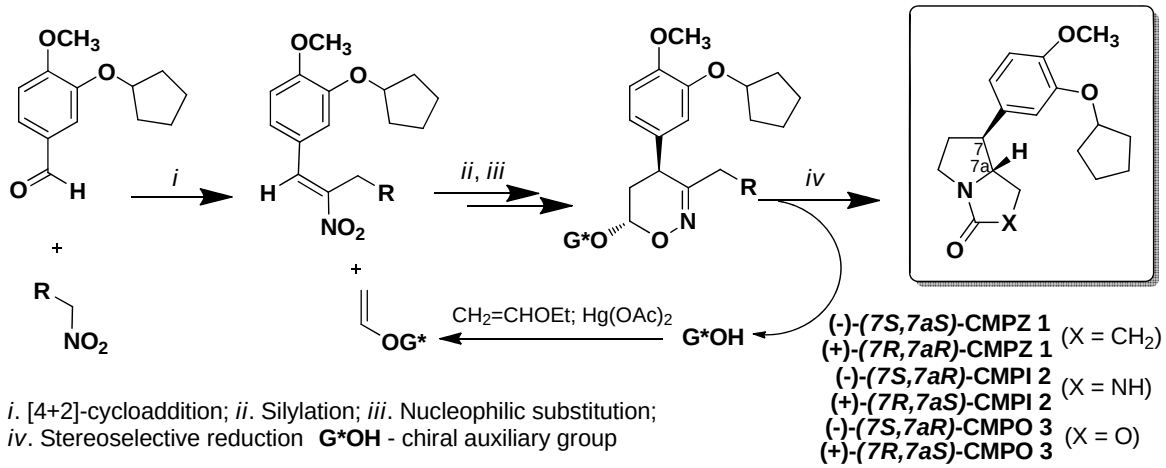
First Asymmetric Syntheses of Three GlaxoSmithKline's Highly Potent Rolipram Analogues

A. Yu. Sukhorukov, Y. D. Boyko, P. A. Zhmurov, S. L. Ioffe, V. A. Tartakovsky
N.D. Zelinsky Institute of Organic Chemistry, 119991, Leninsky prospect, 47, Moscow, Russian Federation
sukhorukov@ioc.ac.ru

Inhibitors of type 4b phosphodiesterase (PDE) such as well-known Rolipram and Cilomilast are considered as innovative drugs against asthma and chronic obstructive lung disease.[1] However, modern PDE 4b inhibitors still suffer from low activity, selectivity and numerous adverse affects, thus making a search for new drug candidates a challenging task.

Scheme



i. [4+2]-cycloaddition; *ii*. Silylation; *iii*. Nucleophilic substitution;
iv. Stereoselective reduction **G*OH** - chiral auxiliary group

Bicyclic pyrrolidine derivatives CMPZ **1**, CMPO **2** and CMPO **3** (Scheme) were introduced by GlaxoSmithKline as highly active PDE 4b inhibitors considerably more potent than Rolipram and Cilomilast. However, biological studies were performed only for racemic samples due to the absence of asymmetric approach to the synthesis of their individual enantiomers. In the present work first total syntheses of enantiopure PDE 4b inhibitors (+)-, (−)-CMPZ **1**, (+)-, (−)-CMPO **2** and (+)-, (−)-CMPO **3** have been developed.[2] The suggested synthetic strategy is based on the original silicon-mediated C−H functionalization of chiral six-membered cyclic nitronates as the key stage.[3]

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1. J.M. Michalski, G. Golden, J. Ikari, S.I. Renard, *Clin. Pharm. Ther.*, **2012**, *91*, 134.
2. (a) A.Yu. Sukhorukov, Y. D. Boyko, Y. V. Nelyubina, S. Gerard, S.L. Ioffe, V.A. Tartakovsky, *J. Org. Chem.*, **2012**, *77*, 5465. (b) A. Yu. Sukhorukov, Y. D. Boyko, Yu. A. Khomutova, Yu. V. Nelyubina, S. L. Ioffe, V. A. Tartakovsky, *J. Org. Chem.*, **2011**, *76*, 7893.
3. A.Yu. Sukhorukov, S.L. Ioffe, *Chem. Rev.*, **2011**, *111*, 5004.