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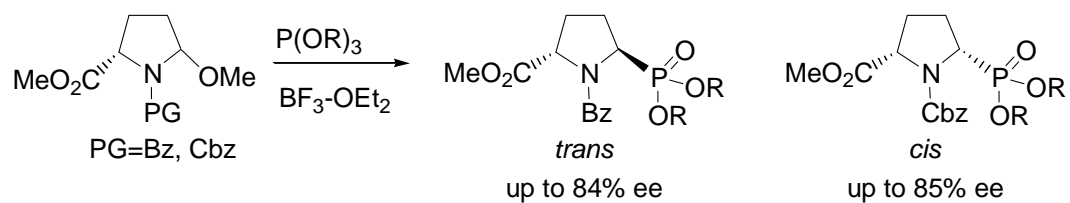
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Facile synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate from L-proline

Shigeo Hirata, Masami Kuriyama, Osamu Onomura*

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

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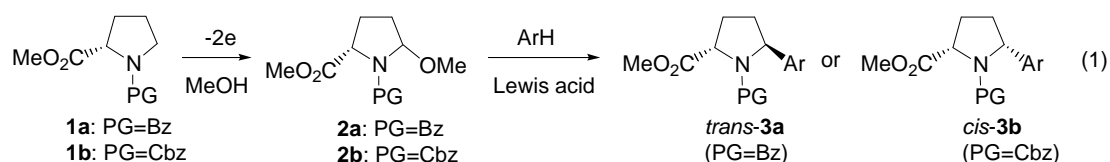
We wish herein to report the effect of N-acyl groups on the diastereoselective introduction of phosphonate groups into L-proline derivatives **2** at the 5-position and its application to synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate **6** (Scheme 1).
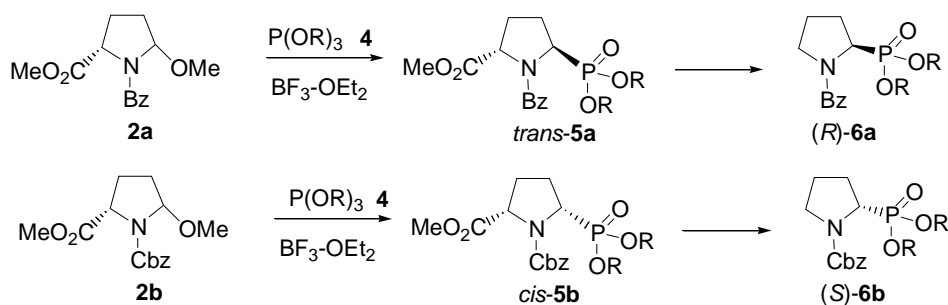
Scheme 1.

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. 3). 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).
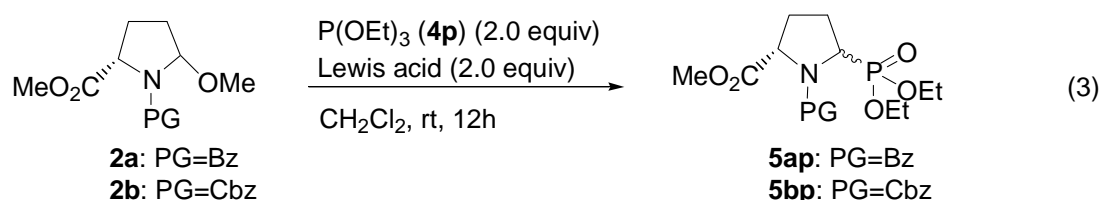

Table 1. Effect of Lewis acid on the Arbusov reaction

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*-ptotecting group on the diastereoselectivity for the Arbusov reaction of **2c-f** with **4p** in the presence of $BF_3 \cdot OEt_2$ (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*-*t*-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).
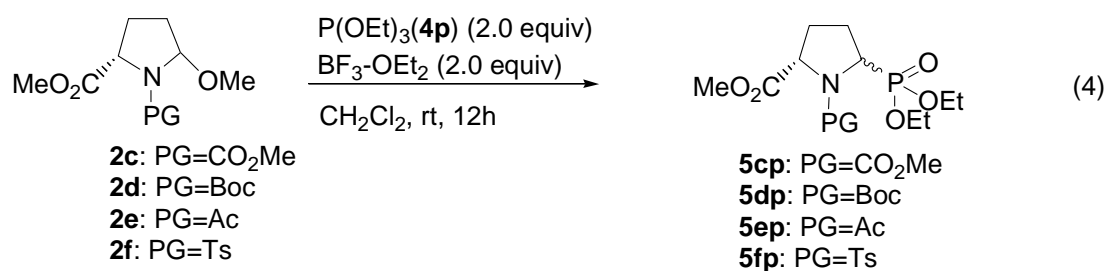
$$
\begin{array}{c}
\text{MeO}_2\text{C} \overset{\text{N}}{\underset{\text{PG}}{\diagdown}} \text{OMe} \quad \xrightarrow[\begin{array}{c}\text{BF}_3\text{-OEt}_2 \text{ (2.0 equiv)} \\ \text{CH}_2\text{Cl}_2, \text{ rt, 12h}\end{array}]{\text{P(OEt)}_3(\textbf{4p}) \text{ (2.0 equiv)}} \quad \text{MeO}_2\text{C} \overset{\text{N}}{\underset{\text{PG}}{\diagdown}} \overset{\text{O}}{\underset{\text{OEt}}{\text{P}}} \text{OEt}
\end{array} \quad (4)
$$

2c: PG=CO₂Me
2d: PG=Boc
2e: PG=Ac
2f: PG=Ts

5cp: PG=CO₂Me
5dp: PG=Boc
5ep: PG=Ac
5fp: PG=Ts

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

Entry	Substrate	PG	Product	Yield (%)[a]	De (%)[b]	Major isomer
1	**2c**	CO₂Me	**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 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 $BF_3 \cdot OEt_2$ (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 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).
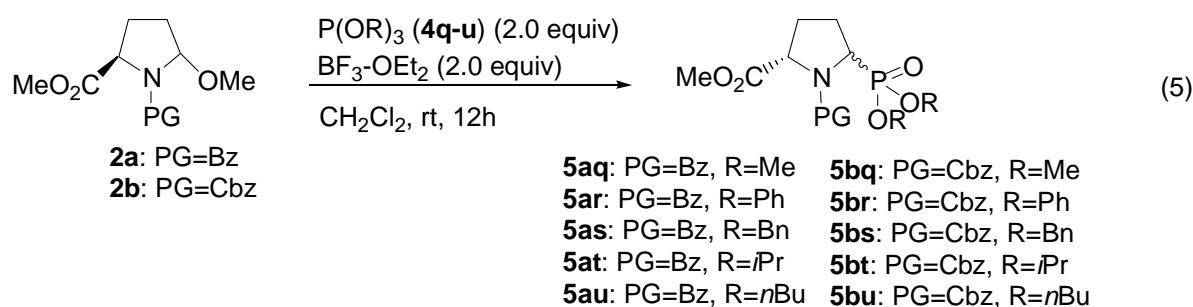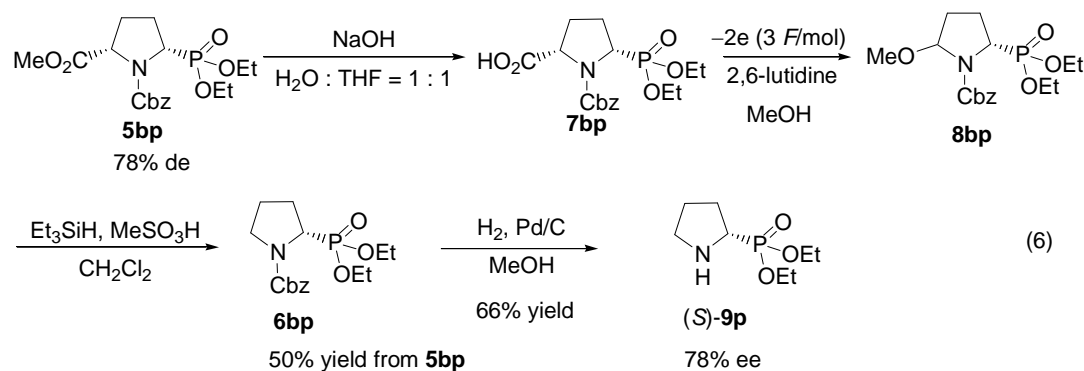

$$\text{2a: PG=Bz} \qquad \text{2b: PG=Cbz}$$

5aq: PG=Bz, R=Me   **5bq**: PG=Cbz, R=Me
5ar: PG=Bz, R=Ph   **5br**: PG=Cbz, R=Ph
5as: PG=Bz, R=Bn   **5bs**: PG=Cbz, R=Bn
5at: PG=Bz, R=*i*Pr   **5bt**: PG=Cbz, R=*i*Pr
5au: PG=Bz, R=*n*Bu   **5bu**: PG=Cbz, R=*n*Bu

(5)

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

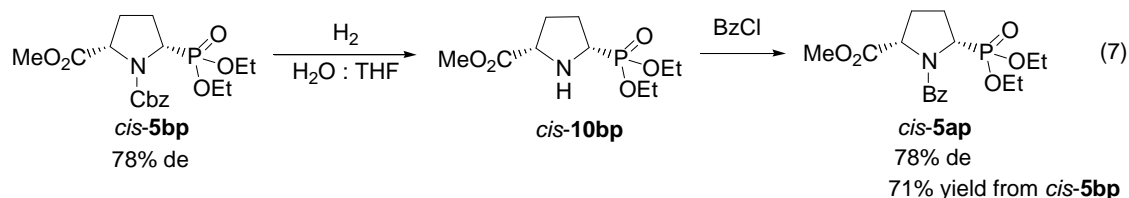| Entry	Substrate	PG	P(OR)$_3$ R		Product	Yield (%)[a]	De (%)[b]	Major isomer
1	**2a**	Bz	Me	**4q**	**5aq**	52	40	*trans*
2	**2a**	Bz	Ph	**4r**	**5ar**	17	57	*trans*
3	**2a**	Bz	Bn	**4s**	**5as**	0	-	-
4	**2a**	Bz	*i*-Pr	**4t**	**5at**	61	84	*trans*
5	**2a**	Bz	*n*-Bu	**4u**	**5au**	28	10	*trans*
6	**2b**	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.
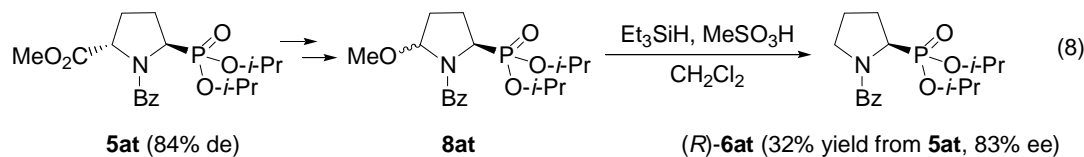
2.4. Determination of stereoconfiguration

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*-benzyloxycarbonyl-2-pyrrolidinylphosphonate **6bp**. Successive debenzyloxycarbonylation of **6bp** afforded (*S*)-**9p**.[3c,11]

MeO₂C group image with reactions:

5bp 78% de → NaOH / H₂O : THF = 1 : 1 → **7bp** → −2e (3 *F*/mol) / 2,6-lutidine / MeOH → **8bp**

Et₃SiH, MeSO₃H / CH₂Cl₂ → **6bp** 50% yield from **5bp** → H₂, Pd/C / MeOH / 66% yield → (*S*)-**9p** 78% ee   (6)

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.

cis-**5bp** 78% de → H₂ / H₂O : THF → *cis*-**10bp** → BzCl → *cis*-**5ap** 78% de / 71% yield from *cis*-**5bp**   (7)

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. 8).

$$\text{5at (84\% de)} \xrightarrow{\quad} \text{8at} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Et}_3\text{SiH, MeSO}_3\text{H}} (R)\text{-6at (32\% yield from 5at, 83\% ee)} \tag{8}$$

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 phosphite in the presence of BF$_3$·OEt$_2$ to majorly afford *trans*-2,5-diphosphorylated pyrrolidine **11ap** in 35% yield from **5ap**.[12]
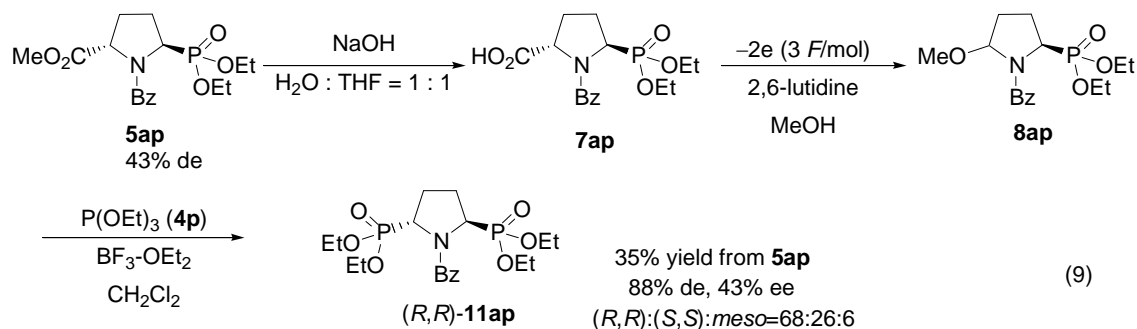
3. Conclusion

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

^{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**,[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$_3$·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; $[\alpha]^{20}_{D}$ −74.3 (*c* 1.1, EtOH, 43% de); ^{1}H-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; $[\alpha]^{20}_D$ −102.9 (*c* 1.9, EtOH, 40% de); ^{1}H-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*=9.3Hz, 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; $[\alpha]^{20}_D$ −148.2 (*c* 0.8, EtOH, 57% de); ^{1}H-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; $[\alpha]^{20}_D$ −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; $[\alpha]^{20}_D$ −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; $[\alpha]^{20}_D$ +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$_7$P [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; $[\alpha]^{20}_D$ −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$_7$P [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; $[\alpha]^{20}_D$ −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=11.7Hz, 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=9.3Hz and 9.2Hz, 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]^{20}$_D$ −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]^{20}$_D$ +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$_7$P [M]$^+$: 455.2073, found : 455.2055; HPLC chiralpak AD column (4.6 mmφ, 250 mm), *n*-Hexane : Isopropanol = 10 : 1, wavelength: 254nm, 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; [α]$^{20}_D$ −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$_7$P [M]$^+$: 323.1134, found: 323.1121; HPLC chiracel 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-buthoxycarbonyl-(2S)-methoxycarbonylpyrrolidin-5-yl]phosphonate (5dp)

Colorless oil; [α]$^{20}_D$ −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$_7$P [M]$^+$: 365.1607, found: 365.1613; HPLC chiracel 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; $[\alpha]^{20}_{D}$ −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 mmφ, 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*).

4.3.14. Diethyl [(2S)-methoxycarbonyl-N-p-toluenesulfonylpyrrolidin-5-yl]phosphonate (5fp)

Colorless oil; $[\alpha]^{20}_{D}$ −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 mmφ, 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** (1.945g, 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 x 30mL). 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 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 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 x 50 mL) and the combined organic layer was dried using anhydrous $MgSO_4$ and filtered. The solvent was removed under *vacuo* 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; $[\alpha]^{20}_D$ +25.3 (*c* 2.3, EtOH, 79% ee); ^{1}H-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$_5$P [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; $[\alpha]^{20}_D$ +6.82 (*c* 1.45, EtOH, 78% ee); ^{1}H-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$_8$H$_{18}$NO$_3$P [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; $[\alpha]^{20}_D$ −49.4 (*c* 1.2, EtOH, 83% ee); ^{1}H-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$_4$P [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 *(5R)-[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$_3$·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; $[\alpha]^{20}_{D}$ −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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7. Recoveries of starting methoxylated compounds caused low yields.

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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.[3f,h]

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