Synthesis and Biological Activities of Optical Isomers of 2-(4-Diphenylmethyl-1-piperazinyl)ethyl 5-(4,6-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate Dihydrochloride (NIP-101)[1)]

Ryozo SAKODA,* Yoshimasa KAMIKAWAJI, and Kiyotomo SETO

Central Research Institute, Nissan Chemical Ind. Co., Ltd., 722–1, Tsuboi-cho, Funabashi-shi, Chiba 274, Japan. *Received December 9, 1991*

Six optical isomers of 2-(4-diphenylmethyl-1-piperazinyl)ethyl 5-(4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate dihydrochloride (NIP-101, 1·2HCl·2H$_2$O), a potent calcium antagonist, were successfully prepared by using optically active (2*R*,4*R*)-(−)- and (2*S*,4*S*)-(+)-2,4-pentanediols, and *cis*-2,4-pentanediol and optically active (*S*)-(+)-2-methoxy-2-phenylethanol. Their proton nuclear magnetic resonance investigations demonstrate that the 1,3,2-dioxaphosphorinane group is conformationally constrained around the C–P bond. Calcium-antagonistic and hypotensive activities of the optical isomers were examined and found to depend mainly on the absolute configuration at a stereogenic center in the 1,4-dihydropyridine ring rather than the configuration of the 1,3,2-dioxaphosphorinane moiety.

Keywords 1,4-dihydropyridine-5-phosphonate; NIP-101; optical isomer; calcium antagonist; hypotensive activity; structure–activity relationship

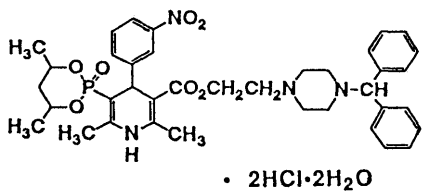
Introduction

2-(4-Diphenylmethyl-1-piperazinyl)ethyl 5-(4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate dihydrochloride (NIP-101, **1**·2HCl·2H$_2$O) is a novel and potent calcium antagonist,[2)] which reduced blood pressure gradually without tachycardia in spontaneously hypertensive rats (SHR) and also demonstrates natriuretic activity.

Reported NIP-101 is considered a mixture of stereoisomers consisting of four possible kinds of enantiomeric pairs.

Heretofore, among a wide variety of drugs containing the optical isomers, many instances of remarkable differences in the potency or profile of the biological activity between the enantiomers as well as among the diastereomers have been illustrated.[3)] It has become increasingly important to obtain information on stereoselectivity for the biological activity and the difference in metabolism between the optical isomers[4)] for progress not only in the search for more valuable drugs but also in basic receptor studies.

The syntheses and biological activities of optically active 1,4-dihydropyridine(DHP)-3,5-dicarboxylates have been studied in this decade. Also, each of the representative compounds such as isradipine,[5)] nicardipine,[6)] nimodipine,[7)] benidipine[8)] and amlodipine[9)] was revealed to consist of enantiomers or diastereomers with large differences in activity. Moreover, there is even an instance in this series where enantiomers show completely opposite effects (antagonism *vs.* agonism) to each other.[10)]



1·2HCl·2H$_2$O (NIP-101)

Fig. 1

Despite the large number of such studies on the optical isomers of the DHP-3,5-dicarboxylates, there has been no study on the DHPs containing the phosphonate group. In the present paper, we describe the synthesis and the calcium-antagonistic and hypotensive activities of the optical isomers in NIP-101.

Results and Discussion

Optical Isomers of NIP-101 A molecule of NIP-101 possesses two and one asymmetric carbons in the 1,3,2-dioxaphosphorinane and DHP parts, respectively. In addition, an asymmetric phosphorus atom is also present in the former part. Possible configurations only in the 1,3,2-dioxaphosphorinane part, *i.e.*, (4*R*,6*R*), (4*S*,6*S*), (2α,4α,6α) and (2β,4α,6α) isomers are shown in Fig. 2.

The (4*R*,6*R*) and (4*S*,6*S*) isomers are enantiomeric, and the (2α,4α,6α) and (2β,4α,6α) isomers are diastereo-

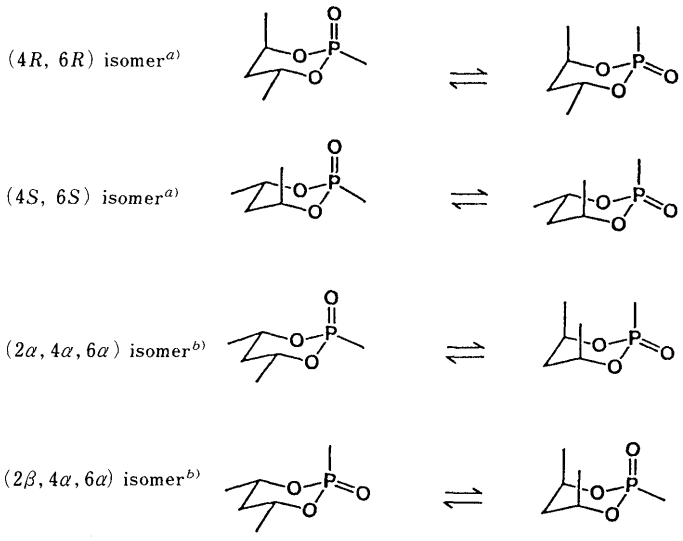


Fig. 2

a) Diastereomeric forms given by a difference in the orientations of the exocyclic substituents on the phosphorus atom can be interconverted by ring-flip; (*R*,*R*) or (*S*,*S*) isomer exists as a mixture of conformational isomers in the equilibrium state.

b) In contrast to (*R*,*R*) or (*S*,*S*) isomers, (2α,4α,6α) and (2β,4α,6α) isomers, which are epimeric with respect to the phosphorus atom, are configurational isomers.

meric to each other. Furthermore, the presence of a stereogenic center in the DHP part provides eight possible stereoisomers falling into four pairs of mirror-image isomers.

The 1,3,2-dioxaphosphorinane skeleton was able to be configurationally constrained by using easily available (2*R*,4*R*)-, (2*S*,4*S*)- and *cis*-2,4-pentanediols (**2R**, **2S**, and **2C**). Although the (2α,4α,6α) and (2β,4α,6α) configurations are possible in *cis* isomers, the method employed for the preparation of NIP-101 afforded only the (2α,4α,6α) isomers as mentioned below. On the other hand, the stereoselective ring-closure to the DHP skeleton, which is known to occur by use of substrates containing specific chiral auxiliaries in the synthesis of optically active DHP-3,5-dicarboxylates,[11] was not observed in this study. The absolute stereochemistry of each of the diastereoisomeric DHPs produced in a variation of the classical Hantzsch synthesis has not been determined; therefore, two isomers, the structural difference between which is only in the configuration at the stereogenic center in the DHP ring, were expressed with A- and B-type isomers. In this definition, either of these two may have an *R* arrangement in this paper. The NIP-101 isomers having the (4*R*,6*R*) configuration in the 1,3,2-dioxaphosphorinane part, $A_R \cdot 2HCl \cdot 2H_2O$ and $B_R \cdot 2HCl \cdot 2H_2O$ isomers, were prepared by a reaction with the structural fragments corresponding to those desired followed by isomer separation. Also those having the (4*S*,6*S*) configuration, $A_S \cdot 2HCl \cdot 2H_2O$ and $B_S \cdot 2HCl \cdot 2H_2O$ isomers, were prepared in the same manner. On the other hand, those having the (2α,4α,6α) configuration, $A_{cis} \cdot 2HCl \cdot 2H_2O$ and $B_{cis} \cdot 2HCl \cdot 2H_2O$ isomers, were prepared in three steps from the intermediary DHP, produced as a diastereomixture of A'_{cis} and B'_{cis} isomers, from the reaction with a substrate containing a selected chiral auxiliary in the carboxylate moiety. From these investigations, NIP-101 used in its pharmacological investigations was revealed to contain six optical isomers.

Preparation of the Optically Active NIP-101 Isomers Bearing the *trans*-4,6-Dimethyl-2-oxo-1,3,2-dioxaphosphorinane Skeleton (4*R*,6*R*)-2-Methoxy-4,6-dimethyl-1,3,2-dioxaphosphorinane (**4R**) was obtained by transesterification with optically active (2*R*,4*R*)-(−)-2,4-pentanediol (**2R**) and trimethyl phosphite (**3**) in 51% yield.[12] The Arbuzov reaction of **4R** with iodoacetone gave the acetonyl phosphonate (**5R**) in 71% yield. The α-acetylstyrylphosphonate (**6R**), which was prepared in 48% yield by Knoevenagel-type condensation of **5R** with 3-nitrobenzaldehyde, was allowed to react with the aminocrotonate (**7**) to give [(2*R*,4*R*),4*RS*]-NIP-101·free base (**1R**, A_R isomer/B_R isomer = 1/1) in 63% yield. The diastereomixture **1R** was treated with ethanolic HCl followed by repeated crystallizations of the resulting 2HCl salt from ethanol to give the pure $A_R \cdot 2HCl \cdot 2H_2O$ isomer (**1Ra**·$2HCl \cdot 2H_2O$, $[\alpha]_D^{25}$ −16.7° (*c* = 0.50, MeOH)) in 37% yield.

Concentration of the filtrates followed by repeated

Table I. Possible Isomers of NIP-101[a]

I	II	III	IV
[(4*R*,6*R*),4*R**] isomer	[(4*S*,6*S*),4*R**] isomer	[(2α,4α,6α),4*R**] isomer	[(2β,4α,6α),4*R**] isomer
[(4*S*,6*S*),4*S**] isomer	[(4*R*,6*R*),4*S**] isomer	[(2α,4α,6α),4*S**] isomer	[(2β,4α,6α),4*S**] isomer

a) 4*R** and 4*S** represent the configuration at 4-position in dihydropyridine ring.

Table II. Solubilities of **1Ra**·$2HCl \cdot 2H_2O$ and **1Rb**·$2HCl \cdot 2H_2O$

Isomer	g/ml at 20 °C	
	EtOH	Me_2CO
1Ra·$2HCl \cdot 2H_2O$	0.2	0.02
1Rb·$2HCl \cdot 2H_2O$	19.5	0.06

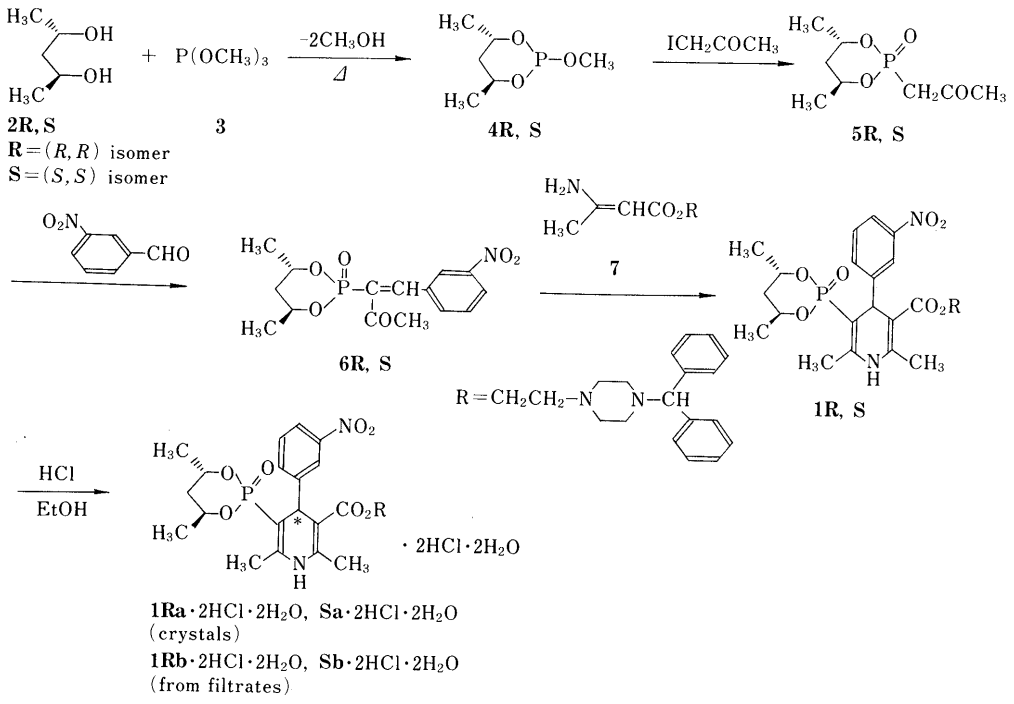


Chart 1

crystallizations of the resulting residue from acetone gave the pure $B_R \cdot 2HCl \cdot 2H_2O$ isomer (**1Rb**·2HCl·$2H_2O$, $[\alpha]_D^{25}$ +38.0° (c=0.50, MeOH)) in 30% yield (Chart 1).

The solubilities of **1Ra**·2HCl·$2H_2O$ and **1Rb**·2HCl·$2H_2O$ in ethanol or acetone were determined and listed in Table II. There is about a 100-fold difference in the solubility in ethanol between these two diastereomers. This difference enables the isolation of **1Ra**·2HCl·$2H_2O$ by crystallizations from ethanol in high yield, whereas a small difference in the solubility in acetone enables the purification of **1Rb**·2HCl·$2H_2O$ by recrystallization from acetone.

In the same manner, the diastereomers, $A_S \cdot 2HCl \cdot 2H_2O$ isomer and $B_S \cdot 2HCl \cdot 2H_2O$ isomer (**1Sa**·2HCl·$2H_2O$, $[\alpha]_D^{25}$ +16.9° (c=0.50, MeOH) and **1Sb**·2HCl·$2H_2O$, $[\alpha]_D^{25}$ −38.0° (c=0.50, MeOH)), were obtained by using (2*S*,4*S*)-(+)-2,4-pentanediol (**2S**) as a starting material.

Preparation of the Optically Active NIP-101 Isomers Bearing the *cis*-4,6-Dimethyl-2-oxo-1,3,2-dioxaphosphorinane Skeleton *cis*-2-Methoxy-4,6-dimethyl-1,3,2-dioxaphosphorinane (**4C**) was obtained by transesterification with *cis*-2,4-pentanediol (**2C**) and trimethylphosphite in 80% yield.[12] Although two possible isomers (**4C** and **4C′**) are present (Fig. 3), **4C** was known as a sole product under these conditions.[13]

The Arbuzov reaction of **4C** with iodoacetone, which was prepared from chloroacetone to be subjected to a subsequent *in situ* derivatization, proceeded with the complete retention of the configuration at the phosphorus atom[14] to give 2α-acetonyl-4α,6α-dimethyl-2β-oxo-1,3,2-dioxaphosphorinan (**5C**) in 76% yield. The α-acetylstyrylphosphonate (**6C**), which was prepared in 73% yield by the reaction of **5C** with bismorpholino-3-nitrophenylmethane by the action of CF_3COOH,[15] was allowed to react with (*S*)-2-methoxy-2-phenylethyl 3-aminocrotonate (**8**) to give [(2α,4α,6α),(*S*),4*RS*]-DHP (**9C**, A'_{cis} isomer/B'_{cis} isomer=1/1) in 70% yield. This diastereomixture **9C** was allowed to react with methoxymethyl (MOM) chloride to give the protected product (**10C**, MOM·A'_{cis} isomer/MOM·B'_{cis} isomer=1/1) in 89% yield. Repeated crystallizations of **10C** from ethyl acetate gave the pure MOM·A'_{cis} isomer (**10Ca**, $[\alpha]_D^{25}$ +0.8° (c=0.50, MeOH)) in 36% yield. Concentration of the filtrates followed by repeated crystallizations of the resulting residue from chloroform–ether gave the pure MOM·B'_{cis} isomer (**10Cb**, $[\alpha]_D^{25}$ +46.0° (c=0.50, MeOH)) in 36% yield. Enantiomeric esters MOM·A_{cis} isomer and MOM·B_{cis} isomer (**12Ca** and **12Cb**), which were obtained by transesterification of the isolated single isomer **10Ca** and **10Cb** with 4-diphenylmethyl-1-piperazineethanol (**11**) in the presence of metal sodium in 73% yield, respectively, was deprotected with ethanolic HCl to give quantitatively the $A_{cis} \cdot 2HCl \cdot 2H_2O$ isomer and $B_{cis} \cdot 2HCl \cdot 2H_2O$ isomer (**1Ca**·2HCl·$2H_2O$, $[\alpha]_D^{25}$ −37.2° (c=0.50, MeOH) and **1Cb**·2HCl·$2H_2O$, $[\alpha]_D^{25}$ +37.2° (c=0.50, MeOH), respectively (Chart 2).

The optically active DHPs have so far been synthesized *via* the isomer separation of the diastereomeric (*S*)-2-methoxy-2-phenylethyl esters followed by transesterification without protection at the amino group in the DHP ring[16]; generally, transesterification in such a method proceeds slowly, besides with low selectivity, to give unsatisfactory results. An easily removable protective group, the MOM group, was employed to solve this problem; the resulting isomers were separated by a simple operation, and the transesterification proceeded smoothly under mild conditions to afford the desired esters in

Fig. 3

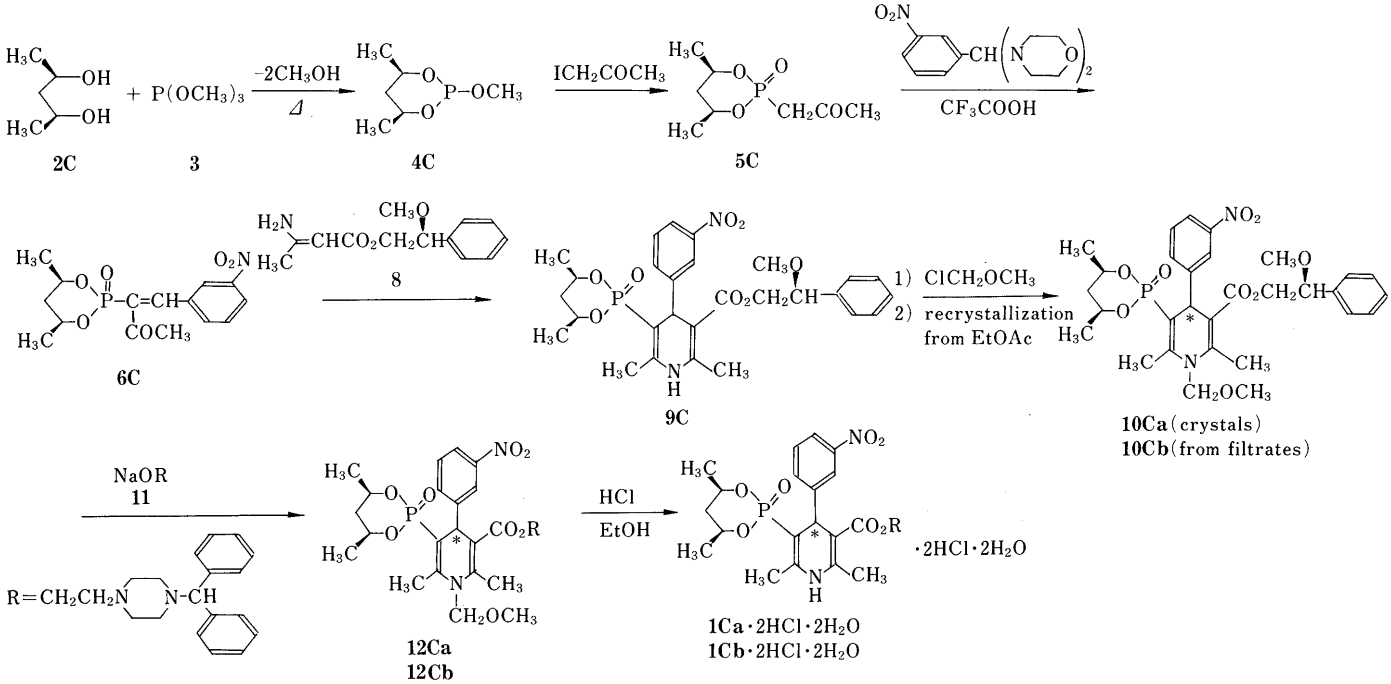
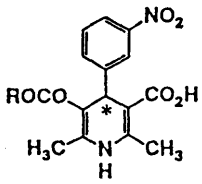
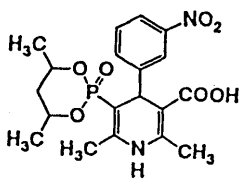


Chart 2



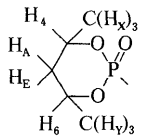
13



14

Fig. 4

TABLE III. ^{1}H-NMR and ^{31}P Spectral Parameters for 1,3,2-Dioxaphosphorinane Part of (*E*)-**6R**, (*E*)-**6C**, **1Ra**, **1Rb** and **1C**



Compd.	Configuration	Chemical shift (ppm)					
		H_4	H_6	H_A	H_E	H_X	H_Y
(*E*)-**6R**	(4*R*,6*R*)	4.78 (eq)	4.95 (ax)	2.00	2.00	1.57 (ax)	1.45 (eq)
(*E*)-**6C**	(2α,4α,6α)	4.81 (ax)	4.81 (ax)	1.70	1.85	1.41 (eq)	1.41 (eq)
1Ra	(4*R*,6*R*)	4.26	4.81	1.76	1.76	1.38	1.32
1Rb	(4*R*,6*R*)	4.48	4.70	1.74	1.74	1.50	1.03
1C	(2α,4α,6α)	4.56	4.70	1.40	1.64	0.97	1.29

Compd.	Coupling constants (Hz)						^{31}P (ppm)
	$J_{4,X}$	$J_{6,X}$	$J_{4,P}$	$J_{6,P}$	$J_{X,P}$	$J_{Y,P}$	δ^{31}P
(*E*)-**6R**	6.4	6.2	11.0	3.9	0	1.7	
(*E*)-**6C**	6.2	6.2	1.2	1.2	2.0	2.0	
1Ra	6.8	6.2	*a)*	*a)*	0	1.3	16.610
1Rb	6.7	6.2	15.1	2.5	0	1.4	16.664
1C	*b)*	*b)*	*b)*	*b)*	*b)*	*b)*	19.347

a) Unable to be determined because of overlapping of the peaks of the another group. *b*) Unable to be determined because determinable sensitivity was not obtained.

good yields. We also attempted to otherwise synthesize these isomers, according to the commonly used method for the preparation of the isomers of the DHP-3,5-dicarboxylates[17] through the chiral acids (**13**), but failed to obtain each single isomer of the acid (**14**) in high optical purity.

Proton Nuclear Magnetic Resonance (^{1}H-NMR) Analysis The ^{1}H-NMR data (500 MHz) of the 1,3,2-dioxaphosphorinane part in the free bases of the NIP-101 isomers and (*E*)-isomrs of **6R**, **6C** ((*E*)-**6R**, (*E*)-**6C**) are listed in Table III.

On the basis of the ^{1}H-NMR comformational analysis studies, both the electronic and steric effects of a substituent were known to govern the conformation of 2-oxo-1,3,2-dioxaphosphorinanes.[18] An equilibrium between the conformers can be explained by the observed couplings of H_4 and H_6 to phosphorus: the phosphorus–proton coupling constant to an equatorial proton is larger than to an axial. The small $J_{6,P}$ (2.5 Hz) compared to $J_{4,P}$ (15.1 Hz) in **1Rb** (free base) indicates the existence of preferential conformation in the 1,3,2-dioxaphosphorinane ring in NIP-101.

TABLE IV. Calcium-Antagonistic and Hypotensive Activities[a]

Compound	pID_{50} (−log[M])	ED_{30} (mg/kg)
NIP-101	7.99	0.039
1Ra·2HCl·2H$_2$O	8.02	0.023
1Rb·2HCl·2H$_2$O	7.12	0.557
1Sb·2HCl·2H$_2$O	7.94	0.048
1Sa·2HCl·2H$_2$O	<6	1.659
1Ca·2HCl·2H$_2$O	8.38	0.027
1Cb·2HCl·2H$_2$O	7.24	0.149

a) Each value represents the mean of 4 animals.

The significant shieldings at H_4 or H_6 and C(H_X or H_Y)$_3$ at either the 4- or 6-position in the 1,3,2-dioxaphosphorinane ring were observed in the ^{1}H-NMR spectra of the free bases of the NIP-101 isomers; equatorial (eq) CH_3 (0.97 ppm) and axial (ax) H (4.56 ppm) in **1C**, ax CH_3 (1.38 ppm) and eq H (4.26 ppm) in **1Ra**, and eq CH_3 (1.03 ppm) and ax H (4.70 ppm) in **1Rb** are shielded, shifting to a high magnetic field. These upfield shifts suggest that the 1,3,2-dioxaphosphorinane groups in NIP-101 are not free to fully rotate around the C–P bond.

Pharmacology The calcium-antagonistic and hypotensive activities of the optical isomers of NIP-101 are listed in Table IV.

The calcium-antagonistic activities were expressed by the pID_{50} values, *i.e.*, the negative logarithm of the molar concentrations of the isomers required to block the Ca^{2+}-induced contractions of K^+-depolarized taenia caecum of guinea pigs (KCl 100 mM; $CaCl_2$ 10 mM) by 50%. The potency order was **1Ca**·2HCl·2H$_2$O > **1Ra**·2HCl·2H$_2$O > **1Sb**·2HCl·2H$_2$O > **1Cb**·2HCl·2H$_2$O > **1Rb**·2HCl·2H$_2$O > **1Sa**·2HCl·2H$_2$O. The (−)-NIP-101 isomers **1Ca**·2HCl·2H$_2$O, **1Ra**·2HCl·2H$_2$O and **1Sb**·2HCl·2H$_2$O showed evidently greater activity than the (+)-NIP-101 isomers **1Cb**·2HCl·2H$_2$O, **1Rb**·2HCl·2H$_2$O and **1Sa**·2HCl·2H$_2$O in every isomeric pair; the activities of **1Ca**·2HCl·2H$_2$O, **1Ra**·2HCl·2H$_2$O and **1Sb**·2HCl·2H$_2$O were 14, 8 and more than 100 times greater than those of **1Cb**·2HCl·2H$_2$O, **1Rb**·2HCl·2H$_2$O and **1Sa**·2HCl·2H$_2$O, respectively. Among the (−)-NIP-101 isomers, a 3-fold difference in activity was observed.

The hypotensive activities were expressed by the ED_{30} values (mg/kg), *i.e.*, the dose that reduced the blood pressure of SHR by 30% when the isomers were administered intravenously. The ED_{30} values were obtained from a linear regression of effects *vs.* log dose. The potency order was approximately consistent with that of the calcium-antagonistic activity. The activities of **1Ca**·2HCl·2H$_2$O, **1Ra**·2HCl·2H$_2$O and **1Sb**·2HCl·2H$_2$O were 6, 24 and 35 times greater than those of **1Cb**·2HCl·2H$_2$O, **1Rb**·2HCl·2H$_2$O and **1Sa**·2HCl·2H$_2$O, respectively. Among the (−)-NIP-101 isomers, a 2-fold difference in the activity was observed. A markedly large difference in both the calcium-antagonistic and hypotensive activities between **1Sa**·2HCl·2H$_2$O and **1Sb**·2HCl·2H$_2$O was observed. The absolute configuration at the stereogenic center in the DHP ring of NIP-101 was found to predominantly govern

the calcium-antagonistic and hypotensive activities, as described in previous studies on the structure–activity relationships of the DHP-3,5-dicarboxylates.[5-9,19] The configuration of the 2-oxo-1,3,2-dioxaphosphorinane moiety apparently influences the magnitude of steroselectivity at the 4-position of the DHP ring to produce the biological effect.

Experimental

Reagent (2*R*,4*R*)-(−)- and (2*S*,4*S*)-(+)-2,4-Pentanediols (**2R** and **2S**) were purchased from Aldrich Chemical Co. (*S*)-(+)-2-Methoxy-2-phenylethanol was prepared by the reduction of (*S*)-(+)-α-methoxyphenylacetic acid (Aldrich) with $LiAlH_4$.[20] *cis*-2,4-Pentanediol (**2C**) was prepared by the Pritchard method.[21] NaI, anhydrous Na_2SO_4 and 35% aqueous HCl were of a special grade purchased from Junsei Kagaku Co., Ltd. All the solvents were of a special grade purchased from Kosoh Kagaku Co., Ltd. or Junsei Kagaku Co., Ltd. Other materials were of a reagent grade from Tokyo Kasei Co., Ltd.

^{1}H-NMR spectra were recorded at 20 °C on JEOL instruments, PMX60SI (60 MHz), FX90Q (90 MHz) and JMN-GSX500 (500 MHz). Unless otherwise specified, PMX60SI was used. Chemical shifts in parts per million for ^{1}H are referenced to tetramethylsilane (TMS) in $CDCl_3$. ^{31}P-NMR spectra were recorded at 20 °C on FX90Q (36.2 MHz). Positive ^{31}P chemical shifts are in delta (parts per million) downfield from external 85% H_3PO_4. Specific rotations were determined at 25 °C on a JASCO DIP-360 Digital Polarimeter. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Mass spectra (MS) were measured on JEOL JMS-DX300.

Chromatography Column chromatography was performed by the use of silica gel (type 60 Merck) as the stationary phase. Thin layer chromatography (TLC) was performed on Silica gel 60F-254 (Merck). Analytical high performance liquid chromatography (HPLC) was performed by use of the system consisting of Shimadzu LC-6A (pump), SPD-6A (ultraviolet (UV) detector, 254 nm), CTO-6A (column oven, 40 °C) and the following column: Unisil NQC185 (4.60 × 250 mm) (Gasukuro Kogyo Co., Ltd.). The mobile phase was MeOH–H_2O (2 : 1, v/v), and the flow rate was 1.0 ml/min.

(4*R*,6*R*)-2-Methoxy-4,6-dimethyl-1,3,2-dioxaphosphorinane (4R) A stirred mixture of 10.0 g (96 mmol) of **2R** and 13.6 g (110 mmol) of trimethyl phosphite (**3**) was heated in an oil bath at 100 °C until the evaporation of methanol ceased. The residue was distilled under reduced pressure to afford 8.0 g (51%) of **4R** as a clear, colorless liquid, bp 70—72 °C (15 mmHg) [lit.[12] bp 75—77 °C (18 mmHg)]. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (d, 3H, J=7 Hz, CH–$_{eq}$C<u>H</u>$_3$), 1.45 (d, 3H, J=7 Hz, CH–$_{ax}$C<u>H</u>$_3$), 1.50—2.20 (m, 2H, CH(CH$_3$)–C<u>H</u>$_2$), 3.50 (d, 3H, J=12 Hz, O–C<u>H</u>$_3$), 4.00—4.80 (m, 2H, O–C<u>H</u> × 2).

(4*S*,6*S*)-2-Methoxy-4,6-dimethyl-1,3,2-dioxaphosphorinane (**4S**) was obtained from (**2S**) in 48% yield in the same way as described above.

(2β,4α,6α)-2-Methoxy-4,6-dimethyl-1,3,2-dioxaphosphorinane (4C) The reaction with 81.0 g (776 mmol) of **2C** and 100 g (806 mmol) of **3** by the same procedure described above afforded 102 g (80%) of **4C** as a clear, colorless liquid, bp 50 °C (10 mmHg) [lit.[12] bp 58—59 °C (11 mmHg)]. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (d, 6H, J=6 Hz, CH–$_{eq}$C<u>H</u>$_3$ × 2), 1.40—1.85 (m, 2H, CH(CH$_3$)–C<u>H</u>$_2$), 3.51 (d, 3H, J=12 Hz, O–C<u>H</u>$_3$), 4.22—4.93 (m, 2H, O–C<u>H</u> × 2).

(4*R*,6*R*)-2-Acetonyl-4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (5R) To a stirred solution of 6.26 g (34.0 mmol) of iodoacetone in 60 ml of benzene was added dropwise a solution of 5.50 g (33.5 mmol) of **4R** in 20 ml of benzene under reflux over a 10 min period. The mixture was heated an additional 1 h under reflux and then concentrated *in vacuo*. Column chromatography of the resulting crude product using ethyl acetate–methanol (9 : 1, v/v) as an eluent afforded 4.92 g (71%) of **5R** as a clear, colorless liquid. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (dd, 3H, J=6.3, 1.5 Hz, CH–$_{eq}$C<u>H</u>$_3$), 1.50 (dd, 3H, J=6.3, 0.5 Hz, CH–$_{ax}$C<u>H</u>$_3$), 1.95 (m, 2H, CH(CH$_3$)–C<u>H</u>$_2$), 2.30 (s, 3H, C(O)–C<u>H</u>$_3$), 3.14 (d, 2H, J=23 Hz, P(O)–C<u>H</u>$_2$), 4.50—5.00 (m, 2H, O–C<u>H</u>(CH$_3$) × 2).

(4*S*,6*S*)-2-Acetonyl-4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (**5S**) was obtained from **4S** in 61% yield in the same way as described above.

2α-Acetonyl-4α,6α-dimethyl-2β-oxo-1,3,2-dioxaphosphorinane (5C) To a mixture of 50 ml of toluene and 30 ml of water were added 15.0 g (162 mmol) of chloroacetone, 29.5 g (197 mmol) of NaI and 0.2 g (0.8 mmol) of tetraethylammonium iodide. The mixture was stirred overnight at room temperature without light. The organic layer was separated and then dried by means of toluene azeotrope. To the stirred, refluxing solution was added 100 ml of a toluene solution containing 25.0 g (152 mmol) of **4C** over a 1-h period. The mixture was stirred an additional 1 h under reflux and then concentrated *in vacuo*. Column chromatography of the resulting crude product using ethyl acetate–methanol (9 : 1, v/v) as an eluent afforded 24.0 g (76%) of **5C** as a clear, colorless liquid. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.35 (dd, 6H, J=6.2, 1.8 Hz, CH–$_{eq}$C<u>H</u>$_3$ × 2), 1.50—1.90 (m, 2H, CH(CH$_3$)–C<u>H</u>$_2$), 2.33 (s, 3H, (CO)–C<u>H</u>$_3$), 3.16 (d, 2H, J=23.5 Hz, P(O)–C<u>H</u>$_2$), 4.70—4.75 (m, 2H, O–C<u>H</u>(CH$_3$) × 2).

(4*R*,6*R*)-2-[1-Acetyl-2-(3-nitrophenyl)ethenyl]-4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (6R) To a solution of 3.38 g (16.4 mmol) of **5R** and 2.40 g (15.9 mmol) of 3-nitrobenzaldehyde in 15 ml of benzene was added 0.5 ml of piperidine. The mixture was stirred for 5 h under reflux and then concentrated *in vacuo*. Column chromatography of the resulting crude product using ethyl acetate–methanol (9 : 1, v/v) as an eluent afforded 2.58 g (48%) of **6R** as a yellow viscous oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.45 (dd, 3H, J=6.4, 1.7 Hz, CH–$_{eq}$C<u>H</u>$_3$), 1.57 (d, 3H, J=6.6 Hz, CH–$_{ax}$C<u>H</u>$_3$), 1.97—2.03 (m, 2H, CH(CH$_3$)–C<u>H</u>$_2$), 2.27 (s, 3H, C(O)–C<u>H</u>$_3$), 4.74—4.82 (m, 1H, O–C(CH$_3$)$_{eq}$<u>H</u>), 4.92—4.98 (m, 1H, O–C(CH$_3$)$_{ax}$<u>H</u>), 7.52—8.35 (m, 5H, Ar<u>H</u> + =C<u>H</u>–Ar).

(4*S*,6*S*)-2-[1-Acetyl-2-(3-nitrophenyl)ethenyl]-4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (**6S**) was obtained from **5S** in 38% yield in the same way as described above.

2α-[1-Acetyl-2-(3-nitrophenyl)ethenyl]-4α,6α-dimethyl-2β-oxo-1,3,2-dioxaphosphorinane (6C) To a stirred suspension of 36.0 g (117 mmol) of bismorpholino-3-nitrophenylmethane in 100 ml of toluene was added 27.6 g (236 mmol) of trifluoroacetic acid at 25 °C. To the mixture heated in an oil bath at 60 °C was added 24.0 g (116 mmol) of **5C**. The mixture was stirred an additional 0.5 h at 60 °C, cooled to 25 °C and then diluted with 150 ml of toluene and 80 ml of water. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. Column chromatography of the resulting crude product using ethyl acetate as an eluent afforded 28.8 g (73%) of **6C** as colorless crystals, mp 130.0—131.0 °C (AcOEt). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.41 (dd, 6H, J=6.2, 1.8 Hz, CH–$_{eq}$C<u>H</u>$_3$ × 2), 1.65—1.89 (m, 2H, CH(CH$_3$)–C<u>H</u>$_2$), 2.29 (s, 3H, C(O)–C<u>H</u>$_3$), 4.80—4.88 (m, 2H, O–C<u>H</u>(CH$_3$) × 2), 7.60—8.29 (m, 5H, Ar<u>H</u> + =C<u>H</u>–Ar). MS *m/z* (%): 69 (100%), 256 (98%), 296 (93%), 339 (M^+, 56%). *Anal.* Calcd for $C_{15}H_{18}NO_6P$: C, 53.10; H, 5.35; N, 4.13. Found: C, 53.03; H, 5.27; N, 3.98.

2-(4-Diphenylmethyl-1-piperazinyl)ethyl (4*RS*)-5-[(4*R*,6*R*)-4,6-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl]-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate, [(4*R*,6*R*),4*RS*]-NIP-101·Free Base (1R) A solution of 1.70 g (5.0 mmol) of **6R** and 1.90 g (5.0 mmol) of 2-(4-diphenylmethyl-1-piperazinyl)ethyl 3-aminocrotonate (**7**) in 10 ml of toluene was stirred for 10 h under reflux and then concentrated *in vacuo*. Column chromatography of the resulting crude product using ethyl acetate–methanol (9 : 1, v/v) as an eluent afforded 2.22 g (63%) of **1R** (A_R isomer/B_R isomer = 1/1) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.50 (m, 6H, CH–C<u>H</u>$_3$ × 2), 1.75 (m, 2H, CH(CH$_3$)–C<u>H</u>$_2$), 2.22—2.70 (m, 16H, N–(C<u>H</u>$_2$)$_2$–N × 2 + N–C(=)–C<u>H</u>$_3$ × 2 + O–CH$_2$C<u>H</u>$_2$–N), 4.11—4.95 (m, 6H, O–C<u>H</u>$_2$CH$_2$–N + C<u>H</u>(Ph) + O–C<u>H</u>(CH$_3$) × 2 + C$_6$H$_4$(NO$_2$)–C<u>H</u>), 6.20 (br s, 1H, N<u>H</u>), 7.10—8.15 (m, 14H, Ar<u>H</u>).

2-(4-Diphenylmethyl-1-piperazinyl)ethyl (4*RS*)-5-[(4*S*,6*S*)-4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl]-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate, [(4*S*,6*S*),4*RS*]-NIP-101·free base (A_S isomer/B_S isomer = 1/1, **1S**) was obtained from **6S** in 65% yield in the same way as described above.

(*S*)-2-Methoxy-2-phenylethyl (4*RS*)-5-(4α,6α-Dimethyl-2β-oxo-1,3,2-dioxaphosphorinan-2α-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate, [(2α,4α,6α),(*S*),4*RS*]-DHP (9C) A solution of 8.30 g (24.5 mmol) of **6C** and 5.70 g (24.2 mmol) of (*S*)-2-methoxy-2-phenylethyl 3-aminocrotonate (**8**) in 40 ml of toluene was stirred for 5 h under reflux. The mixture was cooled to room temperature and then filtered. The cake was washed with two 20 ml portions of cold (10 °C) toluene and then dried *in vacuo* to afford 9.53 g (70%) of **9C** (A'_{cis} isomer/B'_{cis} isomer = 1/1) as pale yellow crystals. HPLC assay: t_R = 21.3/22.2 min. MS *m/z* (%): 121 (100%), 434 (82%), 539 (30%), 556 (M^+, 10%). *Anal.* Calcd for $C_{28}H_{33}N_2O_8P$: C, 60.42; H, 5.98; N, 5.03. Found: C, 60.52; H, 6.08; N, 4.93.

(*S*)-2-Methoxy-2-phenylethyl (4*RS*)-5-(4α,6α-Dimethyl-2β-oxo-1,3,2-dioxaphosphorinan-2α-yl)-1,4-dihydro-1-methoxymethyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate (10C) To a stirred, cooled (0 °C) suspension of 0.50 g (20.8 mmol) of sodium hydride in 50 ml of tetrahydrofuran (THF) was added dropwise a solution of 9.00 g (16.2 mmol)

of **9C** in 20 ml of THF over a 10-min period. The mixture was stirred an additional 1 h at room temperature and then cooled to 0 °C again. To the stirred, cooled (< 5 °C) mixture was added dropwise a solution of 1.35 g (16.7 mmol) of methoxymethyl chloride in 10 ml of THF over a 15-min period. The mixture was stirred for 3 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in 50 ml of chloroform and then washed with 50 ml of water. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. Column chromatography of the resulting crude product using ethyl acetate–ethanol (18 : 1, v/v) as an eluent afforded 8.60 g (89%) of the protected product **10C** (MOM·A'_{cis} isomer/MOM·B'_{cis} isomer = 1/1) as a yellow oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.3 (s, 3H, $CH_2OC\underline{H}_3$), 4.8 (s, 2H, $C\underline{H}_2OCH_3$).

Separation of 1R: Preparation of A_R·2HCl·2H$_2$O Isomer (1Ra·2HCl·2H$_2$O) and B_R·2HCl·2H$_2$O Isomer (1Rb·2HCl·2H$_2$O) To a stirred solution of 5.76 g (8.22 mmol) of **1R** in 28.8 ml of ethanol was added 1.8 g of 35% aqueous HCl at room temperature followed by removal of the solvent *in vacuo*. The resulting viscous 2HCl salt was dissolved in 43 g of hot ethanol and then cooled to 0 °C. The mixture was filtered, and the cake was recrystallized from 45 g of ethanol to afford 2.44 g (37%) of the 2HCl salt of a pure single diastereomer **1Ra**·2HCl·2H$_2$O as pale yellow crystals, mp 190.0—193.0 °C. $[\alpha]_D^{25}$ −16.7° (c = 0.50, MeOH). *Anal.* Calcd for $C_{38}H_{47}Cl_2N_4O_7P\cdot 2H_2O$: C, 56.36; H, 6.35; N, 6.92. Found: C, 56.13; H, 6.15; N, 6.74. ^{1}H-NMR spectral data of the free base **1Ra** at 500 MHz are listed in Table III.

The filtrates were combined and then concentrated *in vacuo*. The residue was crystallized from acetone (acetone : residue, 20 : 1, w/w). The resulting crystals were dissolved in ethanol again and then concentrated. Recrystallization of the residue from acetone gave 1.99 g (30%) of the 2HCl salt of another single diastereomer **1Rb**·2HCl·2H$_2$O as pale yellow crystals. mp 170.0—172.0 °C. $[\alpha]_D^{25}$ +38.0° (c = 0.50, MeOH). *Anal.* Calcd for $C_{38}H_{47}Cl_2N_4O_7P\cdot 2H_2O$: C, 56.36; H, 6.35; N, 6.92. Found: C, 56.62; H, 6.09; N, 6.85. ^{1}H-NMR spectral data of free base **1Rb** at 500 MHz is listed in Table III.

The 2HCl salts of single diastereomers of (**1S**), A_S·2HCl·2H$_2$O isomer (**1Sa**·2HCl·2H$_2$O) and B_S·2HCl·2H$_2$O isomer (**1Sb**·2HCl·2H$_2$O), were obtained from **10S** in the same way as described above. **11S**·2HCl·2H$_2$O: pale yellow crystals, mp 190.0—193.0 °C. $[\alpha]_D^{25}$ +16.9° (c = 0.50, MeOH). *Anal.* Calcd for $C_{38}H_{47}Cl_2N_4O_7P\cdot 2H_2O$: C, 56.36; H, 6.35; N, 6.92. Found: C, 56.18; H, 6.42; N, 6.76. **11Sb**·2HCl·2H$_2$O: pale yellow crystals, mp 170.0—172.0 °C. $[\alpha]_D^{25}$ −38.0° (c = 0.50, MeOH). *Anal.* Calcd for $C_{38}H_{47}Cl_2N_4O_7P\cdot 2H_2O$: C, 56.36; H, 6.35; N, 6.92. Found: C, 56.40; H, 6.26; N, 6.98. ^{1}H-NMR spectral data of the free bases **1Sa** and **1Sb** were identical to those of **1Ra** and **1Rb**, respectively.

Separation of 10C: Preparation of MOM·A'_{cis} Isomer (10Ca) and MOM·B'_{cis} Isomer (10Cb) A stirred suspension of 8.60 g (14.3 mmol) of **10C** in 120 ml of ethyl acetate was heated in an oil bath until **10C** was completely dissolved. The hot homogenous solution was filtered. The filtrate was allowed to come to room temperature and left overnight. The mixture was filtered, and the cake was recrystallized from 60 ml of ethyl acetate to afford 3.10 g (36%) of a single diastereomer **10Ca** as colorless needles, mp 170.5 °C. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.11 (dd, 3H, J = 6.2, 1.5 Hz, O–$CH_{eq}C\underline{H}_3$), 1.35 (dd, 3H, J = 6.2, 1.5 Hz, O–$CH_{eq}C\underline{H}_3$), 1.50—1.90 (m, 2H, $CH(CH_3)$–$C\underline{H}_2$), 2.47 (s, 3H, NH–C(=)–$C\underline{H}_3$), 2.58 (d, 3H, J = 2.4 Hz, NH–C(=)–$C\underline{H}_3$), 3.26 (s, 3H, O–$C\underline{H}_3$), 3.27 (s, 3H, O–CH_3), 4.10—4.90 (m, 5H, P–O–C$\underline{H}$ × 2 + O–$C\underline{H}_2C\underline{H}(OCH_3)$Ph), 4.79 (s, 2H, O–$C\underline{H}_2$–O), 5.00 (d, 1H, J = 13.0 Hz, $(NO_2)C_6H_4$–C$\underline{H}$), 7.32 (s, 5H, $C_6\underline{H}_5$), 7.30—8.15 (m, 4H, $(NO_2)C_6\underline{H}_4$). ^{31}P-NMR (36.2 MHz) δ: 18.93 (s). MS m/z (%): 121 (100%), 317 (8%), 434 (15%), 600 (M^+, 3%). $[\alpha]_D^{25}$ +0.8° (c = 0.50, MeOH). HPLC assay: t_R = 32.4 min. *Anal.* Calcd for $C_{30}H_{37}N_2O_9P$: C, 59.99; H, 6.21; N, 4.66. Found: C, 59.82; H, 6.16; N, 4.54.

The filtrates were combined and concentrated *in vacuo*. The residue was dissolved in chloroform. To the solution, concentrated to such an extent that no precipitate was preformed, was added 40 ml of ether. The mixture was left overnight at room temperature and then filtered. The cake was recrystallized, in the same manner, from chloroform–ether to afford 3.10 g (36%) of another single diastereomer, **10Cb**, as colorless needles, mp 133.0 °C. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.11 (dd, 3H, J = 6.2, 1.5 Hz, O–$CH_{eq}C\underline{H}_3$), 1.36 (dd, 3H, J = 6.2, 1.5 Hz, O–$CH_{eq}C\underline{H}_3$), 1.50—1.90 (m, 2H, $CH(CH_3)$–$C\underline{H}_2$), 2.47 (s, 3H, NH–C(=)–$C\underline{H}_3$), 2.59 (d, 3H, J = 2.4 Hz, NH–C(=)–$C\underline{H}_3$), 3.27 (s, 3H, O–$C\underline{H}_3$), 3.28 (s, 3H, O–$C\underline{H}_3$), 4.10—4.90 (m, 5H, P–O–C$\underline{H}$ × 2 + O–$C\underline{H}_2C\underline{H}(OCH_3)$Ph), 4.79 (s, 2H, O–$C\underline{H}_2$–O), 5.00 (d, 1H, J = 13.0 Hz, $(NO_2)C_6H_4$–C$\underline{H}$), 7.32 (s, 5H, $C_6\underline{H}_5$), 7.30—8.15 (m, 4H, $(NO_2)C_6\underline{H}_4$). ^{31}P-NMR (36.2 MHz) δ: 18.79 (s). MS m/z (%): 121 (100%), 317 (37%), 421 (33%), 600 (M^+, 23%). $[\alpha]_D^{25}$ +46.0° (c = 0.50, MeOH). HPLC assay: t_R = 34.2 min. *Anal.* Calcd for $C_{30}H_{37}N_2O_9P$: C, 59.99; H, 6.21; N, 4.66. Found: C, 59.89; H, 6.22; N, 4.49.

Enantiomeric 2-(4-Diphenylmethyl-1-piperazinyl)ethyl 5-(4α,6α-Dimethyl-2β-oxo-1,3,2-dioxaphosphorinan-2α-yl)-1,4-dihydro-1-methoxymethyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylates, MOM·A_{cis} Isomer (12Ca) and MOM·B_{cis} Isomer (12Cb) To 40 ml of a THF solution containing 8.00 g (27.0 mmol) of 4-diphenylmethyl-1-piperazineethanol (**11**) was added 100 mg (4.35 mmol) of metal sodium. The mixture was stirred overnight at room temperature. To the stirred mixture was added dropwise 10 ml of a THF solution containing 2.00 g (3.33 mmol) of **10Ca** over a 10-min period at room temperature. The mixture was heated in an oil bath at 50 °C for 2 h and then concentrated *in vacuo*. Column chromatography of the resulting crude product using ethyl acetate–ethanol (18 : 1, v/v) as an eluent afforded 1.82 g (73%) of **12Ca** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (dd, 3H, J = 6.2, 1.5 Hz, CH–$_{eq}C\underline{H}_3$), 1.30 (dd, 3H, J = 6.2, 1.5 Hz, CH–$_{eq}C\underline{H}_3$), 1.50—1.90 (m, 2H, $CH(CH_3)$–$C\underline{H}_2$), 2.20—2.60 (m, 8H, N–$C\underline{H}_2C\underline{H}_2$–N × 2), 2.46 (s, 3H, NH–C(=)–$C\underline{H}_3$), 2.53 (d, 3H, J = 2.4 Hz, NH–C(=)–$C\underline{H}_3$), 2.62 (m, 2H, O–$CH_2C\underline{H}_2$–N), 3.22 (s, 3H, O–$C\underline{H}_3$), 4.15 (m, 2H, O–$C\underline{H}_2CH_2$–N), 4.20 (s, 1H, $C\underline{H}(Ph)_2$), 4.50—4.85 (m, 2H, O–$C\underline{H}(CH_3)$ × 2), 4.72 (s, 2H, N–$C\underline{H}_2$–O), 4.94 (d, 1H, J = 10.3 Hz, $C_6H_4(NO_2)$–C$\underline{H}$), 6.9—8.0 (m, 14H, Ar$\underline{H}$). MS m/z (%): 167 (60%), 278 (3%), 405 (3%), 727 (M^+ − 17, 1%), $[\alpha]_D^{25}$ +4.4° (c = 0.50, MeOH).

Another enantiomer **12Cb** was obtained from **10Cb** in the same way as described above. Yellow oil. $[\alpha]_D^{25}$ −4.4° (c = 0.50, MeOH).

Enantiomeric 2-(4-Diphenylmethyl-1-piperazinyl)ethyl 5-(4α,6α-Dimethyl-2β-oxo-1,3,2-dioxaphosphorinan-2α-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate Dihydrochlorides, A_{cis}·2HCl·2H$_2$O Isomer (1Ca·2HCl·2H$_2$O) and B_{cis}·2HCl·2H$_2$O Isomer (1Cb·2HCl·2H$_2$O) A solution of 1.10 g (1.48 mmol) of **12Ca** in 10 ml of 28% ethanolic HCl was stirred at room temperature for 5 h and then concentrated *in vacuo*. The residue was recrystallized from ethanol–ethyl acetate to afford 1.14 g (96%) of **1Ca**·2HCl·2H$_2$O as colorless crystals, mp 180.0—183.0 °C. $[\alpha]_D^{25}$ −37.2° (c = 0.50, MeOH). *Anal.* Calcd for $C_{38}H_{47}Cl_2N_4O_7P\cdot 2H_2O$: C, 56.36; H, 6.35; N, 6.92. Found: C, 56.55; H, 6.19; N, 6.85. ^{1}H-NMR spectral data of the free base **1Ca** at 500 MHz are listed in Table III.

Another enantiomer, **1Cb**·2HCl·2H$_2$O, was obtained from **12Cb** in 96% yield as colorless crystals in the same way as described above, mp 180.0—183.0 °C. $[\alpha]_D^{25}$ +37.2° (c = 0.50, MeOH). *Anal.* Calcd for $C_{38}H_{47}Cl_2N_4O_7P\cdot 2H_2O$: C, 56.36; H, 6.35; N, 6.92. Found: C, 56.09; H, 6.34; N, 6.77.

References and Notes

1) This work was presented at the 107th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1987.
2) T. Sakai, Y. Masuda, M. Iijima, Y. Satho, M. Takeguchi, and S. Tanaka, *Nippon Yakurigaku Zasshi*, **87**, 64P (1986).
3) R. Katho, *Xenobio. Metabol. Dispos.*, **2**, 177 (1987); R. Katho and Y. Yamazoe, *Toxicology Forum*, **10**, 247 (1987).
4) Y. Tokuma, T. Fujiwara, and H. Noguti, *J. Pharm. Sci.*, **76**, 310 (1987).
5) R. P. Hof, A. Hof, U. T. Ruegg, N. S. Cook, and A. Vogel, *J. Cardiovasc. Pharmacol.*, **8**, 221 (1986).
6) T. Takenaka, Y. Miyazaki, M. Asano, S. Higuchi, and H. Maeno, *Jpn. J. Pharmacol.*, **32**, 665 (1982).
7) R. Towart, E. Wehinger, H. Meyer, and S. Kazda, *Arzneim.-Forsch.*, **32**, 338 (1982).
8) K. Muto, T. Kuroda, H. Kawato, A. Karasawa, K. Kubo, and N. Nakamizo, *Arzneim.-Forsch.*, **38**, 1662 (1988).
9) J. E. Arrowsmith, S. F. Campbell, P. E. Cross, J. K. Stubbs, R. A. Burges, D. G. Gardiner, and K. J. Blackburn, *J. Med. Chem.*, **29**, 1696 (1986).
10) S. Kokubun, B. Prod'hom, C. Becker, H. Porzig, and H. Reuter, *Mol. Pharmacol.*, **30**, 571 (1986); R. P. Hof, U. T. Ruegg, A. Hof, and A. Vogel, *J. Cardiovasc. Pharmacol.*, **7**, 689 (1985).
11) F. Bossert, H. Meyer, and E. Wehinger, *Angew. Chem. Int. Ed. Engl.*, **20**, 762 (1981); D. Enders, S. Müller, and A. S. Demir, *Tetrahedron Lett.*, **29**, 6437 (1988).
12) D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Am. Chem. Soc.*, **92**, 7125 (1970).
13) M. Haemers, R. Ottinger, J. Reisse, and D. Zimmermann, *Tetrahedron Lett.*, **1971**, 461; D. Z. Denney and D. B. Denney, *J.*

Am. Chem. Soc., **88**, 1830 (1966); J. Rodgers, D. W. White, and J. G. Verkade, *J. Chem. Soc. (A)*, **1971**, 77.
14) J. A. Mosbo and J. G. Verkade, *J. Org. Chem.*, **42**, 1549 (1977); R. D. Adamcik, L. L. Chang, and D. B. Denney, *J. Chem. Soc., Chem. Commun.*, **1974**, 986.
15) H. Matsumoto, K. Seto, and R. Sakoda, Abstracts of Papers, 54th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1987, p. 948.
16) H. Meyer, F. Bossert, E. Wehinger, K. Stoepel, and W. Vater, *Arzneim. Forsch.*, **31**, 407 (1981).
17) T. Shibanuma, M. Iwanami, K. Okuda, T. Takenaka, and M. Murakami, *Chem. Pharm. Bull.*, **28**, 2809 (1980).
18) A large number of such studies has been reported. Some of them include R. J. M. Hermans and H. M. Buck, *J. Org. Chem.*, **52**, 5150 (1987); K. Taira, K. Lai, and D. G. Gorenstein, *Tetrahedron*, **42**, 229 (1986); D. G. Gorenstein and R. Rowell, *J. Am. Chem. Soc.*, **101**, 4925 (1979); B. E. Maryanoff, R. O. Hutchins, and C. A. Maryanoff, *Top. Stereochem.*, **11**, 187 (1973); W. G. Bentrude and H.-W. Tan, *J. Am. Chem. Soc.*, **95**, 4666 (1973); W. G. Bentrude and K. C. Yee, *J. Chem. Soc., Chem. Commun.*, **1972**, 169.
19) K. Tamazawa, H. Arima, T. Kojima, Y. Isomura, M. Okada, S. Fujita, T. Furuya, T. Takenaka, O. Inagaki, and M. Terai, *J. Med. Chem.*, **29**, 2504 (1986); M. Kajino, Y. Wada, Y. Nagai, A. Nagaoka, and K. Meguro, *Chem. Pharm. Bull.*, **37**, 2225 (1989).
20) D. Valentine, Jr., K. K. Johnson, W. Priester, R. C. Sun, K. Toth, and G. Saucy, *J. Org. Chem.*, **45**, 3698 (1980).
21) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).