Note

Synthesis of Phenylalanine Analogs

Meng-Yang Chang[a]* (張夢揚), Chun-Yu Lin[a] (林俊佑) and Pei-Pei Sun[b] (孫珮珮)
[a]*Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan, R.O.C.*
[b]*Center of General Studies, National Kaohsiung Marine University, Kaohsiung 811, Taiwan, R.O.C.*

A straightforward synthesis of phenylalanine analogs is described. Cerium ammonium nitrate (CAN) mediated addition of azide to cinnamic ester, followed by reaction with sodium acetate afforded the α-azidocinnamate in moderate yield. Hydrogenation of α-azidocinnamate, followed by BOC, CBZ or Fmoc protection gave phenylalanine analogs. A new approach for synthesizing racemic *p*-boronophenylalanine analog was also explored.

Keywords: Phenylalanine; Cerium ammonium nitrate; *p*-Boronophenylalanine; Hydrogenation; Protection.

INTRODUCTION

Among the proteinogenic α-amino acids (AAs), phenylalanine (Phe, P) plays an important structural role in several bioactive peptides. Replacement of phenylalanine with constrained analogs is known to generate more effective therapeutics.[1-3] The pharmacological properties of a peptide with phenylalanine motif are a function of its conformation, which inturn is dictated by the constituent AAs. In this respect, unusual phenylalanine analogs are useful for carrying out more systematic studies (e.g., QSAR).[4] These well-defined structures are responsible for interesting biological properties.

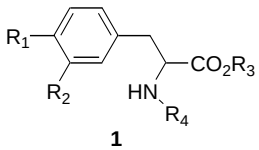
To appreciate the importance of the phenylalanine building block approach, it is useful briefly to review the general synthetic strategies for the preparation of these types of compounds. While attempting the synthesis of complex targets, two different strategies are usually employed.[5] These methods include linear and convergent synthetic approaches. In the linear synthetic strategy, the target molecule is assembled via a step-by-step process; while in the convergent synthesis, advanced intermediates are assembled from smaller fragments in separate sequences.

At an appropriate stage these intermediates are then combined to assemble the final target. In our synthetic strategy, we have pursued the phenylalanine analogs approach, which is different from the above approaches.[5] The highlight of the phenylalanine analogs approach is the potential to prepare libraries of compounds without repeating the whole synthetic sequence. In Fig. 1, the shown representative examples of phenylalanine analogs **1** are commercially available on a large scale because they usually serve as the building blocks for synthesizing peptides or proteins with biological activities in high-throughput combinatorial chemistry.

CAN (cerium ammonium nitrate) was invented by Smith et al. in 1936 and explored extensively in organic reactions in industry and the academic fields.[6] Representative examples include oxidation,[7] oxidative addition,[8] photooxidation,[9] nitration,[10] deprotection,[11] etc. Many research groups successfully developed useful transformations by application of this reagent. For example, Chavan[8h] developed a CAN-mediated azidoalkoxylation of enol ethers and olefins. Hwu[12] provided a practical way to the synthesis of α,β-unsaturated nitroalkenes involving the use of CAN. In this paper, we wish to report on the transformation of α,β-unsaturated esters into phenylalanine analogs **1**, associated with the use of CAN.

RESULTS AND DISCUSSION

In 1999, Chavan[8h] and coworker reported the CAN-mediated azidoalkoxylation of enol ethers and olefins. However reaction of alkyl cinnamate with electron deficient olefins was unsuccessful. The following year, Nair[8b] and coworkers developed that CAN-mediated reaction of alkyl cinnamate with sodium azide in acetonitrile followed by reac-



1

R_1 = H, F, MeO, $(HO)_2B$
R_2 = H, MeO
R_3 = Me, Et
R_4 = CBZ, BOC, Fmoc

Fig. 1.

tion with sodium acetate in dry acetone to afford the sole (*Z*)-α-azidocinnamate in modest yield.[8] In this paper, we want to investigate the ambiguous CAN-mediated reaction of alkyl cinnamate and apply the corresponding results to synthesize phenylalanine analogs **1** with CBZ, BOC or Fmoc protection.

As shown in Scheme I, different benzaldehydes **2** (included benzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 4-fluorobenzaldehyde and *p*-formylbenzeneboronic acid) were treated with stabilized phosphorus ylide of methyl or ethyl triphenylphosphoranylidene acetate ($Ph_3P=CHCO_2Me$ or $Ph_3P=CHCO_2Et$) in dichloromethane to afford methyl or ethyl *trans*-cinnamic ester **3** in good yield. Next, treatment of cinnamic ester **3** with sodium azide and CAN in dry acetonitrile could provide the α-azido-β-nitrato ester as a mixture of *syn*- and *anti*-isomers under the nitrogen system. Without further purification, the resulting crude product was treated with sodium acetate in dry acetone to give α-azidocinnamate **4** as a mixture of (*E*)- and (*Z*)-isomer in two steps with moderate yield. This result is dissimilar to Nair's report.[8b] However, the generated mixture is not influential to the following reaction. In order to obtain phenylalanine analogs **1**, compound **4** was hydrogenated with hydrogen and 10% palladium on activated carbon as a catalyst in methanol or ethanol. The corresponding amine was protected with benzylcarbonyloxy chloride (CBZCl), di-*tert*-butyl dicarbonate (BOC_2O) or 9-fluorenylmethyl succinimidyl carbonate (FmocOSu) to yield phenylalanine analogs **1**. Thus a new and straightforward synthesis of phenylalanine analogs **1** was accomplished *via* Wittig olefination, CAN-mediated reaction, hydrogenation and amino group protection as reaction steps. Compounds **3**, **4**, and **1** were obtained in modest to good yield and are shown in Table 1.

According to the above procedure, the synthesis of phenylalanine analog **1e** was mentioned. Among the boron analogs, *p*-boronophenylalanine (BPA) is a tumor-seeking

Scheme I

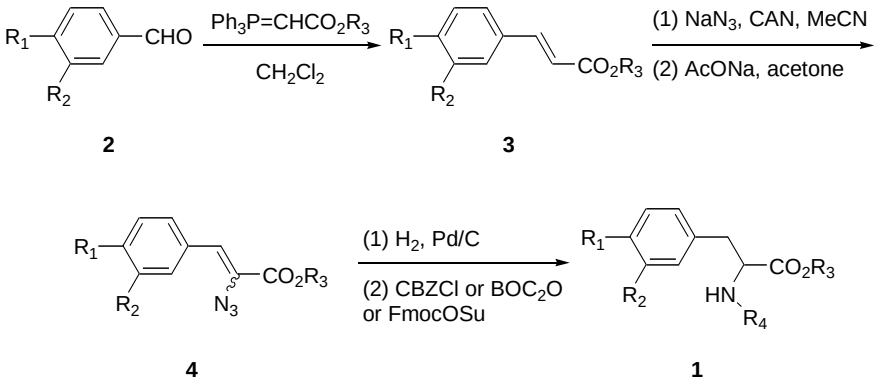


Table 1. The yields[a] of compounds **3**, **4**, and **1**

Entry	Compound **1**, R_1, R_2, R_3, R_4	**3**, yields (%)	**4**, yields (%)	**1**, yields (%)
1	$\mathbf{a_1}$, H, H, Et, CBZ	**3a**, 95%	**4a**, 60%	$\mathbf{1a_1}$, 81%
2	$\mathbf{a_2}$, H, H, Et, BOC			$\mathbf{1a_2}$, 75%
3	$\mathbf{a_3}$, H, H, Et, Fmoc			$\mathbf{1a_3}$, 83%
4	$\mathbf{b_1}$, MeO, H, Me, CBZ	**3b**, 92%	**4b**, 68%	$\mathbf{1b_1}$, 80%
5	$\mathbf{b_2}$, MeO, H, Me, BOC			$\mathbf{1b_2}$, 81%
6	$\mathbf{b_3}$, MeO, H, Me, Fmoc			$\mathbf{1b_3}$, 76%
7	$\mathbf{c_1}$, MeO, MeO, Et, CBZ	**3c**, 87%	**4c**, 66%	$\mathbf{1c_1}$, 83%
8	$\mathbf{c_2}$, MeO, MeO, Et, BOC			$\mathbf{1c_2}$, 82%
9	$\mathbf{c_3}$, MeO, MeO, Et, Fmoc			$\mathbf{1c_3}$, 79%
10	$\mathbf{d_1}$, F, H, Et, CBZ	**3d**, 93%	**4d**, 75%	$\mathbf{1d_1}$, 74%
11	$\mathbf{d_2}$, F, H, Et, BOC			$\mathbf{1d_2}$, 80%
12	$\mathbf{d_3}$, F, H, Et, Fmoc			$\mathbf{1d_3}$, 84%
13	**e**, $(HO)_2B$, H, Et, CBZ	**3e**, 80%	**4e**, 50%	**1e**, 78%

[a] The product yield was adjusted based on isolated product.

amino acid with a specific affinity for tumors and has been used as one of the most effective boron carriers for boron-neutron capture therapy (BNCT) of melanoma cells.[13] Recently, the use of BPA has been exploited for treatment of tumors in clinical trials.[14] Therefore, development of different synthetic methods of BPA are important goals for synthetic chemists and BNCT researchers.[15] The racemic BPA analog **1e** was transferred to L-BPA in enzymatic hydrolysis or D,L-BPA in basic solution in previous literature reports.[16] Herein we also provide a new approach for synthesizing racemic BPA analog **1e** from *p*-formylbenzeneboronic acid using the CAN-mediated methodology as the key step. With these experimental results and observations, we turned our attention to the synthesis of azatyrosine[17a] and pyridylalanine.[17b] But, the CAN-mediated reaction on the β-aromatic heterocyclic group (such as indole, furan and pyridine) of the cinnamic ester was unsuccessful. We attempted to use a variety of reaction conditions, but a complex result was still obtained. For testing the CAN-mediated reaction on a β-aliphatic group (such as methyl and *n*-undecanyl) of the cinnamic ester, we also found there was no reaction. The related limitations and factors in a β-substituted group of cinnamic ester were not clear under the CAN-mediated reaction conditions.

In view of the experimental simplicity, we chose benzaldehyde as the model substrate to synthesize phenylalanine analog **1a$_1$**. Ethyl cinnamate **3a** (53 g, 0.5 mole) was chosen as the starting material to furnish the synthesis of phenylalanine analog **1a$_1$** *via* four steps in moderate yield (65 g, 40%) with only one purification by column chromatography on silica gel. The total procedure was monitored by TLC until the reaction was complete. The overall reaction time is approximately 40 h. In conclusion, a straightforward synthesis of phenylalanine analogs is described. The moderate reaction scale and the relative limitation of β-substituted group of cinnamic ester are studied. A new approach for synthesizing racemic *p*-boronophenylalanine analog was also explored. We are currently studying the related application of cerium ammonium nitrate to other methodologies.

EXPERIMENTAL

General

All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Crude products were purified by column chromatography on silica gel. All reported temperatures are uncorrected.

General preparation of compounds 3[18a]

A solution of benzaldehyde **2** (1.0 mmol) in methylene chloride (10 mL) was added to a rapidly stirred solution of $Ph_3P{=}CHCO_2Me$ or $Ph_3P{=}CHCO_2Et$ (1.1 mmol) in dichloromethane (10 mL). After the reaction mixture was stirred at rt for 4~8 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous magnesium sulfate, filtered, evaporated, and purified to yield **3a**~**3e** (80%~95%).

Ethyl cinnamate (3a)[18a]

IR ($CHCl_3$) 2951, 1717 cm^{-1}; EI-MS: $C_{11}H_{12}O_2$ *m/z* (%) = 176 (M^+, 8); HRMS (EI, M^+) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 15.8 Hz, 1H), 7.27-7.12 (m, 5H), 6.32 (d, *J* = 15.8 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 2H), 1.31 (t, *J* = 6.9 Hz, 3H).

Methyl 4-methoxycinnamate (3b)[18b]

IR ($CHCl_3$) 2951, 1714 cm^{-1}; EI-MS: $C_{11}H_{12}O_3$ *m/z* (%) = 192 (M^+, 5); HRMS (EI, M^+) calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0788; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 15.9 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.1 Hz, 2H), 6.35 (d, *J* = 15.9 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H).

Ethyl 3,4-dimethoxycinnamate (3c)[18a]

IR ($CHCl_3$) 2956, 1719 cm^{-1}; EI-MS: $C_{13}H_{16}O_4$ *m/z* (%) = 236 (M^+, 12); HRMS (EI, M^+) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1047; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 15.9 Hz, 1H), 7.07 (dd, *J* = 1.8, 8.2 Hz, 1H), 7.03 (d, *J* = 1.8 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 3.90 (s, 6H), 4.15 (q, *J* = 6.9 Hz, 2H), 1.32 (t, *J* = 6.9 Hz, 3H).

Ethyl 4-fluorocinnamate (3d)[18a]

IR ($CHCl_3$) 2949, 1709 cm^{-1}; EI-MS: $C_{11}H_{11}FO_2$ *m/z* (%) = 194 (M^+, 3); HRMS (EI, M^+) calcd for $C_{11}H_{11}FO_2$ 194.0743, found 194.0745; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.30 (d, *J* = 8.7 Hz, 2H), 4.18 (q, *J* = 6.9 Hz, 2H), 1.31 (t, *J* = 6.9 Hz, 3H).

Ethyl 4-boronocinnamate (3e)

^{1}H NMR (300 MHz, $CDCl_3$, CD_3OD) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 15.9 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H),

6.38 (d, *J* = 15.9 Hz, 1H), 4.24 (q, *J* = 6.9 Hz, 2H), 1.36 (t, *J* = 6.9 Hz, 3H).

General preparation of compounds 4[8b]

To a deoxygenated solution of **3** (1.0 mmol) and sodium azide (98 mg, 1.5 mmol) in dry acetonitrile, a deoxygenated solution of ceric ammonium nitrate (1.37 g, 2.5 mmol) in the same solvent (10 mL) was added dropwise into an ice bath and stirred well. On completion of the reaction it was worked up using dichloromethane and water, then dried and concentrated. Without further purification, anhydrous sodium acetate (123 mg, 1.5 mmol) was added to a stirred solution of the crude residue in dry acetone (5 mL). After the reaction mixture was stirred at rt for 18~22 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous magnesium sulfate, filtered, evaporated, and purified to yield **4a**~**4e** (50%~75%).

Ethyl 2-azido-3-phenylacrylate (4a)[8b]

IR ($CHCl_3$) 3065, 1706 cm^{-1}; EI-MS: $C_{11}H_{11}N_3O_2$ *m/z* (%) = 217 (M^+, 11); HRMS (EI, M^+) calcd for $C_{11}H_{11}N_3O_2$ 217.0851, found 217.0853; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.81 (m, 2H), 7.40-7.33 (m, 3H), 6.93 (s, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H).

Methyl 2-azido-3-(4-methoxyphenyl)acrylate (4b)

IR ($CHCl_3$) 3058, 1710 cm^{-1}; EI-MS: $C_{11}H_{11}N_3O_3$ *m/z* (%) = 233 (M^+, 8); HRMS (EI, M^+) calcd for $C_{11}H_{11}N_3O_3$ 233.0800, found 233.0801; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10-7.05 (m, 2H), 6.93-6.88 (m, 3H), 3.79 (s, 3H), 3.71 (s, 3H).

Ethyl 2-azido-3-(3,4-dimethoxyphenyl)acrylate (4c)

IR ($CHCl_3$) 3060, 1704 cm^{-1}; EI-MS: $C_{13}H_{15}N_3O_4$ *m/z* (%) = 277 (M^+, 8); HRMS (EI, M^+) calcd for $C_{13}H_{15}N_3O_4$ 277.1063, found 277.1065; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.76-6.63 (m, 3H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.82 (s, 6H), 1.40 (t, *J* = 7.0 Hz, 3H).

Ethyl 2-azido-3-(4-fluorophenyl)acrylate (4d)

IR ($CHCl_3$) 3055, 1706 cm^{-1}; EI-MS: $C_{11}H_{10}FN_3O_2$ *m/z* (%) = 235 (M^+, 2); HRMS (EI, M^+) calcd for $C_{11}H_{10}FN_3O_2$ 235.0757, found 235.0757; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.75 (m, 2H), 7.15-6.98 (m, 2H), 6.88 (s, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H).

Ethyl 2-azido-3-(4-boronophenyl)acrylate (4e)

^1H NMR (300 MHz, $CDCl_3$, CD_3OD) δ 7.76-7.72 (m, 2H), 7.24-7.18 (m, 2H), 6.92 (s, 1H), 4.48-4.40 (m, 2H), 1.39 (t, *J* = 7.0 Hz, 3H).

General preparation of compounds 1

Compound **4** (0.5 mmol) was dissolved in methanol or ethanol (10 mL) and to which was added a catalytic amount of 10% palladium on activated carbon. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 5~8 h. Filtration through a short plug of Celite and washing with ethyl acetate (20 mL) resulted in the desired amine. Without further purification, 0.6 mmol of benzyl chloroformate (CBZCl), di-*tert*-butyl dicarbonate (BOC_2O) or 9-fluorenylmethyl succinimidyl carbonate (FmocOSu) was added to a stirred solution of the crude residue in dry tetrahydrofuran (10 mL). After the reaction mixture was stirred at rt for 2~4 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous magnesium sulfate, filtered, evaporated, and purified to yield **1a$_1$~1e** (74%~83%), **1a$_2$~1d$_2$** (75%~82%) or **1a$_3$~1d$_3$** (76%~84%). The ^1H NMR spectral data of **1a$_1$~1e**, **1a$_2$~1d$_2$** and **1a$_3$~1d$_3$** were in accordance with commercial authentic samples and published reports.

Ethyl *N*-benzyloxycarbonylphenylalaninate (1a$_1$)[19a]

IR ($CHCl_3$) 3320, 1730, 1700 cm^{-1}; EI-MS: $C_{19}H_{21}NO_4$ *m/z* (%) = 327 (M^+, 5); HRMS (EI, M^+) calcd for $C_{19}H_{21}NO_4$ 327.1471, found 327.1474; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.10 (m, 10H), 5.24 (br d, *J* = 7.8 Hz, 1H), 5.12-5.08 (m, 2H), 4.68-4.61 (m, 1H), 4.20-4.12 (m, 2H), 3.13-3.09 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.72, 155.84, 136.51, 135.98, 129.75 (2×), 129.56 (2×), 128.77, 128.60 (2×), 127.31 (2×), 127.21, 67.17, 61.71, 55.07, 38.54, 14.31.

Methyl *N*-benzyloxycarbonyl-4-methoxyphenylalaninate (1b$_1$)[19b]

IR ($CHCl_3$) 3330, 1735, 1704 cm^{-1}; EI-MS: $C_{19}H_{21}NO_5$ *m/z* (%) = 343 (M^+, 4); HRMS (EI, M^+) calcd for $C_{19}H_{21}NO_5$ 343.1420, found 343.1422; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 7.00 (d, *J* = 6.0 Hz, 2H), 6.80 (d, *J* = 6.0 Hz, 2H), 5.23 (br d, *J* = 7.8 Hz, 1H), 5.10-5.07 (m, 2H), 4.70-4.59 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.07-3.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.30, 158.96, 155.87,

136.51, 130.49 (2×), 128.74 (2×), 128.40 (2×), 128.30, 127.84, 114.28 (2×), 67.18, 55.43, 55.16, 52.51, 37.59.

Ethyl *N*-benzyloxycarbonyl-3,4-dimethoxyphenyl-alaninate ($1c_1$)

IR ($CHCl_3$) 3333, 1738, 1703 cm^{-1}; EI-MS: $C_{21}H_{25}NO_6$ *m/z* (%) = 387 (M^+, 4); HRMS (EI, M^+) calcd for $C_{21}H_{25}NO_6$ 387.1682, found 387.1685; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 6.75 (d, *J* = 9.0 Hz, 1H), 6.66-6.61 (m, 2H), 5.23 (br d, *J* = 7.5 Hz, 1H), 5.12-5.06 (m, 2H), 4.65-4.55 (m, 1H), 4.20-4.12 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.18-3.08 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.23, 156.36, 149.37, 148.31, 136.85, 129.11 (2×), 128.83 (2×), 122.07 (2×), 113.16, 111.97 (2×), 67.56, 62.02, 56.63 (2×), 55.36, 38.53, 14.14.

Ethyl *N*-benzyloxycarbonyl-4-fluorophenylalaninate ($1d_1$)[19c]

IR ($CHCl_3$) 3342, 1740, 1710 cm^{-1}; EI-MS: $C_{19}H_{20}FNO_4$ *m/z* (%) = 345 (M^+, 1); HRMS (EI, M^+) calcd for $C_{19}H_{20}FNO_4$ 345.1376, found 345.1375; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 7.08-7.03 (m, 2H), 6.98-6.91 (m, 2H), 5.25 (br d, *J* = 7.8 Hz, 1H), 5.12-5.08 (m, 2H), 4.63-4.58 (m, 1H), 4.19-4.13 (m, 2H), 3.16-3.04 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.53, 163.87, 160.62, 155.78, 136.46, 131.12, 131.01, 128.76, 128.46 (2×), 128.34 (2×), 115.76, 115.47, 67.22, 61.82, 55.06, 37.79, 14.33.

Ethyl *N*-benzyloxycarbonyl-4-boronophenylalaninate (1e)

^1H NMR (300 MHz, $CDCl_3$, CD_3OD) δ 7.76-7.72 (m, 2H), 7.36-7.26 (m, 5H), 7.14-7.08 (m, 2H), 5.26-5.22 (m, 1H), 5.10-5.07 (m, 2H), 4.48-4.40 (m, 3H), 3.09-2.98 (m, 2H), 1.39 (t, *J* = 7.0 Hz, 3H).

Ethyl *N*-*tert*-butoxycarbonylphenylalaninate ($1a_2$)[20a]

IR ($CHCl_3$) 3397, 1740, 1704 cm^{-1}; EI-MS: $C_{16}H_{23}NO_4$ *m/z* (%) = 293 (M^+, 12); HRMS (EI, M^+) calcd for $C_{16}H_{23}NO_4$ 293.1627, found 293.1625; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.12 (m, 5H), 4.98 (br d, *J* = 6.6 Hz, 1H), 4.59-4.53 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.14-3.04 (m, 2H), 1.41 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.11, 155.32, 136.32, 129.59 (2×), 128.71 (2×), 127.20, 80.09, 61.54, 54.67, 38.64, 28.52 (3×), 14.33.

Methyl *N*-*tert*-butoxycarbonyl-4-methoxyphenylalaninate ($1b_2$)[20b]

IR ($CHCl_3$) 3389, 1744, 1706 cm^{-1}; EI-MS: $C_{16}H_{23}NO_5$ *m/z* (%) = 309 (M^+, 15); HRMS (EI, M^+) calcd for $C_{16}H_{23}NO_5$ 309.1576, found 309.1577; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 4.95 (br d, *J* = 7.8 Hz, 1H), 4.59-4.49 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.10-2.94 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.66, 158.90, 155.32, 130.50 (2×), 128.15, 114.21 (2×), 80.11, 55.44, 54.76, 52.39, 37.70, 28.52 (3×).

Ethyl *N*-*tert*-butoxycarbonyl-3,4-dimethoxyphenyl-alaninate ($1c_2$)[20c]

IR ($CHCl_3$) 3395, 1746, 1704 cm^{-1}; EI-MS: $C_{18}H_{27}NO_6$ *m/z* (%) = 353 (M^+, 8); HRMS (EI, M^+) calcd for $C_{18}H_{27}NO_6$ 353.1838, found 353.1840; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 6.0 Hz, 1H), 6.68-6.62 (m, 2H), 4.97 (br d, *J* = 7.8 Hz, 1H), 4.54-4.48 (m, 1H), 4.16 (q, *J* = 6.0 Hz, 2H), 3.85 (s, 6H), 3.10-2.95 (m, 2H), 1.41 (s, 9H), 1.24 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.17, 155.31, 149.08, 148.32, 128.74, 121.68, 112.70, 111.45, 80.07, 61.53, 56.11, 56.03, 54.74, 38.13, 28.54 (3×), 14.39.

Ethyl *N*-*tert*-butoxycarbonyl-4-fluorophenylalaninate ($1d_2$)

IR ($CHCl_3$) 3386, 1745, 1711 cm^{-1}; EI-MS: $C_{16}H_{22}FNO_4$ *m/z* (%) = 311 (M^+, 5); HRMS (EI, M^+) calcd for $C_{16}H_{22}FNO_4$ 311.1533, found 311.1533; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12-7.07 (m, 2H), 7.00-6.94 (m, 2H), 4.99 (br d, *J* = 6.0 Hz, 1H), 4.59-4.50 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.14-3.00 (m, 2H), 1.41 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.94, 163.83, 130.59, 155.24, 132.09, 131.02, 115.68, 115.40, 80.19, 61.64, 54.70, 37.91, 28.51 (3×), 14.35.

Ethyl *N*-9-fluorenylmethoxycarbonylphenylalaninate ($1a_3$)[21]

IR ($CHCl_3$) 3420, 1734, 1717 cm^{-1}; EI-MS: $C_{26}H_{25}NO_4$ *m/z* (%) = 415 (M^+, 2); HRMS (EI, M^+) calcd for $C_{26}H_{25}NO_4$ 415.1784, found 415.1786; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4 Hz, 2H), 7.50-7.45 (m, 2H), 7.34-7.14 (m, 7H), 7.03 (d, *J* = 5.9 Hz, 2H), 5.22 (d, *J* = 8.0 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 4.39-4.02 (m, 5H), 3.04-3.00 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H).

Methyl *N*-9-fluorenylmethoxycarbonyl-4-methoxyphenyl-alaninate ($1b_3$)

IR ($CHCl_3$) 3422, 1733, 1715 cm^{-1}; EI-MS: $C_{26}H_{25}NO_5$ *m/z* (%) = 431 (M^+, 5); HRMS (EI, M^+) calcd for $C_{26}H_{25}NO_5$ 431.1733, found 431.1735; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.59-7.56 (m, 2H), 7.35-7.31 (m,

2H), 7.13 (d, *J* = 7.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.26 (d, *J* = 8.0 Hz, 1H), 4.52-4.48 (m, 1H), 4.44-4.21 (m, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.08-3.00 (m, 2H).

Ethyl *N*-9-fluorenylmethoxycarbonyl-3,4-dimethoxyphenylalaninate (1c$_3$)

IR ($CHCl_3$) 3425, 1730, 1715 cm^{-1}; EI-MS: $C_{28}H_{29}NO_6$ *m/z* (%) = 475 (M^+, 2); HRMS (EI, M^+) calcd for $C_{28}H_{29}NO_6$ 475.1995, found 475.1996; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.59-7.54 (m, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 7.0 Hz, 1H), 6.71-6.68 (m, 2H), 5.29 (d, *J* = 8.0 Hz, 1H), 4.70-4.54 (m, 1H), 4.39-4.20 (m, 5H), 3.58 (s, 6H), 3.1-3.01 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H).

Ethyl *N*-9-fluorenylmethoxycarbonyl-4-fluorophenylalaninate (1d$_3$)

IR ($CHCl_3$) 3430, 1742, 1722 cm^{-1}; EI-MS: $C_{26}H_{24}FNO_4$ *m/z* (%) = 433 (M^+, 1); HRMS (EI, M^+) calcd for $C_{26}H_{24}FNO_4$ 433.1689, found 433.1688; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 2H), 7.32-7.28 (m, 2H), 7.25-7.21 (m, 2H), 5.37 (d, *J* = 8.5 Hz, 1H), 4.67-4.62 (m, 1H), 4.49-4.17 (m, 5H), 3.20-3.08 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H).

ACKNOWLEDGEMENTS

The authors would like to thank the National Science Council (NSC 94-2113-M-390-001) of the Republic of China for financial support.

Received March 11, 2005.

REFERENCES

1. (a) Gavuzzo, E.; Lucente, G.; Mazza, F.; Zecchini, G. P.; Paradisi, M. P.; Pochetti, G.; Torrini, I. *Int. J. Pept. Protein Res.* **1991**, *37*, 268. (b) Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; Beaujouan, J.-C.; Glowinski, J.; Chassaing, G. *J. Med. Chem.* **1994**, *37*, 1586.
2. (a) Torrini, I.; Zecchini, G. P.; Paradisi, M. P.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G.; Spisani, S.; Giuliani, A. L. *Int. J. Pept. Protein Res.* **1991**, *38*, 495. (b) Hsieh, K.-h.; Jorgensen, E. C. *J. Med. Chem.* **1979**, *22*, 1038. (c) Nolan, W. P.; Ratcliffe, G. S.; Rees, D. C. *Tetrahedron Lett.* **1992**, *33*, 6879.
3. (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (b) Liskamp, R. M. J. *Trav. Chim. Pays-Bas* **1994**, *113*, 1. (c) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585. (d) Gibson, S. E.; Guillo, N.; Jones, J. O.; Buck, I. M.; Kalindjian, S. B.; Roberts, S.; Tozer, M. J. *Eur. J. Med. Chem.* **2002**, *37*, 379. (e) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.
4. Griffiths, E. C. In *A Text Book of Drug Design and Development*; Krogsgaard, L., Bundgaard, P. Eds.; Harwood Academic Publishers: Tokyo, 1992; pp 487-528.
5. (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York; 1989. (b) Ho, T.-L. *Tactics of Organic Synthesis*; John Wiley: New York; 1994. (c) Carruthers, W. *Cycloddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (f) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342. (e) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 7703.
6. (a) Smith, G. F.; Sullivan, V. R.; Frank, G. *Ind. Eng. Chem., Anal. Ed*., **1936**, *8*, 449. (b) Molycorp, Inc. Publ. *Cerium: A Guide to its Role in Chemical Technology*; Mountain Pass: California, 1992, p. 10. (c) Ho, T.-L. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley: New York, 1995, vol. 2, p. 1026.
7. (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (b) Zolfigol, M. A.; Borazjani, M. K.; Mallakpour, S. E.; Nasr-Isfahani, H. *Synth. Commun*. **2000**, *30*, 2573. (c) Xiao, J.-P.; Wang, Y.-L.; Jia, X.-S.; Wang, X.-Y.; Wang, H. *Synth. Commun*. **2000**, *30*, 1807. (d) Takemoto, Y.; Ibuka, T.; Furuse, S.-I.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka, T. *Chem. Commun*. **1999**, 2515. (e) Nair, V.; George, T. G.; Nair, L. G.; Panicker, S. B. *Tetrahedron Lett*. **1999**, *40*, 1195. (f) Wang, Y.; Tanko, J. M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2705. (g) Moreno-Vargas, A. J.; Robina, I.; Fernindez-Bolafios, J. G.; Fuentes, J. *Tetrahedron Lett*. **1998**, *39*, 9271. (h) Poigny, S.; Guyot, M.; Samadi, M. *Tetrahedron* **1998**, *54*, 14791.
8. (a) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, 127. (b) Nair, V.; George, T. G. *Tetrahedron Lett.* **2000**, *41*, 3199. (c) Baciocchi, E.; Ruzziconi, R. *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; NATO ASI Series, Kluwer Academic, Dordrecht, 1989, pp. 155-185. (d) Kobayashi, K.; Tanaka, H.; Tanaka, K.; Yoneda, K.; Morikawa, O.; Konishi, H. *Synth. Commun*. **2000**, *30*, 4277. (e) Lee, Y. R.; Kim, B. S.; Kim, D. H. *Tetrahedron* **2000**, *56*, 8845. (f) Nair, V.; Nair, L. G.; Balagopal, L.; Mathew, J. *Indian J. Chem*. **2000**, *B39*, 352. (g) Paolobelli, A. B.; Ruzziconi, R.; Lupattelli, P.; Scafato, P.; Spezzacatena, C. *J. Org. Chem*. **1999**, *64*, 3364. (h) Chavan, S. P.; Subbarao, T. *Tetrahedron Lett*. **1999**, *40*, 5073.
9. (a) Grossi, L.; Strazzari, S. *J. Org. Chem.* **2000**, *65*, 2748. (b) Fokin, A. A.; Peleshanko, S. A.; Gunchenko, P. A.; Gusev, D. V.; Schreiner, P. R. *Eur. J. Org. Chem*. **2000**, 3357.

10. (a) Mellor, J. M.; Mittoo, S.; Parkes, R.; Millar, R. W. *Tetrahedron* **2000**, *56*, 8019. (b) Reddy, M. V. R.; Mehrotra, B.; Vankar, Y. D. *Tetrahedron Lett*. **1995**, *36*, 4861. (c) Chakrabarty, M.; Batabyal, A. *Synth. Commun*. **1996**, *24*, 1.
11. (a) Bull, S. D.; Davies, S. G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D.; Fenton, G. *Chem. Commun*. **2000**, 337. (b) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett*. **1999**, *40*, 1799. (c) Markó, I. E.; Ates, A.; Augustyns, B.; Gautier, A.; Quesnel, Y.; Turet, L.; Wiaux, M. *Tetrahedron Lett*. **1999**, *40*, 5613. (d) DattaGupta, A.; Singh, R.; Singh, V. K. *Synlett* **1996**, 69.
12. (a) Hwu, J. R.; Chen, K.-L.; Ananthan, S.; Patel, H. V. *Organometallics*, **1996**, *15*, 499. (b) Hwu, J. R.; Chen, K.-L.; Ananthan, S. *J. Chem. Soc.*, *Chem. Commun*. **1994**, 1425.
13. (a) Snyder, H. R.; Reedy, A. J.; Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 835. (b) Barth, R. F.; Soloway, A. H.; Fairchild, R. G. *Cancer. Res.* **1990**, *50*, 1061. (c) Hawthorne, M. F. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 950. (d) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F. G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515. (e) Morin, C. *Tetrahedron* **1994**, *50*, 12521.
14. Coderre, J. A.; Bergland, R.; Chadha, M.; Chanana, A. D.; Elowitz, E. H.; Joel, D. D.; Liu, H. B.; Slatkin, D. N.; Wielopolski, L. In *Cancer Neutron Capture Therapy*; Mishima, Y., Ed.; Plenum: New York, 1996; p 533.
15. For synthesis of BPA: (a) Kirihata, M.; Morimoto, T.; Ichimoto, I. *Biosci. Biotech. Biochem.* **1993**, *57*, 1940. (b) Nakao, H.; Morimoto, T.; Kirihata, M. *Biosci. Biotech. Biochem.* **1996**, *60*, 683. (c) Samsel, E. G. U. S. Patent 5,157,149, 1992; *Chem. Abstr.* **1993**, *118*, 125073. (d) Malan, C.; Morin, C. *Synlett* **1996**, 167. (e) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7529. (f) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 231. (g) Park, K. C.; Yoshino, K.; Tomiyasu, H. *Synthesis* **1999**, *12*, 2041.
16. (a) Yoshino, K.; Maruyama, T.; Ogawa, M.; Umeda, I.; Mori, Y.; Takahashi, H.; Mishima, Y.; Ichihashi, M. *Kurri-TR* **1992**, *365*, 5. (b) Roberts, D. C.; Suda, K.; Samanen, J.; Kemp, D. S. *Tetrahedron Lett.* **1980**, *21*, 3455.
17. (a) Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Org. Lett.* **2001**, *3*, 3157. (b) Walker, M. A.; Kaplita, K. P.; Chen, T.; King, H. D. *Synlett* **1997**, 169.
18. (a) Chang, M.-Y.; Lin, J. Y.-C.; Chen, S.-T.; Chang, N.-C. *J. Chin. Chem. Soc.* **2002**, *49*, 1015. (b) Heffner, R. J.; Joullie, M. M. *Synth. Commun.* **1991**, *21*, 2231.
19. (a) Allevi, P.; Cighetti, G.; Anastasia, M. *Tetrahedron Lett.* **2001**, *42*, 5319. (b) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051. (c) Moriniere, J. L.; Danree, B.; Lemoine, J.; Guy, A. *Synth. Commun.* **1988**, *18*, 441.
20. (a) Sameiro, M.; Goncalves, T.; Maia, H. L. S. *Org. Biomol. Chem.* **2003**, *1*, 1480. (b) Chandrasekhar, S.; Ramachandar, T.; Reddy, M. V. *Synthesis* **2002**, 1867. (c) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1990**, *55*, 4246.
21. Bondebjerg, J.; Xiang, Z.; Bauzo, R. M.; Haskell-Luevano, C.; Meldal, M. *J. Am. Chem. Soc.* **2002**, *124*, 11046.