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Synthesis of tertiary propargylic phosphonates by addition of trialkynylaluminum reagents to acyl phosphonates and investigation of their antimicrobial activities

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Abstract: A series of propargylic alcohols containing phosphonates was synthesized by addition reactions of tris-(propynyl) and tris-(phenylethynyl)aluminum reagents to acyl phosphonates in good yields. Aromatic moieties of the acyl phosphonates with electron-withdrawing groups generally resulted in better isolated chemical yield. Selected propargylic phosphonates were tested for antimicrobial activities. Compounds **3a** and **3h** showed noticeable antifungal activity, especially against molds.

Key words: Acyl phosphonates, alkynyl organoaluminum, propargylic alcohols, tris-(phenylethynyl)aluminum, tris-(propynyl)aluminum, antimicrobial activity

1. Introduction

Propargylic alcohols are useful synthetic intermediates and can be easily manipulated into a variety of useful functional groups. For that reason, several methods are available in the literature for their preparation.[1–6] Addition of alkyne to either aldehydes or ketones, reduction of ynones, and direct addition of alkynylzinc reagents to carbonyl compounds are used to obtain related secondary or tertiary propargylic alcohols.[1–6] Moreover, alkynylation of α-keto ester provides synthesis of highly functionalized tertiary alcohols, i.e. propargylic carboxylates.[7–12] Propargylic alcohols having C–P bonds are considered close analogues of propargylic carboxylates.

Addition of organoaluminum reagents to carbonyl compounds for the synthesis of secondary and tertiary alcohols is well known.[13–16] Organoaluminum reagents are easy to handle and are commercially available. However, those not commercially available can be easily prepared according to a literature procedure.[17] Organoaluminum reagents are very attractive for their utilization in asymmetric synthesis.[13–16] Trialkyl aluminum reagents are used as alkyl donor in the addition reaction while trialkynylaluminum reagents are the source of alkynyl type C-based nucleophiles.

$\alpha-$Functionalized phosphonates are medicinally important molecules due to their wide range of biological

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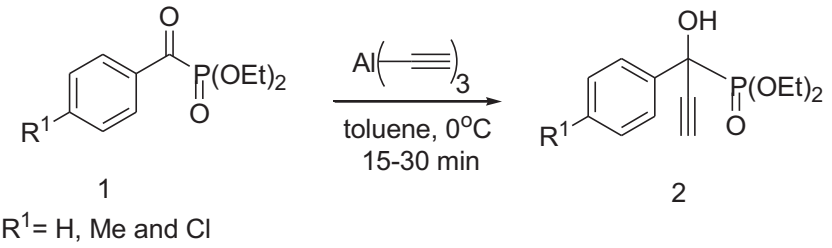
activities. Hence, there are many published procedures for synthesis and investigation of their biological activities.[18–26] For both synthesis and study of their biological activity, tertiary propargylic phosphonates still need more attention. In continuation of our work on acyl phosphonate chemistry, herein we present the synthesis of tertiary propargylic phosphonates by simple addition of trialkynyl organoaluminum reagents to acyl phosphonates and also present our investigation on the antimicrobial activity of selected propargylic phosphonates.

2. Results and discussion

Recently, we have reported that aryl and alkyl acyl phosphonates **1** can react with trialkyl organoaluminum reagents such as Me_3Al and Et_3Al to produce the related secondary and tertiary α-hydroxy phosphonates.[27] In the same article, we also briefly described the alkynylation reactions of acyl phosphonates with the triethynylaluminum reagent to afford the desired α-hydroxy phosphonates **2** in moderate yields, i.e. 67% in the case of R^1=H, 57% in the case of R^1=Me, and 44% in the case of R^1=Cl (Scheme). Encouraged by the results obtained from this preliminary study, we have extended our research and investigated the scope of alkynylation reaction of acyl phosphonates with different trialkynyl organoaluminum reagents to obtain tertiary propargylic phosphonates. In addition, we have studied the capacity of the synthesized propargylic phosphonates as antimicrobial agents.



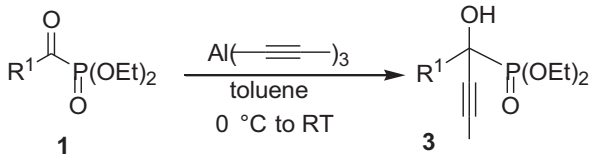
Scheme. Addition of triethynylaluminum reagent to acyl phosphonates.

The acyl phosphonates were prepared by treating the parent chlorides with triethyl phosphites according to the literature procedure.[28] Tris-(propynyl) and tris-(phenylethynyl)aluminum reagents were also prepared by following the literature procedure,[17] i.e. 1-propynyl magnesium bromide solution was reacted with dry $AlCl_3$ to give tris-(propynyl)aluminum.

We initially investigated the addition of tris-(propynyl)aluminum reagent to a variety of acyl phosphonates, **1a**–**m** (Table 1). In all cases, the desired tertiary propargylic alcohols were obtained without cleavage of the C–P bond in good yields. The reaction of benzoyl phosphonate **1a** with tris-(propynyl)aluminum gave the desired tertiary propargylic alcohol **3a** in 56% yield. When the electron donation was increased from $-CH_3$ to –OMe, the yields were lower (entries 2 and 4, Table 1, 53% and 41% yields, respectively).

When the methyl group was at the ortho position (entry 3, Table 1), the desired tertiary propargylic alcohol **3c** was obtained in lower yield (32%) due to the bulkiness around the reactive site. The addition reactions of compounds **1e** and **1h** with tris-(propynyl)aluminum were smooth and afforded compounds **3e** (70%) and **3h** (61%) in good yields. The reaction of 4-trifluoromethyl benzoyl phosphonate with tris-(propynyl)aluminum proceeded efficiently to give compound **3k** in good yield (75%). We also carried out the alkynylation reaction of alkyl phosphonates **1l** and **1m**. However, in these cases the corresponding tertiary propargylic alcohols **3l** and **3m** were obtained in low yields (32% and 38%, respectively).

Table 1. Alkynylation of acyl phosphonates with tris-(propynyl)aluminum reagent.



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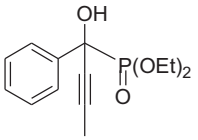
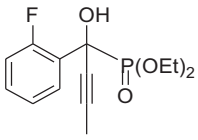
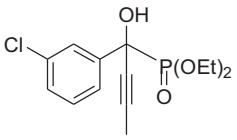
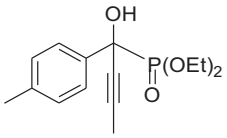
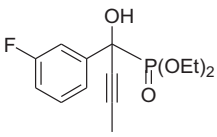
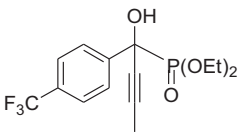
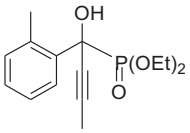
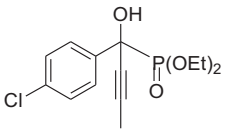
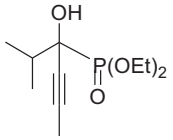
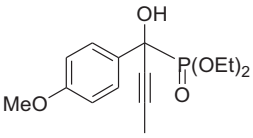
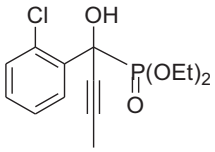
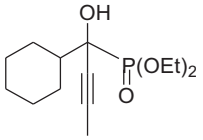
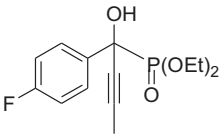
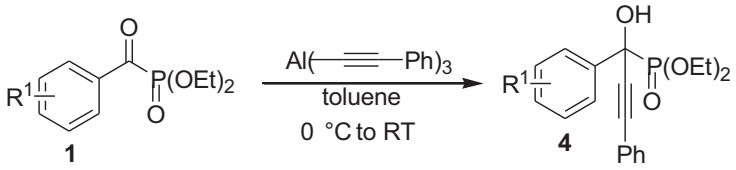
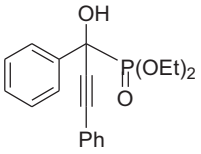
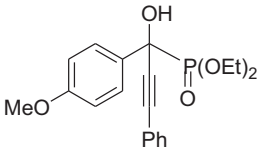
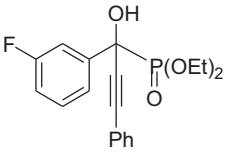
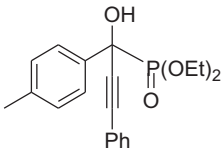
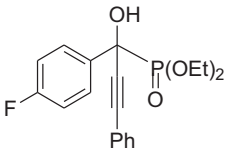
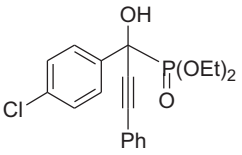
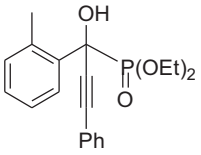
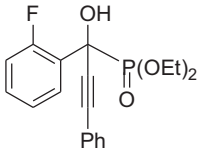
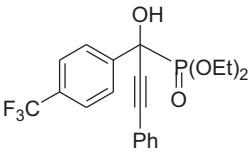
1	 **3a**, [a]	6	 **3f**, 61%	10	 **3j**, 62%
2	 **3b**, 53%	7	 **3g**, 65%	11	 **3k**, 75%
3	 **3c**, 32%	8	 **3h**, 61%	12	 **3l**, 32%
4	 **3d**, 41%	9	 **3i**, 49%	13	 **3m**, 38%
5	 **3e**, 70%				

[a]Yields refer to purified compound

Our next attempt was to use tris-(phenylethynyl) aluminum reagent in alkynylation of the acyl phosphonates (Table 2, entries 1–9) to obtain tertiary propargylic phosphonates. The reaction of benzoyl phosphonate **1a** with freshly prepared tris-(phenylethynyl)-aluminum gave compound **4a** in 61% yield. On the other hand, Zbiral et al.[29] have synthesized compound **4a** by direct addition of organolithium reagent PhC≡CLi to benzoyl phosphonate **1a**, reporting 58% chemical yield.

Table 2. Alkynylation of acyl phosphonates with tris-(phenylethynyl)aluminum reagent.



Entry	Product	Entry	Product	Entry	Product
1	 **4a**, 61%[a]	4	 **4d**, 39%	7	 **4g**, 72%
2	 **4b**, 59%	5	 **4e**, 68%	8	 **4h**, 52%
3	 **4c**, 30%	6	 **4f**, 72%	9	 **4k**, 60%

[a]Yields refer to purified compounds

When the electron-rich benzoyl phosphonates **1b** and **1d** were used, the corresponding alcohols **4b** and **4d** were obtained in decreasing yields (Table 2, entries 2 and 4, 59% and 39% yields, respectively). The electron-poor benzoyl phosphonates entries 5–9 in Table 2 afforded the desired propargylic alcohols in good yields. We generally obtained better chemical yields with tris-(phenylethynyl)aluminum compared to tris-(propynyl)aluminum, probably due to the stability of the resulting propargylic phosphonates.

Compounds **4a**, **4e**, **4k**, **4h**, **3a**, **3e**, **3h**, and **3k** were selected and investigated for antimicrobial activity against 7 different microorganisms and the results are shown in Table 3. Most of the propargylic phosphonates

did not show distinctive and wide antimicrobial activity for bacteria. Only 3 compounds, **4a**, **4e**, and **4h**, showed weak inhibition against 2 of the gram-positive bacteria. On the other hand, while the positive control did not present any meaningful activity, 2 of the compounds, **3a** and **3h**, exhibited clear antifungal activity, especially against molds. When we compare the structures of compounds **4** and **3**, we can see that there is a clear difference in the conjugation of the triple bond with the double bond of benzene. This may change the dipole moment and may help to explain the better activity of compounds **3**.[30,31]

Table 3. Antimicrobial activity of compounds **4a**, **4e**, **4k**, **4h**, **3a**, **3e**, **3h**, and **3k**.

Compounds	Inhibition zone against test organisms (mm)						
	[a]A	B	C	D	E	F	G
4a	15.62	9.39	-	-	-	-	-
4e	15.16	8.59	-	-	-	-	-
4k	-	-	-	-	-	-	-
4h	11.11	6.75	-	-	-	-	-
3a	-	-	7.00	7.34	32.25	33.96	-
3e	-	-	-	-	-	-	-
3h	-	-	7.95	-	21.86	41.42	31.57
3k	-	-	-	-	-	-	-
DMSO	-	-	-	-	-	-	-
[b]VA	29.46	17.50	[c]NT				
B	34.14	12.07					
E	49.98	28.92					
FLU	NT		19.00	-	-	-	-

[a] A: *Micrococcus luteus* NRRL B 4375, B: *Bacillus cereus* LMG 8221, C: *Saccharomyces cerevisiae* NRRL Y 12632, D: *Candida krusei* ATCC 6258, E: *Aspergillus parasiticus* NRRL 465, F: *Aspergillus flavus* NRRL 1957, G: *Penicillium chrysogenum* NRRL 807 [b] VA: Vancomycin (30 μg), B: Bacitracin (10 U), E: Erythromycin (30 μg), FLU: Fluconazole (10 μg) [c] NT: Not tested

The active compounds against the test organisms were examined to determine their minimum inhibitory concentration (MIC) values. The MIC values of selected propargylic phosphonate compounds are presented in Table 4 in comparison to reference antibiotics. All of the studied compounds showed antimicrobial activity against all test microorganisms studied. Compounds **4a**, **4e**, and **4h** exhibited comparatively low MIC values in the range of 12.5–25 μg/mL. However, they were less active than the reference antibiotics, vancomycin, erythromycin, and bacitracin. The MIC value of **3h** against *Saccharomyces cerevisiae* was the same as that of fluconazole. Compounds **3a** and **3h** were determined to exhibit potent antifungal activity against 3 molds with the MIC value of 100 μg/mL. Their activity values were found to be better than those of fluconazole. These compounds can be potential antifungal drugs, especially for molds.

The current work shows that tertiary propargylic alcohols having a C–P bond can be easily prepared in good yields by adding trialkynylaluminum reagents to acyl phosphonates. Alkynylation reactions of acyl phosphonates work better with aryl substituted acyl phosphonates compared to alkyl phosphonates. Moreover, the electronic features of the aromatic moieties affected the chemical yield in such a way that introduction of an electron-withdrawing group on the phenyl ring gave a better chemical yield. This route offers a simple and efficient method for the synthesis of tertiary propargylic alcohols without cleavage of the C–P bond. Future work will focus on the rearrangement of tertiary propargylic phosphonates. Antimicrobial activities of selected propargylic phosphonates against *Micrococcus luteus* NRRL B 4375, *Bacillus cereus* LMG 8221,

Saccharomyces cerevisiae NRRL Y 12632, *Candida krusei* ATCC 6258, *Aspergillus parasiticus* NRRL 465, *Aspergillus flavus* NRRL 1957, and *Penicillium chrysogenum* NRRL 807 were also investigated. Most of the propargylic phosphonates did not exhibit any antimicrobial activity for bacteria. However, when we compare compounds **3a** and **3h** and the reference antibiotic, compounds **3a** and **3h** showed good antifungal activity, especially against molds, according to their MIC values.

Table 4. The minimum inhibitory concentrations (MIC in μg/mL) of compounds **4a**, **4e**, **4h**, **3a**, **3h**, and **3k**.

Compounds	Test organisms						
	[a]A	B	C	D	E	F	G
4a	25	25	-	-	-	-	-
4e	12.5	12.5	-	-	-	-	-
4h	25	12.5	-	-	-	-	-
3a	-	-	200	200	100	100	
3h	-	-	50		100	100	100
VA	1.56	1.56	[b]NT				
B	1.56	200					
E	0.78	0.78					
FLU	-		50	100	< 200	< 200	< 200

[a] All abbreviations used are the same as those in Table 3. [b] NT: Not tested.

3. Experimental section

All the reactions that were sensitive to air and moisture were performed under argon. Organic solvents used in the reactions were distilled prior to use; dichloromethane was freshly distilled from calcium hydride; THF and toluene were distilled from sodium/benzophenone. The progress of all reactions was monitored by TLC, which was carried out on silica gel plates with fluorescent indicator. Crude compounds were purified by flash column chromatography using 230–400-mesh silica gel with hexane-EtOAc mixtures as the eluting solvent. Melting points are uncorrected and were determined on a hot stage microscope. All commercially available reagents were used as received unless otherwise reported. All NMR spectra were recorded at room temperature on a Bruker DPX 400 NMR spectrometer operated at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, and 161 MHz for ^{31}P NMR using $CDCl_3$ as the solvent. ^{1}H NMR and ^{13}C NMR chemical shifts were reported in parts per million relative to tetramethylsilane. ^{31}P NMR chemical shifts were reported in parts per million relative to H_3PO_4. Tris-(phenylethynyl) aluminum and tris-(propynyl) aluminum reagents were prepared by following a literature procedure.[17] Aryl and alkyl acyl phosphonates were also synthesized according to a literature procedure.[28]

3.1. Materials and methods for the antimicrobial activity studies

In vitro antimicrobial susceptibility studies were performed using a panel of gram-positive and -negative bacteria, yeast, and mold species. The panel consisted of a total of 7 microorganism species, namely *Micrococcus luteus* NRRL B 4375, *Bacillus cereus* LMG 8221, *Saccharomyces cerevisiae* NRRL Y 12632, *Candida krusei* ATCC 6258, *Aspergillus parasiticus* NRRL 465, *Aspergillus flavus* NRRL 1957, and *Penicillium chrysogenum* NRRL 807.

First, antimicrobial activities of the synthesized compounds were screened by the disk diffusion method.[32] Overnight grown bacteria and yeast cultures were adjusted to 0.5 McFarland turbidity standards to 10^8 and

10^6 cfu/mL, respectively. Mold spore suspensions were prepared as 10^6 spore/mL. Then 100 μL cell or spore suspensions were spread on the surfaces of Mueller-Hinton Agar (MHA), Sabouraud Dextrose Agar (SDA), and Malt Extract Agar (MEA) for bacteria, yeast, and molds, respectively. Propargylic phosphonates **4a**, **4e**, **4k**, **4h**, **3a**, **3e**, **3h**, and **3k** were dissolved in DMSO and the disks (6 mm dia) including 50 μg of synthesized compounds were placed on the inoculated media. The petri dishes were incubated at 37 °C for 24 h for bacteria and at 30 °C for 2–3 days for fungi. Antimicrobial activity was determined by measuring the radius of the inhibition zones around the disks. Vancomycin (30 μg), erythromycin (30 μg), and bacitracin (10 U) disks were used as positive controls for bacteria and fluconazole (10 μg) disks were used for fungi. DMSO was also used as a negative control. The tests were carried out in triplicate and the results are reported as the average of them. The active compounds in the disk diffusion method were selected to assign MIC values.

In the second step of antimicrobial activity studies, MIC values of selected compounds were determined by the conventional agar diffusion method.[33] To obtain the appropriate concentrations ranging from 200 to 0.78 μg/mL, 2-fold serial dilutions of the selected propargylic phosphonates and reference antibiotics (vancomycin, erythromycin, and bacitracin for bacteria and fluconazole for fungi) were prepared in MHA, SDA, and MEA for bacteria, yeast, and molds, respectively. The inoculants' preparations and incubation conditions were the same as those in the disk diffusion method. Test media supplemented with solvents and without any phosphonate compound and antibiotic were also used as controls. MIC values were described as the lowest concentration of the compound that completely inhibited growth of the test microorganisms on the petri dish.

3.2. General procedure for the synthesis of propargylic phosphonates

To a solution of acyl phosphonate (1 equiv.) in dry toluene (0.5 M) at 0 °C under argon atmosphere was added trialkynylaluminum (3 equiv., 0.23 M solution) dropwise within 2 min. The resultant mixture was stirred at 0 °C, and warmed to room temperature. After the completion of the reaction in 2–3 h, which was monitored by a TLC plate, the reaction mixture was cautiously hydrolyzed with water. The reaction mixture was filtrated over Celite and washed with ethyl acetate. The organic layer was then dried over anhydrous $MgSO_4$, filtered again, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexane–EtOAc mixtures.

3.2.1. Diethyl 1-hydroxy-1-phenylbut-2-ynylphosphonate (3a)

56% yield as a crystalline white solid; mp 157–158 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (6H, dt, J = 7.0 and 2.9 Hz, –$OCH_2\underline{CH}_3$), 1.97 (3H, d, J = 5.1 Hz, –C≡C–$\underline{CH}_3$), 3.66 (1H, d, J = 8.5 Hz, –OH), 3.90–4.22 (4H, m, –$O\underline{CH}_2CH_3$), 7.27–7.42 (m, 3H), 7.69–7.77 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.7 Hz, –C≡C–$\underline{CH}_3$), 16.4 (t, J_{C-P} = 4.0 Hz, –$OCH_2\underline{CH}_3$), 64.4 (dd, J_{C-P} = 73.5 and 4.0 Hz, $O\underline{CH}_2CH_3$), 71.2 (d, J_{C-P} = 167.4 Hz, quaternary C atom), 77.5 (d, J_{C-P} = 2.3 Hz, C≡$\underline{C}$–CH_3) 85.0 (d, J_{C-P} = 8.8 Hz, –$\underline{C}$≡C–CH_3), 126.7 (d, J_{C-P} = 4.2 Hz), 127.8, (d, J_{C-P} = 2.6 Hz), 128.1 (d, J_{C-P} = 3.0 Hz) 137.8 (d, J_{C-P} = 3.0 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 17.36. IR (ATR technique, cm^{-1}): 3241, 2988, 1228, 1015, 972, 757, 703, 577. HRMS: calculated for $C_{14}H_{19}O_4P$ [M], [M+H] = 283.1099 and found 283.1129.

3.2.2. Diethyl 1-hydroxy-1-p-tolylbut-2-ynylphosphonate (3b)

53% yield as a crystalline white solid; mp 127–128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (6H, t, J_{C-P} = 7.1 Hz, –$OCH_2\underline{CH}_3$), 1.96 (3H, d, J_{C-P} = 5.1 Hz, –C≡C–$\underline{CH}_3$), 2.34 (3H, d, J_{C-P} = 1.3 Hz, CH_3), 3.66

(1H, t, –OH, J_{C-P} = 12.2 Hz), 3.90–4.30 (m, 4H, –O$\underline{CH}_2$CH$_3$), 7.16 (2H, d, J_{C-P} = 8.0 Hz), 7.60 (dd, 2H, J_{C-P} = 8.3 and 2.2 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.4 Hz, –C≡C–$\underline{CH}_3$), 16.4 (t, J_{C-P} = 4.0 Hz, –OCH$_2\underline{CH}_3$), 21.0 (s, –CH$_3$), 64.3 (d, J_{C-P} = 7.4 Hz, –O$\underline{CH}_2$CH$_3$), 71.1 (d, J_{C-P} = 168.3 Hz, quaternary C atom), 77.6, 84.9 (d, J_{C-P} = 8.4 Hz), 126.6 (d, J_{C-P} = 4.2 Hz), 128.6 (d, J_{C-P} = 4.2 Hz) 128.6 (d, J_{C-P} = 2.4 Hz), 134.9, 137.9 (d, J_{C-P} = 2.8 Hz). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 17.52. IR (ATR technique, cm^{-1}): 3238, 2986, 1231, 1017, 970, 573. HRMS: calculated for C$_{15}$H$_{21}$O$_4$P [M], [M+H] = 297.1256 and found 297.1289.

3.2.3. Diethyl 1-hydroxy-1-o-tolylbut-2-ynylphosphonate (3c)

32% yield as a crystalline white solid; mp 104–105 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ1.21 (3H, t, J_{C-P} = 7.1 Hz, –OCH$_2\underline{CH}_3$), 1.29 (3H, t, J_{C-P} = 7.1 Hz, –OCH$_2\underline{CH}_3$), 1.95 (3H, d, J_{C-P} = 5.2 Hz, –C≡C–$\underline{CH}_3$), 2.69 (d, 3H, J_{C-P} = 1.5 Hz, CH$_3$), 3.25 (1H, d, –OH, J_{C-P} = 8.0 Hz), 3.80–4.30 (m, 4H, –O$\underline{CH}_2$CH$_3$), 7.12–7.23 (m, 3H), 7.72–7.82 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.5 Hz, –C≡C–$\underline{CH}_3$), 16.4 (dd, J_{C-P} = 9.3 and 5.5 Hz, –OCH$_2\underline{CH}_3$), 21.9 (–CH$_3$), 64.2 (t, J_{C-P} = 8.3 Hz, –O$\underline{CH}_2$CH$_3$), 71.6 (d, J_{C-P} = 167.5 Hz, quaternary C atom), 77.6 (d, J_{C-P} = 2.2 Hz), 85.7 (d, J_{C-P} = 9.0 Hz) 125.4 (d, J_{C-P} = 2.3 Hz), 127.7 (d, J_{C-P} = 4.2 Hz), 128.2 (d, J_{C-P} = 2.7 Hz), 132.3 (d, J_{C-P} = 2.3 Hz), 134.8 (d, J_{C-P} = 1.5 Hz), 137.4 (d, J_{C-P} = 4.8 Hz). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 18.00. IR (ATR technique, cm^{-1}): 3246, 2982, 1229, 1015, 970. HRMS: calculated for C$_{15}$H$_{21}$O$_4$P [M], [M–H] = 295.1099 and found 295.1152.

3.2.4. Diethyl 1-hydroxy-1-(4-methoxyphenyl)but-2-ynylphosphonate (3d)

41% yield as a crystalline white solid; mp 111–112 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.26 (6H, dt, J_{C-P} = 7.0 and 3.7 Hz, –OCH$_2\underline{CH}_3$), 1.97 (3H, d, J_{C-P} = 5.1 Hz, –C≡C–$\underline{CH}_3$), 3.38 (1H, d, –OH, J_{C-P} = 9.0 Hz), 3.81 (s, 3H, –O$\underline{CH}_3$), 3.92–4.20 (4H, m, –O$\underline{CH}_2$CH$_3$), 6.90 (d, 2H, J_{C-P} = 8.7 Hz), 7.64 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.6 Hz, –C≡C–$\underline{CH}_3$), 16.4 (dd, J_{C-P} = 5.2 and 3.6 Hz, –OCH$_2\underline{CH}_3$), 55.3 (–O$\underline{CH}_3$), 64.3 (dd, J_{C-P} = 7.3 and 3.5 Hz, –O$\underline{CH}_2$CH$_3$), 70.9 (d, J_{C-P} = 169.4 Hz, quaternary C atom), 77.5, 85.1 (d, J_{C-P} = 8.8 Hz), 113.3 (d, J_{C-P} = 2.3 Hz) 128.1 (d, J_{C-P} = 4.0 Hz), 129.7 (d, J_{C-P} = 3.4 Hz), 159.6 (d, J_{C-P} = 2.5 Hz). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 17.58. IR (ATR technique, cm^{-1}): 3240, 2980, 1225, 1019, 970. HRMS: calculated for C$_{15}$H$_{21}$O$_5$P [M], [M+H] = 313.1205 and found 313.1247.

3.2.5. Diethyl 1-(4-fluorophenyl)-1-hydroxybut-2-ynylphosphonate (3e)

70% yield as a crystalline white solid; mp 160–161 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.26 (6H, t, J_{C-P} = 7.1 Hz, –OCH$_2\underline{CH}_3$), 1.97 (3H, d, J_{C-P} = 5.2 Hz, –C≡C–$\underline{CH}_3$), 3.96–4.22 (5H, m, –O$\underline{CH}_2$CH$_3$ and –OH), 7.04 (2H, t, J = 8.6 Hz), 7.65–7.75 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.3 Hz, –C≡C–$\underline{CH}_3$), 16.4 (dd, J_{C-P} = 5.2 and J_{C-P} = 4.1 Hz, –OCH$_2\underline{CH}_3$), 64.4 (d, J_{C-P} = 7.4 Hz, –O$\underline{CH}_2$CH$_3$), 70.7 (d, J = 168.9 Hz, quaternary C atom), 77.2, 85.2 (d, J_{C-P} = 8.9 Hz), 114.7 (dd, J_{C-F} = 21.7 Hz and J_{C-P} = 2.6 Hz) 128.7 (dd, J_{C-F} = 8.2 Hz and J_{C-P} =4.2 Hz), 133.8 (t, J_{C-F} = 3.0 Hz) 162.6 (dd, J_{C-F} = 250.0 and J_{C-P} = 3.3 Hz). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 16.42. IR (ATR technique, cm^{-1}): 3233, 1231, 1021, 971, 804, 572. HRMS: calculated for C$_{14}$H$_{18}$FO$_4$P [M], [M+H] = 301.1005 and found 301.1045.

3.2.6. Diethyl 1-(2-fluorophenyl)-1-hydroxybut-2-ynylphosphonate (3f)

61% yield as a crystalline white solid; mp 145–146 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH}_3$), 1.31 (3H, t, J_{C-P} = 7.1 Hz, –$OCH_2\underline{CH}_3$), 1.97 (3H, d, J_{C-P} = 5.1 Hz, –C≡C–$\underline{CH}_3$), 4.04 (1H, s (broad), –OH), 4.08–4.32 (m, 4H, –$O\underline{CH}_2CH_3$), 7.05 (1H, dd, J_{C-F} = 11.9 and J_{C-P} = 8.2 Hz), 7.15 (t, 1H, J_{C-F} = 7.6 Hz), 7.25–7.35 (m, 1H), 7.74 (1H, tt, J_{C-F} = 8.0 and J_{C-P} = 2.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.5 Hz, –C≡C–$\underline{CH}_3$), 16.3 (d, J_{C-P} = 5.5 Hz, –$OCH_2\underline{CH}_3$), 64.6 (dd, J_{C-F} = 7.2 and J_{C-P} = 5.1 Hz, –$O\underline{CH}_2CH_3$), 79.6 (d, J_{C-P} = 168.6 Hz, quaternary C atom), 69.6 (dd, J_{C-P} = 168.6 and J_{C-F} = 2.0 Hz), 76.0 (d, J_{C-P} = 3.8 Hz), 85.3 (dd, J_{C-P} = 8.8 and J_{C-F} = 1.9 Hz), 116.3 (dd, J_{C-F} = 23.0 and J_{C-P} = 2.3 Hz), 123.7 (t, J = 2.3 Hz), 125.1 (dd, J_{C-F} = 9.2 and J_{C-P} = 2.0 Hz), 129.3 (dd, J_{C-F} = 8.7 and J_{C-P} = 2.7 Hz), 160.2 (dd, J_{C-F} = 250.3 and J_{C-P} = 4.3 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.42. IR (ATR technique, cm^{-1}): 3229, 2983, 1235, 1028, 974, 774, 580. HRMS: calculated for $C_{14}H_{18}FO_4P$ [M], [M+H] = 301.1005 and found 301.1040.

3.2.7. Diethyl 1-(3-fluorophenyl)-1-hydroxybut-2-ynylphosphonate (3g)

65% yield as a crystalline white solid; mp 152–153 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (6H, dt, J_{C-P} = 7.0 Hz and J_{C-F} = 5.8 Hz, –$OCH_2\underline{CH}_3$), 1.97 (3H, d, J_{C-P} = 5.2 Hz, –C≡C–$\underline{CH}_3$), 4.03–4.23 (4H, m, –$O\underline{CH}_2CH_3$), 4.37 (1H, d, J_{C-P} = 7.5 Hz, –OH), 6.96–7.05 (1H, m), 7.32 (1H, dt, J_{C-F} = 8.0 and 6.10 Hz), 7.45 (1H, ddd, J = 10.4, 4.2, and 2.3 Hz), 7.51 (1H, td, J = 7.9 and 2.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 4.2 Hz, –C≡C–$\underline{CH}_3$), 16.4 (t, J_{C-P} = 4.2 Hz, –$OCH_2\underline{CH}_3$), 64.5 (dd, J_{C-P} = 7.4 and J_{C-F} =2.0 Hz, –$O\underline{CH}_2CH_3$), 70.8 (dd, J_{C-P} = 167.9 and J_{C-F} = 1.8 Hz, quaternary C atom), 85.2 (d, J_{C-P} = 8.8 Hz), 114.1 (dd, J_{C-P} = 4.0 and J_{C-F} = 23.9 Hz), 114.9 (dd, J_{C-F} = 21.2 and J_{C-P} = 2.8 Hz), 122.6 (t, J = 3.5 Hz), 129.2 (dd, J_{C-F} = 8.1 and J_{C-P} = 2.7 Hz), 140.8 (dd, J_{C-F} = 7.4 and J_{C-P} = 3.1 Hz), 162.4 (dd, J_{C-F} = 247.8 and J_{C-P} = 2.9 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.75. IR (ATR technique, cm^{-1}): 3229, 1228, 1018, 977, 798. HRMS: calculated for $C_{14}H_{18}FO_4P$ [M], [M+H] = 301.1005 and found 301.1055.

3.2.8. Diethyl 1-(4-chlorophenyl)-1-hydroxybut-2-ynylphosphonate (3h)

61% yield as a crystalline white solid; mp 124–125 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (6H, dt, J_{C-P} = 7.0 and J_{C-P} = 1.2 Hz, –$OCH_2\underline{CH}_3$), 1.96 (3H, d, J_{C-P} = 5.2 Hz, –C≡C–$\underline{CH}_3$), 3.95–4.22 (4H, m, –$O\underline{CH}_2CH_3$), 4.26 (1H, d, –OH, J_{C-P} = 7.6 Hz), 7.33 (d, 2H, J = 8.6 Hz), 7.66 (2H, dd, J = 8.7 and J_{C-P} = 2.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.2 Hz, –C≡C–$\underline{CH}_3$), 16.4 (t, J_{C-P} = 4.5 Hz, –$OCH_2\underline{CH}_3$), 64.4 (dd, J_{C-P} = 7.3 and 4.2 Hz, –$O\underline{CH}_2CH_3$), 70.7 (d, J_{C-P} = 168.5 Hz, quaternary C atom), 85.3 (d, J_{C-P} = 8.8 Hz), 127.9 (d, J_{C-P} = 2.7 Hz), 128.3 (d, J_{C-P} = 4.2 Hz) 134.0 (d, J_{C-P} = 3.7 Hz), 136.7 (d, J_{C-P} = 3.0 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.16. IR (ATR technique, cm^{-1}): 3229, 2986, 1230, 1013, 974. HRMS: calculated for $C_{14}H_{18}ClO_4P$ [M], [M+H] = 317.0709 and found 317.0751.

3.2.9. Diethyl 1-(2-chlorophenyl)-1-hydroxybut-2-ynylphosphonate (3i)

49% yield as a crystalline white solid; mp: 137–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (3H, t, J_{C-P} = 7.04 Hz, –$OCH_2\underline{CH}_3$), 1.31 (3H, t, J_{C-P} = 7.1 Hz, –C≡C–$\underline{CH}_3$), 1.96 (3H, d, J_{C-P} = 5.2 Hz), 4.07 (1H,

d, J_{C-P} = 7.7 Hz, –OH,), 4.08–4.32 (4H, m, –O$\underline{CH_2}$CH$_3$), 7.20–7.33 (m, 2H), 7.38 (dd, 1H, J = 7.5 and 1.5 Hz), 7.91 (td, 1H, J = 7.8 and 2.1 Hz). ^{13}C NMR (CDCl$_3$, 100MHz): δ 4.0 (d, J = 2.4 Hz, –C≡C–$\underline{CH_3}$), 6.4 (t, J_{C-P} = 5.8 Hz, –OCH$_2$$\underline{CH_3}$), 64.5 (dd, J_{C-P} = 7.6 and 1.5 Hz, –O$\underline{CH_2}$CH$_3$), 71.3 (d, J_{C-P} = 167.9 Hz, quaternary C atom), 76.3 (d, J_{C-P} = 4.6 Hz), 86.2 (d, J_{C-P} = 9.0 Hz), 126.5 (d, J_{C-P} = 2.1 Hz), 129.4 (d, J_{C-P} = 2.3 Hz), 129.9 (d, J_{C-P} = 4.1 Hz), 131.5 (d, J_{C-P} = 2.0 Hz), 132.4 (d, J_{C-P} = 5.3 Hz), 134.7. ^{31}P NMR (CDCl$_3$, 161 MHz): δ 16.79. IR (ATR technique, cm^{-1}): 3221, 2983, 1231, 1022, 972. HRMS: calculated for C$_{14}$H$_{18}$ClO$_4$P [M], [M+H] = 317.0709 and found 317.0774.

3.2.10. Diethyl 1-(3-chlorophenyl)-1-hydroxybut-2-ynylphosphonate (3j)

62% yield as a crystalline white solid; mp 168–169 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.27 (6H, t, J_{C-P} = 7.1 Hz, –OCH$_2$$\underline{CH_3}$), 1.98 (3H, d, J_{C-P} = 5.2 Hz, –C≡C–$\underline{CH_3}$), 3.80 (1H, d, J_{C-P} = 7.8 Hz, –OH), 4.0–4.23 (m, 4H, –O$\underline{CH_2}$CH$_3$), 7.3 (2H, d, J_{C-P} = 4.8 Hz), 7.55–7.65 (m, 1H), 7.71 (d, 1H, J = 1.5 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 4.0 (d, J_{C-P} = 2.4 Hz, –C≡C–$\underline{CH_3}$), 16.4 (t, J = 4.9 Hz, –CH$_2$$\underline{CH_3}$), 64.5 (dd, J_{C-P} = 7.4 and 2.6 Hz, –O$\underline{CH_2}$CH$_3$), 70.8 (d, J_{C-P} = 167.8 Hz, quaternary C atom), 77.0, 85.5 (d, J_{C-P} = 8.8 Hz), 125.1 (d, J_{C-P} = 3.9 Hz), 127.0 (d, J_{C-P} = 4.0 Hz), 128.3 (d, J_{C-P} = 2.9 Hz), 129.1 (d, J_{C-P} = 2.8 Hz), 133.8 (d, J_{C-P} = 3.0 Hz), 140.1 (d, J_{C-P} = 3.2 Hz). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 16.64. IR (ATR technique, cm^{-1}): 3233, 2981, 1231, 1016, 975, 797, 695. HRMS: calculated for C$_{14}$H$_{18}$ClO$_4$P [M], [M+H] = 317.0709 and found 317.0765.

3.2.11. Diethyl 1-(4-(trifluoromethyl)phenyl)-1-hydroxybut-2-ynylphosphonate (3k)

75% yield as a crystalline white solid; mp 119–120 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.26 (6H, dt, J_{C-P} = 7.0 and J_{C-P} = 5.5 Hz, –OCH$_2$$\underline{CH_3}$), 1.97 (3H, d, J_{C-P} = 5.2 Hz, –C≡C–$\underline{CH_3}$), 4.0–4.26 (4H, m, –O$\underline{CH_2}$CH$_3$), 4.62 (1H, d, OH, J_{C-P} = 6.8 Hz), 7.61 (d, 2H, J_{C-P} = 8.6 Hz), 7.85 (2H, dd, J = 1.5 and J = 8.3 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 3.9 (d, J_{C-P} = 2.2 Hz, –C≡C–$\underline{CH_3}$), 16.3 (t, J_{C-P} = 4.9 Hz, –OCH$_2$$\underline{CH_3}$), 64.5 (t, J_{C-P} = 7.6 Hz, –O$\underline{CH_2}$CH$_3$), 70.9 (d, J_{C-P} = 167.3 Hz, quaternary C atom), 77.2, 85.4 (d, J_{C-P} = 8.9 Hz), 124.7 (t, J_{C-F} = 6.7), 124.1 (d, J_{C-F} = 271.2 Hz), 127.2 (d, J_{C-P} = 3.8 Hz), 129.8 (q, J_{C-F} = 32.2 Hz, –$\underline{C}$F$_3$), 142.3 (d, J_{C-F} = 1.7 Hz). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 15.84. IR (ATR technique, cm^{-1}): 3220, 1238, 1016, 972,883. HRMS: calculated for C$_{15}$H$_{18}$F$_3$O$_4$P [M], [M+H] = 351.0973 and found 351.1018.

3.2.12. Diethyl 3-hydroxy-2-methylhex-4-yn-3-ylphosphonate (3l)

32% yield as a crystalline white solid; mp 68–69 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.09 (6H, d, J = 6.7 Hz, CH$_3$), 1.36 (6H, t, J = 7.1 Hz, –OCH$_2$$\underline{CH_3}$), 1.91 (3H, d, J_{C-P} = 5.2 Hz, –C≡C–$\underline{CH_3}$), 2.08–2.12 (m, 1H, –$\underline{CH}$), 2.85 (1H, d, OH, J_{C-P} = 4.7 Hz), 4.10– 4.33 (m, 4H, –O$\underline{CH_2}$CH$_3$). ^{13}C NMR (CDCl$_3$, 100MHz): δ 3.8 (d, J_{C-P} = 2.6 Hz, –C≡C–$\underline{CH_3}$), 16.5 (d, J_{C-P} = 5.2 Hz, –OCH$_2$$\underline{CH_3}$), 17.0 (d, J_{C-P} = 9.5 Hz), 18.4 (d, J_{C-P} = 1.9 Hz), 34.5 (d, J_{C-P} = 1.0 Hz), 63.8 (dd, J_{C-P} = 20.4 and 7.4 Hz), 73.4 (d, J_{C-P} = 168.7 Hz, quaternary C atom), 75.2, 85.0 (d, J_{C-P} = 9.6 Hz). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 20.92. IR (ATR technique, cm^{-1}): 3270, 2986, 1228, 1021, 962. HRMS: calculated for C$_{11}$H$_{21}$O$_4$P [M], [M+H] = 249.1256 and found 249.1300.

3.2.13. Diethyl 1-cyclohexyl-1-hydroxybut-2-ynylphosphonate (3m)

38% yield as a crystalline white solid; mp 62–63 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08–1.30 (5H, m), 1.36 (6H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH}_3$), 1.66 (1H, d, J = 10.3 Hz), 1.72–1.88 (3H, m), 1.91 (d, 3H, J_{C-P} = 5.3 Hz, –C≡C–$\underline{CH}_3$), 2.04 (2H, t, J = 9.3 Hz), 2.72 (s (broad), 1H, –OH), 4.18–4.32 (m, 4H, –$O\underline{CH}_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 3.9 (d, J_{C-P} = 2.8 Hz, –C≡C–$\underline{CH}_3$), 16.5 (d, J_{C-P} = 5.5 Hz, –$OCH_2\underline{CH}_3$), 26.2 (d, J_{C-P} = 9.5 Hz, CH_2), 26.5 (d, J_{C-P} = 8.6 Hz, CH_2), 28.1 (d, J_{C-P} = 2.1 Hz, CH_2), 44.2, 63.8 (dd, J_{C-P} = 17.1 and 7.5 Hz, –$O\underline{CH}_2CH_3$), 72.9 (d, J_{C-P} = 167.8 Hz, quaternary C atom), 75.8, 84.9 (d, J_{C-P} = 9.5 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 20.71. IR (ATR technique, cm^{-1}): 3263, 2921, 1224, 1017, 983, 939. HRMS: calculated for $C_{14}H_{25}O_4P$ [M], [M+H] = 289.1569 and found 289.1630.

3.2.14. Diethyl 1-hydroxy-1,3-diphenylprop-2-ynylphosphonate (4a)

61% yield as a crystalline white solid; mp 120–121 °C. ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.14 (t, 3H, J_{C-P} = 7.1 Hz, –$OCH_2\underline{CH}_3$), 1.20 (t, 3H, J_{C-P} = 7.1 Hz, –$O\underline{CH}_2CH_3$), 4.0–4.14 (m, 4H, –$O\underline{CH}_2CH_3$), 4.4–4.6 (s (broad), 1H, –OH), 7.20–7.36 (m, 6H), 7.40–7.46 (dd, 2H, J = 7.5 and 1.7 Hz), 7.70–7.75 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.3 (t, J_{C-P} = 5.6 Hz, –$O\underline{CH}_2CH_3$), 63.6 (dd, J_{C-P} = 7.2 and 4.1 Hz, –$O\underline{CH}_2CH_3$), 70.5 (d, J_{C-P} = 166.9 Hz, quaternary C atom), 86.2 (d, J_{C-P} = 2.1 Hz, –C≡$\underline{C}$–Ph), 87.0 (d, J_{C-P} = 9.0 Hz, –$\underline{C}$≡C–Ph), 121.1 (d, J_{C-P} = 3.2 Hz) 125.8 (d, J_{C-P} = 3.9 Hz), 126.9 (d, J_{C-P} = 2.7 Hz), 127.2 (d, J_{C-P} = 2.9 Hz), 127.3, 127.9, 130.9 (d, J_{C-P} = 2.8 Hz), 136.7 (d, J_{C-P} = 3.6 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.13. IR (ATR technique, cm^{-1}): 3187, 2978, 1227, 1049, 1010, 952, 758, 693, 579. HRMS: calculated for $C_{19}H_{21}O_4P$ [M], [M+H] = 345.1255 and found 345.1313.

3.2.15. Diethyl 1-hydroxy-3-phenyl-1-p-tolylprop-2-ynylphosphonate (4b)

59% yield as a crystalline white solid; mp 118–119 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (3H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH}_3$), 1.28 (3H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH}_3$), 2.35 (3H, d, J_{C-P} = 1.6 Hz, –CH_3), 4.05–4.22 (4H, m, –$O\underline{CH}_2CH_3$), 4.66 (1H, d, J = 7.4 Hz, –OH), 7.18 (2H, d, J = 8.4 Hz), 7.28–7.38 (3H, m), 7.51 (2H, dd, J = 7.5 Hz and 1.9 Hz), 7.68 (2H, dd, J_{C-P} = 8.3 and 2.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P} = 5.6 Hz, –$OCH_2\underline{CH}_3$), 21.2 (–CH_3), 64.6 (t, J_{C-P} = 7.5 Hz, –$O\underline{CH}_2CH_3$), 71.4 (d, J = 167.4 Hz, quaternary C atom), 87.4, 88.0 (d, J_{C-P} = 9.5 Hz), 122.2 (d, J_{C-P} = 3.3 Hz) 126.7 (d, J_{C-P} = 4.2 Hz), 128.3, 128.7 (d, J_{C-P} = 2.5 Hz), 128.8, 132.0 (d, J_{C-P} = 2.6 Hz), 134.7 (d, J_{C-P} = 3.7 Hz), 138.0 (d, J_{C-P} = 3.1 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.96. IR (ATR technique, cm^{-1}): 3199, 2979, 1225, 1050, 1018, 952, 757, 691, 573. HRMS: calculated for $C_{20}H_{23}O_4P$ [M], [M+H] = 359.1412 and found 359.1481.

3.2.16. Diethyl 1-hydroxy-3-phenyl-1-o-tolylprop-2-ynylphosphonate (4c)

30% yield as a crystalline white solid; mp 111–112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (dt, 6H, J_{C-P} = 7.1 Hz and 16.0 Hz, –$OCH_2\underline{CH}_3$), 2.76 (d, J_{C-P} = 1.5 Hz, –CH_3), 3.65 (unresolved q, 1H, –OH), 3.92–4.25 (4H, m, –$O\underline{CH}_2CH_3$), 7.12–7.24 (m, 3H), 7.27–7.38 (3H, m), 7.47 (2H, dd, J = 7.5 and 1.9 Hz), 7.79–7.88 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P} = 5.5 Hz, –$OCH_2\underline{CH}_3$), 22.0 (–CH_3), 64.5 (dd, J_{C-P} = 7.5 Hz and 3.9 Hz, –$O\underline{CH}_2CH_3$), 71.8 (d, J_{C-P} = 166.7 Hz), 87.2 (d, J_{C-P} = 2.1 Hz), 88.7 (d, J_{C-P} = 9.5 Hz), 122.2 (d, J_{C-P} = 3.4 Hz), 125.5 (d, J_{C-P} = 2.3 Hz), 127.6 (d, J_{C-P} = 3.9 Hz), 128.3 (d, J_{C-P} =

2.8 Hz), 128.4, 128.9, 131.7 (d, J_{C-P} = 2.8 Hz), 132.4 (d, J_{C-P} = 2.2 Hz), 134.6 (d, J_{C-P} = 2.2 Hz), 137.4 (d, J_{C-P} = 5.0 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 17.43. IR (ATR technique, cm^{-1}): 3187, 2979, 1212, 1053, 1012, 947, 758, 694. HRMS: calculated for $C_{20}H_{23}O_4P$ [M], [M+H] = 359.1412 and found 359.1477.

3.2.17. Diethyl 1-hydroxy-1-(4-methoxyphenyl)-3-phenylprop-2-ynylphosphonate (4d)

39% yield as a crystalline white solid; mp 115–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (3H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH_3}$), 1.28 (3H, t, J_{C-P} = 7.1 Hz, –$OCH_2\underline{CH_3}$), 3.81 (s, 3H, –$O\underline{CH_3}$), 4.0–4.22 (4H, m, –$O\underline{CH_2}CH_3$), 4.24–4.40 (s (broad), 1H, –OH), 6.91 (d, J = 8.7 Hz, 2H), 7.28–7.38 (3H, m), 7.51 (2H, dd, J = 7.5 and 1.9 Hz), 7.72 (dd, 2H, J = 9.0 and 2.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P} = 4.2 Hz, –$OCH_2\underline{CH_3}$), 55.3 (–$O\underline{CH_3}$), 64.5 (dd, J_{C-P} = 7.3 and 2.6 Hz, –$O\underline{CH_2}CH_3$), 71.2 (d, J_{C-P} = 168.6 Hz, quaternary C atom), 87.2, 88.1 (d, J_{C-P} = 9.1 Hz), 113.4 (d, J_{C-P} = 2.2 Hz), 122.1 (d, J_{C-P} = 2.9 Hz), 128.2 (d, J_{C-P} = 4.0 Hz), 128.3, 128.9, 129.6, 131.9 (d, J_{C-P} = 2.7 Hz), 159.6 (d, J_{C-P} = 2.6 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 17.05. IR (ATR technique, cm^{-1}): 3199, 2980, 1225, 1051, 1015, 953, 758, 573. HRMS: calculated for $C_{20}H_{23}O_5P$ [M], [M+H] = 375.1361 and found 375.1426.

3.2.18. Diethyl 1-(4-fluorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate (4e)

68% yield as a crystalline white solid; mp 115–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (3H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH_3}$), 1.27 (3H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH_3}$), 4.04–4.22 (4H, m, –$O\underline{CH_2}CH_3$), 5.11 (1H, d, J_{C-P} = 6.3 Hz, –OH), 7.05 (2H, t, J = 8.6 Hz), 7.28–7.40 (3H, m), 7.51 (2H, dd, J = 7.7 and 1.7 Hz), 7.73–7.81 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P} = 6.3 Hz, –$OCH_2\underline{CH_3}$), 64.6 (dd, J_{C-P} = 9.4 and 7.5 Hz, –$O\underline{CH_2}CH_3$), 71.0 (d, J = 168.2 Hz, quaternary C atom), 87.0 (d, J_{C-P} = 1.1 Hz), 88.2 (d, J_{C-P} = 9.0 Hz), 114.6 (d, J = 2.3 Hz), 114.9.7 (d, J = 2.5 Hz), 122.0 (d, J = 3.0 Hz), 128.3, 128.8 (dd, J_{C-F} = 8.3 and J_{C-P} = 4.1 Hz), 129.0, 132.0 (d, J = 2.6 Hz), 133.7 (t, J = 3.3 Hz), 162.0 (dd, J_{C-F} = 249.7 Hz and J_{C-P} =3.4 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 15.84. IR (ATR technique, cm^{-1}): 3203, 2981, 1233, 1050, 1017, 951, 762, 695, 572. HRMS: calculated for $C_{19}H_{20}FO_4P$ [M], [M+H] = 363.1162 and found 363.1223.

3.2.19. Diethyl 1-(2-fluorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate (4f)

72% yield as a crystalline white solid; mp 122–123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.13 (3H, t, J_{C-P} = 7.0 Hz, –$OCH_2\underline{CH_3}$), 1.32 (3H, t, J_{C-P} = 7.1 Hz, –$OCH_2\underline{CH_3}$), 4.05–4.22 (2H, m, –$O\underline{CH_2}CH_3$), 4.31 (2H, p, J = 7.1 Hz, –$O\underline{CH_2}CH_3$), 5.2 (s (broad), 1H, –OH), 7.06 (1H, dd, J = 11.7 and 8.2 Hz), 7.16 (1H, t, J = 7.6 Hz), 7.22–7.37 (m, 4H), 7.51 (dd, 2H, J = 7.5 and 1.9 Hz), 7.78–7.87 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3 (dd, J_{C-P} = 13.8 and 5.8 Hz, –$OCH_2\underline{CH_3}$), 64.9 (dd, J_{C-P} = 12.3 and 7.3 Hz, –$O\underline{CH_2}CH_3$), 69.3 (dd, J_{C-P} = 168.2 Hz and J_{C-F} = 2.0 Hz, quaternary C atom), 85.8 (d, J_{C-P} = 2.7 Hz), 87.9 (dd, J_{C-P} = 9.3 and J_{C-F} = 2.5 Hz), 116.3 (dd, J_{C-F} = 22.9 and J_{C-P} =2.2 Hz), 122.2 (d, J = 3.1 Hz), 123.8 (t, J = 2.8 Hz), 125.0 (dd, J_{C-F} =9.3 Hz and J_{C-P} =2.7 Hz), 128.3, 128.8, 129.1 (dd, J_{C-F} =4.0 Hz and J_{C-F} =2.0 Hz), 130.1 (dd, J_{C-F} =8.6 and J_{C-P} =2.8 Hz), 131.8 (d, J = 2.7 Hz), 160.0 (dd, J_{C-F} = 251.0 and J_{C-P} =4.2 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.01. IR (ATR technique, cm^{-1}): 3189, 2979, 1224, 1051, 1015, 952, 760, 692. HRMS: calculated for $C_{19}H_{20}FO_4P$ [M], [M+H] = 363.1162 and found 363.1227.

3.2.20. Diethyl 1-(3-fluorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate (4g)

72% yield as a crystalline white solid; mp 113–114 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, t, J = 7.1 Hz, –$OCH_2\underline{CH}_3$), 1.28 (3H, t, J = 7.1 Hz, –$OCH_2\underline{CH}_3$), 4.05–4.27 (4H, m, –$O\underline{CH}_2CH_3$), 5.45–5.60 (s (broad), 1H, –OH), 7.01 (t, 1H, J = 8.3 Hz), 7.27–7.40 (4H, m), 7.47–7.63 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (dd, J = 10.5 and 5.6 Hz, –$OCH_2\underline{CH}_3$), 64.8 (dd, J = 7.4 and 14.4 Hz, –$OCH_2\underline{CH}_3$), 71.0 (d, J_{C-P} = 167.0 Hz, quaternary C atom), 86.8 (d, J_{C-P} = 1.3 Hz), 88.2 (d, J = 9.4 Hz), 114.6 (d, J = 3.8 Hz), 114.3 (d, J = 4.1 Hz), 114.9 (d, J = 2.7 Hz) 115.1 (d, J = 2.9 Hz), 121.9 (d, J = 3.1 Hz), 122.7 (d, J = 3.4 Hz), 128.4, 129.0, 129.3 (dd, J_{C-F} = 8.0 and J_{C-P} = 2.6 Hz), 132.0 (d, J = 2.6 Hz), 140.7 (dd, J_{C-F} = 7.5 and J_{C-P} = 3.6 Hz), 161.3 (dd, J_{C-F} = 242.0 and J_{C-P} =3.1 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.20. IR (ATR technique, cm^{-1}): 3186, 2977, 1226, 1015, 964, 759. HRMS: calculated for $C_{19}H_{20}FO_4P$ [M], [M+H] = 363.1162 and found 363.1226.

3.2.21. Diethyl 1-(4-chlorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate (4h)

52% yield as a crystalline white solid; mp 102–103 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, t, J = 7.0 Hz, –$OCH_2\underline{CH}_3$), 1.26 (3H, t, J = 7.1 Hz, –$OCH_2\underline{CH}_3$), 4.02–4.24 (4H, m, –$O\underline{CH}_2CH_3$), 5.34 (d, J = 5.9 Hz, –OH), 7.28–7.40 (m, 5H), 7.50 (2H, dd, J = 7.8 and 1.6 Hz), 7.73 (2H, dd, J = 8.8 and 2.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (dd, J_{C-P} = 8.5 and 5.7 Hz, –$OCH_2\underline{CH}_3$), 64.7 (dd, J_{C-P} = 14.2 and 7.5 Hz, –$O\underline{CH}_2CH_3$), 71.0 (d, J_{C-P} = 167.8 Hz, quaternary C atom), 86.8 (d, J_{C-P} = 1.52 Hz), 88.2 (d, J_{C-P} = 8.9 Hz) 121.9 (d, J_{C-P} = 3.0 Hz), 128.0 (d, J_{C-P} = 2.7 Hz), 128.4, 129.0, 132.0 (d, J_{C-P} = 2.8 Hz), 134.1 (d, J_{C-P} = 3.5 Hz), 136.6 (d, J_{C-P} = 3.6 Hz). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 15.60. IR (ATR technique, cm^{-1}): 3201, 2985, 1230, 1053, 1012, 949, 754, 688. HRMS: calculated for $C_{19}H_{20}ClO_4P$ [M], [M+H] = 379.0866 and found 379.0935.

3.2.22. Diethyl 1-(4-(trifluoromethyl)phenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate (4k)

60% yield as a crystalline white solid; mp 88–89 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, t, J = 7.1 Hz, –$OCH_2\underline{CH}_3$), 1.28 (3H, t, J = 7.1 Hz, –$OCH_2\underline{CH}_3$), 4.08–4.25 (4H, m, –$O\underline{CH}_2CH_3$), 5.59 (1H, d, J = 5.5 Hz, –OH), 7.3–7.4 (3H, m), 7.52 (2H, dd, J = 7.8 and 1.5 Hz), 7.62 (2H, d, J = 8.3 Hz), 7.92 (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3 (dd, J = 10.5 and 5.5 Hz, $OCH_2\underline{CH}_3$), 64.8 (dd, J = 16.4 and 7.5 Hz, $O\underline{CH}_2CH_3$), 71.2 (d, J = 166.7 Hz, quaternary C atom), 86.6 (d, J_{C-P} = 2.1 Hz), 88.3 (d, J_{C-P} = 9.2 Hz), 121.8 (d, J_{C-P} = 3.2 Hz), 121.4 (q, J_{C-F} = 272.0 Hz, –$\underline{C}F_3$), 124.8 (t, J = 3.2 Hz), 127.3, (d, J = 3.8 Hz), 128.3, 129.1, 129.9 (qd, J_{C-F} = 32.2 Hz and J_{C-P} = 2.9 Hz), 132.0 (d, J = 2.8 Hz), 142.2. ^{31}P NMR ($CDCl_3$, 161 MHz): δ 15.30. IR (ATR technique, cm^{-1}): 3180, 2988, 1227, 1067, 1018, 952, 755, 687. HRMS: calculated for $C_{20}H_{20}F_3O_4P$ [M], [M+H] = 413.1130 and found 413.1226.

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References

1. Auge, J.; Lubin-Germain N.; Seghrouchni, L. *Tetrahedron Lett.* **2003**, *44*, 819–821.
2. Cozzi, P. G.; Rudolph, J.; Bolm, C.; Norrby, P.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 5733–5736.
3. Niwa, S.; Soai, K. *J. Chem. Soc. Perkin Trans.* **1990**, *1*, 937–943.
4. Boobalan, R.; Chen, C.; Lee G. H. *Org. Biomol. Chem.* **2012**, *10*, 1625–1638 and the references related with the addition of alkyne to carbonyl compounds therein.
5. Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339–9341.
6. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
7. Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 15453–15456.
8. Ohshima, T.; Kawabata, T.; Takeuchi, Y.; Kakinuma, T.; Iwasaki, T.; Yonezawa, T.; Murakami, H.; Nishiyama, H.; Mashima, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 6296–6300.
9. Infante, R.; Gago, A.; Nieto, J.; Andres, C. *Adv. Synth. Catal.* **2012**, *354*, 2797–2804.
10. Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451–3453.
11. Aikawa, K.; Hioki, Y.; Mikami, K. *Org. Lett.* **2010**, *12*, 5716–5719.
12. Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem.* **2003**, *115*, 5647–5650.
13. Bauer, T.; Gajewiak, J. *Tetrahedron-Asymmetr.* **2005**, *16*, 851–855.
14. Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2232–2234.
15. Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc.* **1997**, *119*, 4080–4081.
16. Mata, Y.; Dieguez, M.; Pamies, O.; Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159–8165.
17. Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593–9596.
18. Haraguchi, K.; Kubota, Y.; Tanak, H. *J. Org. Chem.* **2004**, *69*, 1831–1836.
19. Pompliano, D. L.; Rands, E.; Schaber, M. D.; Mosser, S. D.; Anthony, N. J.; Gibbs, J. B. *Biochemistry* **1992**, *31*, 3800–3807.
20. Dellaria, J. F., Jr.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 534–542.
21. Tao, M.; Bihovsky, R.; Wells, G. J.; Mallamo, J. P. *J. Med. Chem.* **1998**, *41*, 3912–3916.
22. Asano, M.; Yukita, A.; Matsumoto, T.; Kondo, S.; Suzuki, H. *Cancer Res.* **1995**, *55*, 5296–5301.
23. Yokomatsu, T.; Hayakawa, Y.; Suemune, K.; Kihara, T.; Soed, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2833–2836.
24. Yokomatsu, T.; Abe, H.; Sato, M.; Suemune, K.; Kihara, T.; Soeda, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem.* **1998**, *6*, 2495–2505.
25. Ganzhorn, A. J.; Hoflack, J.; Pelton, P. D.; Strasser, F.; Chanal, M. C.; Piettre, S. R. *Bioorg. Med. Chem.* **1998**, *6*, 1865–1874.
26. Stowasser, B.; Budt, K. H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625–6628.
27. Seven, O.; Polat-Cakir, S.; Hossain, M. S.; Emrullahoglu, M.; Demir, A. S. *Tetrahedron* **2011**, *67*, 3464–3469.
28. Berlin, K. D.; Taylor, H. A. *J. Am. Chem. Soc.* **1964**, *86*, 3862–3866.
29. Hammerschmidt, F.; Schneyder, E.; Zbiral, E. *Chem. Ber.* **1980**, *113*, 3891–3897.
30. Mohammadhosseini, N.; Alipanahi, Z.; Alipour, E.; Emami, S.; Faramarzi, M. A.; Samadi, N.; Khoshnevis, N.; Shafiee, A.; Foroumadi, A. *DARU J. Pharm. Sciences* **2012**, *20*, 1–6.
31. Azerang, P.; Rezayan, A. H.; Sardari, S.; Kobarfard, F.; Bayat, M.; Tabib, K. *DARU J. Pharm. Sciences* **2012**, *20*, 1–5.
32. Bauer, A. W.; Kirby, W. M. M.; Sheris, J. C.; Truck, M. *Am. J. Clin. Pathol.* **1996**, *36*, 493–496.
33. Unsal, T. O.; Ozadali, K.; Yogeeswari, P.; Sriram, D.; Balkan, A. *Med. Chem. Res.* **2012**, *21*, 2388–2394.