# Lipase-Catalyzed Transesterification as a Route to Each Stereoisomer of 2,5-Hexanediol and 3-Hexyne-2,5-diol. Synthesis of (2*R*,5*R*)-2,5-Dimethyltetrahydrofuran

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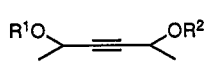
*Received May 28, 1993*

Optically active 2,5-hexanediol is a valuable synthon in the synthesis of chiral auxiliaries[1] and ligands.[2] The methods currently available for its practical synthesis include the microbial reduction of 2,5-hexadione using bakers yeast[3] and the chemical synthesis from 3-oxobutyric acid esters employing Noyori's catalytic hydrogenation and Kolbe decarboxylation coupling.[4] The microbial procedure is applicable to only the (2*S*,5*S*)-enantiomer and frequently suffers from low yields and a tedious workup procedure. Although it is applicable to both enantiomers, the chemical procedure requires rather inconvenient apparatuses. As an alternative to the microbial and chemical method, we herein describe an enzymatic procedure which does not require inconvenient apparatuses and provides high optical purity for both enantiomers. In addition, the same method provides a practical route to monoacetate of *meso*-2,5-hexanediol [(2*S*,5*R*)-5-acetoxy-2-hexanol] of high optical purity, leading to the synthesis of (2*R*,5*R*)-2,5-dimethyltetrahydrofuran. We also describe the utility of the method in the synthesis of other 1,4-diols, especially 3-hexyne-2,5-diol.

This procedure employs, as the starting materials, commercially available 2,5-hexanediol (**1**) which contains three stereoisomers and a lipase from *Pseudomonas* sp. (lipase AK, LAK; 24600 units/g, Amano) as the catalyst for resolution (Scheme I). In a typical procedure, diol **1** was subject to LAK-catalyzed transesterification in the presence of vinyl acetate.[5] The reaction was followed by TLC and stopped when diol **1**, monoacetate **2**, and diacetate **3** were present in a ratio of approximately 1:2:1. The removal of enzymes followed by chromatography afforded **1**, **2**, and **3**, separately. At this time, each compound had high optical purity (>98% ee) but moderate diastereomeric purity (**1**, 75% de; **2**, 78% de, **3**, 90% de). To enhance the diasteromeric purity, each compound was recycled to the LAK-catalyzed transesterification: **2** and **3** had been hydrolyzed to diol, respectively, before being recycled. This recycling increased the diastereomeric purity of **1** and **3** to >98% and that of **2** to 96%. Finally, the hydrolysis of diacetate **3** to (2*R*,5*R*)-**1** completed the resolution process. The overall yield was 18% for unreacted diol [(2*S*,5*S*)-**1**], 36% for monoacetate [(2*S*,5*R*)-**2**], and 17% for (2*R*,5*R*)-**1**, totaling a combined overall yield of 71%.

Some observations from this work deserve a brief comment. First, the lipase AK is *R*-stereoselective in the transesterification of **1**: (2*R*,5*R*)-**1** is the most rapidly converted to diacetate, *meso*-diol (2*R*,5*S*)-**1** rapidly to monoacetate and then slowly to diacetate, and (2*S*,5*S*)-**1** the most slowly to monoacetate and diacetate. Accordingly, the stereoselectivity enables the efficient separation of three stereoisomers of **1** as diacetate, monoacetate, and diol, respectively. Second, the absolute configuration of monoacetate **2** has been established by chemically converting it to (2*R*,5*R*)-**5**[6] (Scheme II). We note that this chemical conversion combined with the LAK-catalyzed transesterification provides the highest optical purity for **5**. Third, the procedure described here is practical since it uses readily available chemicals and enzymes and includes only conventional processes.

To further show the utility of the method described here, we used 3-hexyne-2,5-diol (**6**) as additional substrate. The first round of LAK-catalyzed transesterification provided diol **6**, monoacetate **7**, and diacetate **8** with the following enantiomeric and diastereomeric purity: **6** (>98% ee, 95% de), **7** (>98% ee, 88% ee), and **8** (>98% ee, 86% de). Monoacetate **7** and diacetate **8** were subject to the second round of LAK-catalyzed reaction to amplify the diastereomeric purity. Finally, the hydrolysis of diacetate **8** to (2*R*,5*R*)-**6** completed the resolution process. The yield and optical purity of the final products are as follows (combined overall yield, 87%): (2*R*,5*R*)-**6** (18%, >98% ee and de), (2*S*,5*S*)-**6** (23%, >98% ee and 95% de), and (2*R*,5*S*)-**7** (46%, >98% ee and de). In this case, it is noteworthy that the high enantiomeric and diastereomeric purities for (2*S*,5*S*)-**6** were achieved through the first round of enzyme-catalyzed reaction.




**6**, $R^1 = R^2 = H$
**7**, $R^1 = Ac$, $R^2 = H$
**8**, $R^1 = R^2 = Ac$

In summary, this study has demonstrated that LAK-catalyzed reaction provides an efficient route to enantiomeric 2,5-hexanediol, 3-hexyne-2,5-diol, 5-acetoxy-2-hexanol, 5-acetoxy-3-hexyn-2-ol, and 2,5-dimethyltetrahydrofuran.

## Experimental Section

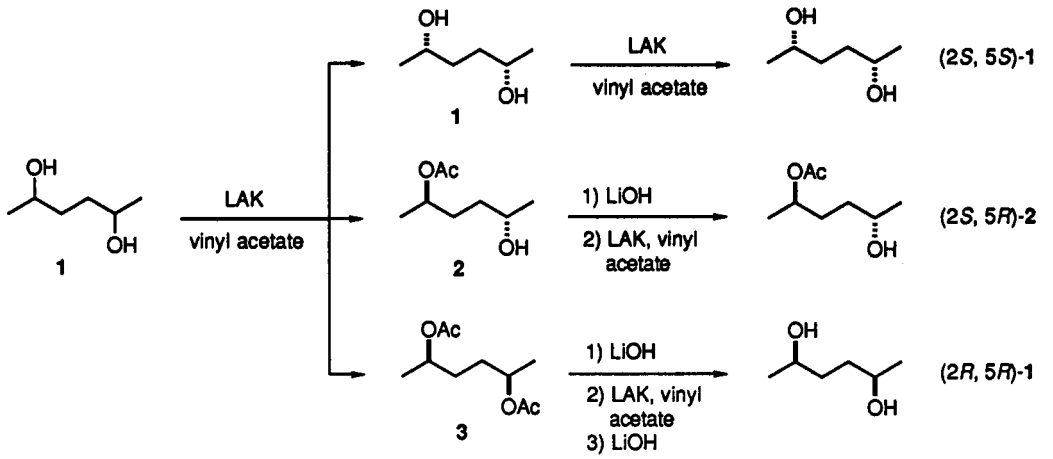
**Materials and Methods.** 2,5-Hexanediol, 3-hexyne-2,5-diol, vinyl acetate, tosyl chloride, and anhydrous ethylene glycol were obtained from Aldrich. Lipase AK from *Pseudomonas* sp. (24600 units/g) was obtained from Amano, Japan. Ethylene glycol was distilled in the presence of Na before use. All other chemicals were reagent grade and used as received.

$^1$H NMR spectra were recorded on a Bruker AM-300 instrument with peaks referenced to TMS in $CDCl_3$. Optical rotations were measured using a Jasco polarimeter. Melting points were measured using a Thomas-Hoover apparatus and uncorrected. Enantiomeric excesses were measured by $^1$H NMR spectroscopy in the presence of Eu(hfc)$_3$ and diastereomeric excesses by both $^1$H and $^{13}$C NMR spectroscopy.[7]

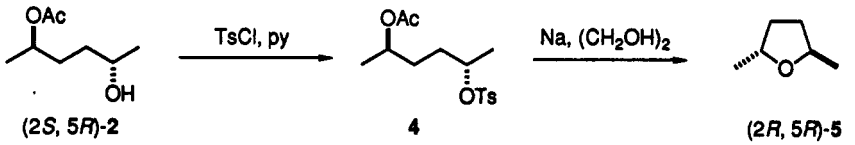
(1) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755.
(2) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653.
(3) Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765.
(4) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedon: Asymmetry* **1991**, *2*, 569.
(5) (a) Wong, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3129. (b) Wang, Y.-F.; Chen, S.-T.; Liu, K. K.-C.; Wong, C.-H. *Tetrahedron Lett.* **1989**, *30*, 1917.
(6) Mihailovic, M. L.; Mamuzic, R. I.; Zigic-Mamuzic, L.; Bosnjak, J.; Cekovic, Z. *Tetrahedron* **1967**, *23*, 215.
(7) Fraser, R. R. In *Asymmetric Syntheis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, p 173.

0022-3263/93/1958-6483$04.00/0 

**Scheme I**




**Scheme II**




**LAK-Catalyzed Transesterification of 2,5-Hexanediol (1).** A solution of 1 (10 g, 84.6 mmol), vinyl acetate (62.4 mL, 677 mmol), and LAK (5 g) was stirred at room temperature. The reaction was followed by TLC and stopped when diol, monoacetate, and diacetate were present in approximately 1:2:1 ratio (32 h). The reaction mixture, after removal of enzymes by filtration, was concentrated and subjected to chromatography (*n*-hexane/ethyl acetate, 4:1) to give diol (1, 2.50 g, 21.2 mmol, 25%), monoacetate (2, 7.10 g, 44.4 mmol, 52%), and diacetate (3, 3.93 g, 19.5 mmol, 23%). For the determination of enantiomeric and diastereomeric purity, small fractions of 1 and 2 were acetylated, respectively, with acetic anhydride in the presence of pyridine to diacetate: 1, >98%, ee, 75% de; 2, >98% ee, 78% de; 3, >98% ee, 90% de.

**(2*R*,5*R*)-2,5-Hexanediol [(2*R*,5*R*)-2].** The diacetate 3 (3.93 g, 19.5 mmol, 90% de) was dissolved in methanol (20 mL) followed by the addition of $LiOH·H_2O$ (4.91 g, 117 mmol). The resulting mixture was stirred at 25 °C for 8 h, filtered, concentrated, and diluted with $H_2O$. The aqueous solution was extracted continuously with ethyl ether for 2 days. The ethereal phase was dried and concentrated to give diol (2.18 g, 18.4 mmol, 95%). The diol was subject to the LAK-catalyzed transesterification (LAK, 1.1 g; vinyl acetate, 13.6 mL; 35 h) to yield diacetate 3 (2.85 g, 14.1 mmol, 76%, >98% ee, >98% de), which then was hydrolyzed ($LiOH·H_2O$, 3.55 g, 84.6 mmol; MeOH, 15 mL) to afford (2*R*,5*R*)-1 (1.70 g, 14.4 mmol, 100%): mp 52–53 °C; $[\alpha]^{25}_D$ −35.7° (*c* 1, $CHCl_3$) [lit.[4] mp 53–54 °C, $[\alpha]^{25}_D$ −39.6° (*c* 1, $CHCl_3$)]; $^1H$ NMR δ 1.19 (d, *J* = 6.2 Hz, 6 H), 1.55 (m, 4 H), 1.68 (br s, 2 H), 3.82 (m, 2 H); $^{13}C$ NMR δ 23.8, 35.8, 68.4.

**(2*S*,5*S*)-2,5-Hexanediol [(2*S*,5*S*)-1].** Diol 1 (2.50 g, 21.2 mmol, 75% de) was subject to the LAK-catalyzed transesterification (LAK, 1.25 g; vinyl acetate, 15.6 mL, 170 mmol; 35 h) to give diol (2*S*,5*S*)-1 (1.79 g, 15.1 mmol, 72%): mp 53.0–53.5 °C; $[\alpha]^{25}_D$ +39.2° (*c* 1, $CHCl_3$) [lit.[8] mp 53.0–53.3 °C, $[\alpha]^{20}_D$ +35.1° (c 9.49, $CHCl_3$)]. The $^1H$ and $^{13}C$ NMR data were identical to those for (2*R*,5*R*)-1. For the analysis of the enantiomeric and diastereomeric purity by $^1H$ NMR spectroscopy, a portion of diol was converted ($Ac_2O$, py) to diacetate (>98% ee, >98% de).

**(2*S*,5*R*)-5-Acetoxy-2-hexanol [(2*S*,5*R*)-2].** The monoacetate 2 (7.10 g, 44.4 mmol, 78% de) was hydrolyzed in the presence of $LiOH·H_2O$ (5.76 g, 137 mmol) in methanol (20 mL). Usual workup, described in the synthesis of (2*R*,5*R*)-1, provided diol (5.16 g, 43.7 mmol, 98%). The diol was recycled to the LAK-catalyzed transesterification (LAK, 2.58 g; vinyl acetate, 32.2 mL, 349 mmol, 35 h) to give monoacetate (2*S*,5*R*)-2 (4.90 g, 30.6 mmol, 70%): $[\alpha]^{25}_D$ +9.6° (c 1, $CHCl_3$); $^1H$ NMR δ 1.19 (d, *J* = 6.2 Hz, 3 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 1.46 (m, 2H), 1.61 (m, 2 H), 2.02 (s, 3 H), 3.78 (m, 1 H), 4.90 (m, 1 H); $^{13}C$ NMR δ 19.8, 21.2, 23.4, 32.1, 34.9, 67.6, 71.0. For the analysis of the enantiomeric and diastereomeric purity by $^1H$ NMR spectroscopy, a portion of monoacetate was converted ($Ac_2O$, py) to diacetate (>98% ee, 96% de).

**(2*R*,5*R*)-2,5-Dimethyltetrahydrofuran [(2*R*,5*R*)-5].** A solution of monoacetate (2*S*,5*R*)-2 (4.40 g, 27.5 mmol), tosyl chloride (7.85 g, 41.2 mmol), and dry pyridine (20 mL) was stirred at 0 °C under nitrogen. After 36 h, the excess tosyl chloride was quenched with methanol. The resulting solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with cold 10% $H_2SO_4$, saturated $NaHCO_3$, and brine in sequence, dried over anhydrous $MgSO_4$, and concentrated to quantitatively give tosylate 4 (8.65 g, 27.5 mmol): $^1H$ NMR δ 1.11 (d, *J* = 6.2 Hz, 3 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 1.4–1.6 (m, 4 H), 1.97 (s, 3 H), 2.41 (s, 3 H), 4.59 (m, 1 H), 4.77 (m, 1 H), 7.30 (d, *J* = 8.1 Hz, 2.H), 7.76 (d, *J* = 8.2 Hz, 2 H). To the tosylate (7.07 g, 22.5 mmol) was added Na (1.04 g, 45.2 mmol) dissolved in dry ethylene glycol (45 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 32 h. From the mixture, the product was evaporated under vacuum (ambient temperature, <1 torr) and trapped using a dry ice–acetone bath to give clear oil of 5 (1.84 g, 18.4 mmol, 82%): $[\alpha]^{25}_D$ −31.3° (*c* 2.91, EtOH), [lit.[6] $[\alpha]^{21}_D$ −22.95° (*c* 2.9, EtOH)]; $^1H$ NMR δ 1.15 (d, *J* = 6.2 Hz, 6 H), 1.41 (m, 2 H), 1.99 (m, 2 H), 4.08 (m, 2 H); $^{13}C$ NMR δ 21.4, 34.1, 74.4.

**LAK-Catalyzed Transesterification of 3-Hexyne-2,5-diol (6).** This procedure followed that for 1 using 6 (10 g, 87.6 mmol), vinyl acetate (60.2 g, 699 mmol), and LAK (5 g). The reaction was carried out for 16 h. The usual workup followed by chromatography afforded diol 6 (2.30 g, 20.2 mmol, 23%), monoacetate 7 (7.12 g, 45.6 mmol, 52%), and diacetate 8 (4.01 g, 20.2 mmol, 23%). For the determination of enantiomeric and diastereomeric purity, small fractions of 6 and 7 were acetylated, respectively, with acetic anhydride in the presence of pyridine to diacetate: 6, >98% ee, 95% de; 7, >98% ee, 88% de; 8, >98% ee, 86% de.

**(2*R*,5*R*)-3-Hexyne-2,5-diol [(2*R*,5*R*)-6].** The diacetate 8 (4.01 g, 20.2 mmol, 86% de) was dissolved in methanol (20 mL) followed by the addition of $LiOH·H_2O$ (5.10 g, 121 mmol). The resulting mixture was stirred at 25 °C for 8 h, filtered, concentrated and diluted with $H_2O$. The aqueous solution was extracted with EtOAc. The organic phase was dried and concentrated to give

(8) Serk-Hanssen, K.; Stallberg-Stenhagen, S.; Stenhagen, E. *Arkiv. Kemi.* **1953**, *5*, 203.

diol (2.30 g, 20.2 mmol, 100%). The diol was subject to the LAK-catalyzed transesterification (LAK, 1.15 g; vinyl acetate, 13.9 mL; 29 h) to yield diacetate 8 (3.14 g, 15.8 mmol, 78%, >98% ee, 98% de), which then was hydrolyzed ($LiOH·H_2O$, 3.98 g, 94.8 mmol; MeOH, 20 mL) to afford (2*R*,5*R*)-6 (1.80 g, 15.8 mmol, 100%): mp 58–60 °C; $[\alpha]^{25}_D$ +70.8° (c 1, $CHCl_3$) [lit.[9] mp 44–46 °C for *dl*-6]; $^1H$ NMR δ 1.39 (d, *J* = 6.5 Hz, 6 H), 3.75 (s, 2 H), 4.49 (q, *J* = 5.8 Hz, 2 H); $^{13}C$ NMR δ 24.0, 57.9, 85.8.

**(2*S*,5*S*)-3-Hexyne-2,5-diol [(2*S*,5*S*)-6].** As described above, the first round of LAK-catalyzed reaction provided diol of high enantiomeric and diastereomeric purity (>98% ee and 95% de). (2*S*,5*S*)-6 (2.30 g, 20.2 mmol, 23%): mp 58–60 °C; $[\alpha]^{25}_D$ −57.3° (c 1.53, $CHCl_3$). The $^1H$ and $^{13}C$ NMR data were identical to those for (2*R*,5*R*)-6.

**(2*S*,5*R*)-5-Acetoxy-3-hexyne-2,5-diol [(2*S*,5*R*)-7].** The monoacetate 7 (7.04 g, 45.1 mmol, 88% de) was hydrolyzed in the presence of $LiOH·H_2O$ (5.67 g, 135 mmol) in methanol (20 mL). Usual workup, described in the synthesis of (2*R*,5*R*)-6, provided diol (5.01 g, 43.9 mmol, 97%). The diol was recycled to the LAK-catalyzed transesterification (LAK, 2.50 g, vinyl acetate, 30.2 g, 351 mmol; 16 h) to give monoacetate (2*S*,5*R*)-2 (6.26 g, 40.1 mmol, 91%): $[\alpha]^{25}_D$ +134.7° (c 1.25, $CHCl_3$); $^1H$ NMR δ 1.36 (d, *J* = 6.8 Hz, 3 H), 1.40 (d, *J* = 6.3 Hz, 3 H), 2.00 (s, 3 H), 2.74 (s, 1 H), 4.47 (q, *J* = 6.7 Hz, 1 H), 5.37 (q, *J* = 6.8 Hz, 1 H); $^{13}C$ NMR δ 20.9, 21.2, 23.9, 57.7, 60.3, 81.9, 86.7, 170.0. For the analysis of the enantiomeric and diastereomeric purity by $^1H$ NMR spectroscopy, a portion of monoacetate was converted ($Ac_2O$, py) to diacetate (>98% ee, >98% de).

**Acknowledgment.** We thank KOSEF and RIST for financial support of this work.

(9) Hill, R. K.; Pendalwar, S. L.; Kielbasinski, K.; Baersky, M. F.; Nugara, P. N. *Synth. Commun.* **1990**, *20*, 1877.