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# Synthesis and characterization of macrocyclic bisphosphonate dimers

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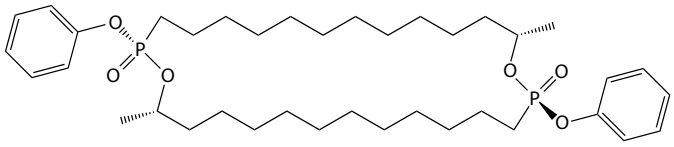
## ABSTRACT

**Background**: Attempts to optimize the synthetic yield of known macrocyclic phosphonates resulted in the discovery of two new macrocyclic bisphosphonate dimers.

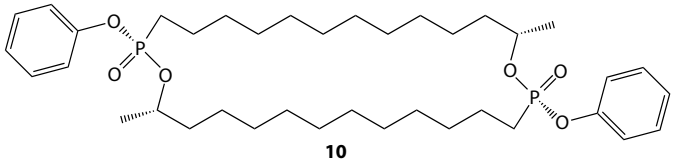
**Methods**: An attempt was carried out to optimize the yield of a known macrocyclic bisphosphonate dimer, **6**, over the yield of monomers **2** and **3**, using the Mitsunobu protocol in the macrocyclization step. Cyclization reactions were carried out at 0.003 M, 0.004 M, 0.005 M, 0.008 M and 0.02 M, compared to 0.002 M in our initial report of the synthesis of monomers.

**Results**: In this attempt to optimize the production of dimer **6**, two new macrocyclic diastereomers of **6**, namely 28-membered bisphosphonates **9** and **10**, were isolated in yields of 3% and 2%, respectively, and characterized by FTIR, LC-MS, $^{1}H$, $^{13}C$ and $^{31}P$ NMR as well as by X-ray crystallography.

**Conclusions**: The results described herein further illustrate the utility of the Mitsunobu macrocyclization (ring-closing) reaction toward the synthesis of macrocyclic phosphonates. The X-ray crystallographic characterization of the three bisphosphonate dimers, together with correlations to specific $^{1}H$ and $^{31}P$ NMR resonances allowed for the assignments of relative stereochemistries between the various dimers.



**9**



**10**

*Keywords:* Synthetic lipids, cyclic phosphonates, Mitsunobu macrocyclization, 28-membered bisphosphonates

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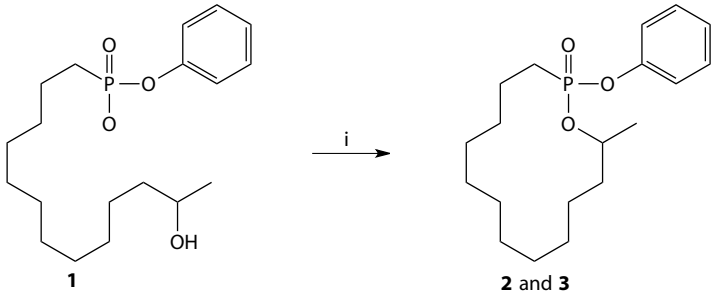
## INTRODUCTION

Cyclic and acyclic phosphonate esters (and the phosphonic acids of their sodium salts) have been used extensively as haptens for the production of catalytic antibodies [1] and as inhibitors of enzymatic processes [2]. In addition, macrocyclic phosphonates have found application as promising inhibitors of barium sulfate crystal growth [3], a problem in off-shore oil production. There exists an extensive literature on the role of bisphosphonates, specifically geminal bisphosphonates, in the treatment of bone diseases [4]. Fewer reports exist describing macrocyclic bisphosphonates. Herm et al. [5] previously described the synthesis of a macrocyclic bisphosphonate containing a flexible bisphosphonate as a chelating unit acting as a host for substrates of the adrenergic receptor. We have previously reported the synthesis of 14-membered ring phenyl phosphonates **2** and **3** from an acyclic hydroxy phosphonic acid precursor, **1** (Scheme 1) [6], and the subsequent application of phosphonates **2** and **3** towards the generation of catalytic antibodies which catalyzed the formation of a 14-membered ring lactone [7]. Subsequently, *N*, *N*-dimethylaminoethanol cyclic phosphonates **4** and **5** were synthesized from **3** and **2**, respectively, and shown to possess DNA binding properties with potential as DNA delivery vectors [8]. In addition to the 14-membered ring phenyl phosphonates **2** and **3**, a 28-membered bisphosphonate dimer, **6**, was isolated from the cyclization of the corresponding acyclic precursor, **1** [6]. The key step in the synthesis of these macrocyclic phosphonates was the use of the Mitsunobu reaction [9] in the ring-closing step, which proceeded in an 82% yield with a 5:1 ratio of the two isomers **2** and **3**. Dimer **6**, an unexpected side-product from this reaction, was formed as a crystalline solid in approximately 5% yield based on the acyclic precursor. Stereochemical information from the X-ray structure of dimer, **6**, together with the $^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra of compounds **2**, **3**, **6** [6] and two 6-membered ring phosphonates, **7** and **8** [10], allowed us to make structural assignments for diastereomers **2** and **3**. Finally, comparison of NOE (nuclear Overhauser enhancement) difference experiments performed on the three compounds allowed us to confirm our relative stereochemical assignments for isomers **2**–**5** as illustrated in Fig. 1.

Our interest in the macrocyclic bisphosphonate **6** stems from its bifunctional nature, and the potential it offers to access novel bolaamphiphiles, amphiphilic molecules with hydrophilic groups at both ends of a hydrophobic hydrocarbon spacer [11–19]. Research into the relationship between the structures and resulting self-assembled constructs of synthetic amphiphiles remains under intense investigation with the ultimate goal of achieving control of the assembling process [20–24]. Bolaamphiphiles have been shown to form varied assemblies [25–32] with distinct features [33–38].

Herein we report the discovery and characterization of two new macrocyclic bis-phosphonate diastereomers of **6**, namely 28-membered bisphosphonates **9** and **10** (Fig. 2), in our attempt to optimize the production of dimer **6** using the Mitsunobu protocol. Finally, a macrocyclic bis-(*N*, *N*-dimethylaminoethanol phosphonate) **11**, was synthesized from the centrosymmetric macrocyclic bisphenoxy phosphonate dimer **6**. The authors believe that compound **11**, a novel bolaamphiphile may have interesting self-assembling and biological activity in applications such as selective nucleic acid G-quadraplex ligands as antitumor agents [39] or gene delivery.




**1** **2** and **3**

**Scheme 1. Reagents and conditions: i) $Ph_3P$, DEAD, benzene, rt, 2 h.**

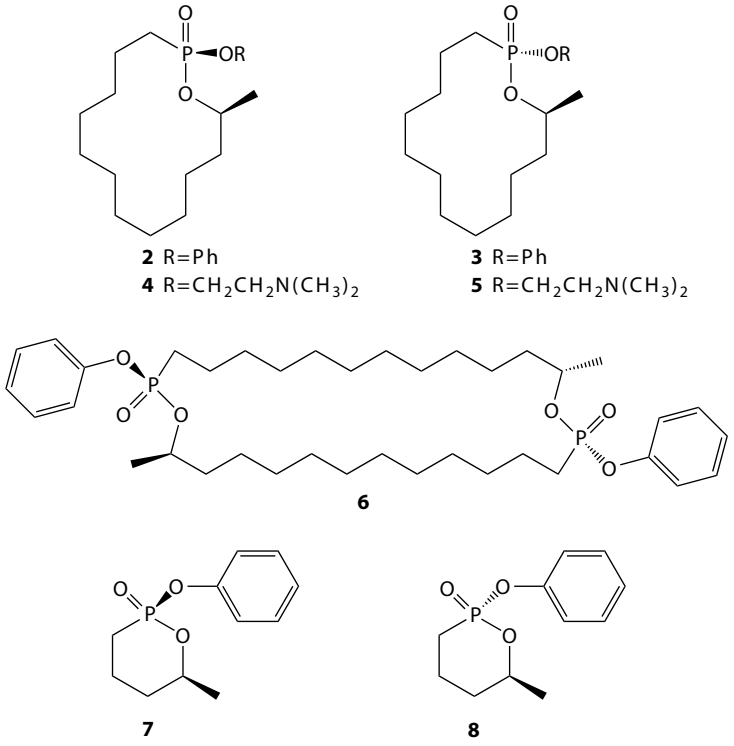



**Figure 1.** Structures and relative stereochemistry of cyclic phosphonates **2**–**8**.

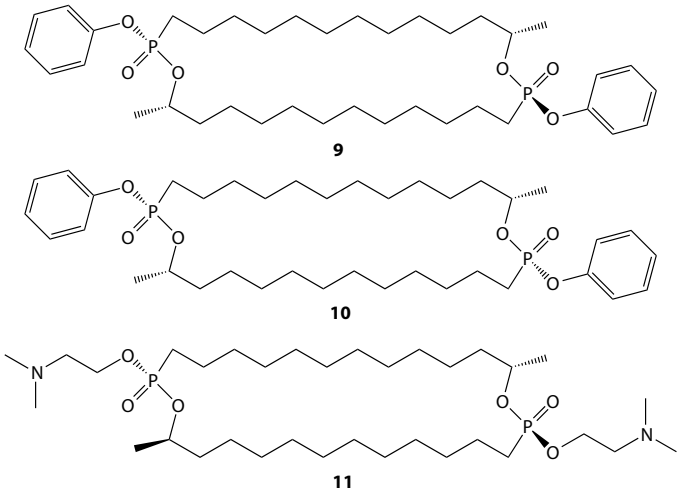



**Figure 2.** Structures and stereochemistry of macrocyclic, 28-membered bisphosphonates **9** and **10**, as well as macrocyclic bis-(*N, N*-dimethylaminoethanol phosphonate) **11**.

## RESULTS AND DISCUSSION

The initial synthesis of the 14-membered ring phosphonates **2** and **3** resulted in the unexpected formation of dimer **6** in approximately 5% yield [6]. In an attempt to optimize production of dimer **6** over monomers **2** and **3**, the cyclization reaction was carried out at 0.003 M, 0.004 M, 0.005 M, 0.008 M and 0.02 M, compared to 0.002 M in our initial report of the synthesis of monomers. In this attempt to optimize the production of dimer **6** using the Mitsunobu protocol in the macrocyclization step, two new macrocyclic diastereomers of **6**, namely 28-membered bisphosphonates **9** and **10**, were isolated. The relative isolated yields of all macrocyclic phosphonates from the various cyclization reactions are reported in Table 1.

**Table 1. Relative yields of macrocyclic phosphonates 2, 3, 6, 9 and 10 isolated from the cyclization reactions.**

| Trial | Conc. of 1 (M) | Percent isolated yield of macrocycles | | | | |
|---|---|---|---|---|---|---|
| | | **2** | **3** | **6** | **9** | **10** |
| **1** [6] | 0.002 | 68 | 14 | 5 | – | – |
| **2** | 0.003 | 45 | 16 | 5 | – | – |
| **3** | 0.004 | 46 | 32 | 5 | – | – |
| **4** | 0.005 | 48 | 31 | 11 | – | – |
| **5** | 0.008 | 14 | 6 | 8 | – | – |
| **6** | 0.02 | 32 | 6 | 6 | 3 | 2 |

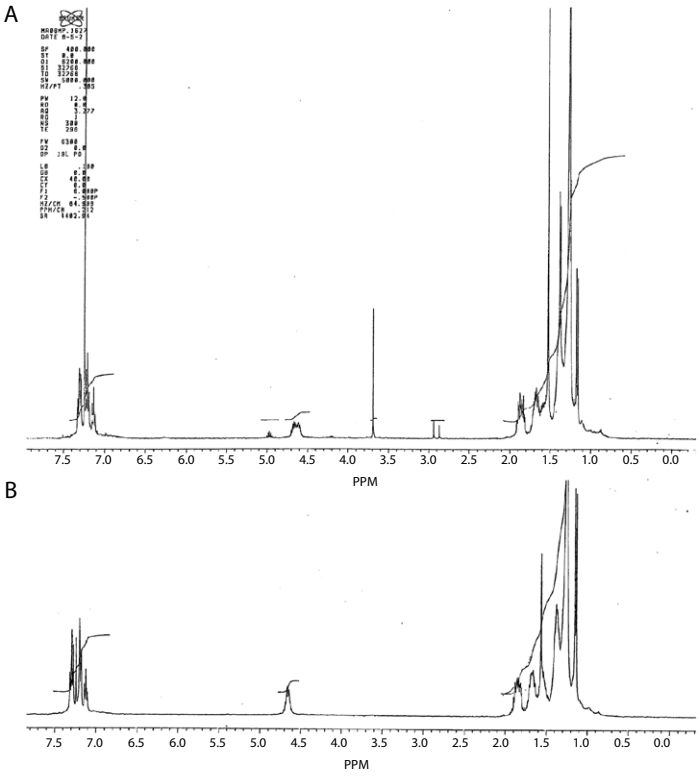



**Figure 3. $^1$H NMR (400 MHz, $CDCl_3$) spectra of dimers 9 (A) and 10 (B).**

Using the Mitsunobu methodology described within, the maximum total yield of cyclic material isolated, as well as the maximum yield of dimer **6** isolated from the cyclization trials (11%) resulted when the concentration of the hydroxy-phosphonic acid starting material (**1**) was 0.005 M. Trial 6, with a concentration of **1** of 0.02 M, resulted in the formation of monomers **2** and **3** in the same 5:1 ratio, respectively, as previously reported, however, the combined yield of **2** and **3** was only 38% as compared to 82% when run at 0.002 M. Dimer **6** was produced in a yield of 6%, compared to 5% at 0.002 M. Dimers **9** and **10** emerged for the first time in trial 6, and were produced in isolated yields of 3% and 2%, respectively. The $^1$H NMR spectra of dimers **9** and **10** are shown in Fig. 3. A lower total isolated yield of cyclic material was generally noted in the trials run at the higher concentrations, perhaps a result of polymerization competing with the cyclization event. All reported yields are isolated yields from purification using normal phase preparative chromatography.

As reported previously, the structure of dimer **6** was determined by single-crystal X-ray diffraction. Dimer **6**, isolated as a racemic mixture of enantiomers, is a centrosymmetric 28-membered ring compound with two parallel chains bridged at both ends by the phosphonate group, and contains four stereogenic centers with R*R* stereochemistry on one bridge, and the mirror image S*S* stereochemistry at the opposite bridge. Dimer **6** has a center of symmetry as a result of the R*R* and S*S* stereochemistry at the bridge ends. Single-crystal X-ray structures were obtained for the newly

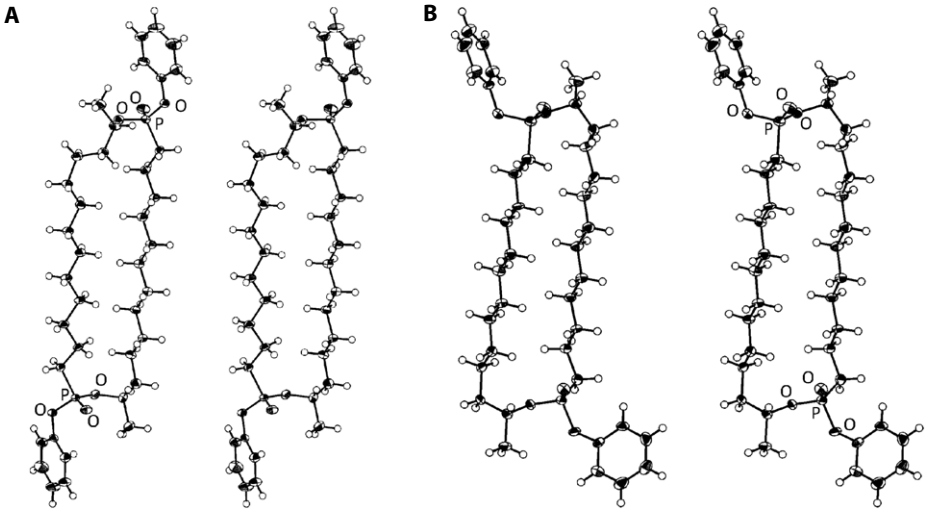



**Figure 4. Stereoviews of ORTEP representations for macrocyclic, 28-membered bisphosphonates 9 (A) and 10 (B).**

**Table 2. Crystal data for phosphonate dimers 6, 9 and 10.**

| Compound | 6[a] | 9[b] | 10[b] |
|---|---|---|---|
| Empirical formula | $C_{38}H_{62}O_6P_2$ | $C_{38}H_{62}O_6P_2$ | $C_{38}H_{62}O_6P_2$ |
| FW | 676.85 | 676.85 | 676.85 |
| $T$ (K) | 294 | 173 | 173 |
| Wavelength (Å) | 1.5418 | 0.7107 | 0.7107 |
| Crystal system | Monoclinic | Monoclinic | Monoclinic |
| Space group | $P2_1/n$ | $P2_1/a$ | $P2_1/c$ |
| $a$ (Å) | 7.841(1) | 21.639(1) | 8.3950(9) |
| $b$ (Å) | 5.664(2) | 7.7552(4) | 46.469(5) |
| $c$ (Å) | 43.378(1) | 22.673(2) | 9.932(1) |
| $\beta$(°) | 90.259(8) | 97.427(3) | 97.914(6) |
| $V$ (Å$^3$) | 1926.4(5) | 3772.9(4) | 3837.5(6) |
| $Z$ | 2 | 4 | 4 |
| $D_{calcd.}$ (g cm$^{-3}$) | 1.17 | 1.19 | 1.17 |
| $\mu$ (cm$^{-1}$) | 13.6 | 1.58 | 1.55 |
| $F$(000) | 736 | 1472 | 1472 |
| No. of reflns. measured | 4757 | 34881 | 18634 |
| No. of unique Reflns., $R_{int}$ | 4447, 0.020 | 8941, 0.093 | 5309, 0.120 |
| $S$ (GoF) on $F^2$ | 2.27 | 0.91 | 0.90 |
| $R$ [$I > 3\sigma(I)$], $Rw$ | 0.030, 0.032 | 0.042, 0.048 | 0.062, 0.094 |
| Largest diff. peak, hole (eÅ$^{-3}$) | 0.14, −0.19 | 0.89, −0.48 | 0.52, −0.57 |

[a] All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu–Kα radiation.
[b] All measurements were made on a Rigaku/ADSC CCD area detector with graphite monochromated Mo–Kα radiation.

isolated dimers **9** and **10** (Fig. 4), the data for which are tabulated in Table 2. The X-ray structures of **9** and **10** reveal that as in dimer **6**, these compounds each contain four stereogenic centers, two at each ends of the dimers. The stereochemical assignments for stereogenic centers, as determined from the X-ray structures of racemic crystals from these racemic compounds, are S*S*S*R*/R*R*R*S* and R*R*R*R*/S*S*S*S* for dimers **9** and **10**, respectively. Furthermore, careful inspection of the stereoviews of **9** and **10** (Fig. 4) reveal that the OPh moiety of the phosphonate center at the top of the structure for **9** (as shown in Fig. 4) occupies a pseudo-axial position relative to the macrocyclic ring, whereas the OPh group associated with the phosphonate center at the bottom of this structure sits in a pseudo-equatorial orientation, as do both OPh moieties within dimer **10**.

Table 3 summarizes key $^1$H and $^{31}$P NMR chemical shifts ($\delta$ values) for phenyl macrocyclic phosphonate dimers, **6**, **9** and **10**, as well as compound **11**. The $^{31}$P NMR signals associated with dimers **9** and **10** support the above mentioned observation that both OPh groups of **10** occupy pseudo-equatorial positions, while only one of the two OPh groups in **9** occupies a pseudo-equatorial position and the second OPh group sits in a pseudo-axial position. These pseudo-axial and

**Table 3. Key $^{1}$H and $^{31}$P NMR chemical shifts ($\delta$ values) for phenyl macrocyclic phosphonate dimers, 6, 9 and 10, as well as bolaamphiphile 11.**

| Compound | $\delta$ $^{1}$H for $CH_3$ protons (ppm) | $\delta$ $^{1}$H for methine proton (ppm) | $\delta$ $^{31}$P (ppm) |
|---|---|---|---|
| **6** [6] | 1.15 [a] | 4.66 [a] | 29.0 [a] |
| **9** | 1.17 [a]/1.39 [b] | 4.67 [a]/4.62 [b] | 27.1 [a]/25.5 [b] |
| **10** | 1.17 [a] | 4.67 [a] | 27.1 [a] |
| **11** | 1.34 [b] | 4.64 [b] | 31.2 [b] |

[a] $^{1}$H and $^{31}$P NMR chemical shifts consistent with P-OR group in pseudo-equatorial position;
[b] $^{1}$H and $^{31}$P NMR chemical shifts consistent with P-OR group in pseudo-axial position.

pseudo-equatorial assignments are supported by previously reported observations, where it has been suggested that the $^{31}$P NMR signal for the equatorial P-OR isomer is lower field than the corresponding axial isomer in the cyclic phosphonates of hexopyranoses [40] and in other six-membered ring phosphonates [41]. This trend supports the observed stereochemical assignments of the OPh groups in **9** and **10** since the $^{31}$P NMR shifts for isomer **10** (both coinciding at 27.1 ppm, with both OPh groups occupying pseudo-equatorial positions) are consistent with one of the two $^{31}$P NMR shifts for isomer **9**, and are approximately 2 ppm downfield from the second $^{31}$P NMR shift for isomer **9** at 25.5 ppm, which we assign to the OPh group at the top of the structure for **9** in Fig. 4, occupying a pseudo-axial position.

In addition to these $^{31}$P NMR correlations, $^{1}$H NMR chemical shift data between the C-1 methyl protons and the C-1 methine proton of **9** and **10** summarized in Table 1, further confirmed the pseudo-equatorial/pseudo-axial assignments made for the OPh moieties associated with these macrocyclic phosphonates. As reported by us previously for similar macrocyclic phosphonate systems [6], the chemical shift separation between the C-1 methine multiplet and the C-1 methyl doublet is greater for cyclic phosphonates possessing P-OR groups in pseudo-equatorial positions, as is the case for dimer **10** (consistent with our dimer **6** assignment previously [6]), and in agreement with one of the two sets of C-1 methine multiplet and C-1 methyl doublet shifts in dimer **9**. Finally, the large chemical shift separation between the C-1 methine multiplet and the C-1 methyl doublet of bolaamphiphile **11**, synthesized by the direct nucleophilic substitution of the OPh groups of **6** at both phosphonate sites with *N*, *N*-dimethylaminoethanol, supports inversion at the phosphorus centers resulting in both P-OR groups occupying pseudo-axial positions.

## MATERIALS AND METHODS

The cyclization reaction was performed in benzene under a $N_2$atmosphere at room temperature using flame-dried glassware. Anhydrous reagents and solvents were purified and prepared according to literature procedures [42]. Chromatographic solvents and reagents were used as received unless noted otherwise. All reagents were supplied by the Aldrich Chemical Co. and unless otherwise stated were used without further purification.

Thin-layer chromatography was performed on Merck silica gel 60 F254 pre-coated aluminum sheets. Visualization was achieved by irradiation with ultraviolet light at 254 nm and/or by spraying with anisaldehyde reagent (a solution of 1 mL anisaldehyde, 5 mL conc. $H_2SO_4$ and 10 mL glacial acetic acid in 90 mL MeOH) followed by heating.

Preparative flash chromatography [43] was performed using 230-400 mesh ASTM silica gel supplied by E. Merck Co. As an indicator of purity, all compounds were purified such that a single spot was evident by thin-layer chromatography (TLC) $R_f$-values.

Except where noted, proton nuclear magnetic resonance ($^{1}$H NMR) spectra were recorded in deuteriochloroform solutions on a Bruker AC-200 (200 MHz) or Bruker WH-400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) on the $\delta$ scale versus chloroform ($\delta$ 7.24 ppm) as an internal standard. Signal multiplicity, spin-spin coupling constants (where possible) and integration ratios are indicated in parentheses. Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded in deuteriochloroform solutions on a Bruker WH-400 (100 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) on the $\delta$ scale versus chloroform ($\delta$ 77.0 ppm) as an internal standard. Phosphorus nuclear magnetic resonance ($^{31}$P NMR) spectra with proton decoupling were recorded in deuteriochloroform solutions on a Bruker AC-200 (81 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) on the $\delta$ scale versus 85% phosphoric acid as an external standard.

Low-resolution electron-impact (EI) mass spectral analyses were performed on a Kratos-AEI model MS 50 mass spectrometer. Ionization energy of 70 eV was used in all measurements.

Melting points (mp) were determined using a Mel-Temp III (Laboratory Devices) melting point apparatus and are uncorrected.

The infrared (IR) spectrum of dimer **6** was recorded as a chloroform solution using NaCl solution cells, whereas the IR spectra of dimers **9** and **10** were obtained in KBr, on a Bomem Michelson 100 FT-IR spectrometer using internal calibration.

Microanalyses were carried out at the microanalytical laboratory of the University of British Columbia Chemistry Department using a Carlo Erba Elemental Analyzer 1106. Samples for microanalysis were purified by column chromatography using the solvent system indicated for each compound.

X-ray crystallographic data and analysis for dimers **9** and **10** were performed at the University of British Columbia, Department of Chemistry on a Rigaku/ADSC CCD area detector with graphite monochromated Mo–Kα radiation.

**Synthesis of dimers 6, 9 and 10.** The synthesis of dimers **6**, **9** and **10** was carried out as reported in *Org. Lett.*, Vol. 3, No. 5, 2001, pp. 643–646, except here we performed the macrocyclization reaction at higher concentrations, namely 0.003 M, 0.004 M, 0.005 M, 0.008 M and 0.02 M in an attempt to optimize dimer over monomer production. In addition, DIAD was used instead of DEAD for the most concentrated attempt (0.02 M), since DEAD is no longer commercially available. Initial investigations in our lab demonstrated that DIAD performs the same as DEAD in this cyclization reaction (unpublished results).

The reaction was carried out as follows: To a stirred solution of compound **1** (1.70 g, 4.77 mmol) in 240 mL of dry benzene at room temperature under nitrogen, triphenylphosphine (5.01 g, 19.1 mmol) was added, followed by DIAD (3.76 mL, 19.1 mmol). After 2 days, the solvent was removed under reduced pressure and the resulting crude mixture was purified by flash chromatography using 2:1 hexane and ethyl acetate to afford the separated diastereomers, **2** (523 mg, 1.55 mmol) and **3** (99 mg, 0.293 mmol), in a 5:1 ratio based on recovered yields, and a combined yield of 38.6%. In addition, 6% (96 mg, 0.145 mmol) of dimer **6** was isolated. While a combined yield of 11% (181 mg, 0.268 mmol) of dimers **9** and **10** was obtained, separation proved challenging, and only 2.8% (46 mg, 0.068 mmol) of dimer **9**, and 1.9% (30 mg, 0.044 mmol) of dimer **10** were isolated as colorless, crystalline solids.

Dimer **6** (as reported previously in Org. Lett., Vol. 3, No. 5, 2001, pp. 643–646):

mp: 103–105 °C; $R_f = 0.36$ (silica gel, diethyl ether : hexane 8:1); FTIR ($CDCl_3$): 2930, 2856, 1593, 1491, 1229, 1012 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 7.10–7.33 (*m*, 10H), 4.66 (*m*, 2H), 1.84 (*m*, 4H), 1.68 (*m*, 4H), 1.56 (*m*, 4H), 1.20–1.45 (*m*, 40H), 1.15 (*d*, $J = 6.2$ Hz, 6H); $^{31}P$ NMR (81 MHz, $CDCl_3$) $\delta$: 29.0; HRMS calcd. for $C_{38}H_{62}O_6P_2$: 676.4022, found 676.4002; Anal. calcd for $C_{38}H_{62}O_6P_2$: C, 67.42; H, 9.24, found: C, 67.51; H, 9.28.

Crystal data for **6**: $C_{38}H_{62}O_6P_2$; monoclinic; $P2_1/n$; $a = 7.841(1)$ Å; $b = 5.664(2)$ Å; $c = 43.378(1)$ Å; $\beta = 90.259(8)°$; $V = 1926.4(5)$ $Å^3$; $Z = 2$; colorless; $T = 294$ K; $R = 0.030$; $GOF = 2.27$.

Dimer **9**: mp: 83–85 °C; $R_f = 0.23$ (silica gel, diethyl ether : hexane 8:1); FTIR (KBr): 2920, 2849, 1596, 1493, 1246, 1216, 1003, 921, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.10–7.38 (*m*, 10H), 4.58–4.72 (*m*, 2H), 1.87 (*m*, 4H), 1.68 (*m*, 4H), 1.56 (*m*, 4H), 1.39 (*d*, $J = 6.5$ Hz, 3H), 1.22–1.48 (*m*, 40H), 1.15 (*d*, $J = 6.5$ Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ (ppm): 129.93, 129.82, 124.90, 120.99, 120.52, 75.25, 74.91, 37.85, 37.49, 30.74, 29.84, 29.73, 29.62, 29.51, 29.39, 25.92, 25.64, 25.39, 24.90, 22.71, 22.31; $^{31}P$ NMR (202 MHz, $CDCl_3$) $\delta$(ppm): 27.1 and 25.5; LC-MS calcd. for $C_{38}H_{62}O_6P_2$ 676.9, found 677.3.

Crystal data for **9**: $C_{38}H_{62}O_6P_2$; monoclinic; $P2_1/a$; $a = 21.639(1)$ Å; $b = 7.7552(4)$ Å; $c = 22.673(2)$ Å; $\beta = 97.427(3)°$; $V = 3772.9(4)$ $Å^3$; $Z = 4$; colorless; $T = 173$ K; $R = 0.042$; GOF = 0.91.

Dimer **10**: mp: 96–98 °C; $R_f = 0.16$ (silica gel, diethyl ether : hexane 8:1); FTIR (KBr): 2919, 2851, 1593, 1493, 1255, 1211, 991, 924, 766 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.12–7.36 (*m*, 10H), 4.67 (*m*, 2H), 1.87 (*m*, 4H), 1.69 (*m*, 4H), 1.56 (*m*, 4H), 1.22–1.48 (*m*, 40H), 1.17 (*d*, $J = 6.5$ Hz, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ (ppm): 129.69, 129.59, 124.69, 120.81, 120.78, 74.77, 74.72, 37.61, 37.56, 30.53, 30.39, 29.78, 29.60, 29.43, 29.36, 29.27, 26.82, 25.69,

25.21, 22.56, 22.19; $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$ (ppm): 27.1; LC-MS calcd. for $C_{38}H_{62}O_6P_2$676.9, found 677.1.

Crystal data for **10**: $C_{38}H_{62}O_6P_2$; monoclinic; $P2_1/c$; $a = 8.3950(9)$ Å; $b = 46.469(5)$ Å; $c = 9.932(1)$ Å; $\beta = 97.914(6)°$; $V = 3837.5(6)$ Å$^3$; $Z = 4$; colorless; $T = 173$ K; $R = 0.062$; GOF = 0.90.

### Synthesis of bolaamphiphile (11)

To 4.0 mL of THF in a 10 mL round bottom flask, was added *N*, *N*-dimethylethanolamine (4.0 μL, 0.040 mmol) via syringe at −78 °C under a $N_2$ atmosphere. The alcohol was treated with 1.6 M *n*-BuLi (20 μL, 0.032 mmol) added via glass syringe. The alkoxide was allowed to form for 5 min before **6** (20 mg, 0.030 mmol) dissolved in 2 mL of THF was cannulated into the reaction vessel via a stainless steel cannula. This mixture was allowed to warm slowly to room temperature and stir for 1.5 hr before fitted with a condenser refluxed for 5.5 hr. The THF was then removed under reduced pressure and the crude was purified by flash column chromatography (5% MeOH in $CH_2Cl_2$) to afford 3.9 mg (20%) of **11** as a colourless oil, together with 11.4 mg (57%) unreacted starting material, **6**.

Bolaamphiphile ( **11**): $R_f = 0.36$ (silica gel, 10% MeOH in $CH_2Cl_2$containing 3 drops, or approximately 1.5%, of ammonium hydroxide); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 4.64 (*m*, 2H), 4.21 (*m*, 2H), 4.15 (*m*, 2H), 2.76 (*m*, 4H), 2.43 (*s*, 12H), 1.80 (*t*, $J = 7.6$ Hz, 2H), 1.77 (*t*, $J = 7.6$ Hz, 2H), 1.63 (*m*, 4H), 1.56 (*m*, 4H), 1.24–1.51 (*m*, 32H), 1.34 (*d*, $J = 6.0$ Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 73.97, 63.15, 59.11, 45.48, 37.37, 28.04, 26.70, 26.35, 26.20, 25.99, 25.97, 25.52, 25.23, 23.36, 22.85, 21.57; $^{31}$P NMR (81 MHz, $CDCl_3$) $\delta$: 31.2; ES-MS calcd. for $C_{34}H_{72}N_2O_6P_2Na(M^+ + Na)$: 689.48, found 689.50.

## CONCLUSIONS

The results described herein further illustrate the utility of the Mitsunobu macrocyclization (ring-closing) reaction toward the synthesis of macrocyclic phosphonates. The X-ray crystallographic characterization of two new macrocyclic bisphosphonate dimers, together with correlations to specific $^1$H and $^{31}$P NMR resonances allowed for the assignments of relative stereochemistries between the various dimers.

This preliminary investigation of these unique macrocyclic bifunctional phosphonates lays the foundation for exploring the physico-chemical and reactivity properties of this class of molecules. Such studies are currently underway and will be the focus of future reports.

## COMPETING INTERESTS:

The authors of this work have no competing interests.

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