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Journal of Organometallic Chemistry 571 (1998) 189–193

Journal of Organometallic Chemistry

Dioxirane oxidation of substituted vinylphosphonates: a novel efficient route to 1,2-epoxyalkylphosphonates

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Received 23 April 1998; received in revised form 6 July 1998

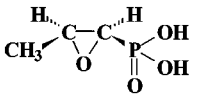
Abstract

A new stereoselective route to substituted 1,2-epoxyalkylphosphonates through oxidation of corresponding alk-1-enylphosphonates by 'in situ' generated ethylmethyldioxirane is described. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Dioxirane; 1,2-Epoxyphosphonate; Vinylphosphonate; Epoxidation; Oxidation

1. Introduction

Epoxyalkylphosphonates are useful intermediates in the synthesis of modified natural and synthetic polymers [1], and also in the preparation of bioactive substances [2–4]. Indeed, since the discovery in 1969 of fosfomycin **1** [3], the preparations of epoxyalkylphosphonates have received much more attention.



1 (-) (1R , 2S)

Since the first review by Redmore in 1971 [5], several improvements in their synthesis have been proposed. The principal routes to 1,2-epoxyalkylphosphonates include: the treatment of halohydrines with a base [5–9], the reaction of α-haloketones [5,10–12] or α-tosyl-ketones [13] with alkali metal derivatives of dialkylphosphonates, the Darzens reaction type of halomethylphosphonates with aldehydes or ketones [5,14–18], an improved variant of Darzens reaction through sulfonio- or ammoniomethylphosphonates [19], and lastly direct epoxidation of α,β-unsaturated phosphonates with either acidic or basic oxidizing reagents [5,20–25].

In the search of synthesis of new analogs of fosfomycin **1** [26], we needed a series of different substituted 1,2-epoxyalkylphosphonates via the corresponding vinylphosphonates whose stereoselective synthesis was previously described [27,28]. First experiments with traditional reagents (*t*BuOOH/catalyst, H_2O_2/Na_2WO_4, H_2O_2/Na_2CO_3), failed in our hands for such substrates: no trace of epoxyphosphonate was either detected, all the vinylphosphonate was recovered at the end of the reaction. These results corroborate the observations by Sturtz et al. [21]. about the very poor reactivity of vinylphosphonates towards most of the classic epoxidation reagents.

2. Results and discussion

So we decided to oxidize the substituted alk-1-enylphosphonates with dioxiranes. Indeed dioxiranes are strong oxidizing compounds [29,30], easy to handle

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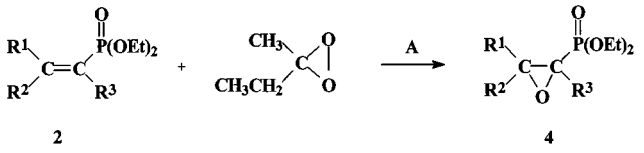
PII S0022-328X(98)00856-0

and can be generated in situ from monopersulfate (caroate) and a ketone in a phase transfer system [31]. Moreover the oxidation could be enantioselective using a chiral ketone [29,31–34]. Herein we report a new and easy synthesis of substituted 1,2-epoxyalkylphosphonates **4** starting from the corresponding alk-1-enylphosphonates **2** oxidized with methyl ethyl dioxirane. We selected butanone rather than acetone (more soluble in water) as dioxirane precursor to mimic chiral unsymetrical ketones and to handle a less volatile dioxirane [35].



2 : R^1 = Alkyl, Ph ; R^2 = Alkyl, Ph, H ; R^3 = Alkyl, H

A : Butanone / H_2O / $nBu_4N^+HSO_4^-$ / pH = 7.3 - 7.5 / 22°C / 24h

Owing the pH-dependence of the dioxirane stability, the reaction, followed by ^{31}P-NMR, needs an accurate control of the pH at 7.4 ± 0.1; and, in order to balance the spontaneous decomposition of dioxirane, the addition of several fresh portions of caroate (up to a maximum of six portions) is necessary to obtain the nearly complete conversion of the starting alk-1-enylphosphonate. Our first attempts were tedious, and the results not very reproducible, due to the variation of pH after addition of caroate. We improved this reaction, by automatizing the addition of caroate and the pH control. We used here a programmable apparatus with electronic comparator, which starts and stops them when the pH orders values are reached.

The results, quoted in Table 1, indicate that the ease of epoxidation depends indeed on the nature and position of the substituents on the double bond: for the 2-mono-substituted (entries **4a**, **4b**, **4c**) and the 2-*cis*-alkyl or 2-*trans*-aryl 2,2-di- or trisubstituted alk-1-enylphosphonates (entries **4d**, **4e**, **4f**, **4j**, **4k**), the conversion rate is high, in agreement with the electrophilic character of dioxirane [36] and the good nucleophilic reactivity of the double bond owing to the electron-donating alkyl groups or the strong conjugation with the aryl groups. On the contrary, for the 2-*cis*-aryl-2,2-disubstituted alkyl-1-enylphosphonates (entries **4g**, **4h**, **4i**), in which the conjugation of the double bond with the aryl group is probably weaken by the steric hindrance between the aryl and phosphonate groups, the conversion rates are low in spite of the addition of six portions of caroate.

The structure of 1,2-epoxyalkylphosphonates **4** have been established unambiguously by ^{1}H-, ^{13}C- and ^{31}P-NMR and elementary analysis (Table 2). This reaction is stereoselective and occurs with full retention of the stereochemistry. Furthermore, except in one case, we almost did not observe any by-products unlike in the other routes.

3. Conclusion

In summary, we propose a stereoselective general way to new substituted 1,2-epoxyalkylphosphonates with moderate to high yields. Corresponding enantioselective syntheses are under investigations.

4. Experimental

Unless otherwise specified, the starting materials were commercially available. IR spectra (film) were recorded using a Perkin-Elmer 377 spectrometer. The NMR spectra in Table 2 were obtained in $CDCl_3$ on Bruker AC-200, AC-250 (^{1}H-NMR at 200.13 and 250.13 MHz, ^{13}C-NMR at 50.32 MHz and ^{31}P-NMR at 81.0 MHz). Chemical shifts refer to signals of tetramethylsilane in the case of ^{1}H and ^{13}C spectra (int.) and to 85% aqueous phosphoric acid (ext.) in the case of ^{31}P spec-

Table 1
Epoxidation of alk-1-enylphosphonates **2** by methyl ethyl dioxirane

Entry	R^1	R^2	R^3	No. of caroate addition	Conversion rate (%)	Yield (%)[a]
4a	*n*Pr	H	H	6	80	58
4b	*n*Bu	H	H	6	100	71.3
4c	Ph	H	H	6	87	73[b]
4d	*n*Pr	Me	H	6	92	75
4e	*n*Pr	Ph	H	2	100	81
4f	*n*Bu	Ph	H	2	100	80
4g	Ph	*n*Oct	H	6	30	19
4h	Ph	*n*Bu	H	6	44	35
4I	Ph	*n*Bu	Me	6	28	20
4j	Ph	*p*MePh	H	2	100	84
4k	*n*Pr	Me	Me	4	100	79

[a] Yields of isolated compounds.
[b] Presence of non identified by-products.

Table 2
Some caracteristic data of epoxyphosphonates **4**

Entry	R_f[a]	^{31}P	$^{13}C_1$ J (Hz)	$^{13}C_2$ J (Hz)
4a[b]	0.45	19.67(s)	49.42(d) $^1J_{P-C}$ = 205	57.4(d) $^2J_{P-C}$ = 1.5
4b	0.44	19.81(s)	49.09(d) $^1J_{P-C}$ = 205	57.72(d) $^2J_{P-C}$ = 1.59
4c	0.22	17.49(s)[c]	52.55(d) $^1J_{P-C}$ = 205.33	57.05(d) $^2J_{P-C}$ = 2.2
4d[b]	0.49	19.53(s)	56.78(d) $^1J_{P-C}$ = 201.7	62.88(s)
4e[b]	0.50	18.18(s)	58.38(d) $^1J_{P-C}$ = 198	65.70(d) $^2J_{P-C}$ = 1.03
4f	0.48	18.13(s)	58.38(d) $^1J_{P-C}$ = 198	65.70(d) $^2J_{P-C}$ = 1.03
4g	0.54	17.23(s)	57.04(d) $^1J_{P-C}$ = 202.21	66.10(d) $^2J_{P-C}$ = 1.52
4h	0.54	17.26(s)	56.9(d) $^1J_{P-C}$ = 202.45	66.11(s)
4i[b]	0.54	20.87(s)	62.21(d) $^1J_{P-C}$ = 197.30	66.11(s)
4j	0.40	15.82(s)	60.00(d) $^1J_{P-C}$ = 199.2	62.68(d) $^2J_{P-C}$ = 1.23
4k[b]	0.61	23.54(s)	60.56(d) $^1J_{P-C}$ = 196	65.78(d) $^2J_{P-C}$ = 3.9

[a] SiO_2, $AcOEt/CH_2Cl_2$ (1/1), revealer: 4-(*p*-nitrobenzylpyridine) or UV.
[b] The elementary microanalysis data are in agreement with the structure: C ± 0.43%; H ± 0.43%; O ± 0.20%.
[c] Other signal at 17.17 ppm: by-product (10%).

tra. Abbreviations of coupling patterns are as follow: s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet; m, multiplet. TLC was conducted on thin Merck silica gel sheets (0.2 mm, 60 F 250) with a mixture (1/1) of ethyl acetate and dichloromethane. The revealer is 4-(*p*-nitrobenzylpyridine) or UV.

4.1. General procedure

In a flask, fitted with a vigorous mechanical stirrer, are introduced: 4.46 mmol of alk-1-enylphosphonate, 100 ml of butanone, 100 ml of CH_2Cl_2, phosphate buffer (prepared by dissolving 0.177 g (1.30 mmol) of KH_2PO_4 and 0.648 g (4.6 mmol) of HNa_2PO_4 in 150 ml of water) and 0.5 g (1.7 mmol) of $Bu_4N^+HSO_4^-$. A solution of aqueous caroate (25 g (77 mmol) in 100 ml H_2O) is then slowly added (over 6 h). The pH of the mixture is maintained between 7.3 and 7.5 by a solution of KOH (5%). Stirring is maintained for eighteen hours, then a new batch of aqueous caroate solution is slowly added (over 6 h) and stirred for an additional period of 18 h.

After completion, solid NaCl is added to the cloudy reaction mixture until saturation, then the organic phase is separated by decantation, and the aqueous phase is extracted with CH_2Cl_2 (4 × 100 ml). The combined organic layers are dried over $MgSO_4$, filtered and then evaporated. The crude product is purified by flash chromatography on silica gel with a (1/1) mixture of ethyl acetate and dichloromethane as eluent.

4.2. Synthesis of (±)diethyl 1,2-epoxy-alkylphosphonates **4**

4.2.1. (±)Cis-diethyl 1,2-epoxy-pentylphosphonates **4a**

58% yield (0.592 g; 2.67 mmol). $R_f = 0.45$. ^{1}H-NMR: $\delta = 0.9$ (t, 3H, $^3J_{H-H} = 7.25$, $CH_3CH_2CH_2$), 1.3 (dt, 3H, $^3J_{H-H} = 7.04$, $^4J_{P-H} = 1.08$, CH_3CH_2O), 1.43–1.53 (m, 2H, $^3J_{H-H} = 7.5$, $CH_3CH_2CH_2$), 1.8 (q, 2H, $^3J_{H-Hb} = 7.13$, $^3J_{H-Hd} = 7.34$, $CH_2CH_bCH_a$), 2.9 (dd, 1H, $J_{P-H} = 27.23$, $^3J_{Ha-Hb} = 4.54$, CH_bCH_aP), 3.10 (ddd, 1H, $^3J_{P-H} = 1.6$, $^3J_{H-Hc} = 7.13$, $^3J_{Hb-Ha} = 4.54$, $CHc_2CH_bCH_aP$), 4.1 (dq, 4H, $^3J_{H-H} = 7.04$, $^3J_{P-H} = 7.09$, CH_3CH_2O). ^{31}P-NMR $\delta = 19.66$ (s). ^{13}C-NMR: $\delta = 57.4$ (d, $^2J_{P-C} = 1.5$, *C*HCHP), 49.42 (d, $^1J_{P-C} = 205$, CH*C*HP), 62.47 and 62.07 (2d, $^2J_{P-C} = 6.30$, CH_3CH_2O), 29.97 (d, $^3J_{P-C} = 8.0$, CH_2CHCHP), 19.37 (s, $CH_3CH_2CH_2$), 16.13 (d, $^3J_{P-C} = 5.81$, CH_3CH_2O), 13.56 (s, CH_3CH_2CH). IR (film): 2960, 2880, 1260, 1030, 795. Anal. calc. for $C_9H_{19}O_4P$: C 48.64, H 8.62, O 28.80. Found: C 48.45, H 9.05, O 28.87%.

4.2.2. (±)Cis-diethyl 1,2-epoxy-hexylphosphonate **4b**

71% yield (0.775g; 3.28 mmol). $R_f = 0.44$. ^{1}H-NMR: $\delta = 0.87$ (t, 3H, $^3J_{H-H} = 7.12$, $CH_3CH_2CH_2$), 1.3 (t, 3H, $^3J_{H-H} = 7.05$, CH_3CH_2O), 1.34–1.44 (m, 4H, $CH_3CH_2CH_2CH_2$), 1.75–1.89 (m, 2H, CH_2CHCH), 2.89 (dd, 1H, $^2J_{PHa} = 27.28$, $^3J_{Hb-Ha} = 4.5$, CH_bCH_aP), 3.12 (ddd, 1H, $^3J_{P-Hb} = 6.37$, $^3J_{Hb-Ha} = 4.5$, $^3J_{H-Hc} = 7.1$, CH_bCHP), 4.12 (dq, 4H, $^3J_{H-H} = 7.05$, $^3J_{P-H} = 7.41$, CH_3CH_2O). ^{31}P-NMR: $\delta = 19.81$ (s). ^{13}C-NMR: $\delta = 57.72$ (d, $^2J_{P-C} = 1.59$, *C*HCHP), 49.09 (d, $^1J_{P-C} = 205$, CH*C*HP), 62.27 (2d, $^2J_{P-C} = 6.39$, CH_3CH_2O), 27.95 (s, $CH_3CH_2CH_2$), 28.86 (d, $^3J_{P-C} = 8.1$, CH_2CHCHP), 22.27 (s, $CH_3CH_2CH_2$). 15.9 (d, $^3J_{P-C} = 5.94$, CH_3CH_2O), 13.63 (s, $CH_3CH_2CH_2$). IR (film): 2960, 2880, 1260, 1040, 795. MS FAB (glycerol), 237 (M + 1).

4.2.3. (±)Cis-diethyl 1,2-epoxy-2-phenyl-ethylphosphonate **4c**

73% yield (0.860 g; 3.36 mmol). $R_f = 0.22$. ^{1}H-NMR: $\delta = 1.08$ and 1.17 (2t, 6H, $^3J_{HH} = 7.06$, CH_3CH_2O), 3.30 (dd, 1H, $^2J_{P-H} = 28.24$, $^3J_{H-H} = 4.49$, C*H*P), 3.5–3.66 (m, 1H, C*H*CHP), 3.70–3.98 (m, 4H, CH_3CH_2O), 7.25–7.52 (m, 5H aromatic). ^{31}P-NMR: δ 17.49 (82%) (s), 17.17 (10%) (s) (by-product), 1.32 (8%) (s) (by-product). ^{13}C-NMR: $\delta = 133.03$ (d, $^3J_{P-C} = 1$, C_{ipso}), 128.01 (s, C_{para}), 127.74 (s, C_{meta}), 126.52 (s, C_{ortho}), 57.05 (d, $^2J_{P-C} = 2.2$, *C*HCHP), 52.55 (d, $^1J_{P-C} = 205.33$, CH*C*HP), 61.98 and 62.19 (2d, $^2J_{P-C} = 6.3$, CH_3CH_2O), 15.96 and 16.08 (2d, 2C $^3J_{P-C} = 2.35$, CH_3CH_2O). IR (film): 2970, 2800, 1600, 1230, 1025, 680.

4.2.4. (±)-(u)-Diethyl 1,2-epoxy-2-methyl-pentylphosphonate ***4d***

75% yield (0.815 g; 3.45 mmol). $R_f = 0.49$. ^{1}H-NMR: $\delta = 0.88$ (t, 3H, $^3J_{H-H} = 7.26$, CH_3CH$_2$CH$_2$), 1.26 (t, 6H, $^3J_{H-H} = 7.12$, CH_3CH$_2$O), 1.29 (s, 3H, C$_3$H$_7$(CH_3)C), 1.39–1.51 (m, 2H, CH$_3$CH_2CH$_2$), 1.8 (quint, 2H, $^3J_{H-H} = 6.92$, $^4J_{P-H} = 2.26$, CH_2CCH), 2.70 (d, 1H, $^2J_{P-H} = 26.60$, CCHP), 4.07 (dq, 4H, $^3J_{H-H} = 7.12$, $^3J_{P-H} = 7.04$, CH$_3$CH_2O). ^{31}P-NMR: $\delta = 19.53$ (s). ^{13}C-NMR: $\delta =$ 62.88 (s, CCHP), 56.78 (d, $^1J_{P-C} = 201.7$, CCHP), 62.57 and 62.03 (2d, $^2J_{P-C} = 6.35$, CH$_3C$H$_2$O), 34.84 (s, CH$_3$CH$_2C$H$_2$), 22.18 (d, $^3J_{P-C} = 0.9$, CH$_3$CCP), 18.91 (s, CH$_3C$H$_2$CH$_2$), 16.25 (d, $^3J_{P-C} = 5.54$, CH$_3$CH$_2$O) 14.01(s, CH$_3$CH$_2$CH$_2$). IR (film): 2960, 2930, 2870, 1250, 1060, 830, 790. MS FAB (NBA), 237 (M + 1); Anal. calc. for $C_{10}H_{21}O_4P$: C 50.84, H 8.96, O 27.09. Found: C 50.82, H 8.92, O 26.89%.

4.2.5. (±)-(l)-Diethyl 1,2-epoxy-2-phenyl-pentylphosphonate ***4e***

81% yield (1.11 g; 3.72 mmol). $R_f = 0.5$. ^{1}H NMR: $\delta = 0.87$ (t, 3H, $^3J_{H-H} = 7.28$, CH_3CH$_2$CH$_2$), 1.25–1.45 (m, 8H, CH$_3$CH_2CH$_2$ and CH_3CH$_2$O), 2.1–2.4 (m, 2H, CH$_3$ CH$_2$CH_2C), 2.8 (d, 1H, $^1J_{P-H} = 27.73$, CH$_2$CCHP), 4.10–4.30 (m, 4H, CH$_3$CH_2O), 7.30–7.45 (m, 5H aromatic). ^{31}P-NMR: $\delta = 18.18$ (s). ^{13}C-NMR: $\delta = 139$ (d, $^3J_{P-C} = 0.57$, C$_{ipso}$), 128.20 (s, C$_{para}$), 127.57–125.5 (C$_{ortho,}$ C$_{meta}$), 65.7 (d, $^2J_{P-C} = 1.03$, CCHP), 62.64 and 62.13 (2d, $^2J_{P-C} = 6.25$, CH$_3C$H$_2$O), 58.38 (d, $^1J_{P-C} =$ 198, CCHP), 33.34 (s, CH$_2$CC), 18.57 (s, CH$_3C$H$_2$CH$_2$), 16.25 (d, $^3J_{P-C} = 6.5$, CH$_3$CH$_2$O), 13.6 (s, CH$_3$CH$_2$CH$_2$). IR (film): 2960, 2920, 2875, 1390–1450, 1260, 1025. Anal. calc. for $C_{15}H_{23}O_4P$: C 60.39, H 7.77, O 21.45. Found: C 60.54, H 7.78, O 21.53%.

4.2.6. (±)-(l)-Diethyl 1,2-epoxy-2-phenyl-hexylphosphonate ***4f***

80% yield (1.15 g; 3.68 mmol). $R_f = 0.48$. ^{1}H-NMR: $\delta = 0.87$ (t, 3H, $^3J_{H-H} = 7.28$, CH_3CH$_2$CH$_2$), 1.20–1.38 (m, 10H, CH$_3$CH_2CH_2CH$_2$ and CH_3CH$_2$O), 2.11–2.45 (m, 2H, CH$_3$CH$_2$CH$_2$CH_2C), 2.88 (d, 1H, $^1J_{P-H} = 27.75$, CH$_2$CCHP), 4.1–4.35 (m, 4H, CH$_3$CH_2O), 7.30–7.45 (m, 5H aromatic). ^{31}P-NMR $\delta = 18.13$ (s). ^{13}C-NMR: δ 139 (d, $^3J_{P-C} = 0.57$, C$_{ipso}$), 128.21 (s, C$_{para}$), 127.57 and 125.5 (C$_{ortho,}$ C$_{meta}$), 65.7 (d, $^2J_{P-C} = 1.07$, CCHP), 62.61 and 62.13 (2d, $^2J_{P-C} = 6.25$, CH$_3$CH$_2$O), 58.38 (d, $^1J_{P-C} = 198$, CCHP), 33.34 (s, CH$_2$CCP), 18.57 (s, CH$_3$CH$_2C$H$_2$), 17.22 (s, CH$_3C$H$_2$CH$_2$), 16.25 (d, $^3J_{P-C} = 6.5$, CH$_3$CH$_2$O), 13.6 (s, CH$_3$CH$_2$CH$_2$). IR (film): 2960, 2920, 2875, 1450, 1390, 1260, 1025.

4.2.7. (±)-(u)-Diethyl 1,2-epoxy-2-phenyl-decylphosphonate ***4g***

19% yield (0.322 g; 0.087 mmol). $R_f = 0.54$. ^{1}H-NMR: $\delta = 0.81$ (t, 3H, $^3J_{H-H} = 7.3$, CH_3CH$_2$CH$_2$), 0.80–0.98 (m, 6H, CH_3CH$_2$O), 1.15–1.33 (m, 12H, CH$_3$(CH_2)$_6$), 1.5–1.7 (m, 1H, CH$_3$(CH$_2$)$_6$CH_2), 1.9–2.2 (m, 1H, CH$_3$(CH$_2$)$_6$CH_2), 3.15 (d, 1H, $^2J_{P-H} = 27.98$, CCHP), 3.30 (dq, 1H, $J_{P-H} = 9.06$, $J_{H-H} = 7.03$, CH$_3$CH_2O), 3.65 (dq, 1H, $J_{P-H} = 10.26$, $J_{H-H} = 7.2$ CH$_3$CH_2O), 3.86–3.98 (m, 2H, CH$_3$CH_2O), 7.23–7.40 (m, 5H aromatic). ^{31}P-NMR: $\delta = 17.23$ (s). ^{13}C-NMR: $\delta = 136.6$ (d, $^3J_{P-C} =$ 0.47, C$_{ipso}$), 127.6, 127.48 and 126.94 (C$_{ortho,}$ C$_{meta}$ C$_{para}$), 66.1 (d, $^2J_{P-C} = 1.52$, CCHP), 61.9 (d, $^2J_{P-C} = 6.55$, CH$_3C$H$_2$O), 57.04 (d, $^1J_{P-C} = 202.21$, CCHP), 38.88 (s, CH$_2$CCHP), 31.56 (s, CH$_2C$H$_2$CH$_2$C), 28.92, 29.13 and 29.15 (s, CH$_3$ CH$_2$CH$_2$(CH_2)$_3$), 24.28 (s, CH$_3$CH$_2C$H$_2$), 22.39 (s, CH$_3C$H$_2$CH), 15.9 (2d, $^3J_{P-C} = 6.35$, CH$_3$CH$_2$O), 13.59 (s, CH$_3$CH$_2$CH$_2$).

4.2.8. (±)-(u)-Diethyl 1,2-epoxy-2-phenyl-2-hexylphosphonate ***4h***

35% yield (0.487 g; 1.561 mmol). $R_f = 0.54$. ^{1}H-NMR: $\delta = 0.82$ (t, 3H, $^3J_{H-H} = 6.86$, CH_3CH$_2$CH$_2$), 0.99 (t, 3H, $^3J_{H-H} = 7.09$, CH_3CH$_2$O), 1.16 (t, 3H, $^3J_{H-H} = 7.05$, CH_3CH$_2$O), 1.15–1.34 (m, 4H, CH$_3$(CH_2)$_2$CH$_2$), 1.5–1.71 (m, 1H, CH$_3$(CH$_2$)$_2$CH_2), 1.9–2.2 (m, 1H, CH$_3$(CH$_2$)$_2$CH_2), 3.19 (1H, $^2J_{P-H} = 28.0$, CCHP), 3.24–3.37 (m, 1H, CH$_3$CH_2O), 3.62–3.71 (m, 1H, CH$_3$CH_2O), 3.92–4.01 (m, 2H, CH$_3$CH_2O), 7.26–7.43 (m, 5H aromatic). ^{31}P NMR $\delta = 17.26$ (s). ^{13}C-NMR: $\delta = 136.54$ (s, C$_{ipso}$), 127.60, 127.49 and 126.90 (C$_{ortho,}$ C$_{meta}$ C$_{para}$), 66.11 (s, CC(H)P), 56.9 (d, $^1J_{P-C} = 202.45$, CCHP), 62.0 (2d, $^2J_{P-C} = 0.13$, CH$_3$CH$_2$O), 38.58 (s, CH$_2$CCHP), 26.39 (s, CH$_2C$H$_2$CH$_2$C), 22.26 (s, CH$_3C$H$_2$CH$_2$), 15.95 (s, CH$_3$CH$_2$O), 13.64 (s, CH$_3$CH$_2$CH$_2$). IR (film): 3000, 2900, 1240, 1027–1052, 800.

4.2.9. (±)-(u)-Diethyl 1,2-epoxy-1-methyl-2-phenylhexylphosphonate ***4i***

20% yield (0.300 g; 0.92 mmol). $R_f = 0.54$. ^{1}H-NMR: $\delta = 0.81$ (t, 3H, $^3J_{H-H} = 6.9$, CH_3CH$_2$CH$_2$), 0.99 (t, 3H, $^3J_{H-H} = 7.09$, CH_3CH$_2$O), 1.14 (t, 3H, $^3J_{H-H} = 7.09$, CH_3CH$_2$O), 1.15–1.26 (m, 4H, CH$_3$(CH_2)$_2$CH$_2$), 1.71 (d, 3H, $^3J_{P-H} = 11.5$, C(CH_3)P), 3.26–3.36 (m, 1H, CH$_3$CH_2O), 3.62–3.74 (m, 1H, CH$_3$CH_2O), 3.90–3.99 (m, 2H, CH$_3$CH_2O), 7.28–7.39 (m, 5H aromatic). ^{31}P NMR $\delta = 20.87$ (s). ^{13}C-NMR: $\delta = 138.75$ (s, C$_{ipso}$), 127.20, 127.25 and 127.49 (C$_{ortho,}$ C$_{meta}$ C$_{para}$), 69.11 (s, CC(CH$_3$)P), 62.21 (d, $^1J_{P-C} = 197.3$, CC(CH$_3$)P, 61.91 and 62.16 (2d, $^2J_{P-C} = 0.14$, CH$_3$CH$_2$O), 35.1 (s, CH$_2$CCHP), 26.8 (s, CH$_2C$H$_2$CH$_2$C), 22.72 (s, CH$_3C$H$_2$CH$_2$), 16.17 (s, CH$_3$CH$_2$O), 15.56 (d, $^2J_{P-C} =$ 0.31 C(CH$_3$)P), 13.8 (s, CH$_3$CH$_2$CH$_2$). IR (film): 3000, 2900, 1240, 1027–1052, 800. MS FAB (NBA), 327 (M + 1). Anal. calc for $C_{17}H_{27}O_4P$: C 62.56, H 8.34, O 19.61. Found: C 62.13, H 8.21, O 19.81%.

4.2.10. (±)-(l)-Diethyl 1-2-epoxy-2-phenyl-2-p-tolylethylphosphonate ***4j***

84% yield (1.34 g; 3.86 mmol). $R_f = 0.40$. ^{1}H-NMR: δ 1.02 (t, 3H, $^3J_{H-H} = 7.0$, CH_3CH$_2$O), 1.23 (t, 3H, $^3J_{H-H}$

$= 7.05$, CH_3CH_2O), 2.29 (s, 3H, $CH_3C_6H_4$), 3.48 (d, 1H, $^2J_{P-H} = 28.21$, CC*H*P), 3.42–3.56 (m, 1H, CH_3CH_2O), 3.79–3.97 (m, 1H, CH_3CH_2O), 3.99–4.09 (m, 2H, CH_3CH_2O), 7.07–7.58 (m, 9H aromatic). ^{31}P-NMR $\delta = 15.82$ (s). ^{13}C-NMR: δ 138 (s, C_{ipso}), 136.68 (C'_{para}), 136.12 (C'_{ipso}), 126.37, 127.81, 127.98 128.08 and 128.98 (C_{meta},C_{ortho},C_{para}, C'_{meta}, C'_{ortho}), 62.68 (d, $^2J_{P-C} = 1.23$, *C*CHP), 62.28 and 62.37 (2d, $^2J_{P-C} = 6.75$ and 6.53, CH_3CH_2O), 60 (d, $^1J_{P-C} = 199.2$, C*C*HP), 20.95 (s, $pCH_3C_6H_4$), 16.02 and 16.16 (2d, $^3J_{P-C} = 6.2$ and 6.01, CH_3CH_2O). IR (film): 2980, 2910, 1490, 1250 (PO), 1027–1052, 800.

4.2.11. (±)-(u)-Diethyl-1,2-dimethyl-pentylphosphonate 4h

79% yield (0.910 g; 3.62 mmol). $R_f = 0.61$. ^{1}H-NMR: $\delta = 0.94$ (t, 3H, $^3J_{H-H} = 7.36$, $CH_3CH_2CH_2$), 1.33 and 1.35 (2t, 6H, $^3J_{H-H} = 5.96$ and 7.08, CH_3CH_2O), 1.34 (d, $^3J_{P-H} = 2.49$, $C_3H_7(CH_3)C$), 1.46 (d, $^3J_{P-H} = 11.24$, $C(CH_3)P$), 1.5 (q, 2H, $^3J_{H-H} = 7.4$, $CH_3CH_2CH_2$), 4.07–4.24(m, 4H, CH_3CH_2O). ^{31}P-NMR: $\delta = 25.57$ (s). ^{13}C-NMR: $\delta = 65.78$ (d, $^2J_{P-C} = 3.9$, *C*CP), 62.10 and 62.65 (2d, $^2J_{P-C} = 6.79$, CH_3CH_2O), 60.56 (d, $^1J_{P-C} =$ 196, C*C*P), 36.47 (s, $CH_3CH_2CH_2$), 19.05 (s, $CH_3CH_2CH_2$), 18.99 (s, CH_3CC), 16.54 (d, $^2J_{P-C} =$ 15.12, $CC(CH_3)P$), 16.38 (d, $^3J_{P-C} = 2.85$, CH_3CH_2O), 14.07 (s, $CH_3CH_2CH_2$). IR (film):. 2997, 2930, 2870, 1245, 1026–1051, 870, 830. MS FAB (glycerol–thioglycerol), 251 (M + 1). Anal. calc. for $C_{11}H_{23}O_4P$: C 52.79, H 9.26, O 25.57. Found: C 52.68, H 9.04, O 25.41%.

Acknowledgements

We thank the Roussel-Uclaf company for the generous gift of the laboratory automaton (Logilab system).

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