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The Synthesis and Reactivity of Alkylaminosubstitutedmethylenediphosphonates

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ABSTRACT: *Reactions of diethyl phosphite with Vilsmeier reagents, $RCONR^1R^2/POCl_3$, afforded various alkylaminosubstitutedmethylenediphosphonates in acceptable yields, which (R = H) were then reacted with aldehydes under the conditions of the Wittig–Horner reaction to furnish vinylphosphonates, and which (R = H) underwent alkylation with alkyl halides to give alkylaminosubstitutedmethylenediposphonates* **8**. *(Z)-Vinylphosphonates could be converted to (E)-isomers in refluxing ethyl acetate.*© 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 271–276, 1999

INTRODUCTION

Much work has been reported in recent literature on the synthesis, reactivity, and bioactivity of alkylaminomethylenediphosphonates [1–7]. Among numerous synthetic methods, two reports have detailed the reaction of dimethylchloroformiminium chloride with triethyl phosphite to give tetraethyl dimethylaminomethylenediphosphonate **1** (Scheme 1) [3,8].

Dimethylchloroformiminium chloride was found to be an efficient reagent for the synthesis of dimethylaminomethylenediphosphonates, in spite of only a few compounds having been prepared according to this method.

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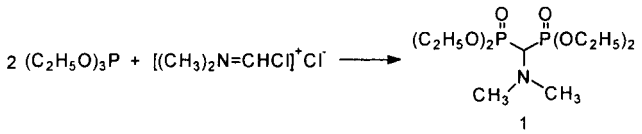
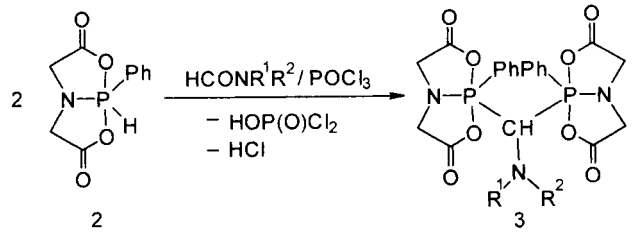
RESULTS AND DISCUSSION

As part of our research on the pesticidal phosphonates, we have been interested in facile and general routes to the synthesis of various alkylaminosubstitutedmethylenediphosphonates. We recently discovered a novel strategy for the preparation of alkylaminomethylenediphosphoranes **3** using the reaction of hydridophosphorane **2** with Vilsmeier reagents (Scheme 2) [9,10].

The interesting results obtained encouraged us to extend our investigation to other phosphorus compounds containing a P–H bond. We selected diethyl phosphite as a starting material because of its ready preparation and remarkable nucleophilicity



SCHEME 1



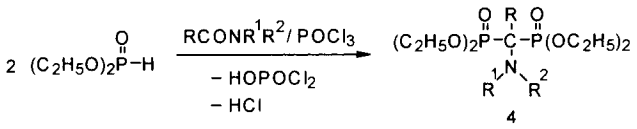
SCHEME 2

and established successfully the following reaction (Scheme 3).

The reaction was carried out under very mild conditions. The preformed Vilsmeier reagents were added to diethyl phosphite. The reaction mixture was stirred at room temperature for 8 ~ 12 hours. The products 4 were purified by column chromatography (Table 1), and their structures were confirmed by ^{1}H NMR, ^{31}P NMR, MS, and quantitative elemental analyses (Table 2).

A more plausible pathway of this reaction might consist of two steps. In the first step, the nucleophilic phosphorus center apparently attacks the electrophilic central carbon of iminium salt **5** with elimination of $HOP(O)Cl_2$ to give the intermediate **6**, which then reacts further with another mole of diethyl phosphite in a manner such that the phosphorus atom attacks the carbon of **6** with elimination of HCl (Scheme 4).

It is noteworthy that phosphorane **2** only reacts with Vilsmeier reagents formed from substituted formamides and phosphorus oxychloride (Scheme 2), but diethyl phosphite can react with various Vilsmeier reagents from substituted formamides, acetylamides, benzoylamides, phenylacetamide, and phosphorus oxychloride (Scheme 3). This difference can be explained by consideration of steric hindrance. X-ray diffraction shows that the steric crowding in compounds **3** is more severe than that in compounds **4** [10].



SCHEME 3

TABLE 1 Products **4** Prepared

Product **4**	*R*	*R*^{1}	*R*^{2}	*Yield*[a] (%)
a	H	CH_3	CH_3	66.1
b	H	C_2H_5	C_2H_5	63.2
c	H	H	CH_3	50.2
d	H	C_3H_7	C_3H_7	58.5
e	H	CH_3	C_6H_5	80.7
f	H	$(CH_2)_5$		75.3
g	H	$(CH_2)_2O(CH_2)_2$		77.9
h	CH_3	CH_3	CH_3	51.3
i	CH_3	C_2H_5	C_2H_5	46.2
j	CH_3	C_3H_7	C_3H_7	57.2
k	CH_3	CH_3	C_6H_5	38.6
l	CH_3	$(CH_2)_5$		50.4
m	CH_3	$(CH_2)_2O(CH_2)_2$		55.3
n	C_6H_5	CH_3	CH_3	30.2
o	$C_6H_5CH_2$	CH_3	CH_3	36.8

[a]Determined by isolation.

Our further investigation deals with reactivity of the compounds **4** (R = H), which react with aldehydes under the conditions of the Wittig–Horner reaction to yield the vinylphosphonates **7** (Scheme 5, Tables 3 and 4).

The reaction provides a mixture of E and Z diasteroisomers, which were separated by column chromatography. The E or Z configuration was deduced from the coupling constant between the phosphorus nucleus and the vinylic proton. The coupling constant of the Z isomer is far larger than that of the E isomer (Tables 3 and 4). ^{31}P NMR spectroscopy shows that the Z isomer is found at a higher field than the E isomer, and the difference is approximately 2–3 ppm (Table 3).

Yields of Wittig–Horner reactions were low due to recovery of starting material. The reactions gave both geometric isomers with low to high stereoselectivity. It was noteworthy that the Z isomer could be converted to the E isomer when an ethyl acetate solution of compound **7** was refluxed for about 8 hours (Table 5, entries **a**, **b**, and **c**(**i**)). However, the E isomer was difficult to be converted to the Z isomer under the same condition (Table 5, entries **c**(**ii**), **d**, and **f**). At sufficiently high temperature, it was possible to secure rupture of the π bond without breaking the sigma bond so that the conversion of the isomers would occur [11]. The experiments have shown that steric interference between groups on the same side of the π bond caused an increase in energy content of that isomer and that the trans isomer (or that isomer with its largest groups on opposite sides) is the lower-energy species.

The sodio-carbanions of compounds **4** could be generated from compounds **4** by deprotonation with NaH, and they reacted with alkyl halides leading to alkylaminosubstitutedmethylenediposphonates **8** (Scheme 6).

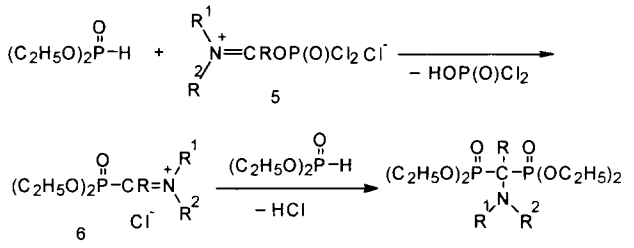
EXPERIMENTAL

^{1}H and ^{31}P NMR spectra were taken on a BRUKER AC-P200 Spectrometer. ^{1}H chemical shifts are reported in parts per million relative to internal tetramethylsilane. ^{31}P chemical shifts are reported in parts per million relative to 85% phosphoric acid (external). Quantitative elemental analyses were run on a Yana MT-3 instrument. Mass spectra were recorded on a Hewlett-Packard 5988 instrument. All operations were carried out under a nitrogen atmosphere. The substituted amides and diethyl phosphite were obtained from commercial sources. Tetrahydrofuran, dried over sodium and distilled, was redistilled from $LiAlH_4$ before use.

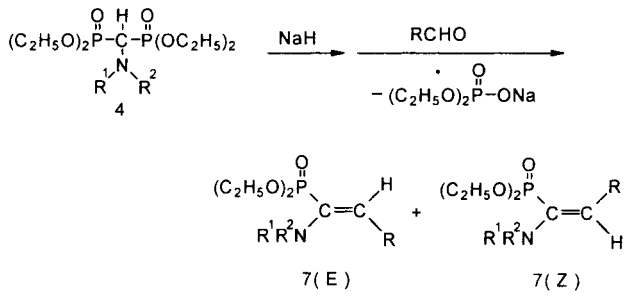
TABLE 2 ^{1}H, ^{31}P NMR, and MS Data of Compounds **4**[a]

Compound 4	^{1}H NMR ($CDCl_3$) CH_3CH_2O	CH_3CH_2O	R	R^1	R^2	^{31}P NMR ($CDCl_3$)	MS, m/z (rel intensity) M^+	M^+-137
a	1.32(m)	4.19(m)	3.42(t, $^2J_{PH}$ = 25.04)	2.67(s)	2.67(s)	18.91	331(2)	194(100)
b	1.22(m)	4.12(m)	3.48(t, $^2J_{PH}$ = 25.04)	2.82(q, $^3J_{HH}$ = 7.01, $N(CH_2CH_3)_2$,	0.96(t, $^3J_{HH}$ = 6.96, $N(CH_2CH_3)_2$	19.38	359(1)	222(100)
c	1.30(m)	4.17(m)	3.17(t, $^2J_{PH}$ = 20.87)	1.95(br)	2.58(s)	19.25	317(3)	180(100)
d	1.31 (t, $^3J_{HH}$ = 7.27)	4.17(m)	3.49(t, $^2J_{PH}$ = 25.04)	2.77(t, $^3J_{HH}$ = 7.3, $N(CH_2CH_2CH_3)_2$, 1.42(m, $^3J_{HH}$ = 7.3, $N(CH_2CH_2CH_3)_2$, 0.84(t, $^3J_{HH}$ = 7.3, $N(CH_2CH_2CH_3)_2$		19.65	387(1)	250(100)
e	1.13(m)	4.00(m)	4.66(t, $^2J_{PH}$ = 25.04)	3.01(s)	6.25–6.80(o,p-NC_6H_5), 7.03–7.12(m-NC_6H_5)	16.15	393(5)	256(100)
f	1.23 (t, $^3J_{HH}$ = 7.16)	4.10(m)	3.22(t, $^2J_{PH}$ = 25.04)	2.85(br, $N(CH_2CH_2)_2CH_2$), 1.43(br, $N(CH_2CH_2)_2CH_2$)		17.77	371(4)	234(100)
g	1.32 (t, $^3J_{HH}$ = 7.10)	4.18(m)	3.28(t, $^2J_{PH}$ = 25.04)	2.99(br, $N(CH_2CH_2)_2O$), 3.63(t, $^3J_{HH}$ = 5.01, $N(CH_2CH_2)_2O$)		17.09	373(1)	236(100)
h	1.30 (t, $^3J_{HH}$ = 7.19)	4.14(m)	16.0(t, $^3J_{PH}$ = 16.95)	2.61(s)	2.61(s)	23.02	345(1)	208(100)
i	1.20 (t, $^3J_{HH}$ = 7.30)	4.09(m)	1.55(t, $^3J_{PH}$ = 16.69)	2.91(q, $^3J_{HH}$ = 7.12, $N(CH_2CH_3)_2$,	0.94(t, $^3J_{HH}$ = 7.13, $N(CH_2CH_3)_2$	22.48	373(2)	236(100)
j	1.25 (t, $^3J_{HH}$ = 6.94)	4.12(m)	1.59(t, $^3J_{PH}$ = 16.66)	2.84(t, $^3J_{HH}$ = 7.47, $N(CH_2CH_2CH_3)_2$, 1.42(br, $N(CH_2CH_2CH_3)_2$, 0.75(t, $^3J_{HH}$ = 7.28, $N(CH_2CH_2CH_3)_2$		23.33	401(4)	264(7)
k	1.34(m)	4.25(m)	1.36(t, $^3J_{PH}$ = 16.69)	3.25(s)	7.04–7.24(o,p-NC_6H_5), 7.29–7.42(m-NC_6H_5)	22.88	407(1)	270(100)
l	1.30 (t, $^3J_{HH}$ = 7.43)	4.18(m)	1.48(t, $^3J_{PH}$ = 16.69)	3.01(br, $N(CH_2CH_2)_2CH_2$), 1.45(br, $N(CH_2CH_2)_2CH_2$)		22.75	385(1)	248(100)
m	1.27(m)	4.14(m)	1.50(t, $^3J_{PH}$ = 16.69)	3.58(br, $N(CH_2CH_2)_2O$), 3.04(br, $N(CH_2CH_2)_2O$)		22.21	387(2)	250(100)
n	1.14 (t, $^3J_{HH}$ = 6.92)	4.07(m)	7.15–7.33(m,p-CC_6H_5) 7.58–7.89(o-CC_6H_5)	2.54(s)	2.54(s)	21.04	407(1)	270(100)
o	1.25(m)	4.06(m)	3.38(t, $^3J_{PH}$ = 13.56, CH_2Ph), 7.18–7.24(o,p-$CH_2C_6H_5$), 7.39–7.42(m-$CH_2C_6H_5$)	2.77(s)	2.77(s)	23.06	421(1)	284(100)

[a]Satisfactory microanalyses obtained: C, ±0.5%; H, ±0.5%; N, ±0.5%.



SCHEME 4



SCHEME 5

TABLE 3 Vinylphosphonates **7** Prepared

Product **7**	R^1	R^2	R	$\delta\ ^{31}P$ ($CDCl_3$)	$^3J_{PH}$ (*Hz*)	*Z/E*[a]	*Yield*[b] (%)
a	$(CH_2)_5$		C_2H_5	(Z)15.8 (E)17.5	42.76 13.56	92/8	34.0
b	$(CH_2)_5$		C_6H_5	(Z)13.3 (E)16.8	40.66 15.64	67/33	40.0
c	CH_2CH_2 OCH_2CH_2		C_6H_5	(Z)13.7 (E)16.9	40.66 15.64	45/55	34.5
d	CH_3	CH_3	C_6H_5	(Z)14.1 (E)17.3	40.66 14.60	10/90	40.3
e	CH_3	CH_3	C_2H_5	(Z)15.7 (E)19.2	42.74 13.54	20/80	29.9
f	CH_3	CH_3	p-O_2N-C_6H_4	(Z)12.7 (E)15.2	40.00 12.00	32/68	46.9

[a]Diasteroisomer ratios were determined by integration of the vinylic proton sigals in the ^1H NMR spectra of compounds **7**.
[b]The isolated yield refered to the total yield of Z and E isomers.

General Procedure for Preparation of Alkylaminosubstitutedmethylenediphosphonates **4** (*R = H, Ph*)

A 15 mmol quantity of substituted foramides, benzoylamides, or phenylacetamide in 5 mL dichloromethane was dropped into phosphorus oxychloride (15 mmol, 2.3 g) contained in an ice-water bath. Then the mixture was stirred at 30°C for 30 minutes. After the mixture had been cooled to 15°C, diethyl phosphite (30 mmol, 4.14 g) in 5 mL dichloromethane was added dropwise. The reaction mixture was kept at 30°C for 10 hours. After the reaction mixture had been poured into 50 g of ice water, the mixture was brought to pH 5 with a solution of sodium carbonate in water. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 50 mL of saturated brine, dried over magnesium sulfate, and filtered. The volatile components were distilled under reduced pressure. The residue was chromatographed on a column of silca gel (dichloromethane and ethyl acetate as eluant) to afford products **4** (yields are shown in Table 1).

General Procedure for Preparation of Alkylaminosubstitutedmethylenediphosphonates **4** (*R = Me, PhCH$_2$*)

To a stirred mixture of a disubstituted acetamide (15 mmol) and diethyl phosphite (30 mmol, 4.14 g) in 15 mL of dichloromethane contained in an ice-water bath was added dropwise phosphorus oxychloride (15 mmol, 2.3 g) over 5 minutes. Then the reaction mixture was stirred at 30°C for 10 hours.

The purification method for the products was similar to that described previously [general procedure for preparation of alkylaminoalkylenediphosphonates **4** (R = H, Ph)]. (Yields are shown in Table 1.)

General Procedure for Preparation of Vinylphosphonates **7**

Under a nitrogen atmosphere, to a suspension of sodium hydride (5 mmol, 0.12 g) in absolute THF (10 mL) at 15°C was added dropwise a solution of compound **4a**, **4f**, or **4g** (5 mmol) in absolute THF (5 mL). The reaction mixture was stirred at 30°C for 1 hour. A solution of benzaldehyde or propanal (5 mmol) in absolute THF (5 mL) was added dropwise. The reaction mixture was kept at 30°C for 4 hours. Water (20 mL) was added to the reaction mixture, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with 50 mL of saturated brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was analyzed by ^1H NMR spectroscopy (ratios of Z and E isomers are shown in Table 3) and isolated by column chromatography or TLC on silica gel using ethyl acetate:petroleum ether (1:8 or 1–2:1) as eluent or developing solvent. E and Z isomers could be obtained respectively. (Yields are shown in Table 3.)

TABLE 4 ^{1}H NMR Data of Vinylphosphonates **7**[a]

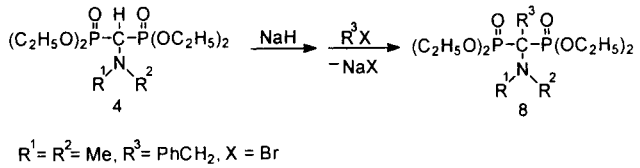
Compound **7**		*CH_3CH_2O*	*CH_3CH_2O*	*R^1*	*R^2*	*CHR*	*R*
a	(Z)	1.24(t, $^3J_{HH}$ = 6.96)	3.99(m)	2.67(t, $^3J_{HH}$ = 5.51, $N(CH_2CH_2)_2CH_2$), 1.51(br, $N(CH_2CH_2)_2CH_2$), 1.37(br, $N(CH_2CH_2)_2CH_2$)		5.39(dt, $^3J_{PH}$ = 42.76, $^3J_{HH}$ = 7.30)	2.33(m, CCH_2CH_3) 0.91(t, $^3J_{HH}$ = 7.49, CCH_2CH_3)
	(E)	1.29(t, $^3J_{HH}$ = 7.03)	4.04(m)	2.65(t, $^3J_{HH}$ = 5.23, $N(CH_2CH_2)_2CH_2$), 1.49(br, $N(CH_2CH_2)_2CH_2$), 1.39(br, $N(CH_2CH_2)_2CH_2$)		6.05(dt, $^3J_{PH}$ = 13.56, $^3J_{HH}$ = 7.02)	2.30(m, CCH_2CH_3) 0.89(t, $^3J_{HH}$ = 7.65, CCH_2CH_3)
b	(Z)	1.04(t, $^3J_{HH}$ = 7.03)	3.88(m)	2.93(t, $^3J_{HH}$ = 5.14, $N(CH_2CH_2)_2CH_2$), 1.60(br, $N(CH_2CH_2)_2CH_2$)		6.47(d, $^3J_{PH}$ = 40.66)	7.20–7.36(m,p-C_6H_5), 7.71–7.76(o-C_6H_5)
	(E)	1.33(t, $^3J_{HH}$ = 6.89)	4.12(m)	2.89(br, $N(CH_2CH_2)_2CH_2$), 1.55(br, $N(CH_2CH_2)_2CH_2$)		6.75(d, $^3J_{PH}$ = 14.93)	7.24–7.33(m,p-C_6H_5), 7.71–7.74(o-C_6H_5)
c	(Z)	1.05(t, $^3J_{HH}$ = 6.92)	3.93(m)	3.78(br, $N(CH_2CH_2)_2O$), 3.02(br, $N(CH_2CH_2)_2O$)		6.47(d, $^3J_{PH}$ = 39.62)	7.24–7.34(m,p-C_6H_5), 7.70–7.74(o-C_6H_5)
	(E)	1.36(t, $^3J_{HH}$ = 6.96)	4.15(m)	3.71(t, $^3J_{HH}$ = 4.31, $N(CH_2CH_2)_2O$), 2.97(t, $^3J_{HH}$ = 4.13, $N(CH_2CH_2)_2O$)		6.85(d, $^3J_{PH}$ = 15.64)	7.24–7.33(m,p-C_6H_5), 7.75–7.80(o-C_6H_5)
d	(Z)	1.04(t, $^3J_{HH}$ = 7.06)	3.90(m)	2.60(s)	2.60(s)	6.30(d, $^3J_{PH}$ = 40.66)	7.22–7.33(m,p-C_6H_5), 7.51–7.75(o-C_6H_5)
	(E)	1.32(t, $^3J_{HH}$ = 6.37)	4.11(m)	2.65(s)	2.65(s)	6.66(d, $^3J_{PH}$ = 14.60)	7.15–7.26(m,p-C_6H_5), 7.50–7.54(o-C_6H_5)
e	(Z)	1.27(t, $^3J_{HH}$ = 6.72)	4.03(m)	2.53(s)	2.53(s)	5.41(dt, $^3J_{PH}$ = 42.74, $^3J_{HH}$ = 6.26)	2.22(m, CCH_2CH_3), 0.88(t, $^3J_{HH}$ = 7.25, CCH_2CH_3)
	(E)	1.33(t, $^3J_{HH}$ = 6.34)	4.11(m)	2.57(s)	2.57(s)	6.12(dt, $^3J_{PH}$ = 13.54, $^3J_{HH}$ = 6.78)	2.26(m, CCH_2CH_3), 0.92(t, $^3J_{HH}$ = 7.31, CCH_2CH_3)
f	(Z)	1.27(t, $^3J_{HH}$ = 6.74)	4.11(m)	2.56(s)	2.56(s)	6.07(d, $^3J_{PH}$ = 40.00)	7.45(d, o-C_6H_4-NO_2-4), 8.05(d, m-C_6H_4-NO_2-4)
	(E)	1.33(t, $^3J_{HH}$ = 6.98)	4.05(m)	2.64(s)	2.64(s)	6.40(d, $^3J_{PH}$ = 12.00)	7.37(d, o-C_6H_4-NO_2-4), 8.01(d, m-C_6H_4-NO_2-4)

[a]Satisfactory microanalyses obtained: C, ±0.5%; H, ±0.5%; N, ±0.5%.

TABLE 5 Z/E Isomers Conversion of Compounds **7**[a]

Compound **7**	*Z:E*[b] (*before heating*)	*Z:E*[b] (*after heating*)
a	92:8	65:35
b	100:0	67:33
c(i)	100:0	59:41
c(ii)	0:100	trace:100
d	10:90	trace:100
f	32:68	trace:100

[a]An ethyl acetate solution of **7** was refluxed for about 8 hours.
[b]Ratios of Z and E isomers were determined by integration of the vinylic proton signals in the ^{1}H NMR spectra of compounds **7**.



$R^1 = R^2 = Me$, $R^3 = PhCH_2$, X = Br

SCHEME 6

Alkylation of N,N-Dimethylaminomethylenedisphosphonate (**4a**) *give to Alkylaminosubstitutedmethylenediphosphonate* **8**

Under a nitrogen atmosphere, to a suspension of sodium hydride (5 mmol, 0.12 g) in absolute THF (10 mL) at 15°C was dropped a solution of N,N-dimethylaminomethylenedisphosphonate (5 mmol) in absolute THF (5 mL). The reaction mixture was stirred at 30°C for 1 hour until the reaction mixture became clear. A solution of benzyl bromide in absolute THF (5 mL) was added dropwise. The reaction was kept at 30°C for 7 hours. The reaction mixture was poured into water (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 50 mL of saturated brine, dried over magnesium sulfate, filtered, and concentrated. The purification of the residue by column chromatography was carried out on silica gel using dichloromethane and ethyl acetate, respectively, as the eluent to afford product **8** (0.656 g, 32.2%). ^{1}H NMR ($CDCl_3$) δ 1.15 (t, $^3J_{HH}$ = 7.25 Hz, 12 H, 4 CH_3), 2.70 (S, 6 H, 2 CH_3), 3.30 (t, $^3J_{PH}$ = 12.51 Hz, 2 H, CH_2), 4.05 (m, 8 H, 4 CH_2), 7.15–7.40 (m, 5 H, C_6H_5); ^{31}P NMR ($CDCl_3$) δ 22.81; MS, m/z (rel intensity) 421 (M^+, 1), 284 (100). Anal. calcd for $C_{18}H_{33}NO_6P_2$: C, 51.30; H, 7.89; N, 3.32. Found: C, 51.73; H, 7.56; N, 3.01.

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