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Chemoenzymatic Synthesis of (*E*)-3,7-Dimethyl-2-octene-1,8-diol Isolated from the Hairpencils of Male *Danaus chrysippus* (African Monarch)

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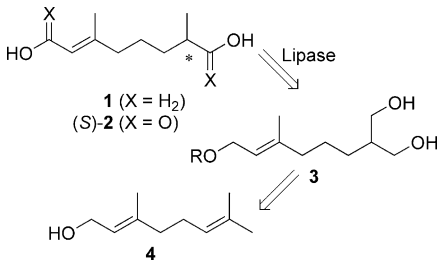
Abstract—The synthesis of (*E*)-3,7-dimethyl-2-octene-1,8-diol (**1**), which was isolated from the hairpencils of male *Danaus chrysippus* (African Monarch), was investigated. The key step of the sequence involves asymmetric desymmetrization of the 1,3-propanediol **7** with lipase, in which high enantioselectivity was observed. Total synthesis afforded (*S*)-**1** in 12 steps and 26% overall yield from readily available geraniol.

(*E*)-3,7-Dimethyl-2-octene-1,8-diol (**1**) has been isolated as a major component from the hairpencils of male *Danaus chrysippus* (African Monarch), which is an Old World member of the subfamily Danainae.[1] Unfortunately, since the amount of this diol **1** in one butterfly is only 0.05 mg, its bioactivity has not been clarified. However, structurally similar dicarboxylic acid (*S*)-**2** is known as a pheromone of the azuki bean weevil, *Callosobruchus chinensis*,[2,3a,7] therefore, the undiscovered bioactivity of **1** is interesting. Successful syntheses of **1** in optically active forms were previously reported, in which the classical approach based on commercially available chiral building blocks was employed.[3,4] Recently, biocatalysts have become one of the most useful catalysts in asymmetric syntheses.[5,6]

Gramatica and Manitto reported that the (*S*)-**1** was synthesized via stereoselective hydrogenation of the carbonyl activated double bond of achiral precursors by baker's yeast,[7] though chemical yield was considerably low. Now we report herein the synthesis of (*S*)-**1** from commercially available and quite inexpensive geraniol (**4**), employing lipase-catalyzed asymmetric desymmetrization of the 1,3-propanediol **3** as shown in Scheme 1.

2-(6-Benzyloxy-4-methyl-4-hexenyl)propane-1,3-diol (**7**) as a substrate for asymmetric desymmetrization was prepared as shown in Scheme 2. Benzylation and epoxidation of geraniol (**4**) gave the epoxide **5** in 78% yield, followed by oxidation, reduction and tosylation to afford the tosylate **6** in 79% yield.[8] Treatment of **6** with the anion derived from diethyl malonate gave the diester, finally, reduction with lithium aluminium hydride (LAH) yielded the 1,3-propanediol **7**.

Lipase-catalyzed asymmetric desymmetrization of the diol **7** was carried out as follows:[9] in a test tube the diol **7** (0.1 mmol) and vinyl acetate (0.15 mmol) were added. To the vessel lipase (0.1 or 0.25 g per 1 g of **7**) was added. The vessel was stirred with a magnetic stirrer at appropriate temperature. On completion of the reaction, the residual mixture was filtered, washed with



Scheme 1. Synthetic plan of **1** from geraniol **4**.

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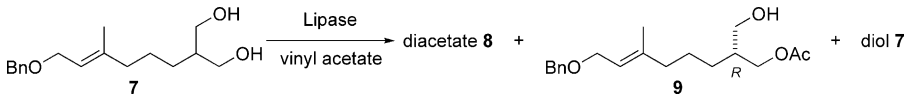
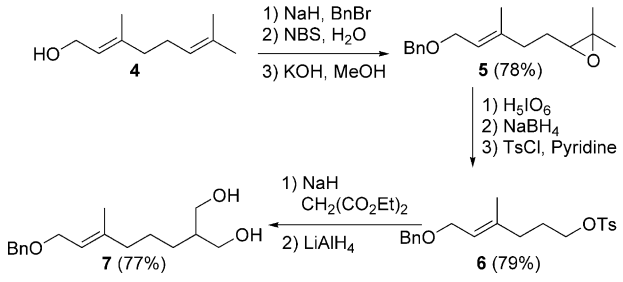
Table 1. Lipase-catalyzed asymmetric desymmetrization of the 1,3-propanediol **7**[a]



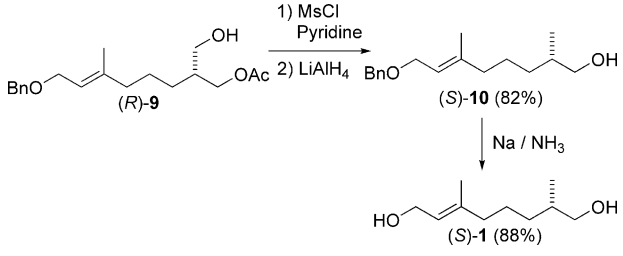
Entry	Lipase[b]	Solvent	Temp (°C)	Time (h)	**8** Yield (%)	**9** Yield (%)	ee[c] (%)	**7** yield (%)
1	AK	*i*-Pr_2O	25	42	41	50	5	9
2	AY	*i*-Pr_2O	25	48	56	36	5	8
3	PL	*i*-Pr_2O	25	30	37	58	12	5
4	CHIRAZYME, L2	*i*-Pr_2O	25	2	7	87	31	6
5	PS-D	*i*-Pr_2O	25	3	6	82	73	12
6	PSA	*i*-Pr_2O	25	52	13	81	77	6
7	PSA	*i*-Pr_2O	0	75	21	75	83	4
8	PSA	—	0	14	25	57	69	18
9	PSA	hexane	0	117	35	53	78	12
10	PSA	THF	0	23	23	75	87	2
11	PSA	acetone	0	48	34	64	88	2
12	PSA	1,4-dioxane	0	2	37	63	89	0
13	PSA	1,4-dioxane:THF = 5:1	0	23	20	75	90	2

[a]The diol **7** (0.1 mmol) and vinyl acetate (0.15 mmol) were used.
[b]0.1 g for entries 1–6 and 0.25 g for entries 7–13 of lipase per 1 g of **7** were used, respectively.
[c]Determined by HPLC analysis (Chiralcel OD, hexane/isopropanol = 97:3, 0.8 mL/min, R_t of (*R*)-isomer: 60.4 min, R_t of (*S*)-isomer:83.6 min).



Scheme 2. Synthesis of the 1,3-propanediol **7**.

ether, and analyzed with HPLC. The results are shown in Table 1. Enantioselectivities were highly affected by the nature of lipases. Lipase AK (*Pseudomonas fluorescence*), AY (*Candida rugosa*) and PL (*Alcaligenes sp.*) gave the monoacetate **9** with low enantioselectivities (entries 1–3). CHIRAZYME®, L-2 (insoluble polymer-supported lipase from *Candida antarctica*, Type B) showed higher reactivity and chemoselectivity except enantioselectivity (entry 4). Lipase PS-D (Celite-supported lipase from *Pseudomonas cepacia*) and PSA (*Pseudomonas cepacia*) improved the enantioselectivity, and the monoacetate **9** was obtained in 81% yield with 77% ee (entries 5–6). Lower reaction temperature increased enantioselectivity up to 83% ee (entry 7). Solvents mainly influenced reactivity and enantioselectivity,[10] in which a polar solvent such as 1,4-dioxane, acetone and tetrahydrofuran (THF) afforded higher enantioselectivity than a nonpolar solvent (entries 8–12). Finally, a mixed solvent in a 1,4-dioxane/THF of 5/1 resulted in the best enantioselectivity (90% ee, *R* configuration) and good chemical yield (75%) (entry 13).



Scheme 3. Transformations of the monoacetate (*R*)-**9** to the desired chiral diol (*S*)-**1**.

The desired diol **1** was synthesized from chiral monoacetate (*R*)-**9** in 3 steps as shown in Scheme 3. Mesylation followed by reduction with LAH of the chiral monoacetate (*R*)-**9** (90% ee) gave the alcohol (*S*)-**10** in 82% yield with slightly decreasing enantiomeric excess (81% ee[11]). Deprotection of the benzyl group by Birch reduction afforded the desired diol (*S*)-**1** ($[\alpha]_D^{15} = -7.18°$ (*c* 0.31, $CHCl_3$))[12] in 88% yield.

In conclusion, lipase-catalyzed asymmetric desymmetrization of the 1,3-propanediol **7** is a valid approach to total synthesis of naturally occurring diol **1**. Total synthesis afforded (*S*)-**1** in 12 steps and 26% overall yield from readily available geraniol. We hope that this simple synthesis of (*S*)-**1** will be helpful for solving unidentified bioactive properties in the future.

Acknowledgements

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9. We also examined the enantioselective hydrolysis of the diacetate **8** in a buffer solution; however, moderate yield (13–78%) and enantioselectivities (22–76% ee) were observed.

10. (a) The correlation between enantioselectivity and such physicochemical characteristics of the solvent as dielectric constant and hydrophobicity is less clear, and various explanations have been suggested. For representative examples, see: Secundo, F.; Riva, S.; Carrea, G. *Tetrahedron: Asymmetry* **1992**, *3*, 267. (b) Fitzpatrick, P. A.; Klibanov, A. M. *J. Am. Chem. Soc*. **1991**, *113*, 3116. (a) For reviews, see: Kvittingen, L. *Tetrahedron* **1994**, *50*, 8253. (b) Theil, F. *Tetrahedron* **2000**, *56*, 2905.

11. The ee was determined by HPLC analysis (Chiralcel OD, hexane/isopropanol = 100:1, 0.8 mL/min, R_t of (*R*)-isomer: 67.5 min, R_t of (*S*)-isomer:83.3 min).

12. A value of optical rotation in literature: (*S*)-**1** (>97% ee): $[\alpha]_D^{25} = -9.1°$ (*c* 4.6, $CHCl_3$),[7] (*R*)-**1** (85% ee): $[\alpha]_D^{20} = +6.9°$ (*c* 3.9, $CHCl_3$).[3a]