JOC Article

In- or In(I)-Employed Tailoring of the Stereogenic Centers in the Reformatsky-Type Reactions of Simple Ketones, α-Alkoxy Ketones, and *β*-Keto Esters

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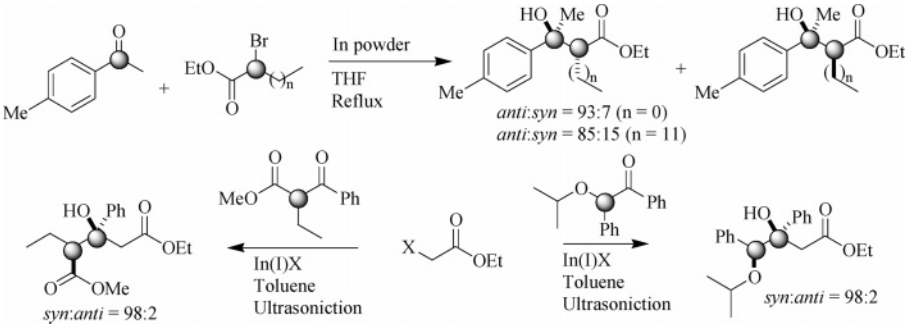

Comprehensive studies were carried out on efficient In- or In(I)-based diastereoselective Reformatsky-type reactions of simple ketones, α-alkoxy ketones, and *β*-keto esters. High *anti* selectivity was established in the addition of the branched α-halo ester derivatives to simple ketones using indium metal under THF-refluxing conditions. The stereochemistry undoubtedly indicated that the involvement of a cyclic transition state, formed from the ketone and stereochemically preferred transient *E*-enolate derived from the branched α-halo ester. Next, with the view of tailoring high degree of stereoselection, the concept of chelation-controlled addition of indium enolates was envisioned. In this line, marvelously *syn* selective additions to α-alkoxy ketones and *β*-keto esters were established. Interestingly, these diastereoselective additions to α-alkoxy ketones and *β*-keto esters require either In(I)X or In−$InCl_3$ systems in toluene under ultrasonication, while very poor efficiency and diastereoselectivity were obtained using indium metal or THF as solvent. The stereochemistry of key products was unambiguously determined by the single-crystal X-ray structure analyses. On the basis of the observed astonishing diastereoselectivities due to strong chelation plausibly, a low-valent RIn(I)-type transient spices could be projected as very reactive spices in the Reformatsky-type reactions.

Introduction

Discovering remarkable stereoselectivity in the C−C bond formation has been the prime objective of organic chemists. Organometallic reactions are among the superior processes for the stereoselective bond formations, and Reformatsky-type reactions are one of the cornerstones.[1] Many processes have been developed using zinc.[2] For very high efficiency, new methods have been reported, e.g., Rieke−Zn,[3a] Zn−Cu couple,[3b] Zn/Ag−graphite;[3c] utilizing other metals such as Cd,[3d] Ni,[3e] Ce,[3f] Mg,[3g,h] and indium;[4a−f] however, some of these reagents must be freshly prepared.[3]

Despite these recent developments, two significant themes still remain to be explored in the Reformatsky-type reactions of ketones:[2] (a) an efficient diastereoselective addition of the branched α-halo ester derivatives to simple ketones (Scheme 1, eq 1) and (b) chelation-controlled stereoselective addition of α-halo esters to α-alkoxy ketones and *β*-keto esters (Scheme 1, eqs 2 and 3).

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(1) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210.

(2) For recent reviews on Reformatsky reactions, see: (a) Fürstner. A. *Synthesis* **1989**, 571. (b) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; New York, 1991; Vol. 2, p 277. (c) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325. (d) Orsini, F.; Sello, G. *Curr. Org. Synth*. **2004**, *1*, 111.

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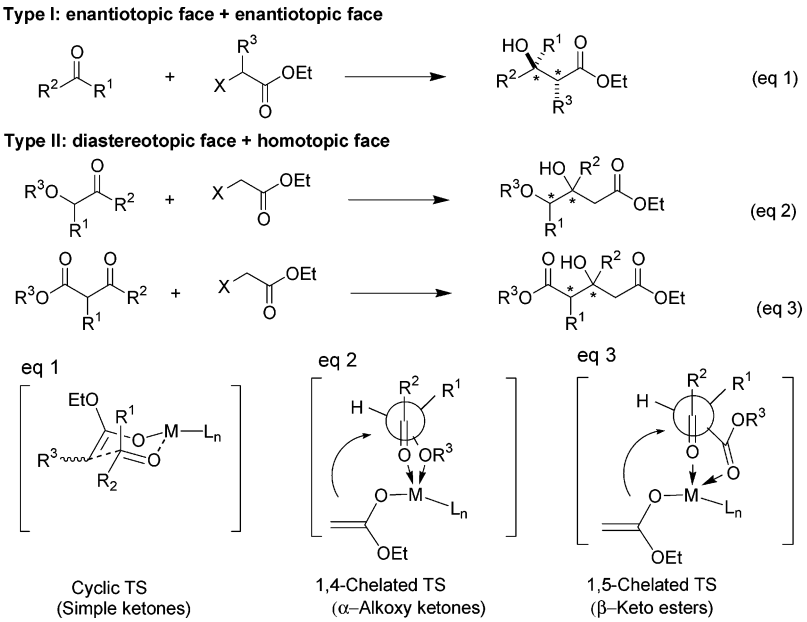
SCHEME 1. Cyclic and Chelation-Controlled Transition States



The former type of stereoselection should own to a usual six-membered cyclic transition state that would result from a transient indium enolate. There have been a few examples with only moderate diastereoselectivity in the case of addition of the branched α-halo ester derivatives to simple ketones. This is probably because the conditions to achieve the additions to ketones are too severe to control the stereoselectivity in contrast to the facile additions to aldehydes. In addition, the difference in the rigid steric demand between the two substituents on the carbonyl carbon of simple ketones importantly decides the degree of stereoselection. This difference is much lower in the case of ketones than aldehydes. In fact, a survey of the existing examples on the addition of the branched α-halo esters to simple ketones revealed the difficulty in achieving good diastereoselectivity,[5,6] e.g., Zn dust/I_2 (*anti/syn* 3:2),[6] Et_2Zn/$RhCl(PPh_3)_3$ (*anti/syn* 1:1),[5a] and low-valent tantalum (ds 17:13).[5b]

For the latter type of chelation-controlled stereoselection, importantly, both of strong coordination acceptance and high nucleophilicity are required for the Reformatsky-type metal enolates. Both of these unique characteristics are more essential in the case of *β*-keto esters than the case of α-alkoxy ketones because of the larger ring size during the chelation and the low electrophilicity of the carbonyl moiety (Scheme 1, eqs 2 and 3).

Taking an impetus from the recently advancing selective reactions based on indium,[4,7] we envisioned the indium-based tailoring of the stereogenic centers in the Reformatsky-type additions.[8] We have recently delineated our preliminary studies on the stereoselective addition of branched α-halo ester derivatives to simple ketones.[9] Next, we also aimed the tailoring of the stereogenic centers through chelation-controlled protocol. Herein, we report the comprehensive studies on three types of the tailoring of the stereogenic centers in the Reformatsky-type reactions of simple ketones, α-alkoxy ketones and *β*-keto esters as shown in Scheme 1, where the different selections of indium species and solvents are essential. Low-valent indium enolates generated from

(3) (a) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452. (b) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698. (c) Csuk, R.; Fürstner, A.; Weidmann, H. *J. Chem. Soc., Chem Commun*. **1986**, 775. (d) Burkhardt, E.; Rieke, R. D. *J. Org. Chem*. **1985**, *50*, 416. (e) Inaba, S.-I.; Rieke, R. D. *Tetrahedron Lett.* **1985**, *26*, 155. (f) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (g) Moriwake, T. *J. Org. Chem.* **1966**, *31*, 983. (h) Borno, A.; Bigley, D. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1311. (i) Paresh, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615. (j) Shibata, I.; Suwa, T.; Sakakibara, H.; Baba, A. *Org. Lett.* **2002**, *4*, 301 and references therein.

(4) For reviews on indium reagents, see: (a) Cintas, P. *Synlett* **1995**, 1087. (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (c) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B.; S. *Tetrahedron* **2004**, *60*, 1959. (d) Araki, S.; Hirashita, T. *Main Group Metals Org. Synth.* **2004**, *1*, 323. (e) Chan, T. H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (f) Loh, T.-P. *Sci. Synth.* **2004**, *7*, 413. (g) Babu, S. A. *Synlett* **2002**, 531. (h) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Curr. Org. Chem.* **2003**, *7*, 1661. (i) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. (j) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (k) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347. (l). Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 1149. (m) Peppe, C. *Curr. Org. Synth.* **2004**, *1*, 227.

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(6) Ross, N. A.; Bartsch, R. A. *J. Org. Chem.* **2003**, *68*, 360 and references therein.

(7) For some recent papers, see: (a) Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186. (b) Loh, T.-P.; Yin, Z.; Song, H.-S.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 911. (c) Yi, X.-H.; Meng, Y.; Li, C.-J. *J. Chem. Soc, Chem. Commun.* **1998**, 449. (d) Hirashita, T.; Kamei, T.; Satake, M.; Horie, T.; Shimizu, H.; Araki, S. *Org. Biomol. Chem.* **2003**, *1*, 3799. (d) Babu, S. A.; Yasuda, M.; Shibata, I., Baba, A. *Synlett* **2004**, 1223. (e) Paquette, L., A. *Synthesis* **2003**, 765. (f) Kumar, S. Kaur, P. *Tetrahedron Lett.* **2004**, *45*, 3413. (g) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464. (h) Khan, F. A.; Dash, J. *E. J. Org. Chem.* **2004**, 2692.

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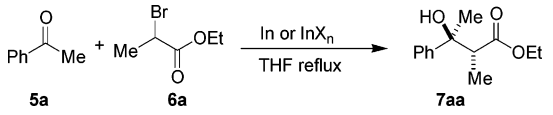
(9) Preliminary report: Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4475.

TABLE 1. Optimization of Indium-Based Diastereoselective Reformatsky-Type Reaction of 5a with 6a[a]



5a 6a 7aa

entry	In or InX_n	time (h)	method[b]	yield (%) (*anti/syn*)
1	In	2.5	B	98 (75:25)
2	In	1.0	A	99 (84:16)
3	InCl	8.0	B	99 (76:24)
4	InBr	3.5	B	84 (84:16)
5	InI	9.0	B	67 (68:32)
6	In	1.0	C	NR
7	$InCl_2$	2.0	A	NR
8[c]	Zn/I_2	40 min	C	13 (50:50)
9	In	2.0	A	65 (88:12)[d]
10	In	2.0	A	NR[e]
11	InBr	2.0	A	NR[d]

[a] **5a** (1 mmol), **6a** (1.8 mmol), indium powder or In(I)X (1.2 mmol), and THF (2 mL) were used unless otherwise specified. [b] Method A: The reaction mixture was dipped into a preheated bath at reflux temperature. Method B: The reaction mixture was gradually heated to reflux for an appropriate period. Method C: Ultrasonication (38 kHz, 120 W) was employed at room temperature. [c] Zn (1.8 mmol) and I_2 (0.2 mmol) in 1,4-dioxane (2.5 mL) were subjected to ultrasonication.[6,10a] [d] Reaction was carried out in toluene at reflux. [e] Reaction was carried out in toluene at 70−75 °C.

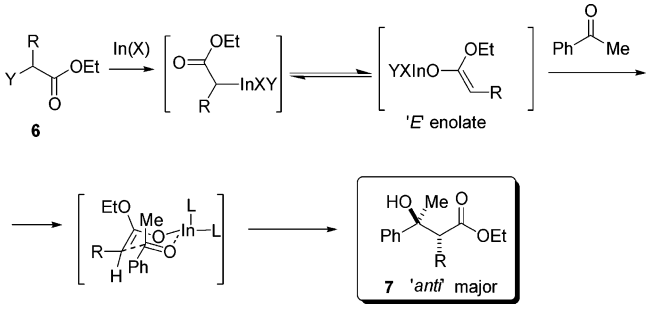
α-iodo esters plausibly act as a key intermediate in these stereoselective reactions.

Results and Discussion

Type I. Reactions of Branched α-Halo Esters with Simple Ketones. In an initial experiment, to a mixture of acetophenone **(5a)** and ethyl-2-bromopropionate **(6a)** in dry THF was added indium metal powder at room temperature, and the resulting mixture was heated to reflux to afford the product **7aa**[5,6] in 98% yield with the diastereoselectivity of 75:25 (*anti/syn*) (Table 1, entry 1). Although both of indium metal and indium(I) halide system have satisfied effect, the former is rather advantageous in terms of a short reaction period. We further found that dipping the flask containing all the substrates, indium metal, and dry THF solvent into a preheated bath (66−69 °C) gave the product (99% yield) with higher selectivity of 84:16 (*anti/syn*) (entry 2). Indium dichloride gave no product, and either the zinc system or indium metal was not efficient using low intensiity ultrasonication (38 kHz, 120 W) in our investigation (entries 6−8).[10a] Toluene solvent gave poor results under similar conditions (entries 10 and 11), and a moderate yield was obtained even under harsh conditions (entry 9). Employing other solvents such as MeCN, DMF, and the systems of MeCH(Cl)COOEt or RX/NaI in DMF/rt were ineffective.[4]

The generality of this important stereoselective reaction was demonstrated with a variety of ketones as summarized in Table 2. Electron-withdrawing and -donating groups slightly altered the diastereoselectivities. The reactions with the α-halo ester derivative **6c** having a long carbon chain, also afforded the products **7ac** and **7dc** with high diastereoselectivities (entries 2 and 8). It can be noted that compared to the existing methods, the indium-based reagents behaved in a distinctive manner with respect to the diastereoselectivity on the addition of branched α-halo esters with simple ketones.

SCHEME 2. Reaction Mechanism for the Formation of *Anti*-Adducts from Simple Ketones



Stereochemistry. We have isolated both the major and minor isomers of β-hydroxy esters in pure form in some cases. The esterification of major isomers **7ca**$_1$ and **7ga**$_1$ was carried out according to the literature method[11,12] to furnish the suitable crystalline for the single-crystal X-ray structure analyses (see the Supporting Information for the X-ray structures and data for the esters **7caB** and **7gaB**). The X-ray analyses unequivocally revealed the formation of *anti* isomers as the major products in the above reactions.

Mechanism. The predominant formation of *anti* isomers can be rationalized by a cyclic model of an *E*-enolate and a ketone as shown in Scheme 2. In this model, one of the two substituents on the carbonyl carbon must be located at the axial position in the six-membered cyclic transition state; of course, it is not hydrogen in contrast to aldehydes. In Scheme 2, the methyl moiety of acetophenone is the case. This hypothesis is also supported by the fact that isopropylphenyl ketone gave a rather lower selectivity (Table 2, entries 9−11). These ideas strongly indicate that a stable and rigid chair form of cyclic model is hardly constructed, and so few reports have achieved the selective addition to ketones in contrast to aldehydes. Thus, the higher selectivity obtained by the indium system is noteworthy.

Type II. Chelation-Controlled Additions to α-Alkoxy Ketones and β-Keto Esters. Despite only a small stereogenic difference between methyl and methoxymethyl groups on the carbonyl moiety of methoxyacetone **5k**, considerable diastereoselectivity was obtained using InBr (77/23) or InCl (72/28) as shown in Scheme 3.[10c] This result could not be rationalized only by the cyclic model shown in Scheme 2. In addition, the fact that indium metal apparently showed less ability than indium(I) halide indicates involvement of an alternative mechanism to the reaction of α-alkoxy ketones.

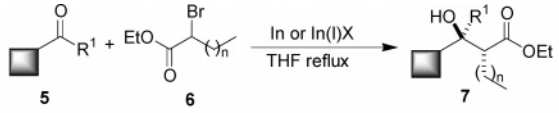
A plausible involvement of a chelated-transition state (chelated-cyclic transition state) as noted in our previous Sn(II) system is strongly envisioned.[13,14] Along this line,

(10) (a) Reported yield for this reaction is 99% (ds 3:2) using HIU (20 kHz, 600 W, 13 mm tip diameter at a power level of 7); see ref 6. (b) In some of the cases, InBr was employed. The results are comparable with indium metal as noted in our preliminary studies; see ref 9. (c) The reactions were carried out using method A.

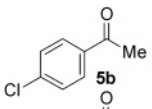
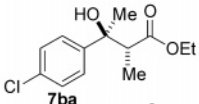
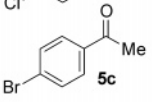
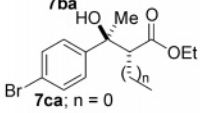
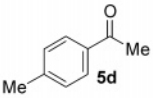
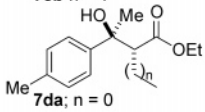
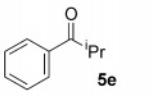
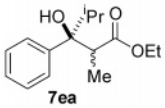
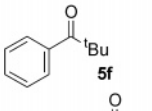
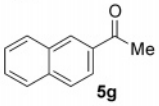
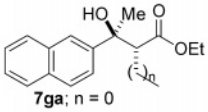
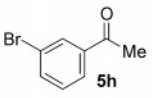
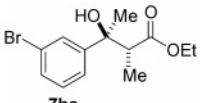
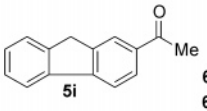
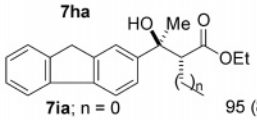
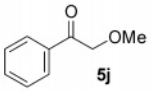
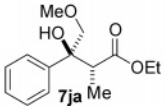
(11) Yasuda, M.; Hirata, K.; Nishino, M.; Yamamoto, A.; Baba, A. J. *Am. Chem. Soc.* **2002**, *124*, 13442.

(12) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702.

TABLE 2. Indium-Based Diastereoselective Reformatsky-Type Reaction of Ketones 5 with 6[a]

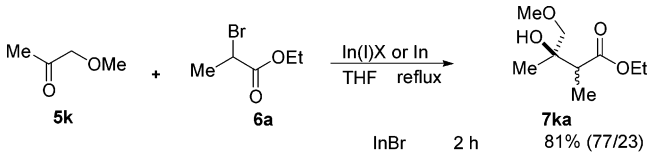


5 6 7

entry	ketone	α-halo ester	In or InX	T (h)	method[b]	product[d]	yield (%) (*anti*/syn)
1	**5a**	**6b**; n = 1	In	2.5	A	**7ab**; n = 1	99 (79:21)[10b]
2[c]	**5a**	**6c**; n = 11	In	8.0	A	**7ac**; n = 11	65 (83:17)[10b]
3	 **5b**	**6a**; n = 0	In	3.0	B	 **7ba**	99 (75:25)[10b]
4	 **5c**	**6a**; n = 0	In	3.0	B	 **7ca**; n = 0	86 (75:25)
5		**6b**; n = 1	In	2.5	A	**7cb** n = 1	97 (82:18)
6	 **5d**	**6a**; n = 0	In	1.0	A	 **7da**; n = 0	88 (93:7)
7			InBr	3.5	B		87 (75:25)
8[c]	**5d**	**6c**; n = 11	In	5.5	A	**7dc**; n = 11	69 (85:15)
9	 **5e**	**6a**; n = 0	In	70 min	A	 **7ea**	60 (69:31)
10			InBr	3.5	A		34 (50:50)
11			InCl	2.5	A		16 (50:50)
12	 **5f**	**6a**; n = 0	In	70 min	A	**7fa**	NR
13	 **5g**	**6a**; n = 0	In	70 min	A	 **7ga**; n = 0	98 (85:15)
14			InBr	4.0	B		97 (85:15)
15	**5g**	**6b**; n = 1	In	3.0	A	**7gb**; n = 1	90 (80:20)[10b]
16	 **5h**	**6a**; n = 0	InBr	3.5	B	 **7ha**	88 (73:27)
17	 **5i**	**6a**; n = 0	In	1.0	A	 **7ia**; n = 0	95 (86:14)
18		**6b**; n = 1	In	1.5	A	**7ib**; n = 1	91 (80:20)
19	 **5j**	**6a**; n = 0	In	3.0	B	 **7ja**	90 (82:18)

[a] **5** (1 mmol), **6** (1.6−1.8 mmol), indium powder, or In(I)X (1.2 mmol) were used in refluxing dry THF (2 mL). [b] See the footnote in Table 1. [c] **5** (1 mmol), **6** (2 mmol), and indium powder (2 mmol) were used. [d] Only the major isomers (*anti*) are drawn.

SCHEME 3. Reaction of Ketone 5k with 6a[a]



[a] **7ka** was isolated as inseparable diastereomers; the stereochemistry was not determined.

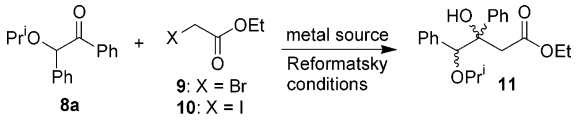
we envisaged three types of reactions: α-alkoxy ketones with α-halo ester (1,4-chelated model, Scheme 1), *β*-keto esters with α-halo ester (1,5-chelated model, Scheme 1), and α-alkoxy ketone with branched α-halo ester.

Primarily, we examined on the additions to α-alkoxy ketones under the optimized conditions for the simple ketones in the above section (Table 3). However, neither indium metal nor InCl system gave positive results

(13) Yasuda, M.; Okamoto, K.; Sako, T.; Baba, A. *Chem. Commun.* **2001**, 157 and references therein.

(14) For selective reactions under the chelation-controlled conditions, see: (a) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (b) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1994**, *23*, 556. For the chelation-controlled aldol-type additions to α-alkoxy aldehydes using enol silanes, see: (c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327. (d) Reetz, M. T.; Raguse, B.; Marth, C. F.; Hugel, H. M.; Bach, T.; Fox, D. N. A. *Tetrahedron* **1992**, *48*, 5731. (e) Reetz, M. T.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119.

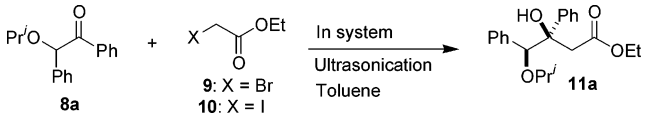
TABLE 3. Reactions of α-Halo Ester with α-Alkoxy Ketone under the Established Conditions[a]



entry	**8a** (mmol)	α-halo ester (mmol)	metal source (mmol)	solvent[b]	conditions (h)	yield (%) (*syn/anti*)
1	0.5	**10** (1.0)	In (1.0)	THF	reflux (2)	99 (50:50)
2	0.5	**10** (1.0)	InCl (1.0)	THF	reflux (2)	50 (50:50)
3	1.0	**10** (1.6)	In (1.1)	THF	US (1.5)	32 (56:46)
4	0.5	**10** (1.0)	InCl (1.0)	THF	US (2)	<5
5[c]	0.5	**10** (1.0)	SmI_2 (0.6)	toluene	US (2)/0−10 °C	<5
6[c]	0.5	**10** (1.0)	SmI_2 (0.6)	THF	−78 °C to rt (2.5)	<5
7	5.0	**9** (5.5)	Zn (6.0)	benzene−Et_2O	reflux	40 (31:69)
8[d]	10.0	**9** (12.0)	Zn (16.0)	Et_2O	35 °C (1)	32 (48:52)
9	0.5	**10** (1.0)	InCl (1.0)	toluene	US (2)	99 (98:2)

[a] US = ultrasonication (38 kHz, 120 W) at room temperature. [b] THF (1.5 mL), toluene (1.5 mL), benzene−Et_2O (5:1, 12 mL), Et_2O (45 mL). [c] SmI_2 0.1 M THF solution was used. [d] Me_3SiCl (0.15 mL) was used for the activation of zinc in ether.

TABLE 4. Optimization of Reaction Conditions: Chelation-Controlled Addition of Indium Enolates to α-Alkoxy Ketones[a]



		In system			
entry	α-halo ester	In or InX	InX_m (mmol)	conditions (h)	**11a** yield (%) (*syn/anti*)
1	**10**	In		110 °C (1)	95 (50:50)
2	**10**	In		US (2)	18 (90:10)
3	**10**	InCl		US (2)	99 (98:2)[b]
4	**10**	InBr		US (2)	91 (98:2)
5	**10**	InI		US (2)	94 (98:2)
6	**10**	In	$InCl_3$ (1)	US (2)	99 (98:2)
7	**10**	In	$InCl_3$ (0.35)	US (2)	99 (98:2)
8	**10**	In	$InBr_3$ (1)	US (1.5)	99 (98:2)
9	**9**	InBr		US (1.5)	<5
10	**10**	In	$InCl_3$ (1)	US (1.5)	<5[c]
11	**10**	In	$InCl_2$ (0.5)	US (1.5)	80 (98:2)

[a] Reactions were carried out using **8a** (0.5 mmol), α-halo ester (1 mmol), and indium powder or InX (1.0 mmol) in dry toluene (1.5 mL) under ultrasonication (US; 38 kHz, 120 W) at room temperature unless otherwise specified. [b] Benzene solvent was used. [c] THF solvent was used.

(entries 1 and 2). THF refluxing gave high yields but suffered from no selectivities. Other solvents such as 1,4-dioxane and DMF were ineffective. Representative other metallic reagents for Reformatsky-type reactions such as zinc[13,15] and samarium(II) iodide[16] gave low yields or low diasteroselectivities (entries 5−8). Fortunately, we succeeded in optimizing the chelation-controlled addition to **8a** using indium(I) halide in dry toluene at ambient temperature under ultrasonication (Table 3, entry 9, and Table 4, entries 3 and 4).

The change of solvent into a nonpolar solvent such as toluene is very much essential, and benzene also acted as an effective solvent (entry 4, Table 4). Surprisingly, the reactivity order of indium metal and In(I)X was completely changed in contrast to the reaction with simple ketones (see Table 1). The use of indium powder at room temperature gave only low yield (18%, entry 2), and heating at 110 °C resulted in losing diastereoselectivity (entry 1). Employing ethyl bromoacetate instead of ethyl iodoacetate was ineffective (entry 9).

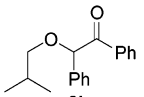
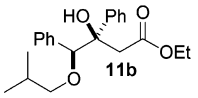
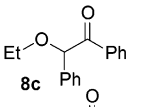
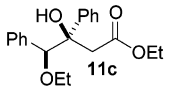
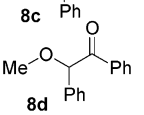
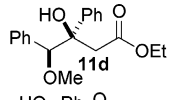
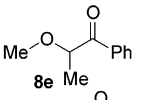
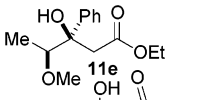
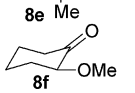
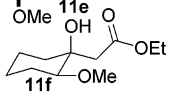
Although indium metal powder did not afford a satisfactory result, strikingly the combined use of indium metal with $InCl_3$ or $InBr_3$ afforded the "*syn*" isomer **11a** in excellent yields under the same conditions employed for In(I)X system (entries 6−8).[17] THF solvent again completely disturbed the addition in this combined system (entry 10), perhaps because of the strong coordination of THF to an active species. It is notable that the use of $InCl_2$ instead of $InCl_3$ also afforded **11a** with excellent diastereoselectivity (>98:2, entry 11). This interesting result does not indicate that $InCl_3$ acts as a simple Lewis acid. We believe that the in situ formation of In(I)X occurs by the disproportionation between indium metal and InX_3 or InX_2 under the experimental conditions.[4m,17]

(15) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796.

(16) SmI_2-mediated Reformatsky-type reactions: (a) Orsini, F.; Lucci, E. M. *Tetrahedron Lett.* **2005**, *46*, 1909 and references therein. (b) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *Acc. Chem. Res.* **1991**, *113*, 8036.

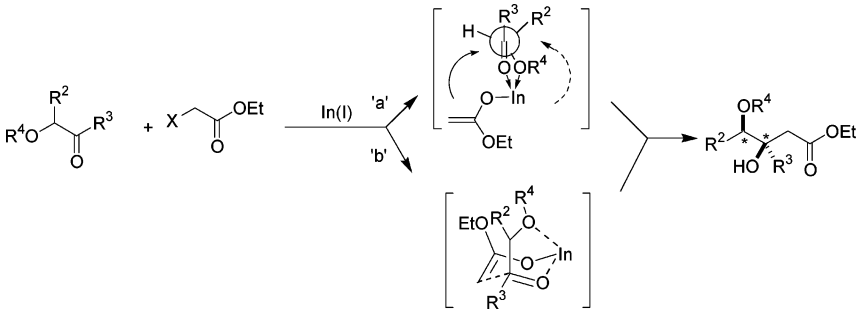
(17) Although the reaction occurs without $InCl_3$ (Table 4, entry 2), addition promoted the reaction very effectively in toluene. (b) Interesting results were obtained. However, at this stage we believe the disproportionation occurs between indium and $InCl_3$; see: Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*; Wiley: New York, 1999; p 203.

TABLE 5. Chelation-Controlled Addition of Indium Enolates to Various α-Alkoxy Ketones in Toluene[a]

entry	substrate	In system: In or InCl (mmol)	In system: InX_3 (mmol)	T (h)	product	yield (%) (*syn*/*anti*)
1	 **8b**	InCl (1.0)	-	2	 **11b**	99 (98:2)
2		In (1.0)	$InCl_3$ (1)	2		99 (98:2)
3		In (1.0)	$InBr_3$ (0.5)	2		94 (98:2)
4	 **8c**	In (1.0)	$InCl_3$ (1)	2	 **11c**	99 (98:2)
5		In (1.0)	$InCl_3$ (1)	2		<5[b]
6	 **8d**	InCl (1.0)	-	2	 **11d**	98 (98:2)
7		In (1.0)	$InCl_3$ (0.5)	2		90 (98:2)
8	 **8e**	InCl (1.0)	-	3	 **11e**	96 (98:2)
9		In (1.6)	$InCl_3$ (0.4)	3		92 (98:2)[c]
10	 **8f**	InCl (1.0)	-	3	 **11f**	96 (75:25)

[a] Reactions were carried out using alkoxy ketone **8** (0.5 mmol) or iodo ester **10** (1 mmol) in dry toluene (1.5 mL) under US (38 kHz, 120 W) at room temperature unless otherwise specified. [b] THF solvent was used. [c] **8e** (1 mmol) and **10** (2 mmol) were used.

SCHEME 4. Mechanism of Chelation-Controlled Addition to α-Alkoxy Ketones



Under the optimized conditions, a variety of α-alkoxy ketones **8** and iodo ester **10** were treated to afford the corresponding "*syn*" isomers **11** exclusively as summarized in the Table 5. When the substitution at 2-position of alkoxy ketone **8** which would crucially direct the chelation-controlled stereochemistry was changed from phenyl to methyl moiety, no decrease in the selectivity was observed (entries 6, 7 vs 8, 9). 2-Methoxycyclohexanone **8f** gave a lower selectivity perhaps because of ring strain (entry 10). The observed very high diastereoselection seems to be explainable through a usual chelation-controlled mechanism (path "a") as shown in Scheme 4. No effect of the bulkiness of R^2, however, suggestively indicates an alternative model like chelated-cyclic transition state (path "b").[11,18]

Next, we were very much interested to widen up the addition to β-keto esters (Scheme 1, eq 3). To the best of our knowledge, there exist no reports on the chelation-controlled diastereoselective Reformatsky-type reactions of β-keto esters.[2] Both In(I)X and In−InX_3 systems could be again applied to this reaction to afford "*syn*" products **13** selectively. Optimizations of reaction conditions as well as the results using a variety of β-keto esters are summarized in Table 6.

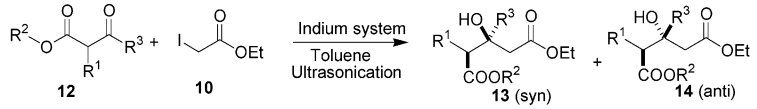
A nonpolar solvent such as toluene is again the choice. The combined use of indium metal and $InCl_3$ under ultrasonication was most effective to give 89% yield with >98% of *syn*-selectivity (entry 4), while InCl gave also a satisfactory yield of 73% with >98% selectivity (entry 1). Employing indium powder, zinc, SmI_2, or THF solvent did not promote the addition (entries 5−8).[19a] A limitation is that no reaction was observed with ketone **12d** bearing *tert*-butyl moiety because of its steric hindrance. Decreasing of the reactivity and selectivity is observed in alkyl ketone **12e**. Reduction of product **13a** was carried out to afford the corresponding triol **13aB** as a colorless solid.[19b] Single-crystal X-ray structure analysis of the triol **13aB** (see the Supporting Information for the ORTEP structure) unambiguously revealed the stereochemistry of products in these reactions. Further, because of a loser 1,5-chelation compared with the 1,4-chelation for α-alkoxy ketone, the chelated-cyclic transition state model is again plausible for the observed high diastereoselectivities (Scheme 5, path b).[11,18]

In the above reactions, we have shown the facile stereoselective construction of two stereogenic centers; next, we aimed to tailor three stereogenic centers. A combination of both the type-I and type-II reaction model that is a chelated cyclic transition state would cleanly complete the stereoselective construction of subsequent three stereogenic centers. In an exemplar reaction, we

(18) Sato, K.; Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429.

(19) (a) Even refluxing the reaction mixture in THF was not effective in this case. (b) Reduction was carried out in THF with an excess of $LiAlH_4$ (6 mmol) for 1 mmol of substrate at room temperature.

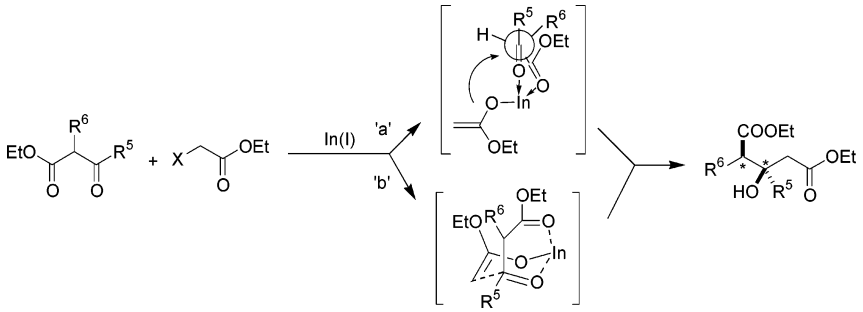
TABLE 6. Concept of Chelation-Controlled Addition of Indium Enolates to β-Keto Esters in Toluene[a]



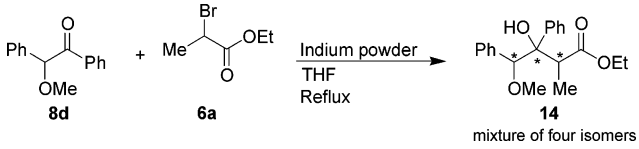
entry	β-keto ester	**10**/ (mmol)	In system (mmol)	$InCl_3$ (mmol)	conditions (h)	product	yield (%) *(syn/anti)*
1		(1.0)	InCl (1.0)	-	US (2.5)		73 (98:2)
2		(1.0)	InBr (1.0)	-	US (2.5)		85 (98:2)
3		(1.0)	In (1.0)	(0.5)[b]	US (2.5)		85 (98:2)
4		(2.3)	In (1.5)	(1.0)	US (2.5)		89 (98:2)[c]
5		(1.0)	In (1.0)	-	US (2.5)		<5
6		(1.0)	In (1.1)	-	70°C (2.0)		<10[d]
7		(2.5)	Zn (2.2)	-	80°C (2.5)		34 (80:20)[e]
8		(0.5)	SmI_2 (0.6)	-	-78°C - rt		<5[f]
9	**12b**	(1.0)	In (1.0)	(1.0)	US (2.5)	**13b**	75 (98:2)
10 11 12	**12c**	(2.0)	In (1.5)	(1.0)	US (4.0)	**13c**	75 (98:2)
13	**12d**	(2.0)	In (1.5)	(1.0)	US (4.0)	**13d**	NR[c]
14	**12e**	(2.3)	In (1.5)	(1.0)	US (3.5)	**13e**	41 (75:25)[c]

[a] Reactions were carried out using **12** (0.5 mmol) and **10** in dry toluene (1.5 mL) under US (38 kHz, 120 W) at room temperature unless otherwise specified. [b] $InBr_3$ was used. [c] **12** (1.0 mmol) was used. [d] THF solvent was used. [e] **12a** (2 mmol). Benzene−ether (5:1) mixture solvent used. [f] SmI_2 0.1 M solution of THF was added.

SCHEME 5. Mechanism of Chelation-Controlled Addition to β-Keto Esters



SCHEME 6. Reaction of 8d with 6a



attempted the addition of branched α-halo ester **6a** to α-alkoxy ketone **8d** as shown in Scheme 6. However, in this stage a mixture of four isomers was produced in >95% combined yield.[20] The establishment of control over three stereogenic centers is under investigation.

Active Species Involved in the Reformatsky-Type Reactions. In our previous ^{1}H NMR studies,[9,21] we observed that two kinds of independent active species (in THF-d_8) at 2.08 ppm (species A) and 1.85 ppm (species B) are forming in the reaction of ethyl iodoacetate (**10**) with In(I)I or indium metal.[22,23] Only the latter species B was found to immediately react with benzaldehyde in THF solution as already noted.[9] The active species B is believed to react fast with simple ketones in THF solution as already discussed. In the nonpolar solvents such as

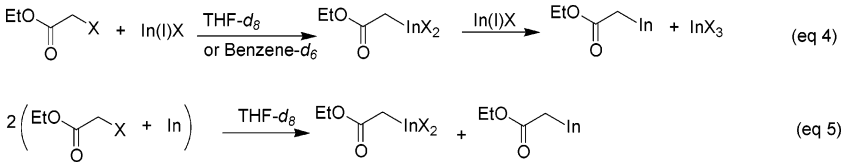
(20) The complete isolation of isomers and the determination of isomeric ratio is under investigation on the stereoselective construction of three subsequent stereogenic centers.

(21) For the H^1 NMR spectra see ref 9 and the Supporting Information therein.

(22) Similar results have been discussed by Chan *et al.* for the generation of allyl- or allenylindiums from indium metal and allyl- or propargyl bromide, respectively, in DMF solution, see: (a) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc*. **1999**, *121*, 3228. (b) Miao, W.; Chung, L., W.; Wu, Y.-D.; Chan, T., H. *J. Am. Chem. Soc.* **2004**, *126*, 13326. Araki et al. reported the formation of allyl-In(III)I_2 from allyl iodide and In(I)I in THF solution; see: (c) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291.

(23) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.

SCHEME 7. Formation of Low-Valent RIn(I)-Type Species in the Reformatsky Reactions



toluene and benzene, the generation of similar species would be expected. In fact, when the mixture of InCl and **10** in benzene-d_6 was subjected to ultrasonication for 45 min, two broad peaks appeared around δ 2.65 (less intensive) and δ 2.59 (more intensive).[24a] Both the new peaks disappeared smoothly by the addition of either benzaldehyde or α-alkoxy ketone **8a** (see the Supporting Information for the spectra). Similarly, an easy generation of the active species was monitored in the combined system of In−InCl$_3$ in benzene-d_6.[24b] In contrast, the appearance of the new peaks corresponding to the active species was very slow in the case of indium metal in benzene-d_6. Perhaps this is the reason indium metal could not promote the reaction in toluene under mild conditions.[25] Since using THF solvent a complete loss chelation control was observed (Table 3), the active species is plausibly a low valent RIn(I)-type rather than RIn(III)X$_2$. In toluene, the low-valent indium species has a high coordination acceptance that can play an important role for both activation of ketones and directing for a high diastereoselective addition without the disturbance of the coordination by the solvent.

From these results and discussions, the formation of RIn(I)-type transient species could be conjectured as given in the Scheme 7. From the ^{1}H NMR spectra it is believed that the facile transformation from RIn(III)X$_2$ to RIn(I) is taking place in toluene (see Supporting Information). The other low reactive species could be RIn(III)X$_2$-type which perhaps cannot be involved in the chelation process. The facile reaction with indium metal would proceed only in THF solution.

In conclusion, an exceedingly important highly diastereoselective C−C bond formation synthetic protocol was established, via In- or In(I)-based Reformatsky-type reactions of simple ketones, α-alkoxy ketones and β-keto esters. We have demonstrated that indium-based reagents exhibit a distinctive diastereoselective pattern for the Reformatsky-type reactions of ketones. The predominant formations of "*anti*" isomers, noticeably suggest the participation of the transient "*E* enolates" in the transition state of the reaction in the case of branched α-halo esters. Diastereoselective tailoring of the stereogenic centers in the chelation-controlled addition of indium enolates to α-alkoxy ketones and β-keto esters was established. In this line, excellent "*syn*" selective products were obtained using In(I)X or In−InCl$_3$ systems in toluene. Based on the astonishing diastereoselectivities and taking the chelation as the key point in the present result, we accomplished that involvement of transient but discrete RIn-type organoindium intermediates in the Reformatsky-type reactions. Interestingly, the establishment of control over two stereogenic center is accounted here, and stereoselective construction of three stereogenic centers would be a challenging target, investigations are under progress in this line.

(24) (a) A similar trend was observed in THF as noted in ref 9. (b) Noticeably, treatment of ethyl iodoacetate and indium and InCl$_3$ also afforded a similar type of spectra and species (see the Supporting Information for the spectra).

(25) Treatment of indium metal with ethyl iodoacetate in benzene-d_6 afforded two new peaks; however, very slow consumption of ethyl iodoacetate was noted and the rate of consumption of ethyl iodoacetate was very high and fast in the cases of In−InCl$_3$ as well as InCl systems. See the Supporting Information for the spectra.

Experimental Section

General Methods. Ultrasonication was carried out using ultrasonic cleaner (38 kHz, 120 W). Melting points are uncorrected. IR spectra were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on 270 or 400 (270/67.9 or 400/100 MHz) spectrometers, respectively, with TMS as internal or external standard. Column chromatography was performed on silica gel (100−200 mesh). Reactions were carried out either under ultrasonication (bath temperature about 10−25 °C, ice was added time to time to the ultrasonication water bath) or at reflux temperature under an inert atmosphere. Solutions were dried with anhydrous magnesium sulfate. Reagents were added to the reaction flask through a syringe. Analytical thin-layer chromatography (TLC) was performed on silica plates, and components were visualized by observation under iodine or UV light. Yields were determined from ^{1}H NMR spectra using internal standards or after isolation in column chromatography. Ratios of diastereomers were determined from ^{1}H NMR of crude reaction mixture.

Materials. Toluene/benzene/Et$_2$O/THF were distilled from sodium and benzophenone. All starting ketones, α-halo esters, indium powder (100 mesh), and In(I)X used in this work are commercially purchased. InI and InBr are available in beads form and used either as beads or particularly, after grinding under an inert atmosphere in the cases of reactions under ultrasonication. InCl is available in powder form. SmI$_2$ (0.1 M solution in THF), Zn powder, InCl$_3$, InCl$_2$, and InBr$_3$ were commercially purchased.

Ethyl 3-Hydroxy-2-methyl-3-phenylbutyrate (7aa). Column chromatographic purification afforded a mixture of diastereomers; see references 5 and 6 for spectral data.

Ethyl 3-Hydroxy-2-ethyl-3-phenylbutyrate (7ab).[5c] Column chromatographic purification afforded a mixture of *anti*/*syn* diastereomers as colorless thick oil: IR (neat) 3502, 3482, 1708, 1376, 1187 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) 7.49−7.17 (m, 5 H), 4.25 (q, J = 7.3 Hz, 2 H),* 3.98 (s, 1 H), 3.95−3.81 (m, 2 H,), 2.80 (dd, J_1 = 10.3, J_2 = 4.9 Hz, 1 H), 2.66 (dd, J_1 = 11.3, J_2 = 3.80 Hz, 1 H),* 1.96−1.67 (m, 2 H), 1.52 (s, 3 H),* 1.49 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H),* 0.95 (t, J = 7.3 Hz, 3 H), 0.89 (t, J = 7.0 Hz, 3 H), 0.75 (t, J = 7.3 Hz, 3 H);* ^{13}C NMR (100 MHz, CDCl$_3$) 176.8,* 176.2, 147. 6, 145.3,* 128.0,* 127.9, 126.7, 126.6,* 124.8,* 124.7, 74.9, 74.4,* 60.7,* 60.2, 57.5,* 56.8, 30.1,* 27.1, 20.8,* 20.4, 14.3,* 13.8, 12.3, 12.1;* MS (EI) *m/z* 236 (M$^+$, 2), 191 (2), 116 (42), 105 (24), 101 (20); HRMS (EI) calcd for C$_{14}$H$_{20}$O$_3$ 236.1412, found *m/z* 236.1420, 236.1418 (M$^+$). Asterisk corresponds to the minor (*syn*) isomer.

(2*S,3*S**)-Ethyl 3-Hydroxy-2-undecanyl-3-phenylbutyrate (7ac$_1$).** Repetitive silica gel column purification afforded *anti* (major) isomer in pure form. **7ac$_1$**: isolated as a colorless thick oil which solidified on standing; mp 46−48 °C; IR (neat) 3502, 3019, 2927, 1700, 1214 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) 7.43−7.18 (m, 5 H), 3.97 (s, 1 H), 3.91−3.79 (m, 2 H), 2.85 (dd, J_1 = 11.00, J_2 = 3.80 Hz, 1 H), 1.80−1.61 (m,

2 H), 1.48 (s, 3 H), 1.20−1.40 (m, 20 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.4, 147.5, 127.9, 126.7, 124.7, 74.9, 60.3, 55.1, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 27.9, 27.3, 27.2, 22.7, 14.1, 13.8; MS (EI) *m/z* 376 (M^+, 0.64), 257 (11), 256 (64), 213 (15), 157 (22), 121 (100), 105 (48), 101 (74), 77 (21); HRMS (EI) calcd for $C_{24}H_{40}O_3$ 376.2977, found *m/z* 376.2971 (M^+). The minor isomer could not be isolated.

Ethyl 3-(4-Chlorophenyl)-3-hydroxy-2-methylbutyrate (7ba).[26] Column chromatographic purification afforded a mixture of *anti/syn* diastereomers as a colorless thick oil: IR (neat) 3490, 2985, 1712, 1492, 1191 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 7.39−7.26 (m, 4 H), 4.27−4.21 (m, 2 H),* 4.15 (s, 1 H),* 4.00 (s, 1 H), 3.93 (q, J = 7.3 Hz, 2 H), 2.96 (q, J = 7.3 Hz, 1 H), 2.78 (q, J = 7.3 Hz, 1 H),* 1.54 (s, 3 H),* 1.43 (s, 3 H), 1.33 (d, J = 7.3 Hz, 3 H), 1.30 (t, J = 7.3 Hz, 3 H),* 1.00 (t, J = 7.3 Hz, 3 H), 0.97 (d, J = 7.3 Hz, 3 H);* ^{13}C NMR (100 MHz, $CDCl_3$) 177.1,* 176.6, 146. 2, 143.6,* 132.5, 128.2,* 128.1, 126.4,* 126.2, 74.4, 74.0,* 61.0,* 60.6, 49.1,* 48.2, 29.8,* 26.8, 14.1,* 13.8, 12.6,* 12.3; MS (EI) *m/z* 256 (M^+, 1), 157 (18), 155 (54), 154 (25), 141 (32), 139 (100), 113 (14), 102 (39), 75 (19); HRMS (EI) calcd for $C_{13}H_{17}ClO_3$ 256.0866, found *m/z* 256.0843, 256.0844 (M^+). Asterisk corresponds to the minor (*syn*) isomer.

Ethyl 3-(4-Bromophenyl)-3-hydroxy-2-methylbutyrate (7ca).[26] Repetitive silica gel column chromatography (three times) afforded both the isomers **7ca**$_1$ and **7ca**$_2$ in pure form. **(2*S**,3*S**)-Ethyl 3-(4-bromophenyl)-3-hydroxy-2-methylbutyrate (7ca$_1$):** *anti* (major) isomer, isolated as a colorless thick oil; IR (neat) 3490, 2981, 1712, 1484, 1191 cm^{-1}; ^{1}H NMR: (270 MHz, $CDCl_3$) 7.43 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 8.4 Hz, 2 H), 4.14 (s, 1 H), 3.93 (q, J = 7.3 Hz, 2 H), 2.95 (q, J = 7.3 Hz, 1 H), 1.42 (s, 3 H), 1.33 (d, J = 7.3 Hz, 3 H), 1.00 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.6, 146.7, 131.1, 126.6, 120.7, 74.2, 60.7, 48.2, 26.8, 13.8, 12.3; MS (EI) *m/z* 302 (M^+ + 2, 2), 300 (M^+, 2), 201 (91), 199 (92), 185 (21), 183 (22), 102 (100), 74 (44); HRMS (EI) calcd for $C_{13}H_{17}BrO_3$ 300.0361, found *m/z* 300.0375 (M^+).

Preparation of Ester Derivative, 4-Chlorobenzoic acid-1-(4-bromophenyl)-2-ethoxycarbonyl-1-methylpropyl ester (7caB) from Major Isomer 7ca$_1$. The esterification was performed according to the literature.[11,12] A flask was charged with dry dichloromethane (10 mL) and **7ca**$_1$ (1.0 mmol) under a nitrogen atmosphere at room temperature. To this solution were sequentially added $MgBr_2$ (2.0 mmol), Et_3N (3.0 mmol), and 4-chlorobenzoic acid anhydride (2.0 mmol). After the mixture was stirred for 15 h, water (10 mL) was added. The water phase was extracted with ethyl acetate, and the organic layer was dried over $MgSO_4$. The solvent was distilled off under reduced pressure. Column chromatographic purification (hexane/AcOEt, 3/1) of the resultant residue on silica gel gave the product **7caB** in 65% yield. Recrystallization from hexane/ether gave the suitable crystals for X-ray structure analysis. See the Supporting Information for the X-ray structure data of product **7caB**.

Spectral data for the ester **7caB** are as follows. The compound was isolated as a colorless solid and repetitively recrystallized from hexane/ether (35 mg of compound in a solution of 1.5 mL diethyl ether and ∼1 mL hexane was subjected to ultrasonication until a clear (diethyl ether can be used if needed more) solution was obtained, which was allowed to stand at rt for ∼1 day to afford the crystals): mp 93−95 °C; IR (Neat) 2985, 1724, 1592, 1488, 1272, 1191 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 7.98 (d, J = 8.4 Hz, 2 H), 7.46 (d, J = 8.4 Hz, 2 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.4 Hz, 2 H), 4.18 (q, J = 7.0 Hz, 2 H), 3.09 (q, J = 7.3 Hz, 1 H), 2.08 (s, 3 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.03 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.2, 163.5, 141.6, 139.5, 131.5, 131.1, 129.3, 128.7, 127.0, 121.8, 84.7, 60.8, 51.3, 18.6, 14.2, 12.4; MS (EI) *m/z* 440 (M^++2, 0.3), 438 (M^+, 0.2), 337 (1.7), 240 (4.8), 209 (1.1), 183 (1.7), 160 (1.2), 139 (100), 112 (0.6), 91 (1.1), 75 (2.5); HRMS (EI) calcd for $C_{20}H_{20}BrClO_4$ 438.0233, found *m/z* 438.0227 (M^+).

(2*R,3*S**)-Ethyl 3-(4-bromophenyl)-3-hydroxy-2-methylbutyrate (7ca$_2$):** *syn* (minor) isomer, isolated as a colorless thick oil; IR (neat) 3502, 2981, 1712, 1484, 1191 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 7.45 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 4.27−4.18 (m, 2 H), 3.99 (s, 1 H), 2.77 (q, J = 7.3 Hz, 1 H), 1.53 (s, 3 H), 1.31 (t, J = 7.3 Hz, 3 H), 0.94 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.1, 144.2, 131.2, 126.8, 120.6, 74.1, 61.0, 49.0, 29.8, 14.1, 12.7; MS (EI) *m/z* 302 (M^+ + 2, 2), 300 (M^+, 2), 201 (78), 200 (10), 199 (80), 185 (33), 183 (34), 102 (100), 74 (46), 57 (6), 56 (8); HRMS (EI) calcd for $C_{13}H_{17}BrO_3$ 300.0361, found *m/z* 300.0369 (M^+).

Ethyl 3-(4-Bromophenyl)-3-hydroxy-2-ethylbutyrate (7cb). Column chromatographic purification afforded a mixture of *anti/syn* diastereomers as a colorless thick oil: IR (neat) 3490, 2973, 1708, 1484, 1187 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.46−7.27 (m, 2 H), 7.32−7.27 (m, 2 H), 4.26 (q, 2 H),* 4.02 (s, 1 H), 3.90 (q, J = 7.3 Hz, 2 H), 2.75 (dd, J_1 = 10.0, J_2 = 5.4 Hz, 1 H), 2.60 (dd, J_1 = 11.3, J_2 = 3.5 Hz, 1 H),* 1.94−1.79 (m, 2 H), 1.49 (s, 3 H),* 1.44 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H),* 0.95 (t, J = 7.0 Hz, 3 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.75 (t, J = 7.3 Hz, 3 H);* ^{13}C NMR (100 MHz, $CDCl_3$) 176.6,* 176.1, 146.8, 144.5,* 131.1,* 131.0, 126.7,* 126.7, 120.6, 120.6,* 74.7, 74.3,* 60.9,* 60.5, 57.2,* 56.4, 30.1,* 27.2, 20.8,* 20.4, 14.3,* 13.9, 12.2, 12.0;* MS (EI) *m/z* 316 (M^+ + 2, 2), 314 (M^+, 1), 301 (4), 300 (1), 299 (4), 201 (43), 199 (45), 185 (29), 183 (30), 157 (7), 116 (100), 101 (35), 88 (14); HRMS (EI) calcd for $C_{14}H_{19}BrO_3$ 314.0518, found *m/z* 314.0534, 314.0514 (M^+). Asterisk corresponds to the minor isomer.

Ethyl 3-(4-Methylphenyl)-3-hydroxy-2-methylbutyrate (7da).[26] Column chromatographic purification afforded a mixture of *anti/syn* diastereomers as a colorless thick oil: IR (neat) 3498, 2985, 1712, 1457, 1191 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 7.31 (d, J = 8.4 Hz, 2 H), 7.11 (d, J = 8.4 Hz, 2 H), 4.23−4.16 (m, 2 H),* 4.04 (s, 1 H), 3.92 (q, J = 7.3 Hz, 2 H), 2.98 (q, J = 7.3 Hz, 1 H), 2.80 (q, J = 7.3 Hz, 1 H),* 2.33 (s, 3 H),* 2.31 (s, 3 H), 1.54 (s, 3 H),* 1.43 (s, 3 H,), 1.31 (d, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.7, 144.6, 136.2, 128.6, 124.5, 74.5, 60.4, 48.4, 26.8, 20.8, 13.8, 12.3; MS (EI) *m/z* 236 (M^+, 1), 191 (2), 136 (10), 135 (100), 119 (20), 102 (5), 91 (14), 65 (4); HRMS (EI) calcd for $C_{14}H_{20}O_3$ 236.1412, found *m/z* 236.1410, 236.1419 (M^+). Asterisk corresponds to the minor isomer.

Ethyl 3-Hydroxy-2-undecanyl-3-(4-methylphenyl)-butyrate (7dc). Repetitive silica gel column chromatography (three times) purification afforded both isomers **7dc**$_1$ and **7dc**$_2$ in pure form. **(2*S**,3*S**)-Ethyl 3-hydroxy-2-undecanyl-3-(4-methylphenyl)butyrate (7dc$_1$):** *anti* (major) isomer, isolated as a colorless thick oil and solidified on standing; mp 47−49 °C; IR (neat) 3502, 2927, 2854, 1708, 1187 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 7.29 (d, J = 8.4 Hz, 2 H), 7.10 (d, J = 8.4 Hz, 2 H), 3.88 (s, 1 H), 3.87 (q, J = 7.3 Hz, 2 H), 2.83 (dd, J_1 = 11.0, J_2 = 3.8 Hz, 1 H), 2.30 (s, 3 H), 1.90−1.65 (m, 2 H), 1.46 (s, 3 H), 1.40−1.10 (m, 20 H), 0.91 (t, J = 7.0 Hz, 3 H), 0.88 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.4, 144.6, 136.2, 128.5, 124.6, 74.8, 60.2, 55.1, 31.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 27.9, 27.3, 27.2, 22.7, 21.0, 14.1, 13.8; MS (EI) *m/z* 390 (M^+, 0.4), 256 (10), 235 (14), 135 (100), 134 (8), 119 (31), 115 (5), 101 (24); HRMS (EI) calcd for $C_{25}H_{42}O_3$ 390.3134, found *m/z* 390.3130 (M^+).

(2*R,3*S**)-Ethyl 3-hydroxy-2-undecanyl-3-(4-methylphenyl)butyrate (7dc$_2$):** *syn* (minor) isomer, isolated as a colorless thick oil; IR (neat) 3525, 2954, 2854, 1708, 1492, 1187 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 7.31 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 4.24 (q, J = 7.3 Hz, 2 H), 3.72 (s, 1 H), 2.71 (dd, J_1 = 11.0, J_2 = 3.8 Hz, 1 H), 2.34 (s, 3 H), 1.70−1.60 (m, 2 H), 1.49 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.20−1.00 (m, 20 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.9, 144.4, 136.1, 128.8, 124.7, 74.4, 60.7, 55.7, 31.9, 30.4, 29.6, 29.6, 29.5, 29.3, 29.2, 27.6, 27.5, 22.7, 21.0, 14.3,

(26) Balsamo, A.; Barili, P., L.; Crotti, P.; Ferretti, M.; Macchia, B.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2548.

14.1; MS (EI) *m/z* 390 (M^+, 0.7), 256 (12), 211 (3), 157 (6), 135 (100), 119 (47), 101 (27), 88 (27); HRMS (EI) calcd for $C_{25}H_{42}O_3$ 390.3134, found *m/z* 390.3139 (M^+).

Ethyl 3-Hydroxy-2-isopropyl-3-phenylbutyrate (7ea). Column chromatographic purification afforded a mixture of diastereomers; see ref 6 for spectral data.

Ethyl 3-Hydroxy-2-methyl-3-naphth-2-ylbutyrate (7ga).[5d] Repetitive column chromatography purification (three times) afforded *anti* (major) isomer **7ga**$_1$ in ~80% of total yield. The *syn* (minor) isomer **7ga**$_2$ was isolated in ~5% yield and the rest as a mixture of diastereomers. **(2*S**,3*S**)-Ethyl 3-hydroxy-2-methyl-3-naphth-2-ylbutyrate (7ga$_1$):** *anti* (major) isomer, isolated as a colorless thick oil; IR (neat) 3490, 2981, 1708, 1454, 1373, 1184 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.91 (s, 1 H), 7.82−7.78 (m, 3 H), 7.56−7.44 (m, 3 H), 4.26 (s, 1 H), 3.85 (q, J = 7.3 Hz, 2 H), 3.14 (q, J = 7.0 Hz, 1 H), 1.54 (s, 3 H), 1.38 (d, J = 7.0 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.7, 145.0, 133.0, 132.3, 128.1, 127.7, 127.3, 125.9, 125.7, 123.4, 123.3, 74.8, 60.5, 48.3, 26.7, 13.7, 12.4; MS (EI) *m/z* 272 (M^+, 1), 254 (1), 172 (4), 171 (33), 170 (58), 155 (100), 127 (89), 57 (14); HRMS (EI) calcd for $C_{17}H_{20}O_3$ 272.1412, found *m/z* 272.1427 (M^+).

Preparation of Ester Derivative 4-Chlorobenzoic acid-2-ethoxycarbonyl-1-methyl-1-naphthalen-2-ylpropyl Ester (7gaB) from Major Isomer 7ga$_1$. The esterification was performed according to the literature method.[11,12] A flask was charged with dry dichloromethane (10 mL) and **7ga**$_1$ (1.0 mmol) under a nitrogen atmosphere at room temperature. To this solution were sequentially added $MgBr_2$ (2.0 mmol), Et_3N (3.0 mmol), and 4-chlorobenzoic acid anhydride (2.0 mmol). After the mixture was stirred for 15 h, water (10 mL) was added. The water phase was extracted with ethyl acetate, and the organic layer was dried over $MgSO_4$. The solvent was distilled off under reduced pressure. Column chromatographic purification (hexane/AcOEt, 3/1) of the resultant residue on silica gel gave the esterified product **7gaB** in 65% yield. Recrystallization from hexane/ether gave the suitable crystals for X-ray analysis. See the Supporting Information for the X-ray structure data.

7gaB. isolated as a colorless solid. Repetitive recrystallization from hexane/ether was carried out (~35 mg of compound in a solution of ~1.5 mL diethyl ether and ~1 mL hexane was subjected to ultrasonication until a clear (diethyl ether can be used if needed more) solution was obtained, which was allowed to stand at rt for ~1 day to afford the crystals): mp 117−115 °C; IR (KBr) 3000, 1720, 1592, 1384, 1272, 1176, 1091 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 8.01 (d, J = 8.1 Hz, 2 H), 7.84−7.81 (m, 4 H), 7.50−7.24 (m, 5 H), 4.21 (m, 2 H), 3.26 (q, J = 7.0 Hz, 1 H), 2.22 (s, 3 H), 1.27 (t, J = 7.3 Hz, 3 H), 1.02 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.6, 163.5, 139.7, 139.4, 132.6, 132.6, 131.1, 129.5, 128.6, 128.4, 128.3, 127.5, 126.3, 126.2, 124.7, 122.8, 85.4, 60.7, 51.2, 18.4, 14.2, 12.5; MS (EI) *m/z* 411 (M^+ + 1, 1), 410 (M^+, 6), 254 (18), 239 (5), 225 (3), 209 (6), 208 (2), 181 (12), 165 (10), 152 (5), 139 (100), 113 (3); HRMS (EI) calcd for $C_{24}H_{23}ClO_4$ 410.1285, found *m/z* 410.1268 (M^+).

(2*R,3*S**)-Ethyl 3-hydroxy-2-methyl-3-naphth-2-ylbutyrate (7ga$_2$):** *syn* (minor) isomer, isolated as a colorless thick oil; IR (neat) 3502, 1712, 1488, 1191 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.99 (s, 1 H), 7.87−7.79 (m, 3 H), 7.49−7.24 (m, 3 H), 4.30−4.14 (m, 2 H), 4.11 (s, 1 H), 2.96 (q, J = 7.3 Hz, 1 H), 1.64 (s, 3 H), 1.31 (t, J = 7.3 Hz, 3 H), 0.97 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.4, 142.3, 133.1, 132.2, 128.2, 127.8, 127.4, 126.0, 125.7, 123.8, 123.1, 74.5, 60.9, 49.0, 30.0, 14.2, 12.8; MS (EI) *m/z* 272 (M^+, 1), 171 (31), 155 (100), 141 (2), 127 (81), 126 (13), 102 (4), 101 (5), 57 (15); HRMS (EI) calcd for $C_{17}H_{20}O_3$ 272.1412, found *m/z* 272.1415 (M^+).

Ethyl 3-Hydroxy-2-ethyl-3-naphth-2-ylbutyrate (7gb). Column chromatographic purification afforded a mixture of *anti/syn* diastereomers as a colorless thick oil: IR (neat) 3494, 3058, 2973, 1704, 1461, 1022 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.99 (s,1 H),* 7.90 (s. 1 H), 7.86−7.62 (m, 3 H), 7.53−7.39 (m, 3 H), 4.27 (m, 2 H),* 4.14 (s, 1 H), 4.00 (s, 1 H),* 3.79 (q, J = 7.3 Hz, 2 H), 2.94 (dd, J_1 = 10.5, J_2 = 4.6 Hz, 1 H), 2.79 (dd, J_1 = 11.6, J_2 = 3.5 Hz, 1 H),* 2.02−1.80 (m, 2 H), 1.60 (s, 3 H),* 1.56 (s, 3 H), 1.31 (t, J = 7.3 Hz, 3 H),* 1.24 (t, J = 7.0 Hz, 3 H),* 0.97 (t, J = 7.3 Hz, 3 H,), 0.76 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.2, 145.0, 133.0, 132.3, 128.1,* 128.2, 127.8,* 127.7, 127.3, 125.9, 125.7, 123.8,* 123.4, 123.2, 123.0,* 75.1, 74.7,* 60.8,* 60.3, 57.2,* 56.5, 30.2,* 27.1, 21.0,* 20.5, 14.3,* 13.7, 12.4, 12.1*; MS (EI) *m/z* 286 (M^+, 6), 172 (13), 171 (100), 155 (28), 141 (3), 127 (25), 116 (6), 101 (6), 73 (4); HRMS (EI) calcd for $C_{18}H_{22}O_3$ 286.1569, found *m/z* 286.1567 (M^+).* Asterisk corresponds to the minor isomer.

Ethyl 3-(3-Bromophenyl)-3-hydroxy-2-methylbutyrate (7ha). Column chromatographic purification afforded a mixture of *anti/syn* diastereomers as a colorless thick oil: IR (neat) 3498, 2981, 1712, 1457, 1191 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.62−7.59 (m, 1 H), 7.39−7.15 (m, 3 H), 4.28−4.18 (m, 2 H),* 4.15 (s, 1 H), 4.01 (s, 1 H,), 4.00−3.84 (m, 2 H), 2.96 (q, J = 7.0 Hz, 1 H), 2.79 (q, J = 7.0 Hz, 2 H),* 1.54 (s, 3 H),* 1.43 (s, 3 H), 1.35−1.26 (m, 3 H), 1.00 (t, J = 7.3 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H);* ^{13}C NMR (100 MHz, $CDCl_3$) 177.0,* 176.5, 150.1, 147.5,* 129.8, 129.7,* 129.7,* 129.6, 128.2,* 128.1, 123.5,* 123.4, 123.5,* 123.4, 74.4, 74.0,* 61.0,* 60.6, 49.0,* 48.2, 29.8,* 26.8, 14.1,* 13.8, 12.7,* 12.3; MS (EI) *m/z* 302 (M^+ + 2, 3), 300 (M^+, 3), 202 (4), 201 (41), 199 (41), 185 (16), 183 (17), 102 (100), 74 (39), 56 (9); HRMS (EI) calcd for $C_{13}H_{17}BrO_3$ 300.0361, found *m/z* 300.0370, 300.0361 (M^+). Asterisk corresponds to the minor isomer.

Ethyl 3-(9*H*-Fluoren-2-yl)-3-hydroxy-2-methylbutyrate (7ia): (2*S,3*S**)-Ethyl 3-(9*H*-Fluoren-2-yl)-3-hydroxy-2-methylbutyrate (7ia$_1$).** Column chromatographic purification afforded a pale yellow thick oil, which solidified as a viscous solid later on: IR (deposit from $CHCl_3$) 3494, 3016, 1704, 1214, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.75 (d, J = 7.6 Hz, 1 H), 7.71 (d, J = 7.6 Hz, 1 H), 7.65 (s, 1 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.42−7.25 (m, 3 H) 4.18 (s, 1 H,), 3.90 (q, J = 7.0 Hz, 2 H), 3.90 (s, 2 H), 3.06 (q, J = 7.0 Hz, 1 H), 1.50 (s, 3 H,), 1.35 (d, J = 7.0 Hz, 3 H), 0.94 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.8, 146.4, 143.4, 143.1, 141.4, 140.2, 126.7, 126.5, 125.0, 123.4, 121.5, 119.8, 119.3, 74.9, 60.5, 48.6, 36.9, 27.0, 13.8, 12.5; MS (EI) *m/z* 310 (M^+, 0.4), 292 (1), 209 (22), 208 (65), 194 (15), 193 (100), 179 (1.5), 165 (88), 164 (12), 163 (16), 139 (6); HRMS (EI) calcd for $C_{20}H_{22}O_3$ 310.1569, found *m/z* 310.1565 (M^+). **(2*R**,3*S**)-Ethyl 3-(9*H*-Fluoren-2-yl)-3-hydroxy-2-methylbutyrate (7ia$_2$).** Isolated as a pale yellow thick oil, solidified as a viscous solid later on: IR (deposit from $CHCl_3$) 3517, 3016, 1708, 1214 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.78−7.67 (m, 2 H), 7.67 (s, 1 H), 7.53 (d, J = 7.0 Hz, 1 H), 7.43−7.25 (m, 3 H), 4.23−4.16 (m, 2 H), 4.01 (s, 1 H,), 3.90 (s, 2 H), 2.90 (q, J = 7.3 Hz, 1 H), 1.66 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.4, 143.8, 143.4, 143.2, 141.4, 140.2, 126.7, 126.5, 125.0, 123.4, 121.6, 119.7, 119.4, 74.6, 60.9, 49.4, 37.0, 30.1, 14.2, 12.8; MS (EI) *m/z* 310 (M^+, 1), 292 (2), 209 (31), 208 (63), 194 (15), 193 (100), 166 (16), 165 (85), 163 (17), 115 (5), 83 (9); HRMS (EI) calcd for $C_{20}H_{22}O_3$ 310.1569, found *m/z* 310.1593 (M^+).

Ethyl 3-(9*H*-Fluoren-2-yl)-3-hydroxy-2-ethylbutyrate (7ib): (2*S,3*S**)-Ethyl 3-(9*H*-Fluoren-2-yl)-3-hydroxy-2-ethylbutyrate (7ib$_1$).** Column chromatographic purification afforded a pale yellow thick oil, which solidified as a viscous solid: IR (deposit from $CHCl_3$) 3490, 2973, 1708, 1461, 1191 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.76 (d, J = 7.0 Hz, 1 H), 7.70 (d, J = 7.0 Hz, 1 H), 7.63 (s, 1 H), 7.53 (d, J = 7.0 Hz, 1 H), 7.42−7.23 (m, 3 H), 4.05 (s, 1 H), 3.85 (q, J = 7. 0 Hz, 2 H), 3.87 (s, 2 H,), 2.87 (dd, J_1 = 10.3, J_2 = 4.9 Hz, 1 H), 1.96−1.86 (m, 2 H), 1.53 (s, 3 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.87 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) 176.3, 146.5, 143.4, 143.1, 141.4, 140.3, 126.7, 126.5, 125.0, 123.5, 121.4, 119.8, 119.3, 75.1, 60.3, 56.9, 36.9, 27.4, 20.6, 13.9, 12.4; MS (EI) *m/z* 324 (M^+, 0.4), 209 (22), 208 (64), 194 (15), 193 (100),

179 (2), 165 (89), 164 (10), 163 (16), 139 (6); HRMS (EI) calcd for $C_{21}H_{24}O_3$ 324.1725, found *m/z* 324.1702 (M^+).

(2*R,3*S**)-Ethyl 3-(9*H*-Fluoren-2-yl)-3-hydroxy-2-ethylbutyrate (7ib$_2$).** Column chromatographic purification afforded a pale yellow oil, solidified as a viscous solid later on: IR (deposit from $CHCl_3$) 3517, 3019, 1704, 1214, 1191 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.78−7.37 (m, 2 H), 7.68 (s, 1 H), 7.53 (d, J = 7.0 Hz, 1 H), 7.43−7.25 (m, 3 H), 4.24 (q, J = 7.3 Hz, 2 H), 3.90 (s, 2 H), 3.89 (s, 1 H), 2.72 (dd, J_1 = 11.3, J_2 = 3.8 Hz, 1 H), 1.78−1.58 (m, 2 H), 1.58 (s, 3 H), 1.33 (t, J = 7.3 Hz, 3 H), 0.76 (t, J = 7.3 Hz, 3 H); ^{13}C NMR: (100 MHz, $CDCl_3$) 176.9, 146.1, 143.4, 143.2, 141.4, 140.2, 126.7, 126.5, 125.0, 123.4, 121.6, 119.8, 119.4, 74.3, 60.8, 57.7, 37.0, 30.4, 21.0, 14.4, 12.2; MS (EI) *m/z* 324 (M^+, 0.3), 209 (21), 208 (67), 194 (16), 193 (100), 166 (14), 165 (85), 163 (17), 115 (4), 97 (5); HRMS (EI) calcd for $C_{21}H_{24}O_3$ 324.1725, found *m/z* 324.1711 (M^+).

(3*S,2*S**)-Ethyl 3-Hydroxy-4-methoxy-2-methyl-3-phenylbutyrate (7ja$_1$).** Column chromatographic purification afforded the major *anti* isomer in pure form as a colorless thick oil: IR (neat) 3482, 2981, 2888, 1712, 1450, 1191, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.50−7.45 (m, 2 H), 7.37−7.24 (m, 3 H), 4.26 (s, 1 H), 4.19 (q, J = 7.4 Hz, 2 H), 3.63 (d, J = 10.0 Hz, 1 H), 3.51 (d, J = 10.0 Hz, 1 H), 3.32 (s, 3 H), 2.93 (q, J = 7.2 Hz, 1 H), 1.30 (t, J = 7.4 Hz, 3 H), 0.94 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) 176.6, 141.8, 128.1, 127.0, 125.1, 80.1, 76.5, 60.7, 59.3, 45.6, 14.1, 12.7; MS (CI) *m/z* 253 (M^+ + 1, 12), 237 (2), 236 (17), 235 (100), 207 (5), 175 (1), 151 (3), 103 (1); HRMS (CI) calcd for $C_{14}H_{21}O_4$ 253.1440, found *m/z* 253.1439 (M^+ + 1). The minor isomer was isolated as a mixture with the major isomer.

Ethyl 3-Hydroxy-4-methoxy-2,3-dimethylbutyrate (7ka). Isolated as a mixture of diastereomers as a colorless oil: IR (neat) 3508, 2981, 2888, 1731, 1461, 1373, 1191 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 4.20−4.11 (m, 2 H), 3.52 (s, 1 H), 3.63, 3.58 (s, 3 H), 3.33−3.24 (m, 2 H), 2.73−2.63 (m, 1 H), 1.31−1.25 (m), 1.22, 1.15 (s, 3 H), 1.21−1.17 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.1, 175.6,* 79.1, 72.8, 72.5,* 60.4, 60.4,* 59.2, 45.6,* 44.8, 22.9,* 21.1, 14.1, 12.3,* 11.8; MS (CI) *m/z* 191 (M^++1, 82), 174 (9), 173 (100), 145 (25), 113 (11), 103 (4), 99 (4); HRMS (CI) calcd for $C_9H_{19}O_4$ 191.1283, found *m/z* 191.1286, (M^+ + 1). Asterisk corresponds to the minor isomer.

(3*S,4*R**)-Ethyl 3-Hydroxy-3,4-diphenyl-4-isopropoxybutanoate (11a).** Column chromatographic purification afforded a colorless solid: mp 77−79 °C; IR (KBr) 3417, 1700, 1454, 852, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.38−7.36 (m, 2 H), 7.26−7.19 (m, 8 H), 4.44 (s, 1 H), 4.37 (s, 1 H), 3.98 (q, J = 7.3 Hz, 2 H), 3.34−3.25 (m, 1 H), 3.14 (d, J = 16.0 Hz, 1 H), 2.94 (d, J = 16.0 Hz, 1 H), 1.09 (t, J = 7.3 Hz, 3 H), 1.02 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) 172.9, 144.0, 138.2, 128.7, 127.4, 127.3, 127.1, 126.8, 126.1, 84.8, 77.5, 70.0, 60.5, 40.6, 23.2, 20.5, 14.0; MS (CI) *m/z* 343 (M^+ + 1, 3), 325 (20), 284 (19), 283 (100), 255 (2), 195 (2), 193 (3); HRMS (CI) calcd for $C_{21}H_{27}O_4$ 343.1909, found *m/z* 343.1905 (M^+ + 1). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.18; H, 7.62.

(3*S,4*R**)-Ethyl 3-Hydroxy-3,4-diphenyl-4-isobutyloxybutanoate (11b).** Column chromatographic purification afforded a colorless thick oil: IR (neat) 3495, 1712, 1454 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.38−7.35 (m, 2 H), 7.27−7.13 (m, 8 H), 4.41 (s, 1 H), 4.29 (s, 1 H), 3.98 (q, J = 7.3 Hz, 2 H), 3.17 (d, J = 16.0 Hz, 1 H), 3.07 (dd, J_1 = 8.8, J_2 = 6.5 Hz, 1 H), 2.97 (d, J = 16.0 Hz, 1 H), 2.83 (dd, J_1 = 8.8, J_2 = 6.5 Hz, 1 H), 1.82−1.72 (m, 1 H), 1.09 (t, J = 7.3 Hz, 3 H), 0.81 (d, J = 8.8 Hz, 3 H), 0.81 (d, J = 8.8 Hz, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) 172.8, 143.8, 137.3, 128.7, 127.5, 127.4, 127.2, 126.9, 126.0, 87.8, 76.6, 60.5, 40.6, 28.6, 19.4, 19.4, 13.9; MS (CI) *m/z* 357 (M^+ + 1, 1), 339 (30), 283 (100), 237 (4), 197 (1), 193 (5), 163 (2); HRMS (CI) calcd for $C_{22}H_{29}O_4$ 357.2066, found *m/z* 357.2057 (M^+ + 1).

(3*S,4*R**)-Ethyl 3-Hydroxy-3,4-diphenyl-4-ethoxybutanoate (11c).** Column chromatographic purification afforded a colorless solid: mp 42−44 °C; IR (KBr) 3417, 1708, 1492, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.46−7.32 (m, 2 H), 7.25−7.12 (m, 8 H), 4.49 (s, 1 H), 4.31 (s, 1 H), 4.00 (q, J = 7.3 Hz, 2 H), 3.43−3.32 (m, 1 H), 3.22−3.11 (m, 1 H), 3.12 (d, J = 16.0 Hz, 1 H), 3.03 (d, J = 16.0 Hz, 1 H), 1.11 (t, J = 7.3 Hz, 3 H), 1.09 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.9, 143.6, 137.4, 128.6, 127.5, 127.4, 127.2, 126.9, 125.9, 87.4, 77.0, 65.1, 60.5, 41.2, 15.0, 13.9; MS (CI) *m/z* 329 (M^+ + 1, 3), 311 (66), 284 (19), 283 (100), 237 (2), 195 (2), 193 (6); HRMS (CI) calcd for $C_{20}H_{25}O_4$ 329.1753, found *m/z* 329.1735 (M^+ + 1).

(3*S,4*R**)-Ethyl 3-Hydroxy-3,4-diphenyl-4-methoxybutanoate (11d).** Column chromatographic purification afforded a colorless solid: mp 94−96 °C; IR (KBr) 3495, 1712, 1203, 748, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.31−7.06 (m, 10 H), 4.51 (s, 1 H), 4.23 (s, 1 H), 4.02 (q, J = 7.3 Hz, 2 H), 3.17 (s, 3 H), 3.07 (s, 2 H), 1.12 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.8, 143.2, 136.5, 128.7, 127.6, 127.5, 127.3, 126.9, 125.8, 89.4, 77.1, 60.6, 57.4, 41.5, 13.9; MS (CI) *m/z* 315 (M^+ + 1, 67), 297 (100), 283 (52), 269 (3), 237 (10); HRMS (CI) calcd for $C_{19}H_{23}O_4$ 315.1596, found *m/z* 315.1584, 315.1624 (M^+ + 1). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.51; H, 7.06. The stereochemistry of the products was established on the basis of similarity in the spectral data and the X-ray structure analysis reported by us.[13]

(3*S,4*R**)-Ethyl 3-Hydroxy-3-phenyl-4-methoxypentanoate (11e).** Column chromatographic purification afforded a colorless thick oil: IR (neat) 3482, 1712, 1450, 1033, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.49−7.22 (m, 5 H), 4.44 (s, 1 H), 4.03 (q, J = 7.3 Hz, 2 H), 3.43 (q, J = 6.4 Hz, 1 H), 3.09 (s, 3 H), 3.06 (d, J = 16.0 Hz, 1 H), 2.83 (d, J = 16.0 Hz, 1 H), 1.11 (t, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.0, 143.6, 128.1, 127.0, 125.4, 83.0, 77.3, 60.5, 57.2, 42.8, 14.0, 12.1; MS (CI) *m/z* 253 (M^+ + 1, 3), 236 (13), 235 (100), 207 (3), 193 (4), 161 (3), 105 (3); HRMS (CI) calcd for $C_{14}H_{21}O_4$ 253.1362, found *m/z* 253.1445 (M^+ + 1).

Ethyl 2-[(1S*,2S*)-1-Hydroxy-2-methoxycyclohexyl]-acetate (11f). Column chromatographic purification afforded a colorless thick oil (data for major isomer): IR (neat) 3494, 1728, 1450, 1327, 1103 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 4.15 (q, J = 7.3 Hz, 2 H), 3.34 (s, 3 H), 3.24 (s, 1 H), 3.05 (dd, J = 10.5, 4.2 Hz, 1 H), 2.59 (d, J = 14.2 Hz, 1 H), 2.43 (d, J = 14.2 Hz, 1 H), 1.85−1.25 (m, 8 H), 1.28 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) 172.1, 82.9, 72.5, 60.3, 56.5, 44.0, 36.1, 25.2, 23.6, 20.8, 14.2; MS (EI) *m/z* 216 (M^+, 29), 198 (27), 184 (45), 170 (13), 143 (36), 138 (27), 97 (53), 84 (100); HRMS (EI) calcd for $C_{11}H_{20}O_4$ 216.1362, found *m/z* 216.1366, 216.1375 (M^+).

(2*S,3*S**)-3-Hydroxy-2-ethyl-3-phenylpentanedioic Acid 5-Ethyl Ester 1-Methyl Ester (13a).** Column chromatographic purification afforded a colorless thick oil: IR (neat) 3482, 2969, 1727, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.41−7.21 (m, 5 H), 4.59 (s, 1 H), 3.96 (double q, 2 H), 3.57 (s, 3 H), 3.27 (d, J = 16.0 Hz, 1 H), 2.81 (d, J = 16.0 Hz, 1 H), 2.67 (dd, J = 12.0, 3.2 Hz, 1 H), 1.76−1.68 (m, 1 H), 1.54−1.47 (m, 1 H), 1.04 (t, J = 7.0 Hz, 3 H), 0.79 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.3, 172.2, 143.8, 128.0, 127.1, 125.1, 75.4, 60.5, 58.7, 51.4, 42.7, 20.4, 13.7, 12.2; MS (CI) *m/z* 295 (M^+ + 1, 87), 278 (17), 277 (100), 245 (31), 231 (5), 207 (4), 193 (9), 103 (2); HRMS (CI) calcd for $C_{16}H_{23}O_5$ 295.1546, found *m/z* 295.1559 (M^+ + 1).

(2*R,3*S**)-2-Ethyl-3-phenylpentane-1,3,5-triol (13aB).** Column chromatographic purification afforded a colorless solid:, mp 94−96 °C; IR (KBr) 3467, 3432, 3401, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.36−7.30 (m, 5 H), 4.97 (s, 1 H), 4.15 (d, J = 11.6 Hz, 1 H), 3.78−3.71 (m, 2 H), 3.49−3.44 (m, 1 H), 3.31 (s, 1 H), 2.56−2.48 (m, 2 H), 2.05−2.00 (m, 1 H), 1.71−1.66 (m, 1 H), 1.41−1.18 (m, 1 H), 1.17−1.08 (m, 1 H), 0.81 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 144.3, 128.0, 126.5, 125.5, 82.5, 61.0, 60.3, 50.5, 40.6, 18.2, 12.5; MS (CI) *m/z* 225 (M^+ + 1, 6), 189 (33), 177 (100), 159 (17), 151 (13), 105 (17); HRMS (CI) calcd for $C_{13}H_{21}O_3$ 225.1491, found

m/z 225.1497 ($M^+ + 1$). See the Supporting Information for the X-ray structure analysis and ORTEP diagram.

(2*S,3*S**)-3-Hydroxy-2-methyl-3-phenylpentanedioic Acid Diethyl Ester (13b).** Column chromatographic purification afforded a colorless thick oil: IR (neat) 3482, 2981, 1727, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.42−7.21 (m, 5 H), 4.62 (s, 1 H), 4.08 (q, $J = 7.2$ Hz, 2 H), 4.06−3.92 (double q, 2 H), 3.21 (d, $J = 16.0$ Hz, 1 H), 2.92 (d, $J = 16.0$ Hz, 1 H), 2.87 (q, $J = 7.6$ Hz, 1 H), 1.18 (t, $J = 7.2$ Hz, 3 H), 1.06 (t, $J = 7.6$ Hz, 3 H), 1.04 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.7, 172.1, 143.5, 128.0, 127.2, 125.3, 75.5, 60.6, 49.9, 43.4, 14.0, 13.9, 12.3; MS (CI) *m/z* 295 ($M^+ + 1$, 21), 278 (17), 277 (100), 232 (9), 231 (60), 207 (7), 193 (10), 103 (2); HRMS (CI) calcd for $C_{16}H_{23}O_5$ 295.1546, found *m/z* 295.1552 ($M^+ + 1$).

(2*S,3*S**)-3-Hydroxy-2-methyl-3-phenylpentanedioic Acid 5-Ethyl Ester 1-Methyl Ester (13c).** Column chromatographic purification afforded a colorless thick oil: IR (neat) 3486, 2981, 1727, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.41−7.22 (m, 5 H), 4.62 (s, 1 H), 3.97 (q, $J = 7.2$ Hz, 2 H), 3.63 (s, 3 H), 3.20 (d, $J = 16.0$ Hz, 1 H), 2.91 (d, $J = 16.0$ Hz, 1 H), 2.88 (q, $J = 7.6$ Hz, 1 H), 1.05 (t, $J = 7.2$ Hz, 3 H), 1.05 (d, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.0, 172.2, 143.5, 128.1, 127.2, 125.3, 75.5, 60.7, 51.7, 49.9, 43.4, 13.9, 12.3; MS (CI) *m/z* 281 ($M^+ + 1$, 36), 264 (26), 263 (100), 232 (5), 231 (33), 217 (9), 194 (4), 193 (35); HRMS (CI) calcd for $C_{15}H_{21}O_5$ 281.1389, found *m/z* 281.1379 ($M^+ + 1$).

(2*S,3*S**)-3-Hydroxy-2,3-dimethylpentanedioic Acid Diethyl Ester (13e).** Column chromatographic purification afforded a mixture of diastereomers as a colorless thick oil: IR (neat) 3502, 2981, 1731, 1457, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.20−4.11 (m, 4 H), 4.06 (s, 1 H),* 4.04 (s, 1 H), 2.78−2.72 (m, 1 H), 2.59 (s, 2 H), 2.51 (d, $J = 16.0$ Hz, 1 H),* 1.30−1.17 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.4, 172.0, 71.8, 62.6,* 60.6, 60.6, 47.7, 43.9, 24.2,* 24.1, 21.8,* 14.1, 14.0,* 12.6; MS (CI) *m/z* 233 ($M^+ + 1$, 100), 216 (3), 215 (28), 187 (8), 169 (34), 145 (7), 131 (8), 103 (2); HRMS (CI) calcd for $C_{11}H_{21}O_5$ 233.1389 found *m/z* 233.1401, 233.1379 ($M^+ + 1$). Asterisk corresponds to the minor isomer.

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Supporting Information Available: General experimental procedures, determination of relative stereochemistry of key products, ^1H NMR spectra of active species determination, details of X-ray structure analyses, and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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