Heteroatom Chemistry
Volume 19, Number 6, 2008

Synthesis of New Functionalized Mono- and Bisphosphinates with 2,6-Di-tert-butyl-4-methylphenol Fragments

Andrey A. Prishchenko, Mikhail V. Livantsov, Olga P. Novikova, Ludmila I. Livantsova, and Elena R. Milaeva

Department of Chemistry, M. V. Lomonosov Moscow State University, Moscow, 119991 Russia

Received 7 April 2008; revised 13 May 2008

ABSTRACT: *Convenient procedures for the synthesis of functionalized mono- and bisphosphinates with 2,6-di-tert-butyl-4-methylphenol (ionol) fragments, starting from the available 3,5-di-tert-butyl-4-benzaldehyde and its derivatives, are proposed, and some properties of the new phosphorus-substituted sterically hindered phenols are presented.*
© 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:562–568, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20475

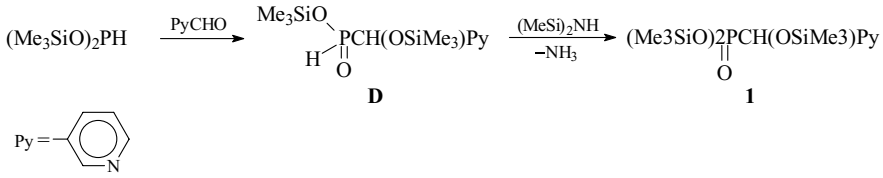
INTRODUCTION

Recently we have proposed the convenient procedures for synthesis of a series of organophosphorus derivatives of 2,6-di-tert-butyl-4-methylphenol (ionol) with one, two, or three phosphorus-containing groups [1]. These compounds were used by us for the preparation of stable phenoxyl radicals and were interesting as biological active compounds [2]. In this work, we propose the convenient methods for the synthesis of new functionalized mono- and bisphosphinates including of ionol fragments, starting from the readily accessible 3,5-di-tert-butyl-4-hydroxybenzaldehyde (**A**), 3,5-di-tert-butyl-4-hydroxybenzalchloride (**B**), and 3,5-di-tert-butyl-4-hydroxybenzoyl chloride (**C**), which were prepared by the procedures described in [3–5], and trimethylsilyl esters of functionalized trivalent phosphorus acids which were prepared by us early as unique organophosphorus synthons [6–8]. In the present study, we found that the aldehyde **A** and its derivatives **B** and **C** smoothly react with various trimethylsilyl esters of trivalent phosphorus acids under mild conditions to form new functionalized phosphorus-containing sterically hindered phenols, which are presented as promising polydentate ligands and effective antioxidants.

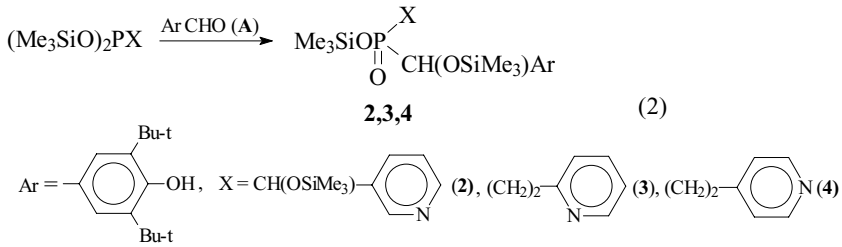
RESULTS AND DISCUSSION

All starting functionalized phosphonites are described in [6–8] except phosphonite **1**, which was specially synthesized in high yield via the addition of bis(trimethylsiloxy)phosphine to the carbonyl group of 3-pyridinecarboxaldehyde after the heating of intermediate **D** with bis(trimethylsilyl)amine (Eq. (1); cf. [7]).

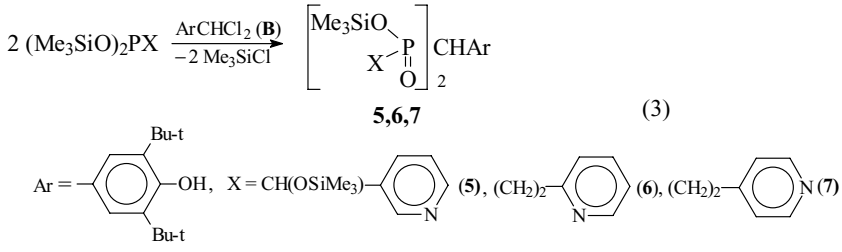
Correspondence to: Andrey A. Prishchenko; e-mail: aprishchenko@yandex.ru.
Contract grant sponsor: Russian Foundation for Basic Research.
Contract grant number: 08-03-00282.
© 2008 Wiley Periodicals, Inc.



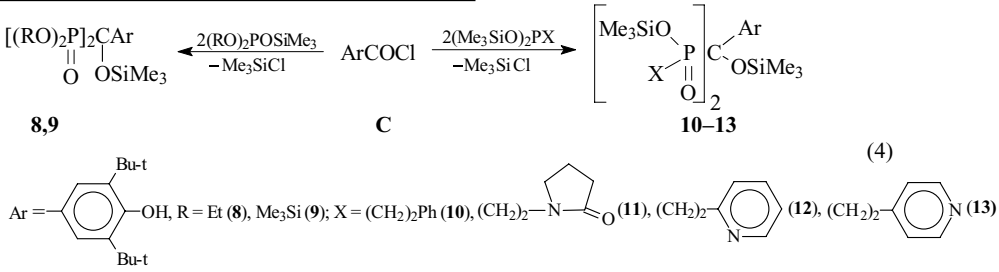
So functionalized bis(trimethylsilyl)phosphonites readily added by the carbonyl group of aldehyde **A** in methylene chloride to give phosphinates **2–4** in high yields (Eq. (2)). Note that under the mild conditions, the sterically hindered hydroxyl group of aldehyde **A** is not trimethylsilylated with excess of bis(trimethylsilyl) phosphonite (cf. [1]).



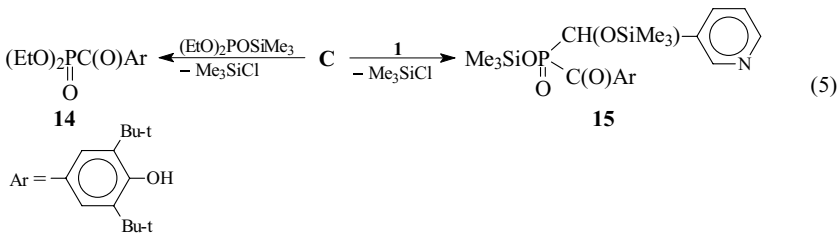
Using functionalized phosphonites, we have devised a convenient method for preparing bisphosphinates, which include trimethylsiloxymethyl groups, pyridine moieties, and sterically hindered phenolic fragments. Thus, trimethylsilyl phosphonites readily react with benzalchloride **B** in a methylene chloride solution by the Arbuzov reaction scheme to form bisphosphinates **5–7** in high yields (Eq. (3)). In these cases, too, the sterically hindered phenolic fragment is preserved (cf. [1]).



Various derivatives of substituted hydroxymethylenebisphosphonic acids are good complexones and are widely used in medicine [9–11]. In this study, we showed that the reactions of trimethylsilyl esters of trivalent phosphorus acids with readily available 3,5-di-tert-butyl-4-hydroxybenzoyl chloride **C** [5] yield new diphosphorylated hydroxymethylene derivatives, containing a sterically hindered phenolic fragment. So trimethylsilyl phosphites and functionalized trimethylsilyl phosphonites taken in excess readily react with acid chloride **C** in methylene chloride to form bisphosphonates **8,9** or bisphosphinates **10–13**, respectively, in high yields (Eq. (4)).

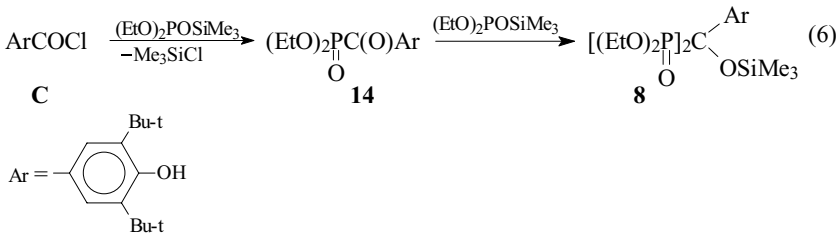


Under similar conditions, the reaction of diethyl trimethylsilyl phosphite or phosphonite **1** with acid chloride **C** in 1:1 ratio gives keto phosphonate **14** or keto phosphinate **15** in high yields (Eq. (5)).



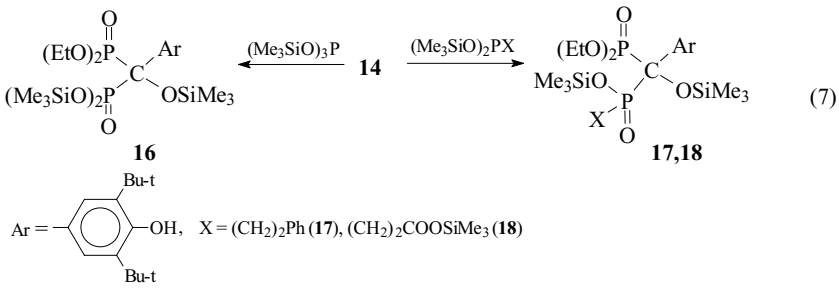
(5)

Thus, the reaction of excess trimethylsilyl phosphite with acid chloride **C** involves two steps: the Arbuzov reaction followed by addition of trimethylsilyl phosphite to the carbonyl group of keto phosphonate **14** to obtain bisphosphonate **8** (cf. [12]; Eq. (6)).



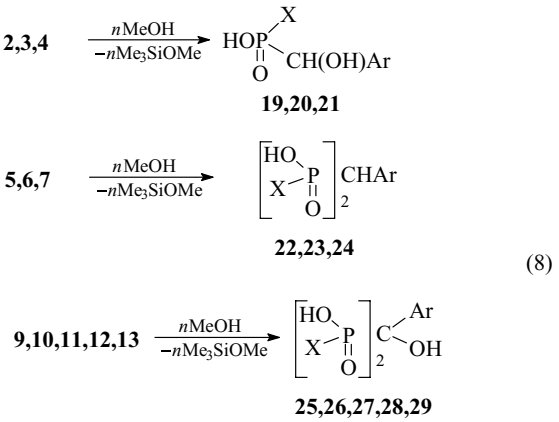
(6)

Here we found a facile route to new derivatives of unsymmetrical hydroxymethylenebisphosphorus acids containing a 2,6-di-*tert*-butylphenol fragment starting from phosphonate **14**. Tris(trimethylsilyl)phosphite as well as functionalized trimethylsilyl phosphonites taken in excess readily add to the carbonyl group of keto phosphonate **14** with the formation of bisphosphonate **16** and phosphonate-phosphinates **17,18**, respectively, in high yields (Eq. (7)).

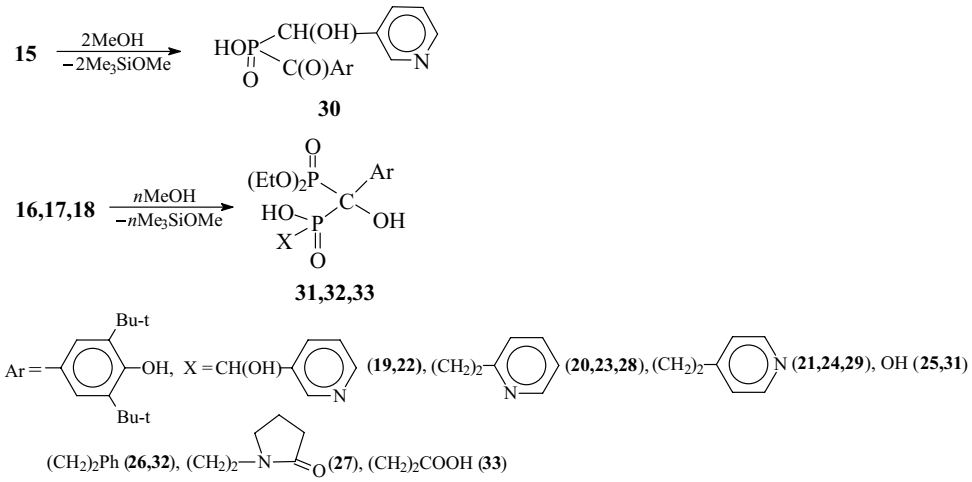


(7)

The reactions of trimethylsilyl esters of organophosphorus acids **2–7** and **9–18** with excess methanol gave functionalized organophosphorus acids **19–33** in high yields containing PCOH and PCP fragments (Eq. (8)).



(8)



Acids **19–31** are obtained as white hygroscopic crystals, and acids **32,33** are viscous oils. Acids **25–27,31** decompose on heating above 120–130°C without definite melting points. In contrast, acids **19–24,28,29** are more stable due to pyridine moieties in their molecules (cf. [12]). Previously unknown hydroxymethylenediphosphoryl compounds containing a sterically hindered phenolic fragment are promising complexing agents and antioxidants. Also the derivatives of substituted unsymmetrical hydroxymethylenediphosphoryl acids containing two phosphoryl groups with different extent of polarization are of interest as unusual ligands and biologically active compounds. The structures of compounds **1–33** were confirmed by the ^{1}H, ^{13}C, ^{31}P NMR spectra, which show characteristic signals of the PCHOH and PCP fragments and signals of substituted aromatic fragments (see Table 1). The elemental analysis data of synthesized compounds are summarized in Table 2.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were registered on a Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ (**1–18**), CD_3OD (**19–24,28–30**), or $(CD_3)_2SO$ (**25–27,31–33**) against TMS (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were performed under dry argon in anhydrous solvents. Aldehyde **A**, dichloride **B**, and benzoyl chloride **C** were prepared according to the procedures described by Coppinger and Campbell [3], Popov et al. [4], Ivakhnenko et al. [5], respectively.

*O,O-Bis(trimethylsilyl)pyrid-3-yl-(trimethylsiloxy)methylphosphonite (**1**)*

A solution of 3-pyridinecarboxaldehyde, 10.7 g in 25 mL of methylene chloride was added with stirring to a solution of 30 g of bis(trimethylsiloxy)phosphine in 60 mL of methylene chloride, and was cooled to 0°C. The mixture was stirred for 0.5 h, the solvent was then distilled off, and 20 g of bis(trimethylsilyl)amine was added to the residue. The mixture was refluxed until ammonia no longer evolved and then distilled to obtain 33.9 g of phosphonite **1** (see Table 1).

*O-Trimethylsilyl[pyrid-3-yl(trimethylsiloxy)-methyl]3,5-di-tert-butyl-4-hydroxyphenyl-(trimethylsiloxy)methylphosphinate (**2**)*

3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde **A**, 4.7 g, was added with stirring to a solution of 7.8 g of phosphonite **1** in 30 mL of methylene chloride, and was cooled to 10°C. The mixture was stirred for 0.5 h, the solvent was then distilled off, the residue was diluted with 5 mL of hexane, and the mixture was cooled to −5°C. The solvent was removed, and it was kept in a vacuum (0.5 mmHg) for 1 h to obtain 10.7 g of phosphinate **2** as a thick oil.

Compounds **3–7** were prepared similarly.

*O,O,O,O-Tetraethyl(3,5-di-tert-butyl-4-hydroxy-phenyl)trimethylsiloxymethylenebisphosphonate (**8**)*

A mixture of 3.8 g of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid, 10 mL hexane, and 8 mL thionyl chloride was refluxed for 0.5 h, the solvent was distilled off in a vacuum, and the residue was kept in a vacuum (0.5 mmHg) for 0.5 h. To a solution of thus obtained benzoyl chloride **C** in 15 mL of methylene chloride, a solution of 8 g of diethyl trimethylsilyl phosphate in 20 mL of methylene chloride was added with stirring and was cooled to 10°C. The mixture was stirred for 0.5 h and heated to reflux, after which the solvent was distilled off,

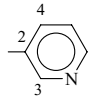
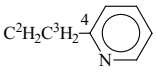
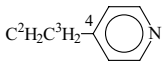
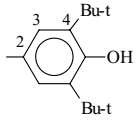
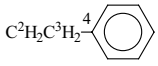
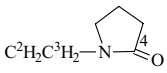
TABLE 1 Yields, Products, Constants, and NMR Spectral Data (δ, ppm; J, Hz) of Compounds **1–33**[a]

Compound	*Yield (%)*	*Mp (°C)*	δ_H C^1H	$^2J_{PH}$	δ (C^1)	$^1J_{PC}$	$\delta(C^1)$, d	J_{PC}	$\delta(C^3)$, s	$\delta(C^4)$, d	J_{PC}	δ_P, s
1	87	118 (1)[a]	4.13 d	4	79.56 d	14	134.59	9	148.57[b]	134.18	4	137.91
2	86	oil	4.83 d	10	70.71 d	108	[c]	–	–	–	–	30.99
			5.19 d	8	71.89 d	107	[c]	–	–	–	–	
			4.57 d	8	68.99 d	110	[c]	–	–	–	–	
			4.94 d	6	70.67 d	112	[c]	–	–	–	–	
3	89	oil	4.78 d	5	74.64 d	120	26.22	90	29.22	160.73	15	41.84
			4.58 d	8	73.93 d	117	26.17	91	29.46	159.28	13	39.94
4	91	oil	4.85 d	5	74.78 d	120	21.71	90	27.39[b]	150.72	14	40.80
			4.66 d	8	74.10 d	118	21.22	89	27.21[b]	150.78	15	38.90
5	89	78	3.75 t	18	42.31 t	78	[c]	–	–	–	–	30.93
			4.81 d	12	72.36 d	115	[c]	–	–	–	–	
			3.49 t	18	43.31 t	80	[c]	–	–	–	–	30.49
			4.88 d	8	71.91 d	113	[c]	–	–	–	–	
6	90	82	3.42 t	16	49.80 t	81	27.47	97	29.18	160.31	18	37.94
			3.38 t	18	52.34 t	80	29.25	106	29.14	160.35	18	29.23
7	88	102	3.41 t	17	49.82 t	80	28.42	84	28.88	147.00	17	36.32
			3.26 t	18	52.40 t	78	28.91	82	28.00	147.22	16	36.56
8	91	127	–	–	80.57 t	152	126.75	s	123.05[b]	136.38	s	16.16
9	90	146	–	–	79.82 t	161	127.67	s	124.05	134.46	s	−0.90
10	92	111	–	–	83.07 t	97	28.74	97	28.16	141.41, 141.49	8 8	39.16
11	93	129	–	–	82.76 t	100	26.04	91	34.50	174.20	s	36.90
12	91	75	–	–	82.91 t	98	27.30	101	28.87	160.37	16	39.46
13	93	85	–	–	82.65 t	96	28.08	94	29.56	150.16	16	38.14
					82.58 t	96	28.21	92	29.46	150.49	18	38.38
14	81	oil	–	–	191.61 d	171	129.44	s	128.07	136.64	s	0.05
15	88	108	–	–	70.63 d	109	[c]	–	–	–	–	14.43
					200.03 d	104	[c]	–	–	–	–	
					69.36 d	120	[c]	–	–	–	–	15.79
					199.61 d	106	[c]	–	–	–	–	
16	87	110	–	–	79.72 dd	151, 163	121.61	s	124.28[b]	134.39	s	16.92 d, −0.58 d, $^2J_{PP}$ 45.4
17	85	oil	–	–	81.25 dd	147, 102	32.08	93	27.82[b]	141.37	16	17.14 d, 39.08 d, $^2J_{PP}$ 43.7
18	90	oil	–	–	81.25 dd	148, 106	22.44	98	28.50	172.45	19	17.15 d, 38.95 d, $^2J_{PP}$ 43.7
19	96	132	5.09 d	7	67.84 d	97	[c]	–	–	–	–	33.23
			5.48 d	10	70.56 d	112	[c]	–	–	–	–	
			4.93 d	8	70.38 d	95	[c]	–	–	–	–	30.15
			5.27 d	9	72.66 d	110	[c]	–	–	–	–	
20	98	139	4.70 d	8	71.86 d	112	24.92	85	28.04	159.27	14	42.85
21	97	117	5.50 d	8	72.66 d	110	27.42	78	27.76[b]	149.36	14	44.0
22	97	235	4.32 t	20	51.38 t	84	[c]	–	–	–	–	31.22
			5.38 d	8	69.95 d	100	[c]	–	–	–	–	
			4.32 t	20	51.38 t	84	[c]	–	–	–	–	31.78
			5.59 d	8	70.30 d	100	[c]	–	–	–	–	
23	96	105	3.77 t	19	50.99 t	77	29.50	93	27.49	158.63	15	37.62
24	97	110	3.84 t	18	50.03 t	78	28.37	74	28.64	162.68	15	39.10
25	98	[d]	–	–	73.75 t	146	127.99	s	123.98	137.53	s	16.51
26	97	[d]	–	–	78.13 t	91	128.53	93	27.73	142.33, 142.41	8 8	45.88
27	94	[d]	–	–	78.18 t	93	24.96	92	35.17	174.0	s	43.76
28	97	119	–	–	78.72 t	91	26.67	96	27.19	158.37	14	39.80
29	97	152	–	–	77.02 t	102	27.40	96	28.36	159.72	17	43.13
30	95	165	5.78 d	8	69.05 d	102	[c]	–	–	–	–	18.78
					205.86 d	115						

(Continued)

TABLE 1 Continued

Compound	*Yield (%)*	*Mp (°C)*	δ_H C^1H	$^2J_{PH}$	δ (C^1)	$^1J_{PC}$	$\delta(C^2)$, d	J_{PC}	$\delta(C^3)$, s	$\delta(C^4)$, d	J_{PC}	δ_P, s
31	91	[d]	–	–	76.54 t	146	127.41	s	123.86	137.76	s	18.54 d, 14.95 d, $^2J_{PP}$ 38.9
32	92	oil	–	–	77.77 dd	148, 96	31.66	94	27.84	142.50	15	17.97 d, 43.59 d, $^2J_{PP}$ 32.4
33	92	oil	–	–	77.70 dd	153, 93	22.21	94	26.83	173.18	15	17.93 d, 43.10 d, $^2J_{PP}$ 35.6

[a]For **1**, Bp in °C (P, mmHg). All signals of alkyl, aryl, and trimethylsilyl groups are in the standard area. The following fragments of compounds **1–33** are presented now: PC^1HO (d), $PC^1{=}O$ (d), PC^1HP (t), PC^1HP (t or dd), and $PC^2C^3C^4$. The ^1H NMR spectra of products fragments show expected signals that look like sometimes as overlapping multiplets. According to the NMR spectra, the compounds **2–7,12,13,15,19,22** are mixtures of two stereoisomers. Their ratio was determined from the ^1H and ^{31}P NMR spectra. The ratio is 55:45 (for **2–4,19**), 60:40 (for **5,15**), 70:30 (for **12,13,22**), 75:25 (for **6,7**). The spectral parameters of the major isomer are given first. The fragments $PC^2C^3C^4$ are  for **1**;  for **3,6,12,20,23,28**;  for **4,7,13,21,24,29**;  for **8,9,14,16,25,31**;  for **10,17,26,32**;  for **11,27**; $C^2H_2C^3H_2C^4{=}O$ for **18,23**.

[b]d (J_{PC}) for compounds: **1** (4), **4** (3), **17** (3), **21** (3); t (J_{PC}) for compounds: **8** (4.5), **16** (4).

[c]In ^{13}C NMR spectra, the signals of pyridine and phenolic fragments of these compounds look as overlapping multiplets.

[d]This compound is decomposed by heating.

TABLE 2 Elemental Analyses Data of Compounds **2–33**[a]

Compound	*Empirical Formula*	*Formula Weight*	*Calcd. (%)*		*Found (%)*	
			C	*H*	*C*	*H*
2	$C_{30}H_{54}NO_5PSi_3$	624.00	57.75	8.72	57.72	8.64
3	$C_{28}H_{48}NO_4PSi_2$	549.84	61.17	8.80	60.98	8.72
4	$C_{28}H_{48}NO_4PSi_2$	549.84	61.17	8.80	60.95	8.69
5	$C_{39}H_{68}N_2O_7P_2Si_4$	851.27	55.03	8.05	54.89	7.94
6	$C_{35}H_{56}N_2O_5P_2Si_2$	702.96	59.80	8.03	59.74	7.96
7	$C_{35}H_{56}N_2O_5P_2Si_2$	702.96	59.80	8.03	59.66	7.91
8	$C_{26}H_{50}O_8P_2Si$	580.73	53.78	8.68	53.59	8.57
9	$C_{30}H_{66}O_8P_2Si_5$	757.23	47.59	8.78	47.48	8.67
10	$C_{40}H_{66}O_6P_2Si_3$	789.17	60.88	8.43	60.65	8.37
11	$C_{36}H_{68}N_2O_8P_2Si_3$	803.16	53.84	8.53	53.66	8.44
12	$C_{38}H_{64}N_2O_6P_2Si_3$	791.15	57.69	8.15	57.52	8.12
13	$C_{38}H_{64}N_2O_6P_2Si_3$	791.15	57.69	8.15	57.55	8.07
14	$C_{19}H_{31}O_5P$	370.42	61.61	8.43	61.48	8.35
15	$C_{27}H_{44}NO_5PSi_2$	549.80	58.99	8.07	58.81	8.01
16	$C_{28}H_{58}O_8P_2Si_3$	668.98	50.27	8.74	49.92	8.68
17	$C_{33}H_{58}O_7P_2Si_2$	684.94	57.87	8.54	57.73	8.49
18	$C_{31}H_{62}O_9P_2Si_3$	725.03	51.36	8.62	51.23	8.52
19	$C_{21}H_{31}NO_5P$	408.45	61.75	7.65	61.59	7.56
20	$C_{22}H_{32}NO_4P$	405.47	65.17	7.95	64.97	8.02
21	$C_{22}H_{32}NO_4P$	405.47	65.17	7.95	64.92	7.99
22	$C_{27}H_{36}N_2O_7P_2$	562.54	57.65	6.45	57.52	6.49
23	$C_{29}H_{40}N_2O_5P_2$	558.60	62.36	7.22	62.12	7.26
24	$C_{29}H_{40}N_2O_5P_2$	558.60	62.36	7.22	62.23	7.28
25	$C_{15}H_{26}O_8P_2$	396.33	45.46	6.61	45.28	6.68

(Continued)

TABLE 2 (Continued)

Compound	Empirical Formula	Formula Weight	Calcd. (%)		Found (%)	
			C	H	C	H
26	$C_{31}H_{42}O_6P_2$	572.62	65.02	7.39	64.89	7.47
27	$C_{26}H_{42}N_2O_8P_2$	572.68	54.54	7.39	54.43	7.35
28	$C_{29}H_{40}N_2O_6P_2$	574.60	60.62	7.02	60.49	7.08
29	$C_{29}H_{40}N_2O_6P_2$	574.60	60.62	7.02	60.47	6.98
30	$C_{21}H_{28}NO_5P$	405.43	62.21	6.96	61.98	7.03
31	$C_{19}H_{34}O_8P_2$	452.43	50.44	7.57	50.07	7.52
32	$C_{27}H_{42}O_7P_2$	540.58	59.99	7.83	59.65	7.74
33	$C_{22}H_{38}O_9P_2$	508.48	51.97	7.57	51.59	7.46

[a]Phosphonite **1** is extremely readily oxidized and hydrolyzed, and therefore it was analyzed in form of the corresponding adduct with aldehyde **A** (phosphinate **2**).

15 mL of hexane was added to the residue, and the mixture was cooled to 0°C. The precipitated white crystals were filtered off and kept in a vacuum (0.5 mmHg) for 1 h. Bisphosphonate **8** was obtained with yield of 8 g.

Compounds **9–18** were prepared similarly.

*Pyrid-3-yl(hydroxy)methyl 3,5-di-tert-butyl-4-hydroxyphenyl(hydroxy)methylphosphinic Acid (**19**)*

Phosphonate **2**, 10.7 g, was added with stirring to 60 mL of methanol and was cooled to 10°C. The mixture was heated to boiling, the solvent was distilled off, and residue was kept in a vacuum (1 mmHg) for 1 h to obtain 6.7 g of acid **19**.

Acids **20–23** were prepared similarly.

REFERENCES

[1] Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Milaeva, E. R. Heteroatom Chem (in press).

[2] Tyurin, V. Yu.; Gracheva, Yu. A.; Milaeva, E. R.; Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Maryashkin, A. V.; Bubnov, M. P.; Kozhanov, K. A.; Cherkasov, V. K. Russ Chem Bull 2007, 744–750.

[3] Coppinger, G. M.; Campbell, T. W. J Am Chem Soc 1953, 75, 734–736.

[4] Popov, L. K.; Egidis, F. M.; Ershov, V. V. Izv Akad Nauk Ser Khim 1968, 902–904 (in Russian).

[5] Ivakhnenko, E. P.; Shif, A. I.; Prokofiev, A. I.; Olekhnovich, L. P.; Minkin, V. I. Zh Org Khim 1989, 25, 357 (in Russian).

[6] Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Petrosyan, V. S. Heteroatom Chem 2008, 19, 345–351.

[7] Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Petrosyan, V. S. Heteroatom Chem 2008, 19, 352–359.

[8] Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Petrosyan, V. S. Heteroatom Chem 2008, 19, 418–428.

[9] Ebetino, F. H. Phosphorus Sulfur Silicon Relat Elem 1999, 144–146, 9.

[10] Matkovskaya, T. A., Popov, K. I.; Yurieva, E. A. Bisphosphonates. Properties, Structure, and Medical Applications; Khimiya: Moscow, 2001 (in Russian).

[11] Kolodiazhnyi, O. I. Usp Khim 2006, 75, 254–282 (in Russian).

[12] Sekine, M.; Hata, T. Chem Commun 1978, 285.