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A Green and Facile Method for the Synthesis of Substituted 1,2-Epoxy Ethyl*gem*bisphosphonates and their Symmetrical Dibutylammmonium Salts

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Abstract

In this paper we report a convenient and environmentally friendly method for the synthesis of substituted 1,2-epoxy ethyl*gem*bisphosphonates using hydrogen peroxide in methanol-water solvent system. This reaction allows easy access to the desired epoxy bisphosphonates in good to excellent yields. It can also be scaled up easily since it requires small amounts of solvents and there are no by-products. The epoxy bisphosphonates were dealkylated with dibutylamine under solvent-free conditions to give novel symmetrical dibutylammonium diethyl (oxirane-2,2-diyl)bisphosphonate salts.

Keywords

Epoxy bisphosphonates; Green epoxidation; Electron-deficient alkenes; Dealkylation; Ammmonium bisphosphonate salts.

Introduction

Bisphosphonates (BP's) continue to receive a great deal of interest due to their industrial uses and other pharmaceutical applications.[1, 2] Bisphosphonates having the epoxy group on the carbon in alpha position are of particular importance because they can be used as intermediates for the synthesis of new drug leads. The oxirane ring is highly strained, so it reacts easily with a wide range of nucleophiles.[3] Epoxy bisphosphonates can also be used in the modification of polymers for flame retardancy and anti-corrosion applications. [4,5] With all these emerging applications and increasing demand, it is therefore necessary to develop environmentally friendly protocols for their synthesis to minimize their environmental impact, especially in the pharmaceutical sector. According to Cespi *et al*, the production of pharmaceuticals has the highest environmental impact, when compared to other sectors of the chemical industry.[6]

Epoxidation of electron-rich alkenes is easily achieved using peroxy acids such meta-chloroperoxybenzoic acid (mCPBA) and tert-butyl hydroperoxide (TBHP). However, this method is limited when it comes to electron-deficient alkenes. [7,8] Ideally, electron-deficient olefins would be epoxidized by hydrogen peroxide in the presence

of metal catalysts [9]. Hydrogen peroxide is an environmentally begnin oxidizing agent; it has high atom efficiency and only produces water as a by-product.[10,11] However, the problem encountered with this method is the insolubility of the metal catalysts in organic solvents. A lot of work has been done to improve epoxidation of electron-deficient olefins by hydrogen peroxide and metal catalysts (usually oxides of manganese, tungsten, molybdenum).[12,13] These metals are usually converted into soluble complexes using salen and porphyrin ligands; this makes the process expensive due to the high cost of the ligands. The use of titanium isopropoxide as a catalyst for hydrogen peroxide epoxidation has also been reported.[14] In this case, the reaction has to be done under dry conditions due to the water sensitivity of titanium isopropoxide. Biphasic solvent systems have also been used with phase transfer catalysts.[11, 15] The use of toxic chlorinated solvents in these systems cancels out the benefits of using hydrogen peroxide as a green epoxidizing agent. Ionic liquids have also been explored as solvents for epoxidation as they have the ability to dissolve a wide range of compounds.[16] Successful epoxidation of 2-substituted vinyl-1,1-bisphosphonate esters has been reported by Fotsing *et al* [17] using dioxirane generated *in situ* by butanone and caroate in water-dichloromethane solvent system. This method required a complex automated set-up to maintain the pH between 7.3 and 7.5 and longer reaction time (over 24 hours). It also generates large volumes of solution (more than 2L per 1g substrate) making the work up procedure very tedious. In this study we have managed to develop a facile, efficient and environmentally friendly method for epoxidation of 2-substituted vinyl*gem*bisphosphonate esters using hydrogen peroxide and sodium tungstate.

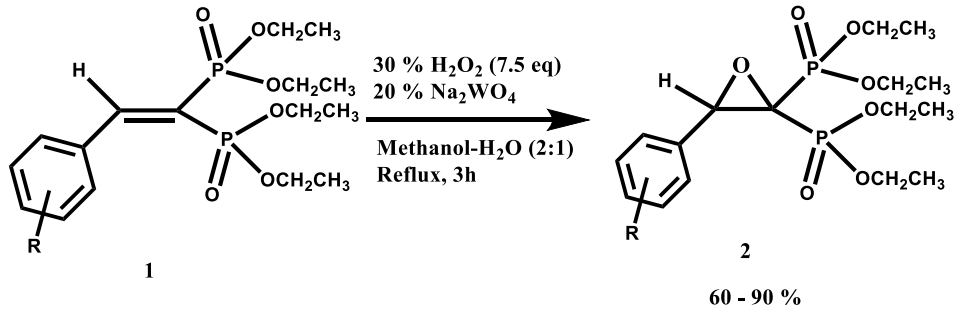
Phosphonic and bisphosphonic acids can be synthesized indirectly via phosphonate esters followed by deprotection/dealkylation to get free acids. The most common and

simple method for the deprotection of phosphonates is by refluxing them with concentrated HCl.[18,19] However, this method is not suitable for acid sensitive functional groups because of the harsh reaction conditions. Phosphonate esters with labile moieties are usually deprotected by reacting with bromotrimethylsilane (TMSBr) followed by solvolysis with water or methanol, a method that was developed by McKenna and co-workers.[20–23] Bisphosphonic acids have also been accessed by palladium-catalyzed hydrogenolysis of tetrabenzyl bisphosphonate esters. This protocol was used by Page *et al* [24] to synthesize 1,2 epoxy*gem*bisphosphonic acids. Partial dealkylation of tetraalkyl methylenebisphosphonates has been reportedly achieved by reacting them with amines such as piperidine and morpholine.[25–28] In this study, substituted epoxy*gem*bisphosphonates were successfully deprotected with dibutylamine to give novel dibutylammonium salts. The bisphosphonates were symmetrically dealkylated to form diammonium salts which can be converted to free acids by ion exchange resins.

Results and Discussion

Synthesis of substituted epoxygembisphosphonates

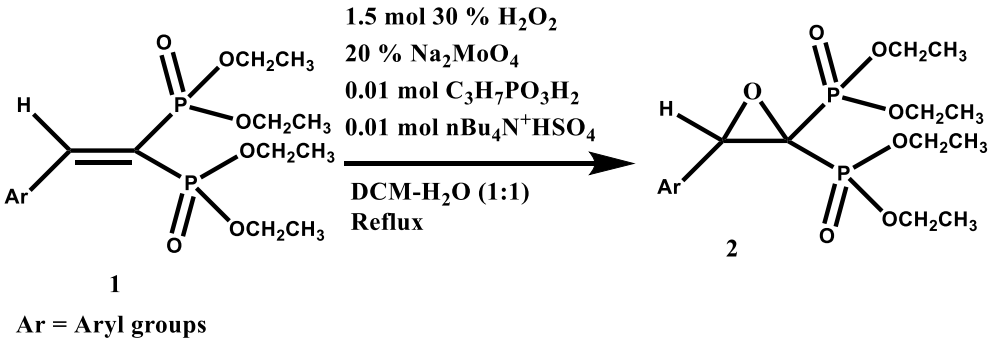
Substituted vinylbisphonates were epoxidized using hydrogen peroxide with sodium tungstate as a catalyst (Scheme 1). Previous attempts to oxidize substituted vinylphosphonates using traditional reagents like hydrogen peroxide and peroxy acids are reported to have failed.[8,17] Our method successfully epoxidized substituted vinyl*gem*bisphosphonates using H_2O_2/Na_2WO_4 in a simple and environmentally friendly solvent system, methanol-water.



R = H (a), 4-F (b), 2-CH_3 (c), 3-NO_2 (d), 2-OCH_3-3-OCH_3 (e).

Scheme 1: Epoxidation using hydrogen peroxide and sodium tungstate

In search of a simple, green and efficient method for the synthesis of substituted 1,2-epoxy ethyl*gem*bisphosphonate esters, we first tried the method reported by Noyori *et al* with modification as shown in Scheme 2.[11] We tried to epoxidize the substituted vinyl bisphosphonates **1** (prepared according to literature [29]) using hydrogen peroxide and sodium molybdate as a catalyst. Tetrabutylammonium bisulfate was added as a phase transfer catalyst and propylphosphonic acid was added an accelerator. The reaction mixture was refluxed in dichloromethane and methanol (1: 1) whilst monitored by ^{31}P NMR. The formation of the epoxide **2** was only observed after 5 days showing less than 30 % conversion of the starting material.



Scheme 2: Epoxidation using hydrogen peroxide and sodium molybdate

The reaction was repeated and sodium molybdate was replaced with sodium tungstate. The reaction was expected to proceed faster in this case but there was no

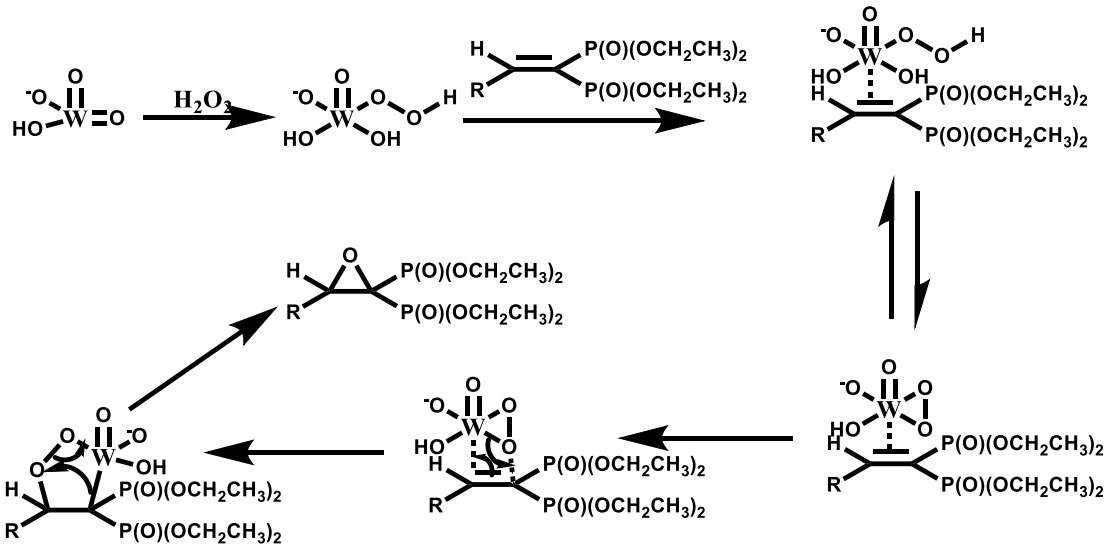
conversion even after 5 days. It was noted that a precipitate was formed when tetrabutylammonium bisulfate was added to the reaction mixture containing sodium tungstate, indicating complex formation between the two. This could be the reason sodium tungstate was ineffective as a catalyst since it was now in the solid phase. The replacement of dichloromethane with THF did not improve the rate of reaction in both cases. We then sought a solvent system that would dissolve all starting materials and catalyst without the requirement of a phase transfer catalyst and came up with a mixture of methanol and water in 2:1 ratio. Repeating the reaction with this simple solvent system yielded the expected product in 3 hours in good to excellent yields (Scheme 1).

Hydrogen peroxide (7.5 eq) was added to the reaction mixture under reflux at 1-hour intervals and the reaction monitored by ^{31}P NMR analysis until all the starting material **1** was converted to the epoxide **2** (in 3 hours). The phosphorus coupling constant (J_{P-P}) changed from 50 Hz (corresponding to the substituted vinyl*gem*bisphosphonate) to about 70 Hz (corresponding to the epoxy*gem*bisphosphonate). ^{31}P-NMR spectra showed two doublets resonating at about 12 ppm and 15 ppm with, $^{2}J_{P-P}$ coupling constants around 70 Hz. This is consistent with the structure of 2-aryl substituted epoxy*gem*bisphosphonates. This is because there is no free rotation around the oxirane ring, therefore the two phosphorus atoms are always in different environments. ^{1}H-NMR spectra showed the triplet corresponding to the oxiranyl proton (H-2) at about 5 ppm with a coupling constant, $^{3}J_{P-H}$ of around 5 Hz.

This is a convenient and environmentally friendly method for epoxidation of substituted vinyl*gem*bisphosphonates. The catalyst and epoxidizing agent are readily available and easy to handle compared to materials used in other epoxidation

protocols. Sodium tungstate is more convenient and cheaper compared to epoxidizing agents composed of salen and porphyrin complexes. It can also be recycled easily because it remains in the aqueous phase when the product is extracted with ethyl acetate. The reaction can also be easily scaled up as the total volume of solvent required for each reach reaction is small (about 70 mL per 1 g of substrate). The reaction is believed to follow a mechanism similar to that described by Wang *et al* [30] as shown in Scheme 3. Sodium tungstate rapidly forms a complex with hydrogen peroxide which in turn forms the dioxocyclic peroxo tungstate. The dioxocyclic tungstate complex is the active species responsible for oxidizing the vinyl*gem*bisphosphonates into epoxy*gem*bisphosphosphonates.

With this method, we have also managed to eliminate the need for phase transfer catalyst and phosphonic acid accelerator which makes the process cost effective as well reduce the complexity of waste produced during the reaction. Replacing toxic dichloromethane with methanol also significantly reduces the environmental impact of the process. Methanol is ranked as one of the most environmentally friendly solvents because its production process has very little impact on the environment.[31] Using hydrogen peroxide also makes the process even greener because it only produces water on decomposition and has high atom efficiency (about 47 %).[10]



Scheme 3: Proposed mechanism for tungstate epoxidation of 2-substituted vinyl-1,1-bisphosphonates in protic solvents.

Dealkylation of substituted epoxy*gem*bisphosphonates

TMSBr mediated deprotection of substituted epoxygembisphosphonates

The epoxy bisphosphonate ester **2** was first reacted with TMSBr without adding a base as we had previously done this reaction successfully with vinyl bisphosphonates **1**. ^{31}P NMR analysis showed that the epoxy bisphosphonate was destroyed due to harsh conditions instead of forming the target epoxy bisphosphonic acid **5**. The reaction was then repeated in the presence of N-methylmorpholine as an acid scavenger (Scheme 4). In this case, ^{31}P NMR analysis showed that the epoxy epoxybisphosphonates were transformed to silyl intermediate **4**. The ^{31}P NMR spectra (Figure 1) showed two doublets at -1.6 ppm and -3.4 ppm with a $^{2}J_{P\text{-}P}$ coupling constant of about 78 Hz. This showed that the oxirane ring was not opened during the reaction.

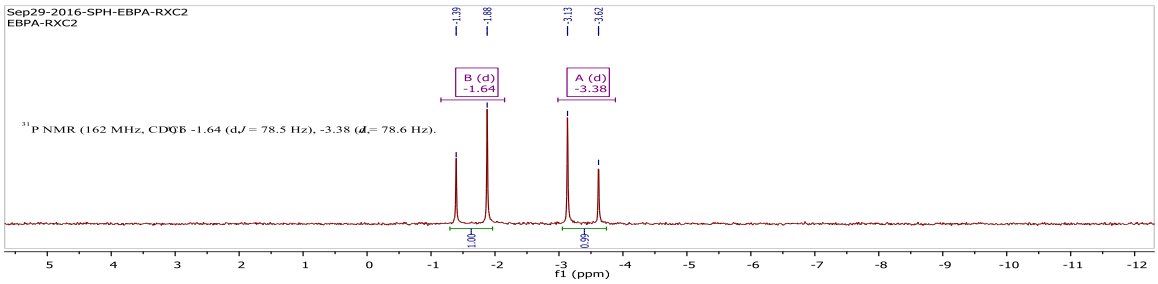
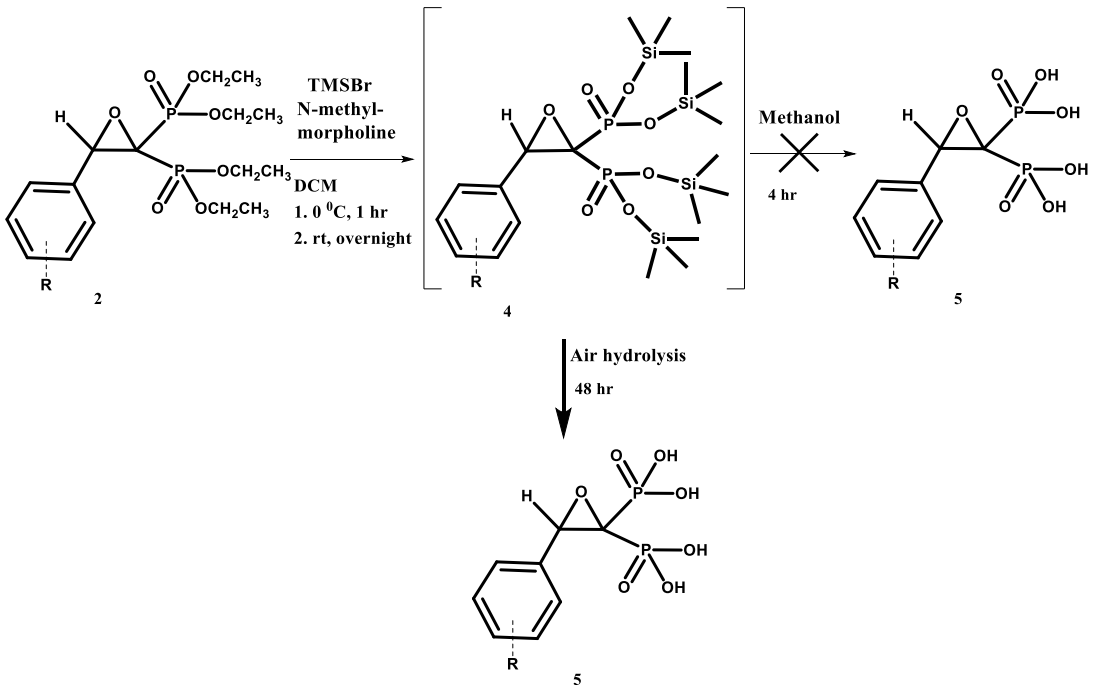


Figure 1 ^{31}P NMR spectrum of epoxy BP silyl intermediate 4.

Solvolysis of the silylated intermediate **4** with methanol led to the destruction of the oxirane ring again as shown in Scheme 4. The reaction was repeated and the silyl intermediate **4** was allowed to hydrolyse slowly in air to give the substituted epoxy bisphosphonic acid **5**. This was confirmed by ^{31}P NMR spectra (Figure 2). The spectra showed two doublets at about 13 ppm and about 10 ppm corresponding to the two phosphorus atoms with a coupling constant $^{2}J_{P\text{-}P}$ of about 67 Hz. Purification of the epoxy bisphosphonic acids by recrystallization led to poor yields, therefore attention was turned to dealkylation using amines.



Scheme 4: TMSBr assisted dealkylation of epoxy BP's

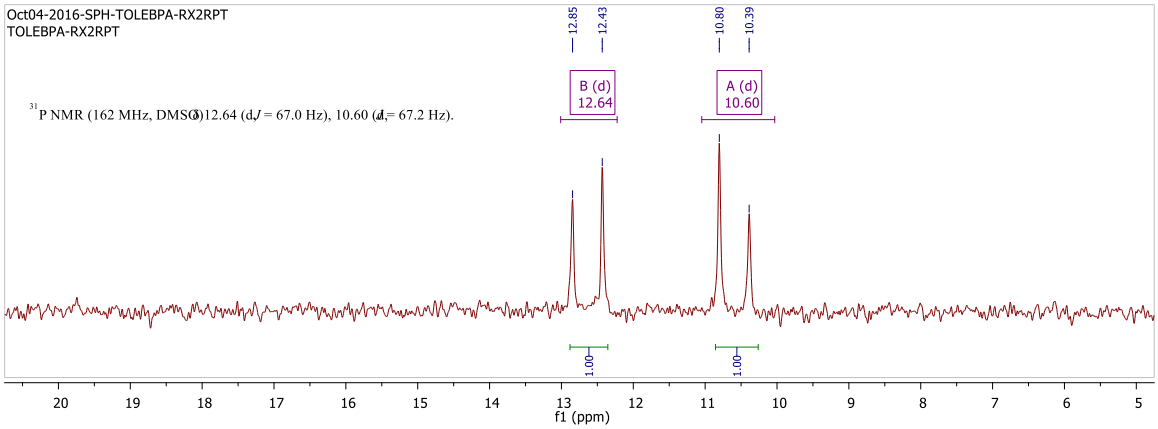
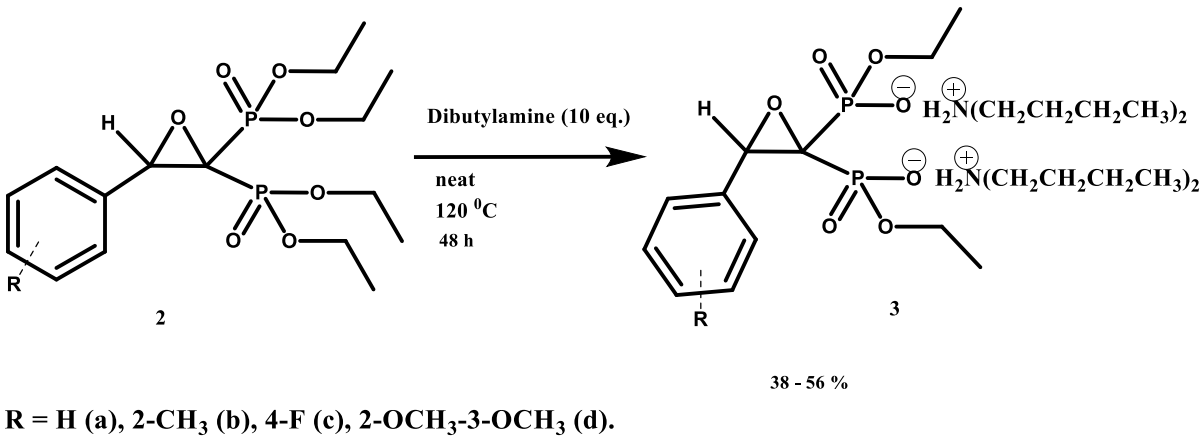


Figure 2: ^{31}P NMR spectrum of (3-(o-tolyl)oxirane-2,2-diyl)bis(phosphonic acid) 5.

Dealkylation of substituted epoxygembisphosphonates with amines

The epoxy BP's **2** were dealkylated using amines after failing to get satisfactory yields when using TMSBr. Cyclohexylamine and dibutylamine were investigated for this purpose, and the latter produced fewer side products making it easier to purify the products. Compounds **2** were heated with excess dibutylamine to give dibutylammonium epoxy*gem*bisphosphonate salts **3** (Scheme 5).



Scheme 5: Reaction of epoxy BP's with dibutylamine.

^{31}P NMR analysis (Figure 3) of the dibutylammonium epoxy BP salts **3** showed that the reaction selectively gave symmetrically dealkylated products; only two doublets were observed at about 10 ppm and 13 ppm with a $^{2}J_{P\text{-}P}$ constant of about 60 Hz.

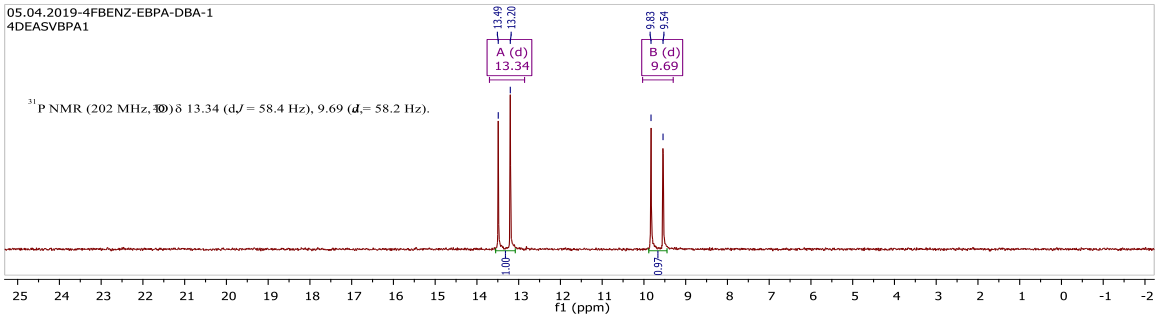
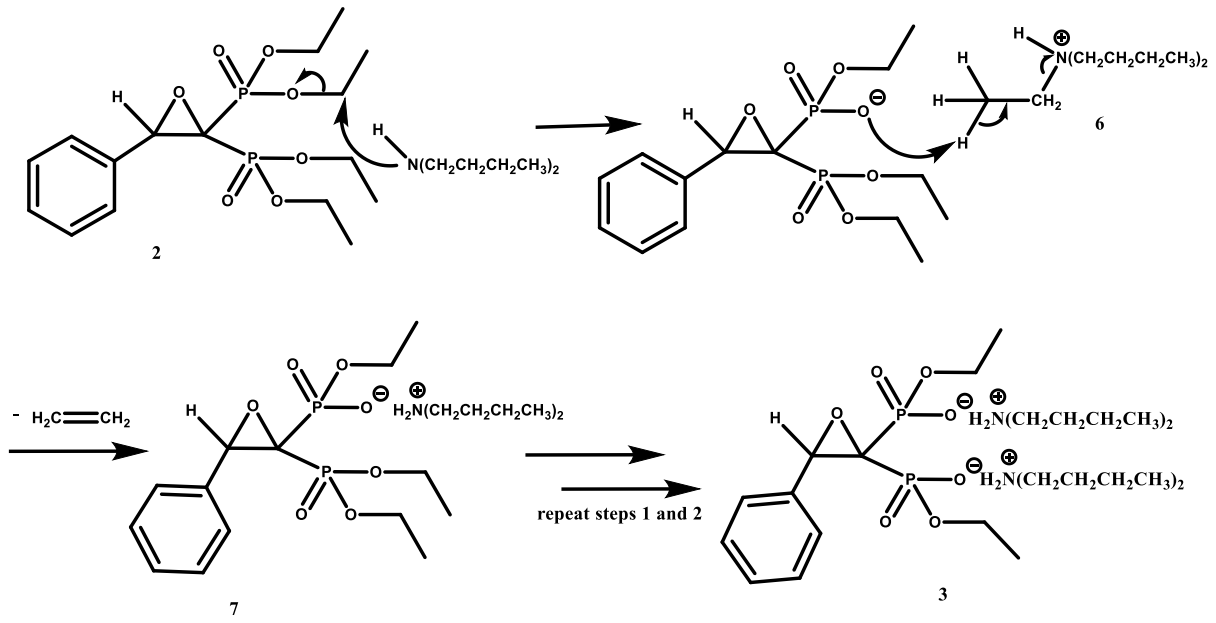


Figure 3: ^{31}P NMR spectrum of dibutylammonium diethyl (3-(4-fluorophenyl)oxirane-2,2-diyl)bis(phosphonate) 3.

^{1}H NMR spectra clearly showed that the structure only had two ethoxy groups (-OCH_2CH_3). The two methyl protons appeared as triplets at about 0.9 ppm and 1.2 ppm whilst the two methylene protons appeared at about 3.7 ppm and 4 ppm as multiplets. Integration of the spectra confirmed the presence of only two dibutylammonium cations in the structure. The oxiranyl proton resonated at about 4.6 ppm displaying a triplet with $^{2}J_{P\text{-}H}$ coupling constant of about 5 Hz. This confirmed that the oxirane ring did not open during the reaction.

The proposed mechanism for dealkylation of epoxy BP's with dibutylamine is shown in Scheme 6. The first step involves the alkylation of dibutylamine by one of the phosphonate groups to form the trialkylammonium ion **6**. The trialkylammonium cation then undergoes Hofmann type rearrangement/ elimination to release ethene and give the dibutylammonium epoxy BP salt **7**. This process is repeated with the second phosphonate group to form the symmetrical dibutylammonium diethyl epoxy*gem*bisphosphonate salt **3**.



Scheme 6: Proposed mechanism for dealkylation of epoxy BP with dibutylamine.

Conclusion

We have successfully developed a facile and environmentally friendly method for the synthesis of substituted 1,2-epoxy ethyl*gem*bisphonates in quantitative yields. Substituted vinyl*gem*bisphosphonates were epoxidized by hydrogen peroxide and sodium tungstate in methanol-water solvent system. We believe this simple and easy method could be extended to other electron deficient alkenes. The epoxy bisphosphonate esters were dealkylated with dibutylamine to give the novel symmetrical epoxy*gem*bisphosphonate ammonium salts. This reaction needs further optimization to improve the yield. The dibutylammonium salts can be easily converted to partial free acids using an acid resin.

Experimental

Starting materials were purchased from Sigma Aldrich or Merck Chemicals unless specified. Solvents were dried using standard procedures in organic chemistry. ^{1}H

NMR (400 MHz), ^{13}C NMR (100 MHz), ^{31}P NMR (160 MHz) were recorded on a Bruker Avance 400 MHz and 1H NMR (500 MHz), 13C NMR (126 MHz), 31P NMR (200 MHz) were measured on a Bruker 500. High resolution mass spectrometry (HRMS) analysis was obtained using the Bruker Compact Q-TOF mass spectrometer.

Procedures

Synthesis of Substituted Vinyl*gem*bisphosphonates

Tetraethyl 2-(phenyl)-ethene-1,1-bisphosphonate 1a: Benzaldehyde (1.06 g, 10 mmol) was dissolved in dry THF (80 mL) and $TiCl_4$ (3 mL, 12 mmol) in toluene (20 mL) was added drop wise. The mixture was stirred for 5 minutes at 0 ^0C. A solution of tetraethyl methylenebisphosphonate (3.46 g, 12 mmol) and N-methylmorpholine (2.43 g, 24 mmol) in dry THF (20 mL) was added drop wise. The mixture was stirred for 1h at 0 ^0C, and then stirred for 3h at room temperature. The reaction was quenched with water (50 mL) and extracted three times with ethyl acetate (100 mL). The organic phase was dried with anhydrous sodium sulphate and purified by column chromatography (acetone: EtOAc, 1: 2) to give the product as a pale yellow oil (2.63 g, 70 %). R_f = 0.3

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.32 (dd, J=47.7, 29.1 H_Z, 1H, H-2), 7.50 – 7.76 (m, 2H, H_{ar}), 7.30 – 7.41 (m, 3H, H_{ar}), 4.17 - 4.25 (m, 4H, -OC**H_2-**), 4.00-4.06 (m, 4H, -OC**H_2-**), 1.39 (t, *J* = 7.1 Hz, 6H, -OCHC**H_3**), 1.16 (t, *J* = 7.1 Hz, 6H, -OCHC**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.18 (d, *J* = 2.1 Hz, C-2), 134.35 (dd, *J* = 21.7, 8.6 Hz, C_{ipso}), 130.30 (s, C_{ar}), 130.09 (t, *J* = 1.5 Hz, C_{ar}), 127.81 (m, C_{ar}), 120.68 (dd, *J* = 170.1, 165.1 Hz, C-1), 62.43 (m, -O**C**H_2-), 62.19 (m, -O**C**H_2-), 16.11 (d, *J* = 6.7 Hz, -OCH**C**H_3), 15.79 (d, *J* = 6.7 Hz, -OCH**C**H_3).

^{31}P NMR (160 MHz, $CDCl_3$) δ (ppm): 12.04 (d, J = 49.6 Hz), 17.25 (d, J = 49.6).

NMR spectra of the substituted vinyl*gem*bisphosphonates consistent with those reported by Fotsing *et al* [17].

General procedure for epoxidation

Tetraethyl 2-phenyl-1,2-epoxyethane-1,1-bisphosphonate 2a: Tetraethyl 2-phenyl-vinyl-1,1-bisphosphonate (0.133g, 0.337 mmol) and sodium tungstate dihydrate (0.024g, 0.0728 mmol) were charged into a three-neck flask containing a mixture of methanol (10 mL) and distilled water (5 mL). A solution of 30 % hydrogen peroxide (0.2 mL) was added while refluxing at 1 hour intervals until the reaction was complete (as monitored by thin layer chromatography). When the reaction was complete, methanol was evaporated under reduced pressure leaving water. The aqueous phase was then extracted three times with ethyl acetate (30 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and evaporated under reduced pressure to give the product as a pale yellow oil (0.102 g, 77%). R_f = 0.45

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H, H_{ar}), 7.38 – 7.27 (m, 3H, H_{ar}), 4.69 (t, *J* = 5.0 Hz, 1H, H-2), 4.37 – 4.23 (m, 4H, -OC**H_2-**), 4.03 – 3.81 (m, 3H, -OC**H_2-**), 3.81 – 3.69 (m, 1H, -OC**H_2-**), 1.43 – 1.37 (m, 6H, -OCHC**H_3**), 1.16 – 1.09 (m, 6H, -OCHC**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 132.38 (dd, *J* = 1.3, 0.7 Hz, C_{ipso}), 128.37 (s, C-Ar), 127.70 (s, C-Ar), 126.95 (d, *J* = 0.7 Hz, C-Ar), 63.95 (d, *J* = 6.4 Hz, C-3), 62.87 (dd, *J* = 16.4, 6.4 Hz, C-3), 61.89 (t, *J* = 2.0 Hz, C-2), 56.00 (dd, *J* = 183.5, 173.1 Hz, C-1), 16.36 (dd, *J* = 5.8, 3.9 Hz, C-4), 16.03 (d, *J* = 6.1 Hz, C-4).

^{31}P NMR (160 MHz, $CDCl_3$) δ (ppm): 15.01 (d, J_{P-P} = 72Hz, 1P); 13.66 (d, J_{P-P} = 72Hz, 1P).

HRMS (ESI^+): m/z [$M+H^+$] calculated for $C_8H_{10}O_6P_2$ [$M+H^+$] = 393.1187; found= 393.1245.

General procedure for dealkylation of epoxy*gem*bisphosphonates with dibutyl amine

Dibutylammonium diethyl (3-(4-fluorophenyl)oxirane-2,2-diyl)bis(phosphonate) 3b: Tetraethyl 2-(4-fluorophenyl)-1,2-epoxyethane-1,1-bisphosphonate **2b** (0.3 g, 0.765 mmol) was heated with excess dibutylamine (10 eq) at 120 ^{0}C for 48 hours. Unreacted dibutylamine was removed under reduced pressure. The residue was washed with acetone to give the product as a white solid (0.262 g, 56 %).

^{1}H NMR (500 MHz, D2O) δ 7.40 – 7.34 (m, 2H, H_{ar}), 6.99 (t, J = 9.0 Hz, 2H, H_{ar}), 4.35 (t, J = 5.4 Hz, 1H, H-2), 4.02 – 3.90 (m, J = 7.2, 2.7 Hz, 2H, -OC**H$_2$-**), 3.73 – 3.62 (m, 2H, -OC**H$_2$-**), 2.95 – 2.85 (m, J = 8.6, 7.0 Hz, 8H, -NC**H**$_2$-), 1.59 – 1.48 (m, 8H, -C**H**$_2$CH$_2$-), 1.32 – 1.21 (m, 8H, -C**H**$_2$CH$_3$), 1.19 (t, J = 7.1 Hz, 3H, -OCHC**H$_3$**), 0.98 (t, J = 7.1 Hz, 3H, -OCHC**H$_3$**), 0.81 (t, J = 7.4 Hz, 12H, -CH$_2$C**H**$_3$).

^{13}C NMR (126 MHz, D2O) δ 163.04, 161.11, 130.67, 128.73 (d, J = 8.4 Hz), 114.44 (d, J = 21.7 Hz), 62.12 (d, J = 5.9 Hz), 61.26 (d, J = 5.7 Hz), 60.97 (m), 60.86, 47.25, 27.50, 19.13, 16.10 (dd, J = 23.7, 5.8 Hz), 12.72.

^{31}P NMR (202 MHz, D2O) δ 13.34 (d, J = 58.4 Hz), 9.69 (d, J = 58.2 Hz).

HRMS (ESI^+): m/z [$M+H^+$] calculated for $C_{28}H_{55}FN_2O_7P_2$ [$M+H^+$] =613.3469; found= 613.3536.

Supporting Information

Supporting information is available on the publisher's website.

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