Diastereoselective construction of azetidin-2-ones by electrochemical intramolecular C-C bond forming reaction

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Abstract- A convenient method for synthesis of optically active azetidin-2-ones using electrochemical oxidation has been exploited. The method consists of a diastereoselective intramolecular C-C bond forming reaction between active methylene and methyne groups through an electrochemical system in which positive iodine species acted as mediators under mild conditions.

Keywords: azetidinone; electrochemical oxidation; diastereoselective; carbon-carbon bond forming reaction, cyclization

1. Introduction

Since the discovery of thienamycin (1),1 a variety of synthetic methods of 1 and its precursors 2 have been exploited (Scheme 1).2 However, new efficient synthetic methods are still of great interest because of economic reasons and the continuing need for novel β-lactamase inhibitors. In 1985, Simig and co-workers reported that the construction of N-protected azetidin-2-ones 4a-c from N-arylated or N-benzylated N-(3-oxobutyryl)aminomalonate diethyl esters 3a-c, which are equilibrated with pyrrolidine-2-ones 5a-c, was achieved by I₂ in the presence of NaOEt (Eq. 1).3

![Scheme 1](image)

Although this reaction is very convenient for the construction of azetidin-2-one skeleton,
there has been no report for its chiral version. We report herein a convenient 
electrochemical diastereoselective construction of azetidin-2-ones 4d-f possessing 
acetyl group at the 3-position and two alkoxylcarbonyl groups at the 4-position from 
easily available N-(3-oxobutyryl)aminomalonate esters 3d-f possessing a chiral 
 auxiliary on a nitrogen atom (Scheme 2). Scheme 2 also shows our strategy for the 
transformation of 4d-f to enantiomerically pure 4-methoxy-3-(1’-silyloxyethyl)azetidin-2-one (2a) which is an important key synthetic 
intermediate for 1.


2. Results and discussion

2.1 Preparation of chiral pyrrolidin-2-ones 5d-f

Pyrrolidin-2-ones 5d-f were prepared in good to high yields using similar method for 
preparation of 5a-c (Eq. 2). The results are shown in Table 1.

Table 1. Preparation of 2-pyrrolidinones 5d-g.

<table>
<thead>
<tr>
<th>entry</th>
<th>R*</th>
<th>R^4</th>
<th>condition</th>
<th>yield (%)</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>Me</td>
<td>Et</td>
<td>rt</td>
<td>80 °C</td>
<td>6d 79</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>t-Bu</td>
<td>80 °C</td>
<td>80 °C</td>
<td>6e 83</td>
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</table>
2.2 Diastereoselective construction of azetidin-2-ones 4d-f

Chemical intramolecular C-C bond forming reaction of 5d-f (Method A) and the corresponding electrochemical reaction (Method B) were examined under various conditions (Eq. 3). The results are summarized in Table 2.

![Diastereoselective construction of azetidin-2-ones 4d-f](image)

**Table 2.** Diastereoselective cyclization of pyrrolidin-2-ones 5d-f.

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>method</th>
<th>conditions</th>
<th>product 4</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>de (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>-</td>
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<tr>
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<td>EtOH</td>
<td>4d</td>
<td>23</td>
<td>58</td>
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<td>7</td>
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<td>11</td>
<td>5f</td>
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<td>MeCN</td>
<td>4f</td>
<td>67</td>
<td>70</td>
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<tr>
<td>12</td>
<td>5f</td>
<td>B</td>
<td>MeCN</td>
<td>4f</td>
<td>89</td>
<td>74</td>
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</tbody>
</table>

<sup>a</sup>Method A: A solution of 5 (0.5 mmol), I<sub>2</sub> (0.5 mmol), and NaOEt (1.5 mmol) in solvent (5 mL) was stirred for 1 h. Method B: 4 F/mol of electricity was passed through a solution of 5 (0.5 mmol) and NaI (0.5 mmol) in solvent (5 mL). <sup>b</sup>Isolated yield (%). <sup>c</sup>Determined by <sup>1</sup>H-NMR. <sup>d</sup>Ambient
temperature (The temperature of the reaction mixture gradually raised from rt to ca 50 °C as electricity was passed.). ° Temperature of bath.

When chemical cyclization of diethyl ester 5d was attempted in ethanol and acetonitrile at room temperature, azetidin-2-one 4d was not obtained at all (entries 1 and 3), however increase of temperature to 85 °C lead to formation of 4d in low yields with moderate diastereoselectivities (entries 5 and 7). On the other hand, electrochemical cyclization of 5d at ambient temperature proceeded to afford 4d in moderate yields (entries 2, 4, 9, and 11). Heat generated during electrochemical oxidation might affect the cyclization. Although the yield of 4d by electrochemical cyclization of 5d in ethanol was not improved at 85 °C compared with at ambient temperature (entries 2 and 6), in acetonitrile somewhat better yield was obtained than that at ambient temperature (entries 4 and 8). The best result was obtained in acetonitrile at 85 °C (entry 8). These optimized conditions were applicable to cyclization of di-\( \tau \)-butyl esters 5e and 5f to afford azetidin-2-ones 4e and 4f in high yields with good to high diastereoselectivities (entries 10 and 12). Recrystallization of 4e from a mixture of diethyl ether and \( n \)-hexane (1/2 V/V) afforded 3\( S \)-4e as a single diastereoisomer.

### 2.3. Reaction mechanism

Plausible reaction mechanism for electrochemical cyclization of 3e is shown in Scheme 3. Briefly, anodically generated positive iodine species “I” react with 3e to afford iodinated intermediate A,\(^5\) which is transformed to enolate B\(^6\) by cathodically generated base “EGB”.\(^7\) Finally cyclization of B affords thermodynamically stable 3\( S \)-4e diastereoselectively. The reason why electrochemical reaction in Table 2 shows higher yields and diastereoselectivity than the corresponding chemical reaction might be explainable by the characteristics of “EGB”. Since “EGB” on cathode simultaneously generated along with “I” on anode in the electrochemical reaction, the electrochemical reaction holds almost neutral. On the other hand, the chemical reaction is always too basic. The strong basicity in the chemical reaction might lower the yield and diastereoselectivity of 4e.
In fact, equilibration of 3S-4e and 3R-4e in the reaction conditions was confirmed by $^1$H-NMR (Scheme 4). Although diastereomerically pure 3S-4e was not epimerized in CDCl$_3$, epimerization of 3S-4e in the presence of potassium carbonate was observed to reach to the equilibrium. Although we can not deny some effect of kinetic control on the diastereoselectivities in these cyclization, thermodynamic control could rationalize the diastereoselectivities.

2.4. Diastereoselective reduction

Diastereoselective reduction of acetyl group in 4d,e was carried out under several reaction conditions (Eq. 4). The results are summarized in Table 3.
Although NaBH₄ majorly reduced ethoxycarbonyl group instead of acetyl group in diethyl ester 4d to afford 8 (entry 1), NaBH₄ or DIBAH in THF reduced acetyl group in di-tert-butyl ester 4e to afford 7e in good to high diastereoselectivity. Epimerization of 4e at the 3-position was not observed under the reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>reductant</th>
<th>condition</th>
<th>product 7</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>de (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
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<td>NaBH₄</td>
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<td>4e</td>
<td>NaBH₄</td>
<td>MeOH</td>
<td>7e</td>
<td>89</td>
<td>12</td>
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<tr>
<td>3</td>
<td>4e</td>
<td>NaBH₄</td>
<td>THF</td>
<td>7e</td>
<td>85</td>
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<td>84</td>
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<tr>
<td>5</td>
<td>4e</td>
<td>DIBAH</td>
<td>THF</td>
<td>7e</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>4e</td>
<td>DIBAH</td>
<td>THF</td>
<td>7e</td>
<td>46</td>
<td>78</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield (%). <sup>b</sup> Determined by ¹H-NMR.

2.5. Determination of absolute stereoconfiguration for 7e

Recrystallization of 7e afforded 3S,1'R-7e as a single diastereoisomer, whose absolute stereoconfiguration was determined to be 1'R by X-ray analysis (Figure 1).<sup>8</sup>
As a result, it was deduced that the major isomer of 4e was 3S-4e.

2.6 Stereochemical course.

The diastereoselectivity might be explained by thermodynamical stability of 3S-4e compared with 3R-4e. Namely, when 1’R-phenylethyl group occupied the lower side of azetidine ring shown as (b) and (d) in Figure 2, there might be steric repulsion between t-butyl group and phenyl group. Additionally, steric repulsion between acetyl group and 1’R-phenylethyl group in 3S-4e might occur ((b) in Figure 2). On the other hand, when 1’R-phenylethyl group occupied the upper side of azetidine ring ((a) and (c) in Figure 2), there might be steric repulsion between acetyl group and 1’R-phenylethyl group in 3R-4e ((c) in Figure 2). Accordingly, 3S-4e shown as (a) in Figure 2 is the most stable conformation. Also, bulkier di-t-butyl ester 4e could be obtained with better diastereoselectivity than that of diethyl ester 4d.
Plausible stereochemical course for the NaBH₄ reduction of 4e are shown in Scheme 5. Sodium ion chelates with the two carbonyl groups, due to this and also the steric repulsion on the re-face between the hydride ion and the tert-butyyl group, the hydride attack therefore takes place on the si-face to afford 1′R-7e diastereoselectively. Higher diastereoselectivity in THF than MeOH seems to support chelation (entries 2 and 3 in Table 3).

Scheme 5. Plausible stereochemical course for NaBH₄ reduction of 3S-4e.

2.7. Preparation of enantiomerically pure azetizin-2-one 2a from 1′R-7e

Enantiomerically pure 4-methoxy-3-(1′-silyloxyethyl)azetidin-2-one (2a) was prepared from 1′R-7e by procedure shown in Scheme 6. Namely, acetylation of 1′R-7e
afforded 9, which was then subjected to acid catalyzed hydrolysis to give dicarboxylic acid 10 in quantitative yield. Decarboxylation of 10 afforded monocarboxylic acid 11, which was then transformed into 4R-methoxylated azetidinone 12 in 73% yield by the non-Kolbe electrolysis. Silylation of 12 and successive hydrogenolysis of chiral auxiliary of 13 afforded desired azetidinone 2a as an enantiomerically pure form (Scheme 6).

![Scheme 6. Preparation of azetidinone 2a from 1'R-7e.](image)

3. Conclusion
A convenient method for the synthesis of optically active azetidin-2-ones using electrochemical oxidation has been exploited. The method consists of diastereoselective intramolecular C-C bond forming reaction between active methylene and methyne groups by electrochemical mediator system in which positive iodine species act as mediators under mild conditions.

4. Experimental section
4.1. General.
Electrochemical reactions were carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. 1H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. 13C NMR spectra were measured on a Varian Gemini 400 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Elemental analyses were carried in Center for Instrumental Analysis, Nagasaki University. Mass spectra were obtained on a JEOL JMS-DX 303 instrument. Specific rotations were measured with Jasco
DIP-1000. All melting points were measured on MICRO MELTING POINT APPARATUS (Yanaco) and are uncorrected.

All solvents were used as supplied without further purification. Diethyl bromomalonate, 1R-phenylethylamine, and 1R-(4-methoxyphenyl)ethylamine are commercially available. Di-tert-butyl bromomalonate was prepared from di-tert-butyl malonate by known procedure.11

4.2. Preparation of aminomalontate 6d-f: general procedure;

To a solution of 1R-phenylethylamine (3.05 g, 25 mmol) and Et3N (2.53 g, 25 mmol) in acetonitrile (25 mL) was added diethyl bromomalonate (8.13 g, 34 mmol). After stirring for 6 h, to the resulting mixture was poured water (30 mL). Organic portion of aqueous layer was extracted with dichloromethane (3 x 25 mL) and washed with sat. aq. NaCl (25 mL). After drying the organic layer over MgSO4, solvent was removed in vacuo, and residue purified by silica gel column chromatography (n-hexane : AcOEt = 10 : 1) to afford diethyl (1R-phenylethyl)aminomalonate (6d)12 in 79 % yield.

Di-tert-butyl (1R-phenylethyl)aminomalonate (6e)

yellow oil; [α]D
28.3
+58.8 (c=1.0, CHCl3); 1H NMR (300MHz CDCl3) δ 1.38 (d, J=6.6Hz, 3H), 1.42 (s, 9H), 1.47 (s, 9H), 2.37 (br s, NH), 3.69 (s, 1H), 3.79 (q, J=6.6Hz, 1H), 7.20-7.39 (m, 5H); IR (neat) 3350, 2978, 2932, 2342, 1750, 1734, 1475, 1493, 1475, 1455, 1395, 1140, 1007, 847, 702 cm⁻¹; HRMS (EI) Calcd for C19H28NO4 (M+) 335.2097, Found: 335.2095.

Di-tert-butyl [(1R-(4-methoxyphenyl)ethyl]aminomalonate (6f)

yellow oil; 1H NMR (300MHz CDCl3) δ 1.36 (d, J=6.6Hz, 3H) 1.42 (s, 9H), 1.47 (s, 9H), 2.38 (br s, NH), 3.75 (q, J=6.6Hz, 1H), 3.80 (s, 3H), 6.85 (d, J=8.7Hz, 2H), 7.25 (d, J=8.7Hz, 2H); IR(neat) cm⁻¹; HRMS (EI) Calcd for C26H31NO5 (M+) 365.2202, Found: 365.2214.

4.3. Preparation of chiral pyrrolidin-2-ones 5d-f: General Procedure

To a solution of 6d (5.59 g, 20 mmol) and Et3N (2.02 g, 20 mmol) in toluene (30 mL) was slowly added dropwise diketene (1.7 mL, 22 mmol) at 0 °C. After the solution was stirred at 80 °C for 1h, the solvent was removed in vacuo at room temperature. The
residue was purified by silica gel column chromatography (n-hexane : AcOEt = 1 : 1) to afford diethyl 3-hydroxy-3-methyl-1-(1'R-phenylethyl) pyrrolidin-5-one-2,2-dicarboxylate (5d) in 93 % yield.

Diethyl 3-hydroxy-3-methyl-1-(1'R-phenylethyl) pyrrolidin-5-one-2,2-dicarboxylate (5d) (a mixture of two diastereomers)

white solid; mp 56-61 °C; $^1$H NMR (400MHz CDCl$_3$) $\delta$ 0.93 and 0.99 (2t, $J=7.3$Hz, 3H), 1.27 and 1.31 (2t, $J=7.3$Hz, 3H), 1.49 and 1.50 (2s, 3H), 1.81 and 1.84 (2d, $J=7.2$Hz, 3H), 2.55-2.80 (m, 2H), 3.68-4.40 (m, 5H), 4.75 and 4.93 (2q, $J=7.3$Hz, 1H), 7.10-7.40 (m, 5H); IR (neat): 3400, 2984, 2940, 1736, 1707, 1686, 1410, 1269, 1231, 1079, 1098, 1053, 704 cm$^{-1}$; HRMS (EI) Calcd for C$_{19}$H$_{25}$NO$_6$ (M$^+$) 363.1682, Found: 363.1684.

Di-tert-butyl 3-hydroxy-3-methyl-1-(1'R-phenylethyl)pyrrolidin-5-one-2,2-dicarboxylate (5e) (a mixture of two diastereomers)

white solid; mp 153-160 °C; $^1$H NMR (400MHz CDCl$_3$) $\delta$ 1.11 and 1.24 (2s, 9H), 1.41 and 1.51 (2s, 9H), 1.48 and 1.63 (2s, 3H), 1.81 and 1.84 (2d, $J=7.3$Hz, 3H), 2.52-2.74 (m, 2H), 3.54 and 4.03 (2s, 1H, OH), 4.76 and 5.02 (2q, $J=7.3$Hz, 1H), 7.15-7.40 (m, 5H); $^{13}$C NMR (100MHz CDCl$_3$) $\delta$ 19.2, 20.1, 23.5, 24.0, 27.3, 27.5, 27.8, 27.9, 46.1, 46.2, 54.5, 55.7, 76.5, 80.0, 84.0, 84.1, 84.5, 84.7, 126.2, 126.3, 126.4, 126.6, 128.1, 142.2, 142.4, 166.3, 166.6, 166.7, 167.1, 174.0, 174.1; IR (neat): 3400, 2980, 2938, 1730, 1692, 1395, 1302, 1250, 1157, 1024, 754, 696 cm$^{-1}$; Anal. Calcd for C$_{23}$H$_{33}$NO$_6$: C, 65.85; H, 7.93; N 3.34. Found: C, 66.25; H, 8.14; N 3.33.

Di-tert-butyl 3-hydroxy-1-[1'R-(4-methoxyphenyl)ethyl]-3-methylpyrrolidin-5-one-2,2-dicarboxylate (5f) (a mixture of two diastereomers)

white solid; mp 186-187 °C; $^1$H NMR (400MHz CDCl$_3$) $\delta$ 1.19 and 1.30 (2s, 9H), 1.47 and 1.53 (2s, 9H), 1.51 and 1.60 (2d, $J=3.0$Hz, 3H), 1.80 and 1.82 (2d, $J=6.8$Hz, 3H), 2.55-2.72 (m, 2H), 3.52 and 3.90 (2s, 1H, OH), 3.74 and 3.75 (2s, 3H), 4.74 and 4.94 (2q, $J=6.8$Hz, 1H), 6.75-6.85 (m, 2H), 7.18 and 7.21 (2d, $J=8.8$Hz, 2H); $^{13}$C NMR (100MHz CDCl$_3$) $\delta$ 13.74, 20.0, 23.6, 23.9, 27.4, 27.6, 27.9, 28.0, 46.2, 46.3, 45.2, 45.5, 55.2, 56.5, 76.6, 80.0, 80.2, 84.0, 84.1, 84.5, 84.6, 113.4, 113.5, 127.5, 128.0, 134.4, 134.6, 158.1, 158.3, 166.2, 166.6, 166.9, 167.0, 173.9, 174.0; IR (neat): 3400, 2980, 2038, 1750, 1732, 1720, 1700, 1868, 1615, 1559, 1514, 1474, 1395, 1370, 1339,
1302, 1248, 1156, 1030, 910, 831, 735 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{24}\)H\(_{35}\)NO\(_7\) (M\(^+\)) 449.2414, Found: 449.2400.

4.4. Preparation of chiral azetidin-2-ones 4d-f:

4.4.1. Typical Procedure for chemical method A (entry 5 in Table 2):

To a solution of 5d (182 mg, 0.5 mmol) in ethanol (5 mL) was added I\(_2\) (127 mg, 0.5 mmol) and Na (35 mg, 1.5 mmol). After stirring for 1 h at 85 \(^\circ\)C, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with 5% Na\(_2\)S\(_2\)O\(_3\) (3 \(\times\) 10 mL) and sat. aqueous NaCl (10 mL). The organic layer was dried over MgSO\(_4\) and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (\(n\)-hexane:AcOEt =1 : 1) to afford 3S-4d in 30% yield with 48% de.

4.4.2. Typical Procedure for electrochemical method B (entry 10 in Table 2):

In an undivided cell equipped with platinum plate electrodes (1 x 2 cm\(^2\)) was placed a solution of 5e (210 mg, 0.5 mmol) and NaI (75 mg, 0.5 mmol) in acetonitrile (5 mL). A constant current (100 mA) was passed through the cell externally warmed in oil-bath (85 \(^\circ\)C). After 4 F/mol of electricity was passed, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with 5% Na\(_2\)S\(_2\)O\(_3\) (3 \(\times\) 10 mL) and sat. aqueous NaCl (10 mL). The organic layer was dried over MgSO\(_4\) and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (\(n\)-hexane:AcOEt =1 : 1) to afford 3S-4e in 94% yield with 80% de, which was recrystalized from a mixture of diethyl ether and \(n\)-hexane (1/2 V/V) to give enantiomerically pure 3S-4e.

**Diethyl 3S-acetyl-1-(1'R-phenylethyl)azetidin-2-one-4,4-dicarboxylate (4d) (3S:3R = 74:26)**

yellow oil; \(^1\)H NMR (300MHz CDCl\(_3\)) \(\delta\) 0.94 (t, \(J=7.2\text{Hz}, 2.22\text{H}\)), 1.06 (t, \(J=7.2\text{Hz}, 0.78\text{H}\)), 1.32 (t, \(J=7.2\text{Hz}, 3\text{H}\)), 1.74 (d, \(J=7.2\text{Hz}, 0.78\text{H}\)), 1.87 (d, \(J=7.2\text{ Hz}, 2.22\text{H}\)), 2.31 (s, 0.78H), 2.35 (s, 2.22H), 3.47-3.62 (m, 0.74H), 3.78-3.90 (m, 0.74H), 3.90-4.02 (m, 0.26H), 4.03-4.15 (m, 0.26H), 4.15-4.45 (m, 2H), 4.57-4.70 (m, 0.74H), 4.75-4.85 (m, 0.26H), 4.68 (s, 0.26H), 4.84 (s, 0.74H), 7.20-7.45 (m, 5H); IR (neat): 2984, 2938, 1779, 1455, 1393, 1300, 1280, 1240,1180, 1096, 1057, 1028, 903, 860, 762, 702 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{19}\)H\(_{23}\)NO\(_6\) (M\(^+\)) 361.1525, Found: 361.1525.
Di-tert-butyl 3S-acetyl-1-(1′R-phenylethyl)azetidin-2-one-4,4-dicarboxylate (4e)
white solid; mp 140-142 °C; [α]D^26.2 = -6.1 (c=1.0, CHCl3); ^1H NMR (300MHz CDCl3) δ 1.07 (s, 9H), 1.55 (s, 9H), 1.85 (d, J=7.2Hz, 3H), 2.35 (s, 3H), 4.66 (q, J=7.2 Hz, 1H), 4.86 (s, 1H), 7.18-7.40 (m, 5H); ^13C NMR (100MHz, CDCl3) δ 22.8, 27.0, 27.8, 30.4, 57.0, 66.5, 67.2, 83.8, 83.9, 125.9, 127.2, 128.7, 143.0, 162.7, 164.9, 165.3, 197.8; IR (neat): 2980, 2930, 1765, 1718, 1495, 1394, 1371, 1001, 970, 851, 764, 702 cm^{-1}; Anal. Calcd for C_{23}H_{31}NO_{6}: C, 66.17; H, 7.48; N, 3.35. Found: C, 65.79; H, 7.62; N, 3.31.

Di-tert-butyl 3S-acetyl-1-[1′R-(4-methoxyphenyl)ethyl]azetidin-2-one-4,4-dicarboxylate (4f)
white solid; mp 107 °C; [α]D^23.8 +3.0 (c=1.0, CHCl3); ^1H NMR (300MHz CDCl3) δ 1.13 (s, 9H), 1.54 (s, 9H), 1.82 (d, J=7.2Hz, 3H), 2.34 (s, 3H), 3.78 (s, 3H) 4.62 (q, J=7.2 Hz, 1H), 4.82 (s, 1H), 6.84 (d, J=8.7Hz, 2H), 7.22 (d, J=8.7Hz, 2H); IR (neat): 2980, 2936, 1771, 1734, 1615, 1559, 1541, 1514, 1474, 1395, 1370, 1302, 1248, 1159, 1032, 831 cm^{-1}; HRMS (EI) Calcd for C_{24}H_{33}NO_{7} (M^+): 447.2257, Found: 447.2268.

4.5. Diastereoselective reduction of 3S-4e:
To a solution of 3S-4e (100 mg, 0.24 mmol) in tetrahydrofuran (3 mL) was added NaBH₄ (18 mg, 0.48 mmol). After stirring for 4 h at -20 °C, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with water (20 mL) and sat. aqueous NaCl (20 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (n-hexane:AcOEt =1 : 1) to afford 1′R-7e in 83% yield with 84% de, which was recrystalized from diethyl ether to give enantiomerically pure 1′R-7e.

3S-(1′R-Hydroxyethyl)-1-(1′R-phenylethyl)azetidin-2-one-4,4-dicarboxylic acid di-tert-butyl ester (7e)
white solid; mp 151-153 °C; [α]D^26.2 +19.7 (c=1.0, CHCl3); ^1H NMR (300MHz CDCl3) δ 1.10 (s, 9H), 1.43 (d, J=3.0Hz, 3H), 1.58 (s, 9H), 1.85 (d, J=5.4Hz, 3H), 2.57 (d, J=2.4Hz, 1H), 3.78 (d, J=6.9Hz, 1H), 4.00-4.07 (m, 1H), 4.58 (q, J=5.4Hz, 1H), 7.18-7.30 (m, 5H); IR (neat): 3500, 2980, 2936, 1759, 1736, 1495, 1456, 1395, 1370, 1343, 1250, 1156, 835, 758, 700 cm^{-1}; HRMS (EI) Calcd for C_{23}H_{33}NO_{6}: C, 65.85; H,
7.93; N, 3.34. Found: C, 66.20; H, 8.07; N, 3.35.

4.6. Acetylation of 1’R-7e:

To a solution of 1’R-7e (420 mg, 1.0 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in pyridine (5 mL) was added dropwise acetyl chloride (236 mg, 3 mmol). After stirring for 2 h at rt, to the reaction mixture was added AcOEt (50 mL). The resulting solution was washed with 3% HCl (3 x 25 mL) and sat. aqueous NaCl (25 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (n-hexane:AcOEt =3 : 1) to afford 9 in 75% yield.

Di-tert-butyl 3S-(1’R-acetoxyethyl)-1-(1’R-phenylethyl)azetidin-2-one-4,4-dicarboxylate (9)

white solid; mp 78-81 ºC; [α]D⁰ +25.4 (c=0.9, CHCl₃); ¹H NMR(300MHz CDCl₃) δ 1.08 (s, 9H), 1.46 (d, J=6.6Hz, 3H), 1.53 (s, 9H), 1.86 (d, J=7.2Hz, 3H), 2.03 (s, 3H), 4.01 (d, J=6.6Hz, 1H), 4.57 (q, J=7.2Hz, 1H), 5.23 (q, J=6.6Hz, 1H), 7.15-7.35 (m, 5H); IR (neat): 2980, 2934, 2380, 1769, 1740, 1495, 1456, 1395, 1341, 1244, 1159, 1144, 1115, 1065, 1048, 905, 849, 834, 760, 733, 700 cm⁻¹; Anal. Calcd for C₂₅H₃₅NO₇: C, 65.06; H, 7.64; N, 3.03. Found: C, 64.95; H, 7.40; N, 2.90.

4.7. Preparation of dicarboxylic acid (10):

To a solution of 9 (462 mg, 1.0 mmol) in dichloromethane (4 mL) was slowly added trifluoroacetic acid (3.7 mL, 50 mmol). After stirring for 2 h at rt, concentration of the reaction mixture under reduced pressure afforded 10 in quantitative yield.

3S-(1’R-Acetoxyethyl)-1-(1’R-phenylethyl)azetidin-2-one-4,4-dicarboxylic acid (10)

white solid; mp 132-136 ºC; [α]D²⁸ +25.3 (c=1.0, CHCl₃); ¹H NMR (300MHz CDCl₃) δ 1.46 (d, J=6.0Hz, 3H), 1.83 (d, J=7.2Hz, 3H), 2.02 (s, 3H), 3.90 (d, J=10.8Hz, 1H), 4.63 (q, J=7.2Hz, 1H), 5.45 (dq, J=6.0Hz, J=10.8Hz, 1H), 7.20-7.40 (m, 5H), 8.55 (m, 2H); IR (neat): 3500, 2984, 2359, 1750, 1541, 1497, 1456, 1375, 1260, 1180, 1160, 1063, 1050, 1028, 963, 912, 760, 700 cm⁻¹; HRMS (EI) Calcd for C₁₇H₁₉NO₇ (M⁺): 349.1162, Found: 349.1135.

4.8. Preparation of monocarboxylic acid (11):

To a solution of 10 (349 mg, 1.0 mmol) in 2,4,6-collidine (2 mL) was heated at 160
°C with oil-bath. After heating for 1 h, to the reaction mixture was added AcOEt (10 mL). The resulting carboxylate ion was collected with sat. NaHCO₃ (3 x 10mL). Combined aqueous layer was acidified with 5% HCl. The carboxylic acid was extracted with AcOEt (3 x 20 mL). The resulting organic layer washed with sat. aqueous NaCl (25 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to afford **11** in quantitative yield.

3S-(1'R-Acetoxyethyl)-1-(1'R-phenylethyl)azetidin-2-one- 4R-carboxylic acid (11)

(4R:4S=72:28)

white solid; mp 86-90 °C; ¹H NMR (300MHz CDCl₃) δ 1.30 (d, J=6.3Hz, 0.84H), 1.42 (d, J=6.3Hz, 2.16H), 1.60 (d, J=6.9Hz, 0.84H), 1.80 (d, J=6.9Hz, 2.16H), 1.89 (s, 0.84H), 1.95 (s, 2.16H), 3.26 (dd, J=1.8Hz, J=10.5Hz, 0.28H), 3.55 (dd, J=5.4Hz, J=10.5Hz, 0.72H), 3.94 (d, J=1.8Hz, 0.28H), 4.07 (d, J=5.4H, 0.72H), 4.53 (q, J=7.2H, 0.72H), 5.57 (q, J=7.2Hz, 0.28H), 5.18-5.34 (m, 1H), 7.26-7.40 (m, 5H), 7.60-7.90 (m, 1H); IR(neat): 3500, 2982, 1748, 1 638, 1541, 1497, 1456, 1379, 1342, 1242, 1200, 1142, 1050, 953, 924, 853, 799, 766, 722 cm⁻¹ ; HRMS (EI) Calcd for C₁₆H₁₉NO₅ (M⁺): 305.1263, Found: 305.1277.

4.9. Decarboxylative methoxylation of **11**: 

In an undivided cell equipped with platinum plate electrodes (1 x 2 cm²) was placed a solution of **11** (101 mg, 0.33 mmol) and NaOMe (54 mg, 1 mmol) in a mixture of acetonitrile (4 mL) and methanol (1 mL). A constant current (50 mA) was passed through the cell externally cooled with water-bath. After 2 F/mol of electricity was passed, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with sat. aqueous NaCl (10 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (n-hexane:AcOEt =2 : 1) to afford **12** as a single diastereomer in 73% yield.

4R-Methoxy-3R-(1'R-hydroxylethyl)-1-(1'R-phenylethyl)azetidin-2-one (12)

colorless oil; ¹H NMR (400MHz CDCl₃) δ 1.27 (d, J=6.4Hz, 3H), 1.63 (d, J=7.3Hz, 3H), 1.80-2.50 (m, 1H), 2.99 (dd, J=3.6Hz, J=5.4Hz, 1H), 3.24 (s, 3H), 4.08 (dq, J=5.4Hz, J=6.4Hz, 1H), 4.73 (d, J=1.0Hz, 1H), 4.93 (q, J=7.3Hz, 1H), 7.26-7.36 (m, 5H); ¹³C NMR (100MHz CDCl₃) δ 19.4, 21.5, 51.4, 54.2, 62.7, 64.0, 84.5, 127.2, 127.7, 128.6, 139.8, 166.5; IR(neat): 3420, 3032, 2975, 2936, 2836, 1740, 1495, 1455, 1395,
1374, 1206, 1184, 1098, 1028, 997, 951, 864, 766, 700 cm\(^{-1}\); HRMS Calcd for C\(_{14}H_{19}NO_3\): 249.1365, Found: 249.1354.

4.10. Silylation of \(12\):

To a solution of \(12\) (60 mg, 0.24 mmol) and 4-dimethylaminopyridine (88 mg, 0.72 mmol) in \(N,N\)-dimethylformamide (1 mL) was added tert-butyldimethylsilyl chloride (109 mg, 0.72 mmol). After stirring for 24 h at rt, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with water (10 mL) and sat. aqueous NaCl (10 mL). The organic layer was dried over MgSO\(_4\) and the solvent was removed under reduced pressure. The residue was subjected on silica gel column chromatography (\(n\)-hexane:AcOEt =5 : 1) to afford \(13\) in 65% yield.

4\(R\)-Methoxy-3\(R\)-[1’\(R\)-tert-butyldimethylsilyloxy)ethyl]-1-(1’\(R\)-phenylethyl)azetidin-2-one (13)
colorless oil; \(^1\)H NMR (400MHz CDCl\(_3\)) \(\delta\) –0.02 (s, 3H), 0.02 (s, 3H), 0.80 (s, 9H), 1.21 (d, \(J=6.4\)Hz, 3H), 1.63 (d, \(J=7.3\)Hz, 3H), 2.90 (dd, \(J=0.6\)Hz, \(J=4.9\)Hz, 1H), 3.20 (s, 3H), 4.05 (dq, \(J=4.9\)Hz, \(J=6.4\)Hz, 1H), 4.71 (d, \(J=0.6\)Hz, 1H), 4.86 (q, \(J=7.3\)Hz, 1H), 7.26-7.39 (m, 5H); \(^{13}\)C-NMR (100MHz CDCl\(_3\)) \(\delta\) –4.7, –4.7, 17.9, 20.0, 22.7, 25.7, 51.7, 54.1, 63.2, 64.4, 84.7, 127.3, 127.6, 128.6, 139.9, 166.2; IR(neat): 3033, 2955, 2930, 2897, 2857, 1765, 1495, 1472, 1389, 1250, 1204, 1183, 1150, 1100, 1040, 1028, 1005, 934, 853, 812, 777, 700 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{20}H_{33}NO_3\) (M\(^+\)): 363.2230, Found: 363.2199.

4.11. Removal of N-protecting group of \(13\):

To anhydrous liq. ammonia (2 mL) was added Na (18 mg, 0.78 mmol) at –78 °C. Successively, a solution of \(13\) (47 mg, 0.13 mmol) in tetrahydrofuran (2 mL) was added to the ammonia. After stirring for 1 h at –78 °C, to the reaction mixture was added sat. aqueous NaCl (10mL). The organic portion was extracted with AcOEt (3 x 10 mL). The resulting organic layer was washed with sat. aqueous NaCl (25 mL). The organic layer was dried over MgSO\(_4\) and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (\(n\)-hexane:AcOEt =2 : 1) to afford \(2a\) in 95% yield.

4\(R\)-Methoxy-3\(R\)-[1’\(R\)-tert-butyldimethylsilyloxy)ethyl]azetidin-2-one (2a)
colorless crystal; mp 56-58 °C; \([\alpha]_D^{27.0}\) –28.9 (c=1.4, CHCl\(_3\)); \(^1\)H NMR (400MHz
CDCl₃) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.26 (d, J=6.4Hz, 3H), 3.00 (dd, J=1.0Hz, J=4.9Hz, 1H), 3.37 (s, 3H), 4.17 (dq, J=4.9Hz, J=6.4Hz, 1H), 5.00 (d, J=1.0Hz, 1H), 6.53 (s, 1H); ¹³C NMR (100MHz CDCl₃) δ −5.1, −4.3, 17.9, 22.5, 25.7, 25.7, 54.9, 64.2, 65.2, 81.5, 167.7.

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References and notes


8. Crystallographic data for structure of azetidin-2-one 7e have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 745174. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.


10. Although the corresponding 4-acetoxylated compound 14 was prepared from 11 by electrochemical oxidation described below, the reduction of 14 with Na in liq. NH₃ did not afford the corresponding N-unsubstituted azetidin-2-one; see, electrochemical decarboxylative acetoxylation: In an undivided cell equipped with platinum plate electrodes (1 x 2 cm²) was placed a solution of 11 (153 mg, 0.5 mmol) and AcOK (98 mg, 1 mmol) in a mixture of acetonitrile (4 mL) and acetic acid (1 mL). A constant current (50 mA) was passed through the cell externally cooled with water-bath. After 4 F/mol of electricity was passed, to the reaction mixture was added sat. NaHCO₃ (30 mL). Organic portion was extracted with AcOEt (3 x 15 mL). The resulting organic layer was washed with sat. aqueous
NaCl (10 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (n-hexane : AcOEt = 2 : 1) to afford 14 in 60% yield.

**4R-Acetoxo-3R-(1'R-acetoxethyl)-1-(1'R-phenylethyl)azetidin-2-one (14):**

colorless oil; 1H NMR (400MHz CDCl₃) δ 1.24 (d, J=6.3Hz, 3H), 1.55 (d, J=7.4Hz, 3H), 1.83 (s, 3H), 1.90 (s, 3H), 3.09 (dd, J=1.0Hz, J=5.8Hz, 1H), 4.80 (q, J=7.3Hz, 1H), 5.09 (quint, J=6.3Hz, 1H), 5.92 (d, J=1.0Hz, 1H), 7.20-7.40 (m, 5H); 13C-NMR (100MHz, CDCl₃) δ 18.2, 19.1, 20.8, 20.8, 52.7, 62.3, 66.1, 78.0, 126.9, 127.9, 128.7, 140.1, 164.3, 169.9, 169.9; IR (neat): 3500, 2984, 2853, 1738, 1640, 1497, 1456, 1377, 1242, 1200, 1140, 1050, 953, 922, 851, 799, 722, 704 cm⁻¹; HRMS (EI) Calcd for C₁₇H₂₁NO₅ (M⁺): 319.1420, Found: 319.1430.


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**GA**

\[\text{HO\,Me}\,C\,O\,\text{CO}_2\text{t-Bu}\,C\,O\,\text{CO}_2\text{t-Bu}\,C\,O\,\text{Me}\,R\,H\,S\,\text{Me} \rightarrow \begin{array}{c}
\text{Me}\,R \,= \, \text{94% yield, 80% de} \\
\text{NaI (0.5 equiv)} \, \text{in MeCN} \, \text{at 85 °C} \\
\text{93% yield, 84% de} \\
\text{NaBH}_4 \, \text{in THF}
\end{array}\]