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Synthesis of New Lipophilic Cyclopentafullerenes from Long-Chain Alka-2,3-dienoates

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Abstract—Long-chain alka-2,3-dienoates were synthesized via the Wittig reaction from the corresponding fatty acids, and the subsequent triphenylphosphine-catalyzed [3+2]-cycloaddition to fullerene C_{60} afforded new lipophilic cyclopentafullerenes.

Keywords: [3+2]-cycloaddition, fatty acids, allenoates, Wittig reaction, cyclopentafullerenes, fullerene C_{60}, amino acids

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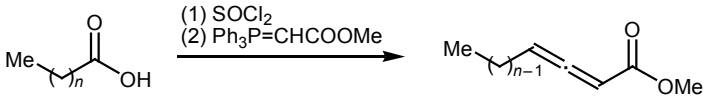
It is widely known that fullerene C_{60} is capable of trapping free radicals, which may be utilized in the design of neuroprotective antioxidants [1–3]. The antioxidant properties of C_{60} originate from its electron deficiency and facile addition of radical species. It should be noted that the antioxidant activity is intrinsic to not only fullerene itself but also its derivatives, both in vitro and in vivo [4]. Administration of fullerene compounds in animals significantly increases their resistance to oxidative stress and prevents them from neurodegenerative processes. It is believed that systematic administration of such medicines could reduce the risk of human diseases related to a high concentration of free radicals, such as Alzheimer's and Parkinson's diseases.

The molecular structure of C_{60} allows it to dissolve in common organic solvents, which is important for conducting chemical reactions. However, the solubility of C_{60} in water is very low, and this factor restricts the use of water as a medium for the synthesis of fullerene-containing compounds. Therefore, preparation of fullerene derivatives with improved solubility is a priority problem. Taking into account that the main source of active oxygen species in cells is located in mitochondria, the key problem is the synthesis of lipophilic mitochondria-addressed antioxidants. Having a positive experience in the field of synthesis of C_{60} conjugates with improved solubility in organic solvents on the basis of various allenic acids, which showed a pronounced antioxidant activity [5, 6], we continued studies in this line and synthesized previously unknown lipophilic conjugates of C_{60} with allenic acids obtained from lauric, miristic, stearic, and begenic acids.

Long-chain methyl alka-2,3-dienoates **2a**–**2d** were prepared by Wittig olefination of the corresponding ketenes derived from lauric, miristic, stearic, and begenic acids (Scheme 1). The structure of **2a**–**2d** was proved by spectral methods. The ^{1}H NMR spectra of **2a**–**2d** showed signals in the region δ 5.53–5.61 ppm for two protons of the allene fragment, and the terminal allenic carbon nuclei resonated in the ^{13}C NMR spectra at δ_C 87.81–95.38 ppm. The central allenic carbon atom gave a signal at δ_C 212.36 ppm [6–9].

According to published data [10–12], phosphine-catalyzed [3+2]-cycloaddition of allenic acids to the fullerene scaffold as dipolarophile gives cyclopenta-

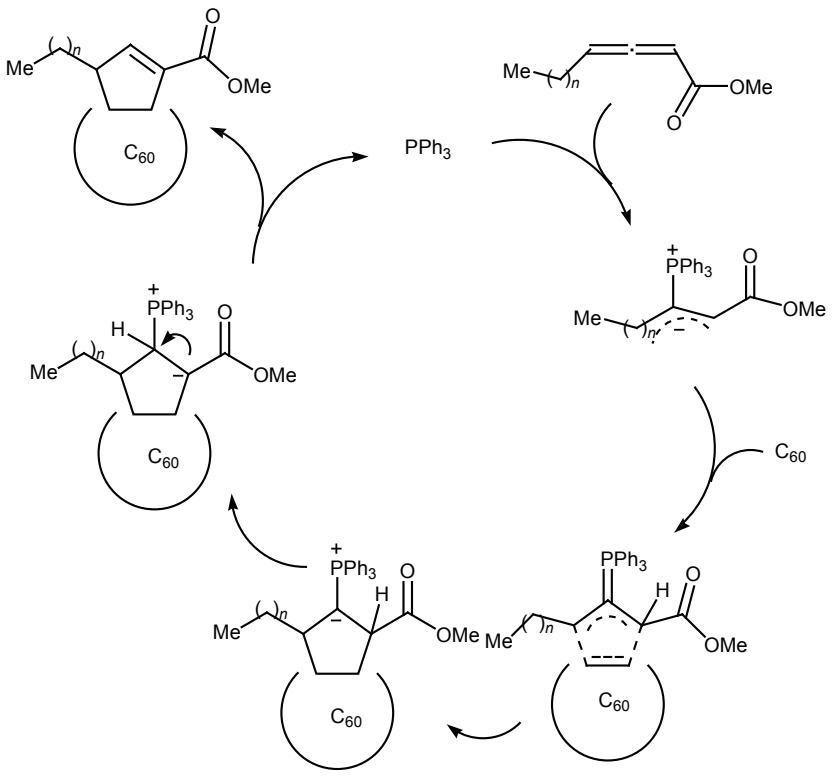
Scheme 1.



1a–1d **2a–2d**

1, **2**, *n* = 10 (**a**), 12 (**b**), 16 (**c**), 20 (**d**).

Scheme 2.



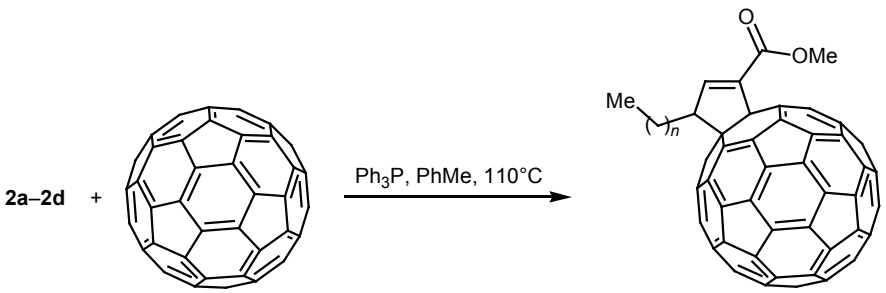
fullerenes. The reaction begins with nucleophilic attack of phosphine on the central allenic carbon atom with the formation of zwitterionic intermediate which acts as 1,3-dipole and adds to C=C double bond of C_{60}. Elimination of the phosphine catalyst from the resulting five-membered phosphorus ylide yields final product (Scheme 2) [5].

By the Morita−Baylis−Hillman reaction [5] of **2a**–**2d** with C_{60} in toluene in the presence of triphenylphosphine we obtained new cyclopentafullerenes **3a**–**3d** that are readily soluble in common organic solvents (Scheme 3). Compounds **3a**–**3d** were moderately soluble in vegetable oils to form 10% solutions.

The structure of **3a**–**3d** was confirmed by spectral methods, including two-dimensional HSQC and HMBC NMR experiments. Figure 1 shows HMBC correlations in the cyclopentene fragment of **3a**. It is seen that protons of the cyclopentene fragment are coupled with all neighboring carbon atoms. However, no correlation is observed between the 5′-H proton and fusion carbon resonating at δ_C 77.28 ppm ($C^{2'}$). This may be due to the fact that the dihedral angle $C^{2'}C^{1'}C^{5'}H$ is close to 90°.

In summary, previously unknown fullerene conjugates have been synthesized by phosphine-catalyzed [3+2]-cycloaddition of long-chain methyl alka-2,3-di-

Scheme 3.



3, n = 9 (**a**), 11 (**b**), 15 (**c**), 19 (**d**).

enoates to C_{60}. The synthesized compounds are characterized by improved solubility in common organic solvents and vegetable oils where their concentration reaches 10%. The products are promising for the design of lipophilic antioxidants of new generation.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR-Prestige-21 spectrometer with Fourier transform (Japan) from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 500 spectrometer at 500.13 and 125.76 MHz, respectively, relative to tetramethylsilane as internal standard. Signals in the NMR spectra were assigned using two-dimensional homo- and heteronuclear correlation techniques (COSY, NOESY, HSQC, HMBC). The progress of reactions was monitored by TLC on Sorbfil PTSKh-AF-A plates; spots were detected under UV light, by treatment with iodine vapor, and by spraying with a ninhydrin solution, followed by heating to 100–120°C. The mass spectra (MALDI) were obtained with a Bruker Ultraflex III instrument (Germany) operating in the linear mode; *p*-nitroaniline was used as matrix. The melting points were measured with a Boetius hot stage coupled with a PHMK 05 microscope. The products were isolated by column chromatography on silica gel (particle size 40–100 or 100–160 μm). Methylene chloride and ethyl acetate were distilled over phophoric anhydride. Toluene, petroleum ether, and benzene were refluxed over metallic sodium and then distilled. Thionyl chloride and triethylamine (Aldrich) were used without further purification.

Compounds 2a–2d (*general procedure*). Thionyl chloride, 31.25 mmol (2.34 mL), was added to a suspension of 6.25 mmol of acid **1a**–**1d** in 15 mL of anhydrous benzene, and the mixture was refluxed for 3 h with protection from atmospheric moisture. The solvent and excess thionyl chloride were removed on a rotary evaporator, and the residue (acid chloride) was used without further purification. Triethylamine, 6.25 mmol, was added dropwise to a solution of 6.25 mmol (2 g) of methyl 2-(triphenyl-λ^5-phosphanylidene)acetate in methylene chloride, the solution was cooled to –10°C, and a cold solution of acid chloride was slowly added dropwise. The mixture was stirred for 0.5 h and left to stand at 0°C for 4–6 h. The solvent was distilled off, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (4:1) as eluent.

Methyl tetradeca-2,3-dienoate (2a). Yield 0.79 g (53%), transparent oil. IR spectrum, ν, cm^{-1}: 1955 (C=C=C), 1724 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t (3H, CH_3), 1.25–1.34 m (14H, CH_2), 1.45–1.46 m (2H, 9-H), 2.12–2.15 m (2H, 10-H), 3.72 s (3H, OCH_3), 5.56–5.62 m (2H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.03 (CH_3), 22.62 (C^2), 27.42 (C^8), 28.63 (C^9), 28.90 (C^{10}), 29.18 (C^4), 29.28 (C^5), 29.38 (C^7), 29.53 (C^6), 31.84 (C^3), 51.84 (OCH_3), 87.81 (=CH), 95.38 (=CH), 166.65 (C=O), 212.33 (=C=). Found, %: C 75.60; H 11.00. $C_{15}H_{26}O_2$. Calculated, %: C 75.58; H 10.99. *M* 238.3657.

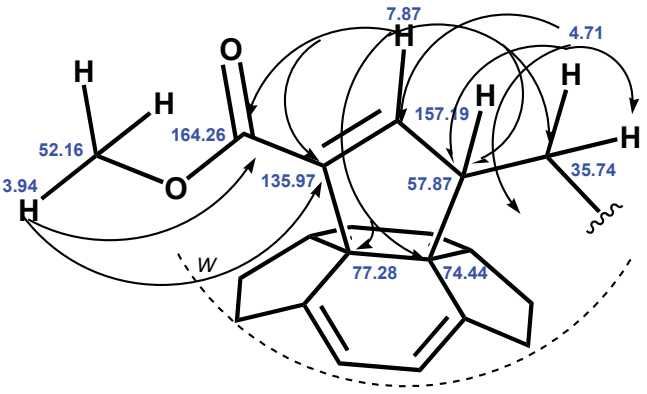


Fig. 1. HMBC correlations for the cyclopentene fragment of compound **3a**.

Methyl hexadeca-2,3-dienoate (2b). Yield 1.40 g (80%), transparent oil. IR spectrum, ν, cm^{-1}: 1962 (C=C=C), 1722 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t (3H, CH_3), 1.14–1.39 m (20H, CH_2), 1.46–1.48 m (2H, 9-H), 2.12–2.14 m (2H, 10-H), 3.94 s (3H, OCH_3), 5.53–5.58 m (2H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.06 (CH_3), 22.67 (C^2), 28.67 (C^{13}), 28.94 (C^7), 29.35 (C^4), 29.58 (C^5), 29.63 (C^6, C^8, C^9), 29.65 (C^{10}), 29.68 (C^{11}, C^{12}), 31.91 (C^3), 51.88 (OCH_3), 87.83 (=CH), 95.10 (=CH), 166.61 (C=O), 212.36 (=C=). Found, %: C 77.10; H 11.52. $C_{18}H_{32}O_2$. Calculated, %: C 77.09; H 11.50. *M* 280.4455.

Methyl icosa-2,3-dienoate (2c). Yield 1.67 g (83%), transparent oil. IR spectrum, ν, cm^{-1}: 1953 (C=C=C), 1723 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.85 m (3H, CH_3), 1.23 s (10H, CH_2), 1.31–1.34 m (2H, 13-H), 1.39–1.40 m (2H, 2-H), 1.41–1.44 m (14H, CH_2), 2.11 m (2H, 15-H), 3.70 s (3H, OCH_3), 5.55–5.59 m (2H, 2NS=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.06 (CH_3), 22.67 (C^2), 28.67 (C^{13}), 28.94 (C^{15}), 29.34 (C^{14}), 29.35 (C^4), 29.58 (C^5), 29.63 (C^6, C^8, C^9), 29.65 (C^{10}), 29.68 (C^{11}, C^{12}), 31.91 (C^3), 51.81 (OCH_3), 87.83 (=CH), 95.37 (=CH), 166.60 (C=O), 212.35 (=C=). Found, %: C 78.18; H 11.87. $C_{21}H_{38}O_2$. Calculated, %: C 78.20; H 11.88. *M* 322.525.

Methyl tetracosa-2,3-dienoate (2d). Yield 2.06 g (87%), white crystalline solid. IR spectrum, ν, cm^{-1}: 1962 (C=C=C), 1722 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87–0.90 m (3H, CH_3), 1.25 s (18H, CH_2), 1.34–1.38 m (2H, 2-H), 1.43–1.46 m (16H, CH_2), 2.12 m (2H, 20-H), 3.72 s (3H, OCH_3), 5.57–5.61 m (2H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.05 (CH_3), 22.64 (C^2), 27.43 (C^{16}, C^{17}, C^{18}, C^{19}, C^{20}), 28.65 (C^{13}), 28.91 (C^{15}), 29.31 (C^{14}), 29.55 (C^4), 29.59 (C^5), 29.65 (C^6, C^7, C^8, C^9, C^{10}, C^{11}, C^{12}), 31.88 (C^3), 51.83 (OCH_3), 87.82 (=CH), 95.38 (=CH), 166.64 (C=O), 212.33 (=S=). Found, %: C 79.32; H 12.27. $C_{25}H_{46}O_2$. Calculated, %: C 79.30; H 12.25. *M* 378.6315.

Cyclopentafullerenes 3a–3d (*general procedure*). A solution of C_{60} (0.1 g, 0.14 mmol) in 35 mL of toluene was kept for 12 h, a solution of 0.14 mmol of ester **2a**–**2d** and 0.14 mmol of triphenylphosphine in 5 mL of toluene was added, and the mixture was refluxed for 12 h. Compounds **3a**–**3d** were isolated by column chromatography using toluene and petroleum ether–ethyl acetate (4:1) as eluents.

Methyl 5′-decyl-5′*H*-cyclopenta[1′,2′:1,9]-(C_{60}-I_h)[5,6]fullerene-3′-carboxylate (3a). Yield 40 mg (30%). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t (3H, CH_3), 1.14–1.39 m (14H, CH_2), 1.46 m (2H, 9-H), 2.12 m (2H, 10-H), 3.94 s (3H, OCH_3), 4.71–4.74 m (1H, CH), 7.87–7.90 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.16 (CH_3), 22.71 (C^2), 28.57 (C^9), 29.37 (C^8), 29.58 (C^5), 29.64 (C^7), 29.70 (C^6), 29.88 (C^4), 31.92 (C^3), 35.74 (C^{11}), 52.16 (OCH_3), 57.87 (CH), 74.44, 77.28, 132.96, 133.65, 133.98, 135.34, 135.70, 135.97, 140.21, 141.57, 141.93, 142.19, 142.41 (=CH), 142.60, 142.72, 143.11, 144.46, 144.87, 144.98, 145.17, 145.96, 146.19, 146.27, 147.25, 147.34, 148.15, 148.31, 157.19, 164.26 (C=O). Found, %: C 93.90; H 3.32. $C_{75}H_{26}O_2$. Calculated, %: C 93.93; H 2.73. *M* 959.0077.

Methyl 5′-dodecyl-5′*H*-cyclopenta[1′,2′:1,9]-(C_{60}-I_h)[5,6]fullerene-3′-carboxylate (3b). Yield 57 mg (41%). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t (3H, CH_3), 1.14–1.39 m (14H, CH_2), 1.46–1.49 m (2H, 9-H), 2.12–2.14 m (2H, 10-H), 3.94 s (3H, OCH_3), 4.71 m (1H, CH), 7.87 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.17 (CH_3), 22.72 (C^2), 28.63 (C^{13}), 28.94 (C^{15}), 29.34 (C^{14}), 29.41 (C^4), 29.58 (C^5), 29.71 (C^6, C^8, C^9), 29.77 (C^{10}), 29.95 (C^{11}, C^{12}), 31.96 (C^3), 52.20 (CH), 57.88 (OCH_3), 74.42, 128.59, 129.65, 131.77, 131.93, 132.00, 132.01, 132.06, 132.14, 132.76, 134.00, 135.27, 135.74, 135.97, 139.19, 139.33, 139.69, 140.22, 141.54, 141.62, 141.87, 141.93, 142.14, 142.19, 142.40 (=CH), 142.71, 143.08, 144.39, 144.47, 144.86, 144.97, 145.10, 145.18, 145.30, 145.34, 145.42, 145.35, 145.96, 146.07, 146.15, 146.26, 146.38, 148.18, 148.35, 157.37, 166.21 (C=O). Found, %: C 93.56; H 3.23. $C_{78}H_{32}O_2$. Calculated, %: C 93.58; H 3.22. *M* 1001.0875.

Methyl 5′-hexadecyl-5′*H*-cyclopenta[1′,2′:1,9]-(C_{60}-I_h)[5,6]fullerene-3′-carboxylate (3c). Yield 75 mg (52%). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 t (3H, CH_3), 1.25 s (8H, CH_2), 1.39–1.41 m (2H, 2-H), 1.41 m (2H, 13-H), 1.42–1.44 m (14H, CH_2), 1.92–1.96 m (2H, 15-H), 3.93 s (3H, OCH_3), 4.71–4.75 m (1H, CH), 7.86–7.90 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.20 (CH_3), 22.74 (C^2), 28.63 (C^{13}), 28.94 (C^{15}), 29.34 (C^{14}), 29.41 (C^4), 29.58 (C^5), 29.71 (C^6, C^8, C^9), 29.77 (C^{10}), 29.95 (C^{11}, C^{12}), 31.96 (C^3), 52.20 (CH), 57.88 (OSH_3), 74.42, 128.59, 129.65, 131.77, 131.93, 132.00, 132.01, 132.06, 132.14, 132.76, 134.00, 135.27, 135.74, 135.97, 139.19, 139.33, 139.69, 140.21, 141.55, 141.61, 141.89, 141.92, 141.98, 142.14, 142.18, 142.23, 142.40 (=CH), 142.63, 142.69, 143.05, 143.10, 144.40, 144.44, 144.88, 144.97, 145.07, 145.16, 145.29, 145.33, 145.44, 145.56, 145.94, 146.07, 146.17, 146.25, 146.35, 147.22, 147.32, 148.15, 148.28, 148.36, 157.17, 164.21 (C=O). Found, %: C 93.28; H 3.65. $C_{81}H_{38}O_2$. Calculated, %: C 93.26; H 3.67. *M* 1043.1672.

Methyl 5′-icosyl-5′*H*-cyclopenta[1′,2′:1,9]-(C_{60}-I_h)[5,6]fullerene-3′-carboxylate (3d). Yield 55 mg (36%). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.91 t (3H, CH_3), 1.28 s (18H, CH_2), 1.39–1.41 m (2H, 2-H), 1.43–1.55 m (16H, CH_2), 2.37–2.40 m (2H, 20-H), 3.95 s (3H, OCH_3), 4.71–4.74 m (1H, CH), 7.72–7.74 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.14 (CH_3), 22.70 (C^2), 28.59 (C^{19}), 29.37 (C^4, C^{17}, C^{18}), 29.67 (C^5, C^{16}), 29.73 (C^6, C^8–C^{15}), 29.90 (C^7), 31.93 (C^3), 35.73 (C^{20}), 52.12 (OCH_3), 57.87 (CH), 128.20, 128.45, 128.50, 128.55, 128.72, 131.97, 132.06, 132.14, 133.64, 133.79, 133.99, 135.34, 135.72, 135.97, 137.01, 137.09, 139.19, 139.32, 139.68, 140.21, 141.55, 141.61, 141.88, 141.91, 141.97,142.13, 142.18, 142.23, 142.40 (=CH), 142.63,142.69, 143.05, 143.10, 144.39, 144.45, 144.49, 144.86, 144.97, 145.07, 145.16, 145.29, 145.34, 145.44, 145.55, 145.91, 145.94, 146.07, 146.17, 146.25, 146.32, 146.34, 147.22, 147.32, 148.15, 148.15, 150.81, 151.08, 153.03, 157.17, 164.17 (C=O). Found, %: C 92.89; H 4.21. $C_{85}H_{46}O_2$. Calculated, %: C 92.87; H 4.22. *M* 1099.2735.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Dumpis, M.A., Nikolaev, D.N., Litasova, E.V., Il'in, V.V., Brusina, M.A., and Piotrovskii, L.B., *Obz. Klin. Farmakol. Lek. Ter*., 2018, vol. 16, p. 4. https://doi.org/10.17816/RCF1614-20
2. Wharton, T. and Wilson, L.J., *Bioorg. Med. Chem*., 2002, vol. 10, p. 3545. https://doi.org/10.1016/s0968-0896(02)00252-3
3. Troshina, O.A., *Cand. Sci. (Chem.) Dissertation*, Chernogolovka, 2007.
4. Injac, R., Prijatelj, M., and Strukelj, B., *Oxidative Stress and Nanotechnology. Methods in Molecular Biology (Methods and Protocols)* (Methods in Molecular Biology vol. 1028), Armstrong, D. and Bharali, D.J., Eds., New York: Springer, 2013, p. 75. https://doi.org/10.1007/978-1-62703-475-3
5. Sakhautdinov, I.M., Malikova, R.N., Biglova, Yu.N., Khusnutdinov, R.A., Gumerov, A.M., Khamitov, E.M., Ivanov, S.P., and Yunusov, M.S., *J. Iran. Chem. Soc*., 2018, vol. 15, p. 1975. https://doi.org/10.1007/s13738-018-1395-y
6. Sakhautdinov, I.M. and Mukhametyanova, A.F., *Russ. J. Org. Chem*., 2019, vol. 55, p. 1280. https://doi.org/10.1134/S1070428019090033
7. Elshater, A.A., Haridy, M.A.M., Salman, M.M.A., Fayyad, A.S., and Hammad, S., *Biomed. Pharmacother*., 2018, vol. 97, p. 53. https://doi.org/10.1016/j.biopha.2017.10.134
8. *Modern Allene Chemistry*, Krause, N. and Hashmi, A.S.K., Eds., Weinheim: Wiley-VCH, 2004, p. 401.
9. Ikuma, N., Inaba, S., Kokubo, K., and Oshima, T., *Chem. Commun*., 2014, vol. 50, p. 581. https://doi.org/10.1039/C3CC45783D
10. Girón, R.M., Reboredo, S., Marco-Martínez, J., Filippone, S., and Martín, N., *Faraday Discuss*., 2014, vol. 173, p. 311. https://doi.org/10.1039/c4fd00065j
11. Shu, L.H., Sun, W.Q., Zhang, D.W., Wu, Sh.H., Wu, H.M., Xu, J.F., and Lao, X.F., *Chem. Commun*., 1997, no. 1, p. 79. https://doi.org/10.1039/A605923F
12. Marco-Martnez, J., Marcos, V., Reboredo, S., Filippone, S., and Mart, N., *Angew. Chem., Int. Ed*., 2013, vol. 52, p. 5115. https://doi.org/10.1002/anie.201301292