Registry No. 1, 107736-03-8; 3, 135192-92-6; 4, 135192-93-7; 7, 135192-94-8; 8, 135192-95-9; 9, 135192-96-0; 10, 135192-97-1; 11, 135192-98-2; MCPBA, 937-14-4; DMD, 74087-85-7; ozone, 10028-15-6.

Supplementary Material Available: ^{1}H NMR spectra of 3, 4, 7–9, and 11 (6 pages). Ordering information is given on any current masthead page.

Di-*tert*-butyl *N*-Acylimidodicarbonates as Isolable Acylating Agents: Mild Conversion of Primary Carboxamides to Substituted Amides

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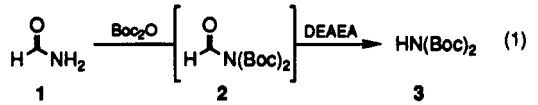
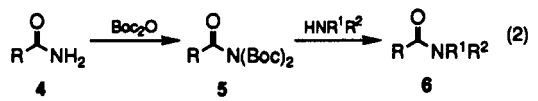
During the course of our work on the synthesis of platelet-activating factor antagonists, we required a mild, general means of converting primary amides to secondary and tertiary amides. This can be accomplished by hydrolysis of amides to acids followed by coupling with the requisite amine; however, this hydrolysis may be incompatible with acid- or base-sensitive functional groups.[1]

A possible solution was suggested by the pioneering work of Grehn and Ragnarsson, which described the exhaustive *tert*-butoxycarbonylation of amide nitrogens[2] and the cleavage of *N*-Boc-acylamides with hydrazine and 2-(diethylamino)ethylamine (DEAEA).[3,4] These workers also describe the synthesis of di-*tert*-butyl imidodicarbonate (3) by exhaustive *tert*-butoxycarbonylation of formamide followed by aminolysis of the unstable di-*tert*-butyl *N*-formylimidodicarbonate (2; eq 1).[5,6] We viewed com-

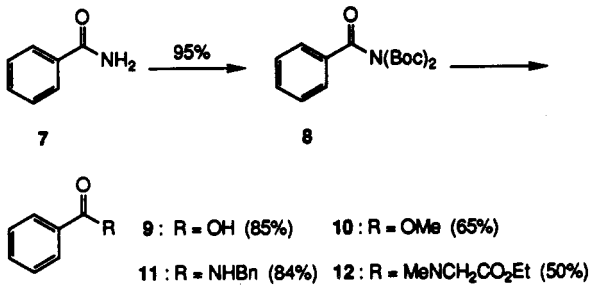




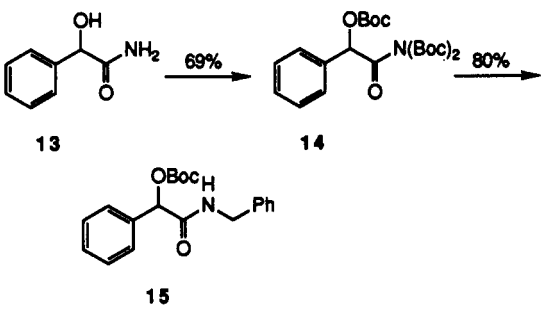
pounds such as 2 as acylating agents rather than a source of 3 and would now like to report that primary amides react with di-*tert*-butyl dicarbonate to give stable, isolable *N*-acylimidodicarbonates 5 (eq 2). These compounds are indeed active acylating agents and cleave selectively at the amide linkage upon reaction with alkoxides to give esters plus di-*tert*-butyl imidodicarbonate (3). This could have been anticipated since Grieco has shown that related *N*-Boc lactams and *N*-Boc secondary amides undergo selective cleavage upon exposure to hydroxide or alkoxides.[7] Imidodicarbonate 5 also bears some similarity to triamides, which Wasserman has shown react as activated carboxylates.[8] We now demonstrate that reaction of 5 with primary and some secondary amines gives the desired amide 6 in moderate to high yields. A series of examples are discussed below.

Treatment of benzamide with di-*tert*-butyl dicarbonate in the presence of DMAP gave a 95% yield of *N*-benzoylimidodicarbonate 8 after silica gel chromatography (Scheme I). This material could be stored indefinitely at room temperature without significant decomposition, as is the case for the other *N*-acylimidodicarbonates described herein (vide infra). Reaction of 8 with sodium hydroxide gave an 85% yield of benzoic acid (9) while methyl benzoate (10) was produced in 65% yield upon exposure to sodium methoxide. Treatment of 8 with benzylamine in methylene chloride at room temperature over 10 h gave an 84% yield of *N*-benzylbenzamide (11), which is on the same order of reactivity as other isolable acylating agents.[9]

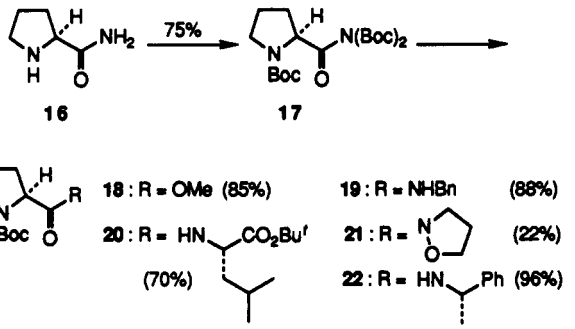
Scheme I



Scheme II



Scheme III



(1) For an overview of methods for amide hydrolysis, see: Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparation*; VCH: New York, 1989; p 988. Also see: Greenlee, W. J.; Thorsett, E. D. *J. Org. Chem.* **1981**, *46*, 5351.

(2) (a) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 510. (b) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand.* **1986**, *40*, 745. (c) Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand.* **1990**, *44*, 944.

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(4) For an example of an intramolecular amine cleavage of an *N*-carbomethoxy γ-lactam, see: Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kameyani, T. *J. Org. Chem.* **1986**, *51*, 3007.

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(6) For an analogous synthesis of benzyl *tert*-butyl imidodicarbonate, see: (a) Grehn, L.; Ragnarsson, U. *Collect. Czech. Chem. Commun.* **1988**, *53*, 2778. (b) Grehn, L.; Lurdes, S.; Ragnarsson, U. *Synthesis* **1988**, 992.

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(8) (a) Wasserman, H. H.; Gambale, J.; Pulwer, J. *Tetraherdron* **1981**, *37*, 4059. (b) Wasserman, H. H.; Lu, T.-J. *Tetrahedron Lett.* **1982**, *23*, 3831. (c) Wasserman, H. H.; Gambale, R. J. *Tetrahedron Lett.* **1981**, *22*, 4849.

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Mandelamide (13) was readily converted to imidodicarbonate 14, which reacted with benzylamine at room temperature over 3 h and gave an 80% yield of benzylamide 15 (Scheme II). It should be noted that α-hydroxy amides such as mandelamide are readily available from the corresponding cyanohydrin;[10] therefore, this route provides a synthesis of α-hydroxy amides from aldehydes under mild conditions.

Some limitations in the acylating capability of *N*-acylimidodicarbonates were encountered with secondary amines. Tertiary amide 12 was produced in only 50% yield after refluxing 8 with sarcosine ethyl ester in acetonitrile over 16 h. Reactions of 14 with sarcosine ethyl ester gave only starting material when conducted at room temperature and produced *N*-Boc-sarcosine ethyl ester at higher temperatures and in the presence of DMAP.

(*S*)-Prolinamide (16) was converted to *N*-acylimidodicarbonate 17 in 75% yield after flash chromatography on silica gel (Scheme III). This white solid was converted to *N*-Boc-(*S*)-proline methyl ester (18) in 85% yield by reaction with sodium methoxide. Reaction of 17 with benzylamine gave an 88% yield of proline amide 19, while dipeptide 20 was produced in 70% by stirring 17 with (*S*)-leucine *tert*-butyl ester at room temperature over 16 h. Heating 17 with isoxazolidine gave the isoxazolidide 21 described by Rapoport;[11] however, as with other secondary amines, the yield was low (22%). Preparation of amide 22 was determined to proceed with <3% racemization by HPLC comparison to amides derived from *N*-Boc-(*S*)- and *N*-Boc-(*R*)-proline.[12]

As a final example, *N*-Boc-(*S*)-asparagine methyl ester (23) may be converted to the stable tetra-Boc analogue 24, although this conversion is inferior to the cases described above.[13] Coupling of this material with benzylamine or (*S*)-phenylalanine methyl ester gave the anticipated product 25 and 26 in 85% and 57% yield, respectively. Reaction with sarcosine ethyl ester in hot acetonitrile gave the tertiary amide 27 in 54% yield. These examples suggest the possibility for selective functionalization of asparagine side chains along a peptide backbone. Efforts in this direction are currently underway.

Kubo and co-workers[14] have demonstrated the regioselective reduction of an *N'*-benzyl-*N*-Boc-2,5-piperazinedione as an intermediate in the synthesis of saframycin. Attempted reduction of imidodicarbonate 17 with diisobutylaluminum hydride or tri-*tert*-butoxyaluminum hydride produced only a meager (<10%) yield of a mixture of aldehyde and alcohol as determined by ^{1}H NMR analysis. Savoia[15] and Hagen[16] have independently reported the nucleophilic ring cleavage of *N*-Boc lactams with Grignard reagents. Addition of Grignards, organolithiums, and organocuprates to 17 have thus far given only complex mixtures, with no identifiable ketone products.

In summary, we have demonstrated that primary amides give isolable di-*tert*-butoxy *N*-acylimidodicarbonates upon reaction with di-*tert*-butyl dicarbonate. These compounds are stable at room temperature and react as acylating agents. Thus, esters and secondary amides are produced by reaction with alkoxides and primary amines, respectively. Secondary amines, however, are slower to react and give coupled products only in some cases. This technique allows for the mild, selective modification of asparagine side chains; applications to asparagine-containing peptides are being investigated.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Elemental analyses were performed by the Analytical Research Department at Abbott Laboratories, Abbott Park and North Chicago. Flash chromatography was carried out with use of E. Merck silica gel (230–400 mesh) as described by Still.[17]

Di-*tert*-butyl *N*-Benzoylimidodicarbonate (8). To a suspension of benzamide 7 (1.00 g, 8.26 mmol) in acetonitrile (20 mL) containing DMAP (100 mg, 0.83 mmol) at room temperature was added a solution of di-*tert*-butyl dicarbonate (3.78 g, 17.35 mmol) in acetonitrile (15 mL), which produced homogeneity and caused evolution of gas. After 2 h, the reaction mixture was concentrated and purified by flash chromatography (9:1 hexane/EtOAc), which gave 2.51 g (95%) of 8 as a thick oil: IR ($CHCl_3$) ν 2980, 1790, 1738, 1710, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 18 H), 7.48 (m, 2 H), 7.60 (m, 1 H), 7.83 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.4, 84.0 (C), 128.5, 130.0, 133.2, 134.1 (C), 149.6 (C), 169.1 (C); MS (CI/NH_3) 339, 322. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.52; H, 7.22; N, 4.36. Found: C, 63.22; H, 7.07; N, 4.17.

Benzoic Acid (9). To a solution of di-*tert*-butyl *N*-benzoylimidodicarbonate (0.50 g, 1.56 mmol) in THF (6 mL) at room temperature was added an aqueous solution of sodium hydroxide (3.43 mL of 0.5 M, 1.71 mmol), and the resulting mixture was stirred for 16 h then concentrated to an aqueous suspension, which was partitioned between water (30 mL) and EtOAc (30 mL). The aqueous phase was acidified to pH 3 with aqueous HCl (1 N) and then extracted with EtOAc (3 × 20 mL), the combined organic phase was dried ($MgSO_4$) and filtered, and solvents were removed, which gave 162 mg (85%) of 9 as a white solid. The spectral and analytical data for 9 were identical with authentic material.

Methyl Benzoate (10). To a solution of di-*tert*-butyl *N*-benzoylimidodicarbonate (8; 0.50 g, 1.56 mmol) in methanol (10 mL) at 0 °C was added a solution of sodium methoxide in methanol (0.39 mL of 4.37 M, 1.71 mmol), and the cooling bath was removed and the reaction stirred for 1 h then concentrated and partitioned between EtOAc (15 mL) and saturated aqueous NH_4Cl (15 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated, which gave a colorless gum that was purified by flash chromatography (98:2 hexane/EtOAc) and gave 138 mg (65%) of 10 as a colorless oil. The spectral and analytical data for 10 were identical with authentic material.

***N*-Benzylbenzamide (11).** To a solution of di-*tert*-butyl *N*-benzoylimidodicarbonate (8; 0.30 g, 0.93 mmol) in methylene chloride (3 mL) at room temperature was added benzylamine (122 μL, 1.12 mmol), and the reaction mixture was stirred for 16 h then diluted with methylene chloride (15 mL), washed with aqueous HCl (10 mL of 0.5 M) and brine (10 mL), and dried ($MgSO_4$). Filtration and removal of solvent gave a tan solid that was purified

(9) For other isolable acylating agents used for the preparation of amides, see: (a) Kovacs, J.; Kisfaludy, L.; Ceprini, M. Q.; Johnson, R. H. *Tetrahedron* **1969**, *25*, 2555. (b) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. *J. Am. Chem. Soc.* **1963**, *85*, 3039. (c) Koziolkiewicz, W.; Janecka, A. *Tetrahedron Lett.* **1989**, *30*, 4423. (d) Bertho, J.-N.; Loffet, A.; Pinel, C.; Reuther, F.; Sennyey, G. *Tetrahedron Lett.* **1991**, *32*, 1303.

(10) Jammot, J.; Pascal, R.; Commeyras, A. *Tetrahedron Lett.* **1989**, *30*, 563.

(11) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972.

(12) Isomers of 22 of known configuration were prepared from *N*-Boc-(*S*)- and *N*-Boc-(*R*)-proline by reaction with (*S*)-(−)-α-methylbenzylamine in the presence of bis(2-oxo-3-oxazolidinyl)phosphinic chloride. These compounds showed base-line separation (retension times of 26.5 and 28.1 min, respectively) when analyzed by reversed-phase HPLC (4.6 mm i.d. × 25 cm Rainin Microsorb C_{18} column, eluting with 65:35 v/v 20 mM aqueous potassium phosphate (pH 3.2)/CH_3CN at 1.0 mL per min with 254 nm UV detection). HPLC analysis of 22 derived from imidodicarbonate 17 indicated that it contained <3% of the *N*-Boc-(*R*)-proline-derived isomer.

(13) Attempted *tert*-butoxycarbonylation of 24 using the procedure described in ref 2a gave a mixture of *tris*- and *tetrakis*-Boc compounds; therefore, an alternative method was used: Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 5196.

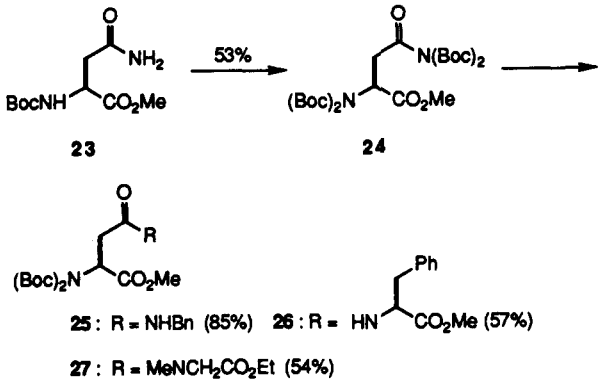
(14) Kubo, A.; Saito, N.; Nakamura, M. *Heterocycles* **1987**, *26*, 1765.

(15) (a) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228. (b) Savoia, D.; Concialini, V.; Roffia, S.; Tarsi, L. *J. Org. Chem.* **1991**, *56*, 1822.

(16) Hagen, T. J. *SynLett* **1990**, 63.

(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme IV



by flash chromatography on silica gel (3:1 hexane/EtOAc) and gave 166 mg (84%) of 11 as a white solid: mp 129–130 °C; IR ($CHCl_3$) ν 3445, 1655, 1515, 1485 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.65 (d, 2 H, J = 6.0), 6.42 (br s, 1 H), 7.25–7.56 (m, 8 H), 7.79 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.0 (CH_2), 127.1, 127.5, 127.6, 127.8, 128.5, 128.6, 134.3 (C), 138.1 (C), 167.3 (C); MS (CI/NH_3) 229, 212. Anal. Calcd for $C_{14}H_{13}NO \cdot 0.1H_2O$: C, 78.54; H, 6.17; N, 6.54. Found: C, 78.46; H, 6.29; N, 6.60.

***N*-Benzoylsarcosine Ethyl Ester (12).** To a solution of di-*tert*-butyl *N*-benzoylimidodicarbonate (8; 0.50 g, 1.56 mmol) in acetonitrile (4 mL) at room temperature was added sarcosine ethyl ester[18] (201 mg, 1.71 mmol), the reaction mixture was heated at reflux for 16 h then cooled and concentrated, and the residue was partitioned between methylene chloride (25 mL) and aqueous HCl (20 mL of 0.5 M). The organic phase was washed with brine (20 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a yellowish oil that was purified by flash chromatography on silica gel (4:1 hexane/EtOAc), which gave 172 mg (50%) of 12 as a colorless oil: IR ($CHCl_3$) ν 2980, 1745, 1635, 1210 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz; 130 °C) δ 1.24 (t, 3 H, J = 7.5), 3.00 (s, 3 H), 4.12 (s, 2 H), 4.16 (q, 2 H, J = 7.5), 7.34–7.52 (m, 5 H); ^{13}C NMR (DMSO-d_6, 75 MHz)[19] δ 13.9, 14.0, 33.9, 38.3, 48.8 (CH_2), 52.6 (CH_2), 60.5 (CH_2), 60.9 (CH_2), 126.2, 126.8, 128.3, 128.5, 129.5, 129.6, 135.6 (C), 168.9 (C), 170.7 (C); MS (CI/NH_3) 239, 222. Anal. Calcd for $C_{12}H_{15}NO_3 \cdot 0.1H_2O$: C, 64.60; H, 6.87; N, 6.28. Found: C, 64.40; H, 6.76; N, 6.20.

***O*,*N*,*N*-Tris(*tert*-butoxycarbonyl)mandelamide (14).** To a slurry of mandelamide (250 mg, 1.6 mmol) and DMAP (40 mg, 0.3 mmol) in acetonitrile (4 mL) at room temperature was added a solution of di-*tert*-butyl dicarbonate (1.19 g, 5.5 mmol) in acetonitrile (2 mL), which caused evolution of gas. This solution was stirred for 4 h then concentrated and purified by flash chromatography (9:1 hexane/EtOAc), which gave 518 mg (69%) of 14 as a slightly yellow oil: IR ($CHCl_3$) ν 2980, 1780, 1750, 1250, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 18 H), 1.50 (s, 9 H), 6.82 (s, 1 H), 7.35 (m, 3 H), 7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.4, 27.6, 76.8, 83.1 (C), 85.0 (C), 128.5, 129.1, 129.3, 132.8 (C), 148.7 (C), 152.5 (C), 169.5 (C); MS (CI/NH_3) 469, 179. Anal. Calcd for $C_{23}H_{33}NO_8$: C, 61.18; H, 7.37; N, 3.10. Found: C, 61.12; H, 7.36; N, 3.10.

***O*-(*tert*-Butoxycarbonyl)-*N*-benzylmandelamide (15).** To a solution of 14 (337 mg, 0.75 mmol) in methylene chloride (4 mL) at room temperature was added benzylamine (98 μL, 0.90 mmol), the reaction mixture was stirred for 3 h then concentrated, and the resulting white solid was collected by suction filtration and washed with hexane, which gave 204 mg (80%) of 15 as a white solid: mp 130–131 °C; IR ($CHCl_3$) ν 1759, 1680, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9 H), 4.45 (dd, 1 H, J = 6.0, 15.0), 4.53 (dd, 1 H, J = 6.0, 15.0), 5.96 (s, 1 H), 6.62 (br s, 1 H), 7.22–7.40 (m, 8 H), 7.46 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.6, 43.2 (CH_2), 77.9, 83.6 (C), 127.0, 127.5, 127.7, 128.7, 128.8, 135.5 (C), 137.7 (C), 151.6 (C), 168.2 (C); MS (CI/NH_3) 359, 285. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.41; H, 6.84; N, 4.05.

***N*$^{\alpha}$,*N*,*N*-Tris(*tert*-butoxycarbonyl)-(*S*)-prolinamide (17).** To a solution (*S*)-prolinamide[18] (1.14 g, 10 mmol) and DMAP (122 mg, 1 mmol) in acetonitrile (30 mL) at room temperature was added a solution of di-*tert*-butyl dicarbonate (6.76 g, 31 mmol) in acetonitrile (10 mL), which caused gas evolution. This solution was stirred for 1 h then concentrated and purified by flash chromatography (4:1 hexane/EtOAc), which gave 3.12 g (75%) of 17 as a white solid: mp 112–113 °C; $[\alpha]_D$ −49.9° (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) ν 2980, 1775, 1750, 1695, 1120 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz)[19] δ 1.32 (s, 7 H), 1.39 (s, 2 H), 1.48 (s, 18 H), 1.76–1.90 (m, 3 H), 2.26 (m, 1 H), 3.28–3.39 (m, 2 H), 4.98 (dd, 1 H, J = 3.0, 9.0); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.8 (CH_2), 23.2 (CH_2), 27.1, 27.6, 28.0, 29.2 (CH_2), 30.0, 46.2 (CH_2), 46.3 (CH_2), 59.0, 59.6, 78.9 (C), 85.0 (C), 148.7 (C), 152.5 (C), 153.3 (C), 173.9 (C); MS (CI/NH_3) 432, 415, 215. Anal. Calcd for $C_{20}H_{34}N_2O_7$: C, 57.95; H, 8.27; N, 6.76. Found: C, 57.88; H, 8.21; N, 6.69.

***N*-(*tert*-Butoxycarbonyl)-(*S*)-proline Methyl Ester (18).** To a solution of imidodicarbonate 17 (0.50 g, 1.21 mmol) in methanol (12 mL) at 0 °C was added a solution of sodium methoxide in methanol (0.30 mL of 4.37 M, 1.33 mmol) and the cooling bath was removed and the solution stirred at room temperature over 1 h then concentrated and partitioned between EtOAc (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated, and the resulting slightly yellow oil was purified by flash chromatography (methylene chloride), which gave 236 mg (85%) of 18 as a colorless oil: $[\alpha]_D$ −48.9° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz)[19] δ 1.41 (s, 6 H), 1.46 (s, 3 H), 1.81–2.03 (m, 3 H), 2.21 (m, 1 H), 3.35–3.59 (m, 2 H), 4.21 (dd, 0.66 H, J = 4.5, 8.5), 4.32 (dd, 0.33 H, J = 4.0, 9.0); MS (CI/NH_3) 230. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.50; H, 8.19; N, 6.00.

***N*$^{\alpha}$-(*tert*-Butoxycarbonyl)-*N*-benzyl-(*S*)-prolinamide (19).** To a solution of imidodicarbonate 17 (0.50 g, 1.21 mmol) in methylene chloride (2 mL) at room temperature was added benzylamine 17 (0.50 g, 1.21 mmol) in methylene chloride (2 mL) at room temperature was added benzylamine (158 μL, 1.45 mmol), and the resulting solution was stirred at room temperature for 16 h then concentrated and the residue partitioned between methylene chloride (20 mL) and aqueous HCl (15 mL of 0.5 M). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and filtered. Removal of solvent gave a tan solid, which was purified by flash chromatography (1:1 hexane/EtOAc) and gave 322 mg (88%) as a white solid: mp 130–131 °C; $[\alpha]_D$ −80.2° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) ν 2980, 1675, 1520, 1445, 1390, 1160 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz)[19] δ 1.29 (s, 5.5 H), 1.42 (s, 4.5 H), 1.72–1.87 (m, 3 H), 2.11 (m, 1 H), 3.29 (m, 1 H), 3.40 (m, 1 H), 4.05–4.25 (m, 2 H), 4.33 (dd, 1 H, J = 7.0, 15.0) 7.18–7.35 (m, 5 H), 8.28–8.41 (m, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.1 (CH_2), 24.0, (CH_2), 27.9, 28.1, 30.0 (CH_2), 31.0 (CH_2), 41.8 (CH_2), 42.0 (CH_2), 46.4 (CH_2), 46.6 (CH_2), 59.7, 59.8, 78.4 (C), 78.5 (C), 126.5, 126.7, 126.8, 127.2, 128.1, 139.6 (C), 153.3 (C), 153.5 (C), 172.2 (C), 172.4 (C); MS (CI/NH3) 305. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.06; H, 7.95; N, 9.20. Found: C, 66.87; H, 7.88; N, 9.17.

***N*-(*tert*-Butoxycarbonyl)-(*S*)-prolyl-(*S*)-leucine *tert*-Butyl Ester (20).** To a solution of imidodicarbonate 17 (0.50 g, 1.21 mmol) in methylene chloride (1 mL) at room temperature was added a solution of (*S*)-leucine *tert*-butyl ester[18] (249 mg, 1.33 mmol) in methylene chloride (1 mL), the reaction stirred at room temperature over 16 h then concentrated, and the residue partitioned between methylene chloride (20 mL) and aqueous HCl (15 mL of 0.5 M). The organic phase was washed with brine (15 mL), dried ($MgSO_4$), and filtered. Removal of solvent gave a yellowish solid that was purified by flash chromatography (3:1 hexane/EtOAc) and gave 326 mg (70%) of 20 as a white solid: mp 111–112 °C $[\alpha]_D$ −72.0° (*c* 4.5, MeOH); IR ($CHCl_3$) ν 2980, 1725, 1695, 1390, 1155 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz)[19] δ

(18) Prepared by addition of triethylamine to a methylene chloride suspension of the commerically available hydrochloride salt. This mixture was stirred until homogeneous then concentrated, and the resulting solid was slurried in anhydrous THF and filtered. Concentration of the filtrate gave the free base as either a liquid or viscous oil.

(19) Doubling of signals in ^1H and ^{13}C NMRs presumably due to restricted rotation, see: Voelter, W.; Fuchs, S.; Seuffer, R. H.; Zech, K. *Monatsch. Chem.* **1974**, *105*, 1110. Compounds 12 and 17 decomposed upon extended heating at 130 °C in DMSO-d_6. Signals for compound 21 did not collase upon heating 130 °C in DMSO-d_6. Variable-temperature NMR experiments were not performed on compounds 18–20 and 27.

0.85 (d, 2.5 H, J = 6.0), 0.90 (d, 3.5 H, J = 6.0), 1.31 (s, 8 H), 1.39 (s, 10 H), 1.40–1.85 (m, 6 H), 2.11 (m, 1 H), 3.22 (m, 1 H), 3.36 (m, 1 H), 4.07–4.17 (m, 2 H), 8.06 (m, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.0, 21.4, 22.7, 23.7, 24.1, 27.5, 27.7, 28.0, 29.6 (CH_2), 30.9 (CH_2), 40.0 (CH_2), 46.4 (CH_2), 50.8, 51.0, 58.9, 59.1, 78.2 (C), 78.3 (C), 80.2 (C), 153.2 (C), 171.6 (C), 171.9 (C), 172.4 (C); MS (CI/NH_3) 385. Anal. Calcd for $C_{20}H_{36}N_2O_4 \cdot 0.25H_2O$: C, 61.73; H, 9.46; N, 7.20. Found: C, 61.74; H, 9.24; N, 7.14.

N-(*tert*-Butoxycarbonyl)-(*S*)-proline Isoxazolidide (21). To a solution of imidodicarbonate **17** (0.50 g, 1.21 mmol) in methylene chloride (1 mL) at room temperature was added a solution of isoxazolidine[18] (115 mg, 1.57 mmol) in methylene chloride (1 mL), and the reaction mixture was refluxed over 16 h then cooled to room temperature, concentrated, and partitioned between methylene chloride (20 mL) and water (20 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting yellowish oil was purified by flash chromatography (4:1 hexane/EtOAc), which gave 72 mg (22%) of **21** as a colorless oil: $[\alpha]_D$ −26.4° (c 2.0, $CHCl_3$); IR ($CHCl_3$) ν 2980, 1680, 1400, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz)[19] δ 1.41 (s, 4 H), 1.45 (s, 5 H), 1.79–2.05 (m, 3 H), 2.11–2.40 (m, 3 H), 3.32–3.65 (m, 3 H), 3.79–4.06 (m, 3 H), 4.63 (dd, 0.45 H, J = 4.0, 9.0), 4.77 (dd, 0.55 H, J = 9.0); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4 (CH_2), 24.2 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 28.3, 28.5, 30.1, (CH_2), 30.9 (CH_2), 43.4 (CH_2), 46.5 (CH_2), 46.8 (CH_2), 56.8, 57.4, 69.3 (CH_2), 69.4 (CH_2), 79.2 (C), 79.3 (C), 153.9 (C), 154.4 (C), 172.6 (C), 173.0 (C); MS (CI/NH_3) 271. Anal. Calcd for $C_{13}H_{22}N_2O_4$: C, 57.76; H, 8.20; N, 10.36. Found: C, 57.74; H, 8.20; N, 10.36.

N^{α}-(*tert*-Butoxycarbonyl)-N-((*S*)-methylbenzyl)-(*S*)-prolinamide (22). To a solution of imidodicarbonate **17** (0.50 g, 1.21 mmol) in methylene chloride (2 mL) at room temperature was added (*S*)-(−)-α-methylbenzylamine (171 μL, 1.33 mmol), and the resulting solution was stirred at room temperature for 1 h then concentrated and partitioned between methylene chloride (20 mL) and aqueous HCl (15 mL of 0.5 M). The organic phase was washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated, and the resulting solid was purified by flash chromatography (2:1 hexane/EtOAc), which gave 369 mg (96%) of **22** as a white solid: mp 105–106 °C; $[\alpha]_D$ −109.8° (c 1.3, $CHCl_3$); IR ($CHCl_3$) ν 2980, 1670, 1365, 1160 cm^{-1}, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.31–1.41 (m, 12 H), 1.65–1.81 (m, 3 H), 2.11 (m, 1 H), 3.21–3.50 (m, 2 H), 4.09 (m, 1 H), 4.92 (m, 1 H), 7.16–7.43 (m, 5 H), 8.23 (m, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.2, 23.0 (CH_2), 28.0, 31.0 (CH_2), 46.5 (CH_2), 47.4, 59.6, 78.3 (C), 125.8, 126.5, 128.1, 144.5 (C), 153.3 (C), 171.5 (C); MS (CI/NH_3) 319, 219. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.66; H, 8.00; N, 8.73.

N^{α},N^{α},N,N-Tetrakis(*tert*-butoxycarbonyl)-(*S*)-asparagine Methyl Ester (24). To a solution of N^{α}-(*tert*-butoxycarbonyl)-(*S*)-asparagine methyl ester **23**[20] (400 mg, 1.63 mmol) in 1,2-dichloroethane (8 mL) at room temperature was added DMAP (100 mg, 0.82 mmol) and triethylamine (1.81 mL, 13.01 mmol) followed by di-*tert*-butyl dicarbonate (1.42 g, 6.50 mmol), which caused evolution of gas. This yellow solution was then heated at 75 °C over 0.75 h, then cooled to room temperature and more di-*tert*-butyl dicarbonate (1.42 g, 13.00 mmol overall) added, then heating continued at 75 °C over an additional 0.75 h. The reaction mixture was then cooled to room temperature, concentrated, and purified by flash chromatography (9:1 hexane/EtOAc), which gave 235 mg (53%) of **24** as a yellowish oil: $[\alpha]_D$ −36.8° (c 2.4, $CHCl_3$); IR ($CHCl_3$) ν 2980, 1780, 1750, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 18 H), 1.52 (s, 18 H), 3.14 (dd, 1 H, J = 6.0, 18.0), 3.72 (s, 3 H), 3.86 (dd, 1 H, J = 7.5, 18.0), 5.59 (dd, 1 H, J = 6.0, 7.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.6, 27.9, 38.4 (CH_2), 52.4, 54.2, 83.3 (C), 84.7 (C), 149.3 (C), 151.4 (C), 170.2 (C), 171.0 (C); MS (FAB) 547, 235. Anal. Calcd for $C_{25}H_{45}N_2O_{11} \cdot 0.5H_2O$: C, 54.04; H, 7.80; N, 5.04. Found: C, 53.97; H, 7.64; N, 4.96.

N^{α},N^{α}-Bis(*tert*-butoxycarbonyl)-N-benzyl-(*S*)-asparagine Methyl Ester (25). To a solution of imidodicarbonate **24** (382 mg, 0.70 mmol) in methylene chloride (4 mL) at room temperature was added benzylamine (92 μL, 0.84 mmol), and this solution was stirred for 3 h then concentrated and the residue partitioned between methylene chloride (10 mL) and aqueous HCl (8 mL of 0.5 M). The organic phase was washed with brine (8 mL), dried ($MgSO_4$), and filtered. Removal of solvent gave a yellowish solid that was purified by flash chromatography (7:3 hexane/EtOAc) and gave 260 mg (85%) of **25** as a white solid: mp 126–127 °C; $[\alpha]_D$ −54.1° (c 1.1, $CHCl_3$); IR ($CHCl_3$) ν 2980, 1745, 1695, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 18 H), 2.66 (dd, 1 H, J = 7.0, 18.0), 3.12 (dd, 1 H, J = 7.5, 18.0), 3.71 (s, 3 H), 4.42 (dd, 1 H, J = 5.5, 15.0), 4.49 (dd, 1 H, J = 5.5, 15.0), 5.51 (dd, 1 H, J = 7.0, 7.5), 5.95 (br s, 1 H), 7.27–7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9, 38.1 (CH_2), 43.6 (CH_2), 52.4, 55.3, 83.4 (C), 127.4, 127.7, 128.6, 138.2, 151.8 (C), 169.3 (C), 170.7 (C); MS (CI/NH_3) 437, 337. Anal. Calcd for $C_{22}H_{32}N_2O_7$: C, 60.54; H, 7.39; N, 6.42. Found: C, 60.78; H, 7.33; N, 6.42.

N^{α},N^{α}-Bis(*tert*-butoxycarbonyl)-(*S*)-β-aspartyl-(*S*)-phenylalanine Dimethyl Ester (26). To a solution of imidodicarbonate **24** (430 mg, 0.79 mmol) in methylene chloride (8 mL) at room temperature was added (*S*)-phenylalanine methyl ester hydrochloride (338 mg, 1.57 mmol) and triethylamine (0.22 mL, 1.57 mmol) followed by DMAP (19 mg, 0.16 mmol), and the slightly cloudy reaction mixture was heated at reflux over 16 h then cooled to room temperature and concentrated. The resulting residue was partitioned between EtOAc (15 mL) and aqueous HCl (10 mL of 0.5 M), and the organic phase was washed with brine (15 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave an orange oil that was purified by flash chromatography (7:3 hexane/EtOAc) and gave 228 mg (57%) of **26** as a colorless oil: $[\alpha]_D$ +8.89° (c 2.6, $CHCl_3$); IR ($CHCl_3$) ν 1790, 1745, 1695, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 18 H), 2.62 (dd, 1 H, J = 7.0, 15.5), 3.12 (dd, 1 H, J = 7.5, 15.5), 3.13 (d, 2 H, J = 6.0), 3.71 (s, 3 H), 3.72 (s, 3 H), 4.87 (dt, 1 H, J = 6.0, 7.0), 5.49 (t, 1 H, J = 7.0), 6.12 (br s, 1 H), 7.08 (m, 2 H), 7.24–7.32 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9, 37.7 (CH_2), 37.9 (CH_2) 52.2, 52.4, 53.3, 55.2, 83.3 (C), 127.0, 128.5, 129.2, 135.8 (C), 151.8 (C); MS (CI/NH_3) 509, 409. Anal. Calcd for $C_{25}H_{36}N_2O_9$: C, 59.04; H, 7.13; N, 5.51. Found: C, 59.38; H, 7.18; N, 5.84.

N^{α},N^{α}-Bis(*tert*-butoxycarbonyl)-(*S*)-β-aspartylsarcosine 1-Ethyl Methyl Diester (27). To a solution of imidodicarbonate **24** (254 mg, 0.46 mmol) and sarcosine ethyl ester hydrochloride (107 mg, 0.70 mmol) in acetonitrile (3 mL) at room temperature was added triethylamine (97 μL, 0.70 mmol) and DMAP (12 mg, 0.09 mmol), and the resulting mixture was heated at 75 °C over 10 h then cooled to room temperature and concentrated. The resulting residue was partitioned between EtOAc (10 mL) and aqueous HCl (7 mL of 0.5 M), and the organic phase was washed with brine (10 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a yellowish oil that was purified by flash chromatography and gave 112 mg (54%) of **27** as a colorless oil: $[\alpha]_D$ −61.1° (c 1.0, $CHCl_3$); IR ($CHCl_3$) ν 1790, 1745, 1695, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz)[19] δ 1.25 (t, 0.25 H, J = 6.0), 1.26 (t, 0.75 H, J = 6.0), 1.51 (s, 18 H), 2.57 (dd, 0.25 H, J = 6.0, 15.0), 2.69 (dd, 0.75 H, J = 6.0, 15.0), 2.99 (s, 0.75 H), 3.11 (s, 2.25 H), 3.24 (dd, 0.25 H, J = 7.5, 15.0), 3.42 (dd, 0.75 H, J = 7.5, 15.0), 3.70 (s, 0.75 H), 3.71 (s, 2.25 H), 3.98 (d, 0.25 H, J = 17.0), 4.04 (d, 0.75 H, J = 17.0), 4.12 (q, 0.25 H, J = 6.0), 4.18 (q, 0.75 H, J = 6.0), 4.20 (d, 0.25 H, J = 17.0), 4.22 (d, 0.75 H, J = 17.0), 5.61 (dd, 0.75 H, J = 6.0, 7.5), 5.62 (dd, 0.25 H, J = 6.0, 7.5); ^{13}C NMR ($CDCl_3$, 75 MHz) major δ 14.1, 28.0, 34.5 (CH_2), 36.3, 49.4 (CH_2), 52.4, 55.4, 61.1 (CH_2), 83.2 (C), 151.8 (C), 169.2 (C), 170.4 (C), 170.8 (C); MS (CI/NH_3) 447, 347. Anal. Calcd for $C_{20}H_{34}N_2O_9 \cdot 0.25H_2O$: C, 53.26; H, 7.71; N, 6.21. Found: C, 53.26; H, 7.49; N, 6.13.

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Registry No. **7**, 55-21-0; **8**, 135364-97-5; **9**, 65-85-0; **10**, 93-58-3; **11**, 1485-70-7; **12**, 100390-89-4; **13**, 4410-31-5; **14**, 135339-63-8; **15**, 135339-64-9; **16**, 7531-52-4; **17**, 135339-65-0; **18**, 59936-29-7; **19**, 92235-33-1; **20**, 82361-29-3; **21**, 135339-66-1; **22**, 135339-67-2; **23**, 124842-28-0; **24**, 135339-68-3; **25**, 135339-69-4; **26**, 135339-70-7; **27**, 135339-71-8; $PhCH_2NH_2$, 100-46-9; Sar-OEt, 13200-60-7; Leu-OBu-*t*, 21691-53-2; (*S*)-(−)-PhCH(Me)NH_2, 2627-86-3; Phe-OMe·HCl, 7524-50-7; isoxazolidine, 504-72-3.

(20) Prepared by addition of excess ethereal diazomethane to a methanolic solution of commercially available N^{α}-Boc-(*S*)-asparagine followed by trituration of the resulting solid with ether.