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Lipase-Catalyzed Transesterification as a Practical Route to Homochiral *syn*-1,2-Diols. The Synthesis of the Taxol Side Chain

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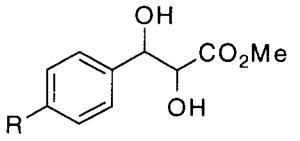
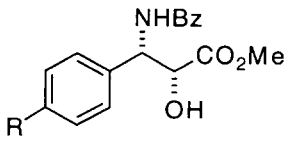
Abstract: *syn*-2,3-Dihydoxy-3-phenyl-propanoic acid methyl ester (**1a**) and its simple derivatives (**1b-e**) are efficiently resolved in LPS-catalyzed transesterification, leading to the synthesis of the taxol side chain and analogs from both resolved enantiomers.

Homochiral 1,2-diols are useful as chiral building blocks in asymmetric synthesis.[1] The catalytic dihydroxylation of olefins using OsO_4 in the presence of cinchona alkaloids provides the most attractive route to these molecules in terms of enantioselectivity and scope.[2] The procedures[3-5] using enzymes also offer useful alternatives to the chemical method. We have recently reported the efficient resolution of *anti*-1,2-diols using lipase PS (LPS, *Pseudomonas cepacia*) and its application in the total synthesis of *endo*-brevicomin.[6] We now wish to report the efficient resolution of *syn*-1,2-diols and its application in the synthesis of the taxol side chain. In this work, *syn*-2,3-dihydoxy-3-phenyl-propanoic acid methyl ester (**1a**) and its simple derivatives (**1b-e**) have been explored as the *syn*-1,2-diol substrates of LPS for the resolution because their optically pure forms are useful in the synthesis of natural products and pharmaceuticals such as taxol[7] and diltiazem.[8] We have found that all of the substrates tested are efficiently resolved in the transesterification reactions catalyzed by LPS and both resolved enantiomers can be utilized in the synthesis of the taxol side chain (**2a**) and analogs (**2b-e**), thus maximizing the overall yield. This paper describes the preliminary results from these studies.



1a R = H
1b R = Cl
1c R = NO_2
1d R = CH_3
1e R = OCH_3



2a R = H
2b R = Cl
2c R = NO_2
2d R = CH_3
2e R = OCH_3

LPS-catalyzed transesterifications of the *syn*-dihydroxy esters were performed in the presence of vinyl acetate at room temperature. The reactions were carried to approximately or slightly over 50% completion. After the removal of enzymes the unreacted diols and the acetylated products were isolated by chromatography. The optical purity of all the isolated molecules were measured in the diacetate forms by the ^1H NMR spectroscopy in the presence of chiral shift reagent. The yields and optical purities are described in Table 1.

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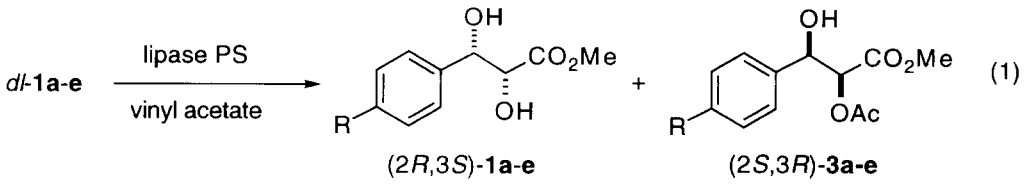
The absolute configurations were confirmed as shown in eqn. 1 based on the sign of the optical rotation of unreacted (2*R*,3*S*)-**1a**.[9]

Table 1. The LPS-catalyzed transesterifications of syn-1,2-diols (*dl*-**1a-e**)



(2*R*,3*S*)-**1a-e** (2*S*,3*R*)-**3a-e**

substrate	yield, %	ee, %	yield, %	ee, %
1a	44	98	54	75
1b	45	>98	55	91
1c	38	91	46	89
1d	45	>98	50	92
1e	36	98	50	91

The results described in Table 1 indicate that all the substrates tested are transformed by LPS with useful enantio- and regioselectivity: *(2S,3R)-enantiomer reacts more rapidly than the other one and the acetylation takes place exclusively at 1-OH*. The optical purity of the monoacetylated enantiomers ranges from 75 to 92% ee and that of the unreacted enantiomers from 91 to >98% ee. Based on these results an empirical rule[10] can be formulated as shown in Figure 1 for predicting and interpreting the enantioselectivity and regioselectivity in the lipase PS-catalyzed transesterification of *syn*-1,2-diols.

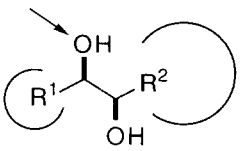
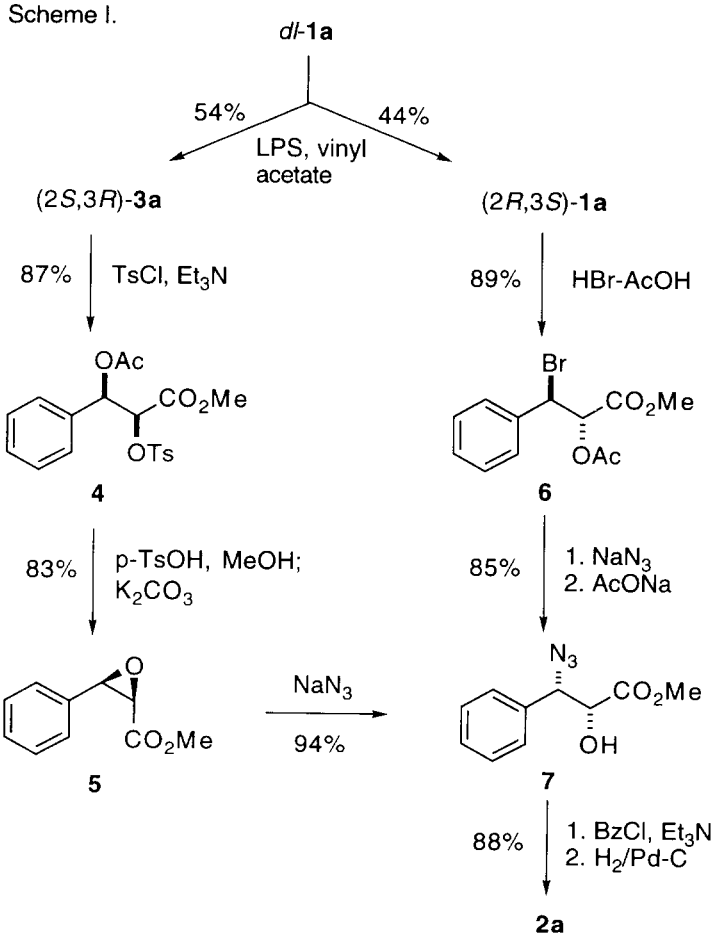


Figure 1. The enantiomer shown reacts more rapidly with enzyme than the other one when two substituents on the ethylene glycol unit differ in size and the acetylation occurs regioselectively at the hydroxyl on the side of smaller substituent.

The enantioselective synthesis of the taxol side chain (**2a**) from enzymatically resolved (2*R*,3*S*)-**1a** and (2*S*,3*R*)-**3a** has been achieved as shown in Scheme I. According to this scheme, both enantiomers were separately converted to the same intermediate **7** and then combined to be transformed to the target molecule. The conversion of (2*S*,3*R*)-**3a** to **7** has been carried out in three steps. The treatment of (2*S*,3*R*)-**3a** with TsCl in the presence of Et_3N provides **4**, the enantiopure form of which is obtained after single recrystallization.[11] The deacetylation of **4** with p-TsOH in MeOH, followed by the treatment with K_2CO_3, gives **5** which is finally transformed by the reaction with NaN_3 in DMF to **7**.[12] The conversion of (2*R*,3*S*)-**1a** to **7** has been accomplished in three steps using the literature procedure.[13] The treatment of (2*R*,3*S*)-**1a** with HBr-AcOH

yields **6** which in turn reacts with NaN_3 in DMF, followed by deacetylation with AcONa in MeOH, to afford **7**. Finally, the synthesis of the taxol side chain (**2a**)[14] has been completed in two steps from **7**. The overall yield from *dl*-**1a** is 62%.

Scheme I.



This synthesis deserves a brief comment. First, both enzymatically resolved enantiomers are used in the synthesis and thus the maxium yield is not limited to 50%.[15] Second, the relatively lower optical purity of enzymatically monoacetylated product is readily enhanced at the stage of tosylate by single crystallization. Third, the tosylation of the monoacetylated product is highly regioselective. The tosylation occurs exclusively at the acetylated 1-OH, not free 2-OH, suggesting that the acetyl group migrates from 1-OH to 2-OH before the 1-OH is tosylated. Finally, the scheme is applicable to the synthesis of taxol side chain analogs (**2b-e**).

This work thus have demonstrated the utility of lipase in the synthesis of homochiral *syn*-1,2-diols, particlularly *syn*-2,3-dihydroxy esters, and the taxol side chain.[16] We conclude that the LPS-catalyzed transesterification provides a useful alternative to the chemical methods for the synthesis of homochiral *syn*-1,2-diol.

Acknowledgenent This work was supported by the Korea Science and Engineering Foundation (SRC-CBM) and the Ministry of Science and Technology, Korea.

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11. **4**: 98% ee; mp 106-108°C; $[\alpha]_D^{21}$ -49.2° (*c* 2.02, CH_2Cl_2); ^1H NMR (ppm, $CDCl_3$) 2.08 (*s*, 3 H), 2.43 (*s*, 3 H), 3.63 (*s*, 3 H), 5.04 (*d*, *J* = 4.7 Hz, 1 H), 6.17 (*d*, *J* = 4.8 Hz, 1 H), 7.22-7.29 (*m*, 7 H), 7.55-7.58 (*m*, 2 H); ^{13}C NMR (ppm, $CDCl_3$) 169.7, 166.8, 145.4, 139.8, 134.8, 130.1, 129.2, 129.0, 128.3, 127.2, 79.6, 74.1, 53.2, 22.0, 21.1. HRMS (M + Cs^+). Calcld for $C_{19}H_{20}O_7S$: 524.9984. Found: 525.0000
12. **7**: mp 55.5-56.5°C; $[\alpha]_D^{21}$ +146° (*c* 1.91, $CHCl_3$) [lit.[7a] mp 56-57°C; $[\alpha]_D^{24}$ +142° (*c* 1.1, $CHCl_3$)].
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