universität wien

DISSERTATION

Titel der Dissertation

„Synthesis of α-aminophosphonic acids and the phosphonate-phosphinate rearrangement“

verfasst von

Mag. Renzhe Qian

angestrebter akademischer Grad

Doktor der Naturwissenschaften (Dr. rer. nat.)

Wien, 2013

Studienkennzahl lt. Studienblatt: A 791 419
Dissertationsgebiet lt. Studienblatt: Dr. Studium der Naturwissenschaften UniStG - Chemie
Betreut von: Ao. Univ.-Prof. Dr. Friedrich Hammerschmidt

For my parents and grandparents

My best thanks to …

Fritz, my boss, my guide in chemistry and also my friend. You have taught and helped me so much (not only in the field of chemistry). You are like my father in Austria. Thank you so much, Fritz!

Jingxia, my love. I can not count how much happiness you have brought me since we met. My life is totally changed. I know that you do not really like the life in Vienna, but for me, you have come again and again. Thank you for being with me. You are my sunshine, the source of my power.

My family, especially my parents, for your support and incomparable love. I am very sorry that, in the last several years, I have spent so little time with you together.

Ania, Petra, Kathi and Thomas, I was very happy to work in the same lab with you during the last four years. I have really learned a lot of things (politics, gardening, customs, cooking, dressing etc.) from you at the coffee breaks and always enjoyed them.

All of my friends who have continually helped me und encouraged me, although quite many of them have left Vienna long ago, to finish this job.

The NMR-department, especially Susanne and Lothar,

Sabine, and Fikret for analytical and preparative HPLC separations,

Petra, again, for reading and correcting my spelling mistakes,

My reviewers,

Everyone who has contributed of this thesis.

Table of Contents

Table of Contents

Table of Contents

Table of Contents

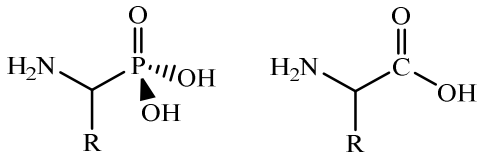
Abbreviations:

Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
Ar	Aromatic substituent
ATR	Attenuated total reflectance
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Conc.	Concentrated
$CyBH_2$	Cyclohexylborane
DBU	1,8-Diazabicycloundec-7-ene
DBAD	Di-*tert*-butyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAH	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
EI	Electrospray ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
HR-MS	High resolution mass spectroscopy
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
MC	Methylene chloride
MeOH	Methanol
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
R	any organic substituent
RT	Room temperature
THF	Tetrahydrofuran
THP	Tetrahydro-2*H*-pyran-2-yl
TLC	Thin layer chromatography
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
TMPH	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl

1. Synthesis of α-aminophosphonic acids

1.1. General comments on α-aminophosphonic acids

α-Aminophosphonic acids **1** are isosteric or bio-isosteric analogs of α-aminoacids **2**, where the carboxyl group is replaced by a phosphonic acid group (Figure 1.01). Aminophosphonic acids have generally similar physical and chemical properties to amino acids, but the exchange also leads to some significant differences. The phosphonic acid group is definitely more acidic than the carboxyl group and has a tetrahedral structure with an extra hydroxyl group, which mimics the tetrahedral transition state involved in the peptide bond cleavage. Furthermore, the phosphorus analogs exhibit an outstanding ability to act as hydrogen bond acceptors or metal cation complexing agents. These properties sometimes hinder their applicability but on the other hand also present new possibilities for the search of bioactive molecules.

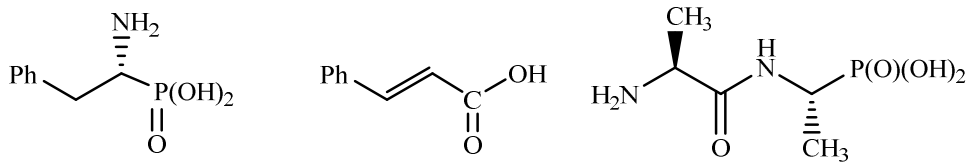


1 **2**

Figure 1.01. Structures of α-aminophosphonic acids **1** and α-amino acids **2**.

Aminophosphonic acids, their esters and the peptides or proteins that contain them generally have a low toxicity against mammals. However, they are found to inhibit e.g. HIV-protease,[1] renin[2] and human prostatic acid phosphatase[3]. Moreover, aminophosphonic acids are used as antibiotics,[4] antiviral drugs,[5] herbicides[6] and antitumor agents[7].

Compound **3**, the phosphonic acid analog of phenylalanine is a very potent inhibitor of phenylalanine ammonia-lyase (PAL) (Figure 1.02).[8] PAL converts *L*-phenylalanine (**4**) to *trans*-cinnamic acid with the release of ammonia. It takes part in at least five metabolic pathways (tyrosine, phenylalanine, and nitrogen metabolism, phenylpropanoid-biosynthesis and alkaloid-biosynthesis II). The concrete mechanism as well as the importance of PAL will be discussed later.

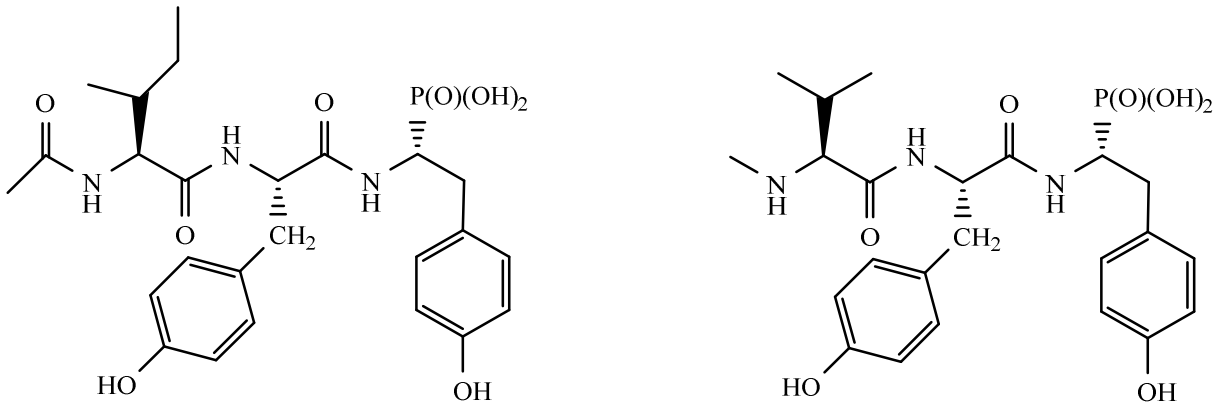


3 **4** **5**

Figure 1.02. 3: phosphonic analog of phenylalanine; **4**: *trans*-cinnamic acid; **5**: Alafosfalin.

The phosphono dipeptide Alafosfalin [*L*-Ala-*L*-Ala(P), **5**] is an antibiotic which is hydrolyzed to alanine and phosphonic alanine in the cell. The latter inhibits the enzyme *D*-alanine-racemase, which is the key enzyme for the biosynthesis of the cell wall.[9] It should be noted that the (*S*,*R*)-diastereomer of Alafosfalin shows a much higher activity against Gram-positive and –negative bacteria than the other three diastereomers.

(*R*)-Phosphotyrosine (the prefix phospho denotes that the carboxyl group has been replaced by a phosphono group in the aminoacid tyrosine) exists in nature as a component of the phosphono tripeptiedes **6** and **7**, which are produced by *Actinomycetes* (Figure 1.03). Both peptides have hypotensive properties.[10]



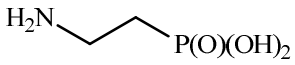
6 **7**

Figure 1.03. (*R*)-Phosphotyrosine.

1.2. Synthesis of racemic α-aminophosphonic acids

In 1959, Horiguchi and Kandatsu isolated the 2-aminoethylphosphonic acid (AEP, **8**) from protozoa, which live in the rumen of sheep (Figure 1.04).[11] With this discovery, the interest in aminophosphonic acids increased. Since then AEP as well as some other phosphonic acids

have been found in a large number of organisms and numerous synthetic methods for the preparation of aminophosphonic acids, especially for α-aminophosphonic acids, have been developed.

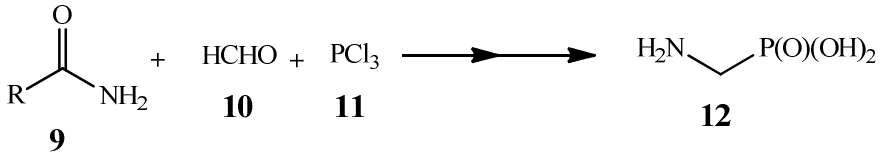


8

Figure 1.04. AEP.

1.2.1. Amidoalkylation of trivalent phosphorus compounds

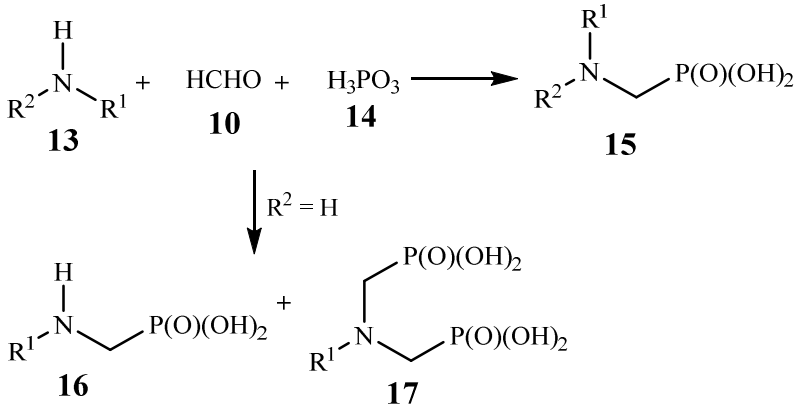
The first synthesis of an α-aminophosphonic acid, the aminomethylphosphonic acid **12**, was achieved by Pikl and Engelmann at the beginning of the 1940s. They reacted amides **9** with formaldehyde **10** and phosphorus trichloride (**11)** and proposed a mechanism for this reaction (Scheme 1.01).[12,13] At first the amide reacts with formaldehyde to form a *N*-hydroxy methylamide. The successive reaction with phosphorus trichloride provides the aminomethylphosphonic acid derivative, which is then treated with acid.



9 **10** **11** **12**

Scheme 1.01. The first synthesis of α-aminophosphonic acid by Pikl and Engelmann.

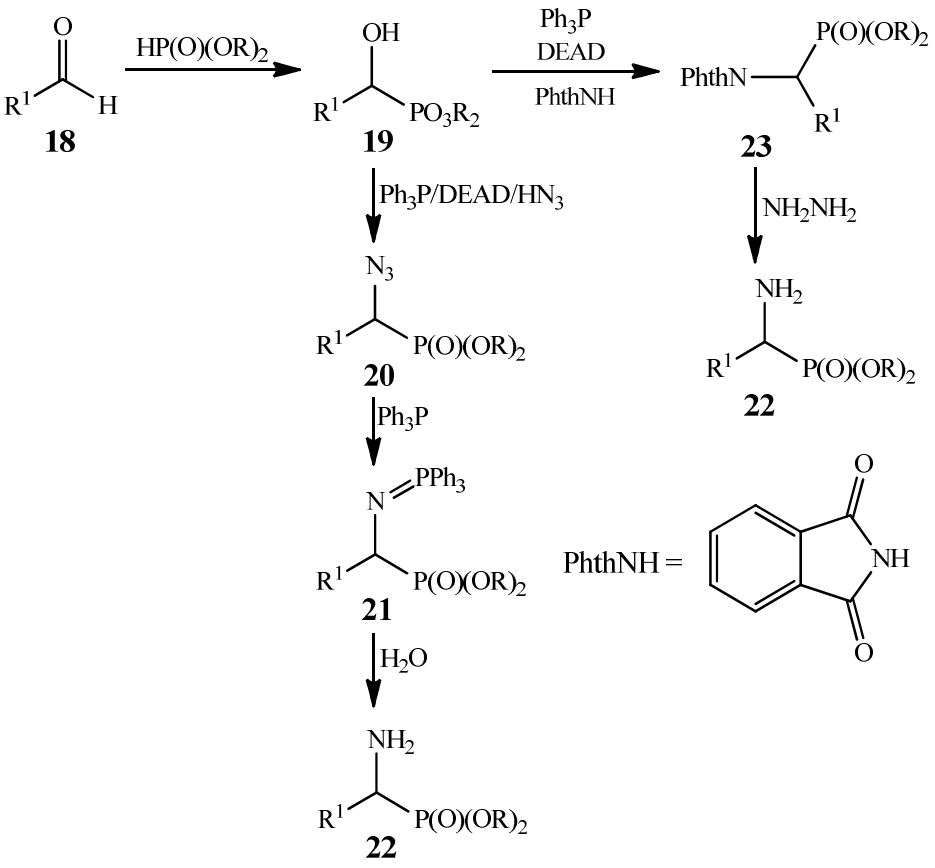
Nowadays, using amine **13** with an easily removable protecting group such as benzyl instead of using amide **9**, and phosphorous acid (**14**) instead of phosphorus trichloride (**11**), has already become a general and reliable method to synthesize aminomethylphosphonic acid derivatives **15** (Scheme 1.02).[14] The removal of benzyl protecting groups from amino group is easier than hydrolysis of amides and a phosphite is more nucleophilic than phosphorus trichloride. However, when a primary amine is applied, the *bis*-methylene phosphonic acid **17** is formed as byproduct. It should be noted that addition of the second phosphonomethyl group to nitrogen is faster than the first one, meaning that the disubstituted product is favored.[15]



Scheme 1.02. The improved method of the first synthesis of α-aminophosphonic acids.

1.2.2. Hydrophosphonylation of aldehydes followed by Mitsunobu reaction

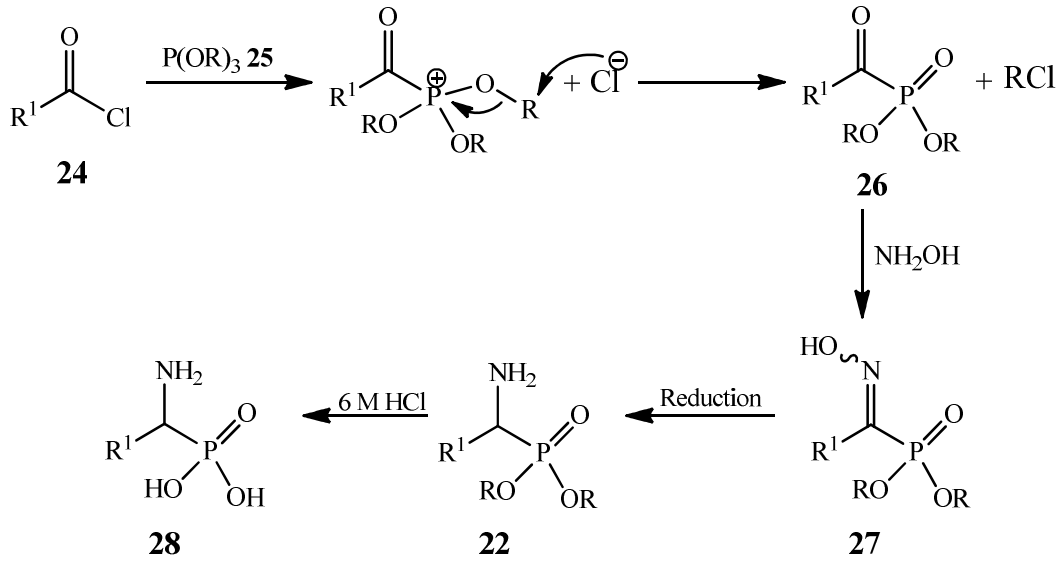
1-Hydroxyphosphonates **19** are proven to be practical starting materials for the synthesis of α-aminophosphonic acids **22**, as they are easily accessible in both racemic[16] and chiral, non-racemic form with high *ee*[17] (Scheme 1.03). A further advantage is that, the yield of the Mitsunobu reaction with hydrazoic acid as the acid component is always high.[18] The isolation of the azide formed is not necessary here, because it can be reduced immediately (Staudinger reaction) to the amine **22** by excess triphenylphosphine. Furthermore, one can use phthalimide instead of hydrazoic acid, whereby *N*-substituted phthalimide **23** is formed and amine **22** is easily released using hydrazine or ammonia (Gabriel reaction).[19]



Scheme 1.03. Hydrophosphonylation of aldehyde followed by Mitsunobu reaction.

1.2.3. Conversion of α-oxophosphonates to α-aminophosphonic acids – the Arbuzov reaction

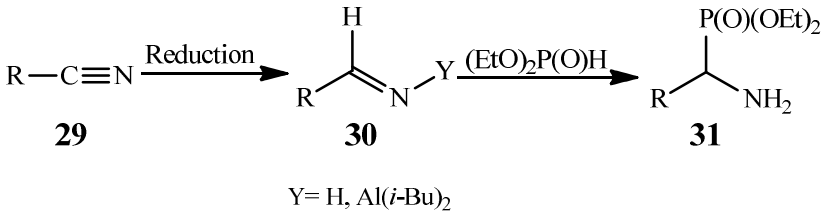
One of the oldest name reactions, the Arbuzov reaction[20] still plays a major role in the synthesis of phosphonic acid esters and their derivatives. To form α-aminophosphonic acids using the Arbuzov reaction, 1-oxoalkylphosphonates **26** are first prepared from acyl chloride **24** and trialkyl phosphites **25** (Scheme 1.04). 1-Oxoalkylphosphonates **26** are converted to oximes **27** with hydroxylamine, which are then reduced to α-aminophosphonic acid esters **22**. The most common methods of reduction are, for example, diborane in THF,[21] catalyzed hydrogenation over Raney-nickel in ethanol,[21] activated zinc powder in formic acid[22] and sodium borohydride[23] or lithium borohydride/trimethylsilyl chloride in dried THF.[24] The α-aminophosphonic acid esters are readily deprotected with boiling 6 M HCl and converted into the α-aminophosphonic acids **28**.



Scheme 1.04. Conversion of α-oxophosphonates to α-aminophosphonic acids.

1.2.4. Reduction of nitriles and subsequent addition of dialkyl phosphites

Nitriles **29** are, in principle, more easily accessible and stable than aldehydes or ketones. The reduction to imines **30** can be carried out for example with titan (II) chloride[25] or DIBAH[26] (Scheme 1.05). It is then followed by the addition of dialkyl phosphite and the hydrolysis in 6 M HCl. Generally, this easy to perform one-pot reaction provides a good yield.

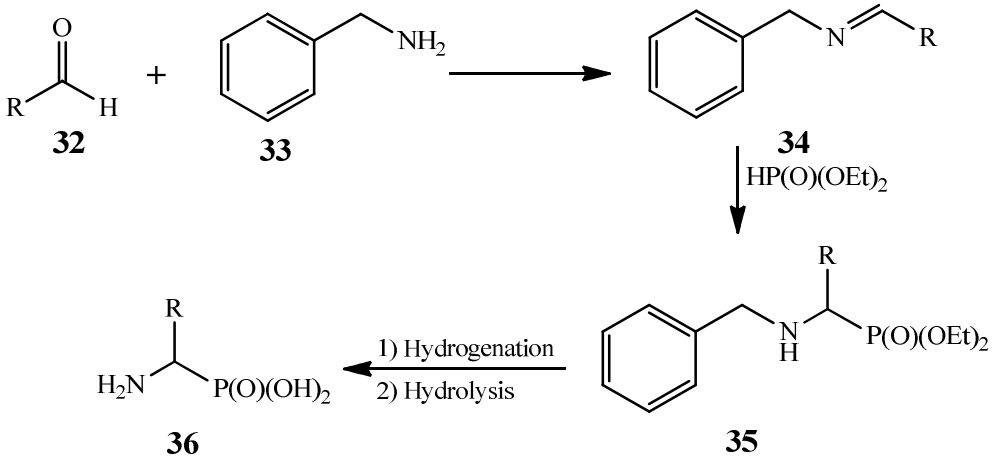


Scheme 1.05. Reduction of nitriles and subsequent addition of dialkyl phosphites.

1.2.5. Addition of dialkyl phosphites to imines prepared from aldehydes and primary amines - the Pudovik reaction

Imine **34** (Schiff base) can be easily obtained by condensation of a primary amine **33** and aldehyde **32** with the formation of water (Scheme 1.06). To synthesize α-aminophosphonic acids **36**, amines with a readily removable protecting group such as benzyl, diphenylmethyl or triphenylmethyl, are preferred. The following hydrophosphonylation of the Schiff base works

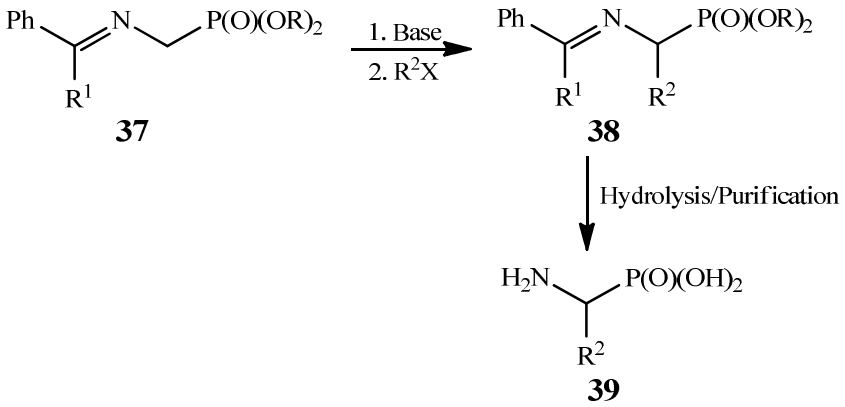
smoothly. This method can also be used to prepare optically active α-aminophosphonic acids,[27] which will be discussed in the next chapter.



Scheme 1.06. Addition of dialkyl phosphites to imines, prepared from aldehydes and primary amines.

1.2.6. Alkylation of Schiff bases derived from aminomethylphosphonic acid esters

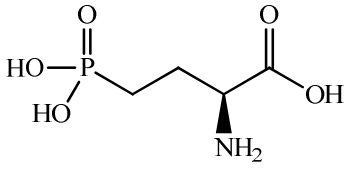
Schiff base **37**, which is formed from an amino methyl phosphonic acid diester and an alkyl aryl ketone, is deprotonated either by LDA[28] or under the conditions of phase-transfer-catalysis (PTC)[29] (for example, KOH with TBAB in MC) and then alkylated (Scheme 1.07). Hydrolysis of imine **38** and removal of the protecting groups from the phosphonate moiety provide α-aminophosphonic acids **39** after the usual purification.



Scheme 1.07. Alkylation of Schiff bases derived from aminomethylphosphonic acid esters.

1.3. Synthesis of optically active α-aminophosphonic acids

It is well known that the biological activity of chemical compounds strongly depends on their absolute configuration. For example, the (*S*)-enantiomer of 2-amino-4-phosphonobutylric acid (**40**) is 20-40 times more active than the (*R*)-enantiomer in suppressing the glutamate-mediated conduction (Figure 1.05).[30] In the last 35 years, the stereoselective synthesis of α-aminophosphonic acids has attracted the interest of many chemists, and numerous applications for these substances have been discovered.[1-7]



40

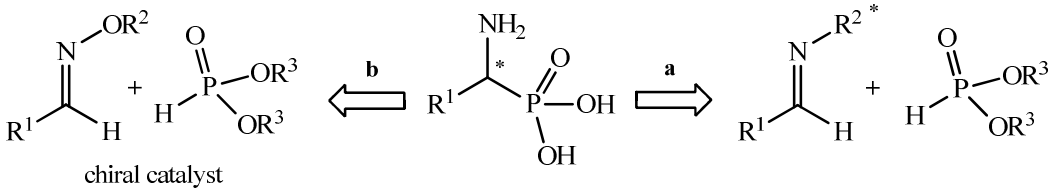
Figure 1.05. (*S*)-2-Amino-4-phosphonobutylric acid.

1.3.1. Stereoselective formation of the C-P bond

The nucleophilic addition of dialkyl- or diaryl phosphites to imines, the Pudovik reaction[31], is one of the best and most important methods for the stereoselective synthesis of α-aminophosphonates, which are critical intermediates in the synthesis of α-aminophosphonic acids. There are two principal alternatives for the stereoselective formation of the C-P bond (Scheme 1.08):

a. Addition of racemic dialkyl phosphites to chiral imines

b. Addition of racemic dialkyl phosphites to racemic imines with chiral catalysts



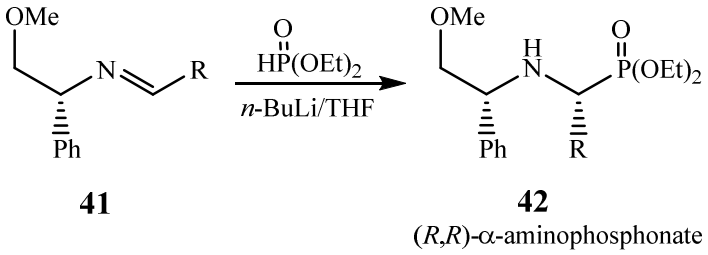
Scheme 1.08. Stereoselective formation of the C-P bond of α-aminophosphonic acids.

1.3.1.1. Stereoselective addition of racemic dialkyl phosphites to chiral imines

The key factor of a stereoselective addition of racemic dialkyl phosphites to chiral imines is the chiral auxiliary attached to nitrogen. It is usually a compound with bulky groups with at least one chiral center.

a. Addition of lithium dialkyl phosphites to (R)-2-methoxy-1-phenyethylimines

One of the most successful examples is the addition of lithium dialkyl phosphite to the imines **41**, which are derived from enantiomerically pure 2-methoxy-1-phenylethylamine (Scheme 1.09).[32] The methoxy group acts as a coordination partner for lithium, which makes the addition of dialkyl phosphite anion more diastereoselective. The dominant diastereomer is the one with the (*R*,*R*)-configuration **42**. The yield and the diastereoselectivity are excellent.

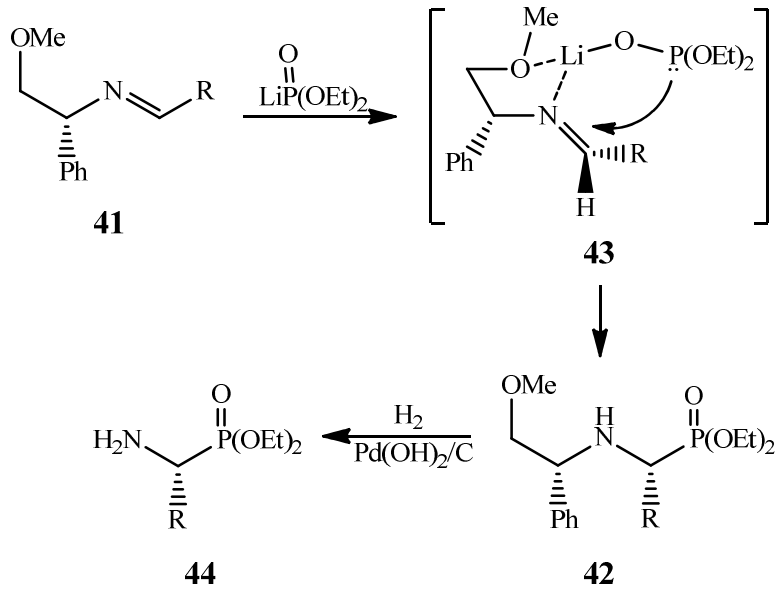


41 **42** (*R*,*R*)-α-aminophosphonate

Scheme 1.09. Addition of lithium dialkyl phosphite to imine **41**.

Mechanism

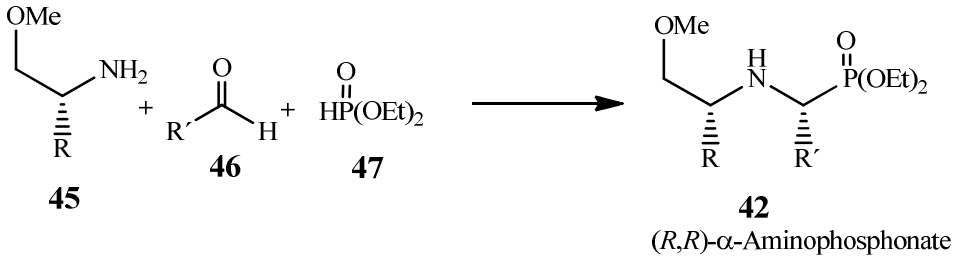
It was suggested by the authors that the complex **43** is responsible for the preferential creation of the (*R*,*R*)-diastereomer (Scheme 1.10). The lithium cation enables the formation of the five membered chelate ring. The phosphite anion, which is attached to the lithium ion, attacks the *re*-side of the imine **41** and provides the (*R*,*R*)-diastereomer.



Scheme 1.10. Proposed mechanism for addition of $(EtO)_2POLi$ to imine **41**.

One-pot reaction

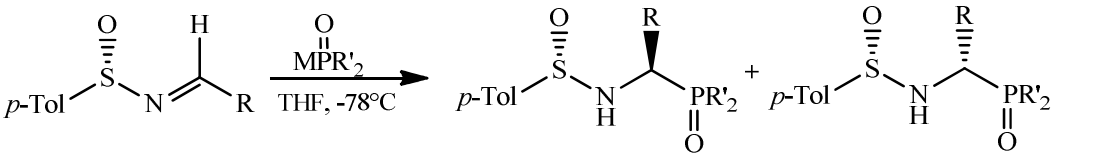
In the one-pot reaction, the imine **41** is generated *in situ* from methylbenzylamine **45** and aldehyde **46**. It gives a higher yield but lower diastereoselectivity (Scheme 1.11).



Scheme 1.11. The one-pot reaction

b. Addition of phosphites to chiral, non-racemic sulfinimines

Addition of phosphites to chiral, non-racemic sulfinimines is another favored method to form enantiomerically pure α-aminophosphonic acids. Chiral sulfinimines can be prepared readily from the Anderson reagent and an aldehyde with formation of water (Scheme 1.12).[33] The addition of lithium or sodium dialkyl phosphites to the (S_s)-sulfinimines **48a-i** provides predominantly the (S_S,R_C)-products **49** in good yield.[34-36] However, the reaction with the (*S*)-sulfinimine **48j** results mainly in the (S_S,S_C)-diastereomer **50j**.[36]



48a-j
(*S*)-Sulfinylimine

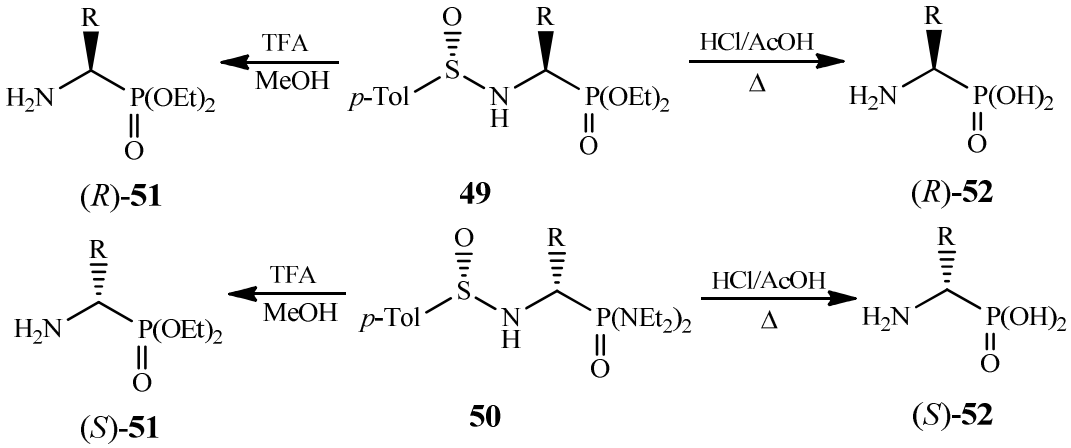
49a-j
(*Ss*,*Rc*)-α-Aminophosphonate

50a-j
(*Ss*,*Sc*)-α-Aminophosphonate

Entry	**48**	R	R´	M	Yield (%)	(S_S, R_C)-**49** : (S_S, S_C)-**50**
1	**a**	Ph	OEt	Li	85	92:08
2	**b**	4-$MeOC_6H_4$	OEt	Li	50	92:08
3	**c**	*n*-Pr	OEt	Li	78	92:08
4	**d**	2-Furyl	OMe	Li	75-80	94:06
5	**e**	2-Thienyl	OMe	Li	75-80	95:05
6	**f**	Ph	OMe	Na	75-80	88:12
7	**g**	Ph	O*i*-Pr	Li	82	74:26
8	**h**	4-$MeOC_6H_4$	O*i*-Pr	Li	55	93:07
9	**i**	*n*-Pr	O*i*-Pr	Na	86	99:01
10	**j**	Ph	NEt_2	Li	75-80	10:90

Scheme 1.12. Addition of phosphites to chiral sulfinimines.

The hydrolysis of diastereomers **49** or **50** with TFA in methanol gives enantiomerically pure α-aminophosphonates **51**, whereas with concentrated HCl in acetic acid the enantiomerically pure α-aminophosphonic acids **52** (Scheme 1.13).



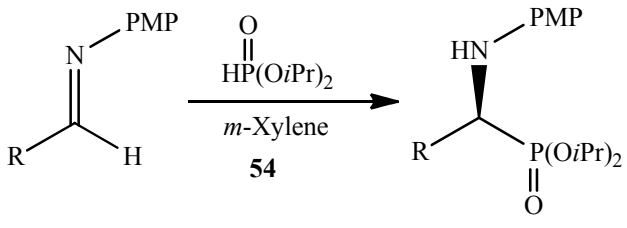
Scheme 1.13. Hydrolysis of α-aminophosphonates **49** or **50**.

1.3.1.2. Addition of racemic dialkyl phosphites to racemic imines with chiral catalysts

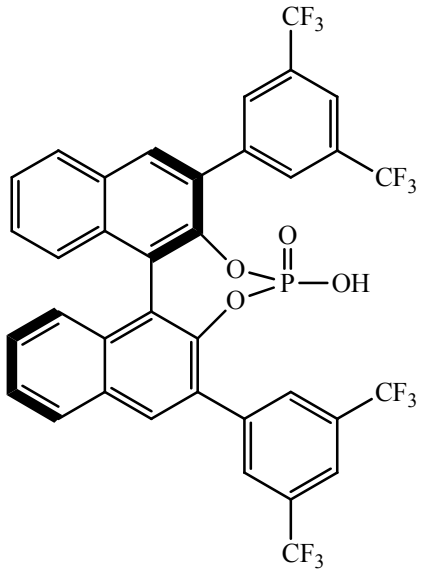
The catalytic asymmetric synthesis is one of the hottest topics in modern synthetic chemistry, because it is the most efficient method for the preparation of chiral, noracemic compounds of high *ee*.[37]

a. Brønsted acid-catalyzed hydrophosphonylation

One of the most successful attempts comes from Akiyama et al.[38] They found that the Brønsted acid, the cyclic phosphoric acid diester **54** derivative of (*R*)-BINOL could catalyze the enantioselective addition of diisopropyl phosphite to the imines **53** at RT. They obtained the (*S*)-α-aminophosphonate **55** in good yield (72-97%) and enantioselectivity (52-90%) (Scheme 1.14).



53 **55**



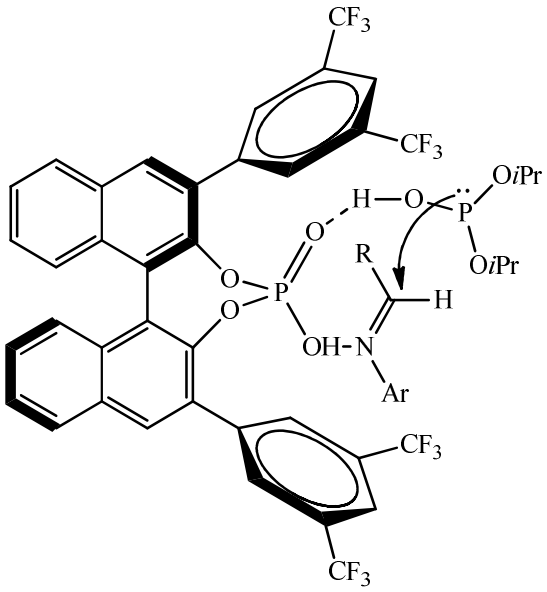
54

Scheme 1.14. Brønsted acid-catalyzed hydrophosphonylation.

In order to explain the high enantioselectivity, the authors proposed a mechanism with **56** as transition state (Figure 1.06). According to their assumption, the phosphoric acid diester **54** has two functions here:

1. As it is a Brønsted acid, it can activate the imine by protonation.

2. The oxygen atom of the P=O group forms a hydrogen bond to the diisopropyl phosphite, which increases the nucleophilicity of the phosphorus atom. The bulky BINOL derivative of phosphorus favors the *re*-facial attack at the C=N bond.

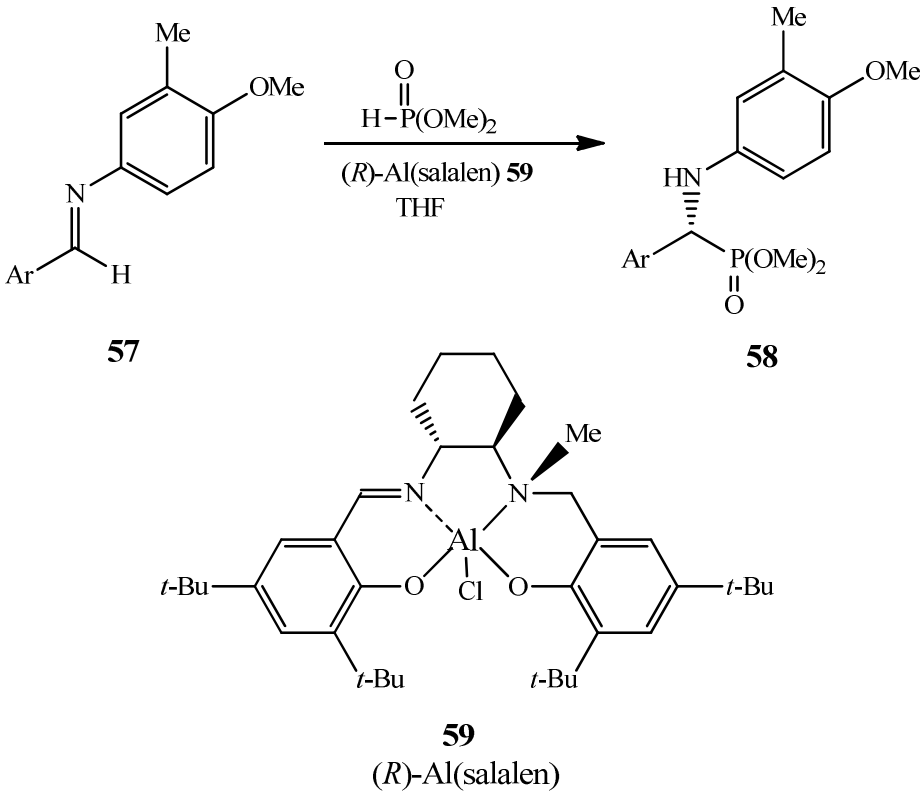


56

Figure 1.06. Proposed transition state for the hydrophosphonylation of imines **53**, catalyzed by Brønsted acid **54**.

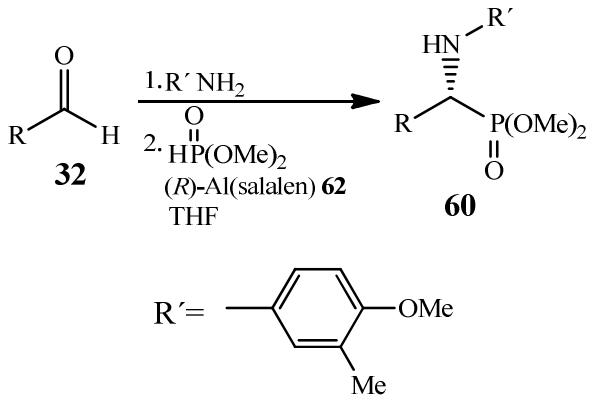
b. Hydrophosphonylation of aromatic aldimines

Another attempt of catalytic hydrophosphonylation was done by Katsuki et al. with good results.[39] They utilized complex (*R*)-Al(salalen) **59** as a catalyst to achieve the stereoselective addition of dimethyl phosphite to the aromatic aldimines **57** (Scheme 1.15). With this method, they obtained α-aminophosphonates **58** in high yields and with very good enantioselectivities. The *ee* value could rise to 95% if the imine had an electron-withdrawing functional group attached to the aromatic ring but it would drop to 85% if an electron-releasing group was present.



Scheme 1.15. Hydrophosphonylation of aromatic aldimines.

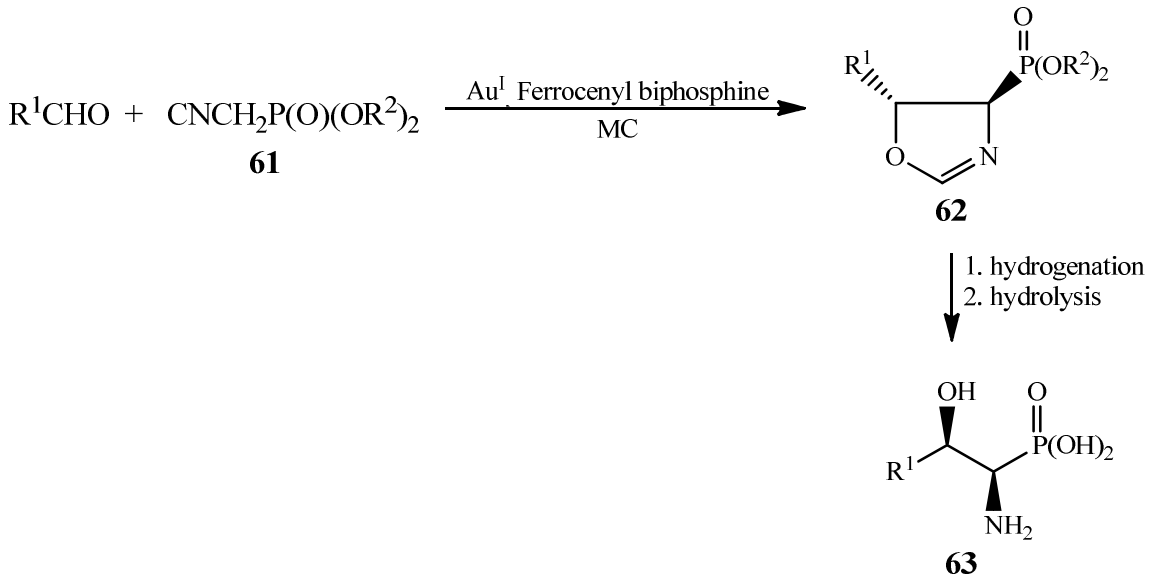
(*R*)-Al(salalen) **59** was also utilized in the one-pot process with aldehydes **32**, 4-methoxy-3-methylaniline or diphenylmethylamine and dimethyl phosphite to achieve a good enantioselectivity (Scheme 1.16).



Scheme 1.16. (*R*)-Al(salalen) in the one-pot process of enantioselective phosphonylation.

1.3.2. Stereoselective formation of the C-C bond

The addition of α-phosphonate carbanions to different electrophilic substrates, through a carbon–carbon bond-forming process, constitutes an important access to α-aminophosphonate synthesis. The Togni and Hayashi groups, independently, reported asymmetric synthesis of α-aminophosphonic acids via an aldol reaction of α-isocyanomethylphosphonates catalyzed by chiral ferrocenyl phosphine-Au(I) complexes.[40,41] Reaction of aldehydes with α-isocyano-methylphosphonates **61** in the presence of only 1 mol% of catalyst gave high yields of *trans*-5-alkyl-2-oxazoline-4-phosphonates **62** with *ee* values between 85–96%. These products were readily converted to the corresponding phosphonic acids **63** upon hydrogenation and hydrolysis (Scheme 1.17).

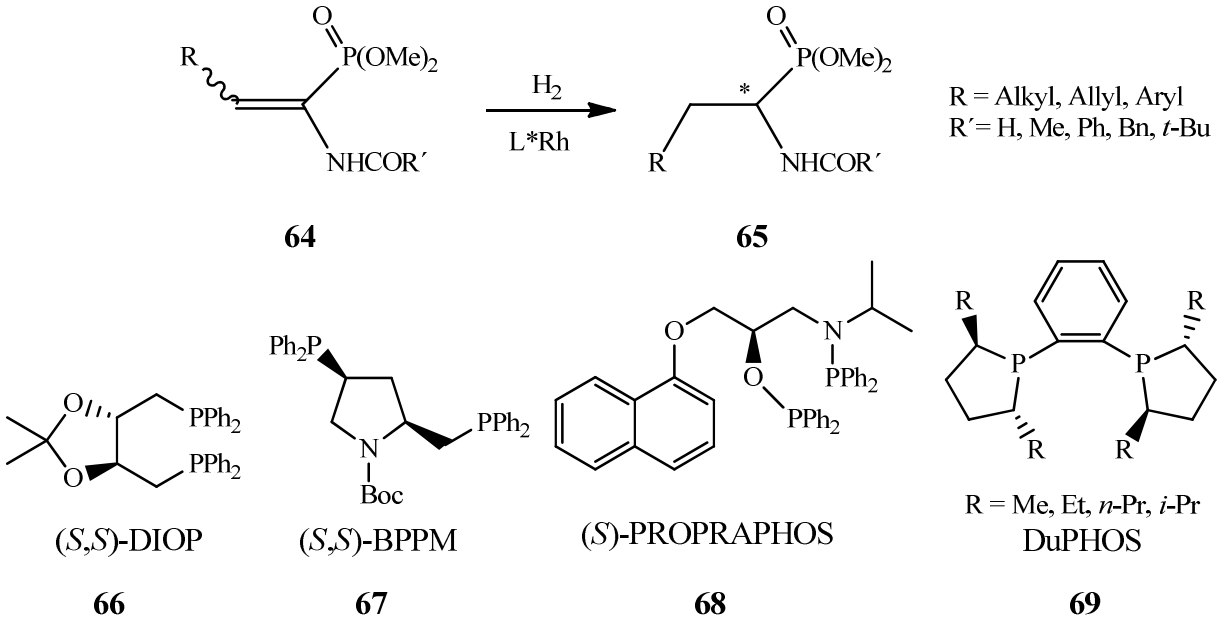


Scheme 1.19. Synthesis of α-aminophosphonic acids via an aldol reaction of α-isocyanomethylphosphonates, catalyzed by chiral ferrocenyl phosphine-Au(I) complexes.

1.3.3. Catalytic hydrogenation

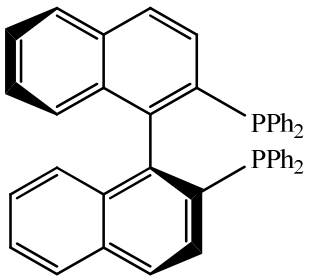
Catalytic asymmetric hydrogenation of dehydroamino acids is a mature area of organic chemistry, and a considerable number of catalytic systems are known to provide α-amino acids with enantioselectivities exceeding 95%.[42] By comparison, there are only a few catalytic hydrogenation methods available to access optically active α-aminophosphonic acid derivatives. The most investigated of them is the homogeneous catalytic hydrogenation of

dehydro aminophosphonates (**64**) using rhodium complexes (Scheme 1.18). Many ligands,[43-45] most of which are diphosphines like **66-69**, have been found to exhibit high enantioselectivities and good yield.



Scheme 1.18. Catalytic hydrogenation by rhodium complex.

Noyori and his colleagues published many papers about the application of Ru(II)-BINAP complex (Figure 1.07) in hydrogenation (Noyori asymmetric hydrogenation) to synthesize stereoselective compounds.[46] They also prepared chiral, nonracemic α-aminophosphonates with 97% *ee* in quantitative yield under very mild reaction conditions (low pressure, 30 °C).[47]



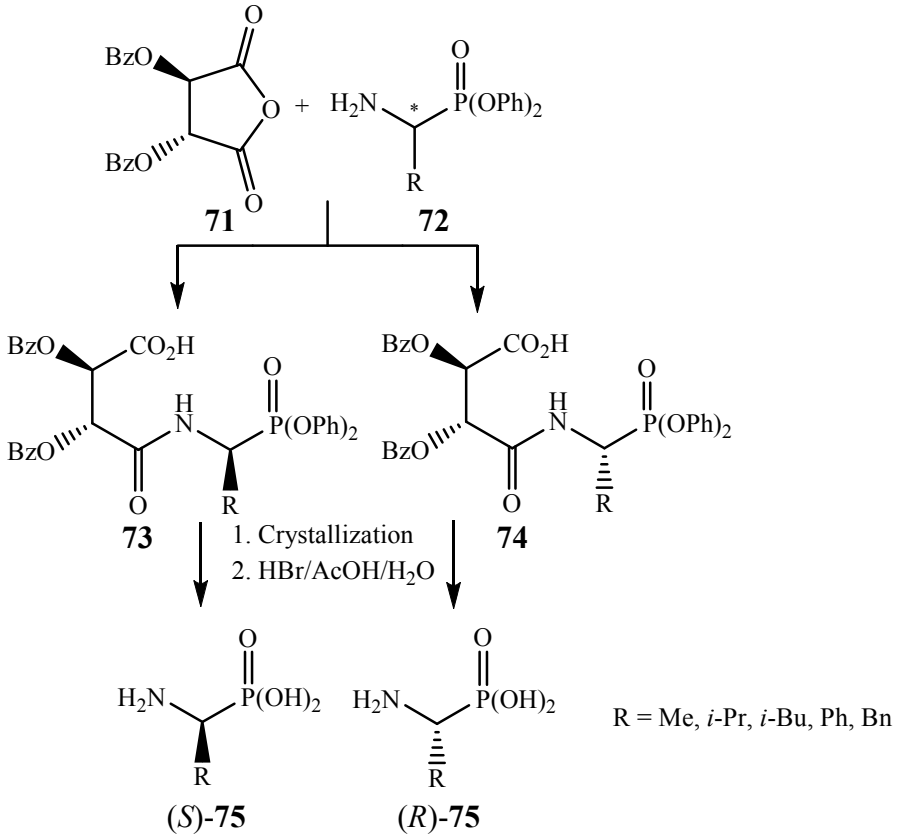
(*S*)-BINAP
70

Figure 1.07. BINAP.

1.3.4. Resolution

1.3.4.1. Resolution by derivatization with dibenzoyl-*L*-tartaric anhydride

This classical method is still of great importance today, especially if both enantiomers of the α-aminophosphonic acid are useful. Probably the most widely used version is derivatization with dibenzoyl-*L*-tartaric anhydride (**71**) (Scheme 1.19).[48] The diastereomeric amides **73** and **74** are separated by fractional crystallization and finally deprotected.

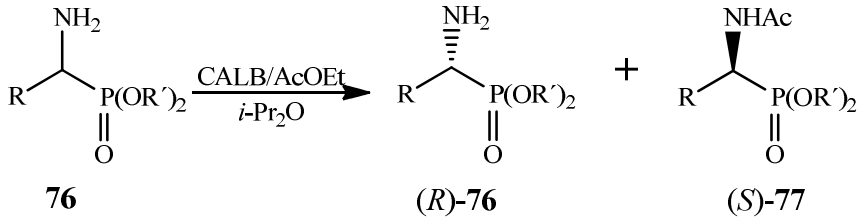


Scheme 1.19. Resolution by derivatization with dibenzoyl-*L*-tartaric anhydride.

1.3.4.2. Enzymatic resolution

The enzymatic resolution is another very practical method of obtaining optically active α-aminophosphonic acids. The advantages of this method are usually mild reaction conditions and low cost as well as high enantioselectivity. For example, the enzyme *Candida antarctica Lipase B* (CALB) catalyzes the enantioselective acylation of racemic α-aminophosphonate **76**

in AcOEt. The (*S*)-aminophosphonate is preferentially acylated and the yield as well as the *ee* are high (Scheme 1.20).[49]



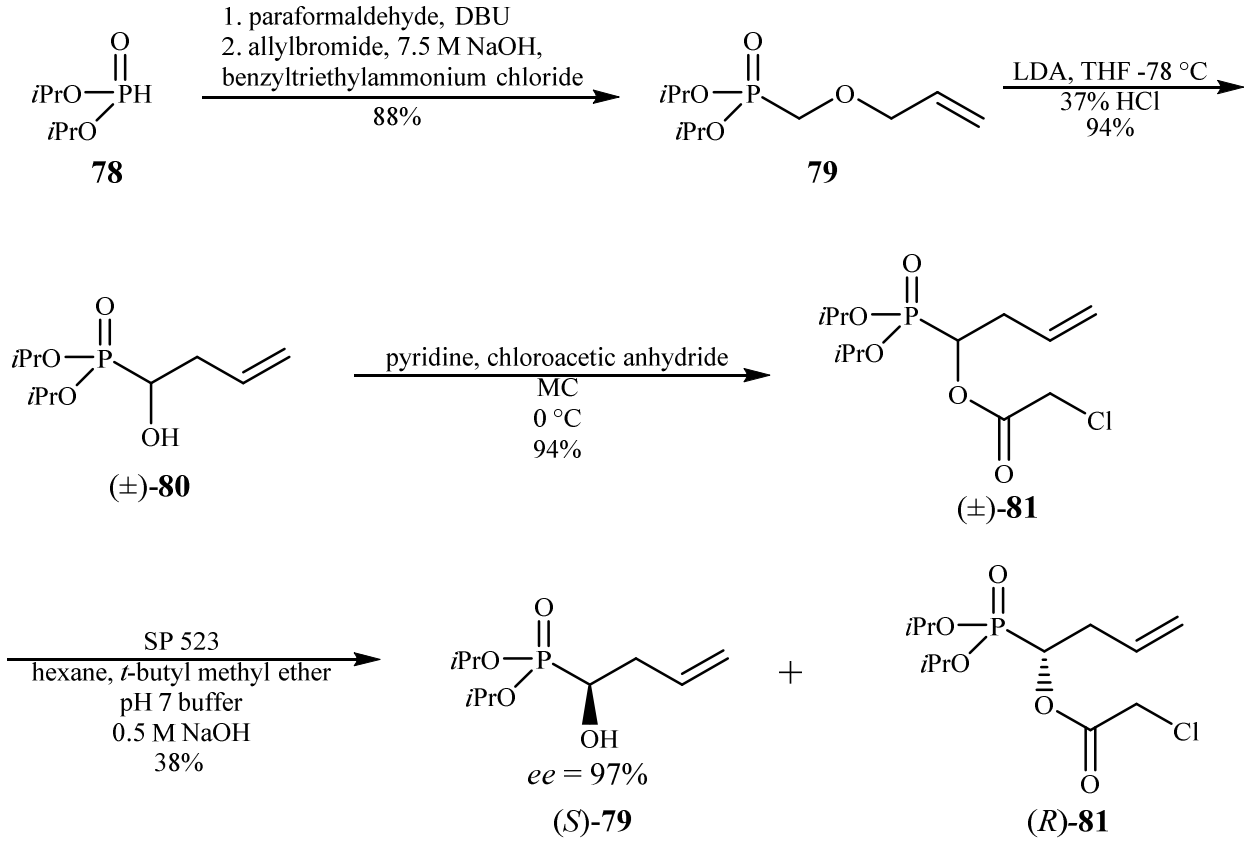
76 (*R*)-**76** (*S*)-**77**

Scheme 1.20. Enzymatic resolution by CALB.

1.4. Results and discussion of the enzyme-catalyzed stereoselective synthesis of α-aminophosphonic acids

1.4.1. Synthesis and enzyme-catalyzed resolution of (±)-1-hydroxy-3-butenylphosphonate

(±)-1-Hydroxyphosphonate **80** was readily synthesized in two steps, starting with very cheap and easily available phosphite, paraformaldehyde, allyl bromide and lithium diisopropylamide in high yield (Scheme 1.21). First, diisopropyl phosphite (**78**) was added to paraformaldehyde, catalyzed by DBU to afford diisopropyl hydroxymethylphosphonate, which was then allylated at oxygen under phase-transfer conditions to give ether **79**. These two reactions were performed as a one pot reaction in 15-20 g quantities (88% yield).

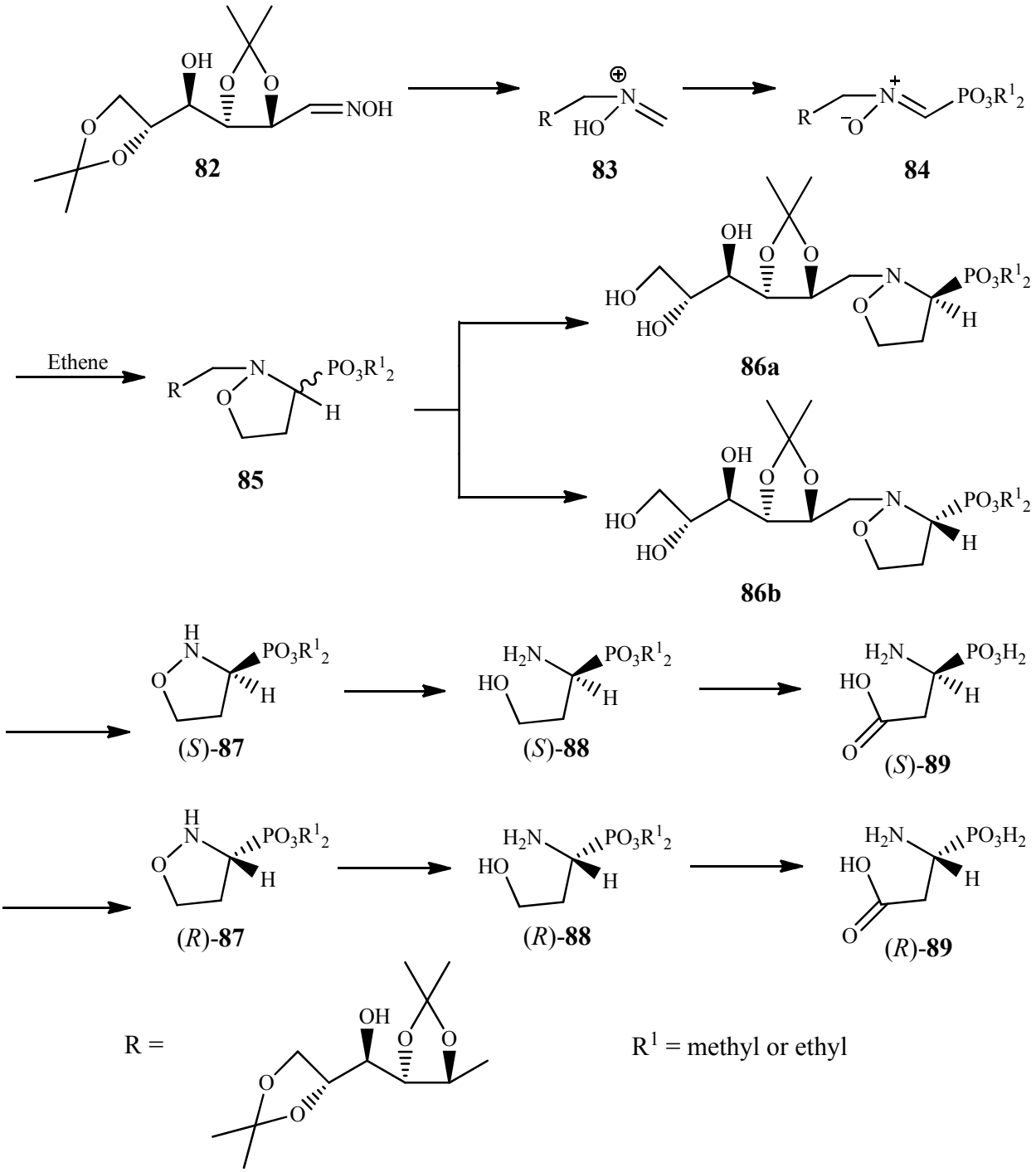


Scheme 1.21. Synthesis and enzyme-catalyzed resolution of (±)-1-hydroxyphosphonate **80**.

(±)-1-Hydroxyphosphonate **80** can be used as a very good starting material for α-aminophosphonic acids for several reasons: (1) The hydroxyl group at α-position can be smoothly converted to amino group by means of the Mitsunobu reaction with HN_3 or substitution of the activated hydroxyl group with NaN_3 in a polar organic solvent, and the enantiopurity stays high with both two methods if the hydroxyl phosphonate is optically active; (2) the carbon chain can be easily shortened by oxidative cleavage of the double bond, and the double bond can be also transformed into a hydroxylethyl group, which can be converted to other functional groups; (3) and moreover, it brings one or two oxygen atoms, which can be readily modified into many functional groups; (4) furthermore, using lipase from *Thermomyces lanuginosus* as enzyme, the chloroacetate of (±)-1-hydroxyphosphonate (±)-**81** can be enantioselectively hydrolyzed to the (*S*)-hydroxyphosphonate (*S*)-**79** with high enantiomeric excess (97%, conversion 38%), which can be determined by ^{1}H NMR spectroscopy of its (*R*)-Mosher ester. If the conversion is higher than 50%, the (*R*)-chloroacetate (*R*)-**81** can also be obtained with very high enantiomeric excess. Therefore (*R*)- and (*S*)-configured α-aminophosphonic acids of >97% *ee* can be prepared from these two α-hydroxyphosphonates.

1.4.2. Synthesis of (*R*)-3-amino-3-phosphonopropanoic acid

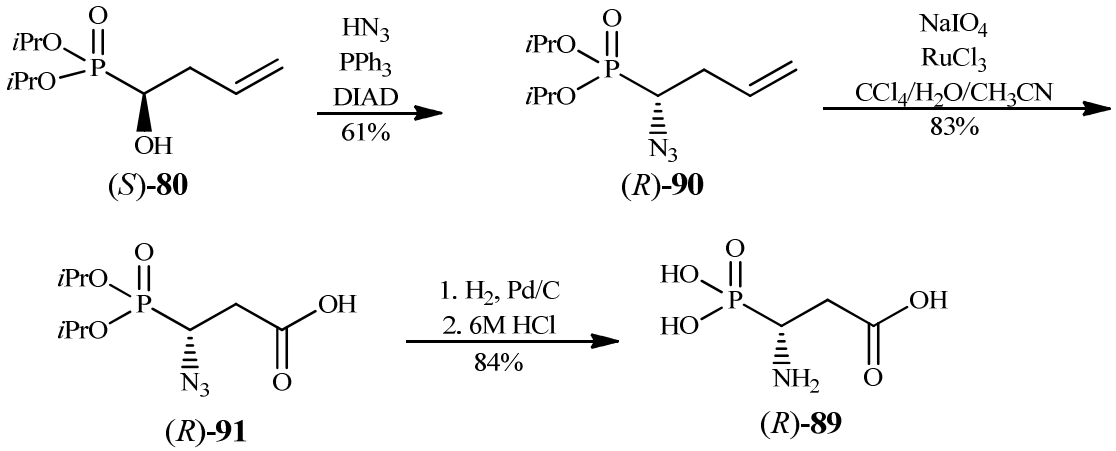
(*R*)-3-Amino-3-phosphonopropanoic acid [(*R*)-**89**] is the phosphonic acid analog of (*S*)-aspartic acid. The first and only synthesis of (*R*)-3-amino-3-phosphonopropanoic acid until now has been achieved by Vasella and Voeffray (Scheme 1.22).[50] The key step of this



Scheme 1.22. Synthesis of (*R*)- and (*S*)-3-amino-3-phosphonopropanoic acid by Vasella and Voeffray.

asymmetric synthesis is a [1,3]-dipolar cycloaddition of *N*-glycosyl-*C*-dialkoxy-phosphonoylnitrone (**84**) and ethene. The monoisopropylidene derivatives (*S*)-**87** and (*R*)-**87** of the cycloaddition product **86** can be separated by chromatography. (*R*)- and (*S*)-3-amino-3-phosphonopropanoic acid (*R*)-**89** and (*R*)-**89**) can be obtained from (*S*)-**87** and (*R*)-**87** by hydrogenation and deprotection.

Using (*R*)-1-hydroxyphosphonate (*S*)-**80** as starting material, my novel synthesis of (*R*)-3-amino-3-phosphonopropanoic acid is much shorter and easier. The α-hydroxyphosphonate (*S*)-**80** was first converted to azide (*R*)-**90** by means of the Mitsunobu reaction and the configuration was inverted (Scheme 1.23). After that, the double bond was oxidized and shortened by ruthenium (VIII) tetroxide formed in situ according to the protocol of Sharpless.[51] The azide (*R*)-**91** was readily reduced by catalytic hydrogenation, which was followed by hydrolytic removal of the protecting groups with refluxing 6 M HCl to give phosphonic acid (*R*)-**89**, the phosphonic acid analog of *L*-aspartic acid.



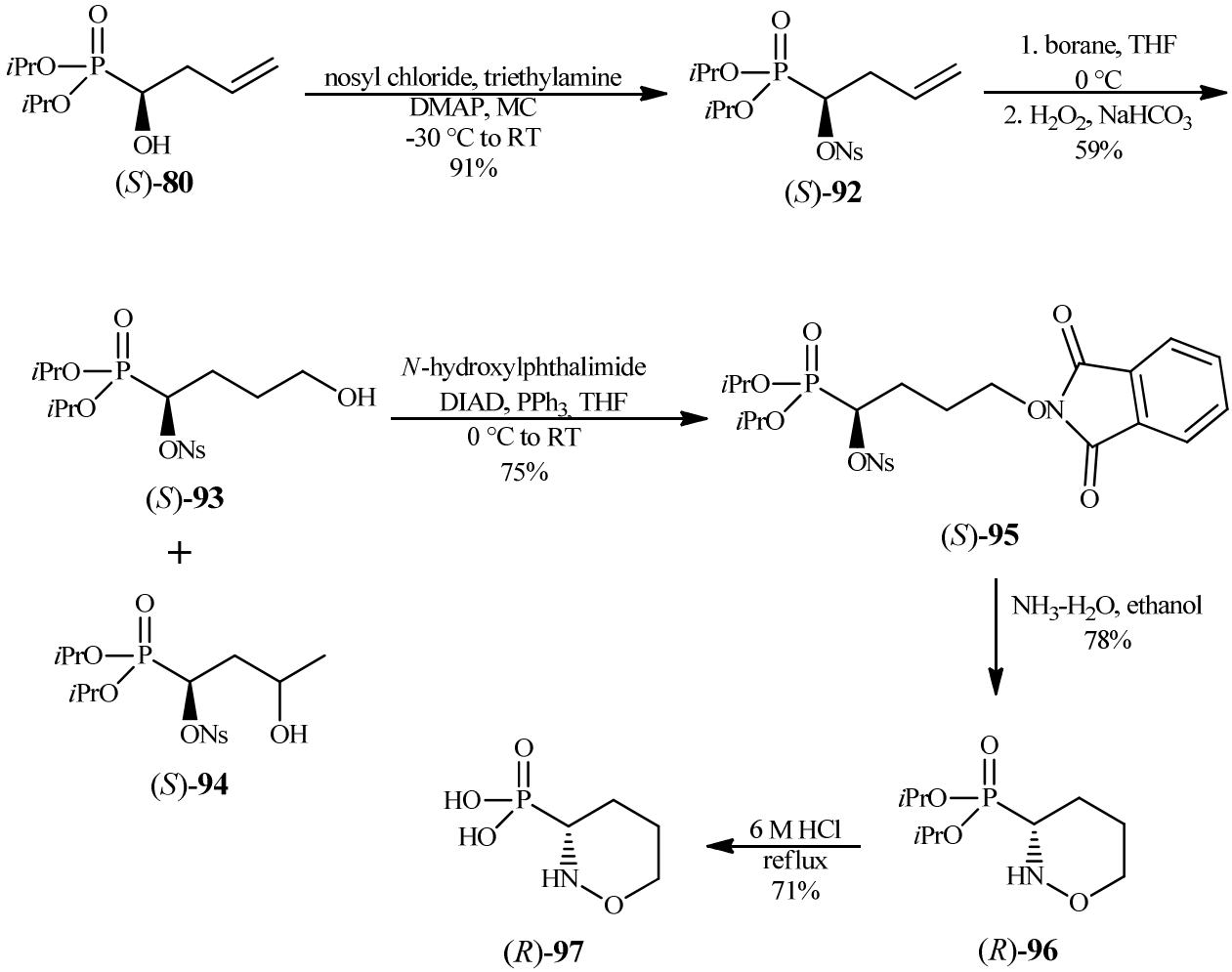
(*S*)-**80** (*R*)-**90** (*R*)-**91** (*R*)-**89**

Scheme 1.23. Synthesis of (*R*)-3-amino-3-phosphonopropanoic acid.

1.4.3. Synthesis of (*R*)-(1,2-oxazinan-3-yl)phosphonic acid

(*R*)-(1,2-oxazinan-3-yl)phosphonic acid [(*R*)-**97**] is a structural analog of (*S*)-proline. It is considered to be a new potential inhibitor of pyrroline-5-carboxylate reductase, which plays an important role in the proline metabolism in plants and will be tested for herbicidal activity.

The synthesis began also with (*S*)-1-hydroxyphosphonate (*S*)-**80**, which was esterified with *p*-nitrobenzene sulfonyl chloride (nosyl chloride) (Scheme 1.24). Having tried this reaction



Scheme 1.24. Synthesis of (*R*)-(1,2-oxazinan-3-yl)phosphonic acid.

several times under various conditions, I found that nosylation worked best when the reaction temperature was −30 °C at the beginning and a stoichiometric amount of DMAP was used as base. Hydroboration in combination with oxidative work up was then tried to get the *anti*-Markovnikov primary alcohol (*S*)-**93** using different boranes under diverse conditions (Table 1.01).

Borane	**Yield**	(*S*)-**94** : (*S*)-**93**
1.5 equiv. BH_3·THF	50%	1:3
0.5 equiv. BH_3·THF	61%	1:3.2
9-BBN	0%	
cyclohexylborane	0%	
Old catecholborane with old Wilkinson´s catalyst	53%	1:10
Old catecholborane with new Wilkinson´s catalyst	30%	1:5
New catecholborane with old Wilkinson´s catalyst	83%	1:10

Table 1.01. Hydroboration of nosylate (*S*)-**92**.

Surprisingly, the best result was obtained when freshly ordered catecholborane and an old (oxidized?) Wilkinson´s catalyst were used. Evans et al. have discussed the effect of catalyst oxidation in the Wilkinson-catalyzed hydroboration, but without mentioning such kind of finding.[52] As the amount of the old catalyst was limited and I did not think that other groups could reproduce this finding even with their own "aged" catalyst, this interesting finding could unfortunately not be utilized for a preparative synthesis. The second best result was obtained using 0.5 equiv. of borane·THF at 0 °C. But the amount of the Markovnikov alcohol in the crude product could hardly be reduced despite having tried different conditions. Nosylate (*S*)-**93** partly cyclized to a substituted tetrahydrofuran when a solution containing it was concentrated at 50 °C under reduced pressure. But the cyclization could be prevented, if the solution was concentrated at RT. The compound was found to be stable in the freezer for several weeks. The experiments performed with 9-BBN and cyclohexylborane failed to give the desired product.

Then the primary alcohol (*S*)-**93** was converted to the protected hydroxylamine (*S*)-**95** in 75% yield, using the Mitsunobu reaction. The following domino-reaction was started by removing the phthalyl protecting group from nitrogen with ammonia in EtOH. The unmasked amino group attacked at C-1 and substituted the nosyloxy group (S_N2) with formation of a six-membered ring. The isopropyl groups were removed by refluxing 6 M HCl to give (*R*)-**97** after ion exchange chromatography (Dowex 50, H^+).

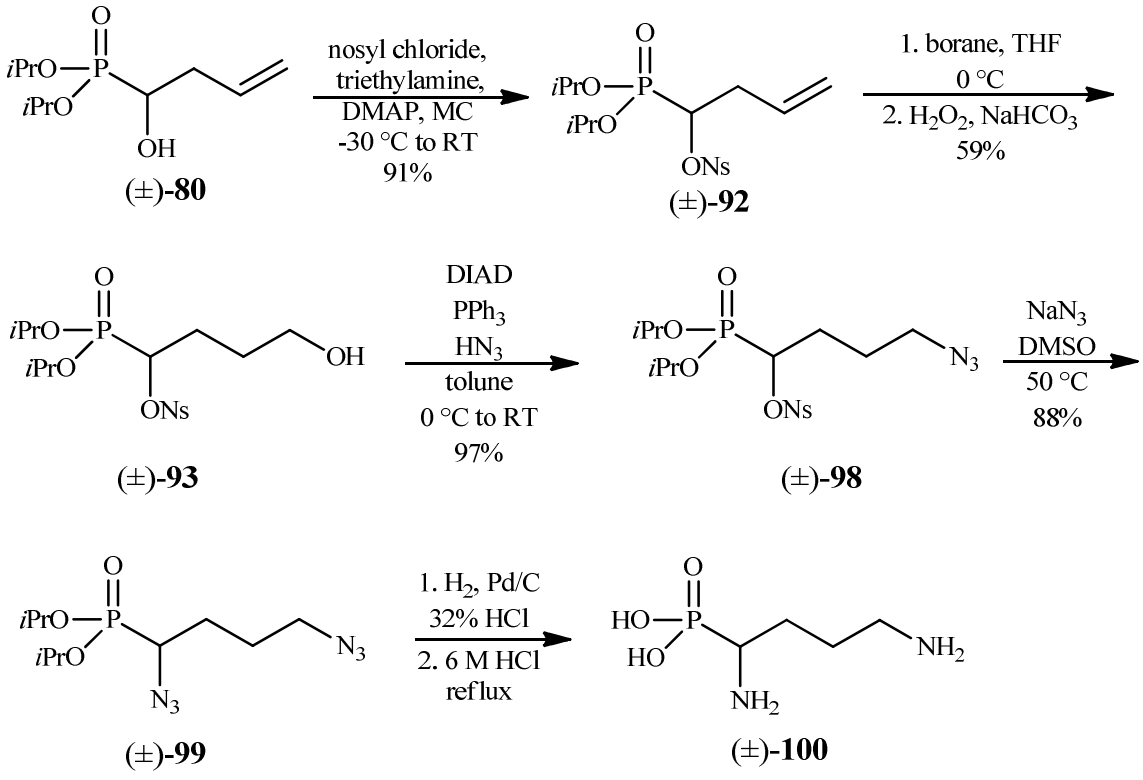
1.4.4. Synthesis of (±)-1,4-diaminobutylphosphonic acid

(*S*)-1,4-Diaminobutylphosphonic acid (**100**) is a structural analog of (*S*)-ornithine, which is an intermediate of the urea cycle. Furthermore, it is the starting material for the biosynthesis of polyamines and cocaine. Polyamines are essential for cell growth, cell division and modulating senescence of organs in plants and are therefore considered plant hormones.[53]

Because of the importance of ornithine in biological systems, its phosphonic acid analog 1,4-diaminobutylphosphonic acid has been synthesized by many groups for diverse purposes.[54-57] The analytical liquid chromatographic enantio-separation has also been furnished by our group several years ago.[58] Nevertheless, I wanted to provide a new synthetic route to this compound, which would be relatively short and easily achievable. Due to the lack of time, only the synthesis of the racemate was performed, but in principle, the route could also be

used for the preparation of the enantiomerically pure diaminophosphonic acid **100**, if the starting hydroxyphosphonate (*S*)-**80** with an *ee* of 98% is used.

The synthesis shares the first two steps (nosylation and hydroboration) with the synthesis of (*R*)-(1,2-oxazinan-3-yl)phosphonic acid (*R*)-**97** (Scheme 1.25). Then the primary alcohol (±)-**93** was converted to azide (±)-**98** by means of the Mitsunobu reaction in very high yield (91%). The nosyloxy group was substituted with azido group (S_N2) in DMSO at 50 °C to afford diazide (±)-**99**, which was easily reduced catalytically, deprotected and purified by ion exchange chromatography to furnish (±)-1,4-diaminobutylphosphonic acid [(±)-**100]**, the structural analog of racemic ornithine.



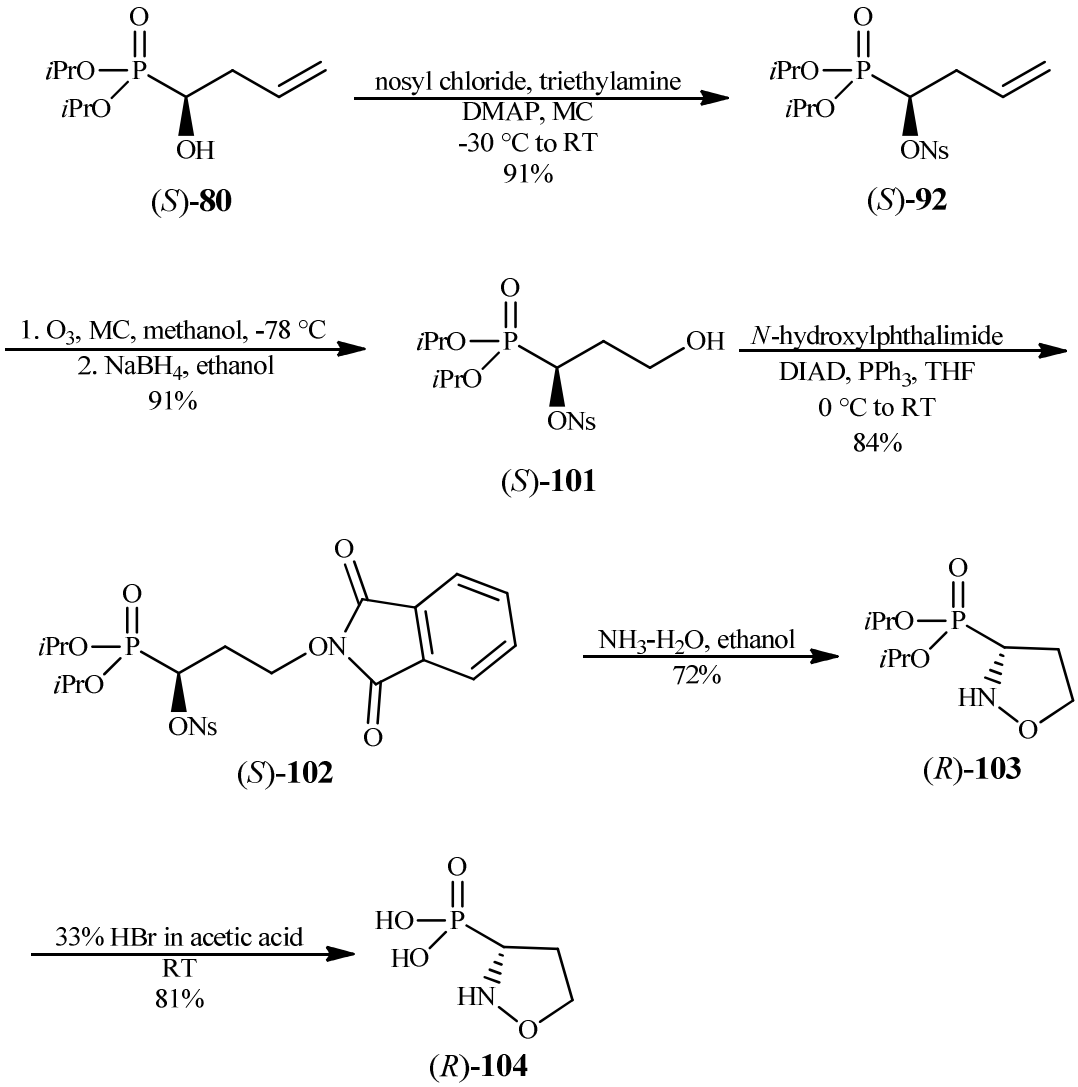
Scheme 1.25. Synthesis of (±)-1,4-diaminobutylphosphonic acid.

1.4.5. Synthesis of (*R*)-(isoxazolidin-3-yl)phosphonic acid

(*R*)-(Isoxazolidin-3-yl)phosphonic acid [(*R*)-**104**] is another structural analog of (*S*)-proline. It is considered to be a potential inhibitor of pyrroline-5-carboxylate reductase, which plays an important role in proline metabolism and will be tested for herbicidal activity.

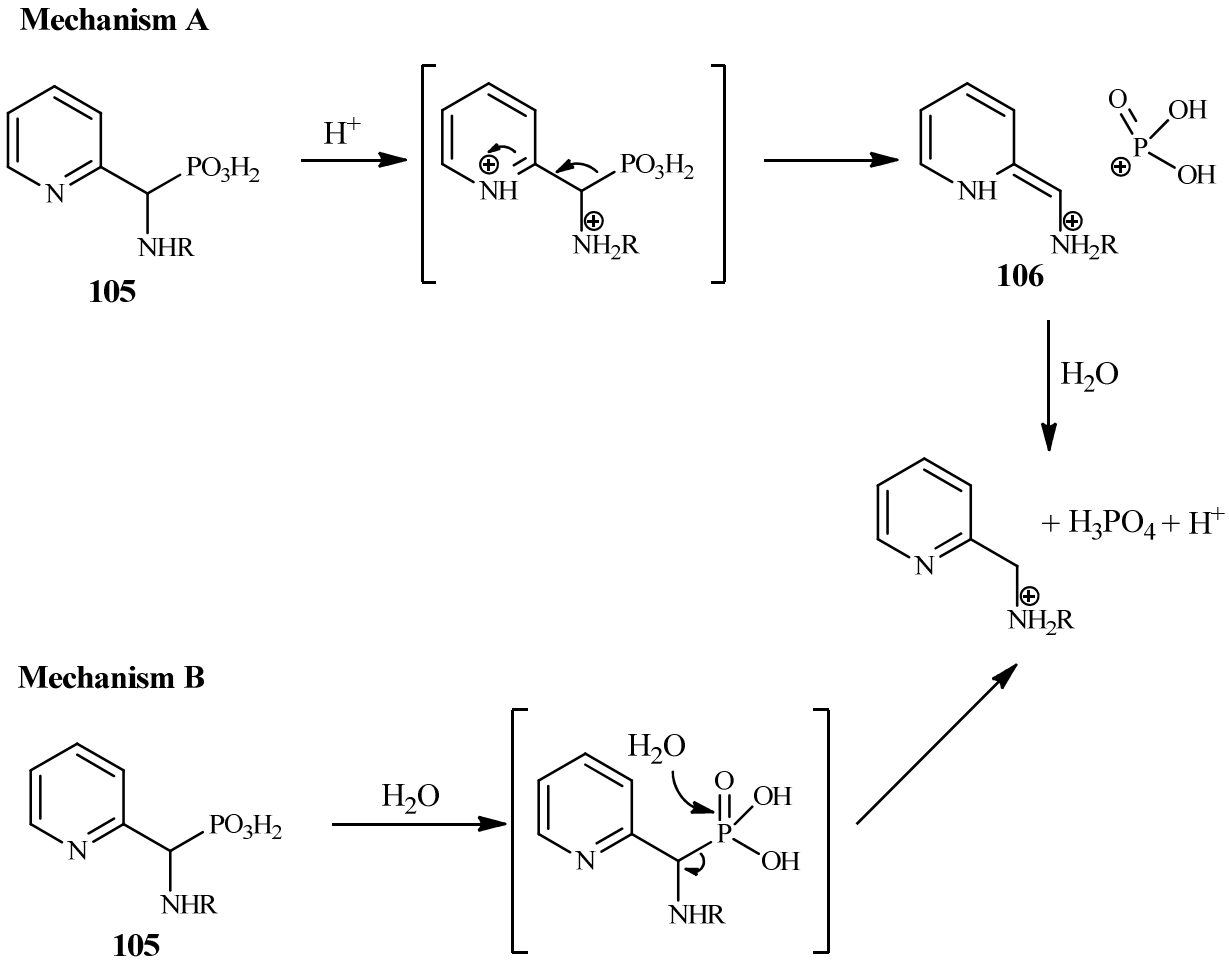
As an intermediate in the synthesis of (*R*)-3-amino-3-phosphonopropanoic acid (*R*)-**99**, (*R*)-(isoxazolidin-3-yl)phosphonic acid [(*R*)-**87**] has also been described by Vasella and Voeffray (see Scheme 1.22).[50] Using the same strategy in the synthesis of (*R*)-(1,2-oxazinan-3-yl)phosphonic acid [(*R*)-**104**], the new asymmetric synthesis of the proline analog was achieved in a relatively short sequence.

To shorten the carbon chain and introduce the hydroxyl group, ozonolysis was performed in a mixture of methanol and dichloromethane at −78 °C (Scheme 1.26). When the solution started to get blue, introduction of ozone was stopped and reductive conditions were applied. Triphenylphosphine was found not to be necessary and sodium borohydride could be added as a solution in ethanol directly to the reaction mixture. The hydroxynosylate (*S*)-**101** was then converted to protected hydroxylamine (*S*)-**102** by means of the Mitsunobu reaction. In the following domino-reaction the cyclic five-membered hydroxylamine (*R*)-**103** was formed more easily than the six-membered analog, because refluxing of the reaction mixture was not necessary. However, two byproducts (phosphate and the phosphonic acid with the opened N-O bond) were formed. The yield for the removal of the isopropyl protecting groups under hydrolytic conditions (refluxing 6 M HCl) was very low for unknown reasons. The yield could also not be improved when trimethylsilyl bromide was used for deprotection and the same byproducts were formed. The desired *L*-proline analog (*R*)-**104** was obtained as a homogenous product only if the phosphonate was deprotected with 33% HBr in acetic acid at RT.[50] The crude phosphonic acid was purified by ion exchange chromatography (Dowex 50, H^+, elution with water). To remove the acetic acid, the product was dissolved in water, freeze-dried, and finally crystallized from water/ethanol. This protocol for deprotection and purification furnished the desired aminophosphonic acid (*R*)-**104**, an analog of *L*-proline in greatly improved yield (81%) and quality.



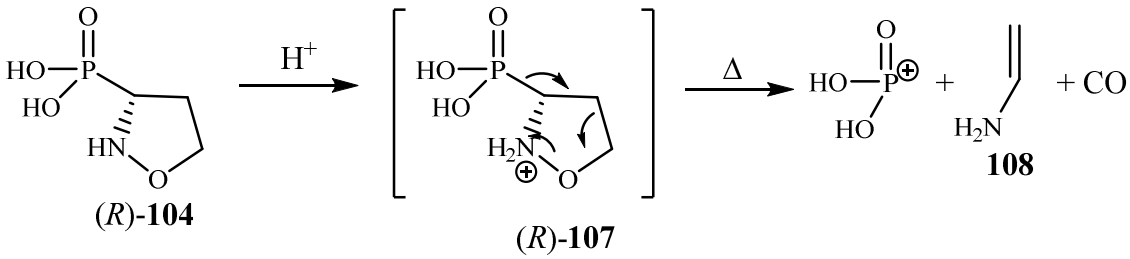
Scheme 1.26. Synthesis of (*R*)-(isoxazolidin-3-yl)phosphonic acid.

α-Aminophosphonic acids are normally chemically very stable compounds under acidic and basic conditions. But those with nitrogen-containing heterocyclic rings are surprisingly labile. Two possible reaction mechanisms for the degradation of 1-amino-(2-pyridyl)-methylphosphonic acid (**105**) to phosphate and 2-pyridylmethylamine (**106**) were proposed by Boduszek et al. (Scheme 1.27).[59] The authors argued that protonation of both nitrogens is necessary to facilitate the heterolytic cleavage of the P-C bond with formation of protonated amine and metaphosphate (mechanism A). The P-C bond in protonated simple α-aminophosphonic acids is not destabilized enough to be split. Therefore, mechanism B is rejected.



Scheme 1.27. Suggested mechanisms for the degradation of 1-amino-(2-pyridyl)methylphosphonic acid

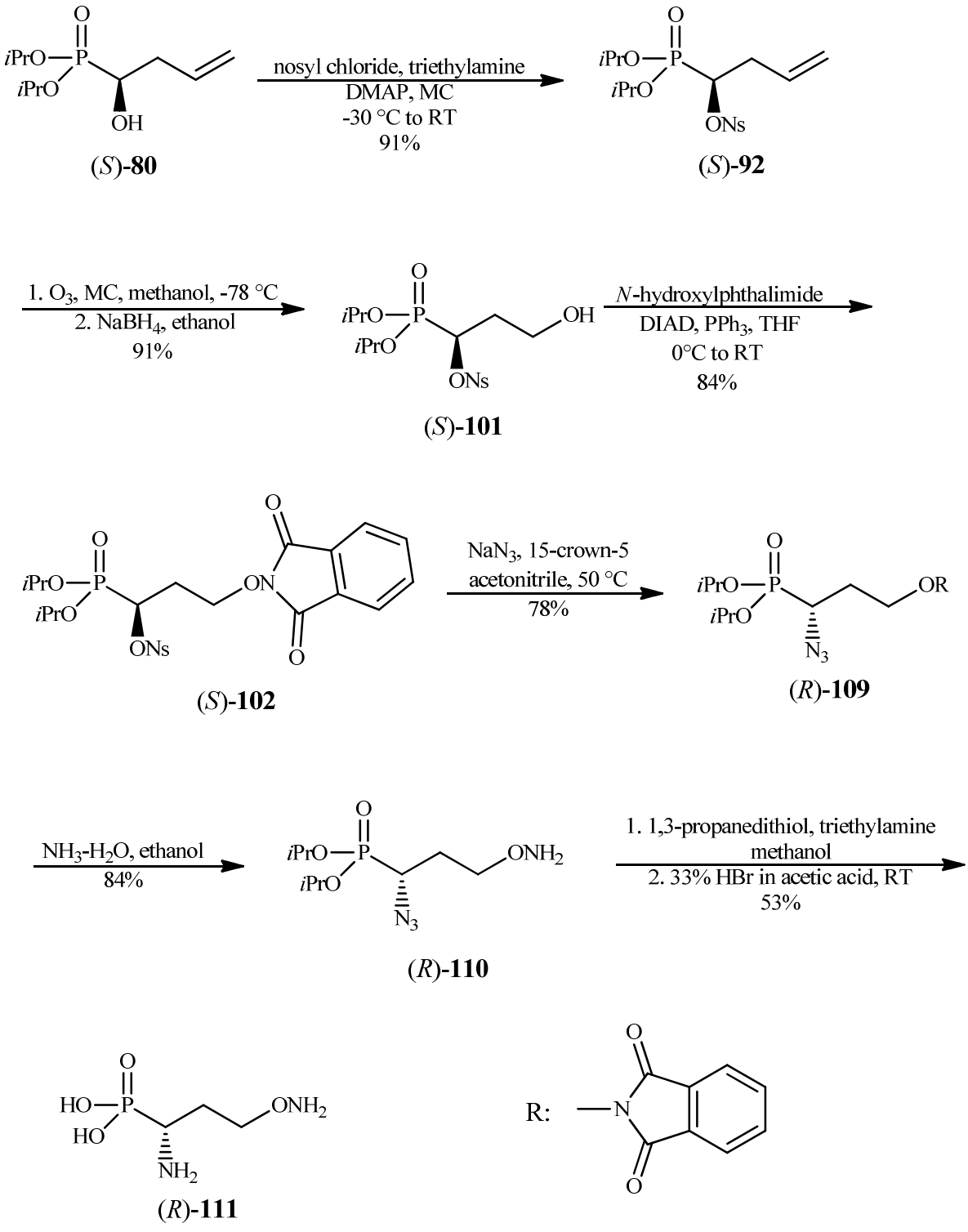
On the basis of the studies by Boduszek et al., I propose a mechanism for the degradation of (*R*)-(isoxazolidin-3-yl)phosphonic acid [(±)-**104**]. During deprotection under acidic conditions (6 M HCl) phosphonic acid (±)-**104** protonated at nitrogen undergoes a fragmentation depicted in Scheme 1.28. Amine **108**, carbon monoxide, and protonated metaphosphate are formed as fragments. Metaphosphate adds water to furnish inorganic phosphate.



Scheme 1.28. Suggested mechanism of degradation of (*R*)-(isoxazolidin-3-yl)phosphonic acid.

1.4.6. Synthesis of (*R*)-1-amino-3-(aminooxy)propylphosphonic acid

(*R*)-1-Amino-3-(aminooxy)propylphosphonic acid [(*R*)-**111**] is another structural analog of (*S*)-ornithine. The synthesis shares the first several steps including the Mitsunobu reaction with the preparation of (*R*)-(isoxazolidin-3-yl)phosphonic acid [(*R*)-**104**] (see Scheme 1.26). The nosyloxy group was substituted with sodium azide in acetonitrile, assisted by 15-crown-5 ether as catalyst to generate naked anions (Scheme 1.29). Thereby the configuration at C-1 was inverted to *R*. Azide (*R*)-**109** was converted to γ-aminooxyphosphonate (*R*)-**110** using ammonia dissolved in water/ethanol. At first I tried to reduce the azido group by catalytic reduction, but the N-O bond was split reductively as well. However, the azido group was selectively reduced to the amino group with 1,3-propanedithiol/triethylamine under very mild conditions.[60] This time the weak N-O bond remained intact. Without purification, the crude product was deprotected at phosphorus with 33% HBr/CH_3CO_2H as the reagent of choice at room temperature. It did not destroy part of the 1-amino-3-(aminooxy)phosphonic acid (*R*)-**111**, which was isolated as crystalline product after purification.

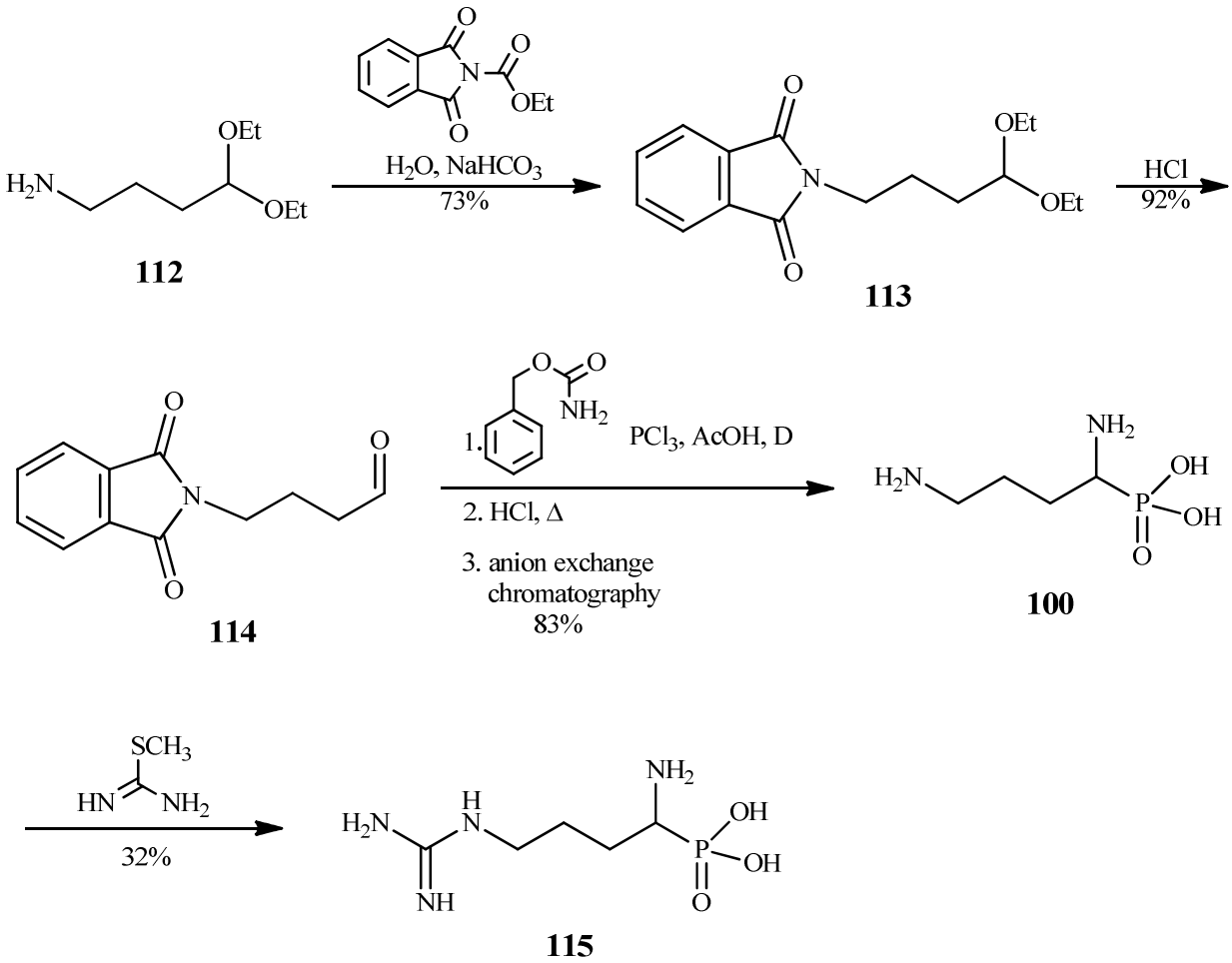


Scheme 1.29. Synthesis of (*R*)-1-amino-3-(aminooxy)propylphosphonic acid.

1.4.7. Synthesis of (*R*)-1-amino-4-guanidinobutylphosphonic acid

(*R*)-1-Amino-4-guanidinobutylphosphonic acid [(*R*)-**115**] is the phosphonic acid analog of proteinogenic amino acid (*S*)-arginine. The synthesis of its racemate was first achieved by

Kerwin et al. in 1996 (Scheme 1.30).[55] No asymmetric synthesis has been reported so far to the best of my knowledge. The preparation of this phosphonic acid containing a guanidino and an amino group is challenging because of the presence of an acid and two basic groups in the molecule. Arginine plays an important role in cell division, the healing of wounds, detoxification of ammonia in mammals (urea cycle), immune functions, and the release of hormones.

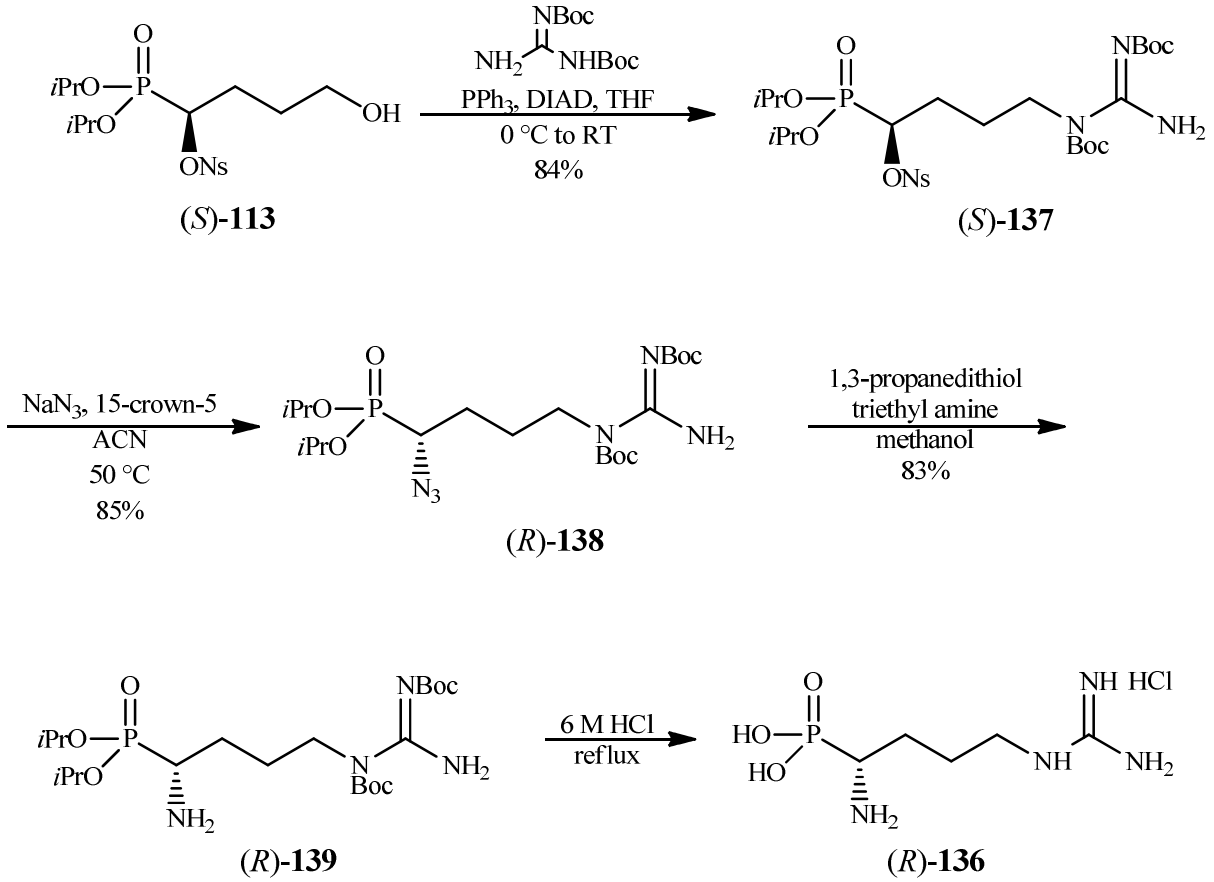


Scheme 1.30. Synthesis of (±)-1-amino-4-guanidinobutylphosphonic acid by Kerwin et al.

The racemic synthesis of phosphoarginine by Kerwin et al. is based on the synthesis of the phosphonic analog of ornithine (±)-**100**, which began with the introduction of the phthalimide group onto the 4,4-diethoxybutan-1-amine [(±)-**112**]. After hydrolysis in HCl, the deprotected aldehyde (±)-**114** afforded the phosphonicacid analog of ornithine (±)-**100** when it was reacted with benzyl carbamate and phosphorous trichloride in boiling acetic acid. In this key step, two amino groups and phosphorus were introduced by means of benzyl carbamate. Benzylcarbamate and the aldehyde formed an imine, which readily added a phosphorous acid derivative. Deblocking gave the. phosphonic acid analog of ornithine,which reacted at the γ-

amino group with *S*-methylisothiourea in the presence of triethylamine in aqueous ethanol to afford the phosphonic acid analog of arginine (±)-**115** with a yield of 32% after purification by ion exchange chromatography.

As the configuration at C-1 of phosphoarginine might be of great importance for its biological activities due to the very high enantioselectivity of enzymes metabolizing the naturally occurring *L*-arginine, the (*R*)-enantiomer was prepared. I envisaged a new approach to (*R*)-phosphoarginine, starting from nosylate (*S*)-**92** and not involving phosphoornithine (*R*)-**100** (Scheme 1.31).



Scheme 1.31. Synthesis of (*R*)-1-amino-4-guanidinobutylphosphonic acid.

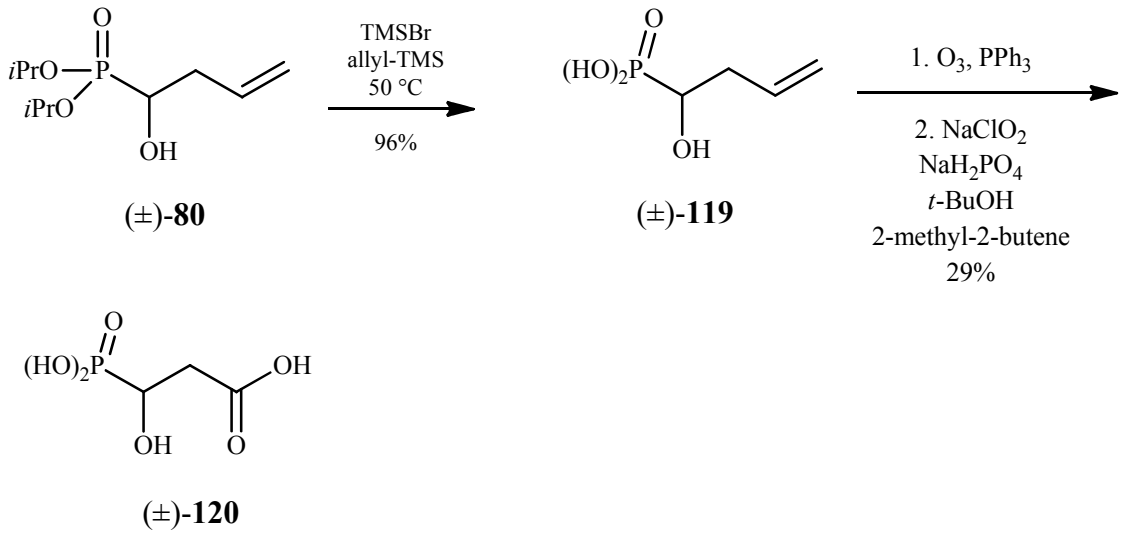
The synthesis began with nosylate (*S*)-**92**, which was already described in the synthesis of (*R*)-(1,2-oxazinan-3-yl)phosphonic acid [(*R*)-**97**]. The guanidino group was introduced smoothly by means of the Mitsunobu reaction with 1,3-bis(*tert*-butoxylcarbonyl)guanidine in high yield (84%).[61] Then the nosyloxy group was substituted by sodium azide in acetonitrile containing a substoichiometric amount of the crown ether 15-crown-5. Formation of the azide (*R*)-**117** was followed an invertive process (S_N2). Azide (*R*)-**117** was reduced with 1,3-

propanedithiol/triethylamine to afford amine (*R*)-**118** at room temperature. The crude and protected phosphoarginine was deprotected with refluxing 6 M HCl to give phosphonic acid analog (*R*)-**115** of (*S*)-arginine hydrochloride as a gum, which could not be crystallized from water/ethanol.

1.4.8. Synthesis of (*R*)-3-hydroxy-3-phosphonopropanoic acid

(*R*)-3-Hydroxy-3-phosphonopropanoic acid is the phosphonic acid analog of malic acid. Malate plays an important role in biochemistry. It is a source of CO_2 in the Calvin cycle, and (*S*)-malate is an intermediate in the citric acid cycle, formed by the stereospecific *anti*-addition of water to fumarate by fumarate hydratase. It is also formed from pyruvate, CO_2, and $NADPH/H^+$ via an anaplerotic reaction catalyzed by malic enzyme and malate dehydrogenase. As a double anion, malate often accompanies potassium cations during the uptake of solutes into the guard cells in order to maintain electrical balance in the cell. The accumulation of these solutes within the guard cell decreases the solute potential, allowing water to enter the cell and promote aperture of the stomata.

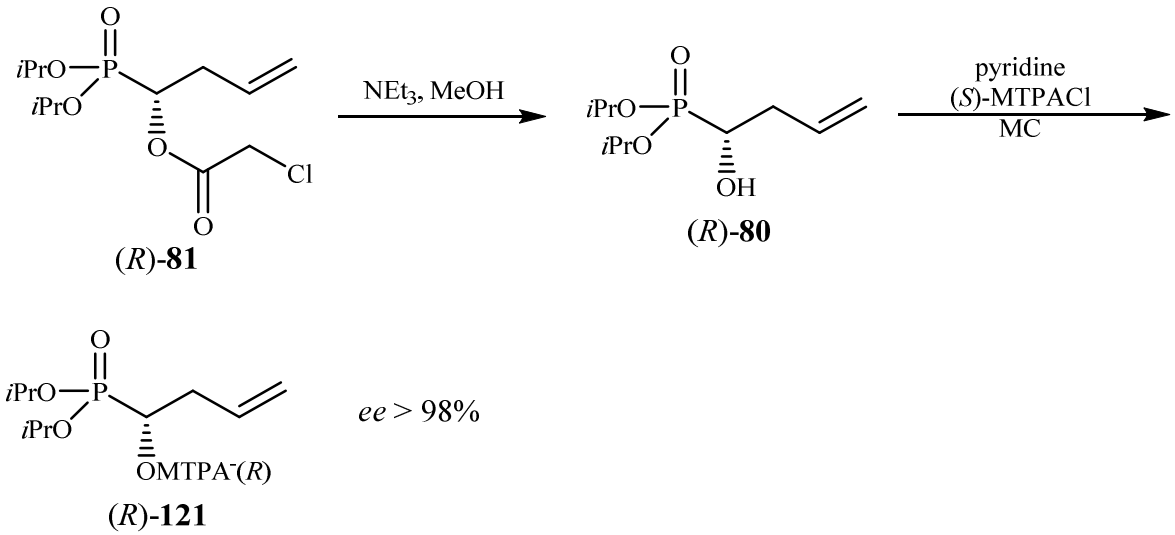
My first approach to synthesize the phosphonic acid analog of malic acid started with racemic 1-hydroxy-3-butenylphosphonate (±)-**80** (Scheme 1.32). It was smoothly deprotected to the phosphonic acid (±)-**119** with trimethylsilyl bromide and then ozonolyzed. The intermediate hydroxyaldehyde was oxidized to the desired phosphonic acid analog (±)-**120** of *L*-malic acid, using the Pinnick protocol.[62] The yield was low dispite many trials to increase it.



(±)-**80** (±)-**119** (±)-**120**

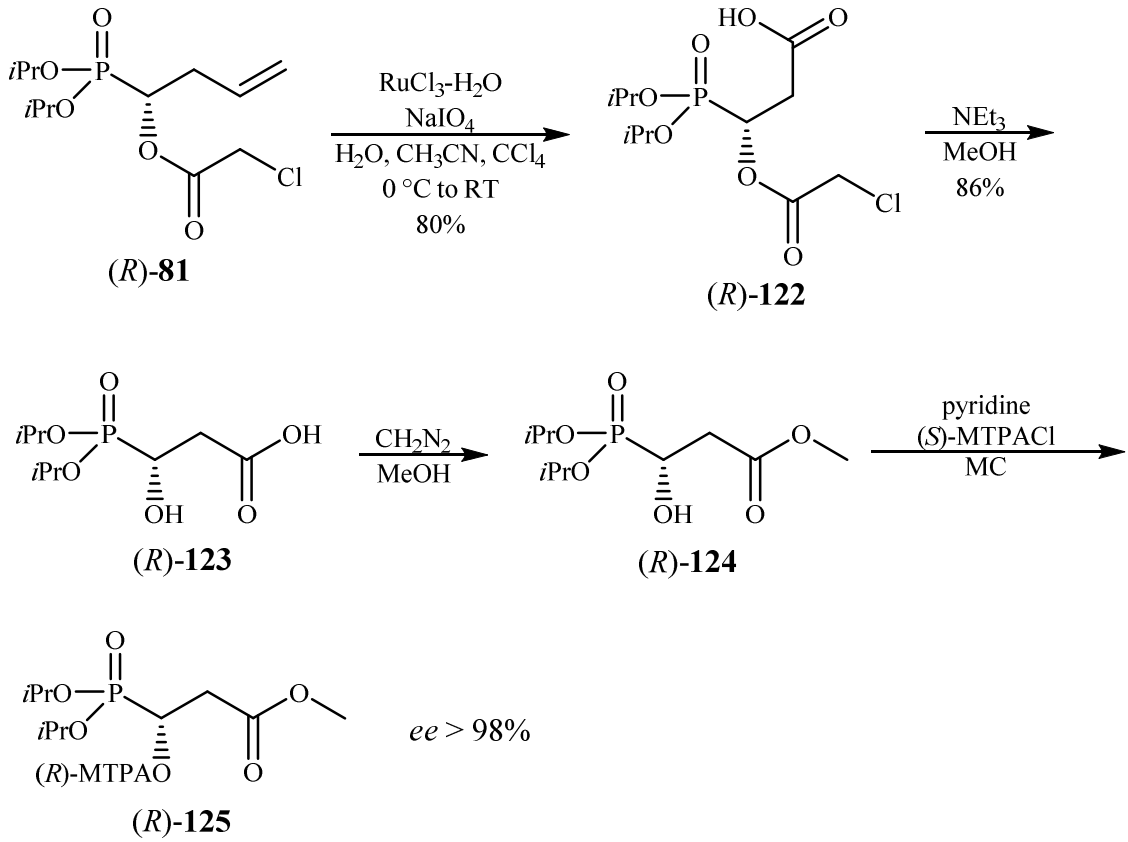
Scheme 1.32. First approach to racemic phosphonic acid analog of malic acid.

As the yield of the first synthesis of the phosphonic acid analog of *L*-malic acid was unsatisfactory, I designed a second one. Contrary to all other phosphonic acids mentioned above, this synthesis started with the chloroacetate (*R*)-**81,** because I reasoned that the low yield could be attributed to the free hydroxyl group. The (*R*)-chloroacetate (*R*)-**81** of 98% *ee* was obtained by lipase-catalyzed resolution of (±)-**81**, when consumption of 0.5 M NaOH stopped (conversion was over 50%). To determine the *ee* of the chloroacetate, it was transesterified (MeOH/triethylamine) and esterified with (*S*)-Mosher chloride [(*S*)-MTPACl] to give diastereomeric (*S*)-Mosher esters (*R*)-**121** (Scheme 1.33). The ^{31}P NMR spectrum allowed the determination of the configuration and the *ee* at C-1.



Scheme 1.33. Determination of the enantiomeric excess of (*R*)-diisopropyl 1-chloroacetoxy-3-butenylphosphonate.

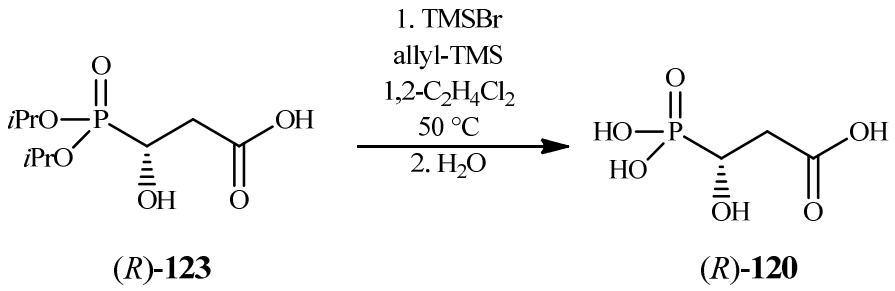
The enantiomerically pure chloroacetate (*R*)-**81** was then oxidized with RuO_4 generated in situ from $RuCl_3 \cdot H_2O$, according to the protocol of Sharpless.[51] The chloroacetic ester (*R*)-**122** was transesterified with triethylamine/MeOH to afford hydroxycarboxylic acid (*R*)-**123**. Its optical purity was evaluated by converting it to the (*R)*-Mosher ester via the methyl ester and recording a^{31}P NMR spectrum. The *ee* of (*R*)-**123** was found to be > 98%, identical to that of the starting material (Scheme 1.34). Therefore, all steps of the sequence had to proceed with retention of configuration without racemization.



Scheme 1.34. Determination of the enantiomeric excess of hydroxypropanoic acid (*R*)-**123**.

-

To finish the synthesis of the (*R*)-phosphonic acid analog of *L*-malic acid [= (*S*)-malic acid], phosphonocarboxylic acid (*R*)-**123** was treated with TMSBr/allylsilane and then hydrolyzed (Scheme 1.35).

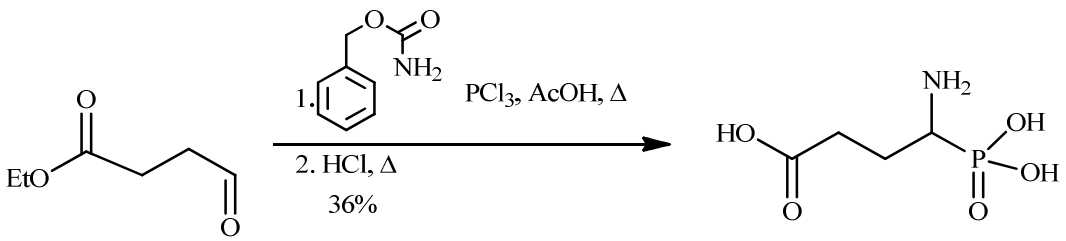


Scheme 1.35. Synthesis of (*R*)-3-hydroxy-3-phosphonopropanoic acid.

1.4.9. Synthesis of (*R*)-4-amino-4-phosphonobutanoic acid

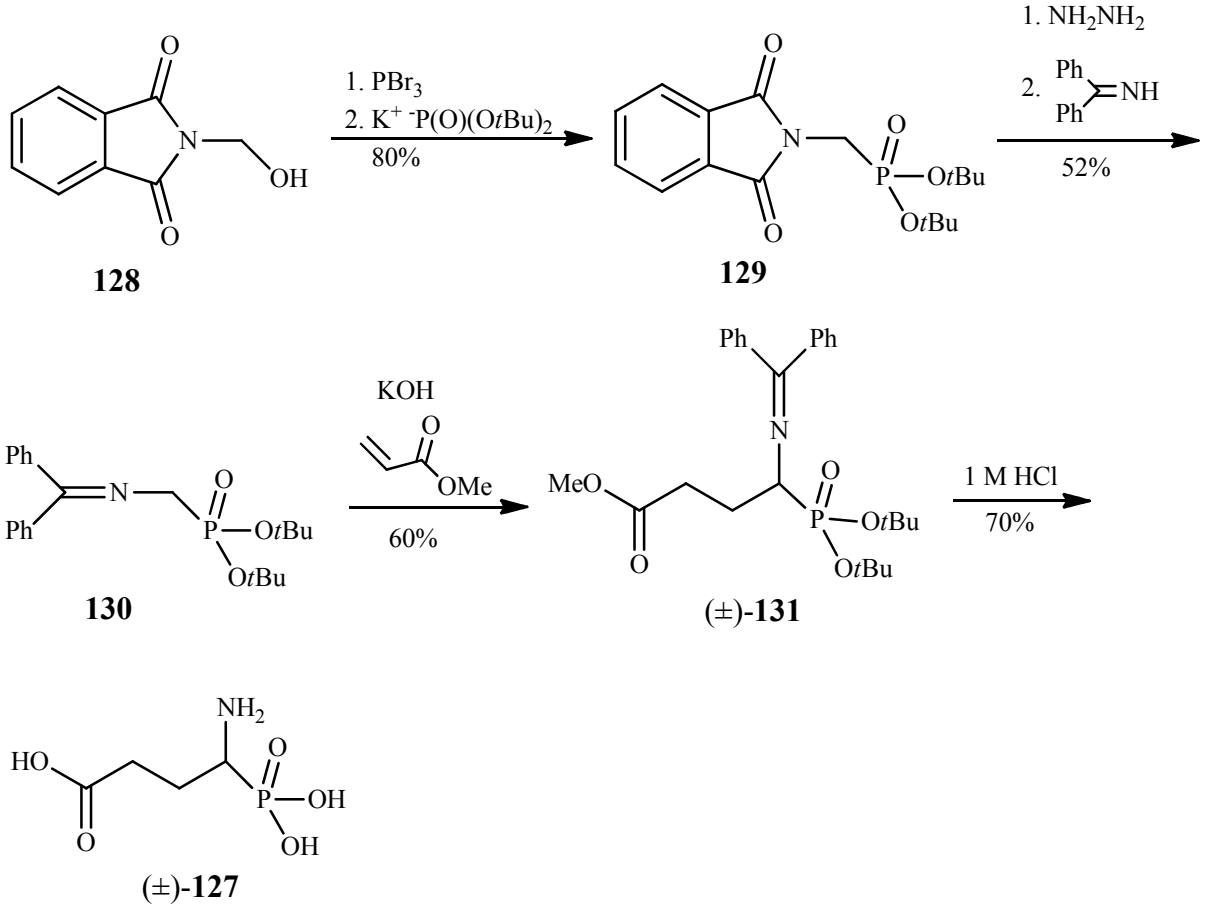
Several syntheses of racemic and two of chiral, nonracemic 4-amino-4-phosphonobutanoic acid (the phosphonic acid analog of glutamic acid) are known. Oleksyszyn´s work[63] is one of

the most attractive ones (Scheme 1.36). His synthesis is a one-pot reaction comprising two steps. Ethyl succinate semialdehyde [(±)-**126]** was added to a stirred mixture of benzyl carbamate, phosphorus trichloride in glacial acetic acid. The resulting mixture was refluxed for 30 min and after the addition of conc. HCl, the mixture was refluxed again to remove all protecting groups. Although the overall yield was not very high (36%), the procedure was simple and very practical.



Scheme 1.36. Synthesis of racemic 4-amino-4-phosphonobutanoic acid by Oleksyszyn et al.

Tanier et al. provided an alternative method for the preparation of (±)-**127** (Scheme 1.37).[64] They utilized the di-*tert*-butyl phosphite, which allowed to deblock the proteced aminophosphonate with 1 M HCl at RT, to prevent the drastic treatment with pure or concentrated hydrochloride acid under reflux. The synthesis involved preparation and alkylation of di-*tert*-butyl *N*-(diphenylmethylene)aminomethylphosphonate (**128**), which could be synthesized on a large scale from easily available *N*-hydroxymethylphthalimide (**130**) in an overall yield of 42%. Chain extension of **130** by the Michael addition to methyl acrylate gave (±)-**131**. Removal of all protecting groups under mild conditions with 1 M HCl at RT afforded the phosphonic acid analog of glutamic acid (±)-**127**.

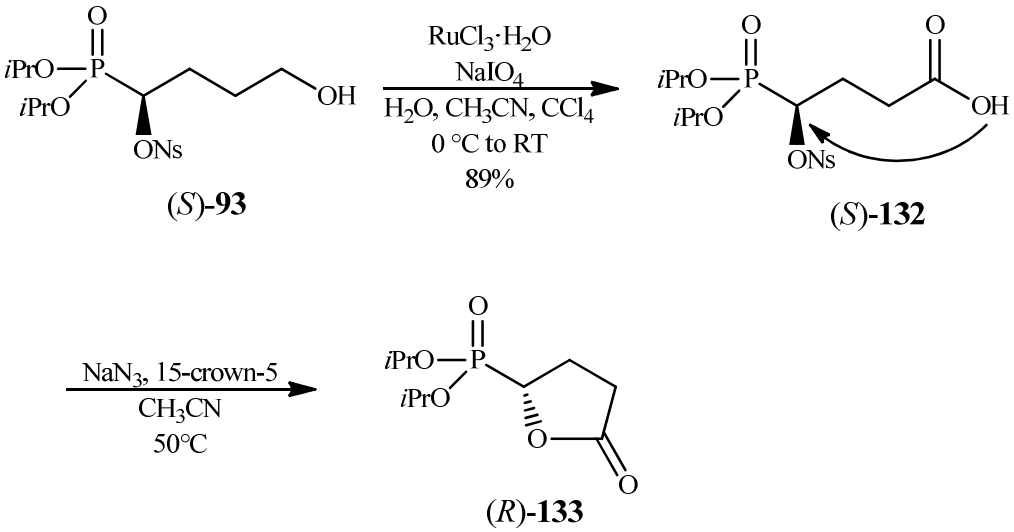


Scheme 1.37. Synthesis of racemic 4-amino-4-phosphonobutanoic acid by Tanier et al.

Resolution of 4-amino-4-phosphonobutyric acid was performed for example by Antczak and Szewczyk by fractional crystallization of the 4-(*N*-carbobenzoxyamino)-4-diethylphosphonobutanoic acid salts of both optically active 1-phenylethylamines.[65]

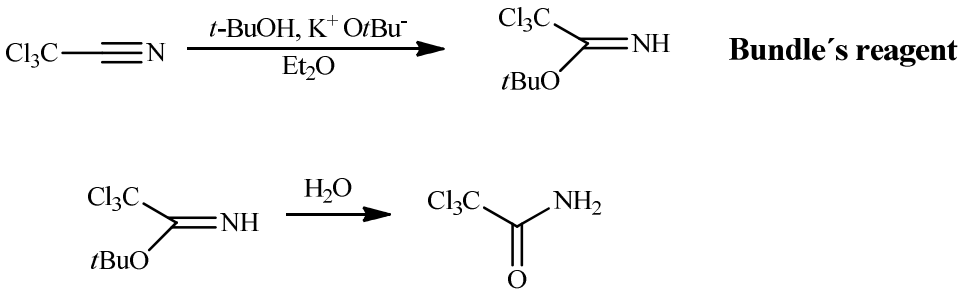
As there is no stereoselective synthesis of the phosphonic acid analog of glutamic acid known, optically pure compounds could only be obtained by inconvenient resolution after derivatization. Based on the synthesis of other similar aminophosphonic acids, I tried the first asymmetric synthesis of (*R*)-4-amino-4-phosphonobutanoic acid by using the easily accessible (*S*)-1-hydroxy-3-butenylphosphonate as starting point. The first several steps to afford 1-nosyloxy-4-hydroxybutylphosphonate [(*S*)-**93**] have already been described in chapter 1.4.3. The primary hydroxyl group of this hydroxyphosphonate was oxidized to a carboxyl group to get carboxylic acid (*S*)-**132** in high yield using RuO_4 regenerated according to the protocol of Sharpless.[51] This compound was found to be stable at 4 °C for at least 2 weeks. When it was added to a mixture of sodium azide and 15-crown-5 ether in acetonitrile, only one product was obtained after stirring for two hours at 50 °C. The IR spectrum of the

isolated compound did not display a signal near 2100 cm^{-1} corresponding to the $–N_3$ group. That meant that cyclization to a lactone had probably occurred, which interfered with substitution of the nosyloxy group by azide (Scheme 1.38).



Scheme 1.38. Cyclization of carboxylic acid (*S*)-**132** in acetonitrile at 50 °C.

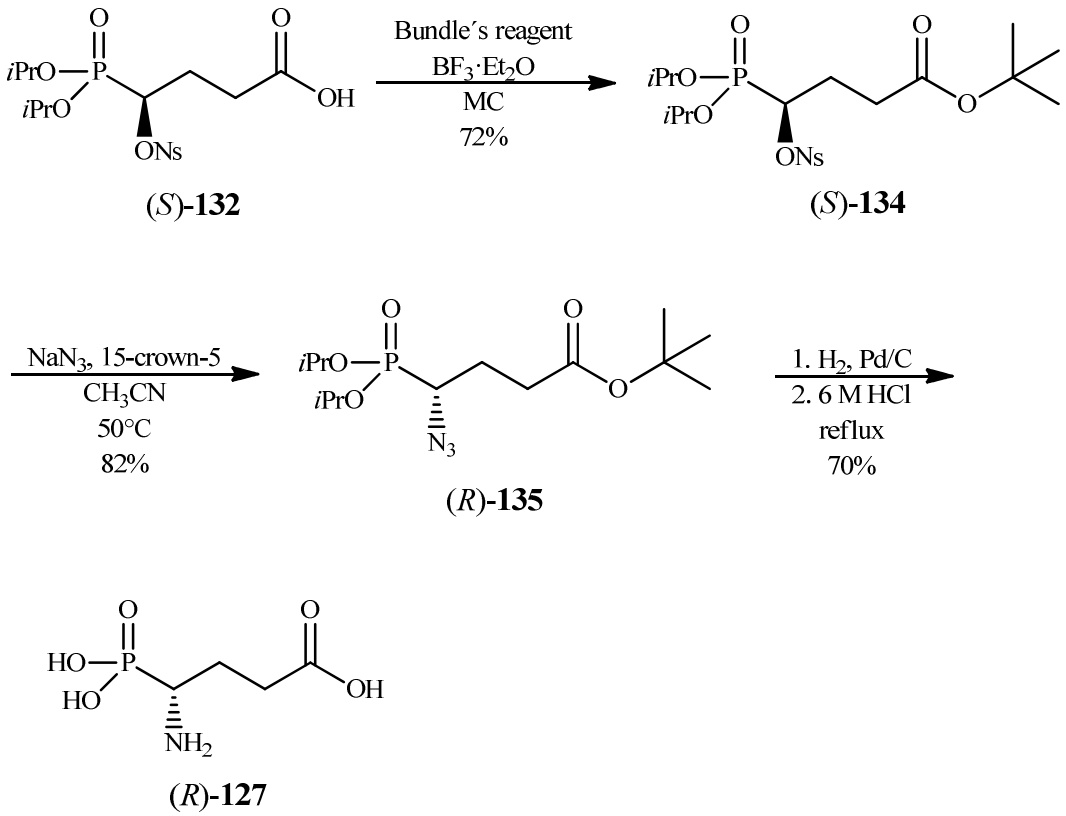
To avoid the undesirable lactone formation, the carboxyl group was protected as *tert*-butyl ester which was formed with Bundle´s reagent. It was synthesized from trichloroacetonitrile and potassium *tert*-butanol in dry ether, catalyzed by potassium *tert*-butoxide. As Bundle´s reagent reacts readily with moisture, it must be prepared in a dry solvent and stored in a well sealed glass bottle (Scheme 1.39).



Scheme 1.39. Synthesis and decomposition of Bundle´s reagent.

The nosyloxy-substituted *tert*-butyl ester (*S*)-**133** was subjected to an S_N2 reaction with sodium azide in presence of 15-crown-5 ether in acetonitrile. Azide (*R*)-**134** was reduced by catalytic hydrogenation, deprotected and purified to furnish (*R*)-4-amino-4-

phosphonobutanoic acid [(*R*)-**127**], a phosphonic acid analog of *L*-glutamic acid (Scheme 1.40).



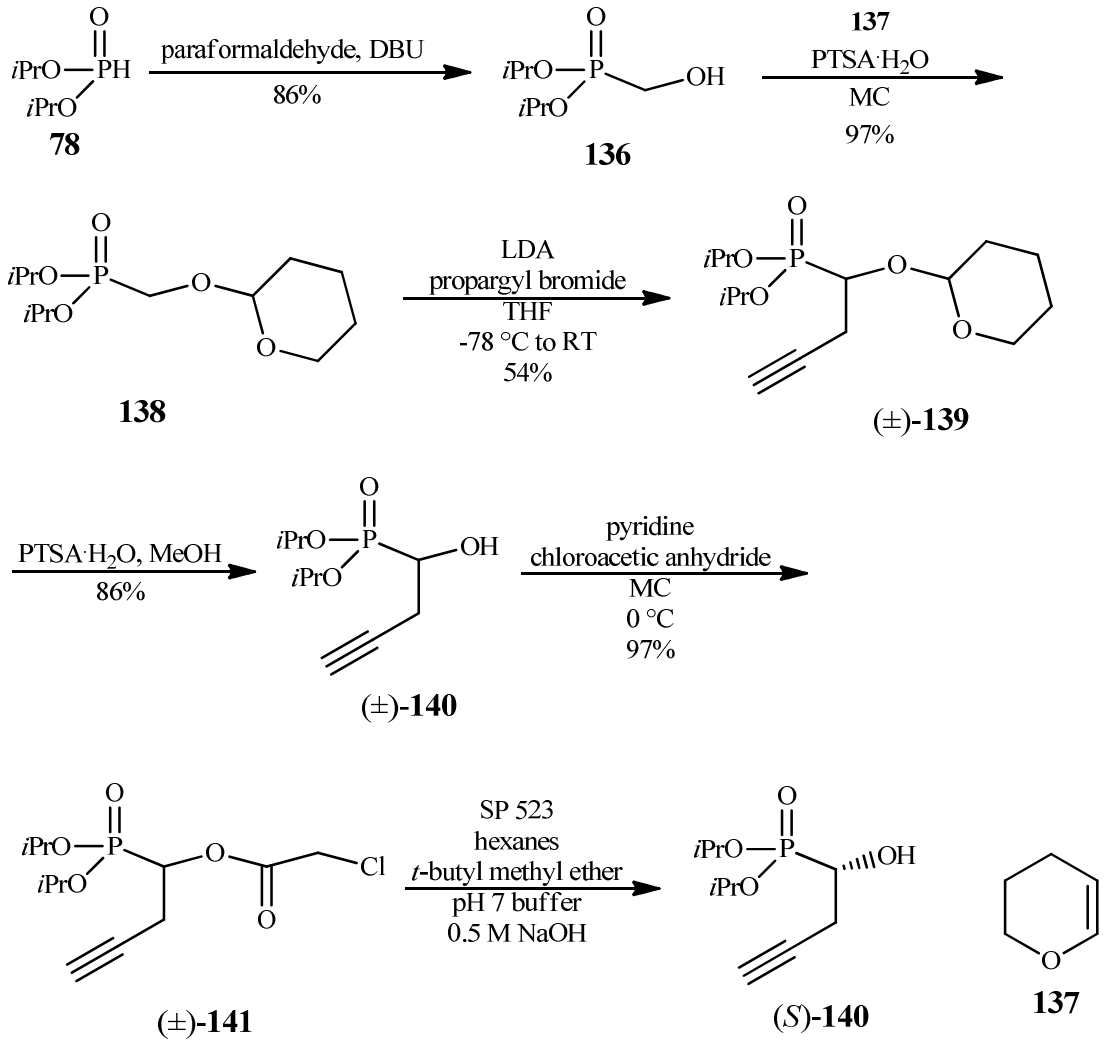
Scheme 1.40. Synthesis of (*R*)-4-amino-4-phosphonobutanoic acid.

1.4.10. Synthesis of (*R*)-1-amino-2-(1,2,3-triazol-4-yl)ethylphosphonic acid

(*R*)-1-Amino-2-(1,2,3-triazol-4-yl)ethylphosphonic acid is a structural analog of the proteinogenic amino acid (*S*)-histidine. It is considered to be a potential inhibitor of histidine ammonia lyase (HAL), which converts histidine into urocanate with release of ammonia. Urocanate is a component of human sweat and protects the skin from UV radiation. When exposed to UV radiation, the *E* form of urocanate is converted into the Z form, which can initiate an immunosuppressive process.[66] The phosphonic acid analog of histidine could be a potential inhibitor of HAL.

The synthesis started with diisopropyl phosphite, which was readily added to formaldehyde to give hydroxymethylphosphonate **136** in 86% yield with DBU as a catalyst (Scheme 1.41).

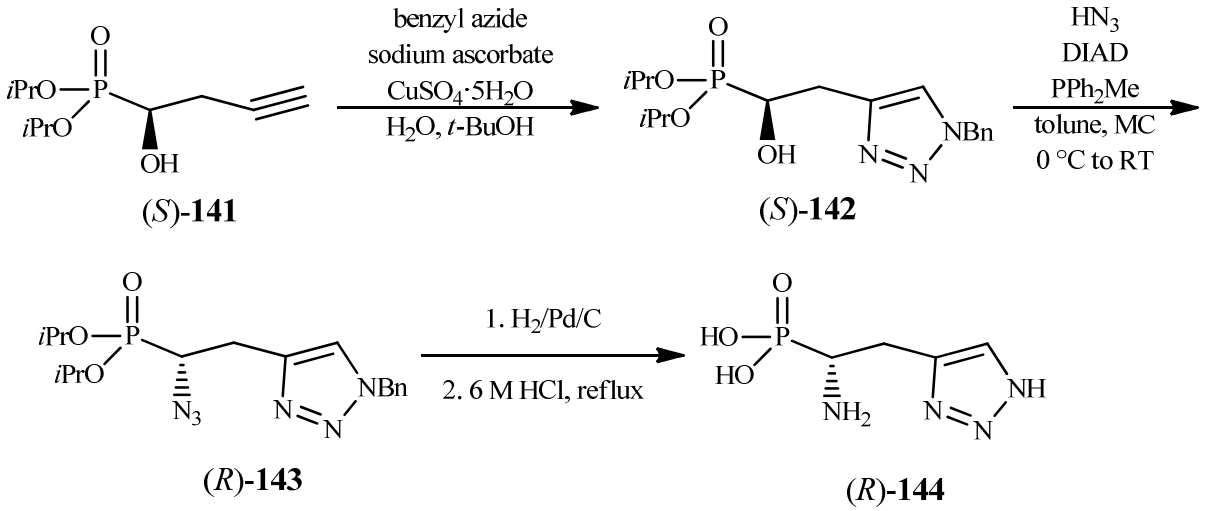
The hydroxyl group was protected with a THP group and the resulting phosphonate **138**, was metalated at –78 °C with LDA and alkylated with propargyl bromide. The THP ether (±)-**139** cleaved with PTSA·H_2O in MeOH and the α-hydroxyphosphonate (±)-**140** was esterified with chloroacetic anhydride/pyridine. The chloroacetate (±)-**141** could be hydrolyzed enantioselectively with the enzyme SP 523 to generate (*S*)-1-hydroxyphosphonate (*S*)-**140** with a high enantiomeric excess (*ee* 92%) as determined by ^{31}P NMR spectroscopy of the (*S*)-Mosher ester.



Scheme 1.41. Synthesis of (*R*)-1-amino-2-(1,2,3-triazol-4-yl)ethylphosphonic acid, part I.

The key step for the synthesis of the phosphonic acid analog of *L*-histidine was the "click reaction", which worked well with benzyl azide, sodium ascorbate and copper sulfate in H_2O/*t*-BuOH (Scheme 1.42). By means of the Mitsunobu reaction, the hydroxyl group was substituted with the azido group in an S_N2 reaction, which inverted the configuration at C-1. Unfortunately, the polarity of azide and triphenylphosphine oxide was very similar, so that

they were hardly separable by flash chromatography. Homogenous azide (*R*)-**143** could only be obtained if methyldiphenylphosphine was used in the Mitsunobu reaction instead of triphenylphosphine, but the isolated yield of the product was low. I hoped to be able to reduce the azide to the amine and remove the benzyl protecting group in one step catalytically with 10% Pd/C/H_2 in methanol. However, only the azido group was reduced. The benzyl group could not be removed before concentrated HCl was added to the reaction mixture. Removal of protecting groups from phosphorus and purification of the crude product as usual gave the phosphonic acid analog (*S*)-**144** of (*L*)-histidine.



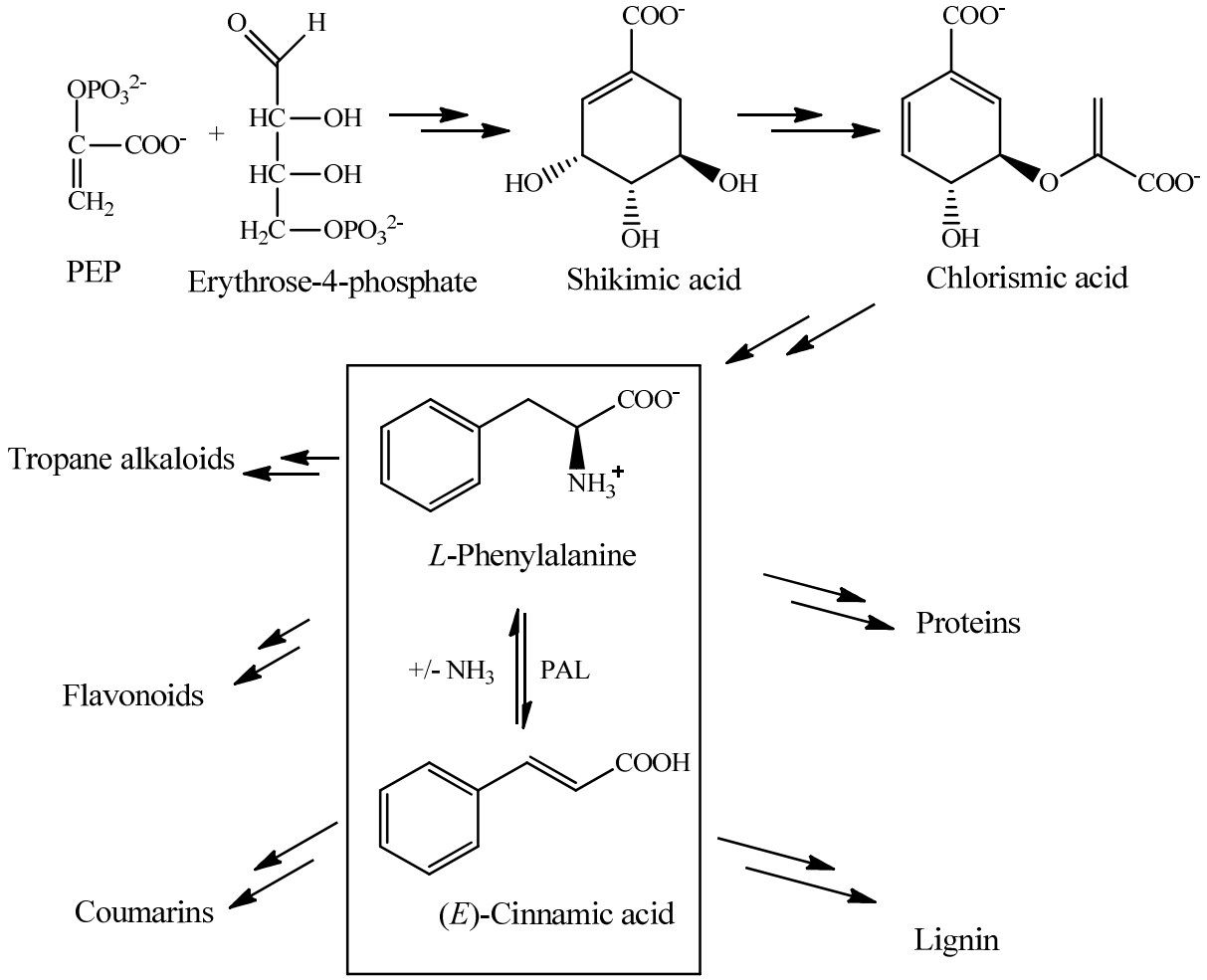
(*S*)-**141** (*S*)-**142** (*R*)-**143** (*R*)-**144**

Scheme 1.42. Synthesis of (*R*)-1-amino-2-(1,2,3-triazol-4-yl)ethylphosphonic acid, part II.

1.5. Inhibitors of phenylalanine ammonia lyase (PAL)

1.5.1. Metabolism of phenylalanine in bacteria, plants and animals

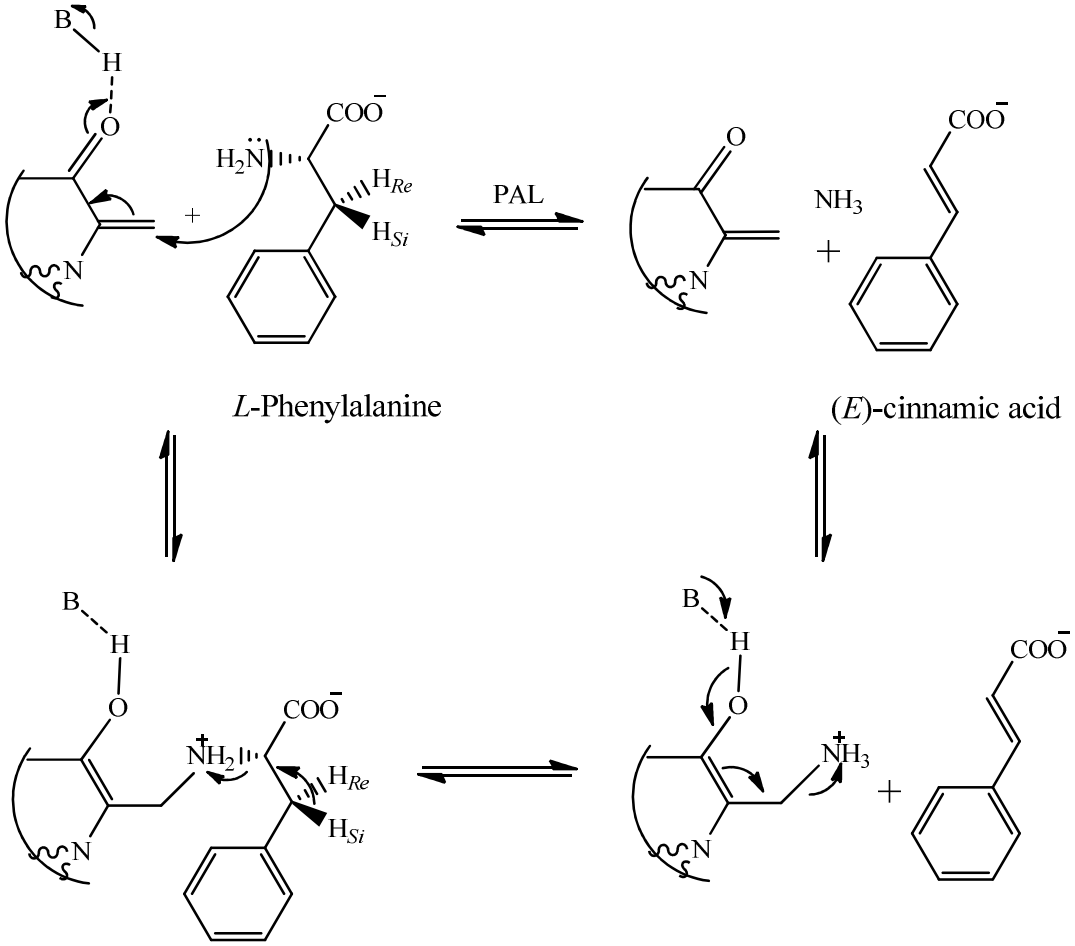
The proteinogenic amino acid *L*-phenylalanine is only synthesized by microorganisms and plants via the shikimic acid pathway, but not by animals. The oxidative degradation of *L*-phenylalanine proceeds via tyrosine to acetoacetyl-CoA. By elimination of ammonia from phenylalanine with the phenylalanine ammonia lyase (PAL), (*E*)-cinnamic acid is generated, which is the starting point for many natural products, especially in plants.[67] These phenylpropanoids include lignin, a major component of wood, flavonoids, of which many plant dyes are derived, and coumarins (Scheme 1.43). Thus, PAL is a key enzyme of plant metabolism.



Scheme 1.43. The shikimic acid pathway.

1.5.2. Mechanism for the elimination of ammonia by PAL

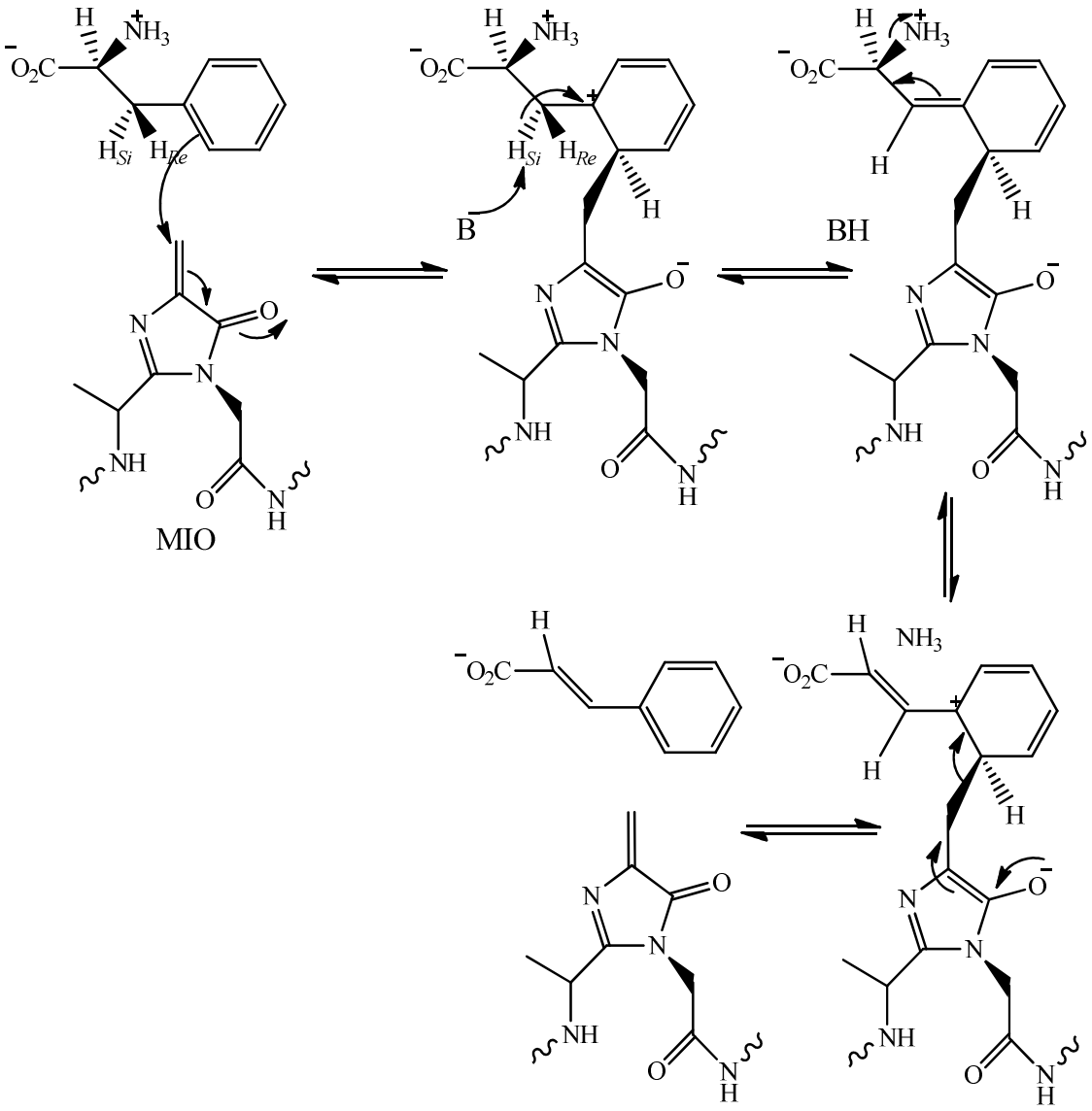
Havir et al. have suspected since over forty years that the dehydroalanine in the active site of PAL acts as electrophile and attacks at the amino group of phenylalanine (Scheme 1.44).[67] The subsequent elimination of H_{si} and the amino group provides cinnamic acid and ammonia intermediately bound to the dehydroalanine (E_1cB elimination). This mechanism does not satisfactorily explain the easy abstraction of H_{si}, whose p*K*a is proven to be over 40,[68] by an enzymatic base. However, the mechanism is strongly supported by the recent crystal structure of a tyrosine ammonia mutase (TAM), showing a covalent adduct of the MIO and the amino group of the substrate.[69]



Scheme 1.44. First presented mechanism for PAL-catalyzed conversion of *L*-phenylalanine to *trans*-cinnamic acid.

To solve the problem of the proton activation, Rétey et al.[70] proposed that the reaction is initiated by electrophilic attack of MIO on the aromatic ring as an alternative mechanism. As a result, the electron density of the phenyl ring is reduced and the acidity of α-protons increases, even if the temporary loss of the aromaticity is energetically unfavorable. Numerous findings indicate that the histidine ammonia lyase (HAL) works according to the same mechanism as the PAL. In 1999, Schulz et al. successfully performed the X-ray structure analysis of HAL from *P. putida* with a resolution of 2.1 Å.[71] They discovered that the prosthetic group in the active site of PAL is the unusual 4-methylidene-imidazole-5-one (MIO), which is significantly more electrophilic than the dehydroalanine. This finding made Rétey´s Friedel-Crafts type mechanism, attack of MIO in *ortho* position of phenyl ring thermodynamically more favorable and plausible (Scheme 1.45). The positive charge on the carbon atom activates the benzylic hydrogen so strongly that it can be abstracted by a relatively weak base (e. g. the phenolate form of tyrosine). This was the first described

biological Friedel-Crafts reaction[72] and was suggested for PAL based on different experiments[73,74].



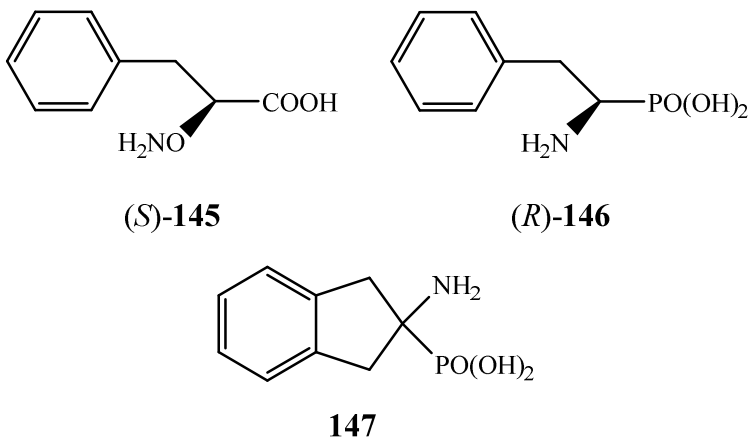
Scheme 1.45. Friedel-Crafts type mechanism proposed by Rétey.

Bornscheuer et al.[75] have provided a possible rationale to explain the difference in substrate specificity between phenylalanine ammonia lyase/mutase (PAL/PAM) and tyrosine ammonia lyase/mutase (TAL/TAM). They suggest that the Glu484 residue in PAL/PAM prevents the MIO group from an attack on the amino group of the substrate, thereby supporting a Friedel-Crafts type mechanism for these two enzymes. This situation is in contrast to TAL/TAM which contains an asparagine residue in this position and undergoes an elimination mechanism. Bornscheuer et al. suppose that both mechanisms, the E_1cB and the Friedel-Crafts

mechanism can occur in aromatic amino acid ammonia lyases and mutases depending on the glutamic acid or asparagine in the active site of the enzyme.

1.5.3. Known inhibitors of PAL

Inhibitors of PAL are potential herbicides and therefore of economic and scientific interest. So many compounds were synthesized, but only some with high activity against PAL were found in recent years. The best of them are the (*S*)-2-aminooxy-3-phenylpropanoic acid (AOPP, (*S*)-**145**), the (*R*)-1-amino-2-phenylethylphosphonic acid (APEP, (*R*)-**146**, a competitive inhibitor) and the achiral 2-aminoindane-2-phosphonic acid (**147**) (Figure 1.08). Although AOPP is the strongest inhibitor of PAL *in vitro* (K_i = 1.4 nM, K_i/K_m = 0.0003 for PAL from buckwheat),[76] it is not so effective in vivo as APEP (K_i = 1.5 μM).[77,78] It was noted that AOPP has a particularly high selectivity to PAL. Both of the latter inhibitors have in place of the carboxyl group, a phosphonic acid group which interacts with the guanidinium group of arginine 354, giving a stronger salt bridge than that with the carboxyl group. Maier et al.[79,80] as well as Zoń et al.[81] have synthesized and tested numerous analogs of **146**, but none of them had a higher inhibitory activity than **146**.



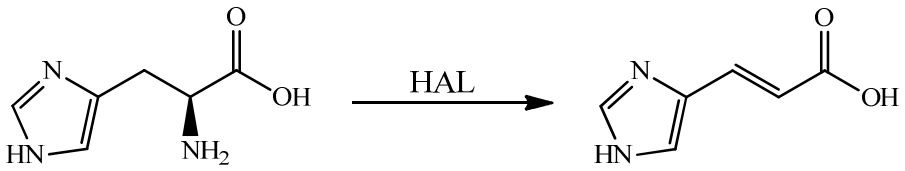
(*S*)-**145** (*R*)-**146**

147

Figure 1.08. Known inhibitors of PAL.

1.6. Results and discussion of the synthesis of (±)-1-amino-2-phenyl-2-propenylphosphonic acid

Histidine ammonia lyase (HAL) is a crucial enzyme for the major oxidative degradation of *L*-histidine in mammals. It converts this proteinogenic amino acid to urocanic acid by removing ammonia (Scheme 1.46).



Scheme 1.46. Degradation of *L*-histidine to urocanic acid by HAL.

A single crystal X-ray structure analysis of HAL allowed to identify the aminoacids involved in this chemical reaction (Figure 1.09).[82,83] The structure analysis revealed that this enzyme contains MIO (4-methylideneimidazole-5-one) as new prosthetic group.

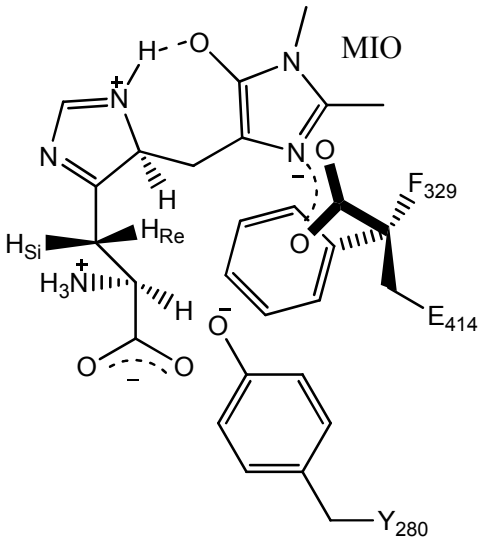
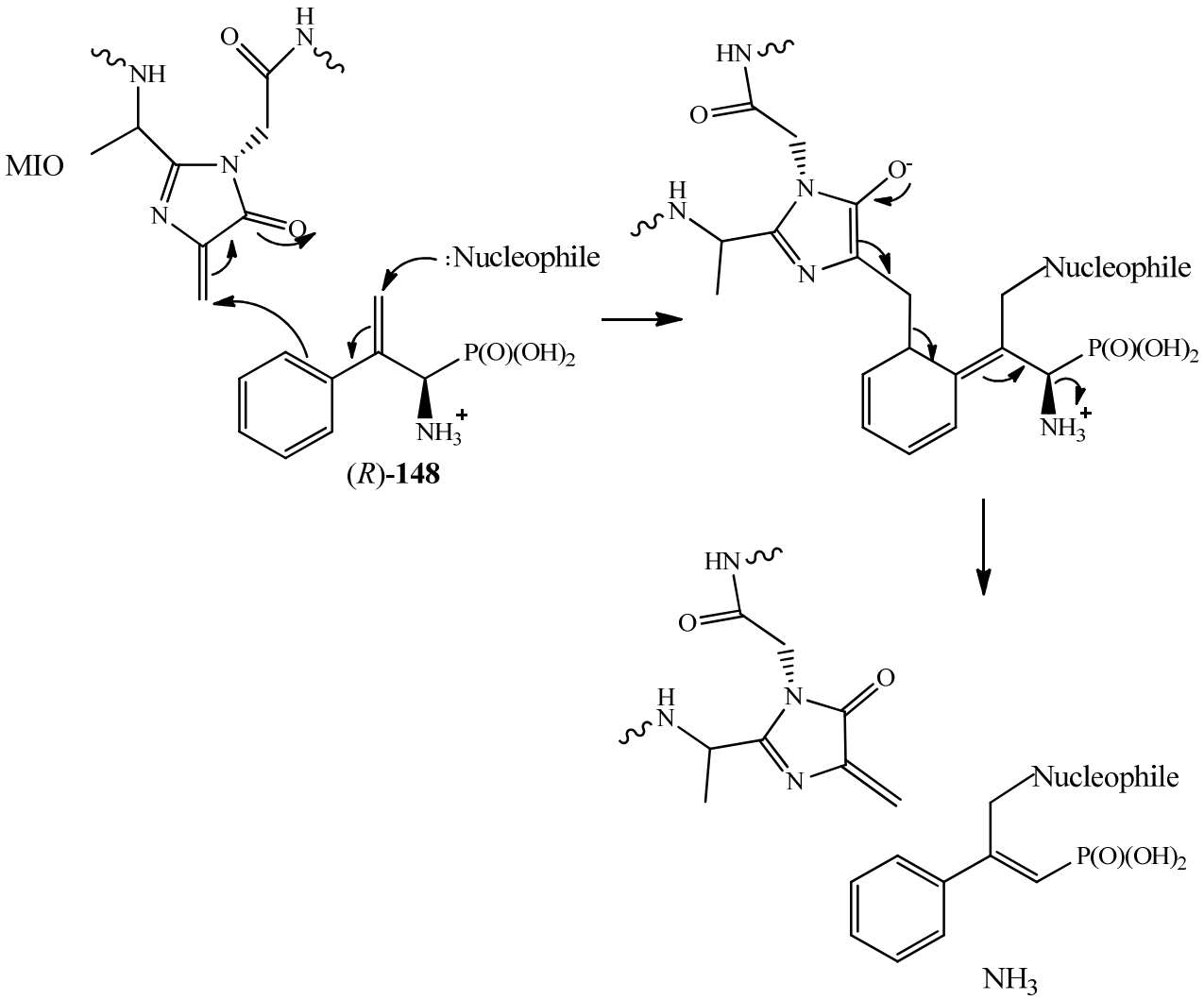


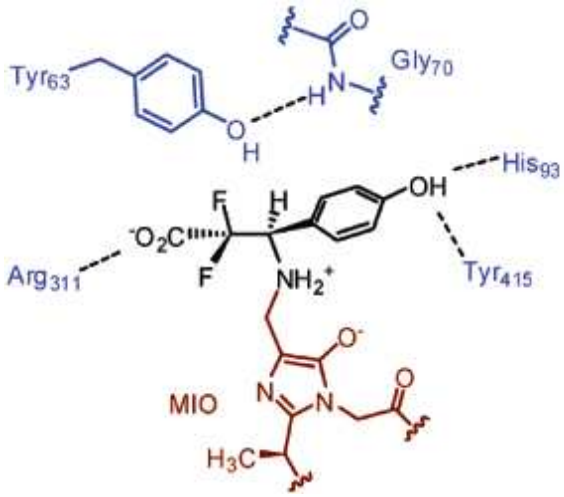
Figure 1.09. X-ray structure of the active site of HAL with MIO (4-methylidene-imidazole-5-one).

It was found that the k_{cat} value of the mutant, in which the glutamic acid 414 was replaced by alanine, was smaller by a factor of 21000 than the wild-type-HAL. Due to the short distance between the carboxylate group of glutamic acid 414 and MIO, it was suggested that it is the base that abstracts a β proton (H_{Re}) of HAL. The Tyr 280 nearby can probably assist the process of abstraction. In contrast, Baedecker and Schulz suggested that the deprotonated hydroxyl group of Tyr 280 acts as base and Glu 414 assists.[84] Both tyrosine and glutamic acid can in principle also function as nucleophiles instead of as bases in their deprotonated forms.[85] In Scheme 1.47, a possible mechanism for the covalent modification of PAL by the potentially irreversible inhibitor (±)-**148** is depicted. The aromatic ring of the β, γ-unsaturated aminophosphonic acid (±)-**148** can attack the electrophile, MIO. Thereby a formal allyl cation is generated, which is neutralized by the addition of a phenolate or carboxylate anion. Thus the enzyme is irreversibly modified even if the cleavage of ammonia is carried out. It is assumed that PAL follows a similar mechanism, but tyrosine probably acts as a base (nucleophile).



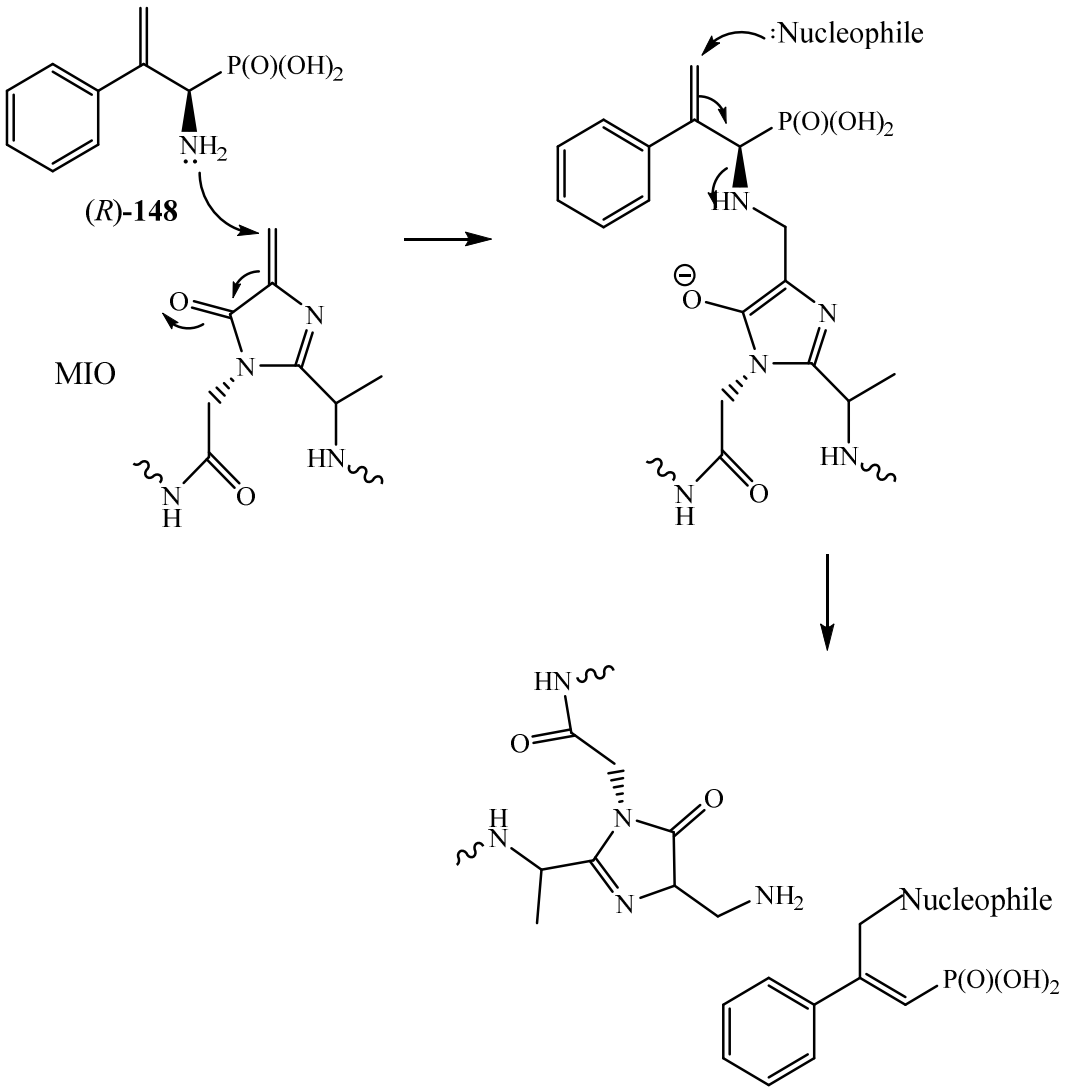
Scheme 1.47. Suggested mechanism I for irreversible inhibition of HAL by (*R*)-**148**.

On the basis of the high structural homology, it was suggested that the mechanism of aminomutases is likely an extension of the lyase chemistry with readdition of the amine via 1,4-conjugate addition. Supporting this mechanism, amminomutase activity has been determined to proceed through a cinnamate intermediate and is reversible.[86] The co-crystals of α,α-difluoro-β-tyrosine and tyrosine ammonia mutase from *Streptomyces globisporus* (SgTAM) by Bruner et al. (Scheme 1.48) showed that only the amine-bound adduct fitted the density and the resulting bound-amine complex was fully refined using simulated annealing and energy minimization. The observed density did not match an MIO/phenyl ring adduct consistent with a Friedel-Crafts mechanism.



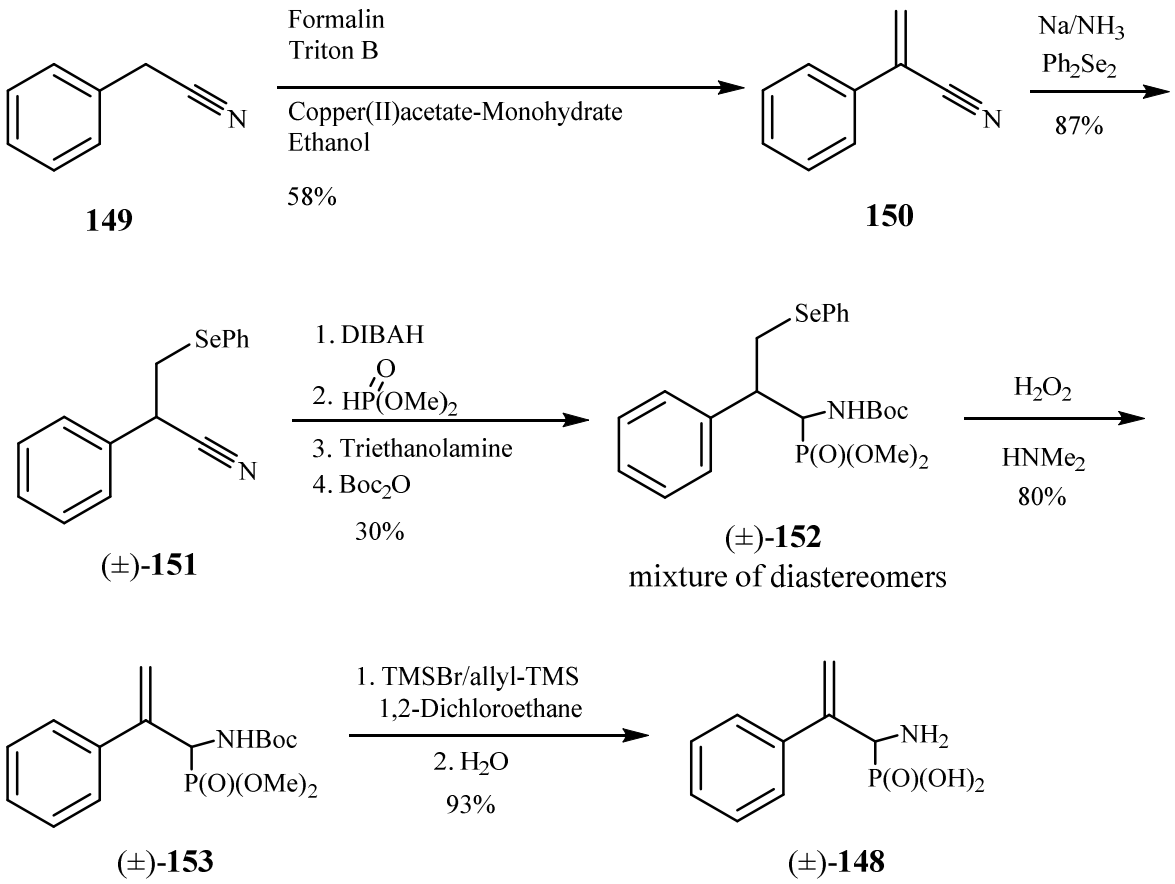
Scheme 1.48. Co-crystals of α,α-difluoro-β-tyrosine and tyrosine amino mutase from *Streptomyces globisporus* (SgTAM) by Bruner et al.

According to this theory, another possible mechanism for the covalent modification of PAL by the designed potential irreversible inhibitor (±)-**148** is depicted in Scheme 1.49. The amino group of the β, γ-unsaturated aminophosphonic acid (±)-**148** can attack the electrophile, MIO like phenylalanine. Then, the double bond is opened and the positive charged amino group leaves with the MIO together. Thus the enzyme is irreversibly modified.



Scheme 1.49. Suggested mechanism II for irreversible inhibition of HAL by (*R*)-**148**.

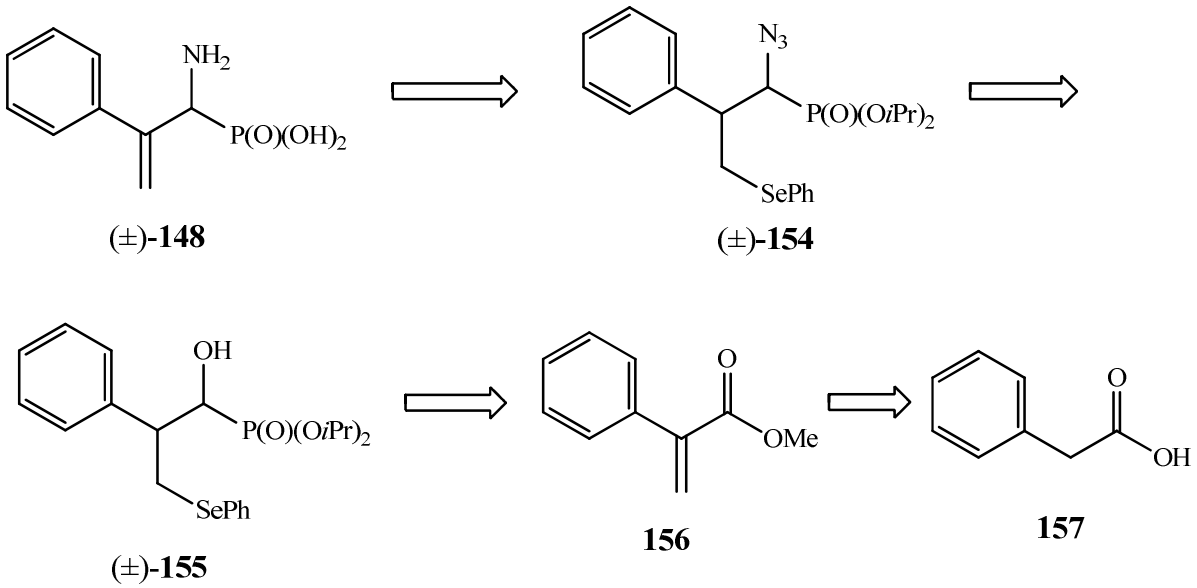
The first synthetic approach to (±)-**148** was performed and described in my master thesis (Renzhe Qian, „Synthese potentieller Inhibitoren der Phenylalanin-Ammoniaklyase“, *University of Vienna*, **2010**). The methylene group was first introduced by a relatively complicated method. Copper(II)acetate-monohydrate was found to be able to block the polymerization of nitrile **149** at higher temperature. Then the methylene group was modified by a phenylselenyl group and the nitrile group was reduced by DIBAH, followed by the addition of dimethyl phosphite. The phenylselenyl group was then oxidized by hydrogen peroxide to recover the double bond and the phosphonate (±)-**150** was hydrolyzed to the corresponding phosphonic acid (Scheme 1.50).



Scheme 1.50. The first synthetic approach to (±)-1-amino-2-phenyl-2-propenylphosphonic acid.

The main drawbacks of this synthesis are (1) the relative low overall yield especially due to the first and third step and (2) the low reproducibility of the first step because of interfering polymerization. To improve the yield, it was necessary to find an easier and more reliable method for the introduction of the methylene and the phosphonate group.

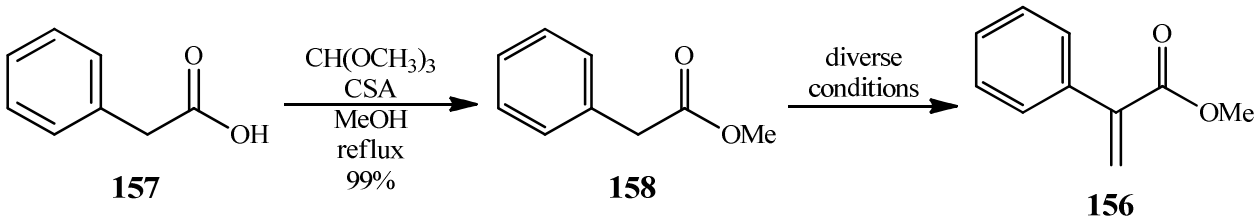
The new synthetic plan used phenylacetic acid (**157**) which should be converted to methyl 2-phenylacrylate (**156**) and the insertion of the methylene group was planned to be achieved in the first step (Scheme 1.51). Addition of phenylselenide would generate a saturated ester, which would be reduced to the aldehyde and react with a silylated phosphite to an α-hydroxyphosphonate **155**. The amino group would be converted by means of the Mitsunobu reaction to form the hydroxyl group, which would stem from the addition of phosphite to aldehyde.



(±)-**148** (±)-**154** (±)-**155** **156** **157**

Scheme 1.51. Retro-synthetic plane of the improved synthesis of (±)-1-amino-2-phenyl-2-propenylphosphonic acid.

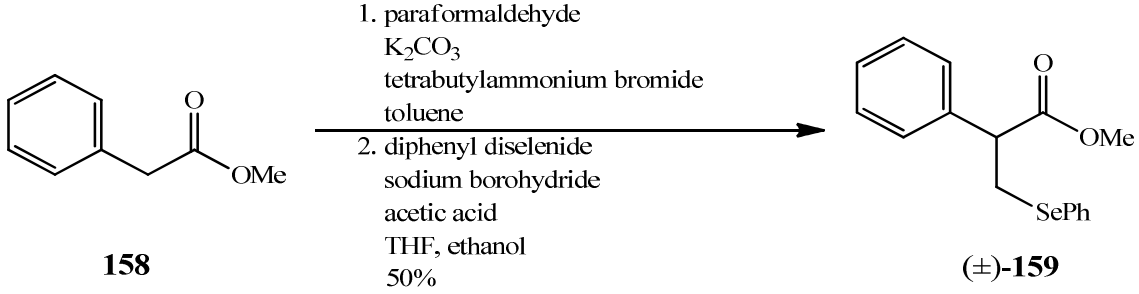
Felpin et al. described a new method for the synthesis of 2-arylacrylates.[87] With the same method, my first approaches were however not as successful as expected. By changing the base, the source of formaldehyde, temperature or solvent, the yield could not be improved. Finally, it was found that the usage of excess powdered anhydrous potassium carbonate was the key to achieving good yields. The best reaction conditions are given in Table 1.02, Entry 10 was proven to be well reproducible.



Entry	Base	Formaldehyde	Temperatur	Solvent	Yield
1	3 equiv. K_2CO_3	paraformaldehyde	50°C	toluene	35%
2	3 equiv. K_2CO_3	formalin	50°C	toluene	23%
3	3 equiv. K_2CO_3	formalin	RT	toluene	0%
4	0.2 ml 35% triton B	formalin	50°C	ethanol	0%
5	0.2 ml 35% triton B	formalin	reflux	ethanol	0%
6	0.1Ä NaOMe	paraformaldehyde	reflux	methanol	0%
7	0.1Ä K*t*OBu	paraformaldehyde	50°C	THF	20%
8	3 equiv. powdered K_2CO_3	paraformaldehyde	50°C	toluene	50%
9	3 equiv. powdered K_2CO_3	paraformaldehyde	50°C	toluene	53%
10	6 equiv. powdered K_2CO_3	paraformaldehyde	50°C	toluene	67%

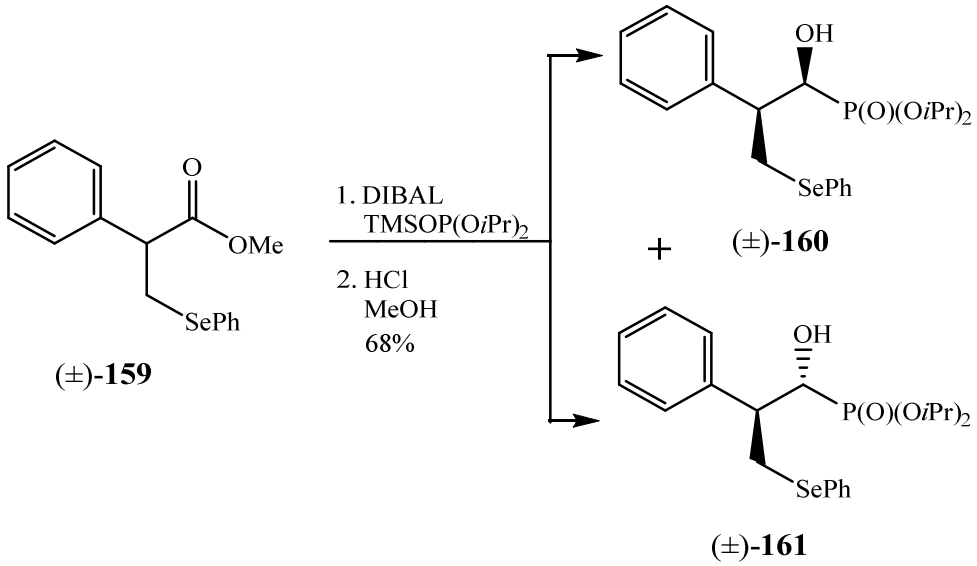
Table 1.02. Reaction conditions and yields for preparation of methyl 2-phenylacrylate.

The addition of phenylselenide generated in situ from diphenyl diselenide/$NaBH_4$ to the Michael acceptor **156** was straightforward. The overall yield of this one-pot reaction was 50% (Scheme 1.52).



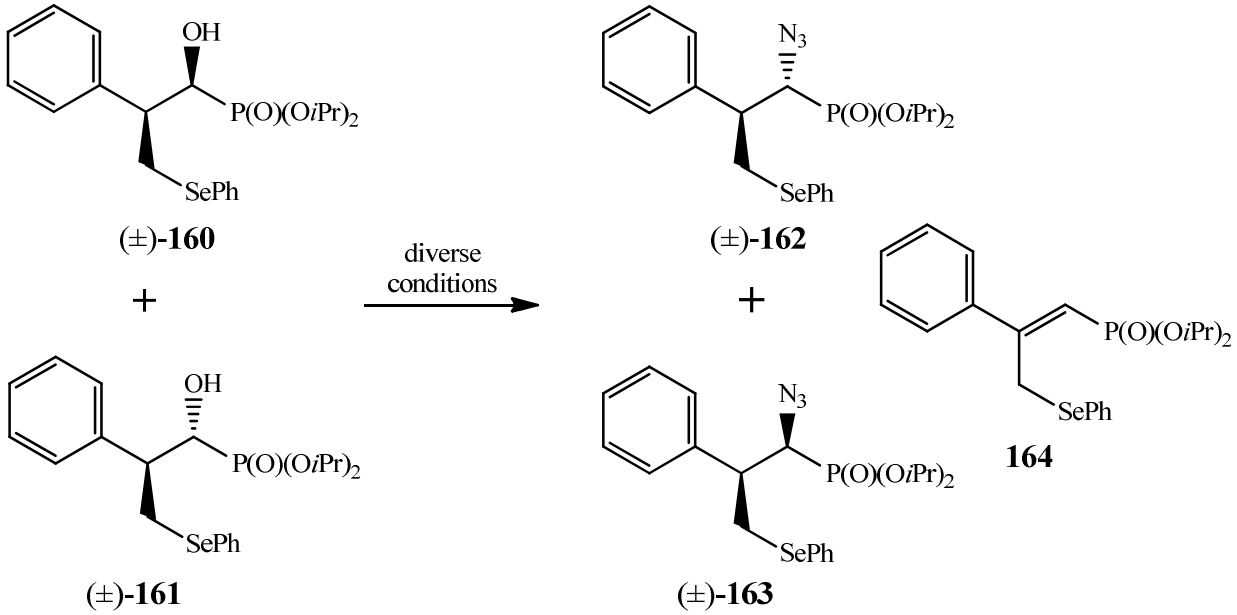
Scheme 1.52. One-pot synthesis of methyl 2-phenyl-3-(phenylselanyl)propanoate.

The ester (±)-**159** was reduced with DIBAH at −78 °C to the aldehyde, which was reacted with diisopropyl trimethylsilyl phosphite to diastereomeric α-silyloxyphosphonates. Workup with 2 M HCl/MeOH resulted in the removal of the silyl group. Flash column chromatography furnished a mixture of two diastereomeric α-hydroxyphosphonates **160** and **161** (ratio 1:3 to 1:4) in 68% yield (Scheme 1.53).



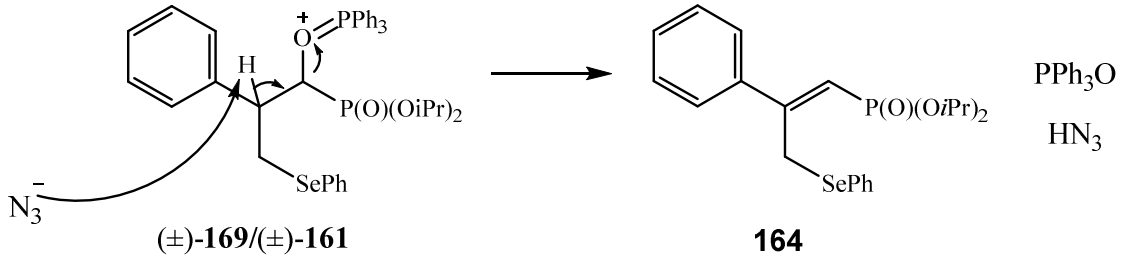
Scheme 1.53. Conversion of ester (±)-**159** to α-hydroxyphosphonates (±)-**160** and (±)-**161**.

The Mitsunobu reaction of this mixture of α-hydroxyphosphonates yielded the desired azides (±)-**162** and (±)-**163** as well as the alkene **164** as byproduct under all conditions by elimination of water (Scheme 1.54). The ratio of both azides to alkene was 1:1.5 to 1:2.



Scheme 1.54. The Mitsunobu reaction products (±)-**162**, (±)-**163**, and **164**.

It is assumed that the olefin was formed by an E2 reaction, which usually occurs when the acidity of proton in the β-position was high enough to be removed by the azide anion, when substitution is sterically hindered (Scheme 1.55).



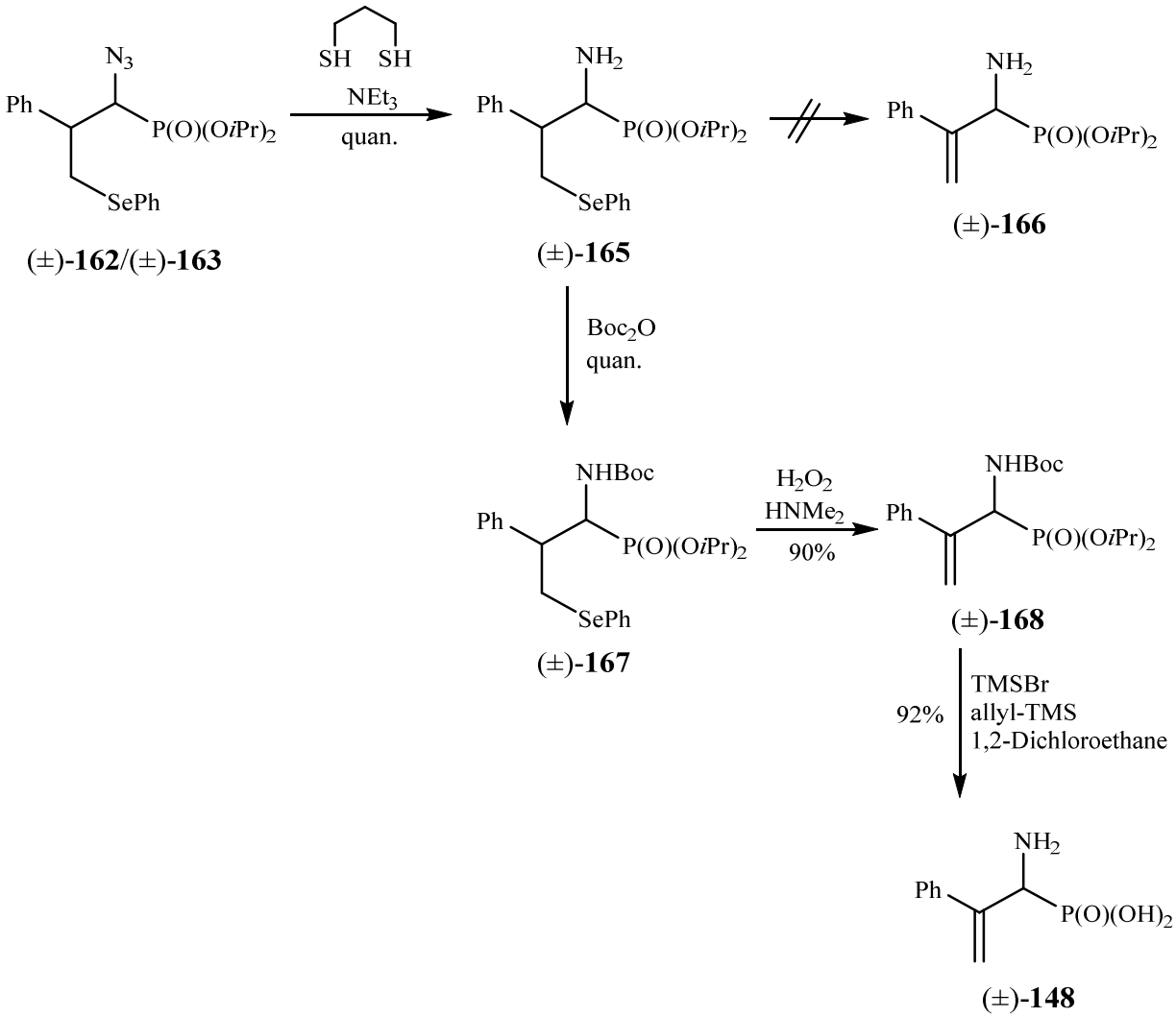
Scheme 1.55. Proposed mechanism for the E2 reaction.

This mechanism was indirectly proved by using phthalimide in place of HN_3 as acid, which is less acidic than HN_3 and more basic than N_3^- in its deprotonated form. Only the E2 product was observed when phthalimide was used (Entry 4, Table 1.03).

Entry	Azodicarboxylate	Temperature	Amine synthon	Solvent	Yield	S_N2 vs. E2
1	DIAD	RT	HN_3	toluene/CH_2Cl_2	59%	2:1
2	DBAD	RT	HN_3	toluene/CH_2Cl_2	58%	2:1
3	DBAD	RT	HN_3	THF	27%	1.5:1
4	DBAD	RT	phthalimide	toluene/CH_2Cl_2	0%	100% E2
5	DBAD	55°C	HN_3	toluene	40%	1:1
6	DBAD	RT	DPPA	toluene/CH_2Cl_2	31%	1.2:1
7	DBAD	60°C	DPPA	toluene	37%	1.2:1

Table 1.03. The approaches with the Mitsunobu reaction.

The azides (±)-**162** and (±)-**163** were then reduced smoothly by 1,3-propanedithiol to a diastereomeric mixture of amines (±)-**165**. Unfortunately, the oxidation of the phenylselenyl substituent to the corresponding selenoxides **166** by hydrogen peroxide did not work. I supposed that it could be due to the free amino group. Protected with the boc group, the phenylselenyl substituent was oxidized, followed readily by elimination of benzeneselenic acid to give the methylene group. The remaining protecting groups were removed as usual (TMSBr/allyl-TMS) to afford the desired free (±)-1-amino-2-phenyl-2-propenylphosphonic acid [(±)-**148**] (Scheme 1.56).



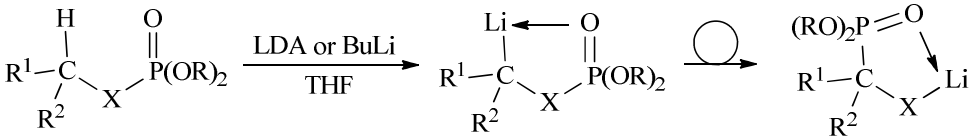
Scheme 1.56. The final steps of the synthesis of (±)-1-amino-2-phenyl-2-propenylphosphonic acid [(±)-**148**].

The new synthesis of (±)-1-amino-2-phenyl-2-propenylphosphonic acid [(±)-**148**] was achieved with an overall yield of 23% compared to 11% for the first synthesis. Every step was reproducible, and the synthesis could be also carried out on a relatively large scale. However, the Mitsunobu reaction needs improvement.

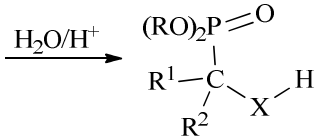
2. The phosphonate–phosphinate rearrangement

2.1. Introduction

The phosphate-α-hydroxyphosphonate,[88-91] thiophosphate-α-mercaptophosphonate[92] and the phosphoramidate-α-aminophosphonate[93,94] rearrangements were studied extensively in the group of Prof. Hammerschmidt (Scheme 2.01). The substrates **169a-c** must contain a hydrogen atom acidified by a heteroatom carrying a phosphinyl group. These isomerization reactions are induced by strong bases such as LDA, *n*BuLi and *s*BuLi at low temperatures, preferentially –78 °C. They metalate **169a-c** and give α-heteroatom-substituted alkyllithiums **170a-c** as intermediates, which undergo an intramolecular rearrangement. The nucleophilic carbon atom immediately attacks the electrophilic phosphinyl group, which migrates from the heteroatom to the carbon atom, giving phosphonate **171a-c**. Aqueous work up yields the phosphonates **172a-c**. The driving force for the rearrangement is the higher stability of the X-Li bond compared to the C-Li bond. It was found that the intermediate dipole-stabilized carbanions **170a-c** are microscopically configurationally stable, in part even for R^1 or R^2 = Ph and not just for alkyl, possibly because of their short half-life. Therefore, the migration follows a retentive course. The stereochemistry at phosphorus remains to be elucidated.



169a-c **170a-c** **171a-c**

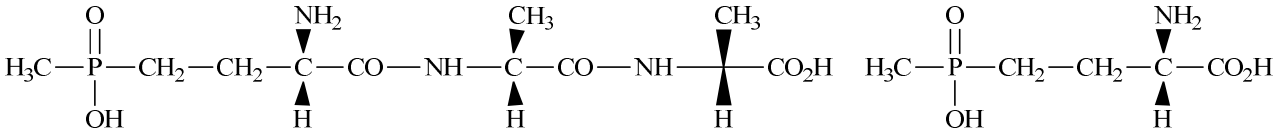


172a-c

169a-172a X = O phosphate-α-hydroxyphosphonate rearrangement
169b-172b X = S thiophosphate-α-mercaptophosphonate rearrangement
169c-172c X = NR phosphoramidate-α-aminophosphonate rearrangement

Scheme 2.01. The phosphate-α-hydroxyphosphonate, thiophosphate-α-mercaptophosphonate and the phosphoramidate-α-aminophosphonate rearrangements.

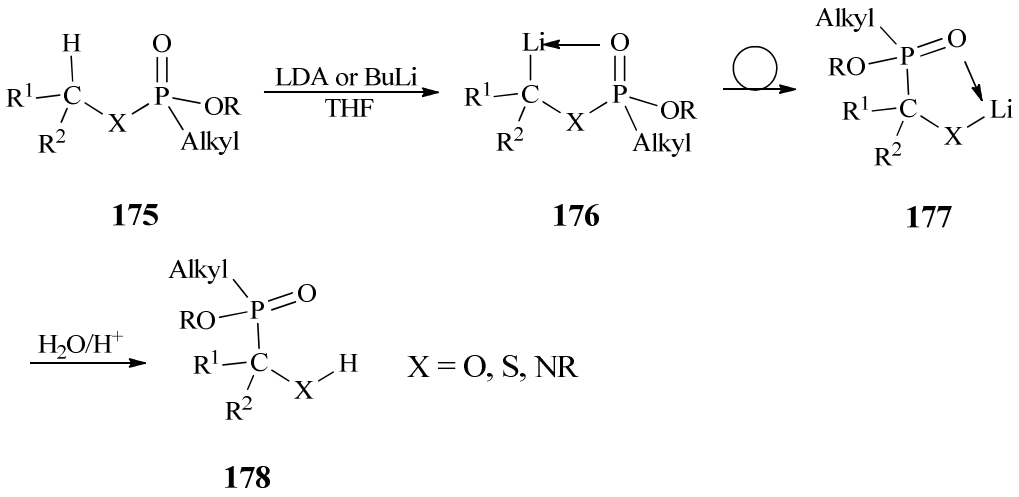
Phosphinates are a class of phosphorus-containing compounds of general structure $R^1R^2PO_2H$, which are of industrial and biological importance.[95] The tripeptide bialaphos (**173**) produced by *Streptomyces hygroscopicus* and *S. viridochromogenes* contains phosphinothricin (**174**) as a component, which is produced chemically as a very important commercial herbicide (Figure 2.01).[96] We reasoned that it should be possible to use a modified phosphate-phosphonate



bialaphos (**173**) phosphinothricin (**174**)

Figure 2.01. Bialaphos and phophinothricin.

rearrangement to access phosphinates. Is it possible to replace one of the OR groups in **169a-c** by a substituted alkyl group? The base-induced rearrangement will then give phosphinate **176** characterized by two P-C bonds (Scheme 2.02). The structure of the substituted alkyl group is

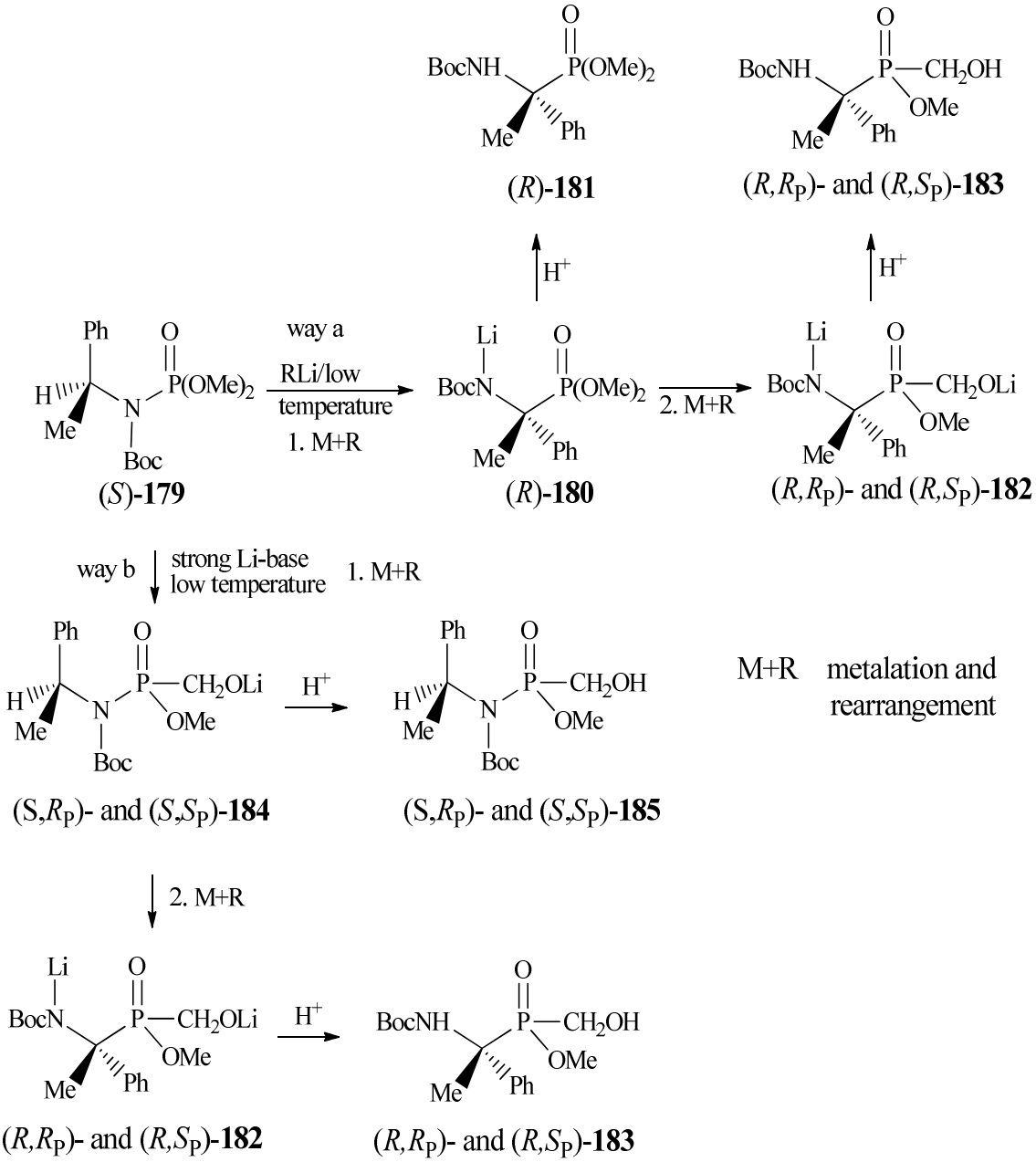


175 **176** **177**

178

Scheme 2.02. Phosphonate-phosphinate rearrangement.

very critical. It should not contain an α-hydrogen atom amenable to deprotonation. Primary and secondary alkyl groups can be metalated by strong bases and are therefore unsuitable substituents at phosphorus. We chose dimethyl phosphoramidate (*S*)-**179** to investigate possible reaction pathways and to perform preliminary experiments (Scheme 2.03). The hydrogen



Scheme 2.03. Rearrangement of dimethyl phosphoramidate (*S*)-**179** to phosphonates and phosphinates.

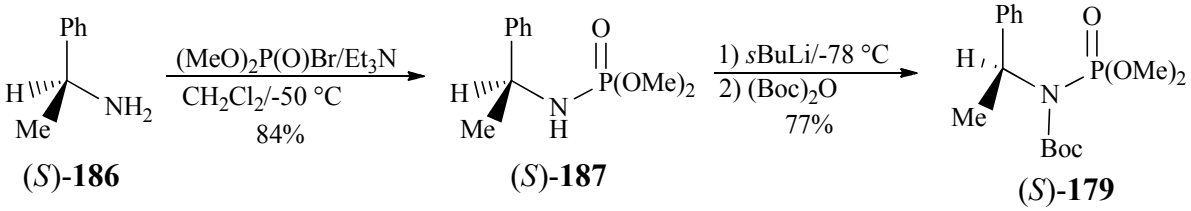
atoms of the MeO group are more acidic than the α-hydrogens of the EtO or *i*PrO group generally used as protecting groups for phosphorus. It is known from previous experiments with the corresponding diethyl ester that it could undergo the well-known phosphoramidate-α-aminophosphonate rearrangement first giving (*R*)-**180** (way a), when treated with 1.2 equiv. of *s*BuLi at –78 °C (first metalation and rearrangement). With excess *s*BuLi (2.5 – 3 equiv.) the MeO group could be metalated as well and the intermediate oxymethyllithiums formed could undergo the phosphonate-phosphinate rearrangement (second metalation and

rearrangement) and give a mixture of diastereomeric phosphinates (R,R_P)- and (R,S_P)-**182**. Acidic workup will give phosphonate (R)-**181** and diastereomeric phosphinates (R,R_P)- and (R,S_P)-**183**, respectively. If the hydrogen atoms of the MeO group are more acidic than the benzylic hydrogen, diastereomeric phosphonamidates (S,R_P)- and (S,S_P)-**184** could be formed first (way b) with 1.2 equiv. of *s*BuLi, followed by the formation of phosphinates (R,R_P)- and (R,S_P)-**182** with 1.5-2 equiv. base, assuming that the configuration at the benzylic carbon atom and at phosphorus will be retained. Acidic workup will yield phosphonamidates **185** and phosphinates **183**, respectively. Taking into account that side reactions could interfere, that individual rearrangements will not be quantitative and both ways could be followed simultaneously, complex reaction mixtures could result.

2.2. Results and discussion

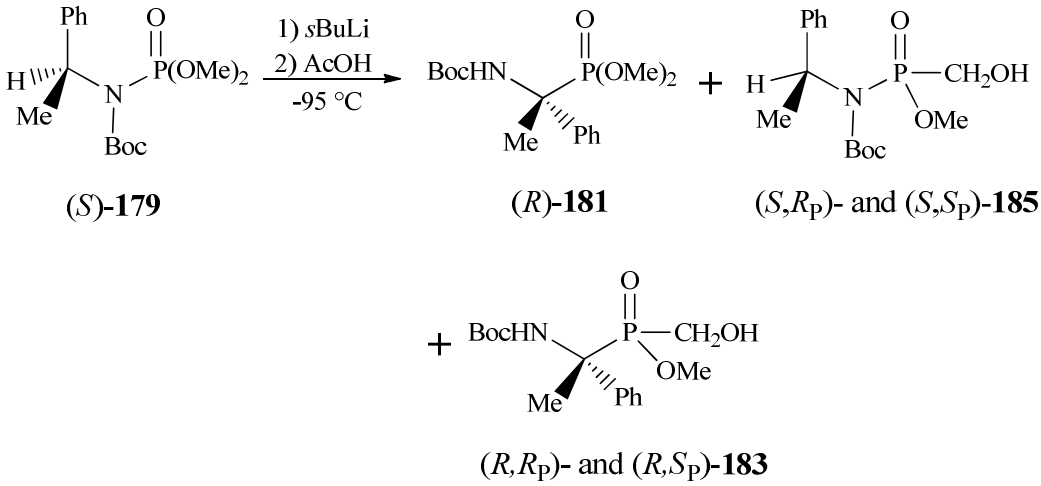
2.2.1. Rearrangement of (*S*)-dimethyl *N*-(*t*-butoxycarbonyl)-*N*-(1-phenylethyl)-phosphoramidate

The phosphoramidate (S)-**179** used to study the reactions outlined in Scheme 2.03 was prepared in two steps from (S)-1-phenylethylamine [(S)-**186**] (98% *ee*) in analogy to the preparation of the diethyl ester (Scheme 2.04).[94] Dimethyl phosphorylbromide generated *in*



Scheme 2.04. Preparation of (S)-**179**.

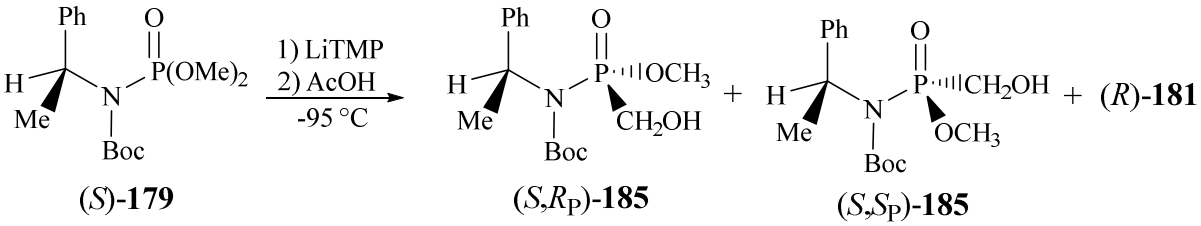
situ from trimethyl phosphite and bromine at –50 °C in CH_2Cl_2 was reacted with (S)-1-phenylethylamine [(S)-**186**] in the presence of triethylamine. The crystalline phosphoramidate (S)-**187** was obtained in 84% yield after purification by flash chromatography. It was metalated at nitrogen in THF using *s*BuLi and then reacted with $(Boc)_2O$ to give *N*-Boc protected phosphoramidate (S)-**179** in 77% yield. Phosphoramidate (S)-**179** was metalated with 1.4 equiv. of *s*BuLi in THF at –95 °C, hoping to have a higher selectivity for the formation of (R)-**181** than at –78 °C (Scheme 2.05).



Scheme 2.05. Formation of (*R*)-**181**.

Under these optimized conditions the crude product was a mixture based on ^{31}P NMR spectroscopy. The main product was undoubtedly the α-aminophosphonate (*R*)-**181** isolated by chromatography in 74%, indicating that the benzylic hydrogen atom is more acidic than a hydrogen atom of the OMe group. As the phosphoramidate-α-aminophosphonate rearrangement follows a retentive course, (*R*)-configuration could be assigned to phosphonate **181**. However, the diastereomeric phosphonamidates **185** and the phosphinates **183** were formed as well in small amounts in unknown ratios. Each pair of diastereomers displayed just one signal in the ^{31}P NMR spectra, but very different ones in the ^{1}H NMR spectra.

Lithium 2,2,6,6-tetramethylpiperidide (LiTMP), a sterically very hindered amide (pK_a 37),[97] was tested as base (2 equiv.) as well at the reaction temperature of –95 °C for 1 h (Scheme 2.06). The crude product contained starting material (*S*)-**179**/phosphonate (*R*)-**181**/phosphonamidates **185** (ratio of two diastereomers about 60:40) in a ratio of 20:6:74, but no phosphinates **183**. The mixture of phosphonamidates **185** was isolated in 55% yield as viscous oil. This result shows that LiTMP metalated the more easily accessible methoxy group preferentially compared to the benzylic position. Furthermore, the pK_a of a OCH_3 group of (*S*)-**179** is estimated to be <37, similar to that of a benzylic hydrogen.



(*S*)-**179** (S,R_P)-**185** (S,S_P)-**185**

(S,S_P)-**185** more polar than (S,R_P)-**185**

OCH_3>O>N>CH_2OH

Scheme 2.06. Rearrangement of (*S*)-**179** induced by LiTMP.

Surprisingly, a further metalation, at the benzylic position to induce a phosphonate-phosphinate rearrangement did not take place (see Scheme 2.03). The two diastereomers **185** were separated by semipreparative HPLC (t_R = 6.01 and 7.25 min) and crystallized from CH_2Cl_2/hexanes. Only the crystals of the less polar diastereomer were suitable for single-crystal X-ray structure analysis. This allowed the assignment of (*R*)-configuration at phosphorus (Figure 2.01).[98] Therefore, the less polar diastereomer **185** has (S,R_P) configuration, the more polar one (S,S_P).

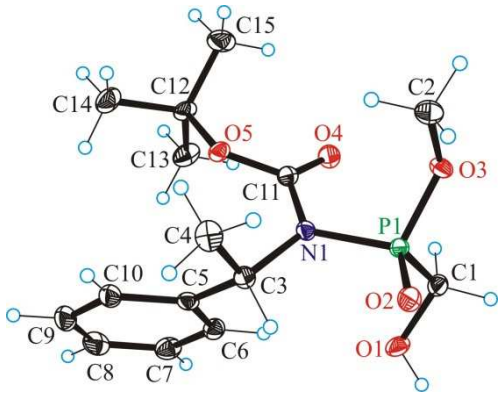
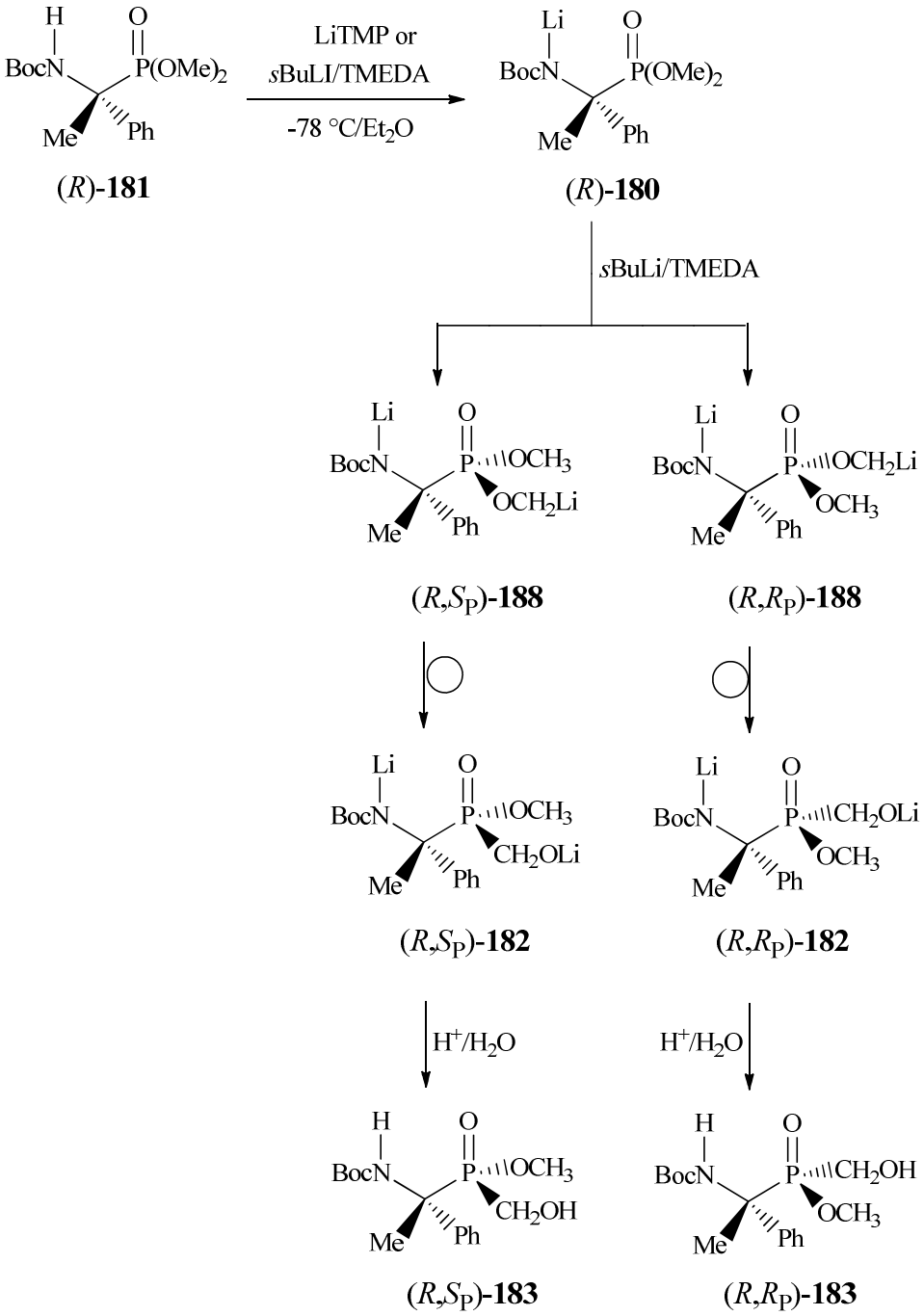


Figure 2.01. 3D-structure of (S,R_P)-**185**.

When LiTMP was replaced by LDA (2.5 equiv.) to induce a rearrangement under otherwise identical conditions, a crude product with a ratio of starting material (*S*)-**179**/phosphonate (*R*)-**181**/phosphonamidates **185**/phosphinates **183** 30:35:35:1 (by ^{31}P NMR) resulted. Flash chromatography gave recovered starting material (*S*)-**179** (0.180 mg 20%), phosphonate (*R*)-**181** (0.181 g, 20%) and diastereomers **185** (0.247 g, 27%). Clearly, the yield of the desired diastereomers **185** decreased and that of phosphonate (*R*)-**179** increased compared to LiTMP, which is evidently the best base for selective metalation at the OCH_3 group of a dimethyl phosphoramidate.

We now had three phosphonates, (*R*)-**181**, (*S*,*R*$_P$)- and (*S*,*S*$_P$)-**185,** in our hands to study the phosphonate-phosphinate rearrangement in detail. Phosphonate (*R*)-**181** was investigated first with 2.5 equiv. of LiTMP in dry THF at –78 °C for 18 h (Scheme 2.07). One equiv. of base



Scheme 2.07. The phosphonate-phosphinate rearrangements of (*R*)-**181**.

is consumed rapidly for converting phosphonate (*R*)-**181** to the lithiated species (*R*)-**180**. Surprisingly, the ratio of phosphonate (*R*)-**181**: phosphinates (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**185** was only 88:12 (by ^{31}P NMR; (*S*,*R*$_P$)-**185**: (*S*,*S*$_P$)-**185** was 22:78 by ^{1}H NMR) despite a reaction time of

18 h. The starting material was recovered in 64% yield. Evidently, metalation at a methoxy group and the ensuing phosphonate-phosphinate rearrangement had occurred only to a small extent. The high electron density at nitrogen of (*R*)-**180** will undoubtedly inductively lower the acidity of the hydrogen atoms of the methoxy group, so that LiTMP is no longer sufficiently basic to metalate (*R*)-**180** at a reasonable quantity. When this phosphonate was reacted with 2.5 equiv. of *s*BuLi/TMEDA in Et_2O for 2h at –78 °C, the crude product contained starting phosphonate and phosphinates (R,R_P)- and (R,S_P)-**183** in a ratio of 63:37 based on ^{31}P NMR spectroscopy (Scheme 2.07). The ratio of (R,R_P)- and (R,S_P)-**183** having the same chemical shift in the ^{31}P NMR spectrum, was determined to be 56:44 by ^{1}H NMR spectroscopy. The inseparable mixture of phosphinates was isolated by flash chromatography in 37% yield. Increasing the amount of base to 3.3 equiv. *s*BuLi/TMEDA (Et_2O, 1 h, –78 °C) increased the yield of the mixture of (R,R_P)- and (R,S_P)-**183** to just 45%. Homogenous diastereomers of **183** were obtained by semipreparative HPLC using EtOAc as eluent. Both compounds were crystallized from CH_2Cl_2/hexanes and the crystals of the more polar one were subjected to a single-crystal structure analysis allowing assignment of (*R*)-configuration at phosphorus (Figure 2.02).[98] Consequently, the less polar diastereomer must have (R,S_P) configuration.

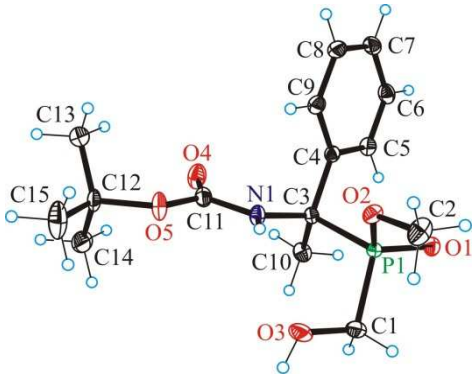
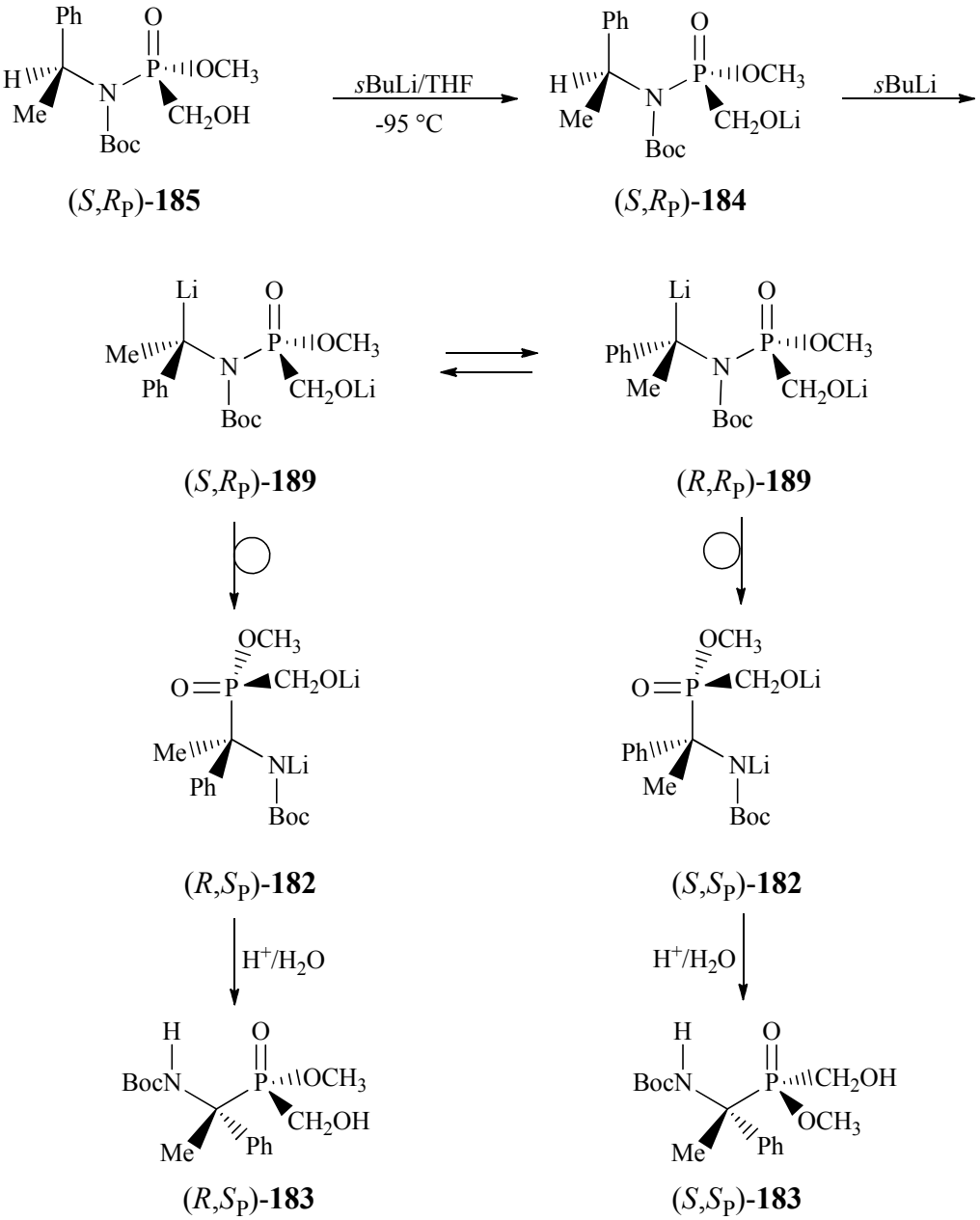


Figure 2.02. 3D-structure of (R,R_P)-**183**.

The alternative approach to obtain (R,S_P)- and (R,R_P)-**183**, started from phosphonamidates (S,R_P)- and (S,S_P)-**185** using 3.3 equiv of *s*BuLi in dry THF at –95 °C (Scheme 2.08). The reaction was quenched after 1 h with AcOH and worked up. The crude product was a mixture of starting phosphonate (S,R_P)-**185** and a mixture of diastereomeric phosphinates **183** (ratio 29:71 by ^{31}P NMR). Flash chromatography furnished recovered reactant in 22% yield and a mixture of diastereomeric phosphinates of unknown relative configuration in 51% yield (ratio



Scheme 2.08. Rearrangement of (*S*,*R*P)-**185** using 3.3 equiv. of *s*BuLi.

89:11 by ^{1}H NMR, 92:8 by HPLC). As we were expecting just one phosphinate, assuming that the phosphonate-phosphinate rearrangement would follow a retentive course as the phosphate-phosphonate rearrangement, a change of configuration at one of the two stereogenic centers had to occur. To determine the relative and absolute configurations at the two centers, the mixture of phosphinates was separated by semipreparative HPLC and compared to the two phosphinates of known relative and absolute configuration obtained according to Scheme 2.07. The major diastereomer was identical in ^{1}H NMR spectrum to (*R*,*S*P)-**183**, so that it could either have (*R*,*S*P) or (*S*,*R*P) configuration. As the specific optical rotation of (*R*,*S*P)-**183** formed from (*R*)-**181** is $[\alpha]_D^{23}$ = +25.1 (*c* = 1.0, acetone) and that of the

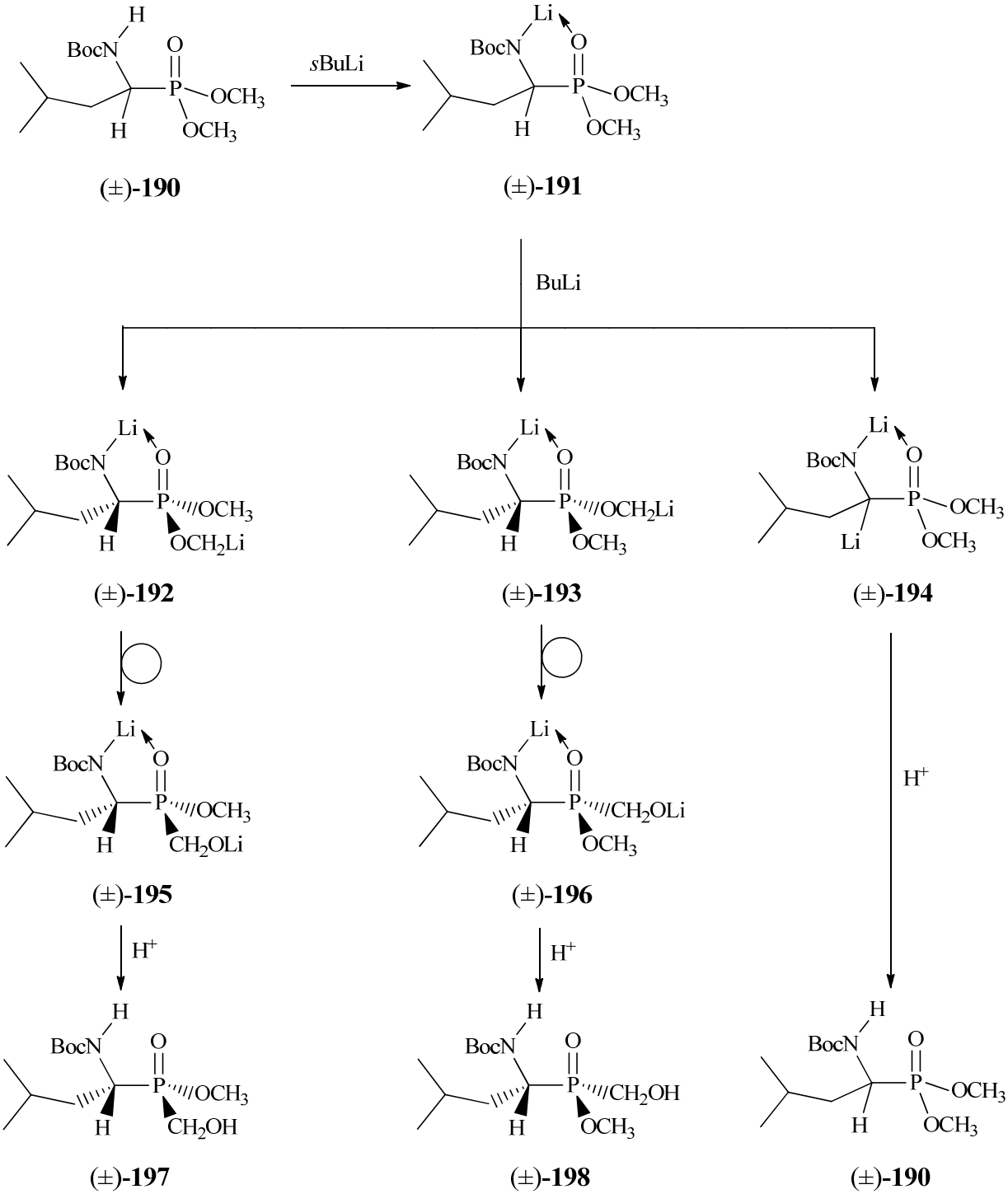
major diastereomer formed from (*S*,R_P)-**185** was $[\alpha]_D^{16}$ = +24.6 (*c* = 1.0, acetone), the latter has indeed (*R*,S_P) configuration. Similarly, the minor diastereomer formed from (*S*,R_P)-**185** was found to have (*S*,S_P) configuration, also based on the specific optical rotation {(*R*,R_P)-**183** formed from (*R*)-**181**: $[\alpha]_D^{23}$ = +15.6 (*c* = 1.0, acetone); minor diastereomer formed from (*S*,R_P)-**185**: $[\alpha]_D^{16}$ = –17.4 (*c* = 0.35, acetone)}. Clearly, part of the molecules changed their configuration at the benzylic stereogenic center despite a reaction temperature of –95 °C. The benzylic carbanion (*S*,R_P)-**189** formed from phosphonate (*S*,R_P)-**184** by metalation is configurationally not stable and enantiomerizes in part to (*R*,R_P)-**189**. Both carbanions undergo a phosphonate-phosphinate rearrangement with retention of configuration and yield the phosphinates (*R*,S_P)-**183** and (*S*,S_P)-**183**, respectively. This result is not quite surprising compared to the phosphoramidate-phosphonate rearrangement of (*R*)-diethyl *N*-(1-phenylethyl)phosphoramidate at temperatures of –78, –30, and 0 °C.[94] The rearrangement followed a retentive course (*ee* 98%) at all temperatures. We think that the major factor influencing the half-life of the benzyllithiums as intermediates of the phosphoramidate-phosphonate and phosphonate-phosphinate rearrangement is the electrophilicity of the phosphorus substitutent. The phosphorus of the $(EtO)_2P(O)$ group is more electrophilic than that of the $(MeO)P(O)(CH_2OLi)$ group. This leads to a longer half-life for the intermediate benzyllithium in the latter case as the reaction rate is smaller and consequently to a higher chance for inversion of the configuration.

Diastereomer (*S*,S_P)-**185** was isomerized in the same way as (*S*,R_P)-**185**. Here more starting phosphonate (*S*,S_P)-**185** was recovered (52%) and the yield of the mixture of phosphinates was lower (25%); (*S*,R_P)-**183** : (*R*,R_P)-**183** = 11: 89 by ^{1}H NMR). Again, a small portion of the molecules changed their configuration at the benzylic stereogenic center.

These experiments demonstrate that the phosphonate-phosphinate rearrangement follows a retentive course at both stereogenic centers, the carbon and phosphorus atoms.

2.2.2. The phosphonate-phosphinate rearrangement of racemic dimethyl 1-(*t*-butoxycarbonyl-amino)-3-methylbutylphosphonate

Finally, a simple *N*-Boc protected racemic dimethyl α-aminophosphonate, (±)-**190**, was studied as substrate for the phosphonate-phosphinate rearrangement (Scheme 2.09). This



Scheme 2.09. The phosphonate-phosphinate rearrangement of racemic dimethyl 1-(*t*-butoxycarbonyl-amino)-3-methylbutylphosphonate (**190**).

compound was prepared easily by a literature procedure from simple precursors[99] and reacted under a variety of conditions with excess BuLi. At first the nitrogen is metalated. Although this protected aminophosphonate (±)-**190** has an acidic α-hydrogen atom, it was reasoned that it would not be metalated because of the neighboring metalated nitrogen atom. Formation of a vicinal dianion was considered highly unlikely, but we were convinced of the opposite later.

The second metalation, the deprotonation of a methoxy group of (±)-**191**, produces α-oxymethyllithiums (±)-**192** and (±)-**193**, the former being possibly preferred, because the required methoxy group is less shielded by the isobutyl substituent. The supposedly short-lived oxymethyllithiums immediately undergo phosphonate-phosphinate rearrangements to phosphinates (±)-**195** and (±)-**196**, respectively. A minimum of 2 equiv. of base are necessary for quantitative transformation. Acidic work up produces a mixture of (±)-**197**, (±)-**198**, and (±)-**190** regenerated from (±)-**191** and (±)-**194**, respectively. Therefore, (±)-**190** was reacted with excess (2.2 to 3 equiv.) LiTMP or *s*BuLi under a variety of conditions (Table 2.01).

Entry	Base	Temp. (°C)	Solvent	Educt: Product[a)]	Yield of phosphin-ates	Recovered Educt
1	2.5 equiv. *s*-BuLi[2)]	-78 °C	Et_2O	only E	0%	81%
2	2.2 equiv. *t*-BuLi[2)]	-78 °C	THF	3:1	Very little	Very little
3	2.2 equiv. *s*-BuLi	-78 °C	THF/DME	2.6:1	5%	13%
4	2.2 equiv. *s*-BuLi	-95 °C	THF/DME	10:1	2%	15%
5	2.5 equiv. LiTMP	-78°C	THF	only E	0%	78%
6	2.5 equiv. LiTMP	-78 °C to -25 °C	THF	only E	0%	51%
7	2.2 equiv. *s*-BuLi[b)]	-78 °C	THF	4:1	17%	50%
8	3 equiv. *s*-BuLi[b)]	-78 °C	THF	1.9:1	19%	42%
9	3.5 equiv. *s*-BuLi[b)]	-78 °C	THF	4.6:1	[c)]	
10	1.2 equiv. *i*PrMgCl, 1.1 equiv. *s*BuLi	-78 °C	THF	only E	0%	
11	1.1 equiv. *i*PrMgClLiCl, 1.5 equiv. *s*-BuLi	-78 °C	THF	only E	0%	
12	2.2 equiv. -*s*BuLi, 2.2 equiv. 12-crown-4	-78 °C	THF	only E	0%	

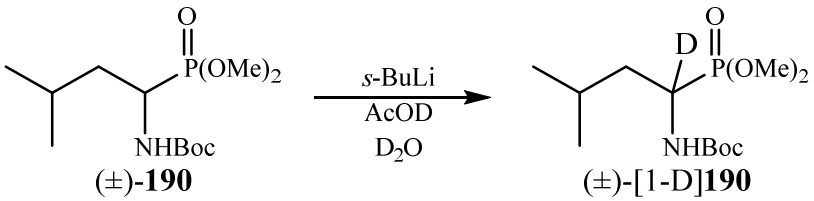
[a)] in crude product by ^{31}P NMR; [b)] with 1 equiv. TMEDA; [c)] not isolated.

Table 2.01. Rearrangements of racemic dimethyl 1-(*t*-butoxycarbonylamino)-3-methylbutylphosphonate (**190**).

The ratio of starting material (±)-**190** and phosphinates was determined by ^{31}P NMR spectroscopy in the crude product. There was only one resonance for phosphinates in the ^{31}P NMR spectra, indicating that there was only one phosphinate formed or that both have the same chemical shift. LiTMP did not effect the phosphonate-phosphinate rearrangement (Entries 5 and 6). *s*-BuLi did not induce the rearrangement in Et_2O (Entry 1), but in THF (Entries 7-9). A combination of *s*BuLi with 12-crown-4 (Entry 12) or *i*PrMgCl with *s*BuLi

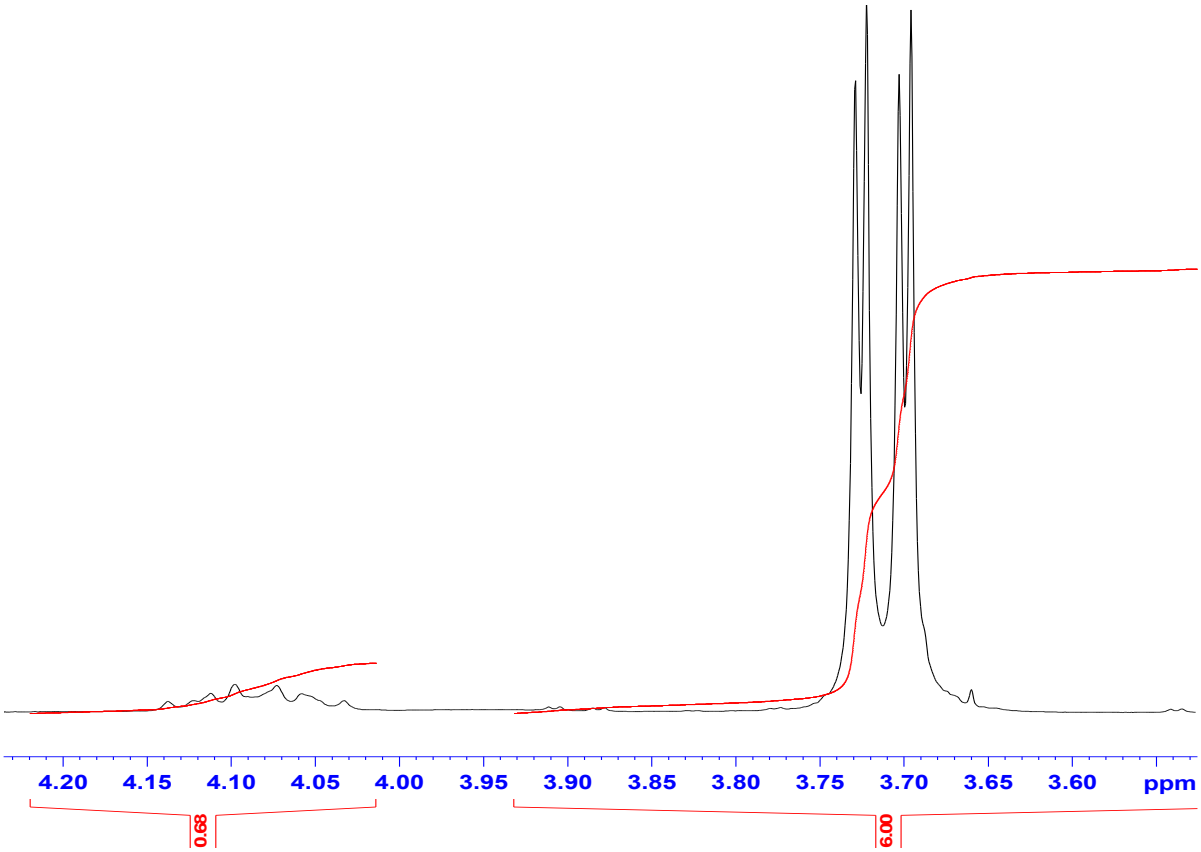
(Entries 10 and 11) did not give the desired phosphinate(s). Flash chromatography furnished an oily phosphinate, (±)-**197** and/or (±)-**198**, of unknown configuration in about 20% yield, which was homogenous by ^{1}H and ^{31}P NMR spectroscopy surprisingly. The two peaks in the ^{31}P NMR spectrum (δ: 52.59 and 50.43, ratio 95:5) were attributed to the two conformers of one of the phosphinates. Furthermore, we assume that the very polar phosphinates should have very similar polarity and should elute together. Unfortunately, the yield of the rearrangement could not be increased to values above 20%. The strong basic conditions induced side reactions, which consumed starting material and thus decreased the yield.

To check whether metalation of (±)-**191** to (±)-**194** (see Scheme 2.09) by BuLi is possible or not, a reaction of (±)-**190** with s-BuLi by the standard procedure was quenched with AcOD (Scheme 2.10).



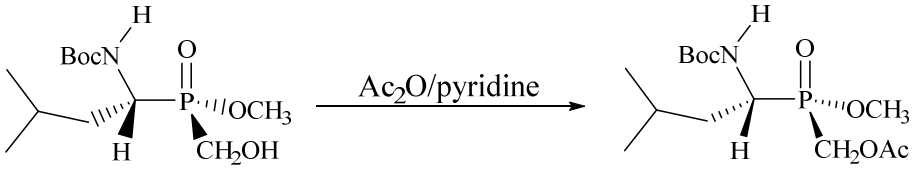
Scheme 2.10. Phosphonate-phosphinate rearrangement quenched with deuterated acetic acid and D_2O.

The starting material was recovered by flash chromatography and investigated by 1H NMR spectroscopy (400 MHz). Surprisingly, 32% of the molecules were deuterated at C-1, indicating that vicinal dianion (±)-**194** was generated (Scheme 2.11). It cannot undergo a phosphonate-phosphinate rearrangement, because the required deprotonation at a methoxy group will not be feasible. This side reaction will undoubtedly reduce the yield of the phosphinate.



Scheme 2.11. ^{1}H NMR spectrum of the recovered phosphonate (the peak on the left side is from the α-hydrogen, the peaks on the right side are from the two methoxy groups).

To ease the interpretation of the ^{1}H NMR spectrum of the isolated phosphinate and get a crystal for a single crystal X-ray structure analysis, phosphinate (±)-**197** was acetylated to give acetate (±)-**199** (Scheme 2.12).



(±)-**197** (±)-**199**

Scheme 2.12. Acetylation of hydroxymethylphosphinate (±)-**197**.

As crystallization from CH_2Cl_2/hexanes gave crystals suitable for single crystal X-ray structure analysis (Figure 2.03),[98] the relative configuration could be determined. The two stereogenic centers were assigned (R^*,S_P^*) configuration, supporting (±)-**192** as the preferred intermediate oxymethyllithium of the phosphonate-phosphinate rearrangement. However, the high diastereoselectivity is noteworthy even if a small amount of (±)-**198** went unnoticed.

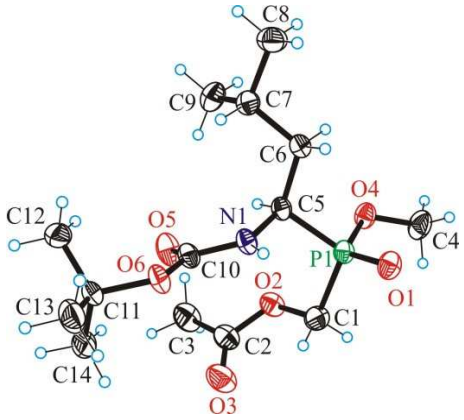


Figure 2.03. 3D-structure of acetoxymethylphosphinate (±)-**199**.

This interesting and new rearrangement in phosphorus chemistry justifies more experiments with other bases and other protecting groups than Boc to improve the yields.

3. Experimental Part

3.1. General

Acetone/dry ice bath was used for reactions between –30 °C and –78 °C, also with addition of liquid nitrogen to achieve –95 °C. Normally, the reaction protocols for racemic and optically active compounds were identical and given for the former.

NMR spectroscopy

^{1}H, ^{13}C (*J* modulated) and ^{31}P NMR spectra were measured on Bruker Avance DRX 400 (^{1}H: 400.13 MHz, ^{13}C: 100.61 MHz, ^{31}P: 161.98 MHz), AV 400 (^{1}H: 400.27 MHz, ^{13}C: 100.65 MHz, ^{31}P: 162.03 MHz) and DRX 600 (^{1}H: 600.13 MHz, ^{13}C: 150.92 MHz, ^{31}P: 242.94 MHz) at 300 K, unless otherwise specified. 2D spectra were measured on DRX 400. Chemical shifts were referenced either to residual $CHCl_3$ (δ_H = 7.24)/H_2O (δ_H = 4.80) or $CDCl_3$ (δ_C = 77.00). All chemical shifts (δ) are given in ppm and *J* values in Hz. The following abbreviations are used to describe spin multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, dsept = doublet of septet etc.

Infrared spectroscopy

IR spectra were run on a Perkin-Elmer 1600 FT-IR or 2000 FT-IR spectrometer or by using ATR on a Bruker VERTEX 70 IR spectrometer. Samples were measured as a film (usually obtained by applying several drops from NMR sample and evaporation of $CDCl_3$) on a silicon disc, or the compound was used directly. IR spectra are reported in wave numbers (cm^{-1}).

Mass Spectroscopy

Mass spectra were recorded on spectrometers from Micro Mass (Fissions Instrument, Trio2000) in EI mode (70 eV). HRMS were measured on Finnigan MAT 8230 with a resolution of 10000.

Chromatography

Flash column chromatography

Preparative flash column chromatography was performed with Merck silica gel (230-400 mesh).

Thin layer chromatography

All reactions were monitored using coated glass plates. TLC was carried out on 0.25 mm thick silica gel 60, F_{254} Merck plates. Spots were detected by UV and/or by dipping the plate into molybdate reagent (a solution of 23.0 g of $(NH_4)_6Mo_7O_{24}\cdot 4\ H_2O$ and 1.0 g of $Ce(SO_4)_2\cdot 4\ H_2O$ in 500 ml of 10% aqueous H_2SO_4). Afterwards, the plate was heated with the heat gun.

Ion-exchange

Three kinds of ion-exchange resins were used to purify the amino phosphonic acids: Dowex® 50 WX8-100 cation exchanger (H^+), Dowex® MWA-1 anion exchanger (OAc^-) and Dowex® 1X8 anion exchanger (HCO_3^-). Solvent for TLC: water/isopropanol/ammonia/water (6:3:1). Spots were detected by dipping the plate into a ninhydrin solution (0.2% ninhydrin in 96% Ethanol) heating with the heat gun.

HPLC

The analytical HPLC was performed by the Jasco System (PU-980 pump, UV 975 and RI 930) with a Chiracel-OD-H-column (Ø 0.46 cm x 25 cm); the preparative HPLC by the Dynamix Model SD-1 with a UV-1 absorption detector and a Chiracel-OD-column (Ø 5 cm x 50 cm).

Polarimetry

Optical rotations were measured on a Perkin-Elmer 141 polarimeter. The length of the cell was 1 dm and the solution in cell was kept normally at 20 °C. The optical rotations were measured with monochromatic sodium light (Na D-line, 598 nm). If the specific rotation was very low, it was also measured at 365 nm (Hg-line).

Melting points

Melting points were measured with a Reichert Thermovar instrument and were uncorrected.

Solvents

The solvents were purified and dried prior to use, according to the following procedures:

- **CH_2Cl_2** was dried by passing through aluminum oxide 90 active, neutral (0.063-0.200 mm, activity I) and stored over molecular sieves (3 Å).
- **Et_2O** was refluxed over $LiAlH_4$ and distilled prior to use.
- **Hexanes** and **EtOAc** used for chromatography were purified by distillation.
- **THF** was refluxed over potassium and freshly distilled prior to use.
- **TMEDA** and **pyridine** were refluxed over CaH_2, distilled and stored over molecular sieves (4 Å).
- **Toluene** was refluxed over sodium/benzophenone, then distilled and stored over molecular sieves (4 Å).

All other solvents were purified and dried by standard methods.

Chemicals

All commercially available reagents were supplied from Aldrich, Alfa Aesar, Fluka, Merck or Acros in the best available quality and used without further purification.

(*S*)-Mosher ester – General Procedure A

A solution of alcohol (0.10 mmol), dry pyridine (0.25 ml) and (*S*)-MTPACl (0.3 ml, 0.15 mmol, 0.5 M in dry CH_2Cl_2) was dissolved in dry CH_2Cl_2 (2 ml) and stirred at room temperature overnight. Afterwards CH_2Cl_2 (10 ml) and HCl (10 ml, 1 M) were added. The organic phase was separated, washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography.

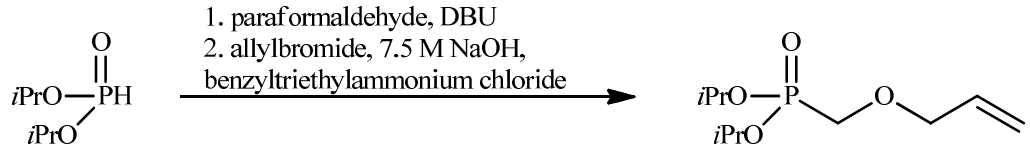
Determination of ee with chiral solvating agent – General Procedure B

First the standard ^1H NMR spectrum was recorded. Then the sample was added to (*R*)-(+)-*t*-butyl(phenyl)phosphinothioic acid (two equiv.) in a vial. The sample was returned into the NMR tube after dissolution and measured again, sometimes on the next day.

3.2. Experimental procedures and compounds characterization

3.2.1. Synthesis of (*R*)-3-amino-3-phosphonopropanoic acid

Diisopropyl (allyloxy)methylphosphonate [79]



78 **79**

Paraformaldehyde (3.150 g, 105 mmol) was added to diisopropyl phosphite (**78**) (16.613 g, 16.8 ml, 100 mmol), and then DBU (20 drops) was added. An exothermic reaction started and the solution became clear. After one hour of stirring at RT, benzyltrimethylammonium chloride (0.089 g, 0.48 mmol), sodium hydroxide (40 ml, 240 mmol, 7.5 M in water) and allyl bromide (14.513 g, 10.4 ml, 120 mmol) were added and vigorous stirring was continued for for 2.5 h. Water (100 ml) and MC (70 ml) were then added. The organic layer was separated and the aqueous one was extracted with MC (2 x 50 ml). The combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was bulb to bulb distilled (95 - 110˚C/0.6 mbar; lit.: 89-92 °C/1.5 mm Hg) to yield allyloxymethylphosphonate **79** (20.718 g, 88%) as a colourless oil; n_D^{20} 1.4327 (lit.: n_D^{20} 1.4312).

IR (Si): ν = 2981, 1387, 1260, 1108, 989.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.83 (tdd, J = 17.2, J = 10.4, J = 5.7 Hz, 1H, C<u>H</u>=CH_2), 5.25 (qd, J = 17.2, J = 1.5 Hz, 1H_{trans}, CH=<u>CH_2</u>), 5.18 (qd, J = 10.4, J = 1.5 Hz, 1H_{cis}, CH=C<u>H_2</u>), 4.71 (septd, J = 7.6, J = 6.3 Hz, 2H, 2 x $(CH_3)_2$C<u>H</u>), 4.05 (td, J = 5.7, J = 1.5 Hz, 2H, OCH_2), 3.66 (t, J = 8.6 Hz, 2H, PCH_2), 1.30 (d, J = 6.3 Hz, 6H, 2 x (<u>CH_3</u>)$_2$CH), 1.29 (d, J = 6.3 Hz, 6H, 2 x (<u>CH_3</u>)$_2$CH).

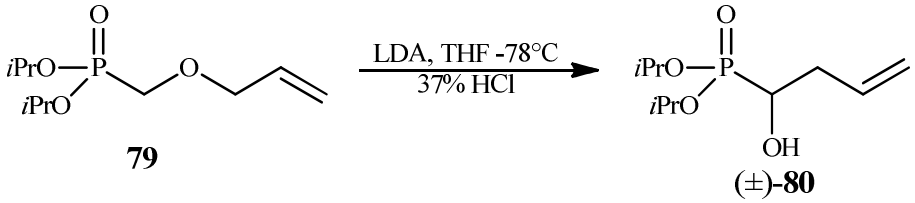
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 133.62 (s, 1C, CH=), 118.02 (s, 1C, CH_2=), 73.76 (d, 1C, J(^{31}P) = 12.2 Hz, OCH_2), 70.86 (d, J(^{31}P) = 6.9 Hz, 1C, $POCH_2$), 64.36 (d, J(^{31}P) = 168.9 Hz, 1C, PCH_2), 23.98 (d, J(^{31}P) = 3.8 Hz, 2C, 2 x CH_3), 23.87 (d, J(^{31}P) = 4.6 Hz, 2C, 2 x CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 20.90 (s, P=O).

The ^{13}C and ^{31}P NMR spectra are not reported in the literature.[100]

Elemental analysis calculated for $C_{10}H_{21}O_4P$ (236.25): C 50.84, H 8.96; found: C 50.73, H 8.86.

(±)-Diisopropyl 1-hydroxy-3-butenylphosphonate [(±)-80]



79 (±)-**80**

Diisopropyl allyloxymethylphosphonate (**79**) (8.90 g, 37.67 mmol) dried by co-evaporation with toluene, was dissolved in dry THF (35 ml) and the solution was cooled to –78 °C under argon atmosphere. LDA (31.3 ml, 45.25 mmol, 1.2 equiv., 1.45 M in THF, freshly prepared) was added and the solution was stirred for 2 h. The reaction was quenched with 32% HCl (12 ml, 10 M) at –78 °C. The organic phase was removed and the aqueous one was extracted with MC (2 x 30 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The α-hydroxyphosphonate (±)-**80** was obtained as a light yellow oil (8.368 g, 94%) and proved to be pure enough (by ^{1}H and ^{31}P NMR spectroscopy) for chloroacetylation. The analytical sample was purified by flash chromatography (EtOAc, R_f = 0.36) to give a colorless oil.

Synthesis of 1.45 M LDA in THF:
Dry diisopropylamine (4.574 g, 6.4 ml, 45.92 mmol) was dissolved in dry THF (6.8 ml) under argon and cooled to –35 °C. *n*-BuLi (18.1 ml, 45.25 mmol, 2.5 M in hexanes) was added dropwise. The solution was ready for use after stirring for 15 min at −30 °C.

IR (Si): ν = 3306, 2980, 2936, 1387, 1224, 1107, 989.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.88 (tdd, J = 7.1, J = 10.1, J = 17.2 Hz, 1H, C<u>H</u>=CH_2), 5.16 (dq, J = 1.5, J = 17.2, 1H, CH=C<u>H</u>$_2$), 5.13 (dd, J = 1.5, J = 10.1 Hz, 1H, CH=C<u>H</u>$_2$), 4.74 (m, 2H, $(CH_3)_2$C<u>H</u>), 3.82 (dt, J = 5.1, J = 9.4 Hz, 1H, CHP), 2.54 (m, 1H, CH_2), 2.40 (m, 1H.

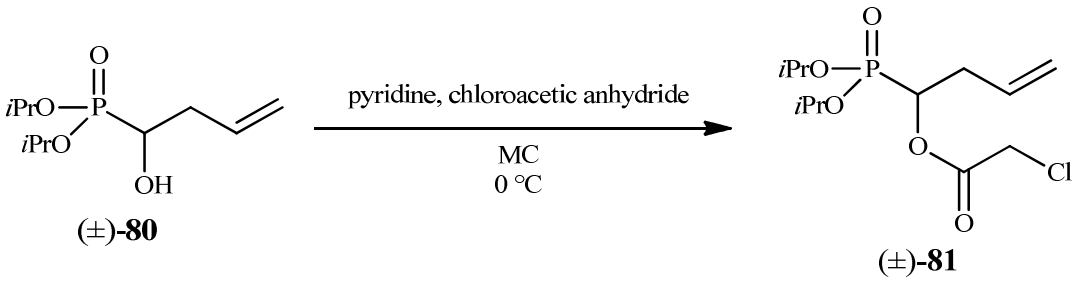
CH_2), 1.33 (d, J = 6.1 Hz, 3H, ($\underline{CH_3}$)$_2$CH), 1.32 (d, J = 6.1 Hz, 3H, ($\underline{CH_3}$)$_2$CH), 1.32 (d, J = 6.1 Hz, 6H, 2 x ($\underline{CH_3}$)$_2$CH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 134.30 (d, J(^{31}P) = 14.5 Hz, 1C, $\underline{C}$H=CH$_2$], 118.64 (s, 1C, CH=$\underline{C}$H$_2$), 71.66 (d, J(^{31}P) = 7.7 Hz, 1C, (CH$_3$)$_2$$\underline{CH}$), 71.60 (d, J(^{31}P) = 6.9 Hz, 1C, (CH$_3$)$_2$$\underline{CH}$), 67.92 (d, J(^{31}P) = 163.7 Hz, 1C, CHP), 36.47 (s, 1C, CH_2), 24.53 (d, J(^{31}P) = 3.8 Hz, 2C, ($\underline{C}$H$_3$)$_2$CH), 24.40 (d, J(^{31}P) = 5.4 Hz, 2C, ($\underline{C}$H$_3$)$_2$CH).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 23.60 (s, P=O).

Elemental analysis calculated for $C_{10}H_{21}O_4P$ (236.25): C 50.84, H 8.96; found: C 50.74, H 8.70.

(±)-Diisopropyl 1-chloroacetoxy-3-butenylphosphonate [(±)-81]



(±)-**80** (±)-**81**

1-Hydroxy-3-butenylphosphonate [(±)-**80**] (7.650 g, 33.38 mmol) and pyridine (8.150 g, 8.3 ml, 103.03 mmol) were dissolved in MC (30 ml) at 0 °C under argon. Chloroacetic anhydride (7.990 g, 46.73 mmol, 1.40 equiv., dissolved in 20 ml of dry MC) was added dropwise and the solution was stirred at 0 °C for 1.5 h. Water (50 ml) was then added and the organic layer was separated. The aqueous layer was extracted with MC (2 x 30 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (2:1), R_f= 0.25] to yield chloroacetate (±)-**81** (9.469 g, 94%) as a yellow oil.

IR (Si): ν = 2981, 2349, 1768, 1645, 1465, 1388, 1261, 1165, 1105, 989.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.69 (AB-sys, J = 6.1, J = 8.1, J = 10.1 Hz, 1H, CHP), 5.25 (ddd, J = 1.0, J = 3.8, J = 10.1 Hz, 1H, $\underline{C}$H=CH$_2$), 5.08 (m, 2H, CH=C$\underline{H_2}$), 4.72 (dsep, J = 6.1, J = 6.3 Hz, 2H, (CH$_3$)$_2$$\underline{C}$H), 4.05 (s, 2H, CH_2Cl), 2.64 (m, 1H, $\underline{CH_2}$CHP), 2.48 (dq, J =

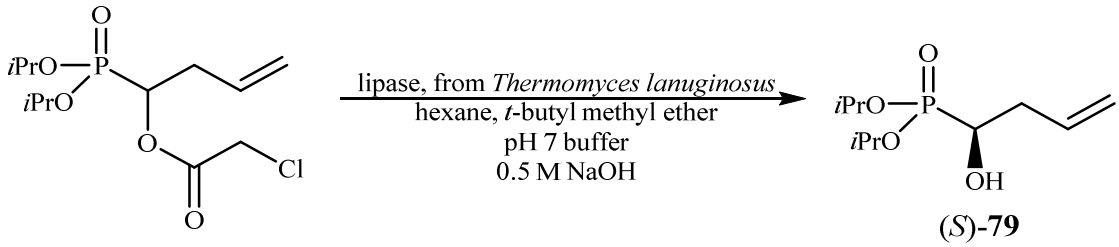
9.3, J = 14.9 Hz, 1H, $\underline{CH_2}CHP$), 1.31 (d, J = 6.1 Hz, 6H, 2 x $(\underline{CH_3})_2CH$], 1.29 (d, J = 6.1 Hz, 3H, 1 x $(\underline{CH_3})_2CH$), 1.28 (d, J = 6.1 Hz, 3H, 1 x $(\underline{CH_3})_2CH$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 166.77 (d, $J(^{31}P)$ = 6.1 Hz, 1C, C=O), 132.78 (d, $J(^{31}P)$ = 13.8 Hz, 1C, $\underline{C}H=CH_2$), 119.19 (s, 1C, $CH=\underline{C}H_2$), 72.43 (d, $J(^{31}P)$ = 6.9 Hz, 1C, $(CH_3)_2\underline{C}H$), 72.27 (d, $J(^{31}P)$ = 7.7 Hz, 1C, $(CH_3)_2\underline{C}H$), 69.57 (d, $J(^{31}P)$ = 171.3 Hz, 1C, CHP], 40.98 (s, 1C, $\underline{C}H_2CHP$), 34.51 (s, 1C, $\underline{C}H_2CHP$), 24.54 (d, $J(^{31}P)$ = 3.1 Hz, 1C, $(\underline{C}H_3)_2CH$), 24.41 (d, $J(^{31}P)$ = 3.1 Hz, 1C, $(\underline{C}H_3)_2CH$), 24.37 (d, $J(^{31}P)$ = 5.4 Hz, 1C, $(\underline{C}H_3)_2CH$), 24.22 (d, $J(^{31}P)$ = 5.4 Hz, 1C, $(\underline{C}H_3)_2CH$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 18.05 (s, P=O).

Elemental analysis calculated for $C_{12}H_{22}ClO_5P$ (312.73): C: 46.09, H: 7.09; found: C: 46.13, H: 6.74

(*S*)-(+)-Diisopropyl 1-hydroxy-3-butenylphosphonate [(*S*)-79]



(±)-**81** (*S*)-**79**

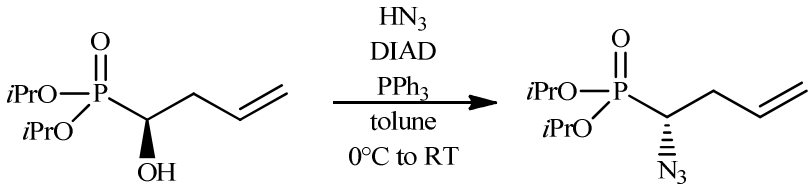
Diisopropyl 1-chloroacetoxy-3-butenylphosphonate [(±)-**81**] (7.509 g, 23.25 mmol) was dissolved in a solvent mixture of hexanes (25 ml), methyl *t*-butyl ether (25 ml) and pH 7 buffer (125 ml, preparation of 500 ml pH 7 buffer: 3.4 g (25 mmol) KH_2PO_4 was dissolved in 300 ml water, adding 1 M NaOH to adjust pH 7, followed by addition of water to a final volume of 500 ml, and then by autoclaving at 121 °C for 20 min). 0.5 M NaOH was added by autotitrator to bring pH to 7.0. Lipase (from *Thermomyces lanuginosus*, ≥100,000 U/g, 0.2 ml of commercial solution from Aldrich) was added, pH again adjusted to 7.0, and kept there by automatic addition of base. The solution was stirred vigorously for 3.5 h at RT. The enzymatic hydrolysis was stopped by adding 2 M HCl to the solution until pH = 4 when the conversion had reached 45% (calculated from the used amount of 0.5 M NaOH). The organic phase was removed and the aqueous one was extracted with EtOAc (3 x 60 ml). The

combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (1:1) for chloroacetate, EtOAc for optically active α-hydroxyphosphonate, R_f = 0.07 for hexanes/EtOAc (1:1)] to yield (*S*)-α-hydroxyphosphonate **79** (2.076 g, 38%) as a colorless oil. $[\alpha]_D^{20}$ = +22.76 (*c* = 2.10, acetone).

(*S*)-Mosher ester:

The α-hydroxyphosphonate (*S*)-**79** was converted to a (*S*)-Mosher ester according to general procedure.; *ee* of (*S*)-**79**: 97%. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 15.91 for (*S*)-**79** and 15.39 for (*R*)-**79**.

(*R*)-(–)-Diisopropyl 1-azido-3-butenylphosphonate [(*R*)-90]



(*S*)-**79** (*R*)-**90**

(*S*)-1-Hydroxy-3-butenylphosphonate (*S*)-**79** (1.979 g, 8.38 mmol) and triphenylphosphine (2.854 g, 10.88 mmol) were dissolved in toluene (30 ml) under argon. At 0 °C, DIAD (94%, 2.343 g, 2.3 ml, 10.89 mmol, dissolved in 3 ml of toluene) was added, followed by HN_3 (8.7 ml, 10.88 mmol, 1.25 M in toluene). The solution was stirred overnight at RT. It was then concentrated under reduced pressure and purified by two flash chromatographies {1. hexanes/EtOAc (2:1), R_f = 0.62 [hexanes/EtOAc (1:1)] and 2. diethyl ether/hexanes 2:1} to yield azide (*R*)-**90** (1.472 g, 67%) as a colorless oil. $[\alpha]_D^{20}$ = –31.02 (c = 1.33, acetone).

IR (Si): ν = 3475, 2983, 2937, 2121, 2102, 1387, 1377, 1258, 1105, 991, 914.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.83 (ddt, J_{trans} = 17.1 Hz, J_{cis} = 10.3 Hz, J = 6.5 Hz, 1H, $\underline{CH}$=CH_2), 5.19 (dd, J_{trans} = 17.1 Hz, J = 1.4 Hz, 1H, CH=$\underline{CH_2}$), 5.15 (d, J_{cis} = 10.3 Hz, 1H, CH=$\underline{CH_2}$), 4.78 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.76 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 3.35 (td, J = 11.9 Hz, J = 3.3 Hz, 1H, CHP), 2.67-2.32 (m, AB-sys, 2H, $\underline{CH_2}CH$=CH_2), 1.34 (d, J = 6.2 Hz, 9H, 3 x $CH(\underline{CH_3})_2$), 1.34 (d, J = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 133.45 (d, $J(^{31}P)$ = 15.2 Hz, 1C, $\underline{CH}=CH_2$), 118.46 (s, 1C, $CH=\underline{CH_2}$), 71.89 (d, $J(^{31}P)$ = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.82 (d, $J(^{31}P)$ = 7.2 Hz, 1C, $\underline{CH}(CH_3)_2$), 57.26 (d, $J(^{31}P)$ = 156.9 Hz, 1C, CHP), 33.03 (s, 1C, $\underline{CH_2}CH=CH_2$), 24.14 (d, $J(^{31}P)$ = 2.8 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 23.96 (d, $J(^{31}P)$ = 4.7 Hz, 2C, 2 x $CH(\underline{CH_3})_2$).

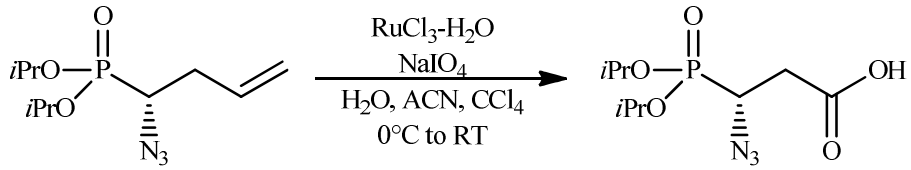
^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 19.44 (s, P=O).

Elemental analysis calculated for $C_{10}H_{20}N_3O_3P$ (261.26): C: 45.97, H: 7.72, N: 16.08; found: C: 46.12, H: 7.73, N: 15.90.

Similarly, (±)-1-hydroxy-3-butenylphosphonate **79** (1.204 g, 5.10 mmol) was converted to (±)-azide **90** (0.679 g, 59%) as a colorless oil.

The spectroscopic data of (±)- and (*R*)-**90** are identical.

(*R*)-3-azido-3-(diisopropoxyphosphinyl)propanoic acid [(*R*)-91]



(*R*)-**90** (*R*)-**91**

1-Azido-3-butenylphosphonate [(*R*)-**90**] (1.462 g, 5.60 mmol) was dissolved in a solvent mixture of H_2O (15 ml), ACN (8 ml) and CCl_4 (8 ml). $RuCl_3 \cdot xH_2O$ (78 mg) and $NaIO_4$ (5.153 g, 24.09 mmol) were added and the solution was stirred vigorously for 5 h from 0 °C to RT. The organic phase was removed and a saturated aqueous solution of $NaHCO_3$ (15 ml) as well as MC (15 ml) were added. The organic layer was separated and extracted with water (1 x 20 ml). 2 M HCl was added to the combined aqueous layers until pH <2, and then the aqueous layer was extracted with MC (2 x 15 ml), washed with brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give azidocarboxylic acid (*R*)-**91** (1.397 g, 89%) as colorless crystals (due to the tiny amounts of Ru, the crystals might be black). Mp. 53-55 °C (ethanol/water).

IR (Si): ν = 2984, 2937, 2132, 2096, 1730, 1389, 1254, 1103, 998.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 9.27 (bs, 1H, COOH), 4.80 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.79 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.02 (ddd, J = 12.3, J = 11.1, J = 3.0 Hz, 1H, CHP), 2.83 (A part of ABX-sys, J_{AB} = 17.0 Hz, J = 7.0, J = 3.0 Hz, 1H, $\underline{CH_2}COOH$), 2.57 (B part of ABX-sys, J_{AB} = 17.1 Hz, J = 11.1, J = 7.4 Hz, 1H, $\underline{CH_2}COOH$), 1.35 (d, J = 6.2 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.34 (d, J = 6.2 Hz, 6H, $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 173.38 (d, $J(^{31}P)$ = 19.7 Hz, 1C, COOH), 72.85 (d, $J(^{31}P)$ = 7.0 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.81 (d, $J(^{31}P)$ = 7.4 Hz, 1C, $\underline{CH}(CH_3)_2$), 54.21 (d, $J(^{31}P)$ = 163.2 Hz, 1C, CHP), 34.11 (s, 1C, $\underline{CH_2}COOH$), 24.06 (d, $J(^{31}P)$ = 6.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.03 (d, $J(^{31}P)$ = 6.4 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.89 (d, $J(^{31}P)$ = 4.9 Hz, 2C, 2 x $CH(\underline{CH_3})_2$).

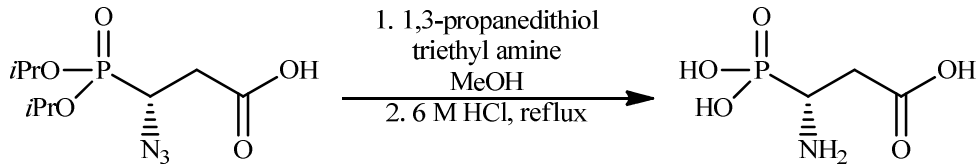
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 19.81 (s, P=O).

Elemental analysis calculated for $C_9H_{18}N_3O_5P$ (279.23): C: 38.71, H: 6.50, N: 15.05; found: C: 39.01, H: 6.68, N: 14.54.

Similarly, (±)-azide **90** (0.410 g, 1.57 mmol) was converted to azidocarboxylic acid (±)-**91** (0.363 g, 83%) as colorless crystals.

The spectroscopic data of (±)- and (*R*)-**91** are identical.

(*R*)-(–)-3-Amino-3-phosphonopropanoic acid [(*R*)-89]



(*R*)-**91** (*R*)-**89**

3-Azidopropanoic acid (*R*)-**91** (0.575 g, 2.06 mmol) was dissolved in methanol (9 ml) under argon. 1,3-Propanedithiol (0.667 g, 0.6 ml, 6.16 mmol) and triethylamine (0.626 g, 0.86 ml, 6.19 mmol) were added and stirring was continued at RT overnight. The solvent was removed under reduced pressure (10 mm Hg) at RT. Water (10 ml) and MC (10 ml) were added. The organic layer was separated and the aqueous one was extracted with MC (2 x 10 ml). The combined organic layers were concentrated under reduced pressure. Then 6 M HCl (40 ml) was added to the residue and solution was refluxed for 4 h. The solution was concentrated

under reduced pressure and purified by ion exchange chromatography [Dowex® 50 WX8, H^+, H_2O] and crystallization (water/ethanol) to yield the aminophosphonic acid (*R*)-**89** (0.205 g, 59%) as colorless crystals. Mp. 233-235 °C (lit.:[107] 234-236 °C).

$[\alpha]_D^{20} = -34.05$ ($c = 0.98$, water) [lit.:[101] $[\alpha]_x^y = -35.2$ ($c = 0.54$, water)].

IR (Si): ν = 3149, 2727 (very broad), 1713, 1608, 1509, 1255, 1203, 1159, 1063, 1029.

^{1}H NMR (400.13 MHz, D_2O): δ = 3.71 (ddd, J (^{31}P) = 14.0 Hz, J = 10.2, J = 3.7 Hz, 1H, CHP), 3.05 (A part of ABX-sys, J_{AB} = 18.0 Hz, J = 8.6, J = 3.7 Hz, 1H, $\underline{CH_2}$COOH), 2.85 (B part of ABX-sys, J_{AB} = 18.0 Hz, J = 10.2, J = 7.1 Hz, 1H, $\underline{CH_2}$COOH).

^{13}C NMR (100.61 MHz, D_2O): δ = 174.55 (d, J(^{31}P) = 15.0 Hz, 1C, COOH), 45.98 (d, J(^{31}P) = 143.0 Hz, 1C, CHP), 33.05 (s, 1C, $\underline{CH_2}$COOH).

^{31}P NMR (161.98 MHz, D_2O): δ = 12.61 (s, P=O).

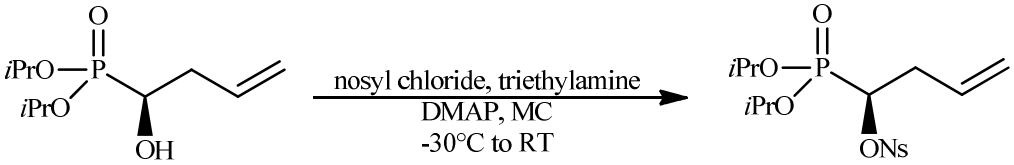
Elemental analysis calculated for $C_3H_8NO_5P$ (169.07): C: 21.31, H: 4.77, N: 8.28; found: C: 21.46, H: 4.68, N: 8.15.

Similarly, azidocarboxylic acid (±)-**91** (0.343 g, 1.23 mmol) was converted to aminophosphonic acid (±)-**89** (0.122 g, 59%) as colorless crystals.

The spectroscopic data of (±)- and (*R*)-**89** are identical.

3.2.2. Synthesis of (*R*)-(1,2-oxazinan-3-yl)phosphonic acid

(*S*)-Diisopropyl 1-(4-nitrobenzenesulfonyloxy)-3-butenylphosphonate [(*S*)-92]



(*S*)-**80** (*S*)-**92**

1-Hydroxy-3-butenylphosphonate [(*S*)-**8**0] (2.570 g, 10.88 mmol) and 4-nitrobenzenesulfonyl chloride (3.616 g, 16.32 mmol) were dissolved in MC (30 ml) and stirred under argon. At –35 °C, DMAP (1.329 g, 10.88 mmol, dissolved in 5 ml of dry MC) was added dropwise and followed by triethylamine (2.198, 3 ml, 21.72 mmol). The solution was allowed to warm up slowly to RT overnight. 2 M HCl (30 ml) was added and the organic layer was separated. The aqueous layer was extracted with MC (2 x 30 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (2:1), R_f = 0.25] to yield nosylated hydroxyphosphonate (*S*)-**92** (4.166 g, 91%) as an oil.

IR (Si): ν = 2984, 1536, 1377, 1351, 1260, 1187, 1104, 995.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.37-8.33 (m, 2H, H_{arom}), 8.15-8.11 (m, 2H, H_{arom}), 5.72 (tdd, J_{trans} = 17.1 Hz, J_{cis} = 10.0 Hz, J = 7.0 Hz, 1H, $\underline{CH}$=CH_2), 5.07 (dd, J_{trans} = 17.1 Hz, J = 1.3 Hz, 1H, CH=$\underline{CH_2}$), 5.03 (d, J_{cis} = 10.2 Hz, 1H, CH=$\underline{CH_2}$), 4.89 (td, J = 9.0 Hz, J (^{31}P) = 4.4 Hz, 1H, CHP), 4.72 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.64 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 2.72-2.50 (m, AB-sys, 2H, $\underline{CH_2}CH$=CH_2), 1.30 (d, J = 6.2 Hz, 6H, 2 x CH($\underline{CH_3}$)$_2$), 1.27 (d, J = 6.2 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.26 (d, J = 6.2 Hz, 3H, CH($\underline{CH_3}$)$_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 150.70 (s, 1C, C_{arom}), 142.84 (s, 1C, C_{arom}), 131.76 (d, J(^{31}P) = 11.4 Hz, 1C, $\underline{CH}$=CH_2), 129.40 (s, 2C, C_{arom}), 124.10 (s, 2C, C_{arom}), 119.50 (s, 1C, CH=$\underline{CH_2}$), 77.47 (d, J(^{31}P) = 170.7 Hz, 1C, CHP), 72.47 (d, J(^{31}P) = 6.7 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.41 (d, J(^{31}P) = 7.2 Hz, 1C, $\underline{CH}(CH_3)_2$), 35.07 (s, 1C, $\underline{CH_2}CH$=CH_2), 24.07 (d, J(^{31}P) = 5.6 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 24.03 (d, J(^{31}P) = 4.9 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.93 (d, J(^{31}P) = 5.2 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.75 (d, J(^{31}P) = 4.9 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$).

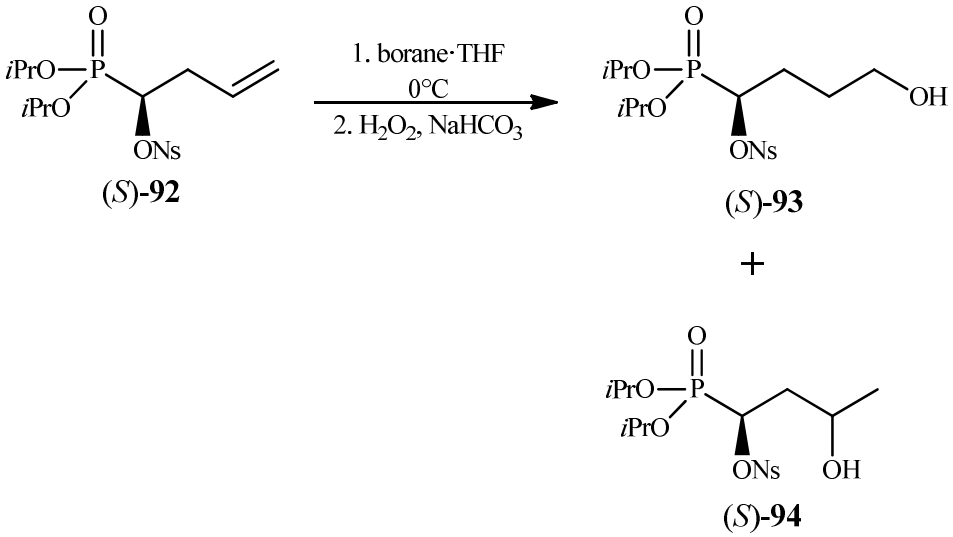
^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 15.54 (s, P=O).

Elemental analysis calculated for $C_{16}H_{24}NO_8PS$ (421.40): C: 45.60, H: 5.74, N: 3.32; found: C: 45.58, H: 5.79, N: 3.34.

Similarly, 1-hydroxyphosphonate (±)-**80** (0.514 g, 2.18 mmol) was converted to nosylated hydroxyphosphonate (±)-**92** (0.818 g, 89%) as colorless crystals. Mp. 73 °C (hexanes).

The spectroscopic data of (±)- and (*S*)-**92** are identical.

(*S*)-Diisopropyl 4-hydroxy-1-(nitrobenzenesulfonyloxy)-butylphosphonate [(*S*)-93]



(*S*)-**92** (*S*)-**93** + (*S*)-**94**

1-Nosyloxy-3-butenylphosphonate [(*S*)-**92**] (4.452 g, 10.56 mmol) was dissolved in dry THF (40 ml) under argon. At 0 °C, BH_3·THF (14.8 ml, 14.8 mmol, 1 M in THF) was added and the solution was stirred for 2 h at this temperature. Then methanol (5 ml) was added and the solution was stirred for 10 min to destroy the excessive borane. After that, H_2O_2 (4.2 ml) (30% in water) and saturated aqueous solution of $NaHCO_3$ (4 ml) were added and the solution was stirred at RT for another 2 h. The organic phase was removed and water (20 ml) as well as MC (20 ml) were added. The organic layer was separated and the aqueous one was extracted with MC (2 x 30 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure at RT (to prevent cyclisation to substituted tetrahydrofuran). The residue was purified by flash chromatography [hexanes/EtOAc (1:1) for the Markovnikov-product (*S*)-**94** and hexanes/EtOAc (1:5) for anti-Markovnikov-product **93** with R_f = 0.21] to yield 4-hydroxyphosphonate (*S*)-**93** (2.745 g,

59%) as a heavy oil, which always contained solvent that could not be removed at room temperature. It could not be characterized and was used immediately for the next step.

IR (Si): ν = 2983, 2101, 1608, 1376, 1536, 1377, 1351, 1249, 995, 913.

Similarly, nosylated hydroxyphosphonate (±)-**92** (0.210 g, 0.50 mmol) was converted to 4-hydroxyphosphonate (±)-**93** (0.138 g, 63%) as a heavy oil.

The spectroscopic data of (±)- and (*S*)-**93** are identical.

Hydroboration with 9-BBN

1-Nosyloxy-3-butenylphosphonate [(±)-**92**] (0.338 g, 0.80 mmol) was dissolved in dry THF (3 ml) under argon. At 0 °C, 9-BBN (1.9 ml, 0.85 mmol, 0.5 M in THF) was added and the solution was stirred for 1 h at this temperature and for 18 h at RT. As the TLC showed that the amount of reactant was still large, stirring was continued for 1 h at 50 °C. Methanol (0.5 ml) was added and the solution was stirred for 10 min to destroy the excessive borane. After that, H_2O_2 (0.3 ml) (30% in water) and saturated aqueous solution of $NaHCO_3$ (0.4 ml) were added and the solution was stirred at 0 °C for 5 h. The organic phase was removed and water (10 ml) as well as MC (10 ml) were added. The organic layer was separated and the aqueous one was extracted with MC (2 x 10 ml). The combined organic layers were washed with brine (5 ml), dried (Na_2SO_4) and concentrated under reduced pressure at RT. No Markovnikov-product was found in the NMR-spectrum of the crude product, instead starting material (42%) and only a small amount of the desired 4-hydroxyphosphonate [(±)-**93]** (16%) and three byproducts were found. No further purification was performed.

Hydroboration with $CyBH_2$

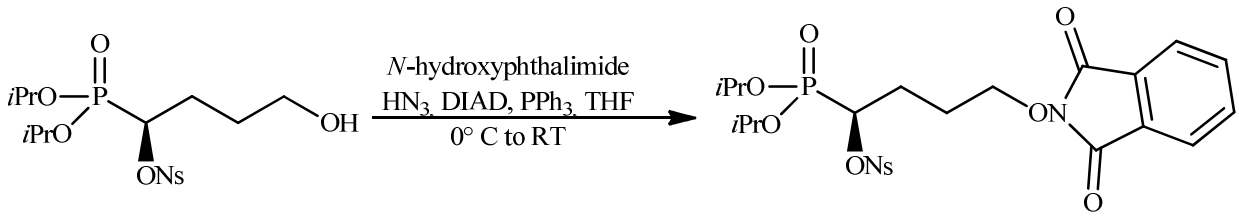
BH_3·THF (0.6 ml, 0.6 mmol, 1 M in THF) was added to cyclohexene (0.050 g, 0.06 ml, 0.61 mmol) at −25 °C under argon and the solution was stirred for 1.5h at −10 °C to yield $CyBH_2$. 1-Nosyloxy-3-butenylphosphonate [(±)-**92]** (0.214 g, 0.51 mmol, dissolved in 1 ml THF) was then added and the solution was stirred 2 h at 0 °C and 3 h at RT. Methanol (0.5 ml) was added and the solution was stirred for 10 min to destroy the excessive borane. After that, H_2O_2 (0.3 ml) (30% in water) and saturated aqueous solution of $NaHCO_3$ (0.4 ml) were added and the solution was stirred at RT overnight. The organic phase was removed and water (10 ml) as well as MC (10 ml) were added. The organic layer was separated and the aqueous one

was extracted with MC (2 x 10 ml). The combined organic layers were washed with brine (5 ml), dried (Na_2SO_4) and concentrated under reduced pressure at RT. The NMR spectrum of the crude product showed 27% reactant, 51% desired product, 10% Markovnikov product and several other byproducts. No further purification was performed.

Hydroboration with catecholborane and Wilkinson´s catalyst

1-Nosyloxy-3-butenylphosphonate [(±)-**92**] (0.277 g, 0.66 mmol) and 24 mg old Wilkinson´s catalyst were dissolved in 1 ml THF under argon. Catecholborane (1.3 ml, 1.3 mmol, 1 M in THF) was added at RT. After 10 min stirring, the solution turned black and the TLC showed that the reaction was already finished. Methanol (0.5 ml) was added and the solution was stirred for 10 min to eliminate the excessive borane. After that, H_2O_2 (0.3 ml) (30% in water) and saturated aqueous solution of $NaHCO_3$ (0.4 ml) were added and the solution was stirred at RT for 2 h. The organic phase was removed and water (10 ml) as well as MC (10 ml) were added. The organic layer was separated and the aqueous one was extracted with MC (2 x 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure at RT and purified by flash chromatography [hexanes/EtOAc (1:1)] to yield 4-hydroxyphosphonate [(±)-**93**] (0.225 g, 78%) as a light yellow oil.

(*S*)-(+)-Diisopropyl 1-(4-nitrobenzenesulfonyloxy)-4-phthalimidooxybutylphosphonate [(*S*)-95]



(*S*)-**93** (*S*)-**95**

4-Hydroxybutylphosphonate (*S*)-**93** (2.580 g, 5.87 mmol), *N*-hydroxyphthalimide (0.958 g, 5.87 mmol) and triphenylphosphine (2.002 g, 7.63 mmol) were dissolved in dry THF (25 ml) under argon. DIAD (1.543 g, 1.5 ml, 7.63 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and was then allowed to warm up to room temperature overnight. The solution was concentrated under reduced pressure and purified by flash chromatography [hexanes/EtOAc (2:1), R_f = 0.30 for hexanes/EtOAc (1:1)] and crystallized (hexanes/MC) to yield phthalimidooxyphosphonate (*S*)-**95** (2.574 g, 75%) as colorless crystals. Mp. 128 °C.

$[\alpha]_D^{20}$ = +5.04 (*c* = 1.29, acetone).

IR (ATR): ν = 1731, 1533, 1374, 1351, 1256, 1186, 986.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.40-8.33 (m, 2H, H_{arom}), 8.22-8.16 (m, 2H, H_{arom}), 7.85-7.78 (m, 2H, H_{arom}), 7.76-7.71 (m, 2H, H_{arom}), 5.00 (ddd, *J* = 9.4 Hz, *J* = 8.7 Hz, *J* (^{31}P) = 4.5 Hz, 1H, CHP), 4.80-4.59 (m, 2H, $\underline{CH}(CH_3)_2$), 4.25-4.15 (m, 2H, CH_2ON), 2.31-2.18 (m, 1H, $\underline{CH_2}CHP$), 2.13-1.94 (m, 2H, $\underline{CH_2}CH_2ON$), 1.94-1.81 (m, 1H, $\underline{CH_2}CHP$), 1.31 (d, *J* = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$), 1.31 (d, *J* = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$), 1.28 (d, *J* = 6.4 Hz, 3H, $CH(\underline{CH_3})_2$), 1.26 (d, *J* = 6.7 Hz, 3H, $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 163.47 (s, 2C, 2 x C=O), 150.74 (s, 1C, C_{arom}), 142.61 (s, 1C, C_{arom}), 134.54 (s, 2C, C_{arom}), 129.45 (s, 2C, C_{arom}), 128.87 (s, 2C, C_{arom}), 124.24 (s, 2C, C_{arom}), 123.55 (s, 2C, C_{arom}), 77.74 (d, J(^{31}P) = 171.5 Hz, 1C, CHP), 77.02 (s, 1C, CH_2ON), 72.52 (d, J(^{31}P) = 6.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.45 (d, J(^{31}P) = 6.0 Hz, 1C, $\underline{CH}(CH_3)_2$), 26.76 (s, 1C, $\underline{CH_2}CHP$), 24.21 (d, J(^{31}P) = 10.0 Hz, 1C, $\underline{CH_2}CH_2ON$), 24.07 (d, J(^{31}P) = 5.4 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.03 (d, J(^{31}P) = 5.4 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.92 (d, J(^{31}P) = 5.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.74 (d, J(^{31}P) = 5.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

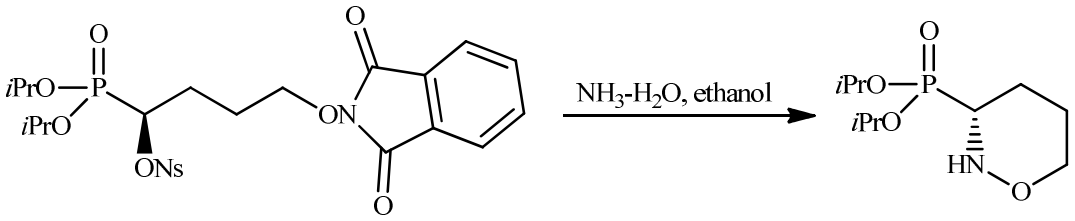
^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 15.65 (s, P=O).

Elemental analysis calculated for $C_{24}H_{29}N_2O_{11}PS$ (584.53): C: 49.31, H: 5.00, N: 4.79; found: C: 49.40, H: 5.13, N: 4.98.

Similarly, 4-hydroxyphosphonate (±)-**93** (0.150 g, 0.34 mmol) was converted to phthalimidooxyphosphonate(±)-**95** (0.139 g, 70%) as colorless crystals. Mp. 128-129 °C.

The NMR spectroscopic data of (±)- and (*S*)-**95** are identical.

(*R*)-Diisopropyl (1,2-oxazinan-3-yl)phosphonate [(*S*)-96]



(*S*)-**95** (*R*)-**96**

Nosylate (*S*)-**95** (0.484 g, 0.83 mmol) was dissolved in ethanol (6 ml). Ammonia (0.6 ml, 25% in water) was added at 0 °C. The solution was allowed to warm up slowly to RT and stirred overnight. Then it was refluxed for 4 h. The solution was concentrated under reduced pressure and purified by flash chromatography [hexanes/EtOAc (1:5), R_f = 0.30] to yield cyclic aminooxyphosphonate (*R*)-**96** (0.163 g, 78%) as a colorless oil, which was used immediately for the next step without characterization.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.41 (bs, 1H, NH), 4.77-4.63 (m, *2*H, $\underline{CH}(CH_3)_2$), 3.99-3.90 (m, 1H, CH_2O), 3.77-3.67 (m, 1H, CH_2O), 3.48-3.36 (m, 1H, CHP), 2.02-1.88 (m, 1H, $\underline{CH_2}CHP$), 1.83-1.65 (m, 1H, $\underline{CH_2}CHP$; m, 2H, $\underline{CH_2}CH_2O$), 1.31 (d, *J* = 6.3 Hz, 3H, $CH(\underline{CH_3})_2$), 1.31 (d, *J* = 4.8 Hz, 3H, $CH(\underline{CH_3})_2$), 1.29 (d, *J* = 6.2 Hz, 6H, 2 x $CH(\underline{CH_3})_2$).

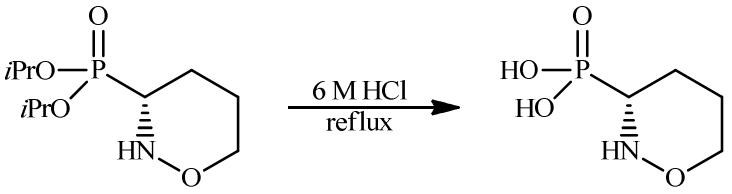
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 71.07 (d, $J(^{31}P)$ = 6.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.01 (d, $J(^{31}P)$ = 6.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 70.51 (s, 1C, CH_2O), 56.52 (d, $J(^{31}P)$ = 150.7 Hz, 1C, CHP), 24.49 (d, $J(^{31}P)$ = 11.6 Hz, 1C, $\underline{CH_2}CH_2O$), 24.07 (d, $J(^{31}P)$ = 3.8 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.03 (d, $J(^{31}P)$ = 3.9 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.95 (d, $J(^{31}P)$ = 5.0 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.92 (d, $J(^{31}P)$ = 4.7 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.63 (d, $J(^{31}P)$ = 3.8 Hz, 1C, $\underline{CH_2}CHP$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 21.27 (s, P=O).

Similarly, phthalimidooxyphosphonate (±)-**95** (0.139 g, 0.24 mmol) was converted to cyclic aminooxyphosphonate (±)-**96** as a colorless oil.

The spectroscopic data of (±)- and (*R*)-**96** are identical.

(*R*)-(1,2-Oxazinan-3-yl)phosphonic acid [(*R*)-97]



(*R*)-**96** (*R*)-**97**

Diisopropyl 1,2-oxazinan-3-ylphosphonate [(*R*)-**96**] (0.093 g, 0.37 mmol) was dissolved in 6 M HCl (5 ml) and refluxed for 4 h. The solution was concentrated under reduced pressure and purified by ion exchange [Dowex® 50WX8, H^+, H_2O] to yield cyclic aminooxyphosphonic acid (*R*)-**97** (0.044 g, 71%) as colorless crystals. Mp. 187-188 °C (decomp.).

$[\alpha]_D^{20} = -15.05$ ($c = 0.51$, water).

IR (ATR): ν = 2300 (very br.), 1216, 1151, 1085, 1071, 1031.

^{1}H NMR (400.13 MHz, D_2O): δ = 4.39-4.31 (m, 1H, CH_2O), 4.28-4.19 (m, 1H, CH_2O), 3.72-3.63 (m, 1H, CHP), 2.30-2.18 (m, 1H, $\underline{CH_2}$CHP), 2.09-1.89 (m, 1H, $\underline{CH_2}$CHP and 2H, $\underline{CH_2}CH_2O$).

^{13}C NMR (100.61 MHz, D_2O): δ = 71.89 (s, 1C, CH_2O), 57.19 (d, $J(^{31}P)$ = 134.7 Hz, 1C, CHP), 22.34 (d, $J(^{31}P)$ = 9.9 Hz, 1C, $\underline{CH_2}CH_2O$), 21.34 (d, $J(^{31}P)$ = 2.4 Hz, 1C, $\underline{CH_2}$CHP).

^{31}P NMR (161.98 MHz, D_2O): δ = 9.11 (s, P=O).

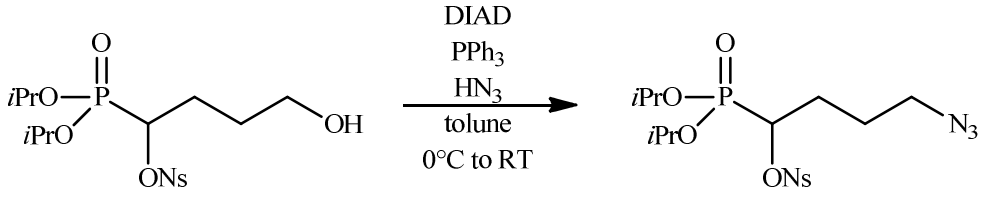
Elemental analysis calculated for $C_4H_{10}NO_4P$ (167.10): C: 28.75, H: 6.03, N: 8.38; found: C: 28.97, H: 5.89, N: 8.12.

Similarly, cyclic aminooxyphosphonate (±)-**96** (0.060 g, 0.24 mmol) was converted to cyclic aminooxyphosphonic acid (±)-**97** as colorless crystals.

The NMR spectroscopic data of (±)- and (*R*)-**97** are identical.

3.2.3. Synthesis of (±)-1,4-diaminobutylphosphonic acid

(±)-Diisopropyl 4-azido-1-(4-nitrobenzenesulfonyloxy)-butylphosphonate [(±)-98]



(±)-**93** (±)-**98**

4-Hydroxybutylphoshonate (±)-**93** (0.305 g, 0.69 mmol) and triphenylphosphine (0.236 g, 0.90 mmol) were dissolved in toluene (2 ml) under argon. DIAD (0.197 g, 0.2 ml, 0.97 mmol, dissolved in 0.5 ml of dry toluene) was added dropwise to the solution and followed by HN_3 (1.5 ml, 0.75 M in toluene, old) at 0 °C. Stirring was continued for 0.5 h at 0 °C and then the reaction mixture was allowed to warm up slowly in the bath to RT overnight. The solution was concentrated under reduced pressure and purified by flash chromatography [hexanes/EtOAc (2:1), R_f = 0.63 for hexanes/EtOAc (1:1)] to yield azide (±)-**98** (0.312 g, 97%) as a light yellow oil.

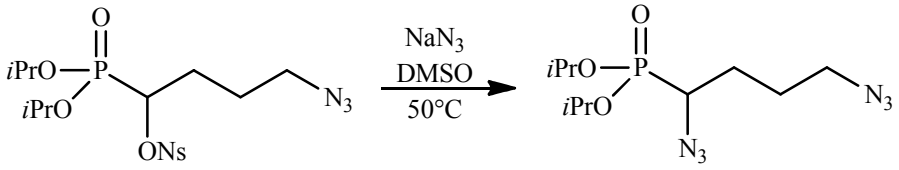
IR (Si): ν = 2983, 2101, 1536, 1376, 1352, 1256, 1188.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.39-8.34 (m, 2H, H_{arom}), 8.18-8.13 (m, 2H, H_{arom}), 4.86 (ddd, J = 9.7 Hz, J = 8.5 Hz, J (^{31}P) = 4.3 Hz, 1H, CHP), 4.74-4.55 (m, 2H, $\underline{CH}(CH_3)_2$), 3.31 (t, J = 6.5 Hz, 2H, CH_2N_3), 2.08-1.64 (m, 4H, $\underline{CH_2}CHP$ + $\underline{CH_2}CH_2N_3$), 1.27 (d, J = 6.2 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.24 (d, J = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$), 1.22 (d, J = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 150.76 (s, 1C, C_{arom}), 142.47 (s, 1C, C_{arom}), 129.31 (s, 2C, C_{arom}), 124.18 (s, 2C, C_{arom}), 77.43 (d, J(^{31}P) = 171.9 Hz, 1C, CHP), 72.49 (d, J(^{31}P) = 6.8 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.36 (d, J(^{31}P) = 7.2 Hz, 1C, $\underline{CH}(CH_3)_2$), 50.57 (s, 1C, CH_2N_3), 27.83 (s, 1C, $\underline{CH_2}CHP$), 24.88 (d, J(^{31}P) = 10.0 Hz, 1C, $\underline{CH_2}CH_2N_3$), 24.01 (d, J(^{31}P) = 3.7 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.94 (d, J(^{31}P) = 3.8 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.90 (d, J(^{31}P) = 4.8 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.69 (d, J(^{31}P) = 5.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 15.58 (s, P=O).

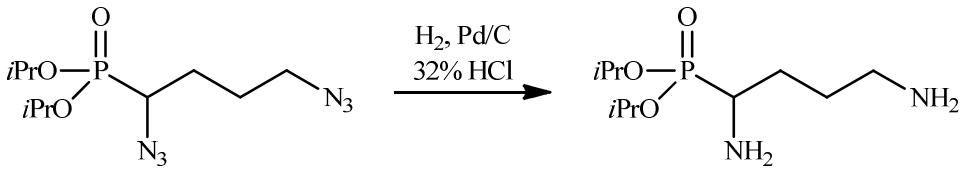
(±)-Diisopropyl 1,4-diazidobutylphosphonate [(±)-99]



(±)-**98** (±)-**99**

4-Azidobutylphosphonate (±)-**98** (0.261g, 0.56 mmol) and NaN_3 (0.110 g, 1.69 mmol) were dissolved in DMSO (3 ml). The mixture was stirred at 50 °C overnight, concentrated under reduced pressure and purified by flash chromatography [hexanes/EtOAc (1:1), R_f = 0.43] to yield diazide (±)-**99** (0.150 g, 88%) as a colorless oil. The spectroscopic data were identical to those of the literature.[102]

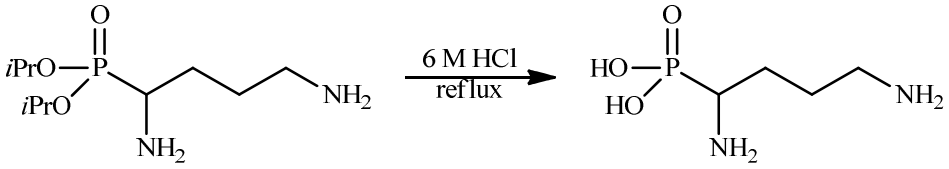
(±)-Diisopropyl 1,4-diaminobutylphosphonate [(±)-99a]



(±)-**99** (±)-**99a**

Diisopropyl 1,4-diazidobutylphosphonate [(±)-**99**] (0.135 g, 0.44 mmol) was dissolved in ethanol (10 ml) with 32 mg 10% Pd/C and 3 drops of 32% HCl in a hydrogenation flask. The hydrogenation was performed at 50 psi overnight. The reaction mixture was filtered through filter paper and washed with ethanol. The filtrate was concentrated under reduced pressure and the residue was used for the next step without further purification.

(±)-1,4-Diaminobutyphosphonic acid [(±)-100]

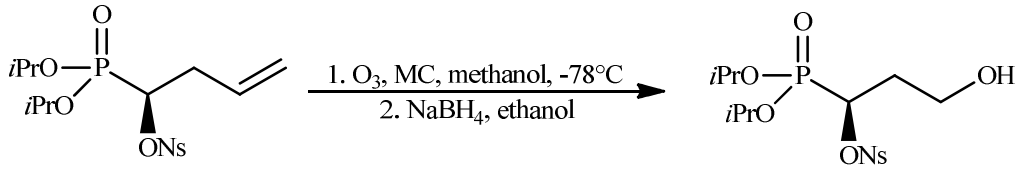


(±)-**99a** (±)-**100**

1,4-Diaminobutylphosphonate (±)-**99a** was dissolved in 6 M HCl (5 ml) and refluxed for 4 h. After cooling the solution was concentrated under reduced pressure. The NMR spectroscopic data are identical to those of the literarture.[102]

3.2.4. Synthesis of (*R*)-(isoxazolidin-3-yl)phosphonic acid

(*S*)-(+)-3-Hydroxy-1-(4-nitrobenzenesulfonyloxy)-propylphosphonate [(*S*)-101]



(*S*)-**92** (*S*)-**101**

Nosylate (*S*)-**92** (0.993 g, 2.36 mmol) was dissolved in a mixture of methanol (5 ml) and MC (5 ml). Ozonolysis was performed at –78 °C for 5 min until the solution turned blue. $NaBH_4$ (0.107 g, 2.83 mmol, dissolved in 1 ml ethanol) was added quickly and the solution was stirred for 2.5 h at RT. The reaction mixture was concentrated under reduced pressure. Water (10 ml) and EtOAc (10 ml) were added to the residue. The organic layer was separated and the aqueous one was extracted with EtOAc (2 x 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (1:1), R_f = 0.17] and crystallization (MC/hexanes) to yield 3-hydroxypropylphosphonate (*S*)-**101** (0.912 g, 91%) as colorless crystals. Mp. 93 °C.

$[\alpha]_D^{20}$ = +25.45 (*c* = 1.15, acetone).

IR (ATR): ν = 3358, 2985, 1608, 1534, 1375, 1350, 1242, 1186, 988.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.40-8.34 (m, 2H, H_{arom}), 8.19-8.14 (m, 2H, H_{arom}), 5.09 (td, *J* = 9.2 Hz, *J* (^{31}P) = 4.5 Hz, 1H, CHP), 4.68 (2 oct overlapping to a dec, *J* = 6.3 Hz, 2H, $\underline{CH}(CH_3)_2$), 3.84-3.65 (m, 2H, $\underline{CH_2}OH$), 2.55 (bs, 1H, OH), 2.22-1.93 (m, 2H, $\underline{CH_2}CH_2OH$), 1.28 (d, *J* = 6.3 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.25 (d, *J* = 6.3 Hz, 6H, 2 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 150.83 (s, 1C, C_{arom}), 142.31 (s, 1C, C_{arom}), 129.46 (s, 2C, C_{arom}), 124.23 (s, 2C, C_{arom}), 75.06 (d, J(^{31}P) = 172.8 Hz, 1C, CHP), 72.64 (d, J(^{31}P) = 6.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.58 (d, J(^{31}P) = 6.5 Hz, 1C, $\underline{CH}(CH_3)_2$), 57.25 (d, J(^{31}P) = 10.3 Hz, 1C, $\underline{CH_2}OH$), 33.48 (s, 1C, $\underline{CH_2}CH_2OH$), 24.03 (d, J(^{31}P) = 5.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.98 (d, J(^{31}P) = 5.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.87 (d, J(^{31}P) = 5.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.73 (d, J(^{31}P) = 4.9 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

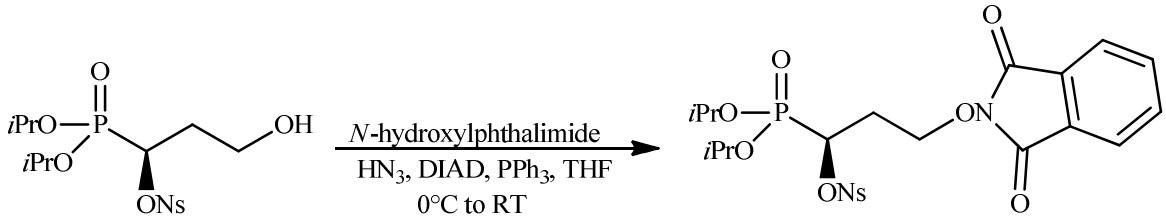
^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 16.74 (s, P=O).

Elemental analysis calculated for $C_{15}H_{24}NO_9PS$ (425.39): C: 42.35, H: 5.69, N: 3.29; found: C: 42.40, H: 5.72, N: 3.29.

Similarly, nosylate (±)-**92** (0.246 g, 0.58 mmol) was converted to hydroxypropylphosphonate(±)-**101** (0.214 g, 85%) as colorless crystals. Mp. 103 °C.

The NMR spectroscopic data of (±)- and (*S*)-**101** are identical.

(*S*)-(+)-Diisopropyl 1-(4-nitrobenzenesulfonyloxy)-3-phthalimidooxypropylphosphonate [(*S*)-102]



(*S*)-**101** (*S*)-**102**

3-Hydroxypropylphosphonate (*S*)-**101** (1.572 g, 3.70 mmol), *N*-hydroxyphthalimide (0.633 g, 3.88 mmol) and triphenylphosphine (1.260 g, 4.80 mmol) were dissolved in dry THF (15 ml) under argon. DIAD (0.973 g, 1.0 ml, 4.81 mmol) was added dropwise at 0 °C and the solution was slowly warmed up to RT and stirred overnight. The solution was then concentrated under reduced pressure and purified by flash chromatography [hexanes/EtOAc (3:2), R_f = 0.33 for hexanes/EtOAc (1:1)] to yield phthalimidooxyphosphonate (*S*)-**102** (1.766 g, 84%) as a colorless foam.

$[\alpha]_D^{20}$ = +15.14 (*c* = 0.35, acetone).

IR (ATR): ν = 1732, 1532, 1374, 1249, 1256, 1185, 982.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.39-8.34 (m, 2H, H_{arom}), 8.25-8.20 (m, 2H, H_{arom}), 7.86-7.80 (m, 2H, H_{arom}), 7.77-7.72 (m, 2H, H_{arom}), 5.31 (td, *J* = 9.1 Hz, *J* (^{31}P) = 4.3 Hz, 1H, CHP), 4.78-4.61 (m, 2H, $\underline{CH}(CH_3)_2$), 4.42-4.24 (m, 2H, CH_2ON), 2.47-2.35 (m, 1H,

$\underline{CH_2}$CHP), 2.27-2.13 (m, 1H, $\underline{CH_2}$CHP), 1.31 (d, *J* = 6.3 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.29 (d, *J* = 6.3 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.28 (d, *J* = 6.1 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.27 (d, *J* = 6.1 Hz, 3H, CH($\underline{CH_3}$)$_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 163.45 (s, 2C, 2 x C=O), 150.82 (s, 1C, C_{arom}), 142.20 (s, 1C, C_{arom}), 134.63 (s, 2C, C_{arom}), 129.73 (s, 2C, C_{arom}), 128.85 (s, 2C, C_{arom}), 124.22 (s, 2C, C_{arom}), 123.63 (s, 2C, C_{arom}), 74.19 (d, J(^{31}P) = 172.2 Hz, 1C, CHP), 73.61 (d, J(^{31}P) = 10.7 Hz, 1C, CH_2ON), 72.72 (d, J(^{31}P) = 4.9 Hz, 1C, $\underline{CH}$(CH_3)$_2$), 72.64 (d, J(^{31}P) = 4.5 Hz, 1C, $\underline{CH}$(CH_3)$_2$), 29.75 (s, 1C, $\underline{CH_2}$CHP), 24.05 (d, J(^{31}P) = 6.3 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 24.01 (d, J(^{31}P) = 6.6 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.87 (d, J(^{31}P) = 5.0 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.73 (d, J(^{31}P) = 4.8 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$).

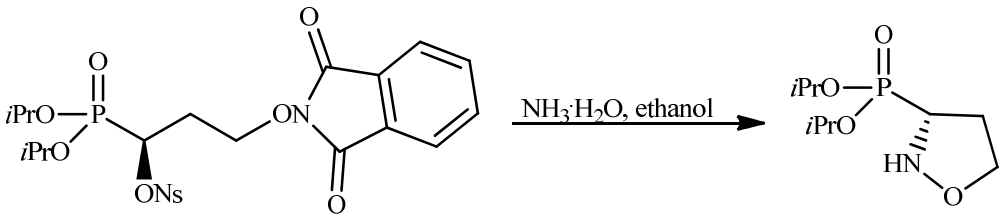
^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 15.42 (s, P=O).

HR-MS (EI, 70 eV): m/z calculated for $C_{23}H_{27}N_2O_{11}PSNa$ $[M + Na]^+$ = 593.0966, found: 593.0961.

Similarly, hydroxypropylphosphonate(±)-**101** (1.260 g, 2.96 mmol) was converted to phthalimidooxyphosphonate(±)-**102** (1.399 g, 83%) as a colorless foam.

The NMR spectroscopic data of (±)- and (*S*)-**102** are identical.

(*R*)-(+)-Diisopropyl (isoxazolidin-3-yl)phosphonate [(*R*)-103]



(*S*)-**102** (*R*)-**103**

Nosylate (*S*)-**102** (0.929 g, 1.63 mmol) was dissolved in ethanol (5 ml). $NH_3 \cdot H_2O$ (2 ml, 25% in water) was added at 0 °C and the solution was slowly warmed up to RT and stirred overnight. A white precipitate formed. The organic phase was removed and a saturated aqueous solution of $NaHCO_3$ (5 ml) as well as MC (5 ml) were added. The organic layer was separated and the aqueous one was extracted with MC (2 x 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was

purified by flash chromatography [hexanes/EtOAc (1:2), R_f = 0.17] to yield the cyclic aminooxyphosphonate (*R*)-**103** (0.279 g, 72%) as a colorless oil.

$[\alpha]_D^{20}$ = +14.27 (*c* = 1.10, acetone).

IR (ATR): ν = 2980, 1458, 1379, 1233, 1108, 982.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 4.82-4.68 (m, 2H, $\underline{CH}(CH_3)_2$), 3.96 (td, $J(^{31}P)$ = 7.7 Hz, J_{AB} = 6.6 Hz, 1H, CH_2O), 3.79 (td, $J(^{31}P)$ = 8.3 Hz, J_{AB} = 6.6 Hz, 1H, CH_2O), 3.45 (q, *J* = 9.0 Hz, 1H, CHP), 3.15 (very bs, 1H, NH), 2.50-2.29 (m, 2H, $\underline{CH_2}CHP$), 1.33 (d, *J* = 6.2 Hz, 9H, 3 x $CH(\underline{CH_3})_2$), 1.33 (d, *J* = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$.

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 71.48 (d, $J(^{31}P)$ = 6.9 Hz, 2C, 2 x $\underline{CH}(CH_3)_2$), 70.04 (d, $J(^{31}P)$ = 8.0 Hz, 1C, CH_2O), 53.60 (d, $J(^{31}P)$ = 155.6 Hz, 1C, CHP), 32.27 (s, 1C, $\underline{CH_2}CHP$), 24.09 (d, $J(^{31}P)$ = 3.5 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.06 (d, $J(^{31}P)$ = 3.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.97 (d, $J(^{31}P)$ = 4.8 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.95 (d, $J(^{31}P)$ = 4.9 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

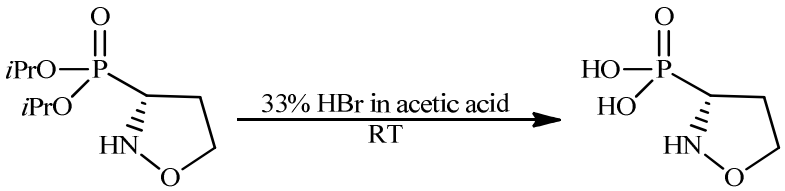
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 22.71 (s, P=O).

Elemental analysis calculated for $C_9H_{20}NO_4P$ (237.23): C: 45.57, H: 8.50, N: 5.90; found: C: 45.64, H: 8.57, N: 5.74.

Similarly, phthalimidooxyphosphonate (±)-**102** (0.229 g, 0.40 mmol) was converted to cyclic aminooxyphosphonate (±)-**103** (0.062 g, 65%) as colorless crystals. Mp. 48-50 °C (hexanes).

The NMR spectroscopic data of (±)- and (*R*)-**103** are identical.

(*R*)-(+)-(Isoxazolidin-3-yl)phosphonic acid [(*R*)-104]



(*R*)-**103** (*R*)-**104**

Diisopropyl (isoxazolidin-3-yl)phosphonate [(*R*)-**103**] (0.122 g, 0.51 mmol) was dissolved in HBr (4 ml, 33% in AcOH) under argon. The solution was stirred at RT overnight. Then it was freeze-dried overnight. The residue was purified by ion exchange [Dowex® 50W8, H^+, H_2O] and crystallization (water/ethanol) to yield phosphonic acid (*R*)-**104** (0.072 g, 81%) as colorless crystals. Mp. 180 °C (decomposition).

$[\alpha]_D^{20}$ = +6.35 (c = 0.63, water).

IR (ATR): ν = 2230 (very broad), 1448, 1256, 1228, 1292, 1162, 1128, 1087, 1018, 995.

^{1}H NMR (400.27 MHz, D_2O): δ = 4.42 (td, J_{AB} = 8.0 Hz, $J(^{31}P)$ = 4.1 Hz, 1H, CH_2O), 4.28 (q, = 7.7 Hz, 1H, CH_2O), 3.92 (q, J = 8.9 Hz, 1H, CHP), 2.87-2.76 (m, 1H, $\underline{CH_2}$CHP), 2.65-2.50 (m, 1H, $\underline{CH_2}$CHP).

^{13}C NMR (100.65 MHz, D_2O): δ = 71.70 (d, $J(^{31}P)$ = 8.3 Hz, 1C, CH_2O), 57.03 (d, $J(^{31}P)$ = 140.1 Hz, 1C, CHP), 30.93 (s, 1C, $\underline{CH_2}$CHP).

^{31}P NMR (162.03 MHz, D_2O): δ = 8.49 (s, P=O).

Elemental analysis calculated for $C_3H_8NO_4P$ (153.07): C: 23.54, H: 5.27, N: 9.15; found: C: 23.56, H: 5.05, N: 8.96.

The NMR spectroscopic data were identical to those of the literature.[50]

Similarly, cyclic aminooxyphosphonate (±)-**103** (0.204 g, 0.86 mmol) was converted to phosphonic acid (±)-**104** as colorless crystals.

The NMR spectroscopic data of (±)- and (*R*)-**103** are identical.

Hydrolysis (*R*)-103 with 6 M HCl

Diisopropyl (isoxazolidin-3-yl)phosphonate [(*R*)-**103**] (0.089 g, 0.38 mmol) was dissolved in 6 M HCl (4 ml) and refluxed for 2.5 h. The solution was concentrated under reduced pressure. The residue was kept in a vacuum desiccator for 18 h over KOH. The ^{31}P NMR spectrum showed that the residue was a mixture of the desired product (43 mol%), phosphate (32

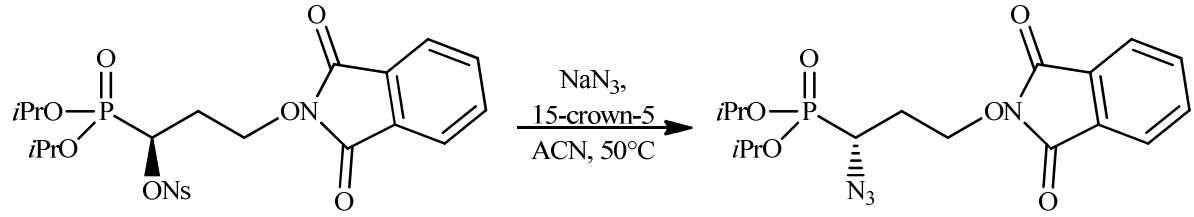
mol%) and the phosphonic acid with an opened N-O bond (18 mol%). The residue was purified by ion exchange chromatography [Dowex® 50WX8, H^+, cation exchange resin, H_2O], but it was not possible to separate the cyclic aminooxyphosphonic acid (*R*)-**125** and the phosphonic acid with an opened N-O bond.

Hydrolysis (*R*)-103 with TMSBr

Diisopropyl (isoxazolidin-3-yl)phosphonate [(*R*)-**103**] (0.204 g, 0.86 mmol) was dissolved in dry 1,2-dichloroethane (5 ml) under argon. TMSBr (0.789 g, 0.68 ml, 5.15 mmol) and allyltrimethylsilane (0.295 g, 0.41 ml, 2.58 mmol) were added and the solution was stirred at 50 °C overnight, before it was concentrated under reduced pressure. The ^{31}P NMR spectrum showed that the desired product was the main product, but a lot of byproducts were also present. The residue was purified by ion exchange [Dowex® 50WX8, H^+ cation exchange resin, H_2O] to yield the cyclic aminooxyphosphonic acid (*R*)-**104**, but the yield was quite low (15%).

3.2.5. Synthesis of (*R*)-1-amino-3-(aminooxy)propylphosphonic acid

(*R*)-(–)-Diisopropyl 1-azido-3-(phthalimidooxy)propylphosphonate [(*R*)-109]



(*S*)-**102** (*R*)-**109**

Nosylate (*S*)-**102** (1.300 g, 2.28 mmol) and NaN_3 (0.444 g, 6.82 mmol) were dissolved in ACN (30 ml) under argon. 15-Crown-5 (0.497 g, 0.45 ml, 2.26 mmol) was added and the solution was then stirred at 50 °C overnight. The reaction mixture was concentrated under reduced pressure and water (20 ml) as well as MC (20 ml) were added to the residue. The organic layer was separated and the aqueous one was extracted with MC (2 x 15 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (1:1), R_f= 0.25] to yield azide (*R*)-**109** (0.734g, 78%) as a colorless oil.

$[\alpha]_D^{20} = -46.77$ (c = 2.20, acetone).

IR (ATR): ν = 2104, 1733, 1468, 1388, 1374, 1258, 1236, 1187, 1129, 1105, 981.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.86-7.80 (m, 2H, H_{arom}), 7.76-7.70 (m, 2H, H_{arom}), 4.87-4.73 (m, 2H, $\underline{CH}(CH_3)_2$), 4.47-4.40 (m, 1H, CH_2ON), 4.29 (td, J = 9.8 Hz, J (^{31}P) = 3.9 Hz, 1H, CH_2ON), 4.09 (td, J = 11.3 Hz, J (^{31}P) = 3.2 Hz, 1H, CHP), 2.37-2.24 (m, 1H, $\underline{CH_2}CHP$), 1.93-1.79 (m, 1H, $\underline{CH_2}CHP$), 1.40-1.33 (overlapping d, 12H, 4 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 163.46 (s, 2C, 2 x C=O), 134.56 (s, 2C, C_{arom}), 128.90 (s, 2C, C_{arom}), 123.62 (s, 2C, C_{arom}), 74.37 (d, J (^{31}P) = 13.4 Hz, 1C, CH_2ON), 71.96 (d, J (^{31}P) = 7.2 Hz, 2C, 2 x $\underline{CH}(CH_3)_2$), 54.11 (d, J (^{31}P) = 159.8 Hz, 1C, CHP), 28.03 (s, 1C, $\underline{CH_2}CHP$), 24.18 (d, J(^{31}P) = 5.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.14 (d, J(^{31}P) = 5.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.99 (d, J(^{31}P) = 4.7 Hz, 2C, 2 x $CH(\underline{CH_3})_2$).

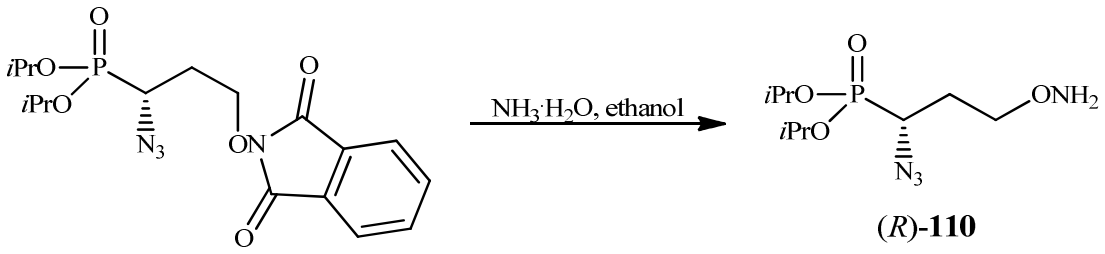
^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 19.76 (s, P=O).

HR-MS (EI, 70 eV): m/z calculated for $C_{17}H_{24}N_4O_6P$ $[M + H]^+$ = 411.1428, found: 411.1424.

Similarly, nosylate (±)-**102** (1.370 g, 2.40 mmol) was converted to azide (±)-**109** (0.808 g, 82%) as a colorless oil.

The NMR spectroscopic data of (±)- and (*R*)-**109** are identical.

(*R*)-diisopropyl 3-aminooxy-1-azidopropylphosphonate [(*R*)-110]

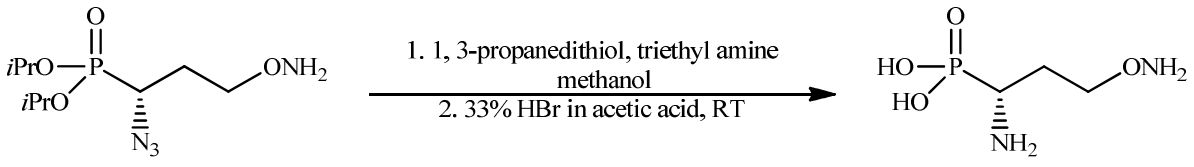


(*R*)-**109** (*R*)-**110**

1-Azido-3-(phthalimidooxy)propylphosphonate [(*R*)-**109**] (0.437 g, 1.06 mmol) was dissolved in ethanol (3 ml). $NH_3 \cdot H_2O$ (4 ml, 25% in water) was added at RT and the solution was stirred for 72 h. The reaction mixture was concentrated under reduced pressure and water (10 ml) as well as MC (10 ml) were added. The organic layer was separated and the aqueous layer was extracted with MC (2 x 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was used for the next step without purification. The crude product (0.248 g, 84%) was found to be a light yellow oil.

Similarly, azide (±)-**109** (0.253 g, 0.62 mmol) was converted to 3-aminooxylphosphonate (±)-**110** (0.150 g, 87%) as colorless crystals.

(*R*)-1-Amino-3-(aminooxy)propylphosphonic acid [(*R*)-111]



(*R*)-**110** (*R*)-**111**

3-Aminooxy-1-azidopropylphosphonate [(*R*)-**110**] (0.248 g, 0.88 mmol) was dissolved in methanol (4 ml) under argon. 1,3-Propanedithiol (0.288 g, 0.26 ml, 2.67 mmol) and triethylamine (0.268 g, 0.37 ml, 2.66 mmol) were added to the solution and it was stirred at RT overnight. The solvent was removed under reduced pressure (10 mm Hg). The residue was then dissolved in 33% HBr (5 ml) in acetic acid under argon. The solution was stirred at RT overnight and then concentrated under reduced pressure. The residue was purified by ion exchange chromatography [Dowex® 1X8, OAc^-, anion exchange resin, H_2O, TLC: water/isopropanol/ammonia/water (6:3:1), R_f = 0.33] and crystallization (water) to yield aminooxyphosphonic acid (*R*)-**111** (0.080 g, 53%) as colorless crystals. Mp. 226-229 °C.

IR (ATR): ν = 1599, 1547, 1057, 976, 921.

^{1}H NMR (400.27 MHz, D_2O): δ = 4.27-4.15 (m, 2H, CH_2O), 3.43 (ddd, J = 13.9 Hz, J = 7.8 Hz, J = 6.0 Hz, 1H, CHP), 2.30-2.17 (m, 1H, $\underline{CH_2}$CHP), 2.15-2.00 (m, 1H, $\underline{CH_2}$CHP).

^{13}C NMR (100.65 MHz, D_2O): δ = 71.81 (d, $J(^{31}P)$ = 6.6 Hz, 1C, CH_2O), 45.71 (d, $J(^{31}P)$ = 146.5 Hz, 1C, CHP), 26.79 (s, 1C, $\underline{CH_2}$CHP).

^{31}P NMR (162.03 MHz, D_2O): δ = 13.45 (s, P=O).

Elemental analysis calculated for $C_3H_{11}N_2O_4P$ (170.10): C: 21.18, H: 6.52, N: 16.47; found: C: 20.87, H: 5.94, N: 15.56.

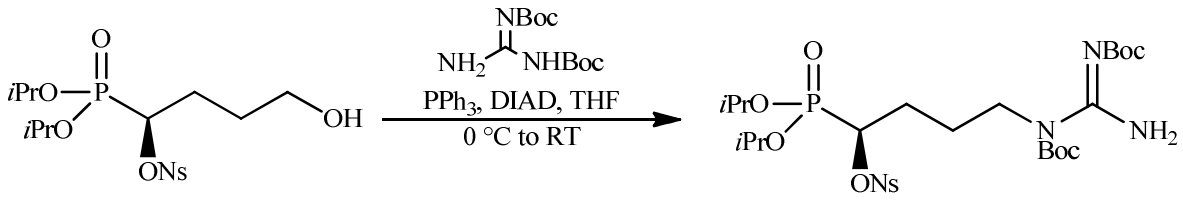
HR-MS (EI, 70 eV): m/z calculated for $C_3H_{12}N_2O_4P$ $[M + H]^+$ = 171.0529, found: 171.0533.

Similarly, 3-aminooxyphosphonate (±)-**110** (0.254 g, 1.00 mmol) was converted to aminophosphonic acid (±)-**111** as colorless crystals. Mp. 223-224 °C (H_2O).

The NMR spectroscopic data of (±)- and (*R*)-**111** are identical.

3.2.6. Synthesis of (*R*)-(1-amino-4-guanidinobutyl)phosphonic acid

(*S*)-Diisopropyl 4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-1-(4-nitrobenzenesulfonyl-oxy)butylphosphonate [(*S*)-116]



(*S*)-**92** (*S*)-**116**

Diisopropyl 4-hydroxy-1-(4-nitrobenzenesulfonyloxy)butylphosphonate [(*S*)-**92**] (2.111 g, 4.50 mmol), 1,3-bis(*tert*-butoxylcarbonyl)guanidine (1.750 g, 6.75 mmol) and triphenylphosphine (1.769 g, 6.74 mmol) were dissolved in dry THF (20 ml) under argon. DIAD (1.440 g, 1.4 ml, 7.12 mmol) was added dropwise at 0 °C. The solution was slowly warmed up to RT and stirred overnight. It was then concentrated under reduced pressure and purified by flash chromatography [hexanes/EtOAc (2:1), R_f = 0.27)] to yield guanidinophosphonate (*S*)-**116** (2.587 g, 84%) as a colorless foam.

IR (Si): ν = 3385, 2982, 1714, 1611, 1536, 1370, 1274, 1254, 1187, 1148, 1100, 993.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 9.32 (bs, 1H, NH_2), 9.18 (bs, 1H, NH_2), 8.38-8.33 (m, 2H, H_{arom}), 8.19-8.13 (m, 2H, H_{arom}), 4.96-4.88 (m, 1H, CHP), 4.66 (oct, J = 6.3 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.59 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 3.96-3.82 (m, 2H, $\underline{CH_2}$NBoc), 1.90-1.63 (m, 4H, $\underline{CH_2}$CHP + $\underline{CH_2}CH_2$NBoc), 1.50 (s, 9H, Boc), 1.47 (s, 9H, Boc), 1.264 (d, J = 6.2 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.26 (d, J = 6.2 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.23 (d, J = 6.3 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.21 (d, J = 6.2 Hz, 3H, CH($\underline{CH_3}$)$_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 163.73 (s, 1C, C=N), 160.53 (s, 1C, C=O), 154.85 (s, 1C, C=O), 150.67 (s, 1C, C_{arom}), 142.72 (s, 1C, C_{arom}), 129.42 (s, 2C, C_{arom}), 124.16 (s, 2C, C_{arom}), 84.02 (s, 1C, $\underline{C}(CH_3)_3$), 78.75 (s, 1C, $\underline{C}(CH_3)_3$), 78.13 (d, J(^{31}P) = 171.5 Hz, 1C, CHP), 72.28 (d, J(^{31}P) = 6.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.21 (d, J(^{31}P) = 6.7 Hz, 1C, $\underline{CH}(CH_3)_2$), 43.58 (s, 1C, $\underline{CH_2}$NBoc), 28.29 (s, 3C, 3 x C($\underline{CH_3}$)$_3$), 27.94 (s, 3C, 3 x C($\underline{CH_3}$)$_3$), 27.63 (s, 1C, $\underline{CH_2}$CHP), 24.88 (d, J(^{31}P) = 10.2 Hz, 1C, $\underline{CH_2}CH_2$N), 24.05 (d, J(^{31}P) = 3.6 Hz, 1C, 1 x

CH($\underline{CH_3}$)$_2$), 23.96 (d, J(^{31}P) = 4.1 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.92 (d, J(^{31}P) = 5.2 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.70 (d, J(^{31}P) = 4.9 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$).

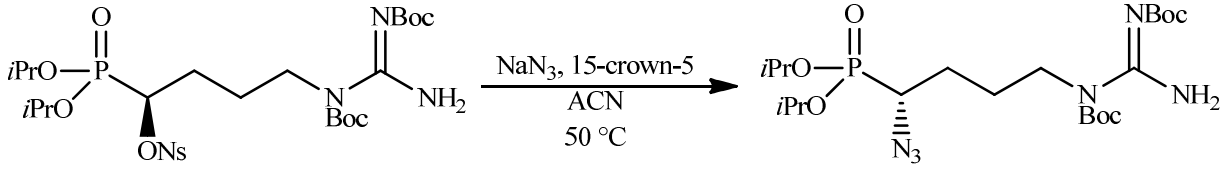
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 15.88 (s, P=O).

Elemental analysis calculated for $C_{27}H_{45}N_4O_{12}PS$ (680.70): C: 47.64, H: 6.66, N: 8.23; found: C: 47.62, H: 6.74, N: 8.10.

Similarly, 4-hydroxylphosphonate (±)-**92** (3.976 g, 9.05 mmol) was converted to guanidinophosphonate (±)-**116** (5.293 g, 86%) as a colorless foam.

The NMR spectroscopic data of (±)- and (*S*)-**116** are identical.

(*R*)-Diisopropyl 4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-1-azidobutylphosphonate [(*R*)-117]



(*S*)-**116** (*R*)-**117**

Diisopropyl 4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-1-(4-nitrobenzenesulfonyloxy)butyl-phosphonate [(*S*)-**116**] (1.580 g, 2.32 mmol) and NaN_3 (0.452 g, 6.94 mmol) were dissolved in ACN (16 ml). 15-Crown-5 (0.511 g, 0.46 ml, 2.32 mmol) was added and the mixture was stirred at 50 °C for 6.5 h and then concentrated under reduced pressure. Water (20 ml) and MC (20 ml) were added and the organic layer was separated. The aqueous layer was extracted with MC (2 x 15 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (2:1), R_f = 0.26] to yield azide (*R*)-**117** (1.027 g, 85%) as a colorless oil.

IR (Si): ν = 3385, 2982, 2105, 1714, 1612, 1369, 1250, 1149, 991, 913.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 9.34 (bs, 1H, NH_2), 9.19 (bs, 1H, NH_2), 4.83-4.68 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 4.00-3.86 (m, 2H, $\underline{CH_2}$NBoc), 3.46 (td, J = 11.6 Hz, J (^{31}P) = 3.2 Hz, 1H,

CHP), 1.91-1.54 (m, 4H, $\underline{CH_2}CHP$ + $\underline{CH_2}CH_2NBoc$), 1.50 (s, 9H, Boc), 1.46 (s, 9H, Boc), 1.33 (d, J = 6.2 Hz, 9H, 3 x $CH(\underline{CH_3})_2$), 1.32 (d, J = 6.0 Hz, 3H, $CH(\underline{CH_3})_2$).

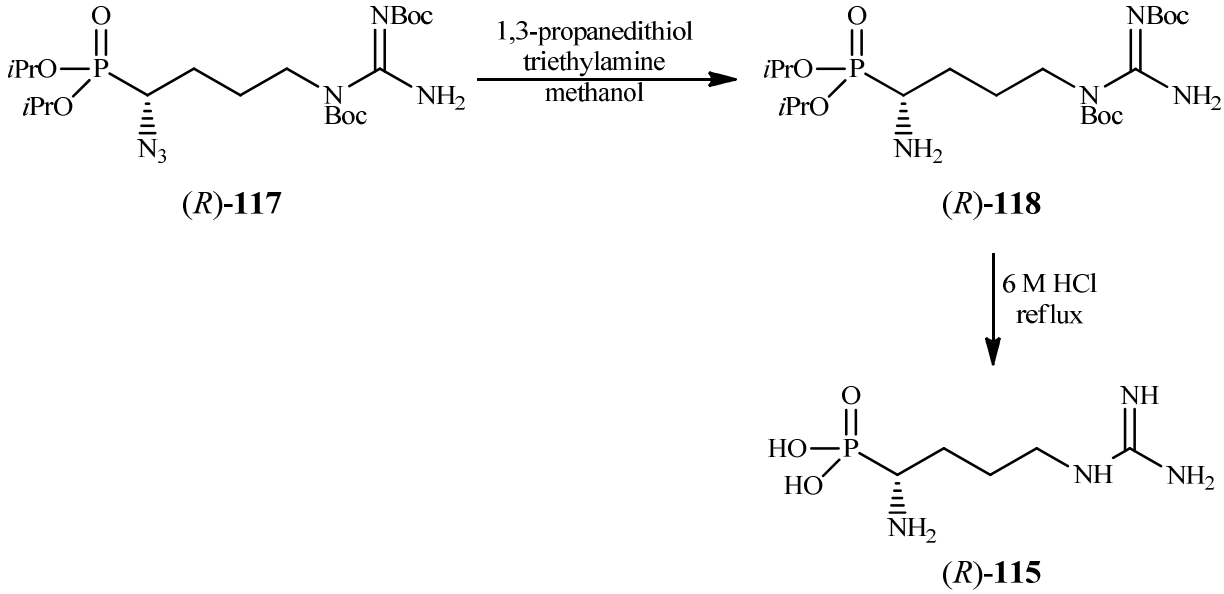
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 163.76 (s, 1C, C=N), 160.49 (s, 1C, C=O), 154.85 (s, 1C, C=O), 154.93 (s, 1C, CNO_2), 83.91 (s, 1C, $\underline{C}(CH_3)_3$), 78.75 (s, 1C, $\underline{C}(CH_3)_3$), 71.74 (d, $J(^{31}P)$ = 7.9 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.66 (d, $J(^{31}P)$ = 7.5 Hz, 1C, $\underline{CH}(CH_3)_2$), 57.33 (d, $J(^{31}P)$ = 167.0 Hz, 1C, CHP), 43.67 (s, 1C, CH_2NBoc), 28.26 (s, 3C, 3 x $C(\underline{CH_3})_3$), 28.00 (s, 3C, 3 x $C(\underline{CH_3})_3$), 25.92 (d, $J(^{31}P)$ = 13.5 Hz, 1C, $\underline{CH_2}CH_2N$), 25.75 (s, 1C, $\underline{CH_2}CHP$), 24.15 (d, $J(^{31}P)$ = 3.1 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 23.99 (d, $J(^{31}P)$ = 5.4 Hz, 2C, 2 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 21.41 (s, P=O).

Similarly, 1-(4-nitrobenzenesulfonyloxy)butylphosphonate (±)-**116** (0.138 g, 0.20 mmol) was converted to 1-azidobutylphosphonate (±)-**117** (0.083 g, 79%) as a colorless foam.

The NMR spectroscopic data of (±)- and (*R*)-**117** are identical.

(*R*)-(1-Amino-4-guanidinobutyl)phosphonic acid [(*R*)-115]



(*R*)-**117** (*R*)-**118** (*R*)-**115**

Diisopropyl 4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-1-azidobutylphosphonate [(*R*)-**117**] (1.496 g, 2.87 mmol) was dissolved in methanol (15 ml) under argon. 1,3-Propanedithiol (0.934 g, 0.86 ml, 8.63 mmol) and triethylamine (0.875 g, 1.2 ml, 8.65 mmol) were added to the solution and it was stirred at RT overnight. The solvent was removed at reduced pressure

at RT. Water (20 ml) was added and the organic phase was separated. The aqueous layer was extracted with MC (2 x 20 ml). The combined organic layers were concentrated under reduced pressure and the residue was purified by flash chromatography [MC/EtOH (20:1), R_f = 0.63] to yield aminophosphonate (*R*)-**118** (1.174 g, 83%) as a colorless oil. Part of this oil (0.524 g, 1.06 mmol) was dissolved in 6 M HCl (10 ml) and refluxed for 4 h. The solution was freeze-dried overnight and purified by crystallization (water/ethanol, + HCl) to yield the aminophosphonic acid hydrochloride analog (*R*)-**115** of arginine (0.141 g, 54%) as a colorless gum, which could not be crystallized from water/ethanol.

IR (Si): ν = 3331, 3154, 1668, 1620, 1529, 1481, 1279, 1141, 935.

^{1}H NMR (400.13 MHz, D_2O): δ = 3.34 (q, J = 6.6 Hz, 1H, CHP), 3.31 (t, J = 6.4 Hz, 2H, CH_2N), 2.06-1.92 (m, 1H, $\underline{CH_2}CHP$), 1.90-1.74 (m, 3H, $\underline{CH_2}CHP$ + $\underline{CH_2}CH_2N$).

^{13}C NMR (100.61 MHz, D_2O): δ = 157.17 (s, 1C, C=N), 49.04 (d, $J(^{31}P)$ = 143.0 Hz, 1C, CHP), 40.92 (s, 1C, $\underline{CH_2}N$), 26.12 (d, $J(^{31}P)$ = 1.3 Hz, 1C, $\underline{CH_2}CHP$), 25.37 (d, $J(^{31}P)$ = 7.9 Hz, 1C, $\underline{CH_2}CH_2N$).

^{31}P NMR (161.98 MHz, D_2O): δ = 14.08 (s, P=O).

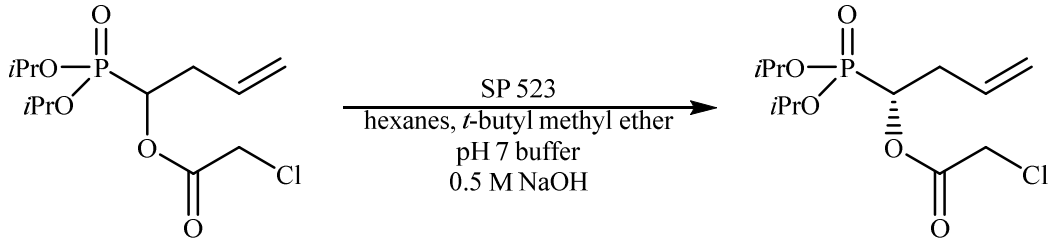
Elemental analysis calculated for $C_5H_{18}ClN_4O_4P$ (264.65): C: 22.69, H: 6.86, N: 21.17, Cl: 13.40; found: C: 22.35, H: 6.62, N: 20.43, Cl: 13.46.

Similarly, 1-azidobutylphosphonate (±)-**117** (0.841 g, 1.62 mmol) was converted to phosphonic acid (±)-**115** (0.183 g, 46%) as colorless crystals. Mp. 157-158 °C.

The spectroscopic data of (±)- and (*R*)-**115** are identical.

3.2.7. Synthesis of (*R*)-3-hydroxy-3-phosphonopropanoic acid

(*R*)-Diisopropyl 1-chloroacetoxy-3-butenylphosphonate [(*R*)-81]

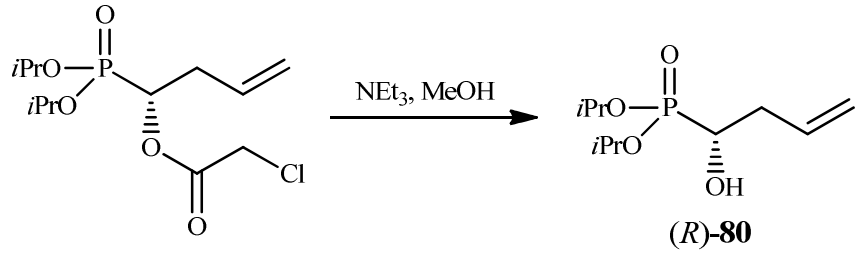


(±)-**81** (*R*)-**81**

Diisopropyl 1-chloroacetoxy-3-butenylphosphonate [(±)-**81**] (3.677 g, 11.76 mmol, already once enzymatically hydrolyzed with the same enzyme with a conversion rate of 42%) was dissolved in a mixture of hexanes (20 ml), *tert*-butyl methyl ether (20 ml) and phosphate buffer [50 mmol, pH 7; preparation of 500 ml of this buffer: 3.4 g (25 mmol) KH_2PO_4 was dissolved in 300 ml H_2O, adding 1 M NaOH to adjust pH to 7, followed by addition of water to a final volume of 500 ml, and then by autoclaving it at 121 °C for 20 min]. 0.5 M NaOH was added by an autotitrator to bring pH to 7.0. Lipase from *Thermomyces lanuginosus* (≥100,000 U/g, 0.2 ml, from Aldrich) was added, pH again adjusted to 7.0, and kept there by automatic addition of base to the vigorously stirred mixture overnight. The enzymatic hydrolysis was stopped by adding 2 M HCl to the solution until pH 4 when the conversion rate reached 16% (calculated from the used amount of 0.5 M NaOH). The organic phase was removed and the aqueous layer was then extracted with EtOAc (3 x 60 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (1:1), R_f = 0.27] to yield chloroacetate (*R*)-**81** (2.314 g, 63%) as a colorless oil.

The optical purity of the ester was estimated by hydrolyzing a sample of (*R*)-**81** and converting it to (*R*)-Mosher ester by general procedure A.

(*R*)-(–)-Diisopropyl 1-hydroxy-3-butenylphosphonate [(*R*)-80]



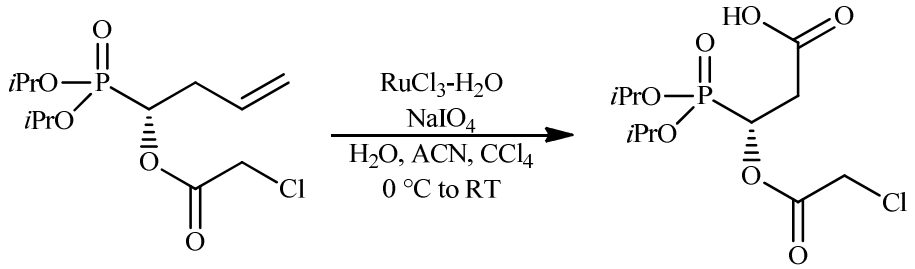
(*R*)-**81** (*R*)-**80**

Diisopropyl 1-chloroacetoxy-3-butenylphosphonate (*R*)-**81** (0.274 g, 0.88 mmol) was dissolved in methanol (2.5 ml). Triethylamine (0.106 g, 0.14 ml, 1.05 mmol) was added. The solution was stirred overnight at RT and quenched with 2 M HCl (1.5 ml). Water (10 ml) and MC (10 ml) were added and the organic layer was separated. The aqueous layer was extracted with MC (2 x 10 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [EtOAc, $R_f = 0.36$] to yield 1-hydroxyphosphonate (*R*)-**80** (0.191 g, 92%) as an oil.

$[\alpha]_D^{20} = -22.38$ ($c = 0.72$, acetone).

An analytical sample of the hydroxyphosphonate (20 mg) was converted to the (*R*)-Mosher ester according to general procedure A; *ee* ≥99%, ^{31}P NMR (161.98 MHz, $CDCl_3$): $\delta = 15.82$ for (*R*)-**80**, no signal of (*S*)-**80** was observed.

(*R*)-(–)-3-(Chloroacetoxy)-3-(diisopropoxyphosphinyl)propanoic acid [(*R*)-122]



(*R*)-**81** (*R*)-**122**

Diisopropyl 1-chloroacetoxy-3-butenylphosphonate **[**(*R*)-**81]** (0.320 g, 1 mmol) was dissolved in a mixture of H_2O (3 ml), ACN (1.6 ml) and CCl_4 (1.6 ml). $RuCl_3 \cdot H_2O$ (13 mg) and $NaIO_4$ (1.280 g, 5.98 mmol) were added to the mixture cooled to 0 °C. The reaction temperature was allowed to rise slowly to RT. After 5 h the organic phase was removed and a saturated aqueous solution of $NaHCO_3$ (5 ml) as well as MC (5 ml) were added. The aqueous layer was

separated and the organic one was extracted with water (1 x 10 ml). 2 M HCl was added to the combined aqueous layers until pH <2. The aqueous layer was extracted with MC (2 x 5 ml), washed with brine (5 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by crystallization (diisopropyl ether/MC) to yield carboxylic acid (*R*)-**122** (0.264 g, 80%) as colorless crystals. Mp. 49-50 °C.

$[\alpha]_D^{20} = -37.16$ ($c = 0.81$, acetone).

IR (Si): ν = 2985, 1758, 1223, 1158, 999, 913.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.45 (bs, 1H, COOH), 5.66 (ddd, J = 10.2 Hz, J = 8.8 Hz, J = 3.7 Hz, 1H, CHP), 4.76 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.75 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.08 (s, 2H, CH_2Cl), 2.91 (A part of ABX-sys, J_{AB} = 17.1 Hz, J = 6.8 Hz, J = 3.7 Hz, 1H, $\underline{CH_2}COOH$), 2.82 (B part of ABX-sys, J_{AB} = 17.1 Hz, J = 10.1 Hz, J = 8.8 Hz, 1H, $\underline{CH_2}COOH$), 1.33 (d, J = 6.1 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.325 (d, J = 6.1 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.32 (d, J = 6.2 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.31 (d, J = 6.1 Hz, 3H, 1 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 172.55 (d, $J(^{31}P)$ = 17.9 Hz, 1C, COOH), 165.79 (d, $J(^{31}P)$ = 4.2 Hz, 1C, $ClCH_2\underline{C}$=O), 72.98 (d, $J(^{31}P)$ = 6.8 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.68 (d, $J(^{31}P)$ = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 66.06 (d, $J(^{31}P)$ = 172.9 Hz, 1C, CHP), 40.50 (s, 1C, CH_2Cl), 34.39 (d, $J(^{31}P)$ = 2.3 Hz, 1C, $\underline{CH_2}COOH$), 24.09 (d, $J(^{31}P)$ = 3.5 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.95 (d, $J(^{31}P)$ = 4.0 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.89 (d, $J(^{31}P)$ = 5.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.73 (d, $J(^{31}P)$ = 5.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

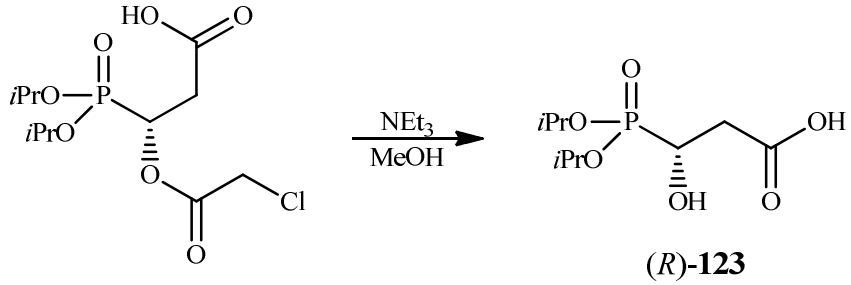
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 16.94 (s, P=O).

Elemental analysis calculated for $C_{11}H_{20}ClO_7P$ (330.70): C: 39.95, H: 6.10; found: C: 40.08, H: 5.87.

Similarly, 1-chloroacetoxyphosphonate (±)-**81** (1.545 g, 4.94 mmol) was converted to propanoic acid (±)-**122** (1.352 g, 83%) as colorless crystals. Mp. 81-82 °C.

The NMR spectroscopic data of (±)- and (*R*)-**122** are identical.

(*R*)-3-(Diisopropoxyphosphinyl)-3-hydroxypropanoic acid [(*R*)-123]



(*R*)-**122** (*R*)-**123**

3-(Chloroacetoxy)-3-(diisopropoxyphosphinyl)propanoic acid [(*R*)-**122**] (0.837 g, 2.53 mmol) was dissolved in methanol (10 ml). Triethylamine (0.308 g, 0.42 ml, 1.05 mmol) was added and the solution was stirred overnight at RT. The reaction was quenched with 2 M HCl (3 ml). The organic layer was removed and water (15 ml) as well as MC (15 ml) were added. The organic layer was separated and the aqueous one was extracted with MC (2 x 10 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by ion exchange chromatography (Dowex® 50W, H^+, H_2O) and crystallization (diisopropyl ether) to yield hydroxyphosphonate (*R*)-**123** (0.555 g, 86%) as colorless crystals. The optical purity was estimated after esterification. Mp. 83-85°C.

IR (ATR): ν = 3359, 2981, 2525, 1697, 1436, 1377, 1196, 1165, 1099, 986.

^{1}H NMR (600.13 MHz, D_2O): δ = 4.83-4.75 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 4.42 (ddd, J = 10.3 Hz, J = 7.7 Hz, J = 3.7 Hz, 1H, CHP), 2.87 (A part of ABX-sys, ddd, J_{AB} = 16.2 Hz, J = 7.7 Hz, J = 3.7 Hz, 1H, $\underline{CH_2}CO_2$), 2.70 (B part of ABX-sys, dt, J_{AB} = 16.2 Hz, J = 10.3 Hz, 1H, $\underline{CH_2}CO_2$), 1.38 (d, J = 6.4 Hz, 6H, 2 x CH($\underline{CH_3}$)$_2$), 1.37 (d, J = 6.2 Hz, 3H, 1 x CH($\underline{CH_3}$)$_2$), 1.36 (d, J = 6.9 Hz, 3H, 1 x CH($\underline{CH_3}$)$_2$).

^{13}C NMR (150.90 MHz, D_2O): δ = 176.81 (d, J(^{31}P) = 19.4 Hz, 1C, CO_2), 76.43 (d, J(^{31}P) = 7.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 76.35 (d, J(^{31}P) = 7.4 Hz, 1C, $\underline{CH}(CH_3)_2$), 66.11 (d, J(^{31}P) = 171.8 Hz, 1C, CHP), 39.07 (d, J(^{31}P) = 4.9 Hz, 1C, $\underline{CH_2}CO_2$), 25.71 (d, J(^{31}P) = 3.7 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 25.69 (d, J(^{31}P) = 3.8 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 25.61 (d, J(^{31}P) = 4.5 Hz, 2C, 2 x CH($\underline{CH_3}$)$_2$).

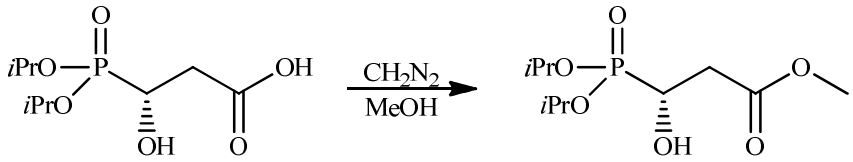
^{31}P NMR (242.94 MHz, D_2O): δ = 25.20 (s, P=O).

Elemental analysis calculated for $C_9H_{19}O_6P$ (254.22): C: 42.52, H: 7.53; found: C: 42.44, H: 7.27.

Similarly, 3-chloroacetoxypropanoic acid (±)-**122** (0.410 g, 1.24 mmol) was converted to 3-hydroxypropanoic acid (±)-**123** (0.280 g, 89%) as colorless crystals. Mp. 78-79 °C (methanol/diisopropyl ether).

The spectroscopic data of (±)- and (*R*)-**123** are identical.

Determination of *ee* of (*R*)-3-(diisopropoxyphosphinyl)-3-hydroxypropanoic acid: Preparation of (*R*)-methyl 3-(diisopropoxyphosphinyl)-3-hydroxypropanoate and (*R*)-Mosher ester thereof



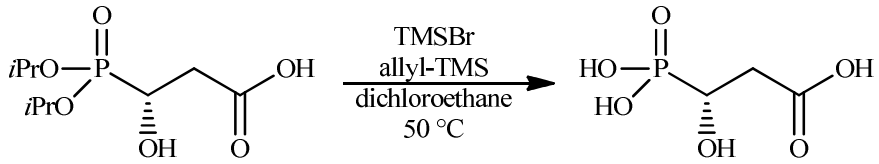
(*R*)-**123** (*R*)-**124**

3-(Diisopropoxyphosphinyl)-3-hydroxypropanoic acid [*R*]-**123**] (0.032 g, 0.13 mmol) was dissolved in methanol (3 ml). A large excess of a freshly distilled solution of diazomethane in diethyl ether was added until the yellow color of diazomethane persisted. The solution was concentrated under reduced pressure immediately. The residue, the methyl ester (*R*)-**124**, was immediately used.

(*S*)-Mosher ester:
The 2-hydroxyester (*R*)-**124** was converted to the (*R*)-Mosher ester according to general procedure A; ee ≥99%, ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 14.68 for (*R*)-**124**. No signal of (*S*)-**124** was observed.

Synthesis of a freshly distilled solution of diazomethane in diethyl ether in a well vented hood:
N-Nitroso-*N*-methylurea (3.0 g, 29.1 mmol) was added to a vigorously stirred mixture of diethyl ether (10 ml) and KOH solution (5 g in 20 ml of water) at −25 °C. When the *N*-nitroso-*N*-methylurea had been consumed, the yellow organic layer was removed and distilled very cautiously. The distillate was collected in a cold test tube (–40 °C) and used.

(*R*)-3-Hydroxy-3-phosphonopropanoic acid [(*R*)-120]



(*R*)-**123** (*R*)-**120**

3-(Diisopropoxyphosphinyl)-3-hydroxypropanoic acid [(*R*)-**123**] (0.465 g, 1.83 mmol) was dissolved in dry 1,2-dichloroethane (10 ml) under argon. TMSBr (3.132 g, 2.7 ml, 20.44 mmol) and allyltrimethylsilane (0.732 g, 1.0 ml, 6.40 mmol) were added and the solution was stirred at 50 °C overnight. Then it was concentrated under reduced pressure. The residue was dissolved in dichloroethane (10 ml) and concentrated again. The residue was purified by ion exchange [Dowex® 50 W, cation exchanger (H^+), H_2O] to yield phosphonic acid (*R*)-**120** as colorless crystals, which could not be recrystallized from water/ethanol.

^{1}H NMR (400.13 MHz, D_2O): δ = 4.08 (ddd, J = 11.3 Hz, J = 7.7 Hz, J = 2.6 Hz, 1H, CHP), 2.65 (A part of ABX-sys, ddd, J_{AB} = 15.5 Hz, J = 5.4 Hz, J = 2.6 Hz, 1H, $\underline{CH_2}CO_2$), 2.44 (B part of ABX-sys, ddd, J_{AB} = 15.5 Hz, J = 11.3 Hz, J = 7.1 Hz, 1H, $\underline{CH_2}CO_2$).

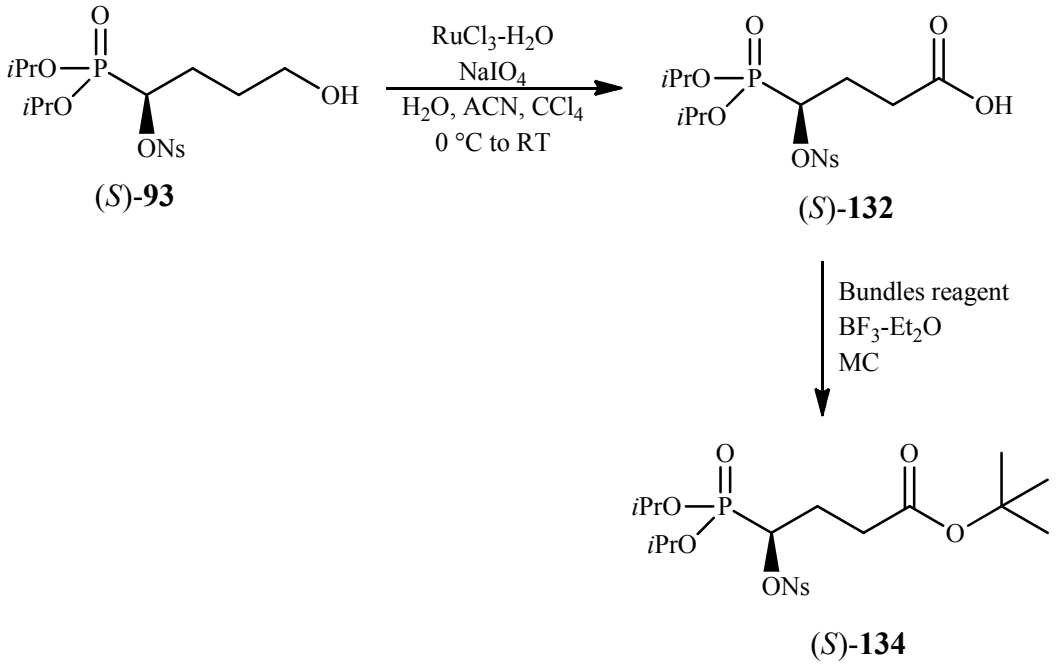
^{13}C NMR (100.61 MHz, D_2O): δ = 180.64 (d, $J(^{31}P)$ = 17.9 Hz, 1C, CO_2), 67.35 (d, $J(^{31}P)$ = 156.7 Hz, 1C, CHP), 40.42 (d, $J(^{31}P)$ = 2.5 Hz, 1C, $\underline{CH_2}CO_2$).

^{31}P NMR (161.97 MHz, D_2O): δ = 20.20 (s, P=O).

Similarly, 1-hydroxyphosphonate (±)-**123** (0.233 g, 0.92 mmol) was converted to 1-hydroxy phosphonic acid (±)-**120** as colorless crystals, which could not be recrystallized from water/ethanol.

3.2.8. Synthesis of (*R*)-4-amino-4-phosphonobutanoic acid

(*S*)-(+)-*tert*-Butyl 4-(diisopropoxyphosphinyl)-4-(4-nitrobenzenesulfonyloxy)butanoate [(*S*)-132]



(*S*)-**93** (*S*)-**132** (*S*)-**134**

Diisopropyl 4-hydroxy-1-(4-nitrobenzenesulfonyloxy)butylphosphonate **[**(*S*)-**93**] (2.221 g, 5.27 mmol) was dissolved in a mixture of H_2O (16 ml), ACN (9 ml) and CCl_4 (9 ml). $RuCl_3 \cdot H_2O$ (45 mg) and $NaIO_4$ (6.113 g, 28.58 mmol) were added and the solution was stirred vigorously for 4.5 h while the reaction mixture was allowed to warm from 0 °C to RT. The organic phase was removed and 2 M HCl (10 ml) as well as MC (15 ml) were added. The organic layer was separated and the aqueous one was extracted with MC (2 x 15 ml), washed with brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The black (Ru compounds!) product (*S*)-**132** (2.128 g, 89%) was used immediately, although it was found to be stable at 4 °C for at least 2 weeks.

The substituted butanoic acid (*S*)-**132** (0.506 g, 1.24 mmol) was dissolved in MC (1.2 ml) under argon. *t*-Butyl 2,2,2-trichloroacetimidate (Bundle´s reagent) (0.541 g, 2.48 mmol) was added followed by $BF_3 \cdot Et_2O$ (20 µl, 1.6 x 10^{-4} mmol) at RT. A grey precipitate formed immediately. The suspension was stirred at RT overnight. Water (10 ml) and MC (10 ml) were added and the organic phase was separated. The aqueous layer was extracted with MC (2 x 10 ml). The combined organic layers were washed with brine (5 ml) and dried (Na_2SO_4)

and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (3:1), R_f = 0.50] to yield *t*-butyl ester (*S*)-**134** (0.412 g, 72%) as a colorless oil.

$[\alpha]_D^{20}$ = +10.65 (*c* = 0.62, acetone).

IR (ATR): ν = 2980, 1725, 1533, 1368, 1350, 1254, 1186, 1153, 985.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.38-8.32 (m, 2H, H_{arom}), 8.19-8.15 (m, 2H, H_{arom}), 4.98 (td, *J* = 9.4 Hz, $J(^{31}P)$ = 4.2 Hz, 1H, CHP), 4.73-4.54 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 2.53-2.33 (m, *2*H, $\underline{CH_2}CO_2$), 2.26-2.15 (m, 1H, $\underline{CH_2}$CHP), 2.08-1.94 (m, 1H, $\underline{CH_2}$CHP), 1.43 (s, 9H, 3 x $C(\underline{CH_3})_3$), 1.28 (d, *J* = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$), 1.285 (d, *J* = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$), 1.24 (d, *J* = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$), 1.23 (d, *J* = 6.3 Hz, 3H, $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 171.29 (s, 1C, C=O), 150.73 (s, 1C, C_{arom}), 142.50 (s, 1C, C_{arom}), 129.51 (s, 2C, C_{arom}), 124.13 (s, 2C, C_{arom}), 80.90 (s, 1C, $\underline{C}(CH_3)_3$), 77.15 (d, $J(^{31}P)$ = 171.8 Hz, 1C, CHP), 72.36 (d, $J(^{31}P)$ = 6.9 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.34 (d, $J(^{31}P)$ = 6.9 Hz, 1C, $\underline{CH}(CH_3)_2$), 30.67 (d, $J(^{31}P)$ = 10.7 Hz, 1C, $\underline{CH_2}CO_2$), 28.06 (s, 3C, 3 x $C(\underline{CH_3})_3$), 25.82 (s, 1C, $\underline{CH_2}$CHP), 24.02 (d, $J(^{31}P)$ = 4.0 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.93 (d, $J(^{31}P)$ = 4.8 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.88 (d, $J(^{31}P)$ = 5.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.71 (d, $J(^{31}P)$ = 4.8 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

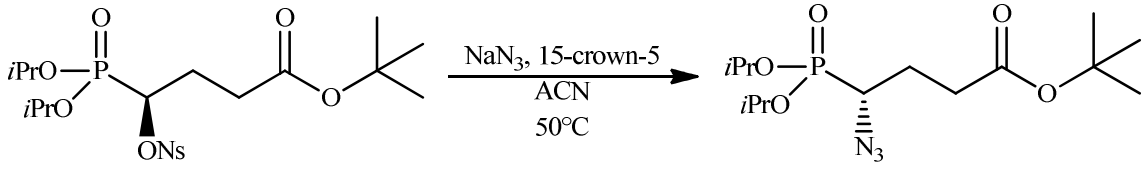
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 15.68 (s, P=O).

Elemental analysis calculated for $C_{20}H_{32}NO_{10}PS$ (509.51): C: 47.15, H: 6.33, N: 2.75; found: C: 47.36, H: 5.97, N: 2.72.

Similarly, butylphosphonate (±)-**93** (0.908 g, 2 mmol) was converted to *t*-butyl ester (±)-**134** (0.709 g, 69%) as a colorless oil.

The NMR spectroscopic data of (±)- and (*S*)-**134** are identical.

(*R*)-(–)-tert-Butyl 4-azido-4-(diisopropoxyphosphinyl)butanoate [(*R*)-135]



(*S*)-**134** (*R*)-**135**

tert-Butyl 4-(diisopropoxyphosphinyl)-4-(4-nitrobenzenesulfonyloxy)butanoate **[**(*S*)-**134**] (0.837 g, 1.64 mmol) and NaN_3 (0.517 g, 7.94 mmol) were mixed in ACN (10 ml) under argon. 15-crown-5 (0.358 g, 0.32 ml, 1.63 mmol) was added and the suspension was then stirred at 50 °C for 7 h. The mixture was concentrated under reduced pressure. Water (20 ml) and MC (20 ml) were added and the organic layer was separated. The aqueous layer was extracted with MC (2 x 15 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (2:1), $R_f = 0.55$] to yield azide (*R*)-**135** (0.469g, 82%) as a light yellow oil.

$[\alpha]_D^{20} = -45.36$ ($c = 1.10$, acetone).

IR (ATR): $\delta = 2980, 2102, 1727, 1368, 1255, 1147, 1105, 980$.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.73 (oct, $J(^{31}P)$ = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.72 (oct, $J(^{31}P)$ = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 3.41 (td, J = 11.4 Hz, $J(^{31}P)$ = 3.7 Hz, 1H, CHP), 2.46-2.28 (m, 2H, $\underline{CH_2}COOH$), 2.13-2.00 (m, 1H, $\underline{CH_2}CHP$), 1.87-1.73 (m, 1H, $\underline{CH_2}CHP$), 1.39 (s, 9H, 3 x $C(\underline{CH_3})_3$), 1.31 (d, J = 6.1 Hz, 3H, $CH(\underline{CH_3})_2$), 1.30 (d, J = 6.2 Hz, 9H, 3 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 171.54 (s, 1C, C=O), 80.63 (s, 1C, $\underline{C}(CH_3)_3$), 71.80 (d, $J(^{31}P)$ = 3.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.73 (d, $J(^{31}P)$ = 3.2 Hz, 1C, $\underline{CH}(CH_3)_2$), 57.07 (d, $J(^{31}P)$ = 157.6 Hz, 1C, CHP), 32.03 (d, $J(^{31}P)$ = 10.7 Hz, 1C, $\underline{CH_2}COOH$), 27.98 (s, 3C, 3 x $C(\underline{CH_3})_3$), 24.31 (s, 1C, $\underline{CH_2}CHP$), 24.06 (d, $J(^{31}P)$ = 3.6 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.04 (d, $J(^{31}P)$ = 3.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.87 (d, $J(^{31}P)$ = 4.8 Hz, 2C, 2 x $CH(\underline{CH_3})_2$).

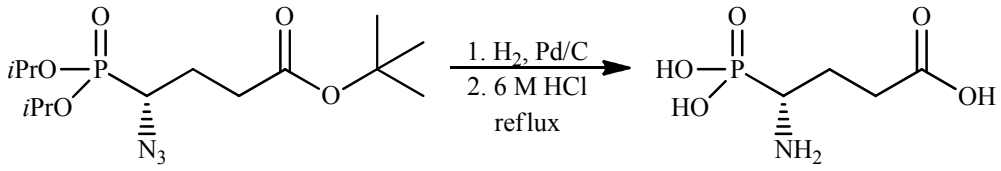
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 20.71 (s, P=O).

Elemental analysis calculated for $C_{14}H_{28}N_3O_5P$ (349.36): C: 48.13, H: 8.08, N: 12.03; found: C: 48.47, H: 7.92, N: 11.48.

Similarly, *t*-butyl ester (±)-**134** (0.697 g, 1.37 mmol) was converted to azide ester (±)-**135** (0.295 g, 62%) as a colorless oil.

The spectroscopic data of (±)- and (*R*)-**135** are identical.

(*R*)-4-Amino-4-phosphonobutanoic acid [(*R*)-127]



(*R*)-**135** (*R*)-**127**

tert-Butyl 4-azido-4-(diisopropoxyphosphinyl)butanoate **[**(*R*)-**135**] (0.290 g, 0.79 mmol) was dissolved in methanol (10 ml) and transferred into a Parr hydrogenation flask. After the addition of 10% Pd/C (30 mg) the flask was mounted to the Parr apparatus. The flask was filled with hydrogen (50 psi) and shaken for 16 h. The catalyst was collected by filtration and washed with methanol. The filtrate was concentrated under reduced pressure. The residue was dissolved in 6 M HCl (10 ml) and refluxed for 4 h. The solution was concentrated under reduced pressure and the residue was purified by ion exchange [Dowex® 50W x 8, H^+, elution with H_2O] to yield phosphonic acid analog (*R*)-**127** of *L*-glutamic acid (0.101 g, 70%) as a gum, which crystallized after a few months, possibly after seeding with crystals of (R)-phosphaglutamic acid from Prof. Kafarski.

IR (ATR): ν = 1683, 1536, 1084, 932.

^{1}H NMR (400.27 MHz, D_2O): δ = 3.35 (ddd, J = 13.7, J = 7.8, J = 6.4 Hz, 1H, CHP), 2.69 (t, J = 7.5 Hz, 2H, CH_2COOH), 2.30-1.98 (m, 2H, CH_2CHP).

^{13}C NMR (100.65 MHz, D_2O): δ = 176.84 (s, 1C, C=O), 48.35 (d, $J(^{31}P)$ = 142.7 Hz, 1C, CHP), 30.59 (d, $J(^{31}P)$ = 9.0 Hz, 1C, CH_2COOH), 23.73 (s, 1C, CH_2CHP).

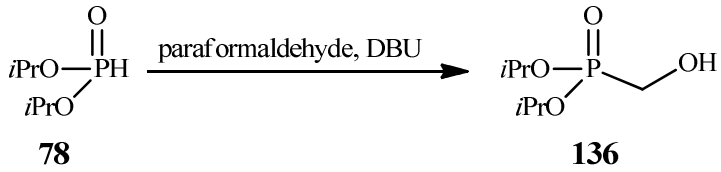
^{31}P NMR (162.03 MHz, D_2O): δ = 12.63 (s, P=O).

Similarly, azide (±)-**135** was converted to phosphonic acid (±)-**127** as colorless crystals.

The NMR spectroscopic data of (±)- and (*R*)-**127** are identical.

3.2.9. Synthesis of (*R*)-1-amino-2-(1H-1,2,3-triazol-4-yl)ethylphosphonic acid

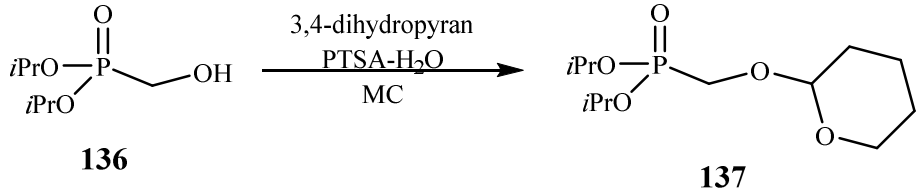
Diisopropyl hydroxymethylphosphonate (136)



78 **136**

Paraformaldehyde (1.890 g, 63 mmol) was added to a stirred mixture of diisopropyl phosphite (**78)** (9.889 g, 60.2 mmol, 10 ml) and then DBU (14 drops) was added dropwise, whereupon a strong exothermic reaction followed, which was not cooled, and the mixture became clear. Stirring was continued for 1h and the mixture cooled down to RT. MC (50 ml) and 2 M HCl (20 ml) were added, and the organic phase was separated. The aqueous layer was extracted with MC (2 x 50 ml). The combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by bulb to bulb distillation (0.2 mbar, 80 – 110 ˚C) to yield hydroxymethylphosphonate **136** (11.17 g, 92%) as a colorless liquid.

Diisopropyl (tetrahydro-2H-pyran-2-yl)oxymethylphosphonate (137)



136 **137**

Diisopropyl hydroxymethylphosphonate (**136)** (4.937 g, 25.17 mmol) and 3,4-dihydro-2H-pyran (2.647 g, 31.47 mmol) were dissolved in MC (50 ml). *p*-Toluenesulfonic acid monohydrate (0.03 g, 0.16 mmol) was added at 0 °C and the solution was stirred for 1.5 h at 0 °C, then 2 h at RT. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 ml). Water (50 ml) was added, and the organic layer was separated. The aqueous layer was extracted with MC (2 x 50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [EtOAc, R_f = 0.53] to yield tetrahydropyranyl ether **137** as a colorless oil (6.870 g, 97%).

IR (ATR): ν = 2978, 2940, 1455, 1385, 1375, 1254, 1123, 1107, 1072, 1038, 981.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.76-4.66 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 4.65 (t, J = 2.7 Hz, 1H, O$\underline{CH}CH_2$), 3.89 (A part of ABX-sys, J_{AB} = 13.8 Hz, $J(^{31}P)$ = 9.0 Hz, 1H, CH_2P), 3.82-3.72 (m, 1H, CH_2O), 3.62 (B part of ABX-sys, J_{AB} = 13.8 Hz, $J(^{31}P)$ = 8.9 Hz, 1H, CH_2P), 3.51-3.42 (m, 1H, CH_2O), 1.83-1.40 (m, 6H, $\underline{CH_2}CHO$, $\underline{CH_2}CH_2O$, $\underline{CH_2}CH_2CHO$), 1.30-1.24 (m, 12H, 4 x $CH(\underline{CH_3})_2$).

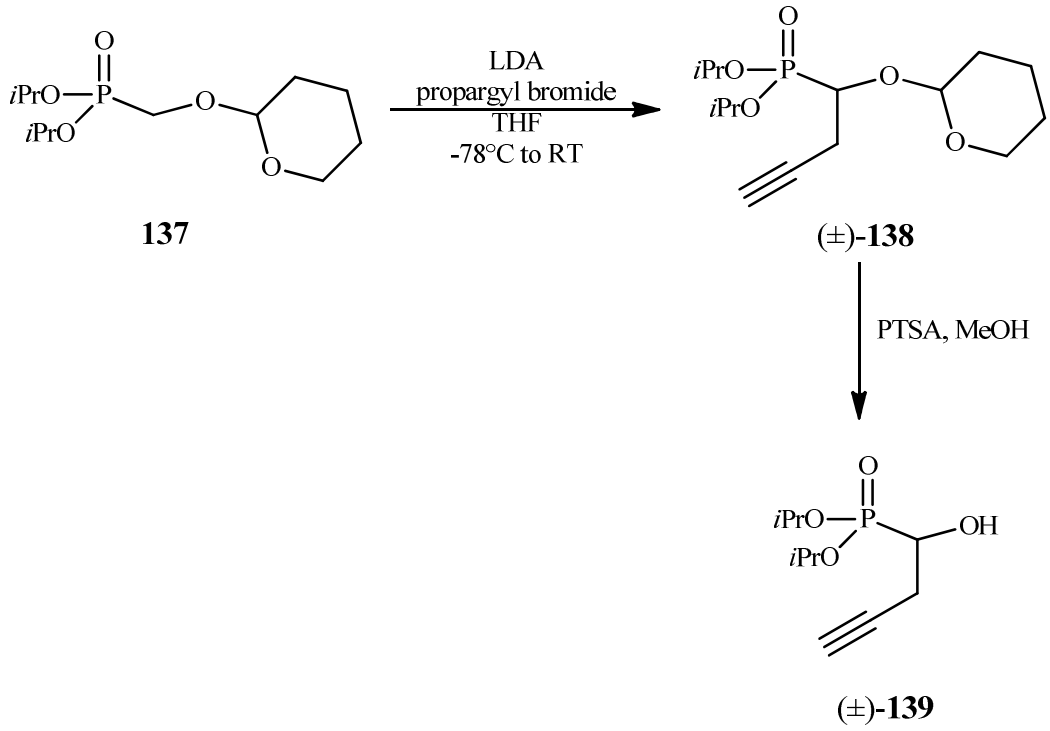
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 99.07 (d, $J(^{31}P)$ = 11.9 Hz, 1C, $\underline{CH}CH_2$), 70.91 (d, $J(^{31}P)$ = 6.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 70.77 (d, $J(^{31}P)$ = 6.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 61.46 (s, 1C, CH_2O), 29.93 (s, 1C, $\underline{CH_2}CHO$), 61.14 (d, $J(^{31}P)$ = 170.4 Hz, 1C, CH_2P), 25.19 (s, 1C, $\underline{CH_2}CH_2O$), 24.03 (d, $J(^{31}P)$ = 2.8 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 23.90 (d, $J(^{31}P)$ = 4.7 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 18.54 (s, 1C, $\underline{CH_2}CH_2CHO$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 21.25 (s, P=O).

Elemental analysis calculated for $C_{12}H_{25}O_5P$ (280.30): C: 51.42, H: 8.99; found: C: 51.86, H: 8.74.

MS (EI, 70 eV): m/z calculated for $C_{12}H_{25}O_5P$ $[M + Na]^+$ = 303.1337, found: 303.1331.

(±)-Diisopropyl (1-hydroxy-3-butynyl)phosphonate [(±)-138]



137 (±)-**138** (±)-**139**

Diisopropyl (tetrahydro-2H-pyran-2-yl)oxymethylphosphonate **(137)** (6.870 g, 24.51 mmol) was dissolved in dry THF (35 ml) under argon. At −78 °C, LDA (26 ml, 28.60 mmol, 1.1 M in THF, freshly prepared) was added and the solution was stirred at this temperature for 1 h. Then propargyl bromide (4.374 g, 3.2 ml, 29.41 mmol, 80% in toluene) was added slowly. The solution was warmed up until RT and stirred overnight, while it turned brown. The reaction was quenched with a saturated aqueous solution of NH_4HCO_3. Water (40 ml) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (1:2), R_f = 0.46] to yield phosphonate (±)-**138** as a brown oil (4.219 g, 54%).

Part of this compound (4.017 g, 12.62 mmol) and *p*-toluenesulfonic acid monohydrate (0.100 g, 0.53 mmol) were dissolved in methanol (50 ml). The solution was stirred at RT for 18 h. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ and concentrated under reduced pressure. Water (30 ml) and MC (30 ml) were added and the aqueous layer was washed with MC (2 x 30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (1:2), R_f = 0.43] to yield hydroxyphosphonate (±)-**139** as crystals (2.529 g, 86%). Mp. 52 °C.

IR (ATR): ν = 3289, 2980, 1386, 1218, 1104, 980.

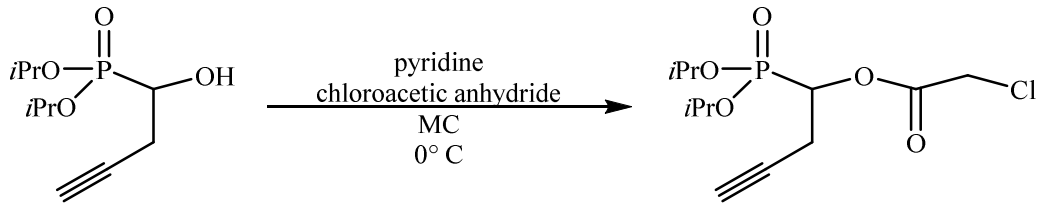
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.78-4.64 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 4.32 (bs, 1H, OH), 3.91 (dt, $J(^{31}P)$ = 9.0 Hz, J = 4.2 Hz, 1H, CHP), 2.67-2.49 (m, 2H, $\underline{CH_2}CH$), 2.00 (t, J = 2.6 Hz, 1H, $\underline{CH}$≡C), 1.31-1.26 (m, 12H, 4 x CH($\underline{CH_3}$)$_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 80.33 (d, $J(^{31}P)$ = 18.6 Hz, 1C, CH≡$\underline{C}$), 71.68 (d, $J(^{31}P)$ = 7.1 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.44 (d, $J(^{31}P)$ = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 70.21 (d, $J(^{31}P)$ = 2.4 Hz, 1C, $\underline{CH}$≡C), 66.56 (d, $J(^{31}P)$ = 165.7 Hz, 1C, CHP), 24.05 (d, $J(^{31}P)$ = 3.6 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 24.00 (d, $J(^{31}P)$ = 3.6 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.88 (d, $J(^{31}P)$ = 3.1 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.83 (d, $J(^{31}P)$ = 3.4 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 22.30 (d, $J(^{31}P)$ = 4.1 Hz, 1C, $\underline{CH_2}$CH).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 22.07 (s, P=O).

Elemental analysis calculated for $C_{10}H_{19}O_4P$ (234.23): C: 51.28, H: 8.18; found: C: 51.29, H: 7.96.

(±)-Diisopropyl (1-chloroacetoxy-3-butynyl)phosphonate [(±)-140]



(±)-**139** (±)-**140**

Diisopropyl (1-hydroxy-3-butynyl)phosphonate [(±)-**139**] (0.514 g, 2.19 mmol) and dry pyridine (0.543 g, 0.55 ml, 6.86 mmol) were dissolved in dry MC(5 ml) at 0 °C under argon. Chloroacetic anhydride (0.548 g, 3.21 mmol, dissolved in 5 ml of dry MC) was added dropwise while the solution was stirred at 0 °C for 2 h. The reaction was quenched with 2 M HCl (5 ml) and the solution was stirred vigorously for 30 min. Water (15 ml) and MC (15 ml) were added and the organic layer was separated. The aqueous layer was extracted with MC (2 x 10 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography

[hexanes/EtOAc (1:1), R_f = 0.23] to yield chloroacetate (±)-**140** (0.658 g, 97%) as a light yellow oil.

IR (ATR): ν = 1771, 1242, 1156, 1103, 980.

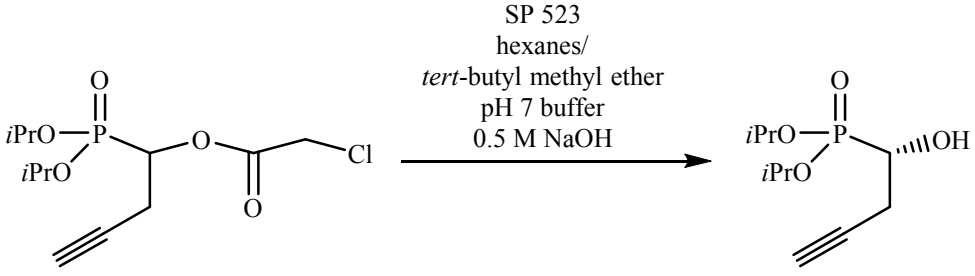
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.42-5.34 (m, 1H, CHP), 4.80-4.67 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 4.13 (s, 2H, CH_2Cl), 2.82-2.64 (m, 2H, $\underline{CH_2}CH$), 1.98 (td, J = 2.7 Hz, $J(^{31}P)$ = 1.0 Hz, 1H, $\underline{CH}$≡C), 1.32 (d, $J(^{31}P)$ = 5.7 Hz, 6H, 2 x CH($\underline{CH_3}$)$_2$), 1.31 (d, $J(^{31}P)$ = 6.0 Hz, 6H, 2 x CH($\underline{CH_3}$)$_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 166.16 (d, $J(^{31}P)$ = 5.4 Hz, 1C, C=O), 78.32 (d, $J(^{31}P)$ = 18.1 Hz, 1C, CH≡$\underline{C}$), 72.35 (d, $J(^{31}P)$ = 6.7 Hz, 1C, $\underline{CH}(CH_3)_2$), 72.18 (d, $J(^{31}P)$ = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 70.94 (d, $J(^{31}P)$ = 2.2 Hz, 1C, $\underline{CH}$≡C), 68.02 (d, $J(^{31}P)$ = 171.1 Hz, 1C, CHP), 40.48 (s, 1C, CH_2Cl), 24.12 (d, $J(^{31}P)$ = 3.4 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 24.00 (d, $J(^{31}P)$ = 4.3 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.95 (d, $J(^{31}P)$ = 5.5 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.81 (d, $J(^{31}P)$ = 5.0 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 20.33 (d, $J(^{31}P)$ = 3.4 Hz, 1C, $\underline{CH_2}CH$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 16.31 (s, P=O).

Elemental analysis calculated for $C_{12}H_{20}ClO_5P$ (310.71): C: 46.39, H: 6.49: found: C: 46.64, H: 6.15.

(*S*)-Diisopropyl (1-hydroxy-3-butynyl)phosphonate [(*S*)-141]

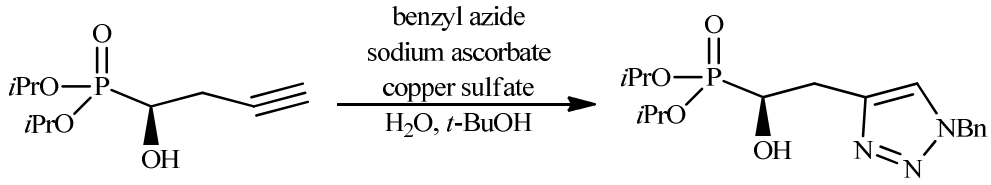


(±)-**140** (*S*)-**141**

Diisopropyl (1-chloroacetoxy-3-butynyl)phosphonate [(±)-**140**] (1.735 g, 5.58 mmol) was dissolved in a mixture of hexanes (5 ml), *tert*-butyl methyl ether (5 ml) and pH 7 phosphate buffer (25 ml). 0.5 M NaOH was added by an autotitrator to bring pH to 7.0. Lipase from *Thermomyces lanuginosus* (≥100,000 U/g, 0.1 ml, Aldrich) was added. The pH was again

adjusted to 7.0 and kept there by automatic addition of base. When the conversion (based on consumption of base) was 45% (after 3.5 h), the enzymatic hydrolysis was stopped by adding 2 M HCl to bring pH to 4. The organic phase was removed and the aqueous layer was then extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with brine (5 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (1:1), R_f = 0.17] to yield 1-hydroxyphosphonate (*S*)-**141** (0.473 g, 36%) as a light yellow oil; the ee of 92% was determined by ^{31}P NMR spectroscopy of the (*R*)-Mosher ester. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 14.46 for (*S*)-**141**, 13.78 for (*R*)-**141**.

(*S*)-(+)-(Diisopropyl [2-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-hydroxyethyl]phosphonate [(*S*)-142]



(*S*)-**141** (*S*)-**142**

Diisopropyl (1-hydroxy-3-butynyl)phosphonate **[**(*S*)-**141**] (2.041 g, 8.71 mmol) and benzyl azide (1.160 g, 1.1 ml, 8.71 mmol) were dissolved in a mixture of water (10 ml) and *t*-butanol (15 ml) at RT. Copper (II) sulfate (0.139 g, 0.87 mmol, dissolved in 2 ml of water) and sodium ascorbate (1.740 g, 8.78 mmol, dissolved in 4 ml of water) were added and the solution was stirred for 3.5 h at RT. The organic phase was removed and the aqueous one was extracted with MC (3 x 15 ml). The combined organic layers were washed with brine (5 ml), an aqueous solution of EDTA to remove traces of copper compounds, then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [EtOAc/EtOH (10:1), R_f = 0.32] and crystallization (diisopropyl ether/MC for enantiomer, diisopropyl ether for racemate) to yield *N*-benzyltriazole (*S*)-**142** (2.640 g, 83%) as colorless crystals. The *ee* was determined using (*R*)-(+)-*t*-butyl(phenyl)phosphinothioic acid as chiral shift reagent, ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 21.27 for (*S*)-**142**, 21.14 for (*R*)-**142**; *ee* before crystallization: 92%; after crystallization: >98%. Mp. 89-90 °C.

$[\alpha]_D^{20}$ = +1.21 (*c* = 0.66, acetone).

IR (ATR): ν = 2979, 1455, 1387, 1374, 1218, 1105, 983.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.39-7.22 (m, 6H, H_{arom}), 5.46 (d, AB-sys, J_{AB} = 14.9 Hz, 2H, $\underline{CH_2}Ph$), 4.79-4.64 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 4.18-4.05 (m, 1H, CHP), 3.66 (dd, J = 10.9 Hz, J = 5.0 Hz, 1H, OH), 3.18 (A part of ABX-sys, J_{AB} = 15.4 Hz, J = 7.7 Hz, J = 2.9 Hz, 1H, $\underline{CH_2}CHP$), 3.00 (B part of ABX-sys, J_{AB} = 15.4 Hz, J = 10.2 Hz, J = 8.5 Hz, 1H, $\underline{CH_2}CHP$), 1.30 (d, J = 6.2 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.28 (d, J = 6.4 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.26 (d, J = 6.4 Hz, 3H, 1 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 134.66 (s, 1C, C_{arom}), 129.08 (s, 2C, C_{arom}), 128.70 (s, 1C, C_{arom}), 128.09 (s, 2C, C_{arom}), 122.10 (s, 1C, C_{arom}), 71.36 (d, $J(^{31}P)$ = 7.7 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.33 (d, $J(^{31}P)$ = 7.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 67.50 (d, $J(^{31}P)$ = 165.8 Hz, 1C, CHP), 54.12 (s, 1C, $\underline{CH_2}Ph$), 28.02 (d, $J(^{31}P)$ = 1.9 Hz, 1C, $\underline{CH_2}CHP$), 24.10 (d, $J(^{31}P)$ = 4.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.06 (d, $J(^{31}P)$ = 4.2 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.96 (d, $J(^{31}P)$ = 4.9 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.94 (d, $J(^{31}P)$ = 4.7 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).
The signal of $\underline{C}N{=}N$ was not found.

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 22.72 (s, P=O).

Elemental analysis calculated for $C_{11}H_{26}N_3O_4P$ (367.38): C: 55.58, H: 7.13, N: 11.44; found: C: 55.25, H: 6.99, N: 11.33.

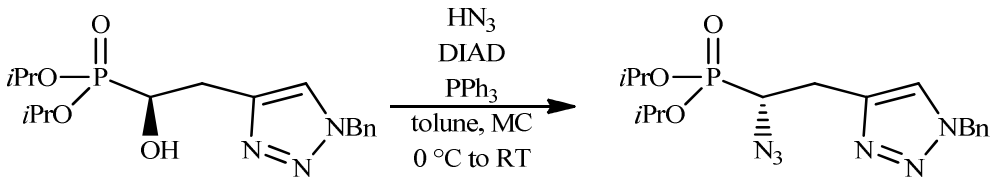
Similarly, diisopropyl (1-hydroxy-3-butynyl)phosphonate [(±)-**141**] (0.407 g, 1.74 mmol) was converted to *N*-benzyltriazole (±)-**142** (0.499 g, 78%) as colorless crystals. Mp. 76-77 °C.

The NMR spectroscopic data of (±)- and (*S*)-**142** are identical.

Preparation of benzyl azide

Benzyl bromide (0.445 g, 0.3 ml, 2.6 mmol) was added to a solution of sodium azide (7.8 ml, 3.9 mmol, 0.5 M in DMSO). The solution was stirred for 72 h. Water (30 ml) and diisopropyl ether (30 ml) were added. The organic layer was separated and washed with water (3 x 20 ml), dried (Na_2SO_4) and concentrated under reduced pressure at RT. The product (0.309 g, 89%) was found to be a colorless oil.

(*R*)-Diisopropyl [1-azido-2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethyl]phosphonate [(*R*)-142]



(*S*)-**142** (*R*)-**143**

1) Mitsunobu reaction with Ph_3P:

Diisopropyl [2-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-hydroxyethyl]phosphonate [(*S*)-**142**] (1.946 g, 5.30 mmol) and triphenylphosphine (1.807 g, 6.89 mmol) were dissolved in 5 ml dry toluene and 10 ml MC under argon. DIAD (1.391 g, 1.4 ml, 6.85 mmol) and then HN_3 (5.7 ml, 7.13 mmol, 1.25 M in toluene) were added dropwise at 0 °C and the solution was slowly warmed up to RT and stirred overnight. The solution was concentrated under reduced pressure and purified by flash chromatography [MC/*i*PrOH (40:1), R_f = 0.25] and crystallization (hexanes/MC) to yield azide (*R*)-**143** (1.632 g, 78%) as colorless crystals.

2) Mitsunobu reaction with methyldiphenylphosphine:

Diisopropyl [2-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-hydroxyethyl]phosphonate [(*S*)-**142**] (0.349 g, 0.95 mmol) and methyldiphenylphosphine (0.248 g, 0.23 ml, 1.24 mmol) were dissolved in 1 ml dry toluene and 2 ml MC under argon. DIAD (0.249 g, 0.25 ml, 1.23 mmol) and then HN_3 (1.1 ml, 1.38 mmol, 1.25 M in toluene) were added dropwise at 0 °C and the solution was slowly warmed up to 40 °C and stirred overnight. The solution was concentrated under reduced pressure and purified by flash chromatography [hexanes/EtOAc (1:5)] and crystallization (hexanes/MC) to yield azide (*R*)-**143** (0.126 g, 34%) as colorless crystals.

$[\alpha]_D^{20} = -23.24$ (*c* = 1.05, acetone).

IR (ATR): ν = 2981, 2120, 1456, 1376, 1252, 1104, 984, 911.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.38-7.28 (m, 4H, H_{arom}), 7.26-7.19 (m, 2H, H_{arom}), 5.49 (d, AB-sys, J_{AB} = 14.9 Hz, 2H, $\underline{CH_2}$Ph), 4.83-4.71 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 3.81 (td, *J* = 11.5 Hz, $J(^{31}P)$ = 3.1 Hz, 1H, CHP), 3.25 (ddd, J_{AB} = 15.3 Hz, *J* = 6.0 Hz, *J* = 3.1 Hz, 1H, A part of ABX-sys, $\underline{CH_2}$CHP), 2.90 (ddd, J_{AB} = 15.3 Hz, *J* = 11.5 Hz, *J* = 8.2 Hz, B part of ABX-sys, 1H, $\underline{CH_2}$CHP), 1.35-1.29 (m, 12H, 4 x CH($\underline{CH_3}$)$_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 143.73 (d, $J(^{31}P)$ = 17.1 Hz, 1C, CN=N), 134.62 (s, 1C, C_{arom}), 129.07 (s, 2C, C_{arom}), 128.70 (s, 1C, C_{arom}), 127.98 (s, 2C, C_{arom}), 122.20 (s, 1C, C_{arom}), 72.04 (d, $J(^{31}P)$ = 7.5 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.98 (d, $J(^{31}P)$ = 7.1 Hz, 1C, $\underline{CH}(CH_3)_2$), 57.47 (d, $J(^{31}P)$ = 158.4 Hz, 1C, CHP), 54.11 (s, 1C, $\underline{CH_2}Ph$), 25.87 (d, $J(^{31}P)$ = 1.9 Hz, 1C, $\underline{CH_2}CHP$), 24.09 (d, $J(^{31}P)$ = 3.5 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 23.94 (d, $J(^{31}P)$ = 4.7 Hz, 2C, 2 x $CH(\underline{CH_3})_2$).

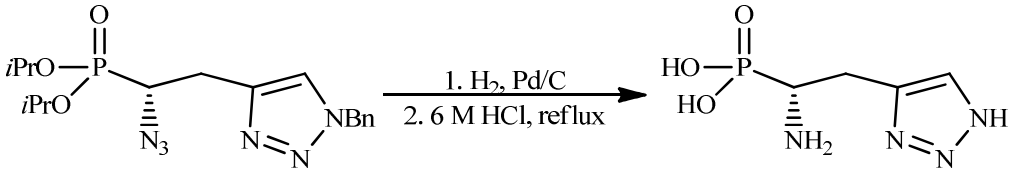
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 19.99 (s, P=O).

Elemental analysis calculated for $C_{17}H_{25}N_6O_3P$ (392.39): C: 52.04, H: 6.42, N: 21.42; found: C: 52.16, H: 6.35, N: 21.33.

Similarly, diisopropyl (2-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-hydroxyethyl)phosphonate [(±)-**142]** was converted to azide (±)-**143** as colorless crystals. Mp. 54 °C.

The NMR spectroscopic data of (±)- and (*R*)-**143** are identical.

(*R*)-1-Amino-2-(1H-1,2,3-triazol-4-yl)ethylphosphonic acid [(*R*)-144]



(*R*)-**143** (*R*)-**144**

Diisopropyl 1-azido-2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethylphosphonate [(*R*)-**143**] (0.177 g, 0.45 mmol) was dissolved in a mixture of methanol (10 ml) and 37% HCl (10 ml) with Pd/C (10%, 100 mg) in a Parr hydrogenation flask. The hydrogenation was operated at a pressure of 5 bar (72.5 psi) over the weekend. Then the suspension was filtered through filter paper and washed with methanol. The filtrate was concentrated under reduced pressure. The residue was dissolved in 6 M HCl (10 ml) and refluxed for 4 h. The solution was purified by ion exchange [Dowex® MWA-1 anion exchanger (OAc^-), 5% AcOH] and crystallization (H_2O/EtOH) to yield the desired 1-amino-2-(1H-1,2,3-triazol-4-yl)ethylphosphonic acid [(*R*)-**144**] (0.043 g, 50%) as colorless crystals. Mp. 179-181 °C.

IR (ATR): ν = 2862, 1636, 1615, 1534, 1245, 1229, 1147, 1130, 1083, 958, 936.

^{1}H NMR (400.13 MHz, D_2O): δ = 7.92 (s, 1H, H_{arom}), 3.67 (ddd, $J(^{31}P)$ = 13.3 Hz, J = 10.7 Hz, J = 4.3 Hz, 1H, CHP), 3.46 (ddd, J_{AB} = 15.8 Hz, J = 7.3 Hz, J = 4.3 Hz, A part of ABX-sys, 1H, $\underline{CH_2}$CHP), 3.22 (ddd, J_{AB} = 15.8 Hz, J = 10.4 Hz, J = 9.0 Hz, B part of ABX-sys, 1H, $\underline{CH_2}$CHP).

^{13}C NMR (100.61 MHz, D_2O): δ = 49.45 (d, $J(^{31}P)$ = 141.7 Hz, 1C, CHP), 24.51 (s, 1C, $\underline{CH_2}$CHP).

^{31}P NMR (161.98 MHz, D_2O): δ = 12.78 (s, P=O).

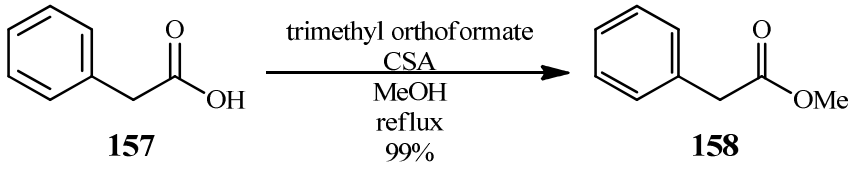
Elemental analysis calculated for $C_4H_9N_4O_3P$ (192.04): C: 25.01, H: 4.72, N: 29.16; found: C: 24.91, H: 4.56, N: 29.06.

Similarly, diisopropyl 1-azido-2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethylphosphonate **[**(±)-**143]** was converted to phosphonic acid (±)-**144** as colorless crystals. Mp. 267-269 °C.

The NMR spectroscopic data of (±)- and (*R*)-**144** are identical.

3.2.10. Synthesis of (±)-1-amino-2-phenyl-2-propenylphosphonic acid

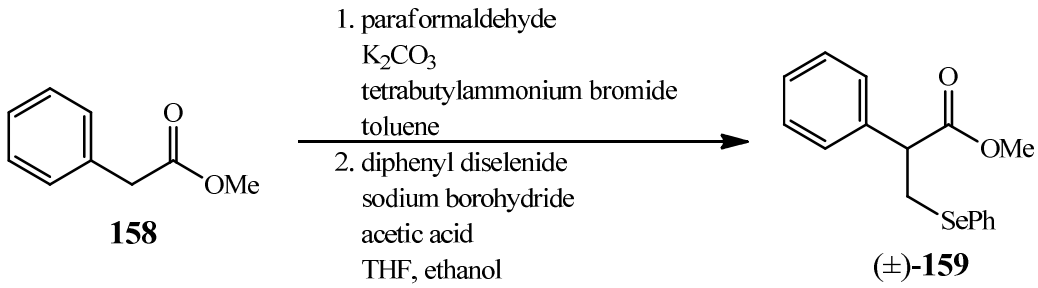
Methyl 2-phenylacetate (158)



157 **158**

Phenylacetic acid (**157)** (4.080 g, 30 mmol), trimethyl orthoformate (3.491 g, 3.6 ml, 32.90 mmol) and camphorsulfonic acid (0.350 g, 1.51 mmol) were dissolved in methanol (25 ml) and refluxed for 18 h. The solution was concentrated under reduced pressure and EtOAc (30 ml) as well as water (30 ml) were added to the residue. The organic layer was separated and the aqueous one was extracted with EtOAc (2 x 20 ml). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (0.4 mbar, 40 °C) to yield methyl ester **158** (4.433 g, 99%) as a light yellow oil.

(±)-Methyl 2-phenyl-3-(phenylselenyl)propanoate [(±)-159]



158 (±)-**159**

Methyl 2-phenylacetate (**158)** (3.350 g, 3.2 ml, 22.38 mmol) and paraformaldehyde (4.5 g, 150 mmol) were dissolved in toluene (50 ml). Tetrabutylammonium bromide (0.8 g, 2.48 mmol) and potassium carbonate (20.665 g, 150 mmol) were added to the solution, and the mixture was stirred vigorously at 50 °C under argon for 5 h. It was cooled and filtered. The filter cake was washed with hexane and the combined filtrates were concentrated under reduced pressure at RT (but not completely, to prevent the polymerization of methyl 2-phenylacrylate). Sodium borohydride (0.860 g, 22.73 mmol, dissolved in 40 ml ethanol) was added to a vigorously stirred solution of diphenyl diselenide (3.550 g, 11.37 mmol) in dry THF (30 ml). A strongly exothermic reaction followed and the yellow color of diphenyl

diselenide disappeared. The solution of benzeneselenol was then added to the methyl 2-phenylacrylate of the first step at −40 °C under argon. The mixture was stirred and slowly warmed up to RT overnight. The solution was concentrated under reduced pressure and EtOAc (50 ml) as well as water (50 ml) were added to the residue. The organic layer was separated and the aqueous one was extracted with EtOAc (2 x 40 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (20:1), R_f = 0.42] to yield methyl 2-phenyl-3-(phenylselanyl)propanoate (±)-**159** (3.587 g, 50%) as a colorless oil.

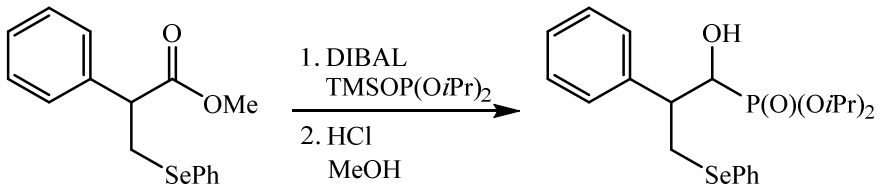
IR (Si): ν = 2950, 1736, 1454, 1325, 1263, 1213, 913.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.57-7.49 (m, 2H, H_{arom}), 7.38-7.24 (m, 8H, H_{arom}), 3.88 (dd, J = 9.6 Hz, J = 6.0 Hz, 1H, CH), 3.69 (s, 3H, OMe), 3.57 (dd, J = 12.4 Hz, J = 9.6 Hz, 1H, $\underline{CH_2}$SePh), 3.21 (dd, J = 12.4 Hz, J = 6.0 Hz, 1H, $\underline{CH_2}$SePh).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 173.14 (s, 1C, C=O), 138.34 (s, 1C, C_{arom}), 133.31 (s, 2C, C_{arom}), 129.55 (s, 1C, C_{arom}), 129.13 (s, 2C, C_{arom}), 128.80 (s, 2C, C_{arom}), 127.77 (s, 1C, C_{arom}), 127.68 (s, 2C, C_{arom}), 127.30 (s, 1C, C_{arom}), 52.34 (s, 1C, OMe), 52.19 (s, 1C, CH), 30.31 (s, 1C, $\underline{CH_2}$SePh).

Elemental analysis calculated for $C_{16}H_{16}O_2Se$ (319.26): C: 60.19, H: 5.05; found: C: 61.69, H: 5.14.

Diastereomeric mixture of (±)-diisopropyl [1-hydroxy-2-phenyl-3-(phenylselanyl)propyl]phosphonate [(±)-160]



(±)-**159** (±)-**160**

Methyl 2-phenyl-3-(phenylselenyl)propanoate [(±)-**159**] (3.587 g, 11.24 mmol) was dissolved in dry toluene (30 ml) under argon. At −78 °C, DIBAH (11 ml, 11 mmol, 1 M in hexanes) was added very slowly and the solution was stirred for 1 h at this temperature. Then

diisopropyl trimethylsilyl phosphite (3.214 g, 13.488 mmol, dissolved in 6 ml MC, self-made) was added and the solution was stirred and warmed up slowly to RT overnight. 2 M HCl (30 ml) was added to quench the reaction and the mixture was stirred for 1 h. Then EtOAc (30 ml) was added and the organic layer was separated. The aqueous layer was washed with EtOAc (2 x 30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in methanol (20 ml) with 37% HCl (10 ml). This solution was stirred for 1 h at RT. After concentration under reduced pressure, EtOAc (30 ml) was added to the residue and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [MC/EtOAc (20:1), R_f = 0.23] to yield the diastereomeric hydroxyphosphonates (±)-**160** (3.500 g, 68%; ratio A/B 3.5:1 by ^{31}P NMR) as a colorless oil.

Mixture of diastereomers: IR (Si): ν = 3265, 2980, 1217, 1105, 992.

To obtain analytical samples of the individual diastereomers, the inseparable mixture (flash column chromatography, HPLC) was converted to chloroacetates, which were separated by semipreparative HPLC (hexanes/EtOAc 3:2; A: t_R = 13.5 min; B: t_R = 15.5 min). The chloroacetates were saponified to give homogenous hydroxyphosphonates A and B of (±)-**160**, respectively.

Oily diastereomer A was derived from less polar chloroacetate (by HPLC):

IR (Si): ν = 3271, 2978, 2926, 1454, 1438, 1385, 1375, 1213, 1105, 1071, 994.

^{1}H NMR (400.13 MHz, $CDCl_3$): ν = 7.47-7.41(m, 2H, H_{arom}), 7.30-7.17 (m, 8H, H_{arom}), 4.61 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.50 (oct, J = 6.3 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.33 (ddd, J = 9.1 Hz, J = 7.6 Hz, J = 4.4 Hz, 1H, CHP), 3.56-3.44 (m, 1H, $\underline{CH}$Ph), 3.34-3.21 (m, 2H, $\underline{CH_2}$SePh), 2.24 (dd, J = 8.5 Hz, J = 7.6 Hz, 1H, OH), 1.21 (d, J = 5.8 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.20 (d, J = 6.1 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.14 (d, J = 6.1 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.04 (d, J = 6.3 Hz, 3H, 1 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 139.42 (d, $J(^{31}P)$ = 5.4 Hz, 1C, C_{arom}), 132.78 (s, 2C, C_{arom}), 130.07 (s, 1C, C_{arom}), 129.17 (s, 2C, C_{arom}), 129.05 (s, 2C, C_{arom}), 128.30 (s, 2C, C_{arom}),

127.40 (s, 1C, C_{arom}), 126.94 (s, 1C, C_{arom}), 71.23 (d, $J(^{31}P)$ = 6.9 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.16 (d, $J(^{31}P)$ = 6.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 70.23 (d, $J(^{31}P)$ = 161.2 Hz, 1C, CHP), 47.18 (d, $J(^{31}P)$ = 3.9 Hz, 1C, $\underline{CH}$Ph), 31.09 (d, $J(^{31}P)$ = 12.2 Hz, 1C, $\underline{CH_2}$SePh), 24.03 (d, $J(^{31}P)$ = 5.4 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.99 (d, $J(^{31}P)$ = 6.1 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.76 (d, $J(^{31}P)$ = 4.6 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.67 (d, $J(^{31}P)$ = 5.3 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 22.19 (s, P=O).

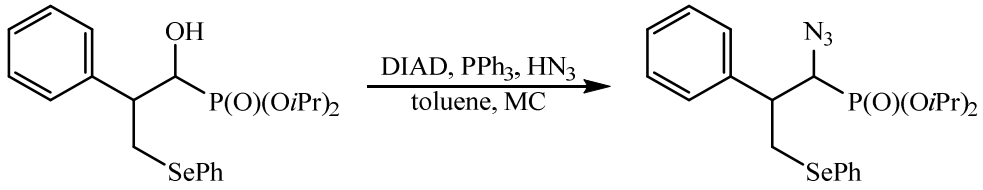
Oily diastereomer B was derived from more polar chloroacetate (by HPLC):
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.51-7.44 (m, 2H, H_{arom}), 7.37-7.21 (m, 8H, H_{arom}), 4.67 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.61 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.14-4.06 (m, 1H, CHP), 3.89-3.77 (m, 1H, $\underline{CH}$Ph), 3.45-3.29 (m, 3H, $\underline{CH_2}$SePh + OH), 1.30 (d, J = 6.2 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.25 (d, J = 6.2 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.19 (d, J = 6.2 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 1.16 (d, J = 6.2 Hz, 3H, 1 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 140.66 (d, $J(^{31}P)$ = 8.0 Hz, 1C, C_{arom}), 132.47 (s, 2C, C_{arom}), 130.75 (s, 1C, C_{arom}), 128.88 (s, 2C, C_{arom}), 128.72 (s, 2C, C_{arom}), 128.25 (s, 2C, C_{arom}), 127.22 (s, 1C, C_{arom}), 126.55 (s, 1C, C_{arom}), 72.09 (d, $J(^{31}P)$ = 159.9 Hz, 1C, CHP), 71.50 (d, $J(^{31}P)$ = 7.4 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.15 (d, $J(^{31}P)$ = 7.5 Hz, 1C, $\underline{CH}(CH_3)_2$), 47.65 (d, $J(^{31}P)$ = 2.3 Hz, 1C, $\underline{CH}$Ph), 29.88 (d, $J(^{31}P)$ = 8.7 Hz, 1C, $\underline{CH_2}$SePh), 24.07 (d, $J(^{31}P)$ = 3.4 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.83 (d, $J(^{31}P)$ = 5.4 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.80 (d, $J(^{31}P)$ = 3.6 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.74 (d, $J(^{31}P)$ = 5.4 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$): = 22.63 (s, P=O).

Elemental analysis calculated for $C_{21}H_{29}O_4PSe$ (455.39) (mixture of diastereomers): C: 55.39, H: 6.42; found: C: 55.20, H: 6.14.

Mixture of diastereomeric (±)-diisopropyl [1-azido-2-phenyl-3-(phenylselanyl)propyl]phosphonates [(±)-162]

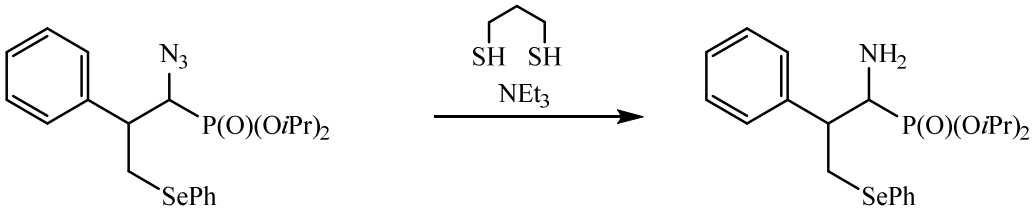


(±)-**160** (±)-**162**

The mixture (ratio of 4:1) of diastereomeric diisopropyl [1-hydroxy-2-phenyl-3-(phenylselanyl)propyl]phosphonates [(±)-**160**] (0.268 g, 0.59 mmol) and triphenylphosphine (0.233 g, 0.89 mmol) were dissolved in dry toluene (3 ml) and dry MC (1 ml) under argon. DIAD (0.9 ml, 0.9 mmol, 1 M in toluene) and then HN_3 (0.7 ml, 0.99 mmol, 1.42 M in toluene, old) were added dropwise at 0 °C. Stirring was continued for 15 min at 0 °C, 3 h at RT and 1 h at 50 °C. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography [first column: hexanes/EtOAc (3:1), R_f = 0.66 in hexanes/EtOAc (1:1) and second column: hexanes/Et_2O (1:2), R_f = 0.44] to yield an inseparable mixture of diastereomeric azides (±)-**162** (0.167 g, 59%; ratio 2:1) as a light yellow oil, containing one alkene as side product (ratio azides/alkene 2:1), which could not be removed. This mixture was used in the next step.

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 18.02 (major azide), 18.35 (minor azide), 14.48 (alkene).

Mixture of diastereomeric (±)-diisopropyl [1-amino-2-phenyl-3-(phenylselenyl)-propyl]phosphonate [(±)-165]



(±)-**162** (±)-**165**

Mixture of diastereomeric diisopropyl [1-azido-2-phenyl-3-(phenylselanyl)propyl]phosphonates **[**(±)-**162**] (0.436 g, 0.9 mmol, 46% pure) was dissolved in methanol (5 ml) under argon. 1,3-Propanedithiol (0.294 g, 0.27 ml, 2.72 mmol) and triethylamine (0.273 g, 0.37 ml, 2.70 mmol) were added to the solution and it was stirred at

RT overnight. The solvent was removed under reduced pressure at RT. CH_2Cl_2 (10 ml) and water (10 ml) were added and the organic layer was separated. The aqueous layer was extracted with MC (2 x 10 ml). The combined organic layers were concentrated under reduced pressure and purified by flash chromatography [MC/EtOH (40:1), R_f= 0.36] to yield mixture of diastereomeric amines (±)-**165** (0.198 g, 99%; ratio 7:3) as a colorless viscous oil. The signals in the ^{13}C NMR spectrum of the mixture could be assigned to the two diastereomers.

IR (Si): ν = 3387, 2979, 1580, 1478, 1454, 1386, 1230, 1178, 1142, 1106, 987, 913.

^1H NMR (400.27 MHz, $CDCl_3$): δ = 7.40-7.35 (m, 2H, H_{arom}), 7.26-7.10 (m, 8H, H_{arom}), 4.63-4.41 (m, 2H, $\underline{CH}(CH_3)_2$), 3.71-3.62 (m, 0.3H, CHP), 3.62-3.52 (m, 0.7H, CHP), 3.46-3.37 (m, 0.7H, $\underline{CH_2}$SePh), 3.37-3.10 (m, 2.3H, $\underline{CH_2}$SePh + $\underline{CH}CH_2$), 1.39 (bs, 2H, NH_2), 1.20 (d, J = 6.2 Hz, 0.9H, $CH(\underline{CH_3})_2$), 1.16 (d, J = 6.0 Hz, 2.1H, $CH(\underline{CH_3})_2$), 1.14 (d, J = 6.0 Hz, 3H, $CH(\underline{CH_3})_2$), 1.13 (d, J = 6.1 Hz, 0.9H, $CH(\underline{CH_3})_2$), 1.11 (d, J = 6.2 Hz, 0.9H, $CH(\underline{CH_3})_2$), 1.10 (d, J = 6.2 Hz, 2.1H, $CH(\underline{CH_3})_2$), 1.00 (d, J = 6.2 Hz, 2.1H, $CH(\underline{CH_3})_2$).

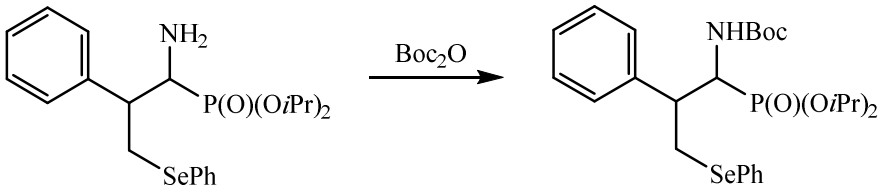
Major diastereomer A:
^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 140.12 (d, $J(^{31}P)$ = 6.5 Hz, 1C, C_{arom}), 132.67 (s, 2C, C_{arom}), 130.33 (s, 1C, C_{arom}), 129.03 (s, 2C, C_{arom}), 129.01 (s, 2C, C_{arom}), 128.25 (s, 2C, C_{arom}), 127.27 (s, 1C, C_{arom}), 126.80 (s, 1C, C_{arom}), 70.65 (d, $J(^{31}P)$ = 7.5 Hz, 1C, $\underline{CH}(CH_3)_2$), 70.42 (d, $J(^{31}P)$ = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 52.47 (d, $J(^{31}P)$ = 150.7 Hz, 1C, CHP), 46.77 (d, $J(^{31}P)$ = 3.5 Hz, 1C, $\underline{CH}$Ph), 31.79 (d, $J(^{31}P)$ = 11.1 Hz, 1C, $\underline{CH_2}$SePh), 24.07 (d, $J(^{31}P)$ = 3.6 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 24.02 (d, $J(^{31}P)$ = 3.9 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.90 (d, $J(^{31}P)$ = 4.7 Hz, 1C, 1 x $CH(\underline{CH_3})_2$), 23.78 (d, $J(^{31}P)$ = 5.6 Hz, 1C, 1 x $CH(\underline{CH_3})_2$).

Minor diastereomer B:
^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 140.12 (d, $J(^{31}P)$ = 6.5 Hz, 1C, C_{arom}), 132.75 (s, 2C, C_{arom}), 130.33 (s, 1C, C_{arom}), 128.94 (s, 2C, C_{arom}), 128.49 (s, 2C, C_{arom}), 128.35 (s, 2C, C_{arom}), 127.16 (s, 1C, C_{arom}), 126.73 (s, 1C, C_{arom}), 70.74 (d, $J(^{31}P)$ = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 70.42 (d, $J(^{31}P)$ = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 54.80 (d, $J(^{31}P)$ = 148.2 Hz, 1C, CHP), 47.22 (d, $J(^{31}P)$ = 3.2 Hz, 1C, $\underline{CH}$Ph), 28.69 (d, $J(^{31}P)$ = 4.3 Hz, 1C, $\underline{CH_2}$SePh), 24.15-23.85 (m 4C, 4 x $CH(\underline{CH_3})_2$).

^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 25.11 (s, integration 0.7, major diastereomer, P=O), 24.70 (s, integration 0.3, minor diastereomer, P=O).

Elemental analysis: calculated for $C_{21}H_{30}NO_3PSe$ (454.40): C: 55.51, H: 6.65, N: 3.08; found: C: 55.25, H: 6.32, N: 3.25.

Mixture of diastereomeric (±)-diisopropyl [1-*t*-butoxycarbonylamino-2-phenyl-3-(phenylselanyl)propyl]phosphonates [(±)-167]



(±)-**165** (±)-**167**

A mixture (ratio 7:3) of diastereomeric (±)-diisopropyl [1-amino-2-phenyl-3-(phenylselanyl)propyl]phosphonates **165** (0.090 g, 0.2 mmol) and Boc_2O (0.134 g, 0.61 mmol) were dissolved in dry ACN (1 ml) under argon. The solution was stirred at RT for 24 h, and then concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (2:1), R_f = 0.33] to yield a mixture of diastereomeric *N*-Boc-protected amines **167** (0.111 g, 99%) as colorless crystals. mp.: 70 °C (diastereomer A,), 124 °C (diastereomer B).

The two diastereomers were separated by preparative HPLC (miniprep., 15 ml/min; hexanes/EtOAc (7:3; A: t_R = 30.80 min; B: t_R = 35.70 min); analytical HPLC (2 ml/min; hexanes/EtOAc (7:3; A: t_R = 7.39 min; B: t_R = 8.32 min).

Diastereomer A: IR (Si): í = 3260, 2979, 1715, 1496, 1291, 1236, 1171, 991.

Diastereomer A (mixture of conformers A and B, ratio 4:1; only those signals are given which could be assigned securely):

^{1}H NMR (400.27 MHz, $CDCl_3$): *ä* = 7.48-7.40 (m, 2H, H_{arom}), 7.30-7.15 (m, 8H, H_{arom}), 4.72-4.58 (m, 1H, $\underline{CH}(CH_3)_2$), 4.58-4.51 + 4.33-4.27 (two m, 1.8H, NH + CHP of A and B), 4.50-4.35 (m, 1H, $\underline{CH}(CH_3)_2$), 3.47-3.30 (m, 2H), 3.27-3.12 (m, 1H), 1.48 (s, 1.8H, 0.6 x $C(\underline{CH_3})_3$

of B), 1.39 (s, 7.2H, 2.4 x C($\underline{CH_3}$)$_3$ of A), 1.26 (d, *J* = 6.1 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.25 (d, *J* = 6.0 Hz, 3H, CH($\underline{CH_3}$)$_2$), 1.17 (d, *J* = 6.1 Hz, 2.4H, 0.8 x CH($\underline{CH_3}$)$_2$ of A), 1.13 (d, *J* = 6.2 Hz, 0.6H, 0.2 x CH($\underline{CH_3}$)$_2$ of B), 0.94 (d, *J* = 6.2 Hz, 2.4H, 0.8 x CH($\underline{CH_3}$)$_2$ of A), 0.85 (d, *J* = 6.1 Hz, 0.6H, 0.2 x CH($\underline{CH_3}$)$_2$ of B).

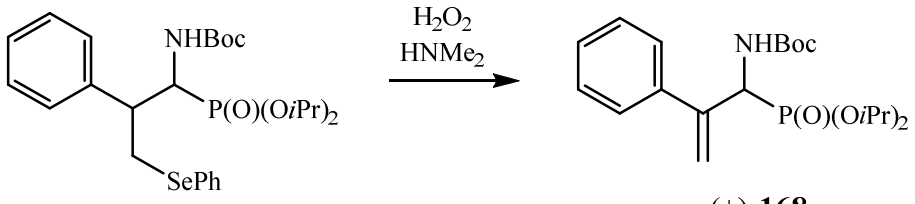
Diastereomer B: IR (Si): í = 3260, 2979, 1713, 1495, 1230, 1172, 994.
Diastereomer B (mixture of conformers A and B, ratio 4:1; only those signals are given which could be assigned securely):
^{1}H NMR (400.13 MHz, $CDCl_3$): *ä* = 7.46-7.39 (m, 2H, H_{arom}), 7.30-7.15 (m, 8H, H_{arom}), 4.88 (dd, *J* = 10.8 Hz, *J* = 3.5 Hz, 0.8H, NH of A), 4.70-4.45 (m, 2.2H, 2 x $\underline{CH}(CH_3)_2$ of A and B + NH of B), 4.34 (ddd, *J* = 19.6 Hz, *J* = 10.8 Hz, *J* = 5.1 Hz, 0.8H, CHP of A), 4.14 (ddd, *J* = 21.2 Hz, *J* = 11.3 Hz, *J* = 3.2 Hz, 0.2H, CHP of B), 3.67-3.55 (m, 1H, $\underline{CH_2}$SePh), 3.45-3.23 (m, 2H, $\underline{CH_2}$SePh + $\underline{CH}CH_2$), 1.38 (s, 7.2H, 2.4 x C($\underline{CH_3}$)$_3$ of A), 1.29-1.17 and 1.15-1.10 (two m, 12H, 4 x CH($\underline{CH_3}$)$_2$), 1.16 (s, 1.8H, 0.6 x C($\underline{CH_3}$)$_3$ of B).

^{13}C NMR (100.61 MHz, $CDCl_3$, only signals of major conformer A are given): *ä* = 154.98 (d, *J*(^{31}P) = 9.1 Hz, 1C, C=O), 140.26 (d, *J*(^{31}P) = 9.1 Hz, 1C, C_{arom}), 133.00 (s, 2C, C_{arom}), 128.93 (s, 2C, C_{arom}), 128.46 (s, 2C, C_{arom}), 128.30 (s, 2C, C_{arom}), 127.74 (s, 1C, C_{arom}), 126.85 (s, 1C, C_{arom}), 80.08 (s, 1C, $\underline{C}(CH_3)_3$), 71.57 (d, *J*(^{31}P) = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.14 (d, *J*(^{31}P) = 7.2 Hz, 1C, $\underline{CH}(CH_3)_2$), 52.48 (d, *J*(^{31}P) = 155.3 Hz, 1C, CHP), 47.16 (d, *J*(^{31}P) = 5.6 Hz, 1C, $\underline{CH}$Ph), 29.56 (d, *J*(^{31}P) = 5.2 Hz, 1C, $\underline{CH_2}$SePh), 28.26 (s, 3C, 3 x C($\underline{CH_3}$)$_3$), 24.11 (d, *J*(^{31}P) = 3.0 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.98 (d, *J*(^{31}P) = 3.4 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.72 (d, *J*(^{31}P) = 5.1 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.57 (d, *J*(^{31}P) = 5.4 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$); signal of SeC_{arom} not detected.

^{31}P NMR (161.98 MHz, $CDCl_3$): *ä* = 21.84 (s, integration 0.8, major diastereomer A, P=O), 21.40 (s, integration 0.2, minor diastereomer B, P=O).

Elemental analysis of mixture of diastereomers calculated for $C_{26}H_{38}NO_5PSe$ (554.52): C: 56.32, H: 6.91, N: 2.53; found: C: 56.26, H: 7.02, N: 2.52.

(±)-Diisopropyl *1-(tert*-butoxycarbonylamino)-2-phenyl-2-propenylphosphonate [(±)-168]



(±)-**167** (±)-**168**

Mixture of diastereomeric diisopropyl [1-*tert*-butoxycarbonylamino-2-phenyl-3-(phenylselanyl)propyl]phosphonates **[(±)-167]** (0.190 g, 0.35 mmol) was dissolved in dry THF (2 ml). Dimethylamine (0.2 ml, 0.4 mmol, 2 M in THF) and hydrogen peroxide (1 ml, 30% in H_2O) were added and the solution was stirred for 5.5 h at RT. The reaction mixture was concentrated under reduced pressure and water (10 ml) and MC (10 ml) were added to the residue. The organic layer was separated and the aqueous one was extracted with MC (2 x 5 ml). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes/EtOAc (2:1), R_f = 0.42] to yield unsaturated *N*-Boc aminophosphonate (±)-**168** (0.123 g, 90%) as colorless crystals. Mp. 104-105 °C.

IR (Si): ν = 3261, 2980, 2934, 1710, 1524, 1495, 1388, 1277, 1238, 1175, 997.

^{1}H NMR (400.13 MHz, $CDCl_3$; possibly two conformers are present in ratio of 6:1; only signals of major one are given): δ = 7.52-7.36 (m, 2H, H_{arom}), 7.34-7.21 (m, 3H, H_{arom}), 5.46 (d, J = 4.8 Hz, 1H, $\underline{CH_2}$=C), 5.43 (d, J = 4.8 Hz, 1H, $\underline{CH_2}$=C), 5.36-5.22 (m, 1H, NH), 4.99 (dd, J = 23.9 Hz, J = 9.8 Hz, 1H, CHP), 4.69 (oct, J = 6.2 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.56 (oct, J = 6.4 Hz, 1H, $\underline{CH}(CH_3)_2$), 1.41 (s, 9H, 3 x C($\underline{CH_3}$)$_3$), 1.28 (d, J = 6.2 Hz, 3H, 1 x CH($\underline{CH_3}$)$_2$), 1.22 (d, J = 6.2 Hz, 3H, 1 x CH($\underline{CH_3}$)$_2$), 1.14 (d, J = 6.2 Hz, 3H, 1 x CH($\underline{CH_3}$)$_2$), 1.09 (d, J = 6.2 Hz, 3H, 1 x CH($\underline{CH_3}$)$_2$).

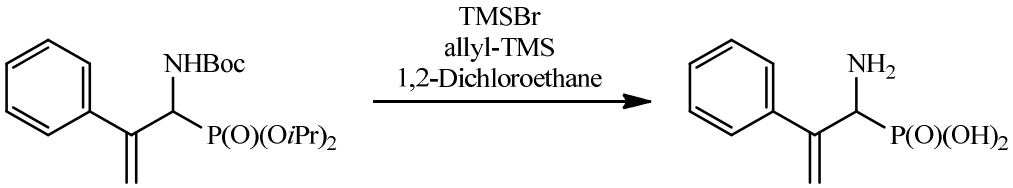
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 145.16 (s, 1C, C_{arom}), 140.37 (s, 1C, $\underline{C}$=CH_2), 128.23 (s, 2C, C_{arom}), 127.72 (s, 2C, C_{arom}), 127.04 (s, 1C, C_{arom}), 116.28 (d, J(^{31}P) = 8.2 Hz, 1C, C=$\underline{CH_2}$), 80.17 (s, 1C, $\underline{C}(CH_3)_3$), 71.83 (d, J(^{31}P) = 7.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.66 (d, J(^{31}P) = 7.6 Hz, 1C, $\underline{CH}(CH_3)_2$), 51.73 (d, J(^{31}P) = 156.5 Hz, 1C, CHP), 28.30 (s, 3C, 3 x C($\underline{CH_3}$)$_3$), 24.16 (d, J(^{31}P) = 3.5 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.90 (d, J(^{31}P) = 3.7 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.63 (d, J(^{31}P) = 4.8 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$), 23.59 (d, J(^{31}P) = 5.2 Hz, 1C, 1 x CH($\underline{CH_3}$)$_2$).

Signal of C=O was not detected.

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 20.92 (s, integration 0.85, major conformer?, P=O), 20.28 (s, integration 0.15, minor conformer?, P=O).

Elemental analysis calculated for $C_{20}H_{32}NO_5P$ (397.45): C: 60.44, H: 8.12, N: 3.52; found: C: 60.30, H: 8.49, N: 3.61.

(±)-1-Amino-2-phenyl-2-propenylphosphonic acid [(±)-148]



(±)-**168** (±)-**148**

Diisopropyl 1-(*tert*-butoxycarbonylamino)-2-phenyl-2-propenylphosphonate [(±)-**168**] (0.035 g, 0.09 mmol) was dissolved in dry 1,2-dichloroethane (2 ml) under argon. TMSBr (1.071 g, 0.9 ml, 6.99 mmol) and allyltrimethylsilane (0.100 g, 0.14 ml, 0.87 mmol) were added and the solution was stirred at 50 °C for 18 h. It was concentrated under reduced pressure after cooling. The residue was dissolved in 1,2-dichloroethane (2 ml) and concentrated again. The residue was dissolved in ethanol/water for desilylation. The solution was concentrated after 30 min and the residue purified by crystallization from water/EtOH to yield racemic 1-aminophosphonic acid (±)-**148** as colorless crystals (11 mg, 60%). Mp. 223-224 °C.

IR (ATR): ν = 3362, 2837, 2738, 2633, 2308, 1609, 1522, 1214, 1157, 1056, 1029, 936.

^{1}H NMR (400.13 MHz, D_2O): δ = 7.62-7.56 (m, 2H, H_{arom}), 7.53-7.43 (m, 3H, H_{arom}), 5.74 (d, J = 4.4 Hz, 1H, CH_2=C), 5.55 (d, J = 4.4 Hz, 1H, CH_2=C), 4.53 (d, $J(^{31}P)$ = 17.5 Hz, 1H, CHP).

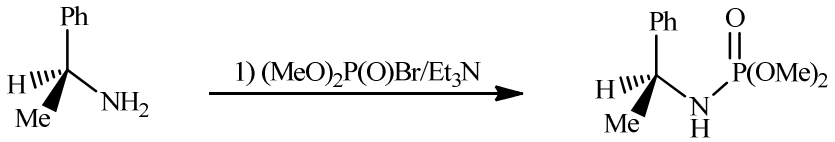
^{13}C NMR (100.61 MHz, D_2O): δ = 142.58 (d, $J(^{31}P)$ = 5.4 Hz, 1C, C_{arom}), 139.87 (d, $J(^{31}P)$ = 3.1 Hz, 1C, C=CH_2), 129.12 (s, 2C, C_{arom}), 128.92 (s, 1C, C_{arom}), 127.10 (s, 2C, C_{arom}), 116.60 (d, $J(^{31}P)$ = 7.4 Hz, 1C, C=CH_2), 52.52 (d, $J(^{31}P)$ = 136.3 Hz, 1C, CHP).

^{31}P NMR (161.98 MHz, D_2O): δ = 10.78 (s, P=O).

Elemental analysis calculated for $C_9H_{12}NO_3P \cdot 0.5H_2O$ (222.18): C: 48.65, H: 5.90, N: 6.30; found: C: 48.62, H: 5.95, N: 6.37.

3.2.11. The phosphonate-phosphinate rearrangement

(*S*)-(–)-Dimethyl *N*-1-phenylethylphosphoramidate [(*S*)-187]



(*S*)-**186** (*S*)-**187**

A solution of bromine in dry CH_2Cl_2 (14.77 mL, 22 mmol, 1.49 M) was added dropwise to a stirred solution of trimethyl phosphite (2.73 g, 2.59 mL, 22 mmol) in dry CH_2Cl_2 (10 mL) under argon at –50 °C. After 30 min (*S*)-1-phenylethylamine (*S*)-**186** (2.42 g, 2.58 mL, 20 mmol, 98% ee) and dry Et_3N (4.04 g, 5.53 mL, 40 mmol) were added and stirring was continued for 30 min at –50 °C and 2 h at room temperature. Water (9 mL) and HCl (16 mL, 2M) were added and the organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc, then EtOAc/EtOH 5:2; R_f = 0.42 for EtOAc) to yield phosphoramidate (*S*)-**187** (3.828 g, 84%) as colorless crystals; mp 53 °C (hexanes/CH_2Cl_2); $[\alpha]_D^{20}$ = –47.78 (*c* = 0.925, acetone). If the crude product was pure enough (as judged by ^{1}H NMR), it was used in the next step without flash chromatography.

IR (Si): ν = 3216, 2951, 1455, 1236, 1035.

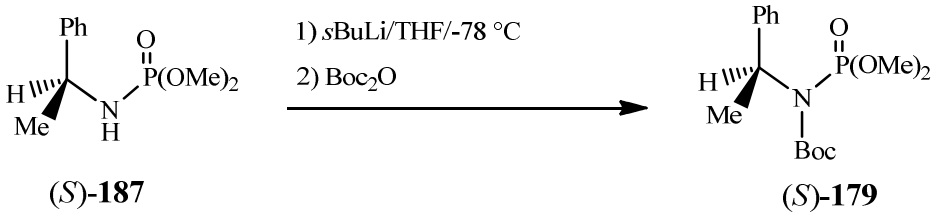
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.36-7.21 (m, 5H, H_{arom}), 4.31 (qdd, *J* = 15.7, 8.6, 6.8 Hz, 1H, CHN), 3.70 (d, *J* = 11.2 Hz, 3H, OCH_3),. 3.49 (d, *J* = 11.2 Hz, 3H, OCH_3), 3.41 (br. t, *J* = 9.9 Hz, 1H, NH, or dd, *J* = 11.1, 8.6 Hz), 1.49 (dd, *J* = 6.8, 0.7 Hz, 3H, CH_3).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 144.97 (d, $J(^{31}P)$ = 4.6 Hz, 1C, C_{arom}), 128.45 (s, 2C, C_{arom}), 127.09 (s, 1C, C_{arom}), 125.75 (s, 2C, C_{arom}), 52.93 (d, $J(^{31}P)$ = 5.4 Hz, 1C, OCH_3), 52.73 (d, $J(^{31}P)$ = 5.3 Hz, 1C, OCH_3), 51.37 (s, 1C, CHN), 25.08 (d, $J(^{31}P)$ = 6.2 Hz, 1C, CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 11.44 (s, P=O).

Elemental analysis calculated for $C_{10}H_{16}NO_3P$ (229.21): C: 52.40, H: 7.04, N: 6.11; found: C: 52.47, H: 6.83, N: 5.99.

(*S*)-(–)-Dimethyl *N*-(*t*-butoxycarbonyl)-N-(1-phenylethyl)phosphoramidate [(*S*)-179]



(*S*)-**187** (*S*)-**179**

*s*BuLi (13.5 mL, 18.85 mmol, 1.2 equiv., 1.4 M in cyclohexane) was added dropwise to a stirred solution of phosphoramidate (*S*)-**187** (3.60 g, 15.71 mmol) in dry THF (25 mL) under argon at –78 °C, followed by Boc_2O (3.77 g, 17.28 mmol, 1.1 equiv.) dissolved in dry THF (4 mL) after 15 min. Stirring was continued for 1 h at –78 °C, then during slow warming to room temperature and finally for 1.5 h at room temperature. AcOH (25 mL, 1 M in CH_2Cl_2) was added to the reaction mixture. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc, R_f = 0.67) to give *N*-Boc-protected phosphonramidate (*S*)-**179** (3.98 g, 77%) as a colorless oil; $[\alpha]_D^{20} = -10.15$ (*c* = 1.3, acetone).

IR (Si): ν = 2979, 1718, 1369, 1289, 1160, 1038.

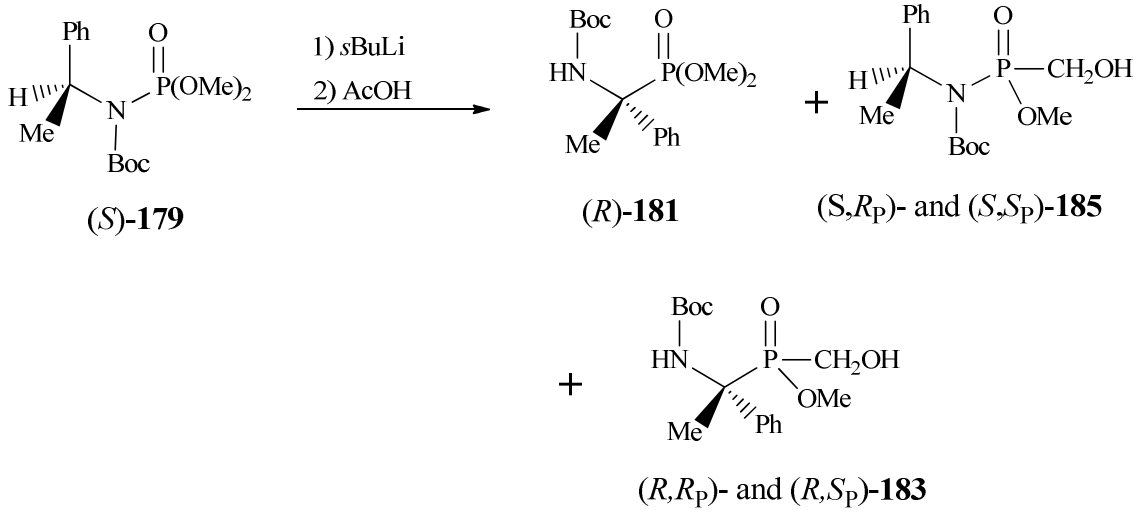
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.42-7.14 (m, 5H, H_{arom}), 5.40 (qd, *J* = 13.8, 7.0 Hz, 1H, CHN), 3.79 (d, *J* = 11.6 Hz, 3H, OCH_3),. 3.70 (d, *J* = 11.8 Hz, 3H, OCH_3), 1.77 (d, *J* = 7.0 Hz, 3H, CH_3), 1.28 (s, 9H, 3 x C($\underline{CH_3}$)$_3$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 153.23 (d, $J(^{31}P)$ = 7.3 Hz, 1C, CO), 142.11 (d, $J(^{31}P)$ = 3.1 Hz, 1C, C_{arom}), 127.96 (s, 2C, C_{arom}), 126.75 (s, 2C, C_{arom}), 126.69 (s, 1C, C_{arom}), 82.49 (s, 1C, $\underline{C}(CH_3)_3$), 54.80 (d, $J(^{31}P)$ = 3.1 Hz, 1C, CHN), 54.29 (d, $J(^{31}P)$ = 6.1 Hz, 1C, OCH_3), 53.69 (d, $J(^{31}P)$ = 6.1 Hz, 1C, OCH_3), 27.85 (s, 3C, 3 x C($\underline{CH_3}$)$_3$), 18.24 (s, 1C, CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 7.23 (s, P=O)

Elemental analysis calculated for $C_{15}H_{24}NO_3P$ (329.33): C: 54.71, H: 7.35, N: 4.25; found: C: 54.28, H: 7.23, N: 4.28.

(*R*)-(+)-Dimethyl 1-*(t*-butoxycarbonylamino)-1-phenylethylphosphonate [(*R*)-181]



(*S*)-**179** (*R*)-**181** (S,R_P)- and (*S*,S_P)-**185**

(*R*,R_P)- and (*R*,S_P)-**183**

*s*BuLi (4.86 mmol, 1.4 equiv., 3.5 mL, 1.4 M in cyclohexane) was added dropwise to a stirred solution of phosphoramidate (*S*)-**179** (1.144 g, 3.47 mmol) in dry THF (10 mL) at –95 °C under argon atmosphere. After stirring for 30 min AcOH (1.9 mL, 5.7 mmol, 3 M in dry CH_2Cl_2) was added, followed by H_2O (10 mL) at room temperature. The organic phase was removed and the aqueous one was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue (^{31}P NMR: (*S*)-**179**/(*R*)-**181**/(*S*,R_P)- and (*S*,S_P)-**185**/(*R*,R_P)- and (*R*,S_P)-**183**/(*S*)-**187** 0:88:7:3:2) was flash chromatographed (hexanes/EtOAc 1:3, R_f = 0.44) to yield phosphonate (*R*)-**181** (0.843 g, 74%) as a colorless oil;

$[\alpha]_D^{20}$ = +2.73 (*c* = 1.5, acetone).

IR (Si): ν = 3443, 3278, 2977, 2957, 1730, 1495, 1251, 1167, 1031.

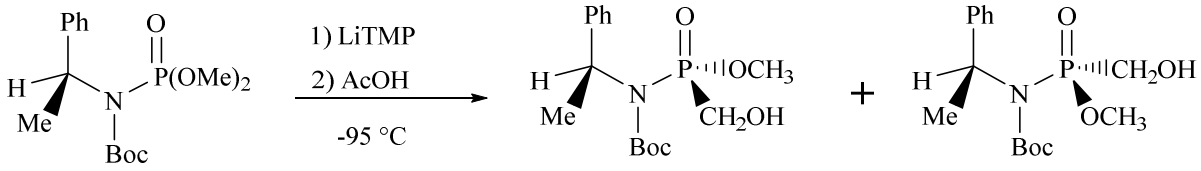
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50-7.44 (m, 2H, H_{arom}), 7.36-7.30 (m, 2H, H_{arom}), 7.28-7.22 (m, 1H, H_{arom}), 5.64 (br. d, *J* = 10.4 Hz, 1H, NH), 3.55 (d, *J* = 10.4 Hz, 3H, OCH_3), 3.48 (d, *J* = 10.4 Hz, 3H, OCH_3),2.03 (d, *J* = 16.2 Hz, 3H, CH_3), 1.32 (br. s, 9H, 3 x C($\underline{CH_3}$)$_3$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 154.07 (br, s, 1C, C=O), 138.85 (s, 1C, C_{arom}), 128.05 (d, $J(^{31}P)$ = 2.3 Hz, 2C, C_{arcom}), 127.34 (d, $J(^{31}P)$ = 3.1 Hz, 1C, C_{arom}), 126.94 (d, $J(^{31}P)$ = 4.6 Hz, 2C, C_{arom}), 79.93 (s, 1C, $\underline{C}(CH_3)_3$), 57.76 (d, $J(^{31}P)$ = 148.4 Hz, 1C, CP), 54.03 (d, $J(^{31}P)$ = 7.3 Hz, 1C, OCH_3), 54.00 (d, $J(^{31}P)$ = 7.3 Hz, 1C, OCH_3), 28.12 (s, 3C, 3 x $C(\underline{CH_3})_3$), 21.22 (br. s, 1C, CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 28.18 (s, P=O).

Elemental analysis calculated for $C_{15}H_{24}NO_3P$ (329.33): C: 54.71, H: 7.35, N: 4.25; found: C: 54.77, H: 7.28, N: 4.26.

(*S*,*R*$_P$)-(–)- and (*R*,*R*$_P$)-(+)-Methyl *N*-*t*-butoxycarbonyl-*N*-(1-phenylethyl)-hydroxy-methylphosphonamidate [(*S*,*R*$_P$)- and (*S*,*S*$_P$)-185]



(*S*)-**179** (*S*,*R*$_P$)-**185** (*S*,*S*$_P$)-**185**

+ (*R*)-**181** + **183** (S,*S*$_P$)-**185** is more polar than (S,*R*$_P$)-**185**

*n*BuLi (2.4 mL, 6 mmol, 2.5 M in cyclohexane) was added to a stirred solution of TMPH (0.848 g, 1.0 ml, 6 mmol) in dry THF (3 mL) at –30 °C under an argon atmosphere. After 15 min the solution was cooled to –95 °C and a solution of phosphoramidate (*S*)-**179** (0.988 g, 3 mmol) in dry THF (total of 3 mL) was added, followed by a solution of AcOH (0.540 g, 0.52 mL, 3 equiv.) in dry THF (1 mL) 1 h later. The cooling bath was removed and when the reaction mixture had reached room temperature, it was diluted with water (10 mL). The organic phase was separated and the aqueous one was extrated with EtOAc (3 x 15 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 5:2 for starting material; EtOAc for **185,** R_f = 0.32 for EtOAc) to yield starting material (0.149 g, 15%) and a mixture of (*S*,*R*$_P$)- and (*S*,*S*$_P$)-**185** (0.545 g, 55%; (*S*,*R*$_P$)-**183** is negligibly less polar by TLC than (*S*,*S*$_P$)-**185**; ratio 60:40 by ^{31}P NMR) as a colorless viscous oil.

Similarly, (*S*)-**179** (0.908 g, 2.8 mmol) was reacted with LDA (2.5 equiv, prepared freshly from *i*Pr_2NH and 2.5 M *n*BuLi). Ratio of starting material (*S*)-**181**/phosphonate (*R*)-**181**/phosphonamidates **185**/phosphinates **183** in crude product 30:35:35:1 (by ^{31}P NMR). Flash chromatography (at first with EtOAc/hexanes 5:2 to recover starting material, then EtOAc) gave recovered starting material (*S*)-**179** (0.180 mg 20%), phosphonate (*R*)-**181** (0.181 g, 20%) and diastereomers **185** (0.247 g, 27%).

(*S*,R_P)-**185**: Less polar diastereomer by HPLC, analytical HPLC, Shimadzu EC 250/4 NUCLEOSIL 50-5 [2 ml/min, EtOAc/hexanes (5:2)], (*S*,R_P)-**185**: t_R = 6.01 min, (*S*,S_P)-**185**: t_R = 7.25 min. (*S*,R_P)- and (*S*,S_P)-**185** were separated by semipreparative HPLC: SemiPrep Superspher RSI 60, (40 ml/min, EtOAc/hexanes (5:2)].

(*S*,R_P)-**185** obtained by semipreparative HPLC was crystallized from CH_2Cl_2/hexanes at +4 °C by slow evaporation of solvent. Crystals were suitable for single crystal X-ray structure analysis. Mp. 88-90 °C.

$[\alpha]_D^{23}$ = –35.03 (*c* = 1.45, acetone);

IR (Si): ν = 3318, 2979, 1709, 1452, 1385, 1370, 1278, 1255, 1158, 1056.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.38-7.33 (m, 2H, H_{arom}), 7.30-7.22 (m, 2H, H_{arom}), 7.21-7.14 (m, 1H, H_{arom}), 5.37 (qd, *J* = 8.4, 7.1 Hz, 1H, CHN), 4.24 (ABP-sys, *J* = 14.7 Hz, 7.7, 3.5 Hz, 2H, PCH_2O), 3.79 (br. s, 1H, OH), 3.73 (d, *J* = 11.6 Hz, 3H, OCH_3), 1.75 (d, *J* = 7.1 Hz, 3H, CH_3), 1.19 (s, 9H, 3 x ($\underline{C}H_3$)$_3$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 154.61 (d, *J*(^{31}P) = 9.9 Hz, 1C, C=O), 141.76 (d, *J*(^{31}P) = 3.8 Hz, 1C, C_{arom}), 127.97 (s, 2C, C_{arom}), 126.69 (s, 1C, C_{arom}), 126.66 (s, 2C, C_{arom}), 83.43 (s, 1C, $\underline{C}(CH_3)_3$), 59.64 (d, *J*(^{31}P) = 143.0 Hz, 1C, CH_2P), 52.83 (s, 1C, CHN), 51.76 (d, *J*(^{31}P) = 7.7 Hz, 1C, OCH_3), 27.72 (s, 3C, 3 x ($\underline{C}H_3$)$_3$), 18.26 (d, *J*(^{31}P) = 2.5 Hz, 1C, CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 31.67 (s, P=O).

Elemental analysis calculated for $C_{15}H_{24}NO_3P$ (329.33): C: 54.71, H: 7.35, N: 4.25; found: C: 54.73, H: 7.44, N: 4.21.

(*S*,*S*$_P$)-**185** obtained by semipreparative HPLC was crystallized from CH_2Cl_2/hexanes at +4 °C by slow evaporation of solvent, thin needles. Mp. 101-103 °C;

$[\alpha]_D^{20} = -5.51$ (*c* = 0.69, acetone).

IR (Si): ν = 3318, 2976, 1711, 1392, 1368, 1272, 1252, 1235, 1160, 1141, 1047.

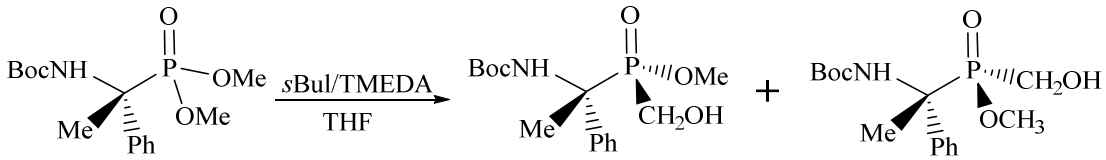
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.42-7.36 (m, 2H, H_{arom}), 7.32-7.26 (m, 2H, H_{arom}), 7.23-7.18 (m, 1H, H_{arom}), 5.38 (qd, *J* = 9.9, 7.1 Hz, 1H, CHN), 4.14 (ABP-sys, *J* = 14.8 Hz, 7.1, 3.4 Hz, 2H, PCH_2O), 3.79 (d, *J* = 11.1 Hz, 3H, OCH_3), 3.20 (br. s, 1H, OH), 1.74 (d, *J* = 7.1 Hz, 3H, CH_3), 1.26 (s, 9H, 3 x ($\underline{CH_3}$)$_3$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 154.68 (d, *J*(^{31}P) = 9.9 Hz, 1C, C=O), 141.87 (s, 1C, C_{arom}), 127.94 (s, 2C, C_{arom}), 126.89 (s, 2C, C_{arom}), 126.73 (s, 1C, C_{arom}), 83.44 (s, 1C, $\underline{C}(CH_3)_3$), 59.31 (d, *J*(^{31}P) = 141.5 Hz, 1C, CH_2P), 53.06 (s, 1C, CHN), 52.49 (d, *J*(^{31}P) = 7.7 Hz, 1C, OCH_3), 27.85 (s, 3C, 3 x ($\underline{CH_3}$)$_3$), 18.21 (d, *J*(^{31}P) = 2.5 Hz, 1C, CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 31.67 (s, P=O).

Elemental analysis calculated for $C_{15}H_{24}NO_3P$ (329.33): C: 54.71, H: 7.35, N: 4.25; found: C: 54.67, H: 7.51, N: 4.24.

Conversion of phosphonamidate (*R*)-181 to diastereomeric phosphinates (*R*,*S*$_P$)-183 and (*R*,*R*$_P$)-183, respectively.



(*R*)-**181** (*R*,*S*$_P$)-**183** (*R*,*R*$_P$)-**183**

more polar than (*R*,*S*$_P$)-**183** by HPLC

Experiment with LiTMP: *s*BuLi (6.4 mmol, 2.5 equiv, 2.56 mL, 2.5 M in cyclohexane) was added to a stirred solution of TMPH (0.904 g, 6.4 mmol, 1.08 mL) in dry THF (3.5 mL) at –30 °C under argon. After 15 min the flask was cooled to –78 °C and the solution of (*R*)-**181** (0.843 g, 2.56 mmol) in dry THF was added slowly. Stirring was continued for 18 h at –78

°C. The cooling bath was removed and AcOH (0.472 g, 7.68 mmol, 2.6 mL of solution, 3 M in dry CH_2Cl_2), HCl (0.5 M, 10 mL) and EtOAc were added. The organic phase was separated and the aqueous one extracted with EOAc (2 x 15 mL). The combined organic layers were washed with water (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product (^{31}P NMR: phosphonate (*R*)-**181**: phosphinates (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**183** = 88:12, by ^{1}H NMR: 81:19; by ^{1}H NMR: (*R*,*S*$_P$)-1**83**:(*R*,*R*$_P$)-**183** = 22:78) was flash chromatographed (hexanes/EtOAc 1:3) to recover only starting phosphonate (*R*)-**181** (0.543 g, 64%).

Experiment with 2.5 equiv of *s*BuLi/TMEDA/Et$_2$O: *s*BuLi (3.75 mmol, 2.5 equiv, 2.7 mL, 1.4 M in cyclohexane) was added dropwise to a stirred solution of (*R*)-**181** (0.483 g, 1.5 mmol) and dry TMEDA (0.436 g, 3.75 mmol, 0.57 mL, 2.5 equiv) in dry Et_2O (1.5 mL) at –78 °C under argon. After stirring for 2 h (at the end of the second h the temperature had risen to –60 °C), AcOH (0.45 g, 7. 5 mmol, 0.43 mL, 5 equiv, 2.5 mL of solution, 3 M in dry CH_2Cl_2), HCl (10 mL, 0.25 M) and EtOAc (15 mL) were added. The phases were separated and the aqueous one was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue (^{31}P NMR: starting phosphonate (*R*)-**181**:phosphinates (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**183** (have same chemical shift) = 63:37, by ^{1}H NMR: (*R*,*S*$_P$)-**183**:(*R*,*R*$_P$)-**183** = 56:44) was purified by flash chromatography (EtOAc/EtOH, 10:1, starting material R_f = 0.49; diastereomers (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**183** formed one spot of R_f = 0.35) to yield mixture of phosphinates (0.184 g, 37%; ratio of phosphinates (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**183** = 58 : 42 by ^{1}H NMR).

Diasteromer (*R*,*S*$_P$)-**183** is less polar than (*R*,*R*$_P$)-**183** by HPLC; analytical HPLC, Shimadzu EC 250/4 NUCLEOSIL 50-5, 2 ml/min, 100% EtOAc, (*R*,*S*$_P$)-**183**: t_R = 6.99 min, (*R*,*R*$_P$)-**183**: t_R = 8.83 min, semipreparative HPLC: SemiPrep Superspher RSI 60, 40 ml EtOAc/min.

Diastereomer (*R*,*S*$_P$)-**183** was crystallized by slow evaporation of solvent from a solution in CH_2Cl_2/hexanes at 4 °C to give very thin colourless crystals, mp 117-120°C;

$[\alpha]_D^{23}$ = +25.1 (*c* = 1.0, acetone).

IR (Si): ν = 3331, 2980, 1727, 1495, 1252, 1168, 1032.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.53-7.45 (m, 2H, H_{arom}), 7.38-7.31 (m, 2H, H_{arom}), 7.30-7.22 (m, 1H, H_{arom}), 5.75 (very br. s, 1H, NH), 3.88 (AB part of ABX-system, J_{AB} = 14.9 Hz, J = 2.8, 2.5 Hz, PCH_2O), 3.66 (br. s, 1H, OH), 3.49 (d, J = 9.9 Hz, 3H, OCH_3), 1.96 (d, J = 14.4 Hz, 3H, CH_3), 1.35 (br. s, 9H, Me_3C);

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 155.00 (d, J = 9.1 Hz, CO), 135.85 (Car), 128.46 (2HCar), 127.68 (Hcar), 126.545 (2HCar), 80.60 (OCq), 59.31 (d, J = 90.3 Hz), 57.53 (d, J = 99.4 Hz, PhCq?), 52.82 (d, J = 7.7 Hz, $POCH_3$), 28.23 (3C, Me_3C), 22.08 (br. s, 1C, CH_3);

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 50.13.

Elemental analysis calculated for $C_{15}H_{24}NO_3P$ (329.33): C: 54.71, H: 7.35, N: 4.25; found: C: 54.46, H: 7.60, N: 4.21.

Diastereomer (R,R_P)-**183** was crystallized by slow evaporation of solvent from a solution in CH_2Cl_2/hexanes at 4 °C to give colourless crystals, suitable for single crystal X-ray structure analysis; mp 132-133 °C,

$[\alpha]_D^{23}$ = +15.6 (c = 1.0, acetone).

IR (Si): ν = 3316, 2979, 1712, 1495, 1368, 1169, 1055, 1033.

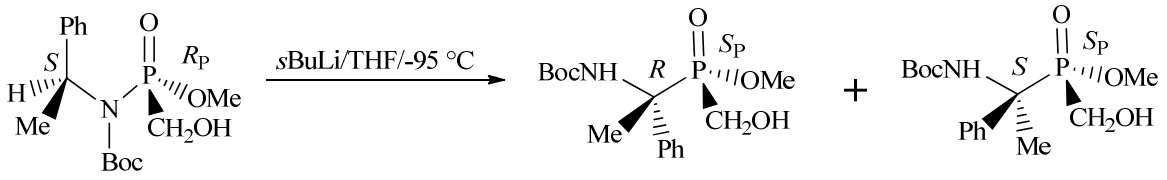
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.48-7.40 (m, 2H, H_{arom}), 7.38-7.30 (m, 2H, H_{arom}), 7.30-7.24 (m, 1H, H_{arom}), 5.91 (br. s, 1H, NH), 3.80 (AB system, J = 14.8, J = 2.6 Hz, 2H, CH_2O), 3.70 (d, J = 9.9 Hz, 3H, CH_3), 3.5 (br. s, 1H, OH), 1.97 (d, J = 14.2 Hz, 3H, CH_3), 1.35 (br. s, 9H, tBu).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 154.92 (d, J = 12.2 Hz, CO), 138.95 (C_{arom}), 128.45 (d, J = 1.5 Hz, 2C, HC_{arom}), 127.59 (d, J = 2.3 Hz, HC_{arom}), 126.43 (d, J = 3.1 Hz, 2C, HC_{arom}), 80.49 (OCq), 59.44 (d, J = 91.0 Hz, PC), 57.18 (d, J = 101.0 Hz, PCH_2O), 53.15 (d, J = 7.7 Hz, OCH_3), 28.20 (s, 3C, Me_3C), 21.82 (CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 50.20.

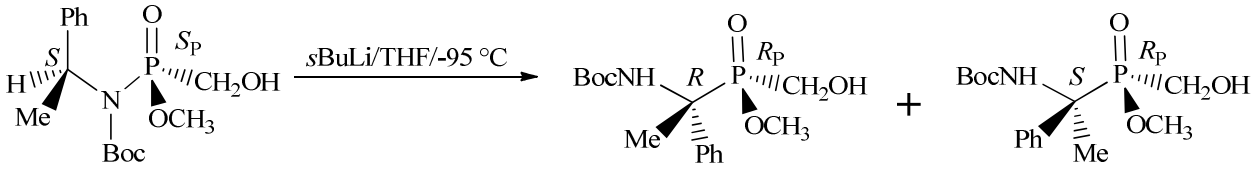
Analysis calcd for $C_{15}H_{24}NO_3P$ (329.33): C 54.71; H 7.35; N 4.25; found: C 54.68; H 7.43; N 4.25.

Conversion of phosphonamidates 185 to methyl (1-*t*-butoxycarbonylamino-1-phenylethyl)-(hydroxymethyl)phosphinates 183, respectively



(S,R_P)-**185** (R,S_P)-**183** (S,S_P)-**183**

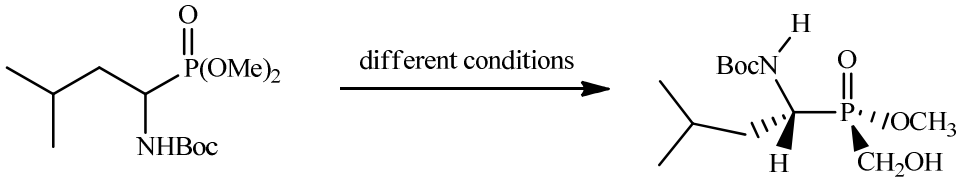
s-BuLi (2.90 mmol, 3.3 equiv, 2.1 mL, 1.4 M in cyclohexane) was added dropwise to a stirred solution of homogenous (S,R_P)-**185** (0.291 g, 0.88 mmol) in dry THF (3 mL) at -95 °C under argon (the reaction mixture turned intensely yellow). After 1 h the reaction was quenched with AcOH (0.349 g, 5.81 mmol, 6.6 equiv, 1.94 mL, 3 M solution in dry CH_2Cl_2) and HCl (5 mL, 0.25 M). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) und concentrated under reduced pressure. The residue was flash chromatographed (EtOAc:EtOH 10:1, educt R_f = 0.74, phosphinates R_f = 0.35) to yield recovered starting (S,R_P)-**185** (63 mg, 22%) and phosphinate **183** (0.148 g, 51%), which was a mixture of (R,S_P)-**183**:(S,S_P)-**183** = 89:11; by HPLC 92:8.



(S,S_P)-**185** (R,R_P)-**183** (S,R_P)-**183**

Similarly to (S,R_P)-**185**, phosphonate (S,S_P)-**185** (132 mg, 0.4 mmol) was reacted with *s*BuLi, (S,S_P)-**185**:**183** = 67 : 33 include product (by ^{1}H NMR), recovered starting material (68 mg, 52%), phosphinates (33 mg, 25%), (R,R_P)-**183**:(R,S_P)-**183** = 89:11 by ^{1}H NMR, 88:12 by HPLC.

3.2.12. The phosphonate-phosphinate rearrangement of (±)-1-(*t*-butoxy-carbonylamino)-3-methylbutylphosphonate



(±)-**190** (±)-**197**

General procedure for phosphonate-phosphinate rearrangement (for details see Table 2.01):

Boc-protected aminophosphonate (±)-**190** (1-2 mmol) dried by co-evaporation with toluene, was dissolved in a dry THF, Et_2O (4 ml/mmol) or a mixture of dry THF/dimethoxyethane (1:1; 4 ml/ mmol) under argon at RT. A strong base (LiTMP freshly prepared from *n*BuLi (1.6 M)/TMP) was added slowly with or without a stoichiometric amount of TMEDA at various temperatures. The solution was stirred for 2 h (except Entry 7, 8: 7 h) and then the reaction was quenched with acetic acid (3 equivalent, 3 M in MC) at low temperature. Excess 2 M HCl and. water were added and the mixture was extracted with MC. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt, R_f = 0.19) to yield phosphinate **197** as a colorless oil.

IR (ATR): ν = 3255, 2957, 1704, 1529, 1391, 1367, 1302, 1275, 1255, 1165, 1036.

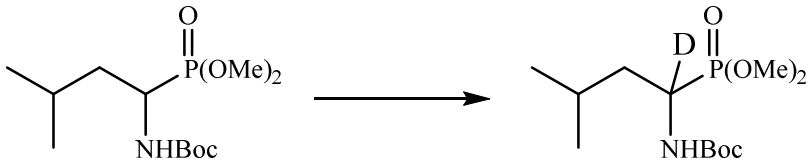
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.61 (d, J = 9.1 Hz, 1H, NH), 4.50-3.91 (m, 2H, CHP + OH), 3.89-3.80 (m, J = 2H, CH_2O), 3.77 (d, $J(^{31}P)$ = 10.1 Hz, 3H, OCH_3), 1.83-1.62 (m, 2H, $\underline{CH_2}CHP$), 1.53-1.44 (m, 1H, $\underline{CH}(CH_3)_2$), 1.42 (bs, 9H, 3 x $C(\underline{CH_3})_3$), 0.93 (d, J = 6.6 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 0.86 (d, J = 6.5 Hz, 3H, 1 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 157.16 (s, 1C, C=O), 81.13 (s, 1C, $\underline{C}(CH_3)_3$), 54.85 (d, $J(^{31}P)$ = 98.3 Hz, 1C, $P\underline{CH_2}OH$), 51.92 (d, $J(^{31}P)$ = 7.4 Hz, 1C, OCH_3), 44.13 (d, $J(^{31}P)$ = 107.6 Hz, 1C, CHP), 34.40 (s, 1C, $\underline{CH_2}CHP$), 28.22 (s, 3C, 3 x $C(\underline{CH_3})_3$), 24.29 (d, $J(^{31}P)$ = 10.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 23.25 (s, 1C, 1 x $CH(\underline{CH_3})_2$), 20.82 (s, 1C, 1 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$; very likely two conformers): δ = 52.59 (s, 0.96P, P=O), 50.43 (s, 0.04P, P=O).

Elemental analysis calculated for $C_{12}H_{26}NO_5P$ (295.31): C: 48.81, H: 8.87, N: 4.74; found: C: 48.52, H: 8.58, N: 4.66.

Quenching of reaction with AcOD/D_2O and isolation of starting material:



(±)-**190** (±)-[1-D]**199**

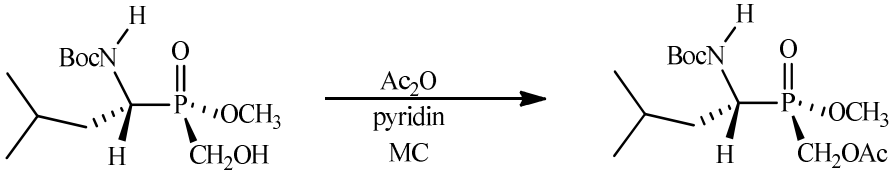
When the rearrangement was quenched with AcOD (2.5 Equiv., dissolved in 0.5 ml D_2O and 2 ml THF), the partly deuterated starting material (45%) was isolated by flash chromatography (AcOEt, R_f = 0.47); 30% of the molecules were deuterated at C-1 (by 1H NMR).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.61 (d, J = 9.3 Hz, 1H, NH), 4.15-4.02 (m, 0.68H, CHP), 3.72 (d, $J(^{31}P)$ = 10.4 Hz, 3H, OCH_3), 3.71 (d, $J(^{31}P)$ = 10.6 Hz, 3H, OCH_3), 1.78-1.61 (m, 1H, $\underline{CH}(CH_3)_2$), 1.56-1.45 (m, 2H, $\underline{CH_2}CHP$), 1.38 (bs, 9H, 3 x $C(\underline{CH_3})_3$), 0.89 (d, J = 6.7 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 0.87 (d, J = 6.7 Hz, 3H, 1 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 155.17 (d, $J(^{31}P)$ = 4.5 Hz, 1C, C=O), 79.87 (s, 1C, $\underline{C}(CH_3)_3$), 53.08 (d, $J(^{31}P)$ = 7.1 Hz, OCH_3), 52.81 (d, $J(^{31}P)$ = 6.7 Hz, OCH_3), 44.80 (d, $J(^{31}P)$ = 155.7 Hz, CHP), 38.39 (d, $J(^{31}P)$ = 2.6 Hz, 0.7C, $\underline{CH_2}CHP$), 38.29 (d, $J(^{31}P)$ = 2.6 Hz, 0.3C, CH_2CDP), 28.19 (s, 3C, 3 x $C(\underline{CH_3})_3$), 24.37 (d, $J(^{31}P)$ = 13.3 Hz, 1C, $\underline{CH}(CH_3)_2$), 23.20 (s, 1C, 1 x $CH(\underline{CH_3})_2$), 20.06 (s, 1C, 1 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$, very likely two conformers): δ = 29.60 (s, 0.86P, P=O), 29.01 (s, 0.14P, P=O); the non-deuterated starting material showed a ratio of 85:15.

Acetylation of phosphinate (±)-197



(±)-**197** (±)-**199**

Phosphinate (±)-**197** (0.055 g, 0.19 mmol) was dissolved in MC (1 ml). Dry pyridine (0.49 g, 0.5 ml, 6.19 mmol) and acetic acid anhydride (0.038 g, 0.04 ml, 0.37 mmol) were added at RT. The solution was stirred overnight, concentrated under reduced pressure at 25 mbar and finally dried for 3 h at 0.5 mbar at 60 °C. The residue was crystallized from hexanes/MC to yield acetate (±)-**199** (0.060 g, 95%) as colorless crystals, suitable for single-crystal X-ray structure analysis. Mp. 80-81°C.

IR (ATR): ν = 3260, 2959, 1756, 1710, 1535, 1370, 1209, 1172, 1044, 913.

^{1}H NMR (400.13 MHz, $CDCl_3$; two conformers): δ = 4.69 (d, J = 10.4 Hz, 0.9H, NH), 4.62-4.50 (m, 0.1H, NH), 4.42 (A part of ABX-system, dd, J = 14.6 Hz, J =3.7 Hz, 1H, CH_2O), 4.36 (B part of ABX-system, dd, J = 14.6 Hz, J = 7.3 Hz, 1H, CH_2O), 4.17 (qd, J = 11.0 Hz, J = 4.0 Hz, 0.9H, CHP), 4.08-3.93 (m, 0.1H, CHP), 3.78 (d, $J(^{31}P)$ = 10.4 Hz, 3H, OCH_3), 2.12 (s, 3H, $C(O)CH_3$), 1.78-1.67 (m, 1H, $\underline{CH}(CH_3)_2$), 1.63-1.47 (m, 2H, $\underline{CH_2}CH(CH_3)_2$), 1.40 (s, 9H, 3 x $C(\underline{CH_3})_3$), 0.94 (d, J = 6.7 Hz, 3H, 1 x $CH(\underline{CH_3})_2$), 0.91 (d, J = 6.5 Hz, 3H, 1 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 170.05 (d, $J(^{31}P)$ = 6.8 Hz, 1C, C=O of Boc), 155.14 (d, $J(^{31}P)$ = 5.2 Hz, 1C, C=O of Ac), 80.30 (s, 1C, $\underline{C}(CH_3)_3$), 55.76 (d, $J(^{31}P)$ = 105.1 Hz, 1C, $P\underline{CH_2}OAc$), 52.30 (d, $J(^{31}P)$ = 7.4 Hz, 1C, OCH_3), 45.45 (d, $J(^{31}P)$ = 111.7 Hz, 1C, CHP), 36.33 (s, 1C, $\underline{CH_2}CHP$), 28.22 (s, 3C, 3 x $C(\underline{CH_3})_3$), 24.38 (d, $J(^{31}P)$ = 11.2 Hz, 1C, $\underline{CH}(CH_3)_2$), 23.32 (s, 1C, CH_3 von Ac), 21.13 (s, 1C, 1 x $CH(\underline{CH_3})_2$), 20.55 (s, 1C, 1 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 47.72 (s, 0.9P, P=O), 45.95 (s, 0.1P, P=O).

To prove the presence of two conformers, ^{31}P NMR spectra were recorded in toluene-d_8 at 25 and 80 °C.

^{31}P NMR (161.97 MHz, C_7D_8, 25 °C): δ = 47.98 (s, 0.94P, P=O), 45.95 (s, 0.06P, P=O); ^{31}P NMR (161.97 MHz, C_7D_8, 80°C): δ = 46.13 (s, P=O).

Elemental analysis calculated for $C_{14}H_{28}NO_6P$ (337.35): C: 49.84, H: 8.37, N: 4.15; found: C: 49.89, H: 8.21, N: 4.07.

4. References:

1. Senten, K.; Daniëls, L.; Var der Veken, P.; De Meester, I.; Lambeir, A.-M.; Scharpé, S.; Haemers, A.; Augustyns, K. J. *Comb. Chem.* **2003**, *5*, 336-344.
2. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587-5590.
3. Beer, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, J. *Bioorg. Med. Chem.* **1996**, *4*, 1693-1701.
4. Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29-40.
5. Huang, J.; Chen, R. *Heteroat. Chem.* **2000**, *11*, 480-492.
6. Yager, K. M.; Taylor, C. M.; Smith, A. B.; III. *J. Am. Chem. Soc.* **1994**, *116*, 9377-9378.
7. Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, J. A. ; Cudennec, C. A.; Pierré, A. *J. Med. Chem.* **1991**, *34*, 1998-2003.
8. Maier, L.; Diel, P. J. *Phosphorus, Sulfur, and Silicon* **1994**, *90*, 259-279.
9. Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56-58.
10. Kase, K.; Yamamoto, M.; Koguchi, T.; Okachi, R.; Kasai, M.; Shirahata, K.; Kawamoto, I.; Shuto, K.; Karasawa, A. *Eur. Pat. Appl. EP* **1982**.
11. Horiguchi, M.; Kandatsu, M. *Nature* **1959**, *184*, 901-902.
12. Engelmann, M.; Pikl, J. **1942**, *US Patent* 2.2304.156.
13. Pikl, J. **1943**, *US Patent* 2.328.358.
14. Moedritzer, K.; Irani, R. R. *J. Org. Chem*. **1966**, *31*, 1603-1607.
15. Iveson, P. B.; Lowe, M. P.; Lockhart, J. C. *Polyhedron* **1993**, *12*, 2313-2323.
16. Cao, X.; Mjalli, A. M. M. *Tetrahedron Lett*. **1996**, *37*, 6073-6076.
17. Drescher, M.; Li, Y.-F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933-4946.
18. Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100-2113.
19. Yamauchi, K.; Mitsuda, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3285-3286.
20. Arbuzov, A. E. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687.
21. Berlin, K. D.; Roy, N. K.; Clauch, R. T.; Bude, D. *J. Am. Chem. Soc*. **1968**, *90*, 4494-4495.
22. Subotkowski, W.; Tyka, R.; Mastalerz, P. *Pol. J. Chem.* **1983**, *57*, 1389-1391.
23. Krzyzanowska, B.; Pilichowska, S. *Pol. J. Chem.* **1988**, *62*, 165-177.

24. Green, D.; Patel, G.; Elgendy, S.; Baban, J. A.; Claeson, G.; Kakkar, V. V.; Deadman, J. *Tetrahedron Lett.* **1993**, *34*, 6917-6920.
25. Gancarz, R.; Wieczorek, J. S. *Synthesis* **1977**, 625.
26. Kudzin, Z. H.; Majchrzak, M. W. *J. Organomet. Chem.* **1989**, *376*, 245-248.
27. Mikołajczyk, M; Drabowicz, J.; Kiełbasiński, P. *Houben-Weyl* **1985**, *E21*, 5701-5731.
28. Seyferth, D.; Marmor, R.S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379-1386.
29. Genet, J. P,; Uziel, J.; Touzin, A. M.; Juge, S. *Synthesis* **1990**, 41-43.
30. Koerner, J. F.; Cotman, C. W. *Brain Res.* **1981**, *216*, 192-198.
31. Pudovik, A. N. *Dokl. Akad. Nauk. SSSR.* **1952**, 83, 865-869.
32. Smith, A. B., III; Yager, K. M.; Phillips, B. W.; Taylor, C. M. *Org. Synth.* **1998**, *75*, 19-29.
33. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett*. **1993**, *34*, 6229-6232.
34. Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem*. **1997**, *62*, 7532-7533.
35. Lefebvre, I. M.; Evans, S. A., Jr. *Phosphorous, Sulfur Silicon Relat. Elem.* **1999**, *144-146*, 397-400.
36. Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991-3994.
37. Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; John Wiley & Sons: New York, NY, **2000**.
38. Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583-2585.
39. Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978-1986.
40. Togni, A.; Pastor, S. D. *Tetrahedron Lett.* **1989**, *30*, 1071-1072.
41. Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247-2250.
42. Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029-3070.
43. Schöllkopf, U.; Hoppe, I.; Thiele, A. *Liebigs ann. Chem*. **1985**, 555-559.
44. Schmidt, U.; Oehme, G.; Krause, H. *Syn. Comm*. **1996**, *26*, 777-781.
45. Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387-390.
46. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc*. **1987**, *109*, 5856-5858.
47. Kitamura, M.; Yoshimura, M.; Tsukamoto, M.; Noyori, R. *Enantiomer* **1996**, *1*, 281-303.
48. Wagner, J.; Lerner, R. A.; Barbas, C. F. III. *Bioorg. Med. Chem*. **1996**, *4*, 901-916.
49. Yuan, C.; Xu, C.; Zhang, Y. *Tetrahedron* **2003**, *59*, 6095-6102.

50. Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65(7)*, 1953-1964.
51. Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.
52. Evans, D.; Fu, G.; Anderson, B. *J. Am. Chem. Soc*. **1992**, *114*, 6679-6685.
53. Pandey, S.; Ranade, S. A.; Nagar, P. K.; Kumar, N. *J. Biosci.* **2000**, *25(3)*, 291-299.
54. Sivaraman, K. K.; Paiardini, A.; Sienczyk, M.; Ruggeri, C.; Oellig, C. A.; Dalton, J. P.; Scammells, P. J.; Drag, M.; McGowan, S. *J. Med. Chem*. **2013**, *56(12)*, 5213-5217.
55. Cowart, M.; Kowaluk, E. A.; Kohlhaas, K. L.; Alexander, K. M.; Kerwin, J. F. Jr. *Bioorg. Med. Chem. Lett.* **1996**, *6(9)*, 999-1002.
56. Sosnovsky, G.; Lukszo, J.; Gravela, E.; Zuretti, M. F. *J. Med. Chem.* **1985**, *28(9)*, 1350-1354.
57. Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Tran. 1: Organic and Bio-Organic Chemistry* **1984**, *12*, 2845-2853.
58. Zarbl, E.; Lammerhofer, M.; Hammerschmidt, F.; Wuggenig, F.; Hanbauer, M.; Maier, N. M.; Sajovic, L.; Lindner, W. *Anal. Chim. Acta* **2000**, *404(2)*, 169-177.
59. Boduszek, B.; Latajka, R.; Leśniak, W. *Phosphorus, Sulfur and Silicon* **2000**, *165*, 53-75.
60. Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633-3634.
61. Dodd, D.; Kozikowski, A. *Tetrahedron Lett.* **1994**, *35*, 977-984.
62. Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J Org. Chem.* **1999**, *64*, 2616-2617.
63. Oleksyszyn, J.; Gruszecka, E.; Kafarski, P.; Mastalerz, P. *Monatshefte für Chemie* **1982**, *113*, 59-71.
64. Genêt, J. P.; Uziel, J.; Port, M.; Touzin, A. M.; Roland, S.; Thorimbert, S.; Tanier, S. *Tetrahedron Lett.* **1992**, *33*, 77-80.
65. Antczak, K.; Szewczyk, J. *Phosphorus, Sulfur and Silicon* **1985**, *22(2),* 247-251.
66. Young, A. R. *Phys. Med. Biol.* **1997**, *42*, 789–802.
67. Hanson, K. R.; Havir, E. A. *Arch. Biochem. Biophys*. **1970**, *141*, 1-17.
68. Bordwell, F. G.; Zhao, Y. *J. Org. Chem.* **1995**, *60*, 3932–3933.
69. Christianson, C. V.; Montavon, T. J.; Festin, G. M.; Cooke, H. A.; Shen, B.; Bruner, S. D. *J. Am. Chem. Soc.* **2007**, *129*, 15744-15745.
70. Langer, M.; Pasuling, A.; Rétey, J. *Angew. Chem*. **1995**, *107*, 1585-1587.
71. Schwede, T. F.; Rétey, J.; Schulz, G. E. *Biochemistry* **1999**, *38*, 5355-5361.
72. Rétey, J. *Naturwissenschaften* **1996**, *83*, 439-447.

73. Schuster, B.; Rétey, J. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 8433-8437.
74. Rettig, M.; Sigrist, A.; Rétey, J. *Helv. Chim. Acta* **2000**, *83*, 2246-2265.
75. Bartsch, S.; Bornscheuer, U. T. *Angew. Chem. Int. Ed*. **2009**, *48*, 3362-3365.
76. Amrhein, N.; Gödeke, K. H. *Plant Sci. Lett.* **1977**, *8*, 313-317.
77. Laber, B.; Kiltz, H. H.; Amrhein, N. Z. *Naturforsch.* C: *Biosci.* **1986**, *41*, 49-55.
78. Amrhein, N. *Rec. Adv. Phytochem*. **1985**, *20*, 83-117.
79. Maier, L.; Diel, P. J. *Phosphorus, Sulfur, and Silicon* **1991**, *62*, 15-27.
80. Maier, L. *Phosphorus, Sulfur, and Silicon* **1990**, 53, 43-67.
81. Zoń, J.; Amrhein, N.; Gancarz, R. *Phytochemistry* **2002**, *59*, 9-21.
82. Schwede, T. F.; Rétey, J.; Schulz, G. E. *Biochemistry* **1999**, *38*, 5355-5361.
83. Baedeker, M.; Schulz, G. E. *Structure* **2002**, *10*, 61-67.
84. Baedeker, M.; Schulz, G. E. *Eur. J. Biochem.* **2002**, *269*, 1790-1797.
85. Gebler, J. C. ; Trimbur, D. E.; Warren, R. A. J.; Aebersold, R.; Namchuck, M.; Withers, S. G. *Biochemistry* **1995**, *34*, 14547-14553.
86. Christenson, S. D.; Wu, W.; Spies, M. A.; Shen, B.; Toney, M. D. *Biochemistry* **2003**, *42*, 12708-12718.
87. Felpin, F.; Miqueu, K.; Sotiropoulos, J.; Fouquet, E.; Ibarguren, O.; Laudien, *Chem. Eur. J.* **2010**, *16*, 5191-5204.
88. Hammerschmidt, F.; Völlenkle, H. *Liebigs Ann. Chem.* **1986**, 2053-2064.
89. Hammerschmidt, F.; Hanninger, A. *Chem. Ber*. **1995**, *128*, 823-830.
90. Hammerschmidt, F.; Schmidt, S. *Chem. Ber.* **1996**, *129*, 1503-1508.
91. Hammerschmidt, F.; Schmidt, S. *Eur. J. Org. Chem.* **2000**, 2239-2245.
92. Philippitsch, V.; Hammerschmidt, F. *Org. Biomol. Chem*. **2011**, *9*, 5220-5227.
93. Hammerschmidt, F:, Hanbauer, M. *J. Org. Chem*. **2000**, *65*, 6121-6131.
94. Kuliszewska, E.; Hanbauer, M.; Hammerschmidt, F. *Chem. Eur. J.* **2008**, *14*, 8603-8614.
95. Houben-Weyl, *Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity*, Kukhar, V. P:, Hudson, H. R., Eds, John Wiley & Sons, Ltd. Chichester, New York, Weinheim, Brisbane, Singapore, Toronto, 2000.
96. Seto, H.; Kuzuyama, T. *Nat. Prods. Rep*. **1999**, 16, 589-696.
97. Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett*. **1986**, *27*, 331-334.
98. Qian, R.; Hammerschmidt, F.; Arion, V. *unpublished results*
99. Klepacz, A.; Zwierzak, A. *Tetrahedron Lett*. **2002**, *43*, 1079-1080.

100. Kolyamshin, O. A.; Kormachev, V. V.; Mitrasov, Y. N. *Russ. J. Gen. Chem*. **1993**, *63*, 750-754.

101. Lyzwa, P.; Blaszczyk, J.; Mikolajczyk, M.; Sieron, L. *Eur. J. Org. Chem*. **2013**, *11*, 2106-2115.

102. Wuggenig, F.; Schweifer, A.; Hammerschmidt, F.; Mereiter, K. *Eur. J. Org. Chem*. *211*, 1870–1879.

5. Summary:

(±)-Diisopropyl 1-hydroxy-3-butenylphosphonate was synthesized easily in three steps from the cheap starting materials diisopropyl phosphite, paraformaldehyde, and allylbromide. It was converted to the chloroacetate and resolved by enantioselective lipase-catalyzed hydrolysis to get (*R*)- or (*S*)-1-hydroxy-3-butenylphosphonate of very high *ee* (>97%). The optically active 1-hydroxyphosphonate was then utilized as key starting material for the synthesis of seven α-amino- and aminooxyphosphonic acids such as 3-amino-3-phosphonopropanoic acid, 1,4-diaminobutyl-, (1,2-oxazinan-3-yl)-, (isoxazolidin-3-yl)-, 1-amino-3-(aminooxy)propyl-, (1-amino-4-guanidinobutyl)phosphonic acid, 4-amino-4-phosphonobutanoic acid and as a phosphonic acid analog of malic acid the 3-hydroxy-3-phosphonopropanoic acid. The diisopropyl 1-hydroxy-3-butinylphosphonate was also prepared in high optical purity (*ee* 92%) and transformed into 1-amino-2-(1H-1,2,3-triazol-4-yl)ethylphosphonic acid of 98% *ee*. All α-aminophosphonic acids except (±)-1,4-diaminobutylphosphonic acid were synthesized in racemic as well as enantiomerically pure form by transforming the double and triple bond of the starting materials in a variety of functional groups. Most of the synthesized phosphonic acids are structural analogs of proteinogenic amino acids and will be tested in due course.

In the second part, the synthesis of (±)-1-amino-2-phenyl-2-propenylphosphonic acid, a potential inhibitor of phenylalanine ammonia lyase (PAL), was achieved via a new route with a doubled overall yield and on a larger scale compared to the previous sequence. PAL is a key enzyme in plant metabolism and an attractive target for developing herbicides. The Mitsunobu reaction, which was used to substitute a hydroxyl for an azido group, produced a significant amount of inseparable olefin as side product (azide:olefin = 2:1). This step has to be improved to achieve a good yield of the desired α-aminophosphonic acid.

In the last part, the phosphonate-phosphinate rearrangement was studied. I chose (*S*)-dimethyl *N*-(*t*-butoxycarbonyl)-*N*-(1-phenylethyl)phosphoramidate to discuss possible reaction pathways and to perform preliminary experiments. The phosphoramidate-aminophosphonate rearrangement could be induced by metalation at the benzylic position or the methoxy group, depending on the base used. The phosphonates formed were subjected to the phosphonate-phosphinate rearrangement, which could be effected only by *s*BuLi at a reasonable rate at –

95°C. It was found that metalation at the benzylic position generated a carbanion partially enantiomerizing even at –95 °C, caused by the longer half-life compared to the one involved in the phosphate-phosphonate rearrangement. Nevertheless, the phosphonate-phosphinate rearrangement follows a retentive course at the carbon and phosphorus atom involved in the formation of a new P-C bond. Finally, a simple *N*-Boc protected racemic dimethyl α-aminophosphonate, (±)-1-(*t*-butoxycarbonylamino)-3-methylbutylphosphonate was studied as substrate for the phosphonate-phosphinate rearrangement. Very surprisingly, the yield of the rearrangement could not be increased to values above 20%. However, only one diastereomer was observed. This interesting and new rearrangement in phosphorus chemistry justifies more experiments with other bases and other protecting groups than Boc to improve the yields and widen the scope of the rearrangement.

6. Zusammenfassung:

(±)-Diisopropyl-1-hydroxy-3-butenylphosphonat wurde in drei Schritten aus den kostengünstigen Ausgangsmaterialien Diisopropylphosphit, Paraformaldehyd und Allylbromid synthetisiert. Es wurde in das Chloracetat überführt, das mittels enantioselektiver Hydrolyse mit einer Lipase je nach Konversion entweder das (*S*)-1-Hydroxy-3-butenylphosphonat oder das (*R*)-Chloracetat mit sehr hohem *ee* (>97%) lieferte. Letzteres wurde zum (*R*)-1-Hydroxyphosphonat (>97%) verseift. Das optisch aktive (*S*)-1-Hydroxyphosphonat wurde dann als Ausgangsmaterial für die Synthese von sieben α-Amino- und Aminooxyphosphonsäuren mit (*R*)-Konfigurtion – der 3-Amino-3-phosphono-propansäure, 1,4-Diaminobutyl-, (1,2-Oxazinan-3-yl)-, (Isoxazolidin-3-yl)-, 1-Amino-3-(aminooxy)propyl-, (1-Amino-4-guanidinobutyl)-phosphonsäure, 4-Amino-4-phosphonobutansäure – verwendet. Aus dem (*R*)-1-Chloracetoxyphosphonat wurde das Phosphonsäureanalogon der Äpfelsäure, die 3-Hydroxy-3-phosphonopropansäure, hergestellt. Auch das (*S*)-Diisopropyl-1-hydroxy-3-butinylphosphonat wurde analog durch enantioselektive Hydrolyse mit der gleichen Lipase mit hohem *ee* (92%) erhalten und in die 1-Amino-2-(1H-1,2,3-triazol-4-yl)ethylphosphonsäure mit 98% *ee* überführt. Alle α-Aminophosphonsäuren außer der (±)-1,4-Diaminobutylphosphonsäure wurden in racemischer sowie enantiomerenreiner (*R*)-Form synthetisiert. Die Doppel- und Dreifachbindung der Ausgangsmaterialien ließen sich in zahlreiche funktionelle Gruppen umwandeln. Die meisten synthetisierten Phosphonsäuren sind Strukturanaloga der proteinogenen Aminosäuren und werden auf ihre biologische Aktivität untersucht werden.

Im zweiten Teil der Dissertation wurde die Synthese der (±)-1-Amino-2-phenyl-2-propenyl-phosphonsäure, ein potentieller Inhibitor der Phenylalanin-Ammoniak-Lyase (PAL), auf einem neuen Weg mit der doppelten Gesamtausbeute im Vergleich zur vorherigen Synthese durchgeführt. PAL ist ein Schlüsselenzym im Metabolismus der Pflanzen und ein attraktives Ziel für die Herbizidentwicklung. Die Mitsunobu Reaktion, welche verwendet wurde, um eine Hydroxyl- durch eine Azidgruppe zu substituieren, lieferte eine erhebliche Menge eines Olefins als Nebenprodukt (Azid:Olefin = 2:1), das sich vom gewünschten Azid nicht abtrennen ließ.

Im letzten Teil wurde erstmals die Phosphonat-Phosphinat-Umlagerung untersucht. Das (*S*)-Dimethyl-*N*-(*t*-butoxycarbonyl)-*N*-(1-phenylethyl)phosphoramidat wurde gewählt, um die möglichen Reaktionswege zu diskutieren und die entsprechenden Versuche durchzuführen. Die Phosphoramidat-Phosphonat-Umlagerung konnte durch Metallierung an der Benzyl- oder Methoxygruppe ausgelöst werden, was von der verwendeten Base abhing. Die gebildeten Phosphonate wurden der Phosphonat-Phosphinat-Umlagerung unterwerfen, die aber nur mit *s*BuLi bei –95°C mit einer angemessen Geschwindigkeit erfolgte. Es wurde gefunden, dass die Metallierung an der bezylischen Position ein Carbanion erzeugte, welches sogar bei –95 °C nicht konfigurationsstabil war. Ein kleiner Teil änderte seine Konfiguration, sodass zwei diastereomere Reaktionsprodukte gebildet wurden. Die Phosphonat-Phosphinat-Umlagerung folgt einem retentiven Verlauf am Kohlenstoff- und Phosphoratom bei der Bildung der neuen P-C-Bindung. Zuletzt wurde ein *N*-Boc-geschütztes racemisches Dimethyl-α-Aminophosphonat, das (±)-1-(*t*-Butoxycarbonylamino)-3-methylbutyl-phosphonat, als Substrat für die Phosphonat-Phosphinat-Umlagerung studiert. Überraschenderweise wurde nur ein Diastereomer beobachtet, dessen Ausbeute trotz vieler Versuche aber nicht über 20% gesteigert werden konnte.

7. Curriculum vitae:

Personal Data

Surname: Qian

First name: Renzhe

Gender: Male

Birth: January 06, 1983, Shanghai, P. R. China

Nationality: Chinese

Marital status: Married

Address: Portnergasse, 1220, Vienna, Austria

E-mail: tsienrenzhe@hotmail.com

Education

2010. 10 – Ph. D. study in organic chemistry

Institute of organic chemistry, University of Vienna, Vienna, Austria

Advisor: Ao. Univ.-Prof. Friedrich Hammerschmidt

2004. 3 – 2010. 6 Diplom-study of chemistry, University of Vienna, Austria (final examination: excellent)

2003. 3 – 2003. 11 Vorstudienlehrgang der Wiener Universitäten (prior school of Vienna universities), Austria

2001. 9 – 2003. 3 Tongji University, Shanghai

2001. 7 Chinese College Entrance Examination (509 points, among the best 1%)

Research Experiences

2010. 8 – now Dissertation

"Synthesis of potentially biologically active α-amino- and α-hydroxyphosphonic acids"

2010. 9 – 2011.2 Cooperation project with Prof. M. Berger of Medical University of Vienna

"[^{3}H]Metyrapol and 4-[^{131}I]Iodometomidate Label Overlapping, but Not Identical, Binding Sites on Rat Adrenal Membranes"

2009. 5 – 2010. 6 Diplom thesis

"Synthesis of potential inhibitors of phenylalanine ammonia lyase"

Teaching Experiences

WS 2011: Biologisch-chemisches Praktikum

SS 2012: Chemisches Grundpraktikum II B; Praktikum - Spezielle Synthesechemie

WS 2012: Biologisch-chemisches Praktikum; Chemisches Grundpraktikum II B

SS 2013: Biologisch-chemisches Praktikum; Chemisches Grundpraktikum II B

WS 2013: Chemisches Grundpraktikum II B

Skills

Extensive experience in a variety of research techniques including: IR, UV, NMR.

Languages

Chinese, English, German

Computer Skills

Windows, Office, Chemoffice, et al.

Publications

1. [^{3}H]Metyrapol and 4-[^{131}I]Iodometomidate Label Overlapping, but Not Identical, Binding Sites on Rat Adrenal Membranes

Berger, M. L.; Hammerschmidt, F.; **Qian, R.**; Hahner, S.; Schirbel, A.; Stichelberger, M.; Schibli, R.; Yu, J.; Arion, V. B.; Woschek, A.; *Mol. Pharmaceutics* **2013**, *10*, 1119-1130.

2. Zinc(II) Complexes with Dangling Functional Organic Groups

Yang, J.; Puchberger, M.; **Qian, R.**; Maurer, C.; Schubert, U., *Eur. J. Inorg. Chem.* **2012**, *27*, 4294-4300.

3. On the phosphonate-phosphinate rearrangement

Qian, R., Arion, V. B., Hammerschmidt, F. *J. Org. Chem.*, in preparation.