Synthesis of Hexahydropyridazine-3-phosphonic Acid

Mamoru KANAME, Kazuo YOSHINAGA, Yasushi ARAKAWA, and Shigeyuki YOSHIFUJI*

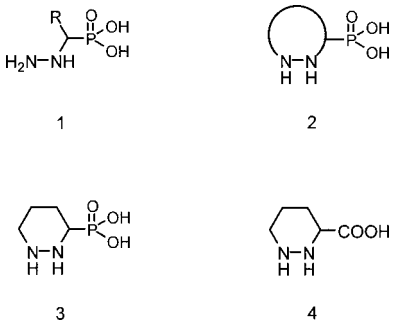
Faculty of Pharmaceutical Sciences, Hokuriku University; Kanagawa-machi Ho-3, Kanazawa 920–1181, Japan.
Received September 12, 2003; accepted October 6, 2003

The synthesis of hexahydropyridazine-3-phosphonic acid (piperidazine-3-phosphonic acid) was performed *via* a hetero-Diels–Alder reaction followed by Lewis acid-catalyzed phosphonylation. This two-step procedure was improved to a one-pot reaction.

Key words hexahydropyridazine-3-phosphonic acid; phosphonylation; one-pot reaction; piperidazine-3-phosphonic acid; α-hydrazinophosphonic acid; hetero-Diels–Alder reaction

As analogues of α-aminophosphonic acids, α-hydrazinophosphonic acids (type **1**, in Fig.1) and their derivatives are of potential biological importance. For example, several of these compounds provide safety against the phytotoxic action of chloroacetanilide herbicides.[1] A few examples of the synthesis of α-hydrazinophosphonic acids have been reported; these include a nucleophilic phosphonylation to either preformed or *in situ* generated C=N bonds (aliphatic aldehyde azines,[2] *N*-protected hydrazones,[3] dimethylhydrazones[4]), a selective reduction of α-hydrazonophosphonic acids,[5] and a nucleophilic substitution of α-mesyloxyalkylphosphonates with hydrazine.[6] However, a simple and general synthetic method for cyclic hydrazine-type compounds (type **2**) has not been established, and most of the reported methods concern acyclic compounds.

Recently, as a model of cyclic α-hydrazinophosphonic acid, we reported the first synthesis of simple hexahydropyridazine-3-phosphonic acid (piperidazine-3-phosphonic acid) **3** in preliminary form,[7] employing the hetero-Diels–Alder (hetero-D–A) reaction and subsequent phosphonylation of the cycloadduct in the presence of a Lewis acid. Piperidazine-3-phosphonic acid is a phosphonic analogue of piperidazine-3-carboxylic acid **4**, the enantiomeric forms of which have been encountered in numerous pharmacologically active molecules, such as the monamycin[8] and azinothricin[9] families. The details of the synthesis of **3** are described here.



1 2 3 4

Fig. 1

In the initial stage, we examined the construction of the 3-substituted pyridazine rings by the application of the reported methods[10,11] of the hetero-D–A reaction, as illustrated in Chart 1. Thus the hetero-D–A reaction of 1-methoxy-1,3-butadiene **5a** with dialkyl azodicarboxylates **6a**—**c** was carried out in dichloromethane (CH_2Cl_2) at room temperature to produce the cycloadducts of 3-methoxy-1,2,3,6-tetrahydropyridazine derivatives **7a**—**c** in nearly quantitative yields. Conversion of the methoxyl group of the cycloadducts **7a**—**c** into a phosphonyl group was conducted smoothly in CH_2Cl_2 at room temperature by treatment of **7a**—**c** with trimethyl phosphite in the presence of trimethylsilyl triflate (TMSOTf) or boron trifluoride etherate ($BF_3 \cdot OEt_2$) as a Lewis acid to afford the corresponding methyl 1,2,3,6-tetrahydropyridazine-3-phosphonates **8a**—**c** in good yields. The results are summarized in Table 1. Despite these satisfactory results, a similar hetero-D–A reaction using trimethylsilyloxybutadiene **5b** or acetoxybutadiene **5c** was not quite as straightforward as expected. These cycloadducts are very unstable. Therefore our attention was directed toward a one-pot reaction including the hetero-D–A reaction and subsequent phosphonylation. After some trials, the one-pot reaction progressed well by slowly adding a Lewis acid to the CH_2Cl_2 solution of three components (diene **5**, dienophile **6**, and trimethyl phosphite) and gave **8a** in satisfactory yields (Table 1), except for the case of acetoxybutadiene **5c**, in which the reaction became complicated. In comparison with the two-step method, this one-pot method appears to be advantageous in terms of reaction efficiency, particularly for the unstable cycloadducts from the hetero-D–A reaction.

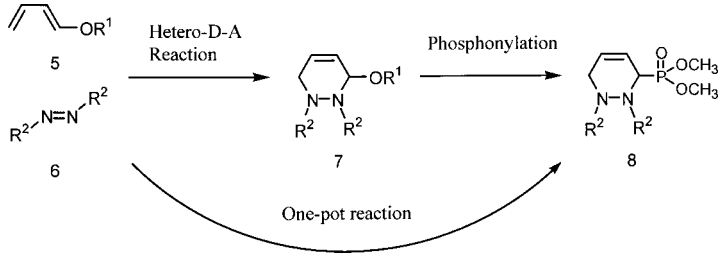


Chart 1

* To whom correspondence should be addressed. e-mail: s-yoshifuji@hokuriku-u.ac.jp

Table 1. Hetero-D–A Reaction and Phosphonylation

Diene		Dienophile[a]		Lewis acid	Hetero-D–A reaction	Yield (%)	Phosphonylation	Yield (%)
	R^1		R^2					
5a	Me	**6a**	Boc	$BF_3 \cdot OEt_2$	**7a**	99	**8a**	81
		6b	Troc	TMSOTf	**7b**	98	**8b**	69
		6c	Z	TMSOTf	**7c**	quant.	**8c**	89
5b	TMS	**6a**	Boc	$BF_3 \cdot OEt_2$	**7d**	64	**8a**	99
5c	Ac	**6a**	Boc			—[b]		
5a	Me	**6a**	Boc	$BF_3 \cdot OEt_2$			**8a**	96
5b	TMS	**6a**	Boc	$BF_3 \cdot OEt_2$	(one-pot reaction)		**8a**	99
5c	Ac	**6a**	Boc	$BF_3 \cdot OEt_2$			**8a**	19

a) Boc, *tert*-butoxycarbonyl; Troc, trichloroethoxycarbonyl; Z, benzyloxycarbonyl. *b*) No product could be isolated.

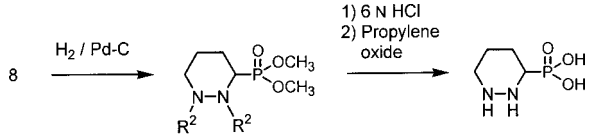


Chart 2

Next, catalytic hydrogenation of tetrahydropyridazines **8a** and **8c**, which have *tert*-butoxycarbonyl (Boc) and trichloroethoxycarbonyl (Troc) groups, using Pd on charcoal in methanol gave the saturated compounds **9a** and **9b** in 89% and 40% yield, respectively, although the reduction of the Troc group ocurred in the latter. Finally, *N*-Boc derivative **9a** was hydrolyzed in boiling 6 N HCl and then treated with propylene oxide[12] in methanol to obtain the salt-free product to give piperidazine-3-phosphonic acid **3** in 62% yield (Chart 2), the structure of which was supported by the analytical and spectral data.

Thus the synthesis of piperidazine-3-phosphonic acid has been accomplished. The present method is simple and will be applicable to the synthesis of a variety of 6-membered cyclic α-hydrazinophosphonic acids.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. NMR spectra were obtained on a JEOL JNM-GSX-400 spectrometer using tetramethylsilane (TMS, δ 0 ppm) or dioxane (δ 3.70 ppm for ^{1}H-NMR and δ 67.4 ppm for ^{13}C-NMR) as an internal standard. IR spectra were recorded on a Horiba FT-720 spectrophotometer. MS and HR-MS were obtained on a JEOL JMS-SX102A spectrometer. Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, Merck). Dialkyl azodicarboxylates and 1-substituted 1,3-butadienes were purchased from commercial sources.

Di-*tert*-butyl 3-Methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7a) A solution of di-*tert*-butyl azodicarboxylate **6a** (690 mg, 3 mmol) in CH_2Cl_2 (3 ml) was stirred under cooling at 0 °C. 1-Methoxy-1,3-butadiene **5a** (0.33 ml, 3.3 mmol) was added to the solution. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 2 h. The reaction solution was evaporated *in vacuo* to leave a residue, which was purified by column chromatography ($CHCl_3$) to give **7a** in 99% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s, C_4H_9), 1.50 (9H, s, C_4H_9), 3.49 and 3.53[13] (3H, each s, OCH_3), 3.55—3.83 (1H, m, C6-Ha), 4.31 and 4.49[13] (1H, d, J=18.7 Hz and dd, J=18.0, 2.9 Hz, C6-Hb), 5.25—5.66 (1H, br, C3-H), 5.77-6.15 (2H, m, C4-H, C5-H). ^{13}C-NMR ($CDCl_3$) δ: 28.26, 28.34 (q), 41.68, 43.64 (t), 56.24 (q), 80.25 (d), 80.84, 81.01, 81.63 (s), 123.82, 124.33 (d), 127.21, 127.73 (d), 154.19, 154.48 (s). IR (neat) cm^{-1}: 1706. MS *m/z*: 314 (M^+). HR-MS *m/z*: 314.1842 (M^+) (Calcd for $C_{15}H_{26}N_2O_5$: 314.1842).

The other cycloadducts **7b**—**d** were prepared in the same manner as described above. Yields of **7b**—**d** are summarized in Table 1.

Bis(2,2,2-trichloroethyl) 3-Methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7b) Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (3H, s, OCH_3), 3.81—3.96 and 4.00—4.11 (1H, m, C6-Ha), 4.53—5.05 (5H, m, C6-Hb and $COOCH_2$×2), 5.57 (1H, br s, C3-H), 5.88—6.09 (2H, m, C4-H, C5-H). ^{13}C-NMR ($CDCl_3$) δ: 43.09, 44.17 (t), 56.72, 57.07 (q), 75.39, 75.62 (t), 81.18, 81.69 (d), 94.72, 94.85 (s), 123.60, 124.04 (d), 126.41, 126.88 (d), 152.67, 153.17 (s). IR (neat) cm^{-1}: 1728. MS *m/z*: 462 (M^+). HR-MS *m/z*: 461.8884 (M^+) (Calcd for $C_{11}H_{12}Cl_6N_2O_5$: 461.8877).

Dibenzyl 3-Methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7c) Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.28 and 3.57[13] (3H, each br s, OCH_3), 3.65—4.00 (1H, m, C6-Ha), 4.41—4.62 (1H, m, C6-Hb), 5.00—5.35 (4H, m, $COOCH_2$×2), 5.50—5.60 (1H, br s, C3-H), 5.81—5.99 (2H, m, C4-H, C5-H), 7.18—7.45 (10H, m, C_6H_5×2). ^{13}C-NMR ($CDCl_3$) δ: 42.52, 42.64 (t), 43.73, 43.87 (t), 56.41 (q), 67.93, 67.99, 68.06, 68.09 (t), 80.78, 80.90, 81.09 (d), 123.65, 124.15 (d), 127.34, 127.58 (d), 127.87, 127.97, 128.11, 128.25, 128.32, 128.43, 128.55, 128.58 (d), 135.64, 135.87 (s), 154.40, 155.24 (s). IR (neat) cm^{-1}: 1716. MS *m/z*: 382 (M^+). HR-MS *m/z*: 382.1529 (M^+) (Calcd for $C_{21}H_{22}N_2O_5$: 382.1529).

Di-*tert*-butyl 3-Trimethylsilyloxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7d) Colorless columns (hexane), mp 58—58.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.21 (9H, s, TMS), 1.48 (18H, s, C_4H_9×2), 3.58 and 3.72[13] (1H, d, J=17.8 Hz and d, J=17.2 Hz, C6-Ha), 4.29 and 4.46[13] (1H, dd, J=17.9, 3.4 Hz and d, J=17.2 Hz, C6-Hb), 5.68—5.95 (3H, m, C3-H, C4-H, C5-H). ^{13}C-NMR ($CDCl_3$) δ: 0.05 (q), 28.27, 28.43 (q), 41.70, 43.60 (t), 73.48, 74.96 (d), 80.72, 81.45 (s), 125.63, 126.00, 126.45, 126.87 (d), 152.59, 153.48, 154.55, 154.64 (s). IR (KBr) cm^{-1}: 1697. MS *m/z*: 372 (M^+). *Anal.* Calcd for $C_{17}H_{32}N_2O_5Si$: C, 54.81; H, 8.66; N, 7.52. Found: C, 54.77; H, 8.49; N, 7.61.

Posphonylation of 7, General Procedure A solution of **7a**—**d** (10 mmol) in CH_2Cl_2 (50 ml) was treated with trimethyl phosphite (3.10 g, 25 mmol) and TMSOTf or $BF_3 \cdot Et_2O$ (15 mmol) at 0 °C. After 15 min the solution was allowed to warm to room temperature and was stirred for a further 12 h. A saturated aqueous $NaHCO_3$ (150 ml) was added to the reaction mixture under ice-cooling. After the mixture was vigorously stirred for 10 min, it was extracted with AcOEt (250 ml×2), which was washed with water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography to give **8a**—**c**. Yields of **8a**—**c** are summarized in Table 1.

Di-*tert*-butyl 3-Dimethylphosphono-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (8a) Colorless prisms (hexane), mp 65—65.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.48, 1.49 and 1.50[13] (18H, each s, C_4H_9×2), 3.61—3.93 (7H, m, OCH_3×2 and C6-Ha), 4.34 and 4.48[13] (1H, dd, J=18.0, 7.0 Hz and dd, J=16.5, 6.6 Hz, C6-Hb), 4.82—5.25 (1H, br, C3-H), 5.95 and 5.98[13] (2H, each br s, C4-H, C5-H). ^{13}C-NMR ($CDCl_3$) δ: 28.14, 28.19, 28.23 (q), 41.17, 43.18 (t), 50.60 (dd, ^1JCP=160.8 Hz, C3), 52.96 (qd, ^2JCP=6.1 Hz, OCH_3), 53.48 (qd, ^2JCP=6.1 Hz, OCH_3), 53.84 (qd, ^2JCP=6.1 Hz, OCH_3), 80.75, 82.23 (s), 120.51, 120.78 (d), 126.00 (d), 152.09, 153.73, 154.28 (s). IR (KBr) cm^{-1}: 1708. MS *m/z*: 392 (M^+). *Anal.* Calcd for $C_{16}H_{29}N_2O_7P$: C, 48.98; H, 7.45; N, 7.14. Found: C, 48.75; H, 7.26; N, 7.12.

Bis(2,2,2-trichloroethyl) 3-Dimethylphosphono-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (8b) Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, d, JHP=11.0 Hz, OCH_3), 3.82 (3H, d, JHP=11.0 Hz, OCH_3), 3.87—3.97 and 4.02—4.12[13] (1H, br, C6-Ha), 4.45—5.26 (6H, m, $COOCH_2$×2, C3-H, C6-Hb), 5.98—6.11 (2H, br, C4-H, C5-H). ^{13}C-NMR ($CDCl_3$) δ: 42.74, 43.75 (t), 51.41, 51.62 (dd, ^1JCP=161.8 Hz, C3), 53.23 (qd, ^2JCP=6.1 Hz, OCH_3), 54.17 (qd, ^2JCP=6.1 Hz, OCH_3), 75.50, 75.62, 75.88 (t), 94.64, 94.90, 95.07 (s), 119.93, 120.37 (d), 124.97, 125.46 (d), 151.99, 153.04, 153.87 (s). IR (neat) cm^{-1}: 1728. MS *m/z*: 540 (M^+). HR-MS *m/z*: 539.8796 (M^+) (Calcd for $C_{12}H_{15}Cl_6N_2O_7P$: 539.8748).

Dibenzyl 3-Dimethylphosphono-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (8c) Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.38—3.99 (7H, m, OCH_3×2 and C6-Ha), 4.41—4.62 (1H, m, C6-Hb), 4.93—5.33 (5H, m, $COOCH_2$×2 and C3-H), 5.97 (2H, br s, C4-H, C5-H), 7.15—7.43 (10H, m, C_6H_5×2). ^{13}C-NMR ($CDCl_3$) δ: 42.06, 43.29, 43.38 (t), 51.19 (dd, ^1JCP=154.1 Hz, C3), 52.93, 53.35, 53.81, 54.20 (q), 67.93, 67.99, 68.56, 68.62, 68.69 (t), 120.01, 120.43 (d), 125.23, 125.71 (d), 127.82, 127.88, 127.94, 128.05, 128.20, 128.29, 128.35, 128.49, 128.55 (d), 135.40, 135.93, 136.07 (s), 153.61, 154.84, 155.34 (s). IR (neat) cm^{-1}: 1716. MS *m/z*: 460 (M^+). HR-MS *m/z*: 460.1399 (M^+) (Calcd for $C_{22}H_{25}N_2O_7P$: 460.1400).

One-Pot Reaction Including the Hetero-D–A Reaction and Phosphonylation Trimethyl phosphite (3.10 g, 25 mmol) was added under ice-cooling to a solution of 1-substituted 1,3-butadiene **5** (11 mmol), di-*tert*-butyl azodicarboxylate **6a** (2.30 g, 10 mmol) in CH_2Cl_2 (10 ml) beforehand stirred for 30 min. A solution of $BF_3 \cdot Et_2O$ (2.13 g, 15 mmol) in CH_2Cl_2 (40 ml) was

added slowly to the reaction mixture under ice-cooling. The reaction mixture was allowed to warm to room temperature and stirred for a further 12 h. The work-up was carried out in a manner similar to that described above for the phosphonylation of **7**. The crude product **8a** was recrystallized from hexane. Yields of **8a** from different butadienes **5a**—**c** are summarized in Table 1.

Di-*tert*-butyl 3-Dimethylphosphono-hexahydropyridazine-1,2-dicarboxylate (9a) A solution of **8a** (4.70 g, 12 mmol) in methanol (100 ml) was hydrogenated over 10% Pd–C (0.3 g) at 4 atm and room temperature for 20 h. The reaction mixture was filtered and concentrated under reduced pressure to leave a crude product, which was subjected to column chromatography ($CHCl_3$, and then 3% MeOH–$CHCl_3$) to give **9a**. Yield 89%. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.48 and 1.49 (each 9H, s, $C_4H_9\times2$), 1.73—2.23 (4H, m, C4-H_2, C5-H_2), 2.83—3.08 (1H, m, C6-Ha), 3.71—3.94 (6H, m, $OCH_3\times2$), 3.79—4.22 (1H, m, C6-Hb), 4.43—4.84 (1H, br, C3-H). ^{13}C-NMR ($CDCl_3$) δ: 19.99 (t), 22.59 (t), 28.22 (q), 42.69, 45.02 (t), 47.74 (dd, ^1JCP=159.8 Hz, C3), 52.50 (qd, ^2JCP=7.4 Hz, OCH_3), 52.74 (qd, ^2JCP=6.1 Hz, OCH_3), 80.32, 81.81 (s), 152.55, 153.92, 154.49, 154.87 (s). IR (KBr) cm^{-1}: 1712. MS *m*/*z*: 394 (M^+). HR-MS *m*/*z*: 394.1869 (M^+) (Calcd for $C_{16}H_{31}N_2O_7P$: 394.1869).

Bis(2,2,2-trichloroethyl) 3-Dimethylphosphono-hexahydropyridazine-1,2-dicarboxylate (9b) A solution of **8b** (6.48 g, 12 mmol) in methanol (100 ml) was hydrogenated over 10% Pd–C (0.3 g) at 1 atm and room temperature for 20 h. The work-up of the mixture was carried out in a manner similar to that described above for **9a**. Yield 40%. Colorless prisms (isopropyl ether), mp 90—90.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.56—1.70 (1H, br, C4-Ha), 1.89—2.31 (3H, m, C4-Hb, C5-H_2), 3.05—3.18 and 3.22—3.33[13] (1H, each m, C6-Ha), 3.80 (3H, d, *J*HP=11.0 Hz, OCH_3), 3.85 (3H, d, *J*HP=11.0 Hz, OCH_3), 4.22—4.34 (1H, m, C3-H), 4.40—4.54 (1H, br, C6-Hb), 4.59—5.25 (4H, m, $COOCH_2\times2$). ^{13}C-NMR ($CDCl_3$) δ: 19.52, 19.84 (t), 22.50, 22.60 (t), 44.55, 45.81 (t), 48.98 (dd, ^1JCP=161.8 Hz, C3), 49.22 (dd, ^1JCP=163.3 Hz, C3), 53.00 (qd, ^2JCP=7.6 Hz, OCH_3), 53.94 (qd, ^2JCP=7.6 Hz, OCH_3), 75.36, 75.56, 75.76 (t), 94.85, 95.07, 95.23 (s), 152.38, 153.14, 154.20 (s). IR (KBr) cm^{-1}: 1753, 1724. MS *m*/*z*: 542 (M^+). *Anal.* Calcd for $C_{12}H_{17}Cl_6N_2O_7P$: C, 26.45; H, 3.14; N, 5.14. Found: C, 26.57; H, 3.05; N, 5.17.

Hexahydropyridazine-3-phosphonic Acid (Piperidazine-3-phosphonic Acid) (3) A solution of **9a** (789 mg, 2 mmol) in 6 N HCl (20 ml) was refluxed under an argon atmosphere for 12 h to give **3** as HCl salt after evaporation to dryness, which was dissolved in MeOH (3 ml) and treated with propylene oxide (1 ml, 14 mmol). The precipitate that resulted was collected by filtration and recrystallized from MeOH–propylene oxide (3 : 1) to give **3** in 62% yield. White powder (MeOH–propylene oxide), mp 158—160 °C. ^{1}H-NMR (D_2O) δ: 1.56—1.85 (2H, m, C4-Ha, C5-Ha), 1.90—2.05 (2H, m, C4-Hb, C5-Hb), 3.03—3.12 (1H, m, C6-Ha), 3.16—3.26 (1H, m, C3-H), 3.30—3.40 (1H, m, C6-Hb), ^{13}C-NMR (D_2O) δ: 21.30 (td, ^3JCP=12.2 Hz, C5), 23.72 (t, C4), 46.04 (t, C6), 54.88 (dd, ^1JCP=146.5 Hz, C3). IR (KBr) cm^{-1}: 3400, 3255 (OH, NH), 1155 (P=O), 1061 (P–O). MS *m*/*z*: 167 (M^++1). HR-MS *m*/*z*: 167.0586 (M^++1) (Calcd for $C_4H_{12}N_2O_3P$: 167.0586).

Acknowledgment This work was supported in part by the Special Research Fund of Hokuriku University.

References and Notes

1) Diel P. J., Maier L., Eur. Pat. Appl. EP 143078 (1985) [*Chem. Abstr.*, **103**, 15544*m* (1985)].
2) Rachon J., Wasielewski C., *Rocz. Chem.*, **50**, 477—487 (1976).
3) Diel P. J., Maier L., *Phosphorus and Sulfur*, **36**, 85—98 (1988).
4) Heydari A., Javidan A., Schaffie M., *Tetrahedron Lett.*, **42**, 8071—8073 (2001).
5) Yuan C., Chen S., Xie R., Feng H., Maier L., *Phosphorus Sulfur Silicon*, **106**, 115—123 (1995).
6) Yuan C., Li C., *Synthesis*, **1996**, 507—510 (1996).
7) Kaname M., Yoshinaga K., Arakawa Y., Yoshifuji S., *Tetrahedron Lett.*, **40**, 7993—7994 (1999).
8) Bevan K., Davies J. S., Hassall C. H., Morton R. B., Phillips D. A. S., *J. Chem. Soc. C*, **1971**, 514—521 (1971).
9) Smitka T. A., Deeter J. B., Hunt A. H., Mertz F. P., Ellis R. M., Boeck L. D., Yao R. C., *J. Antibiot.*, **41**, 726—733 (1988).
10) Alder K., Niklas H., *Liebig's Ann. Chem.*, **585**, 81—96 (1954).
11) Snyder, H. R., Jr., Michels J. G., *J. Org. Chem.*, **28**, 1144—1146 (1963).
12) Langlois N., Rojas-Rousseau A., Decavallas O., *Tetrahedron Asymmetry*, **7**, 1095—1100 (1996).
13) These signals were split due to the rotamers and/or the conformers.