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). This strategy does not belong to any of above three categories. We believe that MOC strategy created the forth 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 α-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. We have developed strategy for asymmetric induction via enolate intermediate A with a chiral C–C axis in 1991 (Chart 1, Eq. 1). The half-life of racemization of the axially chiral enolate A at the reaction temperature (−20°C) was estimated to be ca. 24 d.1) We then developed a method for asymmetric induction via enolate intermediate B with a chiral C–N axis in 2000 (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°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 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°C (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.

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. 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 1-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 Chat 1. Treatment of 5 with sodium hexamethyldisilazide (NaHMDS) in tetrahydrofuran (THF) at −78°C for 1 h gave a 91:9 diastereomeric mixture of 6a:b in a combined

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Logical possibility for asymmetric induction via configurationally stable carbanion B’ (Eq. 4) and racemate formation from the di-tert-butoxycarbonyl (Boc) derivative 2a via achiral enolate intermediate 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
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. These results suggest that the intramolecular conjugate addition of the chiral enolate seems to proceed faster than the corresponding intermolecular 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. 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 intermolecular alkylation via the C–O axially chiral enolate (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 maleonate-type Michael acceptors (Table 2). The reaction of 11 (R1=R2=H, X=CO2Et) 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=CO2F-Bu) and 15 (X=CO2Bn) instead of 11 (X=CO2Et) in the presence of LiHMDS further improved the diastereoselectivity and the enantioselectivity to give a 96:4 diastereomeric mixture of 14a (83% ee) and 14b in a combined yield of 87% (entry 4) and a 96:4 diastereomeric mixture of 16a (86% ee) and 16b 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 (R1=Me, R2=H) with LiHMDS (entry 8), the desired products 18a and 18b 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 R1=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. However, negligible effects of the C(4)-substituent was observed in the asymmetric intramolecular conjugate addition of 19 with R2=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 1. Asymmetric Intramolecular Conjugate Addition of the Enolate Generated from 5, 7, and 9

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

<sup>a</sup> All reactions were run at the substrate concentration of 0.1 M. <sup>b</sup> The diastereomeric ratio was determined by 1H-NMR. <sup>c</sup> The relative configuration of 6a and b was determined based on the reported 1H-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. i) Not determined.
Table 2. Asymmetric Intramolecular Conjugate Addition of Enolates Generated from Substrates with Malonate-Type Michael Acceptors

| Entry | Substrate R1 | R2 | X | Base | Time (h) | Products | Yield (%) | dr a : b | % ee of a<sup>e</sup> vs. b<sup>d</sup> |
|-------|--------------|----|----|------|---------|---------|-----------|---------|-----------------
| 1     | 11           | H  | H  | CO<sub>2</sub>Et | NaHMDS  | 1       | 12a, b    | 60      | 80:20          | 66                |
| 2     | 11           | H  | H  | CO<sub>2</sub>Et | LiHMDS  | 3       | 12a, b    | 67      | 92:8           | 78                |
| 3     | 13           | H  | H  | CO<sub>2</sub>-Bu | NaHMDS  | 1       | 14a, b    | 75      | 90:10          | 74                |
| 4     | 13           | H  | H  | CO<sub>2</sub>-Bu | LiHMDS  | 3       | 14a, b    | 87      | 96:4           | 83                |
| 5     | 15           | H  | H  | CO<sub>2</sub>Bn  | NaHMDS  | 3       | 16a, b    | 90      | 83:17          | 59                |
| 6     | 15           | H  | H  | CO<sub>2</sub>Bn  | LiHMDS  | 3       | 16a, b    | 77      | 96:4           | 86                |
| 7     | 17           | Me | H  | CO<sub>2</sub>Et | NaHMDS  | 3       | 18a, b    | 79      | 67:33          | 96                |
| 8     | 17           | Me | H  | CO<sub>2</sub>Et | LiHMDS  | 3       | 18a, b    | trace<sup>i</sup> | —<sup>i</sup> | —<sup>i</sup>       |
| 9     | 19           | H  | Br | CO<sub>2</sub>Et | NaHMDS  | 1       | 20a, b    | 86      | 75:25          | 67                |
| 10    | 19           | H  | Br | CO<sub>2</sub>Et | LiHMDS  | 3       | 20a, b    | 82      | 92:8           | 77                |
| 11    | 21           | H  | OMe| CO<sub>2</sub>Et | NaHMDS  | 1       | 22a, b    | 94      | 86:14          | 44                |
| 12    | 21           | H  | OMe| CO<sub>2</sub>Et | LiHMDS  | 3       | 22a, b    | 60      | 90:10          | 77                |

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

Chart 3. Determination of the Absolute Configuration of 18<sup>a</sup> and 18<sup>b</sup>

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 18<sup>a</sup>/18<sup>b</sup> were determined by chemical correlation with the known compound 24 (Chart 3). Introduction of a phenylthio group at the α-position of the ester carbonyl group, oxidation of the sulfur atom, followed by thermal β-elimination of resulting sulfoxide gave the unsaturated ester 23. Oxidative cleavage of the double bond of 23 followed by the reduction of the benzylic carbonyl group gave known (R)-24. Accordingly, the absolute configuration of the tetrasubstituted carbon center of 18<sup>a</sup> and 18<sup>b</sup> 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 4<sup>a</sup> would give enantiotomerically enriched enolate D with a chiral C–O axis, which would give product with inversion of configuration. On the other hand, deprotonation of conformer 4<sup>b</sup> would give the product with retention of configuration via enolate ent-D. Due to the better steric accessibility of the α-H in 4<sup>a</sup> than that in 4<sup>b</sup> 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°C based on our previous results in asymmetric intramolecular alkylation reactions. 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...
via asymmetric C–O bond formation.25–28 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** ¹H-NMR were measured in CDCl₃ and referenced from TMS (0.00 ppm) using JEOL ECX-400 (400 MHz) spectrophotometer, unless otherwise noted. ¹³C-NMR were measured in CDCl₃ solution and referenced to CDCl₃ (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) mass spectrometer. 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 245), 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 Wako Pure Chemical Industries, Ltd. and pre-treated with activated MS4Å. Anhydrous DMF, which was purchased from Kanto Kagaku and pre-treated with MS4Å. Wako Pure Chemical Industries, Ltd. was distilled over CaH₂ and kept with MS4Å. Anhydrous NaHMDS was purchased from TCI. LDA and LiHMDS were freshly prepared from the corresponding amine (1 eq) with n-NaHMDS was purchased from TCI. LDA and LiHMDS were freshly prepared from the corresponding amine (1 eq) with n-NaHMDS was purchased from TCI. LDA and LiHMDS were freshly prepared.

**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 drop-wisely 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. NH₄Cl and vigorously stirred for about 1 min. The aqueous layer was extracted with AcOEt and the extracts were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified through silica gel column chromatography.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Optical Rotation</th>
<th>Retention Time (min)</th>
<th>Mass Spectrum (ESI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(R,3R)-2-Ethoxycarbonyl-3-(ethoxycarbonyl)methyl-2,3-dihydrobenzofuran (6a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2(R,3S)-2-Ethoxycarbonyl-3-(ethoxycarbonyl)methyl-2,3-dihydrobenzofuran (6b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2(R,3R)-2,7-Dimethyl-2-ethoxycarbonyl-3-(ethoxycarbonyl)methyl-2,3-dihydrobenzofuran (8a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**General Procedure 2. Asymmetric Intramolecular Conjugate Addition via C–O Axially Chiral Enolates**

![Chart 4. A Possible Mechanism for Asymmetric Intramolecular Conjugate Addition via C–O Axially Chiral Enolates](image-url)
1.05, CHCl₃, 94% ee); IR (neat) cm⁻¹: 3439, 2892, 1736, 1597, 1467, 1377, 1255, 1098, 1028; ¹H-NMR (400 MHz, CDCl₃): δ: 1.26 (3H, t, J = 7.2 Hz), 1.28 (3H, t, J = 7.2 Hz), 1.58 (3H, s), 2.24 (3H, s), 2.57 (1H, dd, J = 8.4, 16.0 Hz), 2.74 (1H, dd, J = 6.8, 16.0 Hz), 4.15–4.24 (5H, m), 6.77 (1H, t, J = 7.2 Hz), 6.93 (1H, d, J = 7.2 Hz), 6.98 (1H, d, J = 7.2 Hz); ¹³C-NMR (100 MHz, CDCl₃): δ: 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 C₁₉H₂₂NaO₇ ([M+Na]⁺): 387.1414. Found: 387.1423.

(2R,3S)-3-Bis(ethoxy carbonyl) methyl-2-ethoxy carbonyl-2-methyl-2,3-dihydrobenzofuran (12b)

Colorless oil; IR (neat) cm⁻¹: 3440, 2983, 1739, 1486, 1463, 1371, 1303, 1254, 1177, 1153, 1022, 755; ¹H-NMR (400 MHz, CDCl₃): δ: 1.14 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 1.34 (3H, t, J = 7.2 Hz), 1.70 (3H, s), 4.01 (1H, d, J = 7.6 Hz), 4.05–4.31 (7H, m), 6.85–6.88 (2H, m), 7.13–7.23 (2H, m);

¹³C-NMR (100 MHz, CDCl₃): δ: 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), 121.51 (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 C₁₉H₂₂NaO₇ ([M+Na]⁺): 387.1414. Found: 387.1420.

(2R,3S)-3-Bis(tert-butoxycarbonyl)methyl-2-ethoxy carbonyl-2-methyl-2,3-dihydrobenzofuran (14a)

Colorless oil; HPLC conditions: Daicel Chiralcel OD-H, hexane/2-propanol=99/1, flow=1.0 mL/min, λ=284 nm, tₚ=29 (major), 32 (minor) [α]°=86.1 (c 1.05, CHCl₃, 82% ee); IR (neat) cm⁻¹: 3437, 2980, 1746, 1595, 1478, 1462, 1254, 1160, 754; ¹H-NMR (400 MHz, CDCl₃): δ: 1.23 (3H, t, J = 7.2 Hz), 1.29 (9H, s), 1.49 (9H, s), 1.71 (3H, s); 3.60 (1H, d, J = 6.8 Hz), 4.18 (2H, q, J = 7.21 Hz), 4.41 (1H, d, J = 6.8 Hz), 6.83–6.86 (2H, m), 7.16 (1H, dd, J = 1.2, 8.0 Hz), 7.26 (1H, d, J = 6.81 Hz); ¹³C-NMR (100 MHz, CDCl₃): δ: 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), 122.24 (d), 136.29 (s), 128.98 (d), 154.86 (s), 165.64 (s), 167.13 (s), 173.23 (s); MS (ESI) m/z 443 ([M+Na]⁺, base peak); HR-MS (ESI) m/z calcd for C₂₃H₃₂NaO₇ ([M+Na]⁺): 443.2034. Found: 443.2033.

(2R,3S)-3-Bis(tert-butoxycarbonyl)methyl-2-ethoxy carbonyl-2-methyl-2,3-dihydrobenzofuran (14b)

Colorless oil; IR (neat) cm⁻¹: 3237, 2979, 2932, 1743, 1480, 1369, 1255, 1147, 752, 734; ¹H-NMR (400 MHz, CDCl₃): δ: 1.30 (9H, s), 1.34 (3H, t, J = 7.21 Hz), 1.48 (9H, s), 1.69 (3H, s), 3.88 (1H, d, J = 7.21 Hz), 4.00 (1H, d, J = 7.21 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); ¹³C-NMR (100 MHz, CDCl₃): δ: 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 (s), 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 C₂₃H₂₄NaO₇ ([M+Na]⁺): 443.2040. Found: 443.2036.

(2R,3R)-3-Bis(benzoylcarbonyl)methyl-2-ethoxy carbonyl-2-methyl-2,3-dihydrobenzofuran (16a)

Colorless oil; HPLC conditions: Daicel Chiralpak AD-H, hexane/2-propanol=99/1, flow=1.0 mL/min, λ=284 nm, tₚ=18 (major), 23 (minor) [α]°=74.5 (c 1.01, CHCl₃, 78% ee); IR (neat) cm⁻¹: 3439, 2982, 1738, 1594, 1478, 1461, 1382, 1159, 1129, 1109, 1018, 753; ¹H-NMR (400 MHz, CDCl₃): δ: 1.21 (3H, t, J = 7.2 Hz), 1.56 (3H, s), 3.84 (1H, d, J = 8.8 Hz), 4.15 (2H, q, J = 7.2 Hz), 4.54 (1H, d, J = 8.8 Hz), 4.96 (1H, d, J = 12.4 Hz), 5.01 (1H, d, J = 12.4 Hz), 5.17 (1H, d, J = 12.4 Hz), 5.22 (1H, d, J = 12.4 Hz), 6.74 (1H, dt, J = 0.8, 7.6 Hz), 6.85 (1H, d, J = 8.0 Hz), 6.98 (1H, d, J = 7.6 Hz), 7.12–7.17 (3H, m), 7.26–7.37
Colorless oil; IR (neat) cm\(^{-1}\): 3448, 2983, 1737, 1371, 1308, 1256, 1177, 1024; \(^{1}^H\)-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.16 (3H, \text{t, } J=7.2Hz), 1.28 (3H, \text{t, } J=7.2Hz), 1.31 (3H, \text{t, } J=7.2Hz), 1.69 (3H, \text{s}), 2.22 (3H, \text{s}), 3.96 (1H, \text{d, } J=8.0Hz), 4.08–4.28 (7H, \text{m}), 6.75 (1H, \text{t, } J=8.0Hz), 6.89 (1H, \text{d, } J=8.0Hz), 7.00 (1H, \text{d, } J=8.0Hz). \(^{13}^C\)-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 13.75 (q), 13.93 (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 C\(_{20}\)H\(_{26}\)NaO\(_7\) ([M+Na]^+): 417.1520. Found: 417.1520. 

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

K\(_2\)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 succinimidyl sulfide (1.17 g, 5.67 mmol)\(^{32}\) was added. The resulting mixture was stirred for 30 min and diluted with CH\(_2\)Cl\(_2\). The mixture was washed with water and brine, and dried over 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 (mCPBA) (0.74 g, 3.09 mmol) was portionwise added to a solution of phenylthio malonate (1.25 g, 2.57 mmol) in CH₂Cl₂ (30 mL) at 0°C. The mixture was gradually warmed to r.t., and stirred for 30 min. The resulting mixture was diluted with CH₂Cl₂ and quenched by addition of aqueous NaHCO₃. The aqueous layer was extracted with CH₂Cl₂. The extracts were washed with water and brine, and dried over MgSO₄, 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 MgSO₄ (0.43 g, 3.61 mmol) in water–acetone (20 mL, 3:2, v/v) was added KMnO₄ (0.52 g, 9.84 mmol) portion-wise at r.t. The mixture was gradually warmed to r.t., and MgSO₄ (0.43 g, 3.61 mmol) in water–acetone (20 mL, 3:2, v/v) was added KMnO₄ (0.52 g, 9.84 mmol) portion-wise at r.t. The mixture was gradually warmed to r.t., and the mixture 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 ketone (0.62 g, 64% yield) as a colorless oil. To a solution of ketone (0.62 g, 1.64 mmol) and NaHMDS in DMF, inversion with LTMP or LiHMDS in THF or DMSO was added. The mixture was stirred for 12 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified through flash silica gel column chromatography to give 24 (13.1 mg, 55% yield) as a colorless oil; [α]D²⁰ = +5.4 (c 1.0, CHCl₃) [lit.] [α]D²⁰ = +8.6 (c 0.9, CHCl₃, 86% ee) for (S)-24. The proton and carbon NMR spectra were identified with reported ones.¹³

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

Colorless oil;¹⁴ ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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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Conflicts of Interest The authors declare no conflict of interest.

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

References and Notes
23) Enantiodiversity was also observed in asymmetric cyclization of the C–N axially chiral enolates generated from α-amino acid derivatives depending on the base-solvent system: retention with KHMDS or NaHMDS in DMF, inversion with LiMP or LiHMDS in THF or toluene, see: Kawabata T., Matsuura S., Kawakami S., Monoguchi D., Moriyama K., J. Am. Chem. Soc., 128, 15394–15395 (2006).