Total Synthesis of Tetrahydrolipstatin and Stereoisomers via a Highly Regio- and Diastereoselective Carbonylation of Epoxymethylalcohol Alcohols


**Synthesis of Tetrahydrolipstatin**

**Significance:** Tetrahydrolipstatin (Xenical®) is a pancreatic lipase inhibitor that is marketed as a treatment for obesity. The eleven-step small-scale synthesis depicted (31% overall yield) features the regioselective carbonylation of the cis-epoxide using the bimetallic [Lewis acid] + [Co(CO)₄]– catalyst to give the trans-β-lactone.

**Comment:** Seven diastereoisomers of tetrahydrolipstatin were also prepared by this epoxide carbonylation route. Attempts to synthesize epoxide via the direct DCC coupling of N-formyl-L-leucine occurred with appreciable amounts of epimerization.

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