Supporting Information

A Concise Route to Structurally Diverse DMP 323 Analogs via Highly Functionalized 1,4-Diamines

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Experimental Section

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General Methods

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon using standard gas-tight syringes, cannulae, and septa. CH_2Cl_2 was purified by distillation over CaH_2 or by passage through a solvent purification system employing activated Al_2O_3 (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* 1996, 15, 1518). THF and Et_2O were purified by passage through the purification system employing activated Al_2O_3 . Pyridine and Et_3N were purified by distillation and each stored over KOH. DMAP was purchased and not purified further. Thin layer chromatography was performed on silica gel 60F₂₅₄ plates (EM-5717, Merck). Visualization of TLC spots was effected using KMnO_4 stain. Flash column chromatography was performed with silica gel (EM-9385-9, 230-400 mesh). Deuteriochloroform (CDCl_3) was stored over molecular sieves (4 Å) at room temperature. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 (unless otherwise mentioned) on either a Bruker DRX-400 MHz spectrometer operating at 400 MHz and 100 MHz, respectively; or a Bruker Avance-500 MHz spectrometer operating at 500 MHz and 125 MHz, respectively. All ^{31}P spectra were recorded in CDCl_3 (unless otherwise noted) on a Bruker DRX-400 MHz spectrometer operating at 162 MHz, or a Bruker Avance-500 MHz spectrometer operating at 202 MHz. Where indicated, nuclei assignments in ^1H and ^{13}C spectra were aided by DEPT, ^1H - ^1H COSY, and ^1H - ^{13}C HMQC experiments recorded on the NMR spectrometers described above. Spectral plots contained in the NMR spectra section (pp S30-S62) were produced from raw FID data using either the SwaN-MR simulation program for Mac operating systems (Balacco, G. *Mol. Biol. Today* 2000, 1, 23-28), or the MestRe-C simulation program for PC/Windows operating systems (<http://qobruue.usc.es/jsigroup/MestRe-C/MestRe-C.html>). High resolution mass spectrometry (HRMS) and FAB spectra were performed by the Mass Spectrometry Laboratory at the University of Kansas using a VG Instrument ZAB double-focusing mass spectrometer.

General Procedure for the Formation of Heterocyclic Diols 1-3

A solution of the heterocyclic alkene, acetone, and water was prepared. *N*-methylmorpholine *N*-oxide monohydrate (NMO•H₂O) was added, followed by the addition of osmium tetroxide (4 wt. % solution of OsO₄ in H₂O). Upon disappearance of starting material by TLC and/or GC, the reaction was quenched with Na₂S₂O₃ (sat'd aq), diluted with EtOAc, and the layers were separated. The aqueous layer was washed with CH₂Cl₂ (3X), and the organic layers were combined, dried (Na₂SO₄), filtered, and concentrated. The crude heterocyclic diol was subjected to flash chromatography for purification. In cases where stereoselectivity was an issue, both NMR (¹H and/or ³¹P) and GC analyses of the crude product were utilized to determine the diastereoselectivity.

Leucine-Derived Cyclic Urea Diol 1a

Following a modified dihydroxylation procedure for the formation of 7-membered heterocyclic diols, C₂-symmetric urea **7b** (58 mg, 0.14 mmol), OsO₄ (27 μL of 4 wt. % solution in H₂O, 4.3 μmol), NMO•H₂O (23 mg, 0.17 mmol), citric acid (33 mg, 0.17 mmol), acetone (1.0 mL), and water (0.30 mL) yielded 63 mg (>95%) of **1a** as a colorless oil after flash chromatography (3:1 hexanes/EtOAc). [α]_D²⁵ = +60.2 (c = 0.96, CHCl₃); FTIR (neat) 3385 (broad), 1604 (-NC(O)N-), 1494, 1481, 1468, 1454, 1385, 1356 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.24 [m, 10H, C(20)-C(25)H], 5.19 [d, *J* = 14.0 Hz, 1H, C(16)H_a or C(17)H_a], 5.04 [d, *J* = 13.9 Hz, 1H, C(17)H_a or C(16)H_a], 3.82 [d, *J* = 14.1 Hz, 1H, C(16)H_b or C(17)H_b], 3.81 [d, *J* = 13.9 Hz, 1H, C(17)H_b or C(16)H_b], 3.58 [dddd, *J* = 7.1, 3.3, 3.3 Hz, 1H, C(4)H or C(5)H], 3.50-3.42 [m, 1H, C(5)H or C(4)H], 3.41-3.32 [m, 2H, C(3)H and C(6)H], 2.53 [d, *J* = 9.1 Hz, 1H, O(26)H or O(27)H], 1.90-1.75 [m, 1H, C(8)H_a, C(8)H_b, C(9)H_a, or C(9)H_b], 1.75-1.62 [m, 1H, C(10)H or C(11)H], 1.55-1.26 [m, 5H, C(8)H_{a,b} and C(9)H_b; C(11)H or C(10)H; and O(27)H or O(26)H], 0.92 [d, *J* = 6.5 Hz, 3H, C(12)H, C(13)H, C(14)H, or C(15)H], 0.88 [d, *J* = 6.6 Hz, 3H, C(13)H, C(14)H, C(15)H,

or C(12)H], 0.85 [d, J = 6.3 Hz, 3H, C(14)H, C(15)H, C(12)H, or C(13)H], 0.79 [d, J = 6.1 Hz, 3H, C(15)H, C(12)H, C(13)H, or C(14)H]; ^{13}C NMR (125 MHz, CDCl_3 , 50 $^\circ\text{C}$) δ 163.40 [C(1)], 138.91 [C(18) or C(19)], 138.36 [C(19) or C(18)], 129.79 [C(22) or C(23)], 129.39 [C(23) or C(22)], 128.84 [C(20) or C(21)], 128.60 [C(21) or C(20)], 127.83 [C(24) or C(25)], 127.66 [C(25) or C(24)], 72.84 [C(4) or C(5)], 69.25 [C(5) or C(4)], 61.54 [C(3) or C(6)], 60.81 [C(6) or C(3)], 25.53 [C(10) or C(11)], 25.35 [C(11) or C(10)], 23.99 [C(12), C(13), C(14), or C(15)], 22.89 [C(13), C(14), C(15), or C(12)], 22.19 [C(14), C(15), C(12), or C(13)], 21.80 [C(15), C(12), C(13), or C(14)]; HRMS calcd for $\text{C}_{27}\text{H}_{39}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ required 439.2961, found 439.2967.

Phenylalanine-Derived Cyclic Urea Diol **1b**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, C_2 -symmetric urea **8** (19 mg, 44 μmol), OsO_4 (8.3 μL of 4 wt. % solution in H_2O , 1.3 μmol), $\text{NMO}\cdot\text{H}_2\text{O}$ (7 mg, 52 μmol), acetone (0.30 mL), and water (0.10 mL) yielded 20 mg (>95%) of **1b** as a colorless oil after flash chromatography (EtOAc). $[\alpha]^{25} = -34.4$ ($c = 0.77$, CHCl_3); FTIR (neat) 3516 (broad), 1739, 1654 ($-\text{NC}(\text{O})\text{N}-$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 50 $^\circ\text{C}$) δ 7.35-7.12 [m, 10H, C(18)-C(23)H], 4.25-4.17 [m, 1H, C(8)H or C(9)H], 4.13 [dd, J = 10.8, 4.7 Hz, 1H, C(9)H or C(8)H], 3.80 [s, 3H, C(12)H or C(13)H], 3.80 [s, 3H, C(13)H or C(12)H], 3.35 [dd, J = 14.1, 5.3 Hz, 1H, C(14)H_a or C(14)H_b; or C(15)H_a or C(15)H_b], 3.32 [dd, J = 14.0, 5.5 Hz, 1H, C(14)H_b or C(14)H_a; or C(15)H_b or C(15)H_a], 3.31-3.25 [m, 1H, C(4)H or C(5)H], 3.22 [dd, J = 14.0, 10.9 Hz, 1H, C(15)H_a or C(15)H_b; or C(14)H_a or C(14)H_b], 3.16 [dd, J = 14.2, 11.0 Hz, 1H, C(15)H_b or C(15)H_a; or C(14)H_b or C(14)H_a], 3.08-3.00 [m, 3H, C(3)H_{a,b} and C(6)H_a; C(3)H_{a,b} and C(6)H_b; C(6)H_{a,b} and C(3)H_a; or C(6)H_{a,b} and C(3)H_b], 2.96-2.82 [m, 1H, C(5)H or C(4)H], 2.68 [dd, J = 14.4, 2.8 Hz, 1H, C(3)H_a, C(3)H_b, C(6)H_a, or C(6)H_b], 2.30-2.10 [bs, 1H, O(24)H or O(25)H], 2.00-1.85 [bs, 1H, O(25)H or O(24)H]; ^{13}C NMR (125 MHz,

CDCl₃, 50 °C) δ 172.66 [C(12) or C(13)], 171.85 [C(13) or C(12)], 163.54 [C(1)], 138.31 [C(16) or C(17)], 138.17 [C(17) or C(16)], 129.21 [C(18), C(19), C(20), or C(21)], 129.16 [C(19), C(20), C(21), or C(18)], 128.85 [C(20), C(21), C(18), or C(19)], 128.51 [C(21), C(18), C(19), or C(20)], 127.13 [C(22) or C(23)], 126.73 [C(23) or C(22)], 68.76 [C(4) or C(5)], 67.57 [C(5) or C(4)], 65.85 [C(8) or C(9)], 64.92 [broad, C(9) or C(8)], 52.19 [C(12) or C(13)], 52.15 [C(13) or C(12)], 51.82 [C(3) or C(6)], 51.82 [C(6) or C(3)], 35.37 [C(14) or C(15)], 35.05 [C(15) or C(14)]; HRMS calcd for C₂₅H₃₁N₂O₇ (M+H)⁺ required 471.2131, found 471.2116.

Leucine/Valine-Derived Unsymmetric Cyclic N-H-Urea Diol **1c**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, unsymmetric urea **9** (36 mg, 127 μ mol), OsO₄ (25 μ L of 4 wt. % solution in H₂O, 4 μ mol), NMO•H₂O (21 mg, 152 μ mol), acetone (0.85 mL), and water (0.25 mL) yielded 32 mg (80%) of **1c** as a colorless oil after flash chromatography (EtOAc). $[\alpha]^{25} = -16.2$ ($c = 1.49$, CHCl₃); FTIR (neat) 3365 (broad), 1739, 1634 (-NC(O)N-), 1492, 1436, 1389, 1369 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.74 [dd, $J = 7.5, 7.5$ Hz, 1H, C(11)H], 4.49 [d, $J = 4.3$ Hz, 1H, N(3)H], 4.15-4.08 [m, 1H, C(6)H], 3.87-3.77 [m, 1H, C(5)H], 3.71 [s, 3H, C(13)H], 3.40 [dd, $J = 13.5, 9.6$ Hz, 1H, C(7)H_a or C(7)H_b], 3.21 [d, $J = 5.9$ Hz, 1H, O(18)H], 3.09 [dd, $J = 13.4, 2.0$ Hz, 1H, C(7)H_b or C(7)H_a], 3.05 [d, $J = 5.5$ Hz, 1H, O(19)H], 2.98 [ddd, $J = 8.0, 5.3, 5.3$ Hz, 1H, C(4)H], 2.21-2.13 [m, 1H, C(8)H], 1.78-1.68 [m, 2H, C(14)H_a and C(14)H_b], 1.67-1.57 [m, 1H, C(15)H], 1.01 [d, $J = 6.9$ Hz, 3H, C(9)H or C(10)H], 0.96 [d, $J = 7.0$ Hz, 3H, C(10)H or C(9)H], 0.94 [d, $J = 6.9$ Hz, 3H, C(16)H or C(17)H], 0.92 [d, $J = 6.7$ Hz, 3H, C(17)H or C(16)H]; ¹³C NMR (100 MHz, CDCl₃) δ 173.40 [C(12)], 162.90 [C(2)], 70.05 [C(4)], 68.22 [C(5)], 60.37 [C(6)], 57.95 [C(11)], 52.17 [C(13)], 46.52 [C(7)], 38.05 [C(14)], 27.99 [C(8)], 25.13 [C(15)], 23.13 [C(16) or C(17)], 21.54 [C(17) or C(16)], 19.82 [C(9) or C(10)], 17.20 [C(10) or C(9)]; HRMS calcd for C₁₅H₂₉N₂O₅ (M+H)⁺ required 317.2076, found 317.2077.

Leucine/Valine-Derived Unsymmetric Cyclic *N*-Bn-Urea Diol **1d**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, unsymmetric urea **10** (13 mg, 35 μ mol), OsO₄ (6 μ L of 4 wt. % solution in H₂O, 1 μ mol), NMO•H₂O (6 mg, 42 μ mol), acetone (0.25 mL), and water (0.10 mL) yielded 12 mg (86%) of **1d** as colorless crystals after flash chromatography (1:1 hexanes/EtOAc). mp 107-110 °C; [α]²⁵ = +76.3 (c = 0.59, CHCl₃); FTIR (neat) 3421 (broad), 1740, 1619 (-NC(O)N-), 1474, 1436, 1388, 1369 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.28 [m, 5H, C(20)H, C(21)H, and C(22)H], 5.29 [d, *J* = 14.3 Hz, 1H, C(18)H_a or C(18)H_b], 4.63 [dd, *J* = 8.3, 6.0 Hz, 1H, C(11)H], 3.89-3.80 [m, 2H, C(5)H and C(6)H], 3.71 [s, 3H, C(13)H], 3.61 [d, *J* = 14.3 Hz, 1H, C(18)H_b or C(18)H_a], 3.20 [dd, *J* = 14.1, 11.0 Hz, 1H, C(7)H_a or C(7)H_b], 2.97 [dd, *J* = 11.2, 3.8 Hz, 1H, C(4)H], 2.92 [dd, *J* = 14.6, 4.2 Hz, 1H, C(7)H_b or C(7)H_a], 2.60-2.15 [bs, 1H, O(23)H or O(24)H], 2.38-2.26 [m, 1H, C(8)H], 1.86 [ddd, *J* = 14.1, 8.1, 6.1 Hz, 1H, C(14)H_a or C(14)H_b], 1.66 [ddd, *J* = 14.0, 8.3, 5.6 Hz, 1H, C(14)H_b or C(14)H_a], 1.61-1.51 [m, 1H, C(15)H], 1.53-1.43 [bs, 1H, O(24)H or O(23)H], 1.08 [d, *J* = 6.6 Hz, 3H, C(9)H or C(10)H], 0.98 [d, *J* = 6.6 Hz, 3H, C(10)H or C(9)H], 0.96 [d, *J* = 6.7 Hz, 3H, C(16)H or C(17)H], 0.95 [d, *J* = 6.6 Hz, 3H, C(17)H or C(16)H]; ¹³C NMR (100 MHz, CDCl₃) δ 172.91 [C(12)], 163.87 [C(2)], 139.34 [C(19)], 129.23 [C(20) or C(21)], 128.73 [C(21) or C(20)], 127.97 [C(22)], 71.23 [C(4)], 68.33 [C(5)], 66.63 [C(6)], 59.42 [C(11)], 56.79 [C(18)], 51.99 [C(13)], 46.71 [C(7)], 38.48 [C(14)], 29.18 [C(8)], 25.39 [C(15)], 22.87 [C(16) or C(17)], 22.30 [C(17) or C(16)], 21.38 [C(9) or C(10)], 20.43 [C(10) or C(9)]; HRMS calcd for C₂₂H₃₅N₂O₅ (M+H)⁺ required 407.2546, found 407.2539.

Phenylalanine-Derived Cyclic Phosphonamide Diol **2a**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, phosphonamide **11a** (50 mg, 97 μmol), OsO_4 (18 μL of 4 wt. % solution in H_2O , 3 μmol), $\text{NMO}\cdot\text{H}_2\text{O}$ (16 mg, 120 μmol), acetone (0.75 mL), and water (0.25 mL) yielded 51 mg (96%) of a 5.6:1 ratio (^{31}P -NMR) of inseparable diastereomers **2a** as white solids after flash chromatography (1:1 hexanes/EtOAc, then EtOAc). FTIR (neat) 1736, 1437, 1198 ($\text{P}=\text{O}$), 747, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (mixture of major/minor isomer peaks) δ 7.74-7.69 (m, 2H), 7.43-7.41 (m, 1H), 7.34-7.31 (m, 2H), 7.19-7.14 (m, 5H), 7.09-7.06 (m, 4H), 7.04-7.01 (m, 1H), 4.74-4.68 (m, 1H), 4.18-4.10 (m, 1H), 3.88-3.85 (m, 1H), 3.70-3.61 (m, 3H), 3.63 (s, 3H), 3.45 (s, 3H), 3.40-3.13 (m, 6H), 3.07-3.02 (m, 1H), 2.95-2.90 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) (major isomer only) δ 173.95 (d, $J_{\text{CP}} = 10.0$ Hz), 172.89 (d, $J_{\text{CP}} = 3.0$ Hz), 137.39, 136.93, 132.37 (d, $J_{\text{CP}} = 9.2$ Hz), 131.63 (d, $J_{\text{CP}} = 2.8$ Hz), 130.33 (d, $J_{\text{CP}} = 158.7$ Hz), 129.18, 129.03, 128.42, 128.34, 128.32, 126.56, 126.56, 69.91, 69.23, 60.16 (d, $J_{\text{CP}} = 5.8$ Hz), 59.85 (d, 6.1 Hz), 52.08, 52.05, 43.66, 42.64, 37.52, 35.64; ^{31}P NMR (162 MHz, CDCl_3) δ 30.32 (5.86, area), 29.81 (1.00, area); HRMS calcd for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_7\text{P}$ ($\text{M} + \text{H}$) $^+$ required 567.2260, found 567.2258.

Leucine-Derived Cyclic Phosphonamide Diol **2b**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, phosphonamide **11f** (115 mg, 0.19 mmol), OsO_4 (36 μL of 4 wt. % solution in H_2O , 6 μmol), $\text{NMO}\cdot\text{H}_2\text{O}$ (30 mg, 0.22 mmol), acetone (1.5 mL), and water (0.50 mL) yielded 119 mg

(98%) of a 5.8:1 ratio (^{31}P -NMR) of inseparable diastereomers **2b** as white solids after flash chromatography (2:1 hexanes/EtOAc). FTIR (neat) 1736, 1455, 1368, 1189 (P=O), 752, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (mixture of major/minor isomer peaks) δ 7.83-7.78 (m, 2H), 7.39-7.31 (m, 10H), 7.28-7.24 (m, 1H), 7.16-7.14 (m, 2H), 5.30-5.06 (m, 2H), 5.02-4.95 (m, 2H), 4.64-4.58 (m, 2H), 3.89-3.80 (m, 1H), 3.75-3.57 (m, 3H), 3.36-3.20 (m, 2H), 2.93-2.83 (m, 2H), 1.72-1.58 (m, 4H), 1.49-1.42 (m, 2H), 0.90 (d, $J = 6.0$ Hz, 3H, major isomer), 0.85 (d, $J = 6.0$ Hz, 3H, major isomer), 0.70 (d, $J = 5.6$ Hz, 3H, major isomer), 0.65 (d, $J = 5.5$ Hz, 3H, major isomer); ^{13}C NMR (100 MHz, CDCl_3) (major isomer only) δ 175.50, 173.39, 135.41, 134.77, 132.23 (d, $J_{\text{CP}} = 6.8$ Hz), 131.72, 128.64, 128.58, 128.50, 128.43, 128.32, 128.28, 128.22, 128.12, 69.89, 68.90, 67.27, 66.82, 56.47 (d, $J_{\text{CP}} = 6.9$ Hz), 55.62, 42.49, 41.70, 39.43, 37.52, 24.70, 24.18, 22.69, 22.38, 22.29, 21.71; ^{31}P NMR (162 MHz, CDCl_3) δ 30.13; HRMS calcd for $\text{C}_{36}\text{H}_{48}\text{N}_2\text{O}_7\text{P}$ ($\text{M} + \text{H}$) $^+$ required 651.3199, found 651.3197.

Leucine/Valine-Derived Unsymmetric Cyclic *N*-H-Phosphonamide Diol **2c**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, unsymmetric phosphonamide *major*-**16a** (295 mg, 0.93 mmol), OsO_4 (178 μL of 4 wt. % solution in H_2O , 28 μmol), $\text{NMO}\cdot\text{H}_2\text{O}$ (15 mg, 1.12 mmol), acetone (6.0 mL), and water (2.0 mL) yielded 181 mg (55%) of *major*-**2c** as a colorless oil and 15 mg (5%) of *minor*-**2c** as a white solid after purification by flash chromatography (5% MeOH in EtOAc, then 10% MeOH in EtOAc). ^{31}P NMR analysis of the crude reaction mixture prior to flash chromatography indicated a 7.6:1.0 mixture of diastereomers.

major-**2c**: $R_f = 0.33$ (10% MeOH in EtOAc); $[\alpha]_D^{25} = -40.8$ ($c = 1.20$, CHCl_3); FTIR (neat) 3358 (broad), 1736, 1167 (P=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.03 [bs, 1H, O(19)H or O(20)H], 3.94-3.87 [m, 2H, C(7)H_a or C(7)H_b; and C(11)H], 3.85-3.81 [m, 1H, C(6)H], 3.78 [s, 3H, C(13)H], 3.38 [dd, $J = 9.2, 2.6$ Hz, 1H, C(5)H], 3.10 [ddd, $J_{\text{HH}} = 15.2, 6.1$ Hz, $J_{\text{HP}} = 15.2$ Hz, 1H,

C(7)H_b or C(7)H_a], 2.82 [dddd, $J_{\text{HH}} = 10.5, 10.5, 3.9$ Hz, $J_{\text{HP}} = 10.5$ Hz, 1H, C(4)H], 2.76 [bs, 1H, O(20)H or O(19)H], 2.44 [dd, $J_{\text{HH}} = 9.3$ Hz, $J_{\text{HP}} = 9.3$ Hz, 1H, N(3)H], 2.38-2.25 [m, 1H, C(8)H], 1.86-1.75 [m, 3H, C(14)H_a, C(14)H_b, and C(15)H], 1.40 [d, $J_{\text{HP}} = 15.0$ Hz, 3H, C(18)H], 0.98 [d, $J = 6.0$ Hz, 3H, C(16)H or C(17)H], 0.96 [d, $J = 6.9$ Hz, 3H, C(17)H or C(16)H], 0.95 [d, $J = 6.4$ Hz, 3H, C(9)H or C(10)H], 0.89 [d, $J = 6.4$ Hz, 3H, C(10)H or C(9)H]; ^{13}C NMR (125 MHz, CDCl_3) δ 173.93 [d, $J_{\text{CP}} = 1.7$ Hz, C(12)], 73.64 [C(5)], 69.58 [C(6)], 57.67 [d, $J_{\text{CP}} = 4.7$ Hz, C(11)], 57.18 [C(4)], 52.07 [C(13)], 45.47 [C(7)], 39.89 [d, $J_{\text{CP}} = 3.3$ Hz, C(14)], 27.22 [d, $J_{\text{CP}} = 6.4$ Hz, C(8)], 24.49 [C(15)], 22.67 [C(16) or C(17)], 21.90 [C(17) or C(16)], 19.85 [C(9) or C(10)], 16.92 [C(10) or C(9)], 12.90 [d, $J_{\text{CP}} = 120.3$ Hz, C(18)]; ^{31}P NMR (162 MHz, CDCl_3) δ 33.88; HRMS calcd for $\text{C}_{15}\text{H}_{32}\text{N}_2\text{O}_5\text{P}$ ($\text{M}+\text{H}$) $^+$ required 351.2049, found 351.2044.

minor-2c: $R_f = 0.21$ (10% MeOH in EtOAc); mp 162-165 °C; $[\alpha]^{25} = -33.7$ ($c = 0.75$, CHCl_3); FTIR (neat) 3450 (broad), 1733, 1164 ($\text{P}=\text{O}$) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.66 [bs, 1H, O(19)H or O(20)H], 4.16 [dd, $J_{\text{HP}} = 11.5$ Hz, $J_{\text{HH}} = 4.5$ Hz, 1H, N(3)H], 4.00-3.87 [m, 2H, C(6)H; and C(7)H_a or C(7)H_b], 3.79-3.69 [m, 1H, C(11)H], 3.74 [s, 3H, C(13)H], 3.61 [bs, 1H, O(20)H or O(19)H], 3.24 [d, $J = 10.1$ Hz, 1H, C(5)H], 3.06 [ddd, $J_{\text{HH}} = 18.0, 1.8$ Hz, $J_{\text{HP}} = 18.0$ Hz, 1H, C(7)H_b or C(7)H_a], 2.40 [ddd, $J_{\text{HH}} = 9.1, 9.1$ Hz, $J_{\text{HP}} = 9.1$ Hz, 1H, C(4)H], 1.86-1.78 [m, 1H, C(8)H], 1.76-1.59 [m, 3H, C(14)H_a, C(14)H_b, and C(15)H], 1.48 [d, $J_{\text{HP}} = 15.0$ Hz, 3H, C(18)H], 1.03 [d, $J = 6.6$ Hz, 3H, C(9)H or C(10)H], 0.98 [d, $J = 6.5$ Hz, 3H, C(10)H or C(9)H], 0.95 [d, $J = 6.8$ Hz, 3H, C(16)H or C(17)H], 0.94 [d, $J = 6.1$ Hz, 3H, C(17)H or C(16)H]; ^{13}C NMR (125 MHz, CDCl_3) δ 173.37 [C(12)], 73.93 [C(5)], 71.86 [C(6)], 59.10 [d, $J_{\text{CP}} = 2.2$ Hz, C(11)], 56.54 [d, $J_{\text{CP}} = 3.7$ Hz, C(4)], 52.27 [C(13)], 43.20 [C(7)], 40.01 [d, $J_{\text{CP}} = 7.5$ Hz, C(14)], 31.37 [d, $J_{\text{CP}} = 9.5$ Hz, C(8)], 24.96 [C(15)], 22.88 [C(16) or C(17)], 22.10 [C(17) or C(16)], 20.35 [C(9) or C(10)], 20.18 [C(10) or C(9)], 12.23 [d, $J_{\text{CP}} = 126.8$ Hz, C(18)]; ^{31}P NMR (162 MHz, CDCl_3) δ 39.19; HRMS calcd for $\text{C}_{15}\text{H}_{32}\text{N}_2\text{O}_5\text{P}$ ($\text{M}+\text{H}$) $^+$ required 351.2049, found 351.2046.

Leucine/Valine-Derived Unsymmetrical Cyclic *N*-H-Phosphonamide Diol **2d**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, unsymmetric phosphonamide *minor*-**16a** (11 mg, 35 μ mol), OsO₄ (6 μ L of 4 wt. % solution in H₂O, 1 μ mol), NMO•H₂O (6 mg, 42 μ mol), acetone (0.25 mL), and water (0.10 mL) yielded a 1.8:1.0-ratio mixture of diastereomers **2d** by crude ³¹P NMR analysis. The product was not isolated.

major-**2d** + *minor*-**2d**: ³¹P NMR (162 MHz, CDCl₃) δ 32.72 (major isomer), 29.55 (minor isomer), see crude ³¹P NMR in the NMR spectra section of the Supporting Information.

Leucine/Valine-Derived Unsymmetric Cyclic *N*-H-Sulfamide Diol **3a**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, unsymmetric sulfamide **13** (30 mg, 94 μ mol), OsO₄ (18 μ L of 4 wt. % solution in H₂O, 3 μ mol), NMO (15 mg, 113 μ mol), acetone (0.65 mL), and water (0.20 mL) yielded 26 mg (79%) of **3a** as an 11.0:1.0 (by ¹H NMR) mixture of inseparable diastereomers after purification by flash chromatography (1:2 hexanes/EtOAc). **For the 11.0:1.0 mixture**: [α]_D²⁵ = -58.9 (c = 1.31, CHCl₃); FTIR (neat) 3479 (broad), 3279 (broad), 1740, 1390, 1370, 1316 (-SO₂-), 1164 (-SO₂-) cm⁻¹; **For major diastereomer major-3a**: ¹H NMR (500 MHz, CDCl₃) δ 5.17 [d, *J* = 11.9 Hz, 1H, O(18)H or O(19)H], 4.49 [d, *J* = 10.2 Hz, 1H, N(3)H], 3.95-3.90 [m, 3H, C(5)H or C(6)H; C(7)H_a or C(7)H_b; and C(11)H], 3.81 [s, 3H, C(13)H], 3.40-3.30 [m, 3H, C(4)H; C(6)H or C(5)H; and C(7)H_b or C(7)H_a], 2.80 [d, *J* = 9.7 Hz, 1H, O(19)H or O(18)H], 2.35-2.29 [m, 1H, C(4)H],

2.06 [ddd, $J = 8.9, 8.9, 19.4$ Hz, 1H, C(14) $\underline{H}_a$ or C(14) $\underline{H}_b$], 1.85-1.76 [m, 2H, C(14) $\underline{H}_b$ or C(14) $\underline{H}_a$; and C(15) $\underline{H}$], 1.02 [d, $J = 6.9$ Hz, 3H, C(16) $\underline{H}$ or C(17) $\underline{H}$], 0.99 [d, $J = 5.9$ Hz, 3H, C(17) $\underline{H}$ or C(16) $\underline{H}$], 0.96 [d, $J = 5.9$ Hz, 3H, C(9) $\underline{H}$ or C(10) $\underline{H}$], 0.85 [d, $J = 6.9$ Hz, 3H, C(10) $\underline{H}$ or C(9) $\underline{H}$]; ^{13}C NMR (125 MHz, CDCl_3) δ 175.11 [C(12)], 72.96 [C(5) or C(6)], 70.61 [C(6) or C(5)], 63.45 [C(11)], 55.67 [C(4)], 53.37 [C(13)], 53.07 [C(7)], 39.47 [C(14)], 26.22 [C(8)], 24.44 [C(15)], 23.30 [C(16) or C(17)], 21.67 [C(17) or C(16)], 19.66 [C(9) or C(10)], 14.59 [C(10) or C(9)]; HRMS calcd for $\text{C}_{14}\text{H}_{29}\text{N}_2\text{O}_6\text{S}$ ($\text{M}+\text{H}$) $^+$ required 353.1746, found 353.1742.

Leucine/Valine-Derived Unsymmetric Cyclic *N*-Bn-Sulfamide Diol **3b**

Following the general dihydroxylation procedure for the formation of 7-membered heterocyclic diols, unsymmetric sulfamide **14** (29 mg, 71 μmol), OsO_4 (14 μL of 4 wt. % solution in H_2O , 2 μmol), NMO (12 mg, 85 μmol), acetone (0.50 mL), and water (0.15 mL) yielded 24 mg (77%) of *major-3b* as a colorless oil and 5 mg (16%) of *minor-3b* as a colorless oil after flash chromatography (1.5:1.0 hexanes/EtOAc).

major-3b: $R_f = 0.26$ (1:1 hexanes/EtOAc); $[\alpha]^{25} = -35.9$ ($c = 1.03$, CHCl_3); FTIR (neat) 3509 (broad), 1740, 1369, 1332 ($-\text{SO}_2-$), 1164 ($-\text{SO}_2-$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44-7.27 [m, 5H, C(20)-C(22) $\underline{H}$], 4.55 [d, $J = 15.7$ Hz, 1H, C(18) $\underline{H}_a$ or C(18) $\underline{H}_b$], 4.54-4.51 [m, 1H, C(11) $\underline{H}$], 4.30 [d, $J = 15.7$ Hz, 1H, C(18) $\underline{H}_b$ or C(18) $\underline{H}_a$], 4.12-4.05 [m, 2H, C(5) $\underline{H}$ and C(6) $\underline{H}$], 3.76 [s, 3H, C(13) $\underline{H}$], 3.43 [dd, $J = 14.9, 7.2$ Hz, 1H, C(7) $\underline{H}_a$ or C(7) $\underline{H}_b$], 3.35-3.28 [m, 2H, C(4) $\underline{H}$; and C(7) $\underline{H}_b$ or C(7) $\underline{H}_a$], 3.27-3.15 [m, 1H, O(23) $\underline{H}$ or O(24) $\underline{H}$], 2.41 [d, $J = 6.2$ Hz, 1H, O(24) $\underline{H}$ or O(23) $\underline{H}$], 2.17-2.07 [m, 1H, C(8) $\underline{H}$], 1.86-1.71 [m, 3H, C(14) $\underline{H}_a$, C(14) $\underline{H}_b$, and C(15) $\underline{H}$], 0.98 [d, $J = 6.2$ Hz, 3H, C(16) $\underline{H}$ or C(17) $\underline{H}$], 0.97 [d, $J = 6.2$ Hz, 3H, C(17) $\underline{H}$ or C(16) $\underline{H}$], 0.93 [d, $J = 6.8$ Hz, 3H, C(9) $\underline{H}$ or C(10) $\underline{H}$], 0.73 [d, $J = 6.7$ Hz, 3H, C(10) $\underline{H}$ or C(9) $\underline{H}$]; ^{13}C NMR (125 MHz, CDCl_3) δ 173.06 [C(12)], 137.33 [C(19)], 128.70 [C(20) or C(21)], 128.46

[C(21) or C(20)], 127.69 [C(22)], 73.83 [C(5) or C(6)], 71.47 [C(6) or C(5)], 66.75 [C(4)], 59.86 [C(11)], 53.56 [C(18)], 52.53 [C(13)], 45.97 [C(7)], 38.88 [C(14)], 30.11 [C(8)], 24.37 [C(15)], 22.99 [C(16) or C(17)], 21.61 [C(17) or C(16)], 20.56 [C(9) or C(10)], 20.11 [C(10) or C(9)]; HRMS calcd for C₂₁H₃₅N₂O₆S (M+H)⁺ required 443.2216, found 443.2219.

minor-3b: R_f = 0.34 (1:1 hexanes/EtOAc); [α]_D²⁵ = -23.0 (c = 0.20, CHCl₃); FTIR (neat) 3499 (broad), 1741, 1387, 1369, 1314 (-SO₂-), 1167 (-SO₂-) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.41 [m, 2H, C(20)H], 7.34-7.27 [m, 3H, C(21)H and C(22)H], 4.71 [d, J = 15.6 Hz, 1H, C(18)H_a or C(18)H_b], 4.59-4.55 [m, 1H, C(11)H], 4.27 [d, J = 16.0 Hz, 1H, C(18)H_b or C(18)H_a], 4.24 [dd, J = 3.6, 3.6 Hz, 1H, C(5)H], 3.96 [ddd, J = 9.9, 2.9, 2.9 Hz, 1H, C(6)H], 3.76 [s, 3H, C(13)H], 3.51 [dd, J = 14.3, 10.0 Hz, 1H, C(7)H_a or C(7)H_b], 3.20 [dd, J = 10.5, 4.0 Hz, 1H, C(4)H], 3.15 [dd, J = 14.3, 2.7 Hz, 1H, C(7)H_b or C(7)H_a], 2.20-2.11 [m, 1H, C(8)H], 1.80-1.71 [m, 3H, C(14)H_a, C(14)H_b, and C(15)H], 1.00 [d, J = 6.0 Hz, 3H, C(16)H or C(17)H], 1.00 [d, J = 6.0 Hz, 3H, C(17)H or C(16)H], 0.95 [d, J = 6.5 Hz, 3H, C(9)H or C(10)H], 0.55 [d, J = 6.6 Hz, 3H, C(10)H or C(9)H]; ¹³C NMR (125 MHz, CDCl₃) δ 172.63 [C(12)], 137.15 [C(19)], 129.14 [C(20) or C(21)], 128.39 [C(21) or C(20)], 127.79 [C(22)], 75.03 [C(5)], 71.03 [C(6)], 66.51 [C(4)], 59.09 [C(11)], 53.85 [C(18)], 52.44 [C(13)], 43.97 [C(7)], 38.87 [C(14)], 28.27 [C(8)], 24.77 [C(15)], 22.98 [C(16) or C(17)], 21.57 [C(17) or C(16)], 20.49 [C(9) or C(10)], 20.42 [C(10) or C(9)]; HRMS calcd for C₂₁H₃₅N₂O₆S (M+H)⁺ required 443.2216, found 443.2224.

Valine-Derived C₂-Symmetric N-H-Cyclic Urea 6a

A solution of symmetric 1,4-diamine **4a** (45 mg, 0.26 mmol) and CH₂Cl₂ (5.0 mL) was prepared, followed by the addition of 1,1'-carbonyl diimidazole (54 mg, 0.33 mmol). The solution was brought to reflux, and the reaction was monitored by TLC and GC. Upon disappearance of starting material (t=12 h), the solvent was removed under reduced pressure. Flash chromatography (EtOAc) afforded 36 mg (69%) of **6a** as a light yellow powder. mp 126-132 °C; $[\alpha]^{25} = +81.9$ (c = 0.27, CHCl₃); FTIR (neat) 3258, 3122, 1701, 1677 (-NC(O)N-), 1520, 1478, 1443, 1385, 1366 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.65 [m, 2H, C(4)H], 4.46 [bs, 2H, N(2)H], 3.66 [dd, *J* = 1.9, 1.9 Hz, 2H, C(3)H], 1.92-1.84 [m, 2H, C(5)H], 0.98 [d, *J* = 6.8 Hz, 6H, C(6)H or C(7)H], 0.98 [d, *J* = 6.8 Hz, 6H, C(7)H or C(6)H]; ¹³C NMR (125 MHz, CDCl₃) δ 164.39 [C(1)], 128.75 [C(4)], 57.59 [C(3)], 34.18 [C(5)], 18.48 [C(6) or C(7)], 18.30 [C(7) or C(6)]; HRMS calcd for C₁₁H₂₁N₂O (M+H)⁺ required 197.1654, found 197.1652.

Leucine-Derived C₂-Symmetric N-H-Cyclic Urea **6b**

A solution of C₂-symmetric 1,4-diamine **4b** (118 mg, 0.60 mmol) and 1,1,2,2-tetrachloroethane (6.0 mL) was prepared in a pear shaped flask under argon. 1,1'-Carbonyl diimidazole (116 mg, 0.71 mmol) was added, and the solution was stirred for 20 minutes at room temperature. The solution was subsequently cannulated into a separate 3-neck flask, equipped with a reflux condenser, containing refluxing 1,1,2,2-tetrachloroethane (6.0 mL), and the resulting solution was stirred at reflux for 15 minutes. The reaction was cooled to room temperature, and the solution was transferred directly to a flash chromatographic column for purification. Flash chromatography (2:1 to elute TCE, then 1:2 hexanes/EtOAc) afforded 94 mg (71%) of **6b** as a white powder. mp 145-148 °C; $[\alpha]^{25} = +154.0$ (c = 1.03, CHCl₃); FTIR (neat) 3243, 3113, 1695 (-NC(O)N-), 1514, 1455, 1382, 1367 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.58 [m, 2H, C(4)H], 4.79 [bs, 2H, N(2)H], 3.85-3.71 [m, 2H, C(3)H], 1.77-1.69 [m, 2H, C(6)H], 1.57 [ddd, *J* = 14.1, 7.4, 7.4 Hz, 2H, C(5)H_a or C(5)H_b], 1.40 [ddd, *J* = 13.8, 7.4, 7.4 Hz, 2H, C(5)H_b or C(5)H_a], 0.92 [d, *J* = 6.8 Hz, 6H, C(8)H or C(7)H], 0.90 [d, *J* = 7.0 Hz, 6H, C(8)H or C(7)H]; ¹³C NMR (125 MHz, CDCl₃) δ 164.02 [C(1)], 129.59 [C(4)], 50.30 [C(3)], 45.39 [C(5)], 24.67 [C(6)], 22.83

[C(7) or C(8)], 21.98 [C(8) or C(7)]; HRMS calcd for $C_{13}H_{25}N_2O$ ($M+H$)⁺ required 225.1967, found 225.1976.

Valine-Derived C₂-Symmetric N-Bn-Cyclic Urea **7a**

A solution of **6a** (12 mg, 61 μ mol), benzyl bromide (24 mg, 141 μ mol), and THF (1.2 mL) was cooled in a 0 °C ice bath. Potassium *t*-butoxide (14 mg, 128 μ mol) was added as a 1.0 M solution in THF, the ice bath was removed, and the reaction was allowed to warm to room temperature and monitored by GC. After 3 h, additional benzyl bromide (24 mg, 141 μ mol) and potassium *t*-butoxide (14 mg, 128 μ mol) were introduced into the reaction. After one hour, additional potassium *t*-butoxide (14 mg, 128 μ mol) was introduced to facilitate consumption of both the starting material and mono-benzylated product. Upon completion of the reaction, the solution was diluted with Et₂O and water. The layers were separated, the aqueous layer washed with Et₂O (3X), the organic layers combined, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Flash chromatography (10:1, then 4:1 hexanes/EtOAc) yielded 18 mg (78%) of **7a** as colorless crystals. mp 64-65 °C; $[\alpha]^{25}_D = +142.2$ ($c = 0.81$, CHCl₃); FTIR (neat) 3029, 1638 (-NC(O)N-), 1468, 1452, 1384, 1366 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.30-7.22 [m, 10H, C(10)H, C(11)H, and C(12)H], 5.73 [d, $J = 3.6$ Hz, 2H, C(4)H], 5.14 [d, $J = 14.9$ Hz, 2H, C(8)H_a or C(8)H_b], 3.97 [d, $J = 14.9$ Hz, 2H, C(8)H_b or C(8)H_a], 3.24 [dd, $J = 8.5, 3.5$ Hz, 2H, C(3)H], 2.25-2.15 [m, 2H, C(5)H], 0.91 [d, $J = 6.8$ Hz, 6H, C(6)H or C(7)H], 0.84 [d, $J = 6.7$ Hz, 6H, C(7)H or C(6)H]; ¹³C NMR (125 MHz, CDCl₃) δ 163.77 [C(1)], 138.57 [C(9)], 128.81 [C(10) or C(11)], 128.71 [C(4)], 128.27 [C(11) or C(10)], 127.02 [C(12)], 65.48 [C(3)], 54.97 [C(8)], 34.24 [C(5)], 21.15 [C(6) or C(7)], 20.00 [C(7) or C(6)]; HRMS calcd for $C_{25}H_{33}N_2O$ ($M+H$)⁺ required 377.2593, found 377.2593.

Leucine-Derived C_2 -Symmetric *N*-Bn-Cyclic Urea **7b**

A solution of **6b** (75 mg, 0.33 mmol), benzyl bromide (343 mg, 2.00 mmol), and THF (7.0 mL) was cooled in a 0 °C ice bath. Potassium *t*-butoxide (225 mg, 2.00 mmol) was added as a 1.0 M solution in THF, the ice bath was removed, and the reaction was allowed to warm to room temperature and monitored by GC. After stirring overnight at room temperature, additional benzyl bromide (172 mg, 1.00 mmol) and potassium *t*-butoxide (113 mg, 1.00 mmol) were introduced into the reaction to facilitate consumption of both the starting material and mono-benzylation product. Upon completion of the reaction, the solution was diluted with Et₂O and water. The layers were separated, the aqueous layer washed with Et₂O (3X), the organic layers combined, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Flash chromatography (1:1 CH₂Cl₂/hexanes, then 4:1 hexanes/EtOAc) yielded 110 mg (81%) of **7b** as colorless crystals. mp 47-49 °C; [α]²⁵ = +163.2 (*c* = 1.36, CHCl₃); FTIR (neat) 3028, 1645 (-NC(O)N-), 1468, 1453, 1385, 1366 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.29 [m, 8H, C(11)H and C(12)H], 7.27-7.23 [m, 2H, C(13)H], 5.65 [dd, *J* = 3.7, 1.2 Hz, 2H, C(4)H], 5.06 [d, *J* = 15.1 Hz, 2H, C(9)H_a or C(9)H_b], 3.93 [d, *J* = 15.1 Hz, 2H, C(9)H_b or C(9)H_a], 3.60-3.50 [m, 2H, C(3)H], 1.71-1.56 [m, 6H, C(5)H_a, C(5)H_b, and C(6)H], 0.88 [d, *J* = 5.9 Hz, 6H, C(7)H or C(8)H], 0.82 [d, *J* = 5.8 Hz, 6H, C(8)H or C(7)H]; ¹³C NMR (125 MHz, CDCl₃) δ 164.45 [C(1)], 138.83 [C(10)], 129.24 [C(13)], 128.46 [C(11) or C(12)], 128.36 [C(12) or C(11)], 127.06 [C(4)], 56.94 [C(3)], 53.19 [C(9)], 43.00 [C(5)], 25.15 [C(6)], 23.47 [C(7) or C(8)], 21.90 [C(8) or C(7)]; HRMS calcd for C₂₇H₃₇N₂O (M+H)⁺ required 405.2906, found 405.2911.

Phenylalanine-Derived C_2 -Symmetric Cyclic Urea **8**

A solution of C_2 -symmetric diamine **4c** (153 mg, 0.37 mmol), Et_3N (94 mg, 0.93 mmol), and CH_2Cl_2 (7.5 mL) was cooled to ca. -78°C in a $\text{CO}_2(\text{s})$ /isopropanol bath. Triphosgene (55 mg, 0.19 mmol) was added as a 1.0 M solution in CH_2Cl_2 , and the reaction was allowed to warm to rt on its own accord. Analysis of the crude reaction by GC showed a significant amount of starting diamine was still present. Therefore, the reaction was re-cooled to ca. -78°C in a $\text{CO}_2(\text{s})$ /isopropanol bath, and additional Et_3N (94 mg, 0.93 mmol) and triphosgene (55 mg, 0.19 mmol, 1.0 M solution in CH_2Cl_2) were introduced into the reaction. After slowly warming to room temperature, starting material had been consumed by GC, and the reaction was concentrated under reduced pressure. Flash chromatography (10:1, then 4:1, then 2:1 hexanes/ EtOAc) afforded 62 mg (38%) of **8** as a colorless oil. $[\alpha]^{25}_D = -52.5$ ($c = 1.34$, CHCl_3); FTIR (neat) 3029, 1740, 1651 ($-\text{NC}(\text{O})\text{N}-$), 1477, 1455 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25-7.13 [m, 10H, C(10) $\underline{\text{H}}$, C(11) $\underline{\text{H}}$, and C(12) $\underline{\text{H}}$], 5.46 [m, 2H, C(4) $\underline{\text{H}}$], 4.54 [dd, $J = 10.6$ Hz, 5.3 Hz, 2H, C(5) $\underline{\text{H}}$], 3.70 [s, 6H, C(7) $\underline{\text{H}}$], 3.52 [d, $J = 15.9$ Hz, 2H, C(3) $\underline{\text{H}}_a$ or C(3) $\underline{\text{H}}_b$], 3.41 [d, $J = 15.7$ Hz, 2H, C(3) $\underline{\text{H}}_b$ or C(3) $\underline{\text{H}}_a$], 3.25 [dd, $J = 14.4$, 5.3 Hz, 2H, C(8) $\underline{\text{H}}_a$ or C(8) $\underline{\text{H}}_b$], 2.93 [dd, $J = 14.4$, 10.7 Hz, 2H, C(8) $\underline{\text{H}}_b$ or C(8) $\underline{\text{H}}_a$]; ^{13}C NMR (125 MHz, CDCl_3) δ 172.49 [C(6)], 165.57 [C(1)], 137.65 [C(9)], 129.12 [C(10) or C(11)], 128.18 [C(11) or C(10)], 126.43 [C(12)], 125.71 [C(4)], 62.10 [C(5)], 51.95 [C(7)], 46.64 [C(3)], 35.67 [C(8)]; HRMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}$) $^+$ required 437.2076, found 437.2062.

Leucine/Valine-Derived Unsymmetric Cyclic N -H-Urea **9**

A solution of **4d** (90 mg, 0.35 mmol) and CH₂Cl₂ (7.0 mL) was prepared, followed by the addition of 1,1'-carbonyl diimidazole (71 mg, 0.44 mmol). The solution was brought to reflux, and the reaction was monitored by TLC and GC. Upon disappearance of starting material (t=24 h), the solvent was removed under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc) afforded 46 mg (46%) of **9** as a colorless oil. $[\alpha]^{25} = -21.9$ (c = 0.31, CHCl₃); FTIR (neat) 3305 (broad), 3247 (broad), 3105, 1743, 1661 (-NC(O)N-), 1473, 1434, 1386, 1368 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.90-5.85 [m, 1H, C(6)H], 5.57 [d, *J* = 11.1 Hz, 1H, C(5)H], 4.85 [dd, *J* = 9.8, 5.0 Hz, 1H, C(11)H], 4.06-4.00 [m, 1H, C(7)H_a or C(7)H_b], 3.99 [bs, 1H, N(3)H], 3.80 [bs, 1H, C(4)H], 3.70 [s, 3H, C(13)H], 3.47 [dd, *J* = 16.7, 6.7 Hz, 1H, C(7)H_b or C(7)H_a], 1.87-1.76 [m, 1H, C(8)H], 1.72-1.55 [m, 3H, C(14)H_a, C(14)H_b, and C(15)H], 0.98 [d, *J* = 6.6 Hz, 3H, C(9)H or C(10)H], 0.97 [d, *J* = 6.8 Hz, 3H, C(10)H or C(9)H], 0.92 [d, *J* = 6.0 Hz, 3H, C(16)H or C(17)H], 0.90 [d, *J* = 5.9 Hz, 3H, C(17)H or C(16)H]; ¹³C NMR (100 MHz, CDCl₃) δ 173.22 [C(12)], 165.16 [C(2)], 129.98 [C(5)], 126.18 [C(6)], 59.17 [C(4)], 56.95 [C(11)], 51.98 [C(13)], 42.49 [C(7)], 38.21 [C(14)], 34.16 [C(8)], 24.84 [C(15)], 23.28 [C(16) or C(17)], 21.28 [C(17) or C(16)], 17.97 [C(9) or C(10)], 17.92 [C(10) or C(9)]; HRMS calcd for C₁₅H₂₇N₂O₃ (M+H)⁺ required 283.2022, found 283.1996.

Leucine/Valine-Derived Unsymmetric Cyclic N-Bn-Urea **10**

A solution of unsymmetric urea **9** (52 mg, 184 μmol) and THF (2.0 mL) was cooled to ca. -78 °C in a CO₂(s)/isopropanol bath. KHMDS (410 μL of 0.91 M in THF, 368 μmol) was added dropwise, and the solution was stirred at -78 °C for 10 min. Benzyl bromide (63 mg, 368 μmol) and 18-crown-6 (49 mg, 184 μmol) were added, and the reaction was allowed to slowly warm to 0 °C. The reaction was quenched with NH₄Cl (sat'd aq), diluted with EtOAc, and the layers were separated. The aqueous layer was washed with EtOAc (3X), and the organic layers combined, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Flash chromatography (10:1 hexanes/EtOAc) yielded 49 mg (71%) of **10** as a colorless oil. $[\alpha]^{25} = +66.5$ (c = 1.14, CHCl₃);

FTIR (neat) 3031, 1741, 1646 (-NC(O)N-), 1470, 1453, 1387, 1368 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.22 [m, 5H, C(20)H, C(21)H, and C(22)H], 5.76-5.68 [m, 2H, C(5)H and C(6)H], 5.13 [d, J = 15.5 Hz, 1H, C(18)H_a or C(18)H_b], 4.37 [dd, J = 6.7, 6.7 Hz, 1H, C(11)H], 4.17 [d, J = 17.2 Hz, 1H, C(7)H_a or C(7)H_b], 3.90 [d, J = 15.5 Hz, 1H, C(18)H_b or C(18)H_a], 3.65 [s, 3H, C(13)H], 3.60 [dd, J = 16.8, 5.3 Hz, 1H, C(7)H_b or C(7)H_a], 3.20-3.16 [m, 1H, C(4)H], 2.30-2.21 [m, 1H, C(8)H], 1.87-1.79 [m, 1H, C(15)H], 1.67-1.55 [m, 2H, C(14)H_a and C(14)H_b], 1.01 [d, J = 6.8 Hz, 3H, C(9)H or C(10)H], 0.94 [d, J = 6.4 Hz, 3H, C(16)H or C(17)H], 0.94 [d, J = 6.4 Hz, 3H, C(17)H or C(16)H], 0.88 [d, J = 6.7 Hz, 3H, C(10)H or C(9)H]; ^{13}C NMR (100 MHz, CDCl_3) δ 173.21 [C(12)], 164.44 [C(2)], 138.90 [C(19)], 129.15 [C(5) or C(6)], 128.35 [C(20) or C(21)], 127.63 [C(21) or C(20)], 126.88 [C(22)], 125.19 [C(6) or C(5)], 65.99 [C(4)], 59.46 [C(11)], 54.75 [C(18)], 51.69 [C(13)], 46.84 [C(7)], 38.45 [C(14)], 34.61 [C(8)], 25.42 [C(15)], 22.64 [C(16) or C(17)], 22.52 [C(17) or C(16)], 21.05 [C(9) or C(10)], 19.80 [C(10) or C(9)]; HRMS calcd for $\text{C}_{22}\text{H}_{33}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ required 373.2491, found 373.2466.

General Procedure for the Formation of Cyclic Phosphonamides 11a-f

A solution of the 1,4-diamine **4c,e-g**, Et_3N , and CH_2Cl_2 was cooled to 0° , and the dichlorophosphine was added dropwise. The reaction was warmed to room temperature for 10 minutes, then concentrated under reduced pressure. The salty slurry was diluted with CH_2Cl_2 , cooled to 0° , and *meta*-chloroperbenzoic acid (*m*-CPBA) was added in three portions. The reaction was warmed to room temperature for 25 minutes, then concentrated under reduced pressure. The resulting slurry was subjected to chromatography for purification.

Phenylalanine-OMe-Derived Cyclic Ph-Phosphonamide 11a

Following the general procedure for the formation of cyclic phosphonamides, 1,4-diamine **4c** (295 mg, 0.716 mmol), Et_3N (300 μL , 2.15 mmol), dichlorophenylphosphine (117 μL , 0.86 mmol), *m*-CPBA (193 mg, 1.12 mmol) and CH_2Cl_2 (2 mL initially, 2 mL for the oxidation step) yielded 332 mg (90%) of the cyclic phosphonamide **11a** as a colorless oil after subjection to flash

chromatography (1:1 hexanes/EtOAc to EtOAc). $[\alpha]^{25} = -59.8$ ($c = 3.18$, CHCl_3); FTIR (neat) 1736, 1454, 1364, 1217 (P=O), 746, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.36 (m, 3H), 7.28-7.09 (m, 11H), 6.96-6.94 (m, 2H), 5.69-5.59 (m, 2H), 4.42 (ddd, $J_{\text{HP}} = 9.5$ Hz, $J_{\text{HH}} = 6.7$, 6.7 Hz, 1H), 4.34 (ddd, $J_{\text{HP}} = 8.8$ Hz, $J_{\text{HH}} = 6.5$, 6.5 Hz, 1H), 3.91-3.74 (m, 2H), 3.64 (s, 3H), 3.61-3.55 (m, 2H), 3.31 (s, 3H), 3.18 (ddd, $J = 13.8$, 8.5, 8.5 Hz, 1H), 3.04-2.94 (m, 2H), 2.77 (ddd, $J = 14.0$, 8.7, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.07, 172.99 (d, $J_{\text{CP}} = 6.4$ Hz), 137.01, 136.67, 132.37 (d, $J_{\text{CP}} = 9.1$ Hz), 131.31 (d, $J_{\text{CP}} = 2.6$ Hz), 129.29, 129.28, 129.02 (d, $J_{\text{CP}} = 163.6$ Hz), 128.28, 128.10, 128.04, 127.99, 127.95, 127.86, 126.43, 126.25, 59.09 (d, $J_{\text{CP}} = 5.8$ Hz), 59.04 (d, $J_{\text{CP}} = 5.1$ Hz), 51.81, 51.20, 41.18 (d, $J_{\text{CP}} = 2.5$ Hz), 40.52 (d, $J_{\text{CP}} = 2.7$ Hz), 36.86, 36.17 (d, $J_{\text{CP}} = 5.2$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ 29.78; HRMS calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_5\text{P}$ ($\text{M} + \text{H}$) $^+$ required 533.2205, found 533.2205.

Phenylalanine-OMe-Derived Cyclic MeO-Phosphonamide **11b**

Following the general procedure for the formation of cyclic phosphonamides, 1,4-diamine **4c** (52 mg, 0.13 mmol), Et_3N (73 μL , 0.525 mmol), methyl dichlorophosphite (14 μL , 0.15 mmol), *m*-CPBA (26 mg, 0.15 mmol) and CH_2Cl_2 (1 mL initially, 1 mL for the oxidation step) yielded 63 mg (91%) of the cyclic phosphonamide **11b** as a colorless oil after subjection to flash chromatography (1:1 hexanes/EtOAc to EtOAc). $[\alpha]^{25} = -74.2$ ($c = 1.20$, CHCl_3); FTIR (neat) 1736, 1453, 1371, 1225 (P=O), 748, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.24-7.15 (m, 10H), 5.51-5.42 (m, 2H), 4.69 (ddd, $J_{\text{HP}} = 9.0$ Hz, $J_{\text{HH}} = 7.6$, 7.6 Hz, 1H), 4.46 (ddd, $J_{\text{HP}} = 10.0$, $J_{\text{HH}} = 7.0$, 7.0 Hz, 1H), 3.62 (s, 3H), 3.61-3.58 (m, 1H), 3.60 (s, 3H), 3.55 (m, 1H), 3.41 (m, 1H), 3.42-3.38 (m, 1H), 3.35 (d, $J_{\text{HP}} = 11.1$ Hz, 3H), 3.19 (dd, $J = 14.2$, 7.6 Hz, 1H), 3.10 (dd, $J = 14.0$, 6.8 Hz, 1H), 2.88-2.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.51 (d, $J_{\text{CP}} = 3.7$ Hz), 172.13 (d, $J_{\text{CP}} = 2.6$ Hz), 137.22, 137.12, 129.40, 129.27, 128.16, 128.13, 127.61, 127.61, 126.42, 126.42, 59.99, 59.94, 52.53 (d, $J_{\text{CP}} = 5.0$ Hz), 51.87, 51.78, 40.67, 40.60, 36.73 (d, $J_{\text{CP}} = 2.9$ Hz), 36.59 (d, $J_{\text{CP}} = 2.8$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ 19.33; HRMS calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6\text{P}$ ($\text{M} + \text{H}$) $^+$ required 487.1998, found 487.1972.

Leucine-OMe-Derived Cyclic Ph-Phosphonamide **11c**

Following the general procedure for the formation of cyclic phosphonamides, 1,4-diamine **4e** (100 mg, 0.292 mmol), Et₃N (142 μ L, 1.02 mmol), dichlorophenylphosphine (46 μ L, 0.34 mmol), *m*-CPBA (55 mg, 0.321 mmol) and CH₂Cl₂ (0.5 mL initially, 0.5 mL for the oxidation step) yielded 122 mg (93%) of the cyclic phosphonamide **11c** as a colorless oil after subsection to flash chromatography (1:1 hexanes/EtOAc). Phosphonamide **11c** was identical in all respects to the previous report of this compound, the synthesis of which was accomplished on a smaller scale (~12 mg, 86% yield). The characterization data for **11c** can be found in the aforementioned report, see: Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000**, *65*, 7913-7918.

Leucine-OMe-Derived Cyclic MeO-Phosphonamide **11d**

Following the general procedure for the formation of cyclic phosphonamides, 1,4-diamine **4e** (61 mg, 0.18 mmol), Et₃N (87 μ L, 0.62 mmol), methyl dichlorophosphite (20 μ L, 0.15 mmol), *m*-CPBA (50 mg, 0.28 mmol) and CH₂Cl₂ (0.5 mL initially, 0.5 mL for the oxidation step) yielded 67 mg (94%) of the cyclic phosphonamide **11d** as a colorless oil after subsection to flash chromatography (1:1 hexanes/EtOAc to EtOAc). [α]_D²⁵ = -38.7 (*c* = 0.84, CHCl₃); FTIR (neat) 1739, 1455, 1437, 1369, 1387, 1236 (P=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.60-5.54 (m, 2H), 4.47 (ddd, *J*_{HP} = 9.9 Hz, *J*_{HH} = 5.8, 5.8 Hz, 1H), 4.21 (ddd, *J*_{HP} = 9.0 Hz, *J*_{HH} = 5.9, 5.9 Hz, 1H), 3.98-3.90 (m, 1H), 3.86-3.76 (m, 1H), 3.69 (d, *J*_{HP} = 11.0 Hz, 3H), 3.67 (s, 3H), 3.67 (s, 3H), 3.55-3.42 (m, 2H), 1.72-1.49 (m, 6H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (d,

$J = 6.5$ Hz, 3H), 0.88 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.99 (d, $J_{\text{CP}} = 1.9$ Hz), 173.29, 128.11, 128.08, 57.40 (d, $J_{\text{CP}} = 4.9$ Hz), 56.72 ($J_{\text{CP}} = 4.2$ Hz), 52.95 (d, $J_{\text{CP}} = 4.9$ Hz), 51.92, 51.79, 41.13 (d, $J_{\text{CP}} = 4.6$ Hz), 40.75 (d, $J_{\text{CP}} = 4.3$ Hz), 39.52 (d, $J_{\text{CP}} = 4.1$ Hz), 39.21 (d, $J_{\text{CP}} = 3.9$ Hz), 24.80, 24.52, 23.10, 23.03, 21.82, 21.72; ^{31}P NMR (162 MHz, CDCl_3) δ 20.39; HRMS calcd for $\text{C}_{19}\text{H}_{36}\text{N}_2\text{O}_6\text{P}$ ($\text{M} + \text{H}$) $^+$ required 419.2311, found 419.2305.

Phenylalanine-Derived Cyclic Phosphonamide **11e**

Following the general procedure for the formation of cyclic phosphonamides, 1,4-diamine **4f** (109 mg, 0.19 mmol), Et_3N (112 μL , 0.808 mmol), dichlorophenylphosphine (31 μL , 0.23 mmol), *m*-CPBA (52 mg, 0.301 mmol) and CH_2Cl_2 (1 mL initially, 1 mL for the oxidation step) yielded 122 mg (96%) of the cyclic phosphonamide **11e** as a colorless oil after subjection to flash chromatography (2:1 hexanes/ EtOAc). $[\alpha]^{25} = -40.3$ ($c = 2.42$, CHCl_3); FTIR (neat) 1734, 1454, 1368, 1214 ($\text{P}=\text{O}$), 742, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.22 (m, 11H), 7.18-7.08 (m, 10H), 6.99-6.93 (m, 4H), 5.59-5.51 (m, 2H), 5.13 (d, $J = 12.2$ Hz, 1H), 5.06 (d, $J = 12.2$ Hz, 1H), 4.83 (d, $J = 12.2$ Hz, 1H), 4.78 (d, $J = 12.2$ Hz, 1H), 4.45 (ddd, $J_{\text{HP}} = 9.5$ Hz, $J_{\text{HH}} = 6.1$, 6.1 Hz, 1H), 4.42 (ddd, $J_{\text{HP}} = 8.7$ Hz, $J_{\text{HH}} = 6.6$, 6.6 Hz, 1H), 3.89-3.76 (m, 2H), 3.59-3.49 (m, 2H), 3.19 (dd, $J = 13.8$, 8.9 Hz, 1H), 3.03 (dd, $J = 14.0$, 6.5 Hz, 1H), 2.98 (dd, $J = 13.8$, 6.1 Hz, 1H), 2.77 (dd, $J = 14.5$, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.45, 171.42 (d, $J_{\text{CP}} = 4.7$ Hz), 137.06, 136.68, 135.44, 135.23, 132.63 (d, $J_{\text{CP}} = 7.3$ Hz), 131.58, 129.47, 129.43, 128.61 (d, $J_{\text{CP}} = 133.7$ Hz), 128.37, 128.34, 128.34, 128.29, 128.22, 128.23, 128.14, 128.11, 128.10, 128.06, 126.56, 126.38, 66.79, 66.33, 59.50 (d, $J_{\text{CP}} = 2.3$ Hz), 59.46 (d, $J_{\text{CP}} = 4.7$ Hz), 41.23, 40.89, 37.17, 37.17, 36.37, 36.33; ^{31}P NMR (162 MHz, CDCl_3) δ 30.15; HRMS calcd for $\text{C}_{42}\text{H}_{42}\text{N}_2\text{O}_5\text{P}$ ($\text{M} + \text{H}$) $^+$ required 685.2831, found 685.2819.

Leucine-OBn-Derived Cyclic Ph-Phosphonamide 11f

Following the general procedure for the formation of cyclic phosphonamides, 1,4-diamine **4g** (320 mg, 0.648 mmol), Et₃N (380 μ L, 2.72 mmol), dichlorophenylphosphine (105 μ L, 0.78 mmol), *m*-CPBA (174 mg, 1.01 mmol) and CH₂Cl₂ (2.5 mL initially, 2.5 mL for the oxidation step) yielded 342 mg (86%) of the cyclic phosphonamide **11f** as a colorless oil after subjection to flash chromatography (2:1 hexanes/EtOAc). $[\alpha]^{25} = -38.0$ ($c = 5.14$, CHCl₃); FTIR (neat) 1734, 1455, 1374, 1214 (P=O), 751, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.84-7.79 (m, 2H), 7.49-7.27 (m, 11H), 7.17-7.15 (m, 2H), 5.63-5.55 (m, 2H), 5.13 (d, $J = 12.3$ Hz, 1H), 5.08 (d, $J = 12.2$ Hz, 1H), 4.94 (d, $J = 12.2$ Hz, 1H), 4.91 (d, $J = 12.2$ Hz, 1H), 4.20 (ddd, $J_{HP} = 9.9$ Hz, $J_{HH} = 7.1$, 7.1 Hz, 1H), 4.14 (ddd, $J_{HP} = 9.6$ Hz, $J_{HH} = 7.4$, 7.4 Hz, 1H), 3.99-3.87 (m, 2H), 3.80-3.72 (m, 1H), 3.67-3.60 (m, 1H), 1.78-1.68 (m, 1H), 1.64-1.60 (m, 2H), 1.58-1.53 (m, 1H), 1.42-1.36 (m, 1H), 1.27-1.18 (m, 1H), 0.89 (d, $J = 6.4$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H), 0.71 (d, $J = 6.5$ Hz, 3H), 0.66 (d, $J = 6.7$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.70 (d, $J_{CP} = 6.4$ Hz), 172.35 (d, $J_{CP} = 2.1$ Hz), 135.64, 135.47, 132.79, 132.72, 131.77 (d, $J_{CP} = 2.2$ Hz), 129.40 (d, $J_{CP} = 125.3$ Hz), 128.37, 128.35, 128.34, 128.21, 128.21, 128.10 (d, $J_{CP} = 8.2$ Hz), 128.09, 128.03, 66.61, 66.31, 56.57 (d, $J_{CP} = 7.1$ Hz), 56.02 (d, $J_{CP} = 6.0$ Hz), 41.16 (d, $J_{CP} = 2.7$ Hz), 40.63 (d, $J_{CP} = 2.9$ Hz), 39.44, 39.06 (d, $J_{CP} = 4.4$ Hz), 24.59, 24.35, 22.85, 22.56, 22.22, 21.96; ³¹P NMR (162 MHz, CDCl₃) δ 29.71; HRMS calcd for C₃₆H₄₆N₂O₅P (M + H)⁺ required 617.3144, found 617.3125.

1,2,7-Thiadiazepane-1-oxide 12

A solution of the 1,4-diamine **4c** (69 mg, 0.17 mmol), Et₃N (98 μ L, 0.70 mmol), and CH₂Cl₂ (0.5 mL) was cooled to 0° in an ice bath. Thionyl chloride (15 μ L, 0.20 mmol) was added dropwise,

and the reaction was warmed to room temperature for 25 minutes, then concentrated under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc) yielded 50 mg (68%) of **12** as a colorless oil. $[\alpha]^{25} = -73$ ($c = 0.74$, CHCl_3); FTIR (neat) 1736, 1436, 1123 (S=O) 746, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.13 (m, 10H), 5.47 (bs, 2H), 4.48 (dd, $J = 8.8, 6.6$ Hz, 1H), 4.40 (dd, $J = 7.9, 7.6$ Hz, 1H), 3.88 (d, $J = 7.9$ Hz, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.58 (d, $J = 7.0$ Hz, 1H), 3.35-3.23 (m, 2H), 3.26 (dd, $J = 15.2, 7.0$ Hz, 1H), 3.16 (dd, $J = 14.1, 7.4$ Hz, 1H), 2.88 (dd, $J = 14.1, 8.2$ Hz, 1H), 2.81 (dd, $J = 14.3, 9.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.09, 171.51, 136.95, 136.52, 129.29, 129.21, 129.14, 128.95, 128.34, 128.11, 126.78, 126.47, 61.11, 59.63, 52.10, 51.95, 40.78, 38.82, 36.76, 36.42; HRMS calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5\text{S}$ ($\text{M} + \text{H}$) $^+$ required 457.1797, found 457.1795.

Leucine-OMe/Valine-Derived Unsymmetric Cyclic N-H-Sulfamide **13**

A solution of unsymmetric 1,4-diamine **4d** (18 mg, 70 μmol) and pyridine (1 mL) was prepared. Sulfamide (7 mg, 74 μmol) was added in one portion, and the solution was brought to reflux for 12 hours. The crude reaction mixture was diluted with EtOAc, washed with 10% $\text{NaHSO}_4(\text{aq})$ (4X), water (1X), and brine (1X). The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated to afford 21 mg (95%) of **13** as a light yellow oil. The product was >99% pure by GC, and >95% pure by ^1H - and ^{13}C -NMR; therefore, the product need not be further purified. $[\alpha]^{25} = -50.5$ ($c = 0.75$, CHCl_3); FTIR (neat) 3279 (broad), 3028, 1741, 1388, 1369, 1319 ($-\text{SO}_2-$), 1172 ($-\text{SO}_2-$) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.79-5.70 [m, 2H, C(5)H and C(6)H], 4.58 [dd, $J = 9.7, 5.2$ Hz, 1H, C(11)H], 4.52 [d, $J = 11.2$ Hz, 1H, N(3)H], 3.96 [ddd, $J = 18.2, 2.6, 2.6$, 1H, C(7)H_a or C(7)H_b], 3.88-3.82 [m, 2H, C(4)H; and C(7)H_b or C(7)H_a], 3.69 [s, 3H, C(13)H], 1.95-1.85 [m, 1H, C(8)H], 1.72-1.54 [m, 3H, C(14)H_a, C(14)H_b, and C(15)H], 1.01 [d, $J = 6.7$ Hz, 3H, C(9)H or C(10)H], 0.96 [d, $J = 5.3$ Hz, 3H, C(10)H or C(9)H], 0.94 [d, $J = 6.5$ Hz, 3H, C(16)H or C(17)H], 0.93 [d, $J = 6.4$ Hz, 3H, C(17)H or C(16)H]; ^{13}C NMR (125 MHz, CDCl_3) δ 172.31 [C(12)], 134.44 [C(5)], 129.22 [C(6)], 57.54 [C(11)], 57.24 [C(4)], 52.00 [C(13)], 41.13 [C(7)],

38.47 [C(14)], 32.27 [C(8)], 24.67 [C(15)], 23.00 [C(16) or C(17)], 21.44 [C(17) or C(16)], 18.66 [C(9) or C(10)], 17.46 [C(10) or C(9)]; HRMS calcd for $C_{14}H_{27}N_2O_4S$ ($M+H$)⁺ required 319.1692, found 319.1693.

Leucine-OMe/Valine-Derived Unsymmetric Cyclic *N*-Bn-Sulfamide **14**

In a flame-dried pressure tube, a solution of unsymmetric sulfamide **13** (30 mg, 94 μ mol) and acetonitrile (1.5 mL) was prepared, followed by the addition of K_2CO_3 (65 mg, 470 μ mol) and benzyl bromide (81 mg, 470 μ mol). The solution was warmed in a 70 °C oil bath, and the reaction was monitored by TLC. Upon disappearance of starting material ($t=96$ h), the solution was diluted with EtOAc and water, the layers were separated, and the aqueous layer was washed with EtOAc (3X). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (7:1 hexanes/EtOAc) yielded 35 mg (92%) of **14** as a colorless oil. $[\alpha]^{25}_D = -48.4$ ($c = 1.41$, $CHCl_3$); FTIR (neat) 3031, 1743, 1388, 1368, 1327 ($-SO_2-$), 1165 ($-SO_2-$) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.39 [d, $J = 7.4$ Hz, 2H, C(20)H], 7.32-7.22 [m, 3H, C(21)H and C(22)H], 5.92-5.87 [m, 1H, C(6)H], 5.81 [dd, $J = 11.0, 4.2$ Hz, 1H, C(5)H], 4.68 [dd, $J = 9.1, 6.0$ Hz, 1H, C(11)H], 4.45 [d, $J = 16.0$ Hz, 1H, C(18)H_a or C(18)H_b], 4.00 [d, $J = 16.0$ Hz, 1H, C(18)H_b or C(18)H_a], 3.92-3.89 [m, 1H, C(4)H], 3.88-3.76 [m, 2H, C(7)H_a and C(7)H_b], 3.72 [s, 3H, C(13)H], 1.81-1.58 [m, 4H, C(8)H, C(14)H_a, C(14)H_b, and C(15)H], 0.98 [d, $J = 6.3$ Hz, 3H, C(16)H or C(17)H], 0.95 [d, $J = 6.3$ Hz, 3H, C(17)H or C(16)H], 0.87 [d, $J = 6.6$ Hz, 3H, C(9)H or C(10)H], 0.73 [d, $J = 6.4$ Hz, 3H, C(10)H or C(9)H]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.36 [C(12)], 138.04 [C(19)], 131.82 [C(5)], 129.11 [C(6)], 128.26 [C(20) or C(21)], 128.23 [C(21) or C(20)], 127.25 [C(22)], 64.20 [C(11)], 58.17 [C(4)], 52.09 [C(13)], 50.33 [C(18)], 40.71 [C(7)], 38.95 [C(14)], 30.47 [C(8)], 24.68 [C(15)], 23.00 [C(16) or C(17)], 21.50 [C(17) or C(16)], 20.39 [C(9) or C(10)], 20.09 [C(10) or C(9)]; HRMS calcd for $C_{21}H_{33}N_2O_4S$ ($M+H$)⁺ required 409.2161, found 409.2152.

Leucine-OMe/Valine-Derived Unsymmetric Cyclic Phosphonamide *major-16a*

A solution of acyclic phosphonamide *major-15a* (126 mg, 0.37 mmol) and CH_2Cl_2 (35 mL) was purged with argon for 10 minutes. Grubbs catalyst (15 mg, 18 μmol) was added, and the solution was brought to reflux and monitored by TLC. Upon disappearance of starting material by TLC, the reaction was concentrated under reduced pressure. Flash chromatography (5% MeOH in EtOAc, then 10% MeOH in EtOAc) afforded 116 mg (>95%) of *major-16a* as a light yellow oil. $[\alpha]^{25} = -12.5$ ($c = 0.91$, CHCl_3); FTIR (neat) 3201 (broad), 3020, 1736, 1197 ($\text{P}=\text{O}$) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.62 [dddd, $J_{\text{HH}} = 11.3, 6.2, 3.8$ Hz, $J_{\text{HP}} = 2.4$ Hz, 1H, C(6)H], 5.46 [ddd, $J_{\text{HH}} = 11.3, 2.1$ Hz, $J_{\text{HP}} = 2.1$ Hz, 1H, C(5)H], 4.09-3.99 [m, 1H, C(7)H_a or C(7)H_b], 3.94-3.88 [m, 1H, C(11)H], 3.64 [s, 3H, C(13)H], 3.43 [dd, $J = 17.0, 6.4$ Hz, 1H, C(7)H_b or C(7)H_a], 3.40-3.32 [m, 1H, C(4)H], 2.58 [dd, $J_{\text{HH}} = 8.6$ Hz, $J_{\text{HP}} = 6.4$ Hz, 1H, N(3)H], 1.91-1.83 [m, 1H, C(8)H], 1.57-1.47 [m, 3H, C(14)H_a, C(14)H_b, and C(15)H], 1.50 [d, $J_{\text{HP}} = 15.1$ Hz, 3H, C(18)H], 0.92 [d, $J = 6.8$ Hz, 3H, C(9)H or C(10)H], 0.89 [d, $J = 6.8$ Hz, 3H, C(10)H or C(9)H], 0.86 [d, $J = 5.6$ Hz, 3H, C(16)H or C(17)H], 0.86 [d, $J = 5.6$ Hz, 3H, C(17)H or C(16)H]; ^{13}C NMR (100 MHz, CDCl_3) δ 172.91 [C(12)], 132.78 [C(5)], 128.49 [C(6)], 56.83 [d, $J_{\text{CP}} = 1.8$ Hz, C(4)], 55.77 [d, $J_{\text{CP}} = 4.3$ Hz, C(11)], 51.89 [C(13)], 39.25 [d, $J_{\text{CP}} = 5.4$ Hz, C(7)], 39.10 [d, $J_{\text{CP}} = 2.2$ Hz, C(14)], 33.31 [d, $J_{\text{CP}} = 9.1$ Hz, C(8)], 24.37 [C(15)], 22.89 [C(16) or C(17)], 21.85 [C(17) or C(16)], 19.28 [C(9) or C(10)], 17.52 [C(10) or C(9)], 11.76 [d, $J_{\text{CP}} = 121.3$ Hz, C(18)]; ^{31}P NMR (162 MHz, CDCl_3) δ 36.20; HRMS calcd for $\text{C}_{15}\text{H}_{30}\text{N}_2\text{O}_3\text{P}$ ($\text{M}+\text{H}$)⁺ required 317.1994, found 317.1994.

Leucine-OMe/Valine-Derived Unsymmetric Cyclic Phosphonamide *minor-16a*

A solution of acyclic phosphonamide *minor-15a* (36 mg, 105 μ mol) and CH_2Cl_2 (10 mL) was purged with argon for 10 minutes. Grubbs catalyst (5 mg, 6 μ mol) was added, and the solution was brought to reflux and monitored by TLC. Upon disappearance of starting material by TLC, the reaction was cooled to room temperature, silica (2.0 g) and DMSO (39 mg, 0.50 mmol) (Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, 3, 1411-1413) were added, and the mixture was allowed to stir open to air overnight. The mixture was filtered, the silica filter cake was washed with acetone (3X), and the crude filtrate was concentrated. The product was recrystallized from EtOAc/heptane to yield 25 mg (76%) of *minor-16a* as a white powder. dec. 190-210 $^\circ\text{C}$; $[\alpha]^{25} = -8.7$ ($c = 0.31$, CHCl_3); FTIR (neat) 3160 (broad), 3012, 1736, 1191 ($\text{P}=\text{O}$) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.69 [dddd, $J_{\text{HH}} = 11.5, 6.8, 2.5$ Hz, $J_{\text{HP}} = 2.5$ Hz, 1H, C(6)H], 5.47 [ddd, $J_{\text{HH}} = 9.4, 1.9$ Hz, $J_{\text{HP}} = 1.9$ Hz, 1H, C(5)H], 4.45 [ddd, $J_{\text{HH}} = 9.7, 4.8$ Hz, $J_{\text{HP}} = 9.7$ Hz, 1H, C(11)H], 4.01-3.91 [m, 1H, C(4)H], 3.85-3.76 [m, 1H, C(7)H_a or C(7)H_b], 3.66 [s, 3H, C(13)H], 3.22 [ddd, $J_{\text{HP}} = 24.0$ Hz, $J_{\text{HH}} = 18.6, 6.9$ Hz, 1H, C(7)H_b or C(7)H_a], 2.40 [dd, $J_{\text{HP}} = 16.0$ Hz, $J_{\text{HH}} = 8.6$ Hz, 1H, N(3)H], 1.91-1.80 [m, 1H, C(8)H], 1.79-1.67 [m, 1H, C(15)H], 1.65-1.49 [m, 2H, C(14)H_a and C(14)H_b], 1.47 [d, $J_{\text{HP}} = 15.1$ Hz, 3H, C(18)H], 0.98 [d, $J = 6.5$ Hz, 3H, C(9)H or C(10)H], 0.95 [d, $J = 6.8$ Hz, 3H, C(16)H or C(17)H], 0.91 [d, $J = 6.9$ Hz, 3H, C(17)H or C(16)H], 0.88 [d, $J = 6.7$ Hz, 3H, C(10)H or C(9)H]; ^{13}C NMR (125 MHz, CDCl_3) δ 174.59 [C(12)], 132.24 [C(5)], 129.39 [C(6)], 56.83 [d, $J_{\text{CP}} = 4.6$ Hz, C(11)], 53.37 [d, $J_{\text{CP}} = 2.5$ Hz, C(4)], 51.74 [C(13)], 41.53 [d, $J_{\text{CP}} = 5.3$ Hz, C(7)], 39.38 [d, $J_{\text{CP}} = 3.7$ Hz, C(14)], 33.00 [d, $J_{\text{CP}} = 8.4$ Hz, C(8)], 24.68 [C(15)], 23.36 [C(16) or C(17)], 21.37 [C(17) or C(16)], 18.13 [C(9) or C(10)], 17.78 [C(10) or C(9)], 10.77 [d, $J_{\text{CP}} = 112.1$ Hz, C(18)]; ^{31}P NMR (162 MHz, CDCl_3) δ 32.96; HRMS calcd for $\text{C}_{15}\text{H}_{30}\text{N}_2\text{O}_3\text{P}$ ($\text{M}+\text{H}$) $^+$ required 317.1994, found 317.1986.

Phenylalanine-OMe /Valine-Derived Unsymmetric Cyclic Phosphonamide *major-16b*

A solution of acyclic phosphonamide **15b** (102 mg, 0.27 mmol, ~8.9:1.0 diastereomeric mixture) and CH_2Cl_2 (25 mL) was purged with argon for 10 minutes. Grubbs catalyst (13 mg, 16 μmol) was added, and the solution was brought to reflux and monitored by TLC. Upon disappearance of starting material by TLC, the reaction was concentrated under reduced pressure. Flash chromatography (EtOAc) afforded 51 mg (54%) of *major-16b* as a light yellow oil.

major-16b: $[\alpha]^{25} = -25.5$ ($c = 2.26$, CHCl_3); FTIR (neat) 3200 (broad), 3026, 1734, 1195 ($\text{P}=\text{O}$) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.24-7.18 [m, 5H, C(16)H, C(17)H, and C(18)H], 5.71-5.66 [m, 1H, C(6)H], 5.54 [d, $J = 11.3$ Hz, 1H, C(5)H], 4.20 [ddd, $J_{\text{HH}} = 10.3, 4.3$ Hz, $J_{\text{HP}} = 10.3$ Hz, 1H, C(11)H], 4.15-4.05 [m, 1H, C(7)H_a or C(7)H_b], 3.70 [s, 3H, C(13)H], 3.43 [ddd, $J_{\text{HH}} = 16.8, 5.9$ Hz, $J_{\text{HP}} = 16.8$ Hz, 1H, C(7)H_b or C(7)H_a], 3.14 [dd, $J = 14.1, 3.9$ Hz, 1H, C(14)H_a or C(14)H_b], 3.01-2.92 [m, 1H, C(4)H], 2.82 [dd, $J = 14.0, 10.7$ Hz, 1H, C(14)H_b or C(14)H_a], 2.63 [dd, $J_{\text{HH}} = 7.0$ Hz, $J_{\text{HP}} = 7.0$ Hz, 1H, N(3)H], 1.85-1.75 [m, 1H, C(8)H], 0.86 [d, $J_{\text{HP}} = 15.6$ Hz, 3H, C(19)H], 0.87 [d, $J = 6.5$ Hz, 3H, C(9)H or C(10)H], 0.84 [d, $J = 6.8$ Hz, 3H, C(10)H or C(9)H]; ^{13}C NMR (125 MHz, CDCl_3) δ 172.08 [C(12)], 137.61 [C(15)], 133.26 [C(5)], 129.60 [C(16) or C(17)], 128.22 [C(17) or C(16)], 127.77 [C(6)], 126.38 [C(18)], 60.31 [d, $J_{\text{CP}} = 4.4$ Hz, C(11)], 56.68 [d, $J_{\text{CP}} = 1.7$ Hz, C(4)], 52.16 [C(13)], 40.23 [d, $J_{\text{CP}} = 2.4$ Hz, C(7)], 36.30 [d, $J_{\text{CP}} = 5.0$ Hz, C(14)], 33.23 [d, $J_{\text{CP}} = 8.6$ Hz, C(8)], 19.21 [C(9) or C(10)], 17.97 [C(10) or C(9)], 11.24 [d, $J_{\text{CP}} = 122.4$ Hz, C(19)]; ^{31}P NMR (202 MHz, CDCl_3) δ 37.47; HRMS calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_3\text{P}$ ($\text{M}+\text{H}$)⁺ required 351.1838, found 351.1838.

minor-16b: ^{31}P NMR (202 MHz, CDCl_3) δ 32.53.

Phenylalanine-OBn/Valine-Derived Unsymmetric Cyclic Phosphonamide *major-16c*

A solution of acyclic phosphonamide **15c** (295 mg, 0.65 mmol, ~5.8:1.0 diastereomeric mixture) and CH_2Cl_2 (65 mL) was purged with argon for 10 minutes. Grubbs catalyst (27 mg, 33 μmol) was added, and the solution was brought to reflux and monitored by TLC. Upon disappearance of starting material by TLC, the reaction was concentrated under reduced pressure. Flash chromatography (EtOAc, then 5% MeOH in EtOAc) afforded 240 mg (87%) of a 5.4:1.0 (^{31}P NMR) mixture of inseparable diastereomers. Recrystallization from Et_2O , CH_2Cl_2 , and heptane gave 160 mg (58%) of major diastereomer *major-16c* as colorless crystals.

major-16c: mp 129-130 $^\circ\text{C}$; $[\alpha]^{25} = -10.4$ ($c = 1.03$, CHCl_3); FTIR (neat) 3186 (broad), 3028, 1731, 1192 ($\text{P}=\text{O}$) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.18 [m, 10H, C(15)H, C(16)H, C(17)H, C(20)H, C(21)H, and C(22)H], 5.70-5.66 [m, 1H, C(6)H], 5.52 [d, $J = 11.3$ Hz, 1H, C(5)H], 5.22 [d, $J = 12.4$ Hz, 1H, C(13)H_a or C(13)H_b], 5.12 [d, $J = 12.4$ Hz, 1H, C(13)H_b or C(13)H_a], 4.25 [ddd, $J_{\text{HH}} = 10.2$, 4.5 Hz, $J_{\text{HP}} = 10.2$ Hz, 1H, C(11)H], 4.24-4.08 [m, 1H, C(7)H_a or C(7)H_b], 3.45 [ddd, $J_{\text{HH}} = 17.4$, 6.1 Hz, $J_{\text{HP}} = 17.4$ Hz, 1H, C(7)H_b or C(7)H_a], 3.18 [dd, $J = 14.0$, 4.1 Hz, 1H, C(18)H_a or C(18)H_b], 3.04-2.94 [m, 1H, C(4)H], 2.83 [dd, $J = 13.9$, 10.5 Hz, 1H, C(18)H_b or C(18)H_a], 2.83-2.25 [m, 1H, N(3)H], 1.81-1.70 [m, 1H, C(8)H], 0.95 [d, $J_{\text{HP}} = 15.2$ Hz, 3H, C(23)H], 0.85 [d, $J = 6.8$ Hz, 3H, C(9)H or C(10)H], 0.82 [d, $J = 6.7$ Hz, 3H, C(10)H or C(9)H]; ^{13}C NMR (125 MHz, CDCl_3) δ 171.29 [C(12)], 137.41 [C(14) or C(19)], 135.44 [C(19) or C(14)], 133.27 [C(5)], 129.50 [C(15), C(16), C(20), or C(21)], 128.30 [C(16), C(20), C(21), or C(15)], 128.11 [C(20), C(21), C(15), or C(16)], 127.99 [C(21), C(15), C(16), or C(20)], 127.96 [C(17) or C(22)], 127.89 [C(6)], 126.54 [C(22) or C(17)], 66.71 [C(13)], 60.48 [d, $J_{\text{CP}} = 4.4$ Hz, C(11)], 56.28 [d, $J_{\text{CP}} = 1.5$ Hz, C(4)], 40.22 [d, $J_{\text{CP}} = 2.1$ Hz, C(7)], 36.38 [d, $J_{\text{CP}} = 5.0$ Hz, C(18)], 33.07 [d, $J_{\text{CP}} = 8.9$ Hz, C(8)], 19.06 [C(9) or C(10)], 17.75 [C(10) or C(9)], 11.30 [d, $J_{\text{CP}} = 122.0$ Hz, C(23)]; ^{31}P NMR (162 MHz, CDCl_3) δ 37.23; HRMS calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_3\text{P}$ ($\text{M}+\text{H}$) $^+$ required 427.2151, found 427.2143.

minor-16c: ^{31}P NMR (162 MHz, CDCl_3) δ 32.88.

The P_S -configuration for compound *major-16c* (entry 5, Table 2) was determined using X-ray crystallography. While *major-16c* exists as colorless crystals, **15a-c** and *major-16a,b* exist as colorless oils. Consequently, the unambiguous assignment of the (*S*)-configuration at phosphorus for *major-16a* was accomplished using the following ^{31}P NMR correlation experiment: the major diastereomers (in red) in both the acyclic and cyclic phosphonamides **15** and **16**, respectively, exhibit a downfield chemical shift in the ^{31}P NMR relative to the minor diastereomers (in blue). This evidence supports the P_S assignment for *major-16a*.

Table 2 ^{31}P NMR Correlation Experiment

entry	acyclic diene	^{31}P δ (ppm)	cyclic olefin	^{31}P δ (ppm)	<i>P</i> -stereochemistry
1	<i>major-15a</i>	34.12	<i>major-16a</i>	36.20	P_S
2	<i>minor-15a</i>	32.41	<i>minor-16a</i>	32.96	P_R
3	<i>major-15b</i>	33.79	<i>major-16b</i>	37.47	P_S
4	<i>minor-15b</i>	32.16	<i>minor-16a</i>	32.53	P_R
5	<i>major-15c</i>	33.46	<i>major-16c</i>	37.23	P_S (from X-ray)
6	<i>minor-15c</i>	31.89	<i>minor-16c</i>	32.88	P_R

Molecular Modeling Program Parameters: SYBYL v. 6.8, MMFF94 force field using default parameter settings except with: NB cutoff = 10 Å; max. iterations: 1000; max. displacement = 0.001; and min. energy change: 0.005.