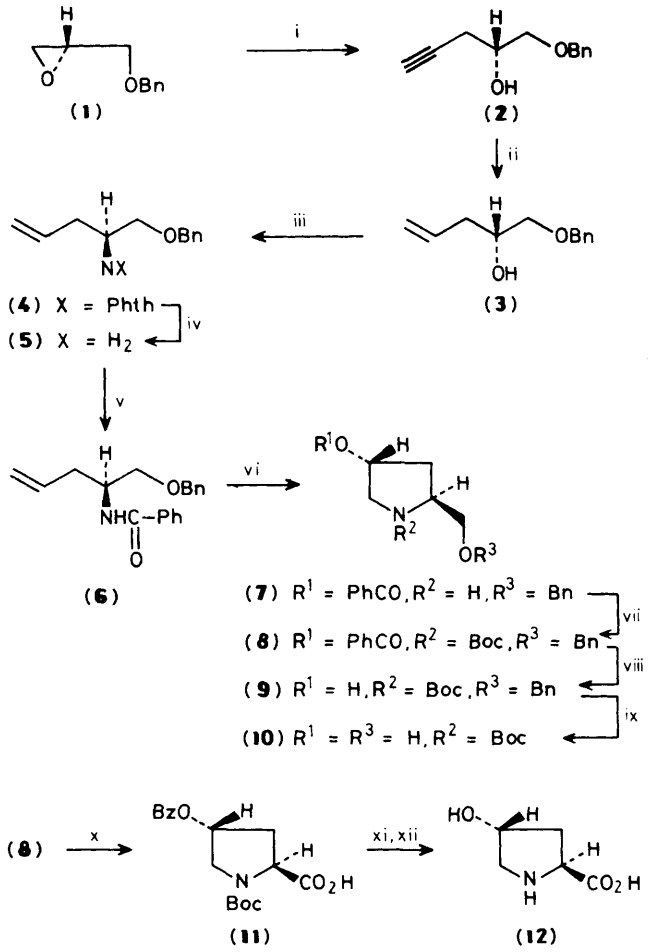
Concise Stereoselective Synthesis of (2*S*,4*R*)-4-Hydroxyproline from (*S*)-*O*-Benzylglycidol by a Novel Cyclization

Seiichi Takano,* Yoshiharu Iwabuchi, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

An efficient stereoselective route to (2*S*,4*R*)-4-hydroxyproline from (*S*)-*O*-benzylglycidol has been established *via* a novel iodine-mediated cyclization of the *N*-benzoyl-γ,δ-unsaturated amide.

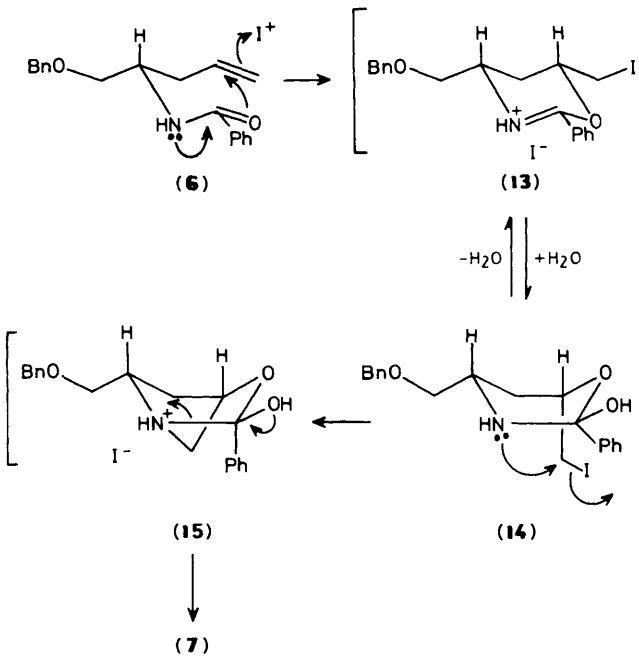
(2*S*,4*R*)-4-Hydroxyproline (**12**) is useful as the key chiral starting material for the synthesis of a variety of valuable materials, such as chiral phosphine ligands,[1] γ-amino-β-hydroxybutanoic acid (GABOB),[2] carbapenems,[3] and Angiotensin Converting Enzyme inhibitors.[4] However, to date, no efficient synthetic method has been reported for both racemic and optically active material.[5] We report here an efficient method for the synthesis of (2*S*,4*R*)-4-hydroxyproline[6] (**12**) from (*S*)-*O*-benzylglycidol[7] (**1**) *via* the *N*-benzoyl-γ,β-unsaturated amide (**6**) by employing a novel double cyclization mediated by iodine.



Scheme 1. *Reagents and conditions:* i, NaH (3.5 equiv.), dimethylsulphoxide (DMSO), acetylene; ii, H_2, $Pd/CaCO_3$ (cat.), AcOEt; iii, phthalimide, di-isopropyl azodicarboxylate, Ph_3P, tetrahydrofuran (THF), −20 °C, 12 h; iv, hydrazine, EtOH, reflux, 6 h; v, benzoyl chloride, Et_3N, CH_2Cl_2; vi, I_2 (3.0 equiv.), THF–H_2O (1 : 1 v/v), 20 °C, 6 h; vii, Boc_2O, Et_3N (0.3 equiv.), CH_2Cl_2; viii, K_2CO_3 (1.1 equiv.), MeOH; ix, H_2, $Pd(OH)_2/C$, MeOH; x, $RuCl_3 \cdot H_2O$ (2.2% mol), $NaIO_4$ (3.0 equiv.), CCl_4–MeCN–H_2O (1 : 1 : 1.5 v/v), room temp., 1 h; xi, K_2CO_3 (1.1 equiv.), MeOH; xii, CF_3CO_2H, anisole. Boc = t-butyoxycarbonyl, Bz = benzoyl, Bn = benzyl.

Treatment of (*S*)-*O*-benzylglycidol (**1**) with sodium acetylide generated by bubbling acetylene in dimethyl sulphoxide (DMSO) containing sodium methylsulphinyl carbanion[8] gave the terminal acetylene[9] (**2**) in 87% yield. The acetylene (**2**) was partially hydrogenated and the hydroxy group of the resulting alkene (**3**) was substituted by phthalimide group with inversion to give the imide† (**4**) in 70% overall yield under the Mitsunobu conditions.[10] Upon brief treatment with hydrazine hydrate, the imide (**4**) yielded the primary amine (**5**) which was benzoylated to give the secondary amide (**6**) in 87% overall yield.

Exposure of (**6**) to iodine (3 equiv.) in aqueous tetrahydrofuran[11] (1 : 1 v/v) at 20 °C allowed facile spontaneous double cyclization to give *O*-benzyl-(2*S*,4*R*)-4-benzoyloxyprolinol (**7**), $[\alpha]_D^{24}$ + 33.6° (*c* 2.0, $CHCl_3$), in 78% yield as a single product.‡ The stereochemistry of the product (**7**) was confirmed unambiguously by transformation into (2*S*,4*R*)-*N*-t-butoxycarbonylprolinol (**10**), $[\alpha]_D^{24}$ −61.4° (*c* 2.0, MeOH), by sequential *N*-t-butoxycarbonyllation, debenzoylation, and debenzylation, which was identical in all respects with an authentic sample of (**10**), $[\alpha]_D^{24}$ −61.3° (*c* 2.0, MeOH),



Scheme 2

† Satisfactory spectral (i.r., ^1H n.m.r., mass) and analytical (combustion and/or high resolution mass) data were obtained for all new compounds.

‡ Stereochemical and optical homogeneity was determined by ^1H n.m.r. (500 MHz) analysis of the (*R*)- and (*S*)-MTPA esters of *N*-benzyl-*O*-benzyl-4-hydroxyproline derived from (**7**).

prepared from (2*S*,4*R*)-4-hydroxyproline (**12**) of natural origin. Conversion of (**7**) into (2*S*,4*R*)-4-hydroxyproline (**12**) was accomplished in five steps. Thus, the carbamate (**8**), $[\alpha]_D^{24}$ −49.7° (*c* 2.05, $CHCl_3$), obtained quantitatively from (**7**), was sequentially debenzylated, oxidized,[12] debenzoylated, and de-*N*-protected to give (2*S*,4*R*)-4-hydroxyproline (**12**), identical in all respects with the authentic material, in 61% overall yield. We believe that the key reaction proceeds through the initial formation of the iododihydro-oxazinium salt (**13**) which was sequentially transformed into (**7**) *via* the iodotetrahydro-oxazine (**14**) and the oxazinium salt (**15**) under the reaction conditions[13] as shown in Scheme 2.

Since we have developed an efficient route[14] to (*R*)-*O*-benzylglycidol (**1**), enantiomeric (2*R*,4*S*)-4-hydroxyproline (**12**) may also be synthesized employing the present methodology.

Received, 19th July 1988; Com. 8/02896F

References

1 K. Achiwa, *J. Am. Chem. Soc.*, 1976, **98**, 8265.
2 T. Shibata, K. Iino, and Y. Sugimura, *Heterocycles*, 1986, **24**, 1331.
3 P. Renand and D. Seebach, *Synthesis*, 1986, 424; J. Hausler, *Monatsh. Chem.*, 1987, **118**, 865.
4 E. M. Smith, G. F. Swiss, B. R. Neustadt, E. H. Gold, J. A. Sommer, A. D. Brown, P. J. S. Chiu, R. Moran, E. J. Sybertz, and T. Baum, *J. Med. Chem.*, 1988, **31**, 875; J. Krapcho, C. Turk, D. W. Cushman, J. R. Powell, J. M. DeForrest, E. R. Spitzmiller, D. S. Karanewsky, M. Duggan, G. Rovnyak, J. Schwartz, Sesha Natarajan, J. D. Godfrey, D. E. Ryono, R. Neubeck, K. S. Atwal, and E. W. Petrillo, Jr., *J. Med. Chem.*, 1988, **31**, 1148.
5 *Cf.* S. G. Ramaswamy and E. Adams, *J. Org. Chem.*, 1977, **42**, 3440.
6 E. Fischer, *Berichte*, 1902, **35**, 2660.
7 S. Takano, M. Akiyama, and K. Ogasawara, *Synthesis*, 1985, 503.
8 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 866.
9 S. Takano, Y. Sekiguchi, N. Sato, and K. Ogasawara, *Synthesis*, 1987, 139.
10 O. Mitsunobu, *Synthesis*, 1981, 1.
11 S. Takano, C. Kasahara, and K. Ogasawara, *Heterocycles*, 1982, **19**, 1443.
12 P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
13 P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry,' Pergamon Press, Oxford, 1983, pp. 101—162.
14 S. Takano, K. Seya, E. Goto, M. Hirama, and K. Ogasawara, *Synthesis*, 1983, 116.