Stereoselective Synthesis of Novel Highly Functionalized β-Aminocyclohexane-carboxylic Acids

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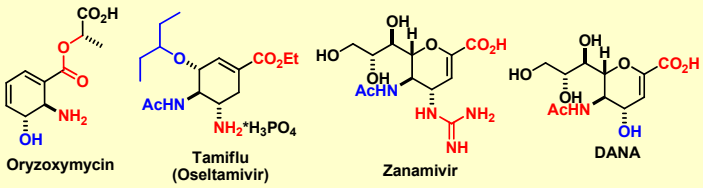
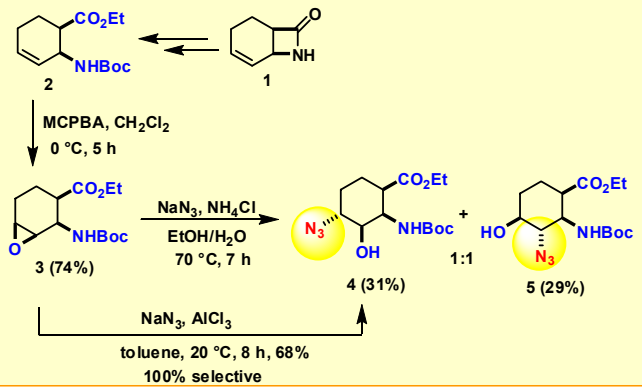
β-Amino acids as a result of their biological importance have exerted increasing interest in synthetic and medicinal chemistry during past twenty years. They are key elements of natural products and precursors of bioactive β-lactams. A number of cyclic β-amino acids, such as cispentacin, oxetin, or icofungipen are important antifungal or antibacterial agents. The conformationally restricted β-amino acids are building blocks in the synthesis of novel biologically active peptides [1]. Multisubstituted cyclic amino acids are important bioactive products. A number of these highly functionalized amino acid derivatives such as Oryzoxymicin, Tamiflu, Zanamivir, Peramivir or 2,3-didehydro-2-deoxy-N-acetylneuraminic acid (DANA) exhibit antiviral, antifungal or antibacterial activities (Scheme 1). An increasing number of functionalized modified analogues of these bioactive compounds have also been reported recent years [2].



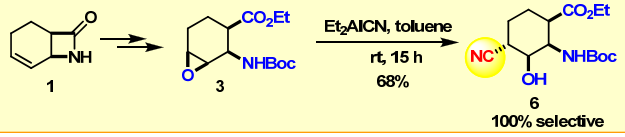
Scheme 1. Highly functionalized bioactive cyclic amino acids.

In this work the regio- and stereoselective synthesis of novel highly functionalized cyclohexane β-amino acid derivatives in racemic or enantiomerically pure form, starting from racemic unsaturated bicyclic β-lactam 1, involving enzymatic resolution, selective transformation of the C=C bond by stereoselective epoxidation, followed by regioselective oxirane opening with azide or cyanide nucleophiles is presented.



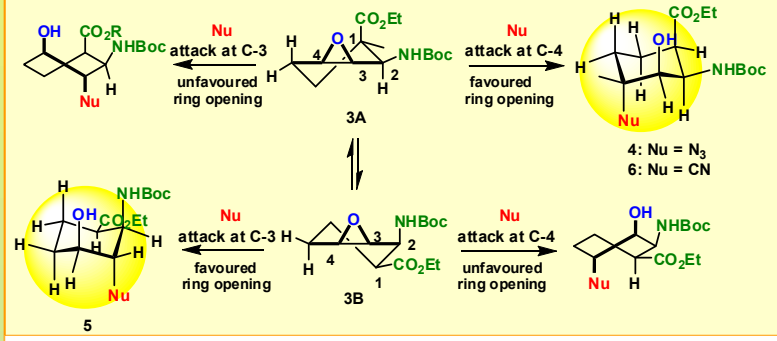
Scheme 2. Synthesis of azido ester regio- and stereosiomers 4 and 5.

Amino ester 2 derived from bicyclic lactam 1 afforded by *cis*-selective epoxidation amino ester 3. When 3 was subjected to oxirane opening with NaN_3/NH_4Cl/EtOH — as a result of the conformational equilibrium 3A-3B (Scheme 4) — the oxirane opening both at C-3 and C-4 led to the favoured chair diaxial conformation in which the hydroxy and azido moieties have *trans* diaxial arrangement giving two regioisomers 4 and 5 (1:1 ratio) which were separated by chromatography (Scheme 2). With the addition of $AlCl_3$, due to the coordinating capability of the Al with the ester and oxirane *O*-atoms the equilibrium is shifted to 3A, with the azide attack exclusively at C-4 through the diaxial conformer the oxirane opening resulted in 100% regioselectively azido ester 4 (Scheme 2 and Scheme 4). The N_3 attack at C-3 would lead to a twiseted chair conformation, due to this 5 is not formed under this condition.



Scheme 3. Regioselective opening of oxirane 3.

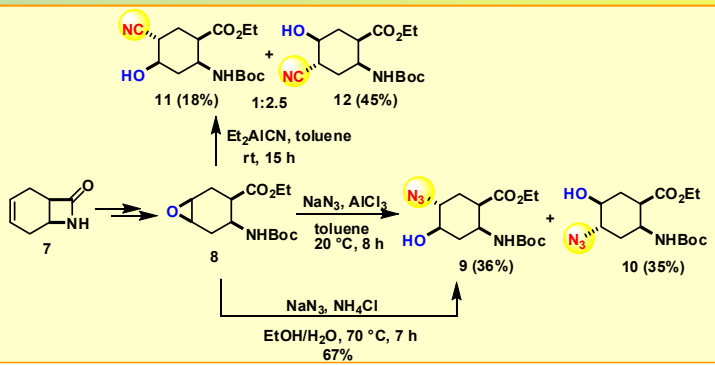
Introduction of a nitril group onto the cyclohexane skeleton of 3 was performed with Et_2AlCN. The oxirane opening reaction afforded 100% regioselectively amino ester 6 (Scheme 3).



Scheme 4. Oxirane opening in amino ester 3.

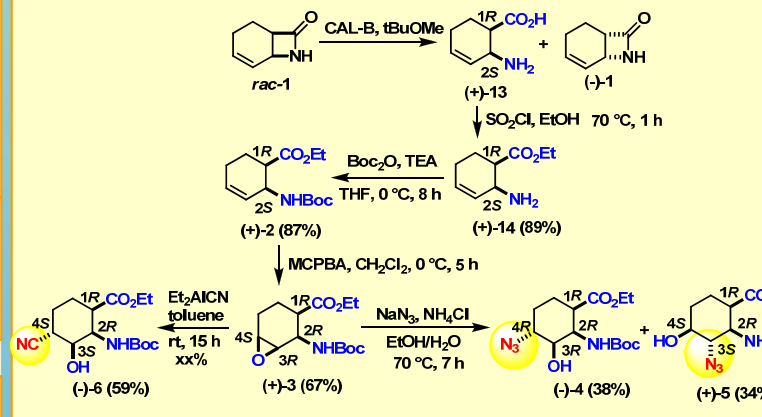
In the presence of Et_2AlCN the equilibrium of epoxide conformers is shifted to 3A, from which the CN attack at C-4 through the diaxial conformation led to 6. The regioselectivity of the reaction is a result of the diaxial chair conformation with the hydroxy and nitrile groups in axial position, affording amino ester 6. Attack of CN at C-3 would generate a twisted chair conformation. For this reason the 3-CN substituted amino ester was not formed.

Epoxide opening with N_3 of amino ester 8 derived from lactam 7 was 100% selective (9) while in contrast to earlier results (Scheme 2) in the presence of $AlCl_3$ furnished azido esters 9 and 10 in 1:1 ratio (Scheme 5). Subsequently epoxide 8 with Et_2AlCN resulted in 11 and 12 in 1:2.5 ratio.



Scheme 5. Synthesis of azido esters 9 and 10 and nitriles 11 and 12.

A simple access to multifunctionalized enantipure aminocyclohexanecarboxylates is presented on Scheme 6, starting from enantiopure amino acid (+)-7 prepared by enzymatic resolution of racemic azetidinone 1. The reaction steps presented on Schemes 2 and 3 were performed, yielding the desired amino esters in optically pure form.



Scheme 6. Synthesis of amino ester enantiomers (-)- 4, (+)-5 and (-)-6.

Summary: Starting from bicyclic β-lactams novel highly functionalized β-amino ester regio- and stereoisomers were prepared in enantiomerically pure form based on diastereoselective epoxidation and regioselective cyclohexaneepoxide opening with azide or cycanide nucleophiles.

[1] (a) Kiss, L.; Forró, E.; Fülöp, F. Amino Acids, Peptides and Proteins in Organic Chemistry. Vol. 1, Ed. A. B. Hughes, Wiley, Weinheim, 2009, 367. (b) Kiss, L.; Fülöp, F. *Synlett* 2010, 1302.
[2] (a) Wen, W-H.; Wang, S-Y.; Tsai, K-C.; Cheng, Y-S. E.; Yang, A-S.; Fang, J-M.; Wong, C-H. Bioorg. Med. Chem. 2010, 18, 4074. (b) Cui, Y.; Jiao, Z.; Gong, J.; Yu, Q.; Zheng, X.; Quan, J.; Luo, M.; Yang, Z. Org. Lett. 2010, 12, 4. (c) Lu, W. J.; Chen, Y. L.; Ma, W. P.; Zhang, X. Y.; Luan, F.; Liu, M. C.; Chen, X. G.; Hu, Z. D. Eur. J. Med. Chem. 2008, 43, 569.