Protecting Group for Carboxyl Function: Mild and Facile Cleavage of 2-Cyanoethyl Ester under Non-hydrolytic Conditions

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The use of the 2-cyanoethyl group for carboxyl-protection is described. This group was readily introduced by esterification using ethylene cyanohydrin and the deprotection was carried out under mild conditions using tetrabutylammonium fluoride in dimethylformamide–tetrahydrofuran.

Keywords 2-cyanoethyl ester; carboxyl protecting group; tetrabutylammonium fluoride; deprotection; β-elimination; peptide synthesis

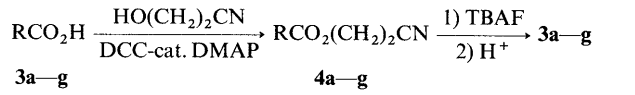
Easy protection of carboxylic acid and removal of the protecting group under mild non-hydrolytic conditions are important in organic synthesis.[1] Although carboxyl groups can be readily protected as the corresponding esters, regeneration of the parent acids is usually carried out in acidic or basic aqueous media. These conditions, however, sometimes cannot be used because of the instability or sensitivity of the given substrate. To overcome this disadvantage, a wide variety of methods have been developed for carboxyl protection based on β-elimination methods.[2] Recently, the 2-cyanoethyl group has been used in peptide synthesis.[3] However, the deblocking was achieved with K_2CO_3 in MeOH–H_2O, and is not suitable for the deprotection of 2-cyanoethyl esters bearing an alkali-sensitive group, such as acetate or 2-trimethylsilylethyl (TMSE) ester in the molecule.[4] We report here an alternative useful deblocking method of 2-cyanoethyl-ester using tetrabutylammonium fluoride (TBAF) under non-hydrolytic conditions, allowing selective deprotection of the 2-cyanoethyl group.

Starting carboxylic acids (**3c, d**) were prepared from methyl 3-(4-hydroxyphenyl)propionate (**1**) by a standard method (Chart 1). The 2-cyanoethyl group was readily introduced[3] by using ethylene cyanohydrin in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane, in high yields (Table I).

Deprotection of the 2-cyanoethyl group was achieved under mild non-hydrolytic conditions. Thus, treatment of 2-cyanoethyl 3-phenylpropionate (**4a**) in tetrahydrofuran (THF) with TBAF at room temperature for 1 h provided the corresponding ammonium carboxylate, from which 3-phenylpropionic acid (**3a**) was obtained in 95% yield. When the reaction was performed in *N,N*-dimethylformamide (DMF)–THF (5 : 1), it proceeded five times faster. Selective cleavage of the 2-cyanoethyl ester was accomplished in the presence of acetate, THP ether, methoxymethyl (MOM) ether, benzyl ester, TMSE ester, and benzyl carbamate. Thus, the 2-cyanoethyl esters (**4b—g**) were treated with TBAF in DMF–THF to give the parent carboxylic acids (**3b—g**) selectively in high yields. It is noteworthy that the cleavage of the 2-cyanoethyl group was faster than that of the TMSE group. These results are summarized in Table I.

Peptide synthesis[5] was carried out with Boc–Phe–OH (**5**). The 2-cyanoethyl ester (**6**) was prepared from **5** by the method mentioned above and treated with TBAF to afford crude **5**. The degree of racemization calculated

TABLE I. Preparation of 2-Cyanoethyl Esters (**4a—g**) and Cleavage of **4a—g** into **3a—g**



R	Yield (%) of **4**	Deprotection conditions (h)	Yield (%) of **3**
$Ph(CH_2)_2$	**4a** (94)	THF, 1	**3a** (95)
		DMF–THF, 0.2	**3a** (98)
$4\text{-}AcOC_6H_4(CH_2)_2$	**4b** (92)	DMF–THF, 0.3	**3b** (84)
$4\text{-}THPOC_6H_4(CH_2)_2$	**4c** (95)	DMF–THF, 0.3	**3c** (88)
$4\text{-}MOMOC_6H_4(CH_2)_2$	**4d** (92)	DMF–THF, 0.3	**3d** (96)
$PhCH_2OCO(CH_2)_2$	**4e** (86)	DMF–THF, 0.2	**3e** (99)
$TMSEOCO(CH_2)_2$	**4f** (92)	DMF–THF, 0.2	**3f** (64)[a]
$PhCH_2OCON$ 	**4g** (97)	DMF–THF, 0.3	**3g** (100)

a) A small amount (4%) of 2-cyanoethyl hydrogen succinate was present.

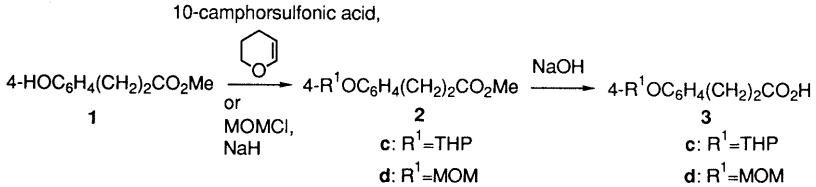


Chart 1

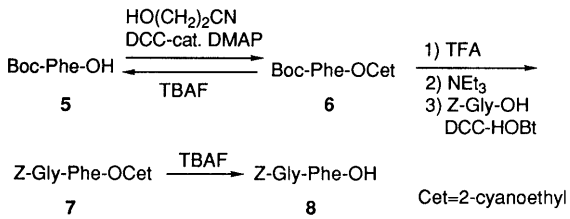


Chart 2

from the optical rotations through this operation (**5**→crude **6**→crude **5**) was 0.4%. Crystallization of crude **5** gave enantiomeric pure **5**. Next, the Boc group of **6** was deprotected by trifluoroacetic acid (TFA) followed by DCC coupling in the presence of 1-hydroxybenzotriazole (HOBt) with Z–Gly–OH to give the dipeptide (**7**). The 2-cyanoethyl ester was cleaved by TBAF to afford crude **8**. The degree of racemization through this operation (**6**→crude **7**→crude **8**) was less than 1.0%. Crystallization of crude **8** gave enantiomeric pure **8**.

Experimental

All melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using a 10 cm cell. Infrared (IR) absorption spectra were recorded on a JASCO HPIR-102 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-HMR) spectra were measured on Varian VXR-200 (200 MHz), Hitachi R-250HT (250 MHz), and JEOL JNM-EX270 (270 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS-D300 [for electron impact (EI)- and exact MS] or a JEOL HX-100 [for fast atom bombardment mass spectra (FAB-MS)] mass spectrometer. E. Merck Silica gel 60 (70—230 mesh ASTM) was used for column chromatography. The known carboxylic acids (**1**,[6] **3b**,[7] **3e**,[8] **3f**,[9] and **3g**[10]) were prepared by the reported methods.

Methyl 3-(4-Tetrahydropyran-2-yloxyphenyl)propionate (2c) 10-Camphorsulfonic acid (65 mg, 0.28 mmol) was added to a solution of **1**[6] (1.0 g, 5.55 mmol) and 3,4-dihydro-2*H*-pyran (2.34 mg, 27.8 mmol) in dry CH_2Cl_2 (10 ml) at 0°C, and the mixture was stirred at the same temperature for 30 min. After quenching of the reaction with saturated aqueous $NaHCO_3$ and CH_2Cl_2, the organic layer was separated. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was chromatographed on silica gel (hexane–AcOEt, 19 : 1) to give **2c** (1.40 g, 96%) as an oil, bp 165—175 °C (0.5 mmHg) (bath temperature). IR ($CHCl_3$) ν: 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.1 (m, 6H), 2.59 (t, 2H, J=7.7 Hz, CH_2CO_2), 2.89 (t, 2H, J=7.7 Hz, CH_2Ph), 3.5—3.7 (m, 1H), 3.66 (s, 3H, CO_2CH_3), 3.8—4.0 (m, 1H), 5.37 (t, 1H, J=3.1 Hz, OCHO), 6.97 (d, 2H, J=8.6 Hz, phenyl protons), 7.10 (d, 2H, J=8.6 Hz, phenyl protons). *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.15; H, 7.59.

Methyl 3-[4-(Methoxymethoxy)phenyl]propionate (2d) A solution of **1**[6] (3.0 g, 16.6 mmol) in dry THF (10 ml) was added to a suspension of NaH (60% dispersion in mineral oil, 731 mg, 18.3 mmol) in dry THF (10 ml) at 0 °C, and the mixture was stirred at room temperature for 30 min. To this mixture, a solution of chloromethyl methyl ether (1.26 ml, 16.6 mmol) in dry THF (15 ml) was added at 0 °C, and the whole was stirred at the same temperature for 1 h. After quenching of the reaction with saturated aqueous NH_4Cl and AcOEt, the organic layer was separated. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was chromatographed on silica gel (hexane–AcOEt, 6 : 1) to give **2d** (3.01 g, 81%) as an oil, bp 120—125 °C (0.1 mmHg) (bath temperature). IR ($CHCl_3$) ν: 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.59 (t, 2H, J=7.5 Hz, CH_2CO_2), 2.90 (t, 2H, J=7.5 Hz, CH_2Ph), 3.46 (s, 3H, OCH_3), 3.66 (s, 3H, CO_2CH_3), 5.14 (s, 2H, OCH_2O), 6.96 (d, 2H, J=8.6 Hz, phenyl protons), 7.11 (d, 2H, J=8.6 Hz, phenyl protons). *Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.05; H, 7.38.

3-(4-Tetrahydropyran-2-yloxyphenyl)propionic Acid (3c) A 1 N NaOH solution (5.3 ml, 5.3 mmol) was added to a solution of **2c** (693 mg, 2.62 mmol) in MeOH (10 ml) at 0°C, and the mixture was stirred at room temperature for 3 h. The MeOH was removed under reduced pressure and the aqueous solution was neutralized with solid citric acid, and then extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was crystallized from CH_2Cl_2–hexane to give **3c** (640 mg, 98%) as colorless prisms, mp 85–86 °C. IR ($CHCl_3$) ν: 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.1 (m, 6H), 2.64 (t, 2H, J=7.7 Hz, CH_2CO_2), 2.90 (t, 2H, J=7.7 Hz, CH_2Ph), 3.5–3.7 (m, 1H), 3.8—4.0 (m, 1H), 5.38 (t, 1H, J=3.1 Hz, OCHO), 6.97 (d, 2H, J=8.6 Hz, phenyl protons), 7.11 (d, 2H, J=8.6 Hz, phenyl protons). Exact MS Calcd for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1210.

3-[4-(Methoxymethoxy)phenyl]propionic Acid (3d) A 0.5 N NaOH solution (12 ml, 6.0 mmol) was added to a solution of **2d** (602 mg, 2.68 mmol) in MeOH (14 ml) at 0 °C, and the mixture was stirred at room temperature for 4 h. The MeOH was removed under reduced pressure and the aqueous solution was neutralized with solid NH_4Cl, and then extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was crystallized from $CHCl_3$–hexane to give **3d** (390 mg, 70%) as colorless prisms, mp 58 °C. IR ($CHCl_3$) ν: 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (t, 2H, J=7.6 Hz, CH_2CO_2), 2.90 (t, 2H, J=7.6 Hz, CH_2Ph), 3.47 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2O), 6.96 (d, 2H, J=8.6 Hz, phenyl protons), 7.12 (d, 2H, J=8.6 Hz, phenyl protons). *Anal.* Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.64; H, 6.76.

Typical Example of the Preparations of 2-Cyanoethyl Esters: 2-Cyanoethyl 3-Phenylpropionate (4a) A solution of DCC (604 mg, 2.93 mmol) in dry CH_2Cl_2 (4 ml) was added to a solution of **3a** (400 mg, 2.67 mmol), ethylene cyanohydrin (189 mg, 2.66 mmol), and DMAP (16.3 mg, 0.13 mmol) in dry CH_2Cl_2 (4 ml) at 0 °C, and the whole was stirred at room temperature for 5 h, and then filtered to remove *N,N'*-dicyclohexylurea (DCU). The filtrate was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and the solution was concentrated under reduced pressure. The oily residue was chromatographed on silica gel (hexane–Et_2O, 3 : 1) to give **4a** (509 mg, 94%) as an oil, bp 139—141 °C (0.3 mmHg). IR ($CHCl_3$) ν: 2250, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (t, 2H, J=6.3 Hz, CH_2CN), 2.69 (t, 2H, J=8.0 Hz, CH_2CO_2), 2.97 (t, 2H, J=8.0 Hz, CH_2Ph), 4.26 (t, 2H, J=6.3 Hz, CO_2CH_2), 7.1—7.4 (m, 5H, phenyl protons). *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.82; H, 6.44; N, 6.87.

2-Cyanoethyl 3-(4-Acetoxyphenyl)propionate (4b) This compound was prepared from **3b**[7] (1.0 g, 4.80 mmol). Purification by chromatography on silica gel (hexane–Et_2O, 1 : 2) gave **4b** (1.16 g, 92%) as an oil, bp 165—175 °C (0.4 mmHg) (bath temperature). IR ($CHCl_3$) ν: 2260, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H, CH_3CO), 2.64 (t, 2H, J=6.3 Hz, CH_2CN), 2.68 (t, 2H, J=7.6 Hz, CH_2CO_2), 2.96 (t, 2H, J=7.6 Hz, CH_2Ph), 4.25 (d, 2H, J=6.3 Hz, CO_2CH_2), 7.01 (d, 2H, J=8.4 Hz, phenyl protons), 7.21 (d, 2H, J=8.4 Hz, phenyl protons). Exact MS Calcd for $C_{14}H_{15}NO_4$: 261.1001. Found: 261.1007.

2-Cyanoethyl 3-(4-Tetrahydropyran-2-yloxyphenyl)propionate (4c) This compound was prepared from **3c** (400 mg, 1.60 mmol). Purification by chromatography on silica gel (hexane–Et_2O, 1 : 1) gave **4d** (460 mg, 95%) as an oil. IR ($CHCl_3$) ν: 2260, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.1 (m, 6H), 2.6—2.7 (m, 4H, CH_2CO_2 and CH_2CN), 2.91 (t, 2H, J=7.6 Hz, CH_2Ph), 3.5—3.7 (m, 1H), 3.8—4.0 (m, 1H), 4.26 (t, 2H, J=6.3 Hz, CO_2CH_2), 5.38 (t, 1H, J=3.3 Hz, OCHO), 6.98 (d, 2H, J=8.6 Hz, phenyl protons), 7.11 (d, 2H, J=8.6 Hz, phenyl protons). *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.03; H, 7.02; N, 4.65.

2-Cyanoethyl 3-[4-(Methoxymethoxy)phenyl]propionate (4d) This compound was prepared from **3d** (1.4 g, 6.7 mmol). Purification by chromatography on silica gel (hexane–Et_2O, 2 : 1) gave **4d** (1.61 g, 92%) as an oil, bp 160—165 °C (0.3 mmHg) (bath temperature). IR ($CHCl_3$) ν: 2250, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.6—2.7 (m, 4H, CH_2CO_2, CH_2CN), 2.91 (t, 2H, J=7.7 Hz, CH_2Ph), 3.46 (s, 3H, OCH_3), 4.25 (t, 2H, J=6.3 Hz, CO_2CH_2), 5.14 (s, 2H, OCH_2O), 6.96 (d, 2H, J=8.8 Hz, phenyl protons), 7.12 (d, 2H, J=8.8 Hz, phenyl protons). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.66; H, 6.71; N, 5.30.

Benzyl 2-Cyanoethyl Succinate (4e) This compound was prepared from **3e**[8] (3.0 g, 14.4 mmol). Purification by chromatography on silica gel (hexane–AcOEt, 6 : 1) gave **4e** (3.24 g, 86%) as an oil, bp 160—170 °C (0.4 mmHg) (bath temperature). IR ($CHCl_3$) ν: 2250, 1725 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 2.64 (t, 2H, J=6.3 Hz, CH_2CN), 2.70 (s, 4H, CH_2CH_2), 4.27 (t, 2H, J=6.3 Hz, OCH_2), 5.14 (s, 2H, CH_2Ph), 7.2—7.5 (m, 5H, phenyl protons). Exact MS Calcd for $C_{14}H_{15}NO_4$: 261.0998. Found: 261.0995.

2-Cyanoethyl 2-(Trimethylsilyl)ethyl Succinate (4f) This compound was prepared from **3f**[9] (127 mg, 0.58 mmol). Purification by chromatography on silica gel (hexane–Et_2O, 2:1) gave **4f** (145 mg, 92%) as an oil, 125—135 °C (0.4 mmHg) (bath temperature). IR ($CHCl_3$) ν: 2260, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (s, 9H, $CH_3\times3$), 0.9—1.1 (m, 2H, CH_2Si), 2.6—2.7 (m, 4H, CH_2CH_2), 2.72 (t, 2H, J=6.3 Hz, CH_2CN), 4.1—4.3 (m, 2H, OCH_2), 4.31 (t, 2H, J=6.3 Hz, OCH_2). *Anal.* Calcd for $C_{12}H_{21}NO_4Si$: C, 53.10; H, 7.80; N, 5.16. Found: C, 52.83; H, 7.71; N, 5.14.

2-Cyanoethyl (1-Benzyloxycarbonyl-4-piperidine)carboxylate (4g) This compound was prepared from **3g**[10] (3.0 g, 11.4 mmol). Purification by recrystallization gave **4g** (3.50 g, 97%) as colorless prisms, mp 78 °C (Et_2O–hexane). IR ($CHCl_3$) ν: 1735, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (m, 2H), 1.8—2.0 (m, 2H); 2.45—2.65 (m, 1H, CHCO), 2.71 (t, 2H, J=6.2 Hz, CH_2CN), 2.8—3.05 (m, 2H), 4.0—4.2 (m, 2H), 4.29 (t, 2H, J=6.2 Hz, CO_2CH_2), 5.13 (s, 2H, CH_2Ph), 7.3—7.4 (m, 5H, phenyl protons). *Anal.* Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.41; H, 6.44; N, 8.84.

Typical Example of the Cleavage of 2-Cyanoethyl Esters with a Base: 3-Phenylpropionic Acid (3a) A solution of 1.0 M TBAF[11] (1.0 ml, 1.0 mmol) in THF was added to a solution of **4a** (200 mg, 0.99 mmol) in DMF (5 ml) at room temperature, and the mixture was stirred for 10 min. The mixture was added to saturated aqueous $NaHCO_3$ and the solution was washed with AcOEt. The aqueous layer was acidified with 10% aqueous HCl and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was solidified to give **3a** (145 mg, 98%) as colorless prisms, mp 47—48 °C (hexane), lit.,[12] mp 48.5 °C. IR ($CHCl_3$) ν: 1713 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (t, 2H, J=7.6 Hz, CH_2), 2.96 (t, 2H, J=7.6 Hz, CH_2), 7.15–7.4 (m, 5H, phenyl protons).

3-(4-Acetoxyphenyl)propionic Acid (3b) By the same procedure as described for the cleavage of **4a**, this compound was recovered from **4b** (200 mg, 0.77 mmol) as colorless plates (134 mg, 84%), mp 95—96 °C (benzene–Et_2O), lit.,[7] mp 93.5—95.5 °C. IR ($CHCl_3$) ν: 1755, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (s, 3H, CH_3CO), 2.68 (t, 2H, J=7.7 Hz, CH_2CO_2), 2.95 (t, 2H, J=7.7 Hz, CH_2Ph), 7.01 (d, 2H, J=8.6 Hz, phenyl protons), 7.22 (d, 2H, J=8.6 Hz, phenyl protons).

3-(4-Tetrahydropyran-2-yloxyphenyl)propionic Acid (3c) By the same procedure as described for the cleavage of **4a**, this compound was recovered from **4c** (200 mg, 0.66 mmol) as colorless prisms (145 mg, 88%), mp 84—85 °C (CH_2Cl_2–hexane).

3-[4-(Methoxymethoxy)phenyl]propionic Acid (3d) By the same procedure as described for the cleavage of **4a**, this compound was recovered from **4d** (200 mg, 0.76 mmol) as colorless prisms (153 mg, 96%), mp 57—58 °C ($CHCl_3$–hexane).

Benzyl Hydrogen Succinate (3e) By the same procedure as described for the cleavage of **4a**, this compound was recovered from **4e** (200 mg, 0.77 mmol) as colorless plates (158 mg, 99%), mp 56—57 °C ($CHCl_3$–hexane), lit.,[8] mp 58—59 °C. IR ($CHCl_3$) ν: 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (s, 4H, CH_2CH_2), 5.13 (s, 2H, CH_2Ph), 7.2—7.4 (m, 5H, phenyl protons), 10.5—11.0 (br, 1H, CO_2H).

The Cleavage of 4f with TBAF By the same procedure as described for the cleavage of **4a**, a mixture of **3f** and **5b** (14:1, 103 mg, 64%) was obtained. This ratio was determined by comparison of the methylene proton signals in the ^{1}H-NMR spectra. The methylene protons (CH_2O) of **3f** appeared as a multiplet (4.14—4.26 ppm). The methylene protons (CH_2O) of 2-cyanoethyl hydrogen succinate[13] appeared as a triplet (4.32 ppm, J=6.3 Hz). The spectral data of **3f**[9] were abstracted from those of the mixture. IR ($CHCl_3$) ν: 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (s, 9H, $CH_3\times3$), 0.95—1.15 (m, 2H, CH_2Si), 2.5—2.8 (m, 4H, CH_2CH_2), 4.14—4.26 (m, 2H, CH_2O).

(1-Benzyloxycarbonyl-4-piperidine)carboxylic Acid (3g) By the same procedure as described for the cleavage of **4a**, this compound was recovered from **4g** (200 mg, 0.63 mmol) as an oil (166 mg, 100%).[10] IR ($CHCl_3$) ν: 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (m, 2H), 1.8—2.05 (m, 2H), 2.4—2.6 (m, 1H, CHCO), 2.8—3.1 (m, 2H), 4.0—4.2 (m, 2H), 5.13 (s, 2H, CH_2Ph), 7.2—7.4 (m, 5H, phenyl protons).

Boc-Phe-OH (5) A solution of 1.0 M TBAF (1.3 ml, 1.3 mmol) in THF was added to a solution of crude **6** (200 mg, 0.63 mmol) in DMF (3 ml) at 0 °C, and the stirring was continued for 40 min at room temperature. The mixture was added to saturated aqueous $NaHCO_3$ and the solution was washed with AcOEt. The aqueous layer was acidified with 5% aqueous $KHSO_4$ and extracted with AcOEt. The extract was washed with water, drid over $MgSO_4$, and concentrated to give crude **5**, $[\alpha]_D^{20}$ +24.5° (c=2, EtOH). Recrystallization from AcOEt–hexane gave pure **5** (145 mg, 87%) as colorless prisms, mp 84—86 °C, $[\alpha]_D^{20}$ +24.7° (c=2, EtOH), lit.,[14] mp 85—87 °C, $[\alpha]_D^{20}$ +24.7±0.5° (c=1.5, EtOH). IR ($CHCl_3$) ν: 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.42 (s, 6H, $CH_3\times2$), 2.8—3.3 (m, 2H, CH_2Ph), 4.5—4.7 (br, 1H, CH), 4.8—5.0 (br, 1H, NH), 7.1—7.4 (m, 5H, phenyl protons).

Z-Gly-Phe-OCet (7) A solution of TFA (5.4 ml) in dry CH_2Cl_2 (25 ml) was added to a solution of **6** (1.5 g, 4.7 mmol) in dry CH_2Cl_2 (5 ml) at 0 °C, and the stirring was continued for 3 h at room temperature. The mixture was evaporated under reduced pressure to remove TFA and CH_2Cl_2. To a solution of the residue in DMF (15 ml), a solution of triethylamine (1.6 ml, 11.5 mmol) in DMF (5 ml) was added at 0 °C. Z–Gly–OH (910 mg, 4.7 mmol), HOBt (680 mg, 5.2 mmol), and DCC (1.04 g, 5.2 mmol) were added to the above solution at 0 °C. The mixture was stirred for 23 h at the same temperature, then DCU precipitated was removed by suction. The filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt and the solution was washed with 5% aqueous $KHSO_4$. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2–Et_2O, 3:1) to give crude **7**, $[\alpha]_D^{20}$ +15.4° (c=2, CH_2Cl_2). Recrystallization from AcOEt–Et_2O gave pure sample of **7** (1.19 g, 62%) as colorless prisms, mp 93—94 °C, $[\alpha]_D^{20}$ +15.8° (c=2.9, CH_2Cl_2). IR ($CHCl_3$) ν: 2250, 1720, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.61 (t, 2H, J=6.4 Hz, CH_2CN), 3.11 (d, 2H, J=6.0 Hz, CH_2Ph), 3.86 (t, 2H, J=4.4 Hz, NCH_2CO), 4.28 (t, 2H, J=6.4 Hz, CO_2CH_2), 4.82 (q, 1H, J=6.0 Hz, CH), 5.12 (s, 2H, OCH_2Ph), 5.3—5.5 (br, 1H, amide NH), 6.4—6.6 (br d, 1H, urethane NH), 7.1—7.5 (m, 10H, phenyl protons). *Anal.* Calcd for $C_{22}H_{23}N_3O_5$: C, 64.53; H, 5.66; N, 10.26. Found: C, 64.54; H, 5.71; N, 10.31.

Z-Gly-Phe-OH (8) A solution of 1.0 M TBAF (1.1 ml, 1.1 mmol) in THF was added to a solution of crude **7** (300 mg, 0.73 mmol) in DMF (5 ml) at 0 °C, and stirring was continued for 2 h at room temperature. The mixture was added to saturated aqueous $NaHCO_3$ and the solution was washed with AcOEt. The aqueous layer was acidified with 5% aqueous $KHSO_4$ and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated to give crude **8**, $[\alpha]_D^{24}$ +37.7° (c=2, EtOH). Recrystallization from AcOEt–Et_2O gave pure **8** (217 mg, 83%) as colorless prisms, mp 126 °C, $[\alpha]_D^{24}$ +38.3° (c=2.4, EtOH), lit.,[15] mp 125—126 °C, $[\alpha]_D^{24}$ +38.5° (c=5, EtOH). IR (KBr) ν: 3275, 1730, 1680, 1650 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 3.0—3.3 (m, 2H, NCH_2CO), 3.83 (d, 2H, J=6.0 Hz, CH_2Ph), 4.75 (q, 1H, J=6.0 Hz, CH), 5.10 (s, 2H, OCH_2Ph), 6.5—6.7 (br, 1H, NH), 7.0—7.7 (m, 10H, phenyl protons).

References and Notes

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5) Amino acids and their derivatives are all of L form. Symbols and nomenclature follow the recommendations published by the IUPAC-IUB Commission on Biochemical Nomenclature for amino acids and peptides: *Eur. J. Biochem.*, **138**, 9 (1984). The following abbreviations for protecting groups in peptide synthesis are used: Boc, *tert*-butoxycarbonyl, Cet, 2-cyanoethyl; Z, benzyloxycarbonyl.
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13) This compound was easily prepared by catalytic hydrogenation of **4e** (72%) as colorless prisms, mp 45—45.5 °C (Et_2O–hexane). IR ($CHCl_3$) ν: 2250, 1740, 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.65—2.8 (m, 6H), 4.32 (t, 2H, $J=6.3$ Hz, CO_2CH_2). *Anal.* Calcd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: C, 48.97; H, 5.34; N, 8.11.

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