Synthesis of Optically Active Dimethyl 3-Isopropylpimelate

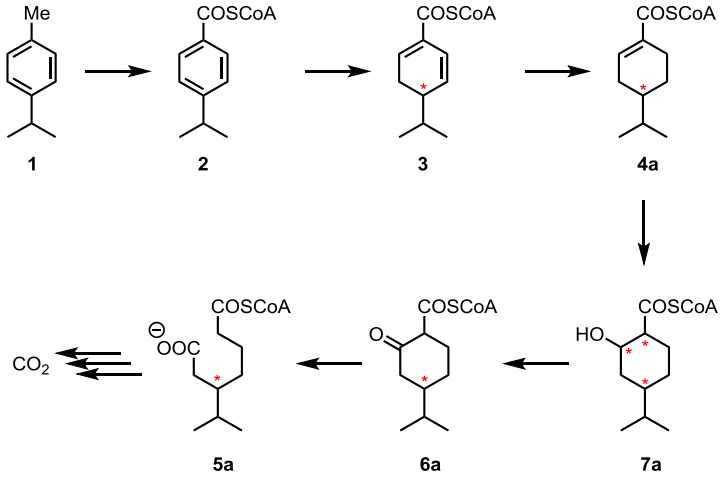
Julian Küppers,[a] Nevenka Cakić,[b] Ralf Rabus,[b] Heinz Wilkes[b] and Jens Christoffers*[a]

[a] Institut für Chemie, [b] Institut für Chemie und Biologie des Meeres
Universität Oldenburg, Carl von Ossietzky-Str. 9–11, D-26111 Oldenburg

An asymmetric synthesis of dimethyl 3-isopropylpimelate was accomplished in five steps from cyclohexenone. This compound is an important reference to study the anaerobic metabolic degradation of *p*-cymene by bacterial strain "*Aromatoleum aromaticum*" pCyN1.

Introduction and Microbiological Background

Within the biological carbon cycle on earth anaerobic microbial processes play the major role in subsurface transformations of organic compounds. In these anoxic environments anaerobic microorganisms have developed special strategies to use hydrocarbons as a source of energy.[1] A suggestion of the anaerobic metabolic degradation of *p*-cymene by bacterial strain "*Aromatoleum aromaticum*" pCyN1 is given in Scheme 1.[2] After oxidation of the methyl group, a biological "Birch-type reduction" leads to the formation of a stereocenter in compound **3**. Its configuration is expected to be retained in the subsequent products **4a–7a** which can be observed by harvesting the strain. Especially the β-alkylated pimelic acid **5a** seems to be a good system to explore the metabolic mechanism.



Scheme 1: Anaerobic metabolic degradation of *p*-cymene by bacterial strain "*Aromatoleum aromaticum*" pCyN1.[2]

Comparison of Synthetic Compounds and Extract

The comparison of the synthetic standards **5c** with the extracted compound (after transesterification) from pCyN1 showed, that during the anaerobic metabolic degradation of *p*-cymene by pCyN1 only the (*S*)-enantiomer is formed (Figure 1).

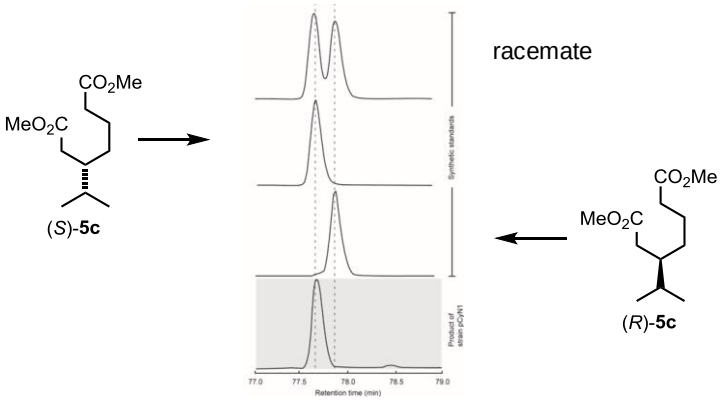
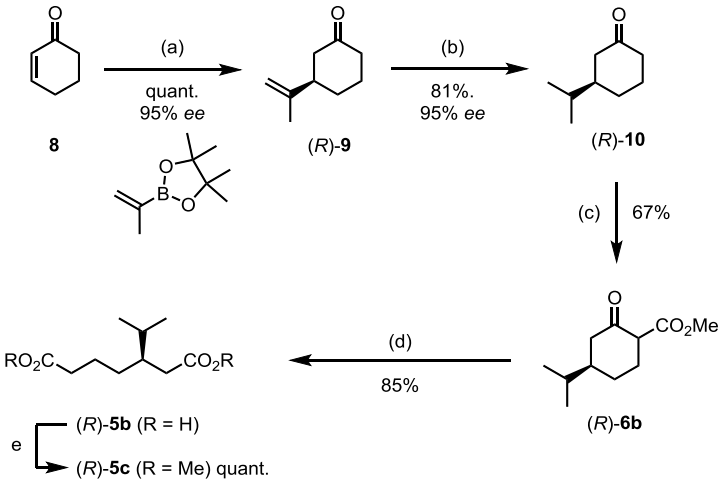


Figure 1: GC-comparison of the synthetic standards **5c** with the extract from pCyN1.

Asymmetric Synthesis

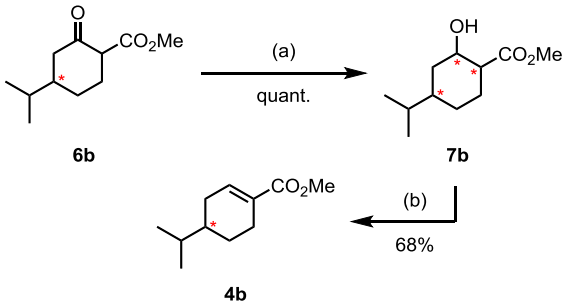
First step of the route to optically active title compound (*R*)-**5c** was the metal-catalyzed conjugated addition of a boronic ester to cyclohexenone (**8**) using a chiral phosphane-ligand followed by Claisen reaction. Retro-Claisen cleavage of the six membered ring lead to the pimelic acid derivative (*R*)-**5b**. The dimethyl ester (*R*)-**5c** was prepared *via* the acid chloride. In a similar manner we synthesized the enantiomer (*S*)-**5c**.



Scheme 2: a) Boronic ester, NEt_3, $[Rh(cod)_2]BF_4$, (*R*)-DTBMSEGPHOS, toluene–water 2:1, 60°C, 19 h; b) 1 atm H_2, PtO_2, EtOH, 23°C, 1.5 h; c) $CO(OMe)_2$, NaH, THF, 75°C, 20 h; d) Na, 1-pentanol, 145°C, 19 h; 2. H_2O, 23°C, 5 min; e) 1. $SOCl_2$, DMF, 23°C, 3 h; 2. pyridine, MeOH, CH_2Cl_2, 23°C, 19 h.

Further Organic Synthesis

In addition to the optically active title compound **5c** we have synthesized three more synthetic standards **4b**, **6b** and **7b** to support our proposed metabolic degradation pathway. Therefore the reduction of **6b** with $NaBH_4$ lead to three different diastereomers of the alcohol **7b** which could be eliminated *via* the mesylate to prepare the α,β-unsaturated ester **4b**.



Scheme 3: a) $NaBH_4$, MeOH, 23°C, 2 h; b) MsCl, pyridine, 120°C, 3 d.

[1] R. Jarling, *Transformations of hydrocarbons in anaerobic bacteria*, Dissertation, Universität Oldenburg, **2016**.
[2] A. Strijkstra, K. Trautwein, R. Jarling, L. Wöhlbrand, M. Dörries, R. Reinhardt, M. Drozdowska, B. T. Golding, H. Wilkes, R. Rabus, *Appl. Environ. Microbiol.* **2014**, *80*, 7592–7603.