Organic & Biomolecular Chemistry

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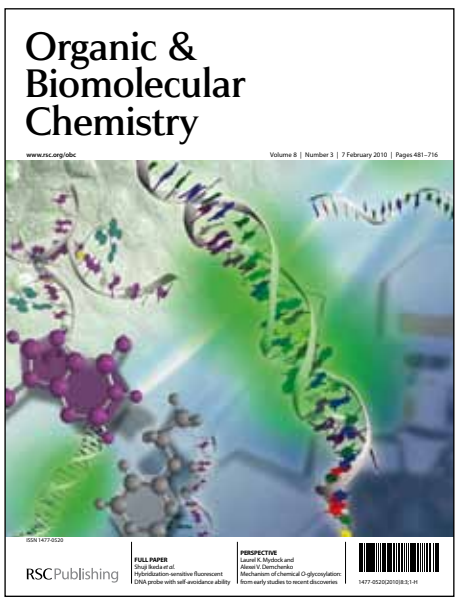

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N,N-Diisopropyl-*N*-phosphonyl Imines Lead to Efficient Asymmetric Synthesis of Aziridine-2-Carboxylic Esters

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Highly diastereoselective asymmetric synthesis of chiral aziridine-2-carboxylic esters is reported for 20 examples with good yields (51-87%) and excellent diastereoselectivities (>99:1 *dr* for most cases). The modified *N*-phosphonyl imines are proven to be superior to previous imine auxiliaries for the *aza* Darzens reaction by using secondary isopropyl to replace primary benzyl group for *N,N*-diamino protection. In the meanwhile, a special operation by slowly adding the pre-cooled imine solution at -78 °C into the preformed β-bromo lithium enolate mixture at this temperature in the presence of 4 Å molecular sieves was found to be crucial in terms of yields and diastereoselectivity. The present method can provide an easy and general access to β-hydroxy α-amino acids and other important amino building blocks.

Introduction

The asymmetric formation of nitrogen heterocycles from readily accessible starting materials has become an important topic for chemical and biomedical research.[1] One of the privileged substructures among the nitrogen-containing heterocycles is represented by the aziridine ring which has been found in a variety of biologically active natural products including mitomycin, azicemycin, azinomycin and maduropeptin.[2a,2b] The structure-activity relationship (SAR) studies on mitosane derivatives revealed that the aziridine ring is crucial for their antitumor activity and selectivity.[2c-2f] This study has led to the finding that mitomycin C can act as the most potent candidate possessing antitumor activities against stomach, breast, oesophagus and bladder tumors.[2b] Many other aziridine-containing derivatives have also been found to exhibit various biological properties.[2a,3a,3b] For example, 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid **1** can serve as a potent irreversible inhibitor of the bacterial enzyme diaminopimelic acid epimerase while 2-(2- carboxyethyl)aziridine-2-carboxylic acid **2** as an irreversible inhibitor of glutamate racemase (Fig. 1).[2a,3a,3b] One of the major reasons for aziridines to play an important role in chemical and biomedical sciences is based on the fact that the strained three-membered rings can undergo regio- and stereoselective ring opening reactions.[4a,4b] For example, the aziridine-2-carboxylic esters can serve as versatile building blocks for making α- and β-amino acids, β-substituted α-amino acids, β-hydroxy α-amino acids, α-amino aldehydes and ketones.[5,9a]

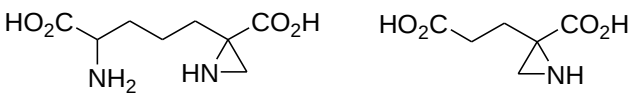

Fig. 1 Biologically active synthetic aziridine-2-carboxylic acids

The asymmetric synthesis of aziridines has been pursued in several research groups for many years;[6] typical known aziridination methods are represented by organocatalytic reactions of imines and enals, and transition metal catalyzed addition of amine or azide onto alkenes.[7,8] Although a great progress has been made on this synthetic topic, it is still remained challenging to develop more efficient and facile approaches to a broad range of structurally diverse aziridines in enantio- and diastereoselective manner. In the past several years, we have designed and synthesized new chiral reagents of *N*-phosphonyl and *N*-phosphinyl amides and imines; we have successfully utilized them in various asymmetric reactions such as asymmetric aza-Darzen reaction,[9a] asymmetric aza-Henry reaction,[9b] asymmetric addition of allylmagnesium bromides,[9c] asymmetric synthesis of *N*-phosphonyl β-amino Weinreb amides,[11a]

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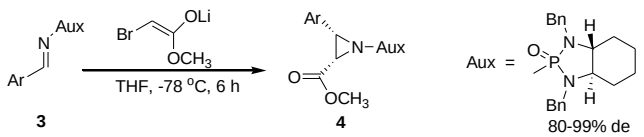
† Electronic Supplementary Information (ESI) available: Copies of ^{1}H, ^{13}C, ^{19}F, ^{31}P NMR spectra, IR spectra and copies of HRMS analysis for all the new compounds. See DOI: 10.1039/b000000x/

asymmetric synthesis of *N*-phosphonyl propargyl amines,[12a] and asymmetric synthesis of α-amino-1,3-dithianes.[12c] In our preliminary work on asymmetric aza-Darzens reaction, we utilized *N,N*-dibenzyl *N*- phosphonyl imines as the electrophiles to react with pre-generated β-bromo lithium enolate to give the aziridine products in good yields and diastereoselectivities.[9a] The important feature of these chiral *N*-phosphonyl imines is shown by the fact that the steric and electronic properties can be optimized by making modifications on different positions of the imine auxiliaries. In the continuing project on *N*-phosphonyl imines, herein we would like to report a more efficient asymmetric aza-Darzens reaction by using isopropyl to replace primary benzyl group for *N,N*-diamino protection on auxiliary and by modifying the synthetic operation.

Results and Discussion

In 1999, one of the great asymmetric methods for synthesizing aziridine-2-carboxylic esters was reported by Davis and coworkers through *N*-*p*-toluenesulfinyl imine-based Darzens reaction.[13] The reaction showed the great success in regard to chemical yields and diastereoselectivity. Despite the above approach to these building blocks, we also made efforts on development of a facile method for the asymmetric synthesis of aziridine-2-carboxylic esters using *N*-phosphonyl imines as electrophiles. The advantages of using chiral *N*-phosphonyl imines would be showed by the following factors: higher thermolytic stability, modification and flexibility at their multiple sites, inertness of phosphonyl group to oxidative conditions, the ^{31}P NMR determination of diastereoselectivity and easy recycling of diamine auxiliary precursors.[9-12] Importantly, our *N*-phosphonyl and *N*-phosphinyl imine-based work has resulted in a new concept called GAP chemistry (Group-Assisted Purification chemistry)[14] which can enable organic synthesis to be performed without using traditional purification techniques such as column chromatography and recrystallization, albeit a few non-GAP exceptions were encountered including the present aziridine formations in which there is no N-H moiety in the products.[15] In our first aza-Darzens synthesis, we utilized *N*-benzyl as the protection group on phosphonyl imine auxiliary. Unfortunately, this auxiliary only showed a limitation on controlling diastereoselectivities in which only one example gave an excellent diastereoselectivity of 99% *de* (Scheme 1).[9a]



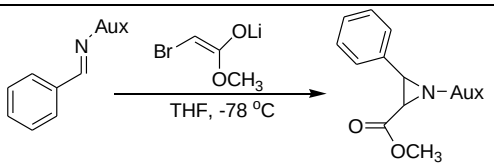
3 **4** 80-99% de

Scheme 1 Synthesis of aziridine-2-carboxylic esters using *N,N*-dibenzylphosphonylimines

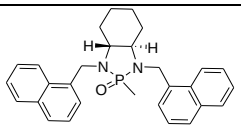
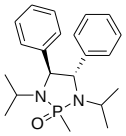
In order to achieve more efficient asymmetric synthesis of aziridine-2-carboxylic esters, we made an effort on the structural modifications on phosphonyl imine auxiliary by using other functional groups to replace the original benzyl and by changing their diamino core structures. We first synthesized the cyclohexane-based *N,N*-di-1-naphthylmethylphosphonyl benzaldimine (**5a**) and subjected it to the reaction with the pre-generated β-bromo lithium enolate. We found the reaction occurred to completion within a prolonged period of over 8.5 hours, but many impurities were formed with the diastereoselectivity of *dr* = 100:42 as revealed by the crude ^{31}P NMR determination. This observation prove that the *N,N*-bisfunctional modifications can result in changes not only on solubility of products but also on the electrophilicity of *N*-phosphonyl imines. We next utilized another chiral imine (**5b**) which was available at that time in our labs and found that the reaction also proceeded at a slower rate with some starting material still remained even after 8.5 h. To make all chiral imine starting materials to be consumed, the reaction was then performed at room temperature. However, the diastereoselectivity was not improved much with *dr* = 100:15 with many impurities co-existing with the major isomeric product.

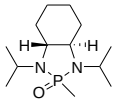
In several of our previous systems, the combination of *N,N*-diisopropyl and diaminocyclohexyl scaffolds have been proven to be superior to others in several nucleophilic addition reactions and syntheses, such as aza-Henry reaction,[9b] the addition reaction of allyl magnesium bromide,[9c] the synthesis of β-amino weinreb amides,[11a] α,β-diamino esters[11d] chiral propargyl amines,[12a] and umpolung reaction with lithium 1,3-dithianes.[12c] Therefore, this combination was considered to enhance the present synthesis of aziridine-2-carboxylic esters. We now found that (1*R*, 2*R*)-diaminocyclohexyl derived *N,N*-diisopropyl-*N*-phosphonyl benzaldimine (**5c**) can react with β-bromo lithium enolate smoothly to completion within 8 hours. Importantly, we found that by slowly adding the pre-cooled benzaldimine (**5c**) solution in THF at -78 °C into preformed β-bromo lithium enolate mixture at the same temperature in the presence of 4 Å molecular sieves is crucial in terms of yields and diastereoselectivity. With the optimized conditions in hand, we successfully synthesized aziridine-2-carboxylic esters with excellent diastereoselectivity (>99%, almost single diastereomer) as revealed by ^{31}P NMR determination of crude products. The results were summarized in Table 1.

Table 1 Optimizing the stereo effect of chiral *N*-phosphonyl imines[a]



5a-5c **6a-6c**

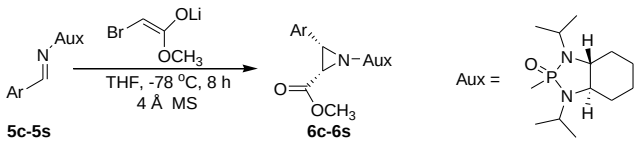
entry	substrate	auxiliary	reaction time	*dr*[b,c]
1	**5a**		>8.5 h	100:42
2	**5b**		>8.5 h	100:15

3	**5c**		8 h	>99:1

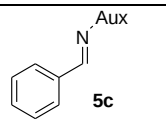
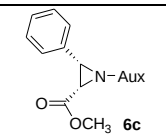
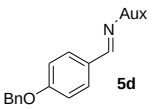
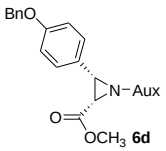
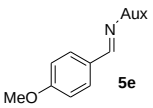
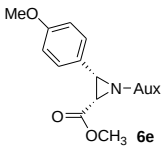
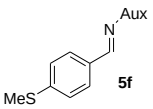
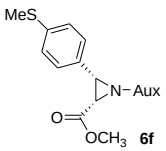
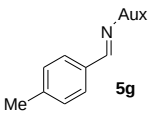
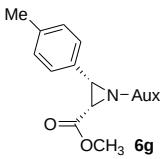
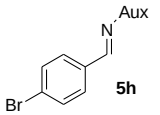
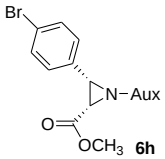
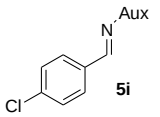
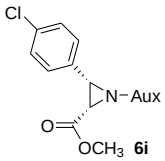
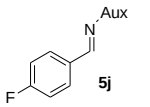
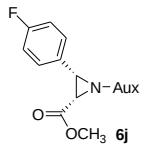
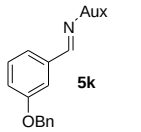
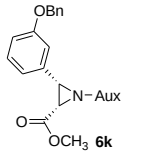
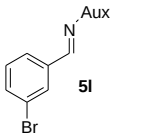
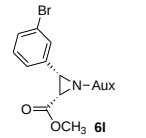
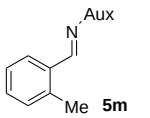
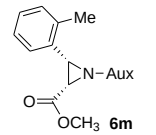
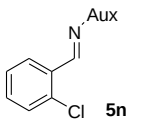
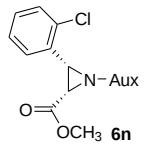
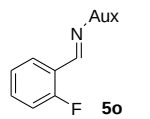
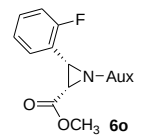
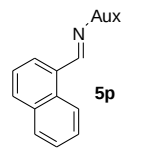
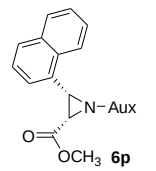
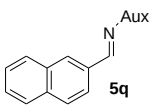
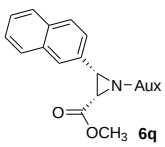
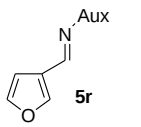
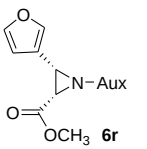
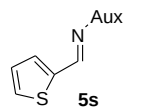
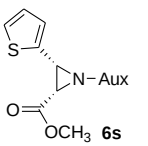
[a]Reaction conditions: 0.57 mmol imine, 1.15 mmol methyl-2-bromo acetate, 1.20 mmol LiHMDS 14 mL solvent, -78 °C. [b]Diastereoselectivities were determined by ^{31}P-NMR analysis of crude products. [c] >99:1 means only one isomer was observed by ^{31}P NMR.

On the basis of the above optimal conditions, the substrate scope of this reaction was next examined. Besides *N*,*N*-diisopropylphosphonyl imines with both electron donating and electron withdrawing groups on the aromatic rings (entries 2-15, Table 2), we also examined substrate scope of two heterocyclic aldimines to give 85% and 76% yields and excellent diastereoselectivities (entries 16 and 17, Table 2). For all cases, isolated yields ranged from 51% to 87% and excellent diastereoselectivities from 96.2:3.8 to >99:1 were obtained. Similar to the previous system,[9a] the major isomeric products were confirmed to be formed in *cis*-geometry (Table 2).

Table 2 Asymmetric addition of lithium enolate of methyl 2-bromoacetate onto *N*,*N*-diisopropylphosphonyl imines[a]



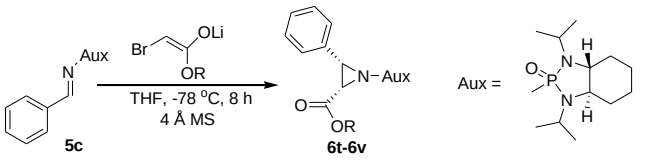
5c-5s 6c-6s

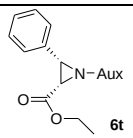
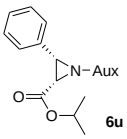
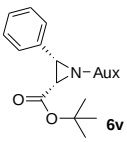
Entry	Substrate	Product	Yield(%)[b]	dr[c,d]
1	 **5c**	 **6c**	78	>99:1
2	 **5d**	 **6d**	70	98.8:1.2
3	 **5e**	 **6e**	84	98.7:1.7
4	 **5f**	 **6f**	71	>99:1
5	 **5g**	 **6g**	87	>99:1
6	 **5h**	 **6h**	69	>99:1
7	 **5i**	 **6i**	70	>98:2
8	 **5j**	 **6j**	79	99:1
9	 **5k**	 **6k**	71	>99:1
10	 **5l**	 **6l**	75	>99:1
11	 **5m**	 **6m**	61	>99:1
12	 **5n**	 **6n**	52	>99:1
13	 **5o**	 **6o**	51	>99:1
14	 **5p**	 **6p**	73	>99:1
15	 **5q**	 **6q**	77	>99:1
16	 **5r**	 **6r**	85	>99:1
17	 **5s**	 **6s**	76	96.2:3.8

[a]Reaction conditions: 0.57 mmol imine, 1.15 mmol methyl-2-bromo acetate, 1.20 mmol LiHMDS 14 mL solvent, -78 °C. [b]Isolated yield of the pure product. [c]Diastereoselectivities were determined by ^{31}P-NMR analysis of crude products. [d]>99:1 means only diasteroisomer was observed in crude ^{31}P-NMR spectrum.

In addition to *N*,*N*-diisopropylphosphonyl imines, we also examined bromo lithium enolates derived from different bromo esters. As shown by Table 3, ethyl, isopropyl and *tert*-butyl group-derived enolates afforded good chemical yields and excellent diastereoselectivities (>99% *dr*). The steric effect of these ester groups did not affect *cis*-geometry and diastereoselectivity of the products.

Table 3 Asymmetric addition of lithium enolates of different 2-bromoacetates onto *N*,*N*-diisopropylphosphonyl benzaldimine[a]

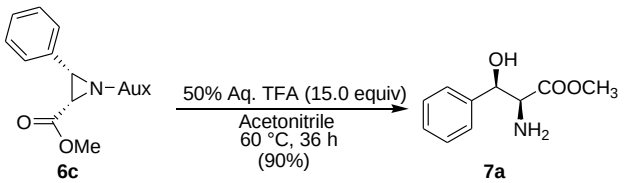


Entry	R	Product	Yield(%)[b]	dr[c,d]
1	Ethyl		78	99.4:0.6
2	Isopropyl		77	>99:1
3	*tert*-Butyl		74	>99:1

[a]Reaction conditions: 0.57 mmol imine, 1.15 mmol methyl-2-bromo acetate, 1.20mmol LiHMDS 14 mL solvent, -78 °C. [b]Isolated yield of the pure product. [c]Diastereoselectivities were determined by ^{31}P-NMR analysis of crude products. [d]>99:1 means only one isomer was observed by ^{31}P NMR.

As compared to our previous aziridination, the present *N*,*N*-diisopropylphosphonyl imine-based synthesis resulted in much higher diastereoselectivity. In most cases, only one isomeric product was observed as proven by the ^{31}P-NMR analysis of resulting crude products. The secondary alkyl group (isopropyl) is superior to its primary counterpart (benzyl) for cyclohexane diamino template in controlling asymmetric induction for this reaction. For many cases, not only diastereoselelectivity but also chemical yields were increased, particularly, for 4-methyl and 4-fluoro substrates, the yields were increased from 76 % and 64% to 87% and 79%, respectively (entries 3 and 8, Table 2). The present synthesis showed the synthesis of twenty (2*S*,3*S*) aziridine-2-carboxylic esters, which may indicate a broader substrate scope than the previous one.

As anticipated the auxiliary can be successfully cleaved by treating the aziridine product (**6c**) with trifluoroacetic acid in acetone and water co-solvents at room temperature to give the ring opening product of (2*S*,3*R*)-β-hydroxy α-amino acid methyl ester (**7a**) as major diastereomer (Scheme 2). The cleavage reaction is used not only for the absolute structure determination, but also for providing an efficient approach to unnatural amino acids.[16]



$[\alpha]^{25}_{D}$ = + 10.1 (c = 0.2, MeOH) for (2*S*,3*R*);
Lit $[\alpha]^{20}_{D}$ = - 10.97 (c =1.4 , MeOH)[17] for (2*R*,3*S*)

Scheme 2 Cleavage of the auxiliary and synthesis of (2*S*,3*R*)-β-hydroxy α-amino acid methyl ester

Similar to the previous system, a six-membered chair like transition state was proposed (Figure 3). The lithium metal cation serves as the Lewis acidic anchor to connect two reaction partners, imine electrophile and enolate nucleophile together, prior to aza Darzens reaction. This anchored reaction manner would be responsible for the excellent control of stereochemistry in which the enolate attacks imine's carbon center on its *Re* face. The asymmetric control is indirectly controlled by two nitrogens that are forced to be the original chirality of the nearby (2*S*,3*S*) vicinal centers on cyclohexane ring.

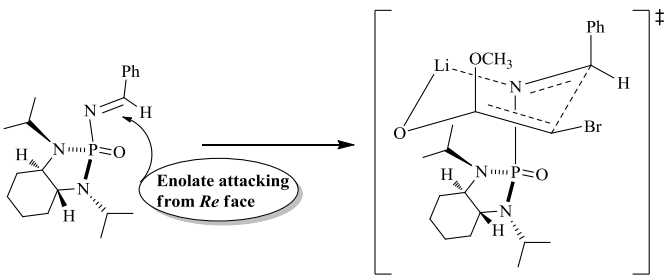


Fig. 3 Proposed transition state model for the asymmetric aza-Darzens reaction.

Conclusions

In conclusion, we have developed an efficient protocol for the asymmetric synthesis of aziridine-2-carboxylic esters by using *N*,*N*-diisopropyl-*N*-phosphonyl imines in which the secondary alkyl is superior to its primary counterpart in providing asymmetric environment. Good yields and excellent diastereoselectivity have been achieved for a good spectrum of twenty substrates. A special operation manner by slowly adding the pre-cooled imine solution at -78 °C into preformed β-bromo lithium enolate mixture at the same temperature in the presence of 4 Å molecular sieves was found to be crucial for the outcomes.

Experimental Section

General experimental methods

All the reactions were carried out in oven-dried glassware under an atmosphere of dry argon, unless otherwise stated. All commercially available reagents were used without further purification. THF used for the reaction was distilled using benzophenone-sodium still under nitrogen prior to use. 4 Å molecular sieves were dried in oven prior to use. Solvents used for extraction and purification were used directly without further distillation. Reaction temperatures are reported as bath temperatures. NMR data was reported as follows: chemical shifts in ppm on the δ scale, multiplicity as (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet), coupling constants in (Hz). ^{1}H NMR spectra were recorded at ambient temperature at 500 MHz. ^{13}C NMR spectra were recorded at ambient temperature at 125 MHz. ^{31}P NMR spectra were recorded at ambient temperature at 202 MHz. ^{19}F NMR were recorded at ambient temperature at 376 MHz. ^{1}H NMR spectra were acquired in $CDCl_3$, chemical shifts were reported as δ values in ppm and were calibrated according to internal $CHCl_3$ (7.26 ppm). For ^{13}C NMR spectra, chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (77.00 ppm). For ^{31}P NMR spectra, chemical shifts are reported as δ values in ppm. For ^{19}F NMR spectra, chemical shifts are reported as δ values in ppm. Infrared spectra (IR) were obtained on an FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). HRMS data was collected at the University of Illinois at Urbana-Champagne instrumentation facility. Optical rotation values were taken using AUTOPOL IV automatic polarimeter. Analytical thin-layer chromatography (TLC) was performed using 0.25mm precoated silica gel plates and the compounds were visualized with UV light (λ = 254 nm) and/or immersing in iodine stain. Compounds were purified using flash column chromatography (forced flow) on silica gel (SiO_2) 60 Å (32-63 μm) particle size.

General synthetic procedure for the asymmetric aza-Darzens reaction

Into an oven dried and argon flushed reaction vial, 4 Å molecular sieves were first taken followed by dry THF (7 mL) and methyl 2-bromoacetate (1.15 mmol, 2 equiv) and stirred. Reaction mixture was then cooled to -78 ^{o}C using dry ice-acetone mixture and lithium bis(trimethylsilylamide) (LiHMDS) (1 M solution in THF, 1.20 mmol, 2.1 equiv) was added slowly dropwise and the resulting reaction mixture was stirred for 45 min at -78 ^{o}C. *N*-phosphonyl imine (0.57 mmol, 1 equiv, dissolved in 7 mL of dry THF) properly sealed with a rubber septum in dry argon atmosphere, was cooled to -78 ^{o}C in the same dry ice-acetone bath for 45 min. After 45 min, the imine was added dropwise *via* a cannula at -78 ^{o}C and stirring was continued for 8h (reaction was monitored by TLC and/or crude NMR) at the same temperature. After confirming the consumption of imine, the reaction mixture was quenched with water (2 mL) and the organic layer was extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography on silica gel (R_f = 0.25) using EtOAc/Hexanes (7:3) as the eluent to afford the aziridine product.

Compound 6c. White solid: mp 99-101 ^{o}C; IR (ATR) *v* 2965, 2938, 1749, 1455, 1361, 1243, 1198, 1170, 1105, 1058, 1033, 1014, 939, 924, 876, 823, 787, 739, 723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7 Hz, 2H), 7.36-7.20 (m, 3H), 3.72 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.66-3.51 (m, 2H), 3.49 (s, 3H), 3.41 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.09-2.92 (m, 2H), 2.11 (d, *J* = 7.5 Hz, 1H), 2.05 (d, *J* = 10.5 Hz, 1H), 1.91-1.61 (m, 2H), 1.34 (d, *J* = 7 Hz, 6H), 1.31-1.24 (m, 1H), 1.21 (dd, *J* = 7.5 Hz and 3.5 Hz, 6H), 1.08 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.54, 134.09, 127.86, 127.78, 59.99, 58.92, 51.79, 45.53, 44.70, 42.70, 41.98, 31.55, 30.27, 24.23, 23.43, 22.65, 20.28, 20.18; ^{31}P (202 MHz, $CDCl_3$) δ 30.82; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{35}N_3O_3P$, 420.2416; found, 420.2425; $[\alpha]_D^{25}$ = -19.9 (c =1, $CHCl_3$).

Compound 6d. Oily liquid; IR (thin film/NaCl) *v* 2935, 2867, 1752, 1728, 1611, 1513, 1455, 1364, 1300, 1243, 1215, 1172, 1107, 1082, 1061, 1024, 929, 826 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.33 (m, 6H), 7.33-7.27 (m, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.00 (s, 2H), 3.67 (dd, *J* = 17.5 Hz and 6 Hz, 1H), 3.63-3.51 (m, 1H), 3.48 (s, 3H), 3.47-3.40 (m, 1H), 3.36 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.05-2.92 (m, 2H), 2.18-2.07 (m, 1H), 2.06-1.95 (m, 1H), 1.76 (s, 2H), 1.33 (d, *J* = 7 Hz, 6H), 1.30-1.23 (m, 1H), 1.2 (d, *J* = 6.5 Hz, 6H), 1.07 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.52, 158.39, 136.79, 128.86, 128.41, 127.83, 127.41, 126.22, 114.10, 69.81, 59.85, 58.81, 51.68, 45.40, 44.57, 42.35, 41.82, 31.43, 30.14, 24.11, 23.33, 22.52, 20.17, 20.05; ^{31}P (202 MHz, $CDCl_3$) δ 30.80; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{41}N_3O_4P$, 526.2835; found, 526.2842; $[\alpha]_D^{25}$ = -25.52 (c =0.76, $CHCl_3$).

Compound 6e. White solid: mp 84-86 ^{o}C; IR (ATR) *v* 2936, 2867, 1748, 1614, 1515, 1456, 1436, 1396, 1367, 1304, 1246, 1217, 1194, 1170, 1107, 1062, 1027, 1010, 995, 921, 879, 829, 764, 746, 725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 9 Hz, 2H), 3.78 (s, 3H), 3.67 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.64-3.53 (m, 1H), 3.51 (s, 3H), 3.49-3.41 (m, 1H), 3.37 (dd, *J* = 17.5 Hz and 6.5 Hz, 1H), 2.99 (s, 2H), 2.11 (d, *J* = 6Hz, 1H), 2.04 (d, *J* = 11 Hz, 1H), 1.78 (s, 2H), 1.34 (d, *J* = 7 Hz, 6H), 1.32-1.25 (m, 1H), 1.21 (d, *J* = 7 Hz, 6H), 1.08 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.68, 159.21, 128.95, 126.07, 113.30, 59.96, 58.93, 55.14, 51.81, 45.52, 44.70, 42.45, 41.94, 31.59, 30.28, 24.27, 23.48, 22.65, 20.27; ^{31}P (202 MHz, $CDCl_3$) δ 30.84; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{37}N_3O_4P$, 450.2522; found, 450.2511; $[\alpha]_D^{25}$ = -31.12 (c =0.75, $CHCl_3$).

Compound 6f. White solid: mp 122-125 ^{o}C; IR (ATR) *v* 2935, 2864, 1749, 1494, 1435, 1368, 1245, 1218, 1194, 1163, 1103, 1098, 1061, 1028, 997, 925, 883, 823, 746, 727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 3.63 (dd, *J* = 15 Hz and 6 Hz, 1H), 3.59-3.50 (m, 1H), 3.47 (s, 3H), 3.45-3.39 (m, 1H), 3.35 (dd, *J* = 15 Hz and 6.5 Hz, 1H),

2.96 (s, 2H), 2.42 (s, 3H), 2.08 (s, 1H), 2.01 (d, *J* = 11.5 Hz, 1H), 1.75 (s, 2H), 1.31 (d, *J* = 7 Hz, 6H), 1.27-1.21 (m, 1H), 1.17 (t, *J* = 6.5 Hz, 6H), 1.04 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.38, 137.86, 130.73, 128.16, 125.62, 59.87, 58.81, 51.74, 45.40, 44.58, 42.33, 41.89, 31.44, 30.14, 24.12, 23.33, 22.52, 20.13, 15.40; ^{31}P (202 MHz, $CDCl_3$) δ 30.72; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{37}N_3O_3PS$, 466.2293; found, 466.2305; $[\alpha]_D^{25}$ = -18.13 (c =0.75, $CHCl_3$).

Compound 6g. White solid: mp 120-122 ^{o}C; IR (ATR) *v* 2937, 2867, 1749, 1396, 1366, 1249, 1217, 1193, 1164, 1107, 1062, 1026, 1010, 923, 881, 821, 759, 746, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8 Hz, 2H), 7.09 (d, *J* = 8 Hz, 2H), 3.68 (dd, *J* = 17.5 Hz and 6 Hz, 1H), 3.63-3.53 (m, 1H), 3.51 (s, 3H), 3.48-3.41 (m, 1H), 3.37 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 2.99 (s, 2H), 2.31 (s, 3H), 2.11 (d, *J* = 6 Hz, 1H), 2.04 (d, *J* = 11 Hz, 1H), 1.78 (s, 2H), 1.34 (d, *J* = 7 Hz, 6H), 1.27 (m, 1H), 1.21 (dd, *J* = 7 Hz, 6H), 1.08 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.62, 137.41, 131.023, 128.59, 127.66, 59.96, 58.89, 51.79, 45.52, 44.69, 42.72, 41.89, 31.55, 30.29, 24.23, 23.46, 22.65, 21.19, 20.22; ^{31}P (202 MHz, $CDCl_3$) δ 30.87; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{37}N_3O_3P$, 434.2573; found, 434.2575; $[\alpha]_D^{25}$ = -29.73 (c =0.76, $CHCl_3$).

Compound 6h. White solid: mp 139-141 ^{o}C; IR (ATR) *v* 2936, 1752, 1487, 1444, 1389, 1362, 1242, 1216, 1192, 1163, 1103, 1063, 1026, 1010, 997, 924, 910, 884, 827, 744, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 3.66 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.62-3.52 (m, 1H), 3.51 (s, 3H), 3.50-3.43 (m, 1H), 3.40 (dd, *J* = 12.5 Hz and 6 Hz, 1H), 3.06-2.90 (m, 2H), 2.14 (d, *J* = 6.5 Hz, 1H), 2.03 (d, *J* = 11.5 Hz, 1H), 1.89-1.67 (m, 2H), 1.37 (d, *J* = 6.5 Hz, 6H), 1.30-1.23 (m, 1H), 1.18 (t, *J* = 7 Hz, 6H), 1.04 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.35, 133.20, 131.05, 129.55, 121.87, 60.01, 58.95, 51.93, 45.50, 44.69, 42.03, 31.51, 30.20, 24.22, 23.38, 22.62, 20.25; ^{31}P (202 MHz, $CDCl_3$) δ 30.59; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{34}BrN_3O_3P$, 498.1521; found, 498.1512; $[\alpha]_D^{25}$ = -19.63 (c =0.83, $CHCl_3$).

Compound 6i. White solid: mp 128-130 ^{o}C; IR (ATR) *v* 2938, 2868, 1752, 1491, 1394, 1362, 1243, 1216, 1192, 1162, 1104, 1086, 1062, 1026, 1011, 998, 923, 909, 886, 825, 745, 727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 3.68 (dd, *J* = 17.5 Hz and 6.5 Hz, 1H), 3.63-3.53 (m, 1H), 3.51 (s, 3H), 3.49-3.37 (m, 2H), 3.08-2.92 (m, 2H), 2.12 (s, 1H), 2.05 (d, *J* = 12 Hz, 1H), 1.80 (s, 2H), 1.46-1.31 (m, 6H), 1.31-1.24 (m, 1H), 1.21 (t, *J* = 7 Hz, 6H), 1.06 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.36, 133.63, 132.65, 129.20, 120.10, 60.00, 58.94, 51.90, 45.48, 44.68, 42.02, 31.51, 30.20, 24.22, 23.37, 22.61, 20.24; ^{31}P (202 MHz, $CDCl_3$) δ 30.63; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{34}ClN_3O_3P$, 454.2026; found, 454.2024; $[\alpha]_D^{25}$ = -35.60 (c =0.86, $CHCl_3$).

Compound 6j. Oily liquid: IR (thin film/NaCl) *v* 2937, 2869, 1752, 1732, 1605, 1511, 1438, 1396, 1364, 1298, 1212, 1175, 1106, 1061, 1026, 929, 881, 831, 770, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.5 Hz, 2H), 6.92 (t, *J* = 9 Hz, 2H), 3.64 (dd, *J* = 15 Hz and 6 Hz, 1H), 3.57-3.46 (m, 1H), 3.43 (s, 3H), 3.42-3.37 (m, 1H), 3.33 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.02-2.84 (m, 2H), 2.06 (s, 1H), 1.99 (d, *J* = 11.5 Hz, 1H), 1.73 (s, 2H), 1.28 (d, *J* = 7 Hz, 6H), 1.25-1.18 (m, 1H), 1.15 (t, *J* = 6.5 Hz, 6H), 1.00 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.25, 163.24, 161.28, 129.62, 129.31, 114.66, 59.84, 58.79, 51.66, 45.32, 44.52, 41.81, 31.36, 30.03, 24.06, 23.18, 22.42, 20.06; ^{31}P (202 MHz, $CDCl_3$) δ 30.68; ^{19}F NMR (376.17 MHz, $CDCl_3$) δ -114.20; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{34}FN_3O_3P$, 438.2322; found, 438.2326; $[\alpha]_D^{25}$ = -30.86 (c =0.75, $CHCl_3$).

Compound 6k. Oily liquid: IR (thin film/NaCl) *v* 2936, 2868, 1754, 1730, 1584, 1488, 1449, 1395, 1364, 1246, 1209, 1175, 1106, 1081, 1060, 1026, 955, 928, 903, 878, 815, 791, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7 Hz, 1H), 7.18 (t, *J* = 8 Hz, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 5.03 (s, 2H), 3.67 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.61-3.49 (m, 1H), 3.47 (s, 3H), 3.46-3.33 (m, 2H), 2.95 (s, 2H), 2.08 (s, 1H), 2.02 (d, *J* = 11.5 Hz, 1H), 1.76 (s, 2H), 1.31 (d, *J* = 7 Hz, 6H), 1.19 (d, *J* = 7 Hz, 7H), 1.07 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.29, 158.31, 136.86, 135.64, 128.79, 128.30, 127.71, 127.28, 120.37, 114.49, 113.77, 77.25, 77.00, 76.74, 69.70, 59.82, 58.75, 51.67, 45.40, 44.53, 42.59, 41.83, 31.38, 30.12, 24.06, 23.38, 22.47, 20.06; ^{31}P (202 MHz, $CDCl_3$) δ 30.69; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{41}N_3O_4P$, 526.2835; found, 526.2829; $[\alpha]_D^{25}$ = -21.01 (c =0.79, $CHCl_3$).

Compound 6l. White solid: mp 130-132 ^{o}C; IR (ATR) *v* 2981, 2932, 1757, 1400, 1361, 1238, 1219, 1198, 1175, 1140, 1105, 1062, 1042, 1018, 927, 909, 879, 843, 788, 758, 723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.44-7.34 (m, 2H), 7.17 (t, *J* = 8 Hz, 1H), 3.66 (dd, *J* = 17.5 Hz and 6.5 Hz, 1H), 3.62-3.54 (m, 1H), 3.52 (s, 3H), 3.50-3.31 (m, 2H), 3.08-2.93 (m, 2H), 2.12 (s, 1H), 2.05 (d, *J* = 11.5 Hz, 1H), 1.79 (s, 2H), 1.36 (s, 2H), 1.33 (d, *J* = 7 Hz, 4H), 1.31-1.24 (m, 1H), 1.21 (dd, *J* = 6.5 Hz and 3 Hz, 6H), 1.08 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.30, 136.54, 130.93, 129.465, 126.52, 121.94, 60.06, 58.93, 51.91, 45.54, 44.68, 41.92, 31.48, 30.27, 24.22, 23.36, 22.71, 20.26; ^{31}P (202 MHz, $CDCl_3$) δ 30.50; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{34}BrN_3O_3P$, 498.1521; found, 498.1522; $[\alpha]_D^{25}$ = -26.00 (c =0.75, $CHCl_3$).

Compound 6m. Oily liquid: IR (thin film/NaCl) *v* 2936, 2867, 1756, 1728, 1460, 1396, 1364, 1201, 1177, 1129, 1106, 1083, 1060, 1028, 930, 830, 780, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (m, 1H), 7.18-7.07 (m, 2H), 7.04 (m, 1H), 3.71 (dd, *J* = 17.5 Hz and 6.5 Hz, 1H), 3.61-3.40 (m, 3H), 3.38 (s, 3H), 3.17-3.05 (m, 1H), 3.03-2.91 (m, 1H), 2.28 (s, 3H), 2.11 (d, *J* = 8 Hz, 1H), 2.04 (d, *J* = 8 Hz, 1H), 1.71 (s, 2H), 1.44-1.26 (m, 7H), 1.19 (dd, *J* = 15 Hz and 7 Hz, 6H), 1.04 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.57, 136.08, 132.09, 129.14, 128.09, 127.30, 125.14, 59.96, 58.72, 51.53, 45.28, 44.55, 41.25, 40.96, 31.34, 30.12, 24.11, 23.09, 22.58, 20.11, 18.57; ^{31}P (202 MHz, $CDCl_3$) δ 31.60; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for

$C_{23}H_{37}N_3O_3P$, 434.2573; found, 434.2563; $[\alpha]_D^{25}$ = -4.20 (c =0.77, $CHCl_3$).

Compound 6n. White solid: mp 122-124 °C; IR (ATR) *v* 2942, 2859, 1751, 1437, 1392, 1360, 1244, 1217, 1199, 1171, 1128, 1105, 1081, 1052, 1030, 1003, 928, 889, 831, 786, 764, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.25-7.14 (m, 2H), 3.92 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.65-3.38 (m, 6H), 3.08 (t, *J* = 7.5 Hz, 1H), 3.00 (t, *J* = 9 Hz, 1H), 2.14 (s, 1H), 2.06 (d, *J* = 10.5 Hz, 1H), 1.80 (s, 2H), 1.37 (s, 3H), 1.33 (d, *J* = 7 Hz, 4H), 1.21 (d, *J* = 6.5 Hz, 6H), 1.09 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.60, 133.77, 132.15, 130.26, 128.86, 128.68, 126.12, 60.10, 58.93, 51.92, 45.49, 44.69, 41.29, 40.96, 31.50, 30.22, 24.25, 23.24, 22.67, 20.29; ^{31}P (202 MHz, $CDCl_3$) δ 31.13; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{34}ClN_3O_3P$, 454.2026; found, 454.2018; $[\alpha]_D^{25}$ = +5.60 (c =0.91, $CHCl_3$).

Compound 6o. White solid: mp 114-116 °C; IR (ATR) *v* 2936, 2867, 1754, 1619, 1492, 1456, 1364, 1234, 1202, 1173, 1094, 1061, 1028, 930, 822, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (t, *J* = 7.5 Hz, 1H), 7.34-7.18 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 3.90 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.64-3.54 (m, 1H), 3.52 (s, 3H), 3.46 (dd, *J* = 16 Hz and 6.5 Hz, 2H), 3.11-2.92 (m, 2H), 2.12 (d, *J* = 6.5 Hz, 1H), 2.06 (d, *J* = 12.5 Hz, 1H), 1.89-1.66 (m, 2H), 1.44-1.29 (m, 7H), 1.22 (d, *J* = 7 Hz, 6H), 1.09 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.52, 162.69, 160.73, 129.98, 129.25, 123.44, 121.52, 114.64, 60.04, 58.94, 51.92, 45.52, 44.70, 43.66, 41.26, 37.38, 31.51, 30.23, 24.25, 23.32, 22.63, 20.26; ^{31}P (202 MHz, $CDCl_3$) δ 30.89; ^{19}F NMR (376.17 MHz, $CDCl_3$) δ -119.49; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{34}FN_3O_3P$, 438.2322; found, 438.2317; $[\alpha]_D^{25}$ = -20.39 (c =0.76, $CHCl_3$).

Compound 6p. White solid: mp 145-147 °C; IR (ATR) *v* 2968, 2944, 2862, 1729, 1440, 1366, 1333, 1729, 1440, 1366, 1333, 1285, 1246, 1232, 1216, 1198, 1173, 1129, 1060, 1030, 1001, 925, 884, 858, 808, 793, 765, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.84 (t, *J* = 7 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.58-7.41 (m, 3H), 4.3 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.73 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.66-3.43 (m, 2H), 3.27 (s, 3H), 3.23 (t, *J* = 9.5 Hz, 1H), 3.04 (t, *J* = 9.5 Hz, 1H), 2.18 (s, 1H), 2.11 (s, 1H), 1.83 (s, 2H), 1.38 (d, *J* = 7 Hz, 7H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.22 (d, *J* = 7 Hz, 3H), 1.07 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.67, 133.12, 131.52, 129.77, 128.59, 128.01, 126.50, 126.18, 125.59, 125.17, 122.76, 60.18, 58.86, 51.69, 45.50, 44.75, 41.70, 40.76, 31.48, 30.28, 24.28, 23.22, 22.78, 20.31; ^{31}P (202 MHz, $CDCl_3$) δ 31.85; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{37}N_3O_3P$, 470.2573; found, 470.2577; $[\alpha]_D^{25}$ = +83.70 (c =0.75, $CHCl_3$).

Compound 6q. White solid: mp 151-153 °C; IR (ATR) *v* 2940, 2860, 1746, 1457, 1392, 1371,1245, 1198, 1166, 1125, 1106, 1080, 1062, 1018, 960, 927, 883, 866, 842, 822, 752, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.88-7.71 (m, 3H), 7.59 (d, *J* = 8 Hz, 1H), 7.44 (p, *J* = 3.5 Hz, 2H), 3.88 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.72-3.55 (m, 1H), 3.54-3.34 (m, 5H), 3.14-2.87 (m, 2H), 2.11 (s, 1H), 2.05 (d, *J* = 10.5 Hz, 1H), 1.78 (s, 2H), 1.36 (d, *J* = 7 Hz, 7H), 1.22 (dd, *J* = 15 Hz and 7 Hz, 6H), 1.07 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.43, 133.01, 132.84, 131.65, 127.80, 127.58, 127.42, 127.05, 125.89, 125.80, 125.39, 59.95, 58.88, 51.74, 45.48, 44.64, 42.88, 42.04, 31.47, 30.22, 24.15, 23.36, 22.64, 20.18; ^{31}P (202 MHz, $CDCl_3$) δ 30.75; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{37}N_3O_3P$, 470.2573; found, 470.2565; $[\alpha]_D^{25}$ = -20.25 (c =0.77, $CHCl_3$).

Compound 6r. White solid: mp 98-100 °C; IR (ATR) *v* 2976, 2937, 2866, 1745, 1436, 1397, 1365, 1233, 1196, 1168, 1124, 1081, 1062, 1019, 981, 925, 873, 819, 801, 767, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.31 (s, 1H), 6.44 (s, 1H), 3.62 (s, 3H), 3.60-3.37 (m, 3H), 3.30 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.03-2.83 (m, 2H), 2.14-1.96 (m, 2H), 1.77 (s, 2H), 1.33 (d, *J* = 7 Hz, 6H), 1.23 (d, *J* = 6.5 Hz, 4H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.78, 142.65, 141.73, 119.90, 110.13, 59.91, 58.86, 51.96, 45.59, 44.68, 40.78, 36.35, 31.56, 30.23, 24.21, 23.52, 22.46, 20.16; ^{31}P (202 MHz, $CDCl_3$) δ 30.33; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{33}N_3O_4P$, 410.2209; found, 410.2219; $[\alpha]_D^{25}$ = -51.20 (c =0.80, $CHCl_3$).

Compound 6s. White solid: mp 109-112 °C; IR (ATR) *v* 2977, 2935, 2865, 1755, 1442, 1397, 1366, 1328, 1255, 1218, 1191, 1171, 1144, 1106, 1081, 1057, 1032, 1007, 928, 903, 877, 848, 803, 770, 746, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 5 Hz, 1H), 7.09 (s, 1H), 6.93 (t, *J* = 4.5 Hz, 1H), 3.85 (dd, *J* = 15 Hz and 6 Hz, 1H), 3.59 (s, 3H), 3.57-3.26 (m, 3H). 2.98 (s, 2H), 2.11 (s, 1H), 2.07 (d, *J* = 10 Hz, 1H), 1.77 (s, 2H), 1.33 (d, *J* = 7 Hz, 7H), 1.21 (t, *J* = 6.5 Hz, 6H), 1.11 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.38, 137.96, 126.59, 125.16, 59.95, 58.80, 51.97, 45.56, 44.74, 42.41, 39.15, 31.49, 30.19, 24.21, 23.42, 22.46, 20.23; ^{31}P (202 MHz, $CDCl_3$) δ 30.17; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{33}N_3O_3PS$, 426.1980; found, 426.1974; $[\alpha]_D^{25}$ = -25.46 (c =0.75, $CHCl_3$).

Compound 6t. Oily liquid: IR (thin film/NaCl) *v* 2974, 2935, 2868, 1751, 1725, 1455, 1394, 1370, 1299, 1246, 1196, 1178, 1107, 1060, 1026, 955, 925, 809, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7 Hz, 2H), 7.32-7.16 (m, 3H), 3.98-3.82 (m, 2H), 3.70 (dd, *J* = 17.5 Hz and 6.5 Hz, 1H), 3.61-3.49 (m, 1H), 3.44 (h, *J* = 7 Hz, 1H), 3.37 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.08-2.90 (m, 2H), 2.10 (s, 1H), 2.02 (d, *J* = 13 Hz, 1H), 1.76 (s, 2H), 1.33 (d, *J* = 6.5 Hz, 6H), 1.19 (dd, *J* = 10 Hz and 7 Hz, 6H), 1.04 (d, *J* = 7 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.01, 134.04, 127.71, 127.60, 77.25, 77.00, 76.74, 60.67, 59.85, 58.83, 45.40, 44.60, 42.43, 42.04, 31.46, 30.14, 24.14, 23.35, 22.50, 20.14, 13.80; ^{31}P (202 MHz, $CDCl_3$) δ 30.95; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{37}N_3O_3P$, 434.2573; found, 434.2570; $[\alpha]_D^{25}$ = -34.19 (c =0.75, $CHCl_3$).

Compound 6u. White solid: mp 114-116 °C; IR (ATR) *v* 2973, 2933, 2859, 1711, 1455, 1393, 1363, 1287, 1241, 1199, 1171, 1143, 1107, 1048, 1032, 978, 910, 883, 838, 785, 754, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7 Hz, 2H), 7.34-7.17 (m, 3H), 4.76 (p, *J* = 6.5 Hz, 1H), 3.72 (dd, *J* = 15 Hz and 6.5 Hz, 1H), 3.64-3.28 (m, 3H), 3.18-2.87 (m, 2H), 2.31-1.99 (m, 2H), 1.78 (s, 2H), 1.36 (d, *J* = 7 Hz, 7H), 1.22 (dd, *J* = 15 Hz and 6.5

Hz, 6H), 1.06 (d, J = 7 Hz, 3H), 0.92 (t, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.66, 134.22, 127.83, 127.67, 127.55, 68.28, 59.89, 58.90, 45.41, 44.66, 42.38, 42.24, 31.54, 30.13, 24.20, 23.41, 22.47, 21.36, 21.25, 20.33, 20.12; ^{31}P (202 MHz, $CDCl_3$) δ 31.09; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{39}N_3O_3P$, 448.2729; found, 448.2727; $[\alpha]_D^{25}$ = -35.13 (c =0.76, $CHCl_3$).

Compound 6v. White solid: mp 130-133 ^oC; IR (ATR) ν 2971, 2934, 2871, 1710, 1455, 1392, 1366, 1348, 1307, 1244, 1214, 1168, 1108, 1084, 1051, 1024, 974, 916, 882, 838, 800, 765, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.5 Hz, 2H), 7.34-7.16 (m, 3H), 3.70 (dd, J = 16.5 Hz and 6.5 Hz, 1H), 3.64-3.51 (m, 1H), 3.51-3.39 (m, 1H), 3.31 (dd, J = 15 Hz and 6.5 Hz, 1H), 3.10-2.93 (m, 2H), 2.13 (s, 1H), 2.05 (d, J = 11.5 Hz, 1H), 1.79 (s, 2H), 1.45-1.28 (m, 7H), 1.24 (d, J = 6.5 Hz, 3H), 1.20 (d, J = 7 Hz, 3H), 1.12 (s, 9H), 1.07 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.25, 134.45, 127.92, 127.65, 127.48, 81.29, 59.94, 58.95, 45.43, 44.69, 42.79, 42.09, 31.57, 30.19, 27.58, 24.25, 23.42, 22.53, 20.34, 20.19; ^{31}P (202 MHz, $CDCl_3$) δ 31.17; HRMS-(ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{41}N_3O_3P$, 462.2886; found, 462.2881; $[\alpha]_D^{25}$ = -33.03 (c =0.77, $CHCl_3$).

Acknowledgements

We thank NIH, the National Institute on Drug Abuse and National Institutes of Health (NIDA, R21DA031860-01, GL). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIDA, NIH. We also thank the Robert Welch Foundation (D-1361, GL), the Fundamental Research Funds for the Key Universities (No. 1107020522, YP) and NSF (CHE-1048553) for NMR-instrument support.

Notes and References

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