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

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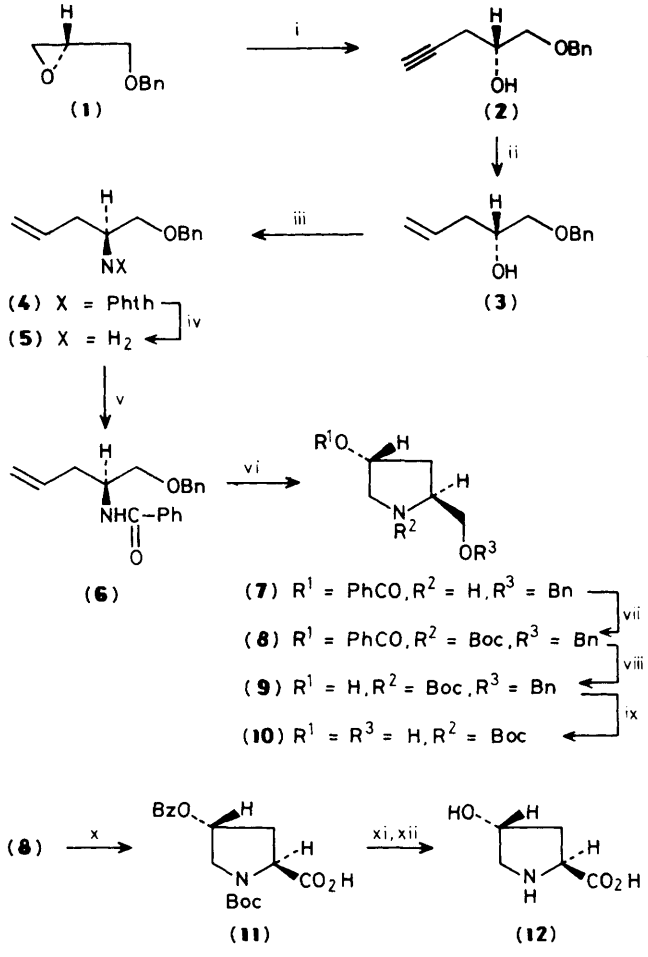
An efficient stereoselective route to (2*S*,4*R*)-4-hydroxyproline from (*S*)-*O*-benzylglycidol has been established *via* a novel iodine-mediated cyclization of the *N*-benzoyl-γ,δ-unsaturated amide.

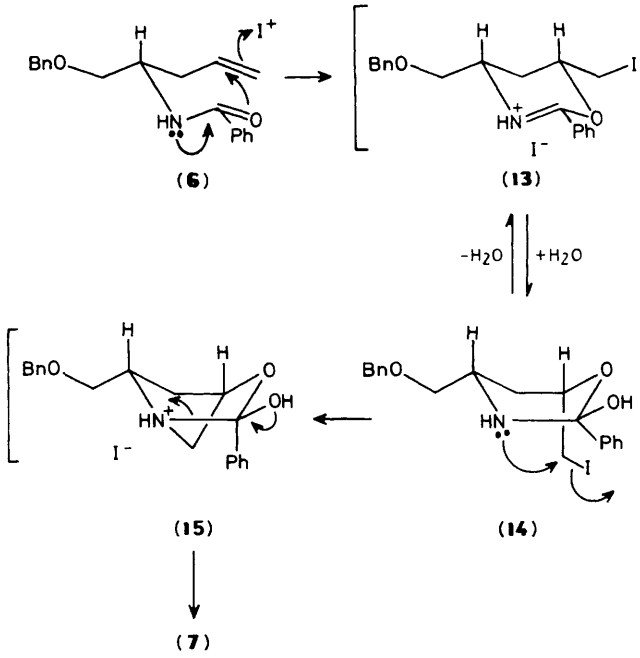
(2*S*,4*R*)-4-Hydroxyproline (**12**) is useful as the key chiral starting material for the synthesis of a variety of valuable materials, such as chiral phosphine ligands,[1] γ-amino-β-hydroxybutanoic acid (GABOB),[2] carbapenems,[3] and Angiotensin Converting Enzyme inhibitors.[4] However, to date, 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.

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