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Dioxirane Oxidation of 2-Aryl-1-vinyl-1,1-diphosphane Dioxide: A Convenient Approach for the Synthesis of Novel 1,2-Epoxy-2-aryl Ethyl*gem*bisphosphonates

Marthe Carine Djuidje Fotsing,[1] Neil Coville,[2] and Xavier Yangkou Mbianda[1]

[1]*Department of Applied Chemistry, University of Johannesburg, Doornfontein Campus, Johannesburg 2028, South Africa*

[2]*Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg 2050, South Africa*

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ABSTRACT: *The synthesis of tetraethyl 1,2-epoxy-2-aryl ethylgembisphosphonates by direct epoxidation of 2-aryl,vinyl-1,1-diphosphonate derivatives with ethyl methyldioxirane generated in situ from potassium hydrogen monopersulfate (caroate) and butanone in a phase transfer system is reported. The epoxides were isolated in excellent yields and fully characterized by spectral and microanalytical data.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem 24:234–241, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21084

INTRODUCTION

Epoxides are interesting versatile intermediate reagents in organic synthesis, because the opening of their ring with different nucleophiles readily leads to diverse 1,2-difunctional systems in a regioselective manner [1–3]. Epoxides with phosphoryl substituents on the α-carbon atom are of particular importance owing to their use as valuable building blocks in the synthesis of bioactive substances [4] and as polymer modifiers [5, 6]. One of the most general and convenient approaches for the preparation of these compounds is through the direct oxidation of the corresponding vinylphosphonates [7]. However, the epoxydation of 1,2-alkenyl phosphonates using the traditional epoxidation reagents (electrophilic peracids or nucleophilic peroxides) generally gives poor results, due to the electron-withdrawing effect of the phosphoryl group on the carbon in the α-position, resulting in a relatively weak electrophilicity of the double bond and also to the appearance of competing side reactions (Michael addition, ring opening of the formed epoxide, isomerization, etc.) [5–7]. As an alternative method free from these limitations, we previously proposed the oxidation reaction with dioxiranes as a simple and efficient route for the obtention of 1,2-epoxyalkylphosphonates [8]. The reaction proceeded regioselectively in mild conditions, with moderate to good yield. We have now applied this reaction to the epoxidation of substituted vinyl*gem*bisphosphonates, and we wish to report here our preliminary results on the synthesis of 2-aryl-1,2-epoxyethyl*gem*bisphosphonate. To the best of our knowledge, the epoxidation of

Correspondence to: X. Y. Mbianda; e-mail: mbianday@uj.ac.za.
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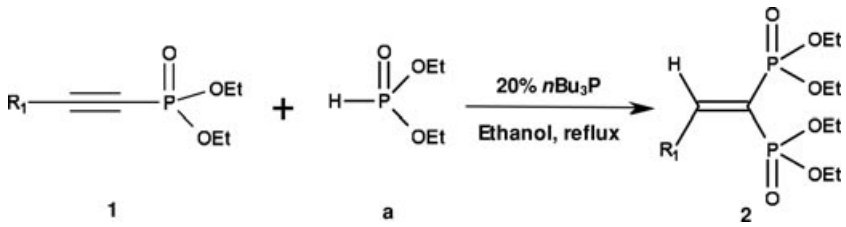


SCHEME 1 Synthesis of 2-aryl-1-vinyl-1,1-diphosphane dioxide.

substituted vinyl*gem*bisphosphonates has never been reported and spectroscopic data featuring this class of epoxides have never been described in the literature. These new structures are of great biological interest, since they might serve as valuable precursors for the preparation of biologically active amino bisphosphonic acids used in the treatment of various human pathologies including cancer [9]; bone- and joint-related diseases such as ostereoporosis, rheumatoid arthritis, Paget's disease [10–12] and parasitic disorders such as malaria, leishmaniasis, and Chaga's disease [13–16].

RESULTS AND DISCUSSION

Synthesis of Aryl-Substituted Vinylgembisphosphonates

Aryl-substituted vinyl*gem*bisphosphonates were synthesized by α-P-addition of diethyl phosphate **a** to readily available alkynylphosphonates **1** using tributylphosphine as a catalyst, according to a method described by Leclerclé and coworkers [17] (Scheme 1).

The reaction progress was monitored by FT-IR spectroscopy, and the reaction completion rested on the appearance of the vinyl (C=C) band (between 1570 and 1678 cm^{-1}), and the total disappearance of the alkyne (C≡C) band at 2200 cm^{-1} in the IR spectra. The regioselective nature of this addition reaction was established by the ^{31}P NMR spectra of the crude products, where only a pair of doublets (around 12 and 17 ppm) with a two-bond P–P coupling of 50 Hz was observed. This clearly indicates that the two phosphorus atoms on carbon C_1 were nonequivalent: each being a doublet resulting from coupling with the other. The reaction selectivity was further substantiated by the ^1H NMR signal of the ethylenic proton that appears as a doublet of doublets in downfield region (around 8.20 ppm), with *cis* and *trans* $^3J_{P\text{-}H}$ vinylic coupling constants ranging from 28.00 to 29.20 Hz and from 46.80 to 48.00 Hz, respectively. These values of the $^3J_{P\text{-}H}$ vinylic coupling constants are consistent with those reported in the literature [18]. Other interesting spectroscopic features of these compounds are listed in Table 1. These include the signal in ^{13}C NMR spectra of the geminal carbon C_1 that appears as a triplet around 120 ppm with very large $^1J_{P\text{-}C}$ coupling constant (around 170 Hz); the signal of the aromatic ipso carbon that appears as a doublet of doublets around 134 ppm with cis and trans $^3J_{P\text{-}C}$ coupling constants ranging from 7.60 to 8.70 Hz and 16.00 to 22.60 Hz, respectively. Previous investigators [17] wrongly assigned this signal to the ethylenic carbon C_2. In fact, carbon C_2 appears as a singlet in the downfield regions (156–161 ppm). The very large value of the $^1J_{P\text{-}C}$ coupling constant for C_1 and the zero value of $^2J_{P\text{-}C}$ for C_2 are common characteristic of the P(V)–C=C– bonding system [19].

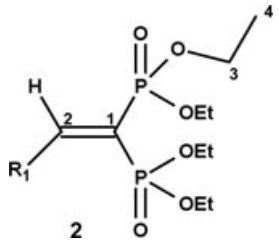
Synthesis of 1,2-Epoxy-2-aryl Ethylgembisphonates

The epoxidation was carried out through dioxirane that was generated in situ from buffered potassium hydrogen monopersulfate (caroate) solution and methylethylketone in a phase transfer system facilitated by the catalytic activity of tetrabutylammonium hydrogensulfate [8] (Scheme 2).

The pH of the reaction was kept strictly between 7.3 and 7.5 to avoid a Bayer–Villiger side reaction involving the ketone [20]. To achieve this, our reaction setup was equipped with a pH control system connected to a pump that maintains the pH range by a controlled addition of a 0.1 mol KOH solution to the reaction mixture. The completion of the reaction was monitored by ^{31}P NMR spectroscopy, where the epoxy *gem*bisphosphonates spectra featured a set of two doublets (around 13 and 15 ppm) similar to those observed in the corresponding vinylbisphosphonates, but with a bigger $^2J_{P\text{-}P}$ coupling constant (around 70 Hz) that reflects the change in the electronic nature of carbon C_1.

The reaction data shown in Table 2 reveals that a 100% conversion (based on ^{31}P NMR) was obtained after 92 h, with a maximum of four additions of caroate solution for all the compounds. These results suggest a relatively faster reaction of

TABLE 1 Spectroscopic Data for **2a–2g**



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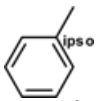
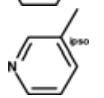
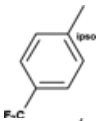
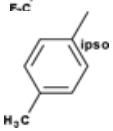
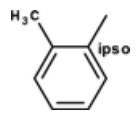
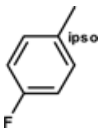
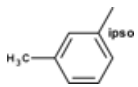
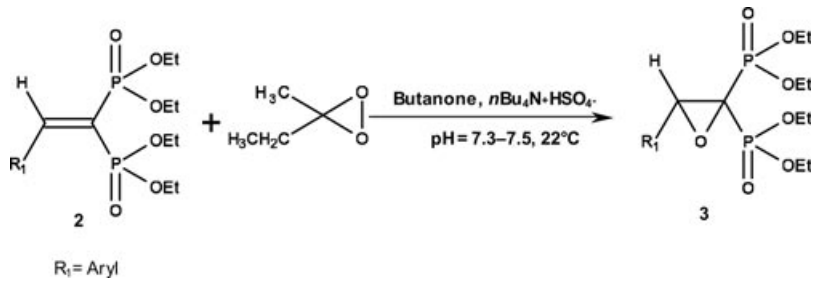
Entry	R_1	Yield (%)	δ ^{31}P NMR (ppm) J (Hz)	δ ^{1}H NMR (ppm) J (Hz) H_2	δ ^{13}C NMR (ppm) J (Hz)			IR (cm^{-1}) ν(C=C)
					C_1	C_2	C_{ipso}	
2a		68	12.16 (d) 17.11 (d) $^{2}J_{P-P} = 49.60$	8.27(dd), $^{3}J_{PH} = 29.20$ (cis) $^{3}J_{PH} = 47.60$ (trans)	120.30 (t) $^{1}J_{PC} = 169.20$	160.51 (s)	133.85 (dd) $^{3}J_{PC} = 8.60$ (cis) $^{3}J_{PC} = 22.60$ (trans)	1648
2b		65	11.16 (d) 15.98 (d) $^{2}J_{P-P} = 48.0$	8.22 (dd) $^{3}J_{PH} = 28.00$ (cis) $^{3}J_{PH} = 46.80$ (trans)	124.26 (t) $^{1}J_{PC} = 168.00$	156.66(s)	130.37 (dd) $^{3}J_{PC} = 9.00$ (cis) $^{3}J_{PC} = 22.00$ (trans)	1670
2c		71	11.84 (d) 16.07 (d) $^{2}J_{P-P} = 48.00$	8.32 (dd), $^{3}J_{PH} = 28.80$ (cis) $^{3}J_{PH} = 47.20$ (trans)	124.36 (t) $^{1}J_{PC} = 168.00$	158.47(s)	137.83 (dd) $^{3}J_{PC} = 7.60$ (cis) $^{3}J_{PC} = 16.00$ (trans)	1637
2d		75	12.55 (d) 17.92 (d) $^{2}J_{P-P} = 48.00$	8.22 (dd) $^{3}J_{PH} = 29.20$ (cis) $^{3}J_{PH} = 48.00$ (trans)	118.48 (t) $^{1}J_{PC} = 169.00$	160.62 (s)	131.16 (dd) $^{3}J_{PC} = 8.30$ (cis) $^{3}J_{PC} = 21.60$ (trans)	1637
2e		49	12.85 (d) 17.49 (d) $^{2}J_{P-P} = 52.80$	8.33 (dd) $^{3}J_{PH} = 28.00$ (cis) $^{3}J_{PH} = 47.60$ (trans)	122.53 (t) $^{1}J_{PC} = 170.40$	160.30 (s).	134.24 (dd) $^{3}J_{PC} = 8.30$ (cis) $^{3}J_{PC} = 20.50$ (trans)	1648
2f		82	12.56 (d) 17.28 (d) $^{2}J_{P-P} = 48.00$	8.19 (dd) $^{3}J_{PH} = 28.80$ (cis) $^{3}J_{PH} = 47.60$ (trans)	119.93 (t) $^{1}J_{PC} = 167.40$	159.30(s)	133.66 (dd) $^{3}J_{PC} = 8.00$ (cis) $^{3}J_{PC} = 25.60$ (trans)	1592
2g		64	12.23 (d) 17.38 (d) $^{2}J_{P-P} = 49.60$	8.22 (dd) $^{3}J_{PH} = 28.80$ (cis) $^{3}J_{PH} = 47.60$ (trans)	120.20 (t) $^{1}J_{PC} = 170.00$	161.37(s)	134.22 (dd) $^{3}J_{PC} = 8.70$ (cis) $^{3}J_{PC} = 21.50$ (trans)	1570



SCHEME 2 Synthesis of 1-2, epoxyarylbisphosphonates.

the vinylbisphosphonates when compared to their monophosphonate counterparts for which a period of 144 h (six additions of the caroate solution) was required for a total conversion [8]. This superior reactivity of the vinyl bisphosphonates could be explained by an increase in the nucleophilicity of the double bond owing to the electron-withdrawing effect brought about by the second phosphoryl group. For two cases (entry **2c** and **2f**), in which the nucleophilicity of the double bonds was further enhanced by the presence of strong electron-withdrawing substituents (CF_3 and F) on the phenyl ring, the reaction was even faster (48 and 73 h, respectively). These observations confirmed the fact that dioxiranes are very efficient oxygen-transfer agents for the epoxydation of electron-poor alkenes under mild conditions [20]. The reaction was chemo- and regioselective, since no by-products were observed in the ^{31}P NMR of the crude products and the compounds were easily isolated in high yields except for two cases (entry **2d** and **2f**), where the products decomposed during the purification process.

The structure of the final product was verified by a combination of ^{1}H, ^{31}P, and ^{13}C NMR and mass spectroscopy (Table 3). Interesting features observed include the ^{1}H NMR signal of the proton H_2 that appears as a triplet around 4.57 ppm with a $^{3}J_{P\text{-}H}$ coupling constant ranging from 4.8 to 5.2 Hz. The large upfield shift of this signal, relative to the

TABLE 2 Epoxidation of 2-Substituted 1,1-Vinylbisphosphonates

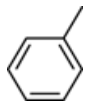
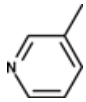
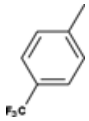
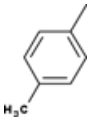
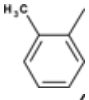
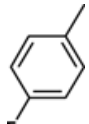
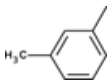
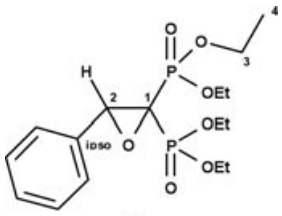
Entry	*R_1*	*Yield (%)*	*Conversion Rate (%)*	*Number of Caroate Additions*	*Reaction Time (h)*
3a		72	100	4	96
3b		86	100	4	96
3c		92	100	2	48
3d		59	100	4	96
3e		79	100	4	96
3f		42	100	3	72
3g		58	100	4	96

TABLE 3 Some Typical Data of Epoxyalkylbisphosphonates



3

Entry	δ ^{31}P NMR (ppm) $^{2}J_{P-P}$ (Hz)	δ ^{1}H NMR (ppm) $^{3}J_{P-H}$ (Hz) H_2	δ ^{13}C NMR (ppm) J (Hz) C_1	C_2	C_{ipso}	m/z
3a	13.43 (d), 15.25 (d) 72.00	4.66 (t) 4.80	55.15 (t) 182.10	60.90 (s)	131.53 (s)	392
3b	12.30 (d), 13.80 (d) 66.56	4.51 (t) 4.80	54.89 (t) 179.80	61.43 (m)	137.83 (s)	393
3c	12.85 (d), 14.46 (d) 68.80	4.67 (t) 4.80	55.62 (t) 184.00	60.85 (s)	136.15 (s)	460
3d	13.58 (d), 15.38 (d) 68.80	4.63 (t) 5.20	55.83 (t) 182.30	61.97 (s)	137.96 (s)	406
3e	13.57 (d), 15.45 (d) 73.60	4.56 (t) 5.20	55.44 (t) 184.00	60.78 (s)	135.65 (s)	406
3f	13.39 (d), 14.94 (d) 72.00	4.61 (t) 5.20	55.93 (t) 182.60	61.32 (s)	128.86 (s)	410
3g	13.55 (d), 15.34 (d) 72.00	4.59 (t) 5.20	55.73 (t) 182.00	61.68 (s)	137.06 (s)	406

corresponding vinylbisphosphonates, could be explained by the fact that the proton is now bonded to a sp^3 carbon linked to an heteroatom. Also noteworthy in the ^{13}C NMR spectrum is the upfield shift of all the signals compared to their vinyl analogs. For instance, the geminal carbon C_1 appears as a triplet around 55 ppm with a coupling constant $^{1}J_{P\text{-}C}$ = 182 Hz and the carbons C_2 and C_{ipso} appear as singlets around 60.90 and 131.53 ppm, respectively.

CONCLUSIONS

In conclusion, we have described a simple and practical method to synthesize 2-aryl 1,2-epoxyethyl *gem*bisphosphonates in good yields through dioxirane oxidation of the corresponding vinyl*gem*bisphosphonates. This new class of compounds has been fully characterized by NMR and mass spectral analysis. They are valuable tools that can give access to a wide range of substituted 1-hydroxymethylene-1,1-bisphosphonates with potent biological applications.

EXPERIMENTAL PROCEDURES AND METHODS

General Experimental Conditions

The starting materials and solvents were commercially available, except for the alkynylphosphonates, which were synthesized in our laboratory, following a procedure described by Aguiar and Chatta [21]. All reactions in nonaqueous solvents were conducted in flame-dried glassware under a positive pressure of argon and with magnetic stirring. IR spectra (film) were recorded using a Nicolet 380 FTIR spectrometer. The NMR spectra were obtained in $CDCl_3$ on a Bruker 400 instrument (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, and ^{31}P NMR at 160 MHz). ^{1}H NMR and ^{13}C NMR chemical shifts refer to signals of residual peaks as internal standard. ^{31}P NMR chemical shifts values are given in ppm relative to 85% H_3PO_4 as external standard. Abbreviations of coupling patterns are as follows: s, singlet; d, doublet; t, triplet; q, quatruplet; m, multiplet. Mass spectra were obtained using a Pegasus 4D GCxGC TOFMS mass spectrometer. TLC was conducted on thin Merck silica gel sheets with ethyl acetate as a mobile phase, and 4-(*p*-nitrobenzylpyridine) and tetraethylenepentamine as a revelator [22].

Synthesis of Aryl-Substituted Vinylgembisphosphonates, **2**

To a solution of phenylethynyl-phosphonic acid diethyl ester (**1**) (119 mg, 0.5 mmol) and diethylphosphite (7 μL, 0.55 mmol) in ethanol (5 mL), *n*-PBu_3 (25 μL, 0.1 mmol) under argon was added. The

mixture was heated under reflux for 8 h and then evaporated. The resulting residue was purified by flash column chromatography on silica gel with the system (acetone-hexane 7:3) as eluent to yield the expected product.

Tetraethyl(2-phenyl)vinyl Bisphosphonate **2a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.11 (t, $6H_4$, $^3J_{HH} = 6.80$ Hz); 1.35 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 3.95–4.09 (m, $4H_3$); 4.11–4.20 (m, $4H_3$); 7.35–7.27 (m, $3H_{ar}$); 7.70–7.71 (m, $2H_{ar}$); and 8.27 (dd, $1H_2$, $^3J_{PH} = 29.20$ Hz, $^3J_{PH} = 47.60$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.21 (d, C_4, $^3J_{PC} = 7.00$ Hz); 15.99 (d, C_4, $^3J_{PC} = 6.00$ Hz); 61.68 (d, C_3, $^2J_{PC} = 6.30$ Hz), 61.92 (d, $C_{3'}$ $^2J_{PC} = 5.60$ Hz), 120.30 (t, C_1, $^1J_{PC} = 169.20$ Hz); 127.29 (s, C_{ar}); 129.53 (s, C_{ar}); 129.77 (s, C_{ar}); 133.85 (dd, C_{ipso}, $J_{PC} = 8.60$ Hz, $J_{PC} = 22.60$ Hz); 160.51 (s, C_2). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 12.02 (d, $J_{PP} = 51.20$ Hz); 17.25 (d, $J_{PP} = 51.20$ Hz). IR (film, cm^{-1}): 3480, 2980, 2360, 1648, 1497, 1570, 1391, 1257, 1020, 776.

Tetraethyl(3-pyridine)vinyl Bisphosphonate **2b**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.31–1.22 (m, $6H_4$); 1.37–1.41 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 4.02–4.13 (m, $4H_3$); 4.15–4.24 (m, $4H_3$); 8.25 (s, $1H_{ar}$); 8.26 (dd, $1H_2$, $^3J_{PH} = 28.2$ Hz, $^3J_{PH} = 46.80$); 8.31 (t, $2H_{ar}$, $^3J_{HH} = 5.2$Hz); 8.71 (s, $1H_{ar}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.69 (d, C_4, $^3J_{PC} = 6.00$ Hz); 15.94 (d, C_4, $^3J_{PC} = 6.00$ Hz); 62.29 (d, C_3, $^2J_{PC} = 7.00$ Hz), 62.53 (d, C_3, $^2J_{PC} = 6.00$ Hz), 115.76 (s, C_{ar}); 122.52 (s, C_{ar}); 124.26 (t, C_1, $^1J_{PC} = 168.00$ Hz); 130.37 (dd, C_{ipso}, $J_{PC} = 9.00$ Hz, $J_{PC} = 22.00$ Hz); 136.76 (s, C_{ar}); 156.66 (s, C_2). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 11.16 (d, $J_{PP} = 48.00$ Hz); 15.98 (d, $J_{PP} = 48$ Hz). IR (film, cm^{-1}): 3480, 2980, 2360, 1648, 1497, 1570, 1391, 1257, 1020, and 776.

Tetraethyl [4-(Trifluoromethyl) Phenyl])vinyl Bisphosphonate **2c**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.21 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 1.33 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 3.72–3.87 (m, $4H_3$); 4.11–4.19 (m, $4H_3$); 7.46 (d, $2H_{ar}$, $^3J_{HH} = 8.00$ Hz); 7.74 (d, $2H_{ar}$, $^3J_{HH} = 8$ Hz); 8.24(dd, $1H_2$, $^3J_{PH} = 28.80$ Hz, $^3J_{PH} = 46.80$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.69–15.69 (m, C_4); 62.36 (d, C_3, $^2J_{PC} = 6.00$ Hz), 62.60 (d, C_3, $^2J_{PC} = 5.00$ Hz), 119.43 (s, C_{ar}); 122.16 (s, C_{ar}); 124.35 (t, C_1, $^1J_{PC} = 165.00$ Hz); 124.84 (s, C_{ar}); 128.71 (s, C_{ar}); 129.56 (s, C_{ar}); 130.62 (m, C_{ar}); 131.94 (s, C_{ar}); 133.61 (s, C_{ar}); 137.98 (m, C_{ipso}); 158.47(s, C_2). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 11.84 (d, $J_{PP} = 48.00$ Hz); 16.07 (d, $J_{PP} = 48$ Hz). IR (film, cm^{-1}): 3482, 2990, 2922, 1626, 1581, 1492, 1447, 1380, 1335, 1257, 1156, 1134, 1033, 865.

Tetraethyl (2-p-tolyl)vinyl Bisphosphonate **2d**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.36 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 1.33 (t, $6H_4$, $^3J_{HH} = 6.80$ Hz); 2.33 (s, 3H); 3.97–4.02 (m, $4H_3$); 4.12–4.17 (m, $4H_3$); 7.15 (d, $2H_{ar}$, $^3J_{HH} = 7.60$ Hz); 7.65 (d, $2H_{ar}$, $^3J_{HH} = 7.60$ Hz); 8.22(dd, $1H_2$, $^3J_{PH} = 29.20$ Hz, $^3J_{PH} = 48.00$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.19 (d, C_4, $^3J_{PC} = 7.00$ Hz); 15.48 (d, C_4, $^3J_{PC} = 6.00$ Hz); 20.63 (s, C); 61.56 (d, C_3, $^2J_{PC} = 6.00$ Hz); 61.75 (d, $C_{3'}$ $^2J_{PC} = 5.00$ Hz); 118.29 (t, C_1, $^1J_{PC} = 167.00$ Hz); 127.90 (d, $C_{ar'}$ $J_{PC} = 14.00$ Hz), 130.03(s, C_{ar}); 130.84 (dd, C_{ipso}, $J_{PC} = 8.00$ Hz, $J_{PC} = 21.00$ Hz); 140.44 (s, C_{ar}); 160.62 (s, C_2). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 12.55 (d, $J_{PP} = 51.20$ Hz); 17.92 (d, $J_{PP} = 48.00$ Hz). IR (film, cm^{-1}): 3440, 2930, 2866, 2844, 1726, 1615, 1581, 1510, 1250, 1033, 955, 832.

Tetraethyl (2-o-tolyl)vinyl Bisphosphonate **2e**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.02 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 1.32 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 2.22 (s, 3H); 3.77–3.93 (m, $4H_3$); 4.08–4.19 (m, $4H_3$); 7.10–7.15 (m, $2H_{ar}$); 7.20 (t, $1H_{ar}$, $^3J_{HH} = 7.60$ Hz); 7.51 (d, $1H_{ar}$, $^3J_{HH} = 8.00$ Hz); 8.33 (dd, $1H_2$, $^3J_{PH} = 28.00$ Hz, $^3J_{PH} = 47.60$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.17 (d, C_4, $^3J_{PC} = 7.00$ Hz); 15.54 (d, C_4, $^3J_{PC} = 3.00$ Hz); 19.05 (s, C); 61.49 (d, C_3, $^2J_{PC} = 6.00$ Hz); 61.91 (d, C_3, $^2J_{PC} = 6.00$ Hz); 124.53 (t, C_1, $^1J_{PC} = 170.40$ Hz); 124.62 (s, C_{ar}); 128.18 (s, C_{ar}); 128.93 (s, C_{ar}); 134.24 (dd, C_{ipso}, $J_{PC} = 8.30$ Hz, $J_{PC} = 20.50$ Hz); 134.98 (s, C_{ar}); 160.30 (s, C_2). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 11.75 (d, $J_{PP} = 51.80$ Hz); 16.38 (d, $J_{PP} = 52.80$ Hz). IR (film, cm^{-1}): 3459, 2978, 2911, 2866, 1659, 1581, 1458, 1391, 1245, 1044, 787.

Tetraethyl (4-fluorophenyl)vinyl Bisphosphonate **2f**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, $6H_4$, $^3J_{HH} = 6.80$ Hz); 1.35 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 3.98–4.11 (m, $4H_3$); 4.14–4.20 (m, $4H_3$); 7.05 (t, $2H_{ar}$, $^3J_{HH} = 8.40$ Hz); 7.77–7.81 (m, $2H_{ar}$); 8.23 (dd, $1H_2$, $^3J_{PH} = 29.20$ Hz, $^3J_{PH} = 47.60$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.37 (d, C_4, $^3J_{PC} = 7.00$ Hz); 15.63 (d, C_4, $^3J_{PC} = 7.00$ Hz); 61.89 (d, C_3, $^2J_{PC} = 7.00$ Hz); 62.08 (d, C_3, $^2J_{PC} = 6.00$ Hz); 113.62 (d, C_{ar}, $J = 21$ Hz); 114.54 (d, C_{ar}, $J = 21$ Hz); 115.27 (d, C_{ar}, $J = 22.00$ Hz); 119.93 (t, C_1, $^1J_{PC} = 167.40$ Hz); 129.04 (d, C_{ar}, $J = 8.80$ Hz); 136.40 (d, C_{ar}, $J = 8.00$ Hz); 133.46 (t, C_{ipso}, $J_{PC} = 8.00$ Hz); 159.30 (s, C_2); and 163.35 (d, C_{ar}, $J = 397.10$ Hz). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 12.56 (d, $J_{PP} = 48.00$ Hz); 17.28 (d, $J_{PP} = 48.00$ Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): −108.60. IR (film, cm^{-1}): 3482, 2990, 2900, 2866, 1603, 1536, 1447, 1413, 1245, 1011, 966, 832.

Tetraethyl (2-m-tolyl)vinyl Bisphosphonate **2g**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.09 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 1.31 (t, $6H_4$, $^3J_{HH} = 7.20$ Hz); 2.30 (s, 3H); 3.90–4.01 (m, $4H_3$); 4.09–4.15 (m, $4H_3$); 7.13 (d, $1H_{ar}$, $^3J_{HH} = 8.00$ Hz); 7.21 (t, $1H_{ar}$, $^3J_{HH} = 8.00$ Hz); 7.48 (d, $2H_{ar}$, $^3J_{HH} = 7.20$ Hz); 8.22 (dd, $1H_2$, $^3J_{PH} = 28.80$ Hz, $^3J_{PH} = 47.80$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.65 (d, C_4, $^3J_{PC} = 7.00$ Hz); 15.96 (d, C_4, $^3J_{PC} = 6.00$ Hz); 20.89 (s, C); 62.65 (d, C_3, $^2J_{PC} = 7.00$ Hz); 62.31 (d, C_3, $^2J_{PC} = 5.00$ Hz); 120.20 (t, C_1, $^1J_{PC} = 170.00$ Hz); 121.08 (s, C_{ar}); 127.61 (s, C_{ar}); 130.57 (s, C_{ar}); 130.94 (s, C_{ar}); 134.22 (dd, C_{ipso}, $J_{PC} = 9.00$ Hz, $J_{PC} = 22.00$ Hz); 137.25 (s, C_{ar}); 161.37(s, C_2). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 12.23 (d, $J_{PP} = 49.60$ Hz); 17.43 (d, $J_{PP} = 49.60$ Hz). IR (film, cm^{-1}): 3471, 2978, 2922, 1648, 1589, 1480, 1402, 1245, 1167, 1033, 787.

Synthesis of 1,2-Epoxy-2-aryl Ethylgembisphosphonates **3** *(Typical Procedure)*

4 mmol of vinyl*gem*bisphosphonates (**2a**), 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 $n Bu_4N^+HSO_4^-$ were introduced in a flask fitted with a vigorous mechanic stirrer. Then a solution of aqueous caroate (25 g (77 mmol) in 100 mL H_2O) was slowly added (over 6 h). The pH of the mixture was maintained between 7.3 and 7.5 by a solution of KOH (5%). Stirring was maintained for 18 h, then a new batch of aqueous caroate solution was slowly added (over 6 h) and the reaction mixture was stirred for an additional period of 18 h. After completion, solid NaCl was added to the cloudy reaction mixture until saturation. The organic phase was separated by decantation, and the aqueous phase was extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then evaporated. The crude product was purified by chromatography on silica gel with ethyl acetate as eluent.

Tetraethyl 1,2-Epoxy-2-phenylbisphosphonate **3a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.11 (m, $6H_4$); 1.37 (m, $6H_4$); 3.90 (m, $4H_3$); 4.27 (m, $4H_3$); 4.66 (t, $1H_2$, $^3J_{P\text{-}H} = 4.80$ Hz); 7.29 (m, $2H_{ar}$); 7.41 (m, $2H_{ar}$, $^3J_{H\text{-}H} = 7.20$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.09 (d, C_4, $^3J_{PC} = 6.00$ Hz); 15.40 (m, C_4, $^3J_{P\text{-}C} = 6.00$ Hz); 55.15 (t, C_1, $^1J_{P\text{-}C} = 182.10$ Hz); 60.90 (s, C_2); 61.77 (d, C_3, $^2J_{P\text{-}C} = 6.10$ Hz); 61.93 (d, C_3, $^2J_{P\text{-}C} = 6.40$ Hz); 62.94 (m, C_3); 126.04 (m, C_{ar}); 126.76 (s, C_{ar}); 127.42 (s, C_{ar}); 131.53 (s, C_{ipso}). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 13.43 (d, 1P, $^2J_{P\text{-}P} = 72.00$ Hz); 15.25 (d, 1P, $^2J_{P\text{-}P} = 72.00$ Hz). IR (film, cm^{-1}): 3488, 2980, 2937, 2913, 1640, 1457, 1396, 1261, 1163, 1028, 808. MS: *m/z* 392.

Tetraethyl 1,2-Epoxy-2-(3-pyridine)bisphosphonate **3b**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (m, $6H_4$); 1.34 (m, $6H_4$); 4.04 (m, $4H_3$); 4.24 (m, $4H_3$); 4.51 (t, $1H_2$, $^3J_{P\text{-}H} = 4.80$ Hz); 7.25 (m, $3H_{ar}$); 8.14 (s, $1H_{ar}$).). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.23 (m, C_4,); 15.40 (m, C_4, $^3J_{PC} = 6.00$ Hz); 54.89 (t, C_1, $^1J_{P\text{-}C} = 179.80$ Hz); 61.43 (m, C_2); 62.43 (d, C_3, $^2J_{P\text{-}C} = 6.30$); 63.22 (d, C_3, $^2J_{P\text{-}C} = 6.40$); 124.15 (s, C_{ar}) 124.56 (s, C_{ar}); 131.63 (s, C_{ar}); 136.80 (s, C_{ar}); 137.83 (s, C_{ipso}). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 12.30 (d, 1P, $^2J_{P\text{-}P} = 67.20$ Hz); 13.74 (d, 1P, $^2J_{P\text{-}P} = 67.20$ Hz). IR (film, cm^{-1}): 3427, 2956, 2925, 2876, 1665, 1469, 1383, 1242, 1163, 1028, 789. MS: *m/z* 393.

Tetraethyl 1,2-Epoxy-2-[4-(trifluoromethyl)phenyl] Bisphosphonate **3c**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.23 (m, $6H_4$); 1.36 (m, $6H_4$); 4.08 (m, $4H_3$); 4.26 (m, $4H_3$); 4.67 (t, $1H_2$, $^3J_{P\text{-}H} = 4.80$); 7.49 (m, $2H_{ar}$); 7.56(m, $2H_{ar}$).). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.48 (m, C_4,); 15.85 (m, C_4); 55.62 (t, C_1, $^1J_{P\text{-}C} = 184.00$ Hz); 60.85 (s, C_2); 61.88 (d, C_3, $^2J_{P\text{-}C} = 5.80$); 62.82 (m, C_3,); 63.83 (m, C_3); 124.56 (s, C_{ar}); 124.16 (m, C_{ar}); 124.36 (m, C_{ar}); 127.19 (s, C_{ar}); 128.76 (d, C_{ar}); 130.25 (m, C); 136.15 (s, C_{ipso}). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 12.85 (d, 1P, $^2J_{P\text{-}P} = 68.80$ Hz); 14.46 (d, 1P, $^2J_{P\text{-}P} = 68.80$ Hz). IR (film, cm^{-1}): 3507, 2980, 2925, 2827, 1720, 1622, 1445, 1389, 1255, 1132, 1016, 789. MS: *m/z* 460.

Tetraethyl 1, 2-Epoxy-2-p-tolylbisphosphonate **3d**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.12 (m, $6H_4$); 1.37 (m, $6H_4$); 3.37 (m, $4H_3$); 4.28 (m, $4H_3$); 4.63 (t, $1H_2$, $^3J_{P\text{-}H} = 5.20$); 7.11 (d, $2H_{ar}$, $^3J_{H\text{-}H} = 7.60$ Hz); 7.29 (d, $2H_{ar}$, $^3J_{H\text{-}H} = 8.00$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.88 (d, C_4, $^3J_{P\text{-}C} = 6.00$ Hz); 16.19 (m, C_4); 21.02 (s, C); 55.83 (t, C_1, $^1J_{PC} = 182.30$ Hz); 61.97 (s, C_2); 62.70 (m, C_3,); 63.73(d, C_3,^{2} $J_{P\text{-}C} = 6.30$ Hz); 126.68(s, C_{ar}); 128.21(s, C_{ar}); 129.14(s, C_{ar}); 137.96 (s, C_{ipso}). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 13.59 (d, 1P, $^2J_{P\text{-}P} = 72.00$ Hz); 15.38 (d, 1P, $^2J_{P\text{-}P} = 72.00$ Hz). IR (film, cm^{-1}): 3507, 2980, 2931, 2864, 1732, 1647, 1451, 1383, 1261, 1022, 802. MS: *m/z* 406.

Tetraethyl 1,2-Epoxy-2-o-tolylbisphosphonate **3e**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.20 (m, $6H_4$); 1.37 (m, $6H_4$); 3.94 (m, $4H_3$); 4.29 (m, $4H_3$); 4.56 (t, $1H_2$, $^3J_{P\text{-}H} = 5.20$ Hz); 7.15 (m, $3H_{ar}$); 7.33 (d, $1H_{ar}$, $^4J_{H\text{-}H} = 7.60$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.58 (d, C_4, $J = 6.00$); 15.80 (m, C_4); 18.12 (s, C); 55.44 (t, C_1, $^1J_{P\text{-}C} = 184.00$ Hz); 60.78 (s, C_2);

62.10 (d, C_3, $^2J_{P\text{-}C}$ = 6.50 Hz); 62.38 (d, C_3, $^2J_{P\text{-}C}$ = 6.10 Hz); 63.27 (dm, C_3); 124.36 (s, C_{ar}); 125.99 (s, C_{ar}); 127.66 (s, C_{ar}); 128.74 (s, C_{ar}); 130.66 (s, C_{ar}); 135.65 (s, C_{ipso}).). ^{31}P NMR ($CDCl_3$, 160 MHz) δ (ppm): 13.57 (d, 1P, $^2J_{P\text{-}P}$ = 75.20 Hz); 15.45 (d, 1P, $^2J_{P\text{-}P}$ = 75.20 Hz). IR (film, cm^{-1}): 3501, 2974, 2925, 2864, 1659, 1457, 1371, 1261, 1169, 1010, 802. MS: *m/z* 406.

Tetraethyl 1,2-Epoxy-2-(4-fluorophenyl)bisphosphonate **3f**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.12 (m, $6H_4$); 1.36 (m, $6H_4$); 3.92 (m, $4H_3$); 4.25 (m, $4H_3$); 4.61 (t, $1H_2$, $^3J_{P\text{-}H}$ = 5.20 Hz); 7.00 (m, $2H_{ar}$); 7.37 (m, $2H_{ar}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.99 (d, C_4, $^3J_{P\text{-}C}$ = 5.90 Hz,); 16.28 (m, C_4); 55.93 (t, $C_{a,}$ $^1J_{P\text{-}C}$ = 182.60); 61.32 (s, C_2); 63.27 (t, C_3, $^2J_{P\text{-}C}$ = 6.10 Hz); 64.01 (m, $C_{3,}$); 114.67 (d, C_{ar}, J = 21.70 Hz); 128.10 (s, C_{ar}); 128.78 (s, C_{ar}); 128.86 (s, C_{ipso}); 162.45 (d, C_{ar}, J = 245.80 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.39 (d, 1P, $^2J_{P\text{-}P}$ = 72.00 Hz); 14.94 (d, 1P, $^2J_{P\text{-}P}$ = 72.00 Hz). IR (film, cm^{-1}): 3488, 2968, 2925, 2852, 1726, 1610, 1518, 1463, 1383, 1261, 1157, 1022, and 802. MS: *m/z* 410.

Tetraethyl 1,2-Epoxy-2-m-tolylbisphosphonate **3g**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): δ 1.04–1.10 (m, $6H_4$); 1.31–1.36 (m, $6H_4$); 2.36 (s, 3H); 3.79–3.98 (m, $4H_3$); 4.19–4.29 (m, $4H_3$); 4.59 (t, $1H_2$, $^3J_{PH}$ = 5.20 Hz); 7.04–7.05 (m, $1H_{ar}$); 7.15–7.19 (m, $3H_{ar}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.83 (d, C_4, J = 6.00 Hz); 16.19 (d, C_4, J = 5.00 Hz); 21.06 (s, C); 55.73 (t, $C_{1,}$ $^1J_{PC}$ = 182.00 Hz); 61.68 (s, C_2); 63.61 (m, C_3); 63.71 (d, C_3, $^2J_{PC}$ = 6.00 Hz); 123.80 (s, C_{ar}); 127.29 (s, C_{ar}); 127.43 (s, C_{ar}); 128.86 (s, C_{ar}); 132.05 (s, C_{ar}); 137.06 (s, C_{ipso}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.55 (d, 1P, $^2J_{PP}$ = 72.00 Hz); 15.34 (d, 1P, $^2J_{PP}$ = 73.60 Hz). IR (film, cm^{-1}): 2979,2931, 2873, 1610, 1591, 1476, 1444, 1391, 1254, 1163, 1014, 974, 886, 830, 789, 696. MS: *m/z* 406.

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