SYNTHESIS OF OPTICALLY PURE 1,4-DIHYDROPYRIDINE DERIVATIVES BY MEANS OF DIASTEREOISOMERIC SEPARATION OF THE HANTZSCH INTERMEDIATES BEARING (*R*)-1-PHENYLETHYLAMINO GROUP

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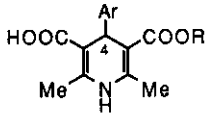
Abstract - Hantzsch intermediates, which were obtained by Michael addition reaction of benzylideneacetoacetates with the enamino esters bearing (*R*)-1-phenylethylamino group as a chiral auxiliary, were separated into two diastereoisomeric mixtures. Each of them underwent cyclization reaction to give optically pure 1,4-dihydropyridine derivatives.

Because of potent calcium channel blocking activity[1] of 4-aryl-1,4-dihydropyridine derivatives, numerous investigations[2] have been carried out for more than twenty years to find new drugs for hypertension disease and many compounds such as nifedipine, manidipine, and benidipine are now in clinical use. Since 4-aryl-1,4-dihydropyridine derivatives which possess different substituents at the 3,5-positions and/or at the 2,6-positions have a chiral center at the 4-position, remarkable difference between both enantiomers in their biological activities have been reported as expected.[3] Thus, it is important to develop efficient methods for introducing a chirality into the 4-position.



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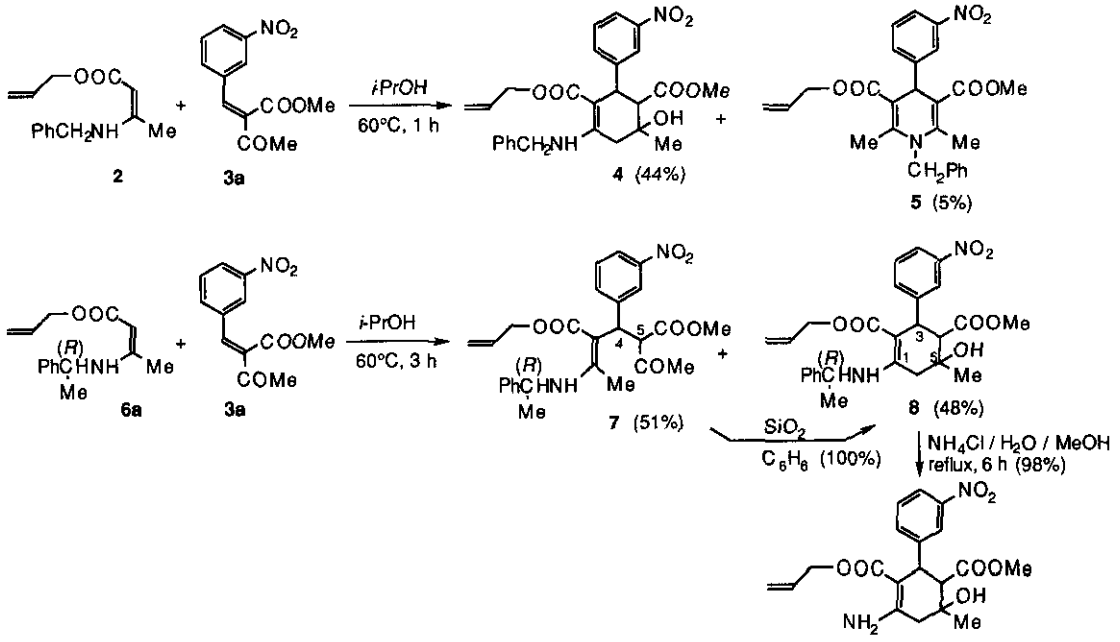
Enantiomeric 1,4-dihydropyridines have been synthesized so far by three respective methods, namely by optical resolution of a key intermediate, racemic monocarboxylic acid (**1**),[4] by enantioselective Hantzsch synthesis using chiral auxiliary,[5] or by chemoenzymatic synthesis of chiral derivatives.[6] In each method, however, it is sometimes difficult to assume the absolute configuration by

chemical correlation with the known compounds, if the product obtained has a new functionality. Besides, the chiral reagent used in the asymmetric Hantzsch synthesis has limited availability. In this paper, we report another method including separation of the Hantzsch intermediate which is useful for preparing chiral 1,4-dihydropyridine derivatives in high optical purity and for assuming their absolute configurations.

Although it is well known that 4-aryl-1,4-dihydropyridines can be produced in high yields by using the usual Hantzsch reaction of 3-aminocrotonates with benzylideneacetoacetates,[7] an unexpected product (**4**)[8] was obtained as the main product along with a small amount of the expected **5**, when allyl 3-benzylaminocrotonate (**2**) was adopted in the same reaction. Moreover, another *N*-substituted aminocrotonate (**6a**), which is readily accessible from allyl acetoacetate and chiral primary amine, (*R*)-(+)-1-phenylethylamine, also underwent similar reaction to obtain **7** and **8** in 51% and 48% yields, respectively. Nmr and tlc analysis of **7** indicated that it exists as a mixture of four diastereoisomers caused by two stereocenters at the 4- and labile 5-positions. Diastereoisomers (**7**) were then treated with silica gel in benzene at room temperature to afford the aldol cyclization product (**8**) as an easily separable mixture of mainly four isomers in quantitative yield. Subsequent removal of the chiral amine moiety with ammonium chloride gave the 1-aminocyclohexen-5-ol derivative (**9**) in almost quantitative yield (Scheme 1).



Scheme 1

A treatment of **6a** with butyllithium in THF, followed by an addition of **3a** even at lower temperature gave a better result providing **7** in 54% yield without formation of the aldol product (**8**). The adduct (**7**), which was crystallized from hexane but was still consisted of a mixture of four isomers at this point, could be separated into two different shapes of crystals (**A**: fine needles and **B**: prisms) with >99% de by fractional recrystallization utilizing sufficient difference of the rate of crystallization. The former, which was crystallized out first from hexane, was identified as a mixture (1:1) of (4*S*,5*R*)-**7** and (4*S*,5*S*)-**7**, and the latter, which was grown slowly from hexane-acetone (10:1), was identified as (4*R*,5*S*)-**7**.[9] Stereochemistry and diastereomeric excess (de) were determined by an nmr study as illustrated in Figure 1 and by further chemical conversion to the known 1,4-dihydropyridine derivative (**10**). High field shift of ester methyl (3.41 ppm) of (4*R*,5*S*)-**7** is probably due to the anisotropic effect of two adjacent aromatic rings (Figure 2).

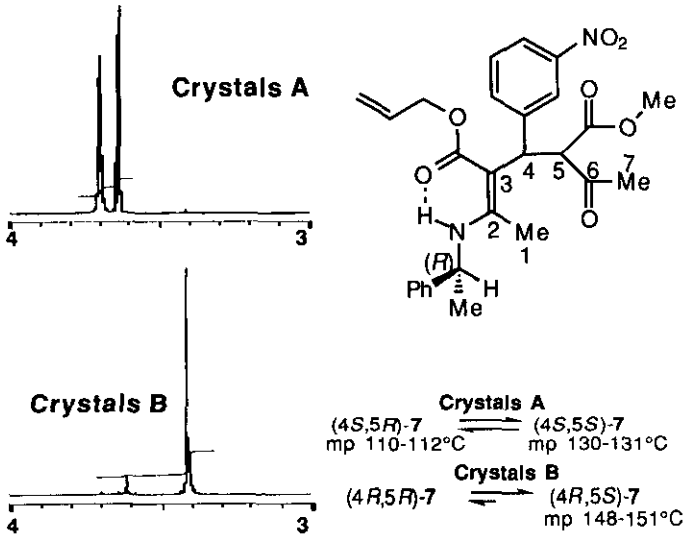


Figure 1. Diastereoisomeric separation of **7** by recrystallization.

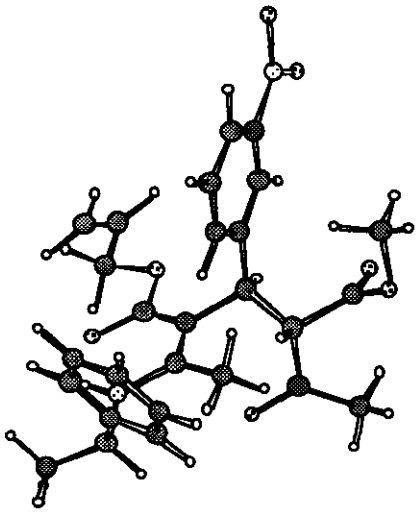


Figure 2. A molecular modeling for (4*R*,5*S*)-**7**.

These observations suggested that *N*-substituted enamino esters, such as **6a**, can not be used for the usual Hantzsch synthesis but can react with benzylideneacetoacetates to form the adducts, which would be separated to each diastereomers and be converted to the desired chiral 1,4-dihydropyridines, even if this reaction has no diastereoselectivity. Furthermore, addition reactions have been investigated by using varaiety of bases and substrates to optimize the yield and selectivity. As shown in Table 1, good to moderate yields were obtained when an equivalent amount of base, such as butyllithium or tertiary amine, was used. 2,3-Dichloro analogues (**12a-d**) could also be isolated by fractional recrystallization from hexane or hexane-acetone without chromatographical separation. However, satisfactory result of stereoselectivity at the 4-position was not

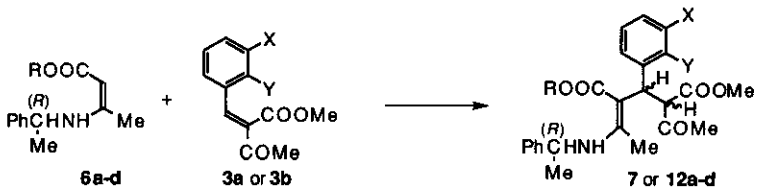


Table 1. Michael addition reaction of chiral enamino esters (**6**) with benzylideneacetoacetetes (**3**).

	R		X	Y	base	solvent	temperature	time	Michael adduct	yield[a]	(4*R*:4*S*) ratio[b]
6a	allyl	**3a**	NO_2	H	*n*-BuLi	THF	−78 → 0°C	2 h	**7**	54%	(1:1)
	allyl		NO_2	H	(*i*-Pr)$_2$EtN	-	room temperature	5 d	**7**	52%	(3:2)
	allyl		NO_2	H	-	$CHCl_3$	50°C	3 h	**7**	21%	(1:1)
	allyl		NO_2	H	K_2CO_3 / PTC[c]	C_6H_6	room temperature	2 d	**7**	10%	(2:1)
	allyl	**3b**	Cl	Cl	*n*-BuLi	THF	−78 → 0°C	2 h	**12a**	51%	(2:1)
	allyl		Cl	Cl	(*i*-Pr)$_2$EtN	-	room temperature	5 d	**12a**	58%	(1:1)
6b	*i*-Pr		Cl	Cl	*n*-BuLi	THF	−78 → 0°C	2 h	**12b**	64%	(1:1)
	i-Pr		Cl	Cl	(*i*-Pr)$_2$EtN	acetone	room temperature	2 d	**12b**	25%	(1:1)
6c	*t*-Bu		Cl	Cl	*n*-BuLi	THF	−78 → 0°C	2 h	**12c**	15%	(1:1)
	t-Bu		Cl	Cl	(*i*-Pr)$_2$EtN	acetone	room temperature	6 d	**12c**	20%	(1:1)
6d	CH_2CH_2CN		Cl	Cl	(*i*-Pr)$_2$EtN	acetone	room temperature	6 d	**12d**	17%	(1:1)

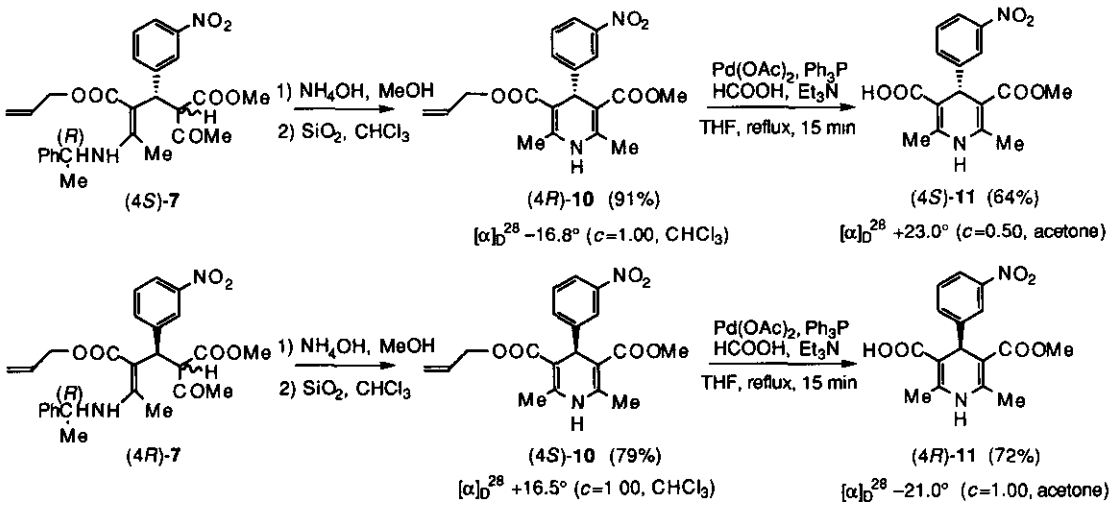
a) isolated yield. b) measured by ^{1}H-nmr. c) PTC : trioctylmethylammonium chloride

Table 2. Chemical shifts of ester methyl protons (ppm) in $CDCl_3$.

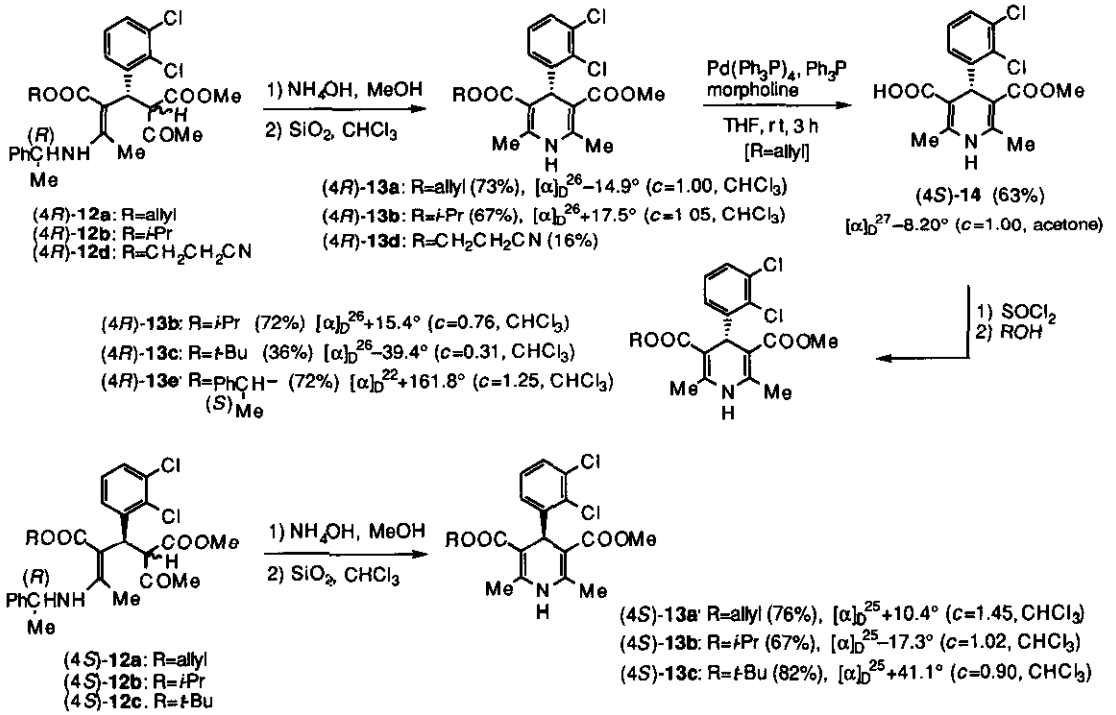
	(4*S*,5*S*)	(4*S*,5*R*)	(4*R*,5*R*)	(4*R*,5*S*)
7	3.70	3.64	3.62	3.41
	(4*R*,5*S*)	(4*R*,5*R*)	(4*S*,5*R*)	(4*S*,5*S*)
12a	3.69	3.56	3.54	3.31
12b	3.68	3.58	3.55	3.31
12c	3.70	3.58	3.55	3.29
12d	3.70	3.59	3.56	3.31

observed. It is noteworthy that the absolute configuration of the adducts could be presumed by comparing the chemical shifts of an ester methyl with those of the corresponding 3-nitro derivatives (**7**) (Table 2).

Conversion of the adducts to the desired enantiomerically pure 1,4-dihydropyridines (**10**) was achieved by two step procedure, namely by amination with 25 % ammonia in methanol followed by treatment with silica gel in chloroform.[10] Palladium catalyzed deallylation[11] gave the monocarboxylic acid (**11**), a key intermediate for the synthesis of clinically useful chiral 1,4-dihydropyridine derivatives[4] (Scheme 2).



Scheme 2



Scheme 3

Cyclization of the 2,3-dichloro analogues to **13a-c** proceeded successfully with an exception of cyanoethyl ester (**13d**). Deallylation of (4*R*)-**13a** with Pd(0)-morpholine[12] occurred even at room temperature to give the monocarboxylic acid ((4*S*)-**14**) with 100% de in 63% yield. Optical purity of (4*S*)-**14** was determined by esterification with the chiral alcohol, (*S*)-(−)-1-phenylethyl alcohol, affording diastereomerically pure (4*R*)-**13e**. Finally, the absolute structure assigned by ^{1}H-nmr was reconfirmed by chemical conversion of (4*S*)-**14** to the diesters ((4*R*)-**13b** and (4*R*)-**13c**), whose optical rotations were in accord with those of the diesters obtained directly from the Michael adducts (Scheme 3).

In conclusion, this procedure provides a useful method to prepare the enantiomerically pure 1,4-dihydropyridine derivatives especially for large scale synthesis because of the use of inexpensive (*R*)-1-phenylethylamine as a chiral auxiliary and the efficient separation of diastereoisomeric mixture of the Michael adducts. It is also indicated that the nmr measurment of a Michael adduct enables us to estimate the stereochemistry of a chiral 1,4-dihydropyridine deriving from that adduct by comparison with the nmr spectrum of **7** or **12a-c**.

EXPERIMENTAL

Melting points were determined by hot stage micro-melting point apparatus (Yanagimoto) and are uncorrected. Ir and mass spectra were measured on a Hitachi 200-10 spectrophotometer and a Hitachi M-80 spectrometer, respectively. ^{1}H-Nmr spectra were recorded on a Varian Gemini-300 spectrometer. Tlc was performed on precorted silica gel plates (Silica gel 60 F_{254}, Merck), and silica gel column (LiChroprep Si60, 15-25 μm, Merck) was used for preparative liquid chromatography (plc). Optical rotations were measured on a JASCO DIP-4 digital polarimeter. *N*-Substituted 3-aminocrotonates (**2** and **6a-d**) were prepared by the reaction of the acetoacetates with primary amines, and were used after vaccum distillation.

Reaction of Allyl 3-Benzylaminocrotonate (2) with Benzylideneacetoacetate (3a)

2 (550 mg, 2.38 mmol) and **3a** (590 mg, 2.37 mmol) were dissolved in *i*-PrOH (2 ml) and the resultant mixture was heated at 60 °C for 1 h. After evaporation of solvent under reduced pressure, the residue was separated and purified by plc using hexane-acetone (10:1–2:1) as an eluent to give **4** (279 mg, 44 %) and **5** (59 mg, 5 %), respectively. 2-Allyl 4-methyl 1-benzylamino-5-hydroxy-5-methyl-3-(3-nitrophenyl)-1-cyclohexene-2,4-dicarboxylate[8] (**4**): A yellow oil. ^{1}H-Nmr ($CDCl_3$) δ: 9.50 and 9.48 (1H, t, *J*=6 Hz, NH), 8.05–7.98 (1H, m, Ar-H) and 7.53–7.28 (8H, m, Ar-H), 5.48–5.27 (1H, m, CH_2=C***H***CH_2), 4.96–4.80 (2H, m, C***H***$_2$=$CHCH_2$), 4.55–4.42 (2H, m, PhC***H***$_2$), 4.30 (1H, d, *J*=11 Hz, C_3-H), 4.27–4.15 (2H, m, CH_2=CHC***H***$_2$), 3.59 and 3.52 (3H, s, CH_3), 3.23 (1H, br s, OH), 2.73 and 2.71 (1H, d, *J*=17 Hz, C_6-H), 2.68 and 2.47 (1H, d, *J*=11 Hz, C_4-H), 2.58 and 2.40 (1H, d, *J*=17 Hz, C_6-H), 1.27 and 1.25 (3H, s, CH_3). 3-Allyl 5-methyl 1-benzyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (**5**): A yellow oil. ^{1}H-

Nmr ($CDCl_3$) δ: 8.10–7.99 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.35 (1H, t, *J*=8 Hz, Ar-H), 7.24 (3H, m, Ar-H), 7.00 (2H, m, Ar-H), 5.92 (1H, m, CH_2=C***H***CH_2), 5.28 (1H, s, C_4-H), 5.30–5.20 (2H, m, C***H***$_2$=CHCH_2), 4.90 (2H, s, PhC***H***$_2$), 4.70–4.58 (2H, m, CH_2=CHC***H***$_2$), 3.71 (3H, s, CH_3), 2.48 (6H, s, CH_3).

Reaction of Allyl 3-((1*R*)-1-phenylethyl)aminocrotonate (6a) with Benzylideneacetoacetate (3a)

6a (260 mg, 1.06 mmol) and **3a** (265 mg, 1.06 mmol) were dissolved in *i*-PrOH (0.5 ml) and the resultant mixture was heated at 60°C for 3 h. After evaporation of solvent under reduced pressure, the residue was separated and purified by plc using hexane-acetone (10:1–5:1) as an eluent to give **7** (268 mg, 51 %) and **8** (256 mg, 48 %), respectively.

2-Allyl 4-Methyl 5-Hydroxy-5-methyl-3-(3-nitrophenyl)-1-((1*R*)-1-phenylethyl)amino-1-cyclohexene-2,4-dicarboxylate (8)

A suspension of SiO_2 (Wakogel C-300) adsorbed with **7** (256 mg, 0.52 mmol) in C_6H_6 (30 ml) at room temperature for 1 h was washed with $CHCl_3$ through a silica gel column. Evaporation of $CHCl_3$ and subsequent separation using plc (C_6H_6-acetone, 100:1–50:1) gave four products (**8**) (totally 256 mg, 100 %) as yellow oils. **8a**: Rf=0.40; **8b**: Rf=0.32; **8c**: Rf=0.28; **8d**: Rf=0.20 (hexane-C_6H_6-acetone, 5:5:1).

2-Allyl 4-Methyl 1-Amino-5-hydroxy-5-methyl-3-(3-nitrophenyl)-1-cyclohexene-2,4-dicarboxylate (9)

To a solution of **8** (250 mg, 0.51 mmol) in MeOH (8 ml) was added a solution of NH_4Cl (500 mg, 9 mmol) in H_2O (2 ml). After refluxing for 6 h, the mixture was evaporated and the residue was chromatographed by plc ($CHCl_3$) to afford **9** (194 mg, 98 %) as white crystals. mp 143–145 °C (hexane–acetone). ^{1}H-Nmr ($CDCl_3$) δ: 8.02, 7.98 and 7.47 (3H, m, Ar-H), 7.39 (1H, t, *J*=8 Hz, Ar-H), 5.37 (1H, m, CH_2=C***H***CH_2), 4.94–4.81 (2H, m, C***H***$_2$=$CHCH_2$), 4.30–4.15 (2H, m, CH_2=CHC***H***$_2$), 4.25 (1H, d, *J*=11 Hz, C_3-H), 3.54 (3H, s, CH_3), 3.28 (1H, d, *J*=2 Hz, OH), 2.64 (1H, dt, *J*=17, 2 Hz, C_6-H), 2.52 (1H, d, *J*=11 Hz, C_4-H), 2.35 (1H, d, *J*=17 Hz, C_6-H), 1.28 (3H, s, CH_3). Ms *m/z*: 390 (M^+).

General Procedure for the Reaction of Enamino Esters with Benzylideneacetoacetates

Method A: To a solution of enamino ester (4 mmol) in THF (20 ml) under Ar was added 2.5 ml (4 mmol) of 1.6 M *n*-BuLi in hexane at −78 °C. After a while, an equivalent of benzylideneacetoacetate was added in portionwise and the resultant mixture was warmed to 0 °C for 2 h. Addition of NH_4Cl (215 mg, 4 mmol) in H_2O (1 ml), followed by extraction with Et_2O gave a yellow oil after dryness and evaporation. Crude crystals, which were formed slowly by adding hexane gradually to the acetone solution of the oil, were recrystallized twice from hexane to obtain a pure product ((4*S*) for **7**) as needles. The remaining mixture was recrystallized from hexane-acetone (10:1 for **7**) to give another product ((4*R*) for **7**), as prisms.

Method B: A mixture of enamino ester (1 eq.), benzylideneacetoacetate (1 eq.), and *i*-Pr_2EtN (1 eq.) was stirred at room temperature. After 5–6 days, undissolved crystals disappeared completely and the resultant yellow oil

was then crystallized by adding hexane. The products mixture was separated by recrystallization in the same procedure as described for method A.

The following compounds were obtained by these procedures.

3-Allyl 5-methyl 4-(3-nitrophenyl)-6-oxo-2-((1*R*)-1-phenylethyl)amino-2-heptene-3,5-dicarboxylate ((4*S*)-**7**): Pale yellow needles. mp 109–111°C (hexane). Ms *m/z*: 494 (M^+). *Anal.* Calcd for $C_{27}H_{30}N_2O_7$: C, 65.58; H, 6.11; N, 5.67. Found: C, 65.67; H, 6.01; N, 5.67. Plc separation (hexane–acetone, 10:1) of this mixture gave two pure isomers ((4*S*,5*R*)-**7** and (4*S*,5*S*)-**7**). (4*S*,5*R*)-**7**: Pale yellow needles. mp 110–112 °C (hexane). ^{1}H-Nmr ($CDCl_3$) δ: 10.12 (1H, d, *J*=7 Hz, NH), 8.04–7.90 (2H, m, Ar-H), 7.40–7.20 (7H, m, Ar-H), 5.83 (1H, m, CH_2=C***H***CH_2), 5.18 (2H, m, C***H***$_2$=$CHCH_2$), 5.05 (1H, d, *J*=11 Hz, C_4-H), 4.73 (2H, m, C_5-H and PhC***H***CH_3), 4.58–4.42 (2H, m, CH_2=CHC***H***$_2$), 3.64 (3H, s, $COOCH_3$), 2.27 (3H, s, CH_3), 2.13 (3H, br s, CH_3), 1.51 (3H, d, *J*=7 Hz, PhCHC***H***$_3$). (4*S*,5*S*)-**7**: Pale yellow needles. mp 130–131 °C (hexane). ^{1}H-Nmr ($CDCl_3$) δ: 10.12 (1H, d, *J*=7 Hz, NH), 7.99–7.90 (2H, m, Ar-H), 7.40–7.20 (7H, m, Ar-H), 5.82 (1H, m, CH_2=C***H***CH_2), 5.15 (2H, m, C***H***$_2$=$CHCH_2$), 4.94 (1H, d, *J*=11 Hz, C_4-H), 4.73 (2H, m, C_5-H and PhC***H***CH_3), 4.58–4.43 (2H, m, CH_2=CHC***H***$_2$), 3.70 (3H, s, $COOCH_3$), 2.29 (3H, s, CH_3), 2.15 (3H, br s, CH_3), 1.51 (3H, d, *J*=7 Hz, PhCHC***H***$_3$).

(4*R*,5*S*)-**7**: Pale yellow prisms. mp 148–151 °C (hexane–acetone). ^{1}H-Nmr ($CDCl_3$) δ: 10.15 (1H, d, *J*=7 Hz, NH), 7.99–7.93 (2H, m, Ar-H), 7.42–7.19 (7H, m, Ar-H), 5.80 (1H, m, CH_2=C***H***CH_2), 5.16–5.07 (2H, m, C***H***$_2$=$CHCH_2$), 4.92 (1H, d, *J*=11 Hz, C_4-H), 4.73 (2H, m, C_5-H and PhC***H***CH_3), 4.50 (2H, m, CH_2=CHC***H***$_2$), 3.41 (3H, s, $COOCH_3$), 2.25 (3H, s, CH_3), 2.14 (3H, br s, CH_3), 1.52 (3H, d, *J*=7 Hz, PhCHC***H***$_3$). Ms *m/z*: 494 (M^+). *Anal.* Calcd for $C_{27}H_{30}N_2O_7$: C, 65.58; H, 6.11; N, 5.67. Found: C, 65.70; H, 6.09; N, 5.69.

3-Allyl 5-methyl 4-(2,3-dichlorophenyl)-6-oxo-2-((1*R*)-1-phenylethyl)amino-2-heptene-3,5-dicarboxylate ((4*R*)-**12a**): White needles. mp 118–120 °C (hexane-acetone). ^{1}H-Nmr ($CDCl_3$) δ: 10.18 and 10.15 (1H, d, *J*=7 Hz, NH), 7.38–7.14 (7H, m, Ar-H), 7.05 and 7.02 (1H, t, *J*=8 Hz, Ar-H), 5.90 (1H, m, CH_2=C***H***CH_2), 5.26–4.19 (2H, m, C***H***$_2$=$CHCH_2$), 5.09 and 4.94 (1H, d, *J*=11 Hz, C_4-H), 4.82–4.65 (2H, m, C_5-H and PhC***H***CH_3), 4.60 and 4.38 (2H, m, CH_2=CHC***H***$_2$), 3.69 and 3.56 (3H, s, $COOCH_3$), 2.28 and 2.09 (6H, s, CH_3), 1.50 and 1.49 (3H, d, *J*=7 Hz, PhCHC***H***$_3$). Ms *m/z*: 517 (M^+), 519 (M^++2). *Anal.* Calcd for $C_{27}H_{29}NO_5Cl_2$: C, 62.60; H, 5.64; N, 2.70. Found: C, 62.70; H, 5.68; N, 2.76.

(4*S*)-**12a**: Colorless prisms. mp 104–108 °C (hexane-acetone). ^{1}H-Nmr ($CDCl_3$) δ: 10.20 and 10.80 (1H, d, *J*=7 Hz, NH), 7.37–7.13 (7H, m, Ar-H), 7.05 and 7.02 (1H, t, *J*=8 Hz, Ar-H), 5.88 (1H, m, CH_2=C***H***CH_2), 5.25–5.17 (2H, m, C***H***$_2$=$CHCH_2$), 5.05 and 4.92 (1H, d, *J*=11 Hz, C_4-H), 4.83 and 4.77 (1H, d, *J*=11 Hz, C_5-H), 4.70 (1H, m, PhC***H***CH_3), 4.60 and 4.43 (2H, m, CH_2=CHC***H***$_2$), 3.54 and 3.31 (3H, s, $COOCH_3$), 2.16 and 2.12 (6H, s, CH_3), 1.49 (3H, d, *J*=7 Hz, PhCHC***H***$_3$). Ms *m/z*: 517 (M^+), 519 (M^++2). *Anal.* Calcd for $C_{27}H_{29}NO_5Cl_2$: C, 62.60; H, 5.64; N, 2.70. Found: C, 62.78; H, 5.70; N, 2.77.

3-Isopropyl 5-methyl 4-(2,3-dichlorophenyl)-6-oxo-2-((1*R*)-1-phenylethyl)amino-2-heptene-3,5-dicarboxylate

((4*R*)-**12b**): Pale yellow needles. mp 104–107 °C (hexane). ^{1}H-Nmr ($CDCl_3$) δ: 10.24 (1H, d, *J*=7 Hz, NH), 7.37-7.18 (7H, m, Ar-H), 7.07 (1H, t, *J*=8 Hz, Ar-H), 5.09 (1H, d, *J*=11 Hz, C_4-H), 5.01 (1H, m, C***H***$(CH_3)_2$), 4.77-4.63 (2H, m, C_5-H and PhC***H***CH_3), 3.68 and 3.58 (3H, s, $COOCH_3$), 2.28, 2.16, 2.13 and 2.05 (6H, s, CH_3), 1.48 (3H, d, *J*=7 Hz, PhCHC***H***$_3$), 1.37 and 0.98 (6H, d, *J*=7 Hz, CH(C***H***$_3)_2$).

(4*S*)-**12b**: Pale yellow prisms. mp 101–105 °C (hexane). ^{1}H-Nmr ($CDCl_3$) δ: 10.28 and 10.25 (1H, d, *J*=7 Hz, NH), 7.35–7.03 (8H, m, Ar-H), 5.04 and 4.93 (1H, d, *J*=11 Hz, C_4-H), 5.02 (1H, m, C***H***$(CH_3)_2$), 4.79 and 4.72 (1H, d, *J*=7 Hz, C_5-H), 4.69 (1H, m, PhC***H***CH_3), 3.55 and 3.31 (3H, s, $COOCH_3$), 2.14, 2.13, and 2.07 (6H, s, CH_3), 1.49 (3H, d, *J*=7 Hz, PhCHC***H***$_3$), 1.40, 1.39, 1.01 and 0.99 (6H, d, *J*=7 Hz, CH(C***H***$_3)_2$).

3-*tert*-Butyl 5-methyl (4*S*)-4-(2,3-dichlorophenyl)-6-oxo-2-((1*R*)-1-phenylethyl)amino-2-heptene-3,5-dicarboxylate ((4*S*)-**12c**): Pale yellow prisms. mp 106–111 °C (hexane). ^{1}H-Nmr ($CDCl_3$) δ: 10.10 and 10.00 (1H, d, *J*=7 Hz, NH), 7.34–7.03 (8H, m, Ar-H), 5.05 and 4.96 (1H, d, *J*=11 Hz, C_4-H), 4.77–4.70 (1H, d, *J*=11 Hz, C_5-H), 4.67 (1H, m, PhC***H***CH_3), 3.55 and 3.29 (3H, s, $COOCH_3$), 2.15, 2.12, 2.11 and 2.02 (6H, s, CH_3), 1.57 (9H, s, *t*-Bu), 1.46 (3H, d, *J*=7 Hz, PhCHC***H***$_3$).

3-(2-Cyanoethyl) 5-methyl (4*R*)-4-(2,3-dichlorophenyl)-6-oxo-2-((1*R*)-1-phenylethyl)amino-2-heptene-3,5-dicarboxylate ((4*R*)-**12d**): White fine needles. mp 112–117 °C (hexane–acetone). ^{1}H-Nmr ($CDCl_3$) δ: 10.23 and 10.21 (1H, d, *J*=7 Hz, NH), 7.37–7.10 (8H, m, Ar-H), 5.16 and 5.14 (1H, d, *J*=11 Hz, C_4-H), 4.78 and 4.73 (1H, d, *J*=11 Hz, C_5-H), 4.70 (1H, m, PhC***H***CH_3), 4.41, 4.32, and 4.00 (2H, m, OC***H***$_2CH_2CN$), 3.70 and 3.59 (3H, s, $COOCH_3$), 2.71 and 2.54 (2H, m, OCH_2C***H***$_2$CN), 2.33, 2.24, 2.16 and 2.13 (6H, s, CH_3), 1.51 (3H, d, *J*=7 Hz, PhCHC***H***$_3$).

3-Allyl 5-Methyl (4*R*)-1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ((4*R*)-**10**)

To a solution of (4*S*)-**7** (267 mg, 0.5 mmol) in MeOH (10 ml) was added 3 ml of conc. NH_4OH. The resultant mixture was heated at 50 °C for 40 min and then evaporated to give a yellow oil, which on extraction with $CHCl_3$ (10 ml) followed by treatment with 0.25 g of SiO_2 (Wakogel C-300) at room temperature for overnight gave (4*R*)-**10** (169 mg, 91 %) as pale yellow crystals after filteration and evaporation. mp 125–127 °C (hexane-acetone). ^{1}H-Nmr ($CDCl_3$) δ: 8.11 (1H, t, *J*=2 Hz, C_2'-H), 8.00 (1H, dd, *J*=8, 2 Hz, C_4'-H), 7.63 (1H, *dt*, *J*=8, 2 Hz, C_6'-H), 7.37 (1H, t, *J*=8 Hz, C_5'-H), 6.09 (1H, br s, NH), 5.88 (1H, m, CH_2=C***H***CH_2), 5.22–5.12 (2H, m, C***H***$_2$=$CHCH_2$), 5.13 (1H, s, C_4-H), 4.55 (2H, m, CH_2=CHC***H***$_2$), 3.65 (3H, s, $COOCH_3$), 2.37 and 2.36 (6H, s, CH_3). $[\alpha]_D^{28}$ −16.8 ° (*c* =1.00, $CHCl_3$).

3-Allyl 5-Methyl (4*S*)-1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ((4*S*)-**10**)

The same procedure as used for (4*R*)-**10** gave (4*S*)-**10** (79 % from (4*R*)-**7**) as pale yellow crystals. mp 127–128 °C (hexane-acetone). $[\alpha]_D^{28}$ +16.5 ° (*c* =1.00, $CHCl_3$)

(4*S*)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3-carboxylic

Acid ((4*S*)-11)

A solution of Ph_3P (10 mg, 0.038 mmol) and $Pd(OAc)_2$ (10 mg, 0.045 mmol) in THF (10 ml) was refluxed under Ar for 10 min. After cooling, (4*R*)-**10** (580 mg, 1.56 mmol), HCOOH (950 mg, 20.7 mmol) and Et_3N (500 mg, 4.95 mmol) were added to the solution and then the resultant mixture was refluxed for 15 min. After the solution was filtered and evaporated, the residue was purified by plc ($CHCl_3$-MeOH) to give (4*S*)-**11** (378 mg, 73 %) as yellow crystals. mp 193–195 °C (decomp.) (acetone). ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 8.56 (1H, br s, NH), 8.07 (1H, t, *J*=2 Hz, C_2'-H), 7.95 (1H, dd, *J*=8, 2 Hz, C_4'-H), 7.63 (1H, dt, *J*=8, 2 Hz, C_6'-H), 7.41 (1H, t, *J*=8 Hz, C_5'-H), 5.06 (1H, s, C_4-H), 3.60 (3H, s, $COOCH_3$), 2.33 and 2.32 (6H, s, CH_3). $[\alpha]_D^{28}$ +23.0° (*c* =0.50, acetone)

(4*R*)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3-carboxylic Acid ((4*R*)-11)

The same procedure as used for (4*S*)-**11** gave (4*R*)-**11** (72 % from (4*S*)-**10**) as yellow crystals. mp 184–185 °C (decomp.) (acetone). $[\alpha]_D^{28}$ –21.0° (*c* =1.00, acetone)

3-Allyl 5-Methyl (4*R*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ((4*R*)-13a)

To a solution of (4*R*)-**12a** (1.55 g, 3 mmol) in MeOH (50 ml) was added 20 ml of conc. NH_4OH. The resultant mixture was heated at 50 °C for 4.5 h and then evaporated to give a colorless oil, which on extraction with $CHCl_3$ (40 ml) followed by treatment with 1 g of SiO_2 (Wakogel C-300) at room temperature for 4 days gave crude product as a pale yellow oil after filteration and evaporation. Plc purification (hexane-acetone, 10:1) afforded pure (4*R*)-**13a** (849 mg, 73 %) as colorless prisms. mp 73–75 °C (hexane). Ir (KBr) cm^{-1}: 3350 (NH), 1700 (C=O), 1660 (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 7.31–7.22 (2H, m, Ar-H), 7.06 (1H, t, *J*=8 Hz, Ar-H), 5.84 (1H, m, CH_2=C***H***CH_2), 5.72 (1H, br s, NH), 5.48 (1H, s, C_4-H), 5.13–5.06 (2H, m, C***H***$_2$=CHCH_2), 4.54 (2H, m, CH_2=CHC***H***$_2$), 3.61 (3H, s, $COOCH_3$), 2.32 and 2.31 (6H, s, CH_3). $[\alpha]_D^{26}$ –14.9° (*c* =1.00, $CHCl_3$). Ms *m/z*: 395 (M^+), 397 (M^++2). *Anal.* Calcd for $C_{19}H_{19}NO_4Cl_2$: C, 57.59; H, 4.83; N, 3.54. Found: C, 57.35; H, 5.17; N, 3.52.

3-Allyl 5-Methyl (4*S*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ((4*S*)-13a)

The same procedure as used for (4*R*)-**13a** gave (4*S*)-**13a** (76 % from (4*S*)-**12a**) as white crystals. mp 73–75 °C (hexane). $[\alpha]_D^{25}$ +10.4° (*c* =1.45, $CHCl_3$)

3-Isopropyl 5-Methyl (4*R*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ((4*R*)-13b)

The same procedure as used for (4*R*)-**13a** gave (4*R*)-**13b** (67 % from (4*R*)-**12b**) as a pale yellow oil. ^{1}H-Nmr ($CDCl_3$) δ: 7.30 and 7.24 (2H, dd, *J*=8, 1.5 Hz, Ar-H), 7.06 (1H, t, *J*=8 Hz, Ar-H), 5.76 (1H, br s,

NH), 5.43 (1H, s, C_4-H), 4.97 (1H, m, $CH(CH_3)_2$), 3.61 (3H, s, $COOCH_3$), 2.31 and 2.29 (6H, s, CH_3), 1.25 and 1.02 (6H, d, J=7 Hz, $CH(CH_3)_2$). $[\alpha]_D^{26}$ +17.5° (c =1.05, $CHCl_3$)

3-Isopropyl 5-Methyl (4*S*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ((4*S*)-13b)

The same procedure as used for (4*R*)-**13a** gave (4*S*)-**13b** (67 % from (4*S*)-**12b**) as a pale yellow oil. $[\alpha]_D^{25}$ −17.3° (c =1.02, $CHCl_3$)

3-*tert*-Butyl 5-Methyl (4*S*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ((4*S*)-13c)

The same procedure as used for (4*R*)-**13a** gave (4*S*)-**13c** (82 % from (4*S*)-**12c**) as white crystals. mp 153–155 °C (hexane). Ir (KBr) cm^{-1}: 3350 (NH), 1685 (C=O), 1660 (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 7.31–7.23 (2H, m, Ar-H), 7.06 (1H, t, J=8 Hz, Ar-H), 5.85 (1H, br s, NH), 5.42 (1H, s, C_4-H), 3.60 (3H, s, $COOCH_3$), 2.26 and 2.23 (6H, s, CH_3), 1.38 (9H, s, t-Bu). $[\alpha]_D^{25}$ +41.1° (c =0.90, $CHCl_3$)

3-(2-Cyanoethyl) 5-Methyl (4*R*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ((4*R*)-13d)

Low yield of (4*R*)-**13d** (5 % from (4*S*)-**12c**) was obtained by the same procedure as used for (4*R*)-**13a**. A treatment of (4*S*)-**12c** with NH_3 in i-PrOH followed by treatment with SiO_2 gave still low yield of (4*R*)-**13d** (16 %) as a pale yellow oil. ^{1}H-Nmr ($CDCl_3$) δ: 7.32-7.25 (2H, m, Ar-H), 7.09 (1H, t, J=8 Hz, Ar-H), 5.82 (1H, br s, NH), 5.45 (1H, s, C_4-H), 4.23 (2H, t, J=7 Hz, CH_2CH_2CN), 3.62 (3H, s, $COOCH_3$), 2.65 (2H, t, J=7 Hz, CH_2CH_2CN), 2.34 and 2.32 (6H, s, CH_3).

(4*S*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethylpyridine-3-carboxylic Acid ((4*S*)-14)

A solution of (4*R*)-**13a** (847 mg, 2.14 mmol) in THF containing morpholine (372 mg, 4.28 mmol), $Pd(Ph_3P)_4$ (50 mg, 0.043 mmol) and Ph_3P (23 mg, 0.088 mmol) was stirred at room temperature for 3 h. After evaporation, the resultant mixture was purified by plc ($CHCl_3$-MeOH) to afford (4*S*)-**14** (474 mg, 62 %) as white fine crystals. mp 186–188 °C ($CHCl_3$). Ir (KBr) cm^{-1}: 3340 (NH and OH), 1690 (C=O). ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 8.01 (1H, br s, NH), 7.35 (1H, dd, J=8, 1.5 Hz, C_4'-H), 7.21 (1H, dd, J=8, 1.5 Hz, C_6'-H), 7.07 (1H, t, J=8 Hz, C_5'-H), 5.42 (1H, s, C_4-H), 3.57 (3H, s, $COOCH_3$), 2.30 and 2.29 (6H, s, CH_3). $[\alpha]_D^{27}$ −8.20° (c =1.00, acetone).

3-((1*S*)-1-Phenylethyl) 5-Methyl (4*R*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ((4*R*)-13e)

A suspension of (4*S*)-**14** (87 mg, 0.244 mmol) in DMF (0.2 ml) was cooled on a ice bath and then a solution of $SOCl_2$ (35 mg, 0.294 mmol) in CH_2Cl_2 (1 ml) was added to this suspension. After 1 h, (*S*)-(−)-1-phenylethyl alcohol (50 mg, 0.410 mmol) and *N*-methylmorpholine (60 mg, 0.594 mmol) were slowly added to the

mixture and the resultant mixture was warmed gradually from 0 °C to room temperature for 1 h. Usual work up and purification by plc (hexane-acetone, 5:1) gave (4*R*)-**13e** (81 mg, 72 %) as a sole product. White crystals. mp 152–153 °C (hexane). Ir (KBr) cm^{-1}: 3360 (NH), 1700 (C=O), 1680 (C=O), 1500. ^{1}H-Nmr ($CDCl_3$) δ: 7.28–7.24 (2H, m, Ar-H), 7.16–7.12 (3H, m, Ar-H), 7.02 (1H, t, *J*=8 Hz, Ar-H), 6.91–6.88 (2H, m, Ar-H), 5.81 (1H, q, *J*=7 Hz, PhC***H***CH_3), 5.76 (1H, br s, NH), 5.49 (1H, s, C_4-H), 3.63 (3H, s, $COOCH_3$), 2.28 and 2.25 (6H, s, CH_3), 1.56 (3H, d, *J*=7 Hz, PhCHC***H***$_3$). $[\alpha]_D^{22}$ +161 ° (*c* =1.25, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{23}NO_4Cl_2$: C, 62.62; H, 5.04; N, 3.04. Found: C, 62.61; H, 5.03; N, 3.04.

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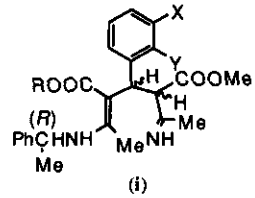
8. ^{1}H-Nmr data suggested that this compound is a 1:1 mixture of diastereomers caused by the stereocenters at C_3 and C_5.
9. Because of epimerization at C_5 during the crystallization process, (4*R*,5*R*)-**7** was disappeared from the product mixture.
10. Production of 6-imino derivatives (**i**) was detected by ^{1}H-nmr analysis.



(i)

The treatment of **7** with NH_4Cl failed to give the desired compound (**10**), but afforded **9** as a main product.

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