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Enantioselective Organocatalyzed Consecutive Synthesis of Alkyl 4,5-Dihydrofuran-2-carboxylates from α-Keto Esters and (Z)-β-Chlro-β-nitrostyrenes

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Abstract
Alkyl 4,5-dihydrofuran-2-carboxylates can be efficiently obtained via an enantioselective organocatalyzed consecutive reaction between α-keto esters and (Z)-β-chloro-β-nitrostyrenes. The overall sequence combines a (R,R)-TUC-catalyzed Michael addition with a DABCO-promoted intramolecular O-alkylation leading to the title products as single diastereomers with enantiomeric excesses from 86% up to 97%.

Keywords dihydrofurans, organocatalysis, domino Michael/alkylation, Takemoto catalyst, (Z)-β-chloro-β-nitrostyrenes

Dihydrofuran is a structural subunit found in a number of important natural products and pharmacologically relevant compounds. In consequence, important efforts have been devoted towards the enantioselective synthesis of dihydrofurans derivatives. Since the pioneer reports of Dauzonne and co-workers twenty-five years ago, the Michael–alkylation domino reaction between (Z)-2-halo-2-nitrostylenes and various bis-nucleophiles has become an attractive strategy to access dihydrofurans enantioselectively (Scheme 1). Hence, the groups of Rueping, Xie, Lu, and Feng employed 1,3-dicarboxyls as 1,3-bis-nucleophiles activated by an hydrogen-bonding organocatalyst to access 3-carbonyl-4,5-dihydrofurans (Scheme 1, eq 1). However, none of these approaches allows for the challenging introduction of a key carbonyl moiety in the 2-position of the final optically active dihydrofuran target. In addition, the 2-carbonyl-4,5-dihydrofuran substructure is present in various families of bioactive natural products such as cheimonophyllal, jiadifenlactone A and no efficient enantioselective method to construct this moiety has been reported so far. Indeed, the 2-carbonyl-4,5-dihydrofuran substructure is present in various families of bioactive natural products such as cheimonophyllal, and jiadifenlactone A and no efficient enantioselective method to construct this moiety has been reported so far.

Scheme 1 Strategies for the construction of optically active dihydrofurans with β-halo-β-nitrostyrenes

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α-Dicarbonyl compounds are privileged substrates for the development of new multiple bond-forming transformations due to their high number of adjacent reactive sites that can participate in the successive creation of several bonds. Therefore, to address this synthetic lack, we propose a sequential enantioselective heterocyclization of α-keto esters with β-chloro-β-nitrostyrenes combining an enantioselective Michael addition promoted by a chiral H-bonding donor bifunctional catalyst with a base-promoted intramolecular O-alkylation (Scheme 1, eq 3).

Optimized conditions for the enantioselective Michael addition leading to 3a were used and our initial efforts focused on the base-promoted heterocyclization from 3a (Table 1). An encouraging result was obtained with the use of 1 equivalent of TMEDA at 60 °C leading to the desired dihydrofuran 4a in only 27% yield, but with excellent stereoselectivities together, with the side product furan 5a (entry 1). Lowering the amount of base to 0.2 equivalents resulted in lower yield (entry 2). Further improvements in yield were achieved using other organic bases even if in the case of DBU (entry 3) a marked erosion of both diastereo- and enantioselectivity was observed as well as an increased proportion of undesired furan 5a compared to the use of DABCO (entry 4). Finally, lowering the temperature had a beneficial impact on the yield (entries 5 and 6), while maintaining excellent diastereo- and enantioselectivities. In this last case, prolonged reaction time was required (72 h) to consume starting materials while keeping a limited ratio of 5a.

Having found conditions that gave good yields and high stereoselectivities in this formal [3+2] heterocyclization, we explored alternative β-chloro-β-nitrostyrenes 1 and α-keto esters 2 (Table 2). Concerning the nitroalkene, the reaction worked well with β-substituted aromatic rings bearing either electron-donating (entries 1–5) or electron-withdrawing groups (entries 6–8), including sterically demanding ortho functionalization (entry 7), or a 2-naphthyl moiety (entry 9). The introduction of an heteroaromatic moiety (3-chromenyl, entry 10) was possible, but a poor yield of 4j was obtained and the reaction was found to be very slow, both for the formation of the Michael adduct and for the heterocyclization step. On the other hand, tert-butyl ester as well as ethyl ester can be employed and the desired

### Table 1 Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>T (°C)</th>
<th>Ratio (3a/4a/5a)</th>
<th>Yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>TMEDA</td>
<td>60</td>
<td>1:13:3</td>
<td>27</td>
<td>12:1</td>
<td>93</td>
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<tr>
<td>2</td>
<td>TMEDA</td>
<td>60</td>
<td>8:6:1</td>
<td>&gt;20:1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>DBU</td>
<td>60</td>
<td>1:16:3</td>
<td>51</td>
<td>14:1</td>
<td>78</td>
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<tr>
<td>4</td>
<td>DABCO</td>
<td>60</td>
<td>1:20:4</td>
<td>47</td>
<td>&gt;20:1</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>DABCO</td>
<td>40</td>
<td>1:18:1</td>
<td>57</td>
<td>&gt;20:1</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>DABCO</td>
<td>25</td>
<td>1:21:1</td>
<td>79</td>
<td>&gt;20:1</td>
<td>95</td>
</tr>
</tbody>
</table>

\(\text{a} \) Reaction conditions: 1. 1a (0.1 mmol), 2a (0.2 mmol), catalyst (R,R)-TUC (10 mol%), EtOAc, 0 °C, stirring, 0 °C, 24 h; 2. base (1 equiv), stirring, T (°C), 24 h; unless otherwise noted.

\(\text{b} \) Determined by \(^1H\) NMR analysis of the crude reaction mixture.

\(\text{c} \) Isolated yield after column chromatography.

\(\text{d} \) Determined by chiral HPLC analysis.

\(\text{e} \) 0.2 equiv of base was used.

\(\text{f} \) 72 h of reaction time after addition of base.
products were obtained in fairly good yields with excellent diastereo- and enantioselectivities (entries 11–14). We noticed also that adding steric bulk around pro-nucleophilic carbon atom of the α-keto ester (use of 2c, 2d, and 2e, entries 12–14) had a negative impact on the kinetics of both the Michael addition as well as on the heterocyclization step.

To evaluate the synthetic usefulness of this methodology, the nitro group of 4a was reduced to the primary amine moiety affording the relatively labile aminal 6 in moderate yield suffering substantial erosion of enantiomeric excess (Scheme 2). Also, an attempt to convert dihydrofuran 4a into the corresponding lactone using the Mioskowski procedure resulted in the formation of nitrofuran 7 in 65% yield.

Table 2 Reaction Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;3&lt;/sup&gt; (%)&lt;sup&gt;e&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;d&lt;/sup&gt; (%)&lt;sup&gt;e&lt;/sup&gt;</th>
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<tbody>
<tr>
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<td>1a</td>
<td>2a</td>
<td>4a</td>
<td>24</td>
<td>90</td>
<td>79</td>
<td>&gt;20:1</td>
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<tr>
<td>2</td>
<td>2-MeOC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1b</td>
<td>2a</td>
<td>4b</td>
<td>24</td>
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<td>54</td>
<td>&gt;20:1</td>
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<tr>
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<td>1c</td>
<td>2a</td>
<td>4c</td>
<td>48</td>
<td>72</td>
<td>48</td>
<td>&gt;20:1</td>
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<tr>
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<td>4-HOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1d</td>
<td>2a</td>
<td>4d</td>
<td>72</td>
<td>72</td>
<td>48</td>
<td>&gt;20:1</td>
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<td>2a</td>
<td>4e</td>
<td>72</td>
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<td>42</td>
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<td>4-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1f</td>
<td>2a</td>
<td>4f</td>
<td>24</td>
<td>48</td>
<td>20</td>
<td>&gt;20:1</td>
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<td>2-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1g</td>
<td>2a</td>
<td>4g</td>
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<td>1h</td>
<td>2a</td>
<td>4h</td>
<td>72</td>
<td>58</td>
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<td>9</td>
<td>2-naphthyl</td>
<td>1i</td>
<td>2a</td>
<td>4i</td>
<td>48</td>
<td>48</td>
<td>61</td>
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<td>10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3-chromeny</td>
<td>1j</td>
<td>2a</td>
<td>4j</td>
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<td>11&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>1a</td>
<td>2b</td>
<td>4k</td>
<td>48</td>
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<td>36</td>
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<td>12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4-MeO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1a</td>
<td>2c</td>
<td>4l</td>
<td>72</td>
<td>72</td>
<td>38</td>
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<tr>
<td>13&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4-MeO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1a</td>
<td>2d</td>
<td>4m</td>
<td>96</td>
<td>72</td>
<td>52</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>14&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4-MeO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1a</td>
<td>2e</td>
<td>4n</td>
<td>96</td>
<td>72</td>
<td>26</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1. 1 (0.1 mmol), 2 (0.2 mmol), catalyst (R,R)-TUC (10 mol%), EtOAc (1.0 mL) stirring, 0 °C, for the indicated time; 2. mixture brought to r.t. followed by addition of DABCO (0.1 mmol).
<sup>b</sup> Isolated yield after column chromatography.
<sup>c</sup> Determined by H NMR analysis of the crude reaction product.
<sup>d</sup> Determined by chiral HPLC analysis.
<sup>e</sup> THF was used as the reaction solvent.
<sup>f</sup> When DABCO was added, the reaction was heated to 40 °C.
In conclusion we have developed an efficient consecutive reaction to optically active alkyldicarbonyltrans-4,5-dihydrofuranyl-2-carboxylic acid by a Michael/0-alkylation sequence between α-keto esters and β-chloro-β-nitrostyrenes. This protocol nicely complements the ones existing using this strategy, making possible the introduction of an ester function in the 2 position of the dihydrofuran structure, ready for further functionalizations. The more challenging activation of α-keto esters in comparison to the well-known 1,3-dicarbonyls explains usually long reaction times for this methodology. But this is well counterbalanced by very high stereoselectivities obtained in all cases.

All reagents were weighed and handled in air at room temperature. 

1H NMR spectra were measured on a Bruker AC 400 (400 MHz) spectrometer. Data were reported as chemical shifts in ppm referenced to the internal solvent signal. 13C NMR spectra were measured on a Bruker AC 400 (100 MHz) spectrometer. The internal solvent signal was used as a reference. Data were reported as chemical shifts in ppm referenced to CDCl3 (δ = 7.26 ppm) or CHCl3 (δ = 7.24 ppm). Melting points (mp) were determined with a Büchi Melting-Point B-450 apparatus and were not corrected. Thin-layer chromatography (TLC) was performed on silica Merck 60F254. Visualization was achieved under UV light (λ = 254 nm). Optical rotations (OR) were measured with a Perkin-Elmer 241 micropolarimeter. Melting points (mp) were determined with a Büchi Melting-Point B-450 apparatus and were not corrected. High-performance liquid chromatography (HPLC) was performed on a chiral phase. The enantiomeric excess (ee) was determined by HPLC analysis on a chiral column.

trans-4,5-Dihydrofuran-2-carboxylic acid; General Procedure

To a solution of nitroalkene 1 (0.1 mmol, 1.0 equiv) and trans-suppliers unless otherwise stated. (Merck, 230–400 mesh). All reagents were obtained from commercial sources. Products were purified by flash column chromatography on silica gel 60 (Merck, 230–400 mesh). All reagents were obtained from commercial suppliers unless otherwise stated.

**Benzyl (4R,5S)-3-Ethyl-4-(2-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4b)**

Isolated as a yellow oil; yield: 21 mg (54%); [α]D = 0.50 (EtOAc/PE, 1:6); δ (400 MHz, CDCl3) = 7.46–7.30 (m, 6 H, ArH), 7.01 (dd, J = 7.7, 1.8 Hz, 1 H, ArH), 6.91–6.88 (m, 2 H, ArH), 5.82 (d, J = 2.2 Hz, 1 H, CHNO), 5.36 (d, J = 3.6 Hz, 2 H, CH2Ph), 4.94 (d, J = 2.2 Hz, 1 H, ArH), 3.87 (s, 3 H, OCH3), 2.86 (dq, J = 14.8, 7.4 Hz, 1 H, CH2CH3), 2.01 (dq, J = 14.8, 7.4 Hz, 1 H, CH2CH3), 0.93 (t, J = 7.4 Hz, 3 H, CH2CH3).


**Benzyl (4S,5S)-3-Ethyl-5-nitro-4-(o-tolyl)-4,5-dihydrofuran-2-carboxylate (4c)**

Isolated as a yellow oil; yield: 18 mg (48%); [α]D = 0.35 (EtOAc/PE, 1:12); δ (300 MHz, CDCl3) = 7.59–7.54 (m, 6 H, ArH), 7.43–7.35 (m, 3 H, ArH), 7.30–7.17 (m, 3 H, ArH), 6.97 (d, J = 7.3 Hz, 1 H, ArH), 5.72 (d, J = 1.9 Hz, 1 H, CHNO), 5.38 (d, J = 3.5 Hz, 2 H, CH2Ph), 4.73 (d, J = 1.9 Hz, 1 H, CH2), 2.87 (dq, J = 15.0, 7.6 Hz, 1 H, CH2CH3), 2.50 (s, 3 H, CH3), 2.02 (dq, J = 15.0, 7.6 Hz, 1 H, CH2CH3), 0.91 (t, J = 7.6 Hz, 3 H, CH2CH3).


**Benzyl (4S,5S)-3-Ethyl-4-(4-hydroxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4d)**

Isolated as a yellow oil; yield: 18 mg (48%); [α]D = 0.10 (EtOAc/PE, 1:6); δ (300 MHz, CDCl3) = 7.40–7.31 (m, 5 H, ArH), 7.06 (d, J = 8.5 Hz, 2 H, ArH), 6.84 (d, J = 8.5 Hz, 2 H, ArH), 6.57 (d, J = 1.8 Hz, 1 H, CHNO), 5.43–5.25 (m, 3 H, CH2Ph, OH), 4.36 (d, J = 1.8 Hz, 1 H, CH2H), 2.81 (dq, J = 15.0, 7.6 Hz, 1 H, CH2CH3), 2.03 (dq, J = 15.0, 7.6 Hz, 1 H, CH2CH3), 0.90 (t, J = 7.6 Hz, 3 H, CH2CH3).

HRMS (ESI+): m/z [M + H]+ calc for C21H22NO5: 345.1785; found: 345.1785.

**Benzyl (4S,5S)-3-Ethyl-4-(4-hydroxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4a)**

Isolated as a yellow oil; yield: 30 mg (79%); [α]D = 0.47 (EtOAc/PE, 1:4); δ (300 MHz, CDCl3) = 7.49–7.31 (m, 5 H, ArH), 7.06 (d, J = 8.5 Hz, 2 H, ArH), 6.84 (d, J = 8.5 Hz, 2 H, ArH), 6.57 (d, J = 1.8 Hz, 1 H, CHNO), 5.43–5.25 (m, 3 H, CH2Ph, OH), 4.36 (d, J = 1.8 Hz, 1 H, CH2H), 2.81 (dq, J = 15.0, 7.6 Hz, 1 H, CH2CH3), 2.03 (dq, J = 15.0, 7.6 Hz, 1 H, CH2CH3), 0.90 (t, J = 7.6 Hz, 3 H, CH2CH3).

HRMS (ESI+): m/z [M + H]+ calc for C21H22NO5: 345.1785; found: 345.1785.
HRMS [ESI+]: m/z [M + NH₄⁺] calc for C₂₇H₂₃N₂O₄: 439.1507; found: 439.1506.

**Benzyl (4S,5S)-4-[(Benzyloxy)phenyl]-3-ethyl-5-nitro-4,5-dihydrofuran-2-carboxylate (4f)**

Isolated as a yellow oily liquid; yield: 8 mg (20%); Rₛ = 0.42 (EtOAc/PE, 1:5); dr anti/syn >20:1; HPLC (Chiralpak IA, heptane/TEOH, 90:10, flow rate = 1.0 ml/min, λ = 254 nm): tₑ = 22.80 (major), 14.28 min (minor); 97% ee; [α]D₂⁰ +210.0 (c 0.64, CHCl₃).

1H NMR (300 MHz, CDCl₃): δ = 7.47–7.32 (m, 6 H, ArH), 7.21–7.06 (m, 3 H, ArH), 5.85 (d, J = 2.1 Hz, 1 H, CHNO), 5.36 (d, J = 1.8 Hz, 2 H, CH₂Ph), 4.83 (d, J = 2.1 Hz, 1 H, CHAr), 2.84 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 2.02 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 0.93 (t, J = 7.6 Hz, 3 H, CH₃). 

13C NMR (75 MHz, CDCl₃): δ = 160.4 (J = 247.2 Hz), 159.3, 140.5, 135.1, 132.8, 130.8 (J = 8.25 Hz), 128.9 (2 C), 128.7, 128.6 (2 C), 125.3 (J = 3.9 Hz), 123.0 (J = 14.3 Hz), 116.4 (J = 21.5 Hz), 108.8, 67.4, 52.0 (J = 3.75 Hz), 18.3, 12.8.

HRMS [ESI+]: m/z [M + NH₄⁺] calc for C₂₇H₂₃N₂O₄: 439.1507; found: 439.1506.

**Benzyl (4S,5S)-4-(3-Chlorophenyl)-3-ethyl-5-nitro-4,5-dihydrofuran-2-carboxylate (4h)**

Isolated as a yellow oily liquid; yield: 17 mg (43%); Rₛ = 0.52 (EtOAc/PE, 1:5); dr anti/syn >20:1; HPLC (Chiralpak IE, heptane/TEOH, 90:10, flow rate = 1.0 ml/min, λ = 254 nm): tₑ = 8.92 (major), 6.64 min (minor); 90% ee; [α]D₂⁰ +136.8 (c 0.90, CHCl₃).

1H NMR (300 MHz, CDCl₃): δ = 7.49–7.32 (m, 7 H, ArH), 7.20 (s, 1 H, ArH), 7.14–7.08 (m, 1 H, ArH), 5.76 (d, J = 2.0 Hz, 1 H, CHNO), 5.37 (d, J = 1.7 Hz, 2 H, CH₂Ph), 4.40 (d, J = 2.0 Hz, 1 H, CHAr), 2.85 (dq, J = 15.0, 7.5 Hz, 1 H, CH₂CH₃), 2.03 (dt, J = 15.0, 7.5 Hz, 1 H, CH₂CH₃), 0.92 (t, J = 7.5 Hz, 3 H, CH₃).

13C NMR (75 MHz, CDCl₃): δ = 159.3, 140.6, 137.8, 135.7, 131.5, 133.0, 131.0, 129.4, 128.9 (2 C), 128.8, 128.6 (2 C), 127.8, 125.9, 108.7, 67.5, 59.1, 18.3, 12.8.

HRMS [ESI+]: m/z [M + NH₄⁺] calc for C₂₇H₂₃ClN₂O₄: 439.1502; found: 439.1507.

**Benzyl (4S,5S)-3-Ethyl-4-(naphthalen-2-yl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4l)**

Isolated as a yellow oily liquid; yield: 25 mg (61%); Rₛ = 0.43 (EtOAc/PE, 1:12); dr anti/syn >20:1; HPLC (Chiralpak AD-H, heptane/TEOH, 50:50, flow rate = 1.0 ml/min, λ = 254 nm): tₑ = 7.80 (major), 97.3 min (minor); 95% ee; [α]D₂⁰ +240.08 (c 1.05, CHCl₃).

1H NMR (400 MHz, CDCl₃): δ = 7.89 (d, J = 8.5 Hz, 1 H, ArH), 7.87–7.82 (m, 2 H, ArH), 7.69 (s, 1 H, ArH), 7.57–7.50 (m, 2 H, ArH), 7.47 (d, J = 6.8 Hz, 2 H, ArH), 7.44–7.35 (m, 3 H, ArH), 5.97 (d, J = 1.0 Hz, 1 H, ArH), 3.19 (d, J = 1.0 Hz, 1 H, CHAr), 2.83 (dq, J = 15.0, 7.5 Hz, 1 H, CH₂CH₃), 2.07 (dq, J = 15.0, 7.5 Hz, 1 H, CH₂CH₃), 0.93 (t, J = 7.6 Hz, 3 H, CH₃).

13C NMR (100 MHz, CDCl₃): δ = 159.5, 140.3, 133.2, 133.6, 133.4, 133.1, 129.3, 128.9 (2 C), 128.7, 128.6 (2 C), 128.1, 127.9, 127.2, 127.1, 126.9, 124.7, 109.2, 67.5, 59.9, 18.4, 12.9.

HRMS [ESI+]: m/z [M + NH₄⁺] calc for C₂₇H₂₃ClN₂O₄: 421.1758; found: 421.1758.

**Benzyl (4S,5S)-3-Ethyl-5-nitro-4-(4-oxo-4H-chromen-3-yl)-4,5-dihydrofuran-2-carboxylate (4o)**

Isolated as a yellow oily liquid; yield: 8 mg (20%); Rₛ = 0.10 (EtOAc/PE, 1:5); dr anti/syn >20:1; HPLC (Chiralpak ID, heptane/TEOH, 50:50, flow rate = 1.0 ml/min, λ = 254 nm): tₑ = 8.99 (major), 8.89 min (minor); 97% ee; [α]D₂⁰ +61.5 (c 0.30, CHCl₃).

1H NMR (400 MHz, CDCl₃): δ = 7.85 (d, J = 8.0 Hz, 1 H, ArH), 7.77–7.71 (m, 2 H, ArH), 7.30–7.27 (m, 7 H, ArH), 5.87 (d, J = 2.4 Hz, 1 H, CHNO), 5.35 (d, J = 4.7 Hz, 2 H, CH₂Ph), 4.76 (d, J = 2.4 Hz, 1 H, CHAr), 2.92 (dq, J = 14.8, 7.5 Hz, 1 H, CH₂CH₃), 2.05 (dq, J = 14.8, 7.5 Hz, 1 H, CH₂CH₃), 1.01 (t, J = 7.5 Hz, 3 H, CH₃).

13C NMR (100 MHz, CDCl₃): δ = 176.1, 159.1, 156.5, 154.2, 141.2, 135.1, 134.6, 131.1, 128.9 (2 C), 128.7, 128.6 (2 C), 126.2, 126.1, 123.7, 119.6, 118.4, 107.9, 67.5, 50.0, 18.4, 13.0.

HRMS [ESI+]: m/z [M + NH₄⁺] calc for C₂₉H₂₄N₂O₅: 439.1500; found: 439.1500.

**Tert-Butyl (4S,5S)-3-Ethyl-4-(4-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4k)**

Isolated as a yellow oily liquid; yield: 25 mg (36%); Rₛ = 0.49 (EtOAc/PE, 1:5); dr anti/syn >20:1; HPLC (Chiralpak IF, heptane/TEOH, 70:30, flow rate = 1.0 ml/min, λ = 254 nm): tₑ = 4.55 (major), 5.20 min (minor); 94% ee; [α]D₂⁰ +259.3 (c 1.05, CHCl₃).
**Benzyl (4S,5S)-3-Isopropyl-4-(4-methoxyphenyl)-5-nitro-4,5-di-hydrofuran-2-carboxylate (4)**

Isolated as a light yellow oil; yield: 30 mg (38%); \( R_f = 0.47 \) (EtOAc/PE, 1:5); \( \text{dr anti/syn} > 20:1 \); HPLC (Chiralpak IB, heptane/EtOH, 80:20, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_f = 6.74 \) (major), 5.11 min (minor); 95% ee; \( [\alpha]_D^{20} +151.4 \) (c 0.80, CHCl\(_3\)).

**Ethyl (4S,5S)-3-Benzyl-4-(4-methoxyphenyl)-5-nitro-4,5-di-hydrofuran-2-carboxylate (4m)**

Isolated as a yellow solid (40 mg; 52%); mp 104–105 °C; \( R_f = 0.51 \) (EtOAc/PE, 1:5); \( \text{dr anti/syn} > 20:1 \); HPLC (Chiralpak IC, heptane/EtOH, 80:20, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_f = 8.66 \) (major), 9.35 min (minor); 86% ee; \( [\alpha]_D^{20} +256.7 \) (c 1.53, CHCl\(_3\)).

**Isobutyrl (4S,5S)-3-Isopropyl-4-(4-methoxyphenyl)-5-nitro-4,5-di-hydrofuran-2-carboxylate (4n)**

Isolated as a light yellow oil; yield: 19 mg (26%); \( R_f = 0.43 \) (EtOAc/PE, 1:4); \( \text{dr anti/syn} > 20:1 \); HPLC (Chiralpak AD-H, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_f = 6.67 \) (major), 5.11 min (minor); 91% ee; \( [\alpha]_D^{20} -198.1 \) (c 0.40, CHCl\(_3\)).

**Benzyl (4S,5S)-5-Amino-3-ethyl-4-(4-methoxyphenyl)-4,5-dihydrofuran-2-carboxylate (6)**

A solution of 4,5-dihydrofuran-2-carboxylate 4a (0.13 mmol, 1.0 equiv) in dry THF (1.0 mL) was added activated zinc powder (18.2 mmol, 140.0 equiv), followed by the addition dropwise of AONH\(_2\) (6.0 mL). The mixture was stirred for 2 h at rt. The mixture was concentrated and extracted with sat. NaHCO\(_3\) solution (2 x 6.0 mL). The combined aqueous phases were extracted with CHCl\(_3\) (2 x 10.0 mL) and the organic layers were washed with water (10.0 mL), dried (NaSO\(_4\)), filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/PE, 40:60). Isolated as a light yellow oil: yield: 17 mg (38%); \( R_f = 0.37 \) (EtOAc/PE, 4:6); \( \text{dr anti/syn} > 20:1 \); HPLC (Chiralpak IA, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_f = 8.73 \) (major), 11.91 min (minor); 57% ee (from 93% ee in the starting material); \( [\alpha]_D^{20} +65.1 \) (c 0.28, CHCl\(_3\)).
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Supporting Information

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References