Improved Stereoselectivity in Intramolecular S_N2' Cyclization through Use of Mechanistic Principles

Woo Duck Seo,[a] Marcus J. Curtis-Long,[b] Seong Hun Jeong,[a] Tae Hong Jun,[a] Min Suk Yang,[a] Ki Hun Park*[a]

[a] Division of Applied Life Science (BK 21 Program), Institute of Agriculture & Life Sciences, Department of Agricultural Chemistry, Gyeongsang National University, Jinju 660-701, South Korea
Fax +82(55)7570178; E-mail: khpark@gshp.gsnu.ac.kr

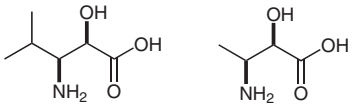
[b] Woodview, 12 New Road, Nafferton, East Yorkshire, YO25 4JP, UK

Received 28 August 2006; revised 17 October 2006

Abstract: Valine and alanine were converted into the corresponding α-hydroxy-β-amino acids through intramolecular S_N2' cyclization. The novel cyclization protocol relied upon the use of *N*-benzyl-protected carbamates derived from α-amino acids

Key words: oxazolidin-2-one, intramolecular cyclization, stereoselectivity, A(1,3) strain, α-hydroxy-β-amino acids

The derivatization of α-amino acids continues to be a vibrant and fruitful area of chemical endeavor because of the high optical purity and varied reactivity of these starting materials.[1] α-Amino acids have been converted efficiently into enantiopure amino epoxides,[2] amino alcohols,[3] amino diols,[4] and a wide range of unsaturated intermediates, as well as into β-amino acids. β-Amino acids[5] are of great chemical significance, and the huge interest in this field has been reflected in the publication of a number of recent reviews on both the general chemical function and the synthesis of this class of compound.[6] However, despite their abundance in important bioactive compounds such as Taxol,[7] highly selective routes to α-hydroxy-β-amino acids (ABHAs; e.g., **1** and **2**, Figure 1) are much rarer, because the controlled generation of two or more stereogenic centers is required. We were able to show that the derivatization of diastereo- and enantiomerically pure oxazolidinones constitutes a powerful route to ABHAs.[4,8]

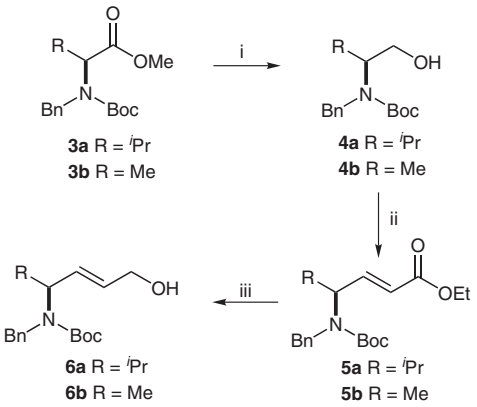


1 **2**

Figure 1 Target compounds

This methodology is based on the conversion of α-amino acids into oxazolidin-2-ones through cyclization of (4-hydroxybutenyl)carbamates, in which the hydroxy group (nucleofuge) has been activated as a sulfonate prior to an internal S_N2' cyclization.[4] This cyclization strategy has been highly effective for substrates derived from α-amino acids containing bulky side chains, but has, sadly, been of low utility in substrates possessing smaller side chains (valine and alanine). The objective of the work reported here has been to extend this methodology to allow stereoselective synthesis of ABHAs possessing smaller side chains. We will also discuss the mechanistic features of the cyclization transition state as elucidated during this work.

Synthesis of the substrates began with chemoselective reduction of *N*-Boc-*N*-Bn-protected α-amino esters **3a** and **3b** with lithium aluminum hydride (Scheme 1).[4] Swern oxidation of the resulting (2-hydroxyethyl)carbamates **4a** and **4b** furnished chiral aldehydes, which underwent an *E*-selective Horner–Wadsworth–Emmons reaction that afforded allylic carbamates **5a** and **5b**. Finally, chemoselective reduction of the ester moiety with diisobutylaluminum hydride generated the cyclization precursors, allylic alcohols **6a** and **6b** (Scheme 1).



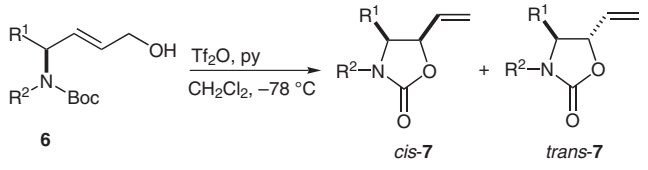
Scheme 1 *Reagents and conditions*: (i) see ref. 4; (ii) (a) Swern oxidation; (b) $(EtO)_2P(O)CH_2CO_2Et$ (2 equiv), NaH (2 equiv), dry THF, 0 °C to r.t., 82% yield; (iii) DIBAL-H (3.0 equiv), THF, –78 °C, 85% yield.

Under our previously reported conditions, namely the use of trifluoromethanesulfonic anhydride in pyridine at –78 °C, allylic alcohols **6c** and **6f** (R^2 = H) gave the corresponding oxazolidinones **7** in 1:2 and 1:5 *cis*/*trans* selectivities, respectively (Table 1, entries 1 and 4). However, when the steric bulk at nitrogen was increased by N-methylation (**6d** and **6g**, R^2 = Me), the cyclization proceeded slightly more selectively, to afford the oxazolidi-

SYNTHESIS 2007, No. 2, pp 0209–0214
Advanced online publication: 21.12.2006
DOI: 10.1055/s-2006-958956; Art ID: F13406SS

none products **7** in improved *cis*/*trans* ratios (Table 1, entries 2 and 5). We subsequently investigated the effect of the more sterically demanding *N*-benzyl substituent (**6e** and **6h**, R^2 = Bn) upon the selectivity (Table 1, entries 3 and 6). Triflation/cyclization of alanine derivative **6e** and valine derivative **6h** led to a dramatic improvement in the selectivities, with the corresponding *trans*-oxazolidinones **7** forming in 15:1 and an excellent 99:1 dr, respectively (Table 1, entries 3 and 6).

Table 1 Optimization of the S_N2' Cyclization Step



Entry	Substrate **6**	R^1	R^2	dr[a]	Yield[b] (%)
1	**6c**	Me	H	1:2	65
2	**6d**	Me	Me	1:4	70
3	**6e**	Me	Bn	1:15	85
4	**6f**	*i*-Pr	H	1:5	76
5	**6g**	*i*-Pr	Me	1:8	83
6	**6h**	*i*-Pr	Bn	1:99	85

[a] The dr (*cis*/*trans*) was determined by ^{1}H NMR integration.
[b] Isolated yield.

Previously, our consideration of the mechanism of the cyclization, as well as molecular modeling studies led us to conclude that minimization of A(1,3) strain[9] by eclipsing of C(2)H and C(4)H is a probable cause for the observed *trans* selectivity in the case of substrates possessing bulky R^1 substituents. However, we noted that for efficient A(1,3) strain control, a substituent bulkier than a proton is generally required in the 2-position (Figure 2) to achieve good selectivity, and this seems to be the grounds for low selectivity when R^1 is small. However, as our results verify, when R^2 becomes an alkyl group, an extra interaction occurs, which destabilizes the transition state leading to the *cis* product. This interaction may be described as a *syn*-pentane interaction between the N–R^2 bond and the olefin. This new interaction is expected to stabilize **B** over **A**, even when R^1 is small enough to allow for significant C(3)–C(4) bond rotation in the absence of other factors.[10]

The conversion of the oxazolidinone products into the corresponding ABHAs was next undertaken (Scheme 2). Dihydroxylation of the vinyl substituent on **7a** and **7b** is achieved with osmium tetroxide followed by cleavage in the presence of periodate, and subsequent oxidation with potassium permanganate yielded acids **8a** and **8b** (Scheme 2). The oxazolidinone ring within these products was easily cleaved, without epimerization at the C(5)-position, by reflux in aqueous potassium hydroxide, to give *N*-benzyl-protected ABHAs **9a** and **9b** in 85% yield. Finally, the amino group was deprotected by hydrogenolysis to give (2*R*,3*S*)-**1**[4] and (2*R*,3*S*)-**2**[11] in 90% yield (Scheme 2).

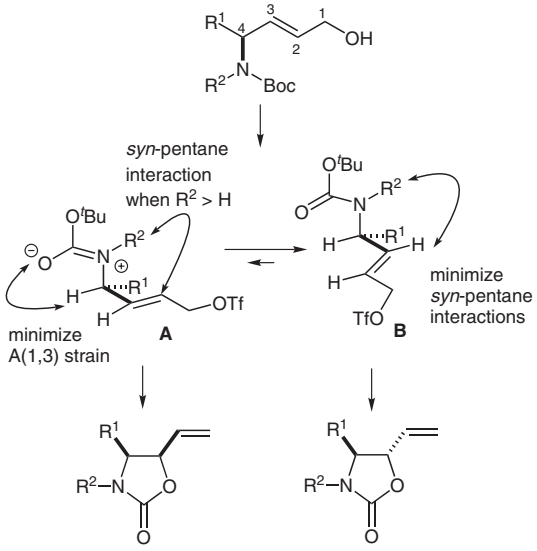
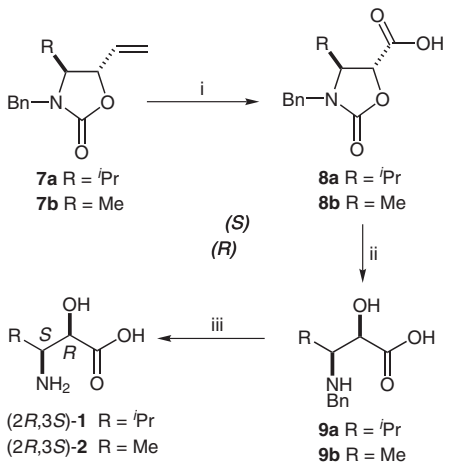


Figure 2 Model explaining increased *anti* selectivity when R^2 = Bn



Scheme 2 *Reagents and conditions*: (i) (a) OsO_4 (10%), NMO (2 equiv), acetone, r.t., 24 h, 90% yield; (b) $NaIO_4$ (1.5 equiv), EtOH–H_2O, 2:1, r.t., 2 h, 80% yield; (c) $KMnO_4$ (1.2 equiv), K_2CO_3 (2.1 equiv), THF–H_2O, 2:1, r.t., 1 h, 75% yield; (ii) 4 M KOH, EtOH, 60 °C, 85% yield; (iii) H_2, MeOH, r.t., 90% yield.

The relative stereochemistry within the target molecules **1** and **2** was determined by 2D-NOESY experiments on oxazolidinone **7a** and **7b**, both of which showed a weak correlation between C(4)H and C(5)H. Vicinal coupling constants between C(4)H and C(5)H ($J_{4,5}$) are also consistent with this analysis (Figure 3).

To prove the enantiomeric purities of the product AHBAs, compounds (2*R*,3*S*)-**1** and (2*R*,3*S*)-**2** were converted first into the *N*-Boc-protected methyl ester derivatives **10** and **12**,[12] and then into the Mosher's esters **11** and **13** (Scheme 3).[4] Analysis of the ^{19}F NMR spectra of the Mosher's esters and comparison with a sample synthesized from racemic α-methoxy-α-(trifluoromethyl)phenyl-

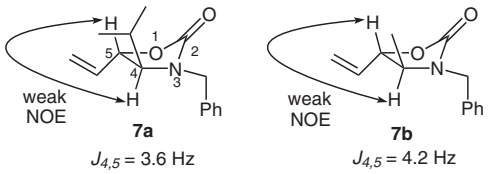
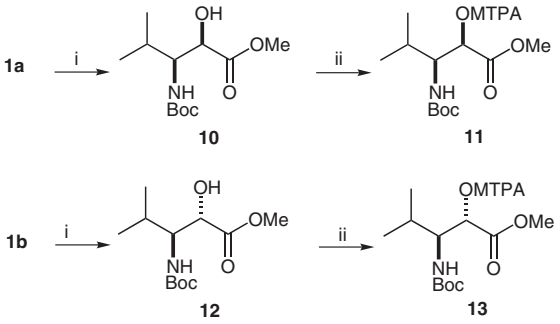


Figure 3 NOESY correlation and coupling constants of oxazolidinones **7a** and **7b**

acetic acid (MTPA) showed that the enantiomeric ratio of the two AHBAs formed in this protocol were >99:1. The absolute configuration was inferred from the known absolute configuration of the starting α-amino acids.



Scheme 3 Preparation of diastereomeric Mosher's esters **11** and **13**. *Reagents and conditions*: (i) (a) HCl, MeOH, r.t., 10 h, 80% yield; (b) Boc_2O, Na_2CO_3, MeOH, r.t., 24 h, 85% yield; (ii) (*R*)-(+)-MTPA (Mosher's acid), DCC, MeCN, r.t., 12 h, 87% yield.

In conclusion, we have synthesized two enantiopure ABHAs using a novel cyclization protocol relying upon the use of *N*-benzyl-protected carbamates derived from α-amino acids. Our study has not only brought about considerable new mechanistic understanding of this potentially highly useful system, but also extended the range of viable substrates to include branched and unbranched aliphatic side chains. We aim to apply these ideas to further development of this protocol by the synthesis of natural products, and by investigating its use in more complex systems.

All non-aqueous reactions were carried out under an inert N_2 atmosphere. Et_3N, DMSO, and CH_2Cl_2 were distilled from CaH_2. All reactions were monitored by TLC on commercially available glass-backed plates. Column chromatography was carried out on 230–400 mesh silica gel. During the workup of reaction mixtures, the final soln before evaporation was washed with brine and dried over anhyd Na_2SO_4. IR spectra were recorded on a Bruker IFS 66 spectrometer. ^1H and ^{13}C NMR spectra were measured relative to TMS in $CDCl_3$, MeOD, and D_2O unless otherwise noted, and recorded on an Avance-300 or a Bruker DRX-500 spectrometer; the 2D NMR experiments were conducted on a Bruker DRX-500 spectrometer. EI-HRMS was carried out on a JEOLJMS-700 mass spectrometer. Elemental analyses were performed on a Leco CHNS-932 instrument. Optical rotations were measured on a Perkin–Elmer polarimeter 343.

***tert*-Butyl (*S*)-Benzyl[1-(hydroxymethyl)-2-methylpropyl]carbamate (4a)**

Compound **4a** was prepared as described in a literature procedure.[4]

$[\alpha]_D^{20}$ –23.1 (*c* 1.0, $CHCl_3$).

IR (KBr): 3450, 3125, 1732 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (m, 6 H), 1.42 (s, 9 H), 1.82 (m, 1 H), 3.53 (s, 1 H), 3.60 (m, 2 H), 4.08 (d, *J* = 9.2 Hz, 1 H), 4.83 (d, *J* = 9.2 Hz, 1 H), 7.26–7.49 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 19.5, 28.4, 29.2, 58.0, 63.7, 72.6, 79.4, 128.1, 128.8, 135.3, 156.8.

Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 68.57; H, 9.26; N, 4.79.

***tert*-Butyl (*S*)-Benzyl(2-hydroxy-1-methylethyl)carbamate (4b)**

Compound **4b** was obtained by the same procedure as that used for compound **4a**.

Oil; $[\alpha]_D^{20}$ +5.6 (*c* 2.0, $CHCl_3$).

IR (KBr): 3356, 2978, 1720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.9 Hz, 3 H), 1.45 (m, 9 H), 3.50 (m, 2 H), 4.00 (d, *J* = 5.7 Hz, 1 H), 4.41 (m, 2 H), 7.23–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 28.4, 48.8, 54.9, 65.6, 80.4, 127.1, 128.5, 139.5, 156.7.

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.91; H, 8.72; N, 5.26.

Ethyl (2*E*,4*S*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]-5-methylhex-2-enoate (5a)

A soln of NaH (0.7 g, 16.5 mmol) in THF (20 mL) was added to $(EtO)_2P(O)CH_2CO_2Et$ (3.3 mL, 16.5 mmol) at 0 °C. The mixture was vigorously stirred until clear and then the corresponding aldehyde **4a** (prepared as described in the literature[4]) (2.4 g, 8.2 mmol) was slowly added at –40 °C. After 30 min, the resulting mixture was warmed to r.t. over 2 h. The mixture was quenched with sat. aq $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed (silica gel, hexane–EtOAc, 6:1); this gave compound **5a** as a solid.

Yield: 2.4 g (81%); mp 72.6–73.4 °C; $[\alpha]_D^{20}$ –15.2 (*c* 0.7, $CHCl_3$).

IR (KBr): 3162, 2978, 1750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.74–0.87 (m, 6 H), 1.28 (m, 2 H), 1.45 (m, 9 H), 2.04 (m, 1 H), 4.19 (m, 2 H), 4.27 (d, *J* = 15.2 Hz, 1 H), 4.47 (d, *J* = 15.1 Hz, 1 H), 5.78 (d, *J* = 15.7 Hz, 1 H), 6.85 (dd, *J* = 6.0, 15.8 Hz, 1 H), 7.20–7.32 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.3, 22.4, 24.6, 28.4, 40.9, 60.4, 77.2, 80.3, 121.8, 127.0, 128.3, 147.4, 155.7, 166.2.

Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 69.76; H, 8.65; N, 3.85.

Ethyl (2*E*,4*S*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]pent-2-enoate (5b)

Compound **5b** was obtained by the same procedure as that used for compound **5a**.

Oil; $[\alpha]_D^{20}$ –8.4 (*c* 1.0, $CHCl_3$).

IR (KBr): 3145, 2955, 1720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.43 (m, 6 H), 1.43 (m, 9 H), 4.19 (m, 3 H), 4.50 (d, *J* = 9.2 Hz, 1 H), 5.79 (d, *J* = 15.7 Hz, 1 H), 6.90 (dd, *J* = 3.8, 15.8 Hz, 1 H), 7.21–7.33 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.5, 28.3, 60.4, 77.5, 80.4, 120.9, 126.9, 128.4, 148.7, 155.5, 166.2.

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.42; H, 8.15; N, 4.21.

***tert*-Butyl Benzyl[(1*S*,2*E*)-4-hydroxy-1-isopropylbut-2-enyl]carbamate (6a)**

To a soln of allylic ester **5a** (2.0 g, 5.5 mmol) in CH_2Cl_2 (27 mL) was added DIBAL-H (16.6 mmol, 3 equiv) at –78 °C and then the mixture was stirred for 10 min at the same temperature. The mixture was quenched with 10% NaOH (5 mL) and filtered. The filtrate was evaporated and chromatographed (silica gel, hexane–EtOAc, 2:1).

Yield: 1.5 g (85%); oil; $[\alpha]_D^{20}$ –14.2 (*c* 1.0, $CHCl_3$).

IR (KBr): 3458, 2970, 1440 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 6 H), 1.41 (s, 9 H), 2.01 (m, 1 H), 3.94 (m, 2 H), 4.02 (m, 1 H), 4.25 (d, *J* = 15.5 Hz, 1 H), 4.49 (d, *J* = 15.4 Hz, 1 H), 5.60 (m, 2 H), 7.17–7.35 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 20.4, 28.9, 30.1, 49.0, 62.9, 77.2, 79.8, 126.7, 128.1, 130.0, 139.7, 155.8.

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.42; H, 9.16; N, 4.36.

***tert*-Butyl Benzyl[(1*S*,2*E*)-4-hydroxy-1-methylbut-2-enyl]carbamate (6b)**

Compound **6b** was obtained by same procedure as that used for compound **6a**.

Oil; $[\alpha]_D^{20}$ –36.0 (*c* 2.0, $CHCl_3$).

IR (KBr): 3480, 2958, 1418 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 15.0 Hz, 3 H), 1.49 (s, 9 H), 2.28 (s, 1 H), 4.04 (m, 2 H), 4.33 (m, 2 H), 5.69 (m, 2 H), 7.20–7.31 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 28.4, 47.2, 62.9, 79.9, 126.6, 128.2, 132.2, 140.1, 155.8.

Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.05; H, 8.64; N, 4.80.

(4*S*,5*S*)-3-Benzyl-4-isopropyl-5-vinyloxazolidin-2-one (7a)

To a soln of allyl alcohol **6a** (0.6 g, 2.5 mmol) in CH_2Cl_2 (13 mL) was added pyridine (0.61 mL, 7.5 mmol) and then diluted Tf_2O (0.8 mL, 5.0 mmol) in CH_2Cl_2 at –78 °C. After being stirred for 0.5 h at –78 °C, the reaction mixture was quenched with sat. aq $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed (silica gel, hexane–EtOAc, 3:1).

Yield: 0.5 g (85%); oil; $[\alpha]_D^{20}$ –28.3 (*c* 0.8, $CHCl_3$).

IR (KBr): 3145, 1724, 1455 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89–0.98 (m, 6 H), 2.06 (m, 1 H), 3.20 (t, *J* = 4.3 Hz, 1 H), 3.99 (d, *J* = 15.2 Hz, 1 H), 4.63 (d, *J* = 4.8 Hz, 1 H), 4.90 (d, *J* = 15.2 Hz, 1 H), 5.23 (d, *J* = 10.9 Hz, 1 H), 5.71 (m, 1 H), 7.25–7.37 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 17.5, 27.6, 45.9, 63.8, 74.4, 117.6, 127.9, 127.9, 128.8, 159.1.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.80; N, 5.72.

(4*S*,5*S*)-3-Benzyl-4-methyl-5-vinyloxazolidin-2-one (7b)

Compound **7b** was obtained by the same procedure as that used for compound **7a**.

Oil; $[\alpha]_D^{20}$ –0.6 (*c* 2.0, $CHCl_3$).

IR (KBr): 3165, 1735, 1447 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 13.2 Hz, 3 H), 3.74 (m, 1 H), 4.05 (d, *J* = 15.2 Hz, 1 H), 4.80 (d, *J* = 15.2 Hz, 1 H), 4.91 (m, 1 H), 5.43 (m, 1 H), 5.82 (m, 2 H), 7.28–7.38 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 45.7, 53.2, 78.1, 120.0, 127.9, 128.8, 131.2, 133.6, 136.0, 157.7.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.85; H, 6.96; N, 6.43.

(4*S*,5*R*)-3-Benzyl-4-isopropyl-2-oxooxazolidine-5-carboxylic Acid (8a)

To a stirred soln of **7a** (0.4 g, 1.6 mmol) and NMO (0.4 g, 3.3 mmol) in acetone–H_2O (10:1, 11 mL) at r.t. was added aq OsO_4 (cat.). The mixture was stirred at r.t. overnight and quenched with aq 10% Na_2SO_3, and extracted with $CHCl_3$ (3 × 5 mL). The organic phase was dried and concentrated under reduced pressure to give the corresponding diol, which was used in the next step without further purification. To a soln of the diol (1.4 mmol) in EtOH–H_2O (2:1, 6 mL) was added $NaIO_4$ (0.6 g, 2.9 mmol) at r.t. After stirring for 2 h, the reaction mixture was evaporated and filtered with EtOAc. The residue was oxidized with $KMnO_4$ (0.4 g, 2.8 mmol) and K_2CO_3 (0.4 g, 2.8 mmol) in THF–H_2O (2:1, 6 mL). After 30 min, the reaction was quenched by the addition of 5% citric acid (6 mL), and then extracted with EtOAc (4 × 10 mL). The organic layer was concentrated and the residue was chromatographed (silica gel, CH_2Cl_2–MeOH, 5:1).

Yield: 0.28 g (74%); oil; $[\alpha]_D^{20}$ –46.0 (*c* 1.0, MeOH).

IR (KBr): 3155, 2910, 1714, 1595 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (dd, *J* = 6.9, 16.9 Hz, 6 H), 2.09 (m, 1 H), 3.61 (t, *J* = 3.4 Hz, 1 H), 4.07 (d, *J* = 15.4 Hz, 1 H), 4.62 (d, *J* = 3.6 Hz, 1 H), 4.88 (d, *J* = 15.2 Hz, 1 H), 7.14–7.38 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 17.4, 27.9, 46.2, 62.7, 70.9, 127.8, 128.1, 128.9, 135.0, 157.4, 172.5.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.85; H, 6.50; N, 5.34.

(4*S*,5*R*)-3-Benzyl-4-methyl-2-oxooxazolidine-5-carboxylic Acid (8b)

Compound **8b** was obtained by the same procedure used for **8a**.

Oil; $[\alpha]_D^{20}$ –2.5 (*c* 2.0, $CHCl_3$).

IR (KBr): 3122, 2940, 1721 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 3.7 Hz, 3 H), 3.78 (t, *J* = 7.4 Hz, 1 H), 4.17 (d, *J* = 9.2 Hz, 1 H), 4.50 (d, *J* = 3.7 Hz, 1 H), 4.75 (d, *J* = 9.2 Hz, 1 H), 7.26–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 46.4, 54.7, 128.4, 128.5, 129.3, 135.5, 157.4, 171.7.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.25; H, 5.58; N, 5.94.

(2*R*,3*S*)-3-(Benzylamino)-2-hydroxy-4-methylpentanoic Acid (9a)

To a soln of **8a** (0.5 g, 1.9 mmol) in EtOH (2 mL) was added 4 M KOH (4 mL), and the mixture was stirred for 4 h at 60 °C. The mixture was washed with Et_2O (20 mL) and the aqueous layer was acidified (pH 2) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed (silica gel, CH_2Cl_2–acetone, 1:1).

Yield: 0.38 g (85%); solid; mp 214–216 °C; $[\alpha]_D^{20}$ –2.6 (*c* 1.0, MeOH).

IR (KBr): 3432, 3010, 1724, 1595 cm^{-1}.

^{1}H NMR (500 MHz, MeOD): δ = 0.92 (dd, *J* = 6.9, 16.9 Hz, 6 H), 2.09 (m, 1 H), 3.61 (t, *J* = 3.4 Hz, 1 H), 4.07 (d, *J* = 15.4 Hz, 1 H), 4.62 (d, *J* = 3.6 Hz, 1 H), 4.88 (d, *J* = 15.2 Hz, 1 H), 7.14–7.38 (m, 5 H).

^{13}C NMR (125 MHz, MeOD): δ = 14.6, 17.4, 27.9, 46.2, 62.7, 70.9, 127.8, 128.1, 128.9, 135.0, 157.4, 172.5.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.82; H, 8.05; N, 5.91.

(2*R*,3*S*)-3-(Benzylamino)-2-hydroxybutanoic Acid (9b)

Compound **9b** was obtained by the same procedure used for **9a**.

Solid; mp 250–252 °C; $[\alpha]_D^{20}$ +3.3 (*c* 0.5, MeOH).

IR (KBr): 3458, 3102, 1765 cm^{-1}.

^{1}H NMR (300 MHz, MeOD): δ = 1.34 (m, 3 H), 3.59 (m, 1 H), 4.22–4.30 (m, 3 H), 7.45–7.91 (m, 5 H).

^{13}C NMR (75 MHz, MeOD): δ = 13.8, 45.7, 63.6, 78.7, 127.9, 128.0, 128.8, 136.1, 171.7.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.12; H, 7.21; N, 6.71.

(2*R*,3*S*)-3-Amino-2-hydroxy-4-methylpentanoic Acid (1)

Compound **9a** (18 mg, 0.08 mmol) was hydrogenated with 20% $Pd(OH)_2$/C in MeOH (3 mL) at r.t. for 12 h. The reaction mixture was filtered and evaporated. The residue was dissolved in MeOH (3 mL) and mixed with Dowex 50W-X8 (0.5 g). The mixture was filtered and then washed with MeOH. The remaining residue was diluted with 3 N NH_4OH soln (5 mL). The soln was evaporated and then co-evaporated with toluene; this gave **1** as a solid.

Yield: 10 mg (90%); mp 208–209 °C; $[\alpha]_D^{20}$ –11.5 (*c* 0.5, MeOH).

IR (KBr): 3434, 2955, 1620 cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 0.97 (m, 6 H), 1.77 (m, 1 H), 3.45 (t, *J* = 6.5 Hz, 1 H), 4.07 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (75 MHz, D_2O): δ = 15.5, 17.8, 28.4, 49.8, 71.3, 174.6.

HRMS (EI): *m/z* calcd for $C_6H_{13}NO_3$: 147.0895; found: 147.0892.

(2*R*,3*S*)-3-Amino-2-hydroxybutanoic Acid (2)

Compound **2** was obtained as a solid by the same procedure used for **1**.

Mp 218–219 °C; $[\alpha]_D^{20}$ +21.4 (*c* 1.0, H_2O).

IR (KBr): 3410, 2930, 1640 cm^{-1}.

^{1}H NMR (500 MHz, D_2O): δ = 1.12 (d, *J* = 6.8 Hz, 3 H), 3.44–3.47 (m, 1 H), 4.08 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (125 MHz, D_2O): δ = 15.0, 49.8, 71.3, 174.6.

Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.33; H, 7.60; N, 11.75.

(*R*)-(+)-Methyl 3-[(*tert*-Butoxycarbonyl)amino]-4-methyl-2-[(3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy]pentanoate (11)

The preparation of **11** is described as a representative example. DCC (47 mg, 0.23 mmol) was added to a soln of (*R*)-(+)-MTPA in MeCN (1.0 mL); this immediately resulted in the formation of a white precipitate of *N*,*N*-dicyclohexylurea. After this mixture had stirred at r.t. for 30 min, the resulting soln of the MTPA anhydride was filtered through a pipette capped with cotton wool, and added to (*R*)-**10** (30 mg, 0.12 mmol). The resulting clear colorless soln was stirred at r.t. for 20 h and then quenched with sat. aq $NaHCO_3$ (5 mL). The reaction mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed (silica gel, hexane–EtOAc, 4:1); this gave compound **11** as an oil, and care was taken to avoid mechanical separation of the diastereomers.

Yield: 47 mg (85%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (m, 6 H), 1.43 (s, 10 H), 3.55 (s, 3 H), 3.69 (s, 3 H), 3.94 (m, 1 H), 4.52 (d, *J* = 10.3 Hz, 1 H), 5.34 (s, 1 H), 7.45 (m, 3 H), 7.70 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7, 19.8, 28.6, 30.4, 53.0, 56.1, 74.2, 80.1, 127.9, 128.8, 130.2, 132.4, 155.7, 166.4, 168.6.

^{19}F NMR (473 MHz, $CDCl_3$): δ = –72.08 (s, >99%, CF_3), –72.48 (s, <1%, CF_3).

Acknowledgment

This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the Regional Animal Industry Research Center at Jinju National University, Jinju, Korea. We are also grateful for the financial support of the Brain Korea 21 Program.

References

(1) (a) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (b) Tietze, L. F.; Burkhardt, O. *Synthesis* **1994**, 1331. (c) Tamura, O.; Yoshida, S.; Sugita, H.; Mita, N.; Uyama, Y.; Morita, N.; Ishiguro, M.; Kawasaki, T.; Ishibashi, H.; Sakamoto, M. *Synlett* **2000**, 1553. (d) Boto, A.; Hernandez, R.; Leon, Y.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 7796. (e) Boto, A.; Hernandez, R.; Leon, Y.; Murguia, J. R.; Rodriguez-Afonso, A. *Tetrahedron Lett.* **2004**, *45*, 6841. (f) Davies, S. B.; Mckervey, M. A. *Tetrahedron Lett.* **1999**, *40*, 1229.

(2) (a) Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10452. (b) Davies, S. G.; Epstein, S. W.; Ichihara, O.; Smith, A. D. *Synlett* **2001**, 1599.

(3) (a) Lee, B. W.; Lee, J. H.; Jang, K. C.; Kang, J. E.; Kim, J. H.; Park, K. M.; Park, K. H. *Tetrahedron Lett.* **2003**, *44*, 5905. (b) Back, T. G.; Parvez, M.; Zhai, H. *J. Org. Chem.* **2003**, *68*, 9389. (c) Minassian, F.; Pelloux-Leon, N.; Valee, Y. *Synlett* **2000**, 242.

(4) (a) Seo, W. D.; Curtis-Long, J. M.; Ryu, Y. B.; Lee, J. H.; Yang, M. S.; Lee, W. S.; Park, K. H. *J. Org. Chem.* **2006**, *71*, 5008. (b) Lei, A.; Lui, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974.

(5) (a) Kobayashi, S.; Kamiyama, K.; Ohno, M. *J. Org. Chem.* **1990**, *55*, 1169. (b) Kamiyama, K.; Kobayashi, S.; Ohno, M. *Chem. Lett.* **1987**, *1*, 29.

(6) For the enantioselective synthesis of β-amino acids, see: (a) Juaristi, E. *Enantioselective Synthesis of β-Amino Acids*; Wiley-VCH: New York, **1997**. (b) Bewley, C. A.; Faulkner, D. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2162. (c) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707. (d) Boger, J.; Lohr, N. S.; Ulm, E. H.; Poe, M.; Blaine, E. H.; Fanelli, G. M.; Lin, T. Y.; Payne, L. S.; Schorn, T. W.; Lamont, B. I.; Vassil, T. C.; Stabilito, I. I.; Veber, D. F.; Rich, D. H.; Bopari, A. S. *Nature* **1983**, *303*, 81. For the use of amino hydroxylation of α,β-unsaturated esters, see: (e) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544.

(7) (a) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181. (b) Cardillo, G.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1995**, *51*, 11831.

(8) (a) Seo, W. D.; Curtis-Long, M. J.; Kim, J. H.; Park, J. K.; Park, K. M.; Park, K. H. *Synlett* **2005**, 2289. (b) Jung, D. Y.; Kang, S.; Chang, S. B.; Kim, Y. H. *Synlett* **2006**, 86. (c) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301.

(9) (a) Bach, T.; Jodicke, K.; Kather, K.; Frohlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 2437. (b) Fernandez-Zertuche, M.; Robledo-Perez, R.; Meza-Avina, M. E.; Ordonez-Palacios, M. *Tetrahedron Lett.* **2002**, *43*, 3777. (c) Kauppinen, P. M.; Koskinen, M. P. *Tetrahedron Lett.* **1997**, *38*, 3103.

(10) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *32*, 1124.

(11) Lee, J. H.; Yang, M. S.; Kang, K. Y.; Moon, Y. H.; Park, K. H. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 714.

(12) Mohan, R.; Chou, Y. L.; Bihovsky, R.; Lumma, W. C.; Erhardt, P. W. Jr.; Shaw, K. J. *J. Med. Chem.* **1991**, *34*, 2402.