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Efficient lipase-catalyzed kinetic resolution of 4-arylmethoxy-3-hydroxybutanenitriles: application to an expedient synthesis of a statin intermediate

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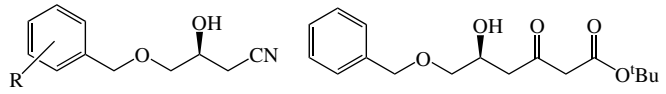
Abstract—The kinetic resolution of 4-arylmethoxy-3-hydroxybutanenitriles was investigated by lipase-catalyzed transesterification in organic solvents. A high enantioselectivity was obtained via reaction with vinyl acetate in a mixed solvent (*n*-heptane/acetonitrile 1:1), which was catalyzed by the lipase from *Artgribacter* sp. A better selectivity was demonstrated when the number of substituents on the aryl ring increased. (*S*)-4-Arylmethoxy-3-hydroxybutanenitriles can be obtained with enantiomeric excesses of up to 98.0% by this method. Furthermore we have developed a novel route to synthesize *tert*-butyl (*S*)-6-benzyloxy-5-hydroxy-3-oxohexanoate, a key intermediate for the preparation of HMG-CoA reductase inhibitors (statins).

1. Introduction

4-Arylmethoxy-3-hydroxybutanenitriles **1** (Scheme 1) have been extensively investigated and employed in synthetic chemistry.[1,2] Chiral 4-arylmethoxy-3-hydroxybutanenitriles are useful chiral building blocks in asymmetric synthesis, as the cyano group is a precursor of many groups, such as amino and carbonyl. Furthermore, substituted benzyl groups can be easily cleaved by methods including hydrogenolysis with catalytic Pd/C[3] and acid hydrolysis in refluxing trifluoroacetic acid (TFA)[4] or $FeCl_3$,[5] which offers potential routes to prepare chiral diols.



a R: H
b R; 4-Cl
c R: 2,4-Cl,
d R: 4-CH_3
e R: 4-CH_3O,
f R: 2,4,6-CH_3
g R: 4-F

Scheme 1.

The resolution of racemic alcohols, catalyzed by lipases in organic solvents, is currently widely used today.[6] However, there are few reports on the preparation of chiral 4-arylmethoxy-3-hydroxybutanenitriles by the method of lipase-catalyzed transesterification. Previously, an enzymatic kinetic resolution of the structurally similar 3-hydroxy-4-phenoxybutanenitrile was reported by utilizing lipase PS (*Pseudomonas cepacia* lipase).[7] There are also other enzymatic methods described for the preparation of similar structures, but most of them are based on lipase catalyzed hydrolysis reactions,[8] such as Anthonsen's researches, which reports on the enzymatic resolution of a similar substrate structure, 3-chloro-1-benzyloxy-2-propanol.[9] To obtain 4-arylmethoxy-3-hydroxybutanenitriles with high ee values by lipase-catalyzed transesterification still remains an attractive target.

Herein we report an enzymatic synthesis to prepare chiral 4-arylmethoxy-3-hydroxybutanenitriles, as well as develop a novel route to synthesize *tert*-butyl (*S*)-6-benzyloxy-5-hydroxy-3-oxohexanoate **2** (Scheme 1), a key intermediate for the preparation of HMG-CoA reductase inhibitors.[10] There are already many reports on the synthesis of *tert*-butyl (*S*)-6-benzyloxy-5-hydroxy-3-oxohexanoate, however,

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most of them have drawbacks such as starting from chiral raw materials,[11,12] employing low temperatures,[13–15] or expensive catalysts.[12,13,15]

2. Results and discussion

2.1. Screening of lipases

Firstly, the enantioselective resolution of racemic 4-benzyloxy-3-hydroxy-butanenitrile **1a** was carried out by employing different lipases in vinyl acetate. The results are listed in Table 1. Of the 11 lipases employed, the lipase from *Artgribacter* sp. and the lipase from *Alcaligenes* sp. showed higher *E*-values (entries 10 and 11). However, the results were far from expected.

2.2. Choice of solvents

Organic solvents play very important roles in enzyme-catalyzed reactions.[16] Therefore, we turned our attention to test different solvents and the results are listed in Table 2. It was observed that two lipases in many solvents produced higher *E*-values than those in vinyl acetate. In most cases, the lipase from *Artgribacter* sp. showed a better selectivity than the lipase from *Alcaligenes* sp.

Table 1. Transesterification of **1a** with vinyl acetate using various lipases

Entry	Source	Supplier	Alcohol ee (%)	Acetate ee (%)	*C* (%)	*E*
1	Novozym 435	Novo Nordisk	11.3	31.4	26.5	2.1
2	*Candida antarctia*	Fluka	4.5	16.2	21.7	1.4
3	*Pseudomos cepacia*	Fluka	2.9	16.1	15.2	1.4
4	*Rhizopus delemar*	Fluka	10.4	30.2	25.5	2.1
5	*Pseudomonas stu.*	Meito Sangyo	4.9	6.1	44.8	1.2
6	Lipase QL	Meito Sangyo	8.1	28.1	22.3	1.9
7	Lipoprime	Novo Nordisk	73.3	24.9	74.1	3.2
8	*Penicilium*	Fluka	1.1	12.8	8.0	1.3
9	*Phizopus* sp.	Fluka	63.6	22.8	73.6	2.8
10	*Alcaligenes* sp.	Fluka	73.7	32.2	69.6	3.9
11	*Artgribacter* sp.	IMCAC	42.8	57.8	42.6	5.6

[a] All reactions were carried out by stirring a mixture of **1a** (50 mg), lipase (10 mg), and vinyl acetate (2 mL) at 30 °C for 24 h.
[b] Lipase from *Artgribacter* sp. was a gift from Professor Xiufen Kou of Institute of Microbiology, Chinese Academy of China (IMCAC).

Table 2. Transesterification of **1a** with vinyl acetate in various solvents

Entry	Solvent	Source	Time (h)	Alcohol ee (%)	Acetate ee (%)	*C* (%)	*E*
1	Toluene	*Artgribacter* sp.	7.5	7.7	34.6	18.3	2.2
		Alcaligenes sp.		19.9	53.5	27.1	4.0
2	THF	*Artgribacter* sp.	34	12.2	66.2	15.6	5.5
		Alcaligenes sp.		24.1	60.2	26.7	6.2
3	*i*-Pr_2O	*Artgribacter* sp.	7.5	11.2	58.6	16.0	4.2
		Alcaligenes sp.		88.7	21.3	80.6	3.8
4	1,4-Dioxane	*Artgribacter* sp.	11.0	16.8	33.6	33.3	2.3
		Alcaligenes sp.	7.5	13.5	26.2	34.0	1.9
5	Cyclohexane	*Artgribacter* sp.	7.5	25.7	63.4	28.8	5.7
		Alcaligenes sp.		96.2	24.4	79.8	5.2
6	*n*-Hexane	*Artgribacter* sp.	11.0	99.0	52.1	65.0	14.8
		Alcaligenes sp.	7.5	95.5	44.4	68.2	8.9
7	*n*-Heptane	*Artgribacter* sp.	11.0	99.0	61.2	61.8	20.3
		Alcaligenes sp.	7.5	95.2	42.4	69.1	8.3
8	Acetonitrile	*Artgribacter* sp.	11	19.8	93.0	17.4	39.4
			20	28.4	92.7	25.4	36.1
			40	33.7	92.5	26.7	35.6
		Alcaligenes sp.	11	29.6	87.2	25.4	19.6
9	*n*-Heptane/acetonitrile (1:1)	*Artgribacter* sp.	15.0	54.3	89.5	37.7	31.2
		Alcaligenes sp.		86.0	68.7	55.6	14.5
10	*n*-Heptane/acetonitrile (1:5)	*Artgribacter* sp.	50.0	32.8	91.6	26.4	31.4
11	*n*-Heptane/acetonitrile (9:1)	*Artgribacter* sp.	15.0	98.0	62.9	60.1	19.0

[a] All reactions were carried out by stirring a mixture of **1a** (40 mg), lipase (10 mg), and vinyl acetate (0.1 mL) in 2 mL solvent at 30 °C.

In acetonitrile (entry 8), the lipase from *Artgribacter* sp. produced a high enantioselectivity, but too low a reaction rate. In non-polar solvents such as *n*-hexane and *n*-heptane (entries 6 and 7), lipase from *Artgribacter* sp. showed high *E*-values and high rates. However, the solubility of the substrate in these solvents was very low. To achieve high *E*-values, adequate rates and good solubilities, we attempted to use mixed solvents (entries 9–11). The mixed solvent (*n*-heptane/acetonitrile = 1:1) was chosen as the reaction solvent.

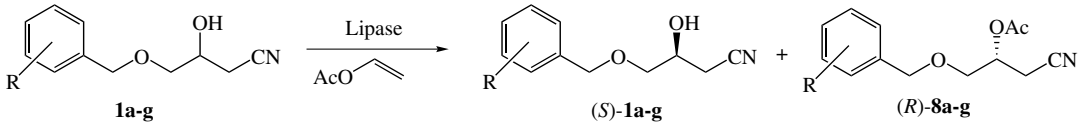
2.3. Effect of substituents

After the solvents were screened, the *E*-value was greatly increased. Here, we continued to study substituent changes on the aryl rings (**1a**–**g**), as shown in Scheme 2. For one reason, the structure of substrates has a great influence in enzymatic selectivity;[17] for another, all the arylmethoxy groups can be removed to give the same product-diols. Besides, the substituents on the aryl rings also make the cleaved reaction more convenient.

Seven substrates **1a**–**g** with substituents on the aryl rings were studied and the results are shown in Table 3. Interestingly, enzymatic selectivity could be improved upon by the introduction of substituents on the aryl rings. With the number of substituents increased, a greater selectivity was seen. The enantioselectivity of the lipase from *Artgribacter* sp. toward **1a**–**g** can be interpreted using a simple rule proposed.[18] For secondary alcohols, the lipase preferentially transforms one enantiomer, and its enantioselectivity is high when the substituents at the stereocenter differ significantly in size. In our case, the size of the group on one side of the stereogenic center increases as the number of substituents on the aryl ring is increased. Therefore, the enantioselectivity of the lipase from *Artgribacter* sp. is improved when the substituent changes from H to a trimethyl group (Table 3).

2.4. Synthesis of *tert*-butyl (*S*)-6-benzyloxy-5-hydroxy-3-oxohexanoate 2

After having obtained (*S*)-4-benzyloxy-3-hydroxybutanenitrile **1a** by an enzymatic resolution, we developed a novel route to synthesize *tert*-butyl (*S*)-6-benzyloxy-5-hydroxy-3-oxohexanoate **2**, which is a key intermediate for the preparation of HMG-CoA reductase inhibitors, as shown in Scheme 3.

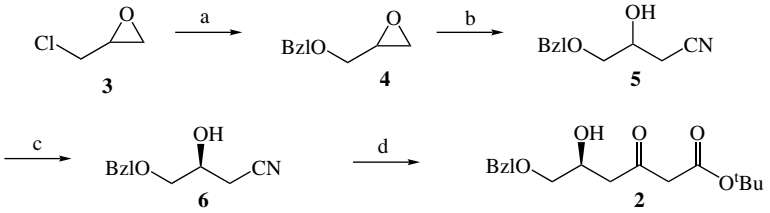


Scheme 2.

Table 3. Kinetic resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1a**–**g**

Substrate	R	Time (h)	Alcohol ee (%)	Acetate ee (%)	*C* (%)	*E*
a	H	45	98.0	70.0	58.3	24.8
b	4-Cl	60	96.2	85.0	53.1	48.5
c	2,4-Cl	70	96.1	90.1	51.6	75.6
d	4-CH_3	52	97.0	81.3	54.4	40.0
e	4-CH_3O	68	96.3	82.3	53.9	40.6
f	2,4,6-CH_3	120	92.7	99.0	48.3	>200
g	4-F	60	99.0	85.0	53.8	63.9

[a] All reactions were carried out by stirring a mixture of **1a**–**g** (5 mmol), lipase from *Artgribacter* sp. (250 mg) and vinyl acetate (25 mmol) in 50 mL solvent (*n*-heptane/acetonitrile = 1:1) at 30 °C.
[b] The reactions were allowed to exceed 50% conversion until the ees of the unreacted (*S*)-alcohols were satisfactory.



Scheme 3. Reagents and conditions: (a) 40% NaOH aq, *n*-Bu_4NBr, 0 °C, 24 h, 85%; (b) NaCN/H_2O, MeOH, H_2SO_4, pH = 8–11, 40 °C, 15 h, 80%; (c) 5 equiv vinyl acetate, lipase from *Artgribacter* sp., *n*-heptane/acetonitrile, 30 °C, 40–60 h; (d) (i) 1.1 equiv TMSCl, 1.2 equiv Et_3N, THF, 0 °C, 12 h; (ii) 2.0 equiv $BrCH_2CO_2{}^tBu$, 3 equiv Zn, 0.01 equiv $MeSO_3H$, THF, reflux 2 h, then, 3 N HCl, 0 °C, 2 h overall 77%.

Firstly, 1-benzyloxy-2,3-epoxypropane **4** was prepared in 85% yield by the reaction of commercially available racemic epichlorohydrin **3** with benzyl alcohol.[19] We then attempted to open the ring of epoxide **4** using NaCN in aqueous–alcoholic conditions. When epoxide **4** was treated with NaCN in aqueous condition under the usual conditions, a complex mixture was obtained. The strong basicity in the course of the reaction most likely prevents hydroxyl group forming. Thus, we kept the pH strictly between 8.0 and 11.0 with H_2SO_4,[20] which eventually allowed β-hydroxynitrile **5** to be pure enough to be directly employed in the next step. The resulting racemic 4-benzyloxy-3-hydroxybutanenitrile was resolved by a lipase-catalyzed esterification using the lipase from *Artgribacter* sp. It was shown by chiral HPLC (Chiralpak AD-H column) that the desired compound **6** could be achieved with high enantiomeric excesses (⩾98% ee) in an isolated yield of 40% from **5**. In the last step, the hydroxyl group of β-hydroxy nitrile **6** was protected by a trimethylsilyl group,[21] then reacted with $BrCH_2CO_2{}^tBu$, according to the literature method,[22] to form the target product **2**, in an overall yield of 77% from **6**.

3. Conclusion

In conclusion, we have developed an efficient enzymatic resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** using the lipase from *Artgribacter* sp. Enantioselective (*S*)-4-arylmethoxy-3-hydroxybutanenitrile **1a** was obtained in the reaction with vinyl acetate in *n*-heptane/acetonitrile solution. This method affords (*S*)-4-arylmethoxy-3-hydroxybutanenitriles with enantiomeric excesses of up to 98.0%. We have also developed a valuable method to synthesize *tert*-butyl (*S*)-6-benzyloxy-5-hydroxy-3-oxohexanoate. Studies on a number of extensions to this work are currently underway.

4. Experimental

4.1. General

All reagents were of commercial grade with purity >98% and used as provided without further purification. *Artgribacter* sp. lipase was a gift from Professor Xiufen Kou of Institute of Microbiology, Chinese Academy of China. Other lipases are commercial enzymes. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on a Brucker Avance-400 (400 MHz) spectrometer with TMS as the internal standard. GC–MS spectra were recorded on a HP-6890/MS-5973 spectrometer. Mass spectra were recorded on an Esquire-LC spectrometer. Melting points were taken on electrothermal melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet 560 spectrometer. Optical rotations were measured on an AUTOPOL IV digital polarimeter. HPLC was performed on a Chiralpak AD-H column (Daicel) and monitored by UV (224 nm). Column chromatography was performed on a Merck silica gel 60 (230–400 mesh). TLC analyses were performed on Merck 60 PF 254 silica gel plates. Conversion and enantiomeric purities were determined by HPLC analyses (solvent: *n*-hexane/EtOH, flow: 1.0 mL/min). The absolute configuration of (*S*)-4-arylmethoxy-3-hydroxybutanenitriles **1a**–**g** was assigned by preparing the standards from (*R*)-epichlorohydrin described in Scheme 3.

4.2. General procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles 1

4-Arylmethoxy-3-hydroxybutanenitrile **1** (5 mmol) was dissolved in a mixed solvent (*n*-heptane/acetonitrile = 1:1, 50 mL), and to this solution lipase from *Artgribacter* sp. (250 mg) and vinyl acetate (25 mmol) were added successively and shaken at 30 °C in an orbital shaker. After about 50% completion of the reaction, as indicated by HPLC analysis, the enzyme was filtered and washed with EtOAc. The solvents were evaporated and purification was accomplished by column chromatography employing EtOAc–hexane (1:4) as the eluent to afford the corresponding (*R*)-acetates **8a**–**g**, followed by the unreacted (*S*)-alcohol **1a**–**g**.

4.2.1. (*S*)-4-Benzyloxy-3-hydroxybutanenitrile 1a. Resolution of (*S*)-4-benzyloxy-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*S*)-**1a** in 40% yield and ee 98.0% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{1a}} = 11.5$ min, $t_{(S)\text{-}\mathbf{1a}} = 12.3$ min, hexane/EtOH 92:8, flow: 1.0 mL/min; $[\alpha]_D^{20} = -3.3$ (*c* 3.3, $CHCl_3$); IR (film): 3432, 3063, 2926, 2253, 1458, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.39 (m, 5H), 4.57 (d, $J = 10.4$ Hz, 2H), 4.06–4.12 (m, 1H), 3.50–3.59 (m, 2H), 2.74 (d, $J = 5.6$ Hz, 1H), 2.60 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.19, 128.45, 127.95, 127.75, 117.25, 73.493, 72.02, 66.34, 22.38; MS (70 eV, EI) *m*/*z* (%): 191 (M^+, 7), 161 (4), 107 (8), 91 (100), 65 (11).

4.2.2. (*S*)-4-(4-Chlorobenzyloxy)-3-hydroxybutanenitrile 1b. Resolution of 4-(4-chlorobenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*S*)-**1b** in 49% yield and ee 96.2% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{1b}} = 26.6$ min, $t_{(S)\text{-}\mathbf{1b}} = 28.7$ min, hexane/EtOH 92:8, flow: 1.0 mL/min; $[\alpha]_D^{20} = -2.6$ (*c* 3.2, $CHCl_3$); IR (film): 3447, 2925, 2253, 1598, 1492, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 4.53 (s, 2H), 4.08–4.12 (m, 1H), 3.50–3.58 (m, 2H), 2.79 (d, $J = 5.2$ Hz, 1H), 2.61 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 135.72, 133.65, 129.02, 128.28, 117.27, 72.64, 72.14, 66.27, 22.43; MS (70 eV, EI) *m*/*z* (%): 225 (M^+, 9), 190 (11), 141 (19), 125/127 (100/33), 89 (29), 42 (6).

4.2.3. (*S*)-4-(2,4-Dichlorobenzyloxy)-3-hydroxybutanenitrile 1c. Resolution of 4-(2,4-dichlorobenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*S*)-**1c** in 45% yield and ee 96.1% as a white solid; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{1c}} = 11.2$ min, $t_{(S)\text{-}\mathbf{1c}} = 14.4$ min, hexane/EtOH 85:15, flow: 1.0 mL/min; mp 54–57 °C; $[\alpha]_D^{20} = -0.6$ (*c* 3.7, $CHCl_3$); IR (KBr): 3448, 3079, 2927, 2250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ

7.40 (d, $J = 1.6$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.25–7.28 (m, 1 Hz), 4.63 (s, 2H), 4.13–4.17 (m, 1H), 3.59–3.68 (m, 2H), 2.62–2.65 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 134.25, 117.79, 133.54, 130.13, 129.24, 127.14, 117.21, 72.56, 70.05, 66.33, 22.46; MS (70 eV, EI) m/z (%): 233 (M^+, 8), 218 (7), 203 (1), 147 (2), 133 (100), 117 (18), 91 (12), 77 (5).

4.2.4. (*S*)-4-(4-Methylbenzyloxy)-3-hydroxybutanenitrile 1d. Resolution of 4-(4-methylbenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*S*)-**1d** in 41% yield and ee 97.0% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{1d}} = 32.2$ min; $t_{(S)\text{-}\mathbf{1d}} = 35.2$ min; hexane/EtOH 95:5, flow: 1.0 mL/min; $[\alpha]_D^{20} = -2.6$ (c 3.0, $CHCl_3$); IR (film): 3445, 2920, 2253, 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.4$ Hz, 2H), 7.18 (d, $J = 8.0$ Hz), 4.52 (s, 2H), 4.07 (m, 1H), 3.48–3.57 (m, 2H), 2.52–2.63 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.78, 134.20, 129.17, 127.96, 117.43, 73.40, 71.94, 66.35, 22.41, 21.09; MS (70 eV, EI) m/z (%): 205 (M^+, 11), 190 (7), 175 (2), 121 (6), 105 (100), 77 (10).

4.2.5. (*S*)-4-(4-Methoxybenzyloxy)-3-hydroxybutanenitrile 1e. Resolution of 4-(4-methoxybenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*S*)-**1e** in 45% yield and ee 96.3% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{1e}} = 29.0$ min, $t_{(S)\text{-}\mathbf{1e}} = 33.5$ min, hexane/EtOH 90:10, flow: 1.0 mL/min; $[\alpha]_D^{20} = -1.8$ (c 3.0, $CHCl_3$); IR (film): 3447, 2958, 2935, 2252, 1611, 1244 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 4.49 (s, 2H), 4.06–4.08 (m, 1H), 3.81 (s, 3H), 3.47–3.57 (m, 2H), 2.56–2.59 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.34, 129.39, 129.19, 117.19, 113.80, 73.11, 71.67, 66.32, 55.13, 22.32; MS (70 eV, EI) m/z (%): 221 (M^+, 8), 203 (3), 137 (29), 121 (100), 43 (15).

4.2.6. (*S*)-4-(2,4,6-Trimethylbenzyloxy)-3-hydroxybutanenitrile 1f. Resolution of 4-(2,4,6-trimethylbenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*S*)-**1f** in 45% yield and ee 92.7% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{1f}} = 13.3$ min, $t_{(S)\text{-}\mathbf{1f}} = 16.5$ min, hexane/EtOH 95:5, flow: 1.0 mL/min; $[\alpha]_D^{20} = +3.0$ (c 3.0, $CHCl_3$); IR (film): 3445, 2920, 2253, 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 2H), 4.58 (s, 2H), 4.05–4.07 (m, 1H), 3.53–3.62 (m, 2H), 2.58 (dd, $J = 6.4$ Hz, $J = 3.6$ Hz, 2H), 2.35 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 138.07, 137.71, 130.33, 129.00, 117.17, 72.00, 67.45, 66.44, 22.27, 20.88, 19.44; MS (70 eV, EI) m/z (%): 233 (M^+, 8), 218 (7), 203 (1), 147 (2), 133 (100), 117 (18), 91 (12), 77 (5).

4.2.7. (*S*)-4-(4-Fluorobenzyloxy)-3-hydroxybutanenitrile 1g. Resolution of (*S*)-4-(4-fluorobenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*S*)-**1g** in 50% yield and ee 99.0% as a colorless oil; HPLC (Daicel Chiralpak AD), $t_{(R)\text{-}\mathbf{1g}} = 34.2$ min, $t_{(S)\text{-}\mathbf{1g}} = 37.3$ min, hexane/EtOH 95:5, flow: 1.0 mL/min; $[\alpha]_D^{20} = -1.4$ (c 3.0, $CHCl_3$); IR (film): 3449, 3072, 2924, 2254, 1604, 1224 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.31 (m, 2H), 7.03–7.07 (m, 2H), 4.53 (s, 2H), 4.09–4.13 (m, 1H), 3.50–3.59 (m, 2H), 2.59–2.62 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.60, 161.15, 133.02, 132.98, 129.57, 129.50, 117.27, 115.42, 115.21, 72.74, 72.01, 66.30, 22.40; MS (70 eV, EI) m/z (%): 209 (M^+, 4), 179 (3), 164 (2), 125 (8), 109 (100), 83 (9).

4.2.8. (*R*)-3-Acetyloxy-4-benzyloxy-3-hydroxybutanenitrile 8a. Resolution of 4-benzyloxy-3-hydroxybutanenitrile **1a** by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitrile **1** afforded (*R*)-**8a** in 53% yield and an ee 70.0% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{8a}} = 6.2$ min, $t_{(S)\text{-}\mathbf{8a}} = 6.6$ min, hexane/EtOH 92:8, flow: 1.0 mL/min; $[\alpha]_D^{20} = +3.4$ (c 3.0, $CHCl_3$); IR (film): 3064, 2959, 2252, 1744, 1232 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.36 (m, 5H), 5.11–5.16 (m, 1H), 4.57 (d, $J = 4.4$ Hz, 2H), 3.58–3.69 (m, 2H), 2.79 (dd, $J = 5.6$ Hz, $J = 1.6$ Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.82, 137.16, 128.45, 127.95, 127.68, 116.18, 73.51, 68.79, 67.43, 20.74, 19.91; MS (70 eV, EI) m/z (%): 233 (M^+, 1), 190 (3), 173 (3), 143 (3), 126 (36), 91 (100), 43 (26).

4.2.9. (*R*)-3-Acetyloxy-4-(4-chlorobenzyloxy)-3-hydroxybutanenitrile 8b. Resolution of 4-(4-chlorobenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*R*)-**8b** in 48% yield and ee 85.0% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{8b}} = 14.5$ min, $t_{(S)\text{-}\mathbf{8b}} = 16.3$ min, hexane/EtOH 92:8, flow: 1.0 mL/min; $[\alpha]_D^{20} = +4.0$ (c 5.0, $CHCl_3$); IR (film): 3053, 2961, 2252, 1744, 1463, 1231 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 5.12–5.14 (m, 1H), 4.53 (d, $J = 4$ Hz, 2H), 3.58–3.69 (m, 2H), 2.79 (dd, $J = 5.2$ Hz, $J = 2.4$ Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.69, 135.66, 133.56, 120.07, 120.50, 116.05, 72.58, 68.90, 67.24, 20.64, 19.82; MS (70 eV, EI) m/z (%): 267 (M^+, 1), 224 (3), 207 (6), 141 (33), 125 (100), 89 (16), 43 (39).

4.2.10. (*R*)-3-Acetyloxy-4-(2,4-dichlorobenzyloxy)-3-hydroxybutanenitrile 8c. Resolution of 4-(2,4-dichlorobenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*R*)-**8c** in 47% yield and ee 90.1% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{8c}} = 9.6$ min, $t_{(S)\text{-}\mathbf{8c}} = 13.1$ min, hexane/EtOH 98:2, flow: 1.0 mL/min; $[\alpha]_D^{20} = +4.6$ (c 4.5, $CHCl_3$); IR (film): 3094, 2958, 1740, 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, $J = 2.0$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 5.14–5.19 (m, 1H), 4.62 (d, $J = 3.6$ Hz, 2H), 3.66–3.77 (m, 2H), 2.82 (dd, $J = 5.6$ Hz, $J = 3.6$ Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.74, 134.08, 133.55, 129.87, 129.09, 127.07, 116.01, 69.96, 69.44, 67.25, 20.67, 19.87; MS (70 eV, EI) m/z (%): 275 (M^+, 1), 216 (1), 147 (5), 132 (100), 117 (15), 91 (9), 43 (12).

4.2.11. (*R*)-3-Acetyloxy-4-(4-methylbenzyloxy)-3-hydroxybutanenitrile 8d. Resolution of 4-(4-methylbenzyloxy)-3-hydroxybutanenitrile by employing the above general

procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*R*)-**8d** in 50% yield and ee 81.3% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{8d}} = 13.0$ min, $t_{(S)\text{-}\mathbf{8d}} = 13.4$ min, hexane/EtOH 95:5, flow: 1.0 mL/min; $[\alpha]_D^{20} = +4.0$ (*c* 3.0, $CHCl_3$); IR (film): 3003, 2977, 2930, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 5.11–5.13 (m, 1H), 4.52 (d, $J = 5.2$ Hz, 2H), 3.55–3.66 (m, 2H), 2.78 (dd, $J = 5.6$ Hz, $J = 1.2$ Hz, 2H), 2.35 (s, 3H), 2.1 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.06, 137.85, 134.22, 129.22, 128.00, 117.40, 73.46, 71.97, 66.45, 22.47, 21.14, 19.97; MS (70 eV, EI) *m*/*z* (%): 247 (M^+,3), 204 (3), 187 (5), 121 (35), 105 (100), 77 (101), 43 (17).

4.2.12. (*R*)-3-Acetyloxy-4-(4-methoxybenzyloxy)-3-hydroxybutanenitrile 8e. Resolution of 4-(4-methoxybenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*R*)-**8e** in 50% yield and ee 82.3% as a white solid; mp 46–49 °C; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{8e}} = 16.5$ min, $t_{(S)\text{-}\mathbf{8e}} = 19.6$ min, hexane/EtOH 90:10, flow: 1.0 mL/min; $[\alpha]_D^{20} = +4.2$ (*c* 5.0, $CHCl_3$); IR (KBr): 2959, 2252, 1744, 1612, 1513, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.0$ Hz, 2H), 5.10–5.12 (m, 1H), 4.50 (d, $J = 6$ Hz, 2H), 3.80 (s, 3H), 3.54–3.65 (m, 2H), 2.77 (dd, $J = 5.2$ Hz, $J = 1.6$ Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.86, 159.44, 129.41, 129.31, 116.31, 113.88, 73.194, 68.56, 67.51, 55.22, 20.77, 19.94; MS (70 eV, EI) *m*/*z* (%): 363 (M^+, 8), 220 (1), 203 (2), 137 (29), 121 (100), 78 (8), 43 (15).

4.2.13. (*R*)-3-Acetyloxy-4-(2,4,6-trimethylbenzyloxy)-3-hydroxybutanenitrile 8f. Resolution of 4-(2,4,6-trimethylbenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*R*)-**8f** in 47% yield and ee 99.0% as a white solid; mp 80–83 °C; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{8f}} = 7.1$ min, $t_{(S)\text{-}\mathbf{8f}} = 7.4$ min, hexane/EtOH 95:5, flow: 1.0 mL/min; $[\alpha]_D^{20} = +8.0$ (*c* 3.0, $CHCl_3$); IR (KBr): 3003, 2965, 2250, 1732, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 2H), 5.08–5.11 (m, 1H), 4.57 (s, 2H), 3.59–3.70 (m, 2H), 2.75 (d, $J = 5.6$ Hz, 2H), 2.34 (s, 6H), 2.26 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.84, 137.97, 137.74, 130.29, 120.90, 116.18, 68.63, 67.53, 20.89, 20.73, 19.88, 19.43; MS (70 eV, EI) *m*/*z* (%): 275 (M^+, 1), 216 (1), 147 (5), 132 (100), 117 (15), 91 (9), 43 (12).

4.2.14. (*R*)-4-Acetyloxy-(4-fluorobenzyloxy)-3-hydroxybutanenitrile 8g. Resolution of 4-(4-fluorobenzyloxy)-3-hydroxybutanenitrile by employing the above general procedure for the resolution of 4-arylmethoxy-3-hydroxybutanenitriles **1** afforded (*R*)-**8g** in 45% yield and ee 85.0% as a colorless oil; HPLC (Daicel Chiralpak AD-H), $t_{(R)\text{-}\mathbf{8g}} = 14.4$ min, $t_{(S)\text{-}\mathbf{8g}} = 15.5$ min, hexane/EtOH 95:5, flow: 1.0 mL/min; $[\alpha]_D^{20} = +3.0$ (*c* 3.0, $CHCl_3$); IR (film): 3072, 2938, 2873, 2253, 1744, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.31 (m, 2H), 7.02–7.06 (m, 2H), 5.10–5.16 (m, 1H), 4.53 (d, $J = 4.4$ Hz, 2H), 3.57–3.68 (m, 2H), 2.79 (dd, $J = 5.2$ Hz, $J = 2.4$ Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.78, 163.57, 161.12, 132.96, 132.93, 129.46, 129.37, 116.10, 115.37, 115.14, 72.71, 68.78, 67.30, 20.65, 19.85; MS (70 eV, EI) *m*/*z* (%): 251 (M^+, 0.5), 208 (3), 191 (5), 161 (3), 125 (25), 109 (100), 43 (25).

4.3. General procedure for the preparation of 2

4.3.1. 1-Benzyloxy-2,3-epoxypropane 4. A mixture of 40% w/w aqueous sodium hydroxide (120 mL), benzyl alcohol (10.37 g, 96.0 mmol), tetrabutylammonium bromide (TBAB) (1.5 g, 4.7 mmol) was vigorously stirred at room temperature and placed in an ice bath. Epichlorohydrin (35.33 g, 384 mmol) was gradually added over 20 min. The progress of the reaction was monitored by TLC. After 24 h, the reaction was complete and the reaction mixture poured on ice/water (60 mL). The aqueous phase was extracted with diethyl ether (2×50 mL). The organic phase was washed with brine to neutrality, dried with magnesium sulfate, filtered, evaporated to dryness, and distilled to yield 1-benzyloxy-2,3-epoxypropane **4** (13.38 g, 85%) as a colorless oil with purity > 98% by GC. IR (film): 2958, 2874, 1598, 1234, 1095; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.35 (m, 5H), 4.62 (dd, $J = 23.2$ Hz, $J = 12.0$ Hz, 2H), 3.78 (dd, $J = 11.6$ Hz, $J = 3.2$ Hz, 1H), 3.46 (dd, $J = 11.6$ Hz, $J = 6.0$ Hz, 1H), 3.16–3.20 (m, 1H), 2.78–2.80 (m, 1H); 2.62 (dd, $J = 4.8$ Hz, $J = 2.4$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.91, 128.43, 127.75, 73.30, 70.81, 50.87, 44.26; MS (70 eV, EI) *m*/*z* (%): 164 (M^+, 9), 107 (72), 91 (100), 79 (29).

4.3.2. (*S*)-4-(Benzyloxy)-3-hydroxybutanenitrile 6. To a solution of **4** (3.94 g, 24 mmol) in MeOH (30 mL) were simultaneously added 30% aqueous solution of NaCN (1.76 g, 36 mmol) and 98% H_2SO_4 (1.65 g, 16.5 mmol) over 1 h at room temperature, keeping its pH strictly between 8 and 11. Then the reaction mixture was stirred at 40 °C for 15 h. The completion of the reaction was confirmed by TLC. After the reaction was completed, methanol was evaporated under reduced pressure. Water (10 mL) was added and extracted with diethylether (40 mL). The organic phase was washed with brine to neutrality, dried with magnesium sulfate, filtered, evaporated to dryness, and distilled to yield 4-(benzyloxy)-3-hydroxybutanenitrile **6** (3.67 g, 80%). Resolution of 4-benzyloxy-3-hydroxybutanenitrile by employing the above general procedure afforded (*S*)-4-benzyloxy-3-hydroxybutanenitrile **6**, ee 98.0%.

4.3.3. *tert*-Butyl (*S*)-6-(benzyloxy)-5-hydroxy-3-oxohexanoate 2. To a stirred solution of **6** (0.95 g, 5 mmol) in THF (30 mL) was added triethylamine (0.61 g, 6 mmol) at 0 °C. To the mixture was added Me_3SiCl (0.59 g, 5.5 mmol) and the mixture warmed to room temperature. After 12 h, aq 10% NH_4Cl solution was added and the organic layer separated. The concentration of the separated organic layer provided (1-(benzyloxy)-3-chloropropan-2-yloxy)trimethylsilane (1.25 g, 95%) as a colorless oil.

To a stirred suspension of commercial zinc powder (0.78 g, 12 mmol) in THF (30 mL) was added $MeSO_3H$ (0.4 mg, 0.04 mmol) at room temperature. The mixture was refluxed for 15 min and (1-(benzyloxy)-3-chloropropan-2-yloxy)tri-

methylsilane (1.05 g, 4.0 mmol) was added. Then to the mixture $BrCH_2CO_2{}^tBu$ (1.44 g, 8 mmol) was added over 1 h. After 2 h, the mixture was cooled to 0–5 °C and aq 3 M HCl (10 mL) was added dropwise. After 2 h, all the organic volatiles were removed in vacuo and the remaining mixture was extracted with EtOAc (2×30 mL) . The separated organic layer was washed with H_2O, dried with $MgSO_4$, and concentrated. Column chromatography (EtOAc/hexane, 1:4) of the residue afforded **2** (1.0 g, 81%) as a colorless oil. $[\alpha]_D^{20} = -13.6$ (c 2.0, $CHCl_3$); IR (film): 3063, 2977, 2930, 1712; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.36 (m, 5H), 4.54 (s, 2H), 4.27–4.29 (m, 1H), 3.43–3.51 (m, 2H), 3.38 (s, 2H), 2.90 (br s, 1H), 2.75 (d, $J = 5.6$ Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 202.96, 166.14, 137.80, 128.40, 127.73, 127.70, 82.14, 73.36, 73.10, 66.67, 51.16, 46.14, 27.91. MS (ESI): $m/z = 639.0$ $(2M+Na)^+$, 331.2 $(M+Na)^+$.

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