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Ring Differentiation of the *trans*-Decahydronaphthalene System *via* Chemo-enzymatic Dissymmetrization of Its σ-Symmetric Glycol: Synthesis of a Highly Functionalized Chiral Building Block for the Terpene Synthesis

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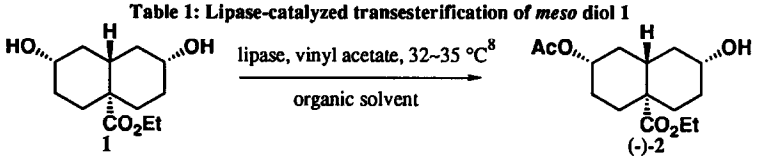
Abstract: The asymmetric ring differentiation by lipase-catalyzed transesterification of a *meso* decahydronaphthalenediol (**1**) was accomplished in extremely high optical and chemical yield. The absolute stereochemistry of the corresponding mono-acetate (-)-**2** was determined by its conversion into a decalone [(-)-**3**] and to an octalone [(+)-**4**], which were key intermediates for the synthesis of (-)-polygodial, (-)-warburganal, and (-)-drimenin.

Recently, we have reported the ring differentiation of the azabicyclic ring-crossed *meso* glycol by lipase, and its conversion into a highly functionalized piperidine as a versatile chiral building block for the 3-piperidinol alkaloid.[1] In our continuous studies on the development of useful chiral building blocks *via* dissymmetrization of the σ-symmetric compound, we have designed a *meso* decahydronaphthalenediol (**1**)[2] and examined its lipase-catalyzed ring differentiation to afford the monoacetate (-)-**2** as a new chiral building block for the enantiodivergent synthesis of sesquiterpenes involving a drimane ring skeleton. Although, many stereoselective syntheses of these sesquiterpenes starting from chiral natural sources have been reported,[3] our approach can equally synthesize not only both enantiomers of the target natural product but also more highly functionalized terpenes bearing an oxygenated angular appendage[4] such as maingayic acid[5] and ajugarin I ~ III.[6] On the lipase-catalyzed transesterification of **1**, the best result was obtained with immobilized lipase AK[7] in diisopropyl ether (iPr_2O) (Table 1).

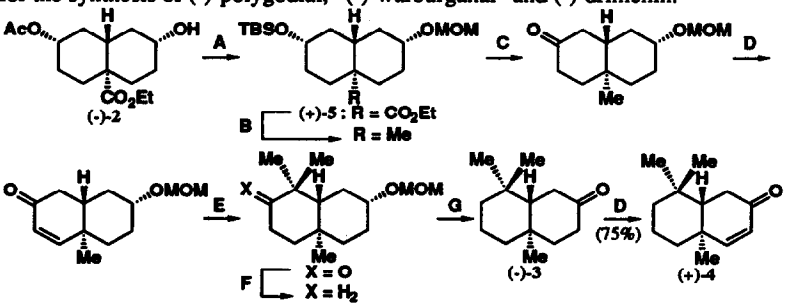
Table 1: Lipase-catalyzed transesterification of *meso* diol 1



Lipase[a]	solvent	Time (h)	Yield (%)[b]	Optical rotation ($[\alpha]_D$)[c]	Optical yield (% ee)
AK[d]	iPr_2O	12	96 (99)	-21.4°	>99[e]
AK[d]	benzene	12	39 (99)	-21.4°	>99[f]
AK[d]	hexane	24	19 (99)	-21.2°	99[f]
AK	iPr_2O	24	89 (99)	-21.2°	99[f]
PS	iPr_2O	24	23 (99)	-20.9°	98[f]
CCL	iPr_2O	24	10 (95)	-20.0°	94[f]
CE	iPr_2O	24	6 (95)	-18.2°	86[f]
AY	iPr_2O	24	17 (94)	-17.2°	81[f]

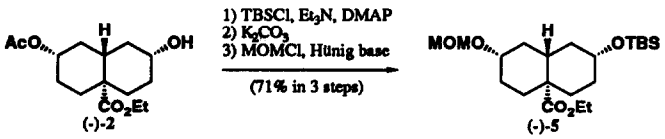
a: Lipase AK (fr. *Pseudomonas fluorescens*), PS (fr. *Pseudomonas cepacia*), CE (fr. *Humicola lanuginosa*) and AY (fr. *Candida rugosa*) were supplied by Amano Pharmaceutical Co., Ltd. We are grateful to Amano Pharmaceutical Co., Ltd. for the generous gift of lipases. CCL (fr. *Candida cylindracea*) was purchased from the Sigma Chemical Co., Ltd. b: Yields in the isolated monoacetate. Yields in parentheses are those based on the conversion rate. c: Optical rotations were taken in chloroform. d: Lipase immobilized on celite was used. e: Determined after benzoylation of (-)-**2** by HPLC analysis using a column packed with CHIRALCEL AD (iPrOH : n-hexane 1 : 30). f: Determined based on the value of optical rotation.

The absolute stereochemistry of the mono-acetate (-)-2 was determined by its conversion into a decalone [(-)-3, $[\alpha]_D$ -13.8°, lit.[9] $[\alpha]_D$ -12.8°] and an octalone [(+)-4, $[\alpha]_D$ +25.6°, lit.[10] $[\alpha]_D$ +7.4°] which were key intermediates for the synthesis of (-)-polygodial,[9] (-)-warburganal[9] and (-)-drimenin.[10]



A: 1) MOMCl, Hünig base (96%); 2) K_2CO_3; 3) TBSCl, Et_3N, DMAP (90% in 2 steps), B: 1) $LiAlH_4$ (95%); 2) I_2, Ph_3P, imidazole (96%); 3) Zn, AcOH, C: 1) TBAF (87% in 2 steps); 2) PCC (92%), D: LDA, TMSCl then $Pd(OAc)_2$ (76%), E: 1) LDA, MeI (86%); 2) LDA, MeI (62%); 3) H_2, 5% Rh/C (98%), F: 1) $TsNHNH_2$, $BF_3{\cdot}Et_2O$; 2) MeLi (82% in 2 steps); 3) H_2, 5% Pd/C ; G: 1) HCl, MeOH; 2) PCC (90% in 3 steps)

Further, the enantiomer [(-)-5, $[\alpha]_D$ -1.2 °] of the silyl ether (+)-5 ($[\alpha]_D$ +1.2 °) was synthesized from the mono-acetate (-)-2.



Thus, we have accomplished ring differentiation of the decahydronaphthalene system *via* dissymmetrization of a *meso* 1,5-glycol (1) by lipase-catalyzed transesterification and provided an efficient approach to the enantio-divergent synthesis of sesquiterpenes having a drimane ring system.

The present method of dissymmetrization is easy to operate on a large scale and under mild conditions, and would provide us with a promising entry to the enantiodivergent synthesis of more highly functionalized terpenes.

REFERENCES AND NOTES

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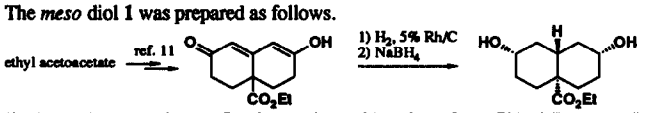
2. Satisfactory analytical and spectra data were obtained for all new compounds. Optical rotations were taken in chloroform unless otherwise stated.
   The *meso* diol 1 was prepared as follows.



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4. The Wieland-Miescher ketone and its homologue have extensively been used in the synthesis of a wide variety of terpenes, however, none of the chiral synthesis of the their analogue bearing an oxygenated angular substituent has been reported to date. See Mander, L. N.; Hamilton, R. J. *Tetrahedron Lett.* 1981, 22, 4115.
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8. The typical procedure is as follows: To a stirred suspension of 1 (0.5 mmol) and vinyl acetate (2 mmol) in iPr_2O (10 mL) was added lipase AK (50 mg) immobilized on celite (200 mg), and the resulting suspension was stirred at 32~35 °C for 12 h. After filteration (celite) and removal of the solvent, an oily residue was fractionated by chromatography on a column (silica gel, 5g) to afford the oily mono-acetate [(-)-2, 136 mg, 96%] and the crystalline diol (1, 4 mg, 3.3%).
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