Design and Synthesis of Haptens for Application to the Preparation of Chiral 1,4-Dihydropyridines

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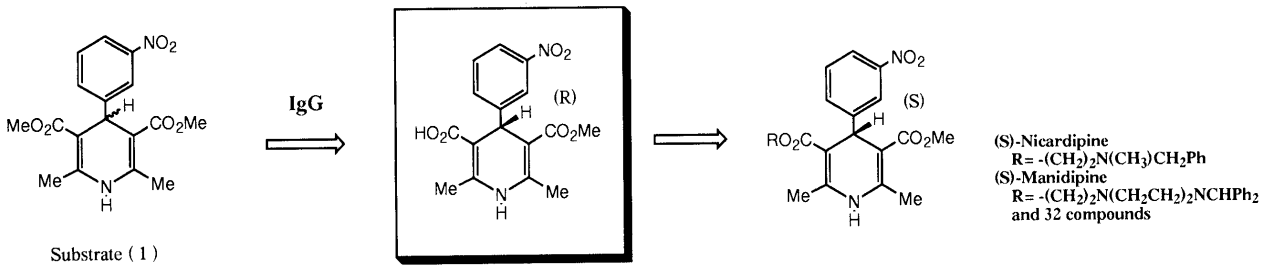
Lipase-catalyzed enzymatic hydrolysis of dimethyl esters of 1,4-dihydropyridines to the monoester, which is an important intermediate for the synthesis of optically active 1,4-dihydropyridines, does not proceed directly. This paper describes the design and synthesis of novel haptens having a phosphonate group containing the requisite oxyanionic character to mimic the tetrahedral intermediate of hydrolysis, and the application of these compounds for generating antibodies with catalytic ability for the enantioselective partial hydrolysis of the dicarboxylic dimethyl ester (1) of a 1,4-dihydropyridine derivative to generate the monocarboxylic acid (2).

Key words 1,4-dihydropyridine; hapten; transition state analog; catalytic antibody; hydrolysis

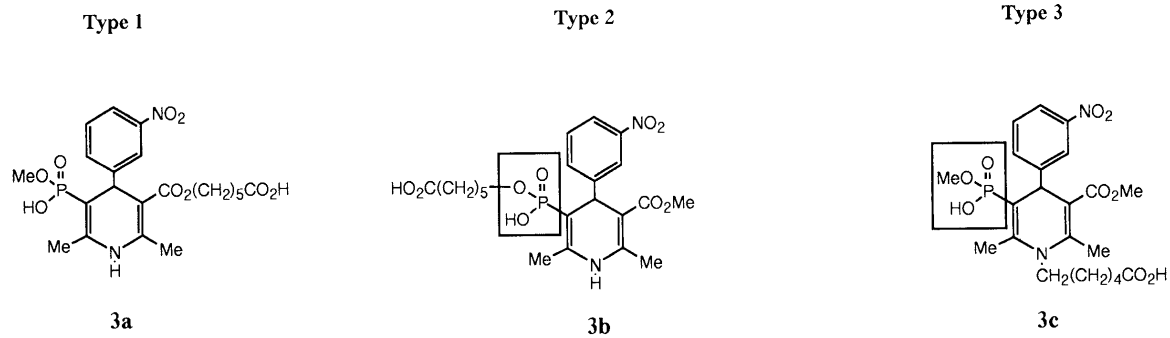
Calcium antagonists are of potential value as antihypertensive drugs.[1] Many 4-aryl-1,4-dihydropyridines have been investigated from a pharmacological point of view, and some of them have already been employed therapeutically.[2] However, most of them have been developed and used as racemates, because of the lack of an efficient asymmetric synthesis, except for the optical resolution of racemates by using chiral alkaloids and the separation of diastereomeric compounds. Our laboratory has already reported the lipase-catalyzed enantioselective synthesis of chiral 1,4-dihydropyridines *via* the hydrolysis of acyloxymethyl esters.[3] The failure of our preliminary enzymatic hydrolysis of the dialkyl esters of 1,4-dihydropyridines suggested that the lipases were not suited for the hydrolysis of sterically hindered carboxylic acid esters such as 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diester (**1**) to the monocarboxylic acid (**2**), which is an important intermediate for commercial products, such as manidipine, nitrendipine and valnidipine. The development of catalytic, enantioselective reactions for the synthesis of optically pure compounds has become an important focus of synthetic organic chemistry. Catalytic antibodies capable of hydrolyzing esters have been generated by using appropriate transition-state analogs (TSAs) in which the ester group has been replaced with a phosphonate group.[4] Enantioselectivity is one of the greatest advantages of using a antibody catalyst. Recently, we have reported the antibody-mediated enantioselective hydrolysis of a glycerol derivative.[5] In this publication, we describe the synthesis of phosphonate analogs (**3a**—**c**) of 1,4-dihydropyridine (**1**), which could be used to generate catalytic antibodies for the enantioselective partial hydrolysis of the diester **1** into the monocarboxylic acid **2** *via* the TSA.



Substrate (1)

Optically Active 1,4-Dihydropyridine (2)

Hapten



3a **3b** **3c**

Fig. 1

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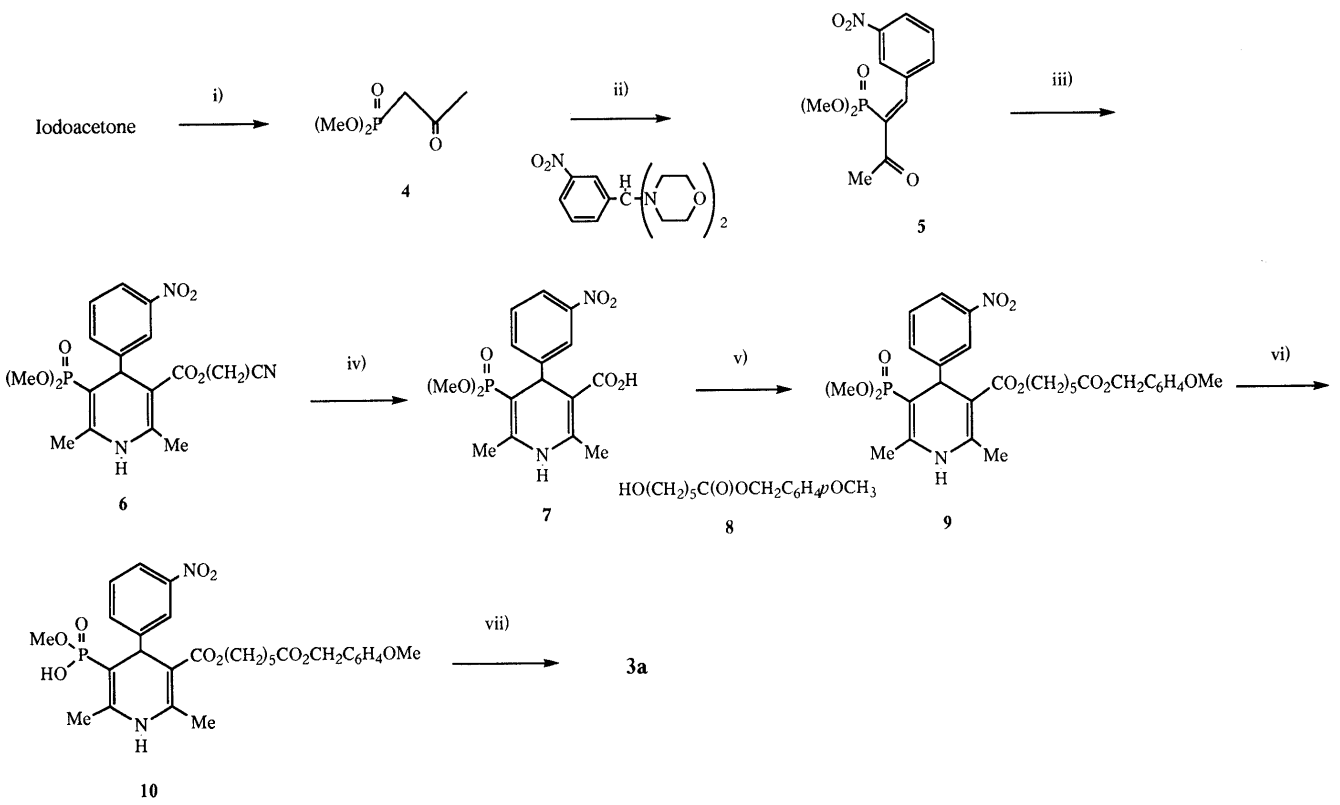
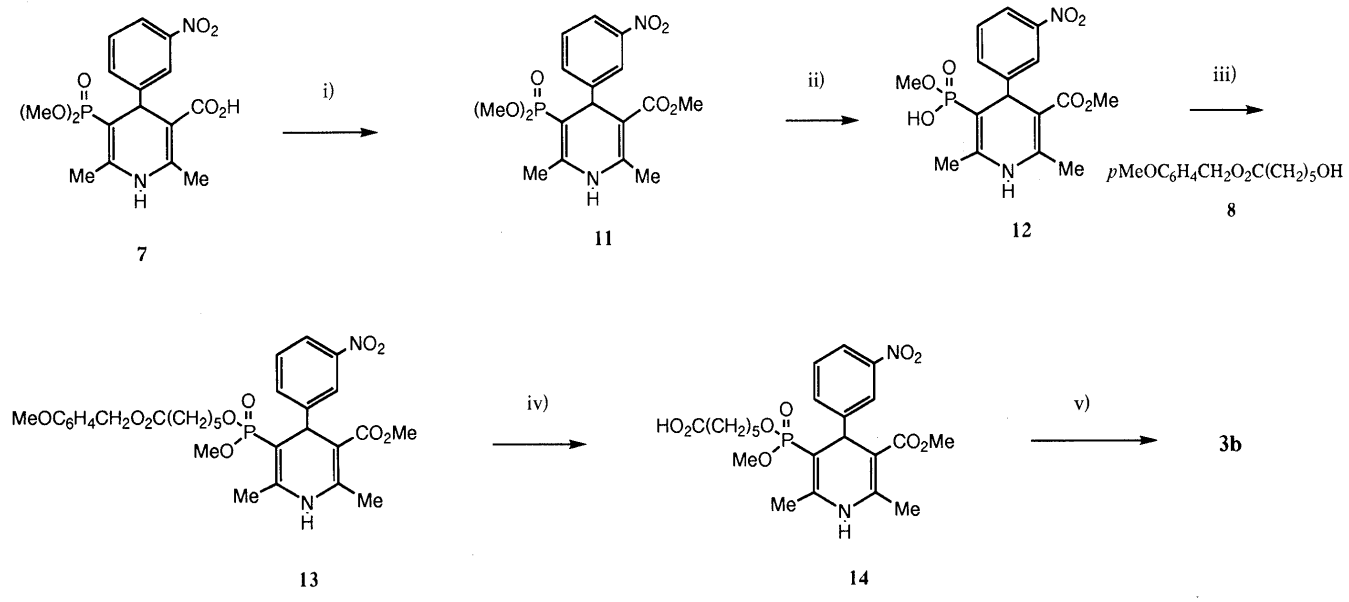


Reagents: i) $P(OCH_3)_3$ in toluene; ii) CF_3CO_2H in toluene; iii) 2-cyanoethyl 3-aminocrotonate in 2-propanol; iv) 1 M NaOH / acetone (1:4); v) DIAD, Ph_3P in THF; vi) *tert*-Butylamine; vii) TFA in CH_2Cl_2

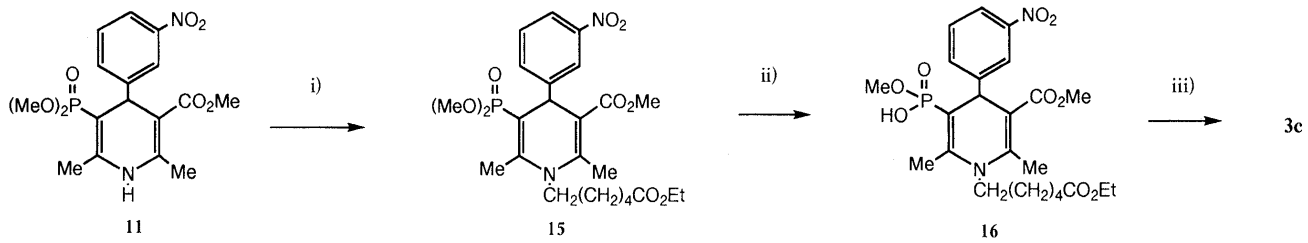
Chart 1



Reagents: i) CH_2N_2 in CH_2Cl_2 / MeOH (1:1); ii) NEt_3, thiophenol; iii) DIAD, Ph_3P in THF; iv) TFA in CH_2Cl_2; v) Me_3SiBr in CH_3CN

Chart 2

We designed three phosphonate TSAs (**3a**—**c**) of 1,4-dihydropyridine, which possess phosphonate groups mimicking the tetrahedral intermediate of ester hydrolysis, to generate catalytic antibodies that can enantioselectively hydrolyze prochiral 1,4-dihydropyridine (**1**) to the monocarboxylic acid (**2**). To obtain an immune response it is necessary to couple the hapten to a carrier protein such as keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA) to the monocarboxylic acid (**2**) and the hexanoyl group was selected as a six-carbon-atom spacer arm for this purpose. Increased immunogenicity due to the nitrophenyl group of the haptens (**3a**—**c**) was



Reagents: i) NaH, $Br(CH_2)_5CO_2Et$, *n*-Bu_4N in DHF; ii) *tert*-butylamine; iii) 0.1 N KOH in MeOH

Chart 3

anticipated.[6] Further, the screening protocols would benefit from a ready spectrophotometric assay. The racemic antigens (**3a**—**c**) were expected to induce antibodies that bind exclusively to either the *R* or *S* substrates.[4a]

The approach used for the synthesis of the hapten **3a** is outlined in Chart 1. The starting material, iodoacetone, was coupled with trimethyl phosphite to give the phosphonate **4** in 74% yield. A Knoevenagel reaction of **4** with 4,4-(3-nitrophenylmethylene)bismorpholine was carried out to give the phosphonate **5** in 76% yield. The condensation of **5** with 2-cyanoethyl 3-aminocrotonate gave **6** in 51% yield. Compound **6** was hydrolyzed with 1 M NaOH to give the monocarboxylic acid **7** in 98% yield. The treatment of **7** with 4-methoxybenzyl 6-hydroxyhexanoate (**8**) was carried out to afford **9** in 98% yield. Compound **9** was treated with *tert*-butylamine to give the monophosphate **10** in 61% yield, and the 4-methoxybenzyl ester was removed by treatment with trifluoroacetic acid (TFA) to afford the desired phosphonic acid monomethyl ester (**3a**) in 35% yield.

Hapten **3b** was synthesized according to Chart 2. Compound **7** was esterified with diazomethane to give the methyl ester **11** in 67% yield. *O*-Demethylation of **11** was achieved with triethylamine and thiophenol to give the monophosphate **12** in 85% yield. The condensation of **12** with **8** gave the phosphonate **13** in 72% yield. After the conversion of **13** to the carboxylic acid **14** with TFA in 98% yield, further treatment with trimethylbromosilane afforded the hapten **3b** in 71% yield.

Finally, the hapten **3c** was synthesized according to Chart 3. Compound **11** was condensed with ethyl 6-bromohexanoate as a spacer in the presence of sodium hydride to afford the *N*-alkyl 1,4-dihydropyridine **15** in 29% yield. After the treatment of **15** with *tert*-butylamine in 91% yield, the hydrolysis of the ethyl ester of **16** with 0.1 N KOH in H_2O–tetrahydrofuran (THF) (1 : 1) gave the hapten **3c** in 60% yield.

In summary, we synthesized three types of haptens (**3a**—**c**) for generating antibody catalysts for the enantioselective hydrolysis of a diester such as prochiral compound **1** to afford an optically active monocarboxylic acid (**2**). Antibodies produced against haptens (**3a**—**c**) may allow efficient enantioselective synthesis of the desired 1,4-dihydropyridines.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO A-202 IR spectrophotometer. MS were measured with a JEOL JMS-SX 102 mass spectrometer. ^{1}H-NMR spectra were taken on a JEOL JNM-GX 270 (270 MHz) spectrometer. ^{1}H-chemical shifts (δ) are given in ppm relative to the signal of Me_4Si ($\delta=0$) in $CDCl_3$, CD_3OD or dimethyl sulfoxide (DMSO)-d_6 as an internal standard. The abbreviations of signal patterns are as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was carried out on Silica gel 60 (70—230 mesh, Merck). Thin-layer chromatography (TLC) on Silica gel 60-F_{254} (Merck) was used to monitor the reaction and to ascertain the purity of the reaction products.

Dimethyl (2-Oxopropyl)phosphonate (4) A mixture of iodoacetone (13 g) and trimethyl phosphite (12 g) was refluxed in toluene for 2 h. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel with AcOEt–*n*-hexane (1 : 4) to give **4** (12.3 g, 74%) as a colorless oil. IR (neat) cm^{-1}: 3470 (enol OH), 1713 (CO), 1246 ($RPO(OR')_2$). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 3.20 (1H, s, CH_AH_B), 3.29 (1H, s, CH_AH_B), 3.87 (6H, d, $J=11.2$ Hz $(CH_3O)_2OP$). GC-MS (*m/z*): 166 $(M)^+$.

Dimethyl ((*Z*)-1-Acetyl-2-(3-nitrophenyl)-1-ethenyl)phosphonate (5) TFA (0.20 mol, 23.0 g) was added to a stirred solution of **4** (0.099 mol, 16.5 g) and 4,4-(3-nitrophenylmethylene)bismorpholine (0.098 mol, 30 g) in toluene (150 ml) at room temperature. The reaction mixture was stirred for 2 h at room temperature, then diluted with water (150 ml), and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel with AcOEt–*n*-hexane (3 : 1) to give **3** (22.5 g, 76%) as a yellow oil. IR (Nujol) cm^{-1}: 3478 (enol OH), 1697 (CO), 1255 ($RPO(OR')_2$). ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s, $COCH_3$), 3.87 (6H, d, $J=11.2$ Hz, $(CH_3O)_2P$), 7.56—8.28 (5H, m, $C_6H_4NO_2$, CH). Positive FAB-MS (*m/z*): 300 $(M+1)^+$.

2-Cyanoethyl 5-Dimethoxyphosphoryl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (6) 2-Cyanoethyl 3-aminocrotonate (0.027 mol, 4.2 g) and **5** (0.027 mol, 8.2 g) were dissolved in 2-propanol (100 ml), and the solution was refluxed for 18 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel with AcOEt–*n*-hexane (3 : 1) to give **6** (7.1 g, 51%) as yellow crystals. mp 142—144 °C. IR (neat) cm^{-1}: 2248 (CN), 1710 (CO), 1231 ($RPO(OR')_2$). ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, d, $J=2.3$ Hz, 2-CH_3), 2.39 (3H, s, 6-CH_3), 2.69 (2H, t, $J=6.3$ Hz, CH_2CN), 3.37, 3.59 (each 3H, d, $J=11.2$ Hz, $(CH_3O)_2P$), 4.28 (2H, q, $J=6.3$ Hz, CO_2CH_2), 4.81 (1H, d, $J=10.2$ Hz, CH), 6.64 (1H, d, $J=5.0$ Hz, NH), 7.40—8.14 (4H, m, $C_6H_4NO_2$). *Anal.* Calcd for $C_{19}H_{22}N_3O_7P$: C, 52.42; H, 5.09; N, 9.65. Found: C, 52.34; H, 4.89; N, 9.55. Positive FAB-MS (*m/z*): 436 $(M+1)^+$.

5-(Dimethoxyphosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylic Acid (7) Compound **6** (0.016 mol, 7.1 g) was added to a stirred solution of 1 M NaOH (14 ml) and acetone (56 ml) at room temperature. The reaction mixture was stirred for 3 h at room temperature, then neutralized with 6 N HCl. After removal of the solvent, the residue was extracted with ether to give **5** (6.2 g, 98%) as pale yellow crystals. mp 168—170 °C. IR (Nujol) cm^{-1}: 1653 (CO), 1212 ($RPO(OR')_2$). ^{1}H-NMR (CD_3OD) δ: 2.14 (3H, d, $J=2.6$ Hz, 2-CH_3), 2.25 (3H, s, 6-CH_3), 3.32, 3.45 (each 3H, d, $J=11.2$ Hz, $(CH_3O)_2P$), 4.66—4.75 (1H, m, CH), 7.41—8.14 (4H, m, $C_6H_4NO_2$). *Anal.* Calcd for $C_{16}H_{19}N_2O_7P$: C, 50.27; H, 5.01; N, 7.33. Found: C, 50.28 H, 5.36; N, 7.28. Positive FAB-MS (*m/z*): 383 $(M+1)^+$.

4-Methoxybenzyl 6-Hydroxyhexanoate (8) A solution of 6-hexanolactone (0.02 mol, 2.28 g) in ethanol (20 ml) was added to 4 N NaOH (5.5 ml) at 0 °C, and the mixture was stirred overnight at room temperature. Removal of the solvent *in vacuo* afforded a residue, to which was added a solution of 4-methoxybenzyl chloride (0.02 mol, 3.13 g) in dimethylformamide (DMF) (15 ml). The mixture was stirred for 2 d at room temperature. The solvent was removed under reduced pressure,

and the residue was chromatographed on silica gel with CH_2Cl_2–acetone (100 : 1) to give **8** (4.3 g, 84%) as a colorless oil. IR (Nujol) cm^{-1}: 3408 (OH), 1729 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.34—1.72 (6H, m, $COCH_2(CH_2)_3$), 2.34 (2H, t, J=7.3 Hz, $COCH_2$), 3.64 (2H, t, J=7.3 Hz, OCH_2), 3.81 (3H, s, OCH_3), 5.05 (2H, s, CO_2CH_2), 6.88, 7.29 (each 2H, d, J=8.6 Hz, C_6H_4). GC-MS (m/z): 252 $(M)^+$.

6-((4-Methoxybenzyl)oxy)-6-oxohexyl 5-(Dimethoxyphosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (9) A mixture of diisopropyl azodicarboxylate (DIAD) (0.42 mmol, 84 mg), triphenylphosphine (PPh_3) (0.39 mmol, 102 mg), and **7** (0.39 mmol, 98 mg) was added to a stirred solution of **8** (0.26 mmol, 99 mg) in THF (5 ml) at room temperature. Stirring was continued overnight at room temperture. After removal of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (100 : 1) to give **9** (156 mg, 98%) as yellow prisms. mp 60—62 °C. IR (Nujol) cm^{-1}: 3204 (NH), 1696 (CO), 1214 (RPO(OR′)$_2$). ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.60 (6H, m, $CO_2CH_2(CH_2)_3$), 2.25 (3H, d, J=2.3 Hz, 2-CH_3), 2.27 (2H, s, $COCH_2$), 2.31 (3H, s, 6-CH_3), 3.32, 3.53 (each 3H, d, J=11.2 Hz, $(CH_3O)_2P$), 3.79 (3H, s, OCH_3), 3.98—4.03 (2H, m, CO_2CH_2), 4.77 (1H, d, J=9.9 Hz, CH), 5.02 (2H, s, CH_2Ar), 6.30 (1H, d, J=5.0 Hz, NH), 6.88, 7.28 (each 2H, d, J=8.9 Hz, $C_6H_4OCH_3$), 7.35—8.12 (4H, m, $C_6H_4NO_2$). FAB-MS (m/z): 617 $(M+1)^+$.

6-((4-Methoxybenzyl)oxy)-6-oxohexyl 5-(Methoxyhydroxyphosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (10) Compound **9** (1.0 mmol, 0.615 g) was dissolved in *tert*-butylamine (10 ml), and the solution was stirred for 7 d at 50—60 °C. Removal of the solvent gave a residue, which was redissolved in MeOH (15 ml). This solution was treated with ion exchange resin (DOWEX (50W-X8)) (1.0 g). The resin was removed by filtration, and the filtrate was concentrated under reduced pressure, and then the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (10 : 1) to give a yellow oil **10** (48 mg, 61%). IR (Nujol) cm^{-1}: 1718 (CO), 1244 (RPO(OH)(OR′)). ^{1}H-NMR ($CDCl_3$) δ: 1.26—2.34 (8H, m, $CO_2CH_2(CH_2)_4$), 2.27 (3H, d, J=7.3 Hz, 2-CH_3), 2.34 (3H, s, 6-CH_3), 3.34 (3H, d, J=12.2 Hz, $POCH_3$), 3.81 (3H, s, OCH_3), 3.85—4.09 (2H, m, $CO_2CH_2CH_2$), 4.83 (1H, d, J=10.2 Hz, CH), 5.04 (2H, s, CO_2CH_2Ar), 6.89, 7.28 (each 2H, d, J=8.9 Hz, C_6H_4), 7.48—8.10 (4H, m, $C_6H_4NO_2$). FAB-MS (m/z): 603 $(M+1)^+$.

6-(((5-(Methoxyhydroxyphosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinyl)carbonyl)oxy)hexanoic Acid (3a) TFA (0.5 ml) was added to a stirred solution of compound **10** (0.51 mmol, 0.295 g) at room temperature. The mixture was stirred for 1 h at room temperature. After removal of the solvent, the residue was chromatographed on silica gel with $CHCl_3$–MeOH–H_2O (65 : 35 : 5) to give **3a** (0.17 g, 35%) as yellow prisms. IR (Nujol) cm^{-1}: 1718 (CO), 1244 (RPO(OH)(OR′)). ^{1}H-NMR (DMSO-d_6) δ: 1.15—1.48 (6H, m, $(COCH_2CH_2)_3$), 2.16 (2H, t, J=7.3 Hz, $COCH_2$), 2.54, 2.57 (each 3H, s, 2-CH_3, 6-CH_3), 3.40 (3H, d, J=11.6 Hz, $POCH_3$), 3.86 (2H, t, J=5.9 Hz, CO_2CH_2), 4.85 (1H, br s, CH), 7.59—8.20 (4H, m, $C_6H_4NO_2$). FAB-MS (m/z): 483 $(M+1)^+$.

Methyl 5-(Dimethoxyphosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (11) A solution of diazomethane in ether was added to a stirred solution of compound **7** (5.2 mmol, 2.0 g) in CH_2Cl_2 (15 ml) and MeOH (15 ml) at room temperature. The mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure, and then the residue was chromatographed on silica gel with AcOEt–*n*-hexane (3 : 1) to give **11** (1.38 g, 67%) as yellow prisms. mp 198—201 °C. IR (KBr) cm^{-1}: 3260 (NH), 1704 (CO), 1209 (RPO(OR′)$_2$). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, d, J=2.3 Hz, 2-CH_3), 2.33 (3H, s, 6-CH_3), 3.34 (3H, d, J=11.2 Hz, $POCH_3$), 3.53 (3H, d, J=11.6 Hz, $POCH_3$), 3.63 (3H, s, CO_2CH_3), 4.79 (1H, d, J=10.3 Hz, CH), 6.82 (1H, d, J=5.0 Hz, NH), 7.35—8.11 (4H, m, $C_6H_4NO_2$). *Anal.* Calcd for $C_{17}H_{21}N_2O_7P \cdot 1/2H_2O$: C, 50.40; H, 5.47; N, 6.91. Found: C, 50.52; H, 5.25; N, 6.97. FAB-MS(m/z): 397 $(M+H)^+$.

Methyl 5-(Methoxyhydroxyphosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (12) Compound **11** (0.5 mmol, 0.198 g) was added to a stirred solution of triethylamine (1.0 ml) and thiophenol (0.5 ml) at room temperature. The mixture was stirred overnight at room temperature, then water (20 ml) was added. The whole was washed with AcOEt, and the aqueous layer was concentrated under reduced pressure. The residue was redissolved in MeOH (10 ml), and treated with ion exchange resin (DOWEX (50W-X8)) (1.0 g). After removal of the resin by filtration, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel with $CHCl_3$–MeOH–H_2O (65 : 35 : 5) to give **12** (164 mg, 85%) as yellow prisms. mp 145—147 °C. IR (Nujol) cm^{-1}: 3548 (NH), 1675 (CO), 1212 (RPO(OH)(OR′)). ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, d, J=2.3 Hz, 2-CH_3), 2.34 (3H, s, 6-CH_3), 3.37 (3H, d, J=11.2 Hz, $POCH_3$), 3.64 (3H, s, CO_2CH_3), 4.86 (1H, d, J=9.9 Hz, CH), 6.83 (1H, br s, NH), 7.36—8.12 (4H, m, $C_6H_4NO_2$). Positive FAB-MS (m/z) : 405 $(M+Na)^+$.

Methyl 5-(Methoxy((6-((4-methoxybenzyl)oxy)-6-oxohexyl)oxy)phosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (13) DIAD (0.63 mmol, 127 mg) was added to a stirred mixture of compound **12** (0.63 mmol, 127 mg), **8** (0.59 mmol, 196 mg), and PPh_3 (0.59 mmol, 154 mg) in THF (5 ml) at room temperature. The mixture was stirred overnight at room temperature. After removal of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (100 : 1) to give **13** (174 mg, 72%) as yellow prisms. mp 50—52 °C. IR (Nujol) cm^{-1}: 3278 (NH), 1701 (CO), 1255 (RPO(OR′)$_2$). ^{1}H-NMR ($CDCl_3$) δ: 1.14—1.63 (6H, m, $CO_2CH_2(CH_2)_3$), 2.23 (2H, t, J=7.3 Hz, $COCH_2$), 2.27 (3H, s, 2-CH_3), 2.35 (3H, s, 6-CH_3), 3.48 (3H, s, $POCH_3$), 3.65 (3H, d, J=4.0 Hz, $C_6H_4OCH_3$), 3.81 (3H, s, CO_2CH_3), 3.47—3.52 (2H, m, $CO_2CH_2CH_2$), 4.82 (1H, d, J=9.9 Hz, CH), 5.04 (2H, s, CO_2CH_2Ar), 6.24 (1H, s, NH), 6.88—7.31 (4H, m, C_6H_4), 7.34—8.11 (4H, m, $C_6H_4NO_2$). *Anal.* Calcd for $C_{30}H_{37}N_2O_{10}P$: C, 58.44; H, 6.05; N, 4.54. Found: C, 58.29; H, 6.31; N, 4.46. FAB-MS (m/z): 617 $(M+1)^+$.

6-(((Methoxy-(5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinyl)phosphoryl)oxyl)hexanoic Acid (14) TFA (0.5 ml) was added to a stirred solution of compound **13** (0.21 mmol, 130 mg) in CH_2Cl_2 at room temperature. The mixture was stirred for 1 h at room temperature. After removal of the solvent, the residue was chromatographed on silica gel with $CHCl_3$–MeOH–H_2O (65 : 35 : 5) to give **14** (102 mg, 98%) as yellow prisms. mp 70—72 °C. IR (Nujol) cm^{-1}: 1701 (CO), 1239 (RPO(OR′)$_2$). ^{1}H-NMR ($CDCl_3$) δ: 1.14—1.64 (6H, m, $CO_2CH_2(CH_2)_3$), 2.24—2.29 (5H, m, 2-CH_3, $COCH_2$), 2.34 (3H, s, 6-CH_3), 3.52 (3H, d, J=11.2 Hz, $POCH_3$), 3.64 (3H, s, CO_2CH_3), 3.72—3.84 (2H, m, CO_2CH_2Ar), 4.80 (1H, d, J=10.6 Hz, CH), 7.36—8.10 (4H, m, $C_6H_4NO_2$). *Anal.* Calcd for $C_{22}H_{29}N_2O_9P \cdot H_2O$: C, 51.36; H, 6.07; N, 5.45. Found: C, 51.34; H, 6.08; N, 4.95. Positive FAB-MS (m/z): 497 $(M+1)^+$, 519 $(M+Na)^+$.

6-((Hydroxy-(5-(methoxycarbonyl)-2,6-dimethyl-4(3-nitrophenyl)-1,4-dihydro-pyridinyl)phosphoryl)oxy)hexanoic Acid (3b) A mixture of compound **14** (0.19 mmol, 96 mg) and trimethylbromosilane (0.19 mmol, 29 mg) in CH_3CN (8 ml) was stirred for 2 d at 40—50 °C. After removal of the solvent, the residue was dissolved in MeOH (5 ml), and treated with ion exchange resin (DOWEX (50W-X8)). After removal of the resin by filtration, the solvent was concentrated under reduced pressure, and the residue was chromatographed on silica gel with $CHCl_3$–MeOH–H_2O (65 : 35 : 5) to give **3b** (66 mg, 71%) as yellow crystals. mp 270 °C (dec.). IR (Nujol) cm^{-1}: 3328 (NH), 1651 (CO), 1232 (RPO(OH)(OR′)). ^{1}H-NMR ($CDCl_3$) δ: 1.27—1.48 (6H, m, $CO_2CH_2(CH_2)_3$), 2.12—2.16 (2H, m, $COCH_2$), 2.21 (3H, s, 2-CH_3), 2.29 (3H, s, 6-CH_3), 3.65 (3H, s, CO_2CH_3), 3.84—3.86 (2H, m, CO_2CH_2), 4.91 (1H, d, J=9.9 Hz, CH), 7.36—8.12 (4H, m, $C_6H_4NO_2$). Positive FAB-MS (m/z): 483 $(M+1)^+$, 505 $(M+Na)^+$, 521 $(M+K)^+$.

Methyl 5-(Dimethoxyphosphoryl)-1-(6-ethoxy-6-oxohexyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (15) Compound **11** (0.35 mmol, 139 mg) was added to a stirred solution of NaH (0.42 mmol, 17 mg) in DMF (1.0 ml) at room temperature under Ar. The mixture was kept for 1 h at room temperature, then a solution of ethyl 6-bromohexanoate (0.42 mmol, 94 mg) in DMF (1.0 ml) was added, and the mixture was stirred overnight at room temperature. After removal of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (15 : 1) to give **15** (55 mg, 29%) as a yellow oil, with recovery of the starting material (85 mg, 61%). IR (neat) cm^{-1}: 1731 (CO), 1234 (RPO(OR′)$_2$). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.3 Hz, CH_2CH_3), 1.11—1.64 (6H, m, $NCH_2(CH_2)_3$), 1.53 (2H, t, J=7.6 Hz, NCH_2), 2.20 (2H, t, J=7.3 Hz, $COCH_2$), 2.40 (3H, d, J=2.6 Hz, 2-CH_3), 2.47 (3H, s, 6-CH_3), 3.53, 3.58 (each 3H, d, J=11.2 Hz, $(CH_3O)_2P$), 3.71 (3H, s, CO_2CH_3), 4.10 (2H, q, J=7.3 Hz, $CO_2CH_2CH_3$), 4.91 (1H, d, J=13.2 Hz, CH), 7.43—8.05 (4H, m, $C_6H_4NO_2$). Positive FAB-MS (m/z): 539 $(M+1)^+$.

Methyl 5-(Methoxyhydroxyphosphoryl)-1-(6-ethoxy-6-oxohexyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (16) A solution of compound **15** (0.10 mmol, 55 mg) was dissolved in *tert*-butylamine (1 ml), and the mixture was stirred for 5 d at 50—60 °C. After removal of the solvent, the residue was redissolved in CH_2Cl_2 and washed with 1 N HCl. The organic layer was concentrated under reduced pressure to give a yellow oil **16** (49 mg, 91%). IR (neat) cm^{-1}: 1733 (CO), 1171 (RPO(OH)(OR′)). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t,

J=7.0 Hz, CH_2CH_3), 1.13—1.71 (6H, m, $NCH_2(CH_2)_3$), 2.20 (2H, t, J=7.3 Hz, $COCH_2$), 2.31 (2H, t, J=7.3 Hz, NCH_2), 2.31 (3H, s, 2-CH_3), 2.49 (3H, s, 6-CH_3), 3.48 (3H, d, J=11.9 Hz, $POCH_3$), 3.71 (3H, s, CO_2CH_3), 4.11 (2H, q, J=7.3 Hz, $CO_2CH_2CH_3$), 4.89 (1H, d, J=13.5 Hz, CH), 7.38—8.05 (4H, m, $C_6H_4NO_2$). Positive FAB-MS(m/z): 525$(M+1)^+$.

6-(3-(Methoxycarbonyl)-5-(methoxyhydroxyphosphoryl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-1-pyridinyl)hexanoic Acid (3c) A solution of compound **16** (0.09 mmol, 49 mg) in H_2O : THF = 1 : 1 (4 ml) and 0.1 N KOH (1 ml), was stirred for 1 h at room temperature. Water was added, and the whole was washed with CH_2Cl_2. The aqueous layer was acidified with 1 N HCl, and extracted with CH_2Cl_2 to give **3c** as a yellow oil (28 mg, 60%). IR (KBr) cm^{-1}: 3448 (NH), 1653 (CO), 1184 (RPO(OH)(OR')). ^{1}H-NMR ($CDCl_3$) δ: 1.10—1.20 (2H, m, $CH_2CH_2CH_2CO_2H$), 1.43 (2H, t, J=6.3 Hz, NCH_2CH_2), 1.52 (2H, t, J=7.6 Hz, $CH_2CH_2CO_2H$), 2.23 (2H, t, J=7.3 Hz, CH_2CO_2H), 2.33 (3H, d, J=2.0 Hz, 2-CH_3), 2.49 (3H, s, 6-CH_3), 3.54 (3H, d, J=11.6 Hz, $POCH_3$), 3.61—3.70 (2H, m, NCH_2), 3.71 (3H, s, CO_2CH_3), 4.98 (1H, d, J=13.5 Hz, CH), 7.33—8.05 (4H, m, $C_6H_4NO_2$). Positive FAB-MS (m/z): 497 $(M+1)^+$, 535 $(M+K)^+$.

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