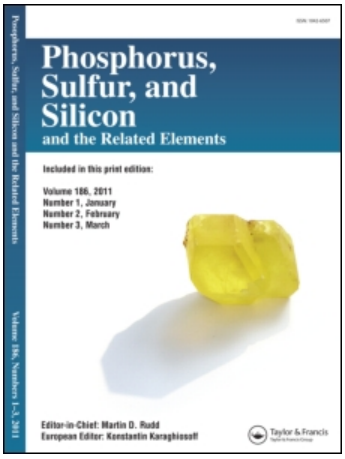


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# OPTICALLY ACTIVE 1-AMINOALKYLPHOSPHONIC ACIDS

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# OPTICALLY ACTIVE 1-AMINOALKYLPHOSPHONIC ACIDS

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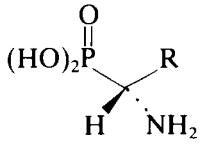
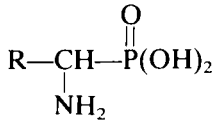
## I. INTRODUCTION

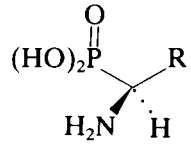
1-Aminoalkylphosphonic acids **1** as analogs of 1-amino-carboxylic acids are important because of their potential biological activity. These act as substrates or inhibitors of enzymes involved in the metabolism of amino acids.[1-2] Several phospho dipeptides and oligopeptides are known to repress bacterial growth.[3-16] Many of these studies have been carried out using racemic 1-amino-alkylphosphonic acids **1** although in several cases their activity has been shown



*R*-Enantiomer



**1**



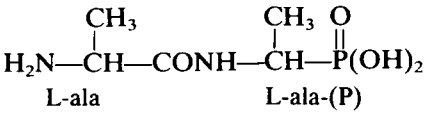
*S*-Enantiomer

| R | | R | |
|---|---|---|---|
| a | $CH_3$ | j | $C_2H_5$ |
| b | $(CH_3)_2CH$ | k | $n\text{-}C_3H_7$ |
| c | $(CH_3)_2CH\,CH_2$ | l | $n\text{-}C_4H_9$ |
| d | $C_6H_5CH_2$ | m | $CH_2CH_2OH$ |
| e | $CH_2OH$ | n | $CH_2Cl$ |
| f | $CH_2COOH$ | o | $CH_2CH_2CH_2COOH$ |
| g | $CH_2CONH_2$ | p | $C_6H_5$ |
| h | $CH_2CH_2COOH$ | q | $CH_3SCH_2CH_2$ |
| i | $p\text{-}HO\text{—}C_6H_4CH_2$ | r | $C(CH_3)_2SH$ |

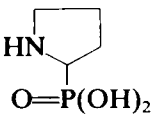
to depend upon their absolute configuration.[11-13] One such example is the high antibacterial activity of alafosfalin **2**, N-(L-alanyl)-L-1-aminoethylphosphonic acid, as compared to that of the other diastereoisomers.[11,13] Alafosfalin[17-19] **2** has been shown to act by facilitated transport into the bacterial cell wall where it is cleaved enzymatically to L-1-aminoethylphosphonic acid **1a** which inhibits alanine racemase and related processes by simulating L-alanine.[20] The analgesic activity of enkephalin analogs containing aminophosphonic acid residues at C-terminal position has been shown to depend on the configuration of the aminophosphonic acid residue.[21-23] Of the two diastereoisomeric pentapeptides Tyr-Gly-Gly-Phe-

* Author to whom all correspondence should be addressed.

† The phosphonic analog of methionine is abbreviated as MetP. Other phosphonic analogs of aminocarboxylic acid are abbreviated accordingly in this Review.




Alafosfalin **2**

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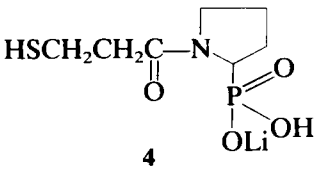


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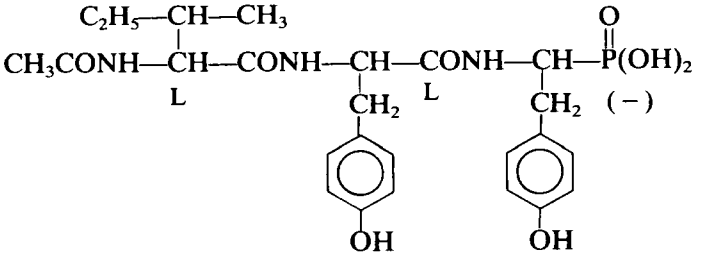


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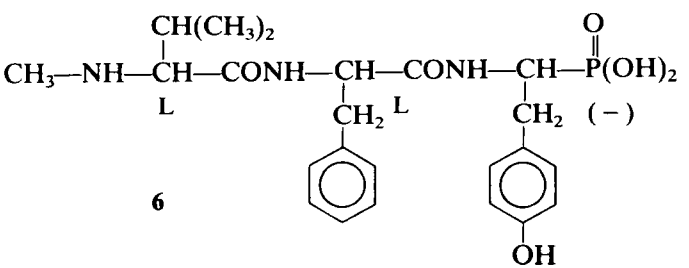



**6**

MetP† differing only in the configuration at the C-terminal phosphonic analog of methionine, only the one with (−)MetP exhibited significant analgesic activity. Unfortunately, the configuration of the phosphonic analog of methionine was not known. (−)-1-Amino-2-phenylethylphosphonic acid **1d**, of then unknown configuration (now known to be *R*), was found to interact with rabbit muscle pyruvate kinase.[24] A derivative **4** of racemic 2-phosphonopyrrolidine (phosphonic analog of proline) **3** was found to be an inhibitor of angiotensin-converting enzyme. The active component of **4** was expected to be the *R*-enantiomer but the study was performed with the racemic **4** presumably for the lack of availability of optically active 2-phosphonopyrrolidine.[25] Thus, there existed an obvious need to have optically active enantiomers of 1-aminoalkylphosphonic acids **1** with known absolute configuration, and this need spurred an interest in the last decade in their synthesis. This review surveys the methods developed to prepare optically active 1-aminoalkylphosphonic acids **1** with known absolute configuration. Several excellent reviews on the synthesis and chemistry of 1-aminoalkylphosphonic acids covering the literature to 1975 are available.[26–28] The chemistry of aminophosphonous acids[29,30] and aminophosphinic acids[31] has also been reviewed.

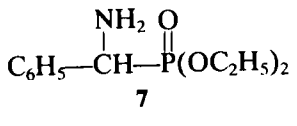
It is interesting to note that the only naturally occurring 1-aminoalkylphosphonic acid is (−)-1-amino-2-(4-hydroxyphenyl) ethylphosphonic acid **1i**.[32] (The absolute configuration of (−)-**1i** has been shown to be *R*, see Reference 61. Thus, natural TyrP belongs to the L-series of amino acids). This has been isolated in the form of hypotensive active tripeptides, N-(N-acetyl-L-isoleucyl-L-tyrosyl)-(−)-1-amino-2-(4-hydroxyphenyl) ethylphosphonic acid **5** from the cultures of actinomycetes K-26 and N-(N-methyl-L-valyl-L-phenylalanyl-(−)-1-amino-2-(4-hydroxyphenyl) ethyl phosphonic acid **6** from the cultures of actinomycetes K-4.



## II. PREPARATION OF OPTICALLY ACTIVE 1-AMINOALKYLPHOSPHONIC ACIDS

### *A. By Resolution*

1. *By Formation of Diastereoisomeric Salts or Compounds with Optically Active Acids.* Aminoalkylphosphonic acids **1** may be resolved both with optically active acids and optically active bases. The first reported attempt to resolve any 1-aminoalkylphosphonic acid or its derivative is that of the resolution of the diethyl 1-amino-1-phenylmethylphosphonate **7** using dibenzoyl-L-(+)-tartaric acid. In this attempt Rogozhin and coworkers[33] were successful in isolating only one of the isomers, namely (−)-diethyl 1-amino-1-phenylmethylphosphonate (−)-**7**. The process involved the treatment of a hot solution of racemic **7** with a solution of dibenzoyl-L-(+)-tartaric acid in methanol from which the diastereoisomeric salt [(−)(+)] preferentially crystallized out. This diastereoisomeric salt was converted to free (−)-**7** by treatment first with HCl and then ammonia. The free (−)-**7** obtained in poor yield had $[\alpha]_D^{20} = -15.6°$ (c 1, methanol) and was of fair optical purity.[34] Dibenzoyl-L-(+)-tartaric acid has been used for the resolution of several other diethyl 1-aminoalkylphosphonates[35] **8a–d**. The ester **8e**



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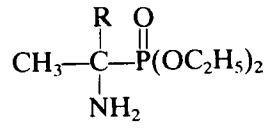
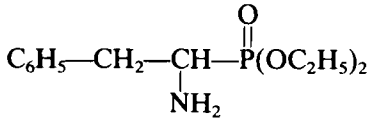


8

a R = $C_2H_5$
b R = $C_4H_9$
c R = i-$C_4H_9$
d R = $C_6H_{13}$
e R = $C_6H_5$

has been resolved with L-(+)-tartaric acid.[35] Several of these optically active esters **8** have been hydrolyzed to the corresponding optically active 1-aminoalkylphosphonic acids.[35] Hydrolysis of (−)-**7** with HCl is reported to yield (−)-1-amino-1-phenylmethylphosphonic acid(−)-**1p**.[36,37]

In the examples cited above only one isomer was isolated in each case. It should be possible to isolate both isomers, and this was achieved in the resolution of diethyl 1-amino-2-phenylethylphosphonate **9** with dibenzoyl-L-(+)-tartaric acid in an ethanol methanol mixture.[38] The diastereoisomeric salt that crystallized preferentially had $[\alpha]_{578}^{20} = -67.2°$ (c 1.95, NaOH). It was converted to free ester and hydrolyzed to give the dextro rotatory 1-amino-2-phenylethyl phosphonic acid (+)-**1d**. From the residue left after the treatment of racemic **9** with dibenzoyl-L(+)-tartaric acid was isolated in the same way (−)-**1d**.

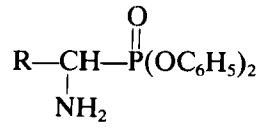


9

The ester **7** has also been resolved by forming diastereoisomeric salts with D-(−)-mandelic acid.[39] Resolution of diphenyl 1-aminoalkylphosphonates **10** by forming diastereoisomeric salts with L-(−)-malic, L-(+)-mandelic, L-(+)-lactic or dibenzoyl-L-(+)-tartaric acids was unsuccessful.[40] The esters **10** have been resolved by reaction with dibenzoyl-L-(+)-tartaric anhydride to form diastereoisomeric amides **11a** and **11b** which were readily separated by crystallization.[40] Hydrolysis of **11a** and **11b** yielded the corresponding enantiomers of 1-aminoalkylphosphonic acids (*S*)-**1** and (*R*)-**1** in high yields.

Optically pure phosphonic analogs of alanine **1a**, valine **1b**, leucine **1c**, phenylglycine **1p**, and phenylalanine **1d** were obtained by this method. Resolution of diphenyl 2-acetoxy-1-aminoethylphosphonate **12** via the diastereoisomeric amides **13** was however not successful.[41] Contrary to the earlier suggestion,[40] diastereoisomeric imides **14** were easily separated by crystallization.[41] Hydrolysis of the resultant diastereoisomers gave the enantiomers of 1-amino-2-hydroxyethylphosphonic acid **1e** in high yields.

1-Aminoalkylphosphonic acids have also been resolved via the phosphonodipeptides. Formation of a peptide bond between an optically active aminoalkylcarboxylic acid and a racemic 1-aminoalkylphosphonic acid yields a mixture of diastereoisomers which can be separated either by crystallization[12,21]



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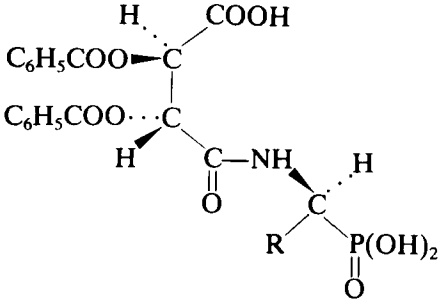
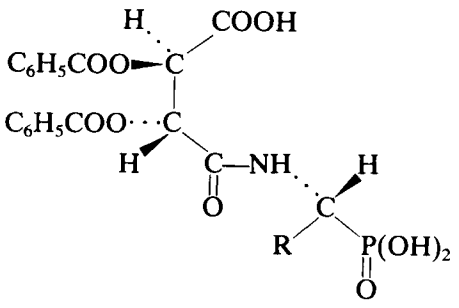
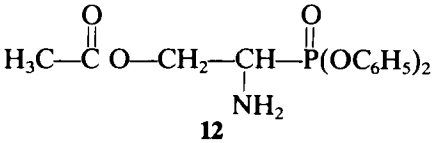


11a



11b



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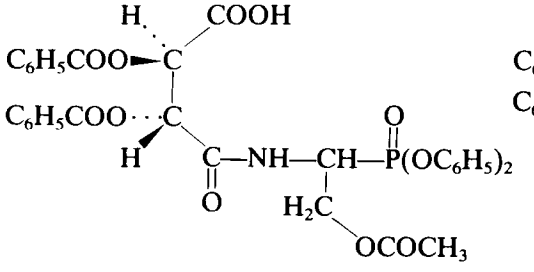

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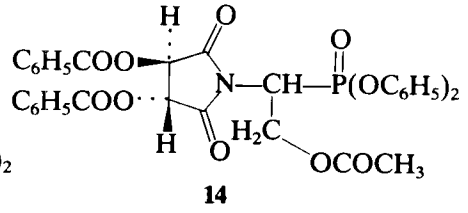
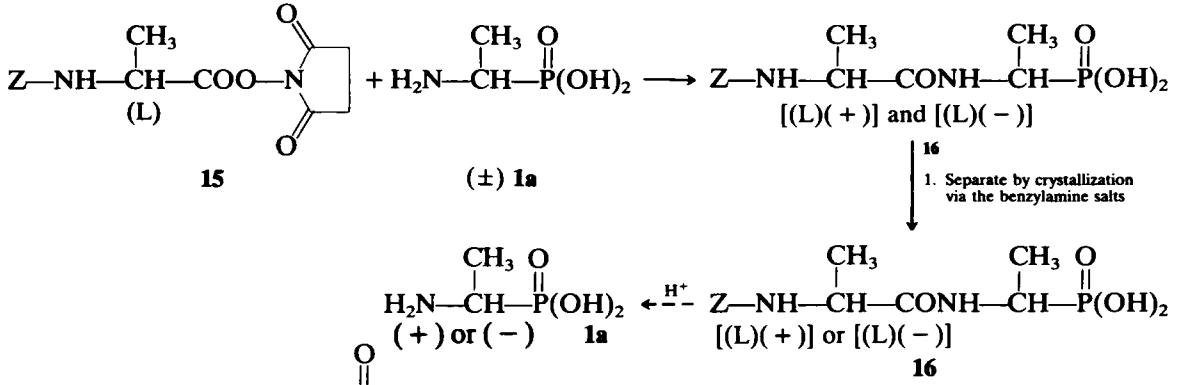


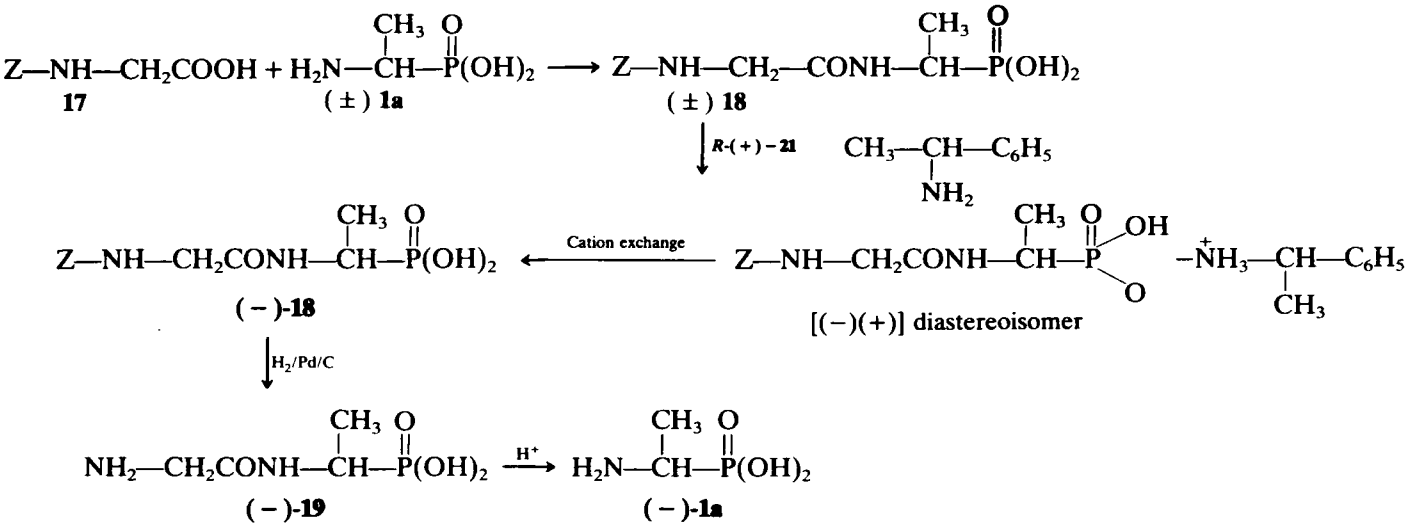
14

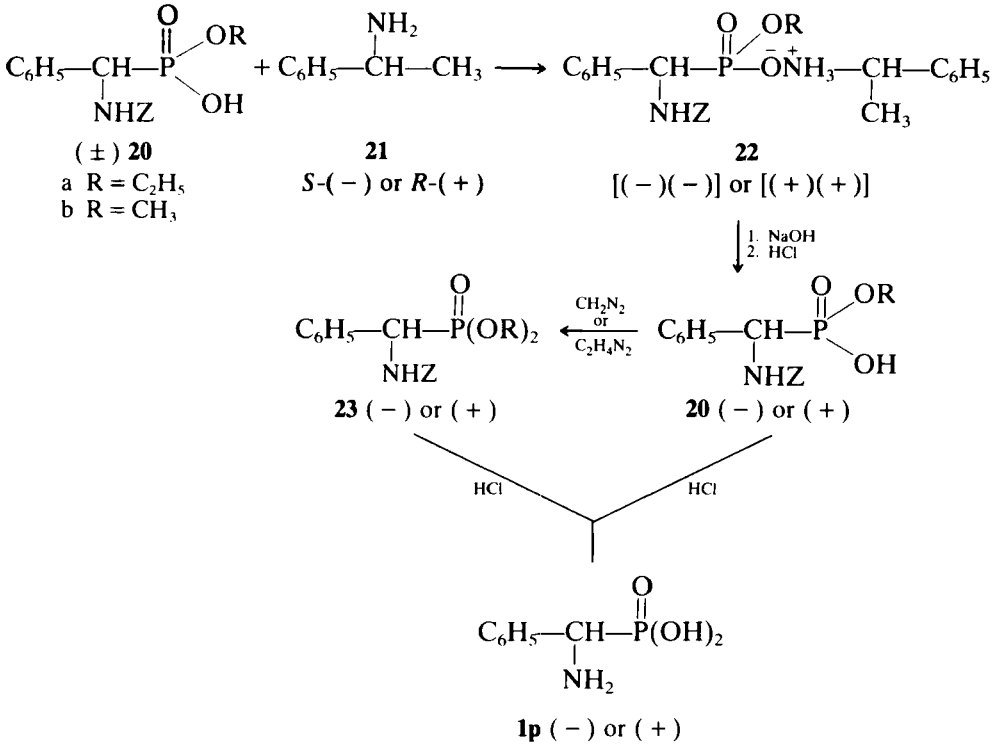
or ion-exchange chromatographic methods.[42–44] For example, the diastereoisomeric mixture of N-protected dipeptide **16** was separated into pure diastereoisomers by the crystallization of benzylamine salts which were then converted into the enantiomers of **1a**.[12] Separation of diastereoisomeric phosphonodipeptides by ion-exchange column chromatography has led to the preparation of the enantiomers of the phosphonic acid analogs of methionine[23] **1q**, glutamic acid **1h**, 2-aminoadipic acid **1o** and proline **3** and enantiomers of 1-aminopropylphosphonic acid[45] **1j**. Differences in the mobility rates of diastereoisomeric peptides on ion-exchange columns have been used in the assignment of the absolute configuration of 1-aminoalkylphosphonic acids.[45] (See Section III, D).

2. *By Formation of Diastereoisomeric Salts with Optically Active Amines.* The peptide **18**, obtained by coupling N-carbobenzyloxyglycine **17** with racemic 1-aminoethylphosphonic acid **1a**, has been resolved[12] with the use of optically active 1-phenylethylamine **21**. Treatment of peptide **18** with *R*-(+)-amine **21** to




(Throughout this review Z=C(=O)—OCH2C6H5)



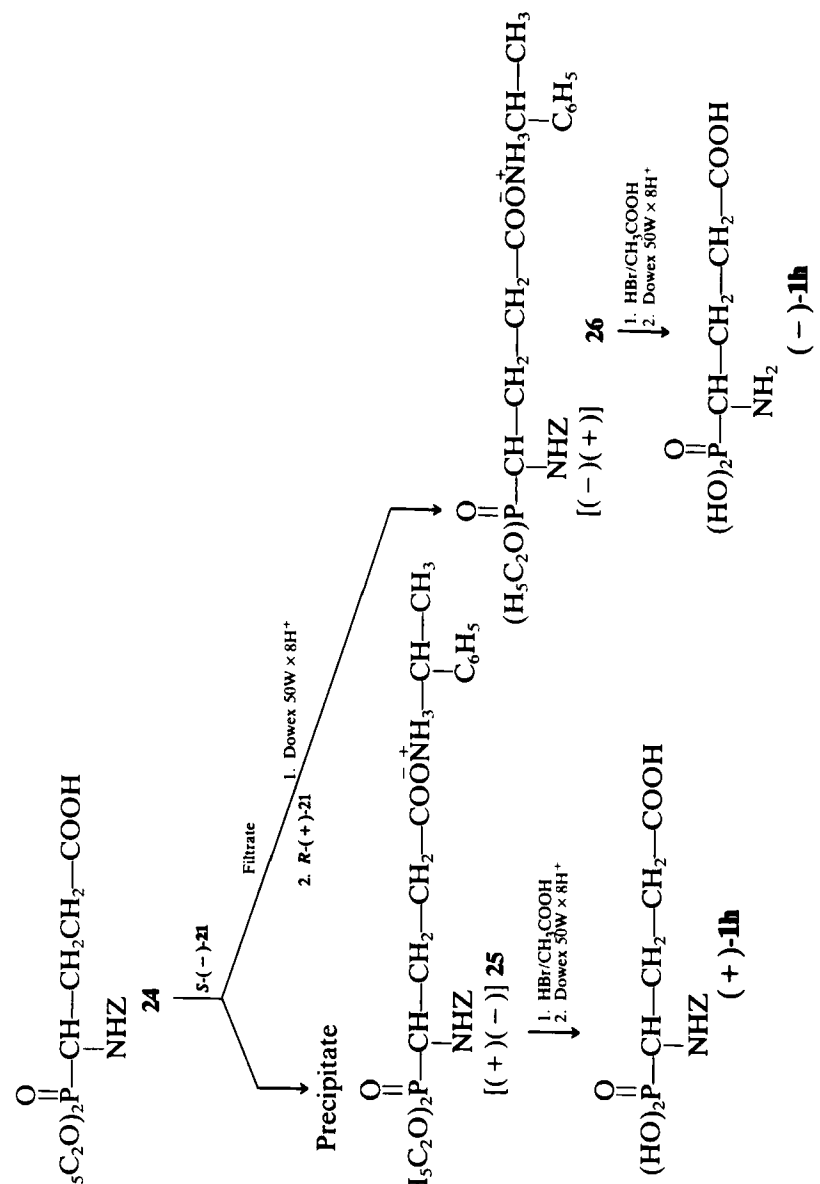


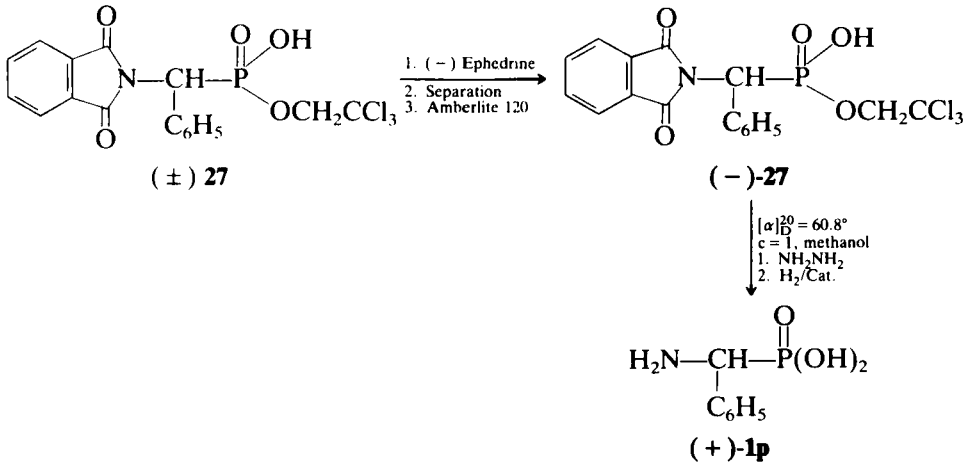

pH 4.00 followed by crystallization from methanol–water mixture gave preferentially the [(−)(+)] diastereoisomer which on hydrogenolysis yielded (−)-N-glycyl-1-aminoethylphosphonic acid (−)-**19**. Hydrolysis of (−)-**19** with HCl then gave (−)-1-aminoethylphosphonic acid (−)-**1a**. Similarly using *S*-(−)-amine **21**, (+) enantiomer of **1a** was obtained.

Monoesters of racemic N-carbobenzyloxy-1-amino-1-phenylmethylphosphonic acid **20** have been resolved[46] by formation of diastereoisomeric salts with optically active 1-phenylethylamine **21**. Treatment of racemic **20** with *S*(−)-amine **21** gives a mixture of [(−)(−)] and [(+)(−)] diastereoisomeric salts from which [(−)(−)] salt **22** can be selectively isolated by fractional crystallization. Similarly by using *R*-(+)-amine **21**, [(+)(+)] diastereoisomeric salt **22** can be obtained. **22** [(−)(−) or (+)(+)] is then converted into optically active monoalkyl ester **20** (− or +). The optically active esters 20 (− or +) and diesters **23** (− or +) on hydrolysis give (− or +) − **1p**.

Resolution of the phosphonic acid analog of glutamic acid **1h** has also been reported.[47] Treatment of racemic phosphonate ester **24** with *S*-(−)-amine **21** resulted in the preferential crystallization of [(+)(−)] diastereoisomer **25**, $[\alpha]_D^0 = +9.8$ (c 2.44, $CH_3OH$). The filtrate after the removal of **25** on treatment with acid ion-exchange resin followed by the addition of *R*-(+)-amine **21** yielded the [(−)(+)] diastereoisomer **26** $[\alpha]_D^0 = -9.6$ (c = 2.5, $CH_3OH$). The resolved diastereoisomers were converted into the corresponding enantiomers of **1h**.

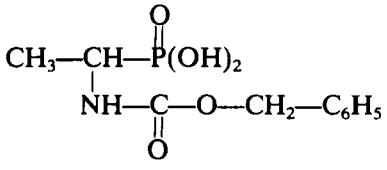
2,2,2-Trichloroethyl monoester of racemic N-phthalyl-1-amino-1-phenylmethyl phosphonic acid **27** has been resolved[48] with (−)ephedrine. The diastereoisomeric






salt that crystallized preferentially from an ethylacetate/hexane solvent mixture, on treatment with Amberlite IR 120 in methanol gave the (−) enantiomer of **27**. The levorotatory **27** yielded (+)-1-amino-1-phenylmethyl phosphonic acid **1p** on removal of protecting groups.

Enantiomers of 1-aminoethylphosphonic acid **1a** have been obtained[12,13] by resolving N-carbobenzyloxy-1-aminoethylphosphonic acid **28** with quinine which formed a salt with the (+) enantiomer. After the removal of this salt, dehydroabietylamine formed a salt with the (−) enantiomer.



**28**

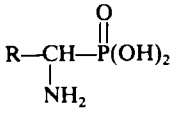
Treatment of these salts with base and hydrogenolysis then gave the enantiomers of **1a**.

3. *Enzymatic Resolution of* 1-*Aminoalkylphosphonic Acids.*[49,50] Treatment of racemic acylaminoalkylphosphonic acid **29** with aminoacylase at pH 7.2–7.5 at 37–40°C results in the selective hydrolysis of the *S*-enantiomer. The acyl *R*-enantiomer **29** is then extracted with hot ethanol from the insoluble *S*-1-aminoalkylphosphonic acid **1**. *R*-1-Aminoalkylphosphonic acid **1** is then obtained by the deacylation of the *R*-enantiomer **29** with HCl.

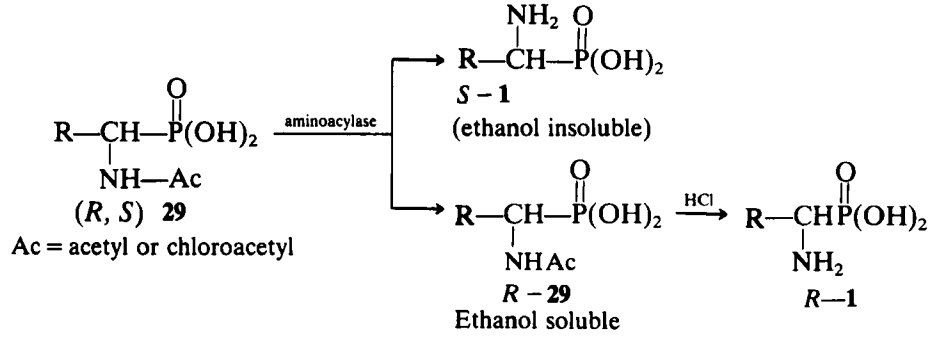
The Table I compares the optical rotations reported by these authors for **1d** and **1p** with the optical rotation values for these reported by other workers.

It may be noted that whereas the optical rotations of the enantiomers of **1p** obtained by the enzymatic method are close to the values reported by other workers,[52] a disagreement exists in the optical rotations of the enantiomers of **1a** and **1d** obtained by the enzymatic method and those values reported for **1a** and **1d** by other workers.[12,13,38,54] Moreover the configuration of levorotatory **1a** and

TABLE I



| R | Configuration | Optical rotation of enantiomers obtained by enzymatic hydrolysis method | Optical rotation reported by other workers | |
|---|---|---|---|---|
| | | $[\alpha]_D^{20}$ $c = 1$, 1N NaOH | $[\alpha]_D^{20}$ $c = 2$, 1N NaOH | |
| **1a** $CH_3$ | *S* | −2.9° | +16.8° | |
| | *R* | +2.8° | −16.9° ([Reference 12 and 13) | |
| | | $[\alpha]_D^{24}$ $c = 1.5$, 1N NaOH | $[\alpha]_{578}^{20}$ $c = 2$, 1N NaOH | $[\alpha]_D^{20}$ $c = 2$, 2N NaOH |
| **1d** $C_6H_5CH_2$ | *S* | −1.5° $c = 1$, 1N NaOH | +49.9° | +37.0° |
| | *R* | +13.9° | −49.9° (Reference 38) | −38.9° (Reference 54) |
| | | $[\alpha]_D^{20}$ $c = 2.0$, 1N NaOH | $[\alpha]_D^{20}$ $c = 2$, 1N NaOH | |
| **1p** $C_6H_5$ | *S* | −17.6° | −18.0° | |
| | *R* | +17.8° | +18.0° (Reference 52) | |




$R = CH_3$, n-$C_3H_7$, n-$C_4H_9$, $C_6H_5$, $C_6H_5CH_2^-$

**1d** have been determined to be *R* by x-ray structural determination (see Table III. Specific Rotations of the 1-aminoalkylphosphonic acids).

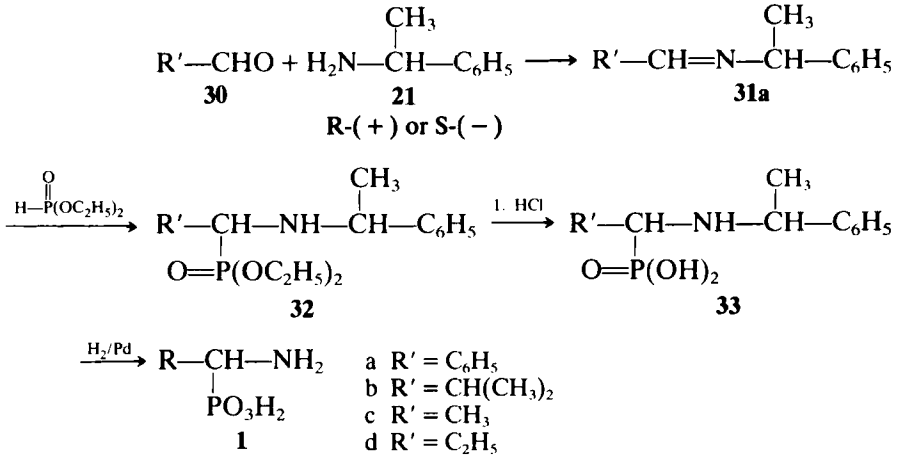
## *B. Asymmetric Induction Methods*

### 1. *By the Addition of a P–H Group to Carbon–Nitrogen Double Bond*

*a. By the addition of diethylphosphite to the C=N double bond of aldimines, obtained by the reaction of aldehydes with optically active 1-phenylethylamine*

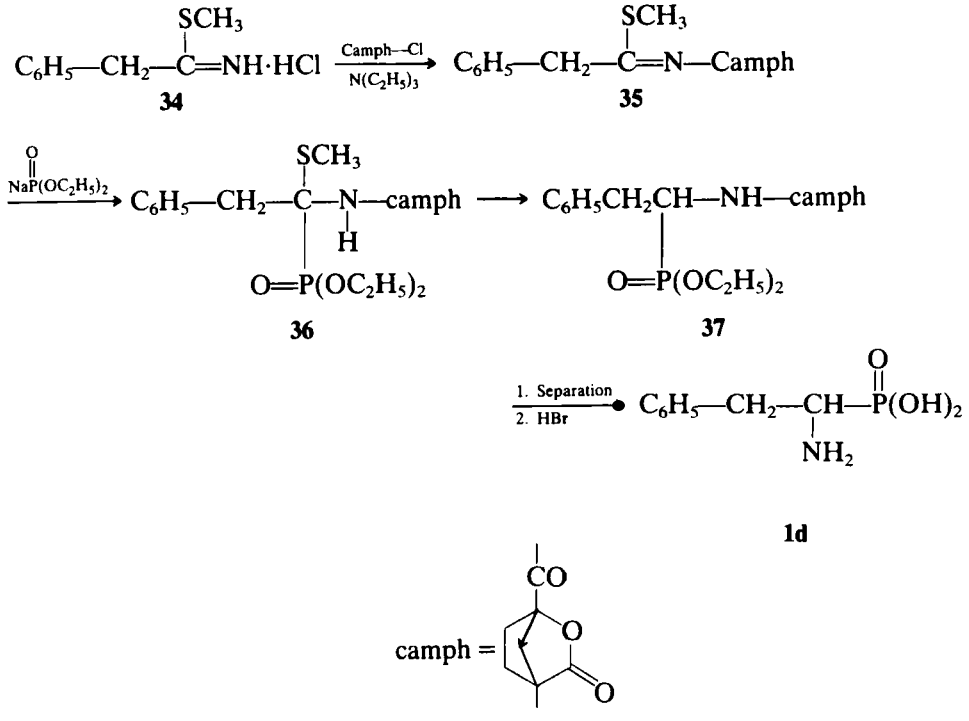
**21**. The first asymmetric induction synthesis of an 1-aminoalkylphosphonic acid was reported by Gilmore and McBride.[51] In this method benzaldehyde **30a** was condensed with either *R*-(+) or *S*-(−)-1-phenylethylamine **21** to form the corresponding aldimine **31a**. Addition of diethylphosphite to the aldimine **31a** at 140°C produced an excess of one of the diastereoisomers **32a** which was isolated, hydrolyzed with HCl, and catalytically hydrogenated to give optically active 1-amino-1-phenylmethyl-phosphonic acid **1p**. A synthesis using *R*-(+)-amine **21** gave the levorotatory enantiomer of **1p**. No details were given by Gilmore and McBride about the asymmetric induction step i.e. addition of diethylphosphite to aldimine **31a** as to what kind of diastereoisomeric excess was obtained.

In a later study by Glowiak and coworkers,[52] it was found that Gilmore's method produced a mixture of diastereoisomers **32a** in a ratio of 2:1. The reaction at room temperature was found to produce better induction and gave **32a** in a diastereoisomeric ratio of 6:1. Similar results were obtained by the addition of diethylphosphite to the aldimine **32b**. With **31c** and **31d**, diethylphosphite addition resulted in poor asymmetric induction.[53]

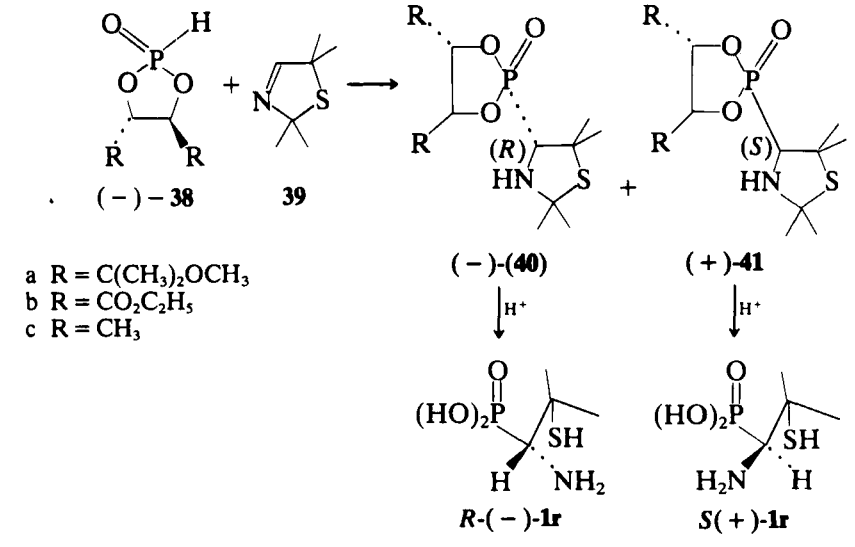



*b. Addition of sodium diethylphosphite to the C=N double bond*[54] *of compound* **35**. Reaction of 1-methylthio-2-phenylethylideneamine hydrochloride **34** with (−)-ω-camphanic acid chloride gave compound **35**. Addition of sodium diethylphosphite to compound **35** yielded the diastereoisomeric mixture **36** which on treatment with Raney Nickel was converted to diastereoisomeric diethyl 1-(camphanyl-amino)-2-phenyl-ethyl-phosphonates **37**. The diastereoisomers **37** were separated by column chromatography and converted into optically active 1-amino-2-phenylethylphosphonic acid **1d** by treatment with HBr. Although no mention is made of the diastereoisomeric excess obtained in the sodium diethylphosphite addition step, it appears from the isolated yields that the diastereoisomer which gives (+)-1-amino-2-phenylethylphosphonic acid **1d** was formed in slight excess.

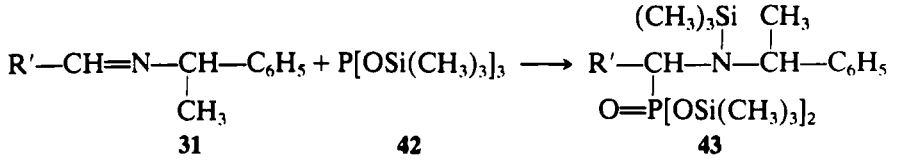
*c. Asymmetric addition of a chiral cyclic phosphite to a cyclic imine.*[55] Addition of a chiral cyclic phosphite (−)-**38** to the carbon-nitrogen double bond of 2,5-dihydro-2,2,5,5-tetramethylthiazole **39** in the presence of boron trifluoride



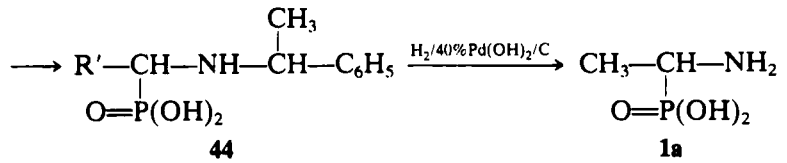
yielded the diastereoisomers (−)-**40** and (+)-**41** in a ratio of 2:1 which were separated chromatographically. The diastereoisomer (−)-**40** that was formed in excess was shown to have the *R*-configuration at C-4 by x-ray structure determination. Hydrolysis of (−)-**40** with conc HCl or 48% HBr gave *R*-(−)-**1r**, the phosphonic acid analog of L-pencillamine. Addition of other chiral phosphites **38b** and **38c** gave diastereoisomers that decomposed during chromatographic separation.



2. *Addition of Tris(trimethylsilyl)phosphite to Aldimine*[53] **31**. Addition of tris(trimethylsilyl)phosphite **42** to the aldimine **31a** in the absence of a catalyst or in a reaction catalyzed by p-toluenesulfonic acid proceeds with about the same amount of asymmetric induction as does the addition of diethylphosphite but chemical yields are better by about 20%. Addition of phosphite **42** to the aldimine **31b** in the presence of zinc chloride followed by methanolysis produced diastereoisomers **44b** in a 2:1 ratio. In the case of **31c** addition of phosphite **42** followed by methanolysis and hydrogenation gave 1-aminoethylphosphonic acid **1a** of 40% optical purity in total yields of 40–50%. Synthesis using *R*-(+)-amine **21** gave *S*-(+)-1-aminoethylphosphonic acid **1a** and *S*-(−)-amine **21** gave *R*-(−)-acid **1a**.



**31** **42** **43**

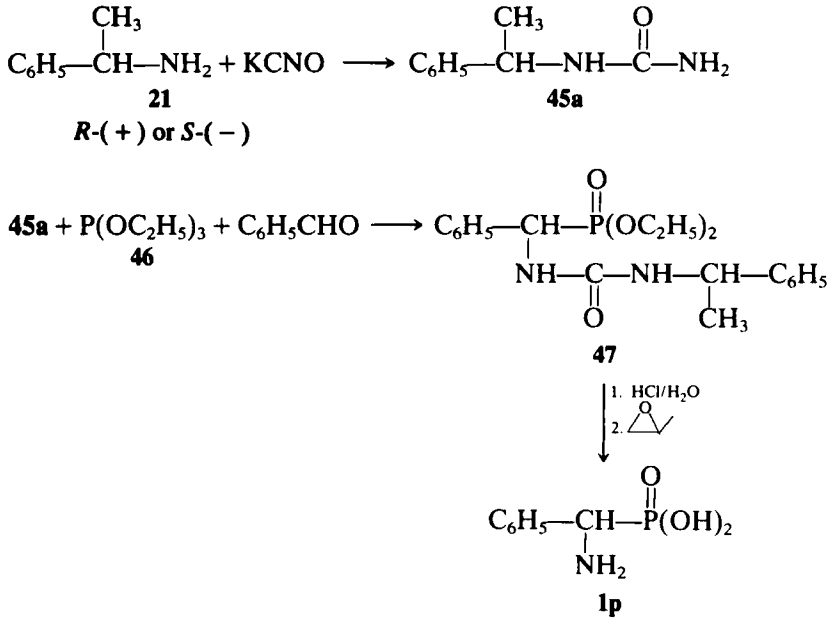


**44** **1a**

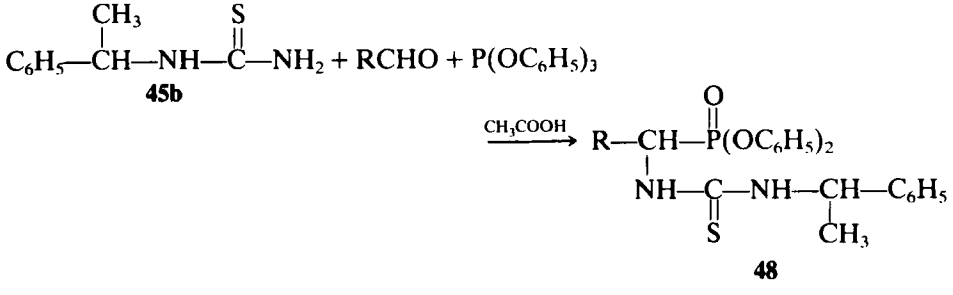
a $R' = C_6H_5$
b $R' = -CH(CH_3)_2$
c $R' = CH_3$

3. *By the Reaction of Optically Active Urea Derived from R-(+)-or S-(−)-1-Phenylethylamine* **21** *with Benzaldehyde and Triethylphosphite.* Monosubstituted ureas react with aldehydes and trivalent phosphorus esters in the presence of an acid to give ureidophosphonates.[56] Huber and Gilmore found that when an optically active urea **45a** derived from *R*-(+) or *S*-(−) amine **21** is reacted with benzaldehyde and triethylphosphite **46**, the hydrolysis of the intermediate diethyl α-[3-(α′-methylbenzyl) ureido] benzyl phosphonate **47** with HCl yields 1-amino-1-phenylmethyl phosphonic acid **1p** of 20% optical purity.[57] Synthesis using *R*-(+)-amine **21** gives dextrorotatory **1p** and synthesis using *S*-(−)-amine **21** gives levorotatory **1p**. It is interesting to note that in both methods using trivalent phosphorus esters (i.e. **42** and **46**), the relationship between the sign of the observed rotation of the product aminophosphonic acid **1** and the starting amine **21** is opposite to that obtained by the dialkylphosphite addition method.

| Method | Starting Amine | Sign of the Observed Rotation of Product Aminophosphonic Acid |
|---|---|---|
| Dialkylphosphite | *R*-(+) | − |
| | *S*-(−) | + |
| Trivalent Phosphorus Esters **42** and **46** | *R*-(+) | + |
| | *S*-(−) | − |

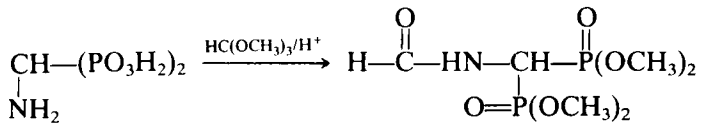


It is important to note that the reaction of optically active N-1-methylbenzylthiourea **45b** with aldehydes and triphenylphosphite in the presence of acetic acid occurs without asymmetric induction[58] and gives a 1:1 mixture of diastereoisomers **48**.

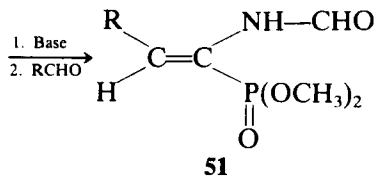


4. *By Catalytic Asymmetric Hydrogenation.*[59] Catalytic hydrogenation of N-[1-(dimethoxyphosphoryl)ethenyl] formamide **51a** with a rhodium catalyst in the presence of (+) DIOP as the chiral ligand followed by hydrolysis of the intermediate N-[1-dimethoxyphosphoryl)ethyl] formamide **52a** gives *R*-(−)-1-aminoethylphosphonic acid **1a** in an enantiomeric excess (e.e) of about 76%. Similarly hydrogenation of E-**51b** gives **52b** with 64% e.e., but an E/Z mixture of **52b** proceeds with only 26% e.e. The formamides **51** are readily available from aminomethylenebisphosphonic acid **49**.

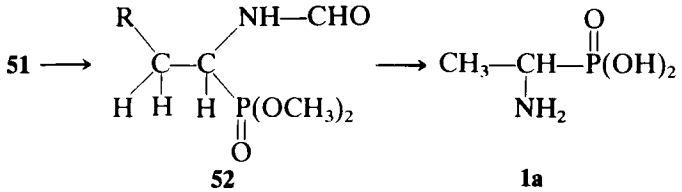
5. *By 1,3-Dipolar Cycloaddition of N-Glycosyl-C-dialkoxyphosphonyl Nitrones* **55** *to Ethylene.*[60] A method involving 1,3-dipolar cycloaddition of N-glycosyl-C-dialkoxyphosphonylnitrones **56** to ethylene as a key step has been developed by Vasella and Voeffray.[60] Addition of dialkylphosphites to the nitrone **54** formed in



49 50



51

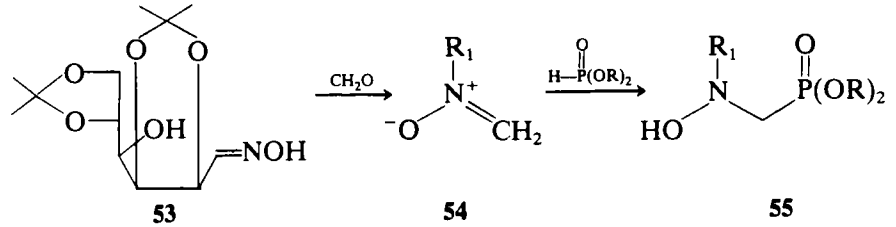


52 1a

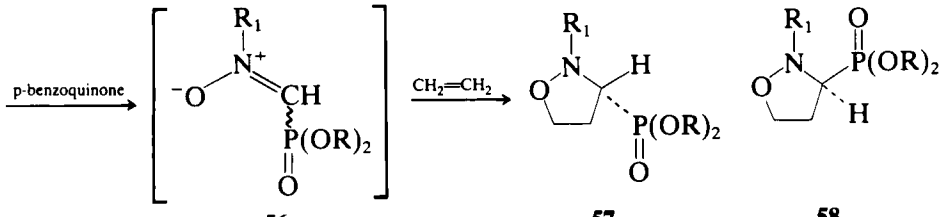
a R = H
b R = $CH_3$

situ from the oxime **53** and formaldehyde gave the hydroxylamines **55**. Oxidation of **55** with p-benzoquinone (to generate **56**) in presence of ethylene gave the cycloaddition products **57** and **58** in a ratio of 3:1.

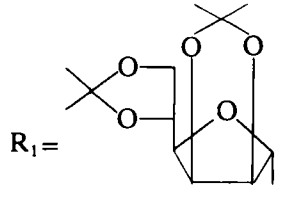
The monoisopropylidene derivatives **59** and **60** obtained by partial deprotection were separated and the major isomers **59** were transformed by standard methods into the phosphonic analogs of L-5-oxaproline **62**, L-homoserine **1m**, L-aspartic acid **1f** and L-asparagine **1g**. From the NMR studies all phosphonic acid analogs **62**, **1m**, **1f**, **1g**, were shown to possess *R*-configuration.



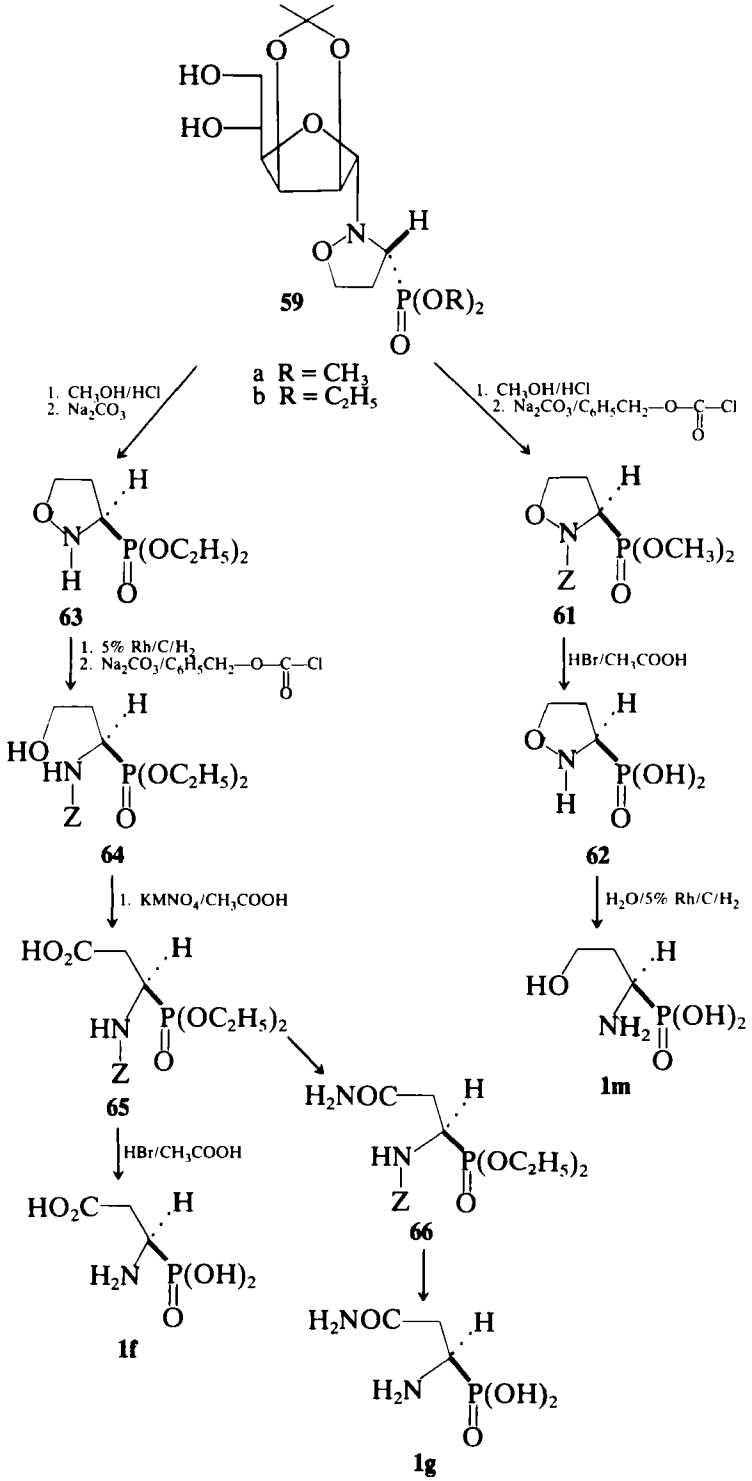
53 54 55



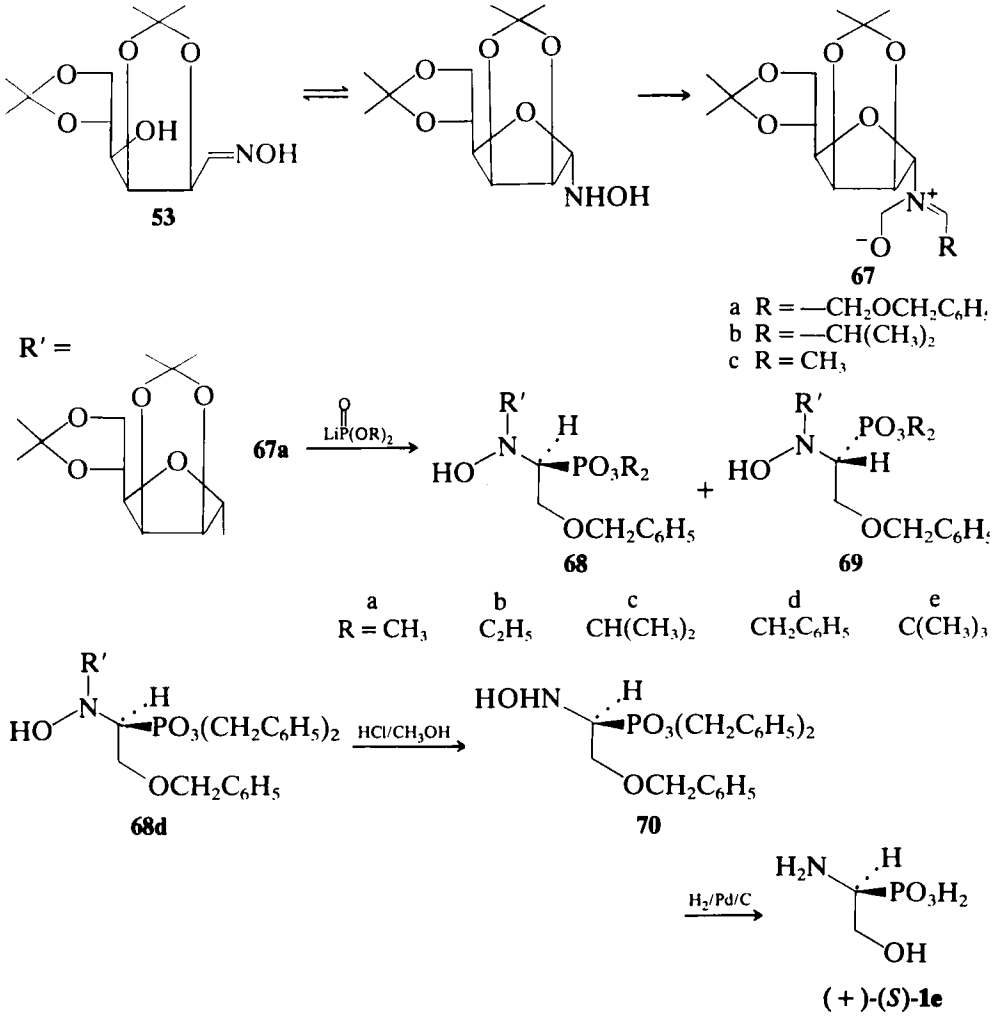
56 57 58

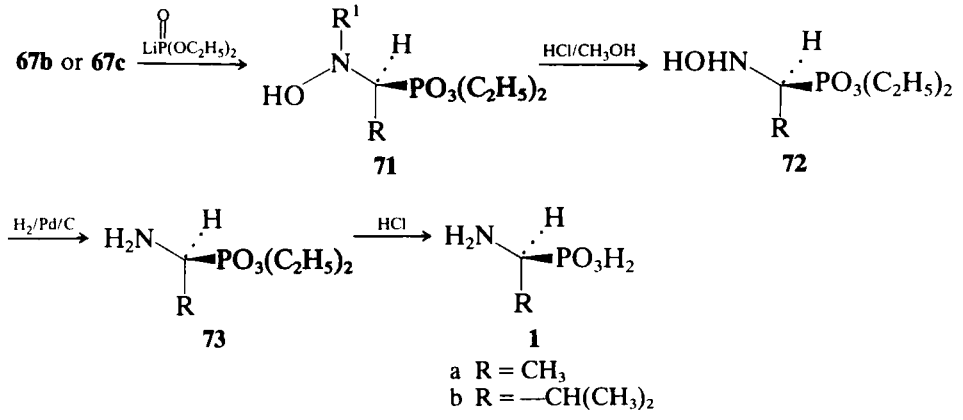


a R = $CH_3$
b R = $C_2H_5$

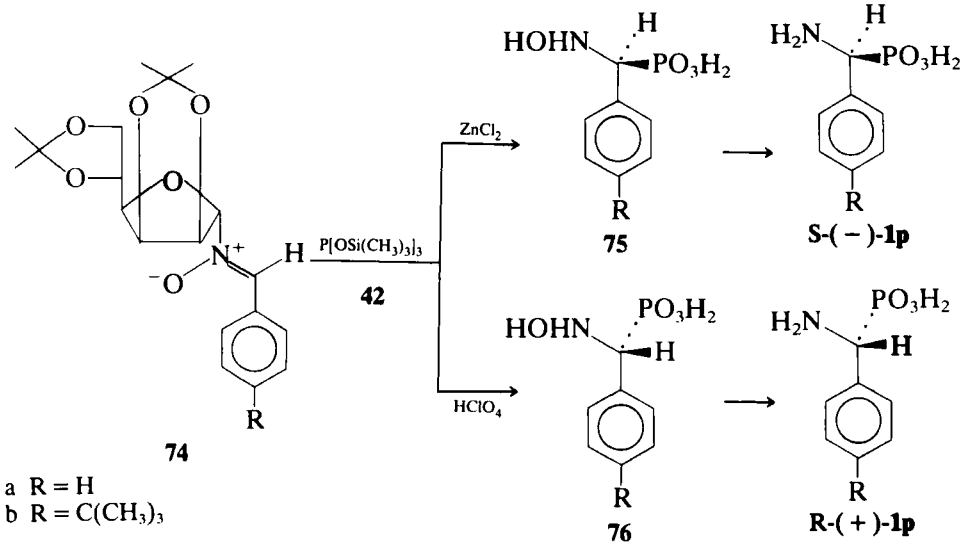


6. *Nucleophilic Addition of Dialkylphosphites to the N-Glycosyl-nitrones.*[61,62] Addition of lithium dialkylphosphites to the crystalline Z-nitrone **67a** in methylene chloride at −60°C gave the N-glycosyl-N-hydroxyaminophosphonates **68** and **69** in high yields and with diastereoisomeric excess 78–92%. The major diastereoisomers **68**, which were easily isolated by crystallization, were converted into *S*-(+)-1-amino-2-hydroxyethylphosphonic acid **1e**. The addition of potassium dialkylphosphites to the nitrone **67a** occurred with much less diastereoselectivity. Similarly the addition of lithium diethylphosphite to the crystalline Z-nitrone **67b** proceeded with a diastereoselectivity of 93%. The major diastereoisomer **71b** was converted into *S*-(+)-1-amino-2-methylpropylphosphonic acid **1b**. (This corresponds to *S*-(−)-disodium 1-amino-2-methyl-propylphosphonate, see Table III). The preparation of *S*-(+)-1-aminoethyl phosphonic acid **1a** by the addition of lithium diethylphosphite to the nitrone **67c** has also been reported. The crude nitrone **67c** was obtained by the reaction of oxime **53** with acetaldehyde.

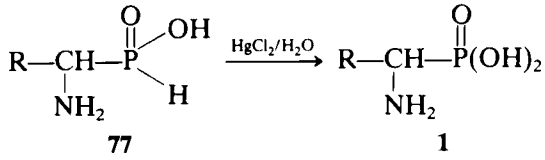





The reaction of lithium diethylphosphite with C-aryl-N-glycosylnitrone **74b** however, gave a complex mixture of products. Reaction of tris(trimethylsilyl)phosphite **42** with nitrone **74a** gave some very interesting results. In presence of catalytic amounts of zinc chloride in refluxing benzene was obtained 84% yield of (−)-**75a** which on hydrogenolysis gave *S*-(−)-**1p** in 61% e.e. However, when the reaction was carried out in the presence of catalytic amounts of $HClO_4$ between −50° and rt, an 83% yield of (+)-**76a** was obtained which on hydrogenolysis gave (+)-**1p** in 94% e.e. Similar results were obtained in the reaction of **74b** with **42** but the reaction of **42** with **67a** under either conditions gave only (+)-(*S*)-**1e**.




7. *By the Oxidation of Optically Active 1-Aminoalkylphosphonous acids*[30] **77.** Oxidation of optically active 1-aminoalkylphosphonous acids **77** with aqueous mercuric chloride at 90–95°C to optically active 1-aminoalkylphosphonic acids **1** has been reported. The known levorotatory phosphonic analogs of alanine **1a**, valine **1b** and leucine **1c** were obtained by this method.




77 1

## III. DETERMINATION OF ABSOLUTE CONFIGURATION

### A. *By X-ray Crystallography*

After an enantiomer of 1-aminoalkylphosphonic acid has been prepared, it is desirable to know its absolute configuration. The best method remains an x-ray crystallographic determination. Absolute configuration of the following enantiomers of 1-aminoalkylphosphonic acids **1** have been determined directly or via derivatives by x-ray crystallographic methods (Table II).

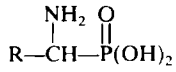
It is not always possible to determine absolute configuration by x-ray crystallographic methods for lack of suitable crystals. In such cases and also for convenience, correlation methods such as comparison of chemical shifts in NMR spectra and chemical transformations to compounds of known configuration are extremely helpful. The following correlation methods have been used for the determination of the absolute configuration of 1-aminoalkylphosphonic acids.



### B. *By NMR Methods*

Vasella and Voeffray[60] used $^{1}H$ and $^{13}C$ NMR spectral data to arrive at the absolute configuration of **78–81**. The $^{1}H$ and $^{13}C$ spectra of **78–81** were compared with those of the corresponding carboxylates **82–85** of known configuration. The chemical shifts of **78** and **80** were very similar to the chemical shifts of **82** and **84** but were distinctly different from the corresponding pairs of compounds epimeric at C(3) (**79–81** and **83**, **85** pairs which between them possess similar spectra). The similarity of the chemical shifts of **78** and **80** with those of **82** and **84** of known

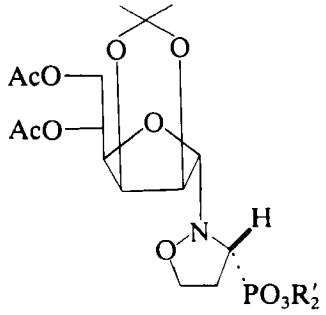
TABLE II



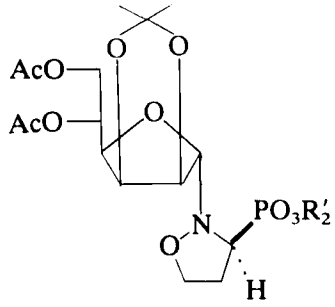

**1**

| Compound | R | Specific Rotation† | Configuration | Reference |
|---|---|---|---|---|
| **1a** | $CH_3$ | +16.8 | *S* | 13 |
| **1b** | $(CH_3)_2CH$ | − 1.0 | *S* | 52, 63 |
| **1d** | $C_6H_5CH_2$ | $[\alpha]_{578}^{20} = +49.9$ | *S* | 38, 64 |
| **1e** | $CH_2OH$ | $[\alpha]_{D}^{25} = +30 (c = 1, H_2O)$ | *S* | 61 |
| **1p** | $C_6H_5$ | +18 | *R* | 52 |
| **1r** | $(CH_3)_2C(SH)$ | −10.8($c = 0.64$) | *R* | 55 |

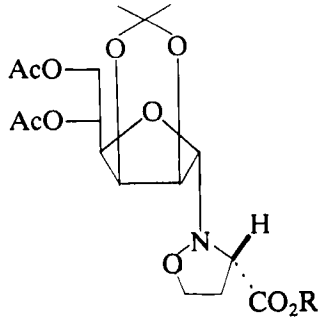
† $[\alpha]_{D}^{20}$, $c = 2$, IN NaOH unless otherwise specified.



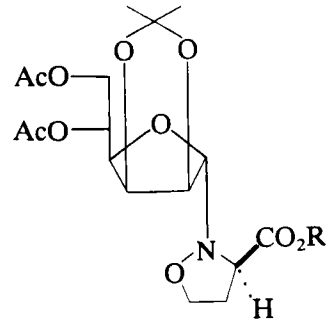
**78** R′ = $CH_3$
**80** R′ = $C_2H_5$



**79** R′ = $CH_3$
**81** R′ = $C_2H_5$



**82** R = t-Bu
**84** R = $C_6H_5$—$CH_2$



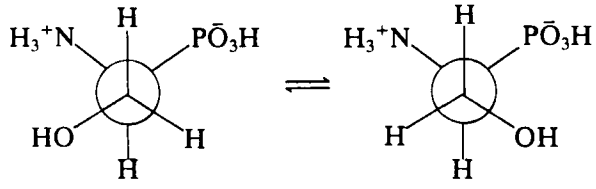
**83** R = t-Bu
**85** R = $C_6H_5$—$CH_2$



L-configuration suggested the same configuration for these phosphonates. This conclusion finds further support in the comparison of the specific rotations.

Since **78** and **80** can be converted to the phosphonic analogs of L-5-oxoproline **62**, homoserine **1m**, aspartic acid **1f** and asparagine **1g** without affecting the appropriate chiral center, all of these must have L-configuration (same as *R*-configuration).

The $^1H$ NMR of (+)-**1e** shows[61] that it exists preferentially in the conformation A.

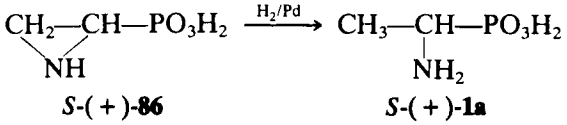


**A** **B**

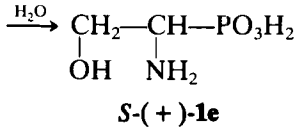
*C. By Chemical Correlation*

In this method the compound whose configuration is to be determined is prepared from or converted to a compound of known absolute configuration. Mastalerz and coworkers[65] have determined the absolute configuration of the phosphonic

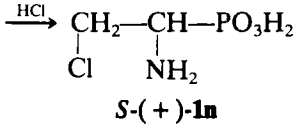
analog of serine by chemical correlation with *S*-(+)-1-aminoethylphosphonic acid **1a**. It is based on the observation that ring opening reactions of 2-aziridine phosphonic acid **86** give exclusively 2-substituted derivatives of 1-aminoethylphosphonic acid[66] and therefore do not affect the chiral atom. (+)-Aziridine phosphonic acid **86** on reduction gives *S*-(+)-1-aminoethylphosphonic acid **1a** and therefore must have the *S*-configuration. Compound (+)-**86** can be converted into the (+) phosphonic analogs of serine **1e** and chloroalanine **1n**, therefore, these have the *S*-configuration.



*S*-(+)-**86** *S*-(+)-**1a**

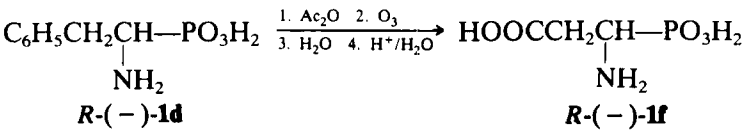


*S*-(+)-**1e**



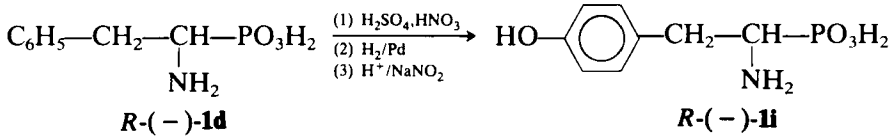
*S*-(+)-**1n**

The configuration of (−)-1-amino-2-phenylethylphosphonic acid **1d** was determined to be *R* by its transformation to *R*-(−)-phosphonic analog of aspartic acid **1f**.



*R*-(−)-**1d** *R*-(−)-**1f**

Further, the laevorotary phosphonic analog of tyrosine **1i** has been shown to have the *R*-configuration by the following sequence of reactions.



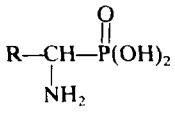
*R*-(−)-**1d** *R*-(−)-**1i**

### *D. By Chromatographic Behaviour*

Coupling of an "N-terminal"-protected L-aminoacid with a racemic dialkyl or diphenyl 1-aminoalkylphosphonate followed by removal of blocking groups yields a mixture of diastereoisomeric peptides **90** and **91**.

TABLE III

Specific rotations of the 1-aminoalkylphosphonic acids



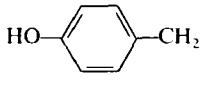
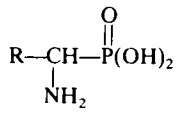
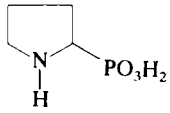
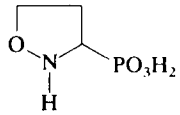
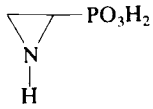
| Compound | R-group | R-configuration $[\alpha]_D$ | R-configuration $[\alpha]_{578}$ | S-Configuration $[\alpha]_D$ | S-Configuration $[\alpha]_{578}$ | Concentration %, Solvent temperature | °C | Reference |
|---|---|---|---|---|---|---|---|---|
| **1a** | $CH_3$ | | −16.0 | | +17.0 | 1,1N NaOH, | 20 | 40 |
| | | | −17.0 | | +17.0 | 1,1N NaOH, | 20 | 45 |
| | | | | | +16.0 | 2,$H_2O$, | 20 | 65 |
| | | −16.9 | | +16.8 | | 2,1N NaOH | 20 | 12, 13 |
| | | +2.8[a] | | −2.9[a] | | 1,1N NaOH, | 20 | 50 |
| | | −16.6 | | | | 2,1N NaOH, | 25 | 30 |
| | | −2.6 | | | | 2,$H_2O$, 25 | 25 | 30 |
| **1b** | $(CH_3)_2CH$ | | | −0.8 | | 2,1N NaOH | 25 | 61 |
| | | | +0.6 | | −0.6 | 5,1 N NaOH | 20 | 40 |
| | | | +0.8 | | −0.8 | 1,1N NaOH | 20 | 45 |
| | | −1.0[b] | | | | 2,$H_2O$, | 24 | 30 |
| | | | | +2.1[b] | | 1.9 $H_2O$ | 25 | 61 |
| **1c** | $(CH_3)_2CH—CH_2$ | | −28.0 | | +27.0 | 1,1NNaOH, | 20 | 45 |
| | | | −24.0 | | +25.0 | 1,1N NaOH, | 20 | 40 |
| | | | −28.0 | | +27.4 | 1,0.25N NaOH | 20 | 23 |
| | | −25.5 | | | | 1,$H_2O$, | 24 | 30 |
| **1d** | $C_6H_5CH_2$- | | −49 | | +52 | 1,1N NaOH, | 20 | 40 |
| | | | −49.9 | | +49.9 | 2,1N NaOH, | 20 | 38 |
| | | −38.9 | | +37.0 | | 2,2N NaOH, | 20 | 54 |
| | | | −38.7 | | +42.9 | 1,0.25N NaOH, | 20 | 23 |
| | | +13.9[a] | | | | 1,1N NaOH, | 24 | 50 |
| | | | | −15.0[a] | | 1.5,1N NaOH, | 24 | 50 |
| | | | −47.0 | | | 2.3,1N NaOH, | 20 | 65 |
| **1e** | $CH_2OH$ | | −30.0 | | +35.0 | 1,1N NaOH, | 20 | 41 |
| | | | | | +27.0 | 2.5, $H_2O$, | 20 | 65 |
| | | | | +30 | | 1, $H_2O$ | 25 | 61 |
| **1f** | $CH_2COOH$ | −32.6 | | | | 1, $H_2O$, | 25 | 60 |
| | | | −35.0 | | | 2.1, $H_2O$, | 20 | 65 |
| **1g** | $CH_2CONH_2$ | −33.0 | | | | 1, $H_2O$, | 25 | 60 |
| **1h** | $CH_2CH_2COOH$ | | −20.0 | | +21.0 | 1,1N NaOH, | 20 | 45 |
| | | | −17.8 | | +17.2 | 5,1N NaOH | 0 | 47 |
| **1i** |  | | −53.0 | | | 1.5,1N HCl, | 20 | 65 |
| **1j** | $C_2H_5$ | | −22.0 | | +21.0 | 1,1N NaOH, | 20 | 45 |
| **1k** | $CH_3CH_2CH_2$ | +8.6 | | −8.3 | | 1,1N NaOH, | 18 | 50 |
| **1l** | $\eta$-$C_4H_9$ | +12.6 | | | | 1.3, 1N NaOH | 22 | 50 |
| | | | | | −12.9 | 2,1N NaOH | 22 | 50 |
| **1m** | $CH_2CH_2OH$ | −6.2 | | | | 1,$H_2O$, | 25 | 60 |
| **1n** | $CH_2Cl$ | | | | +34.0 | 1.6, $H_2O$, | 20 | 65 |
| **1o** | $(CH_2)_3COOH$ | | −12.0 | | +13.0 | | | 45 |
| **1p** | $C_6H_5$ | +18.0 | | −18.0 | | 2,1N NaOH, | 20 | 52 |
| | | +17.8 | | −17.6 | | 2,1N NaOH, | 20 | 50 |

TABLE III (*contd.*)

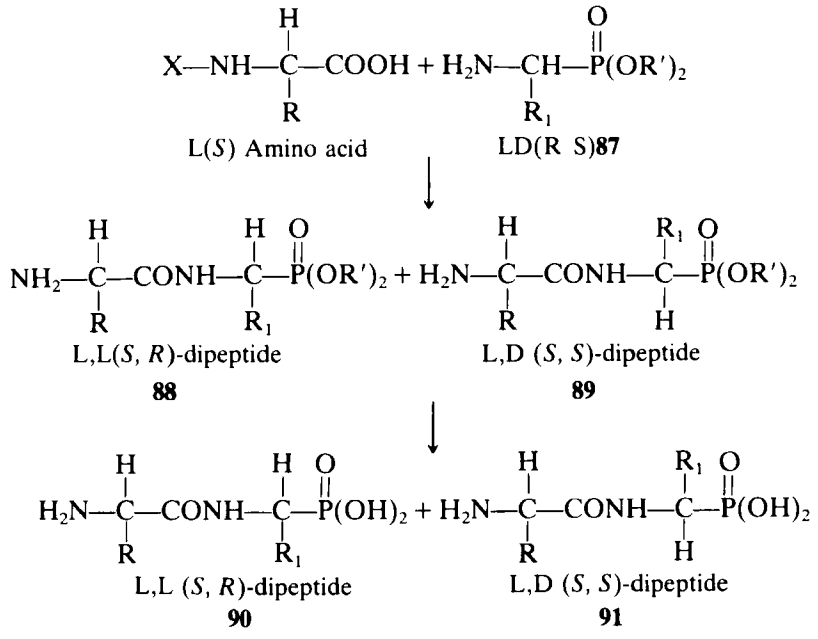


| Compound | *R*-group | *R*-configuration $[\alpha]_D$ | *R*-configuration $[\alpha]_{578}$ | *S*-Configuration $[\alpha]_D$ | *S*-Configuration $[\alpha]_{578}$ | Concentration %, Solvent temperature | °C | Reference |
|---|---|---|---|---|---|---|---|---|
| | | +18.1 | | −18.1 | | 2,1N NaOH, | 25 | 51 |
| | | +19.4 | | −19.4 | | 2,1N NaOH, | 20 | 46 |
| | | | +19.0 | | −20.0 | 1,1N NaOH, | 20 | 40 |
| | | | | −17.90 | | 2,1N NaOH, | 20 | 37 |
| | | +16.0 | | | | 3.5,1N NaOH, | 20 | 48 |
| | | +16.7 | | | | 4,1N NaOH, | 20 | 48 |
| **1q** | $CH_3SCH_2CH_2$ | | −40.4 | | +38.1 | 1,0.25N NaOH, | 20 | 23 |
| **1r** | $C(CH_3)_2SH$ | −10.8 | | | | 0.64,1N NaOH, | 20 | 55 |
| | | | | +10.0 | | 0.72,1N NaOH, | 20 | 55 |
| 3 |  | | *R* $(\alpha)_{578}$ +64.0 | | *S* $(\alpha)_{578}$ −60.0 | 1,1N NaOH, | 20 | 45 |
| 62 |  | | $(\alpha)_D$ +30.8 | | | 1, TFA, | 25 | 60 |
| 76 |  | | | | $(\alpha)_{578}$ +31 | 2.5, $H_2O$, | 20 | 65 |

[a] Seems to be in error.
[b] These values do not agree with each other.

This mixture of diastereoisomeric peptides can be separated into pure diastereoisomers by ion-exchange column chromatography.[42–45] Separation of diastereoisomeric peptides **88** and **89** by silica gel column chromatography has also been reported.[23]

Mastalerz and coworkers[23,44,45] used relative mobilities of the diastereoisomeric peptides **90** and **91** in TLC and on ion exchange columns for the assignments of the configurations of 1-aminoalkylphosphonic acids **1**. It is well established that L, D dipeptides of aminocarboxylic acids migrate faster on paper and in TLC than the corresponding L, L isomers. This relative mobility rule was found to be applicable to phosphonodipeptides **90** and **91**. Thus L, D (*S, S*) phosphonodipeptides **91** were found to migrate faster on TLC and a cation exchange column than the L, L (*S, R*)-isomers **90**. The support for this rule was obtained by the hydrolysis of the resolved diastereoisomeric phosphonopeptides to optically active 1-aminoalkylphosphonic acids **1** of known configuration.




There is one exception to this relative mobility rule. When L-proline is used as the N-terminal amino acid in the phosphonodipeptides, a reversal of relative mobilities occurs. Such an exception is also known for classical dipeptides, where the presence of N-terminal L-proline in a dipeptide causes faster migration of L, L than L, D-isomers.

Ion exchange separation of diastereoisomeric peptides followed by hydrolysis of resolved diastereoisomers has been used for the preparation of enantiomers of phosphonic analogs of glutamic acid (GluP) **1h**, 2-amino adipic acid (adiP) **1o** and proline (pro P) **3**. Enantiomers of 1-aminopropylphosphonic acid **1j** have also been prepared by this method. The configurations of these optically active phosphonic acids were assigned on the basis of the relative mobilities of their peptides.

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