CHEMISTRY LETTERS, pp. 1245−1248, 1991.

Synthesis of Optically Pure 4-Hydroxymethyloxazolidinone as Chiral Serinol Synthon from Glycidol

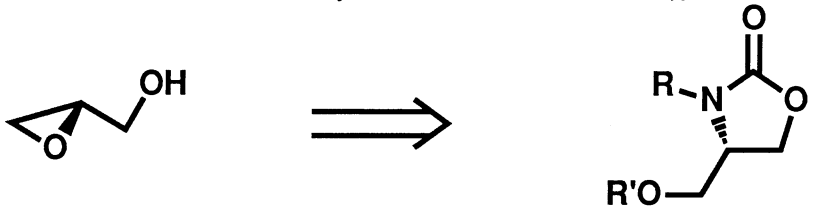
Shigeo KATSUMURA,* Akihiro KONDO, and Qingjun HAN
Faculty of Science, Kwansei Gakuin University,
Uegahara 1-1-155, Nishinomiya, Hyogo 662

Optically pure 3-benzyl-4-hydroxymethyl-2-oxazolidinone and 4-benzoyloxymethyl-2-oxazolidinone as chiral serinol synthons were synthesized from optically active glycidol by intramolecular cyclization via 2,3-epoxycarbamates with strict S_N2 behavior.

Development of new and easily obtainable chiral synthons for various β–substituted-α-amino acids is very important because of the wide range of biological activities exhibited by these molecules. Synthesis of oxazolidine aldehyde as a chiral synthon for β-hydroxy-α-amino acid from serine by Garner is one of the striking solution for this subject,[1] and wide application of this aldehyde to syntheses of sphingolipids, amino acids and amino sugars has proved how important the development of such fundamental chiral synthon is.[2] Most of other approach for synthesis of β-hydroxy-α-amino acids from non amino acids is the utilization of Sharpless asymmetric epoxydation to the appropriate allyl alcohols followed by oxazolidinone ıormation with intramolecular fashion,[3] and is use of sugar as a chiral source.[4,5]

Chiral glycidol bearing highly enantiometric purity has been available based on a biological resolution of epichlorohydrin very recently,[6] and is quite attractive molecule as a source of oxazolidinone derivatives which are not only an ideal chiral synthon for β-hydroxy-α-amino acids but also an ideal chiral auxiliary similar to that derived from amino acids.[7]

We now describe a synthesis of optically pure hydroxymethyloxazolidinone derivatives 2 and 7 as chiral synthons having least carbon unit from glycidol via intramolecular cyclization of both 2,3-epoxy-*N*-benzylcarbamate 1 and -*N*-benzoylcarbamate 6 with strict S_N2 behavior.

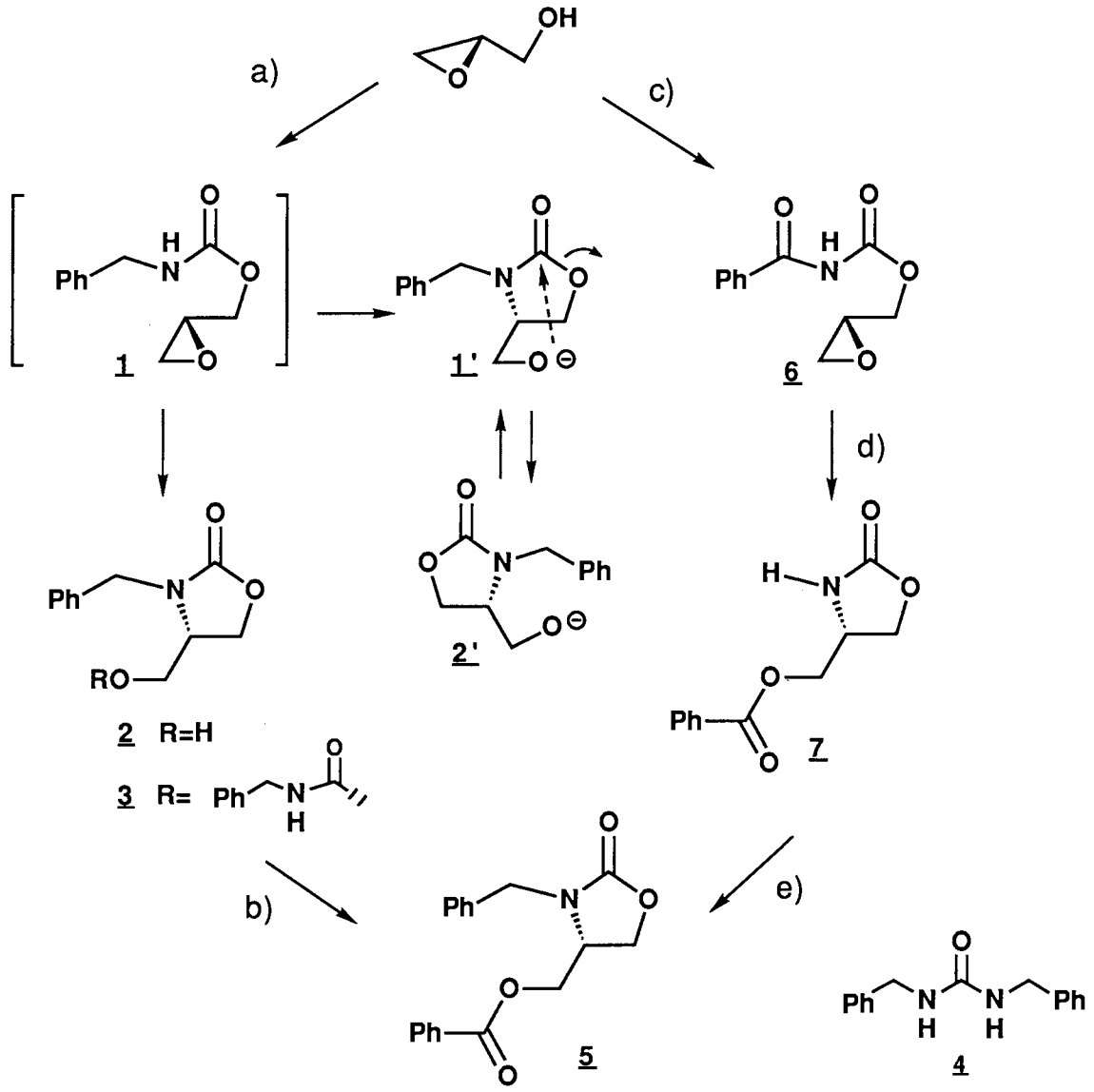


In the preceding papers mentioned about the intramolecular formation of oxazolidinone from 2,3-epoxy-*N*-protected carbamate, isomerization of oxazolidinone ring resulting from acyl transfer from the initially cyclized product was reported as a serious problem in *N*-benzyl compound of 2,3-epoxycarbamate.[3b] In the case of *N*-benzoyl compound of 2,3-epoxycarbamate, benzoyl group is

rearranged from nitrogen of amide to hydroxyl group without isomerization of oxazolidinone ring. Hydrolysis of the resulting *O*-benzoyl group, however, accompanies the isomerization of oxazolidinone in some case.[3d] Probably because these procedures involved initial generation of epoxycarbamate like 1 and subsequent treatment with base, the resulting alcoholate anion of 1' might attack the amide carbonyl group intramoleculary to give its enantiomer 2'.

Keeping the above precedents in mind, we tried to synthesize both optically pure oxazolidinones. Treatment of R-(+)-glycidol, $[\alpha]_D$ +22.2° (c 1.1, $CHCl_3$)(98% ee), with benzylisocyanate (1 equiv., 1.5 M solution of CH_2Cl_2, 35-45 °C, 18 h) in the presence of triethylamine(1.8 equiv.) afforded the desired oxazolidinone 2 in 84% yield as crystals, mp 74-75 °C, $[\alpha]_D$ +29.8°(c 1.03, $CHCl_3$).[8] *N*-Benzylcarbonyl ester of hydroxymethyloxazolidinone 3 and dibenzylurea 4,[9] which showed the same R_f value on TLC of silica gel and were separated by recrystalizations, were obtained as by-products of this reaction.[3f] Use of other bases for cyclization gave unsatisfactory results, for example, reaction with sodium imidazolate in THF[3d] increased the formation of by-products 3 and 4, and treatment with sodium hydrid in THF[3b] or with DBU in CH_2Cl_2 gave decomposed products. The intermediary epoxycarbamate 1, which was isolable quantitatively by a treatment with triethylamine under ice-cooling, afforded desired 2 by the same reaction conditions as mentioned above in less satisfactory yield. *N*-Benzyloxazolidinone 2 obtained above was led to benzoate 5, mp 46-47 °C, $[\alpha]_D$ -35.1°(c 0.87, $CHCl_3$)(benzoyl chloride, triethylamine, DMAP/CH_2Cl_2). The enantiometric purity of the benzoate 5, therefore 2, was determined by a comparison with the one derived from hydroxymethyloxazolidinone-*O*-benzoate 7 by benzylation written as follows.

Glycidol possessing the same enantiometric purity as the one used above was treated with benzoylisocyanate(CCl_4, room temperature) gave epoxycarbamate 6 quantitatively which was treated with potassium carbonate in the presence of benzyltriethylammonium chloride (CH_2Cl_2 / H_2O=1/1, room temperature, 2 h) to afford 4-benzoyloxymethyl-2-oxazolidinone (7) as crystals, mp 112-113 °C, $[\alpha]_D$ +29.6°(c 1.09, $CHCl_3$) in 87% yield. Sodium imidazolate(0.2 equiv.) as a base in dimethyl sulfoxide or acetonitrile[3d] gave less satisfactory results, poorer yield and partial racemization. *N*-Benzylation of benzoate 7 (NaH, benzylbromide, tetraethylammonium iodide / THF-DMF, room temperature) afforded *N*-benzyl derivative 5, $[\alpha]_D$ -34.8°(c 1.31, $CHCl_3$), which was identical with the one derived from 2, and whose value of the optical rotation showed that 2 possessed the same optical purity as the one of 7. Treatment of 5 with base(LiOH in THF-H_2O, Cs_2CO_3 in MeOH, or K_2CO_3 in MeOH) resulted in racemization actually as reported.[3d] Treatment of 5, however, with sodium borohydride went back to 2 without any racemization(0.5 equiv. $NaBH_4$ in EtOH, 79%). Optical purity of 7 was determined by two ways. High performance liquid chromatography of (+)-7 using chiral column showed no peak which corresponded to the other enantiomer.[10] Another way is a direct comparison of 7 derived from (+)-glycidol with the one synthesized independently from (L)-serine . The absolute value of the optical rotation of both compounds was identical.[11] These results demonstrate that the reaction proceeded completely in a S_N2 manner via intermediates 1 and 6 respectively. The mildness of the reaction conditions compared to the reported methods may prevent significant racemization of the products 2 and 7.



a) $PhCH_2NCO$, Et_3N / CH_2Cl_2 b) $PhCOCl$, Et_3N, DMAP / CH_2Cl_2
c) $PhCONCO$ / CCl_4 d) K_2CO_3, $PhCH_2N^+Et_3Cl^-$ / CH_2Cl_2-H_2O
e) NaH, $PhCH_2Br$, Et_4NI / THF-DMF

Thus, optically pure chiral synthons, 2 and 7 were synthesized efficiently from chiral glycidol. Since hydroxymethyl oxazolidinone 2 is transformed into its methyl ester easily(Jones oxidation, diazomethane treatment) and since nitrogen of 7 is protected with *t*-butoxycarbonyl, benzyloxycarbonyl, or trialkylsilyl groups, oxazolidinone 2 and 7 would be concise chiral synthons for synthesis of sphingolipids and β-hydroxy-α-amino acids. The study along this line is now in progress.

We are grateful to Daiso Co. Ltd. for the supply of optically pure glycidol.

References

1) P. Garner and J. M. Park, *J. Org. Chem.*, 52, 2361(1987).

2) P. Garner, J. M. Park, and E. Malecki, *J. Org. Chem.*, 53, 4395(1988); S. Nimkar, D. Menaldino, A. H. Merrill, and D. Liotta, *Tetrahedron Lett.*, 29, 3037(1988); P.Herold, *Helv. Chim. Acta*, 71, 354(1988); P. Garner and J. M. Park, *J. Org. Chem.*, 55, 3772(1990) and references cited there in; N. Sakai and Y. Ohfune, *Symposium paper of 32nd Symposium on the Chemistry of Natural Products*, p662, Chiba(1990), and references cited there in.

3) a) N. Minami, S. S. Ko, and Y. Kishi, *J. Am. Chem. Soc.*, 104, 1109(1982); b) W. R. Roush and M. A. Adam., *J. Org. Chem.*, 50, 3752(1985); c) B. Bernet and A. Vessella, *Tetrahedron Lett.*, 24, 5491(1983); d) S. W. McCombie and T. L. Nagabhushan, *Tetrahedron Lett.*, 28, 5359(1987); e) S. Knapp, P. J. Kukkola, S. Sarma, and S. Pietranico, *Tetrahedron Lett.*, 28, 5399 (1987); S. Knapp, P. J. Kukkola, S. Sarma, T. G. M. Dhar, and A. B. J. Naughton, *J. Org. Chem.*, 55, 5700(1990); f) M. E. Jung and Y. H. Yung, *Tetrahedron Lett.*, 30, 6637(1989).

4) For example, K. Ohashi, Y. Yamagiwa, T. Kamikawa, and M. Kates, *Tetrahedron Lett.*, 29, 1185(1988); K. Ohashi, S. Kosai, M. Arizuka, T. Watanabe, M. Fukunaka, K. Monden, T. Uchikoda, Y. Yamagiwa, and T. Kamikawa, *ibid.*, 29, 1189(1988); A. V. R. Rao, J. S. Yadav, S. Chandrasekhar, and C. S. Rao, *Tetrahedron Lett.*, 30, 6769(1989); M. M. Campbell, A. J. Floyd, T. Lewis, M. F. Mahon and R. J. Ogilvie, *Tetrahedron Lett.*, 30, 1193(1989); A. Dureault, F. Carreaux and J. C. Depezay, *Tetrahedron Lett.*, 30, 4527(1989).

5) As an another approach, intramolecular conjugated addition of carbamoyloxy nitrogen to heteroolefin is reported; M. Hirama, H. Hioki, and S. Ito, *Tetrahedron Lett.*, 29, 3125(1988).

6) N. Kasai, K. Tsujimura, K. Unoura and T. Suzuki, *Agric. Biol. Chem.*, 54, 3185(1990).

7) For example, D. A. Evans, *Aldrichim. Acta*, 15, 23(1982); D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, 110, 1238(1988).

8) Clear separation of the both enantiomers of 2 was unsuccessful by high performance liquid chromatography using chiral column and by NMR using shift reagent.

9) Dibenzylurea 4 might be formed from intermediary epoxycarbamate 1 with competing intermolecular ester exchange.

10) Both enatiomer of 7 were separated clearly by high performance liquid chromatography using chiral column(CHIRALCEL OD supplied by Daisel Co. Ltd, eluted with n-Hexane : *i*-PrOH = 85 : 15, 0.7ml/min). We thank Mr. K.Sakaguchi, Daiso Co. Ltd., for his kind measurement.

11) Benzoate 7 was independently synthesized from (L)-*N*-Boc-*O*-benzyl-serine by the following sequences[1] 1)CH_2N_2 2)DIBAL 3)$NaBH_4$ 4)NaH in DMF 5)O_3 in CH_2Cl_2. The value of optical rotation of 7 derived from L-serine was -28.1°(c 1.0, $CHCl_3$). The value of 7 derived from (+)-glycidol was +29.6°(c 1.09, $CHCl_3$).

(Received April 24, 1991)