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[A0007]

Asymmetric synthesis of *cis*-4,5-disubstituted oxazolidin-2-ones via chiral a-amino epoxides derived from L-Serine

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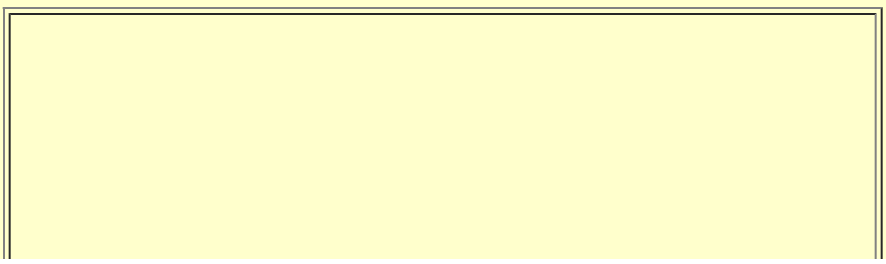
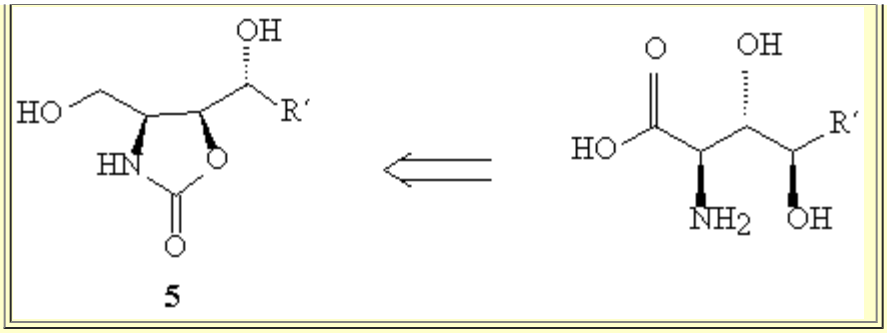
INTRODUCTION

Oxazolidine moieties are widely recognized as very useful chiral auxiliaries in asymmetric reactions,[1] and chiral epoxides have been frequently involved in the design of strategies for the achievement of stereocontrol.[2] However, only few examples reported in literature,[3] combine the influence in the same substrate of both epoxide and oxazolidine moieties, although in any case related with intramolecular reactions.

As a part of our ongoing research program aimed at the synthesis of biologically relevant hydroxylated amino acids,[4] we wish to report an easy strategy which allows the stereoselective preparation of 4,5-disubstituted oxazolidinones **5**, based on the use of the homochiral epoxy oxazolidines derived from L-Serine, which could be precursors of b,g-dihydroxy-a-amino acids (Scheme 1).

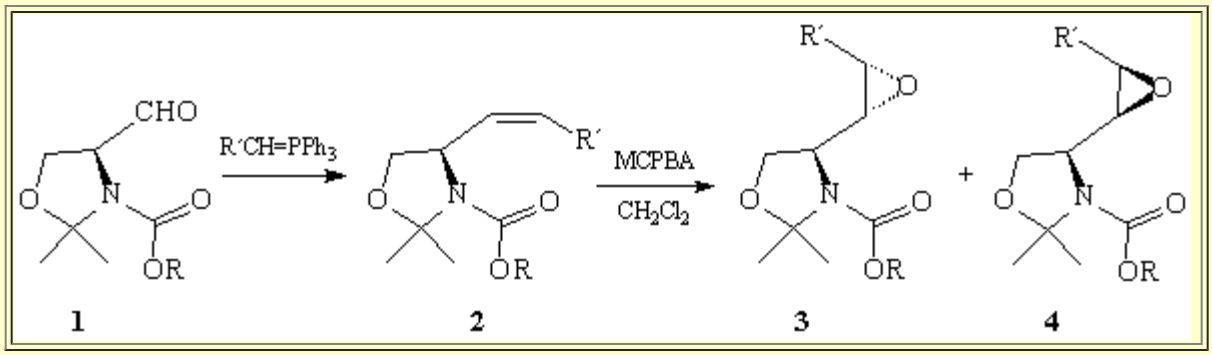




Scheme 1

RESULTS AND DISCUSSIONS

Alkenyl oxazolidines **2a-d** were obtained starting from *Garner´*s protected aldehyde **1a** (R = *tert*-Bu) and its *N*-Cbz analogue **1b** (R = Bn)[5] by using the Wittig olefination standard procedure.[6] Next, epoxidation of each olefin by treatment with MCPBA in dichloromethane, gave the corresponding *threo* **3a-d** and *erythro* **4a-c**, *N*-protected a-amino epoxides, with excellent stereoselectivities.[7] The *threo* diastereomer was always favoured[8] (in the epoxidation of **2d**, the *erythro* isomer **4d**, was not detected) and the resulting mixtures were conveniently separated by conventional column chromatography (Scheme 2).

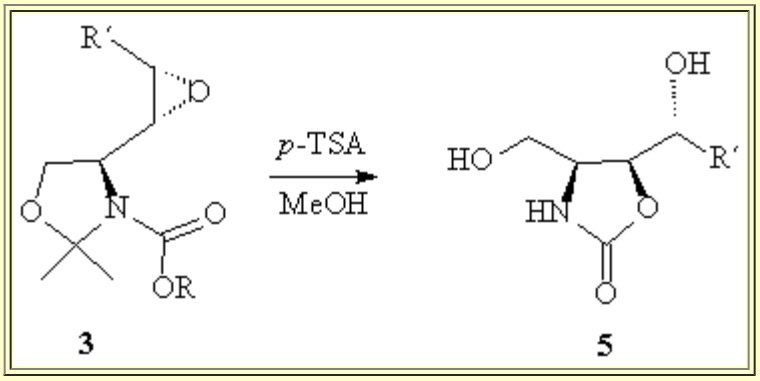


	R	R´	**3**	**4**
2a	*t*-Bu	H	28 %	14 %
2b	Bn	H	35 %	14 %
2c	*t*-Bu	Me	40 %	17 %
2d	Bn	Me	71 %	_

Scheme 2

Addition of p-TSA to a solution of the *threo* amino epoxides **3a-d** in anhydrous methanol at room temperature, afforded the corresponding cyclic carbamates **5a** (R´ = H) and **5b** (R´ = Me). According to the literature,[9] *tert*-butyl carbamates **3a**, **3c** reacted faster and with higher yields than their benzyl analogues **3b**, **3d** and in these cases, the

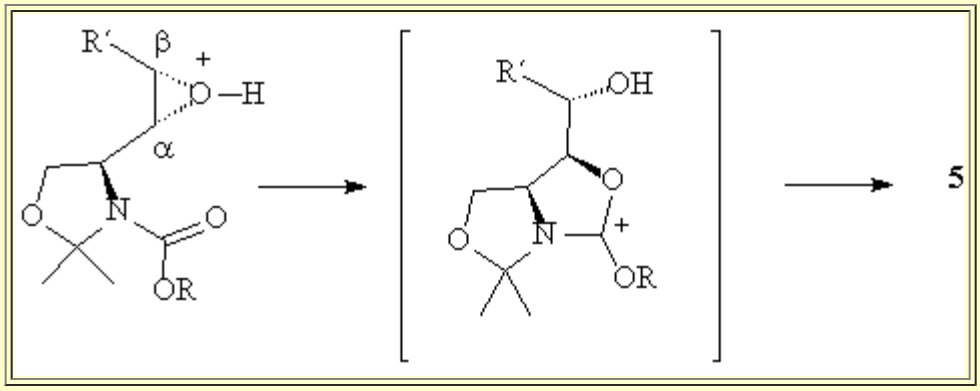
oxazolidinones **5** were isolated with good to excellent yields (Scheme 3).



Epoxide	R	R´	Yields (%) **5**
3a	*t*-Bu	H	60%
3b	Bn	H	41%
3c	*t*-Bu	Me	96%
3d	Bn	Me	86%

Scheme 3

The key-step in the asymmetric synthesis of the oxazolidinones **5** is a fully regio- and stereoselective cyclocarbamation process through an intramolecular nucleophilic attack of the carbamate moiety on the C-a of the protonated epoxide under acidic conditions (Scheme 4). Such participation of a carbamate moiety had been observed in intramolecular epoxide opening under acidic conditions.[9,10] To the best of our knowledge this is the first example of an intramolecular nucleophilic epoxide opening reaction in 4-oxiranyl-oxazolidines.



Scheme 4

The good results obtained in the case of compounds **3a-d**, suggested a similar study with the *erythro N,O*-protected

epoxide **4c**. However, when compound **4c** was submitted under the same conditions, failed to give the expected cyclic product **5**, and compound **6** (Figure 1) was isolated, as a result of an intermolecular reaction with the methanol used as solvent .

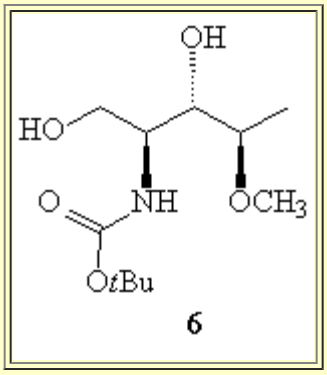
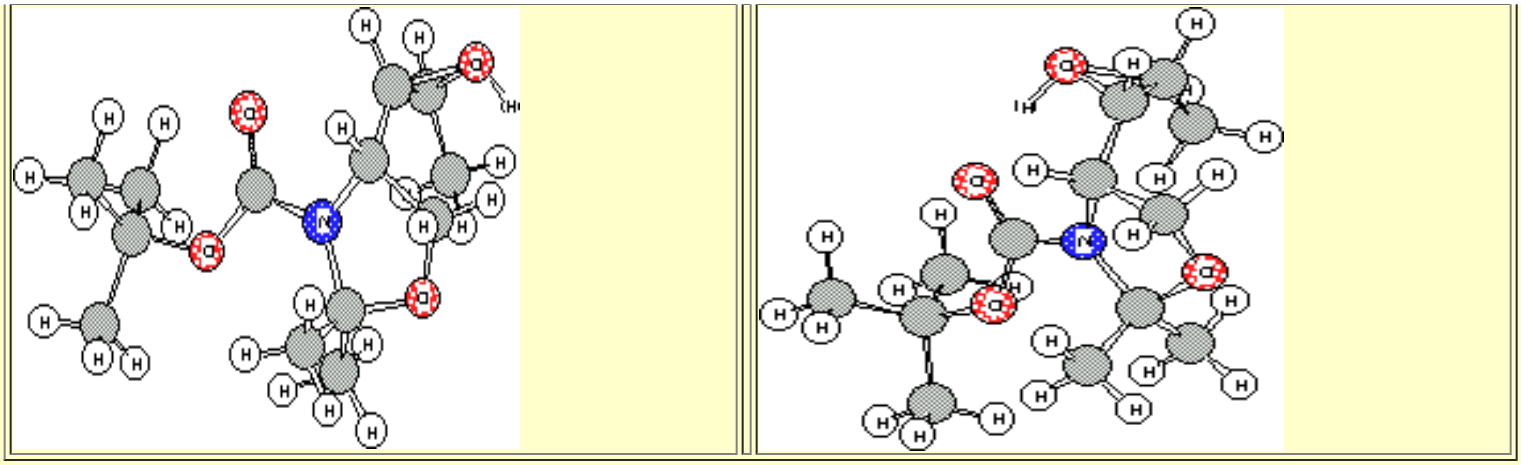


Figure 1

Moreover, theoretical calculations have been performed in order to explain the faster intramolecular rearrangement towards the intermolecular displacement in the case of the *threo* compounds **3**. Calculations were carried out using Gaussian94.[11] Geometries were fully optimized by ab initio calculations using restricted Hartree-Fock level of theory with 6-31G* basis sets. The structures were characterized as a minimun by a frecuency calculation and the RHF/6-31G* energies were corrected for unscaled zero point energies. The optimized structures are shown in Figure 2.
The different behaviour between **4c** and **3c** could be explained by the larger stability of the protonated epoxide **4c** in comparison with the protonated epoxide **3c** (relative stability of 14.59 Kcal/mol). Apparently, one reason for the intermolecular nucleophilic attack of the methanol in the case of the *erythro* compound **4c** is the formation of an intramolecular hydrogen bonding between the carbonylic oxygen atom of *tert*-butoxy carbonyl group and the hydrogen of the protonated oxygen atom of the epoxide group (interatomic distance C=O·····H-O , 1.498 Aº). This hydrogen bonding unables the carbonyl group to act as a nucleophile.
The outcome of the reaction in the case of the *threo* epoxide **3c** could be explained by the model shown in Figure 2. In this case the absence of an intramolecular hydrogen bond places the *N*-Boc group in a such conformation that the nucleophilic attack by the carbonyl oxygen atom is highly favoured.
The natural bond population (NBO) analysis on the protonated epoxide **3c** allows us to understand the total regioselection affording oxazolidinones **5a,b** through a 5-exo mode cyclization. This calculations are in agreement with larger positive charge in C-a position (C-a is 0.17 and C-b is 0.16) leading to the 5-exo closure pathway. Similar calculations performed on the protonated epoxide **4c** revealed that the positive charge is larger on the C-b position (C-a 0.12 and C-b 0.15) and the intermolecular nucleophilic attack occurs on the distal oxiranyl carbon atom (C-b) according to the literature.[1a, 2]



Protonated epoxide **3c** Protonated epoxide **4c**

Figure 2

CONCLUSIONS

In summary, treatment of threo amino epoxides **3a-d**, with catalytic *p*-TSA in anhydrous methanol led to a highly regio- and stereoselective intramolecular epoxide opening reaction, affording *cis*-oxazolidinones **5** via a 5-*exo*-tet process. Theoretical calculations confirm the preference of intramolecular versus intermolecular nucleophilic attack in threo isomers **3a-d**.

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