A Short Stereoselective Synthesis of *cis*- and *trans*-4-Hydroxy-L-proline

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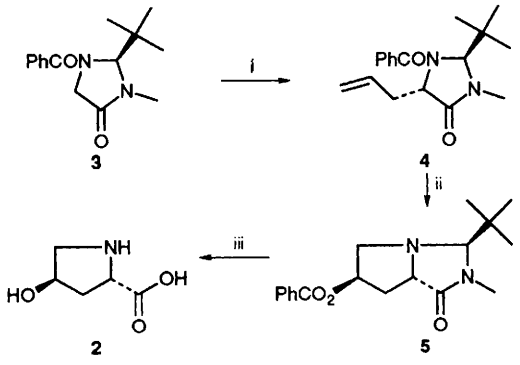
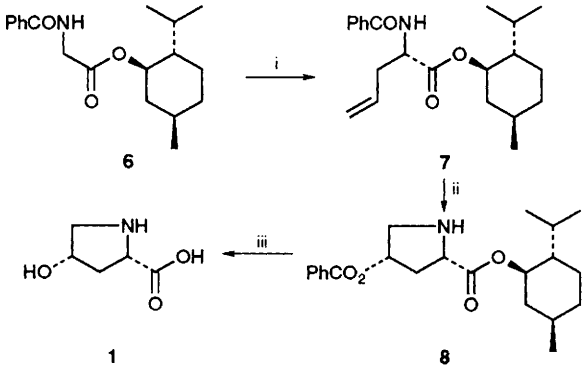
A concise three-step synthesis of *cis*- and *trans*-4-hydroxy-L-proline on a preparative scale has been carried out using readily available starting materials.

Cis-(2*S*,4*S*)- and *trans*-(2*S*,4*R*)-4-hydroxy-L-proline (**1**, **2**) are naturally occurring amino acids. The former is a constituent of phalloidine, the toxic polypeptide of *Amanita phalloides*,[1] whereas the *trans* epimer was found in collagen and gelatin hydrolysates.[2] Takano *et al.*[3] have published a stereoselective ten-step synthesis of *trans*-4-hydroxy-L-proline using (*S*)-*O*-benzylglycidol as starting material. Papaioannou *et al.*[4] have converted *trans*-4-hydroxy-L-proline into the *cis*-epimer *via* a four-step sequence. We now report a three-step stereoselective synthesis of both amino acids based on the methodology described by Takano *et al.*[3]



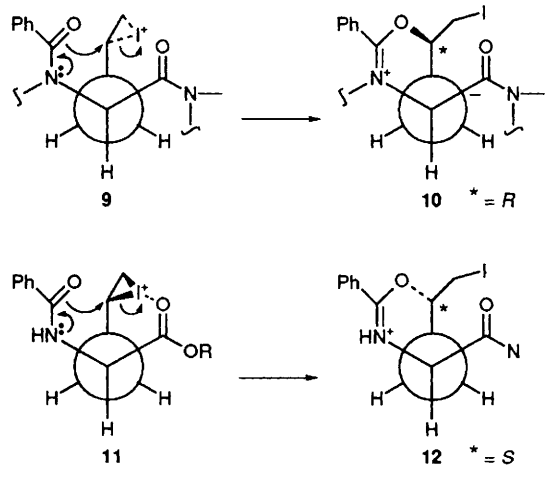
3 **4** **2** **5**

Scheme 1 *Reagents and conditions*: i, LDA (1.2 equiv.), BuLi (1.2 equiv.), allyl bromide (1.5 equiv.), −78 °C → 20 °C, 3 h; ii, I_2 (3.0 equiv.), THF–H_2O (1 : 1 v/v), 20 °C, 3 h; iii, 2 mol dm^{-3} HCl, 140 °C, 2 h



6 **7** **1** **8**

Scheme 2 *Reagents and conditions*: i, LiHMDS (2.0 equiv.), allyl iodide (1.0 equiv.), THF, −78 °C → room temp., 3 h; ii, I_2 (3.0 equiv.), THF–H_2O (1 : 1 v/v), 20 °C, 3 h; iii, HCl (2 mol dm^{-3}, 140 °C, 3 h, sealed tube)



9 **10** **11** **12**

Scheme 3

Trans-4-hydroxy-L-proline **2** was synthesized as outlined in Scheme 1: Seebach's compound (2*S*)-(+)-1-benzoyl-2-*tert*-butyl-3-methyl-4-imidazolidinone **3**[5] was alkylated with 1.2 equiv. of LDA, 1.2 equiv. of *n*-butyllithium and 1.5 equiv. of allyl bromide giving the allylated derivative **4**, $[\alpha]_D^{24}$ +20.5 (*c* 1.0, MeOH), as the only stereoisomer in 90% yield. Treatment of **4** with 3 equiv. of iodine in aqueous THF[6] gave the bicyclic compound **5**, $[\alpha]_D^{24}$ −19.4 (*c* 1.0, MeOH), in 75% yield as the only reaction product. After hydrolysis with 2 mol dm^{-3} HCl (140 °C, 2 h, sealed tube) *trans*-4-hydroxy-L-proline **2**, identical in all respects with a commercially available sample, was obtained in quantitative yield.

For the synthesis of the *cis*-epimer (Scheme 2) the readily available (−)-menthyl ester of hippuric acid **6**[7] was treated with 2 equiv. of lithium hexamethyldisilazide (LiHMDS) and 1 equiv. of allyl iodide in THF resulting in a 2 : 1 mixture of diastereoisomers. Recrystallization from ethyl acetate followed by chromatography of the mother-liquor using cyclohexane–ethyl acetate (100 : 1) gives **7**, $[\alpha]_D^{24}$ −46.4 (*c* 1.0, MeOH), as the main reaction product in 53% yield. Applying the analogous cyclization conditions as above the *cis*-configurated proline derivative **8** $[\alpha]_D^{24}$ −96.1 (*c* 2.0, MeOH) was obtained in 72% yield along with 8% of the *trans*-isomer which could be readily separated by chromatography using cyclohexane–ethyl acetate (5 : 1) as eluent. Hydrolysis of this intermediate with 2 mol dm^{-3} HCl (140 °C, 3 h, sealed tube) gave *cis*-4-hydroxy-L-proline in quantitative yield.

The different stereochemical outcome of the two reactions requires some comment (Scheme 3). As a possible explanation intermediate **9** derived from the allylated imidazolidinone **4** follows the course as depicted in the work described by Takano *et al.*[3] giving bicyclic structure **10** with (*R*)-configuration at position *. The amino acid ester **7**, on the other hand, apparently stabilizes iodonium ion **11** which predominately results in formation of structure **12** with (*S*)-configuration at position *.

The ready availability of the starting materials in both enantiomeric forms makes the two synthetic routes very attractive for the synthesis of both *cis*- and *trans*-4-hydroxy-L-proline as well as their corresponding optical antipodes.

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