A Fast Procedure for the Preparation of Amides/Peptides from Carboxylic Acids and Azides via Two Redox Reactions: Application to the Synthesis of Methionine Enkephalin

Sunil K. Ghosh,* Rekha Verma, Usha Ghosh, and Vasant R. Mamdapur

Bio-Organic Division, Bhabha Atomic Research Centre, Bombay 400085, India

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A one-pot self regulated approach for the synthesis of amides/peptides based on two reduction–oxidation (redox) reactions has been described. The primary and secondary amides/peptides are made by using azidotrimethylsilane and alkyl azides/α-azido acid derivatives respectively as the direct source of amine components. Benzeneselenol, generated in the reaction medium during carboxyl activation, has been found to be an effective reducing agent for the conversion of azides to primary amines. The methodology has been applied to the synthesis of methionine enkephalin.

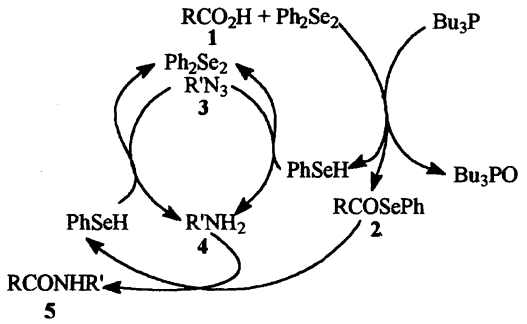
Ammonia and primary amines/amino acid or peptide esters have been used as the amine component for the synthesis of carboxamides and peptides. The reactions are usually performed[1] by the treatment of an activated derivative of the carboxylic acid (carboxyl component) with an appropriate amine component. Racemization and side reactions[2] are unavoidable during amide/peptide bond formation. The racemization problem becomes more serious, especially, in the presence of tertiary bases and quaternary ammonium salts.[3] In the conventional methods of peptide synthesis, the amine component is usually generated from its salt by adding tertiary bases to the reaction medium which increases the risk of racemization. However, this has been minimized to a certain extent by using additives like *N*-hydroxysuccinimide[4] (HOSu), 1-hydroxy-1*H*-benzotriazole[5] (HOBt), and 3-hydroxy-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine[6] (HOAt) during condensation. Conventional methods also have restrictions for the synthesis of the peptides containing unnatural amino acids.[7] In order to obtain such synthetic peptides, one must prepare the chiral amino acid with desired configuration and modified side chains. In this regard, the azide esters hold great promise. Several enantiocontrolled routes to α-azido acid derivatives have been developed[8—11] and the reduction of azido acids has proven to be an extremely attractive approach for the synthesis of proteinogenic as well as non-proteinogenic amino acids which have subsequently been used for the synthesis of biologically active peptides and their analogues.

Methodology

The direct use of azide as amine component for the synthesis of carboxamides and peptides is gaining much attention for minimizing racemization in the peptide synthesis. A few protocols have been reported which include the reaction of an iminophosphorane (derived from an azide and a phosphine) or an azide–phosphine complex with a carboxylic acid,[12,13] or its derivatives like arenethiol/areneselenol esters,[14] and its mixed anhydrides.[14,15] The thiocarboxylic acids[16,17] also react with azides and directly give carboxamides.

The reduction of an azide to the corresponding amine in the presence of a preformed activated carboxyl component would be a better approach for the synthesis of carboxamides. This has been applied for the synthesis of macrolactams[18] by activating the carboxylic acid group of 10- and 9-azidodecanoic acids followed by azido group reduction and cyclization in a separate pot. We envisaged that in situ chemoselective reduction of the azido group to amino group by the by-product generated during carboxylic acid activation would be an attractive approach. The rationale behind this idea are (i) it can be carried out in the same reaction pot, (ii) no interference with the activated carboxyl group, and (iii) it will not require any additional reagents. This will be possible only by judicious selection of suitable redox reactions for carboxylic acid activation and subsequent azide reduction.

In the course of our studies on the formation of a peptide bond under milder conditions, we have reported[19,20] a self-regulated approach to peptide synthesis based on two redox reactions viz. Ph_2Se_2–Bu_3P in presence of a carboxylic acid (RCOOH) (activates the carboxyl component to its *Se*–phenyl carboselenoate ester; see Eq. 1) and PhSeH–NMMNO (NMMNO = *N*-methylmorpholine *N*-oxide) [generates *N*-methylmorpholine (NMM); see Eq. 2]. *N*-Methylmorpholine liberates the free amine from its salt (Eq. 3) which subsequently participates in the condensation reaction (Eq. 4) to give the peptide and a molecule of benzeneselenol. This suggested that benzeneselenol may be a mild effective reducing agent for the reduction of azides in situ. We, therefore, felt that addition of an azide to the reaction pot containing a *Se*–phenyl carboselenoate and benzeneselenol may fulfil both the requirements viz. oxidation of benzeneselenol to diphenyl diselenide with synchronous generation of amine from azide. We report herein that this approach can be used



Scheme 1.

for the synthesis of amides/peptides by direct use of an azido derivative as a source of an amine component. A preliminary communication[21] on part of this work has already been published. Extension of this protocol for the synthesis of primary amide derivatives of protected amino acids and peptides has been carried out using azidotrimethylsilane. The methodology has also been applied for the synthesis of protected methionine enkephalin by condensation of *N*-protected tyrosine with a tripeptide azido derivative.

$$RCO_2H + Ph_2Se_2 + Bu_3P \rightarrow RCOSePh + Bu_3PO + PhSeH \quad (1)$$

$$2PhSeH + NMMNO \rightarrow NMM + Ph_2Se_2 + H_2O \quad (2)$$

$$R'NH_2 \cdot HX + NMM \rightarrow R'NH_2 + NMM \cdot HX \quad (3)$$

$$R'NH_2 + RCOSePh \rightarrow RCONHR' + PhSeH \quad (4)$$

Treatment of a mixture of *N*-protected amino acid/carboxylic acid (RCO_2H) **1** and Ph_2Se_2 with Bu_3P at room temperature generates the intermediate *Se*-phenyl carboselenoate (RCOSePh) **2** and benzeneselenol. Addition of an azido component ($R'N_3$) (alkyl azide, α-azido carboxylic acid derivative, azidotrimethylsilane) **3** oxidizes the benzeneselenol to diphenyl diselenide resulting in its reduction to the amine ($R'NH_2$) **4**. This on subsequent condensation with **2** gives the desired amide/peptide ($RCONHR'$) **5** and a molecule of benzeneselenol which propagates the chain reaction (Scheme 1) consisting a self-regulated one pot amide/peptide synthesis as a result of two successive redox reactions.

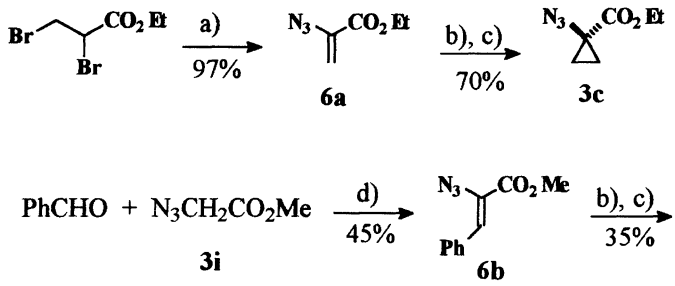
Results and Discussion

Preparation of Azides. Azides **3a**, **3f**, **3g** (Table 1) and **3i** (Scheme 2) used in this study were prepared following the literature procedure[22] from the corresponding bromides under phase transfer conditions. Compound **3b** (Table 1) was prepared following the method of Zaloom and Roberts[23] using alanine methyl ester and trifluoromethanesulfonyl azide. The synthesis of ethyl 1-azidocyclopropanecarboxylate (**3c**) and methyl 1-azido-*t*-2-phenyl-*r*-1-cyclopropanecarboxylate (**3d**) are shown in Scheme 2. The vinyl azide **6a** was prepared from ethyl 2,3-dibromopropionate using 3 molar amounts of sodium azide in dimethylformamide with modifications of the reported procedure[24] (12 h, 60 °C). We found that the reaction proceeded rapidly at 60 °C and gave a quantitative yield of **6a** when heated for 30 min only. The product decomposes on storage at room temperature but reasonably stable when stored in a refregerator. The vinyl azide **6b** was in turn prepared from benzaldehyde and methyl azidoacetate (**3i**) following the literature procedure.[25] Azide **6a** on treatment with an ethereal solution of diazomethane gave pyrazoline adduct[26] which on thermolysis gave the cyclopropyl azide **3c** in 70% yield. The azide **3d** was also prepared from azide **6b** by the addition of diazomethane followed by thermolysis of

Table 1. List of Peptides

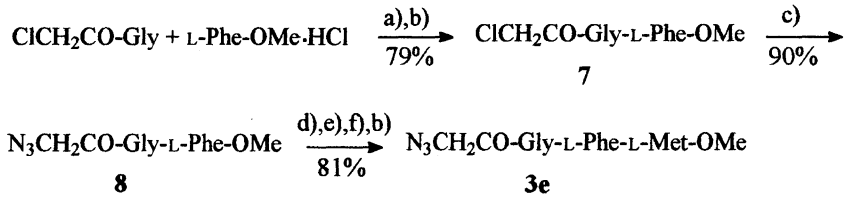
Entry	Carboxyl component[a]	Azide component	Peptide[a]	% Yield[b]	Solvent
1.	Bz–Leu (**1a**)	$N_3CH_2CO_2Et$ (**3a**)	Bz–Leu–Gly–OEt (**5a**)	93	A
	Bz–Leu (**1a**)	$N_3CH_2CO_2Et$ (**3a**)	Bz–Leu–Gly–OEt (**5a**)	85	B
	Bz–Leu (**1a**)	$N_3CH_2CO_2Et$ (**3a**)	Bz–Leu–Gly–OEt (**5a**)	79	C
2.	Z–Gly–Phe (**1b**)	$N_3CH_2CO_2Et$ (**3a**)	Z–Gly–Phe–Gly–OEt (**5b**)	91	A
3.	Bz–Phe (**1c**)	L-$N_3CH(Me)CO_2Et$ (**3b**)	Bz–Phe–Ala–OEt (**5c**)	80	A
4.	Bz–Val (**1d**)	L-$N_3CH(Me)CO_2Et$ (**3b**)	Bz–Val–Ala–OEt (**5d**)	84	A
5.	Ac–Phe (**1e**)	L-$N_3CH(Me)CO_2Et$ (**3b**)	Ac–Phe–Ala–OEt (**5e**)	80	A
6.	Z–Gly (**1f**)	(**3c**)	Z–Gly–Acc–OEt (**5f**)	47	A+C
				(72)	A+C
7.	Boc–Phe (**1g**)	(**3c**)	Boc–PHe–Acc–OEt (**5g**)	(73)	A+C
8.	Z–Val (**1h**)	(**3c**)	Z–Val–Acc–OEt (**5h**)	24	A+C
				(65)	A+C
9.	Z–Gly (**1f**)	DL- (**3d**)	Z–Gly–DL–X–OMe[c] (**5i**)	(50)	A+C
10.	Boc–Tyr (**1i**)	N_3CH_2CO–Gly–Phe–Met–OMe (**3e**)	Boc–Tyr–Gly_2–Phe–Met–OMe (**5j**)	(88)	B
11.	Z–DL–Phe (**1j**)	N_3–$(CH_2)_5CH_3$ (**3f**)	Z–DL–Phe–NH–$(CH_2)_5CH_3$ (**5k**)	78	A
12.	Z–DL–Phe (**1j**)	N_3–$(CH_2)_6CH_3$ (**3g**)	Z–DL–Phe–NH–$(CH_2)_6CH_3$ (**5l**)	80	A
13.	Z–Phe (**1k**)	Me_3SiN_3 (**3h**)	Z–Phe–NH_2 (**5m**)	88	A+C
14.	Z–Ala (**1l**)	Me_3SiN_3 (**3h**)	Z–Ala–NH_2 (**5n**)	89	A+C
15.	Z–Gly–Phe (**1b**)	Me_3SiN_3 (**3h**)	Z–Gly–Phe–NH_2 (**5o**)	83	A

a) All amino acids used are of L-configuration, unless otherwise mentioned. b) Yields given in parentheses corresponding to use of HOBt as catalyst. c) X = 1-amino-*t*-2-phenyl-*r*-1-cyclopropanecarboxylate. Solvents: A = CH_2Cl_2; B = MeCN; C = DMF.



Reagents: a) NaN_3, DMF; b) CH_2N_2, ether; c) CCl_4, heat; d) NaOMe, MeOH

Scheme 2.



Reagents: a) Et_3N,DMAP; b) DCCI; c)NaN_3, DMF; d) NaOH, MeOH, THF; e) H_3O^+ f) L-Met-OMe, HOSu

Scheme 3.

the diazomethane adduct.[26] The azide **3e** used in the synthesis of methionine enkephalin (**5j**) was prepared as shown in Scheme 3. *N*-Chloroacetylglycine was coupled with phenylalanine methyl ester using dicylohexylcarbodiimide (DCCI) in the presence of 4-dimethylaminopyridine (DMAP) to give the peptide **7** in good yield. Nucleophilic displacement of the chlorine in **7** with azide anion (an exceptionally easy process with α-halo acid derivatives) proceeded in dimethylformamide at room temperature to give the azide **8**. This azido-ester **8** was hydrolyzed to give the intermediate azido acid which was coupled with methionine methyl ester using DCCI and *N*-hydroxysuccinimide to give the protected tripeptide azido derivative **3e** in good yield.

Preparation of Amides and Peptides. The amides and peptides synthesized using our protocol are listed in Table 1. Young's peptide,[27] Bz–Leu–Gly–OEt (**5a**) has been synthesized using ethyl azidoacetate (**3a**) in three solvents viz. dichloromethane, acetonitrile, and dimethylformamide. The optical purity of **5a** is >96% in all cases as judged from optical rotation values. Anderson peptide,[28] Z–Gly–Phe–Gly–OEt (**5b**) was also synthesized with retention of chirality. Benzoyl and acetyl protected peptides e.g. Bz–Phe–Ala–OEt (**5c**), Bz–Val–Ala–OEt (**5d**) and Ac–Phe–Ala–OEt (**5e**) were synthesized using the azide L-$N_3CH(CH_3)CO_2Et$ (**3b**). All these products are free from the unwanted diastereoisomers as revealed from their high field ^{1}H NMR.[29] Peptides, containing uncommon amino acids such as 1-aminocyclopropanecarboxylic acid[30] (Acc) e.g. Z–Gly–Acc–OEt (**5f**), Boc–Phe–Acc–OEt (**5g**), and Z–Val–Acc–OEt (**5h**), were synthesized using the azide **3c**. Peptide, containing the cyclopropyl analogue of phenylalanine i.e. 1-amino-2-phenylcyclopropanecarboxylic acvid which is otherwise difficult to prepare[31] can by synthesized. For example, DL-1-(*N*-benzyloxycarbonylglycylamino)-*t*-2-phenyl-*r*-1-cyclopropanecarboxylate (**5i**) has been synthesized from the corresponding azide **3d**. A dramatic improvement on yields of these type of peptides containing hindered amino acids are obtained when HOBt was used as catalyst.[32] Methionine enkephalin (**5j**) was synthesised using Boc–Tyr (**1i**) and the tripeptide azide (**3e**) in overall good yield. In the synthesis of the azide **3e**, the azidoacetyl group acts as a perfect *N*-protecting group and, also a glycine synthon. Therefore, no deprotection was required on the amine component before coupling to Boc–Tyr (**1i**). The method is well applicable for the preparation of secondary amides. For example, amides **5k** and **5l** are synthesized in good yields using hexyl- and heptyl azides (**3f** and **3g**) respectively. Primary amides (**5m**, **5n**, and **5o**) were obtained in very good yields after aqueous work-up when azidotrimethylsilane (**3h**) was used as the azido component. The method is a good alternative to the use of concentrated aqueous ammonia and is devoid of solubility problem as well as allows better control of stoichiometry and pH. The high optical purity of all these products can be explained on the basis that this protocol is totally free from the involvement of any tertiary base or its salts and even the generation of amine component which itself is controlled by the self-regulated reaction.

Experimental

All mps are recorded with a Fisher–Johns apparatus and are uncorrected. The ^{1}H NMR spectra are recorded on a Varian 60 MHz/Bruker 200 MHz/Varian 300 MHz instrument. The ^{1}H decoupled ^{13}C NMR spectra are recorded on a Bruker 200 MHz (proton) instrument. The ^{1}H NMR chemical shifts (δ) are given in ppm

downfield from internal tetramethylsilane (δ=0.00) or from residual chloroform (δ=7.26) or acetone (δ=2.00) and J (coupling constant) values in Hertz. The ^{13}C NMR chemical shifts (δ) are given in ppm downfield from internal tetramethylsilane (δ=0.00) or from internal chloroform-d (δ=77.0). The IR spectra are recorded on a Perkin–Elmer 783 spectrophotometer. Optical rotations are measured on a Perkin–Elmer 243 polarimeter/JASCO DIP-370 polarimeter. Mass spectra are recorded on a Kratos MS 80 or a Shimadzu GCMS-QP1000A instruments.

All reactions were carried out under Ar/N_2 atmosphere. Solvents were freshly dried and distilled prior to use. The *N*-protected amino acids/peptides (**1a**—**1l**) were prepared by standard procedures. The azides **3a**, **3b**, **3f**, **3g**, and **3i** were prepared following the literature procedures and are not included in the experimental. Azidotrimethylsilane (**3h**) (Aldrich) was used as such.

Ethyl *N*-Benzoyl-L-leucylglycinate (Bz–Leu–Gly–OEt) (5a): A General Procedure for the Preparation of Amides and Peptides. Tributylphosphine (98%) (0.77 ml, 3.15 mmol) was added to a stirred solution of *N*-benzoyl-L-leucine (**1a**) (744 mg, 3 mmol), diphenyl diselenide (940 mg, 3.3 mmol) in dichloromethane/acetonitrile/dimethylformamide (DMF) (or any combinations of these solvents) (9 ml) at room temperature under argon atmosphere. After 1—1.5 h at room temperature, the mixture was cooled in an ice-water bath and ethyl azidoacetate (**3a**) (390 mg, 3.3 mmol) was added slowly. A rapid evolution of nitrogen gas was observed. The mixture was allowed to attain room temperature and stirred for overnight (about 20 h). The mixture was diluted with ethyl acetate (50 ml) and washed with sodium hydrogencarbonate solution, with brine solution, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was triturated with petroleum ether (60—80 °C)–ether (5 : 1) (20 ml) to precipitate out the peptide which was filtered and purified by crystallisation; R_f (SiO_2; $CHCl_3$–MeOH, 98 : 2) 0.57; mp 154—155 °C, Lit,[27] 156.5—157 °C; $[\alpha]_D^{25}$ −33.4°C (*c* 3, EtOH), Lit,[27] $[\alpha]_D^{25}$ −34.00° (*c* 3, EtOH) (reaction performed in dichloromethane); 154 °C, $[\alpha]_D^{25}$ −32.8°; (reaction performed in acetonitrile); 154—155°C, $[\alpha]_D^{25}$ −33.0°; (reaction performed in DMF). Liquid products were purified by silica gel chromatography. Solid products, obtained after trituration of the crude product with petroleum ether (60—80 °C)–ether (5 : 1) were crystallized from appropriate solvents. 1-Hydroxybenzotriazole (HOBt) (0.5 molar amount) was added to the reaction mixture along with the azide. Preparation of the primary amides using azidotrimethylsilane (2 molar amounts) was carried out under argon baloon.

Ethyl *N*-Benzyloxycarbonylglycyl-L-phenylalanylglycinate (Z–Gly–Phe–Gly–OEt) (5b). R_f (SiO_2; $CHCl_3$–MeOH, 96 : 4) 0.56; mp 118—119 °C (hexane–ethyl acetate), Lit,[28] 120—120.5 °C; $[\alpha]_D^{25}$ −13.1° (*c* 2, EtOH), Lit,[28] $[\alpha]_D^{25}$ −13° (*c* 2, EtOH).

Ethyl *N*-Benzoyl-L-phenylalanyl-L-alaninate (Bz–Phe–Ala–OEt) (5c). R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.63; mp 150—151 °C (hexane–ethyl acetate); $[\alpha]_D^{25}$ −45.5° (*c* 1, EtOH); IR (KBr) 3280, 1740, 1660, 1635, and 1540 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ=1.27 (t, 3 H, J=7.2 Hz), 1.35 (d, 3 H, J=7.2 Hz), 3.14 (dd, 1 H, J=13.7 and 7.5 Hz), 3.26 (dd, 1 H, J=13.7 and 6 Hz), 4.18 (q, 2 H, J=7.2 Hz), 4.47 (quintet, 1 H, J=7 Hz), 4.87 (q, 1 H, J=7.5 Hz), 6.36 (d, 1 H, J=6.8 Hz), 6.84 (d, 1 H, J=7.2 Hz), 7.22—7.55 (m, 8H), and 7.70—7.75 (m, 2H). Found: C, 68.22; H, 6.68; N, 7.50%. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60%.

Ethyl *N*-Benzoyl-L-valyl-L-alaninate (Bz–Val–Ala–OEt) (5d). R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.66; mp 158 °C (hexane–ethyl acetate); $[\alpha]_D^{25}$ −43.9° (*c* 0.9, EtOH); IR (KBr) 3300, 1750, 1660, 1635, and 1540 cm^{-1}, ^{1}H NMR (200 MHz; $CDCl_3$) δ=1.04 (d, 3 H, J=6.8 Hz), 1.05 (d, 3 H, J=6.7 Hz), 1.29 (t, 3 H, J=7.2 Hz), 1.41 (d, 3 H, J=7.2 Hz), 2.13—2.30 (m, 1 H), 4.21 (q, 2 H, J=7.2 Hz), 4.48—4.64 (m, 2 H), 6.50 (d, 1 H, J=7.5 Hz), 6.84 (d, 1 H, J=8.1 Hz), 7.37—7.55 (m, 3 H), and 7.78—7.84 (m, 2 H). Found: C, 63.75; H, 7.49; N, 8.72%. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.75%.

Ethyl *N*-Acetyl-L-phenylalanyl-L-alaninate (Ac–Phe–Ala–OEt) (5e). R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.34; mp 152—154 °C (hexane–ethyl acetate); $[\alpha]_D^{25}$ −10.8 (*c* 1, EtOH); IR (KBr) 3260, 3080, 1760, 1670, 1640, and 1550 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ=1.26 (t, 3 H, J=7.3 Hz), 1.34 (d, 3 H, J=7.1 Hz), 1.97 (s, 3H), 2.96—3.16 (m, 2 H), 4.17 (q, 2 H, J=7.3 Hz), 4.44 (quintet, 1 H, J=7.2 Hz), 4.66 (q, 1 H, J=7.4 Hz), 6.14 (d, 1 H, J=7.4 Hz), 6.28 (d, 1 H, J=6.8 Hz), and 7.20—7.35 (m, 5 H). Found: C, 62.47; H, 7.10; N, 9.00%. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.15%.

Ethyl 2-Azidopropenoate (6a). This compound was prepared with modification of the reported procedure.[24] A mixture of ethyl 2,3-dibromopropionate (15.6 g, 60 mmol) and sodium azide (11.7 g, 180 mmol) in dimethylformamide (DMF) (60 ml) were heated at 60 °C with stirring under nitrogen for 0.5 h. The mixture was cooled to room temperature, diluted with water (300 ml) and extracted with pentane (3×100 ml). The extract was washed with water and with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give **6a** (8.4 g, 97%); IR (film) 2120, 1730, and 1620 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ=1.35 (t, 3 H, J=6.5 Hz), 4.3 (q, 2 H, J=6.5 Hz), 5.32 (s, 1 H), and 5.87 (s, 1 H).

Methyl (*Z*)-2-Azido-3-phenylpropenoate (6b). A solution of methyl azidoacetate (11.5 g, 100 mmol) and benzaldehyde (5.25 g, 50 mmol) in methanol (10 ml) was added dropwise to a stirred solution of sodium methoxide [prepared using sodium (2.3 g, 0.1 mol)] in methanol (40 ml) at 10 °C with stirring under nitrogen. The mixture was stirred under that condition for 20 min. and 3 h at 25 °C. The solvent was removed under reduced pressure and the residue was acidified with dil HCl (2 M, 50 ml, M=mol dm^{-3}). The reaction mixture was extracted with hexane (3×100 ml). The combined extract was washed with water, brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed (SiO_2; hexane–benzene 95 : 5) to give **6b** (4.5 g, 45%); mp 37 °C, Lit,[25] 38—39 °C; IR (film) 2120, 1720, and 1620 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ=3.92 (s, 3 H), 6.92 (s, 1 H), 7.28—7.5 (m, 3 H, Ar), and 7.75—7.85 (m, 2 H, Ar).

Ethyl 1-Azidocyclopropanecarboxylate (3c). Following the literature procedure,[26] a solution of the vinyl azide **6a** (7.05 g, 50 mmol) in ether (50 ml) at 0 °C was treated dropwise with ethereal diazomethane (200 ml, ca. 0.4 M, 80 mmol) and slowly allowed to attain to room temperature. It was left overnight and the excess diazomethane was removed by bubbling nitrogen through the solution at room temperature. The residual solvent was removed under vaccum to afford crude pyrazoline adduct (9.15 g, 100%) [IR (film) 2120, 1740, and 1555 cm^{-1}]. This adduct (9.15 g, 50 mmol) was dissolved in carbon tetrachloride (125 ml) and heated at 80 °C with stirring under nitrogen for 2 h. The solvent was removed under reduced pressure and the residue was distilled to give **3c** (5.442 g, 70%); bp 60 °C/2 mm Hg (1 mm Hg=133.322 Pa); IR (film) 2120 and 1740 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ=1.18 (dd, 2 H, J=4.5 and 8 Hz), 1.32 (t, 3 H, J=7.5 Hz), 1.48 (dd, 2 H, J=4.5 and 8 Hz) and 4.24 (q, 2 H, J=7.5 Hz).

Methyl 1-Azido-*t*-2-phenyl-*r*-1-cyclopropanecarboxylate (3d). The azide **6b** (4.4 g, 21.67 mmol) in dichloromethane (50 ml) was treated ethereal diazomethane (100 ml, ca. 0.4 M, 40 mmol) at 0 °C and left for 48 h at room temperature. Excess diazomethane was removed by bubbling nitrogen gas through the

solution and the remaining solvent was removed under vaccum to give the crude adduct (5.3 g, 100%) [IR (film), 2120, 1740, and 1600 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=3.72 (dd, 1 H, J=6 and 8 Hz), 3.94 (s, 3 Hz), 4.95 (dd, 1 H, J=18.3 and 6 Hz), 5.14 (dd, 1 H, J=18.3 and 8 Hz), 6.95—7.05 (m, 2 H), 7.27—7.38 (m, 3 H)]. This crude adduct (5.3 g, 21.67 mmol) was dissolved in carbon tetrachloride (50 ml) and heated at 80 °C with stirring over 3.5 h under nitrogen. The solvent was removed and the residue was purified by chromatography (SiO_2; ethyl acetate–hexane, 1.5 : 98.5) to give **3d**[26] (1.65 g, 35%); IR (film) 2110 and 1730 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=1.66 (dd, 1 H, J=6 and 8 Hz), 1.94 (dd, 1 H, J=6 and 10 Hz), 3.01 (dd, 1 H, J=8 and 10 Hz), 3.86 (s, 3 H), and 7.20—7.38 (m, 5 H).

Ethyl *N*-Benzyloxycarbonylglycyl-1-aminocyclopropanecarboxylate (Z–Gly–Acc–OEt) (5f). R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.39; mp 105 °C (hexane–ethyl acetate); IR (KBr) 3300, 1750, 1735, 1670, and 1540 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=1.07—1.15 (m, 2 H), 1.21 (t, 3 H, J=7.4 Hz), 1.52—1.59 (m, 2 H), 3.86 (d, 2 H, J=5.6 Hz), 4.12 (q, 2 H, J=7.4 Hz), 5.12 (s, 2 H), 5.55 (unresolved triplet, 1 H), 6.66 (s, 1 H), 7.22—7.40 (m, 5 H); MS m/z 321 (M+1; 2.2), 320 (M^+; 1), 230 (6.1), 229 (3.6), 135 (10.3), 100 (13.6), 91 (100, $PhCH_2$). Found: C, 60.10; H, 6.37; N, 8.70%. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75%.

Ethyl *N*-*t*-Butoxycarbonyl-L-phenylalanyl-1-aminocyclopropanecarboxylate (Boc–Phe–Acc–OEt) (5g). R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.67; mp 130—131 °C (hexane–ethyl acetate); $[\alpha]_D^{22}$ +4.7° (c 1.9, EtOH); IR (KBr) 3350, 1730, 1690, 1670, and 1525 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=0.82—0.99 (m, 1 H), 0.99—1.13 (m, 1 H), 1.21 (t, 3 H, J=7 Hz), 1.40 (s, 9 H), 1.38—1.63 (m, 2 H), 3.05 (d, 2 H, J=7 Hz), 4.11 (q, 2 H, J=7 Hz), 4.31 (q, 1 H, J=7.3 Hz), 5.1 (bs, 1 H), 6.41 (s, 1 H), 7.20—7.33 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=13.81, 16.92, 17.1, 28.0, 33.0, 38.52, 55.21, 60.96, 79.52, 126.38, 128.08, 129.15, 136.77, 155.36, 171.74, 172.54; MS m/z M^+ absent, 321 (2), 320 (10), 303 (2.8), 259 (11.1), 185 (11.9), 164 (20.4), 120 (50.7), 100 (19.8), 91 (14.2), and 59 (*t*-Butyl; 100). Found: C, 63.60; H, 7.35; N, 7.50%. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44%.

Ethyl *N*-Benzyloxycarbonyl-L-valinyl-1-aminocyclopropanecarboxylate (Z–Val–Acc–OEt) (5h). R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.61; mp 185 °C (hexane–ethyl acetate); $[\alpha]_D^{25}$ −14.8° (c 1.4, EtOH); IR (KBr) 3300, 1740, 1700, 1670, and 1540 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=0.96 (d, 3 H, J=7.2 Hz), 0.99 (d, 3 H, J=7.2 Hz), 1.09—1.15 (m, 2 H), 1.20 (t, 3 H, J=7 Hz), 1.45—1.65 (m, 2 H), 2.05—2.25 (m, 1 H), 3.97 (dd, 1 H, J=8.8 and 6.2 Hz), 4.11 (q, 2 H, J=7 Hz), 5.09 (s, 2 H), 5.44 (d, 1 H, J=8.2 Hz), 6.64 (s, 1 H), 7.33—7.27 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=14.05, 17.34, 17.55, 19.07, 31.05, 33.43, 60.21, 61.36, 66.99, 127.94, 128.13, 128.47, 136.18, 156.38, 172.20; MS m/z 363 (M+1; 2.5), 362 (M^+; 3.1), 361 (M−1; 1), 211 (2.6), 162 (12.2), 100 (7.7), 91 ($PhCH_2$; 100). Found: C, 62.80; H, 7.35; N, 7.70%. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73%.

Methyl DL-1-(*N*-Benzyloxycarbonylglycylamino)-*t*-2-phenyl-*r*-1-cyclopropanecarboxylate (5i). R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.53; IR ($CHCl_3$) 3300, 1730, 1700, 1680, and 1520 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=1.66—1.76 (m, 1 H), 2.16—2.25 (m, 1 H), 2.99 (t, 1 H, J=9 Hz), 3.61—3.80 (m, 2 H), 3.66 (s, 3 H), 5.03 (s, 2 H), 5.21 (unresolved triplet, 1 H), 5.90 (s, 1 H), 7.11—7.35 (m, 10 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=21.07, 32.43, 38.8, 44.32, 52.68, 66.97, 127.38, 127.94, 128.15, 128.35, 128.51, 129.15, 134.01, 136.15, 156.34, 170.39, 171.81. HRMS Found: m/z 382.1539. Calcd for $C_{21}H_{22}N_2O_5$: M, 382.1529.

Methyl *N*-Chloroacetylglycyl-L-phenylalaninate (7). Triethylamine (1.78 ml, 12.8 mmol) was dropwise added to a stirred mixture of *N*-chloroacetylglycine (1.94 g, 12.8 mmol) and L-phenylalanine methyl ester hydrochloride (2.76 g, 12.8 mmol) in dichloromethane–dimehylformamide (1.5 : 1) (32 ml) at 0 °C. After the addition was over, the reaction mixture was stirred at 0 °C for 10 min and 4-dimethylaminopyridine (150 mg, 1.22 mmol) was added followed by a solution of dicyclohexylcarbodiimide (DCCI) (2.9 g, 14 mmol) in dichloromethane (15 ml). The reaction mixture was allowed to attain room temperature and stirred overnight (about 15 h). The reaction mixture was diluted with ethyl acetate (200 ml) and filtered to remove the dicyclohexylurea. The filtrate was washed with dil hydrochloric acid, saturated sodium hydrogencarbonate solution and with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was crystallized from ethyl acetate–hexane to give **7** (3.15 g, 79%); R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.20; mp 115 °C (EtOAc–hexane); $[\alpha]_D^{29}$ 5.0° (c 1, MeOH); IR (KBr) 3300, 3080, 1750, 1640, and 1560 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=3.02—3.22 (m, 2 H), 3.74 (s, 3 H), 3.95 (d, 2 H, J=5.2 Hz), 4.04 (s, 2 H), 4.87 (q, 1 H, J=7.2 Hz), 6.46 (d, 1 H, J=7 Hz), and 7.05—7.40 (m, 6 H). Found: C, 53.51; H, 5.33; N, 8.84%. Calcd for $C_{14}H_{17}ClN_2O_4$: C, 53.76; H, 5.48; N, 8.96%.

Methyl *N*-Azidoacetylglycyl-L-phenylalaninate (8). A mixture of chloride **7** (1.89 g, 6 mmol), sodium azide (0.78 g, 12 mmol) in dry dimethylformamide (20 ml) was stirred at room temperature for overnight (about 20 h). The reaction mixture was poured into water (250 ml) and extracted with ethyl acetate (3×100 ml). The combined extract was washed with water and with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was crystallized from ethyl acetate–petroleum ether to give **8** (1.73 g, 90%); R_f (SiO_2; $CHCl_3$–MeOH 97 : 3) 0.42; mp 132 °C (EtOAc–hexane); $[\alpha]_D^{29}$ 8.0° (c 1, MeOH); IR (KBr) 3260, 3060, 2100, 1750, 1650, and 1550 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=3.03—3.22 (m, 2 H), 3.75 (s, 3 H), 3.95 (d, 2 H, J=5.2 Hz), 3.99 (s, 2 H), 4.87 (q, 1 H, J=7.4 Hz), 6.40 (d, 1 H, J=7.1 Hz), 6.99 (bt, 1 H), 7.07—7.11 (m, 2 H), and 7.25—7.30 (m, 3 H). Found: C, 52.42; H, 5.15; N, 22.10%. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.36; N, 21.93%.

Methyl *N*-Azidoacetylglycyl-L-phenylalanyl-L-methioninate (3e). Sodium hydroxide (5.4 ml of a 1 M solution in water, 5.4 mmol) was added portionwise to a stirred solution of **8** (1.57 g, 4.9 mmol) in methanol–THF (4 : 1) (25 ml) at room temperature. After the addition was over the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, the residue was acidified with hydrochloric acid and extracted with ethyl acetate (3×30 ml). The combined extract was washed with brine, dried (Na_2SO_4), and evaporated to give *N*-azidoacetylglycyl-L-phenylalanine (1.5 g, 100%). A solution of DCCI (1.11 g, 5.4 mmol) in dichloromethane (5 ml) was added dropwise to a stirred solution of the above prepared *N*-azidoacetylglycyl-L-phenylalanine (1.5 g, 4.9 mmol), L-methionine methyl ester (prepared from methionine methyl ester hydrochloride by addition of equimolar amount of triethylamine and removing the triethylammonium hydrochloride) (0.82 g, 5 mmol) and HOSu (0.62 g, 5.4 mmol) in dichloromethane–dimethylformamide (1 : 2) (15 ml) at 0 °C. The reaction mixture was allowed to attain room temperature and stirred overnight (18 h). The reaction mixture was diluted with ethyl acetate (15 ml) and filtered to remove the dicyclohexylurea. The filtrate was washed with dil hydrochloric acid, with saturated sodium hydrogencarbonate solution, water and with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was crystallized from ethyl acetate–petroleum ether 60—80 °C to give **3e** (1.76 g, 81%); R_f (SiO_2; $CHCl_3$–MeOH 95 : 5) 0.49;

mp 141 °C (hexane–ethyl acetate); $[\alpha]_D^{22}$ −26° (*c* 1, MeOH); IR (KBr) 3260, 2100, 1740, 1640, 1530 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.90—2.02 (m, 1 H), 2.06 (s, 3 H), 2.07—2.17 (m, 1 H), 2.43 (t, 2 H, *J*=7.3 Hz), 3.07 (d, 2 H, *J*=6.6 Hz), 3.73 (s, 3 H), 3.88—4.06 (m, 4 H), 4.59—4.66 (m, 1 H), 4.80—4.88 (m, 1 H), 7.05 (bt, 1 H), 7.08 (d, 1 H, *J*=8 Hz), 7.15—7.30 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=15.30, 29.83, 31.17, 38.49, 42.87, 51.55, 52.10, 52.49, 54.37, 127.01, 128.51, 129.36, 136.11, 167.70, 168.27, 170.69, and 171.82. Found: C, 50.40; H, 5.95; N, 18.50%. Calcd for $C_{19}H_{26}N_6O_5S$: C, 50.65; H, 5.82; N, 18.65%.

Methyl *N*-*t*-Butoxycarbonyl-L-tyrosyldiglycyl-L-phenylalanyl-L-methioninate (Boc–Tyr–Gly$_2$–Phe–Met–OMe) (5j). Tributylphosphine (80 μl, 95% Bu_3P, 0.3 mmol) was added dropwise to a stirred solution of *t*-butoxycarbonyl-L-tyrosine (**1i**) (70 mg, 0.25 mmol), diphenyl diselenide (96 mg, 0.3 mmol) in acetonitrile (2 ml) at room temperature. After 1 h at room temperature, the reaction mixture was cooled in an ice-water bath and a solution of the azide **3e** (111 mg, 0.25 mmol) and HOBt (34 mg, 0.25 mmol) in acetonitrile (4 ml) was added. The reaction mixture was stirred at room temperature for overnight (about 20 h). The reaction mixture was diluted with ethyl acetate and washed with sodium hydrogencarbonate solution and with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed to give **5j** (150 mg, 88%); R_f (SiO_2; $CHCl_3$–MeOH 95 : 5) 0.37; mp 113—115 °C (hexane–ethyl acetate); $[\alpha]_D^{25}$ −12.1° (*c* 1, MeOH); IR (KBr) 3300, 1740, 1660, 1540, and 1520 cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) δ=1.37 (s, 9 H), 1.98—2.08 (m, 2 H), 2.06 (s, 3 H), 2.50—2.64 (m, 2 H), 2.84—3.31 (m, 4 H), 3.67 (s, 3 H), 3.56—3.86 (m, 4 H), 4.30 (q, 1 H, *J*=7.5 Hz), 4.51—4.71 (m, 2 H), 6.30 (d, 1 H, *J*=6.8 Hz), 6.74 (d, 2 H, *J*=8.1 Hz), 7.12 (d, 2 H, *J*=8.5 Hz), 7.15—7.32 (m, 5 H), 7.46—7.57 (m, 2 H), 7.67 (unresolved triplet, 1 H), 7.98 (unresolved triplet, 1 H), 8.25 (s, 1 H).

***N*-Hexyl-(*N*-benzyloxycarbonyl-DL-phenylalanin)amide (Z–DL-Phe–NH–$(CH_2)_5CH_3$) (5k).** R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.74; mp 118 °C (benzene–hexane); IR (KBr) 3310, 1690, 1650, 1540 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.87 (t, 3 H, *J*=6.6 Hz), 1.05—1.40 (broad multiplet, 8 H), 2.90—3.15 (m, 4 H), 4.34 (q, 1 H, *J*=7.0 Hz), 5.08 (s, 2 H), 5.47 (bs, 1 H), 5.68 (bs, 1 H), 7.10—7.40 (m, 10 H); MS *m/z* 383 (M+1; 1.0), 382 (M^+; 1.6), 91 ($PhCH_2$; 100). Found: C, 72.06; H, 7.95; N, 7.30%. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.33%.

***N*-Heptyl-(*N*-benzyloxycarbonyl-DL-phenylalanin)amide (Z–DL-Phe–NH–$(CH_2)_6CH_3$) (5l).** R_f (SiO_2; $CHCl_3$–MeOH 98 : 2) 0.73; mp 114—115 °C (benzene–hexane); IR (KBr) 3300, 1685, 1650, 1530 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=0.87 (t, 3 H, *J*=6.0 Hz), 1.00—1.50 (broad multiplet, 10 H), 2.90—3.20 (m, 4 H), 4.40 (q, 1 H, *J*=7.0 Hz), 5.05 (s, 2H), 5.70 (d, 1 H, *J*=8 Hz), 6.05 (broad triplet, 1 H), 7.10—7.40 (m, 10 H). Found: C, 72.50; H, 8.30; N, 7.00%. Calcd for $C_{24}H_{32}N_2O_3$: C, 72.69; H, 8.14; N, 7.07%.

***N*-Benzyloxycarbonyl-L-phenylalaninamide (Z–Phe–NH_2) (5m).** R_f (SiO_2; $CHCl_3$–MeOH 96 : 4) 0.48; mp 164—165 °C (hexane–ethyl acetate), Lit,[33] 164—165 °C, $[\alpha]_D^{22}$ −6.75° (*c* 2, MeOH), Lit,[33] $[\alpha]_D^{22}$ −6.8° (*c* 1, MeOH).

***N*-Benzyloxycarbonyl-L-alaninamide (Z–Ala–NH_2) (5n).** R_f (SiO_2; $CHCl_3$–MeOH 96 : 4) 0.27; mp 133 °C (hexane–ethyl acetate), Lit,[34] 130—131 °C; $[\alpha]_D^{22}$ −4.6° (*c* 2, MeOH), Lit,[34] $[\alpha]_D^{22}$ −4.5° (*c* 2, MeOH).

***N*-Benzyloxycarbonylglycyl-L-phenylalaninamide (Z–Gly–Phe–NH_2) (5o).** R_f (SiO_2; $CHCl_3$–MeOH 97 : 3) 0.20; mp 139—140 °C (hexane–ethyl acetate); $[\alpha]_D^{26}$ 5.4° (*c* 1, MeOH); IR (KBr) 3400, 3360, 3320, 3220, 1690, 1660, and 1550 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=3.07 (d, 2 H, *J*=6.5 Hz), 3.81 (d, 2 H, *J*=5.6 Hz), 4.68 (q, 1 H, *J*=7.3 Hz), 5.69 (s, 2 H), 5.54 (bs, 2 H), 6.05 (bs, 1 H), 6.83 (bd, 1 H), 7.21—7.34 (m, 10 H). Found: C, 64.02; H, 6.05; N, 11.70%. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82%.

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