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Asymmetric synthesis of chiral glutaric acid derivatives via Rh-catalyzed enantioselective hydrogenation

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ABSTRACT

The first Rh-catalyzed enantioselective hydrogenation of dimethyl 2-methyleneglutarate and its derivatives has been reported. For the hydrogenation of dimethyl 2-methyleneglutarate with a chiral ferrocene-based monodentate phosphoramidite ligand (FAPhos), good enantioselectivity (over 90% ee) with full conversions was achieved. In contrast, the hydrogenation of substrates bearing an aryl substituent at a methylene moiety proved to be more difficult, in which the best enantioselectivity of up to 81% ee was obtained by the use of a *P*-stereogenic BoPhoz-type ligand.

1. Introduction

Chiral glutaric acid derivatives, in particular, 2-substituted glutaric analogs, are key structural elements of many natural products and drug intermediates, as well as important building blocks in organic synthesis.[1] Although some enantioselective synthetic methods and resolution procedures have been reported in the past decades,[2] a significantly smaller number of the catalytic methods are known to date. An important advance was reported by Evans et al. who have recently reported a highly enantioselective Michael additions of enolsilanes to the unsaturated imide derivatives in which the resulting adducts could be easily converted into chiral 2-methylglutaric acid.[3] Nevertheless, the development of a catalytic process for the enantioselective synthesis of chiral glutaric acid derivatives is still a great challenge for chemists. Given its inherent efficiency and atom economy, the catalytic asymmetric hydrogenation of prochiral unsaturated precursors of glutaric acid would seem to be an ideal approach to prepare such compounds. Indeed, this method has proved to be a powerful tool for the introduction of stereocenters.[4] To the best of our knowledge, however, the asymmetric synthesis of chiral glutaric acid derivatives via a catalytic hydrogenation process is still an unexplored area. As a part of our ongoing efforts toward the development of new and practical methods for the preparation of optically active compounds,[5] herein, we wish to report our result on the enantioselective synthesis of chiral glutaric acid derivatives via the first Rh-catalyzed asymmetric hydrogenation of 2-methylene-glutarate and 2-benzylideneglutarates.

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2. Results and discussion

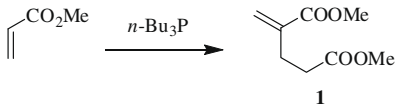
2.1. Asymmetric hydrogenation of dimethyl 2-methyleneglutarate 1

Over past decades, itaconate derivatives have been successfully hydrogenated with a variety of chiral P-ligand/Rh complexes to give enantiomerically pure 2-substituted succinate,[4b,c] which is structurally similar to the 2-methylglutarate of interest.

It should be possible to synthesize a glutarate analog of itaconic acid as a substrate for asymmetric hydrogenation (Fig. 1). Therefore, the search for an efficient method to synthesize 2-methyleneglutarate and its analogs is highly desirable. Gratifyingly, the simplest member, dimethyl 2-methyleneglutarate **1**, can be easily prepared in good yields by the self-condensation of acrylates in the presence of *n*-Bu_3P as shown in Scheme 1.[6]

Figure 1. Itaconate and 2-methyleneglutarate **1**.

With easy access to the substrate, the key to achieving an enantioselective hydrogenation of methyl 2-methyleneglutarate **1** is therefore to find an efficient catalyst. We focused our efforts on searching for an appropriate chiral phosphorus ligand with a demonstrated track record of affecting Rh-catalyzed asymmetric hydrogenations. Exploratory ligand screening employed a diverse array of chiral phosphorus-containing ligands, which are commer-



Scheme 1. Synthesis of dimethyl 2-methyleneglutarate **1**.

cially available or developed within our group. Some representative ligands screened are shown in Figure 2.

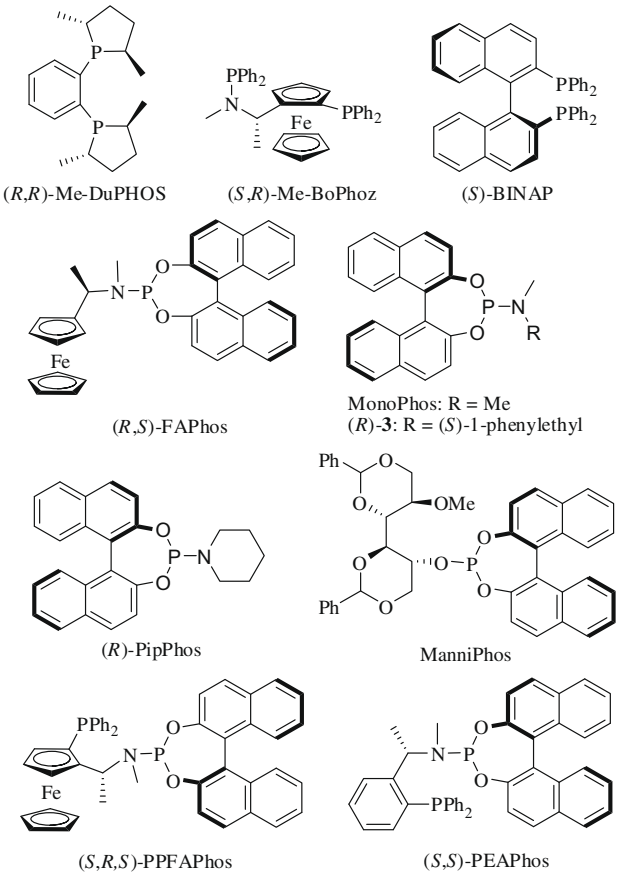
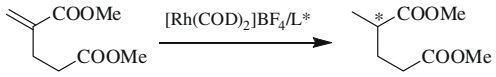


Figure 2. Structure of some representative ligands for asymmetric hydrogenation.

Although having a similar structure, the hydrogenation of dimethyl 2-methyleneglutarate **1** proved to be more difficult than the corresponding dimethyl itaconate. The data summarized in Table 1 revealed that most of the phosphorus-ligand/Rh complexes, which have proved to be highly efficient for the asymmetric hydrogenation of dimethyl itaconate, gave substantially low enantioselectivities for the hydrogenation of dimethyl 2-methyleneglutarate **1**. For instance, DuPHOS[7] only gave moderate enantioselectivity and incomplete conversion (entry 1); while unsymmetrical hybrid ligands such as Me-BoPhoz,[8] PPFAPhos[9] and PEAPhos[10] showed low enantioselectivity although full conversions were observed in these cases (entries 2, 9, and 10). The monodentate phosphite ligand, ManniPhos,[11] gave only 46% ee (entry 8).

To our delight, we found that bidentate BINAP[12] and monodentate FAPhos[13] displayed good enantioselectivities despite the incomplete conversion in the case of using BINAP (entries 3 and 4). More interestingly, subsequent investigations on the effect of monophosphoramidite structure in this hydrogenation showed that the ferrocene fragment in these monodentate ligands has a crucial role in the reactivity and enantioselectivity. Thus, all of

Table 1
Ligand and condition screening for Rh-catalyzed asymmetric hydrogenation of dimethyl 2-methyleneglutarate **1**[a]



Entry	Ligand	Solvent	Conv.[b] (%)	ee[c] (%)
1	(*R*,*R*)-Me-DuPHOS	CH_2Cl_2	89	58
2	(*S*,*R*)-Me-BoPhoz	CH_2Cl_2	100	57
3	(*S*)-BINAP	CH_2Cl_2	**93**	**94**
4	(*R*,*S*)-FAPhos	CH_2Cl_2	**100**	**92**
5	MonoPhos	CH_2Cl_2	74	<10
6	(*R*)-**3**	CH_2Cl_2	<10	—[d]
7	(R)-PipPhos	CH_2Cl_2	70	15
8	ManniPhos	CH_2Cl_2	100	46
9	(*S*,*R*,*S*)-PPFAPhos	CH_2Cl_2	100	25
10	(*S*,*S*)-PEAPhos	CH_2Cl_2	100	21
11	(*R*,*S*)-FAPhos	MeOH	41	<10
12	(*R*,*S*)-FAPhos	THF	12	<10
13	(*R*,*S*)-FAPhos	Toluene	<10	—[d]
14	(*R*,*S*)-FAPhos	*i*-PrOH	100	<10

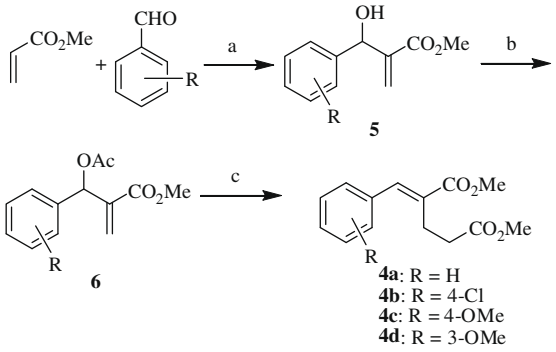
[a] The reactions were performed with 0.25 mmol of substrate at room temperature under a H_2 pressure of 20 bar in 2 mL of the indicated solvent for 12 h with 1 mol % of Rh catalyst.
[b] Conversion was determined by GC.
[c] Ee was determined by GC using a capillary chiral column.
[d] Not determined because of low conversion.

MonoPhos,[14] (*R*)-PipPhos,[15] and the phenyl analog of FAPhos, (*R*)-**3**,[16] gave poor results in this transformation (entries 5–7). Therefore, ferrocene-based monophosphoramidite ligand, FAPhos, was selected as the optimal ligand for the Rh-catalyzed asymmetric hydrogenation of dimethyl 2-methyleneglutarate **1** in terms of enantioselectivity and conversion. Subsequent experiments in an effort to attain higher enantioselectivities by optimizing the reaction conditions, proved unsuccessful. As shown in Table 1, a strong solvent dependency was observed in the reaction. However, no results surpassed that obtained in CH_2Cl_2 (entries 4, 11–14).

2.2. Asymmetric hydrogenation of dimethyl 2-benzylideneglutarates 4

The good results obtained in the hydrogenation of dimethyl 2-methyleneglutarate **1** prompted us to extend the scope of this substrate class. A series of the substrates with an aryl substituent in the methylene moiety were then prepared by a modified method reported by Kim and Murthy et al. independently as outlined in Scheme 2.[17] Initially, the Baylis–Hillman acetates **6** were prepared in good yields according to the standard methods by the treatment of aromatic aldehydes with methyl acrylate, followed by acetylation of alcohol **5**. The reaction of the Baylis–Hillman acetates **6** and (methoxycarbonyl-methylene)triphenylphosphorane in the presence of $Pd(OAc)_2$ in refluxing THF predominantly formed dimethyl (*E*)-2-benzylideneglutarates in good yields. However, an attempt to prepare 2-alkylmethyleneglutarate with the same procedure failed.

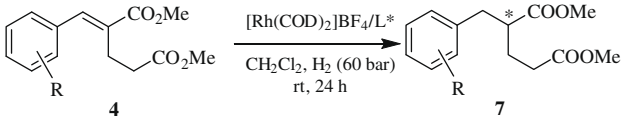
With these substrates in hand, we set out to search for an efficient catalyst for their hydrogenation, and some representative results are summarized in Table 2. Unlike the hydrogenation of dimethyl 2-methyleneglutarate **1**, most of phosphorus-containing ligands including BINAP and FAPhos displayed moderate to low activities for the hydrogenation of these 2-benzylidene substituted substrates even under an H_2 pressure of 60 bar and 2 mol % of catalyst loading (entries 1 and 2). This phenomenon is very similar to that observed in the hydrogenation of itaconic acid derivatives, in



Scheme 2. Synthesis of unsaturated precursors of glutarate **4a–d**. Reagents and conditions: (a) DABCO, rt; (b) AcCl, pyridine, DMAP, CH_2Cl_2; (c) $Pd(OAc)_2$, Ph_3P=CHCOOMe, THF, reflux, 10–13 h.

which β-substituted substrates are found to be hydrogenated less easily than the corresponding parent itaconic acid derivatives.[18]

Table 2
Rh-catalyzed asymmetric hydrogenation of dimethyl 2-benzylideneglutarates **4**[a]



Entry	Ligand	Substrate	Conv.[b] (%)	ee[c] (%)
1	(*S*)-BINAP	**4a**	56	8
2	(*R*,*S*)-FAPhos	**4a**	<5	—[d]
3	(*S*,*R*)-Me-BoPhoz	**4a**	100	66
4	(*S*,*R*)-Et-BoPhoz	**4a**	100	61
5	(S_c,R_{Fc},R_P)-**3a**	**4a**	<5	—[d]
6	(S_c,R_{Fc},R_P)-**3b**	**4a**	100	71
7	(S_c,R_{Fc},R_P)-**3c**	**4a**	100	76
8	(S_c,R_{Fc},R_P)-**3c**	**4b**	100	75
9	(S_c,R_{Fc},R_P)-**3c**	**4c**	100	78
10	(S_c,R_{Fc},R_P)-**3c**	**4d**	100	81

[a] The reactions were performed with 0.25 mmol of substrate at room temperature under a H_2 pressure of 60 bar in 2 mL of CH_2Cl_2 for 24 h with 2 mol % of Rh catalyst.
[b] Conversion was determined by GC.
[c] Ee was determined by HPLC using a chiral column.
[d] Not determined because of low conversion.

After extensively screening phosphorus-ligands, we delightedly found that Me-BoPhoz showed a promising ee-value of up to 66% and full conversions (entry 3). Since the synthetic methodology of BoPhoz-type ligands is highly modular, the optimization of the BoPhoz skeleton was therefore carried out (Fig. 3). After a systematic investigation of a number of BoPhoz-type ligands with varying electronic and steric properties, we determined that (S_c,R_{Fc},R_P)-**3c**, bearing a stereogenic *P*-center in the phosphino moiety and a 4-CF_3 group in phenyl ring of aminophosphino moiety, provided better result than that obtained with Me-BoPhoz, in which up to 76% ee was achieved (entry 7). The hydrogenation of a series of dimethyl (*E*)-2-benzylideneglutarates **4** was examined with the Rh complex of (S_c,R_{Fc},R_P)-**3c** subsequently. The results reveal that there is no major effect on the electronic properties and substitution pattern of the substituent on the phenyl ring of the substrates, and the hydrogenation proceeded to completion and provided the corresponding hydrogenated products with moderate enantioselectivities (entries 7–10). The best enantioselectivity was obtained in the hydrogenation of 3-methoxyphenyl substituted substrate **4d**, in which up to 81% ee was achieved (entry 10).

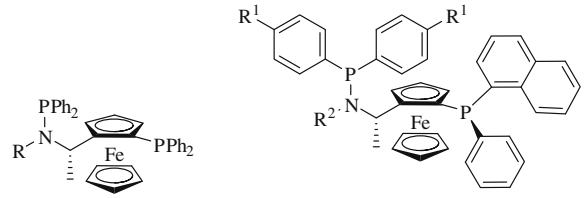


Figure 3. BoPhoz ligands for asymmetric hydrogenation.

3. Conclusion

In summary, we have reported the first asymmetric synthesis of chiral 2-substituted glutarates via the Rh-catalyzed enantioselective hydrogenation. After an extensive ligand screening, the bidentate P-ligand BINAP and monodentate P-ligand FAPhos were found to show good enantioselectivities (94% ee and 92% ee, respectively) in the hydrogenation of dimethyl 2-methyleneglutarate. In contrast, the hydrogenation of 2-benzylideneglutarates was more difficult, and up to 81% ee was obtained by the use of a BoPhoz-type ligand bearing a stereogenic *P* center in the phosphino moiety and a 4-CF_3 group in phenyl ring on aminophosphino moiety. These observations are similar to that observed in the hydrogenation of itaconate, in which the hydrogenation of β-substituted itaconic acid derivatives is found to be less efficient than the hydrogenation of the corresponding parent itaconic acid derivatives. Further investigation of other chiral hydrogenation catalysts is underway and should result in improved hydrogenation enantioselectivity.

4. Experimental

4.1. General methods

All solvents were dried and degassed by standard methods according to the literature[19] and were stored under nitrogen. All the commercially available catalysts and ligands were brought from Strem Chemicals and used without further purification. All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted. NMR spectra were recorded on BRUKER DRX 400 spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from TMS with the solvent resonance as the internal standard. Enantiomeric excess (ee) was determined by GC on a HP 4890 or HPLC analysis on an Agilent HP-1100.

4.2. Synthesis of dimethyl 2-methyleneglutarate 1

Methyl acrylate (21.5 g, 250 mmol) was cooled to −10 °C, followed by the addition of tri-*n*-butylphosphine (5.1 g, 25 mmol). The reaction was allowed to warm to room temperature, and after stirring for 1.5 h, the solution was concentrated on a rotary evaporator and the residue was distilled under reduced pressure to give 12.1 g (56%) of **1** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (s, 1H), 5.61 (s, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 2.63–2.66 (m, 2H), 2.51–2.55 (m, 2H).

4.3. Synthesis of (*E*)-2-benzylideneglutarate derivatives 4

Methyl acrylate (15.0 g, 0.174 mol) and benzaldehyde (15.0 g, 0.141 mol) were stirred in the presence of DABCO (15.9 g, 0.141 mol) for 24 h at room temperature. The reaction mixture

was diluted with ether and washed successively with HCl, $NaHCO_3$, and H_2O. The organic layer was dried over Na_2SO_4, and then the excess methyl acrylate and solvent was removed. The crude product was purified by flash chromatography to give the desired product methyl 2-(1-hydroxybenzyl)acrylate **5a** (23.1 g) in 85.1% yield.

Acetyl chloride (4.0 g, 3.72 mL, 52 mmol) was slowly dropped into a solution of **5a** (40 mmol) and pyridine (40 mL) in CH_2Cl_2 (20 mL), maintained at 0 °C and under nitrogen. After being stirred overnight at room temperature, the solution was poured into ice-water and extracted with ether (3 × 80 mL). The organic phase was dried, and the solvent was evaporated. The crude product was purified by column chromatography.

To a solution of the Baylis–Hillman acetate (16 mmol) in anhydrous benzene (80 mL) were added (methoxycarbonyl-methylene)triphenylphosphorane (16 mmol) and $Pd(OAc)_2$ (6 mol %) and the solution was heated at reflux for 10–13 h (monitored by TLC). After completion of the reaction, H_2O (20 mL) was added to the reaction mixture, which was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, concentrated in vacuum and the crud product was purified by column chromatography.

4.3.1. Dimethyl (*E*)-2-benzylideneglutarate 4a

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.32–7.39 (m, 5H), 3.81 (s, 3H), 3.64 (s, 3H), 2.86–2.90 (m, 2H), 2.54–2.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.11, 168.25, 140.54, 135.21, 131.07, 129.14, 128.66, 52.09, 51.63, 33.28, 23.09. HRMS (EI): calcd for $C_{14}H_{16}O_4$ [M^+] 248.1049, found 248.1049.

4.3.2. Dimethyl (*E*)-2-(4-chlorobenzylidene)glutarate 4b

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.36–7.38 (m, 2H), 7.28–7.31 (m, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 2.82–2.86 (m, 2H), 2.53–2.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.97, 167.99, 139.14, 134.63, 131.69, 130.45, 129.52, 128.91, 52.17, 51.69, 33.12, 23.04. HRMS (EI): calcd for $C_{14}H_{15}ClO_4$ [M^+] 282.0659, found 282.0620.

4.3.3. Dimethyl (*E*)-2-(4-methoxybenzylidene)glutarate 4c

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.34–7.37 (m, 2H), 6.91–6.94 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 2.88–2.92 (m, 2H), 2.55–2.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.29, 160.06, 140.16, 131.11, 128.77, 127.63, 114.16, 55.31, 52.02, 51.66, 33.19, 23.13. HRMS (EI): calcd for $C_{15}H_{18}O_5$ [M^+] 278.1154, found 278.1150.

4.3.4. Dimethyl (*E*)-2-(3-methoxybenzylidene)glutarate 4d

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.28–7.32 (m, 1H), 6.88–6.95 (m, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 2.86–2.90 (m, 2H), 2.54–2.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.06, 168.18, 159.65, 140.42, 136.49, 131.28, 129.65, 121.51, 114.45, 55.20, 52.06, 51.59, 33.29, 23.20. HRMS (EI): calcd for $C_{15}H_{18}O_5$ [M^+] 278.1154, found 278.1147.

4.4. General procedure for asymmetric hydrogenation

In a nitrogen-filled glovebox, to a solution of $[Rh(COD)_2]BF_4$ (1.0 mg, 0.0025 mmol) in anhydrous and degassed CH_2Cl_2 (1 mL) was added ligand (0.00275 mmol for bidentate ligands or 0.005 mmol for monodentate ligands). After stirring the mixture for 30 min, a substrate (0.25 mmol) dissolved in CH_2Cl_2 (1 mL) was added. The reaction mixture was transferred to a Par stainless autoclave. The autoclave was purged three times with hydrogen and the pressure was set to the desired pressure. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen, the solvent was removed. The enantiomeric excess was determined by GC or HPLC after purification on silica gel.

4.4.1. Dimethyl 2-methylglutarate 2

Colorless oil. 92% ee, GC, γ-DEX-225 column (0.25 mm × 30 m), 80 °C, t_1 = 41.8 min, t_2 = 43.6 min. $[\alpha]_D^{25} = -8.1$ (c 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.67–3.68 (m, 6H), 2.49 (m, 1H), 2.32–2.37 (m, 2H), 1.96 (m, 2H), 1.16–1.19 (m, 3H).

4.4.2. Dimethyl 2-benzylglutarate 7a

Colorless oil. 76% ee, HPLC (UV 260 nm, Chiralcel OJ-H (0.46 cm × 25 cm), *i*-PrOH/hexane = 3/97, 1 mL/min), t_1 = 16.7 min, t_2 = 18.7 min. $[\alpha]_D^{20} = -4.8$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.28 (m, 5H), 3.64 (s, 3H), 3.59 (s, 3H), 2.94–2.97 (m, 1H), 2.73–2.78 (m, 2H), 2.29–2.36 (m, 2H), 1.84–1.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 173.2, 138.8, 128.9, 128.5, 126.5, 51.6, 51.6, 46.7, 38.4, 31.7, 26.8. HRMS (EI): calcd for $C_{14}H_{18}O_4$ [M^+] 250.1205, found 250.1210.

4.4.3. Dimethyl 2-(4-chlorobenzyl)glutarate 7b

Colorless oil. 75% ee, HPLC (UV 260 nm, Chiralcel OJ-H (0.46 cm × 25 cm), *i*-PrOH/hexane = 1/99, 0.8 mL/min), t_1 = 37.6 min, t_2 = 39.0 min. $[\alpha]_D^{20} = -8.5$ (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.27 (m, 2H), 7.07–7.09 (m, 2H), 3.65 (s, 3H), 3.60 (s, 3H), 2.90–2.93 (m, 1H), 2.69–2.76 (m, 2H), 2.29–2.37 (m, 2H), 1.87–1.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.99, 173.16, 137.28, 132.31, 130.21, 128.58, 51.66, 46.54, 37.69, 31.62, 26.85. HRMS (EI): calcd for $C_{14}H_{17}ClO_4$ [M^+] 284.0815, found 284.0816.

4.4.4. Dimethyl 2-(4-methoxybenzyl)glutarate 7c

Colorless oil. 78% ee, HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm × 25 cm), *i*-PrOH/hexane = 1/99, 1 mL/min), t_1 = 15.4 min, t_2 = 16.6 min. $[\alpha]_D^{20} = -8.6$ (*c* 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04–7.07 (m, 2H), 6.80–6.82 (m, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 3.61 (s, 3H), 2.88–2.91 (m, 1H), 2.69–2.73 (m, 2H), 2.28–2.36 (m, 2H), 1.87–1.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 173.3, 158.2, 130.8, 129.8, 113.8, 55.2, 51.6, 51.6, 46.9, 37.6, 31.7, 26.7. HRMS (EI): calcd for $C_{15}H_{20}O_5$ [M^+] 280.1311, found 280.1309.

4.4.5. Dimethyl 2-(3-methoxybenzyl)glutarate 7d

Colorless oil. 81% ee, HPLC (UV 254 nm, Chiralcel OJ-H (0.46 cm × 25 cm), *i*-PrOH/hexane = 1/99, 0.8 mL/min), t_1 = 45.0 min, t_2 = 49.4 min. $[\alpha]_D^{20} = -2.7$ (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.21 (m, 1H), 6.70–6.75 (m, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 2.92–2.96 (m, 1H), 2.69–2.76 (m, 2H), 2.29–2.37 (m, 2H), 1.88–1.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 173.2, 159.7, 140.4, 129.5, 121.2, 114.5, 111.9, 55.1, 51.6, 46.5, 38.4, 31.7, 26.8. HRMS (EI): calcd for $C_{15}H_{20}O_5$ [M^+] 280.1311, found 280.1319.

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