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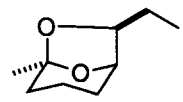
Lipase-Catalyzed Transesterification as a Practical Route to Homochiral Acyclic *anti*-1,2-Diols. A New Synthesis of (+)- and (-)-*endo*-Brevicomin.

Mahn-Joo Kim,* Gil-Bae Choi, Joon-Young Kim, and Hee-Jeong Kim

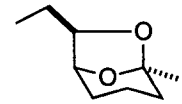
Department of Chemistry and Center for Biofunctional Molecules,
Pohang University of Science and Technology, San 31 Hyoja-Dong, Pohang 790-784, Korea.

Abstract: Several *anti*-1,2-diols (**2a-g**) have been efficiently resolved by using LPS-catalyzed transesterification and the total synthesis of (+)- and (-)-*endo*-brevicomin (**1**) has been achieved starting from one (**2g**) of the resolved diols.

Optically active 1,2-diols are useful as chiral building blocks in asymmetric synthesis.[1] The most attractive route to these molecules in terms of enantioselectivity and scope is the catalytic dihydroxylation of olefins using OsO_4 in the presence of cinchona alkaloids.[2] The chemical method, however, suffers from low to moderate optical purity in the synthesis of *anti*-1,2-diols from *cis*-olefins.[3] A useful alternative for the synthesis of enantiopure *anti*-1,2-diols would be the resolution of their racemic mixtures using lipases. Lipases have been shown to be useful in the sequential kinetic resolution of *dl*-1,3-diols,[4] the enantioselective acylation of *meso*-diols,[5] and the separation of *dl*- and *meso*-diols.[6] Despite of these intensive activities in this area, no systematic studies have been done to demonstrate the utility of lipases in the resolution of acyclic *anti*-1,2-diols. As a part of our research program on the synthesis of *endo*-brevicomin **1**, the pheromone of the bark beetles such as *Dendroctonus frontalis* and *Dryocoetes autographus*, we examined *anti*-1-trityloxy-3,4-hexanediol **2g** as the substrate of lipase PS (LPS) from *Pseudomonas cepacia* in transesterification to see if the diol is efficiently resolved by this enzyme. We found that it was resolved by LPS with high enantioselectivity, thus allowing the preparation of both enantiomers in optically pure form (>98% ee). Accordingly, this encouraging result prompted us to test several additional *anti*-1,2-diols **2a-f** as the substrates of LPS for the resolution. We herein wish to report that all the acyclic *anti*-1,2-diols surveyed are efficiently resolved by LPS in the transesterification reactions.

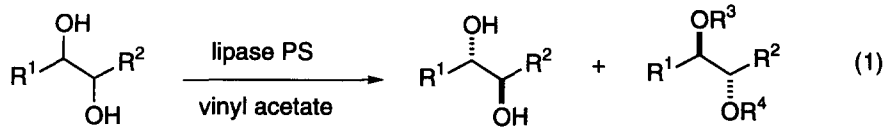


(+)-**1**



(-)-**1**

In a typical procedure, *anti*-1,2-diols were subject to the lipase PS catalyzed transesterification in the presence of vinyl acetate (eqn. 1). The enzyme-catalyzed reactions were carried out at room temperature and stopped when approximately or slightly over 50% of substrates were acetylated. The pattern of the acetylated products varied with the diols used and belonged to one of the following: 1) one single monoacetate (diol **2g**), 2) one major monoacetate and one minor diacetate (diol **2e**), 3) one minor monoacetate and one major diacetate (diol **2f**), 4) one major, one minor monoacetate, and one minor diacetate (diols **2a-d**). After the removal of enzymes the remaining 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



(±)-**2**

(+)- or (-)-**2**

3 R^3 = Ac, R^4 = H
4 R^3 = H, R^4 = Ac
5 R^3 = R^4 = Ac

2-5	R^1	R^2
a	Me	*n*-Pr
b		*n*-Bt
c		*n*-pentyl
d		*n*-hexyl
e		Ph
f	Et	CH_2OTr
g		CH_2CH_2OTr

Table 1. The Results from the LPS-catalyzed transesterifications of **2a-g**[a]

entry	(±)-**2**	unreacted **2** yield (%), ee (%)	**3** yield (%), ee (%)	**4** yield (%), ee (%)	**5** yield (%), ee (%)
1	**a**	35, >98	37, 75	minor	3.7, 98
2	**b**	40, >98	48, 94	minor	6.0, 98
3	**c**	39, >98	52, 81	minor	5.8, 98
4	**d**	32, >98	45, 76	9.6, 11	7.0, 98
5	**e**	47, >98	39, >98	-	10, 98
6	**f**	41, >98	10, >98	-	32, 98
7	**g**	41, >98	42, >98	-	-

[a] A representative procedure is that for (±)-**2g**. A solution containing substrate (1.40g, 3.72 mmol), vinyl acetate (3.50 g, 40 mmol), *tert*-butyl methyl ether (50 mL), LPS (3.3g) was stirred at r.t. for 44 h. The enzymes were removed by filtration and the filtrate then was concentrated and subjected to silica gel chromatography (hexane : ethyl acetate = 4 : 1) to give (-)-**2g** (0.57g, 1.53 mmol, 41%) and **3g** (0.62g, 1.56 mmol, 42%).

of chiral shift reagent. The yields and optical purities are described in Table 1. The stereospecificity of the LPS was confirmed as shown in eqn. 1 based on the sign of the optical rotation for the unreacted **2e**.[7]

Data from Table 1 indicate that all the substrates surveyed are efficiently resolved by LPS and the unreacted enantiomers of high optical purity (>98% ee) are recovered in good yields (32-49%). The optical purity of the acetylated enantiomers ranges from 75 to >98% ee. All the acetylated products from **2e-g** have the optical purity of 98% ee or greater while only the minor diacetates from **2a-d** have the same level of optical purity. These results suggest that the substrates **2e-g** are better resolved than **2a-d**. Based on all of these observations, we can formulate an empirical rule for predicting and interpreting the enantioselectivity in the lipase PS-catalyzed transesterification of 1,2-diols: *the enantiomer **A** shown in Figure 1 reacts more rapidly than the other one **B** and the enantioselectivity is high when the two substituents on the ethylene glycol unit differ significantly in steric bulkiness.*[8] This rule also can serve as a working-hypothesis for selecting a potential substrate of LPS.

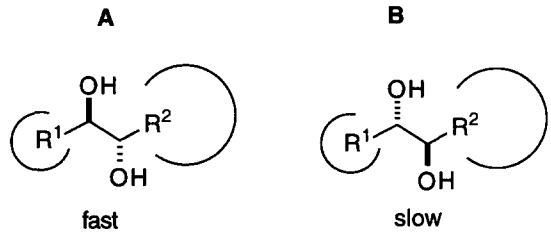
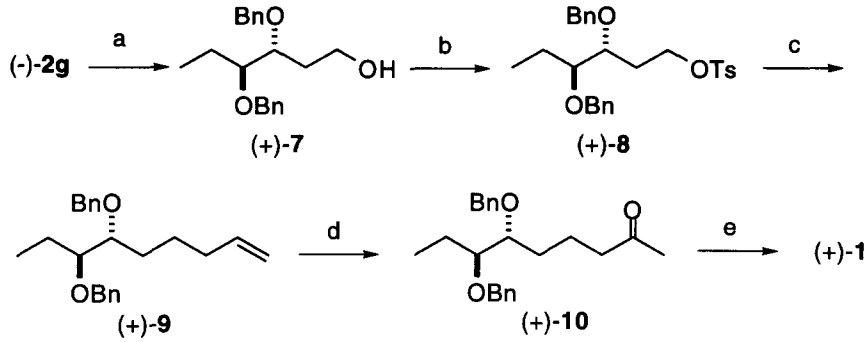


Figure 1

For the synthesis of both enantiomers of *endo*-brevicomin **1** we prepared (+)- and (-)-**2g** in a multi-gram quantity by running a 10g-scale reaction (**2g**, 26.4 mmol; vinyl acetate, 264 mmol; LPS, 20g; 32°C; 16 h) three times with the recycling of the enzymes. After three runs the enzymes were recoverd without a significant loss of catalytic activity. The yield was 48% for (-)-**2g**[9] and 46% for the acetylated product **3g**. The acetylated products were hydrolyzed to yield (+)-**2g**.[9] The synthesis of (+)-**1** was accomplished in six steps from (-)-**2g** (Scheme I). The enantiomeric diol was first converted into dibenzyl ether **6**, which was then treated with acid to remove the trityl group. The resulting alcohol **7** was tosylated and then reacted with allylmagnesium chloride to yield olefin **9**. The olefin was subjected to Wacker oxidation[10] and finally hydrogenated to give the target molecule.[11] The overall yield was 36%. By following the same scheme (-)-**1** was synthesized in 32% yield from (+)-**2g**.[12] We thus have achieved a new synthesis of (+)- and (-)-**1** using combined chemical and enzymatic methods.[13] It should be mentioned that the synthesis of (+)- and -(-)-**1** may be accomplished by starting from the enantiomeric **2f**.

This work has demonstrated the utility of lipase in the synthesis of homochiral *anti*-1,2-diols and natural products. The resolution process using LPS is straightforward and provide high optical purity and good yield. The LPS is readily available,[14] inexpensive, and stable enough to be used for the longer reaction time. We conclude that the LPS-catalyzed transesterification constitutes a useful component of methodology for the synthesis of homochiral *anti*-1,2-diols and provide an alternative complementary to the chemical methods. Further studies to expand the scope of this method to other classes of diols, particularly *syn*-1,2-diols, are in progress and a full account will be reported in the near future.



Scheme 1. *Reagents and conditions*: a) i. BnBr, NaH, reflux, ii. TsOH, 40°C (overall 82%); b) TsCl, DMAP, 0°C to r.t. (94%); c) allylMgCl, r.t. (78%); d) i. $PdCl_2$, CuCl, O_2, r.t. (81%); e) H_2, Pd-C, r.t. (80%)

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References and notes

1. (a) Scott, J. W.: Readily Available Chiral Carbon Fragments and Their Use in Synthesis. In *Asymmetric Synthesis*; Morrison, J. W.; Scott. J. W., Eds.; Academic Press: New York, 1984; Vol 4, pp. 1-226. (b) Fuhrhop, J.; Penzlin, G. *Organic Synthesis*; VCH publisher: Weinheim, 1994; pp. 171-192.
2. For a recent review, see: Wang, L.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.
3. Wang. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568-7570.
4. Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdauskas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942-4945.
5. Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; pp 41-130.
6. (a) Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.* **1992**, *57*, 5231-5239. (b) Kim, M.-J.; Lee, I. S. *J. Org. Chem.* **1993**, *58*, 6483-6485.
7. The unreacted **2e**: $[\alpha]_D^{21}$ -17.5° (*c* 0.85, EtOH) [lit. $[\alpha]_D^{20}$ -11.2° (*c* 4.03, EtOH) for (1*R*,2*S*)-enantiomer (77% ee): Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, J.-Y.; Sancean, Y.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991-1993].
8. Similiar rules were proposed previously for the lipase-catalyzed transformations of secondary alcohols and their esters: (a) Kazlauskas, J. J.; Weissfloch, A. W. E.; Rapport, A. T.; Cuccia, L A. *J. Org. Chem.* **1991**, *56*, 2656-2665. (b) Kim, M.-J.; Cho, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1411-1413.
9. (+)-**2g**: $[\alpha]_D^{21}$ +29.0° (*c* 0.98, $CHCl_3$); m.p. 133-135°C. (-)-**2g**: $[\alpha]_D^{21}$ -29.1° (*c* 1.0, $CHCl_3$); m.p. 133-135°C.
10. Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975-2976.
11. (+)-**1**: $[\alpha]_D^{21}$ +79.2° (*c* 1.10, Et_2O) [lit.[15] $[\alpha]_D^{21}$ +78.8° (*c* 0.5, Et_2O)]. The ^1H and ^{13}C NMR data are in good agreement with those reported in the literature.[15]
12. (-)-**1**: $[\alpha]_D^{21}$ -76.7° (*c* 0.90, Et_2O) [lit.[15] $[\alpha]_D^{21}$ -75.9° (*c* 0.717, Et_2O)]. The ^1H and ^{13}C NMR data are in good agreement with those reported in the literature.[15]
13. For a review on the synthesis of brevicomin, see: Mori, K.: The Synthesis of Insect Phermones. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1992.
14. From Amano.
15. Mori, K.; Seu, Y.-B. *Tetrahedron* **1985**, *41*, 3429-3431.

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