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作品名稱

Asymmetric Total Synthesis of GlaxoSmithKline's Potent Phosphodiesterase PDE IVb Inhibitor

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ABSTRACT

Phosphodiestarase of subtype PDE IVb inhibitors are considered as perspective drugs for the treatment of the central nervous system disorders (depression, Alzheimer's disease, Parkinson's disease). Pyrrolizidinone Glaxo-1, proposed by GlaxoSmithKline, is a highly potent PDE IVb inhibitor (IC_{50} = 63 nM), then conventional phosphodiesterase inhibitors Ro-20-1724, Rolipram and Cilomilast. However the activity of the Glaxo-1 was studied on a racemic sample, since the asymmetric approach to its synthesis has not been developed. Therefore the purpose of this research was the development of an efficient synthetic scheme enabling enantioselective excess to both *(-)*- and *(+)*-Glaxo-1, which can be than subjected to biological studies.

The key stage in proposed asymmetric synthesis *(-)*- and *(+)*-Glaxo-1 is stereoselective [4+2]-cycloaddition of the nitroolefin to an optically activity vinyl ethers, derived from *(-)*- or *(+)-trans*-2-phenylcyclohexanols. The resulting chiral cyclic nitronates are transformed into a functionalized cyclic oxime ethers using tandem sylilation-nucleophilic substitution procedure. Reduction and decarboxylation of these products lead to optically pure Glaxo-1 and the regeneration of chiral 2-phenylcyclohexanols (91%).

Thus both enantiomers *(+)* and *(-)*-Glaxo-1 were obtained selectively in average yield 12% from isovaniline and nitroethane. The study of biological profiles of each enantiomer of Glaxo-1 will be conducted in near future.

評語

A hard work and “improved total yield of the Glaxo Smithkline’s potent phosphodiesterase PEDIVB inhibitor “ synthesis Purity of the effective EE value to 90%.

All the data show the identity of the final product (25% yield, two times increase the literature value), except missing 2DNMR & the chromatography separation of the pure final chiral form.