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Chemoenzymatic Synthesis of Rivastigmine via Dynamic Kinetic Resolution as a Key Step

Synthesis of (S)-Rivastigmine

**Significance:** Rivastigmine (Exelon®) is an acetylcholinesterase inhibitor that is prescribed for the treatment of mild to moderate dementia in patients with Alzheimer’s disease and Parkinson’s disease. The key step in the synthesis depicted is a dynamic kinetic resolution of the benzylic secondary alcohol B involving a lipase (Novozyme 435) coupled with a polymer-bound racemization catalyst (C).

**Comment:** The polymer-bound racemization catalyst C was prepared by heating a polymer-bound benzoyl chloride with $[\text{Ph}_4\text{N}]_2[\eta^5-\text{C}_2\text{CO}]\text{Ru(CO)}_3$ in toluene for one day. The catalyst can be recycled several times. The enzymatic resolution was performed on a 1 mmol scale. For an alternative chemoenzymatic synthesis of rivastigmine, see: J. Mangas-Sánchez et al. J. Org. Chem. 2009, 74, 5304.

**Key words**
- rivastigmine
- dynamic kinetic resolution
- lipases
- racemization

**Synthesis of (S)-Rivastigmine**

1. Et(Me)NCOCl (2.0 equiv) NaH (2.0 equiv)
   CH$_2$Cl$_2$, r.t., 4 h
2. NaBH$_4$ (1.0 equiv)
   MeOH, 0 °C
85%

1. MsCl (1.3 equiv)
   Et$_3$N (3.0 equiv)
   CH$_2$Cl$_2$, 0 °C, 30 min
2. Me$_2$NH (4.0 equiv)
   THF, r.t., 2 d
77%

Novozyme 435 (30 mg/mmol)
isopropenyl acetate (1.5 equiv)
K$_2$CO$_3$ (1.0 equiv)
PhMe (0.3 M), r.t., 1 d
96% (er > 99:1)

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Synfacts 2010, 8, 0853-0853 Published online: 22.07.2010
DOI: 10.1055/s-0030-1257746; Reg-No.: K04210SF