Convenient synthesis of enantiomerically pure bicyclic proline and its \(N\)-oxyl derivatives

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Abstract—Enantiomerically pure bicyclic proline derivative was prepared by \(cis\)-selective allylation and diastereospecific intramolecular alkylation starting from D-pipecolinic acid. In addition, enantiomerically pure azabicyclo \(N\)-oxyls derived from the bicyclic proline worked well as catalyst for enantioselective electrooxidation of racemic sec-alcohols to afford optically active sec-alcohols in moderate optical purity.

Keywords: Bicyclic proline; Quaternary \(\alpha\)-amino acid; Enantioselective oxidation; Electrooxidation; Optically active alcohol

1. Introduction

In the recent past, importance of quaternary \(\alpha\)-amino acids and their peptides have continued to increase in the fields of medicinal chemistry, and protein engineering.\(^1\) Since quaternary \(\alpha\)-amino acids are non-proteinogenic, their synthesis has attracted considerable attention.\(^2\) Among them, bicyclic proline analogues \(A\) bridged at the 2\(^{\text{nd}}\) and 5\(^{\text{th}}\) carbons of the pyrrolidine ring have unique biological\(^3\) and conformational\(^4\) properties. Therefore, several synthetic methods for their preparation have been developed (Figure 1).\(^5\) However, to the best of our knowledge, synthesis of enantiomerically enriched bicyclic proline \(A1\) with an 8-azabicyclo[3.2.1]octane skeleton has not been accomplished to date.\(^6\) We wish herein to report a convenient method for synthesis of \(A1\)\(^7\) starting from D-pipecolinic acid. In addition, chiral \(N\)-oxyls derived from \(A1\) were prepared and used for enantioselective electrooxidation of DL-1-phenylethanol.\(^8\)

![Figure 1. Structure of bicyclic proline analogue A](image-url)
2. Results and discussion
2.1. Synthesis of bicyclic proline derivative 6

Our strategy for synthesis of bicyclic proline derivative 6 is shown in scheme 1, which consists of cis-selective allylation and diastereospecific intramolecular alkylation. To start with, electrochemical methoxylation\(^9\) of D-pipecolinic acid derivative 1 afforded 6-methoxypipecolinate 2, which was allylated with allyltrimethylsilane catalyzed by BF\(_3\)-OEt\(_2\) to give diastereomerically enriched 6-allylated pipecolinate cis-3.\(^{10}\) After isolation of cis-3 by chromatography, transformation of the 6-allyl group to toslyoxyethyl group was carried out by ozonolysis, then NaBH\(_4\) reduction followed by tosylation to obtain 5 in sufficient high yield. Finally, compound 5 underwent a base catalyzed intramolecular alkylation\(^ {3d,11}\) to afford enantiomerically pure 6 with an 8-azabicyclo[3.2.1]octane skeleton in high yield. Further alkaline hydrolysis of 6 gave N-protected bicyclic proline 7 in quantitative yield.

\[
\begin{align*}
\text{N}^\text{CO}_2\text{Me} & \quad \text{N}^\text{CO}_2\text{Me} \quad \text{MeO}^\text{N}^\text{CO}_2\text{Me} \\
1, 99\% & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \чет

Scheme 1.

The stereoconfiguration of 6 was determined by X-ray crystallographic analysis after derivatization of 7 to heterotripeptide 8.\(^{12}\) The transformation was carried out in solution-phase method, employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT) as coupling reagents (Eq. 1). As shown in Figure 2, bicyclic proline analogue has the conformational property similar
to that of proline, which is \( \beta \)-turn inducer.\(^{13}\)

\[
\text{EDC (1.2 equiv)} \\
\text{HOBt (1.2 equiv)} \\
\text{H}2\text{N-(Aib)2-OMe (1.0 equiv)} \\
\text{MeCN, 60°C} \\
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{N} \quad \text{H} \\
\text{N} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

\[
7 \quad 8, \quad 78\%
\]

Figure 2. Ortep drawing of tripeptide 8.

2.2. Synthesis of enantiomerically pure N-oxyls 10, 13, and 16a—d

Enantiomerically pure azabicyclo-\( N \)-oxyl 10 possessing methoxycarbonyl group at the bridgehead position was synthesized from 6 by deprotection of \( N \)-methoxycarbonyl group utilizing \( \text{Me}_3\text{SiI} \) followed by \( m \)-CPBA oxidation (Eq. 2). \( N \)-Oxyl 13 was synthesized as follows: reduction of methyl ester group followed by benzoylation of hydroxyl group gave compound 11 in moderate yield. After deprotection of 11, successive oxidation with \( m \text{CPBA} \) afforded \( N \)-oxyl 13 (Eq. 3).

\[
\begin{align*}
\text{Me}_3\text{SiI (3.0 equiv)} & \quad \text{MeO}_2\text{C} \\
\text{CH}_2\text{Cl}_2, \text{rt} & \quad 9, \quad 73\% \\
\]

\[
\begin{align*}
\text{m-CPBA (1.5 equiv)} & \quad \text{MeO}_2\text{C} \\
\text{CH}_2\text{Cl}_2, \text{rt} & \quad 10, \quad 79\% \\
\end{align*}
\]
Compounds 14a—d substituted with several amide groups were prepared by using solution-phase method (Eq. 4). N-Oxyls 16a—d were prepared in a similar method similar to that described for the preparation of N-oxyl 10. The results are summarized in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RNH₂</th>
<th>Yield of 14a-d (%)</th>
<th>Yield of 15a-d (%)</th>
<th>Yield of 16a-d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-NH₂</td>
<td>14a 70</td>
<td>15a 51</td>
<td>16a 85</td>
</tr>
<tr>
<td>2</td>
<td>Bn-NH₂</td>
<td>14b 78</td>
<td>15b 74</td>
<td>16b 82</td>
</tr>
<tr>
<td>3</td>
<td>Methyl L-Phg</td>
<td>14c 78</td>
<td>15c 86</td>
<td>16c 86</td>
</tr>
<tr>
<td>4</td>
<td>Methyl D-Phg</td>
<td>14d 83</td>
<td>15d 83</td>
<td>16d 68</td>
</tr>
</tbody>
</table>

Table 1. Preparation of enantiomerically pure N-oxyls 16a-d.
Cyclic voltammogram for 10 showed reversible wave pattern similar to that of TEMPO.\textsuperscript{14} This fact strongly suggests that enantiomerically pure azabicyclo-N-oxyls could also play the role of an oxidation mediator just like TEMPO (Figure 3).

\textbf{Figure 3.} Cyclic voltammogram for N-oxyl 10.

2.3. \textit{Enantioselective electrooxidation of DL-1-phenylethanol mediated by chiral azabicyclo-N-oxyls 10, 13, and 16a—d}

The enantioselective electrooxidation of DL-1-phenylethanol (17)\textsuperscript{8a,15} mediated by chiral azabicyclo-N-oxyls 10, 13, and 16a—d was carried out in an undivided beaker-type cell having platinum electrodes as follows (Eq. 5). That is, oxidation was conducted, containing a catalytic amount of N-oxyl, excess amount of sodium bromide, and a mixture of CH\textsubscript{2}Cl\textsubscript{2} and saturated aqueous NaHCO\textsubscript{3} as solvent. After passing through 1.5 \textit{F/mol} of electricity at constant current (20 mA, terminal voltage: ca 3V) at 0°C, acetophenone 18 and (S)-17 were obtained. The results are shown in Table 2. The use of N-oxyls 10 and 16a—d afforded (S)-17 with moderate \textit{s} value\textsuperscript{16} (Entries 1, 3, 4—6), while (S)-17 was recovered with low enantioselectivity when N-oxyl 13 was used (Entry 2).
Table 2. Enantioselective oxidation of DL-phenylethanol (17) mediated by 10, 13, 16a-d

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-oxyl</th>
<th>Yield of 18 (%)</th>
<th>Yield of recovered (S)-17 (%)</th>
<th>% ee of (S)-17</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>59</td>
<td>41</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>50</td>
<td>41</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>16a</td>
<td>64</td>
<td>36</td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>16b</td>
<td>50</td>
<td>50</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>16c</td>
<td>45</td>
<td>51</td>
<td>42</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>16d</td>
<td>53</td>
<td>36</td>
<td>69</td>
<td>6</td>
</tr>
</tbody>
</table>

Enantioselective oxidation of other sec-alcohols 19—24 mediated by 16b were examined (Eq. 6). Table 3 summarizes the results. In all cases, (S)-alcohols 19—24 were recovered with low to moderate s value.
Table 3. Enantioselective oxidation of various sec-alcohols 19-24 mediated by 16b

<table>
<thead>
<tr>
<th>Entry</th>
<th>sec-Alcohol</th>
<th>Yield of ketone (%)</th>
<th>Yield of recovered (S)-alcohol (%)</th>
<th>% ee of (S)-19-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>25 50</td>
<td>48</td>
<td>33 3</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>26 54</td>
<td>45</td>
<td>16 2</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>27 62</td>
<td>35</td>
<td>30 2</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>28 70</td>
<td>29</td>
<td>69 3</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>29 53</td>
<td>46</td>
<td>38 3</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>30 66</td>
<td>24</td>
<td>72 4</td>
</tr>
</tbody>
</table>

Scheme 2 shows our proposed mechanism for kinetic resolution of DL-17 mediated by chiral N-oxyl 16b. Compound DL-17 has prospects to approach 16b' generated by the oxidation of 16b with bromonium ion from path a or path b. In the case of path a, since (R)-17 can smoothly approach 16b' to form the active intermediate, (R)-17 can easily be oxidized to afford acetophenone (18). On the other hand, the formation of intermediate composed of (S)-17 and 16b seems to be somewhat difficult. Also, in the case of path b, the intermediate seems to be somewhat unstable because the distance O-H···O=C is slightly longer for a hydrogen bond.
Scheme 2. Plausible stereochemical course for kinetic resolution of DL-17.
3. Conclusion

We have accomplished a convenient method for synthesis of enantiomerically pure bicyclic proline analogues starting from D-pipecolinic acid. It has similar conformational property to that of proline, which is β-turn inducer. Chiral azabicyclo N-oxyls derived from bicyclic amino acid worked well as catalysts in enantioselective electrooxidation of racemic sec-alcohols to afford optically active sec-alcohols in moderate $s$ value.

4. Experimental Section

4.1. General

Electrochemical reactions were carried out using DC Power Supply (GP 050—2) of Takasago Seisakusho, Inc. $^1$H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. $^{13}$C NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Mass spectra were obtained on a JEOL JMS-DX 303 instrument.

All reagents and solvents were used as supplied without further purification. Although we could not determine optical purity for compounds 7, 9, 10, 11, 12, 13, 14a—d, 15a—d and 16a—d, it was assumed that there was no racemization during their derivation from enantiomerically pure 6.

4.2. Procedure for synthesis of enantiomerically pure proline analogue

Methyl N-methoxycarbonyl-L-pipecolinate (ent-1)$^{10}$ and methyl N-methoxycarbonyl-6-methoxy-L-pipecolinate (ent-2)$^{10}$ are known compounds.

4.2.1. Methyl N-methoxycarbonyl-(6S)-allyl-L-pipecolinate (cis-3)

Under nitrogen atmosphere, BF$_3$-OEt$_2$ (4.2 mL, 34.2 mmol) was added dropwise to 2 (7.5 g, 32.6 mmol) and allyltrimethylsilane (9.8 mL, 61.9 mmol) in CH$_2$Cl$_2$ (200 mL) at $-78^\circ$C then the mixture was stirred for 3 h and allowed to stand until it warmed to $-40^\circ$C. The resulting mixture was poured into ice water and extracted with CHCl$_3$ (300 mL x 3). The combined organic layer was dried over anhydrous MgSO$_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($n$-hexane : AcOEt = 5 : 1; cis-3 was less polar than trans-3) to afford cis-3 as a colorless oil (5.7 g, 72%). $\left[\alpha\right]_D^{20} = +106.6$ (c 1.0, CHCl$_3$); IR (neat) $\nu$ = 2951, 1752, 1713, 1642 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 5.80—5.63 (m, 1H),...
5.07—5.01 (m, 2H), 4.86 (br s, 1H), 4.21 (br s, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.42—2.10 (m, 3H), 1.78—1.47 (m, 5H); 13C NMR (100 MHz, CDCl3) δ = 156.8, 136.0, 116.8, 52.8, 52.3, 52.1, 50.8, 36.3, 26.0, 25.8, 15.3; [HR-FAB(+)]: m/z calcd for C12H20NO4 [M+H]+ 242.1393: found 242.1404.

4.2.2. Methyl N-methoxycarbonyl-(6S)-(2-hydroxyethyl)-D-pipecolinate (4)

Ozone gas was bubbled into a solution of 3 (241 mg, 1.0 mmol) in CH2Cl2 (5.0 mL) at —78°C, and the reaction was monitored by TLC. After disappearance of 3, NaBH4 (304 mg, 8.0 mmol) dissolved in MeOH (1.0 mL) was added dropwise to the mixture and stirred at 50°C for 6 h. The mixture was poured into 3% aqueous HCl and extracted with CHCl3 (20 mL x 3). The combined organic layer was dried over anhydrous MgSO4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 1 : 1) to afford 4 as a colorless oil (198 mg, 81%). [α]D20 = +50.2 (c 1.0, CHCl3); IR (neat) ν = 3500 (br), 2953, 1736, 1700 cm−1; 1H NMR (300 MHz, CDCl3) δ = 4.84 (br s, 1H), 4.50 (br s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.69—3.63 (m, 2H), 2.30 (d, J = 12.0 Hz, 1H), 1.81—1.43 (m, 8H); 13C NMR (100 MHz, CDCl3) δ = 172.8, 157.9, 58.7, 53.3, 52.4, 52.1, 46.8, 35.6, 29.4, 26.0, 16.0; [HR-FAB(+)]: m/z calcd for C11H20NO5 [M+H]+ 246.1342: found 246.1345.

4.2.3. Methyl N-methoxycarbonyl-(6S)-[2-(p-tolunesulfonyloxy)ethyl]-D-pipecolinate (5)

p-TsCl (120 mg, 0.63 mmol), Et3N (88 μL, 0.63 mmol), and 4-DMAP (13.4 mg, 0.11 mmol) were added into 4 (130 mg, 0.53 mmol) in CH2Cl2 (3.0 mL) and the mixture was stirred for 24 h at room temperature. Upon completion of reaction the mixture was poured into 3% aqueous HCl and extracted with CHCl3 (10 mL x 3). The combined organic layer was dried over anhydrous MgSO4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 4 : 1) to afford 5 as a colorless oil (205 mg, 97%). [α]D20 = +61.5 (c 1.0, CHCl3); IR (neat) ν = 2953, 1742, 1701 cm−1; 1H NMR (300 MHz, CDCl3) δ = 7.80 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 4.89 (br s, 1H), 4.36—4.33 (m, 1H), 4.14—4.12 (m, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 2.45 (s, 3H), 2.29 (d, J = 14.4 Hz, 1H), 2.08—1.98 (m, 1H), 1.77—1.40 (m, 6H); 13C NMR (100 MHz, CDCl3) δ = 173.0, 156.8, 144.6, 133.0, 129.8, 128.0, 68.4, 53.0, 52.3, 47.6, 32.0, 28.5, 25.9, 21.6, 15.7; [HR-FAB(+)]: m/z calcd for C18H26NO7S [M+H]+ 400.1432: found 400.1435.

4.2.4. Methyl (1R)-N-methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carboxylate (6)
Under nitrogen atmosphere, 1.9 M NaHMDS (2.5 mL, 4.7 mmol) in n-hexane was added dropwise to 5 (1.56 g, 3.9 mmol) in THF (40 mL) at −78°C, then the mixture was stirred at −78°C for 12 h and allowed to stand until it warmed to room temperature. The mixture was then poured into saturated aqueous NH₄Cl and extracted with AcOEt (40 mL x 3). The combined organic layer was dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 5 : 1) to afford 6 as a colorless oil (761 mg, 86%). [α]D₂₃ = +25.0 (c 1.0, CHCl₃, >99% ee); IR (neat) ν = 2953, 1750, 1709 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 4.33 (br s, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.25—1.39 (m, 10H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.8, 154.9, 65.2, 56.9, 52.4, 52.2, 34.1, 29.8, 29.6, 27.3, 17.0; [HR-FAB(+)]: m/z calcd for C₁₁H₁₈NO₄ [M+H]⁺ 228.1236: found 228.1237. HPLC: Daicel Chiralcel OJ-H column, n-hexane : ethanol = 20 : 1, wavelength: 210 nm, flow rate: 1.0 mL/min, retention time: 8.2 min for (S)-6, 11.1 min for (R)-6.

4.2.5. (1R)-N-Methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carboxylic acid (7)

1M aqueous NaOH (5.0 mL) was added to the stirred solution of 6 (318 mg, 1.4 mmol) in MeOH (5.0 mL), and the solution continued to be stirred at 60°C for 48 h. The solution was then neutralized with 3% aqueous HCl, and then MeOH was evaporated. The residue was diluted with brine, extracted with AcOEt (20 mL x 3), and dried over anhydrous MgSO₄. Removal of the solvent afforded compound 7 (298 mg, quant.) as a colorless oil, which was used for next reaction without further purification. [α]D₂₉ = +21.6 (c 1.0, CHCl₃, >99% ee); IR (neat) ν = 3280 (br), 2955, 1750, 1700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 9.91 (br s, 1H), 4.33 (br s, 1H), 3.72 (s, 3H), 2.34—1.40 (m, 10H); ¹³C NMR (100 MHz, CDCl₃) δ = 177.3, 155.3, 65.4, 57.2, 52.6, 34.6, 29.8, 27.3, 20.8, 17.0; [HR-FAB(+)]: m/z calcd for C₁₀H₁₆NO₄ [M+H]⁺ 214.1079: found 214.1080.

4.2.6. Methyl N-[(1R)-N-methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carbonyl]dimethylglycyl-dimethylglycinate (8)

A solution of 7 (213 mg, 1.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 230 mg, 1.2 mmol), and 1-hydroxybenzotriazole (HOBt, 162 mg, 1.2 mmol) in MeCN (5 mL) was stirred at room temperature for 30 min. Then, a solution of H₂N-(Aib)₂-OMe (202 mg, 1.0 mmol) in MeCN (5 mL) was added to the stirred solution and stirring continued at
60°C for 48 h. The solution was evaporated, diluted with AcOEt (50 mL), washed with 3% aqueous HCl, 5% NaHCO₃, brine, and dried over anhydrous MgSO₄. Evaporation of the solvent gave white solid, which was purified by column chromatography on silica gel (n-hexane : AcOEt = 1 : 5) to afford 8 (310 mg, 78%) as colorless crystals. Mp 165 —167°C; [α]D²⁵ = +25.6 (c 0.5, CHCl₃); IR (KBr) ν = 3324, 3013, 1746, 1736, 1690, 1655 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 7.79 (br s, 1H), 5.91 (br s, 1H), 4.30 (d, J = 6.6 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.21—1.42 (m, 22H); ¹³C NMR (75 MHz, CDCl₃) δ = 175.3, 173.6, 159.8, 156.5, 66.8, 58.0, 56.6, 55.9, 52.8, 52.1, 35.3, 29.5, 28.4, 27.1, 25.4, 24.0, 23.6, 16.9, 14.7; [HR-FAB(+)]: m/z calcd for C₁₉H₃₂N₃O₆ [M+H⁺] = 398.2291; found 398.2314.

Crystallographic data: orthorhombic; space group P2₁2₁2₁; a = 8.7962(5) Å, b = 10.6579(5) Å, c = 22.8155(11) Å; α, β, γ = 90°; V = 2138.93(19) Å³; Z = 4, d calcld = 1.234 g/cm³; 15,490 reflections collected 2763 unique (R int = 0.019); R = 0.0595, wR² = 0.1330.

4.3. Preparation of chiral azabicyclo N-oxyls

4.3.1. Methyl (1R)-8-azabicyclo[3.2.1]octane-1-carboxylate (9)

Me₃SiI (213 μL, 1.5 mmol) was added to stirred solution of 6 (114 mg, 0.5 mmol) in CH₂Cl₂ (2.0 mL), and the solution was stirred at rt for 12 h. The solution was then poured into saturated aqueous NaHCO₃ and extracted with CHCl₃ (20 mL x 3). The combined organic layer was dried over anhydrous MgSO₄ and solvent was removed under reduced pressure to afford 9 as a colorless oil, which was used for next reaction without further purification. [α]D²⁸ = +14.3 (c 0.7, CHCl₃, >99% ee); IR (neat) ν = 3277 (br), 2953, 1717 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 3.74 (s, 3H), 3.06 (br s, 2H), 2.08—1.46 (m, 10H); [HR-El(+)]: m/z calcd for C₉H₁₅NO₂ [M]⁺ 169.1103; found 169.1108.

4.3.2 Methyl (1R)-8-azabicyclo[3.2.1]octane-1-carboxylate-N-oxyl (10)

A solution of amine 9 (34 mg, 0.2 mmol) and m-CPBA (52 mg, 0.3 mmol) in CH₂Cl₂ (1.0 mL) was stirred for 3 h at rt. The solution was then poured into saturated aqueous NaHCO₃ and extracted with CHCl₃ (10 mL x 3). The combined organic layer was dried over anhydrous MgSO₄ and solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 3 : 1) to afford N-oxyl 10 (29 mg, 79%) as a red foam. [α]D²⁹ = —13.9 (c 0.6, CHCl₃, >99% ee); IR (neat) ν = 2955, 1748, 1437 cm⁻¹; [HR-FAB(+)]: m/z calcd for C₉H₁₄NO₃ [M+H⁺] = 184.0974; found 184.0990.
4.3.3. (1R)-N-Methoxycarbonyl-1-benzoyloxymethyl-8-azabicyclo[3.2.1]octane (II)

Under an argon atmosphere, 1M DIBAL-H (3.0 mL, 3.0 mmol) in n-hexane was added dropwise to a solution of 6 (227 mg, 1.0 mmol) in toluene (5 mL) at 0°C. The resulting mixture was stirred for 12 h and allowed to stand until it warmed to room temperature. The solution was then poured into 3% aqueous HCl and extracted with AcOEt (20 mL x 3). The combined organic layer was dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 3 : 1) to afford (1R)-N-methoxycarbonyl-1-hydroxymethyl-8-azabicyclo[3.2.1]octane (6') as a colorless oil (183 mg, 86%). [α]D²⁶ = −21.3 (c 0.9, CHCl₃, >99% ee); IR (neat) ν = 3401 (br), 2946, 1673 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 5.06 (br s, 1H), 4.30 (br s, 1H), 3.77—3.59 (m, 5H), 2.15—1.25 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ = 155.2, 66.6, 66.3, 57.6, 52.2, 31.9, 30.6, 26.0, 17.4; [HR-EI(+)]: m/z calcd for C₁₀H₁₇NO₃ [M]⁺ 199.1208: found 199.1187.

BzCl (98 μL, 0.84 mmol) was added to a stirred solution of 6' (149 mg, 0.7 mmol), Et₃N (147 μL, 1.05 mmol) and DMAP (43 mg, 0.35 mmol) in CH₂Cl₂ (7 mL), and the mixture was stirred at rt for 12 h. The solution was then poured into 3% aqueous HCl and extracted with CHCl₃ (20 mL x 3). The combined organic layer was dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 5 : 1) to afford 11 as a colorless oil (151 mg, 65%). [α]D²⁵ = +51.3 (c 1.2, CHCl₃, >99% ee); IR (neat) ν = 2948, 1721, 1701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 8.02 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 4.71 (s, 2H), 4.38 (br s, 1H), 3.69 (s, 3H), 2.15—1.45 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ = 166.3, 154.9, 132.9, 130.3, 129.6, 128.3, 68.9, 64.1, 57.5, 52.1, 33.0, 32.3, 30.1, 25.7, 17.6; [HR-EI(+)]: m/z calcd for C₁₇H₂₁NO₄ [M]⁺ 303.1471: found 303.1470.

4.3.4. (1R)-Benzoyloxymethyl-8-azabicyclo[3.2.1]octane (12)

Compound 12 was prepared in a similar method to that described for the preparation of 9 (0.5 mmol scale). 122 mg, 99% yield; Colorless oil; [α]D²⁵ = +1.4 (c 0.6, CHCl₃, >99% ee); IR (neat) ν = 3226, 2938, 1721 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 8.05 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 4.34 (dd, J = 11.1, 7.8 Hz, 2H), 3.55—3.78 (m, 1H), 2.40 (br s, 1H), 1.96—1.33 (m, 10H); [HR-EI(+)]: m/z calcd for C₁₅H₁₅NO₂ [M]⁺ 245.1416: found 245.1410.
4.3.5. (1R)-Benzoyloxymethyl-8-azabicyclo[3.2.1]octane-N-oxyl (13)

Compound 13 was prepared in a similar method to that described for the preparation of 10 (0.4 mmol scale). 50 mg, 48% yield; Red foam; $[\alpha]_D^{24} = +48.8$ (c 1.0, CHCl$_3$, >99% ee); IR (neat) $\nu = 2955, 1725$ cm$^{-1}$; [HR-EI(+)]: m/z calcd for C$_{15}$H$_{18}$NO$_3$ [M]$^+$ 260.1287; found 260.1272.

4.3.6. (1R)-N-Methoxycarbonyl-1-N-phenylcarbamoyl-8-azabicyclo[3.2.1]octane (14a)

A solution of aniline (109 $\mu$L, 1.2 mmol), 7 (213 mg, 1.0 mmol), EDC (230 mg, 1.2 mmol), and HOBt (162 mg, 1.2 mmol) in MeCN (10 mL) was stirred at 60°C for 24 h, and then volatiles evaporated. The residue was diluted with AcOEt, washed with cold 3% aqueous HCl, 5% aqueous NaHCO$_3$, and dried over anhydrous MgSO$_4$. After removal of solvent, the residue was purified by column chromatography on silica gel ($n$-hexane : AcOEt = 3 : 1) to give 14a (202 mg, 70%) as colorless crystals. Mp 150—152°C; $[\alpha]_D^{18} = +71.6$ (c 1.0, CHCl$_3$, >99% ee); IR (KBr) $\nu = 3280, 2951, 1700, 1680$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 7.60$ (br s, 1H), 7.50 (d, $J = 7.5$ Hz, 2H), 7.31 (t, $J = 6.3$ Hz, 2H), 7.08 (t, $J = 7.0$ Hz, 1H), 4.39 (br s, 1H), 3.70 (s, 3H), 2.24—1.41 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 171.1$, 156.1, 138.0, 128.9, 123.9, 119.8, 67.0, 58.3, 52.8, 35.9, 28.7, 26.9, 16.9; [HR-FAB(+)]: m/z calcd for C$_{16}$H$_{21}$N$_2$O$_3$ [M+H]$^+$ 289.1552; found 289.1559.

4.3.7. (1R)-N-Methoxycarbonyl-1-N-benzylcarbamoyl-8-azabicyclo[3.2.1]octane (14b)

Compound 14b was prepared in a similar method to that described for the preparation of 14a (1.0 mmol scale). 235 mg, 78% yield; Colorless crystals; Mp 126—128°C; $[\alpha]_D^{25} = +70.8$ (c 1.0, CHCl$_3$, >99% ee); IR (KBr) $\nu = 3280, 2950, 1701, 1660$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 7.31—7.22$ (m, 5H), 6.14 (br s, 1H), 4.45 (br s, 2H), 4.29 (br s, 1H), 3.60 (s, 3H), 2.12—1.36 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 173.0$, 155.9, 138.5, 129.4, 128.5, 128.0, 127.3, 100.5, 66.4, 58.2, 52.4, 43.5, 36.3, 28.9, 26.8, 17.0; [HR-FAB(+)]: m/z calcd for C$_{17}$H$_{23}$N$_2$O$_3$ [M+H]$^+$ 303.1708: found 303.1712.

4.3.8. Methyl N-[(1R)-N-methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carbonyl]-L-phenylglycinate (14c)

Compound 14c was prepared in a similar method to that described for the preparation of 14a (1.6 mmol scale). 449 mg, 78% yield; Colorless oil; $[\alpha]_D^{25} = +53.0$ (c 0.9, CHCl$_3$, >99% ee); IR (neat) $\nu = 2953, 1744, 1702, 1682$ cm$^{-1}$; $^1$H NMR (300
MHz, CDCl₃) δ = 7.38—7.28 (m, 5H), 6.94 (br s, 0.6H), 6.65 (d, J = 7.5 Hz, 0.4H), 5.59 (t, J = 7.0 Hz, 1H), 4.34 (br s, 1H), 3.74—3.36 (m, 6H), 2.34—1.58 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ = 172.5, 171.3, 155.9, 128.9, 128.8, 128.3, 127.5, 127.1, 66.3, 68.3, 58.3, 58.2, 56.1, 52.7, 52.3, 36.1, 28.8, 26.8, 17.0; [HR-El(+)]: m/z calcd for C₁₉H₂₄N₂O₅ [M]+ 360.1685: found 360.1693.

4.3.9. Methyl N-[(1R)-N-methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carbonyl]-D-phenylglycinate (14d)

Compound 14d was prepared in a similar method to that described for the preparation of 14a (1.6 mmol scale). 478 mg, 83% yield; Colorless oil; [α]D²⁵ = +74.7 (c 0.9, CHCl₃, >99% ee); IR (neat) ν = 3300, 2954, 1717, 1699, 1684 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 7.39—7.28 (m, 5H), 6.94 (br s, 0.4H), 6.65 (d, J = 6.9 Hz, 0.6H), 5.59 (t, J = 7.0 Hz, 1H), 4.34 (br s, 1H), 3.73—3.35 (m, 6H), 2.35—1.59 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ = 172.5, 171.5, 155.9, 128.9, 128.8, 128.5, 128.1, 127.5, 127.1, 66.2, 58.4, 58.1, 56.1, 52.6, 52.3, 36.3, 28.8, 26.8, 16.9; [HR-El(+)]: m/z calcd for C₁₉H₂₄N₂O₅ [M]+ 360.1685: found 360.1677.

4.3.10. (1R)-N-Phenylcarbamoyl-8-azabicyclo[3.2.1]octane (15a)

Compound 15a was prepared in a similar method to that described for the preparation of 9 (0.5 mmol scale). 59 mg, 51% yield; Colorless oil; [α]D²⁷ = +74.6 (c 0.6, CHCl₃, >99% ee); IR (neat) ν = 3314, 3278, 2928, 1665 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 9.01 (br s, 1H), 7.58 (d, J = 7.5 Hz, 2H), 7.30 (t, J = 6.9 Hz, 2H), 7.07 (t, J = 7.0 Hz, 1H), 3.67—3.65 (m, 1H), 2.31—1.40 (m, 11H); [HR-FAB(+)]: m/z calcd for C₁₄H₁₉N₂O [M+H]+ 231.1498: found 231.1497.

4.3.11. (1R)-N-Benzylcarbamoyl-8-azabicyclo[3.2.1]octane (15b)

Compound 15b was prepared in a similar method to that described for the preparation of 9 (0.8 mmol scale). 144 mg, 74% yield; Colorless oil; [α]D²⁸ = +28.2 (c 0.6, CHCl₃, >99% ee); IR (neat) ν = 3320, 3252, 2928, 1715, 1659 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 7.33—7.20 (m, 6H), 4.43 (d, J = 9.0 Hz, 2H), 3.57—3.55 (m, 1H), 2.27—1.40 (m, 11H); [HR-FAB(+)]: m/z calcd for C₁₅H₂₁N₂O [M+H]+ 245.1654: found 245.1647.

4.3.12. Methyl N-[(1R)-8-azabicyclo[3.2.1]octane-1-carbonyl]-L-phenylglycinate (15c)

Compound 15c was prepared in a similar method to that described for the
preparation of 9 (1.2 mmol scale). 340 mg, 86% yield; Colorless oil; \([\alpha]_D^{24} = +0.8\ (c\ 0.6, \text{CHCl}_3, >99\% \text{ ee})\); IR (neat) \(\nu = 3366, 3277, 2930, 1748, 1676 \text{ cm}^{-1}\); \(^1\text{H} \text{NMR}\ (300\ \text{MHz, CDCl}_3)\ \delta = 7.93\ (d, J = 7.2\ \text{Hz, 0.5H}), 7.83\ (d, J = 7.2\ \text{Hz, 0.5H}), 7.37—7.25\ (m, 5H), 5.53\ (t, J = 6.9\ \text{Hz, 1H}), 3.72\ (s, 3H), 3.69—3.57\ (m, 1H), 2.25—1.32\ (m, 11H); \([\text{HR-EI(+)}}]: m/z\ \text{calcd for C}_{17}\text{H}_{22}\text{N}_2\text{O}_3\ [\text{M}^+] 302.1630: \text{found 302.1614}.

4.3.13. Methyl N-[(1R)-8-azabicyclo[3.2.1]octane-1-carbonyl]-D-phenylglycinate (15d)

Compound 15d was prepared in a similar method to that described for the preparation of 9 (1.3 mmol scale). 328 mg, 83% yield; Colorless oil; \([\alpha]_D^{25} = +1.4\ (c\ 0.6, \text{CHCl}_3, >99\% \text{ ee})\); IR (neat) \(\nu = 3226\ (\text{br}), 2938, 1721 \text{ cm}^{-1}\); \(^1\text{H} \text{NMR}\ (300\ \text{MHz, CDCl}_3)\ \delta = 7.86\ (d, J = 7.2\ \text{Hz, 0.4H}), 7.77\ (d, J = 7.2\ \text{Hz, 0.6H}), 7.32—7.22\ (m, 5H), 5.46\ (t, J = 7.0\ \text{Hz, 1H}), 3.64\ (s, 3H), 3.55—3.41\ (m, 1H), 2.09—1.26\ (m, 11H); \([\text{HR-FAB(+)}}]: m/z\ \text{calcd for C}_{17}\text{H}_{22}\text{N}_2\text{O}_3\ [\text{M}^+] 302.1628: \text{found 302.1628}.

4.3.14. (1R)-N-Phenylcarbamoyl-8-azabicyclo[3.2.1]octane-N-oxyl (16a)

Compound 16a was prepared in a similar method to that described for the preparation of 10 (0.2 mmol scale). 42 mg, 85% yield; Red foam; \([\alpha]_D^{29} = +72.1\ (c\ 0.9, \text{CHCl}_3, >99\% \text{ ee})\); IR (neat) \(\nu = 3256, 2953, 1686, 1447 \text{ cm}^{-1}\); \([\text{HR-FAB(+)}}]: m/z\ \text{calcd for C}_{14}\text{H}_{18}\text{N}_2\text{O}_2\ [\text{M+H}^+] 246.1369: \text{found 246.1366}.

4.3.15. (1R)-N-Benzylcarbamoyl-8-azabicyclo[3.2.1]octane-N-oxyl (16b)

Compound 16b was prepared in a similar method to that described for the preparation of 10 (0.6 mmol scale). 127 mg, 82% yield; Red foam; \([\alpha]_D^{29} = +18.7\ (c\ 0.6, \text{CHCl}_3, >99\% \text{ ee})\); IR (neat) \(\nu = 3270, 2951, 1721, 1650, 1478 \text{ cm}^{-1}\); \([\text{HR-FAB(+)}}]: m/z\ \text{calcd for C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\ [\text{M+H}^+] 260.1525: \text{found 260.1500}.

4.3.16. Methyl N-[(1R)-8-azabicyclo[3.2.1]octane-1-carbonyl]-L-phenylglycinate-N-oxyl (16c)

Compound 16c was prepared in a similar method to that described for the preparation of 10 (1.1 mmol scale). 300 mg, 86% yield; Red oil; \([\alpha]_D^{25} = +86.1\ (c\ 0.8, \text{CHCl}_3, >99\% \text{ ee})\); IR (neat) \(\nu = 3283, 2953, 1745, 1674 \text{ cm}^{-1}\); \([\text{HR-EI(+)}}]: m/z\ \text{calcd for C}_{17}\text{H}_{21}\text{N}_2\text{O}_4\ [\text{M}^+] 317.1501: \text{found 317.1511}.

4.3.17. Methyl N-[(1R)-8-azabicyclo[3.2.1]octane-1-carbonyl]-D-phenylglycinate-N-oxyl (16d)

Compound 16d was prepared in a similar method to that described for the
preparation of 10 (1.0 mmol scale). 216 mg, 68% yield; Red oil; \([\alpha]_D^{25} = +119.7 (c 1.3, \text{CHCl}_3, >99\% \text{ ee})\); IR (neat) \(\nu = 3277, 2955, 1746, 1676 \text{ cm}^{-1}\); [HR-EI(+)]: \(m/z\) calcd for C\(_{17}\)H\(_{21}\)N\(_2\)O\(_4\) [M]+ 317.1501 : found 317.1488.

4.4. General procedure for enantioselective electrooxidation of DL-sec-alcohols 17, 19-24 with N-oxyls 10, 13, and 16a–d

Anodic oxidation of DL-1-phenylethanol (DL-17) was carried out using platinum electrodes (1 cm x 2 cm) in an undivided beaker-type cell. DL-17 (61 mg, 0.5 mmol), 10 (9.2 mg, 0.05 mmol) and NaBr (206 mg, 2.0 mmol) were added into a mixture of CH\(_2\)Cl\(_2\) (2.5 mL) and saturated aqueous NaHCO\(_3\) (2.5 mL). After passing through 1.5 \(F/\text{mol}\) of electricity at constant current (20 mA) at 0°C, the mixture was poured into water and extracted with AcOEt (20 mL x 3). The combined organic layer was dried over anhydrous MgSO\(_4\) and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (\(n\)-hexane : AcOEt = 10 : 1) to afford acetophenone 18 (35.4 mg, 59% yield) and (S)-17 (24.6 mg, 41% yield) as a colorless oil.

The optical purity of (S)-17 was determined by chiral HPLC: Daicel Chiralcel OB column (4.6 mm\(\phi\), 250 mm), \(n\)-hexane : 2-propanol = 15 : 1, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 13.5 min for (S)-17, 17.5 min for (R)-17.

The optical purity of (S)-19 was determined by chiral HPLC: Daicel Chiralcel OB column (4.6 mm\(\phi\), 250 mm), \(n\)-hexane : 2-propanol = 15 : 1, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 11.9 min for (S)-19, 16.9 min for (R)-19.

The optical purity of (S)-20 was determined by chiral HPLC: Daicel Chiralcel AD column (4.6 mm\(\phi\), 250 mm), \(n\)-hexane : 2-propanol = 100 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 14.0 min for (R)-20, 16.5 min for (S)-20.

The optical purity of (S)-21 was determined by chiral HPLC: Daicel Chiralcel OJ column (4.6 mm\(\phi\), 250 mm), \(n\)-hexane : 2-propanol = 9 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 13.8 min for (S)-21, 16.8 min for (R)-21.

The optical purity of (S)-22 was determined by chiral HPLC: Daicel Chiralcel OJ column (4.6 mm\(\phi\), 250 mm), \(n\)-hexane : 2-propanol = 9 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 12.7 min for (S)-22, 16.0 min for (R)-22.
The optical purity of (S)-23 was determined by chiral HPLC: Daicel Chiralcel OB column (4.6 mm φ, 250 mm), n-hexane : 2-propanol = 15 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 15.0 min for (R)-23, 27.0 min for (S)-23.

The optical purity of (S)-24 was determined by chiral HPLC: Daicel Chiralcel OD-H column (4.6 mm φ, 250 mm), n-hexane : 2-propanol = 50 : 1, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 21.0 min for (S)-24, 22.5 min for (R)-24.

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References and notes


7. Synthesis of racemic proline analogue A1 has been recently reported: Casabona, D.; Jiménez. A. I.; Cativiela, C. Tetrahedron 2007, 63, 5056—5061.


12. Crystallographic data for structure of tripeptide 8 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 699629. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21 EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.


14. Cyclic voltammogram for 10 was measured in 0.1 M Et₄NBF₄/MeCN solution using glassy-carbon as a working electrode, platinum as a counter electrode, and Ag/0.01 M AgNO₃ as a reference electrode. Concentration of 10: 1.0 mM. Scan rate: 30 mV/s. Cyclic voltammogram for other N-oxyls showed reversible wave pattern similar to that for 10. Oxidation potential: 0.83V for 10, 0.82V for 13, 0.58V for 16a, 0.79V for 16b, 0.78V for 16c, 0.80V for 16d.
