Russian Chemical Reviews **75** (3) 227 – 253 (2006) © 2006 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2006v075n03ABEH001193

Chiral hydroxy phosphonates: synthesis, configuration and biological properties

O I Kolodiazhnyi

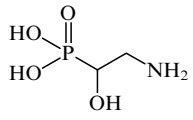
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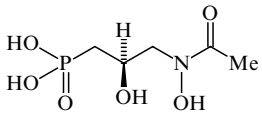
Abstract. Published data on the synthesis, absolute configurations and biological properties of chiral hydroxy phosphonates are generalised and described systematically. Examples of asymmetric synthesis of hydroxy phosphonates by the phospho-aldol reaction, reduction of keto phosphonates, chemo-enzymatic approach, and so on are discussed. Methods for determination of the optical purity and absolute configuration of hydroxy phosphonates using modification by chiral reagents, NMR, circular dichroism, GLC and HPLC on columns with chiral sorbents are considered. The significance of hydroxy phosphonates as promising compounds for the development of new drugs and bioregulators is demonstrated. The bibliography includes 263 references.

I. Introduction

Hydroxy phosphonic acids form an important class of compounds, some of which are encountered in nature. Organophosphorus compounds of natural origin with a C–P bond were unknown before 1959,[1–3] when Horiguchi and Kandatsu[3] first discovered them in living organisms. Soon after this, substantial amounts of amino and hydroxy phosphonates have been isolated from natural sources. The best known natural hydroxy phosphonic acids include 1-hydroxy-2-aminoethylphosphonic acid (HO-AEP), 3-(*N*-acetyl-*N*-hydroxyamino)-2-hydroxypropylphosphonic acid (FR-33289), 1,5-dihydroxy-2-oxopyrrolidin-3-ylphosphonic acid (SF-2312), phosphonothrixin, *etc.*[1,2] Many of these compounds attract attention due to their interesting biological properties as antibacterial, antiviral and antitumour agents, antibiotics, enzyme inhibitors, amino acid mimetics and pesticides.[4–8]



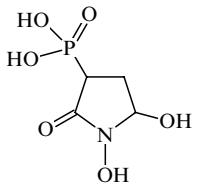
HO-AEP



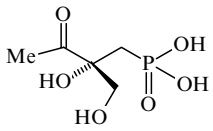
FR-33289

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Received 25 February 2005
Uspekhi Khimii **75** (3) 254 – 282 (2006); translated by Z P Bobkova



SF-2312



phosphonothrixin

The physiological activity of hydroxy phosphonates is due, on the one hand, to their structural similarity to biologically important phosphates with the P–O bond being replaced by P–C and, on the other hand, to the structural analogy between α-hydroxyalkylphosphonic and α-hydroxy carboxylic acids. The replacement of the carboxy group in hydroxy carboxylic acids by a phosphonate group results in hydroxy phosphonic acids exhibiting an inhibitory effect with respect to enzymes and receptors to which natural hydroxy carboxylic acids usually bind. The biological activities of phosphonic acids are largely determined by the absolute configuration of the stereogenic α-carbon atom. For example, of the four possible diastereomers of the antibiotic alaphospholine, the *S*,*R*-diastereomer exhibits the highest activity with respect to the pathogenic microorganisms.[9]

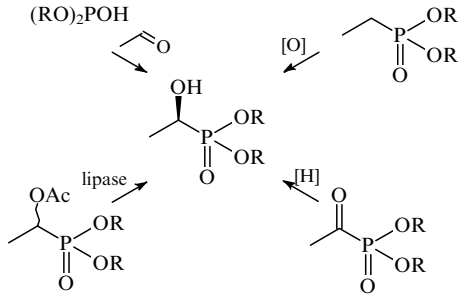
At present, hydroxy phosphonates with various structures containing one or several hydroxy groups in the organic radical have been synthesised and studied in detail; these include derivatives of carbohydrates, purine bases, nucleotides, and so on. The most studied compounds are α- and β-hydroxy phosphonates, β-amino α-hydroxy phosphonates, polyhydroxy phosphonates and fluorine-containing hydroxy phosphonates, which are isosteric analogues of natural compounds exhibiting high biological activity.

The vast factual material accumulated to date on the synthesis, properties and practical application of hydroxy phosphonates still requires systematisation, some contradictory data calling for critical consideration. This stimulated us to write a review paper in which we generalise for the first time the published data on the methods of preparation and properties of chiral hydroxy phosphonates, as well as their applications as biologically active substances or pharmaceutical agents. Hopefully, information surveyed in this review will be useful for chemists engaged in various aspects of organic chemistry and stereochemistry.

II. Asymmetric synthesis of hydroxy phosphonates

The vigorous development of the chemistry and biology of hydroxy phosphonates in the last decade is due to the develop-

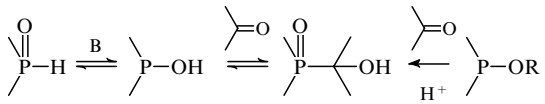
ment of highly efficient methods for their preparation.[10,11] Chiral hydroxy phosphonic acids can be prepared by a number of methods including kinetic resolution of racemic mixtures or enzymatic and asymmetric synthesis. The most important approach to the synthesis of hydroxy phosphonates is phosphorylation of carbonyl compounds leading to formation of a C–P bond (phosphonylation). Two methods for asymmetric phosphonylation of carbonyl compounds are known: phospho-aldol addition and the reaction of phosphonate carbanions with aldehydes or ketones. The phospho-aldol condensation (the Abramov reaction) occupies a leading position in this series, being a highly convenient method for the synthesis of chiral α-hydroxyalkylphosphonates.[12,13]



In recent years, the chemo-enzymatic method for the synthesis of optically active hydroxy phosphonates has been used more and more often.[14] Other routes to these compounds are the enantioselective reduction of keto phosphonates,[15] enantioselective hydroxylation of phosphonate-stabilised carbanions [16] and [2,3]-sigmatropic Wittig rearrangements.[17]

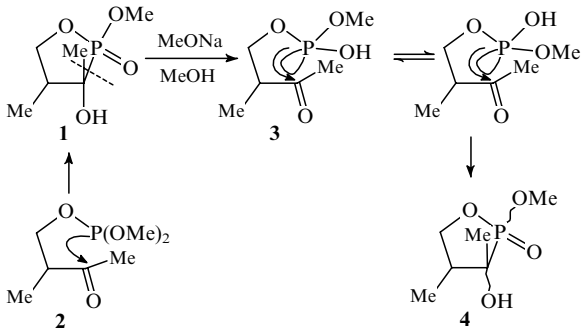
1. Phospho-aldol condensation (the Abramov reaction)

Two types of phospho-aldol condensation are known, namely, the reaction of dialkyl phosphites with carbonyl reagents in the presence of a basic catalyst, which shifts the tautometic equilibrium of dialkyl phosphites towards the P(III)-form, and the reaction of phosphorous triesters with carbonyl compounds in the presence of a proton-donor reagent (phenol, carboxylic acid, tertiary amine hydrochloride, aniline, and so on) or a Lewis acid. Phosphorous triesters react with carbonyl compounds in two steps: first, the reversible addition of a carbonyl reagent to the trivalent phosphorus atom gives a carbon–phosphorus bond and then the ester group at the phosphorus atom is hydrolysed to give α-hydroxy phosphonate.[12,18–20]

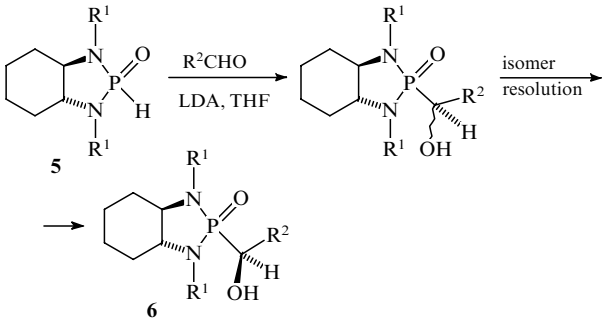


B is base.

In the presence of tertiary amines and some other bases, hydroxyalkylphosphonates decompose into the initial dialkyl phosphite and carbonyl components. This transformation is called the retro-Abramov reaction. Nuclear magnetic resonance [21,22] and kinetic studies [19,20] have shown that the retro-Abramov reaction has a substantial influence on the stereochemistry of the resulting hydroxy phosphonates. For example, the stereochemistry of the sodium methoxide-catalysed decomposition of the diastereomers of 3-hydroxy-2-methoxy-3,4-dimethyl-1,2-oxaphospholan-2-one (**1**) obtained by cyclisation of phosphite **2**, has been studied.[23] Under the action of sodium methoxide in methanol, diastereomerically pure hydroxy phosphonates **1** underwent racemisation. Presumably, the reaction mechanism includes cleavage of the P–C bond (retro-Abramov reaction) and epimerisation of the chiral P-anion **3**, which bring about the formation of a mixture of diastereomers **4** upon the subsequent cyclisation. One more possible reason for racemisation is cleavage of the endocyclic P–O bond in compound **1**.



Chiral phosphonites and phosphinites, having a stereogenic phosphorus atom, and phosphites that contain residues of optically active alcohols, amino alcohols or amines at the phosphorus atom can serve as asymmetric inductors in the Abramov reaction. Phosphites based on chiral 1,2-diaminocyclohexane, ephedrine, binol, menthol, *etc*., are used most often. The addition of chiral dialkyl phosphites and their anions to achiral aldehydes gives rise to α-hydroxy phosphonates with a moderate stereoselectivity.[24–40] For example, the reaction of bicyclic chiral phosphorous diamides **5** with aldehydes yields α-hydroxyalkylphosphonamides **6** in good yields. The presence of bulky substituents in phosphoramidite and aldehyde molecules increases the reaction stereoselectivity.[24–29]

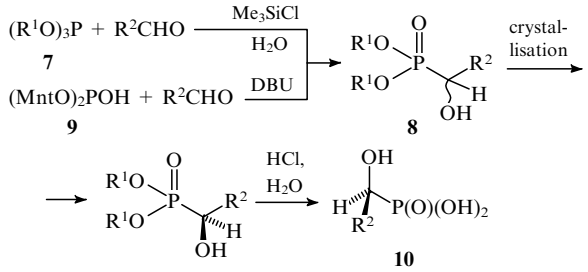


LDA = $LiNPr^i_2$.

R^1	R^2	*dr*	Ref.
2-$MeC_6H_4CH_2$	PhCH=CH	1:1	24
Bn	CH_2=CH	1.4:1	24
1-$NaphCH_2$	PhCH=CH	1.5:1	24
(*S*)-PhMeCH	Ph	1.8:1	29
Bn	PhCH=CH	4.0:1	24
Bu^tCH_2	PhCH=CH	7.9:1	24
Bu^tCH_2	Ph	25:1	24

dr is the diastereomer ratio.

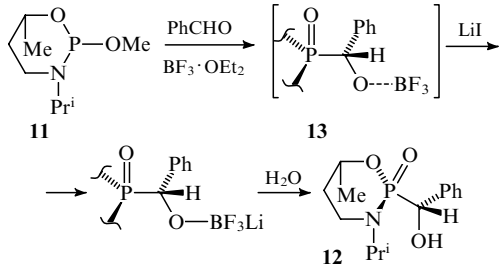
The nature of the chiral alkoxy groups at the phosphorus atom has a pronounced effect on the stereoselectivity of the phospho-aldol condensation. For instance, the reaction of tris(glucofuranosyl) phosphite **7** with benzaldehyde in the presence of chlorotrimethylsilane proceeds with good stereoselectivity to give hydroxy phosphonate **8** mainly as a single isomer with a diastereomeric excess (*de*) of 84%. Meanwhile, trimethyl and tribornyl phosphites react with aldehydes with low stereoselectivity, giving rise to mixtures of hydroxy phosphonate diastereomers **8**.[30,31] The reaction of dimenthyl phosphite (**9**) with aromatic and aliphatic aldehydes in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as the catalyst has a moderate stereoselectivity. The diastereomers **8** were separated and, after hydrolysis of ester groups, acids **10** were formed with enantiomeric purity (*ee*) 96%–98%.[30–33]



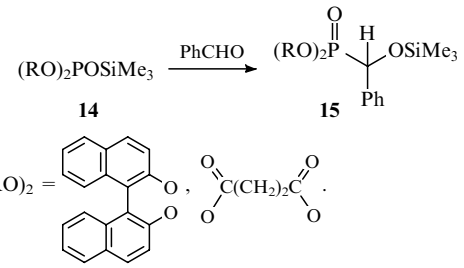
R^1	R^2	*de* (%)	Ref.
GF	Ph	84	31
Mnt	Pr^i	60	31
Mnt	4-$Me_2NC_6H_4$	40	31
Mnt	4-$MeOC_6H_4$	35	30
Mnt	Ph	33	31
Brn	Ph	33	30

GF is (−)-1,2:5,6-di-*O*-isopropylidene-D-glucofuranos-3-yl, Mnt is (1*S*,2*R*,5*S*)-menthyl, Brn is *endo*-bornyl.

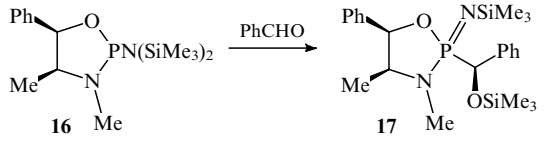
Gordon and Evans have established[34] that the reaction of 2-methoxy-1,3,2-oxazaphosphinane **11** with benzaldehyde in the presence of boron trifluoride etherate affords 2-(α-hydroxybenzyl)-2-oxo-1,3,2-oxazaphosphinane diastereomers **12** in 1 : 2 – 1 : 4 ratio. It was suggested that the reaction proceeds *via* a highly reactive complex of boron trifluoride etherate with benzaldehyde, which reacts with the phosphite to give complex **13**. The reaction stereoselectivity is determined first of all by the step affording complex **13**, which is converted into hydroxyalkylphosphonate **12** after treatment with lithium iodide and hydrolysis.



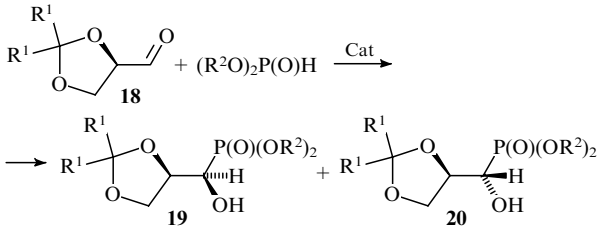
The phospho-aldol reaction of chiral silyl phosphites **14** with benzaldehyde at room temperature gives silyloxy phosphonates **15** with relatively low stereoselectivity.[35]



The addition of chiral diazaphospholidines, which are ephedrine derivatives, to carbonyl compounds also proceeds with moderate stereoselectivity.[36–39] An exception is the modified Mukayama reaction of silylated λ^3-diazaphospholidines **16** with aldehydes, which furnishes only one diastereomer, the adduct **17** (*ee* > 98%).[36] Compound **17** is easily converted into α-hydroxy phosphonate, which possesses a pharmacological activity.[37,38]

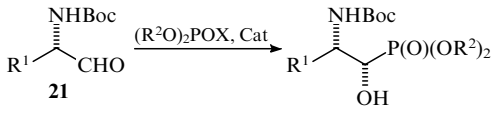


The stereoselectivity of condensation of achiral phosphites with chiral aldehydes is low. For example, the reaction of dialkyl phosphites with 2,3-*O*-protected D-glyceraldehyde **18** in the presence of catalysts such as triethylamine or lithium or cesium fluoride yields mixtures of hydroxy phosphonate diastereomers **19** and **20** in 45 : 55 – 35 : 65 ratio. The use of lithium diethyl phosphite somewhat increases the reaction stereoselectivity.[41] Enantiomerically pure isopropylidene- and cyclohexylidene-protected 1,2,3-trihydroxypropylphosphonates (1*R*,2*R*)-**19** and (1*S*,2*R*)-**20** can be isolated from the diastereomer mixture by column chromatography.[42–44]



R^1_2 = Me_2, $(CH_2)_5$; R^2 = Et, Pr^i; Cat = DBU, Et_3N, CsF, LDA.

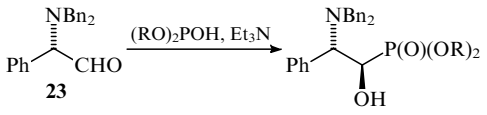
Phosphonylation of chiral α-amino aldehydes is the most convenient and versatile method for the preparation of optically pure stereomeric α-hydroxy-β-aminoalkylphosphonic acids.[45–55] The reaction stereochemistry depends crucially on the number of substituents at the nitrogen atom. For example, the addition of dialkyl phosphites to *N*-*tert*-butoxycarbonyl-(*S*)-phenylglycinal (**21**, R^1 = Ph) yields (1*S*,2*S*)-2-amino 1-hydroxy phosphonate **22**,[48] the phosphonate analogue of the side chain of a natural antitumour agent, paclitaxel. The phosphonylation of *N*-benzoyl-(*S*)-phenylglycinal occurs in a similar way. Meanwhile, the reaction of dialkyl phosphites with *N*,*N*-dibenzylphenylglycinal (**23**) gives mainly (1*R*,2*S*)-diastereomer **24**.[49]



(1*S*,2*S*)-**22**

Boc = $Bu^tOC(O)$.

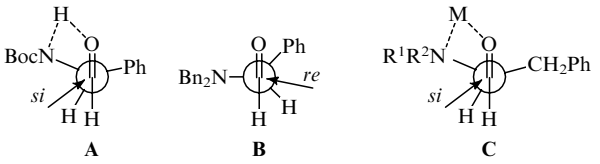
R^1	R^2	X	Cat	*dr*	Ref.
Ph	Me	Li	–	74 : 26	48
Bn	Et	$SiMe_3$	$TiCl_4$	60 : 40	47, 50
Ph	Me	$SiMe_3$	–	83 : 17	48
Bn	Et	$SiMe_2Bu^t$	$TiCl_4$	98 : 2	47
Bn	Et	$SiMe_3$	$SnCl_4$	74 : 26	50
$Bu^tOC_6H_4CH_2$	Et	H	KF	80 : 20	50
Bu^i	Et	H	KF	81 : 19	50



(1*R*,2*S*)-**24** (*de* 50%)

R = Me, Et.

The different stereochemistry of the reaction is due to the fact that in the molecule of (*S*)-*N*-Boc-derivative **21**, the intramolecular hydrogen bond stabilises conformation **A**; therefore, the *si*-stereofacial attack of the dialkyl phosphite on the carbonyl group gives rise to the *S*-adduct. In the case of (*S*)-*N*,*N*-dibenzyl derivative **23**, no intramolecular hydrogen bond is formed; therefore, phosphite attacks preferably the *re*-side of the carbonyl group (model **B**).

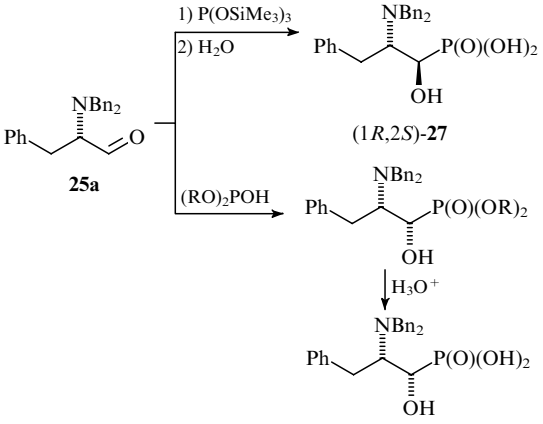


A **B** **C**

M = Ti, Sn.

The stereoselectivity of the reaction of phosphites with aldehydes depends on not only the structure of the initial reactants but also the catalyst.[47–52] For example, titanium and tin tetrachlorides efficiently catalyse the reaction of silyl phosphites with chiral (*S*)-aldehydes **21** and **23** and promote the formation of (1*S*,2*S*)-diastereomers. In this case, the *si*-stereofacial attack is governed by the formation of chelate **C**.[47, 50]

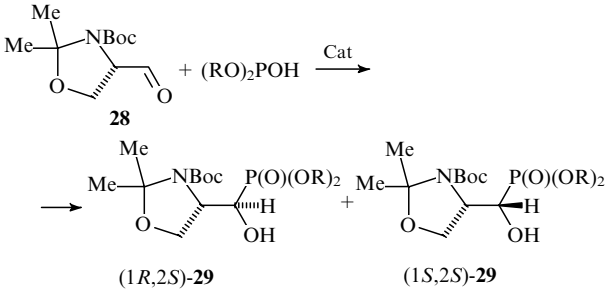
The reaction of chiral aldehyde **25a** with dimenthyl and dibornyl phosphite followed by hydrolysis affords optically pure 2-amino-1-hydroxyalkylphosphonic acid (1*S*,2*S*)-**26**, whereas the addition of the same aldehyde to tris(trimethylsilyl) phosphite results in (1*R*,2*S*)-diastereomer **27**, which was isolated in the crystalline state.[55]



25a (1*R*,2*S*)-**27** (1*S*,2*S*)-**26**

R = Brn, Mnt.

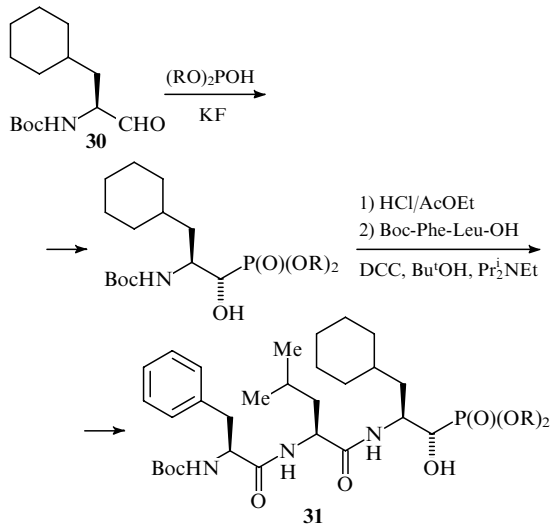
The condensation of dialkyl phosphites with the Garner aldehyde **28** in the presence of triethylamine results in the formation of (1*R*,2*S*)-diastereomers of hydroxy phosphonates **29** (*de* 80%), which were purified by column chromatography. The reaction with titanium(IV) isopropoxide as the catalyst gives a mixture of (1*R*,2*S*)- and (1*S*,2*S*)-diastereomers **29** in ~1 : 1 ratio; pure (1*S*,2*S*)-diastereomer **29** was isolated by column chromatography on silica gel.[53]



28 (1*R*,2*S*)-**29** (1*S*,2*S*)-**29**

R = Me, Et; Cat = Et_3N, $Ti(OPr^i)_4$.

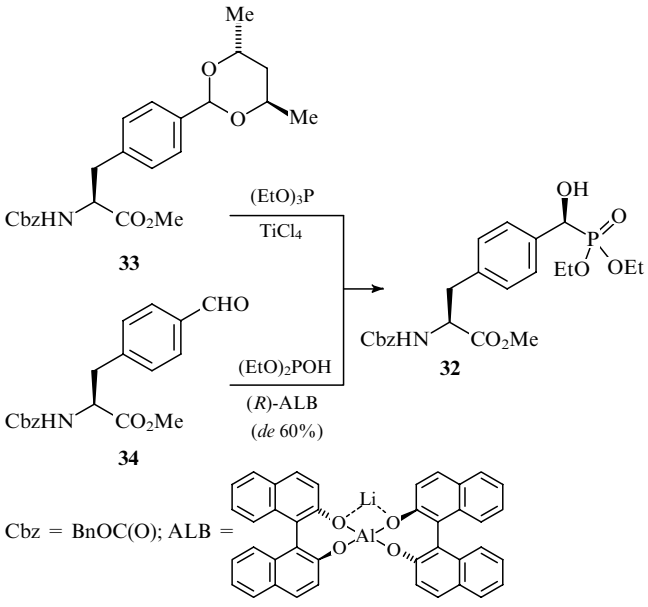
Patel *et al.*[8] used the reaction of dialkyl phosphites with chiral aldehyde **30** for the preparation of enantiomerically pure phosphonate analogues of tripeptides, α-hydroxy phosphonates **31**, which are highly efficient renin inhibitors.



30 **31**

R = Me, Et; DCC = cyclo-$C_6H_{11}-N=C=N-C_6H_{11}$-cyclo.

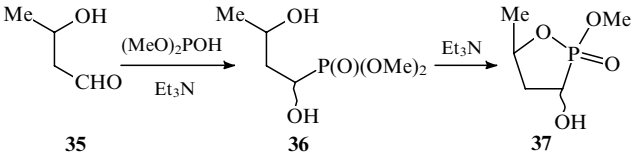
Shibuya and co-workers[54] developed stereocontrolled methods for the synthesis of the hydroxy phosphonate analogue of tyrosine **32** based on the reaction of chiral pentane-2,4-diol acetal of protected 4-formyl-L-phenylalanine **33** with triethyl phosphite in the presence of titanium tetrachloride and by the reaction of diethyl phosphite with methyl ester of *N*-benzyloxycarbonyl-4-formyl-L-phenylalanine (**34**) in the presence of a chiral heterobimetallic catalyst ALB.



33 **34** **32**

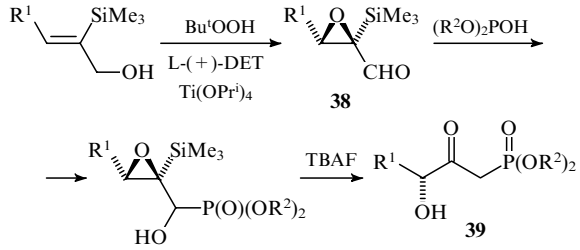
Cbz = BnOC(O); ALB =

The addition of dimethyl phosphite to 3-hydroxybutanal (**35**) results in a diastereomer mixture of 1,3-dihydroxybutylphosphonates **36** in 3 : 7 ratio. The absolute configurations of the C(1) and C(3) atoms in these diols were determined by ^{13}C NMR spectroscopy of their *O*-benzylidene derivatives. The intramolecular cyclisation of phosphonates **36** in the presence of triethylamine gives a mixture of 3-hydroxy-2-methoxy-5-methyl-1,2-oxaphospholan-2-one diastereomers (**37**).[56]



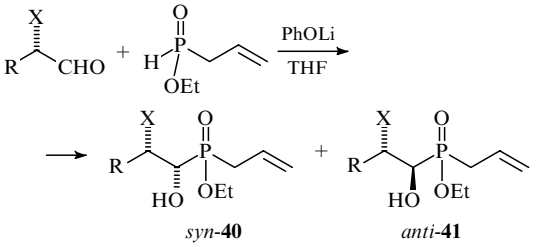
35 **36** **37**

Chiral epoxy aldehydes **38** obtained by asymmetric Sharpless epoxidation of 2-trimethylsilylalk-2-enols reacted with dialkyl phosphites, yielding γ-hydroxy-β-oxo phosphonates **39** with *ee* 96% – 97%.[57]



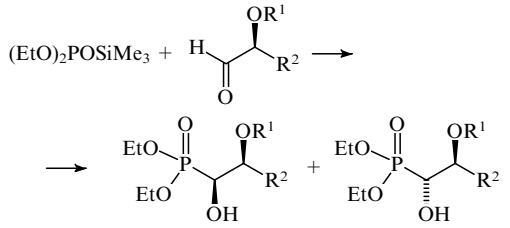
R^1 = n-C_4H_9, n-$C_{10}H_{21}$; R^2 = Me, Ph;
DET is diethyl tartrate; TBAF = $Bu_4N^+F^-$.

β-Substituted α-hydroxy phosphinates **40** and **41** are prepared by lithium phenoxide-catalysed reaction of protected α-hydroxy and α-amino aldehydes with ethyl allylphosphinate.[58]



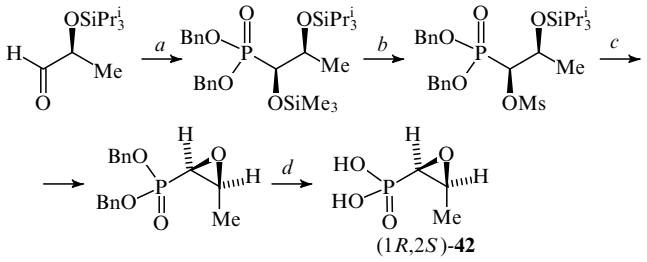
R = Me, Bu^t, Ph, Bn; X = $OSiMe_2Bu^t$, NBn_2.

The phosphonylation of α-silyloxy aldehydes with silyl phosphites was accomplished by Bongini *et al.*[59,60] The reaction stereoselectivity increases with an increase in the bulk of the trialkylsilyl substituents in the phosphite and aldehyde molecules (*dr* 33 : 67 – 92 : 8).



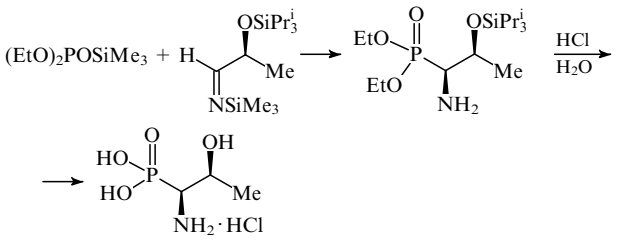
R^1 = $SiEt_3$, $SiPr^i_3$, $SiMe_2Bu^t$; R^2 = Me, Pr^i, n-C_5H_{11}, Ph.

This reaction was used to develop a method for the synthesis of phosphomycin **42**, which is an efficient antibiotic of the natural origin. Phosphomycin **42** was obtained by stereoselective addition of dibenzyl trimethylsilyl phosphite to *O*-triisopropylsilyl-(*S*)-lactaldehyde.[61]



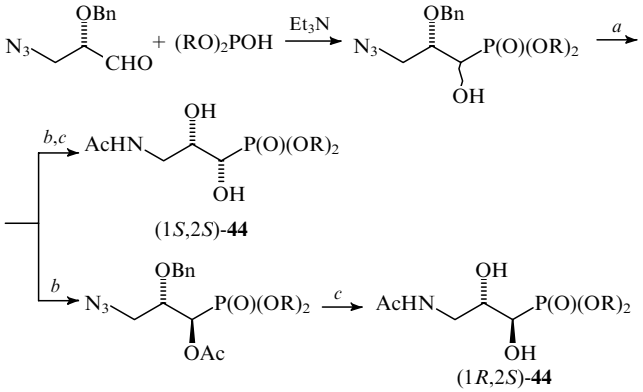
(*a*) $(BnO)_2POSiMe_3$; (*b*) $MeSO_2Cl$ (MsCl), Et_3N, CH_2Cl_2;
(*c*) TBAF, SiO_2, THF, 20 °C; (*d*) H_2, Pd/C;

(1*S*,2*S*)-Phosphothreonine (**43**) with a high diastereomeric purity was prepared in a similar way by the reaction of diethyl trimethylsilyl phosphite with silylated *N*-trimethylsilylimino-(*S*)-lactaldehyde.[62] The other phosphothreonine stereoisomers were prepared by the addition of diethyl trimethylsilyl phosphite to lactaldehyde followed by the Mitsunobu inversion of the corresponding α-hydroxy β-silyloxy phosphonate.[63]



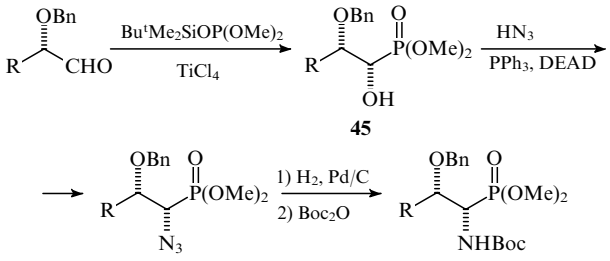
43 (*de* 96%)

Diastereomerically pure (1*R*,2*S*)- and (1*S*,2*S*)-3-amino-1,2-dihydroxypropylphosphonates **44** are prepared by a multistep synthesis, which includes the reaction of (*S*)-3-azido-2-benzyloxypropanal with dialkyl phosphites, chromatographic separation of the stereoisomers on a column with silica gel and debenzylation with hydrogen in the presence of HPd/C.[64]



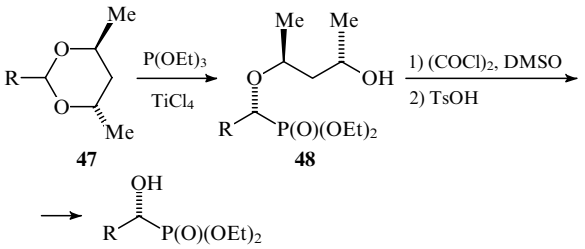
R = Me, Et;
(*a*) chromatography on SiO_2; (*b*) Ac_2O, Et_3N, DMAP; (*c*) H_2, Pd/C;
DMAP =

The stereoselective hydrophosphonylation of α-benzyloxy aldehydes catalysed by titanium tetrachloride is used in the synthesis of the phosphonic analogues of amino hydroxy acids. Shibuya and co-workers[65,66] used the phospho-aldol reaction to prepare β-benzyloxy α-hydroxy phosphonates **45**; their reactions with hydrazoic acid followed by reduction and protection gave substituted α-amino β-hydroxy phosphonates **46**.



R = Pr^i, Ph;
DEAD = $EtO_2CN{=}NCO_2Et$.

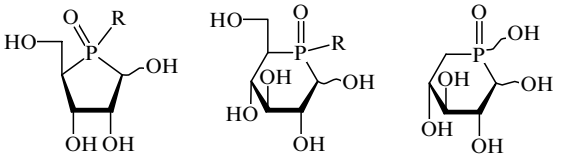
The reaction of triethyl phosphite with homochiral (2*S*,4*S*)-pentanediol acetals **47** in the presence of titanium tetrachloride results in diastereoselective formation of alcohols **48** (*dr* = 93 : 7). The Swern oxidation followed by treatment with *p*-toluenesulfonic acid yields hydroxy phosphonates (*ee* 95%).[67] Yamamoto and co-workers[68] used this strategy to prepare chiral (2*R*)-1-amino-1-deoxy-1-phosphinylglycerols.



47 48

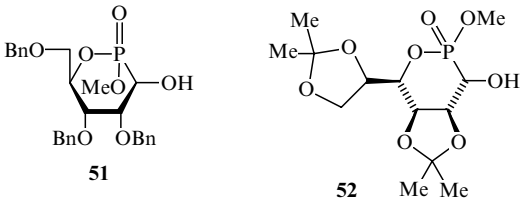
R = Pr^i, Bu^n, Bu^t; Ts = 4-MeC$_6$H$_4$SO$_2$.

The Abramov reaction was used to prepare phosphorus-containing D-ribofuranose (compounds **49**) and D-glucopyranose (**50a**) analogues and 5-deoxy-5-*C*-phosphinyl-D-xylose (**50b**). These compounds were converted into pseudo-carbohydrate nucleoside derivatives that may possess biological activity.[69–71]



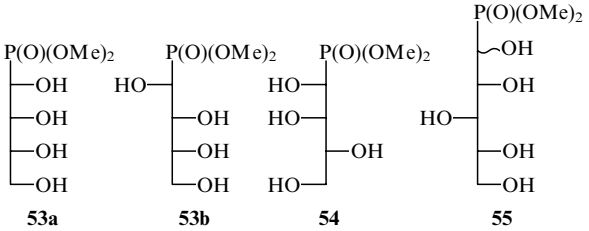
49 50a 50b

The Abramov reaction is also utilised to prepare stereochemically pure δ-phostones **51** and **52**[72] the structures of which were proved by X-ray diffraction analysis.[73]



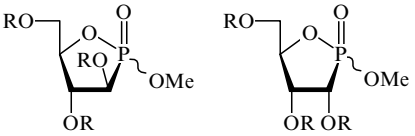
51 52

Polyhydroxyalkylphosphonates **53a**,**b** and **54** were synthesised[74] by the phospho-aldol reaction of dimethyl phosphite with 2,4-*O*-benzylidene derivatives of D-erythrose and D-threose, while the addition of dimethyl phosphite to 2,3:4,5-di-*O*-isopropylidene-D-xylose afforded polyhydroxyalkylphosphonate **55** as a diastereomer mixture.[75]



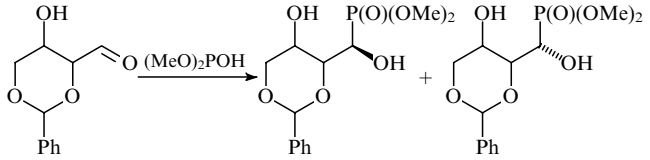
53a 53b 54 55

Wróblewski[76–79] synthesised analogues of D-tetrulose, D-ribose and some other carbohydrates containing phosphorus in the anomeric position. The addition of ethyl trimethylsilyl phosphite to 1,3-di-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-D-tetrulose results in the formation of hydroxy phosphonate diastereomers. The acid-catalysed cyclisation of (1*S*)- and (1*R*)-1-*C*-(dimethoxyphosphoryl)-D-erythritols produces methyl D-arabino- and D-ribofuranoside analogues containing phosphorus in the anomeric position.[77–79]



R = Me, Ph.

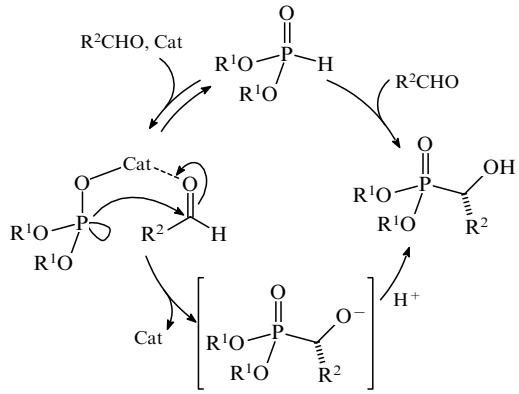
A mixture of (1*S*)- and (1*R*)-2,4-*O*-benzylidene-1-(dimethoxyphosphoryl)-D-threitol diastereomers in 1 : 9 ratio was obtained by the addition of dimethyl phosphite to 2,4-*O*-benzylidene-D-threose in the presence of triethylamine.[79]



Similarly, (1*S*)- and (1*R*)-diastereomeric 2,4-*O*-benzylidene-1-(dimethoxyphosphoryl)-D-erythritols were prepared in 1 : 1 ratio starting from 2,4-*O*-benzylidene-D-erythrose.

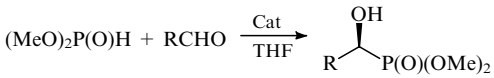
In recent years, asymmetric catalysis of the phospho-aldol condensation gained strong impetus. Scheme 1 shows the tentative reaction mechanism involving an asymmetric catalyst.[80]

Scheme 1

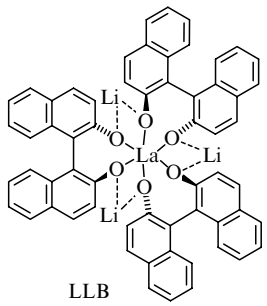


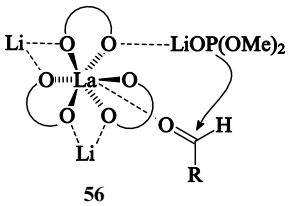
R^1 = Alk, R^2 = Alk, Ar, *etc.*

Several types of asymmetric catalysts have been proposed for the stereochemical control of the phospho-aldol reaction. Shibasaki and co-workers[81] reported that heterobimetallic complexes LLB and ALB containing chiral binaphthol ligands efficiently catalyse asymmetric hydrophosphonylation of aromatic aldehydes. The optical purity (*ee*) of the resulting α-hydroxy phosphonates reaches 95%. The reaction proceeds *via* an intermediate complex of the catalyst with the phosphite and aldehyde (for example, complex **56** in the case of LLB), the nucleophilic attack by the trivalent phosphorus on the aldehyde carbonyl carbon atom taking place within this complex.



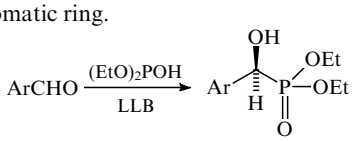
R	Cat = LLB, −78 °C		Cat = ALB, −40 °C	
	yield (%)	*ee* (%)	yield (%)	*ee* (%)
Ph	88	79	95	90
4-MeC$_6$H$_4$	93	78	82	86
4-Me$_2$NC$_6$H$_4$	88	95	–	–
4-MeOC$_6$H$_4$	87	93	88	78
4-NO$_2$C$_6$H$_4$	85	36	85	71
4-ClC$_6$H$_4$	80	63	80	83
PhCH=CH	90	84	85	82
PhCH=C(Me)	94	92	47	56
n-C$_5$H$_{11}$	88	61	95	16





56

Shibuya and co-workers,[82,83] who carried out the same reaction, found that the enantioselectivity of hydrophosphonylation of arylaldehydes in the presence of LLB depends on the electronic nature of the substituent in the *para*-position of the aromatic ring.

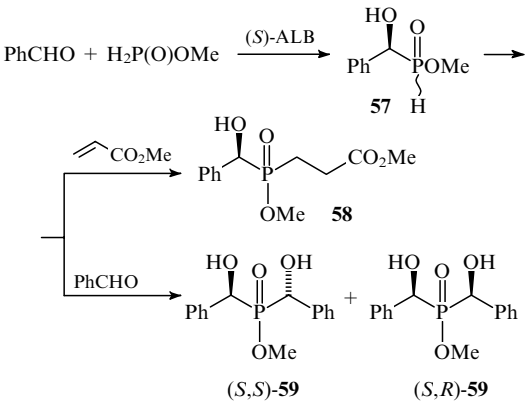


Ar	Yield (%)	*ee* (%)
Ph	98	20
4-$MeOC_6H_4$	95	82
4-MeC_6H_4	94	58
4-ClC_6H_4	99	17

Spilling and Rath[28] reported that the addition of dialkyl phosphites to cinnamaldehyde catalysed by (*R*)-LLB affords (*S*)-hydroxy phosphonates in good yields but the enantioselectivity (*ee*) is only ~30%. Subsequently, for increasing the reaction stereoselectivity, it has been proposed[80] to add the aldehyde to the reaction mixture very slowly, over a period of several hours.

The complexes obtained from titanium(IV) isopropoxide and some chiral diols efficiently catalyse the addition of diethyl phosphite to aromatic aldehydes. For example, the complex obtained from titanium(IV) isopropoxide and diisopropyl L-tartrate ensures the formation of (*R*)-hydroxy phosphonates with *ee* 36%–53%. The reaction enantioselectivity depends on the diol structure, the electronic nature of the substituent at the carbonyl group and the donor properties of the solvent.[83,84]

The addition of methyl hypophosphite to achiral aldehydes in the presence of the ALB catalyst proceeds with a moderate diastereoselectivity, yielding diastereomer mixtures of (*S*)-α-hydroxy-H-phosphinates **57**, which cannot be isolated in a pure state. Compounds **57** react with methyl acrylate and benzaldehyde to give hydroxy phosphinates **58** and an (*S*,*S*)- and (*S*,*R*)-diastereomer mixture of α,α′-dihydroxy phosphinates **59**, from which pure (*S*,*S*)-stereoisomer was isolated after acylation.[85]

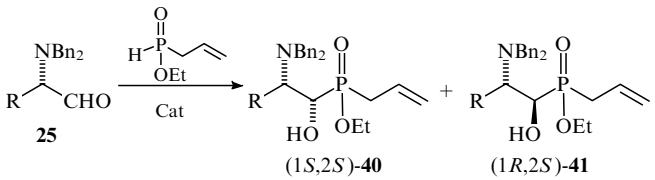


57 **58**

(*S*,*S*)-**59** (*S*,*R*)-**59**

The reaction of hypophosphorous acid with aldehydes initiated by microwave radiation giving rise to bis(α-hydroxyalkyl)-phosphinic acids has been reported.[86]

The catalytic hydrophosphinylation of chiral α-amino aldehydes **25** in the presence of ALB results in β-amino α-hydroxy phosphinic acid derivatives with moderate stereoselectivity.[87–89]

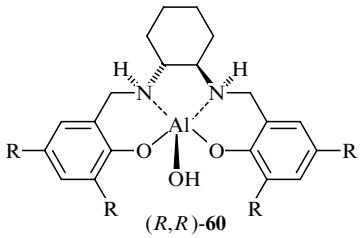


25 (1*S*,2*S*)-**40** (1*R*,2*S*)-**41**

R	Cat	*syn* : *anti*	Yield (%)
Bn	(*R*)-ALB	50 : 50	74
Bn	(*S*)-ALB	7 : 93	63
Bu^i	(*R*)-ALB	58 : 42	71
Bu^i	(*S*)-ALB	5 : 95	51
Me	(*R*)-ALB	24 : 76	48
Me	(*S*)-ALB	6 : 94	52

The formation of a complex diastereomer mixture in the reaction is due to the presence of three asymmetric centres in the product molecule, namely, the α- and β-carbon atoms and the phosphorus atom. Nevertheless, diastereomers (1*S*,2*S*)-**40** and (1*R*,2*S*)-**41** can be separated by column chromatography.[54,87,88]

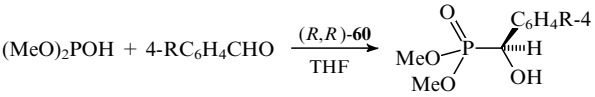
Chiral aluminium salcyan complexes catalyse the enantioselective route of the phospho-aldol reactions.[90] For example, the use of the chiral catalyst (*R*,*R*)-**60** in the reaction of dimethyl phosphite with substituted benzaldehydes results in *S*-isomers of the adducts with *ee* ~50%.



(*R*,*R*)-**60**

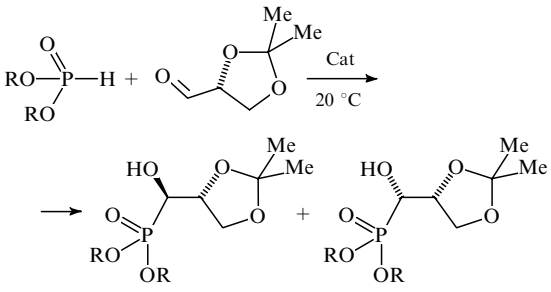
R = H, Bu^t.

R	H	Me	OMe	NO_2	NMe_2
ee (%)	52	57	47	18	22



Optically active quinine catalyses the reaction of *ortho*-nitrobenzaldehyde with dialkyl phosphites giving *S*-enantiomers of hydroxy phosphonates with *ee* 80%.[91,92]

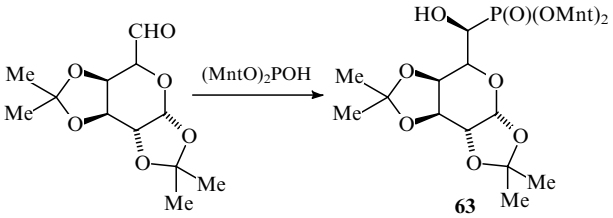
Multiple asymmetric induction, *i.e.*, a reaction proceeding under the stereochemical control of two or more chiral inductors, is an efficient method for increasing the stereoselectivity of the phospho-aldol condensation.[93–98] Thus the reaction of the optically active di-(1*R*,2*S*,5*R*)-menthyl phosphite with 2,3-*O*-isopropylidene-D-glyceraldehyde (both reactants are chiral inductors) occurs with a higher stereoselectivity than the reaction involving one chiral inductor and gives a diastereomeric mixture of α-hydroxy phosphonates **61** and **62** with predominance of the *anti*-stereoisomer (*de* 60%).[43] The introduction of the third asymmetric inductor, the chiral catalyst ALB, increases the stereoselectivity to 90%.[42] The ratio of isomers formed in the reaction depends on the natures of the solvent and the base and on the temperature. The resulting diastereomers (*R*,*R*)-**61** and (*S*,*R*)-**62** were separated by crystallisation and column chromatography on silica gel. The (1*S*,2*R*)-configuration of the adduct was confirmed by X-ray diffraction analysis.



(1*R*,2*R*)-**61** (1*S*,2*R*)-**62**

R	Cat	Solvent	*syn* : *anti*	Ref.
Et	DBU	–	45 : 55	43
Pr^i	DBU	–	45 : 55	43
Mnt	DBU	–	20 : 80	43
Mnt	DBU	MePh	20 : 80	43
Mnt	DBU	THF	28 : 72	43
Mnt	DBU	CH_2Cl_2	35 : 65	43
Mnt	NaOH	THF	30 : 70	43
Mnt	(*S*)-ALB	THF	5 : 95	42
Mnt	(*R*)-ALB	THF	22 : 78	42

The reaction of dimenthyl phosphite with *galacto*-hexodialdose proceeds with high stereoselectivity, owing to double asymmetric induction, resulting in the formation of C(6)-phosphorylated galactose derivative **63** with *de* ~100%. The adducts was isolated as optically pure crystalline compound.[98]

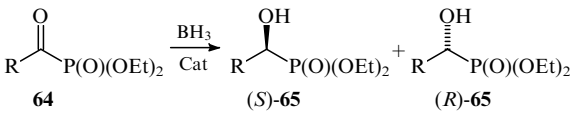


63

2. The reduction of keto phosphonates

The enantioselective reduction of keto phosphonates is a very convenient method for the synthesis of chiral hydroxy phosphonates. Keto phosphonates with optically active substituents, chiral reducing agents or catalysts can serve as asymmetric inductors in this reaction.

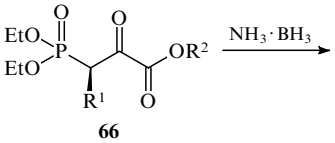
The reduction of diethyl α-keto phosphonates **64** with borane in the presence of chiral β-butyloxazaborolidines as catalysts yields diethyl (*S*)- and (*R*)-1-hydroxyalkylphosphonates **65** in good yields and satisfactory enantiomeric excesses (*ee* 53% – 83%).[99]



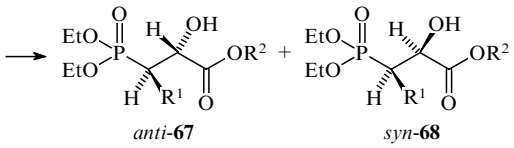
64 (*S*)-**65** (*R*)-**65**

R = Et, Bu^n, Bu^i; Cat — β-butyloxazaborolidine.

The reduction of keto phosphonates **66** with the borane – ammonia complex affords hydroxyphosphonate diastereomers **67** and **68** in 25 : 1 ratio.[100]



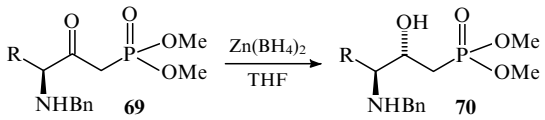
66



anti-**67** *syn*-**68**

R^1 = Me, Et, Pr^n, Bu^n, n-C_5H_{11}; R^2 = Et, Pr^i.

The reaction of γ-*N*-benzylamino β-keto phosphonates **69** with zinc borohydride gives *anti*-γ-amino β-hydroxy phosphonates **70** with good diastereoselectivity.[101]



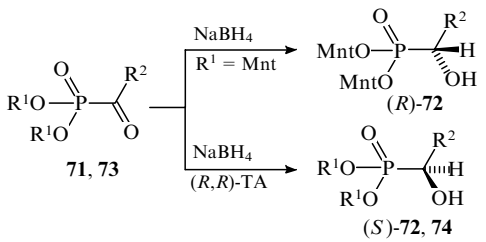
69 **70**

R = Pr^i, Ph.

This strategy has been used to prepare 1,5-dihydroxy-2-oxopyrrolidine-3-phosphonic acid (SF-2312), which is active against Gram-positive and Gram-negative bacteria.[102]

Sodium borohydride reduces sodium acylphosphonates and bis(acylphosphonates) to the corresponding hydroxyalkylphosphonates and dihydroxyalkylenebis(phosphonates).[103]

The reduction of dimenthyl keto phosphonates **71** with sodium borohydride in THF has a low stereoselectivity, (*R*)-1-hydroxybenzylphosphonates **72** were obtained with *de* ~30% – 35%.[104] The stereoselectivity can be increased through the formation of the chiral complex of sodium borohydride with natural D-tartaric acid. The enantioselective reduction of dietyhyl aroylphosphonates **73** with chiral $NaBH_4$ – (*R*,*R*)-TA complex affords diethyl (*S*)-1-hydroxybenzylphosphonates **74** with *ee* ~60%, whereas the reduction of dimenthyl aroylphosphonates **71** yields (*S*)-dimenthyl 1-hydroxybenzylphosphonates **72** with the diastereomeric exess (*de*) 80% – 93%.[105]

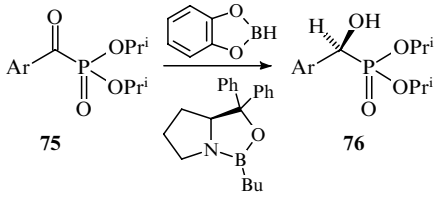


71, **73** (*R*)-**72** (*S*)-**72**, **74**

R^1 = (1*R*,2*S*,5*R*)-Mnt (**71**, **72**), Et (**73**, **74**);
R^2 = Ph, C_6H_4F, C_6H_4OMe; TA is tartaric acid.

Higher stereoselectivity observed in the reduction of dimenthyl aroylphosphonates is due to the double asymmetric induction effect, because in this case the inductions by the menthyl residues and tartaric acid are combined.

It has been proposed[15, 106, 107] to prepare chiral α-, β- and γ-hydroxy phosphonates by the reduction of aroylphosphonates with catecholborane or a borane – dimethyl sulfide complex in the presence of 1,3,2-oxazaborolidine as the catalyst. The enantioselective reduction of diisopropyl α-keto phosphonates **75** with

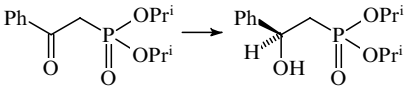


75 **76**

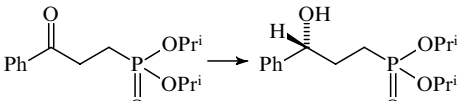
Ar = 2-$MeOC_6H_4$, 2-MeC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-FC_6H_4, 2-BrC_6H_4.

borane or catecholborane controlled by (*S*)-oxazaborolidines leads to (*S*)-1-hydroxybenzylphosphonates **76** with 53% – 83% enantiomeric excess.

Conversely, the reduction of β- (**77**) and γ-keto phosphonates **78** under the same conditions affords β- and γ-hydroxyalkylphosphonates (**79** and **80**) with *R* absolute configuration.



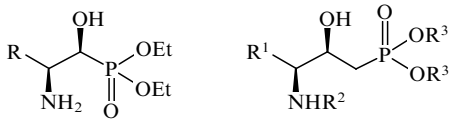
77 **79**



78 **80**

Treatment of α-keto phosphonates **75** with (−)-chlorodiisopinocampheylborane affords diisopropyl (*S*)-1-hydroxybenzylphosphonates **76** with higher enantiomeric excesses than the reaction with catecholborane in the presence of oxazaborolidine.[15]

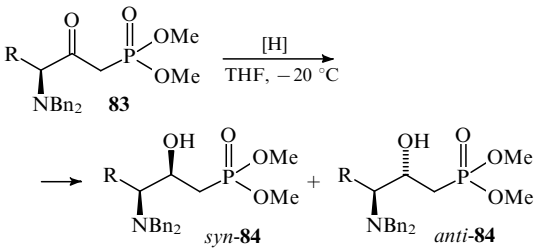
The reduction of α-keto β-phthalimido phosphonates with catecholborane in the presence of oxazaborolidine as the catalyst followed by deprotection of the amino group results in β-amino α-hydroxy phosphonates **81** with a high diastereoselectivity and in good yields.[108] The same procedure was used to convert γ-amino β-keto phosphonates into 3-amino 2-hydroxy phosphonates **82**, which are phosphate mimetics stable against hydrolysis.[109]



81 **82**

R = Me, Pr^i, Bu^i, Bn, 4-BnOC$_6$H$_4$CH$_2$.

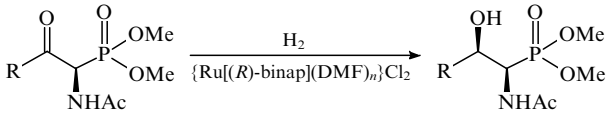
The diastereoselectivity of the reduction of γ-*N*,*N*-dibenzylamino β-keto phosphonates **83** does not depend on steric factors, which are determined by the size of the substituent at C(3). The configurations of hydroxy phosphonates **84** were confirmed by X-ray diffraction analysis and NMR spectroscopy.[110]



83 *syn*-**84** *anti*-**84**

R	Reducing agent	Yield (%)	*syn* : *anti*
Pr^i	AlHBu$^i_2$ (DIBAL-H)	50	82 : 18
Pr^i	$NaBH_4$	44	85 : 15
Pr^i	catecholborane	69	> 98 : 2
Me	catecholborane	85	> 98 : 2
Bn	catecholborane	89	> 98 : 2
Ph	catecholborane	82	90 : 10

The hydrogenation of (*R*)-α-acetamido β-keto phosphonates **85** in the presence of the chiral ruthenium binaphthyl complex gives hydroxy phosphonates (1*R*,2*R*)-**86** with good enantio- and diastereoselectivity.[111]



85 (1*R*,2*R*)-**86**

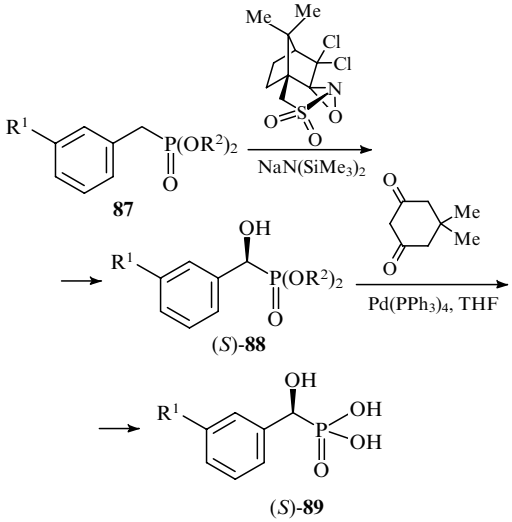
binap is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Tomioka *et al.*[112] carried out photoreduction of dialkyl keto phosphonates, which results in α-hydroxy phosphonates in ~60% – 70% quantum yields.

3. Oxidation

The oxidation of alkyl- and alkenylphosphonates is widely used in the synthesis of hydroxy phosphonates. This method has found wide use since oxidation of double carbon – carbon bonds in the asymmetric epoxidation or the Sharpless dihydroxylation in the case of organophosphorus compounds gives products in high yields and with high optical purity.

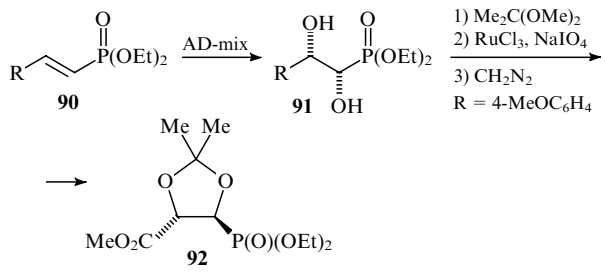
The stereoselective oxidation of benzylphosphonates **87** with chiral oxaziridines gives α-hydroxy phosphonates **88** with a rather high optical purity, *ee* can reach 69% – 98%. De-esterification of α-hydroxy phosphonates **88** with dimedone in the presence of the palladium catalyst occurs with almost no racemisation and affords α-hydroxy phosphonic acids **89** with *ee* 90% – 96%.[16,113]



87 (*S*)-**88** (*S*)-**89**

R^1	R^2	The *ee* of **88** (%)	Ref.
H	Me	93	16
NO_2	Me	80	16
Cl	Me	87	16
OMe	Me	81	16
CF_3	Et	98	113
H	$CH_2=CHCH_2$	96	113
OPh	$CH_2=CHCH_2$	98	113

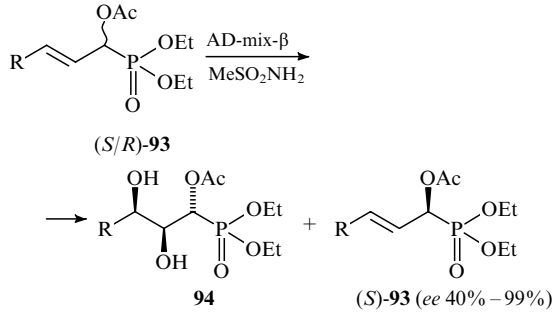
The asymmetric dihydroxylation of (*E*)-alkenylphosphonates **90** by AD-mix-α or AD-mix-β reagents, which represent mixtures of phthalazine adducts with dihydroquinine or dihydroquinidine, potassium ferricyanide, potassium carbonate and potassium osmate, results in the formation of optically active *threo*-α,β-dihydroxy phosphonates **91**.[114–116] The highest enantioselectivity (*ee* > 88%) is attained upon the oxidation of (*E*)-alkenylphosphonates containing an aromatic substituent at the double bond. Diol **91** (R = 4-MeOC$_6$H$_4$) was converted into dioxolane **92** upon the Martin catalytic oxidative degradation of the *p*-methoxyphenyl group. Dioxolanes of type **92** are convenient chiral intermediates for the synthesis of phosphonates containing a heteroatom at the α-carbon atom.[114]



90 **91** **92**

R	AD-mix	The yield of **91** (%)	*ee* (%)
Ph	AD-mix-α	42	91
4-$MeOC_6H_4$	AD-mix-α	71	95
4-$MeOC_6H_4$	AD-mix-β	69	98
3-$MeOC_6H_4$	AD-mix-α	67	96
4-ClC_6H_4	AD-mix-α	65	98
1-Naphthyl	AD-mix-α	80	93
2-Furyl	AD-mix-α	17	88
n-C_7H_{13}	AD-mix-β	63	84

The racemic mixture of (*S*/*R*)-1-acetoxy-2-(*E*)-alkenylphosphonates **93** can be resolved by kinetically controlled dihydroxylation with AD-mix-α or AD-mix-β.[117] The stereochemistry of dihydroxylation depends on the configuration of the α-carbon atom and the nature of substituents at the double bond. For example, AD-mix-β oxidises mainly the (*R*)-enantiomer of compound **93**; hence, in addition to the optically active (1*R*,2*S*,3*R*)-1-acetoxy-2,3-dihydroxyphosphonate **94** formed, the reaction mixture contains non-consumed (*S*)-acyloxyphosphonate **93**, which can be isolated with a good optical purity.

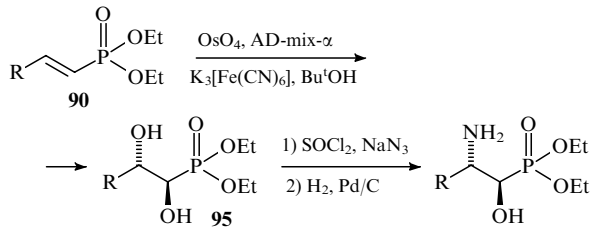


(*S*/*R*)-**93**

94 (*S*)-**93** (*ee* 40% – 99%)

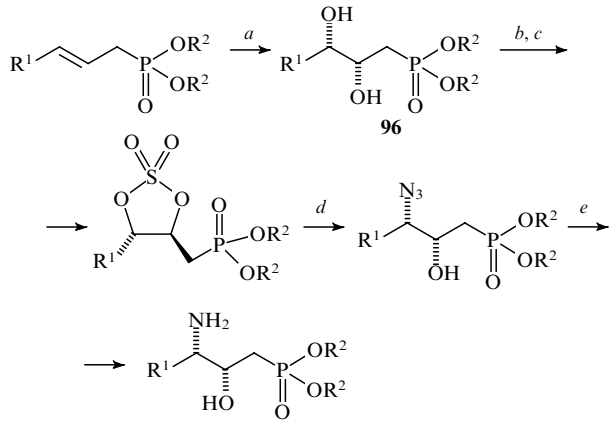
R = H, Ph, 4-$MeOC_6H_4$.

Dihydroxyalkylphosphonates **95** and **96** are prepared by asymmetric dihydroxylation of vinyl- and allylphosphonates. Dihydroxy derivatives **95** and **96** are converted into 2-amino-1-hydroxy- and 3-amino-2-hydroxyalkylphosphonates through formation of azido derivatives and the catalytic reduction of the azide group.[116–119] Chiral 3-amino-2-hydroxyalkylphosphonates are used in the synthesis of phosphocarnitine analogues.[118]



90 **95**

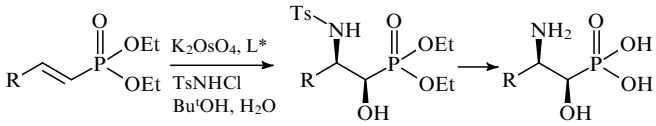
R = H, Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$.



96

R^1 = H, Me, 4-$MeOC_6H_4CO_2CH_2$; R^2 = Et, Bn;
(*a*) AD-mix-α, K_2OsO_4; (*b*) $SOCl_2$, Py; (*c*) $NaIO_4$, $RuCl_2$;
(*d*) NaN_3, H_2SO_4; (*e*) PPh_3, H_2O.

The asymmetric aminohydroxylation of diethyl (*E*)-styrylphosphonates with potassium osmate(VI), tosylamine and AD-mix-α as the chiral inductor results in (1*R*,2*S*)-*threo*-2-amino-1-hydroxyphosphonic acids **97**.[119, 120]

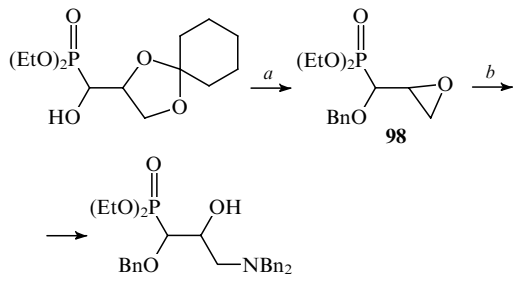


97

L* = AD-mix-α

R	Yield (%)	*ee* (%)
Ph	65	60
4-BrC_6H_4	71	75
4-$O_2NC_6H_4$	75	92
4-$MeOC_6H_4$	72	45
H	55	15

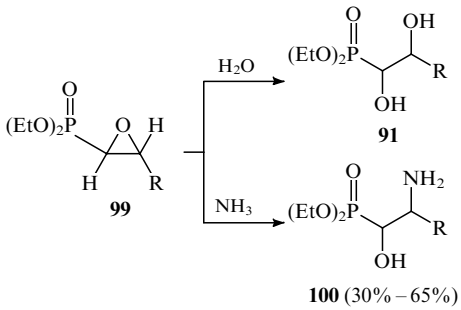
The diastereomeric diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1-benzyloxy-2,3-epoxypropylphosphonates (**98**) were synthesised from 2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonate; its reaction with dibenzylamine yielded (1*R*,2*R*)- and (1*S*,2*R*)-3-dibenzylamino-1-benzyloxy-2-hydroxypropylphosphonates.[121]



98

(*a*): (1) BnBr, Ag_2O; (2) HCl, dioxane; (3) $MeC(OMe)_3$, PPTS; (4) AcBr, K_2CO_3, MeOH; (*b*) $NHBn_2$;
PPTS is pyridinium *p*-toluenesulfonate.

Cristau and co-workers[122, 123] obtained 1,2-dihydroxyethylphosphonates **91** by hydrolysis of ethyl 1,2-epoxy alkylphosphonates **99**. Opening of the oxirane ring in compound **99** by amines resulted in 2-amino-1-hydroxyalkylphosphonates **100**, analogues of HO-AEP.

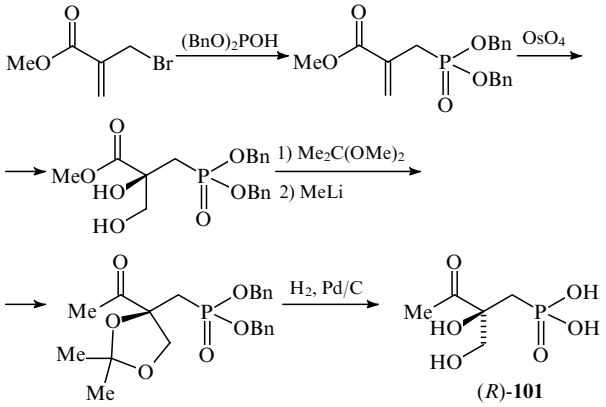


100 (30% – 65%)

R = H, Bu^n, Ph, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-MeOC$_6$H$_4$, 1-naphthyl.

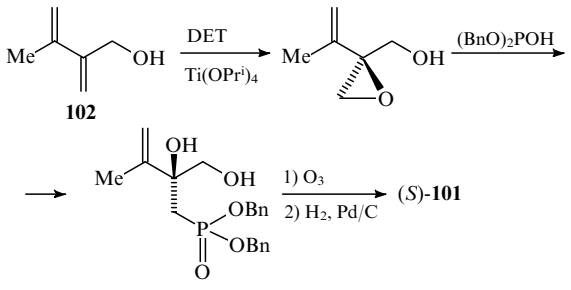
Amino hydroxy phosphonates were also prepared by catalytic methanolysis of 2-phosphorylaziridine.[121]

Nakamura *et al.*[124] developed the synthesis of phosphonothrixin (**101**) starting from methyl bromomethacrylate, which was first converted into allylic phosphonate by the Michaelis – Becker reaction and then hydroxylated with osmium tetroxide. The dihydroxyalkylphosphonate thus formed was converted into (*R*)-phosphonothrixin (**101**), as shown in the scheme.

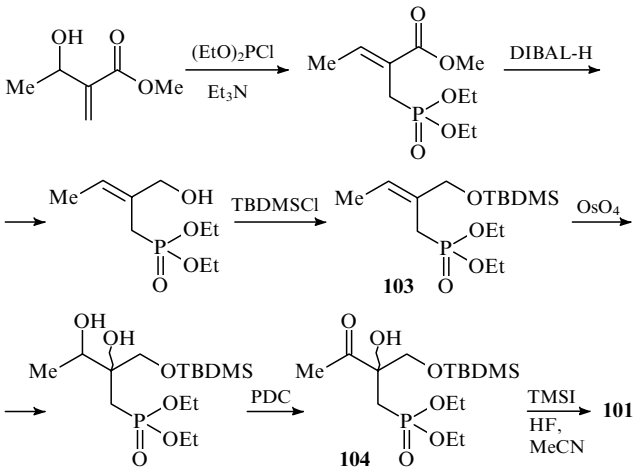


(*R*)-**101**

Another synthetic route to phosphonothrixin, which was also proposed by Nakamura *et al.*,[124, 125] starts with the asymmetric Sharpless epoxidation of the dienic alcohol **102** to give chiral (*R*)-epoxy alcohol (*ee* 92%), which reacts with dibenzyl phosphite to give dihydroxyalkylphosphonate. The subsequent ozonolysis and debenzylation of the dihydroxyalkylphosphonate furnish (*S*)-phosphonothrixin (**101**) with *ee* 92%. The (*R*)-enantiomer of phosphonothrixin was also synthesised by this method.

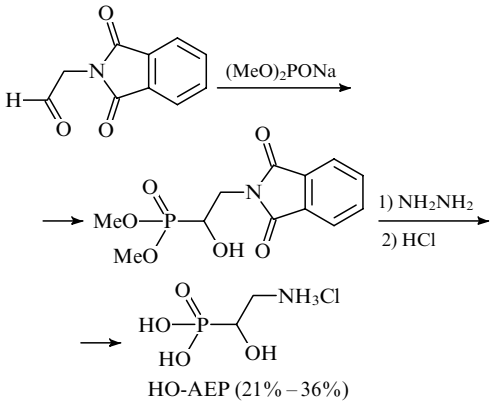


The total six-step synthesis of phosphonothrixin (**101**) was developed on the basis of commercially available methyl 3-hydroxy-2-methylidenebutyrate, which reacts with diethyl phosphorochloridite in the presence of triethylamine; this is followed by reduction of the ester group and yields allylic phosphonate **103** in 60% yield.[126] Dihydroxylation of phosphonate **103** with osmium tetroxide and subsequent oxidation of the secondary alcohol group gives the protected phosphonothrixin **104** in 80% yield. After removal of the protecting groups, free phosphonothrixin (**101**) was obtained in an overall yield of 24%.[126, 127]



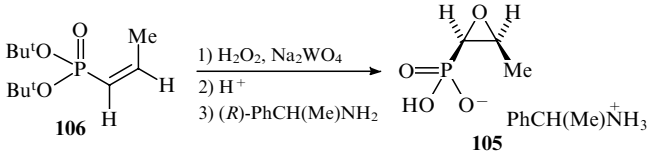
TBDMS = Bu^{t}Me$_2$Si; TMS = Me$_3$Si; PDC is pyridinium dichromate.

Natural 1-hydroxy-2-aminoethylphosphonic acid (HO-AEP), which was isolated from the membrane of the soil amoeba *Acanthamoeba castellanii*, is synthesised by the addition of sodium dimethyl phosphite to *N*-(2-oxoethyl)phthalimide followed by removal of the phthaloyl group with hydrazine and acid hydrolysis of the ester groups.[128]



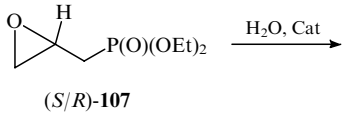
HO-AEP (21% – 36%)

Phosphomycin, (1*R*,2*S*)-(*Z*)-1,2-epoxypropylphosphonic acid (**105**), was prepared by catalytic epoxidation of vinylphosphonate **106** with subsequent hydrolysis and resolution of racemic phosphomycin into enantiomers using (+)-α-phenylethylamine.[129]

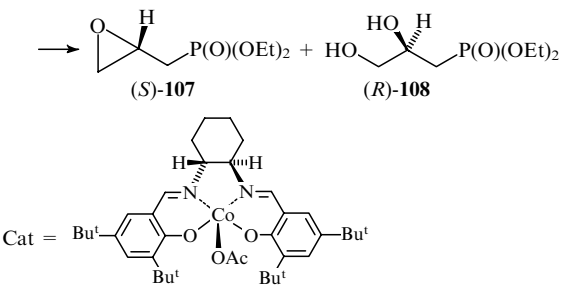


105

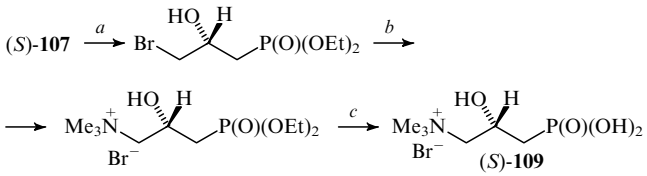
Kinetically controlled hydrolysis was proposed for the enantioselective resolution of racemic epoxyalkylphosphonates.[117 – 130] The conventional acid hydrolysis of epoxide (*S*)-**107** gives diol (*S*)-**108** with *ee* of only 72%. However, partial kinetically controlled hydrolysis of racemic epoxide (*S*/*R*)-**107**, which occurs in the presence of cobalt (*R*,*R*)-salen complex, affords chiral diethyl (*R*)-2,3-dihydroxypropylphosphonate **108** with *ee* 98%.[131, 132] Epoxide (*S*)-**107** with *ee* 82% remains in the reaction mixture.



(*S*/*R*)-**107**



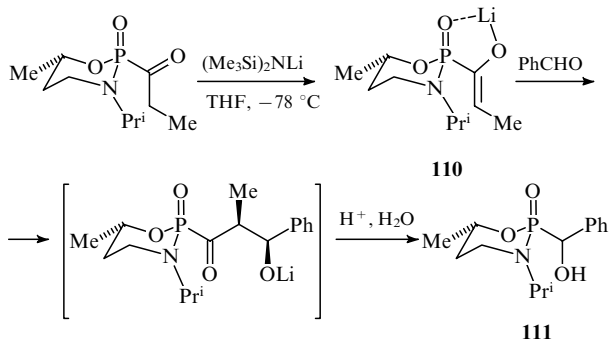
Diethyl (*S*)-2,3-epoxypropylphosphonate **107** is converted into phosphocarnitine (*S*)-**109** according to the following scheme: [132]



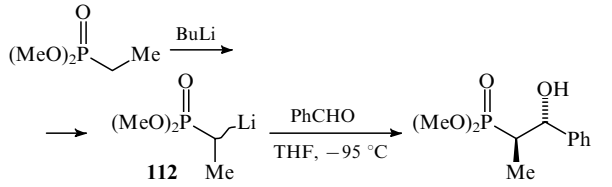
(*a*) $MgBr_2$, (*b*) Me_3N, (*c*) HCl, H_2O.

4. *C*-Modification

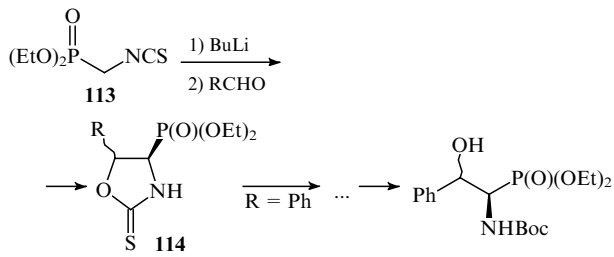
The addition of lithium derivative of (*S,S*)-2-(α-hydroxypropenyl)-2-oxo-l,3,2-oxazaphosphorinane **110** to benzaldehyde results in a diastereomer mixture of α-hydroxy-2-oxo-l,3,2-oxazaphosphorinanes **111** in 3 : 1 ratio.[133]



The reaction of the lithium derivative of dimethyl ethylphosphonate **112** with aromatic aldehydes in THF provides β-hydroxyalkylphosphonates with 85% diastereoselectivity.[134]

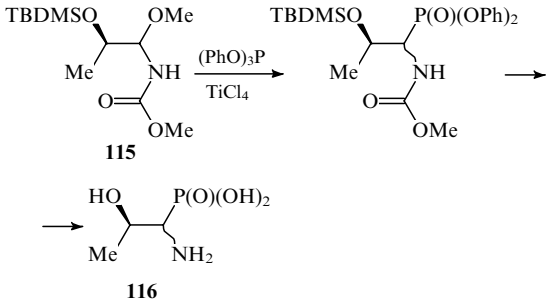


Diethyl isothiocyanomethylphosphonate **113** reacts with butyllithium to give a carbanion, which add to aldehydes yielding a diastereomer mixture of 2-thioxo-1,3-oxazolidin-4-ylphosphonates **114**; these are converted into *N*-Boc-protected 1-amino-2-hydroxyalkylphosphonates in three steps.[135]



R = Pr^i, Bu^t, Ph, PhCH=CH, 1-furyl.

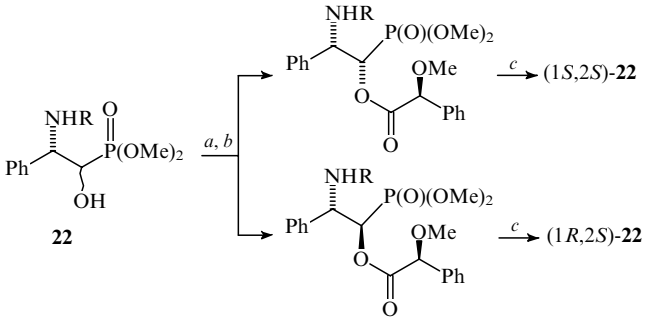
N,O-Acetals **115** containing a chiral group react with triphenyl phosphite in the presence of $TiCl_4$ to give a mixture of (*R,R*)- and (*S,R*)-diastereomeric α-amino-β-hydroxypropylphosphonates **116** in 2 : 1 ratio. Pure diastereomers are obtained by fractional crystallisation.[136]



5. Chromatographic separation

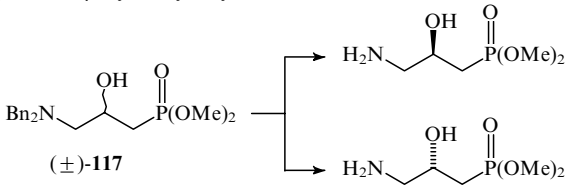
The resolution of racemic hydroxy phosphonates into enantiomers (in the form of diastereomers) by column chromatography is used rather often to obtain chiral hydroxy phosphonates.[137–140] Good results can be attained by using silica gel Merck 60 (70–230 mesh); the course of separation is monitored by TLC. Iodine vapour or, whenever possible, an ultraviolet detector is used to visualise the plates.

Wróblewski and Piotrowska [45,46] separated dimethyl 2-*tert*-butoxycarbonylamino- and dimethyl 2-benzoylamino-1-hydroxy-2-phenylethylphosphonate stereoisomers (**22**) upon esterification with (*S*)-*O*-methylmandelic acid followed by chromatography of the resulting diastereomer mixtures on silica gel. The yield of the less polar diastereomer was 43% and that of the more polar diastereomer, 36%, the latter being obtained in the crystalline state. Enantiomerically pure phosphonates (1*S*,2*S*)-**22** and (1*R*,2*S*)-**22** are formed in good yields upon ammonolysis of the ester.[45,46]



R = Boc, PhC(O);
(*a*) (*S*)-PhCH(OMe)CO_2H, DCC, DMAP; (*b*) chromatography;
(*c*) 25% NH_3, H_2O.

By using a similar approach, Ordóñez *et al.*[138] resolved racemic (*S/R*)-2-hydroxy-3-(*N,N*-dibenzylamino)propylphosphonate **117** into optically pure enantiomers, which are analogues of γ-amino-β-hydroxybutyric acid.



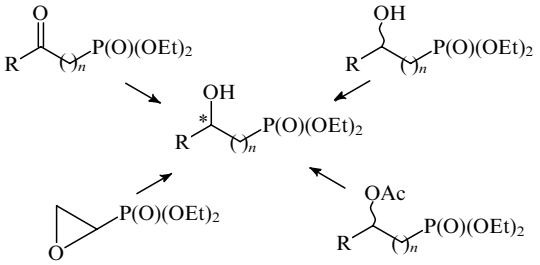
Enantiomeric diethyl hydroxy(aryl)methylphosphonates containing *para*- or *ortho*-substituted benzene or other aromatic rings (naphthalene, thiophene) are separated by HPLC on a chiral stationary phase.[139] The resolution of enantiomers of diethyl

α-hydroxyfarnesylphosphonate, which is a precursor of a farnesyl protein transferase inhibitor, is attained by semipreparative HPLC on a chiral chromatographic column Chiralcel OD.[140]

The separation of stereoisomeric 1-amino-2-hydroxy- and 2-amino-1-hydroxypropylphosphinic acid by capillary electrophoresis using chiral quinine carbamate has been described.[141]

6. Enzymatic synthesis

Enzymatic synthesis is an efficient alternative to the standard chemical synthesis of optically active hydroxy phosphonates. Bacteria, fungi and enzymes can be used as biocatalysts for the preparation of enantiomerically pure hydroxy phosphonates.[142, 143] The following general approaches to the enzymatic synthesis of hydroxyalkylphosphonates are best developed: biocatalytic reduction of keto phosphonates; enantioselective acylation of racemic hydroxy phosphonates using microorganisms or enzymes for the separation of stereoisomers; enantioselective hydrolysis of acyloxyalkylphosphonates and epoxyethylphosphonates.

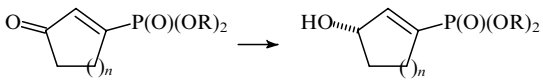


n = 0, 1, 2.

Ketophosphonates are reduced successfully using baker's yeast and some fungi. Baker's yeast is most convenient due to its ready availability, versatility and the ease of application.

Baker's yeast has been used [144–146] for the enantioselective reduction of diethyl β-, γ- and δ-oxoalkylphosphonates, which yielded hydroxy phosphonates with a high optical purity (*ee* > 95%). The reactions were carried out under aerobic conditions. In the case of low reactive compounds, anaerobic reduction was used.[145] This method has also been used to synthesise optically active β-keto γ- and δ-hydroxy phosphonates.[147]

Maffei and co-workers [148] studied the enantioselective reduction of dialkyl 3-oxocycloalk-1-enylphosphonates **118** with baker's yeast and obtained dialkyl (*S*)-3-hydroxycycloalk-1-enylphosphonates **119**, which are important intermediates in the synthesis of a number of biologically active compounds. It was concluded that the reduction of six-membered cyclic keto phosphonates proceeds with a higher enantioselectivity (*ee* 76%) than that involving five- and seven-membered analogues. The highest stereoselectivity is achieved in the reduction of six-membered cyclic keto phosphonates in organic solvents (hexane, benzene, *tert*-butyl methyl ketone); in this case, hydroxy phosphonates **119** are formed with *ee* 65%–82%. An increase in the bulkiness of alkoxy groups at phosphorus (from methoxy to isopropoxy) increases the optical purity of dialkyl 3-hydroxycycloalk-1-enylphosphonates to *ee* 95% irrespective of the reduction conditions.

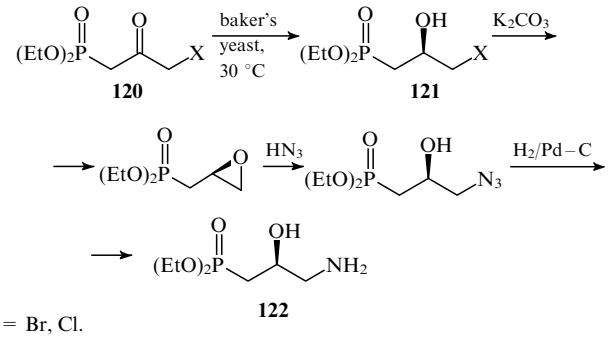


118 **119**

R = Me, Et, Pr^i; n = 1–3.

Solvent	The yield of **119** (%)	*ee* (%)
n-C_6H_{14}	84	65
MeC(O)Bu^t	15	82
C_6H_6	7	69

Yuan *et al.*[149] performed the enantioselective reduction of 3-halo-2-ketopropylphosphonates **120** with baker's yeast; this gave optically active 3-halo-2-hydroxy propylphosphonates **121** in moderate yields and a satisfactory optical purity. Compounds **121** are used in the synthesis of 3-amino-2-hydroxypropylphosphonates **122**.

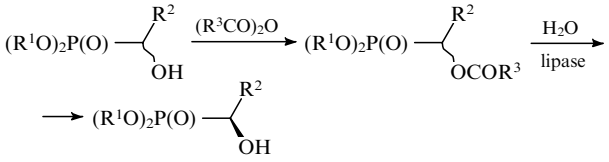


120 **121** **122**

X = Br, Cl.

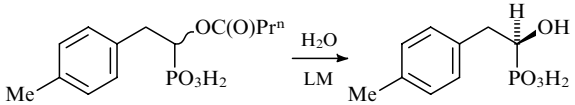
Enzyme-catalysed acylation or hydrolysis constitute convenient methods for the separation of racemic hydroxy phosphonates.[150–161]

Optically pure *S*-enantiomers of the hydroxy phosphonate series have been obtained [154, 157] in satisfactory yields with high enantiomeric excess by enzymatic hydrolysis of the acyl derivatives of racemic hydroxy phosphonates catalysed by lipases from *Aspergillus niger*, *Rhizopus oryzae* and *Candida rugosa*.



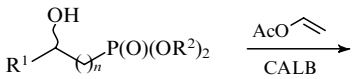
R^1 = Et, Pr^i; R^2 = Et, Pr^n, Pr^i, Bu^n, Bu^i, Bu^t, n-C_5H_{11};
R^3 = $ClCH_2$, Me, Et.

Hydrolysis of racemic 1-butyryloxyalkylphosphonic acid **123** with lipolytic microorganisms (LM), namely, the bacteria *Pseudomonas fluorescence* or the fungi *Penicillium citrinum*, leads to optically pure (*S*)-hydroxy phosphoric acid.[143, 152]

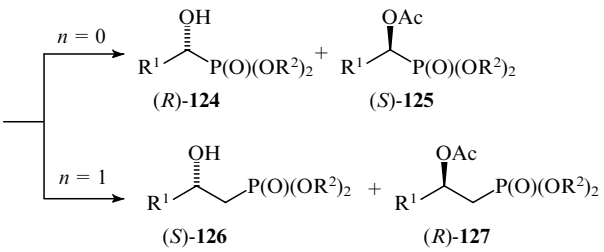


123

Racemic α-hydroxyalkylphosphonates **124** are subjected to acetylation catalysed by lipases from *Candida antarctica B* (CALB) and *Candida rugosa* (CRL); after that, the remaining *R*-isomer of hydroxy phosphonate **124** is separated from the *S*-isomer of acetyl derivative **125**.[147] Yuan and co-workers [153] used CALB in organic solvents for the enantioselective acetylation of racemic β-hydroxyalkylphosphonates **126**. The subsequent separation of the non-consumed alcohol (*S*)-**126** from ester (*R*)-**127** gives pure stereoisomers. In both cases, vinyl acetate was used as the acylation agent. This method for the preparation of chiral hydroxyalkylphosphonates is characterised by high enantioselectivity and experimental convenience.

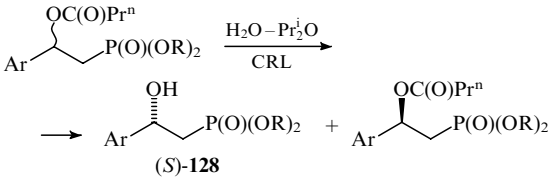


(*S*/*R*)-**124**, **126**



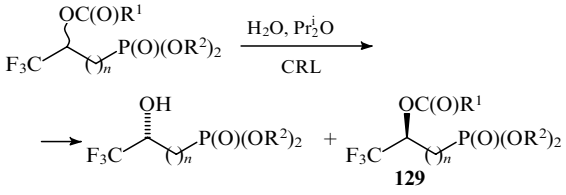
R^1 = Me, Et, CH=CH_2; R^2 = Me, Et; n = 0 (**124**), 1 (**126**).

CRL-catalysed enantioselective hydrolysis of racemic 2-aryl-2-butyryloxyethylphosphonates in a water–diisopropyl ether mixture results in enantiomerically pure (*S*)-2-aryl-2-hydroxyethylphosphonates **128**.[154, 156] The separation of the alcohol from the remaining ester and hydrolysis of the acyl group in the latter yields *S*- and *R*-stereomers of 2-aryl-2-hydroxyethylphosphonates **128** in satisfactory yields (40%–45%) and high optical purity (*ee* > 95%).[147]



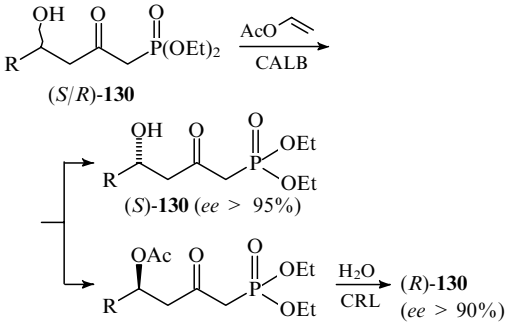
Ar = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 2-naphthyl, 2-furyl;
R = Me, Et, Pr^n, Pr^i.

Using this procedure, highly optically pure 1- and 2-hydroxyalkylphosphonates **129**, containing a trifluoromethyl group, have been obtained. CALB and lipase from *Mucor miehei* catalyse alcoholysis, while CRL catalyses hydrolysis in organic media.[157]



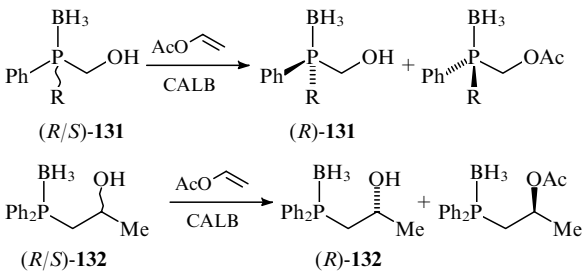
R^1 = Me, Et, Pr^n, Pr^i; R^2 = CH_2Cl, Pr^n; n = 0, 1.

Optically active δ-hydroxy-β-ketoalkylphosphonates (*S*)- and (*R*)-**130** are prepared by CALB-catalysed acetylation of the corresponding racemic alcohols and enantioselective hydrolysis of the resulting (*R*)-acetoxy phosphonate in the presence of CRL.[153]

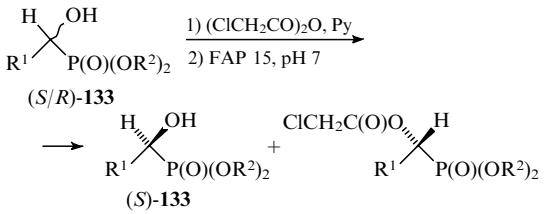


R = Me, Et, CH=CH_2.

Racemic hydroxymethylphenylphosphine – borane complexes **131** can be resolved into enantiomers by enantioselective acetylation catalysed by CALB or the lipase from *Pseudomonas fluorescence* (PFL). The optical purity of the resulting complexes reaches 99%. Racemic 2-hydroxypropyldiphenylphosphine–borane complexes **132** are resolved in a similar way [159]

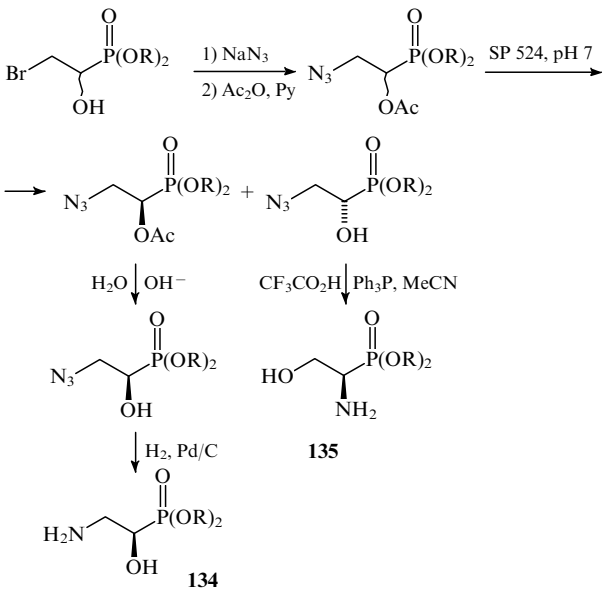


Hammerschmidt *et al.*[14, 162–165] have developed a method for the resolution of racemic α-hydroxy phosphonate **133**, based on acylation and subsequent enzymatic hydrolysis induced by lipases and proteases in an organic solvent–water biphasic system containing a phosphate buffer with pH 7. The highest enantioselectivity is attained by using lipase FAP 15, which hydrolyses only the *S*-enantiomers of α-chloroacetoxyalkylphosphonates to give optically pure alcohols (*S*)-**133**. It was found [14] that lipases SP 524 and AP 6 selectively hydrolyse *S*-isomers of diisopropyl α-bromoacetoxy phosphonates, whereas the protease Chirazyme ® P-2 hydrolyses *R*-isomers of these compounds. The use of lipases AP 6 and FAP 15 permits the preparative resolution of racemates to give gramme amounts of (*S*)-hydroxy phosphonates **133** with *ee* 81%–89%.[162, 163]



R^1 = Et, Pr^i, Bu^i, $MeS(CH_2)_2$, Bu^s; R^2 = Pr^i, Bu^t, $Me_2C(CH_2)_2$.

A method for the synthesis of enantiomerically pure L-phosphoisoserine (**134**) and L-phosphoserine (**135**) from racemic β-bromo-α-hydroxyethylphosphonate using enzymes for isomer separation has been proposed.[165] β-Bromo-α-hydroxyethylphosphonate is first converted into racemic 1-acetoxy-2-azidoethylphosphonate, which is subjected to enzymatic hydrolysis catalysed by lipase SP 524. This yields enantiomerically enriched (*S*)-α-hydroxyphosphonate and its (*R*)-acetyl derivative, whose saponification results in (*R*)-(+)-α-hydroxy-β-azidophosphonate. Enantiomerically pure (*R*)- and (*S*)-β-azido-α-hydroxy-

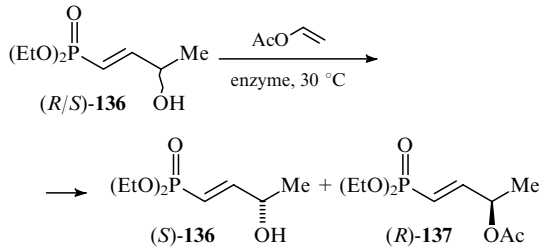


R = H, Pr^i.

phosphonates are converted into L-phosphoisoserine (**134**) and L-phosphoserine (**135**) using catalytic hydrogenation and the Staudinger reaction.

A similar method has been used to prepare chiral methyl sulfides (*ee* 93% – 97%) from racemic α-hydroxy phosphonates, which are resolved using enzymatic hydrolysis of acyl derivatives.[166] The enzymatic acetylation of racemic diisopropyl α-hydroxy phosphonates with isopropenyl acetate in *tert*-butyl methyl ether allows one to obtain (*S*)-diisopropyl-1-hydroxy-(2-thienyl)methyl-, -1-hydroxyethyl-, -1-hydroxycyclohexylmethyl-phosphonate and (*R*)-2-hydroxypropylphosphonate acetates with enantiomeric excesses reaching 99%. Using enzymatic hydrolysis, (*S*)-2-hydroxy-2-phenylethyl- and (*S*)-2-hydroxy-3-methylbutyl-phosphonates can be converted into (1*R*,2*R*)-2-amino-1-hydroxy-phosphonic acids.[167–169] Enzymatic hydrolysis was used in the synthesis of phosphomycin.[169,170]

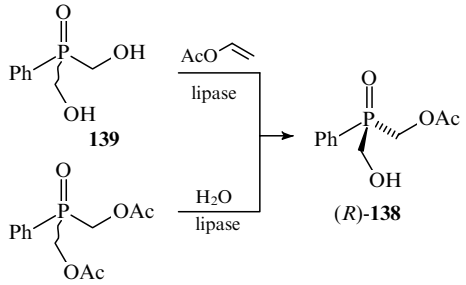
Acetylation of racemic diethyl 3-hydroxybut-1-enylphosphonate (**136**) catalysed by various enzymes and subsequent separation of the components of the reaction mixture affords enantiomerically pure diethyl (*S*)-3-hydroxybut-1-enylphosphonate **136** and diethyl (*R*)-3-acetoxybut-1-enylphosphonate **137** with enantiomeric excesses reaching 99%.[171]



Enzyme	*ee* (%)	
	(*S*)-**136**	(*R*)-**137**
Lipozyme	99	96
Amano AK	97	96
Amano PS	81	98
Acylase from *Asp. melleus*	49	98
CALB	91	14
PPL	22	99
CRL	8	54

Lipases from *Geotrichum candidum*, *Rhizopus niveus*, *Penicillium* species, *Aspergillus usamii*, *Mucor* species and *Pseudomonas cepacia* and porcine pancreatic lipase are used for stereoselective acetylation of racemic hydroxyphosphonates in toluene.[172–181] Thus lipase from *Geotrichum candidum* catalyses the enantioselective acetylation of racemic hydroxy phosphonates to give the acetylated product in a 32% – 34% yield and with optical an purity of 95%.[172]

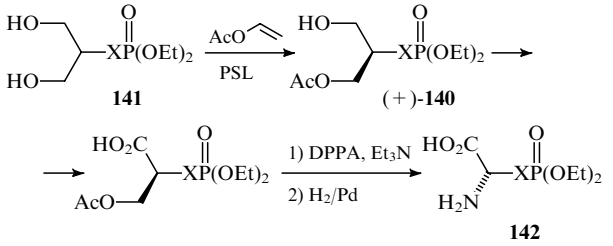
The optically pure monoacetate (*R*)-**138** is prepared from prochiral bis(hydroxymethyl)phenylphosphine oxide (**139**) by



Lipases Amano AK, PFKl (from *Pseudomonas fluorescens*), Amano PS.

enzymatic acetylation with vinyl acetate in an organic solvent or enzymatic hydrolysis of bis(acetoxymethyl)phenylphosphine oxide.[173]

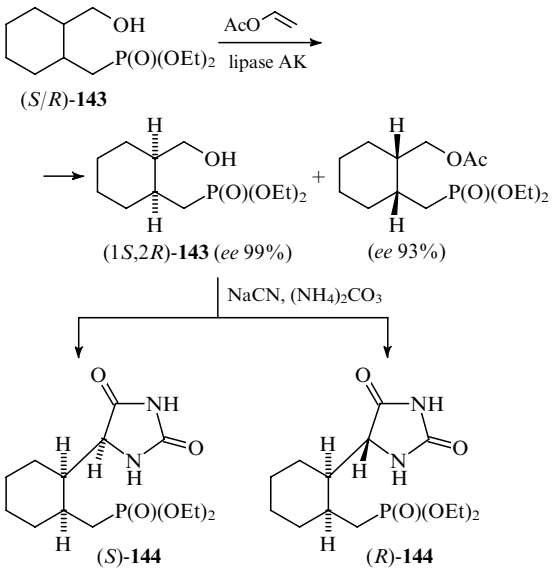
Shibuya and co-workers[174] prepared optically active alcohols **140** by enantioselective acylation of prochiral 2-(ω-phosphonoalkyl)propane-1,3-diols **141** with vinyl acetate in an organic solvent catalysed by lipase from *Pseudomonas cepacia* (PSL). Chiral alcohols (+)-**140** are formed in good yields and high enantiomeric excesses. Alcohols (+)-**140** are then converted into optically active α-amino-ω-phosphono acids **142**, which possess various biological activities and are intermediates in the synthesis of aminopentylphosphonic acid analogues.



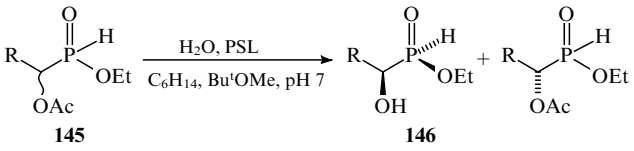
X = CH_2, $(CH_2)_2$, CH_2CF_2; DPPA is diphendiphenoxyphosphoryl azide.

Solvent	The yield of **140** (%)	*ee* (%)
Pr^i_2O	82	98
Pr^i_2O (lipase AK)	98	70
THF	98	98
C_6H_6	94	98
C_6H_{14}	72	79

The same authors[175] carried out the kinetic resolution of racemic 1-diethoxyphosphorylmethyl-2-hydroxymethylcyclohexane (**143**) into enantiomers in good yields and high enantiomeric excesses by acetylation catalysed by lipases PSL or AK. Optically active alcohol (1*S*,2*R*)-**143** was converted into (*S*)- and (*R*)-hydantoins **144**.



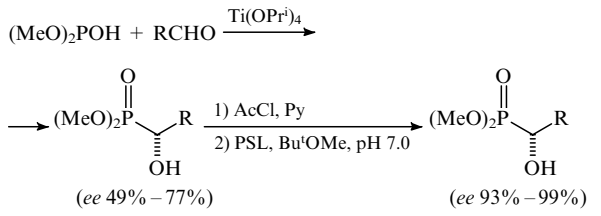
PSL-catalysed hydrolysis of racemic or enantiomerically enriched acetates **145** gives enantiomerically pure α-hydroxyalkylphosphinates (**146**) with *ee* 74% – 99%.[176]



145 **146**

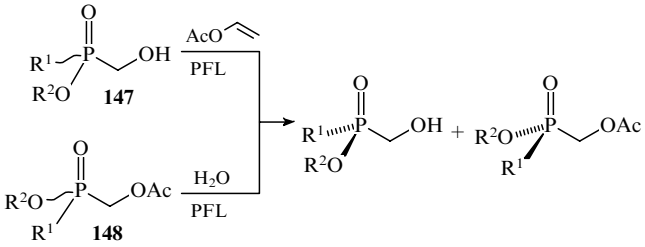
R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, Bn, n-C$_5$H$_{11}$.

The enantiomerically enriched hydroxy phosphonates synthesised by the Abramov reaction can be additionally purified by acetylation and PSL-catalysed hydrolysis; this increases their optical purity to *ee* 93% – 99%.[177]



R = Ph, PhCH=CH, MeCH=CH, C$_5$H$_{11}$CH=CH, PhCH=C(Me).

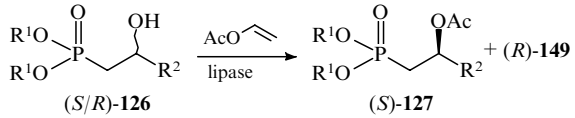
The enzymatic acetylation of racemic hydroxymethylphosphonates and -phosphinates **147** allows one to resolve them into enantiomers with a moderate optical purity and in good yields. Meanwhile, the enantioselective hydrolysis of *O*-acetylated derivatives **148** catalysed by PFL results in hydroxymethylphosphonates and -phosphinates with an optical purity of up to *ee* 92%.[178]



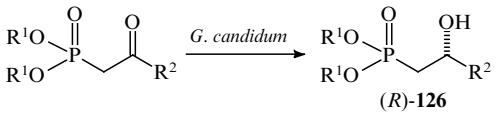
147 **148**

R^1	R^2	Configuration	*ee* (%)
Ph	Me	*R*	80
		S	89
Ph	Et	*R*	54
		S	47
Ph	Pr^i	*R*	80
		S	21
Pr^{i}O	Me	*S*	16
		R	34
Pr^{i}O	Me	*S*	~92
		R	~92

Racemic 2-hydroxyalkylphosphonates **126** are acetylated in the presence of various lipases to give optically pure 2-acetoxyalkylphosphonates (*S*)-**127** with *ee* 93%. In turn, enantiomerically pure 2-hydroxyalkylphosphonates (*R*)-**126** can be obtained by the reduction of 2-keto phosphonates with lipase from *Geotrichum candidum*. For example, diethyl 2-oxopropylphosphonate was converted, under these conditions, into diethyl (*R*)-(+)-2-hydroxypropylphosphonate with *ee* 98%.[179]



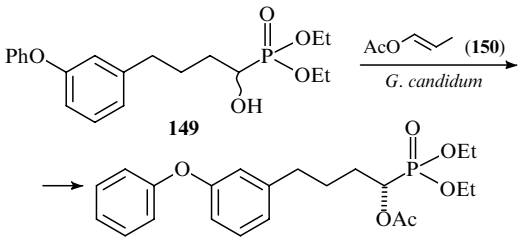
(*S*/*R*)-**126** (*S*)-**127**



(*R*)-**126**

R^1 = Me, Et; R^2 = Me, Bu^n, (CH$_2$)$_3$Ph, 2-pyridyl.

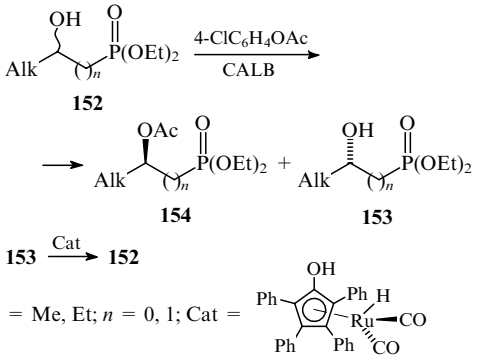
The acetylation of phosphonate **149** with propenyl acetate (**150**) in the presence of the lipase from *Geotrichum candidum* in organic solvents (toluene, hexane, acetone, CH_2Cl_2 and so on) afforded chiral diethyl (*S*)-[1-acetoxy-4-(3-phenoxyphenylene)-butyl]phosphonate **151**, which is a squalene synthase inhibitor. The optical purity (*ee*) of acetylated hydroxyphosphonate **151** obtained by this method reaches 95%.[150]



149

(*S*)-(+)-**151**

The enzymatic acetylation of racemic α- and β-hydroxy phosphonates **152** combined with racemisation *in situ* of the non-consumed substrate **153** catalysed by a ruthenium complex, increases the yield of enantiomerically pure (*ee* > 99%) hydroxy phosphonate acetates **154** to 70% – 87%.[158]



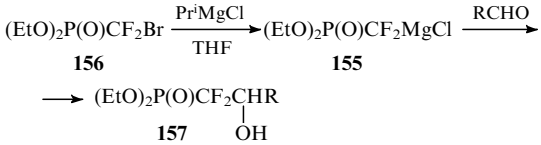
152 **154** **153**

Alk = Me, Et; *n* = 0, 1; Cat =

7. Synthesis of fluorine-containing hydroxy phosphonates

In recent years, fluorine-containing phosphonates, in particular, hydroxy phosphonates where the hydroxy group is separated from the phosphorus atom by a CHF or CF_2 group, have attracted attention of researchers. These compounds are structural analogues of natural phosphates and pyrophosphates in which the oxygen atom has been replaced by a CHF or CF_2 group.[182–202]

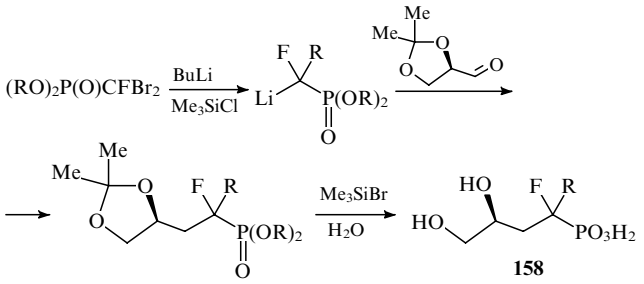
A convenient method for the synthesis of fluorine-containing hydroxy phosphonates by the reaction of organometallic derivatives of fluorophosphonates with aldehydes and ketones has been reported.[184, 185] The organomagnesium derivative of difluoromethylphosphonate (**155**), resulting from the reaction of bromodifluoromethylphosphonate **156** with isopropylmagnesium chloride, reacted with aldehydes, giving 1,1-difluoro-2-hydroxyalkylphosphonates **157** in high yields.



156 **155** **157**

R = Alk, Ph.

This method has been used[186] to prepare monofluorodihydroxybutylphosphonic acid **158**, which is an analogue of glycerol 3-phosphate, the glycerol 3-phosphate dehydrogenase substrate.

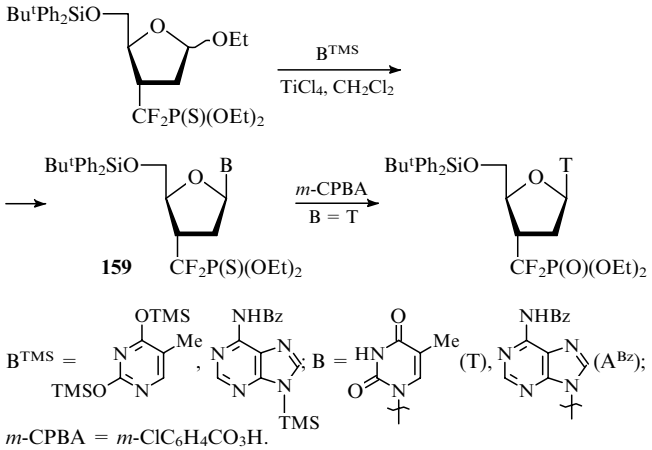


R = H, $SiMe_3$.

The CuBr-activated reaction of (diethylphosphonyl)difluoromethylzinc bromide with aryl iodides results in aryldifluoromethylphosphonates. Treatment of these compounds with trimethylsilyl bromide gives free acids, some of which being low-molecular-mass inhibitors of phosphatase.[187]

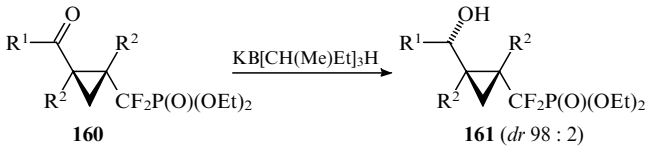
Berkowitz *et al.*[188] described a facile method for the synthesis of difluoroalkylphosphonates; this method was used to prepare difluoromethylphosphonic analogues of L-serine, L-allothreonine and L-threonine.

Shibuya and co-workers[189,190] reported the synthesis of nucleotide analogues containing a phosphoryldifluoromethyl group. Titanium tetrachloride-catalysed glycosylation of the trimethylsilyl derivatives of heterocyclic bases with 2,3-dideoxyribofuranosides containing a thiophosphoryldifluoromethyl group at C(3) is a method for preparing pyrimidine β-nucleosides **159** with high stereoselectivity (*dr* 89 : 11). The oxidation of the thymine-containing nucleoside with *m*-chloroperbenzoic acid gives rise to the difluoromethylphosphonate analogue of thymidine 3′-phosphate.



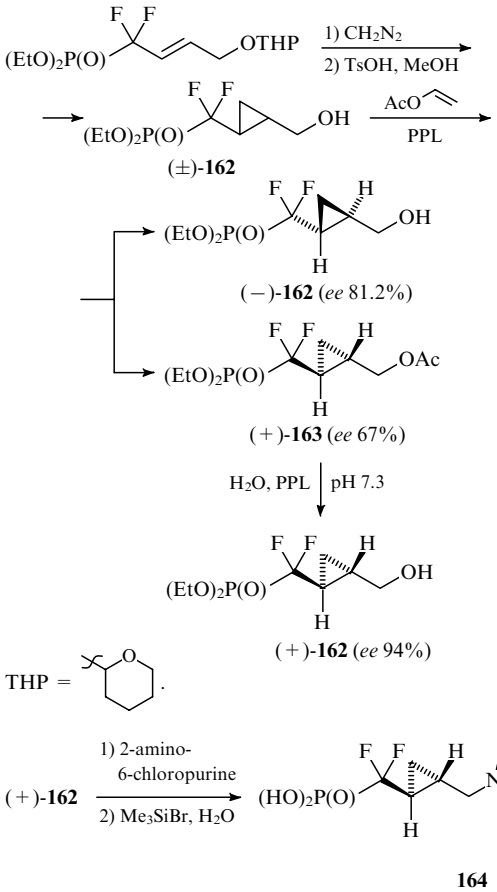
A solid-state method for the synthesis of fluorinated α-hydroxy phosphonates has been proposed.[191] Keen interest is aroused by the fluorophosphonates containing a cyclopropyldifluoromethyl group, which has a pronounced effect on the biological properties of compounds.[192–195] For example, {(1*S*,2*S*)-2-[(1*S*)-1-(6-oxo-1,6-dihydropurin-9-yl)ethyl]cyclopropyl}difluoromethylphosphonate is an efficient inhibitor of purine nucleoside-phosphorylase.[194]

The reduction of [(1*S*,2*S*)-2-acetylcyclopropyl]difluoromethylphosphonates **160** with K-selectride occurs from the less hindered side of the carbonyl group (*si*-stereofacial) and gives cyclopropylethanols **161** with a high diastereoselectivity.

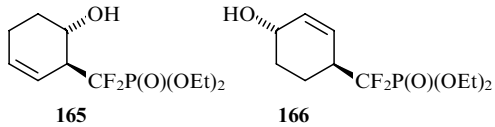


R^1 = Me, Ph, Bn, cyclo-$C_6H_{11}CH_2$, $CH_2=CHCH_2$; R^2 = H, Me.

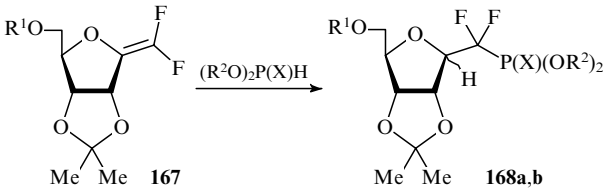
The synthesis of enantiomerically pure diethyl *trans*-4-hydroxy-1,1-difluoro-2,3-methanobutylphosphonate [(+)-**162**] by the reaction of diethyl 4-tetrahydropyranyloxy-1,1-difluorobut-2-enylphosphonate with diazomethane followed by enzymatic double resolution of the resulting racemic hydroxyphosphonates (±)-**162** has been reported.[195] By PPL-catalysed acetylation and hydrolysis of the enantiomerically enriched acetoxy phosphonate (+)-**163**, the optical purity of hydroxy phosphonate (+)-**162** was increased to *ee* 94%. Chiral hydroxy phosphonate (+)-**162**, the structure of which was confirmed by X-ray diffraction, was used for the synthesis of optically active 9-[(2*S*,3*S*)-4-phosphono-4,4-difluoro-2,3-methanobutyl]guanine (**164**),which is a purine nucleoside phosphorylase inhibitor.[195]



Shibuya and co-workers[196] reported the synthesis of (hydroxycyclohexenyl)difluoromethylphosphonates **165** and **166** by the CuBr-catalysed reaction of (diethoxyphosphoryl)difluoromethylzinc bromide with hydroxycyclohex-2-en-1-yl phosphates. Compounds **165** and **166** are intermediates in the stereoselective synthesis of inositol phosphate analogues.

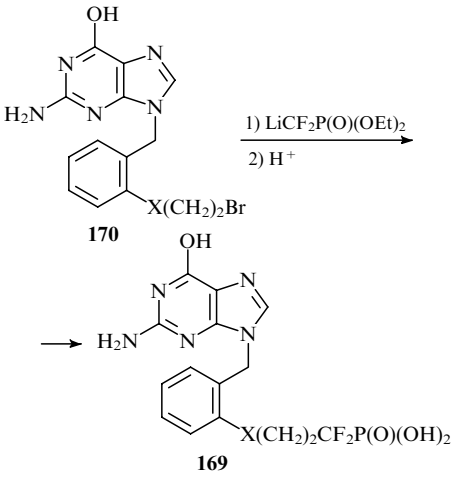


The reaction of dialkyl phosphites and thiophosphites with carbohydrate difluoromethylidene derivatives **167** yields anomeric mixtures of glycosyldifluoromethylphosphonates **168a** and -thiophosphonates **168b** with the isopropylidene protecting group.[197]



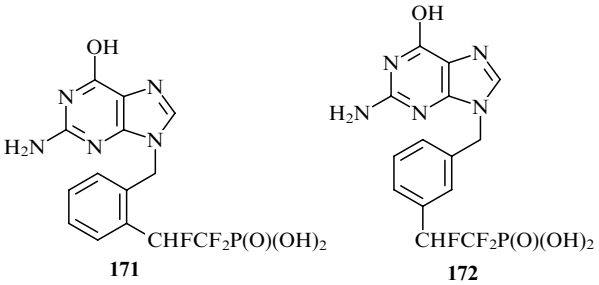
R^1 = H, Bu^tMe_2Si; R^2 = Et, Bn; X = O (**a**), S (**b**).

The synthesis of nucleotides **169**, containing a difluoromethylphosphonate group, which are reverse transcriptase inhibitors, has been reported.[201] Compounds **169** were prepared by the reaction of the lithium derivative of difluoromethylphosphonate with the bromo-containing nucleoside analogue **170** and subsequent hydrolysis of the resulting diester.



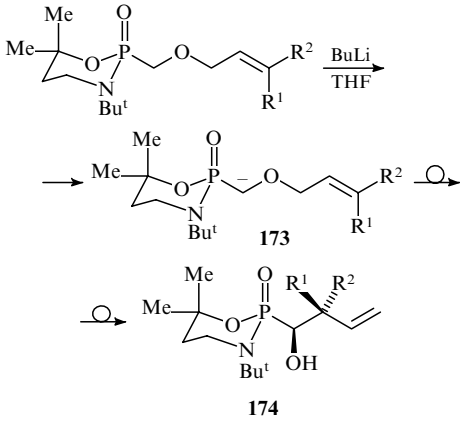
X = CH_2CF_2, $CHFCF_2$, (*E*)-CH=CF, (*E*)-CH=CH, $O(CH_2)_2CF_2$.

Fluorophosphonate derivatives of N^9-benzylguanine **171** and **172**, functioning as purine nucleoside phosphorylase inhibitors, have been synthesised in a similar way.[201]



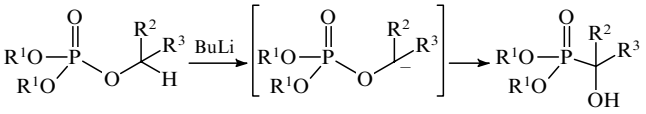
8. Miscellaneous methods for the synthesis of hydroxy phosphonates

The asymmetric [2,3]-sigmatropic Wittig rearrangement of chiral phosphonate carbanions generated from allyloxymethyl and but-2-enyloxymethyl derivatives proceeds with high diastereo- and enantioselectivity.[17, 203] For example, deprotonation of allyl- and but-2-enyloxymethylphosphonamides under the action of butyllithium in THF at −70 °C results in the formation of stable phosphonate carbanions **173**, which readily undergoes the [2,3]-sigmatropic Wittig rearrangement to give hydroxy phosphonate **174** as the only diastereomer.[17]



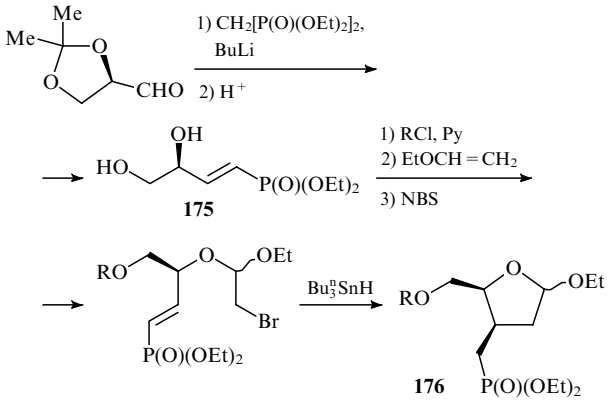
R^1 = R^2 = H; R^1 = Me, R^2 = H; R^1 = H, R^2 = Me.

Hammerschmidt[204] described the phosphate–phosphonate rearrangement, which gives rise to hydroxy phosphonates and is the model reaction for the biosynthesis of compounds with the P–C bond.



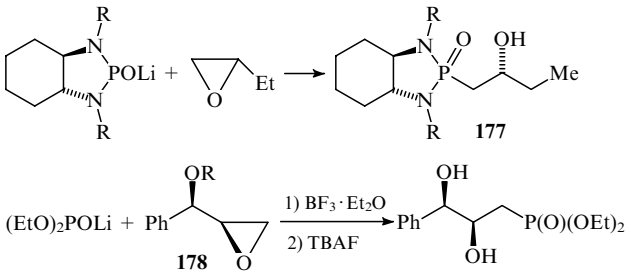
Hydroxy phosphonates are also obtained by the reaction of chiral epoxy chalcones with nucleophiles. In the presence of KF, diethyl phosphite adds preferentially to the *si*-face of the carbonyl group of epoxychalcones to give hydroxy phosphonates with *de* 50%.[205]

Shibuya and co-workers[206] reported the synthesis of dihydroxy phosphonates **175** by the reaction of chiral isopropylideneglyceraldehyde with bis(diethoxyphosphoryl)methane in the presence of butyllithium followed by deprotection of the hydroxy groups. The radical intramolecular cyclisation of the resulting dihydroxy phosphonates **175** yielded phosphonates **176**, which are analogues of 2-deoxyribosyl-3-phosphates, with the stereoselectivity (*de*) 76%–92%.



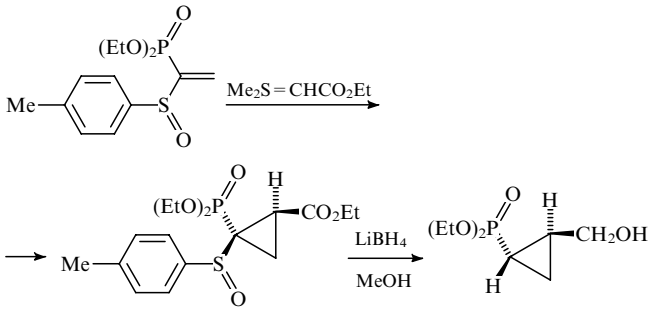
R = $SiPh_2Bu^t$, $SiMe_2Bu^t$; NBS is *N*-bromosuccinimide.

The reaction of optically active lithium *N*,*N*,*N*′,*N*′-tetraalkylphosphorodiamidites with 1,2-epoxybutane leads to hydroxybutylphosphonamides **177** with a diastereoselectivity (*ee*) not exceeding 33%. The reaction of chiral epoxides **178** with achiral lithium diethyl phosphite also proceeds with a low stereoselectivity.[118]

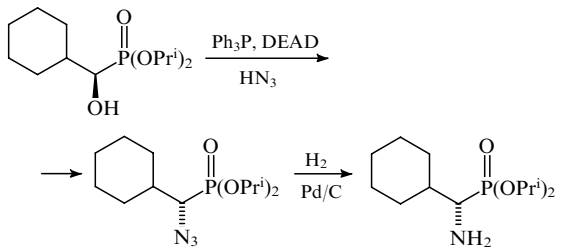


R = $SiMe_2Bu^t$.

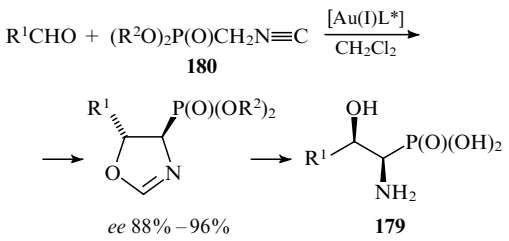
Considerable attention is paid to the synthesis of pharmacologically active hydroxyalkylphosphonates.[207] For example, the Michaelis–Becker reaction of methanesulfonates with dialkyl phosphites furnished nucleoside analogues with a methylenecyclopropylphosphonate fragment, some of which exhibited high antiviral activities.[208] The reaction of [1-(diethoxyphosphoryl)-vinyl] *p*-tolyl sulfoxide with ethyl (dimethylsulfuranylidene)acetate yields (1*S*,2*S*)-1-diethoxyphosphoryl-2-ethoxycarbonylcyclopropyl *p*-tolyl sulfoxide, which is converted into optically pure 2-hydroxymethylcyclopropylphosphonate. This was coupled with adenin and chloropurine under conditions of the Mitsunobu reaction to give conformationally constrained analogues of the antiviral purine nucteotides.[209]



The hydroxy group in hydroxy phosphonates is replaced by the amino group using the Mitsunobu reaction.[210] Diisopropyl (*S*)-(+)- and (*R*)-(−)-hydroxy(cyclohexyl)methylphosphonates, prepared by the kinetic resolution of the racemic mixture using lipase AP 6, are converted by the Mitsunobu reaction, into optically active (*S*)-(+)- and (*R*)-(−)-amino(cyclohexyl)methylphosphonates with an optical purity of not less than 90%. The replacement of the hydroxy group by an amino group is accompanied by the inversion of configuration.

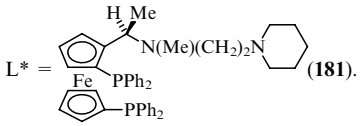


1-Amino-2-hydroxyalkylphosphonic acids **179**, which are isosteric analogues of biologically active and natural compounds, are synthesised by the asymmetric aldol condensation of aldehydes with isocyanomethylphosphonates **180**. The reaction is catalysed by the chiral complex of gold with the ferrocenylphosphine ligand **181**. The optical purity of the reaction products (*ee*) reaches 88%–96%.[211]



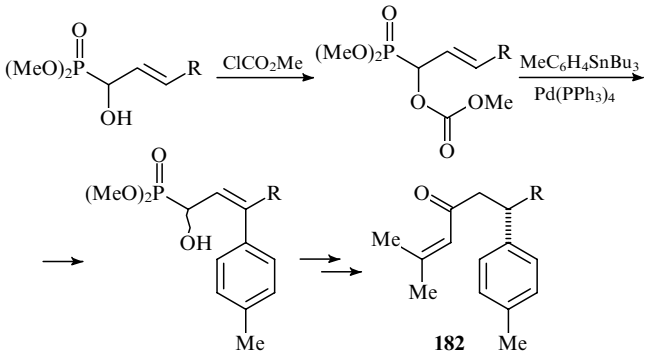
ee 88%–96% **179**

R^1 = Ph, Pr^i, 3,4-$OCH_2OC_6H_3$; R^2 = Et, Ph;

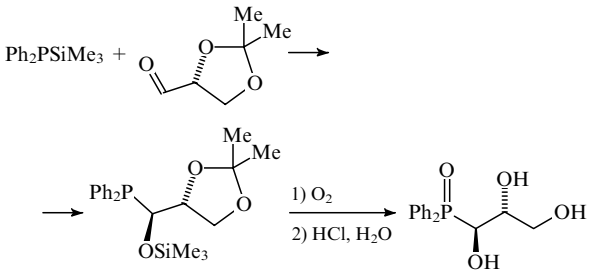


(**181**).

Rowe and Spilling[212] described stereoselective arylation of hydroxyallylphosphonates and used this reaction for the synthesis of (*S*)-(+)-arylturmerone **182**.

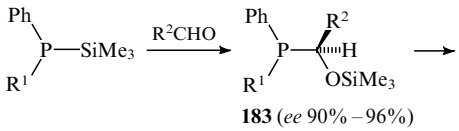


The asymmetric synthesis of (1*S*,2*R*)-(1,2,3-trihydroxypropyl-diphenyl)phosphine oxides, which are structural analogues of the open form of D-erythrose, has been developed.[213]

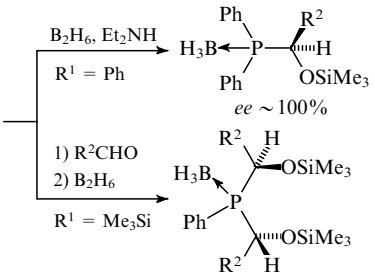


ee 90%

Silylphosphines react with chiral aldehydes with high stereoselectivity to give optically active protected α-hydroxyalkylphosphines **183**. In some cases, the formation of borane complexes is used to increase the optical purity. Bis(hydroxyalkyl)phosphines were also obtained using this reaction and isolated as borane complexes.[213–215]

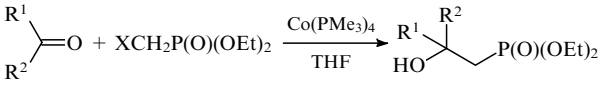


183 (*ee* 90%–96%)



R^1 = Ph, Me_3Si;
R^2 = $H_2N-CH(CH_2Pr^i)-$, $H_2N-CH(CH_2Ph)-$.

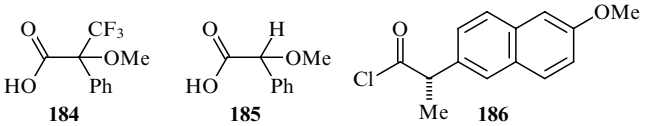
Cobalt complexes are used in the Reformatsky reaction of α-halo phosphonates with ketones or aldehydes to obtain diverse β-hydroxy phosphonates.[216]



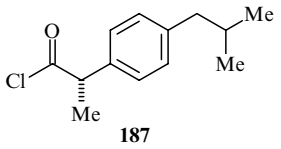
R^1, R^2 = H, Alk, Ar; X = Cl, Br, I.

III. Determination of the absolute configuration of hydroxy phosphonates

To determine the enantiomeric purity of dialkyl 1-hydroxyalkylphosphonates, modification by chiral reagents, resulting in the formation of diastereomeric derivatives, is used most often. In most studies, hydroxy phosphonates are modified by esterification with Mosher's acid **184**,[217–219] camphoric acid[220] and mandelic acid **185**,[221] amino acids[222,223] or with diazaphospholidine derivatives.[224] (*S*)-Naproxen® (**186**) and (*S*)-Ibuprofen® (**187**) chlorides are convenient chiral reagents for determining the enantiomeric purity of 1-hydroxy- and 2-hydroxyalkylphosphonates by means of ^{31}P NMR spectroscopy.[219] The ^1H NMR spectroscopy of chiral 1-(1-naphthyl)ethylammonium salts of hydroxy phosphonic acids,[225] NMR in chiral media, GLC on capillary columns with chiral sorbents[146] and other methods[226,227] are also used.



184 **185** **186**

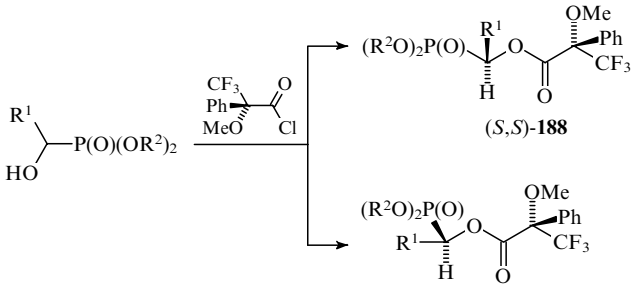


187

Esterification of hydroxy phosphonates with optically active Mosher's acid **184** is a convenient method for determining their optical purity and absolute configuration.[217–219] The diastereomeric esters formed can be analysed by ^1H, ^{19}F and ^{31}P NMR spectroscopy. The signals of the P atoms in the ^{31}P NMR spectra of (*S*)-hydroxy phosphonate esters **188** are usually located in a lower field than those of (*R*)-hydroxyphosphonates **189** (Table 1). This is due to shielding of the phosphorus atom in ester (*R*)-**189** by the phenyl group. The substantial difference between the chemical shifts ($\Delta\delta_P$ = 0.40 – 1.09 ppm) allows reliable determination of the absolute configurations of hydroxyphosphonates.

Table 1. Chemical shifts (δ_P) in the ^{31}P NMR spectra of Mosher's esters.[217–219]

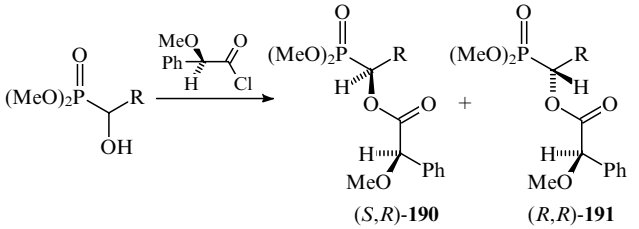
Mosher's ester		δ_P, in the spectrum of		$\Delta\delta$ =
				$=\delta(S)-\delta(R)$
R^1	R^2	*S*-isomer	*R*-isomer	
Et	Me	22.21	21.77	0.44
Pr^i	Et	19.33	18.93	0.40
n-C_5H_{11}	Et	19.90	19.43	0.47
$BnCH_2$	Pr^i	17.42	17.01	0.41



(*S*,*S*)-**188**

(*S*,*R*)-**189**

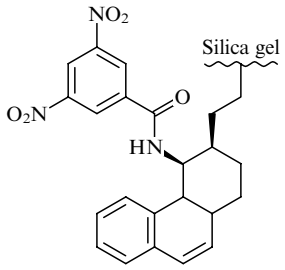
Kozlowski *et al.*[221] determined the enantiomeric purity and the absolute configuration of α-hydroxy phosphonates using esterification with mandelic acid. The upfield or downfield shifts of the signals for the methyl-group protons in the ^1H NMR spectra of compounds **190** and **191** depend on the arrangement of the phenyl group in the molecule and its shielding effect. The absolute configurations of compounds **190** and **191** were additionally proved by X-ray diffraction analysis.



(*S*,*R*)-**190** (*R*,*R*)-**191**

R = PhCH=CH.

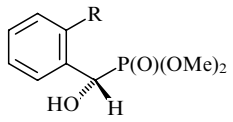
Aryl(hydroxymethyl)phosphonates were separated by HPLC on chiral stationary phase.[228] It was noted that (*R*)-(+)-hydroxyphosphonates are retained by the chiral stationary phase (3*R*,4*S*)-WHELK-01 more strongly than (*S*)-(−)-hydroxyphosphonates. This is due to the formation of a stronger hydrogen bond between the oxygen atom of the P=O group and the hydrogen atom of the amide NH group in the case of *R*-isomers than between the hydroxyl and NH groups in the case of (*S*)-hydroxyphosphonates.



(3*R*,4*S*)-WHELK-01

The absolute configuration of hydroxy phosphonates is also determined by means of circular dichroism spectra.[92,114,178] For example, Wynberg and co-workers[92] used the CD spectra to

determine the absolute configuration of a number of chiral α-hydroxy phosphonates **192**. The enantiomers having *S*-configuration show a negative Cotton effect at 225 nm.



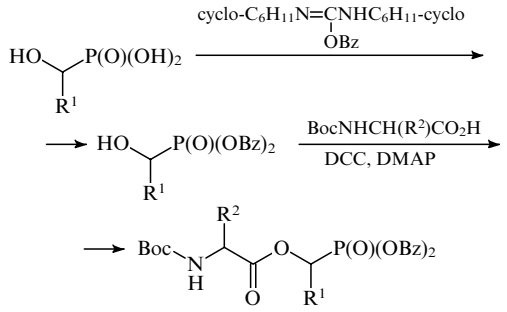
192

R = H, F, Cl, Br, NO_2, NH_2.

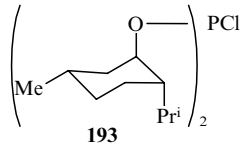
Yokomatsu *et al.*[114] used the CD spectra to determine the absolute configuration of 1,2-dihydroxyphosphonates **91**. It was found that α,β-dihydroxy phosphonates having the (1*S*,2*S*)-configuration show a positive Cotton effect at 210–230 nm, whereas (1*R*,2*R*)-isomers show a negative Cotton effect at these wavelengths.

The enantiomeric composition of hydroxy phosphonates is determined using NMR spectroscopy in the presence of quinine, which is an efficient chiral solvating agent. The hydroxy phosphonate enantiomers are readily distinguished by ^1H and ^{31}P NMR spectroscopy.[227,229,230] No resolution of the enantiomer signals in the ^{31}P NMR spectra of 1-hydroxy- and 2-hydroxyalkylphosphonates was observed where quinine was replaced by brucine, cinchonine, ephedrine or 1-phenylethylamine.

Yet another method for determining the enantiomeric composition of chiral 1-hydroxyalkylphosphonic acids is the ^{31}P NMR study of the diastereomeric derivatives obtained by the reaction of these acids with *N*-substituted L-amino acids.[222]



Dimenthyl phosphorochloridite **193** is a convenient reagent for determination of the enantiomeric composition of hydroxy phosphonates (as well as amines, amino acids and alcohols).[231] The diastereomeric hydroxy phosphonate derivatives formed upon the reaction with this reagent differ appreciably in the chemical shifts δ_P; therefore, the stereomer ratio can be easily determined by integrating the ^{31}P NMR signal intensities.

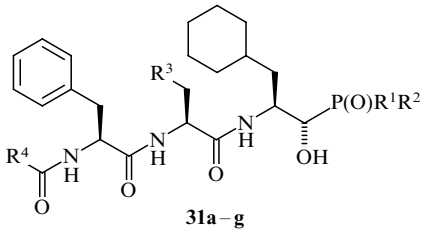


193

IV. Biological activities of hydroxy phosphonates

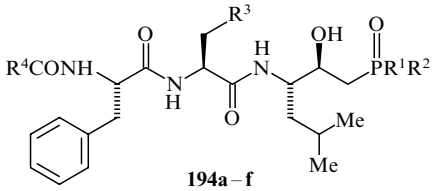
Being structural analogues of hydroxy carboxylic acids, in which the carboxy group has been replaced by the phosphonate group,[2] hydroxy phosphonic acids function as their substrates, as they compete with the carboxy-containing analogues for the active sites of the enzymes and cell receptors.[232–236] The structural differences between the CO_2H and $P(O)(OH)_2$ groups do not prevent hydroxy phosphonic acids from serving as substrates for the enzymes that usually interact with hydroxycarboxylic acids. Thus, hydroxy phosphonic acids inhibit the enzymes involved in the metabolism of hydroxy carboxylic acids, thus affecting various biological processes in the cell.[237] They behave as antibacterial agents, neuroactive compounds, antitumour agents, and so on.[71,72,238] Therefore, study of the biological activities of hydroxy phosphonates appears promising for the development of new bioregulators and drugs.[238–246]

Patel *et al.*[8] found that phosphonopeptides **31a–g**, containing a hydroxy group at the α-carbon atom, inhibit the proteolytic enzyme renin, which possesses an angiotensinogenic action (Table 2). Angiotensin is a powerful octapeptide bioregulator possessing vasoconstrictive properties and increasing blood pressure. It was found that for attaining high activities of compounds **31a–g**, the presence of at least one alkoxyl group at phosphorus is required.



31a–g

Dellaria *et al.*[242] reported renin inhibitors **194a–f** (see Table 2), which are phosphonate analogues of the natural substrate renin **195**. Pseudo-peptides **194a–e** (R^3 = Im) contain both a fragment of the natural structure Phe[8]-His[9] and a new phosphostatine fragment whose presence induces a 130-fold boost in the activities of compounds **194** as compared with the natural substrate **195**.

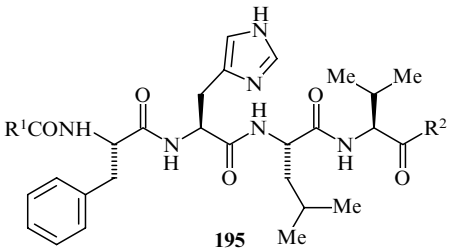


194a–f

Table 2. Effect of the substituent structure in the molecules of phosphonopeptides **31** and **194** on the 50% inhibition concentration (IC_{50}) of renin.[8,242]

Compound [a]	R^1	R^2	R^3	R^4	IC_{50} /nmol litre^{-1}
31a	OEt	OEt	Pr^i	Bu^tO	28±3
31b	OEt	OEt	Pr^i	cyclo-C_5H_9	38±8
31c	OMe	OMe	Pr^i	Bu^tO	10±1
31d	OMe	OMe	Pr^i	cyclo-C_5H_9	16±1
31e	OMe	OMe	Pr^i	$H_2N(CH_2)_5$	31±4
31f	OMe	OMe	Pr^i		8.5±1.4
31g	OMe	OMe	Im [b]		41±14
194a (2*R*)	OMe	OMe	Im	Bu^tO	39
194a (2*S*)	OMe	OMe	Im	Bu^tO	90
194b	OEt	OEt	Im	Bu^tO	72
194c	OMe	OMe	Im	Bu^tCH_2	47
194d	OMe	OMe	Im	EtO	50
194e	$O(CH_2)_2O$		Im	Bu^tO	80
194f	OMe	OMe	Pr^i	Bu^tO	20

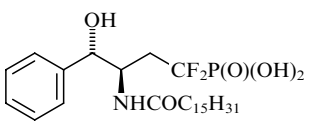
[a] Compounds **31a–g** have 2*S*-configuration; compounds **194b–f** have 2*R*-configuration; [b] Im is imidazolyl.



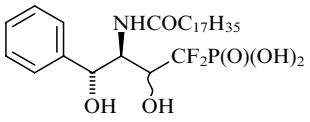
195

R^1, R^2 are peptide residues.

N-Palmitoylsphingosine 1-phosphate analogue **196**, containing a hydrolytically stable difluoromethylphosphonic fragment, is a sphingomyelinase inhibitor (IC_{50} = 3.3 μmol litre^{-1})[240] with the same level of activity as schyphostatin, the most potent known low-molecular-mass inhibitor of this enzyme. Compound **197** inhibits non-competitively neutral sphingomyelinase in bovine brain microsomes, having IC_{50} = 400 μmol litre^{-1} (Ref. 246). Phosphonic acid **197** prevents the action of the tumour necrosis factor TNF-α by inducing neuron PC 12 death at a concentration of 0.1 μmol litre^{-1}.



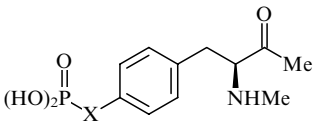
196



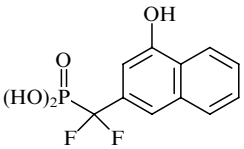
197

Non-competitive sphingomyelinase inhibitors have also been described in another study.[228]

Phosphonic acids **198** and **199** inhibit human phosphoprotein tyrosine phosphatase (PTP-1B) with IC_{50} in the range 57.9–718.1 nmol litre^{-1} (Refs 238, 244–246). Phosphoprotein tyrosine phosphatase catalyses the abstraction of the phosphate group from the tyrosine residue in the molecules of phosphorylated proteins and enzymes, thus inactivating them. Compounds **198** and **199**, which inhibit dephosphorylation of the VEGFR (vein endothelium growth factor), induce fast division of endothelial cells of human umbilical cord vein.[244] The introduction of the second difluoromethylphosphonic fragment into the phosphonic acid molecule increases the inhibitory activity.[247] The protein tyrosine phosphatase inhibitors exhibit a pharmacological action in the therapy of some diseases.[108, 247]



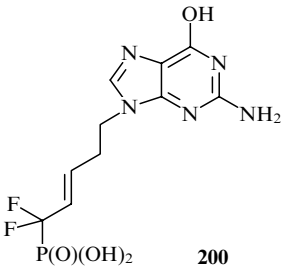
198



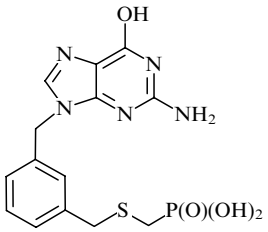
199

X = CF_2, CHF, CHOH.

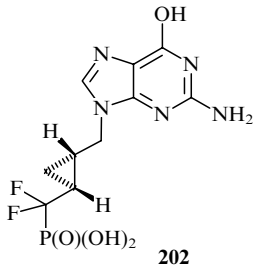
Shibuya and co-workers[195] reported that purine-containing phosphonic acids **200**–**202** inhibit purine nucleoside phosphorylase (PNP). The PNP inhibitors are efficient in the therapy of proliferative diseases (T-cell leukemia, gout, some types of malaria). The introduction of a cyclopropane fragment, restricting the conformational mobility of the molecule, into the *N*-alkyl substituent enhances the inhibitory activity of compounds. For example, compound **202** has a 2400 times higher inhibitory activity with respect to PNP than compound **200**.[195] The replacement of the guanine residue by hypoxanthine also increases the inhibitory activity of hydroxy phosphonates.



200

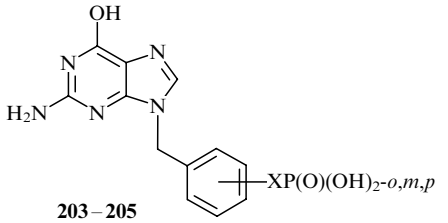


201



202

Phosphonic acid derivatives **203**–**205** of the N^9-benzylguanine series actively inhibit PNP isolated from calf spleen or human erythrocytes. Fluorine-containing compounds are more active than their non-fluorinated analogues.[207]



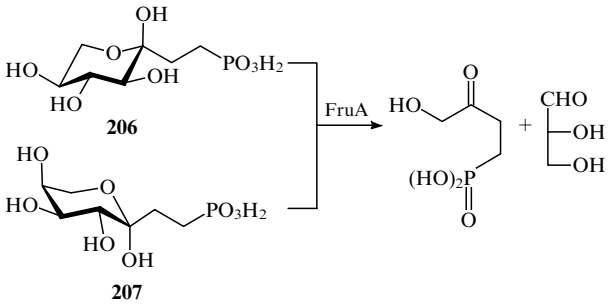
203–**205**

X = CH_2CF_2, $CHFCF_2$, (*E*)-CH=CF, (*E*)-CH=CH, $O(CH_2)_2CF_2$, $O(CH_2)_3$.

Difluoromethylphosphonates **158** behave as effective inhibitors of aspartate-β-semialdehyde dehydrogenase (ASA-DH) from *Escherichia coli*.[202]

Among the biologically active hydroxy phosphonates, interesting antibacterial and antiviral agents have been found;[248–250] an example is (1*R*,2*S*)-(−)-l,2-epoxypropylphosphonic acid (phosphomycin, **42**), isolated from the culture medium of *Streptomyces fradiae* or *Pseudomonas syringae*.[1]

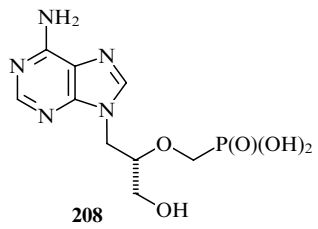
Phosphonic acids **206** and **207** are structural analogues of the aldolase substrate,[249] the enzyme catalysing cleavage of fructosyl 1-phosphate into D-glyceraldehyde and dihydroxyacetone phosphate (DHAP) occurring in the liver.



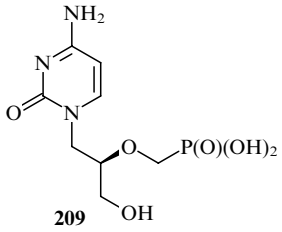
206

207

Hydroxy phosphonate derivatives containing residues of heterocyclic bases exhibit a high antivariolic activity in the epithelial cells and organotypic cultures.[250] The most active compounds of this type are 9-(*S*)-(3-hydroxy-2-phosphonomethoxypropyl)adenine [(*S*)-HPMPA, **208**], 9-(*S*)-(3-hydroxy-2-phosphonomethoxypropyl)-2,6-diaminopurine and 1-(*R*)-(3-hydroxy-2-phosphonomethoxypropyl)cytosine [(*R*)-HPMPC, **209**], known as cidofovir, efficient against human cytomegalovirus and the smallpox virus.

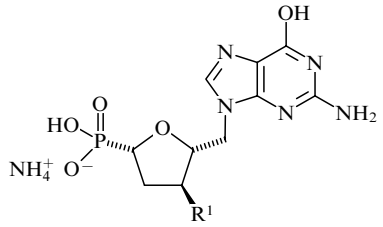


208



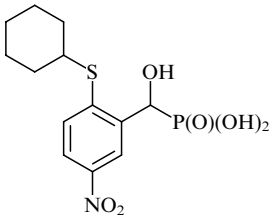
209

On the basis of hydroxy phosphonates, antitumour drugs have been developed.[251–258] Nucleoside phosphate analogues **210** exhibit high antitumour activities in several lines of human malignant cells.[253] Hydroxy phosphonic acids **211** have been proposed as inhibitors of phosphoprotein tyrosine phosphatase CD 45, which plays an important role in the inactivation of the protein growth factors and stabilisation of fast proliferation of the hematopoietic cells.[254] The 5-methylenephosphonate analogue of D-*myo*-inositol-1,4,5-triphosphate **212** behaves as an intracell messenger, favouring the opening of calcium channels and liberation of calcium ions.[251]

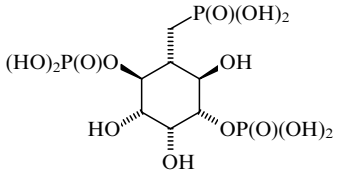


210

R^1 = OH, OMe; R^2 = OH, NH_2.



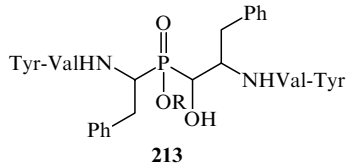
211



212

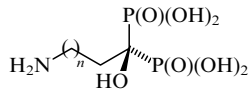
Hydroxy-[4-(5,6,7,8-tetrahydronaphthyl-1-oxy)phenyl]methylphosphonate is an inhibitor of *myo*-inositol monophosphatase, the activity of which with respect to the recombinant bovine brain enzyme corresponds to the inhibition constant K_i = 20 μmol litre^{-1} (Ref. 252).

Compounds **213** inhibit HIV protease and are promising for AIDS therapy.[255] The IC_{50} values of these compounds with respect to HIV protease are in the nanomolar range.

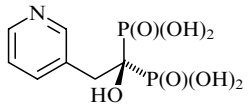


213

Hydroxyalkylbis(phosphonates) are used as pharmacological agents for the therapy of some diseases such as osteoporosis, hypercalcinemia and some kinds of malignant tumours.[257–260] The most important among them are Pamidronate (**214**) (also retards bone resorption), Alendronate (**215**), Risedronate (**216**) and zolendronic acid (**217**).[259]

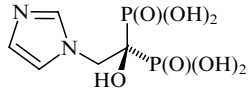


214, **215**



216

n = 1 (**214**), 2 (**215**).



217

The bis-phosphonate derivative of 3-azido-3-deoxythymidine exhibits an antiviral activity in the therapy of AIDS[260] and is registered as Zidovudine.

Some hydroxyalkylphosphonates are plant growth regulators. A number of unsaturated cyclic hydroxy phosphonates synthesised by the reaction of 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphinanes with 2-epoxy-5-aryl-(2*E*,4*E*)-pentadienecarboxaldehydes function as wheat stem growth inhibitors.[261]

Aminohydroxy phosphonates are promising as bidentate ligands for the formation of complexes with transition metals.[262, 263] For example, copper(II) and zinc(II) complexes of alkyl- and aryl-substituted 2-amino 1-hydroxy phosphonates were studied in an aqueous solution by potentiometry and spectroscopy. A comparison of the stability constants shows that these ligands coordinate Cu^{2+} and Zn^{2+} more efficiently than amino phosphonates containing no hydroxy group.[262]

V. Conclusion

The present review considers various methods of asymmetric synthesis, enzymatic, kinetic and chromatographic separation, and some other ways of preparing enantiomers of hydroxy phosphonates with high optical purity. It is noteworthy that, despite the impressive progress attained in the synthesis and study of the properties of hydroxy phosphonates, the problems existing in the chemistry of these compounds are far from being completely solved. The search for enantioselective methods opening an easy route to optically active hydroxy phosphonates still remains topical. Therefore, the development of efficient catalysts for asymmetric phospho-aldol Abramov reaction and for the reduction of keto phosphonates appears especially important. The scope of chemical modification of hydroxy phosphonates aimed at introducing new, more complex, in particular, chiral groups to the carbon, oxygen and especially phosphorus atom is far from being exhausted. The separation of enantiomers and purification of hydroxy phosphonates remain topical tasks. Exact determination of the structure and the absolute configuration of these compounds can be successfully carried out only in some cases.

One can expect that hydroxy phosphonates will remain the subject of intensive research, especially in the field of biological activities and use of these compounds as drugs and bioregulators. In addition, hydroxy phosphonates, their derivatives and analogues can find practical use as synthetic receptors and chiral ligands in metal complexes and selective highly efficient complexones, extractants and analytical reagents.

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[a] — *Russ. J. Gen. Chem. (Engl. Transl.)*
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