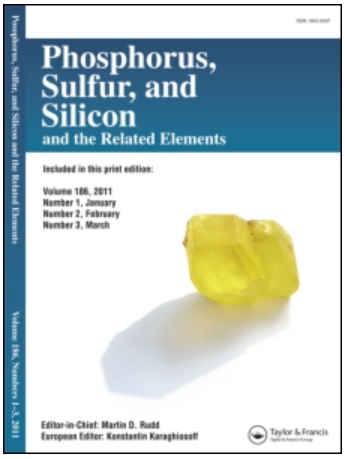

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 78. NEW ASPECTS ON THE INDUCED ASYMMETRIC ADDITION OF DIALKYL PHOSPHITE TO ALDIMINES—AN EFFECTIVE SYNTHESIS OF CHIRAL 1-ARYLPHOSPHONOGLYCINE DERIVATIVES

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 78. NEW ASPECTS ON THE INDUCED ASYMMETRIC ADDITION OF DIALKYL PHOSPHITE TO ALDIMINES—AN EFFECTIVE SYNTHESIS OF CHIRAL 1-ARYLPHOSPHONOGLYCINE DERIVATIVES

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Addition of dialkyl phosphites to Schiff bases derived from (*R*)-2-methoxy-1-phenylethylamine or (*R*)-phenylglycine methyl ester afforded (1*R*,1′*R*)-1-arylphosphonoglycine derivatives with moderate to high diastereoselectivity. The influence of catalysts and solvents and the structural effects of the substrates on this stereochemical process were reported.

Key words: Induced asymmetric addition; dialkyl phosphites; 1-arylphosphonoglycines.

INTRODUCTION

1-Aminophosphonic acids as phosphorus analogs of 1-aminocarboxylic acids are an important class of compounds because of their potential biological activity.[1] As the mimetic tetrahedric intermediates of hydrolyzed esters, amides and peptides, 1-aminophosphonic acid derivatives were used as antibiotics,[2] medicaments[3,4] or enzyme inhibitors.[5]

Since the biological activity of 1-aminophosphonic acids is largely dependent on their absolute configurations,[2,6–7] the asymmetric synthesis of this class of compounds aroused the interest of organic chemists. Although several approaches for the stereoselective synthesis of 1-alkylphosphonoglycine in good enantiomeric purity have been developed,[8,9] only few papers dealt with the preparations of optical active 1-arylphosphonoglycines.

The nucleophilic additions of dialkyl phosphites to imines and oxoiminum derivatives[10–12] constituted the majority of asymmetric synthesis of 1-arylphosphonoglycines up to date. Recently, we have investigated the stereochemical behavior of the addition of dialkyl phosphites to aldimine, resulting from the condensation of substituted benzaldehyde and (*S*)-1-phenylethylamine. The structural effects of substrates and reagents, the influence of reaction conditions including the nature of catalyst and solvent on the diastereomeric excess (de) values and induced direction of the asymmetric additions were reported.[11] A Molecular Mechanics study[13] on this type of reaction revealed that the de values and the induced direction were controlled by the conformation of the imine substrate. Here, we

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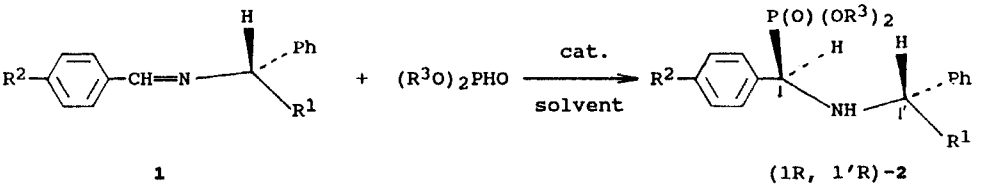
would like to report the asymmetric synthesis of 1-arylphosphonoglycines involving the addition of dialkyl phosphites to Schiff bases with two new amines as chiral auxiliaries.

RESULTS AND DISCUSSION

Introduction of a hetero atom, which is capable of forming a coordinating linkage with a Lewis acid, should have a substantial influence on the conformation of the substrate by the interaction between the Lewis acid and the aldimine. This kind of coordination may change the induced direction and improve the de values. Based on this postulation, in this paper, (*R*)-2-methoxy-1-phenylethylamine[14] and (*R*)-phenylglycine methyl ester[15] were chosen as the chiral auxiliaries. Here the methyl group of the (*S*)-1-phenylethylamine molecule is substituted by CH_2OMe or COOMe, while the relative spatial arrangements of the groups linked to the chiral carbon remains unchanged. This may be conducive to examine the result of our theoretical calculation and investigation on the influence of the substitutent of the chiral auxiliary on the diastereoselectivity of the reaction.



1 (1R, 1'R)-2

R^1 = CH_2OMe(a), COOMe(b); R^2 = H, Me, Me_2N, NO_2, F;
R^3 = Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, Ph

The chiral aldimines **1a** and **1b** were prepared by the condensation of substituted benzaldehyde and the corresponding chiral amine in the presence of anhydrous sodium sulfate and the crude imines thus obtained were used for the subsequent reaction without further purification.

Results of the induced asymmetric addition are listed in Table I.

1. The Influence of Catalysts on de Values

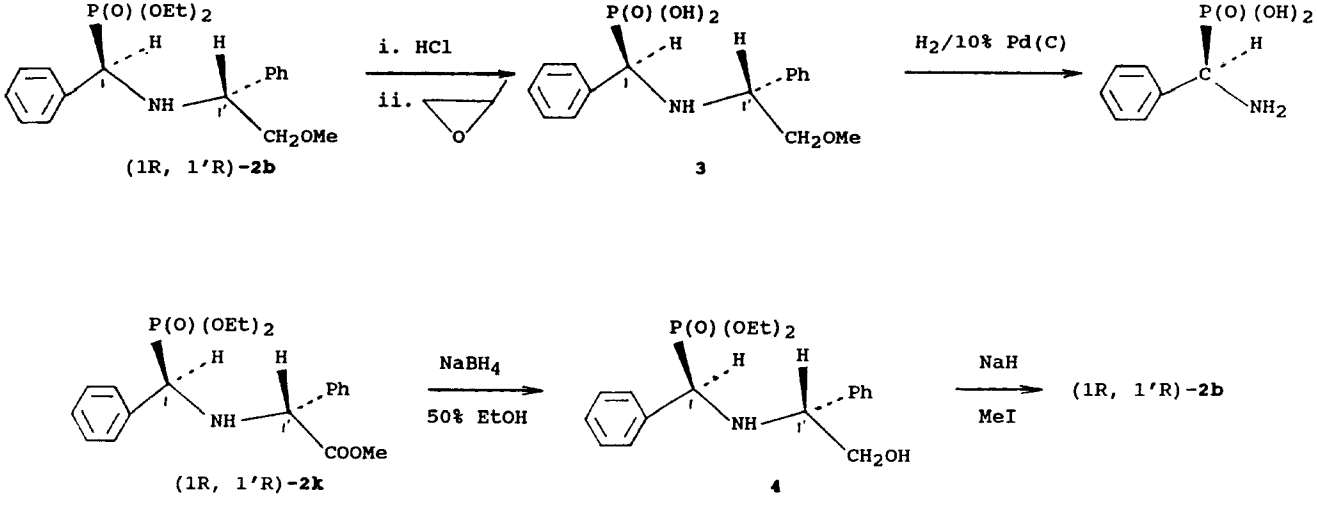
It has been reported that the addition of dialkyl phosphite to C=N double bond was achieved at 140°C without catalyst.[10] Reaction at room temperature in the presence of a Lewis acid was found to produce a better induced effect.[16] With the aid of various types of catalysts in dichloromethane, the aldimines **1a** and **1b** were caused to react with diethyl phosphite to furnish the 1-arylphosphonoglycine derivatives **2** in moderate to high yields. In order to determine the absolute configuration, we converted compounds **2b** to the corresponding 1-amino benzylphosphonic acid. It showed $[\alpha]_D^{20} = +14.7°$ (c = 1.97, 1 N NaOH), which confirms the (*R*)-configuration (lit.,[8] $[\alpha]_D^{20} = +18.0°$ (c = 2.0, 1 N NaOH)). Furthermore, **2k** was transformed into **2b** by reduction with sodium borohydride followed by subsequent methylation. The ^{31}P NMR spectrum gave two peaks at 24.65 and 23.63

TABLE I

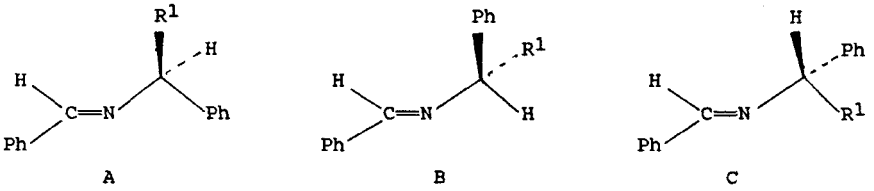
Addition of dialkyl phosphites to aldimines **1a** and **1b**

Entry	Aldimine 1	R^1	Cat.	Solvent	Product 2	R^1	R^2	R^3	yield%	de%	config.
1	**1a**	CH_2OMe	$BF_3.OEt_2$	CH_2Cl_2	**2b**	CH_2OMe	H	Et	88	58	R
2	**1a**	CH_2OMe	$AlCl_3$	CH_2Cl_2	**2b**	CH_2OMe	H	Et	61	71	R
3	**1a**	CH_2OMe	$TiCl_4$	CH_2Cl_2	**2b**	CH_2OMe	H	Et	56	51	R
4	**1a**	CH_2OMe	$ZnCl_2$	CH_2Cl_2	**2b**	CH_2OMe	H	Et	50	67	R
5	**1a**	CH_2OMe	$CdCl_2$	CH_2Cl_2	**2b**	CH_2OMe	H	Et	30	20	R
6	**1a**	CH_2OMe	$NiSO_4$	CH_2Cl_2	**2b**	CH_2OMe	H	Et	34	18	R
7	**1a**	CH_2OMe	$BF_3.OEt_2$	CH_3Ph	**2b**	CH_2OMe	H	Et	85	42	R
8	**1a**	CH_2OMe	$BF_3.OEt_2$	THF	**2b**	CH_2OMe	H	Et	81	4	R
9	**1a**	CH_2OMe	$AlCl_3$	CH_2Cl_2	**2a**	CH_2OMe	H	Me	67	66	R
10	**1a**	CH_2OMe	$AlCl_3$	CH_2Cl_2	**2c**	CH_2OMe	H	n-Pr	61	64	R
11	**1a**	CH_2OMe	$AlCl_3$	CH_2Cl_2	**2d**	CH_2OMe	H	i-Pr	56	60	R
12	**1a**	CH_2OMe	$BF_3.OEt_2$	CH_2Cl_2	**2e**	CH_2OMe	H	i-Bu	72	57	R
13	**1a**	CH_2OMe	$BF_3.OEt_2$	CH_2Cl_2	**2f**	CH_2OMe	Me	Et	55	58	R
14	**1a**	CH_2OMe	$BF_3.OEt_2$	CH_2Cl_2	**2g**	CH_2OMe	Me_2N	Et	54	95	R
15	**1a**	CH_2OMe	$BF_3.OEt_2$	CH_2Cl_2	**2h**	CH_2OMe	F	Et	90	40	R
16	**1a**	CH_2OMe	$BF_3.OEt_2$	CH_2Cl_2	**2i**	CH_2OMe	NO_2	Et	79	49	R
17	**1b**	COOMe	$BF_3.OEt_2$	CH_2Cl_2	**2k**	COOMe	H	Et	84	89	R
18	**1b**	COOMe	$AlCl_3$	CH_2Cl_2	**2k**	COOME	H	Et	75	62	R
19	**1b**	COOMe	$ZnCl_2$	CH_2Cl_2	**2k**	COOMe	H	Et	40	50	R
20	**1b**	COOMe	$TiCl_4$	CH_2Cl_2	**2k**	COOMe	H	Et	51	40	R
21	**1b**	COOMe	$BF_3.OEt_2$	CH_2Cl_2	**2j**	COOMe	H	Me	90	69	R
22	**1b**	COOMe	$BF_3.OEt_2$	CH_2Cl_2	**2l**	COOMe	H	n-Pr	84	75	R
23	**1b**	COOMe	$BF_3.OEt_2$	CH_2Cl_2	**2m**	COOMe	H	i-Pr	70	71	R
24	**1b**	COOMe	$BF_3.OEt_2$	CH_2Cl_2	**2n**	COOMe	H	n-Bu	75	72	R
25	**1b**	COOMe	$BF_3.OEt_2$	CH_2Cl_2	**2o**	COOMe	H	i-Bu	69	82	R
26	**1b**	COOMe	$BF_3.OEt_2$	CH_2Cl_2	**2p**	COOMe	H	Ph	73	89	R
27	**1b**	COOMe	$BF_3.OEt_2$	CH_3Ph	**2k**	COOMe	H	Et	71	56	R
28	**1b**	COOMe	$BF_3.OEt_2$	THF	**2k**	COOMe	H	Et	69	9	R

ppm in the ratio of 75:25, which is consistent with the spectrum of **2b** with the (1*R*,1′*R*) isomer in excess. For compounds **2**, the major isomer, in all cases, was assigned the (1*R*,1′*R*) configuration since substrates **1a** and **1b** and the metal atoms of the Lewis acids with or without empty d-orbital gave the same induced direction



(entries 1, 17 vs. entries 4, 19), which is in contradiction with our previous results using (*S*)-1-phenylethylamine as chiral auxiliary.[11] We presume that the aldimines which we used in the asymmetric induced addition might exist in three comformations A, B and C:



As a result of the coordination with Lewis acid, the conformer C in substrate **1a** or **1b** is predominant. In consequence of the steric effect, the attack of diethyl phosphite took place from the re-face of the imines giving rise to mainly (1*R*,1′*R*)-**2**. Therefore, the de values were increased with the increase of the coordinating ability (entries 1, 2 vs. entries 5, 6). This can also be rationalized by the contribution of the ratio of the conformer C.

2. *Influence of the Solvent on the Asymmetric Induction*

The solvent effect investigation indicated that among the solvents studied, dichloromethane provided the highest de values. When tetrahydrofuran was used as solvent, the de values were rather poor (entries 8, 28). This is due to cyclic ether oxygen of the solvent which can coordinate with the Lewis acid; the ratio of conformer C was thus decreased remarkably.

3. *Steric Effect of Dialkyl Phosphites*

Data in Table I show that the steric effect of the ester alkyl group of dialkyl phosphites is not significant for the de values for both **1a** and **1b**. The de values are around 60% and 80%, respectively. This is notably different from the substrate **1**. This phenonmenon can also be explained by the contribution of conformation C. Since the conformer C has the lowest energy among the three conformers based on our Molecular Mechanics calculation,[13] the coordinating ability of boron trifluoride or aluminum chloride to substrates **1a** or **1b** is very strong. Consequently, conformer C is the most favourable conformation and its ratio is undoubtedly predominant. This situation will make the structural effect of the phosphites not significant and the de values are ranged slightly around the theoretical value.[13]

4. *Electronic Effect of the Nuclear Substituents of the Aldimines*

Various imines derived from para-substituted benzaldehyde and (*R*)-2-methoxy-1-phenylethylamine were examined (entries 13–16). The results in Table I indicate that the electronic effect of the nuclear substituents of imines has a marked influence on both chemical yields and de values. Aldimines with electron withdrawing groups such as F-, NO_2- gave low de values but high chemical yields (entries 15, 16), while electron donating groups increased the de values and decreased the chemical yields

(entry 14). This can be explained by the fact that electron withdrawing groups decrease the electron density of the C=N double bond, consequently the nucleophilic addition of the phosphites would be much easier, and the stereoselectivity should be weakened.

As described above, the method provided a useful way for the stereoselective preparation of 1-arylphosphoglycine derivatives from the chiral auxiliaries prepared from *D*-phenylglycine. For the two chiral auxiliaries used, *R*-phenylglycine methyl ester was more effective. The highest de value was up to 89%, with the (1*R*,1′*R*) configuration as the major isomer.

EXPERIMENTAL

IR spectra were obtained using a Shimadzu IR-440 spectrometer. ^{1}H NMR was recorded on a Varian XL-200 NMR spectrometer in $CDCl_3$ with TMS as internal standard. ^{31}P NMR spectra were taken from a FX-90Q spectrometer, with $CDCl_3$ as solvent and 85% H_3PO_4 as external standard. MS were recorded on a Finnigan-4021 mass spectrometer. The de values of the addition products **2** were evaluated by ^{31}P NMR.

Dialkyl N-[(R)-2-methoxy-1-phenylethyl]amino-p-substituted benzylphosphonate **2a–2i** *and methyl (R)-1-N-[1′-O,O-dialkyl phosphonylbenzyl]amino phenylacetate* **2j–2p**. General procedure: To a solution of imine **1** (1 mmol) in 5 mL solvent, 1 mmol of Lewis acid catalyst was added and then the mixture stirred at room temperature for 10 min. The mixture was then cooled to 0°C and dialkyl phosphite (1 mmol) added. The resulting mixture was stirred for 10 h at 0°C and then diluted to 50 ml with CH_2Cl_2. The organic solution was washed successively with 5% NaOH solution (10 ml) and water (3 × 20 ml), then dried (Na_2SO_4) and concentrated. Crude **2** was obtained as a viscous oil. The de value was estimated by ^{31}P NMR with this crude product. Column chromatography on silica gel using ethyl acetate/petroleum ether as eluent afforded pure samples of **2**.

2a, IR: 3350 (NH); 1240 (P=O); 1020 (P—O—C) cm^{-1}. ^{1}H NMR δ: 3.18, 3.26 (s, 3H (1:3), CH_2OCH_3); 3.31 (dd, 1H, J = 6.0, J = 16 Hz, OCH_ACH_B); 3.41 (d, 3H, J = 9 Hz, $POCH_3$); 3.64 (d, 3H, J = 9 Hz, $POCH_3$); 3.74 (dd, 1H, J = 8, J = 16 Hz, OCH_AH_B); 4.07 (d, 1H, J = 18 Hz, PCH); 4.14 (m, 1H, $NCHCH_2$); 7.08–7.25 (m, 10H, 2xPh). MS (m/e): 350 (M^+ + 1,62); 304 (M^+—CH_2OCH_3, 60); 240 (M^+—P(O)$(OMe)_2$, 100); 194 (M^+—1—P(O)$(OMe)_2$—CH_2OCH_3, 67). Anal. calcd. for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01; P, 8.87%. Found: C, 61.00; H, 6.70; N, 3.96; P, 8.54%.

2b, IR: 3350 (NH); 1245 (P=O); 1020 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 1.10 (m, 3H, OCH_2CH_3); 1.34 (m, 3H, OCH_2CH_3); 3.30, 3.39 (s, 3H, OCH_3); 3.40 (m, 1H, $CH30CH_AH_B$); 3.50 (m, 2H, OCH_2CH_3); 3.76 (m, 2H, CH_2OCH_3); 3.90 (m, 1H, $CH_3OCH_AH_B$); 4.13 (d, 1H, J = 19 Hz, PCH); 4.24 (m, 1H, $NCHCH_2$); 7.20–7.40 (m, 10H, 2xPh). MS (m/e): 378 (M^+ + 1,17); 332 (M^+—CH_2OCH_3, 54); 240 (M^+—P(O)$(OEt)_2$, 81); 194 (M^+—1—P(O)$(OEt)_2$—$CH_{20}CH_3$, 100). Anal. calcd. for $C_{20}H_{28}NO_4P$: C, 63.64; H, 7.48; N, 3.71; P, 8.21%. Found: C, 63.42; H, 7.55; N, 3.65; P, 7.96%.

2c, IR: 3400 (NH); 1240 (P=O); 1000 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 0.82 (m, 3H, $OCH_2CH_2CH_3$); 0.93 (m, 3H, $OCH_2CH_2CH_3$); 1.51 (m, 2H, OCH_2CH_2); 1.67 (m, 2H, OCH_2CH_2); 3.29, 3.37 (s, 3H, OCH_3); 3.50 (m, 1H, $CH_3OCH_AH_B$), 3.60–3.92 (m, 4H, 2x$OCH_2CH_2CH_3$); 3.98 (m, 1H, $CH_3OCH_AH_B$); 4.12 (d, 1H, J = 18 Hz, PCH); 4.26 (m, 1H, $NCHCH_2$); 7.20–7.40 (m, 10H, 2xPh). MS (m/e): 406 (M^+ + 1,44); 360 (M^+—CH_2OCH_3, 63); 240 (M^+—P(O)$(OPr)_2$, 100), 194 (M^+—1—P(O)$(OPr)_2$—CH_2OCH_3, 56). Anal. calcd. for $C_{22}H_{32}NO_4P$: C, 65.17; H, 7.96; N, 3.45; P, 7.64%. Found: C, 64.77; H, 8.18; N, 3.50; P, 7.30%.

2d, IR: 3400 (NH); 1240 (P=O); 990 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 1.16–1.36 (m, 12H, 4xCH_3); 3.27, 3.35 (s, 3H, OCH_3); 3.40–3.56 (m, 2H, OCH_2); 4.03 (d, 1H, J = 19 Hz, PCH); 4.21 (m, 1H, $NCHCH_2$); 4.46 (m, 1H, OCH); 4.68 (m, 1H, OCH); 7.18–7.34 (m, 10H, 2xPh). MS (m/e): 406 (M^+ + 1,100); 360 (M^+—CH_2OCH_3, 11); 240 (M^+—P(O)$(OPr)_2$, 54); 194 (M^+—1—P(O)$(OPr)_2$—CH_2OCH_3, 35). Anal. calcd. for $C_{22}H_{32}NO_4P$: C, 65.17; H, 7.96; N, 3.45; P, 7.64%. Found: C, 65.58; H, 8.29; N, 3.58; P, 7.67%.

2e, IR: 3350 (NH); 1230 (P=O); 1010 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 0.70–1.00 (m, 12H, 4xCH_3); 1.64–2.20 (m, 2H, 2x$CHCH_3$); 3.30, 3.38 (s, 3H, OCH_3); 3.51 (dd, 1H, J = 8, J = 12 Hz, OCH_AH_B);

3.60–3.90 (m, 5H, 2xOCH$_2$CH, OCH$_A$H$_B$); 4.14 (d, 1H, J = 19 Hz, PCH); 4.26 (m, 1H, NCHCH$_2$); 7.20–7.38 (m, 10H, 2xPh). MS (m/e): 434 (M$^+$ + 1,23); 388 (M$^+$—CH$_2$OCH$_3$, 70); 240 (M$^+$—P(O)(OBu)$_2$, 100); 194 (M$^+$—1—P(O)(OBu)$_2$—CH$_2$OCH$_3$, 75). Anal. calcd. for $C_{24}H_{36}NO_4P$: C, 66.49; H, 8.37; N, 3.23; P, 7.14%. Found: C, 66.04; H, 8.66; N, 3.34; P, 7.18%.

2f, IR: 3500 (NH); 1240 (P=O); 1020 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 1.02–1.38 (m, 6H, 2xOCH$_2$CH$_3$); 2.32 (s, 3H, CH$_3$Ph); 3.28, 3.36 (s, 3H, OCH$_3$); 3.44–4.26 (m, 8H, 3xOCH$_2$, PCH, NCHCH$_2$); 7.02–7.34 (m, 9H, 2xAr). MS (m/e): 392 (M$^+$ + 1,48); 346 (M$^+$—CH$_2$OCH$_3$, 13); 254 (M$^+$—P(O)(OEt)$_2$, 100); 208 (M$^+$—1—P(O)(OEt)$_2$—CH$_2$OCH$_3$, 92) Anal. calcd. for $C_{21}H_{30}NO_4P$: C, 64.43; H, 7.73; N, 3.58; P, 7.91%. Found: C, 63.89; H, 7.92; N, 3.47; P, 7.43%.

2g, IR: 3400 (NH); 1240 (P=O); 1025 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 1.16–1.36 (m, 6H, 2xOCH$_2$CH$_3$); 2.04 (s, 6H, NMe$_2$); 3.17 (s, 3H, OCH$_3$); 3.30–4.20 (m, 8H, 3xOCH$_2$, PCH, NCHCH$_2$); 6.66–6.74, 7.16–7.40 (m, 9H, 2xAr). MS (m/e): 421 (M$^+$ + 1,11); 375 (M$^+$—CH$_2$OCH$_3$, 27); 283 (M$^+$—P(O)(OEt)$_2$, 50); 237 (M$^+$—1—P(O)(OEt)$_2$—CH$_2$OCH$_3$, 100).

2h, IR: 3450 (NH); 1240 (P=O); 1020 (P—O—C) cm^{-1}. ^{1}H NMR: 1.02–1.20 (m, 3H, OCH$_2$CH$_3$); 1.24–1.40 (m, 3H, OCH$_2$CH$_3$); 3.30, 3.37 (s, 3H, OCH$_3$); 3.40–4.22 (m, 8H, 3xOCH$_2$, PCH, NCHCH$_2$); 6.90–7.34 (m, 9H, 2xAr). MS (m/e): 396 (M$^+$ + 1,9); 350 (M$^+$—CH$_2$OCH$_3$, 32); 258 (M$^+$—P(O)(OEt)$_2$, 60); 212 (M$^+$—1—P(O)(OEt)$_2$—CH$_2$OCH$_3$, 100). HRMS: Anal. calcd. for $C_{18}H_{22}FNO_3P$(M—CH$_2$OCH$_3$): 350.1321. Found: 350.1351.

2i, IR: 3400 (NH); 1245 (P=O); 1020 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 1.08–1.40 (m, 6H, 2xOCH$_2$CH$_3$); 3.33, 3.40 (s, 3H, OCH$_3$); 3.40–4.23 (m, 8H, 3xOCH$_2$, PCH, NCHCH$_2$); 7.18–7.56, 7.60–8.24 (m, 9H, 2xAr). MS (m/e): 423 (M$^+$ + 1,25); 377 (M$^+$—CH$_2$OCH$_3$, 37); 285 (M$^+$—P(O)(OEt)$_2$, 49); 239 (M$^+$—1—P(O)(OEt)$_2$—CH$_2$OCH$_3$). Anal. calcd. for $C_{20}H_{27}N_2O_6P$: C, 56.86; H, 6.44; N, 6.63; P, 7.33%. Found: C, 56.72; H, 6.71; N, 6.35; P, 7.00%.

2j, IR: 3350 (NH); 1740 (C=O); 1240 (P=O); 1030 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 3.54–3.82 (m, 9H, 3xOCH$_3$); 4.02 (d, 1H, J = 18 Hz, PCH); 4.38 (s, 1H, NCHCO); 7.26–7.46 (m, 10H, 2xPh). MS (m/e): 364 (M$^+$ + 1,19); 304 (M$^+$—COOMe, 15); 255 (M$^+$ + 1—P(O)(OMe)$_2$, 100); 194 (M$^+$—1—P(O)(OMe)$_2$—COOMe, 66). Anal. calcd. for $C_{18}H_{22}NO_5P$: C, 59.50; H, 6.10; N, 3.85; P, 8.52%. Found: C, 59.10; H, 6.11; N, 3.81; P, 8.22%.

2k, IR: 3350 (NH); 1740 (C=O); 1245 (P=O); 1020 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 1.12–1.36 (m, 6H, 2xCH$_2$CH$_3$); 3.64, 3.70 (s, 3H, OCH$_3$); 3.88–4.20 (m, 4H, 2xOCH$_2$), 4.20 (d, 1H, J = 18 Hz, PCH); 4.40 (s, 1H, NCHCO); 7.30–7.50 (m, 10H, 2xPh). MS (m/e): 392 (M$^+$ + 1,2); 254 (M$^+$—P(O)(OEt)$_2$, 100); 194 (M$^+$—1—P(O)(OEt)$_2$—COOMe, 48). Anal. calcd. for $C_{20}H_{26}NO_5P$: C, 61.37; H, 6.70; N, 3.58; P, 7.91%. Found: C, 61.67; H, 6.67; N, 3.53; P, 7.64%.

2l, IR: 3350 (NH); 1740 (C=O); 1200 (P=O); 1010 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 0.80–1.04 (m, 6H, 2xCH$_2$CH$_2$CH$_3$); 1.50–1.80 (m, 4H, 2xCH$_2$CH$_2$CH$_3$); 3.62, 3.70 (s, 3H, OCH$_3$); 3.80–4.14 (m, 4H, 2xOCH$_2$); 4.18 (d, 1H, J = 18 Hz, PCH); 4.38 (s, 1H, NCHCO); 7.26–7.50 (m, 10H, 2xPh). MS (m/e): 420 (M$^+$ + 1,17); 360 (M$^+$—COOMe, 26); 254 (M$^+$—P(O)(OPr)$_2$, 100); 194 (M$^+$—P(O)(OPr)$_2$—COOMe, 17). HRMS: Anal. calcd. for $C_{22}H_{30}NO_5P$: 419.1863. Found: 419.1880.

2m, IR: 3350 (NH); 1740 (C=O); 1240 (P=O); 990 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 0.98–1.24 (m, 12H, 2xCH(CH$_3$)$_2$); 3.52, 3.60 (s, 3H, OCH$_3$); 4.02 (d, 1H, J = 18 Hz, PCH); 4.29 (s, 1H, NCHCO); 4.52 (m, 2H, 2xOCH); 7.18–7.38 (m, 10H, 2xPh). MS (m/e): 420 (M$^+$ + 1,27); 360 (M$^+$—COOME, 4); 255 (M$^+$ + 1—P(O)(OPr)$_2$, 100); 194 (M$^+$—1—P(O)(OPr)$_2$—COOMe, 42). Anal. calcd. for $C_{22}H_{30}NO_5P$: C, 62.99; H, 7.21; N, 3.34; P, 7.38%. Found: C, 62.51; H, 7.21; N, 3.24; P, 7.09%.

2n, IR: 3350 (NH); 1740 (C=O); 1240 (P=O); 1020 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 0.80–1.00 (m, 6H, 2xCH$_2$CH$_2$CH$_2$CH$_3$); 1.20–1.70 (m, 8H, 2xCH$_2$CH$_2$CH$_2$CH$_3$); 3.60, 3.67 (s, 3H, OCH$_3$); 3.82–4.16 (m, 4H, 2xCH$_2$O); 4.16 (d, 1H, J = 18 Hz, PCH); 4.36 (s, 1H, NCHCO); 7.20–7.44 (m, 10H, 2xPh). MS (m/e): 448 (M$^+$ + 1,4); 388 (M$^+$—COOME, 7); 254 (M$^+$—P(O)(OBu)$_2$, 100); 194 (M$^+$—1—P(O)(OBu)$_2$—COOMe, 47). Anal. calcd. for $C_{24}H_{34}NO_5P$: C, 64.41; H, 7.66; N, 3.13; P, 6.92%. Found: C, 64.27; H, 7.88; N, 3.28; P, 6.90%.

2o, IR: 3350 (NH); 1740 (C=O); 1245 (P=O); 1010 (P—O—C) cm^{-1}. ^{1}H NMR, δ: 0.74–1.00 (m, 12H, 2xCH(CH$_3$)$_2$); 1.70–1.98 (m, 2H, 2xCH); 3.60–3.82 (m, 7H, 2xOCH$_2$, OCH$_3$); 4.18 (d, 1H, J = 18 Hz, PCH); 4.37 (s, 1H, NCHCO); 7.24–7.44 (m, 10H, 2xPh). MS (m/e): 448 (M$^+$ + 1,8); 388 (M$^+$—COOMe, 11); 255 (M$^+$ + 1—P(O)(OBu)$_2$, 100); 194 (M$^+$—1—P(O)(OBu)$_2$—COOMe, 70).

Anal. calcd. for $C_{24}H_{34}NO_5P$: C, 64.41; H, 7.66; N, 3.13; P, 6.92%. Found: C, 63.87; H, 7.51; N, 3.03; P, 6.87%.

2p, IR: 3350 (NH); 1740 (C=O); 1210 (P=O); 940 (P—O—C) cm^{-1}. ^1H NMR, δ: 3.60, 3.66 (s, 3H, OCH_3); 4.34 (s, 1H, NCHCO); 4.54 (d, 1H, J = 18 Hz, PCH); 6.70–7.50 (m, 20H, 4xPh). MS (m/e): 488 (M^+ + 1,7); 428 (M^+—COOME, 7); 255 (M^+ + 1—$P(O)(OPh)_2$, 100); 194 (M^+—1—$P(O)(OPh)_2$—COOMe, 72). Anal. calcd. for $C_{28}N_{26}NO_5P$: C, 68.98; H, 5.38; N, 2.87; P, 6.35%. Found: C, 69.24; H, 5.04; N, 2.78; P, 5.95%.

In the ^{31}P NMR spectra of **2a–2i** the downfield peaks were in excess, while for **2j–2p**, the upfield peaks were in excess. The δ ^{31}P data have been published elsewhere.[17]

N-[(R)-2-methoxy-1-phenylethyl]amino benzylphosphonic acid **3** *and its conversion to 1-amino benzylphosphonic acid* **4**. A mixture of **2b** (500 mg, 1.33 mmol) and 5 mL of concentrated HCl was refluxed with stirring for 10 h. After the removal of solvent, the residue was dissolved in minimum amount of ethanol and then treated with propylene oxide until pH = 5–6. The precipitated solid was filtered, dried and recrystallized from aqueous ethanol to afford **3** (299 mg) in 70% yield. The final product **4** was obtained by hydrogenolysis of **3** (250 mg, 0.78 mmol) using 10% Pd/C as catalyst (50 mg) in 10 ml acetic acid at a pressure of 5 Kg/cm^2 at room temperature. Removal of the catalyst and acetic acid gave a white solid which was recrystallized from aqueous ethanol, mp 181–183°C. Its configuration was confirmed to be *R* by comparison of its specific rotation with the reported one of (*R*)-**4**.[8]

Dialkyl N-[(R)-hydroxy-1-phenethyl]amino benzylphosphonate **4** *and its conversion to* **2b**. To a chilled solution of $NaBH_4$ (165 mg, 4.32 mmol) in 10 ml of 50% aqueous ethanol, a solution of **2k** (561 mg, 1.44 mmol) in 50% aqueous ethanol (10 ml) was added dropwise with stirring at 0°C. The resulting suspension was stirred at room temperature for 9 h followed by refluxing for 5.5 h, and then stirred at room temperature for another 9 h. The reaction mixture was then evaporated to remove solvent and extracted with EtOAc (3 × 30 ml). The organic extracts were combined, dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (EtOAc) afforded **4** (335.5 mg) in 64% yield.

A solution of **4** (250 mg, 0.69 mmol) in anhydrous THF (5 ml) was added dropwise to a stirred suspension of 80% NaH (21.9 mg, 0.73 mmol) in THF (5 ml) at room temperature. The resulting mixture was allowed to stand overnight and then a solution of MeI (92 mg, 0.65 mmol) in THF (5 ml) was added dropwise. The reaction mixture was allowed to stand overnight and then poured into 20 ml of cold saturated brine, extracted with EtOAc (3 × 20 ml), dried (Na_2SO_4) and concentrated. Column chromatography on silica gel afforded pure **2b** (160 mg) in 65% yield.

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