Supporting Information

Asymmetric Aza-Mannich Reactions of Sulfinimines: Scope and Application to the Total Synthesis of a Bromopyrrole Alkaloid.

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General Information. Optical Rotations were measured on a Perkin Elmer model 341 polarimeter. ^1H and ^{13}C spectra were measured on either a Bruker 400 MHz or 600 MHz instrument. In the case of ^{13}C spectra, these measurements were taken with full proton decoupling. Data for proton spectra were reported as follows: chemical shifts are reported in ppm, utilizing the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, nd = narrow doublet), coupling constants (Hz). Analytical high performance liquid chromatography (HPLC) was performed on an agilent 1100 series instrument at 280 nM employing either a YMC diol 120 100 x 4.6 mm (achiral) column or a Diacel ChiralPak AD 250 x 4.6 mm (chiral) column using an isocratic solvent mixture noted in Table SI-1 at a flow rate of 1 mL/min. For thin layer chromatography (TLC) analysis throughout this work, Analtech Uniplate precoated plates were used in conjunction with a variety of developing reagents including phosphomolybdic acid (PMA) and para-anisaldehyde (PAA) in addition to UV light. Purification of materials was carried out using an ISCO chromatography system with pre-packed silica gel columns. High resolution mass spectrometry (HRMS) was performed by M-Scan, Inc. and elemental analyses by QTI technologies. All reagents and solvents were used as received from commercial sources.

Determination of absolute configuration:

Scheme SI-1: Absolute Configuration^a.

Although the literature reported the rotation of the (R,S) diastereomer at a concentration of 5 g/100mL, we had difficulty preparing a solution at 2 g/100mL concentration. This observation taken together with a measured rotation of greater magnitude than that reported for the higher concentration suggested that there was a misprint in the original paper and that the concentration should have been reported as “0.5” rather than “5”. To support this hypothesis we re-measured the (R,S) configured diastereomer at a

concentration of 0.7 g/100mL and the (S,S)-diastereomer at 0.5 g/mL and found their respective rotations were in agreement with those reported in the literature.

Mechanistic Discussion:

Placing our process the context of Ellman's work on enamide-aldehyde^{7j} condensations, we discounted approach of our electrophile from the top face of the (*R*)-enamide due to the greater steric bulk of the N-sulfonyl imine nitrogen in comparison to the aldehyde oxygen. This sulfonyl substitution also restricts trajectory of the electrophile to the plane of the electrophile opposite the sulfonyl group where the nitrogen lone pair is available for complexation to the lithium counter ion. Taking these two factors into account, it is apparent that the configuration of the newly formed chiral center will depend on the *E* or *Z* configuration of the electrophile (Figure 1). In the case of the *Z* isomer, A(1,3) strain between R₂ and R₃ in conformer **B** dictates that most if not all of this isomer will exist in conformer **A**. Complexation of the electrophile lone pair in **A** to the lithium counter ion is blocked by unfavorable steric interaction with R₂, resulting in the observed lack of reactivity for the *Z* isomer. Although this same issue exists with conformer **C** of the *E* electrophile, the much smaller A(1,3) interaction between R₂ and the imine proton means that conformer **D**, is sufficiently populated for the reaction to proceed, delivering the observed *S* configuration at the nascent stereocenter. This is born out by the data; condensation of **1a** and **2a** delivered a >99:1 ratio of diastereomers; the corresponding reaction of **1a** with benzaldehyde under the same conditions was reported^{7j} to deliver only a 2.7:1 ratio of diastereomers.

Figure SI-1: Mechanistic Rationale.

Sulfinime Stating Materials: All materials were prepared using Ellman's general procedure as described in the text of the paper utilizing commercially available ketone starting materials.

(*Rs*)-(+)- 2-Methylpropane-2-sulfinic acid (1-pyridin-3-yl-(*E*)-ethylidene)-amide (**1d**)
 $[\alpha]_{\text{D}}^{20} + 6.4^{\circ}$ ($c = 0.68$ in CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 9.02 (s, 1H), 8.61 (d, $J = 5.5$ Hz, 1H), 8.08 (dd, $J = 7.1, 2.3$ Hz, 1H), 7.35 (d, $J = 7.5, 5.5$ Hz, 1H), 2.72 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 195.8, 52.5, 148.9, 134.5, 131.2, 122.6, 54.3, 25.7, 21.6, 21.1. HRMS calculated for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{OS}$ (MH^+) 225.1062, found 225.1077.

(*Rs*)-(-)-2-Methylpropane-2-sulfinic acid (1-pyridin-2-yl-(*E*)-ethylidene)amide (**1e**).
 This material has been reported in racemic form in the literature; the titled enantiomer was found to have $[\alpha]_{\text{D}}^{20} -45.4$ ($c = 0.31$, CHCl_3).

(*Rs*)-(-)-2-Methylpropane-2-sulfinic acid [1-(2-methoxyphenyl)-(*E*)ethylidene]amide (**1f**).
 $[\alpha]_{\text{D}}^{20} -116$ ($c = 0.49$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.45 (d, $J = 7.4$ Hz, 1 H), 7.38 (dd, $J = 7.4, 7.4$ Hz, 1 H), 6.97 (dd, $J = 7.4, 7.4$ Hz, 1 H), 6.92 (d, $J = 7.4$ Hz, 1 H), 3.85 (s, 1 H), 2.71 (s, 2.2 H), 2.46 (s, 0.8 H), 1.30 (s, 6.7 H), 1.22 (s, 2.3 H); ^{13}C NMR (400 MHz, CDCl_3 , major isomer): δ 180.8, 157.2, 131.5, 130.5, 129.4, 120.4, 111.2, 56.8, 55.3, 24.2, 22.2; HRMS (ESI) m/z Calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_2\text{S}$ (MH^+): 254.1215. Found 254.1219.

(Rs)-(-)-2-Methylpropane-2-sulfinic acid isopropylidene-amide (1h)

$[\alpha]_D^{20}$ -230 ($c = 1.07$, CHCl_3); ^1H NMR (600 MHz, CDCl_3): δ 2.33 (s, 3 H), 2.18 (s, 3 H), 1.22 (s, 9 H); ^{13}C NMR (600 MHz, CDCl_3): δ 183.1, 56.2, 30.6, 23.8, 22.2; HRMS (ESI) m/z Calcd for $\text{C}_7\text{H}_{15}\text{NOS}$ (MH^+): 162.0953. Found 162.0948.

Sulfonyl Imine Stating Materials: All materials were prepared using Ruano's general procedure as described in the text of the paper utilizing commercially available aldehyde starting materials.

2-Methylpropane-2-sulfonic acid (E)-propylideneamide (2b).

^1H NMR (400 MHz, CDCl_3): δ 8.66 (t, $J = 3.8$ Hz, 1 H), 2.60 (dq, $J = 3.8, 7.4$ Hz, 2 H), 1.44 (s, 9 H), 1.19 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (400 MHz, CDCl_3): δ 182.0, 57.8, 29.7, 23.8, 22.2; HRMS (ESI) m/z Calcd for $\text{C}_7\text{H}_{16}\text{NO}_2\text{S}$ (MH^+): 178.0902. Found 178.0895.

2-Methylpropane-2-sulfonic acid (E)-(2,2-dimethylpropylidene)amide (2c).

^1H NMR (400 MHz, CDCl_3): δ 8.47 (s, 1H), 1.42 (s, 9 H), 1.19 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 187.0, 58.0, 38.2, 25.9, 23.9; HRMS (ESI) m/z Calcd for $\text{C}_9\text{H}_{20}\text{NO}_2\text{S}$ (MH^+): 206.1215. Found 206.1204.

2-Methylpropane-2-sulfonic acid 4-methoxy-(E)-benzylideneamide (2d).

^1H NMR (400 MHz, CDCl_3): δ 8.94 (s, 1 H), 7.93 (d, J = 8.9 Hz, 2 H), 7.01 (d, J = 8.9 Hz, 2 H), 3.91 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 171.8, 165.2, 133.5, 125.3, 114.6, 58.2, 55.6, 24.0; HRMS (ESI) m/z Calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3\text{S}$ (MH^+): 256.1007. Found 256.1008.

2-Methylpropane-2-sulfonic acid pyridin-2-yl-(E)-methyleamide (2f).

^1H NMR (400 MHz, CDCl_3): δ 9.07 (s, 1 H), 8.76 (d, J = 4.7 Hz, 1 H), 8.15 (d, J = 7.8 Hz, 1 H), 7.83 (dd, J = 7.8 Hz, 1 H), 7.48 (dd, J = 4.7, 7.8 Hz, 1 H), 1.45 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 173.4, 151.1, 150.5, 136.9, 127.6, 123.7, 58.4, 23.8; HRMS (ESI) m/z Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_2\text{S}$ (MH^+): 227.0854. Found 227.0858.

2-Methylpropane-2-sulfonic acid (3-phenyl-(E)-allylidene)amide (2g).

^1H NMR (400 MHz, CDCl_3): δ 8.79 (d, J = 9.4 Hz, 1 H), 7.61-7.59 (m, 2 H), 7.51 (d, J = 15.8 Hz, 1 H), 7.47-7.44 (m, 3 H), 7.06 (dd, J = 9.4, 15.8 Hz, 1 H), 1.47 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 173.6, 153.7, 134.1, 131.6, 129.2, 128.6, 124.7, 58.1, 23.9; HRMS (ESI) m/z Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_2\text{S}$ (MH^+): 252.1058. Found 252.1051.

Condensation Products:

(Rs, S)- (+)-2-Methyl-propane-2-sulfonic acid [3-(4-cyano-phenyl)-3-(2-methyl-propane-2-sulfinylimino)-1-phenyl-propyl]-amide (3b)

$[\alpha]_{\text{D}}^{20} + 85.8^\circ$ (c = 0.31 in CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, J = 7.5 Hz, 2H), 7.73 (d, J = 7.5 Hz, 2H), 7.38 (m, 4H), 7.26 (m, 1H), 6.88 (d, J = 7.2 Hz, 1H), 4.72

(m, 1H), 3.70 (t, $J = 9.5$ Hz, 1H), 3.42 (dd, $J = 9.6, 2.5$ Hz, 1H), 1.45 (s, 9H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 176.1, 142.7, 140.8, 132.6, 129.0, 128.4, 128.0, 118.1, 115.4, 59.1, 58.8, 55.3, 43.3, 23.9, 22.7. HRMS calculated for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3\text{S}_2$ (MH^+) 474.1885, found 474.1880. Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3\text{S}_2$: C 60.86, H 6.60, N 8.87. Found: C 60.80, H 6.39, N 8.70.

(*Rs, S*)- (+)-2-Methyl-propane-2-sulfonic acid [3-(4-methoxy-phenyl)-3-(2-methyl-propane-2-sulfinylimino)-1-phenyl-propyl]-amide (**3c**)

$[\alpha]_{\text{D}}^{20} + 113.6^\circ$ ($c = 0.52$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 6.5$ Hz, 2H), 7.36 (t, $J = 7.0$ Hz, 2H), 7.25 (t, $J = 7.2$ Hz, 1H), 7.14 (d, $J = 6.0$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 2H), 4.71 (m, 1H), 3.88 (s, 3H), 3.62 (t, $J = 9.5$ Hz, 1H), 3.36 (dd, $J = 9.0, 2.3$ Hz, 1H), 1.45 (s, 9H), 1.08 (s, 9H). ^{13}C NMR (400 MHz, CDCl_3) δ 176.1, 163.1, 143.7, 129.8, 129.2, 128.9, 127.7, 126.4, 114.3, 59.1, 58.0, 56.1, 55.4, 22.8, 21.1. HRMS calculated for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{S}_2$ (MH^+) 479.2038, found 479.2052. Anal. Calcd for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{S}_2$: C 60.22, H 7.16, N 5.85. Found: C 60.15, H 7.00, N 6.07.

(*Rs, S*)- (+)-2-Methyl-propane-2-sulfonic acid [3-(2-methyl-propane-2-sulfinylimino)-1-phenyl-3-pyridin-3-yl-propyl]-amide (**3d**).

$[\alpha]_{\text{D}}^{20} + 16.0^\circ$ ($c = 0.52$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 9.12 (s, 1H), 8.76 (d, $J = 2.0$ Hz, 1H), 8.23 (d, $J = 7.0$ Hz, 1H), 7.45 (m, 2H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.29 (m, 1H), 7.01 (d, $J = 6.0$ Hz, 1H), 4.81 (m, 1H), 3.80 (t, $J = 10.5$ Hz, 1H), 3.48 (dd, $J = 9.5, 2.5$ Hz, 1H), 1.45 (s, 9H), 1.08 (s, 9H). ^{13}C NMR (400 MHz, CDCl_3) δ 175.7, 152.7, 148.7, 135.6, 132.6, 128.9, 127.9, 126.4, 123.8, 122.2, 59.1, 58.6, 55.5, 43.2, 23.9, 22.1. HRMS calculated for $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}_3\text{S}_2$ (MH^+) 450.1885, found 450.1886.

(*Rs*, *S*)-(+)-2-Methylpropane-2-sulfonic acid [3-(2-methylpropane-2-sulfinylimino)-1-phenyl-3-pyridin-2-ylpropyl]amide (**3e**).

$[\alpha]_D^{20} +7.77$ ($c = 2.3$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 8.74 (d, $J = 4.5$ Hz, 1 H), 8.14 (d, $J = 7.8$ Hz, 1 H), 7.81 (ddd, $J = 1.7, 7.8, 7.8$ Hz, 1 H), 7.51 (d, $J = 7.4$ Hz, 2 H), 7.43 (ddd, $J = 0.9, 4.5, 7.2$ Hz, 1 H), 7.37 (dd, $J = 7.4, 7.4$ Hz, 2 H), 7.27 (dd, $J = 7.4, 7.4$ Hz, 1 H), 6.89 (d, $J = 7.8$ Hz, 1 H), 5.07 (ddd, $J = 4.6, 7.8, 11.8$ Hz, 1 H), 4.06 (dd, $J = 4.6, 12.1$ Hz, 1 H), 3.54 (dd, $J = 11.8, 11.8$ Hz, 1 H), 1.47 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 177.7, 154.0, 148.9, 143.8, 136.8, 128.6, 127.3, 126.4, 126.1, 123.0, 59.0, 58.3, 55.6, 42.1, 23.9, 22.8; HRMS (ESI) m/z Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_3\text{S}_2$ (MH^+): 450.1885. Found 450.1863. Anal. Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_3\text{S}_2$: C 58.77, H 6.95, N 9.35. Found: C 58.44, H 7.04, N 9.26.

(*Rs*, *S*)-(-)-2-Methylpropane-2-sulfonic acid [3-(2-methoxyphenyl)-3-(2-methylpropane-2-sulfinylimino)-1-phenylpropyl]amide (**3f**).

$[\alpha]_D^{20} -12.5$ ($c = 1.00$, CDCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.67 (d, $J = 7.4$ Hz, 1 H), 7.46 (dd, $J = 7.4, 7.4$ Hz, 1 H), 7.33-7.23 (m, 5 H), 7.08 (dd, $J = 7.4$ Hz, 1 H), 7.02 (d, $J = 6.8$ Hz, 1 H), 6.97 (d, $J = 8.3$ Hz, 1 H), 4.66-4.61 (m, 1 H), 3.23 (s, 3 H), 3.76-3.71 (m, 2 H), 1.40 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 181.2, 157.1, 144.0, 132.4, 132.0, 128.7, 127.4, 127.3, 126.5, 121.1, 111.1, 58.9, 57.9, 55.5, 54.9, 24.0, 22.5; HRMS (ESI) m/z Calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_4\text{S}_2$ (MH^+): 479.2046. Found 479.2038.

(*Rs*, *S*)-(+)-2-Methyl-propane-2-sulfonic acid [3-furan-2-yl-3-(2-methyl-propane-2-sulfinylimino)-1-phenyl-propyl]-amide (**3g**).

$[\alpha]_D^{20} +38.4$ ($c = 0.89$, CDCl_3) ^1H NMR (600 MHz, CDCl_3): δ 7.49 (d, $J = 8$ Hz, 2 H), 7.38 (t, $J = 7.6$ Hz, 2 H), 7.29 (t, $J = 7.2$ Hz, 1 H), 7.20 (nd, $J = 3$ Hz, 1 H), 7.03 (d, $J = 7.3$ Hz, 1 H), 6.60 (nd, $J = 3.2$ Hz, 1 H), 5.05-5.01 (m, 1 H), 3.56 (dd, $J = 14.7, 2.7$ Hz, 1 H), 3.36 (dd, $J = 14.7, 4.8$ Hz, 1 H), 1.40 (s, 9 H), 1.09 (s, 9 H); ^{13}C NMR (600 MHz, CDCl_3): δ 166.9, 152.5, 146.2, 143.7, 128.9, 127.8, 126.5, 115.4, 113.0, 59.3, 58.3, 55.9, 53.6, 43.0, 24.1, 22.7; HRMS (ESI) m/z Calcd for $\text{C}_{21}\text{H}_{31}\text{N}_2\text{O}_4\text{S}_2$ (MH^+): 439.1725 Found 439.1721.

(*Rs*, *S*)-(-)-2-Methyl-propane-2-sulfonic acid [3-(2-methyl-propane-2-sulfinylimino)-1-phenyl-butyl]-amide (**3h**).

$[\alpha]_D^{20} -80.7$ ($c = 0.91$, CDCl_3) ^1H NMR major distereomer (600 MHz, CDCl_3): δ 7.41-7.26 (series of m, 5 H), 7.03 (d, $J = 7.7$ Hz, 1 H), 4.93-4.90 (m, 1 H), 3.50 (dd, $J = 12.5, 12.5$ Hz, 1 H), 2.63 (dd, $J = 13.0, 5.0$ Hz, 1 H), 2.39 (s, 3H), 1.33 (s, 9 H), 1.13 (s, 9 H); ^{13}C NMR (600 MHz, CDCl_3): δ 182.7, 143.3, 129.0, 127.8, 126.6, 59.2, 57.4, 54.9, 48.1, 27.6, 24.2, 22.4; HRMS (ESI) m/z Calcd for $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_3\text{S}_2$ (MH^+): 387.1776 Found 387.1785.

(*Rs, S*)-(-)-2-Methylpropane-2-sulfonic acid [3-(2-methylpropane-2-sulfinylimino)-1-phenylpentyl]-amide (**3i**).

$[\alpha]_D^{20}$ -84.7 ($c = 0.99$, CDCl_3) ^1H NMR (600 MHz, CDCl_3): δ 7.41 (d, $J = 7.4$ Hz, 2 H), 7.35 (t, $J = 7.4$ Hz, 2 H), 7.28 (dd, $J = 7.4, 7.4$ Hz, 1 H), 7.08 (d, $J = 7.6$ Hz, 1 H), 4.91-4.87 (m, 1 H), 3.46 (dd, $J = 12.4, 12.4$ Hz, 1 H), 3.00-2.95 (m, 1 H), 2.63 (dd, $J = 12.7, 4.8$ Hz, 1 H), 2.48-2.42 (m, 1 H), 1.36 (s, 9 H), 1.19 (t, $J = 7.3$ Hz, 3 H), 1.12 (s, 9 H); ^{13}C NMR (600 MHz, CDCl_3): δ 185.7, 143.4, 129.0, 127.7, 126.6, 59.2, 57.7, 55.1, 47.4, 33.3, 24.2, 22.5, 9.7; HRMS (ESI) m/z Calcd for $\text{C}_{19}\text{H}_{33}\text{N}_2\text{O}_3\text{S}_2$ (MH^+): 401.1933 Found 401.1927.

(*Rs, S*)-(-)-2-Methylpropane-2-sulfonic acid [4-benzyloxy-3-(2-methylpropane-2-sulfinylimino)-1-phenylbutyl]amide (**3j**).

$[\alpha]_D^{20}$ -63.3 ($c = 0.31$, CHCl_3) ^1H NMR (400 MHz, CDCl_3): δ 7.41-7.26 (m, 10 H), 6.91 (d, $J = 7.8$ Hz, 1 H), 4.99-4.93 (m, 1 H), 4.69 (d, $J = 11.8$ Hz, 1 H), 4.65 (d, $J = 11.8$ Hz, 1 H), 4.59 (d, $J = 15.2$ Hz, 1 H), 4.33 (d, $J = 15.2$ Hz, 1 H), 3.36 (dd, $J = 12.3, 12.3$ Hz, 1 H), 3.04 (dd, $J = 4.6, 12.3$ Hz, 1 H), 1.33 (s, 9 H), 1.12 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 182.9, 137.6, 128.8, 128.5, 128.0, 127.90, 127.87, 127.5, 126.3, 73.5, 73.4, 59.1, 57.5, 52.8, 40.4, 24.3, 22.4; HRMS (ESI) m/z Calcd for $\text{C}_{25}\text{H}_{37}\text{N}_2\text{O}_4\text{S}_2$ (MH^+): 493.2195. Found 493.2207.

(*Rs, R*)-(+)-2-Methylpropane-2-sulfonic acid [1-ethyl-3-(2-methylpropane-2-sulfinylimino)-3-phenylpropyl]amide (**3k**).

$[\alpha]_D^{20}$ +77.3 ($c = 0.56$, CHCl_3) ^1H NMR (400 MHz, CDCl_3): δ 7.88 (d, $J = 7.4$ Hz, 2 H), 7.53-7.40 (m, 3 H), 5.89 (d, $J = 7.4$ Hz, 1 H), 3.82-3.78 (m, 1 H), 3.43-3.38 (m, 2 H),

1.91-1.86 (m, 1 H), 1.79-1.72 (m, 1 H), 1.37 (s, 9 H), 1.18 (s, 9 H), 1.05 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (400 MHz, CDCl_3): δ 178.9, 136.7, 132.2, 128.7, 127.8, 59.2, 57.5, 53.2, 37.8, 30.6, 24.1, 22.5, 9.3; HRMS (ESI) m/z Calcd for $\text{C}_{19}\text{H}_{33}\text{N}_2\text{O}_3\text{S}_2$ (MH^+): 401.1933. Found 401.1920. Anal. Calcd for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_3\text{S}_2$: C 56.97, H 8.05, N 6.99. Found: C 56.92, H 8.16, N 6.77.

(*Rs*, *S*)-(+)-2-Methylpropane-2-sulfonic acid {2,2-dimethyl-1-[2-(2-methylpropane-2-sulfinylimino)-2-phenylethyl]propyl}amide (**3l**).

$[\alpha]_{\text{D}}^{20} +122.4$ ($c = 1.36$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.89 (d, $J = 7.2$ Hz, 2 H), 7.52-7.43 (m, 3 H), 6.07 (d, $J = 7.0$ Hz, 1 H), 3.85-3.79 (m, 1 H), 3.50-3.41 (m, 2 H), 1.39 (s, 9 H), 1.34 (s, 9 H), 1.07 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 180.5, 136.9, 132.1, 128.6, 128.1, 59.6, 57.7, 57.3, 36.6, 35.7, 26.7, 24.7, 22.6; HRMS (ESI) m/z Calcd for $\text{C}_{21}\text{H}_{37}\text{N}_2\text{O}_3\text{S}_2$ (MH^+): 429.2246. Found 429.2236. Anal. Calcd for $\text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_3\text{S}_2$: C 58.84, H 8.47, N 6.54. Found: C 58.78, H 8.07, N 6.36.

(*Rs*, *S*)-(+)-2-Methylpropane-2-sulfonic acid [3-(2-methylpropane-2-sulfinylimino)-1-(4-nitro-phenyl)-3-phenyl-propyl]-amide (**3m**)

$[\alpha]_{\text{D}}^{20} +19.8$ ($c = 0.66$, CDCl_3) ^1H NMR (600 MHz, CDCl_3): δ 8.25 (d, $J = 9.1$ Hz, 2 H), 7.95 (d, $J = 7.5$ Hz, 2 H), 7.68 (d, $J = 8.7$ Hz, 2 H), 7.62-7.53 (series of m, 3 H), 7.21 (d, $J = 7.3$ Hz, 1 H), 4.94-4.90 (m, 1 H), 3.71 (dd, $J = 13.3, 12.3$ Hz, 1 H), 3.45 (dd, $J = 13.5, 4.8$ Hz, 1 H), 1.46 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR (600 MHz, CDCl_3): δ 177.0, 151.0, 147.6, 136.4, 132.9, 129.3, 127.9, 127.5, 124.4, 59.5, 58.4, 55.4, 53.6, 42.2, 24.0, 22.7; HRMS (ESI) m/z Calcd for $\text{C}_{23}\text{H}_{32}\text{N}_3\text{O}_5\text{S}_2$ (MH^+): 494.1783 Found 494.1805.

(*Rs*, *S*)-(+)-2-Methylpropane-2-sulfonic acid [1-(4-methoxyphenyl)-3-(2-methylpropane-2-sulfinylimino)-3-phenylpropyl]amide (**3n**).

$[\alpha]_D^{20} +19.6$ ($c = 1.05$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.93 (d, $J = 7.2$ Hz, 2 H), 7.56-7.48 (m, 3 H), 7.37 (d, $J = 8.6$ Hz, 2 H), 6.95 (d, $J = 7.6$ Hz, 1 H), 6.91 (d, $J = 8.6$ Hz, 2 H), 4.78 (ddd, $J = 4.8, 7.5, 11.8$ Hz, 1 H), 3.82 (s, 3 H), 3.74 (dd, $J = 11.8, 13.4$ Hz, 1 H), 3.41 (dd, $J = 4.8, 13.4$ Hz, 1 H), 1.44 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 177.6, 159.0, 136.8, 135.7, 132.3, 128.9, 127.8, 127.5, 114.2, 59.0, 58.2, 55.20, 55.18, 43.1, 23.9, 22.7; HRMS (ESI) m/z Calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_4\text{S}_2$ (MH^+): 479.2038. Found 479.2047. Anal. Calcd for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{S}_2$: C 60.22, H 7.16, N 5.85. Found: C 60.11, H 7.26, N 5.66.

(*Rs*, *S*)-(+)-2-Methylpropane-2-sulfonic acid [3-(2-methylpropane-2-sulfinylimino)-3-phenyl-1-pyridin-2-ylpropyl]amide (**3o**).

Condensing sulfinimine **1a** (100 mg, 0.45 mmol) with sulfonyl imine **2g** (132 mg, 0.58 mmol) under the reaction conditions stated in the general procedure yielded, after chromatography (SiO_2 , 50% ethyl acetate/hexanes) as a yellow oil, 123 mg, (61%): $[\alpha]_D^{20} +19.0$ ($c = 2.60$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 8.57 (d, $J = 4.6$ Hz, 1 H), 8.07 (d, $J = 7.3$ Hz, 2 H), 7.72 (ddd, $J = 1.7, 7.6, 7.6$ Hz, 1 H), 7.62 (d, $J = 7.6$ Hz, 1 H), 7.55-7.48 (m, 3 H), 7.20 (ddd, $J = 0.9, 4.6, 7.6$ Hz, 1 H), 6.89 (d, $J = 8.1$ Hz), 5.01 (ddd, $J = 5.0, 8.2, 11.3$ Hz, 1 H), 3.76 (dd, $J = 5.0, 13.5$ Hz, 1 H), 3.59 (dd, $J = 11.3, 13.5$ Hz, 1 H), 1.40 (s, 9 H), 1.08 (s, 9 H); ^{13}C NMR (400 MHz, CDCl_3): δ 177.4, 161.9, 149.1, 137.2, 136.6, 132.4, 128.9, 128.0, 122.5, 120.7, 59.6, 57.9, 57.7, 40.8, 24.0, 22.6; HRMS (ESI) m/z Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_3\text{S}_2$ (MH^+): 450.1885. Found 450.1871. Anal. Calcd for $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}_3\text{S}_2$: C 58.77, H 6.95, N 9.35. Found: C 58.78, H 7.16, N 9.08.

(*Rs*, *S*)-(+)- 2-Methyl-propane-2-sulfonic acid {1-[2-(2-methyl-propane-2-sulfinylimino)-2-phenyl-ethyl]-3-phenyl-allyl}-amide (**3p**)

$[\alpha]_D^{20} +48.3$ (c = 0.91, CDCl_3) ^1H NMR (600 MHz, CDCl_3): δ 7.94 (d, J = 7.3 Hz, 2 H), 7.58-7.28 (series of m, 8 H), 6.62 (d, J = 6.1 Hz, 1 H), 6.42 (d, J = 6.9 Hz, 1 H), 6.29 (d, J = 15.6, 7.6 Hz, 1 H) 4.52-4.48 (m, 1 H), 3.64 (dd, J = 12.4, 12.4 Hz, 1 H), 3.45 (dd, J = 13.6, 5.2 Hz, 1 H), 1.42 (s, 9 H), 1.25 (s, 9 H); ^{13}C NMR (600 MHz, CDCl_3): δ 177.2, 137.0, 136.4, 132.5, 131.4, 130.6, 129.0, 128.8, 128.7, 128.1, 128.0, 126.8, 59.4, 58.3, 54.4, 40.2, 24.3, 22.8; HRMS (ESI) m/z Calcd for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_3\text{S}_2$ (MH^+): 475.2089 Found 475.2097.

Table SI-1: Retention times of selected compounds on achiral and chiral columns.

Compound	Isopropanol (%)	Heptane (%)	T _R achiral (min)	T _R chiral (min)
1d	20	80	2.763	5.255
1f	20	80	1.832	4.515
1h	20	80	1.700	3.709
2g	20	80	1.856	5.355
2h	60	40	1.653	3.575
2i	20	80	1.796	5.037
3d	20	80	2.261	7.671
3f	20	80	1.930	8.610
3g	20	80	1.793	8.618
3h	20	80	1.806	4.918
3i	20	80	1.553	4.513
3j	20	80	1.553	4.956
3m	20	80	1.986	19.899
3o	20	80	1.731	9.268

Manzacidin C Synthesis

(-)-2-Methylpropane-2-sulfonic acid [(1S, 3S)-4-benzyloxy-3-methyl-3-(2-(Rs)-methylpropane-2-sulfinylamino)-1-((E)-styryl)butyl]amide (4).

To a solution of **1j** (3.97 g, 14.8 mmol) and **2h** (4.10 g, 16.3 mmol) in THF (150 mL) at -78 °C was added dropwise during 1 hour LHMDS (14.8 mL, 1M in THF). The mixture was stirred at -78 °C overnight and then quenched cold by the dropwise addition of acetic acid (1.85 mL) in THF (20 mL). Concentration of the reaction mixture followed by purification of the residue by flash chromatography (SiO₂, hexanes : ethyl acetate = 3 : 1) delivered the product as a yellow oil, 6.07 g, (79%): $[\alpha]_D^{20} = -48.1$ ($c = 1.10$, CHCl₃) ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.23 (m, 10 H), 6.54 (d, $J = 15.9$ Hz, 1 H), 6.39 (d, $J = 7.6$ Hz, 1 H), 6.15 (dd, $J = 7.4, 15.8$ Hz, 1 H), 4.65 (s, 2 H), 4.61-4.57 (m, 1 H), 4.51 (d, $J = 15.1$ Hz, 1 H), 4.29 (d, $J = 15.1$ Hz, 1 H), 3.24 (dd, $J = 11.9, 11.9$ Hz, 1 H), 3.01 (dd, $J = 4.4, 11.9$ Hz, 1 H), 1.33 (s, 3 H), 1.31 (s, 3 H); ¹³C NMR (100.6 MHz, CDCl₃): δ 182.5, 137.5, 136.1, 131.0, 130.5, 128.6, 128.4, 127.8, 126.4, 73.5, 73.4, 59.1, 57.5, 52.8, 40.4, 24.3, 22.3; HRMS (ESI) m/z Calcd for C₂₇H₃₉N₂O₄S₂: 519.2351, Found 519.2376.

(-)-2-Methylpropane-2-sulfonic acid [(1S, 3S)-3-amino-4-benzyloxy-3-methyl-1-((E)-styryl)butyl]amide (5).

To a solution of **4** (5.00 g, 9.64 mmol) in dry THF (200 mL) cooled to 0 °C under an argon atmosphere was added dropwise a solution of methylmagnesium bromide (13.0 mL, 3.0 M in THF) over a 10 min period. After 1 hour, tlc analysis indicated consumption of the starting material and the reaction was quenched by the cautious addition of saturated NH₄Cl solution. After extraction with ethyl acetate and concentration of the organic layer, the residue was purified by flash chromatography (SiO₂, hexanes : ethyl acetate = 3 : 1) to afford a pale yellow solid, 3.30 g (65%, single isomer): $[\alpha]_D^{20} = -71.5$ ($c = 1.15$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.20 (m, 10 H), 6.66 (d, $J = 7.0$ Hz, 1 H), 6.43 (d, $J = 15.8$ Hz, 1 H), 6.07 (dd, $J = 7.7, 15.8$ Hz, 1 H), 4.71 (d, $J = 12.0$ Hz, 1 H), 4.64 (bs, 1 H), 4.60 (d, $J = 12.0$ Hz, 1 H), 4.59-4.56 (m, 1 H), 3.74 (d, $J = 8.9$ Hz, 1 H), 3.48 (d, $J = 8.9$ Hz, 1 H), 2.25 (dd, $J = 11.7, 15.2$ Hz, 1 H), 1.99 (dd, $J = 3.3, 15.2$ Hz, 1 H), 1.35 (s, 9 H), 1.32 (s, 3 H), 1.21 (s, 9 H); ¹³C NMR (100.6 MHz, CDCl₃): δ 138.1, 136.7, 132.0, 129.9, 128.5, 128.3, 127.63, 127.59, 127.48, 126.3, 74.4, 73.3, 58.8, 57.3, 55.9, 52.1, 43.1, 26.5, 24.2, 22.6; HRMS (ESI) m/z Calcd for C₂₈H₄₃N₂O₄S₂: 535.2664. Found 535.2674.

A portion of this material (555 mg, 1.04 mmol) was treated with a solution of 2M HCl in 1:1 methanol:1,4-dioxane (4.0 mL) at 0 °C for 2 hours. After adjusting the pH value to

14 by the addition of 10% NaOH solution, the aqueous layer was extracted with ethyl acetate and concentrated to afford **5**, 472mg (99 %): $[\alpha]_D^{20}$ -17.2 (c = 0.41, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 8.03 (bs, 2 H), 7.37-7.23 (m, 10 H), 6.53 (d, *J* = 8.8 Hz, 1 H), 6.41 (d, *J* = 15.9 Hz, 1 H), 6.10 (dd, *J* = 7.8, 15.9 Hz, 1 H), 4.62 (d, *J* = 11.9 Hz, 1 H), 4.59 (d, *J* = 11.9 Hz, 1 H), 4.45-4.43 (m, 1 H), 3.70 (d, *J* = 9.8 Hz, 1 H), 3.60 (d, *J* = 9.8 Hz, 1 H), 2.29 (dd, *J* = 9.6, 15.2 Hz, 1 H), 1.95 (dd, *J* = 3.5, 15.2 Hz, 1 H), 1.40 (s, 3 H), 1.32 (s, 9 H); ¹³C NMR (100.6 MHz, CDCl₃): δ 136.9, 135.8, 131.5, 129.4, 128.7, 128.5, 128.2, 128.1, 126.5, 73.6, 72.4, 59.9, 56.9, 52.7, 42.7, 24.0, 23.2; HRMS (ESI) *m/z* Calcd for C₂₄H₃₅N₂O₃S: 431.2368. Found 431.2374.

(-)-(4*S*, 6*S*)-6-Benzyloxymethyl-6-methyl-4-((*E*)-styryl)-1,4,5,6-tetrahydropyrimidine (**6**). A solution of **5** (472 mg, 1.04 mmol) was dissolved in dry DMF (15 mL) and treated with diethoxymethyl acetate (0.34 mL, 2.08 mmol). After stirring the mixture stirred at ambient temperature for 20 hours, LC-MS analysis indicated the disappearance of the starting material. Removal of the solvent in vacuo delivered the N-Bus pyrimidine as a yellow solid, 429 mg, (94%): $[\alpha]_D^{20}$ -17.7 (c = 0.53, CHCl₃) ¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1 H), 7.37-7.22 (m, 10 H), 6.49 (d, *J* = 15.9 Hz, 1 H), 6.21 (dd, *J* = 5.2, 15.9 Hz, 1 H), 4.77 (bs, 1 H), 4.58 (d, *J* = 11.8 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 3.40 (d, *J* = 8.9 Hz, 1 H), 3.37 (d, *J* = 8.9 Hz, 1 H), 2.53 (d, *J* = 6.1 Hz, 1 H), 2.49 (d, *J* = 6.1 Hz, 1 H), 2.01 (d, *J* = 2.9 Hz, 1 H), 1.97 (d, *J* = 2.9 Hz, 1 H), 1.37 (s, 9 H), 1.23 (s, 3 H); ¹³C NMR (100.6 MHz, CDCl₃): δ 141.0, 138.2, 136.3, 130.2, 129.4, 128.5, 128.2, 127.7, 127.65, 127.56, 126.5, 73.4, 63.5, 54.4, 53.5, 34.9, 25.9, 24.3, 24.2; HRMS (ESI) *m/z* Calcd for C₂₅H₃₃N₂O₃S: 441.2212. Found 441.2214. Anal. Calcd for C₂₅H₃₂N₂O₃S: C 68.15, H 7.32, N 6.36. Found: C 67.85, H 7.19, N 6.45.

A portion of this material (110 mg, 0.25 mmol) was treated with 2 mL of 1.0 M HCl in acetic acid at 90 °C for 2 hours. After cooling to 0 °C the reaction mixture was treated with 10% NaOH solution until the pH was above 13. Extraction with ethyl acetate, concentration in vacuo and acidification of the residue by adding 4M HCl in dioxane (70 μL, 1 eq.) delivered crude **6** as a dark oil. Further purification by flash chromatography (SiO₂, 5%-10% methanol/DCM) afforded **6** as a yellow solid, 79 mg (89%): $[\alpha]_D^{20}$ +248.1 (c = 0.29, MeOH); ¹H NMR (400 MHz, CDCl₃): δ 10.55 (d, *J* = 4.6 Hz, 1 H), 10.17 (d, *J* = 4.6 Hz, 1 H), 8.09 (t, *J* = 4.6 Hz, 1 H), 7.37-7.22 (m, 10 H), 6.62 (d, *J* = 15.9 Hz, 1 H), 6.04 (dd, *J* = 7.1, 15.9 Hz, 1 H), 4.53 (d, *J* = 12.2 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.18-4.12 (m, 1 H), 3.40 (s, 2 H), 2.20 (dd, *J* = 3.9, 13.2 Hz, 1 H), 1.45 (dd, *J* = 11.9, 13.2 Hz, 1 H), 1.40 (s, 3 H); ¹³C NMR (100.6 MHz, CDCl₃): δ 150.6, 137.3, 135.5, 133.6, 128.52, 128.45, 128.2, 127.8, 127.6, 126.6, 125.2, 74.7, 73.3, 53.0, 49.5, 35.3, 24.0; HRMS (ESI) *m/z* Calcd for C₂₁H₂₅N₂O: 321.1967. Found 321.1966.

(+)-(4*S*,6*S*)-6-Benzoyloxymethyl-6-methyl-1,4,5,6-tetrahydropyrimidine-4-carboxylic acid (**7**).

Into a solution of **6** (58 mg, 0.16 mmol) in methanol (10 mL) was bubbled with ozone at -78 °C until a blue color persisted. Air was bubbled through the solution until the blue color disappeared and then dimethyl sulfide (0.5 mL) was added and the solution allowed to warm to rt. After 1 hour, evaporation of the solvent in vacuo afforded a yellow oil which was dissolved in acetonitrile (5.0 mL) and cooled to 0 °C. To this solution was added a solution of sodium chlorite (89 mg, 0.80 mmol) in water (0.5 mL). The reaction mixture was stirred at 0 °C for 2 hours and then concentrated in vacuo. Purification of the residue by reverse-phase flash chromatography (C18, 0-40% acetonitrile/water) afforded **7** as an amorphous white solid, 33 mg (77%): $[\alpha]_D^{20} +179.4$ ($c = 0.20$, MeOH); ^1H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1 H), 7.33-7.25 (m, 5 H), 4.57 (d, $J = 11.9$ Hz, 1 H), 4.52 (d, $J = 11.9$ Hz, 1 H), 4.06 (dd, $J = 5.0, 10.8$ Hz, 1 H), 3.49 (d, $J = 9.5$ Hz, 1 H), 3.45 (d, $J = 9.5$ Hz, 1 H), 3.30 (s, 1 H), 2.48 (dd, $J = 5.0, 14.0$ Hz, 1 H), 1.73 (dd, $J = 10.9, 14.0$ Hz, 1 H), 1.34 (s, 3 H); ^{13}C NMR (100.6 MHz, CD_3OD): δ 174.7, 151.3, 139.3, 129.6, 129.0, 128.9, 77.0, 74.6, 54.2, 54.6, 33.9, 24.4; HRMS (ESI) m/z Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_3$: 263.139. Found 263.1401.

(+)-(4*S*,6*S*)-6-Hydroxymethyl-6-methyl-1,4,5,6-tetrahydropyrimidine-4-carboxylic acid (**8**).

A solution of **7** (183 mg, 0.70 mmol) and 10% palladium on carbon (75 mg, 0.070 mmol) in methanol (30 mL) was degassed and blanketed with 1 atmosphere of hydrogen. The mixture was stirred at ambient temperature for 24 hours, filtered and concentrated in vacuo to afford **8** as colorless amorphous solid (115 mg, 96%): $[\alpha]_D^{20} +125.5$ ($c = 0.24$, MeOH); ^1H NMR (400 MHz, D_2O): δ 8.07 (s, 1 H), 4.48 (dd, $J = 5.4, 10.0$ Hz, 1 H), 3.61 (s, 2 H), 3.34 (d, $J = 0.8$ Hz, 1 H), 2.49 (dd, $J = 5.4, 14.2$ Hz, 1 H), 1.98 (dd, $J = 10.0, 14.2$ Hz, 1 H), 1.32 (s, 3 H); ^{13}C NMR (150.9 MHz, D_2O): δ 174.3, 152.3, 68.6, 54.9, 50.7, 31.7, 23.7; HRMS (ESI) m/z Calcd for $\text{C}_7\text{H}_{13}\text{N}_2\text{O}_3$: 173.0926. Found 173.0924.

Manzacidin C (**9**).

A solution of **8** (16.9 mg, 0.081 mmol) in anhydrous DMF (3 mL) was treated with sodium hydride (16.2 mg, 0.40 mmol, 60% dispersion in mineral oil) and the mixture stirred for 1 hour at room temperature. Solid 4-bromotrichloroacetyl pyrrole (71 mg, 0.24 mmol) was then added to the solution. The mixture was stirred at ambient temperature for 3 hours and then quenched by the cautious addition of aqueous 2M HCl.

The mixture was extracted with ethyl acetate to remove unreacted pyrrole and the concentrated aqueous residue was purified by reverse-phase flash chromatography (C18, 0-40% acetonitrile/water) to afford Manzacidin C as amorphous solid (23 mg, 81%). All spectral data was in accordance with that reported in the literature. $[\alpha]_D^{20} +80.5$ (c = 0.38, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 8.10 (s, 1 H), 7.06 (d, $J = 1.8$ Hz, 1 H), 6.90 (d, $J = 1.8$ Hz, 1 H), 4.53 (ddd, $J = 0.9, 5.1, 10.5$ Hz, 1 H), 4.40 (d, $J = 11.4$ Hz, 1 H), 4.28 (d, $J = 11.4$ Hz, 1 H), 2.63 (dd, $J = 5.4, 14.4$ Hz), 2.03 (DD, $J = 10.5, 14.4$ Hz, 1 H), 1.46 (s, 3 H); ^{13}C NMR (150.9 MHz, CD_3OD): δ 171.3, 160.8, 152.4, 125.7, 123.4, 118.5, 98.4, 69.3, 53.6, 50.4, 32.2, 23.9; HRMS (ESI) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{BrN}_3\text{O}_4$: 344.0246. Found 344.0260.