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A Facile Enzyme Assisted Route to (*R*) - and (*S*)-*t*-Butyloxirane and related β-Amino Alcohols - Catalysts for the Enantioselective Addition of Dialkylzinc Reagents to Aldehydes

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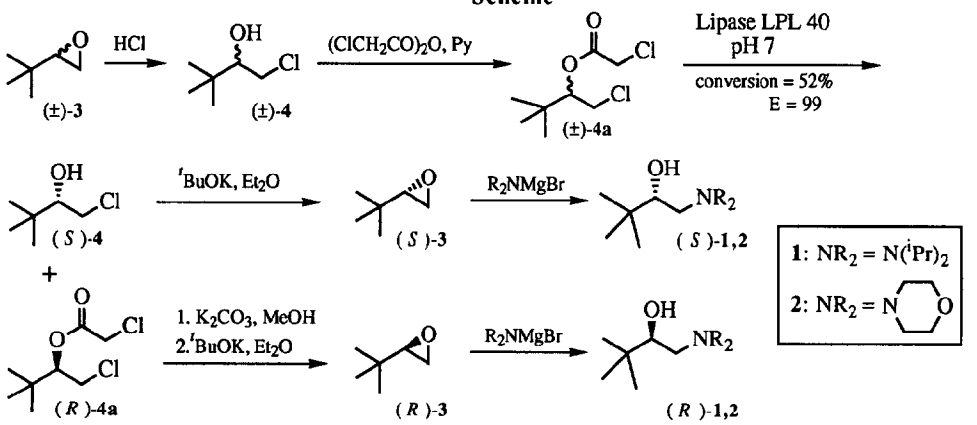
Abstract: (*R*) and (*S*)-*t*-butyloxirane [(*R*)- and (*S*)-**3**] have been prepared in high enantiomeric purity from racemic *t*-butyloxirane (±)-**3** by an enzymatic route. (*S*)-**3** has been used for the preparation of the chiral β-amino alcohols (*R*)- and (*S*)-**1,2**, which are catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes.

Chiral β-amino alcohols of high optical purity, among them (*R*)- and (*S*)-**1,2** carrying bulky *t*-butyl substituents are excellent catalysts for the enantioselective addition of dialkylzinc reagents to a variety of structurally different aldehydes, leading to the corresponding secondary alcohols of high enantiomeric purity both from achiral starting materials[1,2] and also racemates *via* kinetic resolution[3]. Clearly one of the easiest ways to obtain these molecules in high optical purity would be the regioselective, nucleophilic ring opening of (*R*) and (*S*)-*t*-butyloxirane, (*R*)- and (*S*)-**3** with the corresponding amines. Unfortunately, however, the methods hitherto described for the preparation of (*R*)- and (*S*)-**3** are less than satisfactory. These require either lengthy procedures[4], not easily accessible starting materials[5] or lead to products with either modest optical or chemical yields[6].

Scheme



We wish to report here an extremely simple procedure for the preparation of the title compounds using easily accessible and inexpensive starting materials based on the highly selective enzymatic resolution of the corresponding chlorohydrins (*R*)- and (*S*)-**4** (Scheme). (±)-**4** can be prepared easily in high yield (80-85%) *via*

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nucleophilic ring opening of the corresponding racemic *t*-butyloxirane (±)-**3** with aqueous hydrochloric acid. (±)-**4** is then converted into the corresponding racemic chloroacetate (±)-**4a** (chloroacetic anhydride, pyridine). Based on our previous experience with the enzymatic hydrolyses of numerous secondary alcohols in presence of a lipase from *Pseudomonas sp.* (SAM II)[7] it was to be expected that products of high enantiomeric purities should also result from the corresponding lipase catalyzed resolution of (±)-**4a**. Unfortunately, (±)-**4a** was not accepted by the enzyme as substrate. We finally discovered, however, that a very enantioselective hydrolysis of (±)-**4a** can be achieved in presence of the highly active, purified lipoprotein lipase from *Pseudomonas sp.* (LPL 40). In a typical experiment 42.6 g (200 mmol) of (±)-**4a** were suspended in 300 ml 0.1 M phosphate buffer (pH 7) followed by the addtion of 800 mg of the lipase LPL 40 (320000 u) while the pH of the reaction mixture was kept constant by addition of 1 N NaOH solution (pH stat conditions). After 52% conversion (104 h) the reaction was terminated. The products were isolated by extraction and separated by distillation. Obtained were 7.7 g (38%) (*S*)-**4** [b.p.= 156 °C, $[\alpha]_D^{25}$= +42.1(c=1.85, $CHCl_3$), 91%ee (GC on Cyclodex β-I/P)] and 13.43 g (42%) (*R*)-**4a** [$b.p._{40mbar}$= 135 °C, $[\alpha]_D^{25}$= -15.5(c=2.2, $CHCl_3$), >98%ee (GC Cyclodex β-I/P)]. Only the chlorohydrin is accepted as substrate by the enzyme. No conversion was observed with the sterically more demanding bromohydrin ester. The use of activated esters (chloroacetates) was essential for the success of these transformations, both by expediting the rates of hydrolysis of the sterically congested ester function and by facilitating the separation of the products by simple distillation. (*R*)-**4a** was then converted into (*R*)-**4** [$[\alpha]_D^{25}$= -41.0(c=1.3, $CHCl_3$)] by methanolysis in presence of K_2CO_3. Treatment of (*R*)- and (*S*)-**4** with ^{t}BuOK in Et_2O led directly to (*R*)-**3** [$[\alpha]_D^{25}$= -18.4(c=1.7, benzene)], and (*S*)-**3** [$[\alpha]_D^{25}$= +16.4(c=1.8, benzene)], in 65% and 68% isolated yield respectively. The enantiomeric purities of (*R*)- and (*S*)-**3** were unambigously secured both by comparison of the optical rotations with literature data[9] and independently by HPLC using BGIT as chiral auxiliary[10] [(*S*)-**3**: 97%ee, (R)-**3**: 92%ee]. Finally (*S*)-**3** was converted by reaction[11] with diisopropyl amine and morpholine into (*S*)-**1** [$[\alpha]_D^{25}$= +76.7(c=1, $CHCl_3$)] and (*S*)-**2** [$[\alpha]_D^{25}$= +68.1(c=1, $CHCl_3$)] respectively. It should be noted that considerable asymmetric amplification has been observed[12] from catalysts with rather low enantiomeric excess leading to products with high optical purities.

In summary, the above described method allows a rather convenient access to (*R*)- and (*S*)-*t*-butyloxirane and β-amino alcohols derived thereof, e.g. (*S*)-**1,2**. These have been shown to be highly enantioselective catalysts in the addition of dialkylzinc reagents to aldehydes.

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