Synthesis of Optically Active 8-Hydroxy-1-tetralone Derivatives

David Kieslich and Jens Christoffers*

Institut für Chemie, Universität Oldenburg, Carl von Ossietzky-Str. 9–11, D-26111 Oldenburg

Starting from 8-aminonaphthalene-1-sulfonic acid, 8-alkoxy-1-tetralone was synthesized in four steps and was used as starting material for the preparation of optically active 8-hydroxy-1-tetralone derivatives according to the Tsuji-Trost procedure.

1. Introduction

Deprotonated β-dicarbonyl compounds **1** are important ligands ("diketonates") for transition metal complexes.[1] For this reason, they play a considerable role in homogeneous catalysis. In order to access chiral "diketonato" complexes for asymmetric catalysis, we aim to prepare optically active β-dicarbonyl compounds. Actually, to prevent the ligand structure to undergo reactions as a nucleophile in the α-position, we propose that the title structure **2** or the dimer **3** could be a perfect substitute for a β-diketone. Therefore, we have developed a synthetic route to chiral derivatives of tetralone **2**.

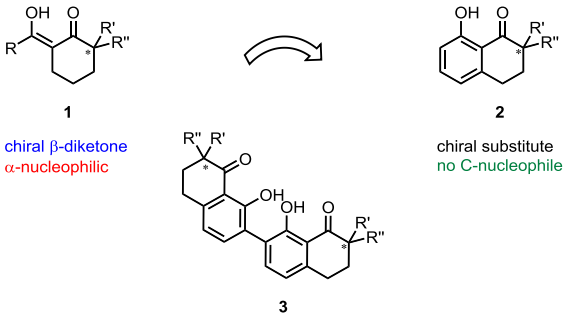
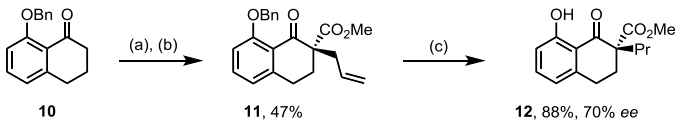


Figure 1: Hydroxytetralone **2** or dimer **3** as a non-nucleophilic substitute for a chiral β-diketone **1**.

3. Synthesis of the 8-Hydroxy-1-tetralone Derivatives Using Asymmetric Allylic Alkylation Reaction

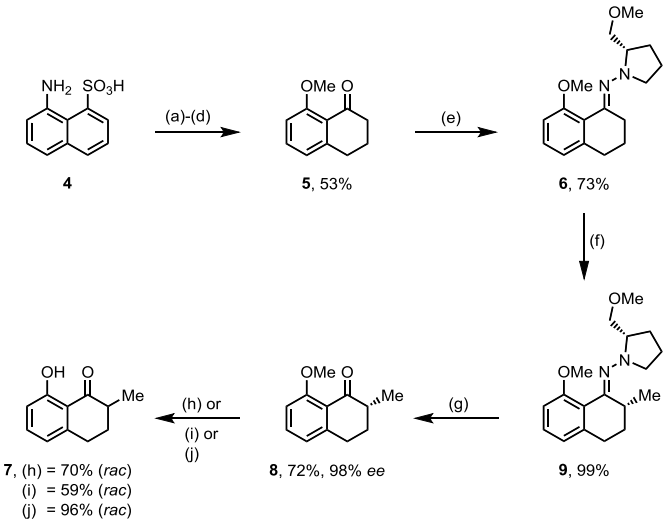
An alternative to access optically active hydroxytetralone derivatives was to use the enantioselective allylic alkylation according to Tsuji-Trost. For this purpose compound **11** was prepared starting from 8-alkoxytetralone **10** over two steps in 47% overall yield. After deprotection of the hydroxyl group and subsequent hydrogenation of the double bond compound **12** could be obtained in 88% yield and an ee of 70%. In order to ensure better complexation of transition metal ions in the future, the next step could be the dimerization of compound **11** to obtain larger ligands for the metal ions with the skeletal structure of compound **3**.



Scheme 2: Reagents and conditions. (a) 1.8 eq. NaH, 10.0 eq. $(MeO)_2CO$, THF, 66°C, 16 h; (b) 1.5 eq. allyl acetate, 1.2 eq. TMG; 0.4 mol% $Pd_2(dba)_3$, 1.6 mol% (*R*,*R*)-DACH, toluene, 0°C → 23°C, 18 h; (c) 5.0 mol% Pd/C, 1 atm H_2, MeOH, 23°C, 2 h.

2. Preparation of 8-Hydroxy-2-methyl-1-tetralone

Starting from 8-aminonaphthalene-1-sulfonic acid **4**, 8-Methoxy-1-tetralone **5** was prepared in 53% yield over four steps. To install the stereocenter in the 2-position, Enders auxiliary (S)-(–)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) was used and hydrazone **6** was obtained in 73% yield. The alkylated compound **9** could be obtained almost quantitatively. For the cleavage of hydrazone **9** different reaction conditions were tried. The use of oxalic acid gave product **8** as a racemate in a low yield. This problem did not occur with SmI_2, but compound **8** could only be obtained in traces.



Scheme 1: Reagents and conditions. (a) 2.5 eq. $NaNO_2$-H_2O, 13% HCl-H_2O, 100°C, 2 h; (b) 12.0 eq. KOH, 12.0 eq. NaOH, 220°C, 1 h; (c) 2.5 eq. $AlCl_3$, cyclohexane, 110°C, 1 h; (d) 6.0 eq. K_2CO_3, 4.4 eq. MeI, acetone, 56°C, 23 h; (e) 1.1 eq. SAMP, 0.1 eq. TosOH, hexane, molecular sieve, 85°C, 16 h; (f) 1.5 eq. LDA, 2.3 eq. MeI, Et_2O, –110°C → 23°C, 13 h; (g) 1.2 eq. $CuCl_2 \cdot 2\ H_2O$, THF, 0°C→ 23°C, 16 h; (h) 1.5 eq. $CeCl_3 \cdot 7\ H_2O$, 1.5 eq. NaI, MeCN, 82°C, 6 h; (i) 3.0 eq. BBr_3, DCM, –90°C → 23°C, 2 h; (j) 2.5 eq. $CH_3(CH_2)_{14}SH$, 2.5 eq. NaH, DMF, 100°C, 3 h.

Other methods, such as the use of SeO_2 or baker's yeast gave product **8** in 57–95% yield with 32–91% *ee*. Finally the best method was the cleavage with $CuCl_2 \cdot 2\ H_2O$ and 98% *ee*. In the last step the arylmethylether should be cleaved. For this purpose various reaction conditions were tested, which gave compound **7** in good to nearly quantitative yields, but only as a racemate. Since the use of other protecting groups such as benzyl or TBS lead to other problems on the synthetic route, a new strategy was proposed and finally the asymmetric allylic alkylation was utilized.[2]

[1] K. Binnemans, K. A. Gschneider Jr., J. C. Bünzli, V. K. Pecharsky, *Handbook on the Physics and Chemistry of Rare Earths*, *35*, Elsevier Verlag, Amsterdam, **2005**, 107–272.

[2] B. M. Trost, B. Schaffner, M. Osipov, D. A. A. Wilton, *Angew. Chem. Int. Ed.* **2011**, *50*, 3548–3551.