SYNTHESIS OF OPTICALLY ACTIVE 2-PIPERIDYLGLYCINE

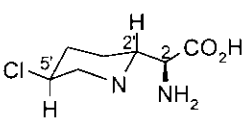
Hyun-kyu Chung, Hyung-woo Kim, and Kyoo-Hyun Chung*

Department of Chemistry, Inha University, Inchon 402-751, Korea

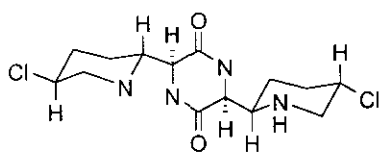
Abstract - Both chiral *threo*- and *erythro*-2-piperidylglycines were synthesized from racemic 2-[(*N*-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid. (4*S*,5*S*)-4-Methyl-5-phenyl-2-oxa-zolidinone was used as a chiral auxiliary in the resolution and azidation.

Many of α,β-diamino acids have displayed various biological activities.[1] Streptolutin [**1**, 2-amino-2-(5-chloropiperidin-2-yl)ethanoic acid], one of α,β-diamino acids, is the parent amino acid of antitumor agent DKP 593A (**2**). The agent was isolated from the soil microorganism, *Streptomyces griseoluteus* and reported to be effective against certain solid tumors.[2,3] The antitumor agent has been synthesized as a racemic mixture.[4] Streptolutine has three chiral centers whose configurations are (*R*) at C-2′, (*S*) at C-5′ and C-2, thus the stereochemical relationship between C-2′ and C-5′ is *trans,* and that of C-2′ and C-2 is *threo*. In the attempted synthesis of streptolutin, the corresponding *erythro* isomer was formed as a major compound.[5]

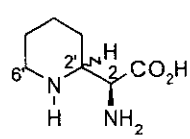
2-Piperidylglycine [**3**, 2-amino-2-(piperidin-2-yl)ethanoic acid] has been studied as a model compound in the preparation of analogs of streptolutin and DKP 593A.[6-8] Heating 7-amino-7-carboxy-8-oxo-1-azabicyclo[4.2.0]octane in 5 M HCl gave a 2:1 mixture of *threo*- and *erythro*-2-piperdylglycines.[7] Hydrogenation of ethyl 2-piperidinylidene-*N*-(ethoxycarbonyl)glycinate on 10% Pd/C gave the corresponding *erythro*-glycine derivative.[8]



1



2



3

In the azidation at the C-2 position of a 2-(piperidin-2-yl)ethanoate, an *erythro*-azide is always predominant over a threo isomer.[9] In the meantime, a few compounds related to 2-piperidylglycine were

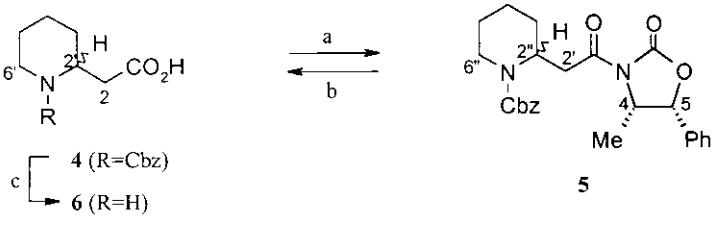
optically resolved. Pig liver esterase catalyzed enantioselectively the hydrolysis of racemic methyl 2-(*N*-acetylpiperidin-2-yl)ethanoate or acetate of 2-(*N*-acetylpiperidin-2-yl)ethan-1-ol to give the corresponding acid or alcohol in 7-24% ee.[10] 2-Piperidineethanol was also resolved through recrystallization of *d*-10-camphorsulfonate salt.[11]

Evans chiral imide enolates have been used in alkylation, aldol condensation and azidation.[12,13] So we thought that a chiral auxiliary may be utilized to obtain chiral 2-(piperidin-2-yl)ethanoic acid from the racemate and to introduce amino group diastereoselectively at the C-2 position.[9] In this note, we described the synthesis of chiral *threo*- and *erythro*-2-piperidylglycines using (4*S*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone as a chiral auxiliary.[12]

Racemic 2-[(*N*-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid (**4**) was reacted with (4*S*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone to give diastereomeric carboxamide (**5**).[9] By column chromatography, the mixture of **5a** and **5b** was separated without any difficulty. When (*S*)-4-benzyl-2-oxazolidinone was used as a chiral auxiliary to prepare a carboxamide, the resulting mixture of two diasteroisomers was difficult to be separated by column chromatography.

The stereochemistry of the piperidine ring was determined by comparison with the known optical rotation. Chiral 2-(piperidin-2-yl)ethanoic acid (**6**) was prepared by the following sequence; hydrolysis of carboxamide (**5**) by LiOH-H_2O_2 followed by hydrogenolysis of the resulting acid on 10% Pd/C. The $[\alpha]_D$ values of **6**, derived from one of **5** having lower Rf value, was +31.2°. Because the $[\alpha]_D$ values of (*S*)-2-(piperidin-2-yl)ethanoic acid (**6b**) was reported to be +33.5°,[14] the compound having lower Rf value was assigned to be **5b** and the other one was **5a** in a mixture of **5** (Scheme1).

Scheme 1. Determination of the Stereochemistry in the Piperidine Ring.



(Chirality of C-2 in the piperidine ring, a:*R*, b:*S*)

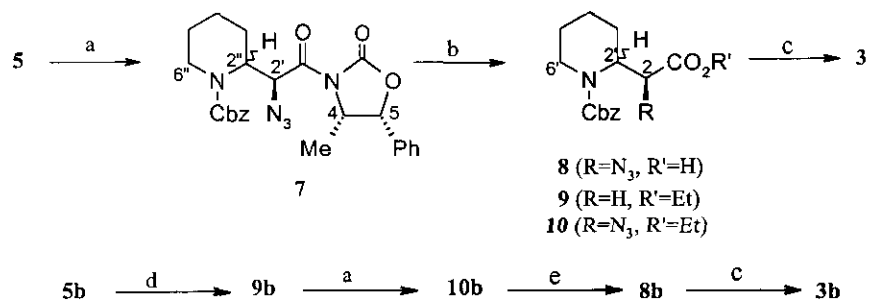
Reaction conditions: (a) i) pivaloyl chloride, Et_3N, ii) (4*S*,5*S*)-4-methyl -5-phenyl-2-oxzolidinone, *n*-BuLi; (b) i) separation, ii) $LiOH,H_2O_2$; (c) H_2, 10% Pd/C.

Carboxamide (**5a**) was treated with KHMDS and 2,4,6-triisopropylbezenesulfonyl azide (trisyl azide) to give azide (**7a**) which has *S* chirality at the C-2′, since the stereochemistry was governed by the methyl

and phenyl groups of the oxazolidinone. As a result, the *threo* isomer was in hand. The reaction of azido carboxamide (**7a**) with LiOH-H_2O_2 gave azido acid (**8a**), which was hydrogenated on 10% Pd/C to afford *threo*-2-piperidylglycine (**3a**). The *threo* stereochemistry was confirmed by comparing its ^{1}H NMR spectra in 2M DCl/D_2O with spectra for *threo*- and *erythro*-2,3-diaminobutanoic acids.[7]

Since azide (**7b**), derived from carboxamide (**5b**), was difficult in separation from the unreacted **5b** upon azidation, other methodology was employed to synthesize *erythro*-2-piperidylglycine (**3b**). Carboxamide (**5b**) was converted to ethyl ester (**9b**) which was reacted with trisyl azide to give a mixture of *erythro*-azide (**10b**) and the enantiomer of **10a** in a ratio of 3.5 : 1.[9] Perpendicular model was suggested to explain the *erythro* preference in the azidation.[15] Ester (**10b**) was purified by flash column chromatography and was converted to *erythro*-2-piperidylglycine (**3b**) by the above mentioned method. The *erythro* stereochemistry was also confirmed by its ^{1}H NMR spectrum (Scheme 2).

Scheme 2. Synthesis of Chiral 2-Piperidylglycine.



(Chirality of C-2 in the piperidine ring, a:*R*, b:*S*)

Reaction conditions: (a) KHMDS, trisyl azide; (b) LiOH,H_2O_2; (c) H_2, 10% Pd/C; (d) NaOEt, EtOH; (e) LiOH.

EXPERIMENTAL

All chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (200MHz) spectrometer in $CDCl_3$ unless otherwise stated. Optical rotations were recorded on a Perkin-Elmer polarimeter 241. Melting points were determined on a Yamato MP-21 and were uncorrected. Elemental analysis was performed by a Xytel EA-1110 at Inha University.

(4*S*,5*S*)-3-[2-((*N*-Benzyloxycarbonyl)piperidin-2-yl)-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone (5). To a solution of 2-[(*N*-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid (**4**, 2.73 g, 9.83 mmol) in THF (25 mL) was added triethylamine (1.30 mL, 12.8 mmol) and pivaloyl chloride (1.30 mL, 10.8 mmol) at -

78℃.[9,13] The slurry was stirred at -78℃ for 10 min and 0℃ for 50 min and then recooled to -78℃. In a separate flask a solution of (4*S*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone (6.80 g, 10.8 mmol) in THF (15 mL) was cooled to -78℃. To this solution was added 1.6M *n*-BuLi in hexane (13.5 mL, 21.6 mmol). The metalated oxazolidinone was added *via* cannula to the white slurry prepared as described above. The resulting slurry was stirred for 15 min at -78℃, warmed to rt, and then stirred for 1.5 h. The reaction was quenched by sodium bisulfate (11.9 g, 4.00 mmol). THF was removed *in vacuo*, and the mixture was diluted with water and extracted with CH_2Cl_2 (40 mL x 3). The extract was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/n-hexane) gave **5a** (1.50 g, 35%) and **5b** (0.86 g, 20%). **5a**: mp 93℃- 95℃(EtOAc/n-hexane). ^{1}H NMR δ 0.79 (d, J = 6.5 Hz, 3H, CH_3), 1.40-1.90 (m, 6H, H-3", H-4", H-5"), 2.93-3.20 (m, 2H, H-2′), 3.32-3.55 (m, 1H, H-6a"), 4.02-4.24 (m, 1H, H-6e"), 4.24-4.48 (m, 1H, H-4), 4.85-5.00 (m, 1H, H-2e"), 5.10-5.17 (m, 2H, benzyl), 5.52-5.68 (m, 1H, H-5), 7.10-7.45 (m, 10H, Ph); ^{13}C NMR δ 168.7, 153.8, 151.6, 135.5, 131.8, 126.87, 126.83, 126.14, 125.6, 124.0, 77.2, 65.2, 53.1, 46.4, 38.0, 34.8, 27.4, 23.6, 17.3, 12.8; $[\alpha]^{20}_D$ +3.3° (c 2.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.74; H, 6.48; N, 6.49.

5b (oil): ^{1}H NMR δ 0.79 (d, J = 4.0 Hz, 3H, CH_3), 1.33-1.85 (m, 6H, H-3", H-4", H-5"), 2.93-3.35 (m,3H, H-2′, H-6a"), 4.00-4.20 (m, 1H, H-6e"), 4.58-4.80 (m, 1H, H-4), 4.85-5.08 (m, 1H, H-2e"), 5.08 (bs, 2H, benzyl), 5.58 (d, J = 7.2 Hz, 1H, H-5), 7.15-7.50 (m, 10H, Ph); ^{13}C NMR δ 168.9, 153.7, 151.4, 135.3, 131.7, 127.1, 126.8, 126.2, 125.9, 124.1, 77.4, 65.2, 53.1, 46.4, 38.0, 34.5, 27.4, 23.5, 17.2, 12.4; $[\alpha]^{20}_D$ -24.2° (c 2.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.74; H, 6.48; N, 6.49.

(3(2*S*),3(2(2*R*)),4*S*,5*S*)-3-[2-Azido-2-((*N*-benzyloxycarbonyl)piperidin-2-yl)-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone (7a). To a solution of **5a** (1.00 g, 2.29 mmol) in THF(15 mL) at -78℃ was added dropwise 0.5M KHMDS in toluene (5.5 mL, 2.75 mmol). The solution was stirred for 30 min and treated with a precooled solution of trisyl azide (0.78 g, 2.52 mmol) in THF (5 mL) *via* cannula . The mixture was stirred for 5 min at -78℃ and then quenched by rapid addition of acetic acid (0.66 mL, 4.80 mmol). After the white slurry was stirred for 2 h at rt, it was diluted with CH_2Cl_2. The mixture was washed with water, and the water layer was extracted with CH_2Cl_2 (50 mL x 3). Combined organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAC/*n*-hexane) gave an oil (0.744 g, 68%). ^{1}H NMR δ 0.89 (d, J = 6.5 Hz, 3H, CH_3), 1.35-1.95 (m, 6H, H-3", H-4", H-5"), 3.05-3.35 (m, 1H, H-6a"), 4.00-4.20 (m, 1H, H-6e"), 4.35-4.52 (m, 1H, H-4), 4.73-4.90 (m, 1H, H-2e"), 5.00-5.35 (m, 2H, benzyl), 5.35-5.57 (m, 1H, H-2′), 5.69 (d, J = 7.2 Hz, H-5), 7.15-7.50 (m, 10H, Ph); ^{13}C NMR δ 169, 153.7, 151.4, 135.3, 131.7, 127.1, 126.9, 126.2, 125.7, 124.1, 77.6, 65.6, 61.7, 53.8, 46.4, 38.9, 28.0, 24.5, 17.8, 12.9; $[\alpha]^{20}_D$ +8.44° (c 2.9, $CHCl_3$). HRMS (FAB+)

calcd for $C_{25}H_{28}N_5O_5$ (MH^+) 478.2090, found 478.2089.

(2*S*,2(2*R*))-2-Azido-[(*N*-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid (8a). To a solution of **7a** (0.68 g, 1.42 mmol) in a mixture of THF and water (3:1, 15 mL) was added slowly LiOH (0.12 g, 2.88 mmol) and H_2O_2 (35%, 1.38 g, 14.2 mmol). The reaction mixture was stirred for 1 h, and quenched by sodium bisulfate (1.97 g, 14.2 mmol). THF was removed *in vacuo*, and the resulting mixture was diluted by water, acidified to pH 1-2 with 1.0N HCl, and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were dried, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% MeOH/CH_2Cl_2) gave a solid (0.41 g, 82%). mp 134℃-135℃ (CH_2Cl_2/ n-hexane); ^{1}H NMR δ 1.40-1.86 (m, 6H, H-3′, H-4′, H-5′), 2.80-2.89 (m, 1H, H-6a′), 4.07-4.25 (m, 2H, H-6e′, H-2), 4.62-4.80 (m, 1H, H-2a′), 5.11-5.28 (m, 2H, benzyl), 7.34 (s, 5H, Ph); ^{13}C NMR δ 19.0, 20.7, 24.7, 26.2, 39.8, 51.9, 61.0, 67.7, 127.9, 128.0, 136.3, 156.0, 173.5; $[\alpha]^{20}_D$ –21.0° (c 0.5, $CHCl_3$). Anal. Calcd For $C_{15}H_{18}N_4O_4$: C 56.60, H 5.70, N 17.60. Found: C 56.03, H 6.08, N 17.41.

(2*S*,2(2*R*))-2-Amino-2-(piperidin-2-yl)ethanoic acid (3a). To a solution of **8a** (0.12 g, 0.38 mmol) in MeOH (15mL) was added 10% Pd/C (0.012 g). The black slurry was stirred under hydrogen at atmospheric pressure for 1 h. The slurry was then filtered through celite, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from MeOH/ Et_2O to give a solid (0.049 g, 81%). mp 204℃-205℃; ^{1}H NMR (2.0M DCl/D_2O) δ 1.18-1.82 (m, 6H, H-3′, H-4′, H-5′), 2.78-2.89 (m, 1H, H-6a′), 3.20-3.27 (m, 1H, H-6e′), 3.44-3.48 (m, 1H, H-2a′), 4.20 (d, J = 3.3 Hz, 1H, H-2); ^{13}C NMR (2.0M DCl/D_2O) δ 18.6, 18.8, 20.6, 44.2, 50.6, 52.9, 164.9; $[\alpha]^{20}_D$ +22.1° (c 0.24, 1.0N HCl). Anal. Calcd For $C_7H_{14}N_2O$: C 53.15, H 8.92, N 17.71. Found: C 53.24, H 8.89, N 17.66.

Ethyl (*S*)-2-[(*N*-benzyloxycarbonyl)piperidin-2-yl]ethanoate (9b).[9] To a precooled solution of **5b** (1.83 g, 4.19 mmol) in EtOH (10 mL) was added slowly NaOEt (0.294 g, 4.19 mmol) in EtOH (5 mL). The reaction mixture was stirred for 2 h and the EtOH was removed *in vacuo*. The residue was added into water and extracted with CH_2Cl_2. The organic layer was dried, filtered, and concentrated *in vacuo* to give an oil. Purification of the crude product by column chromatography (20% EtOAc/n-hexane) gave an oil (1.04 g, 81%). ^{1}H NMR δ 1.21 (t, J=7.2 Hz, 3H, CH_3), 1.35-1.95 (m, 6H, H-3′, H-4′, H-5′), 2.52-2.65 (m, 2H, H-2), 2.78-2.96 (m, 1H, H-6a′), 3.95-4.15 (m, 1H, H-6e′), 4.07 (q, J = 7.4 Hz, 2H, -OCH_2), 4.72-4.86 (m, 1H, H-2e′), 5.13 (br s, 2H, benzyl); ^{13}C NMR δ 12.4, 17.0, 23.5, 26.5, 33.6, 37.8, 46.5, 58.2, 65.3, 126.1, 126.2, 126.8, 135.3, 153.7, 169.6; $[\alpha]^{20}_D$ -7.2° (c 2.1, $CHCl_3$); MS (EI) m/z 305 (M^+).

Ethyl (2*S*,2(2*S*))-2-azido-[(*N*-benzyloxycarbonyl)piperidin-2-yl]ethanoate (10b).[9] The procedure outlined above for the azidation of **5a** was followed employing **9b**. The crude product (**10b**) was purified by column chromatography (20% EtOAc/n-hexane) to give an oil (45%). ^{1}H NMR δ 1.20 (t, J = 7.0 Hz, 3H, CH_3), 1.40-2.02 (m, 6H, H-3′, H-4′, H-5′), 2.85-3.05 (m, 1H, H-6a′), 4.09 (q, J = 7.0 Hz, 2H, OCH_2),

3.98-4.10 (m, 1H, H-6e′), 4.53-4.68 (m, 1H, H-2e′), 5.10 (m, 2H, benzyl), 7.25-7.40 (m, 5H, Ph); ^{13}C NMR 12.3, 17.3, 23.1, 24.4, 37.9, 50.2, 59.0, 60.3, 65.7, 126.3, 126.8, 134.9, 153.9, 167.6; $[\alpha]^{20}_{D}$ +19.8° (c 2.3, $CHCl_3$); MS (CI) m/z 347 (MH^+).

(2*S*,2(2*S*))-2-Azido-[(*N*-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid (8b). To a solution of **10b** (0.469 g, 1.42 mmol) in a mixture of THF and water (3:1, 15 mL) was added slowly LiOH (0.12 g, 2.83 mmol) at 0℃. the reaction mixture was stirred for 1 h, and THF was removed *in vacuo*. The resultant was diluted by water, acidified to pH 1-2 with 1.0N HCl, and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (10% MeOH/CH_2Cl_2) gave an oil (0.42 g, 84%). ^{1}H NMR δ 1.40-1.95 (m, 6H, H-3′, H-4′, H-5′), 2.96-3.08 (m, 1H, H-6a′), 4.06-4.20 (m, 2H, H-6e′, H-2), 4.52-4.64 (m, 1H, H-2a′), 5.03-5.17 (m, 2H, benzyl), 7.34 (br s, 5H, Ph); ^{13}C NMR δ 17.0, 22.8, 23.3, 50.4, 58.7, 66.3, 126.2, 126.9, 134.5, 154.5, 170.8; $[\alpha]^{20}_{D}$ −6.9° (c 1.8, $CHCl_3$). Anal. Calcd For $C_{15}H_{18}N_4O_4$: C 56.60, H 5.70, N 17.60. Found: C 56.03, H 6.08, N 17.41.

(2*S*,2(2*S*))-2-Amino-2-(piperidin-2-yl)ethanoic acid (3b). The procedure outlined above for **3a** was followed employing **8b**. mp 234℃-235℃(MeOH/Et_2O); ^{1}H NMR (2.0 M DCl/D_2O) δ 1.12-1.63 (m, 6H, H-3′, H-4′, H-5′), 2.64-2.75 (m, 1H, H-6a′), 3.10-3.20 (m, 1H, H-6e′), 3.30-3.47 (m, 1H, H-2a′), 4.00 (d, J = 6.4 Hz, 1H, H-2); ^{13}C NMR (2.0 M DCl/D_2O) δ 18.5, 22.2, 43.6, 51.2, 52.7, 164.9; $[\alpha]^{20}_{D}$ −10.0° (c 0.05, 1.0 N HCl). Anal. Calcd For $C_7H_{14}N_2O$: C 53.15, H 8.92, N 17.71. Found: C 53.24, H 8.89, N 17.66.

ACKNOWLEDGMENT

We thank OCRC-KOSEF and the Korea Science and Engineering Fund (No 97-03-01-01-5-L) for partial financial support.

REFERENCES

1. P. Merino, A. Lanaspa, F. L. Merchan, and T. Tejeros, *Tetrahedron Lett.*, 1997, **38**, 1813.
2. G. R. Pettit, R. B. Vondreele, D.L. Herald, M.T. Edger, and. H. B. Wood Jr., *J. Am. Chem. Soc.*, 1976, **98**, 6742.
3. B. H. Arison and J. L. Beck, *Tetrahedron*, 1973, **29**, 2743.
4. T. Fukuyama, R. K. Frank, and C. F. Jewell Jr., *J. Am. Chem. Soc.*, 1980, **102**, 2122.
5. C. Herdeis, W. A. Held, A. Kirfel, and F. Schwabenlander, *Tetrahedron*, 1996, **52**, 6409.
6. K.-H. Chung, D.-R. Lee, and H.-W. Kim, *Bull. Korean Chem. Soc.*, 1996, **17**, 863.
7. B. T. Golding and A. J. Smith, *J. Chem. Soc., Chem. Comm.*, 1980, 702.
8. C. Herdeis and U. J. Nagel, *Heterocycles*, 1983, **20**, 2163.

9. K.-H. Chung and S. O. An, *J. Korean Chem. Soc.*, 1995, **39**, 431.

10. E. J. Toore and J. B. Jores, *Can. J. Chem.*, 1987, **65**, 2722.

11. M. S. Toy and C. C. Prices, *J. Am. Chem. Soc.*, 1960, **82**, 2613.

12. D. A. Evans, R. P. Polniazek, K. M. DeVries, D. E. Guian, and D. J. Marhre, *J. Am. Chem. Soc.*, 1991, **113**, 7613.

13. D. A. Evans, T. C. Britton, J. A. Ellman, and R. L. Dorow, *J. Am. Chem. Soc.*, 1990, **112**, 4011.

14. C. Morlery, D. W. Knight, and A. C. Share, *Tetrahedron: Asymmetry*, 1990, **1**, 147.

15. H.-K. Chung, H.-W. Kim, and K.-H. Chung, *Bull. Korean Chem. Soc.*, 1999, **20**, 325.

Received, 12th July, 1999