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Asymmetric synthesis of *syn* hydroxyphenylalanine via aziridine ring expansion to an oxazoline

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Abstract

The synthesis of (2R,3S)- and (2S,3R)-hydroxyphenylalanine is reported. The main steps are the 1,4-addition of *O*-benzylhydroxylamine to unsaturated imides and the ring expansion of *trans*-aziridines. © 1999 Elsevier Science Ltd. All rights reserved.

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Polyfunctionalized amino acids are present in complex molecules that display high biological and pharmacological activity.¹ β -Hydroxy α -amino acids for instance are present in important antibiotics with either the *syn*- or *anti*-configuration.^{1,2} Recently we developed a synthetic strategy to obtain *syn*-aminoalcohol derivatives based on the ring expansion of *trans*-aziridine-chiral imide to *trans* oxazolines.³

We wish here to report a simple and diastereoselective synthesis of (2R,3S)- and (2S,3R)-phenylserine, the latter being present in the Lysobactin antibiotic backbone.^{2a,b,c}

Recent studies in this laboratory resulted in a straightforward method for the synthesis of *trans*aziridine-2-carboxylates, easily obtained from chiral 3'-benzyloxyamino-imides via titanium and aluminium enolates.⁴ This strategy requires the diastereoselective β -introduction of *O*-benzylhydroxylamine⁵ to α , β -unsaturated chiral imidates. We previously reported the 1,4-addition of *O*-benzylhydroxylamine to alkenyl imides at -78° C, promoted by TiCl₄ or AlMe₂Cl.⁶ This reaction gave an easily separable mixture of isomers in high yield and a diastereomeric ratio which depended on the Lewis acid selected. In fact from TiCl₄ to AlMe₂Cl, a complete inversion of selectivity was observed. On the contrary, any attempt to react the cinnamoyl derivative under these conditions failed and a new effort was required in order to obtain 1,4-addition of *O*-benzylhydroxylamine in good yield (Scheme 1). The results obtained are reported in Table 1.

As shown, the best diastereomeric ratio was obtained with 0.5 equivalents of MgBr₂ as the catalyst at room temperature in CH_2Cl_2 , in ether or in toluene, while the best yield, although with decreased selectivity, was obtained with a catalytic amount of Sc(OTf)₃.

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Scheme 1. Table 1 Conjugate addition of *O*-benzylhydroxylamine to the cinnamoyl derivative **1**

| Entry | Lewis Acid (equiv.) ^a | Solvent | t (h) | 2+3 (%) | 2/3 |
|-------|----------------------------------|---------------------------------|-------|---------|-------|
| 1 | MgBr ₂ (0.2) | CH ₂ Cl ₂ | 72 | 50 | 67:33 |
| 2 | $MgBr_2 (0.5)^b$ | CH ₂ Cl ₂ | 72 | 95 | 80:20 |
| 3 | $MgBr_{2}(0.5)$ | THF | 24 | 95 | 73:27 |
| 4 | $MgBr_{2}(0.5)$ | Et ₂ O | 64 | 90 | 80:20 |
| 5 | $MgBr_{2}(0.5)$ | toluene | 72 | 70 | 75:25 |
| 6 | AlMe ₂ Cl $(0.5)^{c}$ | CH_2Cl_2 | 24 | 60 | 60:40 |
| 7 | $Yb(OTf)_{2}(0.5)$ | CH_2Cl_2 | 72 | 55 | 67:33 |
| 8 | Yb(OTf) ₂ (1.0) | CH ₂ Cl ₂ | 72 | 70 | 61:39 |
| 9 | $Sc(OTf)_3(0.05)$ | CH ₂ Cl ₂ | 8 | 98 | 60:40 |

^{*} All the reactions were carried out from -10 °C to r.t.; ^b The reaction with 1 equivalent of MgBr₂ gave the same diastereomeric ratio but a lower yield; ^c The reaction was carried out from -60 °C to r.t.

In order to prepare the *trans*-aziridines 4 and 5, each 3'-benzyloxylamino derivative was treated in CH_2Cl_2 with 1 equivalent of $AlMe_2Cl$ and transferred via cannula to a solution of TEA in CH_2Cl_2 at 0°C. The corresponding purified aziridine 4 or 5 was isolated in a 75% yield and 100% d.e., accompanied by a 15% of elimination compound 1 (Scheme 2).



Scheme 2.

The (2R,3S) configuration of the aziridine 4, derived from the major isomer, was established by cleavage of the chiral auxiliary with TEA and methanol, following a procedure recently reported by Davies.⁷ This reaction afforded the aziridine methyl ester 6 that was characterized by comparing its optical rotation with data reported in the literature([α]_D -250, c 0.5, CH₃OH).⁸

Compound 4 was treated with benzoyl chloride to give the N-benzoyl derivative which spontaneously afforded the *trans* oxazoline 7 (J=6.4 Hz) through a ring expansion reaction with retention of configuration.⁹ This compound was hydrolysed in 2N HCl/MeOH to the corresponding N-benzoyl-2'-amino-3'-hydroxy derivative 8 in 90% yield (Scheme 3).

To confirm the regiochemical course of the ring expansion reaction, 7 was refluxed in MeOH in the presence of TEA.⁷ With the complete removal of the chiral imidazolidinone auxiliary, the *trans*-2,5-diphenyl-4-methoxycarbonyl oxazoline 9 was obtained in 90% yield and compared with data reported in the literature.¹⁰ When 4 was treated with an excess of acetic anhydride, the *N*,*O*-diacetyl derivative 10



Scheme 3.

was obtained, through the formation of the undetected oxazoline. Treatment of 10 with TEA in MeOH to perform the complete removal of the imidazolidinone auxiliary, gave the corresponding N-acetyl methyl ester 11 (Scheme 4). The stereochemical course of the ring expansion reaction was confirmed by comparing 11 with data reported in the literature (Scheme 4).^{9a}



Scheme 4.

Finally the (2S,3R)-phenylserine derivative 13 was obtained starting from compound 5. In fact, treatment of 5 with benzoyl chloride in the presence of pyridine and DMAP gave oxazoline 12 in 80% yield. The hydrolysis of 12 with HCl/MeOH gave 13 in a 90% yield (Scheme 5).



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