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Chemo-enzymatic synthesis of enantiomerically pure (*R*)-2-naphthylmethoxyacetic acid

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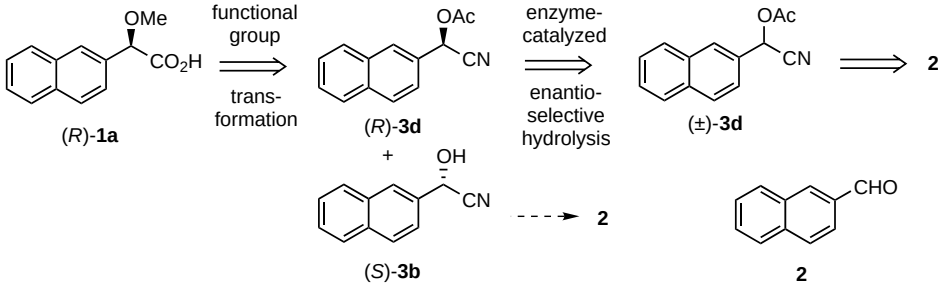
Abstract—Enantiomerically pure (*R*)-2-naphthylmethoxyacetic acid (2-NMA) was synthesized from 2-naphthaldehyde via an integrated chemo-enzymatic procedure. The one-pot, successive use of $SnBr_2$–TMSCN and AcBr worked effectively to give a racemic cyanohydrin acetate. Lipase from *Burkholderia cepacia* then mediated the highly enantioselective hydrolysis of the (*S*)-enantiomer of the racemate, leaving the (*R*)-acetate with an e.e. of >99.9%. The resulting product of this enzyme-catalyzed hydrolysis, an (*S*)-cyanohydrin, spontaneously decomposed into naphthaldehyde, the starting material of this synthetic route, which could be recycled. The hydration of nitrile to amide as well as the hydrolysis of the acetate was performed with a microorganism, *Rhodococcus rhodochrous*, under very mild conditions without any loss of the enantiomeric purity. The amide group was hydrolyzed with nitrosylsulfuric acid, and the product was isolated as an α-hydroxy ester. The α-hydroxyl group was methylated with diazomethane–silica gel and the final task, hydrolysis of the ester, was accomplished under conditions as mild as neutral pH with an esterase from *Krebsiella oxytoca* to give enantiomerically pure 2-NMA.

1. Introduction

An enantiomerically enriched form of 2-naphthylmethoxyacetic acid (2-NMA, **1a**)[1] has been developed as an excellent chiral NMR reagent[2] for the determination of the absolute configuration of secondary alcohols. Currently, to supply pure enantiomers of **1a**, the racemate[3] is separated by chromatography.[4] A recently reported asymmetric carboxylation of the benzylic anion[5] derived from an alkyl benzyl ether is also a promising method. Herein we report our chemo-enzymatic approach to (*R*)-**1a**.

2. Results and discussion

The synthetic plan is shown in Scheme 1. Starting from 2-naphthaldehyde **2**, the key intermediate is the enantiomerically pure (*R*)-cyanohydrin acetate **3d**, for which a variety of chemical and enzymatic approaches have



Scheme 1.

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recently been developed.[6–8] For the preparation of the single enantiomeric form, we chose the lipase-catalyzed enantioselective hydrolysis of the racemate (±)-**3d**.[8e–p] In this process, the concomitantly formed cyanohydrin (*S*)-**3b** would decompose into the starting aldehyde **2**[8m–p] and the undesired enantiomer is converted into the desired one by repetition of the total process. Another very important aspect of this synthesis is the functional group transformation under mild conditions, from nitrile to carboxylate, without any loss in enantiomeric purity.

2.1. Synthesis and resolution of cyanohydrin derivatives

Toward this end, an expeditious synthetic route to (±)-**3d** from **2** is of considerable importance. Our first synthetic efforts toward **3d** from **2** under a biphasic system using NaCN–TBAB[8j] resulted in the formation of **3b** only, even in the presence of acetic anhydride. Based on the well-known procedure through Lewis acid-catalyzed formation of cyanohydrin trimethylsilyl intermediates,[9] we turned our attention to $SnBr_2$, which had been effective for the transformation of trimethylsilyl ether to acetate reported by Oriyama.[10] Indeed, the two-step formation of **3d** from **2** proceeded very smoothly in one pot (92%). This protocol has the advantage of extreme simplicity, compared with the preparation from an aldehyde via acylal[11a] (diacetylated form) or the use of acetyl cyanide.[11b] This one-pot synthesis of cyanohydrin acetates from an aldehyde has so far been reported only from an aromatic aldehyde with very strongly electron-withdrawing substituents.[12]

In addition, $SnBr_2$ also worked very well for the preparation of cyanohydrin methyl ether[13] **3c**. The isolation of an unstable dimethyl acetal was not necessary, and the desired product was obtained in 90% yield (Scheme 2).

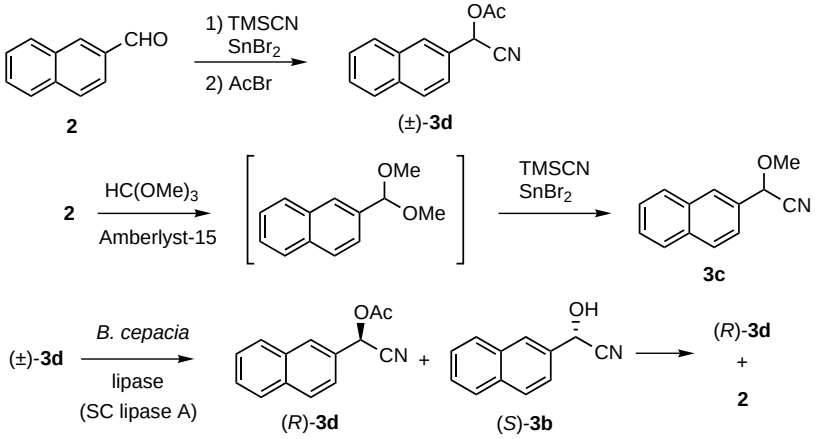
For the kinetic enantiomeric resolution of (±)-**3d**, our first choice was the use of lipoprotein lipase (Toyobo LIP),[14] which had been effective in the enantioselective acylation of the corresponding cyanohydrin.[8c] The revealed moderate enantioselectivity[15] ($E=32$), however, led us to consider another source of lipase. Thus, *Burkholderia cepacia* lipase[6c,6e,8g] (Sumitomo Chemical Industries, SC lipase A) was examined. Extensive investigations of the substrate–enzyme ratio and the effects of immobilization of enzyme and adding a co-solvent provided an elaborated set of incubation conditions (see Section 4), and very high enantioselectivity ($E>500$) in the reaction. The recovered (*R*)-**3d** (45% yield) had an e.e. of >99.9% (Scheme 2). As expected, the hydrolyzed product was obtained as 2-naphthaldehyde due to spontaneous decomposition.

2.2. Hydration of the cyano group

As a mild method of functional group transformation, microorganism-mediated hydration of the nitrile and subsequent hydrolysis of the amide[16] was applied to (*R*)-**3d**. Hydration of the cyano group proceeded very smoothly with *Rhodococcus rhodochrous* IFO 15564 under the two-phase system.[17] Concomitant hydrolysis of acetate[18] occurred, and the product was a hydroxy amide (*R*)-**4b** (75%). No further hydrolysis of the amide to carboxylic acid was observed.

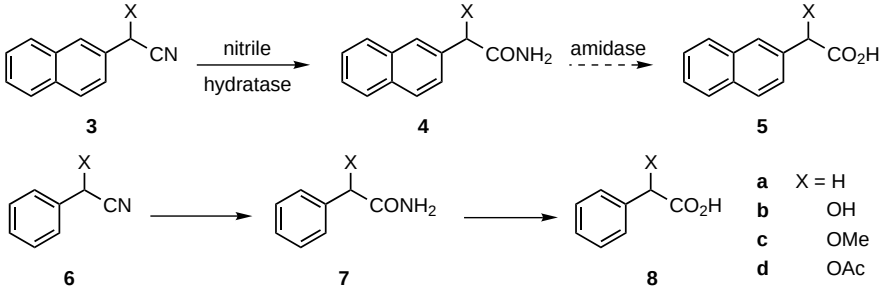
At this stage, we became interested in the structure–activity relationship of nitrile hydratase and amidase on the substrates possessing the related skeleton.[19,20] The effects of both the aromatic nuclei (phenyl or 2-naphthyl) and α-substituent (H, OH, OMe, and OAc) were observed from a set of substrates. The results are summarized in Table 1. In the series of nitriles with a phenyl group, the action of amidase depended upon the steric hindrance by the substituents introduced at the α-position. The increase in size on moving from the phenyl to the 2-naphthyl nucleus severely suppressed the action of the amidase.

Similar retardation was also observed in the action of nitrile hydratase. This is exemplified between the two cyanohydrins **3b** and **6b**. The hydration of naphthyl derivative **3b** was much slower than that of mandelonitrile **6b**, and a considerable portion of this rather unstable substrate **3b** decomposed to aldehyde **2** during the incubation. In this sense, the acetate in **3d** worked as the 'protective group'. From **3d**, the primary product was the acetoxy amide **4d**, and the subsequent hydrolysis by an esterase provided **4b** as mentioned before.



Scheme 2.

Table 1. Hydration and the subsequent hydrolysis of aromatic nitriles with *R. rhodochrous*



Entry	Substrate	Aromatic group	X	Product (%)	
				Amide	Acid
1	**6a**	Phenyl	H	–	**8a** (quant.)
2	**6b**	Phenyl	OH	**7b**[a] (81)	–
3	**6b**	Phenyl	OH	–	**8b**[b] (80)
4	**6c**	Phenyl	OMe	**7c** (quant.)	–
5	**6d**	Phenyl	OAc	**7b** (39), **7d** (35)	–
6	**3a**	2-Naphthyl	H	–	**5a** (87)
7	**3b**	2-Naphthyl	OH	**4b** (8)	–
8	**3c**	2-Naphthyl	OMe	**4c** (88)	–
9	**3d**	2-Naphthyl	OAc	**4b** (75)	–

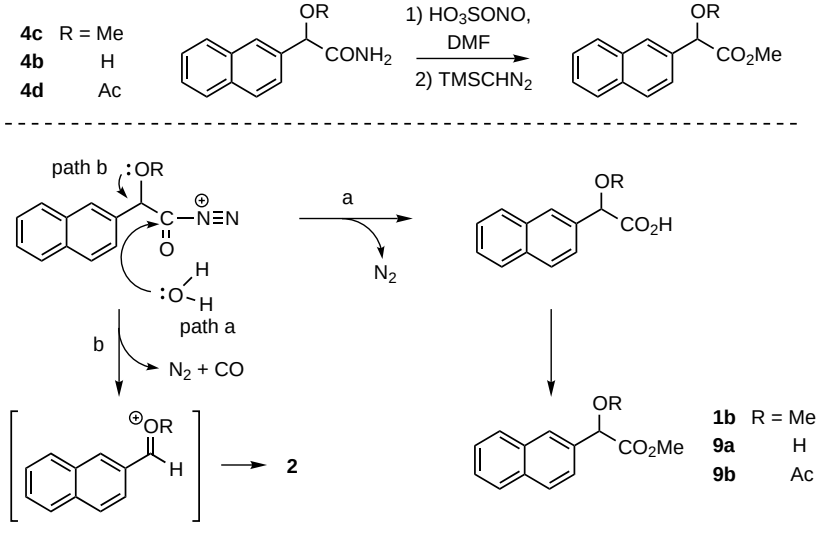
[a] Incubation was performed for 4 h.
[b] Incubation was performed for 18 h.

2.3. Exploring the route from α-hydroxy amide to α-methoxy acid

As mentioned above, the enzyme-catalyzed hydrolysis of the amide failed. At this juncture, toward the synthesis of α-methoxy acid, we prepared the corresponding α-methoxyamide **4c**, and various hydrolytic conditions were examined. This amide, indeed, obstinately resisted hydrolysis, and only activation by means of nitrosation was effective. Use of tetrabutylammonium nitrite[21] and nitrosylsulfuric acid,[22] as the source of NO^+, effected the desired reaction. However, in the use of the former reagent, the reproducibility was low.

An unexpected by-product, 2-naphthaldehyde **2** was formed in the nitrosylsulfuric acid-catalyzed hydrolysis. The formation of an aldehyde is understandable if electron-donation from the methoxy group ejected N_2 and CO (Scheme 3, path b), instead of the desired attack of water (path a) to the possible acyl diazonium intermediate.

This hypothesis prompted us to prepare the substrates **4b** (R = H, Scheme 3) and **4d** (R = Ac) with decreased electron-donating properties, and they were submitted to the same reaction. The acceleration of CO extrusion by means of electron-donating neighboring group was



Scheme 3.

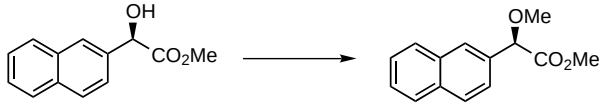
well affirmed by results as shown in Table 2. The by-product formation was considerably suppressed in the latter two substrates. The above study led us to take (*R*)-**4b**, a directly formed product in the previous step of microbial hydration of the cyano group, in this step of amide-hydrolysis.

Table 2. Nitrosation–hydrolysis of α-substituted amides **4a–c**

Entry	Substrate	Product (%)	
		Ester	Aldehyde **2**
1	**4c**	**1b** (55)	35
2	**4b**	**9a** (59)	6
3	**4d**	**9b** (80)	5

We next encountered the difficulty in the step of methylation of the hydroxyl group, since the α-protons of the esters **9a** and **1b** are rather acidic. For example, methylation conditions as mild as MeI–Ag_2O[23] (Table 3, entry 1) caused partial racemization to give **1b** with as low as 57.8% e.e. Thus, acid-catalyzed methylation conditions were extensively examined,[24–26] and the representative entries are also shown in Table 3. It was found that repetitive addition of the diazomethane solution with silica gel worked well (for details, see Section 4) to give **1b** in 86% yield based on the consumed substrate, with no affect on the enantiomeric purity.

Table 3. Methylation of **9a**



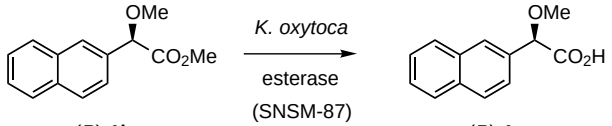
(*R*)-**9a** (*R*)-**1b**

Entry	Reagents	Compound **1b**[a]	
		Yield (%)	E.e. (%)
1	MeI–Ag_2O	18	57.8
2	$CCl_3C(N{=}H)OMe$ –$HBF_4{\cdot}Me_2O$	28	>99.9
3	CH_2N_2–$SnCl_2{\cdot}H_2O$	13	92.8
4	CH_2N_2–silica gel	48 (86)[b]	>99.9

[a] In the case of entry 2, the substrate was methyl (*R*)-mandelate **10a**, and the product was methyl (*R*)-*O*-methylmandelate **10b**.

[b] The yield in parentheses is based on the consumed starting material.

The final problem was the hydrolysis of the methyl ester **1b** under mild conditions. From the screening of enzymes involving lipases, proteases and esterases, *Krebsiella oxytoca* esterase (Nagase, SNSM-87)[27] showed the highest activity (Scheme 4). As this enzyme showed no enantioselectivity, it worked very well as the tool for functional group transformation. Elevated temperature as high as 39°C was necessary to perform an efficient hydrolysis, as the substrate is crystalline at room temperature. In this way, (*R*)-2-NMA, **1a**, with e.e. of over 99.9% was obtained from **1b** in quantitative yield.



(*R*)-**1b** (*R*)-**1a**

Scheme 4.

3. Conclusion

Starting from the readily available 2-naphthaldehyde **2** we have synthesized (*R*)-2-naphthylmethoxyacetic acid (2-NMA, **1a**). Three enzyme-catalyzed procedures were effectively demonstrated, namely, (1) lipase-catalyzed kinetic resolution of cyanohydrin, (2) microbial nitrile hydratase-catalyzed transformation of nitrile to amide, and (3) enzyme-catalyzed hydrolysis of methyl ester under conditions as mild as neutral pH.

4. Experimental

4.1. General

All melting points are uncorrected. IR spectra were measured as thin films for oils or KBr disks of solids on a JASCO FT/IR-410 spectrometer. ^{1}H NMR spectra were measured in chloroform-*d* at 270 MHz on a JEOL JNM EX-270 or at 400 MHz on a JEOL JNM GX-400 spectrometer. HPLC analyses were performed with a SSC-5410 (Senshu Scientific Co., Ltd) liquid chromatographs. Optical rotation values were recorded on a Jasco DIP 360 polarimeter. Silica gel 60 (spherical, 100–210 μm, 37558-79) of Kanto Chemical Co. was used for column chromatography. Peptone and yeast extract were purchased from Kyokuto Pharmaceutical Co, for the cultivation of microorganism. Preparative TLCs were purchased from Merck Co. (1.05744). Acetonitriles **3a**, **6a**, 2-naphthaldehyde **2**, (*R*)-(−)- and (±)-mandelic acid **8b** and 2-naphthylacetic acid **5a** were purchased from Tokyo Kasei Organic Chemicals Co. (P0128, N0366, N003, M0662, M0038, and N0352, respectively) and racemic mandelonitrile **6b** was from Aldrich Co. (11,602-5).

4.2. Syntheses of the substrates

4.2.1. α-Acetoxyphenylacetonitrile 6d. To a solution of benzaldehyde (105 mg, 0.98 mmol) in CH_2Cl_2 (4 mL) was added trimethylsilyl cyanide (TMSCN, 146 mg, 1.47 mmol) and $SnBr_2$ (15 mg, 0.05 mmol). After stirring at room temperature for 10 min under an Ar atmosphere, a solution of acetyl bromide (302 mg, 2.46 mmol) in CH_2Cl_2 (1 mL) was added to a reaction mixture and stirred overnight at the same temperature. Ice-cooled phosphate buffer solution (pH 7.5, 0.1 M) was added and stirred for a further 30 min at 0°C. The

mixture was diluted with AcOEt and the resulting organic layer was poured into ice-cooled aq. $NaHCO_3$ solution. The mixture was extracted with AcOEt (×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (30 g). Elution with hexane–AcOEt (6/1) afforded **6d** as a colorless oil (148 mg, 85%). R_f=0.40 (hexane/AcOEt=9/1); ^{1}H NMR: δ 7.53–7.43 (m, 5H), 6.40 (s, 1H), 2.15 (s, 3H); ^{13}C NMR: δ 168.9, 131.7, 130.4, 129.2, 127.8, 116.1, 62.8, 20.4; IR: ν_{max} 3068, 3038, 2945, 2360, 1755, 1372, 1218, 1024, 962, 697 cm^{-1}. The spectral data were identical to those reported previously.[11a]

4.2.2. α-Acetoxy-2-naphthylacetonitrile 3d. The reaction of 2-naphthaldehyde (154 mg, 0.99 mmol) occurred in the same manner as described above (starting from **6d**) to afford, after chromatographic separation (15 g, hexane/AcOEt=9/1) and PTLC purification (hexane/AcOEt=4/1), **3d** as a yellow solid (205 mg, 92%). R_f=0.44 (hexane/AcOEt=4/1); mp: 44.5–44.8°C; ^{1}H NMR: δ 7.93–7.53 (m, 7H), 6.57 (s, 1H), 2.18 (s, 3H); ^{13}C NMR: δ 168.9, 133.9, 132.8, 129.4, 128.9, 128.4, 128.0, 127.8, 127.6, 127.1, 124.2, 116.1, 63.0, 20.5; IR: ν_{max} 3060, 2940, 1754, 1510, 1371, 1212, 1022, 943, 819 cm^{-1}. Anal. calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.40; H, 4.88; N, 6.23%. The spectral data were identical to those reported previously.[8c]

4.2.3. α-Methoxyphenylacetonitrile 6c. To a solution of benzaldehyde dimethylacetal (1010 mg, 6.66 mmol) in CH_2Cl_2 (7 mL) was added TMSCN (727 mg, 7.33 mmol) and $SnBr_2$ (10 mg, 0.04 mmol) and the mixture was stirred at room temperature for 10 min under an Ar atmosphere. After removing the solvent in vacuo, the reaction mixture was purified by silica gel column chromatography (20 g). Elution with hexane–AcOEt (19/1) afforded **6c** as a colorless oil (962 mg, 98%). R_f=0.32 (hexane/AcOEt=9/1); ^{1}H NMR: δ 7.51–7.42 (m, 5H), 5.21 (s, 1H), 3.54 (s, 3H); IR: ν_{max} 3036, 3004, 2937, 2830, 1455, 1194, 1088, 697 cm^{-1}. The spectral data were identical to those reported previously.[13c]

4.2.4. α-Methoxy-2-naphthylacetonitrile 3c. To a stirred mixture of 2-naphthaldehyde (1.50 g, 9.52 mmol) and Amberlyst-15 (H^+-form, 400–500 mg) was added trimethyl orthoformate (1.6 mL, 14.3 mmol) with ice-cooling. After stirring for 10 min, the reaction mixture was poured into aq. $NaHCO_3$ solution. The resulting mixture was filtered to remove Amberlyst and extracted with Et_2O (×3). The combined organic layer was dried over K_2CO_3 and concentrated. To this resulting mixture were added CH_2Cl_2 (10 mL) and MS 4 Å (1.2 g) and stirred at room temperature for 1 h. Then TMSCN (1.04 g, 10.5 mmol) and $SnBr_2$ (10 mg, 0.04 mmol) were added and the mixture was stirred overnight at the same temperature. The reaction was quenched with aq. HCl solution (2 M, 10.5 mL) and filtered to remove molecular sieves. The two-phase mixture was separated and organic layer was washed with water, aq. $NaHCO_3$ solution and brine, respectively. The extract was then dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (120 g). Elution with hexane–AcOEt (19/1) afforded **3c** as a pale yellow solid (1.69 g, 90%). Recrystallization from ethanol gave an analytically pure sample as colorless needles. R_f=0.46 (hexane/AcOEt=9/1); mp 56.9–57.1°C; ^{1}H NMR: δ 7.99 (s, 1H), 7.93–7.86 (m, 3H), 7.57–7.53 (m, 3H), 5.39 (s, 1H), 3.57 (s, 3H); IR: ν_{max} 3059, 3016, 2938, 2831, 2360, 1600, 1464, 1082, 967, 867, 821, 754 cm^{-1}. Anal. calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10%. Found: C, 79.08; H, 5.53; N, 7.17%.

4.2.5. α-Hydroxy-2-naphthylacetonitrile 3b. To a solution of 2-naphthaldehyde (100 mg, 0.64 mmol) in Et_2O (2 mL) was added NaCN (56 mg, 1.14 mmol) in H_2O (1 mL) and TBAB (10.6 mg, 0.02 mmol). After stirring at 0°C for 15 min, aq. H_2SO_4 solution (2 M, 0.72 mL) was added to the reaction mixture and extracted with Et_2O (×3). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo, afforded **3b** (104.2 mg, 82%) as a crude material. This was purified by silica gel column chromatography (10 g). Elution with hexane–AcOEt (4/1) afforded **3b** as a pale yellow solid (11.8 mg, 10%). R_f=0.20 (hexane/AcOEt=4/1); ^{1}H NMR: δ 10.16 (s, 1H), 8.53–7.53 (m, 7H), 5.91 (s, 1H), 3.41 (s, 1H); IR: ν_{max} 3401, 3258, 3054, 2920, 1644. 1595, 1365, 1072, 825, 742 cm^{-1}. The spectral data were identical to those reported previously.[7d]

4.3. Lipase-catalyzed hydrolysis of cyanohydrin acetate

4.3.1. Hydrolysis with lipoprotein lipase (Toyobo LIP). To a mixture of **3d** (150 mg, 0.67 mmol) in phosphate buffer solution (pH 7.5, 0.1 M, 3 mL) was added LIP (11 mg). While maintaining the pH above 7.1 with a pH controller by continuous addition of aq. NaOH (0.1 M) solution, the reaction mixture was stirred at 40°C for 48 h. The mixture was diluted with AcOEt and filtered through Celite pad. The filtrate was extracted with AcOEt (×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (15 g). Elution with hexane–AcOEt (14/1) afforded (*R*)-**3d** [64.2 mg, 43%, $[\alpha]_D^{18}$ = −22.1 (*c* 1.00, $CHCl_3$)]. The absolute configuration was determined by comparing sign of rotation with that reported previously [lit.[8c] (*S*)-**3d**: $[\alpha]_D^{22}$ +21.7]. ^{1}H NMR: δ 8.35–7.59 (m, 7H), 6.56 (s, 1H), 2.20 (s, 3H); ^{1}H NMR with Eu(hfc)$_3$: δ 2.32 (*S*, minor) and 2.20 (*R*, major); IR: ν_{max} 3059, 2926, 1755, 1511, 1371, 1212, 1020, 816 cm^{-1}. The spectral data were identical to those reported previously.[8c]

4.3.2. Hydrolysis with *B. cepacia* lipase (Sumitomo SC lipase A). To a mixture of **3d** (450 mg, 2.00 mmol) and *n*-decane (4.5 mL) in phosphate buffer solution (pH 7.0, 0.1 M, 40.5 mL), was added immobilized SC lipase A (450 mg).[28] While keeping its pH at 7.0 with a pH controller by continuous addition of aq. NaOH solution (0.1 M), the reaction mixture was stirred at 30°C for 38 h. The mixture was diluted with AcOEt and filtered through Celite pad. The filtrate was extracted

with AcOEt (×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. A small portion of the residue was dissolved in $CDCl_3$ and ^1H NMR spectrum of the mixture was measured. The conversion was estimated to be 54%. The residue was purified by silica gel column chromatography (30 g). Elution with hexane–AcOEt (19/1) afforded (*R*)-**3d** (201 mg, 45%, >99.9% e.e.). $[\alpha]_D^{22} = -17.9$ (*c* 1.00, $CHCl_3$); HPLC analysis: column, Daicel Chemical Ind., Chiralcel OB, 0.46×25 cm; hexane/2-propanol = 98/2; 0.7 ml/min; t_R (min) 75.2 [(*R*)-**3d**, single peak]. In the case of the analysis of racemate, (*S*)-isomer appeared at t_R 60.0 min. Anal. calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.30; H, 4.90; N, 6.09. The IR and NMR data were identical to those of the sample as above.

4.4. Enzyme-catalyzed transformation of nitriles

4.4.1. Pre-cultivation of *R. rhodochrous* IFO 15564. To a sterilized medium (pH 7.2, 100 mL) containing glucose (15 g/L), K_2HPO_4 (0.4 g/L), KH_2PO_4 (1.2 g/L), $MgSO_4 \cdot 7H_2O$ (0.5 g/L), yeast extract (1.0 g/L) and peptone (5.0 g/L) in a 500 mL Erlenmeyer flask with two internal projections was added a solution of ε-caprolactam (0.1 g) and $FeSO_4 \cdot 7H_2O$ (0.3 g) in deionized water (5 mL) via a sterilized membrane filter (ADVANTEC, 25CS020AS, 0.20 μm). A loopful of *R. rhodochrous* IFO15564 was inoculated and the flask was shaken at 30°C on a gyrorotary shaker (180 rpm) for 60 h. Its OD (660 nm) reached to 35 after 48 h incubation. The grown cells (ca. 3 g in wet weight) were harvested by centrifugation (3000 rpm for 15 min at 4°C), washed with 0.1 M KH_2PO_4–K_2HPO_4 buffer (pH 6.0) and collected by centrifugation.

4.5. General procedures for incubation

4.5.1. Method A. To the substrate (150 mg), dissolved in EtOH if needed (1.5 mL for **3a**, **3b**, and **6c**), a suspension of wet cells (0.5 g) in phosphate buffer (15 mL, pH 6.0, 0.1 M) was added and the mixture was stirred at 30°C.

4.5.2. Method B. To the substrate (90 mg), dissolved in EtOH (up to 1 mL for **3a** and **3c**) or DMF (up to 1 mL for **3d**), suspension of wet cells (2 g) in phosphate buffer (50 mL, pH 6.0, 0.1 M) and hexane (20 mL) was added and the mixture was stirred at 30°C.

4.6. Phenylacetic acid 8a

Phenylacetonitrile **6a** was subjected to the microbial hydrolysis using Method A. The hydrolysis completed within 4 h as checked by TLC analysis.

4.7. Mandelamide 7b

Mandelamide **7b** (135 mg, 81%) was obtained from mandelonitrile **6b** (147 mg, 1.11 mmol) using Method A. After stirring at 30°C for 4 h, the reaction mixture was filtered through a Celite pad and washed with H_2O and AcOEt. The filtrate was acidified with 2 M aqueous HCl toward pH 2.0 and saturated with NaCl. The resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Recrystallization of the residue from MeOH gave **7b** as colorless needles. $R_f = 0.30$ (AcOEt); mp 131.9–132.1°C [lit.[29] 133–134°C]; ^1H NMR (C_5D_5N): δ 8.28 (s, 1H), 8.18 (s, 1H), 7.87–7.16 (m, 5H), 5.57 (s, 1H); IR: ν_{max} 3393, 3259, 3056, 2899, 1956, 1894, 1655, 1451, 1182, 1060, 922, 696 cm^{-1}. The spectral data were identical to those reported previously.[29]

4.8. Mandelic acid 8b

Mandelic acid **8b** (135 mg, 80%) was obtained from mandelonitrile **6b** (148 mg, 1.11 mmol) using Method A (30°C, 168 h). Recrystallization of crude product from MeOH gave **8b** as colorless plates. $R_f = 0.08$ (hexane/AcOEt = 1/1); mp 115.7–116.0°C (authentic sample: 119–121°C); ^1H NMR: δ 7.44–7.28 (m, 5H), 5.12 (s, 1H); IR: ν_{max} 3449, 3036, 2664, 2626, 2360, 1726, 1456, 1249, 1191, 1065, 942, 876, 726, 693 cm^{-1}. The spectral data were identical to those of an authentic sample.

4.9. α-Methoxyphenylacetamide 7c

α-Methoxyphenylacetamide **7c** (166.0 mg, quant., 1.00 mmol) was obtained from α-methoxyphenylacetonitrile **6c** (150 mg, 1.09 mmol) using Method A (30°C, 72 h). The crude product was purified by silica gel column chromatography (3 g). Elution with AcOEt–EtOH (9/1) afforded **7c**. $R_f = 0.40$ (AcOEt); mp 100.1–100.6°C [lit.[19] 111–112°C]; ^1H NMR: δ 7.43–7.31 (m, 5H), 6.68 (s, 1H), 4.79 (s, 1H), 3.37 (s, 3H); IR: ν_{max} 3463, 3394, 3186, 2366, 2345, 1656, 1411, 1197, 1091, 704 cm^{-1}. The spectral data were identical to those reported previously.[19]

4.10. Mandelamide 7b and α-acetoxyphenylacetamide 7d

A mixture of mandelamide **7b** and α-acetoxyphenylacetamide **7d** was obtained from α-acetoxyphenylacetonitrile **6d** (150 mg, 0.86 mmol) using Method A (30°C, 19 h). The crude product was purified by silica gel column chromatography (15 g). Elution with hexane–AcOEt (1/1) afforded **7b** (51 mg, 39%) and **7d** (57 mg, 35%).

4.10.1. Mandelamide 7b. $R_f = 0.30$ (AcOEt); mp 131.9–132.1°C. The spectral data were identical to those of the sample as before.

4.10.2. α-Acetoxyphenylacetamide 7d. $R_f = 0.48$ (AcOEt); mp 112.9–113.1°C [lit.[29] 112–113°C]; ^1H NMR: δ 7.28–7.41 (m, 5H), 6.01 (s, 1H), 5.80 (s, 1H), 2.12 (s, 3H); IR: ν_{max} 3389, 3195, 2951, 1743, 1670, 1421, 1227, 1041, 696 cm^{-1}. The spectral data were identical to those reported previously.[29]

4.11. 2-Naphthylacetic acid 5a

2-Naphthylacetic acid **5a** was obtained from 2-naphthylacetonitrile (**3a**, 150 mg, 0.88 mmol) using Method A (30°C, 48 h). Crude **5a** (184 mg, quant., 0.99 mmol) was methylated with diazomethane for purification and purified by silica gel column chromatography (5 g). Elution with hexane–AcOEt (9/1) afforded the methyl ester of **5a** (98 mg, 60%). ^{1}H NMR: δ 7.75–7.31 (m, 7H), 3.71 (s, 2H), 3.62 (s, 3H). Its NMR spectrum was identical with that reported previously.[30]

The same product was also obtained from nitrile **3a** (90 mg, 0.54 mmol) using Method B (30°C, 72 h). PTLC purification of the crude product (CH_2Cl_2/EtOH = 19/1) afforded **5a** (86 mg, 87%). ^{1}H NMR: δ 7.79–7.28 (m, 7H), 3.73 (s, 2H). Its NMR spectrum was identical with that of an authentic sample. The NMR spectrum of the corresponding methyl ester was also identical with that of the sample as above.

4.12. α-Hydroxy-2-naphthylacetamide 4b

α-Hydroxy-2-naphthylacetamide **4b** (13 mg, 8%) was obtained from the corresponding nitrile **3b** (150 mg, 0.82 mmol) using Method A (30°C, 18 h). PTLC purification of the crude product containing 2-naphthaldehyde (hexane/AcOEt = 2/1) afforded **4b** as a colorless solid. R_f = 0.37 (hexane/AcOEt = 2/1); mp 183.1–185.4°C (dec.); IR: ν_{max} 3400, 3053, 2919, 2363, 2333, 1653, 1646, 1072, 825, 742 cm^{-1}. The spectrum was identical with that of (*R*)-**4b** as mentioned later.

4.13. α-Methoxy-2-naphthylacetamide 4c

α-Methoxy-2-naphthylacetamide **4c** (86 mg, 88%) was obtained from nitrile (**3c**, 90 mg, 0.46 mmol) using Method B (30°C, 24 h). The crude product was purified by silica gel column chromatography (3.5 g). Elution with hexane–AcOEt (4/1) afforded **4c** as white powder. Recrystallization from MeOH gave **4c** as colorless needles. R_f = 0.47 (hexane/AcOEt = 4/1); mp 175.8–176.7°C; ^{1}H NMR: δ 7.87–7.44 (m, 7H), 6.74 (s, 1H), 5.57 (s, 1H), 4.77 (s, 1H), 3.40 (s, 3H); IR: ν_{max} 3417, 3157, 2938, 2359, 1691, 1664, 1369, 1099, 747, 607 cm^{-1}. Anal. calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51%. Found: C, 72.32; H, 6.03; N, 6.47%.

4.14. (*R*)-α-Hydroxy-2-naphthylacetamide (*R*)-4b

In a similar manner as described above, (*R*)-α-hydroxy-2-naphthylacetamide (**4b**, 77 mg, 75%) was obtained from nitrile [(*R*)-**3d**, 90 mg, 0.42 mmol] using Method B (30°C, 24 h). Recrystallization of the product from MeOH afforded colorless needles. R_f = 0.50 (hexane/AcOEt = 4/1); mp 222.6–223.4°C; ^{1}H NMR: δ 7.91–7.26 (m, 7H), 7.26 (s, 1H), 6.17–6.16 (d, 1H), 5.02–5.00 (d, 1H); IR: ν_{max} 3393, 3204, 3052, 1711, 1653, 1597, 1437, 1362, 1121, 828, 740, 669 cm^{-1}. Anal. calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96%. Found: C, 71.33; H, 5.52; N, 6.86%. $[\alpha]_D^{22} = -62.8$ (*c* 0.50, DMSO).

4.15. Nitrosation–hydrolysis of amides

4.15.1. Nitrosation–hydrolysis of 4c. To a solution of **4c** (30 mg, 0.14 mmol) in DMF (0.5 mL) was added HO_3SONO (89 mg, 0.70 mmol) and stirred for 24 h at room temperature. The reaction mixture was poured into water, acidified with aq. H_2SO_4 solution (2 M) and extracted with AcOEt. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and to this solution was added trimethylsilyldiazomethane ($TMSCHN_2$). The resulting mixture was concentrated in vacuo. The residue was purified with PTLC (hexane/AcOEt = 9/1) to give **1b** (17.2 mg, 55%) and 2-naphthaldehyde **2** (7.4 mg, 35%). The spectral data were identical to those of the authentic sample as stated later.

4.15.2. Nitrosation–hydrolysis of (*R*)-4b. To a solution of (*R*)-**4b** (>99.9% e.e., 21 mg, 0.10 mmol) in DMF (0.5 mL) was added HO_3SONO (63 mg, 0.50 mmol), stirred for 0.5 h at 0°C and worked-up as in the same manner described above, involving esterification with $TMSCHN_2$. The crude methyl ester was purified with PTLC (hexane/AcOEt = 3/1) to give (*R*)-**9a** (13.0 mg, 59%) and **2** (1.0 mg, 6%). Compound (*R*)-**9a**: R_f = 0.14 (hexane/AcOEt = 3/1); mp 72.8–73.0°C; ^{1}H NMR: δ 7.91–7.48 (m, 7H), 5.36 (s, 1H), 3.77 (s, 3H); IR: ν_{max} 3412, 3056, 2959, 1723, 1440, 1363, 1211, 817; $[\alpha]_D^{28} = -164.0$ (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%. Found: C, 72.14; H, 5.35%.

4.15.3. Nitrosation–hydrolysis of 4d. To a solution of **4d** (11 mg, 0.04 mmol) in DMF (0.2 mL) was added HO_3SONO (50 mg, 0.39 mmol), stirred for 20 h at room temperature and worked up as described above. The residue was purified with PTLC (hexane/AcOEt = 4/1) and gave **9b** (9.2 mg, 80%) and 2-naphthaldehyde 2, (0.3 mg, 4.6%). Compound **9b**: R_f = 0.39 (hexane/AcOEt = 4/1); mp 102.3–102.4°C; ^{1}H NMR: δ 7.95–7.50 (m, 7H), 6.10 (s, 1H), 3.74 (s, 3H), 2.24 (s, 3H); IR: ν_{max} 3885, 3854, 3749, 3744, 1737, 1444, 1375 cm^{-1}. Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46%. Found: C, 69.37; H, 5.31.

4.16. Methylation of α-hydroxyl group

4.16.1. Methylation of 9a with CH_2N_2–silia gel. Silica gel was pre-heated by microwave and cooled in vacuo for 2 h. To a solution of (*R*)-**9a** [>99.9% e.e. at the stage of (*R*)-**4b**, 38 mg, 0.18 mmol] in Et_2O (1 mL) was added silica gel (10 mg) and the ethereal solution of diazomethane as above. Silica gel and diazomethane solution were added again when the yellow color no longer lasts. This procedure was repeated several times over 1 h. Then, the mixture was filtered to remove silica gel and concentrated in vacuo. The residue was purified with PTLC (hexane/AcOEt = 4/1) to give (*R*)-**1b** (19.2 mg, 48%, >99.9% e.e.). The substrate (*R*)-**9a** (16.5 mg, 44%) was also recovered. Compound (*R*)-**1b**: R_f = 0.41 (hexane/AcOEt = 4/1); mp 38.6–39.0°C; ^{1}H NMR: δ 7.92–7.47 (m, 7H), 4.95 (s, 1H), 3.73 (s, 3H), 3.45 (s, 3H); IR: ν_{max} 3057, 2999, 2951, 2360, 1741, 1598, 1508,

1435, 1272, 1193, 1105, 1010, 754. Anal. calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13%. Found: C, 72.85; H, 5.96. $[\alpha]_D^{23} = -140.7$ (c 0.51, $CHCl_3$). HPLC analysis: column, Chiralcel OJ; hexane/2-propanol = 9/1; 0.5 ml/min; t_R (min) 46.9 [(*R*)-**1b**, >99.9%]. In the HPLC analysis of the corresponding racemate, (*S*)-isomer appeared at t_R 62.3 min.

4.16.2. Methylation of 9a with CH_2N_2–$SnCl_2{\cdot}2H_2O$. To a solution of (*R*)-**9a** [99.1% e.e. at the stage of (*R*)-**4b**, 8.7 mg, 0.040 mmol] in acetonitrile (0.4 mL) was added catalytic amount of $SnCl_2{\cdot}2H_2O$ and a solution of diazomethane (3 mmol) in Et_2O. The resulting mixture was filtered and evaporated. The residue was purified with PTLC (hexane/AcOEt = 4/1) and gave **1b** (1.2 mg, 13%). The substrate **9a** (7.3 mg, 84%) was also recovered. The e.e. of the product was 92.8% judged from the HPLC analysis as above.

4.16.3. Methylation of 9a with MeI–Ag_2O. To a solution of (*R*)-**9a** (13.0 mg, 0.006 mmol) in DMF (0.5 mL), methyl iodide (37 μL, 0.59 mmol) and silver(I) oxide (4.2 mg, 0.18 mmol) were added. After stirring overnight at room temperature, the reaction mixture was poured into ice-cooled water and stirred for further 30 min. The mixture was filtered through Celite pad and separated. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified with PTLC (hexane/AcOEt = 3/1) and gave **1b** (5.4 mg, 39%). The substrate **9a** (1.4 mg, 11%) was also recovered. The e.e. of the product was 43.7% according to the HPLC analysis as above, though the e.e. of (*R*)-**4b**, starting material of this route, was 99.2%.

4.16.4. Methylation of (*R*)-10a with methyl trichloroacetimidate–$HBF_4{\cdot}Me_2O$. To a solution of methyl (*R*)-mandelate (**10a**, 100 mg, 0.60 mmol) in CH_2Cl_2 (2 mL), were added methyl 2,2,2-trichloroacetimidate (0.2 mL, 1.62 mmol) and $HBF_4{\cdot}Me_2O$ (40 μL, 0.30 mmol). After stirring over 4 days, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with aq. $NaHCO_3$ solution and H_2O, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give methyl ether **10b** (30.6 mg, 28%) with the recovery of unreacted substrate. Compound **10b**: ^{1}H NMR: δ 7.46–7.33 (m, 5H), 4.78 (s, 1H), 3.72 (s, 3H), 3.41 (s, 3H). The NMR spectrum was identical with that of an authentic sample. HPLC analysis: column, Chiralcel OJ; hexane/2-propanol = 9/1; 0.5 ml/min; t_R (min) 30.8 [(*R*)-**14**, >99.9%]. The (*S*)-enantiomer eluted at t_R 34.3 min in the analysis of racemic sample.

4.17. Enzyme-catalyzed hydrolysis of methyl ester of 1b

4.17.1. Hydrolysis of (*R*)-1a with *K. oxytoca* esterase (Nagase SNSM-87). To a solution of (*R*)-**1b** (30 mg, 0.14 mmol) in phosphate buffer solution (pH 7.0, 0.2 M, 1.2 mL), esterase from *K. oxytoca* (10 mg) was added and stirred at 39°C. After stirring overnight, the reaction mixture was diluted with AcOEt and filtered through Celite pad. The filtrate was acidified with 2 M HCl toward pH 2.0 and saturated with NaCl. The resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. PTLC purification afforded to give (*R*)-**1a** quantitatively. Recrystallization from AcOEt gave analytical sample as colorless prisms. $R_f = 0.25$ (AcOEt/AcOH = 99/1); mp 111.2–111.5°C; ^{1}H NMR: δ 7.91–7.48 (m, 7H), 4.95 (s, 1H), 3.46 (s, 3H); IR: ν_{max} 3193, 3055, 2943, 2835, 1755, 1597, 1444, 1223, 1188, 1092, 757. Anal. calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%. Found: C, 71.89; H, 5.98. $[\alpha]_D^{20} = -162.8$ (c 0.54, $CHCl_3$), $[\alpha]_D^{20} = -173.9$ (c 0.35, MeOH) [lit.[4a] −138.7 (c 0.35, MeOH), lit.[4b] −120.8 (c 0.005, EtOH)]. The spectral data were identical to those reported previously.[4b]

This product was methylated again with $TMSCHN_2$ and PTLC purification afforded methyl ester for the HPLC analysis. The e.e. was confirmed to be >99.9%, according to the HPLC analysis as above.

4.17.2. Attempted hydrolysis of (±)-1b with *Candida rugosa* lipase (Meito OF). To a solution of (±)-**1b** (10 mg, 0.043 mmol) in phosphate buffer solution (pH 7.0, 0.2 M, 0.4 mL), *C. rugosa* lipase (Meito OF, 5 mg) was added and stirred at 27°C. The reactions were monitored by TLC. After 28 h, the mixture was worked-up and purified as above to give (*S*)-**1a** and (*R*)-**1b** (3.9 mg, 38%). The resulting carboxylic acid (*S*)-**1a** was methylated with $TMSCHN_2$ to give (*S*)-**1b** (1.2 mg, 12%).

The e.e.s of (*R*)-**1b** and (*S*)-**1b** [from (*S*)-**1a**] were 24.2 and 40.6%, respectively, determined by the HPLC analysis as above. The E value and the conversion were calculated to be 3 and 37%, respectively. The preference of (*S*)-enantiomer was in good accordance with the result having so far been obtained in an analogous substrate.[31]

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