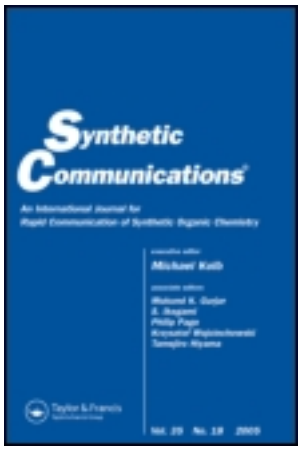

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Resolution of Racemic Rhododendrol by Lipase-Catalyzed Enantioselective Acetylation

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ABSTRACT

Both (*R*)- and (*S*)-enantiomers of rhododendrol were prepared in high enantiomeric exess by lipase from *Pseudomonas cepacia* (Amano PS)-catalyzed acetylation of racemic **1** with vinyl acetate at room temperature. Especially, in the case of using acetonitrile as the solvent, by-products **4** and **5** were minimized.

Key Words: Rhododendrol; Lipase; Kinetic resoluton; Enantioselectivity.

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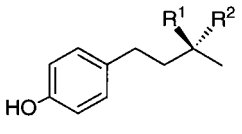
(*S*)-(+)-Rhododendrol; (*S*)-(+)-4-(4′-hydroxyphenyl)-2-butanol **1a**, which has hepato-protective activity,[1] has been isolated from *Rhododendron maximum*,[2] or *Acer nikoense*.[3–5] Furthermore, (*R*)-(−)-rhododendrol **1b** and its glucoside have been isolated from *Rododendron chrysanthem*.[6] Recently, rhododendrol and its glucoside have been used as a melanin-inhibitor and in skin-lightening cosmetics.[7] The absolute configurations of **1a** and **1b** have been determined by X-ray crystallographic analysis and a comparison of their optical rotations[4,8,9] (Fig. 1).

The enantioselective synthesis of **1a** from 4-(4′-hydroxyphenyl)-2-butanone **2** by enzymatic reduction using baker's yeast has been reported by Das et al.[10] However, a useful asymmetric synthesis of **1b** has not been reported so far.

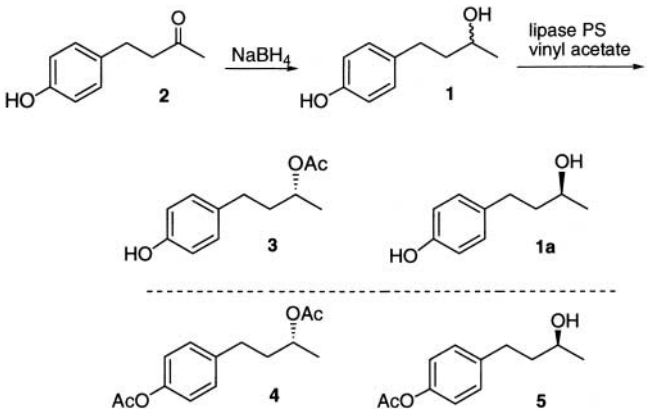
On the other hand, Burgess and Jennings[11] reported that 4-phenyl-2-butanol similar to **1** could be resolved by lipase AK. Aiming at target compound **1a** and **1b**, we made a plan to use the inexpensive lipases as a chiral catalyst. Enzymes, especially lipases are now well established as valuable catalysts in organic syntheses. Moreover, the enzymatic resolution mediated by lipase is attractive because these enzymes are commercially available at a low cost. Kinetic resolution is one of the most useful and convenient methods. In the light of the above considerations, we investigate the enzymatic reaction of phenol-containing alkyl alcohol **1** by lipase which hardly had been reported. We report here the enantioselective and simultaneous syntheses of **1a** and **1b** (Sch. 1).

We first investigated the enzymatic resolution of **1**, which was obtained from the reduction of **2** by $NaBH_4$, with some lipases including *Candida rugosa* lipase (MY), *Pseudomonas cepacia* lipase (PS), *Pseudomonas fluorescense* lipase (AK), and *Alcaligenes sp*. lipase (QLG). The amount of vinyl acetate as the acetate donor and lipase were almost fixed at a 1.5 mol equivalent and a 0.5 mass equivalent with respect to **1** in diisopropyl ether (i-Pr_2O) at room temperature, respectively. The results of the kinetic resolution by transesterification are shown in Table 1. Kinetic transesterification of (*S*)-(+)-alcohol **1a** was found to proceed slower than the (*R*)-(−)-enantiomer under most of



	R^1	R^2
1a	OH	H
1b	H	OH

Figure 1.



Scheme 1.

Table 1. Kinetic resolution of (±)-**1** by lipase-catalyzed acetylation.[a]

Run	Lipase[b]	Solvent	Time (h)	Alcohol **1a** %[c] (%ee)[d]	Acetate **3** %[c] (%ee)[d]	By-product **4** %[c] (%ee)[d]	By-product **5** %[c] (%ee)[d]
1	Lipase MY	*i*-Pr_2O	72	93 (—)	5 (—)	2	—
2	Lipase AK	*i*-Pr_2O	24	25 (99)	32 (46)	21	20
3	Lipase AK	CH_3CN	72	36 (99)	45 (41)	10	8
4	Lipase QLG	CH_3CN	48	54 (53)	40 (85)	4	2
5	Lipase PS	THF	72	86 (10)	12 (—)	1	—
6	Lipase PS	*i*-Pr_2O	96	42 (78)	42 (98)	9 (98)	7 (78)
7	Lipase PS	CH_3CN	72	49 (79)	48 (98)	2	1

[a]All reactions were carried out at room temperature.
[b]Four enzymes were commercially available (MEITO, AMANO).
[c]Product ratio was determined by GC.
[d]The enantiomeric excess (%ee) was determined by HPLC on CHIRALCEL OD-H after hydrolysis with NaOH aqueous solution. The chromatogram showed two signals with $t_r = 35.6$ min and 40.4 min assignable to **1b** and **1a**, respectively.

the lipases. Among the lipases, lipase PS showed high enantioselectivities for this substrate. For lipase MY, transesterification proceed at slower rate (run 1). Whereas for lipase AK and lipase QLG, acetylated **4** and **5** were obtained as by-products (runs 2, 3, and 4).

We then investigated the proper choice of solvent. The influence of solvent in the enantioselectivity for enzyme-catalyzed transesterifications is well documented. In general, enzyme selectivity was good enough for practical use in all of the solvents. However, on using tetrahydrofuran (THF) as the solvent, reaction rate and enantiomeric excess did not give satisfactory result (run 5). The other solvents were also examined, non-polar solvents (for example, hexane, benzene, and toluene) showed poor selectivity and reactivity (data were not shown). Acetonitrile (CH_3CN) gave the best result with regard to enantioselectivity and minimal by-products **4** (2%) and **5** (1%) (run 7).

Enantiomeric excess of the acetylated product **3** was determined by hydrolysis with $NaOH/H_2O$–MeOH to afford **1b**. The optical purities of **1a** and **1b** were directly measured by HPLC on CHIRALCEL OD-H columm. As by-products, the optically active diacetate **4** and monoacetate **5** were isolated by column chromatography. The absolute configuration of these compounds was also determined by hydrolysis with $NaOH/H_2O$–MeOH to afford **1b** and **1a**, respectively. The recrystallization of **1a** (run 6) with 78%ee from $CHCl_3$ afforded **1a** with 99%ee in 54% yield.

In conclusion, we succeed in the preparation of the optically active products (*R*)-(−)- and (*S*)-(+)-rhododendrol with exceedingly high enantiomeric excess by means of enzymatic kinetic resolution. When lipase PS was used in acetonitrile, transesterification of (±)-**1** proceeded in good chemical and optical yield. This method is suitable for large-scale synthesis of (*R*)-(−)- and (*S*)-(+)-rhododendrol.

EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial sources and used without further purification. Lipase MY and QLG were obtained from Meito Co., Ltd. Lipase AK and PS were obtained from Amano Pharm. Co., Ltd. Melting points: Yanagimoto micromelting apparatus, uncorrected values. IR: Jasco IR-810. ^{1}H NMR: (TMS as internal standard): Bruker AM-400 (400 MHz). ^{13}C NMR (TMS as internal standard): Bruker AM-400 (100 MHz). MS: Hitachi M-80A mass spectrometer at 70 eV. Optical rotations: Jasco DIP-4 digital polarimeter. GLC: Shimadzu GC-14A with an FID detector (column, Neutrabond-1, df = 0.15 μm, 0.25 mm ID X 30 m; carrier gas N_2, 0.1 MPa, oven temperature, 100–200°C programmed at 10°C/min; injection temperature, 250°C, detector temperature, 250°C); **1** 14.49 min, **5** 16.79 min, **3** 17.66 min, **4** 19.71 min. HPLC: Hitachi L-6000 [column, CHIRALCEL OD-H,

4.6 mm ID × 250 mm; eluent: 2-propanol/*n*-hexane = 5:95, flow rate, 1 mL/min; detector, Hitachi L-4000 (254 nm)]; **1b** t_r 35.6 min, **1a** t_r 40.4 min. Column chromatography: Merck Kieselgel 60 Art-N: 7734.

Synthesis of Rhododendrol 1

To 4-(4′-hydroxyphenyl)-2-butanone **2** (200 g, 1.22 mol) in EtOH (500 mL) were added small portions of $NaBH_4$ (34.8 g, 0.92 mol) at room temperature. After the reagent was completely added, the mixture was stirred for 2 h and then concentrated at reduced pressure. To the residue was added water (200 mL), 10% HCl (250 mL), and AcOEt (500 mL), and then the organic layer was extracted, washed with brine, and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give crude **1** (214 g). The product was recrystallized from 5% aqueous EtOH solution (1600 mL) at 15°C to give pure **1** (183 g, 90%). M.p. 71°C {lit.[12] 72°C}.

Enzymatic Resolution of Rhododendrol 1 for Determination of Product

To the lipase PS (1.0 g, 0.5 mass equiv.) were added *i*-Pr_2O (30 mL), vinyl acetate (1.5 g, 1.5 mol equiv.), and **1** (2.0 g). The solution was stirred at room temperature for 96 h and the course of the reaction was followed by GC. The product ratios of **1a**, **3**, **4**, and **5** were 42/42/9/7. The solution was filtered and the volatiles were removed under reduced pressure to give an oily product (2.15 g). The crude product was chromatographed on silica gel, then eluted with 5–20% AcOEt/hexane to afford three acetates and an alcohol.

First eluted acetate: (*R*)-(+)-Rhododendrol diacetate, 4-(4′-acetoxyphenyl)-2-butyl acetate **4** (0.2 g) was obtained as a viscous oil. $[\alpha]_D^{24}$ +6.1° (*c* 1.64, EtOH). IR (neat) 2940, 1745, 1510 cm^{-1}. ^1H NMR ($CDCl_3$) 1.24 (3H, d, *J* 8.5), 1.65–1.83 (1H, m), 1.88–1.93 (1H, m), 2.03 (3H, s), 2.28 (3H, s), 2.60–2.69 (1H, m), 4.91–4.97 (1H, m), 6.99 (2H, d, *J* 8.5), 7.17 (2H, d *J* 8.5). ^{13}C NMR ($CDCl_3$) 20.70, 21.78, 21.97, 31.90, 38.18, 71.15, 122.09, 129.88, 139.79, 149.51, 170.30 and 171.43. EIMS: (*m*/*z*) 250 (M^+), 208, 190, 148, 133, 107, 43. HRMS calcd. for [$C_{14}H_{18}O_4$]: 250.2938. Found: $[M]^+$ 250.2939.

4 was hydrolyzed with aqueous NaOH/MeOH at room temperature for 3h to give a (*R*)-(−)-rhododendrol **1b**. The optical purity was 98%ee by HPLC.

Second eluted acetate: (*R*)-(+)-Rhododendrol monoacetate, 4-(4′-hydroxyphenyl)-2-butyl acetate **3** (0.85 g) was obtained as a viscous oil. $[\alpha]_D^{24}$ +2.12° (*c* 1.42, EtOH). IR (neat) 3390, 2970, 1715, 1600, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) 1.24 (3H, d, *J* 6.3), 1.76–1.84 (1H, m), 1.86–1.92 (1H, m), 2.04 (3H, s), 2.53–2.60 (1H, m), 4.90–4.94 (1H, m), 6.75 (2H, d, *J* 8.5), 7.02 (2H, d *J* 8.5). ^{13}C NMR ($CDCl_3$) 20.67, 22.04, 31.53, 38.41, 71.45, 115.95, 130.03, 134.03, 154.67, 171.97. EIMS: (*m*/*z*) 208 (M^+), 148, 133, 107, 43. HRMS calcd. for [$C_{12}H_{16}O_3$]: 208.2566. Found: $[M]^+$ 208.2566.

3 was hydrolyzed with aqueous NaOH/MeOH at room temperature for 3 h to give a (*R*)-(−)-rhododendrol **1b**. $[\alpha]_D^{24}$ −19.4° (*c* 1.03, EtOH).[13] The optical purity was 98%ee by HPLC.

Third eluted acetate: (*S*)-(+)-Rhododendrol monoacetate, 4-(4′-acetoxyphenyl)-2-butanol **5** (0.2 g) was obtained as a viscous oil. $[\alpha]_D^{24}$ +14.43° (*c* 1.32, EtOH). IR (neat) 3390, 2930, 1755, 1510 cm^{-1}. ^1H NMR ($CDCl_3$) 1.22 (3H, d, *J* 8.5), 1.71–1.78 (1H, m), 2.28 (3H, s), 2.63–2.67 (1H, m), 2.69–2.76 (1H, m), 3.79–3.84 (1H, m), 6.99 (2H, d, *J* 8.5), 7.19 (2H, d, *J* 8.5). ^{13}C NMR ($CDCl_3$) 21.78, 24.31, 32.14, 41.41, 68.02, 122.03, 129.96, 140.31, 149.40, 170.37. EIMS: (*m*/*z*) 208 (M^+), 166, 148, 133, 107, 43. HRMS calcd. for [$C_{12}H_{16}O_3$]: 208.2566. Found: $[M]^+$ 208.2568.

5 was hydrolyzed with aqueous NaOH/MeOH at room temperature for 3 h to give a (*S*)-(+)-rhododendrol **1a**. The optical purity was 79%ee by HPLC.

Final eluted alcohol: (*S*)-(+)-Rhododendrol **1a** (0.87 g) was obtained as a solid. The optical purity was 79%ee by HPLC. $[\alpha]_D^{24}$ +12.72° (*c* 1.1, EtOH).[13] The solid was recrystallizated from $CHCl_3$ and the optical purity was 99%ee by HPLC. M.p. 78–78.5°C; $[\alpha]_D^{24}$ +16.9° (*c* 1.06, EtOH).[13] IR (KBr) 3350, 2930, 1610, 1590, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) 1.23 (3H, d, *J* 7.9), 1.68–1.79 (3H, m), 2.58–2.71 (2H, m), 3.81–3.85 (1H, m), 5.25 (1H, brs), 6.75 (2H, d, *J* 8.5), 7.06 (2H, d, *J* 8.5). ^{13}C NMR ($CDCl_3$) 24.25, 31.89, 41.67, 68.36, 115.96, 130.65, 134.65, 154.49. EIMS: (*m*/*z*) 166 (M^+), 148, 133, 107.

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