Rapid Asymmetric Synthesis of Highly Functionalized C5 Chiral Synthons. Practical Preparation of *trans*-3 -Hydroxy-*D*-Proline.

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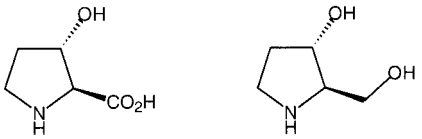
Abstract : A stereocontrolled synthesis of (2*R*, 3*R*)-3-hydroxyproline **5** has been achieved in 33% overall yield from a prochiral β-ketoester : the methyl 5,5-dimethoxy-3-oxopentanoate **6**. The key intermediate is the richly functionalized compound **4** which presented three different oxygenated groups and an *anti* relationship between the alcohol and the amine.

Peptide structures with proline components have received considerable attention over the past few years.[1] *trans*-3-Hydroxy-*L*-proline **1** is a constituent of naturally occurring peptides such as Mucrorin-D,[2] Telomycin[3] and has been isolated from mediterranean sponge and from collagen hydrolysates.[4] The reduced form of **1**, the *trans*-3-hydroxy-*L*-prolinol **2**, occurs in the seeds of the legume *Castanospernum australe*.[5]

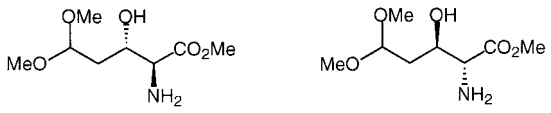


1 2

Scheme 1

Several syntheses of *trans*-3-hydroxyproline and prolinol have been developed in the literature starting from chiral sources such as pyroglutamic acid,[6] *L*-serine[7], *D*-mannitol[8] or *L*-malic acid.[9]

The key intermediates of our approach are the *anti* diastereomers **3** and **4** of the methyl 2-amino-3-hydroxy-5,5-dimethoxypentanoate. These richly functionalized compounds should be useful for the synthesis of various α-amino-β-hydroxy acids of either (*L*) or (*D*) configurations.



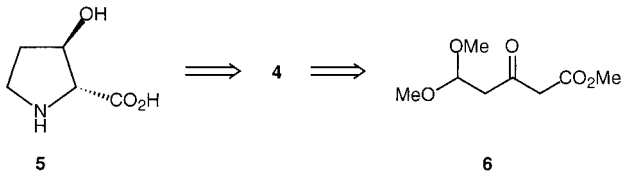
3 4

Scheme 2

Recently, Ciufolini et al. reported the synthesis of the N,O diprotected **4** using the Aza-Achmatowicz reaction[10] in several steps from a chiral furan oxazalone.[11]

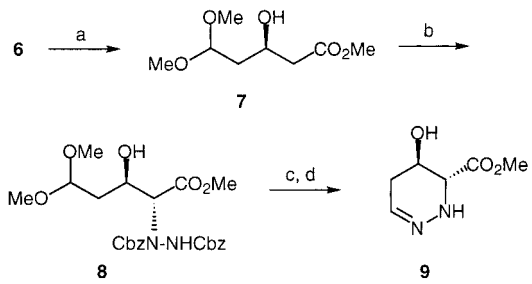
In connection to our continued work on the asymmetric synthesis of α-amino-β-hydroxy acids, our route to **3** and **4** relied on sequential catalytic hydrogenation and electrophilic amination,[12] we report here a concise and stereoselective synthesis of the unnatural *trans*-3-hydroxy-*D*-proline.

(2*R*, 3*R*)-Hydroxyproline **5** was obtained by cyclisation of **4** prepared from β-ketoester **6**.[13] First, we studied the hydrogenation of **6** in the presence of ruthenium catalysts. The C5 acetal functionalized β-ketoester **6** presented two symmetrical oxygens in γ positions to the carbonyl group : this could modify the chelation of the ruthenium complex and influence the enantioselectivity of the reaction.



5 6

Scheme 3



8 9

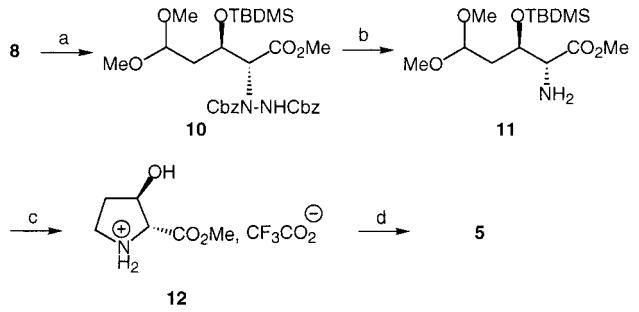
Scheme 4 : (a) H_2, (*R*)-Binap Ru Br_2, 2% mol.; MeOH; 1 atm., R.T., 18 h. (86%, e.e.>95%). (b) MeZnBr, LDA, CbzN=NCbz, -78°C (66%, d.e.>98%). (c) H_2, Pd/C, MeOH, R.T., O.5 h. (d) TFA, H_2O (quant.).

Under classical conditions (20 bars, 50°C) the asymmetric hydrogenation of the β-ketoester **6** was carried out in presence of (*R*)-$BinapRuBr_2$ [14] or [(*R*)-$BinapRuCl_2]_2$-Et_3N[15] and methanol was used as solvent to avoid secondary reactions such as transacetalisation or transesterification. The yields did not exceed 50% and substantial degradation of the substrate was observed. Then, the hydrogenation was performed at room temperature and atmospheric pressure using 2 molecular % of (*R*)-$BinapRuBr_2$ generated *in situ*.[16] Under these mild conditions, the β-hydroxyester **7** was obtained with 86% yield and the enantiomeric excess was higher than 95%. The enantiomeric excess was determinated by chiral gas chromatography.[17]

The diastereoselective amination was carried out with dibenzylazodicarboxylate as electrophilic reagent for the amination step because the conditions of the deprotection of a benzyl carbamate are compatible with the presence of an acetal function. The zinc enolate was generated using methyl zinc bromide and lithium diisopropylamide; its reaction with the dibenzylazodicarboxylate produced the *anti* diastereomer **8** with 66% yield and complete diastereoselectivity.

At this stage, a rapid correlation was done : the benzyl carbamates were hydrogenolyzed and the crude product was treated with aqueous trifluoroacetic acid. The tetrahydropyridazine **9** was obtained quantitatively and its physical data were identical to those reported in the literature.[18] These results confirmed that the absolute configuration of **8** was (2*R*, 3*R*).[19] **9** is a direct precursor of the unnatural (3*R*, 4*R*)-4-hydroxy-2,3,4,5-tetrahydropyridazine carboxylic acid (HPCA).

(3*S*, 4*S*)-HPCA is an aminoacid constituent of the antitumor and anti HIV peptide antibiotics : luzopeptins.[20]



Scheme 5 : (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -78°C (96%). (b) H_2, PtO_2. H_2O, MeOH-H_2O (1/1), R.T. (71%). (c) TFA, H_2O, H_2; $PtO_2.H_2O$, R.T. (d) KOH, MeOH-H_2O, R.T.; Dowex 50x4 (84% from **11**)

The synthesis of the (2*R*, 3*R*)-*trans*-3-hydroxyproline **5** was then developed from the α-hydrazino-β-hydroxyester **8**. The principal step was the cleavage of the hydrazine bond. The hydroxyl function was first protected as *t*-butyldimethylsilyl ether because we noticed that no cleavage of the N-N bond could be perfomed in the presence of a free alcohol. After hydrogenolysis of the benzyl carbamates (H_2, Pd/C), classical conditions such as H_2, PtO_2[21] or H_2, Raney Ni under ultrasounds[22] were used to generate the amine, but degradation of the substrate was observed and no product could be isolated. Then, we tried to deprotect and cleave the hydrazine simultaneously : **10** was exposed to H_2 in presence of $PtO_2.H_2O$ in methanol and 45% of the α-aminoester **11** was recovered after flash chromatography. Using a 1/1 mixture of methanol-water as solvent for these reactions, the yield increased to 71% of purified compound **11**. To our knowledge, we proposed here the first one pot deprotection-cleavage of the N-N bond of a diprotected hydrazine derivative.

The cyclisation to the proline ring was performed using aqueous trifluoroacetic acid and the silyl ether was cleaved under these conditions. The resulting iminium was reduced *in situ* by H_2 in presence of $PtO_2.H_2O$. The trifluoroacetic salt of methyl *trans*-hydroxy-*D*-prolinate **12** was obtained as a crude product and the methyl ester was saponified without further purification. After elution through an ion exchange resin column, the (2*R*, 3*R*)-*trans*-3-hydroxyproline **5** was isolated as a white solid with 84% yield from **11**. All physical data of **5** were identical with those reported in the literature.[8, 23]

The unnatural *trans*-3-hydroxy-*D*-proline **5** was synthesized in 6 steps with 33% overall yield from the prochiral β-ketoester **6**. Using (*S*)-$BinapRuBr_2$ as catalyst in the first step of asymmetric hydrogenation, the natural *trans*-hydroxy-*L*-proline **1** could be obtained in a similar manner. This diastereoselective route is very efficient for the preparation of both *trans*-3-hydroxyprolines.

In conclusion, we proposed in this paper a rapid and stereoselective synthesis of highly functionalized building blocks **3** and **4**. These compounds presented three oxygenated functionalities at different oxydation degrees.This route has also opened an access to the (3*R*, 4*R*)-4-hydroxy-2,3,4,5-tetrahydropyridazine methyl carboxylate **9** and to the *trans*-3-hydroxy-*D*-proline **5** in optically- and diastereomerically-pure form. Both *anti* enantiomers of each product are available from the β-ketoester **6**. The proposed syntheses are very concise : 4 steps for **9** and 6 steps for **5** from the β-ketoester **6**.

The use of the C5 chiral synthons **3** and **4** in further syntheses are under current investigation in our laboratory.

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(17) **Methyl(*R*)-5,5-dimethoxy-3-hydroxypentanoate (7)** : Methyl 5,5-dimethoxy-3-oxopentanoate **6** (1.03 g, 5.4 mmol) was diluted under argon in degassed methanol (10 ml). This solution was canulated into a Schlenk tube containing the (R)-$BinapRuBr_2$ complex (2 mol%). The system was purged 3 times with hydrogen and the reaction mixture was stirred under hydrogen (1 atm.) at RT for 18h. The solution was concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane/ AcOEt (1:1). Yield: 86%. $[\alpha]_D^{20}$ = + 15 (c=1, EtOH). $C_8H_{16}O_5$ (192.21) calcd C 49.98, H 8.39; found C 49.63, H 8.38. GPC : Lipodex A, 80°C, flow : 1ml/mn, r.t. : 62.5 mn.

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(19) **Methyl(*2R,3R*)-5,5-dimethoxy-2-[N,N'-(dibenzyl carbonyl) hydrazino]-3-hydroxypentanoate (8)** : To **7** (1.7 g, 8.8 mmol) in

dry THF (12 ml) at 0°C, was added dropwise a solution of MeZnBr (9.7 mmol) prepared from $ZnBr_2$ (2.18 g, 9.7 mmol) in dry THF (12 ml) and MeLi (6.35 ml, 9.7 mmol, 1.6 M sol. in Et_2O). After stirring for 1h, the mixture was cooled at -78°C and a solution of lithiumdiisopropylamide (17.6 mmol) in THF was added dropwise. After further 1h at -78°C, a solution of dibenzylazodicarboxylate (5.25 g, 17.6 mmol) in THF (24 ml) was added dropwise. The reaction mixture was stirred until no more starting material was detectable by TLC (2.5 h.), hydrolysed at -78°C with a saturated aqueous solution of NH_4Cl (30 ml), warmed at RT, extracted into Et_2O, dried and evaporated. The crude product was purified by flash chromatography eluting with cyclohexane / AcOEt (3:7). Yield : 66%. $[\alpha]_D^{20}$ = +35 (c=1.24, EtOH). $C_{24}H_{29}N_2O_9$ (489.49) calcd C 58.88, H 5.97, N 5.72; found C 58.87, H 6.06, N 5.81.

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5: $[\alpha]_D^{20}$ = +19 (c=1, H_2O); lit.[8] $[\alpha]_D^{20}$ = +18.4 (c=1.2, H_2O); lit.[23] $[\alpha]_D^{20}$ = +18.8 (c=0.14, H_2O).