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Efficient asymmetric synthesis of a functionalized Δ^2-pyrazoline

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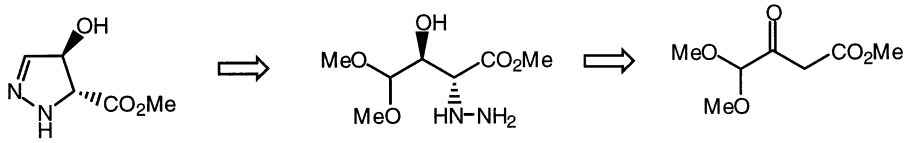
Abstract

The first asymmetric synthesis of the (4*S*,5*R*)-5-carbomethoxy-4-hydroxy-Δ^2-pyrazoline in four steps is described starting from the methyl 4,4-dimethoxy-3-oxobutanoate by sequential catalytic hydrogenation and electrophilic amination.

A large number of Δ^2-pyrazolines have been described in the literature[1] due to their synthetic accessibility and important applications. Δ^2-pyrazolines are also known for their biological activity as anti-inflammatory compounds.[2] Procedures to obtain these systems in enantiomerically pure form are of great interest. Thus, Δ^2-pyrazolines could be used as chiral precursors in the preparation of several heterocyclic derivatives and as building blocks for the asymmetric synthesis of functionalized chiral acyclic synthons.[3] Recently, two routes to enantiomerically pure Δ^2-pyrazolines were reported: the diastereoselective dipolar cycloaddition reaction of Me_3SiCHN_2 to optically active enoates described by Carreira and co-workers[4] and the reaction of diazo compounds with alkenyl Fischer carbenes derived from chiral alcohols reported by Barluenga and co-workers.[5]

In connection with our continued work on the asymmetric synthesis of α-amino β-hydroxy acids and nitrogen heterocycles,[6] we report here a concise and stereoselective synthesis of the chiral functionalized (4*S*,5*R*)-5-carbomethoxy-4-hydroxy-Δ^2-pyrazoline **1**.



1 **2** **3**

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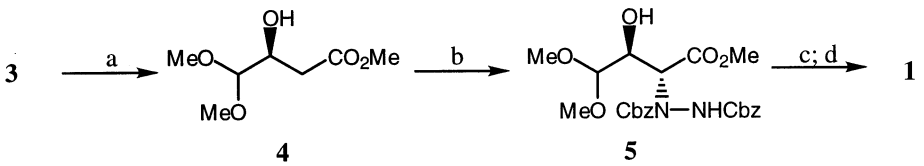
The key intermediate of our approach is the *anti* diastereomer of methyl 2-hydrazino-3-hydroxy-4,4-dimethoxybutanoate **2**. This compound is a chiral C4 synthon highly functionalized by an hydrazino group and three oxygenated substitutions at different oxidation degrees: an alcohol, an acetal and an ester group. Compound **2** was obtained by sequential catalytic hydrogenation and electrophilic amination starting from the β-ketoester **3**.

Compound **3** was prepared by a two carbon homologation of methyl 2,2-dimethoxyethanoate[7] using the Masamune procedure.[8] Asymmetric hydrogenation of the β-ketoester was first carried out in presence of (*R*)-Binap $RuBr_2$ in methanol under classical conditions, but secondary reactions were observed giving methyl-3,4-dihydroxybutanoate and hydroxy-δ-lactone as side products. The use of 1 mol% of [(*R*)-Binap $RuCl_2$]–Et_3N[9] as catalyst gave reproducible results: in methanol at 65°C and under atmospheric pressure,[10] the (*S*)-β-hydroxyester **4** was isolated in 83% yield and 90% enantiomeric excess (Scheme 1).



Scheme 1. (a) H_2 (1 atm), [(*R*)-Binap $RuCl_2]_2$–Et_3N (1%), MeOH, 65°C, 18 h (83%, ee = 90%). (b) 1. MeZnBr (1.1 equiv.), THF, 30 min, 0°C; 2. LDA (2.2 equiv.), THF, 1 h, −78°C; 3. CbzN=NCbz (2 equiv.), THF, 30 min, −78°C (66%, de>95%). (c) H_2, Pd/C, MeOH, rt, 1 h (quant.). (d) TFA, rt, 2 h (70%)

Dibenzyl azodicarboxylate was used as the electrophilic reagent for the amination step giving the hydrazino derivative protected as benzyl carbamates, which can be deprotected in presence of an acetal function. The zinc enolate of **4** was aminated at −78°C to produce the *anti* diastereomer **5** exclusively in 66% isolated yield.

The cyclization was performed after hydrogenolysis of the benzyl carbamates (H_2, Pd/C), by treatment of the crude product with trifluoroacetic acid at room temperature. Compound **1** was purified by silica gel flash chromatography and isolated in 70% yield.[11]

In conclusion, we describe here the first asymmetric synthesis of the (4*S*,5*R*)-5-carbomethoxy-4-hydroxy-Δ^2-pyrazoline **1** in four steps starting from the achiral β-ketoester **3** in 38% overall yield. Its enantiomer could be obtained easily using (*S*)-Binap as chiral ligand for the hydrogenation step. Compound **1** is a new constituent of a novel class of α-amino acids: azaprolines proposed recently by Carreira.[4] These analogs should find important applications as 3-hydroxyproline surrogates. The highly functionalized intermediate **2** should be useful for the preparation of various α-amino-β-hydroxy acids and peptidomimetics.

Acknowledgements

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11. $[\alpha]_D^{25} = -181$ (*c* 0.6, $CHCl_3$).