Synthesis of Optically Active Phthaloyl D-Aminooxy Acids from L-Amino Acids or L-Hydroxy Acids as Building Blocks for the Preparation of Aminooxy Peptides

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For over a decade, many bioorganic and synthetic chemists have made attempts to prepare structurally well-defined and/or biologically active peptidomimetics with novel backbone structures for the creation of new secondary and tertiary structures, as well as for application as agonists, antagonists, and enzyme inhibitors for important pharmaceutical receptors and enzymes.[1] A number of backbone-modified peptides (pseudopeptides) such as oligocarbamates,[2] peptoids,[3] oligoureas,[4] oligosulfonamides,[5] oligopyrrolinones,[6] β-peptides,[7] and flat peptides[8] have been synthesized and characterized for their novel structures and/or biological functions.[9] Recently, structural[10] and theoretical studies[11] of peptides formed by α-aminooxy acids have been reported as a new type of peptidomimetic. It was shown that even short α-aminooxy peptides could adopt a novel secondary structure, namely, eight-membered, hydrogen-bonded turns or N−O turns.[10,11] To provide access to α-aminooxy peptides with more structural diversity and potentially useful biological properties, we have synthesized several optically active phthaloyl aminooxy acids with nonpolar and polar side chains as building blocks for the preparation of diverse α-aminooxy peptides from α-amino acids and α-hydroxy acids.[10b,12] Several methods for the preparation of phthaloyl α-aminooxy acids or esters, including displacement of an α-halo ester or acid with *N*-hydroxyphthalimide (PhthN-OH),[13] the reaction of an α-diazo ester with PhthN-OH,[14] and the Mitsunobu reaction of α-hydroxy ester with PhthN-OH,[15] have been reported. Among the known methods, the Mitsunobu reaction was employed because of the stereospecific conversion of easily prepared α-hydroxy esters to the desired phthaloyl α-aminooxy esters with the inversion of configuration.[15]

Initially, phthaloly D-aminooxy acids (**4**) containing unprotected side chains were effectively prepared in three steps from the corresponding L-hydroxy acids (**1**), which were obtained from commercial suppliers or synthesized by treatment of L-amino acids with $NaNO_2$ in 2.5 N H_2SO_4 or 20% HOAc (Scheme 1).[16] Benzylation of cesium

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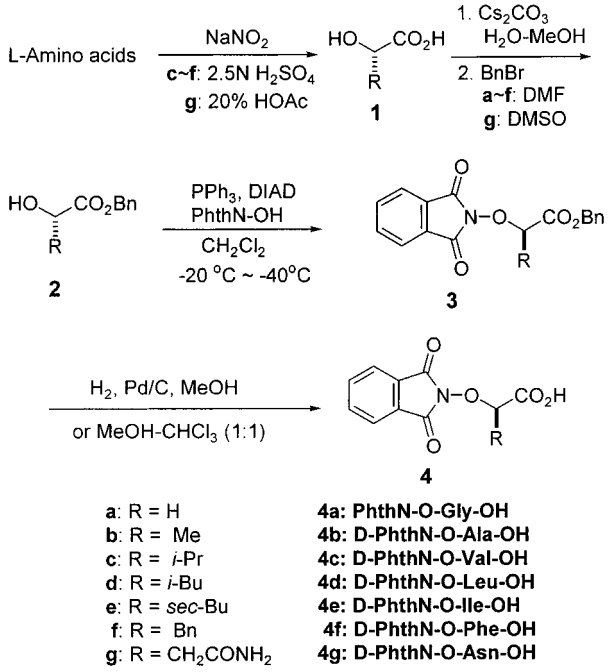
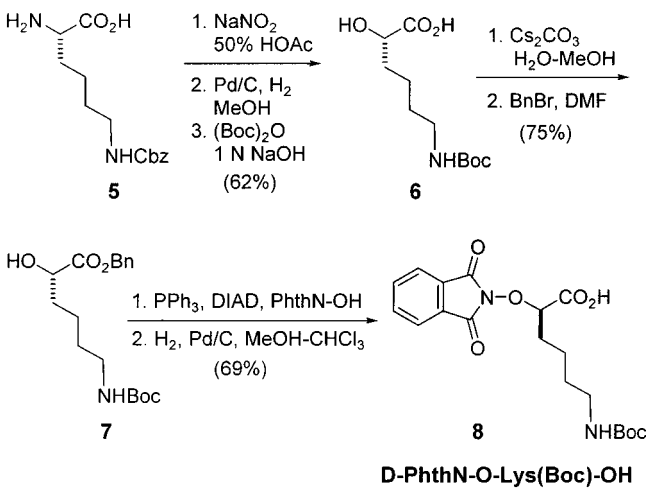
Scheme 1



salts of **1** with benzyl bromide in DMF or DMSO produced benzyl esters **2**.[17] Subsequent conversion of L-hydroxyl groups to phthaloyl D-aminooxy functionalities was performed under Mitsunobu conditions using PhthN-OH, diisopropyl azodicarboxylate (DIAD), and PPh_3 at −20 to −40 °C.[15] Reaction of **2** (except **2c**) with 1.2−1.4 molar equiv each of PPh_3, DIAD, and PhthN-OH proceeded smoothly to afford the corresponding product **3** in high yield. More than 2 equiv each of PPh_3 (2.3 equiv), DIAD (2.3 equiv), and PhthN-OH (2.1 equiv) were necessary in the case of **2c** to give high yield and fast reaction.[18] Products **3a**, **3b**, and **3f** obtained from the Mitsunobu reaction were hardly separated from dihydro-DIAD by flash column chromatography. However, a contaminated dihydro-DIAD was removed by washing with MeOH (**3a**) or precipitation with amines after the next reaction (**3b** and **3f**). Finally, the benzyl group of **3** was removed by hydrogenolysis to furnish **4** in a phthaloyl protected form. It is worthwhile to mention that prolonged hydrogenolysis of benzyl ester **3** resulted in a poor yield of **4** as a result of the cleavage of the N−O bond. Compound **4** was isolated either by flash column chromatography (**4a**), precipitation with cyclohexylamine (**4b**−**e**) or dicyclohexylamine (**4f**)[20] and then acidification of salts with 0.1 N HCl (pH 2), or recrystallization (**4g**).[21]

D-PhthN-*O*-Lys(Boc)-OH (**8**), a lysine analogue, was prepared from commercially available L-NH_2-Lys(Cbz)-OH (**5**) (Scheme 2). Transformation of α-NH_2 in **5** to α-OH

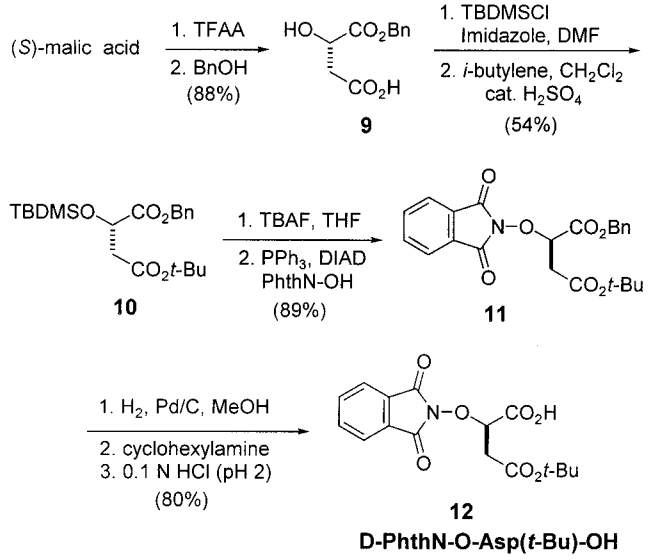
Scheme 2



with $NaNO_2$ in 50% HOAc, followed by removal of a Cbz group and then reprotection of the exposed amine as a Boc group, provided **6** in 62% overall yield. Subsequent steps are analogous to those shown in Scheme 1.

Benzyl (*S*)-malate (**9**) derived from (*S*)-malic acid according to a modified procedure of Miller et al.[22] was used to synthesize D-PhthN-*O*-Asp(*t*-Bu)-OH (**12**) as an aspartic acid analogue (Scheme 3). The hydroxyl group

Scheme 3



and the side chain acid in **9** were sequentially protected as a TBDMS and a *t*-Bu group, respectively, to give **10**. Selective deprotection of a silyl group in **10** with tetrabutylammonium fluoride (TBAF) followed by Mitsunobu reaction with PPh_3 (2.7 equiv), DIAD (2.7 equiv), and PhthN-OH (2.3 equiv) afforded **11** in 89% yield. Removal

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(18) The optical purity of phthaloyl D-aminooxy esters **3c** and **21** was determined by ^{1}H NMR spectra of MTPA amides[19] prepared from the reaction of MTPA-Cl with the corresponding D-aminooxy ester that was produced by the removal of a phthaloyl protecting group by NH_2-NH_2·H_2O (2 equiv for **3c**, 4 equiv for **21**) in MeOH for 15 min at room temperature. It was found that only less than 1% of epimer for both compounds (>98% ee) was present, suggesting that the diazotization of amino acid, the Mitsunobu reaction, and deprotection of a phthaloyl group were highly stereospecific.[15]

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(21) Flash column chromatography of crude **4b**−**g** afforded pure products in very low yield as a result of decomposition of products during chromatography and thus should be avoided.

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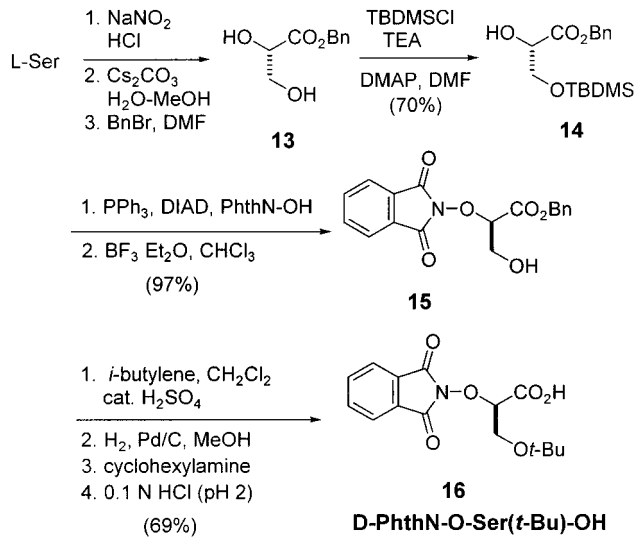
of a benzyl group in **11** and purification by precipitation with cyclohexylamine completed the synthesis of **12**.

Synthesis of D-PhthN-*O*-Ser(*t*-Bu)-OH (**16**) as a serine analogue was initiated by benzylation of the known L-glyceric acid to give **13** in 17% overall yield from L-serine (Scheme 4).[23] Selective protection of a primary

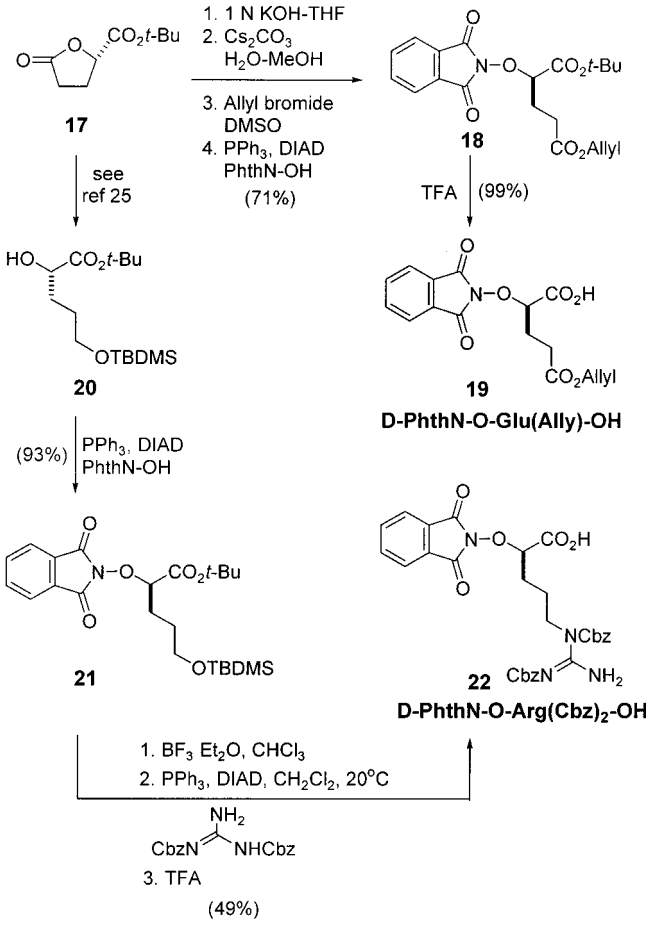
Scheme 4



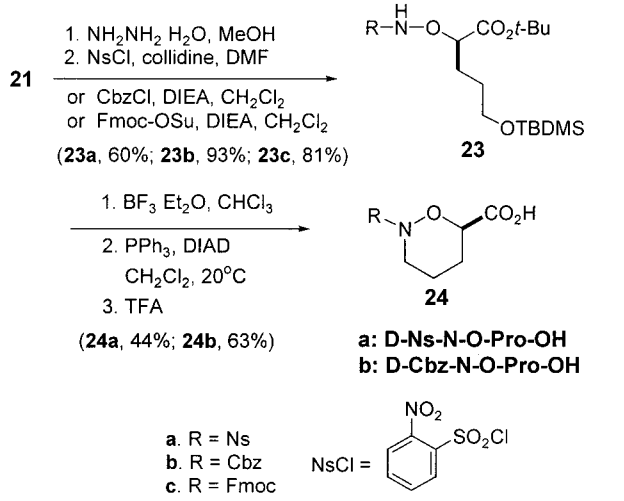
hydroxyl group in **13** as a TBDMS group provided **14** in 70% yield. The conversion of a secondary hydroxyl group in **14** to a phthaloyl aminooxy group under Mitsunobu conditions with PPh_3 (3.4 equiv), DIAD (3.4 equiv), and PhthN-OH (2.5 equiv), and a subsequent desilylation with $BF_3{\cdot}Et_2O$ produced **15** in 97% yield.[24] The use of $BF_3{\cdot}Et_2O$ for the deprotection of a TBDMS group was found to be superior to TBAF because partial cleavage of the phthaloyl group was observed during deprotection reaction with TBAF. Protection of a primary alcohol in **15** as a *t*-Bu group followed by debenzylation of the resulting benzyl ester and purification by precipitation with cyclohexylamine proceeded smoothly to furnish **16** in 69% yield.

Preparation of D-PhthN-*O*-Glu(Allyl)-OH (**19**), D-PhthN-*O*-Arg(Cbz)$_2$-OH (**22**), D-Ns-N-*O*-Pro-OH (**24a**), and Cbz-N-*O*-Pro-OH (**24b**) was efficiently achieved from the common precursor L-glutamic acid by the reactions delineated in Schemes 5 and 6. Hydrolysis of a lactone **17** obtained from L-glutamic acid[25] with 1 N KOH followed by allylation of the resulting acid with allyl bromide via a cesium salt and Mitsunobu reaction afforded **18** in 71% overall yield for three steps (Scheme 5). Deprotection of a *t*-Bu group of **18** with TFA completed the synthesis of **19** as a glutamic acid analogue. A monosilylated hydroxy ester **20** prepared from **17**[25] was converted to **21** under Mitsunobu conditions using 3.4 equiv of PPh_3, 2.5 equiv of PhthN-OH, and 3.4 equiv of DIAD.[18] The final conversion of **21** to an arginine analogue **22** was achieved by removal of a TBDMS group in **21** with $BF_3{\cdot}Et_2O$ and subsequent Mitsunobu reaction with a Cbz protected guanidine[26] and deprotection of a *t*-Bu group.

Scheme 5



Scheme 6



The cyclic amino acid proline induces conformational constraints on amide bond rotation.[27] Thus investigation into cyclic analogues such as **24** would be interesting. The oxy-analogues of nipecotic acid with two different protecting groups, D-Ns-N-*O*-Pro-OH (**24a**) and D-Cbz-N-*O*-Pro-OH (**24b**), were synthesized from **21** in five steps. The treatment of **21** with 4 equiv of $NH_2NH_2{\cdot}H_2O$ in MeOH exposed an aminooxy group, which was subsequently coupled to 2-nitrobenzenesulfonyl chloride (NsCl),[28] CbzCl, and Fmoc-OSu in the presence of collidine or

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(27) Creighton, T. E. In *Proteins: Structures and Molecular Properties*; Freeman: New York, 1993; Chapters 5 and 6.

DIEA to provide **23a**, **23b**, and **23c** in 60%, 93%, and 81% yield, respectively. In case of **23a**, it was found that use of collidine produced the desired product in higher yield than DIEA because less of an *N*,*N*′-bis-2-nitrobenzenesulfonylated product was observed as a side-product. Desilylation of **23a** and **23b** with BF_3·Et_2O followed by intramolecular Mitsunobu reaction of TBDMS deprotected **23a** and **23b** in the presence of PPh_3 and DIAD, and deprotection of *t*-Bu, afforded **24a** and **24b**. An intramolecular Mitsunobu reaction of TBDMS deprotected **23c** did not provide the desired product, but loss of the Fmoc group was observed under these conditions. Currently, synthesis of several aminooxy peptides is in progress for eventual structural studies and evaluation of biological properties.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 250 or 500 MHz for protons and at 62.5 or 125.8 MHz for carbons. Melting points were determined with a Mel-Temp II apparatus and are uncorrected. Microanalyses were carried out by Organic Chemistry Research Center, Korea. Solvents were dried and distilled prior to use.

General Procedure for Conversion of L-Amino Acids to D-Hydroxy Acids (Diazotization). To a stirred solution of L-amino acid (38.0 mmol) in 2.5 N H_2SO_4 (25 mL) was added dropwise a solution of $NaNO_2$ (57.1 mmol) in H_2O (20 mL) for 1 h at 0 °C. After 2 h at the same temperature, the reaction was allowed to stir for 9 h at room temperature. The reaction mixture was extracted with ether, and the combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by recrystallization from $CHCl_3$/hexane or ether/petroleum ether to give D-hydroxy acid.

(*S*)-2-Hydroxy-3-methylbutanoic Acid (1c). $[\alpha]_D$ +17.3 (*c* 1.0, $CHCl_3$) lit. $[\alpha]_D$ +19.0 (*c* 2.08, $CHCl_3$).[16a]

(*S*)-2-Hydroxy-4-methylpentanoic Acid (1d). $[\alpha]_D$ −25.9 (*c* 1.0, 1 N NaOH).

(*2S*,*3S*)-2-Hydroxy-3-methylpentanoic Acid (1e). Compound **1e** was prepared from L-isoleucine and purified by recrystallization from $CHCl_3$/hexane in 71% yield as a crystal: mp 52−54 °C; $[\alpha]_D$ −21.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (d, 1 H, J = 3.0 Hz), 1.90 (bs, 1 H), 1.47−1.38 (m, 1 H), 1.35−1.25 (m, 1 H), 1.04 (d, 3 H, J = 6.8 Hz), 0.95 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 180.1, 74.7, 38.9, 23.6, 15.5, 11.9. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.53; H, 9.29.

(*S*)-2-Hydroxy-3-phenylpropanoic Acid (1f). $[\alpha]_D$ −20.0 (*c* 2.0, H_2O), lit. $[\alpha]_D$ −20.6 (*c* 1.0, H_2O).[16b]

(*S*)-2-Hydroxysuccinamic Acid (1g). $[\alpha]_D$ −10.4 (*c* 1.0, H_2O), lit. $[\alpha]_D$ −10.5 (*c* 1.0, H_2O).[16c]

General Procedure for Benzylation of α-Hydroxy Acids to Benzyl Esters. Benzyl Glycolate (2a). To a stirred solution of glycolic acid (**1a**, 3.0 g, 39.4 mmol) in MeOH (60 mL) and H_2O (6 mL) was added a solution of 20% Cs_2CO_3 in H_2O until pH 7, and then the solvent was removed under reduced pressure. The residue was dissolved in DMF (40 mL), and then benzyl bromide (7.1 g, 41.5 mmol) was added. After stirring for 6 h at room temperature, the reaction mixture was quenched with brine and extracted with EtOAc. The combined organic solution was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 hexane/EtOAc) to give **2a** in 95% yield as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (s, 5 H), 5.21 (s, 2 H), 4.20 (d, 2 H, J = 5.2 Hz), 2.45 (t, 1 H, J = 5.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3, 135.2, 128.8, 128.6, 67.4, 60.8. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.08; H, 6.00.

Benzyl (*S*)-2-Hydroxypropanoate (2b). Compound **2b** was prepared from L-lactic acid (**1b**) as described for **2a** in 65% yield as an oil: $[\alpha]_D$ −15.9 (*c* 4.0, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 5.19 (s, 2 H), 4.35−4.25 (m, 1 H), 2.99 (d, 1 H, J = 5.4 Hz), 1.42 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.6, 135.3, 128.7, 128.6, 128.3, 67.3, 66.9, 20.4. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.66; H, 6.73.

Benzyl (*S*)-2-Hydroxy-3-methylbutanoate (2c). Compound **2c** was prepared from **1c** as described for **2a** in 94% yield as an oil: $[\alpha]_D$ −10.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 5.23 (d, 1 H, J = 12.2 Hz), 5.18 (d, 1 H, J = 12.2 Hz), 4.08 (dd, 1 H, J = 3.5, 6.2 Hz), 2.76 (d, 1 H, J = 6.2 Hz), 2.20−2.00 (m, 1 H), 1.00 (d, 3 H, J = 6.9 Hz), 0.83 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.9, 135.3, 128.8, 128.7, 128.5, 75.1, 67.4, 32.3, 18.9, 16.0. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.22; H, 7.75.

Benzyl (*S*)-2-Hydroxy-4-methylpentanoate (2d). Compound **2d** was prepared from **1d** as described for **2a** in 93% yield as an oil: $[\alpha]_D$ −15.8 (*c* 4.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 5.20 (s, 2 H), 4.27 (t, 1 H, J = 6.8 Hz), 3.13 (s, 1 H), 1.98−1.83 (m, 1 H), 1.60 (t, 2 H, J = 6.8 Hz), 0.96 (d, 3 H, J = 2.3 Hz), 0.93 (d, 3 H, J = 2.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.8, 135.4, 128.7, 128.6, 128.4, 69.3, 67.3, 43.5, 24.5, 23.3, 21.6. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.24; H, 8.15.

Benzyl (*2S*,*3S*)-2-Hydroxy-3-methylpentanoate (2e). Compound **2e** was prepared from **1e** as described for **2a** in 95% yield as an oil: $[\alpha]_D$ −4.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 (s, 5 H), 5.25 (d, 1 H, J = 12.2 Hz), 5.19 (d, 1 H, J = 12.2 Hz), 4.12 (dd, 1 H, J = 3.7, 5.9 Hz), 2.74 (d, 1 H, J = 6.2 Hz), 1.90−1.70 (m, 1 H), 1.40−1.10 (m, 2 H), 0.97 (d, 3 H, J = 6.9 Hz), 0.89 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.3, 135.6, 129.1, 129.0, 128.8, 75.3, 67.7, 39.5, 24.1, 15.9, 12.1. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.19; H, 8.19.

Benzyl (*S*)-2-Hydroxy-3-phenylpropanoate (2f). Compound **2f** was prepared from **1f** as described for **2a** in 97% yield as a solid: mp 25−27 °C; $[\alpha]_D$ −54.2 (*c* 4.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39−7.14 (m, 10 H), 5.15 (s, 2 H), 4.45 (bs, 1 H), 3.09 (dd, 1 H, J = 4.7, 13.9 Hz), 2.95 (dd, 1 H, J = 6.5, 13.9 Hz), 2.83 (bs, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.1, 136.2, 135.1, 129.6, 128.6, 128.7, 128.5, 126.9, 71.4, 67.4, 40.6. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.96; H, 6.32.

Benzyl (*S*)-2-Hydroxysuccinamate (2g). Compound **2g** was prepared from **1g** as described for **2a**, except that DMSO was used as a solvent, in 25% yield as a solid: mp 78−79 °C; $[\alpha]_D$ −17.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 5 H), 5.96 (bs, 1 H), 5.64 (bs, 1 H), 5.23 (s, 2 H), 4.52 (bs, 1 H), 3.79 (bs, 1 H), 2.76 (dd, 1H, J = 3.5, 15.6 Hz), 2.66 (dd, 1H, J = 7.2, 15.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.8, 172.9, 135.5, 129.1, 129.0, 128.8, 68.1, 68.0, 39.8. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.20; H, 5.87; N, 6.27.

General Procedure for Mitsunobu Reaction. Benzyl Phthalimidooxyacetate (3a). To a stirred solution of **2a** (6.0 g, 36.1 mmol), PPh_3 (12.3 g, 47.0 mmol, 1.3 equiv), and PhthN-OH (7.0 g, 43.2 mmol, 1.2 equiv) in CH_2Cl_2 (80 mL) was added DIAD (9.5 g, 47.0 mmol, 1.3 equiv) at −20 to −40 °C. After 40 min at the same temperature, the reaction mixture was concentrated and directly purified by flash column chromatography (4:1 hexane/EtOAc) to give **3a** contaminated by dihydro-DIAD as a solid. Dihydro-DIAD was removed by washing with MeOH to afford a pure **3a** in 91% yield as a solid: mp 128−129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92−7.75 (m, 4 H), 7.36−7.26 (m, 5 H), 5.30 (s, 2 H), 4.85 (s, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.8, 163.0, 135.0, 134.8, 128.9, 128.8, 128.7, 123.9, 73.2, 67.4. Anal. Calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.58; H, 4.22; N, 4.52.

Benzl (*R*)-3-Methyl-2-phthalimidooxybutanoate (3c). Treatment of **2c** (3.71 g, 17.8 mmol), PPh_3 (10.94 g, 41.7 mmol, 2.3 equiv), and PhthN-OH (6.11 g, 37.5 mmol, 2.1 equiv) in CH_2Cl_2 (80 mL) with DIAD (8.88 g, 41.7 mmol, 2.3 equiv) as described for **3a** followed by flash column chromatography (10:1 to 6:1 hexane/EtOAc) gave **3c** in 99% yield as an oil: $[\alpha]_D$ +69.2 (*c* 3.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.82−7.71 (m, 4 H), 7.37−7.28 (m, 5 H), 5.22 (s, 2 H), 4.45 (d, 1 H, J = 7.6 Hz), 2.37−2.29 (m, 1 H), 1.21 (d, 3 H, J = 6.7 Hz), 1.01 (d, 3 H, J = 5.9 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4, 163.2, 135.3, 134.6, 128.9, 128.7, 128.6, 128.5, 123.7, 91.0, 67.3, 30.4, 18.4, 18.2. Anal.

(28) (a) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1998**, *120*, 2690. (b) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.

Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.97; H, 5.44; N, 3.95.

Benzyl (*R*)-4-Methyl-2-phthalimidooxypentanoate (3d). Compound **3d** was prepared from **2d** as described for **3a** and purified by flash column chromatography (10:1 to 6:1 hexane/EtOAc) in 99% yield as an oil: $[\alpha]_D$ +77.8 (*c* 4.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81−7.73 (m, 4 H), 7.35−7.28 (m, 5 H), 5.18 (s, 2 H), 4.85 (dd, 1 H, J = 4.8, 8.4 Hz), 2.05−1.95 (m, 2 H), 1.74−1.68 (m, 1 H), 1.04 (d, 3 H, J = 6.4 Hz), 0.98 (d, 3 H, J = 6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.0, 163.3, 135.3, 134.7, 128.9, 128.6, 128.5, 123.7, 84.3, 67.5, 39.7, 24.5, 23.0, 22.0. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.65; H, 5.79; N, 3.84.

Benzyl (*2R,3S*)-3-Methyl-2-phthalimidooxypentanoate (3e). Compound **3e** was prepared from **2e** as described for **3a** and purified by flash column chromatography (6:1 hexane/EtOAc) in 86% yield as an oil: $[\alpha]_D$ +50.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81−7.71 (m, 4 H), 7.35−7.28 (m, 5 H), 5.20 (s, 2 H), 4.63 (d, 1 H, J = 6.5 Hz), 2.09−2.04 (m, 1 H), 1.65−1.55 (m, 1 H), 1.30−1.24 (m, 1 H), 1.16 (d, 3 H, J = 6.9 Hz), 0.96 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.2, 163.3, 135.5, 134.5, 129.1, 128.6, 128.4, 123.6, 89.2, 67.2, 37.0, 25.3, 14.6, 11.3. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.60; H, 5.81; N, 3.72.

Benzyl (*R*)-2-Phthalimidooxysuccinamate (3g). Compound **3g** was prepared from **2g** as described for **3a** and purified by flash column chromatography (1:1 to 1:3 hexane/EtOAc) in 82% yield as an oil: $[\alpha]_D$ +15.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85−7.75 (m, 4 H), 7.34−7.30 (m, 5 H), 6.60 (bs, 1 H), 5.43 (bs, 1 H), 5.25 (d, 1 H, J = 12.1 Hz), 5.20 (d, 1 H, J = 12.1 Hz), 5.12 (dd, 1 H, J = 5.0, 7.3 Hz), 3.09−2.91 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.1, 168.0, 163.4, 134.4, 132.1, 128.5, 123.9, 81.3, 67.5, 36.6. Anal. Calcd for $C_{19}H_{16}N_2O_6$: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.93; H, 4.26; N, 7.65.

General Procedure for Debenzylation of Benzyl Esters by Hydrogenolysis (Method 1). A suspension of a benzyl ester and 10% Pd/C in a proper solvent system was treated with H_2 under 1 atm and stirred for 1 h. The reaction mixture was filtered through Celite and rinsed with MeOH, and the filtrate was concentrated in vacuo. The crude product was purified either by flash column chromatography, recrystallization, or precipitation with an amine to afford an acid.

Phthalimidooxyacetic Acid (PhthN-*O*-Gly-OH) (4a). Compound **4a** was prepared from **3a** in 1:1 MeOH /$CHCl_3$ as described in Method 1 and purified by flash column chromatography (10:1 $CHCl_3$/MeOH) in 53% yield as a solid: mp 166−168 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 4 H), 4.57 (bs, 2 H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 168.0, 162.6, 134.8, 128.6, 123.2, 72.9. Anal. Calcd for $C_{10}H_7NO_5$: C, 54.31; H, 3.19; N, 6.53. Found: C, 54.29; H, 3.20; N, 6.43.

(*R*)-2-Phthalimidooxypropanoic Acid (D-PhthN-*O*-Ala-OH) (4b). Treatment of **2b**, PPh_3, and *N*-hydroxyphthalimide in CH_2Cl_2 with DIAD as described for **3a** followed by flash column chromatography (6:1 to 3:1 hexane/EtOAc) gave dihydro-DIAD contaminated **3b,** which was used for the next reaction without further purification. A suspension of dihydro-DIAD contaminated **3b** and 10% Pd/C in MeOH was treated with H_2 under 1 atm and stirred for 1 h. The reaction mixture was filtered through Celite and rinsed with MeOH, and the filterate was concentrated in vacuo. The residue was dissolved in EtOAc, and then cyclohexylamine was added. After stirring for 1 h, a precipitated solid was collected by filteration and dried in vacuo. Cyclohexylamine salt was redissolved in H_2O and extracted with CH_2Cl_2 to remove any organic impurity, followed by acidification with 0.5 N HCl to pH 2. The acidic solution was extracted with EtOAc, and the combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated to give **4b** in 68% overall yield from **2b** as a solid: mp 125−130 °C; $[\alpha]_D$ +89.5 (*c* 1.0, $CHCl_3$) ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.74 (bs, 1 H), 7.89−7.78 (m, 4 H), 4.88 (q, 1 H, J = 7.0 Hz), 1.73 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.8, 164.0, 135.2, 128.7, 124.2, 82.4, 16.9. Anal. Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.15; H, 3.91; N, 5.96.

(*R*)-3-Methyl-2-phthalimidooxybutanoic Acid (D-PhthN-*O*-Val-OH) (4c). Compound **4c** was prepared from **3c** in MeOH as described in Method 1 and purified by precipitation with cyclohexylamine in 68% yield as a solid: mp 85−87 °C; $[\alpha]_D$ +99.5 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90−7.79 (m, 4 H), 4.60 (d, 1 H, J = 4.6 Hz), 2.53−2.43 (m, 1 H), 1.26 (d, 3 H, J = 6.9 Hz), 1.17 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.8, 163.6, 134.9, 128.6, 123.8, 90.3, 30.7, 18.3, 17.6. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.33; H, 4.97; N, 5.34.

(*R*)-4-Methyl-2-phthalimidooxypentatanoic Acid (D-PhthN-*O*-Leu-OH) (4d). Compound **4d** was prepared from **3d** in MeOH as described in Method 1 and purified by precipitation with cyclohexylamine in 79% yield as a solid: mp 76−77 °C; $[\alpha]_D$ +103.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.89−7.77 (m, 4 H), 4.86 (dd, 1 H, J = 4.3, 9.1 Hz), 2.16−1.08 (m, 3 H), 1.09 (d, 3 H, J = 6.5 Hz), 1.02 (d, 3 H, J = 6.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.2, 163.6, 134.9, 128.6, 123.8, 83.9, 40.1, 24.4, 22.9, 21.7. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.66; H, 5.49; N, 5.05.

(*2R,3S*)-3-Methyl-2-phthalimidooxypentanoic Acid (D-PhthN-*O*-Ile-OH) (4e). Compound **4e** was prepared from **3e** in MeOH as described in Method 1 and purified by precipitation with cyclohexylamine in 80% yield as an oil: $[\alpha]_D$ +66.1 (*c* 4.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.46 (bs, 1 H), 7.84−7.74 (m, 4 H), 4.70 (d, 2 H, J = 4.3 Hz), 2.12−2.02 (m, 1 H), 1.85−1.70 (m, 1 H), 1.48−1.38 (m, 1 H), 1.11 (d, 3 H, J = 7.0 Hz), 1.01 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.0, 164.0, 135.1, 128.7, 124.0, 88.8, 38.0, 25.6, 14.2, 11.7. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.53; H, 5.68; N, 4.99.

(*R*)-3-Phenyl-2-phthalimidooxypropanoic Acid (D-PhthN-*O*-Phe-OH) (4f). Treatment of **2f**, PPh_3, and *N*-hydroxyphthalimide in CH_2Cl_2 with DIAD as described for **3a** followed by flash column chromatography (6:1 to 3:1 hexane/EtOAc) gave dihydro-DIAD contaminated **3f,** which was used for the next reaction without further purification. A pure sample was obtained by repeated chromatography for characterization purpose: mp 52−54 °C; $[\alpha]_D$ +38.1 (*c* 3.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78−7.69 (m, 4 H), 7.21 (bs, 10 H), 5.11 (s, 2 H), 5.03 (dd, 1 H, J = 6.9, 7.1 Hz), 3.37−3.30 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.5, 163.0, 134.8, 134.6, 134.5, 129.3, 128.7, 128.5, 128.4, 128.3, 127.0, 123.6, 85.7, 67.3, 36.9. Anal. Calcd for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 71.83; H, 4.78; N, 3.57.

A suspension of dihydro-DIAD contaminated **3f** (1.08 g, 2.7 mmol) and 10% Pd/C (100 mg) in MeOH (30 mL) was treated with H_2 under 1 atm and stirred for 1 h. The reaction mixture was filtered through Celite and rinsed with MeOH, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (5 mL), and then dicyclohexylamine (0.34 g, 3.4 mmol) was added. After stirring for 1 h, solvent was removed under reduced pressure. The oily residue was solidified with ether, and a precipitated solid was filtered and rinsed with ether. Dicyclohexylamine salt was redissolved in CH_2Cl_2, washed with 1 N HCl, H_2O and brine, dried ($MgSO_4$), and concentrated to give **4f** in 90% overall yield from **2f** as a solid: mp 135 °C; $[\alpha]_D$ +33.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.88 (bs, 1 H), 7.82−7.72 (m, 4 H), 7.37−7.20 (m, 5 H), 5.05 (dd, 1 H, J = 6.0, 6.3 Hz), 3.47−3.30 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.2, 163.6, 135.0, 134.7, 129.6, 128.6, 127.3, 124.0, 86.0, 37.4. Anal. Calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.58; H, 4.17; N, 4.60.

(*R*)-2-Phthalimidooxysuccinamic Acid (D-PhthN-*O*-Asn-OH) (4g). Compound **4g** was prepared from **3g** in MeOH as described in Method 1 and purified by recrystallization from MeOH/EtOH in 80% yield as a crystal: mp 150−152 °C (decomp); $[\alpha]_D$ +25.7 (*c* 1.0, CH_3OH); ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.87 (s, 4 H), 7.47 (bs, 1 H), 6.97 (bs, 1 H), 5.00 (t, 1 H, J = 6.3 Hz), 2.77 (d, 2 H, J = 6.3 Hz); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 169.9, 169.4, 163.0, 134.9, 128.4, 123.4, 81.1, 36.7. Anal. Calcd for $C_{12}H_{10}N_2O_6$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.85; H, 3.64; N, 10.06.

(*S*)-6-(*tert*-Butyloxycarbonylamino)-2-hydroxyhexanoic Acid (6). Treatment of **5** (5.0 g, 17.8 mmol) in 50% HOAc (350 mL) with $NaNO_2$ (9.8 g, 0.14 mol) in H_2O (40 mL) for 20 min at 0 °C gave a hydroxy acid in 95% yield as a yellow syrup, which was used without further purification. A suspension of a hydroxy acid (2.4 g, 8.5 mmol) and 10% Pd/C (300 mg) in MeOH (100 mL) was treated with H_2 under 1 atm and stirred for 2 h. The reaction mixture was filtered through Celite and rinsed with

MeOH, and the filtrate was concentrated in vacuo. The residue was dissolved in water and extracted with CH_2Cl_2 to remove any organic impurity. The aqueous solution was concentrated to give (*S*)-6-amino-2-hydroxyhexanoic acid in 88% yield as a solid: mp 191−193 °C; $[\alpha]_D$ −14.5 (*c* 2.0, H_2O); ^{1}H NMR (250 MHz, D_2O) δ 4.05 (dd, 1 H, J = 4.8, 6.2 Hz), 3.05−2.99 (t, 2 H, J = 7.4 Hz), 2.15−1.61 (m, 4 H), 1.57−1.36 (m, 2 H); ^{13}C NMR (125.8 MHz, D_2O) δ 182.1, 72.4, 39.9, 33.8, 27.2, 21.9. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.95; H, 8.90; N, 9.52. Found: C, 48.91; H, 8.91; N, 9.50.

To a stirred solution of (*S*)-6-amino-2-hydroxyhexanoic acid (2.0 g, 13.6 mmol) in 1 N NaOH (27.2 mL) and dioxane (27.2 mL) was added $(BOC)_2O$ (5.9 g, 27.0 mmol) at 0 °C. After 2 h at the same temperature, the reaction mixture was concentrated to a half of the volume. The residue was extracted with ether to remove any organic impurity. The aqueous layer was acidified to pH 2 with 0.5 N HCl, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated to give **6** in 74% yield as an oil: $[\alpha]_D$ −4.1 (*c* 1.0, CH_3OH); ^{1}H NMR (250 MHz, CD_3CO_2D) δ 4.30 (dd, 1 H, J = 4.3, 7.4 Hz), 3.10 (m, 2 H), 2.02−1.50 (m, 6 H), 1.45 (s, 9 H); ^{13}C NMR (125.8 MHz, CD_3CO_2D) δ 179.7, 157.5, 71.1, 54.6, 41.1, 34.4, 30.3, 28.7, 23.0. Anal. Calcd for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.38; H, 8.66; N, 5.22.

Benzyl (*S*)-6-(*tert*-butyloxycarbonylamino)-2-hydroxyhexanoate (7). Compound **7** was prepared from **6** as described for **2a** in 75% yield as an oil: $[\alpha]_D$ −16.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 5.19 (s, 2 H), 4.69 (bs, 1 H), 4.21 (m, 1 H), 3.22 (bs, 1 H), 3.08−3.05 (m, 2 H), 1.82−1.64 (m, 2 H), 1.51−1.33 (m, 4 H), 1.42 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4, 163.3, 156.1, 135.2, 134.7, 128.9, 128.7, 128.6, 128.5, 123.8, 85.2, 79.2, 67.5, 40.3, 30.5, 29.6, 28.5, 22.0. Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.10; H, 8.07; N, 4.15.

(*R*)-6-(*tert*-butyloxycarbonylamino)-2-phthalimidooxyhexanoic Acid (D-PhthN-*O*-Lys(Boc)-OH) (8). Compound **8** was prepared from **7** as described for **3a** and purified by flash column chromatography (4:1 hexane/EtOAc) to give a product contaminated by dihydro-DIAD. Dihydro-DIAD was removed by washing with cold MeOH to afford benzyl (*R*)-6-(*tert*-butyloxycarbonylamino)-2-phthalimidooxyhexanoate in 69% yield as a solid: mp 92 °C; $[\alpha]_D$ +37.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−7.73 (m, 4 H), 7.34−7.30 (m, 5 H), 5.22 (d, 1 H, J = 12.1 Hz), 5.17, (d, 1 H, J = 12.1 Hz), 4.76 (dd, 1 H, J = 5.6, 7.3 Hz), 4.57 (bs, 1 H), 3.12 (bs, 2 H), 2.06−2.03 (m, 1 H), 2.00−1.90 (m, 1 H), 1.60−1.47 (m, 4 H), 1.46−1.40 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4, 163.3, 156.1, 135.3, 134.7, 129.0, 128.7, 123.8, 85.2, 67.5, 40.4, 30.6, 29.7, 28.6, 22.1. Anal. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.72; H, 6.27; N, 5.81. Found: C, 64.71; H, 6.36; N, 5.87.

A suspension of benzyl (*R*)-6-(*tert*-butyloxycarbonylamino)-2-phthalimidooxyhexanoate (200 mg, 0.4 mmol) and 10% Pd/C (40 mg) in 1:1 MeOH/$CHCl_3$ (10 mL) was treated with H_2 under 1 atm and stirred for 0.5 h. The reaction mixture was filtered through Celite and rinsed with MeOH, and then the solution was concentrated to afford **8** quantitatively as an oil: $[\alpha]_D$ +12.2 (*c* 2.0 CH_3OH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87−7.77 (m, 4 H), 4.75 (t, 1 H, J = 5.9 Hz), 4.67 (bs, 1 H), 3.17−3.15 (m, 2 H), 2.08−2.00 (m, 2 H), 1.72−1.54 (m, 4 H), 1.59 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.55, 164.09, 135.21, 128.75, 124.23, 40.31, 31.21, 29.62, 28.56; ESI MS calcd for $C_{19}H_{24}N_2O_7$ $(M + H)^+$ 393.4, found 393.4

Benzyl Hydrogen (*S*)-2-Hydroxysuccinate (9). Compound **9** was synthesized according to the modified procedure of Miller et al.[22] Trifluoroacetic anhydride (18.3 g, 87.1 mmol) was added to (*S*)-malic acid (5.0 g, 37.3 mmol) that was pre-cooled in an ice bath. After stirring for 3 h at 0 °C, volatiles were removed by vacuum distillation while the distillation flask was kept at 0 °C. The residual solid was dissolved in BnOH (66.0 g, 0.6 mol) and stirred for 4 h at room temperature. The reaction mixture was diluted with EtOAc and extracted with 10% Na_2CO_3. The combined aqueous solution was acidified to pH 7 with 1 N HCl and extracted with EtOAc to remove unreacted BnOH. The aqueous layer was further acidified to pH 2 with 1 N HCl and extracted with EtOAc. The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated to give **9** in 88% yield as an oil: $[\alpha]_D$ −15.5 (*c* 1.1 $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 (s, 5 H), 5.21 (s, 2 H), 4.54 (dd, 1 H, J = 4.5, 6.1 Hz), 2.95−2.77 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.9, 173.2, 135.0, 128.9, 128.5, 67.9, 67.2, 38.5. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.95; H, 5.49. Found: C, 58.93; H, 5.39.

Benzyl *tert*-Butyl (*S*)-2-(*tert*-Butyldimethylsilyloxy)succinate (10). To a stirred solution of **9** (7.0 g, 31.2 mmol) in DMF (15 mL) was added imidazole (4.5 g, 66.1 mmol) at room temperature. After 30 min, TBDMSCl (5.6 g, 37.2 mmol) was added. The reaction was allowed to proceed for 8 h at room temperature and then quenched with water. The resulting mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (15:1 to 5:1 hexane/EtOAc) to give TBDMS protected **9** in 78% yield as an oil: $[\alpha]_D$ −39.9 (*c* 1.05, CH_3OH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38−7.34 (m, 5 H), 5.20−5.17 (m, 2 H), 4.68−4.63 (m, 1 H), 2.86−2.77 (m, 2 H), 0.86 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.7, 172.0, 135.4, 128.7, 128.6, 69.1, 67.2, 40.6, 25.7, 18.3, −4.8, −5.4. Anal. Calcd for $C_{17}H_{26}O_5Si$: C, 60.32; H, 7.74. Found: C, 60.36; H, 7.79.

Isobutylene (1.7 g, 30.3 mmol) was bubbled through a stirred solution of TBDMS protected **9** (4.0 g, 11.8 mmol) and a catalytic amount of H_2SO_4 (200 μL) in CH_2Cl_2 (25 mL) at −10 °C, and then the reaction mixture was allowed to stir overnight at room temperature. An excess of isobutylene was removed under reduced pressure. The residual solution was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (15:1 hexane/EtOAc) to give **10** in 69% yield as an oil: $[\alpha]_D$ −39.0 (*c* 1.05, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54 (s, 5 H), 5.36 (d, 1 H, J = 12.2 Hz), 5.31 (d, 1 H, J = 12.2 Hz), 4.79 (dd, 1 H, J = 5.4, 6.6 Hz), 2.92−2.78 (m, 2 H), 1.60 (s, 9 H), 1.05 (s, 9 H), 0.17 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.4, 169.5, 135.6, 128.6, 128.5, 128.4, 81.0, 69.3, 66.8, 41.4, 28.1, 25.7, 18.2, −4.8, −5.4. Anal. Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.69. Found: C, 63.90; H, 8.69.

Benzyl *tert*-Butyl (*R*)-2-Phthalimidooxysuccinate (11). To a stirred solution of TBAF (1 M solution in THF, 11.8 mL, 11.8 mmol) was added **10** (3.1 g, 7.9 mmol) at room temperature. After 10 min at the same temperature, the reaction was quenched by dilution with CH_2Cl_2, and the solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (5:1 hexane/EtOAc) to give an alcohol in 92% yield as an oil: $[\alpha]_D$ −12.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 5 H), 5.24 (d, 1 H, J = 12.2 Hz), 5.17 (d, 1 H, J = 12.2 Hz), 4.46 (q, 1 H, J = 5.3 Hz), 3.43 (d, 1 H, J = 5.7 Hz), 2.74 (d, 2 H, J = 4.8 Hz), 1.41 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.4, 169.7, 135.2, 128.6, 128.5, 128.47, 81.5, 67.5, 67.4, 39.7, 27.3. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.30; H, 7.14.

To a stirred solution of an alcohol (1.4 g, 5.0 mmol), PPh_3 (3.5 g, 13.3 mmol, 2.7 equiv), and *N*-hydroxyphthalimide (1.9 g, 11.5 mmol, 2.3 equiv) in CH_2Cl_2 (20 mL) was added DIAD (2.7 g, 13.3 mmol, 2.7 equiv) at −20 °C. After 30 min at the same temperature, the reaction mixture was concentrated and directly purified by flash column chromatography (5:1 to 3:1 hexane/EtOAc) to give **11** in 97% yield as an oil: $[\alpha]_D$ +34.3 (*c* 0.93, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81−7.26 (m, 4 H), 7.35−7.27 (m, 5 H), 5.23 (d, 1 H, J = 12.2 Hz), 5.20 (d, 1 H, J = 12.2 Hz), 5.11 (t, 1 H, J = 6.6 Hz), 3.04 (t, 2 H, J = 6.6 Hz), 1.41 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.0, 167.9, 163.1, 135.0, 134.7, 128.9, 128.6, 128.5, 123.8, 82.0, 81.3, 67.8, 37.0, 28.0. Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.96; H, 5.46; N, 3.31.

Hydrogen *tert*-Butyl (*R*)-2-Phthalimidooxysuccinate (D-PhthN-*O*-Asp(*t*-Bu)-OH) (12). Compound **12** was prepared from **11** in MeOH as described in method 1 and purified by precipitation with cyclohexylamine in 80% yield. The product was slowly crystallized in vacuo: mp 98−100 °C; $[\alpha]_D$ +59.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.89 (bs, 1 H), 7.90−7.78 (m, 4 H), 5.00 (t, 1 H, J = 5.5 Hz), 3.26−3.06 (m, 2 H), 1.45 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.9, 167.9, 163.5, 134.9, 128.1, 123.9, 82.8, 82.1, 37.2, 27.6. Anal. Calcd for $C_{19}H_{15}NO_7$: C, 57.31; H, 5.11; N, 4.18. Found: C, 57.35; H, 5.43; N, 4.12.

Benzyl (*S*)-Glycerate (13). To a stirred solution of L-serine (1 g, 9.5 mmol) in H_2O (50 mL) and concentrated HCl (1.4 mL) was added $NaNO_2$ (571 mg, 8.3 mmol) portionwise at 0 °C. After

24 h at the same temperature, additional $NaNO_2$ (191 mg, 2.8 mmol) was added, stirred for further 24 h at 0 °C, and then allowed to warm to room temperature. After 16 h, the reaction mixture was concentrated, and the residue was dissolved in MeOH and H_2O followed by addition of 20% Cs_2CO_3 in H_2O until pH 7. The solvent was removed under reduced pressure, the residual solid was dissolved in DMF (25 mL), and then benzyl bromide (2.4 g, 14.0 mmol) was added. After stirring for 15 h at room temperature, the reaction mixture was diluted with EtOAc, filtered, concentrated, and directly purified by flash column chromatography (1:1 hexane/EtOAc) to give **13** in 17% yield as an oil: $[\alpha]_D$ −28.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 5.24 (d, 1 H, J = 12.3 Hz), 5.22 (d, 1 H, J = 12.3 Hz), 4.29 (bs, 1 H), 3.87 (m, 2 H), 3.60 (bs, 1 H), 2.78 (bs, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.0, 135.2, 128.8, 128.7, 128.4, 71.9, 67.7, 64.2. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.27; H, 6.18.

Benzyl (*S*)-3-(*tert*-Butyldimethysilyloxy)-2-hydroxypropanoate (14). To a stirred solution of **13** (300 mg, 1.5 mmol), DMAP (9.7 mg, 0.08 mmol), and TEA (314 mg, 3.1 mmol) in DMF (3 mL) was added TBDMSCl (242 mg, 1.6 mmol). The reaction was allowed to proceed for 8 h at room temperature and then quenched with water. The resulting mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (10:1 to 5:1 hexane/EtOAc) to give **14** in 70% yield as an oil: $[\alpha]_D$ −18.0 (*c* 0.45, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (s, 5 H), 5.22 (s, 2 H), 4.27−4.24 (m, 1 H), 4.00−3.85 (m, 2 H), 3.07 (d, 2 H, J = 16.4 Hz), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.8, 135.4, 128.7, 128.6, 128.5, 72.1, 67.3, 65.2, 25.9, 18.4, −5.4, −5.5. Anal. Calcd for $C_{16}H_{26}O_4Si$: C, 61.90; H, 8.44. Found: C, 61.93; H, 8.24.

Benzyl (*R*)-3-Hydroxy-2-phthalimidooxypropanoate (15). Treatment of **14** (320 mg, 1.0 mmol), PPh_3 (936 mg, 3.6 mmol, 3.6 equiv), and *N*-hydroxyphthalimide (426 mg, 2.6 mmol, 2.6 equiv) in CH_2Cl_2 (6 mL) with DIAD (728 mg, 3.6 mmol, 3.6 equiv) as described for **3a** followed by flash column chromatography (10:1 to 5:1 hexane/EtOAc) gave benzyl (*R*)-3-(*tert*-butyldimethylsilyloxy)-2-phthalimidooxypropanoate in 97% yield as an oil: $[\alpha]_D$ +22.34 (*c* 0.44, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.83−7.72 (m, 4 H), 7.37−7.29 (m, 5 H), 5.25 (d, 1 H, J = 12.3 Hz), 5.22(d, 1 H, J = 12.3 Hz), 4.88 (t, 1 H, J = 5.1 Hz), 4.18−4.14 (m, 2 H), 0.84 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.5, 162.9, 135.1, 134.5, 128.8, 128.5, 128.4, 128.4, 123.6, 85.9, 67.3, 62.4, 25.7, 18.2, −5.6. Anal. Calcd for $C_{24}H_{29}NO_6Si$: C, 63.27; H, 6.42; N, 3.07. Found: C, 63.25; H, 6.44; N, 3.11.

To a stirred solution of benzyl (*R*)-3-(*tert*-butyldimethylsilyloxy)-2-phthalimidooxypropanoate (470 mg, 1.0 mmol) in $CHCl_3$ (30 mL) was added $BF_3{\cdot}Et_2O$ (717 mg, 5.05 mmol) at room temperature. After 20 min at the same temperature, the reaction mixture was neutralized by aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated to give **15** quantitatively as a crystal. A pure sample was obtained by recrystallization from CH_2Cl_2/hexane for characterization purpose: mp 126−128 °C; $[\alpha]_D$ +16.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.88−7.77 (m, 4 H), 7.38−7.27 (m, 5 H), 5.28 (s, 2 H), 4.79 (t, 1 H, J = 3.2 Hz), 4.07−3.99 (m, 2 H), 3.65 (t, 1 H, J = 6.9 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.7, 164.2, 135.1, 135.0, 128.7, 128.6, 128.5, 124.1, 86.0, 67.7, 60.9. Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.40; H, 4.35; N, 4.18.

(*R*)-3-*tert*-Butyloxy-2-phthalimidooxypropanoic Acid (D-PhthN-*O*-Ser(*t*-Bu)-OH) (16). Isobutylene (82 mg, 1.5 mmol) was bubbled through a stirred solution of **15** (200 mg, 0.6 mmol) and a catalytic amount of H_2SO_4 (20 μL) in CH_2Cl_2 (10 mL) at −10 °C, and the reaction mixture was allowed to stir overnight at room temperature. An excess of isobutylene was removed under reduced pressure. The residual solution was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (5:1 hexane/EtOAc) to give benzyl (*R*)-3-*tert*-butyloxy-2-phthalimidooxypropanoate in 81% yield as an oil: $[\alpha]_D$ +26.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84−7.72 (m, 4 H), 7.38−7.27 (m, 5 H), 5.28 (d, 1 H, J = 12.2 Hz), 5.23 (d, 1 H, J = 12.2 Hz), 4.93 (t, 1 H, J = 5.4 Hz), 3.92−3.89 (m, 2 H), 1.10 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.7, 163.2, 135.4, 134.7, 129.0, 128.7, 128.7, 128.6, 123.8, 84.9, 74.1, 67.5, 61.4, 27.2. Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.47; H, 5.95; N, 3.44.

A suspension of benzyl (*R*)-3-*tert*-butyloxy-2-phthalimidooxypropanoate (180 mg, 0.5 mmol) and 10% Pd/C (20 mg) in MeOH (6 mL) was treated with H_2 under 1 atm and stirred for 1 h. The reaction mixture was filtered through Celite and rinsed with MeOH, and the solution was concentrated in vacuo. The crude product was dissolved in EtOAc (6 mL), and then cyclohexylamine (54 mg, 0.5 mmol) was added. After stirring for 1 h, a precipitated white solid was filtered and dried in vacuo. Cyclohexylamine salt was redissolved in H_2O and extracted with CH_2Cl_2 to remove any organic impurity followed by acidification with 0.1 N HCl to pH 2. The acidic solution was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated to give **16** in 85% yield as an oil**:** $[\alpha]_D$ +12.5 (*c* 1.85 $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (bs, 1 H), 7.89−7.80 (m, 4 H), 4.93 (s, 1 H), 4.03−3.95 (m, 2 H), 1.13 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.7, 163.9, 135.2, 128.6, 124.1, 85.8, 74.3, 61.5, 27.4. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.65; H, 5.60; N, 4.43.

***tert*-Butyl Allyl (*R*)-2-Phthalimidooxyglutarate (18).** To a stirred solution of **17** (0.70 g, 3.8 mmol) in THF (4 mL) was added 1 N KOH (4.1 mL). After 1 h at room temperature, the reaction was quenched with H_2O, and then washed with CH_2Cl_2 to remove any organic impurity. The aqueous layer was adjusted to pH 2 with 0.5 N HCl and then extracted with EtOAc. The combined organic solution was dried ($MgSO_4$) and concentrated to give *tert*-butyl hydrogen (S)-2-hydroxyglutarate in 90% yield as a solid: mp 72−74 °C; $[\alpha]_D$ −6.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.12 (dd, 1 H, J = 4.2, 7.8 Hz), 2.62−2.40 (m, 2 H), 2.21−2.02 (m, 1 H), 1.97−1.78 (m, 1 H), 1.49 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 179.3, 174.3, 83.4, 69.9, 29.9, 29.5, 28.4. Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.91; H, 7.91.

To a stirred solution of *tert*-butyl hydrogen (*S*)-2-hydroxyglutarate (0.25 g, 1.2 mmol) in MeOH (10 mL) and H_2O (1 mL) was added a solution of 20% Cs_2CO_3 in H_2O until pH 7, and then the solvent was removed in vacuo. The residual solid was dissolved in DMSO (6 mL), and then allyl bromide (0.15 g, 1.2 mmol) was added. After stirring for 4 h at room temperature, the reaction was quenched with brine and extracted with EtOAc. The combined organic solution was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography to give *tert*-butyl allyl (*S*)-2-hydroxyglutarate in 84% yield as an oil: $[\alpha]_D$ −7.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.00−5.84 (m, 1 H), 5.31 (dd, 1 H, J = 1.4, 17.2 Hz), 5.24 (dd, 1 H, J = 1.2, 10.3 Hz), 4.68−4.50 (d, 2 H, J = 5.7 Hz), 4.13−4.06 (m, 1 H), 2.88 (d, 1 H, J = 5.4 Hz), 2.60−2.38 (m, 2 H), 2.22−2.08 (m, 1 H), 1.96−1.82 (m, 1 H), 1.49 (s, 9 H)); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.0, 172.9, 132.2, 118.2, 82.8, 69.7, 65.3, 29.8, 29.6, 28.1. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.04; H, 8.54.

Treatment of *tert*-butyl allyl (*S*)-2-hydroxyglutarate (0.22 g, 0.9 mmol), PPh_3 (0.82 g, 3.1 mmol, 3.4 equiv), and *N*-hydroxyphthalimide (0.48 g, 2.9 mmol, 3.2 equiv) in CH_2Cl_2 (10 mL) with DIAD (0.67 g, 3.1 mmol, 3.4 equiv) as described for **3a** followed by flash column chromatography (6:1 hexane/EtOAc) to give **18** in 94% yield as an oil: $[\alpha]_D$ +37.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.86−7.77 (m, 4 H), 6.01−5.90 (m, 1 H), 5.35 (dd, 1 H, J = 1.2, 17.2 Hz), 5.42 (d, 1 H, J = 10.4 Hz), 4.7 (t, 1 H, J = 6.4 Hz), 4.64 (d, 2 H, J = 5.6 Hz), 2.88−2.66 (m, 2 H), 2.27 (m, 2 H), 1.49 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.9, 167.7, 162.8, 134.4, 132.0, 128.6, 123.3, 117.9, 84.5, 82.5, 65.0, 29.0, 27.6, 25.9. Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.69; H, 5.96; N, 3.57.

Hydrogen Allyl (*R*)-2-Phthalimidooxyglutarate (D-PhthN-*O*-Glu(Allyl)-OH) (19). A solution of **18** (0.24 g, 0.6 mmol) in 50% TFA in CH_2Cl_2 was stirred for 1 h, and then the solution was concentrated in vacuo. The concentration step was repeated several times to remove residual TFA to give **19** in 99% yield as a white solid: mp 81 °C; $[\alpha]_D$ +54.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90−7.79 (m, 4 H), 6.01−5.86 (m, 1 H), 5.33 (dd, 1 H, J = 1.5, 17.2 Hz), 5.24 (dd, 1 H, J = 1.2, 10.3 Hz), 4.86 (dd, 1 H, J = 4.5, 8.3 Hz), 4.62 (d, 2 H, J = 4.7 Hz), 2.97−2.69 (m, 2 H), 2.56−2.26 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.4, 172.2, 163.7, 135.1, 132.1, 128.6, 124.2, 118.5, 84.8, 65.6,

29.3, 26.5. Anal. Calcd for $C_{16}H_{15}NO_7$: C, 57.66; H, 4.54; N, 4.20. Found: C, 57.67; H, 4.58; N, 4.15.

***tert*-Butyl (*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-phthalimidooxypentanoate (21).** Treatment of **20**[25] (1.05 g, 3.5 mmol), PPh_3 (3.08 g, 11.7 mmol, 3.4 equiv) and *N*-hydroxyphthalimide (1.41 g, 8.6 mmol, 2.5 equiv) in CH_2Cl_2 (15 mL) with DIAD (2.50 g, 11.7 mmol, 3.4 equiv) as described for **3a** followed by flash column chromatography (8:1 hexane/EtOAc) gave **21** in 93% yield as a white solid: mp 52 °C; $[\alpha]_D$ +44.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85−7.73 (m, 4 H), 4.69 (t, 1 H, J = 6.5 Hz), 3.74−3.67 (m, 2 H), 2.08−2.01 (m, 2 H), 1.86−1.78 (m, 2 H), 1.55 (s, 9 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.8, 163.3, 134.6, 129.0, 123.7, 85.8, 82.5, 62.4, 28.1, 28.0, 27.8, 26.1, 18.4, −5.2. Anal. Calcd for $C_{23}H_{35}NO_6Si$: C, 61.44; H, 7.85; N, 3.12. Found: C, 61.41; H, 7.92; N, 3.15.

D-PhthN-*O*-Arg(Cbz)$_2$-OH (22). To a stirred solution of **21** (0.25 g, 0.6 mmol) in $CHCl_3$ (3 mL) was added $BF_3{\cdot}Et_2O$ (0.12 g, 0.8 mmol). After 50 min at room temperature, the reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$, H_2O, and brine sequentially, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (2:1 hexane/EtOAc) to give a TBDMS deprotected **21** in 65% yield as an oil: $[\alpha]_D$ +52.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85−7.74 (m, 4 H), 4.71 (dd, 1 H, J = 5.8, 6.6 Hz), 3.85−3.68 (m, 2 H), 2.17−1.98 (m, 2 H), 1.95−1.80 (m, 2 H), 1.47 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.6, 163.4, 134.7, 129.0, 123.7, 85.9, 82.8, 62.4, 28.0, 27.9, 27.7. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.92; H, 6.30; N, 4.19.

To a stirred solution of a TBDMS deprotected **21** (0.12 g, 0.4 mmol), PPh_3 (0.13 g, 0.5 mmol), and *N*,*N*′-bis(benzyloxycarbonyl)guanidine (0.12 g, 0.4 mmol) in CH_2Cl_2 (3 mL) was added DIAD (0.1 g, 0.5 mmol) at room temperature. After 1 h at the same temperature, the reaction mixture was concentrated in vacuo and directly purified by flash column chromatography (8:1 hexane/EtOAc) to give dihydro-DIAD contaminated D-PhthN-*O*-Arg(Cbz)$_2$-O*t*-Bu. A solution of dihydro-DIAD contaminated D-PhthN-*O*-Arg(Cbz)$_2$-O*t*-Bu in 50% TFA in CH_2Cl_2 was stirred for 1.5 h, and then the solution was concentrated in vacuo. The concentration step was repeated several times to remove residual TFA, and then the crude product was purified by short column chromatography (5:1 to 1:1 hexane/EtOAc) to give **22** in 75% yield as a white solid: mp 66 °C; $[\alpha]_D$ +37.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.48 (bs, 1 H), 7.89−7.76 (m, 4 H), 7.44−7.22 (m, 10 H), 5.26 (s, 2 H), 5.12 (d, 1 H, J = 12.5 Hz), 5.05 (d, 1 H, J = 12.5 Hz), 4.95−4.85 (m, 1 H), 4.21−4.08 (m, 2 H), 2.15−1.92 (m, 4 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.8, 163.5, 162.3, 159.8, 155.6, 136.4, 134.8, 134.5, 128.7, 128.6, 128.4, 128.3, 127.9, 123.8, 84.9, 69.3, 67.4, 44.3, 28.1, 23.9. Anal. Calcd for $C_{30}H_{28}N_4O_9$: C, 61.22; H, 4.80; N, 9.52. Found: C, 61.20; H, 4.85; N, 9.51.

***tert*-Butyl (*R*)-5-(*tert*-butyldimethylsilyloxy)-2-(2-nitrobenzenesulfonylaminooxy)pentanoate (23a).** To a stirred solution of **21** (0.45 g, 1.0 mmol) was added $NH_2NH_2{\cdot}H_2O$ (0.20 g, 4.0 mmol) at room temperature. After 15 min at the same temperature, the solvent was remove under reduced pressure. Residual solid was dissolved in 3% Na_2CO_3 and the solution was extracted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give an aminooxy ester, which was used for the next reaction without further purification. The solution of an aminooxy ester, 2-nitrobenzenesulfonyl chloride (0.25 g, 1.1 mmol), and collidine (145 μL) in DMF (600 μL) was stirred for 17 min at room temperature. The reaction was quenched with brine and extracted with EtOAc. The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (6:1 hexane/EtOAc) to give **23a** in 60% yield as a yellow solid: mp 68 °C; $[\alpha]_D$ −115.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 8.19 (d, 1 H, J = 7.9 Hz), 7.93−7.89 (d, 1 H, J = 7.3 Hz), 7.85−7.74 (m, 2 H), 4.55 (dd, 1 H, J = 4.2, 8.1 Hz), 3.62 (t, 2 H, J = 5.9 Hz), 1.93−1.80 (m, 1 H), 1.71−1.57 (m, 3 H), 1.49 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.3, 148.7, 134.9, 133.6, 132.9, 130.5, 125.7, 84.8, 82.5, 62.1, 28.5, 28.2, 27.5, 26.0, 18.4, −5.2. Anal. Calcd for $C_{21}H_{36}N_2O_8SSi$: C, 49.98; H, 7.19; N, 5.55. Found: C, 49.97; H, 7.23; N, 5.51.

***tert*-Butyl (*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-(benzyloxycarbonylaminooxy)pentanoate (23b).** The solution of an aminooxy ester from the previous experiment (0.44 g, 1.0 mmol), benzyloxycarbonyl chloride (0.19 g, 1.1 mmol), and DIEA (245 μL) in CH_2Cl_2 (500 μL) was stirred for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (6:1 hexane/EtOAc) to give **23b** in 93% yield as an oil: $[\alpha]_D$ +52.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.36 (s, 5 H), 5.24−5.08 (m, 2 H), 4.28 (dd, 1 H, J = 4.3, 7.9 Hz), 3.64−3.58 (m, 2 H), 1.98−1.50 (m, 4 H), 1.46 (s, 9 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.0, 156. 9, 135.7, 128.7, 128.5, 128.4, 83.8, 82.2, 67.6, 62.2, 28.3, 28.2, 27.4, 26.0, 18.4, −5.2. Anal. Calcd for $C_{23}H_{39}NO_6Si$: C, 60.89; H, 8.67; N, 3.09. Found: C, 60.81; H, 8.69; N, 3.13.

***tert*-Butyl (*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-(fluorenylmethoxycarbonylaminooxy)pentanoate (23c).** The solution of an aminooxy ester from the previous experiment (0.44 g, 1.0 mmol), FMOC-OSu (0.35 g, 1.04 mmol) and DIEA (180 μL) in CH_2Cl_2 (500 μL) was stirred for 1 h at room temperature. The reaction was diluted with CH_2Cl_2, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (10:1 hexane/EtOAc) to give **23c** in 81% yield as an oil: $[\alpha]_D$ +39.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.73 (d, 2 H, J = 7.4 Hz), 7.65 (d, 2 H, J = 7.4 Hz), 7.40−7.22 (m, 4 H), 4.45 (d, 2 H, J = 6.9 Hz), 4.27−4.21 (m, 2 H), 3.62 (bs, 2 H), 2.01−1.50 (m, 4 H), 1.48 (s, 9 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.0, 156.9, 143.5, 141.3, 127.8, 127.1, 125.0, 120.0, 83.7, 82.1, 67.4, 62.2, 47.0, 28.1, 27.4, 25.9, 18.2, −5.2. Anal. Calcd for $C_{30}H_{43}NO_6Si$: C, 66.51; H, 8.00; N, 2.59. Found: C, 66.52; H, 8.01; N, 2.61.

D-Ns-N-*O*-Pro-OH (24a). To a stirred solution of **23a** (0.28 g, 0.5 mmol) in $CHCl_3$ (5 mL) was added $BF_3{\cdot}Et_2O$ (0.12 g, 0.8 mmol) at room temperature. After 1 h at the same temperature, the reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$, H_2O, and brine sequentially, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (2:1 to 1:2 hexane/EtOAc) to give a TBDMS deprotected **23a** in 51% yield as a solid: mp 95−97 °C; $[\alpha]_D$ −143.4 (*c* 1.07, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 8.23−8.18 (m, 1 H), 7.94−7.90 (m, 1 H), 7.85−7.77 (m, 2 H), 4.58 (dd, 1 H, J = 4.2, 8.2 Hz), 3.68 (dd, 1 H, J = 5.9, 6.2 Hz), 1.92−1.67 (m, 4 H), 1.50 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.2, 148.6, 135.1, 133.5, 133.0, 130.2, 125.7, 84.8, 82.7, 62.0, 28.3, 28.1, 27.4. Anal. Calcd for $C_{15}H_{22}N_2O_8S$: C, 46.15; H, 5.68; N, 7.18. Found: C, 46.12; H, 5.78; N, 7.19.

To a stirred solution of a TBDMS deprotected **23b** (90 mg, 0.2 mmol), PPh_3 (80 mg, 0.3 mmol) in CH_2Cl_2 (1 mL) was added DIAD (70 mg, 0.3 mmol) at 20 °C. After 1 h at the same temperature, the reaction mixture was concentrated in vacuo and directly purified by flash column chromatography (3:1 hexane/EtOAc) to give dihydro-DIAD contaminated D-Ns-N-*O*-Pro-O*t*-Bu. A solution of dihydro-DIAD contaminated D-Ns-N-*O*-Pro-O*t*-Bu in 50% TFA in CH_2Cl_2 was stirred for 1 h, and then the solution was concentrated in vacuo. The concentration step was repeated several times to remove residual TFA, and then the crude product was purified by short column chromatography (1:1 hexane/EtOAc to 1:1 EtOAc/MeOH) to give **24a** in 85% yield as a white solid: mp 125−126 °C; $[\alpha]_D$ +32.6 (*c* 0.5, MeOH); ^{1}H NMR (250 MHz, CD_3CO_2D) δ 8.19 (d, 1 H, J = 7.6 Hz), 7.89−7.66 (m, 3 H), 4.72−4.62 (m, 1 H), 3.70−3.55 (m, 1 H), 3.24−3.08 (m, 1 H), 2.00−1.73 (m, 4 H); ^{13}C NMR (62.5 MHz, CD_3CO_2D) δ 174.1, 150.2, 136.3, 134.1, 132.3, 127.9, 125.0, 80.1, 48.4, 26.8, 23.1. Anal. Calcd for $C_{11}H_{12}N_2O_7S$: C, 41.77; H, 3.82; N, 8.86. Found: C, 41.79; H, 3.77; N, 0.8.79

D-Cbz-N-*O*-Pro-OH (24b). To a stirred solution of **23b** (0.23 g, 0.5 mmol) in $CHCl_3$ (3 mL) was added $BF_3{\cdot}Et_2O$ (0.11 g, 0.8 mmol) at room temperature. After 1 h at the same temperature, the reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$, H_2O and brine sequentially, dried ($MgSO_4$), and concentrated to give a TBDMS deprotected **23b** in 75% yield as an oil: $[\alpha]_D$ +69.2 (*c* 1.02, $CHCl_3$);^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.36 (s, 5 H), 5.24−5.08 (m, 2 H), 4.35 (dd, 1 H, J = 3.8, 8.1 Hz), 3.68 (bs, 2 H), 1.99−1.72 (m, 4 H), 1.47 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.0, 157.3, 135.5, 128.5,

128.4, 128.3, 83.9, 82.3, 67.5, 62.0, 28.3, 28.0, 27.6. Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.14; H, 7.45; N, 4.10.

To a stirred solution of a TBDMS deprotected **23b** (0.12 g, 0.3 mmol), PPh_3 (0.13 g, 0.5 mmol) in CH_2Cl_2 (3 mL) was added DIAD (0.11 g, 0.5 mmol) at 20 °C. After 1 h at the same temperature, the reaction mixture was concentrated in vacuo and directly purified by flash column chromatography (6:1 hexane/EtOAc) to give D-Cbz-N-*O*-Pro-O*t*-Bu in 87% yield as an oil: $[\alpha]_D$ +11.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5 H), 5.24 (d, 1 H, J = 12.4 Hz), 5.16 (d, 1 H, J = 12.4 Hz), 4.30 (dd, 1 H, J = 3.5, 9.1 Hz), 3.96−3.87 (m, 1 H), 3.49−3.38 (m, 1 H), 2.04−1.65 (m, 4 H), 1.46 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.9, 155.3, 135.9, 128.3, 127.9, 127.7, 81.9, 78.5, 67.6, 45.7, 27.8, 26.3, 21.6. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.53; H, 7.21; N, 4.49.

A solution of D-Cbz-N-*O*-Pro-O*t*-Bu (0.10 g, 0.3 mmol) in 50% TFA in CH_2Cl_2 was stirred for 1 h, and then the solution was concentrated in vacuo. The concentration step was repeated several times to remove residual TFA to give **24b** in 97% yield as a sticky solid: $[\alpha]_D$ +30.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 (s, 5 H), 5.21 (s, 2 H), 4.59 (t, 1 H, J = 5.3 Hz), 3.80−3.55 (m, 2 H), 2.22−2.01 (m, 2 H), 1.83−1.70 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3, 155.6, 135.5, 128.6, 128.4, 128.1, 78.8, 68.3, 45.9, 25.8, 21.6. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.86; H, 5.76; N, 5.23.

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