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

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Abstract

The synthesis of (2*R*,3*S*)- and (2*S*,3*R*)-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 (2*R*,3*S*)- and (2*S*,3*R*)-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*-benzylhydroxylamine[5] to α,β-unsaturated chiral imidates. We previously reported the 1,4-addition of *O*-benzylhydroxylamine to alkenyl imides at −78°C, promoted by $TiCl_4$ or $AlMe_2Cl$.[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 $TiCl_4$ to $AlMe_2Cl$, 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 $MgBr_2$ 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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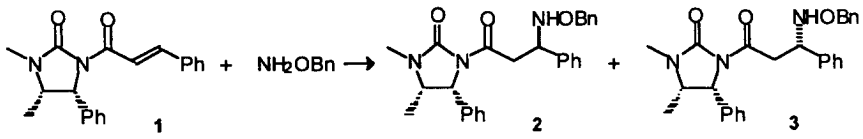


Scheme 1.

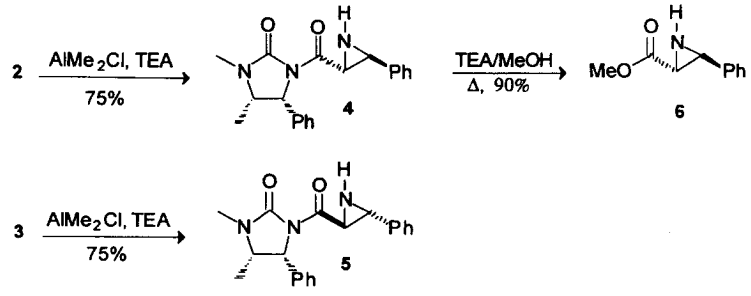
Table 1

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_2Cl_2	72	50	67:33
2	$MgBr_2$ (0.5)[b]	CH_2Cl_2	72	95	80:20
3	$MgBr_2$ (0.5)	THF	24	95	73:27
4	$MgBr_2$ (0.5)	Et_2O	64	90	80:20
5	$MgBr_2$ (0.5)	toluene	72	70	75:25
6	$AlMe_2Cl$ (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_2Cl_2	72	70	61:39
9	$Sc(OTf)_3$ (0.05)	CH_2Cl_2	8	98	60:40

[a] All the reactions were carried out from -10 °C to r.t.; [b] The reaction with 1 equivalent of $MgBr_2$ 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).

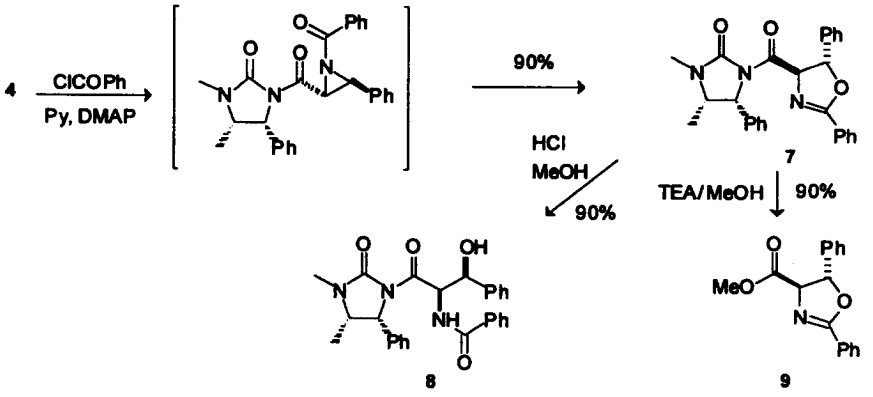


Scheme 2.

The (2*R*,3*S*) 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($[\alpha]_D$ −250, c 0.5, CH_3OH).[8]

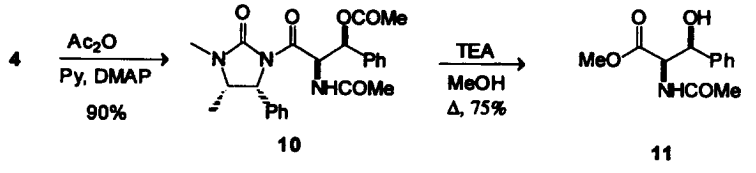
Compound **4** was treated with benzoyl chloride to give the *N*-benzoyl derivative which spontaneously afforded the *trans* oxazoline **7** (J=6.4 Hz) through a ring expansion reaction with retention of configuration.[9] This compound was hydrolysed in 2N HCl/MeOH to the corresponding *N*-benzoyl-2′-amino-3′-hydroxy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



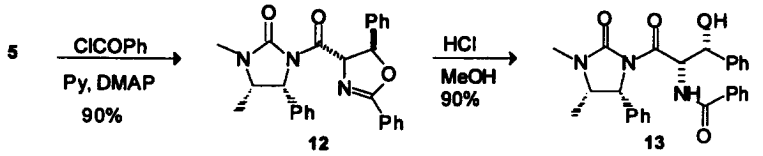
Scheme 3.

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 (2*S*,3*R*)-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).



Scheme 5.

Acknowledgements

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