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<th>Facile synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate from l-proline</th>
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<td>Author(s)</td>
<td>Hirata, Shigeo; Kuriyama, Masami; Onomura, Osamu</td>
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<tr>
<td>Citation</td>
<td>Tetrahedron, 67(48), pp.9411-6416; 2011</td>
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</table>
Facile synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate from L-proline
Shigeo Hirata, Masami Kuriyama, Osamu Onomura*

![Chemical structures and reaction scheme]

Leaves up to 84% ee
Leaves up to 85% ee
Facile synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate from L-proline

Shigeo Hirata, Masami Kuriyama, Osamu Onomura*

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki
852-8521, Japan

Abstract- Diastereoselective introduction of phosphono groups into L-proline derivatives at the 5-position was achieved with suitable selection of N-protecting group. N-Benzoyl-L-prolinate preferentially gave trans-phosphorylated products which could be easily transformed into (S)-(pyrrolidin-2-yl)phosphonates. On the other hand, N-benzylxoy carbonyl-L-prolinate reacted with phosphite to give cis-substituted products which could be easily transformed into (R)-(pyrrolidin-2-yl)phosphonates.

Keywords: Diastereoselective phosphorylation; Arbusov reaction; (Pyrrolidin-2-yl)phosphonate; L-Proline.

1. Introduction

Optically active α-amino phosphonates and their derivatives are biologically important compounds structurally analogous to α-amino acids. A lot of useful methods have been developed for the diastereo- or enantio-selective synthesis of acyclic α-amino phosphonates. On the other hand, there are fewer methods for the diastereoselective synthesis of optically active cyclic α-amino phosphonates which have found promising
applications as surrogates of proline. These methods use (+)- or
(−)-2-hydroxy-3-pinenone, (−)-camphor, (R)- or (S)-phenylglycinol, L-menthol, (S)-(−)-p-toluenesulfonamide as chiral auxiliaries, while easily available L-proline on manufacturing scale has not used for the synthesis.

Recently, we have reported Lewis acid-catalyzed arylation of N-acylated 5-methoxy-L-proline 2 which are electrochemically prepared from L-proline derivatives 1 proceeded diastereoselectively. Namely, N-benzoylated prolinate 2a afforded trans-5-arylated L-proline trans-3a, while N-benzyloxycarbonylated prolinate 2b afforded cis-5-arylated L-proline cis-3b (Eq. 1).

![Chemical structure](image)

We wish herein to report the effect of N-acyl groups on the diastereoselective introduction of phosphonate groups into L-proline derivatives 2 at the 5-position and its application to synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate 6 (Scheme 1).

![Chemical structure](image)

**Scheme 1.**

2. Results and discussion

2.1. Effect of Lewis Acid on the Arbusov reaction

First, we investigated effect of Lewis acid on introduction of triethyl phosphite 4p
into \(N\)-benzoylated or \(N\)-benzyloxycarbonylated 5-methoxylated \(L\)-prolinate\(^6\) \(2a\) or \(2b\) (Eq. 3). The results are shown in Table 1. In the case of \(2a\), \(\text{TiCl}_4\) mediated \(\alpha\)-phosphorylation in good yield but with low diastereoselectivity (entry 1). \(\text{BF}_3\cdot\text{OEt}_2\) promoted the phosphorylation in moderate diastereoselectivity (entry 2), while \(\text{SnCl}_4\) did not work as an effective Lewis acid (entry 3).\(^7\) Using \(\text{Cu(OTf)}_2\), \(\text{AlCl}_3\), \(\text{Hf(OTf)}_4\), or \(\text{In(OTf)}_3\) as Lewis acid afforded phosphorylated product \(5\text{ap}\) in low yields (entries 4-7).\(^7\) In the case of \(2b\), similar tendency for tested Lewis acids was observed (entries 8-14), and \(\text{BF}_3\cdot\text{OEt}_2\) afforded the best result (entry 9).

![Diagram](image)

**Table 1. Effect of Lewis acid on the Arbusov reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>PG</th>
<th>Lewis Acid</th>
<th>Product</th>
<th>Yield (%)(^a)</th>
<th>De (%)(^b)</th>
<th>Major isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^c)</td>
<td>(2a)</td>
<td>Bz</td>
<td>(\text{TiCl}_4)</td>
<td>(5\text{ap})</td>
<td>66</td>
<td>26</td>
<td>\textit{trans}</td>
</tr>
<tr>
<td>2</td>
<td>(2a)</td>
<td>Bz</td>
<td>(\text{BF}_3\cdot\text{OEt}_2)</td>
<td>(5\text{ap})</td>
<td>59</td>
<td>43</td>
<td>\textit{trans}</td>
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<tr>
<td>3</td>
<td>(2a)</td>
<td>Bz</td>
<td>(\text{SnCl}_4)</td>
<td>(5\text{ap})</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(2a)</td>
<td>Bz</td>
<td>(\text{Cu(OTf)}_2)</td>
<td>(5\text{ap})</td>
<td>27</td>
<td>30</td>
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<tr>
<td>5</td>
<td>(2a)</td>
<td>Bz</td>
<td>(\text{AlCl}_3)</td>
<td>(5\text{ap})</td>
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<td>\textit{trans}</td>
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<td>6</td>
<td>(2a)</td>
<td>Bz</td>
<td>(\text{Hf(OTf)}_4)</td>
<td>(5\text{ap})</td>
<td>32</td>
<td>15</td>
<td>\textit{trans}</td>
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<tr>
<td>7</td>
<td>(2a)</td>
<td>Bz</td>
<td>(\text{In(OTf)}_3)</td>
<td>(5\text{ap})</td>
<td>14</td>
<td>32</td>
<td>\textit{trans}</td>
</tr>
<tr>
<td>8(^c)</td>
<td>(2b)</td>
<td>Cbz</td>
<td>(\text{TiCl}_4)</td>
<td>(5\text{bp})</td>
<td>49</td>
<td>51</td>
<td>\textit{cis}</td>
</tr>
<tr>
<td>9</td>
<td>(2b)</td>
<td>Cbz</td>
<td>(\text{BF}_3\cdot\text{OEt}_2)</td>
<td>(5\text{bp})</td>
<td>45</td>
<td>78</td>
<td>\textit{cis}</td>
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<td>10</td>
<td>(2b)</td>
<td>Cbz</td>
<td>(\text{SnCl}_4)</td>
<td>(5\text{bp})</td>
<td>0</td>
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<td>-</td>
</tr>
<tr>
<td>11</td>
<td>(2b)</td>
<td>Cbz</td>
<td>(\text{Cu(OTf)}_2)</td>
<td>(5\text{bp})</td>
<td>35</td>
<td>55</td>
<td>\textit{cis}</td>
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<tr>
<td>12</td>
<td>(2b)</td>
<td>Cbz</td>
<td>(\text{AlCl}_3)</td>
<td>(5\text{bp})</td>
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<td>Cbz</td>
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<td>33</td>
<td>61</td>
<td>\textit{cis}</td>
</tr>
<tr>
<td>14</td>
<td>(2b)</td>
<td>Cbz</td>
<td>(\text{In(OTf)}_3)</td>
<td>(5\text{bp})</td>
<td>26</td>
<td>70</td>
<td>\textit{cis}</td>
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</table>

\(^a\) Yield of isolated product as a mixture of diastereomers after purification by column chromatography.

\(^b\) The diastereomer excess was determined by \(^1\)H-NMR spectroscopy after purification.\(^\circ\) Reaction temperature: \(-78\) °C to rt.
2.2. Effect of N-protective group

Next, we investigated effect of N-protecting group on the diastereoselectivity for the Arbusov reaction of 2c-f with 4p in the presence of BF₃·OEt₂ (Eq. 4). The results are shown in Table 2. Diastereoselectivities of phosphorylated products 5cp and 5dp which were obtained from N-methoxycarbonylated proline 2c and N-ter-butoxycarbonylated proline 2d⁸ (entries 1 and 2 in Table 2) lowered compared with that of N-benzylxycarbonylated proline 5bp (entry 9 in Table 1). Similarly, diastereoselectivities of phosphorylated products 5ep and 5fp which were obtained from N-acetylated proline 2e and N-p-toluenesulfonylated proline 2f (entries 3 and 4 in Table 2) did not exceed that of N-benzoylated proline 5ap (entry 2 in Table 1).

\[
\text{MeO}_2\text{C}^\text{PG}^\text{OMe} \quad \overset{\text{P(}\text{OEt}_3\text{)(4p)} (2.0 \text{ equiv})}{\text{CH}_2\text{Cl}_2, \text{rt, 12h}} \quad \text{MeO}_2\text{C}^\text{PG}^\text{PO}^\text{OEtOEt}
\]

(4)

\text{2c: PG=CO}_2\text{Me} \\
\text{2d: PG=Boc} \\
\text{2e: PG=Ac} \\
\text{2f: PG=Ts}

\text{5cp: PG=CO}_2\text{Me} \\
\text{5dp: PG=Boc} \\
\text{5ep: PG=Ac} \\
\text{5fp: PG=Ts}

Table 2. Effect of N-protective group on the Arbusov reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>PG</th>
<th>Product</th>
<th>Yield (%)ᵃ</th>
<th>De (%)ᵇ</th>
<th>Major isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2c</td>
<td>CO₂Me</td>
<td>5cp</td>
<td>68</td>
<td>50</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>2d</td>
<td>Boc</td>
<td>5dp</td>
<td>20</td>
<td>41</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>2e</td>
<td>Ac</td>
<td>5ep</td>
<td>60</td>
<td>15</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>2f</td>
<td>Ts</td>
<td>5fp</td>
<td>98</td>
<td>29</td>
<td>nd</td>
</tr>
</tbody>
</table>

ᵃ Yield of isolated product as a mixture of diastereomers after purification by column chromatography. ᵇ The diastereomer excess was determined by ¹H-NMR spectroscopy after purification.

2.3. Effect of ester group in phosphite

Next, we investigated effect of ester group of phosphites on the diastereoselectivity for the Arbusov reaction of 2a or 2b in the presence of BF₃·OEt₂ (Eq. 5). The results are shown in Table 3. N-Benzoylated proline 2a reacted with trimethyl phosphite 4q gave
trans-phosphorylated product 5aq in similar yield and diastereoselectivity (entry 1 in Table 3) to those of 5ap (entry 2 in Table 1). Although triphenyl phosphite 4r, tribenzyl phosphate 4s, and tri-n-butyl phosphate 4u were ineffective (entries 2, 3 and 5 in Table 3), triisopropyl phosphate 4t was effective to afford trans-phosphorylated product 5at in good yield with high diastereoselectivity (entry 4 in Table 3). In the case of N-benzyloxy carbonylated proline 2b, similar tendencies were observed with respect to effect of phosphites (entries 6-10 in Table 3). The reaction of 2b with 4t gave the best result to afford cis-5bt in 50% yield with 85% de (entry 9 in Table 3).

Table 3. Effect of alcohol residue of phosphites on the Arbusov reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>PG</th>
<th>P(OR)₃</th>
<th>Product</th>
<th>Yield (%)</th>
<th>De (%)</th>
<th>Major isomer</th>
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<tr>
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<td>2a</td>
<td>Bz</td>
<td>4q</td>
<td>5aq</td>
<td>52</td>
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<td>trans</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>Bz</td>
<td>4r</td>
<td>5ar</td>
<td>17</td>
<td>57</td>
<td>trans</td>
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<tr>
<td>3</td>
<td>2a</td>
<td>Bz</td>
<td>4s</td>
<td>5as</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>Bz</td>
<td>4t</td>
<td>5at</td>
<td>61</td>
<td>84</td>
<td>trans</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>Bz</td>
<td>4u</td>
<td>5au</td>
<td>28</td>
<td>10</td>
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</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>Cbz</td>
<td>4q</td>
<td>5bq</td>
<td>72</td>
<td>59</td>
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<td>7</td>
<td>2b</td>
<td>Cbz</td>
<td>4r</td>
<td>5br</td>
<td>34</td>
<td>84</td>
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<td>8</td>
<td>2b</td>
<td>Cbz</td>
<td>4s</td>
<td>5bs</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>2b</td>
<td>Cbz</td>
<td>4t</td>
<td>5bt</td>
<td>50</td>
<td>85</td>
<td>cis</td>
</tr>
<tr>
<td>10</td>
<td>2b</td>
<td>Cbz</td>
<td>4u</td>
<td>5bu</td>
<td>45</td>
<td>75</td>
<td>cis</td>
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</table>

* Yield of isolated product as a mixture of diastereomers after purification by column chromatography. b The diastereomer excess was determined by H-NMR spectroscopy after purification.
2.4. Determination of stereoconfiguration

Transformation of 5bp into diethyl (S)-(pyrrolidin-2-yl)phosphonate (S)-9p shown in Eq. 6 revealed that the relative stereoconfiguration of 5bp was cis-form. Namely, removal of 2-methoxycarbonyl group of 5bp was accomplished by alkaline hydrolysis of 5bp to afford carboxylic acid 7bp, and decarboxylative methoxylation\(^9\) of 7bp, followed by reduction of N,O-acetal 8bp\(^{10}\) to give N-benzyloxy carbonyl-2-pyrrolidinylphosphonate 6bp. Successive debenzyloxy carbonylation of 6bp afforded (S)-9p\(^{3c,11}\).

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{N} \quad \text{P} \quad \text{O} \quad \text{Et} \quad \text{Et} \\
\text{Cbz} & \quad \text{OEt} \\
5bp & \quad \text{NaOH} \\
\text{NaOH} & \quad \text{H}_2\text{O} : \text{THF} = 1 : 1 \\
\text{HO}_2\text{C} & \quad \text{N} \quad \text{P} \quad \text{O} \quad \text{Et} \quad \text{EtMeO}_2\text{C} \\
\text{Cbz} & \quad \text{OEt} \\
7bp & \quad -2e (3 \text{ F/mol}) \\
\text{2,6-lutidine} & \quad \text{MeOH} \\
\text{MeO}_2\text{C} & \quad \text{N} \quad \text{P} \quad \text{O} \quad \text{Et} \quad \text{Et} \\
\text{Cbz} & \quad \text{OEt} \\
8bp & \quad 66\% \text{ yield} \\
\text{Et_3SiH, MeSO}_3\text{H} & \quad \text{CH}_2\text{Cl}_2 \\
\text{6bp} & \quad 50\% \text{ yield from 5bp} \\
\text{H}_2, \text{Pd/C} & \quad \text{MeOH} \\
\text{N} & \quad \text{P} \quad \text{O} \quad \text{Et} \quad \text{EtMeO}_2\text{C} \\
\text{Cbz} & \quad \text{H}_2\text{O} : \text{THF} \\
9bp \quad 66\% \text{ yield} \\
\text{cis} & \quad 78\% \text{ ee} \\
\end{align*}
\]

Opposite diastereoselectivity for the reaction of 2b with 4p was confirmed by transformation of cis-5bp into cis-5ap shown in Eq. 7. The major diastereomer of cis-5ap in Eq. 7 was consistent with the minor diastereomer obtained in Entry 1 of Table 1. Accordingly, 5ap shown in entry 1 in Table 1 was trans-configuration.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{N} \quad \text{P} \quad \text{O} \quad \text{Et} \quad \text{Et} \\
\text{Cbz} & \quad \text{OEt} \\
cis-5bp & \quad \text{H}_2 \\
\text{H}_2\text{O} : \text{THF} \\
cis-10bp & \quad \text{BzCl} \\
\text{MeO}_2\text{C} & \quad \text{N} \quad \text{P} \quad \text{O} \quad \text{Et} \quad \text{Et} \\
\text{Cbz} & \quad \text{OEt} \\
cis-5ap & \quad 71\% \text{ yield from cis-5bp} \quad 78\% \text{ de} \\
\end{align*}
\]

Similarly, demethoxylation of 8at\(^{10}\) obtained from 5at by hydrolysis and successively decarboxylative methoxylation smoothly proceeded to give diisopropyl N-benzyolated (R)-(pyrrolidin-2-yl)phosphonate 6at (Eq. 8).
2.5. $C_2$-Symmetrical pyrrolidine-2,5-diphosphate

$C_2$-Symmetrical pyrrolidine derivative 11ap was prepared from trans-phosphorylated $N$-benzoylproline 5ap as follows (Eq. 9); Alkaline hydrolysis of 5ap afforded carboxylic acid 7ap. Electrochemical decarboxylative methoxylation$^7$ of 7ap in methanol afforded methoxylated compound 8ap,$^{10}$ which reacted with triethyl phosphate in the presence of BF$_3$·OEt$_2$ to majorly afford trans-2,5-diphosphorylated pyrrolidine 11ap in 35% yield from 5ap.$^{12}$

\[
\begin{align*}
\text{MeO}_2\text{C}_\text{Bz} & \xrightarrow{\text{NaOH, H}_2\text{O : THF = 1 : 1}} \text{NaOH} \\
\text{P(OEt)}_3 & \xrightarrow{\text{2e (3 F/mol)}} \text{MeOH} \\
\text{BF}_3\cdot\text{OEt}_2 & \xrightarrow{\text{CH}_2\text{Cl}_2} (R,R)-11\text{ap}
\end{align*}
\]

35% yield from 5ap

3. Conclusion

We have accomplished diastereoselective introduction of phosphono groups into L-proline derivatives at the 5-position. $N$-Benzoylated L-proline derivative 2a mainly gave trans-phosphorylated products, while $N$-benzyloxy carbonylated L-proline 2b was majorly transformed into cis-phosphorylated products.

4. Experimental Section

4.1. General

$^1$H NMR spectra were measured on a JEOL JNM-AL 400 spectrometer with TMS as
an internal standard. $^{13}$C NMR spectra were measured on a JEOL JNM-AL 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-700N instrument.

All reagents and solvents were used as supplied without further purification.

4.2. Methyl $N$-protected 5-methoxy-L-prolinates 2a-f

$N$-Protected 5-methoxy-L-prolinates 2a, 2b, 2c, 2d, 2e, and 2f were known compounds.

4.3. General procedure for phosphorylation of methyl $N$-protected-5-methoxy-L-prolinates 2a-f

Under an argon atmosphere, BF$_3$·OEt$_2$ (0.246 mL, 2 mmol) was added dropwise to the solution of 2a (291 mg, 1 mmol) and triethyl phosphite 4p (332 mg, 2 mmol) in CH$_2$Cl$_2$ (10 mL) at room temperature. After stirring for 12 h, the solution was poured in brine (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography ($n$-hexane : AcOEt = 1 : 1) to afford a mixture of cis- and trans-5ap as a colorless oil (218 mg, 59%).

4.3.1. Diethyl (5R)-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5ap)

Colorless oil; $[a]_{D}^{20} = -74.3$ (c 1.1, EtOH, 43% de); $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.60-7.30 (m, 5H), 5.30 and 5.02-3.30 (s and m, 9H), 2.90-1.95 (m, 4H), 1.45-1.05 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 171.4, 136.1, 130.0, 128.2, 127.2, 62.0, 54.2, 52.6, 52.1, 30.8, 24.6, 16.3; IR (neat) 1743, 1655, 1394, 1242, 1016, 795 cm$^{-1}$; MS
[EI(+)] : m/z calcd for C₁₁H₂₄NO₆P [M]+: 369.1341, found: 369.1351; HPLC chiralpak AD column (4.6 mmϕ, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 33.7 min (trans), 38.1 min (cis).

4.3.2 Dimethyl (5R)-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5aq):
Colorless oil; [α]"20"D −102.9 (c 1.9, EtOH, 40% de); 1H-NMR (400 MHz, CDCl₃) δ 7.60-7.31 (m, 5H), 5.05-4.96 and 4.78-4.72 (2m, 1H), 4.61 (d, J=9.3Hz, 1H), 3.90-3.50 (m, 6H), 3.42-3.25 (m, 3H), 2.78-2.04 (m, 4H); 13C-NMR (100 MHz, CDCl₃) δ 176.0, 172.3, 136.0, 130.4, 128.3, 127.3, 62.1, 53.8, 53.2, 53.0, 52.2, 30.8, 24.6; IR (neat) 1743, 1655, 1375, 1246, 1061, 833 cm⁻¹; HRMS [EI (+)]: m/z calcd for C₁₅H₂₀NO₆P [M]+: 341.1028, found: 341.1020; HPLC chiralpak AD column (4.6 mmϕ, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 43.3 min (trans), 56.3 min (cis).

4.3.3. Diphenyl (5R)-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5ar)
Colorless oil; [α]"20"D −148.2 (c 0.8, EtOH, 57% de); 1H-NMR (400 MHz, CDCl₃) δ 7.93-6.75 (m, 15H), 5.88-5.29 (m, 1H), 4.93-4.59 (m, 1H), 3.82-3.70 and 3.38 (m and s, 3H), 2.93-2.03 (m, 4H); 13C-NMR (100 MHz, CDCl₃) δ 172.2, 171.7, 150.2, 135.8, 129.8, 129.6, 128.2, 127.4, 125.3, 120.2, 62.2, 55.3, 52.3, 31.0, 24.9; IR (neat) 1746, 1661, 1360, 1210, 1188, 933 cm⁻¹; MS [EI (+)]: m/z calcd for C₂₅H₂₅NO₆P [M]+: 465.1341, found: 465.1339; HPLC chiralpak AD column (4.6 mmϕ, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention
4.3.4. **Diisopropyl (5R)-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5at)**

Colorless oil; $[\alpha]_{20}^{20} -74.6$ (c 4.6, EtOH, 84% de); $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.70-7.32 (m, 5H), 5.30 and 5.10-4.20 (s and m, 4H), 3.90-3.55 and 3.37 (m and s, 3H), 2.87-1.97 (m, 4H), 1.60-1.01 (m, 12H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 172.3, 136.3, 135.9, 129.9, 128.2, 127.3, 62.0, 55.1, 53.4, 52.4, 30.8, 24.7, 23.9; IR (neat) 1747, 1655, 1387, 1242, 1018, 729 cm$^{-1}$; MS [EI(+)]: m/z calcd for C$_{19}$H$_{28}$NO$_6$P [M]$^+$: 397.1654, found: 397.1657; HPLC chiralpak AD column (4.6 mmφ, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 16.1 min (cis), 22.6 min (trans).

4.3.5. **Di-n-butyl (5R)-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5au)**

Colorless oil; $[\alpha]_{20}^{20} -73.4$ (c 4.7, EtOH, 10% de); $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.59-7.31 (m, 5H), 5.04-4.58 (m, 2H), 4.22-3.80 (m, 4H), 3.80-3.37 (m, 3H), 2.87-1.98 (m, 4H), 1.72-1.51 (m, 4H), 1.51-1.13 (m, 4H), 1.01-0.82 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 172.3, 171.2, 136.2, 130.2, 128.2, 127.3, 66.1, 62.1, 54.2, 52.1, 32.5, 30.8, 24.7, 18.6, 13.5; IR (neat) 1744, 1655, 1308, 1240, 1028, 731, 702 cm$^{-1}$; MS [EI (+)] : m/z calcd for C$_{21}$H$_{32}$NO$_6$P [M]$^+$: 425.1967, found: 425.1960; HPLC chiralpak AD column (4.6 mmφ, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 21.8 min (trans), 25.3 min (cis).
4.3.6. Diethyl

(5S)-[(N-benzyloxycarbonyl)-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5bp)
Colorless oil; [\(\alpha\)]\(_{D}^20\) +4.78 (c 1.55, EtOH, 78% de); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45-7.25 (m, 5H), 5.30-4.95 (m, 2H), 4.47-3.90 (m, 6H), 3.90-3.46 (m, 3H), 2.81-1.95 (m, 4H), 1.39-1.24 (m, 6H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.2, 153.6, 136.1, 128.4, 127.8, 67.7, 60.0, 55.8, 54.1, 52.0, 29.6, 16.3; IR (neat) 1759, 1710, 1354, 1248, 1053, 772 cm\(^{-1}\); MS [EI (+)]: \(m/z\) calcd for C\(_{18}\)H\(_{26}\)NO\(_7\)P [M]\(^+\): 399.1447, found : 399.1450; HPLC chiralpak AD column (4.6 mm\(\phi\), 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 18.8 min (cis), 25.9 min (trans).

4.3.7. Dimethyl

(5S)-[(N-benzyloxycarbonyl)-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5bq)
Colorless oil; [\(\alpha\)]\(_{D}^20\) -1.01 (c 4.10, EtOH, 59% de); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55-7.21 (m, 5H), 5.29-4.95 and 4.51-4.25 (2m, 4H), 3.87-3.47 (m, 9H), 2.80-1.85 (m, 4H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.9, 154.5, 136.0, 128.3, 128.1, 127.7, 67.6, 59.9, 53.6, 52.8, 52.0, 29.5, 26.5; IR (neat) 1757, 1701, 1354, 1252, 1055, 833 cm\(^{-1}\); MS [EI (+)]: \(m/z\) calcd for C\(_{16}\)H\(_{22}\)NO\(_7\)P [M]\(^+\): 371.1134, found : 371.1150; HPLC chiralpak AD column (4.6 mm\(\phi\), 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 26.9 min (cis), 37.1 min (trans).

4.3.8. Diphenyl

(5S)-[(N-benzyloxycarbonyl)-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5br)
Colorless oil; [\(\alpha\)]\(_{D}^20\) -43.9 (c 3.85, EtOH, 84% de); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\)
7.40-6.98 (m, 15H), 5.18 and 4.99 (2d, J = 11.7 Hz, 1.2H and 0.8H), 4.88 and 4.80 (2d, J = 9.3 and 9.2 Hz, 0.6H and 0.4H), 4.52 and 4.45 (2d, J = 9.3 Hz and 9.2 Hz, 0.4H and 0.6H), 3.75 and 3.49 (2s, 1.2H and 1.8H), 2.76-1.81 (m, 4H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 172.7, 154.3, 150.1, 135.8, 128.2, 125.2, 124.9, 120.5, 120.2, 67.6, 59.8, 52.1, 29.4, 25.4; IR (neat) 1748, 1707, 1348, 1192, 938 cm$^{-1}$; MS [EI (+)]: m/z calcd for C$_{26}$H$_{26}$NO$_7$P [M]$^+$: 495.1447, found: 495.1465; HPLC chiralpak AD column (4.6 mmΦ, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 40.0 min (trans), 48.7 min (cis).

4.3.9. Diisopropyl

(5S)-[N-benzyloxycarbonyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5bt)

Colorless oil; [α]$^\text{D}$ $^\text{20}$ $-$10.1 (c 3.6, EtOH, 85% de); $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.50-7.08 (m, 5H), 5.30-4.60 (m, 4H), 4.48-3.85 (m, 2H), 3.85-3.37 (m, 3H), 2.72-1.85 (m, 4H), 1.50-1.11 (m, 12H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 172.3, 154.7, 136.1, 128.3, 127.9, 127.8, 71.7, 67.4, 60.1, 55.3, 51.9, 24.4, 23.9, 14.1; IR (neat) 1752, 1717, 1350, 1244, 1013, 772 cm$^{-1}$; MS [EI (+)]: m/z calcd for C$_{20}$H$_{30}$NO$_7$P [M]$^+$: 427.1760, found: 427.1758; HPLC chiralpak AD column (4.6 mmΦ, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 12.8 min (cis), 17.8 min (trans).

4.3.10. Di-n-butyl

(5S)-[N-benzyloxycarbonyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5bu)

Colorless oil; [α]$^\text{D}$ $^\text{20}$ +2.4 (c 5.6, EtOH, 75% de); $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.42-7.22 (m, 5H), 5.29-4.95 and 4.48-4.25(m, 4H), 4.25-3.90 (m, 4H), 3.77-3.45 (m,
4.3.11. Diethyl [N,(2S)-di(methoxycarbonyl)pyrrolidin-5-yl]phosphonate (5cp)

Colorless oil; $[\alpha]_{D}^{20} = -6.2$ (c 0.9, EtOH, 50% de); $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 4.11-3.78 (m, 6H), 3.51-3.24 (m, 3H), 2.51-1.42 (m, 4H), 1.22-0.98 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 171.2, 154.9, 61.7, 59.7, 51.8, 47.8, 20.4, 15.8, 13.6; IR (neat) 1750, 1717, 1448, 1395, 1063, 793 cm$^{-1}$; MS [EI (+)]: $m/z$ calcd for C$_{12}$H$_{22}$NO$_7$P [M]$^+$: 323.1134, found: 323.1121; HPLC chiralcel OD-H column (4.6 mmφ, 250 mm), n-Hexane : Isopropanol = 500 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 7.31 min (cis), 8.78 min (trans).

4.3.12. Diethyl [N-tert-butoxycarbonyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5dp)

Colorless oil; $[\alpha]_{D}^{20} = -2.0$ (c 1.0, EtOH, 41% de); $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 4.42-4.01 (m, 6H), 3.82-3.62 (m, 3H), 2.49-1.70 (m, 4H), 1.66-1.01 (m, 15H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 153.8, 61.8, 51.8, 48.4, 29.5, 28.0, 16.3, 6.4; IR (neat) 1698, 1445, 1395, 1063, 793 cm$^{-1}$; MS [EI (+)]: $m/z$ calcd for C$_{13}$H$_{28}$NO$_7$P [M]$^+$: 365.1607, found: 365.1613; HPLC chiralcel OD-H column (4.6 mmφ, 250 mm), n-Hexane :
Isopropanol = 500 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 7.37 min (cis), 8.62 min (trans).

4.3.13. Diethyl [N-acetyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5ep)
Colorless oil; $[\alpha]_20^\circ$ –21.1 (c 1.1, EtOH, 15% de); $^1$H-NMR (400 MHz, CDCl$_3$) δ 4.76-4.08 (m, 6H), 3.81-3.68 (m, 3H), 2.84-1.90 (m, 7H), 1.39-1.24 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 171.4, 170.6, 59.4, 56.6, 55.0, 52.0, 27.7, 22.2, 16.3; IR (neat) 1755, 1665, 1406, 1244, 1063, 799 cm$^{-1}$; MS [EI (+)]: m/z calcd for C$_{12}$H$_{22}$NO$_6$P [M]$^+$: 307.1185, found: 307.1191; HPLC chiracel OD-H column (4.6 mm$\phi$, 250 mm), n-Hexane : Isopropanol = 500 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 6.9 min (cis), 8.0 min (trans).

Colorless oil; $[\alpha]_20^\circ$ –21.1 (c 1.1, EtOH, 29% de); $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.80 (q, $J$=12.0, 8.6 Hz, 2H), 7.35 and 7.29 (2d, $J$=8.1, 7.6 Hz, 2H), 4.42-3.76 (m, 6H), 3.75 (d, $J$=3.2 Hz, 3H) 2.65-1.93 (m, 7H) 1.37-1.15 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 171.4, 170.6, 59.4, 56.6, 55.0, 52.0, 27.7, 22.2, 16.3; IR (neat) 1755, 1665, 1406, 1244, 1063, 799 cm$^{-1}$; MS [EI (+)]: m/z calcd for C$_{12}$H$_{22}$NO$_6$P [M]$^+$: 307.1185, found: 307.1191; HPLC chiracel AD column (4.6 mm$\phi$, 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254nm, flow rate: 1.0 mL/min, retention time: 31.0 min (trans), 35.2 min (cis).
4.4. Decarboxylation of 5bp

To a solution of 5bp (1.945 g, 5.27 mmol, 78% de) in a mixture of THF and water (1 : 1, 50 mL) was added NaOH (0.422 g, 10.54 mmol). After stirred for 12 h at room temperature, to the resulting mixture was acidified by conc. HCl. Organic portion was extracted with ethyl acetate (3 x 30 mL). Combined organic layer was dried over MgSO4 and then the solvent was removed under reduced pressure to give the corresponding acid 7bp.

The 7bp and 2,6-lutidine (0.798 mL, 6.85 mmol) were placed in a beaker type cell containing a stirring bar. Methanol (50 mL) was added and the mixture was stirred at 0 °C. Graphite anode (10 cm × 5 cm) and platinum cathode (10 cm × 5 cm) were fitted and a 3 F/mol of electricity was passed through. The solvent was evaporated and to the residue was added saturated aqueous NaCl (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layer was dried using anhydrous MgSO4 and filtered. The solvent was removed under vacuo to give the corresponding methoxylated compound 8bp.

To a stirred solution of 8bp (0.731 g, 2.14 mmol) in CH2Cl2 (15 mL) was added Et3SiH (0.410 mL, 2.57 mmol) and MeSO3H (0.208 mL, 3.21 mmol) under nitrogen. After stirring for 4 h at room temperature, to the resulting mixture was added saturated aqueous NaHCO3 (20 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layer was dried using anhydrous MgSO4 and filtered. The solvent was removed under vacuo and the residue was purified using a silica gel column chromatography to give diethyl N-benzylopyrrolidine-(2R)-phosphonate (6bp) in 50% yield from 5bp.
4.4.1. Diethyl (2S)-(N-benzyloxycarbonylpyrrolidin-2-yl)phosphonate (6bp)

Colorless oil; \([\alpha]^{20}_{D} +25.3 \ (c \ 2.3, \text{EtOH}, \ 79\% \ \text{ee})\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.46-7.10 (m, 5H), 5.23-5.01 (m, 2H), 4.38-3.83 (m, 5H), 3.65-3.33 (m, 2H), 2.31-1.62 (m, 4H), 1.38-1.11 (m, 6H); \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.7, 136.4, 128.1, 127.7, 127.6, 66.8, 61.9, 53.3, 46.4, 25.2, 16.1, 6.2; IR (neat) 1717, 1699, 1362, 1244, 1058, 768 cm\(^{-1}\); MS [EI (+)]: \(m/z\) calcd for C\(_{16}\)H\(_{24}\)NO\(_5\)P [M]\(^+\): 341.1392, found : 341.1390; HPLC chiralcel OJ-H column (4.6 mm\(\Phi\), 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 14.2 min (S), 19.7 min (R).

4.5. Deprotection of 6bp

Under a hydrogen atmosphere, to a solution of 6bp (2.148 g, 6.29 mmol) and triethylamine (0.877 mL, 6.29 mmol) in methanol (20 mL) was added 10% palladium-carbon (0.107 g). After stirring at room temperature for 12 h, the resulting mixture was filtered by celite. The filtrate was concentrated under reduced pressure to give diethyl (2S)-(pyrrolidin-2-yl)phosphonate (9p)\(^{3c}\) in 66% yield.

4.5.1. Diethyl (2S)-(pyrrolidin-2-yl)phosphonate (9p)

Colorless oil; \([\alpha]^{20}_{D} +6.82 \ (c \ 1.45, \text{EtOH}, \ 78\% \ \text{ee})\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.25-4.08 (m, 4H), 3.40-3.27 (m, 1H), 3.11-3.00 (m, 1H), 3.00-2.89 (m, 1H), 2.50-2.30 (s, 1H), 2.12-1.70 (m, 4H), 1.34 (t, \(J=6.8\ \text{Hz}, \ 6\)H); MS [EI (+)]: \(m/z\) calcd for C\(_8\)H\(_{18}\)NO\(_3\)P [M]\(^+\): 207.1025, found : 207.1012; HPLC chiralcel AY-H column (4.6 mm\(\Phi\), 250 mm), n-Hexane : EtOH = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 27.1 min (R), 46.9 min (S).
4.6. Preparation of diisopropyl (2R)-(N-benzylopyrrolidin-2-yl)phosphonate [(R)-6at]

In a similar manner to preparation of 6bp from 5bp, diisopropyl (5R)-[N-benzyol-(2S)-methoxycarbonylpyrrolidin-2-yl]phosphonate (5at) was transformed into diisopropyl (2R)-(N-benzylopyrrolidin-2-yl)phosphonate [(R)-6at] in 32% yield.

4.6.1. Diisopropyl (2R)-(N-benzylopyrrolidin-2-yl)phosphonate [(R)-6at]

Colorless oil; \([\alpha]^{20}_{D} -49.4\) (c 1.2, EtOH, 83% ee); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.82-7.31 (m, 5H), 4.91 and 4.29-4.05 (s and m, 4H), 3.83-3.31 (m, 3H), 2.38-1.65 (m, 4H), 1.45-1.12 (m, 6H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.3, 130.3, 128.5, 128.2, 127.5, 62.2, 52.5, 50.3, 25.6, 25.1, 16.3; IR (neat) 1640, 1397, 1246, 1028, 968, 791 cm\(^{-1}\); MS [EI (+)]: \(m/z\) calcd for C\(_{15}\)H\(_{22}\)NO\(_4\)P \([\text{M}^+]\): 311.1287, found : 311.1312; HPLC chiralcel OJ-H column (4.6 mm\(\phi\), 250 mm), n-Hexane : Isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 17.0 min (R), 28.9 min (S).

4.7. Preparation of C\(_2\)-symmetrical (N-benzylopyrrolidin-2,5-diyl)phosphonate

In a similar manner to preparation of 8bp from 5bp, diethyl (5R)-[N-benzyol-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5ap) was transformed into diethyl (2R)-[N-benzyol-5-methoxypyrrolidin-2-yl]phosphonate (8ap). Under an argon atmosphere, BF\(_3\)-OEt\(_2\) (0.246 mL, 2 mmol) was added dropwise to the solution of 8ap (341 mg, 1 mmol) and triethyl phosphite 4p (332 mg, 2 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at room temperature. After stirred for 12 h, the solution was poured in saturated aqueous NaCl (10 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layer was dried over MgSO\(_4\) and the solvent removed under reduced pressure.
The residue was purified by silica gel column chromatography (AcOEt : methanol = 10 : 1) to afford 11ap as a colorless oil (259 mg, 35% yield from 5ap).

4.7.1. Tetraethyl (2R,5R)-[N-benzoylpyrrolidin-2,5-diyl]phosphonate [(R,R)-11ap]
yellow oil; [α]$_{D}^{20}$ −25.5 (c 1.4, EtOH, (S,S): (R,R): meso=26: 68: 6); $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.75-7.33 (m, 5H), 4.78-3.52 (m, 10H), 2.81-2.00 (m, 4H), 1.45-0.88 (m, 12H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 171.3, 136.7, 130.4, 128.1, 128.1, 62.2, 52.2, 26.9, 16.4; IR (neat) 1651, 1362, 1240, 1019, 963 cm$^{-1}$; MS [EI(+)]: m/z calcd for C$_{19}$H$_{31}$NO$_7$P$_2$ [M$^+$]: 447.1576, found : 447.1573; HPLC AS coating type column (4.6 mmφ, 500 mm), n-Hexane : EtOH = 10 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 30.5 min (S,S), 33.4min (R,R), 50.9 min (meso).

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References and notes


7. Recoveries of starting methoxylated compounds caused low yields.

8. In case of N-t-butoxycarbonylated proline 2d, deprotection of the t-butoxycarbonyl group occurred.


10. Diastereoselectivity in these decarboxylative methoxylation was not clear.

11. Hydrolysis of enantiomerically enriched (S)-9p and successive recrystallization of the obtained acid might afford enantiomerically pure
(S)-(pyrrolidine-2-yl)phosphonic acid.\textsuperscript{3f,h}

12. Although similarly 8at was transformed into the corresponding tetraisopropyl ester, its stereochemistry could not be determined.