Asymmetric Synthesis of Cyclic α-Amino Phosphonates Using Masked Oxo Sulfinimines (*N*-Sulfinyl Imines)

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Five-, six-, and seven-membered cyclic α-amino phosphonates, amino acid surrogates, are prepared in enantiomerically pure form via the highly diastereomeric addition of metal phosphonates to masked oxo sulfinimines. Hydrolysis of the resulting masked oxo α-amino phosphonates followed by reduction of the intermediate cyclic imino phosphonates affords the title compounds in good yield.

The importance of unnatural amino acids in the modification of peptides to improve bioactivity and stability and their utility in peptide therapeutics makes the asymmetric synthesis of α- and *β*-amino phosphonic acids a significant objective. α-Amino phosphonic acids are considered to be surrogates for α-amino acids and as such exhibit a broad range of biological activities.[1] For example, they have found utility as enzyme inhibitors,[2−4] haptens for catalytic antibodies,[5] antibacterial agents,[6,7] anti-HIV agents,[8] and biotrytcides.[9] Proline and homoproline analogues of α-amino phosphonates are inhibitors of dipeptidyl peptidase[4b] and HIV.[8]

While a number of methods have been introduced for the asymmetric synthesis of acyclic α-amino phosphonates,[10] the diastereoselective addition of metal phosphites to aldehyde- and ketone-derived sulfinimines (*N*-sulfinyl imines)[11,12] and the regioselective ring-opening of aziridine 2-phosphonates[13] have proven to be particularly useful. Not only are these methods general, providing access to diversely substituted examples, including quaternary and *β*-hydroxy derivatives, they are also highly efficient, highly diastereoselective, and afford the amino phosphonate with predictable stereochemistry.

Fewer methods are available for the asymmetric synthesis of cyclic α-amino phosphonates. For example, Katritzky and co-workers employed the diastereoselective addition of triethyl phosphite (Arbuzov reaction) to a phenylglycinol-derived chiral oxazolopyrrolidine to prepare **1**, the phosphonate analogue of proline (Scheme 1).[14] This cyclic amino phosphonate has also been prepared, in a series of steps, by reducing one of the nitrogen atoms in a chiral piperidazine 3-phosphonic acid.[15] Several asymmetric syntheses of piperidin-2-ylphosphonate **2** (homoproline analogue) have been reported. These include the cyclization of 5-iodo α-amino phosphonates[16]

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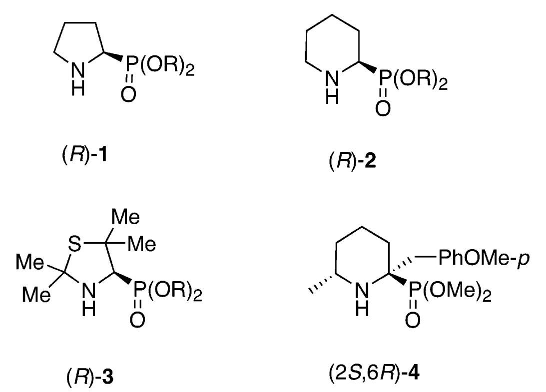
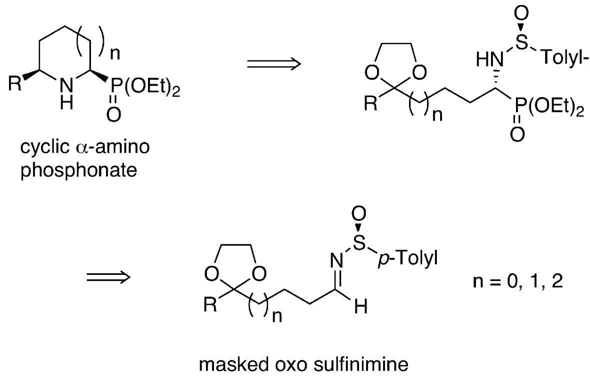
SCHEME 1



SCHEME 2

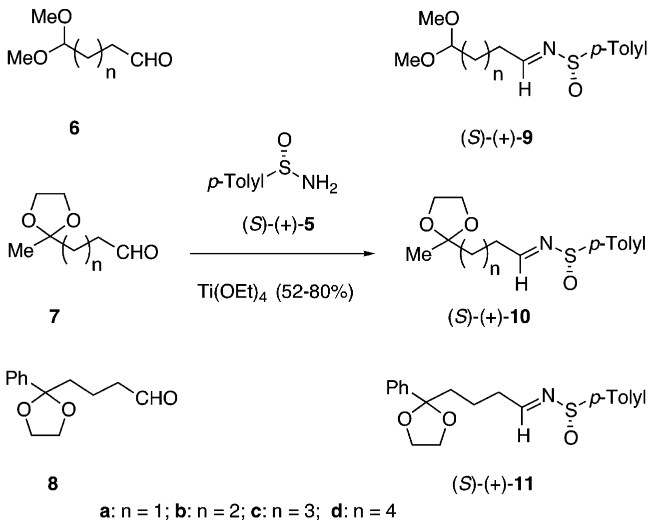


and the treatment of cyano[17] and benzotriazole 6-oxazolopiperidines[18] with phosphites. The enantioselective catalytic hydrophosphonylation of imines to give cyclic amino phosphonates such as **3** has also been reported.[19] Ring-opening of bicyclic aziridines, prepared in the Diels–Alder reaction of dienes and enantiomerically pure 2*H*-azirine 3-phosphonates, affords quaternary piperidine phosphonates such as **4**.[13c] However, many of these procedures are limited by being target specific, lacking in generality, and/or requiring the separation of diastereomeric mixtures having poor de values. Here we report that the highly diastereoselective addition of metal phosphites to masked oxo sulfinimines represents a simple route to stereodefined cyclic α-amino phosphonates derivatives.

Results and Discussion

The general features of our cyclic amino phosphonate synthesis are outlined in Scheme 2. This strategy involves the diastereoselective addition of a metal phosphite to a masked oxo sulfinimine to give the α-amino phosphonate followed by hydrolysis and reduction of an intermediate cyclic imino phosphonate. The sulfinimine-mediated asymmetric Strecker synthesis and this protocol were recently employed in the asymmetric synthesis of proline and pipecolic acid derivatives.[20]

SCHEME 3



Synthesis of Sulfinimines. Masked oxo sulfinimines (*S*)-**9**, (*S*)-**10**, and (*S*)-**11**, new sulfinimine derived polyfunctionalized chiral building blocks,[21] are prepared by condensing commercially available (*S*)-(+)-*p*-toluenesulfinamide (**5**) with the corresponding masked oxo aldehydes **6** to **8** in the presence of 5 equiv of Ti(OEt)$_4$ (Scheme 3).[22] The masked oxo aldehydes were prepared by literature methods that usually involved the careful, −78 °C, DIBAL-H reduction of the corresponding esters.[20]

With the sulfinimines **9**–**11** in hand, treatment with 2 equiv of lithium diethyl phosphite, prepared in situ by reaction of diethylphosphite with LiHMDS, afforded the corresponding α-amino phosphonates **12**–**14** in good to excellent yields (Scheme 4). As summarized in Table 1, the de's for the addition were excellent. The only exceptions were sulfinimines (*S*)-**9c** and (*S*)-**10a** where the diastereoselectivities for **12c** and **13a** were 76 and 88%, respectively (Table 1, entries 3 and 6), and unfortunately, the diastereoisomers were inseparable. In an attempt to improve the de's, the effect of the counterion was evaluated. The use of potassium diethyl phosphite with sulfinimine **10a** afforded the amino phosphate (S_S,R)-**13a** in 98% de and 91% isolated yield (Table 1, entry 8). No improvement in the de was observed for similar additions to **9c** (Table 1, entry 4 and 5).

The stereochemistry at the new stereogenic center is predicted to have the (*R*)-configuration on the basis of our earlier findings.[12c] These findings suggest that metal phosphites add to the *Si*-face of the C−N double bond in sulfinimines via a seven-membered twisted chairlike transition state. This prediction was later confirmed by conversion to a known compound (see below).

Synthesis of Cyclic α-Amino Phosphonates. The next step in the reaction sequence calls for treatment of the masked oxo α-amino phosphonates **12**–**14** with acid to remove the sulfinyl auxiliary and hydrolyze the acetal/

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SCHEME 4

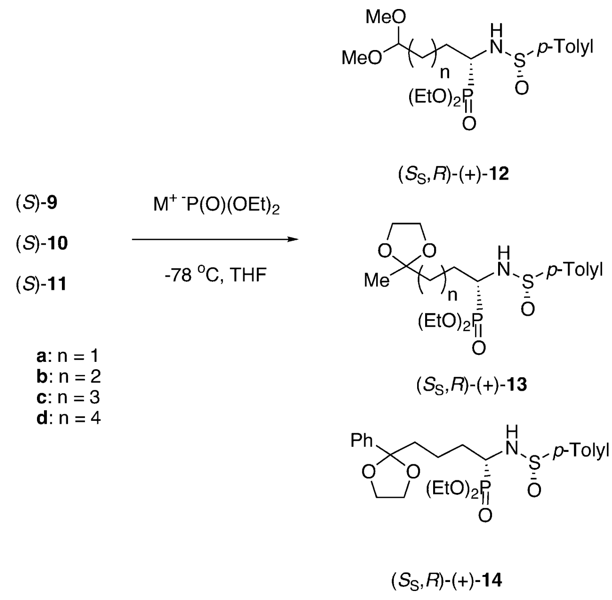

TABLE 1. Addition of Metal Diethyl Phosphite to (*S*)-Sulfinimines at −78 °C in THF

entry	sulfinimines	base (MHMDS) M =	α-amino phosphonate	% yield[a] (% de)[b]
1	**9a** (n = 1)	Li	(S_S,R)-**12a**	92 (93)
2	**9b** (n = 2)	Li	(S_S,R)-**12b**	95 (94)
3	**9c** (n = 3)	Li	(S_S,R)-**12c**	93[c] (76)
4		Na		92[c] (72)
5		K		93[c] (74)
6	**10a** (n = 1)	Li	(S_S,R)-**13a**	91[c] (88)
7		Na		72[c] (82)
8		K		91 (98)
9	**10b** (n = 2)	Li	(S_S,R)-**13b**	74 (98)
10	**10c** (n = 3)	Li	(S_S,R)-**13c**	91 (94)
11	**10d** (n = 4)	Li	(S_S,R)-**13d**	92 (97)
12	**11**	Li	(S_S,R)-**14**	87 (94)

[a] Isolated yield of major diastereoisomer. [b] Determined from the ^{31}P NMR spectra. [c] Mixture of diastereoisomers that were inseparable.

ketal (Scheme 5). This produces the amino carbonyl **15**, which immediately cyclizes to give the imino phosphonates **16** and **17**, and therefore was not detected. The choice of hydrolysis and workup conditions is important. The optimum conditions were hydrolysis with 3 N HCl in THF and neutralizing with solid $NaHCO_3$ at 0 °C. For example, these conditions produced (*R*)-**16b** (R = Me) in 69% isolated yield, but if aqueous saturated $NaHCO_3$ solution were employed to neutralize the reaction, the yield was only 31%. It was also important to minimize the contact times with silica gel to avoid decomposition. Consequently, the imines were flushed through a short pad of silica gel with DCM/MeOH (90:10) in less than 10 min for best results. All attempts to isolate **17a** under any of these conditions met with failure.

The NMR of the crude reaction mixture for the hydrolysis/cyclization of (S_S,R)-(+)-**13c** (n = 3) suggests that it exists as an equilibrating mixture of the amino carbonyl **15** (R = Me, n = 3) and the cyclic imine **18**. This conclusion was based on the appearance of two absorptions in the ^{31}P NMR, at δ 25.7 and 25.9, and the fact that hydrogenation (see below) of the crude reaction mixture gave the corresponding seven-membered cyclic amino phosphonate (2*R*,7*S*)-(−)-**21** in 49% yield (see below). All attempts to obtain identifiable material from the hydrolysis of (S_S,R)-**13d** (n = 4), under any of these conditions, was unsuccessful. Thus, this methodology reaches its limit with the production of seven-membered cyclic α-amino phosphonates.

A variety of hydrogenation catalysts, Pd/C, Pd black, and Raney Ni, were investigated for reduction of the imines to the cyclic amino phosphonates, but these catalysts systems resulted in decomposition and/or recovery of starting material. However, Adam's catalyst (PtO_2) in ethanol for 12 h under atmospheric H_2 afforded the corresponding cyclic α-amino phosphonates **19** to **21** in 49−87% yields. It is interesting to note that reduction of the related cyclic imino carboxylic acids was successful using Pd/C/H_2 within 5 h.[20] In all cases, only a single diastereoisomer was detected on the basis of the ^{31}P NMR spectra. The Mosher amide of (*R*)-−(−)-*O*,*O*-diethyl (pyrrolidin-2-yl)phosphonate (**19a**) indicated that it was >95% enantiomerically pure. Comparison of the specific rotation of (*R*)-(−)-**19a** with a literature value confirms that the predicted absolute configuration (see above) was indeed *R*.[14,23] The cis geometry is expected in all cases because H_2 adds from the least hindered direction. This stereochemical preference was also observed for the hydrogenation of imino acids in the synthesis of cyclic amino acid analogues.[20] Furthermore, a NOESY study of (2*R*,6*R*)-(−)-*O*,*O*-diethyl 6-phenylpiperidin-2-ylphosphonate (**20b**) confirmed the cis relationship of the 2,6-substituents.

Cyclic Quaternary α-Amino Phosphonates. To prepare quaternary α-amino phosphonates using the masked oxo sulfinimine protocol requires a sulfinimine derived from a masked oxo ketone. 4,4-Dimethoxypentanoic acid methyl ester (**22**) was treated with 1.25 equiv of *N*,*O*-dimethylhydroxylamine hydrochloride followed by 8 equiv of methyl or phenylmagnesium bromide (Scheme 6). The corresponding ketones **23** (R = Me, Ph) were isolated in 75−80% yields by chromatography.[24] Next, the masked oxo ketones were treated with (*S*)-(+)-**5** and Ti(OEt)$_4$ in DCM, but the reaction proved to be very slow, affording (*S*)-(+)-**24** (R = Me) in 68% yield after refluxing for 30 h. No reaction between **23** (R = Ph) and (*S*)-**5** was observed, and this may be due to a combination of reduced reactivity of the phenyl ketone and steric hindrance. Because the barrier to planar inversion in ketone-derived sulfinimines is low, (*S*)-(+)-**24** was isolated as a 6:1 mixture of inseparable *E*/*Z* isomers.[12c,25] The sulfinimine mixture was next treated with lithium diethyl phosphite to give a 6:1 mixture of α-amino phosphonate diastereoisomers (S_S,R)-**25** and (S_S,S)-**25**, which were also inseparable by chromatography. Amino phosphonate (S_S,R)-**25** is predicted to be the major isomer based on the stereoinduction model for phosphite addition to sulfinimines (see above).[12c]

When the ketal amino phosphonates were hydrolyzed with 6 N HCl, enantiomers (*R*)- and (*S*)-**26** were obtained in 75% yield. Hydrogenation, as before of (*R*)- and (*S*)-**26**, can in principle give two diastereoisomers if H_2 adds from both faces of the C−N double bond. The fact that

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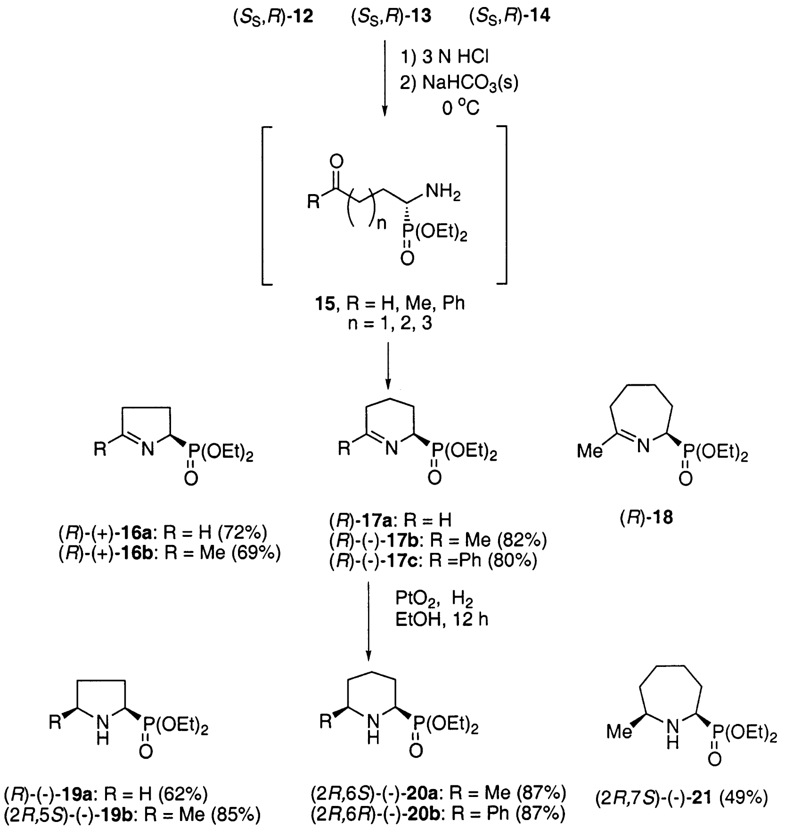
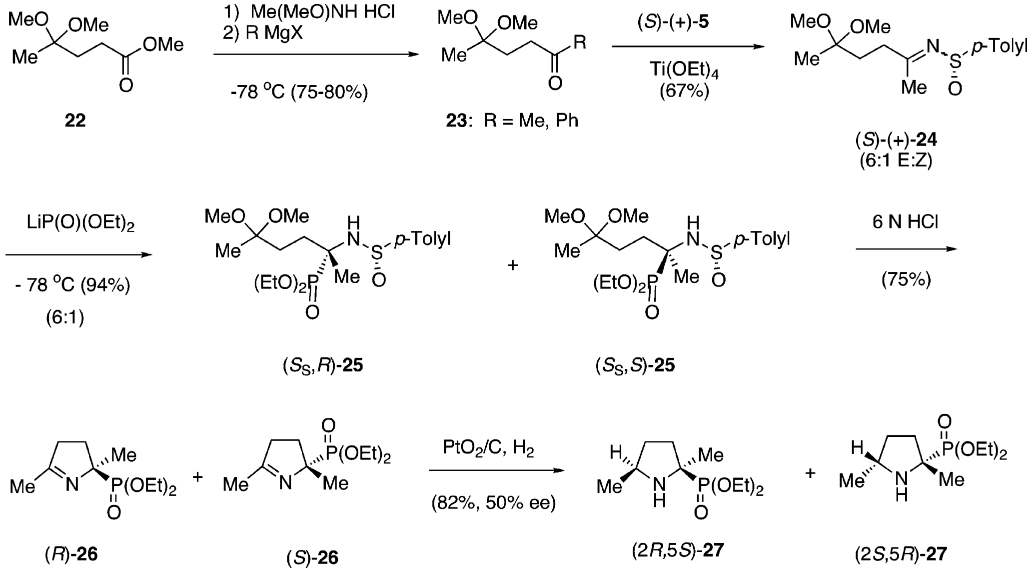
SCHEME 5



SCHEME 6



27 gave a single absorption in the ^{31}P NMR suggests H_2 adds from the least hindered direction affording enantiomers (2*R*,5*S*)-**27** and (2*S*,5*R*)-**27**. The Mosher amide indicates that the enantiomeric purity is 50%, which suggests that somewhere in the transformation of **25** to **27** the enantiomers failed to react at the same rate and/or were lost. The major enantiomer is predicted to have the (2*R*,5*S*) configuration based on the reasonable assumption that amino phosphonate (S_S,*R*)-**25** is the major diastereoisomer for phosphite addition (Scheme 6).

In summary, masked oxo sulfinimines are employed in new methodology for the asymmetric synthesis of five-, six-, and seven-membered cyclic α-amino phosphonates. Modest ee values (50%) were observed in the preparation of quaternary example **27** because the requisite ketone-derived sulfinimines were formed as inseparable *E*,*Z* mixtures.

Experimental Section

4,4-Dimethoxybutanal (**6a**),[20] 5,5-dimethoxypentanal (**6b**),[26] 6,6-dimethoxyhexanal (**6c**),[26] 4,4-(ethylenedioxy)pentanal (**7a**),[20] 5,5-(ethylenedioxy)hexanal (**7b**),[20] 7,7-(ethylenedioxy)octanal (**7d**),[27] methyl 6,6-(ethylenedioxy)heptanoate,[28] 5,5-(ethylenedioxy)-5-phenylpentanal (**8**),[20] (*S*)-(+)-*N*-[5,5-(ethylenedioxy)-5-phenyl-pentanylidene]-*p*-toluenesulfinamide (**11**),[20] (*S*)-(+)-*N*-(5,5-ethylenedipentanylidene)-*p*-toluenesulfinamide (**10a**), and (*S*)-(+)-*N*-[5,5-(ethylenedioxy)hexanylidene]-*p*-toluenesulfinamide (**10b**)[20] were prepared according to literature procedures.

6,6-(Ethylenedioxy)heptanal (7c). In an oven-dried, single-necked, 100-mL, round-bottom flask equipped with a magnetic stir bar and a rubber septum under an argon balloon was placed methyl 6,6-(ethylenedioxy)heptanoate (0.50 g, 2.5 mmol) in DCM (20 mL). The solution was cooled to −78 °C, DIBAL-H (3.2 mL, 3.2 mmol, 1 M solution in CH_2Cl_2) was slowly added, and the reaction mixture was stirred for 2 h. At this time, the reaction was quenched at −78 °C by addition of MeOH (1.0 mL) and saturated Na_2SO_4 (3 mL). After the mixture was stirred at rt for 18 h, anhydrous Na_2SO_4 (4 g) and $MgSO_4$ (1 g) were added and the solution was stirred for 1 h. At this time, the solution was filtered and concentrated. Chromatography (EtOAc/hexane, 10:90) gave 0.31 g (72%) of an oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.47 (m, 2 H), 1.62 (m, 4 H), 2.48 (m, 2 H), 3.99 (m, 4 H), 9.76 (t, J = 2.3 Hz, 1 H). Spectral properties were consistent with literature values.[29]

(*S*)-(+)-*N*-(4,4-Dimethoxybutanylidene)-*p*-toluenesulfinamide (9a). Typical Procedure. In an oven-dried, single-necked, 25-mL, round-bottom flask equipped with a magnetic stir bar and a rubber septum under an argon balloon were placed (*S*)-(+)-**5** (0.16 g, 1 mmol) and **6a** (0.26 g, 2 mmol) in DCM (10 mL). Titanium(IV) ethoxide (1.3 mL, 6 mmol) was added, and the reaction mixture was stirred at rt for 2 h. At this time, the reaction mixture was cooled to 0 °C, H_2O (3 mL) was added, and the reaction mixture was filtered through Celite. The organic phase was washed with H_2O (1 × 5 mL) and brine (1 × 3 mL), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc/hexane, 15:85) gave 0.18 g (67%) of an oil: $[\alpha]^{20}_{D}$ +327 (*c* 1.0 $CHCl_3$); IR (neat) 2945, 1601, 1442, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.99 (m, 2 H), 2.40 (s, 3 H), 2.56 (m, 2 H), 3.28 (s, 3 H), 3.29 (s, 3 H), 4.36 (t, J = 5.9 Hz, 1 H), 7.30 (d, J = 8.1 Hz, 2 H), 7.56 (d, J = 8.1 Hz, 2 H), 8.24 (t, J = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 28.8, 31.7, 53.8, 53.9, 104.3, 125.2, 130.4, 142.3, 142.5, 167.0. Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.84; H, 7.29; N, 5.46.

(*S*)-(+)-*N*-(5,5-Dimethoxypentanylidene)-*p*-toluenesulfinamide (9b). Chromatography (EtOAc/hexane, 15:85) gave an oil: yield 76%; $[\alpha]^{20}_{D}$ +232 (*c* 2.1 $CHCl_3$); IR (neat) 2949, 1620, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 4 H), 2.38 (s, 3 H), 2.49 (m, 2 H), 3.26 (s, 3 H), 3.27 (s, 3 H), 4.33 (t, J = 5.5 Hz, 1 H), 7.28 (d, J = 8.1 Hz, 2 H), 7.52 (d, J = 8.1 Hz, 2 H), 8.21 (t, J = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.8, 32.2, 35.9, 53.2, 104.5, 124.9, 130.2, 142.1, 142.2, 167.1; HRMS calcd for $C_{14}H_{21}NO_3SNa$ (M + Na) 306.1140, found 306.1140.

(*S*)-(+)-*N*-(6,6-Dimethoxyhexanylidene)-*p*-toluenesulfinamide (9c). Chromatography (EtOAc/hexane, 15:85) gave an oil: yield 52%; $[\alpha]^{20}_{D}$ +263 (*c* 0.9 $CHCl_3$); IR (neat) 2945, 1620, 1492, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (m, 2 H), 1.51 (m, 4H), 2.31 (s, 3 H), 2.41 (m, 2 H), 3.20 (s, 3 H), 3.21 (s, 3 H), 4.23 (t, J = 5.6 Hz), 7.21 (d, J = 8.0 Hz, 2 H), 7.47 (d, J = 8.1 Hz, 2 H), 8.14 (t, J = 4.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.5, 25.5, 32.6, 36.1, 53.1, 104.6, 124.9, 130.2, 142.0, 142.3, 167.3; HRMS calcd for $C_{15}H_{23}NO_3SNa$ (M + Na) 320.1296, found 320.1288.

(*S*)-(+)-*N*-[6,6-(Ethylenedioxy)heptanylidene]-*p*-toluenesulfinamide (10c). Chromatography (EtOAc/hexane, 15:85) gave an oil: yield 62%; $[\alpha]^{20}_{D}$ +262 (*c* 1.6 $CHCl_3$); IR (neat) 2945, 1620, 1068 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.59 (m, 2 H), 1.63 (m, 4 H), 2.39 (s, 3 H), 2.48 (m, 2 H), 3.89 (m, 4 H), 7.28 (d, J = 8.4 Hz, 2 H), 7.53 (d, J = 8.2 Hz, 2 H), 8.20 (t, J = 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 24.3, 24.4, 26.2, 36.6, 39.5, 65.3, 110.6, 125.3, 130.5, 142.3, 142.6, 167.7; HRMS calcd for $C_{16}H_{23}NO_3SNa$ (M + Na) 332.1296, found 322.1289.

(*S*)-(+)-*N*-[7,7-(Ethylenedioxy)octanylidene]-*p*-toluenesulfinamide (10d). Chromatography (EtOAc/hexane, 15:85) gave an oil: yield 62%; $[\alpha]^{20}_{D}$ +228 (*c* 2.0 $CHCl_3$); IR (neat) 2942, 1620, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.36 (m, 4 H), 1.60 (m, 4 H), 2.40 (s, 3 H), 2.48 (m, 2 H), 3.93 (m, 4 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.56 (d, J = 8.1 Hz, 2 H), 8.22 (t, J = 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.1, 25.7, 29.6, 36.1, 39.4, 65.0, 110.3, 124.9, 130.2, 142.0, 142.3, 167.5. Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.43. Found: C, 63.05; H, 8.12; N, 4.18.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-Toluenesulfinyl)-1-amino-4,4-dimethoxybutylphosphonate (12a). Typical Procedure. In an oven-dried, 100-mL, single-necked, round-bottom flask fitted with a rubber septum and a magnetic stir bar under an argon balloon was placed (*S*)-(+)-**9a** (0.27 g, 1.0 mmol) in THF (15 mL), which was then cooled to −78 °C. In a separate 50-mL, single-necked, round-bottom flask fitted with a rubber septum and a magnetic stir bar under an argon balloon was placed diethyl phosphite (0.26 mL, 2.0 mmol) in THF (15 mL). The solution was cooled −78 °C, and LiHMDS (2.0 mL, 2.0 mmol) was slowly added. The reaction mixture was stirred for 0.25 h, cannulated to the solution of (+)-**9a**, stirred for 1 h at −78 °C, and quenched by addition of saturated NH_4Cl (2 mL). The organic phase was extracted with EtOAc (3 × 5 mL), washed with H_2O (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (CH_2Cl_2/MeOH, 95:5) followed by recrystallization (EtOAc/hexane, 1:10) afforded 0.37 g (92%) of a solid: mp 74−75 °C; $[\alpha]^{20}_{D}$ +80.7 (*c* 1.0 $CHCl_3$); IR (KBr) 3466, 3222, 2988, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (m, 6 H), 1.92 (m, 4 H), 2.41 (s, 3 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.53 (m, 1 H), 4.12 (m, 4 H), 4.46 (t, J = 5.1 Hz, 1 H), 4.58 (m, 1 H), 7.34 (d, J = 8.1 Hz, 2 H), 7.56 (d, J = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.7, 16.8, 21.7, 27.4, 29.1, 50.1 (d, J_{CP} = 154 Hz), 53.1, 53.3, 62.7 (d, J_{COP} = 6.7 Hz), 63.1 (d, J_{COP} = 6.9 Hz), 104.5, 126.3, 129.9, 141.5, 141.9; ^{31}P NMR ($CDCl_3$) δ 24.59. Anal. Calcd for $C_{17}H_{30}NO_6PS$: C, 50.11; H, 7.42; N, 3.44. Found: C, 49.99; H, 7.67; N, 3.57.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-Toluenesulfinyl)-1-amino-5,5-dimethoxypentylphosphonate (12b). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil; yield 95%; $[\alpha]^{20}_{D}$ +63.2 (*c* 0.7 $CHCl_3$); IR (neat) 3452, 3099, 2977, 1577, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 6 H), 1.54 (m, 4 H), 1.81, (m, 1 H), 1.89 (m, 1 H), 2.34 (s, 3 H), 3.26 (s, 6 H), 3.41 (m, 1 H), 3.98 (m, 4 H), 4.32 (t, 1H, J = 5.1 Hz), 4.47 (m, 1 H), 7.23 (d, J = 8.1 Hz, 2 H), 7.56 (d, J = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.7, 16.8, 21.4, 21.8, 31.4, 32.3, 51.0 (d, J_{CP} = 154 Hz), 53.1, 53.2, 62.8 (d, J_{COP} = 6.7 Hz), 63.1 (d, J_{COP} = 6.8 Hz), 104.6, 126.2, 129.9, 141.7, 142.0; ^{31}P NMR ($CDCl_3$) δ 24.76. Anal. Calcd for $C_{18}H_{32}NO_6PS$: C, 51.29; H, 7.65; N, 3.32. Found: C, 51.41; H, 7.76; N, 3.47.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-toluenesulfinyl)-1-amino-6,6-dimethoxyhexylphosphonate (12c): inseparable mixture (dr 88:12); yield 93% of an oil; $[\alpha]^{20}_{D}$ +40.9 (*c* 1.4 $CHCl_3$); IR (neat) 3312, 3145, 2931, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$) (major) δ 1.27 (m, 8 H), 1.57 (m, 4 H), 1.85, (m, 1 H), 1.92 (m, 1 H), 2.31 (s, 3 H), 3.27 (s, 6 H), 3.41 (m, 1 H), 4.01 (m, 4 H), 4.16 (t, J = 5.0 Hz), 4.36 (m, 1 H), 7.19 (d, J = 8.1 Hz, 2 H), 7.58 (d, J = 8.1 Hz, 2 H); (minor) δ 1.27 (m, 8 H), 1.57 (m, 4 H), 1.85, (m, 1 H), 1.92 (m, 1 H), 2.31 (s, 3 H), 3.26 (s, 6 H), 3.41 (m, 1 H), 4.01 (m, 4 H), 4.16 (t, J = 5.0 Hz), 4.36 (m, 1 H), 7.19 (d, J = 8.1 Hz, 2 H), 7.58 (d, J = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.9, 17.0, 20.4, 25.1, 25.9, 29.8, 30.3, 51.6 (d, J_{CP} = 153 Hz), 54.0, 54.2, 63.9 (d, J_{COP} = 6.7 Hz), 64.2 (d, J_{COP} = 6.7 Hz), 104.6, 125.2, 129.1, 142.6, 143.9; ^{31}P NMR ($CDCl_3$) (major)

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δ 24.88, (minor) δ 25.16. Anal. Calcd for $C_{19}H_{34}NO_6PS$: C, 52.40; H, 7.87; N, 3.22. Found: C, 52.11; H, 7.66; N, 3.38.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-toluenesulfinyl)-1-amino-4,4-(ethylenedioxy)-pentylphosphonate (13a): chromatography (CH_2Cl_2/MeOH, 95:5); yield 91%; mp 96−97 °C; $[\alpha]^{20}_{D}$ +82.7 (*c* 0.6 $CHCl_3$); IR (KBr) 3474, 3179, 2981, 1597, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 6 H), 1.35 (s, 3 H), 1.84, (m, 1 H), 1.92 (m, 1 H), 2.01 (m, 2 H), 2.41 (s, 3 H), 3.56 (m, 1 H), 3.95 (s, 4 H), 4.02 (m, 4 H), 4.52 (m, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.60 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.8, 15.9, 20.7, 23.3, 25.7, 34.2, 49.8 (d, J_{CP} = 154 Hz), 61.8 (d, J_{COP} = 6.5 Hz), 62.1 (d, J_{COP} = 6.8 Hz), 64.0, 64.1, 109.1, 125.2, 128.9, 140.8, 141.0; ^{31}P NMR ($CDCl_3$) δ 24.75. Anal. Calcd for $C_{18}H_{30}NO_6PS$: C, 51.54; H, 7.21; N, 3.34. Found: C, 51.80; H, 7.47; N, 3.39.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-Toluenesulfinyl)-1-amino-5,5-(ethylenedioxy)hexylphosphonate (13b). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil: yield 72%; $[\alpha]^{20}_{D}$ +60.5 (*c* 1.5 $CHCl_3$); IR (neat) 3479, 3188, 2981, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 6 H), 1.32 (s, 3 H), 1.59 (m, 2 H), 1.61 (m, 2 H), 1.71 (m, 1 H), 1.93 (m, 1 H), 2.40 (s, 3 H), 3.51 (m, 1 H), 3.93 (m, 4 H), 4.05 (m, 4 H), 4.48 (m, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 16.9, 20.8, 21.8, 24.3, 32.3, 39.0, 51.0 (d, J_{CP} = 153 Hz), 62.8 (d, J_{COP} = 6.8 Hz), 63.2 (d, J_{COP} = 7.0 Hz), 65.1, 110.3, 126.1, 129.9, 142.0, 142.2; ^{31}P NMR ($CDCl_3$) δ 24.82. Anal. Calcd for $C_{19}H_{32}NO_6PS$: C, 52.64; H, 7.44; N, 3.23. Found: C, 52.38; H, 7.80; N, 2.83.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-Toluenesulfinyl)-1-amino-6,6-(ethylenedioxy)heptylphosphonate (13c). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil: yield 91%; $[\alpha]^{20}_{D}$ +80.2 (*c* 0.5 $CHCl_3$); IR (neat) 3501, 3112, 2941, 1075 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 6 H), 1.31 (s, 3 H), 1.62 (m, 6 H), 1.82 (m, 1 H), 1.94 (m, 1 H), 2.41 (s, 3 H), 3.52 (m, 1 H), 4.01 (m, 4 H), 4.12 (m, 4 H), 4.38 (m, 1 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 7.62 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 21.8, 24.2, 26.4, 26.5, 32.2, 39.3, 51.6 (d, J_{CP} = 154 Hz), 62.9 (d, J_{COP} = 6.9 Hz), 63.1 (d, J_{COP} = 6.9 Hz), 65.0, 110.4, 126.2, 130.0, 141.8, 142.0; ^{31}P NMR ($CDCl_3$) δ 24.90. Anal. Calcd for $C_{20}H_{34}NO_6PS$: C, 53.68; H, 7.66; N, 3.13. Found: C, 53.92; H, 7.89; N, 2.98.

(S_S,*R*)−(+)-*O*,*O*-Diethyl *N*-(*p*-Toluenesulfinyl)-1-amino-7,7-(ethylenedioxy)octylphosphonate (13d). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil: yield 92%; $[\alpha]^{20}_{D}$ +66.1 (*c* 0.8 $CHCl_3$); IR (neat) 3524, 3178, 2940, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 6 H), 1.26 (s, 3 H), 1.54 (m, 8 H), 1.78 (m, 1 H), 1.84 (m, 1 H), 2.34 (s, 3 H), 3.49 (m, 1 H), 3.89 (m, 4 H), 4.11 (m, 4 H), 4.38 (m, 1 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.54 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.7, 16.8, 21.7, 24.3, 26.2, 30.0, 31.7, 32.2, 39.5, 50.8 (d, J_{CP} = 154 Hz), 62.7 (d, J_{COP} = 6.9 Hz), 62.8 (d, J_{COP} = 7.0 Hz), 65.0, 110.5, 126.1, 129.9, 141.9, 142.0; ^{31}P NMR ($CDCl_3$) δ 24.95. Anal. Calcd for $C_{21}H_{36}NO_6PS$: C, 54.65; H, 7.86; N, 3.03. Found: C, 54.52; H, 7.99; N, 2.92.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-Toluenesulfinyl)-1-amino-5,5-(ethylenedioxy)-5-phenylpentylphosphonate (14). Chromatography (CH_2Cl_2/MeOH, 97:3) gave an oil: yield 87%; $[\alpha]^{20}_{D}$ +42.0 (*c* 2.5 $CHCl_3$); IR (neat) 3184, 2926, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 6 H), 1.58 (m, 4 H), 1.83 (m, 2 H), 2.36 (s, 3 H), 3.46 (m, 1 H), 3.74 (m, 2 H), 4.01 (m, 6 H), 4.43 (m, 1 H), 7.23 (m, 5 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 16.9, 20.8, 21.8, 24.3, 32.3, 39.0, 51.0 (d, J_{CP} = 153 Hz), 62.8 (d, J_{COP} = 6.8 Hz), 63.2 (d, J_{COP} = 7.0 Hz), 65.1, 110.3, 126.2, 126.8, 129.2, 129.9, 130.5, 139.6, 141.8, 142.0; ^{31}P NMR ($CDCl_3$) δ 24.82. Anal. Calcd for $C_{24}H_{34}NO_6PS$: C, 58.17; H, 6.92; N, 2.83. Found: C, 58.19; H, 7.06; N, 2.70

(*R*)-(+)-*O*,*O*-Diethyl 3,4-Dihydro-2*H*-pyrrole-2-phosphonate (16a). Typical Procedure. In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stir bar was placed (*S*,*R*)-(+)-**12a** (0.20 g, 0.5 mmol) in THF (15 mL), and the solution was cooled to 0 °C. At this time, 3 N HCl (2 mL) was slowly added, and the reaction mixture was stirred for 2 h at this temperature, neutralized by addition of solid $NaHCO_3$ (0.5 g), dried ($MgSO_4$), and concentrated. Chromatography (CH_2Cl_2/MeOH, 95:5) gave 0.074 g (72%) of an oil: $[\alpha]^{20}_{D}$ +86.5 (*c* 1.0 $CHCl_3$); IR (neat) 2980, 1618, 1248, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (m, 6 H), 2.14 (m, 2 H), 2.68 (m, 2 H), 4.18 (m, 4 H), 4.40 (m, 1 H), 7.74 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 16.9, 22.5, 37.6, 62.6 (d, J_{COP} = 6.6 Hz), 63.0 (d, J_{COP} = 6.7 Hz), 70.2 (d, J_{CP} = 159 Hz), 170.5 (d, J_{CNCP} = 15.4 Hz); ^{31}P NMR ($CDCl_3$) δ 25.45; HRMS calcd for $C_8H_{16}NO_3PNa$ (M + Na) 228.0766, found 228.0773.

(*R*)-(+)-*O*,*O*-Diethyl 5-Methyl-3,4-dihydro-2*H*-pyrrole-2-phosphonate (16b). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil; yield 59%; $[\alpha]^{20}_{D}$ +98.3 (*c* 1.0 $CHCl_3$); IR (neat) 2982, 1643, 1246, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 6 H), 2.08 (m, 3 H), 2.19 (m, 2 H), 2.67 (m, 2 H), 4.15 (m, 4 H), 4.34 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.6, 18.8, 23.3, 38.3, 61.1 (d, J_{COP} = 6.7 Hz), 61,5 (d, J_{COP} = 6.7 Hz), 68.6 (d, J_{CP} = 157 Hz), 177.7 (d, J_{CNCP} = 14.8 Hz); ^{31}P NMR ($CDCl_3$) δ 26.21; HRMS calcd for $C_9H_{19}NO_3P$ (M + H) 220.1103, found 220.1105.

(*R*)-(−)-*O*,*O*-Diethyl 6-Methyl-2,3,4,5-tetrahydropyridine-2-phosphonate (17b). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil; yield 82%; $[\delta]^{20}_{D}$ −15.4 (*c* 0.4 $CHCl_3$); IR (neat) 2941, 1659, 1248, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 6 H), 1.52 (m, 1 H), 1.64 (m, 1 H), 1.87 (m, 2 H), 1.95 (m, 3 H), 2.06 (m, 2 H), 3.81 (m, 1 H), 4.15 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 18.5, 18.6, 21.8, 28.2, 30.4, 57.6 (d, J_{CP} = 166 Hz), 62.4 (d, J_{COP} = 6.8 Hz), 63.1 (d, J_{COP} = 6.9 Hz), 171.7 (d, J_{CNCP} = 15.8 Hz); ^{31}P NMR ($CDCl_3$) δ 25.58; HRMS calcd for $C_{10}H_{21}NO_3P$ (M + H) 234.1259, found 234.1254.

(*R*)-(−)-*O*,*O*-Diethyl 6-Phenyl-2,3,4,5-tetrahydropyridine-2-phosphonate (17c). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil: yield 80%; $[\alpha]^{20}_{D}$ −89.8 (*c* 0.8 $CHCl_3$); IR (neat) 2980, 1660, 1248, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 6 H), 1.70 (m, 1 H), 1.73 (m, 1 H), 2.01 (m, 1 H), 2.13 (m, 1 H), 2.62 (m, 1 H), 2.74 (m, 1 H), 4.22 (m, 5 H), 7.38 (m, 3 H), 7.83 (d, *J* = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 17.1, 21.5, 28.1, 54.8 (d, J_{CP} = 159 Hz), 63.8 (d, J_{COP} = 6.7 Hz), 64.0 (d, J_{COP} = 6.9 Hz), 127.7, 129.3, 133.1, 135.8, 176.5; ^{31}P NMR ($CDCl_3$) δ 24.85; HRMS calcd for $C_{15}H_{23}NO_3P$ (M + H) 296.0.1416, found 296.1420.

(*R*)-(−)-*O*,*O*-Diethyl Pyrrolidine-2-phosphonate (19a). Typical Procedure. In a 25-mL, single-necked, round-bottom flask fitted with a magnetic stir bar under a hydrogen balloon was placed PtO_2 (ca. 4 mg) and (*R*)-(+)-**16a** (0.050 g, 0.24 mmol) in EtOH (5 mL). The reaction mixture was stirred at rt for 16 h, filtered through Celite, and concentrated. Chromatography (CH_2Cl_2/MeOH, 95:5) gave 0.031 g (62%) of an oil: $[\alpha]^{20}_{D}$ −16.7 (*c* 0.5 $CHCl_3$) [lit.[23] $[\alpha]^{20}_{D}$ +16.4 (*c* 1.0, $CHCl_3$) for the (*S*) isomer]. Spectral properties were consistent with literature values.[14,23]

(2*R*,5*S*)-(−)-*O*,*O*-Diethyl 5-Methylpyrrolidine-2-phosphonate (19b). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil: yield 85%; $[\alpha]^{20}_{D}$ −6.8 (*c* 0.5 $CHCl_3$); IR (neat) 3584, 2955, 1236, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (d, *J* = 6.2 Hz, 3 H), 1.26 (m, 6 H), 1.92 (m, 4 H), 2.14 (m, 1 H), 3.10 (m, 1 H), 3.29 (m, 1 H), 4.11 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 6.9, 21.1, 27.3, 33.9, 34.0, 54.8 (d, J_{CP} = 163 Hz), 62.5 (d, J_{COP} = 6.8 Hz), 62.8 (d, J_{COP} = 6.5 Hz); ^{31}P NMR ($CDCl_3$) δ 28.26; HRMS calcd for $C_9H_{21}NO_3P$ (M + H) 222.1259, found 222.1250.

(2*R*,6*S*)-(−)-*O*,*O*-Diethyl 6-Methylpiperidine-2-phosphonate (20a). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil: yield 87%; $[\delta]^{20}_{D}$ −8.4 (*c* 0.5 $CHCl_3$); IR (neat) 3505, 2931, 1234, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, *J* = 6.2 Hz, 3 H), 1.33 (m, 7 H), 1.39 (m, 1 H), 1.58 (m, 1 H), 1.71 (m, 2 H), 1.85 (m, 2 H), 2.57 (m, 1 H), 2.98 (m, 1 H), 4.15 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.9, 23.3, 25.1, 25.2, 26.1, 34.2, 55.0 (d, J_{CP} = 162 Hz), 62.5 (d, J_{COP} = 6.7 Hz), 62.7 (d, J_{COP} = 6.8 Hz); ^{31}P NMR ($CDCl_3$) δ 27.04; HRMS calcd for $C_{10}H_{23}NO_3P$ (M + H) 236.1416, found 236.1414.

(2*R*,6*R*)-(−)-*O*,*O*-Diethyl 6-Phenyl-piperidine-2-phosphonate (20b). Chromatography (CH_2Cl_2/MeOH, 95:5) gave an oil: yield 87%; $[\alpha]^{20}_{D}$ +22.6 (*c* 1.5 $CHCl_3$); IR (neat) 3466, 2933, 1230, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (m, 6 H), 1.42 (m, 2 H), 1.61 (m, 1 H), 1.78 (m, 1 H), 1.94 (m, 3 H), 3.16 (m, 1 H), 3.60 (m, 1 H), 4.18 (m, 4 H), 7.27 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.9, 25.3, 25.4, 25.7, 30.1, 34.4, 55.1 (d, $J_{CP} = 162$ Hz), 62.8 (d, $J_{COP} = 6.5$ Hz), 63.2 (d, $J_{COP} = 6.7$ Hz), 127.3, 127.8, 128.8; ^{31}P NMR ($CDCl_3$) δ 26.61; HRMS calcd for $C_{15}H_{24}NO_3PNa$ (M + Na) 320.1392, found 320.1402.

(2*R*,7*S*)-(−)-*O*,*O*-Diethyl 7-Methylazepane-2-phosphonate (21). In a 25-mL, single-necked, round-bottom flask fitted with a magnetic stir bar was placed (*S*,*R*)-(+)-**13c** (0.12 g, 0.25 mmol) in THF (10 mL). The solution was cooled to 0 °C, 3 N HCl (1 mL) was slowly added, and the reaction mixture was stirred for 2 h at 0 °C. At this time, the reaction mixture was neutralized with solid $NaHCO_3$ (0.5 g), dried ($MaSO_4$), and concentrated. The crude mixture was loaded onto a short pad of silica gel, washed (EtOAc/hexane, 60:40) to remove the sulfinyl byproducts, and eluted (CH_2Cl_2/MeOH, 95:5). The solution was concentrated, and the residue was dissolved in EtOH (5 mL) and hydrogenated over PtO_2 (2 mg) at balloon pressure for 16 h. At this time, the reaction mixture was filtered through Celite and concentrated. Chromatography (CH_2Cl_2/MeOH, 95:5) gave 0.031 g (49%) of an oil: $[\alpha]^{20}_{D}$ −5.8 (*c* 0.7 $CHCl_3$); IR (neat) 3516, 2963, 1212, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, $J = 6.1$ Hz, 3 H), 1.26 (m, 6 H), 1.68 (m, 8 H), 1.97 (m, 1 H), 2.76 (m, 1 H), 2.98 (m, 1 H), 4.12 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.5, 16.6, 21.3, 22,6, 24.1, 25.2, 26.1, 34.2, 56.7 (d, $J_{CP} = 157$ Hz), 61.2 (d, $J_{COP} = 6.9$ Hz), 61.7 (d, $J_{COP} = 6.8$ Hz); ^{31}P NMR ($CDCl_3$) δ 28.45; HRMS calcd for $C_{11}H_{24}NO_3PNa$ (M + Na) 272.1392, found 272.1382.

General Procedure for Preparation of Mosher Amides. In an oven-dried, 10-mL, single-necked, round-bottom flask equipped with a magnetic stir bar and a rubber septum under an argon balloon was placed approximately 0.015 g of (−)-**19a** in dry THF (2 mL). To the solution was added 0.017 g of Mosher's chloride and of Et_3N (0.085 mL). The reaction mixture was stirred for 1 h at rt and quenched by addition of saturated NH_4Cl (1 mL). The solution was extracted with EtOAc (2 × 2 mL), washed with H_2O (1 mL) and brine (1 mL), dried ($MgSO_4$), and concentrated. The racemic Mosher amides were prepared in a similar manner. Evaluation of the ^{19}F, ^1H, and ^{31}P NMR spectra of crude mixtures was used to determine the enantiomeric purity of the ester.

5,5-Dimethoxyhexan-2-one (23). In an oven-dried, single-neck, 250-mL, round-bottom flask equipped with a stirring bar and a rubber septum under argon was placed **22**[30] (2.00 g, 11.35 mmol) and dimethylhydroxylamine hydrochloride (1.38 g, 14.19 mmol) in THF (75 mL). The mixture was cooled to −5 °C, and MeMgCl (38 mL, 114 mmol, 3 M solution in THF) was added in over 2 h while the temperature was maintained at −5 to −2 °C. At this time the reaction mixture was slowly warm to room temperature, stirred for 8 h, and quench with saturated NH_4Cl solution (50 mL). The organic phase was washed with H_2O (2 × 15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Chromatography (EtOAc/hexane 20:80) gave 1.45 g (80%) of a viscous oil: IR (neat) 1720, 1379, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.73 (t, $J = 7.9$ Hz, 2 H), 1.98 (s, 3 H), 2.30 (t, $J = 7.9$ Hz, 2 H), 3.00 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.4, 101.5, 48.6, 39.2, 30.5, 30.4, 21.4. An HMRS could not be obtained due to compound instability.

4,4-Dimethoxy-1-phenylpentan-1-one. Chromatography (EtOAc/hexane 5:95) gave 1.89 g (75%) of a viscous oil: IR (neat) 1687, 1448−1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 2.82 (t, $J = 6.3$ Hz, 2 H), 3.21 (t, $J = 6.3$ Hz, 2 H), 7.39 (m, 2 H), 7.49 (m, 1 H), 7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 30.9, 34.2, 48.7, 101.7, 128.4, 129.0, 130.0, 133.4, 137.3, 200.0; HRMS calcd for $C_{13}H_{18}O_3$ (M + Na), found 245.1145.

(*S*)-(+)-*N*-(4,4-Dimethoxy-1-methylpentylidene)-*p*-toluenesulfinamide (24). In an oven-dried, single-neck, 50-mL, round-bottom flask equipped with a stirring bar and a rubber septum under argon was placed (*S*)-(+)-**5** (0.088 g, 0.57 mmol) and **23** (0.4550 g, 2.84 mmol) in DCM (20 mL). To the solution was added $Ti(OEt)_4$ (1.8 mL, 8.52 mmol) and the solution was refluxed for 30 h. At this time, the reaction mixture was cooled to 0 °C, H_2O (10 mL) was added, and the solution was filtered through Celite. The organic phase was washed with H_2O (2 × 10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. Chromatography (EtOAc/hexane 35:65) gave 0.11 g (67%) of a viscous oil as a 6:1 mixture of inseparable diastereoisomers; $[\alpha]^{20}_{D}$ +30.3 (*c* 0.4, $CHCl_3$); IR (neat) 1618, 1130, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.83 (t, $J = 7.8$ Hz, 2 H), 2.32 (s, 3 H), 2.34 (s, 3 H), 2.36 (m, 2 H), 3.06 (d, $J = 7$ Hz, 6 H), 7.22 (d, $J = 7.8$ Hz, 2 H), 7.57 (d, $J = 8.1$ Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.9, 23.6, 32.3, 38.5, 48.6, 101.5, 125.5, 130.2, 142.2, 143.6, 182.3; HRMS calcd for $C_{15}H_{23}NO_3S$ (M + Na) 320.1296, found 320.1304.

(S_S,*R*)-(+)-*O*,*O*-Diethyl *N*-(*p*-Toluenesulfinyl)-1-amino-4,4-dimethoxy-1-methylpentylphosphonate (25). In an oven-dried, 100-mL, single-neck, round-bottom flask fitted with a rubber septum and a magnetic stir bar under argon was placed (*S*)-**24** (0.23 g, 0.77 mmol) in THF (15 mL) and the solution was cooled to −78 °C. In a second 50-mL, single-neck, round-bottom flask fitted with a rubber septum and a magnetic stirring bar under argon was placed diethyl phosphite (0.20 mL, 1.55 mmol) in THF (15 mL), the solution was cooled to −78 °C, and LiHMDS (1.55 mL, 1.55 mmol) was slowly added. The reaction mixture was stirred for 0.5 h and cannulated to the solution of (*S*)-**24**, and the reaction mixture stirred for 1 h. At this time, the reaction was quenched by addition of saturated NH_4Cl (10 mL). The organic phase was separated, washed with H_2O (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc) gave 0.33 g (94%) of a viscous oil of a 6:1 inseparable mixture of diastereoisomers: $[\alpha]^{20}_{D}$ 56.0 (*c* 0.4, $CHCl_3$); IR (neat) 1390, 1236, 1051, 963 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, $J = 7.2$ Hz, 2 H), 1.22 (s, 3 H), 1.27 (m, 6 H), 1.56, 1.87 (m, 2 H), 1.98 (s, 3 H), 2.33 (s, 3 H), 3.10 (d, $J = 8.8$ Hz, 6 H), 4.07 (m, 4 H), 4.28 (d, $J = 4.8$ Hz, 1 H), 7.21 (d, $J = 7.9$ Hz, 2 H), 7.54 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.9, 21.3, 21.8 (d, $J_{CCP} = 11$ Hz), 30.4, 31.8, 48.5, 58.7 (d, $J_{CP} = 156.2$ Hz), 60.8, 63.2 (d, $J_{COP} = 7.4$ Hz), 63.8 (d, $J_{COP} = 7.0$ Hz), 101.8, 125.8, 130.0, 141.7, 143.6; ^{31}P NMR δ 26.32 (major), 26.62 (minor); HRMS calcd for $C_{19}H_{34}NO_6PS$ (M + Na) 458.1742, found 458.1743.

(*R*)-(+)-*O*,*O*-Diethyl 5-Methyl-3,4-dihydro-2-methylpyrrole-2-phosphonate (26). In a 25-mL, single-neck, round-bottom flask fitted with a magnetic stirring bar was placed **25** (0.22 g, 0.5 mmol) in THF (15 mL). The solution was cooled to 0 °C, 6 N HCl (1 mL) was slowly added, and the reaction mixture was stirred for 2 h. At this time, the reaction was neutralized with solid $NaHCO_3$ (0.5 g), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc/MeOH 90:10) gave 0.087 g (75%) of a viscous oil: $[\alpha]^{20}_{D}$ +20.2 (*c* 0.7, $CHCl_3$); IR (neat) 1643, 1251,1054, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (m, 6 H), 1.42 (d, $J = 16$ Hz, 3 H), 1.60 (m, 1 H), 2.00 (d, $J = 4.0$ Hz, 3 H), 2.40 (m, 1 H), 2.58 (m, 2 H), 4.08 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.9 (d, $J_{CCP} = 4.0$ Hz), 20.2, 24.1, 32.8, 40.1, 62.7 (d, $J_{COP} = 7.0$ Hz), 62.9 (d, $J_{COP} = 7.0$ Hz), 75.8 (d, $J_{CP} = 158.1$ Hz), 177.7 (d, $J_{CNCP} = 13.4$ Hz); ^{31}P NMR δ 28.53; HRMS calcd for $C_{10}H_{20}NO_3P$ (M + Na) 256.1078, found 256.1078.

(2*R*,5*S*):(2*S*,5*R*)-(−)-*O*,*O*-Diethyl 5-Methyl-2-methylpyrrolidine-2-phosphonate (27). In an oven-dried, 25-mL single-neck, round-bottom flask fitted with a magnetic stirring bar was placed PtO_2 (10 mg) (+)-**26** (0.047 g, 0.20 mmol) in EtOH (5 mL). The reaction mixture was stirred under a balloon hydrogen atmosphere for 16 h and filtered through Celite. Chromatography (EtOAc/MeOH 90:10) gave 0.039 g (82%) of a white solid: mp 61−64; $[\alpha]^{20}_{D}$ −3.7 (*c* 0.32, $CHCl_3$); IR (neat)

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1225, 1031, 958 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.25 (d, $J = 2.4$ Hz, 3 H), 1.26 (m, 6 H), 1.30 (d, $J = 16$ Hz, 3 H), 1.36 (m, 1 H), 1.53 (m, 2 H), 1.85 (m, 1 H), 2.24 (m, 1 H), 3.30 (m, 1 H), 4.10 (m, 4 H); ^{13}C NMR (CDCl$_3$) δ 16.9, 21.5 (d, $J_{\mathrm{CCP}} = 7$ Hz), 24.8, 34.4, 35.6, 53.8 (d, $J_{\mathrm{CCP}} = 11.2$ Hz), 60.5 (d, $J_{\mathrm{CP}} = 165.1$ Hz), 62.3 (d, $J_{\mathrm{COP}} = 7.1$ Hz), 63.6 (d, $J_{\mathrm{COP}} = 7$ Hz); ^{31}P NMR δ 30.22; HRMS calcd for $C_{10}H_{22}NO_3P$ (M + Na) 236.1415, found 236.1415. The Mosher amide indicated that the compound was 50% enantiomeric pure. Compound **27** has been prepared in racemic form.[31]

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Supporting Information Available: General experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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