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Stereoselective addition of dialkyl phosphites to di-salicylaldimines bearing the (*R*,*R*)-1,2-diaminocyclohexane moiety

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ABSTRACT

The addition of dialkyl phosphites to the azomethine bond of *N*,*N*′-disalicylidene-1,2-diaminocyclohexane imines, catalyzed by sodium hydride led to bis-aminophosphonates in a high diastereoselectivity. One of the bis-aminophosphonates was analyzed by X-ray diffraction. Another bis-aminophosphonate was converted to a bis-aminophosphonic acid and the structure was studied by X-ray diffraction. Addition of phosphites to a diimine resulted in an aminophosphonate, which was also studied by X-ray diffraction. An explanation of the diastereoselectivity is suggested.

1. Introduction

Salen ligands (**1**) constitute a group of compounds with a large field of applications. First, they have been applied as catalysts in the stereoselective Strecker synthesis of amino acids.[1–3] They have also been used for asymmetric catalysis of the Mannich reaction[4] and the Kabatchnik–Fields reaction.[5,6] Recently, the use of saturated derivatives of salen-ligands, i.e., 1,2-diaminocyclohexane (DACH)-based, *N*-tosylated tetramines has been reported.[7,8] They were applied either to the synthesis of amino acids[7] or to the asymmetric Henry reaction as Cu(I) complexes and were highly stereoselective.[8]

It is well known that aminophosphonic derivatives bearing more than one amino and more than one phosphonic moieties were recognized as good ligands for coordinating metal ions. The phosphonic analogue of EDTA is the most representative example but there are numerous aminophosphonic chelating agents.

There is no wonder that a large number of salen applications concern, in large part, aminophosphonic acids because optically active aminophosphonic acids and their derivatives are biologically active compounds, which are widely used in pharmaceutical applications.[9,10] Therefore much effort has been directed towards the development of asymmetric hydrophosphonylation of carbonyl and imine compounds. Salen-like ligands have also been found to have some in vitro anticancer properties.[11]

All these facts prompted us to perform a study on the catalytic properties of chiral salen-ligand derivatives bearing the phosphonic moieties, which bear saturated, sp^3 nitrogen atoms. Our idea was to construct α-aminophosphonates, which, in structure resemble salen-like ligand derivatives and which combine the chelating abilities of aminophosphonic groups and the strong stereoselection of salen compounds.

We have already published results of salen aminophosphonic derivatives bearing, instead of salicylic moiety, the phenyl one,[12] now, we present the study on the addition of the most common phosphites to its azomethine bond using sodium hydride as a catalyst.

We expected that the presence of this optically active moiety would influence much on the stereoselectivity of the addition. These bis-aminophosphonic systems bearing the (*R*,*R*)-DACH moiety have potential abilities to catalyze asymmetrically the Henry reaction and possibly the Kabachnik–Fields reaction.

2. Results and discussion

The aim of this study is twofold. First, we intended to synthesize a series of bis-aminophosphonate derivatives bearing the (*R*,*R*)-1,2-diaminocyclohexyl (DACH) moiety. These compounds are saturated equivalents of salen-type ligands enriched by phosphonic groups and they may be of value in asymmetric synthesis as catalysts. In future, they will be investigated in view of this aspect.

The second task was to investigate the stereochemistry of addition of alkyl phosphites to salen ligands, namely to *N*,*N*′-disalicylidene-(*R*,*R*)-1,2-diaminocyclohexane derivatives **1a**,**b**. This

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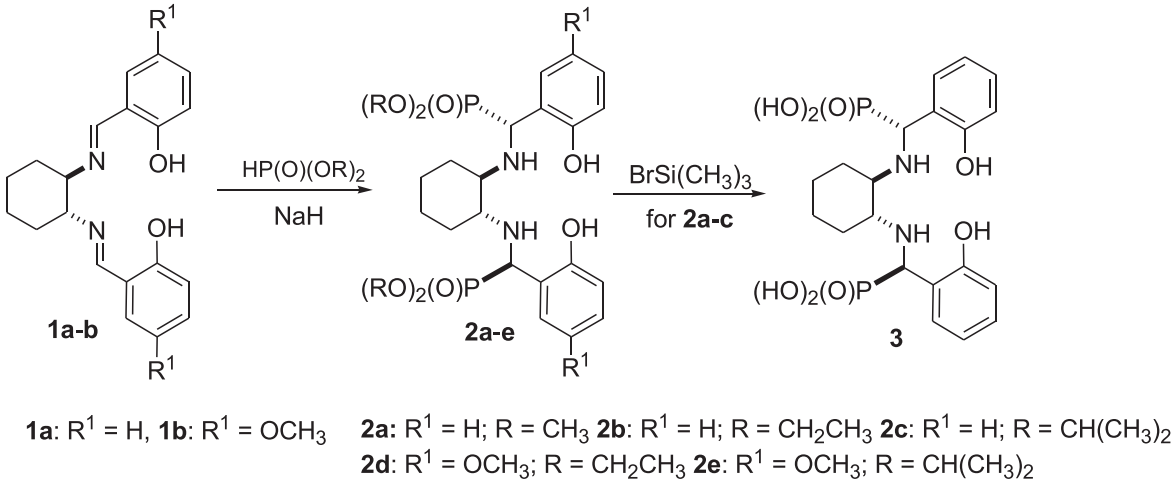
study is a continuation of our previous work, where the stereochemical aspect of phosphite addition to *N*,*N*′-dibenzylidene-(*R*,*R*)-1,2-diaminocyclohexane has been investigated.[12] As reactions occurred with fair diastereoselectivities (dr 100:9:9), we supposed that stereoselection would be even better, when typical salen imines underwent the reaction. For the purpose of the study, we have chosen two salen imines (Scheme 1): *N*,*N*′-disalicylidene-(*R*,*R*)-1,2-diaminocyclohexane (**1a**) and *N*,*N*′-di(5-methoxy-2-hydroxybenzylidene)-(*R*,*R*)-1,2-diaminocyclohexane (**1b**), which were prepared following the slight modification of known methods.[7,12,13] As phosphites, three typical dialkyl esters were used, namely dimethyl, diethyl and diisopropyl one. Additions of dialkyl phosphites were carried out first under similar conditions as in our previous works,[12] i.e., in acetonitrile in the presence of a catalytic amount of trifluoroacetic acid or without any catalyst. Unfortunately, the methods were found to be ineffective, as yields were low, and stereoselectivities were poor. It is probably due to the presence of a phenolic hydroxyl group, which competes with an azomethine bond for reacting with a phosphite.

Table 1
Addition of phosphites to imines **1a**,**b** and **4**

Compd no.	R	R^1	Y[a] [%]	dr	^{31}P NMR	^{31}P NMR of a single diastereoisomer
2a	H	CH_3	74	94:1:5	26.35, 25.43, 24.48	26.35
2b	H	CH_2CH_3	95	92:1:7	24.02, 23.35, 22.19	24.02
2c	H	$CH(CH_3)_2$	72	95:4:1	21.98, 23.82, 25.80	21.98
2d	OCH_3	CH_2CH_3	80	2:96:2	24.89, 24.11, 22.22	24.11
2e	OCH_3	$CH(CH_3)_2$	74	2:95:3	23.65, 22.12, 20.65	22.12
5a	—	CH_2CH_3	63	93:7	22.97, 22.38	22.97
5b	—	$CH(CH_3)_2$	71	86:14	21.71, 20.76	21.71

[a] Yields of isolated, predominant diastereosiomers.



1a: R^1 = H, **1b**: R^1 = OCH_3 **2a:** R^1 = H; R = CH_3 **2b**: R^1 = H; R = CH_2CH_3 **2c**: R^1 = H; R = $CH(CH_3)_2$
2d: R^1 = OCH_3; R = CH_2CH_3 **2e**: R^1 = OCH_3; R = $CH(CH_3)_2$

Scheme 1. Preparation of di(aminophosphonates) **2a**–**e** and aminophosphonic acid **3**.

Considering the acidic character of the substrates, we investigated catalysis to carry out additions in anhydrous ether, in the presence of catalytic amount of sodium hydride. Yields improved much, with a significant increase of diastereoselection as well. Additions to *N*,*N*′-disalicylidene-(*R*,*R*)-1,2-diaminocyclohexane (**1a**) were performed with dimethyl, diethyl and diisopropyl phosphites, where the corresponding bis-aminophosphonates **2a**–**c** were formed in a very high diastereoselectivity with dr values oscillating around 1:4:100. Results are collected in Table 1.

Additions of two phosphites, namely diethyl and diisopropyl ones were performed in the case of *N*,*N*′-di(5-methoxy-2-hydroxybenzylidene)-(*R*,*R*)-1,2-diaminocyclohexane (**1b**), where resulting bis-aminophosphonates **2d**,**e** occurred in a very high diastereoselectivity, with dr values around 1:1:50 (Table 1).

Predominant diastereoisomers of aminophosphonates **2a**–**c** were separated as lyophilisates and any attempts to obtain them in crystalline form failed. Therefore, their absolute configurations could not be determined by means of X-ray structural studies. Hence, they were converted into the corresponding (*R*,*R*)-1,2-cyclohexylenediamino-di[(2-hydroxyphenyl)methylphosphonic acid] (**3**) by cleavage of the phosphonic ester groups with bromotrimethylsilane. This conversion was chosen, because neither racemization nor configuration inversion seemed likely. We could then assume that the configuration of the aminophosphonic acid **3** is the same as configuration of starting esters **2a**–**c**. Fortunately, the acid **3** was a crystalline solid and thus its absolute configuration could obviously be determined by an X-ray study, which revealed that it has the *RRRR* configuration (Fig. 1a). It is therefore assumed that the predominant diastereoisomers of aminophosphonates **2a**–**c** adopted the *RRRR* configuration.

A similar situation occurred in the cases of diaminophosphonates **2d**,**e**. The predominant diastereoisomer of tetraethyl (*R*,*R*)-1,2-cyclohexylenediamino-di[(2-hydroxy-5-methoxyphenyl)-methylphosphonate] (**2d**) was separated as a dense oil, but the predominant diastereoisomer of tetraisopropyl aminophosphonate **2e** crystallized, which allowed the X-ray structural study. This analysis demonstrated that the predominant diastereosiomer of the aminophosphonate **2e** had the *RRRR* configuration (Fig. 1b) and considering the high similarity in structure between aminophosphonates **2d** and **2e**, one can state with a high probability that the predominant diastereomer of **2d** has also the *RRRR* configuration.

Since that above mentioned conditions give high stereoselectivity, in comparison with more common methodologies of phosphite additions to chiral aldimines, we tried to investigate the scope of the method. First, we tested this methodology for non-salicylaldehydes: benzaldehyde and 4-hydroxybenzaldehyde. Clearly, this methodology is only suitable for salicylaldehyde

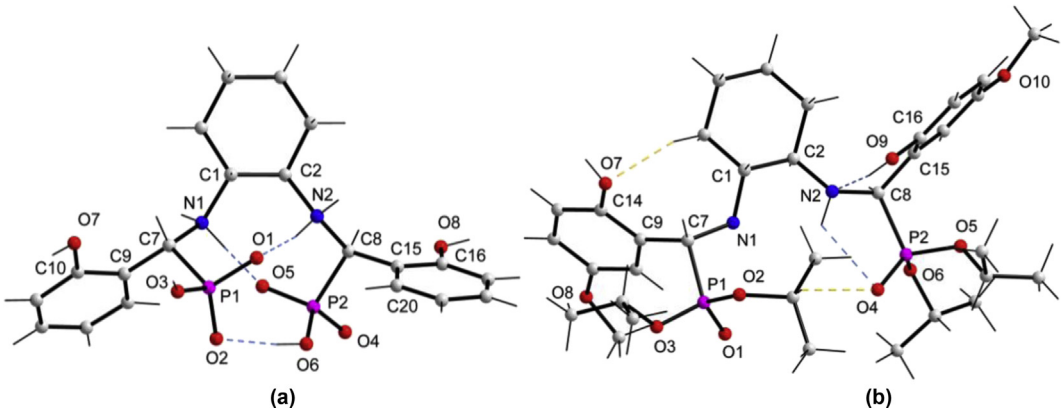
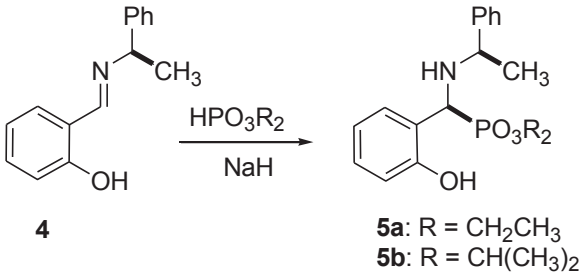


Fig. 1. The X-ray structures of molecules in **3**·MeOH·$2H_2O$ (a) and **2e** (b) showing the intramolecular hydrogen bonds (dashed lines). The disorder in **2e**, **3** and solvent molecules is omitted for clarity [selected torsion angles for **2e**: P1–C7–N1–C1 −142.88(13)°; P2–C8–N2–C2 −148.13(13)°; P1–C7–C9–C14 122.27(18)°; P2–C8–C15–C16–86.04(19)°. Selected torsion angles for **3**: P1–C7–N1–C1 −84.2(3)°; P2–C8–N2–C2 −87.0(4)°; P1–C7–C9–C10 94.7(4)°; P2–C8–C15–C16 100.0(4)°].

derivatives, because addition of phosphites to (*R*,*R*)-*N*,*N*′-bis(benzylidene)-1,2-cyclohexanediamine and to (*R*,*R*)-*N*,*N*′-bis(4-hydroxybenzylidene)-1,2-cyclohexanediamine, when catalyzed by NaH, occurred in extremely low yields (15–20%).

The other problem to investigate was the stereoselectivity of this method in addition of phosphites to imines known to provide a poor chiral assistance. For this purpose, (*R*)-*N*-salicylidene-α-methylbenzylamine (**4**) was chosen, even though the α-methylbenzylamine moiety is known to be a rather poor chiral auxiliary, as the aza-Pudovik reaction occurred in low stereoselectivity with dr not better than 75:25.[14] Surprisingly, additions of diethyl and diisopropyl phosphites to salicylaldimine **4** in anhydrous ether, in the presence of sodium hydride led to the formation of diethyl and diisopropyl (*R*)-α-methylbenzylamino-(2-hydroxyphenyl)-methylphosphonates **5a** and **5b**, respectively (Scheme 2).



Scheme 2. Prepration of aminophosphonates **5a**,**b**.

Diethyl (*R*)-α-methylbenzylamino-(2-hydroxyphenyl)-methylphosphonate **5a** has been mentioned once in the literature,[15] but it has been neither isolated nor characterized. Diastereoselectivities were relatively high, with dr=25:2 and 25:4, respectively, so the catalytic action of sodium hydride improved much the chiral assistance of the α-methylbenzylamine moiety. The separation of the predominant diastereoisomers of **5a**,**b** was performed by column chromatography, but diethyl (*R*)-α-methylbenzylamino-(2-hydroxyphenyl)-methylphosphonate (**5a**) was a dense oil. However, a predominant diastereosiomer of diisopropyl aminophosphonate **5b** crystallized as crystals suitable to perform the X-ray study, which revealed the *S* configuration on the newly formed centre of chirality (Fig. 2).

A tentative model to explain the high diastereoselectivity is presented. First, we considered that the sodium salts of imines **1a**,**b** must have the sodium cation coordinated by the phenolic oxygen

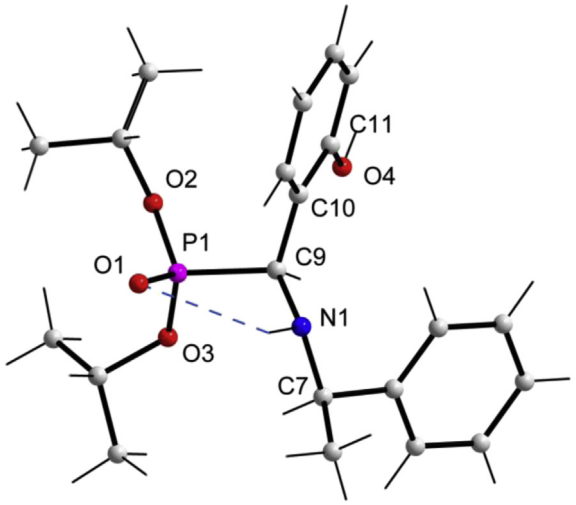


Fig. 2. The X-ray structure of **5b** showing the intramolecular hydrogen bond (dashed line) [selected torsion angles: P1–C9–N1–C7 92.5(2)°; P1–C9–C10–C11–104.1(2)°].

and by the azomethine nitrogen. Thus one can expect the formation of a six-membered ring fused to a phenyl ring. Such a sodium salt **6a**,**b** should adopt an '*anti*–*anti*' conformation, because it seems to be the most convenient due to a distance between two π-electron-rich moieties (Fig. 3). The attack of sodium dialkyl phosphite molecules on the first azomethine bond can be proceeded nearly exclusively from its external side (*Re* side) to form an aminophosphonic moiety adopting the *R* configuration. The formed (*R*)-imino-aminophosphonates **7a**–**e** can be attacked by sodium dialkyl phosphite mainly from the external side too (Fig. 3) leading to the formation of the *RRRR* diastereoisomer as the major product.

Much less obvious is the reason of high diastereoselectivity of addition to the imine **4**. It is, however, probable that its sodium salt is stabilized by intramolecular coordination of a sodium cation by the phenolic oxygen and by azomethine nitrogen. The sodium salt of *N*-salicylidene-(*R*)-α-methylbenzylamine (**4**) would adopt the conformation **4**-bis (Fig. 4). The attack of a phosphite molecule is then most easy from the side opposite to the phenyl ring, and results in the major formation of the *RS* diastereoisomer of **5a**,**b**.

3. Conclusions

The addition of phosphites to chiral salicylaldimines catalyzed by sodium hydride was found to be very highly diastereoselective.

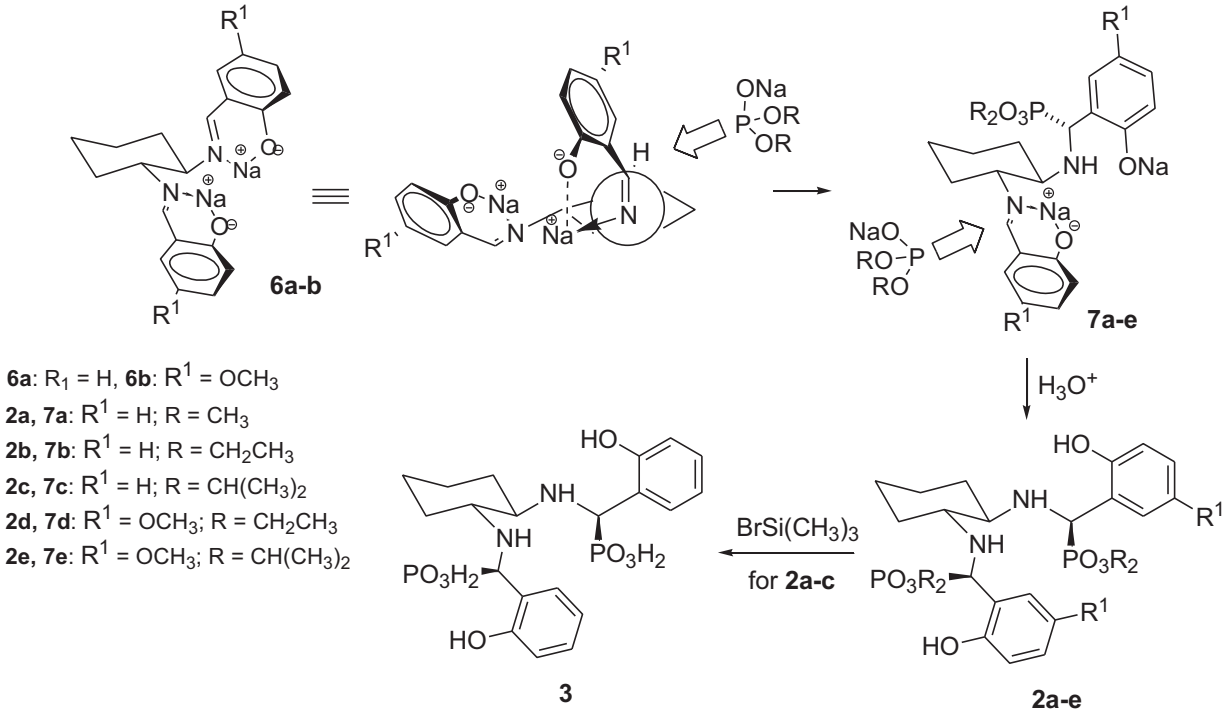


Fig. 3. Probable mechanism of diastereoselective formation of **2a**–**e**.

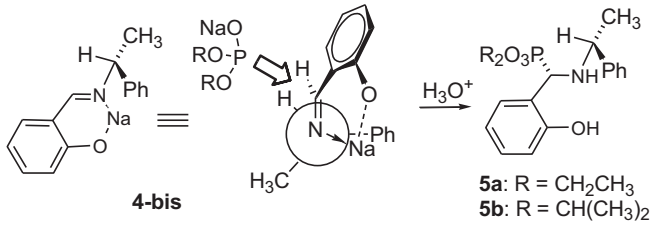


Fig. 4. Probable mechanism of diastereoselective formation of **5a**,**b**.

The diastereoselectivity of addition to *N*,*N*′-disalicylidene-(*R*,*R*)-1,2-diaminocyclohexane imines **1a**,**b** and *N*-salicylidene-(*R*)-α-methylbenzylamine (**4**) can be explained by stabilization of their sodium salts by intramolecular coordination of a sodium cation by the phenolic oxygen and by the azomethine nitrogen. This stabilization enables the predominant formation of the *RRRR* isomers of aminophosphonates **2a**–**e** and the *RS* isomers of **5a**,**b**.

4. Experimental section

4.1. General information and materials

All solvents were routinely distilled and dried prior to use. Commercial reagents were generally used as received. NMR spectra were recorded on a Bruker Avance III 600 MHz apparatus operating at 600 MHz (^{1}H NMR), 150 MHz (^{13}C NMR) and 243 MHz (^{31}P NMR). ^{1}H NMR spectra of imines **1a**,**b** and **4** were recorded on a Varian Gemini 2000BB 200 MHz. Solvent peaks ($CHCl_3/CDCl_3$ δ=7.26/77.16; DMSO-d_6/DMSO-d_6 δ=2.51/39.52) were used as chemical shift references for ^{1}H and ^{13}C NMR spectra, while H_3PO_4 was used as external standard for chemical shift references for ^{31}P NMR. Mass spectra were recorded on a Varian 500-MS LC Ion Trap apparatus using the ESI method. IR spectra were recorded on a Thermo Nicolet Nexus FT-IR spectrometer, while rotations were measured using a Perkin–Elmer 241 MC polarimeter. Melting points were measured using the MelTemp II apparatus, in a capillary. Elemental analyses were performed in the Laboratory of Microanalysis, the Center of Molecular and Macromolecular Studies PAS in Łódź.

4.2. General procedure for synthesis of imines 1a,b

Imines **1a**,**b** were synthesized following the published procedures[7,13] with slight modifications already described in our previous paper.[12] Quantities used: aldehyde (20 mmol) and 1*R*,2*R*-diaminocyclohexane salt (10 mmol).

*4.2.1. (R,R)-N,N′-Bis(salicylidene)-1,2-cyclohexanediamine (**1a**).* Yield 2.90 g, 90%, mp 117–119 °C, lit.[13] 118–119 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.28 (br s, OH, 1H); 8.26 (s, CH=N, 2H); 7.23 (ddd, $^3J_{HH}$=7.3 Hz, $^3J_{HH}$=8.6 Hz and $^4J_{HH}$=1.4 Hz, H_{ortho}, 2H); 7.15 (dd, $^3J_{HH}$=7.3 Hz and $^4J_{HH}$=1.4 Hz, H_{ortho}, 2H); 6.88 (d, $^3J_{HH}$=7.4 Hz, H_{ortho}, 2H); 6.79 (ddd, $^3J_{HH}$=7.4 Hz, $^3J_{HH}$=8.6 Hz and $^4J_{HH}$=1.1 Hz, H_{ortho}, 1H); 3.34–3.29 (m, CH–N, 2H); 1.97–1.70 (m, CH_2, 6H); 1.52–1.44 (m, CH_2, 2H).

*4.2.2. (R,R)-N,N′-Bis(5-methoxysalicylidene)-1,2-cyclohexanediamine (**1b**).* Yield 3.51 g, 92%, mp 115–118 °C, lit.[7] 118–120 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.19 (s, CH=N, 2H); 6.85 (d, $^3J_{HH}$=2.4 Hz, ArH, 2H); 6.84 (s, ArH, 2H); 6.65 (dd, $^3J_{HH}$=2.4 Hz and $^4J_{HH}$=0.9 Hz, ArH, 2H); 3.71 (s, OCH_3, 6H); 3.33–3.28 (m, CH–N, 2H); 1.97–1.70 (m, CH_2, 6H); 1.51–1.42 (m, CH_2, 2H).

4.3. Procedure for synthesis of (*R*,*R*)-1,2-cyclohexylenediamino-di(methylphosphonates) 2a–e

Three-necked flask, equipped with a thermometer, gas inlet and calcium chloride drying tube was charged with imine (2 mmol) and dry diethyl ether (25 mL) and placed on ice-salt bath. After cooling below 0 °C dialkyl phosphite (4.4 mmol) was added. Then sodium hydride 50% suspension in mineral oil (0.5 g) was added in small

portions with care to temperature not rise above 0 °C. The system was kept mixed on ice-salt bath for 30 min and then the bath was removed. Reaction mixture was allowed to warm to ambient temperature and mixed for further 30 min. If imine substrate was still observed on the TLC plates additional portions of phosphite were added. After disappearance of the substrate the mixture was again cooled on ice-salt bath and the reaction was quenched by slow addition of ice pieces. When no more hydrogen was releasing, a thermometer, drying tube and gas inlet were removed and 20 ml of water was added.

Layers were separated. Organic layer was two times extracted by 10% aqueous NaOH (2×15 mL). Pale-yellow or colourless water layers were merged and washed two times with diethyl ether to remove traces of unreacted phosphite. Then the aqueous solution was neutralized up to pH 7 by slow addition of 15% hydrochloric acid (excess of acid must be avoided!) and mixture became milky. Then it was three times extracted with ethyl acetate, organic layer dried and solvent evaporated in vacuo yielding crude amino-phosphonate as light-yellow or colourless dense oil, which was further purified by column chromatography on silica gel.

*4.3.1. Tetramethyl (R,R)-1,2-cyclohexylenediamino-di-(R,R)-[(2-hydroxyphenyl)methylphosphonate] (**2a**).* Predominant diastereo isomer: (0.80 g, 74%), eluent: methanol/ethyl acetate (1:12). Elem anal. calcd for $C_{24}H_{36}N_2O_8P_2$: C, 53.14; H, 6.69; N, 5.16. Found: C, 52.93; H, 6.89; N, 5.42. $[\alpha]_D^{20}$ −47.5 (*c* 0.91, CH_2Cl_2); IR (KBr): 3424 (ν_{OH}); 2951 (ν_{CH}); 1601, 1451 (C−C_{arom}); 1227 (P═O); 1054 (C−O); 1037 (P−O), 828, 755 (C−H_{ortho}), 569. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.43 (br s, OH, 2H); 7.19−7.17 (m, H_{ortho}, 2H); 7.09 (d, $^3J_{HH}$=7.6 Hz, H_{ortho}, 2H); 6.88 (d, $^3J_{HH}$=8.1 Hz, H_{ortho}, 2H); 6.84 (dd, $^3J_{HH}$=7.4 and 7.6 Hz, H_{ortho}, 2H); 4.15 (d, $^2J_{PH}$=21.2 Hz, CHP, 2H); 3.76 (d, $^3J_{PH}$=10.6 Hz, OCH_3, 6H); 3.64 (d, $^3J_{PH}$=10.4 Hz, OCH_3, 6H); 2.90 (br s, NH, 2H); 2.46−2.44 (m, CH−N, 2H); 1.75−1.73 (m, CH_2, 2H); 1.49−1.48 (m, CH_2, 2H); 1.10−1.07 (m, CH_2, 2H); 1.02−1.00 (m, CH_2, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.23 (d, $^3J_{CP}$=5.0 Hz, C−OH); 129.56 (d, $^3J_{CP}$=6.9 Hz, C_{arom}); 120.91 (d, $^2J_{CP}$=3.5 Hz, C_{arom}); 119.90, 118.11, 118.09 (C_{arom}); 63.10 (C_{hex}−N); 58.77 (d, $^1J_{CP}$=152.3 Hz, C−P); 53.88 (d, $^2J_{CP}$=7.0 Hz, POC); 53.70 (d, $^2J_{CP}$=7.3 Hz, POC); 31.23 (C_{hex}); 24.14 (C_{hex}). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 26.35. ESI-MS: *m*/*z*=592 $[M+4H^++2Na^+]$; 569 $[M+4H^++Na^+]$; 560 $[M+2H^++2Na-2CH_3]^+$; 546 $[M+4H^+]$; 552 $[M^+]$.

*4.3.2. Tetraethyl (R,R)-1,2-cyclohexylenediamino-di-(R,R)-[(2-hydroxyphenyl)methylphosphonate] (**2b**).* Predominant diastereo isomer: (1.14 g, 95%), eluent: hexane/ethyl acetate (4:1). Elem anal. calcd for $C_{28}H_{44}N_2O_8P_2$: C, 56.18; H, 7.41; N, 4.68. Found: C, 55.93; H, 7.64; N, 4.75. $[\alpha]_D^{20}$ −57.4 (*c* 1.045, CH_2Cl_2). IR (KBr): 3385 (ν_{OH}); 2981 (ν_{CH}); 1601, 1457 (C−C_{arom}); 1223 (P═O); 1054 (C−O); 1027 (P−O), 969, 754 (C−H_{ortho}). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.51 (br s, OH, 2H); 7.18 (dd, $^3J_{HH}$=7.8 and 7.6 Hz, H_{ortho}, 2H); 7.09 (d, $^3J_{HH}$=7.6 Hz, H_{ortho}, 2H); 6.88 (d, $^3J_{HH}$=8.1 Hz, H_{ortho}, 2H); 6.84−6.81 (m, H_{ortho}, 2H); 4.11−4.01 (m, CHP, OCH_2, 8H); 3.94−3.90 (m, OCH_2, 2H); 2.84 (br s, NH, 2H); 2.54−2.46 (m, CH−N, 2H); 1.77−1.75 (m, CH_2, 2H); 1.49−1.47 (m, CH_2, 2H); 1.30 (t, *J*=7.0 Hz, CH_2CH_3, 6H); 1.22 (t, *J*=7.0 Hz, CH_2CH_3, 6H); 1.13−1.11 (m, CH_2, 2H); 1.08−1.04 (m, CH_2, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.39 (d, $^3J_{CP}$=4.5 Hz, C−OH); 129.82 (C_{arom}); 129.39 (C_{arom}); 121.02, 119.79, 118.27 (C_{arom}); 63.65 (d, $^2J_{CP}$=7.0 Hz, POC); 63.32 (d, $^2J_{CP}$=7.1 Hz, POC); 61.88 (C_{hex}−N); 59.51 (d, $^1J_{CP}$=154.0 Hz, C−P); 30.73 (C_{hex}); 23.73 (C_{hex}); 16.45 (d, $^2J_{CP}$=5.2 Hz, POC); 16.26 (d, $^2J_{CP}$=5.2 Hz, POC). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 24.02. ESI-MS: *m*/*z*=646 $[M+2H^++2Na^+]$; 615 $[M+2Na-CH_2CH_3]$; 602 $[M+4H^+]$.

*4.3.3. Tetraisopropyl (R,R)-1,2-cyclohexylenediamino-di-(R,R)-[(2-hydroxyphenyl)methylphosphonate] (**2c**).* Predominant diastereo isomer: (0.94 g, 72%), eluent: hexane/ethyl acetate (2:1). Elem anal. calcd for $C_{32}H_{52}N_2O_8P_2$: C, 58.70; H, 8.01; N, 4.28. Found: C, 58.69; H, 8.10; N, 4.33. $[\alpha]_D^{20}$ −50.8 (*c* 0.83, CH_2Cl_2). IR (KBr): 3422 (ν_{OH}); 2979 (ν_{CH}); 1603, 1456 (C−C_{arom}); 1224 (P═O); 1054 (C−O); 1037 (P−O), 993, 754 (C−H_{ortho}), 572. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.59 (br s, OH, 2H); 7.17 (dd, $^3J_{HH}$=8.0 and 7.4 Hz, H_{ortho}, 2H); 7.02−7.01 (m, H_{ortho}, 2H); 6.84 (d, $^3J_{HH}$=8.0 Hz, H_{ortho}, 2H); 6.81 (dd, $^3J_{HH}$=7.3 and 7.4 Hz, H_{ortho}, 2H); 4.61−4.53 (m, P−O−CH, 4H); 3.92 (d, $^2J_{PH}$=22.4 Hz, CHP, 2H); 2.75 (br s, NH, 2H); 2.58 (m, CH−N, 2H); 1.79−1.77 (m, CH_2, 2H); 1.47−1.45 (m, CH_2, 2H); 1.31 (d, $^3J_{HH}$=6.1 Hz, CH_3, 6H); 1.30 (d, $^3J_{HH}$=6.1 Hz, CH_3, 6H); 1.24 (d, $^3J_{HH}$=6.1 Hz, CH_3, 6H); 1.18−1.19 (m, CH_2, 2H); 1.13−1.12 (m, CH_2, 2H); 1.08 (d, $^3J_{HH}$=6.1 Hz, CH_3, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.88 (C−OH); 130.58 (d, $^3J_{CP}$=6.6 Hz, C_{arom}); 129.61 (C_{arom}); 121.26 (C_{arom}); 119.97, 118.67 (C_{arom}); 72.94 (d, $^2J_{CP}$=7.6 Hz, OCH); 72.54 (d, $^2J_{CP}$=6.8 Hz, OCH); 60.55 (d, $^1J_{CP}$=151.4 Hz, CH−P); 30.28 (C_{hex}); 24.62 (d, $^4J_{CP}$=3.0 Hz, C_{hex}); 24.48 (d, $^3J_{CP}$=3.1 Hz, C_{hex}); 24.11 (d, $^3J_{CP}$=5.5 Hz, $POCHCH_3$); 23.84 (d, $^3J_{CP}$=5.3 Hz, $POCHCH_3$); 23.42 (C_{hex}). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 21.98. ESI-MS: *m*/*z*=702 $[M+2H^++2Na^+]$; 672 $[M+2Na-2CH_3]^+$.

*4.3.4. Tetraethyl (R,R)-1,2-cyclohexylenediamino-di-(R,R)-[(2-hydroxy-5-methoxyphenyl)methylphosphonate] (**2d**).* Predominant diastereoisomer: (1.05 g, 80%), eluent: diethyl ether. Elem anal. calcd for $C_{30}H_{48}N_2O_{10}P_2$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.89; H, 7.53; N, 4.45. $[\alpha]_D^{20}$ −42.5 (*c* 1.045, CH_2Cl_2). IR (KBr): 3412 (ν_{OH}); 2983 (ν_{CH}); 1617, 1499, 1449 (C−C_{arom}); 1213 (P═O); 1026 (C−O); 969. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.00 (br s, OH, 2H); 6.80 (d, $^3J_{HH}$=8.8 Hz, H_{arom}, 2H); 6.74 (ddd, $^3J_{HH}$=8.8 Hz and $^4J_{HH}$=2.1 Hz and $^6J_{PH}$=2.9 Hz, H_{arom}, 2H); 6.64 (dd, $^4J_{HH}$=2.1 Hz and $^4J_{PH}$=2.3 Hz, H_{arom}, 2H); 4.14−4.02 (m, P−O−CH_2, 6H); 3.96 (d, $^2J_{PH}$=21.8 Hz, CHP, 2H); 3.95−3.90 (m, P−O−CH_2, 2H); 3.75 (s, OCH_3, 6H); 2.87 (br s, NH, 2H); 2.46−2.45 (m, CH−N, 2H); 1.77−1.74 (m, CH_2, 2H); 1.49−1.48 (m, CH_2, 2H); 1.30 (t, $^3J_{HH}$=7.1 Hz, CH_3, 6H); 1.22 (t, $^3J_{HH}$=7.1 Hz, CH_3, 6H); 1.10−1.07 (m, CH_2, 2H); 1.00−0.97 (m, CH_2, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 152.94 (d, $^4J_{CP}$=1.3 Hz, C_{arom}−OCH_3); 151.04 (d, $^3J_{CP}$=4.7 Hz, C−OH); 122.12 (C_{arom}); 119.21 (C_{arom}); 114.90 (C_{arom}); 114.84 (d, $^2J_{CP}$=3.2 Hz, C_{arom}); 63.77 (d, $^2J_{CP}$=7.2 Hz, POC); 63.31 (d, $^2J_{CP}$=7.2 Hz, POC); 59.96 (d, $^1J_{CP}$=151.2 Hz, C−P); 55.73 (OCH_3); 31.08 (C_{hex}); 23.98 (C_{hex}); 16.52 (d, $^2J_{CP}$=5.2 Hz, POC*C*); 16.31 (d, $^2J_{CP}$=5.3 Hz, POC*C*). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 24.11. ESI-MS: *m*/*z*=674 $[M+2Na-2CH_3]^+$.

*4.3.5. Tetraisopropyl (R,R)-1,2-cyclohexylenediamino-di-(R,R)-[(2-hydroxy-5-methoxyphenyl)-methylphosphonate] (**2e**).* Predominant diastereoisomer: (1.06 g, 74%), eluent: diethyl ether, mp 162−163 °C. Elem anal. calcd for $C_{34}H_{56}N_2O_{10}P_2$: C, 57.14; H, 7.90; N, 3.92. Found: C, 57.26; H, 8.08; N, 4.13. $[\alpha]_D^{20}$ −34.0 (*c* 1.06, CH_2Cl_2). IR (KBr): 3420 (ν_{OH}); 2979 (ν_{CH}); 1617, 1498, 1466 (C−C_{arom}); 1209 (P═O); 1023 (C−O); 992, 584. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.09 (br s, OH, 2H); 6.78 (d, $^3J_{HH}$=8.8 Hz, H_{arom}, 2H); 6.75−6.72 (m, H_{arom}, 2H); 6.64 (s, H_{arom}, 2H); 4.61−4.55 (m, P−O−CH, 4H); 3.87 (d, $^2J_{PH}$=22.7 Hz, CHP, 2H); 3.74 (s, OCH_3, 6H); 2.80 (br s, NH, 2H); 2.52 (m, CH−N, 2H); 1.79−1.77 (m, CH_2, 2H); 1.47−1.45 (m, CH_2, 2H); 1.32 (d, $^3J_{HH}$=7.1 Hz, CH_3, 6H); 1.30 (d, $^3J_{HH}$=6.4 Hz, CH_3, 6H); 1.25 (d, $^3J_{HH}$=6.4 Hz, CH_3, 6H); 1.13−1.12 (m, CH_2, 2H); 1.10 (d, $^3J_{HH}$=6.4 Hz, CH_3, 6H); 1.06−1.03 (m, CH_2, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 152.76 (d, $^4J_{CP}$=0.9 Hz, C_{arom}−OCH_3); 151.15 (d, $^3J_{CP}$=4.0 Hz, C−OH); 122.15 (C_{arom}); 119.13 (C_{arom}); 115.05 (d, $^2J_{CP}$=7.0 Hz, C_{arom}); 114.83 (d, $^3J_{CP}$=2.8 Hz, C_{arom}); 72.69 (d, $^2J_{CP}$=7.6 Hz, POC); 72.14 (d, $^2J_{CP}$=7.4 Hz, OCH); 60.45 (d, $^1J_{CP}$=153.6 Hz, CH−P); 55.74 (OCH_3); 30.46 (C_{hex}); 24.36 (d, $^4J_{CP}$=2.9 Hz, C_{hex}); 24.48 (d, $^3J_{CP}$=3.0 Hz, C_{hex}); 23.79 (d, $^3J_{CP}$=5.7 Hz, $POCHCH_3$); 23.53 (d, $^2J_{CP}$=5.7 Hz, $POCHCH_3$); 23.46 (C_{hex}). ^{31}P NMR

($CDCl_3$, 243 MHz): δ 22.12. ESI-MS: m/z=762 [M+2H$^+$+2Na$^+$]; 731 [M+2Na−2CH$_3$]$^+$.

4.4. Procedure for preparation of (*R*,*R*)-1,2−cyclohexylenediamino-di-(*R*,*R*)-[(2-hydroxyphenyl)-methylphosphonic acid] (3)

Tetramethyl (*R*,*R*)-1,2-cyclohexylenediamino-di-(*R*,*R*)-[(2-hydroxyphenyl)methylphosphonate] (**2a**) of 542 mg (1 mmol) was dissolved in 10 ml of a dry acetonitrile. The mixture was cooled down to 0 °C and 2 ml (2.32 g, 15 mmol) of trimethylsilyl bromide was added. The mixture was stirred for 4 h at room temperature. Then 10 ml of methanol was added and stirring was continued for 2 h. Resulting precipitate was filtered and recrystallized from small amount of hot water yielding the *title compound* **3** (102 mg, 21%) as fine crystalline product.

Crystals for X-ray measurements were obtained from solution of the product in water/methanol (1:1) placed in a vial covered with a piece of cotton and slow evaporation of the solvents. Mp 250 °C (decomp.). Elem anal. calcd for $C_{20}H_{28}N_2O_8P_2\cdot 5/2H_2O$: C, 45.20; H, 6.26; N, 5.27. Found: C, 45.30; H, 6.12; N, 5.24. $[\alpha]_D^{20}$ −15.2 (*c* 0.483, CH_2Cl_2). IR (KBr): 3420 (ν_{OH}); 2951 (ν_{CH}); 1618, 1604, 1508, 1458 (C−C$_{arom}$); 1219 (P=O); 1042, 1016 (C−O); 982, 761. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.52 (d, $^3J_{HH}$=7.1 Hz, CH$_{ortho}$, 2H); 7.14 (t, $^3J_{HH}$=7.6 Hz, CH$_{ortho}$, 2H); 6.83−6.81 (m, CH$_{ortho}$, 4H); 4.40 (d, $^2J_{PH}$=18.5 Hz, CHP, 2H); 2.83−2.82 (m, CH−N, 2H); 1.42−1.41 (m, CH$_2$, 4H); 1.16−1.15 (m, CH$_2$, 2H); 0.93−0.91 (m, CH$_2$, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.98 (d, $^2J_{CP}$=5.5 Hz, C$_{arom}$−C−P); 130.78 (d, $^3J_{CP}$=4.7 Hz, C−OH); 129.26 (C$_{arom}$); 123.80 (C$_{arom}$); 119.54 (C$_{arom}$); 117.00 (C$_{arom}$); 63.55 (d, $^3J_{CP}$=9.1 Hz, C$_{hex}$); 57.24 (d, $^1J_{CP}$=143.0 Hz, CH−P); 30.63 (C$_{hex}$); 24.47 (C$_{hex}$). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 13.96.

4.5. Procedure for synthesis of *N*-salicylidene-(*R*)-α-methylbenzylamine (4)

To a vigorously stirred salicylaldehyde (1 g, 8.20 mmol), (*R*)-α-methylbenzylamine (1 g, 8.25 g) was added in one portion. Mixture become yellow with visible droplets of water and the temperature increased.[†] Stirring was continued for some time until the mixture instantaneously crystallized (usually after less than 1 h).[‡] The product was crushed, dried in air-flow and then recrystallized from small amount of *n*-hexane to give the *title product* **4** (1.70 g, 92%) as fine crystals. Mp 72–75 °C, lit.[16] 75 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.55 (br s, OH, 1H); 8.42 (s, CH=N, 1H); 7.38−7.22 (m, PhH, H$_{ortho}$, 7H); 6.98 (dd, $^3J_{HH}$=7.7 Hz and $^4J_{HH}$=0.4 Hz, H$_{ortho}$, 1H); 6.88 (ddd, $^3J_{HH}$=7.4, 8.3 Hz and $^4J_{HH}$=0.9 Hz, H$_{ortho}$, 1H); 4.57 (q, $^3J_{HH}$=6.7 Hz, CH, 1H); 1.65 (d, $^3J_{HH}$=6.7 Hz, CH$_3$, 3H).

4.6. Procedure for synthesis of (*R*)-α-methylbenzylamino-(2-hydroxyphenyl)methylphosphonates 5a,b

Reaction procedure was exactly the same as in case of DACH-derived substrates, however, due to insolubility of the products in basic aqueous solution the workup was done as follows. After quenching the reaction by addition of ice and aqueous layers were separated. Aqueous layer was extracted three times with ethyl acetate. Combined organic layer, containing the product, was washed three times with saturated sodium bicarbonate solution and once with brine. Organic layer was dried over sodium sulfate, filtered. Solvent was removed in vacuo affording pale-yellow or colourless oil. The crude product containing high amount of unreacted phosphite was purified on column chromatography.

*4.6.1. Diethyl (R)-α-methylbenzylamino-(S)-(2-hydroxyphenyl) methylphosphonate (**5a**).* Predominant diastereoisomer: (0.46 g, 63%), eluent: diethyl ether. Elem anal. calcd for $C_{19}H_{26}NO_4P$: C, 62.80; H, 7.21; N, 3.85. Found: C, 62.85; H, 7.35; N, 3.87. $[\alpha]_D^{20}$ +33.2 (*c* 0.91, CH_2Cl_2). IR (KBr): 3156 (ν_{OH}); 2978 (ν_{CH}); 1601, 1492, 1456 (C−C$_{arom}$); 1205 (P=O); 1053 (C−O); 1026 (P−O), 967, 755 (C−H$_{ortho}$), 700. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.28−7.26 (m, PhH, 5H); 7.17−7.15 (m, H$_{ortho}$, 1H); 7.00−6.99 (m, H$_{ortho}$, 1H); 6.82 (d, $^3J_{HH}$=7.8 Hz, H$_{ortho}$, 1H); 6.80−6.77 (m, H$_{ortho}$, 1H); 4.35 (d, $^2J_{PH}$=20.5 Hz, CHP, 1H); 4.07−3.95 (m, OCH$_2$, 4H); 3.87 (q, $^3J_{HH}$=6.6 Hz, CH, 1H); 1.45 (d, $^3J_{HH}$=6.6 Hz, CH$_3$, 3H); 1.26 (t, *J*=6.6 Hz, CH$_2$CH$_3$, 3H); 1.22 (t, *J*=6.6 Hz, CH$_2$CH$_3$, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.82 (d, $^3J_{CP}$=4.9 Hz, C$_{arom}$−OH); 130.12 (d, $^2J_{CP}$=6.2 Hz, C$_{arom}$); 129.42, 128.90, 127.54, 126.72 (C$_{arom}$); 119.37, 119.35 (C$_{arom}$); 117.78 (d, $^3J_{CP}$=7.0 Hz, C$_{arom}$); 117.58 (C$_{arom}$); 63.50 (d, $^2J_{CP}$=7.0 Hz, POC); 63.41 (d, $^2J_{CP}$=7.1 Hz, POC); 58.51 (d, $^1J_{CP}$=149.6 Hz, C−P); 55.35 (d, $^3J_{CP}$=14.3 Hz, C−N); 19.61 (C−C−N); 16.35 (d, $^2J_{CP}$=5.6 Hz, POC); 16.29 (d, $^2J_{CP}$=5.6 Hz, POC). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 20.19. ESI-MS: m/z=381 [M+H$^+$+2Na−2CH$_3$]$^+$.

*4.6.2. Diisopropyl (R)-α-methylbenzylamino-(S)-(2-hydroxyphenyl) methylphosphonate (**5b**).* Predominant diastereoisomer: (0.56 g, 71%), eluent: diethyl ether, mp 106–107 °C. Elem anal. calcd for $C_{21}H_{30}NO_4P$: C, 64.43; H, 7.72; N, 3.58. Found: C, 64.21; H, 7.62; N, 3.66. $[\alpha]_D^{20}$ +26.3 (*c* 0.91, CH_2Cl_2). IR (KBr): 3426 (ν_{OH}); 2975 (ν_{CH}); 1601, 1510, 1496, 1458 (C−C$_{arom}$); 1188 (P=O); 1061 (C−O); 983, 755 (C−H$_{ortho}$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.29−7.26 (m, PhH, 3H); 7.24−7.22 (m, PhH, 2H); 7.16−7.13 (m, H$_{ortho}$, 1H); 6.99 (d, $^3J_{HH}$=7.4 Hz, H$_{ortho}$, 1H); 6.82 (d, $^3J_{HH}$=8.0 Hz, H$_{ortho}$, 1H); 6.78−6.75 (m, H$_{ortho}$, 1H); 4.61−4.57 (m, P−O−CH, 2H); 4.26 (d, $^2J_{PH}$=21.2 Hz, CHP, 1H); 3.86 (q, $^3J_{HH}$=6.6 Hz, CH, 1H); 1.44 (d, $^3J_{HH}$=6.6 Hz, CH$_3$, 3H); 1.28 (d, $^3J_{HH}$=5.6 Hz, CH$_3$, 3H); 1.27 (d, $^3J_{HH}$=5.6 Hz, CH$_3$, 3H); 1.25 (d, $^3J_{HH}$=6.2 Hz, CH$_3$, 6H); 1.15 (d, $^3J_{HH}$=6.2 Hz, CH$_3$, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.67 (d, $^3J_{CP}$=4.9 Hz, C$_{arom}$−OH); 130.33 (d, $^2J_{CP}$=6.5 Hz, C$_{arom}$); 129.24, 128.55, 127.46, 126.74 (C$_{arom}$); 119.21, 118.41, 118.39 (C$_{arom}$); 117.76 (d, $^3J_{CP}$=2.4 Hz, C$_{arom}$); 72.40 (d, $^2J_{CP}$=7.5 Hz, OCH); 72.22 (d, $^2J_{CP}$=7.3 Hz, OCH); 59.01 (d, $^1J_{CP}$=151.4 Hz, CH−P); 55.45 (d, $^3J_{CP}$=14.3 Hz, C−N); 24.14 (d, $^2J_{CP}$=6.5 Hz, CH$_3$); 24.11 (d, $^2J_{CP}$=6.4 Hz, CH$_3$); 23.68 (d, $^2J_{CP}$=5.3 Hz, CH$_3$); 23.58 (d, $^2J_{CP}$=5.5 Hz, CH$_3$); 19.81 (C−C−N). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 21.70. ESI-MS: m/z=410 [M+H$^+$+2Na−2CH$_3$].

4.7. Crystal structures determinations of 2e, 3·MeOH·2H$_2$O and 5b

Data collections for X-ray structure determinations were performed on a Kuma KM4-CCD κ-geometry four-circle diffractometer with a Sapphire2 CCD detector with graphite monochromatized Mo Kα radiation. The data were collected at 100(2) K using an Oxford Cryosystems cooler. Data collection, cell refinement, data reduction and analysis, and absorption correction were carried out with the KM4-CCD software, CrysAlis^{Pro}.[17] The structures were solved by direct methods with the Shelxs,[18] and refined by a full-matrix least-squares technique on F^2 using Shelxl-2013[18] with anisotropic thermal parameters for the non-H-atoms, except for low-occupied positions of disordered atoms. Most of the H atoms were found in difference Fourier maps, but in the final refinement cycles the C-bonded H atoms were repositioned in their calculated positions and refined using a riding model, with C−H=0.95−1.00 Å, and with U_{iso}(H)=1.2U_{eq}(CH, CH$_2$) or 1.5U_{eq}(CH$_3$). Hydroxyl H atoms were refined using a riding model, with O−H=0.84 Å, and with U_{iso}(H)=1.5U_{eq}(O) (**2e**, **5b**) or were refined isotropically with the O−H distances restrained to 0.840(2) Å, and then were constrained to ride

[†] We recommend to not apply this protocol in scale larger than 1–2 g, due to relatively high amount of heat released.

[‡] If the product is already available, small crystal can be added to the mixture to cause immediate crystallization.

on their parent atoms (AFIX 3 instruction in Shelxl-2013; **3**·MeOH·2H_2O). H atoms from disordered water molecules in **3**·MeOH·2H_2O were not found in the difference Fourier maps. N-bonded H atoms in **2e** and **5b** were refined freely, and those in **3**·MeOH·2H_2O were refined using a riding model, with N–H=0.99 Å, and with U_{iso}(H)=1.2U_{eq}(N).

One of diisopropylphosphonate groups in **2e** is disordered and was refined in two sites with s.o.f.=0.783(4) and 0.217(4) (Fig. S1 in Supplementary data). Therefore, in the refinement procedure of the disordered region, some geometrical restrains and constraints/restrains on the fractional coordinates and displacement parameters (SAME, EXYZ, EADP, SIMU instructions in Shelxl-2013) were applied; for details see CIF file. Solvent molecules (methanol and both water molecules) in **3**·MeOH·2H_2O are disordered and refined in two sites each (Fig. S2 in Supplementary data), with s.o.f.=0.802(12) and 0.198(12) for MeOH, 0.799(11) and 0.201(11) for O1W, and 0.758(13) and 0.242(13) for O2W. In addition, one of the phosphonate –OH groups was refined with the H atom disordered into two sites with s.o.f.=0.5 each.

The structure plots were prepared with Diamond.[19] The crystal data and refinement parameters are presented in Table S1 in Supplementary data.

Supplementary data

These Data include NMR spectra for all new compounds **2a**–**e**, **3** and **5a**,**b** as well as crystallographic data, description of molecular structures, geometry of hydrogen bonds and close contacts for **2e**, **3**·MeOH·2H_2O and **5b**. Detailed crystallographic data for the crystals in this paper have been given in the crystallographic information files (CIFs) deposited with the Cambridge Crystallographic Data Center [ref. CCDC 951147 for **2e**, 951148 for **3**·MeOH·2H_2O, and 951149 for **5b**]. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.042.

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