JOC Article
pubs.acs.org/joc

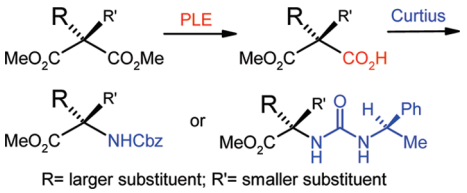
Enantioselective Synthesis of α-Quaternary Amino Acid Derivatives by Sequential Enzymatic Desymmetrization and Curtius Rearrangement of α,α-Disubstituted Malonate Diesters

Violeta Iosub, Anton R. Haberl, Jennifer Leung, Michael Tang, Kannan Vembaiyan, Masood Parvez, and Thomas G. Back*

Department of Chemistry, University of Calgary, Calgary, AB, Canada, T2N 1N4

tgback@ucalgary.ca

Received December 6, 2009



A convenient and versatile enantioselective synthesis of biologically important α-quaternary amino acid derivatives was based on the sequential double alkylation or arylation of dimethyl malonate, followed by desymmetrization with porcine liver esterase (PLE) and Curtius rearrangement. The PLE-mediated hydrolysis of the prochiral dialkylated malonate diesters produced the corresponding chiral half-esters in high yield and with enantiomeric excesses of 43% to >98%. Curtius rearrangement of the latter products, after trapping of the intermediate isocyanates with benzyl alcohol or amines, afforded the corresponding Cbz-protected amino esters or ureas. The absolute configurations of the major products in five examples were established by conversion to compounds with known specific rotations, or by X-ray crystallography of derivatives obtained with chiral amines of known configuration.

Introduction

Peptides and proteins perform myriad structural, signaling, regulatory, and catalytic functions in biological systems and are fundamental components of living organisms. Moreover, the amino acids from which they are composed also serve as biosynthetic and synthetic precursors of numerous alkaloids and other secondary metabolites that are of additional importance in biology and medicine.[1] It is remarkable that such structural complexity and functional diversity is achieved in nature with only 20 proteinogenic amino acids.[2] However, there is growing interest in the construction of designer peptides and proteins that incorporate modified amino acids in order to alter their structural properties, interactions with ligands, and rates of metabolic degradation in biological systems. Since all of the proteinogenic amino acids except glycine contain a single α-substituent, α,α-disubstituted (quaternary) derivatives comprise a potentially useful class of compounds for the preparation of modified peptides and proteins not found in nature. Furthermore, the synthesis of alkaloids and other products containing α-quaternary amine moieties is particularly challenging because the efficient installation of such centers is often precluded by steric constraints. Thus, there is considerable interest in novel methodologies for the efficient enantioselective synthesis of α-quaternary amino acid derivatives.[3]

During our recent enantioselective synthesis of the antiviral alkaloid (−)-virantmycin and its antipode,[4] we employed a

*To whom correspondence should be addressed. Fax: 403-289-9488. Tel: 403-220-6256.

(1) (a) Cordell, G. A. *Introduction to Alkaloids—A Biogenetic Approach*; Wiley: New York, 1981. (b) Dewick, P. M. *Medicinal Natural Products—A Biosynthetic Approach*; Wiley: Chichester, 1997.

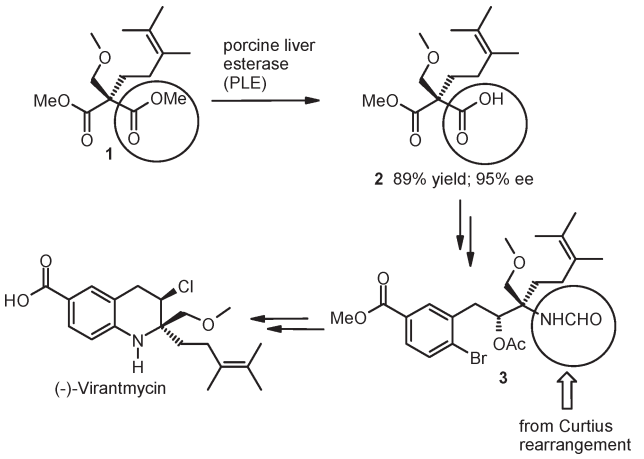
(2) It can be argued that in addition to the 20 classical natural amino acids, several other less common ones such as selenocysteine are also proteinogenic.

(3) For reviews, see: (a) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1–63. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732. (d) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599. (e) Calaza, M. I.; Cativiela, C. *Eur. J. Chem.* **2008**, 3427–3448. (f) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764–1766. (g) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430. (h) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127–5143.

(4) Back, T. G.; Wulff, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6493–6496.

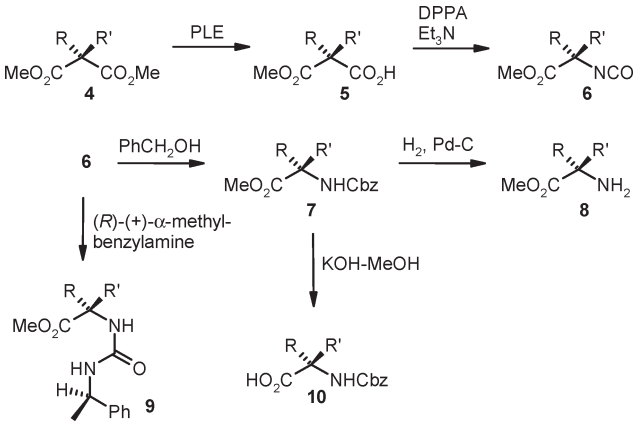
Published on Web 02/04/2010 DOI: 10.1021/jo902584r

SCHEME 1



highly efficient desymmetrization of the α,α-dialkylated malonate diester derivative **1** by porcine liver esterase (PLE) in 95% enantiomeric excess (ee) in order to establish the key stereocenter. The free carboxylic acid group in the resulting half-ester **2** was eventually converted into the corresponding formamide **3** by a stereospecific Curtius rearrangement and finally into the desired product by an intramolecular Buchwald−Hartwig aryl amination, followed by additional functional group modifications (Scheme 1). This suggested that the combination of enzymatic desymmetrization of a disubstituted malonate diester with PLE, followed by Curtius rearrangement, might serve as an exceptionally simple and effective general method for the enantioselective preparation of α-quaternary amino acid derivatives. In addition to the transformations shown in Scheme 1, a few other isolated examples of this and related approaches have been reported. Thus, Kedrowski[5] prepared (*R*)- and (*S*)-2-methylcysteine in 91% ee from desymmetrized dimethyl α-methyl-α-*tert*-butylthiomethylmalonate, while Honda et al.[6] converted diethyl 2-cyclohexene-1,1-dicarboxylate into the corresponding amino ester in 64% ee. The diastereoselective PLE-mediated hydrolysis of a chiral *β*-vinylcyclopropane diester has been employed in the preparation of the corresponding amino acid, but afforded a poor diastereomeric excess (de).[7] In a different approach, α-quaternary amino acid derivatives have been prepared by the Curtius rearrangement of malonate half-esters derivatized with camphor- and menthol-based chiral auxiliaries.[8] We now report

SCHEME 2



our results on the enantioselective preparation of a series of alkyl, cycloalkyl, benzyl, and aryl α,α-disubstituted amino acids by the sequential application of PLE desymmetrization and Curtius rearrangement.

Results and Discussion

The use of PLE for the hydrolytic desymmetrization of prochiral diesters has been extensively investigated.[9] A model of the binding site proposed by Jones et al.[10] provides the means for predicting the configurations of the products, based chiefly on the difference in size of the two α-substituents. Furthermore, Björkling et al.[11] noted that the absolute configurations of α-methyl-α-*n*-alkyl-substituted half-esters changed from *S* to *R* as the second α-substituent increased in length from ethyl to *n*-heptyl, with crossover taking place between the *n*-butyl and *n*-pentyl derivatives. They also observed that enantioselectivities were generally considerably higher with dimethyl than with diethyl esters.

The results from the desymmetrization of a series of variously α,α-disubstituted malonate dimethyl esters **4** are shown in Scheme 2 and Table 1. In general, good to excellent isolated yields of the half-esters **5** were obtained and ee values were measured in entries 1−6 by NMR integration of generally well-separated methyl ester signals of diastereomeric salts produced with (*R*)-(+)-α-methylbenzylamine. In each case, the NMR spectrum was compared with that of the corresponding mixture of diastereomers obtained from racemic **5** (produced by nonenzymatic hydrolysis of **4** with KOH) and (*R*)-(+)-α-methylbenzylamine in order to confirm that the correct signals were being integrated in the enantioselective experiments. Poor resolution of relevant signals precluded such measurements for the half-esters **5g**−***l*** in entries 7−12 and these half-esters were therefore subjected to Curtius rearrangement prior to determination of their ee values. In entries 1−3, a methyl group was chosen as the small substituent, while the larger substituent was varied. The linear *n*-hexyl group of **4a** afforded a higher ee than the branched isopropyl substituent of **4b** (entries 1 and 2),

(5) Kedrowski, B. L. *J. Org. Chem.* **2003**, *68*, 5403–5406.
(6) Honda, T.; Koizumi, T.; Komatsuzaki, Y.; Yamashita, R.; Kanai, K.; Nagase, H. *Tetrahedron: Asymmetry* **1999**, *10*, 2703–2712.
(7) Fliche, C.; Braun, J.; Le Goffic, F. *Synth. Commun.* **1994**, *24*, 2873–2876.
(8) (a) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Nitsuma, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 525–535. (b) Ihara, M.; Takahashi, M.; Nitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Org. Chem.* **1989**, *54*, 5413–5415.
(9) For reviews, see: (a) Domínguez de Maria, P.; García-Burgos, C. A.; Bargeman, G.; van Gemert, R. W. *Synthesis* **2007**, 1439–1452. (b) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis: Regio- and Stereoselective Biotransformations*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 5. (c) Gais, H. J.: Theil, F. In *Enzyme Catalysis in Organic Synthesis*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Vol. 2, Chapter 11. (d) Tamm, C. *Pure Appl. Chem.* **1992**, *64*, 1187–1191. (e) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140. (f) Boland, W.; Frö*β*l, C.; Lorenz, M. *Synthesis* **1991**, 1049–1072. (g) Jones, J. B. *Aldrichim. Acta* **1993**, *26*, 105–112. (h) Jones, J. B. *Can. J. Chem.* **1993**, *71*, 1273–1282. (i) Jones, J. B. *Pure Appl. Chem.* **1990**, *62*, 1445–1448. (j) Zhu, L. M.; Tedford, M. C. *Tetrahedron* **1990**, *46*, 6587–6611. (k) Ohno, M.; Otsuka, M. *Org. React.* **1989**, *37*, 1–55.
(10) (a) Provencher, L.; Jones, J. B. *J. Org. Chem.* **1994**, *59*, 2729–2732. (b) Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946–4952. (c) Provencher, L.; Wynn, H.; Jones, J. B.; Krawczyk, A. R. *Tetrahedron: Asymmetry* **1993**, *4*, 2025–2040. (d) Toone, E. J.; Jones, J. B. *Tetrahedron: Asymmetry* **1991**, *2*, 1041–1052.
(11) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**, *41*, 1347–1352.

TABLE 1. Preparation of Half-Esters and α-Quaternary Amino Acid Derivatives

			yield[a] (ee or de)		
entry	R	R'	half-ester **5**[b]	product **7** or **9**[c]	derivative **8** or **10**[d]
1	$CH_3(CH_2)_5$	Me	**5a** 85 (67)	**7a** 61	**8a** 68 (68)
2	i-Pr	Me	**5b** 82 (42)	**7b** 82 (37)	
3	Me	$HC{\equiv}CCH_2$	**5c** 85 (63)	**7c** 63 (63)	**10c** 66 (61)
4	Cy[e]	Me	**5d** 94 (> 98)	**9d** 52 (> 98)	
5	$CyCH_2$[e]	Et	**5e** 84 (> 98)	**9e** 78 (> 98)	
6	Ph	Me	**5f** 90 (> 98)	**7f** 45	**10f** 70 (96 or 89)
7	$PhCH_2$	Et	**5g** 98	**9g** 70 (52)	
8	$PhCH_2$	*n*-Pr	**5h** 76	**9h** 92 (79)	
9	$PhCH_2CH_2$	Me	**5i** 94	**7i** 67	**10i** 59
				9i 78 (80)	
10	$PhCH_2CH_2$	Et	**5j** 98	**9j** 70 (93)	
11	$PhCH_2CH_2$	*n*-Pr	**5k** 89	**9k** 84 (94)	
12	$PhCH_2CH_2$	*n*-Bu	***5l*** 87	***9l*** 74 (> 98)	

[a]Isolated yields are reported. [b]Enantiomeric excesses (ee) were measured by NMR integration of salts formed with (*R*)-(+)-α-methylbenzylamine, unless otherwise indicated. [c]Enantiomeric excesses (ee) of **7b** and **7c** were measured by HPLC with a chiral column. Diastereomeric excesses (de) of **9** were measured by NMR integration. [d]Enantiomeric excesses were measured as follows: **8a**: NMR integration of salt formed with (*R*)-(−)-*O*-acetylmandelic acid; **10c**: NMR integration of salt formed with (*R*)-(+)-α-methylbenzylamine; **10f and 10i**: comparison of specific rotation to literature values.[16,17] [e]Cy = cyclohexyl.

suggesting that chain length is more important than branching for high enantioselectivity. Surprisingly, however, the linear three-carbon propargyl group of **4c** in entry 3 also provided higher enantioselectivity than the isopropyl substituent of **4b**. Entries 4−6 indicate that structures **4d**−**f**, containing bulky cyclohexyl, cyclohexylmethyl, or phenyl groups, respectively, along with smaller methyl or ethyl groups, afforded single enantiomers of **5d**−**f**, within the limits of detection by NMR spectroscopy.

Porcine pancreatic lipase (PPL) has also been used to desymmetrize prochiral diesters,[12] but appears to have been less thoroughly investigated than PLE for this purpose. Like PLE, PPL is commercially available, inexpensive, and convenient to use. We hoped that complementarity between the two enzymes might permit improvement in the enantioselectivities of examples where PLE was only marginally successful. Unfortunately, attempts at the partial hydrolysis of diesters **4a** and **4b** with PPL Type (II) afforded essentially racemic mixtures of the corresponding half-esters **5a** and **5b**. Thus, PLE proved the more generally efficacious of the two enzymes for the present transformations.

The Curtius rearrangements of **5a**−***l*** were effected with diphenylphosphoryl azide (DPPA).[13,14] The intermediate isocyanates **6** were treated with benzyl alcohol or (*R*)-(+)-α-methylbenzylamine to afford the corresponding *N*-Cbz-protected amino esters **7** or ureas **9**, respectively, which proved easier to isolate than the corresponding primary amines obtained by hydrolysis of **6**. The unusually poor yield of **7f** was attributed to facile decarboxylation during the Curtius rearrangement, as methyl 2-phenylpropanoate was observed as a significant byproduct of this step. Moreover, urea derivatives of amino acids are of special interest, as ureidopeptides can be exploited in the design of new foldamers and other structural motifs.[15] Certain ureidopeptides display potentially useful medicinal properties such as protease inhibition.[15d] We were surprised to note that in compounds **5i**−***l***, where R = phenethyl (entries 9−12), the ee values of products **9i**−***l*** rose as the size of the second substituent R′ increased from methyl to *n*-butyl. This was in contrast to the expectation that enantioselectivities would be enhanced with growing disparity between the size of the two α-substituents. The possibility of kinetic resolution of the enantiomers of the corresponding isocyanates **6** upon treatment with (*R*)-(+)-α-methylbenzylamine was ruled out by treating the racemic isocyanates with the chiral amine and observing equal amounts of the two diastereomeric products in the resulting ^{1}H NMR spectra.

The absolute configurations of the major products (*R*)-**5a**,[11] (*R*)-**5f**,[10d] (*S*)-**10f**,[16a,b] and (*S*)-**10i**[17] were established by comparison of their specific rotations with literature values. X-ray crystallography provided the absolute configurations of the major product (*S*,*S*)-**11e**, formed from isocyanate **6e** and (*S*)-(−)-1-(1-naphthyl)ethylamine (Scheme 3), and of the minor diastereomer (*S*)-**5g** in the form of its salt with

(12) For examples of PPL-mediated desymmetrizations of prochiral diesters, see: (a) Nakazawa, K.; Hayashi, M.; Tanaka, M.; Aso, M.; Suemune, H. *Tetrahedron: Asymmetry* **2001**, *12*, 897–901. (b) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Tetrahedron: Asymmetry* **1996**, *7*, 345–348. (c) Cotterill, I. C.; Cox, P. B.; Drake, A. F.; Le Grand, D. M.; Hutchinson, E. J.; Latouche, R.; Pettman, R. B.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3071–3075. (d) Hultin, P. G.; Mueseler, F.-J.; Jones, J. B. *J. Org. Chem.* **1991**, *56*, 5375–5380. (e) Guibé-Jampel, E.; Rousseau, G.; Salaün, J. J. *Chem. Soc., Chem. Commun.* **1987**, 1080–1081.

(13) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.

(14) For another particularly mild method for converting carboxylic acids, including racemic malonate half-esters, into *t*-Boc-protected amines, see: (a) Lebel, H.; Leogane, O. *Org. Lett.* **2005**, *7*, 4107–4110. (b) Leogane, O.; Lebel, H. *Synthesis* **2009**, 1935–1940. For other recent methods for effecting Curtius rearrangements, see references cited therein.

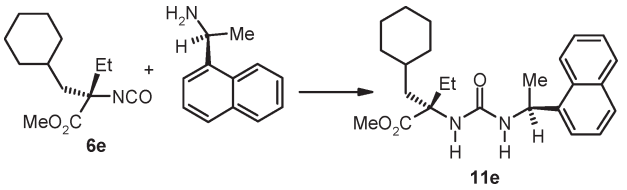
(15) For example, see: (a) Fischer, L.; Didierjean, C.; Jolibois, F.; Semetey, V.; Lozano, J. M.; Briand, J.-P.; Marraud, M.; Poteau, R.; Guichard, G. *Org. Biomol. Chem.* **2008**, *6*, 2596–2610. (b) Violette, A.; Averlant-Petit, M. C.; Semetey, V.; Hemmerlin, C.; Casimir, R.; Graff, R.; Marraud, M.; Briand, J.-P.; Rognan, D.; Guichard, G. *J. Am. Chem. Soc.* **2005**, *127*, 2156–2164. (c) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J.-P.; Marraud, M.; Guichard, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1893–1895. (d) Zhang, X.; Rodrigues, J.; Evans, L.; Hinkle, B.; Ballantyne, L.; Peña, M. *J. Org. Chem.* **1997**, *62*, 6420–6423.

(16) (a) Charette, A. B.; Mellon, C. *Tetrahedron* **1998**, *54*, 10525–10535. (b) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 563–580.

(17) Polese, A.; Formaggio, F.; Crisma, M.; Bonora, G. M.; Toniolo, C.; Broxterman, Q. B.; Kamphuis, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 833–838.

(18) For a general review, see: (a) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971; Chapter 7. For examples of stereochemical studies of the Curtius rearrangement, see : (b) van Well, R. M.; Overkleeft, H. S.; van Boom, J. H.; Coop, A.; Wang, J. B.; Wang, H.; van der Marel, G. A.; Overhand, M. *Eur. J. Org. Chem.* **2003**, *9*, 1704–1710. (c) Hocking, M. B. *Can. J. Chem.* **1968**, *46*, 2275–2282. (d) Denmark, S. E.; Dorow, R. L. *J. Org. Chem.* **1989**, *54*, 5–6.

SCHEME 3



(*R*)-(+)-α-methylbenzylamine (see the Experimental Section and Supporting Information).

The reliable retention of configuration associated with the Curtius rearrangement[18] permits correlation of the absolute configurations of the above products with their respective derivatives in entries 1, 5, 6, 7, and 9. Thus, the dominant enantiomers of **5a**, **5e**, **5f**, **5g**, and **5i** are all assigned the (*R*)-configuration and **7a**, **8a**, **9e**, **11e**, **7f**, **10f**, **9g**, **7i**, **9i**, and **10i** all possess the (S)-configuration.[19] We observed that the optical rotations of all of the half-esters in Table 1 were dextrorotatory, except for **5c**. Thus, by analogy with **5a**, **5e**, **5f**, **5g**, and **5i**, the major enantiomers of the other dextrorotatory half-esters are also assigned the *R*-configuration. This is also consistent with predictions based on the Jones model of PLE, where placement of the larger and smaller α-substituents (R and R′, respectively, in Scheme 2) in the hydrophobic pockets of corresponding size in the active site of the enzyme results in selective ester hydrolysis leading to the (*R*)-half esters. The anomalous levorotatory behavior of **5c** is attributed to the *S*-configuration of its dominant enantiomer, where R = Me and R′ = propargyl in Scheme 2 and Table 1. This in turn is consistent with the previous observation by Björkling et al.,[11] that the PLE desymmetrization of homologuous α-methyl-α-*n*-alkyl diesters produced predominantly the exceptional *S*-enantiomers when the second alkyl substituent was ethyl, *n*-propyl, or *n*-butyl (vide supra). The parallel behavior of the unbranched three-carbon propargyl substituent and the *n*-propyl group is therefore not surprising.

It is worth noting that in our earlier synthesis of (−)-virantmycin, the same desymmetrized malonate half-ester **2** could be converted into (+)-*ent*-virantmycin by protection of the free carboxyl group, saponification of the remaining methyl ester, and eventual Curtius rearrangement of the newly liberated carboxylic acid. A similar protocol can therefore be envisaged for the preparation of the enantiomers of the amino acid derivatives listed in Table 1.

In conclusion, the enantioselective synthesis of α-quaternary amino acid derivatives from prochiral disubstituted malonate diesters can be achieved conveniently, effectively, and often with high ee and predictable absolute configuration by employing PLE desymmetrizations in conjunction with stereospecific Curtius rearrangements.

Experimental Section

All NMR spectra were recorded in deuteriochloroform at 200, 300 or 400 MHz (^{1}H), or at 50, 75 or 100 MHz (^{13}C). Mass spectra were obtained by standard EI or CI techniques as indicated. Chiral HPLC was performed on a Chiralcel OB, 250 × 4.6 mm column; solvent: 5:95 isopropanol/hexanes, 0.5 mL/min; UV detector: 210 nm. PLE[20,21] (lyophilized powder; 17 units/mg) and PPL (Type II, 100−400 units/mg) were purchased from the Sigma Co.

Malonate diesters **4a**,[11] **4b**,[10c] **4c**,[22] **4f**,[10d] and **4g**[23] are known compounds. The preparation of the novel derivative **4d** is provided below. Compounds **4e** and **4h**−***l*** were prepared as in the sample procedure for **4d**.

Preparation of α,α-Dialkylated Dimethyl Malonates. Typical Procedure: Dimethyl 2-Cyclohexyl-2-methylmalonate (4d). Dimethyl 2-cyclohexylmalonate (0.106 g, 0.495 mmol) was added dropwise to a solution of sodium hydride (0.029 g, 60% dispersion in mineral oil, 0.72 mmol) in 20 mL of THF at 0 °C under nitrogen. The mixture was stirred for 20 min and then methyl iodide (0.060 mL, 0.96 mmol) was added. The mixture was refluxed for 5 h. It was then quenched with water and extracted with ether. The ether layer was washed with saturated solutions of ammonium chloride, sodium thiosulfate, and brine, dried, and concentrated in vacuo. Flash chromatography (ethyl acetate: hexanes, 5:95) afforded 0.107 g (95%) of **4d** as a pale yellow oil: IR (film)1735 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.71 (s, 6 H), 2.15 (tt, J = 12.0, 2.9 Hz, 1 H), 1.78−1.74 (m, 2 H), 1.69−1.66 (m, 1 H), 1.59−1.56 (m, 2 H), 1.35 (s, 3 H), 1.34−1.29 (m, 2 H), 1.13−1.05 (m, 3 H); ^{13}C NMR (75 MHz) δ 172.5, 58.0, 52.5, 42.9, 28.4, 26.8, 26.5, 16.4; mass spectrum (CI) (*m*/*z*, %) 229 (12, M^+ + H), 246 (100, M^+ + NH_4). HRMS (CI) calcd for $C_{12}H_{21}O_4$ 229.1440 (M^+ + H), found 229.1448. When the reaction was scaled up to 1.80 g, the crude product was obtained in similar yield and was of sufficient purity for further use without the need for chromatographic purification.

Dimethyl 2-Cyclohexylmethyl-2-ethylmalonate (4e). Pale yellow oil; IR (film) 1742 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.68 (s, 6 H), 1.95 (q, J = 7.6 Hz, 2 H), 1.83 (d, J = 6.0 Hz, 2 H), 1.64−1.53 (m, 5 H), 1.30−1.03 (m, 4 H), 0.98−0.85 (m, 2 H), 0.78 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 172.7, 57.2, 52.1, 39.0, 34.1, 33.3, 26.3, 26.1, 25.7, 8.7; mass spectrum (CI), (*m*/*z*, %) 257 (47, M^+ + H), 274 (100, M^+ + NH_4). HRMS (CI) calcd for $C_{14}H_{25}O_4$: 257.1753 (M^+ + H), found 257.1754.

Dimethyl 2-Benzyl-2-*n*-propylmalonate (4h). Pale yellow oil; IR (film) 1738 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.24−7.19 (m, 3 H), 7.04−7.01 (m, 2 H), 3.68 (s, 6 H), 3.22 (s, 2 H), 1.76−1.70 (m, 2 H), 1.32−1.24 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.0, 136.4, 130.0, 128.5, 127.1, 59.2, 52.4, 38.5, 34.3, 17.8, 14.4; mass spectrum (EI), (*m*/*z*, %) 264 (38, M^+), 204 (93), 91 (100). HRMS (EI) calcd for $C_{15}H_{20}O_4$ 264.1362 (M^+), found 264.1350.

Dimethyl 2-Methyl-2-(2-phenethyl)malonate (4i). Colorless oil; IR (film) 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.33−7.12 (m, 5 H), 3.71 (s, 6 H), 2.62−2.48 (m, 2 H), 2.24−2.09 (m, 2 H), 1.49 (s, 3 H); ^{13}C NMR (75 MHz) δ 172.5, 141.3, 128.4, 128.3, 126.0, 53.6, 52.4, 37.6, 30.8, 20.1; mass spectrum (CI) (*m*/*z*, %) 251 (12, M^+ + H), 268 (100, M^+ + NH_4). HRMS (CI) calcd for $C_{14}H_{19}O_4$ 251.1283 (M^+ + H), found 251.1285.

(19) Note that replacement of the carboxyl group in half-esters **5** by a free or protected amino group with retention of configuration changes the absolute configuration from *R* to *S* because the amino group has a higher priority than the carboxyl group as assigned by the Cahn−Ingold−Prelog rules.

(20) PLE consists of several isozymes, which display different enantioselectivities. While individual isozymes have been obtained by cloning and recombinant expression methods, and may offer advantages over the commercial product, the accessibility and convenience of the latter make it desirable for synthetic applications such as those reported herein.

(21) For lead references to studies of PLE isozymes, see: (a) Hummel, A.; Brüsehaber, E.; Böttcher, D.; Trauthwein, H.; DodererK.; Bornscheuer, U. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8492–8494. (b) Hermann, M.; Kietzmann, M. U.; Ivančić, M.; Zenzmaier, C.; Luiten, R. G. M.; Skranc, W.; Wubbolts, M.; Winkler, M.; Birner-Gruenberger, R.; Pichler, H.; Schwab, H. J. *Biotechnology* **2008**, *133*, 301–310.

(22) Neumeier, R.; Kramp, W.; Maecke, H. R. Eur. Pat. Appl. 417870, 1991; *Chem. Abstr.* **1991**, *115*, 255826.

(23) Björkling, F.; Norin, T.; Szmulik, P.; Boutelje, J.; Hult, K.; Kraulis, P. *Biocatalysis* **1987**, *1*, 87–98.

Dimethyl 2-Ethyl-2-(2-phenethyl)malonate (4j). Colorless oil; IR (film) 1752 cm^{-1}; ^1H NMR (300 MHz) δ 7.27−7.15 (m, 5 H), 3.70 (s, 6 H), 2.52−2.46 (m, 2 H), 2.21−2.16 (m, 2 H), 2.02 (q, J = 7.5 Hz, 2 H), 0.86 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.2, 141.5, 128.5, 128.4, 126.2, 58.2, 52.4, 34.1, 30.7, 25.9, 8.7; mass spectrum (EI) (m/z, %) 264 (2, M^+), 173 (13), 160 (100). HRMS (EI) calcd for $C_{15}H_{20}O_4$ 264.1362 (M^+), found 264.1375.

Dimethyl 2-(2-Phenethyl)-2-*n*-propylmalonate (4k). Colorless oil; IR (film) 1732 cm^{-1}; ^1H NMR (300 MHz) δ 7.28−7.14 (m, 5 H), 3.70 (s, 6 H), 2.50−2.45 (m, 2 H), 2.20−2.15 (m, 2 H), 1.95−1.89 (m, 2 H), 1.25−1.20 (m, 2 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.4, 141.6, 128.7, 128.6, 126.3, 57.9, 52.6, 35.3, 34.7, 30.9, 17.8, 14.6; mass spectrum (EI) (m/z, %) 279 (8, $M^+ + H$), 296 (100, $M^+ + NH_4$). HRMS (EI) calcd for $C_{16}H_{22}O_4$ 278.1518 (M^+), found 278.1525.

Dimethyl 2-*n*-Butyl-2-(2-phenethyl)malonate (4l). Colorless oil; IR (film) 1735 cm^{-1}; ^1H NMR (300 MHz) δ 7.29−7.17 (m, 5 H), 3.73 (s, 6 H), 2.54−2.48 (m, 2 H), 2.23−2.18 (m, 2 H), 2.00−1.95 (m, 2 H), 1.38−1.31 (m, 2 H), 1.23−1.15 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.4, 141.6, 128.62, 128.56, 126.3, 57.8, 52.6, 34.6, 32.8, 30.9, 26.5, 23.1, 14.1; mass spectrum (CI) (m/z, %) 293 (15, $M^+ + H$), 310 (100, $M^+ + NH_4$). HRMS (EI) calcd for $C_{17}H_{24}O_4$ 292.1675 (M^+), found 292.1669.

PLE-Mediated Hydrolysis of α,α-Dialkylated Dimethyl Malonates. Typical Procedure: 2-*n*-Hexyl-2-methylmalonic Acid Monomethyl Ester (5a).[11] Diester **4a** (437 mg, 1.90 mmol) in 28 mL of DMSO was added to 109 mL of 0.2 M sodium phosphate buffer (pH 8). PLE (58 mg) was dissolved in a minimum amount of the buffer solution, which was then added to the DMSO solution of **4a**. The mixture was stirred for 27 h at room temperature. It was then acidified with 1 M HCl and extracted with ether. The organic fractions were filtered through Celite and then extracted with saturated sodium bicarbonate solution. The aqueous layer was reacidified with 1 M HCl and extracted again with ether. The combined organic phases were dried and concentrated in vacuo to yield 351 mg (85%) of **5a** as a colorless oil; IR (film) 1739, 1711 cm^{-1}; ^1H NMR (300 MHz) δ 3.76 (s, 3 H), 1.94−1.84 (m, 2 H), 1.44 (s, 3 H), 1.35−1.19 (m, 8 H), 0.88 (t, J = 6.7 Hz, 3 H); $[\alpha]^{20}_D$ +1.7 (c 9.7, chloroform). The ee (67%) was measured by integration of well-separated methyl ester signals in the ^1H NMR spectrum of an equimolar mixture of **5a** and *R*-(+)-α-methylbenzylamine. Lit.[11] $[\alpha]_D$ +1.1; ee 87%.

A racemic sample of **5a** was prepared as follows. Diester **4a** (215 mg, 0.933 mmol) was dissolved in 5 mL of methanol, and 2.5 mL of 10% aqueous KOH was added. After 6 h, TLC showed the disappearance of starting material and the solution was partitioned between ether and 10% NaOH. The aqueous layer was acidified with use of 1 M HCl and extracted with dichloromethane. The combined organic phases were dried and concentrated in vacuo to afford 89 mg (44%) of the racemic half-ester **5a** as a yellow oil with NMR spectra identical with those of the sample prepared by PLE hydrolysis. Racemic half-ester **5a** was treated with an equimolar amount of *R*-(+)-α-methylbenzylamine to ensure that NMR signals from the resulting diastereomers were well-separated and identified unequivocally.

Compounds **5b**−***l*** were prepared similarly. Their characterization data and any significant differences in their methods of preparation are provided below. The ee values of **5b**−**f** were determined similarly by NMR integration of their salts with *R*-(+)-α-methylbenzylamine. In each case a racemic sample was also prepared for comparison.

2-Isopropyl-2-methylmalonic Acid Monomethyl Ester (5b).[10c] The PLE hydrolysis was performed for 27 h to afford 82% of **5b** as a colorless oil; IR (film) 1734, 1713 cm^{-1}; ^1H NMR (200 MHz) δ 3.76 (s, 3 H), 2.47 (septet, J = 6.7 Hz, 1 H), 1.38 (s, 3 H), 0.97 (d, J = 6.2 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H); $[\alpha]^{20}_D$ +0.88 (c 2.5, chloroform); ee 42%. Lit.[10c] for the (*R*)-enantiomer: $[\alpha]^{25}_D$ ~0 (c 1.3, chloroform); ee 6%.

2-Methyl-2-propargylmalonic Acid Monomethyl Ester (5c).[24] The PLE hydrolysis was performed for 7 h to afford 85% of **5c** as a colorless oil; IR (film) 1734, 1717 cm^{-1}; ^1H NMR (200 MHz) δ 3.79 (s, 3 H), 2.82 (crude t, J = 2.7 Hz, 2 H), 2.07 (crude t, J = 2.7 Hz, 1 H), 1.61 (s, 3 H). $[\alpha]^{20}_D$ −1.3 (c 4.6, chloroform); ee 63%; determined from NMR analysis of the 2-methyl signal.

2-Cyclohexyl-2-methylmalonic Acid Monomethyl Ester (5d). The PLE hydrolysis was performed over 2 d to afford 94% of **5d** as a brown oil; IR (film) 1738, 1708 cm^{-1}; ^1H NMR (400 MHz) δ 3.76 (s, 3 H), 2.13−2.06 (m, 1 H), 1.80−1.58 (m, 5 H), 1.40 (s, 3 H), 1.31−1.26 (m, 2 H), 1.14−1.10 (m, 3 H); ^{13}C NMR (100 MHz) δ 177.3, 172.9, 58.1, 52.8, 43.5, 28.4, 28.3, 26.79, 26.78, 26.4, 16.5; mass spectrum (CI), (m/z, %) 215 (3, $M^+ + H$), 232 (100, $M^+ + NH_4$). HRMS (CI) calcd for $C_{11}H_{19}O_4$ 215.1283 ($M^+ + H$), found 215.1292. $[\alpha]^{20}_D$ +6.0 (c 4.0, chloroform); ee >98%.

2-Cyclohexylmethyl-2-ethylmalonic Acid Monomethyl Ester (5e). The PLE hydrolysis was performed over 5 d to afford 84% of **5e** as a brown oil; IR (film) 1735, 1705 cm^{-1}; ^1H NMR (300 MHz) δ 11.97 (br s, 1 H), 3.82 (s, 3 H), 2.01−1.97 (m, 2 H), 1.89−1.80 (m, 2 H), 1.70−1.40 (m, 5 H), 1.18−1.10 (m, 4 H), 0.87−0.81 (m, 2 H), 0.80 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 176.5, 174.8, 57.2, 52.6, 41.2, 34.0, 33.82, 33.78, 28.4, 26.2, 26.1, 26.0, 9.0; mass spectrum (CI) (m/z, %) 243 (5, $M^+ + H$), 260 (100, $M^+ + NH_4$). HRMS (CI) calcd for $C_{13}H_{23}O_4$ 243.1596 ($M^+ + H$), found 243.1608. $[\alpha]^{20}_D$ +8.5 (c 1.8, chloroform); ee >98%.

2-Methyl-2-phenylmalonic Acid Monomethyl Ester (5f).[10d] The PLE hydrolysis was performed over 4 d to afford 90% of **5f** as a brown oil; ^1H NMR (300 MHz) δ 7.38 (m, 5 H), 3.83 (s, 3 H), 1.93 (s, 3 H); $[\alpha]^{20}_D$ +10.1 (c 8.20, chloroform); ee >98%. Lit.[10d] for the (*R*)-enantiomer: $[\alpha]^{25}_D$ +9.7 (c 3.1, chloroform); ee 81%.

2-Benzyl-2-ethylmalonic Acid Monomethyl Ester (5g). The PLE hydrolysis was performed over 4 d to afford 98% of **5g** as a colorless oil; IR (film) 1732, 1709 cm^{-1}; ^1H NMR (300 MHz) δ 11.28 (br s, 1 H), 7.25−7.23 (m, 3 H), 7.10−7.08 (m, 2 H), 3.75 (s, 3 H), 3.32 (d, J = 13.8 Hz, 1 H), 3.17 (d, J = 13.8 Hz, 1 H), 1.95 (m, 2 H), 0.93 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 175.8, 173.3, 135.7, 129.6, 128.4, 127.2, 59.9, 52.7, 39.6, 27.0, 9.1; mass spectrum (EI) (m/z, %) 236 (14, M^+), 160 (70), 91 (100). HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1048 (M^+), found 236.1035. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.28; H, 6.93. $[\alpha]^{20}_D$ +1.6 (c 6.1, chloroform).

The product was mixed with (*R*)-(+)-α-methylbenzylamine in the molar ratio of 1:1 and the minor diastereomer of the resulting salt crystallized selectively from dichloromethane. X-ray crystallography (see the Supporting Information) established that this product had the *S* configuration at the quaternary carbon atom. The ^1H NMR spectrum of the crystallized material was compared to that of the original mixture of diastereomers, which confirmed that it was the minor diastereomer. The free carboxylic acid of the crystallized isomer was recovered from its salt with (*R*)-(+)-α-methylbenzylamine by treatment with 10% aqueous HCl and extraction with dichloromethane. The dichloromethane solution was concentrated in vacuo to afford recovered **5g** with $[\alpha]^{20}_D$ −2.0 (c 2.9, chloroform), thus further confirming that the crystallized diastereoisomer was the minor one.

2-Benzyl-2-*n*-propylmalonic Acid Monomethyl Ester (5h). The PLE hydrolysis was performed over 6 d to afford 76% of **5h** as a brown oil; IR (neat) 1735, 1708 cm^{-1}; ^1H NMR (300 MHz) δ 11.21 (br s, 1 H), 7.26−7.22 (m, 3 H), 7.09−7.06 (m, 2 H), 3.75

(24) For a racemic preparation of **5c**, see: Arcadi, A.; Cacchi, S.; Delmastro, M.; Marinelli, F. *Synlett* **1991**, 407–409.

(s, 3 H), 3.33 (d, J = 13.7 Hz, 1 H), 3.16 (d, J = 13.7 Hz, 1 H), 1.93−1.82 (m, 2 H), 1.31−1.24 (m, 2H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 176.1, 173.5, 135.9, 129.7, 128.6, 127.4, 59.6, 53.0, 40.2, 36.1, 18.2, 14.3; mass spectrum (EI) (m/z, %) 250 (40, M^+), 204 (93), 189 (24), 91 (100). HRMS (EI) calcd for $C_{14}H_{18}O_4$ 250.1205 (M^+), found 250.1201. $[\alpha]^{20}_D$ +4.3 (c 5.8, chloroform).

2-Methyl-2-(2-phenethyl)malonic Acid Monomethyl Ester (5i). The PLE hydrolysis was performed over 4 d to afford 94% of **5i** as a brown oil; IR (neat) 1738, 1708 cm^{-1}; ^{1}H NMR (300 MHz) δ 11.87 (s, 1 H), 7.30−7.18 (m, 5 H), 3.75 (s, 3 H), 2.65−2.59 (m, 2 H), 2.23−2.17 (m, 2 H), 1.55 (s, 3 H); ^{13}C NMR (75 MHz) δ 177.5, 172.6, 141.3, 128.6, 128.5, 126.3, 53.9, 52.9, 37.8, 31.1, 20.4; mass spectrum (EI) (m/z, %) 236 (5, M^+), 132 (100), 114 (20), 91 (28). HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1049 (M^+), found 236.1056. $[\alpha]^{20}_D$ +2.19 (c 3.60, chloroform).

2-Ethyl-2-(2-phenethyl)malonic Acid Monomethyl Ester (5j). The PLE hydrolysis was performed over 5 d to afford 98% of **5j** as a brown oil; IR (neat) 1735, 1708 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.28−7.14 (m, 5 H), 3.73 (s, 3 H), 2.57−2.47 (m, 2 H), 2.27−2.19 (m, 2 H), 2.06−1.99 (m, 2 H), 0.88 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz) δ 176.4, 173.8, 141.1, 128.7, 128.6, 126.4, 58.4, 53.0, 35.7, 31.2, 27.9, 9.1; mass spectrum (EI) (m/z, %) 250 (5, M^+), 146 (100), 128 (65). HRMS (EI) calcd for $C_{14}H_{18}O_4$ 250.1205 (M^+), found 250.1213. $[\alpha]^{20}_D$ +23.9 (c 1.50, chloroform).

2-(2-Phenethyl)-2-*n*-propyl Malonic Acid Monomethyl Ester (5k). The PLE hydrolysis was performed over 5 d to afford 89% of **5k** as a colorless oil; IR (neat) 1735, 1708 cm^{-1}; ^{1}H NMR (400 MHz) δ 12.08 (br s, 1 H), 7.31−7.21 (m, 5 H), 3.78 (s, 3 H), 2.63−2.56 (m, 2 H), 2.30−2.24 (m, 2 H), 2.04−1.95 (m, 2 H), 1.33−1.30 (m, 2 H), 0.99 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 177.2, 173.2, 141.1, 128.6, 128.5, 126.3, 57.9, 52.9, 36.4, 35.7, 31.1, 17.9, 14.4; mass spectrum (EI) (m/z, %) 264 (1, M^+), 160 (100), 131 (95), 91 (68). HRMS (CI) calcd for $C_{15}H_{21}O_4$ 265.1440 (M^+ + H), found 265.1437. $[\alpha]^{20}_D$ +9.13 (c 8.00, chloroform).

2-*n*-Butyl-2-(2-phenethyl)malonic Acid Monomethyl Ester (5l). The PLE hydrolysis was performed over 4 d to afford 87% of **5l** as a colorless oil; IR (neat) 1738, 1705 cm^{-1}; ^{1}H NMR (400 MHz) δ 12.01 (br s, 1 H), 7.31−7.20 (m, 5 H), 3.78 (s, 3 H), 2.63−2.56 (m, 2 H), 2.30−2.24 (m, 2 H), 2.06−1.99 (m, 2 H), 1.40−1.35 (m, 2 H), 1.29−1.25 (m, 2 H), 0.95 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz) δ 177.0, 173.4, 141.1, 128.6, 128.5, 126.3, 57.8, 52.9, 35.8, 34.1, 31.1, 26.7, 23.0, 14.0; mass spectrum (EI) (m/z, %) 278 (1, M^+), 174 (100), 131 (88), 91 (55). HRMS (CI) calcd for $C_{16}H_{23}O_4$ [M + H]$^+$ 279.1596, found 279.1587. $[\alpha]^{20}_D$ +16 (c 1.7, chloroform).

PPL-Mediated Hydrolysis of 4a. Diester **4a** (0.409 g, 1.78 mmol) in DMSO (27 mL) was added to 94 mL of 0.2 M sodium phosphate buffer (pH 8). PPL (0.400 g) was dissolved in a minimum amount of buffer solution and added to the DMSO solution. This was stirred for 3 d at room temperature. It was then acidified with 10% HCl solution and extracted with dichloromethane. The organic fractions were filtered through Celite and extracted with sodium bicarbonate. The aqueous layer was acidified to pH ~2 and re-extracted with dichloromethane. The combined organic phases were dried and concentrated in vacuo to yield 82 mg (21%) of racemic **5a**.

The similar hydrolysis of diester **4b** also produced essentially racemic product **5b**.

Curtius Rearrangement with Formation of Cbz Derivatives. Typical Procedure: *N*-Carbobenzyloxy-2-(*n*-hexyl)alanine Methyl Ester (7a). Half-ester **5a** (781 mg, 3.61 mmol) was refluxed in 16 mL of toluene with 0.80 mL (3.7 mmol) of DPPA and 0.50 mL (3.6 mmol) of triethylamine for 2 h. The reaction mixture was cooled to room temperature, followed by the addition of DMAP (196 mg, 1.60 mmol) and benzyl alcohol (0.70 mL, 6.8 mmol). Refluxing was then continued for 6 h. The mixture was partitioned between ether and saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ether, the combined organic layers were dried and concentrated in vacuo to yield 1.02 g of yellow oil. This was purified via silica gel chromatography (hexanes:ethyl acetate, 4:1) to yield 704 mg (61%) of **7a** as a clear oil; IR (neat) 3416, 3358, 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.37−7.30 (m, 5 H), 5.60 (s, 1 H), 5.09 (s, 2 H), 3.74 (s, 3 H), 2.15−2.07 (m, 1 H), 1.80−1.70 (m, 1 H), 1.58 (s, 3 H), 1.33−1.17 (m, 7 H), 1.06−0.96 (m, 1 H), 0.87 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz) δ 174.8, 154.6, 136.7, 128.5, 128.04, 128.01, 66.4, 60.1, 52.6, 37.1, 31.6, 29.2, 24.0, 23.4, 22.6, 14.1; mass spectrum (EI) (m/z, %) 321 (M^+, 1), 262 (12), 218 (24), 154 (55), 91 (100). HRMS (EI) calcd for $C_{16}H_{24}NO_2$ [M^+ − CO_2Me] 262.1807, found 262.1829. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.38; H, 8.42; N, 4.63. $[\alpha]^{20}_D$ +5.9 (c 1.0, chloroform).

The following compounds were prepared similarly to **7a**.

***N*-Carbobenzyloxy-2-(isopropyl)alanine Methyl Ester (7b).** The product was obtained in 82% yield from **5b** by the same procedure used in the preparation of **7a** from **5a**; mp 48−51 °C; IR (film) 3371, 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.37−7.20 (m, 5 H), 5.31 (s, 1 H), 5.09 (s, 2 H), 3.72 (s, 3 H), 2.14 (septet, J = 7.1 Hz, 1 H), 1.57 (s, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (50 MHz) δ 174.0, 155.1, 136.4, 128.5, 128.4, 128.0, 66.5, 63.0, 52.2, 35.2, 18.8, 17.3, 17.2; mass spectrum (EI) (m/z, %) 279 (M^+, 2), 236 (12), 220 (18), 192 (12), 91 (100). HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1471 (M^+), found 279.1455. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.51; H, 7.61; N, 4.90. $[\alpha]^{20}_D$ +8.0 (2.2, chloroform). The ee (37%) was measured by chiral HPLC.

***N*-Carbobenzyloxy-2-(propargyl)alanine Methyl Ester (7c).** The product was obtained as a yellow oil in 63% yield from **5c** by the same procedure used in the preparation of **7a** from **5a**; IR 3296, 1718 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.38−7.29 (m, 5 H), 5.69 (s, 1 H), 5.10 (s, 2 H), 3.74 (s, 3 H), 2.94 (d, J = 1.9 Hz, 2 H), 2.03 (t, J = 2.6 Hz), 1.59 (s, 3 H); ^{13}C NMR (50 MHz) δ 173.1, 154.7, 136.2, 128.4, 128.0, 127.9, 79.1, 71.3, 66.6, 58.6, 52.8, 26.9, 23.1; mass spectrum (EI) (m/z, %) 275 (M^+), 236 (6), 216 (15), 192 (8), 172 (14), 108 (26), 91 (100). HRMS (EI) calcd for $C_{15}H_{17}NO_4$ 275.11576 (M^+), found 275.11582. $[\alpha]^{20}_D$ +7.5 (c 1.3, chloroform). The ee (63%) was measured by chiral HPLC.

***N*-Carbobenzyloxy-2-(phenyl)alanine Methyl Ester (7f).** The product was obtained in 45% yield by the same procedure as for the conversion of **5a** to **7a**; pale yellow oil; IR (film) 3352, 1732 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.46−7.27 (m, 10 H), 6.23 (s, 1 H), 5.06 (d, J = 12.3 Hz, 1 H), 5.02 (d, J = 12.3 Hz, 1 H), 3.67 (s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (100 MHz) δ 173.5, 154.5, 140.5, 136.4, 129.9, 128.7, 128.5, 128.1, 128.0, 125.8, 66.6, 62.0, 53.2, 22.7; mass spectrum (EI) (m/z, %), 313 (2, M^+), 254 (68), 210 (31), 91 (100). HRMS (EI) calcd for $C_{18}H_{19}NO_4$ 313.1314 (M^+), found 313.1313. $[\alpha]^{20}_D$ +41.4 (c, 4.02, chloroform).

***N*-Carbobenzyloxy-2-(2-phenethyl)alanine Methyl Ester (7i).** The product was obtained as a colorless oil in 67% yield from **5i** by the same procedure used in the preparation of **7a** from **5a**; IR (film) 3356, 1725 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.40−7.13 (m,10 H), 5.89 (s, 1 H), 5.13 (s, 2 H), 3.69 (s, 3 H), 2.67−2.43 (m, 3 H), 2.21−2.13 (m, 1 H), 1.65 (m, 3 H); ^{13}C NMR (75 MHz) δ 174.6, 154.6, 141.1, 136.6, 128.6, 128.5, 128.4, 128.2, 128.1, 126.0, 66.5, 59.9, 52.7, 38.3, 30.7, 23.7; mass spectrum (EI) (m/z, %) 341 (1, M^+) 237 (67), 91 (100). HRMS (EI) calcd for $C_{20}H_{23}NO_4$ 341.1627 (M^+), found 341.1643. $[\alpha]^{20}_D$ +19 (c 6.5, chloroform).

Preparation of 2-(*n*-Hexyl)alanine Methyl Ester (8a). The Cbz derivative **7a** (117 mg, 0.364 mmol) was dissolved in 25 mL of methanol containing 10 drops of formic acid and 25 mg of 10% palladium on carbon and stirred under hydrogen (1 atm) for 3 d. The mixture was then filtered through Celite, concentrated in vacuo, dissolved in ether, and washed with 10% NaOH

solution. The ether layer was dried and concentrated in vacuo to afford 46 mg (68%) of **8a** as a yellow oil; IR (neat) 3387, 1735 cm^{-1}; ^1H NMR (200 MHz) δ 3.70 (s, 3 H), 1.67−1.40 (m, 4 H), 1.30 (s, 3 H) superimposed on 1.30−1.05 (m, 8 H), 0.86 (t, $J = 6.4$ Hz, 3 H); ^{13}C NMR (50 MHz) δ 178.1, 57.8, 52.0, 41.1, 31.6, 29.4, 26.3, 24.1, 22.5, 14.0; mass spectrum (EI) (*m*/*z*, %) 128 ($M^+ - CO_2Me$, 100), 102 (30). HRMS (EI) calcd for $C_8H_{18}N$ ($M^+ - CO_2Me$) 128.1439, found 128.1443. $[\alpha]^{20}_D$ +8.0 (*c* 1.8, chloroform). The ee (68%) was measured by integration of well-separated methyl ester signals in the ^1H NMR spectrum of an equimolar mixture of **8a** and *R*-(−)-*O*-acetylmandelic acid. This was compared with a 1:1 mixture of diastereomers prepared similarly from racemic **8a**, in turn obtained from the racemic half-ester **5a**.

Curtius Rearrangement with Formation of Ureas. Typical Procedure: 2-Cyclohexyl-2-[3-(1-phenethyl)ureido]propanoic Acid Methyl Ester (9d). A solution of half-ester **5d** (164 mg, 0.765 mmol), triethylamine (0.16 mL, 1.2 mmol), and DPPA (0.17 mL, 0.79 mmol) in 5 mL of toluene was refluxed for 5 h. It was cooled to room temperature and (*R*)-(+)-α-methylbenzylamine (0.18 mL, 1.4 mmol) was added. The mixture was refluxed an additional 20 h, the solvent was evaporated in vacuo, and the residue was chromatographed (20−30% ethyl acetate−hexanes) to afford 133 mg (52%) of product **9d** as a single diastereomer; white solid, mp 184.5−185.5 °C; IR (film) 3346, 1745, 1635 cm^{-1}; ^1H NMR (300 MHz) δ 7.32−7.24 (m, 5 H), 4.91 (br s, 1 H), 4.88 (d, $J = 6.0$ Hz, 1 H), 4.70−4.66 (quintet, $J = 6.5$ Hz, 1 H), 3.62 (s, 3 H), 1.68−1.57 (m, 4 H), 1.41 (s, 3 H), 1.40 (d, $J = 6.8$ Hz, 3 H), 1.23−0.72 (m, 7 H); ^{13}C NMR (100 MHz) δ 175.2, 157.0, 144.3, 128.9, 127.5, 126.1, 62.9, 52.3, 51.0, 45.7, 27.6, 27.4, 26.61, 26.55, 26.4, 23.9, 19.4; mass spectrum (EI) (*m*/*z*, %) 332 (4, M^+), 273 (12), 126 (66), 102 (100). HRMS (EI) calcd for $C_{19}H_{28}N_2O_3$ 332.2100 (M^+), found 332.2118. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.64; H, 8.49; N, 8.43. Found: C, 68.67; H, 8.38; N, 8.09. $[\alpha]^{20}_D$ +42 (*c* 2.9, chloroform). A sample prepared similarly from racemic **5d** for comparison showed clearly separated methyl ester peaks.

The following compounds were prepared similarly to **9d**.

2-Cyclohexylmethyl-2-[3-(1-phenethyl)ureido]butanoic Acid Methyl Ester (9e). The product was obtained in 78% yield as a single diastereomer from the treatment of half-ester **5e** by the same procedure as for the conversion of **5d** to **9d**; white solid; mp 160−162.5 °C; IR (film) 3316, 1738, 1635 cm^{-1}; ^1H NMR (300 MHz) δ 7.35−7.22 (m, 5 H), 5.47 (s, 1 H), 4.93 (d, $J = 6.6$ Hz, 1 H), 4.68 (quintet, $J = 6.8$ Hz, 1 H), 3.66 (s, 3 H), 2.46−2.29 (m, 2 H), 1.80−1.43 (m, 6 H), 1.42 (d, $J = 6.8$ Hz, 3 H), 1.23−0.77 (m, 6 H), 0.64 (t, J = 7.4 Hz, 3 H, superimposed on m, 1 H); ^{13}C NMR (75 MHz) δ 176.3, 155.8, 144.4, 128.9, 127.5, 126.1, 64.3, 52.6, 50.9, 43.4, 34.3, 34.0, 33.1, 30.0, 26.5, 26.42, 26.39, 23.9, 8.4; mass spectrum (CI) (*m*/*z*, %) 361 (100, $M^+ + H$), 329 (25), 257 (28), 120 (48). HRMS (CI) calcd for $C_{21}H_{33}N_2O_3$: 361.2491 ($M^+ + H$); found: 361.2504. Anal. Calcd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95; N, 7.77. Found: C, 70.03; H, 8.99; N, 7.60. $[\alpha]^{20}_D$ +38 (*c* 3.0, chloroform). A sample prepared similarly from racemic **5e** for comparison showed clearly separated methyl ester peaks.

2-Benzyl-2-[3-(1-phenethyl)ureido]butanoic Acid Methyl Ester (9g). The product was obtained in 70% yield as a mixture of diastereomers from the treatment of half-ester **5g** by the same procedure as for the conversion of **5d** to **9d**; colorless oil; IR (film) 3336, 1738, 1632 cm^{-1}; ^1H NMR (400 MHz) major diastereomer δ 7.35−7.15 (m, 8 H), 7.01−6.92 (m, 2 H), 5.42−5.31 (m, 2 H), 4.79−4.73 (m, 1 H), 3.71 (s, 3 H), 3.66 (d, $J = 14.2$ Hz, 1 H), 3.00 (d, $J = 13.3$ Hz, 1 H), 2.56−2.47 (m, 1 H), 1.81 (sextet, $J = 7.2$ Hz, 1 H), 1.37 (d, $J = 6.9$ Hz, 3 H), 0.68 (t, $J = 7.3$ Hz, 3 H); ^{13}C NMR (100 MHz) both diastereomers: δ 174.4, 174.3, 156.2, 156.1, 145.0, 144.5, 137.1, 130.0, 129.9, 128.63, 128.58, 128.1, 127.1, 126.6, 126.13, 126.05, 66.5, 66.0, 52.4, 50.1, 41.2, 41.0, 29.3, 29.2, 23.43, 23.35, 8.7, 8.6; mass spectrum (CI) (*m*/*z*, %) 355 (100, $M^+ + 1$). HRMS (EI) calcd for $C_{21}H_{26}N_2O_3$ 354.1943 (M^+), found 354.1927. $[\alpha]^{20}_D$ −61 (*c* 7.0, chloroform). The de of 52% was calculated by integration of doublets from the major and minor diastereomers at δ 3.00 and 3.07 ppm, respectively. Their chemical shifts matched those observed in a sample obtained similarly from the racemic half-ester **5g**.

2-Benzyl-2-[3-(1-phenethyl)ureido]pentanoic Acid Methyl Ester (9h). The product was obtained in 92% yield as a mixture of diastereomers from the treatment of half-ester **5h** by the same procedure as for the conversion of **5d** to **9d**; colorless oil; IR (film) 3359, 1742, 1632 cm^{-1}; ^1H NMR (400 MHz) major diastereomer: δ 7.40−7.13 (m, 8 H), 6.95−6.87 (m, 2 H), 5.18 (br s, 1 H), 4.83 (br s, 1 H), 4.79−4.72 (m, 1 H), 3.73 (s, 3 H), 3.70 (d, $J = 13.1$ Hz, 1 H), 3.00 (d, $J = 13.3$ Hz, 1 H), 2.56−2.50 (m, 1 H), 1.79−1.72 (m, 1 H), 1.47−1.42 (m, 1 H), 1.43 (d, $J = 6.8$ Hz, 3 H), 1.30−1.15 (m, 1 H), 0.90−0.84 (m, 3 H); minor diastereomer: 3.07 (d, $J = 13.8$ Hz, 1 H), 1.51 (d, $J = 7.3$ Hz, 3 H); ^{13}C NMR (100 MHz) major diastereomer: δ 174.6, 156.1, 144.9, 137.0, 130.0, 128.6, 128.1, 127.2, 126.6, 126.1, 65.7, 52.5, 50.2, 41.4, 38.4, 23.4, 17.7, 14.1; mass spectrum (CI) (*m*/*z*, %) 369 (100, $M^+ + H$). HRMS (CI) calcd for $C_{22}H_{29}N_2O_3$ 369.2178 ($M^+ + H$), found 369.2168. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.47; H, 7.67; N, 7.36. $[\alpha]^{20}_D$ −62 (*c* 2.1, chloroform). The de of 79% was calculated by integration of the doublets from the major and minor diastereomers at δ 3.00 and 3.07 ppm, respectively. Their chemical shifts matched those observed in a sample obtained similarly from the racemic half-ester **5h**.

2-Methyl-2-[3-(1-phenethyl)ureido]-4-phenylbutanoic Acid Methyl Ester (9i). The product was obtained in 78% yield as a mixture of diastereomers from the treatment of half-ester **5i** by the same procedure as for the conversion of **5d** to **9d**; white solid, mp 151−153 °C; IR (film) 3362, 1738, 1629 cm^{-1}; ^1H NMR (300 MHz) major diastereomer: δ 7.36−7.14 (m, 8 H), 7.00−6.98 (m, 2 H), 5.48 (br s, 1 H), 5.23 (d, $J = 6.7$ Hz, 1 H), 4.74 −4.69 (m, 1 H), 3.56 (s, 3 H), 2.48−2.34 (m, 2 H), 2.24−2.12 (m, 1 H), 2.12−1.99 (m, 1 H), 1.53 (s, 3 H), 1.41 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz) major diastereomer: δ 175.8, 156.3, 144.4, 141.4, 128.9, 128.7, 128.4, 127.5, 126.1, 126.0, 60.0, 52.7, 50.8, 38.6, 30.7, 24.2, 23.8; mass spectrum (CI) (*m*/*z*, %) 355 (100, $M^+ + H$). HRMS (CI) calcd for $C_{21}H_{27}N_2O_3$ 355.2022 ($M^+ + H$), found 355.2024. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.77; H, 7.34; N, 7.56. $[\alpha]^{20}_D$ +45 (*c* 1.3, chloroform). The de of 80% was calculated by integration of the methyl ester singlets from the major and minor diastereomers at δ 3.56 and 3.62 ppm, respectively. Their chemical shifts matched those observed in a sample obtained similarly from the racemic half-ester **5i**.

2-Ethyl-2-[3-(1-phenethyl)ureido]-4-phenylbutanoic Acid Methyl Ester (9j). The product was obtained in 70% yield as a mixture of diastereomers from the treatment of half-ester **5j** by the same procedure as for the conversion of **5d** to **9d**; colorless oil; IR (film) 3359, 1738, 1635 cm^{-1}; ^1H NMR (400 MHz) major diastereomer: δ 7.39−7.20 (m, 8 H), 7.03−7.01 (m, 2 H), 5.52 (br s, 1 H), 5.08 (d, $J = 6.7$ Hz, 1 H), 4.76 (quintet, $J = 6.7$ Hz, 1 H), 3.59 (s, 3 H), 2.77−2.69 (m, 1 H), 2.49−2.37 (m, 2 H), 2.14−1.97 (m, 2 H), 1.77−1.68 (m, 1 H), 1.48 (d, $J = 6.8$ Hz, 3 H), 0.72 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (100 MHz) major diastereomer: δ 175.2, 155.9, 144.5, 141.6, 128.9, 128.7, 128.3, 127.5, 126.1, 125.9, 65.0, 52.7, 50.9, 37.3, 30.7, 29.2, 23.9, 8.6; mass spectrum (EI) (*m*/*z*, %) 264 (25), 162 (47), 105 (64), 91 (100). HRMS (EI) calcd for $C_{22}H_{28}N_2O_3$ 368.2100, found 368.2112. $[\alpha]^{20}_D$ +36 (*c* 1.5, chloroform). The de of 93% was calculated by integration of the methyl ester singlets from the major and minor diastereomers at δ 3.59 and 3.65 ppm, respectively. Their chemical shifts matched those observed in a sample obtained similarly from the racemic half-ester **5j**.

2-(2-Phenethyl)-2-[3-(1-phenethyl)ureido]pentanoic Acid Methyl Ester (9k). The product was obtained in 84% yield as a mixture of diastereomers from the treatment of half-ester **5k** by the same procedure as for the conversion of **5d** to **9d**; yellow oil; IR (film) 3362, 1745, 1652 cm^{-1}; ^1H NMR (300 MHz) major diastereomer: δ 7.38−7.09 (m, 8 H), 6.99−6.96 (m, 2 H), 5.66 (br s, 1 H), 5.41 (d, J = 6.8 Hz, 1 H), 4.72 (quintet, J = 6.7 Hz, 1 H), 3.54 (s, 3 H), 2.73−2.65 (m, 1 H), 2.42−2.32 (m, 2 H), 2.09−1.94 (m, 2 H), 1.66−1.56 (m, 1 H), 1.44 (d, J = 6.8 Hz, 3 H), 1.37−1.20 (m, 1 H), 0.95−0.80 (m, 1 H), 0.80 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz) major diastereomer: δ 175.4, 156.1, 144.6, 141.6, 128.8, 128.7, 128.3, 127.4, 126.1, 125.9, 64.3, 52.6, 50.8, 38.4, 37.5, 30.5, 23.8, 17.6, 14.1; mass spectrum (CI) (*m*/*z*, %) 383 (100, $M^+ + H$). HRMS (CI) calcd for $C_{23}H_{31}N_2O_3$ 383.2335 ($M^+ + H$), found 383.2339. Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.33. Found: C, 72.20; H, 7.81; N, 6.94. $[\alpha]^{20}_D$ +49 (*c* 3.4, chloroform). The de of 94% was calculated by integration of the methyl ester singlets from the major and minor diastereomers at δ 3.54 and 3.61 ppm, respectively. Their chemical shifts matched those observed in a sample obtained similarly from the racemic half-ester **5k**.

2-(2-Phenethyl)-2-[3-(1-phenethyl)ureido]hexanoic Acid Methyl Ester (9*l*). The product was obtained in 74% yield as a single diastereomer from the treatment of half-ester **5*l*** by the same procedure as for the conversion of **5d** to **9d**; white solid, mp 99−102.5 °C; IR (film) 3346, 1735, 1632 cm^{-1}; ^1H NMR (400 MHz) δ 7.41−7.14 (m, 8 H), 7.03−6.98 (m, 2 H), 5.58 (br s, 1 H), 5.20 (d, J = 6.8 Hz, 1 H), 4.75 (quintet, J = 6.7 Hz, 1 H), 3.57 (s, 3 H), 2.76−2.70 (m, 1 H), 2.45−2.38 (m, 2 H), 2.08−1.97 (m, 2 H), 1.69−1.62 (m, 1 H), 1.48 (d, J = 6.8 Hz, 3 H), 1.30−1.18 (m, 4 H), 0.84 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz) δ 175.4, 155.9, 144.6, 141.6, 128.9, 128.7, 128.3, 127.4, 126.0, 125.9, 64.3, 52.6, 50.9, 37.5, 35.9, 30.6, 26.5, 23.9, 22.7, 14.2; mass spectrum (EI) (*m*/*z*, %) 292 (32), 190 (43), 91 (52), 69 (100). HRMS (EI) calcd for $C_{24}H_{32}N_2O_3$ 396.2413, found 396.2425. $[\alpha]^{20}_D$ +37 (*c* 2.3, chloroform). A sample obtained similarly from the racemic half-ester **5*l*** showed clearly resolved methyl ester peaks from the two diastereomers.

Preparation of Free Carboxylic Acids. Typical Procedure: *N*-Carbobenzyloxy-2-(propargyl)alanine (10c). Ester **7c** (83 mg, 0.30 mmol) was dissolved in 10 mL of methanol and 17 mL of 10% aqueous KOH solution. The mixture was stirred at 65 °C for 1.5 d and was then partitioned between ether and 10% aqueous NaOH solution. The basic layer was acidified with 10% aqueous HCl and extracted with dichloromethane, then the combined extracts were dried and concentrated in vacuo to afford 52 mg (66%) of **10c** as a colorless oil; IR (film) 3293, 2120, 1715 cm^{-1}; ^1H NMR (300 MHz) δ 7.33−7.29 (m, 5 H), 5.57 (br s, 1 H), 5.10 (s, 2 H), 2.96 (br s, 2 H), 2.02 (t, J = 2.5 Hz, 1 H), 1.61 (s, 3 H); ^{13}C NMR (100 MHz) δ 177.9, 155.3, 136.2, 128.7, 128.4, 128.2, 79.0, 71.9, 67.2, 58.6, 27.0, 23.3; mass spectrum (CI) (*m*/*z*, %) 262 (10, $M^+ + H$), 279 (100, $M^+ + NH_4$). HRMS (EI) calcd for $C_{14}H_{15}NO_4$ 261.1001 (M^+), found 261.0990. $[\alpha]^{20}_D$ +20.7 (*c* 1.23, chloroform). The ee (61%) was measured by integration of well-separated methyl signals in the ^1H NMR spectrum of an equimolar mixture of **10c** and *R*-(+)-α-methylbenzylamine.

The following compounds were prepared similarly to **10c**.

***N*-Carbobenzyloxy-2-(phenyl)alanine (10f).**[16] To a solution of **7f** (92 mg, 0.29 mmol) in 10 mL of methanol was added 2.3 mL of 1 M aqueous KOH solution and the mixture was stirred at room temperature for 19 h. It was then partitioned between 1 M KOH solution and diethyl ether. The aqueous layer was acidified with 10% aqueous HCl solution and extracted with ether. The organic extracts were dried and concentrated in vacuo to afford 60.4 mg (70%) of the product as a colorless oil containing a 1:1 mixture of two rotamers; IR (film) 1718 cm^{-1}; ^1H NMR (200 MHz) major rotamer: δ 8.33 (br s, 1 H), 7.50−7.05 (m, 9 H), 6.71 (br s, 1 H), 5.04 (br s, 1 H), 4.90 (br s, 1 H), 2.05 (s, 3 H); minor rotamer: 6.05 (br s, 1 H); ^{13}C NMR (50 MHz) both rotamers: δ 176.13, 176.06, 158.2, 156.4, 140.4, 140.1, 135.4, 128.5, 128.3, 127.9, 125.8, 125.5, 125.3, 125.2, 67.4, 67.1, 61.9, 23.1; mass spectrum (EI), (*m*/*z*, %) 254 (32, M^+ − COOH), 210 (21), 91 (100). HRMS (EI) calcd for $C_{16}H_{16}NO_2$ 254.1181 (M^+ − COOH), found 254.1179. $[\alpha]^{20}_D$ +34.2 (*c* 1.38, methanol). Lit.[16a] $[\alpha]^{20}_D$ +35.5 (*c* 2.83, methanol); lit.[16b] $[\alpha]_D$ +38.5 (*c* 2.83, methanol) for the *S*-isomer.

***N*-Carbobenzyloxy-2-(2-phenethyl)alanine (10i).**[17] Ester **7i** (128 mg, 0.375 mmol) was dissolved in 8 mL of methanol and 3 mL of 10% aqueous KOH solution. The mixture was refluxed for 20 h and was then partitioned between ether and 10% aqueous NaOH solution. The aqueous layer was acidified with 10% aqueous HCl and extracted with dichloromethane, then the combined extracts were dried and concentrated in vacuo to afford 72 mg (59%) of **10i** as a colorless oil; ^1H NMR (300 MHz) δ 11.60 (s, 1 H), 7.40−7.18 (m, 10 H), 5.78 (s, 1 H), 5.16 (s, 2 H), 2.69−2.56 (m, 3 H), 2.28−2.22 (m, 1 H), 1.71 (s, 3 H); ^{13}C NMR (75 MHz) δ 179.3, 154.6, 140.9, 136.3, 128.6, 128.44, 128.41, 128.3, 128.1, 126.1, 66.7, 59.9, 38.1, 30.6, 23.7. $[\alpha]^{20}_D$ +8.21 (*c* 2.86, methanol); lit.[17] $[\alpha]^{20}_D$ −6.8 (*c* 0.5, methanol) for the *R* isomer.

Determination of the Absolute Configuration of 2-Benzyl-2-ethylmalonic Acid Monomethyl Ester (5e). Preparation of 2-Cyclohexylmethyl-2-{3-[1-(1-naphthyl)ethyl]ureido}butanoic Acid Methyl Ester (11e). A solution of half-ester **5e** (198 mg, 0.818 mmol), triethylamine (0.13 mL, 0.93 mmol), and DPPA (0.20 mL, 0.93 mmol) in 2 mL of toluene was refluxed for 2 h. It was cooled to room temperature and (*S*)-(−)-1-(1-naphthyl)-ethylamine (0.21 mL, 1.31 mmol) was added. The mixture was refluxed an additional 13 h, the solvent was evaporated in vacuo, and the residue was chromatographed (15−30% ethyl acetate−hexanes) to afford 143 mg (43%) of a single product **11e** as the (*S*,*S*)-diastereomer, confirmed by means of X-ray crystallography (see the Supporting Information); white solid, mp 179−184 °C; IR (film) 3356, 1735, 1635 cm^{-1}; ^1H NMR (400 MHz) δ 8.17 (d, J = 8.2 Hz, 1 H), 7.88−7.86 (m, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.57−7.42 (m, 4 H), 5.65 (pentet, J = 6.8 Hz, 1 H), 5.42 (s, 1 H), 4.82 (d, J = 7.3 Hz, 1 H), 3.63 (s, 3 H), 2.51−2.37 (m, 2 H), 1.76−1.50 (m, 10 H), 1.46−1.02 (m, 6 H), 0.65 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz) δ 176.0, 155.2, 139.5, 134.0, 131.0, 128.7, 128.0, 126.3, 125.7, 125.2, 123.4, 122.2, 64.2, 52.3, 45.9, 43.2, 34.2, 34.1, 33.1, 29.9, 26.35, 26.31, 26.2, 22.0, 8.2; mass spectrum (EI) (*m*/*z*, %) 410 (65, M^+), 214 (54), 154 (100). HRMS (EI) calcd for $C_{25}H_{34}N_2O_3$ 410.2569, found 410.2559. $[\alpha]^{20}_D$ +15 (*c* 0.65, chloroform).

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. A.R.H., J.L., and M.T. were undergraduate research assistants who thank PURE, the University of Calgary, and the NSERC USRA program, respectively, for support.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of new compounds; ORTEP diagrams and X-ray crystallographic data for compounds **5g** (salt with (*R*)-(+)-α-methylbenzylamine) and **11e**. This material is available free of charge via the Internet at http://pubs.acs.org.