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AN EFFICIENT, ONE-POT SYNTHESIS OF FOSFOMYCIN DIALKYL ESTERS FROM (*R*)-2-TOSYLOXYPROPANAL

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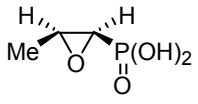
Abstract – (*R*)-2-Tosyloxypropanal (**4**) was prepared from D-mannitol in a 7-step sequence (51% overall yield). Addition of dialkyl phosphonates to **4** in the presence of titanium isopropoxide and the subsequent treatment with DBU stereoselectively afforded, in one-pot, fosfomycin dimethyl (**5a**) and dibenzyl (**5b**) esters both in 58% isolated yield.

INTRODUCTION

(1*R*,2*S*)-1,2-Epoxypropylphosphonic acid (fosfomycin) (**1**) is a clinically used antibiotic which was originally isolated from the fermentation broth of *Streptomyces fradiae*[2] and *Pseudomonas syringae*.[3] Fosfomycin is present on the pharmaceutical market as the disodium,[4] calcium,[5] and tris(hydroxymethyl)ammonium salts.[6] Several synthetic methods for optically active fosfomycin derivatives have been reported as exemplified by catalytic epoxidation of (*Z*)-1-propenylphosphonates and the following optical resolution[7] and bromohydroxylation of (*Z*)-1-propenylphosphonates having a chiral auxiliary and the following ring closure.[8]



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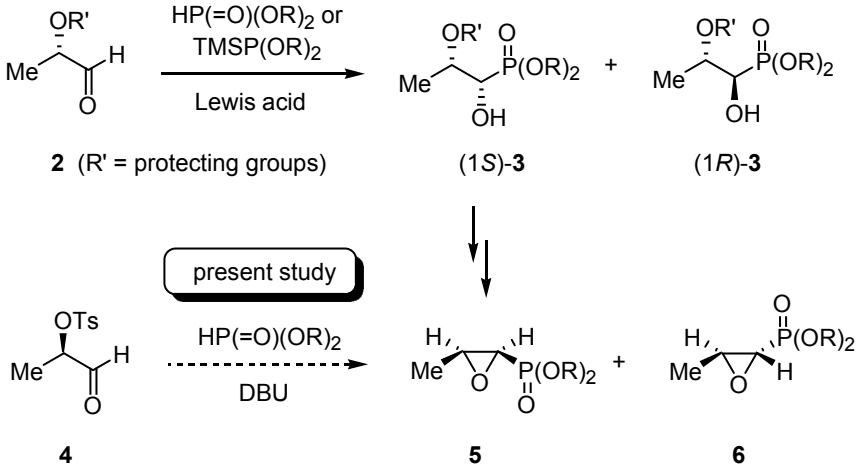
Another synthetic method has also become available by the stereoselective addition of phosphonates (or phosphites) to (*S*)-2-hydroxypropanal derivatives (**2**),[9-11] but the conversion of the resulting α-hydroxyphosphonates (**3**) into fosfomycin derivatives (**5**) requires multi-step procedures (deprotection, tosylation of α-hydroxy group, and ring closure) (Scheme 1). Meanwhile, we have found that 1,2-epoxyphosphonates are readily obtained by the reaction of α-tosyloxyketones with dimethyl phosphonate in the presence of DBU[12] in the course of our studies involving stereoselective C-P bond introduction onto carbohydrates.[13] This procedure is perceived suitable for preparation of fosfomycin derivatives, because the addition of phosphonates and the ring closure would proceed in tandem. We

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

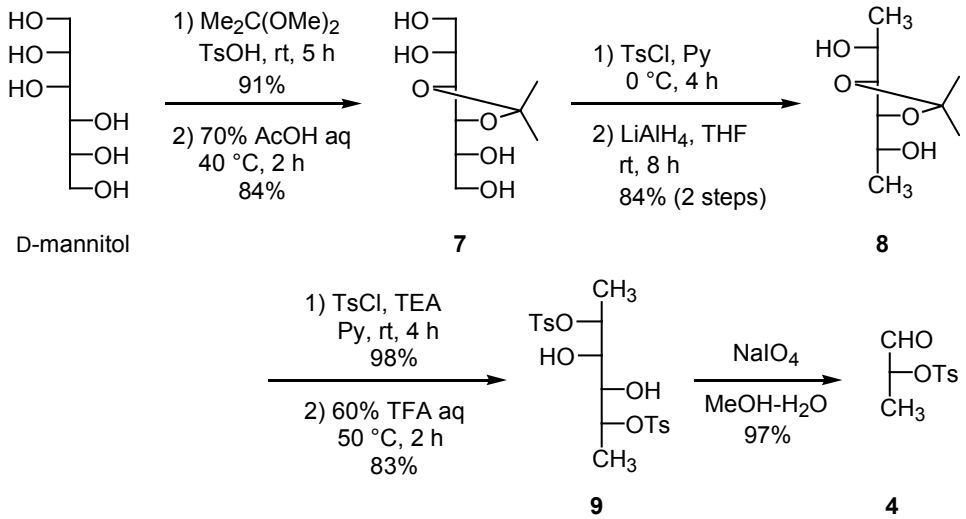
now describe herein a novel, efficient synthesis of fosfomycin derivatives (**5**) based on the stereoselective addition of dialkyl phosphonates to the appropriate precursor (*R*)-2-tosyloxypropanal (**4**).



Scheme 1

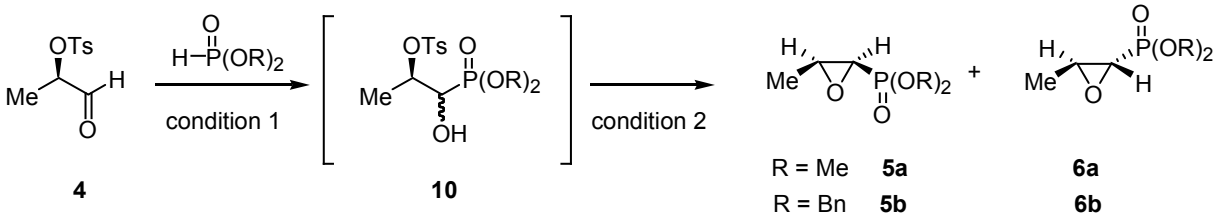
RESULTS AND DISCUSSION

The key intermediate (**4**) was prepared from D-mannitol in 7 steps according to the reported procedures[14–16] with some modifications in a much improved overall yield (51%) (Scheme 2). Namely, acetalization of D-mannnitol with 2,2-dimethoxypropane, followed by hydrolysis with aqueous acetic acid, afforded 3,4-*O*-isopropylidene-D-mannitol (**7**). This was converted into the 1,6-dideoxy compound (**8**) by tosylation of the primary hydroxy groups and the subsequent reduction with lithium aluminum hydride. Tosylation of **8**, followed by hydrolysis with aqueous trifluoroacetic acid (TFA), afforded 1,6-dideoxy-2,5-di-*O*-tosyl-D-mannitol (**9**). Oxidative cleavage of **9** with sodium periodate provided (*R*)-tosyloxypropanal (3-deoxy-2-*O*-tosyl-D-glyceraldehyde) (**4**).



Scheme 2

Conversion of **4** with dialkyl phosphonates to fosfomycin derivatives (**5a,b**) was then examined (Scheme 3) and the results are summarized in Table 1. Compound (**4**) was treated with dimethyl phosphonate (1.5 equiv) in the presence of DBU (2.0 equiv) in THF at 20 °C for 2 h (Entry 1). Under these conditions, addition of the phosphonate and epoxidation of the resulting intermediate (**10**) proceeded simultaneously to afford the *cis*-epoxyphosphonate (**5a**) and its *trans*-isomer (**6a**), in a ratio of 41:59, which were separable by column chromatography. The similar treatment of **4** at a lower temperature (–5 or –40 °C) to give **10**, followed by raising the temperature to 20 °C to afford **5a** and **6a**, resulted in a slight increase in the ratio of the desired **5a** (Entries 2,3). As for the solvent, use of dichloromethane showed a better selectivity for production of **5a** in comparison with THF and acetonitrile (Entries 2,4,5). By employing the same conditions as Entry 5, the reaction of **4** with dibenzyl phosphonate gave the *cis*-epoxide (**5b**) and the *trans*-isomer (**6b**) in a similar yield and ratio (Entry 6).



Scheme 3

Table 1. Reaction of (*R*)-tosyloxypropanal (**4**) with dialkyl phosphonates in the presence of DBU [a]

Entry	Phosphonates	Solvents	Conditions 1	Conditions 2	Yields (%)[b]	Ratio of **5**:**6** [c]
1	R = Me	THF	DBU, 20 °C, 2 h	–	84	41:59
2	Me	THF	DBU, –5 °C, 2 h	20 °C, 2 h	91	46:54
3	Me	THF	DBU, –40 °C, 10 h	20 °C, 2 h	74	50:50
4	Me	MeCN	DBU, –5 °C, 2 h	20 °C, 2 h	80	43:57
5	Me	CH_2Cl_2	DBU, –5 °C, 2 h	20 °C, 2 h	82	57:43
6	Bn	CH_2Cl_2	DBU, –5 °C, 2 h	20 °C, 2 h	86	55:45
7	Me	CH_2Cl_2	$Ti(O^iPr)_4$, 20 °C, 2 h	DBU, 20 °C, 3 h	66	78:22
8	Me	CH_2Cl_2	$Ti(O^iPr)_4$, –5 °C, 10 h	DBU, 20 °C, 3 h	69	84:16
9	Bn	CH_2Cl_2	$Ti(O^iPr)_4$, 20 °C, 2 h	DBU, 20 °C, 3 h	62	76:24
10	Bn	CH_2Cl_2	$Ti(O^iPr)_4$, –5 °C, 10 h	DBU, 20 °C, 3 h	66	88:12

[a] All reactions were carried out by use of 1.5 equiv of phosphonate, 2.0 equiv of DBU, and 1.2 equiv of $Ti(O^iPr)_4$ (for Entries 7–10). [b] Total yield of **5a** (**5b**) and **6a** (**6b**) purified by column chromatography. [c] The ratios were determined by ^1H (in particular, H-1 and H-3 signals) and ^{31}P NMR for the diasteromeric mixture before separation.

In an effort to enhance the diastereoselectivity for production of the (1*R*)-**10**, the precursor for the desired epoxide (**5**), we examined the use of Lewis acids as a chelating agent to promote the addition of phosphonates. Thus, treatment of **4** with dimethyl phosphonate in the presence of titanium isopropoxide (1.2 equiv) in dichloromethane at 20 °C for 2 h gave the α-hydroxyphosphonate intermediate (**10**), which was then treated with DBU (2.0 equiv) to afford **5a** and **6a** in a ratio of 78:22 (Entry 7). The predominant production of **5a** can be perceived as the result of the preferential approach of the phosphonate to a cyclic, titanium-chelated intermediate from the less hindered *re*-face (the opposite side of the methyl group). In contrast, the use of magnesium bromide as a Lewis acid yielded only a trace amount of products. The similar experiment at –5 °C using titanium isopropoxide gave rise more preferentially to the desired **5a** in a ratio of 84:16 (Entry 8), whereas almost no phosphonate addition took place at a further lower temperature (–20 °C). The reaction of **4** with dibenzyl phosphonate under these conditions revealed similar results with those of dimethyl phosphonate (Entries 9,10); the desired *cis*-epoxide (**5b**) was obtained in the highest diastereoselectivity (88:12) (Entry 10). Dibenzyl ester (**5b**) is readily converted into fosfomycin (**1**) by hydrogenolysis according to the reported procedure.[11]

The present work thus demonstrates an efficient synthesis of fosfomycin derivatives from (*R*)-2-tosyloxypropanal with reasonably good diastereoselectivity. This synthetic procedure is highly useful because the addition of a phosphonate and the formation of epoxide can be carried out by a one-pot procedure without isolation of the intermediates.

EXPERIMENTAL

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(*A*) 1:3, (*B*) 1:2, (*C*) 1:1 AcOEt–hexane, and (*D*) AcOEt]. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by exposing the plates to UV light and/or spraying them with 20% sulfuric acid–ethanol (with subsequent heating). Optical rotations were measured with a Jasco P-1020 polarimeter in $CHCl_3$. The NMR spectra were measured in $CDCl_3$ with Varian Unity Inova AS600 (600 MHz for ^1H, 151 MHz for ^{13}C) and Mercury 300 (121 MHz for ^{31}P) spectrometer at 23 °C. Chemical shifts are reported as δ values relative to $CHCl_3$ (7.26 ppm as an internal standard for ^1H), $CDCl_3$ (77.0 ppm as internal standard for ^{13}C), and 85% phosphoric acid (0 ppm as an external standard for ^{31}P).

3,4-*O*-Isopropylidene-D-mannitol (7).[14]

The following modification of the literature procedures[14] was made. To a suspension of D-mannitol (1.80 g, 9.88 mol) in 2,2,-dimethoxypropane (20.0 mL, 165 mmol) was added *p*-toluenesulfonic acid monohydrate (120 mg, 0.63 mmol). The mixture was stirred at rt for 5 h, neutralized with triethylamine, and evaporated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was recrystallized from hexane to give 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (2.71g, 91%) as colorless needles: mp 69–70 °C (lit.,[14] mp 69 °C, 75% yield by using acetone-H_2SO_4), R_f = 0.60 (*A*).

The triacetonide (2.71 g, 8.96 mmol) was dissolved in 70% aqueous acetic acid (30 mL) and stirred at 40 °C for 2 h. The mixture was co-evaporated with toluene in vacuo and the residue was crystallized

with acetone to give **7** (1.67 g, 84%) as colorless needles: mp 88–89 °C (lit.,[14] mp 90 °C, 78% yield), R_f = 0.13 (*D*).

1,6-Dideoxy-3,4-*O*-isopropylidene-D-mannitol (8).[15]

Modification of the literature procedures[14,15] was made as follows. To a solution of **7** (445 mg, 2.00 mmol) in dry pyridine (6.0 mL) was added, with stirring, tosyl chloride (860 mg, 4.51 mmol) at –5 °C. The mixture was stirred at 0 °C for 4 h, diluted with a small amount of cold water, and concentrated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo to give 3,4-*O*-isopropylidene-1,6-di-*O*-tosyl-D-mannitol (1.05 g) as a pale yellow syrup (lit.,[14] mp 86 °C) ; R_f = 0.52 (*C*).

The crude ditosylate was dissolved in dry THF (10 mL) and then lithium aluminum hydride (180 mg, 4.72 mmol) was added in several portions at 0 °C under argon. The mixture was stirred at rt for 8 h and then a small amount of water was added. The mixture was diluted with ethyl acetate (20 mL) and filtered through Celite. The filtrate was evaporated in vacuo and the residue was purified by column chromatography with 1:2 AcOEt-hexane to give **8** (320 mg, 84% from **7**) as colorless needles (from AcOEt-hexane): mp 91–92 °C (lit.,[15] mp 85–88 °C, 50% yield from **7**); R_f = 0.40 (*C*); ^{1}H NMR[17] δ = 1.37 (6H, d, $J_{1,2} = J_{5,6}$ = 6.1 Hz, H_3-1,6), 1.37 (6H, s, Me_2C), 3.25 (2H, br s, HO-2,5), 3.63 (2H, m, H-3,4), 3.78 (2H, qdd, $J_{2,3} = J_{4,5}$ = 5.6, $J_{2,4} = J_{3,5}$ = 1.5 Hz, H-2,5); ^{13}C NMR δ = 20.46 (C-1,6), 26.85 (C*Me*$_2$), 69.28 (C-2,5), 84.03 (C-3,4), 108.74 (*C*Me_2).

1,6-Dideoxy-2,5-di-*O*-tosyl-D-mannitol (9).[16]

Compound (**9**) was prepared from **8** *via* 1,6-dideoxy-3,4-O-isopropylidene-2,5-di-*O*-tosyl-D-mannitol by using the literature procedures.[15,16]

3,4-*O*-Isopropylidene-2,5-di-*O*-tosylate: Colorless needles (98% yield), mp 91–92 °C (from AcOEt-hexane) (lit.,[15] 85% yield, mp 90–91 °C); R_f = 0.55 (*A*).

9: Colorless needles (83%), mp 87–88 °C (from ether) (lit.,[16] 82% yield, mp 84.5–85.5 °C); R_f = 0.20 (*B*).

(*R*)-2-Tosyloxypropanal (3-deoxy-2-*O*-tosyl-D-glyceraldehyde) (4).[16]

The following modification of the literature procedures[16] was made. To a solution of **9** (147 mg, 0.321 mmol) in methanol (3.0 mL) was added dropwise a solution of sodium periodate (89.0 mg, 0.416 mmol) in water (3.0 mL) at 0–5 °C. The mixture was stirred at rt for 1 h and the most of methanol was distilled off in vacuo. The residue was diluted with water and then extracted with ether three times. The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt-hexane to give **4** [142 mg, 97% yield (lit.,[16] 86%)] as a colorless syrup: R_f = 0.20 (*B*).

Dimethyl (1*R*,2*S*)-1,2-epoxypropylphosphonate (5a) and its (1*S*,2*S*)-epimer (6a).

Procedures for Entry 5 in Table 1. To a solution of **4** (114 mg, 0.499 mmol) in dry CH_2Cl_2 (2.0 mL) were added dimethyl phosphonate (0.070 mL, 0.76 mmol) and then DBU (0.150 mL, 1.00 mmol) at –5 °C under argon. The mixture was stirred at the same temperature for 3 h and then at 20 °C for 2 h, and evaporated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and

evaporated in vacuo. The residue was separated by column chromatography with 1:1 AcOEt-hexane to give **5a** (38.9 mg, 47%) and **6a** (29.1 mg, 35%).

5a: Colorless syrup; R_f = 0.35 (*D*); $[\alpha]_D^{30}$ +3.28° (*c* 2.02) [lit.,[9] $[\alpha]_D^{21}$ +5.50° (MeOH)]; ^{1}H NMR[17] δ = 1.57 (3H, dd, $J_{2,3}$ = 5.4, $J_{3,P}$ = 1.0 Hz, H_3-3), 2.95 (1H, dd, $J_{1,P}$ = 27.6, $J_{1,2}$ = 4.4 Hz, H-1), 3.28 (1H, dqd, $J_{2,P}$ = 6.4 Hz, H-2), 3.81, 3.83 [3H each, 2d, J_{POMe} = 10.9 Hz, $P(OMe)_2$]; ^{13}C NMR δ = 14.08 (C-3), 49.40 (d, $^1J_{1,P}$ = 205.0 Hz, C-1), 52.79, 53.21 [2d, $^2J_{C,P}$ = 6.3 Hz, $P(OMe)_2$], 53.31 (d, $^2J_{2,P}$ = 1.7 Hz, C-2); ^{31}P NMR δ = 22.00.

6a: Colorless syrup; R_f = 0.28 (*D*); $[\alpha]_D^{30}$ –18.3° (*c* 2.44); ^{1}H NMR δ = 1.39 (3H, dd, $J_{2,3}$ = 5.1, $J_{3,P}$ = 1.7 Hz, H_3-3), 2.77 (1H, dd, $J_{1,P}$ = 31.0, $J_{1,2}$ = 2.7 Hz, H-1), 3.29 (1H, dqd, $J_{2,P}$ = 5.4 Hz, H-2), 3.80, 3.81 [3H each, 2d, J_{POMe} = 10.7 Hz, $P(OMe)_2$]; ^{13}C NMR δ = 17.44 (C-3), 50.68 (d, $^1J_{1,P}$ = 203.4 Hz, C-1), 52.86 (d, $^2J_{2,P}$ = 1.7 Hz, C-2), 53.13, 53.55 [2d, $^2J_{C,P}$ = 6.3 Hz, $P(OMe)_2$]; ^{31}P NMR δ = 21.18.

Procedures for Entry 8 in Table 1. To a solution of **4** (114 mg, 0.499 mmol) in dry CH_2Cl_2 (2.0 mL) was added titanium isopropoxide (0.180 mL, 0.608 mmol) at –5 °C under argon. The mixture was stirred at the same temperature for 40 min and then dimethyl phosphonate (0.070 mL, 0.76 mmol) was added. After stirring at –5 °C for 10 h, DBU (0.150 mL, 1.00 mmol) was added and the mixture was stirred at 20 °C for 3 h. Then, water (0.5 mL) was added and the resulting precipitate was filtered off through Celite. The filtrate was diluted with water and extracted with $CHCl_3$. The combined organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was separated by column chromatography to give **5a** (48.2 mg, 58%) and **6a** (9.2 mg, 11%).

Dibenzyl (1*R*,2*S*)-1,2-epoxypropylphosphonate (5b) and its (1*S*,2*S*)-epimer (6b).

Procedures for Entry 10 in Table 1. The same procedures described above for Entry 8 were employed. Thus, compound (**4**) (114 mg, 0.499 mmol) was treated with dibenzyl phosphonate (0.170 mL, 0.77 mmol) to give **5b** (92.6 mg, 58%) and **6b** (12.7 mg, 8%), after separation by column chromatography with 1:2 AcOEt-hexane.

5b: Colorless syrup; R_f = 0.40 (*C*); $[\alpha]_D^{23}$ +5.04° (*c* 1.67) [lit.,[11] $[\alpha]_D^{20}$ +4.4° ($CDCl_3$)]; ^{1}H NMR[17] δ = 1.56 (3H, d, $J_{2,3}$ = 5.6 Hz, H_3-3), 2.95 (1H, dd, $J_{1,P}$ = 28.1, $J_{1,2}$ = 4.4 Hz, H-1), 3.24 (1H, dqd, $J_{2,P}$ = 6.4 Hz, H-2), 5.03, 5.09 [1H each, 2dd, $^2J_{CH2}$ = 11.7, J_{POCH} = 8.3 Hz, $POCH_2$], 5.10, 5.13 [1H each, 2dd, $^2J_{CH2}$ = 11 7, J_{POCH} = 8.8 Hz, $POCH_2$], 7.32–7.38 (10H, m, Ph); ^{13}C NMR δ = 14.11 (C-3), 50.13 (d, $^1J_{1,P}$ = 204.4 Hz, C-1), 53.67 (d, $^2J_{2,P}$ = 1.7 Hz, C-2), 67.76, 68.15 [2d, $^2J_{C,P}$ = 6.3 Hz, $POCH_2$], 128.03, 128.09 [2s, Ph(*o*)], 128.55, 128.60 [2s, Ph(*p*)], 128.60, 128.61 [2s, Ph(*m*)], 135.81, 135.89* [2d, $^3J_{C,P}$ = 5.8, 6.3* Hz, Ph(*ipso*)]; ^{31}P NMR δ = 22.56.

6b: Colorless syrup; R_f = 0.33 (*C*); $[\alpha]_D^{23}$ –11.3° (*c* 2.27); ^{1}H NMR δ = 1.28 (3H, d, $J_{2,3}$ = 5.1, $J_{3,P}$ = 1.8 Hz, H_3-3), 2.71 (1H, dd, $J_{1,P}$ = 31.5, $J_{1,2}$ = 2.5 Hz, H-1), 3.23 (1H, quintd, $J_{2,P}$ = 5.1 Hz, H-2), 5.04, 5.08 [1H each, 2dd, $^2J_{CH2}$ = 11.7, J_{POCH} = 7.8 Hz, $POCH_2$], 5.045, 5.09 [1H each, 2dd, $^2J_{CH2}$ = 11.7, J_{POCH} = 8.8 Hz, $POCH_2$], 7.32–7.38 (10H, m, Ph); ^{13}C NMR δ = 14.16 (C-3), 51.38 (d, $^1J_{1,P}$ = 202.1 Hz, C-1), 53.04 (d, $^2J_{2,P}$ = 1.2 Hz, C-2), 68.15, 68.31 [2d, $^2J_{C,P}$ = 6.3 Hz, $POCH_2$], 128.01, 128.09 [2s, Ph(*o*)], 128.55, 128.62 [2s, Ph(*p*)], 128.60, 128.62 [2s, Ph(*m*)], 135.72, 135.86* [2d, $^3J_{C,P}$ = 6.3, 5.6* Hz, Ph(*ipso*)]; ^{31}P NMR δ = 19.89.

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17. The complete parameters for **5a,b** and **8** obtained in the present study are shown here, because ^{1}H NMR data for these compounds reported in Refs. 9, 11 and 15, respectively, include insufficient assignments.