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An asymmetric aminohydroxylation approach to the stereoselective synthesis of *cis*-substituted azetidinone of loracarbef

Jong-Cheol Lee,[a,b] Geun Tae Kim,[a] Young Key Shim[b] and Sung Ho Kang[a,*]

[a]*Dept. of Chemistry, Korea Advanced Institute of Science and Technology, Taejon 305-701, South Korea*
[b]*Bio-Organic Division, Korea Research Institute of Chemical Technology, Taejon 305-600, South Korea*

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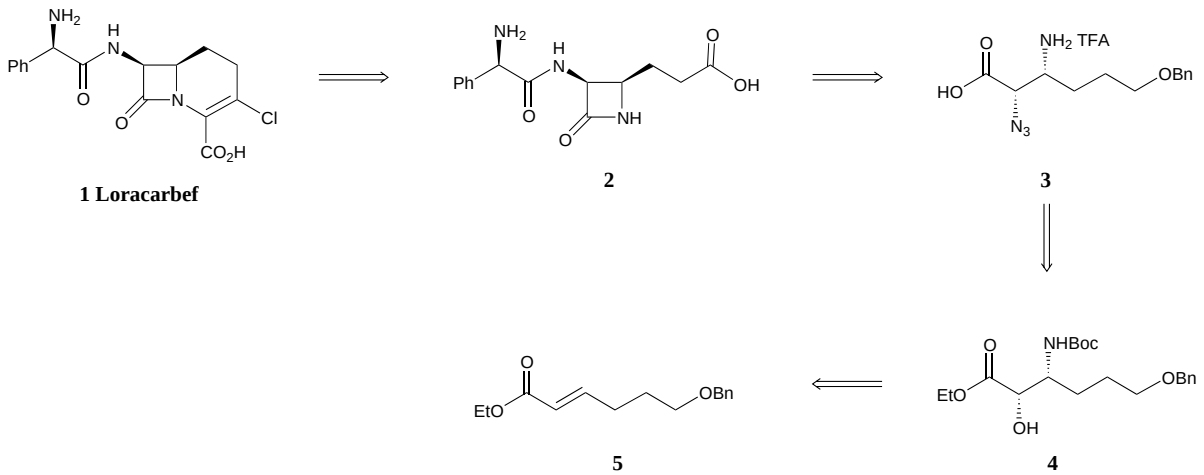
Abstract—A formal synthesis of loracarbef is described. The required key *cis*-substituted azetidinone skeleton was stereoselectively constructed via β-amino acid, which was provided from the asymmetric aminohydroxylation of α,β-unsaturated ester.

Loracarbef is a carbacephalosporin antibiotic with the extended chemical and serum stability.[1] This oral antibiotic is currently on the market and has found specialized use in the treatment of paediatric ear infections. However, unlike cephalosporins, which are usually obtained by partial synthesis from either penicillin sulfoxide esters or side-chain modification of 7-aminocephalosphoranic acid(7-ACA), carbacephalosporins are currently available only by total synthesis.[2]

There are many elegant syntheses of loracarbef.[2–4] It is well known that the most direct access to loracarbef is the utilization of a *cis*-(3*S*,4*R*)azetidinone **2**. Many published syntheses of this key intermediate utilize the classical [2+2] ketene-imine cyclization (Staudinger reaction)[3] or cyclization of β-hydroxy-α-amino acids.[4]

Our synthetic plan for the construction of the *cis*-substituted azetidinone is illustrated in Scheme 1. The α-azido-β-amino acid **3** could be obtained via Sharpless



Scheme 1.

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* Corresponding author.

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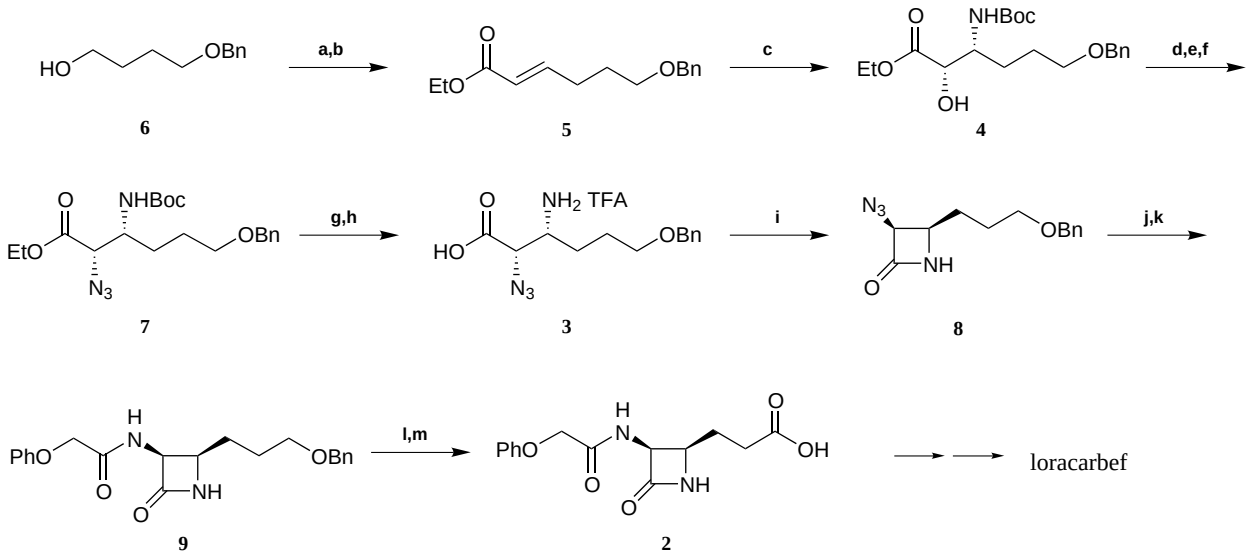

Scheme 2. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 88%; (b) $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, CH_3CN, 0°C, 82%; (c) *t*-Butylcarbamate, NaOH, *t*-BuOCl, $(DHQD)_2PHAL$ (6 mol%), $K_2[OsO_2(OH)_4]$ (4 mol%), *n*-PrOH–H_2O (2/1), 0°C, 65%; (d) $C_6H_5CO_2H$, DEAD, Ph_3P, THF, 84%; (e) K_2CO_3, MeOH, 95%; (f) HN_3 (1.0 mol solution in benzene), DEAD, Ph_3P, THF, 80%; (g) K_2CO_3, MeOH–H_2O (2/1); (h) TFA, 0°C; (i) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_3CN, rt–55°C, 45% (three steps); (j) Ph_3P, THF–H_2O (25/1); (k) $PhOCH_2COCl$, CH_3CN–aq. $NaHCO_3$, 75% (two steps); (l) H_2, 10% Pd–C, EtOH; (m) Jones reagent, acetone, 0°C, 72% (two steps).

asymmetric aminohydroxylation[5] of α,β-unsaturated ester **5** followed by introduction of azide. The intramolecular cyclization of **3** would afford the required *cis*-substituted azetidinone skeleton possessing the appropriate functionalities for further transformation. Introduction of the phenoxy acetyl group and oxidation of primary alcohol would furnish **2**, which is the same intermediate reported by Ternansky et al. at Eli Lilly.[6] Compound **2** was set as the target molecule for our synthetic study.

According to the synthetic plan, monoprotected 1,4-butanediol **6** was then oxidized to the aldehyde (88%), which was subjected to Horner–Emmons olefination with triethyl phosphonoacetate to obtain the α,β-unsaturated ester **5** in 82% yield. The asymmetric aminohydroxylation of **5** with the sodium salt of *t*-butylcarbamate and a 4 mol% $K_2[OsO_2(OH)_2]$/6 mol% $(DHQD)_2PHAL$ admixture in *n*-PrOH–water led to the desired regioisomer [2*S*,3*R*]-**4** in good yield with high regioselectivity (>13:1) and enantioselectivity (89% ee)[7] (Scheme 2).

Next, introduction of the required azide group into α-position of [2*S*,3*R*]-**4** with retention of configuration was accomplished by double Mitsunobu reactions. Treatment of [2*S*,3*R*]-**4** with benzoic acid, Ph_3P, and DEAD afforded the benzoate (84%), which was easily hydrolyzed with K_2CO_3 in MeOH to give the inverted [2*R*,3*R*]-alcohol (95%) at the α-position. Subsequently, the resulting alcohol was treated with a 1.0 mol solution of HN_3 in benzene, Ph_3P, and DEAD to afford [2*S*,3*R*]-**7** in 80% yield. Hydrolysis of the ester **7** with K_2CO_3 in MeOH–water and subsequent TFA deprotection gave a quantitative yield of the β-amino acid **3**. Intramolecular cyclization of **3** using a Mukaiyama's condition[8] afforded the *cis*-substituted azetidinone **8** in 45% yield for the three steps.

Reduction of the azide functionality of **8** with Ph_3P in THF and water, followed by acylation with phenoxyacetyl-chloride in CH_3CN and aq. $NaHCO_3$ provided **9** in 75% yield. Finally, deprotection of the benzyl group of **9** and the following treatment with Jones reagent afforded the desired *cis*-3,4-disubstituted azetidinone **2** in 72% yield.

In conclusion, a formal synthesis of loracarbef was accomplished with high stereoselectivity. The stereoselective construction of the key intermediate *cis*-3,4-disubstituted azetidinone **2** was performed by employing intramolecular cyclization of β-amino acid **3** which was provided from the asymmetric aminohydroxylation of α,β-unsaturated ester **5**.

We are currently undertaking further investigation in our laboratories to enhance the scope of this process for a large-scale production.

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References

1. (a) First public disclosure of loracarbef: Hirata, T.; Matsukuma, I.; Mochida, K.; Sato, K. Presented at the 27th

Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 4–7 October 1987; (b) Sato, K.; Okachi, R.; Matsukuma, I.; Mochida, K.; Hirata, T. *J. Antibiot*. **1989**, *42*, 1844.

2. For a recent review of carbacephalosporins, see: Zhang, T. Y.; Hatfield, L. D. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Scriven, E. F. V.; Rees, C. W., Eds.; Elsevier: London, 1996; Vol. 1, Chapter 20.
3. (a) Matsukuma, I.; Yoshiiye, S.; Mochida, K.; Hashimoto, Y.; Sato, K.; Okachi, R.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 1239; (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett*. **1985**, *26*, 3787; (c) Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem*. **1987**, *59*, 485.
4. (a) Guzzo, P. R.; Miller, M. J. *J. Org. Chem*. **1994**, *59*, 4862; (b) Lotz, B. T.; Miller, M. J. *J. Org. Chem*. **1993**, *58*, 618; (c) Jackson, P. G.; Pedersen, S. W.; Fisher, J. W.; Misner, J. W.; Gardner, J. P.; Staszak, M. A.; Doecke, C.; Rizzo, J.; Aikins, J.; Farkas, E.; Trinkle, K. L.; Vicenzi, J.; Reinhard, M.; Kroeff, E. P.; Higginbotham, C. A.; Gazak, R. J.; Zhang, T. Y. *Tetrahedron* **2000**, *56*, 5667.
5. (a) Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 451; (b) O'Brien, P. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 326.
6. Deeter, J. B.; Hall, D. A.; Jordan, C. L.; Justice, R. M.; Kinnick, M. D.; Morin, Jr., J. M.; Paschal, J. W.; Ternansky, R. J. *Tetrahedron Lett*. **1993**, *34*, 3051.
7. Typical procedure for the synthesis of **4**. A 50 mL round-bottomed flask was charged with *t*-butyl carbamate (364 mg, 3.10 mmol) and *n*-propanol (4 mL). To this stirred solution was added a freshly prepared aqueous solution of NaOH (122 mg, 3.05 mmol in 8 mL water), followed by *t*-butyl hypochlorite (0.35 mL, 3.05 mmol). After stirring for 5 min, a solution of $(DHQD)_2PHAL$ (47 mg, 0.06 mmol) in *n*-propanol (4 mL) was added; the reaction mixture should be homogeneous at this point. Then, a solution of the conjugate ester **5** (248 mg, 1.00 mmol, dissolved in 8 mL of *n*-propanol) was added, followed by addition of $K_2OsO_2(OH)_4$ (14.8 mg, 0.04 mmol). After 1 h at 0°C, the green solution became pale yellow and there was no starting material present by TLC analysis. Saturated aqueous sodium sulfite solution (7 mL) was added and the solution was stirred for 30 min. Then, the two layers were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (25–33% EtOAc–*n*-hexane gradient elution) to afford the desired product (2*S*,3*R*)-6-benzyloxy-3-*tert*-butoxycarbonylamino-2-hydroxy-hexanoic acid ethyl ester **4** (251 mg, 66% yield, 89% ee) as an oil and the regioisomer (2*S*,3*R*)-6-benzyloxy-2-*tert*-butoxycarbonylamino-3-hydroxy-hexanoic acid ethyl ester (19 mg, 5.0% yield) as an oil. Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.31 (m, 5H), 4.79 (br s, 1H), 4.46 (s, 2H), 4.26 (q, $J=6.9$ Hz, 2H), 4.15 (d, $J=2.6$ Hz, 1H), 3.96–4.05 (m, 1H), 3.46–3.49 (m, 2H), 1.65–1.75 (m, 4H), 1.41 (s, 9H), 1.27 (t, $J=6.9$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.99, 26.31, 28.14, 28.20, 29.12, 52.60, 62.03, 69.82, 72.27, 72.84, 79.57, 127.45, 127.57, 128.29, 138.44, 155.31, 173.64; CIHRMS *m*/*z* calcd for $C_{20}H_{32}NO_6(M+H^+)$ 382.2229, found 382.2207; $[\alpha]_D^{27}=+33.7$ ($c=0.95$, $CHCl_3$). The enantiomeric excess of **4** indicated 89% ee by chiral shift analysis with $Eu(hfc)_3$ on the corresponding MTPA ester and **4** was used as its present optical purity without further purification.

(2*S*,3*R*) - 6 - Benzyloxy - 2 - *tert* - butoxycarbonyl - amino - 3-hydroxy-hexanoic acid ethyl ester: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.28 (m, 5H), 5.34 (br s, 1H), 4.47 (s, 2H), 4.17 (q, $J=6.9$ Hz, 2H), 4.10 (d, $J=2.6$ Hz, 1H), 4.07–4.11 (m, 1H), 3.42–3.45 (m, 2H), 1.56–1.78 (m, 4H), 1.40 (s, 9H), 1.25 (t, $J=6.9$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.90, 26.01, 28.01, 28.11, 28.99, 58.80, 64.10, 69.62, 70.70, 73.37, 79.77, 126.55, 126.87, 127.89, 137.34, 156.30, 174.60; $[\alpha]_D^{27}=+30.2$ ($c=0.95$, $CHCl_3$).

8. Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett*. **1984**, 1465.