Enantioselective Synthesis of Diverse α-Amino Phosphonate Diesters

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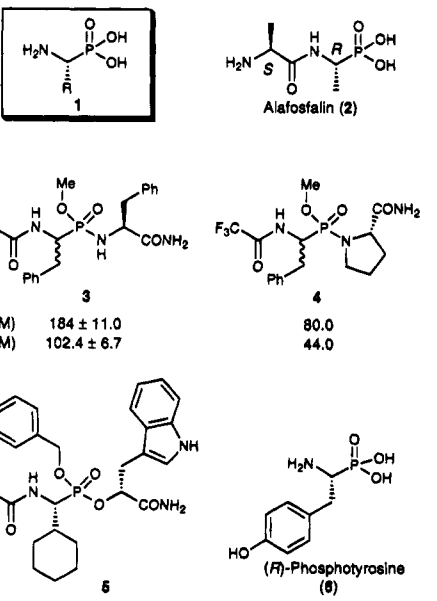
Abstract: An efficient, versatile protocol for the synthesis of highly enantioenriched α-amino phosphonate diesters has been devised. Addition of lithium diethyl phosphite to chiral chelating imines **31a−j**, prepared from a variety of aldehydes and the chiral auxiliary (*R*)-(−)-1-amino-1-phenyl-2-methoxyethane (**29**), generated predominantly the (*R,R*) diastereomers **33**. Hydrogenolysis then furnished α-amino phosphonates **15**; in most examples, the enantiomeric purity exceeded 97% ee.

α-Amino phosphonic acids (**1**) serve as important surrogates for α-amino carboxylic acids, the fundamental building blocks of peptides and proteins. The two pK_a values of dibasic **1** generally bracket the corresponding amino acid pK_a values, yielding peptide analogues (e.g., **2**) with altered isoelectric points and binding properties.[1] Biologically relevant α-amino phosphonate derivatives include the antibacterial agent alafosfalin (**2**),[2] transition-state-analogue inhibitors of proteolytic enzymes (**3** and **4**),[3] and haptens for the generation of catalytic antibodies (e.g., **5**).[4] (*R*)-Phosphotyrosine (**6**) occurs naturally as a component of two hypotensive tripeptides;[5] interestingly, this example embodies the L configuration of the encoded α-amino carboxylic acids.



Earlier Synthetic Approaches. It is not surprising that the biological profiles of α-amino phosphonates are influenced by the absolute configuration of the stereogenic carbon α to phosphorus. For example, the (*S,R*) diastereomer of **2** shows significant activity against both Gram-positive and -negative microorganisms, whereas the other three stereoisomers are considerably less potent.[6] To date, however, racemic α-amino phosphonates have been employed as precursors of many derivatives, underscoring the need for an effective enantioselective synthesis of these materials. Importantly, α-amino phosphonate diesters are more attractive as intermediates for multistep syntheses than the corresponding phosphonic acids, as the insolubility of the latter in both organic and neutral aqueous media complicates derivatization of both the amine and acid functionalities. A simple route to enantiopure α-amino phosphonate diesters therefore held the promise of considerable utility.

The first synthesis of an optically active α-amino phosphonic acid was reported by Gilmore and McBride in 1972.[7] Diastereoselective addition of diethyl phosphite to imine **8**, derived from enantiomerically pure α-methylbenzylamine (**7**), and hydrogenolysis of the chiral auxiliary furnished **11** in unspecified chemical and optical yields (Scheme 1). Soroka and co-workers later demonstrated that the method affords a 2:1 mixture of diastereomeric phosphite adducts **9**.[8] In our published[9] synthesis of the hapten **5**, we employed this protocol to prepare diethyl

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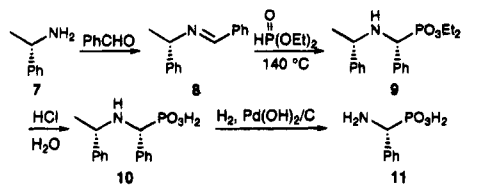
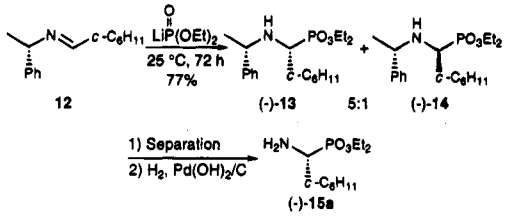
Scheme 1



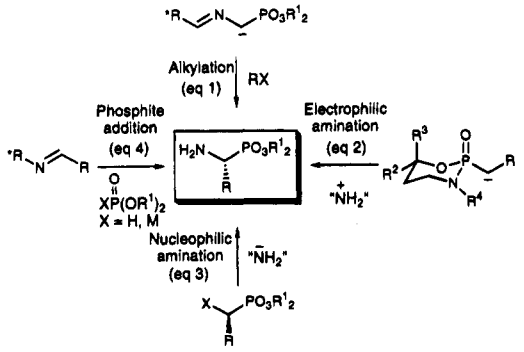
(*R*)-(α-aminocyclohexylmethyl)phosphonate [(−)-**15a**, Scheme 2]. Although workable, the large-scale separation of diastereomers (−)-**13** and (−)-**14** proved highly labor-intensive.

Scheme 2



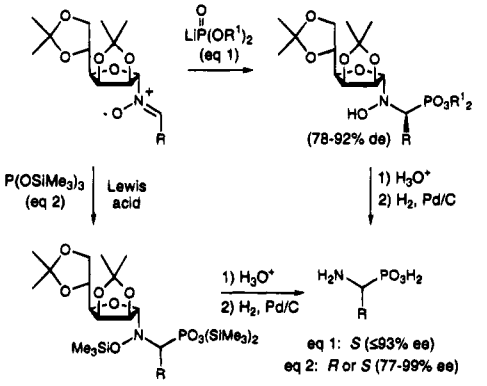
Subsequently, a large number of methods have been devised for the preparation of optically active α-amino phosphonates via chemical and chromatographic resolutions and asymmetric syntheses, as comprehensively reviewed by Dhawan and Redmore.[10] The development of new strategies continues unabated. Recent examples (Scheme 3) include alkylation of chiral phosphonate imines derived from (+)-ketopinic acid[11] and (+)- or (−)-2-hydroxy-3-pinanone (eq 1),[12] electrophilic amination and alkylation of chiral α-alkyl phosphonamides (eq 2),[13] nucleophilic amination of chiral α-hydroxy phosphonate derivatives (eq 3),[14] and addition of di- or trialkyl phosphite derivatives to chiral imines (eq 4).[15]

Scheme 3



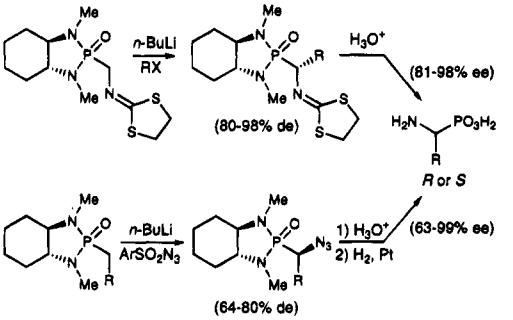
Prior to our work (*vide infra*), the best methods for preparing α-amino phosphonic acid derivatives had been developed by Vasella[16] and Hanessian.[13a,b] Vasella's protocol relies on the stereoselective addition of lithium dialkyl phosphites to *N*-glycosyl nitrones (Scheme 4), affording phosphite addition products with good diastereoselectivities (78−92% de). Acidic hydrolysis and catalytic hydrogenation then provide the derived α-amino phosphonic acids or esters (≤93% ee). This method is useful for generating (*S*)-α-amino phosphonate derivatives, but access to the (*R*) series is difficult at best. A followup study employing tris(trimethylsilyl) phosphite as the nucleophile demonstrated that the configuration of the α carbon could be controlled by variation of the Lewis acid catalyst. Unfortunately, even with this modification, moderate enantiopurities (77−97% ee) and instability of the silyl ester products limit the overall efficiency of the method.

Scheme 4



Hanessian and co-workers developed two complementary approaches to the synthesis of enantioenriched α-amino phosphonic acids (Scheme 5). Alkylation of scalemic bicyclic phosphonamides of either absolute configuration with carbon electrophiles furnishes α-amino phosphonodiamides in 80−98% de; acidic hydrolysis then yields the α-amino phosphonic acids with moderate-to-excellent enantiopurites (81−98% ee). Because this method relies on alkylation, however, derivatives containing branched or aromatic α substituents are inaccessible. The second strategy, based on amination or azidation of chiral α-alkyl phosphonamides, provides adducts with moderate diastereoselectivities (64-80% de). Acidic hydrolysis and catalytic hydrogenolysis again furnishes the α-amino phosphonic acids in 63−99% ee. As noted earlier, further transformations involving the free acids are often problematic. The above limitations defined the three major design objectives for a more effective synthesis of enantiomerically pure α-amino phosphonates: (1) accommodation of a wide range of α substituents, (2) ready access to both product antipodes, and (3) ease of

Scheme 5



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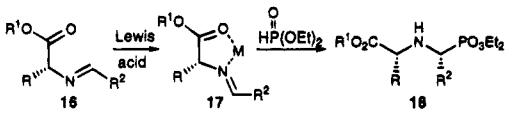
incorporation of the requisite protecting groups. Our ongoing efforts in the catalytic antibody area[4a] prompted us to search for viable solutions to these problems.

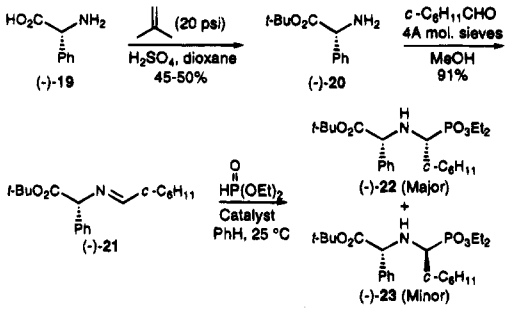
Evolution of the Chelation-Control Strategy. This quest led to earlier work by Zon, who studied the addition of tris(trimethylsilyl) phosphite to chiral imines such as **12**.[17] In some cases, Lewis acid catalysis led to improved yields and diastereoselectivities vis-à-vis the uncatalyzed reactions. These precedents suggested that bidentate coordination of a suitable imine (e.g., **16**; Scheme 6) to the catalyst would generate a rigid chelate, **17**; nucleophilic addition of phosphite anti to the stereodirecting R group would then provide an excess of the (*R,R*) diastereomer **18**. This strategy was exploited previously in the asymmetric hydrocyanation of imines[18] and in conjugate additions of Grignard reagents to α,β-unsaturated imines.[19]

Scheme 6



The preparation of our initial substrate, imine (−)-**21**, began with conversion[20] (isobutylene, H_2SO_4, dioxane) of (*R*)-(−)-phenylglycine (**19**) to the crystalline *tert*-butyl ester (−)-(**20**) in 45−50% yield (Scheme 7). Both enantiomers of **19** are commercially available; we focused on (*R*)-**20** in an effort to obtain (*R*)-α-amino phosphonates, mimics of the coded L-α-amino carboxylic acids (*vide infra*). Condensation with cyclohexanecarboxaldehyde (4 Å molecular sieves, MeOH) gave imine (−)-**21** (91%), to which diethyl phosphite was then added in the presence of the Lewis acids $ZnCl_2$ and $MgBr_2$ and the protic acid TFA (10 mol %; benzene, 25 °C; Scheme 7). Whereas all three catalysts led to increased rates of addition, indicative of the desired imine activation, none afforded enhanced diastereoselectivity; the poor de values indicated that the expected chelate **17** was not formed or that the phenyl group provided insufficient steric bias to control external delivery of the nucleophile.

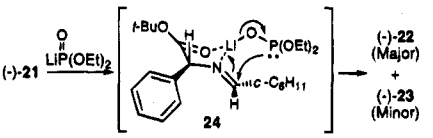
Scheme 7



Catalyst	Time (h)	Yield (%)	de (%)
-	>120	87	38
$ZnCl_2$	7	84	48
$MgBr_2$	>48	40	38
TFA	>48	46	14

Careful analysis of related examples[21] revealed that high facial discrimination might require coordination of the nucleophile with the chelating metal cation, as in Koga's asymmetric addition of Grignard reagents to α,β-unsaturated imines.[19] In phosphite addition this tactic would entail an intermediate structure such as **24**, with a trans relationship between the nucleophile and the stereodirecting phenyl group (Scheme 8). Collapse of **24** would then result in internal delivery of the phosphite nucleophile to the *re* face of the imine double bond.

Scheme 8

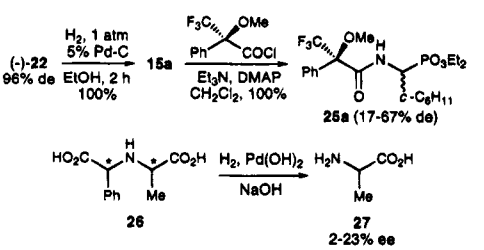


Conditions	Yield (%)	de (%)
HPO_3Et_2, *t*-BuOLi CH_2Cl_2, -70 → 25 °C	38	94
HPO_3Et_2, *n*-BuLi THF, -78 → 25 °C	75-80	94-96

This hypothesis was evaluated with imine (−)-**21** and the lithium salt of diethyl phosphite ($LiPO_3Et_2$), prepared at first by treatment of diethyl phosphite with lithium *tert*-butoxide in dichloromethane at −60 °C. The anion did not react with (−)-**21** at temperatures below 0 °C; even at ambient temperature the addition proved to be slow and inefficient (38% yield), but the selectivity improved dramatically to 94% de (RP-HPLC). We subsequently generated $LiPO_3Et_2$ more effectively by using *n*-BuLi as base; with slightly less than 1 equiv of the anion, the de values increased further. The adverse effect of excess lithium reagent may reflect base-induced epimerization α to phosphorus. Tetrahydrofuran emerged as the solvent of choice, offering minimal inhomogeneity and corresponding improvements in both rate and diastereoselectivity. This optimized sequence routinely provided (−)-**22** both in good yield (75−80%) and in high diastereoselectivity (94−96% de).

A Second-Generation Chiral Auxiliary. At this juncture we sought to remove the benzylic chiral auxiliary. Whereas both **10** and (−)-**13** were readily converted to primary amines via hydrogenolysis with Pearlman's catalyst (Schemes 1 and 2, respectively), to our surprise (−)-**22** proved completely unreactive under these conditions. Equally unrewarding were attempted hydrogenolyses employing Ni, Pt, and Rh catalysts, with and without a protic acid and at elevated hydrogen pressures. Transfer hydrogenolyses (Pd black, ammonium formate)[22] and dissolving metal reductions[23] were also unproductive. Oxidative decarboxylation[24] of the carboxylic acid derived from (−)-**22** followed by hydrolysis of the resultant imine did furnish the target amine **15a**, but in low yield (30%) and with significant epimerization, as ascertained by Mosher amide analysis.[16,25] Almost quantitative hydrogenolysis of (−)-**22** was finally achieved with 5% Pd on activated carbon (Degussa type E101 NO/W) as catalyst in ethanol (Scheme 9).

Scheme 9



Unfortunately, ^1H NMR analysis of the (*S*)-Mosher amides **25a** revealed extensive stereochemical degradation (17−67% de).

(17) Zon, J. *Pol. J. Chem.* **1981**, *55*, 643.
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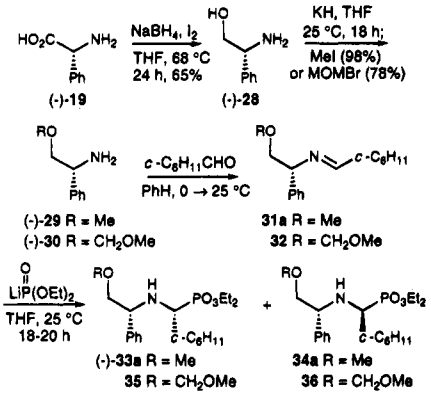
In a related example, Harada and Kataoka observed similar loss of stereochemical integrity upon hydrogenolysis of the phenylglycine–alanine derivative **26** to alanine (**27**).[26]

Because the phosphite adducts of α-phenethylamine-derived imines underwent hydrogenolysis without racemization (Schemes 1 and 2),[8] we turned next to the methyl and methoxymethyl (MOM) ethers of (*R*)-(−)-2-phenylglycinol (**28**, Scheme 10) as prospective chiral auxiliaries. We speculated that the ether oxygen in (−)-**29** and (−)-**30** would participate in bidentate coordination of the lithium cation without compromising the stereochemical integrity of the products upon hydrogenolysis. Both (*R*)-(−)- and (*S*)-(+)-2-phenylglycinol (**28**) are available commercially or by reduction[27] of (−)- and (+)-2-phenylglycine (**19**). The ether derivatives were obtained in quantity (ca. 25 g) from (−)-**28** via the Meyers alkylation procedure[28] (KH, THF,

Scheme 10



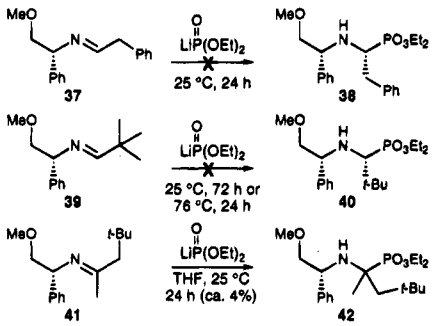
25 °C; MeI or MOMBr; Scheme 10); we again employed the (*R*) enantiomers of the auxiliaries in an effort to generate analogues of the coded α-amino carboxylic acids. Condensation of (−)-**29** and (−)-**30** with cyclohexanecarboxaldehyde (PhH, Na_2SO_4, 0 → 25 °C, 1 h) furnished the hydrolytically unstable imines **31a** and **32** (90% and 92% yields) which were used immediately, without purification. Addition of $LiPO_3Et_2$ (0.95 equiv) to **31a** (R = Me) (THF, ambient temperature, 18–20 h) then furnished a 49:1 mixture (500-MHz ^{1}H NMR) of diastereomeric adducts (−)-**33a** and **34a** in 68% yield after flash chromatography. Moreover, we were delighted to find that hydrogenolysis proceeded uneventfully, catalyzed by $Pd(OH)_2$ in absolute ethanol (*vide infra*). The MOM-protected imine **32** afforded **35** and **36** with identical selectivity, but this addition was exceedingly sluggish, proceeding to only 12% conversion in the time period required for complete reaction of **31**. Accordingly, amine (−)-**29** was employed in all subsequent studies.

The effects of the phosphite counterion on the rate and diastereoselectivity of the addition were investigated with **31a** and the sodium [from $NaN(SiMe_3)_2$] and potassium [$KN(SiMe_3)_2$] salts of diethyl phosphite. Remarkably, neither the sodium nor the potassium reagent gave any detectable product, even after several days at ambient temperature. These observations are in accord with the results of Vasella and co-workers, who obtained poor yields and diastereoselectivities upon addition of KPO_3Et_2 to *N*-glycosyl nitrones. They attributed their findings to competition from single electron transfer mechanisms as well as inferior complexation and lower reactivity of the potassium salt.[16a]

Asymmetric Synthesis of Diverse α-Amino Phosphonates. We then explored the generality of the phosphite addition with a variety of imines; several contained α side chains found in coded α-amino carboxylic acids (Table 1). Authentic mixtures of **33** and **34** (typically ca. 2:1) were prepared by treatment of each imine with diethyl phosphite and anhydrous $ZnCl_2$ (benzene, 25 °C, 20 h). Diastereomer ratios were generally determined via capillary GC prior to purification. When low volatility precluded GC analysis, 500-MHz ^{1}H NMR integration was employed; in every instance the protons α to phosphorus were cleanly resolved. Most substrates reacted with excellent diastereoselectivity (95–98% de).

An anomaly arose in the behavior of **31j** (R = phenyl) which furnished a 7.3:1 mixture of adducts (−)-**33j** and **34j**. In this case, base-induced epimerization of the adducts may be promoted by the phenyl and phosphonyl groups and exacerbated by the lengthy reaction time (48 h). We have thus far been unable to apply the new protocol to the synthesis of the phosphophenylalanine precursor **38**, as the requisite phenylacetaldehyde-derived imine **37** apparently isomerizes to the enamine during reaction with $LiPO_3Et_2$ (Scheme 11). In addition, steric congestion inhibited addition to the pivalaldehyde imine **39** after 72 h at room temperature or 24 h at 67 °C; ketimine **41**, prepared from (−)-**29** and 4,4-dimethyl-2-pentanone, likewise provided only minor amounts (ca. 4% yield) of the α,α-disubstituted amino phosphonate **42** upon reaction with $LiPO_3Et_2$. Although **42** appeared to be a single stereoisomer (500-MHz ^{1}H NMR), the relative configuration was not elucidated in view of the poor chemical yield.

Scheme 11



To account for the high diastereofacial selectivity, we propose the chelated intermediate **43** (Scheme 12), analogous to the structure envisioned earlier (**24**, Scheme 8) in conjunction with the amino ester **20** as chiral auxiliary. The anti disposition of the phenyl and phosphite groups presumably directs the addition to the *re* (i.e., top) face of the imine double bond, generating the (*R,R*) diastereomers **33** (entries **a**–**j**).

Scheme 12

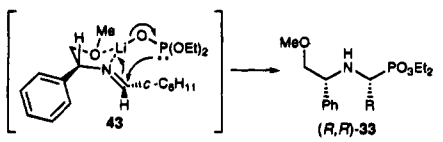


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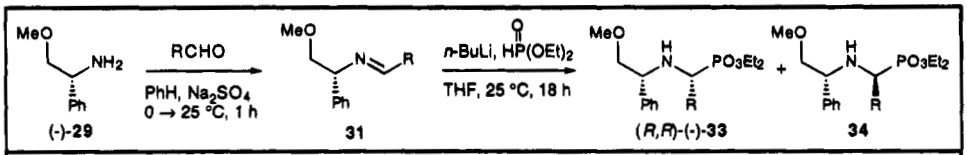
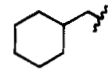
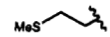
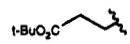
Table 1. Asymmetric Addition of $LiPO_3Et_2$ to Imines Derived from Chiral Auxiliary (*R*)-(−)-**29**

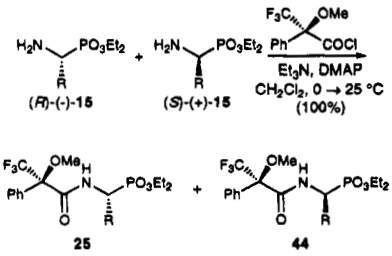


Entry	R	Yields (%): 31[a]	33,34[b]	33:34 Ratio[a]	de (%)
a		90	68	49:1[c]	96.0
b		89	70	114:1[d,e]	98.3
c		82	82	55:1[d]	96.5
d		84	81	>114:1[d,e]	>98.3
e		90	77	41:1[d]	95.2
f		95	78	49:1[b,d]	96.0
g		84	69	55:1[d]	96.5
h		92	38	49:1[c]	96.0
i		95	37	49:1[c]	96.0
j		82	90	7.3:1[c]	76.0

[a] Crude product. [b] After chromatography. [c] Determined by 500-MHz ^1H NMR. [d] Determined by capillary GC. [e] Trace of **34** detectable.

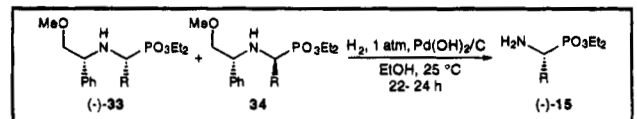
Hydrogenolysis of the chiral directing group in **33a−j** with catalytic palladium hydroxide on carbon in absolute ethanol (25 °C, 22−24 h) afforded the amino esters **15** in 83−100% yields after flash chromatography (Table 2). As anticipated, **15** generally could be unmasked without loss of stereochemical integrity, as ascertained by 500-MHz ^1H NMR analyses of the derived (*S*)-Mosher amides (Scheme 13); the methoxy singlets for each pair of Mosher diastereomers were clearly resolved. For entries **g** and **j** [R = 2-(methylthio)ethyl and phenyl], 21.5% and 5% racemization did occur during hydrogenolysis. In the former example, severe catalyst poisoning by the thioether necessitated the use of forcing conditions [H_2, Pd black (5 equiv), AcOH, 25 °C, 48 h], whereas the phenyl result again probably reflects unusual lability of the α proton. In all other cases, the ee values for **15** were as high or higher than the de values determined for the phosphite adducts; the increases derived from partial separation of the diastereomers **33** and **34** during flash chromatography. No attempt was made to recover the minor isomers **34**, which accounted for less than 2% of each mixture. The minor enantiomers for entries **b**, **d**, and **e** could not be detected by Mosher analysis.

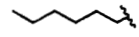
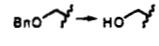
Scheme 13



Determination of Absolute Stereochemistry. The absolute configurations of seven α-amino phosphonates were established via comparison of the signs of optical rotation with literature values (Table 2). The (*R*) configurations of the previously unknown esters **15a** and **15b** were secured by X-ray crystallographic analyses of the derived hydrochloride salt (**15a**•HCl; anomalous dispersion) and (*S*)-Mosher amide (**25b**), respectively

Table 2. Unmasking of α-Amino Phosphonates (−)-**15** via Hydrogenolysis



Entry	R	Yield (%)[a]	$[\alpha]_D^{25}$	Mosher ee (%)
a		94	-52.2° (*c* 1.2, Me_2CO)	96
b		87	-20.9° (*c* 0.6, $CHCl_3$)	≥99
c		86	-0.8° (*c* 1.3, $CHCl_3$)[d]	97
d		89	-20.8° (*c* 1.6, $CHCl_3$)	≥99
e		99	-5.4° (*c* 1.8, $CHCl_3$)[d]	≥99
f		98	-12.2° (*c* 1.1, $CHCl_3$)	≥98
g		89[b,c]	-21.6° (*c* 0.6, $CHCl_3$)	75
h		100	-10.6° (*c* 1.5,$CHCl_3$)[d]	≥98
I		83	-14.3° (*c* 0.7, $CHCl_3$)	96
j		88	-13.3° (*c* 1.9,$CHCl_3$)	71

[a] After chromatography. [b] Corrected for recovered starting material. [c] Pd black (5 equiv), H_2, AcOH, 25 °C, 48 h. [d] Cf. ref 29.

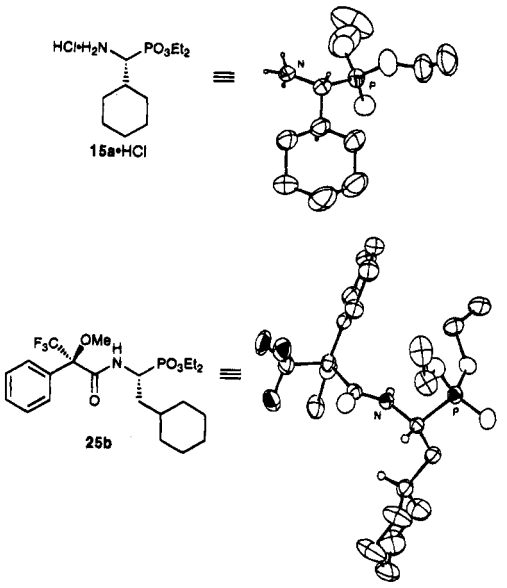
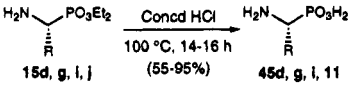


Figure 1. Crystal structures of **15a**·HCl and **25b**.

(Figure 1). The configurations of **33f** and **15f** (R = *n*-hexyl) were inferred from the stereochemical congruity observed within the series as well as the negative Cotton effects (λ_{max} = ca. 200 nm) in all 10 CD curves for **33a**–**j**. Principally in order to obtain polarimetric verification of the absolute stereochemistries, four of the diethyl phosphonates (**15**, entries **d**, **g**, **i**, and **j**) were hydrolyzed in hot concentrated HCl, furnishing the known α-amino phosphonic acids **45d**, **45g**, **45i**, and **11** (Scheme 14). The signs of the product optical rotations were in accord with literature data, but the absolute values suggested that hydrolysis was accompanied by partial racemization, in accord with previous reports.[16a] If desired, the diester **15** can be converted to phosphonic acids without loss of stereochemical integrity; for example, in our synthesis of the hapten **5**, protection of the amine functionality of **15a** (R = cyclohexyl) with the acid-stable (9-fluorenylmethoxy)carbonyl (Fmoc) group permitted acidic hydrolysis of the ethyl esters without interference from racemization. We also anticipate that a variety of basic[30] and nucleophilic[31] protocols can be utilized for conversion of **15** to the corresponding phosphonic acids.

Scheme 14



In summary, we have developed a versatile and efficient three-step asymmetric synthesis of α-amino phosphonate diesters from readily available precursors. This methodology is central to our ongoing research aimed at the development of catalytic antibodies with peptide ligase activities. In addition, the enantioenriched α-amino phosphonate diesters will serve as building blocks for other novel transition state analogues in mechanistic enzymology and non-peptide peptidomimetic research.

(29) Published optical rotation data: (+)-(*S*)-phosphovaline diethyl ester (**15**, entry c) $[\alpha]_D^{25}$ +0.4° (*c* 1.7, $CHCl_3$); (+)-(*S*)-phosphoalanine diethyl ester (**15**, entry e) $[\alpha]_D^{25}$ +7.3° (*c* 1.3, $CHCl_3$); (+)-(*S*)-phosphoserine diethyl ester (**15**, entry h) $[\alpha]_D^{25}$ +9.0° (*c* 1, $CHCl_3$). See reference 15a.

(30) Yamauchi, K; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2528.

(31) Jacques, J.; Leclercq, M.; Brienne, M.-J. *Tetrahedron* **1981**, *37*, 1721.

Experimental Section[32]

(*R*)-Phenylglycine *tert*-Butyl Ester [(−)-20]. Sulfuric acid (10 mL) was added to a suspension of (*R*)-(−)-phenylglycine (**19**) (10.0 g, 66.2 mmol) in 1,4-dioxane (75 mL) in a 400-mL Paar reaction vessel. Isobutylene (75 mL, 0.84 mol) was condensed at −78 °C in a separate flask and then transferred to the Paar vessel cooled to −78 °C via a cannula with a positive pressure of argon. The vessel was attached to a Paar apparatus, and an argon pressure of 20 psi was maintained while the reactor was warmed to room temperature and shaken for 12 h. The vessel was then opened in a fume hood and the excess isobutylene allowed to evaporate. The residue was poured into aqueous NaOH (2 M, 300 mL) and extracted with diethyl ether (3 × 500 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Crystallization from hexanes afforded **20** (6.70 g, 49% yield) as colorless needles: mp 41.5–43 °C; $[\alpha]_D^{25}$ −108° (*c* 1.61, $CHCl_3$); IR ($CHCl_3$) 3400 (w), 3050 (m), 2990 (s), 2950 (m), 1730 (s), 1600 (w), 1500 (w), 1480 (w), 1460 (m), 1400 (m), 1375 (s), 1255 (s), 1155 (s), 1095 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.48 (s, 1 H), 1.98 (s, 2 H), 1.39 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.1, 140.8, 128.5, 127.6, 126.6, 81.4, 59.2, 27.8; high-resolution mass spectrum (CI, CH_4) *m/z* 208.1351 [(M + H)$^+$; calcd for $C_{12}H_{18}NO_2$ 208.1337]. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.47; H, 8.26; N, 6.71.

Phosphite Adduct (−)-(22). Cyclohexanecarboxaldehyde (479.5 mg, 4.28 mmol) was dissolved in anhydrous MeOH (17 mL), and flame-dried 4 Å molecular sieves (ca. 1 g) and (*R*)-phenylglycine *tert*-butyl ester [(−)-**20**] (886.0 mg, 4.28 mmol) were added. The mixture was stirred at room temperature for 12 h and then filtered through Celite, and the filter pad was washed with benzene (80 mL) and CH_2Cl_2 (200 mL). Concentration gave **21** (1.31 g, 91% yield) as a colorless oil: $[\alpha]_D^{25}$ −14.0° (*c* 2.81, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2950 (s), 2870 (m), 1740 (s), 1675 (w), 1460 (w), 1380 (m), 1160 (s), 845 (w), 695 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 5.3 Hz, 1 H), 7.45–7.25 (m, 5 H), 4.80 (s, 1 H), 2.31 (m, 1 H), 1.90–1.60 (m, 5 H), 1.40 (s, 9 H), 1.40–1.20 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.7, 170.1, 138.6, 128.3, 127.6, 127.5, 81.2, 76.9, 43.5, 29.4, 27.8, 25.8, 25.2; high-resolution mass spectrum (CI, CH_4) *m/z* 302.2097 [(M + H)$^+$; calcd for $C_{19}H_{28}NO_2$ 302.2120]. In a separate flask, a solution of freshly distilled diethyl phosphite (1.77 mL, 13.7 mmol) in THF (8.5 mL) was cooled to −78 °C and treated dropwise with *n*-butyllithium (1.54 M in hexane, 2.41 mL, 3.71 mmol). After 0.5 h, the mixture was warmed to room temperature and added via syringe to a solution of **21** (1.18 g, 3.91 mmol) in THF (25 mL) at room temperature. The reaction mixture was stirred for 20 h and quenched with H_2O (15 mL). Most of the THF was removed in vacuo and the residue partitioned between brine (20 mL) and EtOAc (60 mL). The aqueous layer was extracted with EtOAc (25 mL), and the combined

(32) **Materials and Methods.** Except as otherwise indicated, reactions were carried out under argon with dry, freshly distilled solvents, in glassware flame-dried under vacuum, with magnetic stirring. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Benzene was distilled from sodium. Diethyl phosphite was distilled at reduced pressure and stored under argon. *n*-Butyllithium was standardized via titration with diphenylacetic acid. Aldehydes were distilled or prepared immediately prior to use. All reactions were monitored by thin layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Flash chromatography was performed with E. Merck silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as noted. Proton and carbon-13 NMR spectra were recorded on a Bruker AM 500 spectrometer. Proton chemical shifts are reported in δ values relative to internal tetramethylsilane. Carbon chemical shifts are reported relative to solvent. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. High-resolution mass spectra were obtained with a VG Micromass 70/70H or VG ZAB-E spectrometer. Microanalyses were performed by Robertson Labs, Madison, NJ, or by Dr. Rakesh Kohli, Department of Chemistry, University of Pennsylvania. Capillary gas–liquid chromatography was performed with a Hewlett-Packard 5790A instrument equipped with an HP 3390A integrator and a 25 m × 0.2 mm × 0.33 μm HP-1 methylsilicone gum column. Analytical runs were isothermal with oven temperatures of 200 or 230 °C and corresponding injector temperatures of 250 or 280 °C and detector temperatures of 275 or 305 °C. Samples were injected as dilute solutions in anhydrous diethyl ether. Circular dichroism (CD) spectra of the phosphite adducts were recorded on a Jasco J-600 spectropolarimeter as dilute (10^{-3} or 10^{-4} M) solutions in anhydrous trifluoroethanol.

organic solutions were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (gradient elution, 50% → 67% EtOAc/hexanes) furnished **22** (1.18 g, 72% yield) as a colorless oil: 94% de (RP-HPLC). Analytical data for minor isomer: $[\alpha]_D^{25}$ −12.1° (*c* 0.88, $CHCl_3$); IR 3360 (w), 3000 (s), 2940 (s), 2870 (m), 1730 (s), 1455 (m), 1395 (w), 1370 (m), 1240 (s), 1210 (s), 1155 (s), 1100 (w), 1050 (s), 1030 (s), 965 (s), 840 (w), 730 (w), 695 (w), 555 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2 H), 7.33−7.25 (m, 3 H), 4.62 (s, 1 H), 4.12−4.00 (m, 4 H), 2.89 (br s, 1 H), 2.79 (dd, *J* = 3.3, 13.7 Hz, 1 H), 1.86−1.74 (m, 4 H), 1.65 (d, *J* = 13.7 Hz, 1 H), 1.54−1.47 (m, 1 H), 1.38−1.12 (m, 5 H), 1.38 (s, 9 H), 1.28 (td, *J* = 1.7, 7.1, Hz, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.9, 138.3, 128.3, 127.7, 127.6, 81.4, 65.2, (d, J_{CP} = 6.3 Hz), 61.9 (dd, J_{CP} = 3.4, 6.6 Hz), 58.9 (d, J_{CP} = 150 Hz), 39.4, 30.9, 30.7, 28.9, 27.8, 26.7, 26.5, 26.1, 16.4, 16.3; high-resolution mass spectrum (FAB) *m/z* 440.2588 [(M + H)$^+$; calcd for $C_{23}H_{39}NO_5P$ 440.2565]. Analytical data for major isomer: $[\alpha]_D^{25}$ −35.6° (*c* 1.35, $CHCl_3$); IR ($CHCl_3$) 3460 (br, w), 2990 (s), 2940 (s), 2860 (m), 1730 (s), 1450 (m), 1395 (m), 1370 (m), 1245 (s), 1155 (s), 1095 (w), 1050 (s), 1025 (s), 960 (s), 840 (w), 725 (w), 695 (w), 555 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.36 (m, 2 H), 7.33−7.25 (m, 3 H), 4.68 (d, *J* = 3.1 Hz, 1 H), 4.15 (m, 4 H), 3.88 (br s, 1 H), 2.58 (dd, *J* = 11.4, 2.6 Hz, 1 H), 1.84−1.58 (m, 5 H), 1.06 (m, 21 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.6, 138.4, 128.4, 128.2, 127.8, 81.5, 64.2, 62.2 (d, J_{CP} = 7.0 Hz), 61.8 (d, J_{CP} = 7.0 Hz), 57.1 (d, J_{CP} = 140 Hz), 39.1, 30.9, 30.7, 27.8, 26.5, 26.4, 26.0, 16.5; high-resolution mass spectrum (FAB), *m/z* 440.2753 [(M + H)$^+$; calcd for $C_{23}H_{39}NO_5P$ 440.2565]. Anal. Calcd for $C_{23}H_{38}NO_5P$: C, 62.85; H, 8.71; N, 3.18. Found: C, 63.05; H, 8.94; N, 3.17.

(*R*)-(−)-1-Amino-1-phenyl-2-methoxyethane [(−)-29]. In an oven-dried 2-L flask a suspension of potassium hydride (7.82 g, 35% in mineral oil, pentane washed (2 × 75 mL), 195 mmol) in THF (150 mL) was stirred at 25 °C, and a solution of (*R*)-(−)-2-phenylglycinol (**19**) (25.0 g, 182.2 mmol) in THF (370 mL) was added dropwise over 2.5 h via an oven-dried 500-mL pressure-equalizing addition funnel. The resultant pale yellow mixture was stirred overnight and then treated dropwise over 2 h with a solution of methyl iodide (25.2 g, 177.6 mmol) in THF (220 mL). The mixture was stirred for an additional 3 h, poured into cold brine (1.5 L), and extracted with diethyl ether (4 × 250 mL), and the combined organic solutions were dried (Na_2SO_4), filtered, and concentrated. Distillation afforded **29** (25.3 g, 94% yield) as a colorless oil: bp 47−50 °C, 0.2 mmHg; $[\alpha]_D^{25}$ −49° (*c* 6.3, benzene); IR ($CHCl_3$) 3380 (w), 3040 (w), 3000 (w), 2900 (m), 2240 (m), 1580 (m), 1460 (m), 1200 (m), 1120 (s), 905 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.7, 1.6 Hz, 2 H), 7.35 (t, *J* = 7.3 Hz, 2 H), 7.30 (m, 1 H), 4.21 (dd, *J* = 8.7, 3.9 Hz, 1 H), 3.53 (dd, *J* = 9.3, 3.9 Hz, 1 H), 3.41 (s, 3 H), 3.39 (t, *J* = 9.1 Hz, 1 H), 1.75 (br s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.3 (2 C), 127.3, 126.7 (2 C), 78.9, 58.8, 55.4; high-resolution mass spectrum (CI, CH_4) *m/z* 152.1069 [(M + H)$^+$; calcd for $C_9H_{14}NO$ 152.1075].

Cyclohexyl Phosphite Adduct (−)-33a. A solution of amine (−)-**29** (1.80 g, 11.9 mmol) in dry benzene (25 mL) was cooled to 0 °C and treated dropwise with cyclohexanecarboxaldehyde (1.33 g, 11.9 mmol). The mixture was warmed to room temperature, and anhydrous Na_2SO_4 (12 g) was added. The mixture was then stirred for 1.5 h, filtered, and concentrated, affording the crude imine **31a** (R = cyclohexyl) (2.83 g, 97% yield) as a colorless oil. A solution of freshly distilled diethyl phosphite (3.18 g, 23.1 mmol) in THF (15 mL) was cooled to 0 °C and treated dropwise with *n*-BuLi (1.59 M in hexanes, 6.90 mL, 11.0 mmol). The mixture was stirred for 0.5 h, warmed to room temperature, and added via a cannula to a solution of the crude imine (2.83 g, 11.5 mmol) in THF (22 mL) at ambient temperature. The reaction mixture was stirred for 20 h and then quenched with H_2O (20 mL). Most of the THF was removed in vacuo, and the aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (gradient elution, 50% → 67% EtOAc/hexanes) gave **33a** (3.38g, 80% yield) as a colorless oil: 96% de (500-MHz ^1H NMR); $[\alpha]_D^{25}$ −77.5° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3335 (w), 3000 (s), 2920 (s), 1455 (m), 1395 (w), 1230 (s), 1150 (s), 1025 (s), 970 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 6.9 Hz, 2 H), 7.31 (t, *J* = 7.1 Hz, 2 H), 7.25 (m, 1 H), 4.41 (dt, *J* = 9.6, 3.9 Hz, 1 H), 4.17−4.04 (m, 4 H), 3.43 (t, *J* = 9.8 Hz, 1 H), 3.38 (s, 3 H), 3.35 (dd, *J* = 9.6, 3.9 Hz, 1 H), 2.56 (dd, J_{HP} = 12.2 Hz, J_{HH} = 3.0 Hz, 1 H), 1.81−1.60 (m, 5 H), 1.51 (qd, *J* = 11.7, 2.1 Hz, 1 H), 1.35 (q, *J* = 7.0 Hz, 3 H), 1.33 (q, *J* = 7.0 Hz, 3 H), 1.28−1.15 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 128.4 (2 C), 128.1 (2 C), 127.6, 78.0, 61.6 (d, J_{CP} = 7.0 Hz), 60.9 (d, J_{CP} = 7.4 Hz), 59.8, 58.4, 56.5 (d, J_{CP} = 130 Hz), 39.5 (d, J_{CP} = 5.6 Hz), 30.9 (d, J_{CP} = 13.7 Hz), 27.5, 26.6, 26.4, 26.1, 16.6 (d, J_{CP} = 5.9 Hz), 16.5 (d, J_{CP} = 5.9 Hz); high-resolution mass spectrum (CI, CH_4) *m/z* 384.2287 [(M + H)$^+$; calcd for $C_{20}H_{35}NO_4P$ 384.2303]. Anal. Calcd for $C_{20}H_{34}NO_4P$: C, 62.64; H, 8.94; N, 3.65. Found: C, 62.78; H, 9.19; N, 3.85.

Cyclohexylmethyl Phosphite Adduct (−)-33b. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (180.4 mg, 1.193 mmol) cyclohexylacetaldehyde (153.0 mg, 1.212 mmol) and Na_2SO_4 (1.5 g) afforded imine **31b** (R = cyclohexylmethyl) (276.5 mg, 89% yield) as a colorless oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (294.4 mg, 2.132 mmol) and *n*-BuLi (1.59 M, 0.64 mL, 1.0 mmol), provided **33b** (280.7 mg, 70% yield) after flash chromatography (60% EtOAc/hexanes) as a colorless oil: 98.3% de (GC); $[\alpha]_D^{25}$ −93° (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3305 (br, m), 3000 (m), 2850 (s), 2840 (m), 1450 (m), 1230 (s), 1100 (m), 1050 (s), 1025 (s), 960 (s), 910 (s), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.2 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.25 (m, 1 H), 4.50 (dt, *J* = 9.4, 3.8 Hz, 1 H), 4.18−4.07 (m, 4 H), 3.45 (t, *J* = 9.6 Hz, 1 H), 3.38 (s, 3 H), 3.37 (dd, *J* = 9.7, 3.8 Hz, 1 H), 2.69 (ddd, J_{HP} = 10.5 Hz, J_{HH} = 8.5, 3.0 Hz, 1 H), 2.10 (br s, 1 H), 1.68−1.48 (m, 6 H), 1.42 (m, 1 H), 1.35 (q, *J* = 7.0 Hz, 3 H), 1.33 (q, *J* = 7.0 Hz, 3 H), 1.26 (m, 1 H), 1.06 (m, 3 H), 0.89 (qd, *J* = 8.8, 3.2 Hz, 1 H), 0.47 (qd, *J* = 7.8, 3.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 128.3 (2 C), 128.2 (2 C), 127.6, 77.6, 61.8 (d, J_{CP} = 7.4 Hz), 61.4 (d, J_{CP} = 7.1 Hz), 59.6, 58.4, 48.4 (d, J_{CP} = 138 Hz), 38.7, 34.4, 32.9 (d, J_{CP} = 12.5 Hz), 31.6, 26.5 (d, J_{CP} = 6.1 Hz), 25.9, 16.6 (d, J_{CP} = 5.7 Hz), 16.5 (d, J_{CP} = 5.6 Hz); high-resolution mass spectrum (CI, CH_4) *m/z* 398.2453 [(M + H)$^+$; calcd for $C_{21}H_{37}NO_4P$ 398.2460]. Anal. Calcd for $C_{21}H_{36}NO_4P$: C, 63.46; H, 9.13; N, 3.52. Found: C, 63.62; H, 9.39; N, 3.48.

Isopropyl Phosphite Adduct (−)-33c. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (207.9 mg, 1.375 mmol) with isobutyraldehyde (99.0 mg, 1.38 mmol) and Na_2SO_4 (1.5 g) afforded imine **31c** (R = isopropyl) (231.5 mg, 82% yield) as a colorless oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (311.4 mg, 2.255 mmol) and *n*-BuLi (1.59 M, 0.67 mL, 1.1 mmol), for 18 h provided **33c** (301.3 mg, 82% yield) after flash chromatography (50% EtOAc/hexanes) as a colorless oil: 96.5% de (GC); $[\alpha]_D^{25}$ −111° (*c* 3.3, $CHCl_3$); IR ($CHCl_3$) 3360 (br, w), 3000 (s), 2920 (m), 2900 (m), 1460 (m), 1240 (m), 1120 (m), 1095 (m), 1060 (s), 1030 (s), 960 (s), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.0 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.25 (m, 1 H), 4.43 (dt, *J* = 9.7, 3.8 Hz, 1 H), 4.18−4.06 (m, 4 H), 3.45 (t, *J* = 9.7 Hz, 1 H), 3.38 (s, 3 H), 3.35 (dd, *J* = 9.8, 3.8 Hz, 1 H), 2.57 (dd, J_{HP} = 12.2 Hz, J_{HH} = 2.9 Hz, 1 H), 2.25 (br s, 1 H), 2.06 (m, 1 H), 1.34 (q, *J* = 6.0 Hz, 6 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 128.4 (2 C), 128.1 (2 C), 127.6, 77.8, 61.5 (d, J_{CP} = 7.2 Hz), 60.9 (d, J_{CP} = 7.5 Hz), 59.7, 58.3, 56.3 (d, J_{CP} = 131 Hz), 29.1 (d, J_{CP} = 5.8 Hz), 20.8 (d, J_{CP} = 14.9 Hz), 17.2 (d, J_{CP} = 1.6 Hz), 16.5 (d, J_{CP} = 5.8 Hz), 16.4 (d, J_{CP} = 5.9 Hz); high-resolution mass spectrum (CI, CH_4) *m/z* 344.2006 [(M + H)$^+$; calcd for $C_{17}H_{31}NO_4P$ 344.1990]

Isobutyl Phosphite Adduct (−)-33d. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (155.0 mg, 1.026 mmol) with isovaleraldehyde (88.3 mg, 1.03 mmol) and Na_2SO_4 (1.5 g) afforded imine **31d** (R = isobutyl) (189.9 mg, 82% yield) as a pale yellow oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (239.0 mg, 1.732 mmol) and *n*-BuLi (1.59 M, 0.52 mL, 0.82 mmol), for 18 h provided **33d** (252.1 mg, 81% yield) after flash chromatography (60% EtOAc/hexanes) as a colorless oil: >98.3% de (GC); $[\alpha]_D^{25}$ −102° (*c* 2.05, $CHCl_3$); IR ($CHCl_3$) 3340 (br, w), 2985 (s), 2960 (s), 2940 (s), 1460 (m), 1390 (w), 1370 (w), 1230 (s), 1050 (s), 1030 (s), 970 (s), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.2 Hz, 2 H), 7.30 (t, *J* = 7.6 Hz, 2 H), 7.27 (m, 1 H), 4.54 (dt, *J* = 9.4, 3.9 Hz, 1 H), 4.19−4.09 (m, 4 H), 3.46 (t, *J* = 9.6 Hz, 1 H), 3.40 (s, 3 H), 3.38 (t, *J* = 3.9 Hz, 1 H), 2.69 (ddd, J_{HP} = 9.1 Hz, J_{HH} = 7.9, 6.7 Hz, 1 H) , 2.12 (br s, 1 H), 1.95 (m, *J* = 6.5 Hz, 1 H), 1.41 (q, *J* = 7.6

Hz, 2 H), 1.37 (m, J = 7.0 Hz, 6 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.51 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 128.3 (2 C), 128.2 (2 C), 127.6, 77.7, 61.8 (d, J_{CP} = 7.0 Hz), 61.4 (d, J_{CP} = 7.0 Hz), 59.5, 58.4, 49.4 (d, J_{CP} = 138 Hz), 40.5, 23.7 (d, J_{CP} = 7.7 Hz), 23.6 (d, J_{CP} = 4.7 Hz), 20.7, 16.6 (d, J_{CP} = 5.8 Hz), 16.5 (d, J_{CP} = 5.8 Hz); high-resolution mass spectrum (CI, CH_4) m/z 358.2132 [(M + H)$^+$; calcd for $C_{18}H_{33}NO_4P$ 358.2147]. Anal. Calcd for $C_{18}H_{32}NO_4P$: C, 60.49; H, 9.02; N, 3.92. Found: C, 60.70; H, 9.21; N, 3.80.

Methyl Phosphite Adduct (−)-33e. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (202.0 mg, 1.33 mmol) with acetaldehyde (0.3 mL, 5.37 mmol) and Na_2SO_4 (1.5 g) afforded imine **31e** (R = methyl) (212.0 mg, 90% yield) as a colorless oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (330.5 mg, 2.393 mmol) and n-BuLi (1.59 M, 0.72 mL, 1.1 mmol), for 21 h provided **33e** (274.5 mg, 77% yield) after flash chromatography (gradient elution, 50% → 67% EtOAc/hexanes) as a colorless oil: 95.2% de (GC); $[\alpha]_D^{25}$ −83° (c 2.5, $CHCl_3$); IR ($CHCl_3$) 3335 (w), 3000 (s), 2920 (s), 1455 (m), 1395 (w), 1230 (s), 1150 (s), 1025 (s), 970 (s), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.5, 1.4 Hz, 2 H), 7.32 (dt, J = 7.6, 1.5 Hz, 2 H), 7.27 (m, 1 H), 4.40 (td, J = 6.2, 2.7 Hz, 1 H), 4.13 (m, 4 H), 3.38 (d, J = 5.9 Hz, 2 H), 3.37 (s, 3 H), 2.83 (dq, J_{HP} = 9.8 Hz, J_{HH} = 7.3 Hz, 1 H), 2.27 (br s, 1 H), 1.33 (q, J = 6.8 Hz, 6 H), 1.23 (dd, J_{HP} = 16.9 Hz, J_{HH} = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 128.3 (2 C), 127.7 (2 C), 127.5, 77.8, 61.9 (d, J_{CP} = 7 Hz), 61.6 (d, J_{CP} = 7 Hz), 60.3, 58.4, 47.9, 46.8, 17.4, 16.54, 16.52, 16.50, 16.4; high-resolution mass spectrum (CI, CH_4) m/z 316.1689 [(M + H)$^+$; calcd for $C_{15}H_{27}NO_4P$ 316.1677]. Anal. Calcd for $C_{15}H_{26}NO_4P$: C, 57.13; H, 8.31; N, 4.44. Found: C, 56.96; H, 8.58; N, 4.35.

***n*-Hexyl Phosphite Adduct (−)-33f.** Via the procedure described above for **33a**, the reaction of amine (−)-**29** (110.5 mg, 0.731 mmol) with n-heptanal (83.4 mg, 0.731 mmol) and Na_2SO_4 (1.5 g) afforded imine **31f** (R = n-hexyl) (172.2 mg, 95% yield) as a colorless oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (192.3 mg, 1.392 mmol) and n-BuLi (1.59 M, 0.42 mL, 0.66 mmol), for 23 h provided **33f** (208.2 mg, 78% yield) after flash chromatography (gradient elution, 50% → 67% EtOAc/hexanes) as a colorless oil: 96% de (500-MHz ^{1}H NMR); $[\alpha]_D^{25}$ −81° (c 1.8, $CHCl_3$); IR ($CHCl_3$) 3325 (br, w), 3000 (s), 2920 (s), 1460 (m), 1390 (s), 1230 (s), 1120 (m), 1100 (s), 1055 (s), 1030 (s), 970 (s), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.3 Hz, 2 H), 7.31 (t, J = 7.2 Hz, 2 H), 7.25 (m, 1 H), 4.48 (dt, J = 9.3, 3.8 Hz, 1 H), 4.15−4.07 (m, 4 H), 3.42 (t, J = 9.6 Hz, 1 H), 3.37 (s, 3 H), 3.35 (m, 1 H), 2.62 (ddd, J_{HP} = 9.7 Hz, J_{HH} = 9.7, 3.4 Hz, 1 H), 2.13 (br s, 1 H), 1.66 (m, 1 H), 1.55 (m, 1 H), 1.42 (m, 1 H), 1.33 (q, J = 7.1 Hz, 6 H), 1.28−1.16 (m, 5 H), 1.10 (m, 2 H), 0.86 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 128.2 (2 C), 128.1 (2 C), 127.5, 77.8, 61.7 (d, J_{CP} = 7.2 Hz), 61.3 (d, J_{CP} = 7.3 Hz), 59.7, 58.4, 51.2 (d, J_{CP} = 137 Hz), 31.7, 31.2, 28.9, 25.9 (d, J_{CP} = 11.7 Hz), 22.6, 16.57 (d, J_{CP} = 5.7 Hz), 16.52 (d, J_{CP} = 5.6 Hz), 14.0; high-resolution mass spectrum (CI, CH_4) m/z 386.2472 [(M + H)$^+$; calcd for $C_{20}H_{37}NO_4P$ 386.2460]. Anal. Calcd for $C_{20}H_{36}NO_4P$: C, 62.32; H, 9.41; N, 3.63. Found: C, 62.61; H, 9.44; N, 3.53.

2-(Methylthio)ethyl Phosphite Adduct (−)-33g. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (207.2 mg, 1.370 mmol) with 3-(methylthio)propionaldehyde (142.7 mg, 1.370 mmol) and Na_2SO_4 (1.5 g) afforded imine **31g** (R = 2-(methylthio)ethyl) (264.0 mg, 82% yield) as a colorless oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (307.2 mg, 2.224 mmol) and n-BuLi (1.59 M, 0.66 mL, 1.1 mmol), for 18 h generated **33g** (273.6 mg, 69% yield) after flash chromatography (50% EtOAc/hexanes) as a colorless oil: 96.5% de (GC); $[\alpha]_D^{25}$ −93° (c 2.8, $CHCl_3$); IR ($CHCl_3$) 3320 (br, w), 3000 (s), 2910 (s), 1460 (m), 1410 (w), 1240 (s), 1110 (s), 1050 (s), 1025 (s), 965 (s), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.0 Hz, 2 H), 7.32 (t, J = 7.3 Hz, 2 H), 7.28 (m, 1 H), 4.50 (dt, J = 9.6, 3.8 Hz, 1 H), 4.17−4.08 (m, 4 H), 3.41 (t, J = 9.8 Hz, 1 H), 3.38 (s, 3 H), 3.35 (dd, J = 9.8, 3.6 Hz, 1 H), 2.79 (ddd, J_{HP} = 10.3 Hz, J_{HH} = 10.3, 3.4 Hz, 1 H), 2.75 (m, 1 H), 2.43 (dt, J = 7.7, 4.9 Hz, 1 H), 2.24 (br s, 1 H), 1.99 (s, 3 H), 1.96 (m, 1 H), 1.68 (m, 1 H), 1.34 (q, J = 7.6 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 128.3 (2 C), 128.1 (2 C), 127.7, 77.7, 61.8 (d, J_{CP} = 7.5 Hz), 61.5 (d, J_{CP} = 6.6 Hz), 59.7, 58.4, 50.2 (d, J_{CP} = 138 Hz), 30.9 (d, J_{CP} = 4.6 Hz), 30.8 (d, J_{CP} = 14.9 Hz), 16.5 (d, J_{CP} = 5.4 Hz, 2 C), 15.0; high-resolution mass spectrum (CI, CH_4) m/z 376.1703 [(M + H)$^+$; calcd for $C_{17}H_{31}NO_4PS$ 376.1711].

(Benzyloxy)methyl Phosphite Adduct (−)-33h. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (153.0 mg, 1.012 mmol) with α-(benzyloxy)acetaldehyde[33] (152.0 mg, 1.012 mmol) and Na_2SO_4 (1.5 g) afforded imine **31h** [R = (benzyloxy)methyl] (263.2 mg, 92% yield) as a colorless oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (256.5 mg, 1.858 mmol) and n-BuLi (1.59 M, 0.55 mL, 0.88 mmol), for 21 h furnished **33h** (140.0 mg, 38% yield) after flash chromatography (67% EtOAc/hexanes) as a colorless oil: 96% de (500-MHz ^{1}H NMR); $[\alpha]_D^{25}$ −49° (c 0.65, $CHCl_3$); IR ($CHCl_3$) 3325 (br, w), 2995 (s), 2900 (m), 1465 (m), 1240 (s), 1100 (s), 1055 (s), 1025 (s), 960 (m), 695 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 6.8 Hz, 2 H), 7.32 (s, 5 H), 7.27 (m, 3 H), 4.46 (d, 2 H), 4.40 (dt, J = 6.6, 3.1 Hz, 1 H), 4.16−4.07 (m, 4 H), 3.69 (m, 1 H), 3.63 (dd, J = 9.6, 3.7 Hz, 1 H), 3.43 (t, J = 8.4 Hz, 1 H), 3.39 (dd, J = 8.3, 4.5 Hz, 1 H) , 3.36 (s, 3 H), 3.01 (ddd, J_{HP} = 12.7 Hz, J_{HH} = 5.8, 3.8 Hz, 1 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.27 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 138.1, 128.4 (2 C), 128.2 (2 C), 128.0 (2 C), 127.6 (2 C), 127.6, 127.5, 77.9, 73.1, 70.6, 61.9 (d, J_{CP} = 7.4 Hz, 2 C), 60.1, 58.6, 52.8 (d, J_{CP} = 142 Hz), 16.5 (d, J_{CP} = 5.8 Hz), 16.4 (d, J_{CP} = 5.8 Hz); high-resolution mass spectrum (CI, CH_4) m/z 422.2103 [(M + H)$^+$; calcd for $C_{22}H_{33}NO_5P$ 422.2096].

2-(*tert*-Butoxycarbonyl)ethyl Phosphite Adduct (−)-33i. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (120.8 mg, 0.799 mmol) with *tert*-butyl 4-oxobutanoate[34] (126.3 mg, 0.799 mmol) and Na_2SO_4 (1.5 g) afforded imine **31i** [R = 2-(*tert*-butoxycarbonyl)ethyl] (213.0 mg, 92% yield) as a colorless oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (202.0 mg, 1.462 mmol) and n-BuLi (1.59 M, 0.44 mL, 0.70 mmol), for 23.5 h gave **33i** (110.7 mg, 37% yield) after flash chromatography (60% EtOAc/hexanes) as a colorless oil: 96% de (500-MHz ^{1}H NMR); $[\alpha]_D^{25}$ −42° (c 2.2, $CHCl_3$); IR ($CHCl_3$) 3420 (br, w), 2985 (s), 2940 (s), 1730 (s), 1465 (m), 1400 (m), 1370 (m), 1240 (s), 1160 (s), 1040 (s), 970 (s), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.1 Hz, 2 H), 7.33 (t, J = 7.1 Hz, 2 H), 7.26 (m, 1 H), 4.54 (dt, J = 9.6, 3.8 Hz, 1 H), 4.17−4.08 (m, 4 H), 3.41 (t, J = 9.8 Hz, 1 H), 3.37 (s, 3 H), 3.31 (td, J = 9.8, 3.8 Hz, 1 H), 2.63 (ddd, J_{HP} = 10.0 Hz, J_{HH} = 10.0, 3.8 Hz, 1 H), 2.48 (m, 1 H), 2.24 (p, J = 3.6 Hz, 1 H), 2.20 (br s, 1 H), 1.96 (m, 1 H), 1.71 (m, 1 H), 1.36 (s, 9 H), 1.32 (q, J = 7.6 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 140.0, 128.4 (2 C), 128.2 (2 C), 127.7, 80.0, 77.8, 61.9 (d, J_{CP} = 7.3 Hz), 61.4 (d, J_{CP} = 5.3 Hz), 59.0, 58.4, 50.8 (d, J_{CP} = 137 Hz), 32.3 (d, J_{CP} = 12.9 Hz), 28.0 (3 C), 26.4 (d, J_{CP} = 5.3 Hz), 16.5 (d, J_{CP} = 6.1 Hz, 2 C), 15.0; high-resolution mass spectrum (CI, CH_4) m/z 430.2367 [(M + H)$^+$; calcd for $C_{21}H_{37}NO_6P$ 430.2358]. Anal. Calcd for $C_{21}H_{36}NO_6P$: C, 58.73; H, 8.45; N, 3.26. Found: C, 58.49; H, 8.65; N, 3.19.

Phenyl Phosphite Adduct (−)-33j. Via the procedure described above for **33a**, the reaction of amine (−)-**29** (104.0 mg, 0.688 mmol) with benzaldehyde (73.0 mg, 0.688 mmol) and Na_2SO_4 (1.5 g) for 6 h afforded imine **33j** (R = phenyl) (129.2 mg, 82% yield) as a pale yellow oil. Treatment with $LiPO_3Et_2$, prepared from diethyl phosphite (155.6 mg, 1.127 mmol) and n-BuLi (1.59 M, 0.34 mL, 0.54 mmol), for 48 h furnished **33i** (186.8 mg, 90% yield) after flash chromatography (gradient elution, 60% → 67% EtOAc/hexanes) as a colorless oil: 76% de (500-MHz ^{1}H NMR). Analytical data for a 9.3:1 diastereomeric mixture obtained from repurification with the eluent indicated: $[\alpha]_D^{25}$ −86° (c 2.1, $CHCl_3$); IR ($CHCl_3$) 3310 (br, w), 3000 (s), 2905 (m), 1495 (m), 1460 (m), 1240 (s), 1105 (m), 1030 (s), 970 (s), 910 (m), 700 (m), 555 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 10 H), 4.21 (m, 2 H), 3.87 (dq, J_{HP} = 10.1 Hz, J_{HH} = 7.1 Hz, 1 H), 3.76 (d, J_{HP} = 24.9 Hz, 1 H), 3.70 (dq, J = 9.5, 1.8 Hz, 1 H), 3.65 (m, 1 H), 3.44 (t, J = 9.5 Hz, 1 H), 3.32 (dd, J = 9.5, 1.0 Hz, 1 H), 3.28 (s, 3 H), 1.34 (t, J = 7.1 Hz, 3 H), 1.04 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 136.0, 128.6, 128.5 (2 C), 128.0 (2 C),

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127.8, 127.7, 127.6, 77.3, 62.9 (d, J_{CP} = 6.9 Hz), 62.5 (d, J_{CP} = 6.6 Hz), 58.9, 58.6, 57.3 (d, J_{CP} = 158 Hz), 16.5 (d, J_{CP} = 6.3 Hz), 16.1 (d, J_{CP} = 6.2 Hz); high-resolution mass spectrum (CI, CH_4) *m/z* 378.1830 [(M + H)$^+$; calcd for $C_{20}H_{29}NO_4P$ 378.1834]. Anal. Calcd for $C_{20}H_{28}NO_4P$: C, 63.65; H, 7.48; N, 3.71. Found: C, 63.48; H, 7.44; N, 3.60.

Cyclohexyl α-Amino Phosphonate (−)-15a. Phosphite adduct (−)-**33a** (R = cyclohexyl) (19.12 g, 49.83 mmol) was dissolved in absolute ethanol (400 mL), and 20% palladium hydroxide on carbon (21.0 g) was added. The flask was connected to a hydrogenation apparatus equipped with a graduated buret containing water to monitor uptake of hydrogen. The mixture was thoroughly degassed at aspirator pressure and back-filled with hydrogen (3×). The mixture was stirred under hydrogen (1 atm) at room temperature for 15 h and then degassed at aspirator pressure. After filtration through Celite, washing with EtOH (3 × 50 mL), and concentration, flash chromatography (gradient elution, 5% → 10% MeOH/CH_2Cl_2) afforded **15a** (11.97 g, 94% yield) as a colorless oil: $[\alpha]_D^{25}$ −52° (*c* 1.3, acetone); IR ($CHCl_3$) 3000 (br, m), 2950 (m), 2875 (m), 1605 (w), 1520 (w), 1455 (w), 1230 (m), 1100 (s), 980 (w), 620 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (m, 4 H), 2.83 (dd, J_{HP} = 14.3 Hz, J_{HH} = 4.3 Hz, 1 H), 2.00−1.00 (m, 11 H) 1.34 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.6, 61.5, 60.1, 53.9 (d, J_{CP} = 145 Hz), 53.8, 38.9, 30.5, 30.4, 27.5, 27.4, 26.2, 25.9, 25.8, 16.3, 16.2, 13.9; high-resolution mass spectrum (CI, CH_4) *m/z* 250.1598 [(M + H)$^+$; calcd for $C_{11}H_{25}NO_3P$ 250.1572].

Cyclohexylmethyl α-Amino Phosphonate (−)-15b. Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33b** (R = cyclohexylmethyl) (89.0 mg, 0.224 mmol) with 20% $Pd(OH)_2$/C (80 mg) as catalyst gave **15b** (51.2 mg, 87% yield) after flash chromatography (5% MeOH/CH_2Cl_2) as a colorless oil: $[\alpha]_D^{25}$ −21° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3360 (br, m), 3000 (m), 2950 (s), 2850 (m), 1425 (m), 1390 (s), 1235 (s), 1060 (s), 1040 (s), 965 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (m, 4 H), 3.08 (t, *J* = 11.8 Hz, 1 H), 1.79−1.57 (m, 7 H), 1.45 (q, *J* = 10.0 Hz, 1 H), 1.34 (t, *J* = 7.0 Hz, 6 H), 1.32−1.11 (m, 3 H), 0.98 (qd, *J* = 9.6, 3.1 Hz, 1 H), 0.84 (dq, *J* = 9.6, 3.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.1, 62.0, 61.9, 45.9 (d, J_{CP} = 149 Hz), 38.5, 34.3, 33.5, 33.4, 31.8, 26.5, 26.3, 26.0, 16.5 (d, J_{CP} = 5.5 Hz); high-resolution mass spectrum (CI, CH_4) *m/z* 264.1722 [(M + H)$^+$; calcd for $C_{12}H_{27}NO_3P$ 264.1728].

Isopropyl α-Amino Phosphonate (−)-15c. Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33c** (R = isopropyl) (78.4 mg, 0.228 mmol) with 20% $Pd(OH)_2$/C (75 mg) as catalyst gave **15c** (41.0 mg, 86% yield) after flash chromatography (5% MeOH/CH_2Cl_2) as a colorless oil: $[\alpha]_D^{25}$ −0.8° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3680 (br, w), 3400 (w), 3000 (s), 1470 (w), 1390 (w), 1220 (s), 1050 (s), 1030 (s), 960 (s), 750 (br, m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20−4.11 (m, 4 H), 2.85 (dd, J_{HP} = 14.2 Hz, J_{HH} = 4.2 Hz, 1 H), 2.13 (m, 1 H), 1.36 (t, *J* = 7.0 Hz, 6 H), 1.06 (d, *J* = 6.1 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.8 (d, J_{CP} = 7.5 Hz, 2 C), 54.2 (d, J_{CP} = 146 Hz), 29.1, 20.7, 20.6, 17.3 (d, J_{CP} = 4.7 Hz), 16.5 (d, J_{CP} = 5.7 Hz); high-resolution mass spectrum (CI, CH_4) *m/z* 210.1263 [(M + H)$^+$; calcd for $C_8H_{21}NO_3P$ 210.1259].

Isobutyl α-Amino Phosphonate (−)-15d. Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33d** (R = isobutyl) (82.7 mg, 0.231 mmol) with 20% $Pd(OH)_2$/C (83 mg) as catalyst gave **15d** (42.9 mg, 89% yield) after flash chromatography (gradient elution, 2% → 5% MeOH/CH_2Cl_2) as a colorless oil: $[\alpha]_D^{25}$ −21° (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3690 (br, w), 3000 (s), 2940 (m), 1470 (w), 1390 (m), 1230 (s), 1040 (s), 965 (s), 780 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (m, 4 H), 3.04 (ddd, J_{HP} = 10.8 Hz, J_{HH} = 10.8, 3.7 Hz, 1 H), 1.91 (m, *J* = 1.4 Hz, 1 H), 1.56 (br s, 2 H), 1.50 (m, 2 H), 1.34 (td, J_{HH} = 7.0 Hz, J_{HP} = 1.8 Hz, 6 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.1 (d, J_{CP} = 7.1 Hz), 62.0 (d, J_{CP} = 7.0 Hz), 46.7 (d, J_{CP} = 148.3 Hz), 39.9, 24.1 (d, J_{CP} = 13.3 Hz), 23.5, 21.0, 16.5 (d, J_{CP} = 4.5 Hz, 2 C); high-resolution mass spectrum (CI, CH_4) *m/z* 224.1419 [(M + H)$^+$; calcd for $C_9H_{23}NO_3P$ 224.1415]. Anal. Calcd for $C_9H_{22}NO_3P$: C, 48.42; H, 9.93; N, 6.28. Found: C, 48.60; H, 9.93; N, 6.23.

Methyl α-Amino Phosphonate (−)-15e. Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33e** (R = methyl) (86.0 mg, 0.270 mmol) and 20% $Pd(OH)_2$/C (86 mg) as catalyst gave **15e** (49.0 mg, 99% yield) after flash chromatography (gradient elution, 5% → 10% MeOH/$CHCl_3$) as a colorless oil: $[\alpha]_D^{25}$ −5.4° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3390 (br, w), 2995 (s), 1440 (w), 1230 (m), 1060 (s), 1025 (s), 970 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (m, 4 H), 3.12 (m, 1 H), 1.68 (br s, 2 H), 1.35 (t, *J* = 7.3 Hz, 6 H), 1.34 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.0 (d, J_{CP} = 6.9 Hz), 61.9 (d, J_{CP} = 6.8 Hz), 44.1 (d, J_{CP} = 150 Hz), 17.2, 16.5 (d, J_{CP} = 5.5 Hz, 2 C); high-resolution mass spectrum (CI, CH_4) *m/z* 182.0951 [(M + H)$^+$; calcd for $C_6H_{17}NO_3P$ 182.0946].

***n*-Hexyl α-Amino Phosphonate (−)-15f.** Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33f** (R = *n*-hexyl) (86.0 mg, 0.270 mmol) with 20% $Pd(OH)_2$/C (86 mg) as catalyst gave **15f** (49.0 mg, 99% yield) after flash chromatography (5% MeOH/$CHCl_3$) as a colorless oil: $[\alpha]_D^{25}$ −12.2° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3380 (br, w), 3000 (s), 2965 (s), 2940 (s), 1470 (w), 1385 (w), 1225 (s), 1055 (s), 1030 (s), 960 (s), 800 (br, m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19−4.12 (m, 4 H), 2.95 (ddd, J_{HP} = 10.2 Hz, J_{HH} = 10.2, 2.8 Hz, 1 H), 1.80 (m, 1 H), 1.60 (m, 1 H), 1.45 (m, 1 H), 1.35 (q, *J* = 6.4 Hz, 6 H), 1.30 (m, 7 H), 0.90 (t, *J* = 4.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.2 (d, J_{CP} = 7.6 Hz), 62.1 (d, J_{CP} = 6.9 Hz), 49.0 (d, J_{CP} = 149 Hz), 31.9, 31.5, 29.3, 26.4 (d, J_{CP} = 12.7 Hz), 22.8, 16.8 (d, J_{CP} = 5.4 Hz, 2 C), 14.3; high-resolution mass spectrum (CI, CH_4) *m/z* 252.1727 [(M + H)$^+$; calcd for $C_{11}H_{27}NO_3P$ 252.1728].

2-(Methylthio)ethyl α-Amino Phosphonate (−)-15g. A suspension of palladium black (120 mg) in glacial acetic acid (1 mL) was flushed with hydrogen and stirred under hydrogen (1 atm) for 0.5 h at room temperature, and a solution of phosphite adduct (−)-**33g** [R = 2-(methylthio)ethyl] (31.0 mg, 0.083 mmol) in glacial acetic acid (0.5 mL) was added. The resultant mixture was stirred under hydrogen for 48 h and then degassed at aspirator pressure. Following removal of the catalyst by filtration through Celite, concentration and flash chromatography (gradient elution, 5 → 10% MeOH/CH_2Cl_2) afforded **15g** (12 mg, 60% yield) and unreacted **33g** (10 mg) as colorless oils. Data for **15g**: $[\alpha]_D^{25}$ −22° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3390 (br, w), 2990 (s), 2925 (m), 1445 (w), 1235 (s), 1055 (s), 1030 (s), 965 (s), 790 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19−4.11 (m, 4 H), 3.16 (ddd, J_{HP} = 10.1 Hz, J_{HH} = 10.1, 3.8 Hz, 1 H), 2.75 (m, 1 H), 2.68 (dt, *J* = 13.1, 8.0 Hz, 1 H), 2.11 (s, 3 H), 2.08 (m, 1 H), 1.88 (br s, 2 H), 1.75 (m, 1 H), 1.34 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.2 (d, J_{CP} = 6.9 Hz), 62.1 (d, J_{CP} = 7.0 Hz), 47.3 (d, J_{CP} = 149 Hz), 30.7 (d, J_{CP} = 14.4 Hz), 30.4, 16.5 (d, J_{CP} = 5.5 Hz, 2 C), 15.3; high-resolution mass spectrum (CI, CH_4) *m/z* 242.0976 [(M + H)$^+$; calcd for $C_8H_{21}NO_3PS$ 242.0980].

Hydroxymethyl α-Amino Phosphonate (−)-15h. Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33h** [R = (benzyloxy)methyl] (74.8 mg, 0.177 mmol) with 20% $Pd(OH)_2$/C (87 mg) as catalyst gave **15h** (38.0 mg, 100% yield) after flash chromatography (10% MeOH/CH_2Cl_2) as a pale yellow oil: $[\alpha]_D^{25}$ −17.2° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3380 (br, w), 2995 (s), 1520 (w), 1240 (m), 1025 (s), 980 (w), 750 (br, w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (br s, 3 H), 4.27 (m, 4 H), 4.19−4.09 (m, 1 H), 3.98−3.92 (m, 1 H), 3.89−3.82 (m, 1 H), 1.25 (t, *J* = 6.4 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.2, 59.5 (d, J_{CP} = 4.8 Hz, 2 C), 50.5 (d, J_{CP} = 145 Hz), 16.6 (d, J_{CP} = 5.9 Hz, 2 C), 14.3; high-resolution mass spectrum (CI, CH_4) *m/z* 198.0890 [(M + H)$^+$; calcd for $C_6H_{17}NO_4P$ 198.0895].

2-(*tert*-Butoxycarbonyl)ethyl α-Amino Phosphonate (−)-15i. Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33i** [R = 2-(*tert*-butoxycarbonyl)ethyl] (34.7 mg, 0.081 mmol) with 20% $Pd(OH)_2$/C (54 mg) as catalyst gave **15i** (19.8 mg, 83% yield) after flash chromatography (5% MeOH/$CHCl_3$) as a colorless oil: $[\alpha]_D^{25}$ −14° (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) 3400 (br, w), 3000 (s), 1730 (s), 1400 (m), 1370 (m), 1235 (s), 1165 (s), 1060 (s), 1030 (s), 970 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21−4.09 (m, 4 H), 2.97 (ddd, J_{HP} = 10.6 Hz, J_{HH} = 10.6, 4.2 Hz, 1 H), 2.51 (m, 1 H), 2.41 (p, *J* = 7.6 Hz, 1 H), 2.09 (m, 1 H), 1.74 (m, 1 H), 1.44 (m, 1 H), 1.34 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 80.3, 62.1 (d, J_{CP} = 7.0 Hz), 62.0 (d, J_{CP} = 7.1 Hz), 48.1 (d, J_{CP} = 149 Hz), 32.1 (d, J_{CP} = 12.9 Hz), 28.1 (3 C), 26.6, 16.5 (d, J_{CP} = 5.5 Hz, 2 C); high-resolution mass spectrum (CI, CH_4) *m/z* 296.1621 [(M + H)$^+$; calcd for $C_{12}H_{27}NO_5P$ 296.1627].

Phenyl α-Amino Phosphonate (−)-15j. Via the procedure described above for (−)-**15a**, hydrogenolysis of (−)-**33j** (R = phenyl) (82.4 mg, 0.224 mmol) with 20% $Pd(OH)_2$/C (85 mg) as catalyst gave

15j (48.0 mg, 88% yield) after flash chromatography (5% MeOH/$CHCl_3$) as a colorless oil: $[\alpha]_D^{25}$ −13° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3390 (br, w), 3000 (s), 1615 (w), 1465 (m), 1240 (s), 1050 (s), 1020 (s), 965 (m), 800 (m), 700 (m), 550 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.6, 1.9 Hz, 2 H), 7.36 (t, J = 7.4 Hz, 2 H), 7.30 (dd, J = 7.0, 1.4 Hz, 1 H), 4.27 (d, J_{HP} = 17.2 Hz, 1 H), 4.06 (q, J = 7.2 Hz, 2 H), 4.00 (m, 1 H), 3.87 (m, 1 H), 1.84 (br s, 2 H), 1.29 (t, J = 7.0 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 128.4, 127.83, 127.81, 127.7, 127.6, 62.8 (d, J_{CP} = 7.1 Hz), 62.6 (d, J_{CP} = 7.4 Hz), 54.1 (d, J_{CP} = 149 Hz), 16.4 (d, J_{CP} = 5.7 Hz), 16.3 (d, J_{CP} = 5.6 Hz); high-resolution mass spectrum (CI, CH_4) *m/z* 244.1105 [$(M + H)^+$; calcd for $C_{11}H_{19}NO_3P$ 244.1102].

(*R*)-(−)-Phospholeucine (45d). A solution of diethyl phosphonate (−)-**15d** (R = isobutyl) (11.4 mg, 0.051 mmol) in concentrated aqueous HCl (0.3 mL) was heated at 98 °C for 16 h. The mixture was then cooled, concentrated in vacuo, and azeotropically dried with benzene (3 × 5 mL). The residue was dried under vacuum (<1 mmHg) at ambient temperature for 3 h and then dissolved in a minimum of hot (78 °C) absolute ethanol (ca. 2 mL). The solution was cooled to room temperature and treated dropwise with propylene oxide. Filtration furnished **45d** (6.9 mg, 83% yield) as a white solid: mp 281−283 °C; $[\alpha]_D^{25}$ −25° (*c* 0.7, 1 M NaOH) {lit.[35] mp 288−289 °C; $[\alpha]_D^{25}$ −28° (*c* 1, 1 M NaOH)}.

(*R*)-(+)-Phosphomethionine (45g). Via the procedure for **45d** above, hydrolysis of **15g** (R = 2-(methylthio)ethyl) (16.2 mg, 0.067 mmol) gave **45g** (11.8 g, 95% yield) as a pale green, amorphous solid: mp 248−251 °C dec; $[\alpha]_D^{25}$ +39° (*c* 1.1, 0.25 M NaOH) {lit.[36] (*S*)-(−)-phosphomethionine] $[\alpha]_D^{25}$ −40.4° (*c* 1, 0.25 M NaOH)}.

(*R*)-(−)-Phosphoglutamic acid (45i). Via the procedure for **45d** above, hydrolysis of **15i** (R = 2-(*tert*-butoxycarbonyl)ethyl) (19.0 mg, 0.064 mmol) gave **45i** (8.5 mg, 72% yield) as an amorphous white solid: mp 175−177 °C; $[\alpha]_D^{25}$ −7° (*c* 0.7, 1 M NaOH) {lit.[35] mp 183−184 °C; $[\alpha]_D^{25}$ −20° (*c* 1, 1 M NaOH)}.

(*R*)-(+)-Phosphophenylglycine (11). Via the procedure for **45d** above, hydrolysis of **15j** (R = phenyl) (10.0 mg, 0.041 mmol) furnished **11** (4.2 mg, 55% yield) as an amorphous white solid: mp 282−284 °C dec; $[\alpha]_D^{25}$ +17° (*c* 0.42, 1 M NaOH) {lit.[8] $[\alpha]_D^{25}$ +18° (*c* 2, 1 M NaOH)}.

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