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Alkylation of the Isosteviol Terpenoid and Its Oxime with Dibromoalkanes in the KOH–DMSO System

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Abstract — The reaction of 16-hydroximinoisosteviol with dihaloalkanes in the KOH–DMSO results in coupling of two isosteviol carcasses by the carboxy groups. The same products were previously synthesized by hydroximination of isosteviol diesters.
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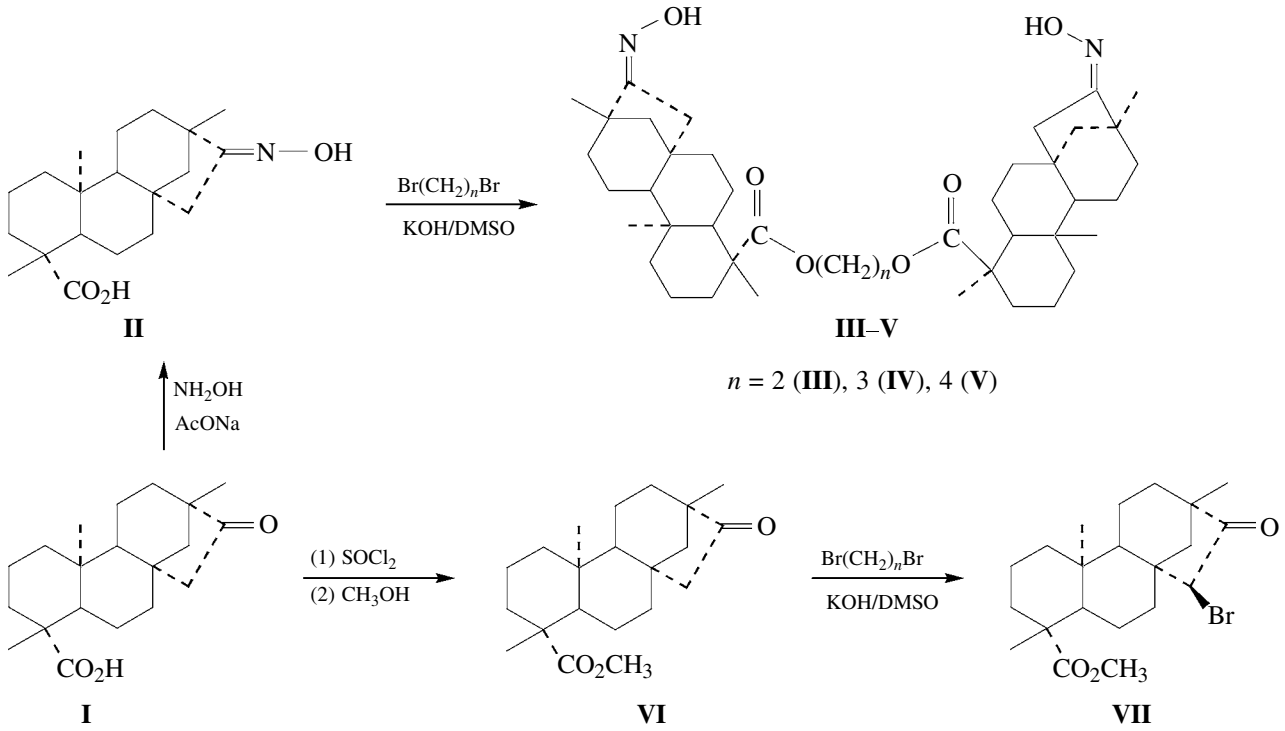
Isosteviol (**I**) (*ent*-16-ketobeyeran-19-oic acid) [1] produced by hydrolysis of glycosides contained in the Stevia rebaudiana Bertoni plant [2] has two reactive groups (carboxy and keto) and can be easily functionalized to prepare novel compounds with useful properties. Owing to its specific molecule geometry (the CO_2H and C=O groups point to one side of the rigid *ent*-beyeran carcass [2]), isosteviol reacts with proton-donor binucleophiles, giving so-called tweezer-like structures with an intramolecular lipophilic cavity [3, 4]. Thus, from isosteviol chloride [5] and diols of various structures we recently obtained crystalline diesters in which, according to X-ray diffraction data, the *ent*-beyeran carcasses lie one above the other, to form an intramolecular lipophilic cavity [4]. The tweezer-like structure of isosteviol diesters is preserved in CCl_4 solutions [6]. The isosteviol keto group is also easily functionalized (oximination, reduction, subsequent acetylation [7–9], and, therewith, the reactions proceed stereospecifically [7, 8].

We set ourselves the task to find a reagent that would react concurrently with the carboxyl and ketone functions of isosteviol (**I**) to couple two *ent*-beyeran carcasses into a macrocyclic structure in one stage. It is known that ketoximes undergo O-alkylation with alkyl halides in the presence of alkali metal hydroxides in dipolar aprotic solvents [10–13]. The use of the superbasic system KOH–DMSO as an activator of nucleophilic substitution [10, 14] would allow isosteviol (**I**) to be alkylated by the carboxy group, too. Therefore, for the starting reagent for the expected macrocyclization of two *ent*-beyeran carcasses we chose 16-hydroximinoisosteviol (**II**).

Oxime **II** synthesized by the oximination of isosteviol (**I**) by the procedure in [9] was slowly added, together with a dibromoalkane (1,2-dibromoethane, 1,3-dibromopropane, and 1,4-dibromobutane) to a homogeneous supebasic suspension prepared by stirring a mixture of crushed KOH and DMSO at room temperature. The reaction mixture was heated with stirring on a water bath for 13 h. The oxime–dibromoalkane–KOH ratio was 1 : 1 : 2, like in [10]. The reaction progress waas monitored by TLC. The reaction products were extracted with ether from the reaction mixture diluted with water and separated by column chromatography on silica. The IR spectra of major reaction products contain, along with strong ester bands at 1136–1220 cm^{-1}, absorption bands of the C=N–OH group at ~935-940 (N–O) and ~1630–1690 cm^{-1} (C=N), which allows us to assign them the structure of isosteviol oxime diesters **III**–**V** and to conclude that the reaction has occurred by the carboxy group exclusively. Evidence for this conclusion comes from the observation in the electron impact (EI) mass spectra of diesters **III** and **IV** of molecular ion peaks at *m/z* 692 and 706, respectively. The intensity of $M^{+\cdot}$ decreases along the series **III**–**V**; therewith, compound **V** gives no molecular ion peak.

The decrease of the stability of the molecular ion under electron impact alone the series **III**–**V** can be explained by increasing length of the hydrocarbon chain tethering two *ent*-beyeran carcasses. The fragmentation of molecules **III**–**V** features loss of the OH group on nitrogen, which gives rise to ions at 675, 689, and 703 for diesters **III**–**V**, respectively. The most informative high-mass spectral region displays



$[M - CH_3]^+$ (*m/z* 677, 691, and 705 for **III**–**V**, respectively) and $[M - H2O]^+$ (*m/z* 674, 688, and 704 for **III**–**V**, respectively) ion peaks. Similar processes we previously observed with other isosteviol imines [9]. The low-mass ions in the spectra of compounds **III**–**V** are formed by consecutive fragmentation of the above ions.

Thus, in our conditions we failed to alkylate isosteviol (**I**) by the oxime group. The formation of diesters **III**–**V**, like the reaction of ketoximes with alkyl halides, which is generally accompanied by side formation of ketones (up to 10%) [10], involves side hydrolysis of oxime **II** to give a little (10%) isosteviol (**I**).

Under more rigid conditions, isosteviol methyl ester **VI** reacts with 1,2-dibromoethane, 1,3-dibromopropane, and propyl bromide, yielding 15-bromo derivative **VII** [15]. The reaction occurs stereospecifically to form a $C^{15}S$ stereoisomer.

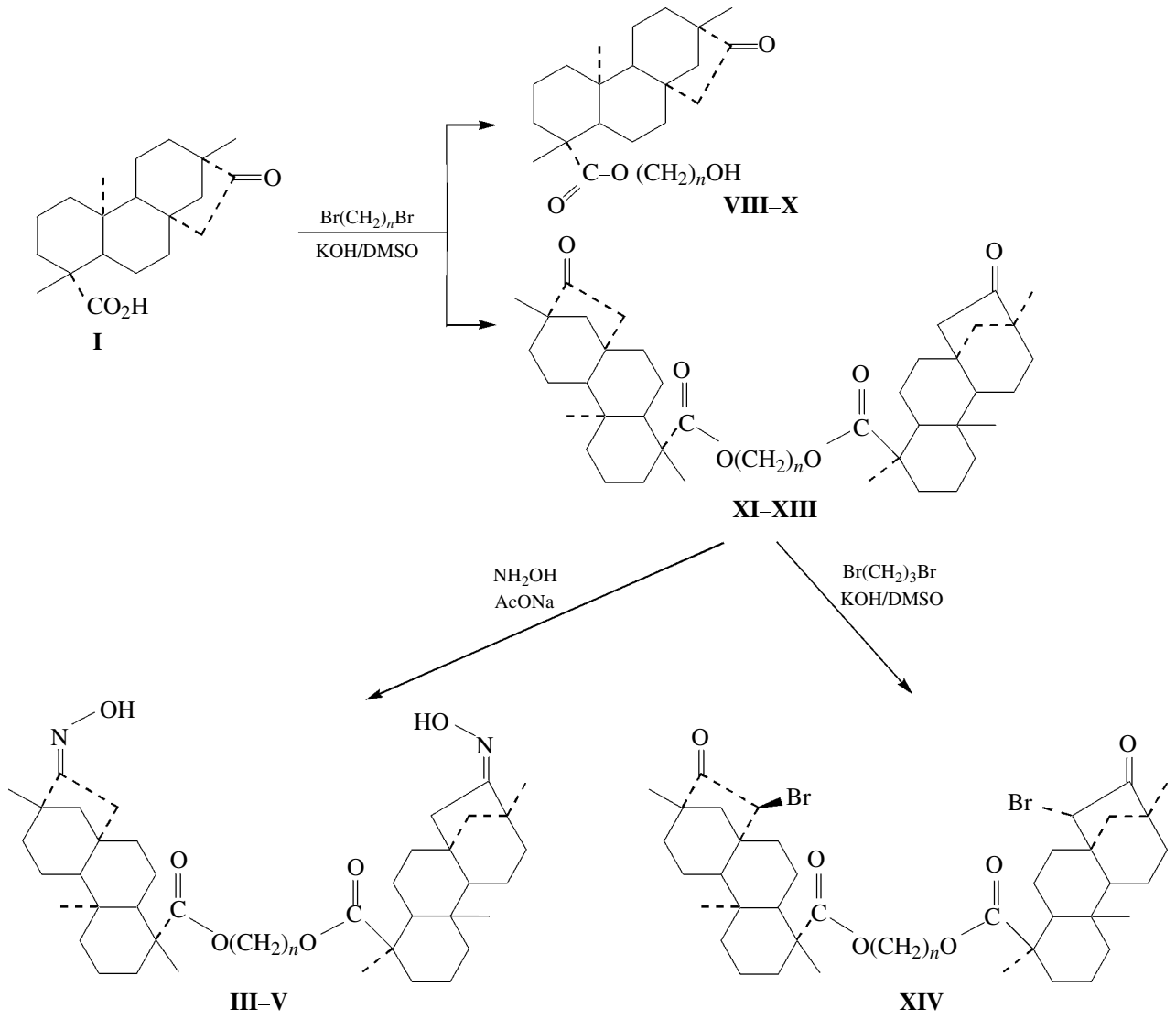
The alkylation of isosteviol (**I**) with in the superbasic KOH–DMSO medium occurs, like with oxime **II**, occurs easily, and the reaction route depends on the stoichiometric ratio of the reagents. At a 1 : 1 ratio, a mixture of keto alcohols **VIII**–**X** (yield 20–30%) and diesters **XI**–**XIII** (yield 20–40%) is formed. The products were isolated individual by column chromatography. At a double excess of isosteviol (**I**), exclusive formation of diesters **XI**–**XIII** (yields 50–80%) are formed. The constants of all the isolated compounds coincide with the constants of the same compounds obtained previously by the reaction of isosteviol chloride with the corresponding diols [4].

The reaction of diesters **XI**–**XIII** with hydroxylamine gave crystalline substances which, according to the IR, ^1H NMR, and mass spectra, are dioximes **III**–**V**. The reaction of isosteviol (**I**) with excess dibromopropane takes an unusual pathway to give isosteviol diester **XIV** brominated by C^{15} [15]. Like the bromination of isosteviol methyl ester **VI** with bromoalkalnes, the reaction occurs stereospecifically to form a $C^{15}S$ stereoisomer.

Thus, 16-hydroiminoisosteviol (**II**) reacts with dibromoalkanes in the superbasic medium KOH–DMSO involves O-alkylation of the isosteviol carcass and produces diesters **III**–**V**.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer at 400–3600 cm^{-1} for suspensions in Vaseline oil (solids) or thin films between KBr plates (liquids). The mass spectra were obtained on an MÆ-1310 instrument, ionizing voltage 60 V, collector current 30 μA; samples were introduced through a direct probe inlet, the ampule was heated from 120 to 250°C. The ^1H NMR spectra were obtained on a Bruker WM-250 instrument. Column chromatography was performed on silica (Chemapol). Reaction mix-



n = 2 (**III, VIII, XI**), 3 (**IV, IX, XII**), 4 (**V, X, XIII**).

tures were analyzed by TLC on Silufol UV-254 plates, eluent petroleum ether–ethyl acetate, 1 : 1.

ent-16-Hydroximinobeyeran-19-oic acid (**II**) was prepared by the reaction of isosteviol (**I**) with hydroxylamine [5]. Commercial DMSO was distilled without preliminary drying.

Isosteviol dioximes III–V. *a*. Reaction of 16-hydroximinoisosteviol **II** with dibromoalkanes. Dihaloalkane, 0.6 mmol, was added to a stirred mixture of 0.6 mmol of compound **II**, 1.2 mmol of KOH, and 4 ml of DMSO at 60°C. The reaction mixture was heated with stirring for 13 h at 70–80°C and diluted with 35 ml of water. The reaction products were extracted with ether (120 ml), and the extract was washed with water and dried with $MgSO_4$. The solvent was removed, and the adducts were purified by column chromatography on silica, eluent chloroform.

b. Reaction of diesters **XI–XIII** with hydroxylamine. Isosteviol diester **XI–XIII**, 1 mmol, was dissolved in 15 ml of CH_3OH and mixed with a solution of 2 mmol of $NH_2OH \cdot HCl$ and 4 mmol of AcONa in 4 ml of water. If the solution got turbid, CH_3OH was added for transparency. The reaction mixture was left to stand at room temperature without stirring until crystals formed.

Ethylene bis(*ent*-16-hydroiminobeyeran-19-oate) (III). Yield 75%, mp 271–272°C (from MeOH). IR spectrum, ν, cm^{-1}: 935 (N–O), 1135, 1160, 1220 (COO), 1690 (C=N), 1730 (C=O), 3180, 3280 (N–OH). ^1H NMR spectrum (C_5D_5N), δ, ppm (*J*, Hz): 0.88 s (3H, 20-CH_3), 1.29 s (3H, 17-CH_3), 1.31 s (3H,

18-CH_3), 3.30 d.d (1H, H_α^{15}, *J* 18.4, 3.3), 4.39 m [4H, $CH_2O(O)C$]. Mass spectrum, *m/z* (I_{rel}, %): 693 (1.3), 692 (2.5) [$M^{+\cdot}$] [1]; 677 (10.1) [$M - CH_3$]$^+$; 674 (11.1) [$M - H_2O$]$^+$; 659 (22.5) [$M - H_2O - CH_3$]$^+$; 658 (12.5), 643 (4.6), 634 (5.7), 621 (4.7), 619 (13.6), 618 (28.6), 603 (5.4), 590 (2.1), 575 (1.3), 446 (5.5), 430 (10.4), 378 (22.6), 360 (65.6), 342 (72.4), 333 (5), 317 (3.4), 316 (8.4), 301 (8.0), 288 (52.8), 272 (60), 270 (100). Found, %: C 72.78; H 9.80; N 3.98. $C_{42}H_{64}N_2O_6$. Calculated, %: C 72.78; H 9.33; N 4.04.

Trimethylene bis(*ent*-16-hydroiminobeyeran-19-oate) (IV). Yield 65%, mp 220–222°C (from MeOH). IR spectrum, ν, cm^{-1}: 940 (N–O), 1150, 1175, 1220 (COO), 1685 (C=N), 1725 (C=O), 3150, 3300 (N–OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.73 s (3H, 20-CH_3), 1.17 s (3H, 17-CH_3), 1.20 s (3H, 18-CH_3), 2.98 d.d (1H, H_α^{15}, *J* 18.2, 3.3), 4.11 m [4H, $CH_2O(O)C$]. Mass spectrum, *m/z* (I_{rel}, %): 707 (0.02), 706 (0.03) [$M^{+\cdot}$] ; 691 (0.2) [$M - CH_3$]$^+$; 689 (0.1) [M – OH]$^+$; 688 (0.2) [M – H2O]$^+$; 673 (0.7) [$M - H_2O - CH_3$]$^+$; 672 (0.7), 671 (0.3), 670 (0.2), 669 (0.1), 661 (0.1), 657 (0.2), 356 (11.4), 350 (3.1), 348 (7.8), 340 (1.6), 333 (42.6), 316 (20.2), 312 (8.0), 300 (8.0), 297 (10.1), 288 (75.3), 287 (100). Found, %: C 72.67; H 10.05; N 4.48. $C_{43}H_{66}N_2O_6$. Calculated, %: C 73.03; H 9.43; N 3.96.

Tetramethylene bis(*ent*-16-hydroiminobeyeran-19-oate) (V). Yield 60%, mp 226–229°C (from MeOH). IR spectrum, ν, cm^{-1}: 935 (N–O), 1160, 1180, 1220 (COO), 1630 (C=N), 1725 (C=O), 3311, 3436 (N–OH). ^{1}H NMR spectrum (250 MHz, C_5D_5N), δ, ppm (*J*, Hz): 0.91 s (3H, 20-CH_3), 1.29 s (3H, 17-CH_3), 1.32 s (3H, 18-CH_3), 3.36 d.d (1H, H_α^{15}, *J* 18.4, 3.1), 4.2 m [4H, $CH_2O(O)C$]. Mass spectrum, *m/z* (I_{rel}, %): 705 (1.1) [$M - CH_3$]$^+$; 703 (0.7) [M – OH]$^+$; 702 (1.1) [M – H2O]$^+$; 687 (11.2) [M – H2O – CH_3]$^+$; 684 (2.8), 674 (9.7), 646 (44.1), 633 (12.5), 577 (10.5), 552 (3.6), 540 (11.6), 486 (4.5), 458 (24.1), 406 (4.7), 388 (17.7), 373 (23.1), 368 (15.7), 299 (13.8), 285 (12.8), 272 (100). Found, %: C 72.43; H 9.94; N 4.02. $C_{44}H_{68}N_2O_6$. Calculated, %: C 73.28; H 9.52; N 3.88.

Reaction of isosteviol (I) with dibromoalkanes. *a*. Component ratio 1 : 1. Dihaloalkane, 0.06 mmol, was added to a mixture of 0.6 mmol of I, 1.2 mmol of KOH, and 4 ml of DMSO at 60°C. The mixture was heated with stirring at 60–70°C for 12 h, after which it was diluted with 40 ml of water. The reaction products were extracted with ether, and the extract was washed with 200 ml of water and dried with $MgSO_4$. The solvent was removed, and the residue was subjected to chromatography on silica, eluent chloroform.

2-Hydroxyethyl-*ent*-16-ketobeyeran-19-oate (VIII). Yield 23%, mp 123–125°C (from MeOH).

Ethylene bis(*ent*-16- ketobeyeran-19-oate) (XI). Yield 34%, mp 183–185°C (from MeOH).

3-Hydroxypropyl-*ent*-16-ketobeyeran-19-oate (IX). Yield 20% (oil).

Trimethylene bis(*ent*-16-ketobeyeran-19-oate) (XII). Yield 40%, mp 153–155°C (from MeOH).

4-Hydroxybutyl-*ent*-16-ketobeyeran-19-oate (X). Yield 29% (oil).

Tetramethylene bis(*ent*-16-ketobeyeran-19-oate) (XIII). Yield 20%, mp 124–126°C (from MeOH).

The IR, ^{1}H NMR, and mass spectra of compounds **VIII**–**XIII** are identical to those reported in [4].

b. Reagent ratio 2 : 1. Dihaloalkane, 0.3 mmol, was added to a mixture of 0.6 mmol of **I**, 1.2 mmol of KOH, and 4 ml of DMSO at 60°C. Further workup was the same as in procedure *a*.

Ethylene bis(*ent*-16-ketobeyeran-19-oate) (XI). Yield 51%, mp 183–185°C (from MeOH).

Trimethylene bis(*ent*-16-ketobeyeran-19-oate) (XII). Yield 80%, mp 153–155°C (from MeOH).

Tetramethylene bis(*ent*-16-ketobeyeran-19-oate) (XIII). Yield 51%, mp 124–126°C (from MeOH).

The IR, ^{1}H NMR, and mass spectra of compounds **XI**–**XIII**, **VIII**–**XIII** are identical to those reported in [4].

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REFERENCES

1. Hanson, R., *The Tetracyclic Diterpenes,* Oxford: Pergamon, 1968.
2. Al'fonsov, V.A., Bakaleinik, G.A., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Litvinov, I.A., Strobykina, I.Yu., and Strobykin, S.I., *Zh. Obshch. Khim.,* 1998, vol. 68, no. 11, p. 1813.
3. Alfonsov, V.A., Bakaleynik, G.A., Gubaidullin, A.T., Kataev, V.E., Kovyljaeva, G.I, Konovalov, A.I., Litvinov, I.A., Strobykina, I.Yu., Andreeva, O.V., and

[1] Ions containing the most abundant isotope are shown.

Korochkina, M.G., *Mendeleev Commun.,* 2000, no. 5, p. 177.

4. Al'fonsov, V.A., Andreeva, O.V., Bakaleinik, G.I., Beskrovnyi, D.V., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Korochkina, M.G., Latypov, Sh.K., Litvinov, I.A., Musin, R.Z., and Strobykina, I.Yu., *Zh. Obshch. Khim.,* 2003, vol. 73, no. 7, p. 1186.
5. Al'fonsov, V.A., Bakaleinik, G.A., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Strobykina, I.Yu., Andreeva, O.V., and Korochkina, M.G., *Zh. Obshch. Khim.,* 2000, vol. 70, no. 8, p. 1406.
6. Kataev, V.E., Strobykin, S.I., Timosheva, A.P., Al'fonsov, V.A., Korochkina, M.G., and Strobykina, I.Yu., *Zh. Obshch. Khim.,* 2005, vol. 75, no. 2, p. 272.
7. Al'fonsov, V.A., Bakaleinik, G.A., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Litvinov, I.A., Strobykina, I.Yu., Strobykin, S.I., Andreeva, O.V., and Korochkina, M.G., *Zh. Obshch. Khim.,* 2000, vol. 70, no. 6, p. 1018.
8. Al'fonsov, V.A., Bakaleinik, G.A., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Litvinov, I.A., Strobykina, I.Yu., Andreeva, O.V., and Korochkina, M.G., *Zh. Obshch. Khim.,* 2001, vol. 71, no. 7, p. 1213.
9. Al'fonsov, V.A., Andreeva, O.V., Bakaleinik, G.I., Beskrovnyi, D.V., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Korochkina, M.G., Litvinov, I.A., Militsina, O.I., and Strobykina, I.Yu., *Zh. Obshch. Khim.,* 2003, vol. 73, no. 8, p. 1330.
10. Tarasova, O.A., Shmidt, E.Yu., Sinegovskaya, M.M., Petrova, O.V., Sobenina, L.N., Mikhaleva, A.I., and Trofimov, B.A., *Zh. Org. Khim.,* 1999, vol. 35, no. 11, p. 1614.
11. *Houben-Weyl. Metoden der organischen Chemie,* Stuttgart: Tieme, 1988, vol. 10/4, p. 217.
12. Nenitescu, C.D., *Chimie Organica, Bucuresti: Didactica si Pedagogica,* 1960, vol. 1. Translated under the title *Organicheskaya khimiya,* Moscow: Inostrannaya Literutura, 1962, vol. 1, p. 695.
13. Yamada, T., Goto, K., Mitsuda, Y., and Tsuji, J., *Tetrahedron,* 1987, vol. 28. no. 39, p. 4557.
14. Tarasova, O.A., Brandsma, L., and Trofimof, B.A., *Synthesis,* 1993, vol. 6, p. 571.
15. Alfonsov, V.A., Andreeva, O.V., Bakaleynik, G.A., Beskrovny, D.V., Kataev, V.E., Kovyljaeva, G.I., Litvinov, I.A., Militsina, O.I., and Strobykina, I.Yu., *Mendeleev Commun.,* 2003, vol. 13, no. 5, p. 234.