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A Simple Total Synthesis of (*S*)-Isoserine

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Abstract : Kinetic enzymatic resolution by *Candida cylindracea* lipase of racemic isoserine diacetate prepared from the cyanohydrin of glyoxylate provided (*S*)-isoserine in good yield and high optical purity.

The β-aminoalcohol functionality associated with a carboxylic group is present in a large number of natural biologically active compounds such as carnitine[1], GABOB[2], isoserine[3] and statine.[4] In recent years their stereoselective synthesis has become a major field in research.

As might be expected for such compounds a number of synthetic routes have been developed. Cyanohydrins are particularly useful intermediates in the synthesis of β-aminoalcohols.[5] In a previous communication[6] we described the stereoselective synthesis of (*S*)- and (*R*)-GABOB by kinetic enzymatic resolution of *O*-acetyl cyanohydrins easily available from ethyl 3,3-diethoxypropionate.[7] Moreover the selective reduction of the nitrile function in the presence of a carboxyl group[6] allowed us to propose a general method for the synthesis of other α-amino-hydroxy carboxylic acids such as isoserine (3-amino-2-hydroxypropionic acid).

A recent publication in this Journal[8] on the enzymatic kinetic resolution of aminoalcohol diacetates by lipases in a buffer solution prompts us to report our own results on a high yield, convenient enantioselective synthesis of (*S*)-isoserine **1** through kinetic resolution of aminoalcohol diacetates in organic solvents.[9]

Several syntheses of racemic[3,10] as well as (*S*)-[11] and (*R*)-isoserine[11c,12] have been reported. In our procedure ethyl glyoxylate was converted quantitatively into cyanohydrine **2a** (ethyl 2-cyano-2-hydroxyacetate) by Me_3SiCN in a pH = 5.4 buffer as already described for ethyl 3-cyano-3-hydroxypropionate.[6] The enzymatic resolution of cyanohydrin **2a** or *O*-acetyl cyanohydrin **2b**[13] by several lipases was unsuccessful probably because of the similar size of the substituents attached to the stereocenter in agreement with the rules recently published by Kazlauskas *et al.*[14] Asymmetrically induced addition of HCN or KCN to ethyl glyoxylate by oxynitrilases[15] was also unsuccessful.

According to our previous results[6] selective reduction of cyanohydrin **2a** using BH_3.THF in the presence of $NiCl_2.6H_2O$ led to a three step synthesis of racemic isoserine **1a** from ethyl glyoxylate (overall yield 85%, scheme 1). Since racemic isoserine possesses substantial differences in the size of substituents attached to the stereocenter the enantioselective transesterification of its diacetate **3a** was undertaken.

The high enzymatic activity in organic solvents discovered by Klibanov[16] has become a method of choice of enzymatic kinetic resolution. Adjustment of the quantity of *n*-butanol (one equivalent) in diisopropyl ether allowed an excellent enantioselective transesterification of **3a** by *Candida cylindracea* lipase (CCL) as described in scheme 1.[17] As predicted by the above mentioned rules[14] the natural (*S*)-isoserine cannot be obtained from the more rapidly hydrolyzed enantiomer. When the asymmetric transesterification of **3a** was stopped after 52% conversion, the enriched (*R*)-alcohol **4** could be easily separated by column chromatography from the unreacted acetate **3**. Acid hydrolysis of **3** followed by ion exchange chromatography on Amberlite IR-120 yielded crude **1** (96%, $[\alpha]_D$= -29 , c=2, H_2O; ee = 90%) which after crystallisation from MeOH/H_2O gave (*S*)-isoserine **1** (mp

191-193°C, Lit.[11a] mp 188-189°C; $[\alpha]_D$= -32.7 , c=0.5, H_2O; Lit.[11b] $[\alpha]_D$= -32.2). In our procedure a single conversion step was sufficient to afford the desired enantiomer **3** in good optical purity demonstrating greater selectivity of lipases in organic solvents[18] as compared to similar attempts in buffered aqueous solution.[8] It should be mentioned that this type of resolution of β-aminoalcohol diacetates occurred with moderate enantioselectivity when carried out on primary alcohol acetates attached to the future chiral center[9] but may be more efficient on secondary alcohol acetates.

Thus (*S*)-isoserine could be prepared in five steps from ethyl glyoxylate with an overall yield of 33% and an good optical purity.

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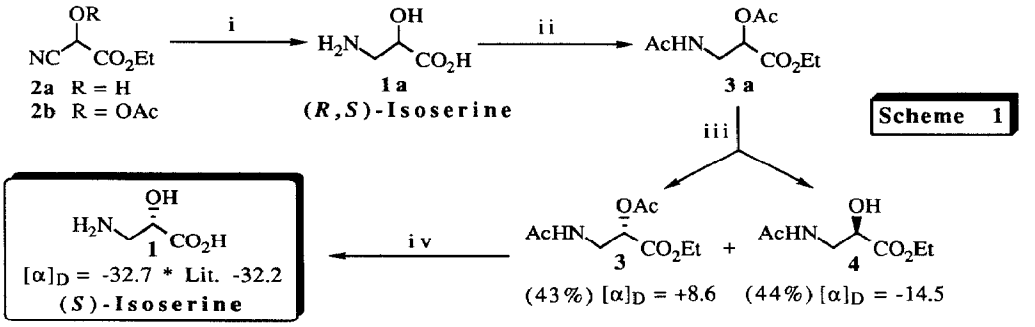

Scheme 1

(i) BH_3•THF,$NiCl_2$•$6H_2O$; 10N HCl; (85%). (ii) EtOH,HCl; Ac_2O/Py; (93%). (iii) CCL,*n*-BuOH, $(Me_2CH)_2O$, 52% conversion ; (iv) HCl/H_2O, Δ, (96%).*after crystallisation from MeOH/H_2O.

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17. 4 g of CCL (Sigma) were added to a solution of 700 mg (3.23 mmol) of **3a** in 15 ml of isopropylether and 270 mg (3.65 mmol) of *n*-butyl alcohol. The mixture was stirred at room temperature for 4 days. After addition of 20 ml of AcOEt and filtration the products were separated by flash chromatography on silica gel, yielding **3** (250 mg, 44%; $[\alpha]_D$= -14.5 , c=1, $CHCl_3$) and **4** (300 mg, 43%; $[\alpha]_D$= +8.6 , c=1, $CHCl_3$).
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