JOC Article

A Novel Synthesis of 5-Functionalized Oxazolidin-2-ones from Enantiomerically Pure 2-Substituted *N*-[(*R*)-(+)-α-Methylbenzyl]aziridines

Tae Bo Sim, Se Hun Kang, Kun Su Lee, and Won Koo Lee*

Department of Chemistry, Sogang University, Seoul 121-742, Korea

Hoseop Yun and Yongkwan Dong

Department of Molecular Science and Technology, Ajou University, Suwon 442-749, Korea

Hyun-Joon Ha*

Department of Chemistry, Hankuk University of Foreign Studies, Yongin 449-791, Korea

wonkoo@ccs.sogang.ac.kr; hjha@hufs.ac.kr

Received July 12, 2002

5-Funtionalized enantiomerically pure oxazolidin-2-ones were prepared in one pot from commercially available chiral aziridines bearing an electron-withdrawing group at C-2 with retention of the configuration in high yields by regioselective aziridine ring-opening followed by intramolecular cyclization.

The importance of functionalized enantiomerically pure oxazolidin-2-ones has been emphasized in organic synthesis. They have been used as not only multipurpose chiral synthons in asymmetric syntheses of biologically active compounds or their synthetic intermediates,[1] but also chiral auxiliaries in many asymmetric transformations.[2,3] Moreover, some suitably substituted chiral oxazolidinones are also being used as biologically active compounds.[4] Although they have been known for their great variety of applicability, merely a few preparative methods exist for the target compounds from L- and D-serine,[5] *N*-sulfonylated allylic carbamates,[6] amino alcohols,[7] chiral aziridines,[8] and allylic amines.[9] Consequently, the development of a new efficient method for the functionalized chiral oxazolidin-2-ones represents a challenging issue. Especially when the C-5 position is functionalized, chiral oxazolidin-2-ones become significantly useful in organic and medicinal chemistry. For

* To whom correspondence should be addresssed.

(1) (a) Bach, J.; Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Tetrahedron Lett.* **1999**, *40*, 6677. (b) O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1189. (c) Lohray, B. B.; Baskaran, S.; Rao, B. S.; Reddy, B. Y.; Rao, I. N. *Tetrahedron Lett.* **1999**, *40*, 4855. (d) Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Kilburn, J. O.; Klemens, S. P.; Glickman, S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680. (e) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673. (f) Grega, K. C.; Barbachyn, M. R.; Brickner, S. J.; Mizsak, S. A. *J. Org. Chem.* **1995**, *60*, 5255. (g) Seneci, P.; Caspani, M.; Ripamonti, F.; Ciabatti, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2345. (h) Park, C.-H.; Brittelli, D. R.; Wang, C. L.-J.; Marsh, F. D.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1992**, *35*, 1156. (i) Gregory, W. A.; Brittelli, D. R.; Wang, C. L.-J.; Kezar, H. S.; Carlson, R. K.; Park, C.-H.; Corless, P. F.; Miller, S. J.; Rajagopalan, P.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1990**, *33*, 2569. (j) Gregory, W. A.; Brittelli, D. R.; Wang, C. L.-J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.

(2) (a) Friestad,G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329. (b) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith A. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3475. (c) Bravo, P.; Fustero, S.; Guidetti, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1999**, *64*, 8731. (d) Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387. (e) Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337. (f) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Chem. Commun.* **1999**, 317. (g) Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 357. (h) Gibson, C. L.; Gillon, K.; Cook, S. *Tetrahedron Lett.* **1998**, *39*, 6733. (i) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1685. (j) Lützen, A.; Köll, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1193. (k) Lützen, A.; Köll, P. *Tetrahedron: Asymmetry* **1997**, *8*, 29. (l) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3. (m) Köll, P.; Lützen, A. *Tetrahedron: Asymmetry* **1996**, *7*, 637. (n) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

(3) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835 and references therein.

(4) (a) Jandu, K. S.; Barrett V.; Brockwell, M.; Cambridge, D.; Farrant, D. R.; Foster, C.; Giles, H.; Glen, R. C.; Hill, A. P.; Hobbs, H.; Honey, A.; Martin, G. R.; Salmon, J.; Smith, D.; Woollard, P.; Selwood, D. L. *J. Med. Chem.* **2001**, *44*, 681. (b) Iwama, S.; Segawa, M.; Fujii, S.; Ikeda, K,; Katsumura, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3495. (c) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673. (d) Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Kilburn, J. O.; Klemens, S. P.; Glickman S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680.

(5) (a) Sibi, M. P.; Christensen, J. W.; Li, B.; Renhowe, P. A. *J. Org. Chem.* **1992**, *57*, 4329. (b) Sibi, M. P.; Renhowe, P. A. *Tetrahedron Lett.* **1990**, *31*, 7407. (c) Sibi, M. P.; Harris, B. J.; Shay J. J.; Hajra, S. *Tetrahedron* **1998**, *54*, 7221. (d) Sibi, M. P.; Li, B. *Tetrahedron Lett.* **1992**, *33*, 4115.

(6) Hirama, M.; Iwashita, M.; Yamazaki, Y.; Itô, S. *Tetrahedron Lett.* **1984**, *25*, 4963.

(7) Gabriele, B.; Salerno, G.; Brindisi, D.; Costa, M.; Chiusoli, G. P. *Org. Lett.* **2000**, *2*, 625

(8) Lucarini, S.; Tomasini, C. *J. Org. Chem.* **2001**, *66*, 727.

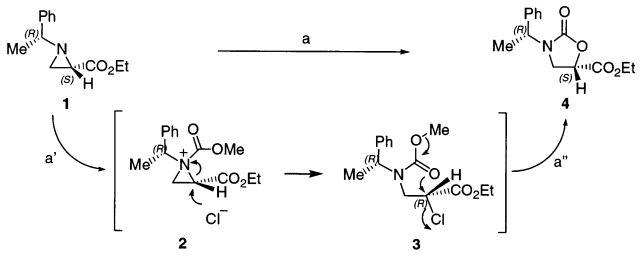
(9) Cardillo, G.; Orena, M.; Sandri, S. *J. Org. Chem.* **1986**, *51*, 713.

10.1021/jo0261911 CCC: $25.00
Published on Web 11/21/2002

instance, Linezolid, having a 5-functionalized chiral oxazolidin-2-one[10] as a key structural unit, has become a new important orally active antibiotic.[11] As its various biological activities and characteristics have been actively tested so far,[12] it is now considered to be even more efficacious than vancomycin used as an antibiotic of last resort. In addition, various isoserine derivatives from chiral oxazolidin-2-ones are highly regarded as protease inhibitors since the hydroxyl group serves as a mimic for the tetrahedral intermediate of proteolysis and is bound tightly to the active site.[13] Unfortunately, toxic reagents (e.g., phosgene, diphosgene, triphosgene, isocyanates) have been usually used with the preparative methods of oxazolidinones from the corresponding amino alcohols;[3] sometimes even very low or high reaction temperatures were needed.[3,14] With those difficulties in mind we developed a novel efficient stereospecific one-pot transformation of 2-functionalized enantiomerically pure aziridines to the corresponding 5-functionalized oxazolidin-2-ones with retention of the configuration at C-2 of the aziridine.

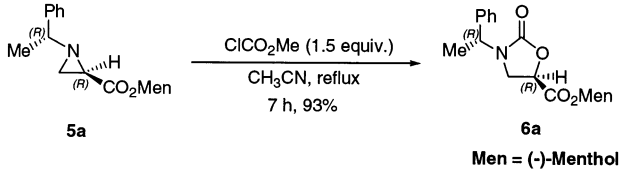
We recently reported the possibilities of the chiral aziridine **1** as a three-carbon chiral building block for the preparation of various biologically active compounds.[15] We found that the aziridine nitrogen was quite basic and also nucleophilic; therefore, ring-opening reactions were initiated by the formation of the aziridinium ion intermediate. We therefore envisaged a regioselective aziridine ring-opening initiated by the acylation of the aziridine nitrogen to produce an activated aziridinium species. The reaction of the enantiomerically pure aziridine-2-carboxylic acid ethyl ester **1** with 1.5 equiv of methyl chloroformate in refluxing CH_3CN proceeded smoothly to provide a 92% yield of the 2-oxazolidinone-5-carboxylic acid ethyl ester **4**.[16] We monitored the reaction carefully and found that the reaction proceeded via two steps with

SCHEME 1[a]



[a] Reagents and conditions: (a) 1.5 equiv of $ClCO_2CH_3$, CH_3CN, reflux, 7 h, 92%. (a′) 1.5 equiv of $ClCO_2CH_3$, toluene, reflux, 2 h, 97%. (a″) CH_3CN, reflux, 7 h, 95%.

SCHEME 2



the formation of the α-chlorocarboxylate **3**, and we proposed a plausible mechanism in Scheme 1. We isolated the intermediate **3** as an oil and obtained all the characterization data including HRMS to support the proposed structure.

There are two possible pathways to form the oxazolidin-2-one from the C-2-substituted aziridine with retention of the configuration: direct CO_2 insertion between the ring nitrogen and C-2 position of the aziridine[17] and a double S_N2 inversion process at C-2. However, the presence of the intermediate **3** suggests that the reaction is going through an S_N2-type double inversion process. Therefore, after acylation on the nucleophilic aziridine nitrogen to form the activated aziridinium species **2**, the C(2)−N bond is regioselectively cleaved by the chloride ion via an S_N2 process, and then following intramolecular cyclization by the carbamate oxygen, the oxazolidinone is obtained with the retention of the configuration at C-2 of the aziridine **1**.[18] Moreover, while screening a suitable reaction solvent, we found that the reaction did not proceed further at the intermediate stage **3** in toluene. Therefore, we isolated and fully characterized the intermediate 2(*R*)-chloro-3-[*N*-methoxycarbonyl-*N*-1(*R*)-phenylethyl]aminopropionic acid ethyl ester (**3**). We also successfully transformed the intermediate **3** to the corresponding oxazolidinone **4** by refluxing in CH_3CN in 95% yield. The above-mentioned stereospecific one-pot transformation of aziridine-2(*R*)-carboxylic acid menthol ester **5a** equally well proceeded to give the corresponding enantiomerically pure oxazolidin-2-one-5(*R*)-carboxylic acid menthol ester **6a** as a white solid in 93% yield (Scheme 2). To confirm the absolute configuration at C-5 of the oxazolidinone **6a**, we obtained the X-ray crystal-

(10) Müller, M.; Schimz K. -L. *Cell. Mol. Life Sci*. **1999**, *56*, 280.

(11) (a) Champney, W. S.; Miller, M. *Curr. Microbiol*. **2002**, *44*, 350. (b) Hamel, J. C.; Stapert, D.; Moerman, J. K.; Ford, C. W. *Infection* **2000**, *28*, 60.

(12) (a) Peláez, T.; Alonso, R.; Pérez, C.; Alcalá, L.; Cuevas, O.; Bouza, E. *Antimicrob. Agents Chemother*. **2002**, *46*, 1617. (b) Conte, J. E., Jr.; Golden, J. A.; Kipps, J.; Zurlinden, E. *Antimicrob. Agents Chemother*. **2002**, *46*, 1475. (c) Gentry-Nielsen, M. J.; Olsen, K. M.; Preheim, L. C. *Antimicrob. Agents Chemother*. **2002**, *46*, 1345. (d) Bassetti, M.; Biagio, A. D.; Cenderello, G.; Bono, B. D.; Palermo, A.; Molfetta, L.; Pipino, F.; Bassetti, D. *J. Orthop. Trauma* **2000**, *3*, 147. (e) Hamilton-Miller, J. M. T.; Shah, S. *Eur. J. Clin. Microbiol. Infect. Dis*. **1999**, *18*, 225.

(13) (a) Kempf, D. J.; Norbeck, D. W.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook., W., Jr; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem*. **1990**, *33*, 2687. (b) Mimoto, T.; Kiso, Y. *Chem. Pharm. Bull*. **1992**, *40*, 2251.

(14) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835. (b) Das, J. *Synth. Commun*. **1988**, *18*, 907.

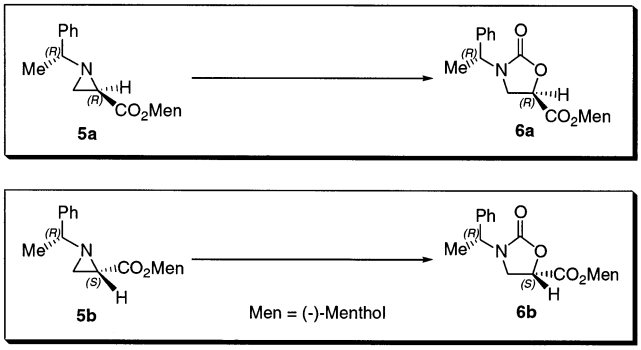
(15) (a) Park, C. S.; Kim, M. S.; Sim, T. B.; Pyun, D. K.; Lee, C. H.; Lee, W. K. *J. Org. Chem*., in press. (b) Chang, J.-W.; Ha, H.-J.; Park, C. S.; Kim, M. S.; Lee, W. K. *Heterocycles* **2002**, *57*, 1143. (c) Pyun, D. K.; Kim, B. J.; Jung, H. J.; Kim, J. H., Lee, J. S.; Lee, W. K.; Lee, C. H. *Chem. Pharm. Bull*. **2002**, *50*, 415. (d) Pyun, D. K.; Lee, C. H.; Ha, H.; Park, C. S.; Chang, J.; Lee, W. K. *Org. Lett*. **2001**, *3*, 4197. (e) Shin, S.; Han, E. Y.; Park, C. S.; Lee, W. K.; Ha, H. *Tetrahedron: Asymmetry* **2000**, *11*, 3293. (f) Park, C. S.; Choi, H. G.; Lee, H.; Lee, W. K.; Ha, H. *Tetrahedron: Asymmetry* **2000**, *11*, 3283. (g) Bae, J. H.; Shin, S.; Park, C. S.; Lee, W. K. *Tetrahedron* **1999**, *55*, 10041. (h) Chang, J.; Bae, J. H.; Shin, S.; Park, C. S.; Lee, W. K. *Tetrahedron Lett*. **1998**, *39*, 9193. (i) Choi, S.; Lee, W. K. *Heterocycles* **1998**, *48*, 1917. (j) Choi, S.; Lee, J.; Kim, J.; Lee, W. K. *J. Org. Chem*. **1997**, *62*, 743. (k) Hwang, G. I.; Chung, J.; Lee, W. K. *Tetrahedron* **1996**, *52*, 12111.

(16) The reaction proceeds equally well with allyl chloroformate, but the reaction rate is dramatically decreased with benzyl chloroformate.

(17) (a) Kawanami, H.; Ikushima, Y. *Tetrahedron Lett*. **2002**, *43*, 3841. (b) Tascedda, P; Duñach, E. *Chem. Commun*. **2000**, 449.

(18) (a) Lucarini, S.; Tomasini, C. *J. Org. Chem*. **2001**, *66*, 727. (b) Benedetti, F.; Norbedo, S. *Tetrahedron Lett*. **2000**, *41*, 10071. (c) Tomasini, C.; Vecchione, A. *Org. Lett*. **1999**, *1*, 2153. (d) Bach, T.; Schröder, J. *Tetrahedron Lett*. **1997**, *38*, 3707. (e) Curran, T. P.; Pollastri, M. P.; Abelleira, S. M.; Messier, R. J.; McCollum, T. A.; Rowe, C. G. *Tetrahedron Lett*. **1994**, *35*, 5409. (f) Lago, M. A.; Samanen, J.; Elliott, J. D. *J. Org. Chem*. **1992**, *57*, 3493.

SCHEME 3



lographic data.[19] We also confirmed the retention of the configuration at C-2 of the aziridine by using 2(*S*)-stereoisomer **5b**[20] to obtain the corresponding 5(*S*)-oxazolidinone **6b** in the same reaction conditions. Therefore, the present transformations show that the absolute configuration at C-5 of the oxazolidinones is controlled by that of the chiral aziridines at the C-2 position (Scheme 3).

The above results show that 5-functionalized chiral oxazolidin-2-ones are available very efficiently from chiral aziridines bearing an electron-withdrawing group at the C-2 position with retention of the configuration. To extend the scope of the reaction, we used various C-2-substituted aziridines which have vinyl or acyl groups to provide more 5-functionalized chiral oxazolidin-2-ones in excellent yields (Table 1). 2-Acylaziridines **7** were prepared from the oxidation of the corresponding secondary alcohols obtained by organometallic addition to the aziridine-2-carboxaldehyde **9**.[21−23] Starting from the 2-acyl-substituted aziridines **7**, we obtained 5-acyl-substituted chiral 2-oxazolidinones **8** in high yields (Scheme 4). Furthermore, aziridine-2-carboxaldehyde **9** was reacted with an ylide to give the coupling product **10** as a *trans* isomer in 96% yield. While the reaction of **10** with methyl chloroformate under the previously described conditions afforded oxazolidinone **11** in 94% yield after purification by silica gel flash chromatography, the formation of the 5-vinyloxazolidin-2-one **13** proceeded without isolation of the 2-vinylaziridine **12** due to the volatility of the compound to give an 85% yield of the vinyloxazolidinone **13** from the aldehyde **9** (Scheme 5).

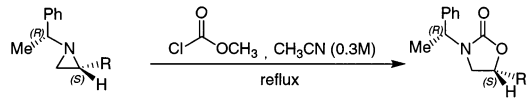
In summary, we developed a novel one-pot pathway to 5-functionalized enantiomerically pure oxazolidinones from the corresponding aziridines bearing an electron-withdrawing group such as ester, vinyl, or acyl at C-2 with retention of the configuration in high yields.

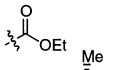
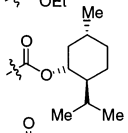
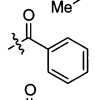
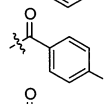
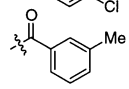
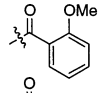
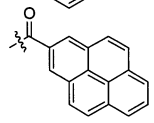
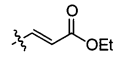
Experimental Section

General Procedures. Flash chromatography was performed with 230−400 mesh silica gel. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on 200, 300, and 500 MHz spectrometers. NMR spectra were recorded in parts per million (δ) relative to the peak for tetramethylsilane (δ = 0.00) as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, t = triplet, q = quartet, m = multiplet), coupling constant, and integration. Elemental analyses were performed using an elemental analyzer. Optical rotations were obtained on a digital polarimeter. Data are reported as follows: $[\alpha]^{25}_D$ (concentration (g/100 mL), solvent). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were reagent grade. All glassware was dried in an oven at 150 °C prior to use. Methylene chloride and triethylamine were dried over calcium hydride prior to use. Small- and medium-scale purifications were performed using flash chromatography. Enantiomerically pure *N*-(*R*)-α-methylbenzylaziridine-2(*R*)-carboxylic acid menthol ester (**5a**) and its 2(*S*)-stereoisomer (**5b**) were obtained commercially.

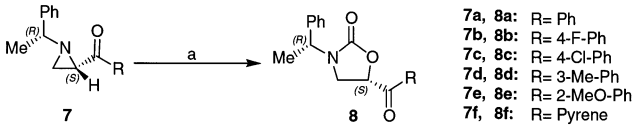
Representative Example of the Formation of Oxazolidin-2-one-5-carboxylates. Preparation of 2-Oxo-3-[1(*R*)-

TABLE 1. Preparation of 5-Functionalized Chiral Oxazolidin-2-ones



entry	R	yield(%)
a		92
b		93
c		92
d		97
e		94
f		88
g		97
h		91
i		97
j		85 (overall yield from **9**)

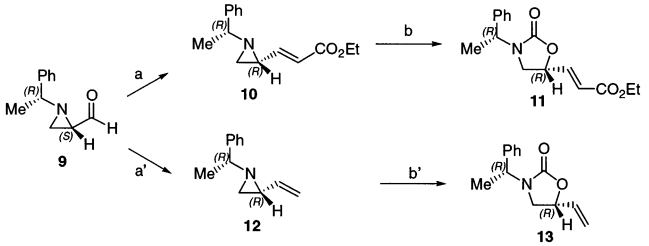
SCHEME 4[a]



[a] Reagents and conditions: (a) 1.5 equiv of $ClCO_2CH_3$, CH_3CN, reflux, 7 h.

(19) The ORTEP drawings and crystal data of **6a** and **6b** are in the Supporting Information.
(20) Both 2(*R*)- and 2(*S*)-aziridinecarboxylic acid menthol esters are available from ChemBioNex.
(21) Lim, Y.; Lee, W. K. *Tetrahedron Lett*. **1995**, *36*, 8431.
(22) Kim, B. C.; Lee, W. K. *Tetrahedron* **1996**, *52*, 12117.
(23) Hwang, G. I.; Chung, J.; Lee, W. K. *J. Org. Chem*. **1996**, *61*, 6183.

SCHEME 5[a]



[a] Reagents and conditions: (a) 1.2 equiv of $(EtO)_2POCH_2CO_2Et$, 1.2 equiv of LiHMDS, THF, at rt, 2 h, 96%. (b) 1.5 equiv of $ClCO_2CH_3$, CH_3CN, reflux, 7 h, 97%. (a′) 2 equiv of $CH_3PPh_3^+I^-$, 1.5 equiv of *n*-BuLi, THF, −78 °C. (b′) 1.5 equiv of $ClCO_2CH_3$, CH_3CN, reflux, 7 h, 85%.

phenylethyl]oxazolidine-5(S)-carboxylic Acid Ethyl Ester (4). To a solution of **1** (100 mg, 0.46 mmol) in 1.50 mL of CH_3CN was added methyl chloroformate (50 μL, 0.68 mmol), and the mixture was stirred for 7 h in refluxing CH_3CN. The mixture was cooled to room temperature and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 30:70) provided 110 mg (92%) of **4** as a colorless oil: $[\alpha]^{22}_D = +68.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.21 (q, *J* = 7.08 Hz, 1H), 4.87 (dd, *J* = 9.58, 5.19 Hz, 1H), 4.19 (q, *J* = 7.14 Hz, 2H), 3.75 (t, *J* = 9.34 Hz, 1H), 3.21 (dd, *J* = 9.28, 5.19 Hz, 1H), 1.59 (d, *J* = 7.14 Hz, 3H), 1.23 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 156.2, 139.0, 128.7, 127.9, 126.8, 69.9, 62.1, 51.5, 43.3, 16.2, 13.9. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.77; N, 5.45.

Data for 6a: mp 65−66 °C; $[\alpha]^{24}_D = -57.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25−7.39 (m, 5H), 5.20 (q, *J* = 7.0 Hz, 1H), 4.72−4.84 (m, 2H), 3.49 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.37 (t, *J* = 9.2 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.24−2.05 (m, 7H), 0.76−1.18 (m, 8H), 0.73 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 168.4, 156.2, 138.6, 128.7, 128.0, 126.9, 76.3, 70.0, 51.4, 46.6, 43.1, 40.4, 33.8, 31.2, 26.0, 23.0, 21.8, 20.6, 16.1, 15.9. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.6; H, 8.42; N, 3.66.

Data for 6b: mp 97−98 °C; $[\alpha]^{24}_D = -1.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24−7.39 (m, 5H), 5.20 (q, *J* = 7.0 Hz, 1H), 4.85 (dd, *J* = 9.6, 5.0 Hz, 1H), 4.71 (td, *J* = 10.8, 4.4 Hz, 1H), 3.74 (t, *J* = 9.6 Hz, 1H), 3.16 (dd, *J* = 9.6, 5.0 Hz, 1H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.29−1.83 (m, 7H), 0.84 (d, *J* = 7.4 Hz, 6H), 0.73−1.09 (m, 2H), 0.65 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 191.5, 167.3, 165.2, 156.0, 138.9, 132.1, 132.0, 128.7, 127.9, 126.8, 116.1, 115.9, 73.2, 51.8, 41.4, 16.6; IR (cm^{-1}) 1762, 1742. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.7; H, 8.35; N, 3.59.

Preparation of 2(*R*)-Chloro-3-[*N*-methoxycarbonyl-*N*-1(*R*)-phenylethyl]aminopropionic Acid Ethyl Ester (3). To a solution of **1** (100 mg, 0.46 mmol) in 1.50 mL of CH_3CN was added methyl chloroformate (50 μL, 0.68 mmol), and the mixture was stirred for 7 h in refluxing toluene. The mixture was cooled to room temperature and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 20:80) gave 140 mg (97%) of **3** as a colorless oil: $[\alpha]^{25}_D = +51.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 5.39 (br, 1H), 4.16−4.08 (m, 2H), 3.74−3.70 (m, 5H), 3.34 (dd, *J* = 14.83, 7.26 Hz, 1H), 1.64 (d, *J* = 7.14 Hz, 3H), 1.25 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 156.7, 140.4, 128.3, 127.3, 126.7, 61.9, 61.4, 54.7, 52.6, 47.8, 17.6, 13.7. HRMS (EI) *m*/*z* calcd for $C_{15}H_{20}ClNO_4$ 313.1081, found 313.1064.

Preparation of *N*-(*R*)-Phenylethylaziridin-2(*S*)-yl Pyren-2-yl Ketone (7f). To a solution of oxalyl chloride (70 μL, 0.80 mmol) in 1.65 mL of CH_2Cl_2 under nitrogen at −78 °C was added DMSO (80 μL, 1.06 mmol). The solution was stirred for 30 min at −78 °C and treated with a solution of a mixture of [*N*-(*R*)-phenylethylaziridin-2(*S*)-yl]pyren-2-ylmethanol (200 mg, 0.53 mmol) in 1.00 mL of CH_2Cl_2. The mixture was stirred for 30 min at −78 °C and treated with Et_3N (0.30 mL, 2.12 mmol) at −78 °C. The mixture was stirred for 15 min and warmed to room temperature. To the mixture was added 2.00 mL of water, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 5), and the combined organic extracts were dried, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 30:70) provided 183 mg (92%) of **7f** as a brown solid: mp 161−162 °C; $[\alpha]^{22}_D = -210.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50−7.23 (m, 14H), 2.95 (q, *J* = 3.05 Hz, 1H), 2.74−2.70 (m, 2H), 1.99 (dd, *J* = 6.23, 1.53 Hz, 1H), 1.55 (d, *J* = 6.53 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 144.2, 133.5, 132.4, 131.0, 130.4, 129.4, 129.4, 129.3, 129.0, 128.6, 127.5, 127.0, 126.3, 126.2, 126.1, 126.0, 124.6, 124.5, 124.2, 123.8, 70.8, 43.5, 37.9, 23.5. Anal. Calcd for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.35; H, 5.82; N, 3.81.

Representative Example of the Preparation of 5-Acyloxazolidin-2-ones. Preparation of 5(*S*)-Benzoyl-3-[1′(*R*)-phenylethyl]oxazolidin-2-one (8a). To a solution of **7a** (166 mg, 0.66 mmol) in 2.20 mL of CH_3CN was added methyl chloroformate (80 μL, 0.99 mmol), and the mixture was stirred for 7 h in refluxing CH_3CN. The mixture was cooled to room temperature and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/CH_2Cl_2, 10:90) gave 179 mg (92%) of **8a** as a white solid: mp 88−89 °C; $[\alpha]^{24}_D = +167.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96−7.26 (m, 10H), 5.59 (dd, *J* = 9.46, 6.04 Hz, 1H), 5.21 (q, *J* = 7.14 Hz, 1H), 3.75 (t, *J* = 9.22 Hz, 1H), 3.59 (dd, *J* = 9.03, 6.04 Hz, 1H), 1.62 (d, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 156.2, 138.9, 134.2, 133.6, 129.1, 128.8, 128.7, 127.9, 126.8, 73.1, 51.7, 41.6, 16.6. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.38; H, 6.03; N, 4.85.

Data for 8b: mp 81−83 °C; $[\alpha]^{23}_D = +162.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02−7.11 (m, 9H), 5.30 (dd, *J* = 9.34, 6.04 Hz, 1H), 5.19 (q, *J* = 7.14 Hz, 1H), 3.73 (t, *J* = 9.22 Hz, 1H), 3.63 (dd, *J* = 9.03, 5.98 Hz, 1H), 1.62 (d, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 167.3, 165.2, 156.0, 138.9, 132.1, 132.0, 128.7, 127.9, 126.8, 116.1, 115.9, 73.2, 51.8, 41.4, 16.6. Anal. Calcd for $C_{18}H_{16}FNO_3$: C, 69.00; H, 5.15; N, 4.47. Found: C, 69.10; H, 5.08; N, 4.51.

Data for 8c: mp 126−127 °C; $[\alpha]^{22}_D = +209.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87−7.24 (m, 9H), 5.70 (dd, *J* = 9.40, 5.80 Hz, 1H), 5.15 (q, *J* = 7.08 Hz, 1H), 3.75 (t, *J* = 9.28 Hz, 1H), 3.56 (dd, *J* = 8.97, 5.86 Hz, 1H), 1.59 (d, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 155.9, 140.5, 138.8, 131.8, 130.4, 129.0, 128.5, 127.7, 126.5, 72.9, 51.6, 41.4, 16.5. Anal. Calcd for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.56; H, 4.92; N, 4.18.

Data for 8d: mp 70−71 °C; $[\alpha]^{22}_D = +163.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−1.24 (m, 9H), 5.60 (dd, *J* = 9.52, 5.92 Hz, 1H), 5.19 (q, *J* = 7.08 Hz, 1H), 3.75 (t, *J* = 9.22 Hz, 1H), 3.53 (dd, *J* = 8.97, 5.92 Hz, 1H), 2.37 (s, 3H), 1.60 (d, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 156.2, 138.9, 138.6, 134.9, 133.6, 129.4, 128.6, 127.7, 126.6, 126.1, 72.9, 51.6, 41.7, 21.1, 16.5. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.76; H, 6.23; N, 4.54.

Data for 8e: $[\alpha]^{23}_D = +12.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−6.93 (m, 9H), 5.68 (dd, *J* = 9.83, 4.52 Hz, 1H), 5.18 (q, *J* = 7.02 Hz, 1H), 3.87−3.84 (m, 4H), 3.20 (dd, *J* = 8.92, 4.52 Hz, 1H), 1.59 (d, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 158.7, 157.1, 139.2, 135.1, 131.0, 128.4, 127.4, 126.4, 123.4, 121.0, 111.5, 75.3, 55.6, 51.0, 42.7, 16.2. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.15; H, 5.71; N, 4.27.

Data for 8f: mp 161−162 °C; $[\alpha]^{22}_D = +210.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64−7.22 (m, 14H), 5.79 (dd, *J* = 9.58, 5.43 Hz, 1H), 5.24 (q, *J* = 7.02 Hz, 1H), 3.80 (t, *J* = 9.34 Hz, 1H), 3.54 (dd, *J* = 9.22, 5.49 Hz, 1H), 1.59 (d, *J* = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 156.4, 139.1,

134.5, 130.8, 130.6, 130.2, 130.2, 128.7, 127.8, 127.4, 126.9, 126.9, 126.8, 126.7, 126.5, 126.4, 124.7, 124.0, 123.8, 74.3, 51.6, 42.4, 16.4. Anal. Calcd for $C_{28}H_{21}NO_3$: C, 80.17; H, 5.05; N, 3.34. Found: C, 80.04; H, 5.05; N, 3.48.

Preparation of 3-[1-(1′*R*)-Phenylethylaziridin-2(*R*)-yl]-acrylic Acid Ethyl Ester (10). To a solution of $(EtO)_2POCH_2CO_2Et$ (0.14 mL, 0.68 mmol) in 1.89 mL of THF under nitrogen with stirring at room temperature was added LiHMDS (1.0 M, 0.69 mL, 0.69 mmol) in THF. The mixture was treated with **9** (100 mg, 0.57 mmol) in 1.00 mL of THF via cannula, stirred for 2 h at room temperature, and then treated with 0.5 mL of aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 mL × 5). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 30:70) provided 136 mg (97%) of **10** as a yellow oil: $[\alpha]^{23}_D = -116.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 6.69−6.64 (m, 1H), 5.91 (d, J = 15.63 Hz, 1H), 4.12 (q, J = 7.14 Hz, 2H), 2.55 (q, J = 6.53 Hz, 1H), 1.20−1.96 (m, 2H), 1.77 (dd, J = 5.80, 1.28 Hz, 1H), 1.41 (d, J = 6.53 Hz, 3H), 1.22 (t, J = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 147.9, 143.9, 128.1, 126.8, 126.2, 121.4, 69.6, 59.9, 38.3, 36.7, 23.2, 14.0. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.87; N, 5.79.

Data for 11: $[\alpha]^{25}_D = +108.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.19 (m, 5H), 6.67 (dd, J = 15.63, 5.13 Hz, 1H), 6.01 (dd, J = 15.63, 1.53 Hz, 1H), 5.11 (q, J = 7.08 Hz, 1H), 5.03−4.98 (m, 1H), 4.09 (q, J = 7.14 Hz, 2H), 3.64 (t, J = 8.91 Hz, 1H), 2.82 (dd, J = 8.73, 6.78 Hz, 1H), 1.50 (d, J = 7.14 Hz, 3H), 1.18 (t, J = 7.14 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 156.4, 142.0, 138.7, 128.4, 127.7, 126.6, 122.8, 71.2, 60.4, 51.3, 44.7, 16.1, 13.8. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.43; H, 6.74; N, 4.52.

Preparation of 3-[1(*R*)-Phenylethyl]-5(*R*)-vinyloxazolidin-2-one (13). To a solution of the phosphonium salt $CH_3PPh_3^+I^-$ (922 mg, 2.28 mmol) in 3.71 mL of THF under nitrogen with stirring and cooling at −78 °C was added *n*-BuLi (1.6 M, 1.07 mL, 1.71 mmol) in hexane. The mixture was stirred for 30 min and treated with **9** (200 mg, 1.14 mmol) in 2.00 mL of THF via cannula at −78 °C. The mixture was stirred for 2 h at −78 °C, warmed to room temperature, and treated with 1 mL of water. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL × 5). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated by air flow to obtain the crude mixture **12**. To a solution of **12** in 3.80 mL of CH_3CN was added methyl chloroformate (0.13 mL, 1.71 mmol), and the mixture was stirred for 7 h in refluxing CH_3CN. The mixture was cooled to room temperature and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 30:70) gave 210 mg (overall 85%) of **13** as a yellow oil: $[\alpha]^{22}_D = +93.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.79−5.72 (m, 1H), 5.35 (td, J = 17.09, 1.04 Hz, 1H), 5.24−5.19 (m, 2H), 4.89 (q, J = 6.78 Hz, 1H), 3.62 (t, J = 8.67 Hz, 1H), 2.85 (dd, J = 8.67, 6.84 Hz, 1H), 1.58 (d, J = 7.08 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 139.3, 134.4, 128.6, 127.7, 126.8, 118.5, 73.9, 51.2, 45.3, 16.4. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.80; H, 7.05; N, 6.56.

Acknowledgment. We thank the Korea Research Foundation (Grant KRF-2002-070-C00060) for financial support. H.-J.H. acknowledges KOSEF for financial support (Grant R01-2000-00048).

Supporting Information Available: X-ray crystallographic data and ORTEP drawings of compounds **6a** and **6b**. This material is available free of charge via the Internet at http//:pubs.acs.org.

JO0261911