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Practical synthesis of (*R*)-(+)-6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-hydroxyphenyl)hexanoic acid: a key intermediate for a therapeutic drug for neurodegenerative diseases

Tatsuya Ito,[a,*] Tomomi Ikemoto,[a] Toru Yamano,[b] Yukio Mizuno[a] and Kiminori Tomimatsu[a]

[a]*Chemical Development Laboratories, Takeda Chemical Industries, Ltd., 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan*

[b]*Medicinal Chemistry Research Laboratories, Takeda Chemical Industries, Ltd., 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan*

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Abstract—A practical method for the preparation of (*R*)-(+)-6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-hydroxyphenyl)hexanoic acid (*R*)-**2**, a key intermediate for a therapeutic drug for neurodegenerative diseases, has been developed. *rac*-Methyl 6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-(propionyloxy)phenyl) hexanoate *rac*-**9b** was synthesized from 2-methylnaphthoquinone in seven steps. An optically active ester (*R*)-**9b** was readily obtained from the corresponding racemic ester by lipase-catalyzed resolution, followed by sulfation or phosphorylation. Sulfation by a sulfur trioxide pyridine complex or phosphorylation by phosphoryl chloride enabled facile isolation of the optically active ester simply by extraction. Optically active acid (*R*)-**2** was synthesized in excellent enantiomeric excess by hydrolysis of (*R*)-**9b** followed by recrystallization. The present synthesis of (*R*)-**2** was accomplished in 10 steps without requiring chromatographic purification.

1. Introduction

In a search for new therapeutic drugs for neurodegenerative diseases, a naphthoquinone derivative **1**[1] was found as a pharmaceutical agent useful for neurodegeneration inhibition in the prevention and treatment of nerve disease (Fig. 1). Hence, the preparation of **1** on a large scale was required to support toxicological evaluation. The key intermediate for the synthesis of **1** was optically active acid (*R*)-**2**.[1,2] As a structural feature, it should be mentioned that (*R*)-**2** has a stereogenic carbon bearing a phenol, a naphthalene moiety and a pentanoic acid. The approach to producing an enantiomerically pure product was examined in detail, and it was found that resolution using alipase was effective. Herein we describe the large-scale production of (*R*)-**2** without chromatographic purification, as outlined in Schemes 1 and 2.

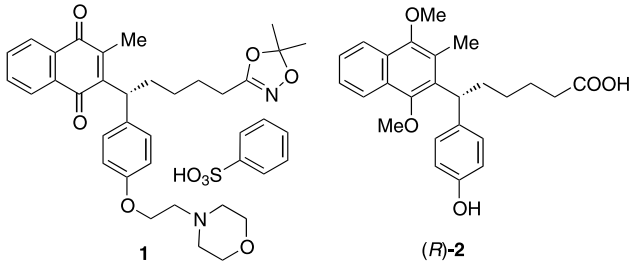

Figure 1.

2. Results and discussion

2.1. Synthesis of *rac*-2

Racemic acid *rac*-**2** was synthesized from a naphthoquinone derivative **3** in five steps, as shown in Scheme 1. A naphthalene derivative **5** was prepared by reduction of **3** with $Na_2S_2O_4$, followed by methylation using Me_2SO_4 in excellent yield (purity 99.2%). Formylation[3] of **5** was carried out with dichloromethyl methyl ether and $TiCl_4$ in dichloromethane to give **6** in 77% yield (purity 97.2%). The reaction temperature was kept at

* Corresponding author. E-mail: ito_tatsuya@takeda.co.jp

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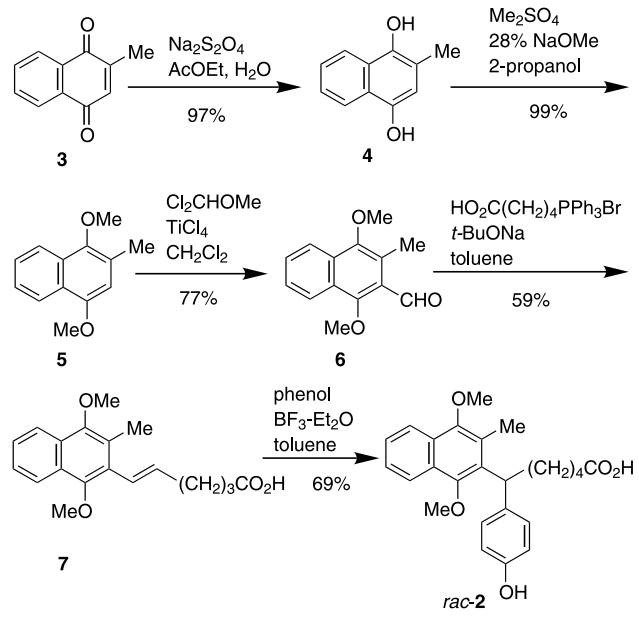
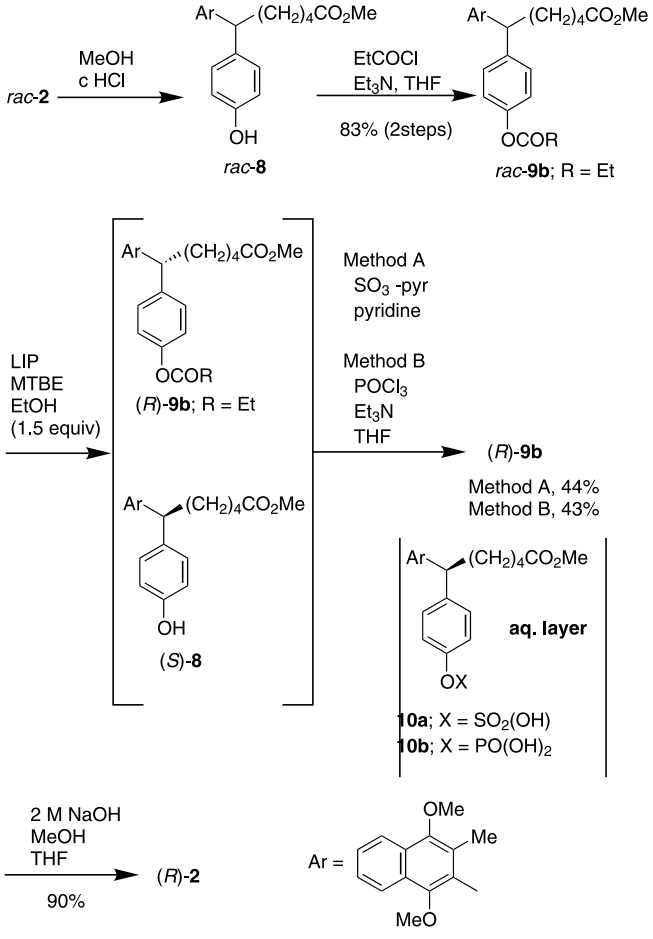


Scheme 1.



Scheme 2.

–20°C while dichloromethyl methyl ether was added. Addition of the dichloromethyl methyl ether at an inappropriate temperature caused an increase in substances that inhibited the crystallization of **6**. Other formylation methods, for example, the Vilsmeier reaction[4] or the Duff reaction,[5] were not effective. In the synthesis of **7** by the Wittig reaction of **6**, we focused on the *E*/*Z* ratio, because only the *E* isomer would react with the phenol in the next step. The utilization of *t*-BuONa as a base in the presence of LiBr[6] increased the amount of the *E* isomer (Table 1, entry 3). However, it was difficult to stir the reaction mixture which contained LiBr for large-scale preparation, since a large amount of insoluble substance appeared. The utilization of THF as a solvent decreased the amount of *E* isomer (entry 4). As a result, the Wittig reaction of **6** in the presence of *t*-BuONa as a base in toluene gave the *E* isomer preferentially (*E*/*Z* ratio = 89/11) (entry 2). The crystallization of the *E*/*Z* mixture (89/11) from the mixture of AcOEt and *n*-hexane produced **7** (contained 1% *Z* isomer) in 59% yield without chromatographic purification. The coupling reaction of **7** with phenol was carried out using BF_3–Et_2O[7] in toluene to give *rac*-**2** in 69% yield (purity 98.8%).

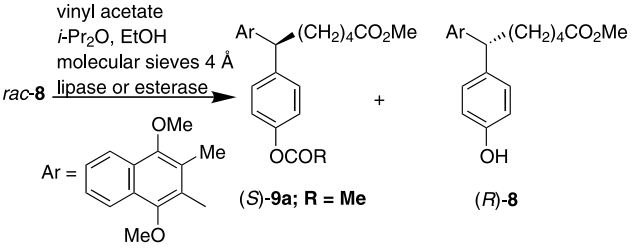
2.2. Resolution

Our attention was focused on developing a facile resolution process (Scheme 2). The resolution of *rac*-**2** using optically active amines was unsuccessful. Hence, we tried the resolution of *rac*-**2** or its derivatives catalyzed by a variety of lipases or esterases.[8] The utilization of phenolic hydroxyl groups, which are remote from chiral centers, has not been well documented.[9] As a result, we found that the resolution of *rac*-**8** by esterification using lipase LIP™ (Toyobo Co., Ltd) or esterase CHE AMANO II™ (Amano Pharmaceutical Co., Ltd) was effective (Scheme 3). However, in spite of all our

Table 1. Wittg reaction of **6**

Entry	Solvent	Base	Additive	*E*/*Z* ratio[a]
1	Toluene	*t*-BuOK	–	85/15
2	Toluene	*t*-BuONa	–	89/11
3	Toluene	*t*-BuONa	LiBr	91/9
4	THF	*t*-BuONa	–	83/17

[a] Ratio by HPLC at 243 nm.



lipase LIP: conversion 34%, (*R*)-**8** (49%ee)
esterase CHE AMANO II: conversion 36%, (*R*)-**8** (50%ee)

Scheme 3.

efforts, the conversions did not exceed 40%, and we speculated that the reactions were reversible. Therefore, we optimized the resolutions by lipase-catalyzed transformation of *rac*-**9** (Table 2). We chose lipase LIP™ for further investigation, since it was comparatively inexpensive. It was found that *rac*-**9b** was suitable as a substrate for the resolution (entries 1, 2, 5, 6, 7). Ester *rac*-**9b** was prepared by methyl esterification of *rac*-**2** with MeOH in the presence of concentrated HCl, followed by propionylation in good yield (purity 99.3%) using propionyl chloride. In the resolution, the utilization of methyl *t*-butyl ether (MTBE) in comparison with *i*-Pr_2O or toluene as a solvent accelerated the reaction and reduced the amount of LIP™ required (entries 3 versus 2, 4). Subsequently, isolation of (*R*)-**9b** from the reaction mixture was needed. In general, the separation of esters and alcohols is achieved by laborious column chromatography, which is extremely difficult and inefficient to carry out on a large scale. We have reported a convenient method to separate esters and alcohols by sulfation of alcohols using the sulfur trioxide pyridine complex (SO_3-pyr).[11] Alcohols are converted into water-soluble compounds, and the isolation of esters is carried out simply by extraction, instead of column chromatography. Hence, we tried the isolation of (*R*)-**9b** using SO_3-pyr (Table 3, entries 1–3). The mixture, which was obtained by the resolution, was treated with SO_3-pyr under the reported conditions to give a mixture consisting of (*R*)-**9b** and phenyl sulfate **10a** (entry 1). After dilution with *i*-Pr_2O, the mixture was washed with water to remove **10a** in the aqueous layer, and (*R*)-**9b** was obtained in the organic layer. High enantiomeric excess, accomplished by the lipase-catalyzed resolution, were not affected by sulfation. However, the sulfation of (*S*)-**8** did not completely proceed and the (*S*)-**8** content in (*R*)-**9b** was 2.0%. After an examination of sulfation under a variety of conditions to minimize the (*S*)-**8** content, we found that the utilization of pyridine alone as the solvent accelerated the reaction, reduced the amount of expensive SO_3-pyr and minimized the (*S*)-**8** content (1.6%) (entry 3). We next tried to isolate (*R*)-**9b** by phosphorylation of (*S*)-**8** using inexpensive phosphoryl chloride (Table 3, entries 4–8). The same mixture was treated with phosphoryl chloride in pyridine to give a mixture consisting of (*R*)-**9b** and phenyl phosphorylate **10b** (entries 4, 5). Extraction with *i*-Pr_2O followed by washing with water removed **10b** from the mixture in a similar way. In the case of phosphorylation by phosphorylchloride, the isolated (*R*)-**9b** did not contain (*S*)-**8** at all, but the phosphorylation caused a slight decrease in the enantiomeric excess: Utilization of triethylamine as the base minimized this (entry 7). The mechanism for the decrease in the enantiomeric excess is currently under investigation. As a result, highly enantiomerically pure (*R*)-**9b** was prepared by the resolution of *rac*-**9b** with lipase, followed by sulfation or phosphorylation in 44 or 43% yield without column chromatography.

2.3. Synthesis of (*R*)-2 in high enantiomeric excess

Hydrolysis of (*R*)-**9b** was carried out with 2 M NaOH in a mixture of MeOH and THF to give (*R*)-**2** (96-97% ee in the reaction mixture) quantitatively. Racemic **2** was less soluble in toluene than (*R*)-**2**, especially above

Table 2. Resolution of *rac*-**9**[a]

Entry	R	LIP/*rac*-**9**	Solvent	Time (h)	Conversion[b] (%)	Ee of (*R*)-**9**[b] (% ee)	*E*[c]
1	Me (**9a**)	0.2	*i*-Pr_2O	24	44	69	33
2	Et (**9b**)	0.3	*i*-Pr_2O	25	52	96	54
3	Et (**9b**)	0.1	MTBE	22	56	99	44
4	Et (**9b**)	0.2	Toluene	2	Trace	–	–
5	Pr (**9c**)	0.2	*i*-Pr_2O	24	53	90	26
6	*t*-Bu (**9d**)	3.0	*i*-Pr_2O	24	Trace	–	–
7	Ph (**9e**)	3.0	*i*-Pr_2O	24	Trace	–	–

[a] The reaction mixtures were stirred at 20–35°C.
[b] Conversion and enantiomeric excess were determined by HPLC.
[c] *E* value was calculated according to the method reported by Chen et al.[10]

Table 3. Sulfation or phosphorylation of the mixture of (*S*)-**8** and (*R*)-**9b**[a]

Entry	Solvent and base (equiv.)	Reagent (equiv.)	Condition	Yield (%) of (*R*)-**9b**[b]	(*S*)-**8** content (%)
1	Pyridine/DMF = 4/1	SO_3-pyr (5)	rt, 5 h	46 (99% ee)	2.0
2	pyridine/DMF = 4/1	SO_3-pyr (2.5)	rt, 24 h	46 (99% ee)	8.6
3	Pyridine	SO_3-pyr (3)	rt, 5 h	44 (99% ee)	1.6
4	Pyridine	$POCl_3$ (5)	rt, 1 h	45 (96% ee)	ND[c]
5	Pyridine	$POCl_3$ (2)	0°C, 1 h	44 (95% ee)	ND[c]
6	THF/pyridine (12)	$POCl_3$ (2)	0°C, 2 h	43 (93% ee)	ND[c]
7	THF/Et_3N (12)	$POCl_3$ (2)	rt, 1 h	43 (97% ee)	ND[c]
8	THF/*i*-Pr_2NEt (12)	$POCl_3$ (4)	rt, 1 h	42 (93% ee)	ND[c]

[a] Enantiomeric purity of initial (*R*)-**9b** was 99% ee.
[b] Yields were based on *rac*-**9b**.
[c] ND = Not detected.

70°C. Therefore, elimination of insoluble substances in toluene at 70°C increased the enantiomeric excess to give (*R*)-**2** in 90% yield (purity 99.4%, 98% ee).

3. Conclusions

We have achieved the practical preparation of (*R*)-**2** for large-scale production without chromatographic purification. This efficient process was based on the resolution of *rac*-**9b**, synthesized from **3** in seven steps, with a lipase followed by sulfation or phosphorylation. Hydrolysis of (*R*)-**9b** followed by elimination of insoluble substances (*rac*-**2**) in toluene gave enantiomerically pure (*R*)-**2**.

4. Experimental

Melting points were recorded on a Büchi B-540 micro melting apparatus and are uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. NMR spectra were run at 300 MHz (^{1}H) and 75.4 MHz (^{13}C), respectively, on a Bruker DPX-300 spectrometer. Chemical shifts are reported as δ values using tetramethylsilane as a reference. Optical rotation values were recorded on a JASCO DIP-370 polarimeter under standard conditions. HPLC was performed on a YMC-Pack ODS-A302 column (4.6 i.d.×150 mm) with 0.05M KH_2PO_4 aqueous solution/MeCN (55/45, and 3/7), a Daicel CHIRALCEL OD column (4.6 i.d.×250 mm) with hexane/EtOH (95/5) or a Daicel CHIRALCEL OJ-R column (4.6 i.d.×250 mm) with 0.5 M $NaClO_4$ aqueous solution/0.5 M $HClO_4$ solution/MeCN (100/1/101) at 25°C. Detection was performed with a Shimadzu SPD-10A spectrophotometric detector at 243, 239, 254 or 280 nm. Purity was determined by HPLC and was presented as an area percentage of the compound peak relative to the total area of all the peaks integrated. The microanalyses and mass spectral analyses were carried out by Takeda Analytical Research Laboratories, Ltd.

4.1. 2-Methylnaphthalene-1,4-diol, 4

To a suspension of 2-methylnaphthoquinone **3** (50 g, 290 mmol) in AcOEt (400 mL) was added a solution of $Na_2S_2O_4$ (100 g, 574 mmol) in water (400 mL) at rt. The resulting mixture was stirred for 0.5 h at the same temperature. The organic layer was separated, washed with water (2×200 mL), and concentrated under reduced pressure. The residue was triturated with *n*-hexane (300 mL). The resulting crystals were collected by filtration, washed with *n*-hexane (100 mL), and dried under reduced pressure to give **4** (48.91 g, 97%) as a pale purple crystalline powder. Mp 117.0–178.9°C; ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H), 6.63 (s, 1H), 7.30–7.43 (m, 2H), 7.99–8.09 (m, 2H), 8.22 (s, 1H), 9.32 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 16.5, 111.0, 118.6, 121.6, 121.8, 123.4, 123.7, 124.7, 126.4, 141.6, 145.7; IR (KBr): 3255, 1602, 1205 cm^{-1}; EIMS: m/z 174 (M^+). Anal. calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.55; H, 5.75%.

4.2. 1,4-Dimethoxy-2-methylnaphthalene, 5

To a solution of **4** (45 g, 258 mmol) and Me_2SO_4 (130 g, 1.03 mol) in 2-propanol (460 mL) NaOMe (28% MeOH solution, 199 g, 1.03 mol) was added dropwise at rt. The resulting mixture was stirred for 0.5 h at 63°C and cooled to 20°C. Water (1.5 L) was added and the mixture was extracted using isopropyl ether (2×1.5 L). The organic layers were combined and washed successively with water (4×500 mL), and concentrated under reduced pressure to give **5** (51.4 g, 98%, purity 99.2%) as a brown solid, which was used directly in further reactions without purification. An analytically pure sample of **5** was obtained by chromatography on alumina with *n*-hexane as a white solid. Mp 35.9–36.3°C; ^{1}H NMR ($CDCl_3$); δ 2.44 (s, 3H), 3.85(s, 3H), 3.95 (s, 3H), 6.59 (s, 1H), 7.40–7.51 (m, 2H), 8.01 (d, 1H, J=8.1 Hz), 8.19 (d, 1H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$): δ 16.3, 55.6, 61.2, 106.8, 121.5, 122.2, 124.6, 125.3, 125.6, 126.4, 128.7, 147.0, 151.6; IR (neat): 3066, 2991, 2900, 1506 cm^{-1}; EIMS: m/z 202 (M^+). Anal. calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.23; H, 7.08%.

4.3. 1,4-Dimethoxy-3-methyl-2-naphthaldehyde, 6

To a solution of **5** (93.5 g, 462 mmol) in dichloromethane (450 mL) was added dropwise $TiCl_4$ (50.7 mL, 462 mmol) at −40°C, followed by Cl_2CHOMe (41.9 mL, 462 mmol) at −20°C. The whole mixture was stirred for 2 h at 0°C and added to water (2 L). The mixture was extracted with AcOEt (3×1 L). The organic layers were combined and washed successively with water (4×400 mL), and concentrated under reduced pressure To the residue dissolved with 2-propanol (500 mL) was added water (700 mL) at 50°C, and then the mixture was stirred for 1 h at rt. The resulting crystals were collected by filtration, washed with water (300 mL) and dried under reduced pressure at 40°C to give **6** (82.2 g, 77%, purity 97.2%) as a white crystalline powder. Mp 93.5–93.7°C; ^{1}H NMR ($CDCl_3$); δ 2.64 (s, 3H), 3.87(s, 3H), 4.07 (s, 3H), 7.25–7.63 (m, 2H), 8.10 (d, 1H, J=8.3 Hz), 8.19 (d, 1H, J=8.3 Hz), 10.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.0, 61.4, 65.4, 122.6, 123.1, 125.1, 126.1, 126.3, 127.1, 129.4, 132.0, 150.7, 160.2, 192.3; IR (KBr): 1685 cm^{-1}; EIMS: m/z 230 (M^+). Anal. calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.97; H, 6.13%.

4.4. (5*E*)-6-(1,4-Dimethoxy-3-methyl-2-naphthyl)hex-5-enoic acid, 7

To a solution of **6** (23 g, 100 mmol) and 4-carboxybutyltriphenylphosphonium bromide (53 g, 120 mmol) in toluene (800 mL) was added *t*-BuONa (23 g, 240 mmol) at 60°C. The resulting mixture was stirred for 3 h at 60°C and cooled to 20°C. Water (500 mL) and *t*-BuOH (50 mL) was added. The aqueous layer was separated and washed with toluene/*t*-BuOH (100/7, 2×200 mL). The aqueous layer was treated with 6 M HCl until the pH was adjusted to 3 and extracted with isopropyl ether/AcOEt (4/6, 2×1 L). The organic layers were combined and washed successively with water (200

mL), 2% aqueous $NaHCO_3$ solution (300 mL), water (200 mL), 0.2 N HCl (200 mL) and water (2×200 mL), and concentrated under reduced pressure. The residue was triturated with *n*-hexane (40 mL) and AcOEt (2 mL). The resulting crystals were collected by filtration and washed with *n*-hexane (3×20 mL), and dried under reduced pressure to give **7** (18.4 g, 59%, $E/Z=99/1$) as a white crystalline powder. Mp 85.2–86.0°C; ^{1}H NMR ($CDCl_3$); δ 1.84–1.95 (m, 2H), 2.35–2.41 (m, 3H), 2.49 (t, 2H, $J=7.5$ Hz), 3.80(s, 3H), 3.86 (s, 3H), 6.18–6.26 (m, 1H), 6.53 (d, 1H, $J=16.1$ Hz), 7.43–7.49 (m, 2H), 8.02–8.10 (m, 2H), 10.80 (br, 1H); ^{13}C NMR ($CDCl_3$): δ 13.7, 24.4, 33.2, 33.4, 60.7, 61.3, 122.0, 122.5, 124.9, 125.5, 125.9, 126.0, 127.5, 127.7, 127.9, 135.7, 149.9, 150.0, 179.6; IR (KBr): 3510, 1708, 1351 cm^{-1}; EIMS: m/z 314 (M^+). Anal. calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.47; H, 7.18%.

4.5. *rac*-6-(1,4-Dimethoxy-3-methyl-2-naphthyl)-6-(4-hydroxyphenyl)hexanoic acid, *rac*-2

To a solution of **7** (34.6 g, 110 mmol) and phenol (28.2 g, 300 mmol) in toluene (300 mL) was added dropwise BF_3–Et_2O (25.2 mL, 200 mmol) at 0°C. The resulting mixture was stirred for 3 h at 40°C and cooled to 20°C. Cold water (1 L) and AcOEt (1 L) were added and the organic layer was separated. The organic layer was extracted with a 10% aqueous Na_2CO_3 solution (4×300 mL). The aqueous layers were combined and washed with isopropylether/AcOEt (1/1, 100 mL). The aqueous layer was treated with 6N HCl until the pH was adjusted to 3 and extracted using AcOEt (2×400 mL). The organic layers were combined and washed successively with water (2×200 mL), and concentrated under reduced pressure. The residue was triturated with toluene (80 mL). The resulting crystals were collected by filtration, washed with toluene (2×20 mL), and dried under reduced pressure to give crude *rac*-**2** (36.4 g) as a white crystalline powder. To a solution of the crude *rac*-**2** (36.4 g) in AcOEt (80 mL) was added toluene (160 mL) at 60°C. The resulting mixture was stirred for 6 h at rt. The resulting crystals were collected by filtration, washed with toluene (2×20 mL), and dried under reduced pressure to give *rac*-**2** (30.8 g, 69%, purity 98.8%) as a white crystalline powder. Mp 121.5–123.5°C; ^{1}H NMR (DMSO-d_6); δ 1.10–1.26 (m, 1H), 1.28–1.48 (m, 1H), 1.49–1.72 (m, 2H), 2.02–2.40 (m, 7H), 3.64 (br, 3H), 3.76 (s, 3H), 4.68 (br, 1H), 6.69 (d, 2H, $J=8.5$ Hz), 7.04 (d, 2H, $J=8.5$ Hz), 7.49–7.52 (m, 2H), 7.97–8.01 (m, 2H), 9.18 (br, 1H), 11.9 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 13.9, 25.7, 28.5, 32.3, 34.4, 41.6, 61.7, 62.7, 115.8, 122.8, 123.4, 126.1, 126.4, 126.1, 127.4, 127.5, 128.0, 128.9, 134.7, 134.9, 150.9, 156.0, 175.3; IR (KBr): 3350, 1698, 1513 cm^{-1}; EIMS: m/z 408 (M^+). Anal. calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.70; H, 6.92%.

4.6. *rac*-Methyl 6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-hydroxyphenyl) hexanoate, *rac*-8

To a solution of *rac*-**2** (121.5 g, 297 mmol) in MeOH (1050 mL) was added concentrated HCl (22.5 mL) at 0°C. The resulting mixture was stirred for 3 h at rt and concentrated under reduced pressure To the residue was added water (200 mL) and the mixture extracted with AcOEt (2×450 mL). The organic layers were combined and washed successively with water (3×300 mL), and concentrated under reduced pressure to give *rac*-**8** (172 g, purity 99.3%) as a colorless liquid, which was used in further reactions without purification. An analytically pure sample of *rac*-**8** was obtained by crystallization from isopropylether as a white crystalline powder. Mp 100.3–100.8°C; ^{1}H NMR ($CDCl_3$); δ 1.10–1.20 (m, 1H), 1.35–1.45 (m, 1H), 1.62–1.75 (m, 2H), 2.10–2.38 (m, 7H), 3.59 (br, 6H), 3.84 (s, 3H), 4.72(br, 1H), 5.65(s, 1H), 6.69 (d, 2H, $J=8.4$ Hz), 7.07 (d, 2H, $J=8.4$ Hz), 7.42–7.49 (m, 2H), 7.96–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 13.5, 25.3, 27.9, 31.9, 33.9, 412, 51.5, 61.3, 62.0, 115.0, 122.2, 122.7, 125.4, 125.7, 127.0, 127.2, 127.8, 128.4, 133.7, 136.3, 150.5, 150.8, 153.7, 174.5; IR (KBr): 3353, 1731, 1513 cm^{-1}; EIMS: m/z 422 (M^+). Anal. calcd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16. Found: C, 73.95; H, 7.23%.

4.7. *rac*-Methyl 6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-(propionyloxy)phenyl) hexanoate, *rac*-9b

To a solution of *rac*-**8** (172 g) and triethylamine (61.4 mL, 441 mmol) in THF (750 mL) was added propionyl chloride (38.4 mL, 441 mmol) at 0°C. The resulting mixture was stirred for 1.5 h at 0°C. After addition of water (300 mL), the whole mixture was concentrated under reduced pressure To the residue was added water (300 mL) and the mixture extracted with AcOEt (2×450 mL). The organic layers were combined and washed successively with water (3×300 mL), 0.1N HCl (2×200 mL), water (200 mL), saturated aqueous $NaHCO_3$ solution (100 mL) and water (100 mL), and then concentrated under reduced pressure. To the residue in isopropylether (1 L) was added activated charcoal (15 g) with the resulting mixture was stirred for 0.5 h at rt. The charcoal was filtered off and washed with isopropylether (200 mL). The filtrate and washings were combined and concentrated under reduced pressure. The residue was triturated with isopropylether (200 mL) and to the resulting suspension was added *n*-hexane (750 mL). The mixture was stirred for 2 h at rt. The resulting crystals were collected by filtration, washed with *n*-hexane (10 mL), and dried under reduced pressure to give *rac*-**9b** (117.8 g, 83% from *rac*-**2**, purity 99.3%) as a white crystalline powder. Mp 71.0–71.5°C; ^{1}H NMR ($CDCl_3$); δ 1.10–1.30 (m, 4H), 1.35–1.50 (m, 1H), 1.55–1.80 (m, 2H), 2.00–2.50 (m, 7H), 2.54 (q, 2H, $J=7.5$ Hz), 3.59 (br, 6H), 3.84 (s, 3H), 4.80 (br, 1H), 6.97 (d, 2H, $J=8.5$ Hz), 7.25 (d, 2H, $J=8.5$ Hz), 7.40–7.55 (m, 2H), 7.90–8.10 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 9.1, 13.6, 25.2, 27.7, 27.9, 31.9, 33.9, 41.5, 51.4, 61.3, 62.0, 121.1, 122.3, 122.7, 125.4, 125.8, 126.8, 127.3, 128.0, 128.3, 133.3, 142.0, 148.6, 150.7, 150.8, 173.0, 174.0; IR (KBr); 1760, 1737, 1506 cm^{-1}; EIMS: m/z 478 (M^+). Anal. calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.83; H, 7.15%.

4.8. (*R*)-(+)-Methyl 6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-(propionyloxy)phenyl) hexanoate, (*R*)-9b (using SO_3-pyr)

To a solution of *rac*-**9b** (110 g, 230 mmol) and EtOH (19.8 mL) in MTBE (1100 mL) was added lipase (LIP™,

Toyobo Co. Ltd.) (11 g) at 25°C. The resulting mixture was stirred for 20 h at 20–35°C. The lipase was filtered off and washed with MTBE (110 mL). The filtrate and washings were combined and concentrated under reduced pressure HPLC analysis of the residue proved that the content of (*R*)-**9b** was 50.2 g (99% ee) and the content of (*S*)-**8** was 59.8g (73% ee). To a solution of the residue in pyridine (330 mL) was added SO_3-pyr (67.6 g, 426 mmol) at rt. The resulting mixture was stirred for 8 h at rt and cooled to 0°C. After addition of water (660 mL), the whole mixture was extracted with isopropylether (2×300 mL). The organic layers were combined and washed successively with a 5% aqueous NaCl solution (3×500 mL), 0.5 M HCl (3×500 mL) and water (3×500 mL), and concentrated under reduced pressure to give (*R*)-**9b** (48.5 g, 44%, purity 96.9%) as a colorless liquid (ee = 99%, CHIRALCEL OD, *n*-hexane/EtOH = 95/5, flow rate: 0.6 ml/min, detection: UV (280 nm), temperature: 25°C). The alcohol (*S*)-**8** content in (*R*)-**9b** was 1.6%. $[\alpha]_D^{20} = +81.1$ (*c* 0.227, AcOEt); ^{1}H NMR ($CDCl_3$); δ 1.10–1.30 (m, 4H), 1.35–1.50 (m, 1H), 1.55–1.80 (m, 2H), 2.00–2.50 (m, 7H), 2.54 (q, 2H, $J = 7.5$ Hz), 3.59(br, 6H), 3.84 (s, 3H), 4.80 (br, 1H), 6.97 (d, 2H, $J = 8.5$ Hz), 7.25 (d, 2H, $J = 8.5$ Hz), 7.40–7.55 (m, 2H), 7.90–8.10 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 9.1, 13.6, 25.2, 27.7, 27.9, 31.9, 33.9, 41.5, 51.4, 61.3, 62.0, 121.1, 122.3, 122.7, 125.4, 125.8, 126.8, 127.3, 128.0, 128.3, 133.3, 142.0, 148.6, 150.7, 150.8, 173.0, 174.0; IR (neat); 1760, 1735, 1506 cm^{-1}; EIMS: *m*/*z* 478 (M^+); HRMS (EI): *m*/*z* 478 (M^+) $C_{29}H_{34}O_6$: calcd 478.2355, found 478.2353.

4.9. (*R*)-(+)-6-(1,4-Dimethoxy-3-methyl-2-naphthyl)-6-(4-hydroxyphenyl)hexanoic acid, (*R*)-2

To a solution of (*R*)-**9b** (48.5 g, 101 mmol) in MeOH (243 mL) and THF (243 mL) was added 2M NaOH (253 mL, 506 mmol) at 0°C. The resulting mixture was stirred for 2 h at rt and treated with 2 M HCl until the pH was adjusted to 7 and then concentrated under reduced pressure. The residue was treated with 2 M HCl until the pH was adjusted to 2 and extracted with AcOEt (2×250 mL). The organic layers were combined and washed successively with water (3×250 mL), a 2.5% aqueous $NaHCO_3$ solution (390 mL), 1 M HCl (1×250 mL) and water (3×250 mL), and then concentrated under reduced pressure. The residue (96.8% ee) was triturated with toluene (830 mL) and the resulting suspension warmed to 70°C. The resulting crystals were filtered off and washed with toluene (40 mL). The filtrate and washings were combined and gradually cooled to 0°C. The resulting crystals were collected by filtration and washed with toluene (100 mL), and dried under reduced pressure to give (*R*)-**2** (37.3 g, 90%, purity 99.4%) as a white crystalline powder (ee = 98%, CHIRALCEL OJ-R, 0.5 M $NaClO_4$ aqueous solution/0.5 M $HClO_4$ solution/MeCN = 100/1/101, flow rate: 0.6 ml/min, detection: UV (254 nm), temperature: 25°C). Mp 65–67°C (lit.[1a] 65–67°C); $[\alpha]_D^{20} = +135.3$ (*c* 0.238, MeOH); ^{1}H NMR (DMSO-d_6); δ 1.10–1.26 (m, 1H), 1.28–1.48 (m, 1H), 1.49–1.72 (m, 2H), 2.02–2.40 (m, 7H), 3.64 (br, 3H), 3.76 (s, 3H), 4.68 (br, 1H), 6.69 (d, 2H, $J = 8.5$ Hz), 7.04 (d, 2H, $J = 8.5$ Hz), 7.49–7.52 (m, 2H), 7.97–8.01 (m, 2H), 9.18 (br, 1H), 11.9 (br, 1H); ^{13}C NMR (DMSO-d_6): δ13.9, 25.7, 28.5, 32.3, 34.4, 41.6, 61.7, 62.7, 115.8, 122.8, 123.4, 126.1, 126.4, 126.1, 127.4, 127.5, 128.0, 128.9, 134.7, 134.9, 150.9, 156.0, 175.3; IR (KBr): 3392, 1720, 1511 cm^{-1}; EIMS: *m*/*z* 408 (M^+). Anal. calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.66; H, 6.79%.

4.10. (*R*)-(+)-Methyl 6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-(propionyloxy)phenyl) hexanoate, (*R*)-9b (using $POCl_3$)

To a solution of *rac*-**9b** (550 mg, 1.15 mmol) and EtOH (0.2 mL) in MTBE (11 mL) was added lipase (LIP™, Toyobo Co. Ltd.) (110 mg) at 25°C. The resulting mixture was stirred for 20 h at 20–35°C. The lipase was filtered off and washed with MTBE (1.1 mL). The filtrate and washings were combined and concentrated under reduced pressure. HPLC analysis of the residue proved that the (*R*)-**9b** content was 235 mg (99% ee) and the (*S*)-**8** content was 278 mg (74% ee). To a solution of the residue and Et_3N (1.1 mL, 7.89 mmol) in THF (2 mL) was added $POCl_3$ (0.12 mL, 1.32 mmol) at 0°C. The resulting mixture was stirred for 1 h at rt and cooled to 0°C. After addition of water (10 mL), the whole mixture was extracted with isopropylether (10 mL). The organic layer was washed successively with water (2×10 mL), 1 M HCl (10 mL) and water (2×10 mL), and concentrated under reduced pressure to give (*R*)-**9b** (238 mg, 43%, purity 98.2%) as a colorless liquid (ee = 97%, Chiralcel OD, *n*-hexane/EtOH = 95/5, flow rate: 0.6 ml/min, detection: UV (280 nm), temperature: 25°C). Alcohol (*S*)-**8** was not detected. Spectroscopic data is identical with (*R*)-**9b** which was isolated by using SO_3-pyr.

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