Heteroatom Chemistry
Volume 12, Number 6, 2001

The Synthesis of Six-Membered P-Heterocycles with Sterically Demanding Substituent on the Phosphorus Atom

György Keglevich,[1] Henrietta Forintos,[1] Melinda Sipos,[1] András Dobó,[2] Krisztina Ludányi,[2] Károly Vékey,[2] Antal Tungler,[3] and László Tőke[4]

[1]*Department of Organic Chemical Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*

[2]*Hungarian Academy of Sciences, Chemical Research Center, 1525 Budapest, Hungary*

[3]*Department of Chemical Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*

[4]*Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*

Received 6 March 2001; revised 30 March 2001

ABSTRACT: *The ring enlargement of 1-(2,4,6-trialkylphenyl)2,5-dihydro-1H-phosphole oxides (**1**) via 6,6-dichloro-3-phosphabicyclo[3.1.0]hexanes (**2**) afforded the double-bond isomers of 1,2-dihydrophosphinine oxides (**3**). Catalytic hydrogenation of the isomeric 1-(di-tert-butyltolyl)-1,2-dihydrophosphinine oxides (**3a**) gave the diastereomers of phosphinane oxide (**4**), while that of the 1-(tri-isopropylphenyl) isomers (**5**) led predominantly to phospholane oxides (**6**) formed by ring contraction.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:528–533, 2001

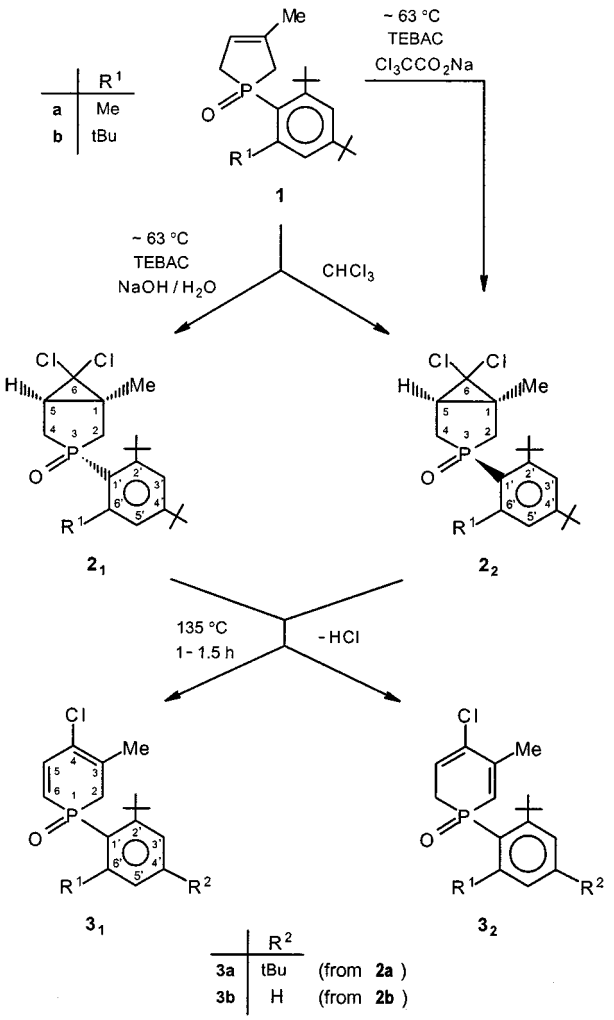
INTRODUCTION

The introduction of sterically demanding substituents on the heteroatom of organophosphorus compounds may affect the physical and the chemical properties of the substrate to a large extent [1]. A bulky P-substituent, such as the 2,4,6-trialkylphenyl group, may have an impact on the geometry around the P-pyramid [2–4]. On the other hand, the reactivity of the P=O moiety is also influenced by the presence of the trialkyphenyl substituent [5,6]. In this article, we describe the synthesis of some 6-membered heterocycles containing a di-*tert*-butyltolyl or a tri-*tert*-butylphenyl group on the phosphorus atom.

RESULTS AND DISCUSSION

We wished to utilize the dichlorocarbene ring enlargement method elaborated by us for the synthesis of 6- and 7-membered P-heterocycles [7–9]. Using this method, dichlorocarbene was added onto the double bond of 2,5-dihydro-1*H*-phosphole oxides **1a,b** to form 3-phosphabicyclo[3.1.0]hexane oxides **2a,b** (Scheme 1). It was observed that the choice of the source of the dichlorocarbene had an impact on the outcome of the dichlorocyclopropanation of dihydrophosphole oxide **1a**. The use of dichlorocarbene generated from chloroform by

Correspondence to: György Keglevich.
Contract Grant Sponsor: Ministry of Higher Education (FKFP).
Contract Grant Number: 363/1999.
Contract Grant Sponsor: Hungarian Scientific Research Fund (OTKA).
Contract Grant Number: T029039.



SCHEME 1

aqueous sodium hydroxide under phase transfer catalytic (PTC) conditions led to two phosphabicyclohexane diastereomers (**2_1a** and **2_2a**); isomer **2_1a** predominated over form **2_2a**. At the same time, using sodium trichloroacetate as the precursor for dichlorocarbene, only isomer **2_2a** was found to have been formed. This was also the case during the synthesis of the tri-*tert*-butylphenyl derivative (**2_2b**). All isomers (**2_1a**, **2_2a**, and **2_2b**) were obtained in a pure form by column chromatography. The stereostructures of isomers **2_1** and **2_2** were assigned on the basis of stereospecific $^3J_{PC}$ couplings. The $^3J_{PC}$ coupling of 5.4 Hz detected on C-6 suggested structure **2_1a**, while the coupling constants of 11.8 and 20.3 Hz confirmed a geometry represented by form **2_2** [10,11]. The phosphabicyclohexanes (**2a,b**) were characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectroscopy. The ^{13}C NMR spectral parameters are listed in Table 1. Elemental composition of the new products (**2a,b**) was supported by HRMS.

In the second step of the ring enlargement, the cyclopropane ring of adducts **2a,b** was opened thermally. The 1,2-dihydrophosphinine oxides (**3a,b**) so formed were obtained as a mixture of two double-bond isomers (**3_1a,b** and **3_2a,b**) (Scheme 1). To our surprise, the *tert*-butyl group in the para position of the aryl ring was also split during the thermolysis of tri-*tert*-butyl derivative **2_2b**. The dihydrophosphinine oxides (**3a,b**) were characterised by ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectroscopic data. The ^{13}C NMR spectral parameters of dihydrophosphinine oxides **3_1a,b** can be found in Table 2. The elemental composition of products **3a,b** was confirmed by high-resolution mass spectrometry (HRMS). The δ_P chemical shifts for the double-bond isomers (**3_1** and **3_2**) of aryl-dihydrophosphinine oxides **3a** and **3b** fall in the expected region of 16–19 ppm. It is noteworthy that, while the 1-(2,4,6-triisopropylphenyl)-4-chloro-3-methyl-1,2-dihydrophosphinine 1-oxide described earlier displayed a δ_P of 19.1, the 5-methyl isomer exhibited a δ_P of 45.9 that is almost 30 ppm downfield of the expected region [11]. Semiempirical calculations suggested that the unique shift is the consequence of an electron distribution due to a special geometry [11].

Disregarding structure identification, there was no need to separate phosphabicyclohexane isomers **2_1** and **2_2**. The thermolysis could be efficiently run on isomeric mixtures. Thermal examinations of adducts **2a,b** suggested 135°C to be the optimum temperature of the thermolyses. At a higher temperature, extensive decomposition of the starting phosphabicyclohexanes (**2a,b**) and the dihydrophosphinine oxides (**3a,b**) was observed to take place. Obviously, the polymerization of the dihydrophosphinine oxide (**3**) also decreased the yield.

We wished to extend the sphere of trialkylphenyl P-heterocycles to phosphinane oxides. For this, the mixture containing the double-bond isomers of dihydrophosphinine oxide **3a** was subjected to catalytic hydrogenation. As expected, the reduction furnished phosphinane oxide **4** as a mixture of diastereomers (**4_1** and **4_2**) (Scheme 2). Product **4** was characterized by ^{31}P and ^{13}C NMR, as well as mass spectroscopic data. The spectral parameters are consistent with those reported earlier for other phosphinane oxides [12,13]. The δ_P of ca. 38 clearly refers to the saturated six-membered heteroring with a phosphine oxide function [12,13]. Interestingly, catalytic hydrogenation of the isomeric mixture of the earlier described triisopropylphenyldihydrophosphinine oxide (**5**) gave predominantly three dimethyl-phospholane oxides (**6_1**, **6_2** and **6_3**); the expected phosphinane-isomers (**7_1** and **7_2**) formed only a minor component of the reaction

TABLE 1 ^{13}C NMR Data for the Isomers (**2_1** and **2_2**) of Phosphabicyclohexane Oxides **2a,b** in $CDCl_3$ Solution

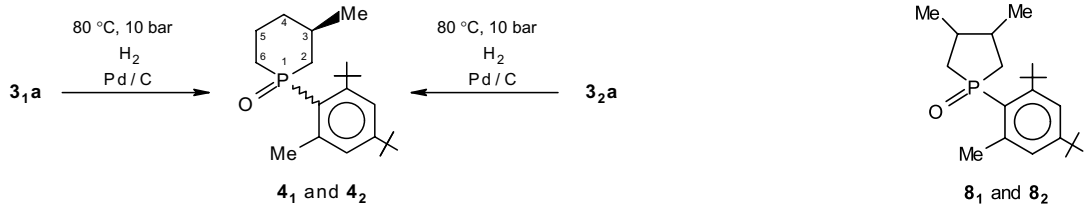
	δ (J_{PC} in Hz)																
Compound	C_1	C_2	C_4	C_5	C_6	C_1-CH_3	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	$C_{2'}-C(CH_3)_3$	$C_{4'}-C(CH_3)_3$	$C_{2'}-CMe_3$	$C_{4'}-CMe_3$	$C_{6'}-CH_3$
2_1a	37.2 (9.2)	40.1 (63.0)	35.6 (66.6)	38.6 (7.2)	71.7 (5.4)	22.3 (8.3)	130.1 (85.0)	158.0 (7.2)	124.3[a] (11.0)	153.3 (2.4)	124.5[a] (10.8)	139.7 (13.0)	31.1[b]	33.2[b]	34.8[c]	38.6[c]	25.1 (4.8)
2_2a	35.9 (9.2)	42.4 (68.9)	36.2 (69.0)	36.9 (7.5)	71.9 (11.8)	21.6 (6.0)	128.4 (92.9)	155.0 (9.0)	123.9[d] (11.6)	152.9 (2.2)	125.2[d] (10.7)	142.1 (9.8)	30.9[e]	33.5[e]	34.5[f]	37.9[f]	24.2 (5.0)
2_2b	35.2 (12.8)	40.7 (65.1)	39.2 (72.3)	33.6 (10.8)	73.7 (20.3)	20.3 (5.1)	124.7 (91.8)	158.9 (8.1)	123.4[g]	152.6 (3.2)			33.4	31.1	33.7	34.8	

[a–f] May be reversed.
[g] Broad signal.

TABLE 2 ^{13}C NMR Data for Dihydrophosphinine Oxides **3_1a,b** in $CDCl_3$ Solution

	δ (J_{PC} in Hz)																
Compound	C_2	C_3	C_4	C_5	C_6	C_3-CH_3	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	$C_{2'}-C(CH_3)_3$	$C_{4'}-C(CH_3)_3$	$C_{2'}-CMe_3$	$C_{4'}-CMe_3$	$C_{6'}-CH_3$
3_1a	38.2 (69.0)	124.0 (20.3)	131.1 (9.3)	139.0	122.9 (94.0)	23.6[a] (9.5)	126.3 (100.6)	158.6 (7.6)	123.6[b] (11.2)	153.6	124.0[b] (10.9)	141.0 (13.0)	30.9[c]	33.3[c]	34.7[d]	38.1[d]	25.0[a] (6.3)
3_1b	36.9 (70.7)	124.1 (19.6)	131.0 (8.9)	144.2	120.0 (93.3)	23.6 (8.5)	[e]	151.6 (12.0)	124.8 (10.8)	126.7			31.5		35.2		

[a–d] May be reversed.
[e] Not resolved.



SCHEME 2

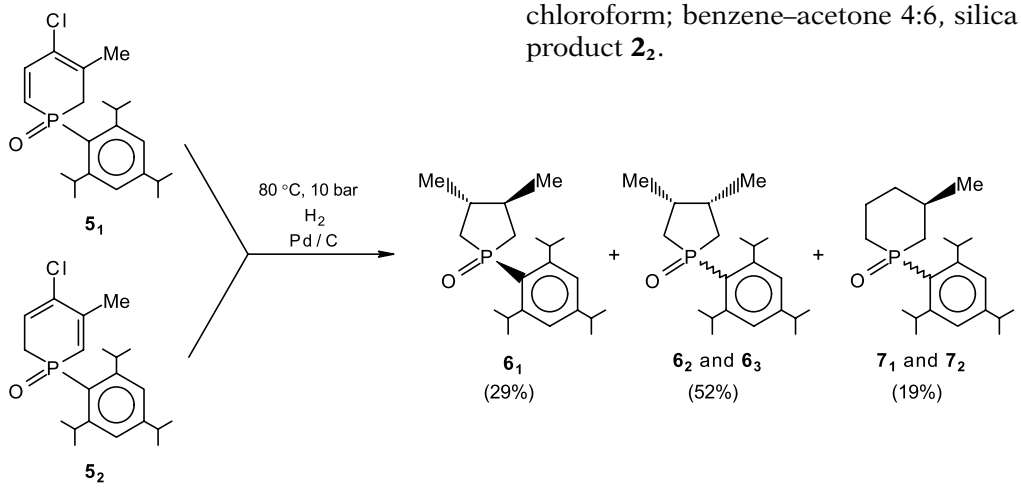
mixture (Scheme 3). Among the phospholane oxides, $\mathbf{6_1}$ is racemic, while $\mathbf{6_2}$ and $\mathbf{6_3}$ are symmetrical. The ^{31}P and ^{13}C NMR spectral parameters of isomers $\mathbf{6_1}$, $\mathbf{6_2}$, and $\mathbf{6_3}$ were identical with those of authentic samples prepared by the hydrogenation of 1-(2,4,6-triisopropylphenyl)-3,4-dimethyl-2,5-dihydro-1H-phosphole oxide [6]. The δ_P values of 52.7, 57.8, and 60.9 obtained for $\mathbf{6_1}$, $\mathbf{6_2}$, and $\mathbf{6_3}$, respectively, fall well in the range that is characteristic of phospholane oxides. Products $\mathbf{7_1}$ and $\mathbf{7_2}$ were characterized by ^{31}P and ^{13}C NMR, as well as mass spectroscopical data. It is noteworthy that under the conditions of the catalytic hydrogenation (80°C and 10 bar), a ring contraction took place. We thought that the hydrochloric acid formed during the reduction might also promote the ring transformation. The result of a hydrogenation carried out in the presence of one equivalent of triethylamine, however, excluded this possibility; moreover, the product composition was shifted in favor of the dimethyl-phospholane oxides (95% vs. 5%). During the catalytic hydrogenation of di-*tert*-butyltolyldihydrophosphinine oxide **3a**, only traces of the corresponding dimethylphospholane oxides ($\mathbf{8_1}$ with δ_P 50.3 and $\mathbf{8_2}$ with δ_P 54.2) could be detected. In the present stage of the work, it is not clear why only in the case of triisopropylphenyl substituent was a significant ring contraction observed. The electron-releasing ability of the P-substituent is probably responsible for the ring contraction that has never been observed.

In the next stage of our work, the P-aryl-heterocycles introduced will serve as suitable starting materials in a study focused on the reactivity of trialkylphenyl derivatives.

EXPERIMENTAL

General Procedure for the Preparation of Phosphabicyclohexanes $\mathbf{2_2}$**a,b** *by the Dichlorocyclopropanation of Dihydrophosphole Oxides* **1a,b** *Using Sodium Trichloroacetate*

A mixture of 5.0 mmol of dihydrophosphole **1**, 0.12 g (0.53 mmol) of TEBAC, and 23.2 g (0.125 mol) of sodium trichloroacetate in 50 mL of chloroform was stirred at reflux for 7 days. The contents of the flask were then filtered, and the solvent of the filtrate evaporated. The residual oil was purified by repeated column chromatography (chloroform; 2% methanol in chloroform; benzene–acetone 4:6, silica gel) to give product $\mathbf{2_2}$.



SCHEME 3

Compound **2_2a**: Yield 32%; δ_P ($CDCl_3$) 80.7; δ_C, Table 1; δ_H 1.27 (s, 9H, CMe_3), 1.51 (s, 9H, CMe_3), 1.68 (s, 3H, C_3–Me), 2.67 (s, 3H, C_6–Me); MS, *m/z* (rel. int.) 400 (M^+, 7), 385 (4), 365 (100), 249 (47); HRMS, M^+_{found} = 400.1515, $C_{21}H_{31}Cl_2OP$ requires 400.1490 for the ^{35}Cl isotopes.

Compound **2_2b**: Yield 41%; δ_P ($CDCl_3$) 80.5; δ_C, Table 1; δ_H 1.29 (s, 9H, C_4–CMe_3), 1.47 (s, 3H, C_3–Me), 1.51 (s, 18H, C_2–CMe_3); MS, *m/z* (rel. int.) 442 (M^+, 7), 407 (14), 385 (100), 291 (34); HRMS, M^+_{found} = 442.1975, $C_{24}H_{37}Cl_2OP$ requires 442.1959 for the ^{35}Cl isotopes.

Synthesis of Phosphabicyclohexane **2_1a** *by the Dichlorocyclopropanation of Dihydrophosphole Oxide* **1a** *Using $CHCl_3$–NaOH/H_2O under PTC*

To the solution of 1.0 g (3.15 mmol) of dihydrophosphole **1** and 0.15 g (0.66 mmol) of TEBAC in 40 mL of chloroform was added dropwise 6.0 g (0.15 mol) of sodium hydroxide in 9 mL of water. The mixture was stirred with heating for 4 hours. After filtration and separation, the organic phase was made up to its original volume, and 0.15 g (0.66 mmol) of TEBAC was added. The reaction mixture was treated with a second portion of aqueous sodium hydroxide as previously. The workup procedure afforded a crude mixture containing 89% of **2_1a** and 11% of **2_2a**. Separation by column chromatography afforded 0.56 g (44%) of isomer **2_1a**. δ_P ($CDCl_3$) 82.9; δ_C, Table 1; δ_H 1.31 (s, 9H, CMe_3), 1.57 (s, 9H, CMe_3), 1.66 (s, 3H, C_3–Me), 2.47 (s, 3H, C_6–Me); MS, *m/z* (rel. int.) 400 (M^+, 6), 385 (4), 365 (100), 249 (31); HRMS, M^+_{found} = 400.1531, $C_{21}H_{31}Cl_2OP$ requires 400.1490 for the ^{35}Cl isotopes.

*General Procedure for the Preparation of the Double-Bond Isomers (***3_1** *and* **3_2***) of dihydrophosphinine oxides* **3a,b**

A 1.5 mmol sample of adduct **2** (either as pure isomer **2_1** or **2_2**, or as an isomeric mixture) was heated in a vial at 135°C until the evolution of hydrochloric acid ceased. The crude product was purified by repeated column chromatography (as previously) to furnish product **3** as the mixture of **3_1** and **3_2** isomers in a purity of 95–97%.

Compounds **3_1a** and **3_2a**: Reaction time 1.5 hours; yield 31%; δ_P 18.9 (79%) and 17.3 (21%); δ_C, Table 2; δ_H 1.32 (s, 9H, CMe_3), 1.66 (s, 9H, CMe_3), 2.11 (s, 3H, Me), 2.28 (s, 3H, Me), 6.31 (dd, $J_1 = J_2 = 12.7$, 1H, C_6–H), 6.72 (dd, $J_1 = 12.7$, $J_2 = 35.3$, 1H, C_5–H); MS, *m/z* (rel. int.) 364 (M^+, 94), 349 (13), 329 (100), 249 (6); HRMS, M^+_{found} = 364.1762, $C_{21}H_{30}ClOP$ requires 364.1723 for the ^{35}Cl isotope.

Compounds **3_1b** and **3_2b**: Reaction time 1 hours; yield 34%; δ_P 17.1 (77%) and 16.2 (23%); δ_C, Table 2; δ_H 1.31 (s, 18H, CMe_3), 2.06 (s, 3H, Me), 6.20 (dd, $J_1 = J_2 = 12.6$, 1H, C_6–H), 6.88 (dd, $J_1 = 12.7$, $J_2 = 34.3$, 1H, C_5–H); HRMS, M^+_{found} = 350.1598, $C_{20}H_{28}ClOP$ requires 350.1566 for the ^{35}Cl isotope.

General Procedure for the Catalytic Hydrogenation of the Double Bond Isomers of Dihydrophosphinimine Oxides **3a** *and* **5**

To the mixture of 1.20 mmol of the dihydrophosphinine oxide (**3a** or **5**) in 35 mL of methanol was added 0.2 g of 5% palladium on carbon, and the suspension was then hydrogenated at 10 bar and 80°C until 3 equivalents of hydrogen were absorbed. The mixture was filtered, the solvent was evaporated, and the residue were purified by column chromatography (silica gel, 3% methanol in chloroform) to give **4_1** and **4_2** (*experiment 1*) or the mixture of **6_1**, **6_2**, **6_3**, **7_1**, and **7_2** (*experiment 2*).

Experiment 1. Yield: 36%; ^{31}P NMR ($CDCl_3$) δ 38.6 (66%) and 37.1 (34%); fast atom bombardment mass spectrometry (FABMS); 335 $(M+H)^+$; $(M+H)^+_{found}$ = 335.2447, $C_{21}H_{36}OP$ requires 335.2504; ^{13}C NMR ($CDCl_3$) for isomer **4_1**: δ 21.8 ($J = 5.4$, C_5), 22.2 ($J = 7.8$, C_3–Me), 23.2 (C_6–Me), 28.9 ($J = 65.1$, C_6), 30.5 ($J = 5.4$, C_3), 30.9 (C_2–C(CH_3)$_3$), 33.4 (C_4–C(CH_3)$_3$), 34.6 ($J = 5.3$, C_4), 34.6 (C_2–CMe_3), 38.4 (C_4–CMe_3), 39.9 ($J = 63.1$, C_2), 123.9 ($J = 9.7$, $C^*_{3'}$), 124.3 (J = 9.2, $C^*_{5'}$), 139.3 ($J = 14.3$, $C_{6'}$), 152.6 ($C_{4'}$), 158.6 ($J = 7.0$, $C_{2'}$). (*,may be reversed.)

Experiment 2. To collect enough material, the hydrogenation was repeated. The combined mixture containing **6_1** (29%), **6_2** (38%), **6_3** (14%), **7_1** (14%) and **7_2** (5%) was refined by repeated column chromatography (as described previously) to afford a fraction containing mainly dimethylphospholane oxides **6_1** (δ_P 52.7, δ_P lit. [6] 52.9), **6_2** (δ_P 57.8, δ_P lit. [6] 57.9) and **6_3** (δ_P 60.9, δ_P lit. [6] 61.0), as well as another fraction consisting of the diastereomers of phosphinane oxide **7**.

Yield of **7_1** and **7_2**: 8%; ^{31}P NMR ($CDCl_3$) δ 38.6 (74%) and 37.4 (26%); FABMS, 335 $(M+H)^+$; ^{13}C NMR ($CDCl_3$) for isomer **7_1**: δ 21.8 ($J = 6.6$, C_5), 23.7 (C_4–CH(CH_3)$_2$), 25.0 ($J = 14.9$, C_3–Me), 25.2 (C_2–CH(CH_3)$_2$), 29.3 (C_4–$CHMe_2$), 30.2 (C_2–$CHMe_2$), 30.6 ($J = 65.3$, C_6), 34.2 (C_3), 35.1 ($J = 5.0$, C_4), 40.0 ($J = 62.7$, C_2), 123.1 ($J = 11.6$, $C_{3'}$), 124.3 ($J = 89.8$, $C_{1'}$), 152.0 ($C_{4'}$), 153.9 ($J = 12.0$, $C_{2'}$).

REFERENCES

[1] Yoshifuji, M. Main Group Chem News 1998, 6, 20.
[2] Quin, L. D.; Keglevich, Gy.; Ionkin, A. S.; Kalgutkar, R.; Szalontai, G. J Org Chem 1996, 61, 7801.
[3] Keglevich, Gy.; Quin, L. D.; Böcskei, Zs.; Keserű, Gy. M.; Kalgutkar, R.; Lahti, P. M. J Organomet Chem 1997, 532, 109.
[4] Keglevich, Gy.; Böcskei, Zs.; Keserű, Gy. M.; Újszászy, K.; Quin, L. D. J Am Chem Soc 1997, 119, 5095.
[5] Keglevich, Gy.; Forintos, H.; Szöllosy, Á.; Tőke, L. Chem Commun 1999, 1423.
[6] Keglevich, Gy.; Forintos, H.; Keserű, Gy. M.; Hegedűs, L.; Tőke, L. Tetrahedron 2000, 56, 4823.
[7] Keglevich, Gy. Synthesis 1993, 931.
[8] Keglevich, Gy.; Petneházy, I.; Miklós, P.; Almásy, A.; Toth, G.; Tőke, L.; Quin, L. D. J Org Chem 1987, 52, 3983.
[9] Keglevich, Gy.; Androsits, B.; Tőke, L. J Org Chem 1988, 53, 4106.
[10] Keglevich, Gy.; Kovács, A.; Tőke, L. Acta Chim Hung 1994, 131, 513.
[11] Keglevich, Gy.; Keseru, Gy. M.; Forintos, H.; Szöllösy, Á.; Ludányi, K.; Tőke, L. J Chem Soc Perkin Trans 1 1999, 1801.
[12] Keglevich, Gy.; Kovács, A.; Újszászy, K.; Tungler, A.; Tóth, G.; Tőke L. Phosphorus Sulfur 1992, 70, 219.
[13] Keglevich, Gy.; Tungler, A.; Novák, T.; Tőke, L. J Chem Res 1996, 528.