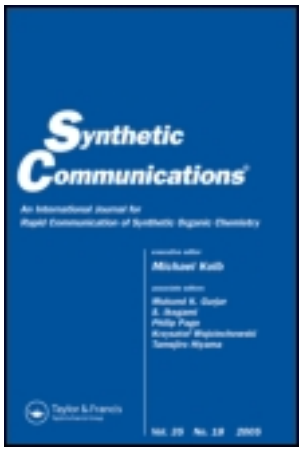

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SIMPLE SYNTHESIS OF OXIRANYLIDENE-2,2-BIS(PHOSPHONIC ACID): TETRABENZYL GEMINAL BISPHOSPHONATE ESTERS AS USEFUL INTERMEDIATES

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SIMPLE SYNTHESIS OF OXIRANYLIDENE-2,2-*BIS*(PHOSPHONIC ACID): TETRABENZYL GEMINAL BISPHOSPHONATE ESTERS AS USEFUL INTERMEDIATES

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ABSTRACT

Tetrabenzyl geminal bisphosphonate esters are shown to be useful synthetic equivalents of 1,1-*bis*(phosphonic acid)s which may be easily functionalized at the central carbon atom without phosphonate ester hydrolysis. The parent *bis*(phosphonic acid) unit is readily regenerated by hydrogenolysis. The chemistry is used to prepare the elusive epoxide oxiranylidene-2,2-*bis*(phosphonic acid) by a short and reliable procedure.

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Geminal bisphosphonates are stable pyrophosphate analogues which bind efficiently to bone surface.[1] They have been used in the clinic to inhibit bone resorption, in most cases with few side effects.[2] Some simple examples, for example etidronate and alendronate, are already marketed for the treatment of osteoporosis and Paget's disease.[3] It has been suggested that bisphosphonates are general metabolic inhibitors.[4] The low level of side effects has been attributed to the rapid absorption of the geminal bisphosphonate to the bone surface and incorporation within the bone matrix, thereby preventing undesired effects within other organs.[2] Other clinically used treatments for osteoporosis, such as hormone replacement therapy, are effective, but can have effects on other tissues.[5] We are interested in using geminal bisphosphonates as bone-targeting moieties for the treatment of bone-related disease;[6] our aim is to use the bone tropism to deliver therapeutics at the desired site of action, thus reducing unwanted side effects in other tissues.

Bis(phosphonic acid)s are typically produced from tetraalkyl bisphosphonate esters either by acid hydrolysis[7] or through silylation-dealkylation using bromotrimethylsilane.[8] While acid hydrolysis is reliable it is often incompatible with other functionalities. Silylation-dealkylation is a milder method, however, in our hands reactions were often incomplete, leading to mixtures of products. This prompted us to investigate the benzyl group as a potential protecting group for *bis*(phosphonic acid)s which might be easily and selectively removed.[9] Hydrogenolysis of benzyl phosphonates has been widely utilized,[10] however, to our knowledge geminal *bis*(phosphonic acid)s have rarely been synthesized in this way. Mioskowski has shown that simple benzyl bisphosphonate esters can be deprotected by the use of catalytic transfer hydrogenolysis[11] or with DABCO in boiling toluene,[12] or even converted into chlorophosphonates.[13] More recently, a 2-substituted geminal *bis*(phosphonic acid) has also been prepared by catalytic transfer hydrogenolysis of the benzyl bisphosphonate.[14]

We chose oxiranylidene-2,2-*bis*(phosphonic acid) **1** as a target around which to develop the chemistry. This epoxide is a notoriously elusive compound potentially valuable as a synthetic intermediate: Johnson has shown that its esters undergo epoxide cleavage followed by an unusual rearrangement upon reaction with nitrogen nucleophiles.[15] Reported briefly in the patent literature twenty-five years ago,[16] two further reports of its attempted synthesis have since appeared: Gatrone reported that the sodium tungstate/hydrogen peroxide oxidation of ethylidene-1,1-*bis*(phosphonic acid) at pH 6–7 produced 1,2-dihydroxy-1,1-*bis*(phosphonic acid), identified by ^{31}P and ^{1}H NMR spectroscopy, rather than **1**.[17] More recently, McKenna described an unambiguous synthesis of **1** *via* the bromohydrin derived from ethylidene-1,1-*bis*(phosphonic acid).[18]

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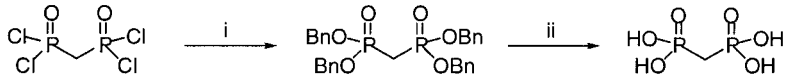
Our initial target, tetrabenzyl methylene bisphosphonate **2**, has previously been reported only rarely, assembled for example by a Michaelis-Arbuzov reaction of tribenzyl phosphite and dibenzyl (chloromethyl)phosphonate,[11] by heating the *bis*(phosphonic acid) with tribenzyl orthoformate,[14] and by a transesterification process.[21] We required relatively large quantities of **2**, and therefore sought a synthesis more amenable to scale-up. Vepsäläinen has synthesized a range of tetraalkyl methylene bisphosphonate esters by reaction of methylene *bis*(phosphonic dichloride) **3** with alcohols using pyridine as the base.[19] Using this method, we found the synthesis of **2** from **3** and benzyl alcohol to be readily achieved on a multigram scale (Scheme 1).



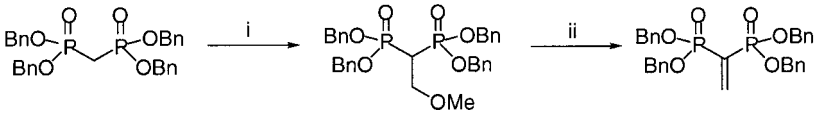
3 **2** **4**

Reagents: i. BnOH, py, tol, 76%; ii. H_2, Pd/C, EtOAc, 94%.

Scheme 1.

Initially we hydrogenolysed **2** to give the known methylene *bis*(phosphonic acid) **4**, the reaction proving efficient and simple.

Elaboration of **2** to tetrabenzyl ethylidene-1,1-bisphosphonate **5** required a modification of Degenhardt's method (Scheme 2).[20] Compound **2** was stirred with paraformaldehyde and diethylamine in methanol at room temperature for four days to give the tetrabenzyl 2-methoxyethylene *bis*-phosphonate intermediate **6**. Attempts to increase the reaction rate by heating led to complicated mixtures of mixed methyl and benzyl ester products. Acid catalysed elimination in toluene under reflux using a soxhlet apparatus containing 4 Å molecular sieves gave **5** in *ca* quantitative yield.



2 **6** **5**

Reagents: i. $(HCHO)_n$, Et_2NH, MeOH; ii. TsOH, tol, Δ, 99%.

Scheme 2.

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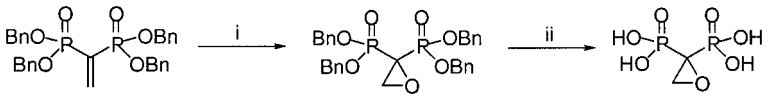
Clean conversion into tetrabenzyl oxiranylidene-2,2-bisphosphonate **7** was accomplished with alkaline hydrogen peroxide in ethanol (Scheme 3);[18] compound **7** was sufficiently pure to be used without further purification. Initially, our attempts to debenzylate **7** by hydrogenolysis in solvents such as methanol, acetone or tetrahydrofuran led to acid **1** together with minor impurities visible by ^{1}H NMR spectroscopy. However, hydrogenolysis in ethanol using 10% Pd(C) yielded acid **1** cleanly and in *ca* quantitative yield after filtration and evaporation (Scheme 3). Acid **1** was converted into the tetrasodium salt by treatment with sodium hydroxide in water. We are currently extending and investigating the use of this mild synthetic procedure for synthesising *bis*(phosphonic acid)s and various conjugates.



5 **7** **1**

Reagents: i. H_2O_2, $NaHCO_3$, EtOH, 94%; ii. H_2, Pd/C, EtOH, 97%.

Scheme 3.

In conclusion, the synthesis of oxiranylidene-2,2-*bis*(phosphonic acid) **1** described here is high yielding, and requires no chromatography and relatively little purification between steps. We have also demonstrated the applicability of the benzyl group as a protecting group for *bis*(phosphonic acid)s and have described the synthesis of several key intermediates.

EXPERIMENTAL SECTION

Tetrabenzyl Methylene Bisphosphonate 2: A suspension of methylene *bis*(phosphonic dichloride) (5.00 g, 20.0 mmol) was stirred rapidly in dry toluene (10 mL) at 0°C. A mixture of dry benzyl alcohol (8.66 mL, 83.0 mmol) and dry pyridine (6.15 mL, 76.1 mmol) was added over 80 min by syringe pump while the temperature was maintained. After the addition was complete the reaction was allowed to reach 20°C and stirred for a further 3 h. The solids were removed by filtration and washed with toluene (2×20 mL). The filtrate was washed with 2 M NaOH (2×15 mL), water (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Removal of benzyl alcohol impurity by distillation (120°C, 1 mmHg) left **2** as a colourless oil

(8.11 g, 76%): IR (liq) 998, 1260. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.51 (2H, t, $J = 21.2$ Hz), 5.02 (8H, dd, $J = 8.7$ and 2.2 Hz), 7.28 (20H, br s). ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 26.7 (t, $J = 136$ Hz), 68.5 (t, $J = 2.9$ Hz), 128.5, 128.9, 129.0, 136.4 (t, $J = 3.4$ Hz). ^{31}P NMR ($CDCl_3$, 101.2 MHz) δ 20.81. MS (EI) 536.15082, $C_{29}H_{30}P_2O_6$ requires 536.1517.

Methylene *bis*(Phosphonic Acid) 4: A solution of **2** (0.100 g, 0.187 mmol) and 10% Pd(C) (10 mg) in dry EtOAc (2 mL) was stirred under a hydrogen atmosphere for 16 h. The Pd(C) was removed by filtration, washed with methanol (2 mL) and the combined filtrate concentrated *in vacuo* to give **4** as a colourless solid (0.031 g, 94%): ^{1}H NMR (D_2O, 400 MHz) δ 2.11 (2H, t, $J = 21.0$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1 (t, $J = 129$ Hz). ^{31}P NMR (D_2O, 101.2 MHz) δ 22.25.

Tetrabenzyl Ethylidene-1,1-bisphosphonate 5: Paraformaldehyde (1.35 g, 45.0 mmol) and diethylamine (0.68 g, 9.33 mmol) were dissolved in dry methanol (30 mL) with warming. A solution of **2** (5.00 g, 9.33 mmol) in dry methanol (30 mL) was added at 20°C and the reaction stirred for 5 d. The reaction was concentrated in vacuo, toluene (20 mL) added and the solution concentrated again. This last step was repeated to remove all traces of methanol, yielding tetrabenzyl methoxymethyl methylene bisphosphonate **6** as a colourless oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.86 (1H, tt, $J = 5.5$ and 23.9 Hz), 3.30 (3H, s), 3.93 (2H, td, $J = 5.6$ and 16.3 Hz), 4.99–5.06 (8H, m), 7.28–7.33 (20H, m).

Intermediate **6**, *p*TSA and toluene (100 mL) were placed into a round bottomed flask fitted with a soxhlet apparatus containing 4 Å molecular sieve. The solution was heated under reflux for 16 h, allowed to cool to 20°C and washed with water (2 × 20 mL). Drying ($MgSO_4$) and concentration *in vacuo* gave **5** as a colourless viscous oil (5.10 g, 99%): IR (liq) 996, 1248. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.95–5.05 (8H, m), 6.98 (2H, dd, $J = 34.4$ and 38.9 Hz), 7.24–7.30 (20H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.5 (d, $J = 3.0$ Hz), 128.4, 128.8, 128.9, 136.3 (t, $J = 3.0$ Hz), 150.1. ^{31}P NMR ($CDCl_3$, 101.2 MHz) δ 15.33 MS (EI) 548.1524, $C_{30}H_{30}P_2O_6$ requires 548.1517.

Tetrabenzyl Oxiranylidene-2,2-bisphosphonate 7: A solution of **5** (1.00 g, 1.82 mmol), $NaHCO_3$ (0.162 g, 193 mmol) and 30% aqueous H_2O_2 (0.40 mL) in ethanol (4 mL) was stirred at 20°C for 16 h. The reaction was diluted with water (10 mL), extracted with CH_2Cl_2 (2 × 40 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **7** as a colourless viscous oil (0.971 g, 94%): IR (liq) 997, 1259. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.23 (2H, t, $J = 5.4$ Hz), 5.01–5.28 (8H, m), 7.25–7.31 (20H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.4 (t, $J = 182.6$ Hz), 50.0, 69.1 (t, $J = 2.4$ Hz), 128.0, 128.1, 128.6, 135.6 (q, $J = 3.3$ Hz). ^{31}P NMR ($CDCl_3$, 101.2 MHz) δ 17.33. Anal. Calcd for $C_{30}H_{30}P_2O_7$: C, 63.83; H, 5.36. Found: C, 63.36; H, 5.36.

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Oxiranylidene-2,2-*bis*(phosphonic Acid) 1: A solution of **7** (0.100 g, 0.177 mmol) and 10% Pd(C) (5 mg) in dry ethanol (1.5 mL) was stirred under an atmosphere of hydrogen for 5 h. The Pd(C) was removed by filtration, washed with ethanol (1 mL) and the combined filtrate concentrated *in vacuo* to give **1** as a colourless viscous oil (0.035 g, 97%): ^{1}H NMR (D_2O, 400 MHz) δ 3.22 (2H, t, $J = 6.0$ Hz). ^{13}C NMR (D_2O, 100 MHz) δ 52.1 (t, $J = 169.7$ Hz), 52.7. ^{31}P NMR (D_2O, 101.2 MHz) δ 17.12.

Oxiranylidene-2,2-*bis*(phosphonic Acid), Tetra Sodium Salt: NaOH (0.0275 g, 0.686 mmol) was added to a solution of **1** (0.035 g, 0.172 mmol) in D_2O (1 mL). Concentration in vacuo gave the product as a colourless solid (0.0500 g, 99%): ^{1}H NMR (D_2O, 400 MHz) δ 2.95 (2H, t, $J = 5.8$ Hz). ^{13}C NMR (D_2O, 100 MHz) δ 51.7, 54.6 (t, $J = 149.1$ Hz), ^{31}P NMR (D_2O, 101.2 MHz) δ 17.33.

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