論文の内容の要旨

応用生命化学専攻
平成 18 年度博士課程　入学
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論文題目　Studies on the Asymmetric Synthesis of Optically Active Odorants

(光学活性な香気成分の不斉合成研究)

Most compounds that support our living have chirality. As the living system can recognize and discriminate chiral isomers, the biological activities depend on their chiral configurations. So, it is very important to make optically pure form of drugs, pheromones, or odorants. Although, the olfactory system of humans and animals can distinguish between optical isomers, the synthetic part of these optically active odorants is underdeveloped.

The methods for preparing an optically pure products can divide into two parts. One is bioconversion and the other is chemical synthesis. In this study, I tried both of these methods for preparing optically active odorant compounds.

Chapter I-1 : Chemo-biological preparation of (*R*)-4-acetoxy-2-methyl-1-butanol

By the bioconversion method, I tried enantioselective reductions of carbon-carbon double bond. 4-Acetoxy-2-methylene-1-butanol (**1)** was used as a substrate of bioconversion, and **1** was able to be synthesized from cheap natural compound itaconic acid in 4 steps. The whole growing cells of microbes were used for the bioconversion, because of their efficiency for no need of co-substrates or co-enzymes.

I screened 6 kinds of microbes, and *Pseudomonas putida* showed the best reduction activity against the double bond of **1**. So I proceeded to the optimization using *P. putida*.

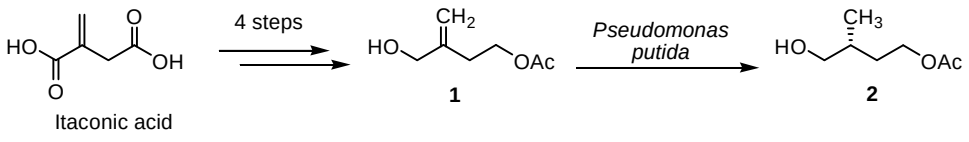

Fig. 1. Chemo-biological preparation of asymmetric chiral alcohol **2**.

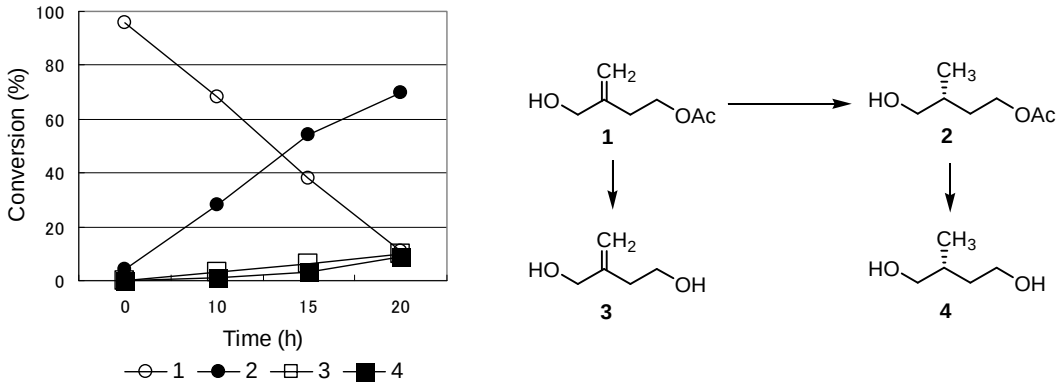

Fig. 2. Bioconversion tendency of **1** by *P. putida*.

The optimized condition of bioconversion with *P. putida* was investigated. After adding **1** and the seed cultured *P. putida* to a new liquid medium, transformation was checked regularly by G.C.

The desired reduction of the double bond of **1** was occurred gradually. But after exponential phase of *P. putida*, it started making undesired byproducts **3** and **4** from **1** and **2** by simultaneous hydrolysis. So, I stopped the process when the peaks of **3** and/or **4** are observed by G.C. The best bioconversion was achieved when 18 h-cultured seed culture medium 1.50 ml (3% of medium) and 0.10 g (0.70 mmol) of substrate in 50 ml (in 500 ml Erlenmeyer flask) of YPD media was cultured at 30°C, 180 rpm. With this method, I could get the optically active asymmetric alcohol **2**, with high conversion rate (>80%) and high optical purity (≥98%).

Chapter I-2 : Synthesis of methyl (*R*)- and (*S*)-3-methyloctanoate

Methyl 3-methyloctanoate has been reported as an odor component of African orchids, *Aerangis* sp. and the odor of this compound is different according to its (*R*)- and (*S*)-configuration. I thought the produced alcohol **2** could be used as chiral building block for the synthesis of these methyl (*R*)- and (*S*)-3-methyloctanoate (Fig. 3).

The synthesis was carried out by simple organic chemical process. I could synthesize the flowery methyl (*S*)-3-methyloctanoate **5** in 4 steps with 60% overall yield, and the fruity (*R*)-form **6** was obtained in 9 steps with 11% overall yield.

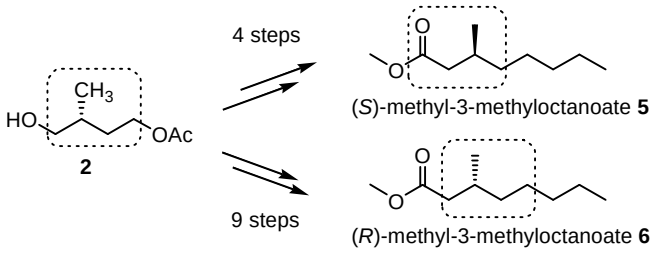

Fig. 3. Synthesis of methyl (*R*)- and (*S*)-3-methyloctanoates.

Chapter II : Sythesis of δ-nonalactone by asymmetric S_N2' reaction

In chemical conversion, I tried to synthesize optically active δ-nonalactone. The δ-lactones are important ingredients for flavor in many foods. They have different flavor according to their absolute configuration, i.e. the (*R*)-form have milky or creamy, while (*S*)-form have peach like flavor.

There are many possible approaches to prepare chiral δ-nonalactone, I tried to use the direct enantioselective alkylation reaction, concretely, S_N2' reaction which is less developed yet.

Compound **7** was designed as an intermediate. It can be prepared from cheap natural compound limonene. It has many efficient points for the S_N2' reaction. At first, it has non-epimerizable ketone, and the direct formation of cyclic carbonate is convenient as a good leaving group. Most of all, the steric effect of neighboring methyl group is expected to enhance the stereoselectivity of S_N2' reaction.

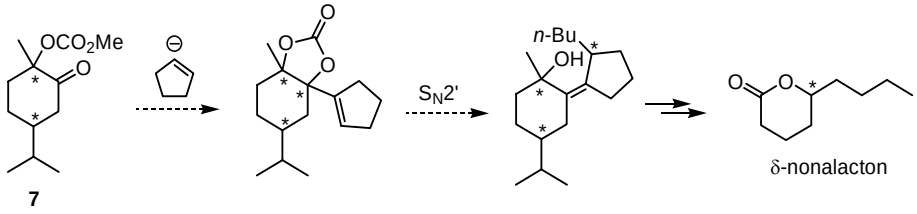

Fig. 4. Synthetic strategy of d-nonalactone by stereoselective SN2' reaction.

(*R*)-(+)-Limonene was converted to carbonate **7** in 4 steps, which was subjected to addition of cyclopentenyl nucleophile. Unexpectedly, I could get two chiral intermediate, epoxide **8** and cyclic carbonate compound **9**. Both of them were possible substrates for the S_N2' reaction, so the reaction was performed with both of them after separation.

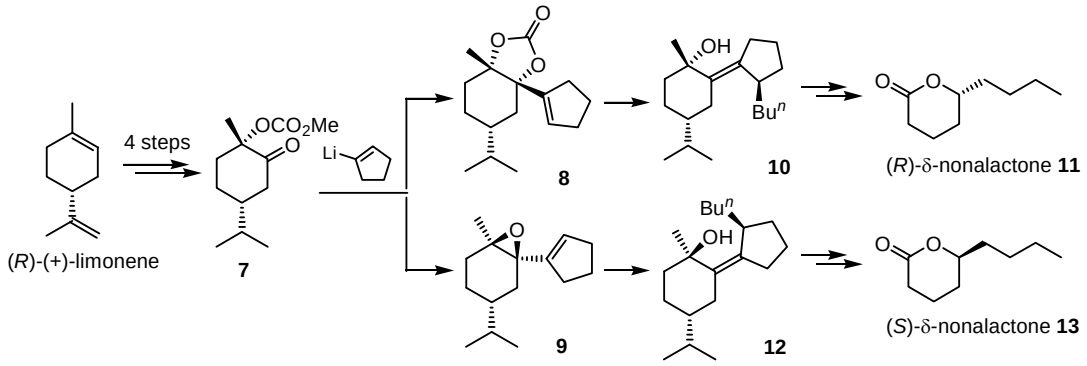

Fig. 5. Synthesis of (*R*)- and (*S*)-δ-nonalactones.

The epoxide **9** was treated with lithium dibutylcuprate to give (*Z*)-product **12** with 65% yield. On the other hand, cyclic carbonate **8** was treated with mono-butylcyanocuprate to give (*E*)-product **10** with 75% yield, while the cyclic carbonate was reductively decarboxylated by the lithium dibutylcuprate. Both S_N2' products were converted to δ-nonalactones by ozonoysis and Baeyer-Villiger reaction to afford (*R*)- and (*S*)-δ-nonalactone, respectively. The e.e. of these products was checked by chiral G.C. The results showed 90% e.e. of (*R*)-δ-nonalactone **11** and 89% of e.e. of (*S*)-form **13**.

Conclusion

In this study, I have synthesized optically active odorants, methyl 3-methyloctanoate and δ-nonalactone, by chemobiological and chemical synthetic method.

At first, by chemobiological method, I could synthesize the optically active alcohol (*R*)-4-acetoxy-2-methyl-1-butanol **2**. The cultured cells of *P. putida* were used for bioconversion with high enantioselectivity. As synthetic application of this chiral alcohol, I synthesized methyl (*R*)-and x(*S*)-3-methyloctanoate, the odor compound of African orchids. The methyl (*S*)-3-methyloctanoate **5** was synthesized from **2** in 4 steps with 60% overall yield, and the methyl (*R*)-3-methyloctanoate **6** was obtained in 9 steps with 11% overall yield.

By chemical synthetic method, I have synthesized both (*R*)-and (*S*)-δ-nonalactone by asymmetric S_N2' reaction with good enantioselectivity. The optically active cyclic carbonate and epoxide, have been developed as S_N2' intermediate. And they produced δ-nonalactone with different manner. I expect they could be applied for the synthesis of other optically active compounds by changing vinyl group and alkyl nucleophile.