The Synthesis of Sterically Demanding Amino Acid-Derived Cyclic Phosphonamides

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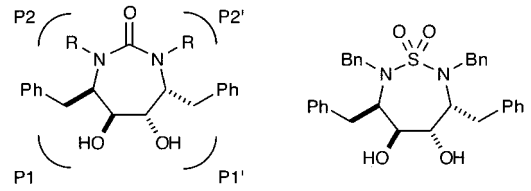
The preparation and utilization of C_2-symmetric 1,4-diamines in the synthesis of amino acid-derived cyclic phosphonamides **1**−**3** are described. The 1,4-diamines are synthesized via three methods: (i) amino acid/fumaryl chloride coupling followed by amide reduction, (ii) amino acid/1,4-diamine coupling followed by amide reduction, and (iii) a template-supported ring-closing metathesis/hydrolysis sequence. The pseudo C_2-symmetric cyclic phosphonamides **1**−**3** are prepared by condensation of the C_2-symmetric 1,4-diamines to P(III) centers, followed by oxidation.

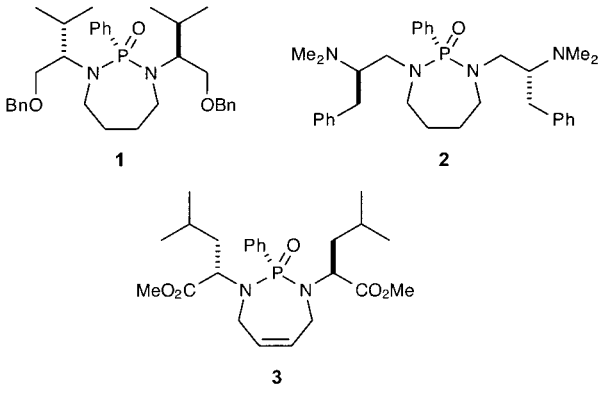
In our pursuit of novel *P*-heterocycles,[1] we have recently become interested in the synthesis of amino acid-based phosphorus containing compounds that may have potential as HIV-1 protease inhibitors. Our efforts in this area have largely been driven by the development of a number of cyclic urea-based HIV-1 protease inhibitors at Dupont-Merck that gave promising biological activity (Scheme 1).[2] The routes described herein allow for incorporation of amino acid side chains into the peripheral P2/P2′ regions (Scheme 1)[3] of the cyclic phosphonamides **1**−**3** (Scheme 2).

Our initial strategy toward the synthesis of cyclic phosphonamides such as **7** centered on the utilization of a ring-closing metathesis (RCM)[4] approach as outlined in Scheme 3. We recently reported the syntheses of a multitude of 5- and 7-membered *P*-heterocycles via RCM sequences.[5] The successful synthesis of other 5- and 7-membered cyclic phosphonamides utilizing a RCM strategy led us down a similar path for the compounds described herein. Although this initial approach was unsuccessful, an alternative pathway has proven to be successful and is the topic of this paper.

Scheme 1. DuPont-Merck HIV-1 Protease Inhibitors



Scheme 2



Our initial proposed synthesis of cyclic phosphonamides **7** involved coupling α-branched amino acid methyl esters **4** to phosphonic dichlorides, followed by allylation of the resulting phosphonamides **5**, and subsequent RCM to derive **7** (Scheme 3).[6] The coupling of various amino acids with methylphosphonic dichloride to yield **5** was facile, however, various attempts to allylate the phosphonamide all proved unsuccessful, and alternate routes were pursued.

Our attention turned to coupling allylated amino acids directly with phosphorus P(V) species (Scheme 4). Coupling of allylated amino acids **8** with phosphonic dichlorides resulted in the quantitative production of two diastereomeric phosphonamidic chloridates **9P*$_S$S*** and **9P*$_R$S***. The monochlorides readily dimerize in the pres-

(1) (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939−3942. (b) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297−3300. (c) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769−1772. (d) Hanson, P. R.; Sprott, K. T.; Wrobleski, A. D. *Tetrahedron Lett.* **1999**, *40*, 1455−1458.

(2) (a) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bachelor, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Vittanen, S. *Science* **1994**, *263*, 380−384. (b) Patel, M.; Kaltenbach, R. F., III; Nugiel, D. A.; McHugh, R. J., Jr.; Jadhay, P. K.; Bacheler, L. T.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Garber, S.; Reid, C.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1077−1082. (c) De Lucca, G. V.; Kim, U. T.; Liang, J.; Cordova, B.; Klabe, R. M.; Garber, S.; Bacheler, L. T.; Lam, G. N.; Wright, M. R.; Logue, K. A.; Erickson-Viitanen, S.; Ko, S. S.; Trainor, G. L. *J. Med. Chem.* **1998**, *41*, 2411−2423. (d) De Lucca, G. V.; Lam, P. Y. S. *Drugs Future* **1998**, *23*, 987−994. (e) Hodge, C. N.; Lam, P. Y. S.; Eyermann, C. J.; Jadhav, P. K.; Ru, Y.; Fernandez, C. H.; De Lucca, G. V.; Chang, C.-H.; Kaltenbach, R. F., III.; Holler, E. R.; Woerner, F.; Daneker, W. F.; Emmett, G.; Calabrese, J. C.; Aldrich, P. E. *J. Am. Chem. Soc.* **1998,** *120*, 4570−4581. (f) Jadhav, P. K.; Woerner, F. J. *Tetrahedron Lett.* **1995**, *36*, 6383−6386. (g) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; De Lucca, G. V.; Rodgers, J. D. US Patent 5,610,294, 1997; *Chem. Abstr.* **1997**, *126*, 293367. h) Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885−897. (i) Baeckbro, K.; Loewgren, S.; Oesterlund, K.; Atepo, J.; Unge, T.; Hulten, J.; Bonham, N. M.; Schaal, W.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 898−902. (j) Hultén, J.; Andersson, H. O.; Schaal, W.; Danielson, H. U.; Classon, B.; Kvarnström, I.; Karlén, A.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 4054−4061.

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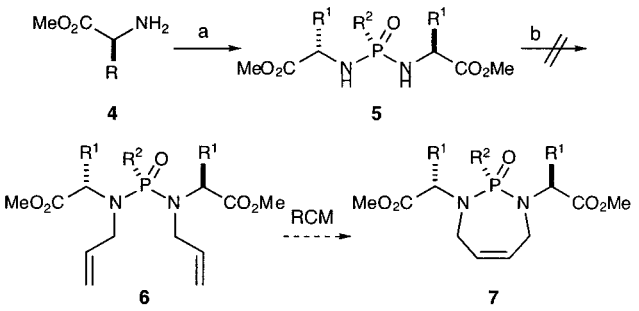
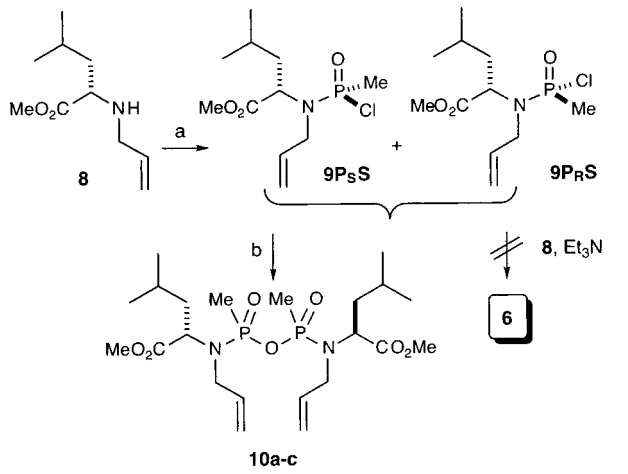
Scheme 3[a]



[a] Key: (a) $CH_3P(O)Cl_2$, Et_3N, CH_2Cl_2, >95%; (b) various allylation procedures.

Scheme 4[a]



[a] Key: (a) $CH_3P(O)Cl_2$, Et_3N, CH_2Cl_2, >95%; (b) Et_3N, 85%.

ence of Et_3N to form 3 diastereomeric phosphonamidic anhydrides **10a**−**c**, but fail to couple with another equivalent of **8** to produce **6**.[7] It became apparent to us that steric factors inherent to secondary α-branched amino acids prevent the coupling routes outlined in Schemes 3 and 4, and thus our original RCM strategy was abandoned.

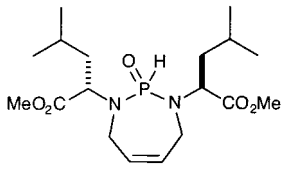
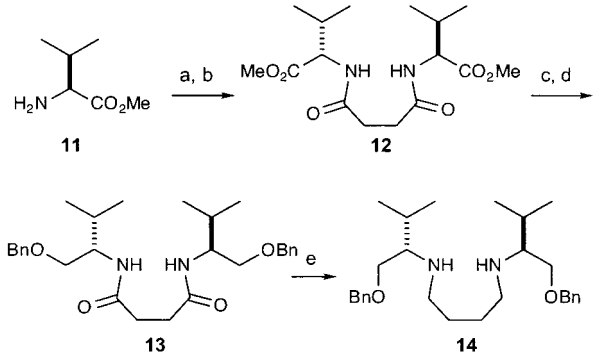


Figure 1.

Scheme 5[a]



[a] Key: (a) fumaryl dichloride, Et_3N, CH_2Cl_2, 99%; (b) H_2/Pd−C, 100%; (c) $NaBH_4$, MeOH, THF, 95%; (d) NaH, BnBr, DMF, 94%; (e) LAH, dioxane, 95%.

We next investigated a P(III) coupling sequence in order to diminish the steric demands imparted by P(V) centers. However, our efforts in coupling two allylated amino acids with various P(III) centers ($MePCl_2$, $MeOPCl_2$, and $PhPCl_2$), followed by oxidation to P(V), were unsuccessful. Despite these shortcomings, we obtained a marginal result from the coupling of allylated leucine **8** to PCl_3, which after hydrolysis and metathesis, afforded a pseudo C_2-symmetric cyclic *P*-H compound in 47% overall yield (Figure 1).[5]

In light of the difficulty associated with attaching two allylated α-branched amino acids to P(V) and P(III) centers, a new strategy involving the synthesis and coupling of 1,4-diamines with phosphorus was undertaken (Scheme 5).[8] Although the issue of steric congestion does not change, we reasoned that the entropic advantage inherent to this route would be favorable.

The route to the phosphonamide **1**, containing two α-branched amino acids is outlined in Schemes 5 and 6. Two equivalents of valine methyl ester **11** were coupled to fumaryl dichloride followed by hydrogenation to afford diamide **12**. Reduction with $NaBH_4$ and protection afforded bis-benzyl ether **13**. Reduction of the amide with LAH produced the 1,4-diamine **14**, which was ready for phosphorus coupling (Scheme 5).

Valine-derived diamine **14** was subjected to both phosphorus(III) and phosphorus(V) coupling procedures (Scheme 6). Compound **14** did not couple with methyl phosphonic dichloride [P(V)], however, it was successfully coupled to dichlorophenylphosphine [P(III)]. Subsequent

(3) Functionalization of the internal P1/P1′ positions and external P2/P2′ positions in other cyclic ureas and sulfamides has been shown to influence the activity of HIV protease inhibitors; see: (a) ref 2 and references therein. (b) Nugiel, D. A.; Jacobs, K.; Worley, T.; Patel, M.; Kaltenbach, R. F., III; Meyer, D. T.; Jadhav, P. K.; De Lucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156−2169. (c) Han, W.; Pelletier, J. C.; Hodge, C. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3615−3620. (d) Patel, M.; Bachelor, L. T.; Rayner, M. M.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 823−828. (e) Dax, S. L.; Cook, S. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 797−802. (f) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; DeLucca, G. V.; Eyermann, C. J.; Chang, C.-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P. N.; McHugh, R. J.; Han, Q.; Li, R.; Markwalder, J. A.; Sietz, S. P.; Sharpe, T. R.; Bachelor, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winslow, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. *J. Med. Chem.* **1996,** *39*, 3514−3525. (g) Han, Q.; Chang, C.-H.; Li, R.; Ru, Y.; Jadhav, P. K.; Lam, P. Y. S. *J. Med. Chem.* **1998,** *41*, 2019−2028. (h) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Erickson-Viitanen, S.; Klabe, R. M.; Bacheler, L.; Cordova, B. C.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1998,** *8*, 715−720.

(4) (a) See ref 1. (b) For other examples of RCM on phosphorus containing compounds using the Grubbs ruthenium catalyst, **4** see: Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119−2123. (d) Trevitt, M.; Gouverneur, V. *Tetrahedron Lett.* **1999**, *40*, 7333−7336. (e) Hetherington, L.; Greedy, B.; Gouverneur, V. *Tetrahedron* **2000**, *56*, 2053−2060.

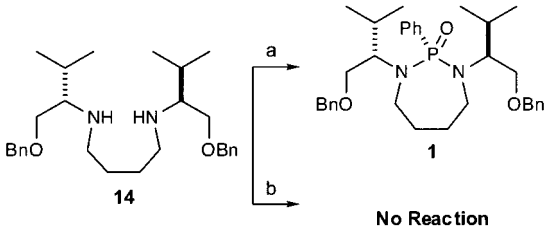
(5) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Synthesis* **2000**, in press.

(6) We have successfully utilized this strategy in the synthesis of amino acid-derived C_2-symmetric sulfamides. Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron*, **2000**, 56, *in press.*

(7) Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000**, *65*, 4721−4728.

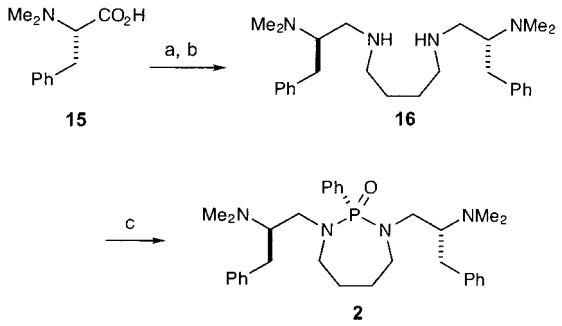
(8) For examples of the coupling of CDI with primary α-branched 1,4-diamines to produce seven-membered cyclic ureas, see: (a) Nugiel ref 3b. For examples of the coupling of SO_2Cl_2 with primary α-branched 1,5-diamines to produce eight-membered cyclic sulfamides, see: (b) Jadhav ref 2f.

Scheme 6[a]



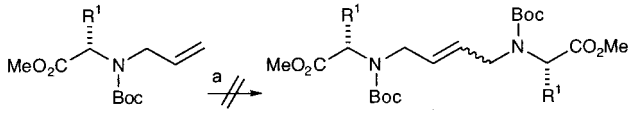
[a] Key: (a) (i) $PhPCl_2$, Et_3N, CH_2Cl_2, (ii) *m*-CPBA, 75%; (b) $CH_3P(O)Cl_2$, Et_3N, CH_2Cl_2.

Scheme 7[a]



[a] Key: (a) HBTU, 1,4-diaminobutane, Et_3N, CH_3CN, 88%; (b) LAH, dioxane, 83%; (c) (i) $PhPCl_2$, Et_3N, CH_2Cl_2, (ii) *m*-CPBA, 85%.

Scheme 8[a]



[a] Key: (a) $Cl_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2.

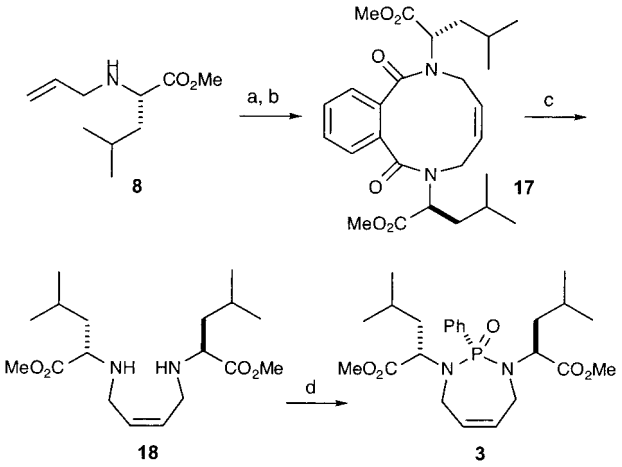
oxidization with *m*-CPBA produced the cyclic phosphonamide **1** in good yield. The lack of coupling to phosphorus (V) and the successful coupling to phosphorus (III) supports the hypothesis that these targets have significant steric issues. Pre-assembly of the 1,4-diamine **14** appears to be crucial in synthesizing these sterically demanding molecules.

A similar synthetic route to phosphonamide **2** containing two β-branched amines is outlined in Scheme 7. Two equivalents of *N*,*N*-dimethyl phenylalanine **15** were coupled to 1,4-diamino butane in good yield to produce the diamide. Subsequent reduction with LAH provided the C_2-symmetric diamine **16**. The coupling of diamine **16** with dichlorophenylphosphine occurred without incidence, and oxidization with *m*-CPBA afforded phosphonamide **2** in good yield (Scheme 7).

To augment this strategy, we investigated the utilization of olefin metathesis to synthesize 1,4-diamines. A number of allylated amino acid analogues were subjected to intermolecular cross-metathesis; however, all proved to be unsuccessful, as consistent with the findings of Grubbs[9] (Scheme 8).

We next pursued a template-promoted RCM route[10] utilizing phthaloyl dichloride to synthesize the amino acid-derived 1,4-diamine (Scheme 9). Two equivalents of N-allylated leucine methyl ester (**8**) was coupled with phthaloyl dichloride to yield the diamide, which was subjected to RCM conditions to yield the bicyclic diamide **17** as predominately the *Z*-geometric isomer (~10:1 *Z*/*E*) in excellent yield. Amide cleavage with MeOH·HCl provided the *Z*-configured 1,4-diamine **18** with complete stereochemical integrity. Cyclic phosphonamide **3** was synthesized in excellent yield by the coupling of **18** with dichlorophenylphosphine, followed by *m*-CPBA oxidation (Scheme 9). The synthesis of **3** completes our original goal and provides an olefin moiety for further functionalization.

Scheme 9[a]



[a] Key: (a) phthaloyl dichloride, Et_3N, DMAP, CH_2Cl_2, 96%; (b) Grubbs catalyst, CH_2Cl_2, 99%; (c) MeOH/HCl, 44%; (d) (i) $PhPCl_2$, Et_3N, CH_2Cl_2, (ii) *m*-CPBA, 86%.

In summary, the synthesis of amino acid-derived pseudo-C_2-symmetric cyclic phosphonamides has been described. Various steric issues have been addressed through the synthesis and coupling of 1,4-diamines with P(III) followed by oxidation. Current efforts toward the synthesis and biological evaluation of these compounds and additional novel *P*-heterocycles are in progress and will be reported in due course.

Experimental Section

General Methods. All reactions were carried out in flame- or oven-dried glassware under an argon atmosphere using standard gastight syringes, cannulaes, and septa. Stirring was accomplished with oven-dried magnetic stir bars. Methylene chloride was purified by distillation over CaH_2. Triethylamine was distilled from CaH_2 and stored over KOH. DMAP was purchased from Reilly Chemicals and was not further purified. *m*-CPBA was purchased from Aldrich at a 75%−85% purity level and was used without further purification. All amino acid precursors were purchased from Advanced Chem Tech. Deuteriochloroform ($CDCl_3$) was purchased from Cambridge Isotope Laboratories and stored over molecular sieves (4 Å) at room temperature. Mass spectra were performed by the Mass Spectrometry Laboratory at the University of Kansas. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230−400 mesh). Thin-layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, Merck). Visualization of TLC spots was effected using $KMnO_4$ stain and UV irradiation.

Valine-Derived Cyclic Phosphonamide (1). A solution of compound **14** (6.5 mg, 0.048 mmol) and CH_2Cl_2 (100ul) was cooled in a 0 °C ice bath, and Et_3N (23 μL, 0.17 mmol) was slowly added. Dichlorophenylphosphine (6.5 μL, 48.0 μmol) was

(9) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689−1690.

(10) (a) Grubbs and co-workers utilized catechol in their strategy, see ref 8. (b) We also employed a similar strategy utilizing catechol to access **18**; however, a 1:1 mixture of cis/trans isomers resulted.

dissolved in CH_2Cl_2 (100 μL) and added dropwise over 1 min. The reaction was warmed to room temperature for 5 min, then recooled in a 0 °C ice bath. mCPBA (17.7 mg, 0.072 mmol) was added to the salt slurry. After being warmed to room temperature, the reaction was concentrated under reduced pressure, and the slurry was subjected to flash chromatography (EtOAc) to afford 18.5 mg (75%) of **1** as a colorless oil: $[\alpha]^{25} = -54.1°$ ($c = 0.15$, $CHCl_3$); FTIR (neat) 1468, 1453, 1384, 1362, 1207 (P═O), 725, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.69 (m, 2H), 7.41−7.24 (m, 13H), 4.61 (d, $J = 11.8$ Hz, 1H), 4.37, (d, $J = 13.0$ Hz, 1H), 4.36 (s, 2H), 3.77−3.67 (m, 2H), 3.66−3.58 (m, 1H), 3.53 (dd, $J = 10.0$, 7.0 Hz, 1H), 3.47−3.38 (m, 2H), 3.34−3.17 (m, 3H), 2.92 (dddd, $J_{HH} = 14.2$ Hz, $J_{HP} = 10.4$ Hz, $J_{HH} = 7.0$, 3.2 Hz, 1H), 1.98−1.87 (m, 2H), 1.78−1.54 (m, 4H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.80 (d, $J = 6.5$ Hz, 3H), 0.80 (d, $J = 6.5$ Hz, 3H), 0.44 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.70, 138.39, 133.71 (d, $J_{CP} = 145.7$ Hz), 130.64 (d, $J_{CP} = 2.8$ Hz), 128.27, 128.14, 127.73, 127.68, 127.60, 127.55, 127.51, 127.27, 73.09, 72.76, 71.57, 71.52, 62.46 (d, $J_{CP} = 7.0$ Hz), 61.44 (d, $J_{CP} = 6.4$ Hz), 42.23, 42.45, 29.32, 28.36, 27.14, 27.09, 21.42, 21.09. 20.37, 20.26; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.05; HRMS calcd for $C_{34}H_{48}N_2O_3P$ $(M + H)^+$ required 563.3403, found 563.3417.

Phenylalanine-Derived Cyclic Phosphonamide (2). In a procedure similar to that of compound **1** compound **16** (47 mg, 0.12 mmol), CH_2Cl_2 (500 μL), Et_3N (66 μL, 0.48 mmol), dichlorophenylphosphine (19 μL, 0.14 mmol), and *m*-CPBA (35 mg, 0.21 mmol) afforded a slurry that was subjected to flash chromatography (10% Et_3N in EtOAc, then 20% Et_3N in CH_3CN) to yield 48 mg (68%, nonoptimized) of **2** as a colorless oil: $[\alpha]^{25} = +18.5°$ ($c = 0.054$, $CHCl_3$); FTIR (neat) 1453, 1437, 1378, 1201 (P═O), 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.78 (m, 2H), 7.52−6.96 (m, 13H), 3.29−2.92 (m, 6H), 2.84−2.55 (m, 5H), 2.35−2.27 (m, 3H), 2.18 (s, 6H), 2.06 (s, 6H), 1.81−1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.93, 140.85, 132.37 (d, $J_{CP} = 8.5$ Hz), 130.64, 129.59 (d, $J_{CP} = 212.0$ Hz), 128.99, 128.85, 128.25, 128.11, 127.79 (d, $J_{CP} = 13.3$ Hz), 125.61, 125.50, 65.25, 65.21, 64.79, 64.79, 64.76, 47.08, 46.94, 40.34, 40.29, 33.00, 32.36, 28.39, 28.02; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.14; HRMS calcd for $C_{32}H_{46}N_4OP$ $(M + H)^+$ required 533.3409, found 533.3427.

Leucine-Derived Cyclic Phosphonamide (3). In a procedure similar to that of compound **1**, compound **18** (10.5 mg, 30.7 μmol), CH_2Cl_2 (1 mL), Et_3N (20 μL, 0.14 mmol), dichlorophenylphosphine (54 μL, 39.9 μmol) and mCPBA (12 mg, 0.05 mmol) afforded a slurry that was subjected to flash chromatography (EtOAc) to yield 12.3 mg (86%) of a colorless oil: $[\alpha]^{25} = +108.3°$ ($c = 0.072$, $CHCl_3$); FTIR (neat) 1731, 1430, 1388, 1368, 1204 (P═O), 748, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, $J_{HP} = 12.1$ Hz, $J_{HH} = 6.8$ Hz, 2H), 7.55−7.50 (m, 1H), 7.47−7.43 (m, 2H), 5.75−5.64 (m, 2H), 4.18 (ddd, $J = 9.1$, 6.3, 6.3 Hz, 1H), 4.08 (ddd, $J_{HP} = 13.3$ Hz, $J_{HH} = 5.8$, 5.8 Hz, 1H), 4.02−3.81 (m, 3H), 3.76−3.70 (m, 1H), 3.68 (s, 3H), 3.46 (s, 3H), 1.78−1.66 (m, 2H), 1.65−1.57 (m, 2H), 1.55 (ddd, $J = 14.3$, 7.2, 7.2 Hz, 1H), 1.40 (ddd, $J = 13.9$, 6.3, 6.3 Hz, 1H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.73 (d, $J = 6.6$ Hz, 3H), 0.68 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.49, 173.16, 132.71 (d, $J_{CP} = 9.0$ Hz), 131.81, 131.78, 129.2 (d, $J_{CP} = 181.1$ Hz), 128.23 (d, $J_{CP} = 13.4$ Hz), 128.22, 56.43 (d, $J_{CP} = 7.0$ Hz), 55.80 (d, $J_{CP} = 6.0$ Hz), 51.88, 51.46, 41.37 (d, $J_{CP} = 2.8$ Hz), 40.53 (d, $J_{CP} = 2.8$ Hz), 39.47, 39.15 (d, $J_{CP} = 4.9$ Hz), 24.62, 24.42, 22.97, 22.61, 22.30, 21.96; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.56; HRMS calcd for $C_{24}H_{38}N_2O_5P$ $(M + H)^+$ required 465.2518, found 465.2521.

Leucine-Derived Methyl Phosphonamidic Chloridates (9P$_S$S, 9P$_R$S). A solution of methylphosphonic dichloride (1.0 mL, 11.04 mmol) and CH_2Cl_2 (20 mL) was cooled in a 0 °C ice bath. Et_3N (6.26 mL, 45.0 mmol) was added dropwise, followed by a catalytic amount of DMAP (5 mol %), and the reaction was stirred for 5 min. Allylated leucine methyl ester **8** (2.0 g, 10.82 mmol) in CH_2Cl_2 (5 mL) was added via cannulae, and the reaction mixture was refluxed and monitored by TLC. Once complete, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc, filtered, and concentrated under reduced pressure. Flash chromatography (3:1 hexanes/EtOAc) afforded 2.94 g (95%) of **9P$_S$S** and **9P$_R$S** as a light yellow oil. Further chromatography (8:1 hexanes/EtOAc) yielded portions of the separated diastereomers for characterization.

A single diastereomer (9P$_S$S or 9P$_R$S): $R_f = 0.39$ (1:1 hexanes/EtOAc); $[\alpha]^{25} = -42.3°$ ($c = 2.44$, $CHCl_3$);. FTIR (neat) 1742, 1445, 1368, 1240 (P═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (dddd, $J = 16.9$, 10.2, 6.5, 6.5 Hz, 1H), 5.22 (dd, $J = 17.2$, 1.2 Hz, 1H), 5.14 (d, $J = 10.1$ Hz, 1H), 4.40 (ddd, $J_{HP} = 12.1$ Hz, $J_{HH} = 7.5$, 7.5 Hz, 1H), 3.75−3.67 (m, 2H), 3.68 (s, 3H), 1.96 (d, $J_{HP} = 16.3$ Hz, 3H), 1.70 (dd, $J = 7.3$, 6.3 Hz, 2H), 1.65−1.52 (m, 1H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.90 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.37, 134.68 (d, $J_{CP} = 3.0$ Hz), 118.04, 55.87, 52.05, 47.16 (d, $J_{CP} = 4.5$ Hz), 38.49 (d, $J_{CP} = 5.7$ Hz), 24.52, 22.65 (d, $J_{CP} = 118.9$ Hz), 22.65, 21.53; ^{31}P NMR (162 MHz, $CDCl_3$) δ 48.02; HRMS calcd for $C_{11}H_{23}ClNO_3P$ $(M + H)^+$ required 282.1026, found 282.1049.

A single diastereomer (9P$_S$S or 9P$_R$S): $R_f = 0.38$ (1:1 hexanes/EtOAc); $[\alpha]^{25} = -13.1°$ ($c = 1.44$, $CHCl_3$); FTIR (neat) 1742, 1440, 1373, 1245 (P═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81−5.69 (m, 1H), 5.20−5.08 (m, 2H), 4.51 (ddd, $J_{HP} = 9.2$ Hz, $J_{HH} = 6.2$, 6.2 Hz, 1H), 3.76−3.66 (m, 2H), 3.62 (s, 3H), 1.98 (d, $J_{HP} = 16.0$ Hz, 3H), 1.73−1.64 (m, 2H), 1.64−1.51 (m, 1H), 0.89 (d, $J = 6.3$ Hz, 3H), 0.88 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.56 (d, $J_{CP} = 6.2$ Hz), 134.08 (d, $J_{CP} = 2.8$ Hz), 118.06, 55.35 (d, $J_{CP} = 2.0$ Hz), 51.97, 46.47 (d, $J_{CP} = 5.1$ Hz), 37.14 (d, $J_{CP} = 2.1$ Hz), 24.31, 22.80, 22.28 (d, $J_{CP} = 117.3$ Hz), 21.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.98; HRMS calcd for $C_{11}H_{23}ClNO_3P$ $(M + H)^+$ required 282.1026, found 282.1047.

Leucine-Derived Methyl Phosphonamidic Anhydrides (10a−c). To a neat mixture of diastereomeric leucine phosphonamidic chloridates **9P$_S$S** and **9P$_R$S** (260 mg, 0.92 mmol) cooled in a 0 °C ice bath was added Et_3N (450 μL, 3.22 mmol). The mixture was heated at 45 °C and monitored by TLC and ^{31}P NMR. The resulting salty slurry was diluted with EtOAc (10 mL), filtered (10 mL), and concentrated under reduced pressure to yield 236 mg (100%) of **10a−c** as a yellow oil. Further purification, to separate **10a** and **10b** sufficiently for characterization purposes, was accomplished by flash chromatography (1:1 Hexanes/EtOAc) and afforded 46 mg (20%) of the pseudo-meso diastereomer **10c**, and 132 mg (56%) of a mixture of C_2-symmetric diastereomers **10a** and **10b**. The mixture was comprised of 16 mg (7%) of a single C_2-symmetric diastereomer **10a** or **10b**, 104 mg (44%) of a mixture of C_2-symmetric diastereomers **10a** and **10b**, and 12 mg (5%) of a sample of C_2-symmetric diastereomer **10a** or **10b** at 90% purity, all as colorless oils.

Pseudo-*meso*-leucine-derived methyl phosphonamidic anhydride (**10c**): $R_f = 0.4$ (EtOAc); $[\alpha]^{25} = -17.1°$ ($c = 0.59$, $CHCl_3$); FTIR (neat) 1749, 1714, 1422, 1363, 1222 (P═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87−5.75 (m, 2H), 5.18 (dd, $J = 17.1$, 1.3 Hz, 1H), 5.14 (dd, $J = 17.1$, 1.3 Hz, 1H), 5.12−5.06 (m, 2H), 4.49 (ddd, $J_{HP} = 10.7$ Hz, $J_{HH} = 10.7$, 5.4 Hz, 1H), 4.34 (ddd, $J_{HP} = 9.2$ Hz, $J_{HH} = 9.2$, 5.3 Hz, 1H), 3.75−3.58 (m, 4H), 3.68 (s, 3H), 3.66 (s, 3H), 1.83−1.60 (m, 6H), 1.74 (d, $J_{HP} = 16.8$ Hz, 3H), 1.69 (d, $J_{HP} = 16.7$ Hz, 3H), 0.92 (d, $J = 6.2$ Hz, 6H), 0.91 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.67 (d, $J_{CP} = 2.2$ Hz), 173.20, 135.34, 135.34, 117.77, 117.48, 56.32 (d, $J_{CP} = 2.9$ Hz), 55.93 (d, $J_{CP} = 3.6$ Hz), 51.94, 51.90, 47.24 (d, $J_{CP} = 4.9$ Hz), 46.45 (d, $J_{CP} = 4.9$ Hz), 38.98 (d, $J_{CP} = 3.7$ Hz), 37.57 (d, $J_{CP} = 2.6$ Hz), 24.51, 24.19, 22.95, 22.87, 21.51, 21.33, 15.49 (dd, $J_{CP} = 129.5$, 4.3 Hz), 14.80 (dd, $J_{CP} = 127.7$, 4.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.19 (d, $J_{PP} = 35.5$ Hz), 28.41 (d, $J_{PP} = 35.5$ Hz); HRMS calcd for $C_{23}H_{43}N_2O_7P_2$ $(M + H)^+$ required 509.2546, found 509.2545.

***C$_2$*-symmetric leucine-derived methyl phosphonamidic anhydride, a single diastereomer (10a or 10b, top R_f):** $R_f = 0.22$ (EtOAc); $[\alpha]^{25} = -37.8°$ ($c = 0.32$, $CHCl_3$); FTIR (neat) 1740, 1437, 1387, 1241 (P═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, $J = 16.9$, 10.2, 6.2, 6.2 Hz, 2H), 5.21 (dd, $J = 15.9$, 1.2 Hz, 2H), 5.12 (dd, $J = 9.8$, 0.9 Hz, 2H), 4.49−4.42 (m, 2H), 3.79−3.57 (m, 4H), 3.67 (s, 6H), 1.81−1.59 (m, 6H), 1.75 (d, $J_{HP} = 17.0$ Hz, 6H), 0.94 (d, $J = 6.0$ Hz, 6H), 0.93 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.33,

135.59, 117.62, 56.11, 51.95, 46.95, 38.71, 24.57, 22.94, 21.31, 15.67 (dd, J_{CP} = 130.9, 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.88; HRMS calcd for $C_{23}H_{43}N_2O_7P_2$ $(M + H)^+$ required 509.2546, found 509.2526.

***C*$_2$-symmetric leucine-derived methyl phosphonamidic anhydride, a single diastereomer (10b or 10a, bottom *R*$_f$ at 90% purity):** R_f = 0.22 (EtOAc); $[\alpha]^{25} = -5.0°$ (c = 0.24, $CHCl_3$); FTIR (neat) 1740, 1437, 1387, 1241 (P=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, J = 16.8, 10.1, 6.6, 6.6 Hz, 2H), 5.17 (dd, J = 16.7, 1.3 Hz, 2H), 5.10 (dd, J = 9.1, 1.0 Hz, 2H), 4.52−4.42 (m, 2H), 3.66−3.54 (m, 4H), 3.68 (s, 6H), 1.80 (d, J_{HP} = 15.8 Hz, 6H), 1.78−1.53 (m, 6H), 0.94 (d, J = 6.0 Hz, 6H), 0.93 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.48, 135.13, 117.47, 55.65, 51.91, 46.35, 37.46, 24.34, 22.99, 21.21, 15.27 (dd, J_{CP} = 130.9, 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.14 HRMS calcd for $C_{23}H_{43}N_2O_7P_2$ $(M + H)^+$ required 509.2546, found 509.2561.

Valine-Derived Diamide (12). A solution of valine methyl ester **11** (3.80 g, 28.9 mmol), Et_3N (5.24 mL, 37.7 mmol), and DMF (30 mL) was cooled in a −10 °C (NaCl saturated) ice bath. Fumaryl dichloride (1.42 mL, 13.2 mmol) was added dropwise over a 1.5 h period. After addition was complete, the reaction was warmed to room temperature and stirred for 15 min. The resulting slurry was portioned between EtOAc (100 mL) and water (100 mL). The water layer was extracted twice with EtOAc (30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting white solid is dissolved in minimal hot CH_2Cl_2, and crystallized from hexanes to afford 4.43 g (98%) of the unsaturated diamide as white crystals: $[\alpha]^{25} = +8.3°$ (c = 0.47, $CHCl_3$); FTIR (neat) 1740, 1637, 1540, 1436, 1355 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 7.05 (d, J = 10.3 Hz, 2H), 4.69 (dd, J = 9.0, 5.3 Hz, 2H), 3.74 (s, 6H), 2.20 (m, 2H), 0.94 (d, J = 6.9 Hz, 6H), 0.91 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.44, 164.24, 133.25, 57.34, 52.26, 31.29, 18.92, 17.84; HRMS calcd for $C_{16}H_{27}N_2O_6$ $(M + H)^+$ required 343.1869, found 343.1840.

The diamide (970 mg, 3.8 mmol) was dissolved in CH_2Cl_2 (50 mL) in a 100 mL flask under argon atmosphere. 10% Pd/C (440 mg) was added to the solution and hydrogen gas was purged over the reaction mixture for 5 min. The solution was then stirred at room temperature under 1 atm of hydrogen gas for 30 min. Filtration over a pad of Celite and concentration yields 973 mg (99%) of **12** as white crystals: $[\alpha]^{25}$ +13.0° (c = 0.83; $CHCl_3$); FTIR (neat) 1748, 1641, 1436, 1374 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, J = 8.6 Hz, 2H), 4.50 (dd, J = 8.7, 5.1 Hz, 2H), 3.70 (s, 6H), 2.67−2.49 (m, 4H), 2.16−2.07 (m, 2H), 0.90 (d, J = 6.9 Hz, 6H), 0.87 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.42, 172.01, 57.16, 52.03, 31.46, 31.05, 18.89, 17.76; HRMS calcd for $C_{16}H_{29}N_2O_6$ $(M + H)^+$ required 345.2026, found 345.2042.

Valine-Derived Bis-Benzyl Ether (13). To a solution of compound **12** (1.21 g, 3.5 mmol) and THF (17 mL) was added $NaBH_4$ (669 mg, 17.6 mmol) at room temperature, and the reaction was equipped with a condenser and heated to 55 °C. MeOH was added dropwise over a 20 min period, and the reaction was monitored by TLC. The reaction was cooled to room temperature, and quenched slowly with a minimal amount of distilled water. The reaction slurry was subjected to flash chromatography (10% MeOH in EtOAc) to afford 954 mg (95%) of the diol as white crystals: $[\alpha]^{25} = -18.2°$ (c = 0.49, 1:1 CH_3CN/H_2O); FTIR (neat) 1635, 1543, 1457, 1418 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, J = 8.9 Hz, 2H), 3.99 (s, 2H), 3.76−3.67 (m, 4H), 3.50 (dd, J = 10.9, 7.8 Hz, 2H), 2.71 (d, J = 9.8 Hz, 2H), 2.49 (d, J = 9.9 Hz, 2H), 1.82−1.74 (m, 2H), 0.93 (d, J = 6.8 Hz, 6H), 0.91 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.63, 63.29, 57.06, 32.27, 29.30, 19.48, 18.79; HRMS calcd for $C_{14}H_{29}N_2O_4$ $(M + H)^+$ required 289.2127, found 289.2152.

A solution of the diol (20 mg, 0.07 mmol) in DMF (150 μL) was cooled in a 0 °C ice bath. NaH (8.4 mg, 0.22 mmol) was added, and the reaction was warmed to room temperature. After gas evolution was complete, the reaction was recooled in a 0 °C ice bath, and benzyl bromide (18.4 μL, 0.16 mmol) was added. The reaction was warmed to room temperature, and allowed to stir for 10 min. The slurry was partitioned between EtOAc (2 mL) and water (2 mL), the layers were separated, and the aqueous layer was reextracted with EtOAc (2 × 2 mL). The organic layers were combined, washed once with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (1:1 Hexanes/EtOAc, then 10% MeOH in EtOAc) afforded 31 mg (95%) of **13** as white crystals: $[\alpha]^{25} = -57.7°$ (c = 0.052, $CHCl_3$); FTIR (neat) 1629, 1540, 1465, 1437, 1387, 1357, 737, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 10H), 6.06 (d, J = 9.3 Hz, 2H), 4.50 (d, J = 12.0 Hz, 2H), 4.45 (d, J = 12.0 Hz, 2H), 3.87−3.82 (m, 2H), 3.55 (dd, J = 9.7, 4.0 Hz, 2H), 3.40 (dd, J = 9.7, 4.2 Hz, 2H), 2.59−2.42 (m, 4H), 1.95−1.86 (m, 2H), 0.90 (d, J = 7.0 Hz, 6H), 0.88 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.74, 138.14, 128.39, 127.61, 127.65, 73.16, 70.03, 54.11, 32.04, 29.26, 19.49, 18.85; HRMS calcd for $C_{28}H_{41}N_2O_4$ $(M + H)^+$ required 469.3066, found 469.3076.

Valine-Derived Diamine (14). LAH (316 mg, 8.3 mmol) was added to a solution of compound **13** (193 mg, 0.42 mmol) and dioxane (2 mL) at room temperature. The flask was equipped with a condenser and heated to reflux for 3 h. The reaction was cooled to room temperature and quenched over a 30 min period with water and Glauber's salt ($Na_2SO_4 \cdot 10H_2O$). The reaction mixture was stirred for an additional 30 min, and filtered over a pad of Celite (EtOAc). The solution was concentrated and subjected to flash chromatography (SiO_2, 10% MeOH in EtOAc) to afford 164 mg (91%) of **14** as a colorless oil: $[\alpha]^{25} = +5.8°$ (c = 1.36, $CHCl_3$); FTIR (neat) 1466, 1383, 1364, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 10H), 4.51 (s, 6H), 3.50 (dd, J = 9.4, 4.4 Hz, 2H), 3.77 (dd, J = 9.4, 6.8 Hz, 2H), 2.62−2.56 (m, 4H), 2.53 (dt, J = 6.6, 4.7 Hz, 2H), 1.54−1.47 (m, 4H), 1.23 (bs, 2H), 0.91 (d, J = 6.9 Hz, 6H), 0.89 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.45, 128.27, 127.54, 127.45, 73.14, 70.33, 62.62, 48.00, 28.86, 28.36, 18.91, 18.25; HRMS calcd for $C_{28}H_{45}N_2O_2$ $(M + H)^+$ required 441.3481, found 441.3504.

Phenylalanine-Derived Diamine (16). *N*,*N*-Dimethyl phenylalanine **15** (1.19 g, 6.2 mmol), Et_3N (1.29 mL, 9.3 mmol), and 1,4-diamino butane (303 μL, 3.0 mmol) were dissolved in CH_3CN (50 mL). HBTU was added, and the reaction was stirred at room temperature for 30 min and then concentrated under reduced pressure. The mixture was vacuum filtered (EtOAc), concentrated under reduced pressure, and subjected to flash chromatography (EtOAc, then 10% Et_3N in EtOAc) to afford 1.06 g (80%, nonoptimized) of the diamide as white crystals: $[\alpha]^{25} = -105.7°$ (c = 0.19, $CHCl_3$); FTIR (neat) 1649, 1455, 1384, 748, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.16 (m, 8H), 6.89 (t, J = 5.7 Hz, 2H), 6.40 (s, 1H), 5.90 (s, 1H), 3.13−3.04 (m, 6H), 3.12 (dd, J = 12.7, 5.3 Hz, 2H), 2.79 (dd, J = 13.4, 5.1 Hz, 2H), 2.23 (s, 12H), 1.24 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.68, 139.44, 128.88, 127.91, 125.69, 70.61, 41.91, 38.25, 32.84, 26.52; HRMS calcd for $C_{26}H_{39}N_4O_2$ $(M + H)^+$ required 439.3073, found 439.3074.

LAH (304 mg, 8.0 mmol) was added to a solution of the diol (433 mg, 0.99 mmol) and dioxane (5 mL) at room temperature. The flask was equipped with a condenser and heated to reflux for 3 h. The reaction was cooled to room temperature and quenched over a 30 min period with water and Glauber's salt ($Na_2SO_4 \cdot 10H_2O$). The reaction mixture was stirred for an additional 30 min, and filtered over a pad of Celite (CH_2Cl_2). The CH_2Cl_2 was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford 338 mg (83%, nonoptimized) of **16** as a colorless oil: $[\alpha]^{25} = +18.8°$ (c = 2.43, $CHCl_3$); FTIR (neat) 1495, 1454, 1373, 740, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 4H), 7.15−7.10 (m, 6H), 2.92−2.82 (m, 4H), 2.52−2.42 (m, 6H), 2.28 (s, 12H), 1.44−1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.02, 128.94, 128.23, 125.71, 64.84, 49.50, 49.46, 40.05, 31.40, 27.63; HRMS calcd for $C_{26}H_{43}N_4$ $(M + H)^+$ required 411.3488, found 411.3495.

Leucine-Derived Bicyclic Diamide (17). A solution of allylated leucine methyl ester **8** (308 mg, 1.67 mmol), DMAP (20 mg, 0.17 mmol), Et_3N (405 μL, 2.91 mmol) and CH_2Cl_2 (7 mL) was cooled in a 0 °C ice bath. Phthaloyl dichloride (120 μL, 0.83 mmol) was added dropwise, and the slurry was warmed to room temperature. After 30 min, the reaction was

partitioned between EtOAc (10 mL) and H_2O (10 mL), and the water layer was extracted twice with EtOAc (5 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc) afforded both a single spot (TLC) and a single peak (GC, 97%) of 398 mg (96%) of phthalic diamide as a mixture of rotamers: $[\alpha]^{25} = -64.8°$ ($c = 0.66$, $CHCl_3$); FTIR (neat) 1743, 1647, 1456, 1436, 1410, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 4H), 5.93−5.79 (m, 2H), 5.23−5.10 (m, 4H), 4.32 (bs, 2H), 3.97−3.87 (m, 2H), 3.78−3.68 (m, 8H), 2.11−1.60 (m, 6H), 0.96−0.70 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.97, 170.75, 136.44, 135.21, 129.07, 126.80, 117.83, 56.78, 52.10, 46.86, 38.74, 25.79, 23.18, 22.99; HRMS calcd for $C_{28}H_{41}N_2O_6$ $(M + H)^+$ required 501.2965, found 501.2971.

A solution the diamide (70 mg, 0.14 mmol) and CH_2Cl_2 (14 mL) was purged with argon gas for 5 min. The solution was brought to reflux and Grubbs catalyst (18 mg, 21.9 μmol) was added in three (6 mg) portions over a 24 h period. After 36 h the reaction was concentrated under reduced pressure and subjected to flash chromatography (1:1 Hexanes/EtOAc) to afford 64 mg (97%) of **17** as a colorless oil: $[\alpha]^{25} = -43.6°$ ($c = 0.51$, $CHCl_3$); FTIR (neat) 1741, 1650, 1430, 1412, 1367, 1331, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2H), 7.39−7.37 (m, 1H), 7.31−7.28 (m, 1H), 5.85 (s, 1H), 5.75 (s, 1H), 5.09 (s, 1H), 4.35 (s, 1H), 4.09−4.01 (m, 1H), 3.96 (dd, $J = 15.2$, 6.0 Hz, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 3.70−3.57 (m, 2H), 2.20−2.13 (m, 1H), 1.98−1.86 (m, 1H), 1.75−1.61 (m, 4H), 1.00−0.96 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 171.75, 169.93, 169.47, 134.62, 134.49, 131.59, 129.54, 129.42, 129.24, 127.44, 126.73, 56.92, 56.02, 52.18, 52.18, 45.66, 42.83, 39.27, 38.37, 25.36, 25.11, 22.76, 22.64, 22.30, 22.18; HRMS calcd for $C_{26}H_{37}N_2O_6$ $(M + H)^+$ required 473.2652, found 473.2646.

Leucine-Derived Diamine (18). In a sealable Pyrex test tube, compound **17** (100 mg, 0.21 mmol) was dissolved in HCl saturated MeOH (3 mL), capped, and heated in a 115° oil bath. After 72 h, the reaction was cooled to room temperature, then concentrated under reduced pressure. EtOAc (2 mL) was added and the reaction was cooled in a 0 °C ice bath. Et_3N (1 mL) was added, then the reaction was slowly warmed to room temperature and stirred for 1 h. The reaction was concentrated under reduced pressure and subjected to flash chromatography (1:1 Hexanes/EtOAc) to afford 24 mg (36%) of **18** as a colorless oil: $[\alpha]^{25} = +12.0°$ ($c = 0.05$, $CHCl_3$); FTIR (neat) 1737, 1468, 1433, 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, $J = 4.5$, 4.5 Hz, 2H), 3.72 (s, 6H), 3.29−3.21 (m, 4H), 3.09 (dd, $J = 13.2$, 4.8 Hz, 2H), 1.76−1.66 (m, 2H), 1.54 (bs, 2H), 1.47−1.43 (m, 4H), 0.92 (d, $J = 6.6$ Hz, 6H), 0.89 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.44, 130.17. 59.34, 51.60, 44.62, 42.85, 24.90, 22.66, 22.35; HRMS calcd for $C_{18}H_{35}N_2O_4$ $(M + H)^+$ required 343.2597, found 343.2619.

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Supporting Information Available: NMR spectra of obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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