Asymmetric Reductive Aldol-Type Reaction with Carbonyl Compounds Using Dialkyl Tartrate as a Chiral Ligand

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An asymmetric reductive aldol-type reaction of *α*,*β*-unsaturated esters with carbonyl compounds using Rh catalyst and Et_2Zn was investigated. A chiral zinc complex from *α*,*β*-unsaturated ester was easily generated as the key intermediate from Et_2Zn and Wilkinson's catalyst with diisopropyl L-(+)-tartrate to give a variety of enantioenriched *β*-hydroxy esters. The reaction was also applied to the intramolecular reductive aldol cyclization.

Key words asymmetric reaction; reductive aldol-type reaction; aldol-type cyclization; $RhCl(PPh_3)_3$; biszinc–tartrate complex

Enantiomerically pure *β*-hydroxy esters are frequently found in bioactive natural products, for example, erythromycin.[1] Furthermore, *β*-hydroxy esters are useful key intermediate to synthesize versatile building blocks of natural products, for example, (+)-tedanolide[2] and (+)-discodermolide[3] (Fig. 1).

Reductive aldol reaction is understood as a sequential reaction involving conjugate reduction of *α*,*β*-unsaturated esters and subsequent aldol reaction of the ester enolate with various carbonyl compounds using metals such as rhodium,[4,5] cobalt,[6–10] and copper[11,12] catalysts. The reductive aldol reaction is one of the most useful tools in organic chemistry because it provides direct access to synthetic *β*-hydroxy esters. Furthermore, the asymmetric variants of ligand-based, auxiliary-based, and catalyst-based reactions have proven to be reliable routes to homochiral aldol adducts.[13–17] On the other hand, Honda and his co-workers reported a Rh catalyzed Reformatsky-type reaction.[18] Based on their report, we reported Reformatsky–Honda reaction using $BrCF_2COOEt$.[19] Furthermore, we recetnly reported a reductive aldol-type reaction of *α*,*β*-unsaturated esters with aldehydes and ketones to give the corresponding products in good to excellent yields by using $RhCl(PPh_3)_3$ and Et_2Zn (Reformatsky–Honda reaction condition)[20,21] (Chart 1). We herein report an asymmetric reductive aldol-type reaction with various aldehydes and ketones.[14,22,23]

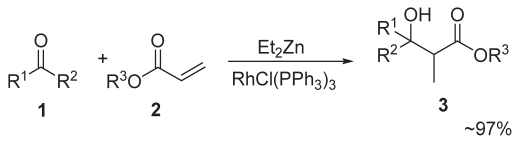

Chart 1. Rh-Catalyzed Reductive Aldol-Type Reaction with Various Carbonyl Compounds

Results and Discussion

First, we conducted a series of reactions to determine the most effective chiral ligand for the asymmetric reductive aldol-type reaction using benzaldehyde (**1a**) and methyl acrylate (**2a**) (Table 1). **1a** and **2a** were treated with Et_2Zn (3.6 eq.) in the presence of $RhCl(PPh_3)_3$ and a ligand to give *β*-hydroxy esters (**3a**) (method A). Using amino alcohol ligands, the desired product **3a** was obtained in moderate to good yield, but poor enantioselectivities were observed, as shown in entries 1–3. Use of diamine, diamide or diol ligands did not give the product at all (entries 4–8). However, use of diisopropyl L-(+)-tartrate **L9** gave the desired reductive aldol-type product in good yield with moderate enantioselectivity for the *anti*-diastereomer (entry 9). Furthermore, once a chiral zinc complex was formed from Et_2Zn with a ligand then used it for the reaction, the enantioselectivity was slightly improved (entry 10, method B). On the other hand, using 2.4 equivalents of Et_2Zn did not give the product at all (entry 11). A further four tartrates **L10**–**13** were also investigated but these did not improve the enantioselectivity and were difficult to separate from the product (entries 12–15). The reaction conditions were found to be optimal using **L9** (Table 1, entry 10).

The scope and limitations of the reaction were examined with various carbonyl compounds, and the results are summarized in Table 2. The reactions proceeded smoothly and gave

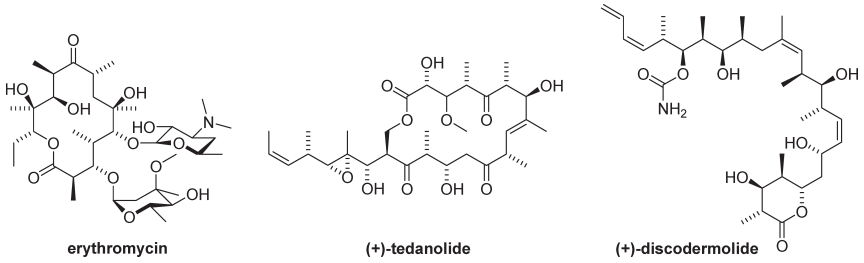

Fig. 1. Some Natural Products That Synthesized from *β*-Hydroxy Esters

The authors declare no conflict of interest.

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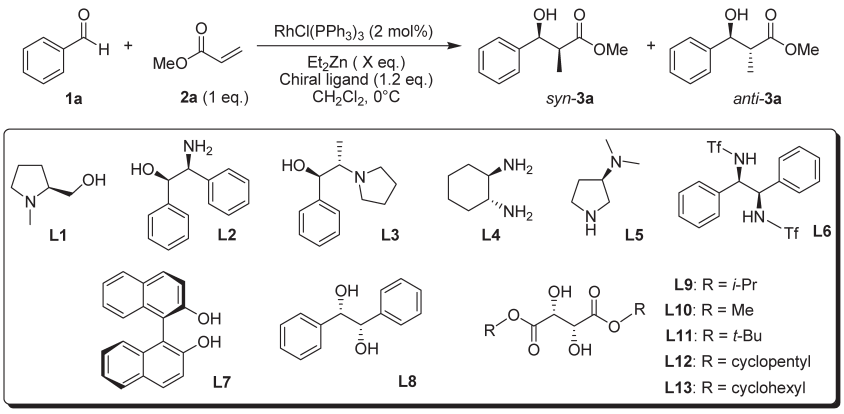
Table 1. Optimization of Reaction Conditions



Entry	Chiral ligand	Et_2Zn (*X* eq.)	Condition[a,b]	Time (h)	Yield (%)[c]		e.e. (%)[d]	
					syn-**3a**	*anti*-**3a**	*syn*-**3a**	*anti*-**3a**
1	**L1**	3.6	Method A	1	32	ND	0	ND
2	**L2**	3.6	Method A	2	35	53	0	3
3	**L3**	3.6	Method A	3	32	62	4	6
4	**L4**	3.6	Method A	5	ND	ND	—	—
5	**L5**	3.6	Method A	3	ND	ND	—	—
6	**L6**	3.6	Method A	3	ND	ND	—	—
7	**L7**	3.6	Method A	1	ND	ND	—	—
8	**L8**	3.6	Method A	1	ND	ND	—	—
9	**L9**	3.6	Method A	1	38	46	7	50
10	**L9**	3.6	Method B	1	40	55	0	64
11	**L9**	2.4	Method B	1	ND	ND	—	—
12	**L10**	3.6	Method B	5	ND	ND	—	—
13	**L11**	3.6	Method B	3	33	33	8	−3
14	**L12**	3.6	Method B	3	42	21	−1	30
15	**L13**	3.6	Method B	1	50	43	−28	53

a) Method A: to a solution of $RhCl(PPh_3)_3$ (2 mol%) in CH_2Cl_2 was added ligand (1.2 eq.), benzaldehyde (**1**; 1 eq.) and *α*,*β*-unsaturated ester (**2**; 1.2 eq.) at 0°C. Then Et_2Zn (3.6 eq.) was slowly added, and stirred for the time.
b) Method B: to a solution of $RhCl(PPh_3)_3$ (2 mol%) in CH_2Cl_2 was added ligand (1.2 eq.), and Et_2Zn (1.2 eq.) at 0°C and stirred for 15 min. Benzaldehyde (**1**; 1 eq.) and *α*,*β*-unsaturated ester (**2**; 1.2 eq.) was added to the mixture, and then Et_2Zn (2.4 eq. or 1.2 eq.) was slowly added and stirred for the time.
c) Isolated yield. *d*) Detected by chiral HPLC.

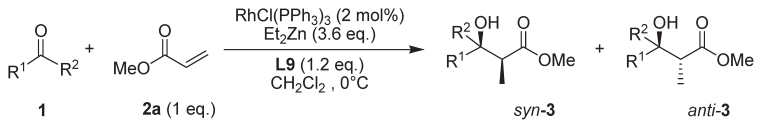
the desired products in good to excellent yields in all cases, although they showed low diastereoselectivity. In the reaction with aromatic aldehydes, the *anti*-form products formed in moderate enantioselectivities (Table 2, entries 1–6). Electron-withdrawing groups decreased the enantioselectivity with the nonasymmetric background reaction being predominant (entries 2–4). It is interesting that the reaction gave the corresponding products in good yields even if ketones were used as substrates (entries 7–9). Cyclohexanone and acetophenone offered moderate enantioselectivities, while benzophenone (entry 8) did not.

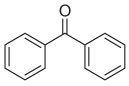
We also examined an intramolecular reductive aldol cyclization to improve diastereoselectivity.[24] Using a model substrate **4**, the reaction proceeded smoothly to give the desired product in moderate yield with slight enantioselectivity, although diastereoselectivity was not improved (Chart 2). However, this result confirmed that the approach would provide a promising route to such a cyclic compound, because a number of studies have reported on the enantioselective reductive aldol cyclization.[13,25,26]

On the basis of previous results and various examinations of reaction conditions,[20,21] we proposed the following mechanism (Fig. 2). $RhCl(PPh_3)_3$ reacted with Et_2Zn to give a rhodium hydride complex **7** *via* the elimination of ethylene from an ethyl rhodium complex **6**. 1,4-Reduction of *α*,*β*-unsaturated ester **1** by **7** to form rhodium enolate **8** is followed by transmetalation with a chiral zinc–tartrate complex **9** to give a chiral zinc intermediate (***Int A****), which then reacts with the carbonyl compound to give the corresponding *β*-hydroxy esters **3** with enantioselectivity. Inomata and coworkers reported reactions that used a combination of organozinc reagent and tartrate, and they proposed the generation of a biszinc–ligand complex.[27–29] A similar biszinc–tartrate complex **9** would have been generated *in situ* in our experiment, as shown in Fig. 3, and would have been involved in generation of the chiral key intermediate (***Int A****). In our method, the fact that the reaction needed more than three molar equivalents of Et_2Zn strongly supports this mechanism.

In conclusion, we investigated an asymmetric reductive aldol-type reaction with various aldehydes and ketones under Reformatsky–Honda reaction conditions. The reaction gave the corresponding products in good to excellent yields with moderate enantioselectivities. This result is significant in that we were able to achieve the enantioselective intramolecular reductive aldol cyclization. We are currently examining ways to further improve the enantioselectivity of the reductive aldol

Table 2. Scope and Limitations of Asymmetric Reductive Aldol-Type Reaction



Entry	Substrate 1		Time (h)	Yield (%)[a]		e.e. (%)[b]	
				syn-**3**	*anti*-**3**	*syn*-**3**	*anti*-**3**
1	X=H	**3a**	1	40	55	0	64
2	X=CF_3	**3b**	3	36	48	4	34
3	X=COOMe	**3c**	7	39	52	7	38
4	X=Cl	**3d**	3	31	42	5	45
5	X=OMe	**3e**	1	40	57	6	56
6	X=Me	**3f**	1	39	54	6	51
7		**3g**	1	78		56	
8		**3h**	5	61		7	
9		**3i**	1	17	65	14	40

a) Isolated yield. *b*) Detected by chiral HPLC.

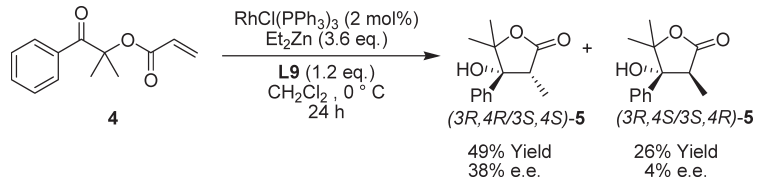


Chart 2. Intramolecular Reductive Aldol Cyclization

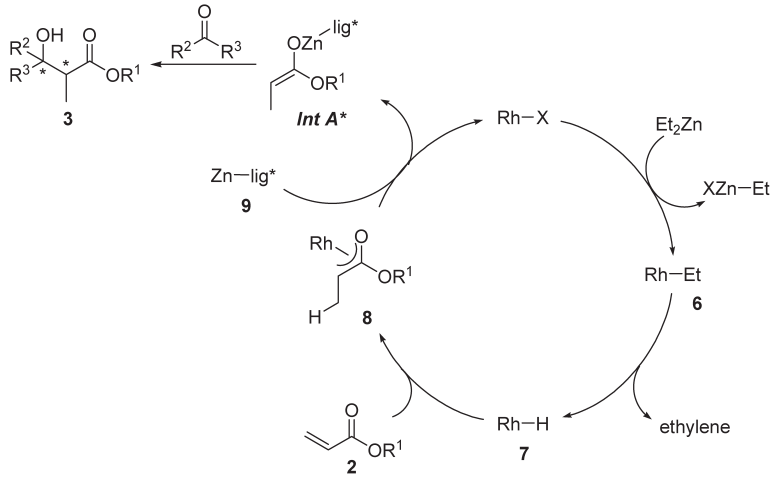


Fig. 2. Proposed Reaction Mechanism

cyclization reaction.

Experimental

General Information ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JNM-GX400 spectrometer. ^{19}F-NMR spectra were recorded on Hitachi FT-NMR R-90H spectrometer. Chemical shifts of ^{1}H-NMR and ^{13}C-NMR are reported in ppm from tetramethylsilane (TMS) as an internal standard at 0 ppm. Chemical shifts of ^{19}F-NMR are reported in ppm from benzotrifluoride (BTF) as an internal standard at 0 ppm. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz). Mass spectra were obtained on JEOL JMS-700T spectrometer.

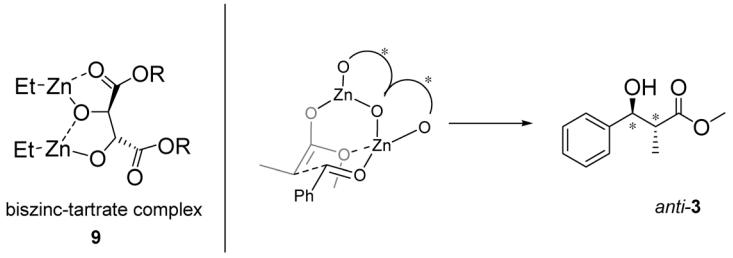


Fig. 3. Biszinc–Tartrate Complex and the Model for Stereochemical Outcome

IR spectra were recorded on JASCO FT/IR-410 spectrophotometer. Melting points were measured on Yanagimoto micro melting point apparatus MP-S3 without correction. Chiral HPLC analysis was performed on a Shimadzu analytical HPLC system with commercial Chiralcel columns (made in Daicel Chemical Ind., Ltd.). Peak areas were calculated on Hitachi D-2500 Chromato-Integrator. Optical rotations were recorded on a JASCO P1020.

Materials Dichloromethane (CH_2Cl_2) was distilled over phosphorus pentoxide just before use. All commercially available liquid aldehyde or ketone were distilled just before use. Other commercially available reagents were used without further purification. All experiments were carried out under argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

Typical Procedure for Asymmetric Reductive Aldol-Type Reaction Method A: To a solution of $RhCl(PPh_3)_3$ (2 mol%) in CH_2Cl_2 (1.25 mL) was added diisopropyl L-(+)-tartrate (0.6 mmol), benzaldehyde (**1**; 0.5 mmol) and methyl acrylate (**2**; 0.5 mmol) at 0°C. Then Et_2Zn (1.8 mmol) was slowly added, and stirred for 1 h. The mixture was quenched with sat. NH_4Cl and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography. After then, enantiomeric ratios were determined using chiral HPLC analysis.

Method B: To a solution of $RhCl(PPh_3)_3$ (2 mol%) in CH_2Cl_2 (1.25 mL) was added diisopropyl L-(+)-tartrate (0.6 mmol), and Et_2Zn (0.6 mmol) at 0°C and stirred for 15 min. Benzaldehyde (**1**; 0.5 mmol) and methyl acrylate (**2**; 0.5 mmol) was added to the mixture, and then Et_2Zn (1.6 mmol) was slowly added and stirred for 1 h. The mixture was quenched with sat. NH_4Cl and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography. After then, enantiomeric ratios were determined using chiral HPLC analysis.

Methyl 3-Hydroxy-2-methyl-3-phenylpropanoate (3a)[20,21] Each diastereomers of the title product (**3a**) were purified by column chromatography (AcOEt : hexane=2 : 3) and were obtained in 40% (39 mg; *syn* form) and 55% yield (53 mg; *anti* form), respectively.

(*syn*-(2*R*,3*R*/2*S*,3*S*)-**3a**) A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.13 (3H, d, J=7.2 Hz), 2.80 (1H, qd, J=7.2, 3.6 Hz), 2.92 (1H, br s), 3.68 (3H, s), 5.11 (1H, d, J=3.6 Hz), 7.25–7.35 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.68, 46.31, 51.86, 73.54, 125.9, 127.4, 128.2, 141.3, 176.1; MS *m*/*z*: 194 (M^+). High resolution-mass spectrum (HR-MS) Calcd for $C_{11}H_{14}O_3$: 194.094 (M^+), Found: 194.094; IR (neat) cm^{-1}: 3478, 1731; $[\alpha]_D^{22}$ −1.01 (c=0.2, $CHCl_3$); HPLC: Chiralcel OD-H hexane/*i*-PrOH (95 : 5, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=9.21 min and t_{major}=10.71 min.

(*anti*-(2*R*,3*S*/2*S*,3*R*)-**3a**) A colorless solid; mp 50.5–51.5°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, d, J=7.2 Hz), 2.82 (1H, dq, J=8.4, 7.2 Hz), 2.93 (1H, d, J=4.2 Hz), 3.73 (3H, s), 4.75 (1H, dd, J=8.4, 4.2 Hz), 7.28–7.39 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.49, 47.08, 51.90, 76.40, 126.6, 128.0, 128.4, 141.4, 176.1; MS *m*/*z*: 194 (M^+). HR-MS Calcd for $C_{11}H_{14}O_3$: 194.094 (M^+), Found: 194.094; IR (KBr) cm^{-1}: 3457, 1711; $[\alpha]_D^{22}$ −3.25 (c=0.2, $CHCl_3$); HPLC: Chiralcel OD-H hexane/*i*-PrOH (95 : 5, v/v), flow 1 mL/min, UV 220 nm, t_{major}=12.6 min and t_{minor}=20.0 min.

Methyl 3-Hydroxy-2-methyl-3-{4′-(trifluoromethyl)phenyl}-propanoate (3b)[20,21] Each diastereomers of the title product (**3b**) were purified by column chromatography (AcOEt : hexane=1 : 4) and were obtained in 36% (47 mg; *syn* form) and 48% yield (62 mg; *anti* form), respectively.

(*syn*-(2*R*,3*R*/2*S*,3*S*)-**3b**) A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, d, J=7.6 Hz), 2.79 (1H, qd, J=7.6, 3.6 Hz), 3.21 (1H, d, J=3.2 Hz), 3.71 (3H, s), 5.19 (1H, br s), 7.47 (2H, d, J=7.6 Hz), 7.61 (2H, d, J=7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.31, 45.98, 52.05, 72.79, 124.1 (q, J=270.6 Hz), 125.2 (m), 126.2, 129.6 (q, J=32.3 Hz), 145.2 (m), 176.0; ^{19}F-NMR (90 MHz, $CDCl_3$) δ: 0.24 (3F, s); MS *m*/*z*: 262 (M^+). HR-MS Calcd for $C_{12}H_{13}O_3F_3$: 262.082 (M^+), Found: 262.083; IR (neat) cm^{-1}: 3480, 1718, 1327; $[\alpha]_D^{22}$ −0.70 (c=1.0, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (90 : 10, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=5.85 min and t_{major}=6.45 min.

(*anti*-(2*R*,3*S*/2*S*,3*R*)-**3b**) A colorless solid; mp 79.0–80.0°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, d, J=7.2 Hz), 2.82 (1H, dq, J=8.0, 7.2 Hz), 3.22 (1H, d, J=4.8 Hz), 3.73 (3H, s), 4.82 (1H, dd, J=8.0, 4.8 Hz), 7.47 (2H, d, J=8.4 Hz), 7.62 (2H, d, J=8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.44, 46.81, 52.03, 75.63, 124.0 (q, J=270.8 Hz), 125.4 (m), 126.9, 130.2 (q, J=32.3 Hz), 145.4 (m), 175.8; ^{19}F-NMR (90 MHz, $CDCl_3$) δ: −0.17 (3F, s); MS *m*/*z*: 262 (M^+). HR-MS Calcd for $C_{12}H_{13}O_3F_3$: 262.082 (M^+), Found: 262.083; IR (KBr) cm^{-1}: 3451, 1715, 1330; $[\alpha]_D^{22}$ −13.6 (c=1.0, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (95 : 5, v/v), flow 1 mL/min, UV 220 nm, t_{major}=9.91 min and t_{minor}=11.67 min.

Methyl 4-(1-Hydroxy-3-methoxy-2-methyl-3-oxopropyl)-benzoate (3c)[21] Each diastereomers of the title product (**3c**) were purified by column chromatography (AcOEt : hexane=2 : 3) and were obtained in 39% (50 mg; *syn* form) and 52% yield (65 mg; *anti* form), respectively.

(*syn*-(2*R*,3*R*/2*S*,3*S*)-**3c**) A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, d, J=7.2 Hz), 2.80 (1H, qd, J=7.2, 3.2 Hz), 3.20 (1H, d, J=3.2 Hz), 3.70 (3H, s), 3.91 (3H, s), 5.18 (1H, t, J=3.2 Hz), 7.42 (2H, d, J=8.4 Hz), 8.02 (2H, d, J=8.4 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.52, 46.13, 52.07, 52.07, 73.10, 125.8, 129.2, 129.5, 146.5, 166.8, 175.8; MS *m/z*: 252 (M^+). HR-MS Calcd for $C_{13}H_{16}O_5$: 252.100 (M^+), Found: 252.100; IR (neat) cm^{-1}: 3496, 1723; $[\alpha]_D^{24}$ −0.59 (*c*=0.7, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (85 : 15, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=8.07 min and t_{major}=9.06 min.

(*anti*-(2*R*,3*S*/2*S*,3*R*)-**3c**) A colorless solid; mp 97.0–98.5°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, d, *J*=7.2 Hz), 2.82 (1H, dq, *J*=8.0, 7.2 Hz), 3.16 (1H, d, *J*=4.8 Hz), 3.72 (3H, s), 3.92 (3H, s), 4.82 (1H, dd, *J*=8.0, 4.8 Hz), 7.42 (2H, d, *J*=8.0 Hz), 8.03 (2H, d, *J*=8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.46, 46.93, 51.99, 52.11, 75.86, 126.5, 129.7, 129.8, 146.6, 166.7, 175.7; MS *m/z*: 252 (M^+). HR-MS Calcd for $C_{13}H_{16}O_5$: 252.100 (M^+), Found: 252.100; IR (KBr) cm^{-1}: 3457, 1717, 1699; $[\alpha]_D^{24}$ −15.7 (*c*=1.0, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (85 : 15, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=11.54 min and t_{major}=13.83 min.

Methyl 3-(4′-Chlorophenyl)-3-hydroxy-2-methylpropanoate (3d)[20,21] Each diastereomers of the title product (**3d**) were purified by column chromatography (AcOEt : hexane=1 : 4) and were obtained in 31% (36 mg; *syn* form) and 42% yield (48 mg; *anti* form), respectively.

(*syn*-(2*R*,3*R*/2*S*,3*S*)-**3d**) A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, d, *J*=7.2 Hz), 2.74 (1H, qd, *J*=7.2, 3.8 Hz), 3.13 (1H, br s), 3.68 (3H, s), 5.07 (1H, d, *J*=3.8 Hz), 7.26–7.32 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.64, 46.20, 51.95, 72.90, 127.3, 128.3, 133.1, 139.8, 176.0; MS *m/z*: 228 (M^+). HR-MS Calcd for $C_{11}H_{13}O_3Cl$: 228.055 (M^+), 229.059 (M^++1), Found: 228.055, 229.061; IR (neat) cm^{-1}: 3478, 1730, 1091; $[\alpha]_D^{22}$ −0.20 (*c*=1.0, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (90 : 10, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=7.21 min and t_{major}=8.01 min.

(*anti*-(2*R*,3*S*/2*S*,3*R*)-**3d**) A colorless solid; mp 67.0–68.0°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.03 (3H, d, *J*=6.8 Hz), 2.77 (1H, qd, *J*=8.4, 6.8 Hz), 3.08 (1H, d, *J*=4.8 Hz), 3.73 (3H, s), 4.73 (1H, dd, *J*=8.4, 4.8 Hz), 7.28 (2H, m), 7.33 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.41, 46.93, 51.99, 75.61, 127.9, 128.6, 133.7, 140.0, 175.9; MS *m/z*: 228 (M^+). HR-MS Calcd for $C_{11}H_{13}O_3Cl$: 228.055 (M^+), 229.059 (M^++1), Found: 228.055, 229.059; IR (KBr) cm^{-1}: 3474, 1714, 827; $[\alpha]_D^{22}$ −17.7 (*c*=1.0, $CHCl_3$); HPLC: Chiralcel OJ-H hexane/*i*-PrOH (90 : 10, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=13.69 and t_{major}=15.35 min.

Methyl 3-Hydroxy-3-(4′-methoxyphenyl)-2-methylpropanoate (3e)[20,21] Each diastereomers of the title product (**3e**) were purified by column chromatography (AcOEt : hexane=1 : 4) and were obtained in 40% (45 mg; *syn* form) and 57% yield (64 mg; *anti* form), respectively.

(*syn*-(2*R*,3*R*/2*S*,3*S*)-**3e**) A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.14 (3H, d, *J*=7.2 Hz), 2.76 (1H, qd, *J*=7.2, 4.6 Hz), 2.87 (1H, br s), 3.65 (3H, s), 3.80 (3H, s), 5.01 (1H, d, *J*=4.6 Hz), 6.87 (2H, d, *J*=8.8 Hz), 7.25 (2H, d, *J*=8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.10, 46.56, 51.79, 55.21, 73.45, 113.6, 127.1, 133.5, 158.9, 176.0; MS *m/z*: 224 (M^+). HR-MS Calcd for $C_{12}H_{16}O_4$: 224.105 (M^+), Found: 224.105; IR (neat) cm^{-1}: 3491, 1731; $[\alpha]_D^{22}$ 0.94 (*c*=1.1, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (90 : 10, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=10.21 min and t_{major}=11.37 min.

(*anti*-(2*R*,3*S*/2*S*,3*R*)-**3e**) A colorless solid; mp 55.0–56.0°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.98 (3H, d, *J*=7.6 Hz), 2.79 (1H, dq, *J*=8.8, 7.6 Hz), 2.88 (1H, d, *J*=4.0 Hz), 3.08 (3H, s), 3.73 (3H, s), 4.70 (1H, dd, *J*=8.8, 4.0 Hz), 6.88 (2H, d, *J*=8.8 Hz), 7.25 (2H, d, *J*=8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.45, 47.18, 51.88, 55.23, 75.99, 113.8, 127.8, 133.6, 159.3, 176.2; MS *m/z*: 224 (M^+). HR-MS Calcd for $C_{12}H_{16}O_4$: 224.105 (M^+), Found: 224.105; IR (KBr) cm^{-1}: 3456, 1716; $[\alpha]_D^{22}$ −24.4 (*c*=1.0, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (90 : 10, v/v), flow 1.25 mL/min, UV 220 nm, t_{minor}=13.95 min and t_{major}=14.91 min.

Methyl 3-Hydroxy-2-methyl-3-*p*-tolylpropanoate (3f)[21] Each diastereomers of the title product (**3f**) were purified by column chromatography (AcOEt : hexane : toluene=1 : 2 : 2) and were obtained in 39% (41 mg; *syn* form) and 54% yield (56 mg; *anti* form), respectively.

(*syn*-(2*R*,3*R*/2*S*,3*S*)-**3f**) A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, d, *J*=7.2 Hz), 2.33 (3H, s), 2.77 (1H, qd, *J*=7.2, 4.0 Hz), 2.91 (1H, br s), 3.66 (3H, s), 5.05 (1H, d, *J*=4.0 Hz), 7.14 (2H, d, *J*=7.6 Hz), 7.22 (2H, d, *J*=7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.88, 21.10, 46.44, 51.83, 73.58, 125.8, 128.9, 137.0, 138.4, 176.1; MS *m/z*: 208 (M^+). HR-MS Calcd for $C_{12}H_{16}O_3$: 208.109 (M^+), Found: 208.110; IR (neat) cm^{-1}: 3475, 1720; $[\alpha]_D^{23}$ −1.09 (*c*=1.0, $CHCl_3$); HPLC: Chiralcel OJ-H hexane/*i*-PrOH (90 : 10, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=14.00 min and t_{major}=15.25 min.

(*anti*-(2*R*,3*S*/2*S*,3*R*)-**3f**) A colorless solid; mp 50.0–51.0°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, d, *J*=7.2 Hz), 2.34 (3H, s), 2.81 (1H, dq, *J*=8.4, 7.2 Hz), 2.82 (1H, d, *J*=4.0 Hz), 3.73 (3H, s), 4.17 (1H, dd, *J*=8.4, 4.0 Hz), 7.16 (2H, d, *J*=8.8 Hz), 7.23 (2H, *J*=8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.45, 21.10, 47.09, 51.79, 76.21, 126.4, 129.0, 137.6, 138.4, 176.0; MS *m/z*: 208 (M^+). HR-MS Calcd for $C_{12}H_{16}O_3$: 208.109 (M^+), Found: 208.111; IR (KBr) cm^{-1}: 3481, 1724; $[\alpha]_D^{23}$ −25.7 (*c*=1.0, $CHCl_3$); HPLC: Chiralcel OJ-H hexane/*i*-PrOH (90 : 10, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=12.07 min and t_{major}=14.25 min.

Methyl 3-Cyclohexyl-3-hydroxy-2-methylpropanoate (3g)[21] Title product (**3g**) was purified by column chromatography (AcOEt : hexane=1 : 4) and obtained in 78% (73 mg). A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, d, *J*=7.2 Hz), 1.20–1.30 (2H, m), 1.35–1.73 (8H, m), 2.52 (1H, q, *J*=7.2 Hz), 2.94 (1H, br s), 3.71 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.60, 21.67, 21.96, 25.74, 33.87, 37.01, 48.04, 51.55, 71.31, 177.1; MS *m/z*: 186 (M^+). HR-MS Calcd for $C_{10}H_{18}O_3$: 186.126 (M^+), Found: 186.126; IR (neat) cm^{-1}: 3475, 1720; $[\alpha]_D^{22}$ −33.0 (*c*=1.1, $CHCl_3$); HPLC: Chiralcel OJ-H hexane/*i*-PrOH (90 : 10, v/v), flow 1 mL/min, UV 220 nm, t_{major}=14.00 min and t_{minor}=15.25 min.

Methyl 4,4-Diphenyl-3-hydroxy-2-methylbutanoate (3h)[20,21] The crude solid of title product (**3h**) was washed with hexane and was obtained in 61% yield (82 mg). A colorless solid; mp 127.0–128.5°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, d, *J*=6.4 Hz), 3.60 (3H, s), 3.66 (1H, q, *J*=6.4 Hz), 4.67 (1H, s), 7.14–7.20 (2H, m), 7.25–7.30 (4H, m), 7.44–7.47 (2H, m), 7.53–7.55 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.94, 46.68, 51.97, 78.02, 125.2, 125.3, 126.5, 126.8, 128.0, 128.2, 143.9, 147.4, 177.8; MS *m/z*: 270 (M^+). HR-MS Calcd for $C_{17}H_{18}O_3$: 270.126 (M^+), Found: 270.125; IR (KBr) cm^{-1}: 3454, 1706; $[\alpha]_D^{24}$ −1.88 (*c*=1.0, $CHCl_3$); HPLC: Chiralcel OJ-H hexane/*i*-PrOH (50 : 50, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=15.00 min and t_{major}=17.77 min.

Methyl 3-Hydroxy-2-methyl-3-phenylbutanoate (3i)[15]

Each diastereomers of the title product (**3i**) were purified by column chromatography (AcOEt : hexane=1 : 9) and were obtained in 17% (18 mg; *syn* form) and 65% yield (67 mg; *anti* form), respectively.

(*syn*-(2*S*,3*R*/2*R*,3*S*)-**3i**) A colorless solid; mp 52.5–54.0°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.96 (3H, d, J=7.2 Hz), 1.56 (3H, s), 2.86 (1H, q, J=7.2 Hz), 3.76 (3H, s), 3.81 (1H, br s), 7.29–7.26 (1H, m), 7.33–7.36 (2H, m), 7.42–7.44 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.85, 30.00, 49.33, 51.92, 74.30, 124.8, 126.6, 128.0, 144.9, 177.5; MS *m*/*z*: 208 (M^+). HR-MS Calcd for $C_{12}H_{16}O_3$: 208.110 (M^+), Found: 208.110; IR (KBr) cm^{-1}: 3494, 1707; $[\alpha]_D^{22}$ 2.52 (c=0.7, $CHCl_3$); HPLC: Chiralcel OJ-H hexane/*i*-PrOH (80 : 20, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=10.25 min and t_{major}=16.32 min.

(*anti*-(2*S*,3*S*/2*R*,3*R*)-**3i**) A colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (3H, d, J=6.8 Hz), 1.46 (3H, s), 3.02 (1H, q, J=6.8 Hz), 3.46 (3H, s), 4.00 (3H, br s), 7.22 (1H, m), 7.31 (2H, m), 7.42 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.56, 26.69, 48.60, 51.66, 74.65, 124.6, 126.7, 128.0, 147.4, 177.0; MS *m*/*z*: 208 (M^+). HR-MS Calcd for $C_{12}H_{16}O_3$: 208.110 (M^+), Found: 208.110; IR (neat) cm^{-1}: 3498, 1713; $[\alpha]_D^{22}$ −15.0 (c=1.1, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (97 : 3, v/v), flow 0.75 mL/min, UV 220 nm, t_{minor}=11.34 min and t_{major}=12.11 min.

2-Methyl-1-oxo-1-phenylpropan-2-yl Acrylate (4) To a solution of 2-hydroxy-2-methylpropiophenone (5 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (8 mmol) and stirred for 30 min. Then, acryloyl chloride (6 mmol) was added to the mixture and stirred for 19 h. The mixture was quenched with 10% HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with sat. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a yellow solid. The solid was purified by recrystallization by hexane and was obtained in 83% (901 mg): A colorless solid; mp 91.0–92.0°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.76 (6H, s), 5.80 (1H, dd, J=10.8, 1.2 Hz), 6.05 (1H, dd, J=17.4, 10.8 Hz), 6.31 (1H, dd, J=17.4, 1.2 Hz), 7.38 (2H, m), 7.48 (1H, m), 8.02 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 25.30, 84.31, 128.0, 128.2, 128.3, 131.4, 132.2, 134.2, 164.8, 198.5; MS *m*/*z*: 218 (M^+). HR-MS Calcd for $C_{13}H_{14}O_3$: 218.094 (M^+), Found: 218.094; IR (KBr) cm^{-1}: 1709, 1679.

4-Hydroxy-3,5,5-trimethyl-4-phenyldihydrofuran-2(3*H*)-one (5) Each diastereomers of the title product (**5**) were purified by column chromatography (AcOEt : toluene=4 : 1) and were obtained in 49% (54 mg; (3*R*,4*R*/3*S*,4*S*) form) and 26% yield (29 mg; (3*R*,4*S*/3*S*,4*R*) form), respectively.

((3*R*,4*R*/3*S*,4*S*)-**5**) A colorless solid; mp 142–146°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.03 (3H, s), 1.23 (3H, d, J=7.2 Hz), 1.56 (3H, s), 2.04 (1H, s), 3.60 (1H, q, J=7.2 Hz), 7.36–7.48 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 7.48, 20.08, 25.28, 42.18, 83.15, 88.20, 126.1, 128.6, 128.8, 138.2, 176.2; MS *m*/*z*: 220 (M^+). HR-MS Calcd for $C_{13}H_{16}O_3$: 220.110 (M^+), Found: 220.110; IR (KBr) cm^{-1}: 3439, 1749; $[\alpha]_D^{24}$ −51.1 (c=1.0, $CHCl_3$); HPLC: Chiralpak AD-H hexane/*i*-PrOH (80 : 20, v/v), flow 1 mL/min, UV 220 nm, t_{minor}=5.57 min and t_{major}=6.23 min.

((3*R*,4*S*/3*S*,4*R*)-**5**) A colorless solid; mp 178.0–182.0°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99 (3H, d, J=6.8 Hz), 1.01 (3H, s), 1.60 (3H, s), 2.19 (1H, br s), 3.28 (1H, q, J=6.8 Hz), 7.29–7.40 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 8.82, 23.69, 24.09, 45.90, 83.38, 87.77, 125.8, 127.8, 128.4, 138.6, 176.4; MS *m*/*z*: 220 (M^+). HR-MS Calcd for $C_{13}H_{16}O_3$: 220.110 (M^+), Found: 220.110; IR (KBr) cm^{-1}: 3424, 1738; $[\alpha]_D^{25}$ −5.48 (c=1.0, $CHCl_3$); HPLC: Chiralcel OJ-H hexane/*i*-PrOH (90 : 10, v/v), flow 0.5 mL/min, UV 220 nm, t_{minor}=20.0 min and t_{major}=20.9 min.

References

1) McGuire J. M., Bunch R. L., Anderson R. C., Boaz H. E., Flynn E. H., Powell H. M., Smith J. W., *Antibiot. Chemother.*, **2**, 281–283 (1952).
2) Dunetz J. R., Julian L. D., Newcom J. S., Roush W. R., *J. Am. Chem. Soc.*, **130**, 16407–16416 (2008).
3) Smith A. B. III, Beauchamp T. J., LaMarche M. J., Kaufman M. D., Qiu Y., Arimoto H., Jones D. R., Kobayashi K., *J. Am. Chem. Soc.*, **122**, 8654–8664 (2000).
4) Revis A., Hilty T. K., *Tetrahedron Lett.*, **28**, 4809–4812 (1987).
5) Willis M. C., Woodward R. L., *J. Am. Chem. Soc.*, **127**, 18012–18013 (2005).
6) Isayama S., Mukaiyama T., *Chem. Lett.*, **18**, 2005–2008 (1989).
7) Baik T. G., Luis A. L., Wang L. C., Krische M. J., *J. Am. Chem. Soc.*, **123**, 5112–5113 (2001).
8) Wang L. C., Jang H.-Y., Roh Y., Lynch V., Schultz A. J., Wang X., Krische M. J., *J. Am. Chem. Soc.*, **124**, 9448–9453 (2002).
9) Lam H. W., Joensuu P. M., Murray G. J., Fordyce E. A. F., Prieto O., Luebbers T., *Org. Lett.*, **8**, 3729–3732 (2006).
10) Lumby R. J. R., Joensuu P. M., Lam H. W., *Org. Lett.*, **9**, 4367–4370 (2007).
11) Ooi T., Doda K., Sakai D., Maruoka K., *Tetrahedron Lett.*, **40**, 2133–2136 (1999).
12) Welle A., Díez-González S., Tinant B., Nolan S. P., Riant O., *Org. Lett.*, **8**, 6059–6062 (2006).
13) Lam H. W., Joensuu P. M. A., *Org. Lett.*, **7**, 4225–4228 (2005).
14) Nishiyama H., Shiomi T., Tsuchiya Y., Matsuda I., *J. Am. Chem. Soc.*, **127**, 6972–6973 (2005).
15) Deschamp J., Chuzel O., Hannedouche J., Riant O., *Angew. Chem. Int. Ed.*, **45**, 1292–1297 (2006).
16) Hashimoto T., Ito J., Nishiyama H., *Tetrahedron*, **64**, 9408–9412 (2008).
17) Shiomi T., Adachi T., Ito J., Nishiyama H., *Org. Lett.*, **11**, 1011–1014 (2009).
18) Kanai K., Wakabayashi H., Honda T., *Org. Lett.*, **2**, 2549–2551 (2000).
19) Sato K., Tarui A., Kita T., Ishida Y., Tamura H., Omote M., Ando A., Kumadaki I., *Tetrahedron Lett.*, **45**, 5735–5737 (2004).
20) Sato K., Isoda M., Ohata S., Morita S., Tarui A., Omote M., Kumadaki I., Ando A., *Adv. Synth. Catal.*, **354**, 510–514 (2012).
21) Sato K., Isoda M., Tokura Y., Omura K., Tarui A., Omote M., Kumadaki I., Ando A., *Tetrahedron Lett.*, **54**, 5913–5915 (2013).
22) Russell A. E., Fuller O. N., Taylor J. S., Aurriset P., Morken P. J., *Org. Lett.*, **6**, 2309–2312 (2004).
23) Zhao D., Oisaki K., Kanai M., Shibasaki M., *J. Am. Chem. Soc.*, **128**, 14440–14441 (2006).
24) Freiría M., Whitehead A. J., Tocher D. A., Motherwell W. B., *Tetrahedron*, **60**, 2673–2692 (2004).
25) Lipshutz B. H., Amorelli B., Unger J. B., *J. Am. Chem. Soc.*, **130**, 14378–14379 (2008).
26) Burns A. R., Solana González J., Lam H. W., *Angew. Chem. Int. Ed.*, **51**, 10827–10831 (2012).
27) Ukaji Y., Shimizu Y., Kenmoku Y., Ahmed A., Inomata K., *Chem. Lett.*, **26**, 59–60 (1997).
28) Wei W., Kobayashi M., Ukaji Y., Inomata K., *Chem. Lett.*, **35**, 176–177 (2006).
29) Konishi A., Wei W., Kobayashi M., Fujinami S., Ukaji Y., Inomata K., *Chem. Lett.*, **36**, 44–45 (2007).