Synthesis of novel carborane-containing terminal alkynes*

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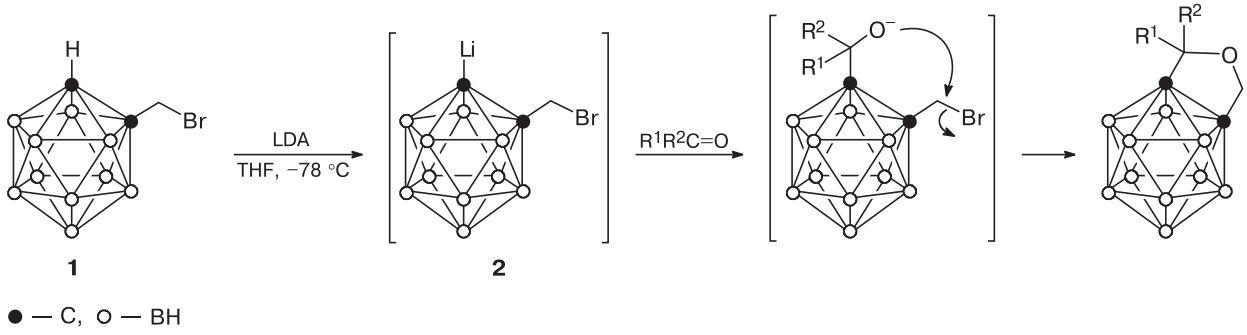
Lithiation of 1-bromomethyl-*o*-carborane with lithium diisopropylamide (LDA) in THF results in the *in situ* formation of 1-lithio-2-bromomethyl-*o*-carborane, the reaction of which with 3-trimethylsilylprop-2-ynal gives 2-(2-trimethylsilylethynyl)-3,4-(*o*-carborano)-2,5-dihydrofuran. Subsequent base-catalyzed desilylation furnishes new terminal alkynes of *closo*- and *nido*-carborane series.

Key words: carboranes, terminal acetylenes, X-ray diffraction.

Terminal acetylenes play an important role in organic synthesis. In particular, the copper-catalyzed [3+2] cycloaddition of azides to alkynes[1] and the Sonogashira cross-coupling reaction[2] make it possible to synthesize substances which are used as materials for nonlinear optics and as medicaments. Discovered more than fifty years ago, carboranes also find a variety of applications.[3,4] Their conjugates with biologically active molecules are used as agents for boron-neutron capture therapy (BNCT) of cancer, radionuclide and IR markers for the diagnosis of cancer, antiviral agents.[5] Terminal alkynes based on polyhedral carboranes can serve as promising synthons for the preparation of such conjugates.

Terminal alkynes based on polyhedral boron hydrides are described mainly for *o*-, *m*-, and *p*-carboranes. Their C-alkynyl derivatives were synthesized by the reaction of their C-lithium or C-copper derivatives with 1-bromo-2-trimethylsilylacetylene with subsequent removal of the silyl protection.[6,7]. The disadvantage of this approach is the low stability and explosion hazard of 1-bromo-2-trimethylsilylacetylene. *B*-Alkynyl derivatives of *o*-, *m*-, and *p*-carboranes turned out to be the most available: they can be prepared by cross-coupling from B-I-derivatives of carboranes and terminal acetylenic Grignard reagents[8] or by the Sonogashira reaction.[9] Similar alkynylated carboranes were used to synthesize new dendrimers[10] and fluorescent nanoparticles.[11] Synthesis of bioconjugates based on carborane terminal alkynes is represented by only a few examples. There is a report[12] on the derivative of 5-ethynyl-2′-deoxyuridine with *o*-carborane synthesized by the Sonogashira reaction from 5-iodo-2′-deoxyuridine and 1-(but-3-ynyl)-2-methyl-*o*-carborane. Conjugates with cholesterols[9] were obtained in our laboratory in collaboration with colleagues from Moscow State University. Recently, the Sonogashira reaction was used to obtain conjugates with 2′-deoxyuridines,[13] deoxyadenosines,[14,15] and ara binoadenosine[16] from 2-ethynyl-*p*-carborane and halogenated nucleosides. From B-alkynyl derivatives of *o*-, *m*-, and *p*-carboranes, the *p*-carborane derivatives are the compounds which found wide application, however,

Scheme 1



* Dedicated to Academician of the Russian Academy of Sciences I. P. Beletskaya.

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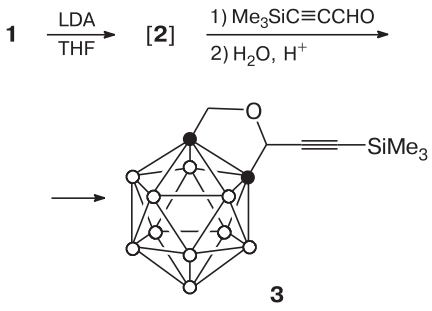
p-carborane itself and its derivatives are incommensur ably expensive compared to *o*-carborane. Therefore, the development of simple methods for the synthesis of new terminal alkynes based on relatively inexpensive *o*-carborane is a very relevant problem.

1-Bromomethyl-*o*-carborane (**1**) is one of the most readily available functionally substituted *o*-carboranes.[17] Earlier, we have proposed a method for its modification by metallation with lithium diisopropylamide (LDA) at −78 °C in THF with the *in situ* formation of 1-lithio-2-bromomethyl-*o*-carborane (**2**).[18] The reaction of this intermediate with carbonyl compounds leads to cyclic dihydrofurans (Scheme 1), which are the products of intramolecular cyclization of intermediate alkoxides. This approach turned out to be an efficient and universal tool and was successfully used for the synthesis of carborane-containing phthalocyanines.[19] In the present work, we present the synthesis of new terminal acetylenes based on *o*-carborane, using the approach described above.

Results and Discussion

To solve this problem, we suggested to carry out the reaction of 1-lithio-2-bromomethyl-*o*-carborane (**2**) obtained *in situ* with acetylenic aldehydes. However, it turned out that the reaction of compound **2** with propiolaldehyde yields only resinification products, which is most likely due to the low stability and tendency to spontaneous polymerization of propiolaldehyde under the action of bases.[20] At the same time, the reaction of derivative **2** with 3-trimethylsilylprop-2-ynal led to the expected new tetrahydrofuran product **3** with an acetylene group (Scheme 2).

Scheme 2



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The structure of the new compound **3** was proved from its NMR spectra and confirmed by X-ray diffraction results (Fig. 1). According to the X-ray diffraction data, compound **3** crystallizes in a centrosymmetric space group ($P2_1/n$), *i.e.*, is a racemate of two enantiomers with the chiral carbon atom C(4). The principal geometric characteristics of molecule **3** correspond to those expected from the analysis of similar structures deposited with the Cambridge Structural Database. For example, the bond lengths C(1)—C(2), C(1)—C(3), C(2)—C(4), C(4)—C(5), and C(5)—C(6) are 1.617(2), 1.514(2), 1.531(2), 1.464(2), and 1.200(2) Å, respectively. The tetrahydrofuran ring is in the flattened envelope conformation with the maximum deviation from the mean square plane for the atom O(1) (0.048(2) Å). Note that the matrix of the atomic displacement parameters is strongly anisotropic for the atom O(1): the maximum value of the matrix is 0.0764 Å^2 and the minimum value is 0.0158 Å^2. This indicates a possible disordering of the atom characteristic of five-membered rings. Unfortunately, the quality of the experimental data did not allow us to localize such a superposition. The anisotropy of the thermal ellipsoid of the oxygen atom indicates the absence of strong intermolecular interactions with this atom. This is confirmed by the analysis of the crystal packing of compound **3**: the shortened are only the contacts between the methylene group of the tetrahydrofuran ring and the alkyne fragment (taking into account the normalized C—H bond lengths, the distance H(3A)...C(5) is 2.789 Å, the angle C(3)—H(3A)...C(5) is equal to 161.3°). Such contacts combine the molecules of two enantiomers into centrosymmetric dimers (see Fig. 2) and can be described as the CH...π-interactions. It is noteworthy that the isotropic parameters of atomic displacements for the hydrogen atoms of the methylene group differ: for the atom H(3A) this parameter is much higher (0.044 Å^2 compared to 0.029 Å^2 for H(3B)). Apparently, the formation of a non-directional CH...π-interaction by the atom H(3A) leads to an increase in the amplitude of its displacements.

We studied the possibility of removing the trimethylsilyl protecting group from compound **3** without deboration of the carborane core to the *nido*-cluster. It was found that the target terminal acetylene **4** can be obtained in a low (28%) yield only by treating silane **3** with tetrabutylammonium fluoride trihydrate at −78 °C (Scheme 3).

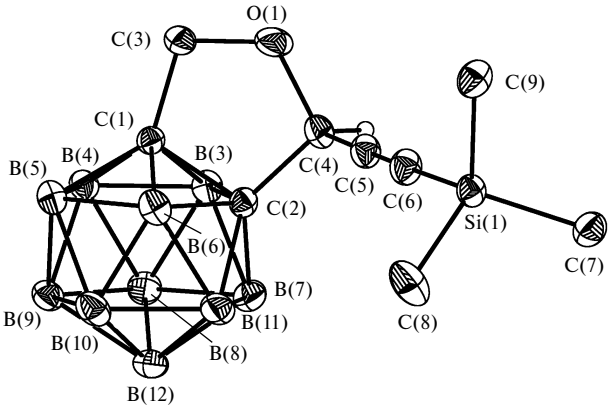


Fig. 1. General view of molecule **3** in crystal according to the X-ray diffraction results. Nonhydrogen atoms are represented by probability ellipsoids of atomic displacements ($p = 0.5$). Hydrogen atoms are omitted, except the hydrogen atom at the optically active atom C(4).

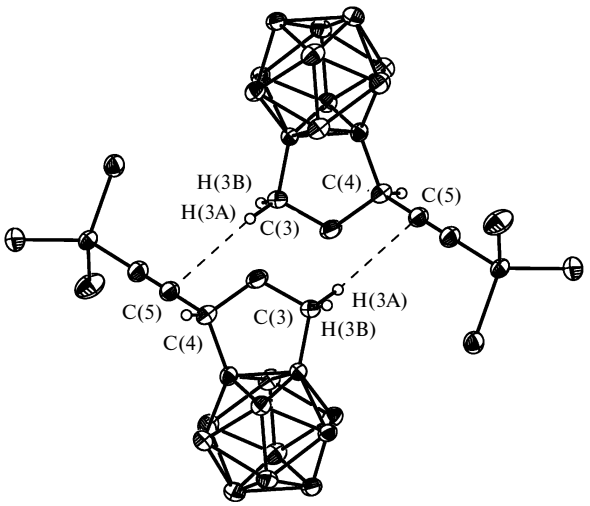
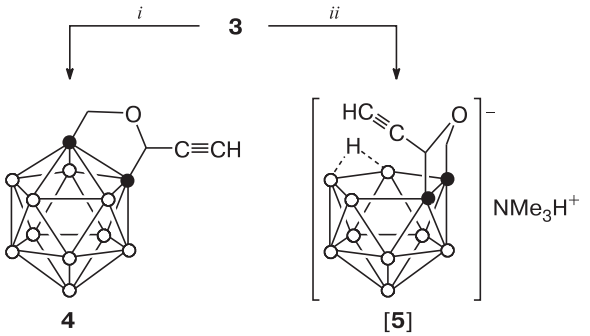


Fig. 2. Centrosymmetric dimer of molecule **3** in crystal. Nonhydrogen atoms are represented by probability ellipsoids of atomic displacements (p = 0.5). Hydrogen atoms are omitted, except the hydrogen atom at the optically active atom C(4) and the atoms H(3A) and H(3B).

Scheme 3

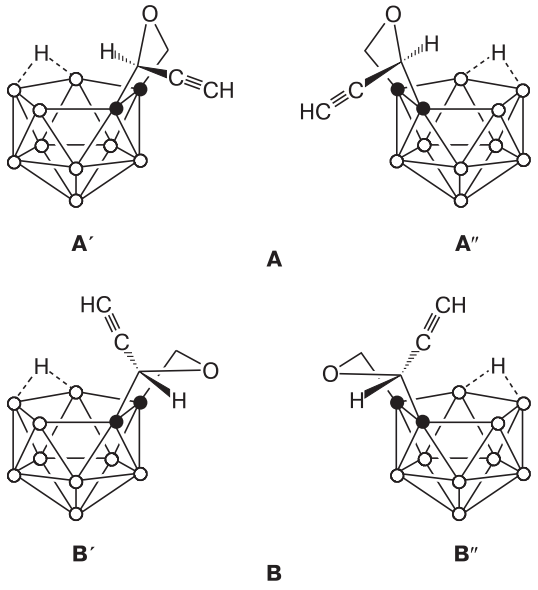


Reagents and conditions: *i*. Bu_4NF, THF, –78 °C, then H_3O^+; *ii*. NaOH, MeOH, then Me_3NHCl, H_2O.

We found that treatment of compound **3** with an excess of NaOH in MeOH results in the simultaneous removal of the silyl protection from the acetylene fragment and deboration of the *o*-carborane core to the undecadicarbaborate anion $[\mathbf{5}]^-$, which was isolated as a trimethylammonium salt $[\mathbf{5}][NMe_3H]$ in the yield close to quantitative (see Scheme 3).

The structure of the salt $[\mathbf{5}][NMe_3H]$ was confirmed by ^1H and ^{13}C NMR spectroscopy. Compound **3** is a mixture of two stereoisomers, therefore, the product of its deboration $[\mathbf{5}][NMe_3H]$ is two diastereomers **A** and **B**, each of which is a mixture of two enantiomers **A′**, **A″** and **B′**, **B″**, respectively.

The ^1H NMR spectrum of salt $[\mathbf{5}][NMe_3H]$ exhibits two sets of signals for the protons of the tetrahydrofuran ring and acetylene group in the ratio 5 : 1, respectively, δ: 4.78 (s, CHO); 3.91 (d, HC<u>H</u>O); 3.64 (d, HC<u>H</u>O), 2.75 (d, C≡CH) and 4.36 (s, CHO); 4.13 (d, HC<u>H</u>O); 3.60 (d, HC<u>H</u>O), 2.75 (d, C≡CH). Analysis of the ^1H NMR spectra suggests that the diastereomeric pair **B** predominates, whose terminal acetylene group is located above the negatively charged open face of the carborane core, which leads to a downfield shift of the signal for the acetylenic proton and to an upfield shift of the H—C—O proton signal. Separation of these regioisomers was unsuccessful.



In conclusion, new *o*-carboranyl terminal acetylenes were obtained by the reaction of 1-lithio-2-bromomethyl-*o*-carborane with silyl-protected propiolaldehyde, which were further desilylated to terminal alkynes of *closo*- or *nido*-*o*-carboranes. The products obtained are promising in the synthesis of bioinorganic conjugates of carboranes with a variety of biomolecules.[21]

Experimental

1-Bromomethyl-*o*-carborane (**1**) was synthesized according to the procedure described in the literature.[17] Diethyl ether and tetrahydrofuran were distil led over sodium benzophenone ketyl immediately before use. Dimethylformamide was distilled over calcium hydride *in vacuo* of a membrane pump (12 Torr). Diisopropylamine was distilled over KOH. ^1H, ^{11}B, and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (400.13, 128.38, and 100.61 MHz, respectively for ^1H, ^{11}B, and ^{13}C nuclei). A residual NMR signal of the solvent with respect to tetramethylsilane was taken as an internal standard for ^1H and ^{13}C NMR spectra. For ^{11}B NMR spectra, $BF_3 \cdot Et_2O$ was used as an external standard.

2-(2-Trimethylsilylethynyl)-3,4-(*o*-carborano)-2,5-dihydrofuran (3). A solution of 1-bromomethyl-*o*-carborane (**1**) (1.51 g, 6.36 mmol) in THF (5 mL) was added dropwise to lithium diisopropylamide (prepared from 1.6 *M* solution of butyllithium in hexane (4.3 mL) and diisopropylamine (0.91 mL) in THF (10 mL)) at –78 °C. The resulting solution was stirred for 1 h at –78 °C, which was accompanied by the formation of a white

precipitate. Then, 3-trimethylsilylprop-2-ynal (0.88 g, 7 mmol) was added to the mixture at −78 °C, which was stirred for 30 min, raising the temperature to ambient. The reaction mixture was poured into 1 *M* HCl (25 mL), the organic phase was separated, the aqueous phase was extracted with diethyl ether (10 mL). The combined organic extracts were dried with Na_2SO_4. The solvent was evaporated, the residue was recrystallized from methanol (5 mL). The yield was 0.92 g (3.25 mmol, 51%), colorless crystals. Found (%): C, 37.86; H, 7.81. $C_9H_{22}B_{10}OSi$. Calculated (%): C, 38.27; H, 7.85. ^{1}H NMR ($CDCl_3$), δ: 5.13 (s, 1 H, CHO); 4.38 (d, 1 H, HC<u>H</u>O, *J* = 8.6 Hz); 4.26 (d, 1 H, HC<u>H</u>O, *J* = 8.8 Hz); 3.13—1.47 (br.m, 10 H, BH); 0.24 (s, 9 H, CH_3Si). ^{13}C NMR ($CDCl_3$), δ: 97.6 (HC<u>C</u>≡C); 95.6 (C≡<u>C</u>Si); 80.3 (C_{carb}); 78.5 (C_{carb}); 73.5(CHO); 73.0 (CH_2O); 0.5 (CSi). ^{11}B NMR ($CDCl_3$), δ: −5.8 (d, 2 B, *J* = 166 Hz); −7.6 (d, 1 B, *J* = 148 Hz); −8.2 (d, 2 B, *J* = 160 Hz); −10.2 (d, 1 B); −12.4 (d, 2 B, *J* = 159 Hz); −13.2 (d, 2 B, *J* = 175 Hz).

2-Ethynyl-3,4-(*o*-carborano)-2,5-dihydrofuran (4). The compound **3** (0.2 g, 0.7 mmol) was dissolved in THF (20 mL). The reaction mixture was cooled to −78 °C, followed by the addition of $NBu_4F \cdot 3H_2O$ (0.22 g, 0.7 mmol). The temperature of the mixture was raised to 0 °C, the mixture was poured into 10% aqueous HCl (10 mL) and extracted with diethyl ether (2×20 mL). The organic extracts were combined and dried with sodium sulfate, the solvent was evaporated. The product was purified by column chromatography (eluent hexane). The yield was 0.042 g (0.20 mmol, 28%), a white foam. Found (%): C, 34.01; H, 6.73. $C_6H_{14}B_{10}O$. Calculated (%): C, 34.27; H, 6.71. ^{1}H NMR ($CDCl_3$), δ: 5.16 (s, 1 H, CHO); 4.39 (d, 1 H, HC<u>H</u>O, *J* = 8.7 Hz); 4.29 (d, 1 H, HC<u>H</u>O, *J* = 8.8 Hz); 2.78 (d, 1 H, C≡CH, *J* = 2.1 Hz); 3.13—1.47 (br.m, 10 H, BH). ^{13}C NMR ($CDCl_3$), δ: 80.0 (C_{carb}); 78.5 (C_{carb}); 77.7 (C≡<u>C</u>H); 76.9 (<u>C</u>≡CH); 73.2(CHO); 73.1 (CH_2O). ^{11}B NMR ($CDCl_3$), δ: −5.8 (d, 2 B, *J* = 151 Hz); −7.5 (d, 1 B, *J* = 154 Hz); −8.2 (d, 2 B, *J* = 163 Hz); −10.1 (d, 1 B, *J* = 180 Hz); −12.4 (d, 2 B, *J* = 170 Hz); −13.1 (d, 2 B, *J* = 154 Hz).

2-Ethynyl-3,4-(dodecahydro-*nido*-undecadicarbaborato)-2,5-dihydrofuran, trimethylammonium salt [5][NMe_3H]. The compound **3** (0.2 g, 0.7 mmol) was dissolved in MeOH (10 mL), after addition of two granules of NaOH, the mixture was refluxed for 1 h with a reflux condenser. Then, MeOH was evaporated, the residue was dissolved in 10% aqueous HCl (10 mL), followed by the addition of an excess of the saturated aqueous solution of trimethylamine hydrochloride. The product was collected by filtration and dried in air. The yield was 0.174 g (0.67 mmol, 96%), a white foam. Found (%): C, 41.17; H, 9.28; N, 5.43. $C_9H_{24}B_9NO$. Calculated (%): C, 41.64; H, 9.32; N, 5.40. ^{1}H NMR (acetone-d_6), δ: 4.78 (d, 1 H, CHO, *J* = 2.2 Hz); 3.91 (d, 1 H, HC<u>H</u>O, *J* = 7.8 Hz); 3.64 (d, 1 H, HC<u>H</u>O, *J* = 7.8 Hz); 3.22 (s, 9 H, NMe_3); 2.75 (d, 1 H, C≡CH, *J* = 2.2 Hz); 3.13—1.47 (br.m, 9 H, BH); −2.67 (br.m, BH-bridging). ^{13}C NMR (acetone-d_6), δ: 81.0 (<u>C</u>≡CH); 76.8 (C≡<u>C</u>H); 72.8 (C_{carb}); 72.5 (C_{carb}); 71.8 (CHO); 71.6 (CH_2O). ^{11}B NMR ($CDCl_3$), δ: −12.4 (d, 2 B, *J* = 135 Hz); −16.1 (m, 1 B); −19.4 (m, 4 B); −31.3 (d, 1 B, *J* = 136 Hz); −36.1 (d, 1 B, *J* = 141 Hz).

X-ray diffraction study of crystals of compound **3** was performed on a Bruker APEX II Duo diffractometer (Mo-Kα radiation, graphite monochromator, ω-scan technique). The structures were solved by direct method and refined by the least squares method in anisotropic full-matrix approximation with respect to F^2_{hkl}. Hydrogen atoms were localized from difference Fourier syntheses of electron density and refined in isotropic approximation. The full X-ray diffraction data and crystallographic parameters are available from the Cambridge Crystallographic Database (CCDC 1584790, www.ccdc.ac.uk).

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References

1. J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.,* 2010, **39**, 1302.
2. R. Chinchilla, C. Nájera, *Chem. Soc. Rev.,* 2011, **40**, 5084.
3. R. N. Grimes, *Carboranes*, 3rd ed., Academic Press, London, 2016.
4. V. I. Bregadze, *Russ. Chem. Bull.*, 2014, **63** 1021.
5. N. S. Hosmane, *Boron Science: New Technologies and Applications*, CRC Press, Boca Raton, 2011.
6. M. A. Fox, A. M. Cameron, P. J. Low, M. A. J. Paterson, A. S. Batsanov, A. E. Goeta, D. W. H. Rankin, H. E. Robertson, J. T. Schirlin, *Dalton Trans.*, 2006, 3544.
7. L. I. Zakharkin, A. I. Kovredov, V. A. Ol´shevskaya, *Bull. Acad. Sci., Div. Chem. Sci.*, 1986, **35**, 1260.
8. A. Himmelspach, M. Finze, *Eur. J. Inorg. Chem.*, 2010, 2012.
9. I. P. Beletskaya, V. I. Bregadze, V. A. Ivushkin, G. G. Zhigareva, P. V. Petrovskii, I. B. Sivaev, *Zh. Org. Khim.*, 2005, **41**, 1386 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2005, **41**].
10. R. Djeda, J. Ruiz, D. Astruc, R. Satapathy, D. Rashmirekha, Barada Prasanna, N.S. Hosmane, *Inorg. Chem.*, 2010, **49**, 10702.
11. J. F. Morin, T. Sasaki, Y. Shirai, J. M. Guerrero, J. M. Tour, *J. Org. Chem.*, 2007, **72**, 9481.
12. G. W. Kabalka, R. N. Kesavulu, C. Narayana, in *Cancer Neutron Capture Therapy*, Vol. **21**, Ed. Y. Mishima, Plenum Press, New York, 1996, p. 157.
13. M. Białek-Pietras, A. B. Olejniczak, E. Paradowska, M. Studzińska, P. Suski, A. Jabłońska, Z. J. Leśnikowski, *J. Organomet. Chem.*, 2016, **798**, 99.
14. K. Bednarska, A. B. Olejniczak, B. A. Wojtczak, Z. Sułowska, Z. J. Lesnikowski, *ChemMedChem.*, 2010, **5**, 749.
15. K. Bednarska, A. B. Olejniczak, A. Piskala, M. Klink, Z. Sułowska, Z. J. Lesnikowski, *Bioorg. Med. Chem.*, 2012, **20**, 6621.
16. J. D. Żołnierczyk, A. B. Olejniczak, A. Mieczkowski, J. Z. Błoński, Z. M. Kiliańska, T. Robak, Z. J. Leśnikowski, *Bioorg. Med. Chem.*, 2016, **21**, 5076.
17. M. M. Fein, D. Grafstein, J. E. Paustian, J. Bobinski, B. M. Lichstein, N. Mayes, N. N. Schwartz, M. S. Cohen, *Inorg. Chem.*, 1963, **2**, 1115.
18. A. A. Semioshkin, M. V. Vichuzhanin, K. A. Lyssenko, V. I. Bregadze, *Zh. Org. Khim.*, 2003, **39**, 380 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2003, **39**].
19. D. Wöhrle, O. Tsaryova, A. Semioshkin, D. Gabel, O. Suvorova, *J. Organomet. Chem.*, 2013, **747**, 98.
20. J. C. Sauer, *Organic Syntheses, Coll. Vol. 4*, 1963, 813.
21. S. B. Alyabyev, I. P. Beletskaya, *Russ. Chem. Rev.*, 2017, **86**, 689.

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