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1-(α-Aminobenzyl)-2-naphthol: A New Chiral Auxiliary for the Synthesis of Enantiopure α-Aminophosphonic Acids

Kirill E. Metlushka,[a, b] Boris A. Kashemirov,[b] Viktor F. Zheltukhin,[a] Dilyara N. Sadkova,[a] Bernd Büchner,[c] Christian Hess,[c] Olga N. Kataeva,[a, c] Charles E. McKenna,[b] and Vladimir A. Alfonsov*[a]

Abstract: A new diastereoselective synthesis of α-aminophosphonates has been developed, based on the reaction, in the presence of trifluoroacetic acid, of trialkyl phosphites with chiral imines derived from (*R*)- or (*S*)-1-(α-aminobenzyl)-2-naphthol. The reaction proceeds at room temperature in toluene with high diastereoselectivity. The major diastereomer can be separated by crystallization from an appropriate solvent. The relative configuration of both chiral centers of the major diastereomer was determined by single-crystal X-ray structure analysis. The desired α-aminophosphonic acids can be obtained in enantiopure form by treatment of the corresponding diastereomers with HCl.

Keywords: aminophosphonic acids · asymmetric synthesis · Betti bases · chiral auxiliaries · imines

Introduction

α-Aminophosphonic acids are analogues of amino acids in which the carboxylic acid group is replaced by a phosphonic acid group. A number of α-aminophosphonic acids exhibit biological activities, including inhibitory activity against bacteria and fungi.[1] As a result, the synthesis of racemic α-aminophosphonates has been extensively investigated.[2] The bioactivity of such compounds is usually found to depend on their absolute configuration, so considerable attention is now being focused on the preparation of enantiopure α-aminophosphonates.[3] Stereoselective hydrophosphonylation of imines (the Pudovik reaction) offers an attractive route to the synthesis of such compounds. Chiral imines,[4] chiral hydrophosphoryl compounds,[5] and various types of asymmetric catalysts[6] have been employed to induce chiral preference; however, there is a continuing need to find new, accessible, cheaper, and more efficient approaches to the stereoselective synthesis of α-aminophosphonic acids.

Recently, we reported a new synthesis and the enantioseparation of benzylidenes obtained from 1-(α-aminobenzyl)-2-naphthols (Betti bases).[7] In the present work, we demonstrate the potential of these readily available Betti adducts as chiral inductors for the synthesis of enantiopure α-aminophosphonates.

Results and Discussion

It is well known that addition of trivalent phosphorus acid derivatives to polar unsaturated compounds containing a C=O group proceeds under mild conditions to form α-substituted alkyl phosphonates. For example, α-hydroxyphosphonates can be easily obtained from trialkyl phosphites and aldehydes in the presence of chlorotrimethylsilane and mineral acids.[8] However, relatively few reactions of trialkyl phosphites with compounds containing a C=N group have been documented. The addition of triethylphosphite to Schiff bases in phenol[9] was the first example described, and trialkyl phosphites were subsequently shown to condense with imino acids[10] and α,β-unsaturated aldimines in the presence of formic acid.[11] It was established[11] that the acid plays crucial roles by activating the imine and also by deal-

[a] K. E. Metlushka, Dr. V. F. Zheltukhin, D. N. Sadkova, Dr. O. N. Kataeva, Prof. Dr. V. A. Alfonsov
Kazan Scientific Center of the Russian Academy of Sciences
A. E. Arbuzov Institute of Organic and Physical Chemistry
Arbuzov str. 8, Kazan 420088 (Russia)
Fax: (+7) 8432-75-5322
E-mail: alfonsov@iopc.knc.ru

[b] K. E. Metlushka, Dr. B. A. Kashemirov, Prof. Dr. C. E. McKenna
Department of Chemistry, University of Southern California
Los Angeles, CA 90089-0744 (USA)

[c] Prof. Dr. B. Büchner, Dr. C. Hess, Dr. O. N. Kataeva
IFW Dresden, Institute for Solid State Research
P.O. Box 270116, 01171 Dresden (Germany)

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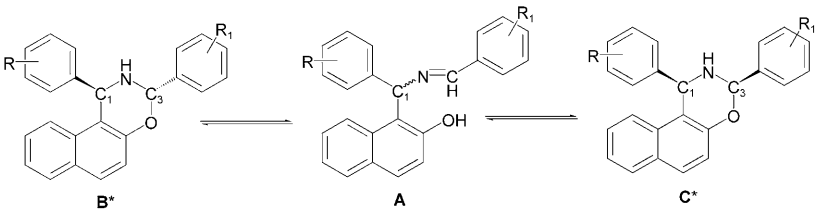
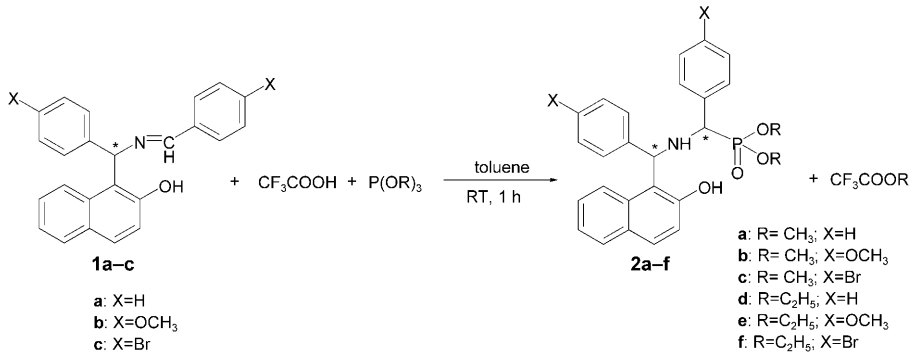
kylating the phosphonium intermediates formed en route to the final products.

Our attempts to use formic or acetic acids to promote the reaction of trialkyl phosphites with the Betti base imine **1a** (prepared from β-naphthol and hydrobenzamide[7a]; Scheme 1) revealed reactions that proceeded very sluggishly, albeit with moderate stereoselectivity (Table 1). Surprisingly, when TFA or trichloroacetic acid was substituted for these standard acids, the desired aminophosphonate products were obtained in much higher yield and with substantially better stereoselectivity (Table 1; Scheme 1). Other strong acids (HCl, *p*-toluenesulfonic acid) also accelerated the condensation with **1a**, but with somewhat decreased diastereoselectivity.



Scheme 2. Cyclic/acyclic tautomers of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. * Only one member from each pair of enantiomers **B** and **C** is shown.



Scheme 1. Reaction of Betti base imines **1a**–**1c** with trialkyl phosphites in the presence of trifluoroacetic acid (TFA).

Table 1. Influence of various acids on the rate and stereoselectivity of **2a** formation.

Acid	pK_a[12]	Reaction time	
		1 h	24 h
acetic	4.76	no reaction	initial imine: 94% products: 6% *de* = 48%
formic	3.75	traces of products	initial imine: 91% products: 9% *de* = 43%
trichloroacetic	0.65	reaction complete, *de* = 80%	–
trifluoroacetic	0.23	reaction complete, *de* = 80%	–
p-toluenesulfonic	−4.12	reaction complete, *de* = 62%	–
4 M HCl in 1,4-dioxane	−8	reaction complete, *de* = 55%	–

The condensation products of 1-(α-aminobenzyl)-2-naphthol with benzaldehydes are systems of equilibrating tautomers comprising acyclic imine structures with corresponding naphthoxazines (Scheme 2).[13]

We investigated the influence of TFA on the tautomeric equilibrium of 1,3-di(*p*-methoxyphenyl)-2,3-dihydro-1*H*-naphth-[1,2-*e*][1,3]oxazine with ^{1}H NMR spectroscopy by using an equimolar ratio of the starting reagents in $CDCl_3$. A comparison of the proton NMR spectra obtained in the absence or presence of TFA revealed the following effects due to the acid: 1) the proton signals at carbon atoms C1 and C3 of tautomers **B** and **C** are greatly diminished, and the resonances shift to lower field; 2) the C1 proton resonance of tautomer **A** is shifted to the aromatic region; and 3) the proton signal (doublet, $^3J_{HH} = 9.5$ Hz) of the HC=N group of tautomer **A** is shifted downfield.

The ratio of the tautomers was 87.4 (**A**):12.6 (**B**+**C**). In the absence of TFA, this ratio was only 57:43. These data suggest that the added TFA protonates the imine nitrogen atom in **A** (that is, it activates the C=N group for nucleophilic attack) and diminishes the formation of the oxazine tautomers **B** and **C**. These data are in accordance with the literature.[14]

Reactions of trimethyl- or triethylphosphite with imines **1a–1c** (Scheme 1) were carried out in dry toluene with vigorous stirring at room temperature for 1 h. The ratio of reagents was imine/TFA/trialkyl phosphite = 1:1.1:3, and the reactions were monitored by ^{31}P NMR spectroscopy. Unreacted trialkyl phosphite, the TFA alkyl ester byproduct, and other volatiles were removed in vacuo, and the products were purified by column chromatography on silica gel. Total yields and diastereomeric excesses (*de*) of the products are given in Table 2. It is obvious from the results that trifluoroacetic acid affords a rapid and complete reaction to give the desired products in good yields and with good stereoselectivities.

We studied the influence of different solvents on the stereoselectivity of the reaction of imine **1a**, TFA, and triethylphosphite (molar ratio of **1a**:TFA:triethylphosphite acid = 1:1.1:3) at room temperature (Table 3). The data show that the diastereoselectivity is significantly decreased (from 80 to 33%) if the solvent is changed from toluene to acetonitrile. A possible explanation for this result is participation of the

Table 2. Diastereoselectivity of hydrophosphonylation of compounds **1a–1c**

Product	X	Yield [%]	δ_P [ppm] D_1[a]	D_2[a]	*de* value[b] [%]
R = CH_3					
2a	H	74.5	24.55	25.88	83
2b	OCH_3	76.7	25.79	27.09	81
2c	Br	81.7	23.74	24.98	79
R = C_2H_5					
2d	H	76.0[c]	22.19[d]	23.71[d]	80[d]
2e	OCH_3	86.2	22.51	24.03	66
2f	Br	90.3	21.19	22.56	84

[a] D_1: major diastereomer; D_2: minor diastereomer. [b] Values of diastereomeric excesses were measured before and after purification by column chromatography. [c] Yield of isolated pure diastereomer D_1 (see the Experimental Section). [d] Chemical shifts and diastereomeric excesses were measured in the reaction mixture (see the Experimental Section).

Table 3. Influence of different solvents on reaction stereoselectivity.

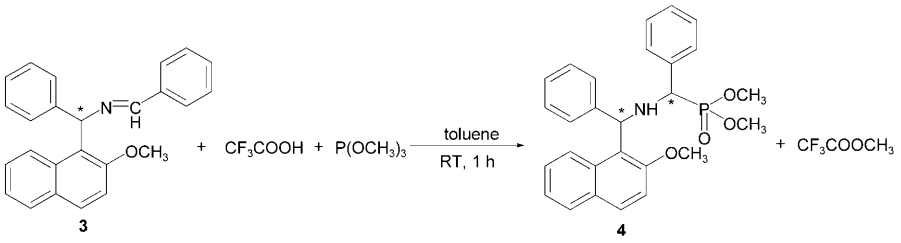
Solvent	*de* [%]
toluene	80
benzene	79
carbon tetrachloride	77
chloroform	77
dichloromethane	56
1,4-dioxane	44
nitrobenzene	41
tetrahydrofuran	35
acetonitrile	33

naphthol hydroxy group in a polar bond to the solvent, which would disfavor intramolecular stabilization of one diastereomer relative to the other. To test this surmise, the OMe derivative of **1a** was prepared[15] and allowed to react with trimethylphosphite in the presence of TFA (Scheme 3). As predicted, the stereoselectivity was significantly lower (*de* = 32%), which confirms that the OH group of the naphthol moiety plays a key role in the stereocontrol of the reaction of **1a** with trialkyl phosphites in the presence of TFA.

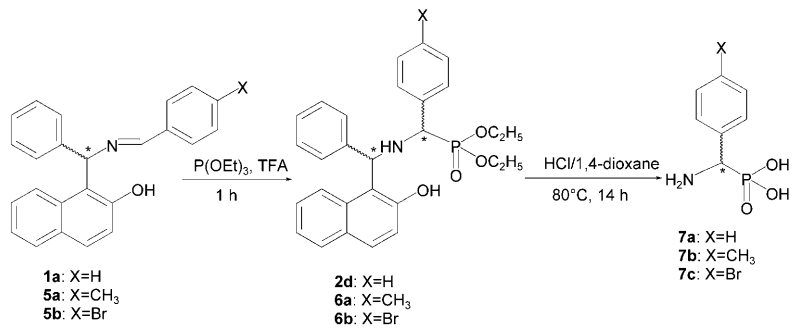
When (*R*)-(−)-**1a** was used, enantiopure (>98%) (*R,R*)-(−)-**2d** was obtained after recrystallization of the diastereomerically enriched **2d** product from toluene. A single crystal derived from this preparation was studied by X-ray diffraction, which established the absolute configuration and revealed four independent molecules in the asymmetric unit, all of which have different ethoxy-group conformations (see Figure 1 in the Supporting Information). This conformational flexibility allows close packing in the crystal. (*S,S*)-(+)-**2d**, (*S,S*)-(+)-**6a**, and (*S,S*)-(+)-**6b** were obtained similarly from imine enantiomers (*S*)-(+)-**1a**, (*S*)-(+)-**5a** and (*S*)-(+)-**5b**, respectively (Scheme 4).

For comparison, (±)-**2d** obtained from racemic **1d** was recrystallized from both toluene and benzene. X-ray diffraction analysis of resultant single crystals showed isostructural solvates in the unit cell, with a 2:1 solute/solvent ratio (see Figure 2 in the Supporting Information).

To complete the new synthetic route, there remained the task of converting the chiral phosphonate esters into the corresponding α-aminophosphonic acids with preservation of the stereochemistry at the α-carbon atom. (*R*)-(+)-**7a**, (*S*)-(−)-**7a**, (*S*)-(−)-**7b**, and (*S*)-(−)-**7c** were obtained from (*R,R*)-(−)-**2d**, (*S,S*)-(+)-**2d**, (*S,S*)-(+)-**6a**, and (*S,S*)-(+)-**6b** in 76–88% yield by treatment at 80 °C with concentrated HCl in 1,4-dioxane (Scheme 4). The specific optical rotations of the acid products were identical to the literature values, and the enantiopurity was confirmed by NMR spectroscopy by using α-cyclodextrin as a chiral shift reagent.[16] It should be noted that the configurations in the final products (*R* or *S*) are the same as those of the chiral inductors used to produce them.



Scheme 3. Reaction of the methylated derivative of 1,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (**3**) with trimethylphosphite and TFA.



Scheme 4. α-Aminobenzylphosphonic acid synthesis.

Conclusions

We have demonstrated a simple, inexpensive, and efficient approach to enantiopure α-aminophosphonic acids, based on the reaction of chiral benzylidenes derived from 1-(α-aminobenzyl)-2-naphthol (Betti bases) with trialkyl phosphites in the presence of TFA, isolation of the major diastereomeric products by crystallization from an appropriate solvent, and hydrolysis with hydrochloric acid.

Experimental Section

General: ^{1}H NMR spectra were recorded on an AVANCE-400 spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as the external reference. ^{31}P NMR spectra were recorded on a CXP-100 spectrometer with $CDCl_3$ as the solvent and 85% H_3PO_4 as the external reference. The following abbreviations are used to indicate multiplicities: s: singlet; d: doublet; t: triplet; m: multiplet. IR spectra were recorded on a Vector 22 spectrometer (from KBr pellets). Column chromatography was performed on silica gel (silica gel L 100/400). EI mass spectra were obtained by using a TRACE MS "Finnigan MAT" instrument operating at 70 eV with an ion-source temperature of 200 °C. Data processing was carried out by using the "Xcalibur" program. Optical rotations were measured on a Perkin–Elmer 341 polarimeter.

General synthesis of α-aminophosphonate dialkyl esters: Trimethyl- or triethylphosphite (2.7 mmol) in absolute toluene (3 mL) was added to a rapidly stirred suspension of compounds **1a**–**1c** and **3** (0.9 mmol) in absolute toluene (3 mL). Excess phosphite is required due to a minor side reaction that forms the dialkyl ester. TFA (0.113 g, 0.99 mmol) in absolute toluene (3 mL) was added dropwise to the resulting suspension over 2–3 min to form a homogeneous solution. After the mixture had been stirred at room temperature for 1 h, the solvent, TFA ester, and excess trialkyl phosphite were removed in vacuo at or below 50 °C. The viscous residue was analyzed by ^{31}P NMR spectroscopy to determine the *de* value and was then purified on silica gel with elution with benzene and ethyl acetate (1:1 for **2b**, 2:1 for **2a**, 3:1 for **2c** and **4**, 4:1 for **2e**, and 6:1 for **2f**).

***O*,*O*-Diethyl-[1-{(2′-hydroxynaphth-1′-yl)}(phenyl)methylamino]-1-(phenyl)methylphosphonate (2d)**: Triethylphosphite (4.482 g, 27 mmol) in absolute toluene (9 mL) was added to a vigorously stirred suspension of **1a** (3.033 g, 9 mmol) in absolute toluene (15 mL). Within 3 min, TFA (1.129 g, 9.9 mmol) in absolute toluene (9 mL) was added dropwise to produce a homogeneous solution, which was stirred at room temperature for 1 h. After partial evaporation to a volume of 10 mL, the mixture was kept cold for 1 week. The resulting crystals were filtered off, washed with a small amount of diethyl ether, and dried in vacuo to give aminophosphonate **2d** (3.25 g, 76%); *de* > 98%; m.p. 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03, 1.46 (2t, ^3J(H,H) = 6.9 Hz, 6H; CH_3CH$_2$OP), 3.59–3.69 (m, 1H; CH$_3$CH_2OP), 3.85–3.95 (m, 1H; CH$_3$CH_2OP), 4.12 (d, ^2J(P,H) = 22.6 Hz, 1H; H–C–P), 4.20–4.32 (m, 2H; CH$_3$CH_2OP), 5.56 (s, 1H; C_{naphth}–C–H), 7.21–7.78 ppm (m, 16H; H_{arom}); ^{31}P NMR (100 MHz, $CDCl_3$): δ_P = 22.25 ppm; IR: $\tilde{\nu}$ = 1019, 1047 (C–O–P), 1237 (P=O), 3226 cm^{-1} (NH); EIMS (70 eV): *m*/*z* (%): 475.2 (100) [M^+], 338.2 (100) [M^+–{P(O)(OEt)$_2$}], 231.1 (100) [M^+–{P(O)(OEt)$_2$}–{Ph–CH$_2$–NH$_2$}]; elemental analysis: calcd (%) for $C_{28}H_{30}NO_4P$: C 70.72, H 6.36, N 2.95, P 6.51; found: C 70.94, H 6.27, N 2.89, P 6.37.

***(R*,*R*)-*O*,*O*-Diethyl[1-{(2′-hydroxynaphth-1′-yl)}(phenyl)methylamino]-1-(phenyl)methylphosphonate ((*R*,*R*)-(−)-2d)**: This compound was obtained by using the same procedure as that for **2d**, from (*R*)-(−)-**1a**. The scale was decreased 3 times, and the reaction mixture was partially evaporated to 1.5 mL before crystallization. The resulting crystals were filtered off, washed with a small amount of diethyl ether, and dried in vacuo to give aminophosphonate (*R*,*R*)-(−)-**2d** (0.74 g, 52%); *de* > 98%; m.p. 125–126 °C; $[\alpha]_D^{20}$ = −208 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03, 1.44 (2t, ^3J(H,H) = 7 Hz, 6H; CH_3CH$_2$OP), 3.59–3.68 (m, 1H; CH$_3$CH_2OP), 3.85–3.94 (m, 1H; CH$_3$CH_2OP), 4.10 (d, ^2J(P,H) = 22.4 Hz, 1H; H–C–P), 4.20–4.29 (m, 2H; CH$_3$CH_2OP), 5.55 (s, 1H; C_{naphth}–C–H), 7.21–7.77 ppm (m, 16H; H_{arom}); ^{31}P NMR (100 MHz, $CDCl_3$): δ_P = 22.2 ppm; IR: $\tilde{\nu}$ = 1021, 1049 (C–O–P), 1241 (P=O), 3226 cm^{-1} (NH); EIMS (70 eV): *m*/*z* (%): 475.2 (38) [M^+], 338.2 (100) [M^+–{P(O)(OEt)$_2$}], 231.1 (100) [M^+–{P(O)(OEt)$_2$}–{Ph–CH$_2$–NH$_2$}]; elemental analysis: calcd (%) for $C_{28}H_{30}NO_4P$: C 70.72, H 6.36, N 2.95, P 6.51; found: C 70.59, H 6.34, N 2.94, P 6.52.

***(S*,*S*)-*O*,*O*-Diethyl[1-{(2′-hydroxynaphth-1′-yl)}(phenyl)methylamino]-1-(phenyl)methylphosphonate ((*S*,*S*)-(+)-2d)**: This compound was obtained by using the same procedure as that for **2d**, from (*S*)-(+)-**1a**. The crystalline product was filtered off, washed with a small amount of diethyl ether, and dried to give aminophosphonate (*S*,*S*)-(+)-**2d** (0.68 g, 48%); *de* > 98%; m.p. 125–126 °C; $[\alpha]_D^{20}$ = +205 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03, 1.44 (2t, ^3J(H,H) = 7 Hz, 6H; CH_3CH$_2$OP), 3.59–3.69 (m, 1H; CH$_3$CH_2OP), 3.84–3.94 (m, 1H; CH$_3$CH_2OP), 4.10 (d, ^2J(P,H) = 22.4 Hz, 1H; H–C–P), 4.19–4.29 (m, 2H; CH$_3$CH_2OP), 5.55 (s, 1H; C_{naphth}–C–H), 7.18–7.77 ppm (m, 16H; H_{arom}); ^{31}P NMR (100 MHz, $CDCl_3$): δ_P = 22.2 ppm; IR: $\tilde{\nu}$ = 1022, 1049 (C–O–P), 1241 (P=O), 3227 cm^{-1} (NH); EIMS (70 eV): *m*/*z* (%): 475.2 (36) [M^+], 338.2 (100) [M^+–{P(O)(OEt)$_2$}], 231.1 (100) [M^+–{P(O)(OEt)$_2$}–{Ph–CH$_2$–NH$_2$}]; elemental analysis: calcd (%) for $C_{28}H_{30}NO_4P$: C 70.72, H 6.36, N 2.95, P 6.51; found: C 70.55, H 6.24, N 2.89, P 6.47.

***(S*,*S*)-*O*,*O*-Diethyl[1-{(2′-hydroxynaphth-1′-yl)}(phenyl)methylamino]-1-(4-tolyl)methylphosphonate ((*S*,*S*)-(+)-6a)**: This compound was obtained by using the same procedure as that for **2d**, from **(*S*)-(+)-5a**. Crystallization method: the solvent was evaporated, the oily residue taken up in toluene and cyclohexane (1:1; 1 mL), and the mixture was left to stand in the cold for 1 week. The crystalline product was filtered off, washed with a small amount of diethyl ether, and dried to give aminophosphonate **(*S*,*S*)-(+)-6a** (0.65 g, 44%); *de* > 98%; m.p. 115–116 °C; $[\alpha]_D^{20}$ = +175 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05, 1.43 (2t, ^3J(H,H) = 7 Hz, 6H; CH_3CH$_2$OP), 2.44 (s, 3H; CH$_3$), 3.59–3.69 (m, 1H; CH$_3$CH_2OP), 3.85–3.95 (m, 1H; CH$_3$CH_2OP), 4.05 (d, ^2J(P,H) = 22.2 Hz, 1H, H–C–P), 4.18–4.27 (m, 2H; CH$_3$CH_2OP), 5.56 (s, 1H; C_{naphth}–C–H), 7.18–7.77 ppm (m, 15H, H_{arom}); ^{31}P NMR (100 MHz, $CDCl_3$): δ_P = 21.8 ppm; IR: $\tilde{\nu}$ = 1021, 1051 (C–O–P), 1246 (P=O), 3233 cm^{-1} (NH); EIMS (70 eV): *m*/*z* (%): 489.2 (2) [M^+], 352.3 (10) [M^+–{P(O)(OEt)$_2$}], 231.2 (52) [M^+–{P(O)(OEt)$_2$}–{*p*-CH$_3$–C$_6$H$_4$–CH$_2$–NH$_2$}]; elemental analysis: calcd (%) for $C_{29}H_{32}NO_4P$: C 71.15, H 6.59, N 2.86, P 6.33; found: C 71.11, H 6.44, N 2.84, P 6.32.

***(S*,*S*)-*O*,*O*-Diethyl[1-{(2′-hydroxynaphth-1′-yl)}(phenyl)methylamino]-1-(4-bromophenyl)methylphosphonate ((*S*,*S*)-(+)-6b)**: This compound was obtained by using the same procedure as that for **2d**, from (*S*)-(+)-**5b**. Crystallization method: the solvent was evaporated, the residue was dissolved in benzene and cyclohexane (1:1; 1 mL), and the mixture was left to stand in the cold for 1 week. The resulting crystals were filtered off, washed with a small amount of diethyl ether, and dried to give aminophosphonate (*S*,*S*)-(+)-**6b** (0.95 g, 57%); *de* > 98%; m.p. 162–163 °C; $[\alpha]_D^{20}$ = +142 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07, 1.44 (2t, ^3J(H,H) = 7 Hz, 6H; CH_3CH$_2$OP), 3.67–3.77 (m, 1H; CH$_3$CH_2OP), 3.89–3.98 (m, 1H; CH$_3$CH_2OP), 4.07 (d, ^2J(P,H) = 22.4 Hz, 1H; H–C–P), 4.20–4.28 (m, 2H; CH$_3$CH_2OP), 5.51 (s, 1H; C_{naphth}–C–H), 7.22–7.78 ppm (m, 15H; H_{arom}); ^{31}P NMR (100 MHz, $CDCl_3$): δ_P = 21.37 ppm; IR: $\tilde{\nu}$ = 1023, 1058 (C–O–P), 1229 (P=O), 3224 cm^{-1} (NH); EIMS (70 eV): *m*/*z* (%): 554.2 (8) [M^+], 417.2 (20) [M^+–{P(O)(OEt)$_2$}], 231.2 (100) [M^+–{P(O)(OEt)$_2$}–{*p*-Br–C$_6$H$_4$–CH$_2$–NH$_2$}]; elemental analysis: calcd (%) for $C_{28}H_{29}BrNO_4P$: C 60.66, H 5.27, Br 14.41, N 2.53, P 5.59; found: C 60.54, H 5.34, Br 14.30, N 2.48, P 5.52.

General procedure for the synthesis of α-aminophosphonic acids: 12 N HCl (1.2 g) was added to a solution of phosphonate ester ((*R*,*R*)-(−)-**2d**, (*S*,*S*)-(+)-**2d**, (*S*,*S*)-(+)-**6a**, or (*S*,*S*)-(+)-**6b**; 0.63 mmol) in 1,4-dioxane (3 mL). The reaction mixture was kept at 80 °C for 7 h, then 12 N HCl (1.2 g) was again added and the reaction mixture was maintained at 80 °C for 7 h. After evaporation of the volatile compounds, the solid residue was washed with ethyl acetate heated to reflux (2×5 mL) to leave a brownish solid, which was filtered off. The ethyl acetate layer was extracted with distilled water (3×5 mL). The solid was dissolved in the combined aqueous phases, and the resulting mixture was heated to reflux with charcoal to give a colorless solution, which, after evaporation of the solvent, gave the α-aminophosphonic acid product as a crystalline solid (dried in vacuo). The optical purity of the enantiomeric products was established through comparison of the experimental specific optical rotations with those reported in the literature (see the Supporting Information) and also by ^{31}P NMR spectroscopy with α-cyclodextrin as a chiral discriminating agent, according to the procedure of Kafarski and coworkers.[16]

Complete experimental procedures for the preparation of enantiopure (*R*)-(−)-**1a**, (*S*)-(+)-**1a**, (*S*)-(+)-**5a**, and (*S*)-(+)-**5b**, synthetic methods and physical data for compounds **2a**, **2b**, **2c**, **2e**, **2f**, **4**, (*R*)-(+)-**7a**, (*S*)-(−)-**7a**, (*S*)-(−)-**7b**, and (*S*)-(−)-**7c**, ^{1}H NMR spectra for (*R*,*R*)-(−)-**2d**,

(*S*,*S*)-(+)-**2d**, (*S*,*S*)-(+)-**6a**, and (*S*,*S*)-(+)-**6b**, ^{31}P NMR spectra from the experiments with α-cyclodextrin, specific optical rotation analysis data, and crystallographic data for single crystals of **2d** are presented in the Supporting Information.

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