JOC*Note*

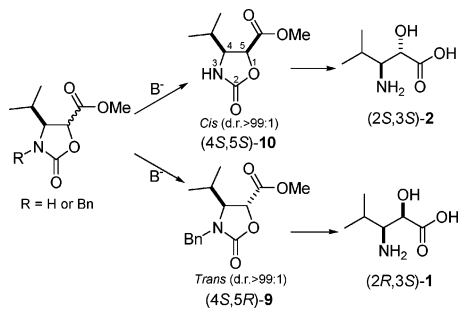
Highly Diastereoselective Epimerization: Stereodivergent Synthesis of α-Hydroxy-*β*-amino Isopentanoic Acid

Woo Duck Seo, Marcus J. Curtis-Long,† Young Bae Ryu, Jin Hwan Lee, Min Suk Yang, Woo Song Lee,‡ and Ki Hun Park*

Division of Applied Life Science (BK 21 Program), Department of Agricultural Chemistry, Research Institute of Life Science, Gyeongsang National University, 660-701, Korea, Trout Beck, Wansford, Driffield, East Yorkshire, YO25 8NX, United Kingdom, and Korea Research Institute of Bioscience and Biotechnology, Daejeon 305-333, Korea

khpark@gshp.gsnu.ac.kr

Received February 15, 2006



The high diastereoselectivity of the base-catalyzed epimerization of oxazolidin-2-ones **7** and **8** is shown to depend on the nature of the *N*-substituent (R group); when R = Bn, the 4,5-*trans*-product (4*S*,5*R*)-**9** is formed, whereas when R = H the 4,5-*cis*-product (4*S*,5*S*)-**10** is formed, both with >99:1 dr. The successful hydrolysis of the oxazolidin-2-one group in both *cis*- and *trans*-derivatives show this to be a stereodivergent route to enantiopure α-hydroxy-*β*-amino isopentanoic acids (2*R*,3*S*)-**1** and (2*S*,3*S*)-**2**.

Over the recent years, there has been an increased interest in synthetic routes to optically pure α-hydroxy-*β*-amino acids, not only because of their wide-ranging chemical utility,[1] but also because this functionality is a key component in a number of biologically active natural products.[2] Although α-hydroxy-*β*-amino acids have been implicated in the development of both supermolecular drugs[3] and conformationally stable oligo-[4] and dipeptide species,[5] the scope for the development of this important functional group is still very broad. Accordingly, a number of methods have been reported for the stereoselective syntheses of α-hydroxy-*β*-amino acid derivatives using different strategies,[6] including epoxidation,[7] amino hydroxylation,[8] derivatization of amino aldehydes,[9] nitro aldol reaction,[10] nucleophilic addition to chiral aldehydes,[11] and amides.[12] In the previous report,[13] we described that chiral oxazolidin-2-ones possessing a vinyl group on the 5 position can be generated by the internal cyclization of a chiral carbamate onto an allylic cation. This synthetic route is appealing, not only because it represents an ideal basis for an asymmetric synthetic sequence, but also because we were able to show that the products were easily transformed into α-hydroxy-*β*-amino acid derivatives. Although the diastereoselectivity of the reaction was moderated, it was realized that the cyclic nature of the oxazolidin-2-one cyclization products coupled with the acidity of the ester α-protons could enable us both to improve this selectivity and to access the epimeric product. In this article we focus on the development of a stereodivergent base-promoted strategy to access both *cis*- and *trans*-carbomethoxy oxazolidin-2-one intermediates (**7** and **8**). Because in the original communication of our cyclization reaction we only used secondary carbamates, which afforded secondary oxazolidin-2-ones, we began by synthesizing the *N*-benzylated tertiary oxazolidin-2-one analogue, which allowed us to conduct the initial epimerization studies on the monoanion. Synthesis began with L-valinal **3**, which was easily prepared form L-valine.[14,15] The addition of

* Corresponding author. Tel.: +82-55-751-5472. Fax: +82-55-757-0178.
† Trout Beck.
‡ Korea Research Institute of Bioscience and Biotechnology.

(1) (a) Kotake, T.; Rajesh, S.; Yoshio, H.; Mukai, Y.; Ueda, M.; Kimura, T.; Kiso, Y. *Tetrahedron Lett.* **2004**, *45*, 3651−3654. (b) Guenard, D.; Gueritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160−167. (c) Zhao, Y.; Jiang, N.; Chen, S.; Peng, C.; Zhung, X.; Zou, Y.; Zhang, S.; Wang, J. *Tetrahedron* **2005**, *61*, 6546−6552. (d) Harada, T.; Inui, C. *J. Org. Chem.* **2006**, *71*, 1277−1279.

(2) (a) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707−2714. (b) 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*, 81−84. (c) Rich, D. H.; Moon, B. J.; Boparai, A. S. *J. Org. Chem.* **1980**, *45*, 2288−2290. (d) Nezami, A.; Luque, I.; Kimura, T.; Kiso, Y.; Freire, E. *Biochemistry* **2002**, *41*, 2273−2280.

(3) (a) Righi, G.; Rumboldt, G. *J. Org. Chem.* **1996**, *61*, 3557−3560. (b) Ha, H. J.; Park, G. S.; Ahn, Y. G.; Lee, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1619−1622. (c) Cardillo, G.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1995**, *51*, 11831−11840.

(4) (a) Wee, A. G. H.; McLeod, D. D. *J. Org. Chem.* **2003**, *68*, 6268−6273. (b) Shuto, D.; Kasai, S.; Kimura, T.; Liu, P.; Hidaka, K.; Hamada, T.; Shibakawa, S.; Hayashi, Y.; Hattori, C.; Szabo, B.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4273−4276.

(5) (a) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1990**, *55*, 2232−2234. (b) Gill, D. M.; Pegg, N. A.; Rayner, C. M. *Tetrahedron Lett.* **1995**, *45*, 8237−8330.

(6) For a review, see: (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576. (b) Liu, Mei.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035.

(7) (a) Denis, J. N.; Greene, A. E.; Serra, A. A.; Luche, M. J. *J. Org. Chem.* **1986**, *51*, 46−50. (b) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320−4323.

(8) (a) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637. (b) Donohoe, T. J.; Johnson, P. D.; Pye, R. J. *Org. Biomol. Chem.* **2003**, *1*, 2025−2028.

(9) 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*, 5905−5907.

(10) Kudyba, I.; Raczko, J.; Jurczak, J. *J. Org. Chem.* **2004**, *69*, 2844−2850.

(11) (a) Denis, J. N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939−6942. (b) Manickam, G.; Nogami, H.; Kanai, M.; Groger, H.; Shibasaki, M. *Synlett* **2001**, *5*, 617−620.

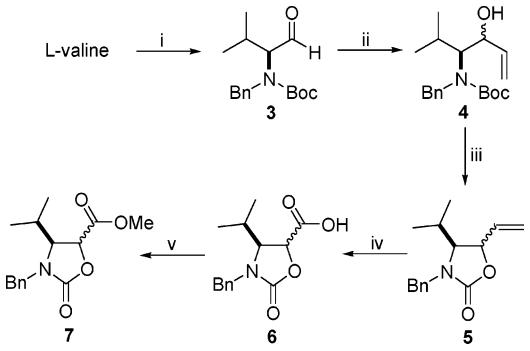
(12) (a) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570−6573. (b) Iwanowicz, E. J.; Lin, J.; Robert, D. G. M.; Michael, I. M.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607−1612.

(13) Seo, W. D.; Curtis-Long, M. J.; Kim, J. H.; Park, J. K.; Park, K. M.; Park, K. H. *Synlett* **2005**, *15*, 2289−2292.

(14) (a) Disadee, W.; Ishikawa, T. *J. Org. Chem.* **2005**, *70*, 9399−9406. (b) Davis, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387−3391.

10.1021/jo060309m CCC: $33.50
Published on Web 05/25/2006

SCHEME 1. Preparation of Carbomethoxy Oxazolidin-2-one[a]



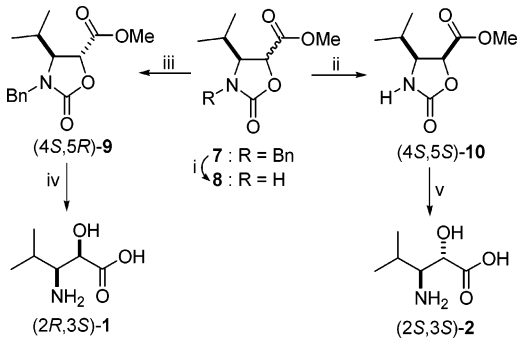
[a] Reagents and conditions: (i) refs 14 and 15; (ii) vinylMgBr, THF, −10 °C, 2 h, 90%; (iii) *t*-BuOK, THF, −78 °C → rt, 12 h, 80%; (iv) (a) OsO_4, NMO, acetone, rt, 24 h, 86%; (b) $NaIO_4$, EtOH/H_2O (2:1), 1 h, 85%; (c) $KMnO_4$, K_2CO_3, THF/H_2O (2:1), rt, 1 h, 70%; (v) CH_3I, K_2CO_3, DMF, 0 °C → rt, 2 h, 85%.

vinylmagnesium bromide to aldehyde **3** afforded a 2:1 trans/cis mixture of allylic alcohol products **4**. Stirring this in the presence of *t*-BuOK at −78 °C over 12 h allowed efficient cyclization to generate the oxazolidin-2-one **5** as a 2:1 mixture of trans/cis distereoisomers. To progress toward the amino acid motif, oxidation of the vinyl group using OsO_4 followed by periodate cleavage of the product diol, in the presence of $KMnO_4$, gave the corresponding carboxylic acid **6**. Treatment with CH_3I gave ester **7** with no epimerization (Scheme 1).

Investigations then began into base-catalyzed epimerization. Treatment of *N*-benzyl **7** with 2 equiv of LHMDS afforded the lithium enolate, which upon treatment with either methanol or TBP [2,4,6-tri-(*tert*)-butylphenol] afforded as a single product the *trans*-diastereoisomer (4*S*,5*R*)-**9** in >99:1 dr. Then a sequence of catalytic *N*-debenzylation followed by base-catalyzed hydrolysis of the oxazolidin-2-one gave the fully deprotected α-hydroxy-*β*-amino acid (2*R*,3*S*)-**1** as a single diastereoisomer in 53% overall yield. Since the *cis*-product was elusive in this manifold, our attention turned to epimerization of the secondary oxazolidinone **8**, which was available as a 2:1 mixture of diastereoisomers by *N*-debenzylation of the cyclization product **7** under Birch reduction conditions.[14] Thus, treatment of **8** with 2 equiv of LHMDS at − 78 °C generated the dianion, and the facial selectivity of protonation with a range of different Bronsted acids was investigated. In contrast to the anion of **7**, treatment of the dianion of **8** with MeOH led to a 1:2 cis/trans mixture of diastereoisomers. However, exposing the dianion to the more sterically demanding proton source, TBP, gave (4*S*,5*S*)-**10** as a >99:1 cis/trans mixture. As before, base-catalyzed hydrolysis of the oxazolidin-2-one **10** gave the fully deprotected α-hydroxy-*β*-amino acid (2*S*,3*S*)-**2** in 57% yield with no epimerization at the α center. The spectroscopic data for **1** and **2** are consistent with those of the diastereomic mixture.[16]

Because it appears that the *N*-alkyl substituent has a significant effect on the protonation selectivity, to gain a deeper understanding of the effect of steric environment on the selectivity of the epimerization, the *N*-methyl analogue was synthesized using a similar strategy to that shown above in 76% overall yield. In general, the lithium anion of this species showed similar reactivity to the dianion of **7**. Thus, its protonation with MeOH led to a small excess of the *trans*-product, while protonation with a bulky proton source gave a 10-fold excess of the *cis*-moiety (Scheme 2).

SCHEME 2. Epimerization of Carbomethoxy Oxazolidin-2-ones[a]



[a] Reagents and conditions: (i) Li, liq NH_3, Et_2O, −70 °C, 5 min, 76%; (ii) LHMDS, TBP, THF, −78 °C, 8 h, 70%; (iii) LHMDS, TBP, THF, −78 °C, 4 h, 85%; (iv) (a) 4 N KOH, EtOH, reflux, 10 h, 78%; (b) 20% $Pd(OH)_2$/C, MeOH, rt, 12 h, 80%; (v) 4 N KOH, EtOH, reflux, 12 h, 82%.

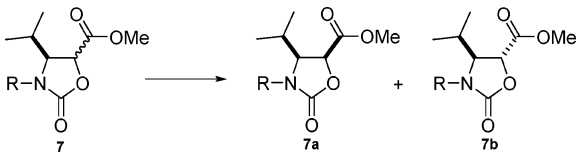
With these results in hand, a plausible rational for the stereoselectivity of the epimerization can be given by considering the steric effects of both the isopropyl group and the *N*-substituent in terms of A(1,3) strain. In the case of **8**, formation of the dianion is expected to lead to considerable A(1,3) strain between the enolate and the 4-isopropyl group. This will force the latter to adopt a pseudoaxial position and, hence, disfavor protonation cis to it. The efficiency of steric shielding has then been shown to be dependent upon the steric presence of the proton source: in the case of sterically undemanding MeOH, 1,2-steric interactions between the acid and the isopropyl group are not sufficient to induce a facial bias, and, thus, the *trans*-product is marginally favored, giving a 3:1 mixture of diastereoisomers; whereas when the bulky acid, TBP, is used, the increase in 1,2-steric interactions between the acid and the isopropyl group results in the formation of the *cis*-derivative, the kinetic product, in 99:1 dr.

In the case of the enolate of *N*-benzyl **7**, A(1,3) strain is also believed to force the isopropyl group to be in a pseudoaxial environment, as before. However, to further minimize steric interactions, the phenyl appendage of the *N*-benzyl group is forced to adopt a position trans to the isopropyl group. In contrast to the dianion of **8**, protonation of the enolate of **7** using either acid (MeOH or TBP) leads to the *trans*-derivative [proven to be the thermodynamic product, as it is the only stereoisomer present after epimerization of the 2:1 trans/cis diastereoisomeric mixture of **8** under equilibrating conditions (treatment with *t*-BuOK/EtOH)]. Thus, as the phenyl group is larger than the isopropyl moiety, it consistently overrides the sterically dependent directing influence of the isopropyl group, leading exclusively to the *trans*-product. Consistent with the phenyl group being the important stereocontrol element, protonation of the enolate of the *N*-methyl derivative showed similar selectivity to that of the dianion of **8**. The outline of the construction of the oxazolidin-2-one is illustrated in Table 1. The stereochemistry of carbomethoxy oxazolidin-2-ones **9** and

(15) (a) Golebiowski, A.; Jacobsson, U.; Raczko, J.; Jurczak, J. *J. Org. Chem.* **1989**, *54*, 3759−3760. (b) Ginesta, X.; Pericas, M. A.; Riera, A. *Synth. Commun.* **2005**, *35*, 289−297.

(16) (a) Mohan, R.; Chou, Y. L.; Bihovsky, R.; Lumma, W. C.; Erhardt, P. W., Jr.; Shaw, K. J. *J. Med. Chem.* **1991**, *34*, 2402−2410. (b) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394−407.

TABLE 1. Preparation of Epimerized Carbomethoxy Oxazolidin-2-one



entry	R	solvent/ H^+ source	base	ratio[b] (**7a**:**7b**)	yield[c] (%)
1	H	THF/CH_3OH	LHMDS	1:3	65
2	H	THF/TBP[a]	LHMDS	99:1	70
3	H	EtOH	*t*-BuOK	1:3	68
4	CH_3	THF/CH_3OH	LHMDS	1:6	75
5	CH_3	THF/TBP[a]	LHMDS	10:1	76
6	Bn	THF/CH_3OH	LHMDS	1:99	80
7	Bn	THF/TBP[a]	LHMDS	1:99	85
8	Bn	EtOH	*t*-BuOK	1:99	82

[a] 2,4,6-Tri-(*tert*)-butylphenol. [b] Determined by ^{1}H NMR integration. [c] Isolated yields.

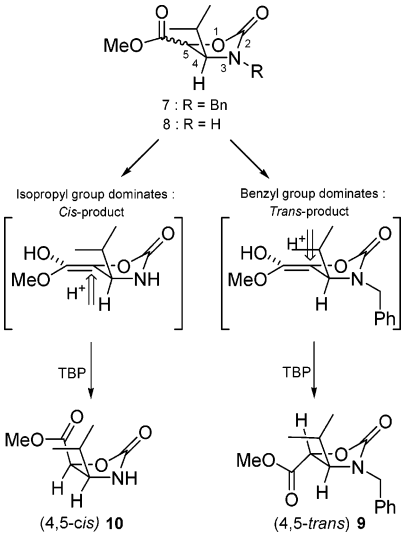


FIGURE 1. Plausible mechanism of stereodivergent transformation of carbomethoxy oxazolidin-2-ones.

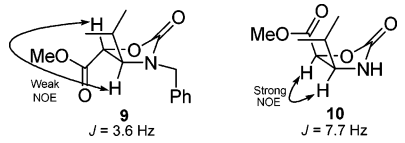
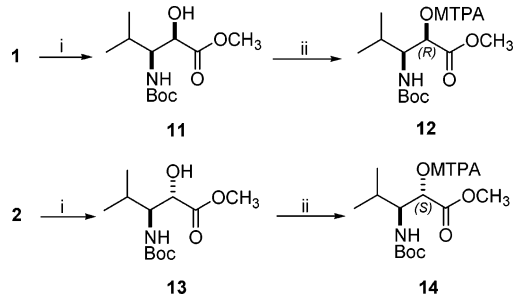


FIGURE 2. NOESY correlations and coupling constants of cis/trans diastereomers.

10 (Figure 1) were determined by NOESY experiments and coupling constants (cis, $J = 7.7$ Hz; trans, $J = 3.6$ Hz; Figure 2). It is known that the *cis*-derivative has a larger coupling constant than the *trans*-derivative in oxazolidin-2-ones.[17]

To demonstrate the enantiomeric purities of **1** and **2**, both compounds were derivatized to N−Boc esters **11** and **13** by a well-established method.[16] Compounds **11** and **13** were subsequently converted to the diastereomerically pure Mosher's esters **12** and **14** (Scheme 3) by treatment with (*R*)-(+)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid [(MTPA) "Mosher's acid"] with DCC in acetonitrile, as previously described.[18] Analysis of **12** and **14** by ^{19}F NMR established the enantiomeric ratio in **1** and **2** to be >99:1 after spectral comparison to the two diastereoisomers formed at each instance upon coupling racemic MTPA with **11** and **13**, respectively.

SCHEME 3. Preparation of Diastereomeric Mosher's Esters[a]



[a] Reagents and conditions: (i) (a) HCl, MeOH, rt, 10 h, 80%; (b) Boc_2O, Na_2CO_3, MeOH, rt, 24 h, 85%; (ii) *R*-(+)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid, DCC, CH_3CN, rt, 12 h, 87%.

In conclusion, we have shown that the stereochemical outcome of the base-catalyzed epimerization of ester-substituted oxazolidinones can be effectively controlled using selective protonation agents. We have proved the viability of this methodology toward the synthesis of enantio- (>99:1, er) and diastereopure (>99:1, dr) α-hydroxy-*β*-amino isopentanoic acids.

Experimental Section

***tert*-Butyl Benzyl(4-hydroxy-2-methylhex-5-en-3-yl)carbamate (4).** To a solution of aldehyde **3** (4.0 g, 13.7 mmol) in THF (120 mL) was added 1.0 M vinylmagnesium bromide (41.1 mL, 41.1 mmol) at −10 °C. After being stirred for 40 min at room temperature, the reaction mixture was quenched with satd aqueous NH_4Cl and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 3/1) to give compound **4** (3.95 g, 90%) as an oil. IR (KBr): 3420, 2754, 1728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (1H, m), 1.43 (9H, m), 2.53 (1H, m), 3.98 (1H, d, $J = 15.3$ Hz), 4.36 (1H, m), 4.87 (2H, m), 5.73 (1H, m), 7.27∼7.34 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 26.9, 28.4, 54.3, 72.3, 80.6, 114.2, 127.4, 127.9, 128.2, 129.2, 138.4, 157.0. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.59; H, 9.35; N, 4.49.

3-Benzyl-4-isopropyl-5-vinyl Oxazolidin-2-one (5). To a solution of allyl alcohol **4** (3.9 g, 12.2 mmol) in THF (40 mL) was added a solution of *t*-BuOK (2.7 g, 24.4 mmol) in THF at −78 °C. After being stirred for 10 h at room temperature, the reaction mixture was quenched with satd aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 4/1) to give compound **5** (2.4 g, 80%) as an oil. IR (KBr): 3145, 1724, 1655 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89∼0.98 (6H, m), 2.06 (1H, m), 3.20 (1H, t, $J = 4.3$ Hz), 3.99 (1H, d, $J = 15.2$ Hz), 4.63 (1H, d, $J = 4.8$), 4.90 (1H, d, $J = 15.2$ Hz), 5.23 (1H, d, $J = 10.9$ Hz), 5.71 (1H, m), 7.25∼7.37 (1H, m).

(17) (a) Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893−3914. (b) Kobayashi, S.; Isobu, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079−5082.

(18) Mazaleyrat, J. P.; Goubard, Y.; Azzini, M. V.; Wakselman, M.; Peggion, C.; Formaggio, F.; Toniolo, C. *Eur. J. Org. Chem.* **2002**, 1232−1247.

^{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. HRMS calcd for $C_{15}H_{19}NO_2$, 245.1416; found, 245.1415.

Methyl 3-Benzyl-4-isopropyl-2-oxooxazolidine-5-carboxylate (7). To a solution of acid **6** (1.4 g, 5.3 mmol) in DMF (26 mL) was added K_2CO_3 (1.5 g, 10.6 mmol) and CH_3I (0.7 mL, 10.6 mmol) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was added to a mixture of EtOAc (10 mL) and 1 N HCl (5 mL). The reaction mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/ EtOAc = 2/1) to give compound **7** (1.25 g, 85%) as an oil. IR (KBr): 3252, 2954, 1755, 1586 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74∼0.91 (6H, m), 2.06 (1H, m), 3.50 (1H, t, J = 3.6 Hz), 4.05 (1H, d, J = 15.3 Hz), 4.60 (1H, d, J = 3.1 Hz), 4.91 (1H, d, J = 15.3 Hz), 7.25∼7.63 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 17.5, 28.0, 46.2, 52.9, 62.3, 71.1, 127.9, 128.1, 128.9, 135.3, 157.0, 170.0. HRMS calcd for $C_{15}H_{19}NO_4$, 277.1314; found, 277.1315.

Methyl 4-Isopropyl-2-oxooxazolidine-5-carboxylate (8). To a solution of compound **7** (0.8 g, 2.88 mmol) in Et_2O (3 mL) was slowly added a solution of Li (80 mg, 11.5 mmol) in liquid ammonia (8 mL) at −70 °C under argon. After being stirred for 5 min at the same temperature, it was quickly quenched with water (10 mL). The reaction mixture was extracted with EtOAc (3 × 8 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/ EtOAc = 1/1) to give compound **8** (0.41, 76%) as an oil. IR (KBr): 2954, 2504, 1755 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89∼0.94 (6H, m), 2.08 (1H, m), 3.49 (1H, t, J = 3.5 Hz), 3.76 (3H, s), 4.07 (1H, d, J = 15.3 Hz), 4.60 (1H, d, J = 3.6 Hz), 4.98 (1H, d, J = 15.2 Hz), 7.25∼7.45 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 17.5, 28.0, 46.2, 52.8, 62.3, 71.1, 127.9, 128.1, 128.8, 135.9, 157.0, 170.0. HRMS calcd for $C_8H_{13}NO_4$, 187.0845; found, 187.0792.

(4*S*,5*R*)-Methyl-3-benzyl-4-isopropyl-2-oxooxazolidine-5-carboxylate (9). To a solution of compound **7** (60 mg, 0.22 mmol) in THF (2 mL) was added slowly dropwise 1.0 M LHMDS (0.4 mL, 0.44 mmol) at −78 °C. After being stirred for 30 min, TBP (0.22 g, 0.88 mmol) in THF (0.4 mL) was added slowly dropwise to the reaction mixture over 5 min at −78 °C. The reaction mixture was maintained at −78 °C for 4 h and then quenched with satd aqueous $NaHCO_3$ (2 mL). The reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 2:1) to give compound **9** (51 mg, 85%) as an oil. $[\alpha]^{20}_D$ −37.5 (*c* 0.5, $CHCl_3$). IR (KBr): 3252, 2954, 1755 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89∼0.94 (6H, m), 2.08 (1H, m), 3.49 (1H, t, J = 3.5 Hz), 3.76 (3H, s), 4.07 (1H, d, J = 15.3 Hz), 4.60 (1H, d, J = 3.6 Hz), 4.98 (1H, d, J = 15.2 Hz), 7.25∼7.45 (5H, m). ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.7, 17.5, 28.0, 46.2, 52.8, 62.3, 71.1, 127.9, 128.1, 128.8, 135.9, 157.0, 170.0. HRMS calcd for $C_{15}H_{19}NO_4$, 277.1314; found, 277.1315.

Representative Example of the Preparation of Mosher's Ester. Preparation of (*R*)-(+)-α-Methoxy-α-trifluoromethyl-α-phenylacetic Acid Ester (12). DCC (78 mg, 0.38 mmol) was added to a solution of (*R*)-(+)-MTPA in acetonitrile (1.5 mL), which immediately resulted in the formation of a white precipitate of *N*,*N*-dicyclohexylurea. After this had stirred at room temperature for 15 min, the resulting solution of the MTPA anhydride was filtered through a pipet capped with cotton wool and added to samples of (*R*)-**12** (50 mg, 0.19 mmol). The resulting clear colorless solutions were stirred at room temperature for 20 h and then quenched with satd aqueous $NaHCO_3$ (3 mL). The reaction mixture was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 4:1) to give compound **12** (79 mg, 87%) as an oil, with care being taken not to exercise a mechanical separation of one of the diastereoisomers over the other. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (m, 6H), 1.43 (s, 10 H), 3.55 (s, 3H), 3.69 (s, 3H), 3.94 (m, 1H), 4.52 (d, 1H, J = 10.3 Hz), 5.34 (s, 1H), 7.45 (m, 3H), 7.70 (m, 2H). ^{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, $CDCl_3$): −72.08 {s (>99%), CF_3}, −72.48 {s (<1%), CF_3}.

(2*S*,3*S*)-3-Amino-2-hydroxy-isopentanoic Acid (2). To a solution of **10** (80 mg, 0.10 mmol) in 95% EtOH (1.5 mL) was added 4 N KOH (1.5 mL). The reaction mixture was refluxed for 12 h, cooled to room temperature, and then quenched with 10% HCl (3 mL), filtered, and evaporated. The residue was dissolved in MeOH (3 mL) without further purification and mixed with Dowex 50W-X8 (1 g). The mixture was filtered and then washed with MeOH. The remaining residue was diluted with 3 N NH_4OH solution. The solution was evaporated and then coevaporated with toluene to give compound **2** (15 mg, 82%) as a solid. Mp 215−216 °C; $[\alpha]^{20}_D$ +19.2 (*c* 0.5, MeOH). IR (KBr): 2986, 1768, 1641 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): δ 0.87 (6H, m), 2.02 (1H, m), 3.82 (1H, t, J = 3.4 Hz), 4.51 (1H, d, J = 3.4 Hz). ^{13}C NMR (75 MHz, D_2O): δ 18.3, 19.6, 29.2, 49.5, 70.4, 174.4. HRMS calcd for $C_6H_{13}NO_3$, 147.0895; found, 147.0892.

(2*R*,3*S*)-3-Amino-2-hydroxy-isopentanoic Acid (1). Compound **9** was hydrolyzed with 4 N KOH in 95% EtOH (1.5 mL) for 10 h, using the same procedure as compound **2**. The residue was hydrogenated with 20% $Pd(OH)_2$/C (10 mg) in MeOH (2 mL) at room temperature for 12 h. The reaction mixture was filtered and evaporated. The residue was dissolved in MeOH (3 mL) and mixed with Dowex 50W-X8 (1 g). The mixture was filtered and then washed with MeOH. The remaining residue was diluted with 3 N NH_4OH solution. The solution was evaporated and then coevaporated with toluene to give compound **1** (18 mg, 62%) as a solid. Mp 208−209 °C; $[\alpha]^{20}_D$ −11.3 (*c* 0.5, MeOH). IR (KBr): 2954, 1755, 1600 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): δ 0.97 (6H, m), 1.77 (1H, m), 3.45 (1H, t, J = 6.5 Hz), 4.07 (1H, d, J = 4.8 Hz). ^{13}C NMR (75 MHz, D_2O): δ 15.5, 17.8, 28.4, 49.8, 71.3, 174.6. HRMS calcd for $C_6H_{13}NO_3$, 147.0895; found, 147.0892.

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.

Supporting Information Available: General procedures, product characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060309M