Synthesis of highly functionalized β-aminocyclopentane- or cyclohexanecarboxylate stereoisomers via selective nitrile-oxide dipolar cycloaddition

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Introduction

The 1,3-dipolar cycloaddition of nitrile oxides to alkenes has become widely used and a highly efficient method for the synthesis of isoxazolines. It is a powerful technique to functionalize olefins since the isoxazoline ring formed may be regarded as a masked iminoalcohol, hydroxyketone or aminoalcohol [1]. The multifunctionalized cyclohexane or cyclopentane amino acids (Oryzoxymycin, Tamiflu, Zanamivir, DANA, Peramivir) are important derivatives, which exhibit strong antiviral, antifungal or antibacterial activities [2].

Recently, our group reported a regio- and stereoselective procedure for the formation of a series isoxazoline-fused cispentacin and transpentacin stereoisomers (2-6) from the bicyclic β-lactam 1 [1] (Scheme 1).

Our aim was to synthesize highly functionalized β-aminocyclopentane carboxylate regio- and stereoisomers starting from the earlier prepared isoxazoline-fused cispentacin and transpentacin derivatives by reduction of the isoxazoline ring (Scheme 2).

The nitrile-oxide attack to the C=C bond of lactone 12 occurred, via H-bonding directing effect, from the carbamate-side, leading to the all-cis derivative 17 (Figure 2). The reduction reaction of the isoxazoline in 2 proceeded selectively with the H attack from carbamate side of the cyclopentane skeleton (Figure 1) giving 7. Next the reductions of other isoxazoline-fused cispentacin and transpentacin stereoisomers (4, 5 and 6) were effected in order to increase the number of diastereomers of the multifunctionalized amino esters (9-11, Scheme 3).

Nitroethane (derived form nitroethane) addition to 12 resulted in regio- and stereoselectively isoxazoline 17 in which the isoxazoline ring and the carbamate group have cis-relative stereochemistry, while the O-atom of the isoxazoline ring is closest to the carbamate. Next, compound 17 was subjected to lactone opening with NaOEt affording 15 and 16 (Scheme 4).

On treatment with NaOEt 23 by lactone ring opening resulted in the corresponding hydroxylated ester 24, and the isoxazoline ring opening with NaBH4/NiCl2 furnished in the corresponding highly functionalized amino ester 25 (Scheme 6).

Results

Conclusion

In conclusion eight highly functionalized cyclopentane and cyclohexane β-amino ester stereoisomers were prepared by regio- and stereoselective nitro-oxide cycloaddition, followed by reductive isoxazoline ring opening.

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References


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