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Synthesis of *R*-(−)-2-phenylpropanal: a potentially new route towards chiral 2-phenylalkanals

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Abstract

A facile two step synthesis of (*R*)-2-phenylpropanal in high enantiomeric excess is described, starting from commercial (*S*)-styrene oxide, involving as a key step a Dess–Martin oxidation. © 1998 Elsevier Science Ltd. All rights reserved.

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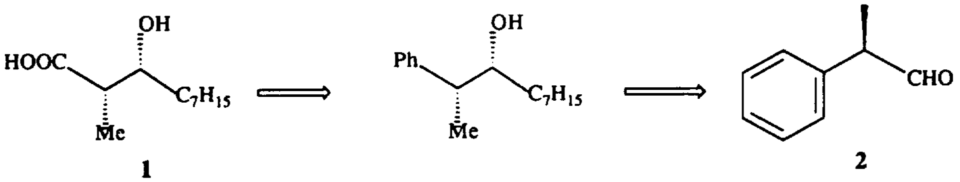
1. Introduction

(2*S*,3*R*)-3-Hydroxy-2-methyldecanoic acid **1** is a component of hapalosin, a cyclic depsipeptide which exhibits an anti-multidrug resistance (MDR), a phenomenon encountered in cancer chemotherapy.[1] Compound **1** is usually obtained by an aldol reaction utilizing n-octanaldehyde.[2] Another possibility would be a condensation of n-heptyllithium with (*R*)-2-phenylpropanal **2** through a Cram model selectivity,[3] followed by oxidation of the phenyl group (Scheme 1).



Scheme 1.

For this purpose, we turned our attention towards the preparation of enantiomerically pure **2** and we were surprised to find no simple method describing its optically pure synthesis.[4] Besides the transition metal catalysed asymmetric hydroformylation of vinyl benzene,[4a] the only useful method described until now was the stereocontrolled 1,4-addition of trimethylaluminium to a chiral α,β-unsaturated acetal.[4b] Two kinetic resolutions by enantioselective addition of diethylzinc to racemic 2-phenylpropanal,[4c] and

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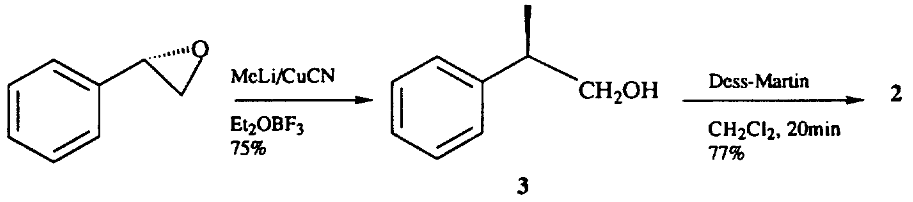
enzymatic ester hydrolysis in rather low enantiomeric excess (ee)[4d] were also described. Consequently, we set out for a convenient method to access **2**.

Here, we wish to describe a two step synthesis of **2** in high enantiomeric excess starting from (*S*)-styrene oxide (Scheme 2).



Scheme 2.

2. Results and discussion

Epoxide opening of (*S*)-styrene oxide[5] with methyllithium under our previously described conditions[6] led to 2-phenylpropan-1-ol **3**, contaminated with a small amount of the regioisomer (about 5%). Separation of the two regioisomers was achieved by chromatography over silica gel. In order to determine the enantiomeric excess, **3** was converted into its trifluoroacetate derivative, and submitted to gas chromatography using a chiral column (gamma-cyclodextrin butyryl/40 m×0.25 mm/type G-BP/Interchim) revealing an ee of 96%. However, owing to the rather low rotatory power observed, we presume that a trace amount (not detectable by GC) of the regioisomer, 1-phenyl-1-propanol, still remained; indeed, this minor regioisomer showed an opposite sign of rotation.[7]

The next step proved more troublesome. Our initial idea was to use the Swern oxidation,[8] since it proceeds under rather mild conditions; unfortunately, subsequent GC measurement of the ee, after reduction of the carbonyl with $NaBH_4$ and transformation of the resulting alcohol (see above) revealed almost complete racemisation. Among a variety of oxidizing reagents that were tested (tetra-n-butylammonium per-ruthenate,[9] chromium trioxide/Celite,[10] etc.), it appeared that the only reagent to give **2** in good chemical yield and without loss of enantiomeric excess was the Dess–Martin periodinane.[11]

Since a variety of alkyllithiums can be used in the ring opening of styrene oxide, this method could be seen as a general procedure to access phenyl-2-alkanals.

3. Experimental

Infrared spectra were taken on an FT Nicolet 210 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ using a Bruker AC-200 E apparatus. Chemical shifts are expressed in ppm from internal TMS. Flash chromatography was performed using silica gel 60 (Merck, 230–400 mesh). Optical rotations were measured on a Perkin–Elmer 141 polarimeter.

3.1. (R)-2-Phenyl-1-propanol 3

A 1.6 M ether solution of methyllithium (15.6 mL, 25 mmol) was added to a suspension of CuCN (2.24 g, 25 mmol) in THF (30 mL) cooled to −40°C. The solution was allowed to warm to −20°C for 30 min. The homogeneous pink solution was cooled to −80°C and $BF_3\cdot Et_2O$ (3.2 mL, 25 mmol) was slowly added. After 5 min stirring at the same temperature, a solution of styrene oxide (2 g, 16.6

mmol) in THF (10 mL) was added and the resulting solution was stirred for 15 min. The reaction was quenched with a solution of 1/1 saturated NH_4Cl/10 M NH_4OH (40 mL) and stirred for 1 h until the copper salts were completely dissolved. After extraction with Et_2O (3×20 mL), the organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography over silica gel to give the alcohol **3** (1.7 g, 75%) whose spectral ^1H NMR data were in full accordance with the literature;[12] $[\alpha]_D^{22}$=+13.2 (neat); literature: $[\alpha]_D^{20}$=+16.6 (neat), 95.4% enantiomeric excess.[13]

*3.2. (*R*)-2-Phenylpropanal 2*

To a solution of 2-phenyl-1-propanol (1 g, 7.3 mmol) in dry dichloromethane (40 mL) was added the Dess–Martin periodinane (5.3 g, 12.4 mmol) in one portion (a gentle warming was observed). The reaction was stirred for 20 min at room temperature. A buffer solution of NaH_2PO_4/$KHPO_4$ (25 mL) was added to the reaction flask and the mixture was stirred for 10 min. The reaction mixture was filtered through Celite and washed with dichloromethane. The solution was extracted with CH_2Cl_2 and dried over magnesium sulfate. The organic layer was filtered and evaporated to give a colourless liquid with a strong characteristic odour.[14] The latter was diluted with pentane and filtered again over Celite. After evaporation of the solvent, the product was quickly purified by flash chromatography using cyclohexane:ethyl acetate (95:5) as eluent to give the pure aldehyde **2** (0.76 g, 77%), whose spectral data were in full accordance with the literature;[4e] $[\alpha]_D^{22}$=−229 (c 0.68, diethyl ether); literature: $[\alpha]_D$=+192 (c 0.69, ether)[4b] and $[\alpha]_D^{22}$=−205.3 (neat).

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