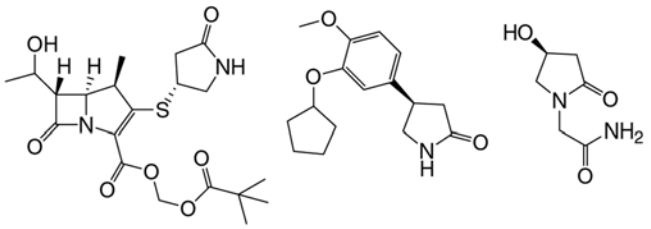
Synthesis of Enantiomerically Pure *N*-Substituted 4-Hydroxypyrrolidin-2-one Derivatives

Yong-Chul Jeong, Sung Kwan Hwang,† and Kwang-Hyun Ahn*

College of Environment and Applied Chemistry, and MRCID, Kyung Hee University, Yongin 449-701, Korea
**E-mail: khahn@khu.ac.kr*
†Dae He Chemical Co, 1 Ra 301, Shihwa Industrial Complex, Shihung 429-450, Korea
Received February 28, 2005

Key Words : 4-Hydroxypyrrolidin-2-ones, Oxiracetame, Chiral epoxide, Kinetic resolution

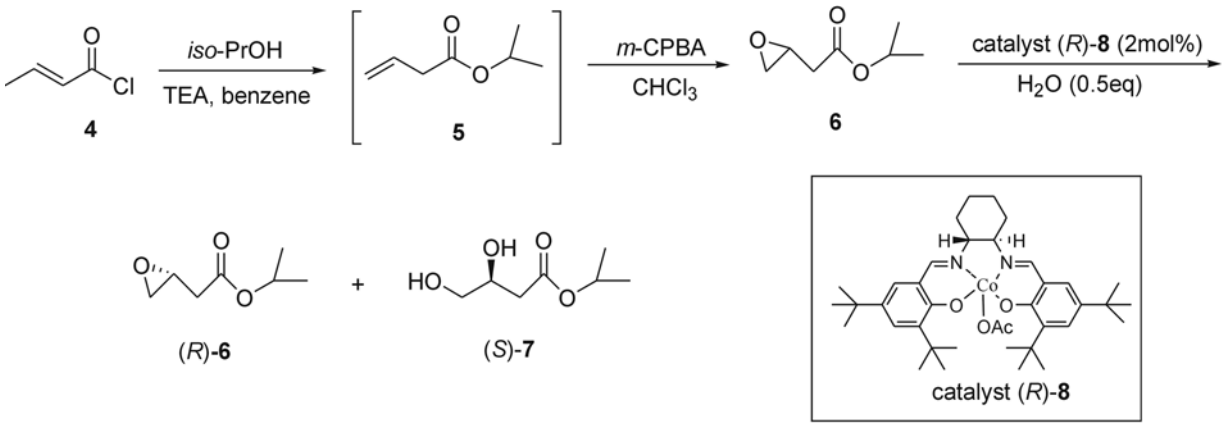
Optically active 4-substituted pyrrolidin-2-one substructures can be found in various biologically active compounds such as CS-834, **1**, an oral carbapenem antibiotic drug,[1] rolipram, **2**, an antidepressant agent[2] and oxiracetame, **3**, a nootropic drug for the Alzheimer's disease.[3-6] Chiral 4-hydroxypyrrolidin-2-one and its *N*-substituted derivatives are versatile intermediates for the synthesis of those compounds. Therefore, several methods for the synthesis of optically active 4-hydroxypyrrolidin-2-one derivatives have been developed including methods using enzymatic reaction and multistep synthsis from a chiral natural intermediate. [7-12]



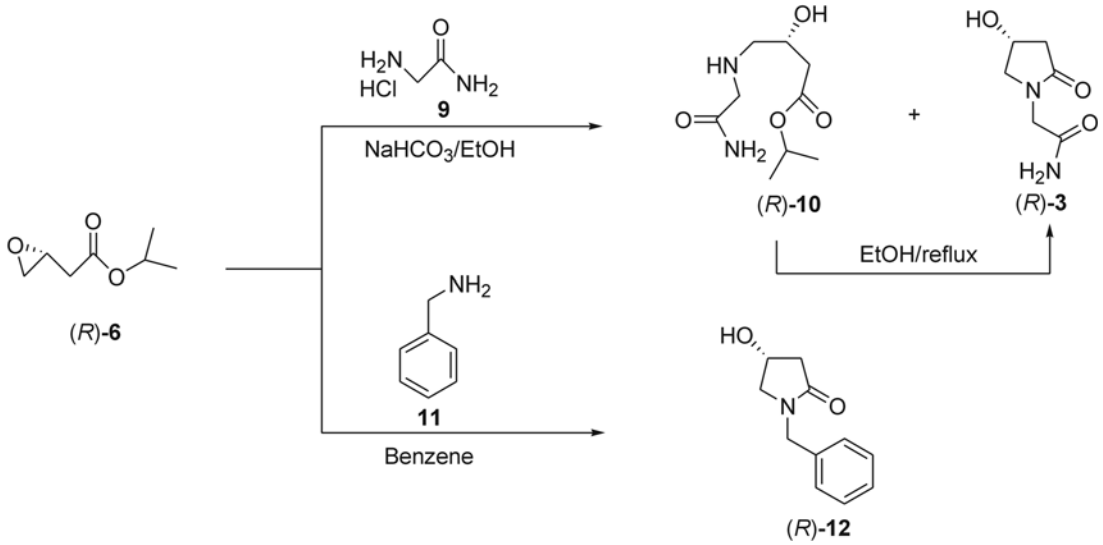
1 **2** **3**

Recently, we reported an efficient synthetic method for chiral epoxides using asymmetric epoxidation of olefins[13,14] and have also tried to use the chiral epoxides for the synthesis of optically active amino alcohols which are important intermediates for the synthesis of chiral drugs and natural products. For example, we were able to synthesize chiral cathinone and ephedrine derivatives efficiently from a chiral aryl epoxide.[15] In a continuation of this research, we found that chiral *N*-substituted 4-hydroxypyrrolidin-2-one derivatives such as oxiracetame can also be readily prepared from the reaction between chiral epoxide and amines. Thus, here we report a simple synthetic method for (*R*)-*N*-substituted 4-hydroxypyrrolidin-2-ones from a chiral 3,4-epoxybutanoic acid ester.

In order to synthesize the chiral 3,4-epoxybutanoic acid ester that is the key intermediate for this research, we decided to use Jacobson's hydrolytic kinetic resolution reaction of racemic epoxide.[16-19] Thus, we prepared epoxide (*R*)-**6** from crotonyl chloride **4** according to the Scheme 1. In the esterification of crotonyl chloride **4**, we found that the double bond was shifted to terminal position to give olefin **5**.[20,21] The olefin **5** was oxidized *in situ* by *m*-CPBA to produce racemic epoxide (±)-**6**, that was distilled under reduced pressure to afford colorless liquid, (±)-**6** in 73% yield (2-steps). The kinetic resolution of epoxide (±)-**6** by 0.5 equivalent of H_2O was performed with 2 mol % of the Jacobson's Co-salen (III) complex, (*R*)-**8**, prepared *in situ* from the (*R,R*)-(-)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine cobalt (II) in the presence of acetic acid under air. The reaction, which was followed by GC analysis, was completed within 15 hours. After the resolution was complete, epoxide (*R*)-**6** was isolated by partitioning the products between hexane and water. It was



Scheme 1. Synthesis of chiral epoxide, (*R*)-6.



Scheme 2. Syntheses of (*R*)-oxiracetame, (*R*)-3 and (*R*)-*N*-benzyl-4-hydroxypyrrolidin-2-one, (*R*)-12.

found that the hexane phase contained epoxide (*R*)-**6** and residual catalyst (*R*)-**8**, while the diol (*S*)-**7** was remained in water. The distillation of mixtures of epoxide (*R*)-**6** and residual catalyst (*R*)-**8** under reduced pressure afforded the chiral epoxide (*R*)-**6** in 84% yield and 99% ee.

To prepare the (*R*)-oxiracetame, (*R*)-**3**, the epoxide (*R*)-**6** was reacted with glycinamide hydrochloride **9** in the presence of $NaHCO_3$ (Scheme 2). The reaction produced (*R*)-**3** in 31% yield along with the intermediate (*R*)-**10** in 15% yield. The isolated (*R*)-**10** was readily cyclized in refluxing ethanol to give (*R*)-oxiracetame in 80% yield indicating that (*R*)-oxiracetame can be obtained from the epoxide (*R*)-**6** in overall 43% yield. We tried to optimize the reaction condition to improve the total yield of (*R*)-**3** and (*R*)-**10**. However, the combined total yield was always remained in *ca*. 45-50%.

Similarly, we also synthesized (*R*)-*N*-benzyl-4-hydroxypyrrolidin-2-one, (*R*)-**12**, from the reaction between the epoxide, (*R*)-**6** and benzylamine **11** in 47% yield. In this reaction, we were not able to isolate any ring-opened intermediate.

In summary, we have developed a simple and practical synthetic method for enantiomerically pure *N*-substituted 4-hydroxypyrrolidin-2-one derivatives such as (*R*)-**3** and (*R*)-**12** from the readily available crotonyl chloride, **4**.

Experimental Section

Generals. Chemicals were supplied by Aldrich and Merck. $CHCl_3$, benzene and ethanol were purified by standard procedures. Meting points were taken on a Mel-Temp 3.0 (Laboratory Devices Inc., USA) melting point apparatus. The ^1H and ^{13}C NMR spectra were obtained using Varian AS-400 spectrometer at 400 MHz and 100 MHz and Jeol JNM-AL300 spectrometer at 300 MHz and 75 MHz respectively with tetramethylsilane as the internal reference. MS spectra were obtained on a Jeol JMS-700 spectrometer. Optical rotations were taken on an AUTOPOL® III automatic polarimeter (Rudolph Research Inc). GC spectra were obtained on a Younglin M600D. Flash column chromatography was performed with Merck silicagel 60 (70-230 mesh).

***iso*-Propyl 3,4-epoxybutanoate, (±)-6.** *iso*-Propyl alcohol (21 mL, 270 mmol), triethylamine (32 mL, 230 mmol) and benzene (57 mL) were placed in a round-bottomed flask. Crotonyl chloride **4** (18 mL, 190 mmol) was added slowly into the mixture with stirring at 0 °C. After 30 min, the slurry was filtered through Celite to remove $Et_3N{\cdot}HCl$, and concentrated *in vacuo* to provide the crude *iso*-propyl 3-butenoate **5**. Into a stirred solution of *m*-CPBA (40 g, 230 mmol) in $CHCl_3$ (300 mL) held at 0 °C was added the above crude *iso*-propyl 3-butenoate **5** for 30 min. The mixture was stirred overnight at room temperature. The reaction mixture was filtered to remove *m*-chlorobenzoic acid, washed with saturated aqueous $NaHCO_3$ and dried with $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by distillation under reduced pressure to afford colorless liquid product (±)-**6** (20 g, 73% two steps).

R_f 0.7 (hexane : ethyl acetate = 2 : 1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.09-5.03 (m, 1H, -O-C<u>H</u>-$(CH_3)_2$), 3.31-3.27 (m, 1H, H-C(3)), 2.76 (dd, 1H, J_1 = 4.4 Hz, J_2 = 8.8 Hz, H-C(4)), 2.48 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.4 Hz, H-C(4)), 2.54-2.51 (m, 2H, H-C(2)), 1.26 (d, 6H, J = 6.4 Hz, -CH-(C<u>H</u>$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.42 (-CO), 67.94 (C(2)), 47.74 (C(3)), 46.28 (C(4)), 38.04 (-<u>C</u>H-$(CH_3)_2$), 21.52 (-CH-(<u>C</u>$H_3)_2$); MS(EI) *m/e* 145 (M^+), 129, 102, 86, 71, 60, 58, 54.

Hydrolytic kinetic resolution of *iso*-propyl 3,4-epoxybutanoate, (±)-6. *iso*-Propyl 3,4-epoxybytanoate (±)-**6** (15 g, 100 mmol), (*R,R*)-(−)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine cobalt (II) (1.3 g, 2.1 mmol), acetic acid (0.24 mL, 4.1 mmol) were placed in 25 mL round-bottom flask. The flask was cooled to 0 °C, to which were added THF (1.0 mL) and H_2O (0.93 mL, 52 mmol). The reaction was allowed to warm up to room

temperature and stirred for 15 hr. The reaction monitored by GC analysis (Hewlett Packard HP-101 column) indicated diol **7** to present in 50% yield. Hexane (100 mL) was added, and filtered to remove Co-salen (III) catalyst. The residue was stirred with a 1 : 1 hexane: water mixture (200 mL) and separated. The hexane layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to afford colorless liquid (*R*)-**6** (6.2 g, 84%). The optical purity determined with Supelco chiral cyclo α-DEX GC column was 99%ee. $[\alpha]_D^{25}$ = +7.0 (c = 0.5, $CHCl_3$).

(*R*)-4-Hydroxy-2-oxopyrrolidine-*N*-acetamide, (*R*)-3 (Oxiracetame). (*R*)-*iso*-Propyl 3,4-epoxybutanoate (*R*)-**6** (1.4 g, 10 mmol), $NaHCO_3$ (0.84 g, 10 mmol), glycinamide ·HCl (**9**, 1.1 g, 10 mmol) and ethanol (10 mL) were stirred and refluxed for 24 hr. After completion of the reaction, the warm reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford the white solid (*R*)-**3** (0.49 g, 31%), and (*R*)-**10** (0.35 g, 15%).

(*R*)-10: R_f 0.6 ($CHCl_3$: methanol = 8 : 3); m.p. 80-81 °C; $[\alpha]_D^{25}$ = +10.2 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H, -N<u>H</u>$_2$), 6.09 (s, 1H, -N<u>H</u>$_2$), 5.09-5.01 (m, 1H, -O-C<u>H</u>-(CH_3)$_2$), 4.14-4.10 (m, 1H, -C<u>H</u>OH-), 3.31 (s, 2H, -N<u>H</u>-, -O<u>H</u>), 2.74-2.40 (m, 6H, -CO-C<u>H</u>$_2$-NH-C<u>H</u>$_2$-CHOH-C<u>H</u>$_2$-CO-), 1.25 (d, 6H, J = 6.0 Hz, -CH-(C<u>H</u>$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.98 (-CO-), 171.99 (-CO-), 68.40 (-<u>C</u>HOH-), 66.86 (-CHOH-<u>C</u>H$_2$-NH-), 54.72 (-NH-<u>C</u>H$_2$-CO-NH$_2$), 52.12 (-CHOH-<u>C</u>H$_2$-COO-), 39.48 (-<u>C</u>H-(CH_3)$_2$), 21.74 (-CH-(<u>C</u>H$_3$)$_2$); MS(EI) *m/e* 219 (M^+), 218, 200, 174, 156, 142, 132, 114, 96, 87, 84, 72, 70, 59.

(*R*)-3: R_f 0.4 ($CHCl_3$: methanol = 8 : 3); m.p 163-167 °C (Merck index 165-168); $[\alpha]_D^{25}$ = +34.4 (c = 0.5, H_2O) [ref.[22] +36.4 (c = 1.0, H_2O)]; ^{1}H NMR (400 MHz, DMSO) δ 7.30 (s, 1H, -N<u>H</u>$_2$), 7.11 (s, 1H, -N<u>H</u>$_2$), 5.21 (d, 1H, J = 4.4 Hz, -O<u>H</u>), 4.30-4.25 (m, 1H, -C<u>H</u>OH-), 3.85 (d, 1H, J = 16.8 Hz, -N-C<u>H</u>$_2$-CO-NH$_2$), 3.64 (d, 1H, J = 16.8 Hz, -N-C<u>H</u>$_2$-CO-NH$_2$), 3.60 (dd, 1H, J_1 = 10.2 Hz, J_2 = 6.0 Hz, -NC<u>H</u>$_2$-CHOH-), 3.13 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.0 Hz, -N-C<u>H</u>$_2$-CHOH-), 2.54 (dd, 1H, J_1 = 16.8 Hz, J_2 = 6.0 Hz, -CO-C<u>H</u>$_2$-CHOH-), 2.06 (dd, 1H, J_1 = 16.8 Hz, J_2 = 2.0 Hz, -CO-C<u>H</u>$_2$-CHOH-); ^{13}C NMR (100 MHz, DMSO) δ 172.92 (-<u>C</u>ON-), 169.83 (-<u>C</u>ONH$_2$), 63.49 (-<u>C</u>HOH-), 56.93 (-N<u>C</u>H$_2$-CHOH-), 44.96 (-N-<u>C</u>H$_2$-CO-NH$_2$), 40.54 (-CO-<u>C</u>H$_2$-CHOH-); MS (EI) *m/e* 159 (M^+), 140, 123, 115, 114, 97, 96, 84, 72, 71, 59, 55.

Oxiracetame (*R*)-3 [from the (*R*)-10]. (*R*)-**10** (0.80 g, 3.4 mmol) was dissolved in ethanol (5 mL). The solution was stirred and refluxed for 24 hr. The reaction mixture was cooled to room temperature and filtered. The solvent was removed under reduced pressure. The residue was purified by column chromatography to afford the white solid (*R*)-**3** (0.43 g, 80%).

(*R*)-*N*-Benzyl-4-hydroxypyrrolidin-2-one, (*R*)-12. (*R*)-*iso*-Propyl 3,4-epoxybutanoate (*R*)-**6** (0.50 g, 3.5 mmol) and benzylamine **11** (0.38 mL, 3.5 mmol) were dissolved in benzene (5 mL). The solution were stirred and refluxed for 18 hr. The reaction mixture was cooled to room temperature and filtered. The solvent was removed under reduced pressure. The residue was purified by column chromatography to afford the (*R*)-**12** (0.31 g, 47%).

R_f 0.2 (ethyl acetate); m.p. 105-106 °C [ref[11] (*S*)-**12**, 107.5-109 °C]; $[\alpha]_D^{25}$ = +32.4 (c = 0.5, $CHCl_3$), [ref.[11] (*S*)-**12**, –35.2 (c = 1.3, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H, aromatic H), 4.52-4.40 (m, 3H, -N-C<u>H</u>$_2$Ph, -C<u>H</u>OH-), 3.49 (dd, 1H, J_1 = 11.2 Hz, J_2 = 5.6 Hz, -N-C<u>H</u>$_2$-CHOH-), 3.20 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.0 Hz, -N-C<u>H</u>$_2$-CHOH-), 2.72 (dd, 1H, J_1 = 17.4 Hz, J_2 = 6.4 Hz, -CO-C<u>H</u>$_2$-CHOH-), 2.44 (dd, 1H, J_1 = 17.4 Hz, J_2 = 2.0 Hz, -CO-C<u>H</u>$_2$-CHOH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.75 (-<u>C</u>O-), 135.86, 128.63, 127.91, 127.54 (aromatic C), 64.33 (-<u>C</u>HOH), 55.71 (-N-<u>C</u>H$_2$Ph), 46.34 (-N-<u>C</u>H$_2$-CHOH-), 41.20 (-CO-<u>C</u>H$_2$-CHOH-); MS(EI) *m/e* 191(M^+), 146, 132, 118, 104, 91, 89, 65, 57.

Acknowledgement. This work was supported by the Kyung Hee University Research Fund in 2004 (20040211).

References

1. Miyauchi, M.; Endo, R.; Hisaoka, M.; Yasuda, H.; Kawamoto, I. *J. Antibiot.* **1997**, *50*, 429.
2. Mulzer, J.; Zuhse, R.; Schmiechem, R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 870.
3. Pifferi, G.; Pinza, M. *US 4118396*, **1978**.
4. Aschwanden, W.; Kyburz, E. *US 4,476,308*, **1984**.
5. Iriuchijima, S.; Kobayashi, H.; Aoki, K.; Oda, T.; Shinoyama, M.; Nosaka, Y. *US 4,686,296*, **1987**.
6. Pinza, M.; Pfeiffer, U. C. *US 4,797,496*, **1989**.
7. Almeida, J. F.; Anaya, J.; Martin, N.; Grande, M.; Moran, J. R.; Carballero, M. C. *Tetrahedron: Asymmetry* **1992**, *3*, 1431.
8. Monguzzi, R.; Pifferi, G.. *US 4,124,594*, **1978**.
9. Chiodini, L.; Pepeu, G. *WO 93/06826*, **1993**.
10. Banfi, S.; Dugnano, P.; Pellegata, R.; Pifferi, G.; Pinza, M. *US 4,173,569*, **1979**.
11. Huang, P. Q.; Zheng, X.; Wang, S. L.; Ye, J. L.; Jin, L. R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 3309.
12. Chang, D.; Witholt, B.; Li, Z. *Org. Lett.* **2000**, *2*, 3949.
13. Ahn, K.-H.; Park, S. W.; Choi, S.; Kim, H.-J.; Moon, C. J. *Tetrahedron Lett.* **2001**, *42*, 2485.
14. Jeong, Y.-C.; Choi, S.; Yu, K.; Ahn, K.-H. *Bull. Korean Chem. Soc.* **2003**, *24*, 537.
15. Choi, S., *Master thesis*; Kyung Hee university, 2002.
16. Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.
17. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *227*, 936.
18. Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.
19. Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086.
20. Ozeki, T.; Kusaka, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1995.
21. Panek, J. S.; Liu, P. *J. Am. Chem. Soc.* **2000**, *122*, 11090.
22. Miyamoto, S.; Mori, A. *Neuroscience* **1985**, *11*, 1.