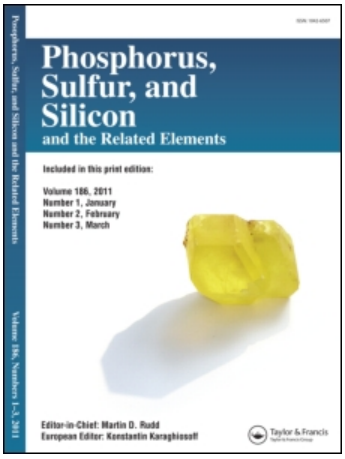

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SYNTHESIS OF ACID-LABILE GEMINAL BIS- AND TRISPHOSPHONIC ACIDS[1]

H. Gross[a]; I. Keitel[a]; B. Costisella[a]; C. E. McKenna[b]
[a] Zentralinsititut fur Organische Chemie, Berlin-Adershof, Germany [b] Department of Chemistry, University of Southern California, Los Angeles, California, USA

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SYNTHESIS OF ACID-LABILE GEMINAL BIS- AND TRISPHOSPHONIC ACIDS[1]

H. GROSS, I. KEITEL and B. COSTISELLA
Zentralinsititut fur Organische Chemie, Rudower Chaussee 5, 0-1199 Berlin-Adershof, Germany

and

C. E. McKENNA
Department of Chemistry, University of Southern California, Los Angeles, California 90089-0744, USA

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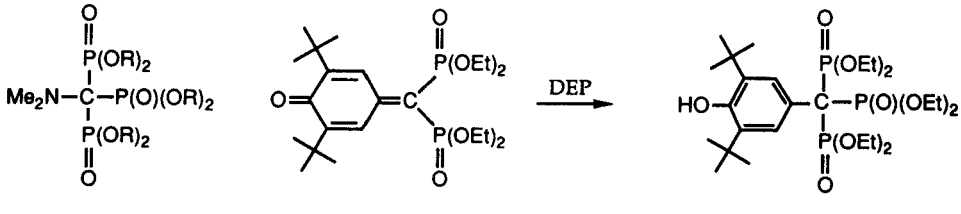
Sodium salts (**7**, **8** respectively) of the unsaturated bisphosphonic acid **5** (2,6-di-*tert*-butyl-7,7-bis(phosphono)-1,4-benzoquinone-4-methide) and the trisphosphonic acid **6** (4-hydroxy-3,5-di-*tert*-butylphenylmethane tris(phosphonic acid), were prepared by buffered hydrolysis of the corresponding trimethylsilyl esters. The structures of **7** and **8** were determined by ^{13}C and ^{31}P NMR analysis. Compound **8** is the first well-established example of a *gem* trisphosphonic acid salt.

Key words: 7-phosphono-quinonemethide salts; arylmethane trisphosphonate; bromotrimethylsilane; silyldealkylation; ^{13}C, ^{23}Na, ^{31}P NMR data.

INTRODUCTION

The first example of a *gem* trisphosphonate derivative was the hexaester **1a** prepared by V. Kuchar *et al.*[2] Recently, Gross *et al.* prepared the first arylmethane trisphosphonate ester (**3**) by addition of diethylphosphite (DEP) to the bisphosphonoquinone methide **2**.[3] In general, phosphonic acid esters of this type are not very stable, undergoing phosphoryl group migrations[4] or other P—C bond cleavage reactions.[5]

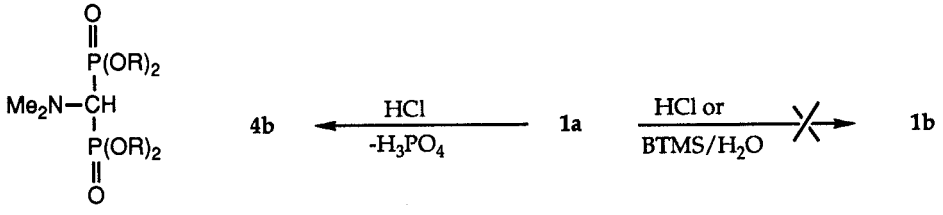


1 **2** **3**

1	a	b
R	Et	H

SCHEME 1

Previous efforts to prepare a *gem* trisphosphonic acid have been unsuccessful. For example, cleavage of one P—C bond was observed on attempted hydrolysis of the trisphosphonic acid ester **1a** under acidic conditions. Specifically, treatment with a.q. HCl, which hydrolyzes the bisphosphonic ester **4a** almost quantitatively to the corresponding acid **4b**,[6] under the same conditions converts **1a** not to the expected trisphosphonic acid **1b**, but instead to the dephosphorylation product **4b**. Even with bromotrimethylsilane (BTMS/H_2O) de-esterification under mild conditions,[7] **1a** yields only **4b**.[5]

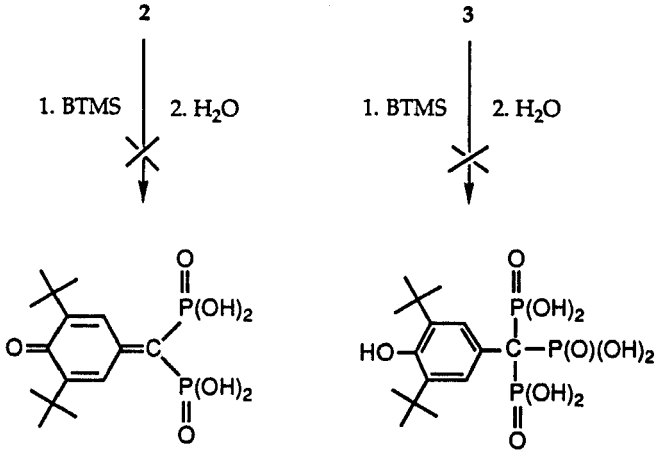


4b

4	a	b
R	Et	H

SCHEME 2

P—C bond cleavage is also observed in H_2O after silyldealkylation of the bisphosphono-quinone methide **2** or its trisphosphonate analog **3**.[8]



5 **6**

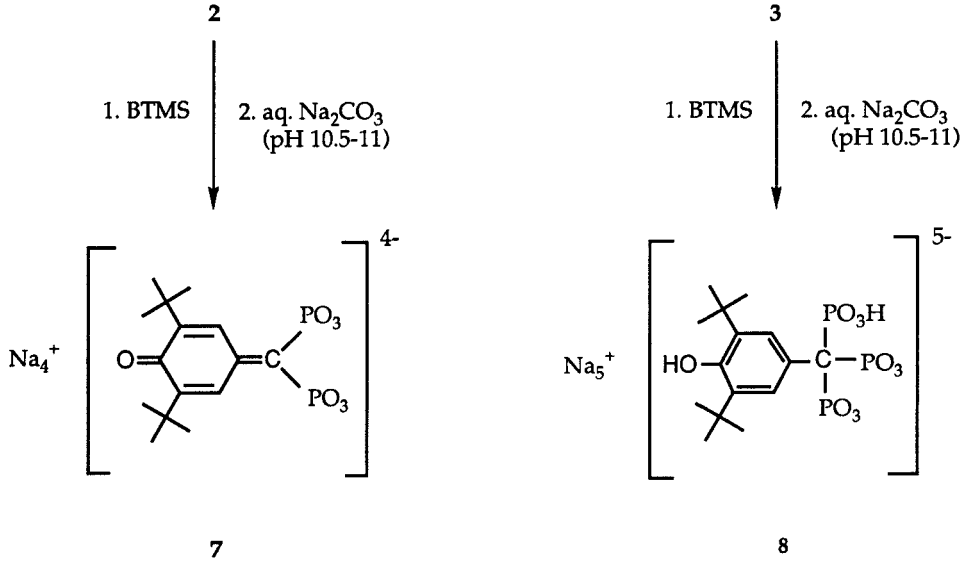
SCHEME 3

Recently, it was reported that a sodium salt of an acid-labile phosphonic acid (thiophosphonoformic acid) could be prepared with minimal P—C scission by solvolysis of the corresponding tris(trimethylsilylester) under weakly alkaline condi-

tions.[9] This method has now been applied successfully to the silyldealkylation-hydrolysis of **2** and **3**.

RESULTS AND DISCUSSION

The trimethylsilyl esters of **5** and **6**, respectively, prepared by reflux with excess BTMS for several hours in methylene chloride, were reacted *in situ* with a slight excess of aqueous Na_2CO_3 at 0°. The aqueous phases of the mixtures were then adjusted to pH 10.5–11 with 3 M NaOH. The sodium salts **7** and **8** were isolated in nearly quantitative yield by precipitation with methanol.



SCHEME 4

TABLE I

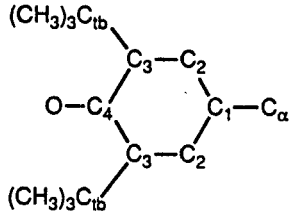
NMR data for sodium salts of **5** and **6**

Cpd.	^{31}P δ, ppm[a]	^{23}Na δ, ppm[b]	^{13}C δ, ppm[c] (J in Hz)						
			C_1	C_2	C_3	C_4	C_α	C_{tb}	CH_3
7	9.1	-0.4	160.2 (2.0)	137.4 (14.7)	151.4	191.6	156.0 (124.7)	37.4	31.8
8	17.4	-0.3	132.8 (5.8)	131.2 (6.8)	139.9	152.4	60.5 (96.0)	34.3	32.2

[a] In H_2O; reference, external 85% H_3PO_4.
[b] In H_2O; reference, external 4 M NaCl.
[c] In D_2O; reference, external HMDS (std: Na^+ salt of 3-trimethylsilyl-1-propanesulfonic acid).

Attempted hydrolysis of the hexakis(trimethylsilyl) trisphosphonate corresponding to **1a**, using the same procedure, resulted in P—C scission, forming the bisphosphonate **4b**.

The structures of the products **7** and **8** were established unambiguously by their NMR spectra (Table I). The ^{13}C-NMR chemical shift values and coupling patterns of the two compounds are characteristic, generally paralleling those previously reported for **2** and **3**.[3] In particular, the methide C-atom (C_α) and the C_1- and C_2-ring-atoms of **7** give triplets due to coupling with two equivalent P-nuclei, and the corresponding C-atoms of **8** give quadruplets due to coupling with three equivalent P-nuclei. The quinone-methide character of **7** is suggested by the typical carbonyl ^{13}C δ of 191.6 ppm and the phosphonovinyl ^{13}C δ of 156.0 ppm, assigned to C_4 and C_α, respectively. The NMR spectra revealed no evidence for any P—C cleavage products.



SCHEME 5

In conclusion, carbonate-buffered hydrolysis of phosphonic acid trimethysilyl esters has made possible preparation of the first example of a *gem* trisphosphonic acid salt.

EXPERIMENTAL

2,6-Di-tert-butyl-7,7-bis(phosphono)-1,4-benzoquinone-4-methide, tetrasodium salt (**7**) *and 4-hydroxy-3,5-di-tert-butylphenylmethane tris(phosphonic acid), pentasodium salt* (**8**). A solution of 4 mmol **2** or **3** in 10 mL of dry CH_2Cl_2 was refluxed with 15 mL BTMS or 25 mL of BTMS, resp., for 4 h. The reaction mixtures were concentrated *in vacuo*. The resulting residues were then treated with 9 mmol Na_2CO_3 in 6 mL of H_2O, or 13.5 mmol of Na_2CO_3 in 9 mL of H_2O. The pH of the solutions was adjusted to 10.5–11 with 3 M NaOH and 60 mL of MeOH was added. After 1 h of stirring at room temperature, the desired products were separated by filtration at the pump and dried *in vacuo* (50°C, 10^{-2} torr). The salts **7** and **8** were recrystallized from aqueous methanol for elemental analysis (Table II).

TABLE II

Yield and elemental analysis data for sodium salts of **5** and **6**

Cpd.	Yield (%)	Formula (MW)	Elemental Analysis Calcd.	Found
7	87	$C_{15}H_{20}Na_4O_7P_2 \cdot 2H_2O$ (502.26)	C 35.87 H 4.82	35.94 4.94
8	82	$C_{15}H_{22}Na_5O_{10}P_3 \cdot 2H_2O$ (606.23)	C 29.72 H 4.32	29.73 4.39

ACKNOWLEDGEMENT

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