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A Synthesis of Optically Active 4-Diethoxyphosphinyl-3-(1-hydroxyethyl)-2-azetidinone: A Potential Precursor to (1-Aminoalkyl)-phosphonic Acid Derivatives

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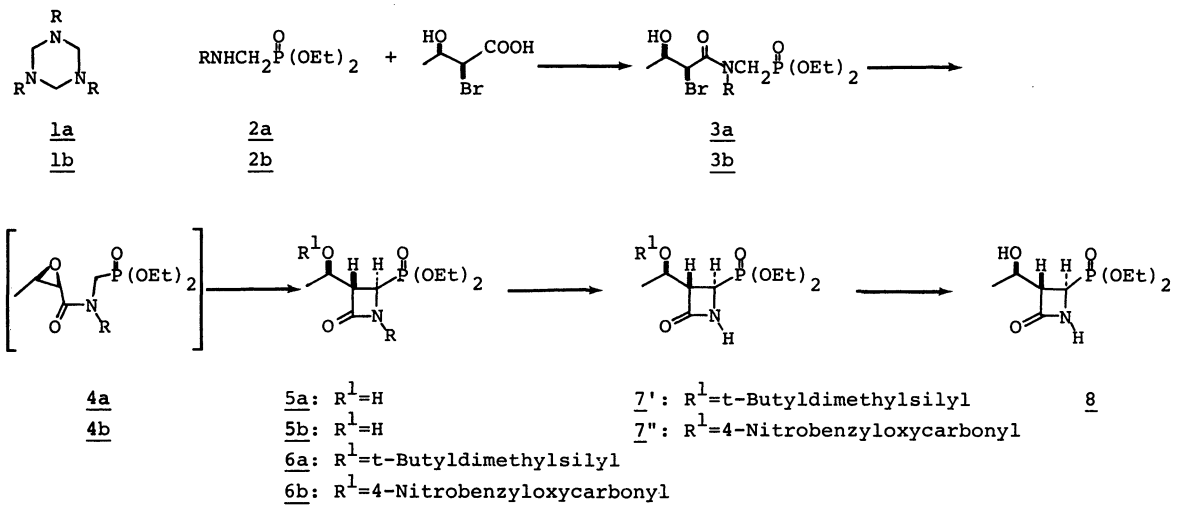
Optically active 4-diethoxyphosphinyl-3-(1-hydroxyethyl)-2-azetidinone (**8**) was synthesized from (2*R*,3*R*)-*N*-diethoxyphosphinylmethyl-2,3-epoxybutyramide derivatives, and compound **8** was alternatively synthesized from (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone via 3-[1-(*t*-butyldimethylsilyloxy)-ethyl] derivative.

4-Dialkoxyphosphinyl-2-azetidinone derivatives obtained by a treatment of the corresponding 4-acetoxy-2-azetidinone derivatives with trialkyl phosphites have already been reported by Campbell[1] as the starting material of alanyl dipeptide-containing organophosphorus moiety via β-phosphono-β-alanine derivatives. Such organophosphorus-containing molecules as the (1-aminoalkyl)phosphonic acid dipeptide (for example: alaphosphine-an inhibitor of alanine racemase) are becoming increasingly important for pharmaceutical use.

In this paper we wish to describe a new synthetic procedure for optically active 4-diethoxyphosphinyl-3-(1-hydroxyethyl)-2-azetidinone (**8**), as a potential precursor to one of the (1-aminoalkyl)phosphonic acid derivatives, by a ring closure of 2-bromo-3-hydroxybutyramides via the corresponding 2,3-epoxybutyramides which possess an activated methylene adjoining the amide nitrogen. This type of intramolecular concerted ring-closure reaction accompanied by an epoxide cleavage reaction to form a β-lactam derivative has already been reported.[2] On the other hand, (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)-ethyl]-2-azetidinone (**9**) is one of the key intermediates to carbapenem antibiotics,[3] and **9** may become a commercially available material. Therefore, we attempted to utilize compound **9** for the synthesis of **8**. As a result, it was revealed that **9** is a promising intermediate for the synthesis of **8**. Thus, we also wish to report here this alternative procedure.

The starting phosphorus-containing butyramides were synthesized as follows: A treatment of 4-methoxybenzylamine or *p*-anisidine with paraformaldehyde according to the procedure reported by Ratcliffe et al.[4] gave hexahydro-1,3,5-triazines, **1a** (95% yield; mp 113—115 °C) or **1b** (72% yield; mp 128—130 °C). A reaction of the hexahydro-1,3,5-triazines (**1a** and **1b**) with diethyl phosphite at 100 °C for 4—6 h gave secondery amines (**2a** and **2b**: 65 and 61% yields, respectively). An amide-formation reaction of the amines (**2a** and **2b**) with 1 equivalent of (2*S*,3*R*)-2-bromo-3-hydroxybutyric acid[5] in tetrahydrofuran



Scheme 1.

(THF) in the presence of 1 equivalent of dicyclohexylcarbodiimide (DCC) gave **3a** (77% yield) and **3b** (21% yield).

Next, these phosphorus-containing butyramides were cyclized to β-lactams in a stereospecific manner. A treatment of **3a** and **3b** with 1 equivalent of lithium hexamethyldisilazanide in tetrahydrofuran at ice-cooling temperature for 5 min, and then another 1 equivalent of $LiN(SiMe_3)_2$ at 24 °C gave chiral 4-diethoxyphosphinyl-3-(1-hydroxyethyl)-2-azetidinone derivatives (**5a** (37% yield) and **5b** (61% yield) via *cis*-epoxides, **4a** and **4b**); *cis*-β-lactams were not isolated. The protection of the hydroxyl group of **5b** with 4-nitrobenzyl chloroformate by use of 4-dimethylaminopyridine (DMAP) as a base in CH_2Cl_2 gave **6b** (79% yield) as a foam. The deprotection of the methoxyphenyl group of **6b** with 3 equivalents of cerium(IV) ammonium nitrite (CAN) in acetone-H_2O (3 : 2) gave **7″** (81% yield) as a crystalline solid; mp 74—76 °C. The hydrogenolysis of **7″** with 5% Pd-C/H_2 at room temperature gave **8** (92% yield); mp 70—71 °C; $[\alpha]_D^{24}$ −4.9° (*c* 0.59, $CHCl_3$). Similarly, protection of the hydroxyl group of **5a** with *t*-butyldimethylsilyl chloride by use of 4-dimethylaminopyridine (DMAP) as a base in *N*,*N*-dimethylformamide (DMF) gave **6a** (67%). Deprotection of the methoxybenzyl group of **6a** with $K_2S_2O_8$-K_2HPO_4 in MeCN-H_2O (1 : 1) at 70—75 °C under argon for 30 min gave *N*-unsubstituted β-lactam **7′** (57% yield) as a gum. This 3,4-trans compound (**7′**) was also alternatively synthesized in good yield without detecting the 3,4-cis isomer[1b] by a treatment of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)-ethyl]-2-azetidinone (**9**) with triethyl phosphite according to Campbell's method,[1] and **7′**, obtained from both routes was identical in all respects. Compound **7′** was converted to **8** in 72% yield by a treatment with a tetrabutylammonium fluoride solution in tetrahydrofuran.

These compounds **5a**, **b**, **6a**, **b**, **7′**, **7″**, and **8** should be potential precursors to new 1-aminoalkylphosphonic acid analogues.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and were uncorrected. Optical rotations were obtained by the use of a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were recorded at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as an internal standard (δ value). The IR absorption spectra were determined on a Jasco IR A-2 spectrophotometer. Mass spectra were obtained on a JMS-01SG mass spectrometer. Preparative TLC was performed on silica-gel plates (Merck 60 PF_{245}), and column chromatography was carried out on columns packed with Merck silica-gel 60 using slightly increased pressure (1.5 atm) for elution. Elemental analyses were performed by the Analytical Center of the Analytical and Metabolic Research Laboratories, Sankyo Co., Ltd.

1,3,5-Tris(4-methoxybenzyl)hexahydro-1,3,5-triazine (1a). To a solution of 4-methoxybenzylamine (13.72 g, 0.10 mol) in dry ethanol (10 ml) was added formaldehyde (37 wt% solution in water, 7.5 ml) at room temperature with stirring. After 15 min, the reaction mixture was dissolved in EtOAc (100 ml). The solution was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a triazine (14.22 g, 95% yield) as a crystalline solid; mp 113—115 °C. ^1H NMR ($CDCl_3$) δ=3.35 (6H, s), 3.55 (6H, s), 3.75 (9H, s), 6.65—7.25 (12H, m). MS *m*/*z* 447 (M^+). Found: C, 72.48; H, 7.38; N, 9.39%. Calcd for $C_{27}H_{33}O_3N_3$: C, 72.00; H, 7.40; N, 9.15%.

1,3,5-Tris(4-methoxyphenyl)hexahydro-1,3,5-triazine (1b). Treatment of *p*-anisidine and formaldehyde as described above gave **1b** in 72% yield as a crystalline solid; mp 128—130 °C. ^1H NMR ($CDCl_3$) δ=3.73 (3H, s), 4.65 (2H, s), 6.65—7.15 (4H, m). MS *m*/*z* 405 (M^+). Found: C, 70.63; H, 6.65; N, 10.22%. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36%.

***N*-(Diethoxyphosphinylmethyl)-4-methoxybenzylamine (2a).** A solution of the triazine **1a** (6.27 g, 14 mmol) in diethyl phosphite (5.4 ml, 42 mmol) was stirred for 6 h at 100 °C. After cooling, the reaction mixture was diluted with EtOAc (100 ml), which was washed with sat. $NaHCO_3$ aq and brine, dried over $MgSO_4$, and concentrated in vacuo to give an oily residue. Chromatography of the remaining residue on a silica-gel column (elution with cyclohexane-EtOAc (1 : 4)) gave an amine (7.30 g, 60.1%) as a viscous oil. ^1H NMR ($CDCl_3$) δ=1.25 (6H, t, *J*=6 Hz), 1.65 (1H, bs), 2.85 (2H, d, *J*=13 Hz), 3.65 (3H, s), 3.8—4.3 (6H, m), 6.6—7.25 (4H, m).

***N*-(Diethoxyphosphinylmethyl)-4-methoxyaniline (2b).** The same treatment of **1b** as described above in the formation of **2a** from **1a** gave **2b** in 61% yield as an oil. ^1H NMR ($CDCl_3$) δ=1.16 (6H, t, *J*=6 Hz), 3.30 (2H, d, *J*=6 Hz), 3.67 (3H, s), 3.8—4.3 (4H, m), 6.68 (4H, s). IR ν_{max}(film) cm^{-1}; 3300, 1520, 1260. MS *m*/*z* 273 (M^+).

(2*S*,3*R*)-*N*-(Diethoxyphosphinylmethyl)-*N*-(4-methoxybenzyl)-2-bromo-3-hydroxybutyramide (3a). To a solution of the amine **2a** (6.88 g, 24 mmol) and (2*S*,3*R*)-2-bromo-3-hydroxybutyric acid (4.39 g, 24 mmol) in THF (50 ml) was added DCC (4.66 g, 24 mmol) with stirring at room temperature. After 10 min, the reaction mixture was filtered to remove the precipitated DCC-H_2O. The filtrate was concentrated in vacuo to give an oily mixture, which was chromatographed on a silica-gel column. Elution with EtOAc gave an amide **3a** (8.32 g, 77% yield). ^1H NMR ($CDCl_3$) δ=1.1—1.4 (9H, m), 3.80 (3H, s), 3.85—4.45 (8H, m), 4.5—4.8 (2H, m), 6.85—7.20 (4H, m). MS *m*/*z* 451 (M^+).

(2*S*,3*R*)-*N*-(Diethoxyphosphinylmethyl)-*N*-(4-methoxyphenyl)-2-bromo-3-hydroxybutyramide (3b). The same treatment of **2b** as described above in the formation of **3a** from **2a** gave **3b** in 21% yield as a crystalline solid; mp 76—79 °C (from diisopropyl ether). ^1H NMR ($CDCl_3$) δ=1.22 (3H, t, *J*=8 Hz), 1.28 (6H, t, *J*=8 Hz), 3.78 (3H, s), 3.88—4.28 (8H, m), 6.74—7.30 (4H, m). MS *m*/*z* 437 (M^+). Found: C, 44.00; H, 5.78; N, 3.14; Br, 18.43; P, 7.70%. Calcd for $C_{16}H_{25}NO_6BrP$: C, 43.81; H, 5.70; N, 3.19; Br, 18.23; P, 7.16%.

(3*S*,4*R*)-4-Diethoxyphosphinyl-3-[(*R*)-1-hydroxyethyl]-1-(4-methoxybenzyl)-2-azetidinone (5a). To a solution of the amide **3a** (2.26 g, 5 mmol) in THF (10 ml) was added dropwise a solution of lithium hexamethyldisilazanide (15 mmol), which was prepared from hexamethyldisilazane (2.42 g) in THF (10 ml) and butyllithium (1.6 M in hexane, 9.38 ml), under nitrogen with stirring at 0—5 °C. After 30 min, the reaction mixture was diluted with EtOAc (100 ml), which was washed with 5% HCl, sat. $NaHCO_3$ and brine,

dried over Na_2SO_4, and concentrated in vacuo to give an oily mixture. Chromatography of the mixture on preparative silica-gel plates (developed with EtOAc) gave a β-lactam **5a** (0.68 g, 36.6% yield). IR ν_{max}(film) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.15—1.45 (9H, m), 2.95 (1H, bs), 3.20—3.55 (1H, m), 3.6—4.4 (7H, m), 4.75 (1H, d, J=15 Hz), 6.65—7.35 (4H, m). MS m/z 371 (M^+).

(3*S*,4*R*)-4-Diethoxyphosphinyl-3-[(*R*)-1-hydroxyethyl]-1-(4-methoxyphenyl)-2-azetidinone (5b). Treatment of **3b** with lithium hexamethyldisilazanide as described above in the formation of **5a** from **3a** gave **5b** in 61% yield as an oil. IR ν_{max}(film) cm^{-1}; 3400, 1760, 1260, 1520. ^1H NMR ($CDCl_3$) δ=1.20 (3H, d, J=6 Hz), 1.22 (6H, t, J=6 Hz), 2.15 (1H, bs), 3.70 (3H, s), 3.28—4.45 (7H, m), 6.68—7.48 (4H, m). MS m/z 357 (M^+).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-diethoxyphosphinyl-1-(4-methoxybenzyl)-2-azetidinone (6a). To a solution of **5a** (520 mg, 1.4 mmol) and *t*-butyldimethylsilyl chloride (320 mg, 2.1 mmol) in DMF (2 ml) was added DMAP (260 mg, 2.1 mmol) at room temperature with stirring. After 15 h, the reaction mixture was diluted with EtOAc (100 ml), which was washed with 5% HCl aq, sat. $NaHCO_3$ and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give an oily product which was chromatographed on a silica-gel column. Elution with cyclohexane-EtOAc (1 : 1) gave a silyl ether (**6a**, 451 mg, 67.2% yield). ^1H NMR ($CDCl_3$) δ=0.05 (6H, s), 0.75 (9H, s), 1.05—1.40 (6H, dt, J=8, 2 Hz; 3H, d, J=6 Hz), 3.27 (1H, dt, J=8, 3 Hz), 3.73 (3H, s), 3.73—4.30 (7H, m), 4.57 (1H, d, J=14 Hz), 6.65—7.30 (4H, m). IR ν_{max}(film) 1760, 1260 cm^{-1}. MS m/z 485 (M^+).

(3*S*,4*R*)-4-Diethoxyphosphinyl-1-(4-methoxyphenyl)-3-[(*R*)-1-(4-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (6b). To a solution of **5b** (140 mg, 0.4 mmol), 4-nitobenzyloxycarbonyl chloride (260 mg, 1.2 mmol) in dichloromethane (4 ml) was added DMAP (150 mg, 1.2 mmol) with stirring at room temperature. After 2 h, the reaction mixture was diluted with EtOAc, which was washed with dil. HCl, water, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give a residual oil. Preparative TLC of the residue on silica-gel plates gave **6b** (210 mg, 97% yield) as an oil. IR ν_{max}(film) cm^{-1}; 1760, 1610, 1520, 1260. ^1H NMR ($CDCl_3$) δ=1.24 (6H, dt, J=6, 2 Hz), 1.49 (3H, d, J=4 Hz), 3.48—3.68 (1H, m), 3.79 (3H, s), 3.84—4.38 (6H, m), 5.20 (2H, s), 6.78—8.25 (8H, m). MS m/z 536 (M^+).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-diethoxyphosphinyl-2-azetidinone (7′). (a) To a solution of **6a** (140 mg, 0.3 mmol) in MeCN-H_2O (1 : 1, 20 ml) was added K_2HPO_4 (490 mg, 2.8 mmol) and $K_2S_2O_8$ (900 mg, 3.3 mmol) under argon. The mixture was heated at 73 °C for 30 min with stirring. After concentration in vacuo, the residue was diluted with water (50 ml), and extracted with EtOAc (100 ml×2). The combined organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an oily residue. Chromatography on a preparative TLC plate (developed with cyclohexane-EtOAc (1 : 2) gave *N*-unsubstituted product **7′** (60 mg, 57% yield) as a gum. ^1H NMR ($CDCl_3$) δ=0.05 (6H, s), 0.85 (9H, s), 1.15 (3H, d, J=6 Hz), 1.35 (6H, t, J=8 Hz), 3.35 (1H, dt, J=8, 3 Hz), 3.7—4.5 (7H, m), 6.30 (1H, bs). MS m/z 366 (M^+).

(b) A mixture of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**9**, 1.2 g) and triethyl phosphite (4 ml) was heated to 100 °C for 1 h. The reaction mixture was concentrated in vacuo with a pump, and chromatographed on a silica-gel column. Elution with EtOAc-cyclohexane (1 : 1) gave **7′** in 92% yield, which was identical with that obtained in (a).

(3*S*,4*R*)-4-Diethoxyphosphinyl-3-[(*R*)-1-(4-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (7″). To a solution of **6b** (110 mg, 0.2 mmol) in acetone (1.5 ml) and water (1 ml) was added CAN (330 mg, 0.6 mmol) at 0 °C with magnetic stirring. After 30 min at 0 °C, the reaction mixture was diluted with EtOAc, which was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give an oily residue. The residue was chromatographed on a silica-gel column to give **7″** (88 mg, 81% yield) as a crystalline solid: Mp 77—78 °C. ^1H NMR ($CDCl_3$) δ=1.25 (3H, d, J=6 Hz), 1.42 (6H, t, J=6 Hz), 3.41—3.70 (1H, m), 3.84 (1H, dd, J=8, 2 Hz), 4.12 (2H, dq, J=16, 2 Hz), 4.28 (2H, dq, J=16, 2 Hz), 5.26 (2H, s), 7.00 (1H, bs), 7.49—8.35 (4H, A_2B_2-quartet). MS m/z 430 (M^+). Found: C, 47.48; H, 5.27; N, 6.39; P, 7.09%. Calcd for $C_{17}H_{23}N_2O_9P$: C, 47.44; H, 5.35; N, 6.51; P, 7.21%.

(3*S*,4*R*)-4-Diethoxyphosphinyl-3-[(*R*)-1-hydroxyethyl]-2-azetidinone (8). (a) A solution of **7″** (106 mg, 0.246 mmol) in MeOH (5 ml) and 5% Pd-C (100 mg) was stirred for 2 h at room temperature under hydrogen. Filtration, concentration and column chromatography on silica gel (eluted with EtOAc-EtOH=19 : 1) gave **8** (56 mg, 91% yield) as a crystalline solid; mp 70—71 °C (from EtOAc-cyclohexane). $[\alpha]_D^{24}$ −4.9° (*c* 0.59, $CHCl_3$). IR ν_{max}(KBr) cm^{-1}; 3350, 3200, 1750. ^1H NMR δ=1.24 (3H, d, J=6 Hz), 1.32 (6H, t, J=8 Hz), 3.29 (1H, dt, 9, 3 Hz, C_3-H)), 3.61—4.41 (7H, m, containing OH), 7.40 (1H, bs, NH). MS m/z 233 (M^+−18). Found: C, 43.03; H, 7.12; N, 5.67; P, 11.53%. Calcd for $C_9H_{18}NO_5P$: C, 43.02; H, 7.16; N, 5.57; P, 12.34%.

(b) A solution of **7′** (140 mg, 0.383 mmol) in THF (2 ml) and *n*-Bu_4NF (1.0 M solution in THF, 0.6 ml) was allowed to stand overnight at room temperature. The solution was concentrated in vacuo to give an oily mixture which was chromatographed on a silica-gel column. Elution with EtOAc and then 10% EtOH in EtOAc gave **8** (70 mg, 72% yield), which was identical with that obtained from **7″** in procedure (a).

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