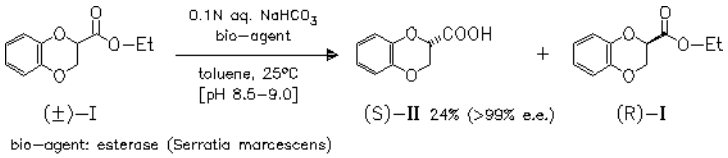
pyrazine derivatives

R 0550

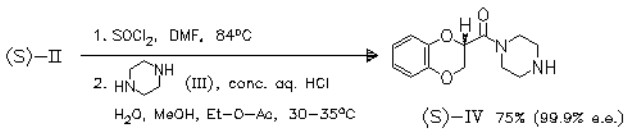
06 - 175

Practical Chemical and Enzymatic Technologies for (S)-1,4-Benzodioxanyl-2-carboxypiperazine Intermediate in the Synthesis of (S)-Doxazosin Mesylate. — Two different methods for the synthesis of optically active benzodioxanylcarbonylpiperazine (IV) are presented. The first method involves the enzymatic resolution of benzodioxanylcarboxylate (I), followed by condensation of the so-formed enantiopure acid (II) with piperazine. Due to an unfavorable eutectic point of the crystallization mixture, however, the crystallization of enantiopure compound (II) is not effective. The second method involves the chemical resolution of racemic amide (IV) with D-tartaric acid. Optically active amide (IV) is isolated in 20% yield and 99.3% e.e. after crystallization. Condensation of (S)-amide (IV) with chloroquinazoline (V) then provides doxazosin (VI). — (FANG, Q. KEVIN; GROVER, PAUL; HAN, ZHENGXU; MCCONVILLE, FRAN X.; ROSSI, RICHARD F.; OLSSON, DAMASE J.; KESSLER, DONALD W.; WALD, STEPHEN A.; SENANAYAKE, CHRIS H.; Tetrahedron: Asymmetry 12 (2001) 15, 2169-2174; Chem. Res. Dev., Sepracor Inc., Marlborough, MA 01752, USA; EN)

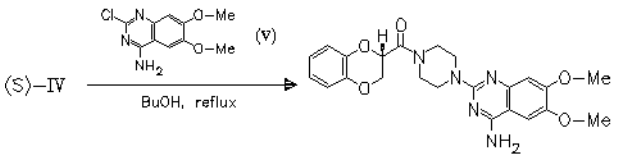


(±)–I (S)–II 24% (>99% e.e.) (R)–I

bio–agent: esterase (Serratia marcescens)



(S)–IV 75% (99.9% e.e.)



(S)–VI 95% (99.8% e.e.)