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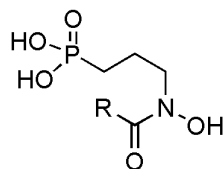
AN EFFICIENT SYNTHESIS OF ANTIBIOTIC SF-2312 (3-DIHYDROXYPHOSPHORYL-1,5-DIHYDROXY-2-PYRROLIDONE)

Tadashi Hanaya* and Chika Itoh

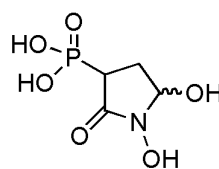
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Abstract – *N*-Benzyloxy-2-(diethoxyphosphoryl)pent-4-enamide (**6**) was prepared from ethyl diethoxyphosphorylacetate in a 3-step sequence. Oxidative cleavage of the terminal olefin of **6** with osmium tetroxide and sodium periodate afforded 1-benzyloxy-3-diethoxyphosphoryl-5-hydroxy-2-pyrrolidone (**7**). The first synthesis of racemic SF-2312 was achieved by treatment of **7** with trimethylsilyl bromide, followed by hydrogenolysis.

Phosphonic acid antibiotics containing a hydroxamic acid function have attracted considerable interest in medicinal chemistry because of their antimicrobial activities. For example, fosmidomycin (**1**)¹ and its *N*-acetyl analog FR-900098 (**2**),² isolated from *Streptomyces lavendulae* and *S. rubellomurinus* sp., respectively, were found to be potent inhibitors for the 1-deoxy-D-xylulose 5-phosphate reductoisomerase.³ In recent years, a number of analogs of these compounds have been synthesized owing to the investigation of structure-activity relationships and development of antimalarial agents.^{4,5}



1 R = H (fosmidomycin)
2 R = Me (FR-900098)

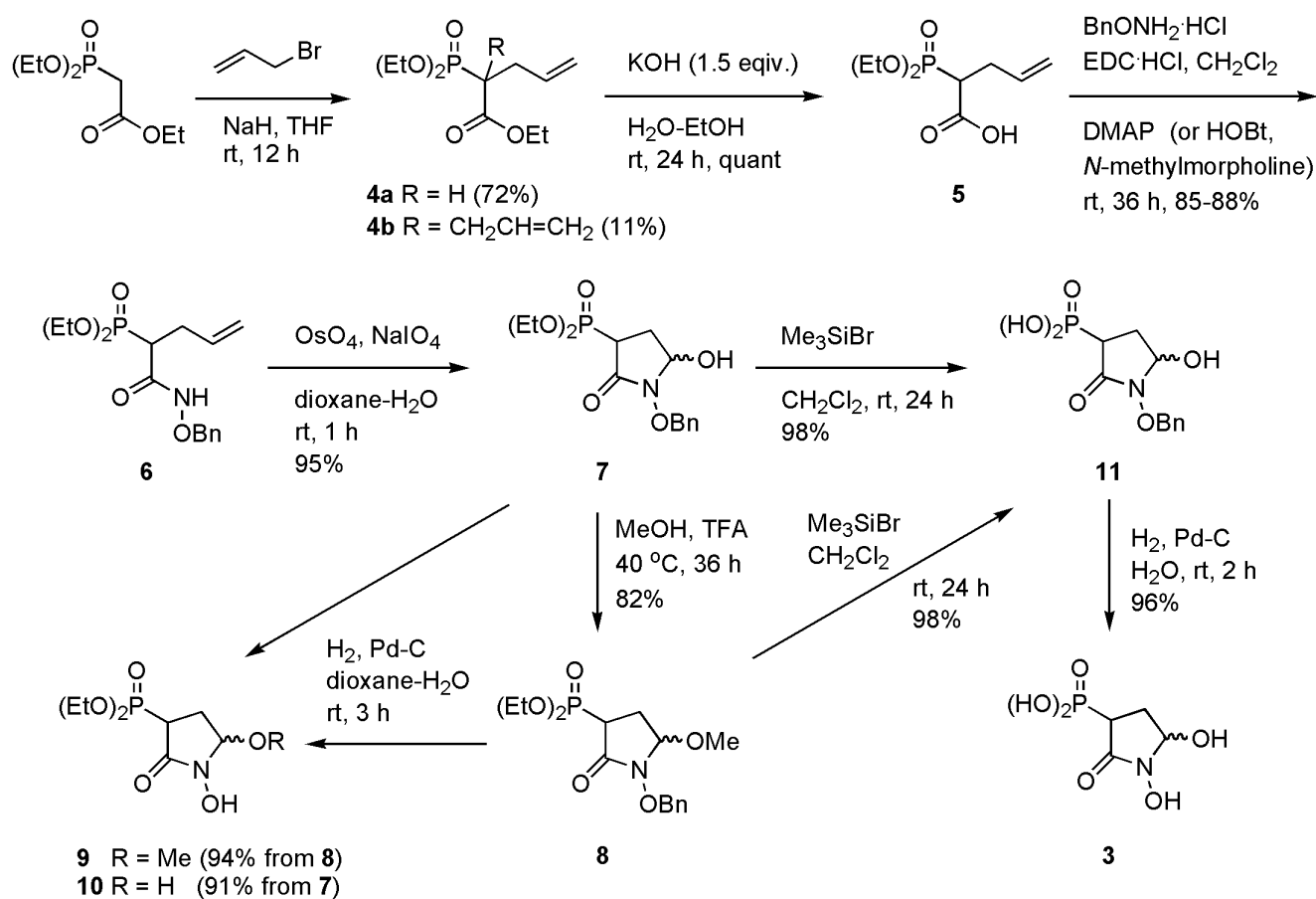


3 (SF-2312)

Meanwhile, SF-2312 (**3**), a phosphonic acid antibiotic active against Gram-positive and Gram-negative bacteria, was isolated from *Micromonospora* sp.^{6,7} Despite its unique structure in having a 1,5-dihydroxy-2-pyrrolidone ring, attempts at preparation of **3** and the assignment of the stereochemistry have not been made so far. We describe herein the first, efficient synthesis of racemic SF-2312 (**3**) as a preliminary study for asymmetric synthesis of **3**.

Ethyl diethoxyphosphorylacetate served as the starting material for preparation of the 2-phosphorylpent-4-enohydroxamate derivative (**6**), the key precursor for the 1,5-dihydroxy-2-pyrrolidone ring formation (Scheme 1). The reported procedures⁸ for preparation of ethyl 2-(diethoxyphosphoryl)pent-4-enoate (**4a**) from ethyl diethoxyphosphorylacetate was slightly modified and thus **4a** was obtained in an improved yield (72%) together with the diallyl-substituted compound (**4b**) (11%). Chemoselective hydrolysis of **4a** in aqueous ethanol containing potassium hydroxide provided the corresponding pent-4-enoic acid (**5**) in a quantitative yield.

Condensation of **5** with *O*-benzylhydroxylamine in the presence of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDC) hydrochloride and 4-dimethylaminopyridine (DMAP) afforded the *O*-benzyl hydroxamate (**6**) in 88% yield. The same condensation in the presence of EDC hydrochloride, 1-hydroxybenzotriazole (HOBt), and *N*-methylmorpholine, provided **6** in a similar yield.



Scheme 1

The 1,5-dihydroxy-2-pyrrolidone ring formation of **6** was carried out by the intramolecular hemiacetalization of the hydroxamate with the terminal aldehyde. Namely, the oxidative cleavage of the terminal olefin of **6** with osmium tetroxide and sodium periodate afforded the aldehyde intermediate, which was immediately cyclized to give the 5-hydroxy-2-pyrrolidone derivative (**7**) as a 65:35 diastereomeric mixture. The structural assignments of these isomers were made by ¹H-NMR with the

aid of 2D NOESY measurement and thus the *cis* form of the major isomer and the *trans* form of the minor one were confirmed (Table 1, Figure 1).

As the hemiacetal (hydroxylactam) moiety of **7** seemed to be susceptible to the conditions required for the following cleavage of the benzyl and phosphonic ester moieties, the 5-hydroxy group of **7** was protected as a methyl acetal (methoxylactam) by way of precaution. Namely, **7** was treated with trifluoroacetic acid (TFA) in methanol at 40 °C to give the 5-methoxy-2-pyrrolidone derivative (**8**) in 82% yield. The product was confirmed by NOE experiments to be a 28:72 mixture of *cis* and *trans* isomers in the reverse ratio to that of **7** (Table 1, Figure 1).

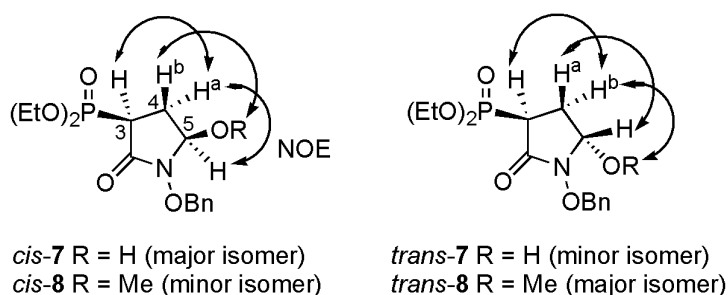


Figure 1. Relative configurations of 1-benzyloxy-3-phosphoryl-2-pyrrolidone derivatives (**7**, **8**) and the observed NOEs

Hydrogenolysis of **8** in the presence of 10% Pd-C afforded the debenzylated product (**9**) and the same treatment of the hemiacetal compound (**7**) also yielded the deprotected compound (**10**) without formation of byproducts. Therefore protection of the hemiacetal moiety seems to be unnecessary for such a reductive condition. However cleavage of the phosphonic ester of **9** and **10** with trimethylsilyl bromide in dichloromethane resulted in the formation of an inseparable mixture of unidentified products and a minor amount of the desired product **3**.

We thus attempted removal of protecting groups of **7** and **8** in the alternative sequence: the phosphonic ester of **7** was first cleaved by the treatment with trimethylsilyl bromide to afford **11** quantitatively. It is noteworthy that the similar treatment of **8** also provided **11** quantitatively, as a result of simultaneous cleavage of the methyl acetal. Judging from these results, it seems that the functional group necessary for protection of the 1,5-dihydroxy-2-pyrrolidone moiety against the action of trimethylsilyl bromide is not the 5-hydroxy but 1-hydroxy group.

The final removal of the benzyl group of **11** by hydrogenolysis furnished 3-dihydroxyphosphoryl-1,5-dihydroxy-2-pyrrolidone (**3**) as a diastomeric mixture (*cis/trans* = 41:59).⁹ The NMR data of **3** were found to be identical with those reported for the natural product.^{6,7}

The present work thus demonstrates the first synthesis of racemic SF-2322 (**3**) by a short and efficient route. Extension of this work including applications of these findings in synthesizing optically active SF-2322 is in progress.

Table 1. 600 MHz ¹H-NMR Spectral parameters for 3-dihydroxyphosphoryl-1,5-dihydroxy-2-pyrrolidone derivatives (**3**, **7–11**)^a

Com- pound	Chemical shifts (δ)							
	H-3	H ^a -4	H ^b -4	H-5	CH ₂ CH ₃	CH ₂ CH ₃ ^b	CH ₂ Ph ^{c,d}	Other signals
<i>cis-7</i>	2.85	2.45	2.18	4.98	4.26–4.11	1.365, 1.35	5.12, 5.10	5.58 (HO, $J_{5,OH} = 12.4$ Hz)
<i>trans-7</i>	3.09	2.42	2.10	4.95	4.26–4.11	1.34, 1.335	5.44, 4.98	3.60 (HO, $J_{5,OH} = 3.9$ Hz)
<i>cis-8</i>	2.87	2.43	2.24	4.67	4.32–4.16	1.35, 1.33	5.14, 5.00	3.47 (MeO)
<i>trans-8</i>	3.03	2.35	2.08	4.47	4.32–4.16	1.37, 1.35	5.01, 5.00	3.40 (MeO)
<i>cis-9</i>	2.99	2.55	2.18	4.97	4.30–4.10	1.34, 1.31	e	3.56 (MeO)
<i>trans-9</i>	3.11	2.54	2.12	5.20	4.30–4.10	1.34, 1.31	e	3.54 (MeO)
<i>cis-10</i>	2.97	2.60	2.16	5.20	4.30–4.11	1.36, 1.34	e	f
<i>trans-10</i>	3.36	2.50	2.18	5.30	4.30–4.11	1.33, 1.30	e	f
<i>cis-11</i>	2.82	2.57	2.01	5.11			5.02, 5.01	
<i>trans-11</i>	3.00	2.38	2.11	5.07			5.01, 4.96	
<i>cis-3</i>	2.88	2.65	1.97	5.18				
<i>trans-3</i>	3.01	2.49	2.09	5.27				

	Coupling constants (Hz)								
	$J_{3,4a}$	$J_{3,4b}$	$J_{3,P}$	$J_{4a,4b}$	$J_{4a,5}$	$J_{4a,P}$	$J_{4b,5}$	$J_{4b,P}$	$J_{5,P}$
<i>cis-7</i>	9.5	1.0	21.7	14.2	6.1	27.1	0.8	16.8	0
<i>trans-7</i>	7.8	9.8	22.7	13.9	6.1	18.7	2.0	8.3	0
<i>cis-8</i>	10.8	5.4	23.1	14.2	7.1	13.6	3.2	20.4	2.9
<i>trans-8</i>	8.1	9.3	22.0	13.9	6.1	19.1	1.5	6.8	0
<i>cis-9</i>	10.5	5.4	22.7	14.2	7.3	14.0	2.9	20.5	3.2
<i>trans-9</i>	8.1	9.3	21.7	14.2	6.4	19.2	1.5	7.6	0
<i>cis-10</i>	10.0	5.4	22.0	14.2	6.6	14.5	3.2	19.0	2.5
<i>trans-10</i>	7.6	9.0	21.7	14.0	6.6	19.0	1.5	8.5	0
<i>cis-11</i>	10.0	4.2	21.5	14.2	6.6	14.5	2.7	17.7	1.5
<i>trans-11</i>	7.1	9.5	21.5	13.9	6.6	18.8	2.0	7.5	0
<i>cis-3</i>	10.3	5.1	21.2	13.9	7.1	12.5	3.2	18.8	2.2
<i>trans-3</i>	6.1	9.8	21.2	14.2	6.8	19.1	2.9	10.5	0

^a **7–10** in CDCl₃, **11**, **3** in D₂O. ^b $J_{CH_2CH_3} = 7.1$ Hz. ^c $J_{CH_2} = 10.3–10.8$ Hz. ^dδ 7.47–7.45 [dd, $J_{o,m} = 7.8$, $J_{o,p} = 1.8$ Hz, Ph(*o*)], 7.40–7.35 [m, Ph(*m,p*)]. ^eδ 9.80–9.10 (br s, HO-N). ^fThe 5-OH signal was not detected.

EXPERIMENTAL

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by spraying them with 20% sulfuric acid–ethanol or 20% phosphomolybdic acid–ethanol (with subsequent heating). The NMR spectra were measured in CDCl₃ with Varian Unity Inova AS600 (600

MHz for ^1H , 151 MHz for ^{13}C) and Mercury 300 (121 MHz for ^{31}P) spectrometers at 23 °C, unless otherwise stated. Chemical shifts are reported as δ values relative to CHCl_3 (7.26 ppm in CDCl_3) and DOH (4.79 ppm in D_2O) as an internal standard for ^1H NMR, CDCl_3 (77.0 ppm in CDCl_3) and 1,4-dioxane (67.2 ppm in D_2O) as an internal standard for ^{13}C NMR, and 85% phosphoric acid (0 ppm) as an external standard for ^{31}P NMR. The IR spectra were recorded on a Thermo Nicolet Avatar360. The MS spectra were measured on a VG-70SE instrument.

Ethyl 2-(diethoxyphosphoryl)pent-4-enoate (4a) and ethyl 2-diethoxyphosphoryl-2-(prop-2-enyl)pent-4-enoate (4b)

Modification of the literature procedures⁸ was made as follows. To a solution of ethyl diethoxyphosphorylacetate (500 mg, 2.23 mmol) in dry THF (5 mL) was added sodium hydride (60% in oil, 98 mg, 2.45 mmol) at 0 °C. After stirring at the same temperature for 1 h, allyl bromide (0.210 mL, 2.40 mmol) was added and the mixture was stirred at rt for 12 h. The mixture was treated with saturated aqueous NH_4Cl at 0 °C and then most of THF was distilled off in vacuo. The resulting solution was diluted with water and extracted with CHCl_3 (3 x 10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was separated by column chromatography with 3:1 AcOEt-hexane to give **4a** [423 mg, 72% (lit.,⁸ 47% yield by distillation)] and **4b** (75 mg, 11%).

4a: Colorless oil; R_f = 0.43 (1:1 AcOEt-hexane); ^1H NMR δ = 1.27 (3H, t, $J_{\text{CH}_2\text{CH}_3}$ = 7.2 Hz, COCH_2CH_3) 1.33, 1.34 (3H each, 2t, $J_{\text{CH}_2\text{CH}_3}$ = 7.1 Hz, POCH_2CH_3), 2.58, 2.70 (1H each, 2m, H^a, H^b -3), 3.01 (1H, ddd, $J_{2,\text{P}}$ = 22.3, $J_{2,3a}$ = 11.4, $J_{2,3b}$ = 4.0 Hz, H-2), 4.12–4.22 (4H, m, POCH_2), 4.17 (2H, q, COCH_2), 5.04 [1H, dq, $J_{4,5E}$ = 10.2, $J_{3,5E} = J_{5E,5Z}$ = 1.5 Hz, $\text{H}_{(E)}$ -5], 5.11 [1H, dq, $J_{4,5Z}$ = 17.0, $J_{3,5Z}$ = 1.5 Hz, $\text{H}_{(Z)}$ -5], 5.76 (1H, ddt, $J_{3a,4} = J_{3b,4}$ = 6.7 Hz, H-4); ^{31}P NMR δ = 22.46.

4b: Colorless oil; R_f = 0.55 (1:1 AcOEt-hexane); ^1H NMR δ = 1.28 (3H, t, $J_{\text{CH}_2\text{CH}_3}$ = 7.1 Hz, COCH_2CH_3) 1.32 (6H, t, $J_{\text{CH}_2\text{CH}_3}$ = 7.1 Hz, POCH_2CH_3), 2.67 (4H, ddt, $J_{3,\text{P}}$ = 14.8, $J_{3,4}$ = 7.1, $J_{3,5E} = J_{3,5Z}$ = 1.3 Hz, H-3), 4.12–4.17 (4H, m, POCH_2), 4.21 (2H, q, COCH_2), 5.09 [2H, ddt, $J_{4,5E}$ = 10.2, $J_{5E,5Z}$ = 2.3 Hz, $\text{H}_{(E)}$ -5], 5.11 [2H, dq, $J_{4,5Z}$ = 17.1 Hz, $\text{H}_{(Z)}$ -5], 5.86 (2H, ddt, $^4J_{4,\text{P}}$ = 0.6 Hz, H-4); ^{31}P NMR δ = 22.91.

2-(Diethoxyphosphoryl)pent-4-enoic acid (5).

To a solution of **4** (500 mg, 1.89 mmol) in EtOH (5.0 mL) was added 10 M aq. KOH (0.28 mL, 2.8 mmol). The mixture was stirred at rt for 24 h and then neutralized with Amberlite IR-120 (H^+). The resin was filtered off and the filtrate was evaporated in vacuo to give **5** (447 mg, quant) as a colorless syrup, which was used for the next step without further purification: R_f = 0.08 (1:1 AcOEt-hexane).

^1H NMR δ = 1.33, 1.335 (3H each, 2t, $J_{\text{CH}_2\text{CH}_3}$ = 7.1 Hz, CH_2CH_3), 2.52, 2.68 (1H each, 2m, H^a, H^b -3), 3.03 (1H, ddd, $J_{2,\text{P}}$ = 22.5, $J_{2,3a}$ = 11.0, $J_{2,3b}$ = 3.9 Hz, H-2), 4.16, 4.20 (2H each, 2m, CH_2CH_3), 5.04 [1H, dq, $J_{4,5E}$ = 10.3, $J_{3,5E} = J_{5E,5Z}$ = 1.2 Hz, $\text{H}_{(E)}$ -5], 5.12 [1H, dq, $J_{4,5Z}$ = 17.0, $J_{3,5Z}$ = 1.2 Hz, $\text{H}_{(Z)}$ -5], 5.78 (1H, ddt, $J_{3a,4} = J_{3b,4}$ = 6.6 Hz, H-4), 5.90 (1H, br s, CO_2H); ^{31}P NMR δ = 23.57.

N-Benzyloxy-2-(diethoxyphosphoryl)pent-4-enamide (6).

A. With EDC-DMAP. To a solution of **5** (200 mg, 0.847 mmol) and *O*-benzylhydroxylamine

hydrochloride (170 mg, 1.07 mmol) dissolved in dry CH_2Cl_2 (10 mL) were added DMAP (265 mg, 2.17 mmol) and EDC hydrochloride (200 mg, 1.04 mmol). After stirring for 36 h at rt, the mixture was diluted with CHCl_3 (20 mL) and washed with 1M HCl (10 mL) and then brine (2 x 10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography with 3:1 AcOEt-hexane to give **6** (253 mg, 88%) as a colorless syrup: $R_f = 0.35$ (AcOEt). ^1H NMR $\delta = 1.31$ (6H, t, $J_{\text{CH}_2\text{CH}_3} = 7.1$ Hz, CH_2CH_3), 2.52 (1H, m, H^b -3), 2.70 (2H, m, H-2, H^a -3), 4.11 (4H, m, CH_2CH_3), 4.90 (2H, s, CH_2Ph), 5.04 [1H, dt, $J_{4,5E} = 10.3$, $J_{3,5E} = J_{5E,5Z} = 1.2$ Hz, $\text{H}_{(E)}$ -5], 5.10 [1H, dt, $J_{4,5Z} = 16.9$, $J_{3,5Z} = 1.2$ Hz, $\text{H}_{(Z)}$ -5], 5.75 (1H, ddt, $J_{3a,4} = J_{3b,4} = 6.4$ Hz, H-4), 7.36 [3H, m, $\text{Ph}(m,p)$], 7.40 [2H, m, $\text{Ph}(o)$], 9.09 (1H, br s, NH); ^{13}C NMR $\delta = 16.30$ (d, $^3J_{\text{C,P}} = 4.5$ Hz, CH_2CH_3), 16.33 (d, $^3J_{\text{C,P}} = 5.8$ Hz, CH_2CH_3), 30.64 (C-3), 43.58 (d, $^1J_{2,P} = 130.1$ Hz, C-2), 62.73 (d, $^2J_{\text{C,P}} = 5.8$ Hz, CH_2CH_3), 63.32 (d, $^2J_{\text{C,P}} = 6.9$ Hz, CH_2CH_3), 78.24 (CH_2Ph), 117.35 (C-5), 128.45 [$\text{Ph}(m)$], 128.58 [$\text{Ph}(p)$], 129.12 [$\text{Ph}(o)$], 134.37 (d, $^3J_{4,P} = 15.0$ Hz, C-4), 135.30 [$\text{Ph}(ipso)$], 165.20 (C-1); ^{31}P NMR $\delta = 24.07$. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_5\text{P}$: C, 56.30; H, 7.09. Found: C, 56.21; H, 7.20.

B. With EDC-HOBt. To a solution of **5** (120 mg, 0.508 mmol) and *O*-benzylhydroxylamine hydrochloride (100 mg, 0.627 mmol) dissolved in dry CH_2Cl_2 (5 mL) were added HOBt (83.0 mg, 0.614 mmol), *N*-methylmorpholine (140 mL, 1.27 mmol) and EDC hydrochloride (120 mg, 0.626 mmol). After stirring at rt for 24 h, the reaction mixture was purified by use of same procedures described above, giving **6** (147 mg, 85%).

1-Benzyloxy-3-diethoxyphosphoryl-5-hydroxy-2-pyrrolidone (**7**).

To a solution of **6** (57.6 mg, 0.169 mmol) in 50% aqueous 1,4-dioxane (5.0 mL) was added osmium tetroxide (4.4 mg, 0.017 mmol). The mixture was stirred at rt for 30 min and then sodium periodate (110 mg, 0.514 mmol) was added gradually. The mixture was stirred at rt for 1 h, diluted with water (15 mL), and extracted with CHCl_3 (3 x 10 mL). The combined organic layers were washed with water (15 mL), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography with 1:19 MeOH- CHCl_3 to give a diastereomeric mixture (*cis/trans* = 65:35) of **7** (55.2 mg, 95%) as a colorless solid: $R_f = 0.50, 0.43$ (1:9 MeOH- CHCl_3). Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_6\text{P}$: C, 52.48; H, 6.46. Found: C, 52.60; H, 6.55.

cis-**7**: ^1H NMR, see Table 1; ^{13}C NMR $\delta = 16.28, 16.37$ (2d, $^3J_{\text{C,P}} = 6.3$ Hz, CH_2CH_3), 28.69 (d, $^2J_{4,P} = 4.0$ Hz, C-4), 37.24 (d, $^1J_{3,P} = 135.9$ Hz, C-3), 62.72, 65.16 (2d, $^2J_{\text{C,P}} = 6.3$ Hz, CH_2CH_3), 78.31 (CH_2Ph), 81.79 ($^3J_{5,P} = 0$ Hz, C-5), 128.46 [$\text{Ph}(m)$], 128.88 [$\text{Ph}(p)$], 129.56 [$\text{Ph}(o)$], 134.79 [$\text{Ph}(ipso)$], 164.19 (d, $^2J_{2,P} = 3.5$ Hz, C-2); ^{31}P NMR $\delta = 25.70$.

trans-**7**: ^1H NMR, see Table 1; ^{13}C NMR $\delta = 16.32, 16.41$ (2d, $^3J_{\text{C,P}} = 6.3$ Hz, CH_2CH_3), 26.86 (d, $^2J_{4,P} = 3.5$ Hz, C-4), 36.11 (d, $^1J_{3,P} = 148.6$ Hz, C-3), 62.54, 63.33 (2d, $^2J_{\text{C,P}} = 6.3$ Hz, CH_2CH_3), 77.94 (CH_2Ph), 80.46 (d, $^3J_{5,P} = 9.2$ Hz, C-5), 128.59 [$\text{Ph}(m)$], 129.00 [$\text{Ph}(p)$], 129.59 [$\text{Ph}(o)$], 134.98 [$\text{Ph}(ipso)$], 166.27 (d, $^2J_{2,P} = 3.5$ Hz, C-2); ^{31}P NMR $\delta = 23.26$.

1-Benzyloxy-3-diethoxyphosphoryl-5-methoxy-2-pyrrolidone (**8**).

To a solution of **7** (50.6 mg, 0.147 mmol) in dry MeOH (4.0 mL) was added TFA (0.010 mL, 0.13 mmol).

The mixture was stirred at 40 °C for 36 h and then triethylamine (0.20 mL) was added at rt. The mixture was evaporated in vacuo and the residue was purified by column chromatography with 1:19 MeOH-CHCl₃ to give a diastereomeric mixture (*cis/trans* = 28:72) of **8** (43.2 mg, 82%) as a colorless syrup: *R_f* = 0.55, 0.49 (1:9 MeOH-CHCl₃). Anal. Calcd for C₁₆H₂₄NO₆P: C, 53.78; H, 6.77. Found: C, 53.89; H, 6.59.

cis-8: ¹H NMR, see Table 1; ¹³C NMR δ = 16.37, 16.46 (2d, ³J_{C,P} = 6.3 Hz, CH₂CH₃), 24.95 (d, ²J_{4,P} = 3.5 Hz, C-4), 36.62 (d, ¹J_{3,P} = 144.5 Hz, C-3), 56.46 (MeO), 62.74, 63.40 (2d, ²J_{C,P} = 6.3 Hz, CH₂CH₃), 78.02 (CH₂Ph), 88.25 (d, ³J_{5,P} = 4.7 Hz, C-5), 128.53 [Ph(*m*)], 128.96 [Ph(*p*)], 129.55 [Ph(*o*)], 134.77 [Ph(*ipso*)], 164.99 (d, ²J_{2,P} = 4.8 Hz, C-2); ³¹P NMR δ = 21.92.

trans-8: ¹H NMR, see Table 1; ¹³C NMR δ = 16.37, 16.46 (2d, ³J_{C,P} = 6.3 Hz, CH₂CH₃), 25.70 (d, ²J_{4,P} = 3.5 Hz, C-4), 36.20 (d, ¹J_{3,P} = 149.1 Hz, C-3), 56.82 (MeO), 62.44, 63.35 (2d, ²J_{C,P} = 6.3 Hz, CH₂CH₃), 77.82 (CH₂Ph), 87.99 (d, ³J_{5,P} = 9.2 Hz, C-5), 128.56 [Ph(*m*)], 128.99 [Ph(*p*)], 129.76 [Ph(*o*)], 134.94 [Ph(*ipso*)], 165.43 (d, ²J_{2,P} = 4.5 Hz, C-2); ³¹P NMR δ = 23.32.

3-Diethoxyphosphoryl-1-hydroxy-5-methoxy-2-pyrrolidone (**9**).

Compound **8** (24.3 mg, 0.0680 mmol) was dissolved in 50% aqueous 1,4-dioxane (5.0 mL) and 10% Pd-C (8.5 mg, 0.0080 mmol) was added. The mixture was stirred at rt for 3 h under atmospheric pressure of hydrogen. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was purified by short-path column chromatography with 1:19 MeOH-CHCl₃ to give a diastereomeric mixture (*cis/trans* = 30:70) of **9** (17.1 mg, 94%) as a colorless syrup: *R_f* = 0.46, 0.40 (1:9 MeOH-CHCl₃). Anal. Calcd for C₉H₁₈NO₆P: C, 40.45; H, 6.79. Found: C, 40.28; H, 6.88.

cis-9: ¹H NMR, see Table 1; ¹³C NMR δ = 16.27, 16.33 (2d, ³J_{C,P} = 6.3 Hz, CH₂CH₃), 24.75 (d, ²J_{4,P} = 4.0 Hz, C-4), 36.77 (d, ¹J_{3,P} = 145.7 Hz, C-3), 56.57 (MeO), 62.93, 63.50 (2d, ²J_{C,P} = 6.3 Hz, CH₂CH₃), 88.79 (d, ³J_{5,P} = 5.2 Hz, C-5), 165.12 (d, ²J_{2,P} = 4.5 Hz, C-2); ³¹P NMR δ = 22.65.

trans-9: ¹H NMR, see Table 1; ¹³C NMR δ = 16.29, 16.36 (2d, ³J_{C,P} = 6.3 Hz, CH₂CH₃), 25.59 (d, ²J_{4,P} = 3.5 Hz, C-4), 36.58 (d, ¹J_{3,P} = 150.3 Hz, C-3), 57.10 (MeO), 62.55, 63.86 (2d, ²J_{C,P} = 6.3 Hz, CH₂CH₃), 89.02 (d, ³J_{5,P} = 9.2 Hz, C-5), 165.09 (d, ²J_{2,P} = 4.0 Hz, C-2); ³¹P NMR δ = 24.15.

3-Diethoxyphosphoryl-1,5-dihydroxy-2-pyrrolidone (**10**).

By use of same procedures described for **9** from **8**, compound **7** (26.6 mg, 0.0775 mmol) was treated with 10% Pd-C (8.7 mg, 0.0082 mmol) to give a diastereomeric mixture (*cis/trans* = 38:62) of **10** (17.9 mg, 91%) as a colorless syrup: *R_f* = 0.26, 0.19 (1:9 MeOH-CHCl₃). Anal. Calcd for C₈H₁₆NO₆P: C, 37.95; H, 6.37. Found: C, 37.79; H, 6.53.

cis-10: ¹H NMR, see Table 1; ¹³C NMR δ = 16.26, 16.30 (2d, ³J_{C,P} = 5.8 Hz, CH₂CH₃), 27.59 (d, ²J_{4,P} = 4.5 Hz, C-4), 37.32 (d, ¹J_{3,P} = 145.1 Hz, C-3), 62.83, 64.60 (2d, ²J_{C,P} = 6.3 Hz, CH₂CH₃), 82.11 (d, ³J_{5,P} = 4.6 Hz, C-5), 164.74 (d, ²J_{2,P} = 3.8 Hz, C-2); ³¹P NMR δ = 24.82.

trans-10: ¹H NMR, see Table 1; ¹³C NMR δ = 16.30, 16.32 (2d, ³J_{C,P} = 5.8 Hz, CH₂CH₃), 27.33 (d, ²J_{4,P} = 4.1 Hz, C-4), 36.60 (d, ¹J_{3,P} = 149.1 Hz, C-3), 63.18, 63.45 (2d, ²J_{C,P} = 6.3 Hz, CH₂CH₃), 81.76 (d, ³J_{5,P} = 8.6 Hz, C-5), 165.53 (d, ²J_{2,P} = 4.0 Hz, C-2); ³¹P NMR δ = 24.16.

1-Benzyloxy-3-dihydroxyphosphoryl-5-hydroxy-2-pyrrolidone (11).

A. From 7. Compound **7** (24.0 mg, 0.0699 mmol) was dissolved in dry CH₂Cl₂ (1.0 mL) and trimethylsilyl bromide (0.140 mL, 1.07 mmol) was added. The mixture was stirred at rt for 24 h and then evaporated in vacuo. The residue was dissolved in water (5 mL) and washed with AcOEt (10 mL). The aqueous layer was evaporated in vacuo to give a diastereomeric mixture (*cis/trans* = 39:61) of **11** (19.7 mg, 98%) as a pale yellow syrup, which was spectrometrically pure and was used directly for the next step: *R_f* = 0.55 (3:7 H₂O-EtOH); ¹H NMR (D₂O), see Table 1. HRMS(FAB): *m/z* calcd for C₁₁H₁₅NO₆P [M + H]⁺ 288.0637, found 288.0650.

B. From 8. By use of same procedures describe above, compound **8** (23.5 mg, 0.0657 mmol) was treated with trimethylsilyl bromide (0.140 mL, 1.07 mmol) at rt for 24 h, giving **11** (18.5 mg, 98%).

3-Dihydroxyphosphoryl-1,5-dihydroxy-2-pyrrolidone (3).

To a solution of **11** (19.7 mg, 0.0685 mmol) in water (1.5 mL) was added 10% Pd-C (9.0 mg, 0.0085 mmol). The mixture was stirred at rt for 2.5 h under atmospheric pressure of hydrogen. The catalyst was filtered off and the filtrate was diluted with water. The mixture was treated with active charcoal and filtered. The filtrate was evaporated in vacuo to give a diastereomeric mixture (*cis/trans* = 41:59) of **3** (13.0 mg, 96%) as a colorless hygroscopic syrup: *R_f* = 0.18 (3:7 H₂O-EtOH); IR (neat) 3390 (OH), 1685 cm⁻¹ (C=O). HRMS(FAB): *m/z* calcd for C₄H₉NO₆P [M + H]⁺ 198.0168, found 198.0175. Anal. Calcd for C₄H₈NO₆P·H₂O: C, 22.34; H, 4.69. Found: C, 22.06; H, 4.82.

cis-3: ¹H NMR (D₂O), see Table 1; ¹³C NMR (D₂O) δ = 27.70 (d, ²*J*_{4,P} = 3.5 Hz, C-4), 38.84 (d, ¹*J*_{3,P} = 133.0 Hz, C-3), 82.44 (d, ³*J*_{5,P} = 3.7 Hz, C-5), 169.35 (d, ²*J*_{2,P} = 8.2 Hz, C-2); ³¹P NMR (D₂O) δ = 17.70.

trans-3: ¹H NMR (D₂O), see Table 1; ¹³C NMR (D₂O) δ = 26.64 (d, ²*J*_{4,P} = 2.9 Hz, C-4), 38.20 (d, ¹*J*_{3,P} = 135.9 Hz, C-3), 82.01 (d, ³*J*_{5,P} = 6.0 Hz, C-5), 169.52 (d, ²*J*_{2,P} = 8.2 Hz, C-2); ³¹P NMR (D₂O) δ = 18.19.

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