I. General Experimental

All reactions were carried out under a nitrogen atmosphere with dry solvents and under anhydrous conditions unless otherwise noted. Reagents and solvents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25mm E. Merck silica gel plates (60F-254) using UV light as visualization agent and ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size, 0.040–0.063 mm) was used for flash column chromatography. NMR were recorded on a Bruker DRX-500 and calibrated using
undeuterated solvent as an internal reference. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Thermo Orbi-trap Discovery instrument.

II. Experimental and Spectral data

**Preparation of sodium salt 7:** Crude (3R,4R)-ethyl 1-benzyl-3-hydroxypiperidine-4-carboxylate 5 (1.0 equiv, 9.27 g, 35.21 mmol; prepared from 9.2 g of ketoester 4) was placed in a 250 mL round bottom flask, followed by ethanol (97 mL). To the resulting dark solution, sodiumtrimethylsilanolate (1.65 equiv, 6.50 g, 57.94 mmol,) was added in one portion. The reaction was maintained at ambient temperature under nitrogen for 12 hours. The resulting solids were collected by filtration using a Buchner funnel. The crude product was rinsed with two 10 mL portion of ethanol followed to 10 mL of MTBE. The resulting material was dried under vacuum for 4 hours to yield 7 (7.79 g, 30.28 mmol, 86%) as an off-white solid.

7: mp = decomposition >250 °C; $[\alpha]^{25}_D = -9.0$ (c = 1, water);; IR (film): $\nu_{\text{max}} = 3488, 3355, 3275, 3030, 2950, 2794, 2759, 1553, 1401, 1094, 1040 \text{ cm}^{-1}$; $^1$H NMR (MeOD, 500 MHz): $\delta = 7.34 - 7.28$ (m, 4H), 7.27 - 7.22 (m, 1H), 3.77 (td, $J=9.9, 4.4$ Hz, 1H), 3.57 (d, $J=12.9$ Hz, 1H), 3.50 (d, $J=12.9$ Hz, 1H), 3.00 (ddd, $J=10.7, 4.4, 1.6$ Hz, 1H), 2.93 - 2.78 (m, 1H), 2.02 - 1.91 (m, 3H), 1.81 (t, $J=10.4$ Hz, 1H), 1.69 - 1.58 (m, 1H) ppm; $^{13}$C NMR (MeOD, 125 MHz): $\delta = 182.40, 138.95, 130.72, 129.37, 128.42, 70.58,$
Preparation of carbamate 9: Sodium (3S,4R)-1-benzyl-3-hydroxypiperidine-4-carboxylate (1.0 equiv, 4.98 g, 19.36 mmol) was placed in a 250 mL round bottom flask, followed by acetonitrile (100 mL). The resulting heterogeneous solution was stirred for 5 minutes under nitrogen before being placed in a 75 °C bath. After stirring in bath for 10 minutes, diphenylphosphonic azide (1.1 equiv, 4.62 mL, 21.29 mmol) was added dropwise over a period of 30 minutes. Reaction stirred in bath for 5 hours before heating stopped and solution allowed to cool to room temperature. The crude reaction solution was combined with 60 mL ethyl acetate and extracted with three 100mL portion of saturated sodium bicarbonate solution. Aqueous solution back extracted with 100 mL ethyl acetate and organic solution combined. The organic was dried with MgSO₄ and concentrated under reduced pressure to a pale yellow solid. The crude product was purified by flash column chromatography (silica, 20–80% MTBE:hexanes) to yield cyclic carbamate 9 (3.52 g, 15.19 mmol, 78%) as a colorless as a white crystalline solid.

9: mp = 155-157 °C; R_f = 0.11 (silica, MTBE:Hexane, 1:1); [α]^{25}_D = 14.7 (c = 1.0, MeOH); IR (film): v_{max} = 3315, 2923, 2807, 1766, 1731, 1401, 1246, 1139, 1005, 912, 752, 703 cm⁻¹; ^1H NMR (MeOD, 500 MHz): δ = 7.35 - 7.30 (m, 4H), 7.29 - 7.23 (m, 1H), 4.01 (td, J = 10.8, 3.6 Hz, 1H), 3.71 - 3.67 (m, 1H), 3.67 - 3.62 (m, 1H), 3.30 - 3.26 (m, 1H), 3.24 (dd, J = 9.6, 3.0 Hz, 1H), 3.00 - 2.94 (m, 1H), 2.35 (t, J = 9.9 Hz, 1H), 2.25 (td, J = 12.0, 2.8 Hz, 1H), 2.01 - 1.94 (m, 1H), 1.69 (qd, J = 11.9, 4.1 Hz, 1H) ppm; ^13C NMR (MeOD, 125 MHz): δ = 163.29, 139.15, 130.35, 129.54, 128.60, 81.80, 63.28,
61.49, 55.10, 52.36, 29.61 ppm; HRMS calcd for C_{13}H_{16}N_{2}O_{2}H^+ [M + H^+] 233.1290, found 233.1287.

**Preparation of methyl glycoside of 2-deoxy-D-ribose 10:** 2-deoxy-D-ribose (1.0 equiv, 30.93 g, 230.59 mmol,) was placed in a 1L round bottom flask, followed by methanol (450 mL). After dissolution (~20 min), the flask was cooled in an ice water/methanol bath (–5 to 0 °C). Acetyl chloride (0.15 equiv, 2.5 mL, 35.15 mmol,) was added over 5 minutes. The reaction was maintained at this temperature under nitrogen for 3 hours, then solid sodium bicarbonate (25.0 g) was added. The slurry was stirred for 30 minutes at 0 °C, after which it was filtered through a pad of celite. Upon concentration under reduced pressure, some solid material was present (sodium bicarbonate/sodium chloride that was dissolved in the methanol). Dichloromethane (750 mL) was added, and the slurry was stirred for 1 h at room temperature. The solids were removed by filtration through celite (any unreacted starting material is also in soluble in dichloromethane), and the solvent removed under reduced pressure to yield 10 (33.41 g, 225.4 mmol, 98%, 5:4 mixture of anomers, contaminated with 8% combined of the hexose anomers) as a colorless oil. The analytical data matched that reported by Gottschald (Koth, D.; Fiedler, A.; Scholz, S.; Gottschald, M. *J. Carbohydr. Chem.* 2007, 26, 267-278).

**Preparation of bis-tosylate 11:** Compound 10 (1.0 equiv, 12.00 g, 80.99 mmol, contains 8% combined of the hexose anomers) was dissolved in dichloromethane (120 mL) and pyridine (5.0 equiv, 32.75 mL, 405.0 mmol). The system was purged with nitrogen for 15 minutes, placed in an ice bath and then p-toluenesulfonyl chloride (4.0 equiv 61.77 g, 323.97 mmol) was added.
The reaction was stirred in the ice bath for 1 hour, at room temperature for 1 hour, and then heated to 40 °C for 17 hours. The reaction was diluted with dichloromethane (300 mL), washed with 1M HCl (4 × 125 mL), saturated sodium bicarbonate (2 × 125 mL). The organic was dried with MgSO₄ and concentrated under reduced pressure to a pale yellow oil. This material was purified by flash column chromatography (silica, 10–50% EtOAc:hexanes) to yield bis-tosylate 11 (32.33 g, 70.85 mmol, 87%, 5:4 mixture of anomers, contaminated with 8% combined of the hexose anomers) as a colorless oil that formed a low-melting solid upon standing. A small sample (60 mg) was purified by preparative TLC to separate the two pentose anomers (elute 6x’s with EtOAc:hexanes, 1:4) so that they could be characterized.

*Data for faster eluting anomer on silica:*  
R_f = 0.26 (silica, EtOAc/hexanes, 1:4); IR (film): ν_max = 3070, 2928, 2843, 1588, 1497, 1450, 1357, 1174, 1103, 983, 916, 854, 814, 667 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 7.78–7.76 (m, 4 H), 7.37–7.35 (m, 4 H), 5.03 (dd, J = 5.0, 2.5 Hz, 1 H), 4.91–4.87 (m, 1 H), 4.21–4.18 (m, 1 H), 3.97–3.91 (m, 2 H), 3.20 (s, 3 H), 2.46 (s, 3 H), 2.45 (s, 3 H), 2.24–2.15 (m, 2 H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ = 145.44, 145.07, 132.82, 132.58, 130.13, 129.90, 127.97, 127.92, 105.15, 80.51, 80.12, 68.78, 55.26, 39.12, 21.69, 21.66 ppm; HRMS calcd for C₂₀H₂₄O₈S₂NH₄⁺ (M + NH₄⁺) 474.1251, found 474.1248.

*Data for slower eluting anomer on silica gel - R_f = 0.20 (silica, EtOAc:hexnaes, 1:4); IR (film): ν_max = 3061, 2959, 2919, 2843, 1593, 1490, 1454, 1375, 1205, 1157, 1099, 992, 925, 814 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 7.77–7.75 (m, 4 H), 7.36–7.34 (m, 4 H), 4.93 (d, J = 5.5 Hz, 1 H), 4.79 (ddd, J = 5.5, 3.5, 2.0 Hz, 1 H), 4.31 (m, 1 H), 4.11 (m, 2 H), 3.29 (s, 3 H), 2.46 (s, 6 H), 2.15 (ddd, J = 13.0, 8.0, 5.0 Hz, 1 H), 1.97 (app. d, J =
Preparation of benzyl glycoside 12: Compound 11 (1.0 equiv, 5.00 g, 10.95 mmol, contains 8% combined of the hexose anomers) was dissolved in dichloromethane (60 mL), then benzyl alcohol (5.0 equiv, 5.67 g, 54.76 mmol) and TsOH (0.38 g, 2.19 mmol, 0.2 equiv) was added. The system was purged with nitrogen, then refluxed for 60 hrs, after which the glycoside exchange reached approximately 80% conversion. Additional TsOH (0.1 equiv, 0.19 g, 1.09 mmol) was added, and the reaction refluxed for an additional 45 hours. The reaction was cooled to room temperature, and the organic layer washed with saturated sodium bicarbonate (3 × 25 mL), dried with magnesium sulfate and concentrated under reduced pressure to yield a pale yellow oil (4:3 mixture of anomers). It was difficult to separate the 6 from the excess benzyl alcohol, so this material was used directly in the next step. Upon standing, approximately 10% of the minor anomer crystallized from solution and the characterization data is provided. Approximately 30 mg of the anomer pair was purified by preparative TLC (elute 5x’s with EtOAc:hexanes, 1:4). Characterization data is provided.

Characterization data for mixture of anomers 12: Rf = 0.37 (silica, EtOAc:hexnaes, 1:4); IR (film): νmax = 3061, 3030, 2959, 2919, 1592, 1490, 1450, 1366, 1192, 1179, 1099, 979, 925, 814, 667 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz, 4:3 mixture of anomers, a single proton of the major anomer was given an integration of 1): δ = 7.78–7.74 (m, 7 H), 7.37–7.21 (m, 15.75 H), 5.23 (dd, J = 5.0, 2.5 Hz, 0.75 H), 5.12 (d, J = 4.5 Hz, 1 H), 4.93
(ddd, \(J = 7.0, 5.5, 3.5, 0.75 \) Hz), 4.84 (ddd, \(J = 5.0, 3.5, 2.0 \) Hz, 1 H), 4.69 (d, \(J = 12.5 \) Hz, 1 H), 4.56 (d, \(J = 13.5 \) Hz, 0.75 H), 4.43 (d, \(J = 12.5 \) Hz, 1 H), 4.35 (dd, \(J = 6.0, 3.0 \) Hz, 1 H), 4.33 (d, \(J = 14.0 \) Hz, 0.75 H), 4.26–4.23 (m, 0.75 H), 4.16–4.11 (m, 2 H), 4.02–3.95 (m, 1.5 H), 2.46 (s, 2.25 H), 2.45 (s, 3 H), 2.45 (s, 3 H), 2.43 (s, 2.25 H), 2.30–2.21 (m, 2.5 H), 2.07 (app. d, \(J = 15.0 \) Hz, 1 H) ppm; \(^{13}\text{C} \) NMR (CDCl\(_3\), 125 MHz, all signals are listed): \(\delta = 145.44, 145.18, 145.09, 145.06, 137.57, 136.96, 133.16, 132.85, 132.58, 132.53, 130.13, 129.99, 129.90, 128.43, 128.37, 127.96, 127.90, 127.88, 127.62, 127.58, 103.20, 102.56, 80.71, 80.60, 80.14, 79.13, 69.61, 68.96, 68.91, 68.50, 39.19, 39.03, 21.69, 21.68, 21.66 ppm; HRMS calcd for C\(_{26}\)H\(_{28}\)O\(_8\)S\(_2\)NH\(_4^+\) \([M + NH\(_4^+\)]\) 550.1564, found 550.1560.

Characterization data for minor anomer: \(R_f = 0.37\) (silica, EtOAc:hexnaes, 1:4); IR (film): \(v_{\text{max}} = 3066, 3030, 2954, 2928, 2879, 1597, 1495, 1455, 1361, 1174, 1094, 979, 921, 814, 671\) cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\), 500 MHz): \(\delta = 7.77\) (d, \(J = 8.0 \) Hz, 2 H), 7.74 (d, \(J = 8.5 \) Hz, 2 H), 7.38–7.29 (m, 7 H), 7.23–7.20 (m, 2 H), 5.23 (dd, \(J = 5.0, 2.5 \) Hz, 1 H), 4.93 (ddd, \(J = 7.0, 5.5, 3.5 \) Hz, 1 H), 4.56 (d, \(J = 13.5 \) Hz, 1 H), 4.33 (d, \(J = 13.5 \) Hz, 1 H), 4.26–4.23 (m, 1 H), 4.02–3.95 (m, 2 H), 2.46 (s, 3 H), 2.43 (s, 3 H), 2.30–2.21 (m, 2 H) ppm; \(^{13}\text{C} \) NMR (CDCl\(_3\), 125 MHz): \(\delta = 145.44, 145.06, 136.96, 132.85, 132.53, 130.13, 129.90, 128.44, 127.96, 127.95, 127.92, 127.88, 103.20, 80.71, 80.14, 69.61, 68.91, 39.19, 21.70, 21.65 ppm; HRMS calcd for C\(_{26}\)H\(_{28}\)O\(_8\)S\(_2\)NH\(_4^+\) \([M + NH\(_4^+\)]\) 550.1564, found 550.1561.

Preparation of bis-benzylamine 13a and 13b: Crude compound 12 (1.0 equiv, 5.84 g, 10.96 mmol, concentrated reaction from glycoside exchange above, contains excess benzyl alcohol) was placed in 100 mL round bottom flask. Ethanol (25 mL) was added,
and a white precipitate formed, which dissolved upon addition of benzylamine (8.0 equiv, 9.40 g, 87.72 mmol). The system was purged with nitrogen for 30 minutes, and then heated to reflux for 48 hours. The reaction was concentrated, and an initial silica gel column (eluent gradient = 100% CH₂Cl₂ to 2% methanol in CH₂Cl₂) removed most of the excess benzyl alcohol and benzylamine to yield 4.20 g of a pale yellow oil. The anomers could be separated by a second silica column (eluent gradient = 50% ethyl acetate in hexanes to 100% ethyl acetate) to yield 1.18 g of the faster eluting anomer, and 1.13 g of the slower eluting anomer (2.31 g, 5.74 mmol, 52% combined yield) as colorless oils.

**Characterization data for faster eluting anomers on silica gel:** Rₕ = 0.30 (silica, ethyl acetate); [α]²⁵_D = +46.7 (c = 1.5, CHCl₃); IR (film): ν_max = 3301, 3087, 3066, 3030, 2914, 2830, 1663, 1610, 1495, 1459, 1357, 1099, 1027, 907, 750, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.34–7.23 (m, 15 H), 5.25 (dd, J = 5.5, 1.5 Hz, 1 H), 4.70 (d, J = 12.0 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 4.30–4.27 (m, 1 H), 3.82–3.74 (m, 3 H), 3.67–3.59 (m, 2 H), 2.93 (dd, J = 12.0, 5.0 Hz, 1 H), 2.85 (dd, J = 12.0, 5.0 Hz, 1 H), 2.25 (ddd, J = 8.5, 7.0, 1.0 Hz, 1 H), 2.03 (brs, 2 H), 1.94 (ddd, J = 12.0, 7.0, 4.5 Hz, 1 H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ = 140.27, 140.18, 138.14, 128.34, 128.34, 128.20, 127.99, 127.82, 127.52, 126.93, 126.91, 101.99, 78.31, 69.04, 57.90, 54.27, 52.36, 49.15, 40.32 ppm; HRMS calcd for C₂₆H₃₀N₂O₂H⁺ [M + H⁺] 403.2380, found 403.2377.

**Characterization data for slower eluting anomer on silica gel:** Rₕ = 0.10 (silica, ethyl acetate); [α]²⁵_D = −67.3 (c = 1.2, CHCl₃); IR (film): ν_max = 3320, 3061, 3021, 2910, 2839, 1601, 1499, 1450, 1357, 1201, 1357, 1201, 1094, 1042, 912, 734, 703 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 7.32–7.21 (m, 15 H), 5.19 (dd, J = 5.0, 2.0 Hz, 1 H), 4.71
(d, \(J = 12.0 \text{ Hz}, 1 \text{ H}\)), 4.42 (d, \(J = 12.0 \text{ Hz}, 1 \text{ H}\)), 4.24 (dd, \(J = 12.5, 6.5 \text{ Hz}, 1 \text{ H}\)), 3.86 (d, \(J = 12.8 \text{ Hz}, 1 \text{ H}\)), 3.80 (s, 2 H), 3.61 (d, \(J = 12.8 \text{ Hz}, 1 \text{ H}\)), 3.34–3.31 (m, 1 H), 2.95–2.87 (m, 2 H), 2.18–2.08 (m, 4 H) ppm; \(^{13}\text{C}\) NMR (CDCl\(_3\), 125 MHz): \(\delta = 140.28, 140.21, 128.33, 128.31, 128.12, 128.10, 127.74, 127.52, 126.88, 126.80, 102.99, 81.23, 69.21, 57.66, 54.22, 52.07, 50.41, 37.84 \text{ ppm}; \) HRMS calcd for C\(_{26}\)H\(_{30}\)N\(_2\)O\(_2\)H\(^+\) [M + H\(^+\)] 403.2380, found 403.2374.

**Preparation of acetonide 15:** 2-deoxy-D-ribose (1.0 equiv, 25.01 g, 186.46 mmol,) and pyridinium \(p\)-toluenesulfonate (0.025 equiv, 1.15 g, 4.58 mmol) were placed in a 500 mL round bottom flask, followed by ethyl acetate (300 mL). The resulting heterogeneous mixture was stirred at room temperature under nitrogen for 10 minutes. At room temperature, 2-methoxypropene (1.3 equiv, 24.0 mL, 250.13 mmol) was charged in one portion. The reaction was stirred for 5 hours at room temperature and then filtered using a Buchner funnel to remove any undissolved material. Triethylamine (0.054 equiv, 1.4 mL, 10 mmol) was added to filtrate and the solution was removed under reduced pressure. This material was purified by flash column chromatography (silica, 20–60\% EtOAc:heptane) to yield the protected sugar 15 (21.80 g, 125.14 mmol, 67\%) as a colorless oil. The analytical data matched that reported by Winssinger (Jogireddy, R.; Dakas, P.-Y.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem. Eur. J.* **2009**, *15*, 11498-11506).

**Preparation of bis-mesylate 16:** A solution of acetonide 15 (1.0 equiv, 5.11 g, 29.33 mmol,) in THF (100 mL) was added dropwise over a period of one hour to a ice bath cooled suspension of lithium aluminum hydride (2.0 equiv, 2.28 g, 60.0 mmol) in THF
The reaction was allowed to stir in the ice bath for one hour and then at ambient temperature for an additional two hours. The reaction returned to the ice bath and quenched using a Fieser workup by sequential addition water (2.3 mL), 15% NaOH (2.3 mL), and water (6.9 mL). The solution was removed from the ice bath and allowed to stir at room temperature for 30 minutes. The reaction was charged with MTBE (100 mL) and then filtered through a pad of celite to remove undesired solids. The solids were rinse with two 20 mL potions of MTBE. The organic filtrate was evaporated to afford the diol (R_f = 0.22 (silica, MeOH:DCM, 1:19) as a colorless oil that was immediately transferred to a 250 mL round bottom flask and dissolved in DCM (100 mL). The solution was placed in an ice bath and stirred for 20 minutes. Triethylamine (3.2 equiv, 15.0 mL, 107.61 mmol) was added to the solution followed by dropwise addition of methanesulfonyl chloride (3.0 equiv, 6.8 mL, 87.87 mmol) over 30 minutes. Solution was stirred at 0 °C for 2 hours and then allowed to warm to room temperature over 30 minutes. The reaction was diluted with additional DCM (100 mL), transferred to a separatory funnel and sequentially washed with water (50 mL), and brine (50 mL). The DCM solution was dried over Na_2SO_4, filtered and evaporated to afford an orange oil. The crude product was purified by flash column chromatography (silica, 20–80% EtOAc:hexanes) to yield bis-mesylate 16 (7.98 g, 24.00 mmol, 82%) as a colorless oil.

16: (R_f = 0.16 (silica, EtOAc:hexanes, 1:1); [α]_{D}^{25} = -5.3 (c = 1, CHCl_3); IR (film): \nu_{max} = 3030, 2944, 2905, 1352, 1183, 1103, 967, 836 cm^{-1}; ^1H NMR (CDCl_3, 500 MHz): \delta = 4.46 - 4.33 (m, 2H), 4.27 - 4.17 (m, 2H), 3.06 (d, J=18.0 Hz, 6H), 2.05 (dddd, J=14.2, 9.1, 6.4, 2.8 Hz, 1H), 1.99 - 1.90 (m, 1H), 1.46 (s, 3H), 1.36 (s, 3H) ppm; ^13C NMR
Preparation of piperidine acetonide 17: In a 50 mL round bottom flask combine benzylamine (10.0 equiv, 3.22 g, 30.08 mmol) with ethanol (10 mL). To the reaction add freshly prepared bis-mesylate 16 (1.0 equiv, 1.00 g, 3.01 mmol) via a tared syringe. The solution is stirred at room temperature for 30 minutes before being heated to reflux for 12 hours. The solution was allowed to cool to room temperature and then evaporated to afford a viscous crude oil. The crude product was purified by flash column chromatography (silica, 20–100% EtOAc:hexanes) to yield piperidine 17 (0.68 g, 2.75 mmol, 93%) as a pale yellow oil.

17: (Rf = 0.16 (silica, EtOAc:hexanes, 1:1); [α]25D = (c = 1, CHCl3); IR (film): v_max = 2944, 2932, 2820, 1450, 1370, 1246, 1210, 1059, 863, 698 cm⁻¹; 1H NMR (CDCl₃, 500 MHz): δ = 7.36 - 7.31 (m, 4H), 7.30 - 7.25 (m, 1H), 4.25 - 4.21 (m, 1H), 4.18 (dt, J =8.3, 5.6 Hz, 1H), 3.57 - 3.50 (m, 2H), 2.85 (ddd, J =11.4, 6.2, 1.6 Hz, 1H), 2.54 - 2.48 (m, 1H), 2.28 - 2.21 (m, 2H), 1.54 (s, 3H), 1.38 (s, 3H) ppm; 13C NMR (CDCl₃, 125 MHz): δ = 138.1, 129.0, 128.2, 127.0, 108.3, 72.7, 71.7, 62.7, 55.8, 48.4, 28.4, 27.3, 26.4 ppm; HRMS calcd for C₁₅H₂₁NO₂H⁺ [M + H⁺] 248.1651, found 248.1654.

Preparation of piperidine diol 18: Piperidine acetonide 17 (1.0 equiv, 0.68 g, 2.75 mmol), THF (12 mL) and water (12 mL) were combined in a 100 mL round bottom flask. To the solution 2M aqueous HCl (5.0 equiv, 6.9 mL, 13.80 mmol) was added dropwise over 30 minutes using an addition funnel. The resulting acidic solution was stirred at
room temperature for two hours. The reaction mixture was transferred to a separatory funnel and extracted with MTBE (3 x 20 mL).

Combined organic extracts were washed with saturated aqueous NaHCO₃ (20 mL) and brine (20 mL) before being dried over MgSO₄, filtered and evaporated afford the crude product as an amorphous solid. The crude product was purified by flash column chromatography (silica, 0–10% MeOH:DCM) to yield piperidine 18 (0.48 g, 2.31 mmol, 84%) as a white solid.

18: mp = 61 - 63 °C; [α]²₅° = -33.7 (c = 1, CHCl₃); IR (film): v max = cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 7.41 - 7.18 (m, 5H), 3.84 - 3.74 (m, 1H), 3.62 - 3.51 (m, 3H), 2.88 (br. s., 1H), 2.74 (d, J=10.7 Hz, 1H), 2.29 (d, J=11.3 Hz, 1H), 2.11 (t, J=9.9 Hz, 1H), 1.88 - 1.79 (m, 1H), 1.77 - 1.66 (m, 1H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ = 137.7, 129.0, 128.4, 127.3, 69.4, 68.7, 62.1, 57.0, 50.5, 29.8 ppm; HRMS calcd for C₁₂H₁₇NO₂H⁺ [M + H⁺] 208.1338, found 208.1336.

Preparation of piperidine epoxide 19: Piperidine diol 18 (1.0 equiv, 0.054g, 0.26 mmol) was combined with DCM (1 mL) in a 10mL round bottom flask. To the solution stirring at room temperature was added 2-acetoxyisobutyryl chloride (1.2 equiv, 45 µL, 0.31 mmol) in DCM (0.5 mL) dropwise over 10 minutes. The solution was allowed to stir at room temperature for 2 hours. The reaction was placed in an ice bath and quenched by addition of saturated aqueous NaHCO₃ (3mL). The aqueous layer was extracted with DCM (2 x 1mL) and the combined organic solution was evaporated to afford the crude chloroacetate intermediate which was diluted with methanol (1.5 mL). The reaction was stirred to give a homogeneous mixture before addition of an aqueous solution of K₂CO₃ (4.0 equiv,
0.133g, 0.97 mmol). The reaction was stirred for 12 hours at room temperature. The reaction was extracted with ethyl acetate (3 x 1mL). Combined organic extracts were washed with brine (2 mL) before being dried over MgSO₄, filtered and evaporated to afford an oil. The crude product was purified by flash column chromatography (silica, 10–80% EtOAc:heptane) to yield piperidine 19 (0.013 g, 0.068 mmol, 26%) as a clear oil.

19: [α]²⁵ D = -46.5 (c = 1, CHCl₃); IR (film): νmax = 3061, 3003, 2914, 2803, 2762, 1490, 1450, 1357, 1290, 1165, 1027, 801, 743, 694 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 7.36 - 7.29 (m, 4H), 7.28 - 7.23 (m, 1H), 3.47 (s, 2H), 3.28 - 3.21 (m, 2H), 3.04 (ddd, J=13.5, 4.2, 1.3 Hz, 1H), 2.69 (d, J=13.6 Hz, 1H), 2.39 - 2.31 (m, 1H), 2.26 - 2.17 (m, 1H), 2.10 - 1.95 (m, 2H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ δ = 137.97, 129.04, 128.25, 127.11, 62.35, 52.37, 51.33, 50.69, 45.80, 45.61ppm; HRMS (observed as protonated carboxylic acid) calcd for C₁₂H₁₅NO₂H⁺ [M + H⁺] 190.1232, found 190.1226.

N-benzyl 3,4-epoxy piperidine fumarate salt (±)-21. To a stirred suspension of 20 (1.0 equiv, 40.2 g, 0.232 mol) in H₂O (320 mL) was added TFA (1.1 equiv, 19.31 mL, 0.255 mol) dropwise. The resulting mixture was then heated to 70 °C and NCS (1.2 equiv, 37.2 g, 0.278 mol) was added solid in one portion. The reaction mixture was maintained at 70 °C for 4 h before being cooled to ambient temperature and quenched with 10 N NaOH (final pH = 8–9). The resulting heterogeneous mixture was extracted with CH₂Cl₂ (2 × 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to a red colored crude oil. This crude mixture was dissolved into MeOH (280 mL) and K₂CO₃ (2.5 equiv, 80.2 g, 0.580 mol) was added.
The resulting reaction mixture was heated to 50 °C for 5 h, cooled to ambient temperature and diluted with H2O (500 mL). The reaction mixture was extracted with CH2Cl2 (2 × 150 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to a crude oil. The crude oil was diluted with acetone (400 mL) and heated to 50 °C. To this stirred solution was added fumaric acid (1.0 equiv, 26.9 g, 0.232 mol) portion wise as a solid over 5 min Upon completion of the addition, the resulting slurry was cooled to ambient temperature (1 h), filtered, and the isolated solid was washed with acetone (100 mL) to give the titled fumarate salt (±)-21 (51.7 g, 0.152 mol, 73 % yield). (±)-21: mp = 161–163 °C; IR (film): νmax = 3412brs, 3029s, 2589brs, 1712s, 1654s, 1526s cm⁻¹; ¹H NMR (d6-DMSO, 500 MHz): δ = 7.29 (m, 5 H), 6.61 (s, 2 H), 3.46 (d, J = 1.5 Hz, 2 H), 3.19 (m, 2 H), 2.96 (ddd, J = 13.5, 4.0, 1.5 Hz, 1 H), 2.55 (d, J = 13.5 Hz, 1 H), 2.31 (ddt, J = 11.5, 5.0, 1.5 Hz, 1 H), 2.13 (ddd, J = 6.0, 5.0, 2.5 Hz, 1 H), 1.91 (m, 2 H) ppm; ¹³C NMR (d6-DMSO, 125 MHz): δ = 166.60, 136.43, 134.34, 129.26, 128.31, 127.46, 60.68, 51.09, 49.88, 49.57, 45.24, 24.40 ppm; HRMS calcd for C12H15NOH⁺ [M + H⁺] 190.1232, found 190.1221.

BMS-281 (±)-1: To a stirred slurry of fumarate salt (±)-21 (1.0 equiv, 51.7 g, 0.152 mol) in MTBE (200 mL) was added aq. KOH (2N, 200 mL). The resulting mixture was stirred at ambient temperature for 30 in before being transferred to a separation funnel. The organic layer was collected and dried over Na2SO4, filtered, and concentrated to a crude oil. The crude oil was diluted with CH3CN (250 mL) and BnNH2 (1.2 equiv, 20 mL, 0.183 mol) and LiCl (1.0 equiv, 6.4 g, 0.152 mol) were added successively. The reaction mixture was stirred at 20 °C for 24 h. The reaction was
quenched with H₂O (500 mL) and extracted with CH₂Cl₂ (2 × 200 mL). The organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to a light yellow solid. The crude solid was dissolved into toluene (100 mL) and heated to 85 °C. Heptane (200 mL) was added to the stirred solution dropwise by addition funnel (30 min). Upon completion of the addition, the solution was cooled to 20 °C over 1 h and then placed into an ice bath (0 °C) and stirred for an additional 1 h. The resulting slurry was filtered and washed with heptane (100 mL) to afford (±)-1 (38.4 g, 0.152 mol, 85% yield) as an off-white crystalline solid. (±)-1: mp = 103–105 °C; Rf = 0.55 (silica, MeOH: CH₂Cl₂, 1:4); IR (film): vₘₐₓ = 3292m, 3127brs, 3034m, 2945m, 2820s, 1500m, 1454s, 1370s cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 7.35-7.29 (m, 8 H), 7.27-7.23 (m, 2 H), 3.95 (d, J = 13.0 Hz, 1 H), 3.73 (d, J = 13.0 Hz, 1 H), 3.56 (d, J = 13.5 Hz, 1 H), 3.52 (d, J = 13.5 Hz), 3.45 (dt, J = 9.0, 4.5 Hz, 1 H), 3.07 (m, 1 H), 3.0 (brs, 1 H), 2.84 (m, 1 H), 2.36 (m, 1 H), 2.09-2.03 (m, 2 H), 1.96 (t, J = 10 Hz, 1 H), 1.36 (m, 1 H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ = 140.47, 138.13, 129.05, 128.43, 128.19, 128.03, 127.05, 70.96, 62.65, 61.11, 58.33, 52.24, 50.73, 29.53 ppm; HRMS calcd for C₁₉H₂₄N₂OH⁺ [M + H⁺] 297.1967, found 297.1956.

**R-O-acetyl mandelic acid salt of BMS-281 (+)-23:** To a stirred solution of (±)-1 (38.4 g, 0.129 mol) in EtOH (200 proof, 500 mL) at 80 °C was added dropwise a solution of R-O-acetyl mandelic acid (1.0 equiv, 25.16 g, 0.129 mol) in EtOH (200 proof, 150 mL) over 10 min. Upon completion of the addition, the reaction mixture was slowly cooled to 60 °C (30 min) during which time the crystalline solid began to form. The resulting slurry was then cooled to 20 °C (2 h).
Stirring was maintained at 20 °C for 8 h before being filtered and washed with EtOH (200 proof, 50 mL) affording (+)-23 (27.9 g, 0.056 mol, 43.9 yield, 90.6 %ee) as a white crystalline solid. Recrystallization from EtOH (200 proof) could provide an ee upgrade to 99.5 %ee (ee was determined by chiral HPLC see section III. Chromatograms). (+)-23: mp (DSC) (10 °C/min) = onset 171 °C, peak 173 °C; [α]_D^{25} = –63.9 (c = 1.0, MeOH); IR (film): \nu_{\text{max}} = 3123\text{m}, 3024\text{m}, 2972\text{m}, 2438\text{m}, 1730\text{s}, 1637\text{s}, 1583\text{s} 1374\text{s}, 1250\text{s} \text{ cm}^{-1}; ^1H NMR (CD3OD, 500 MHz): \delta = 7.54–7.40 (m, 7 H), 7.35–7.25 (m, 8 H), 5.77 (s, 1 H), 4.25 (d, J = 13.5 Hz, 1 H), 4.22 (d, J = 13.5 Hz, 1 H), 3.75 (dt, J = 9.5, 4.5 Hz, 1 H), 3.63 (d, J =13.0 Hz, 1 H), 3.56 (d, J = 13.0 Hz, 1 H), 3.08 (ddd, J = 11.0, 5.0, 2.0 Hz, 1 H), 2.96 (m, 1 H), 2.82 (m, 1 H), 2.13 (s, 3 H), 2.15–2.04 (m, 2 H), 1.95 (t, J = 10.0 Hz, 1 H), 1.68 (ddd, J = 13.5, 12.0, 4.5 Hz, 1 H) ppm; ^13C NMR (CD3OD, 125 MHz): \delta = 176.10, 172.58, 138.74, 138.19, 133.83, 130.92, 130.67, 130.42, 130.35, 129.61, 129.41, 129.25, 128.98, 128.85, 78.98, 69.16, 63.01, 61.80, 59.87, 52.27, 50.23, 27.38, 21.23 ppm; HRMS calcd for C_{19}H_{24}N_{2}O_{2}H^+ [M + H^+] 297.1967, found 297.1956.

Figure 1. X-ray derived ORTEP of bis-HCl salt 24.
Bis-HCl salt 24 (MeOH co-solvate) was serendipitously prepared from 23 while attempting its recrystallization (from MeOH / CH$_2$Cl$_2$) to generate crystals appropriate for single crystal X-ray analysis.

III. Microbial Assays

Table 1: Enantioselective hydrolysis of epoxide 19a/b by using microorganisms.

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>SC Number</th>
<th>Conversion (dil, 20)</th>
<th>Ee of epoxide *</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aureobasidium pullulans</td>
<td>13849</td>
<td>60.4%</td>
<td>-32.4%</td>
<td>2.0</td>
</tr>
<tr>
<td>Cunninghamella echinulata</td>
<td>13973</td>
<td>88.2%</td>
<td>-42.9%</td>
<td>1.5</td>
</tr>
<tr>
<td>Mortierella ramanniana</td>
<td>13842</td>
<td>60.6%</td>
<td>50.1%</td>
<td>3.1</td>
</tr>
<tr>
<td>Curvularia lunata</td>
<td>13918</td>
<td>96.9%</td>
<td>53.7%</td>
<td>1.4</td>
</tr>
<tr>
<td>Aspergillus ustus</td>
<td>16248</td>
<td>80.0%</td>
<td>-27.8%</td>
<td>1.4</td>
</tr>
<tr>
<td>Aspergillus restrictus</td>
<td>16394</td>
<td>82.5%</td>
<td>-64.5%</td>
<td>2.2</td>
</tr>
<tr>
<td>Aspergillus niger</td>
<td>2164</td>
<td>48.3%</td>
<td>-26.5%</td>
<td>2.3</td>
</tr>
<tr>
<td>Aspergillus niger</td>
<td>9719</td>
<td>57.4%</td>
<td>-28.3%</td>
<td>2.0</td>
</tr>
<tr>
<td>Aspergillus terreus</td>
<td>16061</td>
<td>71.7%</td>
<td>-50.6%</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Aspergillus niger</strong></td>
<td><strong>16295</strong></td>
<td><strong>50.4%</strong></td>
<td><strong>-97.1%</strong></td>
<td><strong>184.8</strong></td>
</tr>
<tr>
<td>Aspergillus caespitosus</td>
<td>16312</td>
<td>78.8%</td>
<td>-100.0%</td>
<td>9.8</td>
</tr>
<tr>
<td>Aspergillus ochraceus</td>
<td>16337</td>
<td>68.5%</td>
<td>-78.8%</td>
<td>4.7</td>
</tr>
<tr>
<td>Aspergillus oryzae</td>
<td>16388</td>
<td>64.1%</td>
<td>-34.1%</td>
<td>2.0</td>
</tr>
<tr>
<td>Beauveria bassiana</td>
<td>16102</td>
<td>52.4%</td>
<td>-49.1%</td>
<td>4.1</td>
</tr>
<tr>
<td>Nocardia autotrophica</td>
<td>14721</td>
<td>59.5%</td>
<td>-48.2%</td>
<td>3.1</td>
</tr>
<tr>
<td>Beauveria bassiana</td>
<td>16103</td>
<td>42.8%</td>
<td>-46.2%</td>
<td>6.6</td>
</tr>
<tr>
<td>Aspergillus restrictus</td>
<td>16394</td>
<td>48.0%</td>
<td>-85.3%</td>
<td>68.1</td>
</tr>
</tbody>
</table>

* Enantiomeric excess with positive value is for epoxide (→)-19 and enantiomeric excess with negative value is for epoxide (+)-19. Conversion and ee were calculated based on HPLC response at 220 nm.

Materials and method

Growth medium and sample analysis-

The microorganisms were grown on soybean meal glucose medium. The medium was prepared from dextrose anhydrous 20 g/L, yeast extract 5.0 g/L, nutrisoy 5.0 g/L, sodium chloride 5.0 g/L and potassium hydrogen phosphate 5.0 g/L. The pH of the medium was adjusted to 7.0 and medium was autoclaved for 15 min. prior to use. The microorganism screening experiments were done by using two methods. **Method 1:** In 24-well plate
formet 50 µL spore suspension of a microorganism was incubated with 2.0 mL of the same medium for two days at 28°C, 600 rpm. A stock solution of the racemic epoxide (2.0 mg/10 µL) was prepared in DMSO and 10 µL stock solution was added per well. The incubation was continued for five days at 28°C, 600 rpm. Biotransformation mixture from each well was extracted with ethyl acetate, solvent was removed, and the residue was dissolved in 1.5 mL acetonitrile and analyzed by HPLC. **Method 2:** Soybean glucose medium 10 mL per flask was inoculated with 0.2 mL culture of the microorganism and the flasks were incubated at 28°C, 250 rpm for two days. Second stage culture was prepared by inoculating 9.0 mL of same medium with 1.0 mL broth from first stage culture. The second stage culture was incubated under same conditions for one day. A stock solution of the racemic epoxide (2.0 mg/10 µL) was prepared in DMSO and 50 µL stock solution was added per well. The incubation was continued for five days under same conditions. Biotransformation mixture from flasks was centrifuged, supernatant was extracted with ethyl acetate, solvent was removed and the residue was analyzed by using HPLC.
IV. Chromatograms

1. Classical Resolution

![Chemical structures](image)

Samples were analyzed on HPLC column, Chiralpak IA (DEA only) 4.6 × 150mm by using solvent A (0.05% DEA in heptane) and solvent B (0.05% DEA in MeOH:EtOH, 1:1) with an isocratic gradient of 20% solvent B (stop time 15 min.) at a flow rate of 0.7 mL/min. The detection was done by UV at 220 nm. The retention times for two enantiomers are 7.3 min (desired) and 9.1 min (undesired).

Chromatogram of 1 (racemic).

Chromatogram of the mother liquor (−91.9 % ee).

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2012
Chromatogram of 1 (enantioenriched, +90.6 %ee).

\[ (-)-1 \]

\[
\begin{array}{c}
\text{AP} \\
95.34 \\
4.68 \\
\end{array}
\]

Chromatogram of 1 after recrystallization (+99.6 %ee).

\[ (-)-1 \]

\[
\begin{array}{c}
\text{AP} \\
97.77 \\
0.22 \\
\end{array}
\]
2. Biocatalytic Resolution

Samples were analyzed on HPLC column, Chiralpak AS-RH 4.6x150mm by using solvent A (10 mM ammonium acetate in water-acetonitrile, 90:10) and solvent B (10 mM ammonium acetate in Water-acetonitrile, 10:90) with a gradient of 0 % to 10% of B in 35 min (stop time 37 min.) at a flow rate of 0.5 mL/min. The detection was done by UV at 220 nm. The retention times for two enantiomers are 25.38 min and 28.59 min. Diol appears at retention time 6.51 min.
V. Copies of $^1$H NMR and $^{13}$C NMR Spectra

$^1$H NMR (CD$_3$OD, 500 MHz) for 7

$^{13}$C NMR (CD$_3$OD, 125 MHz) for 7
$^1$H NMR (CD$_3$OD, 500 MHz) for 9

$^{13}$C NMR (CD$_3$OD, 125 MHz) for 9
$^1$H NMR (CDCl$_3$, 500 MHz) for 11 (bottom anomer)

11 (bottom anomer)

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 11 (bottom anomer)
\[^1H\ NMR\ (CDCl_3,\ 500\ MHz)\ for\ \textbf{11}\ (top\ anomer)\]

\[
\begin{align*}
\text{TsO} & \quad \text{TsO}\ \\
\text{OMe} & \quad \text{OMe}
\end{align*}
\]

\[
\textbf{11}\ (top\ anomer)
\]

\[^{13}C\ NMR\ (CDCl_3,\ 125\ MHz)\ for\ \textbf{11}\ (top\ anomer)\]

\[
\begin{align*}
\text{13C NMR} & \quad (CDCl_3,\ 125\ MHz)\ for\ \textbf{11}\ (top\ anomer)
\end{align*}
\]
$^1$H NMR (CDCl$_3$, 500 MHz) for 12 (anomeric mixture)

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 12 (anomeric mixture)
$^1$H NMR (CDCl$_3$, 500 MHz) for 12 (anomeric mixture)

12 (minor anomer)

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 12 (anomeric mixture)
$^1$H NMR (CDCl$_3$, 500 MHz) for 13a (faster eluting anomer)

13a (faster eluting anomer)

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 13a (faster eluting anomer)
$^1$H NMR (CDCl$_3$, 500 MHz) for 13b (slower eluting anomer)

13b (slower eluting anomer)

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 13b (slower eluting anomer)
$^1$H NMR (CDCl$_3$, 500 MHz) for 17

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 17
$^1$H NMR (CDCl$_3$, 500 MHz) for 18

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 18
$^1$H NMR (CDCl$_3$, 500 MHz) for 19

$^{13}$C NMR (CDCl$_3$, 125 MHz) for 19
\begin{align*}
\text{\textsuperscript{1}H NMR (\textit{d}_6\text{-DMSO, 500 MHz}) for 21} \\

(\pm)-21 \\

\text{\textsuperscript{13}C NMR (\textit{d}_6\text{-DMSO, 125 MHz}) for 21} \\
\end{align*}
**1H NMR (CDCl₃, 500 MHz) for 1**

**13C NMR (CDCl₃, 125 MHz) for 1**
$^{1}H$ NMR (CD$_3$OD, 500 MHz) for 23

$^{13}$C NMR (CD$_3$OD, 125 MHz) for 23