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Preparation of (R)-2-Azidoesters from 2-((p-Nitrobenzene)sulfonyl)oxy Esters and Their Use as Protected Amino Acid Equivalents for the Synthesis of Di- and Tripeptides Containing D-Amino Acid Constituents

Robert V. Hoffman* and Hwa-Ok Kim
Department of Chemistry
New Mexico State University
Las Cruces, NM 88003-0001

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Abstract: (R)-2-Azidoesters and their derived (R)-2-azido acids are readily prepared from common amino acids by an inversion methodology that employs (S)-2-nosyloxyesters as key intermediates. The (R)-2-azidoesters can be used as protected amino acid equivalents in peptide synthesis. Basic hydrolysis frees the carboxyl group. Triphenylphosphine / water is used to free the amine group. By these reactions a variety of L-D and D-L dipeptides, L-D-L tripeptides, and depsipeptides can be prepared easily in good yields, and without detectable epimerization.

Introduction

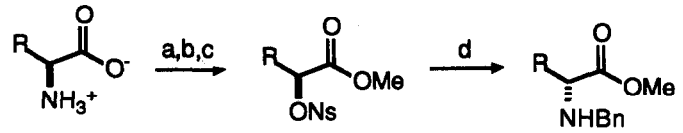
The preparation of D-α-amino acids has received a great deal of attention because their incorporation in both naturally[1] and unnaturally[2] occurring peptides often results in interesting biological activity of the peptide. A variety of asymmetric syntheses used to prepare L-α-amino acids can be utilized for producing the D-antipode by reversing the chirality of the asymmetric element (chiral auxiliary, chiral catalyst, or chiral precursor) used in the synthesis.[3]

An alternate strategy for gaining access to D-α-amino acids is to simply invert the configuration of readily available L-α-amino acids. Despite the apparent simplicity of this approach, it has not been effectively reduced to practice until recently when Effenberger showed that 2-triflyloxyesters derived from optically active 2-hydroxyesters undergo enantiospecific nucleophilic substitution with amines to give α-aminoesters with inverted configuration.[4, 5] In addition to amine nucleophiles, hydroxylamines can be employed to prepare N-hydroxy-α-aminoesters.[6] Hydrazides can also be used as nucleophiles to prepare 2-hydrazinylesters with high optical purities.[7]

Our interest in the use of 2-((p-nitrobenzene)sulfonyl)oxyesters (2-nosyloxyesters) as synthetic intermediates[8] led to the observation that optically active 2-nosyloxyesters also undergo substitution by benzylamine to give N-benzyl-α-aminoesters in good yields with complete inversion of configuration.[9] This substitution for nosylate (or triflate) coupled with the preparation of enantiomerically pure (S)-2-nosyloxyesters from L-amino acids represents a straightforward method for inverting the configuration of L-amino acids in high chemical and stereochemical yields. (Scheme 1).[9]

We wished to extend this inversion methodology to the synthesis of (R)-2-azidoesters. The azide group of (R)-2-azidoesters is easily converted to the amine group,[10] thus (R)-2-azido esters can be thought of as azide protected

Scheme 1



a. $NaNO_2$, 1N H_2SO_4, 85-95%. b. K_2CO_3, CH_3I, acetone, 69-96%, c. NsCl, TEA, DMAP, CH_2Cl_2, 80-100%, d. $BnNH_2$, CH_3CN, 80-95%, ee=100%.

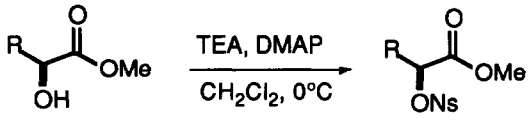
equivalents of D-amino acid esters. However, as a masking function for amines, the azide group confers distinct chemical properties to the protected amine compared to N-benzylated aminoesters or N-acylated aminoesters. In particular, they are very easy to process, and they are neither acidic or basic. Inversion methodology for the preparation of (R)-2-azidoesters would provide a useful alternative to their preparation by asymmetric synthesis described in an exceptional recent paper from the Evans group.[11] In that report direct asymmetric azido transfer was used to prepare 2-azidoimides in either enantiomeric configuration at C-2. The azidoimide could be converted to an amino acid of high optical purity. The imide itself can be used as a 2-azido ester surrogate, or it can be converted to an optically pure 2-azido ester.

In addition to asymmetric azide transfer, asymmetric halogenation has been used to give optically active 2-haloimides, which upon azide substitution produce 2-azidoesters with good enantioselection.[11] Other chiral auxiliaries have also been employed for the preparation of optically active 2-azidoesters by asymmetric halogenationation followed by azide substitution.[12]

Unmasking the azide-protected amine group of 2-azido esters has usually involved catalytic reduction of the azide to an amine hydrochloride, followed by neutralization and subsequent reaction of the amino group. This protocol is required by the propensity of free aminoesters to polymerize unless isolated as the hydrochloride. It was felt that if deprotection (reduction of the azide group) could be carried out under mild, neutral conditions, reaction of the amino group could succeed without isolation of the aminoester intermediate. Accordingly, a second goal of this work was to develop a method to use D-2-azidoesters themselves for peptide synthesis.

Results and Discussion

(S)-2-Hydroxyesters **1a-g**, prepared from L-amino acids,[7] were treated with p-nitrobenzenesulfonyl chloride in the presence of TEA and DMAP to give (S)-methyl 2-nosyloxy esters **2a-g** in excellent yields (Eqn. 1) The optical rotations of **2a-g** are given in the Experimental Section. These materials (with the possible exception of **2g**) are of high optical purity (>95%) since substitution by amines[9] and azide (vide infra) gives inverted products of high optical purity.



(1)

1a, R = CH_3	**2a**, 100%
1b, R = i-Bu	**2b**, 96%
1c, R = CH_2Ph	**2c**, 97%
1d, R = CH_2CO_2Me	**2d**, 80%
1e, R = i-Pr	**2e**, 70%
1f, R = sec-Bu	**2f**, 94%
1g, R = Ph	**2g**, 97%

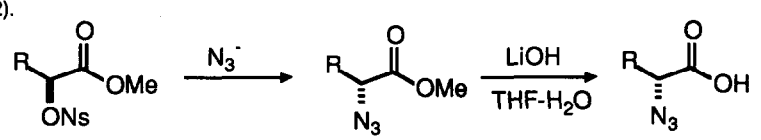
Table 1. Preparation of (R)-Methyl 2-Azidoesters **3a-g** and (R)-2-Azido Acids **4a-g** from (S)-Methyl 2-Nosyloxyesters **2a-g**.

Entry	2-Nosyloxyester	2-Azidoester (%)[a]	2-Azido Acid(%)[a]	ee(%)
1.	**2a**	**3a** (83)	**4a** (87)	92
2.	**2b**	**3b** (90)	**4b** (90)	97
3.	**2c**	**3c** (92)	**4c** (93)	93
4.	**2d**	**3d** (78)[b]	-	>95
5.	**2e**	**3e** (92)	**4e** (90)	97
6.	**2f**	**3f** (95)	**4f** (88)	94
7.	**2g**	**3g** (100)[b]	**4g** (56)	35

a. Yields are isolated yields of pure products.

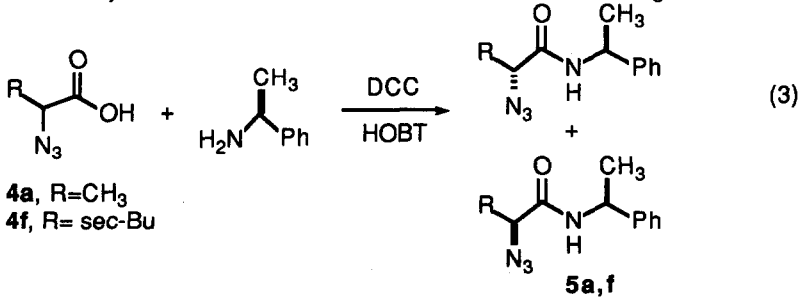
b. 1,1,3,3-Tetramethylguanidinium azide was used as the azide source.

Nosyloxyesters **2a-c,e,f** were reacted with sodium azide in warm DMSO (55°C), and **2d,g** were treated with 1,1,3,3-tetramethyguanidinium azide[11] in dichloromethane at room temperature to give 2-azidoesters **3a-g** in excellent yields (Table 1). The crude products were quite pure by ^{1}H nmr spectroscopy, and were used directly in subsequent reactions very effectively without the need for further purification. In order to prove the identity of **3a-g** and to determine their optical purity, they were converted to azido acids **4a-g** in high yields by treatment with lithium hydroxide in aqueous THF (Eqn. 2).



2a-g **3a-g** **4a-g** (2)

Azido acids **4b,c,e,g** are known compounds,[11] thus their optical purities and hence the optical purities of the corresponding 2-azidoesters **3b,c,e,g** were determined by optical rotations. The optical purity of azido acids **4a** and **4f**, and hence azido esters **3a** and **3f**, were determined by coupling the carboxyl group of **4a** and **4f** with (S)-α-methylbenzylamine to give amides **5a** and **5f** (Eqn. 3). The diastereomers of **5a** were not distinguishable by ^{1}H nmr, however, analysis of the crude product by HPLC showed two diastereomers to be present in the ratio of 96 : 4. A reference mixture of diastereomers, made from racemic **1a** by the same route, was used to confirm the HPLC peak identities. The diastereomers of **5f** gave individual ^{1}H nmr signals for the C-2 methine proton in a diastereomeric ratio of 97 : 3. In both cases the major diastereomer was assumed to have the inverted R-configuration at C-2 by analogy to the

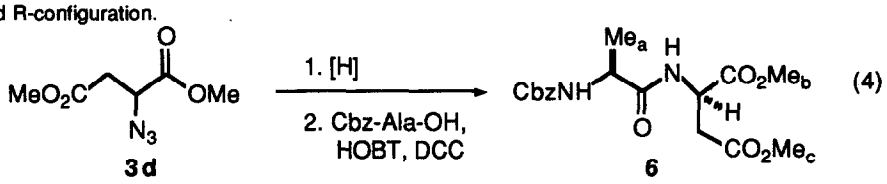


4a, R=CH_3
4f, R= sec-Bu

5a,f (3)

stereochemistry found for **4b,c,e,g**.

Determination of the optical purity of **3d** was complicated by the fact that there are two carboxyl groups which could couple with (S)-α-methylbenzylamine. Therefore the azide group was reduced to the amine and coupled with Cbz-L-alanine to give dipeptide **6**. Only one diastereomer could be detected by ^{1}H nmr analysis (Eqn. 4). A diastereomeric mixture of **6**, which was prepared by carrying out the same sequence starting with racemic **2d**, revealed that each diastereomer gave unique signals for the methyl protons of the alanine fragment (Me_a) and the methoxy methyl groups of the aspartate fragment (Me_b, Me_c). Only one set of signals was found for **6** prepared from (R)-**2d** indicating that only a single diastereomer had been produced. The stereochemistry at C-2 of the aspartate fragment was assumed to be the inverted R-configuration.

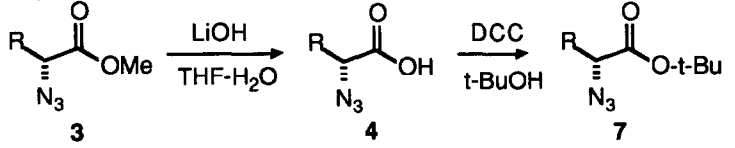


(4)

The results show that the substitution for the nosylate group in 2-nosyloxy esters **2** by azide takes place with high stereoselectivity with inversion of configuration. The results also demonstrate that each step of the reaction sequence starting from L-amino acids is highly stereoselective. The single exception is **2g** which gives azido ester products with only 35% ee. An α-phenyl substituent is well-known to reduce the stereoselectivity of substitution of both 2-nosyloxyesters and 2-triflyloxyesters by several classes of nucleophiles,[6,7] and thus constitutes a structural limitation of the method.

The utilization of 2-azido esters as substrates for peptide synthesis would be very attractive if a) the ester group could be easily converted to the free acid for coupling at the carboxyl group, and b) an alternative to catalytic reduction for the "unmasking" of the azide-protected amine could be found which does not require isolation of the amino ester, and which would permit the use of readily available Cbz- or Boc-protected amino acids or other 2-azido acids as coupling partners. Depending on the mode of peptide coupling that is planned (through the azide first or through the carboxyl group first), these operations might be performed in different sequence, therefore the protecting group chemistries must be compatible.

(R)-Methyl 2-azidoesters **3** can be efficiently converted to the corresponding t-butyl esters **7** without racemization by hydrolysis of **3** to the azido acid **4** and reesterification with t-butanol (or other alcohols) (Eqn, 5). The ester exchange of t-butyl for methyl permits facile deprotection of the carboxyl group with TFA, and the byproducts do not interfere with subsequent coupling procedures.



(5)

For unmasking the amine function, the Staudinger reaction was attractive since the reaction conditions are mild and the byproducts are neutral and unreactive towards peptide coupling reagents.[13] Reaction of azides with triphenylphosphine in the presence of water is a common method for generating amines from azides.[14] The resulting amines can be acylated to give amides easily. On the other hand it has been reported that amides can be produced by the reaction of azides with carboxylic acids in the presence of triphenyl phosphine.[15] The reaction presumably involves

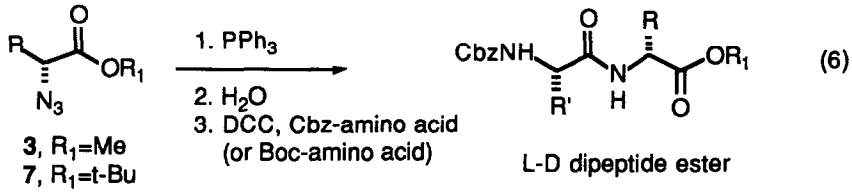
Table 2. Preparation of Cbz-L-D Dipeptide Esters from (R)-2-Azido Esters and Cbz-Amino Acids.

Cbz-Amino Acid	(R)-2-Azido Ester	Dipeptide	Yield (%)[a]
Cbz-Ala-OH	**3 d**	Cbz-Ala-D-Asp(OMe)-OMe, **6**	95
Boc-Phe-OH	**3 a**	Boc-Phe-D-Ala-OMe, **8**	90
Cbz-Ala-OH	**7 e**	Cbz-Ala-D-Val-O-t-Bu, **9**	75
Cbz-Val-OH	**7 e**	Cbz-Val-D-Val-O-t-Bu, **10**	87

a. Yields are isolated yields of pure products.

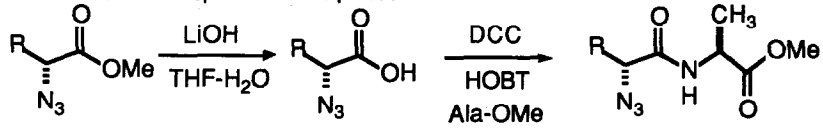
reaction of phosphazene intermediates from the Staudinger reaction with carboxylic acids. While several optically active substrates were used, no data concerning racemization was presented.

The excellent success of carbodiimide-based peptide coupling methodology suggested that the best use of the Staudinger reaction for amine deprotection from the azide would be to use it to produce the α-amino ester, which could then be coupled with an α-amino acid using carbodiimide-based methodology. As a test of the hypothesis, several (R)-2-azidoesters **3a,d** and **7e** were treated with triphenylphosphine and then water and, without isolation, coupled with Cbz-protected L-amino acids. Excellent yields of Cbz-L-D dipeptide esters **6, 8, 9, 10** were obtained, each as a single diastereomer, thus ruling out racemization of either amino acid component in the process (Eqn. 6, Table 2). Furthermore the procedure is very simple since only a single flask is used and only the final dipeptide is isolated.



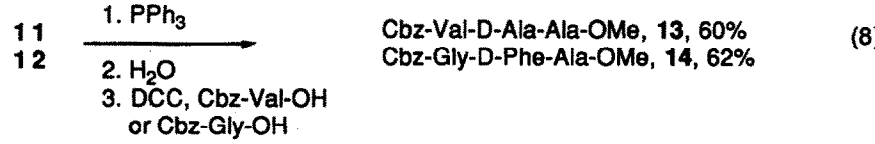
(6)

(R)-2-Azido esters **3** can also be employed to give azido-D-L-dipeptides efficiently (Eqn. 7). Thus hydrolysis of **3a,c** to the (R)-2-azido acids **4a,c** followed by standard peptide bond formation with Ala-OMe was used to prepare N_3-D-Ala-Ala-OCH_3, **11**, (53%) and N_3-D-Phe-Ala-OMe, **12**, (89%).[16] No evidence of epimerization in the azido dipeptide product was found in the ^1H nmr spectrum of the product.



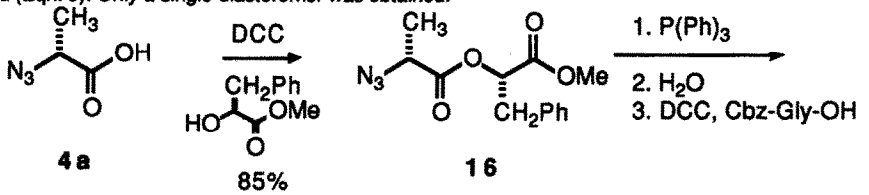
(7)

Azide-protected dipeptides can likewise be coupled selectively to give L-D-L tripeptide esters by standard methodology. Azide deprotection-coupling of dipeptides **11** and **12** gives L-D-L tripeptide esters **13** and **14**, respectively, in good yields (Eqn. 8). Alternatively, t-butyl-protected dipeptide Cbz-Ala-D-Val-O-t-Bu, **9**, (produced by coupling through the azide group first) gives the L-D-L tripeptide Cbz-Ala-D-Val-Ala-OMe, **15**, in 94% yield upon removal of the t-butyl group with TFA followed by coupling with Ala-OMe. This example illustrates the utility of (R)-t-butyl 2-azidoesters **7** in the sequence, as a t-butoxide group can be removed more easily in peptides than a methoxide group.

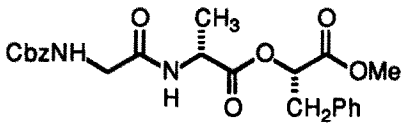


(8)

Besides the utility of 2-azidoesters in peptide synthesis, (R)-2-azido acids **4** are also well-suited for the preparation of depsipeptides. One class of these materials contain ester linkages in place of amide linkages in the peptide skeleton, and they have a variety of interesting biological activities.[17] The synthesis of depsipeptides using azido esters is very straightforward. For example, **4a** was esterified with (S)-methyl 2-hydroxy-3-phenylpropanoate, **1c**, using DCC (85%). The resulting azido ester **16** was coupled with Cbz-Gly-OH to give the D-L depsipeptide Cbz-Gly-D-Ala-(O)-Phe **17** in 81% yield (Eqn. 9). Only a single diasteromer was obtained.



(9)



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In summary, we have shown that (R)-2-azidoesters and their derived (R)-2-azido acids are readily prepared from common amino acids by an inversion methodology that employs (S)-2-nosyloxyesters as key intermediates. The (R)-2-azidoesters can be used as protected amino acid equivalents in peptide synthesis. Basic hydrolysis frees the carboxyl group. Triphenylphosphine / water is used to free the amine group. By these reactions a variety of L-D and D-L dipeptides, L-D-L tripeptides, and depsipeptides can be prepared easily in good yields, and without detectable epimerization.

Experimental Section

Melting points are uncorrected. ^{1}H nmr spectra were recorded at 200 MHz on a Varian XL-200 spectrometer. Thin-layer chromatography was performed on silica gel 60 F_{254} plates and visualized by UV irradiation and/or iodine. Analytical HPLC was performed with the indicated solvent systems and flow rates on a Rainin HP chromatograph equipped with a 8 mm x 25 cm Dynamax-60A 8 mm silica gel column and UV detector (254 nm). Flash chromatography was performed using silica gel 60 (230 -400 mesh). Radial chromatography was performed on a Chromatotron Model 7924T from Harrison Research using a 2 mm layer of silica gel 60 PF_{254} containing gypsum. Elemental analyses were carried out by M-H-W Laboratories, Tuscon, AZ. Amino acids and Cbz-protected amino acids were purchased (Sigma). (S)-Methyl 2-hydroxyesters **1b-f** were prepared from the corresponding L-amino acids by a diazotization[18] -esterification[19] sequence. L-Methyl lactate, **1a**, and L-methyl mandelate, **1g**, were purchased commercially (Aldrich).

(S)-Methyl 2-((*p*-nitrobenzene)sulfonyl)oxy Esters (2). General Procedure. The (S)-2-hydroxy methyl ester was dissolved in a mixture of dichloromethane, triethylamine (1.0 equivalent), and 4-dimethylaminopyridine (DMAP)

(0.1 equivalent) and cooled to 0°C. A solution of p-nitrobenzenesulfonyl chloride (1.1 equivalent) in dichloromethane was added dropwise. After stirring at 0°C for 2 - 3 h, the mixture was washed with 1N HCl, brine, passed through a short pad of $MgSO_4$ and silica gel 60, and concentrated to provide the corresponding 2-nosyloxy esters . In most cases, the crude material was sufficiently pure to be used in the next reaction without further purification. Silica gel chromatography or recrystallization was used to give material of analytical purity.

(S)-Methyl 2-(((*p*-Nitrobenzene)sulfonyl)oxy)propanoate (2a) was prepared from (S)-methyl lactate **1a** (1.04 g, 10 mmol), triethylamine (1.5 mL), DMAP (250 mg), and p-nitrobenzenesulfonyl chloride (2.22 g, 10.0 mmol) as white solid (3.12 g, quantitative). A small amount of sample was purified for analysis by preparative TLC (hexane: ethyl acetate= 9: 1): mp 52 -53°C; $[\alpha]_D^{25}$ - 9.9 (c 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.59 (d, 3H, *J* = 7.0 Hz, $CHCH_3$), 3.71 (s, 3H, OCH_3), 5.12 (q, 1H, *J* = 7.0 Hz, $CHCH_3$), 8.17 and 8.42 (ABq, 4H, *J* = 9 Hz, aromatic CH); FTIR ($CDCl_3$) 3105, 2957, 1755, 1536, 1352, 1189 cm^{-1}. The ^1H NMR and IR were in good agreement with a racemic sample.[20] Anal. Calcd for $C_{10}H_{10}NO_7S$: C, 41.52; H, 3.83; N, 4.84. Found: C, 41.63; H, 3.87; N, 4.79.

(S)-Methyl 4-Methyl-2-((*p*-nitrobenzene)sulfonyl)oxy pentanoate (2b) was prepared from (S)-methyl 2-hydroxy-4-methylpentanoate **1b** (1.46 g, 10.0 mmol), triethylamine (1.5 mL), DMAP (250 mg), and p-nitrobenzenesulfonyl chloride (2.22 g, 10.0 mmol) as a pale yellow oil (3.19 g, 96%). A small amount of the crude product was purified for analysis by flash chromatography (hexane : ethyl acetate = 80 : 20): $[\alpha]_D^{25}$ -18.06 (c 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$,) δ 0.85 (two d, 6H, *J* = 6.4 Hz, $CH(CH_3)_2$), 1.57 - 1.90 (m, 3H, $CH_2CH(CH_3)_2$), 3.62 (s, 3H, OCH_3), 5.00 (dd, 1H, CHC=O), 8.10 and 8.35 (AB q, 4H, *J* = 9 Hz, aromatic CH). Anal. Calcd for $C_{13}H_{17}NO_7S$: C, 47.13; H, 5.14; N, 4.23. Found: C, 47.27; H, 5.04; N, 4.13.

(S)-Methyl 2-((*p*-Nitrobenzene)sulfonyl)oxy 3-phenylpropanoate (2c) was prepared from (S)-methyl 2-hydroxy-3-phenylpropanoate **1c** (1.80 g, 10.0 mmol), triethylamine (1.5 mL), DMAP (100 mg), and p-nitrobenzenesulfonyl chloride (2.22 g, 10.0 mmol) as a white solid (3.55 g, 97%). A small amount of the crude product was purified for analysis by flash chromatography (hexane : ethyl acetate = 90 : 10 to 80 : 20): mp 80 - 81°C; $[\alpha]_D^{25}$ -51.18 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.03 (two d, 1H, *J* = 15, 10 Hz, CH_2CH), 3.23 (two d, 1H, *J* = 15, 4 Hz, CH_2CH), 3.79 (s, 3H, OCH_3), 5.02 (dd, 1H, J = 10, 4 Hz, CH_2CH), 7.15 (m, 5H, aromatic CH), 7.75 and 8.16 (AB q, 4H, *J* = 9 Hz, aromatic CH). Anal. Calcd for $C_{16}H_{15}NO_7S$: C, 52.60; H, 4.11; N, 3.84. Found: C, 52.49; H, 4.07; N, 3.66.

(S)-Dimethyl 2-((*p*-Nitrobenzene)sulfonyl)oxy succinate (2d) was prepared from (S)-dimethyl 2-hydroxysuccinate **1d**(1.62 g, 10.0 mmol), triethylamine (1.5 mL), DMAP (250 mg), and p-nitrobenzenesulfonyl chloride (2.22 g, 10.0 mmol) as a pale yellow solid (2.75 g, 80%). A small amount of the crude product was purified for analysis by flash chromatography (hexane : ethyl acetate = 80 : 20 to 60 : 40): mp 56 - 61°C; $[\alpha]_D^{25}$ -18.86 (c 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.98 (m, 2H, CH_2CH), 3.66 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.41 (dd, 1H, CH_2CH), 8.16 and 8.42 (AB q, 4H, *J* = 9 Hz, aromatic CH); IR (neat) 3100, 2950, 1740 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_9S$: C, 41.50; H, 3.75; N, 4.03. Found: C, 41.79; H, 3,77; N, 3.88.

(S)-Methyl 3-Methyl-2-((*p*-nitrobenzene)sulfonyl)oxy butanoate (2e) was prepared from (S)-methyl 2-hydroxy-3-methylbutanoate **1e**(2.0 g, 15.1 mmol), triethylamine (2.2 mL), DMAP (200 mg), and p-nitrobenzenesulfonyl chloride (3.37 g, 15.2 mmol) as a pale yellow oil (3.36 g, 70%). A small amount of the crude product was purified for analysis by flash chromatography (hexane : ethyl acetate =80 : 20): $[\alpha]_D^{25}$ -4.4 (c 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 and 0.98 (two d, 6H, *J* =6.8, 6.8 Hz, $CH(CH_3)_2$), 2.25 (m, 1H, $CH(CH_3)_2$), 3.69 (s, 3H, OCH_3), 4.84 (d, 1H, *J* = 4.4 Hz, $CHCH(CH_3)_2$), 8.16 and 8.42 (AB q, 4H, *J* = 9 Hz, aromatic CH). Anal. Calcd for $C_{12}H_{15}NO_7S$: C, 45.43; H, 4.73; N, 4.42. Found: C, 45.43; H, 4.84; N, 4.46.

(2S, 3S)-Methyl 3-Methyl-2-((*p*-nitrobenzene)sulfonyl)oxy pentanoate (2f) was prepared from (2S,3S)-methyl 2-hydroxy-3-methylpentanoate **1f** (1.46 g, 10 mmol), triethylamine (1.5 mL), DMAP (250 mg), and p-nitrobenzenesulfonyl chloride (2.22 g, 10 mmol) as a colorless oil (2.86 g, 94%) after purification by flash chromatography (hexane : ethyl acetate = 95 : 5 to 80 : 20): $[\alpha]_D^{25}$ -3.51 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 0.95 (d, 3H, *J* = 6.8 Hz, $CHCH_3$), 1.2 - 1.5 (set of m, 3H, CH_2CH_3, $CHCH_3$), 3.68 (s, 3H, OCH_3), 4.89 (d, 1H, *J* = 4.8 Hz, $NsOCHCOOCH_3$), 8.16 and 8.41 (AB q, 4H, *J* = 9 Hz, aromatic CH); FTIR (neat) 3109, 2967, 1758, 1536, 1352, 1189 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_7S$: C, 47.12; H, 5.17; N, 4.23. Found: C, 47.22; H, 5.13; N, 4.21.

(S)-Methyl 2-((*p*-Nitrobenzene)sulfonyl)oxy 2-phenylacetate (2g) was prepared from (S)-methyl mandelate **1g** (1.0 g, 6.0 mmol), triethylamine (1.0 mL), DMAP (100 mg), and p-nitrobenzenesulfonyl chloride (1.56 g, 7.0 mmol) as a pale yellow oil (2.04 g, 97%). A small amount of the crude product was purified for analysis by flash chromatography (hexane : ethyl acetate = 80 : 20): $[\alpha]_D^{25}$ +10 .08 (c 1.2, DMF). Spectral data were in good agreement with an authentic racemic sample.[20]

(R)-Methyl 2-Azidoalkanoates (3) and (R)-Methyl 2-Azidoalkanoic Acids (4). General Procedure. To a stirred solution of (S)-methyl-2-((*p*-nitrobenzene)sulfonyl)oxy alkanoate (2) (3.0 mmol) in dimethylsulfoxide (10 mL) was added sodium azide (6.0 mmol). The mixture was heated to 55-60 °C for 16 hours. After cooling to room temperature, the resulting solution was poured into water (50 mL) and extracted with ether (4 x 50 mL). The ethereal extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated by rotary evaporator (bath temperature 30 °C) to provide a pale yellow oil. Most of the crude products obtained were pure by ^1H nmr spectroscopy

Further structure proof was obtained by hydrolysis. Solid $LiOH{\cdot}H_2O$ (2 equivalents) was added to a stirred solution of the azido alkanoate **3** in THF and H_2O at room temperature. The resulting solution was stirred for 30 min. After saturated $NaHCO_3$ was added, the solution was washed with ether and acidified by 6N HCl solution (pH 2) and extracted with ethyl acetate . The combined ethyl acetate extracts were washed with brine, passed through the short pad of $MgSO_4$ and silica gel 60 to provide a colorless oil. Most of the crude products obtained were spectroscopically pure.

(R)-Methyl 2-Azidopropanoate (3a) was obtained by using (S)-methyl 2-((*p*-nitrobenzene)sulfonyl)oxypropanoate **2a** (2.29 g, 7.9 mmol) and sodium azide (1.04 g, 16 mmol) as a colorless oil (750 mg, 83 %). ^1H NMR ($CDCl_3$) δ 1.48 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 3.80 (s, 3H, OCH3), 3.97 (q, 1H, *J* = 7.2 Hz, $CHCH_3$); FTIR (neat) 2980, 2950, 2080, 1740, 1445, 1200 cm^{-1}.

Azido acid **4a** was prepared from **3a** (640 mg, 5.6 mmol) and $LiOH{\cdot}H_2O$ (470 mg, 11.1 mmol) as a colorless oil (490 mg, 87%): $[\alpha]_D^{25}$ -21.0 (c 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.54 (d, 3H, *J* = 7.4 Hz, $CHCH_3$), 4.04 (q, 1H, *J* = 7.2 Hz, $CHCH_3$), 11.67 (brs, 1H, COOH); FTIR (neat) 3500 - 2500 (br), 2104, 1720, 1456, 1232 cm^{-1}.

Coupling of azido acid **4a** with (S)-α-methylbenzylamine was carried out by adding dicyclohexyl carbodiimide (1.42 g, 7.0 mmol) to a cooled (0 °C), stirred solution of **4a** (540 mg, 5.35 mmol), (S)-α-methylbenzylamine (730 mg, 6.0 mmol) and 1-hydroxybenzotriazole hydrate (HOBT) (810 mg, 6.0 mmol) in THF (50 mL). The resulting solution was stirred at 0 °C for 3 h and allowed to stir at room temperature overnight. After concentration, the white residue was taken up in ethyl acetate (100 mL) and filtered. The filtrate was washed with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **5a** as a white solid (890 mg, 81%) after purification by flash chromatography (hexane : ethyl acetate = 95 : 5 to 80 : 20): mp 78 - 79°C; $[\alpha]_D^{25}$ -99.5 (c 0.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.51 (two d, 6H, *J* = 7.0, 6.8 Hz, $CH(CH_3)_2$), 4.10 (q, 1H, *J* = 7.0 Hz, $CHCH_3$), 5.09 (m, 1H, $CHCH_3$), 6.66 (brs, 1H, NH), 7.31 (m, 5H, phenyl); FTIR($CHCl_3$) 3409, 3310, 3014, 2981, 2116, 1662, 1519, 1216

cm^{-1}; HPLC (hexane : ethyl acetate = 50 : 50, 1 mL/min, t_R = 4.34 and 4.73 in the ratio of 4 : 96). Anal. calcd for $C_{11}H_{14}N_4O$: C, 60.54; H, 6.47; N, 25.66. Found: C, 60.46; H, 6.47; N, 25.80.

For comparison racemic 2-azidopropanoic acid was prepared by the same procedure from (±)-lactic acid and condensed with (S)-α-methylbenzylamine to provide racemic azido amide **5a**.

(R)-Methyl 2-Azido-4-methylpentanoate (3b) was obtained from **2b** (1.0 g, 3.0 mmol) and sodium azide (400 mg, 6.1 mmol) as a colorless oil (460 mg, 90 %) after purification by flash chromatography (hexane : ethyl acetate = 100 : 0 to 95 : 5): ^{1}H NMR ($CDCl_3$) δ 0.96 (two d, 6H, *J* = 4.2 Hz, -CH(C*H*$_3$)$_2$), 1.67 (m, 3H, -C*H*$_2$C*H*(CH$_3$)$_2$), 3.80 (s, 3H, OCH$_3$), 3.80 (m, collapsed with OCH$_3$, N$_3$C*H*CO$_2$CH$_3$); FTIR (neat) 2950, 2080, 1735, 1430, 1190 cm^{-1}.

Azido acid **4b**was obtained from **3b** (460 mg, 2.7 mmol) and LiOH·H$_2$O (250 mg, 6 mmol) as a colorless oil (380 mg, 81 % for two steps): $[\alpha]_D^{25}$ +35.2 (c 1.25, MeOH) (Lit.[11] +36.3); ^{1}H NMR ($CDCl_3$) δ 0.99 (two d, 6H, *J* =4.4, 4.2 Hz, CH(C*H*$_3$)$_2$), 1.73 (m, 3H, C*H*$_2$C*H*(CH$_3$)$_2$), 3.88 (dd, 1H, *J* = 6.2, 5.8 Hz, N$_3$C*H*CO$_2$H), 11.0 (brs, 1H, CO$_2$H); FTIR(neat) 3500 - 2500(br), 2116, 1718, 1470, 1420, 1267, 1224 cm^{-1}. Spectral data were in good agreement with the literature values.[11]

(R)-Methyl 2-Azido-3-phenylpropanoate (3c) was obtained from **2c** (1.40 g, 3.8 mmol) and sodium azide (520 mg, 8.0 mmol) as a colorless oil (720 mg, 92 %): ^{1}H NMR ($CDCl_3$) δ 3.08 (ABX, 2H, C*H*$_2$Ph), 3.76 (s, 3H, OCH3), 4.07 (two d, 1H, *J* = 5.4, 5.8 Hz, N$_3$C*H*CO$_2$CH$_3$), 7.30 (m, 5H, phenyl); FTIR(neat) 3029, 2954, 2112, 1746, 1274, 1209 cm^{-1}.

Azido acid **4c** was obtained from **3c** (710 mg, 3.5 mmol) and LiOH·H$_2$O (300 mg, 7.1 mmol) as a colorless oil (620 mg, 93%): $[\alpha]_D^{25}$ +64.0 (c 1.4, $CHCl_3$) (Lit.[11] +68.6); ^{1}H NMR ($CDCl_3$) δ 3.15 (ABX, 2H, C*H*$_2$Ph), 4.15 (two d, 1H, N$_3$C*H*COOH), 7.32 (m, 5H, phenyl), 10.0 (brs, 1H, COOH); IR (neat) 3500 - 2500 (br), 2100, 1710, 1460, 1220 cm^{-1}. Spectral data were in agreement with literature values.[11]

(R)-Dimethyl 2-Azidosuccinate (3d) was obtained by reacting **2d** (2.21 g, 6.3 mmol) with 1,1,3,3-tetramethylguanidium azide[11] (3.0 g, 18 mmol) in dichloromethane at room temperature for 4 h as a white solid (920 mg, 78 %) after purification by flash chromatography (hexane : ethyl acetate = 95 : 5): ^{1}H NMR ($CDCl_3$) δ 2.82 (ABX, 2H, *J* = 7.6, 5.4 Hz, CHC*H*$_2$CO$_2$CH$_3$), 3.80 (s, 3H, OCH3), 3.84 (s, 3H, OC*H*3), 4.42 (dd, 1H, *J* = 6.0, 5.6 Hz, C*H*CH$_2$CO$_2$CH$_3$); FTIR (neat) 2957, 2112, 1754, 1439, 1212 cm^{-1}. The crude product **3d** was quite pure by ^{1}H nmr and was used without further purification. Further structure proof was obtained by the conversion to Cbz-Ala-D-Asp(OMe)-OMe, **6**, described below.

(R)-Methyl 2-Azido-3-methylbutanoate (3e) was obtained from **2e** (3.02 g, 9.5 mmol) and sodium azide (1.30 g, 20 mmol) as a colorless oil (1.37 g, 92 %): ^{1}H NMR ($CDCl_3$) δ 0.99 (two d, 6H, *J* = 4.0 Hz, CH(C*H*$_3$)$_2$), 2.19 (m, 1H, C*H*(CH3)2), 3.68 (d, 1H, *J* = 6.2 Hz, N$_3$C*H*CO$_2$CH$_3$), 3.80 (s, 3H, OCH3); FTIR(neat) 2968, 2112, 1747, 1264, 1204 cm^{-1}.

Azido acid **4e** was obtained from **3e** (1.20 g, 7.6 mmol) and LiOH·H$_2$O (640 mg, 15 mmol) as a colorless oil (980 mg, 90%): $[\alpha]_D^{25}$ +69.2 (c 2.3, MeOH) (Lit.[11] +71.5); ^{1}H NMR ($CDCl_3$) δ 1.05 (two d, 6H, *J* = 7.0, 6.8 Hz, CH(C*H*$_3$)$_2$), 2.26 (m, 1H, C*H*(CH$_3$)$_2$), 3.79 (d, 1H, *J* = 5.6 Hz, N$_3$C*H*COOH), 11.72 (brs, 1H, COOH); IR (neat) 3500 - 2500 (br), 2100, 1710, 1460, 1260, 1220 cm^{-1}. Spectral data were in agreement with literature data.[11]

(2R, 3S)-Methyl 2-Azido-3-methylpentanoate (3f) was obtained from **2f** (2.39 g, 7.2 mmol) and sodium azide (1.04 g, 16 mmol) as a colorless oil (1.17 g, 95 %): ^{1}H NMR ($CDCl_3$) δ 0.95 (overlapping d and t, *J* = 6.6 Hz, 6H, 2 x C*H*$_3$), 1.2 - 1.6 and 2.0 (set of m, 3H, C*H*$_2$CH$_3$, C*H*CH$_3$), 3.81 (s, 3H, OCH$_3$), 3.91 (d, 1H, *J* = 5.0 Hz, N$_3$C*H*CO$_2$CH$_3$); FTIR (neat) 2965, 2107, 1747, 1460, 1261, 1203 cm^{-1}.

Azido acid **4f** was obtained from **3f** (560 mg, 3.27 mmol) and LiOH·H$_2$O (280 mg, 6.7 mmol) as a colorless oil (450 mg, 88%): $[\alpha]_D^{25}$ +73.5 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97 (overlapping t and d, 6H, 2 x CH$_3$), 1.40 (set of m, 2H,

CH_2CH_3), 2.00 (m, 1H, $CHCH_3$), 4.00 (d, 1H, J = 4.4 Hz, $N_3CHCOOH$); FTIR (neat) 2968 (br), 2110, 1719, 1460, 1419, 1384 cm^{-1}.

Coupling of **4f** with (S)-α-methylbenzylamine was carried out by adding DCC (720 mg, 3.5 mmol) to a THF solution of **4f** (440 mg, 2.87 mmol), (S)-α-methylbenzylamine (370 mg, 3.0 mmol), and HOBT (410 mg, 3.0 mmol). Amide **5f** was obtained as a white solid (450 mg, 60%) after purification by flash chromatography (hexane : ethyl acetate = 95 : 5 to 90 : 10): mp 92 - 93 °C; $[\alpha]_D^{25}$ -0.8 (c 1.0, $CHCl_3$), -117.6 (c 1.1, MeOH); ^1H NMR ($CDCl_3$) δ 0.75 (d, J = 6.8 Hz, 3H, $CHCH_3$), 0.98 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.40 (set of m, 2H, CH_2CH_3), 1.53 (d, 3H, J = 7.0 Hz, $NHCHCH_3$), 2.13 (m, 1H, $CHCH_3$), 4.02 (d, 1H, J = 3.0 Hz, $N_3CHC{=}O$), 5.17 (m, 1H, J = 7.4 Hz, $NHCHCH_3$), 6.68 (br, 1H, NH), 7.32 (m, 5H, phenyl). A minor NMR doublet at δ 3.92 (J=3Hz) was assigned to the $N_3CHC{=}O$ proton of the (2S)-diastereomer thus a 97 : 3 ratio of the diastereomers was calculated. FTIR($CHCl_3$) 3409, 2968, 2111, 1665, 1513, cm^{-1}. Anal. calcd for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.50; H, 7.72; N, 21.46.

(R)-Methyl 2-Azidophenylacetate (3g) was prepared from **2g** (1.06 g, 3.0 mmol) and 1,1,3,3-tetramethylguanidinium azide (1.43 g, 9.0 mmol) as a pale yellow oil in quantitative yield: ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H, $OCH3$), 5.00 (s, 1H, $N_3CHCO_2CH_3$), 7.41 (m, 5H, phenyl); FTIR (neat) 3033, 2954, 2107, 1745, 1455, 1196 cm^{-1}. Azido acid **4g** was obtained from **3g** (570 mg, 3.0 mmol) and $LiOH{\cdot}H_2O$ (250 mg, 6 mmol) as a colorless oil (300 mg, 56%): $[\alpha]_D^{25}$ -62.0 (c 1.0, $CHCl_3$) (Lit.[11] -175); ^1H NMR ($CDCl_3$) δ 5.03 (s, 1H, $N_3CHCOOH$), 7.42 (m, 5H, phenyl), 9.40 (br, 1H, $COOH$); FTIR (neat) 3034 (br), 2110, 1726, 1455, 1226 cm^{-1}. The spectral data agreed with the literature values.[11]

Synthesis of L-D Dipeptide (6) Using (R)-2-Azidoesters. General Procedure for L-D Dipeptides. Triphenylphosphine (1.31 g, 5.0 mmol) was added to a stirred solution of (R)-dimethyl 2-azidosuccinate **3d** (460 mg, 2.46 mmol) in THF (20 mL) at room temperature. The resulting solution was stirred for 2 days and H_2O (65 mL, 3.6 mmol) was added and stirring was continued 2 additional days. The reaction mixture was diluted with THF (30 mL) and cooled to 0 °C, and HOBT (500 mg, 3.7 mmol), Cbz-Ala-OH (670 mg, 3.0 mmol), followed by DCC (820 mg, 4.0 mmol) were added. The solution was stirred at 0 °C for 3 h and at room temperature overnight. After concentration by rotary evaporation, the residue was taken up into ethyl acetate (100 mL) and filtered. The filtrate was washed with 1N HCl (100 mL), saturated $NaHCO_3$(100 mL), and brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel 60, and concentrated to provide Cbz-Ala-D-Asp(OMe)-OMe **6** as a pale yellow oil. The crude product was purified by flash chromatography (hexane : ethyl acetate = 80 : 20 to 50 : 50) to provide a white solid (860 mg, 95 %): mp 97 - 98°C; $[\alpha]_D^{25}$ -43.2 (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (d, 3H, J = 7.0 Hz, $CHCH_3$), 2.94 (m, 2H, $CH_2CO_2CH_3$), 3.68 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.31 (m, 1H, $NHCH$), 4.86 (m, 1H, $NHCH$), 5.12 (s, 2H, CH_2Ph), 5.37 (br, 1H, NH), 7.10 (br, 1H, NH), 7.36 (s, 5H, phenyl). NMR showed no detectable evidence of a second diasteromer. Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.89; H, 6.12; N, 7.65.

It was subsequently found that reduction of the azide function could be carried out without racemization by refluxing the azidoester with triphenylphosphine for 5 h followed by addition of water and refluxing for an additional 5 h.

Boc-Phe-D-Ala-OMe (8) was prepared from **3a** (610 mg, 4.7 mmol), Ph_3P (2.5 g, 9.5 mmol) at reflux in THF (100 mL) for 5 h and addition of H_2O (130 mL, 7.0 mmol) with additional reflux for 5 h. The coupling reaction was carried out by using Boc-Phe-OH (1.32 g, 5mmol), HOBt (680 mg, 5 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (1.54 g, 8 mmol) to provide **8** as a white soild (1.48 g, 90 %) after purification by flash chromatohraphy (hexane : ethyl acetate = 90 : 10 to 80 : 20): mp 63-66°C (Lit.[21] 63-64°C); $[\alpha]_D^{25}$ +18.31 (c 1.06, MeOH) (lit.[21] -21.1); ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 7.2 Hz, $CHCH_3$), 1.41 (s, 9H, $OC(CH_3)_3$), 3.06 (d, 2H, J = 7Hz, CH_2Ph), 3.72 (s, 3H, OCH_3), 4.38 (m, 1H, $NHCH$), 4.52 (m, 1H, $NHCH$), 5.08 (br, 1H, NH), 6.30 (brd, 1H, NH), 7.27 (m, 5H, phenyl). The spectral data

agreed with the literature values.[21] No evidence for the L-L diastereomer of **8** was observed by comparison with an authentic sample Boc-Phe-Ala-OMe, prepared by the reaction of Boc-Phe-OH with HCl·-Ala-OMe in the presence of DCC and HOBt.

Cbz-Ala-D-Val-O-t-Bu (9). To a stirred, 0 °C solution of (R)-2-azido-3-methylbutanoic acid **4e** (760 mg, 5.3 mmol) in dichloromethane (50 mL) was added t-butanol (2 mL), DMAP (70 mg), followed by DCC (1.24 g, 6.0 mmol). The resulting solution was stirred for 3 h at 0°C and at room temperature overnight. After concentration by rotary evaporation, the residue was taken up into the ethyl ether (100 mL) and filtered. The filtrate was washed with 1N HCl (100mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated to provide a (R)-t-butyl 2-azido-3-methylbutanoate **7e** (940 mg, 89 %) as pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.98 and 1.01 (two d, 6H, J = 4.2 Hz, CH(C*H*$_3$)$_2$), 1.51 (s, 9H, OC(C*H*$_3$)$_3$), 2.16 (m, 1H, C*H*(CH$_3$)$_2$), 3.50 (d, 1H, N$_3$C*H*CO). Above oil was used for the next reaction without further purification.

A solution of **7e** (940 mg, 4.7 mmol) and Ph_3P (2.5 g, 9.5 mmol) in THF (80 mL) was heated at reflux for 12 h. After the solution was cooled to room temperature, H_2O (130 mL, 7.2 mmol) was added, and the resulting solution was heated at reflux for an additional 12 hours. After the solution was cooled to 0°C, Cbz-Ala-OH (1.11 g, 5.0 mmol), HOBt (680 mg, 5.0 mmol), and DCC (1.5 g, 7.3 mmol) were added successively. After 3 h stirring at 0°C and at room temperature overnight, the milky solution was concentrated by rotary evaporator. The residue was taken up into ethyl acetate (100 mL) and filtered. The filtrate was washed with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel 60 to provide **9** as a white solid (1.33 g, 75 %) after purification by flash chromatography (hexane : ethyl acetate = 95 : 5 to 80 : 20): mp 50 - 52 °C; $[\alpha]_D^{25}$ -18.65 (c 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (two d, 6H, CH(C*H*$_3$)$_2$), 1.41 (d, 3H, J = 7.2 Hz, CHC*H*$_3$), 1.47 (s, 9H, OC(C*H*$_3$)$_3$), 2.14 (m, 1H, C*H*(CH$_3$)$_2$), 4.27 (m, 1H, NHC*H*CH$_3$), 4.43 (two d, 1H, J = 4.4 Hz, NHC*H*COO-), 5.13 (s, 2H, C*H*$_2$Ph), 5.40 (br, 1H, N*H*), 6.50 (br, 1H, N*H*), 7.36 (s, 5H, phenyl). NMR showed no detectable evidence for the L-L diastereomer. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.22; H, 7.70; N, 7.43.

Cbz-Val-D-Val-O-t-Bu (10) was prepared by using (R)-t-butyl 2-azido-3-methylbutanoate **7e** (330 mg, 1.65 mmol) and Ph_3P (870 mg, 3.3 mmol) at reflux for 6 h, and H_2O (50 mL, 2.8 mmol) at reflux for 12 h. The coupling reaction was carried out by using Cbz-Val-OH (450 mg, 1.8 mmol), HOBt (240 mg, 1.8 mmol), and EDCI (580 mg, 3 mmol) to provide **10** as a colorless oil (580 mg, 87 %) after purification by flash chromatography (hexane : ethyl acetate = 90 : 10 to 80 : 20): $[\alpha]_D^{25}$ -11.09 (c 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.95 (set of m, 12 H, 2 x CH(C*H*$_3$)$_2$), 1.46 (s, 9H, OC(C*H*$_3$)$_3$), 2.16 (m, 2H, 2 x C*H*(CH$_3$)$_3$), 4.11 (m, 1H, NHC*H*), 4.44 (dd, 1H, J = 4.2 Hz, NHC*H*), 5.12 (s, 2H, C*H*$_2$Ph), 5.43 (br, 1H, NH), 6.38 (brd, 1H, NH), 7.35 (s, 5H, phenyl). Anal. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 64.88;H, 8.23; N, 6.82.

N$_3$-D-Ala-Ala-OMe (11) was prepared by adding **4a** (970 mg, 8.4 mmol), HOBt (1.21 g, 9.0 mmol), and then DCC (1.85 g, 9.0 mmol) to a 0 °C solution of Ala-OMe (8.5 mmol) in THF (40 mL) and dichloromethane (10 mL).The resulting solution was stirred at 0 °C for 3 h and at room temperature overnight. After concentration by rotary evaporation, the residue was taken up in ethyl acetate (100 mL) and filtered. The filtrate was washed with 1N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL), passed through a short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **11** as a colorless oil (890 mg, 53 %) after purification by flash chromatography (hexane : ethyl acetate = 80 : 20 to 60 : 40): $[\alpha]_D^{25}$ -34.6 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3H, J = 7.0 hz, CHC*H*$_3$), 1.55 (d, 3H, J = 7.0 Hz, CHC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.10 (q, 1H, J = 7.0 Hz, C*H*CH$_3$), 4.57 (pentet, 1H, J = 7.4 Hz, C*H*CH$_3$), 6.90 (br, 1H, N*H*); FTIR(neat) 3312, 2987, 2117, 1746, 1662, 1532, 1454, 1214, 1159 cm^{-1}. Anal Calcd for $C_7H_{12}N_4O_3$: C, 42.00; H, 6.04; N, 27.99. Found: C, 41.90; H, 6.19; N, 28.11. No evidence of the L-L diastereomer was observed in the ^{1}H nmr spectrum.

N_3-D-Phe-Ala-OMe (12) was prepared by adding **4c** (2.87 g, 15 mmol), HOBt (2.03g, 15 mmol), and then DCC (3.45 g, 17 mmol) to a 0°C solution of Ala-OMe (16 mmol) in THF (80 mL) and dichloromethane (20 mL). The resulting solution was stirred at 0 °C for 3 h and at room temperature overnight. After concentration by rotary evaporation, the residue was taken up in ethyl acetate (200 mL) and filtered. The filtrate was washed with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **12** as a colorless oil (3.31 g, 89 %) after the crude product was purified by flash chromatography (hexane : ethyl acetate = 95 : 5 to 80 : 20): $[\alpha]_D^{25}$ -20.4 (c 0.47, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 2.98 (A of ABX, 1H, CH_2Ph), 3.36 (B of ABX, 1H, CH_2Ph), 3.75 (3H, OCH_3), 4.14 (m, 1H, CHCO), 4.56 (m, 1H, CHCO), 6.73 (br, 1H, NH), 7.31 (m, 5H, phenyl); FTIR (neat) 3317, 3064, 2953, 2108, 1744, 1662, 1528, 1454, 1214 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, H, 5.84; N, 20.28. Found: C, 56.72; H, 5.84; N, 20.14.

Cbz-Ala-D-Val-Ala-OMe (15) was prepared by treating Cbz-Ala-D-Val-O-t-Bu **9** (950 mg, 2.45 mmol) in dichloromethane (10 mL) with trifluoroacetic acid (2 mL). The resulting soluting was stirred at room temperature for 3 hours. After concentration in vacuo, a sticky oil was obtained. To a solution of this oil in THF (10 mL) was added a solution of Ala-OMe (prepared by adding triethylamine (0.42 mL, 3 mmol) to a stirred suspension of HCl-Ala-OMe (420 mg, 3mmol) in THF (80 mL) at 0 °C). Next was added HOBt (410 mg, 3 mmol), followed by DCC (620 mg, 3 mmol). The resulting mixture was stirred at 0 °C for 3 h and at room temperature overnight. After concentration by roatary evaporator, the residue was taken up in ethyl acetate (100 mL) and filtered. The filtrate was washed with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), passed through a short pad of $MgSO_4$ and silica 60, and concentrated to provide **15** as a white solid (940 mg, 94 %) after purification of the crude product by flash chromatography (hexane : ethyl acetate = 80 : 20 to 60 : 40): mp 200 - 202 °C; $[\alpha]_D^{25}$ -10.4 (c 0.5, DMF); ^1H NMR (400 MHz, DMSO-d_6) δ 0.81 (dd, 6H, *J* = 7.6 Hz, $CH(CH_3)_2$), 1.21 and 1.27 (two d, 6H, *J* = 7.2 Hz, 2 x $CHCH_3$), 2.00 (m, 1H, $CH(CH_3)_2$), 3.61 (s, 3H, OCH_3), 4.25 (set of m, 3H, 3 x NHCH), 5.02 (s, 2H, CH_2Ph), 7.35 (m, 5H, phenyl), 7.50 (brd, 1H, NH), 7.85 (brd, 1H, NH), 8.25 (brd, 1H, NH). Anal. Calcd for $C_{20}H_{29}N_3O_6$: C, 58.95; H, 7.17; N, 10.31. Found: C, 58.71; H, 6.94; N, 10.14.

Synthesis of Cbz-L-D-L-Tripeptide Esters. Cbz-Gly-D-Phe-Ala-OMe (14).General Procedure. A mixture of N_3-D-Phe-Ala-OMe **12** (740 mg, 2.8 mmol) and Ph_3P (1.58 g, 6 mmol) in THF (80 mL) was heated at reflux for 10 h. After cooling to room temperature, H_2O (90 mL, 5 mmol) was added, and the resulting solution was heated at reflux for 12 h. After cooling the reaction mixture to 0 °C, Cbz-Gly-OH (700 mg, 3.5 mmol) and HOBt (480 mg, 3.5 mmol), followed by EDCI (960 mg, 5 mmol) were added. The resulting solution was stirred at 0°C for 3 h and at room temperature for overnight. After concentration, the residue was taken up into ethyl acetate (100 mL) and 1N HCl (100 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phases were washed with sat. $NaHCO_3$ (100 mL), brine (100 mL), passed through the short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **14** as a white solid (480 mg, 62 %) after purification by flash chromatography (hexane : ethyl acetate = 80 : 20 to 50 : 50): mp 123 - 127 °C; $[\alpha]_D^{25}$ +9.54 (c 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 (d, 3H, *J* = 7.4 Hz, $CHCH_3$), 3.06 (m, 2H, $CHCH_2Ph$), 3.67 (s, 3H, OCH_3), 3.85 (d, 2H, *J* = 5.4 Hz, $NHCH_2CO$), 4.47 (m, 1H, NHCHCO), 4.77 (m, 1H, NHCHCO), 5.10 (s, 2H, CH_2Ph), 5.64 (br, 1H, NH), 6.63 (br, 1H, NH), 6.92 (br, 1H, NH), 7.10 - 7.50 (m, 10 H, phenyl). Anal Calcd for $C_{23}H_{27}N_3O_6$: C, 62.57; H, 6.16; N, 9.52. Found: C, 62.35; H, 6.23; N, 9.42. No evidence of epimerization was observable in the ^1H nmr spectrum.

Cbz-Val-D-Ala-Ala-OMe (13) was prepared by using N_3-D-Ala-Ala-OMe **11**, (400 mg, 2.0 mmol), Ph_3P (1.06 g, 4.0 mmol), and then H_2O (50 mL, 2.8 mmol) in THF (50 mL) at room temperature for 2 days, respectively. The coupling reaction was carried out by using Cbz-Val-OH (500 mg, 2.0 mmol), HOBt (270 mg, 5 mmol), and EDCI (580 mg, 3 mmol) to

provide **11** as a white solid (480 mg, 60 %) after purification by flash chromatography (hexanae : ethyl acetate = 80 : 20 to 50 : 50): mp 185 - 187 °C; $[\alpha]_D^{25}$ +18.04 (c 0.77, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (two d, 6H, *J* = 6.4 Hz, $CH(CH_3)_2$), 1.38 (d, 6H, *J* = 7.2 Hz, 2 x $CHCH_3$), 2.13 (m, 1H, $CH(CH_3)_2$), 3.69 (s, 3H, OCH_3), 3.96 (t, 1H, $NHCHCH(CH_3)_2$), 4.56 (two q, 2H, 2 x $NHCHCH_3$), 5.10 (ABq, 2H, CH_2Ph), 5.58 (brd, 1H, NH), 6.76 (brd, 1H, NH), 7.12 (brd, 1H, NH), 7.35 (s, 5H, phenyl). Anal. Calcd for $C_{20}H_{29}N_3O_6$: C, 58.95; H, H, 7.17; N, 10.31. Found: C, 58.81; H, 7.06; N, 10.28. No evidence for epimerization was observable by ^1H nmr.

(S)-Methyl O-[(R)-2-azidopropanoyl]-2-oxy-3-phenylpropanoate (16) was prepared by adding (S)-methyl 2-hydroxy-3-phenylpropanoate **1c** (830 mg, 5 mmol), DMAP (70 mg), and then DCC (1.13 g, 5.5 mmol) to a stirred, 0 °C solution of (R)-2-azidopropanoic acid **4a** (575 mg, 5.0 mmol) in dichloromethane (80 mL). The resulting solution was stirred at 0 °C for 3 h and at room temperature overnight. After concentration by rotary evaporation, the residue was taken up in ethyl acetate (150 mL) and filtered. The filtrate was washed with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **16** as a colorless oil (1.18 g, 85 %) after purification by flash chromatography (hexane : ethyl acetate = 95 : 5 to 90 : 10): $[\alpha]_D^{25}$-23.6 (c 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.36 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 3.20 (ABq, 2H, CH_2COOCH_3), 3.76 (s, 3H, OCH_3), 3.96 (q, 1H, J = 7.2 Hz, $CHCH_3$), 5.32 (dd, 1H, *J* = 4.2 Hz, $CHCH_2$), 7.29 (m, 5H, phenyl); FTIR (neat) 3014, 2943, 2109, 1749, 1455, 1255, 1185 cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.53; H, 5.66; N, 15.12.

Cbz-Gly-D-Ala-(O)-Phe-OMe (17) was prepared by treating **16** (1.10 g, 3.97 mmol) in THF (100 mL) with Ph_3P (2.2 g, 8.4 mmol) and refluxing for 8 h. After addition of H_2O (110 mL, 6.1 mmol), the reaction was kept at room temperature for 2 days. The coupling reaction was carried out by adding Cbz-Gly-OH (880 mg, 4.2 mmol), HOBt (570 mg, 4.2 mmol), and DCC (1.45 g, 7.0 mmol) as before to provide **17** as a colorless semi-solid (1.43 g, 81 %) after purification of the crude product by flash chromatography (hexanae : ethyl acetate = 50 : 50): $[\alpha]_D^{25}$ -10.6 (c 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (d, 3H, *J* = 7.0 Hz, $CHCH_3$), 3.16 (ABq, 2H, $CHCH_2Ph$), 3.74 (s, 3H, OCH_3), 3.85 (d, 2H, $NHCH_2CO$), 4.65 (m, 1H, $NHCHCH_3$), 5.12 (s, 2H, CH_2Ph), 5.30 (dd, 1H, $CHCH_2Ph$), 5.50 (br, 1H, NH), 6.60 (br, 1H, NH), 7.2 - 7.5 (m, 10H, phenyls). Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.23; H, 6.04; N, 6.46.

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