Synthesis of polycyclic cyclopropanecarboxylic acids and their esters based on catalytic cyclopropanation of 6,6-dimethylfulvene

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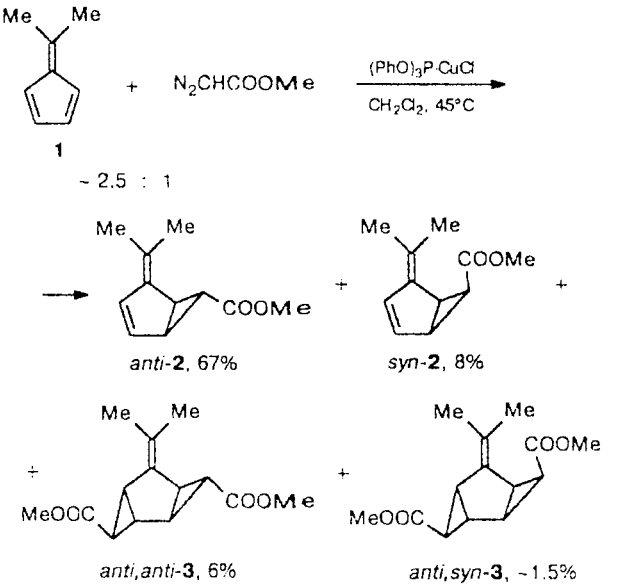
Reactions of 6,6-dimethylfulvene with methyl diazoacetate in the presence of Cu compounds is accompanied by methoxycarbonylmethylenation of the endocyclic double bonds to give the corresponding mono- and diadducts in total yields of up to 85% with marked predominance of *anti*-isomers. The subsequent cyclopropanation of monoadducts with diazomethane in the presence of Pd compounds also involves the endocyclic double bond and gives esters of tricyclo[4.1.0.0^{2,4}]heptanecarboxylic acid in high yields.

Key words: diazomethane, diazoesters, cyclopropanation, esters of bicyclo[3.1.0]hex-2-ene-6- and tricyclo[4.1.0.0^{2,4}]heptane-3-carboxylic acids

(β,β-Dimethylvinyl)cyclopropanecarboxylic acid derivatives are of considerable interest, because this moiety is incorporated into some natural and synthetic pyrethroids.[1,2] In the present work, we studied successive catalytic cyclopropanation of 6,6-dimethylfulvene (**1**) with methyl diazoacetate (MDA) and diazomethane to give derivatives of bi- and tricycloalkanecarboxylic acids in which the cyclopropanecarboxylic acid fragment is fused with a five-membered carbocyclic ring.

Fulvene **1** is known[3] to be a good indicator of the philicity of carbenes: electrophilic carbenes, for example, $:CCl_2$, add to its endocyclic double bonds, while nucleophilic carbenes, for example, $:C(OMe)_2$, add to the exocyclic double bonds. However, reactions of **1** with diazoacetates in the presence of dediazotization catalysts have not been reported. The reaction of the closest analog of **1**, *gem*-dimethylbenzofulvene, with ethoxycarbonylcarbene generated by the decomposition of ethyl diazoacetate in the presence of $Rh_2(OAc)_4$ results in a mixture of regioisomers in which the product of cyclopropanation of the endocyclic double bond predominates (~4:1).[4] It should be noted that selective ethoxycarbonylmethylenation of the exocyclic double bond occurs when compound **1** reacts with ethyl (dimethylsulfuranylidene)acetate; however, this reaction obeys second-order kinetics and does not involve intermediate formation of a carbene.[5]

We found that the slow addition of MDA to a boiling solution of a 2–3-fold molar excess of **1** in CH_2Cl_2 in the presence of ~0.2 mol.% $Cu(acac)_2$ or $(PhO)_3P{\cdot}CuCl$ results in intense decomposition of MDA accompanied by the addition of methoxycarbonylcarbene to the endocyclic double bonds in **1**. This yields methyl *anti*-4-(1-methylethylidene)bicyclo[3.1.0]hex-2-ene-6-carboxylate (*anti*-**2**) as the major reaction product (up to 68%). This product was isolated in a pure state by vacuum distillation and preparative TLC. In addition, *syn*-**2** (yield ~8%) and isomeric dimethyl *anti,anti*- and *anti,syn*-5-(1-methylethylidene)tricyclo[4.1.0.0^{2,4}]heptane-3,7-dicarboxylates (**3**) (overall yield ~7.5%) were obtained as minor products.



The proportions of dimethyl maleate and dimethyl fumarate in the reaction mixture did not exceed 3%, and the products of cyclopropanation of the exocyclic double bond of **1** were not detected in the distilled fractions at all.

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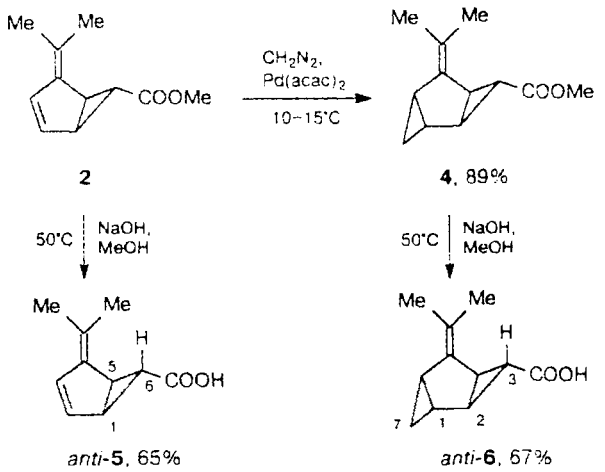
The use of 0.1–0.5 mol.% $Rh_2(OAc)_4$ at 20°C as the catalyst is less effective than the use of copper compounds; in addition, in this case, the selectivity of the process also markedly decreases, which is apparently due to side transformations of the dimethylfulvene itself under the action of the Rh catalyst.

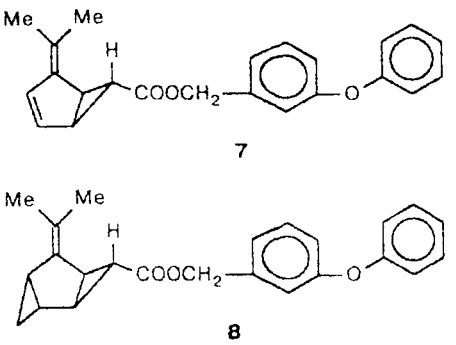
The structures of bicyclic esters **2** and tricyclic esters **3** were determined from their ^1H and ^{13}C NMR spectra; the configurations of the methoxycarbonyl groups were found taking into account the multiplicities of the signals corresponding to the methine protons in the cyclopropane rings; vicinal spin-spin coupling constants were 6–8 Hz for *cis*-protons and 2.4–3.2 Hz for *trans*-protons.

The subsequent cyclopropanation of monoester **2** was carried out by the procedure that we described previously.[6] This procedure involves simultaneous generation and catalytic decomposition of diazomethane in the presence of $Pd(acac)_2$. For this purpose, *N*-nitroso-*N*-methylurea (NMU) was slowly added to a stirred mixture of 45% aqueous KOH, olefin **2**, a catalyst, and an organic solvent at an NMU : **2** : $Pd(acac)_2$ molar ratio of 2.5:1:0.003. Cyclopropanation of compound **2** with diazomethane formed involves only the endocyclic double bond and gives methyl tricycloheptanecarboxylate **4** in 89% yield (for the distilled product); compound **4** is mostly formed as the *trans,anti*-isomer (no less than 95%, according to GLC and ^1H NMR spectrum).



Hydrolysis of esters **2** and **4** with methanolic NaOH at 50 °C gave acids **5** and **6** in 65–67% yields; according to ^1H and ^{13}C NMR spectra, they were formed as single *anti*-isomers. This is indicated, first of all, by the small spin-spin coupling constants for the proton at the C(6) atom in acid **5** (J_{trans} = 2.4 Hz) and the proton at C(3) in acid **6** (J_{trans} = 2.9 Hz). It should be noted that spectral characteristics of the acid **5** synthesized by us differ substantially from those reported[7] for the isopropylidenebicyclohexenecarboxylic acid prepared by the Favorsky rearrangement of bicyclic α-chloroketone under the action of alkali; the initial α-chloroketone was synthesized from the adduct of dichloroketene and fulvene **1** followed by reduction leading to the removal of one chlorine atom. Since in the paper cited[7] the isomeric composition of the acid was not studied, it can be assumed that the distinctions between the ^1H and ^{13}C NMR spectra of these two samples of acid **5** are due to their different isomeric compositions.

In view of the fact that the *m*-phenoxybenzyl fragment can be a promising alcoholic component for some pyrethroids, it was of interest to study the possibility of preparing the corresponding esters from cyclopropanecarboxylic acids **5** and **6**. Unfortunately, we had to reject the most obvious and widely used method of the synthesis of esters, *viz.*, the reaction of acid chlorides with alcohols, because we did not succeed in preparing the corresponding acyl chlorides by treating these polycyclic acids with thionyl chloride. Nevertheless, we accomplished the synthesis of *m*-phenoxybenzyl esters **7** and **8** by treatment of the sodium salts of acids **5** and **6** with *m*-phenoxybenzyl chloride in triethylamine; the yields of the products were 65 and 78%, respectively.



It should be noted that all the obtained compounds containing an *exo,endo*-diene group are markedly less stable than their cyclopropanated analogs, *viz.*, tricyclo[4.1.0.$0^{2,4}$]heptanes **4**, **6**, and **8**. For example, at 20°C without a solvent, the diene ester **7** is converted over a period of 2 weeks into a paraffin-like compound that is poorly soluble in organic solvents and exhibits non-characteristic broad signals in the ^1H NMR spectrum. Conversely, ester **8** does not undergo any substantial changes over the same period.

Experimental

GLC analysis was carried out on an LKhM-8MD chromatograph with a flame ionization detector and an I-02 integrator (a 300×0.3 cm column with 5% SP-2100, helium as the carrier gas, 30 mL min^{-1}). ^1H NMR spectra were recorded using a Bruker WM-250 instrument (250 MHz) for 10–13% solutions in $CDCl_3$ with tetramethylsilane as the internal standard. GC/MS analysis was carried out on a Finnigan MAT

INCOS-50 instrument (70 eV) with a 30-m-long OV-1701 capillary column.

Methyl 4-(1-methylethylidene)bicyclo[3.1.0]hex-2-ene-6-carboxylate (2). Methyl diazoacetate (8.0 g, 0.08 mol) was added over a period of 2 h with permanent stirring to a boiling solution of 6,6-dimethylfulvene **(1)** (21.5 g, 0.2 mol) and $(PhO)_3P \cdot CuCl$ (0.065 g) in 20 mL of CH_2Cl_2. When the reaction was completed (evolution of N_2 ceased), the solvent and excess **1** were distilled off *in vacuo*. A mixture of hexane (15 mL) and ether (10 mL) was added to the residue, and the mixture was filtered through a small layer of silica gel. Vacuum distillation gave 10.8 g (76%) of ester **2**, b.p. 70–71 °C (1.2 Torr), as a mixture of *anti*- and *syn*-isomers in a ratio of ~8.5:1, according to GLC and ^{1}H NMR data, and 0.75 g (~7.5%) of a colorless liquid with a boiling point of 110–124 °C (1.2 Torr) that contained diesters **3** (see below). The individual isomers of ester **2** were isolated from the first fraction by preparative TLC (silica gel L, 40–100 mm, hexane–ether, 5 : 1, R_f = 0.38 and 0.52 for the *syn*- and *anti*-isomers, respectively).

anti-**2**. ^{1}H NMR, δ: 6.09 (br.d, 1 H, H-3, $J_{2,3}$ = 5.6 Hz), 6.06 (br.d.d, 1 H, H-2, $J_{2,3}$ = 5.6 Hz, $J_{1,2}$ = 2.2 Hz), 3.65 (s, 3 H, OMe), 2.77 (br.d.d, 1 H, H-5, $J_{1,5}$ = 6.2 Hz, $J_{5,6}$ = 2.6 Hz), 2.63 (br.d.t, 1 H, H-1, $J_{1,5}$ = 6.2 Hz, $J_{1,2} \sim J_{1,6} \sim$ 2.5 Hz), 1.87 (s, 3 H, Me), 1.78 (s, 3 H, Me), 1.21 (t, 1 H, H-6, $J_{1,6} = J_{5,6}$ = 2.6 Hz). ^{13}C NMR, δ: 172.5 (CO), 138.3 and 127.9 (C=C), 133.1 and 128.5 (HC=CH), 50.9 (OMe), 33.7, 32.9, 28.5 (C-1, C-5, C-6), 21.4 (Me), 20.4 (Me). MS, *m/z* (*I* (%)): 178 (19) M^+, 163 (15), 147 (10), 119 (87), 103 (15), 91 (100). Found (%): C, 74.02; H, 7.80. $C_{11}H_{14}O_2$. Calculated (%): C, 74.13; H, 7.92.

syn-**2**. ^{1}H NMR, δ: 6.27 (br.d, 1 H, H-3, $J_{2,3}$ = 5.5 Hz), 5.85 (m, 1 H, H-2), 3.57 (s, 3 H, OMe), 2.65 (m, 2 H, H-1 and H-5), 1.99 (t, 1 H, H-6, J = 8.0 Hz), 1.88 (s, 3 H, Me), 1.85 (s, 3 H, Me). MS, *m/z* (*I* (%)): 178 (16) M^+, 163 (13), 147 (11), 119 (81), 103 (14), 91 (100). Found (%): C, 73.93; H, 7.84. $C_{11}H_{14}O_2$. Calculated (%): C, 74.13; H, 7.92.

Dimethyl 5-(1-methylethylidene)tricyclo[4.1.0.0^{2,4}]heptane-3,7-dicarboxylate (3). Preparative TLC (silica gel L, 40–100 mm, hexane–ether, 3:1) of the second fraction with a boiling point of 110–124 °C (1.2 Torr) obtained in the previous experiment, gave two isomeric diesters: *anti,anti*-**3** and *anti,syn*-**3** in a ratio of ~4:1 (R_f = 0.26 and 0.18, respectively).

anti,anti-**3**. ^{1}H NMR, δ: 3.67 (s, 3 H, OMe), 2.23 (ddd, 2 H, H-4 and H-6, $J_{1,6} = J_{2,4}$ = 6.0 Hz, $J_{3,4} = J_{6,7}$ = 3.0 Hz, J = 1.0 Hz), 2.07 (br.d.d, 2 H, H-1 and H-2, $J_{1,6} = J_{2,4}$ = 6.0 Hz, $J_{3,4} = J_{6,7}$ = 3.0 Hz), 1.74 (s, 6 H, 2 Me), 1.51 (t, 2 H, H-3 and H-7, $J_{3,4} = J_{6,7}$ = 3.0 Hz). MS, *m/z* (*I* (%)): 250 (10) M^+, 235 (8), 218 (15), 190 (31), 159 (42), 137 (30), 131 (100). Found (%): C, 67.34; H, 7.31. $C_{14}H_{18}O_4$. Calculated (%): C, 67.18; H, 7.25.

anti,syn-**3**. ^{1}H NMR, δ: 3.67 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 2.28 and 2.22 (both br.d.d, 2×1 H, H-6 and H-1, $J_{1,6}$ = 6.2 Hz, $J_{1,7}$ and $J_{6,7}$ = 3.2 Hz), 2.14 and 2.04 (both br.d.d, 2×1 H, H-4 and H-2, $J_{2,4}$ = 5.6 Hz, $J_{2,3}$ and $J_{3,4}$ = 7.8 Hz), 1.89 (t, 1 H, H-3, $J_{2,3} = J_{3,4}$ = 7.8 Hz), 1.77 and 1.72 (both s, 2×3 H, Me), 1.48 (t, 1 H, H-7, $J_{1,7} = J_{6,7}$ = 3.2 Hz). MS, *m/z* (*I* (%)): 250 (8) M^+, 235 (8), 218 (13), 190 (32), 159 (40), 137 (32), 131 (100).

Methyl 5-(1-methylethylidene)tricyclo[4.1.0.0^{2,4}]heptane-3-carboxylate (4). A solution of ester **2** (5 g, 0.028 mol) (*anti* : *syn* ≈ 8.5 : 1) in a mixture of hexane (10 mL) and CH_2Cl_2 (15 mL) and $Pd(acac)_2$ (0.025 g) were added at 10°C to 50 mL of 45% aqueous KOH. Then *N*-nitrosomethylurea (7.2 g, 0.07 mol) was added in small portions with permanent stirring. After 30 min, 10 mL of hexane was added, and the organic layer was separated, washed with water, and dried with Na_2SO_4. Removal of the solvents and distillation *in vacuo* gave 4.8 g (89%) of a colorless liquid, b.p. 103–108 °C (2.5 Torr), whose major component (no less than 95%) was identified as the *anti*-isomer of ester **4**. ^{1}H NMR, δ: 3.66 (s, 3 H, OMe), 2.17 (ddd, 1 H, H-4, $J_{2,4}$ = 6.3 Hz, $J_{3,4}$ = 3.1 Hz, J = 1.0 Hz), 2.03 (br.d.d, 1 H, H-2, $J_{2,4}$ = 6.3 Hz, $J_{2,3}$ = 3.0 Hz), 1.71 and 1.72 (both s, 6 H, 2 Me), 1.64 and 1.46 (both m, 2×1 H, H-1 and H-6), 1.48 (t, 1 H, H-3, J = 3.0 Hz), 0.80 (dt, 1 H, *anti*-H-7, J_{cis} = 7.5, J_{gem} = 4.0 Hz), 0.29 (q, 1 H, *syn*-H-7, $J_{trans} = J_{gem}$ = 4.0 Hz). ^{13}C NMR, δ: 172.8 (CO), 136.9 and 123.4 (C=C), 52.1 (OMe), 33.3, 30.3, 29.3 (C-2, C-3, C-4), 22.0 and 20.9 (2 Me), 18.4, 14.3 (C-1, C-6), 14.8 (C-7).

4-(1-Methylethylidene)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (5). A solution of ester **2** (*anti* : *syn* ≈ 8.5 : 1) (5 g, 0.028 mol) in 8 mL of toluene was slowly added with stirring at 50 °C to a solution of NaOH (2 g, 0.05 mol) in 5 mL of MeOH, and the mixture was stirred for 2h. The organic layer was separated, 15% HCl was added to the reaction mixture to pH ~3, and the products were extracted with toluene. The toluene solution was dried with Na_2SO_4, and the solvents were removed using a rotary evaporator. The residue consisted of 3.0 g (65%) of the *anti*-isomer of acid **5**, m.p. 135–136 °C. ^{1}H NMR, δ: 6.14 (br.d, 1 H, H-3, $J_{2,3}$ = 5.6 Hz), 6.10 (br.d.d, 1 H, H-2, $J_{2,3}$ = 5.6 Hz, $J_{1,2}$ = 2.0 Hz), 2.86 (br.d.d, 1 H, H-5, $J_{1,5}$ = 6.1 Hz, $J_{5,6}$ = 2.4 Hz), 2.75 (br.d.t, 1 H, H-1, $J_{1,5}$ = 6.1 Hz, $J_{1,2} \sim J_{1,6} \sim$ 2.3 Hz), 1.91 (s, 3 H, Me), 1.83 (s, 3 H, Me), 1.22 (t, 1 H, H-6, $J_{1,6} = J_{5,6}$ = 2.4 Hz), 10.6 (br.s, 1 H, COOH). ^{13}C NMR, δ: 179.9 (CO), 138.3 and 129.8 (C=C), 133.4 and 129.2 (HC=CH), 34.3, 34.2, 29.9 (C-1, C-5, C-6), 21.4 (Me), 20.4 (Me).

5-(1-Methylethylidene)tricyclo[4.1.0.0^{2,4}]heptane-3-carboxylic acid (6) was obtained by the hydrolysis of ester **4** (3.85 g, 0.02 mol), similarly to the synthesis of acid **5**. Extraction of the acidified reaction mixture with toluene followed by drying of the organic layer and the removal of the solvents gave 2.39 g (67%) of acid **6** as small colorless crystals, m.p. 138–140 °C. ^{1}H NMR, δ: 2.28 (br.d.d, 1 H, H-4, $J_{2,4}$ = 6.0 Hz, $J_{3,4}$ = 3.0 Hz), 2.13 (br.d.d, 1 H, H-2, $J_{2,4}$ = 6.0 Hz, $J_{2,3}$ = 2.9 Hz), 1.76 (s, 6 H, 2 Me), 1.69 and 1.54 (both m, 2×1 H, H-1 and H-6), 1.50 (t, 1 H, H-3, J = 2.9 Hz), 0.83 (dt, 1 H, *anti*-H-7, J_{cis} = 7.6 Hz, J_{gem} = 4.1 Hz), 0.31 (q, 1 H, *syn*-H-7, $J_{trans} = J_{gem}$ = 4.1 Hz), 10.2 (br.s, 1 H, COOH). ^{13}C NMR, δ: 179.5 (CO), 136.5 and 124.1 (C=C), 34.1, 30.4, 30.3 (C-2, C-3, C-4), 22.1, 18.3 (C-1, C-6), 21.1 and 21.0 (2 Me), 14.9 (C-7). Found (%): C, 74.01; H, 7.98. $C_{11}H_{14}O_2$ Calculated (%): C, 74.13; H, 7.92.

***m*-Phenoxybenzyl 4-(1-methylethylidene)bicyclo[3.1.0]hex-2-ene-6-carboxylate (7).** A mixture of 4-(1-methylethylidene)bicyclo[3.1.0]hex-2-ene-6-carboxylate **(5)** (1.98 g, 0.012 mol), powdered NaOH (0.50 g, 0.012 mol), and triethylamine (1.5 mL) was heated in an inert atmosphere to 70 °C, then *m*-phenoxybenzyl chloride (2.64 g, 0.012 mol) was added, and the mixture was kept at this temperature for 2.5 h. After extraction with benzene (20 mL) followed by removal of the solvent, the target product was isolated by column chromatography (silica gel L, 40–100 mm). First, elution with hexane was used to separate unreacted *m*-phenoxybenzyl chloride, and then elution with a benzene–hexane mixture (1:1) gave 2.70 g (65%) of ester **7** as a yellowish highly viscous material. ^{1}H NMR, δ: 7.36 and 7.08

(both m, 3 H, 6 H, C_6H_4OPh), 6.15 (br.d, 1 H, $J_{2,3}$ = 5.6 Hz, H-3), 6.11 (m, 1 H, H-2), 5.14 (br.s, 2 H, OMe), 2.88 and 2.74 (both m, 2×1 H, H-5 and H-1), 1.93 and 1.83 (both s, 2×3 H, 2 Me), 1.35 (t, H-6, J_{trans} = 3.0). Found (%): C, 79.48; H, 6.31. $C_{23}H_{22}O_3$ Calculated (%): C, 79.74; H, 6.40.

***m*-Phenoxybenzyl 5-(1-methylethylidene)tricyclo[4.1.0.0^{2,4}]-heptane-3-carboxylate (8).** The experiment was carried out similarly to the previous one. The reaction of 5-(1-methylidene)tricyclo[4.1.0.0^{2,4}]heptane-3-carboxylate **(6)** (1.78 g, 0.01 mol), NaOH (0.41 g), triethylamine (1.5 mL), and *m*-phenoxybenzyl chloride (2.20 g, 0.01 mol) gave 2.81 g (78%) of ester **8** as a slightly yellowish high-viscosity material. ^{1}H NMR, δ: 7.35 and 7.06 (both m, 3 H, 6 H, C_6H_4OPh), 5.12 (br.s, 2 H, OMe), 2.26 (br.d.d, 1 H, H-4, $J_{2,4}$ = 7.2 Hz, $J_{3,4}$ = 3.1 Hz), 2.12 (m, 1 H, H-2), 1.78 and 1.76 (both s, 2×3 H, 2 Me), 1.68 and 1.51 (both m, 2×1 H, H-1 and H-6), 1.60 (t, 1 H, H-3, J_{trans} = 3.1 Hz), 0.85 (d.t, 1 H, *anti*-H-7, J_{cis} = 8.1 Hz, J_{gem} = 4.4 Hz), 0.33 (q, 1 H, *syn*-H-7, J_{trans} = J_{gem} = 4.4 Hz). Found (%): C, 79.80; H, 6.58. $C_{24}H_{24}O_3$. Calculated (%): C, 79.97; H, 6.71.

References

1. N. N. Mel'nikov. *Pestitsidy. Khimiya, Tekhnologiya i Primenenie* [*Pesticides. Chemistry, Technology, and Applications*], Khimiya, Moscow, 1987, p. 170 (in Russian).
2. *Piretroidy. Khimiko-Tekhnologicheskie Aspekty* [*Pyrethroids. Chemico-Technological Aspects*], Ed. V. K. Promonenkov, Khimiya, Moscow, 1992, p. 36 (in Russian).
3. R. A. Moss, C. M. Young, L. A Perez, and K. Krogh-Jespersen, *J. Am. Chem. Soc.*, 1981, **103**, 2413.
4. F. Z. Galin, V. K. Ignatyuk, S. N. Lakeev, R. G. Rakhimov, V. S. Sultanova, and G. A. Tolstikov, *Zh. Org. Khim.*, 1989, **25**, 103 [*J. Org. Chem. USSR*, 1989, **25** (Engl. Transl.)].
5. G. A. Tolstikov, F. Z. Galin, V. N. Iskanderova, and V. D. Komissarov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 715 [*Bull. Acad. Sci. USSR, Div. Chem.*, 1986, **35**, 656 (Engl. Transl.)].
6. O. M. Nefedov, Yu. V. Tomilov, A. B. Kostitsyn, U. M. Dzhemilev, and V. A. Dokichev, *Mendeleev Commun.*, 1992, 13.
7. W. T. Brady, S. J. Norton, and J. Ko, *Synthesis*, 1983, 1002.

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