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Facile synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate from L-proline

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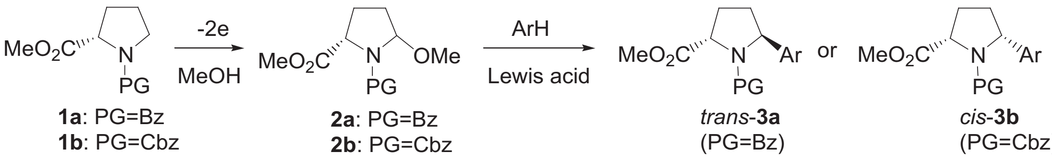
ABSTRACT

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*-benzyloxycarbonyl-L-prolinate reacted with phosphite to give *cis*-substituted products, which could be easily transformed into (*R*)-(pyrrolidin-2-yl)phosphonates.

1. Introduction

Optically active α-amino phosphonates and their derivatives are biologically important compounds structurally analogous to α-amino acids.[1] A lot of useful methods have been developed for the diastereo- or enantio-selective synthesis of acyclic α-amino phosphonates.[2] 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.[3] These methods use (+)- or (−)-2-hydroxy-3-pinenone,[3b] (+)-camphor,[3c] (*R*)- or (*S*)-phenylglycinol,[3d,e] L-menthol,[3f] (*S*)-(+)-*p*-toluenesulfinamide[3g] 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).[4]



1a: PG=Bz
1b: PG=Cbz
2a: PG=Bz
2b: PG=Cbz
trans-**3a** (PG=Bz)
cis-**3b** (PG=Cbz)

(1)

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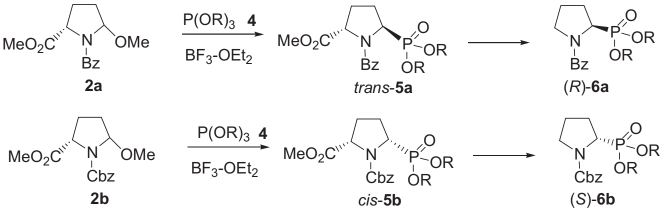
We wish herein to report the effect of *N*-acyl groups on the diastereoselective introduction of phosphonate groups into L-proline derivatives **2** at the 5-position and its application to synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate **6** (Scheme 1).

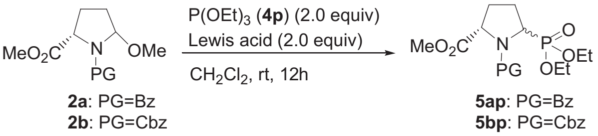


Scheme 1.

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**[5] into *N*-benzoylated or *N*-benzyloxycarbonylated 5-methoxylated L-prolinate[6] **2a** or **2b** (Eq. 2). The results are shown in Table 1. In the case of **2a**, TiCl$_4$ mediated α-phosphorylation in good yield but with low diastereoselectivity (entry 1). BF$_3$·OEt$_2$ promoted the phosphorylation in moderate diastereoselectivity (entry 2), while SnCl$_4$ did not work as an effective Lewis acid (entry 3).[7] Using Cu(OTf)$_2$, AlCl$_3$, Hf(OTf)$_4$, or In(OTf)$_3$ as Lewis acid afforded phosphorylated product **5ap** in low yields (entries 4–7).[7] In the case of **2b**, similar tendency for tested Lewis acids was observed (entries 8–14), and BF$_3$·OEt$_2$ afforded the best result (entry 9).



(2)

Table 1
Effect of Lewis acid on the Arbusov reaction

Entry	Substrate	PG	Lewis acid	Product	Yield[a] (%)	de[b] (%)	Major isomer
1[c]	**2a**	Bz	TiCl$_4$	**5ap**	66	26	trans
2	**2a**	Bz	BF$_3$·OEt$_2$	**5ap**	59	43	trans
3	**2a**	Bz	SnCl$_4$	**5ap**	0	—	—
4	**2a**	Bz	Cu(OTf)$_2$	**5ap**	27	30	trans
5	**2a**	Bz	AlCl$_3$	**5ap**	37	53	trans
6	**2a**	Bz	Hf(OTf)$_4$	**5ap**	32	15	trans
7	**2a**	Bz	In(OTf)$_3$	**5ap**	14	32	trans
8[c]	**2b**	Cbz	TiCl$_4$	**5bp**	49	51	cis
9	**2b**	Cbz	BF$_3$·OEt$_2$	**5bp**	45	78	cis
10	**2b**	Cbz	SnCl$_4$	**5bp**	0	—	—
11	**2b**	Cbz	Cu(OTf)$_2$	**5bp**	35	55	cis
12	**2b**	Cbz	AlCl$_3$	**5bp**	44	29	cis
13	**2b**	Cbz	Hf(OTf)$_4$	**5bp**	33	61	cis
14	**2b**	Cbz	In(OTf)$_3$	**5bp**	26	70	cis

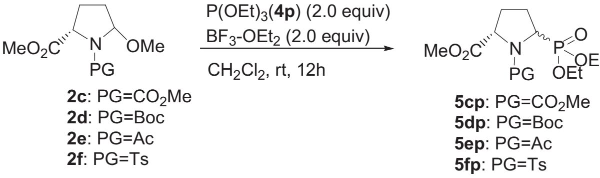
[a] Yield of isolated product as a mixture of diastereomers after purification by column chromatography.

[b] The diastereomer excess was determined by ^{1}H NMR spectroscopy after purification.

[c] 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 BF$_3$·OEt$_2$ (Eq. 3). The results are shown in Table 2. Diastereoselectivities of phosphorylated products **5cp** and **5dp**, which were obtained from *N*-methoxycarbonylated proline **2c** and *N*-*tert*-butoxycarbonylated proline **2d**[8] (entries 1 and 2 in Table 2) lowered compared with that of *N*-benzyloxycarbonylated 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).



(3)

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

Entry	Substrate	PG	Product	Yield[a] (%)	de[b] (%)	Major isomer
1	**2c**	CO$_2$Me	**5cp**	68	50	nd
2	**2d**	Boc	**5dp**	20	41	nd
3	**2e**	Ac	**5ep**	60	15	nd
4	**2f**	Ts	**5fp**	98	29	nd

[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.

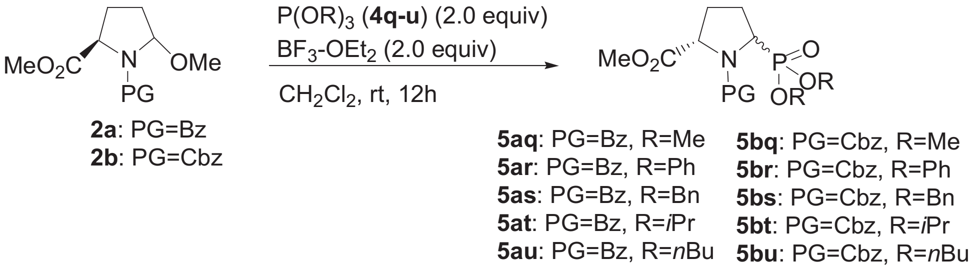
2.3. Effect of ester group in phosphite

Next, we investigated effect of ester group of phosphites on the diastereoselectivity for the Arbusov reaction of **2a** or **2b** in the presence of BF$_3$·OEt$_2$ (Eq. 4). 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 phosphite **4s**, and tri-*n*-butyl phosphite **4u** were ineffective (entries 2, 3, and 5 in Table 3),[7] triisopropyl phosphite **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*-benzyloxycarbonylated proline **2b**, similar tendencies were observed with respect to effect of phosphites (entries 6–10 in Table 3).[7] 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).

2.4. Determination of stereoconfiguration

Transformation of **5bp** into diethyl (*S*)-(pyrrolidin-2-yl)phosphonate (*S*)-**9p** shown in Eq. 5 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*-benzyloxycarbonyl-2-pyrrolidinylphosphonate **6bp**. Successive debenzyloxycarbonylation of **6bp** afforded (*S*)-**9p**.[3c,11]

Opposite diastereoselectivity for the reaction of **2b** with **4p** was confirmed by transformation of *cis*-**5bp** into *cis*-**5ap** shown in Eq. 6. The major diastereomer of *cis*-**5ap** in Eq. 6 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.



2a: PG=Bz
2b: PG=Cbz

5aq: PG=Bz, R=Me
5ar: PG=Bz, R=Ph
5as: PG=Bz, R=Bn
5at: PG=Bz, R=*i*Pr
5au: PG=Bz, R=*n*Bu

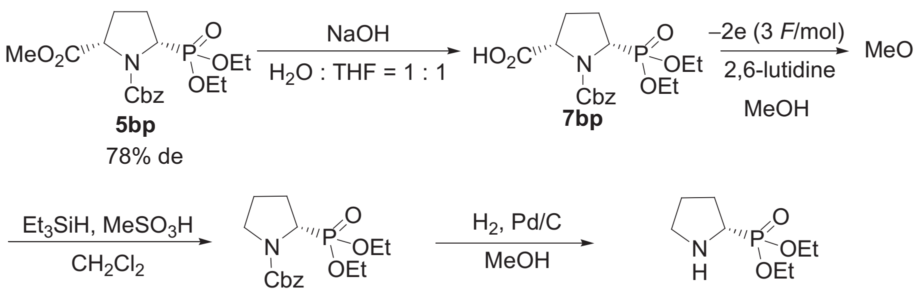
5bq: PG=Cbz, R=Me
5br: PG=Cbz, R=Ph
5bs: PG=Cbz, R=Bn
5bt: PG=Cbz, R=*i*Pr
5bu: PG=Cbz, R=*n*Bu

(4)

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

Entry	Substrate	PG	P(OR)$_3$		Product	Yield[a] (%)	de[b] (%)	Major isomer
			R					
1	**2a**	Bz	Me	**4q**	**5aq**	52	40	trans
2	**2a**	Bz	Ph	**4r**	**5ar**	17	57	trans
3	**2a**	Bz	Bn	**4s**	**5as**	0	—	—
4	**2a**	Bz	*i*-Pr	**4t**	**5at**	61	84	trans
5	**2a**	Bz	*n*-Bu	**4u**	**5au**	28	10	trans
6	**2b**	Cbz	Me	**4q**	**5bq**	72	59	cis
7	**2b**	Cbz	Ph	**4r**	**5br**	34	84	cis
8	**2b**	Cbz	Bn	**4s**	**5bs**	0	—	—
9	**2b**	Cbz	*i*-Pr	**4t**	**5bt**	50	85	cis
10	**2b**	Cbz	*n*-Bu	**4u**	**5bu**	45	75	cis

[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.



5bp
78% de

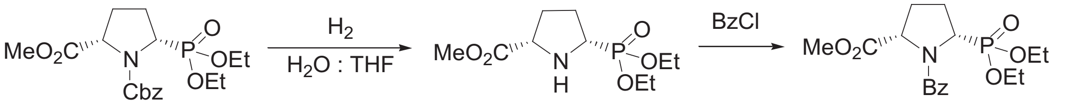
7bp

8bp

6bp
50% yield from **5bp**

(*S*)-**9p**
78% ee

(5)



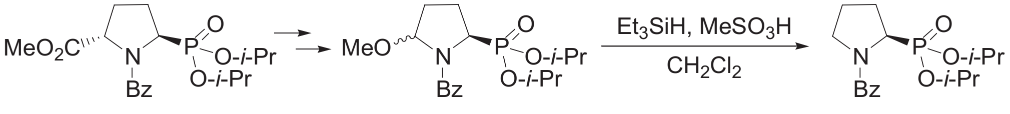
cis-**5bp**
78% de

cis-**10bp**

cis-**5ap**
78% de
71% yield from *cis*-**5bp**

(6)

Similarly, demethoxylation of **8at**[10] obtained from **5at** by hydrolysis and successively decarboxylative methoxylation smoothly proceeded to give diisopropyl *N*-benzoylated (*R*)-(pyrrolidin-2-yl) phosphonate **6at** (Eq. 7).



(7)

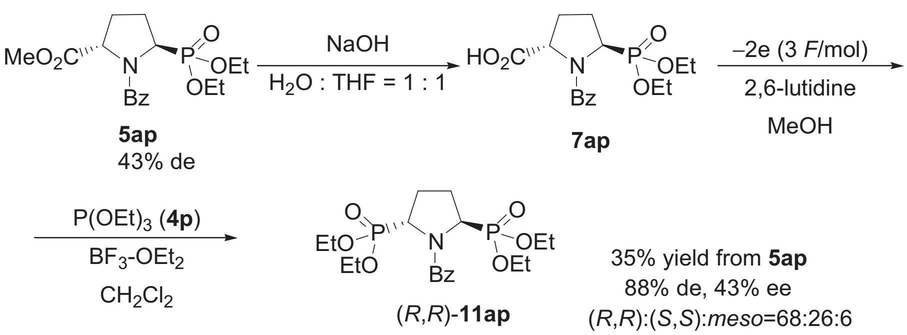
5at (84% de)

8at

(*R*)-**6at** (32% yield from **5at**, 83% ee)

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. 8);



(8)

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 phosphite in the presence of $BF_3\cdot OEt_2$ to majorly afford *trans*-2,5-diphosphorylated pyrrolidine **11ap** in 35% yield from **5ap**.[12]

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*-benzyloxycarbonylated L-proline **2b** was majorly transformed into *cis*-phosphorylated products.

4. Experimental section

4.1. General

^1H-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**,[6b] **2b**,[6e] **2c**,[6a] **2d**,[6c] **2e**,[6d] and **2f**[5b] were known compounds.

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

Under an argon atmosphere, $BF_3\cdot OEt_2$ (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_2Cl_2 (10 mL) at room temperature. After stirring for 12 h, the solution was poured in brine (10 mL) and extracted with CH_2Cl_2 (3×10 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; $[\alpha]_D^{20}$ −74.3 (*c* 1.1, EtOH, 43% de); ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{17}H_{24}NO_6P$ $[M]^+$: 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), 38.1min (cis).

*4.3.2. Dimethyl (5R)-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (**5aq**).* Colorless oil; $[\alpha]_D^{20}$ −102.9 (*c* 1.9, EtOH, 40% de); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.31 (m, 5H), 5.05–4.96 and 4.78–4.72 (2m, 1H), 4.61 (d, *J*=9.3 Hz, 1H), 3.90–3.50 (m, 6H), 3.42–3.25 (m, 3H), 2.78–2.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{20}NO_6P$ $[M]^+$: 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; $[\alpha]_D^{20}$ −148.2 (*c* 0.8, EtOH, 57% de); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, 1273, 1210, 1188, 933 cm^{-1}; MS [EI (+)]: *m/z* calcd for $C_{25}H_{25}NO_6P$ $[M]^+$: 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 time:49.2 min (trans), 58.2 min (cis).

*4.3.4. Diisopropyl (5R)-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (**5at**).* Colorless oil; $[\alpha]_D^{20}$ −74.6 (*c* 4.6, EtOH, 84% de); ^1H 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 $C_{19}H_{28}NO_6P$ $[M]^+$: 397.1654, found: 397.1657; 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: 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; $[\alpha]_D^{20}$ −73.4 (*c* 4.7, EtOH, 10% de); ^1H 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 $C_{21}H_{32}NO_6P$ $[M]^+$: 425.1967, found: 425.1960; 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: 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{18}H_{26}NO_7P$ $[M]^+$: 399.1447, found: 399.1450; 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: 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{16}H_{22}NO_7P$ $[M]^+$: 371.1134, found: 371.1150; 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: 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, $CDCl_3$) δ 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 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 $C_{26}H_{26}NO_7P$ $[M]^+$: 495.1447, found: 495.1465; 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: 40.0 min (trans), 48.7 min (cis).

*4.3.9. Diisopropyl (5S)-[N-benzyloxycarbonyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (**5bt**).* Colorless oil; $[\alpha]_D^{20}$ −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 $C_{20}H_{30}NO_7P$ $[M]^+$: 427.1760, found: 427.1758; 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: 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; $[\alpha]_D^{20}$ +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, 3H), 2.81–1.85 (m, 4H), 1.70–1.56 (m, 2H), 1.56–1.28 (m, 2H), 0.93–0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.4, 136.0, 128.2, 127.9, 127.5, 66.9, 65.6, 59.9, 54.8, 51.8, 32.4, 29.4, 26.5, 18.5, 13.4; IR (neat) 1759, 1717, 1352, 1248, 1030, 752 cm^{-1}; MS [EI (+)]: *m/z* calcd for $C_{22}H_{34}NO_7P$ $[M]^+$: 455.2073, found: 455.2055.

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: 11.9 min (cis), 18.4 min (trans).

*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, $CDCl_3$) δ 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, $CDCl_3$) δ 171.2, 154.9, 61.7, 59.7, 52.2, 51.5, 47.8, 20.4, 15.8, 13.6; IR (neat) 1750, 1717, 1448, 1375, 1049, 776 cm^{-1}; MS [EI (+)]: *m/z* calcd for $C_{12}H_{22}NO_7P$ $[M]^+$: 323.1134, found: 323.1121; HPLC chiracel OD-H column (4.6 mmϕ, 250 mm), *n*-hexane/isopropanol=500:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 7.31 min (cis), 8.78 min (trans).

*4.3.12. Diethyl [N-tert-buthoxycarbonyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (**5dp**).* Colorless oil; $[\alpha]_D^{20}$ −2.0 (*c* 1.0, EtOH, 41% de); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{28}NO_7P$ $[M]^+$: 365, 1607, found: 365.1613; HPLC chiracel OD-H column (4.6 mmϕ, 250 mm), *n*-hexane/isopropanol=500:1, wavelength: 254 nm, 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; $[\alpha]_D^{20}$ −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 $C_{12}H_{22}NO_6P$ $[M]^+$: 307.1185, found: 307.1191; HPLC chiracel OD-H column (4.6 mmϕ, 250 mm), *n*-hexane/isopropanol=500:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 6.9 min (cis), 8.0 min (trans).

*4.3.14. Diethyl [(2S)-methoxycarbonyl-N-p-toluenesulfonylpyrrolidin-5-yl]phosphonate (**5fp**).* Colorless oil; $[\alpha]_D^{20}$ −21.1 (*c* 1.1, EtOH, 29% de); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (q, *J*=12.0 and 8.6 Hz, 2H), 7.35 and 7.29 (2d, *J*=8.1 and 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 $C_{12}H_{22}NO_6P$ $[M]^+$: 307.1185, found: 307.1191; HPLC chiracel AD column (4.6 mmϕ, 250 mm), *n*-hexane/isopropanol=10:1, wavelength: 254 nm, 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** (1.945g, 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 (3×30 mL). Combined organic layer was dried over $MgSO_4$ 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 (3×50 mL) and the combined organic layer was dried over 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 CH_2Cl_2 (15 mL) was added Et_3SiH (0.410 mL, 2.57 mmol) and $MeSO_3H$ (0.208 mL, 3.21 mmol) under nitrogen. After stirring for 4 h at room temperature, to the resulting mixture was added saturated aqueous

$NaHCO_3$ (20 mL). The mixture was extracted with ethyl acetate (3×50 mL) and the combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under *v*acuo and the residue was purified using a silica gel column chromatography to give diethyl *N*-benzoylpyrrolidine-(2*R*)-phosphonate (**6bp**) in 50% yield from **5bp**.

*4.4.1. Diethyl (2S)-(N-benzyloxycarbonylpyrrolidin-2-yl)phosphonate (**6bp**).* Colorless oil; $[\alpha]_D^{20}$ +25.3 (*c* 2.3, EtOH, 79% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{16}H_{24}NO_5P$ $[M]^+$: 341.1392, found: 341.1390; HPLC Chiralcel OJ-H column (4.6 mmϕ, 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 (2*S*)-(pyrrolidin-2-yl)phosphonate (**9p**)[3c] in 66% yield.

*4.5.1. Diethyl (2S)-(pyrrolidin-2-yl)phosphonate (**9p**).* Colorless oil; $[\alpha]_D^{20}$ +6.82 (*c* 1.45, EtOH, 78% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 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 Hz, 6H); MS [EI (+)]: *m*/*z* calcd for $C_8H_{18}NO_3P$ $[M]^+$: 207.1025, found: 207.1012; HPLC Chiralcel AY-H column (4.6 mmϕ, 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 (2*R*)-(*N*-benzoylpyrrolidin-2-yl)phosphonate [(*R*)-6at]

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

*4.6.1. Diisopropyl (2R)-(N-benzoylpyrrolidin-2-yl)phosphonate [(R)-**6at**].* Colorless oil; $[\alpha]_D^{20}$ −49.4 (*c* 1.2, EtOH, 83% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{22}NO_4P$ $[M]^+$: 311.1287, found: 311.1312; HPLC Chiralcel OJ-H column (4.6 mmϕ, 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*-benzoylpyrrolidin-2,5-diyl)phosphonate

In a similar manner to preparation of **8bp** from **5bp**, diethyl (5*R*)*-[N-benzoyl-(2S)-methoxycarbonylpyrrolidin-*5*-yl]phosphonate* (**5ap**) was transformed into diethyl (2*R*)-[*N*-benzoyl-5-methoxypyrrolidin-2-yl]phosphonate (**8ap**). Under an argon atmosphere, $BF_3 \cdot OEt_2$ (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_2Cl_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_2Cl_2 (3×20 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; $[\alpha]_D^{20}$ −25.5 (*c* 1.4, EtOH, (*S*,*S*):(*R*,*R*):*meso*=26:68:6); ^1H 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 $C_{19}H_{31}NO_7P_2$ $[M]^+$: 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*), 33.4 min (*R*,*R*), 50.9 min (*meso*).

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