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Efficient Synthesis of Enantiomerically Pure β^2-Amino Acids via Chiral Isoxazolidinones

Hee-Seung Lee,† Jin-Seong Park,‡
Byeong Moon Kim,‡ and Samuel H. Gellman*,†

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706-1396, and School of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

gellman@chem.wisc.edu

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Abstract: We report a practical and scalable synthetic route for the preparation of α-substituted β-amino acids (β^2-amino acids). Michael addition of a chiral hydroxylamine, derived from α-methylbenzylamine, to an α-alkylacrylate followed by cyclization gives a diastereomeric mixture of α-substituted isoxazolidinones. These diastereomers are separable by column chromatography. Subsequent hydrogenation of the purified isoxazolidinones followed by Fmoc protection affords enantiomerically pure Fmoc-β^2-amino acids, which are useful for β-peptide synthesis. This route provides access to both enantiomers of a protected β^2-amino acid.

β-Amino acids have long been employed as precursors for β-lactams and other medicinally important molecules.[1,2] More recently, β-amino acids have gained attention as building blocks for oligomers with well-defined folding behavior (foldamers).[3] Short β-amino acid oligomers (β-peptides) can take on a variety of secondary structures; the substitution patterns of the individual residues within a β-peptide are critical determinants of the folding pattern.[4]

Seebach et al. have pioneered the use of monosubstituted β-amino acids to create β-peptide foldamers.[5] Oligomers containing exclusively β-substituted β-amino acids (β^3-amino acids) or exclusively α-substituted β-amino acids (β^2-amino acids) tend to adopt the 14 helix, which is defined by 14-membered ring C═O(*i*)- -H—N(*i* − 2) hydrogen bonds. Oligomers containing both β^2- and β^3-amino acid residues can form the 10/12 helix, a very different conformation that contains two distinct types of backbone hydrogen bonds.[6] Di-β-peptide segments containing a β^3-residue followed by a β^2-residue, with the appropriate relative configurations, adopt a reverse turn conformation. Seebach et al. have developed somatostatin mimics based on this turn motif.[7]

Our group's β-peptide studies began with conformationally preorganized residues, e.g., β-amino acids rigidified by small rings.[8] We have shown that these residues confer unique properties on β-peptides, including high conformational stability in aqueous solution and folding patterns that are inaccessible without backbone constraints.[9] β-Peptides containing both cyclically constrained residues and acyclic β^3-residues combine the conformational stability provided by the former with the ease of the side-chain introduction provided by the latter.[10] This synergy should extend to mixtures of constrained and β^2-residues. Furthermore, combining β^2-residues, β^3-residues, and constrained residues in a single sequence should provide great versatility in orienting specific sets of side chains along a folded β-peptide scaffold. Exploration of these latter two possibilities has been hampered, however, because β^2-amino acids are more difficult to prepare than are β^3-amino acids.

β^3-Amino acids are readily available from the corresponding α-amino acids via Arndt—Eistert methodology.[11] This simple and enantiospecific route provides access to building blocks with a wide range of side chains. Several routes to β^2-amino acids have been reported,[12] but none is as efficient or general as the Arndt—Eistert route to

† University of Wisconsin.
‡ Seoul National University.

(1) For reviews on the synthesis of β-amino acids, see: (a) *Enantioselective Synthesis of β-amino acids*; Juaristi, E., Ed.; Wiley—VCH: New York, 1997. (b) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983.

(2) (a) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479. (b) Floreancig, P. E.; Swalley, S. E.; Trauger, J. W.; Dervan, P. B. *J. Am. Chem. Soc.* **2000**, *122*, 6342. (c) Reinelt, S.; Merce, M.; Dedier, S.; Reitinger, T.; Folkers, G.; Lopez de Castro, J. A.; Rognan, D. *J. Biol. Chem.* **2001**, *276*, 24525. (d) For biologically active β-peptides, see: Werder, M.; Hausre, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774. Hamuro, Y.; Schneider, J. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 12200. Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.

(3) For reviews, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905. (c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (d) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.

(4) DeGrado, W. F.; Schneider, J. P.; Hamuro, Y. *J. Pept. Res.* **1999**, *54*, 206.

(5) (a) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. (b) Hintermann, T.; Seebach, D. *Synlett* **1997**, 437.

(6) (a) Seebach, D.; Schreiber, J. V.; Abele, S. *Helv. Chim. Acta* **2000**, *83*, 34. (b) Schreiber, J. V.; Seebach, D. *Helv. Chim. Acta* **2000**, *83*, 3139.

(7) (a) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1595. (b) Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. *J. Med. Chem.* **2001**, *44*, 2460.

(8) (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071. (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381. (c) Wang, X.; Espinosa, J. F.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 4821. (d) Lee, H.-S.; LePlae, P. R.; Porter, E. A.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 3597. (e) LePlae, P. R.; Umezawa, N.; Lee, H.-S.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 5629.

(9) Lee, H.-S.; Syud, F. A.; Wang, X.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 7721.

(10) LePlae, P. R.; Fisk, J. D.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 6820.

(11) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 187.

(12) (a) For use of Evans' chiral auxiliary, see: Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093. Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2141. Micuch, P.; Seebach, D. *Helv. Chim. Acta* **2002**, 85, 1567. Sibi, M. P.; Deshpande, P. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1461. (b) For use of Oppolzer's sultam, see: Posinet, R.; Chassaing, G.; Vaissermann, J.; Lavielle, S. *Eur. J. Org. Chem.* **2000**, 83. (c) For use of pseudoephedrin, see: Myers, A.; Schnider, P.; Kwon, S.; Kung, D. *J. Org. Chem.* **1999**, *64*, 3322. Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527. (d) For use of chiral pyrimidinone, see: Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723. (e) For C—H activation, see: Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197.

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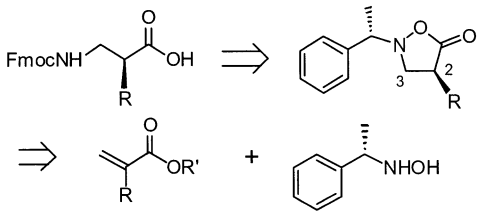
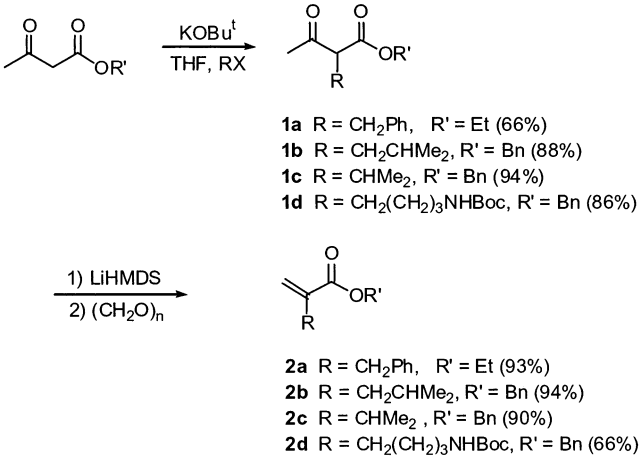
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Preparation of α-Alkylacrylates



β^3-amino acids. Most reported routes to β^2-amino acids involve chiral auxiliaries, the removal of which requires basic or acidic conditions. Epimerization at the α-position can arise under basic conditions. The acidic removal conditions preclude the use of acid-labile protecting groups for side-chain functionality, like Boc, which are convenient when Fmoc-based oligomer synthesis is planned.

We present a new route to β^2-amino acids that offers significant advantages relative to the existing methods. Our approach is outlined in Scheme 1. The enantiomerically pure Fmoc-β^2-amino acid is envisioned to arise from the corresponding isoxazolidinone via hydrogenolysis, which removes the chiral auxiliary and cleaves the N−O bond without any possibility of racemization, followed by N-protection. The α-substituted isoxazolidinone intermediate should be available from the appropriate α-alkylacrylate ester and enantiomerically pure α-methylbenzylhydroxylamine. Related routes have been used for the stereoselective preparation of β^3- and $\beta^{2,3}$-amino acids, although in some cases the chiral auxiliary has been linked to the acrylate, via esterification, rather than to the hydroxylamine.[13] Baldwin and Aubé were the first to employ a chiral hydroxylamine for isoxazolidinone synthesis, but these workers examined only β-substituted acrylate substrates.[13b] We explored the reaction of a chiral hydroxylamine that is readily available in enantiomerically pure form with achiral α-substituted acrylates because we anticipated that this approach would provide access to protected β^2-amino acids with protein-like side chains.

Scheme 2 summarizes the synthesis of α-alkylacrylate esters in which the α-substituent will ultimately become the side chain of the β^2-amino acid. Monoalkylation of acetoacetate esters with various alkyl halides (RX) gave **1a**−**d** in moderate to good yields. Deprotonation followed by the addition of paraformaldehyde afforded the desired α-alkylacrylates **2a**−**d** in good yields.[14]

Scheme 3 outlines the preparation of four Fmoc-β^2-amino acids bearing side chains found on proteinogenic α-amino acids. Ethyl α-benzylacrylate (**2a**) was treated with (*S*)-α-methylbenzylhydroxylamine oxalic acid salt (**3**)[15] and triethylamine in refluxing ethanol to give adduct **4a** as the major product (72%) along with a diastereomeric mixture of the isoxazolidinones **5a** and **6a** (17%). Hydroxylamine adducts analogous to **4a** with β-substituents rather than α-substituents are known to cyclize to the corresponding isoxazolidinones in some cases,[13b] but the in situ cyclization of **4a** was sluggish. We could obtain the α-substituted isoxazolidinone mixture **5a**/**6a** efficiently via the reaction of **4a** with a base (LHMDS) or a Lewis acid (*n*-Bu_2SnO). The treatment of **4a** with LHMDS in THF at −78 °C for 10 min gave mixture **5a**/**6a** in excellent yield (92%) but with little diastereoselectivity (**5a**/**6a** = 1.5:1). Alternatively, refluxing **4a** in benzene with *n*-Bu_2SnO provided the mixture **5a**/**6a** in excellent yield (99%) but again with little diastereoselectivity (**5a**/**6a** = 1.5:1). Fortunately, the isoxazolidinones **5a** and **6a** (and the other isoxazolidinone mixtures we examined, **5b**−**d**/**6b**−**d**) proved to be very easy to separate preparatively via column chromatography. The ^{1}H NMR analysis of the α-substituted isoxazolidinones such as **5a** and **6a** was hampered by nitrogen inversion, which is slow on the NMR time scale at rt.[13a] Enantiomeric excesses of these and the other isoxazolidinones discussed below were readily determined via chiral HPLC (Chiralcel OD column) after diastereomer separation by preparative chromatography (99% de). The isoxazolidinones **5a** and **6a** are precursors to the Fmoc-β^2-phenylalanine enantiomers **7a** and **8a**, and it is valuable to have access to both β^2-amino acid enantiomers from a single preparation.

Low yields were obtained when the route in Scheme 3 was pursued by starting with ethyl α-isopropylacrylate (i.e., the ethyl ester analogue of **2c**). Switching to the benzyl ester **2c**[13d] significantly improved the reaction efficiency. We found that changing the solvent from ethanol to DMF and running the reaction at rt gave the intermediate **4c** exclusively (no isoxazolidinone byproducts). Use of the benzyl ester in place of the ethyl ester enhanced the subsequent cyclization reaction to produce **5c**/**6c**, presumably because benzyloxy is a better leaving group than ethoxy. Another benefit of the switch to the benzyl ester is that the acrylate intermediate is less volatile, which simplifies product isolation after the reactions outlined in Scheme 2.

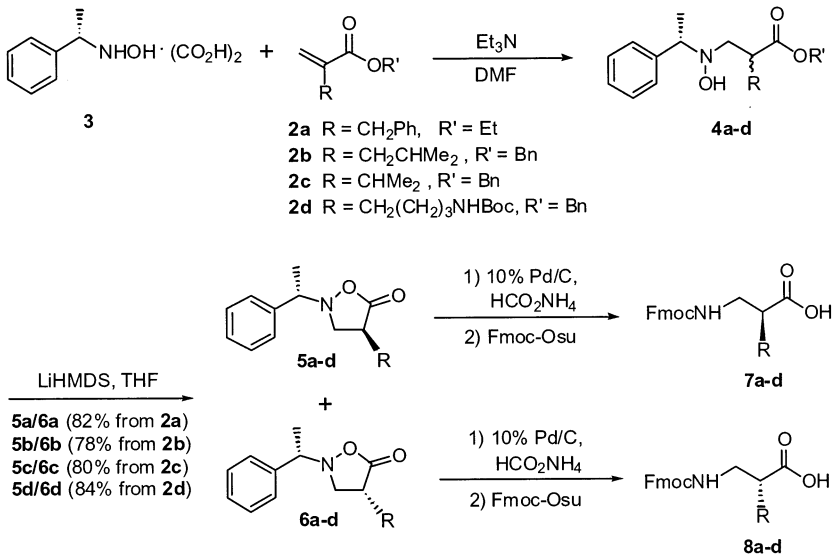
Th intermediates **4b**−**d**, as diastereomeric mixtures, were treated with LHMDS in THF at −78 °C to give the

(13) (a) Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363. (b) Baldwin, S. W.; Aubé, J. *Tetrahedron Lett.* **1987**, *28*, 179. (c) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1995**, 1171. (d) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1998**, 1291. (e) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456. (f) Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *2*, 3393.

(14) Ueno, Y.; Setoi, H.; Okawara, M. *Tetrahedron Lett.* **1978**, *39*, 3753.

(15) (a) Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, *9*, 1299. (b) Traber, B.; Jung, Y.-G.; Park, T. K.; Hong, J.-I. *Bull. Korean Chem. Soc.* **2001**, *22*, 547.

SCHEME 3. Synthetic Route for Either Enantiomer of Fmoc-β^2-amino Acids



SCHEME 4. Alternative Route for Fmoc-β^2-homovaline-OH

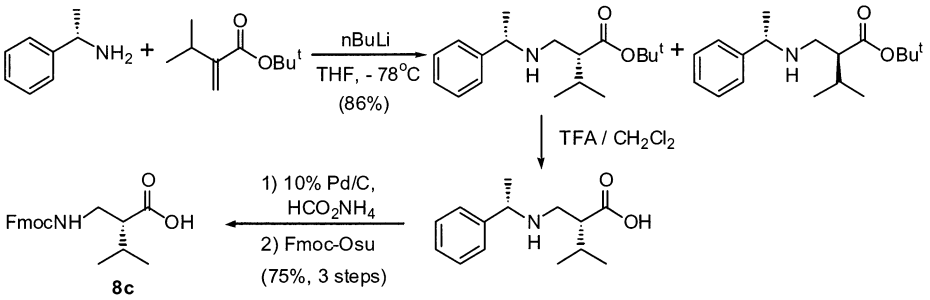


TABLE 1. Determination of Absolute Configuration

	yield (%)[a]	$[\alpha]^{25}_D$ (observed)	$[\alpha]^{rt}_D$ (literature)
7a	82	+11.8	+8.2 (**7a**, *c* 0.91, $CHCl_3$)[b]
7b	80	+10.8	+10.8 (**7b**, *c* 0.6, $CHCl_3$)[b]
8c	84	−12.1	+11.5 (**7c**, *c* 0.97, $CHCl_3$)[b]
8d	78	−4.6	+4.8 (**7d**, *c* 0.54, $CHCl_3$)[c]

[a] Yield from **5** or **6**. [b] Reference 11. [c] Reference 7b.

isoxazolidinone mixtures **5b−d/6b−d** in excellent yield (>95%). Transfer hydrogenolysis of the isolated α-substituted isoxazolidinone isomers with 10% Pd/C and ammonium formate in refluxing methanol led to efficient N−O bond cleavage and removal of the α-methylbenzyl group to give the corresponding β^2-amino acids. N-protection then provided the desired Fmoc-β^2-amino acids. The absolute configurations of the Fmoc-β^2-amino acids were established by the comparison of the optical rotations with the values reported in the literature (Table 1). In each case, the isoxazolidinone retrospectively assigned to series **5** eluted more rapidly during preparative chromatography than did the diastereomer assigned to series **6**.

In the case of Fmoc-β^2-homovaline, we examined an alternate synthetic route (Scheme 4) that is based on chemistry reported by Davies and Fenwick.[16] In this case, we used enantiomerically pure α-methylbenzylamine as the nucleophile rather than the corresponding hydroxylamine, and we used the *tert*-butyl ester form of the acrylate. The Michael adducts were formed in an approximate 1:1 ratio, but as observed with the isoxazolidinones, the diastereomeric products were readily separated by preparative chromatography. Acid treatment removed the *tert*-butyl esters of the isolated diastereomers. Hydrogenolysis then removed the chiral auxiliary, and N-protection provided the desired product. This route may be a useful alternative to the one shown in Scheme 3 for β^2-amino acid derivatives that do not bear acid-labile protecting groups in their side chains.

We have developed an efficient synthetic route that provides both enantiomers of Fmoc-β^2-amino acids. The reaction sequence can be run on a reasonably large scale, and this route can therefore conveniently support exploratory β-peptide studies. The ready availability of α-acrylate esters such as **2a−d** should allow one to generate a wide range Fmoc-β^2-amino acids, including versions that contain functional groups with acid-labile protection in the side chains [exemplified by Fmoc-β^2-(ϵ-*N*-Boc)homolysine]. This route avoids expensive chiral auxiliaries and potential epimerization problems. Our method is complementary to an elegant approach recently reported by Davies and Venkataramani that involves asymmetric C−H insertion and gives access to β^2-amino acids bearing aryl and vinyl side chains.[12e] The broad range of Fmoc-β^2-amino acids available through our route

(16) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109.

and that of Davies and Venkataramani should provide access to new β-peptides with specific shapes and specific functions.

Experimental Section

General Procedures. Melting points were determined on a capillary melting-point apparatus and are uncorrected. Optical rotations were measured using sodium light (D line, 589.3 nm). THF was distilled from sodium benzophenone ketyl under N_2. Unless otherwise noted, all other commercially available reagents and solvents were used without further purification. Analytical thin-layer chromatography (TLC) was carried out on Whatman TLC plates precoated with silica gel 60 (250-μm layer thickness). Visualization was accomplished using either a UV lamp, potassium permanganate stain (2 g of $KMnO_4$, 13.3 g of K_2CO_3, 3.3 mL of 5% (w/w) NaOH, and 200 mL of H_2O), or phosphomolybdic acid stain (10% phosphomolybdic acid in ethanol). Column chromatography was performed on EM Science silica gel 60 (230−400 mesh). The solvent mixtures used for TLC and column chromatography are reported in v/v ratios. Diastereomeric excesses of **5a**−**d** and **6a**−**d** were determined by chiral HPLC (250 × 4.6 mm Chiralcel OD column, 1.0 mL/min).

A representative synthetic procedure is provided below. Other procedures may be found in the Supporting Information.

2-Benzyl-3-oxobutyric Acid Ethyl Ester (1a). To a suspension of *t*-BuOK (8.8 g, 76.8 mmol) in THF (200 mL) were added ethyl acetoacetate (9.6 mL, 75.3 mmol) and *t*-BuOH (7.0 mmol) at 0 °C. The resulting clear solution was stirred for 30 min, and then benzyl bromide (8.9 mL, 74.8 mmol) was added to the solution. The solution was stirred at 70 °C for 12 h. The reaction was quenched with water, and then a saturated aqueous sodium bicarbonate solution was added. The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. The crude product was purified by silica gel column chromatography (1:10 EtOAc/hexanes, $R_f = 0.18$) to give **1a** (10.9 g) in 66% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.31−7.16 (m, 5H), 4.05 (q, $J_{HH} = 7.2$ Hz, 2H), 3.78 (t, $J_{HH} = 7.5$ Hz, 1H), 3.16 (d, $J_{HH} = 7.5$ Hz, 2H), 2.18 (s, 3H), 1.20 (t, $J_{HH} = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 202.37, 169.09, 138.14, 128.76, 128.54, 126.64, 110.10, 61.43, 61.31, 33.97, 29.56, 13.99. ESI−MS *m*/*z*: 243.0 (M + Na, calcd 243.1), 463.1 (2M + Na, calcd 463.2).

2-Benzylacrylic Acid Ethyl Ester (2a). To a stirred solution of compound **1a** (6.60 g, 30.0 mmol) in THF (200 mL) was added LHMDS (33.0 mL, 33.0 mmol, and 1.0 M solution in THF) at −78 °C. The solution was stirred for 30 min, and then paraformaldehyde (4.2 g, excess) was added as a solid in one portion. The resulting suspension was stirred at rt for 6 h and then filtered through Celite to remove the excess paraformaldehyde. The filtrate was concentrated, and the residue was purified by column chromatography (1:19 EtOAc/hexanes, $R_f = 0.37$) to give **2a** (5.3 g) in 93% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34−7.20 (m, 5H), 6.25 (t, $J_{HH} = 0.6$ Hz, 1H), 5.46 (m, 1H), 4.20 (q, $J_{HH} = 7.2$ Hz, 2H), 3.65 (s, 2H), 1.28 (t, $J_{HH} = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 166.87, 140.38, 138.77, 129.02, 128.35, 126.26, 125.90, 60.69, 38.05, 14.11. ESI−MS *m*/*z*: 213.1 (M + Na, calcd 213.1).

4-Benzyl-2-[(1*S*)-phenylethyl]isoxazolidin-5-one (5a/6a). To a stirred solution of **2a** (4.95 g, 26.0 mmol) in DMF (100 mL) were added (1*S*)-phenylethylhydroxylamine oxalate (**3**;[15a] 11.8 g, 52.0 mmol) and triethylamine (36.2 mL, 260 mmol) at rt. The resulting clear solution was stirred at rt for 24 h. The resulting cloudy suspension was concentrated via vacuum-rotary evaporation and then purified by column chromatography on silica gel (1:10 EtOAc/hexanes, $R_f = 0.12$) to afford **4a** (7.31 g) as a colorless oil in 86% yield. This material was dissolved in THF (100 mL), the solution was cooled to −78 °C, and then LHMDS (24.5 mL, 24.5 mmol, 1.0 M solution in THF) was added. The yellow solution was stirred at −78 °C for 30 min. Water (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give a crude diastereomeric mixture of isoxazolidinones as a yellow oil. The mixture could be separated by column chromatography on silica gel [5 (diameter) × 20 (height) cm column, 1:10 EtOAc/hexanes] to afford **5a** (3.76 g) and **6a** (2.51 g), each in diastereomerically pure form and in 82% overall yield from **2a**. The diastereomeric excesses (de) were determined by chiral HPLC (250 × 4.6 mm Chiralcel OD column, 1.0 mL/min, 2:98 2-propanol/hexanes); $t_R = 15.69$ min (**5a**) and $t_R = 20.53$ min (**6a**).

(4*S*)-Benzyl-2-[(1*S*)-phenylethyl]isoxazolidin-5-one (5a). 99% de. $R_f = 0.23$ (1:10 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 600 MHz, 54 °C) δ: 7.40−7.10 (10H), 3.95 (s, 1H), 3.50−3.10 (br, 3H), 3.05 (m, 1H), 2.80 (s, 1H), 1.40 (br s, 3H). ESI−MS *m*/*z*: 304.1 (M + Na, calcd 304.1), 585.3 (2M + Na, calcd 585.3).

(4*R*)-Benzyl-2-[(1*S*)-phenylethyl]isoxazolidin-5-one (6a). 99% de. $R_f = 0.17$ (1:10 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 600 MHz, 54 °C) δ: 7.40−7.10 (10H), 3.95 (s, 1H), 3.42 (br, 1H), 3.20 (s, 1H), 3.10 (m, 1H), 2.95 (s, 1H), 2.80 (m, 1H), 1.30 (br s, 3H). ESI−MS *m*/*z*: 304.1 (M + Na, calcd 304.1), 585.3 (2M + Na, calcd 585.3).

(2*S*)-Benzyl-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-propionic Acid (Fmoc-(*S*)-β^2-HPhe-OH; 7a). Isoxazolidinone **5a** (3.00 g, 10.7 mmol) was dissolved in methanol (50 mL). Ammonium formate (6.7 g, 107 mmol) and 10% Pd/C (1.0 g) were added to the solution. The mixture was stirred at 60 °C for 2 h. After the reaction was complete (the disappearance of starting material was monitored by TLC), the resulting mixture was filtered through Celite, and the filtrate was concentrated to give a white solid. The crude amino acid was characterized but not purified. ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.28−7.16 (m, 5H), 3.21 (m, 1H), 2.89−2.60 (m, 4H). ESI−MS *m*/*z*: 178.1 (M − H, calcd 178.1).

The crude solid was dissolved in 1:1 THF/H_2O (100 mL) and cooled to 0 °C, and then Fmoc-OSu (3.6 g, 10.7 mmol) and $NaHCO_3$ (9.0 g, 107 mmol) were added. The reaction mixture was stirred at rt for 2 h, and THF was removed under reduced pressure. The aqueous residue was washed with diethyl ether (2 × 50 mL), and the organic layers were discarded. The aqueous layer was acidified with a $NaHSO_4$ solution and extracted with methylene chloride (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (1:50 MeOH/CH_2Cl_2) to afford the desired product **7a** as a white solid (3.52 g, 82.0% yield for two steps). This solid was recrystallized from chloroform/hexane: mp 148−152 °C; $[\alpha]^{25}_D$ +11.8° (*c* 0.91, $CHCl_3$), $[\alpha]^{rt}_D$ +8.2° (**7a**,[11] *c* 0.91, $CHCl_3$). This compound exists as a mixture of slowly interconverting rotamers according to NMR spectroscopy. ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.76 (d, $J_{HH} = 7.2$ Hz, 2H), 7.63 (d, $J_{HH} = 7.5$ Hz, 2H), 7.39−7.16 (m, 9H), 4.31 (d, $J_{HH} = 6.2$ Hz, 2H), 4.18 (t, $J_{HH} = 6.6$ Hz, 1H), 3.40−3.05 (m, 2H), 2.98−2.60 (m, 3H). ^{13}C NMR (CD_3OD, 75.4 MHz) δ: 177.45, 158.70, 145.22, 142.50, 140.13, 129.93, 129.36, 128.70, 128.09, 127.37, 126.15, 120.87, 67.72, 48.36, 43.38, 36.78. ESI−MS *m*/*z*: 178.1 (M − $C_{15}H_{11}O_2$ (Fmoc), calcd 178.1), 400.1 (M − H, calcd 400.2), 801.3 (2M − H, calcd 801.3).

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Supporting Information Available: Experimental procedures for **1b**−**d**, **2b**−**d**, **5b**−**d**/**6b**−**d**, **7b**, **8c**, and **8d** and ^{1}H NMR and ^{13}C NMR spectra of compounds **1**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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