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The first asymmetric synthesis of (2*S*,3*S*,4*R*)-3-amino-2-hydroxymethyl-4-hydroxypyrrolidine

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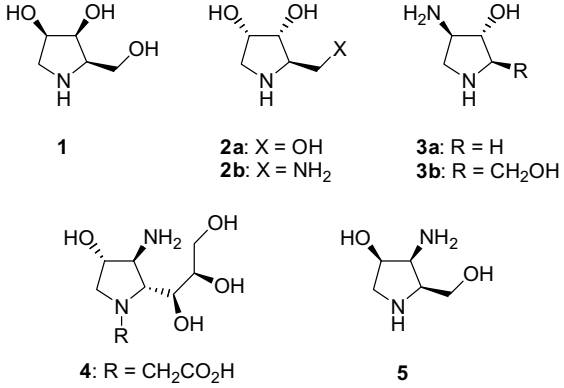
Abstract—The novel (2*S*,3*S*,4*R*)-3-amino-2-hydroxymethyl-4-hydroxypyrrolidine **5** has been produced in an efficient synthesis from *trans*-4-hydroxy-L-proline **8**. The key step involves a tethered aminohydroxylation of the alkene **7** to introduce regio- and stereoselectively the amino alcohol functionality in the resulting products **6** and **13**. Subsequent deprotection steps furnish the target molecule **5** as well as several differentially protected analogues.

Polyhydroxylated *N*-heterocycles are of great chemical interest primarily due to the wide range of biological activity they display.[1] These iminosugars are often strong inhibitors of glycosidase enzymes and have consequently been investigated as potential therapies in the treatment of diabetes, HIV and cancer.[2] Structurally, the most simple iminosugars are those based on the pyrrolidine motif. Hence, the triol **1** is a strong competitive inhibitor of α-galactosidase[3] whilst the diastereomeric compound **2a** displays weak activity against several glycosidase enzymes.[4] Amino pyrrolidines have also been utilised in glycosidase inhibition studies with intriguing results. For example, the 2-aminomethyl pyrrolidine **2b** has been shown to be a more potent inhibitor of α-mannosidase than the corresponding triol **2a**.[4] In addition, the presence of the primary amine in **2b** allowed for further functionalisation at this position giving the potential for combinatorial-based methods of inhibitor discovery.[5,6] Related 2-aminomethyl pyrrolidines have also found use as ligands in analogues of the anti-cancer agent cisplatin.[7]

In contrast, the introduction of amine substituents at either the C3- or C4-position of a hydroxy pyrrolidine has received only limited attention. Syntheses of the 4-amino pyrrolidines **3a**[8] and **3b**[9] have been described and the former was shown to inhibit α-mannosidase with a K_i (40 μM) comparable to that for 1-deoxymannojirimycin. Additionally, Vasella and co-workers have synthesised the 3-amino pyrrolidine **4** as an analogue of *N*-acetylneuraminic acid and found that it inhibits *Vibrio cholerae* sialidase.[10] Similar 3-amino pyrrolidines have also been synthesised by other groups although biological testing was not reported.[11,12] The potential biological activity associated with 3-amino-4-hydroxy pyrrolidines makes them attractive synthetic targets especially since further functionalisation through the two amine groups is also possible. In view of these potential benefits we wish to report the first synthesis of the 3-amino analogue of **1** namely (2*S*,3*S*,4*R*)-3-amino-2-hydroxymethyl-4-hydroxypyrrolidine **5**.



Our synthetic strategy to the target diamine **5** is outlined in Scheme 1. We envisaged that **5** could be accessed

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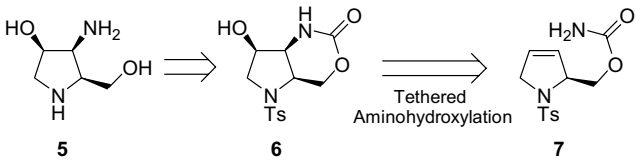


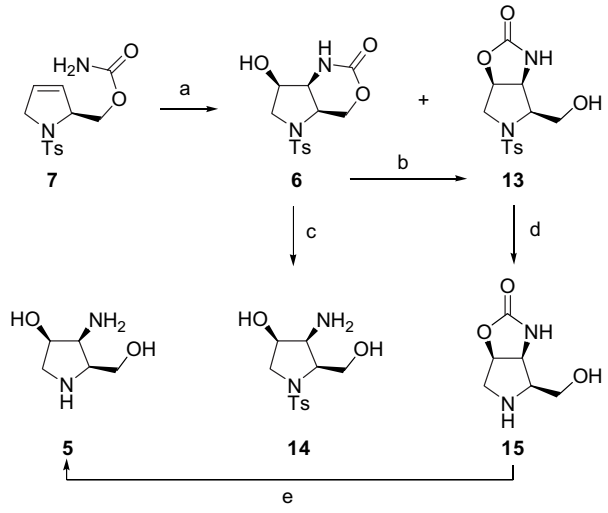
Scheme 1.

from the differentially protected intermediate **6** which in turn could be formed from homoallylic carbamate **7** using the regio- and stereoselective tethered aminohydroxylation (TA) reaction recently developed by Donohoe et al.[13] Three points should be noted in considering the proposed conversion of **7** to **6**. Firstly, only a limited number of homoallylic systems have been reported to undergo the TA reaction[13c,d,14] and therefore successful reaction of **7** would extend the scope of this new methodology. Additionally, five-membered endocyclic alkenes have been shown to be incompatible with the allylic TA reaction due to proposed strain in the azaglycolate osmate intermediate involved.[13b] However, we believed that the relief of strain associated with the extra carbon atom in homoallylic substrates such as **7** would facilitate successful reaction. Finally we were unsure of the effect, if any, the electron withdrawing *N*-tosyl substituent would have on the reactivity of the alkene towards aminohydroxylation.

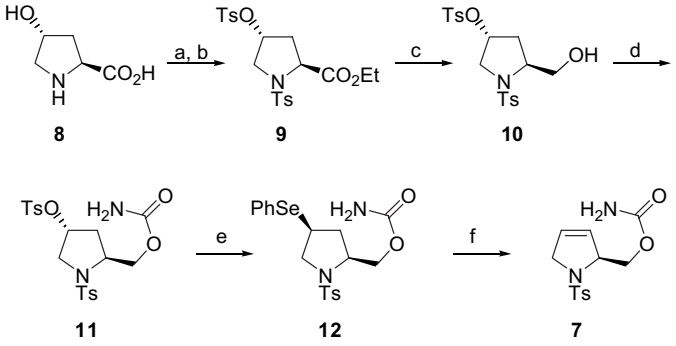
The key homoallylic carbamate **7** was synthesised from *trans*-4-hydroxy-L-proline **8** using a modified version of the route reported by Schofield and co-workers[12] as shown below (Scheme 2).[15]

Initial conversion of **8** to the corresponding ethyl ester was followed by reaction with excess *p*-toluenesulfonyl chloride simultaneously to protect the amine and activate the hydroxyl functional group giving **9** in excellent yield.[16] Reduction of the ethyl ester using $LiBH_4$ (generated in situ from $NaBH_4$–LiCl)[17] then furnished the alcohol **10** which was converted to the carbamate **11** under standard conditions.[13b] Subsequent nucleophilic displacement of the *p*-toluenesulfonate ester by phenylselenide anion (generated by reaction of $(PhSe)_2$ with $NaBH_4$) proceeded smoothly to give the selenide **12** in excellent yield.[18] Finally, oxidation of the selenide resulted in spontaneous elimination of the product selenoxide to furnish the target carbamate **7** in six steps from **8** and in 38% overall yield.[19]

With sufficient quantities of the carbamate **7** to hand we next turned our attention to the key TA reaction (Scheme 3). Pleasingly reaction of **7** under the conditions reported by Donohoe et al.[13] led to the formation of the anticipated 5:6 bicyclic carbamate **6** (21–40%) together with variable amounts of the isomeric 2-oxazolidinone **13** (10–28%) resulting from migration of the carbamate group.[20] The two products were readily separated by flash column chromatography and their stereostructures confirmed by X-ray crystallographic analysis as shown (Figs. 1 and 2).[21] Although the relative proportion of **6** and **13** varied, the combined yield of both products was found to be consistently in the region of 50% (together with ca. 40% recovered starting material **7**) over a number of repeated reactions. These yields are comparable to those previously reported for the TA reaction of homoallylic carbamates.[13c,d,14] Additionally, we found



Scheme 3. Reagents and conditions: (a) NaOH, ^{t}BuOCl, ^{i}Pr$_2$NEt (5 mol%), $K_2Os(OH)_4O_2$ (4 mol%), ^{n}PrOH–H_2O (1:1), rt, 2–6 h, (**6**—21–40%; **13**—10–28%; recovered **7**—38–40%); (b) $LiAlH_4$, Et_2O, reflux, 6 h, (100%); (c) LiOH, H_2O–MeOH (4:1), reflux, 1.5 h, (57%); (d) Na–NH_3, −78°C to rt, (95%); (e) LiOH, H_2O–MeOH (4:1), reflux, 1.5 h, (35%).



Scheme 2. Reagents and conditions: (a) $SOCl_2$, EtOH, reflux, 5 h, (98%); (b) NEt_3, TsCl, DMAP, CH_2Cl_2, rt, 48 h, (96%); (c) $NaBH_4$, LiCl, THF–EtOH (1:1), 0 °C, 3.5 h, (91%); (d) $Cl_3CCONCO$, CH_2Cl_2, 0 °C, 2 h; then K_2CO_3, MeOH, 0 °C, 4 h, (91%); (e) $(PhSe)_2$, $NaBH_4$, THF–EtOH (1:1), reflux, 2 h, (94%); (f) H_2O_2, pyridine, CH_2Cl_2, 0 °C, 2 h, (52%).

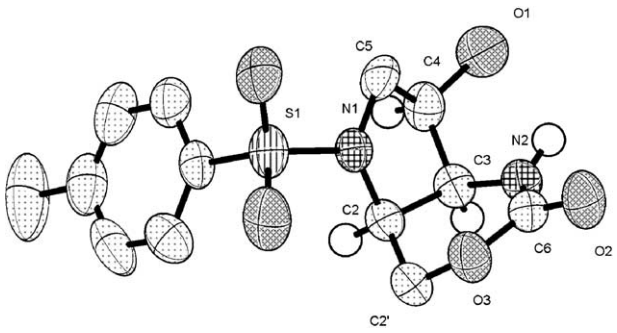


Figure 1. X-ray crystal structure of **6**. Only one of the unique molecules (the difference between them is minimal) of the unit cell is shown. Only some atoms labelled and selected H-atoms shown for clarity.[21]

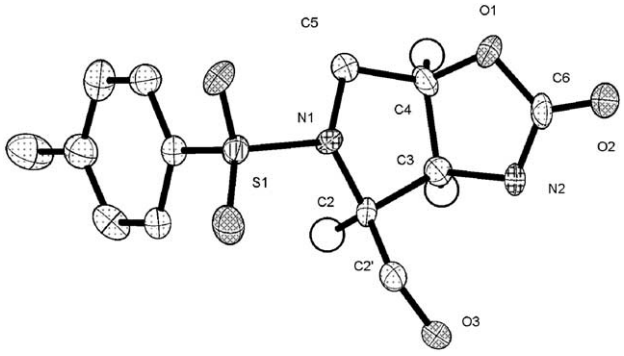


Figure 2. X-ray crystal structure of **13**. Only one of the unique molecules (they differ only in slight orientations of the *N*-Ts group) of the unit cell is shown. Only some atoms labelled and selected H-atoms shown for clarity.[21]

that longer reaction times gave **13** as the major product suggesting that it is thermodynamically favoured over **6** and this was further indicated by conversion of **6** to **13** on prolonged standing in MeOH-d_4. Finally, it should be noted that whilst the TA reaction of **7** was reproducible on a relatively large scale (i.e. >0.5 mmol), in our hands small scale reactions (i.e., <0.1 mmol) were much more capricious and gave overall yields for **6**+**13** which varied unpredictably from 4% to 40%.

Initial attempts to deprotect the carbamate group in **6** using $LiAlH_4$ were unsuccessful and only resulted in quantitative conversion to the 2-oxazolidinone **13** (Scheme 3). However, hydrolysis of **6** to give **14** was possible using LiOH in refluxing aqueous methanol,[22,23] but unfortunately all efforts to deprotect **14** to furnish **5** met with failure. Fortunately, simple reversal of the deprotection steps proved more successful. Thus, treatment of **13** with sodium in ammonia resulted in efficient removal of the *N*-tosyl group to generate **15** which could be hydrolysed using LiOH to give the target compound **5** in moderate yield. We found the amino pyrrolidine **5** to be somewhat unstable as the free base and so it was characterised and stored at pH 2–3.[24]

In summary, we have reported the first synthesis of (2*S*,3*S*,4*R*)-3-amino-2-hydroxymethyl-4-hydroxypyrrolidine **5** the 3-amino analogue of the known glycosidase inhibitor **1**. The synthetic route described also provides access to a number of differentially protected analogues of **5** (viz. **6**, **13** and **15**) which potentially allow for selective further functionalisation of the pyrrolidine core. In addition, we have expanded the scope of the TA methodology to include five-membered endocyclic alkenes containing a homoallylic carbamate group. Biological testing of **5** and some of the other intermediates produced in the course of this work is currently in progress. These results together with synthetic routes to diastereoisomers of **5** will be reported in due course.

Acknowledgements

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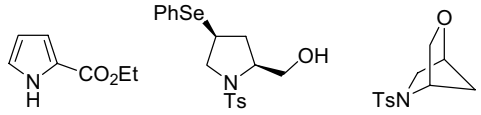
18. Attempts to introduce the phenylselenide moiety by reaction of either **9** or **10** under similar conditions were less successful resulting in the isolation of **16** (10%) from **9** and **17** (25%) and **18** (25%) from **10** as the only identifiable products.



16 **17** **18**

19. For **7**, white solid, mp: 149–152 °C; $[\alpha]_D^{20}$ −208.8 (*c* 1.02, MeOH); δ_H (300 MHz; $CDCl_3$): 2.41 (3H, s, Ar 4-Me), 4.06–4.14 (2H, m, 2 × H-5), 4.15 (1H, dd, *J* = 11.1, 5.4 Hz, C*H*HO), 4.40 (1H, dd, *J* = 11.1, 3.9 Hz, CH*H*O), 4.61–4.65 (1H, m, H-2), 4.92 (2H, br s, NH_2), 5.50 (1H, dapp q, *J* = 6.3, 2.1 Hz, H-3), 5.70 (1H, ddd, *J* = 6.3, 5.4, 2.1 Hz, H-4), 7.30 (2H, d, *J* = 8.1 Hz, Ar H-3), 7.70 (2H, d, *J* = 8.1 Hz, Ar H-2); δ_C (75 MHz; $CDCl_3$): 21.47 (CH_3), 55.67 (CH_2), 66.06 (CH), 66.65 (CH_2), 126.73 (CH), 126.77 (CH), 127.40 (2 × CH), 129.77 (2 × CH), 134.21 (C), 143.70 (C), 156.62 (C). Accurate mass (FAB) found: 297.0908 ($M+H^+$ $C_{13}H_{17}O_4N_2S$ requires 297.0909).
20. For **6**, white solid, mp: 104–108 °C; $[\alpha]_D^{20}$ −24.7 (*c* 0.29, MeOH); δ_H (300 MHz; CD_3OD): 2.45 (3H, s, Ar 4-Me), 3.23 (1H, dd, *J* = 11.1, 6.0 Hz, *H*H-5). 3.45, (1H, dd, *J* = 11.1, 6.0 Hz, H*H*-5), 3.73 (1H, dd, *J* = 6.9, 4.2 Hz, H-3), 3.80 (1H, app td, *J* = 6.0, 4.2 Hz, H-4), 4.00 (1H, ddd, *J* = 6.9, 6.0, 3.0 Hz, H-2), 4.33 (1H, *J* = 11.4, 3.0 Hz, C*H*HO), 4.54 (1H, dd, *J* = 11.4, 6.0 Hz, CH*H*O), 7.45 (2H, d, *J* = 8.1 Hz, Ar H-3), 7.78 (2H, d, *J* = 8.1 Hz, Ar H-2); δ_C (75 MHz; CD_3OD): 22.36 (CH_3), 54.20 (CH_2), 54.94 (CH), 57.63 (CH), 69.96 (CH_2), 71.83 (CH), 129.59 (2 × CH), 131.20 (2 × CH), 136.08 (C), 146.721 (C), 157.80 (C). Accurate mass (FAB) found: 313.0858 ($M+H^+$ $C_{13}H_{17}O_5N_2S$ requires 313.0858).
For **13**, white solid, mp: 100–102 °C; $[\alpha]_D^{20}$ −49.0 (*c* 1.14 MeOH); δ_H (400 MHz; CD_3OD): 2.45 (3H, s, Ar 4-Me), 2.91 (1H, app td, *J* = 9.0, 5.2 Hz, H-2). 3.06, (1H, dd, *J* = 12.0, 5.2 Hz, *H*H-5), 3.66 (1H, dd, *J* = 11.2, 9.0 Hz, C*H*HO), 3.72 (1H, dd, *J* = 12.0, 0.8 Hz, H*H*-5), 4.25 (1H, dd, *J* = 11.2, 5.2 Hz, CH*H*O), 4.35 (1H, dd, *J* = 9.0, 6.0 Hz, H-3), 4.91 (1H, ddd, *J* = 6.0, 5.2, 0.8 Hz, H-4), 7.47 (2H, d, *J* = 8.4 Hz, Ar H-3), 7.72 (2H, d, *J* = 8.4 Hz, Ar H-3); δ_C (100.6 MHz; CD_3OD): 20.10 (CH_3), 55.82 (CH_2), 58.42 (CH), 59.46 (CH_2), 63.44 (CH), 76.33 (CH), 127.91 (2 × CH), 129.69 (2 × CH), 131.22 (C), 144.76 (C), 160.04 (C). Found: 313.0858 ($M+H^+$ $C_{13}H_{17}O_5N_2S$ requires 313.0858). Anal. found: C, 49.75; H, 5.16; N, 8.81; $C_{13}H_{16}O_5N_2S$ requires: C, 49.99; H, 5.16; N, 8.97.
21. Crystal data for **6**: $C_{13}H_{16}N_2O_5S$, *M* = 312.34, orthorhombic, space group *P*2(1)2(1)2(1), *a* = 5.6923(7), *b* = 15.7807(17), *c* = 33.089(4) Å, *V* = 2972.3(6) Å^3, *T* = 290(2) K, *Z* = 8, D_c = 1.391 g cm^{-3}, μ (Mo Kα) = 0.240 mm^{-1}. Final, R_1 = 0.0582 (for 3796 reflections with $I > 2\sigma(I)$) and *wR*2 = 0.1274 for all data. Crystal data for **13** (the structure includes a molecule of solvent $CHCl_3$): $C_{14}H_{17}Cl_3N_2O_5S$, *M* = 431.71, monoclinic, space group *P*2(1), β = 90.174(2)°, *a* = 7.5405(10), *b* = 23.062(3), *c* = 10.2684(14) Å, *V* = 1785.7(4) Å^3, *T* = 150(2) K, *Z* = 4, D_c = 1.606 g cm^{-3}, μ (Mo Kα) = 0.658 mm^{-1}. Final, R_1 = 0.0813 (for 5413 reflections with $I > 2\sigma(I)$) and *wR*2 = 0.2176 for all data. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers: **6**, CCDC 269573; **13**, CCDC 269574. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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23. The same hydrolysis could also be applied to a mixture of the isomers **6** and **13** to give **14** in 68% yield.
24. Selected spectroscopic data for **5** at pH 2–3: δ_H (400 MHz, D_2O+DCl): 3.49 (1H, dd, *J* = 12.8, 3.6 Hz, *H*H-5), 3.54 (1H, dd, *J* = 12.8, 2.0 Hz, H*H*-5), 4.02 (1H, dd, *J* = 12.4, 6.0 Hz, C*H*HO), 4.06 (1H, dd, *J* = 12.4, 4.8 Hz, CH*H*O), 4.16 (1H, ddd, *J* = 9.2, 6.0, 4.8 Hz, H-2), 4.24 (1H, dd, *J* = 9.2, 4.8 Hz, H-3), 4.79–4.81 (1H, m obscured by HOD peak, H-4); δ_C (100.6 MHz; D_2O+DCl): 50.69 (CH_2), 52.18 (CH), 57.10 (CH_2), 58.10 (CH), 67.79 (CH).