New synthetic approach to (*o*-hydroxyphenyl)methylphosphonic acid derivatives

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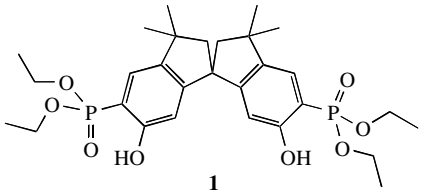
10.1070/MC2003v013n04ABEH001784

2,6-Dimethylphenols and 5,5′-dimethyl-6,6′-spirobiindanol react with diethylphosphite to give phosphates, which are easily transformed by LDA to (*o*-hydroxyphenyl)methylphosphonates.

(*o*-Hydroxyphenyl)methylphosphonic acids are compounds with significant binding properties towards heavy metals[1] and lanthanides.[2] These compounds can be prepared by reaction of benzyl halides with trialkyl phosphites according to the Michaelis–Arbuzov reaction.[3] For phenolic benzylphosphonic acids, especially with the phenolic OH in the *ortho*-position relative to the phosphonomethyl group, the direct reaction of *o*-hydroxybenzyl alcohols with trialkyl phosphites is also possible.[4,5]

Our interest in phosphonic acid derivatives led us to the synthesis of new building blocks bearing phosphonic groups,[6] one of which is spirobiindane biphosphonate unit **1**. This dissymetric molecule containing ancillary groups (phosphonic) shows flame-retarding properties for epoxy resins,[7] and, after the hydrolysis to a monoester, opens new frontiers in applications as a negatively charged receptor.[8,9]



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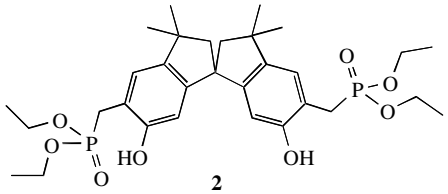


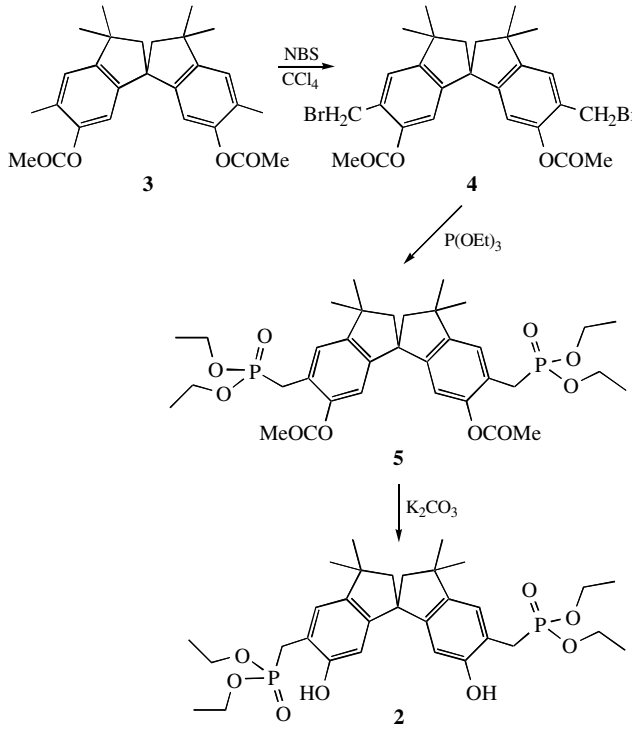
2

In search for novel building blocks to be incorporated into new types of molecular scaffolds, we have been attracted by compound **2**, where the phosphonic groups are attached to the benzylic methylenes of the spirobiindane frame.

Here, we report on a new and general one-pot procedure for the synthesis of (*o*-hydroxyphenyl)methylphosphonic acid derivatives using *ortho*-disubstituted methyl phenol and lithium diisopropylamide (LDA), with the idea of synthesising chiral bis-chelating phosphonates, which can include neutral guests and act as ligands for lanthanides. Furthermore, these molecules, after hydrolysis to the corresponding bis-monoesters, could become water-soluble receptors for positively charged molecules and thus act as potential resolving agents for antipods of biologically relevant molecules.

As an example, Scheme 1† demonstrates the most usual synthetic pathway for obtaining compoud **2**. The first step proceeds with a 60% yield, and the second one, with a 40% yield. Then, the hydrolysis of ester **5** affords compound **2** with only a 18% overall yield.

Therefore, considering our experience in the production of *ortho*-hydroxyaryl phosphonates[6] by the 1,3-phosporotropic rearrangement reaction performed on aryl phosphates and LDA at a low temperature, we decided to follow a more simple and direct way to compound **2**, *i.e.*, to use the LDA rearrangement for the preparation of (*o*-hydroxyphenyl)methylphosphonic acids. In order to optimise the new reaction, mesitol and 2,6-dimethylphenol were chosen as model compounds. The synthesis is conceptually based on the phosphorilation of the OH phenolic group, which yields the phosphate derivative; the use of lithium salts at low temperature, in case of bis(orthomethyl)-substituted phenols rearranges the phosphate to the benzylic phosphonate as reported in Scheme 2.‡



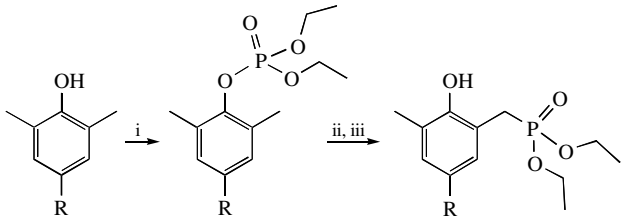
Scheme 1

The first step proceeds in almost quantitative yield; the second one, which represents the crucial step, occurs with a 60–70% yield depending on the starting phenols. We found that the yields of (*o*-hydroxyphenyl)methylphosphonic acid derivatives are little affected by the molar ratio LDA:phosphate. On going from a stoichiometric amount to a large excess of LDA, the best results were obtained when a molar ratio of 4:1 (LDA:phosphate) was used. In other words, the treatment of phosphate esters with an excess of lithium diisopropylamide

† Compound **3** was prepared according to the published procedure.[11]

5,5′-Dibromomethyl-6,6′-diacetoxy-3,3,3′,3′-tetramethyl-1,1′-spirobiindane **4**: 0.75 g (65%), mp 170–172 °C. ^{1}H NMR ($CDCl_3$) δ: 7.18 (s, 2H, spiroArH), 6.54 (s, 2H, spiroArH), 4.42 (dd, 4H, CH_2Br, J_{HH} 10 Hz), 2.29 (s, 6H, MeCO), 2.31 (dd, 4H, spiroCH_2, $^2J_{HH}$ 13 Hz), 1.4 (s, 6H, spiroMe), 1.37 (s, 6H, spiroMe). ^{13}C NMR ($CDCl_3$) δ: 169.06, 152.03, 150.18, 148.6, 128.44, 124.15, 118.76, 59.14, 57.54, 43.36, 31.52, 30.16, 28.48, 26.91, 20.29. FAB-MS, *m/z* (%): 579 (8) $[M + H]^+$, 601 (70) $[M + Na]^+$.

5,5′-Diethylphosphonomethyl-6,6′-diacetoxy-3,3,3′,3′-tetramethyl-1,1′-spirobiindane **5**: 0.44 g (40%). ^{1}H NMR ($CDCl_3$) δ: 7.15 (d, 2H, spiroArH, $^4J_{HP}$ 2.8 Hz), 6.53 (s, 2H, spiroArH), 4.03 (m, 8H, POCH_2Me), 3.09 (m, 4H, CH_2P), 2.28 (dd, 4H, spiroCH_2, $^2J_{HH}$ 13.3 Hz), 1.36 (s, 6H, spiroMe), 1.32 (s, 6H, spiroMe), 1.25 (t, 6H, POCH_2*Me*, $^3J_{HH}$ 7 Hz), 1.24 (t, 6H, POCH_2*Me*, $^3J_{HH}$ 7.2 Hz). FAB-MS, *m/z* (%): 693.72 (25) $[M + H]^+$, 715 (23) $[M + Na]^+$.



Scheme 2 *Reagents and conditions*: i, $HP(O)(OEt)_2/CCl_4$, NEt_3, 0 °C; ii, LDA/THF, –78 °C; iii, saturated NH_4Cl/H_2O.

generates the methyl anion, which undergoes migration of the phosphorus from oxygen to carbon. Although O → C migrations of phosphorus are not without precedent,[6,10] this new reaction represents the first example of a phosphate → phosphonate rearrangement involving the methyl group.

A comment on the selectivity of the reaction is necessary. In principle, when 2,6-dimethylphenol is employed as a substrate, if a double 1,3-sigmatropic rearrangement of the phosphate group is operating, one should expect that the compound containing the phosphonic group attached to the aromatic carbon in the *para*-position of the phenol must be formed. No evidence was found for the formation of such a derivative, indicating that a double sigmatropic rearrangement is not operating.

Then, using the synthetic procedure outlined in Scheme 2, compound **2** was easily synthesised starting from 5,5′-dimethyl-6,6′-spirobiindanol, which is readily converted into its diphosphate ester upon treatment with diethyl phosphite and CCl_4 in the presence of triethylamine, and then rearranged to crystalline product **2** by treatment of the diphosphate with a strong base (LDA). The possibility that the phosphonic group goes to the 7,7′-position of the spirobiindanol skeleton by 1,3-rearrangement is very low and impossible because of the high steric congestion of such aromatic carbon atoms.

Phosphorus, carbon and proton NMR data provided convincing evidence for the structure assigned. Diphosphate of compound **2** showed a single phosphorus resonance at δ –5.76 ppm, while the rearrangement product **2** showed a single phosphorus resonance at δ 30.22 ppm, which is also so far from the resonance δ 22.12 ppm of compound **1**, where the phosphorus atoms are directly attached to the aromatic carbons.

In summary, our new general synthetic procedure allows to produce *o*-hydroxyphenyl methyl phosphonic acids in a very convenient and easy way.

This study was supported by MURST.

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Received: 28th April 2003; Com. 03/2110

‡ *General procedure for the synthesis of* (o-*hydroxyphenyl)methylphosphonic acid diethyl esters* **2**, **6** and **7**. In a typical procedure, to a stirred mixture of bis(hydroxyphenyl) derivatives (0.05 mol) and diethyl phosphite (0.11 mol) in carbon tetrachloride (100 ml) cooled at 0 °C, triethylamine was added dropwise and the reaction temperature was maintained below 10 °C by external cooling. The mixture was stirred overnight at room temperature; then, the ammonium salt formed was filtered off and the organic solution was washed with 2 N sodium hydroxide and water and dried over anhydrous Na_2SO_4. The removal of the solvent in a vacuum left the bis(phosphate) precursor as a colourless oil, a part (0.01 mol) of which in a THF solution (50 ml) was added from a dropping funnel to a lithium diisopropylamide (LDA) (0.04 mol) solution in 100 ml of THF at –78 °C. After the addition was completed, the reaction mixture was stirred at –78 °C for 6 h; then, the reaction mixture was quenched with 200 ml of saturated aqueous ammonium chloride. The organic mass was extracted with diethyl ether and chloroform and dried over anhydrous Na_2SO_4; after evaporation of the solvents at reduced pressure, it was purified by column chromatography on silica gel using gradient elution with ethyl acetate in cyclohexane to give pure dialkyl-(*o*-hydroxyaryl)methylphosphonate.

5,5′-Diethylphosphonomethyl-6,6′-dihydroxy-3,3,3′,3′-tetramethyl-1,1′-spirobiindane **2**: 3.65 g (60%), mp > 220 °C. ^{1}H NMR ($CDCl_3$) δ: 6.82 (d, 2H, spiroArH, $^4J_{HP}$ 2 Hz), 6.38 (s, 2H, spiroArH), 4.03 (m, 8H, POCH_2Me), 3.21 (m, 4H, CH_2P), 2.25 (dd, 4H, spiroCH_2, $^2J_{HH}$ 13 Hz), 1.34 (s, 6H, spiroMe), 1.28 (s, 6H, spiroMe), 1.22 (m, 12H, POCH$_2$*Me*). ^{13}C NMR ($CDCl_3$) δ: 154.8 (d, J_{CP} 5 Hz), 151.6, 144.95, 124.27 (d, J_{CP} 7.75 Hz), 117.62 (d, J_{CP} 9.1 Hz), 114.53, 63.23 (d, J_{CP} 6.75 Hz), 62.84 (d, J_{CP} 6.87 Hz), 59.58, 42.91, 31.82, 30.4, 30.18 (d, $^1J_{CP}$ 136.5 Hz), 16.25. ^{31}P NMR ($CDCl_3$) δ: 30.218. FAB-MS, *m/z*: 609.2 (100%) $[M + H]^+$.

6-Methyl-2-phosphonomethylphenol **6**: 1.68 g (65%). ^{1}H NMR ($CDCl_3$) δ: 7.05 (d, 1H, ArH, $^3J_{HH}$ 7.5 Hz), 6.88 (d, 1H, ArH, $^3J_{HH}$ 7.5 Hz), 6.76 (t, 1H, ArH, $^3J_{HH}$ 7.5 Hz), 4.02 (m, 4H, POCH_2Me), 3.15 (d, 2H, ArCH_2P, $^2J_{HP}$ 21 Hz), 2.27 (s, 3H, Ar*Me*), 1.24 (t, 6H, POCH$_2$*Me*, $^3J_{HH}$ 7 Hz). ^{13}C NMR ($CDCl_3$) δ: 153.69 (d, J_{HP} 4.7 Hz), 130.19 (d, J_{HP} 3.4 Hz), 128.79 (d, J_{HP} 7.6 Hz), 128.05 (d, J_{HP} 3.4 Hz), 120.52 (d, J_{HP} 2.1 Hz), 118.32 (d, J_{HP} 9.4 Hz), 62.96 (d, J_{HP} 7.3 Hz), 30.12 (d, $^1J_{HP}$ 136.9 Hz), 16.30, 16.16 (d, J_{HP} 6.0 Hz). ^{31}P NMR ($CDCl_3$) δ: 30.204. FAB-MS, *m/z* (%): 259.2 (99) $[M + H]^+$.

4,6-Dimethyl-2-phosphonomethylphenol **7**: 1.91 g (70%). ^{1}H NMR ($CDCl_3$) δ: 8.1 (s, 1H, ArO*H*), 6.87 (s, 1H, Ar*H*), 6.69 (s, 1H, Ar*H*), 4.05 (m, 4H, POCH_2Me), 3.11 (d, 2H, ArCH_2P, $^2J_{HP}$ 21 Hz), 2.24 (s, 3H, Ar*Me*), 2.21 (s, 3H, Ar*Me*), 1.25 (t, 6H, POCH$_2$*Me*, $^3J_{HH}$ 7 Hz). ^{13}C NMR ($CDCl_3$) δ: 151.39 (d, J_{HP} 4.5 Hz), 130.92 (d, J_{HP} 3.62 Hz), 129.677, 129.17 (d, J_{HP} 8.25 Hz), 127.91 (d, J_{HP} 3.25 Hz), 118.13 (d, J_{HP} 9.12 Hz), 62.97 (d, J_{HP} 6.75 Hz), 30.24 (d, $^1J_{HP}$ 136.5 Hz), 20.33, 16.26 (m). ^{31}P NMR ($CDCl_3$) δ: 30.393. FAB-MS, *m/z* (%): 273.2 (99) $[M + H]^+$.