

This article is dedicated to Professor Satoshi Ōmura in celebration of his 2015 Nobel Prize.

### Regular Article

## Asymmetric Synthesis of Multisubstituted Dihydrobenzofurans by Intramolecular Conjugate Addition of Short-Lived C–O Axially Chiral Enolates

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**Enantioselective intramolecular conjugate addition reactions of short-lived C–O axially chiral enolates have been developed. The reactions proceeded with inversion of the configuration and provided dihydrobenzofurans with contiguous tetra- and trisubstituted carbon centers in up to 96% enantiomeric excess (ee).**

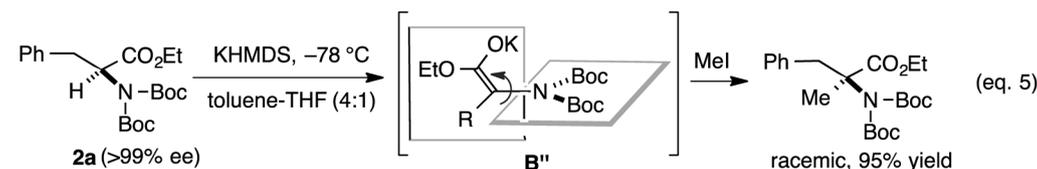
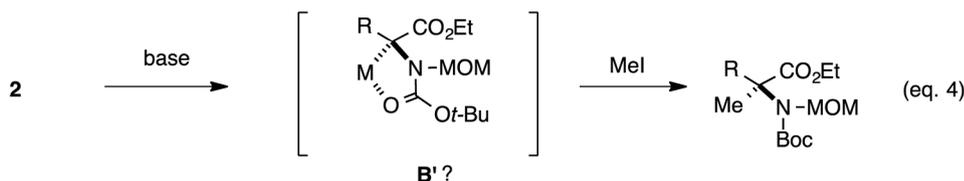
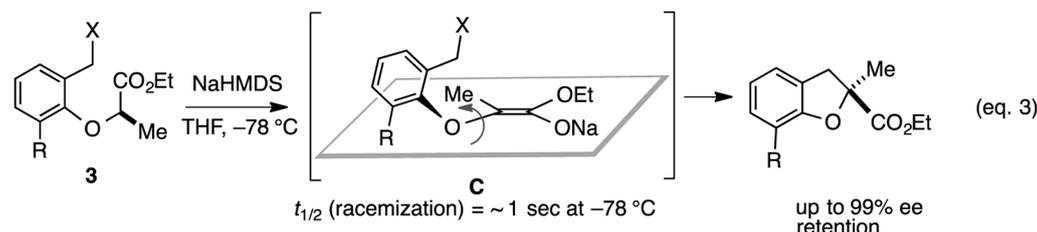
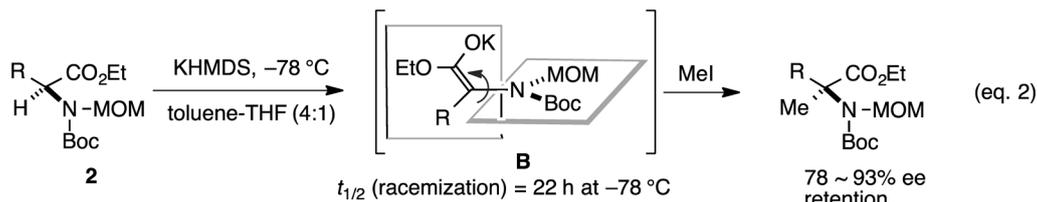
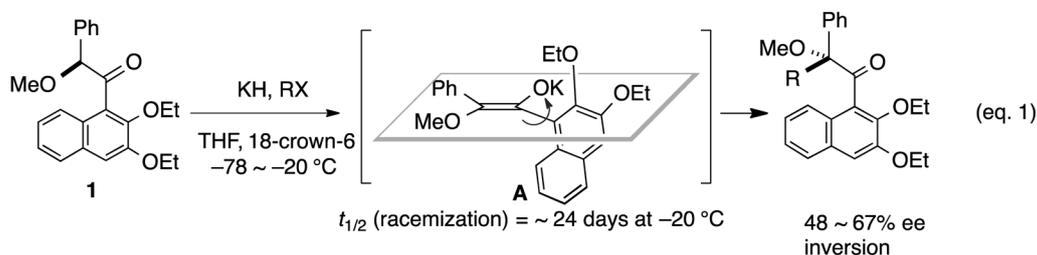
**Key words** axially chiral enolate; asymmetric synthesis; chiral C–O axis; dihydrobenzofuran; conjugate addition; restricted bond rotation

Asymmetric synthesis had been classified into three categories: 1) optical resolution of the racemate by diastereomer formation, 2) diastereoselective synthesis using chiral auxiliaries, and 3) enantioselective synthesis using chiral catalysts or chiral reagents. On the other hand, we have studied asymmetric reactions that proceed *via* enolate intermediates with intrinsic axial chirality (MOC: memory of chirality).<sup>1–6</sup> This strategy does not belong to any of above three categories. We believe that MOC strategy created the fourth category of asymmetric synthesis. The characteristic feature of the asymmetric reactions based on MOC strategy is asymmetric reactions take place at the original stereogenic center of the starting material in the absence of external chiral sources. Accordingly, when the optically active starting materials are abundant and ubiquitous  $\alpha$ -amino acids, asymmetric synthesis based on MOC strategy is especially advantageous. MOC strategy also has salient feature in the mechanistic point of view. The asymmetric synthesis proceeds *via* the transient chiral species with limited half-lives of racemization.<sup>1–13</sup> We have developed strategy for asymmetric induction *via* enolate intermediate **A** with a chiral C–C axis in 1991<sup>1</sup> (Chart 1, Eq. 1). The half-life of racemization of the axially chiral enolate **A** at the reaction temperature ( $-20^{\circ}\text{C}$ ) was estimated to be *ca.* 24 d.<sup>1</sup> We then developed a method for asymmetric induction *via* enolate intermediate **B** with a chiral C–N axis in 2000<sup>2</sup> (Chart 1, Eq. 2). The half-life of racemization of the axially chiral enolate **B** was determined to be 22 h at the reaction temperature ( $-78^{\circ}\text{C}$ ) by the measurement of the time-dependent racemization of enolate **B**. As logical possibility, the asymmetric induction might take place *via* configurationally stable carbanion **B'** (Chart 1, Eq. 4). However, this possibility was eliminated because di-Boc derivative **2a** (>99% enantiomeric excess (ee)) gave the racemic product by the same treatment for **2** (Chart 1, Eq. 5). Since the enolate **B''** generated from **2a** cannot to be axially

chiral along the C–N axis even through rotation of the C–N bond is restricted, racemate formation is a reasonable consequence. We finally succeeded to develop asymmetric synthesis *via* short-lived C–O axially chiral enolates with the supposed half-life of racemization as short as *ca.* 1 s at  $-78^{\circ}\text{C}$ <sup>6</sup> (Chart 1, Eq. 3). The reaction shown in Eq. 3 was the first example of asymmetric reaction that proceeds *via* an axially chiral enolate with the restricted rotation of the C–O axis as the sole source for asymmetric induction. We report here asymmetric intramolecular conjugated addition reactions *via* C–O axially chiral enolates as further extension of this novel asymmetric induction (Chart 2). The key to success in this asymmetric induction is to design fast reactions to minimize racemization of the chiral enolate intermediates with extremely short half-lives of racemization. The products obtained by this transformation, chiral 2,2,3-trisubstituted dihydrobenzofurans, have been frequently found in important pharmacophores and biologically active compounds.<sup>14–21</sup>

In the asymmetric cyclization shown in Eq. 3, substituent R in **3** played a crucial role for the asymmetric induction. For example, **3** with R=H gave a racemic dihydrobenzofuran, whereas **3** with R=*i*-Pr gave the corresponding dihydrobenzofuran in 99% ee under the similar reaction conditions.<sup>6</sup> Based on these backgrounds, precursors **4** with substituents R (compounds **5**, **7**, and **9** in Table 1) for the asymmetric intramolecular conjugate addition were prepared starting from L-ethyl lactate *via* the Mitsunobu reaction with the corresponding phenol derivatives (see Supplementary Materials for the preparation of the substrates **4**). We first examined the reaction of **5** (R=H) under the optimized conditions for asymmetric intramolecular alkylation *via* the C–O axially chiral enolate in Eq. 3 in Chart 1.<sup>6</sup> Treatment of **5** with sodium hexamethyldisilazide (NaHMDS) in tetrahydrofuran (THF) at  $-78^{\circ}\text{C}$  for 1 h gave a 91 : 9 diastereomeric mixture of **6a/b**<sup>22</sup> in a combined

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Logical possibility for asymmetric induction *via* configurationally stable carbanion  $\text{B}'$  (Eq. 4) and racemate formation from the di-*tert*-butoxycarbonyl (Boc) derivative  $\mathbf{2a}$  *via* achiral enolate intermediate  $\text{B}''$ .

Chart 1. Asymmetric Reactions *via* Memory of Chirality and the Proposed Chiral Enolate Intermediates with Chiral C–C (Eq. 1), C–N (Eq. 2), and C–O (Eq. 3) Axes

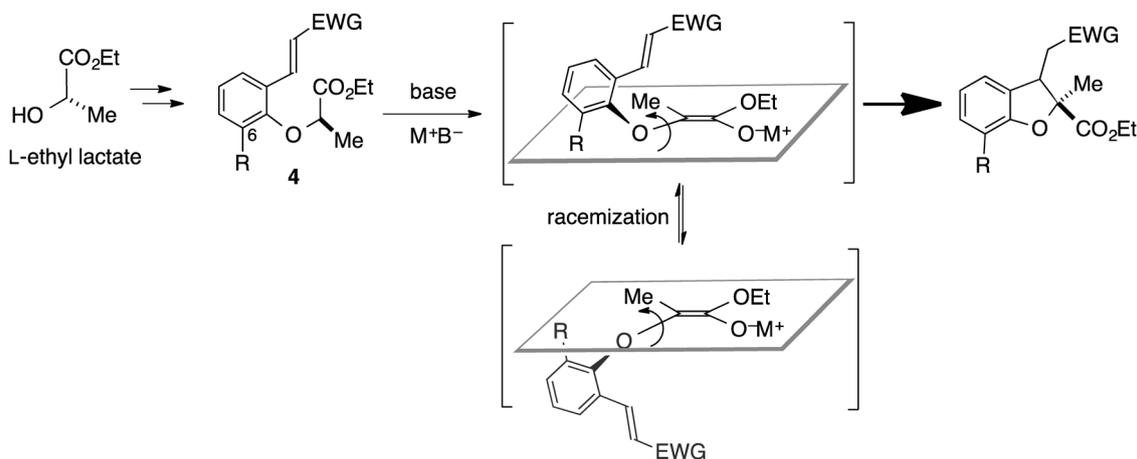
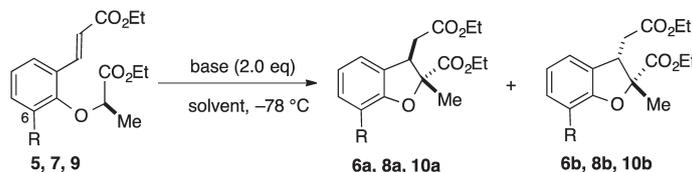


Chart 2. Strategy for Asymmetric Intramolecular Conjugate Addition of Axially Chiral Enolates with a Chiral C–O Axis

Table 1. Asymmetric Intramolecular Conjugate Addition of the Enolate Generated from **5**, **7**, and **9**<sup>a)</sup>

Entry	Substrate	R	Base	Solvent	Time (h)	Products	Yield (%)	dr <b>a</b> : <b>b</b> <sup>b,c)</sup>	% ee of <b>a</b> <sup>d,e,f)</sup>
1	<b>5</b>	H	NaHMDS	THF	1	<b>6a, b</b>	82	91:9	41
2	<b>5</b>	H	LDA	THF	1	<b>6a, b</b>	37	75:25	-30
3	<b>5</b>	H	LiHMDS	THF	2	<b>6a, b</b>	26	91:9	53
4	<b>5</b>	H	KHMDS	THF	0.5	<b>6a, b</b>	43	89:11	-11
5	<b>5</b>	H	NaHMDS	Toluene	2.5	<b>6a, b</b>	74	92:8	-24
6 <sup>g)</sup>	<b>5</b>	H	NaHMDS	DMF/THF (6:1)	2.5	<b>6a, b</b>	58	86:14	21
7	<b>5</b>	H	LiHMDS	Toluene	3	<b>6a, b</b>	— <sup>h)</sup>	— <sup>i)</sup>	— <sup>i)</sup>
8	<b>5</b>	H	LiHMDS	DMF/THF (11:1) <sup>g)</sup>	2	<b>6a, b</b>	81	90:10	28
9	<b>7</b>	Me	NaHMDS	THF	3.5	<b>8a, b</b>	50	90:10	95
10	<b>9</b>	Br	NaHMDS	THF	3	<b>10a, b</b>	9	— <sup>i)</sup>	— <sup>i)</sup>

<sup>a)</sup> All reactions were run at the substrate concentration of 0.1 M. <sup>b)</sup> The diastereomeric ratio was determined by <sup>1</sup>H-NMR. <sup>c)</sup> The relative configuration of **6a** and **b** was determined based on the reported <sup>1</sup>H-NMR data of **6a** and **b** (ref. 22). The relative configuration of **8** and **10** was tentatively assigned by analogy. <sup>d)</sup> ee's were determined by HPLC analysis with a chiral stationary phase. <sup>e)</sup> Absolute configurations were tentatively assigned. <sup>f)</sup> ee's of **b** were not determined. <sup>g)</sup> Run at -60°C. <sup>h)</sup> Recovery of **5**. <sup>i)</sup> Not determined.

yield of 82% (Table 1, entry 1). The ee of the major diastereomer was found to be 41% (entry 1). This result was contrary to the asymmetric intermolecular alkylation shown in Chart 1, Eq. 3, where the racemate was obtained from substrate **3** with R=H.<sup>6)</sup> These results suggest that the intramolecular conjugate addition of the chiral enolate seems to proceed faster than the corresponding intramolecular alkylation. We next investigated the effects of bases on the asymmetric intramolecular conjugate addition of **5**. Use of lithium diisopropylamide (LDA) as a base gave the product with diminished diastereoselectivity and yield (entry 2). The absolute configuration of the major diastereomer (30% ee) was found to be opposite to that obtained in the reaction with NaHMDS.<sup>23)</sup> On the other hand, the reaction of **5** with lithium hexamethyldisilazide (LiHMDS) gave product **6a** with the same absolute configuration as that with NaHMDS (entries 1, 3). Solvent effects in the reactions with NaHMDS and LiHMDS were examined (entries 5–8). Use of neither a less coordinating solvent (toluene) nor a strongly coordinating solvent *N,N*-dimethylformamide (DMF) improved the efficiency. Since dramatic improvement of the enantioselectivity was attained by employing the substrate **3** with R=Me in asymmetric intramolecular alkylation *via* the C–O axially chiral enolate<sup>6)</sup> (Chart 1, Eq. 3), the effects of the substituent R at C(6) were then investigated in the intramolecular conjugate addition of the chiral enolates (entries 9 and 10). Substrate **7** (R=Me) was treated with NaHMDS in THF for 3.5 h at -78°C to give a 90:10 diastereomeric mixture of **8a/b** in a combined yield of 50% (entry 9). The ee of the major diastereomer **8a** was found to be much improved (95% ee) compared with 41% ee of **6a** obtained by the reaction of **5** with R=H (entries 9 vs. 1). The reaction of **9** with R=Br gave product **10** in only 9% yield (entry 10).

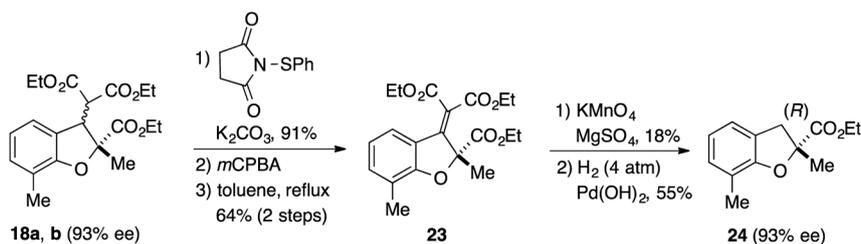
According to the strategy shown in Chart 2, minimization of racemization of the intermediary chiral enolate seems to be the key to achieve high asymmetric induction. Therefore, higher asymmetric induction is expected if the relative rate of intramolecular conjugate addition of the enolate increased compared to that of enolate racemization. Introduction of

the stronger electron-withdrawing groups in the Michael acceptor moiety was expected to be effective in increasing the rate of intramolecular conjugate addition of the enolate. We then examined substrates with malonate-type Michael acceptors (Table 2). The reaction of **11** (R<sup>1</sup>=R<sup>2</sup>=H, X=CO<sub>2</sub>Et) with NaHMDS in THF at -78°C gave an 80:20 diastereomeric mixture of **12a/b** in a combined yield of 60% (Table 2, entry 1). The ee of the major diastereomer was found to be 66%, which was improved compared to 41% obtained by the reaction of the corresponding mono-ester derivative **5**. (Table 2, entry 1 vs. Table 1, entry 1). The reaction of **11** with LiHMDS gave dihydrobenzofuran **12a** in 78% ee (**12a/b**=92:8, 67% yield, entry 2). Use of **13** (X=CO<sub>2</sub>*t*-Bu) and **15** (X=CO<sub>2</sub>Bn) instead of **11** (X=CO<sub>2</sub>Et) in the presence of LiHMDS further improved the diastereoselectivity and the enantioselectivity to give a 96:4 diastereomeric mixture of **14a** (83% ee) and **b** in a combined yield of 87% (entry 4) and a 96:4 diastereomeric mixture of **16a** (86% ee) and **b** in a combined yield of 77% (entry 6), respectively. The effects of the substituents on the aromatic ring were next investigated. While only trace amount of dihydrobenzofuran derivatives were obtained by treatment of **17** (R<sup>1</sup>=Me, R<sup>2</sup>=H) with LiHMDS (entry 8), the desired products **18a** and **b** were obtained by treatment of **17** with NaHMDS as a 67:33 diastereomeric mixture in a combined yield in 79% (entry 7). The ee of the major diastereomer **18a** was much improved to be 96% compared to that (66%) of the product obtained by the reaction of the corresponding substrate with R<sup>1</sup>=H, **11** (Table 2, entries 7 vs. 1). We next investigated the effects of the substituent at C(4), because dramatic enhancement of the enantioselectivity was observed by introducing the substituent at C(4) in asymmetric intramolecular six-membered cyclization *via* the C–O axially chiral enolate.<sup>6)</sup> However, negligible effects of the C(4)-substituent was observed in the asymmetric intramolecular conjugate addition of **19** with R<sup>2</sup>=Br. Dihydrobenzofuran derivative **20a** was obtained in 66–77% ee by the reaction of **19** (entries 9, 10), which was comparable to the enantioselectivity (66–78% ee) obtained in the intramolecular conjugate addition of **11**

Table 2. Asymmetric Intramolecular Conjugate Addition of Enolates Generated from Substrates with Malonate-Type Michael Acceptors<sup>a)</sup>

Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	X	Base	Time (h)	Products	Yield (%)	dr <b>a</b> : <b>b</b> <sup>b,c,d)</sup>	% ee of <b>a</b> <sup>e,f,g)</sup>
1	<b>11</b>	H	H	CO <sub>2</sub> Et	NaHMDS	1	<b>12a, b</b>	60	80:20	66
2	<b>11</b>	H	H	CO <sub>2</sub> Et	LiHMDS	3	<b>12a, b</b>	67	92:8	78
3	<b>13</b>	H	H	CO <sub>2</sub> <i>t</i> -Bu	NaHMDS	1	<b>14a, b</b>	75	90:10	74
4	<b>13</b>	H	H	CO <sub>2</sub> <i>t</i> -Bu	LiHMDS	3	<b>14a, b</b>	87	96:4	83
5	<b>15</b>	H	H	CO <sub>2</sub> Bn	NaHMDS	3	<b>16a, b</b>	90	83:17	59
6	<b>15</b>	H	H	CO <sub>2</sub> Bn	LiHMDS	3	<b>16a, b</b>	77	96:4	86
7	<b>17</b>	Me	H	CO <sub>2</sub> Et	NaHMDS	3	<b>18a, b</b>	79	67:33	96
8	<b>17</b>	Me	H	CO <sub>2</sub> Et	LiHMDS	3	<b>18a, b</b>	trace <sup>h)</sup>	— <sup>i)</sup>	— <sup>i)</sup>
9	<b>19</b>	H	Br	CO <sub>2</sub> Et	NaHMDS	1	<b>20a, b</b>	86	75:25	67
10	<b>19</b>	H	Br	CO <sub>2</sub> Et	LiHMDS	3	<b>20a, b</b>	82	92:8	77
11	<b>21</b>	H	OMe	CO <sub>2</sub> Et	NaHMDS	1	<b>22a, b</b>	94	86:14	44
12	<b>21</b>	H	OMe	CO <sub>2</sub> Et	LiHMDS	3	<b>22a, b</b>	60	90:10	77

a) All reactions were run at the substrate concentration of 0.1 M. b) Diastereomeric ratio was determined by <sup>1</sup>H-NMR. c) The relative configuration of **18a** was estimated by its NOE spectra. The relative configuration of **18b** was determined by NOESY spectra after its conversion into the corresponding bicyclic analogue. For detail, see Supplementary Materials. d) Relative configuration of **12**, **14**, **16**, **20**, and **22** was tentatively assigned by analogy. e) ee's were determined by HPLC analysis with a chiral stationary phase. f) The absolute configurations of **18a** and **b** was determined by chemical correlation with (*R*)-**24**, see Chart 3. The absolute configurations of **12**, **14**, **16**, **20**, and **22** was tentatively assigned by analogy. g) ee's of **b** were not determined. h) Recovery of **17**. i) Not determined.

Chart 3. Determination of the Absolute Configuration of **18a** and **b**

with R<sup>2</sup>=H (entries 1, 2). Even decrease in the enantioselectivity was observed in the reaction of **21** (R<sup>2</sup>=OMe) compared to that of the reaction of **11** (44–77% ee in entries 11, 12 vs. 66–78% ee in entries 1, 2).

The absolute configurations of **18a/b** were determined by chemical correlation with the known compound **24** (Chart 3). Introduction of a phenylthio group at the  $\alpha$ -position of the ester carbonyl group,<sup>24)</sup> oxidation of the sulfur atom, followed by thermal  $\beta$ -elimination of resulting sulfoxide gave the unsaturated ester **23**. Oxidative cleavage of the double bond<sup>25)</sup> of **23** followed by the reduction of the benzylic carbonyl group gave known (*R*)-**24**.<sup>6)</sup> Accordingly, the absolute configuration of the tetrasubstituted carbon center of **18a** and **b** was determined to be *R*, and the intermolecular conjugate addition of **17** was disclosed to proceed with inversion of the configuration.

A hypothetical model for the mechanism of intramolecular conjugate addition of **4** is shown in Chart 4. Deprotonation of conformer **4a** would give enantiomerically enriched enolate **D** with a chiral C–O axis, which would give product with inversion of configuration. On the other hand, deprotonation of conformer **4b** would give the product with retention of configuration *via* enolate *ent-D*. Due to the better steric accessibility of the  $\alpha$ -H in **4a** than that in **4b** on deprotonation, formation of the chiral enolate **D** seems to be preferable, and

the overall reaction would proceed in inversion of the configuration. Both enolates **D** and *ent-D* are expected to readily undergo racemization in the reaction medium. The half-life of racemization of the C–O axially chiral enolates might be supposed to be roughly 1 s at  $-78^\circ\text{C}$  based on our previous results in asymmetric intramolecular alkylation reactions.<sup>6)</sup> Because the enolate racemization and asymmetric intramolecular conjugate addition of the chiral enolate are competing to each other, the relative rate between them is critically involved in the enantioselectivity of the reaction. The rate of racemization of the chiral enolate generated from the substrates with R=Me is assumed to be relatively smaller compared to that from the substrates with R=H, because the C–O bond rotation responsible for the enolate racemization is expected to be affected by the steric bulkiness of the R group. This would explain the substituent effects at C(6) observed among **5** and **7** (Table 1, entries 1 vs. 9) and those among **11** and **17** (Table 2, entries 1 vs. 7).

In conclusion, we have developed a novel method for asymmetric intramolecular conjugate addition *via* short-lived axially chiral enolates with a chiral C–O axis. This method provides a unique entry to chiral dihydrobenzofuran derivatives with contiguous tetra- and trisubstituted chiral centers. While the chiral dihydrobenzofuran skeleton has been constructed

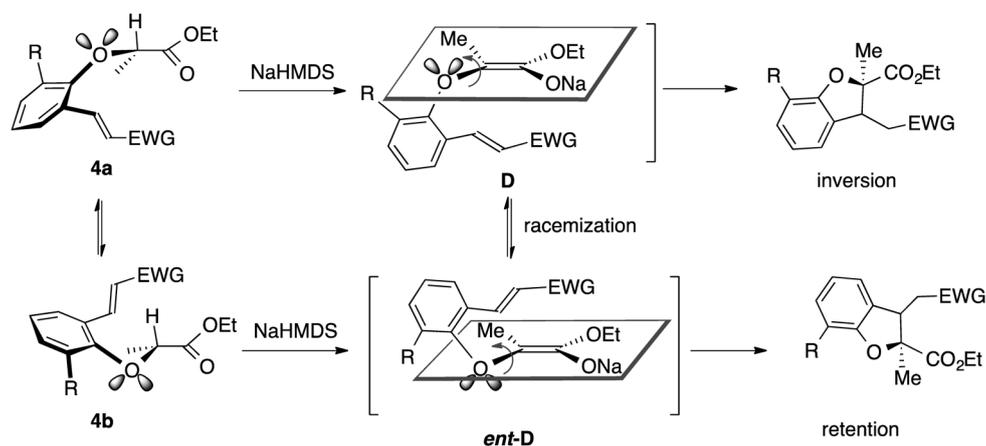


Chart 4. A Possible Mechanism for Asymmetric Intramolecular Conjugate Addition via C–O Axially Chiral Enolates

via asymmetric C–O bond formation,<sup>25–28</sup> asymmetric C–C bond formation at the original chiral center was employed in the present method. Readily available and abundant L-ethyl lactate is used not only as a functionalized carbon resource, but also as a chiral source for asymmetric induction.

## Experimental

**General Remarks** <sup>1</sup>H-NMR were measured in CDCl<sub>3</sub> and referenced from TMS (0.00 ppm) using JEOL ECX-400 (400 MHz) spectrophotometer, unless otherwise noted. <sup>13</sup>C-NMR were measured in CDCl<sub>3</sub> solution and referenced to CDCl<sub>3</sub> (77.0 ppm) using JEOL ECX-400 (100 MHz) spectrophotometer, unless otherwise noted. Chemical shifts are reported in ppm. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet; br, broadened. IR spectra were recorded on JASCO FT/IR-4200 spectrometer. Mass spectra were obtained on JEOL JMS-700 electron ionization (EI) or Bruker impact-HD electrospray ionization (ESI) mass spectrometers. Elemental analyses were performed with CHN J-science-lab. Microcoder JM10 analyzer. Optical rotations were determined on HORIBA SEPA-200 or JASCO P-2200 polarimeters. Flash column chromatography was performed on Silica Gel (SiliaFlash® F60 or 60N (KANTO)). TLC was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60F<sub>245</sub>), and compounds were visualized with UV light followed by *p*-anisaldehyde stain or phosphomolybdic acid stain. All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. Anhydrous THF was purchased from Kanto Kagaku and pre-treated with activated MS4Å for 1 d or longer. Anhydrous toluene purchased from Wako Pure Chemical Industries, Ltd. was distilled over CaH<sub>2</sub> and kept with MS4Å. Anhydrous DMF, which was purchased from Wako Pure Chemical Industries, Ltd. and pre-treated with MS4Å for 1 d, was distilled over P<sub>2</sub>O<sub>5</sub> and kept with MS4Å. NaHMDS was purchased from TCI. LDA and LiHMDS were freshly prepared from the corresponding amine (1 eq) with *n*-BuLi (1 eq) in THF or toluene at 0°C for 30 min. KHMDS was prepared from HMDS with KH in THF or toluene.

**General Procedure 1. Asymmetric Conjugate Addition of Acrylates (5, 7, 9) with Bases (Table 1)** A solution of the substrate in the solvent indicated in Table 1 was added dropwise to a solution of base (2.0 eq) in the solvent indicated in

Table 1 at –78°C (for THF or toluene solutions) or –60°C (for DMF solution) (the final concentration of the substrate: 0.1 M). After being stirred at the same temperature, the mixture was poured into aqueous sat. NH<sub>4</sub>Cl and vigorously stirred for about 1 min. The aqueous layer was extracted with AcOEt and the extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified through silica gel column chromatography.

(2*R*,3*R*)-2-Ethoxycarbonyl-3-(ethoxycarbonyl)methyl-2-methyl-2,3-dihydrobenzofuran (**6a**)

Colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol=99/1, flow=1.0 mL/min, λ=284 nm, retention time (*t<sub>R</sub>*)=15 (minor enantiomer), 25 (major enantiomer) min; [α]<sub>D</sub><sup>20</sup> –37.5 (c 0.60, CHCl<sub>3</sub>, 49% ee); IR (neat) cm<sup>-1</sup>: 3447, 2983, 1736, 1597, 1479, 1462, 1377, 1244, 1110, 1081, 1021, 753; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.27 (3H, t, *J*=6.8 Hz), 1.29 (3H, t, *J*=6.8 Hz), 1.57 (3H, s), 2.59 (1H, dd, *J*=8.8, 16.0 Hz), 2.77 (1H, dd, *J*=6.8, 16.0 Hz), 4.17–4.26 (5H, m), 6.86–6.90 (2H, m), 7.12 (1H, d, *J*=7.6 Hz), 7.17 (1H, brt, *J*=7.6 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 13.97 (q), 14.06 (q), 18.71 (q), 35.56 (t), 44.33 (d), 60.77 (t), 61.70 (t), 88.91 (s), 109.89 (d), 121.15 (d), 124.40 (d), 128.46 (s), 128.80 (d), 157.65 (s), 171.34 (s), 172.88 (s); MS (ESI) *m/z* 315 ((M+Na)<sup>+</sup>, base peak); high resolution (HR)-MS (ESI) *m/z* Calcd for C<sub>16</sub>H<sub>20</sub>NaO<sub>5</sub> ((M+Na)<sup>+</sup>): 315.1203. Found: 315.1202.

(2*R*,3*S*)-2-Ethoxycarbonyl-3-(ethoxycarbonyl)methyl-2-methyl-2,3-dihydrobenzofuran (**6b**)

Colorless oil; IR (neat) cm<sup>-1</sup>: 3444, 2982, 1735, 1598, 1481, 1376, 1251, 1166, 1125, 1088, 1021, 752; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.28 (3H, t, *J*=7.2 Hz), 1.29 (3H, t, *J*=7.2 Hz), 1.71 (3H, s), 2.56 (1H, dd, *J*=8.0, 16.4 Hz), 2.64 (1H, dd, *J*=6.8, 16.4 Hz), 3.86 (1H, brt, *J*=7.2 Hz), 4.15–4.32 (4H, m), 6.86–6.89 (2H, m), 7.10–7.12 (1H, m), 7.16–7.20 (1H, m); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 14.14 (q), 24.66 (q), 36.68 (t), 47.87 (d), 60.83 (t), 61.64 (t), 89.90 (s), 110.07 (d), 121.06 (d), 124.41 (d), 128.17 (s), 128.99 (d), 158.06 (s), 171.15 (s), 171.23 (s); MS (ESI) *m/z* 315 ((M+Na)<sup>+</sup>, base peak); HR-MS (ESI) *m/z* Calcd for C<sub>16</sub>H<sub>20</sub>NaO<sub>5</sub> ((M+Na)<sup>+</sup>): 315.1203. Found: 315.1198.

(2*R*,3*R*)-2,7-Dimethyl-2-ethoxycarbonyl-3-(ethoxycarbonyl)-methyl-2,3-dihydrobenzofuran (**8a**)

Colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol=99/1, flow=0.5 mL/min, λ=284, *t<sub>R</sub>*=25 (minor enantiomer), 46 (major enantiomer) min; [α]<sub>D</sub><sup>22</sup> –57.4 (c

1.05,  $\text{CHCl}_3$ , 94% ee); IR (neat)  $\text{cm}^{-1}$ : 3438, 2982, 1736, 1597, 1467, 1377, 1255, 1098, 1028;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.26 (3H, t,  $J=7.2\text{Hz}$ ), 1.28 (3H, t,  $J=7.2\text{Hz}$ ), 1.58 (3H, s), 2.24 (3H, s), 2.57 (1H, dd,  $J=8.4, 16.0\text{Hz}$ ), 2.74 (1H, dd,  $J=6.8, 16.0\text{Hz}$ ), 4.15–4.24 (5H, m), 6.77 (1H, t,  $J=7.2\text{Hz}$ ), 6.93 (1H, d,  $J=7.2\text{Hz}$ ), 6.98 (1H, d,  $J=7.2\text{Hz}$ );  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.01 (q), 14.13 (q), 15.14 (q), 18.75 (q), 35.77 (t), 44.72 (d), 60.79 (t), 61.63 (t), 88.64 (t), 120.12 (s), 121.00 (d), 121.71 (d), 127.83 (s), 130.04 (d), 156.33 (s), 171.48 (s), 173.19 (s); MS (ESI)  $m/z$  329 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{17}\text{H}_{22}\text{NaO}_5$  ((M+Na) $^+$ ): 329.1359. Found: 329.1353.

(2*R*,3*S*)-2,7-Dimethyl-2-ethoxycarbonyl-3-(ethoxycarbonyl)-methyl-2,3-dihydrobenzofuran (**8b**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3448, 2982, 2920, 1737, 1597, 1467, 1376, 1264, 1028, 760;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.276 (3H, t,  $J=7.2\text{Hz}$ ), 1.283 (3H, t,  $J=7.2\text{Hz}$ ), 1.72 (3H, s), 2.24 (3H, s), 2.56 (1H, dd,  $J=7.6, 16.4\text{Hz}$ ), 2.62 (1H, dd,  $J=7.6, 16.4\text{Hz}$ ), 3.86 (1H, t,  $J=7.6\text{Hz}$ ), 4.13–4.27 (4H, m), 6.78 (1H, t,  $J=7.6\text{Hz}$ ), 6.91 (1H, d,  $J=7.6\text{Hz}$ ), 6.99 (1H, d,  $J=7.6\text{Hz}$ );  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.09 (q), 14.17 (q), 15.20 (q), 24.72 (q), 36.70 (t), 48.26 (d), 60.80 (t), 61.48 (t), 89.59 (s), 120.14 (s), 120.84 (d), 121.51 (d), 127.42 (s), 130.17 (d), 156.70 (s), 171.35 (s); MS (ESI)  $m/z$  329 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{17}\text{H}_{22}\text{NaO}_5$  ((M+Na) $^+$ ): 329.1359. Found: 329.1354.

7-Bromo-2-ethoxycarbonyl-3-(ethoxycarbonyl)methyl-2-methyl-2,3-dihydrobenzofuran (**10**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3440, 2983, 1733, 1604, 1584, 1449, 1377, 1255, 1022, 772;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.26 (3H, t,  $J=7.2\text{Hz}$ ), 1.28 (3H, t,  $J=7.2\text{Hz}$ ), 1.62 (3H, s), 2.57 (1H, dd,  $J=8.8, 16.0\text{Hz}$ ), 2.77 (1H, dd,  $J=6.4, 16.0\text{Hz}$ ), 4.17–4.28 (5H, m), 6.76 (1H, t,  $J=8.0\text{Hz}$ ), 7.05–7.07 (1H, m), 7.32 (1H, d,  $J=8.0\text{Hz}$ );  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.00 (q), 14.15 (q), 18.58 (q), 35.72 (t), 45.33 (d), 60.99 (t), 61.97 (t), 89.59 (s), 102.96 (s), 122.55 (d), 123.56 (d), 130.19 (s), 132.02 (d), 155.45 (s), 171.13 (s), 172.42 (s); MS (ESI)  $m/z$  393 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{16}\text{H}_{19}\text{BrNaO}_5$  ((M+Na) $^+$ ): 393.0308. Found: 393.0302.

**General Procedure for Asymmetric Conjugate Addition of Benzylidenemalonate (11, 13, 15, 17, 19, 21) with Bases (Table 2)**

A solution of the substrate (1.0eq) in THF was added dropwise to a solution of the base (2.0eq or 1.5eq) in THF at  $-78^\circ\text{C}$  (the final substrate concentration: 0.1M). After being stirred for the time indicated in Table 2, the mixture was poured into aqueous sat.  $\text{NH}_4\text{Cl}$ , and the resulting mixture was extracted with  $\text{AcOEt}$ . The extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residual oil was purified through silica gel column chromatography to give dihydrobenzofuran derivatives.

(2*R*,3*R*)-3-Bis(ethoxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**12a**)

Colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol=99/1, flow=1 mL/min,  $\lambda=284\text{nm}$ ,  $t_R=12.6$  (minor enantiomer), 15.4 (major enantiomer) min;  $[\alpha]_D^{22}=-86.9$  ( $c$  1.09,  $\text{CHCl}_3$ , 72% ee); IR (neat)  $\text{cm}^{-1}$ : 3441, 2983, 1732, 1478, 1462, 1370, 1250, 1109, 1027, 755;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.12 (3H, t,  $J=7.2\text{Hz}$ ), 1.24 (3H, t,  $J=7.2\text{Hz}$ ), 1.30 (3H, t,  $J=7.2\text{Hz}$ ), 1.65 (3H, s), 3.74 (1H, d,  $J=8.4\text{Hz}$ ), 4.07 (2H, q,  $J=7.2\text{Hz}$ ), 4.16–4.22 (2H, m), 4.27 (2H, q,  $J=7.2\text{Hz}$ ), 4.51 (2H, d,  $J=8.4\text{Hz}$ ), 6.83–6.88 (2H, m), 7.12 (1H, d,  $J=7.2\text{Hz}$ ),

7.15–7.19 (1H, m);  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.73 (q), 13.96 (q), 14.02 (q), 18.65 (q), 46.93 (d), 53.27 (d), 46.93 (d), 53.27 (d), 61.70 (t), 61.93 (t), 61.99 (t), 89.14 (s), 109.94 (d), 121.13 (d), 125.66 (d), 125.76 (s), 129.39 (d), 158.44 (s), 167.37 (s), 167.82 (s), 172.89 (s); MS (ESI)  $m/z$  387 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{19}\text{H}_{24}\text{NaO}_7$  ((M+Na) $^+$ ): 387.1414. Found: 387.1423.

(2*R*,3*S*)-3-Bis(ethoxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**12b**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3440, 2983, 1739, 1486, 1463, 1371, 1303, 1254, 1177, 1153, 1022, 755;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.14 (3H, t,  $J=7.2\text{Hz}$ ), 1.29 (3H, t,  $J=7.2\text{Hz}$ ), 1.34 (3H, t,  $J=7.2\text{Hz}$ ), 1.70 (3H, s), 4.01 (1H, d,  $J=7.6\text{Hz}$ ), 4.05–4.31 (7H, m), 6.85–6.88 (2H, m), 7.13–7.23 (2H, m);  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.70 (q), 13.92 (q), 13.97 (q), 25.69 (q), 50.37 (d), 53.74 (d), 61.57 (t), 61.81 (t), 61.85 (t), 88.99 (s), 110.23 (d), 120.94 (d), 125.11 (s), 125.67 (d), 129.40 (d), 157.96 (s), 167.44 (s), 167.82 (s), 170.85 (s); MS (ESI)  $m/z$  387 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{19}\text{H}_{24}\text{NaO}_7$  ((M+Na) $^+$ ): 387.1414. Found: 387.1420.

(2*R*,3*R*)-3-Bis(*tert*-butoxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**14a**)

Colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol=99.5/0.5, flow=0.5 mL/min,  $\lambda=284\text{nm}$ ,  $t_R=29$  (major), 32 (minor) min;  $[\alpha]_D^{21}=-81.6$  ( $c$  1.05,  $\text{CHCl}_3$ , 82% ee); IR (neat)  $\text{cm}^{-1}$ : 3437, 2980, 1746, 1595, 1478, 1462, 1254, 1160, 754;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.23 (3H, t,  $J=7.2\text{Hz}$ ), 1.29 (9H, s), 1.49 (9H, s); 1.71 (3H, s); 3.60 (1H, d,  $J=6.8\text{Hz}$ ), 4.18 (2H, q,  $J=7.2\text{Hz}$ ), 4.41 (1H, d,  $J=6.8\text{Hz}$ ), 6.83–6.86 (2H, m); 7.16 (1H, dd,  $J=1.2, 8.0\text{Hz}$ ), 7.26 (1H, d,  $J=6.8\text{Hz}$ );  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.93 (q); 18.80 (q), 27.42 (q); 27.73 (q); 46.67 (d), 55.05 (d), 61.72 (t), 82.04 (s), 82.11 (s), 89.11 (s), 109.67 (d), 120.89 (d), 126.24 (s), 126.39 (d), 128.98 (d), 158.46 (s), 166.64 (s), 167.13 (s), 173.23 (s); MS (ESI)  $m/z$  443 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{23}\text{H}_{32}\text{NaO}_7$  ((M+Na) $^+$ ): 443.2040. Found: 443.2033.

(2*R*,3*S*)-3-Bis(*tert*-butoxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**14b**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3237, 2979, 2932, 1743, 1480, 1369, 1255, 1147, 752, 734;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.30 (9H, s), 1.34 (3H, t,  $J=7.2\text{Hz}$ ), 1.48 (9H, s), 1.69 (3H, s), 3.88 (1H, d,  $J=7.2\text{Hz}$ ), 4.00 (1H, d,  $J=7.2\text{Hz}$ ); 4.29–4.31 (2H, m), 6.84–6.88 (2H, m), 7.15–7.19 (1H, m), 7.25–7.27 (1H, m);  $^{13}\text{C-NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.03 (q), 25.89 (q), 27.54 (q), 27.86 (q), 50.17 (d), 55.40 (d), 61.75 (t), 81.94 (s), 82.21 (s), 88.93 (s), 110.11 (d), 120.79 (d), 125.81 (s), 126.49 (d), 129.09 (d), 158.02 (s), 166.82 (s), 167.41 (s), 170.87 (s); MS (ESI)  $m/z$  443 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{23}\text{H}_{32}\text{NaO}_7$  ((M+Na) $^+$ ): 443.2040. Found: 443.2036.

(2*R*,3*R*)-3-Bis(benzyloxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**16a**)

Colorless oil; HPLC conditions: Daicel Chiralpak AD, hexane/2-propanol=99/1, flow=1.0 mL/min,  $\lambda=284\text{nm}$ ,  $t_R=18$  (major), 23 (minor) min;  $[\alpha]_D^{22}=-74.5$  ( $c$  1.01,  $\text{CHCl}_3$ , 78% ee); IR (neat)  $\text{cm}^{-1}$ : 3439, 2982, 1738, 1594, 1478, 1461, 1382, 1159, 1129, 1109, 1018, 753;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.21 (3H, t,  $J=7.2\text{Hz}$ ), 1.56 (3H, s), 3.84 (1H, d,  $J=8.8\text{Hz}$ ), 4.15 (2H, q,  $J=7.2\text{Hz}$ ), 4.54 (1H, d,  $J=8.8\text{Hz}$ ), 4.96 (1H, d,  $J=12.4\text{Hz}$ ), 5.01 (1H, d,  $J=12.4\text{Hz}$ ), 5.17 (1H, d,  $J=12.4\text{Hz}$ ), 5.22 (1H, d,  $J=12.4\text{Hz}$ ), 6.74 (1H, dt,  $J=0.8, 7.6\text{Hz}$ ), 6.85 (1H, d,  $J=8.0\text{Hz}$ ), 6.98 (1H, d,  $J=7.6\text{Hz}$ ), 7.12–7.17 (3H, m), 7.26–7.37

(8H, m);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.93 (q), 18.54 (q), 46.95 (d), 53.25 (d), 61.87 (t), 67.47 (t), 67.66 (t), 89.01 (s), 109.94 (d), 125.51 (s), 125.54 (d), 128.32 (d), 128.37 (d), 128.40 (d), 128.42 (d), 128.45 (d), 128.51 (d), 129.37 (d), 134.57 (s), 134.82 (s), 158.32 (s), 166.98 (s), 167.43 (s), 172.70 (s); MS (ESI)  $m/z$  511 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{29}\text{H}_{28}\text{NaO}_7$  ((M+Na) $^+$ ): 511.1727. Found: 511.1737.

(2*R*,3*S*)-3-Bis(benzyloxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**16b**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3392, 2981, 2918, 1737, 1481, 1459, 1376, 1255, 1153, 751;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.23 (3H, t,  $J=7.6\text{Hz}$ ), 1.67 (3H, s), 4.06–4.15 (4H, m), 4.98 (1H, d,  $J=12.4\text{Hz}$ ), 5.03 (1H, d,  $J=12.4\text{Hz}$ ), 5.15 (2H, s), 6.75 (1H, brt,  $J=7.2\text{Hz}$ ), 6.82 (1H, d,  $J=8.0\text{Hz}$ ), 6.97 (1H, d,  $J=7.2\text{Hz}$ ), 7.13–7.37 (11H, m);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.94 (q), 25.61 (q), 50.42 (d), 53.88 (d), 61.87 (t), 67.42 (t), 67.51 (t), 88.96 (s), 110.30 (d), 121.02 (d), 124.93 (s), 125.58 (d), 128.28 (d), 128.36 (d), 128.38 (d), 128.43 (d), 128.50 (d), 128.52 (d), 129.45 (d), 157.91 (s), 167.15 (s), 167.53 (s), 170.84 (s); MS (ESI)  $m/z$  511 ((M+Na) $^+$ ), 999 ((2M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{29}\text{H}_{28}\text{NaO}_7$  ((M+Na) $^+$ ): 511.1727. Found: 511.1739.

(2*R*,3*R*)-3-Bis(ethoxycarbonyl)methyl-2-ethoxycarbonyl-2,7-dimethyl-2,3-dihydrobenzofuran (**18a**)

Colorless oil; HPLC conditions: Daicel Chiralpak ID, hexane/2-propanol=99/1, flow=1.0 mL/min,  $\lambda=284\text{nm}$ ,  $t_{\text{R}}=17.7$  (minor), 22.4 (major) min;  $[\alpha]_{\text{D}}^{22}-107.4$  ( $c$  0.98,  $\text{CHCl}_3$ , 96% ee); IR (neat)  $\text{cm}^{-1}$ : 3446, 2983, 1737, 1596, 1467, 1370, 1251, 1176, 1097, 1027, 759;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.13 (3H, t,  $J=7.2\text{Hz}$ ), 1.23 (3H, t,  $J=7.2\text{Hz}$ ), 1.30 (3H, t,  $J=7.2\text{Hz}$ ), 1.64 (3H, s), 2.24 (3H, s), 3.71 (1H, d,  $J=8.8\text{Hz}$ ), 4.05–4.11 (2H, m), 4.13–4.21 (2H, m), 4.26 (2H, q,  $J=7.2\text{Hz}$ ), 4.49 (1H, d,  $J=8.8\text{Hz}$ ), 6.74 (1H, t,  $J=7.6\text{Hz}$ ), 6.92 (1H, d,  $J=7.6\text{Hz}$ ), 6.98 (1H, d,  $J=7.6\text{Hz}$ );  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.69 (q), 13.92 (q), 13.94 (q), 15.10 (q), 18.54 (q), 47.20 (d), 53.35 (d), 61.60 (t), 61.73 (t), 61.90 (t), 88.81 (s), 120.07 (s), 120.89 (d), 122.81 (d), 125.00 (s), 130.46 (d), 156.99 (s), 167.38 (s), 167.80 (s), 173.00 (s); MS (ESI)  $m/z$  401 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{20}\text{H}_{26}\text{NaO}_7$  ((M+Na) $^+$ ): 401.1571. Found: 401.1570.

(2*R*,3*S*)-3-Bis(ethoxycarbonyl)methyl-2-ethoxycarbonyl-2,7-dimethyl-2,3-dihydrobenzofuran (**18b**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3448, 2983, 1737, 1594, 1468, 1371, 1301, 1267, 1177, 1156, 1028, 766;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.16 (3H, t,  $J=7.2\text{Hz}$ ), 1.28 (3H, t,  $J=7.2\text{Hz}$ ), 1.31 (3H, t,  $J=7.2\text{Hz}$ ), 1.69 (3H, s), 2.22 (3H, s), 3.96 (1H, d,  $J=8.0\text{Hz}$ ), 4.08–4.28 (7H, m), 6.75 (1H, t,  $J=8.0\text{Hz}$ ), 6.89 (1H, d,  $J=8.0\text{Hz}$ ), 7.00 (1H, d,  $J=8.0\text{Hz}$ );  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.75 (q), 13.93 (q), 15.21 (q), 25.53 (q), 50.88 (d), 54.09 (d), 61.57 (t), 61.69 (t), 61.79 (t), 88.72 (s), 120.28 (s), 120.68 (d), 122.70 (d), 124.39 (s), 130.55 (d), 156.61 (s), 167.60 (s), 167.81 (s), 170.94 (s); MS (ESI)  $m/z$  401 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{20}\text{H}_{26}\text{NaO}_7$  ((M+Na) $^+$ ): 401.1571. Found: 401.1569.

(2*R*,3*R*)-3-Bis(ethoxycarbonyl)methyl-5-bromo-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**20a**)

Colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol=99/1, flow=1.0 mL/min,  $\lambda=284\text{nm}$ ,  $t_{\text{R}}=12$  (minor), 18 (major) min;  $[\alpha]_{\text{D}}^{22}-49.7$  ( $c$  1.10,  $\text{CHCl}_3$ , 77% ee); IR (neat)  $\text{cm}^{-1}$ : 3450, 2983, 1733, 1471, 1370, 1305, 1255, 1027, 758;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.14 (3H, t,  $J=7.2\text{Hz}$ ),

1.25 (3H, t,  $J=7.2\text{Hz}$ ), 1.31 (3H, t,  $J=7.2\text{Hz}$ ), 1.66 (3H, s), 3.73 (1H, d,  $J=8.0\text{Hz}$ ), 4.04–4.13 (2H, m), 4.20 (2H, q,  $J=7.2\text{Hz}$ ), 4.27 (2H, q,  $J=7.2\text{Hz}$ ), 4.46 (1H, d,  $J=8.0\text{Hz}$ ), 6.75 (1H, d,  $J=8.4\text{Hz}$ ), 7.26–7.29 (2H, m);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.72 (q), 13.90 (q), 13.96 (q), 18.54 (q), 46.85 (d), 52.94 (d), 61.85 (t), 62.06 (t), 62.10 (t), 89.70 (s), 111.44 (d), 112.96 (s), 128.23 (s), 128.79 (d), 132.16 (d), 157.65 (s), 167.08 (s), 167.53 (s), 172.41 (s); MS (ESI)  $m/z$  465 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{19}\text{H}_{23}\text{BrNaO}_7$  ((M+Na) $^+$ ): 465.0519. Found: 465.0507.

(2*R*,3*S*)-3-Bis(ethoxycarbonyl)methyl-5-bromo-2-ethoxycarbonyl-2-methyl-2,3-dihydrobenzofuran (**20b**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3448, 2982, 1737, 1473, 1371, 1308, 1256, 1177, 1024;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.16 (3H, t,  $J=7.2\text{Hz}$ ), 1.29 (3H, t,  $J=7.2\text{Hz}$ ), 1.33 (3H, t,  $J=7.2\text{Hz}$ ), 1.68 (3H, s), 4.00 (1H, d,  $J=7.6\text{Hz}$ ), 4.06–4.14 (3H, m), 4.16–4.30 (4H, m), 6.74 (1H, d,  $J=8.4\text{Hz}$ ), 7.26–7.30 (2H, m);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.75 (q), 13.91 (q), 13.94 (q), 25.61 (q), 50.25 (d), 53.36 (d), 61.75 (t), 61.96 (t), 61.98 (t), 89.60 (s), 111.77 (d), 112.73 (s), 127.63 (s), 128.77 (d), 132.20 (d), 157.17 (s), 167.20 (s), 167.58 (s), 170.34 (s); MS (ESI)  $m/z$  465 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{19}\text{H}_{23}\text{BrNaO}_7$  ((M+Na) $^+$ ): 465.0519. Found: 465.0510.

(2*R*,3*R*)-3-Bis(ethoxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-5-methoxy-2,3-dihydrobenzofuran (**22a**)

Colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol=99/1, flow=1.0 mL/min,  $\lambda=284\text{nm}$ ,  $t_{\text{R}}=25$  (minor), 30 (major) min;  $[\alpha]_{\text{D}}^{21}-60.9$  ( $c$  1.21,  $\text{CHCl}_3$ , 61% ee); IR (neat)  $\text{cm}^{-1}$ : 3437, 2983, 1733, 1488, 1370, 1227, 1175, 1149, 1106, 1031;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.13 (3H, t,  $J=7.2\text{Hz}$ ), 1.24 (3H, t,  $J=7.2\text{Hz}$ ), 1.30 (3H, t,  $J=7.2\text{Hz}$ ), 1.64 (3H, s), 3.71 (3H, s), 3.73 (1H, d,  $J=8.4\text{Hz}$ ), 4.05–4.10 (2H, m), 4.19 (2H, dq,  $J=0.8, 7.2\text{Hz}$ ), 4.28 (2H, q,  $J=7.2\text{Hz}$ ), 4.47 (1H, d,  $J=8.4\text{Hz}$ ), 6.68–6.74 (2H, m), 6.77–6.79 (1H, m);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.66 (q), 13.87 (q), 13.94 (q), 18.58 (q), 47.19 (d), 53.09 (d), 55.74 (s), 61.61 (t), 61.81 (t), 61.91 (t), 109.88 (d), 111.60 (d), 114.56 (d), 126.64 (s), 152.49 (s), 154.31 (s), 167.25 (s), 167.68 (s), 173.02 (s); MS (ESI)  $m/z$  417 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{20}\text{H}_{26}\text{NaO}_8$  ((M+Na) $^+$ ): 417.1520. Found: 417.1521.

(2*R*,3*S*)-3-Bis(ethoxycarbonyl)methyl-2-ethoxycarbonyl-2-methyl-5-methoxy-2,3-dihydrobenzofuran (**22b**)

Colorless oil; IR (neat)  $\text{cm}^{-1}$ : 3393, 2983, 1737, 1480, 1307, 1227, 1148, 1032;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.14 (3H, t,  $J=7.2\text{Hz}$ ), 1.28 (3H, t,  $J=7.2\text{Hz}$ ), 1.33 (3H, t,  $J=7.2\text{Hz}$ ), 1.67 (3H, s), 3.72 (3H, s), 4.01 (1H, d,  $J=7.6\text{Hz}$ ), 4.03–4.12 (3H, m), 4.17–4.30 (4H, m), 6.71–6.77 (3H, m);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.77 (q), 13.96 (q), 14.02 (q), 25.71 (q), 50.73 (d), 53.61 (d), 55.92 (q), 61.62 (t), 61.86 (t), 89.21 (s), 110.29 (d), 111.75 (d), 114.72 (d), 126.06 (s), 152.08 (s), 154.31 (s), 167.44 (s), 167.86 (s), 170.97 (s); MS (ESI)  $m/z$  417 ((M+Na) $^+$ , base peak); HR-MS (ESI)  $m/z$  Calcd for  $\text{C}_{20}\text{H}_{26}\text{NaO}_8$  ((M+Na) $^+$ ): 417.1520. Found: 417.1520.

#### Determination of Absolute Configuration of **18a/b**

$\text{K}_2\text{CO}_3$  (0.59 g, 4.23 mmol) was added to a solution of a diastereomeric mixture of **18a/b** (1.07 g, 2.82 mmol) in MeCN (28 mL) at r.t. After being stirred for 30 min at r.t., phenyl succinimide sulfide (1.17 g, 5.67 mmol)<sup>24</sup>) was added. The resulting mixture was stirred for 30 min and diluted with  $\text{CH}_2\text{Cl}_2$ . The mixture was washed with water and brine, and dried over  $\text{MgSO}_4$ , filtered, and concentrated. The residue was puri-

fied through flash silica gel column chromatography to give phenylthio malonate (1.25 g, 91% yield). *m*-Chloroperbenzoic acid (*m*CPBA) (0.74 g, 3.09 mmol) was portionwise added to a solution of phenylthio malonate (1.25 g, 2.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0°C. The mixture was gradually warmed to r.t., and stirred for 30 min. The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and quenched by addition of aqueous sat. NaHCO<sub>3</sub>. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with water and brine, and dried over MgSO<sub>4</sub>, filtered, and concentrated to give an oil, which was dissolved in toluene (30 mL). The stirring mixture was refluxed for 12 h. After removal of volatiles, the residue was purified through flash silica gel column chromatography to give **23** (0.62 g, 64% yield) as a colorless oil. To a solution of **23** (0.62 g, 1.64 mmol) and MgSO<sub>4</sub> (0.43 g, 3.61 mmol) in water–acetone (20 mL, 3:2, v/v) was added KMnO<sub>4</sub> (0.52 g, 9.84 mmol) portion-wise at r.t. After being stirred for 13 h, the mixture was diluted with water and extracted with AcOEt. The extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified through silica gel column chromatography to give ketone (69.1 mg, 18% yield). A mixture of ketone (23.7 mg, 0.10 mmol) and Pd(OH)<sub>2</sub>/C (6.8 mg, 0.01 mmol) was stirred under H<sub>2</sub> atmosphere (4 atm) for 54 h at r.t. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified through silica gel column chromatography to give **24** (13.1 mg, 55% yield) as a colorless oil; [α]<sub>D</sub><sup>20</sup>+5.4 (*c* 1.0, CHCl<sub>3</sub>) [lit.<sup>1)</sup> [α]<sub>D</sub><sup>19</sup>–8.6 (*c* 0.9, CHCl<sub>3</sub>, 86% ee) for (*S*)-**24**]. The proton and carbon NMR spectra were identified with reported ones.<sup>1)</sup>

(*R*)-Diethyl 2-(2-(Ethoxycarbonyl)-2,7-dimethylbenzofuran-3(2*H*)-ylidene) Malonate (**23**)

Colorless oil; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.22 (3H, t, *J*=7.3 Hz), 1.28 (3H, t, *J*=7.3 Hz), 1.38 (3H, t, *J*=6.9 Hz), 1.83 (3H, s), 2.23 (3H, s), 4.10–4.29 (4H, m), 4.38–4.47 (2H, m), 6.88 (1H, dd, *J*=0.5, 7.8 Hz), 7.19–7.23 (2H, m); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 13.87 (q), 13.94 (q), 14.02 (q), 20.93 (q), 61.37 (t), 61.63 (t), 61.77 (t), 91.67 (s), 115.62 (s), 120.78 (s), 121.76 (d), 122.07 (s), 122.30 (d), 135.33 (d), 156.05 (s), 161.90 (s), 163.46 (s), 166.35 (s), 167.25 (s).

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**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this article contains supplementary materials.

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