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Stereospecific Transformation of Protected P−H Group into P−O or P−N Group in One-Pot Reaction

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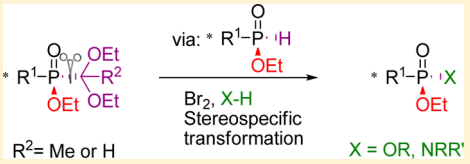
Supporting Information

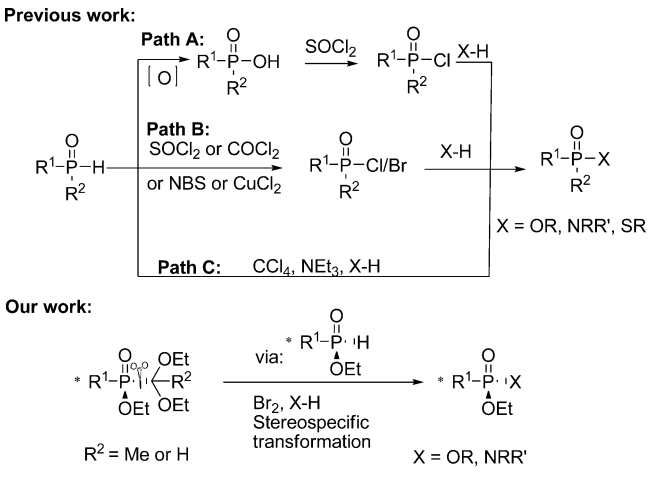
ABSTRACT: A general and efficient procedure for converting 1,1-diethoxyalkylphosphinates into phosphonates or phosphonamides is described by the application of bromine with moderate to high yields and good purity in a one-pot reaction. *H*-Phosphinate reacts stereospecifically with bromine and subsequently couples with nucleophile to form the corresponding optically active $R^1P(O)(OEt)X$ with retention of configuration at the phosphorus center. For α-amino-*H*-phosphinates, the transformation could be realized without the protection of the amino group.



Organophosphorus acid derivatives, more specifically α-amino or α-hydroxy phosphonates or phosphonamides are useful as intermediates for the preparation of antibacterial, antipsoriatic, anti-HIV, and anticancer agents, and they have been found to possess herbicidal and defoliating activity.[1]

The transformation of the P−H group into a P−X group is useful for the syntheses of various organophosphorus acid derivatives, and the stereospecific transformation is especially important for optically active compounds. The most common strategies for such transformation are shown in Scheme 1 as

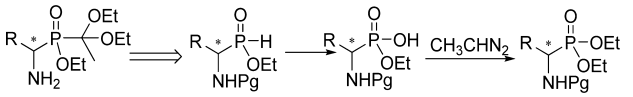
Scheme 1. Transformation of P−H Group to P−X Group



path A[2] and path B,[3] both of which require several steps. Achieving these transformations is somewhat troublesome because of the difficulties in purifying phosphonic acid (Path A) and because of highly reactive phosphorochloridate or phosphorobromidate. Although the Atherton−Todd reaction provides direct transformation with the activation of the P−H group by CCl_4[4] (Scheme 1 Path C), this procedure could not be applied for the sterically hindered or unstable *H*-phosphinates in our study. Above all, all of the described processes need to have the α-amino group of the *H*-phosphinates protected.

To determine the absolute configuration and d.r. values of α-aminophosphinates, as was done by Haruki and co-workers,[5] the α-aminophosphinates need to be converted to α-aminophosphonates and the amino group should be blocked (Scheme 2).

Scheme 2. Transformation of α-Aminophosphinates into α-Amidophosphonate[5]



Here we report an efficient procedure for the stereospecific transformation of 1,1-diethoxyalkyl protected *H*-phosphinates into phosphonates or phosphonamides in the presence of bromine and nucleophile in a one-pot reaction (Scheme 1). Because *H*-phosphinates are sometimes unstable and the 1,1-diethoxyalkyl group is easily introduced and labile to hydrolysis, it is used as temporary protecting group for the P−H function.

In our previous study of converting α-aminophosphinate **1a** into α-aminophosphonate to determine the d.r. value of **1a**, we first hydrolyzed the 1,1-diethoxymethyl group of **1a** by TMSCl to give α-amino-*H*-phosphinate,[6] which was too unstable to be isolated. So it was directly subjected to the oxidization reaction by bromine in dichloromethane and ethanol. Unexpectedly, the diethylphosphonate **2a** instead of ethyl hydrogen phosphonate was separated in good yields (Table 1, entry 1, 2). The transformation went through the formation of the P−H group, and sequential bromination and in situ transferring into diethylphosphonate **2a**. During optimization studies, we

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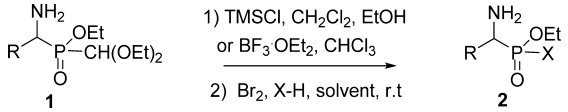
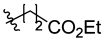
Table 1. Transformation of α-Aminophosphinates to α-Aminophosphonates and α-Aminophosphonamides[a]



Entry	1 R	X-H	2	Yield (%)[b]
1[c]	**1a** 		**2a**	80
2[c]	**1a** 		**2a**	80 (33)[d]
3[c]	**1b** 	EtOH	**2b**	79
4[e]	**1c** i-Pr		**2c**	40
5[e]	**1d** 		**2d**	45
6[e]	**1e** 		**2e**	55
7[c]	**1f** 	MeOH	**2f**	82
8[c]	**1a** 	n-$C_7H_{15}NH_2$ (5 eq.)	**2g**	24
9[c]	**1f** 	H-Gly-OEt (8 eq.)	**2h**	42

[a]Reaction for step 2 was carried out with *H*-phosphinate after the hydrolysis of **1** (0.1 mmol), EtOH (1 mL) or MeOH (1 mL) or corresponding RNH_2 in DCM (1 mL, entry 1, 3–6) or CH_3CN (1 mL, entry 2, 7–9), and a slight excess of bromine was added until yellow color persisted at rt. [b]Isolated yield for two steps. [c]TMSCl for step 1. [d]Isolated yield in parentheses with 2 equiv of NEt_3. [e]$BF_3{\cdot}Et_2O$ for step 1.

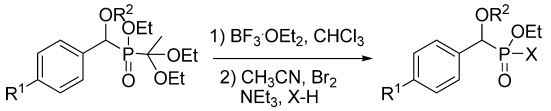
found the addition of NEt_3 was disadvantageous and resulted in lower yield (entry 2). Under the optimized conditions, the substrate scope was studied, and it was proved that the reaction could tolerate different protecting groups including benzyl, phthalyl and alkoxylcarbonyl (entry 1, 3, 5, 6). Next, the nucleophile was investigated, and methanol was a good substrate for this reaction with good yield (entry 7). Phosphonamides could be prepared as well when reacted with amine or glycine ethyl ester, but the yields are low to moderate (entry 8, 9).

As shown in Table 1, the process is direct and highly efficient. This provides a convenient method to elucidate the absolute configuration and d.r. values of α-aminophosphinates. The partial protection of the amino group as a result of the intramolecular hydrogen bonding of the amino group with the phosphoryl group makes the protection of the α-amino group not necessary.[7] As far as we know, no report of such process with the free α-amino group as substrate has been revealed yet, and no method of direct conversion of the P–H group into a P–O or P–N group by bromine has ever been developed.

Therefore, we decided to expand this procedure for special phosphinate derivatives such as α-acetoxyphosphinate **3a** and α-Fmoc-oxyphosphinate **3b** (Table 2) that constitute an important class of biologically active compounds.

As described in Table 2, phosphinates **3** were converted to **4** in moderate to high yields in one pot reaction. For **3a**, the addition of NEt_3 gave a higher yield (entry 1), which was the opposite of the result of α-aminophosphinates **1**. It might be reasoned by the acid-capture nature of the amino group in α-amino-*H*-phosphinates, whereas **3a** needs additional base to

Table 2. Transformation of 3 to 4[a]



3a R^1 = Cl, R^2 = Ac
3b R^1 = H, R^2 = Fmoc

4

entry	3	X–H	4	yield (%)[b]
1	**3a**	EtOH (5 equiv)	**4a**	76 (61)[c]
2	**3a**	L-menthol (2 equiv)	**4b**	37
3	**3a**	H-Gly-OEt·HCl (2 equiv)	**4c**	61[d]
4	**3a**	*n*-$C_7H_{15}NH_2$ (2 equiv)	**4d**	70
5	**3a**	*n*-$C_7H_{15}NH_2$ (5 equiv)	**4d**	77[e]
6	**3a**	(*S*)-α-methylbenzylamine (5 equiv)	**4e**	quant.[d,f]
7	**3b**	EtOH (10 mL $mmol^{-1}$)	**4f**	73[c,e]
8	**3b**	MeOH (10 mL $mmol^{-1}$)	**4g**	quant.[c,e]

[a]Reaction for step 2 was carried out with *H*-phosphinate after the hydrolysis of **3** (0.1 mmol), appropriate X–H, NEt_3 (0.2 mmol) and bromine (0.15 mmol) in CH_3CN (2 mL) at rt. [b]Isolated yield for two steps. [c]Isolated yield in parentheses without NEt_3. [d]NEt_3 (0.4 mmol) was used. [e]Bromine (0.2 mmol) was used. [f]Bromine (0.5 mmol) was used.

neutralize the acid generated from the bromination of *H*-phosphinate. The sterically hindered L-menthol gave a slightly low yield (entry 2), and the glycine ethyl ester, as well as amine, gave corresponding phosphonamide with high purity and good yields (entry 3–6). The addition of X–H from 2 to 5 equiv would slightly improve the yield (entry 4, 5), and **3b** was a good substrate for this reaction with good yields (entry 7, 8).

The enantiomerically pure α-amidophosphinates **5**,[8] which are important biologically active compounds, are difficult to be converted into phosphonates or phosphonamides **6** for their steric hindrance and low stability. Thus, an endeavor was made to achieve the stereospecific transformation of **5** to prepare optically active **6** by this procedure (Table 3). Gladly, the conversion went through quite well at 0 °C within several hours to generate **6** with moderate to high yields. Partly decomposed *H*-phosphinates were detected, which could be ascribed to the instability of these compounds. It should be pointed out that by the procedure of $CuCl_2$[3c] (entry 2) or CCl_4[4b] (entry 3), no product was given at all, which indicated the steric hindrance and the low stability of these *H*-phosphinates. Each product gave a single peak in its ^{31}P NMR, indicating that its de % was more than 95% and the transformation was stereospecific.

The single crystals of deprotected **5c**, **6c** and **6f** indicate that the products have retention of configuration at the phosphorus center.[9] Thus we are able to convert the stereospecific P–H group into a P–X group with retention of configuration for bulky and instable *H*-phosphinates. To achieve the stereospecific transformation with retention at the phosphorus center is rather rare in the literature,[10] so this reaction could provide a protocol to investigate the stereochemistry of phosphorus compounds.

Following the progress of the reaction by ^{31}P NMR spectroscopy reveals several aspects of the mechanism (Scheme 3, Figure 1). Phosphinate **3a** is hydrolyzed to *H*-phosphinate **A** and then activated by Br_2, producing an intermediate **B**, which is phosphorobromidate and HBr. Since **B** is generated in the presence of EtOH, it is coupled in situ and side reactions are minimized (Scheme 3). If the nucleophile is omitted from the reaction mixture, byproducts are formed because of intermolecular reactions of the phosphorus derivatives.

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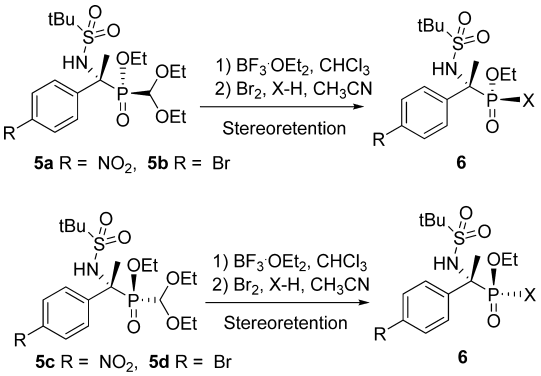
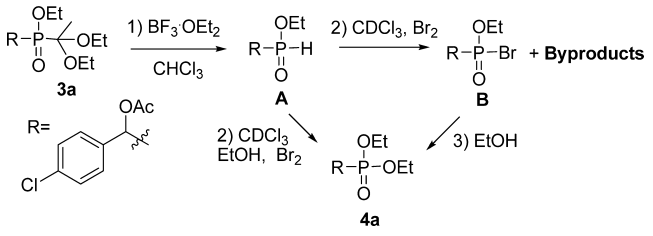
Table 3. Stereospecific Transformation of 5 to 6[a]



entry	5	X–H	Br_2 (equiv)	6	yield (%)[b]
1	**5a**	MeOH (10 mL mmol^{-1})	2	**6a**	86
2	**5b**	MeOH (10 mL mmol^{-1})	2	**6b**	86 (0)[c]
3	**5b**	H-Gly-OEt·HCl (2 equiv)	1.5	**6c**	48[d] (0)[e]
4	**5b**	*n*-$C_7H_{15}NH_2$ (5 equiv)	4	**6d**	80
5	**5b**	(*S*)-α-methylbenzylamine (5 equiv)	4	**6e**	50
6	**5c**	MeOH (10 mL mmol^{-1})	2	**6f**	quant.
7[f]	**5d**	MeOH (10 mL mmol^{-1})	2	**6g**	79
8[f]	**5d**	*n*-$C_7H_{15}NH_2$ (5 equiv)	4	**6h**	46[g]

[a]Reaction for step 2 was carried out with *H*-phosphinate after the hydrolysis of **5** (0.1 mmol), appropriate X–H and bromine in CH_3CN (2 mL) at 0 °C. [b]Isolated yield; each product gave a single peak in its ^{31}P NMR, indicating single diastereoisomer. [c]Yield in parentheses with the procedure of $CuCl_2$ and then NEt_3, MeOH and THF.[3c] [d]NEt_3 (0.4 mmol) was added, and the reaction was carried out at room temperature. [e]Yield in parentheses with the procedure of NEt_3, CH_3CN, CH_2Cl_2, CCl_4.[4b] [f]CH_2Cl_2 (2 mL) was used instead of CH_3CN. [g]The reaction was carried out at room temperature.

Scheme 3. Process Revealed by ^{31}P NMR



In conclusion, this procedure offers a general and effective method for the direct transformation of a protected P–H group into a P–O or P–N group stereospecifically. Bromine is first applied for such one-pot transformation. This is the first time achieving the conversion of α-aminophosphinates without protection of the amino group. Stereospecific retention at phosphorus center in such chemical conversion is quite rare and interesting. The high reactivity of phosphorobromidate makes the preparation of sterically hindered phosphonates or phosphonamides much more realizable.

EXPERIMENTAL SECTION

General Methods. Reactions were performed under nitrogen unless otherwise noted. Materials were obtained from commercial suppliers and used without further purification. 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.

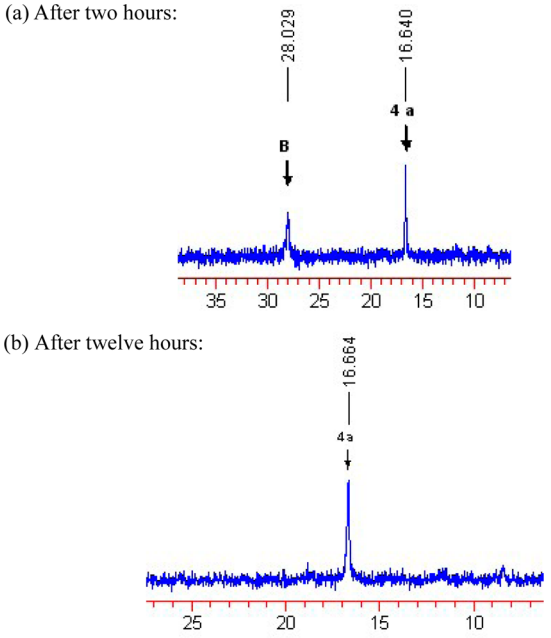


Figure 1. ^{31}P NMR of **A** reacted with Br_2 (2 equiv) and EtOH (5 equiv).

General Procedure for the Transformation of the P–H Group into a P–O or P–N Group. *H*-Phosphinate (0.1 mmol) generated by the hydrolysis of 1,1-diethoxyalkyl group[11] was used directly in the next step without further purification. *H*-Phosphinate was dissolved in DCM (2 mL) or CH_3CN (2 mL). The corresponding X–H and, for some instances, NEt_3 were added. Bromine was added at room temperature, except for **5**, where it was added at 0 °C. After completion of the reaction monitored by TLC, it was quenched by 2 mL of 5% $NaHCO_3$ and 2 mL of 5% Na_2SO_3 and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude product was purified by silica gel column chromatography with petroleum ether/ethyl acetate (1:1) or preparative TLC. Data for compounds **2a**,[12] **2c**,[13] **2d**,[14] **3a**,[5b] **4a**,[15] **5a**[8] and **5c**[8] were in accordance with reported data.

Compound 2b. White solid (28 mg, 79%): mp 92–94 °C; IR (film) 3463, 3383, 3305, 2981, 2934, 1771, 1716, 1397, 1055, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (q, *J* = 2.8 Hz, 2H), 7.73 (q, *J* = 2.8 Hz, 2H), 4.14 (m, 4H), 3.73 (t, *J* = 6.8 Hz, 2H), 3.02 (td, J_1 = 10.4 Hz, J_2 = 3.2 Hz, 1H), 2.02 (m, 1H), 1.84 (m, 2H), 1.65 (m, 2H), 1.56 (m, 1H), 1.33 (td, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2 (s), 133.8 (s), 132.0 (s), 123.1 (s), 62.0 (m), 48.1 (d, *J* = 148.1 Hz), 37.4 (s), 28.3 (s), 25.2 (d, *J* = 12.4 Hz), 16.4 (m); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 28.42; MS (ESI) *m*/*z* (%) 355.1 [M + H]$^+$; HRMS (MALDI) calcd for $C_{16}H_{24}N_2O_5P$ 355.1417, found 355.1432.

Compound 2e. Colorless oil (20 mg, 55%): IR (film) 3455, 2937, 1770, 1712, 1397, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (q, *J* = 2.8 Hz, 2H), 7.71 (q, *J* = 2.8 Hz, 2H), 4.14 (m, 4H), 3.71 (t, *J* = 7.2 Hz, 2H), 2.93 (td, J_1 = 10.2 Hz, J_2 = 3.6 Hz, 1H), 1.83 (m, 1H), 1.69 (m, 5H), 1.48 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5 (s), 133.9 (s), 132.1 (s), 123.2 (s), 62.1 (m), 48.6 (d, *J* = 148.0 Hz), 37.7 (s), 30.8 (s), 28.3 (s), 23.5 (d, *J* = 12.4 Hz), 16.6 (d, *J* = 5.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 28.91; MS (ESI) *m*/*z* (%) 369.3 [M + H]$^+$; HRMS (MALDI) calcd for $C_{17}H_{26}N_2O_5P$ 369.1574, found 369.1585.

Compound 2f. Colorless oil (18 mg, 82%): Two diastereomers; IR (film) 3465, 2957, 1637, 1236, 1057, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.16 (m, 2H), 3.78 (m, 3H), 3.06 (td, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 1.91 (m, 1H), 1.54–1.43 (m, 4H), 1.35 (m, 3H), 0.93 (dd, J_1 = 26.0 Hz, J_2 = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 62.3 (m), 52.7 (m), 46.6 (d, *J* = 147.3 Hz), 39.9 (s); 24.1 (d, *J* = 13.1

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Hz), 23.5 and 21.0 (s), 16.6 (m); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 30.92, 30.87; MS (ESI) m/z (%) 210.1 $[M + H]^+$; HRMS (MALDI) calcd for $C_8H_{21}NO_3P$ 210.1254, found 210.1259.

Compound 2g. Colorless oil (9 mg, 24%): Two diastereomers; IR (film) 3222, 2926, 1454, 1208, 1039, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.28 (m, 5H), 4.58−4.50 (m, 2H), 4.14−3.98 (m, 2H), 3.82−3.63 (m, 2H), 3.33−3.16 (m, 1H), 3.01−2.88 (m, 2H), 2.72 (m, 1H), 1.43 (m, 2H), 1.32−1.25 (m, 13H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.82 (s), 137.75 (s), 128.5 (s), 127.8 (s), 73.5 (m), 71.1 (d, J = 41.5 Hz), 60.2 (m), 50.5 and 50.0 (d, J = 136.4 and 139.2 Hz), 40.9 (s), 32.5 (m), 31.8 (s), 29.0 (s), 26.6 (s), 22.6 (s), 16.5 (m), 14.1 (s).; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 33.52, 33.05 (1:1); MS (ESI) m/z (%) 357.3 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{34}N_2O_3P$ 357.2302, found 357.2306.

Compound 2h. Colorless oil (12 mg, 42%): Two diastereomers; IR (film) 3200, 2957, 2928, 1750, 1202, 1150, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.21 (q, J = 7.2 Hz, 2H), 4.16−3.98 (m, 2H), 3.83 (dd, J_1 = 9.6 Hz, J_2 = 6.8 Hz, 2H), 3.12 (m, 1H), 3.02 (td, J_1 = 10.4 Hz, J_2 = 3.6 Hz, 1H), 1.88 (m, 1H), 1.59−1.36 (m, 2H), 1.30 (m, 6H), 0.96 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1 (d, J = 4.4 Hz) and 171.9 (d, J = 5.2 Hz), 61.4 (m), 60.2 (m), 48.2 (d, J = 141.4 Hz) and 47.6 (d, J = 140.0 Hz), 43.0 (m), 40.1 and 39.4 (s), 24.3 and 24.2 (s), 23.6 and 21.0 (s), 16.4 (m), 14.2 (m); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 33.52, 33.05; MS (ESI) m/z (%) 281.2 $[M + H]^+$; HRMS (MALDI) calcd for $C_{11}H_{26}N_2O_4P$ 281.1625, found 281.1626.

Compound 4b. Attained as four diastereomers; Light yellow oil (16 mg, 37%): IR (film) 3480, 2956, 2928, 2870, 1752, 1223, 1014, 998 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.40 (m, 2H), 7.34−7.31 (m, 2H), 6.03 (m, 1H), 4.30−4.17 (m, 1H), 4.14−3.91 (m, 2H), 2.15 (m, 3H), 2.03−1.74 (m, 1H), 1.65−1.24 (m, 10H), 1.20−1.12 (m, 1H), 0.91−0.88 (m, 3H), 0.83−0.55 (m, 6H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2 (m), 133.5 (m), 131.4 (m), 128.6 (m), 127.5 (m), 77.7 (m), 70.0−68.1 (m), 62.6 (m), 47.3 (m), 42.0 (m), 32.8 (m), 30.4 (m), 28.6 (m), 24.5 (m), 21.7 (m), 20.8 (m), 19.8 (m), 15.4 and 14.5 (m); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 16.54, 16.45, 16.28, 16.18; MS (ESI) m/z (%) 453.2 $[M + Na]^+$; HRMS (MALDI) calcd for $C_{21}H_{32}O_5PClNa$ 453.1568, found 453.1563.

Compound 4c. Attained as two diastereomers; Light yellow oil (23 mg, 61%): IR (film) 3222, 2983, 1747, 1226, 1031, 963 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.40 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.08 and 6.03 (d, J = 12.4 Hz and J = 12.4 Hz, 1H), 4.19 (m, 2H), 4.14−4.03 (m, 2H), 3.77−356 (m, 2H), 3.21−3.10 (m, 1H), 2.165 and 2,160 (s, 3H), 1.30−1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (m), 169.5 and 169.4 (s), 134.5 (m), 132.4 and 132.4 (d, J = 2.9 Hz and J = 2.7 Hz); 129.2 (m), 128.7 (m), 71.6 and 70.9 (d, J = 156.1 Hz and J = 156.1 Hz), 61.61 (m), 61.57 (m), 42.9 and 42.8 (s), 20.9 (s), 16.3 (m), 14.1 (s); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 21.23, 21.18 (1.4:1); MS (ESI) m/z (%) 378.1 $[M + H]^+$; HRMS (MALDI) calcd for $C_{15}H_{21}NO_6PClNa$ 400.0687, found 400.0691.

Compound 4d. Attained as two diastereomers; Colorless oil (27 mg, 70%): IR (film) 3418, 2929, 1743, 1627, 1227, 1046, 564 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.05 and 6.01 (d, J = 12.4 Hz and J = 12.0 Hz, 1H), 4.13−3.96 (m, 2H), 2.94−2.82 (m, 2H), 2.53 and 2.44 (m, 1H), 2.17 (s, 3H), 1.40 (m, 2H), 1.29−1.22 (m, 11H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6 (m), 134.4 (m), 132.9 (m); 129.2 (s), 128.6 (s), 71.2 (m), 61.1 (m), 41.4 (d, J = 4.4 Hz), 32.2 (d, J = 4.3 Hz), 31.8 (s), 28.9 (s), 26.5 (s), 22.6 (s), 20.9 (m), 16.4 (m), 14.1 (s); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 21.86, 21.71; MS (ESI) m/z (%) 390.2 $[M + H]^+$; HRMS (MALDI) calcd for $C_{18}H_{29}NO_4PClNa$ 412.1415, found 412.1429.

Compound 4e. Attained as four diastereomers; Sticky white solid (40 mg, quantitative): mp 62 °C; IR (film) 3218, 2977, 1745, 1492, 1225, 1038, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.18 (m, 9H), 6.04−5.83 (m, 1H), 5.24−4.36 (m, 1H), 4.13−3.61 (m, 2H), 3.18−2.98 (m, 1H), 2.27−1.99 (m, 3H), 1.57−1.41 (m, 3H), 1.27−1.02 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9 (m), 143.8 (m), 133.3 (m), 131.8 (m), 131.5 (m), 128.2 (m), 127.5 (m), 126.3 (m), 124.6 (m), 71.3−69.0 (m), 60.2 (m), 50.2 (m), 24.8 (m), 19.7 (m), 15.2 (m); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 21.11, 20.77, 20.64, 20.61; MS (ESI) m/z (%) 396.2 $[M + H]^+$; HRMS (MALDI) calcd for $C_{19}H_{23}NO_4PClNa$ 418.0946, found 418.0944.

Compound 4f. Colorless oil (34 mg, 73%): IR (film) 3479, 2983, 1754, 1258, 1050, 1023, 974, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 8.0 Hz, 2H), 7.59 (m, 2H), 7.53 (m, 2H), 7.42−7.35 (m, 5H), 7.32−7.25 (m, 2H), 5.96 (d, J = 13.6 Hz, 1H), 4.42 (m, 2H), 4.26 (t, J = 7.4 Hz, 1H), 4.14−3.95 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4 (d, J = 1.2 Hz), 143.2 (d, J = 2.2 Hz), 141.3 (s), 133.0 (d, J = 1.5 Hz), 129.0 (d, J = 2.9 Hz), 128.6 (d, J = 2.2 Hz), 127.6 (d, J = 1.5 Hz), 127.8 (d, J = 5.8 Hz), 127.2 (s), 125.2 (d, J = 3.7 Hz), 120.1 (s), 74.6 (d, J = 169.2 Hz), 70.6 (s), 63.7 and 63.5 (dd, J = 6.5 and 6.6 Hz), 46.7 (s), 16.4 and 16.3 (d, J = 5.1 and 5.8 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 16.59; MS (ESI) m/z (%) 467.3 $[M + H]^+$; HRMS (MALDI) calcd for $C_{26}H_{27}O_6PNa$ 489.1438, found 489.1441.

Compound 4g. Colorless oil (45 mg, quantitative): IR (film) 3480, 2955, 1754, 1258, 1027, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 8.0 Hz, 2H), 7.58 (m, 2H), 7.53 (m, 2H), 7.42−7.35 (m, 5H), 7.27 (m, 2H), 5.98 (d, J = 13.6 Hz, 1H), 4.42 (m, 2H), 4.26 (t, J = 7.4 Hz, 1H), 4.16−4.02 (m, 2H), 3.68 (d, J = 10.8 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.3 (d, J = 11.6 Hz), 143.2 (s), 141.3 (s), 132.7 (d, J = 2.2 Hz), 129.0 (d, J = 2.9 Hz), 128.7 (d, J = 2.2 Hz), 128.0 (d, J = 1.4 Hz), 127.8 (d, J = 5.8 Hz), 127.2 (s), 125.2 (d, J = 2.9 Hz), 120.1 (s), 74.3 (d, J = 169.2 Hz), 70.6 (s), 63.9 (d, J = 7.3 Hz), 53.7 (d, J = 6.5 Hz), 46.7 (s), 16.5 (d, J = 5.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 17.87; MS (ESI) m/z (%) 453.3 $[M + H]^+$; HRMS (MALDI) calcd for $C_{25}H_{25}O_6PNa$ 475.1281, found 475.1274.

Compounds **5** were prepared according to reported procedure[8] as single diastereomer.

Compound 5b. Colorless oil, yield 92% (477 mg): $[\alpha]_D^{25.4}$ 38.7 (c 1.0, $CHCl_3$); IR (film) 3288, 2979, 2932, 1483, 1313, 1129, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 2H), 7.50 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.4 Hz, 1H), 4.40 (d, J = 10.4 Hz, 1H), 4.12 (m, 2H), 3.87−3.70 (m, 2H), 3.64−3.43 (m, 2H), 2.13 (d, J = 15.2 Hz, 3H), 1.43 (s, 9H), 1.29(t, J = 7.0 Hz, 3H), 1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8 (s), 131.3 (s), 129.3 (s); 122.2 (d, J = 3.6 Hz), 100.8 (dd, J_1 = 142.2 Hz, J_2 = 4.4 Hz), 66.9 (m), 65.6 (m), 63.6 (m), 62.5 (d, J = 347.2 Hz), 60.5 (s), 24.3 (s), 19.8 (s), 16.7 (s), 15.1 (s); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 33.94 ppm; MS (ESI) m/z (%) 536.1, 538.1 $[M + Na]^+$; HRMS (MALDI) m/z calcd for $C_{19}H_{33}BrNO_6PSNa$ 536.0842, found 536.0849.

Deprotected 5c. White solid (49 mg, 89%): mp 144 °C; $[\alpha]_D^{25.2}$ 52.8 (c 0.94, $CHCl_3$); IR (film) 3149, 2985, 2933, 1606, 1521, 1348, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.01 (d, J = 580.0 Hz, 1H), 5.28 (d, J = 8.8 Hz, 1H), 3.98−3.78 (m, 2H), 2.09 (d, J = 20.4 Hz, 3H), 1.44 (s, 9H), 1.15 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6 (s), 145.2 (d, J = 3.0 Hz), 128.5 (d, J = 4.4 Hz); 123.5 (d, J = 2.1 Hz), 64.1 (d, J = 7.3 Hz), 60.9 (s), 60.5 (d, J = 97.0 Hz), 24.3 (s), 19.3 (s), 16.1 (d, J = 5.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 35.89; MS (ESI) m/z (%) 379.3 $[M + H]^+$; HRMS (MALDI) calcd for $C_{14}H_{23}N_2O_6PSNa$ 401.0907, found 401.0905.

Compound 5d. Light yellow oil, yield 98% (365 mg): $[\alpha]_D^{25.9}$ 55.7 (c 1.0, $CHCl_3$); IR (film) 3289, 2979, 1484, 1313, 1129, 1058, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.03 (d, J = 7.6 Hz, 1H), 4.34 (d, J = 11.6 Hz, 1H), 4.19 (m, 2H), 3.86 (m, 1H), 3.69 (m, 2H), 3.36 (m, 1H), 2.07 (d, J = 14.8 Hz, 3H), 1.44 (s, 9H), 1.31 (m, 6H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1 (s), 131.5 (s), 129.2 (s); 122.2 (d, J = 3.6 Hz), 102.3 (s), 68.1 (d, J = 5.9 Hz), 66.1 (m), 63.8 (d, J = 8.0 Hz), 63.1 (d, J = 89.7 Hz), 60.3 (s), 24.2 (s), 19.2 (s), 16.7 (d, J = 5.1 Hz), 15.1 (d, J = 24.8 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 32.80 ppm; MS (ESI) m/z (%) 536.2, 538.2 $[M + Na]^+$. Elemental analysis (%) calcd for $C_{19}H_{33}BrNO_6PS$: C 44.36, H 6.47, N 2.72. Found: C 44.13, H 6.38, N 2.54.

Compound 6a. White solid (35 mg, 86%): mp 138−139 °C; $[\alpha]_D^{27.4}$ 40.9 (c 0.93, $CHCl_3$); IR (film) 3155, 2987, 1605, 1520, 1350, 1312, 1245, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J =

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8.8 Hz, 2H), 7.86 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 2H), 5.22 (d, J = 8.8 Hz, 1H), 4.12 (m, 2H), 3.51 (d, J = 10.8 Hz, 3H), 2.14 (d, J = 16.8 Hz, 3H), 1.44 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.4 (s), 147.3 (s), 128.5 (d, J = 4.3 Hz), 123.3 (d, J = 2.9 Hz), 64.4 (d, J = 7.3 Hz), 61.1 (d, J = 148.8 Hz), 60.7 (s), 54.5 (d, J = 7.3 Hz), 24.3 (s), 20.5 (d, J = 6.5 Hz), 16.5 (d, J = 5.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 23.36; MS (ESI) m/z (%) 409.3 $[M + H]^+$; HRMS (MALDI) calcd for $C_{15}H_{25}N_2O_7PSNa$ 431.1012, found 431.1008.

Compound 6b. White solid (38 mg, 86%): mp 84−87 °C; $[\alpha]_D^{26.5}$ 34.5 (c 0.5, $CHCl_3$); IR (film) 3153, 2981, 1481, 1314, 1242, 1130, 1025, 967, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55−7.50 (m, 4H), 5.11 (d, J = 8.8 Hz, 1H), 4.09 (m, 2H), 3.44 (d, J = 10.8 Hz, 3H), 2.06 (d, J = 16.8 Hz, 3H), 1.41(s, 9H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8 (d, J = 2.1 Hz), 131.4 (s), 129.1 (d, J = 4.3 Hz); 122.3 (d, J = 3.7 Hz), 64.1 (d, J = 7.3 Hz), 61.1 (d, J = 90.9 Hz), 60.5 (s), 54.5 (m), 24.3 (s), 20.0 (d, J = 3.7 Hz), 16.5 (d, J = 5.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 24.15; MS (ESI) m/z (%) 442.2, 444.2 $[M + H]^+$; HRMS (MALDI) calcd for $C_{15}H_{25}NO_5PSBrNa$ 464.0267, found 464.0282.

Compound 6c. White solid (25 mg, 48%): mp 141−142 °C; $[\alpha]_D^{27.0}$ 36.6 (c 0.93, $CHCl_3$); IR (film) 3204, 2984, 2930, 1731, 1311, 1209, 1127, 1082, 851 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 6.04 (d, J = 8.8 Hz, 1H), 4.18 (q, J = 9.3 Hz, 2H), 4.06 (m, 2H), 3.46 (m, 2H), 2.78 (m, 1H), 2.07 (d, J = 16.4 Hz, 3H), 1.42 (s, 9H), 1.31−1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2 (d, J = 4.3 Hz), 139.9 (s), 131.3 (d, J = 2.2 Hz); 129.2 (d, J = 4.4 Hz), 122.0 (d, J = 4.3 Hz), 61.88 (d, J = 7.3 Hz), 61.87 (s), 61.8 (d, J = 139.3 Hz), 60.5 (s), 42.8 (s), 24.3 (s), 19.8 (d, J = 5.0 Hz), 16.3 (d, J = 6.5 Hz), 14.1 (s); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 26.89; MS (ESI) m/z (%) 513.1 $[M + H]^+$; HRMS (MALDI) calcd for $C_{18}H_{31}N_2O_6PSBr$ 513.0818, found 513.0815.

Compound 6d. White solid (42 mg, 80%): mp 135−137 °C; $[\alpha]_D^{25.8}$ 38.5 (c 1.04, $CHCl_3$); IR (film) 3336, 2928, 2857, 1483, 1312, 1127, 1034, 547 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52−7.47 (m, 4H), 5.27 (t, J = 8.4 Hz, 1H), 4.20−4.0 (m, 2H), 2.70 (m, 1H), 2.53 (m, 1H), 2.28 (m, 1H), 2.02 (d, J = 16.0 Hz, 3H), 1.40 (s, 9H), 1.32 (t, J = 7.0 Hz, 3H), 1.30−1.10 (m, 10H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.8 (d, J = 2.1 Hz), 131.2 (d, J = 3.0 Hz), 129.1 (d, J = 4.4 Hz); 122.0 (d, J = 3.7 Hz), 61.9 (d, J = 7.3 Hz), 61.8 (d, J = 134.9 Hz), 60.3 (s), 42.2 (s), 32.2 (d, J = 5.1 Hz), 31.7 (s), 28.8 (s), 26.4 (s), 24.3 (s), 22.6 (s), 20.0 (d, J = 5.1 Hz), 16.5 (d, J = 5.9 Hz), 14.0 (s); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 28.06; MS (ESI) m/z (%) 525.4, 527.4 $[M + H]^+$; HRMS (MALDI) calcd for $C_{21}H_{38}N_2O_4PSBrNa$ 547.1366, found 547.1360.

Compound 6e. White solid (27 mg, 50%): mp 172−174 °C; $[\alpha]_D^{26.8}$ 32.9 (c 1.0, $CHCl_3$); IR (film) 3340, 2979, 1455, 1310, 1127, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (s, 4H), 7.36−7.23 (m, 3H), 7.08 (d, J = 6.8 Hz, 2H), 5.04 (d, J = 8.8 Hz, 1H), 4.21 (m, 1H), 4.05 (m, 1H), 3.81 (m, 1H), 2.70 (t, J = 10.4 Hz, 1H), 1.98 (d, J = 16.8 Hz, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.31 (s, 9H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0 (d, J = 3.6 Hz), 139.7 (d, J = 2.2 Hz), 131.1 (d, J = 2.9 Hz), 129.2 (d, J = 4.4 Hz), 128.8 (s), 127.4 (s), 125.4 (s), 122.0 (d, J = 3.6 Hz), 62.0 (d, J = 7.3 Hz), 61.8 (d, J = 137.1 Hz), 60.4 (s), 52.3 (s), 26.6 (d, J = 4.4 Hz), 24.2 (s), 19.9 (d, J = 5.1 Hz), 16.3 (d, J = 5.8 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 26.70; MS (ESI) m/z (%) 531.3 $[M + H]^+$; HRMS (MALDI) calcd for $C_{22}H_{32}N_2O_4PSBrNa$ 553.0896, found 553.0886.

Compound 6f. White solid (41 mg, quantitative): mp 129−130 °C; $[\alpha]_D^{24.8}$ 47.9 (c 1.0, $CHCl_3$); IR (film) 3444, 3150, 2986, 1606, 1520, 1349, 1311, 1245, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J = 8.8 Hz, 2H), 7.86 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 2H), 5.26 (d, J = 8.8 Hz, 1H), 3.98−3.75 (m, 2H), 3.76 (d, J = 10.8 Hz, 3H), 2.14 (d, J = 16.8 Hz, 3H), 1.44 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.4 (s), 147.3 (d, J = 2.9 Hz), 128.6 (d, J = 5.1 Hz), 123.2 (d, J = 2.1 Hz), 64.6 (d, J = 8.0 Hz), 61.1 (d, J = 148.8 Hz), 60.7 (s), 54.4 (d, J = 7.3 Hz), 24.3 (s), 20.5 (d, J = 6.6 Hz), 16.5 (d, J = 5.8 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 23.40; MS (ESI) m/z (%) 409.3 $[M + H]^+$; HRMS (MALDI) calcd for $C_{15}H_{25}N_2O_7PSNa$ 431.1012, found 431.1010.

Compound 6g. White solid (35 mg, 79%): mp 128−129 °C; $[\alpha]_D^{27.4}$ 40.9 (c 0.93, $CHCl_3$); IR (film) 3448, 2987, 1638, 1480, 1315, 1243, 1130, 1050, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56−7.49 (m, 4H), 5.15 (d, J = 8.8 Hz, 1H), 3.94−3.61 (m, 2H), 3.72 (d, J = 10.8 Hz, 3H), 2.06 (d, J = 16.8 Hz, 3H), 1.41 (s, 9H), 1.15 (t, J = 13.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8 (d, J = 2.2 Hz), 131.4 (s), 129.2 (d, J = 5.1 Hz); 122.3 (d, J =3.7 Hz), 64.4 (d, J =7.2 Hz), 60.8 (d, J = 150.2 Hz), 60.5 (s), 54.2 (m), 24.3 (s), 20.1 (d, J = 5.0 Hz), 16.3 (d, J = 4.2 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 24.16; MS (ESI) m/z (%) 442.0, 444.0 $[M + H]^+$; HRMS (MALDI) calcd for $C_{15}H_{25}NO_5PSBrNa$ 464.0267, found 464.0261.

Compound 6h. Colorless oil (24 mg, 46%): $[\alpha]_D^{27.7}$ 18.2 (c 1.0, $CHCl_3$); IR (film) 3307, 2928, 2856, 1647, 1312, 1128, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (br, 4H), 5.27 (d, J = 11.6 Hz, 1H), 3.88 (m, 2H), 3.83 (m, 2H), 2.47 (m, 1H), 2.05 (d, J = 16.8 Hz, 3H), 1.44−1.40 (m, 10H), 1.24 (s, 9H), 1.17 (t, J = 7.0 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.9 (d, J = 2.9 Hz), 131.1 (s), 129.2 (s); 121.8 (d, J = 3.6 Hz), 62.0 (d, J = 7.3 Hz), 61.7 (d, J = 135.6 Hz), 60.4 (s), 42.4 (s), 32.5 (d, J = 5.1 Hz), 31.7 (s), 28.9 (s), 26.5 (s), 24.3 (s), 22.6 (s), 20.2 (m), 16.2 (m), 14.0 (s); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 27.80; MS (ESI) m/z (%) 525.3, 527.3 $[M + H]^+$; HRMS (MALDI) calcd for $C_{21}H_{39}N_2O_4PSBr$ 525.1546, found 525.1546.

Mechanism Studied by ^{31}P NMR Spectroscopy. **3a** (50 μmol) was hydrolyzed by $BF_3{\cdot}Et_2O$ and concentrated to give crude *H*-phosphinate **A**.

A (50 μmol in 0.5 mL of $CDCl_3$) reacted with Br_2 (100 μmol) and EtOH (100 μmol). The progress of the reaction was monitored by ^{31}P NMR spectroscopy. After 2 h, the intermediate **B** and product **4a** were formed (Figure 1a). Twelve hours later, only **4a** was detected (Figure 1b).

A (50 μmol in 0.5 mL of $CDCl_3$) reacted with Br_2 (100 μmol). After 5 min, partial conversion of **A** to intermediate **B** and byproducts was detected (Scheme S2a, Supporting Information). After 3 h, **A** was completely consumed and **4a** was detected which was from the reaction of **B** with EtOH, a residue from the hydrolysis of **3a** (Scheme S2b, Supporting Information). After that, EtOH (100 μmol) was added. Two hours later, **B** was partly consumed and **4a** was formed (Scheme S2c, Supporting Information). Twelve hours later, **B** was completely consumed. However, the byproducts were present during the entire process (Scheme S2d, Supporting Information).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of compounds **2b**, **2e−h**, **4b−g**, **5b**, deprotected **5c**, **5d** and **6a−h**; crystallographic data for deprotected **5c**, **6c** and **6f**. 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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