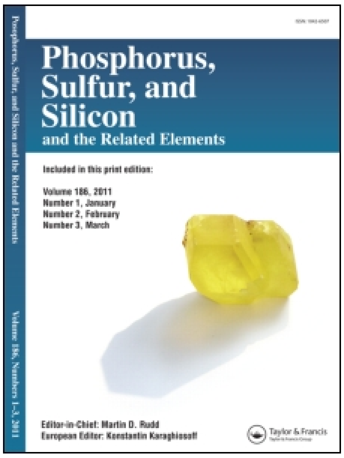


**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# REARRANGEMENT OF DI-T-BUTYL ARYL PHOSPHATES TO DI-T-BUTYL(2-HYDROXYARYL)PHOSPHONATES. PREPARATION OF (2-HYDROXY-1,3-PHENYLENE)BISPHOSPHONIC ACIDS

Balram Dhawan[a]; Derek Redmore[a]
[a] Petrolite Corporation, St. Louis, MO

**To cite this Article** Dhawan, Balram and Redmore, Derek(1989) 'REARRANGEMENT OF DI-T-BUTYL ARYL PHOSPHATES TO DI-T-BUTYL(2-HYDROXYARYL)PHOSPHONATES. PREPARATION OF (2-HYDROXY-1,3-PHENYLENE)BISPHOSPHONIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 42: 3, 177 — 182

**To link to this Article: DOI:** 10.1080/10426508908054893

**URL:** http://dx.doi.org/10.1080/10426508908054893

*Phosphorus, Sulfur, and Silicon*, 1989, Vol. 42, pp. 177–182
Reprints available directly from the publisher
Photocopying permitted by license only

# REARRANGEMENT OF DI-T-BUTYL ARYL PHOSPHATES TO DI-T-BUTYL(2-HYDROXYARYL)PHOSPHONATES. PREPARATION OF (2-HYDROXY-1,3-PHENYLENE)BISPHOSPHONIC ACIDS

BALRAM DHAWAN† and DEREK REDMORE
*Petrolite Corporation, St. Louis, MO 63119*

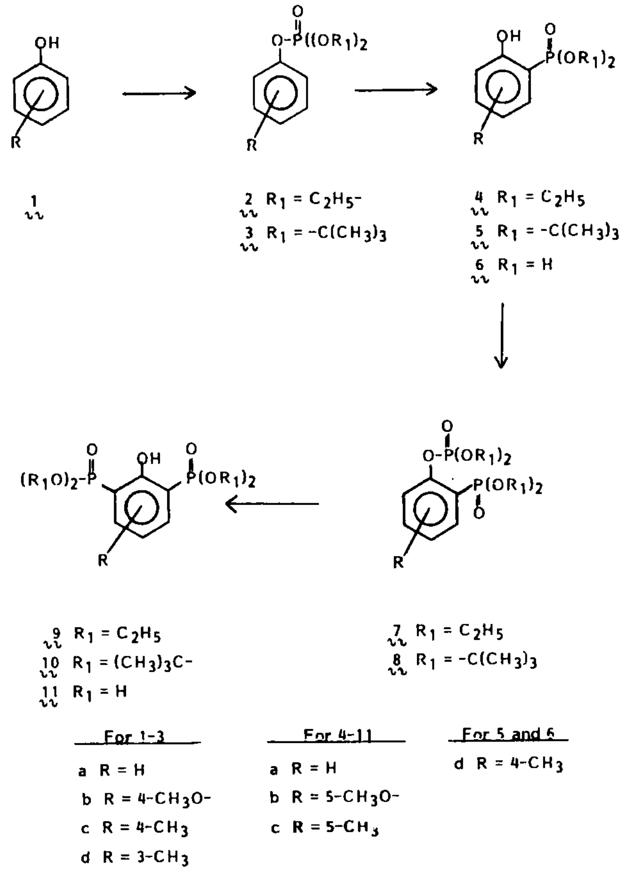
*(Received July 22, 1988; in final form August 13, 1988)*

Di-t-butyl aryl phosphates **3** on treatment with lithium diisopropylamide rearrange to di-t-butyl (2-hydroxyaryl)phosphonates **5**. A di-t-butyl (2-hydroxyaryl) phosphonate on reaction with di-t-butyl phosphorochloridate yields a phosphate–phosphonate **8** which on treatment with lithium diisopropylamide gives a tetra-t-butyl (2-hydroxy-1,3-arenediyl) bisphosphonate **10**. Treatment of these phosphonate esters **5** and **10** with trifluoroacetic acid in benzene results in loss of t-butyl groups to yield (2-hydroxyaryl) phosphonic acids **6** and (2-hydroxy-1,3-arenediyl) bisphosphonic acids **11** respectively.

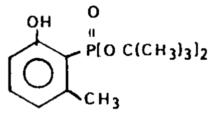
*Key words:* Phosphate–phosphonate rearrangement; preparation (2-hydroxy-1, 3-phenylene)bisphosphonic acids.

In an earlier paper[1] we reported the preparation of (2-hydroxyaryl)phosphonic acids **6** and (2-hydroxy-1,3-arenediyl) bisphosphonic acids **11** by the hydrolysis of diethyl (2-hydroxyaryl) phosphonates **4** and tetraethyl (2-hydroxyl,3-arenediyl) bisphosphonates **9** respectively. The hydrolysis of **4** and **9** was achieved via transesterification with trimethylsilyl chloride/sodium iodide in acetonitrile followed by treatment with water. The products **6** and **11** (**a** and **b**) were isolated as anilinium salts. In a later communication[2] we reported that the use of t-butyl esters instead of ethyl esters allowed the preparation of **6** (**a** and **b**) in free form (i.e. not as anilinium salts) as white crystalline solids. It was possible because de-t-butylation of di-t-butyl (2-hydroxyaryl) phosphonates **5** (**a** and **b**) could be carried out in an aprotic solvent benzene with trifluoroacetic acid (TFA). In this paper we describe the preparation of (2-hydroxy-1,3-phenylene) bisphosphonic acids **11** (**a** and **c**) and show that use of t-butyl esters instead of ethyl esters offers certain additional advantages. In addition two more examples of **6** (**c** and **d**) are reported.

Treatment of sodium phenoxides **1** with di-t-butyl phosphorochloridate yielded di-t-butyl aryl phosphates **3** which on treatment with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) rearranged to di-t-butyl (2-hydroxyaryl)phosphonates **5**. Rearrangement of **3d** gave a crystalline solid that was identified as di-t-butyl (2-hydroxy-4-methylphenyl) phosphonate **5d**, on the basis of the spectral data.[3,4] In the $^{13}$C NMR of **5d**, the methyl carbon of Ar–$CH_3$ appeared as a singlet and in the $^1$H NMR, there was a downfield aromatic quartet with $J_{PH} = 14$ Hz and $J_{H-H} = 9$ Hz showing the presence of an ortho proton to the phosphonate group.[5] The alternative structure di-t-butyl (2-hydroxy-6-



methylphenyl)phosphonate **V** is ruled out because it is expected to show a doublet for the methyl carbon of Ar–$CH_3$ and the absence of an ortho proton to the phosphonate group. Both new phosphonates **5c** and **5d** were de-t-butylated with TFA in benzene to give (2-hydroxy-5-methyl) phenylphosphonic acid **6c** and (2-hydroxy-4-methylphenyl) phosphonic acid **6d** respectively which were characterized by spectral data and elemental analysis.



V

Treatment of the sodium salts of **5a** and **5c** with di-t-butyl phosphorochloridate yielded di-t-butyl 2-(di-t-butoxyphosphinyl)phenyl phosphate **8a** and di-t-butyl 2-(di-t-butoxyphosphinyl)-5-methylphenyl phosphate **8c** respectively. Both **8a** and **8c** are crystalline solids and were readily isolated and purified. In the case of ethyl esters, the corresponding compounds **7** were liquids and could not be isolated pure.

In the $^{31}P$ NMR spectra, both **8a** and **8c** exhibited two phosphorus signals (both

TABLE I

Spectral data of compounds **8a–11c**

| Compound | $^{31}P$ | $^{1}H$ NMR | $^{13}C$ NMR |
|---|---|---|---|
| **8a** | +6.52 ($J_{P-P} = 2.44$ Hz)<br>−16.60 ($J_{P-P} = 2.44$ Hz) | 1.44 and 1.50 (2xs, 36H, $CH_3$)<br>6.98–8.16 (m, 4H, Ar) | 29.67 [d, 3.02 Hz, C(Ç$H_3$)$_3$], 30.21 [d, 3.02 Hz, C(Ç$H_3$)$_3$] 82.09 [d, 9.05 Hz, Ç($CH_3$)$_3$], 83.33 [d, 7.09, Ç($CH_3$)$_3$], 118.11 (dd, 3.02 Hz, 7.09 Hz, $C_3$) 122.87 (d, 13.05, $C_5$), 123.74 (dd, 12.14 Hz, 190.3 Hz, $C_1$), 132.60 (d, 4.00 Hz, $C_4$), 134.71 (d, 7.09 Hz, $C_6$), 152.47 (d, 5.05 Hz, $C_2$) |
| **8c** | +6.82 ($J_{P-P} = 2.44$ Hz)<br>−16.53 ($J_{P-P} = 2.44$ Hz) | 1.50 and 1.56 (2xs, 36H, $CH_3$)<br>2.36 (s, 3H, Ar–$CH_3$), 7.15–8.00 (m, 3H, Ar) | 20.21 ($CH_3$), 29.63 [d, 6.03 Hz, C(Ç$H_3$)$_3$], 30.19 [d, 6.03 Hz, C(Ç$H_3$)$_3$], 81.93 [d, 9.05 Hz, Ç($CH_3$)$_3$], 83.09 [d, 7.01 Hz, Ç($CH_3$)$_3$], 117.83 (dd, 9.13 Hz, 4.00 Hz, $C_3$), 123.17 (dd, 9.13 Hz, 189.40 Hz, $C_1$), 132.24 (d, 16.14 Hz, $C_5$), 133.09 ($C_4$), 134.88 (d, 10.10 Hz, $C_6$), 150.28 (d, 6.03 Hz, $C_2$) |
| **10a** | +9.80 | 1.44 (s, 36H, $CH_3$), 6.75–7.02 (m, 1H, Ar) 7.60–7.90 (m, 2H, Ar) 11.06 (s, 1H, OH) | 29.89 [C(Ç$H_3$)$_3$], 82.60 (t, Ç($CH_3$)$_3$), 117.93 (dd, 189.40 Hz, 7.09 Hz, $C_1$, $C_3$), 118.06 (t, 14.10 Hz, $C_5$), 137.36 ($C_4$, $C_6$), 161.40 (t, 7.01 Hz, $C_2$) |
| **10c** | +10.16 | 1.50 (s, 36H, $CH_3$), 2.30 (s, 3H, $CH_3$) 7.62 (dd, $J_{P-C-CH} = 11.5$ Hz, $J_{P-C-C-C-C-H} = 4.5$ Hz, 2H, Ar), 10.88 (s, 1H, OH) | 19.98 ($CH_3$), 30.02 [C(Ç$H_3$)$_2$], 82.63 [t, Ç($CH_3$)$_3$], 117.70 (dd, 187.37 Hz, 10.11 Hz, $C_1$, $C_3$), 127.26 (t, 14.10 Hz, $C_5$), 137.73 ($C_4$, $C_6$), 159.40 (t, 6.03 Hz, $C_2$) |
| **11a** | +14.76 | 7.52 (tt, $J_{H-H} = 7.5$ Hz, $J_{P-C-C-C-H} = 3$ Hz, 1H, Ar), 8.25 (apparent q, $J_{H-H} = 7.5$ Hz, $J_{P-C-C-H} = 15$ Hz, 2H, Ar) | 118.56 (dd, 7.81 Hz, 179.69 Hz, $C_1$, $C_3$), 121.55 (t, 13.67 Hz, $C_5$), 138.56 (s, $C_4$, $C_6$), 161.81 (t, 3.91 Hz, $C_2$) |
| **11c** | +14.96 | 2.68 (s, 3H, $CH_3$), 8.02 (d, $J_{P-C-C-H} = 15$ Hz, 2H, Ar) | 20.39 (s, $CH_3$), 117.52 (dd, 9.77 Hz, 177.73 Hz, $C_1$, $C_3$), 130.51 (t, 13.67 Hz, $C_5$), 138.04 (s, $C_4$, $C_6$), 158.82 (t, 5.82 Hz, $C_2$) |

doublets) as expected, the phosphate ester at ca. −16.50 ppm and the phosphonate ester at ca. +6.50 ppm. The four bond P-P coupling constant was 2.44 Hz. In the $^{1}$H NMR spectra of **8**, two singlets of 18 H each corresponding to the methyl protons of two different kinds of t-butyl groups were seen. In the $^{13}$C NMR spectra, two kinds of t-butyl groups were also clearly evident, each kind of t-butyl group exhibiting a doublet for the methyl carbons and a doublet for the $\underset{\cdot}{C}(CH_3)_3$. The splitting pattern observed due to the coupling with phosphorus helped the assignment of signals to the aromatic ring carbons. In **8c**, $C_1$ appeared as a doublet of doublet showing one bond C–P coupling constant of ca. 190 Hz and a three bond P–O–C–C coupling constant of ca. 9 Hz, $C_3$ also appeared as a doublet of doublet exhibiting three bonds coupling to both the phosphorus, $C_5$ and $C_6$ appeared as doublets due to coupling with phosphonate phosphorus, $C_2$ appeared as a doublet showing two bond coupling only to one of the phosphorus and $C_4$ was singlet. In **8a**, four bond P–C coupling constant of 4.00 Hz with $C_4$ was observed. (Table I).

The compounds **8** when treated with LDA in THF underwent clean rearrangement to yield tetra-t-butyl (2-hydroxy-1,3-arendiyl)bisphosphonates **10**. The bisphosphonates **10** are white crystalline solids and exhibited a single phosphorus signal in their $^{31}$P spectra at ca. 10.00 ppm. $^{1}$H NMR showed only one kind of t-butyl groups, a singlet corresponding to 36 H for the t-butyl protons. In the $^{13}$C NMR of **10**, only four kinds of aromatic ring carbons were observed unambiguously proving the assigned structures. (Table I). The ring carbon $C_2$ appeared as a triplet exhibiting two bond P–C coupling constant of 7–10 Hz. The ring carbon $C_5$ appeared as a triplet exhibiting three bond P–C coupling constant of ca. 14.00 Hz. The ring carbon $C_1$ and $C_3$ appeared as a doublet of doublet exhibiting one bond P–C coupling ($J = 187$–$189$ Hz) and three bond P–C coupling of 7–10 Hz. The two bond coupling between phosphorus and proton bearing carbon ($C_4$ and/or $C_6$) was not observed.

In compounds **10**, the $^{13}$C signal from $\underset{\cdot}{C}(CH_3)_3$ was a *triplet* with a visible coupling of ca. 4 Hz which is half of the value of P–O–$\underset{\cdot}{C}$ coupling normally observed say, in **8**. This appears to be a case of 'virtual coupling' in which the phosphorus that is six-bond away from $\underset{\cdot}{C}$–$CH_3$ contributes to the multiplicity of the signal but not to the coupling.[6] The observed coupling is the average of the actual couplings i.e. 8 Hz with P that is 2 bond away and ca. zero Hz with the phosphorus that is 6 bonds away.

Treatment of **10a** and **10c** with trifluoroacetic acid results in loss of t-butyl groups to yield (2-hydroxy-1,3-phenylene)bis(phosphonic acid) **11a** and (2-hydroxy-5-methyl-1,3-phenylene)bis(phosphonic acid) **11c**, respectively. These were characterized by $^{1}$H, $^{13}$C and $^{31}$P NMR spectra (Table I) and elemental analysis.

## EXPERIMENTAL

Melting points were obtained either on a Fisher Johns melting point apparatus or a Melt Temp melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith Laboratories, Knoxville, TN and Petrolite Corporation, Analytical Section. $^{1}$H NMR spectra were obtained with a Perkin-Elmer R-32 spectrometer (90 MHz). $^{31}$P spectra were obtained with a Jeol FX-60 spectrometer operating at 24.15 MHz. $^{13}$C NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) either on a Jeol FX-60 spectrometer operating at 15.04 MHz or Varian-XL-300 spectrometer[7] operating at 75.429 MHz.

The chemical shift (+$\delta$) values are downfield from $H_3PO_4$ (cap) for $^{31}P$ spectra and from $Me_4Si$ for $^1H$ and $^{13}C$ spectra.

*Di-t-butyl aryl phosphates* **3**. These were prepared as reported[2] for di-t-butyl phenyl phosphate **3a**.

*Di-t-butyl (4-methylphenyl) phosphate* **3c**. Starting with 40 mmol of 4-methylphenol, the yield of crude product was 8.5 g (71%). $^1H$ NMR ($CDCl_3$) 1.52 (s, 18H, $CH_3$), 2.32 (s, 3H, $CH_3$), 7.12 (s, 4H, Ar). $^{31}P$ NMR ($CDCl_3$) −15.4.

*Di-t-butyl (3-methylphenyl) phosphate* **3d**. Starting with 55 mmol of 3-methylphenol, the yield was 13.0 g (79%). $^1H$ NMR ($CDCl_3$) 1.50 (s, 18H, $CH_3$), 2.30 (s, 3H, $CH_3$), 6.70–7.30 (m, 4H, Ar). $^{31}P$ NMR ($CDCl_3/H_3PO_4$) −15.6.

*Di-t-butyl (2-hydroxyaryl)phosphonates* **5**. The rearrangement of di-t-butyl aryl phosphates to di-t-butyl(2-hydroxyarylphosphonates) was carried out as reported earlier.[2]

*Di-t-butyl (2-hydroxy-5-methylphenyl) phosphonate* **5c**. Starting with 10.2 g of **3c**, the yield of the crude product was 8.4 g (82%). $^1H$ NMR ($CDCl_3$) 1.46 (s, 18H, $CH_3$), 2.26 (s, 3H, $CH_3$), 6.68–7.30 (m, 3H, Ar). $^{31}P$ ($CDCl_3$) + 14.1.

*Di-t-butyl (2-hydroxy-4-methylphenyl) phosphonate* **5d**. Starting with 12.0 g of **3d**, the yield of **5d** was 6.5 g (54%), colorless needles, mp 83–84°C (from pet. ether, b.p. 35–60°C). $^1H$ NMR ($CDCl_3$) 1.45 (s, 18H, $CH_3$), 2.30 (s, 3H, $CH_3$), 6.60–6.80 (m, 2H, Ar), 7.10–7.38 (q, $J_{H-H} = 9$ Hz, $J_{P-C-C-H} =$ 14 Hz, 1H, Ar), 10.44 (s, 1H, OH). $^{13}C$ NMR ($CDCl_3$) 21.55 (s, $CH_3$), 30.14 (d, 4.00 Hz, $C(\underset{\smile}{C}H_3)_3$), 83.28 (d, 6.03 Hz, $\underset{\smile}{C}(CH_3)_3$, 111.37 (d, 189.33 Hz, $C_1$), 117.42 (d, 11.09 Hz, $C_3$), 120.25 (d, 14.10 Hz, $C_5$), 131.58 (d, 6.03 Hz, $C_6$), 144.82 (d, 3.01 Hz, $C_4$), 160.17 (d, 8 Hz, $C_2$). $^{31}P$ NMR ($CDCl_3$) + 14.3. *Analysis* calcd for $C_{15}H_{25}O_4P$: C, 60.00; H, 8.33; P, 10.33. Found: C, 60.22; H, 7.86; P, 10.33.

*(2-Hydroxyaryl) phosphonic Acids* **6.** These were prepared by the method reported earlier.[2]

*(2-Hydroxy-5-methylphenyl) phosphonic Acid* **6c**. Starting with 8.2 g of crude **5c**, the yield of **6c** was 3.3 g (64%) mp 144°C. $^1H$ NMR ($D_2O/Me_4Si$ cap.) 2.72 (s, 3H, $CH_3$), 7.20–7.45 (m, 1H, Ar), 7.64–8.02 (m, 2H, Ar). $^{13}C$ NMR ($D_2O/Me_4Si$ cap.) 20.52 ($CH_3$), 116.74 (d, 179.69 Hz, $C_1$), 117.13 (d, 11.72 Hz, $C_3$), 130.83 (d, 13.67 Hz, $C_5$), 133.37 (d, 7.81 Hz, $C_6$), 135.83 ($C_4$), 156.74 (d, 3.91 Hz, $C_2$). $^{31}P$ NMR ($D_2O$) + 16.07. *Analysis* calcd for $C_7H_9O_4P$: C, 44.68; H, 4.79; P, 16.49. Found: C, 44.14; H, 4.74; P, 16.46.

*(2-Hydroxy-4-methylphenyl) phosphonic acid* **6d**. Starting with 5.5 g of **5d**, the yield was 3.0 g (87%), mp 136–137°C. $^1H$ NMR ($D_2O/Me_4Si$ cap.) 2.74 (s, 3H, $CH_3$), 7.18–7.38 (m, 2H, Ar), 7.95 (dd, $J_{H-H} = 8$ Hz, $J_{P-C-C-H} = 14$ Hz, 1H, Ar). $^{13}C$ NMR ($D_2O/Me_4Si$ cap.) 21.82 ($CH_3$), 113.50 (d, 183.59 Hz, $C_1$), 117.59 (d, 9.77 Hz, $C_3$), 122.13 (d, 13.67 Hz, $C_5$), 133.50 (d, 7.81 Hz, $C_6$), 146.87 ($C_4$), 159.21 (d, 3.91 Hz, $C_2$). $^{31}P$ NMR ($D_2O$) + 16.53. *Analysis* calcd for $C_7H_9O_4P$: C, 44.68; H, 4.79; P, 16.49. Found: C, 44.70; H, 4.83; P, 16.29.

*Di-t-butyl 2-(di-t-butoxyphosphinyl)phenyl Phosphate* **8a**. To an ice-cooled solution of crude **5a** (10.87 g, 0.038 mole) in tetrahydrofuran (30 ml) was added carefully a slurry of sodium hydride (0.912 g, 0.038 mole) in tetrahydrofuran (30 ml). After the evolution of hydrogen has ceased, di-t-butyl phosphorochloridate (8.68 g, 0.038 mole) was added dropwise. The reaction mixture was then kept in a refrigerator for 72 h. It was next stirred at rt for 3 h. The solvent was removed on a rotary evaporator. Methylene chloride (100 ml) and water (50 ml) were added to the residue. After stirring for 30 min, the organic layer was separated, dried over anhydrous sodium sulfate to obtain a dark oil. It was dissolved in 4 ml of petroleum ether and refrigerated when **8a** separated out as a white crystalline solid. It was collected by filtration and washed with a small amount of petroleum ether. The yield was 9.20 g (51%) mp 103.5°C. *Analysis* calcd for $C_{22}H_{40}O_7P_2$: C, 55.23; H, 8.37; P, 12.97. Found: C, 54.91; H, 8.28; P, 12.99.

*Di-t-butyl 2-(di-t-butoxyphosphinyl)-5-methylphenyl Phosphate* **8c**. When the starting material was 8.5 g (0.0283 mole) of **5c**, the yield of **8c** was 8.0 g (58%), mp. 97°C. *Analysis* calcd for $C_{23}H_{42}O_7P_2$: C, 56.10; H, 8.54; P, 12.60. Found: C, 55.89; H, 8.05; P, 12.71.

*Tetra-t-butyl (2-hydroxy-1,3-phenylene)bis(phosphonate)* **10a**. To a solution of diisorpopylamine (2.02 g, 0.02 mole) in tetrahydrofuran cooled to −78°C was added n-butyllithium[8] (12.5 ml of a 1.6 M solution). The mixture was stirred for 30 min and then a solution of **8a** (4.78 g, 0.01 mole) in 15 ml THF was syringed into the reaction mixture. It was next stirred at −78°C for 1 h and then dry ice-acetone bath was removed. Stirring was continued for an additional 1.5 h. It was next poured over a mixture of 100 ml saturated aq. ammonium chloride and 150 ml methylene chloride. The organic layer was separated, dried over anhydrous sodium sulfate and solvent was removed on rotary evaporator. The crude product was recrystallized from petroleum ether. The yield was 3.00 g (63%) mp 103.5°C. *Analysis* calcd for $C_{22}H_{40}O_7P_2$: C, 55.23; H, 8.37; P, 12.97. Found: C, 55.18; H, 8.30; P, 12.95.

*Tetra-t-butyl (2-hydroxy-5-methyl-1,3-phenylene)bis(phosphonate)* **10c**. When the starting material was 4.92 g of **8c**, the yield of **10c** was 4.00 g (81%), mp 133–134°C. *Analysis* calcd for $C_{23}H_{42}O_7P_2$: C, 56.10; H, 8.54; P, 12.60. Found: C, 56.08; H, 8.62; P, 12.46.

*(2-Hydroxy-1,3-phenylene)bis(phosphonic acid)* **11a**. To a stirred solution of 1.95 g of **10a** in benzene was added 1.46 g trifluoroacetic acid. After about 15 min, a solid began to separate. After 24 h, the white solid was collected by filtration. The crude product was dissolved in ethanol, the solution was filtered and then ethanol was removed on rotary evaporator. Addition of methylene chloride to the residue gave **11a** as a white crystalline solid, 1.0 g (97%), mp 179–180°C. *Analysis* calcd for $C_6H_8O_7P_2$: C, 28.34; H, 3.15; P, 24.41. Found: C, 28.55; H, 3.28; P, 23.96.

*(2-Hydroxy-5-methyl-1,3-phenylene)bis(phosphonic acid)* **11c**. Starting with 2.0 g of **10c**, the yield of **11c** was 0.95 g (87%), mp 183–184°C. *Analysis* calcd for $C_7H_{10}O_7P_2$: C, 31.34; H, 3.73; P, 23.13. Found: C, 31.87; H, 3.79; P, 22.62.

## REFERENCES

1. B. Dhawan and D. Redmore, *J. Org. Chem.* **49,** 4018 (1984).
2. B. Dhawan and D. Redmore, *Synthetic Communication,* **15,** 411 (1985).
3. L. S. Melvin, *Tetrahedron Lett.* 3375 (1981).
4. B. Dhawan and D. Redmore, *J. Org. Chem.,* **51,** 179 (1986).
5. C. E. Griffin, R. B. Davidson and M. Gordon, *Tetrahedron,* 561 (1966).
6. J. I. Musher and E. J. Corey, *Tetrahedron,* 791 (1962).
7. We are grateful to Dr. C. D. Gutsche for $^{13}C$ spectra obtained on Varian XL-300 spectrometer.
8. Fisher certified tetrahydrofuran was used without any further drying. Excess *n*-butyl lithium was used which may not be necessary.