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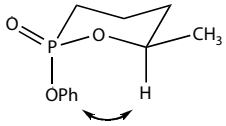
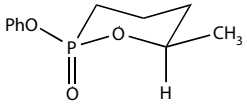
# Synthesis and stereochemistry of 6-membered ring phosphonates

Michael D. Pungente[1,*] Larry Weiler[2,**]

## ABSTRACT




1a




1b

*Background*: Organophosphorus compounds have important industrial and biomedical applications as pharmaceutical and agrochemical agents, as well as transition state analogs for the production of monoclonal antibodies.
*Methods*: Two diastereomers of a 6-membered ring, cyclic phenyl phosphonate were synthesized in 8 steps from 1,3-butanediol.
*Results*: The stereochemistry of the diastereomers was elucidated on the basis of $^{31}P$ NMR signals, together with $^{1}H$ NMR nuclear Overhauser effects (NOE) difference experiments.
*Conclusions*: Such cyclic phosphonates may have utility serving as transition state analogs for the production of monoclonal antibodies.

*Keywords:* Cyclic phosphonates, 6-membered, stereochemistry, NOE

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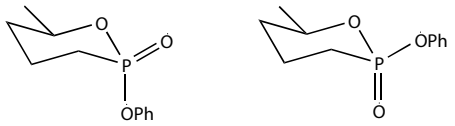
## INTRODUCTION

Organophosphorus compounds have received widespread interest as pharmaceutical [1–7] and agrochemical [8] agents as a result of the inherent physiological stability associated with the carbon–phosphorus bond capable of avoiding enzymatic degradation by phosphatases. Notably cyclic phosphonate analogues of hexopyranoses [9–14] are potential inhibitors of glycosidases [15]. Furthermore, cyclic phosphonate esters have found use as haptens for the production of catalytic antibodies [16–18]. Previously we reported [16] the production of a monoclonal antibody raised against a macrocyclic phosphonate transition state analogue that catalyzed an intramolecular transesterification of the corresponding hydroxy ester to give a 14-membered ring lactone. Furthermore, the synthesis and stereochemical elucidation of the 14-membered ring phenyl phosphonate leading to the hapten has been reported [19]. Herein we report the synthesis of the cyclic phosphonate **1a** and **1b** (Fig. 1), along with the stereochemical assignments of these diastereomers elucidated on the basis of $^{31}$P NMR signals, together with $^{1}$H NMR nuclear Overhauser effects (NOE) difference experiments.




**1a** **1b**

**Figure. 1 Cyclic phosphonates 1a and 1b.**

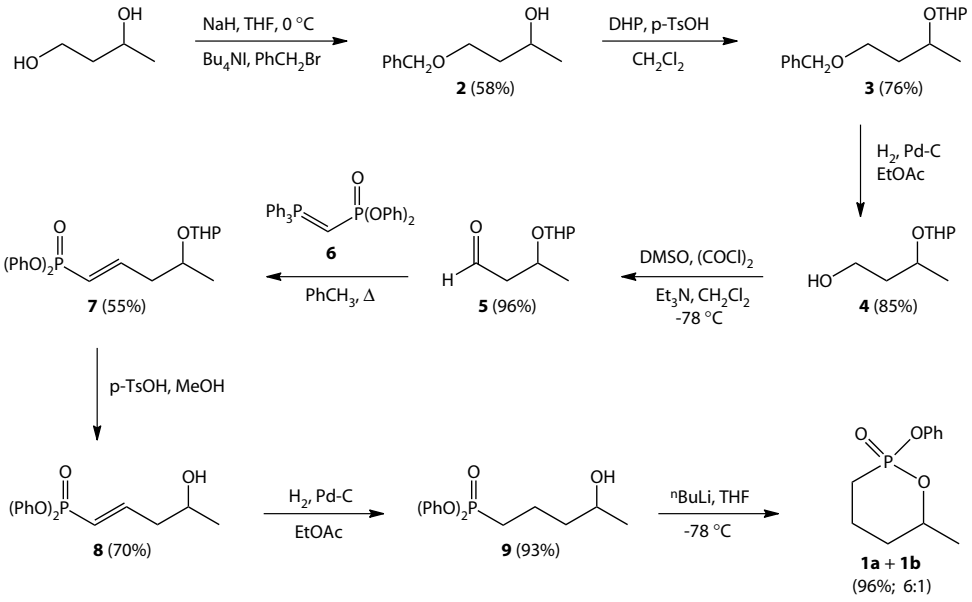
## RESULTS AND DISCUSSION

### The synthesis of diastereomeric cyclic phosphonates, 1a and 1b

The synthesis of **1a** and **1b** (Scheme 1) began with the conversion of the primary hydroxyl of 1,3-butanediol to the corresponding benzyl ether to give **2** in 58% yield. The secondary hydroxyl of **2** was then protected as the tetrahydropyranyl (THP) ether **3** in 76% yield. This addition of the THP group created a second chiral center in **3**, and therefore, two diastereomers of **3** were obtained. The two diastereomers were obtained in a 1:1 ratio according to the $^{1}$H NMR spectrum of **3**, which reveals two methyl doublets of equal intensity and two methine multiplets, corresponding to the methine proton of the THP group (data not shown). Hydrogenolysis of the benzyl moiety of compound **3** gave alcohol **4** in an isolated yield of 85%. Alcohol **4** was then oxidized under the Swern conditions to give the aldehyde **5** in 96% yield. Aldehyde **5** was subsequently reacted with the stabilized Wittig reagent **6** [20] to give the trans vinyl phosphonate **7** in a moderate yield of 55%. The vinyl phosphonate **7** was then reacted with p-toluenesulphonic acid to liberate the secondary hydroxyl compound **8** in 70% yield. Removal of the THP group from **7** eliminated one of two stereogenic centers in the molecule giving a single set of optical isomers, reflected in the $^{1}$H NMR spectrum of **8**, which contains only one methyl doublet. The alkene **8** was then reduced to give the saturated diphenyl phosphonate **9** in 93% yield. Finally, the hydroxy diphenyl phosphonate **9** was reacted with n-butyl lithium in THF at −78°C to produce the cyclic diastereomeric phosphonates **1a** and **1b** in isolated yields of 82% and 16% (5:1 ratio), respectively, as colorless oils upon purification by silica gel flash chromatography using 1:1 petroleum ether and ethyl acetate.

### Stereochemical elucidation of diastereomeric cyclic phosphonates, 1a and 1b

Figure 2 illustrates the relative stereochemical assignments of three sets of cyclic phosphonates, including **1a** and **1b**, cyclic phosphonate analogs of pentoses, **10a** and **10b** [15], and finally macrocyclic phosphonates **11a** and **11b** [19]. Support for the axial assignment of the OPh moiety on the phosphorus atom of **1a** comes from correlations between the $^{31}$P NMR chemical shift data (Table 1). It has been observed that the $^{31}$P NMR signal for the axial P-OR isomer is approximately 2-ppm higher field than the corresponding equatorial isomer in the cyclic phosphonates of hexopyranoses [15,21,22] and in other six-membered ring phosphonates [23,24]. The $^{31}$P NMR shifts for compounds **1a** and **1b**, listed in Table 1, are in agreement with the trends described above for the pair of cyclic phosphonate analogs of pentoses, **10a** and **10b**, reported by Harvey et al., [15] and those described by Pungente et al. [19] for the pair of 14-membered ring phosphonates, **11a** and **11b**.




**Scheme 1** Synthesis of cyclic phosphonates **1a** and **1b**.

**Table 1.** $^{31}$P NMR chemical shifts ($\delta$ values) for cyclic phosphonates.

| Compound | P-OR stereochemistry | $\delta\,^{31}$P (ppm) | $\Delta$(eq-ax) |
|---|---|---|---|
| 1a | ax | 20.49 | |
| 1b | eq | 23.39 | 2.9 |
| 10a [15] | ax | 14.06 | |
| 10b [15] | eq | 16.37 | 2.3 |
| 11a [19] | pseudo-ax | 27.80 | |
| 11b [19] | pseudo-eq | 29.60 | 1.8 |

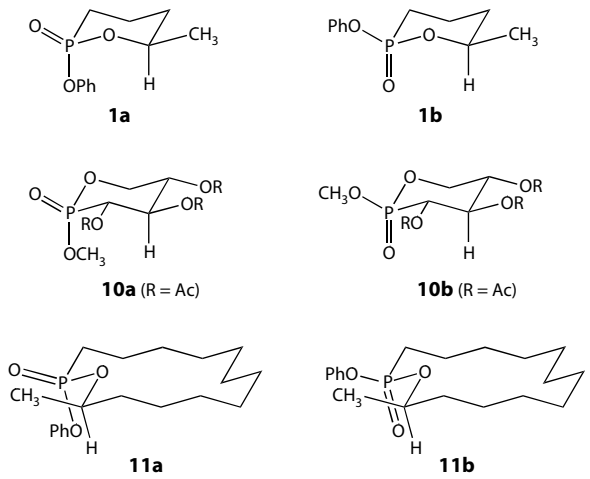



**Figure. 2** Relative stereochemical assignments of 6-membered ring phosphonates **1a** and **1b**, cyclic phosphonate analogs of pentoses, **10a** and **10b** [15], and finally macrocyclic phosphonates **11a** and **11b** [19].

That is, the $^{31}$P signal for phosphonate **1a**, with the OPh group in the axial position, is at higher field than the corresponding equatorial isomer, **1b**.

Finally, the stereochemical assignments for compounds **1a** and **1b** were confirmed on the basis of $^{1}$H NMR NOE difference experiments. Irradiation of the methine signal at 4.51 ppm of phosphonate **1a** resulted in enhancement of the phenyl signal between 7.4 and 7.2 ppm, whereas, irradiation of the corresponding methine signal for **1b** failed to produce an enhanced signal in the phenyl region

(Fig. 3). This NOE data is consistent with the stereochemical assignments for compounds **1a** and **1b**. Furthermore, these NOE results are consistent with those obtained from the pair of cyclic phosphonate analogs of pentoses, **10a** and **10b**, reported by Harvey et al. [15]. They reported an NOE enhancement of H-2 in **10a** when the phosphorus methyl was irradiated, consistent with these two substituents having a 1,3-diaxial relationship.

## GENERAL CHEMICAL METHODS

Unless otherwise stated, all reactions were performed under a $N_2$ atmosphere using flame-dried glassware. Cold temperature baths were prepared as follows: −78°C (dry ice–acetone) and 0°C (ice–water). Anhydrous reagents and solvents were purified and prepared according to literature procedures [25]. Chromatographic solvents and reagents were used as received unless noted otherwise. The low boiling fraction (35–60°C) of petroleum ether was used. All reagents were supplied by the Aldrich Chemical Co. and unless otherwise stated were used without further purification. n-Butyl lithium (n-BuLi) was standardized by titration against 2,2-diphenylacetic acid in THF at room temperature to the appearance of a faint yellow color.

All reactions were monitored by thin layer chromatography (TLC) and judged to be complete when the starting material was consumed as determined by TLC. In the description of reaction work-ups, washing with brine refers to a saturated solution of NaCl, drying of the organic phase was accomplished with $MgSO_4$ and removal of solvent in vacuo or concentration of solvent refers to the use of a rotary evaporator using a water aspirator and heating using a water bath.

Preparative flash chromatography [26] 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 TLC.

Infrared (IR) spectra were recorded on a Bomem Michelson 100 FT-IR spectrometer using internal calibration. IR spectra were recorded on the neat liquid or as a chloroform solution using NaCl solution cells.

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 (13C 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 (31P 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.

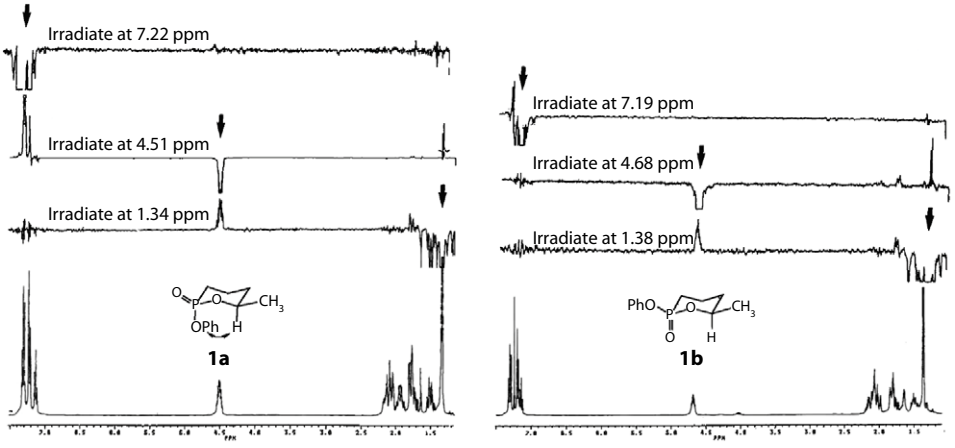



**Figure. 3** Selected $^1$H NMR NOE difference experiments that distinguish between the two diastereomers of cyclic phosphonates **1a** and **1b.**

Low- and high-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. Low-resolution desorption chemical ionization (DCI) mass spectral analyses, using $CH_4$ or $NH_3$ reagent gas as indicated, were recorded on a Delsi Nermag R10-10C mass spectrometer. High-resolution DCI mass spectral analyses, using $CH_4$ or $NH_3$ reagent gas as indicated, were recorded on a Kratos MS 80 RFA mass spectrometer.

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.

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.

## EXPERIMENTAL

### 1-Benzyloxy-3-butanol (2).

1,3-Butanediol (5.0 g, 56 mmol) was dissolved in 125 mL of dry THF, and cooled to 0°C under $N_2$ prior to the addition of a 60% dispersion of NaH in mineral oil (2.7 g, 67 mmol) over a 10 min period. Upon addition of the NaH, the mixture was stirred for 10 min, and $Bu_4NI$ (1.0 g, 2.8 mmol) was added, followed by the drop wise addition of benzyl bromide (8.0 mL, 67 mmol). The ice–water bath was removed, and the reaction mixture was stirred at room temperature for 2.5 h before diluting the mixture with $Et_2O$, and quenching with water, followed by 1 M HCl. The mixture was then extracted with $Et_2O$, and the combined $Et_2O$ extracts were dried over anhydrous $MgSO_4$, filtered and solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using 1:1 petroleum ether and ethyl acetate to afford 5.8 g (58%) of **2** as a colorless oil.

$^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.32 (m, 5H), 4.52 (s, 2H), 4.00 (m, 1H), 3.653 (m, 2H), 2.63 (s, 1H), 1.73 (m, 2H), 1.18 (d, J = 6.2 Hz, 3H); LRMS (EI) *m/z* (relative intensity): 180 (2), 161 (11), 120 (15), 108 (11), 107 (46), 92 (16), 91 (100), 79 (16), 65 (12).

### 1-Benzyloxy-3-(Tetrahydropyranyloxy) butane (3).

To a stirred solution of **2** (260 mg, 1.44 mmol) in 5 mL of $CH_2Cl_2$ was added DHP (158 μL, 1.73 mmol) and p-TsOH (14 mg, 0.072 mmol), and the mixture was stirred at room temperature under $N_2$ for 2 h. The solvent was then removed and the residue was diluted with $Et_2O$. The ether layer was washed with 2 × 25 mL of saturated $NaHCO_3$, 1 × 25 mL water and 1 × 50 mL of brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using 5:1 petroleum ether and ethyl acetate to afford 288 mg (76%) of **3** as a colorless oil.

$^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.30 (m, 5H), 4.70 (m, 0.4H), 4.55 (m, 0.6H), 4.49 (m, 2H), 3.75–4.08 (m, 2H), 3.62 (m, 1H), 3.48 (m, 2H), 1.60–2.00 (m, 4H), 1.40–1.60 (m, 4H), 1.24 (d, J = 6.2 Hz, 1.5H), 1.11 (d, J = 6.2 Hz, 1.5H); LRMS (DCI, $NH_3$) *m/z* (relative intensity): 282 ($M^+ + 18$, 4), 265 ($M^+ + 1$, 4), 181 (66), 179 (16), 91 (88), 85 (100); HRMS (DCI, $CH_4$) calcd. for $C_{16}H_{24}O_3$: 264.1725, found 264.1648.

### 3-(Tetrahydropyranyloxy) butan-1-ol (4).

A spatula tip of Pd-C (10%) stirring in 20 mL of EtOAc was saturated with $H_2$ for 12 h before a solution of compound **3** (230 mg, 0.871 mmol) in 5 mL of EtOH was added via a steel cannula. This mixture was allowed to stir for an additional five hours under $H_2$ pressure of one atmosphere. The reaction mixture was filtered through a Celite bed and concentrated under reduced pressure to give 146 mg of crude product, which was purified by flash chromatography using 1:1 petroleum ether and ethyl acetate to afford 129 mg (85%) of **4** as a colorless oil.

IR (neat): 3408, 2918, 1447, 1376, 1322, 1260, 1201, 1128, 1027, 1001, 907, 868, 811 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 4.68 (m, 0.2H), 4.55 (m, 0.8H), 3.40–4.13 (m, 6H), 2.35 (br s, 1H), 1.28 (d, J = 6.2 Hz, 0.6H), 1.15 (d, J = 6.2 Hz, 1.4H); LRMS (DCI, $NH_4$) *m/z* (relative intensity): 192 ($M^+ + 18$, 1), 175 ($M^+ + 1$, 4), 173 (2), 108 (6), 101 (13), 86 (10), 85 (100), 55 (18).

**3-(Tetrahydropyranyloxy) butanal (5).**

To a stirred solution of oxalyl chloride (75 μL, 0.86 mmol) in 10 mL of dry $CH_2Cl_2$ under $N_2$ at −78°C was added DMSO (102 μL, 1.44 mmol) dissolved in 2 mL $CH_2Cl_2$ via a stainless steel cannula. After 10 min. of stirring, compound **4** (102 mg, 0.575 mmol) in 5 mL of $CH_2Cl_2$ was added to the activated DMSO via a stainless steel cannula. Finally, after stirring an additional 10 min, $Et_3N$ (410 μL, 2.95 mmol) was syringed in, and the reaction mixture was allowed to warm to room temperature while maintaining stirring. After 3 h, the solution was diluted with 50 mL of $Et_2O$ followed by 50 mL of water. The aqueous layer was further extracted with 3 × 50 mL of $Et_2O$ and the combined $Et_2O$ extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to a yellow oil. The crude product was then purified by flash chromatography using 4:1 petroleum ether and ethyl acetate to afford 95 mg (96%) of **5** as a colorless oil.

$^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 9.80 (m, 1H), 4.68 (m, 0.8H), 4.55 (m, 0.2H), 4.18–4.43 (m, 1H), 3.63–3.99 (m, 2H), 3.48 (m, 1H), 2.55 (m, 2H), 1.40–1.85 (m, 8H), 1.26 (d, J = 6.2 Hz, 0.6H), 1.20 (d, J = 6.2 Hz, 2.4H).

**1-Diphenylphosphinyl-4-(tetrahydropyranyloxy)-1-pentene (7).** The Wittig reagent **6** [20] (1.9 g, 3.8 mmol) and aldehyde **5** (0.43 g, 2.5 mmol) were dissolved in 40 mL of toluene and refluxed under $N_2$ for three days. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using 5:1 petroleum ether and ethyl acetate to afford 0.55 g (55%) of **7** as a colorless oil.

IR (neat): 2941, 2870, 1629, 1592, 1489, 1455, 1379, 1341, 1271, 1214, 1192, 1163, 1127, 1074, 1026, 994, 934, 767 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.10–7.38 (m, 10H), 7.00 (m, 1H), 5.95 3 (m, 1H), 4.68 (m, 0.5H), 4.55 (m, 0.5H), 3.73–4.00 (m, 2H), 3.35-3.60 (m, 1H), 2.30–2.55 (m, 2H), 1.35–1.90 (m, 6H), 1.18 (d, J = 6.2 Hz, 1.5H), 1.08 (d, J = 6.2 Hz, 1.5H); $^{31}$P NMR (81 MHz, $CDCl_3$) $\delta$: 10.8; LRMS (EI) *m/z* (relative intensity): 402 (1), 318 (28), 301 (22), 275 (26), 274 (100), 259 (17), 181 (13), 162 (10), 141 (13), 133 (15), 118 (18), 117 (96), 116 (65), 115 (47), 94 (85), 77 (87); HRMS calcd. for $C_{22}H_{27}O_5P$: 402.1596, found 402.1605.

**4-Hydroxy-1-diphenylphosphinyl-1-pentene (8).**

p-TsOH (26 mg, 0.14 mmol) was added to a stirred solution of compound **7** (0.55 g, 1.4 mmol) in 20 mL of MeOH at room temperature. After 5 h, the MeOH was removed under reduced pressure and the resulting oil was dissolved in $Et_2O$, washed with 2 × 20 mL of water followed by 2 × 20 mL of brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography using 1:1 petroleum ether and ethyl acetate to afford 0.31 g (70%) of alcohol **8** as a colorless oil.

IR (neat): 3403, 2971, 1629, 1592, 1489, 1456, 1198, 1164, 1120, 1072, 1025, 937, 814, 767 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.12–7.35 (m, 10H), 6.94 (ddt, J = 7.2, 17.1, 23.1 Hz, 1H), 5.94 (ddt, J = 1.4,17.1, 23.1 Hz, 1H), 3.88 (m, 1H), 2.37 (dt, J = 1.4, 7.7 Hz, 2H), 1.61 (br s, 1H), 1.14 (d, J = 6.2 Hz, 3H); $^{31}$P NMR (81 MHz, $CDCl_3$) $\delta$: 10.8; LRMS (EI) *m/z* (relative intensity): 318 (16), 274 (48), 259 (8), 181 (6), 133 (7), 117 (830), 94 (82), 77 (100); HRMS calcd. for $C_{17}H_{19}O_4P$: 318.1021, found 318.1014; Anal. Calcd. for $C_{17}H_{19}O_4P$: C, 64.13; H, 6.02. Found: C, 64.03; H, 6.11.

**1-Diphenylphosphinyl pentan-4-ol (9).**

A spatula tip of Pd-C (10%) in 20 mL of EtOAc was saturated with $H_2$ for 16 h before compound **8** (0.31 g, 0.97 mmol) in 3 mL of EtOAc was added via a steel cannula. This mixture was allowed to stir for an additional two days under $H_2$ gas at a pressure slightly greater than one atmosphere. The reaction mixture was filtered through a Celite bed and concentrated under reduced pressure to afford 0.29 g (93%) of **9** as a colorless oil.

IR (neat): 3411, 2940, 1592, 1490, 1456, 1374, 1202, 1164, 1126, 1069, 1025, 1007, 935, 763 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.13–7.37 (m, 10H), 3.84 (m, 1H), 2.02–2.22 (m, 2H), 1.76–2.02 (m, 3H), 1.61 (dt, J = 6.4, 7.5 Hz, 2H), 1.21 (d, J = 6.2 Hz, 3H); $^{31}$P NMR (81 MHz, $CDCl_3$) $\delta$: 25.6; LRMS (EI) *m/z* (relative intensity): 320 (1), 305 (10), 227 (100), 185 (15), 172 (25), 140 (25), 95 (57), 94 (96), 91 (75), 77 (86).

**6-Methyl-2-oxo-2-phenoxy-1,2-oxaphosphorinane (1a and 1b).**

Compound **9** (495 mg, 1.55 mmol) was dissolved in 30 mL of dry THF and stirred under $N_2$, then cooled to −78°C with a dry-ice acetone bath. 1.2 M *n*BuLi (94 μL, 1.1 mmol) was then added via syringe, and after stirring at −78°C for 2.5 h, the dry-ice acetone bath was removed. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography using 1:1 petroleum ether and ethyl acetate to afford 0.286 g (82%) of **1a** and 0.057 g (16%) of **1b** colorless oils.

Isomer **1a:** IR (neat): 2946, 1592, 1491, 1455, 1384, 1302, 1255, 1209, 1161, 1079, 1049, 1032, 980, 921, 839, 789, 765 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 7.11–7.34 (m, 5H), 4.51 (m, 1H), 2.02–2.20 (m, 2H), 1.94 (m, 1H), 1.68–1.84 (m, 2H), 1.51 (m, 1H), 1.35 (dd, J = 2.3, 6.3 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 129.80 (s), 124.68 (s), 119.99 (d, J = 4.50 Hz), 78.99 (d, J = 7.73 Hz), 33.14 (d, J = 6.30 Hz), 22.61 (d, J = 7.95 Hz), 22.08 (d, J = 127.20 Hz), 21.48 (d, J = 8.10 Hz); $^{31}P$ NMR (81 MHz, $CDCl_3$) $\delta$: 20.5; LRMS (EI) *m/z* (relative intensity): 226 (29), 211 (6), 185 (23), 172 (25), 144 (24), 115 (9), 94 (100), 77 (18); HRMS calcd. for $C_{11}H_{15}O_3P$: 226.0759, found 226.0756;

Isomer **1b:** IR (neat): 2943, 1593, 1491, 1383, 1291, 1250, 1210, 1153, 1026, 951, 783 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 7.11–7.34 (m, 5H), 4.68 (m, 1H), 1.96–2.22 (m, 3H), 1.71–1.86 (m, 2H), 1.45–1.54 (m, 1H), 1.36 (dd, J = 2.3, 6.3 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 129.67 (s), 124.92 (s), 120.55 (d, J = 4.65 Hz), 77.59 (d, J = 5.25 Hz), 33.30 (d, J = 5.63 Hz), 22.41 (d, J = 126.80 Hz), 22.31 (d, J = 7.05 Hz), 20.42 (d, J = 7.13 Hz); $^{31}P$ NMR (81 MHz, $CDCl_3$) $\delta$: 23.4; LRMS (EI) *m/z* (relative intensity): 226 (41), 211 (7), 185 (27), 172 (30), 144 (26), 115 (9), 94(100), 77 (18); HRMS calcd. for $C_{16}H_{24}O_3P$ : 226.0759, found 226.0759; Anal. Calcd. for $C_{11}H_{15}O_3P$: C, 58.39; H, 6.69. Found: C, 58.07; H, 6.71.

## CONCLUSIONS

Two 6-membered ring, cyclic phenyl phosphonate diastereomers, **1a** and **1b** were prepared in a 6:1 ratio, respectively, in 8 steps from 1,3-butanediol. The stereochemistry of **1a** and **1b** was elucidated on the basis of $^{31}P$ NMR signals, together with $^1H$ NMR nuclear Overhauser effects (NOE) difference experiments. Such cyclic phosphonates may have utility serving as transition state analogs for the production of monoclonal antibodies.

**Competing interests:**

The authors of this work have no competing interests.

## ACKNOWLEDGEMENTS

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