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Reactions of acyl phosphonates with organoaluminum reagents: a new method for the synthesis of secondary and tertiary α-hydroxy phosphonates

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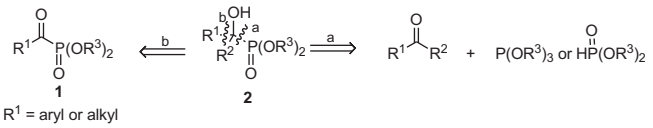
ABSTRACT

The reactions of organoaluminum reagents (trimethylaluminum, triethylaluminum, etc.) with aryl and alkyl acyl phosphonates, which lead to the formation of α-hydroxy phosphonates in moderate to good yields, are reported. This method provides easy access to secondary and tertiary α-hydroxy phosphonates depending on the reaction conditions. The reactions of triethylaluminum with a series of acyl phosphonates at 0 °C gave the secondary α-hydroxy phosphonates, while at −100 °C they afford the tertiary α-hydroxy phosphonates.

1. Introduction

α-Hydroxy phosphonates[1] are close analogs of α-hydroxy phosphonic acids, which are important compounds of a wide range of enzyme inhibitors, including farnesyl protein tranferase (FPT),[2] human renin,[3] human protein tyrosine phosphatase (PTP),[4] purine nucleoside phosphorylase (PNP),[5] and 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase.[6] They also show antiproliferative activity against several human cancer cell lines and[7a–e,8] human immunodeficiency virus (HIV).[8]

There are two routes that are most commonly used to synthesize α-hydroxy phosphonates, where either dialkyl phosphites are mostly added to an aldehyde known as Pudovik reaction or trialkyl phosphites are added to an aldehyde known as an Abramov reaction as shown in Scheme 1 path **a**. To date, the synthesis of tertiary α-hydroxy phosphonates has not received much attention. We are currently interested in acyl phosphonates,[9] which led us to investigate the synthesis of α-hydroxy phosphonates where our path **b**, as shown in Scheme 1, simply involves the addition of organoaluminum reagents to acyl phosphonates.



Scheme 1. Synthetic pathways for the synthesis of α-hydroxy phosphonates.

In order to synthesize the tertiary α-hydroxy phosphonates, Maeda et al.[10] have utilized the addition of Grignard and organolithium reagents to **1a** (Table 1, entry 1), but their chemical yields were very low. For instance, **2a** was obtained by the addition of MeMgBr to compound **1a** in around 50% yield while the addition of MeLi resulted in 0% yield. The reactions of either Grignard or organolithium reagents with benzoyl phosphonate gave the desired products, but in low yield or no product at all, suggesting these carbon-based nucleophiles are not reactive enough a good candidates for a carbon-based nucleophile are organoaluminum or organozinc reagents. It is known that organozinc reagents are very reactive and unstable and not easy to handle compared to organoaluminum reagents, which are commercially available and are excellent carbon-based nucleophiles due to high reactivity and great Lewis acidity of the metal center. Organoaluminum reagents are well known for their addition to carbonyl compounds for the synthesis of secondary and tertiary alcohols. Another advantage of using organoaluminum reagents is the possibility to use them in asymmetric synthesis.[11]

Herein, we report a new method for the synthesis of tertiary and secondary α-hydroxy phosphonates. Acyl phosphonates (entries **1a**–**i**) were treated with trialkyaluminum and trialkynylaluminum reagents to afford α-hydroxy phosphonates in moderate to good yields.

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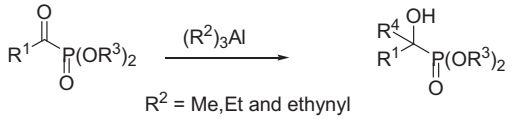
Table 1
Addition of $(R^2)_3Al$ to acyl phosphonates



1
R^1 = Aryl and alkyl
R^3 = Me, Et

2
R^1 = Aryl and alkyl
R^3 = Me, Et
R^4 = H, Me, Et and ethynyl

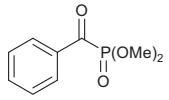
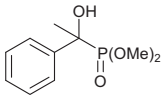
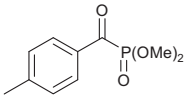
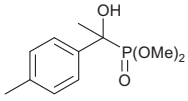
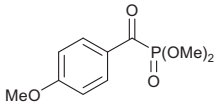
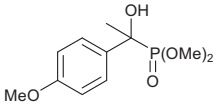
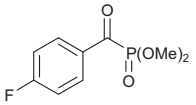
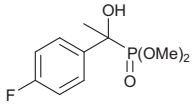
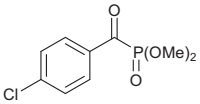
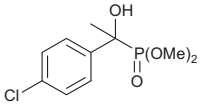
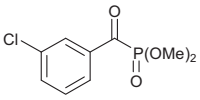
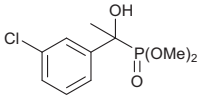
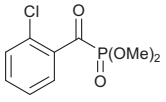
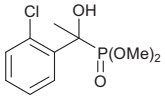
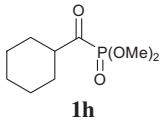
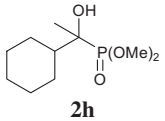
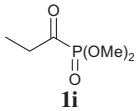
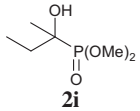
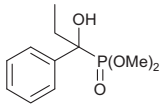
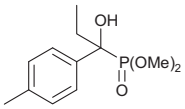
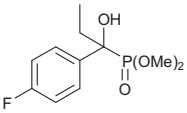
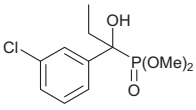
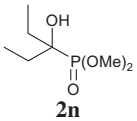
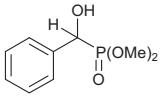
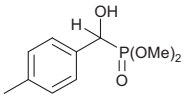
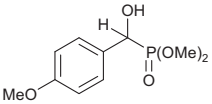
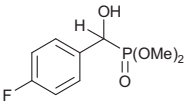
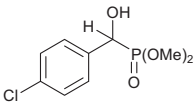
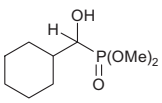
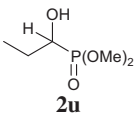
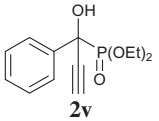
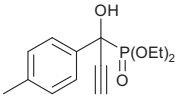
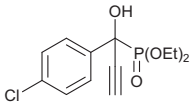
Entry	Acyl phosphonate	Product	Yield[a] (%)
1	 **1a**	 **2a**	85
2	 **1b**	 **2b**	83
3	 **1c**	 **2c**	77
4	 **1d**	 **2d**	72
5	 **1e**	 **2e**	64
6	 **1f**	 **2f**	73
7	 **1g**	 **2g**	77
8	 **1h**	 **2h**	78
9	 **1i**	 **2i**	63
10	**1a**, R^3=Me	 **2j**	44

Table 1 (*continued*)

Entry	Acyl phosphonate	Product	Yield[a] (%)
11	**1b**, R^3=Me	 **2k**	35
12	**1d**, R^3=Me	 **2l**	10
13	**1f**, R^3=Me	 **2m**	32
14	**1i**, R^3=Me	 **2n**	9
15	**1a**, R^3=Me	 **2o**	75
16	**1b**, R^3=Me	 **2p**	81
17	**1c**, R^3=Me	 **2q**	80
18	**1d**, R^3=Me	 **2r**	56
19	**1e**, R^3=Me	 **2s**	58
20	**1h**, R^3=Me	 **2t**	85
21	**1i**, R^3=Me	 **2u**	48
22	**1a**, R^3=Et	 **2v**	67

(*continued on next page*)

Table 1 (*continued*)

Entry	Acyl phosphonate	Product	Yield[a] (%)
23	**1b**, R^3=Et	 **2w**	57
24	**1e**, R^3=Et	 **2x**	44

[a] Yields refer to purified compounds.

2. Results and discussion

Acyl phosphonates **1a**–**i** were easily prepared by following the procedure described in the literature by the addition of trimethyl phosphites to either aryl or alkyl chlorides at 0 °C, which is known as a Michaelis–Arbuzov reaction.[12]

With these organonoaluminum reagents, most of the time stronger coordinating solvents, such as Et_2O or THF rather than toluene and CH_2Cl_2, are used to help breaking the dimeric species of trialkyaluminum reagents to increase its reactivity. In the 1,2-addition reaction of the trimethylaluminum reagent to benzoyl phosphonate **1a**, we have first screened the following solvents; THF, toluene, CH_2Cl_2, and hexane at 0 °C. Among these solvents, toluene gave the best results in terms of yield and afforded the α-hydroxy phosphonates, thus we then used toluene as our reaction solvent in subsequent trials. Secondly, we have screened the number of equivalents of the Me_3Al reagent and found that 3 equiv of Me_3Al reagent were necessary to give the desired compound **2a** in good yield.

Encouraged by the result obtained with benzoyl phosphonate **1a**, we investigated the 1,2-addition reactions of trimethylaluminum reagents with a variety of other benzoyl phosphonates, most of which gave tertiary α-hydroxy phosphonates in good yields (entries 1–9). When the electron donation was increased from $-CH_3$ to $-OMe$, the reactivity was reduced and the yields are lowered (entries 2 and 3, Table 1). When the −F and −Cl were used on the *para* position of benzoyl phosphonate, the compounds **2d** and **2e** were obtained in 72% and 64% yields, respectively. A fluorine substituent on the benzoyl phosphonate can either decrease the electron density by removing the electrons from the system inductively or increase the electron density by donating electrons to the system through resonance. Based on our experimental results by comparing the yield with −Cl substituted benzoyl phosphonate, it decreases the electron density of benzoyl phosphonate and acts as an electron withdrawing group and gives better yield in the addition reaction of a trimethylaluminum reaction. The reactions of 3-chloro benzoyl phosphonate **1f** and 2-chloro benzoyl phosphonate **1g** with Me_3Al were smooth to afford compounds **2f** (73%) and **2g** in good yield (77%). The reactions of Me_3Al with alkyl phosphonates **1h** and **1i** (entries 8 and 9) proceeded efficiently again to afford the compounds **2h** and **2i** in 78% and 63% yields.

Our next attempt was to use the Et_3Al reagent as an ethyl donor in the 1,2-addition reactions of acyl phosphonates (Table 1, entries 10–14). At 0 °C the addition of Et_3Al to benzoyl phosphonate **1a** solely gave the hydride-donor product **2o**. Then, we scrutinized the addition reactions of Et_3Al to different acyl phosphonates at 0 °C in order to obtain secondary α-hydroxy phosphonates. In all cases (entries 15–21), secondary α-hydroxy phosphonate derivatives were isolated in moderate yields. After decreasing the temperature from 0 °C to −100 °C, we were able to increase the yield of **2j** from 0% to 44% (entry 10). The reactions of Et_3Al at −100 °C were also examined with both substituted benzoyl phosphonates and alkyl phosphonates (entries 10–14) to afford tertiary α-hydroxy phosphonates, albeit in low yields.

$Al(i\text{-}bu)_3$ was also used as an alkylating agent in the 1,2-addition reaction of dimethyl benzoyl phosphonate **1a**. As we expected, only the hydride-donor product-secondary α-hydroxy phosphonate **2o** was obtained in 67% yield.[13] When the reaction was repeated at −100 °C instead of at 0 °C, the yield drop to 32%.

We also attempted to carry out the alkynylation of acyl phosphonates by using the triethynylaluminum reagent, which was prepared by following the literature procedure.[14] After the optimization of the reaction condition, we found that it is necessary to use 3 equiv of triethynylaluminum reagent at 0 °C just like the addition of the trialkylaluminum reagent. As shown in the table (entries 22–24), the desired α-hydroxy phosphonates were obtained in moderate yields.

3. Conclusion

In summary, we have reported 1,2-addition of commercially available trimethylaluminum reagent to a series of substituted benzoyl phosphonates and alkyl phosphonates for the syntheses of tertiary α-hydroxy phosphonates in good to moderate yields without the cleavage of the phosphonate group. Depending on the reaction temperature, we were able to obtain both secondary and tertiary α-hydroxy phosphonates, i.e., secondary α-hydroxy phosphonates (hydride addition product) at 0 °C in good yields and tertiary α-hydroxy phosphonates (ethylation product) at −100 °C albeit in low yields. Alkynylation of acyl phosphonates by using triethynylaluminum reagent were also performed and the desired α-hydroxy phosphonates were obtained in moderate yields. This method provides a convenient access to synthesize secondary and tertiary α-hydroxy phosphonates in terms of yields, short reaction time, and easy preparation of various acyl phosphonates via a Michaelis–Arbuzov reaction and the commercial availability of trialkylaluminum reagents. Efforts toward the asymmetric syntheses of these α-hydroxy phosphonates by using organoaluminum reagents are currently in progress.

4. Experimental section

4.1. General methods

Reactions sensitive to air and moisture were performed under argon. 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. TLC plates were initially visualized by UV light source, and then dipped into an ethanolic solution of phosphomolybdic acid. Flash column chromatography was performed using 230–400-mesh silica gel using ethyl acetate/hexane mixture as 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. Both ^1H NMR and ^{13}C NMR spectra were obtained in chloroform-*d*. ^1H NMR chemical shifts were reported in parts per million, and tetramethylsilane was used as an internal reference. ^{13}C NMR chemical shifts were reported in parts per million and the chloroform solvent signals were used as an internal reference. Triethynylaluminum reagent was prepared by following to literature procedure.[14] Aryl and alkyl acyl phosphonates were synthesized according to literature procedure.[12]

4.2. General procedure (a)

To a solution of acyl phosphonate (1 equiv) in dry toluene (0.5 M) at 0 °C under argon atmosphere was added trimethylaluminum (3 equiv, 2 M solution in heptane) dropwise. After stirring for 10 min at the same temperature, the reaction mixture was cautiously hydrolyzed with water (warning: these hydrolyze are exothermic and are accompanied by gas evolution). The reaction mixture was filtrated over Celite and washed with ethyl acetate. After evaporation of solvent in vacuo, the crude product was purified by flash column chromatography on silica gel using ethyl acetate as the eluting solvent.

*4.2.1. Dimethyl 1-hydroxy-1-phenylethylphosphonate (**2a**).* Yield 85%, crystalline white solid (mp: 142–143 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.75 (d, 3H, J=15.7 Hz, $-CH_3$), 3.56 (d, 3H, J=10.3 Hz, $(CH_3O)_2P$), 3.66 (d, 3H, J=10.2 Hz, $(CH_3O)_2P$), 4.40 (d, 1H, J=4.7 Hz, –OH), 7.17–7.21 (1H, m), 7.27 (2H, t, J=7.5 Hz), 7.51–7.54 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.8 (d, J_{C-P}=3.8 Hz, $-CH_3$), 53.7 (d, J_{C-P}=7.8 Hz, $(CH_3O)_2P$), 54.1 (d, J_{C-P}=7.3 Hz, $(CH_3O)_2P$), 73.6 (d, J_{C-P}=159.1 Hz, quaternary *C*-atom in –C(OH)), 125.8 (d, J_{C-P}=4.4 Hz), 127.4 (d, J_{C-P}=2.9 Hz), 128.0 (d, J_{C-P}=2.3 Hz), 141.0 (d, J_{C-P}=0.9 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.18; IR (ATR technique, cm^{-1}): 3278, 2980, 1447, 1225, 1202, 1186, 1055, 1023; HRMS: calculated for $C_{10}H_{15}O_4P$ 230.0708 and found 230.0715.

*4.2.2. Dimethyl 1-hydroxy-1-p-tolylethylphosphonate (**2b**).* Yield 83%, crystalline white solid (mp: 156–157 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (3H, d, J=15.5 Hz), 2.28 (3H, s), 3.54 (3H, d, J=10.2 Hz), 3.67 (3H, d, J=10.2 Hz), 7.10 (2H, d, J=8.2 Hz), 7.40 (2H, dd, J=2.2, 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 25.9 (d, J=3.8 Hz), 53.7 (d, J=7.6 Hz), 54.0 (d, J=8.0 Hz), 73.6 (d, J=159.6 Hz), 125.7 (d, J=4.4 Hz), 128.8, 137.0, 138.0 (d, J=8.4 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.38; IR (ATR technique, cm^{-1}): 3265, 2980, 1451, 1410, 1224, 1203, 1185, 1124, 1099, 1017; HRMS: calculated for $C_{11}H_{17}O_4P$ 244.0864 and found 244.0865.

*4.2.3. Dimethyl 1-hydroxy-1-(4-methoxyphenyl) ethylphosphonate (**2c**).* Yield 77%, crystalline white solid (mp: 172–173 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.72 (3H, d, J=15.5 Hz), 3.25 (1H, d (broad), J=5.4 Hz), 3.54 (3H, d, J=10.2 Hz), 3.66 (3H, d, J=10.2 Hz), 3.74 (3H, s), 6.81 (2H, d, J=9.0 Hz), 7.43 (2H, dd, J=2.3 and 9.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.8 (d, J=4.5 Hz), 53.9 (t, J=7.4 Hz), 55.2, 73.4 (d, J=160.0 Hz), 113.5 (d, J=2.1 Hz), 127.0 (d, J=4.5 Hz), 132.7, 159.0 (d, J=2.7 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.46; IR (ATR technique, cm^{-1}): 3283, 2993, 1580, 1455, 1438, 1250, 1205, 1172, 1068, 1045, 1019; HRMS: calculated for $C_{11}H_{17}O_5P$ 260.0814 and found 260.0808.

*4.2.4. Dimethyl1-(4-fluorophenyl)-1-hydroxyethylphosphonate (**2d**).* Yield 72%, crystalline white solid (mp: 157–158 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.82 (3H, d, J=5.6 Hz), 3.66 (3H, d, J=10.3 Hz), 3.75 (3H, d, J=10.3 Hz), 4.44 (1H, d, J=4.8 Hz), 7.03 (2H, t, J=9.0 Hz), 7.59 (1H, ddd, J=9.0, 5.2, and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.9 (d, J=4.2 Hz), 53.8 (d, J=7.6 Hz), 54.2 (d, J=7.3 Hz), 73.3 (d, J=160.4 Hz), 114.8 (dd, J=21.4 and 2.3 Hz), 127.6 (dd, J=8.1 and 4.4 Hz), 136.7 (d, J=2.7 Hz), 160.9 (dd, J=246.3 and 3.2 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.96; IR (ATR technique, cm^{-1}): 3283, 2984, 1507, 1452, 1411, 1223, 1201, 1161, 1128, 1080, 1064, 1030; HRMS: calculated for $C_{10}H_{14}FO_4P$ 248.0614 and found 248.0615.

*4.2.5. Dimethyl 1-(4-chlorophenyl)-1-hydroxyethylphosphonate (**2e**).* Yield 64%, crystalline white solid (mp: 161–162 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (3H, d, J=15.6 Hz), 3.60 (3H, d, J=10.2 Hz), 3.68 (3H, d, J=10.2 Hz), 4.44 (1H, s (broad)), 7.25 (2H, d, J=8.5 Hz), 7.46 (2H, dd, J=2.3 and 8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.9 (d, J=3.8 Hz), 53.7 (d, J=7.9 Hz), 54.3 (d, J=7.0 Hz), 73.4 (d, J=159.8 Hz), 127.3 (d, J=4.3 Hz), 128.2 (d, J=2.4 Hz), 133.5 (d, J=3.3 Hz), 139.6; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.64; IR (ATR technique, cm^{-1}): 3266, 2950, 1489, 1225, 1203, 1182, 1090, 1071, 1030; HRMS: calculated for $C_{10}H_{14}ClO_4P$ (^{35}Cl-isotope) 264.0318 and found 264.0313.

*4.2.6. Dimethyl 1-(3-chlorophenyl)-1-hydroxyethylphosphonate (**2f**).* Yield 73%, crystalline white solid (mp: 136–137 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (3H, d, J=15.7 Hz), 3.63 (3H, d, J=10.3 Hz), 3.69 (3H, d, J=10.0 Hz), 7.17–7.23 (2H, m), 7.38–7.41 (1H, m), 7.54–7.56 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.84, 53.8 (d, J=7.9 Hz), 53.4 (d, J=7.8 Hz), 73.4 (d, J=159.9 Hz), 124.1 (d, J=4.1 Hz), 126.1 (d, J=4.4 Hz), 127.6 (d, J=1.9 Hz), 129.2 (d, J=2.1 Hz), 134.2, 143.3; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.51; IR (ATR technique, cm^{-1}): 3260, 2954, 1456, 1423, 1228, 1194, 1122, 1084, 1049; HRMS: calculated for $C_{10}H_{14}ClO_4P$ (^{35}Cl-isotope) 264.0318 and found 264.0321.

*4.2.7. Dimethyl 1-(2-chlorophenyl)-1-hydroxyethylphosphonate (**2g**).* Yield 77%, crystalline white solid (mp: 143–144 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.93 (3H, d, J=15.5 Hz), 3.64 (3H, d, J=10.3 Hz), 3.70 (3H, d, J=10.3 Hz), 7.12–7.22 (2H, m), 7.29 (1H, dd, J=1.1 and 7.6 Hz), 7.70 (1H, td, J=7.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0, 54.0 (t, J=5.9 Hz, –C=OPO(OCH_3)$_2$, both –OMe groups are overlapping), 75.1 (d, J=160.9 Hz), 126.7 (d, J=1.8 Hz), 129.0 (d, J=2.3 Hz), 129.7 (d, J=4.5 Hz), 131.8 (d, J=1.7 Hz), 132.0 (d, J=5.8 Hz), 137.7 (d, J=3.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.44; IR (ATR technique, cm^{-1}): 3260, 2954, 1456, 1423, 1228, 1194, 1122, 1084, 1049, 1021; HRMS: calculated for $C_{10}H_{14}ClO_4P$ (^{35}Cl-isotope) 264.0318 and found 264.0322.

*4.2.8. Dimethyl 1-cyclohexyl-1-hydroxyethylphoshonate (**2h**).* Yield 78%, crystalline white solid (mp: 82–83 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.97–1.17 (5H, m), 1.26 (3H, d, J=16.0 Hz), 1.60–1.90 (6H, m), 3.74 (6H, dt, J=1.6 and 10.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (d, J=4.2 Hz), 26.0 (d, J=8.2 Hz), 26.4 (d, J=4.0 Hz), 26.5, 27.8 (d, J=2.6 Hz), 44.5 (d, J=5.4 Hz), 53.0 (d, J=7.9 Hz), 53.6 (d, J=7.4 Hz), 75.3 (d, J=157.1 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.46; IR (ATR technique, cm^{-1}): 3319, 2994, 2849, 1146, 1224, 1190, 1077, 1054, 1028; HRMS: calculated for $C_{10}H_{21}O_4P$ 236.1170 and found 236.1172.

*4.2.9. Dimethyl 2-hydroxybutan-2-yl phosphonate (**2i**).* Yield 63%, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (3H, t, J=7.5 Hz), 1.30 (3H, d, J=16.0 Hz), 1.57–1.68 (1H, m), 1.71–1.84 (1H, m), 3.73 (3H, d, J=10.1 Hz), 3.72 (3H, d, J=10.1 Hz), 4.45 (1H, s (broad)); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.8 (d, J=8.6 Hz), 21.1 (d, J=4.7 Hz), 29.8 (d, J=5.3 Hz), 53.3 (t, J=6.2 Hz), 72.0 (d, J=161.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 30.03; IR (ATR technique, cm^{-1}): 3311, 2956, 1460, 1226, 1167, 1131, 1023; HRMS: calculated for $C_6H_{15}O_4P$ 182.0708 and found 182.0701.

4.3. General procedure (b)

To a solution of acyl phosphonate (1 equiv) in dry toluene (0.5 M) at –100 °C under argon atmosphere was added triethylaluminum (3 equiv, 1 M solution in heptane) dropwise. After stirring for 10 min at the same temperature, the reaction mixture was cautiously hydrolyzed with water. The reaction mixture was filtrated over Celite and washed with ethyl acetate. After evaporation of solvent in vacuo, the crude product was purified by flash column chromatography on silica gel using ethyl acetate as the eluting solvent.

*4.3.1. Dimethyl 1-hydroxy-1-phenylpropylphosphonate (**2j**).* Yield 44%, crystalline white solid (mp: 120–121 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.71 (t, J=7.4 Hz, 3H), 2.05–2.62 (m, 2H), 3.48 (d, J=10.2 Hz, 3H), 3.68 (d, J=10.2 Hz, 3H), 7.20–7.24 (m, 1H), 7.29 (t

(broad), J=8.1 Hz, 2H), 7.48–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.2 (d, J=11.0 Hz), 30.4 (d, J=4.5 Hz), 53.7 (d, J=7.4 Hz), 54.0 (d, J=7.6 Hz), 76.9 (d, J=157.0 Hz), 126.1 (d, J=4.5 Hz), 127.4 (d, J=3.0 Hz), 128.1 (d, J=2.6 Hz), 138.1; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.23; IR (ATR technique, cm^{-1}): 3283, 2968, 2938, 1220, 1058, 1020, 833; HRMS: calculated for $C_{11}H_{17}O_4P$ 244.0864 and found 244.0858.

*4.3.2. Dimethyl 1-hydroxy-1-p-tolylpropylphosphonate (**2k**).* Yield 35%, crystalline white solid (mp: 114–115 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77 (t, J=7.4 Hz, 3H), 2.11–2.31 (m, 2H), 2.34 (d, J=1.7 Hz, 3H), 3.05 (d, J=5.8 Hz, 1H), 3.55 (d, J=10.2 Hz, 3H), 3.74 (d, J=10.2 Hz, 3H), 7.18 (d, J=8.3 Hz, 2H), 7.45 (dd, J=8.3, 2.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.1 (d, J=11.0 Hz), 21.0, 30.1 (d, J=4.3 Hz), 53.7 (d, J=7.6 Hz), 53.9 (d, J=7.6 Hz), 76.7 (d, J=157.7 Hz), 126.0 (d, J=4.6 Hz), 128.8 (d, J=2.4 Hz), 135.1, 136.9 (d, J=3.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.32; IR (ATR technique, cm^{-1}): 3253, 2977, 2951, 1220, 1054, 1022; HRMS: calculated for $C_{12}H_{19}O_4P$ 258.1021 and found 258.1014.

*4.3.3. Dimethyl 1-(4-fluorophenyl)-1-hydroxypropylphosphonate (**2l**).* Yield 10%, crystalline white solid (mp: 153–155 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77 (d, J=7.3 Hz, 3H), 2.28–2.09 (m, 2H), 3.0 (d, J=5.3 Hz, 1H), 3.56 (d, J=10.2 Hz, 3H), 3.75 (d, J=10.2 Hz, 3H), 7.04 (t, J=8.4 Hz, 2H), 7.54 (dtd, J=7.8, 5.3, 2.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.2 (d, J=10.8 Hz), 30.5 (d, J=4.9 Hz), 53.8 (d, J=7.4 Hz), 53.9 (d, J=7.6 Hz), 76.5 (d, J=146.9 Hz), 114.9 (dd, J=21.3, 2.7 Hz), 128.0 (dd, J=7.8, 4.6 Hz), 134.0 (d, J=3.2 Hz), 162.2 (d, J=250.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.96; IR (ATR technique, cm^{-1}): 3246, 2956, 2923, 1507, 1221, 1047, 1012, 812; HRMS: calculated for $C_{11}H_{16}FO_4P$ 262.0770 and found 262.0764.

*4.3.4. Dimethyl 1-(3-chlorophenyl)-1-hydroxypropylphosphonate (**2m**).* Yield 32%, crystalline white solid (mp: 129–130 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.74 (t, J=7.4 Hz, 3H), 2.13–2.24 (m, 2H), 3.67 (d, J=10.3 Hz, 3H), 3.76 (d, J=10.2 Hz, 3H), 4.16 (d, J=2.2 Hz, 1H), 7.27–7.23 (m, 2H), 7.43 (ddd, J=7.5, 4.0, 2.0 Hz, 1H), 7.58 (dd, J=4.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.2 (d, J=11.5 Hz), 30.2 (d, J=4.1 Hz), 53.8 (d, J=7.7 Hz), 54.1 (d, J=7.7 Hz), 75.7, 124.4 (d, J=4.2 Hz), 126.6 (d, J=4.6 Hz), 127.4 (d, J=2.9 Hz), 129.2 (d, J=2.7 Hz), 134.3 (d, J=2.7 Hz), 141.0; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.42; IR (ATR technique, cm^{-1}): 3241, 2956, 1413, 1223, 1189, 1058, 1026, 777; HRMS: calculated for $C_{11}H_{16}ClO_4P$ 278.0475 and found 278.0471.

*4.3.5. Dimethyl 3-hydroxypentan-3-ylphosphonate (**2n**).* Yield 9%, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J=7.5 Hz, 6H), 1.62–1.78 (m, 4H), 2.30 (d, J=3.7 Hz, 1H), 3.74 (d, J=10.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.3 (d, J=5.6 Hz), 27.2 (d, J=4.8 Hz), 53.2 (d, J=5.7 Hz), 75.4 (d, J=157.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 30.03; IR (ATR technique, cm^{-1}): 3309, 2981, 2955, 1460, 1219, 1027, 823; HRMS: calculated for $C_7H_{17}O_4P$ 196.0864 and found 196.0867.

4.4. General procedure (c)

To a solution of acyl phosphonate (1 equiv) in dry toluene (0.5 M) at 0 °C under argon atmosphere was added triethylaluminum (3 equiv, 1 M solution in heptane) dropwise. After the completion of reaction in 10 min, 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. After evaporation of solvent in vacuo, the crude product was purified by flash column chromatography on silica gel using ethyl acetate as the eluting solvent.

*4.4.1. Dimethyl hydroxy(phenyl)methylphosphonate (**2o**).* Yield 75%, crystalline white solid (mp: 106–107 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.66 (3H, d, J=10.3 Hz), 3.70 (3H, d, J=10.3 Hz), 5.03 (1H, d, J=10.9 Hz), 7.28–7.37 (3H, m), 7.47–7.48 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 53.5 (d, J=7.5 Hz), 53.9 (d, J=6.4 Hz), 70.7 (d, J=159.1 Hz), 127.1 (d, J=5.9 Hz), 128.2 (d, J=2.8 Hz), 128.4 (d, J=2.1 Hz), 136.5; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 22.92; IR (ATR technique, cm^{-1}): 3258, 2956, 1192, 1049, 1023, 774; HRMS: calculated for $C_9H_{13}O_4P$ 216.0551 and found 216.0547.

*4.4.2. Dimethyl hydroxy(p-tolyl)methylphosphonate (**2p**).* Yield 81%, crystalline white solid (mp: 102–103 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (3H, d, J=1.7 Hz), 3.66 (3H, d, J=10.3 Hz), 3.71 (3H, dd, J=10.3 Hz), 4.16 (1H, dd, J=8.7 and 5.7 Hz), 4.98 (1H, dd, J=10.5 and 5.1 Hz), 7.16 (2H, J=8.0 Hz), 7.35 (2H, dd, J=8.0 and 2.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 53.4 (d, J=7.3 Hz), 53.7 (d, J=6.7 Hz), 70.1 (d, J=161.1 Hz), 126.9 (d, J=6.0 Hz), 128.8 (d, J=2.2 Hz), 133.5, 137.6 (d, J=3.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 23.91; IR (ATR technique, cm^{-1}): 3258, 2957, 1204, 1046, 1022, 818; HRMS: calculated for $C_{10}H_{15}O_4P$ 230.0708 and found 230.0708.

*4.4.3. Dimethyl hydroxy(4-methoxyphenyl)methylphosphonate (**2q**).* Yield 80%, crystalline white solid (mp: 94–95 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.58 (3H, d, J=10.3 Hz), 3.63 (3H, d, J=10.3 Hz), 3.73 (3H, s), 4.90 (1H, d, J=10.2 Hz), 6.81 (2H, d, J=8.5 Hz), 7.33 (2H, dd, J=8.5 and 2.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 53.5 (d, J=7.3 Hz), 53.8 (d, J=7.1 Hz), 55.1, 70.1 (d, J=162.0 Hz), 113.8 (d, J=1.5 Hz), 128.4 (d, J=6.2 Hz), 128.5 (d, J=1.0 Hz), 159.5 (d, J=1.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 24.06; IR (ATR technique, cm^{-1}): 3258, 2956, 1205, 1190, 1047, 1022, 833, 774; HRMS: calculated for $C_{10}H_{15}O_5P$ 246.0657 and found 246.0658.

*4.4.4. Dimethyl (4-fluorophenyl)(hydroxy)methylphosphonate (**2r**).* Yield 56%, crystalline white solid (mp: 97–98 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.17 (1H, dd, J=9.2 and 4.6 Hz), 3.69 (3H, d, J=10.4 Hz), 3.72 (3H, d, J=10.4 Hz), 5.03 (1H, dd, J=10.2 and 3.8 Hz), 7.06 (2H, t, J=8.4 Hz), 7.45–7.49 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 53.5 (d, J=7.4 Hz), 54.0 (d, J=6.9 Hz), 69.9 (d, J=161.0 Hz), 115.3 (d, J=2.3 Hz), 128.8 (d, J=6.0 Hz), 128.9 (d, J=6.0 Hz), 132.4, 160.6 (dd, J=246.6 and 3.5 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 23.25; IR (ATR technique, cm^{-1}): 3258, 2956, 1205, 1047, 1022, 833, 790; HRMS: calculated for $C_9H_{12}FO_4P$ 234.0457 and found 234.0454.

*4.4.5. Dimethyl (4-chlorophenyl)(hydroxy)methylphosphonate (**2s**).* Yield 58%, crystalline white solid (mp: 104–105 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.63 (3H, d, J=10.3 Hz), 3.64 (3H, d, J=10.3 Hz), 4.95 (1H, d, J=11.0 Hz), 7.25 (2H, d, J=8.3 Hz), 7.34 (2H, dd, J=8.3 and 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 53.6 (d, J=7.4 Hz), 54.1 (d, J=7.1 Hz), 69.9 (d, J=160.0 Hz), 128.4 (d, J=5.8 Hz), 128.5 (d, J=2.5 Hz), 134.0 (d, J=3.7 Hz), 135.1 (d, J=1.2 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 22.58; IR (ATR technique, cm^{-1}): 3258, 2956, 1204, 1191, 1047, 1022, 833, 773; HRMS: calculated for $C_9H_{12}ClO_4P$ 250.0162 and found 250.0158.

*4.4.6. Dimethyl cyclohexanecarbonylphosphonate (**2t**).* Yield 85%, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04–1.27 (5H, m), 1.58–1.69 (5H, m), 1.93 (1H, d (broad), J=11.8 Hz), 3.11 (1H, s (broad)), 3.63 (1H, d (broad), J=5.2 Hz), 3.72 (3H, d, J=3.0 Hz), 3.75 (3H, d, J=3.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.0, 26.2 (d, J=2.7 Hz), 27.8 (d, J=7.4 Hz), 29.8 (d, J=8.8 Hz), 39.7 (d, J=1.9 Hz), 52.9 (d, J=6.9 Hz), 53.1 (d, J=7.3 Hz), 72.4 (d, J=156.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.58; IR (ATR technique, cm^{-1}): 3262, 2923, 2851, 1210, 832; HRMS: calculated for $C_9H_{19}O_4P$ 222.1021 and found 222.1023.

*4.4.7. Dimethyl 1-hydroxypropylphosphonate (**2u**).* Yield 48%, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, J=7.4 Hz), 1.60–1.80 (2H, m), 3.73 (3H, d, J=10.3 Hz), 3.74 (3H, d, J=10.3 Hz), 4.46 (1H, dd, J=6.7 and 2.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.3

(d, J=13.6 Hz), 24.7 (d, J=1.2 Hz), 53.0 (d, J=7.3 Hz), 53.2 (d, J=7.2 Hz), 69.0 (1H, d, J=160.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 27.71; IR (ATR technique, cm^{-1}): 3259, 2956, 1205, 1046, 1022, 833, 774; HRMS: calculated for $C_5H_{13}O_4P$ 168.0551 and found 168.0548.

4.5. General procedure (d)

Triethynylaluminum reagent was prepared by following a literature procedure.[14] Freshly prepared triethynylaluminum reagent (3 equiv) was added to a solution of acyl phosphonate (1 equiv) in dry toluene (0.25 M) at 0 °C. After stirring for 15–30 min, the reaction mixture was carefully quenched with water and then filtrated over Celite. The solvent was evaporated and crude product was purified by flash column chromatography to afford corresponding α-hydroxy phosphonates.

*4.5.1. Diethyl 1-hydroxy-1-phenylprop-2-ynylphosphonate (**2v**).* Yield 67%, crystalline white solid (mp: 112–113 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (3H, dt, J=5.6 and 0.6 Hz), 1.28 (3H, dt, J=5.6 and 0.6 Hz), 2.82 (1H, d, J=5.3 Hz), 3.89 (1H, d, J=8.5 Hz), 4.16–4.01 (4H, m), 7.40–7.30 (3H, m), 7.74–7.71 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3 (d, J=2.5 Hz), 16.4 (d, J=2.7 Hz), 64.6 (t, J=6.3 Hz), 71.0 (d, J=166.4 Hz), 76.5 (d, J=9.2 Hz), 82.1 (d, J=1.7 Hz), 126.7 (d, J=4.0 Hz), 127.9 (d, J=2.5 Hz), 128.4 (d, J=2.9 Hz), 136.9 (d, J=3.8 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.49; IR (ATR technique, cm^{-1}): 3246, 3188, 2993, 1234, 1004, 972, 950, 699; HRMS: calculated for $C_{13}H_{17}O_4P$ 268.0864 and found 268.0859.

*4.5.2. Diethyl 1-hydroxy-1-p-tolylprop-2-ynylphosphonate (**2w**).* Yield 57%, crystalline white solid (mp: 96–98 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (3H, t, J=7.0 Hz), 1.22 (3H, t, J=7.0 Hz), 2.29 (3H, d, J=1.6 Hz), 2.72 (1H, d, J=5.3 Hz), 4.09–3.96 (4H, m), 4.13 (d, J=8.1 Hz, 1H), 7.09 (d, J=8.3 Hz, 2H), 7.51 (dd, J=2.2 and 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.36 (d, J=2.8 Hz), 16.4 (d, J=2.6 Hz), 21.0, 64.4 (d, J=7.3 Hz), 70.8 (d, J=167.2 Hz), 76.3 (d, J=9.2 Hz), 82.2, 126.6 (d, J=4.0 Hz), 128.6 (d, J=2.4 Hz), 134.0 (d, J=3.8 Hz), 138.0 (d, J=3.8 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.72; IR (ATR technique, cm^{-1}): 3275, 3255, 3214, 2961, 2925, 1073, 1011, 961, 799; HRMS: calculated for $C_{14}H_{19}O_4P$ 282.1021 and found 282.1021.

*4.5.3. Diethyl 1-(4-chlorophenyl)-1-hydroxyprop-2-ynylphosphonate (**2x**).* Yield 44%, crystalline white solid (mp: 105–107 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (6H, q (broad), J=7.4 Hz), 2.74 (1H, d, J=5.3 Hz), 4.12–4.00 (4H, m), 4.29 (1H, d (broad), J=7.0 Hz), 7.27 (2H, d, J=8.4 Hz), 7.58 (2H, dd, J=8.4 and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.29 (d, J=3.7 Hz), 16.3 (d, J=3.6 Hz), 64.7 (d, J=7.4 Hz), 70.6 (d, J=166.7 Hz), 76.8 (d, J=9.1 Hz), 81.6 (d, J=1.2 Hz), 128.1 (d, J=2.6 Hz), 128.2, 134.4 (d, J=4.0 Hz), 135.6 (d, J=3.4 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.09; IR (ATR technique, cm^{-1}): 3289, 3212, 2924, 1236, 1006, 946; HRMS: calculated for $C_{13}H_{16}ClO_4P$ 302.0475 and found 302.0471.

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Supplementary data

The copies of ^{1}H, ^{13}C, and ^{31}P NMR and HRMS spectra of these synthesized compounds are presented. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.036. This data includes MOL file and InChIKey of the most important compound described in this article.

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