Heteroatom Chemistry
Volume 11, Number 7, 2000

A New and Efficient Asymmetric Synthesis of 1-Amino-1-Alkylphosphonic Acids

Chengye Yuan, Shusen Li, and Guoqiang Wang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P.R. China; yuancy@pub.sioc.ac.cn

Received 25 May 2000; revised 28 July 2000

ABSTRACT: *A new and efficient method for the asymmetric synthesis of 1-amino-1-alkyl phosphonic acids is described. It involves a diastereoselective alkylation of a bicyclic chloromethyl phosphonamide derived from (S)-2-anilinomethylpyrrolidine, with subsequent conversions leading to an amino compound by the Staudinger method. Acid hydrolysis affords the target molecule of high enantiomeric purity and good yield.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:528–535, 2000

INTRODUCTION

As phosphorus analogs of aminoacids, 1-amino-1-alkylphosphonic acids are an important class of compounds with biological activity [1]. As the mimetic tetrahedral intermediates of the hydrolysis of esters, amides, and peptides, 1-aminoalkylphosphonic acid derivatives have been used as antibiotics [2], medicaments [3], or enzyme inhibitors [4].

Since the biological activity of 1-amino-1-alkylphosphonic acids is largely dependent on their absolute configurations [5,6], the asymmetric synthesis of this class of compounds has aroused the interest of organic chemists. Several review articles relating to the preparation of optically active 1-amino-1-alkyl-phosphonic acids are available [7–9]. Among various methods reported, the nucleophilic addition of dialkyl phosphites to imines and oxoimimum derivatives containing an sp^2C atom constituted the majority of asymmetric syntheses of 1-arylphosphonoglycines to date. We have investigated the stereochemical behavior of the addition of dialkyl phosphites to aldimines, resulting from the condensation of substituted benzaldehydes with (*S*)-1-phenylethylamine. The structural effects of substrates and reagents, the influence of reaction conditions including the nature of the catalyst and solvent on the diastereomeric excess (de) value and induced directions of the asymmetric addition were reported [10]. A molecular mechanics study [11] on this type of reaction revealed that the de value and the induced direction were controlled by the conformation of the aldimines used as substrates.

Introduction of a heteroatom, which is capable of forming a coordinating bond with a Lewis acid, should have a substantial influence on the conformation of the substrate by the interaction between the Lewis acid and the aldimine. This kind of coordination may change the induced direction and improve the de value. Based on this postulation, (*R*)-2-methoxy-1-phenylethylamine and (*R*)-phenylalanine methyl ester were chosen as the chiral auxiliaries [12]. Structurally, the methyl group of the (S)-1-phenylethylamine molecule is substituted by CH_2OMe or COOMe, while the relative spatial arrangement of the group linked to the chiral carbon remains unchanged. Our experimental data demonstrated that the reaction system under investigation provided a useful way for the stereoselective

Correspondence to: Chengye Yuan.
Contract Grant Sponsor: National Natural Science Foundation of China (NNSFC).
Contract Grant Number: 29832050.

preparation of 1-arylphosphonoglycine derivatives. The *R*-phenylalanine methyl ester was a more effective substrate with the de value up to 89%, with the R-configuration as the major isomer.

Furthermore, the induced asymmetric addition of a dialkyl phosphite to a chiral aldimine can also be considered to be a convenient method for the synthesis of an optically active 1-amino-1-alkylphosphonic acid, but the scope of the application of this method is limited only to the preparation of phosphonophenylglycine derivatives. Since the presence of a phenyl group on the 1-methylene carbon atom is essential due to a structural requirement for the formation of a complex with a Lewis acid type of metal as a catalyst. However, Hanessian's report [8], which was based on the alkylation of a chiral bicyclic phosphonamide derived from (*R,R*)- and (*S,S*)-1,2-diaminocyclohexane, can be considered as one of the general synthetic routes to 1-aminophosphonic acids of high optical purity in either enantiomeric series. In order to examine the influence of structure of a bicyclic phosphonamide on the stereochemical process, we modified Hanessian's procedure by using (*S*)-2-anilinomethylpyrrolidine as the chiral auxiliary. The significant improvement in our method is based on the use of this readily available starting material. We should also mention that molecular mechanics calculations were introduced by us to assign the absolute configurations of the alkylation products [13]. The preliminary result was published by us as a communication [14]. In this article, in addition to experimental details, we plan to discuss the stereochemistry involved in this process.

RESULTS AND DISCUSSION

Preparation and Separation of Bicyclic Chloromethylphosphonamides

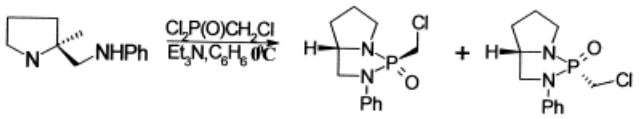
We used (*S*)-2-anilinomethylpyrolidine(**1**) as the chiral auxiliary, and this was obtained by reduction of (*S*)-5-oxopyrrolidine-2-carboxanilide [7]. The latter was prepared in 46% yield by heating L-glutamic acid with aniline as described in the literature. We found that the yield of this reaction could be markedly increased to 94% by refluxing the reaction mixture at about 190°C using a Dean-Stark trap to effect the automatic separation of water produced during the cyclization.

Reaction of **1** with chloromethanephosphonyl dichloride gave a mixture of bicyclic chloromethyl phosphonamides **2** and **3**, namely (2*S*, 5*S*) and (2*R*, 5*S*)-2-chloromethyl-2-oxo-3-phenyl-1,3-diaza-2-phospha-bicyclo-[3.3.0]-octane. These two diastereomers could be separated by column chromatography on silica-gel using ethyl acetate/petroleum ether (8:3) as eluent, the total yield being 85% with a 4:5 ratio of isomer *2*:*3* (Scheme 1). The absolute configurations at the phosphorus in diastereomeric **2** and **3** were readily assigned through examination of their ^{1}HNMR data on the basis of the downfield shift of the hydrogen resonance in a 1,3-*cis* relationship to the P=O group [14]. The relevant ^{1}HNMR data is presented in Table 1, among which H-4, H′-4 and H-8, H′-8 also followed this empirical rule (Table 1).

As reported by Fiaud [15], for such types of bicyclic phosphonamides, when P=O is in a 1,3-*cis* relationship to H-5, the ^{31}P NMR chemical shift should be at higher field, while in the 1,3-*trans* relationship, the ^{31}P NMR signal should be located downfield. Our experimental data in Table 1 are consistent with such a rule.

Asymmetric Alkylation of the Chiral Bicyclic Chloromethylphosphonamide and the Absolute Configuration of the Product

Diastereoselective alkylation is the key step in our synthetic scheme. The isolated **2** was alkylated with an appropriate alkyl iodide at −78°C in THF using LDA as base. Compounds **4** were obtained in high yields and with excellent optical purity (Scheme 2) (Table 2). The R-configurations were established, based on the absolute configuration of the 1-chloro-1-alkylphosphonic acid derivative (**5*R***) derived by hydrolysis of the related **4**. Analogously, compounds **6** were obtained by alkylation of compound **3** and provided good results. The *S*-configuration of compounds **7** was demonstrated similarly (Scheme 2) (Table 3). Similarly, alkylation of **3** offered compound **6** (Table 3).

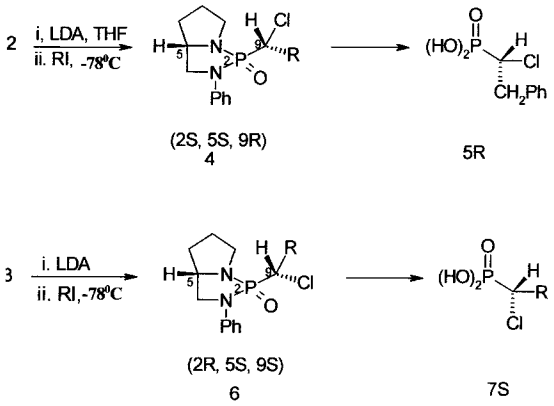


1 2 (36%) 3(45%)

SCHEME 1

TABLE 1 The Partial ^{1}HNMR Data of **2** and **3**

Compound	Config. at P	Chemical Shift (ppm)					
		H-4	*H′-4*	*H-5*	*H-8*	*H′-8*	^{31}P(δ)
2	*S*	3.76	3.35	3.80	3.70	3.00	32.82
3	*R*	3.06	3.74	4.14	3.06	5.59	24.48



SCHEME 2

Conversion of Compounds **4** *and* **6** *to Optically Active 1-Amino-1-alkylphosphonic Acids*

Nucleophilic displacement on compounds **4** and **6** by the azide ion gave the corresponding azido compounds **8** that were readily converted to amino derivatives **9** by the Staudinger reaction. Acid hydrolysis of compounds **9** provided each compound (*R*)-10 (Scheme 3) (Table 5), which was identified as the corresponding (*R*)-1-aminopropylphosphonic acid.

EXPERIMENTAL

All melting points and boiling points are uncorrected. The IR spectra were taken on a Shimadzu IR400 spectra meter. The ^{1}HNMR spectra were recorded in $CDCl_3$ solutions on EM-360A (60MHz), FX-90Q (90MHz), Varian XL-200 (200MHz), or Bruker AC-300 (300MHz) spectrometers using TMS as an internal standard. The ^{31}P NMR spectra were taken on a FX-90Q or Bruker AC-300 instrument(rs. external 85% H_3PO_4). Mass spectra were performed on a Finnigan-4021 apparatus. HRMS data were recorded on a Finnigan MAT 8430 Spectrometer. The molecular mechanics calculations were performed on a VAX-780 computer at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. All solvents used in these experiments were dried by standard techniques. All the reactions with carbanions were carried on in a nitrogen atmosphere.

(*S*)-*2-anilinomethylpyrrolidine* (**1**)

To a dried three-necked flask fitted with a Dean-Stark trap, thermometer, and stirrer, was added L-glutamic acid (20 g 136mmole) and freshly redistilled aniline (150 mL). The reaction mixture was heated under reflux and kept at the reaction temperature of about 183°C for 2 hours. After that, the excess aniline was removed by distillation under reduced pressure. Acetone (100 mL) was added to the cooled residue (20 mL). The pale yellow solid that separated was washed with acetone and recrystallized from methanol; *S*-2-oxopyrrolidine-2-carboxanilide was obtained as colorless crystalline plates; m.p. 189–190°C (lit. m.p. 189–191°C yield 46%), yield 26 g or 93.6%.

To an ice-cold suspension of lithium aluminum hydride (6.8 g, 179 mmol) in THF (200 mL), was added (*S*)-2-oxopyridine-2-carboxanilide (14.5 g, 71 mmole), and the mixture was heated under reflux for 3 hours. The mixture was then cooled and treated with water (3 mL), followed by 2N NaOH aqueous solution (80 mL). The mixture was filtered, and the resulting clear solution was extracted with dichloromethane (3 × 50 mL). The residue was washed with dichloromethane (3 × 50 mL). The combined dichloromethane solution was evaporated and distilled. The fraction boiling at 101–104°C/0.2 mmHg. was collected; (*S*)-2-anilinomethylpyrroline was obtained as pale yellow liquid. Yield 10.2 g or 81.5% (literature [7] yield 85%).

Bicyclic chloromethylphosphonamide (*2S,5S*) *and* (*2R,5S*)*-2-phospha-bicyclo[3.3.0]-octane* (**2,3**)

To an ice-cold solution of *1* (5.1 g, 30 mmol) and triethylamine (6.7 g, 6.6 mmol) in benzene (100 mL) was added dropwise a benzene solution (60 mL) of chloromethylphosphonyl dichloride (5 g, 30 mmol). The rate of addition was controlled so that the reaction temperature did not exceed 5°C during 2 hours. The reaction mixture was stirred for an additional 1 hour at 10°C and then allowed to stand overnight. The separated triethylamine hydrochloride was filtered off and then washed with benzene. Upon removal of the benzene, the resultant mixture was separated by column chromatography on silica gel using EtOAc/Petroleum ether 8:2 as eluent. Compound **2** was obtained as a viscous oil (Rf = 0.75) yield 3.1 g or 36%. *3* was obtained as a crystalline powder (Rf = 0.65). Yield 3.8 g or 45%.

2; (viscous oil) the less polar isomer, $[a]_D^{20} = -30.58°$ IR (KBr): 1240(P=O), 1060(P–N)cm^{-1}. ^{1}HNMR ($CDCl_3$, 200 MHz: 1.58(m, 1H, H′-6), 1.92(m,3H,H-6,CH_2-7), 3.00(M, 1H, H′-8), 3.35 (m,1H,H′-4), 3.62–3.90 (m, 5H, H-8,H-4,H-5,PCH_2), 6.94(m, 1H, Ar-para), 7.20(m, 4H, Ar-ortho and meta). ^{31}P NMR ($CDCl_3$, 90MHz): 32.82. MS (EI): 270 (M,51) 221 (M-CH_2Cl, 39), 116(M-CH_2Cl-$PhNCH_2$,100) ppm.

3: (colorless crystals) the more polar isomer m.p.

TABLE 2 Compounds **4** from C-alkylation of **2**

	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**
R	Me	Et	*n*-Pr	*i*-Pr	*n*-Bu	Bz	$CH_2CH=CH_2$
yield (%)[a]	80	78	76	74	76	82	75
de (%)[b]	>95	80	78	60	>95	>95	>95
m.p. (°C)	109–111	oil	oil	101–102	oil	90–92	oil
$[\alpha]_D^{20c}$	−34.2°	−12.2°	−15.3°	−38.3°	−11.4°	−19.1°	−20.6°
	(c,1.11)	(c,0.9)	(c,0.6)	(c,1.03)	(c,1.44)	(c,0.42)	(c,0.97)
Config[d]	*R*	*R*	*R*	*R*	*R*	*R*	*R*

[a]Isolated yields.
[b]Evaluated by ^{31}PNMR using 85% H_3PO_4 as an external reference, de > 95% means only one diastereometer being detacted.
[c]Measured in MeOH.
[d]Established based on the absolute configuration [8] of 1-chloroalkyl phosphonic acids derived from the hydrolysis of compound **4**.

TABLE 3 Compounds **6** from C-Alkylation of **3**

	6a	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**
R	Me	Et	*n*-Pr	*i*-Pr	*n*-Bu	Bz	$CH_2CH=CH_2$
Y	83	81	72	72	75	82	73
yield (%)[a]							
de (%)[b]	>95	86	55	16	>95	78	>35
m.p. (°C)	138–140	107–109	117–119	104–105	82–83	55–57	72–73
$[\alpha]_D^{20c}$	+43.9°	+31.5°	+13.4°	−23.2°	+9.4°	+21.8°	+29.3°
	(c,1.08)	(c,1.0)	(c,0.9)	(c,1.02)	(c,1.22)	(c,0.98)	(c,0.98)
Config[d]	*S*	*S*	*S*	*R*	*S*	*S*	*S*

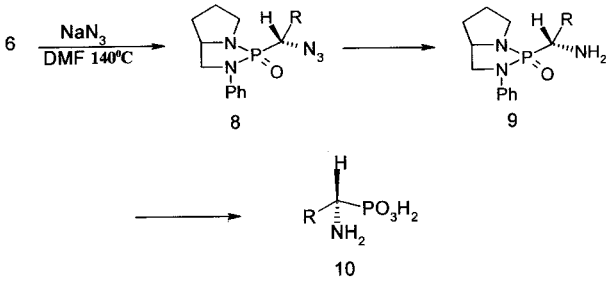
[a]Isolated yields.
[b]Evaluated by ^{31}PNMR using 85% H_3PO_4 as an external reference, de > 95% means only one diastereometer being determined.
[c]Measured in MeOH.
[d]Established based on the absolute configuration [2] of 1-chloroalkyl phosphonic acids derived from the hydrolysis of compounds **6**.

TABLE 4 Amino Compounds **9** Synthesized

	9a	**9b**	**9c**	**9d**	**9′e**	**9′f**
R	Me	Et	*n*-Pr	*n*-Bu	Et	*n*-Pr
yield (%)	78	75	70	72	67	69
de (%)	>95	82	92	>92	90	>92
$[\alpha]_D^{20}$	−9.75°	−5.83°	−18.3°	−15.68°	+12.0°	+10.4°
	(c,1.28)	(c,0.36	(c,1.18)	(c,0.44)	(c,1.00)	(c,0.80)
Config.	*R*	*R*	*R*	*R*	*S*	*S*

TABLE 5 1-Amino-1-Alkylphosphonic Acids

	10a	**10b**	**10c**	**10e**	**10′b**	**10′c**
R	Me	Et	n-Pr	n-Bu	Et	n-Pr
yield (%)	97	80	98	97	95	97
m.p. (°C)	278	276	270	289	275	274
$[\alpha]_{578}$	−15.5°	−21.6°	−17.0°	−17.7°	+21.2°	+12.2°
de (%)	78	85	85	80	98	97
Config.	*R*	*R*	*R*	*R*	*S*	*S*



SCHEME 3

90°C, $[a]_D^{20}$ = +53.31 IR (KCl)υ: 1240(P=O), 1080(P–N)cm^{-1} ^{1}HNMR ($CDCl_3$, 200 MHz) 1.64(m, 1H, H-6), 2.06(m, 3H, H′-6, CH_2-7), 3.26(m, 2H, H-4, H-8), 3.59(m, 1H, H′-8), 3.74 (m, 1H, H′-4), 3.84(d,2H, J = 8 Hz,PCH_2), 4.14(m, 1H, H-5), 6.95 (m, 1H, Ar-para), 7.23(m, 4H, Ar-ortho and meta). ^{31}PNMR ($CDCl_3$, 90MHz): 24.48ppm. MS (EI): 270(M,45), 221(M-CH_2Cl,40), 116(M-CH_2Cl-$PhNCH_2$,100).

Alkylation of **2**: To a cold (−78°C) solution of diisopropylamine (0.43 mL, 3.3 mmol) in THF (10 mL)

was added carefully a 2.0N *n*-BuLi solution in *n*-hexane (1.65 mL, 3.3 mmol) under a nitrogen atmosphere. Then, a THF (2 mL) solution of 2 (811 mg, 3 mmol) was added during 20 minutes at −78°C. After that, at the same temperature, the alkyl iodide (3.3 mmol) (benzyl bromide being used for benzylation) was introduced, and the reaction mixture was stirred for an additional 2 hours. Methanol was added at −78°C to terminate the alkylation process. After having been allowed to warm to room temperature, the mixture was treated with salinated aqueous NH_4Cl solution (25 mL) and then extracted repeatedly with ethyl acetate (3 × 30 mL). This solution was dried over Na_2SO_4, and the solvent was then removed. The de value was estimated by ^{31}PNMR spectroscopy. Pure alkylation products of **2** and **3** can be obtained by column chromatography on silica-gel using ethyl acetate and petroleum ether as eluent.

4a *was obtained by alkylation of* **2** *with methyl iodide as described previously. Column chromatography on silica-gel using EtOAC:petroleum ether 5:5 as eluent afforded* **3a** *as an oil.* IR(υ)1220(P=O), 1080(P–N)cm^{-1}. ^{1}HNMR(δ): 1.65(m, 1H, H′-6), 1.75(dd, 3H, J = 7.3, J = 15.5 Hz, $PCH_2C\underline{H}_3$), 1.85–2.15(m, 3H, H-6, CH_2-7), 3.10(m, 1H, H′-8), 3.45(m, 1H, H′-4), 3.90(m, 3H, H-4, H-5, H-8), 4.30(m, 1H, PCH), 7.00(m, 1H, Ar-Para), 7.30(m, 4H, Ar-ortho and meta) ppm. ^{31}PNMR 37.04 ppm. MS (EI) 284(M,100), 211(M-CHMeCl, 89), 116(M-CHMeCl-$PhNCH_2$,86) Elemental analysis ($C_{13}H_{18}N_2OPCl$) Calculated (%) C, 54.84; H, 6.37; N, 9.84; P, 10.88; Cl, 12.45 Found (%) C, 55.08; H, 6.40; N, 9.79; P, 10.05; Cl, 12.72.

4b *was obtained analogously as for* **4a** *by use of ethyl iodide as the alkylation agent.* IR(υ) 1230 (P=O), 1070 (P-N)cm^{-1}, ^{1}HNMR(δ) 1.10(t, 3H, J = 7.3 Hz, CH_3), 1.65(m, 1H, H′-6), 1.90–2.15(m, 4H, H-6, CH_2-7, CH-1, H-2, CH_3), 2.30 (m, 1H, CH-1, H-2, CH_3), 3.05(m, 1H, H′-8), 3.40(m, 1H, H′-4), 3.85(m, 3H, H-4, H-5, H-8), 4.15(m, 1H, PCH), 7.00(m, 1H, Ar-para), 7.30 (m, 4H, Ar-ortho and meta) ppm. ^{31}PNMR(δ) 36.04, 28.43 (90:10)ppm. MS (EI) 298(M, 87), 221(M-CHEtCl, 100), 116(M-CHEtCl-$PhNCH_2$, 83), HRMS. Anal. 298.0971 required 289.0998.

4c *was obtained analogously as for* **4a** *by use of propyl iodide as the alkylation agent and EtOAc: petroleum ether = 4:6 as the eluent.* IR(υ) 1230 (P=O), 1070 (P–N)cm^{-1}. ^{1}HNMR(δ) 0.90(t, 3H, J = 7.4, CH_3), 1.45(m, 1H, $CH_2CH^1H^2CH_3$), 1.65(m, 2H, H′-6, $CH_2C\underline{H}_2CH_3$), 1.80–2.25(m, 5H, H-6, CH_2-7, $C\underline{H}_2CH_2CH_3$), 3.05(m, 1H, H′-8), 3.45(m, 1H, H′-4), 3.85(m, 3H,H-4,H-5,H-8), 4.15(m, 1H, PCH), 7.00(m, 1H, Ar-para), 7.25(m, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 36.02, 28.16 (89:11)ppm. MS(EI): 312(M,43); 221(M-CHPrCl, 100), 116(M-CHPrCl-$PhNCH_2$, 76). Elemental analysis ($C_{15}H_{22}N_2PCl$): Calculated (%) C, 57.60; H, 7.09; N, 8.96; P, 9.90; Cl, 11.33. Found (%) C, 57.95; H, 7.08; N, 9.05; P, 9.72; Cl, 10.84.

4d *was obtained analogously as for* **4c** *by use of isopropyl iodide as alkylation agent.* IR(υ) 1215 (P=O), 1090 (P–N)cm^{-1}, ^{1}HNMR(δ) 1.00(d, 3H, J = 6.4Hz, CH_3), 1.05(d, 3H, J = 6.6Hz, CH_3), 1.65 (m, 1H, H′-6), 1.85–2.15(m, 3H, H-6, CH_2-7), 2.65(m, 1H, CHMe-2), 3.05(m, 1H, H′-8), 3.40(m, 1H, H′-4), 3.90(m, 3H, H-4, H-5, H-8), 4.15(dd, 1H, J = 2.8, J = 8.9 Hz, PCH), 7.00(m, 1H, Ar-para), 7.30(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 34.81, 28.50 (80:20)ppm. MS(EI): 312(M, 23), 221(M–CHPrCl, 71), 116(M–CHPrCl–$PhNCH_2$,100). Elemental analysis ($C_{15}H_{22}N_2OPCl$): Calculated (%) C, 57.60; H, 7.09; N, 8.96; P, 9.90; Cl, 11.33. Found (%): C, 57.57; H, 6.96; N, 8.94; P, 9.63; Cl, 11.56.

4e *was obtained analogously as for* **4a** *by use of butyl iodide as the alkylation agent and EtOAc: petroleum ether = 4:6 as the eluent.* IR(υ) 1225 (P=O), 1070 (P–N)cm^{-1}, ^{1}HNMR(δ) 0.90(t, 3H, J = 7.2, CH_3), 1.40(m, 4H, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.65(m, 2H, H′-6, $C\underline{H}^1H^2CH_2CH_2CH_3$), 1.80–2.30(m, 4H, H-6, CH2-7, $CH^1\underline{H}^2CH_2CH_2CH_3$), 3.05(m, 1h, H′-8), 3.45(m, 1H, H′-4), 3.85(m, 3H, H-4, H-5, H-8), 4.2(m, 1H, PCH), 6.95(m, 1H, Ar-para, 7.25(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ) 35.82. MS(EI): 326(M, 19), 221(M-CHBuCl, 100), 116(M–CHBuCl–$PhNCH_2$, 74). HRMS: Anal. 326.1329; Required 326.1316.

4f *was obtained analogously as for* **4c** *by use of benzyl chloride as the alkylation agent.* IR(υ) 1235 (P=O), 1060 (P–N)cm^{-1}, ^{1}HNMR(δ): 1.65(m, 1H, H′-6), 1.95(m, 1H, H′-7), 2.10(m, 2H, H-6, H-7); 3.05(m, 2H, H′-8, $ArC\underline{H}^1H^2$), 3.45(m, 1H, H′-4), 3.65(m, 1H, $ArCH^1\underline{H}^2$), 3.85(m, 1H, H-8), 3.95(m, 2H, H-4, H-5), 4.40(m, 1H, PCH), 7.00(m, 1H, Ar-para), 7.25(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 35.57ppm. MS(EI): 360(M, 36), 325(M-Cl, 100), 221(M–CHBzCl, 89), 116(M–CHBzCl–$PhNCH_2$,77), 91($PhCH_2$, 12). Elemental analysis ($C_{19}H_{22}N_2OPCl$) Calculated (%) C, 63.24; H, 6.15; N, 7.77; P, 8.58; Cl, 9.83. Found (%) C, 62.97; H, 6.12; N, 7.70; P, 8.18; Cl, 9.64.

4g *was obtained analogously as for* **4a** *by use of allyl chloride as the alkylation agent and EtOAc: petro-*

leum ether = 5:5 as eluent in the chromatographic separation. IR(υ) 1230 (P=O), 1070 (P–N)cm^{-1}, ^{1}HNMR(δ): 1.65(m, 1H, H′-6), 2.00(m, 3H, H-6, CH_2-7), 2.65(m, 1H, $CH_2=CHC\underline{H}^1H^2$), 3.00(m, 2H, H′-8, $CH_2=CHCH^1\underline{H}^2$) 3.40(m, 1H, H′-4), 3.85(m, 3H, H-4, H-5, H-8), 4.20(m, 1H, PCH), 5.10(d, 1H, J = 11.1 Hz, $C\underline{H}^1H^2=$), 5.15(d, 1H, J = 17.3 Hz, $CH^1\underline{H}^2$), 7.00(m, 1H, Ar-para), 7.25(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 35.55ppm. MS(EI): 310(m, 32), 275(M-Cl, 36), 221(M-CH(CH_2CHCH_2)Cl, 80), 116(M-CH($CH_2CH=CH_2$)Cl-PhNCH$_2$, 100). HRMS: Anal. 310.0952; Required 310.0998.

Alkylations of **3** were carried out analogously with the method used for **2**. By using various alkylating agents various derivatives of **9** with the 2R,5S,9S configuration were synthesized.

6a *was separated by column chromatography on silica-gel using EtOAc:petroleum ether = 8:2 as eluent.* IR(υ) 1225 (P=O), 1100 (P–N)cm^{-1}, ^{1}HNMR(δ): 1.66(m, 1H, H-6), 1.79(dd, 3H, J = 7.6, J = 14.6 Hz, $PCH_2C\underline{H}_3$), 2.10(m, 3H, H′-6, CH_2-7), 3.25(m, 1H, H-8), 3.60(m, 2H, H-4, H′-8), 3.80(m, 1H, H′-4), 4.12(m, 1H, H-5), 4.38(m, 1H, PCH), 6.98(m, 1H, Ar-para), 7.29(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 24.67ppm. MS(EI): 284(M, 35), 221(M-CHMe-Cl, 100), 116(M-CHMeCl-PhNCH$_2$, 86). Elemental analysis ($C_{13}H_{18}N_2OPCl$) Calculated (%): C, 54.84; H, 6.37; N, 9.84; P, 10.88; Cl, 12.45. Found (%) C, 54.77; H, 6.16; N, 9.84; P, 10.47; Cl, 12.35.

6b *was separated by column chromatography on silica-gel using EtOAc:petroleum ether=7:3 as eluent.* IR(υ) 1220 (P=O), 1095 (P–N)cm^{-1}, ^{1}HNMR(δ): 1.09(t, 3H, J = 7.0 Hz, CH_3), 1.65(m, 1H, H-6), 1.90(m, 1H, $CH^1H^2CH_3$), 2.10(m,3H, H′-6, CH_2-7), 2.50(m, 1H, $CH^1H^2CH_3$), 3.32(m, 1H, H-8), 3.47(m, 1H, H-4), 3.68(m, 2H, H-4, H-8), 4.10(m, 2H, H-5, P-CH), 6.98(m, 1H, Ar-para), 7.24(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 24.61, 24.22(93:7)ppm. MS(EI):298(M, 47), 221(M-CHEtCl, 100), 116(M-CHEtCl-PhNCH$_2$, 52). Elemental analysis ($C_{14}H_{20}N_2OPCl$) Calculated (%): C, 56.28; H, 6.75; N, 9.38; P, 10.37; Cl, 11.87. Found (%): C, 56.08; H, 6.39; N, 9.24; P, 10.05; Cl, 11.95.

6c *was separated by column chromatography on silica-gel using EtOAc: petroleum ether=6:4 as eluent.* IR(υ) 1200(P=O), 1090 (P–N)cm^{-1}. ^{1}HNMR(δ):0.93 (t, 3H, J = 7 Hz, CH_3), 1.4(m, 1H, $CH_2C\underline{H}^1H^2CH_3$), 1.70(m, 2H, H-6, $CH_2CH^1\underline{H}^2CH_3$), 1.90(m, 1H, $C\underline{H}^1H^2CH_2CH_3$), 2.12(m, 3H, H′-6, CH_2-7), 2.40(m, 1H, $CH^1\underline{H}^2CH_2CH_3$), 3.34(m, 1H, H-8), 3.50(m, 1H, H-4), 3.70(m, 3H, H′-4, H′-8), 4.18(m, 2H, H-5, P-CH), 7.00 (m, 1H, Ar-para), 7.27(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 24.75, 24.33 (77.5:22.5). MS(EI): 312(M, 28), 221(M-CHPrCl, 100), 116(M-CH(Pr)Cl-PhNCH$_2$, 82). Elemental analysis ($C_{15}H_{22}N_2OPCl$), Calculated (%) C, 57.60; H, 7.09; N, 8.96; P, 9.90; Cl, 11.33). Found (%) C, 57.23; H, 6.83; N, 8.51; P, 9.63; Cl, 11.31.

6d *was separated by column chromatography on silica-gel using EtOAc:petroleum ether = 6:4 as eluent.* IR(υ) 1240 (P=O), 1100 (P–N)cm^{-1}, ^{1}HNMR(δ): 0.90(d, 3H, J = 7.0 Hz, CH_3), 1.15(d, 3H, J = 6.0Hz, CH_3), 1.64(m, 1H, H-6), 2.15(m, 3H, H′-6, CH_2-7), 2.25(m, 1H, $CHMe_2$), 3.28(m, 2H, H-4, H-8), 3.70(m, 2H, H′-4, H′-8), 4.17(m, 1H, H-5), 4.29(dd, 1H, J = 4.0, J = 9.0 Hz, PCH), 7.00(m, 1H, Ar-para), 7.30(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 23.72, 23.58 (42:58) ppm. MS(EI): 312(M, 23), 221(M–CHPrCl, 100), 116(M–CHPrCl–PhNCH$_2$, 74). Elemental analysis ($C_{15}H_{22}N_2OPCl$): Calculated (%): C, 57.60; H, 7.09; N, 8.96; P, 9.90; Cl, 11.33; Found (%): C, 57.70; H, 7.05; N, 8.96; P, 9.55; Cl, 11.52.

6e *was separated by column chromatography on silica-gel using EtOAc:petroleum ether=6:4 as eluent.* IR(υ) 1240 (P=O), 1110 (P–N)cm^{-1}, ^{1}HNMR(δ): 0.90(d, 3H, J = 7.0Hz, CH_3), 1.33 (m, 3H, H-6, $CH_2CH_2C\underline{H}_2CH_3$), 1.66(m, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 1.90(m, 1H, $C\underline{H}^1H^2CH_2CH_2CH_3$), 2.10(m, 3H, H′-6, CH_2-7), 2.44(m, 1H, $CH^1\underline{H}^2CH_2CH_2CH_3$), 3.34(m, 1H, H-8), 3.50(m, 1H, H-4), 3.70(m, 2H, H′-4, H′-8), 4.16(m, 2H, H-5, PCH), 7.00(m, 1H, Ar-para), 7.28(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 24.70ppm. MS(EI): 326(M, 47), 221(M–CHBuCl, 100), 116(M–CHBuCl–PhNCH$_2$, 58). Elemental analysis ($C_{16}H_{24}N_2OPCl$): Calculated (%) C, 58.80; H, 7.40; N, 8.57; P, 9.48; Cl, 10.85. Found (%): C, 583.65; H, 7.62; N, 8.26; P, 9.10; Cl, 10.70.

6f *was separated by column chromatography on silica-gel using EtOAc:petroleum ether=5:5 as eluent.* IR(υ) 1225 (P=O), 1080 (P–N)cm^{-1}, ^{1}HNMR(δ): 1.66(m, 1H, H-6), 2.05(m, 3H, H′-6, CH_2-7), 2.50(m, 1H, $ArC\underline{H}^1CH^2$), 3.24(m, 2H, H-4, H-8), 3.70(m, 3H, H′-4, H′-8, $ArCH^1\underline{H}^2$), 4.10(m, 1H, H-5), 4.40(m, 1H, PCH), 7.00(m, 1H, Ar-para), 7.25(m, 4H, Ar-ortho and meta)ppm. ^{31}PNMR(δ): 23.70, 24.03 ppm (75:25). MS(EI): 360(M, 31), 325(M-Cl, 83), 221(M–CHBzCl, 100), 116(M–CH_1BzCl–PhNCH$_2$, 92). HRMS: Anal. 325.1482 (M-Cl); Required 325.1465.

6g *was separated by column chromatography on silica-gel using EtOAc:petroleum ether = 6:4 as*

eluent. IR(υ) 1215 (P=O), 1110 (P–N)cm^{-1}, ^{1}HNMR(δ): 1.67(m, 1H, H-6), 2.10(m,3H,H′-6, CH_2-7), 2.65(m, 1H, CH_2=CHC$\underline{H}^1H^2$), 3.15(m, 1H, H-8), 3.30(m, 1H, H-4), 3.50(m, 1H, CH_2=CHC$H^1\underline{H}^2$), 4.20(m, H, H-5, PCH), 5.10(d, 1H, J = 9.3 Hz, C$\underline{H}^1H^2$=), 5.15(d, 1H, J = 16.0 Hz, C$H^1\underline{H}^2$=), 7.00(m, 1H, Ar-para), 7.27(m,4H, Ar-ortho and meta)ppm ^{31}PNMR(δ):23.80,23.43(67.5:32.5)ppm MS(EI):310(M,13), 275(M–Cl,36), 221(M–CHAIICl, 80), 116(M–CHAIICl –PhNCH_2, 100), Elemental analysis ($C_{15}H_{24}N_2OPCl$): Calculated (%) C, 57.97; H, 6.49; N, 9.02; P, 9.97; Cl, 11.41. Found (%): C, 57.85; H, 6.47; N, 8.97; P, 9.58; Cl, 11.47.

(*R*)-*α-chloro-β-phenylethylphosphonicacid*(**5R**) was prepared by heating a mixture of **4f** (0.27 g), in benzene(10 mL) in the presence of hydrochloric acid (1:1, 4 mL) at 60°C for 6 hours. After removal of benzene, the aqueous residue was treated with NaOH to pH 13 followed by extraction with ethyl acetate (3 × 30 mL). The resultant aqueous solution was treated with concentrated HCl to pH 3, and after removal of water under diminished pressure, the residue was extracted with chloroform.

The inorganic salt thus obtained was removed by filtration. After removal of chloroform the residue was recrystallized from Ethanol-ethyl acetate to give pure **5*R***(yield 160 mg or 90%), m.p. 100°C $[a]_D^{20}$ = +30° (c = 0.12 MeOH).

(*S*)-*α-chloro-β-butylphosphonic acid* (**7S**) was prepared analogously as for **5R**. Yield of **7S**: 140 mg or 85%. $[a]_D^{20}$ = −20° (c = 1.55 MeOH).

Conversion of **4** *to* **7** *via* **6**. Replacement of the chlorine atom in **4** by the azado group was achieved as follows: To a mixture of **4** (3 mmol) in DMF (10 mL) was added NaN_3 (390 mg, 6 mmol) and then heated for 24 hours at 140°C. DMF was removed below 50°C, and the residue was dissolved in ethyl acetate, an inorganic salt being removed by filtration. Upon removal of ethyl acetate by evaporation, compound (**6**) was obtained. Since **4d** gave no reaction while **4f** and **4g** provided compounds with elimination of HCl, consequently we were able to obtained only **6a**, **6b**, **6c**, and **6e**, that could be converted, without purification, directly to the corresponding *compounds* **7**.

9a: A mixture consisting of crude **6a** (1.5 mmol), benzene (10 mL) and triphenylphosphine (393 mg, 1.5 mmol) was stirred at room temperature for 4 hours. Following evolution of nitrogen gas, to the mixture was added 2 mL of water, and the resulting mixture was stirred for an additional 4.5 hours at 50–55°C. After having been cooled to 5°C, the separated aqueous layer was extracted with chloroform (2 × 5 mL). The combined organic solution was dried over anhydrous Na_2SO_4. Removal of the solvent gave a residue that was treated by column chromatography on silicon-gel using EtOAc:MeOH as eluent IR(υ): 3350(NH_2), 1195(P–O), 1060(P–N)cm^{-1}, ^{1}HNMR(δ): 1.10 (dd, 3H, J = 7.2 Hz, J = 18.4 Hz, CH_3), 1.65(m, 1H, H′-6), 1.80–2.20(m, 3H, H-6, CH_2-7), 3.05(m, 1H, H-8), 3.40(m, 2H, H′-3, H-8), 3.80 (m, 3H, H-4, H-5, PCH), 6.95(m, 1H, Ar-para), 7.25(m, 4H, Ar-meta, ortho)ppm, ^{31}PNMR(δ):42.90ppm. MS(EI):266(M + 1, 70), 222(M + 1-CHMeNH_2, 64), 117(M + 1-CHMeNH_2, 64), 117(M + 1-CHMeNH_2PhNCH_2, 100). HRMS Anal. 265.1331, Required 265.1340.

9b *was obtained analogously as for* **9a**. IR(υ): 3300(NH_2), 1190(P=O), 1060(P–N)cm^{-1}. ^{1}HNMR(δ): 0.90(t, 3H, J = 7.4 Hz, CH_3), 1.65(m, 2H, H′-6, C$\underline{H}$)$^1H^2CH_3$), 2.00(m, 4H, H-6, CH_2-7, C$H^1\underline{H}^2CH_3$), 3.00(m, 1H, H′-8), 3.15(m, 1H, H′-4), 3.35(m, 1H, H-8), 3.80(m, 3H, H-4, H-5, PCH), 6.95(m, 1H, Ar-para, 7.25(m, 4H, Ar-meta, para)ppm. ^{31}PNMR(δ): 42.94, 35.95 (91:9)ppm. MS(EI): 280(M + 1, 27), 222(M + 1-CHEtNH_2, 48), 117(M + 1-CHEtNH_2-PhNCH_2, 100). HRMS: Anal. 279.1536, Required 279.1469.

9c *was obtained analogously as for* **7a**. IR(υ): 3350(NH_2), 1180(P=O), 1060(P–N)cm^{-1}. ^{1}HNMR(δ): 0.75(t, 3H, J = 6.8Hz, CH_3), 1.25(m, 2H, $CH_2C\underline{H}_2CH_3$), 1.50(m, 1H, C$\underline{H}^1H^2CH_2CH_3$), 1.65(m, 2H, H′-6, C$H^1\underline{H}^2CH_2CH_3$), 1.80–2.10(m, 3H, H-6, CH_2-7), 3.50(m, 1H, H′-8), 32.5(m, 1H, H′-4), 3.40(m, 1H, H-8), 3.80(m, 3H, H-4, H-5, PCH), 6.95(m, 1H, Ar-para), 7.25(m, 4H, Ar-meta, ortho)ppm. ^{31}PNMR(δ): 42.49, 36.33 (96:4)ppm. MS(EI): 293(M, 2), 222(M + 1-CHPrNH_2, 44), 117(M + 1-CHPrNH_2-PhNCH_2, 100). HRMS: Anal. 293.1717, Required 293.1652.

7e *was obtained analogously as for* **7a**. IR(υ): 3350(NH_2), 1200(P = O), 1060(P–N)cm^{-1}. ^{1}HNMR(δ): 0.65(t, 3H, J = 7.1 Hz, CH_3), 1.20(m, 4H, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.50(m, 1H, C$\underline{H}^1H^2CH_2CH_2CH_3$), 1.65(m, 1H, H′-6), 2.00(m, 4H, H-6, CH_2-7, C$H^1\underline{H}^2CH_2CH_2CH_3$), 3.00(m, 1H, H′-8), 3.20(m, 1H, H′-4), 3.40(m, 1H, H-8), 3.80(m, 3H, H-4, H-5, PCH), 6.95(m, 1H, Ar-para), 7.25(m, 4H, Ar-meta, ortho)ppm. ^{31}PNMR(δ): 42.35ppm. MS(EI): 308(M + 1, 44), 222(M + 1-CHBuNH_2, 58), 117(M + 1-CHBu-PhNCH_2, 100). HRMS: Anal. 307.1822 Required 307.1808.

(*R*)-*1-Aminopropylphosphonic acid* (**10b**). A mixture of **7b** (250 mg) in 1:1 hydrochloric acid (5

mL) was stirred at 40°C for 4 hours. The aqueous component was removed on a rotatory evaporator and to the residue thus obtained was added ethanol (2 mL) to form a solution. To this was added propylene oxide until precipitate formation was completed. The white precipitate was collected by filtration and washed successively with ethanol (5 mL) and EtOAc (3 × 10 mL). **10b** was obtained as a colorless powder. m.p. 276°C. Yield 100 mg or 80%. $[\alpha] = 18.7°$ ($c = 0.1$, 1N NaOH) (literature [2]), $[\alpha] = -22°$, ($c = 0.1$, 1N NaOH).

REFERENCES

[1] Kafarski, P.; Lejczak, B. Phosphorus Sulfur Silicon 1991, 63, 193–215.
[2] Atherton, F. R.; Hassell, C. H.; Lambert, R. W. J Med Chem 1986, 29, 29–40.
[3] Giannousis, P. P.; Bartlett, P. A. J Med Chem 1987, 30, 1603–1609.
[4] Kupczyk-Subotkowska, L.; Mastalertz, M. Int J Peptide Protein Res 1983, 21, 485–490.
[5] Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassell, C. H.; Holmes, S. W.; Lambert, R. W. Nature 1978, 272, 56–58.
[6] Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W. Antimicrob Agents Chemotherapy 1979, 15, 659–663.
[7] Iriuchijima, S. Synthesis 1978, 684–685.
[8] Hanessian, S.; Bennani, Y. L. Tetrahedron Lett 1990, 31, 6465–6468.
[9] Kukhar, V. P. in Aminophosphonic and Aminophosphinic Acids; Kukhar, V. P., Hudson, H. R. (Eds.) John Wiley & Sons: Chichester, U.K., 2000; Chapter 5, pp. 127–168.
[10] Yuan, C. Y.; Cui, S. H. Phosphorus Sulfur Silicon 1991, 55, 159.
[11] Li, S. S.; Wang, G. Q. Acta Chimica Sinica 1993, 51, 713.
[12] Yuan, C. Y.; Li, S. S.; Ma, Y. L. Phosphorus Sulfur Silicon 1993, 81, 27.
[13] Wang, G. Q. Ph.D. Dissertation, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 1993.
[14] Yuan, C. Y.; Li, S. S.; Wang, G. Q. Chinese Chem Lett 1993, 9, 753.
[15] Peyronel, J. F.; Samuel, O.; Fiaud, J. C. J Org Chem 1987, 52, 5320.