FORMATION OF 5-METHYLENE-1,3-DIOXEPANES BY THE REACTION OF 2,2,2-TRIPHENYL-1,2λ^5-OXAPHOSPHOLANES WITH PARAFORMALDEHYDE

Kentaro Okuma,* Yuichiro Tanaka, Ichiro Shuzui, and Kosei Shioji
Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-0180, Japan

Abstract— Reaction of 2,2,2-triphenyl-1,2λ^5-oxaphospholanes with paraformaldehyde yielded novel 7-membered cyclic methylene acetals (5-methylene-1,3-dioxepanes) in good yields. Phosphonium betaines reacted with paraformaldehyde to give new betaines, which further reacted with paraformaldehyde to afford olefins *via* Wittig reaction. The mechanism of this reaction was discussed.

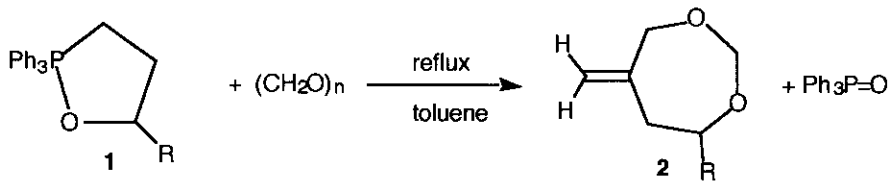
Oxaphospholanes (**1**) are interesting compounds because of their unique structure and synthetic utility.[1] In 1967, Hands and Mercer reported the first isolation of the parent 2,2,2-triphenyl-1,2λ^5-oxaphospholane (**1a**).[2] Because their synthetic utility in the formation of homoallylic alcohols appeared promising, it was surprising to find that very few substituted derivatives of **1** had been prepared.[3] Enholm and co-workers have reported the sequential Wittig-oxyanion accelerated Cope reaction of 2,2,2-triphenyl-5-vinyl-1,2λ^5-oxaphospholane.[3] Recently, enantiomerically pure 2,2,2-triphenyl-1,2λ^5-oxaphospholanes (**1**) were synthesized and the reaction of **1** with aldehydes afforded the corresponding enantiomerically pure homoallylic alcohols in nearly quantitative yields.[4] In a previous communication, we have reported the novel formation of 5-methylene-1,3-dioxepanes (**2**) by the reaction of **1** with paraformaldehyde.[5] We report herein the details of the reactions of **1** with paraformaldehyde.

RESULTS AND DISCUSSION

Reaction of 1 with Paraformaldehyde

Oxaphospholanes (**1**) were prepared by the reaction of 3-hydroxyalkyltriphenylphosphonium iodides with sodium hydride or by the direct cyclization of methylenetriphenylphosphorane with epoxides.[4,6] Treatment of **1a** with paraformaldehyde resulted in the formation of 5-methylene-1,3-dioxepane (**2a**), which was identified based on its spectroscopic data. The ^{1}H NMR spectrum of **2a** displayed signals at δ 4.93 (s, 2H) of exo methylene protons, at δ 2.54 (br t, 2H, *J*=5 Hz, allyl CH_2), 3.76 (t, 2H, *J*=5 Hz, OCH_2), 4.32 (br s, 2H, Allyl CH_2O), and 4.80 (s, 2H, OCH_2O) for four aliphatic methylene protons. The ^{13}C NMR spectrum of **2a** showed four aliphatic carbons (δ 37.9, 68.8, 73.4, and 95.8) and two olefinic carbons (δ 113.4 and 146.4) (Scheme 1).

In the case of 2,2,2-triphenyl-1,2λ-oxaphospholane (**1a**), the reaction proceeds at relatively low temperature. Even in refluxing ether, the reaction was completed within 5 h. However, elevated temperature is required in the cases of **1b**, **1c**, and **1d** (Table 1). Normal Wittig reaction products, homoallylic alcohols were not observed in the reaction mixture by ^{1}H NMR analysis.

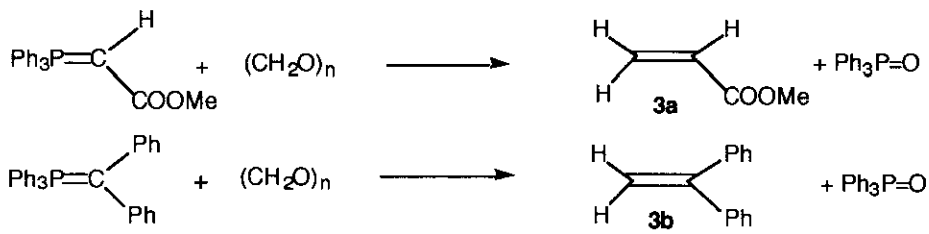


Scheme 1. Formation of 5-methylene-1,3-dioxepanes (**2**).

Table 1. Reaction of Oxaphospholanes **1** with Paraformaldehyde

	1		Conditions		Products (Yield/%)	
	R	Time/h	Solvent	Temp.	**2**	$Ph_3P=O$
1a	H	0.2	benzene	reflux	**2a** 80	95
1b	Me	6	benzene	reflux	**2b** 70	75
1b	Me	1	toluene	reflux	**2b** 90	90
1c	Et	1	toluene	reflux	**2c** 90	90
1d	Ph	1	toluene	reflux	**2d** 90	90

Since oxepanes (**2**) were obtained in good yields, the reaction of stable Wittig reagents with paraformaldehyde was then carried out. Treatment of carbomethoxymethylenetriphenylphosphorane with paraformaldehyde gave only methyl acrylate (**3a**) together with triphenylphosphine oxide in 90% yield. Other Wittig reagents such as diphenylmethylenetriphenylphosphorane gave the same result; normal Wittig reaction product, diphenylethylene (**3b**), was obtained (Scheme 2).



Scheme 2. Reaction of stable phosphorus ylides with paraformaldehyde.

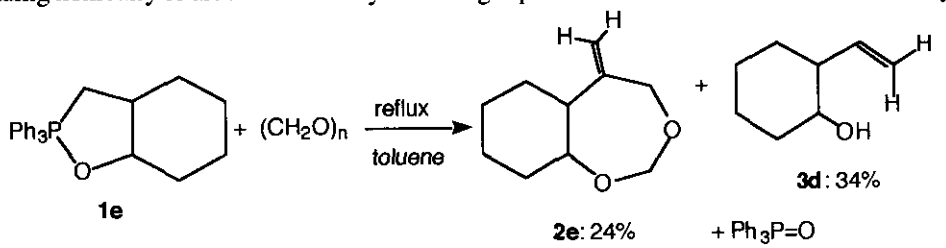
The reaction of **1b** with benzaldehyde afforded only the corresponding Wittig reaction product (**3c**: 5-phenyl-4-penten-2-ol), suggesting that polymeric aldehydes are required in this reaction.

To confirm the possibility of the formation of bicyclic dioxepane, the reaction of oxaphospholane (**1e**) with paraformaldehyde was carried out. The desired product (**2e**) was obtained together with 2-vinylcyclohexanol (**3d**) (Scheme 3).

The reaction might proceed as follows: oxaphospholane (**1**) reacts with two equivalents of formaldehyde to give the corresponding betaine (**4**), which further reacts with another molecule of formaldehyde followed by dehydration to afford **2** (Scheme 4) Thus, **1** reacts with three equivalents of formaldehyde to afford dioxepanes (**2**).

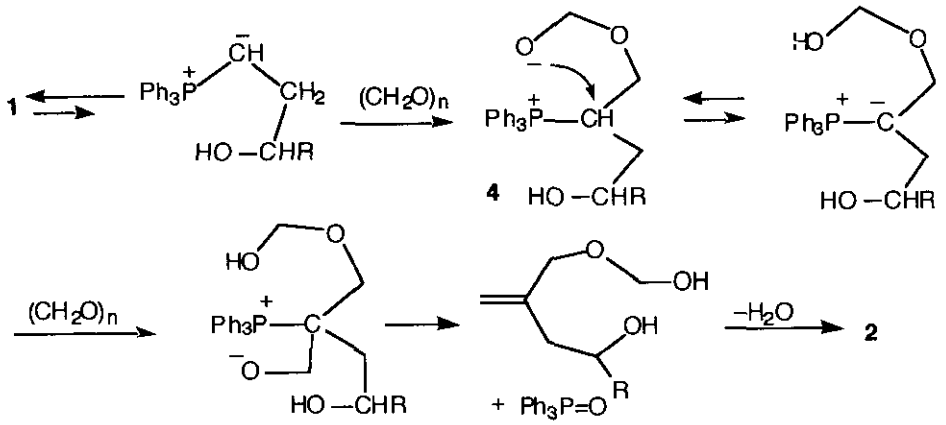
The present reaction is quite different from others. The typical reaction of 2,2,2-triphenyl-1,2-oxaphospholanes includes the preparation of homoallylic alcohols by the reaction with aldehydes. For example, Hands and Mercer reported that the reaction of oxaphospholanes with aldehydes afforded the

corresponding homoallylic alcohols.[3] Corey and Kang reported that the reaction of α-lithiomethylenetri-



Scheme 3. Reaction of **1e** with paraformaldehyde.

phenylphosphorane with epoxides afforded the corresponding homoallylic alcohols.[8] Other types of the reactions were also reported. Le Corre and Hercouet prepared 2,3-dihydrofurans by the intramolecular cyclization of ω-acyloxy-*n*-propylidenephosphorane.[9] Denny *et al.* reported that ethyl 2-phenylcyclopropanecarboxylate was produced in the reaction of carbethoxymethylenetriphenylphosphorane with styrene oxide at 200 °C.[10] Schweizer and Creasy reported that thermolysis of 5-benzoyl-2,2,2,5-tetraphenyl-1,2-oxaphospholane afforded benzil, triphenylphosphine, and an olefin.[11] However, there is no report on the reaction with paraformaldehyde to give cyclic alkylidene acetals.

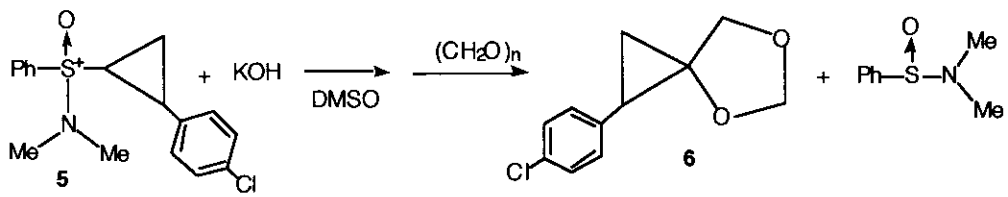


Scheme 4. Reaction mechanism.

Reaction of Sulfoxonium Ylide with Paraformaldehyde

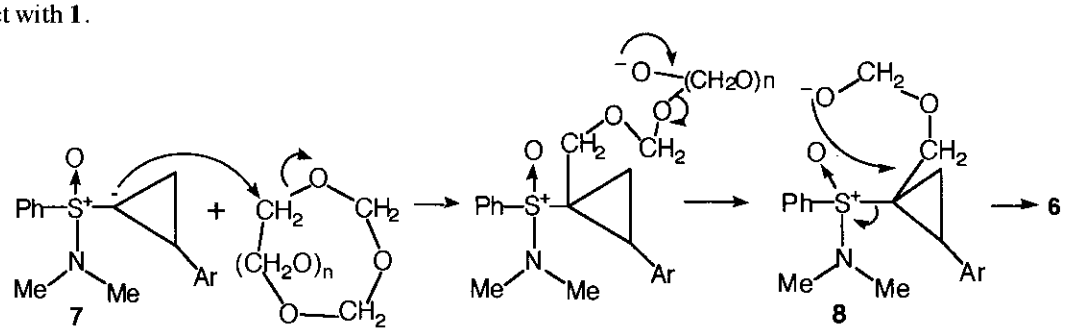
We then tried the reaction of sulfoxonium ylides with paraformaldehyde to investigate the scope and limitation of this methodology. Previously, we have synthesized 2-*p*-chlorocyclopropyl-(dimethylamino)phenylsulfoxonium tetrafluoroborate (**5**) in a remarkably simple procedure,[12] which seems to be a good substrate to react with paraformaldehyde. Treatment of **5** with potassium hydroxide followed by the addition of paraformaldehyde resulted in the formation of 1-(*p*-chlorophenyl)-4,6-dioxaspiro[2.4]heptane (**6**) in 70 % yield (Scheme 5). The structure of **6** was confirmed by its NMR spectroscopic analysis. The ^{1}H NMR spectrum of **6** displayed signals at δ 1.16, 1.64, and 2.47 for cyclopropyl protons, at δ 3.53, 3.70, 5.00, and 5.09 for four geminal methylene protons, at 6.99 and 7.26 for aromatic protons.

The reaction might proceed as follows. Cyclopropylide (**7**) produced from **5** and KOH attacked the carbon of paraformaldehyde, which afforded the corresponding betaine (**8**). The obtained betaine was further subjected to intramolecular substitution to give **6** (Scheme 6).



Scheme 5. Formation of dioxaspiro[2,4]heptane (**6**).

This result is different from that of the reaction of **1** with paraformaldehyde. In the reaction of **5**, two moles of formaldehyde react with one mole of cyclopropylide (**7**), whereas three moles of formaldehyde react with **1**.



Scheme 6. Mechanism of the reaction of **7** with paraformaldehyde.

The present result is quite different from those described by Johnson *et al.*[12] and Trost *et al.*[13] They reported that the reaction of sulfonium or sulfoxonium cyclopropylides with aldehydes afforded the corresponding cyclopropylidene transfer products (oxaspiropentanes). Thus, oxaspiropentane should be formed by the usual methylene transfer reaction in the present case. 4,6-Dioxaspiro[2.4]heptane (**6**) might be more stable than oxaspiropentane because of its smaller ring strain. When paraformaldehyde, polymeric form of formaldehyde, is used as a substrate, the formation of **6** is much favorable than that of oxaspiropentane.

The present reaction is interesting that it can introduce two or three oxymethylene groups to sulfoxonium or phosphonium salts in one operation. This is the first example of the synthesis of 7-membered cyclic acetals from oxaphospholanes, representing a new type of reaction for oxaphospholanes.

ACKNOWLEDGMENT

This work was partly supported by Grants-in-Aid for Scientific Research (06640706 and 07804046) from the Ministry of Education, Science, Culture, and Sports of Japan.

EXPERIMANTAL

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a JEOL FX-90Q or a JEOL GSX-400 spectrometer. Chemical shifts are given in ppm units downfield from tetramethylsilane. TLC analyses were done using Merck Silica gel 60 F254 aluminum plates.

Material 2,2,2-Triphenyl-1,2λ^5-oxaphospholanes (**1**) were prepared by the reaction of 3-hydroxyalkyltriphenylphosphonium salts with sodium hydride[4] or by the reaction of methylenetriphenylphosphorane with epoxides.[6] Sulfoxonium salt (**5**) was prepared by a method described by us.[11]

Reaction of 1a with Paraformaldehyde

To a solution of **1a** (1.67 g, 5.4 mmol) in benzene (5 mL) was added paraformaldehyde (0.45 g, 15 mmol) in one portion. After refluxing for 12 min, the reaction mixture was subjected to silica gel column

chromatography by elution with pentane. The eluant was concentrated to give crude 5-methylene-1,3-dioxepane (**2a**) (0.51 g, 80 %), which was distilled to afford pure **2a** (0.27 g, 43 %). **2a**: bp 100°C/760 mm Hg, HRMS; Found: m/z 114.0670. Calcd for $C_6H_{10}O_2$ (M^+): 114.0681.

Reaction of **1b** with paraformaldehyde was carried out in a similar manner by using **1b** (0.67 g, 2.0 mmol), paraformaldehyde (0.30 g, 10 mmol), and benzene (5 mL). Flash chromatography using pentane gave 7-methyl-5-methylene-1,3-dioxepane (**2b**) (0.18 g, 70 %). **2b**: bp 45-55°C/17 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3 H, *J*=4 Hz, CH_3), 2.39-2.48 (m, 2 H, allyl CH_2), 3.70 (m, 1 H, OCH), 4.26 (d, 1 H, *J*=14 Hz, allyl C<u>H</u>HO), 4.41 (d, 1 H, *J*=14 Hz, allyl CH<u>H</u>O), 4.65 (d, 1 H, *J*=7 Hz, OC<u>H</u>HO), 4.93 (br s, 2H, $=CH_2$), 4.98 (d, 1H, J=7 Hz, OCH<u>H</u>O). ^{13}C NMR ($CDCl_3$) δ 21.88 (CH_3), 44.89 (CH_2), 73.41 (allyl CH_2O), 75.50 (OCH), 94.21 (OCH_2), 113.98 ($=CH_2$), 145.56 (=C). HRMS: Found: m/z 128.0837. Calcd for $C_7H_{12}O_2$ (M^+); 128.0823.

Reaction of **1c** with paraformaldehyde was carried out in a similar manner by using **1c** (0.70 g, 2.0 mmol), paraformaldehyde (0.30 g, 10 mmol), and toluene (5 mL). Flash chromatography using pentane gave 7-ethyl-5-methylene-1,3-dioxepane (**2c**) (0.26 g, 90 %). **2c**: bp 80-90 °C/20 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3 H, *J*=7 Hz, CH_3), 1.66 (m, 2 H, CH_2), 2.45-2.50 (m, 2 H, allyl CH_2), 3.42 (m, 1 H, OCH), 4.24 (d, 1 H, *J*=14 Hz, allyl C<u>H</u>HO), 4.38 (d, 1H, *J*=14 Hz, allyl CH<u>H</u>O), 4.65 (d, 1H, *J*=7 Hz, OC<u>H</u>HO), 4.92 (br s, 2H, $=CH_2$), 5.01 (d, 1H, *J*=7 Hz, OCH<u>H</u>O). ^{13}C NMR ($CDCl_3$) δ 10.21 (CH_3), 28.92 (CH_2), 42.86 (CH_2), 73.18 (allyl CH_2O), 80.51 (OCH), 94.65 (OCH_2), 113.91 ($=CH_2$), 145.69 (=C). HRMS: Found: m/z 142.0994. Calcd for $C_8H_{14}O_2$ (M^+); 142.0960.

Reaction of **1d** with paraformaldehyde was carried out in a similar manner by using **1d** (0.80 g, 2.0 mmol), paraformaldehyde (0.30 g, 10 mmol), and toluene (5 mL). Flash chromatography using pentane gave 7-phenyl-5-methylene-1,3-dioxepane (**2d**) (0.36 g, 90 %). **2d**: ^{1}H NMR ($CDCl_3$) δ 2.64 (dd, 1 H, J=15 and 3 Hz, =CC<u>H</u>H), 2.76 (dd, 1 H, *J*=15 and 11 Hz, =CCH<u>H</u>), 4.34 (d, 1 H, *J*=14 Hz, allyl C<u>H</u>HO), 4.49 (d, 1H, *J*=14 Hz, allyl CH<u>H</u>O), 4.58 (dd, 1H, *J*=12 and 3 Hz, PhCH), 4.81 (d, 1 H, *J*=7 Hz, OC<u>H</u>HO), 5.02 (s, 2 H, $=CH_2$), 5.13 (d, 1 H, *J*=7 Hz, OCH<u>H</u>O), 7.25-7.42 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ 45.52 (CH_2), 73.20 (allyl CH_2O), 80.91 (OCH), 94.51 (OCH_2O), 114.79 ($=CH_2$), 125.86 (Ph), 127.72 (Ph), 128.17 (Ph), 142.24 (=C), 145.24 (Ph). HRMS: Found: m/z 190.0981. Calcd For $C_{12}H_{14}O_2$ (M^+): 190.0994. Found: C, 75.40; H, 7.26. Calcd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.37.

Preparation of Bicyclic Oxaphospholane (1e)

A solution of 2-hydroxycylohexylmethyltriphenylphosphonium iodide (5.02 g, 10.0 mmol) in THF (20 mL) was added a suspension of sodium hydride (0.44 g, 60% mineral oil dispersion, 11 mmol) in THF (15 mL) and the suspension was refluxed for 3 h. The reaction mixture was filtered and the filtrate was concentrated to give crude crystals of **1e**. Recrystallization from dichloromethane-hexane to give colorless crystals (1.92 g, 51 %). **1e**: mp 151-153 °C. ^{1}H NMR (C_6D_6) δ 0.92-1.36 (m, 4 H, CH_2), 1.43-1.58 (m, 3 H, CH_2 and CH), 1.70-1.78 (m, 1 H, C<u>H</u>H), 1.83-1.88 (m, 1 H, CH<u>H</u>), 2.01-2.15 (m, 1 H, PC<u>H</u>H), 2.69-2.82 (m, 2 H, PCH<u>H</u> and OCH), 6.96-7.09 (m, 9 H, Ar). ^{13}C NMR (C_6D_6) δ 25.22 (CH_2), 26.63 (CH_2), 30.40 (d, J_{PC}=20 Hz, CH_2), 33.19 (d, J_{PC}=7 Hz, CH2), 45.30 (CH), 73.48 (d, J_{PC}=92 Hz, PCH), 76.62 (d, J_{PC}=6 Hz, OCH), 127.34, 127.45, 132.13, 132.22 (Ar). Found: C, 80.20; H, 7.36. Calcd for $C_{25}H_{27}OP$: C, 80.19; H, 7.27.

Reaction of 1e with Paraformaldehyde

To a solution of **1e** (0.75 g, 2.0 mmol) in toluene (10 mL) was added paraformaldehyde (0.30 g, 10 mmol) in one portion. After refluxing for 6 h, the solution was evaporated to give a colorless oil, which was chromatographed over silica gel by elution with hexane-dichloromethane (1:1) to give bicyclic acetal **2e** (0.084 g, 24 %) and **3d** (0.086 g, 34 %). **2e**: bp 190-200 °C/20 mmHg; ^{1}H NMR ($CDCl_3$) δ=1.19-1.44 (m, 4 H, CH_2), 1.69-1.82 (m, 2 H, CHH), 1.88-1.92 (m, 1 H, CHH), 2.00-2.04 (m, 1 H, C<u>H</u>H), 2.11-2.17 (m, 1 H, CH<u>H</u>), 3.17 (dt, 1 H, *J*=4 and 10 Hz, OCH), 4.21 (d, *J*=12 Hz, 1 H, allyl C<u>H</u>HO),

4.34 (d, 1 H, *J*=12 Hz, allyl CHHO), 4.72 (d, 1 H, *J*=6 Hz, OCHHO), 4.95 (d, 1 H, *J*=6 Hz, OCHHO), 5.02 (br s, 1 H, $=CH_2$), 5.06 (br s, 1 H, $=CH_2$). ^{13}C NMR ($CDCl_3$) δ 24.75 (CH_2), 25.26 (CH_2), 29.89 ($CCHCH_2$), 33.60 ($OCHCH_2$), 48.51 (CCH), 73.62 (allyl CH_2O), 81.59 (OCH), 93.31 (OCH_2O), 114.40 ($=CH_2$), 149.27 (=C). HRMS: Found: 168.1150. Calcd for $C_{10}H_{16}O_2$ (M^+); 169.1194. **3d**: ^1H NMR ($CDCl_3$) δ=1.15-1.32 (m, 4 H, CH_2), 1.66-1.92 (m, 4 H, CH_2), 2.03 (m, 1H, CH), 3.25 (dt, 1 H, *J*=4 and 10 Hz, CHOH), 5.11 (m, 2 H, $=CH_2$), 5.68 (ddd, 1 H, J=9, 10, and 17 Hz, =CH). ^{13}C NMR ($CDCl_3$) δ 24.75 (CH_2), 25.12 (CH_2), 31.08 (CH_2), 33.79 (CH_2), 51.20 (CH), 72.74 (CHOH), 116.70 ($=CH_2$), 140.79 (=CH). HRMS: Found: m/z 126.1048. Calcd for $C_8H_{14}O$ (M^+): 126.1044.

Reaction of 5 with Potassium Hydroxide followed by the Addition of Paraformaldehyde

To a solution of salt **5** (0.85 g, 2.08 mmol) and paraformaldehyde (0.19 g, 6.24 mmol) in DMSO (5 mL) was added powdered potassium hydroxide (0.29 g, 5.20 mmol). After being stirred for 72 h, the reaction mixture was poured into water (30 mL), and extracted with dichloromethane (10 mL) for three times. The combined extracts were dried over $MgSO_4$ and evaporated to afford a brown oil. This oil was dissolved in dichloromethane (10 mL) and H_2O_2 (30 %, 0.5 mL) was added to this solution. The suspension was stirred for 24 h, and washed with water. The separated dichloromethane solution and the combined dichloromethane extracts were dried over $MgSO_4$ and evaporated to give a pale yellow oil. This oil was subjected to Kugel Rohr distillation to give a colorless oil of 1-(*p*-chlorophenyl)dioxaspiro[2.4]heptane (**6**) (0.31 g, 70 %). **6**: colorless oil, ^1H NMR ($CDCl_3$) δ 1.16 (t, 1 H, *J*=7 Hz, cyclopropyl CHH), 1.64 (t, 1 H, *J*=7 Hz, cyclopropyl CHH), 2.47 (t, 1 H, *J*=7 Hz, cyclopropyl CH), 3.53 (d, 1 H, *J*=8 Hz, *gem* CHH), 3.70 (d, 1H, *J*=8 Hz, *gem* CHH), 5.00 (s, 1 H, *gem* CHH), 5.09 (s, 1 H, *gem* CHH), 6.99 (d, 2 H, *J*=9 Hz, Ar), 7.26 (d, 2 H, *J*=9 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 13.43 (cyclopropyl CH_2), 25.59 (cyclopropyl CH), 65.05 (CH_2), 66.10 (C), 95.07 (OCH_2), 127.05, 128.62, 128.84, 135.77 (Ar). Found: m/z 210.0447. Calcd for $C_{11}H_{11}{}^{35}ClO_2$ (M^+): 210.0448.

REFERENCES AND NOTES

1. For recent reports, see T. Kawashima, K. Kato, and R. Okazaki, *J. Am. Chem. Soc.*, 1992, **114**, 4008. C. K. McClure, C. W. Grote, and B. A. Lockett, *J. Org. Chem.*, 1992, **57**, 5195. T. Kawashima and R. Okazaki, *Synlett*, 1996, 600.
2. A. R. Hands and A. J. H. Mercer, *J. Chem. Soc. (C)*, 1967, 1099.
3. Unsubstituted oxaphospholane: A. R. Hands, and A. J. H. Mercer, *J. Chem. Soc. (C)*, 1968, 2448. Vinyloxaphospholane: E. J. Enholm, H. Satici, and G.Prasad, *J. Org. Chem.*, 1990, **55**, 324.
4. S. Yamamoto, K. Okuma, and H. Ohta, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4476. S. Yamamoto, H. Takeuchi, Y. Tanaka, K. Okuma, and H. Ohta, *Chem. Lett.*, 1991, 113. K. Okuma, Y. Tanaka, S. Hirabayashi, K. Shioji, and H. Matsuyama, *Heterocycles*, 1997, **45**, 1385. K. Okuma, S. Hirabayashi, M. Ono, K. Shioji, H. Matsuyama, and H. J. Bestmann, *Tetrahedron*, 1998, **54**, 4243.
5. K. Okuma, Y. Tanaka, and H. Ohta, *Tetrahedron Lett.*, 1993, **34**, 4233.
6. H. J. Bestmann, C. Riemer, and R. Dötzer, *Chem. Ber.*, 1992, **125**, 225.
7. E. J. Corey and J. Kang, *J. Am. Chem. Soc.*, 1982, **104**, 4724.
8. A. Hercouet and M. L. Corre, *Tetrahedron*, 1981, **37**, 2855.
9. D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, 1959, **81**, 6330.
10. E. E. Schweizer and W. S. Creasy, *J. Org. Chem.*, 1971, **36**, 2244.
11. K. Okuma, Y. Sato, and H. Ohta, *J. Org. Chem.*, 1994, **59**, 2390.
12. C. R. Johnson, G. E. Katekar, R. E. Huxol, and E. R. Janiga, *J. Am. Chem. Soc.*, 1971, **93**, 3771. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, 1973, **95**, 7692.
13. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 1973, **95**, 5298. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 1973, **95**, 5311. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 1973, **95**, 5321. For a review, see B. M. Trost and L. S. Melvin, "Sulfur Ylides" Academic Press, New York, 1975. Chapter 5.

Received, 4th June, 1998