The Stereoselective Synthesis of 2-Aryl-2-hydroxybutanoic Acid *via* Menthyl Chiral Auxiliaries

by **Ji-Ming Xiang**[a])[b]) and **Bao-Lin Li***[a])

[a]) School of Chemistry and Material Sciences, Shaanxi Normal University, Xi'an 710062, P. R. China (phone: +86-915-3261322; fax: +86-915-3261322; e-mail: baolinli@snnu.edu.cn; jimingxiang@aktc.net.cn)

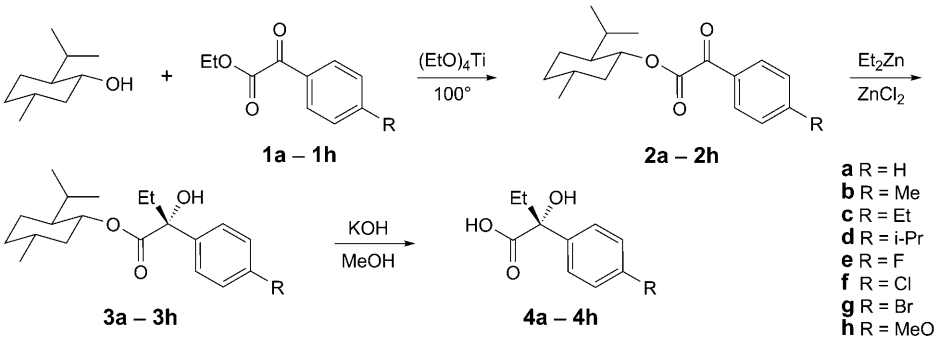
[b]) Department of Chemistry, Ankang University, Ankang 725000, P. R. China

In the presence of titanium(IV) tetraethoxide ($(EtO)_4Ti$), menthyl arylglyoxylates are prepared by transesterification of ethyl arylglyoxylates and natural (−)-(1*R*,2*S*,5*R*)-menthol. Using menthyl as a chiral auxiliary, the corresponding novel (*R*)-menthyl 2-aryl-2-hydroxybutanoates are synthesized by the addition of Et_2Zn with menthyl arylglyoxylates. The structures of the products are characterized by IR and ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry, and elemental analysis. The diastereoselectivities are analyzed by HPLC. The addition reactions are completed with good yields and high diastereoisomeric excess (de up to 95%), and, after hydrolysis, the (*R*)-2-aryl-2-hydroxybutanoic acids are obtained with high optical purities.

Introduction. – The synthesis of chiral α-hydroxy compounds by the asymmetric addition of organometallics to aldehydes and ketones have extensively been reported [1]. We anticipate that α-keto esters will display a reactive intermediate similar to that of aldehydes and ketones [2]. Furthermore, the resultant α-alkyl-α-hydroxy esters are amenable to derivatization and useful starting components for the synthesis of pharmaceutical agents and natural products [3]. Diastereoselective addition of organometallic reagents to α-keto esters by means of a chiral auxiliary is a methodology to obtain chiral tertiary α-hydroxy carboxylic acids. Among various chiral auxiliaries employed for the stereoselective synthesis of tertiary alcohols, molecules based on a cyclohexane frame such as menthol (= 5-methyl-2-(1-methylethyl)cyclohexanol) are powerful, because they provide a higher asymmetric effect, and they are readily accessible natural products. Using menthol as the chiral auxiliary provides many advantages such as low cost, availability, good selectivity, and a tendency of intermediates to be crystalline [4].

Here, we present a novel stereoselective synthesis of tertiary α-hydroxy carboxylic acids. First, ethyl arylglyoxylates (= 2-aryl-2-oxoacetates) were synthesized as described in the literature [5][6]. Subsequently, the (−)-menthyl (= 5-methyl-2-(1-methylethyl)cyclohex-1-yl) arylglyoxylates were prepared by transesterification conditions with a catalyst of $(EtO)_4Ti$. Finally, the diastereoselective addition to (−)-menthyl α-keto esters employed organozinc or *Grignard* reagents to afford the α-hydroxy esters. The esters were saponified to afford the chiral tertiary α-hydroxy carboxylic acids. The synthetic route is illustrated in *Scheme 1*.

Scheme 1. *Synthetic Route to (*R*)-2-Aryl-2-hydroxybutanoic Acids*

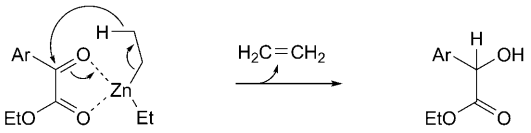


Results and Discussion. – 1. *Conditions of Transesterification.* Starting from ethyl arylglyoxylates, the (−)-menthyl esters were prepared through transesterification [7]. The amount of (−)-menthol had an impact on the progress of the transesterification reaction. The yield was low when the amount of (−)-menthol is less than the amount of ethyl arylglyoxylates. Treatment of ethyl arylglyoxylates with (−)-menthol (1.2 equiv.) in the presence of a catalytic amount of $(EtO)_4Ti$ (20 mol-%) in toluene at 100° provided (−)-menthyl aryl glyoxylate in $\geq$70% yield. (−)-Menthol, less than 1.2 equiv, led to incomplete conversion; it is presumably because the ethoxide ligands on the catalyst undergo an exchange with menthol during the reaction. The transesterification reaction between ethyl arylglyoxylate and (−)-menthol needed to be catalyzed by $(EtO)_4Ti$, as the reaction did not occur if there was no catalyst. Addition of $(EtO)_4Ti$ can facilitate the reaction, however the amount of $(EtO)_4Ti$ cannot be less than 10 mol-%, otherwise, the yield decreases dramatically. There is also no advantage for increasing the amount of catalyst to more than 30 mol-%, thus, the appropriate amount is deemed to be 20 mol-%. The transesterification reaction is also apparently affected by reaction time and temperature. When the temperature is lower than 80°, it is difficult to drive the transesterification to completion. However, when the temperature was higher than 110°, the color of reactant was deepened and more by-products appeared. The optimal reaction conditions as determined by TLC were found to be 100° and 10 h. The reaction was pushed to completion by passing a stream of N_2 to the reaction vessel to remove the generated EtOH.

2. *Addition of an Organometallic Reagent to α-Keto Esters.* Ketones and aldehydes are suitable electrophiles to *Grignard* reagents; however, they are generally inert toward dialkylzinc reagents and organozinc halides in the absence of catalyst. While many catalysts give rise to an accelerated asymmetric addition of alkylzinc reagents to aldehydes [8], the corresponding addition to ketones is more difficult due to greater steric hindrance. Assuming that the steric and electronic properties of α-keto esters confer a reactivity profile intermediate to that of aldehydes and ketones [9], we have discovered that α-keto esters react spontaneously and often uncontrollably with *Grignard* reagents and organozinc reagents, although the reactivity can be suppressed by low temperature.

The alkylation of α-keto esters is further complicated due to competing reduction pathways [10]. Two main products (*via* addition and reduction) are encountered in the addition of Et_2Zn to α-keto esters at $-20°$. We assume that the reduction product arises *via* a metal lone pair pathway as illustrated in *Scheme 2*. Reduction is, therefore, possible with any anionic organometallics that contain a β-H-atom [11].

Scheme 2. *Possible Mechanism for the Reduction of α-Keto Esters by Et_2Zn*



We have found out that the reduction pathway may be a major contributor in the addition of Et_2Zn and EtMgCl at room temperature. With decreasing the temperature, the addition product was appropriately increased, but the reduction product was still the major one. Thus, in order to accelerate the addition reaction, a catalyst is necessary. We concluded that $ZnCl_2$ is a good catalyst for the addition of Et_2Zn to α-keto esters. Our investigation demonstrated that the reduction was the major reaction at $0°$ in the absence of the catalyst for the reaction of Et_2Zn with (−)-menthyl phenylglyoxylate. A slight improvement in the yield of the addition product was achieved at $-40°$ (*Table 1*, *Entry 2*). In contrast, when adding $ZnCl_2$ as a catalyst to the mixture, 96% addition resulted with very little reduction product (*Table 1*, *Entries 4–6*). It is possible that $ZnCl_2$ as a *Lewis* acid coordinates with the α-keto ester to promote the addition reactivity of the keto C=O group [12]. By pre-mixing 1.2 equiv. of $ZnCl_2$ with the α-keto ester before introduction of the nucleophile reagent, which is implicated in the pre-complexation of the dicarbonyl moiety *via* a π-stacked chelated complex [13], the effect of catalyst $ZnCl_2$ on the reduction and addition is shown in *Table 1*.

Table 1. *Effect of $ZnCl_2$ on the Addition of Et_2Zn to (−)-Menthyl Phenylglyoxylate*

Entry	Catalyst	T [°]	t [h]	Reduction conversion [%]	Addition conversion [%]
1	None	0	3	62	38
2	None	−40	4	56	44
3	None	−60	5	46	54
4	$ZnCl_2$	0	3	4	96
5	$ZnCl_2$	−40	4	2	98
6	$ZnCl_2$	−60	5	1	99

3. *Stereoselectivity of the Addition of Et_2Zn to* (−)*-Menthyl Arylglyoxylates.* The yields and diastereoselectivities of the addition of Et_2Zn to (−)-menthyl arylglyoxylate catalyzed by $ZnCl_2$ are compiled in *Table 2*. The diastereoselectivity of the reaction was studied by high-performance liquid chromatography (HPLC). The addition reactions afford high yield when there is an electron-withdrawing group in the benzene ring such

as a halogen (*Table 2*, *Entries 5–7*). When one weak electron-donating group is in the *p*-position of the benzene ring, such as **3b–3d**, only moderate chemical yields were obtained (*Table 2*, *Entries 2–4*). An active electron-donating group, such as a MeO group, in the benzene ring results in a lower chemical yield (*Table 2*, *Entry 8*). The diastereoselective addition to (−)-menthyl phenylglyoxylate employing EtMgCl afforded menthyl 2-hydroxy-2-phenylbutanoate in a 1.8:1 diastereomeric ratio (dr) at room temperature, while pretreatment at a low temperature (−40°) afforded slightly better selectivity (2.4:1). The nucleophilic addition of the Et_2Zn reagent to the (−)-menthyl α-keto esters gave more than 4:1 dr at −40°. The diastereoselectivity was >90% when there is an electron-donating group such as alkyl in the *p*-position of the benzene ring (*Table 2*, *Entries 2–4*). When a weaker electron-withdrawing group such as halogen is in the *p*-position of the benzene ring, the procedure led to a moderate diastereoselectivity (*Table 2*, *Entries 5–7*). An active electron-donating group such as MeO group in the *p*-position of the benzene ring also provides good diastereoselectivity (*Entry 8*).

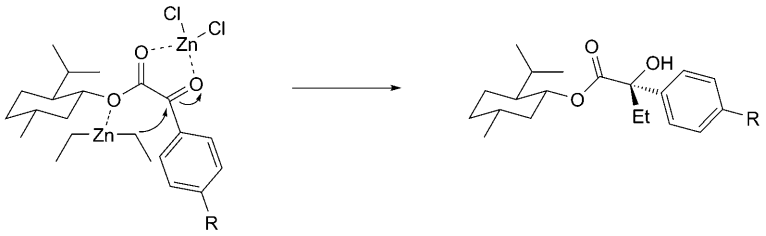
Table 2. *Stereoselectivity for the Addition of Et_2Zn to (−)-Menthyl Arylglyoxylate*

Entry	R	*t* [h]	*T* [°]	Yield [%]	de [%]	Absolute configuration
1	H	6	−40	86	94	(*R*)
2	Me	6	−40	82	95	(*R*)
3	Et	6	−40	80	94	(*R*)
4	i-Pr	6	−40	80	91	(*R*)
5	F	6	−40	92	80	(*R*)
6	Cl	6	−40	91	81	(*R*)
7	Br	6	−40	93	83	(*R*)
8	MeO	6	−40	73	85	(*R*)

The stereochemical course of the reaction can be rationalized by a steric model as depicted in *Scheme 3*. The two C=O groups are likely to adopt a *syn*-coplanar conformation due to formation of a $ZnCl_2$ chelate. The C=O groups are predicted to be between the small and the medium by *Prelog*, so the favored direction of approach goes through the small-sized group. The alkyl group may play a role as a diastereoface-discriminating group to induce high levels of enantioselectivity. When the Et_2Zn combines with the ester O-atom, the polarization of the carbanion of the Et_2Zn is increased, favoring the addition of the organozinc reagent to the α-keto ester *via* a five-membered ring conformation [14]. Because the i-Pr group effectively shields one face of the keto C=O chelated with $ZnCl_2$ [15], the Et_2Zn reagent attacks the keto C=O group from the opposite face to the i-Pr group to avoid steric repulsion. It leads to the preferential formation of the (*R*)-isomer [16]. The approach of the addition *via* a chelated conformation is shown in *Scheme 3*.

Conclusions. – In conclusion, our study provided a convenient synthesis strategy for 2-aryl-2-hydroxybutanoic acid. Using (−)-menthol as a chiral auxiliary, an efficient method for highly stereoselective synthesis of the chiral tertiary alcohols was achieved through the diastereoselective addition of the Et_2Zn to (−)-menthyl arylglyoxylate in

Scheme 3. *Stereochemical Course of Addition of Et_2Zn to (−)-Menthyl Arylglyoxylate*



the presence of catalyst $ZnCl_2$. These asymmetric aryl-α-hydroxy esters are valuable chiral synthons for the further preparation of complex chiral compounds. The fact that a stereogenic center of bearing OH group can be generated under mild conditions may lead to new opportunities in pharmaceutically relevant syntheses.

Experimental Part

1. *General.* All chemicals used were of anal. grade and obtained from commercial sources. TLC: glass sheets precoated with silica gel GF_{254} (SiO_2). Optical rotations: *Wzz-3* digital polarimeter. The ee and de values of the products were determined using a *Shimadzu LC-10ATVP* HPLC machine equipped with an ultraviolet detector, 150 mm × 4.6 mm *Daicel OD-H*, and compounds were eluted with petroleum ether (PE)/AcOEt 9:1. IR Spectra: *Nicolet FT-IR 200* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker AVANCE 300* spectrometer, in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. FAB-MS: *VG ZAB-HS* spectrometer; in *m/z* (rel. %). Elemental analyses: *Vario EL III*.

2. *General Procedure for the Preparation of (−)-Menthyl Aryl Glyoxylates* **2a**–**2h**. A suitably equipped reaction vessel was charged with ethyl arylglyoxylate (0.05 mol), (−)-menthol (0.075 mol), $(EtO)_4Ti$ (10 mmol), and toluene (30 ml). The mixture was stirred at 100° for 6 h under N_2. The EtOH generated and the partial toluene were distilled off with the aid of N_2 flow. The reaction progress was monitored by TLC and considered complete when the ethyl arylglyoxylate was fully consumed. The solvent and volatile material were removed through rotating distillation, and the crude product was purified by column chromatography (CC) on SiO_2 using PE/AcOEt 9:1 as the eluent. The first eluate was collected, and the solvent was removed to give the corresponding products.

2.1. *(−)-Menthyl Phenylglyoxylate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl Oxo(phenyl)acetate*; **2a**). Light yellow solid. Yield 68%. M.p. 43–44°. $[\alpha]_D^{20} = -45.6$ ($c = 0.51$, $CHCl_3$). IR: 2963, 2854, 1723 (keto C=O), 1670 (ester C=O), 1597, 1517, 1452, 1370, 1203, 710, 681. ^{1}H-NMR (300 MHz): 7.97 (*d*, *J* = 7.5, 2 arom. H); 7.66 (*t*, *J* = 7.0, 1 arom. H); 7.52 (*t*, *J* = 7.5, 2 arom. H); 5.01 (*m*, CH–O); 2.18 (*d*, *J* = 11.2, 1 H); 1.96 (*t*, *J* = 5.2, 1 H); 1.73 (*d*, *J* = 11.2, 2 H); 1.62–1.53 (*m*, 2 H); 1.25–1.10 (*m*, 3 H); 0.96 (*d*, *J* = 6.5, 6 H); 0.85 (*d*, *J* = 6.9, 3 H). ^{13}C-NMR (75 MHz): 186.78; 163.89; 134.74; 132.62; 129.90 (2 C); 128.88 (2 C); 76.98; 46.87; 40.67; 34.08; 31.55; 26.20; 23.40; 21.94; 20.65 (2 C).

2.2. *(−)-Menthyl (4-Methylphenyl)glyoxylate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (4-Methylphenyl)(oxo)acetate*; **2b**). Light yellow oil. Yield 70%. $[\alpha]_D^{20} = -52.4$ ($c = 0.55$, $CHCl_3$). IR: 2961, 2869, 1728 (keto C=O), 1697 (ester C=O), 1605, 1513, 1455, 1200, 1176, 840. ^{1}H-NMR (300 MHz): 7.85 (*d*, *J* = 7.8, 2 arom. H); 7.27 (*d*, *J* = 7.8, 2 arom. H); 4.97 (*m*, CH–O); 2.39 (*s*, Me); 2.17–2.14 (*m*, 1 H); 1.99–1.92 (*m*, 2 H); 1.71–1.60 (*m*, 2 H); 1.52–1.45 (*m*, 2 H); 1.21–1.10 (*m*, 2 H); 0.89 (*d*, *J* = 6.6, 6 H); 0.84 (*d*, *J* = 6.9, 3 H). ^{13}C-NMR (75 MHz): 186.38; 164.06; 146.01; 130.76; 129.95 (2 C); 129.60 (2 C); 76.67; 46.82; 40.62; 34.05; 31.50; 25.90; 23.35; 22.22; 20.96; 16.48 (2 C).

2.3. *(−)-Menthyl (4-Ethylphenyl)glyoxylate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (4-Ethylphenyl)(oxo)acetate*; **2c**). Light yellow oil. Yield 65%. $[\alpha]_D^{20} = -64.6$ ($c = 0.51$, $CHCl_3$). IR: 2961, 2871, 1728 (keto C=O), 1684 (ester C=O), 1606, 1570, 1456, 1370, 1208, 1175, 846. ^{1}H-NMR (300 MHz): 7.91 (*d*, *J* = 7.9, 2 arom. H); 7.33 (*d*, *J* = 7.9, 2 arom. H); 5.01 (*m*, CH–O); 2.70 (*q*, *J* = 7.5, CH_2); 2.17–1.98

(*m*, 3 H); 1.71–1.52 (*m*, 2 H); 1.26 (*t*, *J* = 7.5, Me); 1.23–1.20 (*m*, 2 H); 0.96–0.92 (*m*, 2 H); 0.90 (*d*, *J* = 6.9, 6 H); 0.82 (*d*, *J* = 4.8, 3 H). ^{13}C-NMR (75 MHz): 186.40; 164.09; 158.21; 132.10; 130.11 (2 C); 128.45 (2 C); 76.67; 46.86; 40.66; 34.09; 31.53; 9.12; 26.17; 23.38; 21.94; 20.65; 16.17 (2 C).

2.4. *(−)-Menthyl [4-(1-Methylethyl)phenyl]glyoxylate* (= *(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl [4-(1-Methylethyl)phenyl](oxo)acetate*; **2d**). Light yellow oil. Yield 65%. $[\alpha]_D^{20} = -54.0$ (*c* = 0.59, $CHCl_3$). IR: 2971, 2868, 1729 (keto C=O), 1682 (ester C=O), 1605, 1455, 1387, 1369, 1182, 857. ^{1}H-NMR (300 MHz): 7.93 (*d*, *J* = 7.8, 2 arom. H); 7.37 (*d*, *J* = 7.8, 2 arom. H); 5.02 (*m*, CH−O); 2.99 (*m*, 1 H); 2.21–2.17 (*m*, 1 H); 1.98–1.91 (*m*, 2 H); 1.75–1.72 (*m*, 2 H); 1.53–1.37 (*m*, 2 H); 1.28 (*d*, *J* = 6.6, 6 H); 1.17–1.07 (*m*, 2 H); 0.91 (*d*, *J* = 6.3, 6 H); 0.86 (*d*, *J* = 6.9, 3 H). ^{13}C-NMR (75 MHz): 186.40; 164.11; 156.64; 130.19 (2 C); 127.05 (2 C); 126.35; 76.7; 46.85; 40.66; 34.09; 31.54; 26.16; 23.70; 23.38; 21.95; 20.66 (2 C); 16.17 (2 C).

2.5. *(−)-Menthyl (4-Fluorophenyl)glyoxylate* (= *(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (4-Fluorophenyl)(oxo)acetate*; **2e**). Colorless oil. Yield 70%. $[\alpha]_D^{20} = -53.0$ (*c* = 0.65, $CHCl_3$). IR: 2956, 2871, 1729 (keto C=O), 1693 (ester C=O), 1589, 1507, 1456, 1313, 1201, 858. ^{1}H-NMR (300 MHz): 7.99 (*q*, *J* = 5.7, 2 arom. H); 7.13 (*t*, *J* = 8.4, 2 arom. H); 4.94 (*m*, CH−O); 2.12–2.09 (*m*, 1 H); 2.03–1.85 (*m*, 1 H); 1.68–1.65 (*m*, 2 H); 1.50–1.43 (*m*, 2 H); 1.18–0.94 (*m*, 3 H); 0.88 (*d*, *J* = 7.2, 6 H); 0.81 (*d*, *J* = 9.8, 3 H). ^{13}C-NMR (75 MHz): 184.76; 168.34; 158.12; 132.74 (2 C); 129.07; 116.30 (2 C); 76.90; 46.78; 40.53; 33.99; 31.46; 26.14; 23.32; 21.83; 20.41 (2 C).

2.6. *(−)-Menthyl (4-Chlorophenyl)glyoxylate* (= *(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (4-Chlorophenyl)(oxo)acetate*; **2f**). Light yellow solid. Yield 72%. M.p. 54–56°. $[\alpha]_D^{20} = -68.1$ (*c* = 0.40, $CHCl_3$). IR: 2954, 2872, 1736 (keto C=O), 1687 (ester C=O), 1589, 1456, 1371, 1178, 845. ^{1}H-NMR (300 MHz): 7.93 (*d*, *J* = 7.8, 2 arom. H); 7.47 (*d*, *J* = 7.8, 2 arom. H); 4.81 (*m*, CH−O); 2.06–2.03 (*m*, 1 H); 1.89–1.85 (*m*, 1 H); 1.70–1.67 (*m*, 2 H); 1.51–1.47 (*m*, 2 H); 1.18–1.04 (*m*, 3 H); 0.90 (*d*, *J* = 6.3, 6 H); 0.82 (*d*, *J* = 7.2, 3 H). ^{13}C-NMR (75 MHz): 185.60; 158.17; 140.02; 137.45; 131.25 (2 C); 129.29 (2 C); 77.70; 46.69; 40.24; 34.02; 31.39; 26.38; 23.42; 21.88; 20.50 (2 C).

2.7. *(−)-Menthyl (4-Bromophenyl)glyoxylate* (= *(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (4-Bromophenyl)(oxo)acetate*; **2g**). Light yellow solid. Yield 72%. M.p. 68–70°. $[\alpha]_D^{20} = -36.9$ (*c* = 0.46, $CHCl_3$). IR: 2963, 2850, 1747 (keto C=O), 1690 (ester C=O), 1584, 1486, 1454, 1399, 1168, 841. ^{1}H-NMR (300 MHz): 7.88 (*d*, *J* = 8.4, 2 arom. H); 7.67 (*d*, *J* = 7.8, 2 arom. H); 5.00 (*m*, CH−O); 2.15–2.06 (*m*, 1 H); 1.94–1.77 (*m*, 1 H); 1.73–1.58 (*m*, 2 H); 1.54–1.39 (*m*, 2 H); 1.27–1.13 (*m*, 3 H); 0.94 (*d*, *J* = 6.6, 6 H); 0.85 (*d*, *J* = 6.6, 3 H). ^{13}C-NMR (75 MHz): 186.52; 163.21; 132.32; 131.54 (2 C); 130.03 (2 C); 128.90; 77.26; 46.83; 40.61; 34.04; 31.55; 26.22; 23.37; 21.94; 20.65 (2 C).

2.8. *(−)-Menthyl (4-Methoxyphenyl)glyoxylate* (= *(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (4-Methoxyphenyl)(oxo)acetate*; **2h**). Yellow solid. Yield 70%. M.p. 55–56°. $[\alpha]_D^{20} = -38.7$ (*c* = 0.51, $CHCl_3$). IR: 2955, 2870, 1728 (keto C=O), 1677 (ester C=O), 1599, 1511, 1458, 1309, 1209, 1166, 839. ^{1}H-NMR (300 MHz): 7.96 (*d*, *J* = 6.6, 2 arom. H); 6.97 (*d*, *J* = 6.9, 2 arom. H); 4.97 (*m*, CH−O); 3.88 (*s*, 3 H); 2.19–2.15 (*m*, 1 H); 1.96 (*m*, 1 H); 1.74–1.71 (*m*, 2 H); 1.56–1.52 (*m*, 2 H); 1.24–1.05 (*m*, 3 H); 0.94 (*d*, *J* = 6.6, 6 H); 0.84 (*d*, *J* = 6.6, 3 H). ^{13}C-NMR (75 MHz): 185.29; 164.94; 164.21; 132.37 (2 C); 125.61; 114.25 (2 C); 76.66; 55.60; 46.83; 40.64; 34.08; 31.53; 26.16; 23.37; 21.95; 20.65 (2 C).

3. *General Procedure for the Preparation of Menthyl (*R*)-2-Aryl-2-hydroxybutanoates* **3a**–**3h**. A soln. of 1M $ZnCl_2$ (12 mmol) in CH_2Cl_2 was added to a keto ester (10 mmol) in CH_2Cl_2 (10 ml) in a suitably equipped reaction vessel. The mixture was stirred at r.t. for 20 min and then cooled to −40°. A soln. of 1M Et_2Zn in hexane (10 mmmol) was injected into the soln. of the pre-complexed keto ester with $ZnCl_2$ and then stirred at −40° for 6 h. After complete conversion (TLC), the mixture was warmed to 0°, the reaction was quenched with 1M HCl (20 ml), and the mixture was extracted with Et_2O (3 × 30 ml). The combined org. layer was dried (anh. $MgSO_4$). Then, the solvent and volatile material were removed by rotating distillation, and the crude solid product was purified by CC (SiO_2; PE/AcOEt 9:1). The second fraction of the elution was collected, and the solvent was removed to give the corresponding product.

3.1. *Menthyl (*R*)-2-Hydroxy-2-phenylbutanoate* (= *(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-Hydroxy-2-phenylbutanoate*; **3a**). White solid. Yield 86%. M.p. 83.2–84.1°. de 94%. $[\alpha]_D^{20} = -69.3$ (*c* = 0.20, acetone). IR: 3453 (OH), 2956, 1721 (C=O), 1495, 1454, 1389, 1262, 735, 693. ^{1}H-NMR (300 MHz): 7.26–7.40 (*m*, 5 arom. H); 4.63–4.80 (*m*, CH−O); 2.17 (*s*, OH); 1.76–1.87 (*m*, 1 H); 1.56–1.64 (*m*, 2 H); 1.38–1.42 (*m*, 3 H); 0.97–1.05 (*m*, 2 H); 0.90 (*d*, *J* = 6.2, 6 H); 0.84 (*s*, 3 H);

0.77 (*t*, *J* = 6.7, 3 H); 0.58 (*d*, *J* = 7.6, 3 H). ^{13}C-NMR (75 MHz): 173.5; 138.7; 128.5; 126.6; 126.4; 76.6; 73.1; 47.1; 40.7; 34.1; 31.4; 26.4; 25.4; 23.5; 22.0; 20.7; 16.4. FAB-MS: 318 (24, M^+), 300 (100, $[M - H_2O]^+$). Anal. calc. for $C_{20}H_{30}O_3$ (318.45): C 75.43, H 9.50; found: C 75.49, H 9.66.

3.2. *Menthyl (*R*)-2-Hydroxy-2-(4-methylphenyl)butanoate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-Hydroxy-2-(4-methylphenyl)butanoate*; **3b**). White solid. Yield 82%. M.p. 103.2–106.3°. de 95%. $[\alpha]_D^{20} = -64.3$ (*c* = 0.13, acetone). IR: 3460 (OH); 2954, 1730 (C=O), 1612, 1513, 1458, 1388, 1262, 825, 794. ^{1}H-NMR (300 MHz): 7.12–7.29 (*m*, 4 arom. H); 4.63–4.76 (*m*, CH–O); 2.33 (*s*, 3 H); 2.17 (*s*, OH); 1.75–1.90 (*m*, 1 H); 1.56–1.67 (*m*, 2 H); 1.38–1.55 (*m*, 3 H); 1.04–1.10 (*m*, 2 H); 0.91 (*d*, *J* = 6.7, 6 H); 0.85 (*s*, 3 H); 0.79 (*t*, *J* = 6.0, 3 H); 0.59 (*d*, *J* = 7.6, 3 H). ^{13}C-NMR (75 MHz): 173.5; 143.0; 138.1; 129.2; 126.6; 76.6; 73.0; 47.1; 40.7; 34.1; 31.4; 26.4; 25.3; 23.5; 22.0; 21.2; 20.7; 16.4. FAB-MS: 332 (19, M^+), 314 (100, $[M - H_2O]^+$). Anal. calc. for $C_{21}H_{32}O_3$ (332.48): C 75.86, H 9.70; found: C 75.88, H 9.76.

3.3. *Menthyl (*R*)-2-(4-Ethylphenyl)-2-hydroxybutanoate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-(4-Ethylphenyl)-2-hydroxybutanoate*; **3c**). White solid. Yield 80%. M.p. 58.8–61.1°. de 94%. $[\alpha]_D^{20} = -67.3$ (*c* = 0.26, acetone). IR: 3461 (OH), 2955, 1732 (C=O), 1512, 1458, 1388, 1263, 833, 784. ^{1}H-NMR (300 MHz): 7.15–7.36 (*m*, 4 arom. H); 4.62–4.80 (*m*, CH–O); 3.30 (*s*, OH); 2.62 (*q*, *J* = 7.1, 2 H); 1.76–1.88 (*m*, 1 H); 1.55–1.67 (*m*, 2 H); 1.39–1.43 (*m*, 3 H); 1.22 (*t*, *J* = 7.1, 3 H); 0.97–1.04 (*m*, 2 H); 0.91 (*d*, *J* = 4.8, 6 H); 0.85 (*s*, 3 H); 0.79 (*t*, *J* = 6.8, 3 H); 0.58 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR (75 MHz): 173.5; 142.8; 136.1; 128.0; 126.6; 76.5; 73.0; 47.1; 40.7; 34.1; 31.4; 28.6; 26.3; 25.3; 23.4; 21.9; 20.7; 16.4; 15.8. FAB-MS: 346 (18, M^+), 328 (100, $[M - H_2O]^+$). Anal. calc. for $C_{22}H_{34}O_3$ (346.50): C 76.26, H 9.89; found: C 76.32, H 9.91.

3.4. *Menthyl (*R*)-2-Hydroxy-2-[4-(1-methylethyl)phenyl]butanoate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-Hydroxy-2-[4-(1-methylethyl)phenyl]butanoate*; **3d**). White solid. Yield 80%. M.p. 64.9–65.7°. de 91%. $[\alpha]_D^{20} = -55.7$ (*c* = 0.17, acetone). IR: 3454 (OH), 2957, 1725 (C=O), 1513, 1462, 1388, 1372, 1260, 832, 785. ^{1}H-NMR (300 MHz): 7.17–7.34 (*m*, 4 arom. H); 4.65–4.78 (*m*, CH–O); 3.41 (*s*, OH); 2.89 (*m*, 1 H); 1.86–1.90 (*m*, 1 H); 1.63–1.77 (*m*, 2 H); 1.43–1.55 (*m*, 3 H); 1.24 (*d*, *J* = 5.1, 6 H); 0.96–1.10 (*m*, 2 H); 0.91 (*d*, *J* = 5.3, 6 H); 0.85 (*s*, 3 H); 0.79 (*t*, *J* = 7.2, 3 H); 0.56 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR (75 MHz): 173.6; 149.2; 136.3; 126.7; 126.4; 76.3; 72.9; 47.1; 40.8; 34.1; 31.4; 26.3; 25.3; 24.0; 23.4; 22.9; 21.9; 20.7; 16.3. FAB-MS: 360 (17, M^+), 342 (100, $[M - H_2O]^+$). Anal. calc. for $C_{23}H_{36}O_3$ (360.53): C 76.62, H 10.06; found: C 76.69, H 10.10.

3.5. *Menthyl (*R*)-2-(4-Fluorophenyl)-2-hydroxybutanoate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-(4-Fluorophenyl)-2-hydroxybutanoate*; **3e**). White solid. Yield 92%. M.p. 103.5–104.6°. de 80%. $[\alpha]_D^{20} = -64.1$ (*c* = 0.12, acetone). IR: 3450 (OH), 2957, 1719 (C=O), 1603, 1512, 1461, 1389, 1234, 1201, 840, 810. ^{1}H-NMR (300 MHz): 7.02–7.36 (*m*, 4 arom. H); 4.63–4.79 (*m*, CH–O); 3.56 (*s*, OH); 1.82–1.90 (*m*, 1 H); 1.55–1.74 (*m*, 2 H); 1.37–1.41 (*m*, 3 H); 0.96–1.04 (*m*, 2 H); 0.90 (*d*, *J* = 7.0, 6 H); 0.84 (*s*, 3 H); 0.78 (*t*, *J* = 6.7, 3 H); 0.61 (*d*, *J* = 7.7, 3 H). ^{13}C-NMR (75 MHz): 173.3; 161.4; 134.6; 128.4; 115.4; 76.7; 72.4; 46.8; 40.7; 34.0; 31.4; 26.4; 25.5; 23.4; 21.9; 20.6; 16.4. FAB-MS: 336 (19, M^+), 318 (100, $[M - H_2O]^+$). Anal. calc. for $C_{20}H_{29}FO_3$ (336.44): C 71.40, H 8.69; found: C 71.48, H 8.76.

3.6. *Menthyl (*R*)-2-(4-Chlorophenyl)-2-hydroxybutanoate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-(4-Chlorophenyl)-2-hydroxybutanoate*; **3f**). Light yellow solid. Yield 91%. M.p. 82.5–83.4°. de 81%. $[\alpha]_D^{20} = -53.2$ (*c* = 0.22, acetone). IR: 3454 (OH), 2954, 1720 (C=O), 1598, 1501, 1458, 1386, 1201, 1189, 830, 795. ^{1}H-NMR (300 MHz): 7.12–7.45 (*m*, 4 arom. H); 4.62–4.77 (*m*, CH–O); 3.60 (*s*, OH); 1.80–1.97 (*m*, 1 H); 1.56–1.71 (*m*, 2 H); 1.30–1.41 (*m*, 3 H); 0.95–1.04 (*m*, 2 H); 0.90 (*d*, *J* = 6.2, 6 H); 0.84 (*s*, 3 H); 0.77 (*t*, *J* = 7.1, 3 H); 0.63 (*d*, *J* = 7.7, 3 H). ^{13}C-NMR (75 MHz): 170.2; 139.1; 134.6; 130.5; 129.6; 77.9; 73.6; 47.1; 41.2; 34.0; 31.5; 26.4; 25.6; 23.4; 22.1; 20.6; 16.4. FAB-MS: 352 (15, M^+), 334 (100, $[M - H_2O]^+$). Anal. calc. for $C_{20}H_{29}ClO_3$ (352.90): C 68.07, H 8.28; found: C 68.00, H 8.21.

3.7. *Menthyl (*R*)-2-(4-Bromophenyl)-2-hydroxybutanoate* (=*(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-(4-Bromophenyl)-2-hydroxybutanoate*; **3g**). Light yellow solid. Yield 93%. M.p. 78.8–79.6°. de 83%. $[\alpha]_D^{20} = -47.6$ (*c* = 0.23, acetone). IR: 3455 (OH), 2955, 1737 (C=O), 1591, 1487, 1457, 1388, 1201, 1180, 828, 780. ^{1}H-NMR (300 MHz): 7.15–7.51 (*m*, 4 arom. H); 4.61–4.76 (*m*, CH–O); 3.78 (*s*, OH); 1.80–2.00 (*m*, 1 H); 1.56–1.66 (*m*, 2 H); 1.23–1.41 (*m*, 3 H); 0.96–1.03 (*m*, 2 H);

0.89 (*d*, *J* = 6.1, 6 H); 0.84 (*s*, 3 H); 0.75 (*t*, *J* = 8.0, 3 H); 0.63 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR (75 MHz): 172.9; 137.8; 131.8; 129.2; 122.6; 76.8; 72.5; 47.0; 40.7; 34.0; 31.4; 26.4; 25.7; 23.4; 22.0; 20.7; 16.4. FAB-MS: 398 (16, $[M+2]^+$), 396 (16, M^+), 380 (100, $[M+2-H_2O]^+$), 378 (100, $[M-H_2O]^+$). Anal. calc. for $C_{20}H_{29}BrO_3$ (397.35): C 60.45, H 7.36; found: C 60.41, H 7.40.

3.8. *Menthyl (*R*)-2-Hydroxy-2-(4-methoxyphenyl)butanoate* (= *(1*R,*2*S,*5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*R*)-2-Hydroxy-2-(4-methoxyphenyl)butanoate*; **3h**). Pink solid. Yield 73%. M.p. 89.2–90.6°. de 85%. $[\alpha]_D^{20} = -68.8$ (*c* = 0.17, acetone). IR: 3445 (OH), 2956, 1731 (C=O), 1612, 1512, 1459, 1253, 1203, 1175, 829, 797. ^{1}H-NMR (300 MHz): 7.30 (*t*, *J* = 5.8, 2 H); 6.86 (*t*, *J* = 6.6, 2 H); 4.62–4.78 (*m*, CH–O); 3.79 (*s*, MeO); 3.46 (*s*, OH); 1.78–1.88 (*m*, 1 H); 1.63–1.73 (*m*, 2 H); 1.23–1.41 (*m*, 3 H); 0.96–1.06 (*m*, 2 H); 0.89 (*d*, *J* = 4.4, 6 H); 0.84 (*s*, 3 H); 0.78 (*t*, *J* = 7.1, 3 H); 0.60 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR (75 MHz): 173.7; 159.7; 131.1; 127.9; 113.9; 76.4; 72.7; 55.3; 47.1; 40.7; 34.1; 31.4; 26.3; 25.4; 23.4; 22.0; 20.7; 16.4. FAB-MS: 348 (19, M^+), 330 (100, $[M-H_2O]^+$). Anal. calc. for $C_{21}H_{32}O_4$ (348.48): C 72.38, H 9.26; found: C 72.31, H 9.21.

4. *General Procedure for the Preparation of (*R*)-2-Aryl-2-hydroxybutanoic acids* **4a**–**4h**. A soln. of KOH (25 mmol) in H_2O (20 ml) was added to compound **3** (5 mmol) in MeOH (20 ml). The resulting mixture was heated to reflux until complete conversion of the starting material (monitored by TLC). The org. solvent was removed by rotating distillation, H_2O (20 ml) was added, and the aq. layer was extracted with Et_2O (2 × 30 ml). A soln. of 2N aq. HCl was added until an acidic pH was reached, and the aq. layer was further extracted with AcOEt (3 × 30 ml). The combined org. layers were dried (anh. $MgSO_4$), filtered, and concentrated under vacuum to afford pure compounds **4a**–**4h**. All anal. data corresponding to the series of compound **4** were identical to those reported in the literature [17].

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