Synthesis of Optically Active Dimethyl 3-Isopropylpimelate

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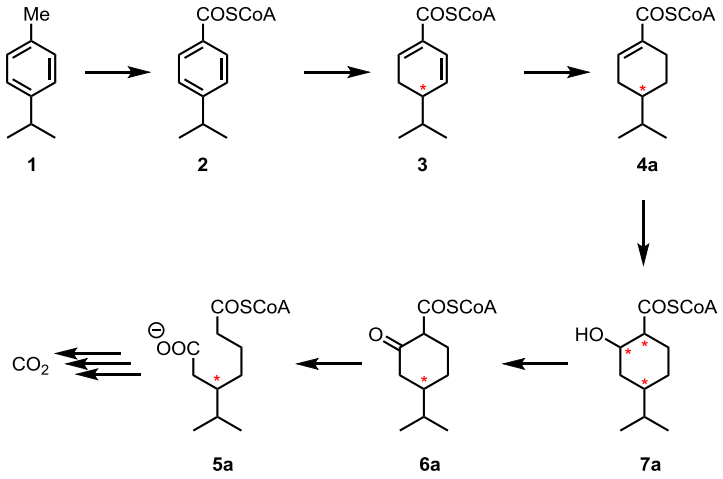
An asymmetric synthesis of dimethyl 3-isopropylpimelate was accomplished in five steps from cyclohexenone. This compound is an important reference standard to study the anaerobic metabolic degradation of *p*-cymene by bacterial strain *A. aromaticum* pCyN1.

Microbiological Background

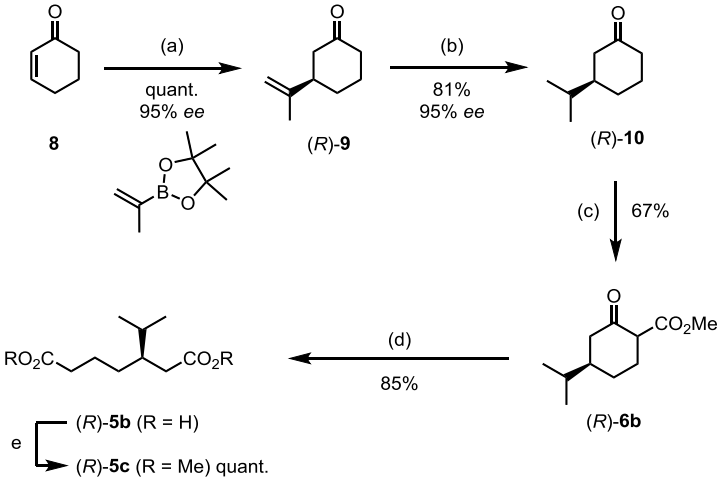
A suggestion of the anaerobic degradation of *p*-cymene by bacterial strain *Aromatoleum aromaticum* pCyN1 is given in Scheme 1. After oxidation of the methyl group, a biological "Birch-type reduction" leads to the formation of a stereocenter in compound **3**. Its configuration is expected to be retained in the subsequent products **4a–7a**. Especially the β-alkylated pimelic acid **5a** seems to be a good system to explore the metabolic mechanism.[1]



Scheme 1: The proposed anaerobic metabolic degradation pathway of *p*-cymene (**1**) by denitrifying betaproteobacterium *Aromatoleum aromaticum* pCyN1.[1]

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*)-DTBM-SEGPHOS, 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.

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).

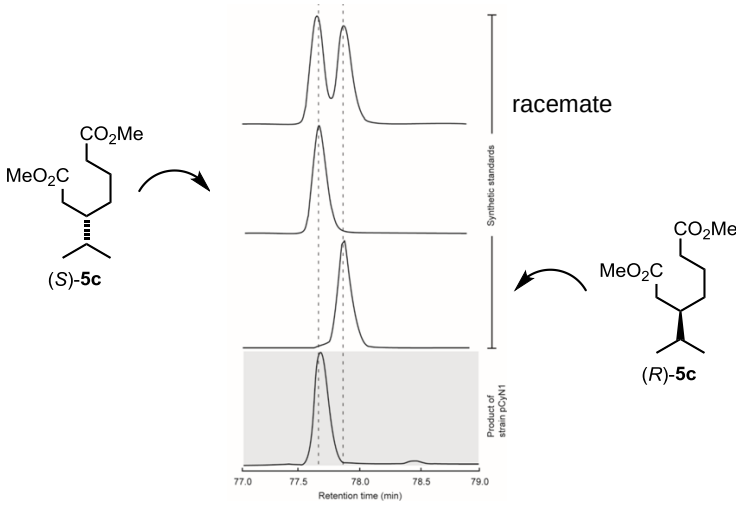
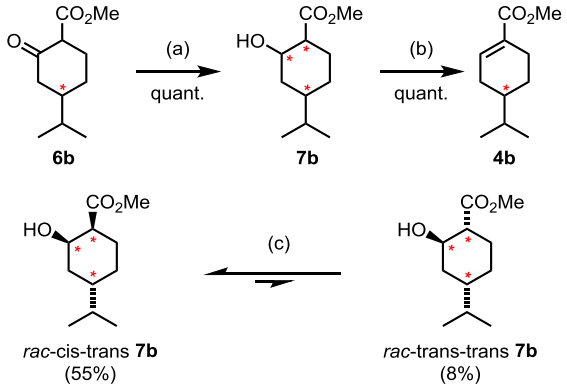


Figure 1: Comparison of the synthetic standards **5c** with the culture extract from *A. aromatoleum* pCyN1 after transesterification by gas chromatography.

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 brosylate to prepare the α,β-unsaturated ester **4b**. The fourth diastereomer of **7b** was obtained by epimerization at the 1-position with NaOMe in MeOH.



Scheme 3: a) $NaBH_4$, MeOH, 23°C, 2 h; b) 1. 4-$BrC_6H_4SO_2Cl$, pyridine, 23°C, 1 d; 2. $NaNO_2$, DMF, 90°C, 3 h; c) NaOMe, MeOH, 23°C, 1 d.

[1] J. Küppers, P. Becker, R. Jarling, M. Dörries, N. Cakić, M. Schmidtmann, J. Christoffers, R. Rabus, H. Wilkes, *Chem. Eur. J.* **2019**, *in press*. (doi: 10.1002/chem.201805837).