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

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Supplementary Information:

(2S,4R)-2-Ethoxycarbonyl-4-hydroxypyrrolidinium chloride

Thionyl chloride (11.18 g, 6.82 ml, 94.0 mmol) was added to a 0 °C solution of trans-hydroxy-L-proline 12 (11.20 g, 85 mmol) dissolved in ethanol (100 ml). The solution was refluxed for 5 h before being cooled and the solvent was removed under reduced pressure. The resulting crude material was purified by recrystallisation (from ethanol) to give the title compound (16.20 g, 98%) as a white solid; mp 150-153 ºC (from ethanol) (Lit.1 153-153.5 ºC); [α]D 20 –26.4 (c=2.5 MeOH); νmax (solid)/cm⁻¹ 3311br (OH), 2954m, 2699s, 1698 (C=O), 1593m, 1401m, 1273s, 1236s, 1076s, 956s; δH (300 MHz; D₂O) 1.41 (3H, t, J 7.1, CH₃CH₂O), 2.40 (1H, ddd, J 14.2, 10.4, 4.4, H₃-3), 2.61 (1H, ddt, J 14.2, 7.8, 1.8, HH-3), 3.52 (1H, dt, J 12.6, 1.8, HH-5), 3.64 (1H, dd, J 12.6, 3.7, HH-5), 4.42 (2H, q, J 7.1, CH₃CH₂O), 4.74-4.84 (2H, m, H-2, H-4); δC (75 MHz; D₂O) 13.1 (CH₃), 36.7 (CH₂), 53.4 (CH₂), 58.2 (CH), 63.9 (CH₂), 69.4 (CH), 169.8 (C); (ES) m/z (%) 160 (M+H +, 100%); Accurate mass (FAB) Found 160.0974 (M+H + C₇H₁₄NO₃ requires 160.0974); Anal. Found C, 43.18; H, 7.13; N, 7.24; C₇H₁₄NO₃Cl requires C, 42.97; H, 7.21; N, 7.13.

(2S,4R)-2-Ethoxycarbonyl-1-(toluene-4-sulfonyl)-4-(toluene-4-sulfonyloxy)pyrrolidine (13)

Triethylamine (16.30 g, 22.5 ml, 161 mmol) and DMAP (0.05 g, 0.06 mmol) were added to a stirring solution of (2S,4R)-2-ethoxycarbonyl-4-hydroxypyrrolidinium chloride (6.30 g, 32.2 mmol) in dichloromethane (41 ml). The reaction mixture was stirred for 1 h before a solution of p-toluenesulfonyl chloride (15.40 g, 80.7 mmol) dissolved in dichloromethane (80 ml) was added dropwise. The reaction mixture was stirred for a further 48 h before being diluted with dichloromethane (50 ml). The organic layer was washed with water (3 × 50 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The resulting crude material was purified by recrystallisation from ethanol to give 13 (14.47 g, 96%) as a white solid; mp 76-78 ºC (from ethanol) (Lit.2 75-76 ºC); [α]D 20 –74.2 (c=2.43 MeOH); νmax (solid)/cm⁻¹ 2878s, 1737s (C=O), 1596m, 1358s, 1346s, 1196m, 1166s, 1159s, 953s; δH (300 MHz; CDCl₃) 1.20 (3H, t, J 7.2, CH₃CH₂O), 2.16 (1H, ddd, J 14.0, 7.5, 5.1, HH-3), 2.32...
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(1H, dddd, J 14.0, 7.5, 3.0, 1.5, H H-3), 2.39 (3H, s, Ar 4-Me), 2.41 (3H, s, Ar 4-Me), 3.54 (1H, dapp t, J 12.3, 1.5, H H-5), 3.66 (1H, dd, J 12.3, 4.2, H H-5), 4.07-4.21 (3H, m, CH3C2H2O, H-2), 4.92-4.97 (1H, m, H-4), 7.27 (2H, d, J 8.1, 2 × Ar H-3), 7.29 (2H, d, J 8.1, 2 × Ar H-3), 7.67 (2H, d, J 8.1, 2 × Ar H-2); δC (75 MHz; CDCl 3) 14.0 (CH 3), 21.2 (CH 3), 21.6 (CH 3), 37.2 (CH 2), 53.8 (CH2), 59.2 (CH), 61.8 (CH2), 78.2 (CH), 127.6 (2 × CH), 127.6 (2 × CH), 127.6 (2 × CH), 127.6 (2 × CH), 133.0 (C), 141.1 (C), 145.3 (C), 171.1 (C); (ES) m/z (%) 468 (M+H +, 100%), 485 (58, M+NH 4 +); Accurate mass (FAB) Found 468.1150 (M+H+ C21H26NO7S2 requires 468.1151); Anal. Found C, 54.17; H, 5.55; N, 2.94; C21H25NO7S2 requires C, 53.95; H, 5.39; N, 2.97.

(2S,4R)-2-(Hydroxymethyl)1-(toluene-4-sulfonyl)-4-(toluene-4-sulfonyloxy)pyrrolidine (14)

LiCl (2.07 g, 42.0 mmol) and NaBH 4 (1.86 g, 42.0 mmol) were added to a 0 ºC solution of 13 (6.53 g, 14.0 mmol) dissolved in a 1:1 mixture of ethanol (80 ml) and THF (80 ml). The solution was stirred for 3.5 h before being quenched with water (50 ml). Ethanol was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 × 50 ml). The organic layers were combined, dried (MgSO4) and the solvent was removed under reduced pressure to give 14 (5.41 g, 91%) as a white solid; mp 82-84 ºC (Lit. 3 86-87 ºC); [α]20 D –21.5 (c=1.03 MeOH);

v max (solid)/cm -1 3532br (OH), 2963m, 1597m, 1335s, 1173s, 1090m, 889s, 812s; δH (300 MHz; CDCl 3) 1.88-1.94 (1H, br dd, J 14.1, 7.8, H H-3), 2.03 (1H, ddd, J 14.1, 8.4, 4.8, H H-3), 2.33 (3H, s, Ar 4-Me), 2.34 (3H, s, Ar 4-Me), 3.28 (1H, br s, OH), 3.51-3.67 (4H, m, CHH2O, 2 × H-5, H-2), 3.81 (1H, dd, J 11.4, 3.3, CH3/O), 4.86-4.92 (1H, m, H-4), 7.22 (4H, d, J 8.1, 4 × Ar H-3), 7.48 (2H, d, J 8.1, 2 × Ar H-2), 7.62 (2H, d, J 8.1, 2 × Ar H-2); δC (75 MHz; CDCl 3) 21.2 (CH3), 21.2 (CH3), 34.8 (CH2), 53.0 (CH2), 59.9 (CH), 62.7 (CH2), 78.6 (CH), 127.2 (2 × CH), 127.4 (2 × CH), 129.4 (2 × CH), 129.6 (2 × CH), 132.8 (C), 133.0 (C), 143.8 (C), 144.8 (C); (ES) m/z (%) 254 ((M+H+)HOOSOC6H4CH3, 100%), 443 (97, M+NH 4 +), 426 (72, M+H+); Accurate mass (FAB) Found 426.1045 (M+H+ C19H24NO6S2 requires 426.1045); Anal. Found C, 53.64; H, 5.54; N, 3.06; C21H25NO7S2 requires C, 53.63; H, 5.45; N, 3.29.

(2S,4R)-2-(Carbamoyloxymethyl)-1-(toluene-4-sulfonyl)-4-(toluene-4-sulfonyloxy)pyrrolidine (15)

Trichloroacetylisocyanate (0.38 g, 0.24 ml, 3.8 mmol) was added to a 0 ºC solution of 14 (1.38 g, 3.2 mmol) in dichloromethane (5 ml). After 2 h TLC analysis confirmed
all starting material had been consumed. Dichloromethane was removed under reduced pressure and the resulting crude material was dissolved in methanol (6.5 ml). The solution was cooled to 0 °C and aqueous potassium carbonate (19.4 ml, 0.5 moldm\(^{-3}\), 9.7 mmol) was added. The solution was stirred for 4 h before the solvent was removed under reduced pressure. Water (10 ml) was added and the resulting solution extracted with ethyl acetate (3 × 20 ml), the organic layers were combined, dried (MgSO\(_4\)) and the solvent removed under reduced pressure to give 15 (1.37 g, 91%) as a white solid; mp 94-97 °C; \([\alpha]_{20}^{D} –36.1\) (c=1.95 MeOH); \(\nu_{\text{max}}(\text{solid})/\text{cm}^{-1}\) 2957s, 1723s (C=O), 1597s, 1401m, 1331s, 1346s, 1174s, 1089m, 956s, 889s; \(\delta_{\text{H}}\) (300 MHz; CDCl\(_3\)) 1.95-2.05 (2H, m, 2 × H-3), 2.44 (3H, s, Ar 4-Me), 2.46 (3H, s, Ar 4-Me), 3.55 (1H, ddd, \(J_1 12.6, 3.3, 0.9\), H\(H\)-5), 3.61 (1H, dd, \(J_1 12.6, 4.2\), H\(H\)-5), 3.84-3.91 (1H, m, H-2), 4.19 (1H, dd, \(J_1 11.4, 5.7\), CH\(O\)), 4.38 (1H, dd, \(J_1 11.4, 3.3\), CH\(O\)), 4.81-4.88 (3H, m, H-4, NH 2), 7.30 (2H, d, \(J_2 8.1\), 2 × Ar H-3), 7.32 (2H, d, \(J_2 8.1\), 2 × Ar H-3), 7.59 (2H, d, \(J_2 8.1\), 2 × Ar H-2), 7.70 (2H, d, \(J_2 8.1\), 2 × Ar H-2); \(\delta_{\text{C}}\) (75 MHz; CDCl\(_3\)) 21.6 (CH\(_3\)), 21.6 (CH\(_3\)), 33.7 (CH\(_2\)), 36.3 (CH), 55.7 (CH\(_2\)), 66.7 (CH\(_2\)), 127.3 4 (2 × CH), 127.2 9 (C), 128.2 (CH), 129.8 (2 × CH), 129.9 (2 × CH), 133.1 (C), 133.6 (C), 144.1 (C), 145.2 (C), 156.3 (C); (ES) m/z (%) 469 (M+H +, 100%), 486 (51, M+NH\(_4\)+); Accurate mass (FAB) Found 469.1103 (M+H +C\(_{20}\)H\(_{25}\)N\(_2\)O\(_7\)S\(_2\) requires 469.1103).

\((2S,4S)-2-(\text{Carbamoyloxymethyl})-4-\text{phenylselanyl}-1-(\text{toluene-4-sulfonyl})\text{pyrrolidine (16)}\)

Sodium borohydride (0.19 g, 5.13 mmol) was added to a solution of diphenyldiselenide (0.84 g, 2.70 mmol) in ethanol (10 ml). The solution was degassed (3 cycles freeze-pump-thaw) and to this mixture a degassed (3 cycles freeze-pump-thaw) solution of 15 (1.93 g, 4.28 mmol) in THF (10 ml) was added. The reaction mixture was refluxed for 2 h before solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography on silica (40:60, ethyl acetate:petroleum-ether) to give 16 (1.76 g, 94%) as a white solid; mp 125-128 °C; \([\alpha]_{20}^{D} +27.0\) (c=1.15 MeOH); \(\nu_{\text{max}}(\text{solid})/\text{cm}^{-1}\) 3460br (NH), 2920s, 1698s (C=O), 2163s, 1306s, 1152s, 1084m, 733s; \(\delta_{\text{H}}\) (300 MHz; CDCl\(_3\)) 1.71 (1H, ddd, \(J_1 13.2, 10.2, 7.5\), H\(H\)-3), 2.29 (1H, dapp t, \(J_1 13.2, 7.5\), H\(H\)-3), 2.43 (3H, s, Ar 4-Me), 2.80 (1H, app tdd, \(J_1 10.2, 7.5, 6.6\), H-4), 3.26 (1H, dd, \(J_1 12.3, 10.2\), H\(H\)-5), 3.78 (1H, dd, \(J_1 12.3, 6.6\), H\(H\)-5), 3.90-3.98 (1H, m, H-2), 4.17 (1H, dd, \(J_1 11.1, 5.7\), CH\(O\)), 4.26 (1H, dd, \(J_1 11.1, 5.1\), CH\(H/O\)), 4.76 (2H, s br, NH\(_2\)), 7.25-7.37 (5H, m, 3 × Ph-H, 2 × Ar H-3), 7.40-7.44 (2H, m, 2 × Ph-H), 7.67 (2H, d, \(J_2 8.4\), 2 × Ar H-2); \(\delta_{\text{C}}\) (75 MHz; CDCl\(_3\)) 21.5 (CH\(_3\)), 33.7 (CH\(_2\)), 36.3 (CH), 55.7 (CH\(_2\)), 58.7 (CH), 66.7 (CH\(_2\)), 127.3 (2 × CH), 127.2 (C), 128.2 (CH), 129.2 (2 × CH), 129.9 (2 × CH), 134.4 (C), 134.8 (2 × CH), 143.9 (2 × C), 156.4 (C); (ES) m/z (%) 394 (M-CONH\(_2\), 100%), 455 (67, M+H+); Accurate mass (FAB) Found 455.0543 (M+H+C\(_{19}\)H\(_{23}\)N\(_2\)O\(_4\)Se requires 455.0544); Anal. Found C, 49.99; H, 4.89; N, 6.32; C\(_{19}\)H\(_{22}\)N\(_2\)O\(_4\)Se requires C, 50.33; H, 4.89; N, 6.18.
Pyridine (0.32 ml, 3.9 mmol) and hydrogen peroxide (0.75 ml, 30% solution) were added to a 0 °C solution of 16 (1.33 g, 2.9 mmol) dissolved in dichloromethane (16 ml). The reaction mixture was stirred for 2 h before being diluted with dichloromethane (20 ml). The organic layer was washed with 5% aqueous KHSO₄ (2 × 10 ml), saturated aqueous NaHCO₃ (2 × 10 ml) and water (2 × 10 ml) before being dried (MgSO₄). The solvent was removed under reduced pressure and the resulting crude material was purified by flash column chromatography on silica (2:98, methanol:dichloromethane) to give 11 (0.45 g, 52%) as an off-white solid; mp 149-152 °C; [α]₂₀° D -208.8 (c=1.02 MeOH); ν_max (solid)/cm⁻¹ 3461br (NH), 2921s, 1730s (C=O), 1706s, 1600m, 1402m, 1311m, 1049s, 817s; δ_H (300 MHz; CDCl₃) 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, CHHO), 4.40 (1H, dd, J 11.1, 3.9, CHHO), 4.61-4.65 (1H, m, H-2), 4.92 (2H, brs, NH₂), 5.50 (1H, dapp q, J 6.3, 2.1, H-3), 5.70 (1H, ddd, J 6.3, 5.4, 2.1, H-4), 7.30 (2H, d, J 8.1, Ar H-3), 7.70 (2H, d, J 8.1, Ar H-2); δ_C (75 MHz; CDCl₃) 21.5 (CH₃), 55.7 (CH₂), 66.1 (CH), 66.7 (CH₂), 126.7 (CH), 126.8 (CH), 127.4 (2 × CH), 129.8 (2 × CH), 134.2 (C), 143.7 (C), 156.6 (C); (ES) m/z (%) 236 (M-OCONH₂, 100%), 297 (22, M+H⁺); Accurate mass (FAB) Found 297.0908 (M+H⁺ C₁₃H₁₇N₂O₄S requires 297.0909).

**Alternative synthesis of 25:**

(S)-2-(tert-butyl diphenylsilyloxymethyl)-1-(Toluene-4-sulfonyl)-2,5-dihydro-1H-pyrrole

Imidazole (0.045 g, 0.67 mmol) and DMAP (0.0081 g, 0.066 mmol) were added to a 0 °C solution of 28 (0.14 g, 0.556 mmol) dissolved in dichloromethane (5 ml) and the solution was stirred for 15 min. tert-Butyldiphenylsilyl chloride (0.18 g, 0.17 ml, 0.67 mmol) was added and the mixture stirred for a further 4 h. The reaction mixture was diluted with dichloromethane (10 ml) and was washed with water (10 ml). The organic layer was dried (MgSO₄), and the solvent removed under reduced pressure. The resulting crude material was purified by flash column chromatography on silica (10:90, ethyl acetate:petroleum-ether) to give the title compound (0.22 g, 81%) as a white solid; mp 69-71 °C; [α]₂₀° D -172.6 (c= 1.0 MeOH); ν_max (CH₂Cl₂)/cm⁻¹; 3055m, 2551m, 2523m, 2362m, 2112m, 1721s, 1508m, 1392m, 1249s, 1131s, 1042m, 820s; δ_H (300 MHz; CDCl₃) 5.96 (1H, s, Ar 4-Me), 5.99 (1H, s, Ar 3-Me), 7.29 (2H, d, J 8.1, Ar H-3), 7.68 (2H, d, J 8.1, Ar H-2); δ_C (75 MHz; CDCl₃) 21.5 (CH₃), 55.7 (CH₂), 66.1 (CH), 66.7 (CH₂), 126.7 (CH), 126.8 (CH), 127.4 (2 × CH), 129.4 (2 × CH), 134.2 (C), 143.7 (C), 156.6 (C); (ES) m/z (%) 236 (M-OCONH₂, 100%), 297 (22, M+H⁺); Accurate mass (FAB) Found 297.0908 (M+H⁺ C₁₃H₁₇N₂O₄S requires 297.0909).
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2928m, 1593m, 1464m, 1428m, 1346s, 1264s, 1093s, 1029w, 823m, 765s; δH (300 MHz, CDCl3) 1.07 (9H, s, C(CH3)3), 2.42 (3H, s, Ar 4-Me), 3.77 (1H, dd, J 9.9, 7.2, C/H/O), 4.02 (1H, dd, J 9.9, 3.9, CH/H/O), 4.10-4.14 (2H, m, 2 × H-5), 4.43-4.46 (1H, m, H-2), 5.69 (1H, dd, J 6.3, 3.6, 1.8, H-3), 5.76 (1H, dapp q, J 6.3, 2.4, H-4), 7.27 (2H, d, J 8.1, 2 × Ar H-3), 7.37-7.48 (6H, m, 6 × Ph-H), 7.62 (2H, d, J 8.1, 2 × Ar H-2), 7.63-7.69 (4H, m, 4 × Ph-H); δC (75 MHz; 300 MHz, CDCl3) 19.2 (C), 21.5 (CH3), 26.8 (3 × CH3), 55.9 (CH2), 67.1 (CH2), 68.0 (CH), 125.7 (CH), 127.4 (2 × CH), 127.7 (4 × CH), 128.6 (CH), 128.6 (2 × CH), 129.7 (2 × CH), 135.6 (4 × CH), 133.3 (C), 137.1 (2 × C), 143.2 (C); (ES) m/z (%) 414 (M-Ph, 100%), 509 (23, M+NH4+), 492 (16 M+H+); Accurate mass (FAB) 492.2029 Found (M+H+ C28H34NO3SSi requires 492.2029).

(2R,3R,4S)-3,4-Epoxy-2-(tert-butyldiphenylsilyloxymethyl)-1-(toluene-4-sulfonyl)pyrrolidine

Na2EDTA (0.75 ml, 4x10⁻⁴ moldm⁻³, 0.00032 mmol) and trifluoroacetone (0.19 g, 0.16 ml, 1.77 mmol) were added to a 0 °C solution of the alkene from the previous reaction 11 (0.231 g, 0.78 mmol) dissolved in acetonitrile (12 ml). Solid NaHCO3 (0.11 g, 1.29 mmol) mixed with oxone® (0.50g, 0.81 mmol) was then added to the solution portion-wise over 1 h. The reaction mixture was stirred a further 2 hr before sodium sulphate (0.5 g) was added. The solution was diluted with dichloromethane (10 ml), filtered and the filtrate was concentrated under vacuum. The resulting material was purified by flash column chromatography on silica (10:90, ethyl acetate:petroleum-ether) to afford the title compound (0.048 g, 60%) as a white solid; mp 118-119 °C; [α]20D –86.0 (c= 1.18 MeOH); νmax (CH2Cl2)/cm⁻¹ 1748w, 1430w, 1343s, 1235m, 1156s, 1090s, 1045s, 1010m, 928w, 847s; δH (300 MHz, CDCl3) 1.07 (9H, s, C(CH3)3), 2.43 (3H, s, Ar 4-Me), 3.55 (1H, d, J 3.0, H-3 or H-4), 3.57 (1H, d, J 12.6, H-5), 3.58 (1H, d, J 3.0, H-3 or H-4), 3.67 (1H, d, J 12.6, H-5), 3.91 (1H, dd, J 10.5, 5.4, CH/H/O), 3.93 (1H, dd, J 10.5, 6.6, CH/H/O), 3.88-3.98 (1H, m overlapping, H-2), 7.28 (2H, d, J 8.1, 2 × Ar H-3), 7.39-7.48 (6H, m, 6 × Ph-H), 7.60-7.69 (6H, m, 4 × Ph-H, 2 × Ar H-2); δC (75 MHz; 300 MHz, CDCl3) 19.1 (C), 21.6 (CH3), 26.8 (3 × CH3), 49.6 (CH2), 55.1 (CH), 57.7 (CH), 61.7 (CH), 64.9 (CH2), 127.5 (2 × CH), 127.9 (4 × CH), 129.5 (2 × CH), 129.9 (CH), 129.9 (2 × CH), 132.7 (C), 132.9 (C), 135.2 (C), 135.6 (3 × CH), 143.4 (C); (ES) m/z (%) 509 (23, M+NH4+), 430 (M-Ph, 100%), 525 (22, M+NH4+), 508 (7, M+H+); Accurate mass (FAB) 508.1977 Found (M+H+ C28H34NO3SSi requires 508.1978); Anal. Found C, 66.14; H, 6.56; N, 2.60; C28H33NO4SSi requires: C, 66.29; H, 6.55; N, 2.75.

(2R,3R,4S)-3,4-Epoxy-2-hydroxymethyl-1-(toluene-4-sulfonyl)pyrrolidine
Tertiary butyl ammonium fluoride (0.081 ml of a 1 moldm\(^{-3}\) solution in THF, 0.081 mmol) was added to a 0 °C solution of the epoxide from the previous step (0.037 g, 0.073 mmol) dissolved in THF (1.9 ml). The reaction mixture was stirred for 2 h before the solvent was removed under vacuum. The resulting material was purified by flash column chromatography on silica (50:50, ethyl acetate:petroleum-ether) to give the title compound (0.016 g, 84%) as a white solid; Mp: 127-129 °C (Lit.\(^4\) 131-133 °C); \([\alpha]^{20}_D\) –91.0 (c= 1.53 MeOH); \(v_{\text{max}}\) (CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 3503br (OH), 1332s, 1317s, 1219m, 1155s, 1092m, 1008m, 848s, 816m, 670s; \(\delta_h\) (300 MHz, CDCl\(_3\)) 2.43 (3H, s, Ar 4-Me), 3.51 (1H, d, \(J\) 3.0, H-3 or H-4), 3.57 (1H, d, \(J\) 3.0, H-3 or H-4), 3.58 (1H, d overlapping, \(J\) 12.6, H-5), 3.68 (1H, d, \(J\) 12.6, H-5), 3.80 (1H, dd, \(J\) 12.6, 6.0, C/HOO), 3.88 (1H, dd, \(J\) 12.6, 4.2, CH/HOO), 3.90 (1H, dd, \(J\) 6.0, 4.2, H-2), 7.31 (2H, d, \(J\) 8.1, 2 × Ar H-3), 7.66 (2H, d, \(J\) 8.1, 2 × Ar H-2); \(\delta_c\) (75 MHz; 300 MHz, CDCl\(_3\); Me\(_4\)Si): 21.6 (CH\(_3\)), 49.5 (CH\(_2\)), 55.0 (CH), 57.2 (CH), 62.5 (CH), 63.2 (CH\(_2\)), 127.6 (2 × CH), 129.6 (2 × CH), 134.5 (C), 143.9 (C); (ES) m/z (%) 252 (M+H\(^+\)-H\(_2\)O, 100%), 270 (7, M+H\(^+\)); Accurate mass (FAB) 270.0800 Found (M+H\(^+\) C\(_{12}\)H\(_{16}\)NO\(_{4}\)S requires 270.0800); Anal. Found C, 53.34; H, 5.40; N, 5.03; C\(_{12}\)H\(_{15}\)NO\(_{4}\)S requires: C, 53.50; H, 5.61; N, 5.20.

\((2R,3R,4S)-2\)-(Carbamoyloxymethyl)-3,4-epoxy-1-(toluene-4-sulfonyl)pyrrolidine

Trichloroacetylisocyanate (0.036 g, 0.0023 ml, 0.031 mmol) was added to a 0 °C solution of the alcohol from the previous step (0.0056 g, 0.021 mmol) in dichloromethane (1 ml). After 8 h TLC analysis confirmed all starting material had been consumed. The crude material was dissolved in methanol (1 ml) and hydrolysis was carried out using potassium carbonate (1ml, 0.5 moldm\(^{-3}\), 0.5 mmol). After 18 h the reaction was worked up to yield 25 (0.0054 g, 78%) as a white solid. Analytical data reported in the main paper.

A single crystal of 25 was obtained by recrystallisation from CHCl\(_3\). Crystal data:

\[C_{13}H_{16}N_2O_5S, \ M = 312.34, \ \text{orthorhombic}, \ a = 7.7577 \ (8), \ b = 17.7377 \ (19), \ c = 20.872 \ (2) \ \AA, \ U = 2872.0 \ (5) \ \AA^3, \ T = 150(2) \ K, \ \text{space group} \ P2_12_12_1, \ Z = 8, \ \text{absorption coefficient} = 0.249 \ \text{mm}^{-1}, \ 20984 \ \text{reflections measured}, 5053 \ \text{unique} \ (R_{int} = 0.0491), \ \text{absolute structure parameter} = 0.12(6). \]  

The final \(wR(F^2)\) was 0.0699 for all data. CCDC deposition number 656329.
X-Ray structure for 25 (ellipsoids are shown at 50% probability). There are two unique molecules in the asymmetric unit of which only one is shown.

**Attempted selanylation of 14:**

Sodium borohydride (0.012 g, 0.32 mmol) was added to a solution of diphenyldiselenide (0.054 g, 0.17 mmol) in ethanol (2 ml). The solution was degassed (3 cycles freeze-pump-thaw) and to this mixture a degassed (3 cycles freeze-pump-thaw) solution of 14 (0.116 g, 0.273 mmol) in THF (2 ml) was added. The reaction mixture was refluxed for 3 h before solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography on silica (40:60, ethyl acetate:petroleum-ether) to give 18 (0.028 g, 25%) and 19 (0.029 g, 42%) as colourless oils:

**18:** δ\( _{H} \) (250 MHz; CDCl\(_3\)) 1.64-1.76 (1H, m, HH-3), 2.18-2.28 (1H, m, HH-3), 2.44 (3H, s, Ar 4-Me), 2.68-2.82 (1H, m, H-4), 3.31 (1H, dd, \( J = 12.0, 10.3 \), HH-5), 3.62-3.82 (4H, m, HH-5, H-2, CH\(_2\)O), 7.24-7.33 (5H, m, \( 3 \times \) Ph-H, \( 2 \times \) Ar H-3), 7.39-7.42 (2H, m, \( 2 \times \) Ph-H), 7.65 (2H, d, \( J = 8.3 \), \( 2 \times \) Ar H-2).

**19:** δ\( _{H} \) (250 MHz; CDCl\(_3\)) 1.32 (1H, dd, \( J = 9.9, 2.5 \), HH-7), 1.70 (1H, brd, \( J = 9.9, HH-7 \)), 2.42 (3H, s, Ar 4-Me), 3.21 (1H, dd, \( J = 9.8, 1.5 \), H-6exo), 3.40 (1H, d, \( J = 9.8, H\text{-}6\text{-endo} \)), 3.65 (1H, dd \( J = 7.8, 1.6 \), H-3exo), 3.88 (1H, d \( J = 7.8, H\text{-}3\text{-endo} \)), 4.45 (1H, brs, H-1 or H-4), 4.50 (1H, brs, H-1 or H-4), 7.32 (2H, d, \( J = 8.2, 2 \times \) Ar H-3), 7.72 (2H, d, \( J = 8.4, 2 \times \) Ar H-2); (ES) m/z (%) 254 (M+H\(^{+}\), 100%)
Glycosidase inhibition

All enzymes and substrates were purchased from Sigma. Enzyme and substrate solutions were made using 0.2 M sodium phosphate buffers at suitable pH and protein concentrations (pH 6.5 and 0.2 U mL$^{-1}$ for α-galactosidase (green coffee beans), pH 7.3 and 2.0 U mL$^{-1}$ for β-galactosidase (bovine liver), pH 6.0 and 1.5 U mL$^{-1}$ for α-glucosidase (Saccharomyces cerevisiae), pH 5.0 and 0.2 U mL$^{-1}$ for β-glucosidase (algod, Prunus sp.), pH 4.5 and 0.2 U mL$^{-1}$ for α-mannosidase (jack bean, Canavalia ensiformis), pH 4.0 and 1.0 U mL$^{-1}$ for naringinase (Penicillium decumbens) and pH 4.25 and 0.2 U mL$^{-1}$ for N-acetyl-β-D-glucosaminidase (bovine kidney)). PNP-glycosides were used as substrates at a concentration of 5 mM.

Compounds tested for enzyme inhibition were dissolved in distilled water at a concentration of 1 mg mL$^{-1}$. Where required, compounds were dissolved in methanol (ca. 20 µL) before dilution using distilled water. Inhibitor solutions were stored at −20 °C. All assays were carried out in triplicate using water as a blank in place of the inhibitor. Reaction time was determined based on the length of time needed to give a final absorbance of 0.3–1.5 units. Linearity of the reaction time course was checked using a series of incubation times. Rate of colour development after the addition of Trinder glucose reagent was determined using a linear time course.

Enzyme solution (10 µL) inhibitor solution (10 µL) and substrate solution (50 µL) were combined in the well of a flat-bottomed 96-well (300 µL) microtitre plate. The reaction mixture was incubated at 25 °C for 5–20 min and was stopped using glycine solution (70 µL, 0.4 M, adjusted to pH 10.4 using NaOH). Absorbance at 405 nm was measured immediately in a microtitre plate reader (Molecular Devices VersaMax microplate reader). Percentage activity was calculated by reference to the control reaction for each assay and percentage inhibition determined by subtraction from 100%.

References: