Synthesis and Crystal Structure of Optically Active 2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate (NZ-105)

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(*S*)-2-[Benzyl(phenyl)amino]ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate ((*S*)-NZ-105) and *R* isomer were synthesized through the fractional crystallization of (*S*)-2-Methoxy-2-phenylethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate. Calcium antagonism activity was found to reside in the *S* isomer from single crystal X-ray diffraction analysis

Keywords optical resolution; X-ray diffraction analysis; calcium antagonist; 2-[benzyl(phenyl)amino]ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate; NZ-105

2-[Benzyl(phenyl)amino]ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate hydrochloride ethanol (NZ-105) is a novel calcium antagonist with potent hypotensive and selective cerebral vasodilating activities.[1] This agent is known to exhibit its vasodilative action by selectively antagonizing against the vascular calcium channel and is expected to be a new type of drug.

NZ-105 has a stereogenic center in the dihydropyridine skeleton. Investigating the stereoselectivity of calcium antagonism, observed in many 1,4-dihydropyridine-3,5-dicarboxylates containing unsymmetrical ester groups,[2] strong activity was found to reside with the *S* enantiomer in NZ-105. The present article intends to report the method recently established for the synthesis of each enantiomer and absolute configuration determined by single crystal X-ray diffraction analysis.

Results

Synthesis of Optically Active Isomers Synthesis of optically active isomers was carried out as shown in Chart 1. 5,5-Dimethyl-2-[1-(3-nitrophenyl)-3-oxo-1-buten-2-yl]-2-oxo-1,3,2-dioxaphosphorinane (**1**) was obtained in good yield by the aminal method,[3] and (*S*)-(2-methoxy-2-phenyl)ethyl 3-aminocrotonate ((*S*)-**2**) from (*S*)-(2-methoxy-2-phenyl)ethanol by a conventional procedure.[4] A reaction of **1** with (*S*)-**2** gave (*RS*,*S*)-**3** as a 1 : 1 mixture of diastereomers in 74% yield. Crystallization of crude (*RS*,*S*)-**3** from ethyl acetate gave a single diastereomer (*S*,*S*)-**3** in 37% yield as pale yellow crystals. Diastereomer (*S*,*S*)-**3** was converted to (*S*)-**5** by protection of the amino group in the dihydropyridine ring by $ClCH_2OCH_3$ (MOM

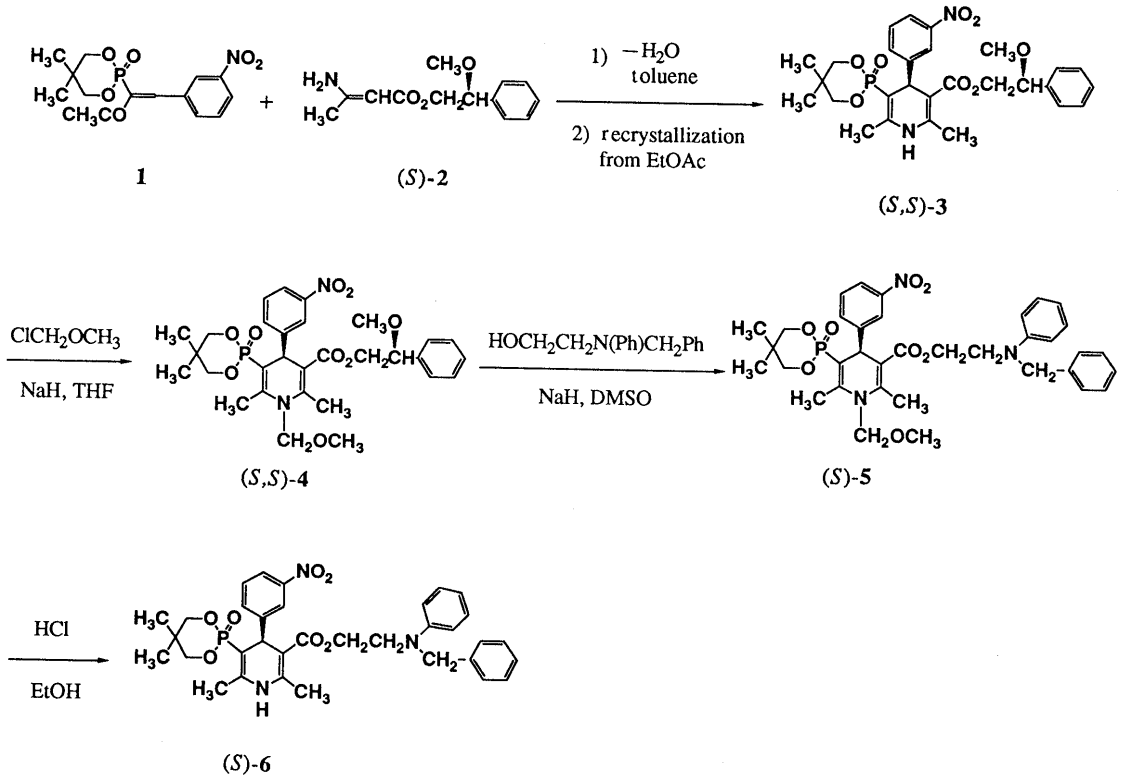

Chart 1

chloride), followed by transesterification with 2-[benzyl-(phenyl)amino]ethanol in the presence of sodium hydride. Deprotection of (*S*)-**5** with hydrochloric acid gave (*S*)-**6** quantitatively. Another enantiomer, (*R*)-**6**, was prepared as follows. The mother liquor containing (*RS*,*S*)-**3** was condensed, and the residue was crystallized from toluene to give pale yellow crystals, which were composed of equimolecular amounts of (*S*,*S*)-**3**, (*R*,*S*)-**3**, and toluene. Because an attempt to separate them by repeated recrystallization was unsuccessful, the diastereomeric mixture of **3** was subjected to subsequent reactions, from which **6** was derived, and finally, (*R*)-**6** was obtained in 100% enantiomeric purity by recrystallizations from ethanol.

Calcium Antagonism *In vitro* calcium antagonist activity was assessed against calcium (10 mM)-induced constriction of potassium-depolarized rabbit aorta. As the concentrations of (*S*)-**6** and (*R*)-**6** required to induce relaxation

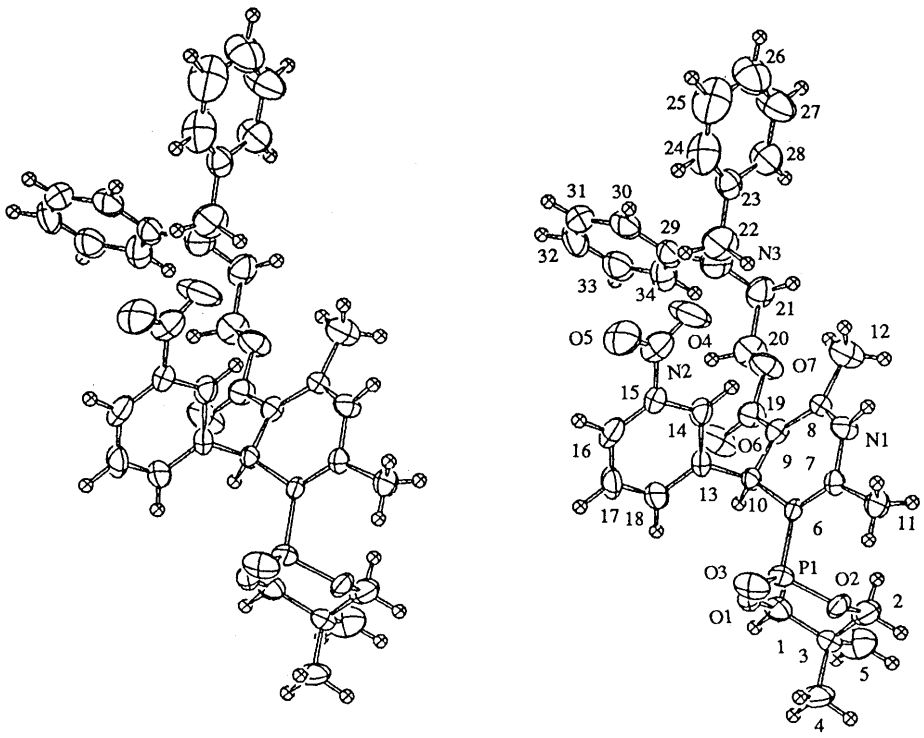

Fig. 1. An ORTEP Stereo-Drawing of (*S*)-**6** with Atomic Numbering

Thermal ellipsoids are drawn at the 50% probability level, H atoms given orbitary thermal parameters for clarity.

TABLE I. Atomic Positional and Thermal Parameters with Their e.s.d.'s in Parentheses

Atom	*x*	*y*	*z*	B_{eq} (Å^2)	Atom	*x*	*y*	*z*	B_{eq} (Å^2)
P(1)	0.7456 (2)	0.66973 (9)	0.8934 (2)	2.75 (9)	C(13)	0.6974 (6)	0.6653 (4)	1.2366 (8)	2.6 (4)
O(1)	0.7946 (4)	0.6119 (2)	0.9092 (5)	3.0 (3)	C(14)	0.6461 (6)	0.7013 (4)	1.325 (1)	3.3 (4)
O(2)	0.7097 (4)	0.6727 (2)	0.7414 (5)	3.3 (3)	C(15)	0.7051 (7)	0.7283 (4)	1.420 (1)	3.2 (4)
O(3)	0.8189 (4)	0.7128 (2)	0.9212 (7)	4.5 (3)	C(16)	0.8055 (8)	0.7218 (4)	1.435 (1)	4.0 (5)
O(4)	0.5588 (6)	0.7634 (4)	1.5132 (9)	8.7 (5)	C(17)	0.8560 (7)	0.6862 (4)	1.349 (1)	4.1 (5)
O(5)	0.6996 (6)	0.7971 (3)	1.5781 (8)	6.3 (4)	C(18)	0.7994 (7)	0.6586 (4)	1.253 (1)	4.0 (5)
O(6)	0.5856 (5)	0.5407 (2)	1.2614 (8)	5.9 (4)	C(19)	0.5204 (7)	0.5744 (4)	1.249 (1)	3.3 (4)
O(7)	0.4313 (4)	0.5684 (3)	1.3126 (7)	4.6 (3)	C(20)	0.4083 (8)	0.5169 (4)	1.372 (1)	4.5 (5)
N(1)	0.4714 (5)	0.7016 (3)	1.0557 (7)	3.2 (3)	C(21)	0.3165 (8)	0.5252 (5)	1.463 (1)	5.1 (6)
N(2)	0.6493 (8)	0.7664 (3)	1.5083 (9)	5.0 (5)	C(22)	0.3431 (9)	0.6047 (5)	1.613 (1)	6.3 (6)
N(3)	0.3460 (7)	0.5459 (4)	1.591 (1)	5.4 (5)	C(23)	0.2587 (7)	0.6249 (4)	1.704 (1)	4.1 (5)
C(1)	0.7472 (7)	0.5644 (3)	0.8452 (8)	3.3 (4)	C(24)	0.271 (1)	0.6651 (5)	1.797 (1)	6.7 (7)
C(2)	0.6588 (7)	0.6254 (4)	0.686 (1)	4.2 (5)	C(25)	0.196 (1)	0.6838 (5)	1.877 (2)	9 (1)
C(3)	0.7253 (6)	0.5745 (4)	0.6985 (9)	3.3 (4)	C(26)	0.097 (1)	0.6641 (5)	1.859 (1)	7.4 (8)
C(4)	0.8206 (7)	0.5812 (4)	0.618 (1)	5.0 (5)	C(27)	0.0834 (8)	0.6255 (5)	1.770 (1)	7.3 (7)
C(5)	0.6664 (8)	0.5249 (4)	0.647 (1)	5.7 (6)	C(28)	0.1600 (8)	0.6049 (5)	1.691 (1)	6.1 (6)
C(6)	0.6357 (6)	0.6697 (3)	0.9970 (7)	2.3 (3)	C(29)	0.3831 (7)	0.5118 (4)	1.692 (1)	4.0 (5)
C(7)	0.5586 (6)	0.7030 (3)	0.9736 (8)	2.5 (4)	C(30)	0.4142 (7)	0.5323 (5)	1.816 (1)	5.1 (6)
C(8)	0.4529 (6)	0.6591 (4)	1.1408 (8)	2.9 (4)	C(31)	0.4514 (8)	0.4962 (6)	1.909 (1)	5.9 (7)
C(9)	0.5311 (6)	0.6237 (3)	1.1709 (8)	2.6 (4)	C(32)	0.4610 (8)	0.4419 (6)	1.886 (1)	6.0 (7)
C(10)	0.6369 (6)	0.6368 (3)	1.1263 (8)	2.5 (4)	C(33)	0.4284 (8)	0.4222 (5)	1.768 (1)	5.5 (6)
C(11)	0.5491 (6)	0.7444 (4)	0.8608 (8)	3.7 (5)	C(34)	0.3921 (7)	0.4559 (4)	1.670 (1)	4.8 (6)
C(12)	0.3464 (7)	0.6573 (4)	1.190 (1)	4.9 (5)					

TABLE II. Selected Bond Lengths (Å), Angles (°), and Torsion Angles (°) with Their e.s.d.'s in Parentheses
[Intramolecular distances]

Atom	Atom	Distance	Atom	Atom	Distance	Atom	Atom	Distance
P(1)	O(3)	1.457 (6)	C(1)	C(3)	1.51 (1)	C(17)	C(18)	1.39 (1)
P(1)	O(1)	1.565 (5)	C(2)	C(3)	1.53 (1)	C(20)	C(21)	1.52 (1)
P(1)	O(2)	1.588 (5)	C(3)	C(4)	1.50 (1)	C(22)	C(23)	1.52 (1)
P(1)	C(6)	1.776 (8)	C(3)	C(5)	1.53 (1)	C(23)	C(24)	1.36 (1)
O(1)	C(1)	1.467 (9)	C(6)	C(7)	1.32 (1)	C(23)	C(28)	1.39 (1)
O(2)	C(2)	1.45 (1)	C(6)	C(10)	1.52 (1)	C(24)	C(25)	1.34 (2)
O(4)	N(2)	1.19 (1)	C(7)	C(11)	1.52 (1)	C(25)	C(26)	1.40 (2)
O(5)	N(2)	1.22 (1)	C(8)	C(9)	1.38 (1)	C(26)	C(27)	1.31 (2)
O(6)	C(19)	1.20 (1)	C(8)	C(12)	1.49 (1)	C(27)	C(28)	1.38 (1)
O(7)	C(19)	1.34 (1)	C(9)	C(19)	1.44 (1)	C(29)	C(34)	1.39 (1)
O(7)	C(20)	1.43 (1)	C(9)	C(10)	1.50 (1)	C(29)	C(30)	1.40 (1)
N(1)	C(8)	1.37 (1)	C(10)	C(13)	1.53 (1)	C(30)	C(31)	1.38 (1)
N(1)	C(7)	1.41 (1)	C(13)	C(18)	1.36 (1)	C(31)	C(32)	1.35 (2)
N(2)	C(15)	1.48 (1)	C(13)	C(14)	1.42 (1)	C(32)	C(33)	1.35 (2)
N(3)	C(29)	1.39 (1)	C(14)	C(15)	1.39 (1)	C(33)	C(34)	1.36 (1)
N(3)	C(21)	1.43 (1)	C(15)	C(16)	1.34 (1)			
N(3)	C(22)	1.46 (1)	C(16)	C(17)	1.39 (1)			

TABLE II. (continued)
[Intramolecular bond angles]

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
O(3)	P(1)	O(1)	111.4 (3)	C(4)	C(3)	C(1)	112.1 (7)
O(3)	P(1)	O(2)	110.2 (4)	C(4)	C(3)	C(2)	110.2 (8)
O(3)	P(1)	C(6)	115.4 (4)	C(4)	C(3)	C(5)	109.3 (8)
O(1)	P(1)	O(2)	105.1 (3)	C(1)	C(3)	C(2)	109.0 (7)
O(1)	P(1)	C(6)	106.0 (3)	C(1)	C(3)	C(5)	107.1 (8)
O(2)	P(1)	C(6)	108.2 (3)	C(2)	C(3)	C(5)	109.1 (7)
C(1)	O(1)	P(1)	120.0 (5)	C(7)	C(6)	C(10)	118.9 (7)
C(2)	O(2)	P(1)	117.7 (5)	C(7)	C(6)	P(1)	121.5 (6)
C(19)	O(7)	C(20)	118.6 (7)	C(10)	C(6)	P(1)	119.0 (5)
C(8)	N(1)	C(7)	121.6 (6)	C(6)	C(7)	N(1)	120.5 (7)
O(4)	N(2)	O(5)	124 (1)	C(6)	C(7)	C(11)	127.2 (8)
O(4)	N(2)	C(15)	118.7 (9)	N(1)	C(7)	C(11)	112.3 (7)
O(5)	N(2)	C(15)	117.4 (9)	N(1)	C(8)	C(9)	118.8 (7)
C(29)	N(3)	C(21)	122 (1)	N(1)	C(8)	C(12)	113.3 (7)
C(29)	N(3)	C(22)	120 (1)	C(9)	C(8)	C(12)	127.9 (8)
C(21)	N(3)	C(22)	118 (1)	C(8)	C(9)	C(19)	124.8 (8)
O(1)	C(1)	C(3)	111.8 (7)	C(8)	C(9)	C(10)	119.7 (7)
O(2)	C(2)	C(3)	110.8 (7)	C(19)	C(9)	C(10)	115.4 (7)
C(9)	C(10)	C(6)	110.8 (6)	N(3)	C(22)	C(23)	115.3 (9)
C(9)	C(10)	C(13)	111.7 (7)	C(24)	C(23)	C(28)	115 (1)
C(6)	C(10)	C(13)	111.8 (6)	C(24)	C(23)	C(22)	124 (1)
C(18)	C(13)	C(14)	118.0 (9)	C(28)	C(23)	C(22)	121 (1)
C(18)	C(13)	C(10)	123.0 (9)	C(25)	C(24)	C(23)	125 (1)
C(14)	C(13)	C(10)	119.0 (7)	C(24)	C(25)	C(26)	119 (1)
C(15)	C(14)	C(13)	116.9 (8)	C(27)	C(26)	C(25)	118 (1)
C(16)	C(15)	C(14)	125 (1)	C(26)	C(27)	C(28)	123 (1)
C(16)	C(15)	N(2)	120 (1)	C(27)	C(28)	C(23)	120 (1)
C(14)	C(15)	N(2)	115.4 (8)	C(34)	C(29)	N(3)	121 (1)
C(15)	C(16)	C(17)	118 (1)	C(34)	C(29)	C(30)	118 (1)
C(16)	C(17)	C(18)	118.2 (8)	N(3)	C(29)	C(30)	121 (1)
C(13)	C(18)	C(17)	123 (1)	C(31)	C(30)	C(29)	118 (1)
O(6)	C(19)	O(7)	120.0 (8)	C(32)	C(31)	C(30)	123 (1)
O(6)	C(19)	C(9)	124.4 (8)	C(33)	C(32)	C(31)	118 (1)
O(7)	C(19)	C(9)	115.6 (8)	C(32)	C(33)	C(34)	121 (1)
O(7)	C(20)	C(21)	107.2 (8)	C(33)	C(34)	C(29)	121 (1)
N(3)	C(21)	C(20)	111.3 (8)				

TABLE II. (continued)
[Torsion or conformation angles]

(1)	(2)	(3)	(4)	Angle	(1)	(2)	(3)	(4)	Angle
P(1)	O(1)	C(1)	C(3)	50.6 (8)	O(4)	N(2)	C(15)	C(16)	−164 (1)
P(1)	O(2)	C(2)	C(3)	−56.7 (8)	O(4)	N(2)	C(15)	C(14)	15 (1)
P(1)	C(6)	C(7)	N(1)	178.9 (6)	O(5)	N(2)	C(15)	C(16)	12 (1)
P(1)	C(6)	C(7)	C(11)	1 (1)	O(5)	N(2)	C(15)	C(14)	−168.7 (9)
P(1)	C(6)	C(10)	C(9)	−158.0 (6)	O(6)	C(19)	O(7)	C(20)	−13 (1)
P(1)	C(6)	C(10)	C(13)	76.7 (8)	O(6)	C(19)	C(9)	C(8)	171 (1)
O(1)	C(1)	C(3)	C(4)	66 (1)	O(6)	C(19)	C(9)	C(10)	−11 (1)
O(1)	C(1)	C(3)	C(2)	−56.3 (9)	O(7)	C(19)	C(9)	C(8)	−11 (1)
O(1)	C(1)	C(3)	C(5)	−174.2 (7)	O(7)	C(19)	C(9)	C(10)	166.4 (8)
O(1)	P(1)	O(2)	C(2)	43.8 (6)	O(7)	C(20)	C(21)	N(3)	−83 (1)
O(1)	P(1)	C(6)	C(7)	−155.9 (7)	N(1)	C(8)	C(9)	C(19)	−173.9 (8)
O(1)	P(1)	C(6)	C(10)	33.1 (7)	N(1)	C(8)	C(9)	C(10)	9 (1)
O(2)	C(2)	C(3)	C(4)	−63 (1)	N(1)	C(7)	C(6)	C(10)	−10 (1)
O(2)	C(2)	C(3)	C(1)	60 (1)	N(2)	C(15)	C(16)	C(17)	−179.2 (8)
O(2)	C(2)	C(3)	C(5)	176.5 (7)	N(2)	C(15)	C(14)	C(13)	178.7 (8)
O(2)	P(1)	O(1)	C(1)	−40.7 (6)	N(3)	C(29)	C(34)	C(33)	180 (6)
O(2)	P(1)	C(6)	C(7)	−43.6 (8)	N(3)	C(29)	C(30)	C(31)	−179 (1)
O(2)	P(1)	C(6)	C(10)	145.5 (6)	N(3)	C(22)	C(23)	C(24)	140 (1)
O(3)	P(1)	O(1)	C(1)	−159.9 (6)	N(3)	C(22)	C(23)	C(28)	−44 (1)
O(3)	P(1)	O(2)	C(2)	163.9 (6)	C(1)	O(1)	P(1)	C(6)	73.8 (6)
O(3)	P(1)	C(6)	C(7)	80.3 (8)	C(2)	O(2)	P(1)	C(6)	−69.2 (6)
O(3)	P(1)	C(6)	C(10)	−90.7 (7)	C(6)	C(7)	N(1)	C(8)	−15 (1)
C(6)	C(10)	C(9)	C(8)	−30 (1)	C(15)	C(14)	C(13)	C(18)	2 (1)
C(6)	C(10)	C(9)	C(19)	152.1 (7)	C(19)	O(7)	C(20)	C(21)	167.5 (8)
C(6)	C(10)	C(13)	C(18)	−88 (1)	C(20)	C(21)	N(3)	C(29)	−81 (1)
C(6)	C(10)	C(13)	C(14)	91 (1)	C(20)	C(21)	N(3)	C(22)	95 (1)
C(7)	C(6)	C(10)	C(9)	31 (1)	C(21)	N(3)	C(29)	C(34)	0 (1)
C(7)	C(6)	C(10)	C(13)	−94.5 (9)	C(21)	N(3)	C(29)	C(30)	178.4 (9)
C(7)	N(1)	C(8)	C(9)	16 (1)	C(21)	N(3)	C(22)	C(23)	108 (1)
C(7)	N(1)	C(8)	C(12)	−164.2 (8)	C(22)	N(3)	C(29)	C(34)	−176 (1)
C(8)	N(1)	C(7)	C(11)	163.4 (7)	C(22)	N(3)	C(29)	C(30)	3 (1)
C(8)	C(9)	C(10)	C(13)	95.3 (9)	C(22)	C(23)	C(24)	C(25)	179 (1)
C(9)	C(19)	O(7)	C(20)	169.4 (8)	C(22)	C(23)	C(28)	C(27)	−177 (1)
C(9)	C(10)	C(13)	C(18)	147.1 (9)	C(23)	C(24)	C(25)	C(26)	−5 (2)
C(9)	C(10)	C(13)	C(14)	−34 (1)	C(23)	C(28)	C(27)	C(26)	1 (2)
C(10)	C(9)	C(8)	C(12)	−172 (1)	C(23)	C(22)	N(3)	C(29)	−76 (1)
C(10)	C(6)	C(7)	C(11)	171.8 (7)	C(24)	C(25)	C(26)	C(27)	4 (2)
C(10)	C(13)	C(18)	C(17)	177.1 (8)	C(24)	C(23)	C(28)	C(27)	−1 (2)
C(10)	C(13)	C(14)	C(15)	−177.0 (7)	C(25)	C(24)	C(23)	C(28)	3 (2)
C(12)	C(8)	C(9)	C(19)	6 (1)	C(25)	C(26)	C(27)	C(28)	−2 (2)
C(13)	C(18)	C(17)	C(16)	1 (2)	C(29)	C(34)	C(33)	C(32)	−3 (2)
C(13)	C(14)	C(15)	C(16)	−2 (2)	C(29)	C(30)	C(31)	C(32)	1 (2)
C(13)	C(10)	C(9)	C(19)	−82 (1)	C(30)	C(31)	C(32)	C(33)	−3 (2)
C(14)	C(15)	C(16)	C(17)	1 (2)	C(30)	C(29)	C(34)	C(33)	1 (1)
C(14)	C(13)	C(18)	C(17)	−2 (1)	C(31)	C(32)	C(33)	C(34)	4 (2)
C(15)	C(16)	C(17)	C(18)	−1 (1)	C(31)	C(30)	C(29)	C(34)	0 (2)

TABLE III. The Deviations of Atoms (Å) from the Least-Squares Best Plane through Each of 4 Atoms

Atoms	Distance	Atoms	Distance
C(6)	−0.005 (7)	C(8)	−0.005 (8)
C(7)	0.006 (8)	C(9)	0.005 (8)

by 50% were 2.57 nM and 2190 nM, respectively, (*S*)-**6** exhibited no less than 850-fold activity compared with that of (*R*)-**6**.

X-Ray Diffraction Analysis An ORTEP[5] stereo drawing of (*S*)-**6** with atomic labeling is shown in Fig. 1. The atomic positional parameters and equivalent isotropic thermal parameters are listed in Table I,[6] and Table II presents selected bond lengths, angles and torsion angles.

As shown in Fig. 1, the absolute configuration at the 4-position [C(10)] in the dihydropyridine ring is an *S* configuration. While the carbonyl group, C(19)=O(9), in the 3-position [C(9)] is antiperplanar (171°) with respect to C(8)–C(9), which is same as in the case of 1,4-dihydropyridine-3,5-dicarboxylic acid derivatives,[7] the P(1)=O(3) bond is practically perpendicular (80.3°) to the C(6)–C(7) bond. The nitro group in the phenyl ring in the 4-position [C(10)] points out of the dihydropyridine ring, which is reverse of its configuration in the racemic compound.[8]

The dihydropyridine ring was in a boat-type conformation, the deviation of N(1) and C(10) atoms from

the least-squares best plane of C(6)–C(7)–C(8)–C(9) being 0.156 Å and 0.378 Å in the same direction, respectively (Table III). The dioxaphosphorinane ring, on the other hand, presented a chair-type conformation carrying an axial P–C bond.

The bond distances and angles in the molecule are normal and compare well with the average values derived from diffraction experiments.[9]

Discussion

Optically active poly-substituted 1,4-dihydropyridines have been prepared by several methods,[2a,10] among which is the widely used method developed by Shibanuma *et al.*[10a] The method comprised of the optical resolution of the carboxylic acid, conversion of the separated single enantiomer to the corresponding acid chloride and final esterification has given the desired enantiomeric ester. However, this method was not suitable for the synthesis of the optical isomers of NZ-105, because racemization occured. So, an efficient diastereomeric separation and synthesis without isomerization were investigated, and a synthetic route of optically active NZ-105 was established, as shown in Chart 1.

Applicating the reported manner for the synthesis of the optical isomers of 1,4-dihydropyridine-3,5-dicarboxylates,[2a,10b] transesterification without protection at the site of nitrogen in the dihydropyridine ring gave unsatisfactory results as follows. The direct conversion of (*S*,*S*)-**3** into the desired product (*S*)-**6** caused not only a significant decrease in the yield of (*S*)-**6**, but also the formation of by-products difficult to remove. Under comparatively severe conditions (the presence of a strong base and high temperature), decomposition of the cyclic phosphonate moiety proceeded. Consequently, (*S*)-**6** was synthesized after protection with MOM to be obtained in 100% of enantiomeric purity in 33% yield based on (*S*,*S*)-**3**. In spite of the multistep-route, this method proved to be suitable for the preparation of the optical isomers of dihydropyridine-carboxylates bearing substituents labile toward the strong base. Although the racemic compound **6** was treated with HCl in ethanol to give HCl salts incorporating ethanol (NZ-105) as yellow crystals, crystallization of the HCl salts of (*S*)-**6** was not observed. The presence of an enantiomeric pair was considered to play a great role in the formation of stable crystals of HCl salts.

Experimental

High-performance liquid chromatography (HPLC) was done on a Shimadzu Model LC-6A and performed on a Unisil Pack 5C18-250A (Gasukuro Kogyo) column at 40 °C (MeOH : H_2O = 2 : 1, 1.0 ml/min) for analysis of diastereomers or on a Chiralcel OC (Daicel Chem. Ind.) column at 30 °C (250 mm × 4.6 mm i.d., MeOH, 1.0 ml/min) for analysis of enantiomers. Column chromatography was performed with Merck Silica gel 60 (70—230 mesh), and thin-layer chromatography (TLC) was performed on Merck Pre-Coated TLC Plates Silica gel 60 F-254. Melting points are uncorrected and determined on a Yanako micro melting point apparatus. 60 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectra ($CDCl_3$) were recorded on a JEOL PMX60SI spectrometer, and chemical shifts are reported in the δ scale (ppm) relative to tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS D-300 instrument at an ionizing voltage of 70 eV. Optical rotations were measured on a JASCO DPI-360 digital polarimeter. X-Ray diffraction analysis was performed at Tray Research Center, Inc.

5,5-Dimethyl-2-[1-(3-nitrophenyl)-3-oxo-1-buten-2-yl]-2-oxo-1,3,2-dioxaphosphorinane (1) To a solution of 30.7 g (100 mmol) of dimorpholino-3-nitrophenylmethane and 20.4 g (200 mmol) of trifluoroacetic acid in 20 g of toluene was added 20.6 g (100 mmol) of 5,5-dimethyl-2-oxo-2-(2-oxopropyl)-1,3,2-dioxaphosphorinane. The mixture was stirred for 30 min at 60 °C and then for 3 h at < 10 °C in an ice-water bath. To the vigorously stirred mixture was added 20 g of water. The precipitations were filtered and recrystallized from toluene to 31.5 g (93%) of colorless crystals of **1**, which was a mixture of (*E*)- and (*Z*)-isomers (95 : 5, from NMR analysis). mp 150—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83, 1.06 [s, 3H, *E*/*Z* = 95/5, $C(CH_3)$-$_{eq}C\underline{H}_3$], 1.16, 1.21 [s, 3H, *E*/*Z* = 95/5, $C(CH_3)$-$_{ax}C\underline{H}_3$], 2.32, 2.58 [(s, 3H, *E*/*Z* = 95/5, $C(O)C\underline{H}_3$], 3.56—4.47 (m, 4H, $OC\underline{H}_2 \times 2$), 7.05—8.40 (m, 5H, $Ar\underline{H}$ + P–C = C$\underline{H}$).

(2*S*)-2-Methoxy-2-phenylethyl (4*S*)-5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate ((*S*,*S*)-3) To a solution of 11.2 g (33.0 mmol) of **1** in 50 ml of toluene was added dropwise a solution of 7.81 g (33.2 mmol) of (*S*)-2-methoxy-2-phenylethyl 3-aminocrotonate (**2**) in 30 ml of toluene under reflux with the azeotropical removal of water. The solution was heated for an additional 3 h under reflux with the removal of water and then concentrated *in vacuo*. The residue was chromatographed on silica gel (EtOAc : EtOH = 10 : 1) to give 13.62 g (74%) of (*RS*,*S*)-**3** as a 1 : 1 diastereomeric mixture as a yellow viscous oil. Crystallization of the resultant crude product from 13.6 g of ethyl acetate gave 5.04 g (37%) of pure (*S*,*S*)-**3** (100% de) as pale yellow crystals: mp 200—203 °C. $[\alpha]_D^{25}$ +48.9° (*c* = 0.50, EtOH). ^{1}H-NMR δ: 0.93 (s, 3H), 1.04 (s, 3H), 2.0—2.5 (m, 6H), 3.22 (s, 3H), 3.3—4.7 (m, 7H), 4.97 (br d, *J* = 11 Hz, 1H), 6.8—8.4 (m, 10H). MS *m*/*z*: 556 (M^+, 8), 539 (22), 434 (100), 300 (12), 121 (41). *Anal.* Calcd for $C_{28}H_{33}N_2O_8P$: C, 60.42; H, 5.98; N, 5.03. Found: C, 60.06; H, 6.01; N, 4.94.

(2*S*)-2-Methoxy-2-phenylethyl (4*S*)-5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-1-methoxymethyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate ((*S*,*S*)-4) To a solution of 4.95 g (8.89 mmol) of (*S*,*S*)-**3** in 61.5 g of dry tetrahydrofuran (THF) was added 0.47 g (10.8 mmol, 55% in mineral oil) of NaH under ice-water cooling. After the mixture was stirred for 30 min in an ice-water bath, 0.87 g (10.8 mmol) of chloromethyl methyl ether was added to the solution. The mixture was stirred for 30 min at room temperature and then quenched with 150 ml of brine, followed by extraction with 150 ml of $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (EtOAc) to give 3.89 g (75%) of pure (*S*,*S*)-**4** (100% de) as a pale yellow oil. ^{1}H-NMR δ: 0.95 (s, 3H), 1.02 (s, 3H), 2.29 (s, 3H), 2.54 (d, *J* = 2.2 Hz, 3H), 3.22 (s, 6H), 3.3—4.6 (m, 7H), 4.76 (s, 2H), 4.97 (d, *J* = 13 Hz, 1H), 6.9—8.3 (m, 9H); MS *m*/*z*: 600 (M^+, 36), 451 (69), 421 (75), 317 (100), 269 (20), 135 (30), 121 (26).

(*S*)-2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-1-methoxymethyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate ((*S*)-5) To a solution of 17.6 g (77.4 mmol) of 2-[benzyl(phenyl)amino]ethanol in 52.1 g of dimethyl sulfoxide (DMSO) was added 0.32 g (7.3 mmol, 55% in mineral oil) of NaH. The mixture was stirred for 20 min at room temperature. A solution of 3.88 g (6.46 mmol) of (*S*,*S*)-**4** in 22 g of benzene was added to the mixture. The mixture was stirred for 30 min at room temperature and then poured in 350 ml of brine and extracted with 350 ml of $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (EtOAc) to give 2.09 g (45%) of crude (*S*)-**5** as a yellow-redish viscous oil containing 6% of the starting material. This oil was used in the next reaction without further purification: MS *m*/*z*: 675 (M^+, 9), 209 (100), 196 (20), 91 (15).

(*S*)-2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate ((*S*)-6) A solution of 2.09 g (2.91 mmol) of (*S*)-**5** in 15.8 g of 28% HCl–EtOH was allowed to stand for 1.5 h at room temperature. After removal of the solvent *in vacuo*, the residue was diluted with 100 ml of $CHCl_3$ and washed with 100 ml of 5% Na_2CO_3 aqueous solution. The organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (EtOAc) to give 1.89 g (99%) of (*S*)-**6** as a yellow oil, which was slowly solidified on standing. Three recrystallizations of the resultant solid from 10 (w/v) times of ethanol gave 1.14 g of pure (*S*)-**6** (100% ee) as pale yellow crystals: mp 190—192 °C. $[\alpha]_D^{25}$ +7.0° (*c* = 0.50, $CHCl_3$). HPLC (t_R) 5.1 min. ^{1}H-NMR δ: 0.90 (s, 3H), 0.99 (s, 3H), 2.1—2.5 (m, 6H), 3.1—4.7 (m, 10H), 4.89 (br d, *J* = 11 Hz, 1H), 6.4—8.2 (m, 15H). *Anal.* Calcd for $C_{34}H_{38}N_3O_7P$: C, 64.65; H, 6.06; N, 6.65; P, 4.90. Found: C, 64.70; H, 6.12; N, 6.54; P, 4.90.

(*R*)-2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate ((*R*)-6) The filtrate on recrystallization of (*S*,*S*)-**3** from ethyl

acetate was concentrated *in vacuo*. Without further purification, 3.9 g of residue which contains (*R*,*S*)-**3** (78% de) as a major component was successively subjected to methoxymethylation, transesterification, and demethoxymethylation, as mentioned above. The obtained crude product of (*R*)-**6** was recrystallized three times from EtOH to give 540 mg of optically pure (*R*)-**6** (100% ee) as pale yellow crystals: mp 190—192 °C. $[\alpha]_D^{25}$ −7.0° ($c=0.50$, $CHCl_3$). HPLC (t_R) 6.4 min. *Anal.* Calcd for $C_{34}H_{38}N_3O_7P$: C, 64.65; H, 6.06; N, 6.65; P, 4.90. Found: C, 64.55; H, 6.21; N, 6.44; P, 4.70.

X-Ray Crystal Structure Determination Crystal data: $C_{34}H_{38}O_7PN_3$, $M_r=631.66$, $P2_12_12_1$, $a=13.162(3)$, $b=24.506(4)$, $c=9.960(3)$ Å, $V=3212(1)$ Å^3, $D_x=1.306$ Mg m^{-3}, $Z=4$, $F(000)=1336$, $\mu(CuK_\alpha)=11.98$ cm^{-1}, the final R was 0.051 for 1663 observed [$I>3\sigma(I)$] reflections.

Crystals of (*S*)-**6** suitable for X-ray diffraction were obtained upon recrystallization from an ethanol solution. The unit cell parameters were obtained by least-squares from 2θ values for 25 reflections measured in a diffractometer. The intensities of 5510 (2757 unique) reflections were collected on a Rigaku AFC5R four-circle diffractometer up to an angle of $2\theta=120°$ with graphite monochromated CuK_α radiation, using the 2θ–ω scan technique and scan range of $(0.79+0.30\tan\theta)°$ in ω at room-temperature. The scan speed was 16.0°/min, and stationary background counts were recorded in each side of the reflection. The ratio of peak counting time to background counting time was 2:1. As three standard reflections, which were measured after every 150 reflections, declined by 1.50%, a linear correction factor was applied to the data. Lorentz and polarization effects and empirical absorption correction (transmission factors ranging 0.83 to 1.28) were also applied.

The structure was solved by direct methods[11] which located all the non-hydrogen atoms. A full-matrix least-squares anisotropic procedure was applied for non-hydrogen atoms, and hydrogen atoms were included in the structure factor calculation in idealized positions ($d_{C-H}=0.95$ Å) with isotropic thermal parameters which were 20% greater than the B_{eq} value of the atom to which they were bonded.

The absolute configuration was determined after parallel refinement of both enantiomers. The f'' term for phosphorus is relatively small, 0.434, so the differences in R values were small but convincing. The correct enantiomer was chosen over the other on the basis of the lower weighted R value[6] (0.051 as opposed to 0.053), and a complete set of Bijvoet pairs was also collected to assist in the determination of the absolute configuration.

Function minimized was $\sum w(|F_o|-|F_c|)^2$ with $w=4F_o^2/\sigma^2(F_o^2)$, where $\sigma(F_o^2)$ is the standard deviation based on counting statistics. Final refinement gave $R=0.051$, $wR=0.062$. Neutral atom scattering factors and $\Delta f'$, $\Delta f''$ were taken from International Tables for X-Ray Crystallography.[12]

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