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New bicyclic phosphonates of unsymmetrical structure

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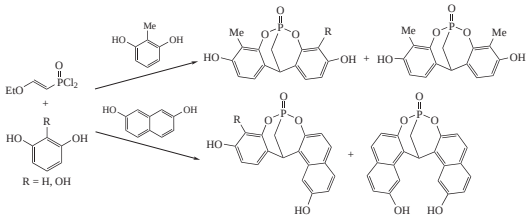
New unsymmetrical bicyclic cage phosphonates have been obtained by refluxing two different phenols with (2-ethoxyvinyl)phosphonic dichloride in toluene in the presence of trifluoroacetic acid.

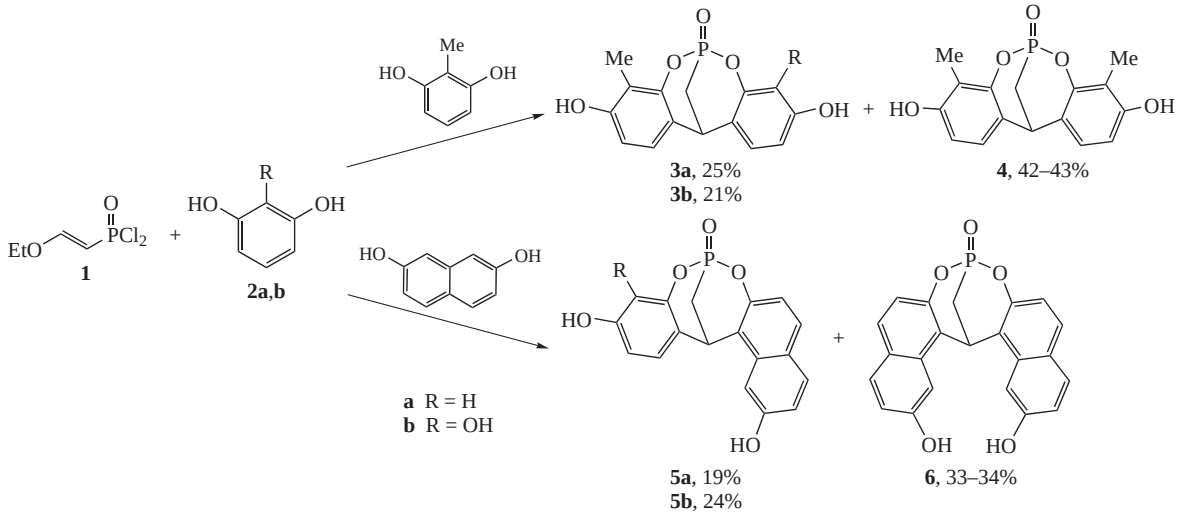


Cage compounds are of interest since the rigid framework provides strict localization of the substituents, which gives a clear knowledge of their spatial arrangement.[1,2] Organophosphorus cage compounds with endocyclic phosphorus–carbon bonds possess unusual reactivity and physical properties and look promising from fundamental and practical viewpoints.[3–7] Such compounds can be employed as complexing agents, ligands in metal-complex catalysis, organocatalysts,[8] and multifunctional drugs possessing antiviral,[9] anticancer,[10] and other types of activities.[11,12]

We have previously obtained symmetrical cage phosphonates with all endocyclic bonds by the reaction of (2-ethoxyvinyl)-phosphonic dichloride **1** with resorcinol and some other active phenols.[13–15] It seemed challenging to extend the scope of this reaction to access unsymmetrical structures. Herein, new unsymmetrical bicyclic phosphonates were prepared by multicomponent reaction of compound **1** with two different phenols. In fact, dissolution of equimolar amounts of resorcinol **2a** or pyrogallol **2b** with 2-methylresorcinol in boiled toluene in the presence of trifluoroacetic acid followed by the dropwise addition of phosphonic dichloride **1** led to novel unsymmetrical phosphonates **3a**,**b** (Scheme 1). Note that symmetrical bicyclic phosphonate **4** was also formed, while formation of symmetrical phosphonates based on resorcinol or pyrogallol was not observed. The reaction of resorcinol **2a** or pyrogallol **2b** with naphthalene-2,7-diol proceeded in the same way giving unsymmetrical phosphonates **5a**,**b**, along with symmetrical one **6**. All physicochemical data for compounds **4**[13] and **6**[16] coincide with our previous data.

Structures of phosphonates **3a**,**b** and **5a**,**b** were elucidated from NMR (^{1}H, ^{31}P, and ^{13}C) and IR spectroscopy, mass spectrometry (MALDI) and elemental analysis. Structures of compounds **5a** and **5b** were also confirmed using 1D/2D correlation NMR experiments (for details, see Online Supplementary Materials).

In the case of compound **5a**, individual spin systems were resolved in the course of ^{1}H–^{1}H COSY experiment, while carbon atoms corresponding to these protons were found by ^{1}H–^{13}C HSQC experiment. The fragment P–CH_2–CH is clearly resolved in ^{1}H spectra due to the intrinsic range of proton resonance, as well as due to the presence of coupling constants J_{HH} and J_{PH} ($^3J_{HH}$ 3.9 Hz, $^2J_{PH}$ 16.1 Hz, and $^3J_{HH}$ 3.9 Hz, $^2J_{PH}$ 34.6 Hz in the case of



Scheme 1 *Reagents and conditions*: CF_3COOH, toluene, reflux.

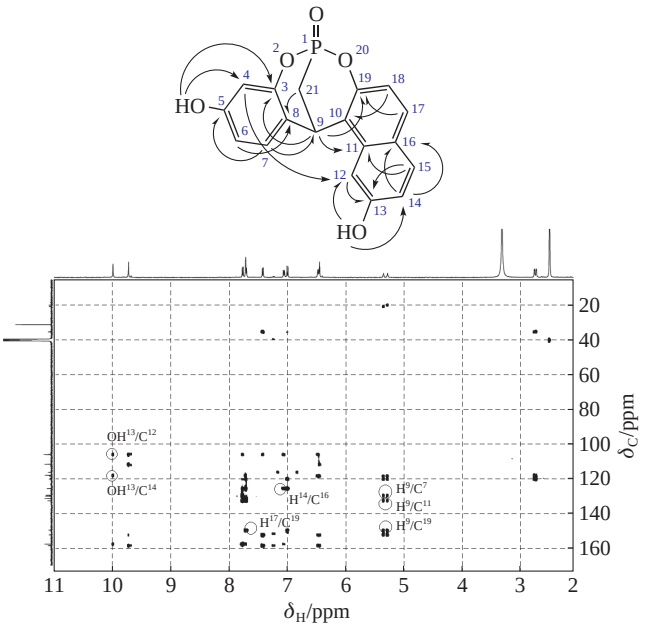
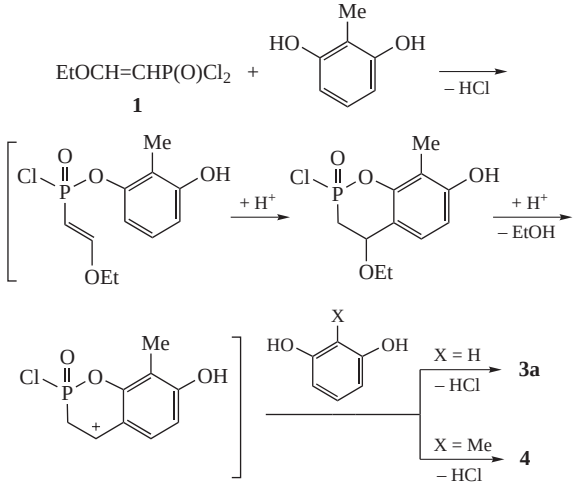


Figure 1 $^{1}H–^{13}C$ HMBC spectrum of compound **5a** and its structure with key NMR correlations.

H^{21} and H^{9}, respectively). Then, the $^{1}H–^{13}C$ HMBC correlations along the chain from H^{9} to H^{3}, from H^{6} to C^{8}, and from OH^{5} to C^{4} and C^{3} were established. The presence of the constant $^{3}J_{CP}$ 8.4 Hz allowed as to distinguish $C^{4}H$ group from $C^{12}H$ one. Analogously, the structure of naphthol fragment and its correlation with P–CH_2–CH fragment were determined based on a series of $^{1}H–^{13}C$ HMBC correlations between H^{9}/C^{19}, H^{9}/C^{11}, H^{17}/C^{19}, H^{15}/C^{13}, OH^{13}/C^{12}, and H^{14}/C^{16} (Figure 1). The structure was additionally confirmed by the observed carbon–phosphorus coupling constants. The spatial structure was confirmed on the basis of NOE experiments; the effects H^{9}/H^{7} and H^{9}/H^{12} gave an unambiguous proof of their spatial proximity.



Scheme 2

A plausible mechanism for formation of unsymmetrical bicyclic phosphonates is outlined on the example of phosphonic dichloride **1**, 2-methylresorcinol and resorcinol as the reactants (Scheme 2). Initially, phosphorylation of one hydroxyl group of 2-methylresorcinol occurs with the formation of phosphonochloridoate. The further cascade reactions, intermolecular cyclization, elimination of EtOH and subsequent attack by the second molecule of 2-methylresorcinol or resorcinol at carbocation centre, lead to the final bicyclic phosphonates (see Scheme 2).

In summary, the first representatives of unsymmetrical bicyclic phosphonates were synthesized by the one-pot reaction of (2-ethoxyvinyl)phosphonic dichloride with two different phenols.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.032.

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