



## Long range phosphorus–phosphorus coupling constants in bis(phosphorylhydroxymethyl)benzene derivatives

Marek Doscoczek, Barbara Malinowska\*, Piotr Młynarz, Barbara Lejczak, Paweł Kafarski

Department of Bioorganic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

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### ABSTRACT

Long range spin–spin couplings found between two phosphorus atoms are quite rare phenomena. A new example of such a coupling through seven bonds is described for 1-[(diethoxyphosphoryl)butyryloxymethyl]-4-[(diethoxyphosphoryl)hydroxymethyl]benzene and 1,4-bis[phosphorylhydroxymethyl]benzene and through six bonds for tetraethyl phenylene-1,3-(bishydroxymethylphosphonate). Coupling constants in this system are also well predicted by theoretical studies.

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### 1. Introduction

Nuclear Magnetic Resonance (NMR) is a useful technique for the characterization of the three dimensional structure of chemical and biological systems ranging from small molecules<sup>1,2</sup> to complex biological polymers such as nucleic acids and proteins. Coupling constants are one of the most important parameters here since they supply information on the geometry and dynamics of individual moieties in a molecule, leading to the determination of its conformation.<sup>3</sup> In phosphorus organic chemistry, the NMR technique is based on the magnetic properties of phosphorus nuclei.<sup>1,3</sup>

Coupling constants across more than four bonds have been named ‘Long Range Couplings’ (LR). In phosphorus compounds the LR between <sup>31</sup>P and <sup>1</sup>H (<sup>n</sup>J<sub>PH</sub>) and <sup>31</sup>P and <sup>13</sup>C atoms (<sup>n</sup>J<sub>PC</sub>) have been studied by many researchers.<sup>4</sup> Khaleeluddin, Scott, Gordon, and Griffin reported such couplings via five to seven bonds.<sup>5–7</sup> The origin of LR lies in that fragments of the molecule are rich in π-electrons (aromatic rings, double or triple bonds). Another type of coupling interaction between phosphorus atoms involves spin–spin interactions across hydrogen bonds (<sup>nh</sup>J<sub>XY</sub>, where *n* is the number of bonds between coupled atoms (X,Y) and couplings via hydrogen bond denoted as *h*), for example, in phosphazene sponges (<sup>4h</sup>J<sub>PP</sub> P=NH<sup>+</sup>...N=P),<sup>8,9</sup> N–H...O=P, and O–H...O=P (<sup>3h</sup>J<sub>PN</sub>, <sup>2h</sup>J<sub>PH</sub>) in *Desulfovibrio vulgaris* flavodoxin,<sup>10–14</sup> C–H...O=P (<sup>3h</sup>J<sub>PC</sub>, <sup>2h</sup>J<sub>PH</sub>) in model phosphate-guanine, and bishydroxybisphosphonates.<sup>15,16</sup> LR couplings may also occur via ‘through-space’ interactions (<sup>ts</sup>J<sub>XY</sub>), for example, in tetraphosphine ferrocenyl derivatives, as a result of overlapping of lone pairs of orbitals in two close elements.<sup>17</sup> Representative examples of structures exemplifying each of these types of couplings are collected in Table 1.

Long range couplings between two phosphorus atoms are quite rarely observed (Table 1). In many cases the mechanism of spin–spin transfer interactions between atoms is a cumulative effect of several factors, which are impossible to define precisely.

In this Letter, we report a new class of phosphonates represented by 1-[(diethoxyphosphoryl)butyryloxymethyl-oxymethyl]-4-[(diethoxyphosphoryl)hydroxymethyl]benzene (**A**), 1,4-bis[phosphorylhydroxymethyl]benzene (**B**), and 1,3-bis[(diethoxyphosphoryl)hydroxymethyl]benzene (**C**) (Scheme 1),<sup>30</sup> in which such long range coupling constants have been detected.

Compound **A** was obtained as a single enantiomer by biocatalysis (*RR*), whereas compound **B** was a single diastereomer (*RR,SS*), while compound **C** was a mixture (*RR/SS* and *meso*). Consequently in the <sup>31</sup>P NMR spectra of **B** the phosphorus signal is a singlet and in **C**, it is a doublet. Here we present an experimental and theoretical examination of long range coupling phenomenon in these compounds.

### 2. Registration of J<sub>PP</sub> couplings

Interpretation of the <sup>31</sup>P{<sup>1</sup>H} NMR spectra of the studied compounds indicated the presence of intramolecular couplings. Determination of coupling constants may not always be straightforward, especially taking into consideration the fact that the studied compounds may appear as diastereoisomers and signals may overlap. Therefore, the correlation of several NMR techniques was required.

Experimental investigations to determine <sup>n</sup>J<sub>PP</sub> couplings were carried out according to standard procedures applying 1D and 2D NMR techniques. There are a few known NMR methods delineating P–P interactions.

The simplest method of determining <sup>n</sup>J<sub>PP</sub> couplings is interpretation of the multiplet structure of <sup>31</sup>P{<sup>1</sup>H} NMR spectra of compounds with different chemical shifts for each phosphorus atom belonging to the same molecule, as is the case in compound **A**.

\* Corresponding author. Tel.: +48 071 320 46 14; fax: +48 071 328 40 64.  
E-mail address: [barbara.malinowska@pwr.wroc.pl](mailto:barbara.malinowska@pwr.wroc.pl) (B. Malinowska).

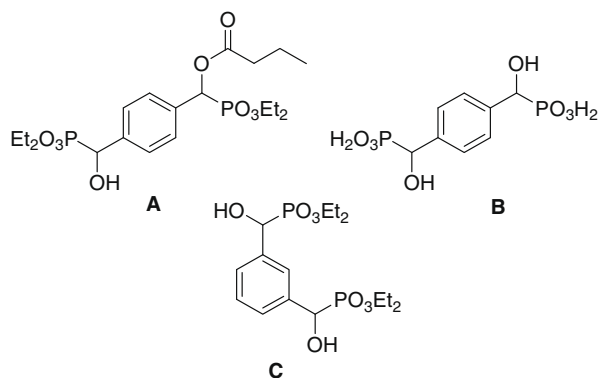
**Table 1**  
Selected examples of compounds with long range coupling constants between phosphorus atoms

Compound	Coupling constants $J_{PP}$ (Hz)	Ref.
	2,6- $^9J_{PP}$ = 4.09 2,3- $^5J_{PP}$ = 5.35 2,7- $^8J_{PP}$ = 1.48 1,5- $^7J_{PP}$ = 1.47 1,6- $^8J_{PP}$ = 1.88	18
	<i>ortho</i> $^5J_{PP}$ = 9.05 <i>meta</i> $^6J_{PP}$ = 3.16 <i>para</i> $^7J_{PP}$ = 7.87	18
	For the unprotonated form $J_{PP}$ = 107.0 For the protonated form $J_{PP}$ = 221.6	19
	$^4J_{PP}$ = 1.6	8,20
	$^{15}J_{PP}$ = 60	17
	$^{10}J_{PP}$ = 8.0	21
	$^6J_{PP}$ detected	22
	$^5J_{PP}$ = 1.7	23
	$^6J_{PP}$ = 27.3	24
a)	a) $^7J_{PP}$ = 30.3	
b)	b) $^8J_{PP}$ = 30.6	25

(continued on next page)

Table 1 (continued)

Compound	Coupling constants $J_{PP}$ (Hz)	Ref.
	In dendrimers $3.8 < {}^7J_{PP} < 4.5$	26
	For phosphite inositol derivatives ${}^5J_{PP} = 2.93\text{--}6.7$	27,28
	${}^5J_{PP} = 3.0$	29

Scheme 1. Structures of compounds **A** (*RR*), **B** (*RR/SS*), and **C** (*RR/SS/meso*).

An additional verification of these values was obtained by recording the NMR spectra at enhanced resolution (Fig. 1).

The confirmation of the presence of LR coupling and verification of the value of the coupling constant came from application of the selective homodecoupling technique. The selective decoupling of phosphorus nuclei resulted in signal simplification for each spin-spin-coupled phosphorus atom. This method requires a triple-tuned NMR probe. An unequivocal method of confirmation of the presence of coupling between homological nuclei is the application of two dimensional  ${}^{31}\text{P}\{^1\text{H}\}\text{--}{}^{31}\text{P}\{^1\text{H}\}$  spectra ( ${}^{31}\text{P}$  COSY spectra) (Fig. 2). Signals appearing on the cross diagonal axis correspond to the observed couplings. This technique gives reliable results only in cases when the value of the  ${}^nJ_{PP}$  coupling exceeds several Hz as in the case of compound **A**.

The last, although quite rare, method relies on recording one-dimensional  ${}^{31}\text{P}\{^1\text{H}\}$  NMR spectra using a large number of scans ( $n_s < 1\text{ k}$ ) or using a sufficient concentration of the compound to allow couplings between phosphorus and the  ${}^{13}\text{C}$  carbon atom to be observed.<sup>31</sup> Typical values of the  ${}^2J_{PC}$  coupling determined for compounds with direct carbon-to-phosphorus bonds are around 160 Hz. For molecules with two phosphorus atoms, it is also possible to observe  ${}^1J_{P\text{--}^{13}\text{C}}$  coupling (157, 162 Hz found in the case of compound **A**) besides coupling between phosphorus atoms  ${}^nJ_{PP}$ . This effect allows differentiation of phosphorus atoms bonded with various isotopes of carbon atoms, due to the existence of  ${}^{12}\text{C}\text{--}{}^{31}\text{P}$ ,

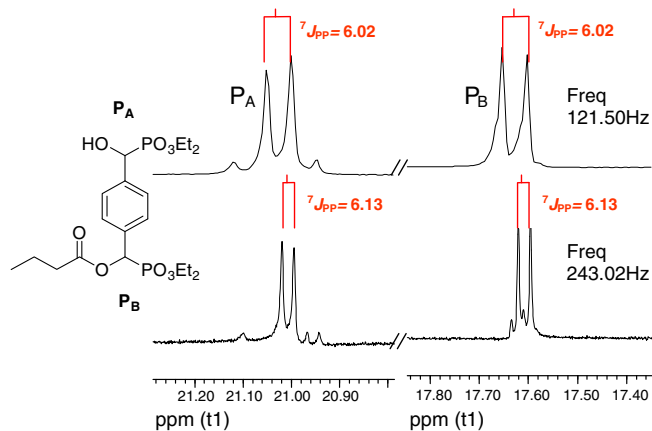


Figure 1. The  ${}^{31}\text{P}\{^1\text{H}\}$  NMR spectra of compound **A** recorded at frequencies of 121.50 MHz (Bruker DRX300) and 243.02 MHz (Bruker AMX600). Slight disparities between the obtained coupling constants result from inaccuracy of the measurements.

${}^{13}\text{C}\text{--}{}^{31}\text{P}$  systems. This isotope effect typically equals a few ppbs,<sup>31</sup> but is sufficient to record  ${}^nJ_{PP}$  couplings. This type of experiment is simple and convenient, and especially favorable when measuring couplings in symmetric molecules such as compounds **B** (Fig. 3) and **C**. The same procedure was successfully applied to calculate the couplings transferred across hydrogen bonds ( ${}^4nJ_{PP}$ ) in imino-phosphorane-substituted proton sponges.<sup>20</sup>

Application of the same method based on isotope effects with oxygen atoms did not lead to expected results. Oxygen has three stable isotopes,  ${}^{16}\text{O}$  (abundance 99.760%),  ${}^{17}\text{O}$  (0.037%), and  ${}^{18}\text{O}$  (0.201%) of which only  ${}^{17}\text{O}$  has a nuclear spin (5/2) with a moderately strong quadrupole moment resulting in fairly short T2 relaxation times and hence broad resonances.<sup>32</sup>

The expected values of the coupling constants  ${}^1J_{P\text{--}^{16}\text{O}}$  and  ${}^1J_{P\text{--}^{17}\text{O}}$  should be 253 and 176 Hz (as found by calculations using B3LYP/6-31G(*d,p*)/B3LYP/IGLO II). Unfortunately, the signals originating from coupling with the oxygen atom were not found even in the  ${}^{31}\text{P}\{^1\text{H}\}$  NMR spectra recorded with a long measurement time. We were able to observe only singular signals (Fig. 3 and Supplementary data) derived from the  ${}^{31}\text{P}\text{--}{}^{18}\text{O}$  and  ${}^{31}\text{P}\text{--}{}^{16}\text{O}$  isotope effects.

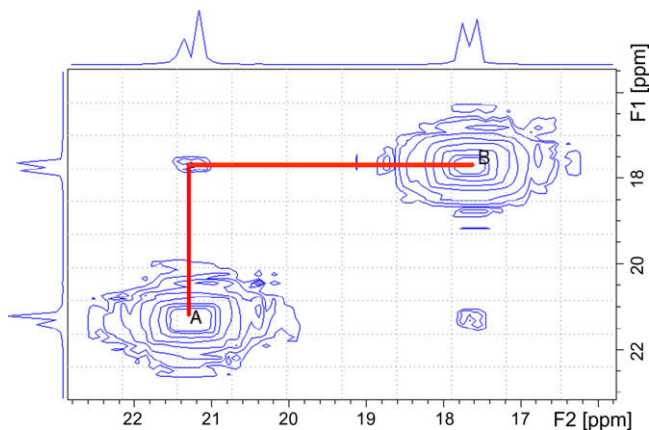


Figure 2. The  $^{31}\text{P}\{^1\text{H}\}$ - $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum of compound A.

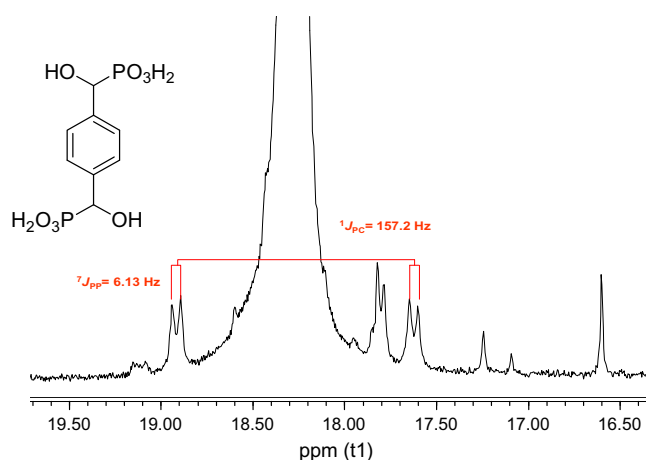


Figure 3. The  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum of compound B measured at a concentration of 30 mg/0.6 mL DMSO- $d_6$  with indicated selected couplings of  $^7J_{\text{PP}}$  and  $^1J_{\text{PC}}$ .

Additionally, we recorded long range couplings of the  $^nJ_{\text{CP}}$  type (for compound A:  $^6J_{\text{CP}} = 0.34$  Hz, for compound B:  $^6J_{\text{CP}} = 1.03$  Hz in  $\text{CDCl}_3$  and  $^6J_{\text{CP}} = 1.18$  Hz in DMSO, as well as  $^7J_{\text{PC}} = 2.07$  Hz in DMSO for compound C). Experimental details are in the Supplementary data.

### 3. Long range $^nJ_{\text{PP}}$ coupling—theoretical investigations

The calculations were performed using the GAUSSIAN 03 program<sup>33</sup> (see Supplementary data). Long range couplings between phosphorus atoms, transferred via aromatic rings as  $\text{P}-\text{CHX}-\text{C}_{\text{Ar}}-\text{C}_{\text{Ar}}-\text{C}_{\text{Ar}}-\text{CH}(\text{X})-\text{P}$ , were registered for the first time by Ernst in 1977 who also postulated that coupled phosphorus atoms cannot be located in the same plane as the benzene ring.<sup>18</sup> Similar couplings were also found in phosphonic dendrimers.<sup>26</sup>

The LR coupling observed in this work for compound A was additionally confirmed by theoretical methods using the simplified structure of compound A2 as a model (Fig. 4). Conformers with the lowest energy levels were found by calculation of the potential energy depending on the  $\text{P}-\text{C}-\text{C}-\text{C}$ ,  $\text{P}'-\text{C}-\text{C}-\text{C}$  (D1 and D2) angles.

The potential energy surface (PES) showed that this compound has flat energetic minima. The barrier of rotation versus the  $\text{P}-\text{C}-\text{C}-\text{C}$  angle is about 2–3 kcal/mol. The  $^7J_{\text{PP}}$  coupling constants were calculated from two cross-sections of the PES graph: for the energetic minimum at  $\text{D2} = -65.0$  and the energetic maximum at  $\text{D2} = -5.0$  degrees (Fig. 5).

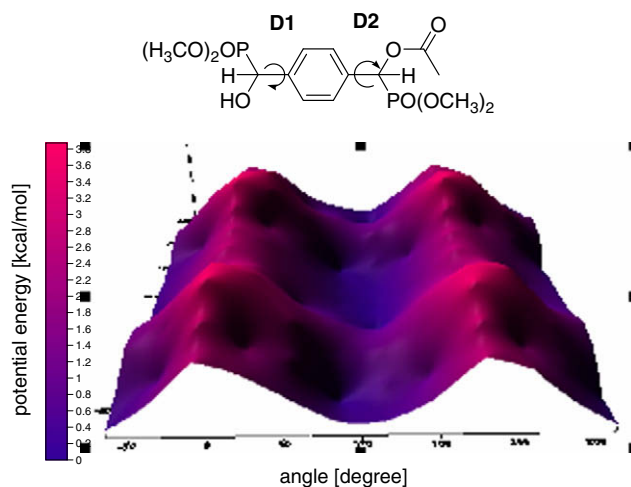


Figure 4. Chemical formula of model compound A2 and the dependence of potential energy (kcal/mol) on D1 and D2 angles. The torsion angle was varied by  $30^\circ$  in the B3LYP//6-31G(d) procedure.

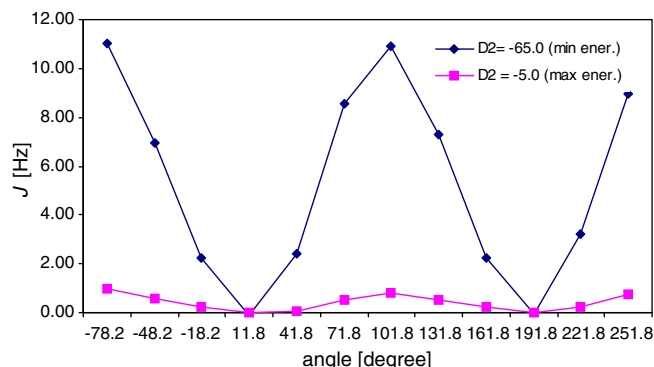
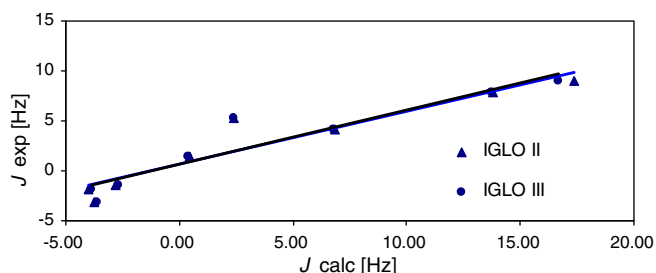


Figure 5. The dependence of coupling constant values  $^7J_{\text{PP}}$  [Hz] on the D1 angle [degrees] for two cross-sections of the potential energy graph  $\text{D2} = -65.0$  and  $-5.0$  (from Fig. 4) as calculated using B3LYP//IGLOII.

The  $^7J_{\text{PP}}$  coupling constant for structures characterized by the  $\text{D2} = -65.0^\circ$  angle varies from 0 to 12 Hz, whereas the potential energy found for this structure varies from 0 to 1.3 kcal/mol. Due to the relatively insignificant energy differences, free rotation of the phosphonic moiety is possible, which is confirmed by calculation of the Boltzmann distribution for 24 analyzed conformers, for which the coupling constants were calculated. Conformers characterized by the  $\text{D2} = -65.0$  and  $\text{D1} = -18.0$  angles, which energy is near to the transition state of rotation of phosphonic moiety, constitute 2.1% of population.

The values of the coupling constants for the second cross-section ( $\text{D2} = -5.0$ ) are in the narrow range of 0–1 Hz and dependent on the values of the D1 angle, but the energy in the same cross-section of the PES plane oscillates between 2.50 and 3.87 kcal/mol. Thus, participation of these conformers is insignificant to the whole population. The highest value of  $^7J_{\text{PP}}$  was observed for angles  $\text{D2} = -65.0$  with  $\text{D1} = -78.2$  and  $\text{D1} = 101.8$ . The values of calculated angles result in location of both phosphonic moieties on the same or opposite sides of phenyl ring, respectively. Comparison of the orbitals of the conformers with maximal and minimal values of coupling constants suggests that the considered geometry of the molecule determines the orbital shape and interactions of the nuclear spins. Theoretical calculations of long range coupling con-



**Figure 6.** Regression analysis of experimentally measured versus calculated coupling constants using eight compounds for the calibration, as measured by Ernst.<sup>19</sup> A sign of values of coupling was matched on the basis of theoretical calculations. IGLO II ( $y = 0.5346x + 0.6444$ ,  $R^2 = 0.8888$ ), IGLO III ( $y = 0.5494x + 0.6204$ ,  $R^2 = 0.8901$ ).

stants for particular conformers in their global minimum give values with some errors in calculation (Fig. 6).

The experimental value of  ${}^7J_{PP}$  for compound **A** is 6.13 Hz, whereas the calculated  ${}^7J_{PP}$  values for a model acetyl derivative in its energetic minimum was found to be 3.22 Hz and 6.02 Hz, and thus with respect to the weighted average of conformers is 6.02 Hz (Fig. 6). The last value corresponds well with the experimental one. The estimates of the remaining coupling constants ( $J_{PH}$ ,  $J_{PC}$ ) calculated using this method are also in good accord with the experimental data (see Supplementary data). It was also possible to observe the dependence of coupling constants on conformation by comparison of the coupling constants found in the NMR spectra recorded in polar and non-polar solvents. Thus, the value of  ${}^7J_{PP} = 6.13$  Hz recorded in chloroform (non-polar solvent) is different from the value ( ${}^7J_{PP} = 6.68$  Hz) determined in DMSO (polar solvent) for compound **A**, using the same experimental conditions.

The values of the coupling constants are strongly dependent on the location of the coupled substituents on the phenyl ring.<sup>19</sup> Ernst ordered the values of coupling constants between phosphorus atoms in 1,*n*-phenylene-bis(methyl-phosphonate) esters as *ortho* > *para* > *meta* ( ${}^5J_{PP} = 9.05 > {}^7J_{PP} = 7.87 > {}^6J_{PP} = 3.16$  Hz for experimental values and calculated values as  ${}^5J_{PP} = 17.36 > {}^7J_{PP} = 13.78 > {}^6J_{PP} = -3.78$  Hz). He states that ‘This geometry is most favorable for  $\sigma$ – $\pi$  exchange polarization which transmits the coupling information to the aromatic *n*-system and it is responsible for the large magnitude of the observed  $J_{PP}$ ’. Measured values for compound **C** ( ${}^7J_{PP} = 6.13$  Hz) and its isomers *ortho* ( ${}^5J_{PP} = 4.30$  Hz)<sup>17</sup> and *meta* ( ${}^6J_{PP} = 2.78$  Hz) align the other way (see Supplementary data). This phenomenon may be explained by the different conformation of –CHOH–P(O)(OEt)<sub>2</sub> compared to the –CH<sub>2</sub>P(O)(OEt)<sub>2</sub> moieties, especially in terms of intermolecular hydrogen bond formation.

Progress in the development of NMR techniques allows long range couplings to be measured more precisely. For compounds **A**, **B**, and **C** possessing two phosphorus atoms, it is possible to measure these couplings with application of both 1D and 2D spectra. In addition, the isotope effect in the  ${}^{31}\text{P}\{^1\text{H}\}$  NMR spectra and observed  ${}^{13}\text{C}$ – ${}^{31}\text{P}$  couplings appear to support the observations made using simple 1D or 2D techniques. The  $J_{PP}$  coupling constant value depends on the spatial arrangement of the coupling moieties in the molecule. Analysis of these data indicated that in the case of compound **A** both CH(OH)–PO(OEt)<sub>2</sub> groups do not lie in the aromatic ring plane.

Theoretical methods give an advantage in interpretation and understanding of the obtained results (as the dependence of coupling constants on angles in the investigated structures). Methods taking into consideration the representative population of conformers give results in good accordance with the experimental measurements.

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## Supplementary data

Supplementary data (experimental and computational details, all NMR spectra for compounds **A**, **B**, **C** and other derivatives, orbital shapes, their conformations are presented. Comparison of measured and calculated values of selected coupling  $J_{PC}$ ,  $J_{PH}$ ,  $J_{PO}$  are given) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.107.

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