

Tandem eneyne-phosphaallene/Myers type cyclization via base-induced isomerisation of enediynephosphine

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Dedicated to Professor François Mathey on the occasion of his 60th birthday

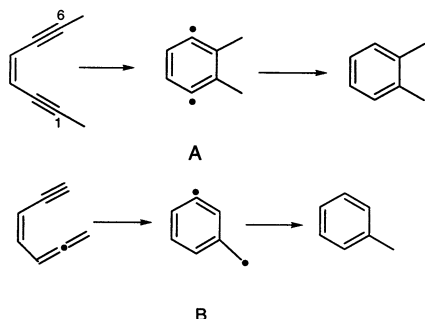
Abstract

A reaction cascade involving room temperature base-induced ynephosphine-phosphaallene rearrangement and Myers–Saito type cycloaromatization of the ene-yne-allenephosphine intermediate is described. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Ene-diyne; Ene-yne-allenephosphine; Phosphaallene; Ynephosphine; Rearrangement; Cycloaromatization

1. Introduction

Thermal cycloaromatization of ene-diyne (Bergman type cyclization A) and enyne-allene (Myers–Saito type cyclization B) play a fundamental role in the mode of action of natural enediynes antitumor antibiotics [1]. The DNA cleaving ability of these structures is related to the formation of a diradical intermediate.



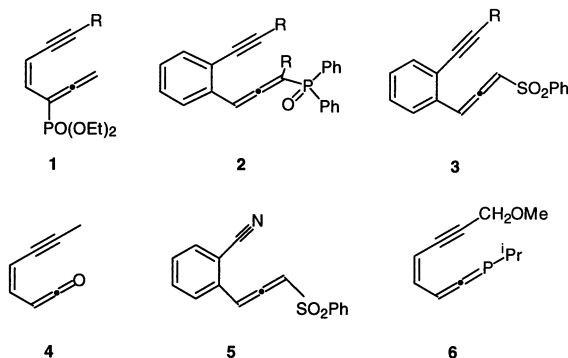
Bergman reactions usually proceed at high temperature (150 °C). The ease of cyclization of these conjugated enediynes strongly depends on the distance between carbons C₁ and C₆ [2]. By contrast, the

Myers–Saito cyclization occurs usually at lower temperature (80 °C) [3] or at the physiological temperature for some simple acyclic mimic structures of natural products such as **1–3** [4–7]. A cyclization at a subambient temperature (10 °C) has even been observed with a compound bearing a substituted allenic sulfide [8]. The ease of the Myers–Saito cycloaromatization is related to the short distance between yne and allene functions. Efforts have been also oriented towards cycloaromatization of conjugated structures containing hetero-substituted chromophores such as **4** [9] and **5** [10] (Scheme 1).

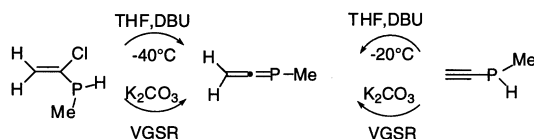
All the eneyne-allene mimic chromophores **1–5** are highly reactive species. Most of them have however, been isolated and characterized. Due to their high reactivity, they are commonly formed by a reaction cascade starting from stable precursors and in situ thermally transformed into the corresponding aromatic derivatives via a biradical intermediate in the presence of [1–4]-dimethylbutadiene as hydrogen donor atom. Compounds such as **1–5** are of interest both for mechanistic studies and for their potential DNA cleaving abilities. More generally, chromophores, which are able to induce cycloaromatization at the physiological temperature via a biradical intermediate, are potentially useful for the design of new antibiotic agents. Herein, we report that the ene-ynephosphaallene **6** formed by

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Scheme 1.



Scheme 2.

base-induced rearrangement of the ene-diyne **7b** phosphine precursor led at room temperature to the corresponding phenylphosphine structure **16** via a Myers–Saito type cyclization.

2. Results and discussion

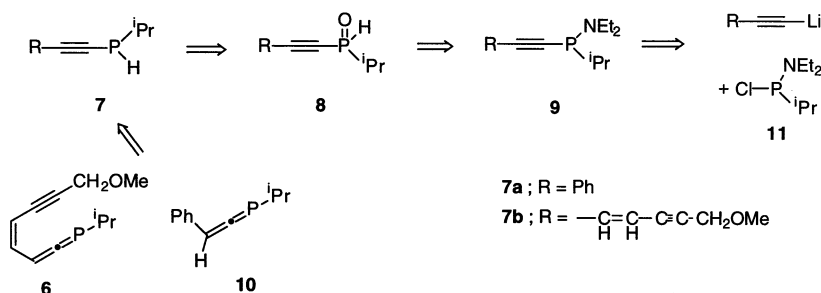
1-Phosphaallenes $\text{P}=\text{C}=\text{C}<$ are isoelectronic to ketenes. Their syntheses and chemical properties are well documented [11]. The bulky substituted derivatives are stable at room temperature. They are obtained by various synthetic routes, such as phospho-Wittig and Peterson-type reactions. The simple derivatives substituted by primary alkyl groups are not stable at room temperature and consequently need special approaches. As an example, $\text{H}_2\text{C}=\text{C}=\text{P}-\text{Me}$ was prepared in solution or under vacuum gas–solid reaction (VGSR) [12], either by dehydrohalogenation of chlorovinylphosphine or by base-induced rearrangement of the ethynylmethylphosphine (Scheme 2). Oligomerization was observed in solution around -20°C (detection by ^{31}P)

[13]. Only the VGSR technique allowed the complete characterization of the structure (^1H -, ^{31}P - and ^{13}C -NMR).

The phenyl P-phosphaallene **10** bearing an isopropyl group on the phosphorus atom was expected to be more stable than the corresponding P-methylphosphaallene. However, access by the VGSR technique should be not possible since volatility of the product was expected to be too weak to allow vaporization on a solid base (K_2CO_3). We choose consequently another way involving the base-induced rearrangement in solution of the enediynes P-*i*-propylphosphine precursor **7b**. The synthesis was first developed on a simple structure **7a** ($\text{R}=\text{Ph}$) to precise the experimental conditions and was then extended to **7b** in which the ene-yne chromophore takes the place of the phenyl group. The *retrosynthetic route* was presented on Scheme 3. Ynephosphines **7a,b** were prepared by reduction of the phosphine oxides **8a,b** with silane as a reducing agent [14], the later compounds being themselves obtained by condensation of the corresponding alkynyl lithium on P-chlorodiethylaminophosphine **11** followed by acidic hydrolysis of the resulting ynephosphine **9a,b**.

2.1. Ynephosphine **7a** and phosphaallene **10**

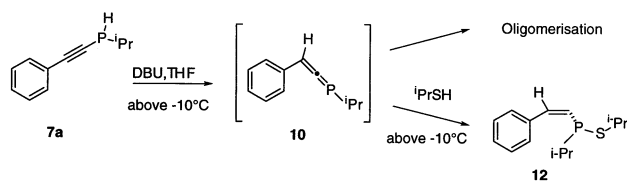
The P-chlorodiethylaminophosphine starting material **11** was obtained on molar scale by monoamination of PCl_3 at -40°C with diethylamine followed by condensation of the Grignard reagent derived from $i\text{-PrCl}$ (overall yield 64% in distilled compound) [15]. Reaction of lithium phenylacetylide at -78°C on $\text{ClP}(\text{NEt}_2)i\text{-Pr}$ **11** led to the phenylaminophosphine **9a** (79% yield after distillation). The product was fully characterized by NMR spectroscopy (^1H , ^{13}C , ^{31}P) and HRMS. The crude phosphine oxide **8a** (purity $>95\%$, yield 78%) was then obtained in good yield by acidic hydrolysis of **9a** on solid acid (Amberlyst 15) in THF in the presence of one equivalent of water [16]. Like other secondary ethynylphosphine oxides, **8a** is not thermally stable. Polymerization and C–P bond cleavage were observed during the distillation. The crude product can however, be kept in the fridge for months without decomposition. NMR and HRMS data are in good agreement



7a; $\text{R}=\text{Ph}$

7b; $\text{R}=\text{—C}(\text{H})=\text{C}(\text{H})\text{—C}\equiv\text{C—CH}_2\text{OMe}$

Scheme 3.



Scheme 4.

with the structure. The product was used in the subsequent reaction as such.

An important C–P cleavage was observed by reduction of **8a** with AlHCl_2 [17]. Reduction with PhSiH_3 in pentane for 2 h at 30 °C gave the expected free phosphine **7a** in 70% yield [13]. The stability of this compound is too weak to allow distillation. The residual impurities which were present after evacuation of volatile compounds under vacuum are mainly polysiloxanes (around 5%). The NMR and HRMS data confirmed the structure. The crude product can be kept for weeks in solution under neutral gas in the fridge.

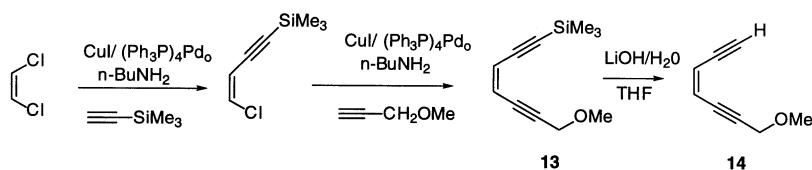
Attempts to detect the phosphallaene **10** by low temperature base-induced rearrangement of the free ynephosphine **7a** with DBU were unsuccessful. By monitoring the ^{31}P -NMR experiments, the signal of **7a** ($\delta_{\text{P}} = -73$ ppm, $^1J_{\text{PH}}$ 217 Hz, d) was continuously observed from -78 to -10 °C, but intensity decreased slowly above this temperature to completely disappear around 0 °C. This transformation was accompanied by the formation of a complex mixture (signals 17 and 33 ppm) attributed to the products resulting from the oligomerization of phosphallaene **10**. We have previously observed that the rearrangement of secondary phosphines substituted by a primary alkyl group on phosphorus occurred around -20 °C, allowing thus the characterization of the phosphallaene before oligomerization [13]. Due to the presence of the isopropyl group the temperature required for the rearrangement of the P-isopropylphosphine **7a** is higher

(0 °C). Consequently, the decomposition of the phosphallaene at this temperature is probably too fast to allow observation by NMR spectroscopy. Evidence for the formation of **10** was however, given by performing the reaction from -20 to 20 °C in the presence of an excess of i propanethiol. The two expected vinylphosphine diastereomeric adducts **12'**, **12''** ($\delta^{31}\text{P}$ 16.3 and 32.6 ppm) were isolated as an oil and characterized by ^1H - and ^{31}P -NMR and by HRMS (Scheme 4).

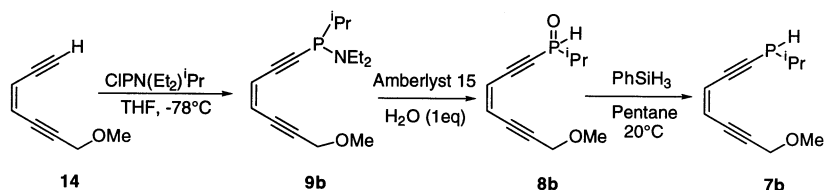
2.2. Ynephosphine **7b**

The methodology developed above was then extended to the synthesis of the ene-diynephosphine **7b** (Schemes 5 and 6). (*Z*)-methoxy-ene-diyne **13** was obtained by coupling silylacetylene on (*Z*)-dichloroethylene in the presence of $\text{Pd}(\text{PPh}_3)_4$, copper iodide and n butylamine [18] followed by coupling the resulting (*Z*)-chloroene-yne silane on propargylic ether under similar catalytic conditions (Scheme 5) [19]. Desilylation of **13** with lithium hydroxide in a THF– H_2O mixture [20] led to the terminal acetylene **14** which was fully characterized after purification by flash chromatography. The overall yield from dichloroethene was 35%. Compound **14** was not very stable and should be kept in the fridge.

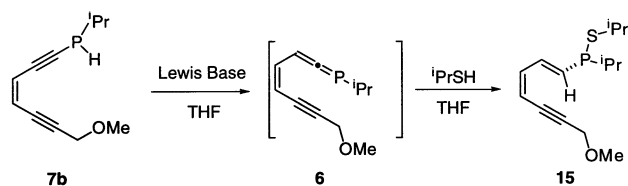
Ene-diyne P-phosphineamine **9b** was obtained by P-alkylation of the lithium ene-yne acetylide with $\text{CIPN}(\text{Et}_2)^i\text{Pr}$ **11** in THF at -78 °C (Scheme 6). The crude oil was purified by distillation to afford **9b** in 76% yield (b.p. 87 °C, 1 mmHg). The product was fully characterized by NMR (^{31}P , ^{13}C , ^1H) and HRMS. Acidic hydrolysis of **9b** on Amberlyst 15 in the presence of one equivalent of water led to the ene-diynephosphine oxide **8b** [15]. The compound is not stable at room temperature and should be kept in solution in the fridge (yield estimated for the crude product 85%, determination by ^{31}P , purity > 95%). However, it can be purified by flash chromatography on silica gel (yield of the



Scheme 5.



Scheme 6.



Scheme 7.

purified compound 52%) and was fully characterized by NMR spectroscopy and HRMS.

Reduction of the ene-diyne phosphine oxide **8b** was critical. With Cl_2AlH in THF the desired free phosphine **7b** was formed in a poor yield, the main products resulting from a C–P cleavage. Reduction with HSiCl_3 in pentane gave the expected product **7b** in a poor yield, accompanied by undetermined by-products. Reduction by phenylsilane in pentane gave the best results (yield 60%). The free phosphine **7b** was too unstable to be purified by distillation or by flash chromatography. The crude mixture obtained after elimination under vacuum of excess of reagent and volatile siloxanes was analyzed by NMR spectroscopy. The ^{31}P -NMR presented a signal at $^{31}\delta - 73$ ppm, ($^1J_{\text{PH}} 217.5$ Hz), in good agreement with the structure. The presence of polysiloxanes (15%) and ene-diyne **14** (20%) resulting from a partial C–P cleavage did not allow to fully attribute all the carbons of the chromophore. Finally, the structure was completely assigned by NMR and HRMS analysis of the recovered phosphine oxide **8b** resulting from a spontaneous oxidation of **7b** in the presence of air (Scheme 6). Compound **7b** presented a lower stability than **7a**. It was thermally unstable above 40°C and should be used as prepared or kept in a freezer at -16°C .

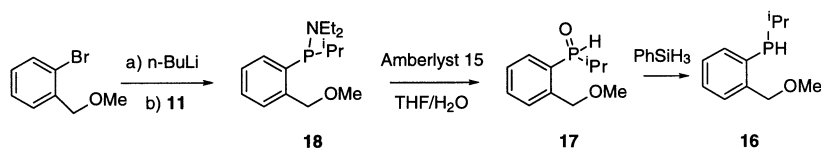
2.3. Phosphaallene **6** and cycloaromatization

Attempts to detect the transient phosphaallene **6** by low temperature rearrangement of **7b** with a Lewis base and monitoring the low temperature ^{31}P -NMR experiments were unsuccessful. The temperature of the rearrangement with DBU was observed at a lower temperature for **7b** (-40°C) than that observed for **7a** (-20°C). With pyridine, the rearrangement of **7b** was also observed (20°C , 4 days), but not that of **7a**. These properties probably result from a stronger P–H acidity of **7b** with regard to **7a**, induced by the ene-diyne

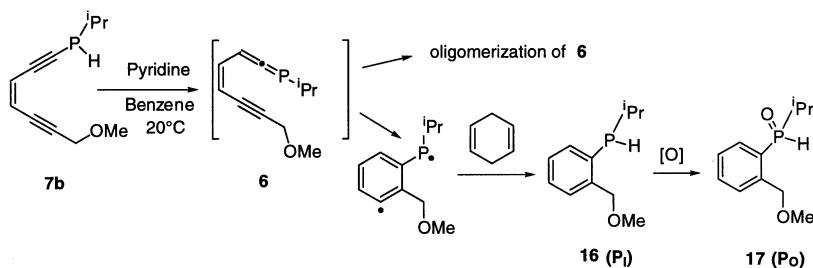
chromophore. Signals observed from 17 to 33 ppm are resulting from the oligomerization of the phosphaallene intermediate **6**.

As expected, the thiophosphine isomeric adducts **15'** and **15''** were obtained by a sequence involving low temperature rearrangement of **7b** ($-80 \geq 20^\circ\text{C}$) induced by a strong Lewis (DBU or DABCO) and trapping in situ the reactive phosphaallene intermediate **6** by iPrSH (Scheme 7). Adducts were also observed with triethylamine and pyridine, but with the later base at a higher temperature (20°C). Adducts **15** were fully characterized by ^1H -, ^{13}C - and ^{31}P -NMR ($\delta_{\text{P}} 16.6$ and 32.3 ppm) and HRMS spectrometry.

As shown in Section 1, electrocyclization of the mimic structures of natural products such as **1–5** occurred at the physiological temperature. Since the ene-ynephosphine phosphaallene intermediate **6b** was formed at room temperature in the presence of a weak base (pyridine) under high dilution conditions, the cycloaromatization of this chromophore was expected. The rearrangement of **7b** was consequently performed at room temperature with pyridine as a Lewis base in a benzene solution containing [1–4]cyclohexadiene as a hydrogen donor atom. The resulting solution analyzed by ^{31}P after 2 days showed that **7b** nearly disappeared. The signals from 17 to 33 ppm corresponding to the oligomerization of phosphaallene **6** were observed. However, a new signal at $\delta - 33$ ppm ($^1J_{\text{PH}} 213$ Hz) corresponding to a secondary free phosphine (P_1) appeared. A similar reaction was then performed in a flask in a 10 mmol scale. After evacuation of the solvent and oxidation in air, a secondary phosphine oxide (P_O) was observed by ^{31}P -NMR analysis ($\delta_{\text{P}} 42$ ppm, $^1J_{\text{PH}} 467$ Hz) of the crude mixture and then isolated by flash chromatography on silica gel. This product can result from electrocyclization of **6** (compound **16**) followed by oxidation of the resulting free phosphine P_1 . The ^{31}P -NMR data and HRMS (molecular ion 228.091, calculated 228.091) for P_O are in favor of the expected phenylphosphine oxide **17**. However, the amount of product was too small (yield $< 5\%$) to get a complete characterization. The synthesis of the authentic samples **16** and **17** was carried out to confirm the structures of P_1 and P_O (Scheme 8). Synthesis of phosphine oxide **17** involved the condensation of the lithium derivative of 2-bromo benzylmethylether on the chloroaminophosphine **11** followed by acidic hydrolysis with Amberlyst 15 of the resulting 2-aminoisopropyl-



Scheme 8.



Scheme 9.

phosphine benzylmethylether **18**. The product **17** was fully characterized by NMR (^1H , ^{13}C , ^{31}P) and by HRMS. The free phosphine **16** was finally obtained by reduction of **17** with phenylsilane ($\delta_{\text{P}} - 33$ ppm, $^1J_{\text{PH}} 213$ Hz) and was fully characterized.

These results confirmed the former analysis: ^{31}P and HRMS data of **17** correspond to those of **P_O**, the free phosphine **16 (P_i)** resulted from the electrocyclization of the transient intermediate **6** (Scheme 9).

3. Conclusion

A secondary ene-diynephosphine was converted at room temperature in the presence of a weak base (pyridine) into a phenylphosphine derivative in a reaction cascade involving base-induced ynephosphine-phosphaallene rearrangement and Myers–Saito electrocyclization of the ene-yneallene phosphine intermediate. Efforts have to be carried out to do this sequence potentially useful for the design of bioactive molecules. This work shows the interest of low-coordinate species such as phosphaallenes for extension of fundamental reactions and for the design of new intermediates.

4. Experimental

4.1. General

Caution: Free phosphines are highly oxidizable and potentially toxic molecules. All reactions should be carried out under an inert atmosphere in a well-ventilated hood. ^1H (300 MHz)-, ^{13}C (75 MHz)- and ^{31}P (121 MHz)-NMR spectra were recorded on a Bruker AC-300P spectrometer and HRMS (high resolution mass spectrometry) experiments were performed on a Varian MAT 311 instrument. THF was freshly distilled under Ar from LiAlH_4 . All the reactions involving water- and air-sensitive chemicals were carried out under nitrogen.

4.2. Preparation of **9a**

A solution of butyllithium (62.6 ml, 110 mmol, 1.6 M in C_6H_{14}) was added at -78°C to a solution of phenyl acetylene (100 mmol, 10.2 g) in THF (250 ml). The reaction was stirred at this temperature for 30 min and a solution of P-chlorodiethylaminoisopropylphosphine **11** [14] (98 mmol) in THF (20 ml) was slowly added. The reaction was slowly warmed to room temperature (r.t.). The solvent was then removed under vacuum and the residue washed with C_5H_{12} (30 ml). The C_5H_{12} solution was then filtered on celite under a nitrogen pressure. The resulting oil obtained after evaporation of the solvent was distilled. B.p. 60°C (1 mmHg), yield 68%.

^{31}P -NMR (CDCl_3): δ 42.0 (m). ^1H -NMR (300 MHz, CDCl_3): δ 0.89 (dd, 3H, $^3J_{\text{PHa}} = 8.1$ Hz, $^3J_{\text{HaH}} = 7.0$ Hz, CH_3CH); 0.93 (t, 6 H, $^3J_{\text{HH}} = 7.0$ Hz, CH_2CH_3); 0.95 (dd, 3H, $^3J_{\text{PHa'}} = 9.3$ Hz, $^3J_{\text{Ha'H}} = 6.7$ Hz, CHCH_3); 1.95 (dh, H, $^2J_{\text{PH}} = 8.4$ Hz, $^3J_{\text{HH}} = 7.0$ Hz, CH_3CH); 2.88 (qd, 4H, $^3J_{\text{PH}} = 9.8$ Hz, $^3J_{\text{HH}} = 7.1$ Hz, CH_2CH_3); 7.09 and 7.23 (m, 5 H_{arom}). ^{13}C -NMR (75 MHz, CDCl_3): δ 14.74 (qdm, $^1J_{\text{CH}} = 125.5$ Hz, $^3J_{\text{CP}} = 4.0$ Hz, CH_3CH_2); 17.56 (qddq, $^1J_{\text{CHa}} = 126.7$ Hz, $^2J_{\text{CP}} = 23.2$ Hz, $^2J_{\text{CH}} = 5.0$ Hz, $^3J_{\text{CH}} = 4.7$ Hz, CH_3CH); 18.68 (qddq, $^1J_{\text{CHa'}} = 127.5$ Hz, $^2J_{\text{CP}} = 22.0$ Hz, $^2J_{\text{CH}} = 4.6$ Hz, $^3J_{\text{CH}} = 4.0$ Hz, CHCH_3); 28.26 (dh, $^1J_{\text{CH}} = 131.3$ Hz, $^2J_{\text{CH}} = 4.0$ Hz, CHCH_3); 44.86 (tdm, $^1J_{\text{CH}} = 134.5$ Hz, $^2J_{\text{CP}} = 13.6$ Hz, CH_2CH_3); 90.73 (dd, $^1J_{\text{CP}} = 35.6$ Hz, $^3J_{\text{CH}} = 3.1$ Hz, $\text{C}\equiv\text{C}-\text{P}$); 104.17 (dm, $^2J_{\text{CP}} = 3.6$ Hz, $\text{C}\equiv\text{C}-\text{P}$); 123.5; 128.25 and 131.47, C_{arom}). HRMS Calc. for $\text{C}_{15}\text{H}_{22}\text{NP}$: 247.1499. Found: 247.146.

4.3. Preparation of **8a**

Amberlyst® 15 (4.7 meq g^{-1} , 6.4 g, 30 mmol) were added to a solution of THF (30 ml) containing 0.2 ml of water. The mixture was stirred under nitrogen and then cooled at -40°C . A solution of phenylaminophosphine **9a** (2.47 g, 10 mmol) in THF (10 ml) was then slowly added and the stirring was maintained for 30 min. The reaction mixture was then warmed to r.t. After filtration, the residue was washed with C_5H_{12} (2×10 ml) and the combined organic layer was con-

centrated under reduced pressure. The yield in the crude product **8a** was 78%, (purity > 95%). For analytical purpose, the resulting oil was purified by flash chromatography (eluent: EtOAc) to afford a colourless oil (yield of purified product 32%). The oil can be kept on the fridge under a nitrogen mantle.

³¹P-NMR: δ 12.00 (ddh, $^1J_{\text{PHc}} = 507.5$ Hz, $^2J_{\text{PHb}} = 20.8$ Hz, $^3J_{\text{PHa}} = 13.6$ Hz). ¹H-NMR (300 MHz, CDCl₃): δ : 126 (dd, 6H, $^3J_{\text{PHa}} = 13.6$ Hz, $^3J_{\text{HaHb}} = 7.1$ Hz, CH_{a3}CH_c); 2.08 (dhd, H, $^2J_{\text{PHb}} = 20.8$ Hz, $^3J_{\text{HbHa}} = 7.1$ Hz, $^3J_{\text{HbHc}} = 2.4$ Hz, CH_bCH_{a3}); 7.21 (dd, H, $^1J_{\text{PHc}} = 507.5$ Hz, $^3J_{\text{HcHb}} = 2.4$ Hz, P-H_c); 7.32 and 7.51 (m, 5 H_{arom}). ¹³C-NMR (75 MHz, CDCl₃)□: δ 14.28 (qdm, $^1J_{\text{CHa}} = 128.7$ Hz, $^2J_{\text{CP}} = 14.0$ Hz, CH_bCH_{a3}); 28.96 (ddm, $^1J_{\text{CHb}} = 129.4$ Hz, $^1J_{\text{CP}} = 80.5$ Hz, CH_bCH_{a3}); 79.58 (ddd, $^1J_{\text{CP}} = 148.5$ Hz, $^2J_{\text{CHc}} = 16.2$ Hz, $^3J_{\text{CHb}} = 2.6$ Hz, C≡C-P); 104.54 (dm, $^2J_{\text{CP}} = 26.2$ Hz, C≡C-P); 119.28; 128.53; 130.79 and 132.36, C_{arom}). HRMS, Calc. for C₁₁H₁₃OP: 192.0704. Found: 192.069; m/z (%): 192 (45.14); 150 (100); 149 (89.98); 102 (70.77); 43 (35.60); 41 (35.62); 28 (54.59).

4.4. Preparation of **7a**

Phenylsilane (2.7 mmol) in C₅H₁₂ (3 ml) was slowly added to a solution of phosphine oxide **8a** (2.6 mmol) in C₅H₁₂ (4 ml). After heating for 4 h at 30 °C, the mixture was allowed to r.t. Solvent, excess of reagent and siloxane were then removed under vacuum. The crude phosphine (yield 70%) was used in this state in the following (main impurities polysiloxanes 5%).

³¹P-NMR (121 MHz, CDCl₃): δ -73 (dhd, $^1J_{\text{PH}} = 217.5$ Hz, $^3J_{\text{PH}} = 16.0$ Hz, $^2J_{\text{PH}} = 12.4$ Hz). ¹H-NMR (300 MHz, CDCl₃): δ 1.33 (ddd, 6H, $^3J_{\text{PH}} = 16.0$ Hz, $^3J_{\text{HH}} = 6.9$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, (CH₃)₂CH); 2.20 (dhd, H, $^2J_{\text{PH}} = 12.4$ Hz, $^3J_{\text{HH}} = 6.9$ Hz, $^3J_{\text{HH}} = 5.4$ Hz, CHCH₃); 4.12 (dd, H, $^1J_{\text{PH}} = 217.5$ Hz, P-H); 7.32 and 7.51 (m, 5 H_{arom}). ¹³C-NMR (75 MHz, CDCl₃): δ 21.97 (qdm, $^1J_{\text{CH}} = 127.1$ Hz, $^2J_{\text{CP}} = 13.3$ Hz, CH₃CHCH₃); 22.12 (qdm, $^1J_{\text{CH}} = 126.8$ Hz, $^2J_{\text{CP}} = 14.7$ Hz, CH₃CHCH₃); 23.03 (dh, $^1J_{\text{CH}} = 132.1$ Hz, $^1J_{\text{CP}} = 3.4$ Hz, $^2J_{\text{CH}} = 4.1$ Hz, CHCH₃); 83.00 (m, $^1J_{\text{CP}} = 19.5$ Hz, C≡C-P); 105.30 (m, $^2J_{\text{CP}} = 1.5$ Hz, C≡C-P); 123.2; 128.6; 131.74 and 133.4; C_{arom}). HRMS for C₁₁H₁₃P: Calc. 176.0755. Found: 176.075; m/z (%): 177 (7); 176 (37); 135 (5); 134 (25); 133 (100); 77 (2); 44 (42); 43 (19); 41 (13). HRMS for C₈H₆P [M - *i*Pr] Calc. 133.0207. Found: 133.019.

4.5. Preparation of **12'**, **12''**

A solution of DBU (1.52 g, 10 mmol) in C₆H₅CH₃ (5 ml) was slowly added to a cooled (-40 °C) C₆H₅CH₃ solution (10 ml) containing of 2-propanethiol (1.52 g, 20 mmol) and **7a** (0.88 g, 5 mmol). The mixture was then quenched at 0 °C with a solution of HCl in ether

(1 N) in excess (15 mmol). After elimination of the ammonium salts by filtration under a nitrogen pressure, volatile products were eliminated under reduced pressure. The crude oil was analyzed (³¹P and ¹H).

As a mixture of the two isomers **12'**, **12''**. ³¹P-NMR (121 MHz, CDCl₃): δ 16.30 and 32.6 ppm. ¹H-NMR (300 MHz, CDCl₃): δ 1.1 (m, 3H, (CH₃)₂CHS); 1.2 (dd, 6H, $^3J_{\text{HH}} = 6.8$ Hz, $^3J_{\text{PH}} = 2.2$ Hz, (CH_{a3})₂CHP); 1.28 (dd, 3H, $^3J_{\text{HH}} = 6.8$ Hz, $^3J_{\text{PH}} = 3.8$ Hz, (CH_{a3})₂CHP); 1.85 (m, H, (CH₃)₂CHS); 2.95 (m, H, (CH₃)₂CHP); 6.2; 6.65–6.7 and 7–7.1 (vinyl protons); 7.15–7.60 (H_{arom}). HRMS for C₁₄H₂₁PS, Calc.: 252.1102. Found: 252.107. HRMS for C₁₁H₁₄PS [M - *i*Pr]: Calc. 209.0554. Found: 209.056; m/z (%): 252 (22); 210 (17); 209 (53); 135 (12); 134 (21); 133 (100).

4.6. Preparation of **9b**

Ene-diyne P-phosphineamine **9b** was prepared by following the protocol already described for **9a**. At the end of the reaction, the solvent was removed under vacuum and the residue washed with C₅H₁₂ (30 ml). The C₅H₁₂ solution was then filtered on celite under a nitrogen pressure. The organic phase was concentrated under vacuum and the resulting crude oil (yield 87%, purity > 95%) was used in the state in the following.

³¹P-NMR (121 MHz, CDCl₃)□: δ 42.25 (m). ¹H-NMR (300 MHz, CDCl₃): δ 0.96 (dd, 3H, $^3J_{\text{HaHc}} = 7.0$ Hz, $^3J_{\text{PHa}} = 5.2$ Hz, CH_{a3}CH_c); 1.01 (t, 6H, $^3J_{\text{HH}} = 7.2$ Hz, 2 CH₃CH₂); 1.03 (dd, 3H, $^3J_{\text{Ha'Hc}} = 7.0$ Hz, $^3J_{\text{PHa'}} = 6.0$ Hz, CH_{a3}CH_c); 2.02 (dh, H, $^2J_{\text{PHc}} = 8.5$ Hz, $^3J_{\text{HcHa'}} = 7.0$ Hz, CH_cCH₃); 2.96 (dq, 4H, $^3J_{\text{PH}} = 9.9$ Hz, $^3J_{\text{HH}} = 7.1$ Hz, 2 CH₂CH₃); 3.32 (s, 3H, OCH₃); 4.18 (d, 2H, $^5J_{\text{HH}} = 2.0$ Hz, CH₂O); 5.74 (ddm, H, $^3J_{\text{Hb'Hb}} = 10.9$ Hz, $^5J_{\text{PHb'}} = 1.0$ Hz, CH_b = CH_{b'}); 5.87 (dd, H, $^3J_{\text{HbHb'}} = 10.9$ Hz, $^4J_{\text{PHb}} = 1.4$ Hz, CH_b = CH_{b'}). ¹³C-NMR (75 MHz, CDCl₃): δ 14.63 (qdm, $^1J_{\text{CH}} = 126.0$ Hz, $^3J_{\text{CP}} = 4.4$ Hz, CH₂CH₃); 17.32 (qddq, $^1J_{\text{CHa}} = 126.7$ Hz, $^2J_{\text{CP}} = 23.3$ Hz, $^2J_{\text{CHc}} = 5.2$ Hz, $^3J_{\text{CHa'}} = 4.4$ Hz, CHCH_{a3}); 18.53 (qddq, $^1J_{\text{CHa'}} = 127.2$ Hz, $^2J_{\text{CP}} = 22.7$ Hz, $^2J_{\text{CHc}} = 5.1$ Hz, $^3J_{\text{CHa}} = 4.3$ Hz, CHCH_{a3}); 28.00 (dh, $^1J_{\text{CHc}} = 131.6$ Hz, $^2J_{\text{CHa}} = 2J_{\text{CHa'}} = 3.9$ Hz, CH_cCH₃); 44.89 (tdm, $^1J_{\text{CH}} = 134.7$ Hz, $^2J_{\text{CP}} = 13.4$ Hz, CH₂CH₃); 57.57 (qt, $^1J_{\text{CH}} = 141.7$ Hz, $^3J_{\text{CH}} = 5.3$ Hz, OCH₃); 60.34 (tq, $^1J_{\text{CH}} = 147.7$ Hz, $^3J_{\text{CH}} = 5.5$ Hz, CH₂O); 83.92 (dt, $^2J_{\text{CH}} = 14.2$ Hz, $^3J_{\text{CH}} = 5.0$ Hz, C≡C-CH₂O); 92.71 (td, $^2J_{\text{CH}} = 7.2$ Hz, $^3J_{\text{CH}} = 5.0$ Hz, C≡C-CH₂O); 99.58 (dm, $^1J_{\text{CP}} = 38.1$ Hz, C≡C-P); 101.47 (dd, $^2J_{\text{CHb}} = 12.2$ Hz, $^2J_{\text{CP}} = 3.5$ Hz, C≡C-P); 118.06 (dd, $^1J_{\text{CH}} = 143.8$ Hz, $^3J_{\text{CP}} = 3.2$ Hz, CH_b=CH_{b'}); 119.96 (dd, $^1J_{\text{CH}} = 142.4$ Hz, $^4J_{\text{CP}} = 2.5$ Hz, CH_b=CH_{b'}). HRMS for C₁₅H₂₄NOP: Calc. 265.1595. Found: 265.159; m/z (%): 265 (26); 223 (14); 222 (100); 193 (14); 151 (5); 119 (4); 107 (6); 95 (5); 69 (5); 43 (5); 42 (12); 41 (11).

4.7. Preparation of **8b**

Compound **8b** is prepared according to the protocol already used for the preparation of **8a** (yield 85% in crude product, purity >95%). For analytic purpose, the product was purified by flash chromatography (eluent, EtOAc) in a 50% yield.

^{31}P -NMR (121 MHz, CDCl_3): δ 11.69 (ddh, $^1J_{\text{PHd}} = 506.6$ Hz, $^2J_{\text{PHc}} = 20.8$ Hz, $^3J_{\text{PHa}} \approx ^3J_{\text{PHa}'} \approx 15.7$ Hz). ^1H -NMR (300 MHz, CDCl_3): δ 1.16, 3H, $^3J_{\text{PHa}} = 14.7$ Hz, $^3J_{\text{HaHc}} = 7.1$ Hz, $\text{CH}_c\text{CH}_{a3}$; 1.24 (dd, 3H, $^3J_{\text{PHa}'} = 13.6$ Hz, $^3J_{\text{Ha'Hc}} = 7.1$ Hz, $\text{CH}_c\text{CH}_{a'3}$); 2.11 (dhd, H, $^2J_{\text{PHc}} = 20.8$ Hz, $^3J_{\text{HcHa}} = ^3J_{\text{HcHa}'} = 7.3$ Hz, $^2J_{\text{HcHd}} = 2.0$ Hz, CH_cCH_3); 3.33 (s, 3H, OCH_3); 4.21 (d, 2H, $^5J_{\text{HHb}'} = 1.8$ Hz, CH_2O); 5.88 (dd, H, $^3J_{\text{HbHb}'} = 11.0$ Hz, $^4J_{\text{PHb}} = 2.7$ Hz, $\text{CH}_b=\text{CH}_{b'}$); 6.09 (dd, H, $^3J_{\text{Hb'Hb}} = 11.0$ Hz, $^5J_{\text{PHb}'} = 0.5$ Hz, $\text{CH}_b=\text{CH}_{b'}$); 7.04 (dd, H, $^1J_{\text{PHd}} = 506.6$ Hz, $^3J_{\text{HdHc}} = 2.0$ Hz, P-H_d). ^{13}C -NMR (75 MHz, CDCl_3): δ 14.4 (qdm, $^1J_{\text{CHa}} = ^1J_{\text{CHa}'} = 128.9$ Hz, $^2J_{\text{CP}} = 17.6$ Hz, $\text{CH}_{a3}\text{CH}_c$); 29.07 (ddm, $^1J_{\text{CHc}} = 130.2$ Hz, $^1J_{\text{CP}} = 80.4$ Hz, CH_cCH_3); 57.82 (qt, $^1J_{\text{CH}} = 141.8$ Hz, $^3J_{\text{CH}} = 5.4$ Hz, OCH_3); 60.24 (tq, $^1J_{\text{CH}} = 147.7$ Hz, $^3J_{\text{CH}} = 5.7$ Hz, CH_2O); 82.86 (dt, $^2J_{\text{CHb}'} = 13.9$ Hz, $^3J_{\text{CH}} = 5.0$ Hz, $\text{C}\equiv\text{C-CH}_2\text{O}$); 86.60 (ddm, $^1J_{\text{CP}} = 145.1$ Hz, $^2J_{\text{CHd}} = 15.0$ Hz, $\text{C}\equiv\text{C-P}$); 96.21 (td, $^2J_{\text{CH}} = 7.4$ Hz, $^3J_{\text{CHb}'} = 4.9$ Hz, $\text{C}\equiv\text{C-CH}_2\text{O}$); 100.64 (ddd, $^2J_{\text{CP}} = 25.5$ Hz, $^3J_{\text{CHd}} = 15.4$ Hz, $^2J_{\text{CHb}} = 5.5$ Hz, $\text{C}\equiv\text{C-P}$); 116.62 (dd, $^1J_{\text{CH}} = 171.8$ Hz, $^3J_{\text{CP}} = 4.5$ Hz, $\text{CH}_b=\text{CH}_{b'}$); 125.30 (dd, $^1J_{\text{CH}} = 168.9$ Hz, $^4J_{\text{CP}} = 3.1$ Hz, $\text{CH}_b=\text{CH}_{b'}$). HRMS, Calc. for $\text{C}_{11}\text{H}_{15}\text{O}_2\text{P}$: 210.0810. Found: 210.080, m/z (%): 210 (11); 195 (44); 179 (11); 168 (3.46); 95 (14); 70 (11); 69 (27).

4.8. Preparation of **7b**

Free ene-diyne phosphine **7b** was formed according to the protocol used for **7a**. Yield in crude product 60%. ^{31}P -NMR (121 MHz, CDCl_3): δ -73 pp (dm); $^1J_{\text{PH}} = 217.5$ Hz. Presence of impurities prevents obtention of all the NMR data. The product was indirectly characterized by spontaneous oxidation in air and comparison of the corresponding oxide with the authentic sample **8b**.

4.9. Preparation of **15'**, **15''**

A solution of DBU (0.152 g, 1 mmol) in $\text{C}_6\text{H}_5\text{CH}_3$ (1 ml) was slowly added to a cooled (-20°C) $\text{C}_6\text{H}_5\text{CH}_3$ solution (1 ml) containing of *i*-propanethiol (0.152 g, 2 mmol) and **7b** (0.21 g, 1 mmol). The mixture was then quenched at 0°C with a solution of HCl in ether (1 N) in excess (15 mmol). After elimination of the ammonium salts by filtration under a nitrogen pressure, volatile products were eliminated under reduced pres-

sure. The crude oil was analyzed (^{31}P and ^1H) as a mixture of the two isomers **15'**, **15''**.

^{31}P -NMR (121 MHz, CDCl_3): δ 32.3 and 16.6 ppm. ^1H -NMR (300 MHz, CDCl_3): δ : 1.06 (m, 6H, $(\text{CH}_3)_2\text{CHS}$); 1.29 (dd, 6 H, $^3J_{\text{HH}} = 6.6$ Hz, $^2J_{\text{PH}} = 0.7$ Hz, $(\text{CH}_3)_2\text{CHP}$); 1.85 (m, H, $(\text{CH}_3)_2\text{CHP}$); 2.95 (m, 6 H, $(\text{CH}_3)_2\text{CHS}$); 3.36 (s, 3H, OCH_3); 4.25 (s, 2H, CH_2O); 5.45 (d, $^3J_{\text{HH}} = 12.7$ Hz, P-H); 6.20–6.45; 7–7.20. HRMS, Calc. for $\text{C}_{14}\text{H}_{23}\text{OPS}$: 270.12072. Found: 270.120; m/z (%): 43 (100); 42 (12); 41 (43); 39 (14); 28 (12).

4.10. Preparation of 2-aminoisopropylphosphine benzylmethylether (**18**)

18s obtained by oxiethoxyphenylpA solution of butyllithium (10.4 ml, 16.6 mmol in 1.6 M in hexane) was added at -78°C to a solution of bromo-2 benzylmethylether (14.9 mmol, 3 g) in THF (30 ml). The solution was stirred at this temperature for 30 min, then slowly allowed to warm to -60°C and finally cooled at -78°C . Diethylaminophosphine **11** (2.17 g, 14.87 mmol) in THF (5 ml) was then adduct and the reaction mixture was allowed to warm at r.t. The solvent was removed under vacuum and the residue washed with C_5H_{12} (2×30 ml). The C_5H_{12} solution was then filtered on celite under a nitrogen pressure. The resulting oil obtained after evaporation of the combined organic layer was distilled. B.p. 85°C (1 mmHg), yield 80%.

^{31}P -NMR (121 MHz, CDCl_3): δ 53 ppm. ^1H -NMR (300 MHz, CDCl_3): δ 0.30 (t, 6H, $^3J_{\text{HH}} = 7.1$ Hz, CH_2CH_3); 0.70 (dd, 3 H, $^3J_{\text{PH}} = 18.5$ Hz, $^3J_{\text{HH}} = 6.8$ Hz, CH_3CHCH_3); 0.98 (dd, 3H, $^3J_{\text{PH}} = 15.2$ Hz, $^3J_{\text{HH}} = 6.9$ Hz, CH_3CHCH_3); 2.26 (h, H, $^3J_{\text{HH}} = 7.0$ Hz, CH_3CH); 2.71 (m, 4H, CH_2CH_3); 3.23 (s, 3H, CH_3O); 4.52 (d, H, $^2J_{\text{Ha'Hb}} = 12.7$ Hz, $\text{CH}_a\text{H}_b\text{O}$); 4.75 (dd, H, $^2J_{\text{Hb'Hb}} = 12.7$ Hz, $^4J_{\text{PH}} = 3.3$ Hz, $\text{CH}_a\text{H}_b\text{O}$); H_{arom} : 7.03 (td, H, $^3J_{\text{HH}} = 7.4$ Hz, $^5J_{\text{PH}} = 1.4$ Hz); 7.12 (td, H, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.5$ Hz); 7.26 (dt, H, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.9$ Hz); 7.33 (ddd, H, $^3J_{\text{HH}} = 7.5$ Hz, $^3J_{\text{PH}} = 3.7$ Hz, $^4J_{\text{HH}} = 0.6$ Hz). ^{13}C -NMR, (75 MHz, CDCl_3): δ 14.60 (qdm, $^1J_{\text{CH}} = 125.4$ Hz, $^3J_{\text{CP}} = 3.1$ Hz, CH_2CH_3); 18.0 (m, $^2J_{\text{CP}} = 27.6$ Hz, CH_3CHCH_3); 19.22 (m, $^2J_{\text{CP}} = 18.9$ Hz, CH_3CHCH_3); 22.67 (ddm, $^1J_{\text{CH}} = 128$ Hz, $^1J_{\text{CP}} = 9.2$ Hz, CH_3CH); 44.22 (tdq, $^1J_{\text{CH}} = 133.6$ Hz, $^2J_{\text{CP}} = 14.3$ Hz, $^2J_{\text{CH}} = 4.3$ Hz, CH_2CH_3); 58.29 (qt, $^1J_{\text{CH}} = 140.8$ Hz, $^3J_{\text{CH}} = 3.9$ Hz, CH_3O); 72.31 (tdq, $^1J_{\text{CH}} = 141.7$ Hz, $^3J_{\text{CP}} = 26.8$ Hz, $^3J_{\text{CH}} = 5.0$ Hz, CH_2O); C_{arom} : 126.62 (dd, $^1J_{\text{CH}} = 160.4$ Hz, $^2J_{\text{CH}} = 7.7$ Hz); 127.46 (ddm, $^1J_{\text{CH}} = 160.0$ Hz, $J_{\text{CP}} = 4.7$ Hz); 128.65 (dt, $^1J_{\text{CH}} = 160.5$ Hz, $^2J_{\text{CH}} = 7.6$ Hz); 128.77 (dt, $^1J_{\text{CH}} = 159.4$ Hz, $^2J_{\text{CH}} = 8.3$ Hz); 136.36 (dm, $^3J_{\text{CP}} = 21.9$ Hz); 143.15 (dm, $^1J_{\text{CP}} = 22.6$ Hz).

4.11. Preparation of 2-isopropylphosphineoxide benzylmethylether **17**

Prepared by following the protocol used for **8a**. Yield 85% after purification by flash chromatography on silica gel (eluent EtOAc).

^{31}P -NMR (121 MHz, CDCl_3): δ 42.0 (d, $^1J_{\text{PH}} = 465$ Hz), ^{31}P -NMR (121 MHz, C_6D_6): δ 39 (d, $^1J_{\text{PH}} = 466.4$ Hz). ^1H -NMR (200 MHz, CDCl_3) δ : 1.15 (dd, 3H, $^3J_{\text{PH}} = 20$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, CH_3CHCH_3); 1.20 (dd, 3H, $^3J_{\text{PH}} = 17.5$ Hz, $^3J_{\text{HH}} = 7.1$ Hz, CH_3CHCH_3); 2.30 (dh, H, $^2J_{\text{PH}} = 10.8$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, CH_3CH); 3.40 (s, 3H, OCH_3); 4.6 and 4.7 ($2 \times 2\text{H}$, $^2J_{\text{HH}} = 11.7$ Hz, CH_2O); 7.16 (dd, H, $^1J_{\text{PH}} = 465$ Hz, $^3J_{\text{HH}} = 3.4$ Hz, P-*H*); 7.4–7.8 (m, 4 H_{arom}). ^{13}C -NMR (50 MHz, CDCl_3): δ 15.0 (qm, $^1J_{\text{CH}} = 128.3$ Hz, CH_3CH); 27.78 (ddm, $^1J_{\text{CH}} = 128.0$ Hz, $^1J_{\text{CP}} = 59.2$ Hz, CH_3CH); 57.10 (qt, $^1J_{\text{CH}} = 142.6$ Hz, $^3J_{\text{CH}} = 3.5$ Hz, OCH_3); 71.64 (tq, $^1J_{\text{CH}} = 143$ Hz, $^3J_{\text{CH}} = 5.0$ Hz, $^3J_{\text{CP}} = 4.6$ Hz, CH_2O); 124.22–139.14 (C_{arom}). HRMS, Calc. for $\text{C}_{10}\text{H}_{14}\text{O}_2\text{P}$ [$\text{M} - \text{CH}_3$] $^+$: 197.0731. Found: 177.0725.

4.12. Preparation of the free 2-*i*-propylphosphine benzylmethylether **16**

Prepared by following the protocol used for **7a**.

^{31}P -NMR (121 MHz, CDCl_3): δ -33.5 (d, $^1J_{\text{PH}} = 213$ Hz). ^1H -NMR (300 MHz, CDCl_3) δ : 1;10 (dd, 3H, $^3J_{\text{PH}} = 10.4$ Hz, $^3J_{\text{HH}} = 6.9$ Hz, CH_3CHCH_3); 1.12 (dd, 3H, $^3J_{\text{PH}} = 17.4$ Hz, $^3J_{\text{HH}} = 7.0$ Hz, CH_3CHCH_3); 2.10 (hd, H, $^3J_{\text{HH}} = 7.0$ Hz, $^2J_{\text{PH}} = 1.5$ Hz, CH_3CH); 3.3 (s, 3H, OCH_3); 3.8 (dd, H, $^1J_{\text{PH}} = 2.3$ Hz, $^3J_{\text{HH}} = 7.4$ Hz, P-*H*); 4.4 and 4.5 (d, $2 \times 2\text{H}$, $^2J_{\text{HH}} = 5.3$ Hz, CH_2O); 4 H_{arom} : 7.03 (td, H, $^3J_{\text{PH}} = 7.3$ Hz, $^4J_{\text{HH}} = 1.3$ Hz); 7.21 (td, H, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.5$ Hz); 7.31 (ddd, H, $^3J_{\text{HH}} = 7.4$ Hz, $J_{\text{PH}} = 2.7$ Hz, $J_{\text{HH}} = 1.2$ Hz); 7.40 (ddd, H, $^3J_{\text{PH}} = 12.7$ Hz, $^3J_{\text{PH}} = 7.0$ Hz, $^4J_{\text{HH}} = 1.2$ Hz). ^{13}C -NMR (75 MHz, CDCl_3): δ 21.42 (m, $^1J_{\text{CH}} = 126.3$ Hz, $^2J_{\text{CP}} = 19.0$ Hz, CH_3CHCH_3); 22.94 (qm, $^1J_{\text{CH}} = 126.4$ Hz, $^2J_{\text{CP}} = 3.7$ Hz, CH_3CHCH_3); 24.28 (ddm, $^1J_{\text{CH}} = 131.8$ Hz, $^1J_{\text{CP}} = 8.1$ Hz, CH_3CH); 58.07 (qt, $^1J_{\text{CH}} = 141.0$ Hz, $^3J_{\text{CH}} = 3.6$ Hz, CH_3O); 73.84 (tdq, $^1J_{\text{CH}} = 141.6$ Hz, $^3J_{\text{CP}} = 14.7$ Hz, $^3J_{\text{CH}} = 4.9$ Hz, CH_2O); C_{arom} : 127.60 (dddm, $^1J_{\text{CH}} = 161.4$ Hz, $^3J_{\text{CH}} =$

7.7 Hz, $^2J_{\text{CP}} = 2.7$ Hz); 128.70 (ddm, $^1J_{\text{CH}} = 160.6$ Hz, $^3J_{\text{CH}} = 7.6$ Hz, $^3J_{\text{CP}} = 3.5$ Hz); 134.59 (dm, $^1J_{\text{CP}} = 16.5$ Hz); 136.24 (dm, $^1J_{\text{CH}} = 165.8$ Hz); 141.72 (dm, $^3J_{\text{CP}} = 5.7$ Hz). HRMS, Calc. for $\text{C}_{11}\text{H}_{17}\text{OP}$: 196.1017. Found: 196.102.

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