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Stereoselective Addition of Dimethyl Thiophosphite to Imines

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Dimethyl thiophosphite (DMTP) was synthesized from dimethyl phosphite, and the diastereoselective addition of DMTP to benzaldimines bearing chiral auxiliary groups was examined. Yields of the product α-aminophosphonothionates ranged from 17% to 75% after chromatography. The addition of DMTP to the benzaldimine derived from (*S*)-phenylglycinol afforded the highest diastereoselectivity (83:17), whereas addition of DMTP to the benzaldimine derived from threonine methyl ester and alanine methyl ester were far less diastereoselective, affording 38:62 and 61:39 ratios, respectively. Addition of DMTP to the benzaldimine derived from (*R*)-α-methylbenzylamine (78:22) and (*S*)-serine methyl ester (73:27) were intermediate in selectivity. DMTP addition to the imines formed between serine methyl ester and acetaldehyde and isobutyraldehyde gave 55:45 and 70:30 ratios, respectively, with the diastereoselectivity corresponding roughly to the size of the α-alkyl group. The stereochemistry of the newly formed α-stereocenters resulting from the addition of DMTP to (*S*)- and (*R*)-phenylglycinol benzaldimines was confirmed by conversion of the product α-aminophosphonothionates to the known enantiomers of phosphonophenylglycine.

Introduction

(*S*,*R*)-Alafosfalin and (*R*)-phospholeucine are α-aminophosphonic acids (APAs), a class of α-amino acid isosteres in which the carboxylic acid group has been replaced by a phosphonic acid group (Figure 1). Like natural amino acids, the biological activity of APAs correlates with the stereochemistry at the α-carbon center. For example, (*S*,*R*)-alafosfalin shows higher antibacterial activity than any of its other diastereomers,[1] and (*R*)-phospholeucine is a more potent inhibitor of leucine aminopeptidase than the *S* enantiomer.[2,3]

To incorporate the desired configuration at the α-center of α-aminophosphonic acids, a number of approaches have been devised.[4−11] In many of these synthetic strategies, the P−C bond and α-chiral center are formed by asymmetric addition of a phosphite to an imine. The resulting enantioenriched α-aminophosphonate is generally converted to the APA following straightforward synthetic manipulations.

Despite significant progress in the preparation of enantioenriched APAs, there have been very few syntheses of the corresponding phosphonothionate analogues of APAs, the α-aminophosphonothioic acids (APTAs;

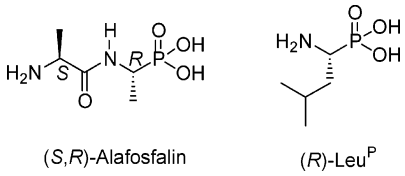

FIGURE 1. Structures of alafosfalin and (*R*)-phospholeucine.

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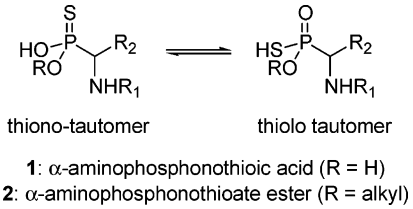


FIGURE 2. General structures of α-aminophosphonothioic acids (**1**) and phosphonothioate esters (**2**) and their possible thiolo tautomers.

Figure 2).[4,8,12−14] Phosphonothioic acids are sulfur-containing analogues of phosphate groups that are well-known in nucleoside chemistry and are of value because the thiol group imparts chemical characteristics that differ greatly from the corresponding phosphate group, namely, nucleophilicity, metal binding, etc.[15] Such novel properties would be useful additions to phosphorus analogues of amino acids and peptides. Further benefits of installing a sulfur-containing ligand at phosphorus include the production of a tautomerically nonequivalent acid (thiono−thiolo equilibrium; Figure 2)[16] and the capability to generate a new asymmetric center at phosphorus (in the monoester form, **2**).[13,14]

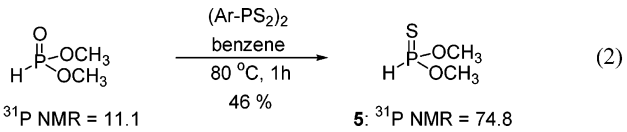
One straightforward approach to prepare APTAs would be to convert the phosphoryl (P═O) of an APA into a thiophosphoryl (P═S) by use of Lawesson's reagent or a related thionating agent.[17] Unfortunately, this route fails because of preferred reactivity of thionating agents at the amino group or amine protecting group.[13] Displacement of a phosphorus ester group (P−OR) by SH^- (P−SH), which would form the asymmetric APTA monoester, also fails owing to competing dealkylation reactions at the phosphorus ester groups. As a result, a convergent approach in which the P═S is directly installed in the product is needed. As noted, dialkyl phosphites (e.g., dimethyl phosphite, **3**) add to imines (prepared from chiral amines) with stereocontrol to afford α-aminophosphonates (**4**).[6,9a,11] In previous work from this laboratory, dimethyl thiophosphite (**5**; DMTP) was found to add rapidly and in high yield to a variety of electrophiles including imines.[18] Adaptation of the addition of DMTP to imines containing chiral auxiliaries (R^1) would form the α-aminophosphonothionates (**6**) bearing an enantioenriched α-carbon center and would allow direct access to the desired APTAs (eq 1).

(1)

In this study, reactions between DMTP and imines that vary in a chiral auxiliary group were conducted and the diastereoselectivity was determined. Because suitably positioned hydroxyl groups are known to influence diastereocontrol,[19] we specifically studied the effect of pendant heteroatom groups on the diastereoselectivity of thiophosphite addition. The mechanism and diastereofacial orientation of the addition reaction could be established by conversion of a select α-aminophosphonothionate diastereomer product into a single enantiomer of an α-aminophosphonic acid having known absolute configuration.

Results and Discussion

Synthesis of Dimethyl Thiophosphite. Although dimethyl thiophosphite (**5**; DMTP) has been synthesized previously,[18,20,21] specific spectral and experimental details are lacking for characterization. Dimethyl phosphite (**3**; DMP) was reacted with Lawesson's reagent (10 equiv)[17] to afford **5** in 46% yield following distillation (eq 2). DMTP shows a characteristic ^{31}P NMR downfield shift (δ 74.8 ppm) relative to DMP (δ 11.1 ppm) with a large J_{P-H} coupling constant of 652 Hz.[22] Monitoring for reaction progress and completion by ^{31}P NMR is recommended since the reaction times vary despite rigorous control of the reaction parameters. Allowing the thionation reaction to proceed to greater than 95% completion (disappearance of DMP) simplifies purification, although unreacted DMP may be separated from DMTP by fractional distillation.



(2)

A survey of the reaction of DMTP with electrophiles (aldehydes, ketones, imines, and Michael acceptors) and a brief relative rate study (**3** vs **5**) have been reported.[18]

Addition of Dimethyl Thiophosphite to Imines. There are only a handful of investigations that have

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SCHEME 1

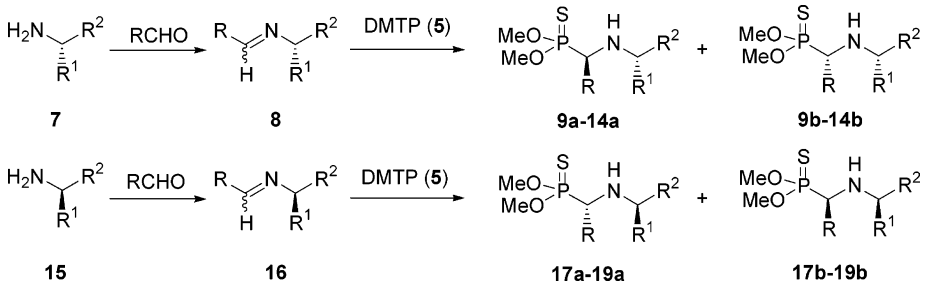

TABLE 1. Addition of Dimethyl Thiophosphite to Imines Containing Chiral Auxiliary Groups (Scheme 1)

products	chiral auxiliary	R	R^1	R^2	$^{31}P^a$ (δ)	yield[b] (%)	^{31}P ratio[c] [isolated ratio][d]
9a/9b	(*R*)-phenylglycinol	Ph	CH_2OH	Ph	100.5/98.1	75.5	75:25 [80:20]
10a/10b	(*S*)-L-alanine, methyl ester	Ph	Me	CO_2Me	98.4/97.3	17.0	53:47 [55:45]
11a/11b	(*S*)-L-serine, methyl ester	Me	CH_2OH	CO_2Me	102.6/101.9	32.7	55:45
12a/12b	(*S*)-L-serine, methyl ester	^{i}Pr	CH_2OH	CO_2Me	102.9/101.4	15.0	30:70
13a/13b	(*S*)-L-serine, methyl ester	Ph	CH_2OH	CO_2Me	97.8/97.2	62.4	73:27 [82:18]
14a/14b	(2*S*,3*R*)-L-threonine, methyl ester	Ph	CH(Me)OH	CO_2Me	97.2/96.8	33.6	38:62
17a/17b	(*S*)-phenylglycinol	Ph	CH_2OH	Ph	100.5/98.1	63.4	83:17 [95:5]
18a/18b	(*R*)-α-methyl benzylamine	Ph	Me	Ph	101.6/98.9	63.8	76:24 [90:10]

[a] Relative to H_3PO_4 in $CDCl_3$. [b] Following column chromatography; total for both diastereomers. [c] ^{31}P ratio based on integration of the crude reaction mixture averaged from three trials. [d] Isolated ratio represents the fractional purified amount of a single diastereomer.

reported the reactions of DMTP,[4,18,23] and none have investigated the formation of α-aminophosphonothionates (**6**) containing asymmetric centers. DMTP is at least 100-fold more reactive than DMP toward electrophiles, and importantly, DMTP does not undergo demethylation as a side reaction to addition as does DMP. Because of this enhanced reactivity, the diastereoselective addition of DMTP to imines can be conducted under mild conditions. Because a number of enantioenriched α-aminophosphonic acid analogues have been prepared by the analogous addition of dialkyl phosphites to asymmetric imines, the absolute configuration of a representative α-amino phosphonothionate product can be determined by conversion to a known APA by oxidation of the P═S bond to P═O.

As this study sought to preliminarily evaluate the influence of chiral auxiliaries (**7**, **15**) on the stereoselective addition of DMTP to imines (Scheme 1), substituents attached to the imine were varied (**8**, **16**; R = Me, ^{i}Pr, Ph) to identify key interactions that would furnish favorable diastereomer ratios. Benzaldehyde was chosen due to the ease of imine formation and the need to correlate the product diastereomer structures to (*R*)- and (*S*)-phosphono(phenylglycine), for which absolute configurations have been established.[2,7,24,25] Imines of acetaldehyde and isobutyraldehyde were examined to evaluate the role of sterics on the diastereoselectivity and the potential for these addition reactions to afford the α-aminophosphonic acid analogues of alanine and leucine. Phenylglycinol, α-methylbenzylamine, and the methyl esters of alanine, serine, threonine, and cysteine were selected because a number of comparative studies with these amines as chiral auxiliaries have been conducted and they have the potential for examining the presence/absence of a hydroxy directing group.

Aldimines **8** and **16** (R = Me, ^{i}Pr and Ph) were prepared by reaction between the aldehyde and amines in the presence of 3 Å sieves. Aldimine formation progress was evaluated by the appearance of the aldimine proton (δ. 8.5 ppm) of the crude reaction mixture and estimated to be greater than 95% prior to addition of DMTP.

Imine solutions were reacted with DMTP (1 equiv) for up to 12 h at room temperature or 0 °C. The addition of DMTP to the asymmetric imines (Scheme 1, Table 1) underwent reaction readily and in relatively good conversion as evidenced by ^{31}P NMR. The products were identified by the pentavalent thionate (P═S) ^{31}P NMR peaks near 100 ppm (Table 1).[26] Despite near-quantitative conversion by ^{31}P NMR, both liquid extraction and direct separation on silica gel led to significant loss of material as evidenced by the large range in isolated yields. The crude products were typically isolated by flash chromatography following evaporation of the solvent.

Where possible, the individual diastereomers were isolated from chromatography and the isomer ratio was measured (Table 1). Most mixtures were preparatively unseparable, affording only small amounts of one [major] diastereomer that was of adequate quantity for spectroscopic and elemental analyses. The observed diastereomer ratios are not readily comparable to the corresponding reaction of dialkyl phosphites with imines because most routes to APAs have used the sterically more discriminating diethyl phosphite or the lithio salt.[9,11]

Interestingly, phenylglycinol had no additional influence on the diastereomer ratio relative to α-methylbenzylamine, whereas the presence/absence of a hydroxy group on the amino acids did alter the diastereoselectivity. For example, changing the auxiliary from alanine to

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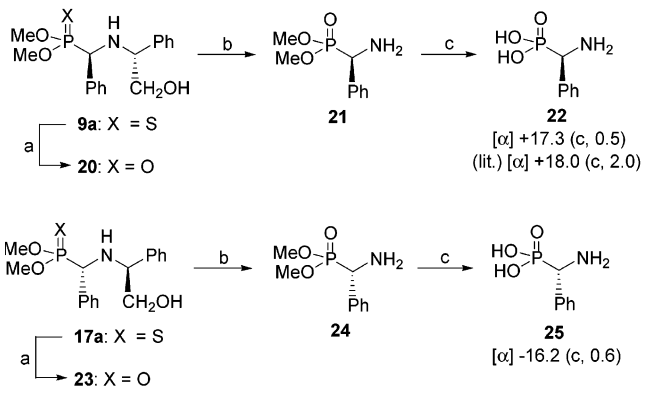
SCHEME 2[a]



[a] (a) H_2O_2, 1:1 H_2O/MeOH, rt, 9 h. (b) H_2/Pd(OH)$_2$, MeOH, rt. (c) HCl, 100 °C (sealed tube), 12 h.

serine increased the ratio from 61:39 to 73:27. Conversely, the use of threonine (branching at the hydroxyl group) led to lowered diastereoselectivity, possibly the result of compensating steric and conformational effects. Attempts to use cysteine methyl ester as auxiliary failed because the reaction with benzaldehyde formed the tetrahydrothiazole prior to imine formation.

DMTP was reacted with the imines of (*R*)- and (*S*)-phenylglycinol to afford **9a/9b** and **17a/17b**. The NMR data supported the formation of a 3:1 mixture of diastereomers, however, the relative configuration of the newly formed α-carbon (PαC) could not be directly assigned because neither the products (**9a/9b, 17a/17b**) nor the corresponding oxidized analogue (P═O) had known configurations (diethyl α-aminophosphonic acids have had absolute and/or relative configurations assigned[24]). Therefore, to unambiguously assign the stereochemistry at the PαC, synthetic routes were undertaken to convert **9a/9b** [from (*R*)-phenylglycinol] and **17a/17b** [from (*S*)-phenylglycinol] to the known phosphonophenylglycine enantiomers **22** and **25** (Scheme 2).[25]

Oxidation of the thionates (P═S) to form the phosphonyl (P═O) was attempted with *m*-chloroperoxybenzoic acid (*m*-CPBA), *t*-BuOOH, monoperoxyphthalic acid, magnesium salt (MMPP),[27] and H_2O_2. When **9a** or **17a** was oxidized with *m*-CPBA or MMPP, significant decomposition of the starting material was observed even when the number of molar equivalents was limited. The reaction did not occur at all when *t*-BuOOH was used, indicating that **9a/17b** might be more sterically hindered than expected. Reacting **9a** or **9b** with a 50% H_2O_2 (5 mL) and CH_3OH (5 mL) mixture for 9−12 h resulted in 29% yield of oxidized product **20** and **23** after chromatography. The reaction was monitored by ^{31}P NMR (δ 27.1 ppm) and stopped before completion to reduce the formation of several byproducts that have R_f values nearly identical with those of the desired product. Phosphonates **20** and **23** showed identical spectra with $[\alpha]_D^{20}$ rotations of −27.4 and +23.6, respectively.

Phosphonates **20** and **23** were hydrogenolyzed with Pd(OH)$_2$/H_2 to afford the dimethyl α-aminophosphonates **21** and **24** in 49% yield (Scheme 2), which led to a reversal in the optical rotation to $[\alpha]_D^{20}$ +25.7 and −24.2 for **21** and **24,** respectively. Dimethyl α-aminophosphonates **21** and **24** were hydrolyzed in sealed tubes (HCl, 100 °C) to afford the (α-amino-α-phenyl)methylphosphonic acid **22** and **25** (phosphonophenylglycine) (Scheme 2) after neutralization.

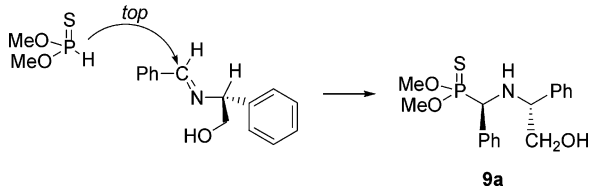


FIGURE 3. Proposed orientation of addition of DMTP to **9a**.

Compound **22** showed an optical rotation of $[\alpha]_D^{20}$ +17.3 (92% ee), and compound **25** showed an optical rotation of $[\alpha]_D^{20}$ −16.2 (80% ee). The rotation of the (*R*)-phosphonophenylglycine previously correlated with an X-ray crystal structure showed an $[\alpha]_D^{20}$ +18.0 (*c* 2.0, 1 N NaOH),[24] thereby allowing the relative assignment of the *R* configuration to the PαC of the major phosphonothionate isomer (**9a**) formed from (*R*)-phenylglycinol, and likewise, the *S* configuration for the PαC of the major isomer (**17a**) formed from (*S*)-phenylglycinol.

A second convergent synthesis was conducted to confirm that the mode of addition by DMTP was identical to that of dimethyl phosphite (DMP). The benzaldimine of (*R*)-phenylglycinol (**8**; R = Ph, R^1 = Me, R^2 = Ph) was reacted with DMP, resulting in a diastereomer pair of α-aminophosphonate adducts. The diastereomers were separated and the major product showed a ^{31}P NMR signal at δ 27.1 and $[\alpha]_D^{20}$ −31.83 ($CHCl_3$), which strongly correlate with **20**, the product obtained from the oxidation of **9a** (Scheme 2), indicating the expected identical mode of addition by DMP and DMTP.

The preferred formation of the (*R*,*R*)-**9a** and (*S*,*S*)-**17a** diastereomers may result from the fact that the benzaldimine may predominantly adopt an *E* configuration that reacts with DMTP on the face opposite to the larger phenyl substituent (smaller CH_2OH), resulting in the *R* configuration at the new PαC center (Figure 3). A similar orientation of addition could be operative for the methyl aldimine (acetaldehyde), but the products would be less diastereoselective. It is unknown whether the DMTP protonates the imine prior to addition, which could shift the configurational equilibrium.

The influence of the hydroxyl group on the diastereoselectivity was unclear. α-Methylbenzylamine yielded the same diastereoselectivity as phenylglycinol. However, serine showed an improved product ratio of **73:27** (for **13a/13b**) as compared to 62:38 for threonine (**14b/14a**) and 53:47 for alanine (**10a/10b**). The trend suggests that the hydroxyl influences the mode the addition, but since the alanine products **10a/10b** were obtained in poor yield, a strict comparison of these results is not possible. The reason that the α-methylbenzylamine group gave near-identical diastereoselectivity to phenylglycinol may be due to the fact that the mode of addition to α-methylbenzaldimine closely resembles that attained by the phenylglycinol aldimine and therefore affords similar diastereoselectivity.

In conclusion, DMTP adds to imines containing N-chiral auxiliaries in good diastereoselectivity in certain cases and in identical orientation to DMP. By use of

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readily available, optically active amines, α-aminophosphonothionates may be prepared in good yield and high stereoselectivity. With these findings, the synthesis of APTAs containing a P-chiral group will be possible.

Experimental Section

Dimethyl Thiophosphite 5.[21] A solution of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent; 25 g, 0.062 mol) and freshly distilled dimethyl phosphite (11 mL, 13.2 g, 0.12 mol) in benzene (88 mL) was heated at 85−90 °C for 45 min. The reaction mixture was cooled to room temperature, and hexane (80 mL) was added to precipitate sulfur- and phosphorus-containing byproducts. The reaction mixture was passed through filter paper and Celite, and the solution was concentrated to an oil under reduced pressure. The product, dimethyl thiophosphite **5,** distilled at 60 °C at 12−16 mM Hg (oil bath 85−95 °C) as a colorless liquid (6.93 g, 0.055 mol, 45.8% yield): ^{1}H NMR δ 7.64 (dd, J = 651.7 and 3.4 Hz, 1 H), 3.69 (d, J = 14.0 Hz, 3 H), 3.68 (d, J = 14.0 Hz, 3 H); ^{13}C NMR δ 52.3 (d, J_{P-OCH_3} = 10 Hz); ^{31}P NMR δ 74.8.

General Procedure for the Synthesis of α-Aminophosphonothioates. To a suspension of the amine hydrochloride (1 equiv) in THF (25 mL) was added TEA (1.1 equiv). The mixture was stirred for 30 min, filtered, and evaporated to yield the free base that was dissolved in a mixture of toluene (10 mL) and the aldehyde (1.0 equiv). Molecular sieves (3 Å) were added and the mixture was stirred at room temperature for 2 h. The mixture was filtered through Celite (aliquot showed imine formation; singlet at δ 8.42 ppm) and chilled to 0 °C, and dimethyl thiophosphite **5** (1.1 equiv) was added. The reaction mixture was stirred at 0 °C for 48 h or until ^{31}P NMR showed loss of **5** and/or the sole appearance of signals at δ 97−103 ppm. The reaction mixture was evaporated to an oil and chromatographed on silica gel (hexanes/Et_2O) to afford the product α-aminophosphonothioates.

***O,O*-Dimethyl (*R*)-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}(phenyl)methylphosphonate 20.** A solution of **9a** (0.360 g, 0.26 mmol) in 50% H_2O_2 (5 mL), and CH_3OH (5 mL) was stirred at room temperature for 8−10 h (^{31}P NMR monitoring). The reaction was stopped with 2.5% $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (5 × 40 mL) to afford crude **20** (0.292 g) that was chromatographed with hexanes/Et_2O/CH_3OH (10:10:0.5). The phosphonate **20** was obtained as a yellowish oil (0.104 g, 0.309 mmol, 29%): TLC R_f = 0.14 (hexanes/Et_2O/CH_3OH = 4.25:4.25:0.5); $[\alpha]^{23}_D$ = −25.53 (c = 1.90, $CHCl_3$); ^{1}H NMR δ 7.33−7.19 (m, 10 H), 4.10 (d, J_{PCH} = 18.8 Hz, 1H), 4.01−3.98 (m, 1H), 3.78−3.73 (m, 1H), 3.73 (d, J_{POCH_3} = 10.4 Hz, 3H), 3.63−3.59 (m, 1H), 3.49 (d, J_{POCH_3} =10.4 Hz, 3 H), 3.08 (br s, 1H); ^{13}C NMR δ 140.4, 136.2, 128.4, 128.4, 128.2, 128.2, 127.9, 127.5, 127.3, 66.1, 62.8, 62.7, 58.1 (d, J_{PC} = 152.6 Hz), 53.6 (d, J_{POCH_3} = 9.2 Hz), 53.2 (d, J_{POCH_3} = 9.2 Hz); ^{31}P NMR δ 27.1; Anal. Calcd for $C_{17}H_{22}NO_4P$: C, 60.89; H, 6.61; N, 4.18. Found: C, 60.57; H, 6.62; N, 4.12.

Compound **20** was also prepared by the addition of dimethyl phosphite to the benzaldimine of (*R*)-phenylglycinol. To a solution of (*R*)-(−)-2-phenylglycinol (0.57 g, 4.19 mmol) in toluene (10 mL) containing molecular sieves (3 Å, 0.5 g) was added benzaldehyde (0.43 mL, 0.44 g, 4.19 mmol). After 3 h at room temperature, the mixture was filtered through Celite, dimethyl phosphite (0.38 mL, 0.46 g, 4.19 mmol) was added, and the reaction was stirred for 48 h. The reaction mixture was purified by chromatography (hexanes/Et_2O/MeOH 4.25/4.25/0.5) to give dimethyl phosphonate **20** (0.79 g, 2.34 mmol, 56%) as a yellowish oil: $[\alpha]^{25}_D$ −31.83 (c 1.99, $CHCl_3$).[10,11]

Dimethyl (*R*)-Amino(phenyl)methylphosphonate 21. A solution of **20** (0.121 g, 0.36 mmol) and Pearlman's catalyst (0.03 g) in CH_3OH (15 mL) was stirred for 12 h under H_2 at room temperature. The reaction mixture was degassed and filtered through Celite; the solids were triturated with CH_3OH, and evaporated to dryness. The residue was extracted from CH_2Cl_2/2.5% $NaHCO_3$ to afford crude product (0.093 g) that was purified by column chromatography (hexanes/Et_2O/CH_3OH 10:10:0.5) to afford α-aminophosphonate **21** as yellowish oil (0.038 g, 0.18 mmol, 49%): TLC R_f = 0.10 (hexanes/Et_2O/CH_3OH = 4.5:4.5:1); $[\alpha]^{23}_D$ = +25.75 (c = 1.90, $CHCl_3$); ^{1}H NMR δ 7.44−7.25 (m, 5H), 4.29 (d, J_{PCH} = 16.8 Hz, 1 H), 3.69 (d, J_{POCH_3} = 10.4 Hz, 3 H), 3.56 (d, J_{POCH_3} = 10.4 Hz, 3 H), 2.18 (br s, 2H); ^{13}C NMR δ 137.4, 128.6, 128.0, 127.6, 127.6, 53.7 (d, J_{CP} = 149.6 Hz), 53.6 (d, J_{POCH_3} = 6.1 Hz), 53.5 (d, J_{POCH_3} = 12.2 Hz); ^{31}P NMR δ 27.5; HRMS calcd for M + H^+ of $C_9H_{14}NO_3P$ 216.0790, found 216.0782; Anal. Calcd for $C_9H_{214}NO_3P$·0.25H_2O: C, 49.20; H, 6.65; N, 6.38. Found: C, 48.85; H, 6.74; N, 6.33.

(*R*)-Phosphonophenylglycine 22.[24] A solution of **21** (0.046 g, 0.20 mmol) was dissolved in HCl_{conc} (2 mL) and heated in a sealed tube at 100 °C for 12 h. The mixture was evaporated to a solid white residue that was dissolved in EtOH (2 mL) and treated with propylene oxide (10 mL), resulting in a white precipitate. The white precipitate was isolated by centrifugation, triturated with Et_2O, filtered, and dried to give **22** as a white solid (0.025 g, 0.13 mmol, 66.8% yield): $[\alpha]^{23}_D$ = +17.3 (c = 0.52, 1 N NaOH); ^{1}H NMR (D_2O) δ 7.34−7.20 (m, 5H), 4.21 (d, J_{PCH} = 16.0 Hz, 1 H); ^{13}C NMR (D_2O) δ 134.1, 129.9, 129.6, 128.6, 54.7 (J_{PC} = 137.4 Hz); ^{31}P NMR ($CDCl_3$) δ 10.9; HRMS calcd for M + H^+ of $C_7H_{11}NO_3P$ 188.0476, found 188.0491.

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Supporting Information Available: Procedures and physical data for compounds **9a/9b**, **10a/10b**, **11a/11b**, **12a/12b**, **13a/13b**, **14a/14b**, **17a/17b**, **18a/18b**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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