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# Enantioselective Synthesis of *H*-Phosphinic Acids Bearing Natural Amino Acid Residues

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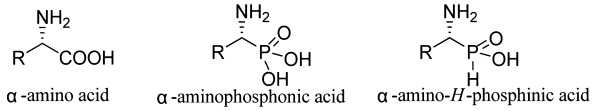
Supporting Information

**ABSTRACT:** The first systematic study on the asymmetric synthesis of *H*-phosphinic acids bearing natural protein amino acid residues was reported on the basis of the asymmetric addition of ethyl diethoxymethylphosphinate to *N*-*tert*-butanesulfinyl imines. Good yields and moderate to high enantioselectivities were obtained. Reliable methods were developed for the elucidation of the stereochemistry of these phosphinic acids and derivatives thereof. The transformation of the side chains of these analogues was studied. Methods for the conversion of the α-aminophosphinates to oligopetides were reported.


## INTRODUCTION

As a phosphorus analogue of natural α-aminocarboxylic acid, α-aminophosphonic acid is of great interest to chemists (Scheme 1). Many procedures have been developed for their preparation in both racemic and optically pure forms,[1] and their biological studies have revealed diverse activities.[2]

**Scheme 1. α-Amino Acid and Its Phosphorus Analogues**




However, direct comparison of α-aminophosphonic acids with α-aminocarboxylic acids is not reasonable, since the former belongs to dibasic acids while the latter are monobasic acids in nature. From this structural point of view, α-amino-*H*-phosphinic acids are much closer to natural α-aminocarboxylic acids (Scheme 1). It is well documented that optically active α-aminocarboxylic acids play an irreplaceable role in the biological metabolism. Consequently, it is reasonable to assume that better bioactivities can be expected for *H*-phosphinic analogues of α-amino acids than for corresponding phosphonic acids. Previous work by George et al. demonstrates that *N*-methyl-*N*-amidinoaminomethylphosphinic acid is much more reactive as analogue of creatine in the creatine kinase reaction than the corresponding phosphonic acid or its monoester.[3a] Similar effects were found for inhibitors of nitric oxide synthase (NOS).[3b] In fact, derivatives of *H*-phosphinic acids have already demonstrated varieties of activities;[4] also, the precursor of α-aminophosphinates are excellent synthons for the preparation of various organophosphorus compounds.[5]

Unfortunately, probably because of the unique structure, it is difficult to synthesize chiral α-amino-*H*-phosphinic acids. Most of the available methods only lead to racemates.[6] Thus, almost all current literature data recordings used racemic *H*-phosphinic acids directly in their biological studies. As far as we know, only five α-amino-*H*-phosphinic acids have been described in the literature for their asymmetric syntheses.[7] This might be due to three reasons. First, the high reactivity of P−H group usually makes the preparation of *H*-phosphinic acid difficult. Second, the stereochemistry for organophosphorus compounds is complex because of the delocalization of P═O bond due to d−p π bond. To be specific, reliable methods to elucidate the stereochemistry of *H*-phosphinic acids or phosphinates are lacked. Finally, additional functionalization of amino acids emphasizes the difficulty toward the asymmetric syntheses of *H*-phosphinic analogues of the natural α-amino acids. For these reasons, studies on the asymmetric synthesis and biological studies of this type of compound are challenging.

Recently, a convenient procedure for the preparation of optically active α-aminophosphinates by using *N*-tertbutanesulfinyl imines as chiral auxiliaries was described.[8] $Rb_2CO_3$ was found to have suitable basicity in the asymmetric synthesis of phosphinates. Also, a procedure describing a one-pot transformation of protected P−H group into P−O or P−N group by bromine, which provides a convenient method to elucidate the absolute configuration and dr values of α-aminophosphinates, was developed.[5] Herein, as a part of our systematic efforts in the study of *H*-phosphinic acids and their derivatives, we describe the first systematic stereoselective synthesis of *H*-phosphinic isosteres of α-amino acids (Scheme 2). Nucleophilic attack of ethyl diethoxymethylphosphinate on sulfinamide **1** bearing a side chain of a natural amino acid gave phosphinate **2**, which was then subsequently converted to α-amino-*H*-phosphinate **3** or α-amino-*H*-phosphinic acid **4**.

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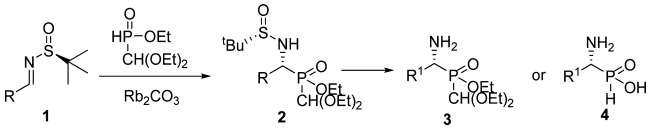
**Scheme 2. Asymmetric Syntheses of α-Amino-*H*-phosphinic Acids**

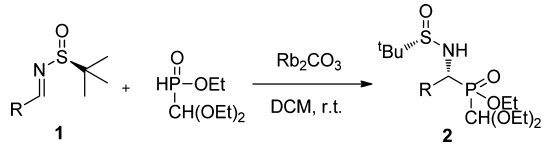


## RESULTS AND DISCUSSION

Amino acids can be catalogued as follows: (i) nonfunctionalized amino acids (alanine, glycine, phenylalanine, valine, and leucine); (ii) amino acids with additional functionalities, including hydroxyl (serine, tyrosine, and threonine), sulfanyl (methionine and cysteine), amino (tryptophan, arginine, and proline), and amide linkage (asparagines, pyroglutamic acid, and glutamine); (iii) dicarboxylic acids (aspartic acid and glutamic acid); and (iv) amino acids containing two amino groups (lysine). In order to achieve the asymmetric synthesis of their phosphinic analogues, protection of additional functional group is necessary.

Consequently, (*S*)-sulfinamide **1** was first prepared by condensation of (*S*)-2-methylpropane-2-sulfinamide and corresponding aldehyde by $Ti(OPr^i)_4$ or $CuSO_4$,[9] followed by a nucleophilic reaction with diethoxymethylphosphinate to give phosphinates **2** with $Rb_2CO_3$ as a base at room temperature (Table 1). For most of substrates **1** with side chains of natural amino acids, the reactions proceeded successfully and gave good to high yields. Except for **1k** (entry 11), the product **2k** underwent debromination and decomposed, so it was directly subjected to the next reaction without further purification. (*R*)-Sulfinamide (−)-**1l** was used in this reaction as well (entry 13).

**Table 1. Preparation of Phosphinates 2**[a]

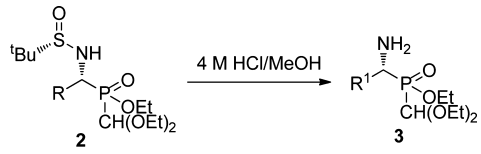


| entry | 2 | R | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | **2a** | Me | 30 | 84 |
| 2 | **2b** | $PhtN(CH_2)_3$ | 17 | 92 |
| 3 | **2c** | $BnSCH_2$ | 10 | 91 |
| 4 | **2d** | $FmSCH_2$ | 40 | 90 |
| 5 | **2e** | $MeOCO(CH_2)_2$ | 13 | 87 |
| 6 | **2f** | (*S*)-sec-Bu | 36 | 80 |
| 7 | **2g** | *i*-Bu | 24 | 90 |
| 8 | **2h** | $PhtN(CH_2)_4$ | 36 | 94 |
| 9 | **2i** | $MeS(CH_2)_2$ | 24 | 98 |
| 10 | **2j** | Bn | 15 | 64 |
| 11 | **2k** | $Br(CH_2)_3$ | 36 | –[c] |
| 12 | **2l** | $BnOCH_2$ | 72 | 50 |
| 13 | (−)-**2l** | $BnOCH_2$[d] | 17 | 88 |
| 14 | **2m** | (*R*)-MeCH(OBn) | 17 | 92 |
| 15 | **2n** | 3′-indolyl-$CH_2$ | 36 | 96 |
| 16 | **2o** | 4-$MeOC_6H_4CH_2$ | 36 | 93 |
| 17 | **2p** | *i*-Pr | 24 | 70 |

[a]The reaction was carried out with **1** (5 mmol), ethyl diethoxymethylphosphinate (4 mmol) and $Rb_2CO_3$ (25 mmol) in 50 mL of DCM at room temperature. [b]Separated yield after column chromatography. [c]The product was unstable, and debromination was detected, so it was subjected to the next reaction without further purification. [d](*R*)-Sulfinamide was used as substrate instead of (*S*)-sulfinamide.

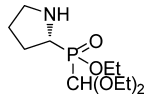
The removal of the protecting groups of phosphinate **2** was attempted. The conditions of 4 M HCl in the solvent of methanol at room temperature was found to be suitable to remove the *tert*-butylsulfinyl group to give phosphinate **3** with good to excellent yields (Table 2). This mild condition does not affect the phosphinate group at all, but side chains with a methyl ester group (**2e**, entry 4) would undergo transesterification to give an ethyl ester group when the reaction was performed with 1 M HCl in EtOH. When prolonging the reaction of **2e** with 1 M HCl in EtOH, partial hydrolysis was detected as well (entry 4). Phosphinate **2k** with a bromine-substituted side chain underwent cyclization to give phosphinate **3k** under the acidic condition (entry 10).

**Table 2. Removal of *tert*-Butylsulfinyl Group of 2 to Phosphinates 3**[a]



| entry | 3 | $R^1$ | yield (%)[b] |
|---|---|---|---|
| 1 | **3b** | $PhtN(CH_2)_3$ | quant. |
| 2 | **3c** | $BnSCH_2$ | 90 |
| 3 | **3d** | $FmSCH_2$ | 83 |
| 4 | **3e** | $EtOCO(CH_2)_2$ | 65[c,d] |
| 5 | **3f** | (*S*)-sec-Bu | 82 |
| 6 | **3g** | *i*-Bu | 90 |
| 7 | **3h** | $PhtN(CH_2)_4$ | 94 |
| 8 | **3i** | $MeS(CH_2)_2$ | 99 |
| 9 | **3j** | Bn | quant. |
| 10 | **3k** | –[f] | 80[e] |
| 11 | **3l** | $BnOCH_2$ | quant. |
| 12 | (−)-**3l** | $BnOCH_2$ | 92 |
| 13 | **3m** | (*R*)-MeCH(OBn) | 96 |
| 14 | **3n** | 3′-indolyl-$CH_2$ | 93 |
| 15 | **3p** | *i*-Pr | 98 |

[a]The reaction was carried out with **2** (0.5 mmol) in 2.5 mL of 4 M HCl in MeOH at room temperature for 75 min. [b]Separated yield after column chromatography. [c]The reaction was carried out for 20 h with 1 M HCl in EtOH. [d]When the reaction was carried out for 33 h in 1 M HCl in EtOH, 16% **3e** and 29% product with conversion of the ester group to carboxylic group ($R^1$ = $CH_2CH_2COOH$) were given. [e]Separated yield for 2 steps from **1k**. [f]The structure of product **3k** is as follows:



Next, the removal of the protecting groups leading to final product **4** was investigated. Our initial study showed that when phosphinate **2** was directly treated with 4 M HCl by heating to reflux for 15 h, *H*-phosphinic acid **4** was obtained for specific substrates without any additional functional group (Table 3, entries 1, 4, 9, 10). However, this procedure often led to byproducts that may be caused by the sulfinamide group, especially for functionalized substrates. After an exploration of the reaction conditions, simply by the reaction of phosphinate **3** in 4 M aqueous HCl by heating to reflux for 1.5 h, the


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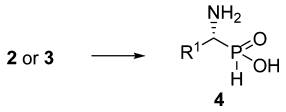
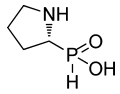
**Table 3. Preparation of Phosphinic Acids 4**




| entry | substrate | 4 | $R^1$ | yield (%) |
|---|---|---|---|---|
| 1 | **2a** | **4a** | Me | 80[a] |
| 2 | **3c** | **4c** | $BnSCH_2$ | 95[b] |
| 3 | **3f** | **4f** | (*S*)-sec-Bu | 97[b] |
| 4 | **2g** | **4g** | *i*-Bu | 33[a] |
| 5 | **3h** | **4h** | $PhtN(CH_2)_4$ | 49[b] |
| 6 | **3i** | **4i** | $MeS(CH_2)_2$ | 84[b] |
| 7 | **3j** | **4j** | Bn | 86[b] |
| 8 | **3k** | **4k** | –[c] | 63[b] |
| 9 | **2o** | **4o** | $4\text{-}MeOC_6H_4CH_2$ | 60[a] |
| 10 | **2p** | **4p** | *i*-Pr | 40[a] |

[a]Procedure A: **2** (0.2 mmol) in 4 M aqueous HCl (4 mL) was heated to reflux for 15 h and then treated with 20 mL of propylene oxide. [b]Procedure B: **3** (0.5 mmol) in 4 M aqueous HCl (2.5 mL) was heated to reflux for 1.5 h and then treated with 20 mL of propylene oxide. [c]The structure of product **4k** is as follows:

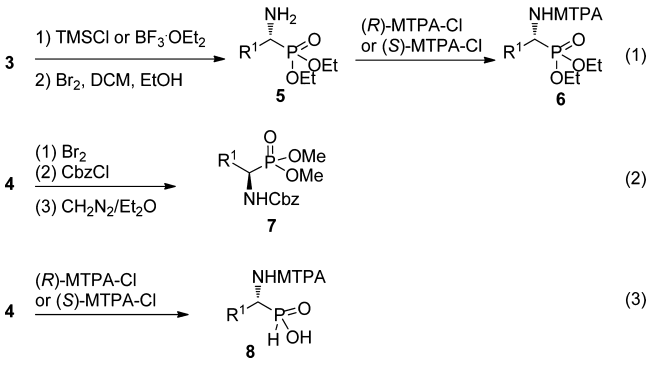



formation of byproducts was excluded (Table 3, entries 2, 3, 5–8).

Finally, the stereochemistry of these addition reactions was studied. $^{31}P$ NMR analysis indicates that phosphinate **2** has two isomers as major products and additional two as minor products. However, it is difficult to separate these isomers by chromatography for most substrates except **2c** and **2m**, and the chirality at the phosphorus center increased the difficulty. Thus to discriminate the absolute configuration of each isomer is almost impossible. Nevertheless, *N*-*tert*-butanesulfinyl imines do not have asymmetric inductive effect to the phosphinates group,[8] so just confirming the stereochemistry of the $\alpha$-substituent is adequate and realizable. For phosphinate **2** and **3**, although its dr value can be detected by $^{31}P$ NMR spectrum, we can not know the relative value between the isomer of ($R_c$) and ($S_c$), which actually reflects the enantioselectivities of these reactions.

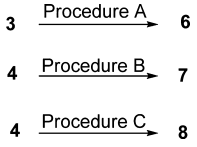
Thus, methods to determine of the constituents of the $\alpha$-carbon were studied (Scheme 3). To achieve this, phosphinate **3** was transferred to the diethyl phosphonate **5** by our previously developed one-pot procedure (Scheme 3, eq 1),[5]

**Scheme 3. Methods to Determine the Ratio of ($R_c$)/($S_c$)**




and then analysis of the NMR spectra of the Mosher's derivative **6** reflected its dr value. Also, oxidation and subsequent transformation of phosphinic acid **4** give phosphonate **7** (Scheme 3, eq 2). Further determination of the er value of compound **4** can be achieved by analysis of the HPLC spectrum of compound **7**. Direct conversion of **4** to its Mosher's derivative **8** provides another procedure to determine the er value of **4** (Scheme 3, eq 3) in the condition that diastereoisomers of **8** are distinguishable in their NMR or HPLC spectra. By the above procedures, the relative ratio of ($R_c$) and ($S_c$) isomers of **3** and **4** was determined (Table 4).

**Table 4. The Ratio of ($R_c$)/($S_c$) for 3 or 4**




| entry | substrate | $R^1$ | procedure[a] | ratio of ($R_c$)/($S_c$) |
|---|---|---|---|---|
| 1 | **4a** | Me | B | 90:10 |
| 2 | **3b** | $PhtN(CH_2)_3$ | A | 90:10 |
| 3 | **3c** | $BnSCH_2$ | – | single isomer separated |
| 4 | **3e** | $EtOCO(CH_2)_2$ | A | 88:12 |
| 5 | **4f** | (*S*)-sec-Bu | B | 97:3 |
| 6 | **4g** | *i*-Bu | B | 88:12 |
| 7 | **4h** | $PhtN(CH_2)_4$ | B | 89:11 |
| 8 | **4i** | $MeS(CH_2)_2$ | C | 81:19 |
| 9 | **4j** | Bn | B | 90:10 |
| 10 | **4k** | – | B | 79:21 |
| 11 | **3l** | $BnOCH_2$ | A | 66:34 |
| 12 | (–)-**3l** | $BnOCH_2$ | A | 69:31 |
| 13 | **3m** | (*R*)-MeCH(OBn) | – | single isomer separated |
| 14 | **3n** | 3′-indolyl-$CH_2$ | A[b] | 95:5 |
| 15 | **4o** | $4\text{-}MeOC_6H_4CH_2$ | B | 88:12 |
| 16 | **3p** | *i*-Pr | A | >95:5 |
| 17 | **4p** | *i*-Pr | B | >99:1 |

[a]Procedure A: Ratio of ($R_c$)/($S_c$) was measured by NMR spectra of **6**. Procedure B: Ratio of ($R_c$)/($S_c$) was determined by chiral HPLC analysis of **7**. Procedure C: Ratio of ($R_c$)/($S_c$) was estimated by NMR spectra and HPLC spectrum of **8**. [b]The indolyl group of **3n** was dibrominated.

For sterically hindered substrates such as **4f** (entry 5), **3n** (entry 14), and **3p** (entry 16, 17), excellent enantioselectivities were obtained, while less sterically hindered substrates (entry 1, 2, 4, 6–9, 15) provide good enantioselectivities. For **3l** or (–)-**3l** with a side chain of benzyloxy methyl group, relatively low dr values resulted for both (*S*) and (*R*)-sulfinamide (entry 11, 12), indicating that the asymmetric inductive effect of these two isomers was similar. Similar ratios were measured by both procedure A (entry 16) and procedure B (entry 17), indicating that both these two methods are liable to elucidate the enantioseletivity of these reactions. The major isomer of **2c** and **2m** were separated in yields of 48 and 45%, respectively. Subsequently they were subjected to the reaction providing single isomer of **3c** and **3m**, respectively (entry 3, 13).

Next, the absolute configuration of the $\alpha$-carbon atom was investigated by analyses of $^1H$ NMR spectra of Mosher's derivatives **6p**, which are single isomers, and it can be confirmed to be *R* (Table 5, Figure 1). Similar analyses of the derivatives of the Mosher's derivatives of the major isomer of **3m** go to the same conclusion.[10] These results indicate that


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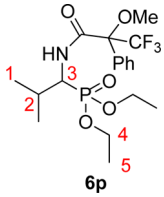
**Table 5. $^1$H NMR Data of (*S*) and (*R*)-Mosher's Derivative 6p**




6p

| | $\delta_{1\ (CH_3)_2}$ | $\delta_{2\ CH}$ | $\delta_{3\ CH}$ | $\delta_{4\ CH_2*2}$ | $\delta_{5\ CH_3*2}$ |
|---|---|---|---|---|---|
| (*R*)-MTPA | 1.06 | 2.31 | 4.35 | 4.06 | 1.26 |
| (*S*)-MTPA | 0.93 | 2.25 | 4.35 | 4.14 | 1.33 |
| $\Delta\delta_{(S)-(R)}$ | −0.13 | −0.06 | 0 | 0.08 | 0.07 |
| $\Delta\delta_{(S)-(R)}$ | <0 | <0 | 0 | >0 | >0 |

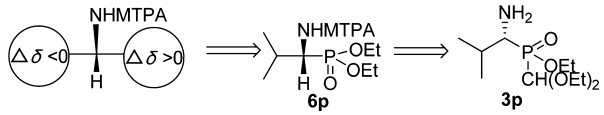
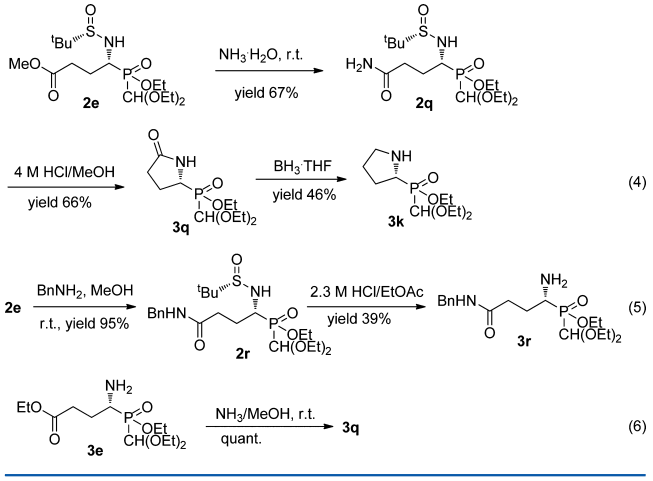



**Figure 1.** Absolute configuration of **3p** elucidated by Mosher's method.

the major isomer of **3** or **4** has the absolute configuration of *R* at the $\alpha$-carbon atom.

Further conversion of the side chains of the compounds **3** was studied. Transformation of the ester group of **2e** to amide group proceeded successfully in aqueous ammonia or $BnNH_2$ leading to **2q** (Scheme 4, eq 4) or **2r** (Scheme 4, eq 5),

**Scheme 4. Transformation of Ester Group to Amide Group**

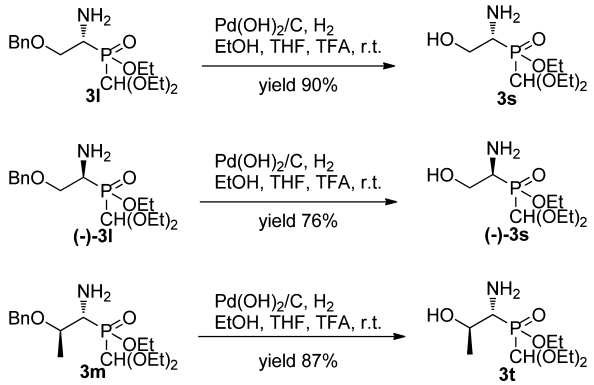



respectively. Quite interestingly, when **2q** was reacted with 4 M HCl in MeOH, intramolecular amidation took place and **3q** was obtained in 66% yield. As we know, **3q** is the intermediate toward the analogue of L-pyroglutamic acid. Also, **3q** can be transferred to **3k**, the intermediate of the analogue of L-proline. **3e** was converted to **3q** by aqueous ammonia in quantitative yield too (Scheme 4, eq 6), so the intramolecular amidation could take place under either acidic or basic conditions.

Trying to remove the benzyl group of **3l**, (−)-**3l** or **3m** by Pd/C and hydrogen failed. However, under the conditions of $Pd(OH)_2/C$ and hydrogen, this group could be deprotected successfully to give corresponding alcohols (Scheme 5).

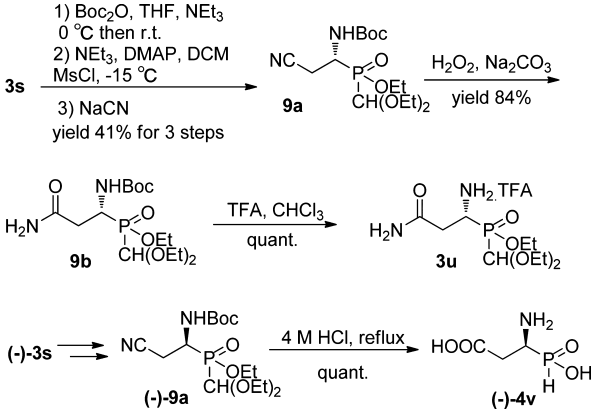
The $\beta$-hydroxyl group of phosphinate **3s** or (−)-**3s** can be transferred into amide group or carboxylic group via a cyano

**Scheme 5. Removal of Benzyl Group**




intermediate **9a** or (−)-**9a** (Scheme 6). First, **3s** or (−)-**3s** was converted to **9a** or (−)-**9a**. Then in hydrogen peroxide, **9a** was

**Scheme 6. Transformation of the Analogues of Serine to Asparagine and Aspartic Acid**




converted to **9b**, after removal of the Boc group of which, **3u**, which is the intermediate of asparagine, was obtained in quantitative yield. The cyano group of (−)-**9a** was transferred to carboxylic group when refluxed in 4 M HCl giving the analogue of D-aspartic acid (−)-**4v**.

As demonstrated in our previous work,[5] the P−H group of phosphinate **3** can be transferred to different groups such as P−O or P−N group. Also, condensation of phosphinate **3** with *N*-protected amino acids or dipeptides (Table 6) leads to phosphorus-oligopeptide **10** in moderate to quantitative yields by EDCI and HOBt.

These phosphorus-oligopeptides could be functioned as peptidomimetics for natural peptides. Previous studies have revealed their diverse bioactivity.[4] Initiate study on the bioactivity of these compounds indicates that compound **10a** may have inhibitive effect toward cell division cycle 25 homologue B (*Schizosaccharomyces pombe*) (CDC25B), which has oncogenic properties.[11]

## CONCLUSIONS

The first systematic enantioselective preparation of *H*-phosphinic analogues of $\alpha$-amino acids has been studied on the basis of the asymmetric addition of phosphinates to *N-tert*-butanesulfinyl imines. Good yields and moderate to excellent enantioselectivities have been obtained for 17 substrates with side chains of natural $\alpha$-amino acids. The transformation of the


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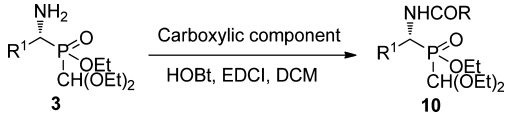
**Table 6. Preparation of Oligopeptide 10 from Phosphinate 3**[a]




| entry | 3 | $R^1$ | carboxylic component | 10 | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **3f** | (*S*)-sec-Bu | Boc-Phe-OH | **10a** | 79 |
| 2 | **3f** | (*S*)-sec-Bu | Boc-Val-OH | **10b** | quant. |
| 3 | **3j** | Bn | Boc-Val-OH | **10c** | 81 |
| 4 | **3g** | *i*-Bu | Fmoc-Ala-OH | **10d** | quant. |
| 5 | **3h** | $PhtN(CH_2)_4$ | Cbz-Gly-OH | **10e** | 93 |
| 6 | **3f** | (*S*)-sec-Bu | Boc-Phe-Val-OH | **10f** | 76 |
| 7 | **3g** | *i*-Bu | Boc-Phe-Val-OH | **10g** | 49 |
| 8 | **3j** | Bn | Boc-Phe-Val-OH | **10h** | 35 |
| 9 | **3p** | *i*-Pr | Boc-Phe-Val-OH | **10i** | 67 |
| 10 | **3p** | *i*-Pr | Boc-Phe-OH | **10j** | 98 |
| 11 | **3g** | *i*-Bu | Boc-Phe-OH | **10k** | 82 |
| 12 | **3r** | $BnNHCO(CH_2)_2$ | Boc-Phe-OH | **10l** | 44 |
| 13 | **3f** | (*S*)-sec-Bu | Boc-Trp-OH | **10m** | 78 |

[a]The reaction was carried out with 0.55 mmol carboxylic compound, 0.6 mmol HOBt, 0.6 mmol EDCI and 0.5 mmol **3** in 5.5 mL of DCM at 0 °C and then room temperature. [b]Separated yield after column chromatography.

analogue of glutamic acid to glutamine and pyroglutamic acid, and transformation of the analogue of serine to asparagine and aspartic acid analogues are studied as well. This study provides guidelines for the investigation of the stereochemistry of organophosphorus compounds in future studies. Furthermore, phosphorus-containing peptides are prepared from α-amino-phosphinates, and their potent biological activities as peptidomimetics could be expected in the future.

## EXPERIMENTAL SECTION

**General Methods.** Reactions were performed under nitrogen unless otherwise stated. Materials were obtained from commercial suppliers and used without further purification unless otherwise indicated. Preparative thin-layer chromatography (TLC) was performed with plates precoated with silica gel G.F. Flash chromatography was performed using silica gel (300−400 mesh). HRMS were detected by FT-ICR MS.

**Procedure for Preparation of 1.**[7] Procedure A: To a solution of (*S*)-2-methylpropane-2-sulfinamide (1820 mg, 15 mmol) in 30 mL of DCM, $CuSO_4$ (4849 mg, 30 mmol) and 20 mmol aldehyde were added at room temperature. After completion of the reaction monitored by TLC, the solution was filtered by Celite, washed by EtOAc, and then purified by silica gel column chromatography with petroleum ether/ethyl acetate (1:15 to 1:7) to give **1a**, **1e**, **1j** or **1p**. Data for compounds **1a**,[12] **1j**,[9b] and **1p**[9b] were in accordance with reported data. Compounds **1** are mainly in *E* form, but at times *Z* form can be detected by NMR. Most of them were unstable at room temperature, so they should be used as soon as they were purified.

Procedure B: To (*S*)-2-methylpropane-2-sulfinamide (623 mg, 5 mmol), $Ti(OPr^i)_4$ (2840 mg, 10 mmol), 6 mmol aldehyde and 1.5 mL of THF were added at room temperature. After completion of the reaction monitored by TLC, the solution was quenched by 1 mL of water with stirring, and 100 mL of ethyl acetate was added and then filtered by Celite. The solid was washed by 30 mL of ethyl acetate. The combined ethyl acetate phases were dried over anhydrous $Mg_2SO_4$ and then purified by silica gel column chromatography with petroleum ether/ethyl acetate (1:15 to 1:7) to give **1b**, **1c**, **1d**, **1f**, **1g**, **1h**, **1i**, **1k**, **1l**, (−)-**1l**, **1m**, **1n**, and **1o**. Data for compounds **1g**[13] and (−)-**1l**[14] were in accordance with reported data.

*Compound* ***1b***. Yield 86%, 1.38 g; white solid: mp 77 °C; $[\alpha]_D^{21}$ 158.6 (*c* 1.0, $CHCl_3$); IR (film) 2957, 2925, 1712, 1396, 1083, 720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.09 (t, *J* = 3.6 Hz, 1H), 7.85 (dd, $J_1$ = 2.8 Hz, $J_2$ = 5.2 Hz, 2H), 7.72 (dd, $J_1$ = 3.2 Hz, $J_2$ = 5.2 Hz, 2H), 3.79 (t, *J* = 6.8 Hz, 2H), 2.60 (m, 2H), 2.05 (m, 2H), 1.19 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 168.4, 167.9, 134.0, 132.1, 123.3, 56.7, 37.4, 33.5, 24.2, 22.3; MS (ESI) *m*/*z* (%) 343.1 [M + Na]$^+$; HRMS (ESI) Calcd for $C_{16}H_{20}N_2O_3SNa$ 343.1087, found 343.1101. Elemental analysis (%) calcd for $C_{16}H_{20}N_2O_3S$: C 59.98, H 6.29, N 8.74. Found: C 59.96, H 6.36, N 8.54.

*Compound* ***1c***. Yield 63%, 0.85 g; colorless oil: $[\alpha]_D^{22}$ 265.7 (*c* 1.0, $CHCl_3$); IR (film) 3028, 2977, 2959, 2924, 1611, 1454, 1087, 701 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.98 (t, *J* = 5.2 Hz, 1H), 7.35−7.24 (m, 5H), 3.70 (s, 2H), 3.35 (t, *J* = 5.6 Hz, 2H), 1.23 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 164.1, 137.3, 129.2, 128.7, 127.4, 57.0, 35.6, 34.4, 22.4; MS (ESI) *m*/*z* (%) 270.1 [M + H]$^+$; HRMS (ESI) Calcd for $C_{13}H_{19}NNaOS_2$ 292.0800, found 292.0801.

*Compound* ***1d***. Yield 71%, 1.27 g; yellow solid: mp 72−73 °C; $[\alpha]_D^{22}$ 191.4 (*c* 1.0, $CHCl_3$); IR (film) 3064, 2959, 2923, 2863, 1610, 1450, 1086, 743 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.96 (t, *J* = 5.6 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 4.11 (t, *J* = 6.4 Hz, 1H), 3.48−3.34 (m, 1H), 3.39−3.34 (m, 1H), 3.13−2.98 (m, 1H), 3.03−2.98 (m, 1H), 1.20 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 164.0, 145.6, 141.1, 127.7, 127.1, 124.8, 120.0, 57.0, 46.6, 36.1, 35.6, 22.4; MS (ESI) *m*/*z* (%) 358.1 [M + H]$^+$. Elemental analysis (%) calcd for $C_{20}H_{23}NOS_2$: C 67.19, H 6.48, N 3.92. Found: C 66.79, H 6.55, N 3.73.

*Compound* ***1e***. Yield 44%, 1.44 g; colorless oil: *E*/*Z* ≈ 5.2:1; $[\alpha]_D^{26}$ 187.8 (*c* 1.1, $CHCl_3$); IR (film) 2954, 2870, 1739, 1625, 1475, 1438, 1365, 1213, 1169, 1085, 998, 583 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.13 (t, *J* = 2.8 Hz, 1H), 3.68 (s, 3H), 2.84 (m, 2H), 2.68 (m, 2H), 1.17 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 172.7, 167.2, 56.8, 51.8, 31.0, 29.1, 22.2; MS (ESI) *m*/*z* (%) 220.1 [M + H]$^+$; HRMS (EI) Calcd for $C_9H_{17}NO_3S$ 219.0929, found 219.0933.

*Compound* ***1f***. Yield 38%, 0.36 g; colorless oil: $[\alpha]_D^{27}$ 208.7 (*c* 1.0, $CHCl_3$); IR (film) 2964, 2929, 2875, 1620, 1458, 1363, 1087, 1016, 725, 586 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, *J* = 5.1 Hz, 1H), 2.55 (m, 1H), 1.66 (m, 1H), 1.50 (m, 1H), 1.20 (s, 9H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.8 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 173.3, 56.4, 41.6, 26.7, 22.3, 16.4, 11.5; MS (ESI) *m*/*z* (%) 190.1 [M + H]$^+$; HRMS (ESI) Calcd for $C_9H_{20}NOS$ 190.1266, found 190.1265.

*Compound* ***1h***. Yield 72%, 1.21 g; colorless oil: $[\alpha]_D^{28}$ 154.5 (*c* 1.4, $CHCl_3$); IR (film) 3466, 2947, 1771, 1712, 1622, 1467, 1397, 1364, 1081, 1047, 721 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.06 (t, *J* = 4.8 Hz, 1H), 7.84 (dd, $J_1$ = 3.2 Hz, $J_2$ = 5.6 Hz, 2H), 7.72 (dd, $J_1$ = 3.2 Hz, $J_2$ = 5.6 Hz, 2H), 3.73 (t, *J* = 6.8 Hz, 2H), 2.59 (m, 2H), 1.77 (m, 2H), 1.71 (m, 2H), 1.18 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 168.8, 168.3, 134.0, 132.1, 123.2, 56.5, 37.5, 35.4, 28.1, 22.6, 22.3; MS (ESI) *m*/*z* (%) 335.2 [M + H]$^+$; HRMS (ESI) Calcd for $C_{17}H_{22}N_2O_3SNa$ 357.1243, found 357.1255.

*Compound* ***1i***. Yield 80%, 0.83 g; colorless oil: $[\alpha]_D^{25}$ 69.4 (*c* 2.0, $CHCl_3$); IR (film) 2960, 2917, 2867, 1623, 1428, 1363, 1184, 1087, 1018, 687, 582 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.09 (t, *J* = 2.8 Hz, 1H), 2.84−2.80 (m, 4H), 2.13 (s, 3H), 1.21 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 167.4, 56.7, 35.6, 29.5, 22.3, 15.5; MS (ESI) *m*/*z* (%) 208.1 [M + H]$^+$; HRMS (ESI) Calcd for $C_8H_{17}NOS_2Na$ 230.0644, found 230.0646.

*Compound* ***1k***. Yield 70%, 0.89 g; colorless oil: $[\alpha]_D^{28}$ 187.3 (*c* 1.0, $CHCl_3$); IR (film) 3480, 2964, 2926, 1629, 1455, 1363, 1247, 1081, 583 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.11 (t, *J* = 4.0 Hz, 1H), 3.50 (m, 2H), 2.72 (m, 2H), 2.23 (m, 2H), 1.20 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 167.8, 56.7, 34.4, 32.6, 28.1, 22.4; MS (ESI) *m*/*z* (%) 254.0 [M + H]$^+$; HRMS (EI) Calcd for $C_8H_{16}NOSBr$ 253.0136, found 253.0137.

*Compound* ***1l***. Yield 56%, 0.71 g; colorless oil: $[\alpha]_D^{23}$ 220.6 (*c* 0.8, $CHCl_3$); IR (film) 3063, 3031, 2960, 2926, 2866, 1632, 1274, 1455, 1363, 1085, 739, 699 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.13 (t, *J* = 3.2 Hz, 1H), 7.37−7.31 (m, 5H), 4.64 (s, 2H), 4.41 (t, *J* = 2.4 Hz,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2H), 1.22 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 166.8, 137.2, 128.6, 128.1, 127.9, 73.3, 71.3, 57.0, 22.4; MS (ESI) $m/z$ (%) 254.1 $[M + H]^+$; HRMS (EI) Calcd for $C_{13}H_{19}NO_2S$ 253.1137, found 253.1140.

*Compound* ***1m***. Yield 79%, 1.06 g; colorless oil: $[\alpha]_D^{27}$ 327.4 ($c$ 1.0, $CHCl_3$); IR (film) 3031, 2929, 2868, 1624, 1455, 1365, 1088, 699 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.06 (d, $J$ = 4.4 Hz, 1H), 7.36−7.26 (m, 5H), 4.65 (d, $J$ = 11.6 Hz, 1H), 4.53 (d, $J$ = 11.6 Hz, 1H), 4.34 (m, 1H), 1.39 (d, $J$ = 6.8 Hz, 3H), 1.21 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 170.6, 137.6, 128.5, 127.9, 127.8, 76.3, 71.7, 57.0, 22.4, 18.7; MS (ESI) $m/z$ (%) 268.1 $[M + H]^+$; HRMS (ESI) Calcd for $C_{14}H_{21}NO_2SNa$ 290.1185, found 290.1197.

*Compound* ***1n***. Yield 48%, 0.63 g; yellow oil: $[\alpha]_D^{26}$ 205.3 ($c$ 1.0, $CHCl_3$); IR (film) 3290, 3059, 2960, 1620, 1457, 1064, 742 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.32 (br, 1H), 8.16 (t, $J$ = 5.2 Hz, 1H), 7.58 (d, $J$ = 8.0 Hz, 1H), 7.36 (d, $J$ = 8.0 Hz, 1H), 7.20 (dt, $J_1$ = 1.2 Hz, $J_2$ = 8.0 Hz, 1H), 7.12 (dt, $J_1$ = 0.8 Hz, $J_2$ = 8.0 Hz, 1H), 7.05 (d, $J$ = 2.0 Hz, 1H), 3.95 (d, $J$ = 5.2 Hz, 2H), 1.19 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 167.7, 136.3, 127.2, 122.7, 122.4, 119.7, 118.7, 111.3, 109.0, 56.8, 32.5, 22.4; MS (ESI) $m/z$ (%) 263.0 $[M + H]^+$; HRMS (ESI) Calcd for $C_{14}H_{19}N_2OS$ 263.1213, found 263.1220.

*Compound* ***1o***. Yield 66%, 0.84 g; yellow oil: $[\alpha]_D^{24}$ 267.0 ($c$ 2.0, $CHCl_3$); IR (film) 2958, 2835, 1620, 1512, 1248, 1177, 1086, 831, 667 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.10 (t, $J$ = 4.8 Hz, 1H), 7.14 (d, $J$ = 8.4 Hz, 2H), 6.86 (d, $J$ = 8.8 Hz, 2H), 3.79 (s, 3H), 3.76 (m, 2H), 1.18 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 167.7, 158.7, 130.3, 126.7, 114.3, 56.8, 55.3, 41.8, 22.4; MS (ESI) $m/z$ (%) 254.1 $[M + H]^+$; HRMS (ESI) Calcd for $C_{13}H_{20}NO_2S$ 254.1209, found 254.1209.

**Procedure for Preparation of 2.** To $Rb_2CO_3$ (5770 mg, 25 mmol), ethyl diethoxymethylphosphinate (3920 mg, 20 mmol), and 50 mL of DCM were added at room temperature. After 15 min, compound **1** (5 mmol) was added to the solution. After completion of the reaction monitored by TLC, the reaction was quenched by 30 mL of water and then extracted with ethyl acetate (50 mL × 3) and washed with 30 mL of brine. The combined organic phases were dried over anhydrous $Na_2SO_4$ and then purified by silica gel column chromatography with petroleum ether/ethyl acetate (2:3 to 1:5) to give **2**.

*Compound* ***2a***. Yield 84%, 1.44 g; colorless oil: $[\alpha]_D^{25}$ 64.1 ($c$ 2.0, $CHCl_3$); IR (film) 3465, 3184, 2978, 2931, 1740, 1653, 1476, 1391, 1365, 1296, 1216, 1061, 959, 557 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.97 (m, 1H), 4.27 (m, 2H), 4.12 (m, 1H), 3.93−3.73 (m, 5H), 1.50−1.41 (m, 3H), 1.39−1.34 (m, 3H), 1.29−1.27 (m, 6H), 1.23 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 100.3 (d, $J$ = 140.3 Hz), 66.1 (d, $J$ = 9.3 Hz), 65.4 (d, $J$ = 8.8 Hz), 62.3 (d, $J$ = 7.4 Hz), 55.8 (d, $J$ = 0.9 Hz), 46.8 (d, $J$ = 95.4 Hz), 22.3 (s), 16.5 (d, $J$ = 5.1 Hz), 15.1 (d, $J$ = 7.5 Hz), 14.5 (d, $J$ = 0.9 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.11, 38.89, 38.72, 38.24; MS (ESI) $m/z$ (%) 344.2 $[M + H]^+$, 366.3 $[M + Na]^+$; HRMS (MALDI) Calcd for $C_{13}H_{31}NO_5PS$ 344.1655, found 344.1648.

*Compound* ***2b***. Yield 92%, 1.46 g; colorless oil: $[\alpha]_D^{26}$ 33.6 ($c$ 1.0, $CHCl_3$); IR (film) 3471, 3198, 2977, 1713, 1396, 1060, 722 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.83 (m, 2H), 7.72 (m, 2H), 5.07 (m, 1H), 4.26 (m, 2H), 3.95−3.75 (m, 4H), 3.70 (m, 4H), 2.0 (m, 2H), 1.83−1.64 (m, 2H), 1.26−1.22 (m, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 168.3 (s), 133.9 (s), 132.1 (s), 123.2 (s), 99.6 (d, $J$ = 139.3 Hz), 66.1 (d, $J$ = 10.2 Hz) and 65.2 (d, $J$ = 9.5 Hz), 62.7 (d, $J$ = 6.6 Hz), 56.8 (s), 52.0 (d, $J$ = 89.0 Hz), 37.6 (s), 27.2 (s), 25.0 (d, $J$ = 9.5 Hz), 22.7 (s), 16.7 (d, $J$ = 5.1 Hz), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 40.11, 39.59, 39.07, 38.70; MS (ESI) $m/z$ (%) 517.4 $[M + H]^+$; HRMS (ESI) Calcd for $C_{23}H_{37}N_2O_7PSNa$ 539.1951, found 539.1972. Elemental analysis (%) calcd for $C_{23}H_{37}N_2O_7PS$: C 53.48, H 7.22, N 5.42. Found: C 53.67, H 7.45, N 5.37.

*Compound* ***2c***. Yield 91%, 2.12 g; colorless oil: data for the major isomer (yield approximately 48%), $[\alpha]_D^{23}$ −14.2 ($c$ 1.0, $CHCl_3$); IR (film) 3187, 2977, 2927, 2360, 1495, 1221, 1061, 1031, 702 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33−7.21 (m, 5H), 5.06 (d, $J$ = 9.6 Hz, 1H), 4.27 (m, 2H), 3.94−3.76 (m, 5H), 3.74 (s, 2H), 3.69 (m, 1H), 3.06 (m, 1H), 2.74 (m, 1H), 1.34 (t, $J$ = 7.2 Hz, 3H), 1.29−1.21 (m, 15H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.0 (s), 129.0 (s), 128.6 (s), 127.2 (s), 99.7 (d, $J$ = 140.7 Hz), 66.2 (d, $J$ = 10.9 Hz) and 65.2 (d, $J$ = 8.8 Hz), 62.9 (d, $J$ = 6.5 Hz), 57.3 (s), 52.2 (d, $J$ = 86.1 Hz), 36.8 (s), 33.0 (d, $J$ = 4.4 Hz), 22.8 (s), 16.7 (d, $J$ = 4.3 Hz), 15.4 (d, $J$ = 6.6 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 36.59; MS (ESI) $m/z$ (%) 466.1 $[M + H]^+$; HRMS (ESI) Calcd for $C_{20}H_{36}NO_5PS_2Na$ 488.1665, found 488.1667. Elemental analysis (%) calcd for $C_{20}H_{36}NO_5PS_2$: C 51.59, H 7.79, N 3.01. Found: C 51.25, H 7.89, N 3.03.

*Compound* ***2d***. Yield 90%, 2.49 g; light yellow oil: $[\alpha]_D^{23}$ 3.1 ($c$ 1.0, $CHCl_3$); IR (film) 3190, 2977, 2927, 2863, 1476, 1448, 1218, 1060, 1033, 743 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.73 (m, 2H), 7.67 (m, 2H), 7.37 (t, $J$ = 7.2 Hz, 2H), 7.30 (m, 2H), 5.11−4.75 (m, 1H), 4.27 (m, 2H), 4.12 (t, $J$ = 5.6 Hz, 1H), 3.96−3.53 (m, 6H), 3.22−2.78 (m, 4H), 1.34 (t, $J$ = 6.8 Hz, 3H), 1.29−1.24 (m, 6H), 1.22−1.21 (m, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 145.9 (m), 141.2 (m), 127.6 (s), 127.0 (s), 124.9 (m), 119.9 (m), 100.3 (m), 66.3 (m) and 65.3 (m), 62.9 (m), 57.4 (m), 52.3 (m), 46.8 (m), 37.0 (m), 34.5 (m), 22.7 (m), 16.7 (m), 15.4 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 37.22, 37.16, 36.95, 36.69; MS (ESI) $m/z$ (%) 554.3 $[M + H]^+$; HRMS (ESI) Calcd for $C_{27}H_{40}NO_5PS_2Na$ 576.1978, found 576.1979.

*Compound* ***2e***. Yield 87%, 1.81 g; colorless oil: $[\alpha]_D^{27}$ 37.5 ($c$ 1.0, $CHCl_3$); IR (film) 3459, 3203, 2978, 1737, 1440, 1390, 1366, 1302, 1213, 1163, 1061, 959, 838, 593 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.10 (m, 1H), 4.29 (m, 2H), 4.0−3.72 (m, 6H), 3.68 (s, 3H), 2.78−2.45 (m, 2H), 2.29 (m, 1H), 1.98 (m, 1H), 1.37 (t, $J$ = 6.8 Hz, 3H), 1.30−1.25 (m, 15H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 173.0 (s), 99.7 (d, $J$ = 140.0 Hz), 66.5 (d, $J$ = 9.5 Hz) and 65.2 (d, $J$ = 9.5 Hz), 62.7 (d, $J$ = 7.3 Hz), 56.7 (s), 51.5 (s), 51.4 (d, $J$ = 89.7 Hz), 30.2 (d, $J$ = 8.8 Hz), 25.3 (d, $J$ = 2.9 Hz), 22.6 (s) 16.5 (d, $J$ = 5.1 Hz), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 39.94, 39.41, 38.89, 38.64; ESI ($m/z$) 416.5 $[M + H]^+$; HRMS (ESI) Calcd for $C_{16}H_{34}NO_7PSNa$ 438.1686, found 438.1707. Elemental analysis (%) calcd for $C_{16}H_{34}NO_7PS$: C 46.25; H 8.25; N 3.37. Found: C 46.04; H 8.37; N 3.22.

*Compound* ***2f***. Yield 59%, 1.14 g; colorless oil: $[\alpha]_D^{27}$ 76.5 ($c$ 1.1, $CHCl_3$); IR (film) 3479, 3334, 2974, 2931, 2876, 1644, 1462, 1390, 1365, 1216, 1061, 958, 870, 559, 497 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.16 (d, $J$ = 7.2 Hz, 1H), 4.28 (m, 2H), 3.96−3.65 (m, 6H), 2.11 (m, 1H), 1.70 (m, 1H), 1.35 (m, 3H), 1.31−1.25 (m, 15H), 1.21 (m, 1H), 1.01 (m, 3H), 0.92 (m, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 99.0 (d, $J$ = 137.8 Hz), 65.9 (d, $J$ = 11 Hz) and 64.8 (d, $J$ = 8.0 Hz), 62.4 (d, $J$ = 7.3 Hz), 57.2 (d, $J$ = 86.0 Hz), 57.0 (s), 35.9 (d, $J$ = 2.1 Hz), 24.3 (d, $J$ = 1.4 Hz), 22.9 (s), 16.7 (d, $J$ = 18.9 Hz), 16.6 (d, $J$ = 5.1 Hz), 15.4 (d, $J$ = 3.7 Hz), 11.9 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 40.23, 39.10, 39.06, 37.90; ESI ($m/z$) 386.3 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{16}H_{37}NO_5PS$ 386.2125, found 386.2123.

*Compound* ***2g***. Yield 90%, 1.73 g; colorless oil: $[\alpha]_D^{25}$ 33.8 ($c$ 1.2, $CHCl_3$); IR (film) 3466, 3188, 2957, 2870, 1500, 1387, 1366, 1294, 1215, 1062, 958, 795, 561 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.06 (d, $J$ = 7.5 Hz, 1H), 4.18 (m, 2H), 3.87−3.58 (m, 6H), 1.78 (m, 1H), 1.52 (m, 2H), 1.28−1.08 (m, 18H), 0.84 (dd, $J_1$ = 4.5 Hz, $J_2$ = 19.5 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 99.4 (d, $J$ = 137.1 Hz), 65.9 (d, $J$ = 9.4 Hz) and 64.9 (d, $J$ = 8.8 Hz), 62.5 (d, $J$ = 7.3 Hz), 56.9 (s), 50.7 (d, $J$ = 89.7 Hz), 38.3 (d, $J$ = 2.2 Hz), 23.8 (d, $J$ = 10.2 Hz), 23.4 (s), 22.7 (s), 20.5 (s), 16.6 (d, $J$ = 5.1 Hz), 15.3 (d, $J$ = 6.6 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.92, 39.24, 38.70, 38.66; ESI ($m/z$) 386.3 $[M + H]^+$; HRMS (ESI) Calcd for $C_{16}H_{37}NO_5PS$ 386.2125, found 386.2109.

*Compound* ***2h***. Yield 94%, 2.49 g; colorless oil: $[\alpha]_D^{28}$ 20.8 ($c$ 1.0, $CHCl_3$); IR (film) 3466, 3195, 2977, 2932, 1771, 1713, 1438, 1396, 1366, 1216, 1060, 958, 872, 722 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.76 (m, 2H), 7.64 (m, 2H), 5.03 (m, 1H), 4.19 (m, 2H), 3.80 (m, 4H), 3.67−3.53 (m, 4H), 1.88 (m, 1H), 1.61 (m, 4H), 1.35 (m, 1H), 1.27 (t, $J$ = 6.8 Hz, 3H), 1.23−1.11 (m, 15H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 168.3 (s), 133.9 (s), 132.1 (s), 123.2 (s), 99.6 (d, $J$ = 138.6 Hz), 66.1 (d, $J$ = 10.2 Hz) and 65.2 (d, $J$ = 8.7 Hz), 62.6 (d, $J$ = 7.3 Hz), 56.8 (s), 52.3 (d, $J$ = 89.0 Hz), 37.6 (s), 29.3 (s), 28.2 (s), 23.3 (d, $J$ = 9.5 Hz), 22.6 (s), 16.6 (d, $J$ = 4.3 Hz), 15.4 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.27, 38.92, 38.39, 38.0; ESI ($m/z$) 531.5 $[M +$


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H]$^+$; HRMS (ESI) Calcd for $C_{24}H_{39}N_2O_7PSNa$ 553.2108, found 553.2104.

*Compound* ***2i***. Yield 98%, 1.49 g; colorless oil: $[\alpha]_D^{25}$ 23.5 (*c* 2.0, $CHCl_3$); IR (film) 3448, 3192, 2978, 2919, 1475, 1443, 1390, 1296, 1216, 1163, 1060, 960, 562 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.10 (d, *J* = 9.6 Hz, 1H), 4.28 (m, 2H), 3.95−3.72 (m, 6H), 2.72 (m, 2H), 2.09 (m, 1H), 2.09 (s, 3H), 1.91 (m, 1H), 1.36 (t, *J* = 6.8 Hz, 3H), 1.29 (m, 6H), 1.25 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 99.7 (d, *J* = 139.2 Hz), 66.1 (d, *J* = 9.5 Hz) and 65.1 (d, *J* = 8.7 Hz), 62.7 (d, *J* = 7.2 Hz), 56.8 (s), 51.0 (d, *J* = 89.7 Hz), 30.2 (d, *J* = 10.9 Hz), 29.6 (d, *J* = 2.1 Hz), 22.7 (s), 16.7 (d, *J* = 5.1 Hz), 15.3 (d, *J* = 3.7 Hz), 15.0 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.12, 38.80, 38.29, 37.95; ESI (*m*/*z*) 404.3 [M + H]$^+$. Elemental analysis (%) calcd for $C_{15}H_{34}NO_5PS_2$: C 44.65; H 8.49; N 3.47. Found: C 44.21; H 8.72; N 3.34.

*Compound* ***2j***. Yield 64%, 1.34 g; colorless oil: $[\alpha]_D^{26}$ 3.9 (*c* 1.0, $CHCl_3$); IR (film) 3446, 3184, 3063, 2978, 2929, 1475, 1214, 1166, 1060, 959, 598 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.44−7.19 (m, 5H), 5.03 (m, 1H), 4.28 (m, 2H), 4.10−3.64 (m, 6H), 3.09 (m, 2H), 1.39−0.92 (m, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.4 (d, *J* = 11.7 Hz), 129.5 (m), 128.4 (m), 126.7 (m), 99.7 (d, *J* = 137.8 Hz), 66.2 (m) and 65.2 (d, *J* = 8.7 Hz), 62.9 (m), 56.7 (m), 53.9 (m), 36.0 (d, *J* = 4.4 Hz), 22.4 (m), 16.7 (m), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 66.34, 65.24, 64.93, 64.84; ESI (*m*/*z*) 420.3 [ M+ H]$^+$. Elemental analysis (%) calcd for $C_{19}H_{34}NO_5PS$: C 54.40; H 8.17; N 3.34. Found: C 54.51; H 8.26; N 2.94.

*Compound* ***2l***. Yield 50%, 1.12 g; colorless oil: $[\alpha]_D^{21}$ 36.4 (*c* 1.0, $CHCl_3$); IR (film) 3177, 2978, 2929, 2869, 1476, 1455, 1364, 1217, 1108, 1060, 958, 738, 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.40−7.28 (m, 5H), 5.0 (m, 1H), 4.54 (m, 2H), 4.39−3.94 (m, 4H), 3.93−3.72 (m, 5H), 3.60 (m, 1H), 1.35−1.21 (m, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 137.6 (s), 128.4 (s), 128.0 (s), 127.8 (s), 99.8 (d, *J* = 145.2 Hz), 73.5 (s), 69.0 (s), 66.0 (d, *J* = 10.9 Hz) and 65.5 (d, *J* = 8.7 Hz), 62.6 (d, *J* = 7.3 Hz), 56.6 (s), 52.3 (d, *J* = 88.2 Hz), 22.5 (s), 16.6 (m), 15.4 (m); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 38.26, 38.21, 37.89, 37.33; ESI (*m*/*z*) 450.3 [M + H]$^+$; HRMS (ESI) calcd for $C_{20}H_{37}NO_6PS$ 450.2074, found 450.2072.

*Compound (−)-***2l***.* Yield 88%, 1.98 g; colorless oil: $[\alpha]_D^{27}$ −34.4 (*c* 1.0, $CHCl_3$); IR (film) 3486, 3182, 2978, 2870, 1641, 1476, 1455, 1364, 1301, 1218, 1106, 1058, 959, 739, 700, 560 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.38−7.28 (m, 5H), 5.0 (m, 1H), 4.54 (m, 2H), 4.22 (m, 2H), 4.15−3.71 (m, 7H), 3.60 (m, 1H), 1.35−1.21 (m, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 137.6 (s), 128.3 (s), 127.9 (s), 127.8 (s), 99.7 (d, *J* = 145.1 Hz), 73.4 (s), 68.9 (s), 65.9 (d, *J* = 10.2 Hz) and 65.4 (d, *J* = 8.8 Hz), 62.5 (d, *J* = 7.3 Hz), 56.5 (s), 52.3 (d, *J* = 88.3 Hz), 22.4 (s), 16.5 (m), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 37.03, 36.68, 36.13; ESI (*m*/*z*) 450.5 [M + H]$^+$; HRMS (ESI) calcd for $C_{20}H_{36}NO_6PSNa$ 472.1893, found 472.1896.

*Compound* ***2m***. Yield 92%, 2.13 g; colorless oil: $[\alpha]_D^{26}$ 29.1 (*c* 1.0, $CHCl_3$); IR (film) 3478, 2977, 2929, 1455, 1390, 1217, 1060 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.40−7.26 (m, 5H), 5.27−4.67 (m, 1H), 4.62 (m, 1H), 4.48 (m, 1H), 4.31 (m, 1H), 4.26−2.84 (m, 8H), 1.53−1.12 (m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.0 (m), 128.1 (m), 127.7 (m), 127.3 (m), 100.6 (m), 77.1 (m), 72.1 (m), 67.3 (m), 64.8 (m), 62.3 (m), 57.1 (m), 22.7 (m), 16.8 (m), 16.3 (m), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.37, 37.12, 36.53, 35.58; ESI (*m*/*z*) 464.4 [M + H]$^+$; HRMS (MALDI) calcd for $C_{21}H_{38}NO_6PSNa$ 486.2050, found 486.2035.

*Compound* ***2n***. Yield 93%, 2.13 g; sticky yellow oil: $[\alpha]_D^{26}$ 4.7 (*c* 1.0, $CHCl_3$); IR (film) 3244, 2978, 2929, 1456, 1206, 1058, 960, 742 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.43 (s, 1H), 7.65 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.17 (dt, $J_1$ = 0.4 Hz, $J_2$ = 7.2 Hz, 1H), 7.13−7.07 (m, 2H), 4.79 (d, *J* = 10.4 Hz, 1H), 4.28 (m, 2H), 4.15 (m, 1H), 3.95−3.65 (m, 4H), 3.43 (m, 2H), 3.14 (m, 1H), 1.38−1.24 (m, 6H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 136.3 (s), 127.6 (s), 123.6 (s), 122.0 (s), 119.5 (s), 118.9 (s), 111.2 (s), 111.0 (s), 100.2 (d, *J* = 137.9 Hz), 66.3 (d, *J* = 8.8 Hz) and 65.3 (d, *J* = 10.3 Hz), 62.8 (d, *J* = 7.3 Hz), 56.6 (s), 52.7 (d, *J* = 88.2 Hz), 26.1 (d, *J* = 3.7 Hz), 22.3 (s), 16.6 (d, *J* = 5.1 Hz), 15.3 (d, *J* = 14.6 Hz); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 39.54, 38.72; ESI (*m*/*z*) 459.2 [M + H]$^+$; HRMS (ESI) Calcd for $C_{21}H_{35}N_2O_5PSNa$ 481.1897, found 481.1913. Elemental analysis (%) calcd for $C_{21}H_{35}N_2O_5PS$: C 55.00; H 7.69; N 6.11. Found: C 54.68; H 7.92; N 5.93.

*Compound* ***2o***. Yield 96%, 2.16 g; colorless oil: $[\alpha]_D^{26}$ 1.4 (*c* 1.3, $CHCl_3$); IR (film) 3184, 2978, 2931, 1613, 1514, 1456, 1391, 1248, 1060, 960, 831 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.14 (m, 2H), 6.83 (m, 2H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.26 (m, 2H), 4.2−3.6 (m, 6H), 3.78 (s, 3H), 3.34−2.76 (m, 2H), 1.39−0.96 (m, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 158.5 (s), 130.7 (s), 129.2 (d, *J* = 11.6 Hz), 113.8 (s), 99.7 (d, *J* = 138.6 Hz), 66.2 (d, *J* = 10.3 Hz) and 65.1 (d, *J* = 8.7 Hz), 62.7 (d, *J* = 7.3 Hz), 56.6 (s), 55.3 (s), 54.1 (d, *J* = 87.5 Hz), 35.0 (d, *J* = 3.6 Hz), 22.3 (s), 16.6 (d, *J* = 5.1 Hz), 15.4 (d, *J* = 5.9 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 36.52, 35.46, 35.25, 35.02; ESI (*m*/*z*) 450.4 [M + H]$^+$; HRMS (ESI) Calcd for $C_{20}H_{36}NO_6PSNa$ 472.1893, found 472.1915. Elemental analysis (%) calcd for $C_{20}H_{36}NO_6PS$: C 53.44; H 8.07; N 3.12. Found: C 53.12; H 8.18; N 2.97.

*Compound* ***2p***. Yield 70%, 1.30 g; colorless oil: $[\alpha]_D^{25}$ 44.5 (*c* 0.67, $CHCl_3$); IR (film) 3480, 3000, 2931, 2875, 1653, 1475, 1390, 1366, 1213, 1059, 952, 599 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.22−4.74 (m, 1H), 4.76−3.50 (m, 8H), 2.5−2.2 (m, 1H), 1.38−1.26 (m, 24H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 99.6 (m), 67.7−64.8 (m), 63.4−62.3 (m), 58.4−55.2 (m), 57.2 (s), 30.3−28.2 (m), 23.0−22.9 (m), 20.8 (m), 16.9 (m), 15.4 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.87, 38.95, 38.86, 37.70; ESI (*m*/*z*) 372.1 [M + H]$^+$; HRMS (MALDI) Calcd for $C_{15}H_{35}NO_5PS$ 372.1968, found 372.1954.

*Compound* ***2q***. **2q** was prepared from **2e**. To **2e** (420 mg, 1 mmol) was added 10 mL of aqueous ammonia and stirred overnight. The reaction was extracted by chloroform (20 mL × 5), washed with brine and then dried over anhydrous $Na_2SO_4$. The crude product was purified by column chromatography giving 267 mg colorless oil in 67% yield: $[\alpha]_D^{25}$ 40.8 (*c* 1.0, $CHCl_3$); IR (film) 3369, 3196, 2978, 1673, 1213, 1057, 594 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.80 (br, 1H), 6.28 (br, 1H), 5.03 (m, 1H), 4.69−4.41 (m, 1H), 4.27 (m, 2H), 3.90 (m, 2H), 3.83−3.65 (m, 3H), 2.52 (m, 1H), 2.42 (m, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.38−1.25 (m, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 175.2 (s), 99.7 (d, *J* = 139.3 Hz), 66.3 (d, *J* = 9.5 Hz) and 65.7 (d, *J* = 9.5 Hz), 62.9 (d, *J* = 7.3 Hz), 55.8 (s), 51.6 (d, *J* = 91.1 Hz), 31.9 (d, *J* = 8.0 Hz), 26.1 (s), 22.6 (s), 16.6 (m), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.22, 38.60, 38.44, 38.15; ESI (*m*/*z*) 401.4 [M + H]$^+$; HRMS (ESI) Calcd for $C_{15}H_{34}N_2O_6PS$ 401.1870, found 401.1878.

*Compound* ***2r***. **2r** was prepared from **2e**. To **2e** (414 mg, 1 mmol) in 5 mL of MeOH, 5 mL of $BnNH_2$ was added and stirred for 2 days. The solution was concentrated and then purified by column chromatography with DCM:MeOH ($NH_3$) (50:1), giving 467 mg colorless oil in 95% yield: $[\alpha]_D^{25}$ 33.9 (*c* 1.0, $CHCl_3$); IR (film) 3281, 2977, 1655, 1546, 1215, 1058, 699 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33−7.23 (m, 5H), 6.89−6.70 (m, 1H), 5.03 (m, 1H), 4.41 (m, 2H), 4.23 (m, 2H), 4.11 (m, 1H), 3.87 (m, 2H), 3.80−3.56 (m, 3H), 2.52 (m, 1H), 2.42 (m, 1H), 2.26 (m, 1H), 2.09 (m, 1H), 1.35−1.22 (m, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 172.1 (s), 138.5 (s), 128.6 (s), 127.7 (s), 127.3 (s), 99.9 (d, *J* = 140.0 Hz), 66.3 (d, *J* = 9.5 Hz) and 65.7 (d, *J* = 9.5 Hz), 62.8 (d, *J* = 7.3 Hz), 56.8 (s), 51.4 (d, *J* = 91.2 Hz), 43.4 (s), 32.8 (d, *J* = 7.3 Hz), 26.8 (s), 22.6 (s), 16.6 (d, *J* = 5.1 Hz), 15.3 (d, *J* = 5.8 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.97, 38.30, 38.25, 37.64; ESI (*m*/*z*) 491.5 [M + H]$^+$; HRMS (ESI) Calcd for $C_{22}H_{40}N_2O_6PS$ 491.2339, found 491.2347.

**Procedure for Preparation of 3.** To 0.5 mmol phosphinate **2**, 2.5 mL of 4 M HCl in MeOH was added at room temperature. After 75 min, the reaction monitored by TLC was completed. The solution was concentrated under a vacuum and then dissolved in DCM. MeOH saturated with ammonia was added to neutralize the residual acid. The crude product was purified by silica gel column chromatography with DCM/MeOH ($NH_3$) (50:1) to give phosphinate **3**.

*Compound* ***3b***. Yield >99%, 206 mg; colorless oil: $[\alpha]_D^{30}$ 1.0 (*c* 0.97, $CHCl_3$); IR (film) 3595, 3462, 3384, 2977, 2932, 1771, 1716, 1440, 1397, 1370, 1213, 1034, 722 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.83 (m, 2H), 7.72 (m, 2H), 4.88 (d, *J* = 7.2 Hz, 1H), 4.21

(m, 2H), 3.87 (m, 2H), 3.71 (m, 4H), 3.10 (m, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.82 (m, 1H), 1.53 (m, 1H), 1.42 (m, 2H), 1.33 (m, 3H), 1.24 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 168.2 (s), 133.8 (s), 132.0 (s), 123.0 (s), 100.6 (d, $J$ = 132.0 Hz), 65.4 (m), 61.7 (m), 48.6 (d, $J$ = 91.1 Hz), 37.5 (s), 27.3 (d, $J$ = 9.5 Hz), 25.2 (d, $J$ = 11.7 Hz), 16.6 (m), 15.1 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 41.44, 41.14; MS (ESI) $m/z$ (%) 413.3 $[M + H]^+$; HRMS (ESI) Calcd for $C_{19}H_{30}N_2O_6P$ 413.1836, found 413.1852. Analysis of $^{31}$P NMR and HPLC spectra of (*S*)-Mosher's derivate **6b**: retention time = 148.6 min, 170.6 min (89.9:10.1).

*Compound* ***3c***. Yield 90%, 162 mg; colorless oil: $[\alpha]_D^{30}$ −50.3 (*c* 1.0, $CHCl_3$); IR (film) 3370, 3292, 1221, 1109, 1057, 1035, 701 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.34−7.22 (m, 5H), 4.87 (d, $J$ = 7.2 Hz, 1H), 4.21 (m, 2H), 3.85 (m, 2H), 3.74 (s, 2H), 3.66 (m, 2H), 3.19 (m, 1H), 3.06 (m, 1H), 2.56 (m, 1H), 1.31 (t, $J$ = 6.8 Hz, 3H), 1.23 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.2 (s), 128.9 (s), 128.6 (s), 127.1 (s), 100.4 (d, $J$ = 136.4 Hz), 65.7 (d, $J$ = 8.0 Hz) and 65.4 (d, $J$ = 8.7 Hz), 62.1 (d, $J$ = 7.3 Hz), 48.8 (d, $J$ = 93.3 Hz), 36.5 (s), 33.6 (d, $J$ = 3.7 Hz), 16.7 (d, $J$ = 4.3 Hz), 15.3 (d, $J$ = 5.1 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.84; MS (ESI) $m/z$ (%) 362.1 $[M + H]^+$; HRMS (ESI) Calcd for $C_{16}H_{28}NO_4PSNa$ 384.1369, found 384.1383. Elemental analysis (%) calcd for $C_{16}H_{28}NO_4PS$: C 53.17, H 7.81, N 3.88. Found: C 52.88, H 7.79, N 3.95.

*Compound* ***3d***. Yield 82%, 184 mg; colorless oil: $[\alpha]_D^{24}$ −16.5 (*c* 1, $CHCl_3$); IR (film) 3063, 3039, 2977, 2928, 1477, 1448, 1295, 1216, 1108, 1057, 1034, 955, 744, 540 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.74 (d, $J$ = 7.6 Hz, 2H), 7.70 (d, $J$ = 7.2 Hz, 1H), 7.66 (d, $J$ = 7.2 Hz, 1H), 7.38 (t, $J$ = 7.2 Hz, 2H), 7.31 (t, $J$ = 7.6 Hz, 2H), 4.89 (t, $J$ = 7.6 Hz, 1H), 4.22 (m, 2H), 4.13 (t, $J$ = 6.0 Hz, 1H), 3.86 (m, 2H), 3.68 (m, 2H), 3.27−3.02 (m, 4H), 2.65 (m, 1H), 1.70 (s, 2H), 1.32 (m, 3H), 1.23 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 145.9 (s), 141.1 (d, $J$ = 3.6 Hz), 127.6 (s), 127.1 (s), 124.8 (d, $J$ = 18.3 Hz), 119.9 (s), 100.5 (d, $J$ = 137.1 Hz), 65.8 (m), 62.3 (m), 48.6 (d, $J$ = 93.3 Hz), 46.9 (s), 36.7 (s), 35.2 (s), 16.8 (d, $J$ = 5.1 Hz), 15.3 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 40.28, 39.89; MS (ESI) $m/z$ (%) 450.3 $[M + H]^+$; HRMS (ESI) Calcd for $C_{23}H_{33}NO_4PS$ 450.1862, found 450.1845.

*Compound* ***3e***. Yield 65%, 106 mg; colorless oil: $[\alpha]_D^{24}$ −2.5 (*c* 1.0, $CHCl_3$); IR (film) 3389, 2979, 2933, 2904, 1732, 1446, 1208, 1056, 1034, 956 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.86 (d, $J$ = 7.2 Hz, 1H), 4.23 (m, 2H), 4.13 (q, $J$ = 7.2 Hz, 2H), 3.88 (m, 2H), 3.71 (m, 2H), 3.08 (m, 1H), 2.62 (m, 1H), 2.51 (m, 1H), 2.20 (m, 1H), 1.80 (m, 1H), 1.64 (br, 2H), 1.35 (t, $J$ = 6.8 Hz, 3H), 1.26 (m, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 173.4 (s), 101.0 (d, $J$ = 131.2 Hz), 65.8 (d, $J$ = 8.0 Hz) and 65.6 (d, $J$ = 9.7 Hz), 61.9 (d, $J$ = 7.3 Hz), 60.4 (s), 48.6 (d, $J$ = 89.7 Hz), 31.0 (d, $J$ = 11.7 Hz), 25.5 (d, $J$ = 3.6 Hz), 16.7 (d, $J$ = 5.1 Hz), 15.2 (d, $J$ = 2.9 Hz), 14.2 (s); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 42.32, 42.03; MS (ESI) $m/z$ (%) 326.2 $[M + H]^+$; HRMS (ESI) Calcd for $C_{13}H_{29}NO_6P$ 326.1727, found 326.1717. Analysis of the $^{31}$P NMR and $^{19}$F NMR spectra of the (*S*)-Mosher's derivate **6e**: dr = 88:12.

*Compound* ***3f***. Yield 82%, 115 mg; colorless oil: $[\alpha]_D^{24}$ 10.4 (*c* 1.0, $CHCl_3$); IR (film) 3391, 2974, 2932, 2876, 1213, 1112, 1058, 953 cm$^{-1}$; $^1$H NMR ($CD_3OD$, 400 MHz) $\delta$ 4.99 (d, $J$ = 6.8 Hz, 1H), 4.24 (m, 2H), 4.92 (m, 2H), 3.74 (m, 2H), 3.13 (dd, $J_1$ = 4.0 Hz, $J_2$ = 6.8 Hz, 1H), 1.93 (m, 1H), 1.76 (m, 1H), 1.37 (t, $J$ = 7.2 Hz, 3H), 1.28 (m, 7H), 1.07 (d, $J$ = 36.4 Hz, 3H), 0.96 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CD_3OD$, 100 MHz) $\delta$ 100.7 (d, $J$ = 181.2 Hz), 66.0 (d, $J$ = 12.1 Hz) and 65.8 (d, $J$ = 11.6 Hz), 62.0 (d, $J$ = 10.2 Hz), 52.4 (d, $J$ = 121.5 Hz), 35.6 (s), 24.1 (s), 15.6 (s), 15.5 (d, $J$ = 5.9 Hz), 14.1 (d, $J$ = 20.0 Hz), 10.8 (s); $^{31}$P NMR ($CD_3OD$, 121 MHz) $\delta$ 44.10, 43.80; MS (ESI) $m/z$ (%) 282.2 $[M + H]^+$; HRMS (ESI) Calcd for $C_{12}H_{29}NO_4P$ 282.1829, found 282.1829.

*Compound* ***3g***. Yield 90%, 126 mg; colorless oil: $[\alpha]_D^{26}$ −5.8 (*c* 1.0, $CHCl_3$); IR (film) 3380, 2957, 2931, 1389, 1204, 1113, 1057, 825 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.88 (d, $J$ = 7.6 Hz, 1H), 4.23 (m, 2H), 3.89 (m, 2H), 3.71 (m, 2H), 3.16 (m, 1H), 1.96 (m, 1H), 1.56 (m, 1H), 1.46 (m, 1H), 1.35 (t, $J$ = 7.2 Hz, 3H), 1.27 (t, $J$ = 7.2 Hz, 6H), 0.97 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 100.7 (d, $J$ = 131.3 Hz), 65.7 (d, $J$ = 7.3 Hz) and 65.3 (d, $J$ = 8.8 Hz), 61.8 (d, $J$ = 7.3 Hz), 46.8 (d, $J$ = 91.9 Hz), 38.5 (s), 23.9 (d, $J$ = 12.4 Hz), 23.6 (s) and 20.8 (s), 16.7 (d, $J$ = 4.4 Hz), 15.2 (d, $J$ = 5.8 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 42.05; MS (ESI) $m/z$ (%) 282.3 $[M + H]^+$; HRMS (ESI) Calcd for $C_{12}H_{29}NO_4P$ 282.1829, found 282.1831.

*Compound* ***3h***. Yield 79%, 168 mg; colorless oil: $[\alpha]_D^{26}$ −10.9 (*c* 1.8, $CHCl_3$); IR (film) 3237, 2976, 2931, 2866, 1771, 1713, 1397, 1120, 1056, 722 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.84 (dd, $J_1$ = 3.2 Hz, $J_2$ = 5.2 Hz, 2H), 7.71 (dd, $J_1$ = 2.8 Hz, $J_2$ = 5.2 Hz, 2H), 4.86 (d, $J$ = 7.2 Hz, 1H), 4.21 (m, 2H), 3.87 (m, 2H), 3.71 (m, 4H), 3.04 (m, 1H), 1.89 (m, 1H), 1.78−1.68 (m, 3H), 1.47 (m, 2H), 1.33 (m, 3H), 1.26 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 168.4 (s), 133.9 (s), 132.2 (s), 123.2 (s), 100.9 (d, $J$ = 131.2 Hz), 65.7 (d, $J$ = 8.1 Hz) and 65.6 (d, $J$ = 8.8 Hz), 61.8 (m), 48.9 (d, $J$ = 91.1 Hz), 37.8 (s), 29.6 (d, $J$ = 6.6 Hz), 28.4 (s), 23.6 (d, $J$ = 11.6 Hz), 16.7 (d, $J$ = 4.4 Hz), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 40.96, 40.26; MS (ESI) $m/z$ (%) 427.5 $[M + H]^+$; HRMS (ESI) Calcd for $C_{20}H_{32}N_2O_6P$ 427.1992, found 427.2012.

*Compound* ***3i***. Yield 79%, 118 mg; colorless oil: $[\alpha]_D^{26}$ −8.8 (*c* 1.0, $CHCl_3$); IR (film) 3983, 2977, 2919, 1633, 1444, 1205, 1109, 1058, 957 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.87 (m, 1H), 4.23 (m, 2H), 3.88 (m, 2H), 3.70 (m, 2H), 3.38 (m, 1H), 2.80 (m, 1H), 2.68 (m, 1H), 2.16 (m, 1H), 2.11 (s, 3H), 1.76 (m, 1H), 1.35 (m, 3H), 1.27 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 101.0 (d, $J$ = 132.0 Hz), 65.8 (d, $J$ = 8.0 Hz) and 65.6 (d, $J$ = 8.8 Hz), 61.9 (d, $J$ = 8.0 Hz), 47.7 (d, $J$ = 90.4 Hz), 30.8 (d, $J$ = 13.1 Hz), 29.40 (s), 29.37 (s), 16.8 (d, $J$ = 5.1 Hz), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 42.78, 42.55; MS (ESI) $m/z$ (%) 300.3 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{11}H_{26}NO_4PSNa$ 322.1212, found 322.1212.

*Compound* ***3j***. Yield >99%, 158 mg; light yellow oil: $[\alpha]_D^{26}$ −9.6 (*c* 1.0, $CHCl_3$); IR (film) 3378, 2977, 2929, 1454, 1217, 1111, 1057, 953, 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.32 (m, 2H), 7.27−7.22 (m, 3H), 4.84 (m, 1H), 4.26 (m, 2H), 3.89 (m, 2H), 3.69 (m, 2H), 3.34 (m, 1H), 3.29 (m, 1H), 2.69 (m, 1H), 2.68 (m, 1H), 1.35 (t, $J$ = 6.8 Hz, 3H), 1.27 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 138.2 (d, $J$ = 13.2 Hz), 129.4 (s), 128.6 (s), 126.6 (s), 100.7 (d, $J$ = 136.3 Hz), 66.1 (d, $J$ = 8.0 Hz) and 65.6 (d, $J$ = 9.4 Hz), 62.1 (d, $J$ = 7.3 Hz), 50.2 (d, $J$ = 98.4 Hz), 36.6 (s), 16.8 (d, $J$ = 5.1 Hz), 15.3 (d, $J$ = 2.9 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 41.62, 41.22; MS (ESI) $m/z$ (%) 316.3 $[M + H]^+$; HRMS (ESI) Calcd for $C_{15}H_{27}NO_4P$ 316.1672, found 316.1673.

*Compound* ***3k***. Yield 80%, 106 mg; colorless oil: $[\alpha]_D^{25}$ −1.8 (*c* 1.0, $CHCl_3$); IR (film) 3444, 2976, 2932, 2876, 1445, 1210, 1108, 1059, 958, 540 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.87 (m, 1H), 4.24 (m, 2H), 3.88 (m, 2H), 3.72 (m, 2H), 3.43 (m, 1H), 3.03 (m, 1H), 2.91 (m, 1H), 2.10−2.01 (m, 3H), 1.85 (m, 1H), 1.73 (m, 1H), 1.34 (t, $J$ = 6.8 Hz, 3H), 1.26 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 100.3 (d, $J$ = 140.1 Hz), 65.5 (m), 62.5 (d, $J$ = 7.3 Hz), 53.6 (d, $J$ = 101.3 Hz), 47.4 (d, $J$ = 7.3 Hz), 25.6 (s), 25.5 (m), 16.6 (d, $J$ = 5.1 Hz), 15.2 (d, $J$ = 5.8 Hz); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 43.38, 42.90; MS (ESI) $m/z$ (%) 266.6 $[M + H]^+$; HRMS (ESI) Calcd for $C_{11}H_{25}NO_4P$ 266.1516, found 266.1528.

*Compound* ***3l***. Yield >99%, 173 mg; light yellow oil: $[\alpha]_D^{26}$ 0.44 (*c* 1.0, $CHCl_3$); IR (film) 3453, 2977, 2929, 2870, 1478, 1454, 1212, 1106, 1068, 1035, 956, 740, 700, 556 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.34−7.27 (m, 5H), 4.83 (m, 1H), 4.55 (m, 2H), 4.21 (m, 2H), 3.80 (m, 4H), 3.62 (m, 2H), 3.40 (m, 1H), 1.30 (m, 3H), 1.22 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 137.8 (s), 128.4 (s), 127.9 (s), 127.8 (s), 101.0 (d, $J$ = 137.1 Hz), 73.5 (s), 70.0 (d, $J$ = 19.6 Hz), 65.8 (m), 62.2 (m), 49.8 (d, $J$ = 91.1 Hz), 16.7 (m), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 40.18, 39.95; MS (ESI) $m/z$ (%) 346.3 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{16}H_{29}NO_5P$ 346.1775, found 346.1773. Analysis of the $^{19}$F NMR and $^{31}$P NMR spectra of the (*S*)-Mosher's derivative **6l**: dr = 66.0:34.0.

*Compound (−)-***3l***.* Yield >99%, 173 mg; light yellow oil: $[\alpha]_D^{27}$ 0.21 (*c* 1.0, $CHCl_3$); IR (film) 3453, 3385, 2988, 2871, 1641, 1604, 1454, 1212, 1106, 1058, 1034, 740, 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33−7.28 (m, 5H), 4.83 (m, 1H), 4.54 (m, 2H), 4.21 (m, 2H), 3.80 (m, 4H), 3.60 (m, 2H), 3.40 (m, 1H), 1.29 (m, 3H), 1.21


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(m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 137.8 (s), 128.3 (s), 127.8 (s), 127.7 (s), 100.9 (d, $J$ = 136.4 Hz), 73.4 (s), 69.9 (d, $J$ = 2.9 Hz), 65.6 (m), 61.9 (d, $J$ = 6.6 Hz), 49.7 (d, $J$ = 91.9 Hz), 16.6 (m), 15.1 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 40.05, 39.80 (1:0.8); MS (ESI) $m/z$ (%) 346.3 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{16}H_{29}NO_5P$ 346.1778, found 346.1787. Analysis of the $^{19}$F NMR and $^{31}$P NMR spectra of the (*S*)-Mosher's derivative (−)-**6l**: dr = 68.7:31.2.

*Compound* ***3m***. Yield 96%, 172 mg; colorless oil; the major isomer had a yield of about 45%, and it could be separated as single isomer with the following data: $[\alpha]_D^{23}$ −5.9 (*c* 1.0, $CHCl_3$); IR (film) 3455, 3389, 3310, 2977, 2930, 2898, 1606, 1454, 1392, 1219, 1034, 557 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.38−7.26 (m, 5H), 4.82 (d, $J$ = 7.2 Hz, 1H), 4.64 (d, $J$ = 10.8 Hz, 1H), 4.49 (d, $J$ = 10.8 Hz, 1H), 4.16 (m, 1H), 4.08 (m, 2H), 3.85 (m, 2H), 3.64 (m, 2H), 3.15 (dd, $J_1$ = 7.2 Hz, $J_2$ = 3.2 Hz, 1H), 1.36 (dd, $J_1$ = 6.0 Hz, $J_2$ = 0.8 Hz, 3H), 1.23 (dt, $J_1$ = 2.8 Hz, $J_2$= 7.2 Hz, 6H), 1.20 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.4 (s), 128.3 (s), 128.0 (s), 127.6 (s), 100.8 (d, $J$ = 137.8 Hz), 72.9 (s), 71.0 (s), 65.5 (d, $J$ = 8.8 Hz) and 65.3 (d, $J$ = 8.7 Hz), 61.8 (d, $J$ = 6.6 Hz), 54.4 (d, $J$ = 91.1 Hz), 16.5 (d, $J$ = 5.1 Hz), 16.3 (d, $J$ = 8.8 Hz), 15.3 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 40.14; MS (ESI) $m/z$ (%) 360.2 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{17}H_{30}NO_5PNa$ 382.1754, found 382.1746. Analysis of the $^1$H NMR spectra of the (*S*)-Mosher's and (*R*)-Mosher's derivatives of **5m** indicated the absolute configuration of (1*R*). But the configuration of the phosphorus atom could not be confirmed.

*Compound* ***3n***. Yield 74%, 131 mg; light yellow oil: $[\alpha]_D^{25}$ −13.7 (*c* 0.56, $CHCl_3$); IR (film) 3399, 3241, 2977, 1633, 1205, 1102, 1056, 1034, 742 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.45 (br, 1H), 7.64 (m, 1H), 7.37 (d, $J$ = 8.0 Hz, 1H), 7.17 (m, 2H), 7.11 (m, 1H), 4.90−4.77 (m, 1H), 4.27 (m, 2H), 3.85 (m, 2H), 3.77−3.49 (m, 3H), 3.41 (m, 1H), 2.95 (m, 1H), 2.39 (br, 2H), 1.36 (m, 3H), 1.28−1.21 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.5 (s), 133.9 (s), 127.5 (d, $J$ = 37.9 Hz), 123.6 (s), 122.1 (s), 119.5 (s), 118.9 (s), 111.4 (s), 100.7 (d, $J$ = 134.9 Hz), 65.9 (d, $J$ = 8.0 Hz) and 65.5 (d, $J$ = 8.8 Hz), 62.3 (d, $J$ = 7.3 Hz), 49.1 (d, $J$ = 94.8 Hz), 26.2 (s), 16.8 (m), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 41.23, 40.89; MS (ESI) $m/z$ (%) 355.1 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{17}H_{27}N_2O_4PNa$ 377.1601, found 377.1599. Analysis of the $^{19}$F NMR and $^{31}$P NMR spectra of the (*S*)-Mosher's derivative **6n** indicated the dr value was 94.8:5.2.

*Compound* ***3p***. Yield 98%, 131 mg; colorless oil: $[\alpha]_D^{26}$ 3.9 (*c* 1.2, $CHCl_3$); IR (film) 3390, 2975, 2931, 1208, 1113, 1057, 952, 551 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.87 (m, 1H), 4.23 (m, 2H), 3.89 (m, 2H), 3.71 (m, 2H), 3.0 (m, 1H), 2.25 (m, 1H), 1.34 (t, $J$ = 6.8 Hz, 3H), 1.26 (m, 6H), 1.08−1.0 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 100.9 (d, $J$ = 131.3 Hz), 65.6 (m), 61.6 (d, $J$ = 7.3 Hz), 53.4 (d, $J$ = 90.4 Hz), 27.7 (m), 20.8 (m), 17.0 (m), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 42.32, 41.82; MS (ESI) $m/z$ (%) 268.3 $[M + H]^+$; HRMS (ESI) Calcd for $C_{11}H_{27}NO_4P$ 268.1672, found 268.1674. Analysis of the $^1$H NMR, $^{19}$F NMR and $^{31}$P NMR spectra of the (*S*)-Mosher's derivative **6p** indicated the dr value was >95:5.

*Compound* ***3q***. **3q** was prepared from **2q** by the conditions of 4 M HCl/MeOH in a yield of 66% or from **3e** as the following procedure. **3e** (34 mg, 0.1 mmol) was dissolved in 10 mL of MeOH, which was previously saturated with $NH_3$ at room temperature. The reaction was stirred overnight. Then the solution was concentrated to give 30 mg colorless oil in quantitative yield: $[\alpha]_D^{28}$ 10.4 (*c* 1.0, $CHCl_3$); IR (film) 3434, 3234, 2979, 1699, 1209, 1106, 1056, 544 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.12−6.05 (m, 1H), 4.81 (m, 1H), 4.23 (m, 2H), 3.98 (m, 1H), 3.87 (m, 2H), 3.71 (m, 2H), 2.55−2.30 (m, 4H), 1.35 (m, 3H), 1.28 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 177.9 (d, $J$ = 3.7 Hz), 101.2 (d, $J$ = 140.0 Hz), 66.2 (m), 62.6 (d, $J$ = 7.3 Hz), 49.6 (d, $J$ = 100.6 Hz), 29.2 (d, $J$ = 2.2 Hz), 20.4 (d, $J$ = 3.7 Hz), 16.7 (d, $J$ = 5.1 Hz), 15.2 (d, $J$ = 4.4 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.28, 39.10; MS (ESI) $m/z$ (%) 302.2 $[M + Na]^+$; HRMS (ESI) Calcd for $C_{11}H_{22}NO_5PNa$ 302.1128, found 302.1134.

*Compound* ***3r***. **3r** was prepared by the reaction of **2r** with 2.3 M HCl in EtOAc instead of 4 M HCl in MeOH. Yield 39%, 73 mg; colorless oil: $[\alpha]_D^{26}$ 2.6 (*c* 1.0, $CHCl_3$); IR (film) 3282, 2977, 2930, 1657, 1548, 1206, 1056, 956, 699 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33−7.23 (m, 5H), 6.80 (br, 1H), 4.84 (m, 1H), 4.41 (d, $J$ = 5.6 Hz, 2H), 4.18 (m, 2H), 3.85 (m, 2H), 3.68 (m, 2H), 3.08 (m, 1H), 2.53 (m, 1H), 2.44 (m, 1H), 2.19 (m, 1H), 1.85 (m, 1H), 1.32 (t, $J$ = 6.8 Hz, 3H), 1.24 (t, $J$ = 6.8 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 172.5 (d, $J$ = 3.6 Hz), 138.5 (s), 128.6 (s), 127.7 (s), 127.3 (s), 100.8 (d, $J$ = 133.4 Hz), 65.8 (m), 62.0 (m), 48.4 (d, $J$ = 90.4 Hz), 43.5 (s), 33.2 (d, $J$ = 10.2 Hz), 26.6 (d, $J$ = 3.0 Hz), 16.7 (d, $J$ = 4.4 Hz), 15.3 (d, $J$ = 3.7 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 41.3; MS (ESI) $m/z$ (%) 387.5 $[M + H]^+$; HRMS (ESI) Calcd for $C_{18}H_{32}N_2O_5P$ 387.2043, found 387.2025.

*Compound* ***3s***. The product was obtained after the removal of the benzyl group of **3l** according to the following procedure. **3l** (37 mg, 0.1 mmol) was dissolved in 3.8 mL of EtOH, and 1.2 mL of THF, $Pd(OH)_2/C$ (37 mg, 20%, moisture) and TFA (41 $\mu$L, 0.5 mmol) were added subsequently. The reaction was stirred under hydrogen at 27 °C overnight. After the completion of the reaction, the mixture was filtered through Celite and washed by ethyl acetate. The solution was concentrated and then purified by silica gel column chromatography with DCM/MeOH ($NH_3$) (30:1) to give 23 mg colorless oil in a yield of 90%: $[\alpha]_D^{27}$ 2.2 (*c* 1.0, $CHCl_3$); IR (film) 3373, 2978, 2931, 1680, 1445, 1394, 1203, 1110, 1056, 958, 560 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.84 (m, 1H), 4.24 (m, 2H), 3.88 (m, 4H), 3.72 (m, 2H), 3.25 (m, 1H), 2.36 (br, 3H), 1.36 (m, 3H), 1.27 (t, $J$ = 6.8 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 101.2 (d, $J$ = 137.1 Hz), 66.2 (m), 62.3 (m), 61.9 (m), 50.9 (d, $J$ = 89.7 Hz), 16.7 (s), 15.2 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 41.36, 40.82; MS (ESI) $m/z$ (%) 256.1 $[M + H]^+$; HRMS (ESI) Calcd for $C_9H_{23}NO_5P$ 256.1308, found 256.1309.

*Compound* ***(−)-3s***. The product was obtained similar to that for **3s** as a colorless oil. Yield 76%, 19 mg; colorless oil: $[\alpha]_D^{27}$ −2.4 (*c* 1.0, $CHCl_3$); IR (film) 3370, 2977, 2931, 1393, 1203, 1107, 1056, 957 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.85 (m, 1H), 4.24 (m, 2H), 3.88 (m, 4H), 3.72 (m, 2H), 3.27 (m, 1H), 2.73 (br, 3H), 1.35 (t, $J$ = 7.2 Hz, 3H), 1.27 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 101.2 (d, $J$ = 137.1 Hz), 66.2 (m), 62.3 (m), 61.7 (m), 50.9 (d, $J$ = 87.5 Hz), 16.7 (s), 15.2 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 41.14, 40.71; the rest data are the same as compound **3s**.

*Compound* ***3t***. The product was obtained after the removal of the benzyl group from the single isomer of **3m** similar to that of **3s**. Yield 87%, 23 mg; colorless oil: $[\alpha]_D^{21}$ 4.1 (*c* 0.44, $CHCl_3$); IR (film) 3378, 2976, 2931, 1446, 1393, 1204, 1104, 1058, 669 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.83 (d, $J$ = 6.4 Hz, 1H), 4.32−4.18 (m, 3H), 3.89 (m, 2H), 4.16 (m, 1H), 3.72 (m, 2H), 3.06 (dd, $J_1$ = 4.8 Hz, $J_2$ = 8.0 Hz, 1H), 1.38−1.33 (m, 6H), 1.27 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 101.3 (d, $J$ = 135.3 Hz), 66.3 (d, $J$ = 8.6 Hz) and 66.0 (d, $J$ = 8.6 Hz), 65.6 (d, $J$ = 2.0 Hz), 62.3 (d, $J$ = 7.5 Hz), 54.0 (d, $J$ = 87.5 Hz), 19.8 (d, $J$ = 9.1 Hz), 16.7 (d, $J$ = 4.9 Hz), 15.2 (d, $J$ = 2.9 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 40.61; MS (ESI) $m/z$ (%) 270.1 $[M + H]^+$; HRMS (ESI) Calcd for $C_{10}H_{25}NO_5P$ 270.1465, found 270.1471.

*Compound* ***9a***. **9a** was prepared from **3s** according to the following procedure. **3s** (93 mg, 0.36 mmol) dissolved in 2 mL of THF at 0 °C, then $NEt_3$ (0.1 mL, 0.72 mmol) was added. $Boc_2O$ (0.17 mL, 0.72 mmol) in 0.8 mL of THF was added dropwise to the solution. After the reaction was stirred at 0 °C for 3 h, it was warmed to room temperature and stirred overnight. Then the solution was concentrated to give the crude product, which was directly subjected to next reaction. The crude product was dissolved in 6 mL of DCM, cooled to −15 °C, and then $NEt_3$ (0.15 mL, 1.08 mmol) and DMAP (44 mg, 0.36 mmol) were added. Then MsCl (0.14 mL, 1.8 mmol) in 1 mL of DCM was added dropwise. After about 3 h, the reaction was completed as indicated by TLC. Then 2 mL of diluted $NaHCO_3$ was added to quench the reaction. The aqueous phase was extracted with 10 mL × 3 EtOAc. The combined organic phases were washed with brine and then dried over anhydrous $Na_2SO_4$. The crude product passed through a short silica gel column to remove byproducts and gave 119 mg colorless oil in 76% yield. The product (119 mg, 0.268 mmol) was dissolved in 5 mL of DMF, and NaCN (131 mg, 2.68 mmol) was added. The reaction was warmed to 40 °C. After 2 h, the solution turned yellow. The reaction was completed as indicated by


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TLC. Twenty milliliters of EtOAc was added. The solution was washed by sat. $FeSO_4$ until the color of the organic phase remained. The organic phase was dried over anhydrous $Na_2SO_4$, and then purified by silica gel column chromatography with petroleum ether/ethyl acetate (1:1 to 1:5) to give 49 mg light yellow oil in 54% yield: $[\alpha]_D^{22}$ 3.2 (*c* 1.0, $CHCl_3$); IR (film) 3244, 2979, 2933, 2248, 1717, 1522, 1367, 1167, 1059, 1033, 561 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 5.56−5.27 (m, 1H), 4.80 (m, 1H), 4.43 (m, 1H), 4.27 (m, 2H), 3.87 (m, 2H), 3.71 (m, 2H), 2.92 (m, 2H), 1.46 (s, 9H), 1.37 (m, 3H), 1.28 (m, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ for the major isomer, 155.0 (d, *J* = 7.3 Hz), 116.7 (d, *J* = 11.0 Hz), 101.7 (d, *J* = 146.6 Hz), 80.7 (s), 67.1 (d, *J* = 8.1 Hz) and 66.6 (d, *J* = 10.2 Hz), 63.3 (m), 44.4 (d, *J* = 97.7 Hz), 28.2 (s), 19.4 (d, *J* = 5.9 Hz), 16.6 (m), 15.2 (m); $^{31}P$ NMR ($CDCl_3$, 162 MHz) $\delta$ 35.20, 34.73; MS (ESI) *m*/*z* (%) 387.1 $[M + Na]^+$; HRMS (ESI) Calcd for $C_{15}H_{30}N_2O_6P$ 365.1836, found 365.1847.

*Compound* ***9b***. **9b** was prepared from **9a** according to the following procedure. To **9a** (25 mg, 0.068 mmol), a mixture of 1.6 mL of acetone, 0.13 mL of sat. $Na_2CO_3$, and 0.66 mL of $H_2O_2$ was added. After the reaction was stirred at room temperature for 2 days, the reaction was completed as indicated by TLC. The solution was concentrated, and the crude product was purified by silica gel column chromatography with DCM/MeOH($NH_3$) (40:1) to give 22 mg of white sticky oil in 84% yield: $[\alpha]_D^{21}$ 1.6 (*c* 1.0, $CHCl_3$); IR (film) 3418, 3292, 3202, 2978, 1673, 1516, 1308, 1167, 1058, 545 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.84 (s, 1H), 5.86 (s, 1H), 5.79−5.70 (m, 1H), 4.81 (m, 1H), 4.52 (m, 1H), 4.24 (m, 2H), 3.86 (m, 2H), 3.70 (m, 2H), 2.74 (m, 2H), 1.44 (s, 9H), 1.34 (t, *J* = 6.8 Hz, 3H), 1.27 (m, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 172.5 (m), 155.6 (m), 100.8 (m), 80.3 (s), 66.7−66.2 (m), 62.9 (m), 45.0 (m), 35.7 (m), 20.2 (s), 16.6 (m), 15.2 (m); $^{31}P$ NMR ($CDCl_3$, 162 MHz) $\delta$ 38.44, 37.97; MS (ESI) *m*/*z* (%) 405.1 $[M + Na]^+$; HRMS (ESI) Calcd for $C_{15}H_{32}N_2O_7P$ 383.1942, found 383.1948.

*Compound* ***3u***. **3u** was prepared from **9b** as the following procedure. **9b** (7.8 mg, 0.02 mmol) wa dissolved in 0.4 mL of chloroform, and 0.2 mL of TFA was added. After the reaction was stirred at room temperature for 1 h, the reaction was completed as indicated by TLC. The solution was concentrated to give 8 mg light yellow oil in quantitative yield: $[\alpha]_D^{23}$ 3.8 (*c* 0.5, MeOH); IR (film) 3350, 3187, 2983, 1677, 1421, 1204, 1057, 1028, 800, 722 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 400 MHz) $\delta$ 5.00−4.96 (m, 1H), 4.22 (m, 2H), 3.94 (m, 1H), 3.82 (m, 2H), 3.66 (m, 2H), 2.88 (m, 1H), 2.67 (m, 1H), 1.30 (q, *J* = 6.8 Hz, 3H), 1.18 (t, *J* = 6.8 Hz, 6H); $^{13}C$ NMR ($CD_3OD$, 100 MHz) $\delta$ 173.7 (m), 102.4 (m), 68.6−68.0 (m), 65.7 (m), 45.6−44.2 (m), 32.8−32.3 (m), 17.0 (m), 15.6 (m); $^{19}F$ NMR ($CD_3OD$, 376 MHz) $\delta$ −77.33; $^{31}P$ NMR (MeOD-4, 162 MHz) $\delta$ 34.55, 33.92; MS (ESI) *m*/*z* (%) 282.9 $[M + H]^+$; HRMS (ESI) Calcd for $C_{10}H_{24}N_2O_5P$ 283.1417, found 283.1412.

**Procedure for Preparation of 4.** Procedure A: 4 mL of 4 M aqueous HCl was added to 0.2 mmol phosphinate **2** at room temperature. The reaction was heated to reflux. After 15 h, it was cooled to room temperature. The solution was washed by DCM (2 mL × 3). The aqueous phase was concentrated under a vacuum below the temperature of 40 °C. The residue was dissolved in 0.3 mL of EtOH, and then 20 mL of propylene oxide was added dropwise to the solution. White precipitate was formed. The mixture was stirred at room temperature overnight and then filtered to give white solid. Drying over the vacuum gave product **4a**, **4g**, **4o** or **4p**. Data for compound **4a** and **4g** were in accordance with reported literature.[6]

Procedure B: 2.5 mL of 4 M aqueous HCl was added to 0.5 mmol phosphinate **3** at room temperature. The reaction was heated to reflux for 1.5 h and then cooled to room temperature. The rest procedure was the same as Procedure A to give product **4c**, **4f**, **4h**, **4i**, **4j** or **4k**. Data for compound **4i** and **4j** were in accordance with reported literature.[6]

*Compound* ***4a***. Yield 80%, 17 mg. HPLC analysis of its dimethyl phosphonate derivate **2**−**7a**: Chiralpak PC-2, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL $min^{-1}$, retention time = 12.9 min, 10.8 min (89.8:10.2).

*Compound* ***4c***. Single isomer prepared from the major isomer of **3c**. Yield 95%, 110 mg; white solid: mp 225−227 °C; $[\alpha]_D^{26}$ −96.0 (*c* 0.97, MeOH); IR (film) 3409, 3024, 2920, 1601, 1494, 1199, 963, 700 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 400 MHz) $\delta$ 7.29 (d, *J* = 6.8 Hz, 2H), 7.24 (t, *J* = 6.8 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 3.75 (s, 2H), 3.38 (m, 1H), 2.91 (m, 1H), 2.68 (m, 1H); $^{13}C$ NMR ($CD_3OD$, 100 MHz) $\delta$ 138.8 (s), 130.2 (s), 129.8 (s), 128.5 (s), 49.0 (d, *J* = 127.6 Hz), 36.6 (s), 28.7 (s); $^{31}P$ NMR ($CD_3OD$, 121 MHz) $\delta$ 21.10, 20.55, 20.01 (1:1:1); MS (ESI) *m*/*z* (%) 232.1 $[M + H]^+$; HRMS (ESI) Calcd for $C_9H_{15}NO_2PS$ 232.0556, found 232.0563.

*Compound* ***4f***. Yield 97%, 73 mg; white solid: mp 229−231 °C; $[\alpha]_D^{27}$ −4.6 (*c* 1.0, $H_2O$); IR (film) 3414, 2966, 2388, 1639, 1608, 1536, 1458, 1170, 1044, 1020, 564, 452 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 400 MHz) $\delta$ 7.03 (d, *J* = 520.4 Hz, 1H), 2.74 (m, 1H), 1.88 (m, 1H), 1.62 (m, 1H), 1.21 (m, 1H), 1.05 (d, *J* = 5.6 Hz, 3H), 0.89 (m, 3H); $^{13}C$ NMR ($CD_3OD$, 100 MHz) $\delta$ 57.1 (d, *J* = 102.9 Hz), 35.4 (s), 26.6 (s), 16.2 (d, *J* = 5.9 Hz), 11.6 (s); $^{31}P$ NMR ($CD_3OD$, 121 MHz) $\delta$ 16.18; MS (ESI) *m*/*z* (%) 150.1 $[M - H]^-$; HRMS (MALDI) Calcd for $C_5H_{14}NO_2PNa$ 174.0654, found 174.0654. HPLC analysis of its dimethylphosphonate derivative **7f**: AD-H, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL $min^{-1}$, retention time = 5.18 and 6.18 min (97.2:2.8).

*Compound* ***4g***. Yield 33%, 10 mg. HPLC analysis of its dimethylphosphonate derivative **7g**: Chiralpak PC-2, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL $min^{-1}$, retention time = 9.6 and 7.2 min (87.7:12.3).

*Compound* ***4h***. Yield 49%, 72 mg; white solid: mp 206−208 °C; $[\alpha]_D^{28}$ −8.1 (*c* 0.83, $H_2O$); IR (film) 3448, 2940, 1773, 1706, 1542, 1400, 1173, 1044, 963, 894, 719 $cm^{-1}$; $^1H$ NMR ($D_2O$, 400 MHz) $\delta$ 7.70 (m, 4H), 6.92 (d, *J* = 532.8 Hz, 1H), 3.58 (m, 2H), 3.04 (m, 1H), 1.86 (m, 1H), 1.75−1.58 (m, 3H), 1.46 (m, 2H); $^{13}C$ NMR ($D_2O$, 100 MHz) $\delta$ 170.7 (s); 134.7 (s); 131.3 (s); 123.3 (s); 50.4 (d, *J* = 91.2 Hz), 37.3 (s), 27.4 (s); 25.9 (s); 22.7 (d, *J* = 8.7 Hz); $^{31}P$ NMR ($D_2O$, 121 MHz) $\delta$ 21.08; ESI (*m*/*z*) 295.0 $[M - H]^-$; HRMS (MALDI) Calcd for $C_{13}H_{17}N_2O_4PNa$ 319.0818, found 319.0815. HPLC analysis of its dimethylphosphonate derivative **7h**: Chiralpak PC-2, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL $min^{-1}$, retention time = 39.4 and 28.8 min (89.4:10.6).

*Compound* ***4i***. Yield 84%, 71 mg. Analysis of the $^{31}P$ NMR and $^{19}F$ NMR spectra of its Mosher's derivative **8i** indicated a er value of 81.3:18.7.

*Compound* ***4j***. Yield 86%, 80 mg. HPLC analysis of its dimethylphosphonate derivative **7j**: Chiralpak PC-2, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL $min^{-1}$, retention time = 23.0 and 11.9 min (90.3:9.7).

*Compound* ***4k***. Yield 37%, 25 mg; white solid: mp 211 °C; $[\alpha]_D^{28}$ −6.7 (*c* 0.75, $H_2O$); IR (film) 3416, 2962, 2301, 1632, 1448, 1192, 1056, 966, 560 $cm^{-1}$; $^1H$ NMR ($D_2O$, 400 MHz) $\delta$ 6.98 (d, *J* = 537.6 Hz, 1H), 3.42 (m, 1H), 3.30 (t, *J* = 6.8 Hz, 2H), 2.19 (m, 1H), 2.07−1.90 (m, 3H); $^{13}C$ NMR ($D_2O$, 100 MHz) $\delta$ 57.5 (d, *J* = 91.2 Hz), 46.9 (d, *J* = 4.4 Hz), 24.0 (s), 23.8 (d, *J* = 7.3 Hz); $^{31}P$ NMR ($D_2O$, 121 MHz) $\delta$ 19.69; ESI (*m*/*z*) 134.1 $[M - H]^-$; HRMS (ESI) Calcd for $C_4H_9NO_2P$ $[M - H]^-$ 134.0373, found 134.0380. HPLC analysis of its dimethylphosphonate derivative **7k**: Chiralpak PA-2, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL $min^{-1}$, retention time = 17.7 and 15.1 min (79.4:20.6).

*Compound* ***4o***. Yield 60%, 26 mg; white solid: mp 228−230 °C; $[\alpha]_D^{26}$ −28.6 (*c* 1.4, $H_2O$/NaOH); IR (film) 2934, 1613, 1514, 1250, 1173, 1032, 817, 726, 568, 515 $cm^{-1}$; $^1H$ NMR ($D_2O$, 300 MHz) $\delta$ 6.98 (m, 2H), 6.66 (m, 2H), 6.47 (d, *J* = 508.8 Hz, 1H), 3.49 (s, 3H), 2.89−2.4 (m, 2H), 2.20 (m, 1H); $^{13}C$ NMR ($D_2O$, 100 MHz) $\delta$ 157.5 (s); 130.9 (d, *J* = 14.6 Hz); 130.5 (s); 114.1 (s); 55.3 (s), 52.4 (d, *J* = 99.2 Hz), 34.3 (s); ESI (*m*/*z*) 213.9 $[M - H]^-$; HRMS (MALDI) Calcd for $C_9H_{13}NO_3P$ $[M - H]^-$ 214.0638, found 214.0643. HPLC analysis of its dimethylphosphonate derivative **7o**: Chiralpak PC-2, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL $min^{-1}$, retention time = 26.5 and 17.0 min (88.0:12.0).

*Compound* ***4p***. Yield 40%, 11 mg; white solid: mp 230−232 °C; $[\alpha]_D^{27}$ −2.44 (*c* 1.05, $H_2O$/NaOH); IR (film) 2962, 2359, 1640, 1548, 1468, 1177, 1042, 972, 548, 462 $cm^{-1}$; $^1H$ NMR ($D_2O$/NaOH, 300


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MHz) $\delta$ 6.93 (d, $J$ = 530.4 Hz, 1H), 2.75 (m, 1H), 2.10 (m, 1H), 0.96 (m, 6H); $^{13}$C NMR ($D_2O$/NaOH, 75 MHz) $\delta$ 56.4 (d, $J$ = 91.6 Hz), 28.8 (s), 19.4 (d, $J$ = 9.4 Hz) and 18.0 (d, $J$ = 8.7 Hz); $^{31}$P NMR ($D_2O$/NaOH, 121 MHz) $\delta$ 19.58; ESI ($m/z$) 136.1 $[M - H]^-$; HRMS (ESI) Calcd for $C_4H_{11}NO_2P$ $[M - H]^-$ 136.0533, found 136.0533. HPLC analysis of its dimethylphosphonate derivative **7p**: Chiralpak PC-2, *n*-hexane/2-propanol 50:50, $\lambda$ = 214 nm, flow rate = 0.7 mL min$^{-1}$, retention time = 8.9 and 7.5 min (99.6:0.4). Analysis of the NMR spectra of (*S*) and (*R*)-Mosher's derivatives of **5p** in which only one isomer was detected indicated similar dr value.

*Compound (−)-**4v**.* (−)-**4v** was prepared from (−)-**9a** according to the following procedure. (−)-**9a** (12 mg, 0.033 mmol) was dissolved in 0.66 mL of 4 M HCl, and the solution was heated to reflux for 2 h. The reaction was concentrated to give 6 mg of product in quantitative yield: $[\alpha]_D^{27}$ −0.39 (*c* 0.43, $H_2O$); IR (film) 3116, 3021, 1716, 1404, 1182, 1045, 668 cm$^{-1}$; $^1$H NMR ($D_2O$, 400 MHz) $\delta$ 6.99 (d, $J$ = 545.6 Hz, 1H), 3.47 (m, 1H), 2.91 (m 1H), 2.73 (m, 1H); $^{13}$C NMR ($D_2O$, 100 MHz) $\delta$ 173.6 (d, $J$ = 11.7 Hz), 46.9 (d, $J$ = 92.6 Hz), 30.5 (s); $^{31}$P NMR ($D_2O$, 162 MHz) $\delta$ 17.16; ESI ($m/z$) 152.0 $[M - H]^-$; HRMS (ESI) Calcd for $C_3H_7NO_4P$ $[M - H]^-$ 152.0118, found 152.0125.

**General Procedure for the Preparation of 10.** To 0.55 mmol carboxylic compound in 3 mL of DCM, HOBt (90 mg, 0.6 mmol) and EDCI (130 mg, 0.6 mmol) were added at 0 °C. After 15 min, 0.5 mmol **3** in 2.5 mL of DCM was added. After 3 h, the reaction was warmed to room temperature and then stirred overnight. After completion of the reaction monitored by TLC, the reaction was quenched by 5 mL of sat. $NaHCO_3$ and then extracted with EtOAc (20 mL × 3). The combined organic phases were washed with 10 mL of brine, dried over anhydrous $Na_2SO_4$ and then purified by silica gel column chromatography with petroleum ether/ethyl acetate (2:3 to 1:2) to give **10**.

*Compound **10a**.* Yield 79%, 209 mg; sticky colorless oil: $[\alpha]_D^{28}$ −28.7 (*c* 1.3, $CHCl_3$); IR (film) 3278, 2976, 2932, 1681, 1519, 1498, 1366, 1170, 1058, 558 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.23−7.13 (m, 5H), 6.46 (d, $J$ = 10.4 Hz, 1H), 5.0 (d, $J$ = 6.0 Hz, 1H), 4.44 (m, 2H), 4.30 (q, $J$ = 7.2 Hz, 1H), 4.04 (m, 2H), 3.75 (m, 2H), 3.54 (m, 2H), 3.10 (m, 1H), 2.95 (m, 1H), 1.95 (m, 1H), 1.63 (m, 1H), 1.33 (s, 9H), 1.16 (m, 9H), 1.01 (m, 1H), 0.89 (d, $J$ = 6.4 Hz, 3H), 0.80 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.0 (d, $J$ = 5.1 Hz), 155.6 (s), 136.7 (s), 129.3 (s), 128.6 (s), 126.8 (s), 99.8 (d, $J$ = 140.0 Hz), 80.2 (s), 66.2 (d, $J$ = 10.2 Hz) and 64.9 (d, $J$ = 8.0 Hz), 61.9 (d, $J$ = 6.6 Hz), 55.7 (s), 49.9 (d, $J$ = 94.1 Hz), 37.1 (s), 35.0 (s), 29.6 (s), 28.2 (s), 24.4 (s), 16.6 (m), 15.2 (m), 11.6 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.43; ESI ($m/z$) 551.6 $[M + Na]^+$; HRMS (MALDI) Calcd for $C_{26}H_{45}N_2O_7PNa$ 551.2857, found 551.2837.

*Compound **10b**.* Yield >99%, 240 mg; sticky colorless oil: $[\alpha]_D^{28}$ −31.3 (*c* 1.25, $CHCl_3$); IR (film) 3278, 2974, 2933, 1716, 1673, 1521, 1366, 1209, 1173, 1060, 557 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.57−6.30 (m, 1H), 4.96 (d, $J$ = 8.0 Hz, 1H), 4.69 (d, $J$ = 9.2 Hz, 1H), 4.56−4.42 (m, 1H), 4.21 (m, 2H), 3.92−3.82 (m, 3H), 3.69 (m, 2H), 2.20 (m, 1H), 2.06 (m, 1H), 1.76 (m, 1H), 1.45 (s, 9H), 1.34−1.22 (m, 9H), 1.14 (m, 1H), 1.04−0.88 (m, 12H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.5 (m), 155.8 (s), 100.0 (d, $J$ = 140.0 Hz), 79.7 (s), 66.1 (m) and 64.7 (m), 61.8 (d, $J$ = 5.1 Hz), 60.4 (s), 49.8 (d, $J$ = 93.3 Hz), 35.0 (s), 29.9 (s), 28.1 (s), 24.3 (s), 19.3 (s), 17.7 (s), 16.5 (m), 15.1 (m), 11.5 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.67, 38.56; ESI ($m/z$) 481.7 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{22}H_{45}N_2O_7PNa$ 503.2857, found 503.2837.

*Compound **10c**.* Yield 81%, 208 mg; colorless oil: $[\alpha]_D^{26}$ −40.4 (*c* 1.14, $CHCl_3$); IR (film) 3271, 2977, 2931, 1716, 1681, 1497, 1206, 1172, 1060, 1038, 751 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.22−7.09 (m, 5H), 6.92−6.77 (m, 1H), 4.93 (m, 1H), 4.81 (m, 1H), 4.67−4.60 (m, 1H), 4.16 (m, 2H), 3.85−3.45 (m, 5H), 3.20 (m, 1H), 2.83 (m, 1H), 1.92 (m, 1H), 1.38−1.31 (m, 9H), 1.27−1.17 (m, 9H), 0.72−0.57 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.1 (m), 155.7 (m), 136.8 (d, $J$ = 11.9 Hz), 129.4 (s), 128.3 (s), 126.7 (s), 101.2 (d, $J$ = 143.7 Hz), 79.7 (s), 66.6 (m), 62.9 (m) and 60.4 (m), 46.7 (d, $J$ = 97.7 Hz), 34.4 (s), 30.5 (s), 28.3 (s), 19.2 (s), 17.3 (s) and 16.6 (s), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.90, 38.64, 38.49, 38.11; ESI ($m/z$) 515.6 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{25}H_{43}N_2O_7PNa$ 537.270, found 537.2708.

*Compound **10d**.* Yield 85%, 244 mg; white solid: mp 66 °C; $[\alpha]_D^{30}$ −31.9 (*c* 1.0, $CHCl_3$); IR (film) 3256, 3064, 2977, 1721, 1670, 1536, 1450, 1246, 1208, 1059, 1036, 741 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) 7.75 (d, $J$ = 7.2 Hz, 2H), 7.59 (d, $J$ = 7.6 Hz, 2H), 7.38 (t, $J$ = 7.6 Hz, 2H), 7.30 (t, $J$ = 7.6 Hz, 2H), 7.15 (br, 1H), 5.75 (br, 1H), 4.78 (d, $J$ = 9.2 Hz, 1H), 4.64 (m, 1H), 4.35 (m, 3H), 4.19 (m, 3H), 3.86 (m, 2H), 3.69 (m, 2H), 1.62 (m, 3H), 1.42 (d, $J$ = 6.8 Hz, 3H), 1.26 (m, 9H), 0.91 (m, 6H); $^{13}$C NMR ($CDCl_3$, 126 MHz) $\delta$ 172.3 (s), 155.8 (s), 143.8 (s), 141.3 (s), 127.7 (s), 127.1 (s), 125.1 (s), 120.0 (s), 100.4 (d, $J$ = 137.1 Hz), 67.0 (s), 66.4 (d, $J$ = 8.7 Hz) and 64.9 (d, $J$ = 8.8 Hz), 62.5 (d, $J$ = 7.3 Hz), 50.5 (s), 47.1 (s), 44.1 (d, $J$ = 94.8 Hz), 37.4 (s), 24.5 (d, $J$ = 12.4 Hz), 23.5 (s), 21.1 (s), 19.4 (s), 16.7 (d, $J$ = 5.1 Hz), 15.3 (d, $J$ = 3.6 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.51, 39.22, 38.80, 38.46; ESI ($m/z$) 597.5 $[M + Na]^+$; HRMS (MALDI) Calcd for $C_{30}H_{43}N_2O_7PNa$ 597.270, found 597.2670.

*Compound **10e**.* Yield 93%, 287 mg; colorless oil: $[\alpha]_D^{30}$ −22.9 (*c* 1.0, $CHCl_3$); IR (film) 3264, 2977, 2934, 1713, 1525, 1397, 1056, 721 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.80 (m, 2H), 7.67 (m, 2H), 7.35−7.30 (m, 5H), 6.92 (br, 1H), 5.89 (br, 1H), 5.11 (s, 2H), 4.76 (d, $J$ = 8.8 Hz, 1H), 4.52 (m, 1H), 4.17 (m, 2H), 3.92 (m, 2H), 3.84 (m, 2H), 3.70−3.63 (m, 4H), 1.94 (m, 1H), 1.76−1.58 (m, 3H), 1.40 (m, 2H), 1.29−1.21 (m, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 169.0 (s), 168.5 (s), 156.5 (s), 136.3 (s), 133.9 (s), 132.0 (s), 128.5 (s), 128.2 (s), 128.1 (s), 123.2 (s), 100.5 (d, $J$ = 140.0 Hz), 67.0 (s), 66.3 (d, $J$ = 9.5 Hz) and 65.3 (d, $J$ = 8.8 Hz), 62.6 (d, $J$ = 7.3 Hz), 45.7 (d, $J$ = 95.6 Hz), 44.5 (s), 37.3 (s), 28.0 (s), 27.9 (s), 22.8 (d, $J$ = 11.6 Hz), 16.7 (m), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.64, 38.48, 38.38; ESI ($m/z$) 618.6 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{30}H_{40}N_3O_9PNa$ 640.2394, found 640.2387.

*Compound **10f**.* Yield 76%, 237 mg; white solid: mp 78−85 °C; $[\alpha]_D^{30}$ −16.4 (*c* 1.29, $CHCl_3$); IR (film) 3280, 2975, 2932, 1713, 1648, 1535, 1212, 1059, 755 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.65−7.41 (m, 1H), 7.24 (m, 5H), 6.88 (m, 1H), 5.91 (m, 1H), 4.74 (m, 1H), 4.59 (m, 2H), 4.44 (m, 1H), 4.21 (m, 2H), 3.88 (m, 2H), 3.71 (m, 2H), 3.07 (d, $J$ = 5.6 Hz, 2H), 2.05 (m, 2H), 1.87 (m, 1H), 1.39−1.36 (m, 9H), 1.30−1.21 (m, 9H), 1.18−0.83 (m, 13H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.8 (m), 171.3 (m), 155.7 (s), 137.0 (s), 129.2 (s), 128.4 (s), 126.6 (s), 100.5 (d, $J$ = 137.1 Hz), 79.5 (s), 66.2 (d, $J$ = 8.7 Hz), 64.9 (m) and 62.0 (m), 58.3 (s), 55.9 (s), 50.2 (d, $J$ = 89.7 Hz), 37.4 (s), 35.1 (s), 30.9 (s), 28.2 (s), 24.3 (m), 19.3 (s), 17.9 (s), 16.5 (m), 15.2 (m), 11.8 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.75; ESI ($m/z$) 650.8 $[M + Na]^+$; HRMS (ESI) Calcd for $C_{31}H_{54}N_3O_8PNa$ 650.3541, found 650.3521. Elemental analysis (%) calcd for $C_{31}H_{54}N_3O_8P$: C 59.31; H 8.67; N 6.69. Found: C 59.18; H 8.55; N 6.49.

*Compound **10g**.* Yield 78%, 253 mg; white solid: mp 78 °C; $[\alpha]_D^{30}$ −18.7 (*c* 1.0, $CHCl_3$); IR (film) 3268, 2975, 2931, 1716, 1648, 1537, 1211, 1058, 754 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.63−7.41 (m, 1H), 7.23 (m, 5H), 6.90 (m, 1H), 5.62 (m, 1H), 4.82 (m, 1H), 4.63 (m, 1H), 4.54−4.40 (m, 2H), 4.21 (m, 2H), 3.87 (m, 2H), 3.70 (m, 2H), 3.05 (m, 2H), 2.13 (m, 1H), 1.61 (m, 2H), 1.38 (s, 9H), 1.32−1.24 (m, 9H), 0.90−0.76 (m, 13H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.5 (m), 170.7 (m), 155.3 (m), 136.8 (s), 129.3 (s), 128.5 (s), 126.7 (s), 100.3 (d, $J$ = 137.1 Hz), 79.7 (s), 66.2 (d, $J$ = 8.0 Hz), 64.7 (m) and 62.4 (m), 58.1 (s), 55.9 (s), 44.0 (d, $J$ = 105.0 Hz), 37.4 (m), 31.0 (m), 28.2 (s), 24.4 (m), 23.5 (s), 21.0 (s), 19.3 (s) and 17.7 (s), 16.6 (m), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.65, 39.31, 38.90, 38.62; ESI ($m/z$) 650.8 $[M + Na]^+$; HRMS (MALDI) Calcd for $C_{31}H_{54}N_3O_8PNa$ 650.3541, found 650.3522.

*Compound **10h**.* Yield 35%, 116 mg; white solid: mp 99 °C; $[\alpha]_D^{27}$ −29.8 (*c* 1.0, $CHCl_3$); IR (film) 3266, 2975, 1714, 1647, 1542, 1214, 1170, 1058, 668 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.22−7.10 (m, 10H), 6.68 (br, 1H), 6.35 (br, 1H), 5.25−4.90 (m, 1H), 4.75 (m, 1H), 4.59 (m, 1H), 4.27 (m, 1H), 4.18 (m, 2H), 4.01 (m, 1H), 3.80−3.64 (m, 3H), 3.49 (m, 1H), 3.18 (m, 1H), 3.07−2.78 (m, 3H), 1.87 (m, 1H), 1.31 (s, 9H), 1.27−1.17 (m, 9H), 0.72−0.52 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.3 (m), 170.4 (m), 155.4 (m), 136.9 (m),


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136.8 (s), 136.7 (s), 129.3 (s), 128.7 (s), 128.4 (s), 126.9 (m), 126.7 (s), 100.6 (d, $J$ = 138.5 Hz), 80.2 (m), 66.5 (m), 65.2 (m) and 62.8 (m), 58.4 (m), 56.1 (m), 47.0 (d, $J$ = 94.0 Hz), 38.6 (m), 34.7 (m), 30.6 (m), 28.3 (s), 19.0 (m) and 17.5 (m), 16.6 (m), 15.3 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.33, 38.03, 37.74; ESI ($m/z$) 662.8 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{34}H_{52}N_3O_8PNa$ 684.3384, found 684.3392.

*Compound* ***10i***. Yield 67%, 206 mg; white solid: mp 90 °C; $[\alpha]_D^{27}$ −5.5 ($c$ 1.33, $CHCl_3$); IR (film) 3279, 2976, 2931, 1714, 1649, 1535, 1391, 1366, 1211, 1173, 1058, 756 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.44 (m, 1H), 7.15 (m, 5H), 6.74 (m, 1H), 5.93 (m, 1H), 4.70−4.31 (m, 4H), 4.21 (m, 2H), 3.82−3.42 (m, 4H), 2.99 (m, 2H), 2.20 (m, 1H), 2.02 (m, 1H), 1.29 (s, 9H), 1.24−1.12 (m, 9H), 0.96−0.70 (m, 12H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.8 (m), 171.4 (m), 155.7 (m), 137.2 (m), 129.2 (s), 128.4 (s), 126.6 (s), 100.7 (m), 79.5 (m), 66.9 (m), 66.2 (m), 62.7 (m), 58.3 (m), 56.0 (m), 50.0 (m), 37.5 (m), 31.2 (m), 30.6 (m), 28.2 (s), 20.8 (m) and 19.4 (m), 18.4 (m) and 17.7 (m), 16.6 (m), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.90, 38.70, 38.64; ESI ($m/z$) 614.8 $[M + H]^+$; HRMS (MALDI) Calcd for $C_{30}H_{52}N_3O_8PNa$ 636.3384, found 636.3399.

*Compound* ***10j***. Yield 98%, 252 mg; colorless oil: $[\alpha]_D^{26}$ −21.1 ($c$ 1.0, $CHCl_3$); IR (film) 3271, 2977, 2931, 1714, 1668, 1522, 1498, 1366, 1210, 1171, 1058, 557 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.18 (m, 5H), 6.62 (br, 1H), 5.22 (br, 1H), 4.63−4.48 (m, 1H), 4.37 (m, 2H), 4.10 (m, 2H), 3.73 (m, 2H), 3.56 (m, 2H), 3.15−2.89 (m, 2H), 2.23 (m, 1H), 1.32−1.30 (m, 9H), 1.25−1.12 (m, 9H), 0.93−0.75 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.4 (m), 155.6 (m), 136.8 (s), 129.2 (m), 128.5 (m), 126.8 (m), 100.4 (m), 80.1 (m), 66.3 (m), 64.8 (m), 62.5 (m) and 62.0 (m), 55.8 (m), 49.6 (m), 37.2 (m), 28.2 (m), 20.6 (m), 16.6 (m), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 38.61, 38.31, 38.25; ESI ($m/z$) 515.6 $[M + H]^+$; HRMS (ESI) Calcd for $C_{25}H_{43}N_2O_7PNa$ 537.270, found 537.2718.

*Compound* ***10k***. Yield 82%, 217 mg; colorless oil: $[\alpha]_D^{26}$ −31.0 ($c$ 1.0, $CHCl_3$); IR (film) 3258, 2977, 1715, 1668, 1523, 1498, 1366, 1209, 1366, 1209, 1172, 1058, 563 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.27−7.18 (m, 5H), 6.41 (br, 1H), 4.90 (br, 1H), 4.67 (d, $J$ = 9.5 Hz, 1H), 4.59 (q, $J$ = 9.5 Hz, 1H), 4.37 (d, $J$ = 6.5 Hz, 1H), 4.11 (m, 2H), 3.82 (m, 2H), 3.63 (m, 2H), 3.13−3.09 (m, 1H), 3.02 (m, 1H), 1.60 (m, 1H), 1.49 (m, 2H), 1.37 (s, 9H), 1.28−1.19 (m, 9H), 0.90 (d, $J$ = 6.0 Hz, 3H), 0.87 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 126 MHz) $\delta$ 170.8 (d, $J$ = 3.8 Hz), 155.4 (s), 136.5 (s), 129.4 (s), 128.6 (s), 126.9 (s), 100.6 (d, $J$ = 141.5 Hz), 80.2 (s), 66.2 (d, $J$ = 9.6 Hz), 64.8 (d, $J$ = 7.7 Hz), 62.2 (d, $J$ = 6.7 Hz), 55.6 (s), 44.0 (d, $J$ = 95.5 Hz), 37.2 (s), 28.2 (s), 24.2 (d, $J$ = 11.5 Hz), 23.5 (s), 20.9 (s), 16.7 (d, $J$ = 4.8 Hz), 15.2 (d, $J$ = 5.8 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.14, 39.02; ESI ($m/z$) 529.8 $[M + H]^+$; HRMS (ESI) Calcd for $C_{26}H_{45}N_2O_7PNa$ 551.2857, found 551.2838.

*Compound* ***10l***. Yield 44%, 139 mg; white solid: mp 133−139 °C; $[\alpha]_D^{27}$ −21.5 ($c$ 1.0, $CHCl_3$); IR (film) 3285, 2977, 2930, 1660, 1536, 1168, 1058, 1032, 699 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.33−7.19 (m, 10H), 6.82−6.59 (m, 2H), 4.94 (m, 1H), 4.73−4.66 (m, 1H), 4.49 (m, 1H), 4.42 (d, $J$ = 5.5 Hz, 2H), 4.33 (m, 1H), 4.14 (m, 2H), 3.82 (m, 2H), 3.64 (m, 2H), 3.18−3.14 (m, 1H), 2.98 (m, 1H), 2.27 (m, 3H), 1.92 (s, 1H), 1.36−1.34 (m, 9H), 1.28 (m, 3H), 1.25−1.21 (m, 6H); $^{13}$C NMR ($CDCl_3$, 126 MHz) $\delta$ 172.0 (s), 171.8 (m), 155.5 (m), 138.5 (s), 136.4 (s), 129.3 (s), 128.7 (s), 128.6 (s), 127.8 (s), 127.3 (s), 127.0 (s), 100.2 (d, $J$ = 142.5 Hz), 80.3 (s), 66.4 (m), 65.5 (m), 62.5 (m), 55.9 (s), 45.8 (d, $J$ = 96.5 Hz), 43.5 (s), 37.5 (s), 32.8 (d, $J$ = 12.5 Hz), 28.2 (s), 25.6 (d, $J$ = 3.9 Hz), 16.6 (m), 15.2 (m); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 37.70, 37.66, 37.41; ESI ($m/z$) 634.7 $[M + H]^+$; HRMS (ESI) Calcd for $C_{32}H_{48}N_3O_8PNa$ 656.3071, found 656.3070.

*Compound* ***10m***. Yield 78%, 221 mg; white solid: mp 68−70 °C; $[\alpha]_D^{26}$ −26.9 ($c$ 1.0, $CHCl_3$); IR (film) 3293, 2976, 2932, 1696, 1511, 1210, 1168, 1058, 742, 558 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.95 (br, 1H), 7.63 (d, $J$ = 7.6 Hz, 1H), 7.37 (d, $J$ = 8.0 Hz, 1H), 7.18 (t, $J$ = 6.8 Hz, 1H), 7.12−7.08 (m, 2H), 6.50 (dd, $J_1$ = 10.4 Hz, $J_2$ = 1.6 Hz, 1H), 5.07 (d, $J$ = 7.2 Hz, 1H), 4.57−4.46 (m, 3H), 4.17−4.02 (m, 2H), 3.80 (m, 2H), 3.60 (m, 2H), 3.26 (m, 2H), 1.97 (m, 1H), 1.64 (m, 1H), 1.40 (s, 9H), 1.22 (m, 9H), 1.02 (m, 1H), 0.91 (d, $J$ = 6.8 Hz, 3H), 0.84 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.7 (d, $J$ = 5.1 Hz), 155.8 (s), 136.4 (s), 127.4 (s), 123.5 (s), 122.0 (s), 119.5 (s), 118.6 (s), 111.4 (s), 110.0 (s), 99.8 (d, $J$ = 140.7 Hz), 80.3 (s), 66.4 (d, $J$ = 9.5 Hz), 65.0 (d, $J$ = 8.8 Hz), 62.1 (d, $J$ = 7.3 Hz), 55.4 (s), 49.8 (d, $J$ = 94.0 Hz), 35.0 (s), 28.2 (s), 24.5 (d, $J$ = 2.2 Hz), 16.6 (d, $J$ = 5.1 Hz), 16.5 (d, $J$ = 11.0 Hz), 15.3 (d, $J$ = 4.4 Hz), 11.6 (s); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 39.20, 38.84, 38.75; ESI ($m/z$) 568.7 $[M + H]^+$; HRMS (ESI) Calcd for $C_{28}H_{46}N_3O_7PNa$ 590.2966, found 590.2953.

**NMR data for 6p and (−)-6p.** *(R)-Mosher's Derivative of* ***5p*** *(****6p****).* $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.55 (m, 2H), 7.40 (m, 3H), 7.17 (d, $J$ = 10.4 Hz, 1H), 4.35 (m, 1H), 4.11 (m, 2H), 4.01 (m, 2H), 3.38 (s, 3H), 2.31 (m, 1H), 1.30−1.20 (m, 6H), 1.06 (d, $J$ = 6.4 Hz, 6H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$ −69.42; $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 24.56; ESI ($m/z$) 426.3 $[M + H]^+$.

*(S)-Mosher's Derivative of* ***5p*** *((−)-****6p****).* $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.57 (m, 2H), 7.40 (m, 3H), 6.84 (d, $J$ = 9.6 Hz, 1H), 4.35 (m, 1H), 4.18−4.10 (m, 4H), 3.52 (s, 3H), 2.25 (m, 1H), 1.33 (dt, $J_1$ = 2.8 Hz, $J_2$ = 7.2 Hz, 6H), 0.93 (dd, $J_1$ = 6.8 Hz, $J_2$ = 21.2 Hz, 6H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$ −69.12; $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 24.47; ESI ($m/z$) 426.3 $[M + H]^+$.

**NMR Data for Mosher'S Derivative of the Major Isomer of 3m.** *(R)-Mosher's Derivative of the Major Isomer of* ***3m***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.58 (m, 2H), 7.52 (m, 1H), 7.40 (m, 3H), 7.36 (m, 2H), 7.34−7.28 (m, 2H), 5.31 (s, 1H), 4.66 (d, $J$ = 11.2 Hz, 1H) and 4.51 (d, $J$ = 11.2 Hz, 1H), 4.54 (td, $J_1$ = 10.4 Hz, $J_2$ = 1.6 Hz, 1H), 4.48 (d, $J$ = 10.0 Hz, 1H), 4.36 (m, 1H), 4.13−3.95 (m, 2H), 3.84−3.44 (m, 4H), 3.89 (d, $J$ = 1.2 Hz, 3H), 1.26 (dd, $J_1$ = 1.6 Hz, $J_2$ = 6.4 Hz, 3H), 1.16 (q, $J$ = 7.2 Hz, 6H), 1.11 (t, $J$ = 7.2 Hz, 3H); $^{19}$F NMR ($CDCl_3$, 376 MHz) $\delta$ −69.13; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 36.23.

*(S)-Mosher's Derivative of the Major Isomer of* ***3m***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.60 (m, 2H), 7.40 (m, 3H), 7.31−7.24 (m, 5H), 5.30 (s, 1H), 4.61 (d, $J$ = 10.4 Hz, 1H), 4.55 (td, $J_1$ = 10.4 Hz, $J_2$ = 1.6 Hz, 1H), 4.55 (d, $J$ = 11.2 Hz, 1H) and 4.46 (d, $J$ = 11.2 Hz, 1H), 4.32 (m, 1H), 4.21−4.03 (m, 2H), 3.92−3.49 (m, 4H), 1.21 (t, $J$ = 7.2 Hz, 3H), 1.20 (q, $J$ = 7.1 Hz, 6H), 1.08 (dd, $J_1$ = 1.6 Hz, $J_2$ = 6.4 Hz, 3H); $^{19}$F NMR ($CDCl_3$, 376 MHz) $\delta$ −68.75; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 35.98.

## ■ ASSOCIATED CONTENT

### Supporting Information

NMR spectra of new compounds **1**−**4**, **9**, **10**, **6p**, (−)-**6p**, Mosher's derivatives of the major isomer of **3m**; HPLC data for **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) Selective reviews for the preparation of amino phosphonic acids: (a) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorus Sulfur Relat. Elem.* **1994**, *92* (1−4), 239−264. (b) Ma, J. *Chem. Soc. Rev.* **2006**, *35*, 630−636. (c) Mario, O.; Haydee, R.; Carlos, C. *Tetrahedron* **2009**, *65*, 17−49. (d) Albrecht, Ł.; Albrecht, A.; Krawczyk, H.; Jørgensen, K. A. *Chem—Eur. J.* **2010**, *16*, 28−28. (e) Lefebvre, I. M.; Evans, S. A. *J. Org. Chem.* **1997**, *62*, 7532−7533.

(2) Selective reviews for biological studies of phosphonic acids: (a) Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010**, *17* (3), 264−

289. (b) Galezowska, J.; Gumienna-Kontecka, E. *Coord. Chem. Rev.* **2012**, *256*, 105−124.
(3) (a) Gerald, L. R.; Arno, L. G.; George, L. K. *J. Am. Chem. Soc.* **1971**, *93*, 5542−5551. (b) Marion, C.; Elizabeth, A. K.; Kathy, L. K.; Karen, M. A.; James, F. K. *Bioorg. Med. Chem. Lett.* **1996**, *6* (9), 999−1002.
(4) Selective reviews for biological studies of phosphinic acids, see: (a) Berlicki, L.; Kafarski, P. *Curr. Org. Chem.* **2005**, *9*, 1829−1850. (b) Yiotakis, A.; Georgiadis, D.; Matziari, M.; Makaritis, A.; Dive, V. *Curr. Org. Chem.* **2004**, *8*, 1135−1158. (c) Collinsova, M.; Jiracek, J. *Curr. Med. Chem.* **2000**, *7* (6), 629−647.
(5) Yao, Q.; Yuan, C. *J. Org. Chem.* **2012**, *77*, 10985−10990 and references cited therein.
(6) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2845−2853.
(7) To be specific, the following analogues were synthesized asymmetrically. (a) Analogues of Ala and Phe: Patrick, P. M.; Brian, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1319−1329. (b) Analogues of Ala, Phe, Val, and Leu: Hamilton, R.; Walker, B.; Walker, B. J. *Tetrahedron Lett.* **1995**, *36* (25), 4451−4454. (c) Analogue of Met: Kirill, V. A.; Yurii, N. Z.; Nikolai, G. F.; Elena, N. K.; Radii, M. K. *Mendeleev Commun.* **2003**, *13* (3), 127−128.
(8) Zhang, D. H.; Yuan, C. Y. *Chem.—Eur. J.* **2008**, *14*, 6049−6052.
(9) (a) David, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651−3653. (b) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284.
(10) See Experimental Section and Supporting Information for detailed NMR data.
(11) Galaktionov, K.; Beach, D. *Cell* **1991**, *67* (6), 1181−1194.
(12) Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5* (22), 4215−4218.
(13) Asada, M.; Obitsu, T.; Kinoshita, A.; Nagase, T.; Yoshida, T.; Yamaura, Y.; Takizawa, H.; Yoshikawa, K.; Sato, K.; Narita, M.; Nakai, H.; Toda, M.; Tobe, Y. *Bioorg. Med. Chem.* **2010**, *18* (9), 3212−3223.
(14) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772−8778.