%.

Table 1 Epoxidation of alcohol **28**

Reagents	Yield (%)	Ratio (**29**–**30**)[a]
*m*CPBA	90	3 : 2
Oxone®, CF_3COCH_3	16	4 : 1
$Mo(CO)_6$, ^{t}BuO$_2$H	96	5 : 2
$VO(acac)_2$, ^{t}BuO$_2$H	—[b]	—

[a] Determined by ^{1}H-nmr. [b] Complex mixture of unidentifiable products.

hydroxyl-directed epoxidation of the alcohol **28** which could be produced from **11** by alkaline hydrolysis (Scheme 6). Epoxidation of **28** was explored with a number of reagents (Table 1) but in all cases the reaction was selective for the *anti*-epoxide **29** over the *syn*-isomer **30**; in addition the two products proved to be inseparable by chromatography. The facial selectivity seen with **28** in these reactions is in stark contrast to the results reported for the corresponding cyclopentene analogue, where up to 90% selectivity for the *syn*-epoxide can be achieved.[28]

With the failure to effect selective *syn*-epoxidation of **28** we turned our attention to an alternative approach as outlined in Scheme 7. Reaction of **28** with NBS in THF–H_2O generated the bromohydrin **31** whose stereostructure was established by X-ray analysis (Fig. 3). The selective formation of **31** again shows the preference for the alkene in **28** to undergo reaction from the opposite face to the C-2 substituent, producing the *anti*-bromonium ion which is regioselectively attacked by water at the

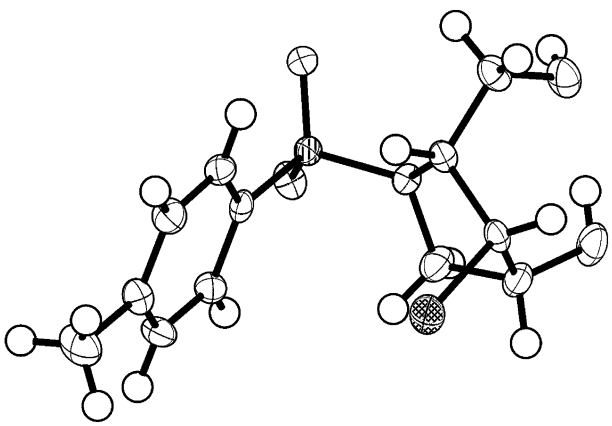
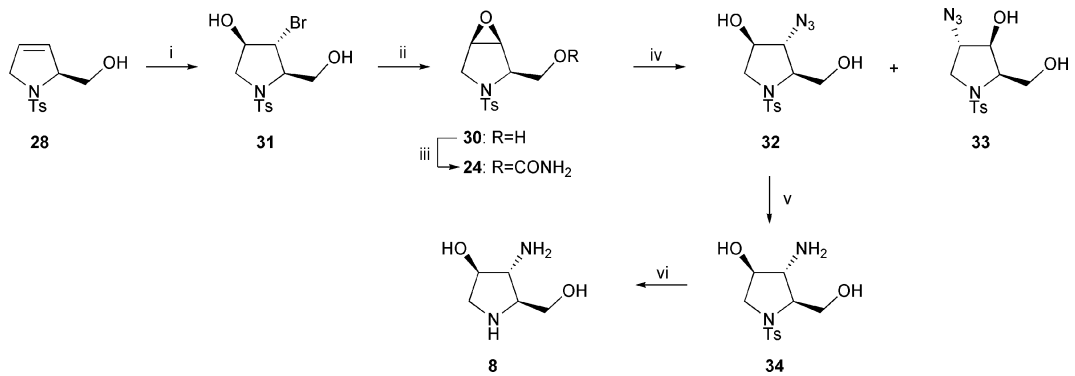


Fig. 3 X-Ray structure for **31** (ellipsoids are shown at 50% probability).



Scheme 7 *Reagents and conditions*: i, NBS, THF–H_2O, rt, 59%; ii, ^{t}BuOK, toluene, rt, 99%; iii, $Cl_3CCONCO$, CH_2Cl_2, 0 °C; then K_2CO_3, MeOH, 0 °C, 65%; iv, NaN_3, NH_4Cl, acetone–water, reflux, **32**: 58%, **33**: 32%; v, H_2, Pd/C, THF–H_2O, 97%; vi, Na–NH_3, −78 °C to rt, 38%.

C-4 position. Treatment of **31** with base gave the *syn*-epoxide **30**, which was converted to the carbamate **24** under standard conditions. All attempts at intramolecular epoxide ring-opening with **24** (using the same conditions as for the transformation **25** → **26**) were unsuccessful, giving only recovered starting material or generating the hydrolysis product **30**. Fortunately, an intermolecular reaction proved much more successful and treatment of **30** with sodium azide gave the ring-opened products **32**–**33** in a 2 : 1 ratio. The X-ray structure of the major isomer **32** (Fig. 4) revealed that it had arisen from nucleophilic attack by the azide at the C-3 position. The regioselectivity observed in this reaction may be due to the presence of unfavourable eclipsing interactions between the C-2 and C-3 substituents in the minor isomer **33** and the transition state leading to it. However, ring-opening of a similar pyrrolidine *syn*-epoxide has been reported to take place with preferential nucleophilic attack at the C-4 position under the same reaction conditions,[14] and so the origin of selectivity is far from clear.

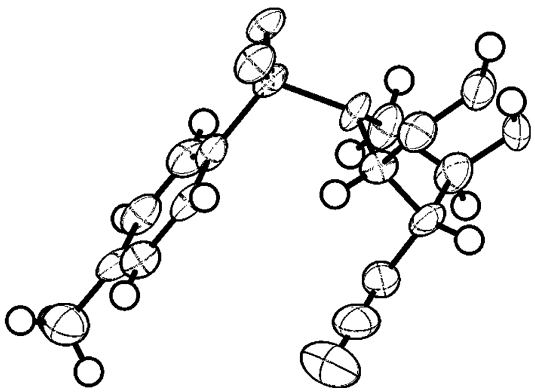


Fig. 4 X-Ray structure for **32** (ellipsoids are shown at 50% probability and some hydrogen atoms have been omitted for clarity). There are two unique molecules in the asymmetric unit of which only one is shown.

To complete the synthesis, reduction of the azide **32** gave the amine **34** and removal of the *N*-tosyl protecting group generated the novel amino pyrrolidine **8**, which was characterised and stored as its hydrochloride salt.

Glycosidase inhibition

Inhibition assays were performed with two of the novel amino pyrrolidines. Both **6** and **7** were moderately active against bovine liver β-galactosidase with 57 and 52% inhibition respectively (at 1 mg ml^{-1} of the corresponding hydrochloride salt; *ca.* 0.85 mM under the assay conditions). Compound **6** also displayed 36% inhibition of α-galactosidase (from green coffee beans) under these conditions. No significant activity (<20% inhibition) was seen with **6** or **7** against a variety of other glycosidase enzymes in these preliminary screens. These activities can be compared with those for the corresponding hydroxy pyrrolidines. Thus, triol **1** is a much stronger inhibitor of α-galactosidase (50% inhibition at 0.2 μM)[4] than the corresponding 3-amino pyrrolidine **6**. The triol analogue of **7** has been reported to be a moderate inhibitor of β-glucosidase ($K_i = 7.1$ mM) and α-galactosidase (50% inhibition at 0.32 mM),[29] whereas amino pyrrolidine **7** showed no significant activity against these enzymes.

Conclusions

We have reported the asymmetric synthesis of 3 stereoisomers of 3-amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine **6**–**8** by a divergent route starting from *trans*-4-hydroxy-L-proline. Preliminary biological testing indicates that two of these novel compounds are moderate inhibitors of β-galactosidase. In addition, the synthetic routes described provide access to a number of differentially protected intermediates of **6**–**8** which potentially allows for further derivatisation of the pyrrolidine core as an approach to discover novel glycosidase inhibitors.

Experimental

General

All reactions were performed under an inert atmosphere of nitrogen in flame dried glassware unless otherwise stated. Organic solvents were dried by distillation from the following as required: THF (sodium–benzophenone), diethyl ether ($LiAlH_4$), CH_2Cl_2, MeOH and triethylamine (CaH_2). All other reagents and solvents were purified by standard literature procedures.[30] Thin layer chromatography (TLC) analysis was performed using silica gel 60 F254 aluminium TLC plates, Merck 5554. Flash column chromatography was carried out using sorbsil C60 silica gel. Melting points were measured using a Kofler hotstage and are uncorrected. Infrared (IR) spectra were collected as liquid films between NaCl discs using a Perkin Elmer 1600 FT-IR spectrometer, IR spectra of solids were recorded using a Perkin Elmer FT-IR spectrometer with an ATR attachment. Fast atom bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H spectrometer using xenon and *m*-nitrobenzyl alcohol as the matrix. Electrospray (ES) mass spectra were recorded on a Micromass Quattro LC spectrometer. High resolution mass spectrometry was measured on a Kratos Concept 1H spectrometer using peak matching to stable reference peaks, depending on the technique used. Optical rotations were measured using a Perkin Elmer 341 polarimeter at a wavelength of 598 nm. NMR spectra were recorded using Bruker ARX 250, AM 300 or DRX 400 spectrometers. Chemical shifts are reported in parts per million downfield from TMS and using residual protic solvent as an internal standard. *J* coupling constants are reported in Hz and the measured values are corrected to one decimal place. ^{13}C NMR experiments were all accumulated with proton decoupling and DEPT experiments were used to aid carbon assignment. Where required, assignments were confirmed by two-dimensional homonuclear (^1H–^1H) and heteronuclear (^1H–^{13}C) correlation spectroscopy.

(2*S*,3*S*,4*R*)-4-Hydroxy-2,3-(oxazin-2-one)-1-(toluene-4-sulfonyl)-pyrrolidine (20) and (2*S*,3*S*,4*R*)-2-hydroxymethyl-3,4-(oxazol-2-one)-1-(toluene-4-sulfonyl)pyrrolidine (21)

All but a few drops of a freshly prepared solution of aqueous NaOH (11.4 ml, 0.08 mol dm^{-3}, 0.91 mmol) was added to a solution of **11** (0.30 g, 1.0 mmol) in ^{n}PrOH (12.1 ml). After 5 min ^{t}BuOCl (0.13 g, 1.0 mmol) was added to the reaction which was stirred for a further 5 min before ^{i}Pr$_2$NEt (0.005 g, 0.007 ml, 0.05 mmol) was added. After another 5 min period $K_2Os(OH)_4O_2$ (0.015 g, 0.04 mmol), dissolved in the remaining aqueous NaOH

solution, was also added and a green colour was observed, which slowly changed to a dark brown–black. After 2 h sodium sulphite (0.5 g) was added and the solution stirred for 30 min. The reaction mixture was then extracted with ethyl acetate (3 × 20 ml), the organic layers were combined and washed with water (20 ml) and brine (20 ml). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting crude material was purified by flash column chromatography on silica (1 : 99, methanol–ethyl acetate) to give **20** (0.066 g, 21%) as a white solid and **21** (0.091 g, 28%) as an off-white solid, together with recovered **11** (0.115 g, 38%).

Data for **20**: mp 104–108 °C; $[\alpha]_D^{20}$ −24.7 (c = 0.29 MeOH); ν_{max}(solid)/cm^{-1} 3260 br (NH/OH), 1701 s (C=O), 1480 w, 1424 m, 1340 m, 1285 w, 1157 s, 1065 m, 993 m, 769 m, 666 s; δ_H (300 MHz, CD_3OD) 2.45 (3H, s, Ar 4-Me), 3.23 (1H, dd, J 11.1, 6.0, *H*H-5), 3.45 (1H, dd, J 11.1, 6.0, H*H*-5), 3.73 (1H, dd, J 6.9, 4.2, H-3), 3.80 (1H, app td, J 6.0, 4.2, H-4), 4.00 (1H, ddd, J 6.9, 6.0, 3.0, H-2), 4.33 (1H, dd, J 11.4, 3.0, C*H*HO), 4.54 (1H, dd, J 11.4, 6.0, CH*H*O), 7.45 (2H, d, J 8.1, 2 × Ar H-3), 7.78 (2H, d, J 8.1, 2 × Ar H-2); δ_C (75 MHz, CD_3OD) 22.4 (CH_3), 54.2 (CH_2), 54.9 (CH), 57.6 (CH), 70.0 (CH_2), 71.8 (CH), 129.6 (2 × CH), 131.2 (2 × CH), 136.1 (C), 146.7 (C), 157.8 (C); (ES) m/z (%) 313 (M + H$^+$, 100%), 330 (65, M + NH_4^+); accurate mass (FAB) found 313.0858 (M + H$^+$ $C_{13}H_{17}N_2O_5S$ requires 313.0858)

A single crystal of **20** was obtained by recrystallisation from $CHCl_3$–MeOH.§

Data for **21**: mp 100–102 °C; $[\alpha]_D^{20}$−49.0 (c = 1.14 MeOH); ν_{max}(solid)/cm^{-1} 3289 br (NH/OH), 1730 s (C=O), 1599 m, 1404 w, 1349 m, 1242 m, 1160 s, 970 w; δ_H (400 MHz, CD_3OD): 2.45 (3H, s, Ar 4-Me), 2.91 (1H, app td, J 9.0, 5.2, H-2), 3.06 (1H, dd, J 12.0, 5.2, *H*H-5), 3.66 (1H, dd, J 11.2, 9.0, C*H*HO), 3.72 (1H, dd, J 12.0, 0.8, H*H*-5), 4.25 (1H, dd, J 11.2, 5.2, CH*H*O), 4.35 (1H, dd, J 9.0, 6.0, H-3), 4.91 (1H, ddd, J 6.0, 5.2, 0.8, H-4), 7.47 (2H, d, J 8.4, 2 × Ar H-3), 7.72 (2H, d, J 8.4, 2 × Ar H-2); δ_C (100.6 MHz, CD_3OD) 20.1 (CH_3), 55.8 (CH_2), 58.4 (CH), 59.5 (CH_2), 63.4 (CH), 76.3 (CH), 127.9 (2 × CH), 129.7 (2 × CH), 131.2 (C), 144.8 (C), 160.0 (C); (ES) m/z (%): 313 (M + H$^+$, 100%), 330 (68, M + NH_4^+); accurate mass (FAB) found 313.0858 (M + H$^+$ $C_{13}H_{17}N_2O_5S$ requires 313.0858); anal. found C, 49.75; H, 5.16; N, 8.81; $C_{13}H_{16}N_2O_5S$ requires C, 49.99; H, 5.16; N, 8.97%.

A single crystal of **21** (together with a molecule of $CHCl_3$) was obtained by recrystallisation from $CHCl_3$–MeOH.§

(2*S*,3*S*,4*R*)-3-Amino-4-hydroxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine (22)

LiOH (0.036 g, 1.5 mmol) was added to a solution of **20** (0.055 g, 0.18 mmol) dissolved in MeOH (0.4 ml) and water (1.6 ml) and the mixture was heated at reflux for 1.5 h. The solution was cooled and the solvent removed under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica (20 : 80, methanol–ethyl acetate) to give **22** (0.029 g, 57%) as a white solid; mp 132–135 °C; $[\alpha]_D^{20}$ −57.6 (c = 2.6 MeOH); ν_{max}(solid)/cm^{-1} 3330 w (OH/NH), 2888 w, 1599 w, 1467 w, 1341 m, 1236 w, 1152 s, 1030 m, 809 m, 675 s; δ_H (400 MHz, D_2O) 2.39 (3H, s, Ar 4-Me), 3.06 (1H, dd, J 8.8, 4.4, H-3), 3.28 (1H, dd, J 11.6, 3.6, *H*H-5), 3.38 (1H, dd, J 11.6, 1.2, H*H*-5), 3.69 (1H, app td, J 4.4, 2.8, H-2), 3.72 (1H, dd, J 12.4, 2.8, C*H*HO), 3.85 (1H, dd, J 12.4, 4.4, CH*H*O), 3.93 (1H, ddd, J 8.8, 3.6, 1.2, H-4), 7.44 (2H, d, J 8.0, 2 × Ar H-3), 7.72 (2H, d, J 8.0, 2 × Ar H-2); δ_C (100.6 MHz, D_2O) 20.7 (CH_3), 54.4 (CH_2), 58.9 (CH), 59.8 (CH_2), 61.7 (CH), 70.3 (CH), 127.5 (2 × CH), 130.2 (2 × CH), 131.3 (C), 145.7 (C); (ES) m/z (%) 287 (M + H$^+$, 100%), 573 (28, 2 M + H$^+$); accurate mass (FAB) found 287.1066 (M + H$^+$ $C_{12}H_{19}N_2O_4S$ requires 287.1066).

The above reaction was also carried out on a mixture of **20**–**21** (*ca.* 1 : 1) to give **22** in 68% yield.

(2*S*,3*S*,4*R*)-2-Hydroxymethyl-3,4-(oxazol-2-one)pyrrolidine (23)

The carbamate **21** (0.011 g, 0.036 mmol) was placed in a three necked flask fitted with a dry ice condenser and dissolved in a minimal amount of liquid ammonia (*ca.* 5 ml) at −78 °C. Sodium metal (0.0021 g, 0.09 mmol) was then added portion-wise to the stirring reaction mixture. After the addition of sodium was complete the reaction was warmed to room temperature and the liquid ammonia allowed to evaporate. The crude residue was dissolved into water and transferred to a round bottom flask. The water was removed under reduced pressure and the resulting crude material was purified by flash column chromatography on silica (25 : 75, methanol–ethyl acetate) to give **23** (0.0054 g, 95%) as a yellow oil; $[\alpha]_D^{20}$ −18.5 (c = 0.8 MeOH); ν_{max}(film)/cm^{-1} 3255 w (OH/NH), 1736 s (C=O), 1558 s, 1406 s, 1228 w, 1097 w, 1036 m, 956 w; δ_H (400 MHz, CD_3OD) 2.87 (1H, dd, J 13.2, 4.8, *H*H-5), 2.95 (1H, ddd, J 7.2, 6.4, 4.8, H-2), 3.23 (1H, d, J 13.2, H*H*-5), 3.64 (1H, dd, J 10.8, 7.2, C*H*HO), 3.73 (1H, dd, J 10.8, 6.4, CH*H*O), 4.31 (1H, dd, J 7.2, 4.8, H-3), 5.12 (1H, dd, J 7.2, 4.8, H-4); δ_C (100.6 MHz, CD_3OD) 52.5 (CH_2), 57.9 (CH), 59.6 (CH_2), 61.3 (CH), 81.8 (CH), 160.8 (C); (ES) m/z (%) 159 (M + H$^+$, 100%); accurate mass (FAB) found 159.0770 (M + H$^+$ $C_6H_{11}N_2O_3$ requires 159.0770).

(2*S*,3*S*,4*R*)-3-Amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine (6)

LiOH (0.025 g, 1.04 mmol) was added to a solution of **23** (0.011 g, 0.06 mmol) in MeOH (0.14 ml) and water (0.56 ml). The mixture was heated at reflux for 1.5 h before being cooled and the solvent was then removed under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica (100% methanol basified with NH_3) to give **6** (0.032 g, 35%) as an orange oil. To aid analysis dilute HCl (aq) was added to the amine in water until the solution was pH 2–3, yielding the corresponding hydrochloride salt of **6**; ν_{max}(solid)/cm^{-1}: 3323 w (OH/NH), 2032 w, 1393 w, 1347 w, 1151 m, 1020 m, 978 m; δ_H (400 MHz, D_2O) 3.49 (1H, dd, J 12.8, 3.6, *H*H-5), 3.54 (1H, dd, J 12.8, 2.0, H*H*-5), 4.02 (1H, dd, J 12.4, 6.0, C*H*HO), 4.06 (1H, dd, J 12.4, 4.8, CH*H*O), 4.16 (1H, ddd, J 9.2, 6.0, 4.8, H-2), 4.24 (1H, dd, J 9.2, 4.8, H-3), 4.79–4.81 (1H, m obscured by HOD peak, H-4); δ_C (100.6 MHz, D_2O) 50.7 (CH_2), 52.2 (CH), 57.1 (CH_2), 58.1 (CH), 67.8 (CH); accurate mass (FAB) found 133.0975 (M + H$^+$ $C_5H_{13}N_2O_2$ requires 133.0977).

§ CCDC reference numbers 656329–656332 and 656489. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b711994a

(2*R*,3*S*,4*R*)-2-Carbamoyloxymethyl-3,4-epoxy-1-(toluene-4-sulfonyl)pyrrolidine (24) and (2*R*,3*R*,4*S*)-2-carbamoyloxymethyl-3,4-epoxy-1-(toluene-4-sulfonyl)pyrrolidine (25)

Na_2EDTA (3.92 ml, 4×10^{-4} mol dm^{-3}, 0.0015 mmol) and trifluoroacetone (0.97 g, 0.77 ml, 8.6 mmol) were added to a 0 °C solution of **11** (0.231 g, 0.78 mmol) dissolved in acetonitrile (12 ml). Solid $NaHCO_3$ (0.52 g, 6.3 mmol) mixed with oxone® (2.41 g, 3.9 mmol) was then added to the solution portion-wise over 1 h. The reaction mixture was stirred a further 2 h before sodium sulphate (~1 g) and dichloromethane (30 ml) were added. The mixture was filtered and the filtrate was concentrated under vacuum to yield an inseparable 1 : 3 mixture of **24** and **25** (0.239 g, 98%). Data for isomeric mixture; minor isomer **24**: δ_H (300 MHz, $CDCl_3$) 2.45 (3H, s, Ar 4-Me), 3.27 (1H, dd, *J* 11.7, 1.8, *H*H-5), 3.65 (1H, dd, *J* 3.0, 1.8, H-4), 3.69 (1H, dd, *J* 9.3, 4.5, 1.8, H-2), 3.72 (1H, dd, *J* 3.0, 1.8, H-3), 3.75 (1H, d, *J* 11.7, H*H*-5), 3.14 (1H, dd, *J* 10.5, 9.3, C*H*HO), 4.73 (2H, s br, NH_2), 4.84 (1H, dd, *J* 10.5, 4.5, CH*H*O), 7.35 (2H, d, *J* 8.0, 2 × Ar H-3), 7.74 (2H, d, *J* 8.0, 2 × Ar H-2); δ_C (75 MHz, $CDCl_3$) 21.6 (CH_3), 50.5 (CH_2), 54.8 (CH), 57.7 (CH), 57.9 (CH), 63.5 (CH_2), 127.8 (2 × CH), 129.9 (2 × CH), 133.5 (C), 144.2 (C), 156.1 (C). Major isomer **25**: δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s, Ar 4-Me), 3.53 (1H, d, *J* 12.9, *H*H-5), 3.55 (2H, s, H-3, H-4), 3.68 (1H, d, *J* 12.9, H*H*-5), 4.07 (1H, dd, *J* 5.7, 4.2, H-2), 4.27 (1H, dd, *J* 11.4, 5.7, C*H*HO), 4.41 (1H, dd, *J* 11.4, 4.2, CH*H*O), 4.69 (2H, br s, NH_2), 7.32 (2H, d, *J* 8.0, 2 × Ar H-3), 7.65 (2H, d, *J* 8.0, 2 × Ar H-2); δ_C (75 MHz, $CDCl_3$) 19.6 (CH_3), 47.2 (CH_2), 52.9 (CH), 54.7 (CH_2), 57.8 (CH), 62.7 (CH), 125.6 (2 × CH), 127.6 (2 × CH), 132.9 (C), 141.9 (C), 154.5 (C).

A pure sample of **25** was also produced by an alternative synthetic route—full details are given in the ESI.†

(2*S*,3*S*,4*S*)-4-Hydroxy-2,3-(oxazin-2-one)-1-(toluene-4-sulfonyl)pyrrolidine (26)

Potassium *tert*-butoxide (0.20 g, 0.66 mmol) was added to a solution of **25** (0.200 g, 0.66 mmol; 3 : 1 mixture of isomers **25**–**24**) dissolved in ^{n}PrOH (8 ml). The solution was stirred for 5 min, ^{t}BuOCl (0.073 g, 0.66 mmol) was added and the reaction mixture was stirred for a further 2 h before the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography on silica (1 : 99, methanol–ethyl acetate) to give **26** (0.064 g, 31%; 43% based on **25**) as a white solid; mp 216–219 °C; $[a]_D^{20}$ −115.3 (*c* = 1.04 MeOH); ν_{max}(solid)/cm^{-1} 3262 br (NH/OH), 1702 s (C=O), 1596 w, 1408 w, 1341 m, 1157 s, 1065 m, 958 w; δ_H (300 MHz, CD_3OD) 2.41 (3H, s, Ar 4-Me), 3.40 (1H, d, *J* 12.0, *H*H-5), 3.55 (1H, dd, *J* 12.0, 3.3, H*H*-5), 3.73 (1H, d, *J* 5.4, H-3), 3.91–3.94 (2H, br m, H-4, H-2), 4.36 (1H, d, *J* 12.0, C*H*HO), 4.67 (1H, dd, obscured by HOD peak, *J* 12.0, 2.4, CH*H*O), 7.37 (2H, d, *J* 8.1, 2 × Ar H-3), 7.74 (2H, d, *J* 8.1, 2 × Ar H-2); δ_C (75 MHz, CD_3OD) 22.4 (CH_3), 56.0 (CH), 57.1 (CH_2), 62.3 (CH), 69.2 (CH_2), 75.2 (CH), 129.9 (2 × CH), 131.6 (2 × CH), 136.5 (C), 146.2 (C), 157.1 (C); (ES) *m*/*z* (%) 252 (M − (OH + CONH), 100%), 313 (33, M + H^+), 236 (M − ($OHNHCO_2$)); accurate mass (FAB) found 313.0858 (M + H^+ $C_{13}H_{17}N_2O_5S$ requires 313.0858). Anal. found C, 49.82; H, 4.91; N, 8.80; $C_{13}H_{16}N_2O_5S$ requires C, 49.99; H, 5.16; N, 8.97%.

The same procedure could be carried out with a pure sample of **25** to give **26** in 50% yield.

A single crystal of **26** was obtained by recrystallisation from CH_2Cl_2–MeOH. Crystal data: $C_{13}H_{16}N_2O_5S$, M = 312.34, monoclinic, a = 11.501 (3), b = 6.2268 (17), c = 19.785 (6) Å, U = 1416.6 (7) Å^3, T = 150(2) K, space group $P2_1$, Z = 4, absorption coefficient = 0.252 mm^{-1}, 9300 reflections measured, 4877 unique (R_{int} = 0.0988), absolute structure parameter = 0.1(2). The final $wR(F^2)$ was 0.2799 for all data. CCDC deposition number 656330.‡§

(2*S*,3*S*,4*S*)-3-Amino-4-hydroxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine (27)

LiOH (0.016 g, 0.66 mmol) was added to a solution of **26** (0.026 g, 0.08 mmol) dissolved in MeOH (0.1 ml) and water (0.4 ml) and the mixture was heated at reflux for 1.5 h. The solution was cooled and the solvent removed under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica (20 : 80, methanol–ethyl acetate) to give **27** (0.016 g, 68%) as a white solid; mp 54–56 °C; $[a]_D^{20}$ −18.9 (*c* = 1.0 MeOH); ν_{max}(solid)/cm^{-1} 3361 br (NH/OH), 2944 w, 1597 m, 1402 w, 1335 m, 1090 m, 1025 m, 816 w; δ_H (400 MHz, D_2O) 2.44 (3H, s, Ar 4-Me), 3.02 (1H, dd, *J* 10.4, 7.0, *H*H-5), 3.11 (1H, app t, *J* 7.0, H-3), 3.77 (1H, dd, *J* 10.4, 7.0, H*H*-5), 3.81 (1H, ddd, *J* 7.0, 4.8, 3.2, H-2), 3.87 (1H, dd, *J* 12.4, 3.2, C*H*HO), 3.92 (1H, dd, *J* 12.4, 4.8, CH*H*O), 4.27 (1H, app q, *J* 7.0, H-4), 7.48 (2H, d, *J* 8.0, 2 × Ar H-3), 7.77 (2H, d, *J* 8.0, 2 × Ar H-2); δ_C (100.6 MHz, D_2O) 20.7 (CH_3), 52.5 (CH_2), 58.0 (CH), 60.5 (CH_2), 61.3 (CH), 73.3 (CH), 127.6 (2 × CH), 130.1 (2 × CH), 133.3 (C), 145.7 (C); (ES) *m*/*z* (%): 287 (M + H^+, 100%); accurate mass (FAB) found 287.1065 (M + H^+ $C_{12}H_{19}N_2O_4S$ requires 287.1066).

(2*S*,3*S*,4*S*)-3-Amino-4-hydroxy-2-(hydroxymethyl)pyrrolidine (7)

The carbamate **26** (0.031 g, 0.098 mmol) was placed in a three necked flask fitted with a dry ice condenser and dissolved in a minimal amount of liquid ammonia (*ca.* 5 ml) at −78 °C. Sodium metal (0.0056 g, 0.24 mmol) was then added portion-wise to the stirring reaction mixture. After the addition of sodium was complete the reaction was warmed to room temperature and the liquid ammonia was allowed to evaporate. The crude residue was dissolved in water and transferred to a round bottom flask. Water was removed under reduced pressure and the resulting crude material was purified by flash column chromatography on silica (100% methanol) to give **7** (0.0061 g, 41%) as a yellow oil. To aid analysis dilute HCl (aq) was added to the amine in water until the solution was pH 2–3, yielding the corresponding hydrochloride salt of **7**. $[a]_D^{20}$ +7.8 (*c* = 0.61 MeOH) ν_{max}(solid)/cm^{-1} 3326 w (OH/NH), 2022 w, 1599 w, 1396 w, 1347 w, 1157 m, 1037 m, 978 m, 767 m; δ_H (400 MHz, D_2O) 3.36 (1H, dd, *J* 12.8, 4.4, *H*H-5), 3.73 (1H, dd, *J* 12.8, 5.2, H*H*-5), 3.98 (1H, dd, *J* 12.4, 3.6, CH*H*O), 4.02 (1H, dd, *J* 7.2, 4.0, H-3), 4.07 (1H, dd, *J* 12.4, 3.6, CH*H*O) 4.31 (1H, d app t, *J* 7.2, 3.6, H-2), 4.63–4.74 (1H, m obscured by HOD peak, H-4); δ_C (100.6 MHz, D_2O) 49.6 (CH_2), 56.6 (CH_2), 57.1 (CH), 58.4 (CH), 71.9 (CH); (ES) *m*/*z* (%) 133 (M + H^+, 100%); accurate mass (FAB) found 133.0976 (M + H^+ $C_5H_{13}N_2O_2$ requires 133.0977).

(*S*)-2-Hydroxymethyl-1-(toluene-4-sulfonyl)-2,5-dihydro-1*H*-pyrrole (28)

An aqueous solution of NaOH (2.2 ml of a 0.5 M solution) was added to **11** (0.11 g, 0.37 mmol) dissolved in ^{n}PrOH (4.4 ml). The reaction mixture was refluxed for 1 h before the solvent was removed under reduced pressure. The resulting aqueous material was extracted with ethyl acetate (3 × 10 ml), the organic layers were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to give **28** (0.08 g, 87%) as an off-white solid; mp 99–100 °C; $[a]_D^{20}$ −162.5 (c = 1.28 MeOH); ν_{max}(solid)/cm^{-1} 3524 (OH), 2941 w, 1595, 1492 w, 1377 m, 1334 s, 1203 w, 1155 s, 1089 m, 1036 s, 844 w, 816 s; δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, Ar 4-Me), 3.69 (1H, dd, J 11.7, 5.5, C*H*HO), 3.79 (1H, dd, J 11.7, 3.5, CH*H*O), 4.12 (1H, d app q, J 15.0, 2.2, *H*H-5), 4.21 (1H, dd app t, J 15.0, 5.5, 2.2, H*H*-5), 4.43–4.48 (1H, m, H-2), 5.54 (1H, dq, J 6.3, 2.2, H-3), 5.71 (1H, ddd, J 6.3, 5.5, 2.2, H-4), 7.32 (2H, d, J 8.4, 2 × Ar H-3), 7.71 (2H, d, J 8.4, 2 × Ar H-2); δ_C (100.6 MHz, $CDCl_3$) 21.6 (CH_3), 56.4 (CH_2), 65.8 (CH_2), 69.4 (CH), 126.6 (CH), 126.8 (CH), 127.6 (2 × CH), 129.9 (2 × CH), 133.9 (C), 144.0 (C); (ES) m/z (%) 236 (M − OH, 100%), 254 (98, M + H$^+$), 155 (92, $CH_3C_6H_4SO_2^+$); accurate mass (FAB) found 254.0851 (M + H$^+$ $C_{12}H_{16}NO_3S$ requires 254.0851).

(2*R*,3*R*,4*R*)-3-Bromo-4-hydroxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine (31)

NBS (1.37 g, 7.70 mmol) was added to a solution of **28** (0.97 g, 3.85 mmol) in THF (27.7 ml) and water (3.18 ml) and the mixture stirred in the dark for 4 h. The reaction mixture was diluted with diethyl ether (50 ml) and washed with water (50 ml). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting crude material was purified by flash column chromatography on silica (40 : 60, ethyl acetate–petroleum ether) to give **31** (0.54 g, 41%) as a white solid. The yield of **31** was increased to 0.786 g (59%) by recrystallisation of a mixed fraction with chloroform; mp 164–168 °C; $[a]_D^{20}$ −43.6 (c = 1.09 MeOH); ν_{max}(CH_2Cl_2)/cm^{-1} 3175 w, 2877 w, 1596 m, 1455 m, 1348 m, 1165 s, 1074 m, 1032 m, 822 m, 663 s; δ_H (300 MHz, $CDCl_3$) 2.45 (3H, s, Ar 4-Me), 3.65 (2H, d, J 3.0, CH_2O), 3.82 (1H, dd, J 12.0, 1.8, *H*H-5), 4.01 (1H, ddd, J 3.6, 3.3, 1.8, H-4), 4.08 (1H, br s, H-3), 4.15 (1H, dd, J 12.0, 3.6, H*H*-5), 4.19 (1H, br s, H-2), 7.36 (2H, d, J 8.1, 2 × Ar H-3), 7.74 (2H, d, J 8.1, 2 × Ar H-2); δ_C (75 MHz, 300 MHz, $CDCl_3$) 21.5 (CH_3), 53.5 (CH), 55.3 (CH_2), 65.0 (CH_2), 71.5 (CH), 77.5 (CH), 127.6 (2 × CH), 129.6 (2 × CH), 134.5 (C), 143.9 (C); (ES) m/z (%) 352 (M(^{81}Br) + H$^+$, 100%), 350 (90, M(^{79}Br) + H$^+$); accurate mass (FAB) 350.0061 found (M + H$^+$ $C_{12}H_{17}{}^{79}BrNO_4S$ requires 350.0062); anal. found C, 41.12; H, 4.82; N, 3.82; $C_{12}H_{16}BrNO_4S$ requires C, 41.15; H, 4.60; N, 3.99%.

A single crystal of **31** was obtained by recrystallisation from CH_2Cl_2–MeOH. Crystal data: $C_{12}H_{16}BrNO_4S$, M = 350.23, orthorhombic, a = 7.5443 (6), b = 10.6588 (9), c = 17.4366 (15) Å, U = 1402.1 (2) Å^3, T = 150(2) K, space group $P2_12_12_1$, Z = 4, absorption coefficient = 3.089 mm^{-1}, 11010 reflections measured, 2752 unique (R_{int} = 0.0337), absolute structure parameter = −0.003(7). The final $wR(F^2)$ was 0.0661 for all data. CCDC deposition number 656331.§

(2*R*,3*S*,4*R*)-3,4-Epoxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine (30)

Potassium *tert*-butoxide (0.062 g, 0.55 mmol) was added to a solution of **31** (0.18 g, 0.50 mmol) in toluene (5 ml) and the reaction mixture stirred for 2 h. The mixture was diluted with diethyl ether (10 ml) and the organic extract washed with water (10 ml). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give **30** (0.135 g, 99%) as a white solid; mp 128–131 °C; $[a]_D^{20}$ −104.9 (c = 1.45 MeOH); ν_{max}(CH_2Cl_2)/cm^{-1} 3547 m (OH), 2961 w, 2896 w, 1597 w, 1405 w, 1336 s, 1306 m, 1160 s, 1092 s, 1038 s, 864 s, 817 s, 707 m; δ_H (300 MHz, $CDCl_3$) 2.33 (1H, br s, OH), 2.46 (3H, s, Ar 4-Me), 3.27 (1H, dd, J 11.7, 1.8, *H*H-5), 3.56 (1H, app td, J 5.2, 2.1, H-2), 3.61 (1H, dd, J 3.0, 1.8, H-4), 3.76 (1H, dd, J 3.0, 2.1, H-3), 3.80 (1H, d, J 11.7, H*H*-5), 3.98 (1H, dd, J 11.7, 5.2, C*H*HO), 4.15 (1H, dd, J 11.7, 5.2, CH*H*O), 7.36 (2H, d, J 8.1, 2 × Ar H-3), 7.72 (2H, d, J 8.1, 2 × Ar H-2); δ_C (75 MHz, $CDCl_3$) 21.6 (CH_3), 50.9 (CH_2), 53.8 (CH), 58.4 (CH), 61.7 (CH), 63.0 (CH_2), 127.7 (2 × CH), 129.9 (2 × CH), 133.2 (C), 144.3 (C); (ES) m/z (%) 292 (M + Na$^+$, 100%), 270 (49, M + H$^+$); accurate mass (FAB) 270.0800 found (M + H$^+$ $C_{12}H_{16}NO_4S$ requires 270.0800); anal. found C, 53.38; H, 5.77; N, 5.05; $C_{12}H_{15}NO_4S$ requires C, 53.50; H, 5.61; N, 5.20%.

(2*R*,3*S*,4*R*)-1-(Toluene-4-sulfonyl)-2-(carbamoyloxymethyl)-3,4-epoxypyrrolidine (24)

The alcohol **30** (0.057 g, 0.21 mmol) was dissolved in dichloromethane (0.45 ml) and formation of the carbamate was achieved following the procedure described for **15** using trichloroacetylisocyanate (0.38 g, 0.024 ml, 0.32 mmol). After 1 h TLC analysis confirmed all starting material had been consumed. The crude material was dissolved in methanol (1 ml) and hydrolysis was achieved using aqueous potassium carbonate (1.28 ml, 0.5 mol dm^{-3}, 0.64 mmol). After 18 h the reaction was worked up as before to give **24** as a white solid (0.043 g, 65%); NMR data as above. Additional data; mp 185–188 °C; $[a]_D^{20}$ −122.32 (c = 0.89 MeOH); ν_{max}(solid)/cm^{-1} 3450 w (NH_2), 3355 w, 2974 w, 1698 m (C=O), 1666 s, 1599 w, 1482 w, 1414 m, 1340 s, 1156 s, 1119 w, 1092 s, 855 s; (ES) m/z (%) 313 (M + H$^+$, 100%), 252 (81, M − $OCONH_2$); accurate mass (FAB) found 313.0859 (M + H$^+$ $C_{13}H_{17}N_2O_5S$ requires 313.0858).

(2*S*,3*R*,4*R*)-3-Azido-4-hydroxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine (32) and (2*R*,3*R*,4*S*)-4-azido-3-hydroxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine (33)

Sodium azide (0.12 g, 1.84 mmol) was added to a solution of **30** (0.098 g, 0.36 mmol) in acetone (10.2 ml) and water (1.3 ml). Ammonium chloride (0.019 g, 0.84 mmol) was added and the solution heated at reflux (80 °C) for 18 h. After cooling, acetone was removed under reduced pressure and the resulting aqueous layer was washed with ethyl acetate (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting material was purified by flash column chromatography on silica (100% diethyl ether) to give **32** (0.660 g, 58%) as a white solid and with **33** (0.036 g, 32%) as a colourless oil.

Data for **32**; mp 94–96 °C; $[a]_D^{20}$ −78.3 (c = 1.24 MeOH); ν_{max}(CH_2Cl_2)/cm^{-1} 3260 br (OH), 2927 w, 2098 s (N_3), 1597 w,

1343 m, 1239 w, 1163 s, 1089 m, 1032 s, 973 w, 823 m, 663 s; δ_H (300 MHz, $CDCl_3$) 2.46 (3H, s, Ar 4-Me), 3.33 (1H, dd, *J* 10.8, 4.8, *H*H-5), 3.54–3.60 (2H, m, H-2, H*H*-5), 3.83 (1H, dd, *J* 11.7, 2.1, C*H*HO), 3.92–3.95 (2H, m, H-3, H-4), 4.21 (1H, dd, *J* 11.7, 3.6, CH*H*O), 7.36 (2H, d, *J* 8.1, 2 × Ar H-3), 7.73 (2H, d, *J* 8.1, 2 × Ar H-2); δ_C (75 MHz, $CDCl_3$) 21.6 (CH_3), 55.7 (CH_2), 63.9 (CH_2), 66.1 (CH), 69.5 (CH), 73.1 (CH), 127.7 (2 × CH), 129.9 (2 × CH), 132.5 (C), 144.4 (C); (ES) *m*/*z* (%) 313 (M + H^+ 100%), 330 (42, M + NH_4^+); accurate mass (FAB) 313.0970 found (M + H^+ $C_{12}H_{17}N_4O_4S$ requires 313.0971); anal. found C, 46.04; H, 5.02; N, 17.84; $C_{12}H_{16}N_4O_4S$ requires C, 46.14; H, 5.16; N, 17.94%.

Data for **33** $[\alpha]_D^{20}$ +5.2 (*c* = 0.36 MeOH); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3269 br (OH), 2101 s (N_3), 1599 m, 1328 s, 1268 m, 1151 s, 1089 s, 1031 m, 991 m, 864 m; δ_H (300 MHz, $CDCl_3$) 2.46 (3H, s, Ar 4-Me), 3.21 (1H, dd, *J* 11.4, 4.2, *H*H-5), 3.47 (1H, ddd, *J* 6.0, 4.2, 3.9, H-2), 3.87 (1H, dd, *J* 11.4, 5.4, H*H*-5), 3.95–4.04 (3H, m, H-3, H-4, C*H*HO), 4.26 (1H, dd, *J* 12.3, 3.9, CH*H*O), 7.36 (2H, d, *J* 8.1, 2 × Ar H-3), 7.71 (2H, d, *J* 8.1, 2 × Ar H-2); δ_C (75 MHz, $CDCl_3$) 21.6 (CH_3), 51.2 (CH_2), 61.2 (CH), 61.9 (CH_2), 64.4 (CH), 77.3 (CH), 127.6 (2 × CH), 129.9 (2 × CH), 132.9 (C), 144.4 (C); (ES) *m*/*z* (%) 642 (2 M + NH_4^+ 100%), 313 (68, M + H^+), 330 (46, M + NH_4^+); accurate mass (FAB) 313.0972 found (M + H^+ $C_{12}H_{17}N_4O_4S$ requires 313.0971).

A single crystal of **32** was obtained by recrystallisation from $CHCl_3$. Crystal data: $C_{12}H_{16}N_4O_4S$, $M = 312.35$, monoclinic, $a = 7.539$ (4), $b = 17.643$ (9), $c = 11.223$ (5) Å, $U = 1468.1$ (12) Å^3, $T = 150(2)$ K, space group $P2_1$, $Z = 4$, absorption coefficient = 0.242 mm^{-1}, 10263 reflections measured, 5092 unique (R_{int} = 0.1254), absolute structure parameter = 0.17(14). The final $wR(F^2)$ was 0.1542 for all data. CCDC deposition number 656332.§

(2*S*,3*R*,4*R*)-3-Amino-4-hydroxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine (34)

10% Palladium on charcoal catalyst (6.3 mg) was added to a solution of **32** (0.021 g, 0.067 mmol) in THF (4 ml) and water (2 ml). The mixture was stirred for 3 h under hydrogen at atmospheric pressure (balloon). The reaction mixture was diluted with THF (10 ml), filtered and the filtrate was concentrated under reduced pressure to give **34** (0.018 g, 97%) as a white solid; mp 92–93 °C; $[\alpha]_D^{20}$ −62.3 (*c* = 1.16 MeOH); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3284 br (OH/NH), 2924 br, 1597 m, 1492 w, 1455 w, 1333 s, 1182 w, 1152 s, 1089 m, 1010 m, 948 w, 812 m, 659 s; δ_H (300 MHz, D_2O) 2.45 (3H, s, Ar 4-Me), 3.14 (1H, app t, *J* 5.6, H-3), 3.195–3.26 (2H, m, *H*H-5, H-2), 3.49 (1H, d app t, *J* 9.6, 5.6, H-4), 3.53 (1H, dd, *J* 10.5, 5.6, H*H*-5), 3.75 (1H, dd, *J* 12.0, 3.6, CH*H*O), 3.82 (1H, *J* 12.0, 5.4, CH*H*O), 7.43 (2H, d, *J* 8.1, 2 × Ar H-3), 7.72 (2H, d, *J* 8.1, 2 × Ar H-2); δ_C (75 MHz, D_2O) 20.7 (CH_3), 53.3 (CH_2), 58.8 (CH), 62.0 (CH_2), 67.1 (CH), 74.2 (CH), 127.4 (2 × CH), 130.3 (2 × CH), 131.5 (C), 145.8 (C); (ES) *m*/*z* (%): 111 (100%), 287 (42, M + H^+); accurate mass (FAB) 287.1065 found (M + H^+ $C_{12}H_{19}N_2O_4S$ requires 287.1066).

(2*S*,3*R*,4*R*)-2-Hydroxymethyl-3-amino-4-hydroxy-pyrrolidine (8)

The tosylate **34** (0.018 g, 0.064 mmol) was placed in a three necked flask fitted with a dry ice condenser and dissolved in a minimal amount of liquid ammonia (*ca.* 5 ml) at −78 °C. Sodium metal (0.0044 g, 0.19 mmol) was then added portion-wise to the stirring reaction mixture. After the addition of sodium was complete the reaction was warmed to room temperature and the liquid ammonia was allowed to evaporate. The crude residue was dissolved into water and transferred to a round bottom flask, water was removed under reduced pressure and the resulting crude material was purified by flash column chromatography on silica (100% methanol bubbled with NH_3) to give **8** (0.0032 g, 38%) as a clear oil. To aid analysis dilute HCl (aq) was added to the amine in water until the solution was pH 2–3, affording the hydrochloride salt of **8**; $[\alpha]_D^{20}$ +26.9 (*c* = 0.32 MeOH); ν_{max}(solid)/cm^{-1}: 3334 br (OH/NH), 2901 br, 1599 br, 1408 w, 1102 m, 1026 m, 970 w, 922 m; δ_H (400 MHz, D_2O) 3.38 (1H, dd, *J* 12.4, 4.0, *H*H-5), 3.61 (1H, dd, *J* 12.4, 4.0, H*H*-5), 3.60–3.62 (1H, m overlapping, H-3), 3.81 (1H, app td, *J* 5.1, 4.4, H-2), 3.87 (1H, dd, *J* 12.0, 5.1, C*H*HO), 3.97 (1H, dd, *J* 12.0, 4.4, CH*H*O), 4.56 (1H, app q, *J* 4.0, H-4); δ_C (100.6 MHz, CD_3OD) 50.2 (CH_2), 56.9 (CH), 58.7 (CH_2), 62.6 (CH), 72.1 (CH); (ES) *m*/*z* (%): 133 (M + H^+, 100%); accurate mass (FAB) found 133.0975 (M + H^+ $C_5H_{13}N_2O_2$ requires 133.0977).

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Notes and references

1 For selected reviews see: E. B. de Melo, A. D. Gomes and I. Carvalho, *Tetrahedron*, 2006, **62**, 10277; V. H. Lillelund, H. H. Jensen, X. F. Liang and M. Bols, *Chem. Rev.*, 2002, **102**, 515; T. D. Heihtman and A. T. Vasella, *Angew. Chem., Int. Ed.*, 1999, **38**, 750.
2 N. Asano, R. J. Nash, R. J. Molyneux and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645; N. Asano, *Glycobiology*, 2003, **13**, 93R; A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux and R. J. Nash, *Phytochemistry*, 2001, **56**, 265; S. Gerber-Lemaire and L. Juillerat-Jeanneret, *Mini–Rev. Med. Chem.*, 2006, **6**, 1043.
3 A. E. Stütz, in *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley VCH, Weinheim, 1999.
4 G. W. J. Fleet, S. J. Nicholas, P. W. Smith, S. V. Evans, L. E. Fellows and R. J. Nash, *Tetrahedron Lett.*, 1985, **26**, 3127.
5 F. Popowycz, S. Gerber-Lemaire, R. Demange, E. Rodriguez-Garcia, A. T. C. Asenjo, I. Robina and P. Vogel, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2489; K. Yasuda, H. Kizu, T. Yamashita, Y. Kameda, A. Kato, R. J. Nash, G. W. J. Fleet, R. J. Molyneux and N. Asano, *J. Nat. Prod.*, 2002, **65**, 198.
6 For selected examples see: C. Laroche, J.-B. Behr, J. Szymoniak, P. Bertus, C. Schütz, P. Vogel and R. Plantier-Royona, *Bioorg. Med. Chem.*, 2006, **14**, 4047; J. H. Kim, M. J. Curtis-Long, W. D. Seo, J. H. Lee, B. W. Lee, Y. J. Yoon, K. Y. Kanga and K. H. Parka, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4282; N. Asano, K. Ikeda, M. Kasahara, Y. Arai and H. Kizu, *J. Nat. Prod.*, 2004, **67**, 846.
7 F. Popowycz, S. Gerber-Lemaire, E. Rodriguez-Garcia, C. Shütz and P. Vogel, *Helv. Chim. Acta*, 2003, **86**, 1914; S. Gerber-Lemaire, F. Popowycz, E. Rodriguez-Garcia, A. T. C. Asenjo, I. Robina and P. Vogel, *ChemBioChem*, 2002, **3**, 466; H. Fiaux, C. Schütz, P. Vogel, L. Juillerat-Jeanneret and S. Gerber-Lemaire, *Chimia*, 2006, **60**, 185; S. Favre, H. Fiaux, C. Schütz, P. Vogel, L. Juillerat-Jeanneret and S. Gerber-Lemaire, *Heterocycles*, 2006, **69**, 179.
8 D. Kim, Y. Kim, T. Kim and K. H. Kim, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 643.
9 C. Herdeis, A. Aschenbrenner, A. Kirfel and F. Schwabenlander, *Tetrahedron: Asymmetry*, 1997, **8**, 2421.
10 G. Limberg, I. Lundt and J. Zavilla, *Synthesis*, 1999, 178.
11 L. Czollner, J. Kuszmann and A. Vasella, *Helv. Chim. Acta*, 1990, **73**, 1338.

12 E. Falb, Y. Bechor, A. Nudelman, A. Hassner, A. Albexk and H. E. Gottlieb, *J. Org. Chem.*, 1999, **64**, 498.
13 C. Palomo, P. C. Fernando, C. Cuevas, J. M. Ontoria, J. M. Odriozola and S. Munt, *Bull. Soc. Chim. Belg.*, 1992, **101**, 541.
14 J. K. Robinson, V. Lee, T. D. W. Claridge, J. E. Baldwin and C. J. Schofield, *Tetrahedron*, 1998, **54**, 981.
15 K. L. Curtis, J. Fawcett and S. Handa, *Tetrahedron Lett.*, 2005, **46**, 5297.
16 (*a*) T. J. Donohoe, P. D. Johnson, A. Cowley and M. Keenan, *J. Am. Chem. Soc.*, 2002, **124**, 12934; (*b*) T. J. Donohoe, P. D. Johnson and R. Pye, *Org. Biomol. Chem.*, 2003, 2025; (*c*) T. J. Donohoe, P. D. Johnson, R. Pye and M. Keenan, *Org. Lett.*, 2004, **6**, 2583.
17 N. B. Westwood and R. T. Walker, *Tetrahedron*, 1998, **54**, 13391.
18 T. Ibuka, T. Taga, H. Habashita, K. Nakai, H. Tamamura, F. Nobutaka, C. Yukiyasu, N. Hisao and Y. Yoshinori, *J. Org. Chem.*, 1993, **58**, 1207.
19 F. Busqé, P. de March, M. Figueredo, J. Font, T. Gallagher and S. Milan, *Tetrahedron: Asymmetry*, 2002, **13**, 437.
20 (*a*) J. L. Cohen and A. R. Chamberlin, *Tetrahedron Lett.*, 2007, **48**, 2533; (*b*) T. J. Donohoe, M. J. Chughtai, D. J. Klauber, D. Griffin and A. D. Campbell, *J. Am. Chem. Soc.*, 2006, **128**, 2514.
21 M. N. Kenworthy, G. D. McAllister and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 6661; M. N. Kenworthy and R. J. K. Taylor, *Org. Biomol. Chem.*, 2005, 603.
22 A more efficient version of the TA reaction has now been developed: see reference 20*b* and also: T. J. Donohoe, C. J. R. Bataille, W. Gattrell, J. Kloesges and E. Rossignol, *Org. Lett.*, 2007, **9**, 1725.
23 J. R. Dehli and V. J. Gotor, *J. Org. Chem.*, 2002, **67**, 6816.
24 C. B. Hudson, A. V. Robertson and W. R. J. Simpson, *Aust. J. Chem.*, 1975, **28**, 274.
25 A similar intramolecular epoxide ring-opening strategy has recently been reported: Y. Wang, A. Benn, N. Flinn, T. Monk, M. Ramjee, J. Watts and M. Quibell, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1327.
26 J. D. Aebi, D. T. Deyo, C. Sun, D. Guillaume, B. Dunlap and D. H. Rich, *J. Med. Chem.*, 1990, **33**, 999; L. F. Garcia-Alles, J. Magdalena and V. Gotor, *J. Org. Chem.*, 1996, **61**, 6980; M. Yamamoto, M. Suzuki, K. Kishikawa and S. Kohmoto, *Synthesis*, 1993, 307; S. Knapp, P. J. Kukkola, S. Sharma, T. G. M. Dhar and A. B. J. Naughton, *J. Org. Chem.*, 1990, **55**, 5700.
27 C. Bachand, H. Driguez, J. M. Paton, D. Touchard and J. Lessard, *J. Org. Chem.*, 1974, **39**, 3136.
28 Y. Morizawa, T. Nakayama, Y. Matsumura, K. Uchida and A. Yasuda, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2714.
29 G. Buchanan, K. W. Lumbard, R. J. Sturgeon, D. K. Thompson and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1990, 699; Y. Ryu and G. Kim, *J. Org. Chem.*, 1995, **60**, 103.
30 D. D. Penin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, NY, 3rd edn, 1988.