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Efficient one-pot synthesis of β-hydroxyphosphonates: regioselective nucleophilic ring opening reaction of epoxides with triethyl phosphite catalyzed by $Al(OTf)_3$

Sara Sobhani *, Asieh Vafaee

Department of Chemistry, College of Sciences, Birjand University, Birjand 414, Iran

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ABSTRACT

A variety of β-hydroxyphosphonates were produced in high yields by ring opening reaction of different types of epoxides with di/trialkyl phosphite esters catalyzed by $Al(OTf)_3$. The reactions proceeded with complete chemo- and regioselectivity to give the title compounds. This method is new, simple and efficient for the one-pot synthesis of β-hydroxyphosphonates via direct C–P bond formation.

1. Introduction

Amongst phosphonates, β-hydroxyphosphonates are an important class of compounds. They exhibit a variety of interesting and useful properties that make them attractive as herbicides, antibiotics, pesticides, antioxidants and horticulture agents.[1–6] Many of these diverse properties have been attributed to the relatively inert nature of the C–P bond and to the physical and structural similarity of phosphonic and phosphinic acids to the biologically important phosphate ester and carboxylic acid functional groups.[7] Furthermore, β-hydroxyphosphonates serve as precursors for the preparation of different types of phosphonate derivatives such as: α,β-unsaturated,[8] β-azido-,[9] β-amino-,[9] β-tosyloxy-,[10] and β-acyloxyphosphonates.[11] β-Acyloxyphosphonates have been also used as intermediates in the synthesis of optically active β-hydroxyphosphonates by enzymetic hydrolysis.[12]

There are several multistep approaches for the synthesis of β-hydroxyphosphonates: a) reduction of β-ketophosphonates,[13–18] b) oxidation of the β-H in alkylphosphonates,[19] c) hydrolysis of acyl derivatives,[20] d) reaction of some Grignard reagents with β-ketophosphonates[21] and e) Reformatsky-type addition of α-halophosphonates to carbonyl compounds.[22–24] β-Hydroxyphosphonates can also be prepared by one-pot reaction via direct C–P bond formation of phosphite esters with epoxides in the presence of acids or bases. These methods are similar to Arbuzov reaction of alkyl halides with phosphite esters.[25] However, a few reported methods exist for the one-pot synthesis of β-hydroxyphosphonates[26–32] and all of these methods suffer from at least one of the following drawbacks: low yields,[26] the use of excess of epoxides,[27] miosture sensitive catalysts or reagents,[28–32] drastic reaction conditions,[28] strong bases,[29] stoichiometric amounts of the catalyst[30–32] and the formation of by-products (e.g. cyclopropane or olefin).[26,33]

In recent years, we have focused our attention on the development of useful methods for the synthesis of phosphonate derivatives.[34–39] In this connection, we have found that metal triflates [$M(OTf)_x$; M=Al, Li, Mg, Ce, Cu] are efficient catalysts for the synthesis of α-amino-, α-trimethylsilyloxy- and α-acyloxyphosphonates.[40–45] These observations prompted us to examine the catalytic efficiency of these metal triflates for the one-pot synthesis of β-hydroxyphosphonates by a ring opening reaction of epoxides with triethyl phosphite.

2. Results and discussion

At first, we examined the feasibility of the ring opening reaction of glycidyl phenyl ether (**1a**) with triethyl phosphite (molar ratio: 1/5) using metal triflates [$M(OTf)_x$; M=Al, Li, Mg, Ce, Cu] in *n*-hexane under reflux conditions. Amongst metal triflates tested, $Al(OTf)_3$ turned out to be the most effective catalyst for this purpose (Table 1, Entry 1). The desired product (**2a**) was obtained in lower yields and after longer reaction times, when 1 or 3 equiv of triethyl phosphite were used (Table 1, Entries 2 and 3). The reaction proceeded with low yields in solvents such as toluene, CCl_4, or CH_3CN under reflux conditions (Table 1, Entries 8–10). No yields were obtained when the reaction was carried out in CH_2Cl_2, Et_2O or acetone as solvent (Table 1, Entries 11–13). A similar reaction in the absence of solvent led to the formation of the desired product (**2a**) in low yield due to the formation of a mixture of by-products (Table 1, Entry 14).

In the next step, the applicability of this method for the ring opening reaction of various types of epoxides with triethyl phosphite using $Al(OTf)_3$ in *n*-hexane under reflux condition were investigated (Scheme 1). The results of these studies are summarized in Table 2.

* Corresponding author. Tel.: +98 561 2502008; fax: +98 561 2502009.
E-mail addresses: ssobhani@birjand.ac.ir, sobhanisara@yahoo.com (S. Sobhani).

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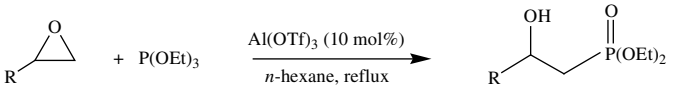
Table 1
Ring opening reaction of glycidyl phenyl ether with triethyl phosphite catalyzed by different metal triflates $M(OTf)_x$ [M=Al, Li, Mg, Ce, Cu]

Entry	Catalyst	Solvent	Temp.	Time (h)	Yield[a] (%)
1	$Al(OTf)_3$	*n*-hexane	Reflux	0.75	93
2	$Al(OTf)_3$	*n*-Hexane	Reflux	2	90[d]
3	$Al(OTf)_3$	*n*-hexane	Reflux	10	85[d]
4	LiOTf	*n*-Hexane	Reflux	10	8
5	$Mg(OTf)_2$	*n*-Hexane	Reflux	10	12
6	$Ce(OTf)_4$	*n*-Hexane	reflux	3	40
7	$Cu(OTf)_2$	*n*-Hexane	Reflux	18	0
8	$Al(OTf)_3$	Toluene	Reflux	72	20
9	$Al(OTf)_3$	CCl_4	Reflux	72	10
10	$Al(OTf)_3$	CH_3CN	Reflux	72	40
11	$Al(OTf)_3$	CH_2Cl_2	rt	24	0[c]
12	$Al(OTf)_3$	Et_2O	rt	24	0[c]
13	$Al(OTf)_3$	Acetone	rt	24	0[c]
14	$Al(OTf)_3$	—	80 °C	0.25	40[b]

[a] Isolated yield. Conditions: triethyl phosphite (5 equiv, except for entries 2 and 3), catalyst (10 mol %).
[b] Conversion of epoxide was 100% but desired product besides a mixture of by-products were formed.
[c] 100% Consumption of epoxide was observed but a mixture of by-products were formed.
[d] Conditions: triethyl phosphite (3 and 1 equiv for entries 2 and 3, respectively).



1a-h **2a-h**

Scheme 1. $Al(OTf)_3$ catalyzed ring opening reaction of epoxides with triethylphosphite.

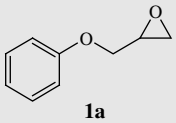
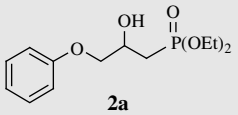
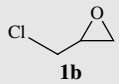
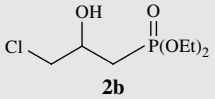
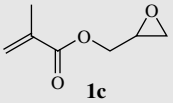
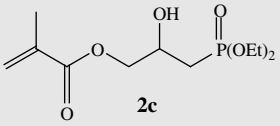
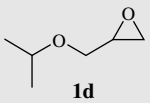
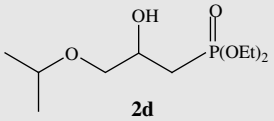
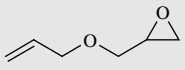
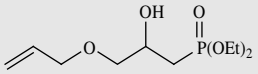
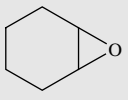
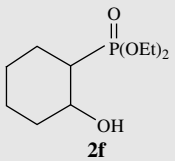
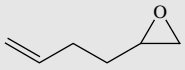
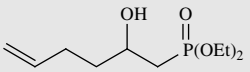
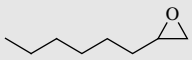
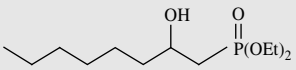
It is worthy of mention that $Al(OTf)_3$ was used as an efficient catalyst for the ring opening reaction of epoxides by oxygen and nitrogen nucleophiles in recent years.[46–48] To the best of our knowledge, there is no report in the literature on the conversion of epoxides to β-hydroxyphosphonates by phosphorus nucleophiles in the presence of $Al(OTf)_3$.

As indicated in Table 2, the reactions of different types of epoxides with triethyl phosphite proceeded with complete regioselectivity to afford the corresponding β-hydroxyphosphonates (**2a**–**h**) in high yields. No by-product was formed in any of these transformations. Moreover, the results show that triethyl phosphite attacked the epoxide ring even in the presence of functional groups susceptible to Arbuzov reaction and Michael addition (Entries 2 and 3). These observations are a good indication of the presence of an excellent chemoselectivity in this method.

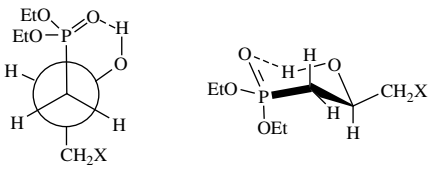
All the products were isolated and identified by their spectral data such as ^1H NMR, ^{13}C NMR, ^{31}P NMR, IR and MS. The β-hydroxyphosphonates (**2a**–**h**) exist predominantly as their *anti*-conformers **3a**–**h** (Scheme 2) as can be juged from the large values of their $^3J_{C,P}$ couplings (15.5–20.1 Hz). The predominant formation of the *anti* conformer **3a**–**h** can be a result of the hydrogen bond formation within a six-membered ring. It adopts a chair conformation (**4a**–**h**) with C-3 substituents in the equatorial positions (Scheme 2).[50] These obervations are in agreement with the formation of the regioisomer resulting from the nucleophilic attack on the less substituted carbon of the epoxide. Appearance of a signal at 1.61–2.35 ppm with the integration equivalent to two hydrogens in ^1H NMR spectrum of the products is another indication for this regioiomer formation.

All mass spectral data consist of molecular peaks with weak intensities due to the readily cleavage of C_2–C_3 bond followed by loss of two fragments of C_2H_4 (Scheme 3). The appearance of two peaks at *m*/*e*=181 and 125 are the results of the above mentioned cleavages. These two peaks are observed as common peaks in mass spectra of all the products except for **2f** (M^++1=237, 100%).

Table 2
$Al(OTf)_3$ catalyzed ring opening reaction of various types of epoxides with triethylphosphite in *n*-hexane under reflux conditions

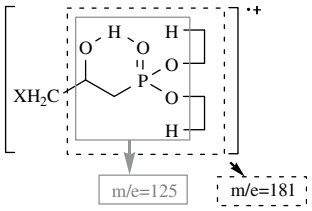
Entry	Epoxide	Product	Yield[a] (%)
1	 **1a**	 **2a**	93
2	 **1b**	 **2b**	88
3	 **1c**	 **2c**	86
4	 **1d**	 **2d**	95
5	 **1e**	 **2e**	93
6	 **1f**	 **2f**	98[b]
7	 **1g**	 **2g**	98
8	 **1h**	 **2h**	95

[a] Isolated yield. All products gave satisfactory spectral data in accordance with the known literature data.[10,11,26–32,49,50]
[b] dr=100%, trans isomer is formed.[10]



3a-h **4a-h**

Scheme 2. *anti* and Chair conformers of the products.



Scheme 3. Common fragmentation of β-hydroxyphosphonates.

After performing the preparation reaction of diethyl β-hydroxyphosphonate **2a** under the conditions described in Table 2, the reaction mixture was washed with water. The aqueous layer containing the catalyst was separated. Evaporation of the solvent under reduced pressure gave the catalyst, which was re-used for a consecutive run under the same reaction conditions. The average isolated yields of **2a** and the catalyst for five consecutive runs were 90.8 and 96.8, respectively (Fig. 1). This reusability demonstrates the high stability and turnover of $Al(OTf)_3$ under the employed conditions. It is noteworthy that the recyclability test was stopped after five runs.

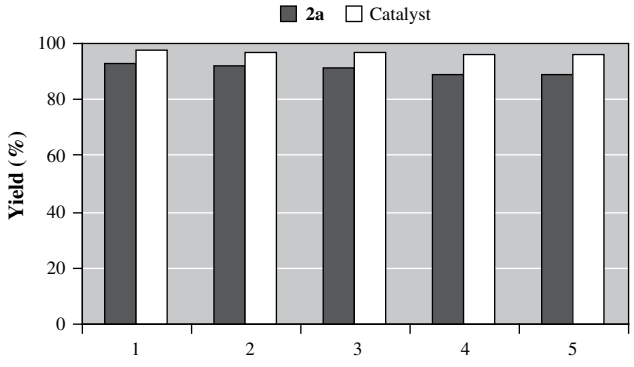
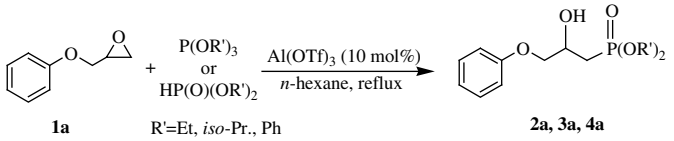


Figure 1. Reusability of $Al(OTf)_3$ as a catalyst for the synthesis of **2a**.

We have also compared the catalytic activity of $Al(OTf)_3$ with some common Lewis acids [e.g. $Al(OH)_3$, $AlCl_3$, $FeCl_3$, I_2, $LiClO_4$, $ZrCl_4$], BrØnsted acids [e.g. TfOH, $HClO_4$, $H_3PW_{12}O_{40}$, NH_2SO_3H] and metal oxides [e.g. CdO, Sb_2O_3, SnO, PbO, MoO_3, W_2O_3, ZnO] for the ring opening reaction of glycidyl phenyl ether with triethyl phosphite in refluxing *n*-hexane (Table 3). As it is evident from Table 3, $Al(OTf)_3$ is the most effective catalyst for this purpose leading to the formation of diethyl β-hydroxyphosphonate **2a** in high yields. In the absence of $Al(OTf)_3$, the starting materials remain intact even after prolonged reaction times (Table 3).

Furthermore, we have evaluated the generality of the presented method for the ring opening reaction of glycidyl phenyl ether with different phosphite esters (Scheme 4). The results of these studies are presented in Table 4.



Scheme 4. Ring opening reaction of glycidyl phenyl ether with various phosphite esters.

Table 3
Comparison of the catalytic efficiency of $Al(OTf)_3$ with various catalysts in the reaction of glycidyl phenyl ether with triethyl phosphite[a]

Entry	Catalyst[b]	Time (h)	Yield[c] (%)
1	$Al(OTf)_3$	1	93
2	$Al(OH)_3$	24	47[e]
3	$AlCl_3$	9	20
4	$FeCl_3$	2	35
5	I_2	24	0
6	$LiClO_4$	24	40[g]
7	$ZrCl_4$	5	15[g]
8	TfOH	9	0
9	$HClO_4$	0.25	50[g]
10	$H_3PW_{12}O_{40}$	—[f]	0[e]
11	NH_2SO_3H	2	50[g]
12	CdO[d]	48	Trace
13	Sb_2O_3[d]	24	0[e]
14	SnO[d]	24	0[e]
15	PbO[d]	24	0[e]
16	MoO_3[d]	48	15
17	W_2O_3[d]	24	0[e]
18	ZnO[d]	24	0 (40)[g,h]
19	—	72	0

[a] Conditions: at reflux in *n*-hexane (except for entry 19). triethyl phosphite (5 equiv).
[b] Catalyst (10 mol %).
[c] Isolated yield.
[d] Catalyst (100 mol %).
[e] 100% Consumption of epoxide was observed but a mixture of by-products was observed.
[f] Immediately.
[g] 100% Consumption of epoxide was observed but the desired product besides a mixture of by-products was obtained.
[h] Diethyl phosphite (5 equiv) was used.

Table 4
Ring opening reaction of glycidyl phenyl ether with various phosphite esters catalyzed by $Al(OTf)_3$ in *n*-hexane under reflux conditions

Entry	Phosphite[a]	Product	Time (min)	Yield[b] (%)
1	$P(OEt)_3$	**2a**	45	93
2	$P(O\text{-}i\text{-}Pr)_3$	**3a**	60	90
3	$HP(O)(OEt)_2$	**2a**	45	96
4	$HP(O)(O\text{-}i\text{-}Pr)_2$	**3a**	120	92
5	$P(OPh)_3$	**4a**	50	97

[a] Conditions: phosphite (5 equiv), $Al(OTf)_3$ (10 mol %).
[b] Isolated yield.

As is obvious from Table 4, the catalytic ring opening reaction of glycidyl phenyl ether proceeded well with different nucleophilic phosphite esters such as tri-*iso*-propyl/triphenyl phosphite and diethyl/di-*iso*-propyl phosphite as well as triethyl phosphite.

3. Conclusion

In conclusion, $Al(OTf)_3$ was found as a re-usable and efficient catalyst for the one-pot synthesis of a variety of β-hydroxyphosphonates by ring opening reaction of epoxides with different phosphite esters. This method not only provides a novel protocol for the synthesis of biologically important β-hydroxyphosphonates, but also extends the applicability of $Al(OTf)_3$ for the ring opening reaction of epoxides by phosphorus nucleophiles. High yields, excellent chemo- and regioselectivity, easy work-up, no by-product formation and using a catalytic amount of $Al(OTf)_3$ make this method attractive and a useful contribution to the present methodologies.

4. Experimental

4.1. General

Chemicals were purchased from Merck and Fluka Chemical Companies. All of the products were identified by their physical and spectral data. IR spectra were run on a Perkin Elmer 780 instrument. NMR spectra were recorded in ppm in $CDCl_3$ on a Bruker Avance DPX-250 instrument using TMS as an internal standard for ^1H NMR and ^{13}C NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR. Mass spectra were recorded on a Shimadzu GC–MS-QP5050A. Elemental analysis for C, H and N were obtained using a Heraeus CHN-O-Rapid analyzer. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates or by GC on Shimadazu model GC-14A instrument.

4.2. General procedure for the preparation of β-hydroxyphosphonates (2a–h, 3a and 4a)

$Al(OTf)_3$ (0.01 mmol) was added to a solution of epoxide (1 mmol) and $P(OEt)_3$ (5 mmol) in *n*-hexane (5 ml). The reaction

mixture was stirred at reflux conditions for 1 h and then washed with water (2×10 mL). The organic layer was separated and dryed over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product. The pure product was isolated by chromatography on silica gel.

4.3. Spectral data for diethyl 2-hydroxyphosphonates (2a–h, 3a and 4a)

*4.3.1. Diethyl 2-hydroxy-3-phenoxypropylphosphonate (**2a**)*

Pale yellow oil; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3320 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 7.31–7.25 (m, 2H, Ar), 6.99–6.89 (m, 3H, Ar), 4.46–4.34 (m, 1H, C*H*OH), 4.26–4.14 [m, 4H, P(O)(OCH_2CH$_3$)$_2$], 4.06–3.94 (m, 2H, CH_2), 2.32–2.23 (m, 1H, CH_2P), 2.20–2.07 (m, 1H, CH_2P), 1.48–1.25 [m, 6H, P(O)(OCH$_2$CH_3)$_2$]; δ_C (62.9 MHz, $CDCl_3$): 158.3, 129.5, 121.2, 114.5 (Ar), 71.2 (d, $^3J_{C,P}$=15.7 Hz, *C*H$_2$), 65.4 (d, $^2J_{C,P}$=4.0 Hz, *C*HOH), 62.1 [d, $^2J_{C,P}$=5.7 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 62.0 [d, $^2J_{C,P}$=5.7 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 30.2 (d, $^1J_{C,P}$=140.5 Hz, *C*H$_2$P), 16.4 [P(O)(OCH$_2$*C*H$_3$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 30.16; *m*/*z* 289 (6.58M$^+$+1), 288 (1.46M$^+$), 181 (83.54), 125 (100%).

*4.3.2. Diethyl 3-chloro-2-hydroxypropylphosphonate (**2b**)*

Pale yellow oil; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3516 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 4.33–4.25 [m, 5H, P(O)(OCH_2CH$_3$)$_2$, C*H*OH], 4.02 (br s, O*H*), 3.61–3.59 (m, 2H, CH_2Cl), 2.35–2.25 (m, 2H, CH_2P), 1.36 [t, 6H, $^3J_{H,H}$=6.7 Hz, P(O)(OCH$_2$CH_3)$_2$]; δ_C (62.9 MHz, $CDCl_3$): 66.3 (d, $^2J_{C,P}$=5.0 Hz, *C*HOH), 64.4 [d, $^2J_{C,P}$=7.5 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 64.2 [d, $^2J_{C,P}$=7.5 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 49.1 (d, $^3J_{C,P}$=20.1 Hz, *C*H$_2$Cl), 30.7 (d, $^1J_{C,P}$=145.5 Hz, *C*H$_2$P), 16.2 [d, $^3J_{C,P}$=6.3 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 31.13; *m*/*z* 233 (4.17M$^+$+3), 231 (12.59M$^+$+1), 195 (2.80), 181 (65.52), 125 (100), 43 (24.10%).

*4.3.3. 3-(Diethylphosphoryl)-2-hydroxypropyl methacrylate (**2c**)*

Pale yellow oil; R_f (30% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3562 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 6.17 (s, 1H, CH_2=C), 5.61 (s, 1H, CH_2=C), 4.31–4.06 [m, 8H, P(O)(OCH_2CH$_3$)$_2$, C*H*OH, CH_2, –O*H*], 2.34–2.10 (m, 2H, CH_2P), 1.96 (s, 3H, CH_3), 1.41–1.35 [m, 6H, P(O)(OCH$_2$CH_3)$_2$]; δ_C (62.9 MHz, $CDCl_3$): 167.7 (*C*=O), 135.6 (CH$_2$=*C*), 126.5 (*C*H$_2$=C), 68.1 (*C*HOH), 65.3 (d, $^3J_{C,P}$=17.0 Hz, *C*H$_2$), 63.9 P(O)(O*C*H$_2$CH$_3$)$_2$], 38.7 (d, $^1J_{C,P}$=144.0 Hz, *C*H$_2$P), 18.3 (C=*C*CH$_3$), 16.1 [P(O)(OCH$_2$*C*H$_3$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 31.5; *m*/*z* 279 (4.36M$^+$−1), 181 (68.76), 125 (100%).

*4.3.4. Diethyl 2-hydroxy-3-isopropoxypropylphosphonate (**2d**)*

Pale yellow oil; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3394 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 4.13–4.08 [m, 5H, P(O)(OCH_2CH$_3$)$_2$, O*H*], 3.58–3.48 [m, 2H, C*H*(CH$_3$)$_2$, C*H*OH], 3.34 (d, 2H, $^3J_{H,H}$=5.0 Hz, CH_2), 2.08–1.96 (m, 2H, CH_2P), 1.25 [t, 6H, $^3J_{H,H}$=7.5 Hz, P(O)(OCH$_2$CH_3)$_2$], 1.06 [d, 6H, $^3J_{H,H}$=6.3 Hz, CH(CH_3)$_2$]; δ_C (62.9 MHz, $CDCl_3$): 72.1 [*C*H(CH$_3$)$_2$], 71.9 (d, $^3J_{C,P}$=16.3 Hz, *C*H$_2$), 65.5 (d, $^2J_{C,P}$=4.4 Hz, *C*HOH), 62.8 [d, $^2J_{C,P}$=6.3 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 62.7 [d, $^2J_{C,P}$=6.3 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 30.3 (d, $^1J_{C,P}$=111.5 Hz, *C*H$_2$P), 21.9 [CH(*C*H$_3$)$_2$], 16.2 [d, $^3J_{C,P}$=6.3 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 31.49; *m*/*z* 253 (3.06M$^+$−1), 181 (46.22), 125 (64.88), 57 (51.46), 43 (100%).

*4.3.5. Diethyl 3-(allyloxy)-2-hydroxypropylphosphonate (**2e**)*

Pale yellow oil; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3464 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 5.93–5.77 (m, 1H, CH$_2$=C*H*), 5.26–5.12 (m, 2H, CH_2=CH), 4.13–3.97 [m, 7H, C*H*OH, CH_2, P(O)(OCH_2CH$_3$)$_2$], 3.42 (d, 2H, $^3J_{H,H}$=5.0 Hz, CH_2), 3.19 (br s, O*H*), 2.01–1.91 (m, 2H, CH_2P), 1.28 [t, 6H, $^3J_{H,H}$=7.0 Hz, P(O)(OCH$_2$CH_3)$_2$]; δ_C (62.9 MHz, $CDCl_3$): 134.4 (CH$_2$=*C*H), 117.2 (*C*H$_2$=CH), 73.8 (d, $^3J_{C,P}$=15.7 Hz, *C*H$_2$), 72.2 (*C*H$_2$), 65.6 (d, $^2J_{C,P}$=4.0 Hz, *C*HOH), 61.9 [d, $^2J_{C,P}$=6.2 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 61.8 [d, $^2J_{C,P}$=6.2 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 30.1 (d, $^1J_{C,P}$=139.6 Hz, *C*H$_2$P), 16.3 [d, $^3J_{C,P}$=6.2 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 30.34; *m*/*z* 253 (10.86M$^+$+1), 181 (89.11), 125 (100), 64 (47.01), 41 (61.42%).

*4.3.6. Diethyl 2-hydroxycyclohexylphosphonate (**2f**)*

Pale yellow oil; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3448 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 4.07–3.98 [m, 5H, P(O)(OCH_2CH$_3$)$_2$, OH], 3.64–3.61 (m, 1H, C*H*OH), 2.00–1.61 (m, 5H, C*H*P, CH_2), 1.29–1.20 [m, 10H, P(O)(OCH$_2$CH_3)$_2$, CH$_2$]; δ_C (62.9 MHz, $CDCl_3$): 68.7 (d, $^2J_{C,P}$=5.5 Hz, *C*HOH), 62.1 [d, $^2J_{C,P}$=6.2 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 61.8 [d, $^2J_{C,P}$=6.2 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 43.2 (d, $^1J_{C,P}$=135.2 Hz, *C*HP), 34.5 (d, $^3J_{C,P}$=15.5 Hz, *C*H$_2$), 25.1 (d, $^3J_{C,P}$=19.5 Hz, *C*H$_2$), 25.0, 24.1 (*C*H$_2$), 16.4 [d, $^3J_{C,P}$=5.5 Hz, P(O)(OCH$_2$CH$_3$)$_2$], 16.3 [d, $^3J_{C,P}$=5.5 Hz, P(O)(OCH$_2$CH$_3$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 32.39; *m*/*z* 237 (100M$^+$+1), 165 (90.02%).

*4.3.7. Diethyl 2-hydroxyhex-5-enylphosphonate (**2g**)*

Pale yellow oil; [Found: C, 50.70; H, 8.82. $C_{10}H_{21}O_4P$ requires C, 50.84; H, 8.96%]; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3473 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 5.85–5.69 (m, 1H, CH$_2$=C*H*), 5.03–4.91 (m, 2H, CH_2=CH), 4.22–4.04 [m, 5H, P(O)(OCH_2CH$_3$)$_2$, C*H*OH], 3.75 (br s, –O*H*), 2.19–2.00 (m, 4H, CH_2P, CH_2), 1.71–1.52 (m, 2H, CH_2), 1.31 [t, 6H, $^3J_{H,H}$=7.0 Hz, P(O)(OCH$_2$CH_3)$_2$]; δ_C (62.9 MHz, $CDCl_3$): 137.8 (CH$_2$=CH), 115.0 (*C*H$_2$=CH), 65.7 (d, $^2J_{C,P}$=6.3 Hz, *C*HOH), 63.4 [d, $^2J_{C,P}$=6.3 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 63.3 [d, $^2J_{C,P}$=6.3 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 37.5 (d, $^3J_{C,P}$=17.0 Hz, *C*H$_2$), 33.5 (d, $^1J_{C,P}$=140.9 Hz, *C*H$_2$P), 29.6 (*C*H$_2$), 16.2 [d, $^3J_{C,P}$=6.3 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 32.06; *m*/*z* 237 (15.76M$^+$+1), 181 (74.21), 125 (100), 99 (8.54), 82 (12.15), 41 (20.47%).

*4.3.8. Diethyl 2-hydroxyoctylphosphonate (**2h**)*

Pale yellow oil; [Found: C, 54.01; H, 10.00. $C_{12}H_{27}O_4P$ requires C, 54.12; H, 10.22%]; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3512 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 4.20–3.85 (m, 5H, C*H*OH, P(O)(OCH_2CH$_3$)$_2$], 3.36 (br s, O*H*), 2.00–1.85 (m, 2H, CH_2P), 1.50–1.24 [m, 16H, P(O)(OCH$_2$CH_3)$_2$, CH_2], 0.83 (t, 3H, $^3J_{H,H}$=7.0 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$): 66.4 (d, $^2J_{C,P}$=4.5 Hz, *C*HOH), 61.8 [d, $^2J_{C,P}$=5.7 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 38.2 (d, $^3J_{C,P}$=17.0 Hz, *C*H$_2$), 33.4 (d, $^1J_{C,P}$=138.0 Hz, *C*H$_2$P), 31.7, 28.9, 25.3, 22.5 (*C*H$_2$), 16.4 [d, $^3J_{C,P}$=6.3 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$], 14.0 (*C*H$_3$); δ_P (101.2 MHz, $CDCl_3$): 31.56; *m*/*z* 267 (12.43, M$^+$+1), 181 (100), 125 (74.22), 43 (20.96%).

*4.3.9. Diisopropyl 2-Hydroxy-3-phenoxypropylphosphonate (**3a**)*

Pale yellow oil; R_f (50% *n*-hexane/EtOAc) 0.25; υ_{max} (neat): 3266 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 7.31–7.25 (m, 2H, Ar), 6.98–6.90 (m, 3H, Ar), 4.79–4.69 [m, 2H, P(O)(O*C*H(CH$_3$)$_2$)$_2$], 4.45–4.25 (m, 1H, C*H*OH), 4.03–3.94 (m, 2H, CH_2), 3.73 (br s, O*H*), 2.23–1.95 (m, 2H, CH_2P), 1.34 [d, 12H, $^2J_{H,H}$=5.2 Hz, P(O)(OCH(CH_3)$_2$)$_2$]; δ_C (62.9 MHz, $CDCl_3$): 158.4, 129.4, 121.1, 114.5 (Ar), 71.3 (d, $^3J_{c,p}$=15.7 Hz, *C*H$_2$), 70.9 [d, $^2J_{C,P}$=5.0 Hz, P(O)(O*C*H(CH$_3$)$_2$)$_2$], 70.8 [d, $^2J_{C,P}$=5.0 Hz, P(O)(O*C*H(CH$_3$)$_2$)$_2$], 65.5 (d, $^2J_{C,P}$=5.0 Hz, *C*HOH), 31.1 (d, $^1J_{c,p}$=184.6 Hz, *C*H$_2$P), 24.0 [P(O)(OCH(*C*H$_3$)$_2$)$_2$]; δ_P (101.2 MHz, $CDCl_3$): 28.06; *m*/*z* 317 (16.14, M$^+$+1), 209 (17.37), 125 (100), 43 (21.89%).

*4.3.10. Diphenyl 2-hydroxy-3-phenoxypropylphosphonate (**4a**)*

Brown-red oil; R_f (10% *n*-hexane/CH_2Cl_2) 0.35; υ_{max} (neat): 3387 (–OH) cm^{-1}; δ_H (250 MHz, $CDCl_3$): 7.3–7.1 (m, 7H, Ar), 6.92–6.82 (m, 8H, Ar), 4.30–4.15 (m, 2H, CH_2), 4.10–3.85 (m, 2H, C*H*OH, O*H*), 2.95–2.65 (m, 2H, CH_2P); δ_C (62.9 MHz, $CDCl_3$): 158.4, 156.6, 155.6, 129.5, 121.3, 120.6, 115.3, 114.5 (Ar), 68.7 (d, $^3J_{c,p}$=18.9 Hz, *C*H$_2$), 65.9 (*C*HOH), 29.7 (d, $^1J_{C,P}$=140.0 Hz, *C*H$_2$P); δ_P (101.2 MHz,

$CDCl_3$): 22.47; *m*/*z* 384 (2.75, M^+), 366 (4.11), 326 (45.56), 77 (100%).

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