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Convenient Synthetic Route to an Enantiomerically Pure FMOC α-Amino Acid

Douglass F. Taber,* James F. Berry, and Timothy J. Martin†

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

taberdf@udel.edu

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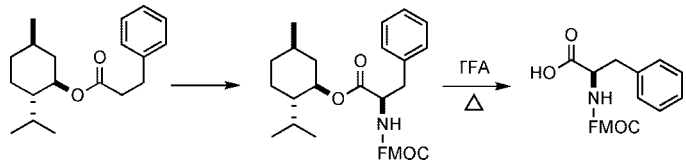

A strategy for the facile α-amination of carboxylic acid menthyl esters is described. The resulting diastereomers, readily separable, can be individually carried on to each enantiomer of the FMOC α-amino acid. A variety of unnatural side chains were compatible with this approach. The menthyl ester was easily removed from the FMOC α-amino acid without racemization.

Introduction

The incorporation of unnatural amino acids into peptides and proteins has gained importance in recent years.[1] Methods such as nonsense codon suppression have come to the fore as viable strategies for integrating unnatural amino acids into peptides.[2] Unnatural amino acids serve as probes for the identification of interactions between proteins,[3] and for identifying structural domains[4] as well as changes in conformation that take place.[5] A plethora of unnatural amino acids have been prepared, with side chains incorporating, inter alia, perfluorinated tryptophan derivatives,[6] nitrobenzyl groups,[7] azides,[8] and cyanoanthracene groups.[9]

There are two methods for the construction of enantiomerically pure α-amino acids, enantioselective homologation, and α-amination of the carboxylic acid. To effect enantioselective homologation, Belokon has developed achiral nickel(II) complexes used in conjunction with a NOBIN (2-amino-2′-hydroxy-1,1′-binaphthyl) catalyst.[10] Johnson has used Pd-catalyzed Suzuki cross coupling of halides with enantiopure vinyloxazolidine derivatives.[11] Krische has shown rhodium-catalyzed reductive coupling of alkynes with (*N*-sulfinyl)iminoacetates to be a promising method for achieving high regio- and stereo-

† Undergraduate research participant, University of Delaware.

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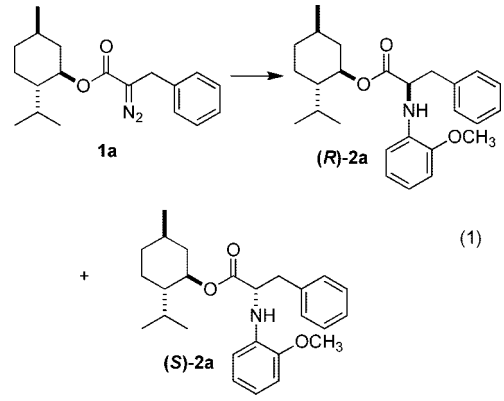
control in amino acid ester construction.[12] Phase transfer catalysts have also been used for glycine alkylation. O'Donnell reported the use of a chiral quaternary ammonium salt, derived from *Cinchona* alkaloids, to prepare the α-amino acid derivatives in high yield and high ee from the corresponding imine and alkyl halide.[13] Marouka has also developed a series of chiral quaternary ammonium salts which catalyze the enantioselective synthesis of α-alkyl-α-amino acid derivatives with very low catalyst loading.[14]

An alternative approach is α-amination of the carboxylic acid. Evans has developed a chiral magnesium bis(sulfonamide) complex for electrophilic amination with high enantioselectivity.[15] Lectka has employed *o*-benzoquinone imides with chiral ketene enolates.[16] Zheng has shown the capability of chiral amide cuprates to be coupled with lithium *tert*-butyl-*N*-tosyloxycarbamate in high diastereoselectivity and high yield.[17] In the laboratory of Badía, arylacetamide enolate coupling with di-*tert*-butylazidocarboxylate gave the corresponding arylglycine amino acid precursor with excellent enantioselectivity.[18] Zhou[19] and Fu[20] have both employed chiral copper complexes to effect NH insertion into the carbene derived from an α-diazoester, yielding the respective α-amino acid derivative in high enantiomeric excess. Although these last methods of preparing α-amino acid derivatives via NH insertion are useful, there are no examples of derivatives containing side chains that include alkenes or alkynes.

There are two challenges with each of these approaches. The first is that the products, although enantiomerically enriched, are not directly enantiomerically pure. Further, preparation of the alternate enantiomer of the target amino acid requires preparation of the enantiomeric chiral auxiliary or catalyst. We have shown that diazo esters[21] couple smoothly with aryl amines.[22] We envisioned (eq 1) the extension of this process to the production of enantiomerically pure α-amino acids. Several issues had to be addressed for this approach to be practical. The first was the discovery of an enantiomerically pure alcohol such that the diastereomeric esters resulting from amine NH insertion could be efficiently separated. It was also important that the protective aromatic group could be removed from the amine, and that hydrolysis of the ester could be effected without racemization of the stereogenic center.



Results and Discussion

Menthol had been used previously for the crystallization,[23] separation,[24,25] and determination of enantiopurity[26] of subsequent esters. In this study, we were pleased to observe (Scheme 1) that the 1:1 mixture of diastereomers of the α-aminated menthyl esters were readily separable by preparatory column chromatography. Here, the inexpensive L-menthol has three roles: protection of the sensitive carboxylic acid as an ester, as a resolving agent for separation of the diastereomers formed through NH insertion of *o*-anisidine into the corresponding diazo ester, and as a reporter of diastereomeric purity. A methyl group of the L-menthol showed distinct doublets ((*R*)-**2a**: δ 0.48; (*S*)-**2a**: δ 0.60) in the ^{1}H NMR spectrum for the two diastereomers. With use of these doublets, diastereomeric ratios were established through integration of the peak areas.

The menthyl esters for this study were prepared by DCC-mediated coupling[27] of menthol with the appropriate acid. Of these menthyl esters, only **5a** and **5e** had previously been prepared.[28] It had been reported previously that acylation of an ester with benzoyl chloride (**5a** → **6a**) proceeded in high yield by sequential addition of NEt_3 and $TiCl_4$, followed by heating in MeCN for 15 min.[22] We found that overnight reaction at room temperature was more efficient. These milder reaction conditions should allow for more sensitive substrates to be used without decomposition.

We observed (eq 2) that with aromatic side chains (X = H, Br, OCH_3) one of the diastereomers (the less polar diastereomer, *S* configuration at the α carbon as established by X-ray analysis) of the aromatic β-keto ester crystallized out. By using this approach, most of the mixture could be converted to the single

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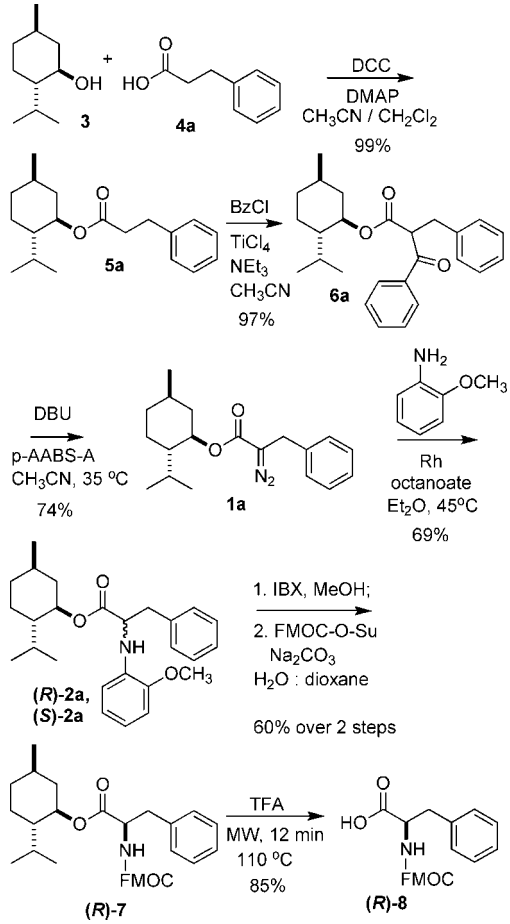
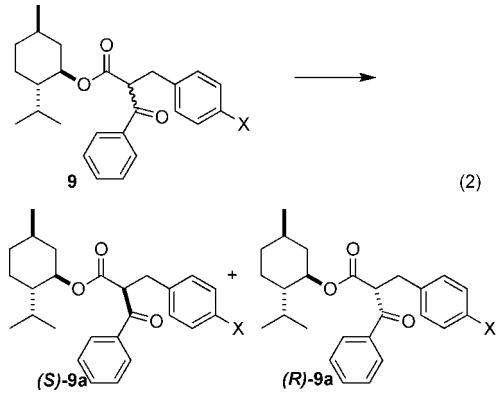
SCHEME 1



crystalline diastereomer. This may have promise as a practical method for the preparation of enantiomerically pure β-keto esters.



The next step in the sequence was conversion of β-keto ester **6** to the corresponding diazo ester **1** (Scheme 2). Our initial report described the use of *p*-acetaminobenzenesulfonyl azide (*p*-AABS-A) at room temperature for this conversion.[22] We found that gentle warming was required to drive the reaction of the menthyl esters to completion. The yields for diazo transfer to the several esters are summarized in Table 1.

The most important step in the synthesis was the rhodium-catalyzed NH insertion of *o*-anisidine into the diazo ester **1** to afford the corresponding amine diastereomers (*R*)-**2** and (*S*)-**2**

SCHEME 2

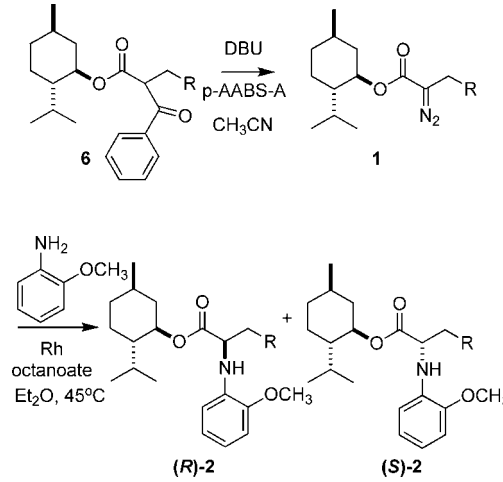
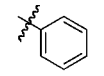
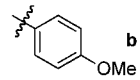
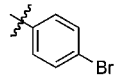


TABLE 1. Yields for the Diazo Transfer and NH Insertion Reactions

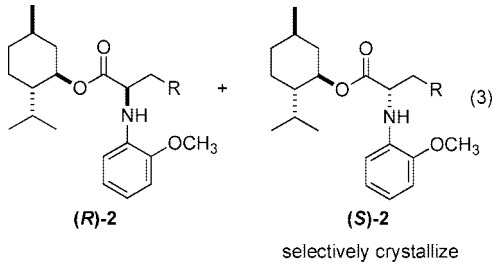
R group		diazo transfer yield (%)	NH insertion yield (%)[a]
	a	74[b]	69
	b	72[c]	72
	c	70[b]	70
	d	77[c]	68
	e	72[b]	73

[a] Based on diazo ester charged. [b] 35 °C, 3 h. [c] Room temperature, overnight.

(Scheme 2), in a 1:1 ratio (^{1}H NMR). With use of the phenyl diazo ester **1a**, the best results (69% yield, based on diazo ester) were obtained by adding the diazo ester dropwise to a solution of *o*-anisidine and catalytic rhodium octanoate in dry Et_2O at reflux. We were pleased (Table 1) to observe that alkenyl (**1d**) and alkynyl (**1e**) functional groups were compatible with these reaction conditions.

It became apparent that side product formation prevented the consumption of the entire quantity of *o*-anisidine, which eluted with the product diastereomers. Fortunately, we found that addition of 0.1% triethylamine to the elution solvent assisted separation. We also discovered that if only 0.8 equiv of *o*-anisidine was employed, TLC monitoring of the reaction mixture showed very little residual *o*-anisidine, with no decrease in the yield of the products.

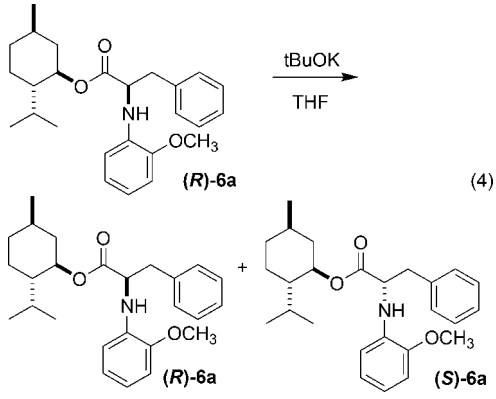
We observed (eq 3) that, after column chromatography, crystallization of the product diastereomers (dissolving the compounds in a minimal amount of PE and cooling the solution to temperatures below 0 °C) afforded the more polar diastere-



(3)

omer (*S*)-**2** as a crystalline solid (as established by X-ray analysis), leaving the less polar diastereomer (*R*)-**2** in solution (eq 3). The more polar diastereomer was recovered in >99% diastereomeric purity as established by ^{1}H NMR.

We also found (eq 4) that a 7:1 mixture of (*R*)-**2a**:(*S*)-**2a** could be epimerized using potassium *tert*-butoxide to afford a 2:1 mixture of diastereomers. Through separation and epimerization, the two NH insertion products obtained can thus be converted to a single desired diastereomer.



(4)

After some exploration, we settled (Scheme 1) on the Hoveyda protocol[29] as the best for the removal of the protective aromatic group. The crude free amine mixture was immediately exposed to FMOC protection conditions (FMOC-O-Su and Na_2CO_3 in a 1:1 H_2O:dioxane mixture[30] at room temperature for 24 h). The resulting yield of FMOC amine (*R*)-**7** was 60% over two steps with little decomposition.

The final step in the sequence was the removal of the menthyl group to liberate the FMOC protected amino acid. We were concerned that the use of a strong acid such as TFA could epimerize the enantiopure center that we had carefully established. Use of TFA at 110 °C for 12 min under microwave conditions did effectively remove the menthyl group. To check for racemization during the dementhylation step, the resulting FMOC-D-phenylalanine (*R*)-**8** was subjected to the DCC/DMAP coupling procedure used previously. To our delight, the ^{1}H NMR showed the presence of three clear menthyl doublets, indicating the chiral center had not undergone racemization in the dementhylation step.[31] The use of acetone-d_6 as the NMR solvent is preferred because the three menthyl doublets that are present are completely distinguishable (*RR* δ 0.68, 0.77, 0.88), whereas using $CDCl_3$ causes the chemical shifts to overlap (*RR* δ 0.73, 0.83−0.88).

Currently most syntheses of α-amino acids employ *tert*-butyl esters as protecting groups for the carboxylic acid. Our methodology described here should be of value since menthyl esters enable the diastereomeric integrity to be evaluated directly. Use of this reporter function of the menthyl ester could also facilitate the preparation of unnatural amino acids from the corresponding natural amino acids. Esterification with menthol followed by subsequent transformations could be effected, with the intermediates easily monitored for diastereomeric purity by ^{1}H NMR.

Conclusion

Adventitious racemization is always a hazard when manipulating the esters of α-amino acids. We have developed a simple procedure for the preparation of single enantiomer FMOC α-amino acids from the corresponding carboxylic acids. The use of L-menthol as the coupling partner has three distinct roles: protection of the sensitive carboxylic acid functionality, separation of the resulting diastereomers formed through NH insertion, and determination of the diastereomeric purity through integration of the methyl doublets ((*R*)-**2a**: δ 0.48; (*S*)-**2a**: δ 0.60) in the ^{1}H NMR spectrum. The menthyl ester was easily removed without epimerization. Although other NH insertion methods[19,20] are limited to α-aryl and α-methyl side chains, our methodology enables the incorporation of longer aliphatic side chains. We believe that this will be a practical method for the laboratory-scale preparation of a variety of unnatural amino acids.

Experimental Section

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 3-Phenylpropanoate (5a). L-Menthol (2.01 g, 12.9 mmol), hydrocinnamic acid (1.962 g, 13.1 mmol), and *N*,*N*-dimethylaminopyridine (DMAP) (0.39 g, 3.19 mmol) were combined in a round-bottomed flask along with 13 mL of a 1:1 mixture of CH_2Cl_2 and CH_3CN. 1,3-Dicyclohexylcarbodiimide (DCC) (2.92 g, 14.2 mmol) in 2 mL of dry CH_2Cl_2 was added dropwise over 10 min at 0 °C. The solution was warmed to rt and stirred overnight. The white precipitate was filtered out and the filtrate was partitioned between CH_2Cl_2 and, sequentially, 1 N aqueous HCl, 10% aqueous $NaHCO_3$, and water. The combined organic extract was dried (Na_2SO_4) and concentrated to yield (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 3-phenylpropanoate (**5a**) (3.69 g, 99% yield) as a clear oil. The ^{1}H NMR agreed with that of the previously synthesized material.[28a] ^{1}H NMR δ 7.21 (m, 2H), 7.11 (m, 3H), 4.59 (td, 1H, J = 11.2 Hz, J = 4.4 Hz), 2.87 (t, 2H, J = 7.6 Hz), 2.53 (t, 2H, J = 7.6 Hz), 1.84 (d, 1H, J = 12.8 Hz), 1.53−1.69 (m, 3H), 1.39 (m, 1H), 1.25 (m, 1H, J = 11.2 Hz, J = 2.8 Hz), 0.72−1.01 (m, 9H), 0.62 (d, 3H, J = 6.8 Hz); ^{13}C NMR[32] δ u: 172.5, 140.5, 40.9, 36.2, 34.2, 31.1, 23.4; ^{13}C NMR[32] δ d: 128.4, 128.3, 126.2, 74.1, 46.9, 31.4, 26.1, 22.0, 20.8, 16.2.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-Benzoyl-3-oxo-3-phenylpropanoate (6a). To a solution of the phenyl ester (3.995 g, 13.9 mmol), benzoyl chloride (6.024 g, 43.0 mmol), triethylamine (8.411 g, 83.3 mmol), and 14 mL of dry CH_3CN was added titanium tetrachloride (1.0 M in toluene; 20.8 mL, 20.8 mmol) over 10 min at 0 °C under N_2 atmosphere. The reaction mixture was warmed to rt and stirred overnight, then partitioned between water and EtOAc. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield a diastereomeric mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-benozyl-3-oxo-3-

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(31) A slight impurity in the commercial menthol was present at δ 0.56. This impurity did not interfere with the analysis.

(32) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" and for methylene and quaternary carbons as "u".

phenylpropanoate (**6a**) (5.278 g, 97% yield) as an off-white solid. The solid was then recrystallized from a 4:1 mixture of MeOH:PE. TLC R_f (MTBE/PE = 0.4:9.6) = 0.29; $[\alpha]^{15}_D$ −64.5 (*c* 1.00, CH_2Cl_2); mp 116−118 °C; ^{1}H NMR (recrystallized compound) δ 7.99 (dd, 2H, J = 8.8 Hz, J = 1.6 Hz), 7.56 (tt, 1H, J = 7.2 Hz, J = 1.6 Hz), 7.45 (t, 2H, J = 8 Hz), 7.25 (m, 4H), 7.19 (m, 1H), 4.58 (m, 2H), 3.32 (m, 2H), 1.79 (d, 1H, J = 11.6 Hz), 1.58 (m, 2H), 1.37 (m, 1H), 1.20 (m, 2H), 0.72−0.97 (m, 6H), 0.65 (d, 3H, J = 7.2 Hz), 0.41 (d, 3H, J = 6.4 Hz); ^{13}C NMR δ u: 194.0, 168.8, 138.4, 136.2, 40.3, 34.5, 34.1, 22.9; ^{13}C NMR δ d: 133.4, 129.0, 128.6, 128.6, 128.5, 126.6, 75.5, 56.9, 46.7, 31.3, 25.5, 21.9, 20.6, 15.7; IR 1718, 1686 cm^{-1}; HRMS calcd for $C_{26}H_{33}O_3$ (MH^+) 393.2430, obsd 393.2428.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-Diazo-3-phenylpropanoate (1a). Keto ester **6a** (1.001 g, 2.6 mmol) was combined with *N*-acetoaminobenzenesulfonyl azide (1.228 g, 5.1 mmol) in 1 mL of dry CH_3CN. The mixture was stirred at 0 °C under N_2 atmosphere for 5 min. DBU (0.583 g, 3.8 mmol) was added dropwise over 5 min to the solution at 0 °C. The mixture was stirred for 10 min and additional *N*-acetoaminobenzenesulfonyl azide (0.625 g, 2.6 mmol) and DBU (0.193 g, 1.3 mmol) were added. The solution was heated to 35 °C and stirred for 3 h, then partitioned between water and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-diazo-3-phenylpropanoate (**1a**) as a yellow oil (0.592 g, 74% yield). TLC R_f (MTBE/PE = 0.4:9.6) 0.46; ^{1}H NMR δ 7.31 (m, 2H, J = 7.6 Hz), 7.23 (m, 3H), 4.76 (td, 1H, J = 10.8 Hz, J = 4.4 Hz), 3.61 (s, 2H), 2.03 (d, 1H, J = 8.8 Hz), 1.80 (br s, 1H), 1.66 (m, 2H), 1.48 (m, 1H), 1.36 (m, 1H, J = 12 Hz, J = 4.8 Hz), 0.93−1.11 (m, 2H), 0.83−0.91 (m, 7H), 0.75 (d, 3H, J = 6.8 Hz); ^{13}C NMR δ 167.1, 137.4, 128.7, 128.3, 127.0, 77.2, 74.9, 47.1, 41.3, 34.2, 31.4, 29.4, 26.4, 23.6, 22.0, 20.7, 16.5; IR 2082, 1688 cm^{-1}; HRMS calcd for $C_{19}H_{27}N_2O_2$ (MH) 315.2073, obsd 315.2063.

(R)-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl) 2-(2-Methoxyphenylamino)-3-phenylpropanoate ((*R*)-2a) and (*S*)-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl) 2-(2-Methoxyphenylamino)-3-phenylpropanoate ((*S*)-2a). *O*-Anisidine (0.147 g, 1.2 mmol) and rhodium(II) octanoate dimer (0.023 g, 2 mol %) were added to a round-bottomed flask along with 1.75 mL of dry Et_2O. The flask was equipped with a reflux condenser and the solution was heated to 45 °C (oil bath temperature) under N_2 atmosphere for 10 min. Diazo ester **1a** (0.475 g, 1.5 mmol) in 1.5 mL of dry Et_2O was added dropwise over 10 min. The solution was then allowed to stir at 45 °C for 3 h. After cooling, the mixture was immediately concentrated and chromatographed via TLC mesh silica gel to afford diastereomers (*R*-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-(2-methoxyphenylamino)-3-phenylpropanoate ((*R*)-**2a**) and (*S*-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-(2-methoxyphenylamino)-3-phenylpropanoate ((*S*)-**2a**) as clear oils: ((*R*)-**2a** (less polar diastereomer) 0.090 g, (*S*)-**2a** (more polar diastereomer) 0.133 g, mixture of diastereomers 0.203 g, 69% yield overall). The mixture of diastereomers (0.203 g) was then dissolved in a minimal amount of PE and placed in the freezer overnight to induce crystallization of (*S*)-**2a**, the more polar diastereomer (0.075 g). (*R*)-**2a** (*less polar diastereomer*, clear oil): TLC R_f (MTBE/PE = 0.4:9.6) 0.45; $[\alpha]^{15}_D$ −23.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (acetone-d_6) δ 7.30 (m, 4H), 7.23 (m, 1H), 6.82 (d, 1H, J = 8 Hz), 6.75 (td, 1H, J = 8 Hz, J = 1.2 Hz), 6.62 (t, 2H, J = 7.6 Hz), 4.83 (d, 1H, exchanges, J = 10 Hz), 4.54 (td, 1H, J = 10.8 Hz, J = 4.4 Hz), 4.37 (m, 1H), 3.81 (s, 3H), 3.14 (d, 2H, J = 6.8 Hz), 1.86 (d, 1H, J = 12 Hz), 1.62 (m, 3H), 1.40 (m, 1H), 1.28 (m, 1H, J = 11.6 Hz, J = 3.2 Hz), 0.82−1.03 (m, 6H), 0.70 (d, 3H, J = 7.2 Hz), 0.48 (d, 3H, J = 6.8); ^{13}C NMR (acetone-d_6) δ u: 173.2, 148.1, 138.2, 137.7, 41.6, 39.4, 34.9, 23.5; d: 130.2, 129.1, 127.5, 121.8, 118.2, 111.5, 110.8, 75.2, 59.0, 55.9, 47.7, 32.1, 25.9, 22.3, 21.2, 15.9; IR 3401, 1731 cm^{-1}; HRMS calcd for $C_{26}H_{35}NO_3Na$ (M + Na) 432.2513, obsd 432.2511. (*S*)-**2a** (*more polar diastereomer*, crystalline solid): TLC R_f (MTBE/PE = 0.4:9.6) 0.41; $[\alpha]^{15}_D$ −47.1 (*c* 1.00, CH_2Cl_2); mp 68−72 °C; ^{1}H NMR (acetone-d_6) δ 7.27 (m, 4H), 7.21 (m, 1H), 6.80 (dd, 1H, J = 8 Hz, J = 1.6 Hz), 6.74 (td, 1H, J = 8 Hz, J = 1.2 Hz), 6.61 (m, 2H), 4.83 (d, 1H, J = 9.6 Hz), 4.57 (td, 1H, J = 10.8 Hz, J = 4 Hz), 4.38 (m, 1H), 3.79 (s, 3H), 3.13 (d, 2H, J = 6.8 Hz), 1.84 (m, 1H), 1.62 (m, 3H), 1.26−1.44 (m, 2H), 1.00 (m, 1H), 0.77−0.85 (m, 7H), 0.71 (m, 1H), 0.60 (d, 3H, J = 6.8 Hz); ^{13}C NMR (acetone-d_6) δ u: 173.4, 148.1, 138.0, 137.7, 41.3, 39.2, 34.9, 23.7; ^{13}C NMR (acetone-d_6) δ d: 130.3, 129.1, 127.5, 121.8, 118.1, 111.5, 110.9, 75.2, 58.4, 55.9, 47.7, 32.0, 26.6, 22.2, 21.1, 16.3; IR 3401, 1731 cm^{-1}; HRMS calcd for $C_{26}H_{35}NO_3Na$ (M + Na) 432.2515, obsd 432.2514.

Epimerization. The protected amine (0.023 g, mmol, 7:1 ratio of (*R*)-**2a** to (*S*)-**2a**) was dissolved in 3 mL of dry THF. To this solution was added dropwise 5 mL of a 1 mg/mL solution of potassium *tert*-butoxide in dry THF. The reaction mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure and an additional 5 mL of potassium *tert*-butoxide in dry THF was added. The mixture was then stirred overnight at rt. The residue was chromatographed to yield a 2:1 mixture ((*R*)-**2a** to (*S*)-**2a**) of diastereomers (0.017 g, 74% yield). The ^{1}H NMR matched the aforementioned compounds.

(*R*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl) 2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanoate ((*R*)-7). To a solution of iodobenzene diacetate (0.236 g, 0.73 mmol) and 0.1 mL of acetic acid in 5 mL of MeOH at 0 °C was added the protected amine (*R*)-**2a** (0.075 g, 0.18 mmol) in 2 mL of MeOH dropwise over 5 min. The solution was stirred for 10 min at 0 °C and then warmed to rt and stirred for 30 min. Then, 5 mL of 1 N aqueous HCl was added and the mixture was stirred for an additional 30 min. Next, 10 mL of 10% aqueous $Na_2S_2O_3$ was added and the solution was stirred for 30 min. The solution was brought to pH ∼10−11 with solid Na_2CO_3 and stirred for 1.5 h. The mixture was partitioned between CH_2Cl_2 and H_2O and the combined organic layers were dried (Na_2SO_4) and concentrated to give the crude free amine. A mixture of FMOC-O-Su (0.081 g, 0.24 mmol) and Na_2CO_3 (0.038 g, 0.36 mmol) in 1.5 mL of a 1:1 dioxane:H_2O mixture was then stirred for 5 min at rt. The crude free amine, dissolved in 1 mL of dioxane, was added and the solution was stirred for 24 h at rt. The mixture was partitioned between CH_2Cl_2 and H_2O and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield (*R*)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanoate ((*R*)-**7**) (0.057 g, 60% yield over two steps) as an off white solid. TLC R_f (MTBE/PE 1.0:9.0) 0.26; $[\alpha]^{15}_D$ +28.0 (*c* 1.00, CH_2Cl_2); mp 86−89 °C; ^{1}H NMR (acetone-d_6) δ 7.84 (d, 2H, J = 7.6 Hz), 7.64 (t, 2H, J = 6.4 Hz), 7.40 (t, 2H, J = 7.6 Hz), 7.20−7.33 (m, 7H), 6.86 (d, 1H, exchanges, J = 8.8 Hz), 4.66 (td, 1H, J = 10.8 Hz, J = 4.4 Hz), 4.47 (m, 1H), 4.24 (m, 2H), 4.18 (q, 1H, J = 6.8 Hz), 3.20 (dd, 1H, J = 14 Hz, J = 6 Hz), 3.00 (dd, 1H, J = 14 Hz, J = 9.2 Hz), 1.95 (d, 1H, J = 12.8 Hz), 1.76 (m, 1H, J = 6.8 Hz, J = 2.4 Hz), 1.65 (m, 2H), 1.47 (m, 1H), 1.36 (m, 1H, J = 12 Hz, J = 2.8 Hz), 0.93−1.11 (m, 2H), 0.85−0.91 (m, 4H), 0.77 (d, 3H, J = 6.8 Hz), 0.68 (d, 3H, J = 7.6 Hz); ^{13}C NMR (acetone-d_6) δ u: 172.2, 156.8, 145.0, 142.0, 138.2, 67.2, 41.5, 38.3, 34.9, 23.7; ^{13}C NMR (acetone-d_6) δ d: 130.1, 129.2, 128.5, 127.9, 127.5, 126.1, 120.8, 67.2, 56.9, 47.9, 47.7, 32.1, 26.4, 22.3, 21.1, 16.3; IR 3588, 3327, 1721, 1702 cm^{-1}; HRMS calcd for $C_{34}H_{39}NO_4Na$ (M + Na) 548.2777, obsd 548.2769.

FMOC-D-Phenylalanine ((*R*)-8). The FMOC-protected amine (0.075 g, 0.14 mmol) was dissolved in 1.5 mL of TFA and placed in a microwave reactor for 12 min (5 min warming to 110 °C, followed by 7 min at 110 °C) at 250 psi. The TFA was then bubbled off under N_2 and the residue was taken up in 3 mL of CH_2Cl_2 and evaporated onto flash silica gel. Chromatography of the residue afforded FMOC-D-Phe ((*R*)-**8**) (0.047 g, 85% yield) as a white solid. The ^{1}H NMR and ^{13}C NMR matched that of the commercial material. Subsequent

re-esterification with L-menthol was then used to determine the stereochemical integrity of the amino acid (see below).

Re-esterification of FMOC-D-Phenylalanine. L-Menthol (0.020 g, 0.129 mmol), commercial FMOC-D-phenylalanine ((*R*)-**8**) (0.050 g, 0.129 mmol), and DMAP (0.016 g, 0.129 mmol) were combined in a round-bottomed flask along with 1 mL of dry CH_2Cl_2. 1,3-Dicyclohexylcarbodiimide (DCC) (0.032 g, 0.154 mmol) in 0.5 mL of dry CH_2Cl_2 was added dropwise over 5 min at 0 °C. The solution was warmed to rt and stirred overnight. The mixture was evaporated onto silica gel and chromatographed to yield (*R*)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanoate ((*R*)-**7**) (0.060 g, 88% yield) as a white solid. The ^{1}H NMR and ^{13}C NMR matched that of the previously synthesized material.

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Supporting Information Available: Experimental data and ^{13}C NMR and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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