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Stereoselective synthesis, solution structure and metal complexes of (1*S*,2*S*)-2-amino-1-hydroxyalkylphosphonic acids

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Abstract—The highly stereoselective synthesis of (1*S*,2*S*)-2-amino-1-hydroxyalkylphosphonic acids was achieved by addition of dimethyl phosphite to *N*-protected aminoaldehydes. Relative configuration and solution conformations of (1*S*,2*S*)-2-amino-1-hydroxy-alkylphosphonic acids (in D_2O) and their dimethyl esters (in $CDCl_3$ and CD_3OD) were established by means of NMR basing on the dependence between observed values of coupling constants ($^3J_{HH}$, $^3J_{PC}$, $^3J_{HP}$) and corresponding dihedral angles. Potentiometric and spectroscopic methods were used for the evaluation of the structure of the complexes of (1*S*,2*S*)-2-amino-1-hydroxy-alkylphosphonic acids with Zn(II) and Cu(II) ions in aqueous solutions.

1. Introduction

Phosphonic acids bearing heteroatoms in the α and β positions have attracted considerable interests because of their well recognized interesting biological properties.[1] Most importantly, they act as inhibitors of proteolytic enzymes, such as renin[2] and human immunodeficiency virus (HIV) protease,[3] as agents affecting the growth of plants[4] or as haptens for the development of catalytic antibodies.[5] They also represent structural analogues of statine and bestatine, the compounds of potential use as anti-cancer agents and potent inhibitors of proteases involved in apoptosis, as well as might be considered as interesting and promising analogues of non-terpenic fragment of paclitaxel and docetaxel—one of the most important natural anti-cancer agents.[6] Moreover, the presence of neighboring amino and hydroxy groups close to each other makes them interesting chelating agents able to bind zinc ions present in the active centers of metalloproteases.[7]

These properties have stimulated the studies on their synthesis with special attention paid to their stereoselective synthesis. Although, the synthesis of aromatic analogues of β-amino-α-hydroxyphosphonates have been satisfactorily achieved in recent years, the literature reports describing the synthesis of 2-amino-1-hydroxy-alkylphosphonates bearing aliphatic substituents in their side chains are rather scarce.[4,8,9] Additionally, their conformations in aqueous solutions as well as their abilities to coordinate metal ions have not been described so far, although these properties are known to have significant influence on the biological activity exerted by aminophosphonic acids.

In this paper we have described the stereocontrolled synthesis and properties of optically active (1*S*,2*S*)-2-amino-1-hydroxyalkanephosphonic acids, determination of their structure by means of NMR spectroscopy basing on the dependence between observed values of coupling constants ($^3J_{HH}$, $^3J_{PC}$, $^3J_{HP}$) and corresponding dihedral angles,[10] as well as evaluation of complexing abilities of these new ligands towards Zn(II) and Cu(II) ions.

2. Results and disscussion

2.1. Stereoselective synthesis

The (*S*)-α-amino acids were transformed into their methyl ester hydrochlorides followed by protection of their amino groups with Boc_2O. *N*-Protected esters

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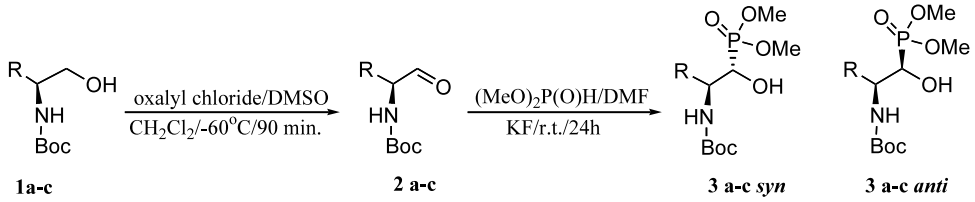


Scheme 1. Reagents and conditions used during synthesis of **3a–c** (R = -CH_3, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$).

were then reduced to the appropriate alcohols **1** by treatment with $NaBH_4$/LiCl in THF/EtOH. All the steps in the preparation of *N*-protected amino alcohols were carried out according to literature procedures.[11] The synthesis of the aliphatic (*S*)-*N*-Boc-α-amino aldehydes **2** was performed by the oxidation of the (*S*)-*N*-Boc-α-amino alcohols **1** using DMSO–oxalyl chloride in dry CH_2Cl_2 (Swern oxidation)[12] (Scheme 1). To avoid the undesired decomposition and racemisation of the aldehydes, the obtained crude products were used immediately in the next step of the synthesis. According to our experience, the racemisation of (*S*)-*N*-Boc-α-amino aldehydes **2** occurs at 5–7% per hour upon silica gel during their purification.[13]

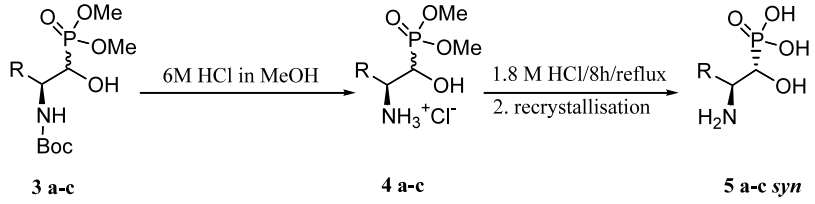
The appropriate (*S*)-*N*-Boc-α-aminoaldehyde **2** was treated with dimethyl phosphite in DMF using solid KF as a catalyst to give the mixture of dimethyl (1*S*,2*S*)/(1*R*,2*S*)-2-(Boc-amino)-1-hydroxyalkylphosphonates **3**, in which the *syn* adduct predominates (Table 1).[14a] This method was chosen because its succesful application for the stereoselective synthesis of α-hydroxyphosphonates bearing cycloaliphatic side-chains was reported earlier.[14] The observed stereoselective course of the reaction is in a good agreement with literature where the strong dominance of production of *syn*-diastereomers upon addition of various nucleophilic species to *N*-monosubstitued α-amino aldehydes was reported. This is, on the other hand, in contrast to *N*,*N*-disubstitued α-amino aldehydes, where *anti*-isomers predominate.[15] Ratios of *syn*- to *anti*-diastereoisomers established from the ^{31}P NMR spectra are shown in Table 1.

Table 1. Diastereoselectivity of the addition of dimethyl phosphite to (*S*)-*N*-Boc-α-aminoaldehydes **2**

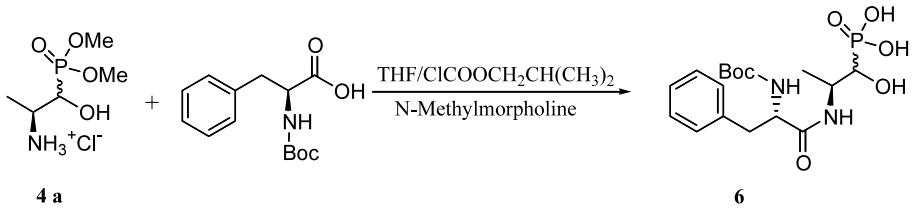
Entry	R	Stereoselectivity *syn*:*anti*	Yield (%)
3a	-CH_3	80:20	78
3b	-$CH_2CH(CH_3)_2$	88:12	81
3c	$CH(CH_3)(CH_2CH_3)$	83:17	82

They show, that the presence of a bulky side chain improved the stereoselectivity of addition of dimethyl phosphite to (*S*)-*N*-Boc-α-aminoaldehyde **2**, which in turn indicates, that the stereoselectivity in this reaction is not only dependent on reaction conditions, but also on the structure of the substrate.[14] The obtained mixtures of dimethyl-[Boc-amino]-1-hydroxyalkylphosphonic esters **3** were then sequentially deprotected and recrystallised to yield the desired (1*S*,2*S*)-2-amino-1-hydroxyalkylphosphonic acids **5** (Scheme 2). Reaction of esters **3** with 6 M hydrogen chloride in methanol (saturated solution) led to dimethyl (1*S*,2*S*)/(1*R*,2*S*)-2-amino-1-hydroxyalkylphosphonate hydrochlorides **4** with quantitative yields. In the next step, the obtained hydrochlorides **4** were deprotected by refluxing in 8 M HCl to give the desired 2-amino-1-hydroxyalkylphosphonic acids **5** as mixtures of two diastereomers with the ratio of (1*S*,2*S*) to (1*R*,2*S*) isomers being identical to that for the Boc-protected methyl esters **3**. The separation of the pure diastereomers of (1*S*,2*S*)-**5a**,**b** and (1*S*,2*S*,3*S*)-**5c** was achieved by fractional crystallisation. According to the interest in the synthesis of **5**-*syn* (1*S*,2*S*) derivatives, and the observed small amount of the **5**-*anti* (1*R*,2*S*) diastereomers formed, we have not undertook efforts to obtain the second ones as pure enantiomers.

In order to prove that there is a lack of racemisation of the aldehyde **2** upon addition of dimethyl phosphite, we coupled the obtained mixture of dimethyl (1*S*,2*S*)/(1*R*,2*S*)-2-amino-1-hydroxypropylphosphonate hydrochloride **4a** with (*S*)-Boc-phenylalanine (Scheme 3). This was done in order to incorporate an additional, defined stereogenic center into the molecule, which in turn should result in appearance of additional peaks in ^{31}P NMR spectra if the racemisation of substrate **2** would take place.[16] To avoid undesired racemisation of the substrates during the coupling step, the reaction was performed by mixed carboxylic–carbonic anhydride procedure (with the use of isobutyl chloroformate) at −20°C in dry THF and in the presence of *N*-methylmorpholine. ^{31}P NMR spectra of the mixture



Scheme 2. Deprotection of phosphonate **3**.



4 a 6

Scheme 3. Preparation of phosphonodipeptide **6**.

Table 2. Values of the coupling constants (Hz) found for *syn*-esters **3** and **4**

R	Entry	$^3J_{CP}$ (Hz)			$^3J_{HP}$ (Hz)		
		$CDCl_3$	CD_3OD	D_2O	$CDCl_3$	CD_3OD	D_2O
$-CH_3$	**3a**	8.2	9.6	Insolouble	9.8	10.0	Insolouble
$-CH_3$	**4a**	Insolouble	9.8	10.6	Insolouble	8.1	10.1
$-CH_2CH(CH_3)_2$	**3b**	10.6	9.8	Insolouble	9.8	10.2	Insolouble
$-CH_2CH(CH_3)_2$	**4b**	4.9	10.4	8.5	9.0	9.5	9.5
$CH(CH_3)(CH_2CH_3)$	**3c**	11.8	12.8	Insolouble	10.0	10.5	Insolouble
$CH(CH_3)(CH_2CH_3)$	**4c**	4.2	10.7	9.4	9.8	10.2	10.5

of isomers of peptide **6** showed the presence of two dominating signals at 25.28 ppm (16%) and 25.48 ppm (84%) corresponding to (1*S*,2*S*,2′*S*) and (1*R*,2*S*,2′*S*) diastereoisomers, and only traces (less than 1%) of the second pair of diastereomers at 25.62 and 25.78 ppm.

Our results are in accordance with earlier report of Tao, who had performed a similar reaction, in which dimethyl (2*S*)-amino-1-hydroxy-4-methylpentylphosphonate hydrochloride **4b** was coupled with (*S*)-Cbz-Leucine gave the final product as a mixture of only two desired diastereomers.[16] This allowed us to postulate, that the aliphatic (*S*)-*N*-Boc-α-amino aldehydes **2** did not racemise in applied reaction conditions (DMF, KF, $HPO(OMe)_2$).

2.2. Determination of absolute configuration and conformational analysis

In order to assign a tentative absolute configuration to the obtained compounds we have used NMR conformational analysis of esters **3** and **4** and acids **5** basing on our recent studies, which were done in order to study the influence of hydrogen bonding on conformational behavior of diethyl (1*R*,2*S*)-2-amino-1-hydroxy-2-arylalkylphosphonates.[10]

The presence of amino, hydroxyl and phosphonyl groups in the same molecule creates the possibility of various hydrogen bonds, of which the dominating ones determine the molecule conformation in the solution. In the case of compounds **3**–**5** we would expect a competition in the formation of hydrogen bonds between three functional groups present in the molecule, namely amino, hydroxy and phosphonate moieties. In order to determine, which one predominates we have performed measurements of NMR spectra for dimethyl esters **3** and **4** in non-polar ($CDCl_3$) and polar (CD_3OD and D_2O) solvents and compared the results with those obtained for phosphonic acids **5** in D_2O. In order to eliminate the possible formation of intermolecular hydrogen bonding, we have performed NMR investigations in dilute solutions (concentration of phosphonates = 5 mg/ml). We have also limited conformational analysis only to the dominant *syn* (1*S*,2*S*)-diastereomers. This is because the presence of only a small amount of *anti* (1*R*,2*S*)-diastereomers in the mixtures caused problems with exact determination of coupling constants values, which is indispensable step in such studies. Coupling constants determined for *syn*-esters **3** and **4** are shown in Table 2, whereas those found for respective acids **5** in Table 3. Interpretation of the experimental data was based on the dependence of the observed coupling constants $^3J_{HP}$ and $^3J_{PC}$ for esters **3** and **4**, and $^3J_{HH}$, $^3J_{PC}$, $^3J_{HP}$ for acids **5**, on respective values of dihedral angles between these atoms, which enabled us to assign tentative absolute configurations, as well as the most probable conformations of the studied molecules in solution.[10]

Table 3. Values of the coupling constants (Hz) found for *syn*-acids **5**

Entry	R	D_2O solution			
		$^3J_{PC}$	$^3J_{HH}$	$^2J_{HP}$	$^3J_{HP}$
5a	$-CH_3$	8.7	5.3	5.8	8.9
5b	$-CH_2CH(CH_3)_2$	9.6	2.2	4.6	10.5
5c	$CH(CH_3)(CH_2CH_3)$	10.7	2.0	5.2	11.3

In Tables 4 and 5 the comparison of the coupling constants determined for (1*S*,2*S*) and (1*R*,2*S*) diastereomers (2*S*-center was predetermined by using

Table 4. Conformational analysis—comparison of calculated and experimental data for dimethyl 2-amino-1-hydroxyalkylphosphonates **3** and **4**

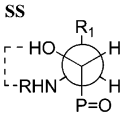
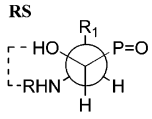
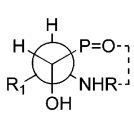
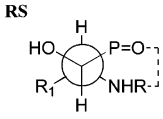
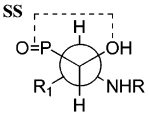
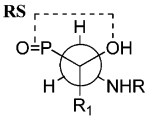
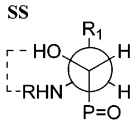
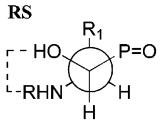
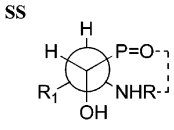
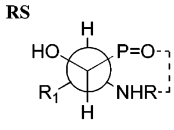
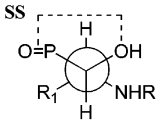
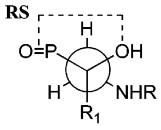
	EXPERIMENTAL	EXPECTED FROM CALCULATIONS											
		HO---NH HYDROGEN BOND				NH---P=O HYDROGEN BOND				HO---P=O HYDROGEN BOND			
Entry	$CDCl_3$/ CD_3OD/ D_2O Observed coupling constants	SS 		RS 		SS 		RS 		SS 		RS 	
		Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values
3	$^3J_{HP}$ ($CDCl_3$) 9.8–10.0 Hz	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+
3	$^3J_{CP}$ ($CDCl_3$) 8.2-11.8 Hz	>8	+	0-8	_	>8	+	>8	+	0-8	-	>8	+
3	$^3J_{HP}$ (CD_3OD) 10.0–10.5Hz	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+
3	$^3J_{CP}$ (CD_3OD) 9.6 – 12.8 Hz	>8	+	0-8	_	>8	+	>8	+	0-8	-	>8	+
4	$^3J_{HP}$ ($CDCl_3$) 9.0-9.8 Hz	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+
4	$^3J_{CP}$ ($CDCl_3$) 4.2 – 4.9 Hz	>8	-	0-8	+	>8	-	>8	-	0-8	+	>8	-
4	$^3J_{HP}$ (CD_3OD) 8.1-10.2 Hz	7-12	+	7-12	+	7-12	+	7-12	+	7-12	-	7-12	+
4	$^3J_{CP}$ (CD_3OD) 9.8 – 10.7	>8	+	0-8	_	>8	+	>8	+	0-8	-	>8	+
4	$^3J_{HP}$ (D_2O) 9.5-10.1 Hz	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+	7-12	+
4	$^3J_{CP}$ (D_2O) 8.5 – 10.6 Hz	>8	+	0-8	_	>8	+	>8	+	0-8	-	>8	+

Table 5. Conformational analysis—comparison of calculated and experimental data for 2-amino-1-hydroxyalkylphosphonic acids **5**

	Experimental	EXPECTED FROM CALCULATIONS											
	D_2O	HO---NH HYDROGEN BOND				NH---P=O HYDROGEN BOND				HO---P=O HYDROGEN BOND			
		SS 		RS 		SS 		RS 		SS 		RS 	
	observed coupling constants	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values	Hz	Agreement between predicted and observed values
	$^3J_{HH}$ 2.0 – 5.3 Hz	1 - 6	+	1 – 6	+	1 - 6	+	>10	-	>10	_	>10	_
	$^3J_{PC}$ 8.7 – 10.7 Hz	>8	+	0 – 8	_	>8	+	>8	+	0 - 8	_	>8	+
	$^3J_{HP}$ 8.9-11.3 Hz	4 - 12	+	4 – 12	+	4-12	+	4-12	+	4 - 12	+	4 - 12	+

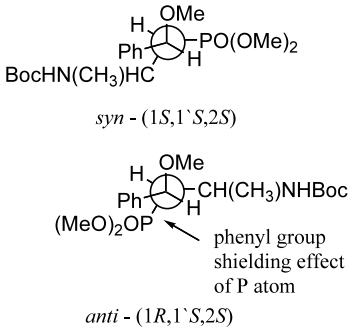
appropriate isomer of amino acid as substrate) obtained with those calculated from conformational analysis of three sets of species having their conformations constrained by the presence of hydrogen bonding are collected. The first set was established assuming the formation of hydrogen bond between hydroxyl- and amino-moieties, in the second set the formation of such a bond between amino- and phosphonate groups was proposed, whereas the third set considers the possibility of formation of hydrogen bonds between hydroxyl and

phosphonyl functions. The last set considers free rotation around the P–C bond (both groups are attached to the same carbon atom) and the presented results are limited to the most energetically probable conformers with hydrogen atoms being *trans* to each other. Formation of hydrogen bonds results in fixing the dihedral angles, which is reflected by certain values of the corresponding coupling constants. For $^3J_{PC}$ these values fall into two categories: 0–8 Hz for *gauche* like conformations and >8 Hz for *trans* conformations, whereas for $^3J_{HH}$ and $^3J_{HP}$ they lie in narrow defined ranges (see Tables 4 and 5).

Results of the analysis suggests the formation of hydrogen bonds between either $(NH_2)\cdots(P{=}O)$ or $(NH_2)\cdots(OH)$ moieties in (1*S*,2*S*) esters and acids. From the obtained results we can not determine, which of the two bonds predominate and thus establish the strict conformation of these compounds in the solution. The similar environment of both conformations rather suggests the existence of a dynamic equilibrium between them. Anyway, the presence of *trans* conformation and the lack of a *gauche* like one was shown to exist in all the solutions of esters and acids. In the case of acids **5** we have obtained an acceptable agreement between experimental and calculated data only for (1*S*,2*S*) isomers, which confirms the expected steric course of the reaction and provides tentative absolute configuration for the major isomer obtained in this work.

IR spectra of the acids showed broad bands in the region of 3100–2400 cm^{-1}, which is very characteristic for strongly hydrogen-bonding systems, particularly $NH_3^+\cdots X^-$ system.[17] The lack of strong absorption at 3500 cm^{-1} indicates involvement of the hydroxyl group in hydrogen bonding, which suggests the formation of a hydrogen bond between amino and hydroxyl groups in crystalline state in the case of acids.

In order to confirm the tentative assignment of the absolute configuration of the obtained compounds, we have performed an additional experiment, namely esterification (NMR scale experiment) of **3a** with (*S*)-*O*-methyl mandelic acid upon action of DCC, according to the procedure described by Kozlowski.[18] In our case, the application of the proposed model would result in shielding of the phosphorus atom in the case of (1*R*,1′*S*,2*S*)-ester and thus its signal shifting upfield in ^{31}P NMR spectra relative to the (1*S*,1′*S*,2*S*)-ester (Scheme 4). This in the case of (*S*)-*O*-methyl mandelate derivatised alcohols should enlarge the distance between peaks of the observed diastereomers in the ^{31}P NMR spectra comparing to the non-esterified alcohols. The obtained experimental results confirm this assumption, because the $\Delta\delta$ between diastereomers of alcohol **3a** is 0.51 ppm (25.62 ppm (1*R*,2*S*), 26.13 ppm (1*S*,2*S*)), whereas for its (*S*)-*O*-methyl mandelates 0.74 ppm (19.61 ppm (1*R*,1′*S*,2*S*), 20.35 ppm (1*S*,1′*S*,2*S*)). Our data are in a good agreement with those reported by Kozlowski and enabled us to assign determine tentatively the absolute configuration of dimethyl (1*S*,2*S*)/(1*R*,2*S*)-2-amino-1-hydroxylakanephosphonate **3a** and confirm that major isomer appears to have ascertained



Scheme 4. (*S*)-*O*-Methyl mandelate derivative of **3a**.

by the NMR experiments (1*S*,2*S*) cofiguration.

The absolute configuration of the obtained acids **5** was additionally confirmed by comparision of the specific rotation and spectroscopic parameters of (1*S*,2*S*)-2-amino-1-hydroxypropylphosphonic acid **5a**, with the data reported for this compound earlier.[19]

2.3. Coordination studies

An inhibitory effect of phosphonic acids with heteroatoms (hydroxy, amino) in α and β positions may result from the good binding abilities of these groups to metal ions present in the active centers of enzymes. Therefore, we have studied complexing abilities of the obtained acids **5** for Cu(II) and Zn(II) ions.

The obtained results show that each ligand behaves as the H_2L acid with two protonation constants at amino ($\log K = 10.88$–11.31) and phosphonic group (5.65–5.85) (Table 6). The second protonation at the phosphonic group occurs below pH 1.5 and therefore the pK value could not be evaluated. The basicity of the amino donor is higher for **5b** and **5c** having large substituents adjacent to the amino group.

Cu(II) forms two major complex species with the studied acids **5** (Table 6). The stabilities of the equimolar complexes ($\log K = 9.64$–9.78) and bis-complexes ($\log \beta = 16.74$–17.39) are relatively high indicating the strong coordination ability of all three acids. In the case of ligands **5a** and **5b**, which form slightly weaker bis-complexes than **5c**, the $[CuL_2]^{2-}$ species underwent

Table 6. Stability constants of the proton ($\log K$) for copper(II) and zinc(II) complexes ($\log \beta$) of acids **5** at 25°C and $I = 0.1$ M (KNO_3)

Ligand	**5a**	**5b**	**5c**	α-Ala-P
Log K(HL)	10.88(1)	11.20(1)	11.31(1)	10.11
Log $K(H_2L)$	5.85(1)	5.65(1)	5.68(1)	5.55
[CuL]	9.75(1)	9.64(1)	9.78(2)	8.29
$[CuL_2]^{2-}$	16.74(1)	17.10(2)	17.39(2)	14.94
$[CuH_{-1}L_2]^3$	4.91(10)	5.77(5)	–	–
$[ZnHL]^+$	13.36(3)	13.56(3)	13.53(2)	11.79
[ZnL]	6.45(2)	6.26(6)	6.39(3)	5.99
$[ZnH_{-1}L]^-$	1.59(2)	–	–	–

deprotonation to $[CuH_{-1}L_2]^{3-}$ complex at pH above 10. The energy of the d–d transitions at 715 nm (Table 7) for equimolar species clearly indicate the involvement of one amino group in the Cu(II) ion coordination. Thus, the chelation of the metal ion involves the [NH_2, PO_3^{2-}] donor set.[20] Also EPR parameters (Table 7) agree with such a coordination mode. The coordination of the second ligand shifts the d–d transition energy to 632–665 nm region (Table 7), which is characteristic for coordination of two amino nitrogen atoms and two phosphonate oxygen atoms to Cu(II) ion.[20a,b] The changes in the EPR parameters also well agree with this binding mode.

Table 7. Spectroscopic parameters for copper(II) complexes formed by studied acids **5**

Ligand	λ	ε	A_{II}	g
5a				
[CuL]	715	54	155	2.32
$[CuL_2]^{2-}$	665	74	170	2.26
$[CuH_{-1}L_2]^{3-}$	665	74	170	2.26
5b				
[CuL]	713	54	152	2.32
$[CuL_2]^{2-}$	632	68	167	2.26
$[CuH_{-1}L_2]^{3-}$	632	68	167	2.26
5c				
[CuL]	704	57	155	2.32
$[CuL_2]^{2-}$	653	82	170	2.26
$[CuH_{-1}L_2]^{3-}$	653	82	170	2.26

Zn(II) ions form two major complexes as well. However, the species formed are equimolar with stability constants for [ZnL] species distinctly lower than those obtained for the Cu(II) ions (Table 6). In the protonated complexes $[ZnHL]^+$ proton sits most likely on the amino group causing that ligand binds to metal ion via monodentate coordination through the phosphonate oxygen. In the high pH the [ZnL] complex (L = **5a**) deprotonates into $[ZnH_{-1}L]^-$ species. The proton dissociation with $\log K \sim 8$ occurs most likely from the bound water molecule. In the two other cases potentiometric titration were performed only up to pH around 7 due to precipitation of the zinc complex.

All the studied ligands are much more effective in Cu(II) ion coordination than, for example, phosphonic analogues of simple amino acids. This could suggest some role of hydroxyl group in stabilization of the complexes formed. In the case of Zn(II) ions only equimolar species are formed, while for phosphonic analogue of alanine also ZnL_2 complexes were found.[20a] The bulky substituent as well as some involvement of hydroxyl group could protect the binding of the second aminophosphonate to Zn(II) ion.

3. Conclusions

We have performed highly stereoselective synthesis of 2-amino-1-hydroxyalkylphosphonic esters by the addition of dimethyl phosphite to (*S*)-*N*-Boc-α-amino aldehydes **2**. The subsequent deprotection and purification of the obtained compounds resulted in pure *syn*-diastereomers of 2-amino-1-hydroxyalkylphosphonic acids of (1*S*,2*S*) configuration in the case of **5a**,**b** and (1*S*,2*S*,3*S*) in the case of **5c**. Additionally, we have shown that esters **4** could be easily converted into phosphono dipeptides with a very good stereoselectivity.

The configuration of the obtained compounds was determined by both conformational analysis of their dilute solutions, as well as by analysis of NMR spectra of their derivatives with (*S*)-*O*-methylmandelic acid, the methods, which have been recently standardly used for the assignment of absolute configurations of optically active hydroxyalkylphosphonates.[9d,19,21] In our case the configuration of major isomer appeared as (1*S*,2*S*).

The coordination abilities of acids **5** towards Cu(II) and Zn(II) prove that they are potent chelating agents binding these ions stronger than structurally related simple aminophosphonic acids. This suggests vital role of hydroxyl moiety in complex formation.

4. Experimental

4.1. General remarks

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Dichloromethane was dried over P_2O_5 and distilled. THF was dried over sodium with benzophenone as indicator and distilled. Reaction progress was monitored by thin-layer chromatography on Merck 60 F_{254} 0.1 m silica plates. Unless otherwise specified, extracts were dried over $MgSO_4$ and solvents were removed with a rotary evaporator. IR spectra were recorded with Perkin–Elmer 1600 Series Fourier transform spectrometer as thin films or KBr pellets. NMR spectra were recorded on a Bruker Avance DRX 300 MHz instrument, operating at 300.13 MHz (^{1}H), 121.499 MHz (^{31}P) and 75.46 MHz (^{13}C). Measurements were made in $CDCl_3$ (99.5 at.% D), CD_3OD (99.5 at.% D) and D_2O (99.8 at.% D) solutions containing 3,5 mg of sample in 0.7 ml of solvent at temperature 300 K, all solvents were supplied by Dr Glaser AG (Basel, Switzerland). Proton decoupling was achieved by power gated decoupling using the Waltz 16 sequence. Chemical shifts are reported in parts per million relative to TMS, and coupling constants are reported in hertz. Melting points were determined on a Electrothermal 9200 apparatus and are reported uncorrected. Elemental analyses were performed at Chemistry Department of the University of Wroclaw and Wroclaw University of Technology on Perkin Elmer 2400 CHN. Electrospray mass spectra were recorded at Chemistry Department of the University of Wroclaw using Finnigan Mat TSQ 700 Electrospray mass spectrometer. Titrations involved an ionic background of 0.1 M KNO_3, ligand concentration of 2 mM and metal-to-ligand ratios of 1:2, 1:3, 1:4 and 1:5 were applied. Initial solutions of 2 mL were titrated with sodium hydroxide delivered by a

0.25 mL micrometer syringe previously calibrated by weight titrations and titrations of standard materials. The pH-metric titrations were performed at 25°C in pH range 2.5–11.0 using a MOLSPIN automatic titration system with a Russell CMAW 711 microcombined electrode calibrated daily in hydrogen-ion concentration using HNO_3.[22] Titrations were performed in triplicate and the SUPERQUAD computer program was used for calculations of stability constants ($\beta_{pqr}=[M_pH_rL_q]/[M]^p[H]^r[L]^q$).[23] Standard deviations quoted refer to random errors only. They are, however, a good indication of the importance of a particular species in the equilibrium. Absorpion spectra were recorded on a Beckman DU 650 spectrophotometer. Electron paramagnetic resonance (EPR) spectra were performed in ethylene glycol–water (1:2 v/v) solution at 77 K on a Bruker ESP 300E spectrometer at the X-band frequency (about 9.45 GHz) and equipped with the Bruker NMR gaussmetter ER 035M and the Hewlett–Packard microwave frequency counter HP 5350B. The concentrations used in the spectroscopic measurements were the same as those used in potentiometric titrations.

4.2. General procedure for the synthesis of *N*-Boc-α-amino alcohols 1

The methyl ester of the appriopriate *N*-Boc-α-aminoacid (0.08 mol) was dissolved in THF (100 ml) followed by addition of lithium chloride (0.16 mol) and sodium borohydride (0.16 mol). After addition of dry ethanol (150 ml), the mixture was stirred overnight. When the reaction was completed (TLC), the mixture was cooled in an ice–water bath and pH adjusted to 3 by addition of 10% citric acid. After concentration in vacuo, water was added (200 ml), and extraction with dichloromethane (4×70 ml) performed. Standard work-up of the organic phase gave desired product **1**. Spectral and analytical data for *N*-Boc-α-amino alcohols were identical with those published earlier for **1a**,[11e] **1b**[11f] and **1c**.[11d]

4.3. General procedure for the synthesis of *N*-Boc-α-amino aldehydes 2

Oxalyl chloride (0.035 mol) was dissolved in 100 ml of dry dichloromethane and cooled to −60°C. Then dry DMSO (0.105 mol) in 10 ml of dichloromethane was added dropwise. After 5 min, *N*-Boc-α-amino alcohol **1** (0.03 mol) in 10 ml of dichloromethane was added dropwise and the mixture was stirred intensively for 1 h, while the temperature was maintained between −60 and −50°C. After completion of the reaction (TLC), triethylamine (0.15 mol) was added and the mixture was stirred for additional 15 min. Next, 100 ml of saturated aqueous solution of ammonium chloride and 100 ml of water were added and the mixture was stirred for additional 5 min. The mixture was left to reach room temperature. Then the organic phase was washed with: 5% aqueous solution of citric acid (2×70 ml), water and brine. Standard work-up of the organic phase gave desired product **2** as yellowish solid, which was immediately used for the next step without further purification.

4.3.1. *N*-Boc-(*S*)-α-aminoalaninal, 2a. 82% yield, ^{1}H NMR ($CDCl_3$): $\delta=1.34$ (d, 3H, ^3J(H,H)=7.3 Hz, CH_3), 1.46 (s, 9H, Boc), 4.23 (m, 1H, CH), 6.88 (bs, 1H, NH) 9.56 (s, 1H, formyl).

4.3.2. *N*-Boc-(*S*)-α-aminoleucinal, 2b. 66% yield, ^{1}H NMR ($CDCl_3$): $\delta=0.96$ (d, 6H, ^3J(H,H)=6.3 Hz, CH_3), 1.37 (m, 1H, CH), 1.45 (s, 9H, Boc), 1.66 (m, 2H, CH_2), 4.23 (m, 1H, CH), 6.95 (bs, 1H, NH) 9.58 (s, 1H, formyl).

4.3.3. *N*-Boc-(*S*)-α-amino-*i*-leucinal, 2c. 63% yield, ^{1}H NMR ($CDCl_3$): $\delta=0.89$ (m, 6H, 2×CH_3), 1.19 (m, 1H, CH), 1.38 (s, 9H, Boc), 1.41 (m, 2H, CH_2), 4.22 (m, 1H, CH), 7.10 (bs, 1H, NH), 9.59 (s, 1H, formyl).

4.4. General procedure for the synthesis of dimethyl (1*S*,2*S*)/(1*R*,2*S*)-(2-*tert*-butoxycarbonyloamino-1-hydroxy)alkylphosphonates 3

N-Boc-α-amino aldehyde **2** (0.01 mol) was dissolved in 50 ml of DMF and dimethyl phosphite (0.01 mol) and KF (0.05 mol) were added. The mixture was stirred for 24 h, solid components were filtered off and solvent removed under reduced pressure. The oily residue was dissolved in dichloromethane and washed with: 10% aqueous citric acid solution (50 ml), water (50 ml) and brine (50 ml). After drying and removal of solvent final product was obtained as yellowish oil of satisfactory purity. Because of the low ratio of the minor diastereomer **3**-(1*R*,2*S*), their peaks in ^{1}H and ^{13}C spectra are hidden under the peaks of major epimer (1*S*,2*S*), and therefore the detail determination of these signals was omitted during analysis.

4.4.1. Dimethyl (1*S*,2*S*)/(1*R*,2*S*)-(2-*tert*-butoxycarbonyloamino-1-hydroxy)propylphosphonate (80/20 mixture), 3a. 78% yield, IR: $\nu=1048$, 1118, 1248, 1367, 1523, 1697, 2935, 2978, 3327 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta=$ 1.27 (d, 3H, ^3J(H,H)=6.3 Hz, CH_3), 1.43 (s, 9H, Boc) 3.49 (dd, 1H, ^3J(H,H)=5.1 Hz, ^2J(H,P)=11.5 Hz, CH), 3.82 and 3.91 (2d, 6H, ^3J(H,P)=10.5 Hz, 2× OCH_3), 4.04 (m, 1H, CH), 5.65 (d, 1H, ^3J(H,H)= 12.1Hz, NH) ^{13}C NMR ($CDCl_3$): $\delta=17.23$ (d, ^3J(C,P)=8.2 Hz), 28.32 (s), 47.59 (s), 53.20 (d, ^2J(C,P)=6.2 Hz), 54.02 (d, ^2J(C,P)=6.0 Hz), 71.36 (d, ^1J(C,P)=164.2 Hz), 79.60 (s), 155.15 (s); ^{31}P NMR: $\delta=25.62$ (1*R*,2*S*), 26.13 (1*S*,2*S*); ESI=283.9, 305.8 $(M+Na)^+$.

4.4.2. Dimethyl (1*S*,2*S*)/(1*R*,2*S*)-(2-*tert*-butoxycarbonyloamino-1-hydroxy-4-methyl)pentylphosphonate (88/12 mixture), 3b. 81% yield, IR: $\nu=1043$, 1173, 1249, 1367, 1505, 1713, 2871, 2958, 3335 cm^1. ^{1}H NMR ($CDCl_3$): $\delta=0.86$ (d, 6H, ^3J(H,H)=4.4 Hz, 2×CH_3), 1.37 (s, 9H, Boc), 1.57 (m, 3H, CH, CH_2), 3.74 and 3.79 (2d, 6H, ^3J(H,P)=10.6 Hz, 2×OCH_3), 3.89 (m, 2H, 2×CH), 5.40 (d, 1H, ^3J(H,H)=9.0 Hz, NH). ^{13}C NMR ($CDCl_3$): $\delta=21.58$ (s), 22.14 (s), 28.31 (s), 40.60 (d, ^3J(C,P)=10.6 Hz), 49.73 (s), 53.20 (d, ^2J(C,P)=6.8 Hz), 53.58 (d, ^2J(C,P)=6.0 Hz), 70.2 (d, ^1J(C,P)=161.8 Hz), 79.31

(s), 156.17 (s). ^{31}P NMR: $\delta = 25.87$ (1*R*,2*S*), 26.41 (1*S*,2*S*); ESI = 325.8, 347.9 $(M+Na)^+$.

4.4.3. Dimethyl (1*S*,2*S*,3*S*)/(1*R*,2*S*,3*S*)-(2-*tert*-butoxycarbonyloamino-1-hydroxy-3-methyl)pentylphosphonate (83/17 mixture), 3c. 82% yield, IR: $\nu = 1044$, 1176, 1250, 1367, 1506, 1714, 2875, 2958, 3329 cm^1. ^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (m, 6H, 2×CH_3), 1.13 (m, 1H, CH) 1.42 (s, 9H, Boc), 1.5 (m, 2H, CH_2), 3.54 (m, 1H, CH), 3.80 (d, 6H, ^3J(H,P) = 10.6 Hz, 2×OCH_3), 3.84 (m, 1H, CH), 5.60 (d, 1H, ^3J(H,H) = 8.2 Hz, NH). ^{13}C NMR ($CDCl_3$): $\delta = 11.12$ (s), 15.64 (s), 25.40 (s), 28.33 (s), 35.85 (d, ^3J(C,P) = 11.8 Hz), 53.16 (d, ^2J(C,P) = 7.4 Hz), 53.75 (d, ^2J(C,P) = 7.0 Hz), 55.24 (s), 67.64 (d, ^1J(C,P) = 163.1 Hz), 79.17 (s), 156.34 (s). ^{31}P NMR: $\delta = 25.41$ (1*R*,2*S*,3*S*), 26.02 (1*S*,2*S*,3*S*); ESI = 325.8, 347.6 $(M+Na)^+$.

4.5. General procedure for the synthesis of dimethyl (2-amino-1-hydroxy)alkylphosphonates hydrochlorides 4

The dimethyl (2-*tert*-butoxycarbonyloamino-1-hydroxy)alkylphosphonate **3** was stirred in 6 M hydrogen chloride saturated in methanol for 30 min. The solvent was removed under reduced pressure, and the residue treated with diethyl ether (20 ml). Evaporation of this solvent on rotary evaporator gave compound **4** in quantitative yield as white semisolid.

4.5.1. Dimethyl (1*S*,2*S*)/(1*R*,2*S*)-(2-amino-1-hydroxy)-propylphosphonate hydrochloride (81/19 mixture), 4a. IR: $\nu = 1051$, 1185, 1242, 1370, 1507, 1611, 2959, 3329 cm^{-1}. ^{1}H NMR (CD_3OD): $\delta = 1.43$ (d, 3H, ^3J(H,H) = 6.7 Hz, CH_3), 3.74 (m, 1H, CH), 3.82 (d, 6H, ^3J(P,H) = 10.6 Hz, 2×OCH_3), 3.92 (m, 1H, CH), 8.08 (bs, 4H, OH, NH_3^+) ^{13}C NMR (CD_3OD): $\delta = 15.10$ (d, ^1J(C,P) = 9.8 Hz), 52.37 (d, ^2J(C,P) = 6.2 Hz), 54.05 (d, ^2J(C,P) = 7.4 Hz), 54.48 (d, ^2J(C,P) = 7.5 Hz), 66.73 (d, ^1J(C,P) = 167.1 Hz). ^{31}P NMR (CD_3OD): $\delta = 23.73$ (1*R*,2*S*), 24.56 (1*S*,2*S*); ESI = 184.0.

4.5.2. Dimethyl (1*S*,2*S*)/(1*R*,2*S*)-(2-amino-1-hydroxy-4-methyl)pentylphosphonate hydrochloride (88/12 mixture), 4b. IR: $\nu = 1050$, 1216, 1470, 1506, 1608, 2960 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 0.98$ (d, 6H, ^3J(H,H) = 5.0 Hz, 2×CH_3), 1.57 (m, 2H, CH_2), 1.74 (m, 1H, CH), 3.82 (2d, 6H, ^3J(H,P) = 10.5 Hz, 2×OCH_3), 4.02 (m, 2H, 2×CH), 6.10 (bs, 4H, NH_3^+, OH). ^{13}C NMR ($CDCl_3$): $\delta = 22.65$ (s), 24.26 (s), 38.02 (d, ^3J(C,P) = 4.9 Hz), 53.61 (d, ^2J(C,P) = 7.0 Hz), 54.76 (d, ^2J(C,P) = 7.0 Hz), 65.75 (d, ^1J(C,P) = 166.6 Hz). ^{31}P NMR: $\delta = 24.77$ (1*R*,2*S*), 24.93 (1*S*,2*S*); ESI = 225.6.

4.5.3. Dimethyl (1*S*,2*S*,3*S*)/(1*R*,2*S*,3*S*)-(2-amino-1-hydroxy-3-methyl)pentylphosphonate hydrochloride (83/17 mixture), 4c. IR: $\nu = 1050$, 1216, 1371, 1471, 1508, 1610, 2961 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.12$ (m, 6H, 2×CH_3), 1.22 (m, 1H, CH), 1.59 (m, 2H, CH_2), 3.76 (m, 1H, CH), 3.81 (d, 3H, ^3J(H,P) = 10.3 Hz, OCH_3), 3.86 (d, 3H, ^3J(H,P) = 10.5 Hz, OCH_3), 4.02 (m, 1H, CH), 6.11 (bs, 4H, NH_3^+, OH). ^{13}C NMR ($CDCl_3$): $\delta = 12.82$ (s), 18.36 (s), 24.02 (s), 35.27 (d, ^3J(C,P) = 4.2 Hz), 52.57 (d, ^2J(C,P) = 7.0 Hz), 53.08 (d, ^2J(C,P) = 7.0 Hz), 62.10 (s), 66.97 (d, ^1J(C,P) = 167.8 Hz). ^{31}P NMR: $\delta = 24.29$ (1*R*,2*S*,3*S*), 25.11 (1*S*,2*S*,3*S*); ESI = 226.

4.6. General procedure for the synthesis of (1*S*,2*S*)-2-amino-1-hydroxyalkylphosphonates 5

The dimethyl (2-amino-1-hydroxy)alkylphosphonate hydrochloride **4** was refluxed in 50 ml of 8 M HCl for 8–10 h. After evaporation of the volatile products in vacuo, the residue was dissolved in 100 ml of ethanol and treated with propylene oxide (pH = 6). The precipitated acid was filtered off and recrystallized 3–5 times from water to give pure *syn* diastereomer of **5**. In the case of **5c** the final product was obtained by the recrystallisation from water and isopropanol.

4.6.1. (1*S*,2*S*)-(2-Amino-1-hydroxy)propyl phosphonic acid, 5a. 72% yield, mp = 247–250°C, $[\alpha]_D^{26.7} = +19.3$ (*c* 1, water), IR: $\nu = 916$, 1040, 1096, 1143, 1509, 1628, 2361, 3154 cm^{-1}. ^{1}H NMR (D_2O): $\delta = 1.28$ (d, 3H, ^3J(H,H) = 6.6 Hz, CH_3), 3.47 (ddq, 1H, ^3J(H,H) = 5.3 Hz, 6.6 Hz, ^2J(H,P) = 5.8 Hz, CH), 3.60 (dd, 1H, ^3J(H,H) = 5.3 Hz, ^3J(H,P) = 8.9, CH). ^{13}C NMR (D_2O): $\delta = 15.4$ (d, ^3J(C,P) = 8.7 Hz), 49.02 (s), 68.41 (d, ^1J(C,P) = 156.2 Hz). ^{31}P NMR (D_2O): $\delta = 17.27$. Anal. calcd for $C_3H_{10}NO_4P$: C, 23.23; H, 6.45; N, 9.03. Found: C, 23.21; H, 6.08; N, 8.77%.

4.6.2. (1*S*,2*S*)-(2-Amino-1-hydroxy-4-methyl)pentyl phosphonic acid, 5b. 78% yield, mp = 235.5–238.5°C, $[\alpha]_D^{25.9} = +8.7$ (*c* 1, water), IR: $\nu = 937$, 1015, 1076, 1134, 1526, 1618, 2881, 3145 cm^{-1}. ^{1}H NMR (D_2O): $\delta = 0.84$ (d, 6H, ^3J(H,H) = 7.0 Hz, 2×CH_3), 1.42 (m, 1H, CH), 1.57 (m, 2H, CH_2), 3.50 (m, 1H, CH), 3.71 (dd, 1H, ^3J(H,H) = 2.2 Hz, ^3J(H,P) = 10.5 Hz, CH). ^{13}C NMR (D_2O): $\delta = 21.38$ (s), 23.56 (s), 38.18 (d, ^3J(C,P) = 9.6 Hz), 57.37 (s), 65.83 (d, ^1J(C,P) = 155.4 Hz). ^{31}P NMR (D_2O): $\delta = 17.57$. Anal. calcd for $C_6H_{16}NO_4P$: C, 36.52; H, 8.11; N, 7.10. Found: C, 36.43; H, 7.89; N, 6.88%.

4.6.3. (1*S*,2*S*,3*S*)-(2-Amino-1-hydroxy-3-methyl)pentyl phosphonic acid, 5c. 66% yield, mp = 216–220°C. $[\alpha]_D^{28.3} = +8.2$ (*c* 1, water), IR: $\nu = 942$, 1013, 1080, 1134 1528, 1616, 2881, 3145 cm^{-1}. ^{1}H NMR (D_2O): $\delta = 0.76$ (t, 3H, ^3J(H,H) = 7.3 Hz, CH_3), 0.83 (d, 3H, ^3J(H,H) = 6.7 Hz, CH_3), 1.05 (m, 1H, CH), 1.60 (m, 2H, CH_2), 3.12 (m, 1H, CH), 3.86 (dd, 1H, ^3J(H,H) = 2.0 Hz, ^3J(H,P) = 11.3 Hz, CH). ^{13}C NMR (D_2O): $\delta = 9.82$ (s), 14.19 (s), 24.22 (s), 33.86 (d, ^3J(C,P) = 10.1 Hz), 56.40 (s), 63.92 (d, ^1J(C,P) = 155.1 Hz). ^{31}P NMR (D_2O): $\delta = 17.10$. Anal. calcd for $C_6H_{16}NO_4P$: C, 36.52; H, 8.11; N, 7.10. Found: C, 36.52; H, 8.13; N, 6.77%.

4.7. Synthesis of Boc-(*S*)-Phe-(*S*)-Ala-PO_3Me_2, 6

Boc-(*S*)-phenylalanine (5 mmol) was dissolved in 10 ml of dry THF and 12 mmol of *N*-methylmorpholine was added dropwise to the mixture. The mixture was then cooled in an ice–water bath to −20°C and 5.5 mmol of isobutyl chloroformate was added. After 1 h, 5 mmol of (1*S*,2*S*)/(1*R*,2*S*) dimethyl (2-amino-1-hydroxy)propylphosphonate hydrochloride **3a** was added and the mixture was stirred overnight at room temperature. THF

was removed on rotary evaporator and the residue was dissolved in 40 ml of ethyl acetate and washed with 10% aqueous solution of citric acid, saturated solution of $NaHCO_3$, water and brine. Drying and evaporation of the solvent gave crude **6**, which was purified by means of column chromatography on silica gel using CH_2Cl_2/MeOH (50:2, v/v) as eluent. Pure phosphonopeptide **6** was obtained as a white solid.

Mixture of two diastereoisomers: (1*S*,2*S*,2′*S*), 84%; (1*R*,2*S*,2′*S*), 16%; 38% yield, mp = 45–49°C. IR: ν = 978, 1023, 1070.60, 1173, 1225, 1445, 1479, 1527, 1651, 1691, 2982, 3339 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.26$ (d, 3H, $^3J(H,H) = 5.7$ Hz, CH_3), 1.37 (s, 9H, Boc), 3.01 (m, 2H, CH_2), 3.82 (d, 6H, $^3J(P,H) = 10.5$ Hz, 2×OCH_3), 3.89 (dd, 1H, $^3J(H,H) = 3.8$ Hz, $^2J(H,P) = 8.9$, CH), 4.27 (m, 2H, 2×CH), 7.02 (d, 1H, NH), 7.23–7.31 (m, 5H, aromat.); ^{13}C NMR for (1*S*,2*S*,2′*S*) ($CDCl_3$): δ = 17.6 (d, $^3J(C,P) = 9.7$ Hz), 28.22 (s), 38.50 (s), 47.46 (s), 53.50 (d, $^2J(C,P) = 7.0$ Hz), 56.50 (s), 70.74 (d, $^1J(C,P) = 161.4$ Hz), 80.20 (s), 126.8 (s), 128.51 (s), 129.40 (s), 136.67 (s), 155.37 (s), 172.04 (s). ^{31}P NMR: $\delta = 25.28$ (1*R*,2*S*,2′*S*), 25.48 (1*S*,2*S*,2′*S*). Anal. calcd for $C_{19}H_{31}N_2O_7P$: C, 52.98; H, 7.20; N, 6.51. Found: C, 53.21; H, 7.40; N, 6.77%. ESI = 430.5, 452 $(M+Na)^+$.

4.8. Derivatization of 3b with (*S*)-*O*-methylmandelic acid

To a solution of **3b** (30 mg) in 1 ml of CH_2Cl_2 (*S*)-*O*-methylmandelic acid (15.4 mg, 1 equiv.) was added followed by addition of small crystal of DMAP and DCC (24 mg, 1.3 equiv.). After 24 h of stirring DCU was filtered off, solvent removed under reduced pressure and the sample subjected to ^1H and ^{31}P NMR ($CDCl_3$) analysis without purification.

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