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Asymmetric synthesis of hydroxyphosphonates

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Abstract—Hydroxyphosphonates have attracted considerable attention as biologically active compounds, enzyme inhibitors, and drugs. Over the last few years significant interest in the asymmetric synthesis and practical application of chiral hydroxyphosphonates has been reported, which shows the theoretical interest and the practical importance of hydroxyphosphonates. An overview of recent synthetic approaches to chiral hydroxyphosphonates and determinations of their absolute configuration is presented. Data on the practical applications of hydroxyphosphonates are also discussed.

Contents

1. Introduction

Hydroxyphosphonic acids are an important class of compounds, which occur in Nature. Until 1959, naturally occurring organophosphorus compounds containing the C–P bond were unknown.[1–3] In 1959, Horiguchi and Kandatzu[3] first isolated from living things compounds containing a C–P bond. Soon after many new types of related compounds have been found in hundreds of aquatic and terrestrial animals and microorganisms. Typical representatives of natural hydroxyphosphonic acids are phosphonothrixin **1** (PTX) (Scheme 1), dihydroxyphosphonic acid (FR-33289) **2**, hydroxy-2-aminoethylphosphonic acid (HO-AEP), 1,5-dihydroxy-2-oxopyrrolidinphosphonic acid (SF-2312), and others.[1,2] There has been significant interest in (1*R*,2*S*)-(−)-(l,2-epoxypropyl) phosphonic acid, also known as fosfomycin, which is a cell-wall active antibiotic isolated from the fermentation broth of *Streptomyces fradiae* or *Pseudomonas syringae*.[1] Many of these compounds have attracted attention because of their antibacterial, antiviral, antibiotic, pesticidal, anticancer, and enzyme inhibitor properties.[4–8]

Substituted hydroxyphosphonic acids constitute a class of mimics of natural hydroxycarboxylic acids, in which a carboxylic group is replaced by phosphonic or related

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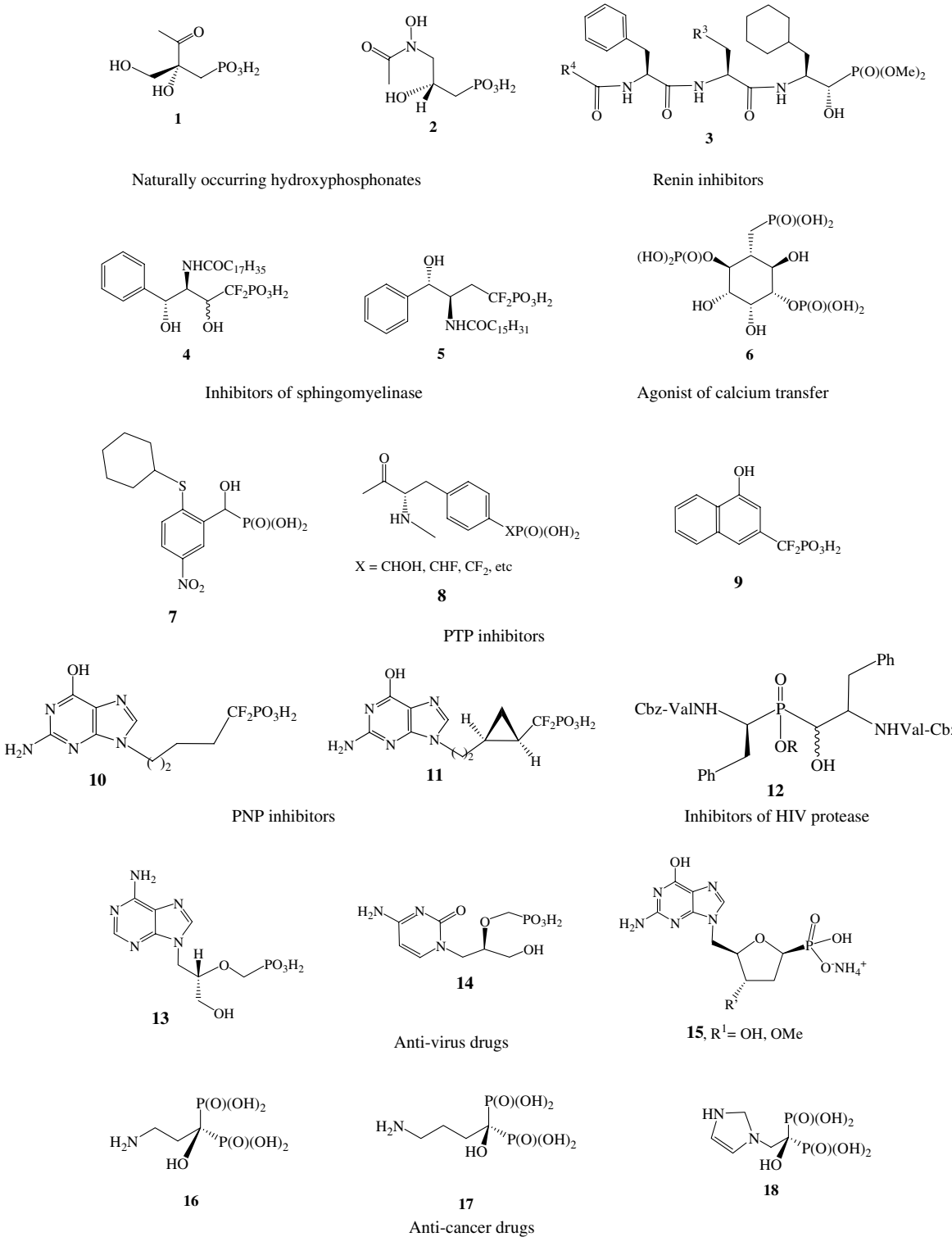


Scheme 1. Selected examples of natural and synthetic biologically active hydroxyphosphonates.

function.[4] The replacement of the carboxyl group in 'normal' hydroxycarbonic acids by a phosphonic group, means that they display an inhibiting effect to fermentation receptors which usually interact with natural hydroxycarboxylic acids.[9–13] Acting as antagonists of these acids, hydroxycarboxylic acids inhibit enzymes involved in carboxylic acid metabolism and thus affect a variety of physiological processes.[14–16] For example, phosphonopeptide **3** efficiently inhibits human renin, the enzyme which specifically catalyses the conversion of angiotensinogen to angiotensin.[17]

The phosphonic acid derivatives β-hydroxyphosphonates, α-hydroxy-β-aminophosphonates, polyhydroxyphosphonates, and difluoromethylenephosphonates all show potent biological activity as inhibitors of

enzymes.[18–31] Some hydroxyphosphonates act as inhibitors of the enzyme *myo*-inositol monophosphatase.[29,30] For example, the inhibitory potency of hydroxy-[4-(5,6,7,8-tetrahydronaphthyl-1-oxy)phenyl]methylphosphonate toward the recombinant bovine brain enzyme was on the level $K_i = 20$ μM.[30] The C–P analogues of *N*-palmitoylsphingosine-1-phosphates **4** and **5** efficiently inhibit sphingomyelinase,[15] with the same level of inhibitory activity as schyphostatin, the most potent of the few known small molecular inhibitors of sphingomyelinase.[22] The 5-methylenphosphonate analogue of *myo*-inositol-1,4,5-triphosphate **6** is an agonist of calcium transfer.[29] Hydroxyphosphonate **7** is an inhibitor of CD-45 tyrosine phosphatase, which is an important player in the regulation of cell activation and proliferation in haematopoetic cells.[32]

Phosphonic acids **8** and **9** inhibit human protein tyrosine phosphatase (PTP).[18–24] Inhibitors of PTP have been shown to have high pharmacological activity in the treatment of different diseases.[25] 1,1-Difluoroalkylphosphonic acids **10** and **11** inhibit purine nucleoside phosphorylase (PNP).[26] These substances treat a leukaemia of T-cages, podagra, and malaria.

It was found that the introduction of cyclopropyl groups in a side chain of hydroxyphosphonates increases the PNP inhibiting activity of compound **10**.[27] The conformationally constrained compound **11**, containing a cyclopropyl group is 2400-fold more potent than compound **10**.

Hydroxyphosphonates display high antibacterial, antiviral, anticancer activity,[28–39] for example, compound **12** inhibits HIV protease, and are prospective drugs for the treatment of AIDS.[33] Hydroxyphosphonates **13**–**15** are efficient medicines against smallpox. Compound **14**, known as Cidofovir, is used as an antiviral medication for the treatment of cytomegalovirus infections as well as smallpox.[28]

Some hydroxyphosphonates possessing potent antitumour activity are used for the treatment of cancer.[29–36] For example, hydroxyalkyl-bis-phosphonates **16**–**18** demonstrate antiproliferative activity in several human cancer cell lines with IC_{50} values in the μM range.[31] Compounds **16**–**18** have also been applied in the treatment of bony rarefication, hypercalcaemia, and malignant tumours.[35–38] The bis-phosphonate derivative of 3-azido-3-deoxythymidine (AZT), which has the commercial name 'Zidovudine', was registered as an anti-HIV drug and used in the treatment of AIDS.[36]

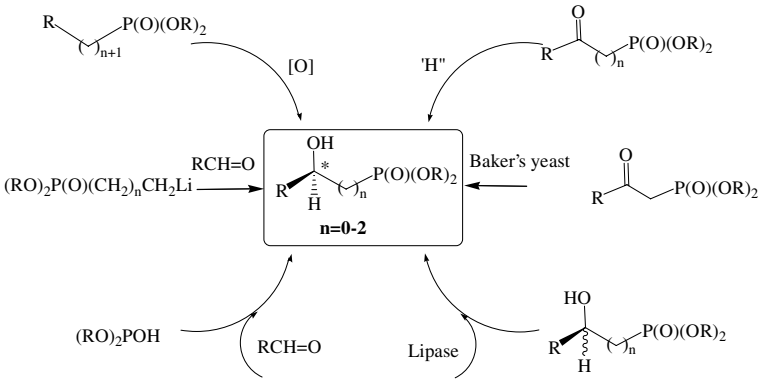
It has been established that the biological activity of phosphonic acids is largely determined by the absolute configuration of the stereogenic α-carbon atom. For example, of the four possible diastereomers of the antibiotic Alaphospholine, the greatest activity against pathogenic microorganisms is shown by the (*S*,*R*)-diastereomer. The three other stereoisomers are much inferior to this compound in activity (see Ref. 39 and the literature referred to therein).

Over the last 10 years, a significant number of methods for the asymmetric synthesis and practical application of chiral hydroxyphosphonates has been reported, which clearly show the theoretical interest and practical importance of hydroxyphosphonates. The aim herein is to systematize and generalize the data published over the last 10–15 years related to the study of chiral hydroxyphosphonates.

2. Asymmetric synthesis of hydroxyphosphonates

The fast development of the chemistry and biology of hydroxyphosphonates over the last decade has been determined by the development of highly effective methods for their preparation.[40,41] Chiral hydroxyphosphonic acids can be prepared by various methods such as kinetic resolution, chemoenzymatic synthesis, and asymmetric synthesis.

The main method for the synthesis of hydroxyphosphonates is the phosphonylation of carbonyl compounds. Two methods for asymmetric phosphonylations of carbonyl compounds are known: the phospho-aldol addition (the Abramov reaction) and reaction of phosphonate carbanions with aldehydes or ketones (Scheme 2).[42,43] Chemoenzymatic synthesis also constitutes a widespread methodology for the preparation of optically active hydroxyphosphonates.[44] Other useful methods for the



Scheme 2. Synthetic routes to chiral hydroxyphosphonates.

synthesis of hydroxyphosphonates are the enantioselective reduction of ketophosphonates,[45] enantioselective hydroxylation of phosphonate stabilized carbanions,[46] and [2,3]-sigmatropic Wittig rearrangements.[47]

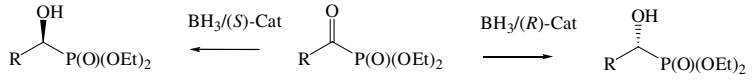
2.1. Asymmetric reduction

The asymmetric reduction of ketophosphonates is one of the most convenient methods for the synthesis of chiral hydroxyphosphonates.[48–59] The asymmetric reduction can occur under the control of chiral auxiliaries, which are included in the ketophosphonate, under the control of asymmetric catalysts, or chiral reagents.

The reduction of diethyl α-ketophosphonates **19** with borane in the presence of chiral β-butyloxazoborolidines as a catalyst (Cat) yielded the diethyl 1-hydroxyalkylphosphonates (*S*)-**20** or (*R*)-**20** in good yields and moderate enantiomeric excesses (53–83% ee).[48] Acylphosphonic and bis-acylphosphonic acid sodium salts were directly reduced by sodium borohydride to the corresponding hydroxyphosphonates and dihydroxyalkanebisphosphonates.[50] The reduction of [(*N*-*p*-toluenesulfonyl)amino]-β-ketophosphonates **21** with different borohydrides gave [(*N*-*p*-toluenesulfonyl)amino]-β-hydroxyphosphonates **22** and **23** in good chemical yields and moderate diastereoselectivity. Only the zinc borohydride reduction of **21** resulted in the formation of *anti*-β-hydroxy-γ-aminophosphonates **22** with good diastereoselectivity (Scheme 3).[52]

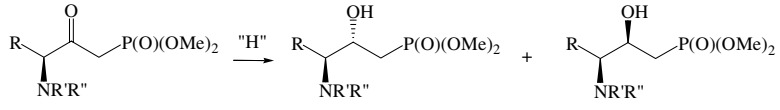
The reduction of ketophosphonates **26** with sodium borohydride in THF proceeded with low stereoselectivity (~30–35% de),[51] which was increased via the formation of a chiral complex of sodium borohydride with natural (*R*,*R*)-tartaric acid.[54b] The reduction of ketophosphonates **26** with this chiral complex afforded the diethyl (1*S*)-α- and β-hydroxyphosphonates with ~ 60–85% ee and the dimenthyl (1*S*)-α-hydroxyphosphonate **28** with diastereomeric purities of 80–93% (Scheme 4). The reduction of dimenthyl ketophosphonates with the unnatural (*S*,*S*)-tartaric acid/$NaBH_4$ proceeded with lower stereoselectivity than in case of diethyl ketophosphonates. For example, the reduction of dimenthyl 1-phenylketophosphonate with this complex afforded the corresponding hydroxyphosphonate only with 45% de. Evidently the asymmetric inductions of (1*R*,2*S*,5*R*)-menthyl groups and of (*R*,*R*)-tartaric acid went in the same direction and increased the resulting stereoselectivities (entry 5, matched double asymmetric induction), whereas the asymmetric inductions of (1*R*,2*S*,5*R*)-menthyl groups and of (*S*,*S*)-tartaric acid act in opposite directions, reducing the resulting stereoselectivities (entry 6, mismatched double asymmetric induction).[54c]

This methodology was applied to the synthesis of (*S*)- and (*R*)-phosphocarnitines **32** and **33** with both enantiomers being prepared using the (*R*,*R*)- and (*S*,*S*)-tartaric acid (Scheme 5).[54] In the first step, the diethyl 3-chloro-2-oxopropylphosphonate **29** was reduced with the formation of diethyl 3-chloro-2-oxopropylphosphonate **30**, which is the precursor of the phosphocarnitine. Additionally, phosphonate **30** was dealkylated and the free phosphonic acid **31** treated with an aqueous solution of trimethylamine to provide the phosphocarnitines



(*S*)-**20** **19** (*R*)-**20**

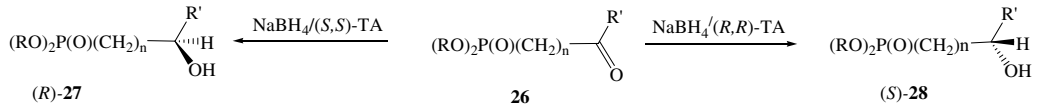
Cat=β-butyloxazoborolidine, R=Et (80% *ee*), Bu (53% *ee*), *i*-Bu (76% *ee*), Ph (82% *ee*)



21 **22**, *Anti* **23**, *Syn*

R	R'	R"	"H"=Hydride	Yield (%)	*dr*	Ref
i-Pr	H	*p*-Ts	$LiBH_4$/THF	98	53: 47	51a
i-Pr	H	*p*-Ts	$NaBH_4$/MeOH	99	81: 19	51a
i-Bu	H	*p*-Ts	$NaBH_4$/MeOH	98	29: 71	51a
Ph	H	*p*-Ts	$NaBH_4$/MeOH	97	63: 37	51a
Ph	H	Bn	$NaBH_4$/MeOH	75	63: 37	51b
i-Pr	Bn	Bn	$NaBH_4$/THF	44	85: 15	52
i-Pr	H	*p*-Ts	$Zn(BH_4)_2$/THF	91	77: 23	51a
Ph	H	Bn	$Zn(BH_4)_2$/THF	80	88: 12	51b
i-Pr	H	Bn	$Zn(BH_4)_2$/THF	85	96: 4	51b

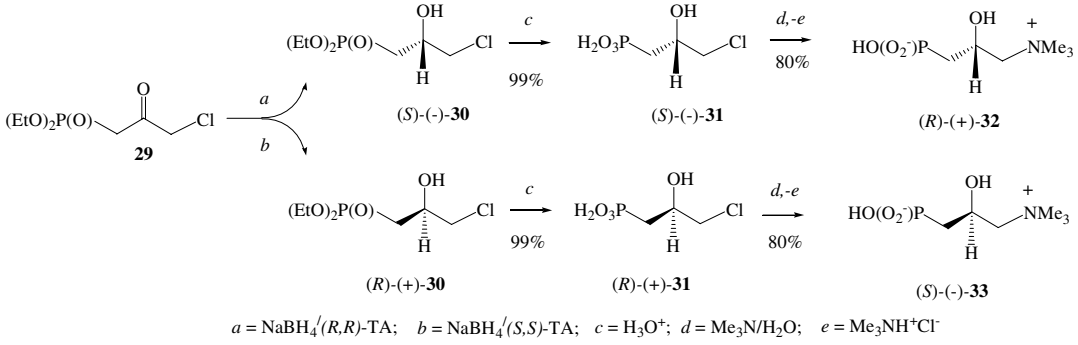
Scheme 3. Borane reduction of ketophosphonates.



entry	R	R'	*n*	TA	Yield of **27**,**28** (%)	*ee (or de)* of **27**,**28**(%)	Config
1	EtO	CH_2Cl	1	*R*,*R*	80	85	*S*
2	EtO	CH_2Cl	1	*S*,*S*	80	85	*R*
3	EtO	Ph	1	*R*,*R*	95	60	*S*
4	EtO	Ph	0	*R*,*R*	95	80	*S*
5	Mnt	Ph	0	*R*,*R*	95	93	*S*
6	Mnt	Ph	0	*S*,*S*	95	46	*R*
7	Mnt	C_6H_4F-2	0	*R*,*R*	97	82	*S*
8	Mnt	Bu-*t*	0	*R*,*R*	90	~100	*S*
9	Mnt	C_6H_4OMe-2	0	*R*,*R*	96	71	*S*
10	Mnt	Pr-*i*	0	*R*,*R*	98	68	*S*
11	Mnt	*a*	0	*R*,*R*	97	96	*S*

a–4-Substituted *O*,*O*-methyleneresorcine; TA = tartaric acid

Scheme 4. Stereoselective reduction of ketophosphonates **26**.



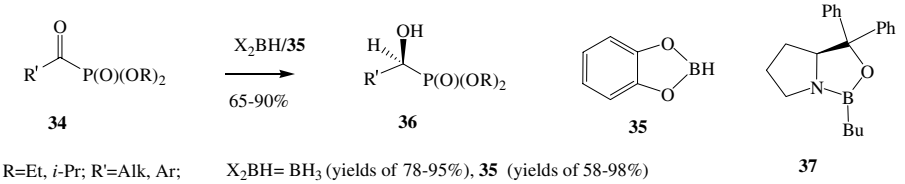
Scheme 5. Synthesis of (*S*)- and (*R*)-phosphocarnitines **32** and **33**.

in good enantiomeric excesses. The phosphocarnitines **32** and **33** were isolated as colourless pure solids.

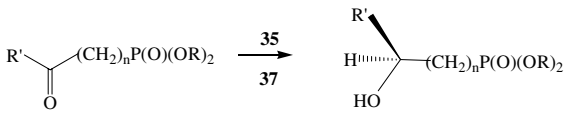
The enantioselective reduction of arylketophosphonates **34** with either catecholborane **35** or borane/dimethylsulfide complex in the presence of a 1,3,2-oxazaborolidine catalyst **37** provided chiral α-,β- and γ-hydroxyphosphonates **36**. The reduction of α-ketophosphonates **34** with (*S*)-oxazaborolidine-catecholborane led to the formation of (*S*)-1-hydroxylkylphosphonates **36** and, correspondingly, the reduction with the (*R*)-oxazaborolidine-catecholborane afforded (*R*)-1-hydroxylkylphosphonates **36** with the same stereoselectivity (53–83% ee) (Scheme 6).[45,55,56] Both α-aryl- and α-alkylketophosphonates were reduced using the (*S*)-oxazaborolidine catalyst leading to the (*S*)-configuration in the hydroxyphosphonates.

The reduction of β-phthalimido-α-ketophosphonates with boranes **35** and oxazaborolidine catalyst **37** afforded β-phthalimido-α-hydroxyphosphonates in good yields and high diastereoselectivities.[58] The reduction of β- and γ-ketophosphonates **38** under the same conditions resulted in the β- and γ-hydroxyalkylphosphonates **39** of (*R*)-configurations in moderate yields (~60%) and good stereoselectivities (70–80% ee) (Scheme 7).

The reduction of α-ketophosphonates **40** with (−)-chlorodiisopinocampheylboranes (Ipc_2B–Cl) yielded (*S*)-α-hydroxyphosphonates **41** in 65% enantiomeric



Scheme 6. Oxazaborolidine-catecholborane reduction of α-ketophosphonates **34**.



38 **39**

R=Pr-*i*. R'= XC_6H_4, X=2-MeO, 2-Me, 2Cl, 3Cl, 4Cl, 2F, 2Br, 2MeO, 2Me; n=1,2

Scheme 7. Asymmetric synthesis of β-, γ-ketophosphonates **39**.

excess.[45,56] This method allowed access to α-hydroxy-β-aminophosphonates **42** and β-hydroxy-γ-iminophosphonates **43** (Scheme 8).

The reduction of the γ-*N*-benzylamino-β-ketophosphonate derived from readily available (*S*)-tribenzylated amino acids was achieved with catecholborane to afford γ-amino-β-hydroxyphosphonates in high diastereoselectivity.[51] The reduction of β-keto-γ-*N*,*N*-dibenzylaminophosphonates **44** derived from readily available (*S*)-tribenzylated amino acids with catecholborane resulted in the β-hydroxy-γ-aminophosphonates **45** and **46** in high diastereoselectivity and good yields.[57,58] The results summarized in Table 1 show that the diastereoselectivity of the reduction of *N*,*N*-dibenzylamino-β-ketophosphonates **44** is independent of the steric parameters of the R group at C(3). Diastereomers **44** and **45** were separated and their configuration confirmed by X-ray analysis and NMR spectroscopy. The reduction of dimethyl 3-*N*,*N*-di(α-methylbenzyl)amino-2-ketophosphonates **44** with catecholborane at −78 °C in the presence of $LiClO_4$ gave γ-amino-β-hydroxyphosphonates **45** and **46** in good yield and very good diastereoselectivity (Scheme 9).[53]

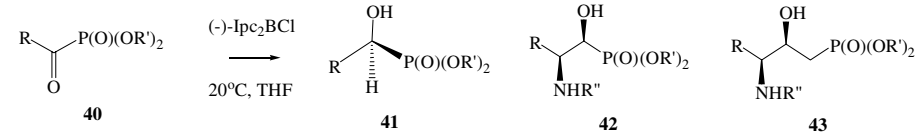
Table 1. Reduction of ketophosphonates **44**

A	Yield (%)	*syn*:*anti*
DIBAL-H	50	82:18
$NaBH_4$	44	85:15
Catecholborane	69	>98:2
Catecholborane	85	>98:2
Catecholborane	89	>98:2
Catecholborane	82	90:10

Enantioselective hydrogenation of (*R*)-α-acetamido-β-ketophosphonate **50** in the presence of a chiral BINAP–Ru(II) complex led to the formation of (1*R*,2*R*)- or (1*S*,2*S*)-hydroxyphosphonates **51** in good yields (54–76%) with high enantio- and diastereoselectivity (~94–98% ee) (Scheme 10).[59a] Asymmetric hydrogenation of β-ketophosphonates and β-ketothiophosphonates **52** with chiral Ru(II) catalysts were described with enantiomeric excesses of **53** of up to 99% being obtained.[59b]

The reduction of Schiff bases obtained from diethyl 1-oxoethyl-2,2,2-trifluorophosphonates and (−)-α-phenylethylamine as chiral auxiliary resulted in the formation of chiral phosphonate analogues of trifluoroalanine in 22% ee.[60]

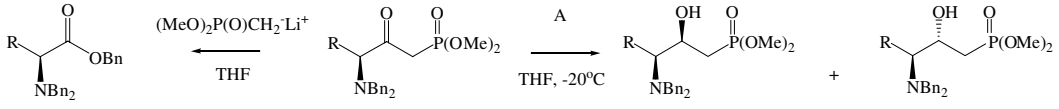
Tomioka et al.[61] reported the photo-reduction of dialkyl ketophosphonates and ethyl acetoacetate. Ketophosphonates have been photo-reduced with the formation of α-hydroxyphosphonates, with quantum yields for the disappearance of ketones ranging from 0.6 to 0.7.



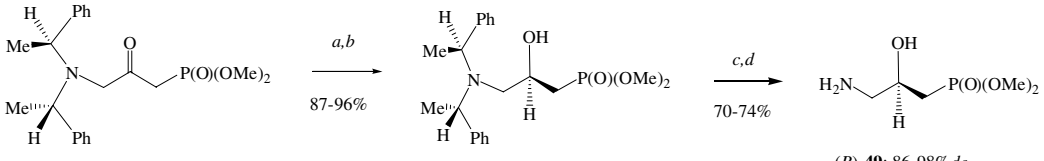
40 **41** **42** **43**

R=Me, Pr-*i*, Bn, Ph; R'=Me, Et, Pr-*i*

Scheme 8. Asymmetric reduction of ketophosphonates **40** with (−)-Ipc_2BCl.



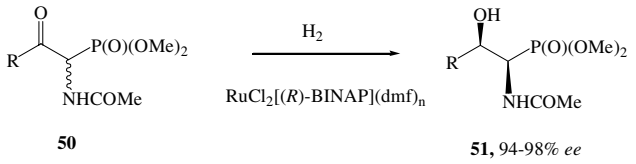
R=Me, Pr-*i*, Bn, Ph **44** *Syn*-**45** *Anti*-**46**



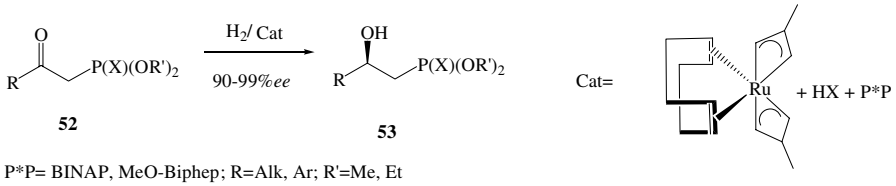
(*S*,*S*)-**47** (*R*,*S*,*S*)-**48**; 86-98%*de* (*R*)-**49**; 86-98%*de*

a = CB; *b*=$LiClO_4$; THF, -20°C; *c* = Me_3SiBr; *d* = H_2, $Pd(OH)_2/C$

Scheme 9. Stereoselective hydroboration of *N*,*N*-dibenzylamino-β-ketophosphonates **44** and **47**.



50 **51,** 94-98% *ee*



52 **53**

P*P= BINAP, MeO-Biphep; R=Alk, Ar; R'=Me, Et

R	R'	Ligand (P'P)	Yield. %	Config	Ee(%)
Me	Et	(*S*)-Binap	100	*S*	99
C_5H_{11}	Me	(*S*)-Binap	100	*S*	98
c-Pr	Et	(*S*)-Binap	100	*S*	94
		(*R*)-MeOBiphep	100	*R*	93
2-thiophen	Et	(*S*)-Binap	93	*S*	70
		(*S*)-MeOBiphep	97	*S*	77
3-thiophen	Et	(*S*)-Binap	100	*S*	94
		(*S*)-MeOBiphep	96	*S*	86
C_0H_{11}	Me	(*S*)-Binap	100	*S*	90
		(*S*)-MeOBiphep	100	*S*	94
i-Pr	Me	(*S*)-MeOBiphep	100	*S*	93
		(*R*)-Binap	100	*R*	92

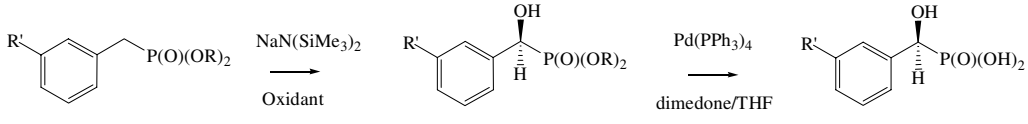
Scheme 10. BINAP–Ru(II) catalyzed hydrogenation of ketophosphonates.

2.2. Asymmetric oxidation

The asymmetric oxidation of carbon–carbon bonds or carbanions is a useful route to a variety of hydroxyl- and dihydroxyphosphonates.[62–72] For example, chiral α-hydroxyphosphonates **55** of high enantiomeric excess (96–98% ee) were prepared by the stereoselective oxaziridine-mediated hydroxylation of dialkyl benzylphosphonates **54**. α-Hydroxyphosphonates **55** were converted into corresponding free phosphonic acids and retained a high degree of stereochemical purity (90–98% ee) (Scheme 11).[46,62]

Asymmetric dihydroxylation of (*E*)-alkenylphosphonates **56** with AD-mix-α or AD-mix-β reagents led to the formation of optically active *threo*-α,β-dihydroxyphosphonates **57** (Scheme 12).[63–65] The highest level of enantioselectivity (>88% ee) was observed in the oxidation of (*E*)-alkenylphosphonates with conjugated aromatic substituents. Enantioselectivities and yields were significantly improved when the dihydroxylation reaction was carried out with the dimethyl phosphonate instead of diethyl phosphonate (Table 2). α,β-Dihydroxyphosphonates **57** reacted regioselectively with *t*-$BuMe_2SiCl$/pyridine/DMF to give the corresponding β-siloxy derivatives **58** in good yield (83%), which under Mitsunobu reaction conditions were converted into the optically active *erythro*-α-amino-β-siloxyphosphonates **59** in moderate yield.[64] Diol **57** (R = *p*-An) via a two-step synthesis (oxidization with $RuCl_3/NaIO_4$ and reduction with $NaBH_4$) was transformed into dioxolane **60** which is a chiron for the asymmetric synthesis of α-heteroatom-substituted phosphonates.[65]

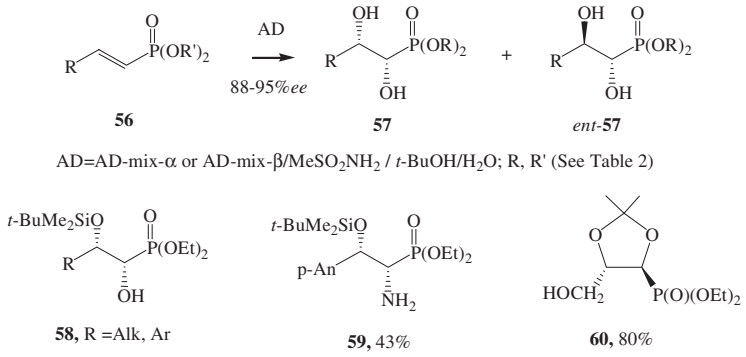
The racemic mixture of 1-acyloxy 2-(*E*)-alkenylphosphonates (*RS*)-**60** was resolved by kinetically controlled



54 (*S*)-**55**, 54-76%

R	R'	Oxidant	X	*ee (%)*	Refs
Me	H		H	69	46
Me	H		Cl	93	46
Me	NO_2		Cl	80	46
Me	Cl		Cl	87	46
Me	MeO		Cl	81	46
Et	CF_3		Cl	98	62
CH_2=$CHCH_2$	H		Cl	96	62
CH_2=$CHCH_2$	PhO		Cl	98	62

Scheme 11. Enantioselective oxidation of benzylphosphonates **26** with chiral oxaziridines.



Scheme 12. Synthesis of *threo*-α,β-dihydroxyphosphonates **57** and their transformations.

Table 2. Asymmetric dihydroxylation of dialkyl 1(*E*)-alkenylphosphonates **56**

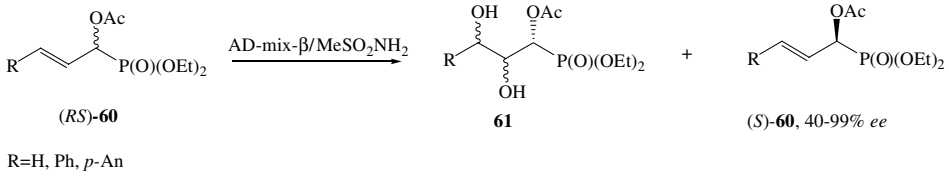
R′	R	AD	Yields (%)	ee (%)
Me	Ph	AD-mix-β	52	97
Et	Ph	AD-mix-α	42	91
Et	4-$MeOC_6H_4$	AD-mix-α	71	95
Et	4-$MeOC_6H_4$	AD-mix-β	69	98
Et	4-ClC_6H_4	AD-mix-α	65	98
Et	1-Naphthyl	AD-mix-α	80	93
Et	*n*-C_7H_{13}	AD-mix-β	63	84
Et	3-$MeOC_6H_4$	AD-mix-α	67	96
Et	2-Furyl	AD-mix-α	17	88

dihydroxylation with AD-mix-α- or AD-mix-β-reagents.[66] The kinetic rate of dihydroxylation was highly dependent upon the configuration of the 1-acyloxy functional group, as well as the nature of substituents at the 3-position. For example, the reaction of a racemic diethyl (*E*)-3-phenyl-1-acetyloxy-2-propenylphosphonate **60** with an AD-mix-β reagent preferentially dehydroxylated the (*R*)-enantiomer with the formation of an inseparable mixture of diastereomers **61** and left the unreacted (*S*)-enantiomer **60** in high enantiomeric purity (99% ee). Conversely the reaction of (*RS*)-**60** with an AD-mix-α reagent allowed to obtain the (*R*)-**60** with 99% ee (Scheme 13).

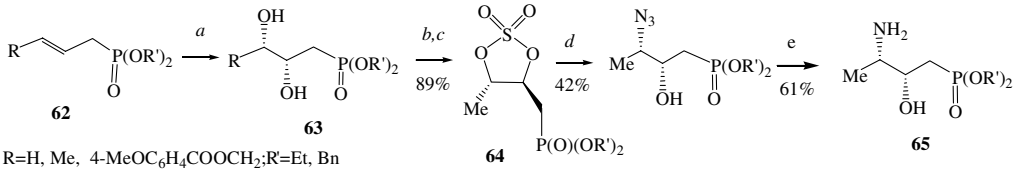
Dihydroxyalkylphosphonates **63** were prepared by asymmetric dihydroxylation of allylphosphonates **62**, which were then transformed into 2-hydroxy-3-aminoalkylphosphonates **65** via the formation of azides **64** and catalytic reduction of the azide groups (Scheme 14).[65,66] Chiral 3-amino-2-hydroxyalkylphosphonates **65** were used in the synthesis of phosphonate analogues of (*R*)-carnitine.[67]

Asymmetric aminohydroxylation of diethyl (*E*)-styrylphosphonates **66** with potassium osmate(VI) dihydrate, toluene sulfonchloramide T and $(DHQD)_2PHAL$ as a chiral ligand led to the (1*R*,2*S*)-*threo*-1-hydroxy-2-aminophosphonic acids **67** in good yields (55–75%) and enantioselectivities from 45% to 92% ee (Scheme 15).[68,69]

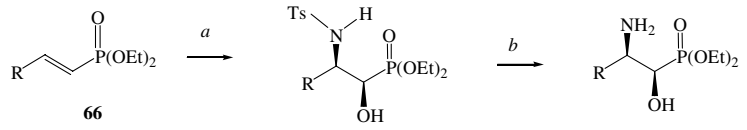
1,2-Dihydroxy-2-arylethylphosphonates and α-hydroxy-β-aminoethylphosphonic acid were prepared via the oxirane ring opening of *trans*-1,2-epoxy-2-arylethylphosphonates.[71,72] Thus, the diastereomeric diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1-benzyloxy-2,3-epoxypropylphosphonates **69**



Scheme 13. Kinetic controlled asymmetric dihydroxylation of alkenylphosphonates.



Scheme 14. Synthesis of aminohydroxyphosphonates **65** via the formation of azides **64**.



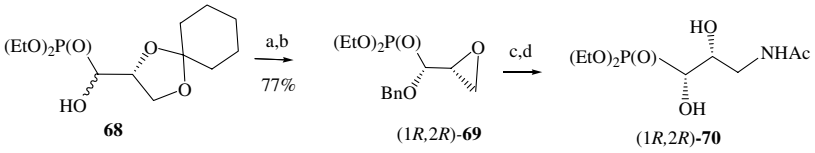
a = OsO_4, $(DHQD)_2PHAL$; TsNHCl; t-BuOH:H_2O; b = HBr, AcOH, propylene oxide
R=H (55%, 15% *ee*), Ph(65%, 60% *ee*), 4-An(72%, 45% *ee*), 4-BrC_6H_4(71%, 75% *ee*), 4-$NO_2C_6H_4$ (75%, 92% *ee*)

Scheme 15. Asymmetric aminohydroxylation of diethyl (*E*)-styrylphosphonates.

were obtained from the 1-hydroxy-2,3-*O*-cyclohexylidenepropylphosphonate **68** and by reaction with dibenzylamine were converted into (1*R*,2*R*)- and (1*S*,2*R*)-α-hydroxy-β-aminopropylphosphonates **70**.[70a] Aminohydroxyphosphonates were also synthesized by acid catalyzed methanolysis of 2-phosphonyl aziridine (Scheme 16).[70b]

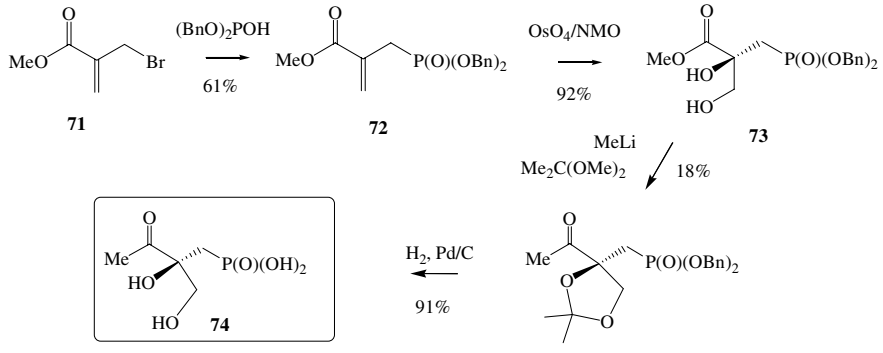
Asymmetric epoxidation of allylphosphonates was extensively used in the asymmetric synthesis of naturally occurring hydroxyphosphonates.[73–81] In particular, the synthesis of phosphonothrixine **74** has been developed by Nakamura et al.,[73] starting from bromomethylallylketone **71**, which via a Michaelis–Becker reaction was converted into allylphosphinate **72**. This was oxidized by dihydroxylation with osmium tetroxide to give the dihydroxyphosphonate **73**, which was converted into phosphonothrixine **74** (Scheme 17).

The asymmetric synthesis of phosphonothrixine **74** by the same authors employed the dienyl-alcohol as the starting reactant. Catalytic asymmetric epoxidation of dienyl-alcohol **75** using D-DETA furnished the chiral (*R*)-epoxy alcohol **76** (92% ee, 57% yield). The C–P bond was formed by adding the chloromagnesium of dibenzyl phosphite. Ozonolysis and debenzylation gave (*S*)-PTX in 79% yield and 92% ee. The (*R*)-enantiomer of phosphonothrixine **74** was also prepared using this methodology. On the basis of the specific rotation and biological activity, the natural product was determined to have (*S*)-configuration (Scheme 18).[73,74]

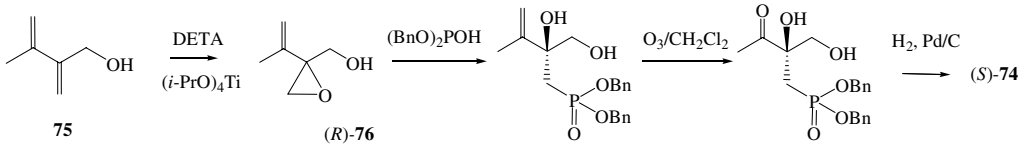


a = BnBr, $Me_2C(OMe)_2$, column chromatography, b = PPTS, AcBr, K_2CO_3, MeOH; c = $HNBn_2$, NEt_3,
d = H_2-Pd(O)$_2$/C

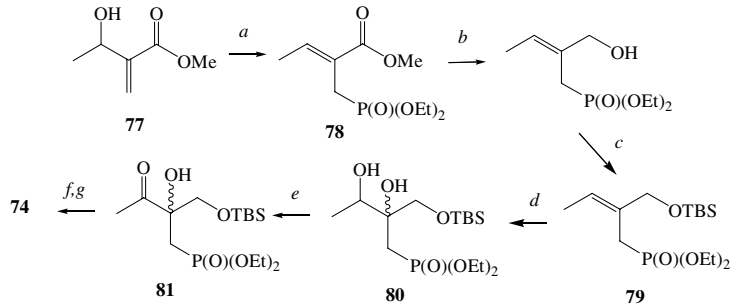
Scheme 16. Synthesis of hydroxyphosphonates **68**, **70** via the oxirane ring opening.



Scheme 17. Synthesis of phosphonothrixine starting from bromomethylallylketone.



Scheme 18. Synthesis of phosphonothrixine **74** starting from dienyl-alcohol **75**.



a = $(EtO)_2PCl/Et_3N$; b = DIBAL-H; c = TBSCl; d = OsO_4; e = PDC; f = TMSCl, HF/MeCN; g = column chromatography

Scheme 19. Synthesis of phosphonothrixine **74** starting from methyl 3-hydroxy-2-methylene butyrate **77**.

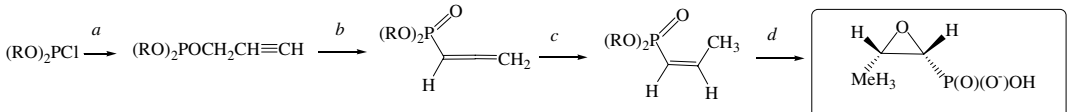
The synthesis of phosphonothrixine **74** was also accomplished in six steps and 24% overall yield from the commercially available methyl 3-hydroxy-2-methylene butyrate **77**, which was phosphorylated with diethyl chlorophosphite in the presence of triethylamine to give the *E*-allylphosphonate **78** (60% yield) forming the key C–P bond via an intramolecular Arbusov rearrangement.[75] The vicinal dihydroxylation to diol **80** followed by the oxidation of **79** led to the formation of protected phosphonothrixine **81** in 80% yield. Deprotection of **81** to salt-free protonated PTX **74** was achieved using excess TMSI in CH_2C1_2 and aqueous HF in MeCN (Scheme 19).

(1*R*,2*S*)-1,2-Epoxypropenylphosphonic acid, also known as Fosfomycin, was synthesized by a catalytic epoxidation of vinylphosphonate **82** with the subsequent resolution of racemic Fosfomycin to enantiomer **83** with the (+)-phenylethylamine (Scheme 20).[77]

Hydrolytic kinetic resolution of terminal epoxides was successfully applied to the enantioselective separation of diethyl 2,3-epoxypropylphosphonates.[66–79] Acid-catalyzed hydrolysis of (*RS*)-epoxide **84** gave the corresponding (*S*)-diol in only 72% ee due to low C-3 regioselectivity of the reaction. At the same time the partial, kinetically controlled hydrolysis of racemic (*RS*)-**84**, catalyzed by (*R*,*R*)-salen-Co(III)-OAc complex **86** led to the formation of chiral (*S*)-epoxide **84** in 82% ee and (*R*)-2,3-dihydroxypropylphosphonate **85** in 71% yield and 98% ee (Scheme 21).[80,81]

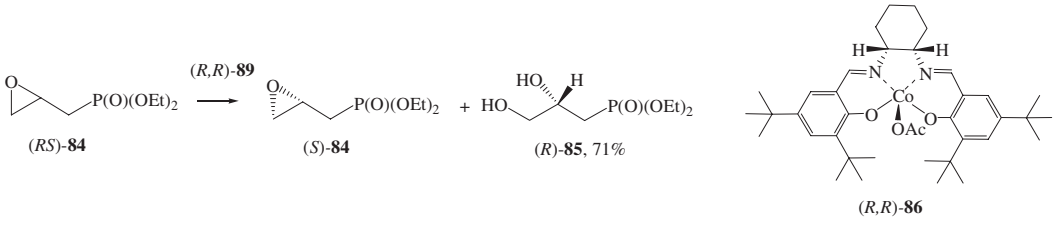
Two reliable methods for the synthesis of the enantiomerically pure (*S*)-3-amino-2-hydroxypropylphosphonic acids (phosphonate analogues of L-GABOB) from diethyl (*S*)-epoxypropylphosphonate **84** were reported (Schemes 22 and 23). Ring opening in the epoxypropylphosphonate (*S*)-**84** with *N*-trityl- and *N*-benzhydrylamines occurred exclusively at C(3) leading to the formation of 3-*N*-trityl or 3-*N*-benzhydrylamino-2-hydroxypropylphosphonates **87** and **90**, which were obtained in good yields and with good ee after column chromatography. Compounds **87** and **90** were converted into Boc-derivatives (*S*)-**88**. The phosphonate (*S*)-**88** was transformed into the enantiomerically pure phosphonate analogue of L-GABOB **89** (Scheme 22).[81b,c]

Diethyl (*S*)-2,3-epoxypropylphosphonate **84** was transformed into phosphonocarnitine (*S*)-**33** according to Scheme 24.[81a,b] A similar method for the synthesis of

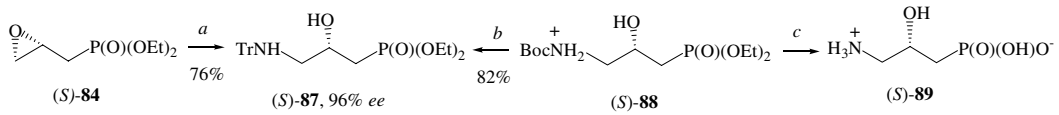


R=*t*-BuO; a = $HOCH_2CH{\equiv}CH$; b = Et_3N; c = H_2/Pd-C;
d= $H_2O_2/NaWO_4$, (*R*)-Ph(Me)$CHNH_2$

Scheme 20. Synthesis of (1*R*,2*S*)-fosfomycin.

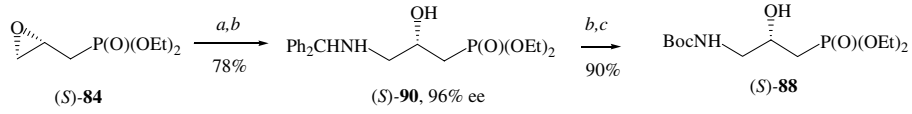


Scheme 21. Kinetically controlled resolution of 2,3-epoxypropylphosphonates **84**.



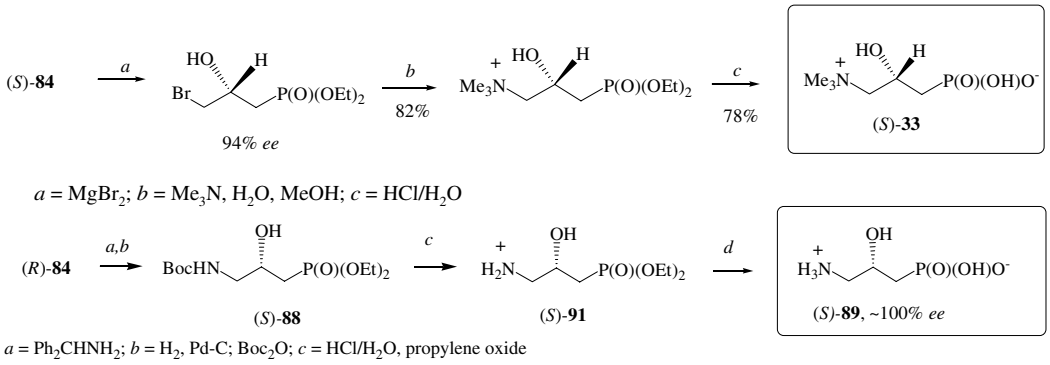
a = $TrNH_2$, b = H_2, Pd-C, Boc_2O, c = column chromatography, d = 12N HCl, propylene oxide

Scheme 22. Asymmetric synthesis of phosphonate analogue of L-GABOB (*S*)-**89**.



a = Ph_2CHNH_2, b = column chromatography, c = H_2, Pd-C, Boc_2O

Scheme 23. Stereoselective synthesis of Boc-derivative (*S*)-**88**.



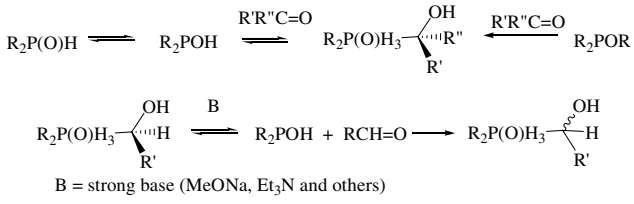
Scheme 24. Asymmetric synthesis of (*S*)-phosphonocarnitine **33** and phosphonate analogue of L-GABOB **90**.

the enantiomerically pure (*S*)-3-amino-2-hydroxypropylphosphonic acid **89**, a phosphonate analogue of L-GABOB, from the diethyl (*S*)-2,3-epoxypropylphosphonate was also elaborated (Scheme 24).[81a]

2.3. Asymmetric addition reactions

The main method for the synthesis of hydroxyphosphonates is the phosphonylation of carbonyl compounds, mainly via the phosphoaldol reaction (the Abramov reaction). Two types of phospho-aldol reaction are possible: (a) the reaction of dialkylphosphites with carbonyl reagents, proceeding in the presence of base catalyst, which shifts the P(O)H ⇌ P–OH tautomeric equilibrium towards the D(O) form, and (b) the addition reaction of phosphoric acid triesters to carbonyl compounds, proceeding in the presence of proton donating reagents (phenol, carboxylic acid, hydrochloride of aniline, etc.), or Lewis acids. The addition reaction of phosphorus acid esters with carbonyl compounds involves two steps: first the formation of a P–C bond and second the cleavage of the ester function with formation of phosphonyl group. The first step of the addition reaction is reversible.[42,82–84]

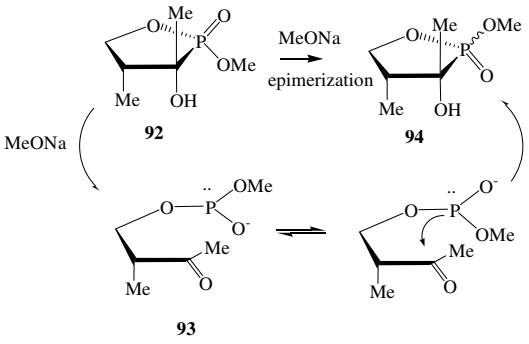
In the presence of strong bases, hydroxyalkylphosphonates dissociate with the formation of the initial dialkylphosphite and carbonyl compound. This transformation is known as the *retro*-phospho-aldol reaction (or *retro*-Abramov reaction). The *retro*-Abramov reaction has been studied by Gancarz[85] (NMR spectroscopy) and Cherkasov[83,84] (kinetic methods). They found that the *retro*-Abramov reaction causes the epimerization of hydroxyphosphonates (Scheme 25).



Scheme 25. Abramov and *retro*-Abramov reactions.

For example, the diastereomerically pure 3,4-dimethyl-2-methoxy-2-oxo-1,2-oxaphospholan-3-ol **92** in the presence of sodium methoxide in methanol afforded diastereomeric mixtures of **92** and **94**. The mechanism of the *retro*-Abramov reaction involves the P–C bond cleavage and epimerization of chiral anion **93** (Scheme 26).[86]

Chiral substrates in the asymmetric phospho-aldol reaction can be chiral phosphonites, having a stereogenic phosphorus atom, or phosphites derived from chiral alcohols, amino alcohols, or amines. The addition of achiral aldehydes to chiral trialkylphosphites **95** or

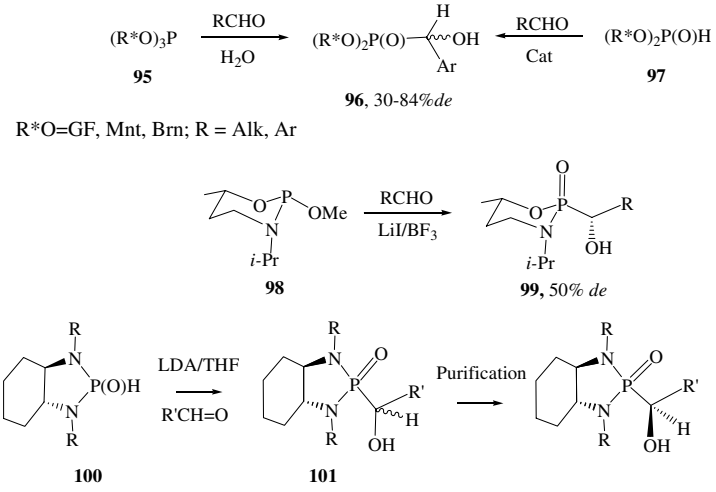


Scheme 26. Example of *retro*-Abramov reaction.

chiral dialkylphosphites **97** results, as a rule, in the formation of α-hydroxyphosphonates **96** in good yields and moderate stereoselectivity.[1,83–104] For example, chiral 1,3,2-oxazaphosphites **98**, derived from ephedrine, reacted with carbonyl compounds in the presence of boron trifluoride etherate to give the diastereomerically enriched α-hydroxy-2-oxo-1,3,2-oxazaphosphorinanes **99** in the ratio of 1:2–1:4.[102] The addition of chiral lithium diamidophosphite **100** to aldehydes led to the formation of α-hydroxyalkylphosphonamides **101** in good yield and moderate stereoselectivity. However the increase in the steric bulk of the alkyl groups in molecules of amidophosphite and aldehyde increased the stereoselectivity of reaction (Scheme 27).[87–93]

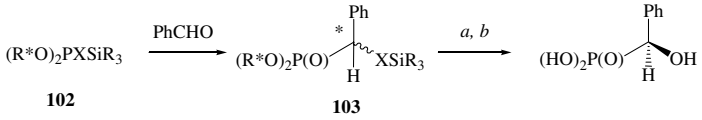
Silylphosphites **102** reacted with benzaldehyde to afford silyloxyphosphonates **103** in moderate stereoselectivity.[103] The exception to the rule is the modified Mukayama reaction of silylated λ^3-diazaphospholidines **102** (X = NR) with aldehydes, which resulted in the formation of the addition product in >98% ee.[98] Compounds **103** were converted into the α-hydroxyphosphonic acids, which possessed pharmacological activity (Scheme 28).[99,100]

The configuration of the hydroxyphosphonates depends on the catalyst and reaction conditions. Thus, the reaction of dimenthylphosphite with arylaldehydes in the presence of DBU preferentially provides (1*R*)-hydroxyphosphonates **105**, whereas the reaction catalyzed by (−)-quinine led to the formation of (1*S*)-hydroxy-



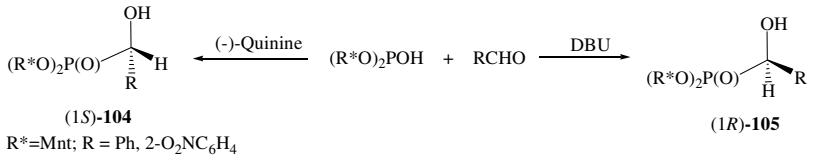
R	R'	*dr*	*Refs*
PhCH=CH	2-MeC_6H_4	1:1	88
CH_2=CH	Bn	1.4:1	88
PhCH=CH	l-Naphth-CH_2	1.5:1	88
(S)-PhMeCH	Ph	1.8:1	93
PhCH=CH	Bn	4.0:1	88
PhCH=CH	t-$BuCH_2$	7.9:1	89
Ph	t-$BuCH_2$	25: 1	88

Scheme 27. Asymmetric phospho-aldol reaction proceeding under the control of a chiral P(III) compound.



$(R^*O)_2$ = Binol, DETA, DIPT; *a* = crystallization or column chromatography; *b*=H_3O^+; X= O, NR

Scheme 28. Reaction of silylphosphites with aldehydes.

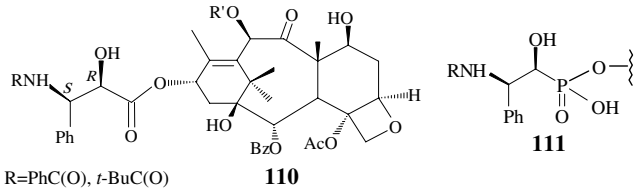


Scheme 29. Reaction of chiral phosphites with achiral aldehydes.

phosphonates **104**. The hydroxyphosphonates **104** and **105** were purified by crystallization and converted to hydroxyphosphonic acids in 96–99% ee (Scheme 29).[97]

The reaction of achiral phosphites with chiral aldehydes proceeds in general also with a moderate stereoselectivity.[105–134] For example, the reaction of dialkylphosphites with 2,3-*O*-substituted-D-glyceraldehyde, in the presence of such catalysts such as triethylamine, lithium, or caesium fluorides, furnished diastereomeric mixtures of hydroxyphosphonates **106** and **107** in the ratio of 45:55–35:55. Application of lithium diethylphosphonate improved the diastereoselectivity.[105] The diethyl 1,2,3-trihydroxypropylphosphonates (1*R*,2*R*)-**106** and (1*S*,2*R*)-**107** were isolated by column chromatography and obtained in a pure state after recrystallization (Scheme 29).[106–108] The reaction of dialkylphosphites with the Garner aldehyde in the presence of triethylamine resulted in the (1*R*,2*S*)-2-amino-1,3-dihydroxypropylphosphonate **109** in 80% de. At the same time, this reaction in the presence of titanium(IV) isopropoxyde as a catalyst yielded the diastereomeric mixture (1*S*,2*S*)-**108**/(1*R*,2*S*)-**109** in a ratio of ~1:1, which were separated by column chromatography to furnish the minor (1*S*,2*S*)-diastereomer **108** (Scheme 30).[117]

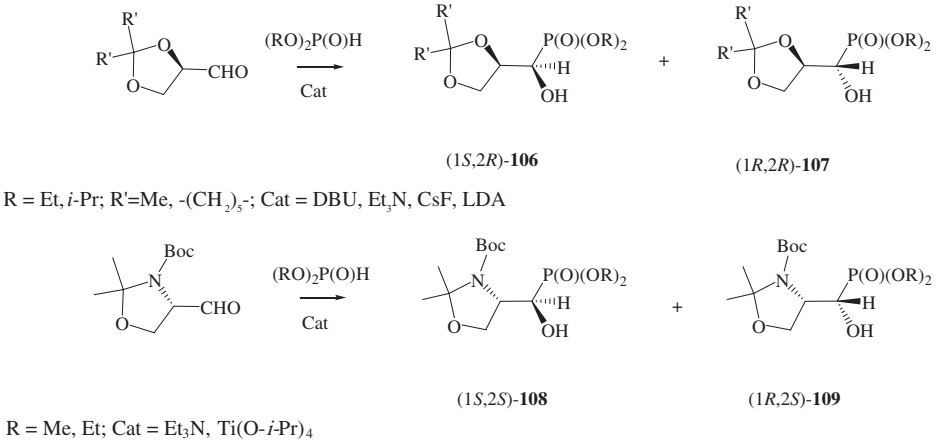
Phosphonate analogues of natural anticancer substances, the taxoids, and fragments of taxoids **110** have been synthesized with use of phospho-aldol reaction.[109] For example, chiral phosphonate analogues of the paclitaxel side chain **111** have been obtained by reaction of diethylphosphite with chiral α-aminoaldehyde (Scheme 31).[110]



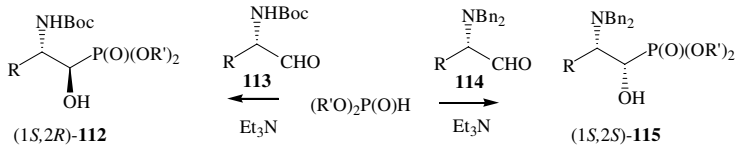
Scheme 31. Taxol and phosphotaxol.

The phosphonylation of chiral α-aminoaldehydes is a convenient and versatile method for the preparation of optically active stereoisomers of α-amino-β-hydroxyalkylphosphonic acids.[111–122] The stereochemistry of the reaction depends on the substituents at the nitrogen atom. For example, the addition of dialkyl phosphites to (*S*)-*N*,*N*-dibenzylphenylglycinal **114** in the presence of triethylamine resulted in (1*S*,2*S*)-1-hydroxy-2-aminophosphonate **115**,[112] whereas the reaction of dialkylphosphites with (*S*)-*N*-Boc-phenylglycinal **113** under the same conditions, yielded the (1*S*,2*R*)-diastereomer **112** (Scheme 32).[110]

The stereoselectivity of the phospho-aldol reaction depends on the structure of the initial reagents and catalyst.[111–116] For example, the titanium tetrachloride catalyzed the reaction of silylphosphites with chiral (*S*)-aldehydes **113** and **114** to increase the stereoselectivity in favour of the (1*S*,2*S*)-diastereomer. The highly stereoselective synthesis of (1*S*,2*S*)-2-amino-1-hydroxyalkylphosphonic acids was achieved by the addition of dimethyl phosphite to the *N*-protected aminoaldehyde with KF as catalyst in DMFA.[113] The reaction of lithium dialkylphosphites with *N*-Boc-phenylglycinal



Scheme 30. Asymmetric phosphoaldol reaction proceeding under control of chiral aldehyde.



Scheme 32. Asymmetric synthesis of 1-hydroxy-2-aminophosphonates.

Table 3. Stereoselective reaction of chiral aldehyde **114** with dialkylphosphites $(R'O)_2POX + \mathbf{113} + (Cat) \rightarrow \mathbf{112}$

R′	R	X	Cat	Yield (%)	dr	Refs
Me	Ph	H	Et_3N	62	56	113b
Me	Ph	Li	—	>100	14	113b
Et	Bn	Me_3Si	$TiCl_4$	63	20	111,114
Et	Bn	*t*-$BuMe_2Si$	$TiCl_4$	86	96	111
Et	Bn	Me_3Si	$SnCl_4$	53	48	114
Et	*t*-$BuOC_6H_4CH_2$	H	KF	82	60	104
Et	Bn	H	CsF	92	42	104

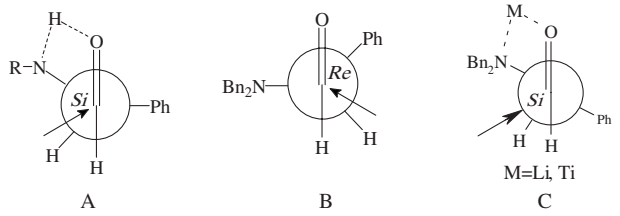


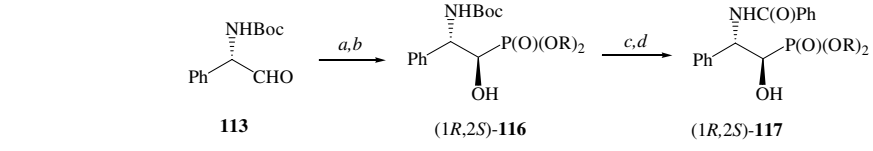
Figure 1. Modelling of the phosphoaldol reaction of chiral aldehydes **113** and **114** with dialkyl phosphites.

(*S*)-**113** predominantly gave the (1*R*,2*S*)-diastereomer **112** (Table 3).[112] Subsequent deprotection of *N*-Boc- and their α-benzoyl-groups, allowed access to the (1*R*, 2*S*)-phosphonate analogue of the paclitaxel side chain (Scheme 33).

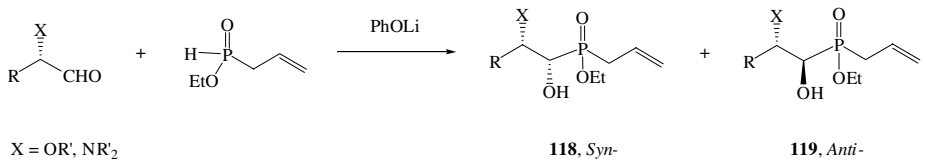
These results were rationalized by modelling of transition states in the addition of dialkyl phosphites to aldehydes. In the (*S*)-*N*-Boc-derivative, the intramolecular hydrogen bond stabilizes the conformation A and the dialkyl phosphite attacks the *Si* face of the carbonyl group, thus leading to the formation of the *syn*-adduct (model A). In the presence of triethylamine the chelation is not possible, therefore the dialkyl phosphite preferentially attacks the *Re* face of the carbonyl group in the (*S*)-aldehyde (model B). Addition of a metalated phosphite (Li, Mg, and Ti) to the (*S*)-aldehyde led to an increase in the *syn*-diastereomer due to the involvement of the chelated conformation C (Fig. 1).[111–114]

β-Substituted α-hydroxyphosphinates **118**, **119** have been obtained by reaction of α-hydroxyaldehydes and α-aminoaldehydes with the ethyl allylphosphinate catalyzed by lithium phenoxide (Scheme 34).[122]

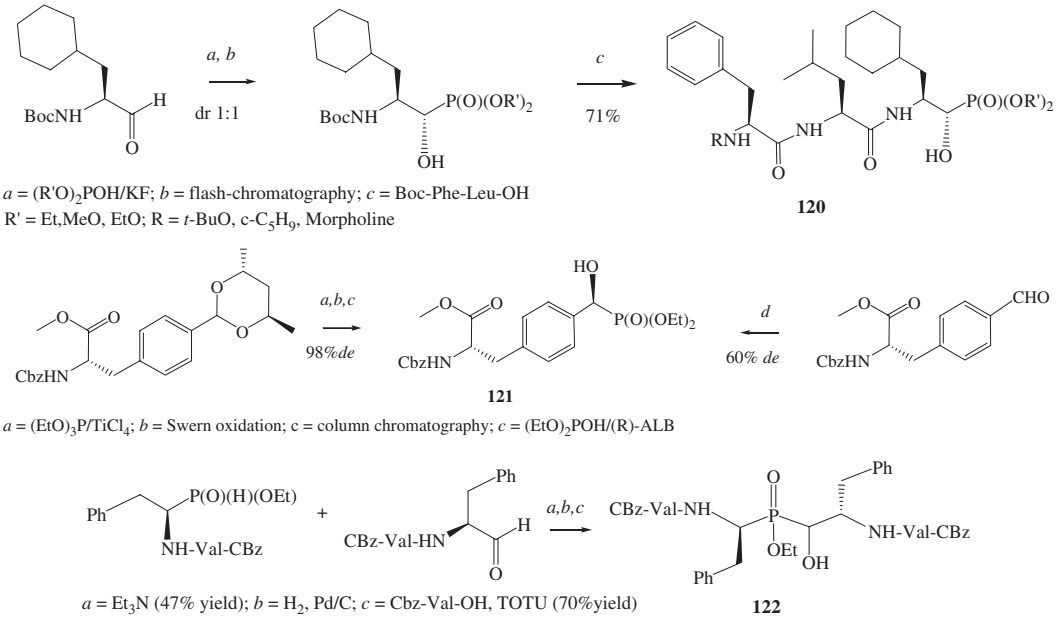
The phospho-aldol reaction of chiral aldehydes with dialkyl phosphites was used for the stereoselective syntheses of various biologically active compounds.[123–134] For example, Patel et al.[6] prepared the tripeptidyl α-hydroxyphosphonates **120**, which are highly effective renin inhibitors (Scheme 35). Shibuya et al.[118] reported the synthesis of the hydroxyphosphonate analogues of tyrosine **121** while Stowasser[33,34] discovered new inhibitors of HIV-protease **122**, active in the lower nanomolar range, which are very promising drugs for AIDS therapy. Compounds **122** were prepared as a mixture of three diastereomers in 3.4:1.7:1 ratio because of fast racemization of chiral aldehyde under coupling conditions.



Scheme 33. Synthesis of phosphonate analogue of the paclitaxel side chain.



Scheme 34. Phosphoaldol addition of chiral aldehydes to ethyl allylphosphinate.



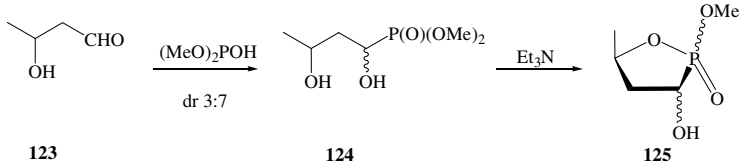
Scheme 35. Synthesis of renin inhibitors **120**, tyrosine analogues **121**, and HIV-protease inhibitors **122**.

The addition of dimethyl phosphite to β-hydroxyaldehyde **123** led to the diastereomeric mixture of ethane (1,3-dihydroxybutyl)phosphonates **124** in a ratio of 3:7. The intramolecular transesterification of the phosphonates **124** in the presence of triethylamine afforded the diastereomers of five-membered heterocycles **125**, which were separated by column chromatography (Scheme 36).[123]

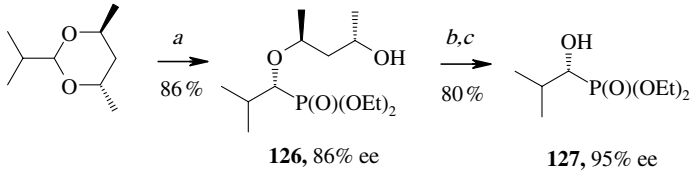
The diastereoselective reaction of triethyl phosphite with enantiomerically pure acetals of (2*S*,4*S*)-pentandiole in the presence of titanium tetrachloride, has afforded alcohol **126**, which was treated with *p*-toluenesulfonic acid and then converted into hydroxyphosphonate **127** by Swern oxidation.[133] Yamamoto et al. (Scheme 37)[134] obtained by this method the chiral (2*R*)-1-amino-1-deoxy-1-phosphinylglyceroles.

Bongini[126,127] reported the stereoselective phosphonylation of α-silyloxyaldehydes **129** with silylphosphites **128**. The stereoselectivity of reaction increased proportionally to the size of the trialkylsilyl substituents in the phosphite and aldehyde. (1*S*,2*S*)-Phosphothreonine **131** was synthesized analogously in good yield and high diastereomeric purity by reaction of trimethylsilyldiethylphosphite **128** with *N*-trimethylsilylimino-(*S*)-lactate aldehyde **130**.[129] Other stereoisomers of phosphothreonine were prepared by the phospho-aldol addition of a trimethylsilyldiethylphosphite to lactaldehyde, followed by Mitsunobu inversion of the corresponding α-hydroxy-β-silyloxyphosphonate (Scheme 38).[130]

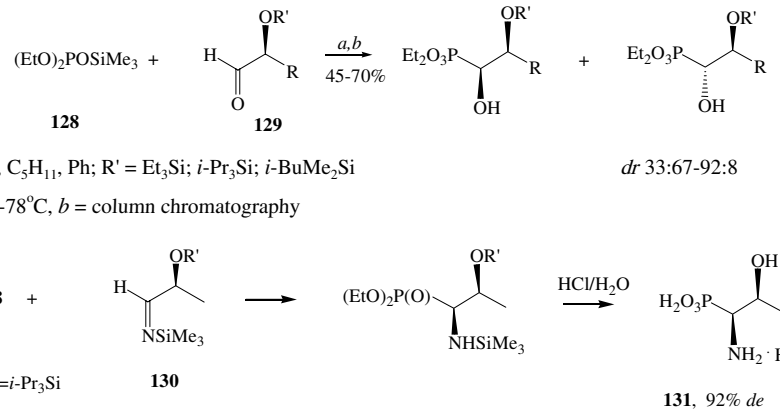
This reaction has been used in the synthesis of natural antibiotic (1*R*,2*S*)-fosfomycin **132b** (Scheme 39).[128]



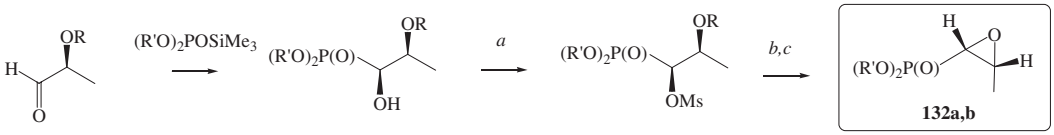
Scheme 36. Asymmetric synthesis of hydroxy-1,2-oxaphospholan-2-ones.



Scheme 37. Diastereoselective reaction of triethyl phosphite with homochiral acetals.



Scheme 38. Examples of asymmetric phosphoaldol reaction.



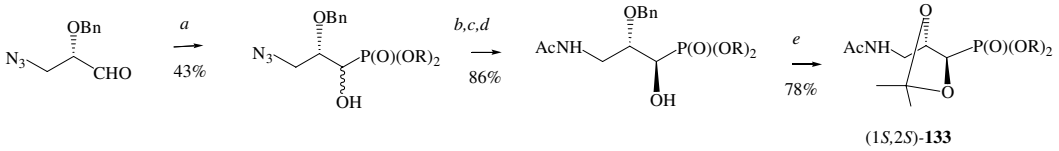
Scheme 39. Synthesis of enantiomerically pure fosfomycin **132b**.

Diastereomerically pure acetonide of dimethyl (1*S*,2*S*)-1,2-dihydroxy-3-aminopropylphosphonates **133** was prepared by a multistep synthesis, including phospho-aldol reaction of (2*S*)-3-azido-2-benzyloxypropanal with dialkylphosphites and subsequent hydrogenation of the addition product.[131] Shibuya et al. have described a stereoselective hydrophosphonylation of α-benzyloxyaldehydes, catalyzed by titanium tetrachloride which resulted in the formation of phosphonic analogues of oxyamino acids. They used the phospho-aldol reaction for the preparation of α-hydroxy-β-oxyphosphonates **134**, which reacted with HN_3 to convert into α-azido-β-oxyphosphonic acids **135** and then into α-amino-β-oxyphosphonic acids **136** (Scheme 40).[132,133]

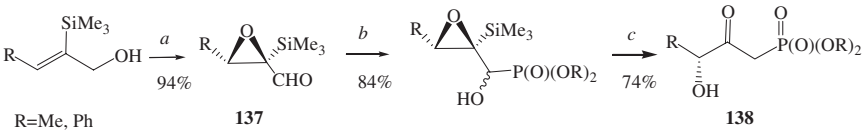
Chiral epoxy-aldehydes **137** (97% ee) were prepared by the asymmetric Sharpless epoxidation of 1-trimethylsiloxy-1-alkynes[121] and then reacted with the dialkyl phosphites to afford the β-keto-γ-hydroxyphosphonates **138** in 96–97% ee (Scheme 41).

The phospho-aldol reaction was applied to the preparation of phosphonate carbohydrates.[134–145] Phosphorus analogues of D-ribofuranose, D-glucopyranose, synthetic heteroatomic carbohydrates, pseudo-sugar nucleosides, and others were synthesized and tested for biological activity.[134–137]

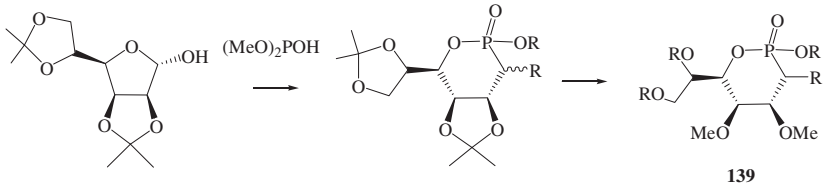
Thieme and Guenter used the phosphoaldol reaction for the preparation of δ-phoston **139**, which was isolated as a stereochemically pure material (Scheme 42).[138,139] Wroblewski[140] described the synthesis of the tetrafuranoside analogues of D-glycerotetrulose, D-erythritol, and other carbohydrates, bearing phosphorus in the anomeric position. Acid catalyzed cyclization of (1*S*)- and (1*R*)-1-*C*-(dimethoxyphosphinyl)-D-erythritols



Scheme 40. Asymmetric synthesis of 1-amino-2-alcoxyphosphonates.



Scheme 41. Asymmetric synthesis of β-keto-γ-hydroxyphosphonates.



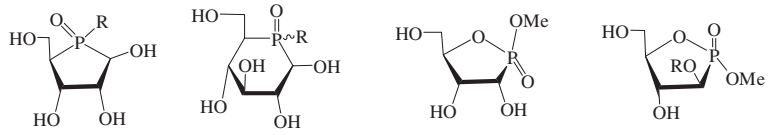
Scheme 42. Asymmetric synthesis of δ-phoston.

resulted in the formation of P-epimeric analogues of methyl D-ribo- and D-arabino-furanosides with phosphorus in the anomeric position (Scheme 43).[141–143]

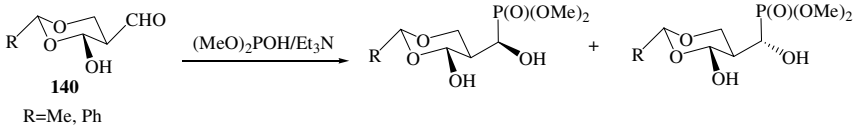
Diastereomers of (1*S*)- and (1*R*)-2,4-*O*-benzylidene-l-*C*-(dimethoxyphosphoryl)-D-erythritol in the 1:1 ratio (75% yield) and diastereomers of (−)-(1*S*)- and (1*R*)-2,4-D-benzylidene-1-(dimethoxyphosphoryl)-D-threitol in a 1:9 proportion (15% yield) were prepared by addition of dimethyl phosphite to the 2,4-*O*-benzylidene derivatives of D-erythrose or D-threose **140** in the presence of triethylamine (Scheme 44). The compounds were separated by column chromatography and purified by recrystallization.[144]

A number of polyhydroxyphosphonates **141**, **142**,[106–108] and **143**–**146**,[145] were synthesized by phospho-aldol reaction.[106–108,145] For example, the 2,3:4,5-di-D-isopropyliden-D-xylose was reacted with dimethyl phosphite to yield the diastereomeric mixture of polyhydroxyphosphonates **146** (Scheme 45).[145]

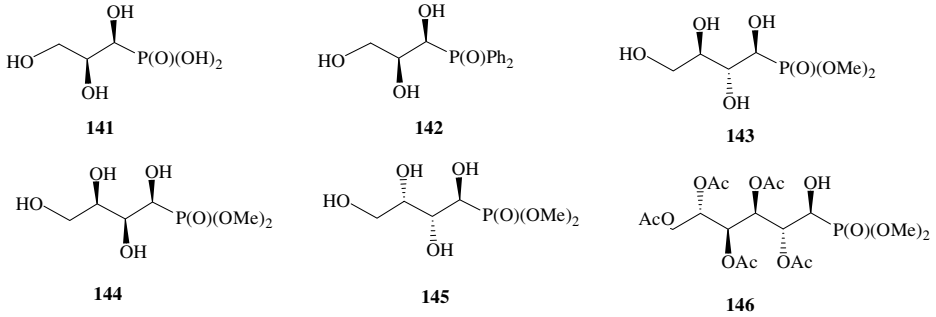
Over the last few years, the enantioselective synthesis of hydroxyphosphonates by a catalytic phospho-aldol



Scheme 43. Phosphorus analogues of carbohydrates.

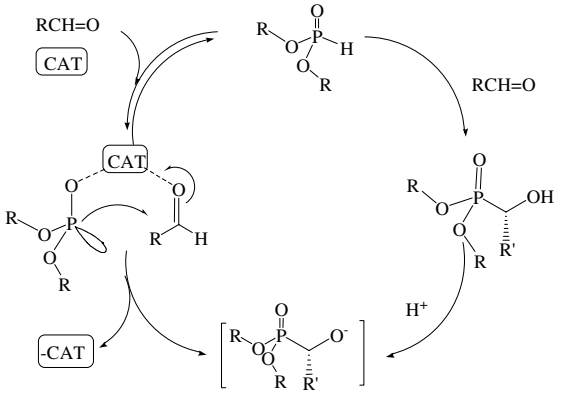


Scheme 44. The synthesis of D-erythritol and D-threitol derivatives.



Scheme 45. Polyhydroxyphosphonates.

reaction has attracted considerable interest.[146–156] A number of chiral catalysts have been proposed for the phospho-aldol reaction and some of them have exhibited a high catalytic efficiency. Scheme 46 shows a possible mechanism of the catalytic phospho-aldol reaction.[146]



Scheme 46. Mechanism of catalytic phosphoaldol reaction.

For the stereochemical control of the phospho-aldol reaction, different types of asymmetric catalysts have been proposed. For example, Shibazaki[146b] reported that heterobimetallic complexes, containing chiral BINOL ligands, are effective catalysts in the hydrophosphonylation of aldehydes to give hydroxyphosphonates **147** in up to 95% ee. The reaction proceeded via the intermediate complex **148** of LLB with phosphite and aldehyde (Scheme 47). Heterobimetallic binol complexes LLB and ALB catalyzed the reaction between the dimethyl phosphite and arylaldehydes to yield α-hydroxyphosphonates **147** with ~90% ee (Table 4).[147]

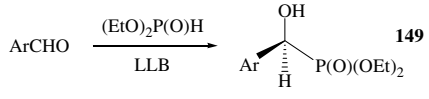
Shibuya et al.[89,92] and Spilling et al.[148–150] studied the catalytic activity of LLB in phospho-aldol reactions and obtained α-hydroxyphosphonates **149** with lower enantioselectivity than Shibazaki (Table 5). However Shibazaki, in the latest publication explained that the very slow addition of catalyst into the reaction medium improves the enantioselectivity of the phospho-aldol reaction ('the effect of slow addition').[146]

Shibuya et al.[148,149] reported that the complexes (Cat) derived from $(i\text{-PrO})_4$Ti and chiral 1,2-diols [diisopropyl-L-tartrate **151**, (*S*,*S*)-cyclohexanediol **152**, etc.] are effective catalysts and induce the stereoselective addition of alkylphosphites to arylaldehydes more efficiently than LLB (53% ee). The enantioselectivity of the phosphonylation depended on the nature of the solvent, the carbonyl compound and the chiral diol.[150] In particular the (*S*,*S*)-cyclohexanediol efficiently increased the catalytic activity of titanium alkoxide to yield (*R*)-hydroxyphosphonates in 65–70% ee (Scheme 48).

Table 4. LLB catalyzed phospho-aldol reaction (Shibazaki results)[147]

R	Cat* = LLB (−78 °C)		Cat* = ALB (−40 °C)	
	Yield (%)	ee (%)	Yield (%)	ee (%)
Ph	88	79	95	90
p-Tl	93	78	82	86
p-$Me_2NC_6H_4$	88	95	—	—
p-An	87	93	88	78
PhCH=CH–	90	84	85	82
PhCH=C(Me)	94	92	47	56
C_6H_{13}	88	61	95	16

Table 5. LLB catalyzed phosphoaldol reaction (Shibuya and Spilling results)



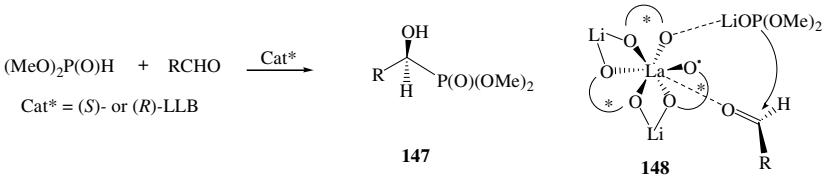
149

Ar	Yield (%)	ee (%)	Refs
Ph	98	20	150
4-$MeOC_6H_4CH$=CH	87	74	89
4-$MeOC_6H_4CH$=CH	67	79	149
4-$MeOC_6H_4CH$=CH	95	82	149
4-MeC_6H_5CH=CH	94	58	149
PhCH=CH	98	20	149
4-ClC_6H_4CH=CH	99	17	149

The reaction of ethyl ethylphosphinate with chiral *N*,*N*-dibenzyl-α-aminoaldehyde catalyzed by (*S*)-ALB led to the formation of hydroxyphosphonates as a mixture of several diastereomers arising from the stereogenicity of three asymmetric centres on both the α- and β-carbon atoms and the phosphorus atom. Nevertheless, some of these diastereomers were separated by column chromatography, purified by recrystallization and their stereochemistry confirmed by X-ray crystallographic analysis.[152]

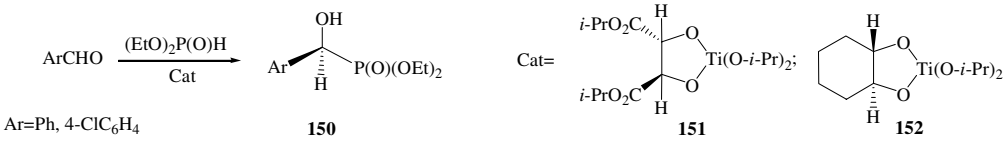
The hydrophosphonylation using ethyl phosphinate afforded both the *syn*- and *anti*-β-amino-α-hydroxy-*H*-phosphinates with high diastereoselectivity by tuning the chirality of ALB (Table 6).

The reaction of methylphosphinate with benzaldehyde, catalyzed with (*S*)-ALB and initiated by microwave irradiation, led to the formation of (*S*)-α-hydroxy-*H*-phos-



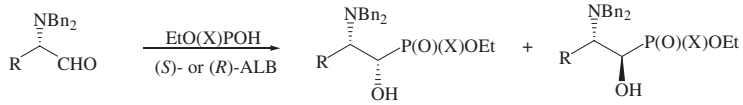
147 **148**

Scheme 47. Catalytic phospho-aldol reaction.



Scheme 48. Chiral alkoxide titanium catalyzed phospho-aldol reaction.

Table 6. Phospho-aldol reaction controlled by ALB-complex



R	X	ALB	*syn*:*anti*	Yield (%)	Refs
Bn	H	*R*	87:13	66	151
Bn	H	*S*	6:94	56	151
Bn	Et	*R*	43:57	55	151
Bn	Et	*S*	11:89	51	151
Me	$CH_2CH{=}CH_2$	*R*	24:76	48	120,152
Me	$CH_2CH{=}CH_2$	*S*	6:94	52	120,152
i-Bu	$CH_2CH{=}CH_2$	*R*	58:42	71	120,152
i-Bu	$CH_2CH{=}CH_2$	*S*	5:95	51	120,152
Bn	$CH_2CH{=}CH_2$	*R*	50:50	74	120,152
Bn	$CH_2CH{=}CH_2$	*S*	7:93	63	120,152

phinate **155** (85% ee) and (*S*,*S*)-bis(α-hydroxyalkyl)phosphinate derivatives **156** and **157** (80% ee) as shown in Scheme 49.[122]

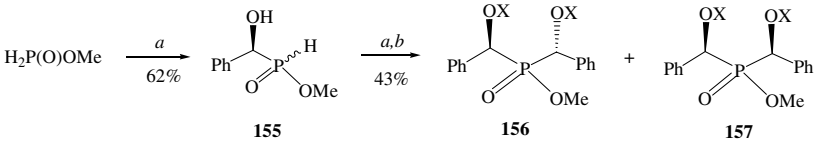
Chiral salcyan and salen aluminium complexes were used as catalysts of the phospho-aldol reaction under aerobic conditions.[153] For example chiral catalyst **159** allowed the addition of dimethylphosphite to substituted benzaldehydes, to give the hydroxyphosphonates **160** with ~50% ee (Scheme 50).

Enantioselective hydrophosphonylation of the arylaldehydes was performed in a two-phase (NaOH/toluene) system mediated by chiral crown ethers, incorporating one or two sugar units. The best ee (42%) was achieved for the α-*m*-methoxyphenylphosphonate formed from dimethylphosphite and *m*-methoxybenzaldehyde (Scheme 51).[155]

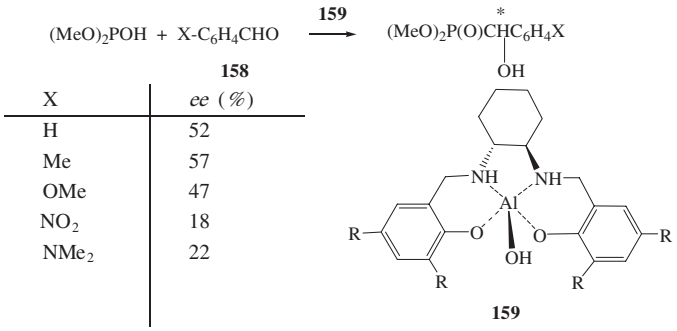
The multiple asymmetric induction (multistereoselectivity) is an efficient method for increasing the stereoselectivity of the phosphoaldol reaction by employing more then one chiral auxilary.[157–162] Thus the reaction of chiral dialkylphosphites **161** with the chiral 2,3-D-isopropylidene-(*R*)-glyceraldehyde **162**, under the control by two chiral auxiliaries, which reinforced one another, was more stereoselective than under the control of one chiral auxiliary to yield the diastereomers of (1*R*,2*R*)-**163**/(1*S*,2*R*)-**163** with 60% de (Table 7).

Chiral di(1*R*,2*S*,5*R*)-menthylphosphite reacted with chiral aldehydes in the presence of chiral ALB catalyst with the triple asymmetric induction increasing the stereoselectivity of the reaction to 90%. The (*R*,*R*)/(*S*,*R*)-diastereomers were separated either by crystallization or column chromatography on silica gel. The stereoselectivity of the reaction depended on the solvent, the nature of the bases and the temperature. The (1*S*,2*R*)-configuration of the addition product was proven by NMR spectroscopy and X-ray analysis. Chiral aldehydes **114** reacted with the (1*R*,2*S*,5*R*)-dimenthylphosphite and di-*endo*-bornyl phosphite with the formation of either chiral (1*S*,2*S*)- or (1*R*,2*S*)-1-hydroxy-2-aminophosphonic acids. At the same time, the reaction of dibenzylphenylalaninal with tris(trimethylsilyl)phosphite afforded the (1*S*,2*S*)-α-hydroxy-β-aminoalkyl phosphonic acid **164**, which was purified by recrystallization (Scheme 52).[161]

C-Phosphorylated galactose derivatives **165** were prepared by a phospho-aldol reaction under the control of double asymmetric induction, which raised the stereoselectivity up to ~100% de. The compounds were isolated as enantiomerically pure solids (Scheme 53).[162]

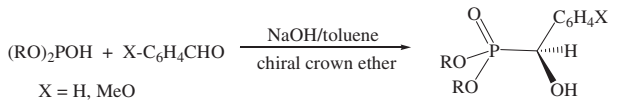


Scheme 49. ALB catalysis of phospho-aldol reaction.



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

Scheme 50. [(*R*,*R*)-salcyan]AlX catalysis of the phospho-aldol reaction.

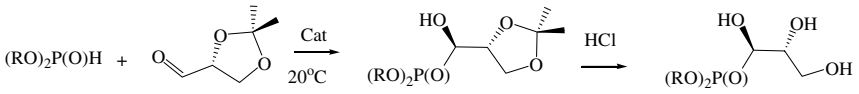


Scheme 51. Enantioselective phase transfer catalysis of the phospho-aldol reaction.

The aldol addition of lithium (*S*,*S*)-2-propionyl-2-oxo-l,3,2-oxazaphosphorinane **166** to benzaldehyde led to the formation of a diastereomeric mixture of the α-hydroxy-2-oxo-1,3,2-oxazaphosphorinanes **167** in the ratio of 3:1 (Scheme 54).[163]

β-Hydroxyalkylphosphonates were prepared with moderate diastereoselectivity by the reaction of phosphonate carbanions with carbonyl compounds in THF.[164] The lithium derivative of diethyl isothiocyanomethylphosphonate **168** was reacted with aldehydes to afford a mixture of *cis*- and *trans*-(2-thioxo-oxazolidine-4-yl)-phospho-

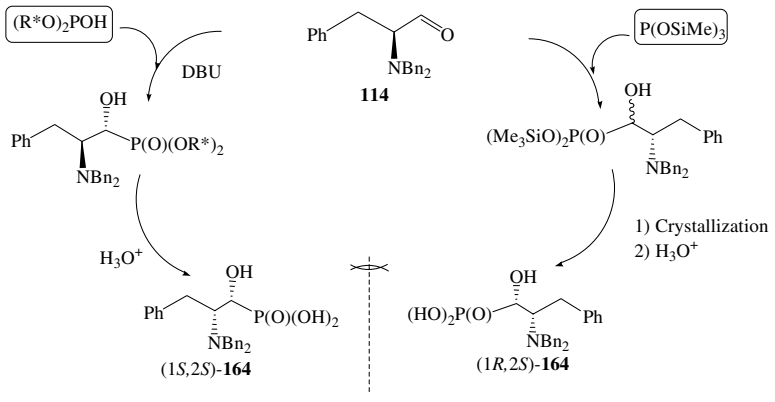
Table 7. Double and triple asymmetric induction in the phospho-aldol reaction



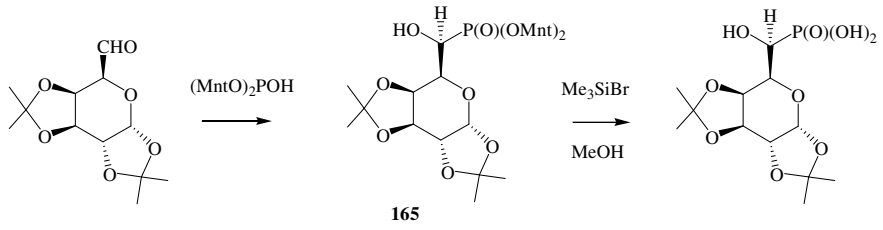
161 **162** (1*R*,2*R*)-**163a-c** (1*R*,2*R*)

R	Cat	Solvent	de (%)	Refs
Et	DBU	[a]	10	107
i-Pr	DBU	[a]	10	107
Mnt	DBU	[a]	60	107
Mnt	DBU	Toluene	60	107
Mnt	DBU	THF	44	107
Mnt	DBU	CH_2Cl_2	30	107
Mnt	NaOH	THF	40	107
Mnt	(*S*)-ALB	THF	90	106
Mnt	(*R*)-ALB	THF	56	106

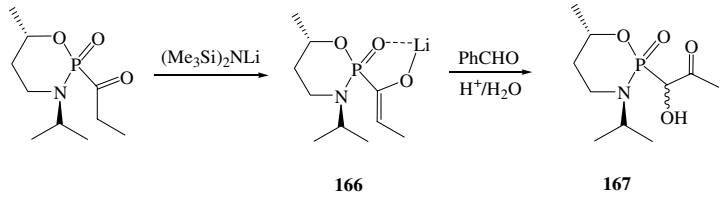
[a] Without solvent.



Scheme 52. Asymmetric catalytic synthesis of 2-amino-1-hydroxyphosphonates.



Scheme 53. Double asymmetric synthesis of hydroxygalactosophosphonates.



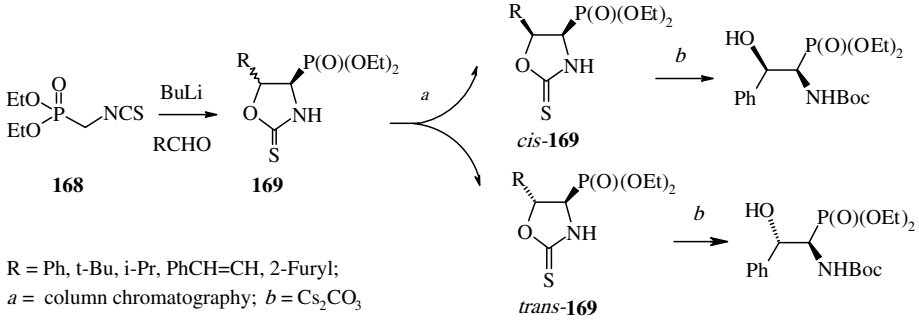
Scheme 54. Synthesis of oxazaphosphorinanes **167**.

nates **169**, which were separated by column chromatography and converted into the *N*-Boc-1-amino-2-hydroxyalkylphosphonates (Scheme 55).[165]

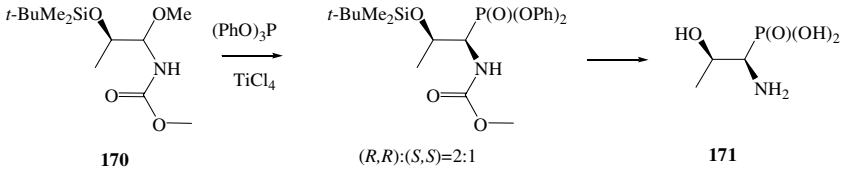
The reaction of achiral *N*,*O*-acetals **170** with triphenylphosphite in the presence of $TiCl_4$ led to the formation of *N*-acetylated α-aminophosphonates **171** in low diastereoselectivity. Pure diastereomers **171** were obtained by fractional recrystallization (Scheme 56).[166]

Diastereomerically enriched hydroxyphosphonates prepared by a phospho-aldol reaction were additionally purified by preparative column chromatography.[167–171] For example, Wroblewsky and Petrovska[75,76] obtained the pure enantiomers of *syn*- and *anti*-dimethyl 1-hydroxy-2-(benzoylamino)-2-phenylethylphosphonate by resolution of their esters with *O*-methylmandelate acid followed by column chromatography. Enantiomerically pure phosphonates (1*S*,2*S*)-**172** and (1*R*,2*R*)-**172** were obtained after the removal of the resolving ester moiety by ammonolysis with 25%-aqueous NH_3 (Scheme 57).[75,76]

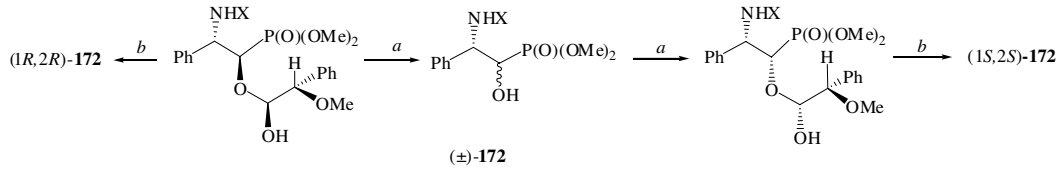
This methodology was used for the purification of a number of hydroxyphosphonates. For example, Ordones et al.[168] resolved the diastereomers of (±)-3-(*N*,*N*-dibenzylamino)-2-hydroxyphosphonates **173** derived with (*S*)-*O*-methylmandelic acids by column chromatography and then converted them into enantiomerically pure enantiomers of β-hydroxy-γ-aminopropylphosphonic acid (*S*)-**91** and (*R*)-**91**, which are analogues of GABOB.[168a] The same method was used



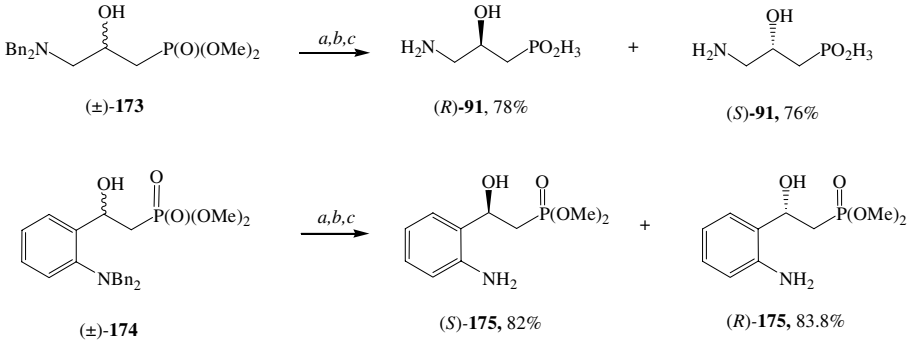
Scheme 55. Synthesis of α-amino-β-hydroxyalkylphosphonates.



Scheme 56. Synthesis of the α-amino-β-hydroxyphosphonates **171**.



Scheme 57. Resolution of hydroxyphosphonates (+/−)-**172** by column chromatography.



Scheme 58. Separation of racemic hydroxyphosphonates.

for the resolution of both enantiomers of 2-aminophenyl-2-hydroxyethylphosphonate **174**, which are starting compounds for the preparation of non-ionic selective X-ray contrast agents (Scheme 58).[168b]

Preparative HPLC was used in the separation of enantiomerically enriched or racemic hydroxyphosphonates. Enantiomers of diethyl hydroxybenzylphosphonate, containing aryl rings (1-naphthyl, 2-naphthyl, and 2-thienyl) were separated by HPLC on the O1 chiral stationary phase.[169] Enantiomers of ethyl α-hydroxyfarnesylphosphonate, a precursor of a farnesyl protein transferase inhibitor has been separated by semi-preparative HPLC on a chiral column using a Chiralcel OD chiral stationary phase.[169,170] Caccamese described the direct chiral HPLC separation of the enantiomers of fluorinated phosphonates.[171]

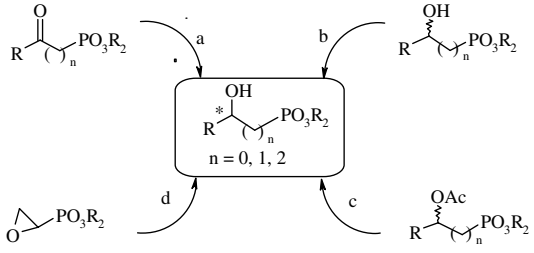
The stereoisomers of 1-amino-2-hydroxy- and 2-amino-1-hydroxypropylphosphonic acids were resolved by capillary electrophoresis using chiral quinine carbamate.[172]

2.4. Chemoenzymatic synthesis

Chemoenzymatic synthesis represents an effective and sometimes preferable alternative to the standard synthesis of fine chemicals in their optically active forms. The use of enzymatic synthesis in organophosphorus chemistry is surprisingly scarce and generally limited to the synthesis of optically active hydroxyphosphonic acids and their esters. Bacteria, fungi, and various lipases can be used as biocatalysts for the preparation of optically active hydroxyphosphonates.[173]

There are four general processes applied to the enzymatic synthesis of hydroxyalkylphosphonates, namely: (a) the use of baker's yeast and other fungi for the bioreduction of ketophosphonates; (b) the use of microorganisms and lipases for the enantioselective separation of hydroxyphosphonates via acylation; (c) the use of lipolytic organisms either for enantioselective hydrolysis of acyloxyalkanephosphonates; (d) the use of bacteria and fungi for hydrolytic oxirane ring opening in substituted 1,2-epoxyethanephosphonates (Scheme 59).

Carbonyl reductions are probably the most thoroughly studied and exploited biotransformations performed by baker's yeast, because the catalyst is inexpensive and versatile and the process is easy to perform. Zymanczyk-Duda et al.[174–176] have applied baker's yeasts for the enantioselective reduction of diethyl β-, γ-, and δ-oxoalkylphosphonates resulting in hydroxyphosphonates in good yields and with high enantiomeric excesses (>95% ee). The reaction was carried out



Scheme 59. Enzymatic synthesis of hydroxyphosphonates.

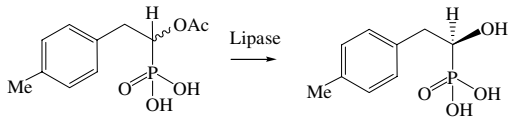
in water under aerobic conditions. With less reactive compounds, anaerobic reduction was applied.[175]

Yuan et al.[177] used this method to prepare optically active β-keto-γ-hydroxyphosphonates and β-keto-δ-hydroxyphosphonates. Maffei et al.[178] studied the enantioselective reduction of cyclic dialkyl (3-oxo-1-cycloalkenyl)phosphonates **176** by baker's yeast to give dialkyl (3-hydroxy-1-alkenyl)phosphonates, which are important synthetic blocks in the synthesis of bioactive compounds. They came to the conclusion that the reduction of six-membered cyclic ketophosphonates with dry or fermented baker's yeast in organic solvents proceeded more enantioselectively (70–82% ee) than the reduction of their seven-membered or five-membered analogues, which yielded racemic diethyl (3-oxocyclopentyl)phosphonates (Scheme 60).

The bioreduction of 2-keto-3-haloalkane phosphonates by baker's yeast afforded optically active 3-halo-β-hydroxyalkylphosphonates in 35–82% chemical yields and ~72% ee.[179] These compounds were used as chirons for the stereoselective synthesis of phosphorus analogues of biologically active compounds including the phosphorus analogue of (*R*)-GABOB (Scheme 61).

The lipase-catalyzed kinetic resolution of enantiomers is an important tool to obtain optically active hydroxyphosphonates.[180–191] The resolution of racemic acylated hydroxyphosphonates was achieved by enzymatic hydrolysis with the lipolytic microorganisms *Pseudomonas fluorescens* and *Penicillium citrinum* (Scheme 62).[182]

Racemic α-hydroxyalkylphosphonates were resolved by catalytic acetylation with *Candida antarctica* B lipases (CALB) and *Candida rugosa* lipases (CRL) to (*R*)- and (*S*)-isomers in high enantiomeric excess.[177,178] Yuan et al.[183] used the lipase CALB in organic solvents for

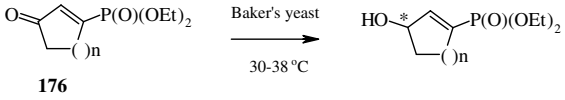


Scheme 62. Enzymatic hydrolysis of racemic 1-hydroxyphosphonates.

enantioselective acetylation and resolution of racemic β-hydroxyalkylphosphonates (*SR*)-**177**. The subsequent separation of unreacted alcohol (*S*)-**177** and ester (*R*)-**178** has afforded the pure stereoisomers. This method is simple and furnishes chiral hydroxyalkylphosphonates in high enantiomeric excess (85–95%) (Scheme 63).

Enantiomerically pure 2-hydroxy-2-arylethylphosphonates **179** were prepared by the enantioselective hydrolysis of butyryloxy-2-oxoarylethylphosphonates, catalyzed with CRL in a mixture of water–isopropyl ether.[184,186] As a result the (*S*)- and (*R*)-stereoisomers of 2-hydroxy-2-arylethylphosphonates were obtained in moderate chemical yields (40–45%) and high enantiomeric excesses (>95% ee). The method was used in the preparation of various types of hydroxyphosphonates, in particular for the preparation of enantiomerically pure 1- and 2-hydroxyalkylphosphonates **180**, bearing a trifluoromethyl group. The hydrolysis was controlled by lipases: *C. antarctica* B., *Mucor miehei* and *C. rugosa* in an organic medium (Scheme 64).[187]

Optically active β-keto-δ-hydroxyalkylphosphonates in moderate yield and high enantiomeric excesses were prepared by double enzymatic resolution, at first with *C. antarctica* lipase *B*-catalyzed acetylation of racemic alcohols and then with *C. rugosa* lipase-catalyzed enantioselective hydrolysis of acetoxyphosphonate (Scheme 65).[184]

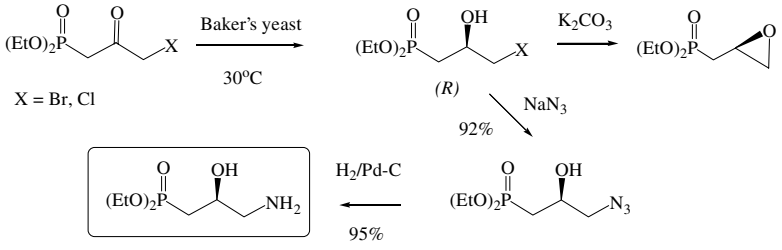


176

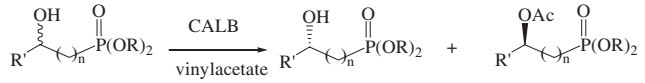
1 (n=2), 2 (n=1), 3 (n=3)

Solvent	Yield (%)	*ee (%)*	Config
n-Hexane	84	65	*S*
Methyl *tert*-butyl ether	15	82	*S*
Benzene	7	69	*S*

Scheme 60. Enantioselective reduction of ketophosphonates by baker's yeast.



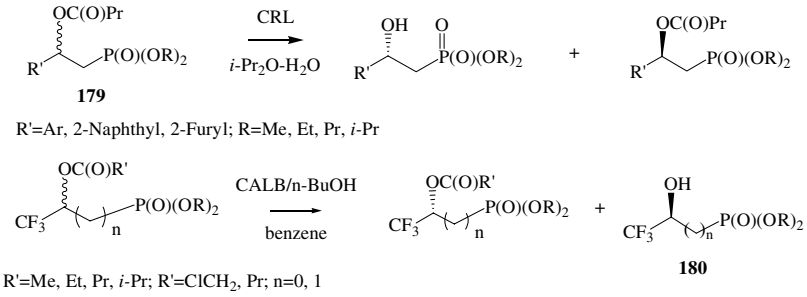
Scheme 61. Bioreduction of 2-keto-3-haloalkane phosphonates by baker's yeast.



(*SR*)-**177** (*S*)-**177** (*R*)-**178**

R=Me, Et, vinyl; R=Me, Et; n=0 (41-50% yield, >95%ee), 1 (35-45% yield, 85-95% ee),

Scheme 63. CALB catalyzed enzymatic acylation of racemic hydroxyphosphonates.



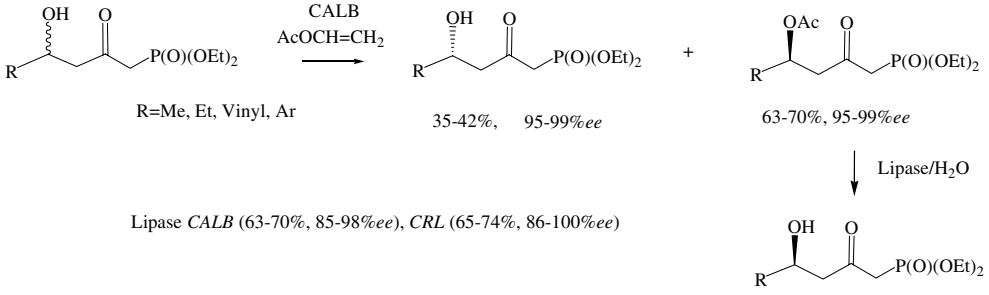
179

R'=Ar, 2-Naphthyl, 2-Furyl; R=Me, Et, Pr, *i*-Pr

R'=Me, Et, Pr, *i*-Pr; R'=$ClCH_2$, Pr; n=0, 1

180

Scheme 64. Enzymatic synthesis of enantiomerically pure β-hydroxyphosphonates.



R=Me, Et, Vinyl, Ar

35-42%, 95-99%*ee*

63-70%, 95-99%*ee*

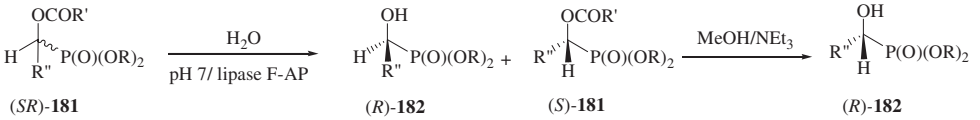
Lipase *CALB* (63-70%, 85-98%*ee*), *CRL* (65-74%, 86-100%*ee*)

Scheme 65. Enzymatic resolution of racemic 2-keto-4-hydroxyphosphonates.

Hammerschmidt[190–198] reported a method for the resolution of racemic α-hydroxyphosphonates **181** by lipases and proteases in a two-phase system (organic solvent–water) containing a phosphate buffer at pH 7. Under these conditions chiral α-hydroxyphosphonates were prepared in an enantiomeric excess of 98%. For instance, the protease Chirazime® P-2 hydrolyzed racemic α-chloracetoxyphosphonates to afford (*R*)-α-hydroxyalkylphosphonates with 31–97% ee.[185] Acetates of racemic α-hydroxyphosphonates **182** underwent enzymatic hydrolysis controlled with various lipases, including esterase of pig liver in the two-phase system. The highest enantioselectivity was achieved with lipase FAP 15 and (acetoxy)phenylmethylphosphonates as substrate. Only the (*S*)-enantiomers of phosphonates were hydrolyzed to afford enantiomerically pure (*S*)-alcohols. Lipases AP 6 and FAP 15 were used for the preparation of (*S*)-phosphonates on a preparative scale with 81–89% ee (Scheme 66).[192,193]

Diisopropyl α-hydroxy-β-bromoethylphosphonates **183** were separated by catalytic enzymatic hydrolysis (92–99% ee).[194,195] Lipases (SP 524, AP 6) hydrolyzed (*S*)-esters, whereas Chirazyme® P-2 protease hydrolyzed only (*R*)-esters. Replacement of isopropyl groups with *tert*-butyl groups slowed down the reaction rate; but the replacement of *i*-Pr groups with 2,2-dimethylpropan-1,3-diyl groups increased the reaction rate (Scheme 67).[44,194]

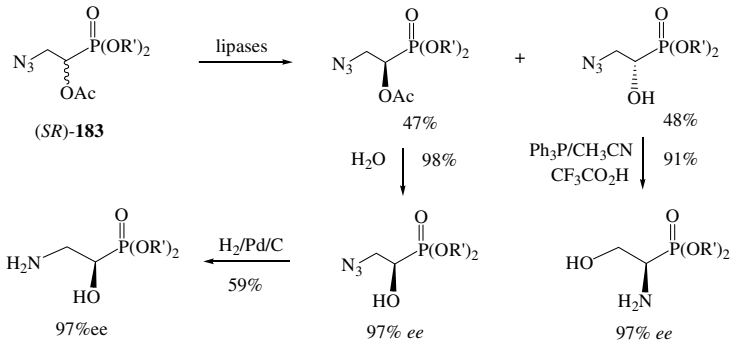
Racemic diisopropyl 2-azido-1-acetoxyethylphosphonate, SP 524, was resolved by lipase-catalyzed hydrolysis to enantiomerically enriched (*S*)-α-hydroxy-β-azidophosphonate and (*R*)-(−)-ester, which was hydro-



(*SR*)-**181** (*R*)-**182** (*S*)-**181** (*R*)-**182**

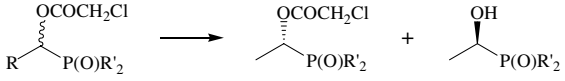
R= Et, *i*-Pr, t-Bu, $MeS(CH_2)_2$; R'= CH_2Cl, Pr; R"=*i*-Pr, $Me_2C(CH_2)_2$

Scheme 66. Enzymatic resolution of racemic hydrophosphonates in two-phase system.



Scheme 67. Lipase-catalyzed resolution of racemic hydroxyphosphonates.

lyzed with the formation of (*R*)-(+)-α-hydroxy-β-azidophosphonates. The corresponding methylsulfides were synthesized in three steps, from chiral α-hydroxyphosphonates obtained by enzymatic resolution.[196] Enzymatic acetylation of racemic diisopropyl α-hydroxyphosphonates with isopropyl acetate in methyl-*tert*-butyl ether furnished the acetates of (*S*)-α-hydroxy-(β-thienyl)methyl, α-hydroxyethyl-, α-hydroxycyclohexylphosphonates, and (*R*)-β-hydroxypropylphosphonates in 99% ee. Enzymatic hydrolysis of chloroacetoxyphosphonates with *Candida cylindracea* lipase and *Subtilisin* protease in a two-phase system resulted in the formation of (*S*)-hydroxyphosphonates in 51–92% ee (Scheme 68).



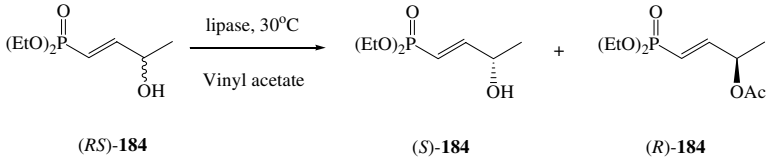
Scheme 68. Enzymatic hydrolysis of chloroacetoxyphosphonates.

(*S*)-2-Phenyl-β-hydroxyethyl- and (*S*)-γ-methyl-β-hydroxybutylphosphonates were transformed into (*R*)-β-aminophosphonic acids with the same enantiomeric excesses.[197–199] Enzymatic hydrolysis was used also for the synthesis of fosfomycine.[199,200]

Lipases *Geotrichum candidum*, *Rhizopus niveus*, *Penicillum* sp., *Aspergillus usamii*, *Mucor* sp., *Pseudomonas cepacia*, *Geotrichum candidum*, and pig liver were used for the stereoselective acetylation of racemic hydroxyphosphonates in organic solvents.[202] Lipases *Liposyme*, *Amano AK*, *Amano Ps*, *CALB*, *PPL* were applied to the resolution of racemic diethyl (3-hydroxy-1-butenyl)phosphonate. The reaction led to the formation of acetylated product (*R*)-**185** and unreacted hydroxyphosphonate (*S*)-**184**, which were subsequently converted into (*S*)- and (*R*)-diethyl (3-acetoxy-1-butenyl) phosphonates **184** in moderate yields and high enantiomeric excesses (Scheme 69).[201]

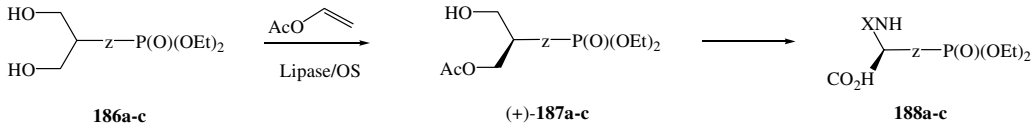
Shibuya et al.[204] prepared the optically active alcohol **187** by *PS*-lipase (from *Pseudomonas cepariei*) catalyzed acylation of prochiral 2-(ω-phosphono)alkyl-1,3-propandiols **186**. Transesterification of (±)-hydroxyalkylphosphonate **186** with vinyl acetate in the presence of lipase in an organic solvent (diisopropyl ether, THF, and benzene) proceeded with the formation of chiral alcohols (+)-**187** in good yields and high enantiomeric excesses. Alcohol (+)-**187** was converted into the optically active ω-phosphino-α-amino acids **188**, which are intermediates in the synthesis of AP-5 analogues (Scheme 70).

The same authors have performed the kinetic resolution of racemic diethylphosphonomethyl-2-hydroxymethylcyclohexanes **189** by PS lipase-catalyzed transesterification acetylation of diols in an organic solvent in moderate yields (~40%) and high enantiomeric excess. The optically active alcohol **190** was transformed into hydantoins **191** (Scheme 71).[205]



Lipase	**184,** *ee* (%)	**185**, *ee* (%)
Lipozyme	96	99
Amano Ak	96	97
CALB	14	91
PPL	99	22
CRL	54	8

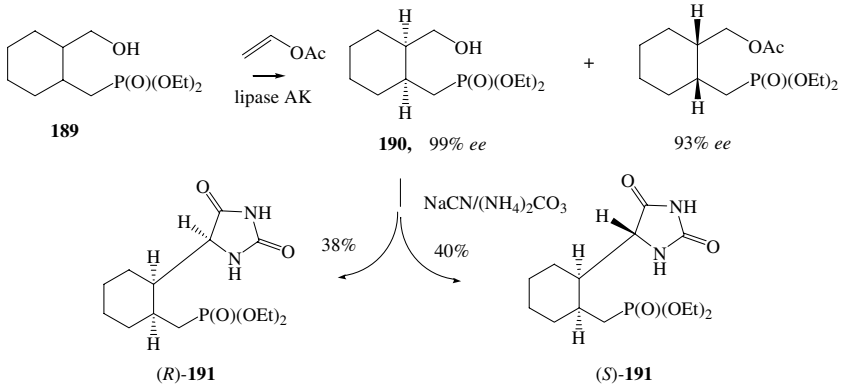
Scheme 69. Enzymatic synthesis of enantiomerically enriched (3-acetoxy-1-butenyl) phosphonates.



Z=CH_2 (a), CH_2CH_2 (b), CH_2CF_2 (c), X=Boc, Cbz=BnOCO; OS = Organic Solvent

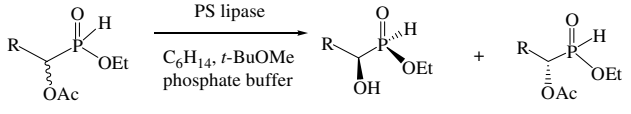
Lipase	Solvent	Yield of **187a** (%)	*ee* of **187a** (%)
AK	*i*-Pr_2O	98	70
PS	*i*-Pr_2O	92	98
PS	*i*-Pr_2O	88	83
PS	THF	98	98
PS	C_6H_6	94	98
PS	C_6H_{14}	72	79

Scheme 70. Enzymatic enantiodiscrimination of prochiral diols.



Scheme 71. Lipase catalyzed kinetic resolution of hydroxyphosphonates.

Shibuya et al.[206] used a *Pseudomonas cepacia* lipase-controlled hydrolysis of racemic or enantiomerically enriched acetates for the preparation of α-hydroxy-*H*-phosphinates in 74–99% ee. Enantiomerically enriched hydroxyphosphonates **192**, which were prepared by an Abramov reaction, were then additionally purified by *P. cepacia* lipase-controlled acetylations and enzymatic hydrolysis (Scheme 72). This methodology allowed us to increase the enantiomeric excess of hydroxyphosphonates **193** up to 93–99% ee (Scheme 73).[207]



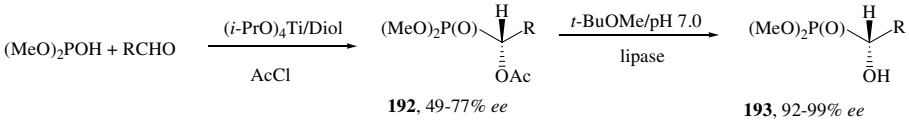
R= 4-MeC_6H_4, Ph, 4-ClC_6H_4, Bn, n-C_5H_{11}

Scheme 72. Lipase controlled preparation of α-hydroxy-*H*-phosphinates.

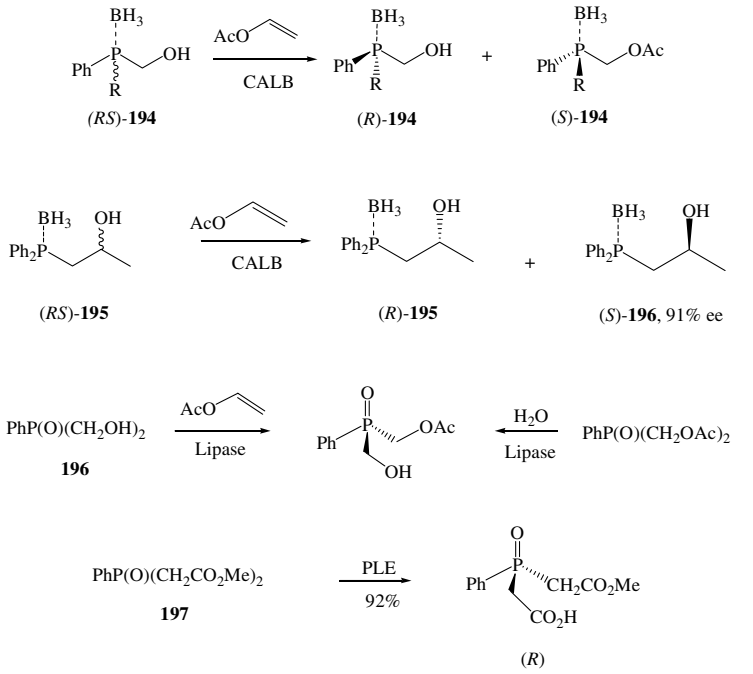
In recent years, the enzymatic resolutions have been used for the preparation of chiral hydroxyalkylphosphines derivatives. For example, the racemic phosphine–borane complexes **194** and **195** were resolved to enantiomers by lipase-catalyzed acetylation with CALB or *Pseudomonas fluorescence* enzymes in good yields and high enantiomeric excess.[189] The prochiral bis(hydroxymethyl)phenylphosphine oxide **196** was dessymetrized by means of enzymatic acetylation of vinyl acetate in an organic solvent. The prochiral *tertiary* phosphine oxides **197** were transformed into chiral (*R*)-monoacetate by PLE-controlled hydrolysis in 92% yield and with 72% ee (Scheme 74).[203]

Enantioselective hydrolysis of *O*-acetyl derivatives **198** controlled by PFL resulted in the formation of hydroxyalkylphosphonates in good enantiomeric excess (~92% ee) (Table 8).[208]

Racemic 2-hydroxyalkylphosphonates **199** were acetylated under kinetic resolution conditions in the presence

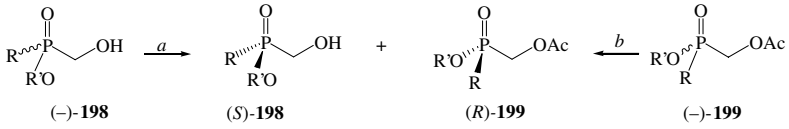


Scheme 73. Enzymatic post treatment of enantiomerically enriched hydroxyphosphonates.



Scheme 74. Enzymatic preparation of tertiary phosphine derivatives.

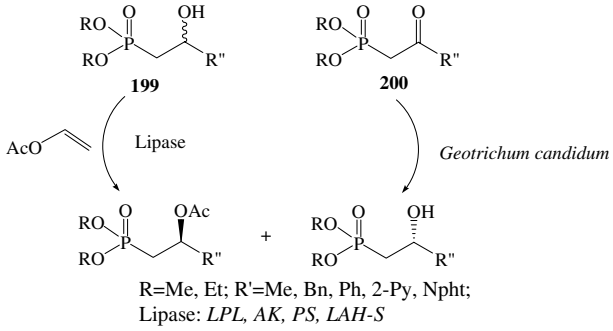
Table 8. Enzyme promoted resolution of racemic *O*-acetyl hydroxyphosphonates



a= vinylacetate, PFL; b=H_2O/PFL

R	R′	Method a			Method b		
		Yield (%)	ee of **198** (%)	Config	Yield (%)	ee of **199** (%)	Config
Ph	Me	44	80	*R*	39	89	*S*
Ph	Et	42	54	*R*	44	47	*S*
Ph	*i*-Pr	37	80	*R*	46	21	*S*
Pr^iO	Me	55	~92	*S*	45	~92	*R*

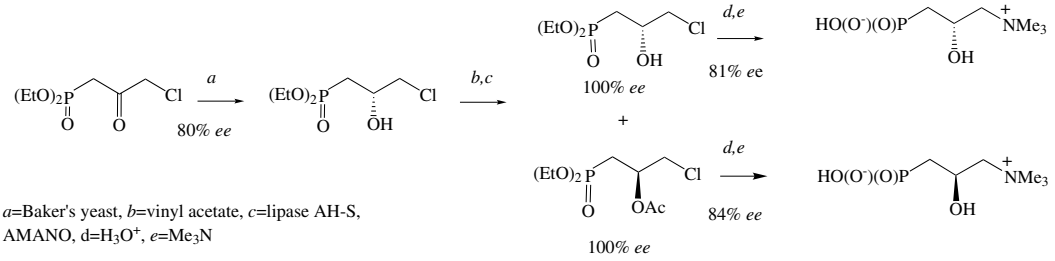
of various lipases with formation of enantiomerically pure (*S*)-2-acetoxyalkylphosphonates and reduced alcohols in good yield and with ee up to 93%. The enantiomerically pure (*R*)-(+)-diethyl 2-hydroxypropanphosphonates were also prepared by a *Geotrichum candidum* controlled reduction of the corresponding 2-ketophosphonate. *G. candidum* is a fungus which is very effective in the stereoselective reduction of ketones. For example, diethyl 2-oxopropylphosphonate **200** was converted into diethyl (*R*)-(+)-2-hydroxypropylphosphonate in 47% yield and 98% ee (Scheme 75).[209]



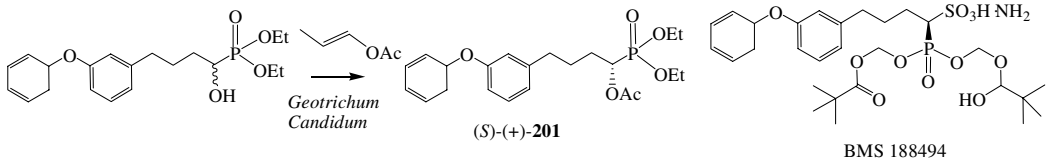
Scheme 75. Enzymatic synthesis of 2-hydroxyalkylphosphonates.

Glyphosate analogues and bis(hydroxymethyl)phosphorylmethylphosphonic acids were synthesized in good yields, using a bis(benzyloxymethyl)chloromethylphosphine oxide as a starting reagent.[210]

Baker's yeast reduction and enzymatic kinetic resolution afforded the enantiomerically pure (*R*)- and (*S*)-precursors of (*R*)- and (*S*)-phosphocarnitine, which were converted to (*R*)- and (*S*)-phosphocarnitine. Mikolajczyk et al. used chemoenzymatic synthesis for the preparation of both enantiomerically pure stereoisomers of phosphocarnitine (Scheme 76).[211]



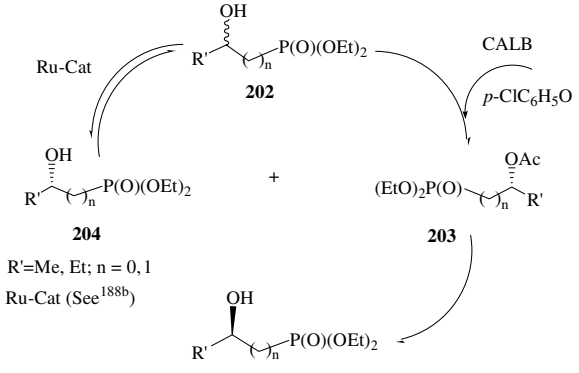
Scheme 76. Chemoenzymatic synthesis of phosphocarnitine.



Scheme 77. Synthesis of inhibitor squalene synthase BMS 188494.

The stereoselective acetylation of racemic [l-(hydroxy)-4-(3-phenyl)butyl]phosphonate with isopropenyl acetate was performed in toluene using *G. candidum* lipase. The chiral (*S*)-[1-(acetoxy)-4-3-phenylbutyl]phosphonate **201** was prepared as an intermediate for the total synthesis of a squalene synthase inhibitor, BMS 188494. The chiral hydroxyphosphonate **201** was obtained by this method in 37% yield and 95% ee (Scheme 77).[180]

Pàmies and Bäckvall[188] developed a method of dynamic kinetic separation of hydroxyphosphonates which increased the yield of the major product (Scheme 78). Enzymatic kinetic separation of racemic α- and β-hydroxyphosphonates **202** was combined with ruthenium catalyzed racemization of substrate **204** to afford the enantiomerically pure acetate of (*R*)-hydroxyphosphonates **253** in 99% ee.



Scheme 78. Dynamic kinetic separation of hydroxyphosphonates.

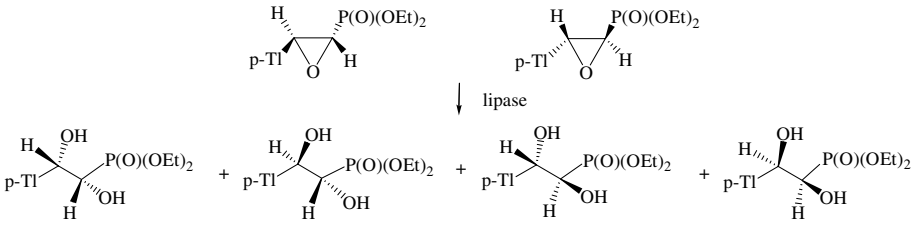
Hydrolytic opening of the oxirane ring using epoxide hydrolases or microbial cell cultures was used for the preparation of enantiomerically pure hydroxyphosphonates.[212] In contrast to chemical hydrolysis, biocatalysis gave *erythro*-1,2-dihydroxyphosphonates, with *threo*-isomers being the minor ones. Thus the chemical hydrolysis of epoxyphosphonate afforded the 85:15 mixture of *threo*- and *erythro*-stereoisomers in 79% yield, whereas the enzymatic hydrolysis with *Beauveria bassiana* afforded the 42:58 ratio of these stereoisomers in 59% yield. This pattern of reaction is typical for all the microorganisms used, namely *Aspergillus niger*, *Cunninghamella elegans*, *B. bassiana*, *Beauveria brongnartii*, *R. glutinis* and *Rhodococcus* sp. In all the cases the major *threo*-isomer formed in high enantiomeric excess (Scheme 79).

2.5. Asymmetric synthesis of hydroxyfluorophosphonates

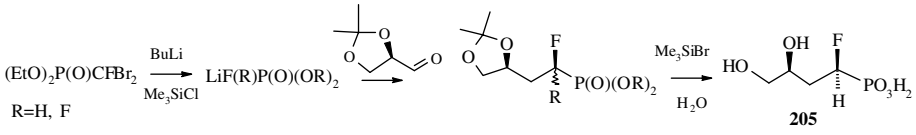
α-Monofluoromethyl and α,α-difluoromethylphosphonates are isosteres of natural phosphates and the pyrophosphates formed by the replacement of the bridging ester oxygen atom by CHF or CF_2-group. Replacement of the oxygen atom in natural phosphates on CH_2 group allowed us to retain the approximate geometry of a molecule and simultaneously to increase the resistance of a molecule to hydrolysis by phosphatase. However, electronegativity of the oxygen atom is higher than the electronegativity of the CH_2 group. Therefore, the replacement of the CH_2 group by CHF or CF_2 groups allows us to improve the conformational characteristics and biological properties of hydroxyphosphonates.[213–232]

For example, O'Hagan[215] described the synthesis of monofluoro- and difluoromethylphosphonates **205**, which are fluorinated phosphonate analogues of *sn*-glycerol-3-phosphate, where the bridging phosphate ester oxygen is replaced by CHF or CF_2 (Scheme 80).[221] Kinetic studies for the oxidation with NADH linked glycerol-3-phosphate dehydrogenase reveal that the CHF-phosphonate performs similarly to the natural substrate *sn*-glycerol-3-phosphate, and is a better substrate than the CF_2-phosphonate. The X-ray analysis of these compounds showed that the geometry of CF_2-phosphonate is the closest to that of *sn*-glycerol-3-phosphate (Scheme 81).[215]

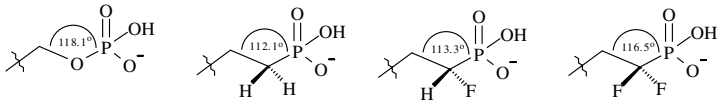
Several methods have been proposed for the preparation of fluorophosphonates. For example, the important



Scheme 79. Representative example of biocatalytic ring opening in epoxyethylphosphonates.



Scheme 80. Synthesis of hydroxyl(fluoro)alkylphosphonates via a metal–halogen exchange reaction.

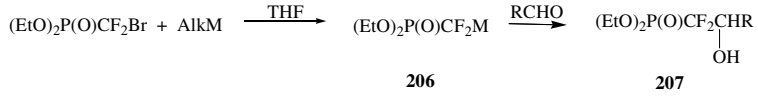


Scheme 81. C–X–P angles of *sn*-glycerol-3-phosphate analogues obtained from X-ray structure data.

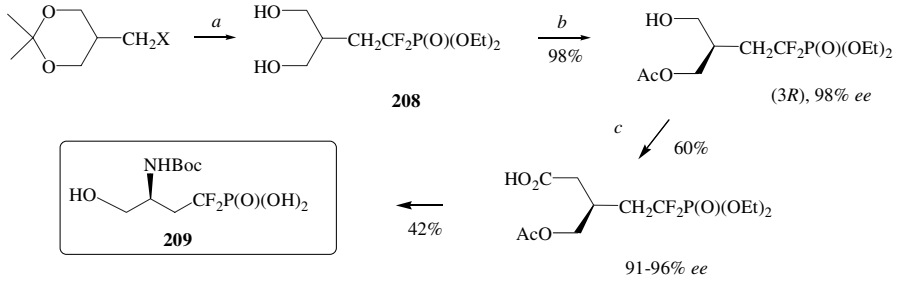
method for the preparation of hydroxyfluorophosphonates is metal–halogen exchange reaction of halogen methylphosphonates with metal alkanes (butyl lithium or organomagnesium).[214] 1,1-Difluoro-2-hydroxyphosphonates were prepared from diethyl bromodifluoromethylphosphonate by this method via a metal–halogen exchange reaction with isopropylmagnesium chloride. Organomagnesium derivate **206** reacted with aldehydes and ketones to yield, in high yields, the 1,1-difluoro-2-hydroxyphosphonates **207** (Scheme 82).[214a] This method was used for the preparation of free acids inhibitors of protein phosphatases.[214b]

Enzymatic methods have been used for the preparation of chiral hydroxyfluorophosphonates. Lipase PS catalyzed acetylation of prochiral 2-(ω-phosphono)alkyl-1,3-propanediols **208** was found to proceed with high enantioselectivity (98% ee). Application of the phosphonic chirons thus obtained was illustrated by the stereocontrolled synthesis of ω-phosphono-α-aminoacids **209** (98% ee) (Scheme 83).[204]

Yokomatzu described sphingomyelin analogues **212** and **213**, in which the long alkenyl chain and the phosphodiester moiety of sphingomyelin were replaced by a phenyl and an isosteric difluoromethylenephosphonic acid. The analogues **212** and **213** were synthesized from aldehyde **210**[213] (Scheme 84). Aldehyde **210** was treated with lithium diethyl difluoromethylphosphonate to give a 1:1 diastereomeric mixture of phosphoaldol adducts **211**.

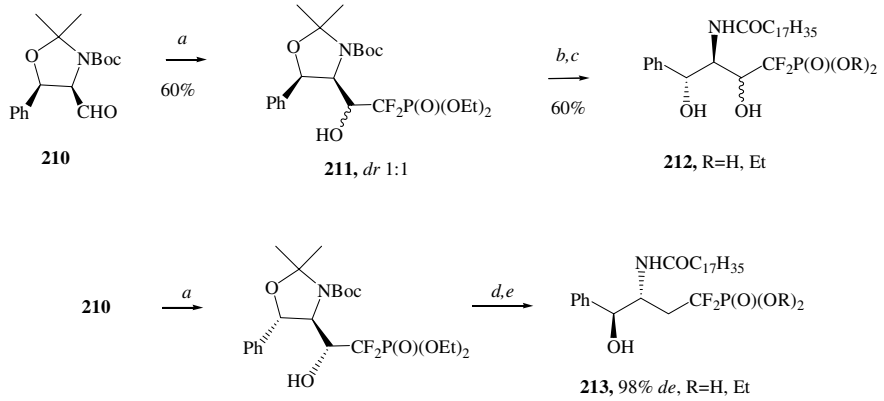


Scheme 82. Preparation of difluoromethylhydroxyphosphonates **206**.



a=$LiCF_2P(O)(OEt)_2$; *b*=Lipase *PS*, vinyl acetate; *c*=$RuCl_3$, $NaIO_4$; *d*=DPPA, Et_3N, BnOH

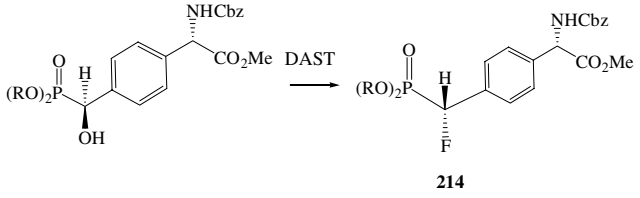
Scheme 83. Enzymatic synthesis of chiral hydroxyfluorophosphonates.



Scheme 84. Asymmetric synthesis of non-competitive inhibitors of Sphingomyelinases. Reagents: (a) **211**,[213] $LiCF_2P(O)(OEt)_2$, (b) HCl, palmitoyl chloride, Et_3N; (c) TMSRr, MeOH; (d) *n*-BuLi, ClC(S)OPh; (e) Bu_3SnH, AIBN.

The deprotection of the diethyl ester afforded **212** in virtually quantitative yield. Analogues of *N*-palmitoylsphingosine-1-phosphate **213** were prepared with very high stereoselectivity (98% de). Deoxygenation of β-hydroxyfluorophosphonate into δ-hydroxyfluorophosphonate **213** was achieved via the corresponding phenylthionocarbonate by the Martin procedure.[22b] Compound **212** had the ability to suppress tumour necrosis factor α-induced apoptosis of PC-12 neurons at a low concentration of 0.1 mM (Scheme 84).[15,22]

Fluorophosphonates can be prepared by treatment of hydroxyphosphonates with DAST leading to the replacement of CH–OH group with CHF-group.[138,212] Analogues of phosphorylated tyrosine **214** were stereoselectively prepared by DAST deoxofluorination of obtained hydroxyphosphonates. The reaction proceeded via the S_N2 mechanism and inversion of a configuration



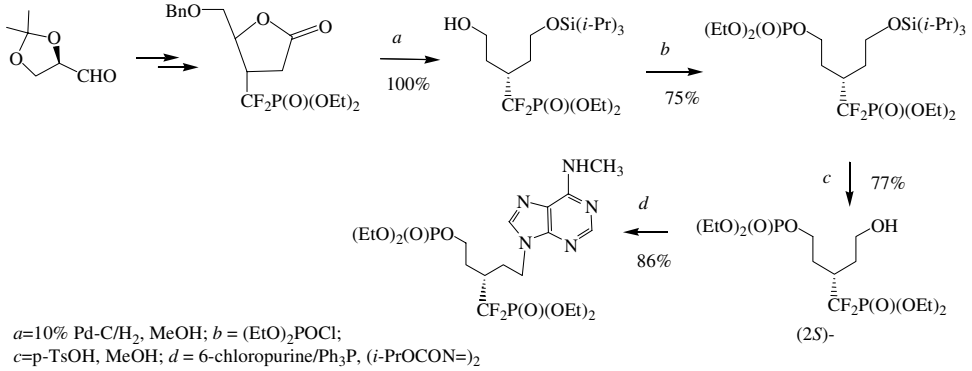
Scheme 85. Synthesis of α-fluorophosphonates by action of DAST.

to give chiral monofluoromethylene phosphonates (Scheme 85).[84,138,213]

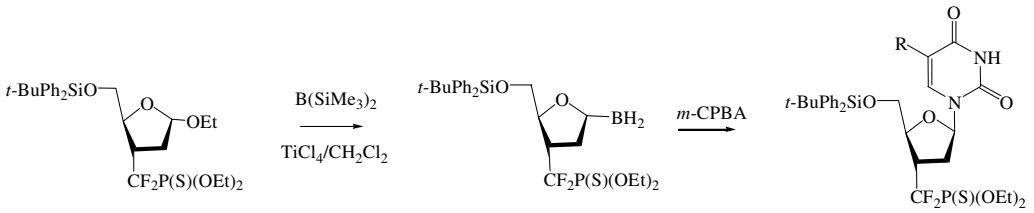
A synthetic approach to a new type of acyclic nucleotide analogues, having difluoromethylene phosphonyl group in a lateral chain was recently reported.[217] These compounds were enantio-divergently prepared in good yields and high enantiomeric purity as their ester-protecting derivatives from a highly differentiated 1,5-pentanediol derivative possessing a difluoromethylenephosphonyl group at the 3-position. The prepared compounds are acyclic modification of MRS 2179, containing the isosteric difluoromethylenephosphonyl group, which are $P2Y_1$-antagonists (Scheme 86).

Recently, a three-step synthesis of γ-fluoroallylphosphonates starting from α,β-unsaturated aldehydes was described.[218] The treatment of (*E*)-diethyl 3-fluoro-2-hexenylphosphonate with $LiN(TMS)_2$ and benzaldehyde in THF led to the preferential formation of *syn*-(*Z*)-diethyl 3-fluoro-1-(hydroxybenzyl)-2-butenylphosphonate. Hammond et al.[219] proposed an improved synthesis of α-fluorinated propargylphosphonates and the solid-phase synthesis of α-hydroxy-γ-TIPS propargylphosphonates.

The titanium tetrachloride-mediated *N*-glycosylation of 2,3-dideoxyribofunanosides having a (diethoxyphosphorothioyl)difluoromethyl group at the 3α-posi-



Scheme 86. The synthesis of difluoromethylene isosteric analogues of MRS 2179.



Selectivity:X=Me, *dr*=89:11; H, *dr*=87:13; F, *dr* 76:24

215

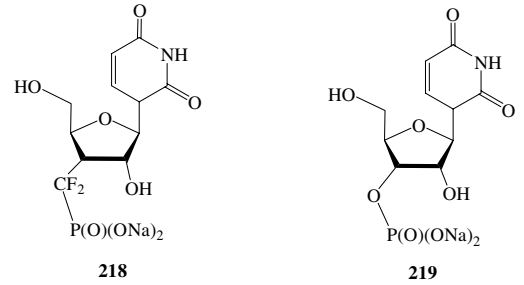
Scheme 87. *N*-Glycosylation of 2,3-dideoxyribofuranosides.

tion with silylated nucleobases was described.[220] The nucleotide analogues were transformed into the difluoromethylenephosphonate analogue of thymidine-3′-phosphate **215** by oxidation with *m*-CPBA, followed by aqueous work-up (Scheme 87).

Radical cyclization of allylic α,α-difluorophosphonates was applied to construct the α,α-difluorophosphonate-functionalized oxacycles **216**. Hydroxyphosphonates **216** were used for the preparation of 1,1-difluoro-2-(tetrahydro-3-furanyl)ethylphosphonic acids **217** possessing a (purine-9-yl)methyl functionality at the ring, which were tested as 'multi-substrate analogue' inhibitors for purine nucleoside phosphorylases. The stereochemistry of inhibitors **217** was found to significantly affect the inhibitory potency. The trans-isomers were about 4-fold less potent than the corresponding *cis*-isomers (Scheme 88).[11,21]

A conformational analysis of nucleoside-3′-phosphates **218** and difluorophosphonates **219** reveals that the difluorophosphonate function, a phosphate mimic, governs the conformational behaviour of the ribofuranose.[223] The discrepancy between the difluorophosphonate group-modified **218** and the natural nucleoside **219** clearly shows that the introduction of a difluorophosphonate group at the C3' position strongly affects the conformational distribution, although the difluorophosphonate group are considered as close mimics of the phosphate function (Scheme 89).

Over the last few years, chemists have become attracted to fluorophosphonates containing cyclopropyldifluoromethyl groups.[222–224,227] 1,1-Difluoro-2-(tetrahydro-3-furanyl)ethylphosphonic acids possessing the (purine-

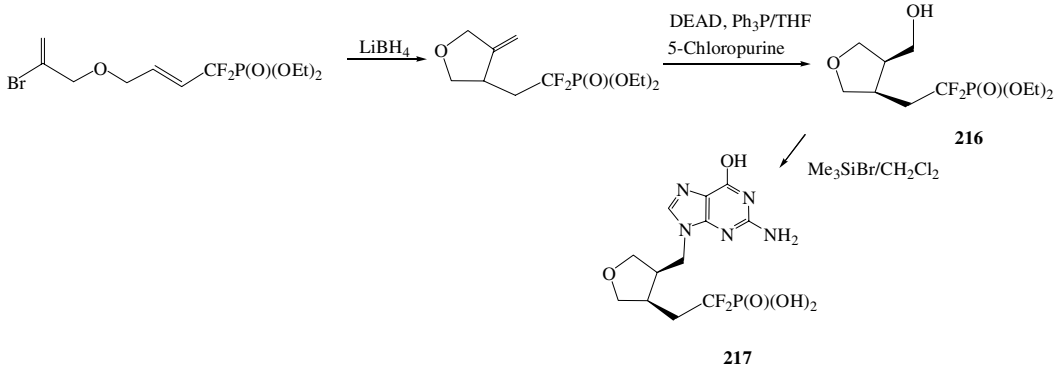


218 **219**

Scheme 89. Conformational analysis of nucleoside-3′-phosphates and difluorophosphonates.

9-yl)methyl functionality in the ring were synthesized and tested as 'multi-substrate analogue' inhibitors for purine nucleoside phosphorylases.[26,224] The reduction of diethyl [(1*S**,2*S**)-2-acetylcyclopropyl](difluoro)-methylphosphonate **220** with potassium-selectride proceeded from the less-hindered face of the carbonyl in the bisected *s-cis* conformation to give the corresponding cyclopropylalkanol **221** in high diastereoselectivity (96% de).[224] The 1,1-difluoro-5-(1*H*-9-purinyl)-2-pentenylphosphonic acids,[222] *cis*- and *trans*-isomers of 1,1-difluoro-2-(tetrahydro-3-furanyl)ethylphosphonic acids were synthesized analogously.[223] The cyclopropane ring and the hypoxanthine residue increased the profile of inhibitory activity (Scheme 90).[222]

Conformationally constrained analogues of *ent*-9-(difluorophosphonopentyl)guanines, a multi-substrate analogue inhibitor of PNP, were prepared from optically active *trans*-1-(diethoxyphosphinyl)difluoromethyl-2-hydroxymethylcyclopropanes **222**.[227] Enzymatic double



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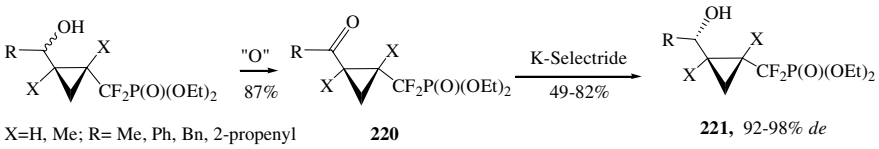
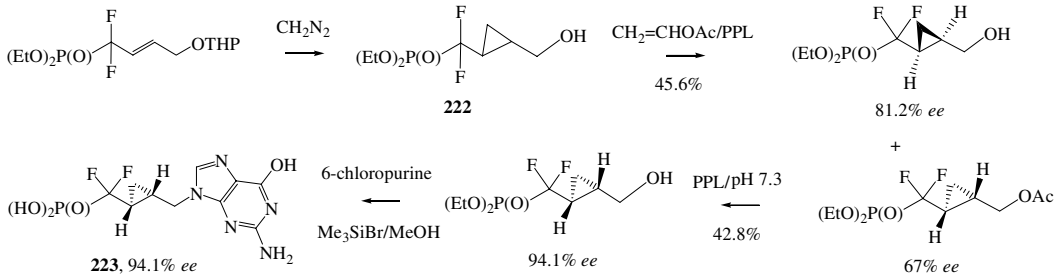
217

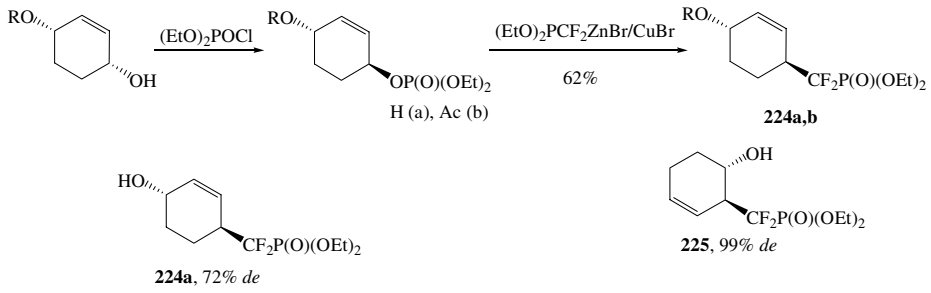
Scheme 88. Asymmetric synthesis of inhibitors for purine nucleoside phosphorylase.



Scheme 90. Asymmetric synthesis of cyclopropyl(difluoro)methylphosphonates.



Scheme 91. The synthesis of conformationally constrained analogue of PNP inhibitors.



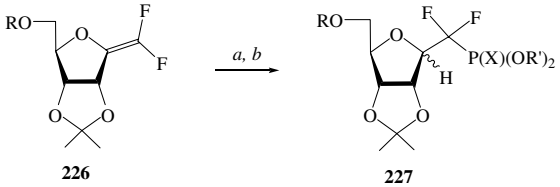
Scheme 92. The synthesis of cyclohexenedifluoromethylphosphonates **224** and **225**.

resolution with PPL was applied to obtain (+)-**223** and (−)-**223** in high enantiomeric purity. (Scheme 91).[26] The synthesis of enantiomerically pure (2′*S*,3′*S*)-9-(4′-phosphono-4′,4′-difluoro-2′,3′-methanobutyl) guanine possessing properties of purine nucleoside phosphorylase inhibitors has been also when described.[27]

Shibuya[228] has described the synthesis of cyclohexenedifluoromethylphosphonates **224** and **225**, from cyclohex-2-enyl-1-phosphates, which are intermediates in the stereoselective synthesis of inositol phosphate analogues.[226] The reaction of diethoxyphosphoryldifluoromethylzinc bromide ($BrZnCF_2PO_3Et_2$) with highly functionalized cyclohex-2-enyl-1-phosphates in the presence of CuBr in THF provides a facile method for introducing a difluoromethylenephosphonate unit to the allylic position within a cyclic array in a stereo- and regioselective manner (Scheme 92).

The reaction of dialkylthiophosphites with difluoroalkylidene carbohydrates **226** resulted in the formation of anomeric difluoromethylenephosphonates **227a** and difluoromethylenethiophosphonates **237b** (Scheme 93).[230]

The method for the synthesis of the fluorophosphonate analogues of *N*9-benzylguanine, which possesses the properties of PNP inhibitors, has been developed.[231]

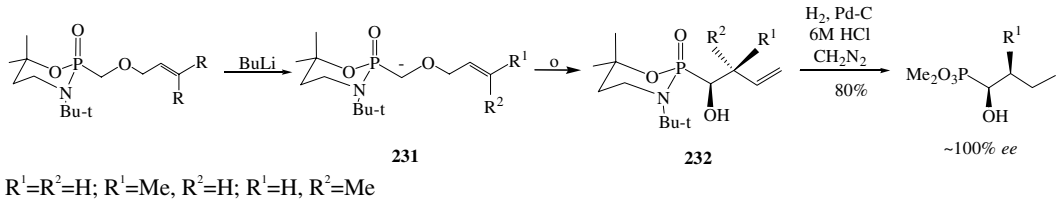


a = H-P(X)(OR)$_2$;R=Et, Bn; *b* = PhSP(O)(OEt)$_2$, *n*-Bu$_3$SnH; X= O,S
R=H, R';=Et, X=O, 44%, 1:9 dr; R= t-BuMe$_2$Si, R'=Bn, X=S, 76%, 1:9 dr;
R= *t*-BuMe$_2$Si, R'=Et, X=S, 94%,1:9 dr;

Scheme 93. Anomeric difluoromethylenephosphonates and difluoromethylenethiophosphonates.

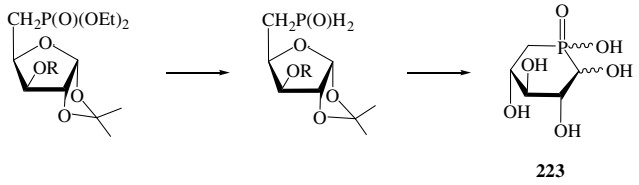
2.6. Miscellaneous reactions

An asymmetric [2,3]-sigmatropic Wittig rearrangement was used in the synthesis of α-hydroxyphosphonates.[47,233,234] The asymmetric [2,3]-Wittig rearrangement of chiral phosphonate carbanions proceeded with high diastereo- and enantioselectivities in the case of allyloxymethyl- and (*Z*)-2-butenyloxymethyl derivatives. Deprotonation of allylphosphonates with butyllithium in THF at −70 °C afforded the stable phosphonate carbanion **231**, which easily underwent the [2,3]-sigmatropic Wittig rearrangement to convert into the single diastereomer **232** (Scheme 94).[47]



Scheme 94. Asymmetric [2,3]-sigmatropic Wittig rearrangement.

Analogues of D-glucose-, 5-deoxy-5-*C*-(hydroxyphosphinyl)-D-xylose, 5-deoxy-5-*C*-[(*R*,*S*)-methoxyphosphinyl]-α,β-D-xylo-pyranoses[236] were also described (Scheme 95).[101]



Scheme 95. Synthesis of phosphinylcarbohydrates.

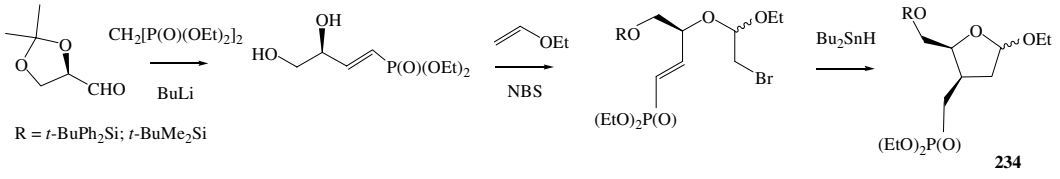
Shibuya reported the synthesis of methylenephosphonate analogues of 2-deoxyriboso-3-phosphates **234** via an intramolecular addition and radical ring formation of vinylphosphonates with diastereoselectivity of 92% de. Diastereomerically pure **234** was isolated after column chromatography on silica gel (Scheme 96).[237]

The reaction of dialkylphosphite with chiral chalcon–epoxides was reported.[235] The reaction of optically active bis-dialkylamidophosphite lithium with achiral 1,2-epoxybutane resulted in hydroxyalkylphosphonates **235** with 33% de. The reaction of chiral epoxides **236** with the achiral lithium diethylphosphite also proceeded with a low stereoselectivity to afford racemic **237** (Scheme 97).[148]

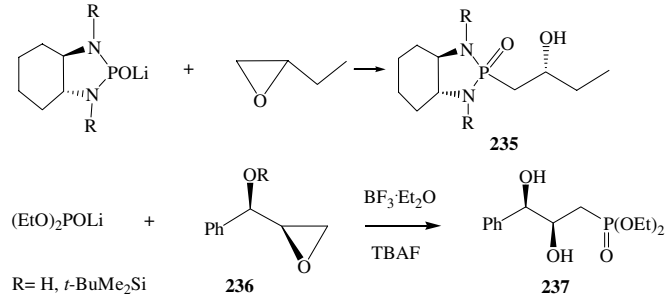
The synthesis of pharmacologically active hydroxyalkyl-bis-phosphonates attracted special attention. For example Michaelis–Becker reaction of methylenesulfonates with dialkyl phosphites afforded methylenecyclopropylphosphonate nucleosides possessing antiviral activity.[238] The reaction of (*S*)-(+)-(1-diethoxyphosphoryl) vinyl-*p*-tolylsulfoxide with the ethyl (dimethyl-sulfuranylidene)acetate has resulted in the formation of (1*S*,2*S*)-(1-diethoxyphosphoryl)-2-ethoxycarbonyl-cyclopropyl-*p*-tolylsulfoxide, which was converted into enantiomerically pure cyclopropylphosphonate.[238]

Hydroxyl groups of hydroxyphosphonates were substituted into amino groups via the Mitsunobu reaction.[239] (*R*)-(−)- and (*S*)-(+)-diisopropyl 1-hydroxycyclohexylmethylphosphonates **238**, which were obtained by kinetic resolution of racemic compounds with lipase AP6, were then converted into the optically active (*S*)-(+)- and (*R*)-(−)-α-aminocyclohexyl-methylphosphonic acids **239** in ~90% ee. The substitution of the hydroxyl group with an azide group proceeded with inversion of the absolute configuration (Scheme 98).

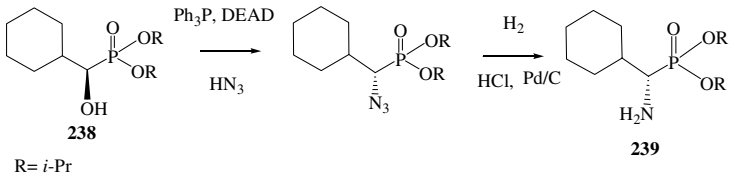
The α-amino-β-hydroxyalkylphosphonic acids **240**, isosteric analogues of phenylalanine and β-alkylserines, were synthesized by asymmetric aldol condensation of aldehydes with (isocyanomethyl) phosphonates, catalyzed with the chiral complex of ferrocenylphosphine



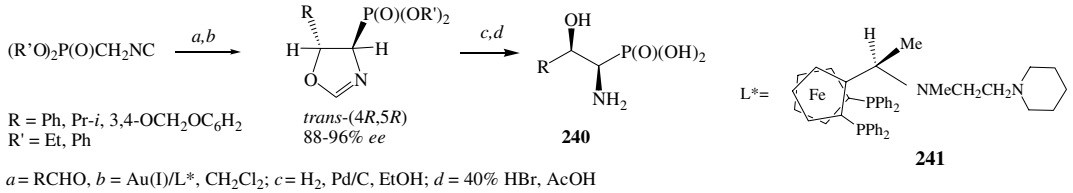
Scheme 96. Synthesis of methylenephosphonate analogues of 2-deoxyriboso-3-phosphates.



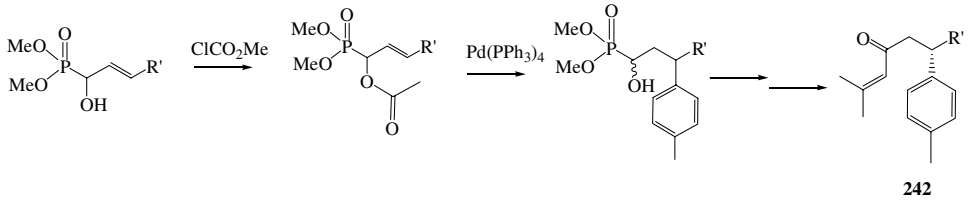
Scheme 97. Reaction of lithium phosphites with epoxides.



Scheme 98. Substitution of OH-groups in hydroxyphosphonates on NH_2 via the Mitzunobu reaction.



Scheme 99. Asymmetric aldol condensation catalyzed with the chiral complex of ferrocenylphosphine gold(I).

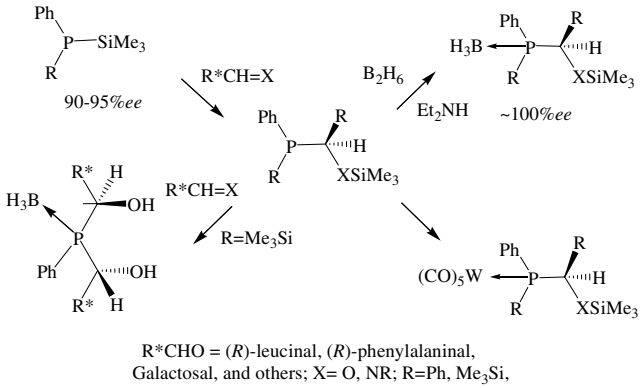


Scheme 100. The synthesis of (*S*)-(+)-*ar*-turmorene.

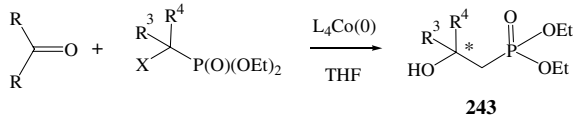
gold(I) **241**. The enantiomeric excess of the reaction products attained 88–96% ee (Scheme 99).[240]

Spilling[241,242] described the stereoselective arylation of hydroxyallylphosphonates and has applied this reaction for the synthesis of (*S*)-(+)-*ar*-turmorene **242** (Scheme 100).

Hydroxyphosphonic acids and organophosphorus analogues of carbohydrates attracted a growing interest as potential biologically active materials. The asymmetric synthesis of diphenyl (1*S*,2*R*)-1,2,3-trihydroxypropylphosphine oxides was developed from structural analogues of the erythrose open form. Silylphosphines reacted with chiral aldehydes to give the optically active tertiary α-hydroxyalkylphosphines in high stereoselectivity, obtaining in some cases 98% de. These compounds were purified and isolated in good yields as borane complexes (Scheme 101).[243–245]



Scheme 101. The optically active tertiary α-hydroxyalkylphosphines.



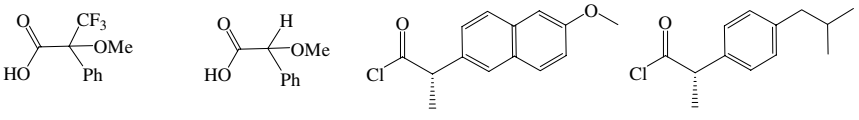
Scheme 102. The preparation of β-hydroxyphosphonates via the Reformatsky reaction.

Low-valent cobaltous complexes were used in the Reformatsky reaction of α-halogenephosphonates with ketones and aldehydes for the preparation of various β-hydroxyphosphonates **243** (Scheme 102).[246]

Shuster et al.[246b] developed an enantioselective synthesis of dihydroxylated pyrrolidines bearing an ethylphosphonyl substituent. Starting from achiral reactants, two stereoisomeric phosphonylated dihydroxypyrrolidines containing four stereogenic centres were synthesized enantioselectively by employing a combination of enzymatic and transition-metal-mediated methods.

3. Absolute configuration of hydroxyphosphonates

The enantiomeric purity of dialkyl 1-hydroxyalkylphosphonates can be determined by derivatization



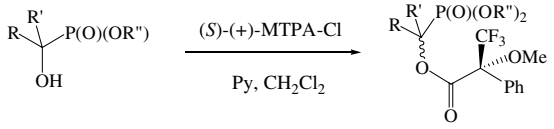
244 245 246 247

Scheme 103. Chiral derivatizing reagents.

with chiral reagents resulting in the diastereomers of these compounds. In particular, the derivatization of hydroxyphosphonates with α-methoxy(trifluoromethyl)phenylacetic acid **244** (MTPA, Mosher acid),[214,247–249] camphoric acid,[250] mandelic acid **245**,[215,251] phosphono-didepsipeptides,[251–253] and diazaphospholidine chloride[254] was described. (*S*)-Naproxen® chlorides **246** and (*S*)-ibuprofen® chlorides **247** are convenient chiral derivatizing reagents for the determination of the enantiomeric purity of α- and β-hydroxyalkylphosphonates by ^{31}P NMR spectroscopy.[249] The ^{1}H NMR spectroscopy of chiral 1-(1-naphthyl)ethylamine salts of hydroxyphosphonic acids,[255] NMR in chiral medium, GLC with chiral stationary phase,[176] and others[256] were also used (Scheme 103).

The Mosher's method for the determination of the absolute configuration of chiral phosphonates has become very popular in recent years. The absolute configuration of α-hydroxyphosphonates was determined by derivatization with Mosher reagent **194** and application of ^{1}H, ^{19}F and ^{31}P NMR spectroscopy.[247–249] Chemical shifts δ_P of derivatized (*S*)-hydroxyphosphonates are usually in down field relationship to signals of the corresponding (*R*)-hydroxyphosphonates. The difference in chemical shifts δ_P (0.40–1.09 ppm) allows us to determine absolute configurations of hydroxyphosphonates (Scheme 104).

The conformation model of Mosher's esters derived from α-hydroxyphosphonates (Scheme 105), shows that

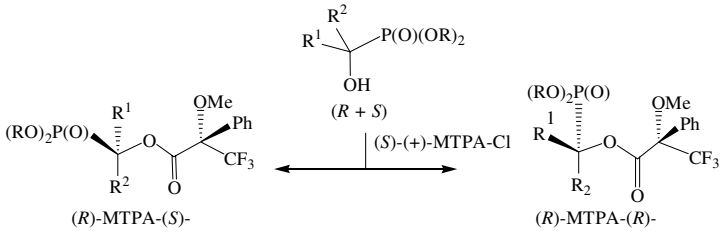


Scheme 104. Preparation of Mosher's esters from α-hydroxyphosphonates.

the trifluoromethyl group and the carbinyl hydrogen at C=O group (R_2 = H, D) are eclipsed by the carbonyl oxygen. The phosphorus atom in the (*R*)-MTPA ester was shielded by the phenyl group if the chiral alcohol had an (*R*)-configuration at C-1 relative to alcohol having an (*S*)-configuration. Therefore, the chemical shift of the phosphorus atom in the ^{31}P NMR spectra of the (*R*)-MTPA derivatives of (*R*)-hydroxyphosphonates will be upfield when compared with those of the (*S*)-alcohol.

The ^{31}P NMR spectra of (*R*)-MTPA esters with (*S*)-hydroxyphosphonates confirmed that their signals δ_P are indeed downfield and that signals δ_P of (*R*)-hydroxyphosphonates derivatized with (*R*)-MTPA esters are upfield. The shift differences were within 0.28–0.50 ppm (Table 9).[248]

Yokomatzu et al.[227,226] determined the absolute configuration of dihydroxyphosphonates **248** by converting them into the cyclic acetonides **249**. The dihedral angles between HCCP were calculated by MOPAC semiempirical program. On the basis of these calculations and the phosphorus version of Karplus equations, a large vicinal proton–phosphorus coupling constant ($^{3}J_{PH}$ = 17.2 Hz) was expected for *trans*-**249**, while a small coupling constant ($^{3}J_{PH}$ = 1.7 Hz) was assumed for the *cis*-isomer. Careful analysis of the ^{1}H NMR spectrum of *cis*- and *trans*-**249** established the vicinal coupling constant to be 10.1 and 9.8 Hz, respectively, suggesting their *trans* relative stereochemistry. The (*S*)-absolute configuration of compounds **250** was confirmed also by means of ^{31}P NMR analysis of their (*R*)-MTPA esters. The δ_P chemical shifts of (*S*)-diastereomers in low field of the ^{31}P NMR spectra were assigned to the (*S*)-configuration. Hence the results obtained by the two alternative methods coincided and consequently the absolute configuration of initial compounds was unambiguously established as (1*S*,2*S*) (Scheme 106).

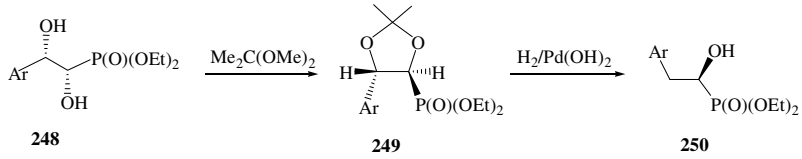


Scheme 105. Conformation model of Mosher esters derived from α-hydroxyphosphonates.

Table 9. Assignment of configuration of α-hydroxyphosphonates via their Mosher esters

$(RO)_2P(O)H + R'CH{=}O \longrightarrow (RO)_2P(O)CH(OH)R'$

R^1	R^2	R^3	δ_P, ppm		$\Delta\delta$
			(*S*)	(*R*)	$[\delta(S) - \delta(R)]$
Et	H	Me	22.21	21.77	0.44
i-Pr	H	Et	19.33	18.93	0.40
C_5H_{11}	H	Et	19.90	19.43	0.47
$PhCH_2CH_2$	H	*i*-Pr	17.42	17.01	0.41



248 **249** **250**

Scheme 106. Determination of absolute configuration of dihydroxyphosphonates **248**.

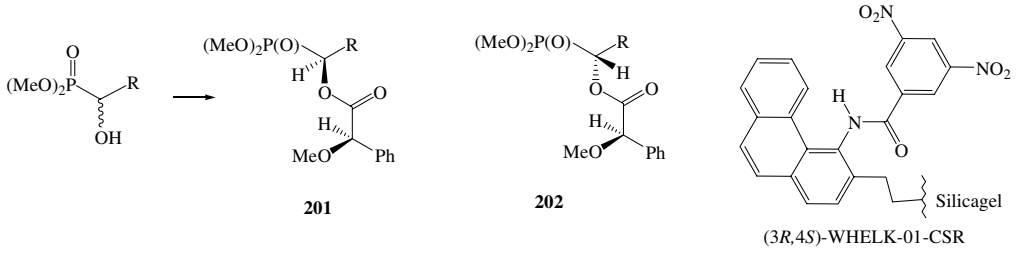
The enantiomeric purity and absolute configuration of α-hydroxyphosphonates can be determined by ^1H and ^{31}P NMR spectroscopy of the mandelate ester derivatives.[251] The observed chemical shifts allowed the assignment of the absolute configuration of the hydroxyphosphonates by the position of phenyl group in compounds and its shielding effect. Thus, the ^1H NMR spectra of (1*S*,2*R*)-diastereomers **251** and **252** showed a downfield shift of signals for the *O*-methyl protons, relative to the parent alcohol. The absolute configuration of compounds **252** was additionally determined by X-ray analysis.

Pirkle et al.[257] analyzed α-aryl-α-hydroxymethanphosphonates by liquid chromatography on chiral stationary phase, CSP1. They found that the *dextro*-enantiomers of hydroxyphosphonates were preferentially retained by the chiral (3*R*,4*S*)-WHELK-O1 stationary phase and assigned the (+)-(*S*)-configuration (Scheme 107). The hydroxyphosphonates contain the basic centre and acceptor of hydrogen bond on the stereogenic centre which approved the efficient differentiation of enantiomers of these compounds with chiral CSP-1. The phosphinyl oxygen forms more strong hydrogen bonding to the amide of N–H of the selector, than is the hydroxyl oxygen. Therefore, the (*R*)-enantiomers of these hydroxylphosphonates should be the more retained on the chiral (3*R*,4*S*)-CSP-1.

The absolute configuration of the hydroxyphosphonates was defined by CD spectra.[63,156,208] For example, Wynberg et al.[156] determined the absolute configurations of some chiral α-hydroxyphosphonates **253** by CD spectra (X = H, HO_2, F, Cl, Br, NH_2; R = Me). The α-hydroxyphosphonates, which had an (*S*)-configuration, showed negative Cotton effect at 225 nm. Yokomatzu et al.[63] by means of CD-spectra have determined an absolute configuration of some 1,2-dihydroxyphosphonates. They observed, that the α,β-dihydroxyphosphonates **255** having a (1*S*,2*S*)-configuration showed the positive Cotton effect at 230–210 nm, whereas the (1*R*,2*R*)-isomers **254** showed the negative Cotton effect at these wavelengths (Scheme 108).

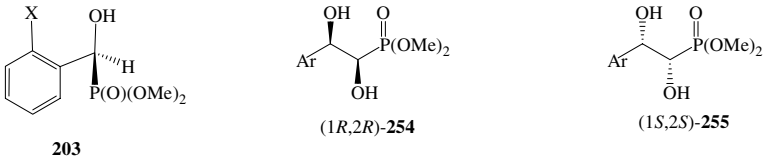
Enantiomerically pure (*Rp*)-*tert*-butylphenylphosphinothioic acid, quinine,[258] cinchonine, and cinchonidine[259] were successfully used for the direct determination of the enantiomeric purity of α-[259] and β-hydroxyphosphonates.[260–262] Enantiomers of hydroxyphosphonates were distinguished by means of both ^1H NMR and ^{31}P NMR.[258–262] Cinchonidine and quinine were the most effective as a chiral solvating agent for the determination of the enantiomeric excess of hydroxyphosphonates.

N-Substituted L-amino acids were used for the determination of the enantiomeric composition of chiral 1-



201 **202** (3*R*,4*S*)-WHELK-01-CSR

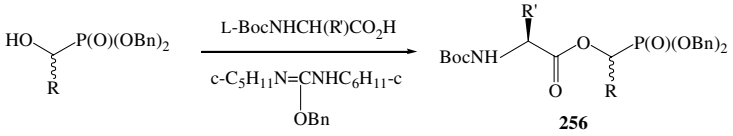
Scheme 107. Analysis of α-hydroxymethanphosphonates by HPLC on chiral stationary phase.



203 (1*R*,2*R*)-**254** (1*S*,2*S*)-**255**

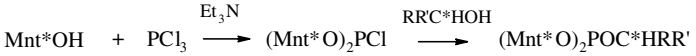
X=H, NO_2, Cl, Br, F, NH_2 Ar = 3-$MeOC_6H_4$, 4-ClC_6H_4, Furyl, 1-Naphthyl

Scheme 108. Chiral phosphonates.



256

Scheme 109. Determination of the enantiomeric excess by means of N-substituted L-amino acids.



257

Scheme 110. The dimenthyl chlorophosphite as derivatizing reagent.

hydroxyalkylphosphonic acids by means of ^{31}P NMR spectroscopy (Scheme 109).[251]

Dimenthylchlorophosphites **257** are convenient chemical derivatizing agents for the determination of the enantiomeric purity of hydroxyphosphonates by ^{31}P NMR (Scheme 110).[263,264]

The measurement of the specific rotations is a convenient method for the determination of enantiomeric purity and absolute configuration of hydroxyphosphonates. We have collected the specific rotation data of α- and β-hydroxyalkylphosphonates, as well as of α,β-dihydroxyphosphonates, carefully analyzed and summarized in Tables 10–12. Some data were additionally verified in our laboratory. Consideration of these rotation data allows us to conclude that (*S*)-hydroxyphosphonates are very often laevororotatory, whereas (*S*)-hydroxyphosphonates are dextrorotatory, however, there are many exceptions.

Table 10. α-Hydroxyalkylphosphonates $(R'O)_2P(O)CH(OH)R$

Entry	R	R′	$[\alpha]_D^{20}$	C (%)	Solvent	ee (%)	Config	Refs
1	Me	Et	−5.5	0.5	MeOH	95	R	183
			+13.6	1.1	$CHCl_3$			183
2	Me	*i*-Pr	+5.9	1.07	Me_2CO	89	*S*	192
3	Me	*i*-Pr	−6.1	2.0	$CHCl_3$	95	*R*	183
4	Me	*t*-Bu	+2.0	1.3	$CHCl_3$	82	*S*	55,250
5	Et	Et	+11.0	3.6	$CHCl_3$	80	*R*	48
			−4.9	1.5				183
6	Et	Me	−4.3	0.5	$CHCl_3$	50.8	*R*	183
7	Et	*i*-Pr	+16.5	1.2	Me_2CO	97	*S*	147
8	*i*-Pr	Et	−4.0	1.0	$CHCl_3$	>95	*R*	133
9	*i*-Pr	*i*-Pr	+9.8	1.0	Me_2CO	92	*S*	147
10	*i*-Pr	*i*-Pr	−9.0	1.4	Me_2CO	96	*R*	193
11	*i*-Pr	*t*-Bu	−2.5	1.0	$CHCl_3$	80	*S*	55,250
12	*i*-Pr	Mnt	−91.5	1.0	Toluene	90	*S*	95
13	Bu	Et	+16.6	2.24	$CHCl_3$	53	*S*	48
14	*i*-Bu	Me	−25.0	0.92	$CHCl_3$	>99	*R*	89
15	*i*-Bu	Et	−16.5	0.5	$CHCl_3$	>95	*R*	133
16	*i*-Bu	Et	+6.40	3.49	$CHCl_3$	76	*R*	48
17	*i*-Bu	*i*-Pr	+25.4	1.0	Me_2CO	99	*S*	154
18	*i*-Bu	*i*-Pr	−23.9	1.9	Me_2CO	96	*R*	193

(*continued on next page*)

Table 10 (*continued*)

Entry	R	R′	$[\alpha]_D^{20}$	C (%)	Solvent	ee (%)	Config	Refs
19	*i*-Bu	*t*-Bu	+12.7	0.7	$CHCl_3$	90	*S*	55,250
20	*s*-Bu	*i*-Pr	+10.5	1.2	Me_2CO	99	1*S*,2*S*	154
21	C_5H_{11}	*i*-Pr	−14.2	0.9	Me_2CO	83	*R*	193
22	C_5H_{11}	Et	−14.5	1.0	Me_2CO	70	*R*	193
23	C_9H_{19}	Et	−14.5	1.0	Me_2CO	32	*R*	193
24	*c*-C_4H_7	*i*-Pr	−18.6	1.0	Me_2CO	92	*R*	193
25	*c*-C_6H_{11}	*i*-Pr	−8.8	1.0	Me_2CO	95	*R*	193
26	Bn	Et	−21.3	0.5	$CHCl_3$	>95	*R*	133
27	Bn	*i*-Pr	+14.1	0.8	$CHCl_3$	95	*S*	55,250
28	Bn	*i*-Pr	−14.8	1.0	Me_2CO	44	*R*	193
29	Ph	Me	−46.0	100	Me_2CO	99	*S*	46,89,192
30	Ph	Me	+41.1	1.0	EtOH	⩾99	*R*	46,192
31	Ph	Et,H	+59.4	1.4	$CHCl_3$	99	R,S_P	206
32	Ph	Et	−14.4	1.0	$CHCl_3$	96	*S*	250
			−13.5			42		
33	Ph	Et	+18.65	3.63	$CHCl_3$	82	*R*	48,148
				1.00		53		257
34	Ph	*t*-Bu	−13.3	0.8	$CHCl_3$	92	*S*	250
35	Ph	*i*-Pr	−28.2	1.29	Me_2CO	>99	*S*	192
36	Ph	All	−29	1.0	$CHCl_3$	96	*S*	62
37	Ph	Mnt	−88.9	1.0	Toluene	98	*S*	94
38	Ph	Brn	−39	1.0	Toluene	98	*S*	94
39	4-$Me_2NC_6H_4$	Mnt	−69.2	1.0	Toluene	98	*S*	94
40	2-$O_2NC_6H_4$	Mnt	−396	0.6	$CHCl_3$	90	*R*	97
41	$PhCH_2CH_2$	*t*-Bu	+14.1	0.8	$CHCl_3$	95	*S*	55
42	2-Tl	*i*-Pr	−60	0.9	$CHCl_3$	97	*S*	55,250
43	4-Tl	*t*-Bu	−12.8	0.8	$CHCl_3$	76	*S*	55,250
44	3-$CF_3C_6H_4$	Me	−37	0.6	$CHCl_3$	>98	*S*	62
45	3-$CF_3C_6H_4$	Et	−27	2.4	$CHCl_3$	98	*S*	62
46	3-$CF_3C_6H_4$	All	−27	2.8	$CHCl_3$	96	*S*	62
47	4-*t*-BuC_6H_4	*i*-Pr	−15.6	1.0	$CHCl_3$	52	*S*	45,68
48	4-An	Et	−31.1	1.0	$CHCl_3$	82	*S*	257
49	2-An	*i*-Pr	−22.5	0.9	$CHCl_3$	69	*S*	250
50	3-An	*i*-Pr	−9.0	1.0	$CHCl_3$	52	*S*	45,68
51	4-An	*i*-Pr	−12.3	0.8	$CHCl_3$	55	*S*	55,250
52	4-An	Me	−40	1.0	$CHCl_3$	81	*S*	46
53	2-An	Mnt	−56.4	1.0	Toluene	98	*R*	94,265
54	4-$MeSC_6H_4$	*i*-Pr	−18.8	1.1	$CHCl_3$	63	*S*	68
55	4-$MeSO_2C_6H_4$	*i*-Pr	−19.2	0.8	$CHCl_3$	85	*S*	68
56	2-FC_6H_4	*i*-Pr	−18.1	0.7	$CHCl_3$	91	*S*	55,250
57	2-ClC_6H_4	Me	−74	1.0	$CHCl_3$	100	*S*	46,122,250
58	2-ClC_6H_4	Et	−42.0	0.8	$CHCl_3$	67	*S*	250
59	2-ClC_6H_4	*i*-Pr	−65.8	0.9	$CHCl_3$	97	*S*	55,250
60	2-ClC_6H_4	*t*-Bu	−41.4	0.9	$CHCl_3$	92	*S*	250
61	3-ClC_6H_4	*i*-Pr	−16.8	0.8	$CHCl_3$	77	*S*	250
62	3-ClC_6H_4	*t*-Bu	−10.8	0.9	$CHCl_3$	83	*S*	250
63	4-ClC_6H_4	Et	+21.9	1.0	$CHCl_3$	52	*R*	148,257
64	4-ClC_6H_4	*t*-Bu	−17.3	0.8	$CHCl_3$	81	*S*	250
65	2-BrC_6H_3	*i*-Pr	−59.0	1.5	$CHCl_3$	95	*S*	55,250
66	2-IC_6H_3	*i*-Pr	−65.2	1.2	$CHCl_3$	92	*S*	55
67	2,6-FC_6H_3	*i*-Pr	−6.9	1.0	$CHCl_3$	99	*S*	55
68	2,4-ClC_6H_3	*i*-Pr	−55.0	1.0	$CHCl_3$	94	*S*	55,250
69	2-$H_2NC_6H_4$	Me	+49	1.0	$CHCl_3$	100	*S*	122
70	4-$MeSC_6H_4$	*i*-Pr	−18.8	1.1	$CHCl_3$	63	*S*	45
71	CH_2=CH	Et	−12.7	0.8	$CHCl_3$	95	*R*	183
72	CH_2=CH	*i*-Pr	−14.4	0.7	$CHCl_3$	95	*R*	183
73	PhCH=CH	Me	+38.5	1.0	EtOH	⩾99	*R*	192,207
74	PhCH=CH	Me	−23.6	2.74	$CHCl_3$	>99	*S*	89
75	PhCH=CH	*i*-Pr	−4.5	0.9	EtOH	56	*R*	207
76	PhCH=C(Me)-	Me	+4.0	0.5	EtOH	⩾99	*R*	207
77	MeCH=CH	Me	−9.5	0.95	Me_2CO	82	*S*	192
78	$C_5H_{11}C$≡C	Me	+25.9	1.0	EtOH	92	*R*	207
79	4-$O_2NC_6H_4$	Me	−54.2	1.0	$CHCl_3$	80	*S*	46
80	2-$O_2NC_6H_4$	Me	−417	1.0	$CHCl_3$	100	*S*	156
81	2-$O_2NC_6H_4$	*i*-Pr	−193.2	1.0	$CHCl_3$	60	*S*	156
82	2-$O_2NC_6H_4$	H	−497	1.0	MeOH	100	*S*	154,156

Table 10 (*continued*)

Entry	R	R′	$[\alpha]_D^{20}$	C (%)	Solvent	ee (%)	Config	Refs
83	3-$PhOC_6H_4$	Me	−39	0.9	$CHCl_3$	94	*S*	62
84	3-$PhOC_6H_4$	Et	−19	1.0	$CHCl_3$	86	*S*	62
85	3-$PhOC_6H_4$	All	−16	0.9	$CHCl_3$	98	*S*	62
86	$MeSC_2H_4$	*i*-Pr	+42.8	1.0	Me_2CO	98	*S*	147
87	4-$MeSC_6H_4$	*i*-Pr	−18.8	1.1	$CHCl_3$	63	*S*	45
88	CH(Me)OSi(*i*-Pr)$_3$	Et	+6.25	1.38	$CHCl_3$	—	1*S*,2*S*	126
89	CH(Me)OSi(*i*-Pr)$_3$	Et	+1.75	0.8	$CHCl_3$	—	1*R*,2*S*	126
90	CH(Ph)OSi(*i*-Pr)$_3$	Bn	+17.5	1.93	$CHCl_3$	—	1*S*,2*S*	126
91	$CH(NBn_2)Ph$	Me	+73.5	0.95	EtOAc	100	1*S*,2*S*	113
92	$CH(NBn_2)Ph$	Me	+73.8	2.0	EtOAc	100	1*R*,2*S*	113
93	$CH(NBn_2)Ph$	Et	+81.4	1.88	EtOAc	100	1*S*,2*S*	113
94	CH(NHBoc)Ph	Et	+18.1	0.91	EtOAc	100	1*S*,2*S*	113
95	CH(NHBoc)Ph	Me	+22.4	1.16	EtOAc	100	1*S*,2*S*	109,113
96	CH(NHBoc)Ph	Me	−21.7	1.3	EtOAc	100	1*R*,2*R*	109
97	CH(NHBz)Ph	Me	−44.6	1.2	EtOAc	100	1*S*,2*S*	109
98	CH(NHBz)Ph	Me	+42.4	1.3	EtOAc	98	1*R*,2*R*	109
99	CH(NHBz)Ph	Et	−37.7	0.25	EtOAc	98	1*S*,2*S*	109
100	CH(NHBz)Ph	Et	+35.1	1.0	EtOAc	98	1*R*,2*R*	110
101	$CH(NBn_2)Bn$	Et	+28.6	1.0	$CHCl_3$	>98	2*R*,3*S*	111
102	$CH(NBn_2)Bn$	Et	+39.0	1.1	$CHCl_3$	>98	2*S*,3*S*	111
103	2-Furyl	Et	−4.2	1.0	$CHCl_3$	18	*S*	257
104	3-Furyl	Et	−11.7	1.0	$CHCl_3$	64	*S*	257
105	3-Thienyl	Et	−13.4	1.0	$CHCl_3$	67	*S*	257
106	CH_2N_3	Me	+2.6	3.45	MeOH	97	*R*	247
107	CH_2Cl	Et	+15.4	0.8	MeOH	95	*S*	267
108	CH_2NH_2	H	−31.4	0.52	H_2O	97	*R*	195,247
109	CH_2NH_2	H	+31.8	0.52	H_2O	97	*S*	247
110	$CH(NH_2)(i-Bu)$	H	+8.7	1.0	H_2O	100	1*S*,2*S*	113
111	$CH(NH_2)$(*s*-Bu)	H	+8.2	1.0	H_2O	100	1*S*,2*S*,3*S*	113
112	$CH(NH_2)Me$	H	19.3	1.0	H_2O	100	1*S*,2*S*	113
113	PhCH=CH	H	−3.0	0.68	H_2O	>99	*S*	89
114	Ph	H[a]	+14	1.0	MeOH–H_2O	96	*R*	264
115	Ph	H[a]	−13.8	0.78	H_2O	86	*S*	89
116	2-An	H[a]	+30	1.0	$CHCl_3$	96	*R*	265
117	3-$PhOC_6H_4$	Na	−22	0.2	H_2O	94	*S*	62
118	3-$CF_3C_6H_4$	Na	−16	1.1	H_2O–Me_2CO	>98	*S*	62

[a] Dicyclohexylammonium salt.

4. Conclusions and application perspectives

It is hoped that this review devoted to chiral hydroxyphosphonates and their application as biologically active materials or pharmaceuticals will be useful to chemists interested in various aspects of organic chemistry and stereochemistry.

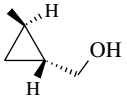
It is necessary to note that despite the impressive progress achieved in the synthesis and studies of properties of hydroxyphosphonates, not all problems have been solved. The problem of the development of enantioselective methods giving easy access to both optical antipodes of hydroxyphosphonates still remains. The creation of highly effective catalysts for the asymmetric phospho-aldol reaction, or for the reduction of ketophosphonates is an important problem, which is currently waiting a solution.

It is easy to predict that the basic efforts in studying the chemistry of hydroxyphosphonates will be concentrated in this direction and phospho-aldol reaction is promising for solving these problems. The prospects of chemical modification of hydroxyphosphonates with the introduction of new, more and more complex groups including those with definite configuration to C-, and, especially, to P-centres are far from exhausted.

The actual problem is the resolution of enantiomers and purification of chiral hydroxyphosphonates. The exact definition of a structure and of an absolute configuration can only be successfully solved in limited cases. We have considered the various chiral hydroxyphosphonates, which are generated, using methods of asymmetric synthesis, enzymatic kinetic resolution, chromatographic fractionation, and some other methods. These methods allowed us to obtain a series of enantiomerically pure compounds of high enantiomeric excess.

Looking at the future, it seems that hydroxyphosphonates will be the subject of intensive studies, especially in their range of application as pharmaceuticals and biological products. The most interesting opportunities lie in the development of the application of reagents and catalysts, allowing us to obtain hydroxyphosphonates by the most accessible methods. It is believed that the area of the application of hydroxyphosphonates will

Table 11. β-Hydroxyalkylphosphonates $(RO)_2P(O)CH(R^1)CH(OH)R^2$

Entry	R^2	R^1	R	$[\alpha]_D^{20}$	C	Solvent	ee (%)	Configuration	Physical data	Refs
1	Me	H	Me	+5.7	1.0	$CHCl_3$	100	*S*	Oil	183
2	Me	H	Et	+7.2	1.0	MeOH	98	*R*	Oil	209
3	Me	H	Et	+15.2	0.25	$CHCl_3$	95	*S*	Oil	183
4	Me	H	H	−10.3	2.04	H_2O	100	*S*	Oil	168a
5	Et	H	Et	+13.1	0.21	$CHCl_3$	85	*S*	Oil	183
6	$CH{=}CH_2$	H	Et	+5.6	5.6	$CHCl_3$	9.5	*S*	Oil	183
7	Ph	H	Et	+3.0	2.0	MeOH	99	*R*	Oil	176
8	Ph	H	*i*-Pr	+25.1	0.8	$CHCl_3$	91	*R*	Solid	250
9	α-Py	OH	Et	−18.8	1.0	Mc	62	*S*		209
10	2-$C_6H_4NH_2$	H	Me	+13.3	1.2	$CHCl_3$	—	*S*	Yellow oil	168b
11	2-$C_6H_4NH_2$	H	Me	−13.7	1.4	$CHCl_3$	—	*R*	Oil	168b
12	CH_2Cl	H	Et	−10.7	1.8	$CHCl_3$	85	*S*	Oil	267
				−7.77	5.1	MeOH	100			81,211
13	CH_2Cl	H	Et	−13.3	3.0	$CHCl_3$	93	*R*	Oil	267
				+7.8	5.0	MeOH	100			81,211
14	CH_2Br	H	Et	+12.4	4.12	$CHCl_3$	100	*R*	Oil	81
15	CH_2NHBoc	H	Et	−2.6	2.8	$CHCl_3$	100	*S*	Oil	81
16	CH_2NBn_2	H	Me	−31.7	1.42	$CHCl_3$	100	*S*	Oil	168
17	$CH_2N[CH(Me)Ph\text{-}S]_2$	H	Me	+23.1	0.59	$CHCl_3$	98	*R*	Mp 115–118 °C	53
18	CH_2OH	H	Et	−17.8	1.43	EtOH	98	*R*	Oil	80
19	CH(OH)Me	H	Bn	−7.9	1.01	$CHCl_3$	100	2*S*,3*S*	Mp 93–95 °C	67
20	CH_2NH_2	H	H	+10.8	2.04	H_2O	100	*R*	Solid, PF 175–178	168
				−10.3	2.04				Solid, PF 175–178	168
21	CH_2NH_2	H	H	−41.4	0.9	H_2O	100	*S*	White powder	81b
				+15.2	1.3				Oil	267
22	CH_2N_3	H	Et	−6.8	1.75	$CHCl_3$	90	*S*	Oil	267
				−24.3	2.3	MeOH–H_2O	100		Oil	211b
23	$CH_2N^+Me_3$	H	H	−17.4	1.15	H_2O	100	*S*	Solid, mp 270 °C	267
				−17.8	2.0	H_2O	90		Solid, mp 250 °C	54c
24	$CH_2N^+Me_3$	H	H	+24.1	2.09	MeOH–H_2O	100	*R*	Oil	211b
25	Me	NH_2	H	+8.5	0.28	H_2O	78	1*S*,2*S*	Oil	130
26	Me	NH_2	H	−8.9	0.208	H_2O	80	1*R*,2*R*	Oil	130
27	Me	NH_2	H	−8.9	0.294	H_2O	84	1*R*,2*S*	Oil	130
28	Me	NH_2	H	+8.8	0.218	H_2O	85	1*S*,2*R*	Oil	130
29	H	NH_2	H	−30.2	1.27	H_2O	>98	*R*	Mp 95–110 °C	247
				−17.0	1.22	1N NaOH				
30	H	NH_2	H	+30.4	4.2	H_2O	100	*S*	Mp 95–110 °C	247
				+18.2	1.1	1N NaOH				
31	Me	Cl	Et	+2.7	3.1	$CHCl_3$	95	1*S*,2*R*	Oil	267
32	Me	Cl	Et	−2.6	3	$CHCl_3$	90	1*R*,2*S*	Oil	267
33	2-$C_6H_4NH_2$	H	Me	+13.3	1.2	$CHCl_3$		*S*	Yellow oil	168
34	2-$C_6H_4NH_2$	H	Me	−13.7	1.4	$CHCl_3$		*R*	Viscous oil	168
33	2-$C_6H_4NBn_2$	H	Me	+5.9	1.4	$CHCl_3$	93	*S*	Mp 115–118 °C	168
33	2-$C_6H_4NBn_2$	H	Me	−6.1	1.14	$CHCl_3$		*R*	Mp 115–118 °C	168
35	Ph_3CNH	H	Et	−5.6	3.3	$CHCl_3$	96	*S*	Mp 80–81 °C	266
36	Ph_2CHNH	H	Et	−4.05	2.0	$CHCl_3$	100	*S*	Oil	266
37	BocNH	H	Et	−2.6	2.8	$CHCl_3$	—	*S*	Oil	266
38	$Ph_2CHN(Boc)$	H	Et	+6.6	1.9	$CHCl_3$	100	*S*	Oil	266
39	BnN(OH)	H	Et	−14.3	1.68	$CHCl_3$	98	*S*	Oil	266
40	BnONH	H	Et	−12.8	1.79	$CHCl_3$	97	*S*	Oil	266
41	BnONH	H	Et	+12.0	1.20	$CHCl_3$	97	*R*	Oil	266
42	$CH(Bn)NHSO_2Tl\text{-}4$	H	Me	−79.4	1.89	$CHCl_3$	100	3*S*,2*R*	Mp 131–132 °C	51a
43	$CH(Ph)NHSO_2Tl\text{-}4$	H	Me	+0.5	1.19	$CHCl_3$	100	3*S*,2*S*	Mp 169–170 °C	51a
44	$CH(Ph)NHSO_2Tl\text{-}4$	H	Me	+0.6	1.23	$CHCl_3$	100	3*S*,2*R*	Mp 150–153 °C	51a
42			Et	−24.0	0.19	Me_2CO	100	1*R*,2*S*	—	242

be expanded greatly. For example, some interesting regulators of plant growth have been found amongst hydroxyalkylphosphonates. In addition to the search for new highly effective biologically active compounds among hydroxyphosphonates, their derivatives and analogues, it is necessary to expect increasing interest to practical application related to their complex-forming properties. These applications should primarily include the use of hydroxyphosphonates as synthetic receptors and chiral ligands in metal complexes, as well as selec-

Table 12. α,β-Dihydroxyphosphonates $(RO)_2P(O)CH(OH)CH(OH)R'$

Entry	R	R′	$[\alpha]_D^{20}$	C	Solvent	*ee* (%)	Config	Refs
1	Na	Me	+23.1	10.22	H_2O	—	1*S*,2*S*	126
2	Na	*i*-Pr	−4.65	3.87	H_2O	—	1*S*,2*S*	126
3	Na	Ph	+106.9	1.45	H_2O	—	1*S*,2*S*	126
4	Et	Me	+3.73	1.0	MeOH	33	1*S*,2*S*	64,122
5	Et	Ph	+33.7	1.0	MeOH	92	1*S*,2*S*	64,122
6	Et	Ph	−30.8	1.0	MeOH	92	1*R*,2*R*	64,122
7	Et	Ph	−22.5	1.0	$CHCl_3$	98	1*R*,2*R*	212
8	Et	2-Tl	−37.5	1.0	$CHCl_3$	98	1*R*,2*R*	212
9	Et	3-Tl	−11.6	1.0	$CHCl_3$	98	1*R*,2*R*	212
10	Et	4-Tl	+28.8	1.0	$CHCl_3$	98	1*S*,2*S*	212
11	Et	3-An	+32.7	1.0	MeOH	96	1*S*,2*S*	122,64
12	Et	4-An	+28.8	1.0	MeOH	95	1*S*,2*S*	64,122
13	Et	4-An	−31.6	1.0	MeOH	28.8	1*R*,2*R*	64,122
14	Et	4-ClC_6H_4	+43.7	1.0	$CHCl_3$	98	1*S*,2*S*	122,212
15	Et	4-BrC_6H_4	+20.8	1.0	$CHCl_3$	98	1*S*,2*S*	212
16	Et	CH_2NHAc	+19.0	0.98	$CHCl_3$	100	1*R*,2*R*	70
17	Et	CH_2NHAc	−77.2	1.01	$CHCl_3$	100	1*S*,2*R*	70
18	Me	CH_2NHAc	+35.6	1.81	$CHCl_3$	100	1*R*,2*S*	131
19	Me	CH_2NHAc	−12.4	2.12	$CHCl_3$	100	1*S*,2*S*	131
20	Et	CH_2NBn_2	−4.0	0.73	$CHCl_3$	100	1*R*,2*R*	70
21	Et	CH_2NBn_2	−77.2	1.01	$CHCl_3$	100	1*S*,2*R*	70
22	Et	*t*-$BuMe_2SiOCH_2$	−8.25	1.0	MeOH	38	1*S*,2*S*	64,122
23	Et	C_7H_{15}	−0.8	1.0	MeOH	84	1*R*,2*R*	64,88
24	Et	C_7H_{15}	+1.8	1.0	MeOH	84	1*S*,2*S*	64,88
25	Et	1-Naphthyl	+63.2	1.0	MeOH	93	1*S*,2*S*	64,88
26	Et	2-Furyl	+14.7	1.0	MeOH	88	1*S*,2*S*	64,88
27	Et	4-$MeOC_6H_4CO_2CH_2$	+3.87	1.0	MeOH	97	1*S*,2*S*	64,88
28	MntO	CH_2OH	−60	2	$CHCl_3$	98	1*S*,2*R*	106,108
29	Ph	CH_2OH	+5	2	$CHCl_3$	98	1*S*,2*R*	107

tive highly effective complexes, extraction agents and analytical reagents.

Throughout this review, we employ the following abbreviation: Ac—acetyl; ALB—lithium aluminum binol complex; All—allyl; Alk—alkyl; An—anysyl; Ar—aryl group; AD—asymmetric dihydroxylation; AE—asymmetric epoxidation; BINOL—bis(binaphthol); Boc—*t*-BuOCO; Bn—benzyl; Brn—*endo*-bornyl; Bz—benzoyl; CALB—*Candida antarctica* lipase B; Cat—catalyst; CRL—*Candida rugosa* lipase; Cy—cyclohexyl; DBU—1,5-diazabicyclo-[5,4,0]-undec-7-ene; de—diastereomeric excess; dr—diastereomer ratio; DETA—diethyl tartrate; DIBAL—diisobutylaluminum hydride; DIPT—diisopropyl tartrate; ee—enantiomeric excess; GF—(−)-1:2; 5:6-diisopropyliden-D-glucofuranosyl; HMPA—hexamethylphosphoric triamide; HO–AEP—hydroxy-2-aminoethylphosphonic acid; KHMDS—potassium hexamethyldisilazide; L—ligand; IC_{50}—inhibiting concentration of 50%; LDA—lithium diisopropylamide; LHMDS—lithium hexamethyldisilazide; LLB—lithium–lantan–binol complex; Mnt—menthyl; (+)-Mnt—(1*S*,2*R*,5*S*)-menthyl; (−)-Mnt—(1*R*,2*S*,5*R*)-menthyl; MTPA—α-methoxy-α-(trifluoromethyl)phenylacetyc acid (Mosher acid); NaHMDS—sodium hexamethyldisilazide; PNP—purine nucleoside phosphorylase, PTP—protein tyrosine phosphatase; PTX—phosphonothrixin; R_S, R_M, R_L—small, medium and large groups; R*—alkyl or aryl group, containing stereogenic centre or element of chirality; TBDMS—*tert*-butyldimethylsilyl; TBS—*tert*-butyldimethylsilyl; THF—tetrahydrofuran; Tl—tolyl; TMS—trimethylsilyl; TOTU—*O*-[(etoxycarbonyl)cyanomethylenamino]-*N*,*N*,*N*′,*N*′-tetramethyluroniumtetrafluoroborate; X—group containing heteroatom; X*—chiral auxiliary group.

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