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A new and facile preparation of *tert*-butyl (3*R*,5*S*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate

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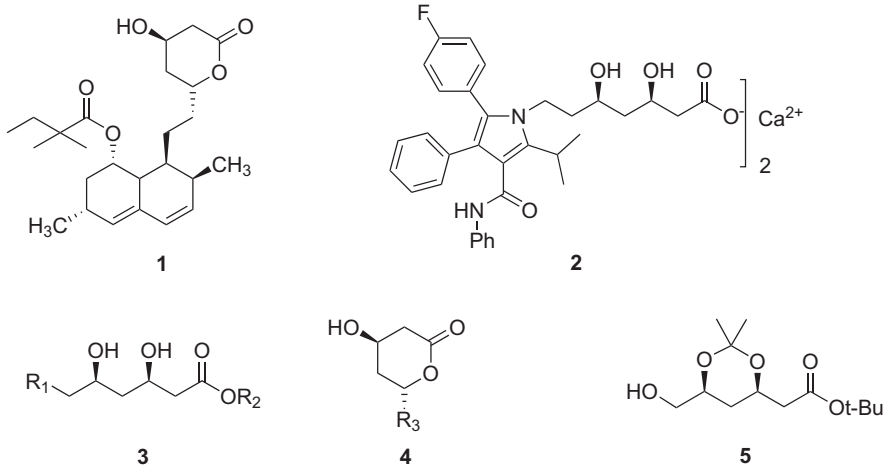
Abstract—A facile method for the preparation of *tert*-butyl (3*R*,5*S*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate is described by a chemoenzymatic approach. In this method, one hydroxyl stereocenter at C5 is obtained with a high ee value (up to 98.0%) via an enzymatic transesterification resolution of l-chloro-3-(4-methylbenzyloxy)-2-propanol. The other hydroxyl stereocenter at C3 was built with 98.0% de, by acid-hydrolysis of a 1,3-diol-acetonide *syn*/*anti*-**10**. It is noteworthy that the reduction of β-hydroxy ketone **8** with sodium borohydride can be carried out smoothly in aqueous isopropyl alcohol with a high diastereomeric ratio *syn*/*anti* ($dr_{s:a}$) of 4.0:1.

1. Introduction

HMG-CoA reductase inhibitors (statins), such as simvastatin[1] **1** and atorvastatin[2] **2** (Fig. 1), have been widely used to reduce low density lipoprotein (LDL) levels in blood with less side effects. Statins have a common structure, β,δ-dihydroxycarboxylate **3** or its closed chain analogue **4**.[3] A convenient synthesis of enantiomerically and diastereomerically pure β,δ-dihydroxycarboxylate moiety is crucial for the preparations of statins. Much research has been published regarding this topic since 1980. In most research, one chiral hydroxyl group is introduced by chiral raw materials[4] or asymmetric synthesis,[5] and the other chiral hydroxyl group can be obtained by sodium borohydride



1 2 3 4 5

Figure 1. Statins and key intermediates.

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reduction in the presence of triethylborane or diethyl(methoxy)borane as complexing agents.[6] Recently, Wolberg[7] described the stereoselective synthesis of a chiral β,δ-dihydroxy ester, which comprised of a Baker's yeast reduction and a *syn*-selective borohydride reduction. However, all these methods were all involved rather low reaction temperatures (below −60 °C), and flammable and expensive borane reagents. Reduction of the β,δ-diketo ester by the method of ruthenium catalysts[8] or biocatalysts[9] is a straightforward and flexible approach. For example, Carpentier succeeded in providing *syn*-3,5-dihydroxyesters via ruthenium-catalyzed transfer hydrogenation. The diastereomeric excess achieved was, nevertheless, limited to 80% at best.[8a] Highly enantioselective reduction of ethyl 6-benzyloxy-3,5-dioxohexanoate by the microbe of *Acinetobacter*. sp. SCI 13874 was reported, although the diastereoselectivity given was unsatisfactory (63% de).[9b]

Herein, we report a facile route to the synthesis of *tert*-butyl (3*R*,5*S*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate **5** by a chemoenzymatic approach (Scheme 1). The advantage of this approach is that two hydroxyl stereocenters (C3 and C5) could be obtained with high enantiomeric and diastereomeric purity by an enzymatic transesterification at 30 °C and diastereomer-differentiating hydrolysis at the room temperature, respectively.

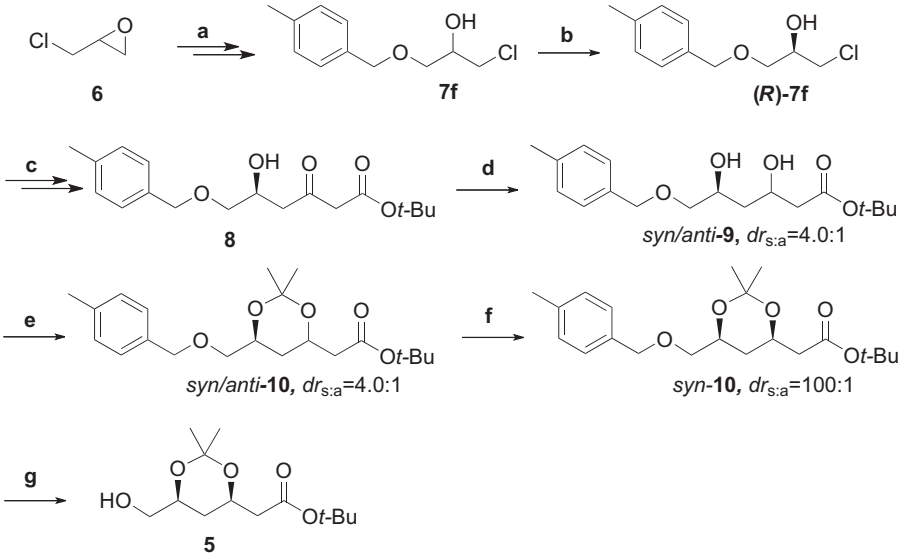
2. Results and discussion

2.1. Synthetic route

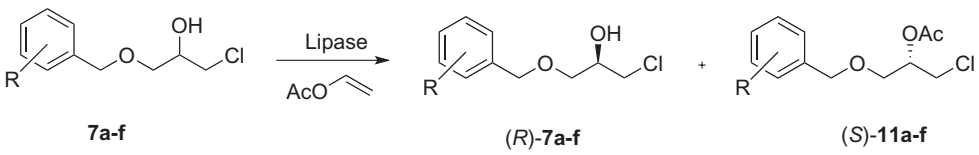
In the present synthetic strategy, commercially available racemic epichlorohydrin **6** was used as the starting material (Scheme 1). Treatment of **6** with *p*-methylbenzyl alcohol in the presence of a base gave epoxide in high yields.[10] l-Chloro-3-(4-methylbenzyloxy)-2-propanol **7f** was formed after the epoxide was treated with NH_4Cl in DMSO.[11] Compound (*R*)-**7f** was obtained by a lipase-catalyzed asymmetric esterification in the mixed solvent (*n*-hexane/acetonitrile, 3:1, v/v) with 98.0% ee (chiral HPLC analysis). β-Hydroxy ketone **8** was formed in an overall yield of 58% from (*R*)-**7f** by the addition with sodium cyanide, followed by hydroxyl group protection[12] and condensation with *tert*-butyl 2-bromoacetate.[13] Compound **8** was then reduced by sodium borohydride in aqueous isopropyl alcohol in 0 °C, giving *syn*/*anti*-**9** with $dr_{s:a}$ 4.0:1. After the acid-catalyzed protection of *syn*/*anti*-**9** with 2,2-dimethoxypropane, *syn*/*anti*-**10** was treated with aqueous acid to fulfill the selective preparation of *syn*-**10**.[14] The resulting *syn*-**10** was easily separated from *anti*-**9** by silica gel chromatography in 65% yield with $dr_{s:a}$ 100:1 (GC analysis). Finally, hydrogenolysis of the benzyl protecting group afforded **5** with 98.0% de.

2.2. Synthesis of hydroxyl stereocenters at C5

Considering our interest in building the chiral C5 of **5** by an enzymatic method, we aimed to resolve 1-chloro-3-arylmethoxy-2-propanols **7a**–**f** (Scheme 2) by lipase-catalyzed esterification and to find a suitable substrate used in the synthetic route. Although optically active 1-chloro-3-benzyloxy-2-propanol could be prepared from chiral epichlorohydrin, which could be obtained from racemic epichlorohydrin by catalytic asymmetric synthesis,[15] enzymatic methods afforded an alternative and effective way for the synthesis of chiral 1-chloro-3-benzyloxy-2-propanol. Many enzymatic methods have been reported, but most of them were based on lipase-catalyzed hydrolysis reactions.[16] In our previous report,[17] (*S*)-4-arylmethoxy-3-hydroxybutanenitriles were prepared by the method of lipase-catalyzed esterification, but only moderate enantio-



Scheme 1. Reagents and conditions: (a) (i) epichlorohydrin, 40% NaOH aq, *n*-Bu_4NBr, 10 °C, 24 h, 80%; (ii) DMSO, NH_4Cl, 75–80 °C, 8 h, 85%; (b) vinyl acetate, the lipase from *Alcaligenes* sp. (PL), a mixed solvent (*n*-hexane/acetonitrile = 3:1, v/v), 30 °C, 25 h, 48%; (c) (i) NaCN, DMSO, 70 °C, 7 h, 80%; (ii) TMSCl, Et_3N, THF, 0 °C, 12 h, 95%; (iii) $BrCH_2CO_2{}^tBu$, Zn, $MeSO_3H$, THF, reflux 4 h, then, 3 M HCl; 0 °C, 3 h, 76%; (d) $NaBH_4$, *i*-PrOH/H_2O, 0 °C, 4 h, 85%; (e) $Me_2C(OMe)_2$, cat. camphor sulfonic acid, rt, 4 h, 95%; (f) 0.50 M *p*-TsOH, CH_2Cl_2, rt, 10 h, 65%; (g) 20 atm H_2, cat. 10% Pd/C, EtOAc, 32 °C, 16 h, 90%.



Scheme 2.

meric ratios (mostly from 24 to 75) were obtained. In order to obtain better enantiomeric ratios, we continued our research to resolve **7a**–**f** (Scheme 2), since these compounds can be easily converted to 4-arylmethoxy-3-hydroxybutanenitriles by treating with sodium cyanide.

2.2.1. Lipase screening. Firstly, the resolution of racemic 1-chloro-3-benzyloxy-2-propanol **7a** was performed by employing different lipases in vinyl acetate and the results are listed in Table 1. It was observed that the reactions catalyzed by the lipase from *Alcaligenes* sp. (QL) (Table 1, entry 6) proceeded with good enantioselectivity, but with only relatively low conversions after 20 h. The uses of some enzymes resulted in low-selective reactions (Table 1, entries 1–5). The lipase from *Alcaligenes* sp. (PL) showed higher *E*-values and better reaction rates (Table 1, entry 7). Therefore, the lipase from *Alcaligenes* sp. (PL) was chosen in the following reactions.

2.2.2. Effect of solvent. Solvent variation in a lipase-catalyzed kinetic resolution is known to influence the enantioselectivity as well as the reaction rate.[18] In the present study, eight solvents were examined by using *Alcaligenes* sp. (PL) lipase (Table 2). It was observed that *i*-Pr_2O and toluene were not suitable for obtaining good enantioselectivities (Table 2, entries 1 and 2). In *n*-hexane, the reaction proceeded very quickly, but the *E*-value was unsatisfactory (Table 2, entry 3). Moreover, it took a long reaction time to reach 50% conversion in pure acetonitrile (Table 2, entries 4 and 5). To achieve high *E* value and an adequate rate, we attempted to mixed solvents (Table 2, entries 6–8). In these solvents, they both gave high enantioselectivities and good reaction rates. Therefore, the mixed solvent (*n*-hexane/acetonitrile, 3:1, v/v) was selected as the suitable reaction solvent.

2.2.3. Effect of the substituent. Here we continued to study the effects of different substituents on the aryl rings on the enzymatic resolution of the substrates, as shown in Scheme 2 and Table 3. For one reason, the structure of the substrates plays a great role on enzymatic selectivity.[19] For another, the substituted benzyl groups can be easily cleaved by the method of hydrogenolysis with catalytic Pd/C.[20]

Seven substrates **7a**–**f** were studied and the results are given in Table 3. When **7a**–**d** were chosen as the substrates, the selectivity was dropped. Better results with *E*-values higher than 200 were obtained when substrates **7e** and **7f** were catalyzed by the lipase from *Alcaligenes* sp. (PL). The lipase was particularly selective toward the (*R*)-**7f** enantiomer. At nearly 50% conversion, unreacted alcohol (*R*)-**7f** was obtained in 98% ee and the corresponding acetate (*S*)-**11f** in 96% ee. Therefore, **7f** was chosen as the intermediate in our synthetic route to build the hydroxyl stereocenter at C5 of **5**.

2.3. Synthesis of hydroxyl stereocenter at C3

In general, *syn*-dihydroxy esters were synthesized according to Prasad's method.[6] However, this method involved using flammable triethylborane or diethyl(methoxy)borane, and a very low temperature (<−60 °C). We found a facile way to prepare the protected *syn*-diol *syn*-**10** by a three-step method; first the asymmetric reduction of β-hydroxy ketone **8**; then the acetonide protection of *syn*/*anti* **9**, and lastly, the acid-catalyzed hydrolysis of *syn*/*anti*-**10** (Scheme 1).

Solvents may affect the stereochemistry of reduction with sodium borohydride.[21] Therefore, we first attempted to reduce **8** with sodium borohydride in different solvents (Table 4). It was found that in aqueous ethyl alcohol, the diastereomeric ratio ($dr_{s:a}$) of *syn*/*anti*-**9** was 2.0:1. When aqueous isopropyl alcohol was chosen,**a** higher $dr_{s:a}$ value (4.0:1) was obtained. This exciting result encouraged us to develop an effective acid-catalyzed hydrolysis method for the synthesis of *syn*-**10**.[14]

After acetonide protection of *syn*/*anti*-**9**, *syn*/*anti*-**10** was treated with aqueous acid to fulfill the selective preparation

Table 1. Transesterification of **7a** with vinyl acetate using various lipases[a]

Entry	Lipase source	Time (h)	ee (%)		Conversion (%)	*E*
			Alcohol	Acetate		
1	*Candida antarctica*	15	33.5	33.8	49.8	2.7
2	*Lipoprime.TM*	7.5	66.3	57.3	53.6	7.1
3	*Pseudomonas* sp.	15	14.3	65.2	18.0	5.5
4	*Rhizopus delemar*	15	33.7	42.9	44.0	3.4
5	*Artgribacter* sp.	7.5	51.3	71.2	41.8	9.8
6	*Alcaligenes* sp.(QL)	20	13.3	81.5	14.0	11.2
7	*Alcaligenes* sp.(PL)	7.5	66.2	78.4	47.1	16.2

[a] All reactions were carried out by stirring a mixture of **7a** (50 mg), lipase (5 mg), and vinyl acetate (2 mL) at 30 °C.

Table 2. Transesterification of **7a** with vinyl acetate in various solvents[a]

Entry	Solvent	Time (h)	ee (%)		Conversion (%)	*E*
			Alcohol	Acetate		
1	Toluene	15.0	52.3	68.5	56.8	9.0
2	*i*-Pr_2O	9.5	74.8	74.2	50.2	15.0
3	*n*-Hexane	6.5	95.0	70.7	57.3	20.9
4	Acetonitrile	31.0	44.1	98.0	33.1	153
5	Acetonitrile	60.0	70.5	96.6	41.9	123
6	*n*-Hexane/acetonitrile (1:3)	50.0	97.1	90.3	51.8	82.8
7	*n*-Hexane/acetonitrile (1:1)	35.0	96.3	89.8	51.7	74.2
8	*n*-Hexane/acetonitrile (3:1)	25.0	97.5	88.2	52.5	69.3

[a] All reactions were carried out by stirring a mixture of **7a** (40 mg), the lipase from *Alcaligenes* sp. (PL) (5 mg) and vinyl acetate (0.1 mL) in 2 mL solvent at 30 °C.

Table 3. Kinetic resolution of 1-chloro-3-arylmethoxy-2-propanols **7a–f**[a]

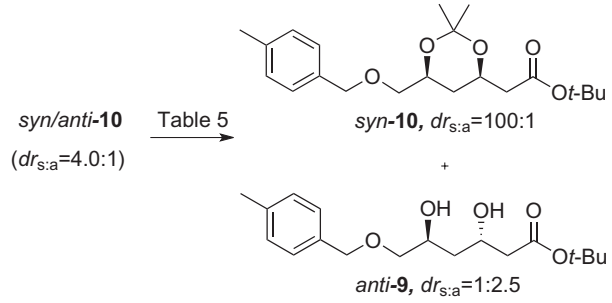
Entry	Substrate	R	Time (h)	ee (%)		Conversion (%)	*E*
				Alcohol	Acetate		
1	**7a**	H	25	97.3	88.5	52.3	70
2	**7b**	2,4-Cl	35	96.8	84.5	53.4	49
3	**7c**	4-CH_3O	20	98.2	90.1	52.1	90
4	**7d**	4-F	30	98.1	91.5	51.7	103
5	**7e**	4-Cl	30	96.7	96.0	50.1	200
6	**7f**	4-CH_3	30	98.0	96.0	50.5	226

[a] All reactions were carried out by stirring a mixture of **7a–f** (5 mmol), the lipase from *Alcaligenes* sp. (PL) (125 mg) and vinyl acetate (15 mmol) in the 50 mL mixed solvent (*n*-hexane/acetonitrile, 3:1,v/v) at 30 °C.

Table 4. Reduction of **8** in different solvents[a]

Entry	Solvent	*syn*/*anti*-**9** ($dr_{s:a}$)	Yield (%)
1	Ethyl alcohol/H_2O (4:1,v/v)	2.0:1	86
2	Methyl alcohol/H_2O (4:1,v/v)	3.2:1	87
3	Isopropyl alcohol/H_2O (4:1,v/v)	4.0:1	85

[a] 4.0 g (12.4 mmol) **8**, 0.54 g (14.6 mmol) $NaBH_4$, 0 °C, 4 h.



Scheme 3. Diastereomer-differentiating hydrolysis of *syn*/*anti*-**10**.

of *syn*-**10** (Scheme 3). In order to optimize the reaction conditions, the effects of acid species and reaction time on the reaction were examined (Table 5). It was found that the aqueous solution of *p*-TsOH (0.50 M) was most effective in this reaction.

3. Conclusion

In conclusion, an efficient asymmetric synthesis of **5** has been described by a chemoenzymatic approach. To obtain the hydroxyl stereocenter at C5, l-chloro-3-(4-methylbenzyloxy)-2-propanol **7f** was enantioselectively resolved by lipase from *Alcaligenes* sp. (PL) in the mixed solvent (*n*-hexane/acetonitrile, 3:1) with a high ee value (up to 98.0%). Another hydroxyl stereocenter at C3 was built by a three-step method; first the sodium borohydride reduction of β-hydroxy ketone **8** in aqueous isopropyl alcohol with a high diastereomeric ratio ($dr_{s:a} = 4.0:1$), then acetonide protection, followed by hydrolysis of *syn*/*anti*-**10** with *p*-TsOH solution (0.50 M). Compound *syn*-**10** was obtained in 65% yield and 98.0% de. By hydrogenolysis of the benzyl protecting group, compound **5** was obtained with high enantiomeric and diastereomeric purity (98.0% ee, 98.0% de).

4. Experimental

4.1. General

All reagents were of commercial grade with purity >98% and used as provided without further purification. *Candida antarctica* (*Novozym 435*) and *Lipoprime.TM* were purchased from Novo Nordisk; *Alcaligenes* sp. (PL), *Alcaligenes* sp. (QL) from Meito Sangyo; *Pseudomonas* sp.,

Table 5. Resolution of *syn*/*anti*-**10** in different conditions

Entry	Conditions	*syn*-**10** ($dr_{s:a}$)	Yield of *syn*-**10** (%)	*anti*-**9** ($dr_{s:a}$)	Yield of *anti*-**9** (%)
1	1 M HCl (8 mL),[a] 30 h	4.0:1	/	/	/
2	2 M HCl (3 mL),[a] 20 h	8.0:1	80	1:5.0	10
3	3 M HCl (3 mL),[a] 15 h	70.0:1	60	1:1.5	21
4	0.35 M *p*-TsOH (4 mL),[a] 20 h	9.0:1	80	1:6.0	11
5	0.50 M *p*-TsOH (4 mL),[a] 10 h	100:1	65	1:2.5	25

[a] Aqueous solution, CH_2Cl_2 (5 mL), (2 g, 7.6 mmol) *syn*/*anti*-**10** ($dr_{s:a} = 4.0:1$), 18 °C.

Rhizopus delemar from Fluka and *Artgribacter* sp. was a gift from Professor Xiufen Kou of the Institute of Microbiology, Chinese Academy of China (IMCAC). ^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. 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). Conversion and enantiomeric purities of 1-chloro-3-arylmethoxy-2-propanols were determined by HPLC analyses (solvent: *n*-hexane/EtOH); the ees of the corresponding acetates were calculated by using standard curves. Diastereomeric purities were determined by GC analyses on AT.SE-30 column (30 m × 0.20 mm × 0.33 μm). The absolute configurations of 1-chloro-3-arylmethoxy-2-propanols **7a**–**f** were assigned by preparing standards from (*R*)-epichlorohydrin.

4.2. General procedure for the resolution of 1-chloro-3-arylmethoxy-2-propanols 7a–f

Racemic **7a**–**f** (5 mmol) was dissolved in a mixed solvent (*n*-hexane/acetonitrile = 3:1, 50 mL). To this solution, the lipase from *Alcaligenes* sp. (PL) (125 mg) and vinyl acetate (15 mmol) were added successively and shaken at 30 °C for 20–30 h. After about 50% conversion was reached (monitored by HPLC), the enzyme was filtered and washed with ethyl acetate (30 mL). The solvent was evaporated and purification was accomplished by chromatography on silica gel, employing EtOAc/hexane (1:4) as the eluent to afford the corresponding acetate (*S*)-**11a**–**f**, followed by the unreacted alcohol (*R*)-**7a**–**f**.

4.2.1. (*R*)-1-Chloro-3-benzyloxy-2-propanol (*R*)-7a. This compound was obtained as a colorless oil in 43% yield and 97.3% ee; $[\alpha]_D^{20} = +1.5$ (*c* 3.3, $CHCl_3$); HPLC (Daicel Chiralpak AD-H), $t_{(S\text{-}\mathbf{7a})} = 12.0$ min, $t_{(R\text{-}\mathbf{7a})} = 12.8$ min, hexane/EtOH 92:8, flow: 0.9 mL/min; ^1H NMR (400 Hz, $CDCl_3$): δ 7.30–7.38 (m, 5H), 4.56 (s, 2H), 3.97–4.02 (m, 1H), 3.58–3.67 (m, 2H), 3.59 (d, $J = 4.0$ Hz, 2H), 2.59 (br s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): 137.5, 128.4, 127.8, 127.7, 73.43, 70.8, 70.2, 45.9; MS (70 eV, EI) *m*/*z* (%): 200/202 (M^+, 15/5), 126/128 (6/2), 107 (10), 91 (100), 65 (12).

4.2.2. (*R*)-1-Chloro-3-(2,4-dichlorobenzyloxy)-2-propanol (*R*)-7b. This compound was obtained as a colorless oil in 44% yield and 96.8% ee; $[\alpha]_D^{20} = +2.2$ (*c* 3.4, $CHCl_3$); HPLC (Daicel Chiralpak AD-H), $t_{(S\text{-}\mathbf{7b})} = 9.2$ min, $t_{(R\text{-}\mathbf{7b})} = 10.1$ min, hexane/EtOH 90:10, flow: 1.0 mL/min; ^1H NMR (400 Hz, $CDCl_3$): δ 7.27–7.36 (m, 3H), 4.61 (s, 2H), 4.01–4.05 (m, 1H), 3.60–3.70 (m, 4H), 2.51 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): 134.1, 133.9, 133.7, 129.9, 129.2, 127.1, 71.3, 70.2, 70.0, 46.0; MS (70 eV, EI) *m*/*z* (%): 268/270 (M^+, 5/5), 194/196 (4/4), 159/161 (100/66), 123 (12), 89 (13).

4.2.3. (*R*)-1-Chloro-3-(4-methyoxybenzyloxy)-2-propanol (*R*)-7c. This compound was obtained as a yellow oil in 45% yield and 98.2% ee; $[\alpha]_D^{20} = +1.9$ (*c* 3.9, $CHCl_3$); HPLC (Daicel Chiralpak AD-H), $t_{(S\text{-}\mathbf{7c})} = 82.6$ min, $t_{(R\text{-}\mathbf{7c})} = 87.9$ min, hexane/EtOH 99:1, flow: 1.0 mL/min; ^1H NMR (400 Hz, $CDCl_3$): δ 7.25 (d, $J = 7.2$ Hz, 2H), 6.89 (d, $J = 8.4$ Hz, 2H), 4.49 (s, 2H), 3.96–3.99 (m, 1H), 3.57–3.65 (m, 2H), 3.55 (d, $J = 5.2$ Hz, 2H), 3.00 (s, 3H), 2.56 (br s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): 159.2, 129.6, 129.3, 113.7, 73.07, 70.4, 70.17, 55.1, 45.9; MS (70 eV, EI) *m*/*z* (%): 230/232 (M^+, 15/5), 137 (10), 121 (100), 91 (5), 78 (10).

4.2.4. (*R*)-1-Chloro-3-(4-fluorobenzyloxy)-2-propanol (*R*)-7f. This compound was obtained as a yellow oil in 45% yield and 98.1% ee; $[\alpha]_D^{20} = +2.4$ (*c* 1.8, $CHCl_3$); HPLC (Daicel Chiralpak AD-H), $t_{(S\text{-}\mathbf{7d})} = 17.1$ min, $t_{(R\text{-}\mathbf{7d})} = 18.2$ min, hexane/EtOH 93:7, flow: 1.0 mL/min; ^1H NMR (400 Hz, $CDCl_3$): δ 7.27–7.31 (m, 2H), 7.02–7.06 (m, 2H), 4.52 (s, 2H), 3.99–4.01 (m, 1H), 3.58–3.67 (m, 2H), 3.59 (d, $J = 5.2$ Hz, 2H), 2.51 (br s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): 163.6, 161.2, 133.4, 133.3, 129.6, 129.5, 115.5, 115.2, 72.8, 70.8, 70.2, 45.9; MS (70 eV, EI) *m*/*z* (%): 218 (M^+, 7), 165 (1), 144/146 (4/1.3), 125 (10), 109 (100), 83 (10).

4.2.5. (*R*)-1-Chloro-3-(4-chlorobenzyloxy)-2-propanol (*R*)-7e. This compound was obtained as a colorless oil in 47% yield and 96.7% ee; $[\alpha]_D^{20} = +2.2$ (*c* 3.2, $CHCl_3$); HPLC (Daicel Chiralpak AD-H), $t_{(S\text{-}\mathbf{7e})} = 18.8$ min, $t_{(R\text{-}\mathbf{7e})} = 19.6$ min, hexane/EtOH 95:5, flow: 1.0 mL/min; ^1H NMR (400 Hz, $CDCl_3$): δ 7.33 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 4.52 (s, 2H), 3.98–4.01 (m, 1H), 3.59–3.67 (m, 2H), 3.58 (d, $J = 4.8$ Hz, 2H), 2.57 (br s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): 136.0, 133.5, 128.9, 128.5, 72.6, 70.8, 70.1, 45.9; MS (70 eV, EI) *m*/*z* (%): 234/236 (M^+, 10/6), 160 (7/4), 141 (14), 125/127 (100/34), 89 (15).

4.2.6. (*R*)-l-Chloro-3-(4-methylbenzyloxy)-2-propanol (*R*)-7f. This compound was obtained as a colorless oil in 47% yield and 98.0% ee; $[\alpha]_D^{20} = +2.0$ (*c* 3.5, $CHCl_3$); HPLC (Daicel Chiralpak AD-H), $t_{(S\text{-}\mathbf{7f})} = 21.9$ min, $t_{(R\text{-}\mathbf{7f})} = 23.4$ min, hexane/EtOH 92:8, flow: 0.9 mL/min; ^1H NMR (400 Hz, $CDCl_3$): δ 7.23 (d, $J = 8.0$ Hz, 2H), 7.17 (d,

$J = 7.6$ Hz, 2H), 4.52 (s, 2H), 3.96–4.01 (m, 1H), 3.58–3.67 (m, 2H), 3.58 (d, $J = 4.4$ Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): 137.6, 134.4, 129.1, 127.8, 73.3, 70.6, 70.2, 45.9, 21.1; MS (70 eV, EI) *m/z* (%): 214 (M^+, 11), 199 (2), 140/142 (5/1.7), 121 (9), 105 (100), 77 (10).

4.2.7. (*S*)-2-Acetoxy-1-chloro-3-benzyloxy-2-propanol (*S*)-11a. This compound was obtained as a colorless oil in 42% yield and 88.5% ee; $[\alpha]_D^{20} = +7.3$ (*c* 3.3, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.29–7.37 (m, 5H), 5.15–5.17 (m, 1H), 4.56 (d, $J = 4.8$ Hz, 2H), 3.67–3.78 (m, 2H), 3.64–3.66 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): 170.0, 137.5, 128.3, 127.7, 127.6, 73.3, 71.58, 68.1, 42.7; MS (70 eV, EI) *m/z* (%): 242 (M^+, 1), 207 (5), 147 (10), 135/137 (18/6), 107 (19), 91 (100), 77 (4).

4.2.8. (*S*)-2-Acetoxy-1-chloro-3-(2,4-dichlorobenzyloxy)-2-propanol (*S*)-11b. This compound was obtained as a colorless oil in 43% yield and 84.5% ee; $[\alpha]_D^{20} = +6.8$ (*c* 3.4, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.26–7.38 (m, 3H), 5.16–5.21 (m, 1H), 4.60 (d, $J = 4.0$ Hz, 2H), 3.67–3.8 (m, 4H), 2.11 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): 170.0, 133.9, 133.9, 133.4, 129.7, 129.0, 127.0, 71.4, 69.8, 68.7, 42.5, 42.2, 20.8; MS (70 eV, EI) *m/z* (%): 311 (M^+, 1), 275/277 (7/5), 267/269 (5/5), 174 (31), 159 (100), 123 (13).

4.2.9. (*S*)-2-Acetoxy-1-chloro-3-(4-methyoxybenzyloxy)-2-propanol (*S*)-11c. This compound was obtained as a colorless oil in 45% yield and 90.1% ee; $[\alpha]_D^{20} = +8.8$ (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.25 (d, $J = 8.0$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 5.13–5.15 (m, 1H), 4.48 (d, $J = 6.4$ Hz, 2H), 3.80 (s, 3H), 3.64–3.76 (m, 2H), 3.60–3.62 (m, 2H), 2.09 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): 170.1, 159.3, 129.6, 129.2, 113.7, 73.0, 71.6, 67.7, 55.1, 42.7, 20.8; MS (70 eV, EI) *m/z* (%): 272/274 (M^+, 7/2.5), 229 (2), 177 (4), 137 (50), 121 (100), 78 (11).

4.2.10. (*S*)-2-Acetoxy-1-chloro-3-(4-fluorobenzyloxy)-2-propanol (*S*)-11d. This compound was obtained as a colorless oil in 45% yield and 91.5% ee; $[\alpha]_D^{20} = +8.4$ (*c* 3.7, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.27–7.30 (m, 2H), 7.01–7.05 (m, 2H), 5.14–5.17 (m, 1H), 4.52 (d, $J = 5.6$ Hz, 2H), 3.66–3.76 (m, 2H), 3.63–3.65 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): 170.1, 163.5, 161.1, 133.3, 133.29, 129.4, 129.3, 115.3, 115.1, 72.6, 71.5, 68.0, 42.5, 20.8; MS (70 eV, EI) *m/z* (%): 260 (M^+, 0.5), 225 (4), 207 (6), 167 (7), 147 (11), 135 (24), 109 (55), 91 (100).

4.2.11. (*S*)-2-Acetoxy-1-chloro-3-(4-chlorobenzyloxy)-2-propanol (*S*)-11e. This compound was obtained as a colorless oil in 47% yield and 96.0% ee; $[\alpha]_D^{20} = +8.9$ (*c* 3.1, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.33 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 5.14–5.17 (m, 1H), 4.52 (d, $J = 5.2$ Hz, 2H), 3.67–3.77 (m, 2H), 3.63–3.66 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): 170.1, 136.1, 133.5, 128.9, 128.5, 72.5, 71.5, 68.2, 42.6, 20.8; MS (70 eV, EI) *m/z* (%): 276 (M^+, 1), 241 (10), 181 (13), 140 (39), 125/127 (100/34), 89 (16).

4.2.12. (*S*)-2-Acetoxy-l-chloro-3-(4-methylbenzyloxy)-2-propanol (*S*)-11f. This compound was obtained as a colorless oil in 48% yield and 96.0% ee; $[\alpha]_D^{20} = +8.7$ (*c* 2.2, $CHCl_3$); δ 7.23 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 5.15–5.58 (m, 1H), 4.52 (d, $J = 5.2$ Hz, 2H), 3.66–3.77 (m, 2H), 3.62–3.65 (m, 2H), 2.35 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): 170.1, 137.5, 134.5, 129.0, 127.7, 73.2, 71.6, 67.9, 42.7, 21.1, 20.8; MS (70 eV, EI) *m/z* (%): 256 (M^+, 4), 221 (3), 161 (6), 135/137 (18/6), 121 (37), 105 (100), 77 (9).

4.3. Experimental procedure for the synthesis of 5

4.3.1. (*R*)-1-(4-methylbenzyloxy)-3-chloro-2-propanol (*R*)-7f. A mixture of DMSO (100 mL), NH_4Cl (42.8 g, 800.0 mmol), 1-(4-methybenzyloxy)-2,3-epoxypropane (71.2 g, 400.0 mmol) prepared according to the literature method[10] was vigorously stirred at room temperature and then heated at 75–80 °C for 8 h. After the reaction was complete, water (60 mL) was added and the mixture was extracted with ethyl acetate (2×100 mL). The organic phase was separated, dried with magnesium sulfate and distilled to yield **7f** as a colorless oil (72.8 g, 85%). Resolution of **7f** (40.0 g, 18.7 mmol) by employing the above general procedure **4.2** afforded (*R*)-**7f** (18.8 g, 47% yield, 98.0% ee).

4.3.2. *tert*-Butyl (*S*)-6-(4-methybenzyloxy)-5-hydroxy-3-oxohexanoate 8. DMSO (60 mL), (*R*)-**7f** (18.0 g, 87.8 mmol) and sodium cyanide (5.2 g, 106.1 mmol) were added to a 250 mL flask and heated at 70 °C for 7 h. After the reaction was complete, water (60 mL) and ethyl acetate (2×100 mL) were added. The organic phase was separated, dried, and distilled. The residue was purified by chromatography on silica gel to afford (*S*)-4-(4-methybenzyloxy)-3-hydroxybutanenitrile as a colorless oil (14.4 g, 80%).

To a stirred solution of (*S*)-4-(4-methybenzyloxy)-3-hydroxybutanenitrile (12.4 g, 60.5 mmol) in THF (100 mL) was added triethylamine (6.8 g, 67.3 mmol) at 0 °C. To the mixture was added Me_3SiCl (6.8 g, 63.0 mmol). The reaction mixture was stirred at rt for 12 h, then filtered, and evaporated to give (*S*)-4-(4-methybenzyloxy)-3-(trimethylsilylhydroxy)butanenitrile (15.8 g, 95%) as a colorless oil.

To a stirred suspension of commercial zinc powder (7.8 g, 120.0 mmol) in THF (60 mL) was added $MeSO_3H$ (4 mg, 0.4 mmol) and refluxed for 15 min. To the mixture (*S*)-4-(4-methybenzyloxy)-3-(trimethylsilylhydroxy)butanenitrile (15.8 g, 57.0 mmol) and $BrCH_2CO_2{}^tBu$ (20.6 g, 114.4 mmol) were added. The reaction mixture was refluxed for 4 h, then cooled to 0–5 °C after which 3 M HCl (200 mL) was added dropwise. After 3 h, ethyl acetate (120 mL) was added and the organic layer washed with saturated $NaHCO_3$ (50 mL). The separated organic layer was dried and concentrated. Column chromatography on silica gel (EtOAc/hexane, 1:4) of the residue afforded **8** (13.4 g, 76%) as a colorless oil. $[\alpha]_D^{20} = -13.0$ (*c* 2.5, $CHCl_3$); IR (film): 3442, 3063, 2978, 2926, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 7.6$ Hz, 2H), 4.51 (s, 2H), 4.28 (m, 1H), 3.41–3.50 (m, 2H), 3.39 (s, 2H), 2.97 (br s, 1H), 2.75 (d, $J = 6.4$ Hz, 2H), 2.35 (s, 3 H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.0, 166.2, 137.5, 134.7, 129.1, 127.8, 82.1,

73.2, 72.9, 66.6, 51.1, 46.1, 27.9, 21.1; MS (ESI): 666.4 $(2M+Na)^+$, 345.0 $(M+Na)^+$.

4.3.3. *tert*-Butyl (5*S*)-6-(4-methybenzyloxy)-3,5-dihydroxyhexanoate *syn*/*anti*-9. Compound **8** (11.0 g, 34.2 mmol), isopropanol (60 mL), and H_2O (10 mL) were added to a 150 mL flask and cooled to 0 °C. $NaBH_4$ (1.5 g, 40.5 mmol) dissolved in H_2O (5 mL) solution was added dropwise for 30 min. After 4 h, 3 M HCl was added to neutrality. Isopropanol was removed and the remaining mixture was extracted with ethyl acetate (2×60 mL). The separated organic layer was dried with magnesium sulfate and concentrated to yield *syn*/*anti*-**9** (9.4 g, 85%) as a colorless oil; $dr_{s:a} = 4.0{:}1$. The value of $dr_{s:a}$ was determined by GC after **9** was converted to **10**; IR (film): 3445, 1731, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 7.6$ Hz, 2H), 4.51 (s, 2H), 4.23–4.29 (m, 1H), 4.06–4.12 (m, 1H), 3.61, 3.90 (br s, 1H), 3.46–3.51 (m, 1H), 3.37–3.43 (m, 1H), 2.11, 3.05 (br s, 1H), 2.42 (d, $J = 6.4$ Hz, 2H), 2.35 (s, 3H), 1.64 (dt, $J = 16.0$ Hz, 4.8 Hz, 1H), 1.46 (s, 9H); MS (ESI): 347 $(M+Na)^+$.

4.3.4. *tert*-Butyl (5*S*)-6-(4-methybenzyloxy)-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate *syn*/*anti*-10. To a stirred solution of *syn*/*anti*-**9** (9.0 g, 27.8 mmol) in 2,2-dimethoxypropane (20 mL) was added camphorsulfonic acid (0.1 g). The mixture was stirred for 4 h at room temperature. After the reaction was completed, the mixture washed with saturated sodium hydrogen carbonate to neutrality. The organic phase was dried with magnesium sulfate, filtered, and distilled to yield *syn*/*anti*-**9** (9.6 g, 95%, $dr_{s:a} = 4.0{:}1$). GC (AT.SE-30), $t_{anti\text{-}(3R,5R)\text{-}\mathbf{10}} = 7.9$ min, $t_{syn\text{-}(3R,5S)\text{-}\mathbf{10}} = 8.1$ min, 180 °C isothermal.

4.3.5. *tert*-Butyl (3*R*,5*S*)-6-(4-methybenzyloxy)-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate *syn*-10. Compound *syn*/*anti*-**9** (5.0 g; 13.7 mmol) was added to a solution of *p*-TsOH (0.68 g; 4.0 mmol) in CH_2Cl_2 (10 mL) and water (8 mL). The reaction mixture was stirred at 18 °C for 10 h, then washed with saturated sodium hydrogen carbonate (20 mL), extracted with CH_2Cl_2 (2×20 mL). The separated organic layer was dried with magnesium sulfate and concentrated. The residue was purified by chromatography on silica gel with EtOAc/hexane (1:4) as the eluent to afford the corresponding *syn*-**10** (3.3 g, 65% yield, 98.0% de) as a colorless oil; $[\alpha]_D^{20} = -6.5$ (*c* 2.0, $CHCl_3$); IR (film): 1731, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, $J = 7.6$ Hz, 2H), 7.16 (d, $J = 7.6$ Hz, 2H), 4.58 (dd, $J = 23.6$ Hz, 12.8 Hz, 2H), 4.25–4.32 (m, 1H), 4.08–4.14 (m, 1H), 3.51 (dd, $J = 10.0$ Hz, 6.0 Hz, 1H), 3.38 (dd, $J = 10.0$ Hz, 4.8 Hz, 1H), 2.47 (dd, $J = 15.6$ Hz, 7.2 Hz, 1H), 2.35 (s, 3H), 2.34 (dd, $J = 15.2$ Hz, 6.0 Hz, 1H), 1.63 (dt, $J = 12.8$ Hz, 2.8 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 9H), 1.40 (s, 3H), 1.29 (dd, $J = 24.0$ Hz, 12.0 Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): δ 170.1, 137.2, 135.0, 128.9, 127.8, 98.7, 80.4, 73.18, 73.16, 68.3, 65.8, 42.6, 33.2, 30.0, 28.0, 21.1, 19.6; MS (70 eV, EI) *m*/*z* (%): 365 (M^+, trace), 349 (6), 307 (4), 291 (3), 249 (23), 190 (34), 105 (100), 77 (4), 57 (14).

4.3.6. *tert*-Butyl (3*R*,5*S*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate 5. Pd/C (10%, 0.8 g) was added to a solution of *syn*-**10** (3.0 g, 8.2 mmol) in EtOAc (70 mL) contained in a 250 mL autoclave. The autoclave was purged with H_2 and then filled with H_2 (20 atm). The mixture was stirred at constant pressure with heating at 32 °C inner temperature for 16 h. TLC (EtOAc/hexane, 1:4) indicated quantitative clean reaction. The catalyst was filtered and the solvent was evaporated. The residue was dried to give a colorless oil **5** (1.9 g, 90%). $[\alpha]_D^{20} = +9.9$ (*c* 2.0, $CHCl_3$); −6.8 (*c* 1.5, MeOH), {lit. $[\alpha]_D^{20} = -7.57$ (*c* 2.0, MeOH)[5d]}; IR (film): 3446, 1731, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.19–4.26 (m, 1H), 3.91–3.97 (m, 1H), 3.54 (dd, $J = 11.6$ Hz, 3.6 Hz, 1H), 3.46 (dd, $J = 11.6$ Hz, 6.4 Hz, 1H), 2.56 (br s, 1H), 2.40 (dd, $J = 15.2$ Hz, 7.2 Hz, 1H), 2.28 (dd, $J = 15.2$ Hz, 6.0 Hz, 1H), 1.46 (dt, $J = 12.8$ Hz, 2.4 Hz, 1H), 1.41 (s, 3H), 1.38 (s, 9H), 1.32 (s, 3H), 1.29 (d, $J = 12.4$ Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): δ 170.0, 98.7, 80.5, 69.5, 65.68, 65.64, 42.5, 31.7, 29.8, 27.9, 19.6; MS (70 eV, EI) *m*/*z* (%): 260 (M^+, trace), 245 (3), 229 (1), 189 (100), 173 (34), 147 (6), 129 (93), 111 (81), 87 (24), 57 (66).

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