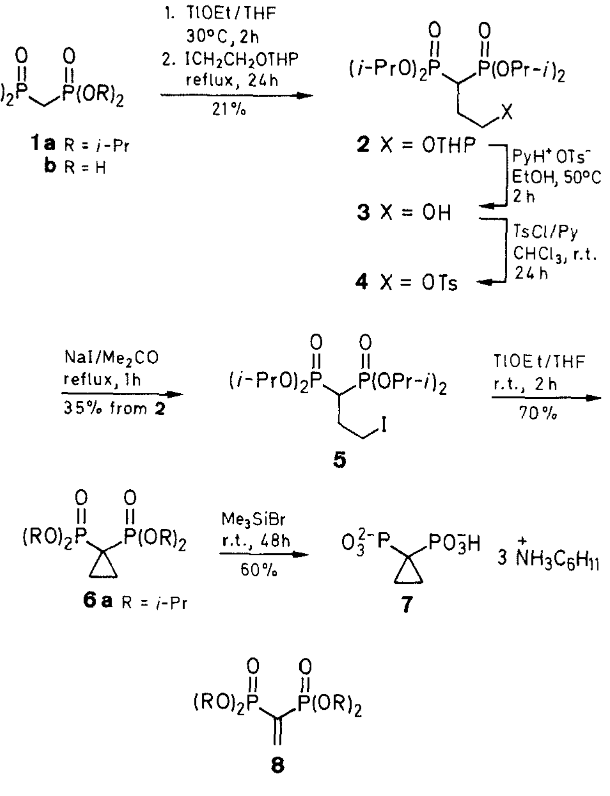
The Synthesis of 1,1-Cyclopropanediylbis(phosphonic acid)

David W. Hutchinson,* David M. Thornton
Chemistry Department, Warwick University, Coventry CV4 7AL, England

Tetraisopropyl 1,1-cyclopropanediylbis(phosphonate) has been synthesised by an intramolecular cyclisation of the thallium(I) salt of tetraisopropyl (3-iodo-1,1-propanediyl)bis(phosphonate). Dealkylation of the tetraisopropyl ester gave 1,1-cyclopropanediylbis(phosphonic acid) in good yield.

Methylenebis(phosphonic acids), for example **1b** (R = H) have a number of useful biochemical properties which appear to be related to their ability to chelate metal ions.[1,2] The stereochemical restraints imposed by a three-membered ring could have an important effect on the biochemical properties of alicyclic methylenebis(phosphonic acids) such as 1,1-cyclopropanediylbis(phosphonic acid) **7** and hence the synthesis of these alicyclic compounds is of interest. No synthesis of **7** has been reported although a synthesis of 1-phosphono-1-cyclopropanecarboxylic acid has been described.[3] We now report a route for the synthesis of **7** which could be used for the synthesis of related alicyclic bis(phosphonic acids).

We were unable to synthesise 1,1-cyclopropanediylbis(phosphonates) **6** from tetraalkyl ethenyldiylbis(phosphonates)[4] **8** via a Simmons–Smith reaction.[5] Furthermore, the carbon–carbon double bond in **8** does not undergo epoxidation with 3-chloroperoxybenzoic acid under conditions when electron deficient carbon–carbon double bonds are epoxidised. The reaction of alkylidenephosphoranes with **8**[6] appeared a promising synthetic route to **6** as this reaction formally resembles the Michael reaction which we had already observed.[7] However, we were unable to obtain **6** by this route.



1-Phosphono-1-cyclopropanecarboxylic acid[3] and diethyl 1-cyanocyclopropylphosphonate[8] have been prepared, respectively, by treatment of *tert*-butyl (diethoxyphosphoryl)acetate or diethyl cyanomethylphosphonate with 1,2-dibromoethane in the presence of base. Hence, we have developed a synthesis of **6** from a *C*-alkyl methylenebisphosphonate which could undergo intramolecular nucleophilic displacement leading to cyclisation and the formation of the cyclopropane ring.

We have observed[9] that alkylation of the thallium(I) salt of **1a** with primary iodides can occur in almost quantitative yield. However, when the thallium(I) salt of **1a**[9,10] was treated with an excess of 1,2-diiodoethane, little alkylation (< 5%) could be observed by ^{31}P-NMR and no tetraisopropyl (3-iodo-1,1-propanediyl)bis(phosphonate) (**5**) could be detected, possibly because the bis-primary iodide was unstable under the conditions of the reaction.

Treatment of the thallium(I) salt of ester **1a** with 2-iodoethyl tetrahydropyranyl ether gave the alkylated product **2**.[11] Removal of the tetrahydropyranyl group with pyridinium *p*-toluene sulphonate,[12] tosylation of the hydroxy group and displacement of the tosyl group with iodide gave tetraisopropyl bisphosphonate **5**. Formation of the thallium(I) salt of this ester was followed by very rapid cyclization to give tetraisopropyl 1,1-cyclopropanediylbis(phosphonate) **6a** in high yield. This tetraester could be dealkylated without ring opening upon treatment with bromotrimethylsilane to yield the free acid **7** which was isolated as its tris(cyclohexylammonium) salt. The stability of the cyclopropane ring in **6** contrasts with our observation that the dealkylation of diethyl 1-phosphono-1-cyclopropanecarboxylic acid with bromotrimethylsilane is accompanied by partial opening of the cyclopropane ring. This synthetic route to alicyclic bisphosphonic acids should be of general application provided the appropriate homologue of 2-iodoethyl tetrahydropyranyl ether is used.

Tetraisopropyl methylenebis(phosphonate) (Lancaster Synthesis Ltd) bromotrimethylsilane, iodoethanol and thallium(I) ethoxide (Aldrich Chemical Co) were commercially available. All solvents were dried and distilled before use.

NMR Spectra: ^{1}H spectra were recorded on a Perkin-Elmer R34 spectrometer at 220 MHz. ^{13}C and ^{31}P spectra were recorded with broad band decoupling at 100.62 and 162.0 MHz respectively on a Bruker WH400 spectrometer, using 85% H_3PO_4 as external reference for ^{31}P spectra (downfield shifts +ve). Ammonia chemical ionisation mass spectra were determined as previously reported.[13]

2-Iodoethyl Tetrahydropyranyl Ether:

To a solution of 2-iodoethanol (25.0 g, 0.145 mol) and pyridinium p-toluene sulphonate[12] (3.65 g, 14.5 mmol) in dry CH_2Cl_2 (40 mL) is added dihydropyran (19.9 mL, 0.218 mol) dropwise over 30 min. Stirring is continued at r. t. for 20 h. After Et_2O has been added, the solution is washed with brine (125 mL) followed by water (2 x 50 mL). The ether extracts are dried ($MgSO_4$), filtered through

Celite and the solvent removed *in vacuo* to give the title compound as a yellow oil which was purified by distillation; yield: 34.9 g (94%); bp 49–50 °C/0.13 mbar.

$C_7H_{13}IO_2$	calc.	C 32.83	H 5.12	I 49.56
(256.1)	found	32.44	5.14	47.73

MS (NH_3, CI): *m/z* = 257 (M + 1).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.5–2.0 (m, 6 H, CH_2-THP), 3.35 (t, 2 H, CH_2I, J = 6.7 Hz), 3.60 (dt, 1 H, J = 5.7, 6.9 Hz, $OC\underline{H}_2$-THP), 3.80 (dt, 1 H, J = 5.7, 6.9 Hz, $O\underline{C}H_2$-THP), 3.8–4.1 (m, 2 H, $OC\underline{H}_2CH_2I$), 4.75 (t, 1 H, J = 3.4 Hz, $OC\underline{H}O$).

Tetraisopropyl [(3-Tetrahydropyranyloxy)-1,1-propanediyl]bis(phosphonates) (2):

To a solution of tetraisopropyl methylenebis(phosphonate) (6.0 g, 17.4 mmol) in dry THF (20 mL) is added thallium(I) ethoxide (1.73 mL, 24.4 mmol) in a single portion. The solution is stirred at 30–35 °C for 2 h during which time a white precipitate forms. 2-Iodoethanol tetrahydropyranyl ether (31.24 g, 0.122 mol) is then added with stirring and the solution heated under reflux for 24 h. The reaction mixture is then applied to a column of Florisil (2 × 15 cm) which is eluted with acetone/petroleum ether (1 : 1, 500 mL). The eluate is concentrated *in vacuo* and the residue chromatographed on silica[14] [elution with acetone/petroleum ether (1 : 14)] followed by rechromatography of the product obtained on silica eluting with MeOH/Et_2O (1 : 50) to give **2** as a colorless oil; yield: 3.21 g. By NMR spectroscopy, this oil is an approximate 1 : 1 mixture of the title compound and tetraisopropyl methylenebis(phosphonate.) A small sample was rechromatographed for NMR analysis but the remainder is used directly in the next stage of the synthesis.

^{1}H-NMR ($CDCl_3$) δ = 1.38 (dd, 24 H, J = 6.1, 2.8 Hz, CH_3), 1.5–1.9 (m, 6 H, CH_2–THP), 2.20 (m, 2 H, J = 6.1, 16.4 Hz, $C\underline{H}_2CHP_2$), 2.42 (tt, 1 H, J = 6.1, 24.4 Hz, PCHP), 3.50 (m, 2 H, OCH_2–THP), 3.90 (m, 2 H, CH_2O), 4.65 (t, 1 H, J = 3.3 Hz, OCHO), 4.80 (m, 4 H, $Me_2C\underline{H}O$).

Tetraisopropyl (3-Hydroxy-1,1-propanediyl)bis(phosphonates) (3):

To a solution of the crude tetrahydropyranyl ether **2** (1.6 g) in absolute EtOH (30 mL) is added pyridinium *p*-toluenesulphonate (171 mg, 0.68 mmol).[12] The solution is stirred at 45–50 °C for 12 h and the solvent evaporated *in vacuo* to leave a colourless oil. Flash chromatography of this oil on silica eluting with MeOH/Et_2O (1 : 30) gives the title compound as a colourless oil; yield: 0.48 g (66 % based on the content of tetrahydropyranyl ether in the crude starting material).

$C_{15}H_{34}O_7P_2$	calc.	C 46.39	H 8.82
(388.4)	found	46.34	8.82

MS (NH_3 CI): *m/z* = 389 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 1.31 (d, 12 H, J = 7.0 Hz, CH_3), 1.33 (dd, 12 H, J = 7.0, 2.0 Hz, CH_3), 2.12 (tq, 2 H, J = 6.1, 16.8 Hz, $C\underline{H}_2CHP_2$), 2.36 (tt, 1 H, J = 6.1, 25 Hz, PCHP), 3.76 (t, 2 H, J = 6.1 Hz, $C\underline{H}_2OH$). 4.73 (m, 4 H, J = 7.0, 7.4 Hz, $Me_2C\underline{H}O$.

^{31}P-NMR ($CDCl_3$): δ = 22.2 (s).

Tetrapropyl [3-(4-Toluenesulfonyloxy)-1,1-propanediyl]bis(phosphonate) (4):

To alcohol **3** (0.44 g, 1.1 mmol) dissolved in $CHCl_3$ (5 mL) is added *p*-toluene sulphonylchloride (0.43 g, 2.2 mmol) in pyridine (0.72 mL, 9 mmol) and the reaction set aside for 24 h. Excess 5 % aq. HCl is then added and the mixture extracted with $CHCl_3$ (2 × 25 mL). The $CHCl_3$ extracts are dried ($MgSO_4$), filtered and evaporated to a colourless oil which is purified by flash chromatography on silica [elution with MeOH/Et_2O (1 : 40)] The title compound is obtained as a colourless oil; yield: 0.44 g (72 %).

$C_{22}H_{40}O_9P_2S$	calc.	C 48.70	H 7.43
(542.6)	found	50.73	7.83

MS (NH_3 CI): *m/z* = 543 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 1.29 (dd, 24 H, J = 5.7, 1.0 Hz, CH_3), 2.20 (m, 2 H, J = 6.2, 6.6, 16 Hz, $C\underline{H}_2CHP_2$), 2.24 (tt, 1 H, J = 6.2, 24 Hz, PCHP), 2.42 (s, 3 H, $C\underline{H}_3C_6H_4$), 4.23 (t, 2 H, J = 6.6 Hz, CH_2OS), 4.72 (m, 4 H, J = 5.7 Hz, $Me_2C\underline{H}O$), 7.31 (d, 2 H_{arom}, J = 8.4 Hz), 7.77 (d, 2 H_{arom}, J = 8.4 Hz).

^{31}P-NMR ($CDCl_3$): δ = 20.2 (s).

Tetraisopropyl (3-Iodopropanediyl)bis(phosphonates) (5):

To tosylate **4** (0.41 g, 0.75 mmol) dissolved in dry acetone (10 mL) is added anhydrous NaI (0.57 g, 3.8 mmol) and the mixture refluxed under N_2 for 1 h. The reaction is then cooled, filtered through Celite and the acetone removed *in vacuo*. Flash chromatography of the residue on silica eluting with MeOH/Et_2O (1 : 40) gives the title compound as a colourless oil; yield: 0.27 g (73 %).

$C_{15}H_{33}IO_6P_2$	calc.	C 36.16	H 6.68
(498.3)	found	36.81	6.89

MS (NH_3 CI): *m/z* = 499 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 1.34 (td, 24 H, J = 6.4, 1.7 Hz, CH_3), 2.32 (tt, 1 H, J = 6.2, 28 Hz, PCHP), 2.35 (m, 2 H, J = 6.2, 7.2 Hz, $C\underline{H}_2CHP_2$), 3.46 (t, 2 H, J = 7.2 Hz, CH_2I), 4.77 (m, 4 H, J = 6.4, 6.5 Hz, $Me_2C\underline{H}O$.

^{31}P-NMR ($CDCl_3$): δ = 22.2 (s).

Tetraisopropyl 1,1-Cyclopropanediylbis(phosphonic acid) (6):

A solution of thallium(I) ethoxide in THF (0.5 mL, 0.5 mmol TlOEt) is added dropwise over 2 min. to a solution of the iodo compound **5** (0.25 g, 0.5 mmol) in dry THF (10 mL) under N_2. The mixture is stirred for 2 h then applied to a Florisil column (10 cm × 2 cm) which is eluted with acetone/petroleum ether (150 mL, 1 : 1). Evaporation of the eluate followed by flash chromatography of the residue on silica eluting with MeOH/Et_2O (1 : 40) gives the title compound as a colourless oil; yield: 0.13 g (70 %).

$C_{15}H_{32}O_6P_2$	calc.	C 48.64	H 8.71
(370.4)	found	47.79	8.20

MS (NH_3 CI): *m/z*, $C_{15}H_{33}O_6P_2$ calc.: 371.1753 (M + 1); found: 371.1707 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 1.31 (t, 4 H, J = 13.9 Hz, CH_2-cyclopropyl), 1.32 (dd, 24 H, J = 62, 4.1 Hz, CH_3), 4.68 (m, 4 H, J = 6.6, 7.7 Hz, Me_2CHO).

^{31}P-NMR ($CDCl_3$): δ = 23.5 (s).

^{13}C-NMR ($CDCl_3$): δ = 10.8 (s, CH_2-cyclopropyl), 11.6 (t, J = 181 Hz, CP_2), 24.0 (s, CH_3), 70.9 (s, $Me_2\underline{C}HO$).

1,1-Cyclopropanediylbis(phosphonic acid), Tris(cyclohexylammonium) Salt (7):

Bis(phosphonate) **6** is dealkylated with bromotrimethylsilane and the product isolated as the tris(cyclohexylammonium) salt[7] which is recrystallised from MeOH/Et_2O as a white solid; yield: 83 mg (60 %).

$C_{21}H_{47}N_3O_6P_2$	calc.	C 49.83	H 9.48
(499.6)	found	49.81	9.20

^{1}H-NMR (D_2O): δ = 0.95 (t, 4 H, J = 14.2 Hz, CH_2-cyclopropyl), 1.1–1.15 (m, 15 H, CH_2-cyclohexyl), 1.65 (m, 3 H, CH_2-cyclohexyl), 1.80 (m, 6 H, CH_2-cyclohexyl), 2.00 (m, 6 H, CH_2-cyclohexyl), 3.18 (m, 3 H, CHN).

^{31}P-NMR (D_2O): δ = [^{1}H coupled] 21.4 (quint, J = 14.2 Hz).

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