*Russian Journal of Organic Chemistry, Vol. 40, No. 10, 2004, pp. 1521–1525. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 10, 2004, pp. 1569–1573.*


# Reactions of 2,3,5-Trichloro-4,4-ethylenedioxy-2-cyclopentenone with Some Ambident Nucleophiles. Sterically Loaded Functionalized 6-Azabicyclo[3.1.0]hex-5-enes

**G. A. Shavaleeva, N. A. Ivanova, F. G. Usmanova, R. R. Akhmetvaleev, and M. S. Miftakhov**

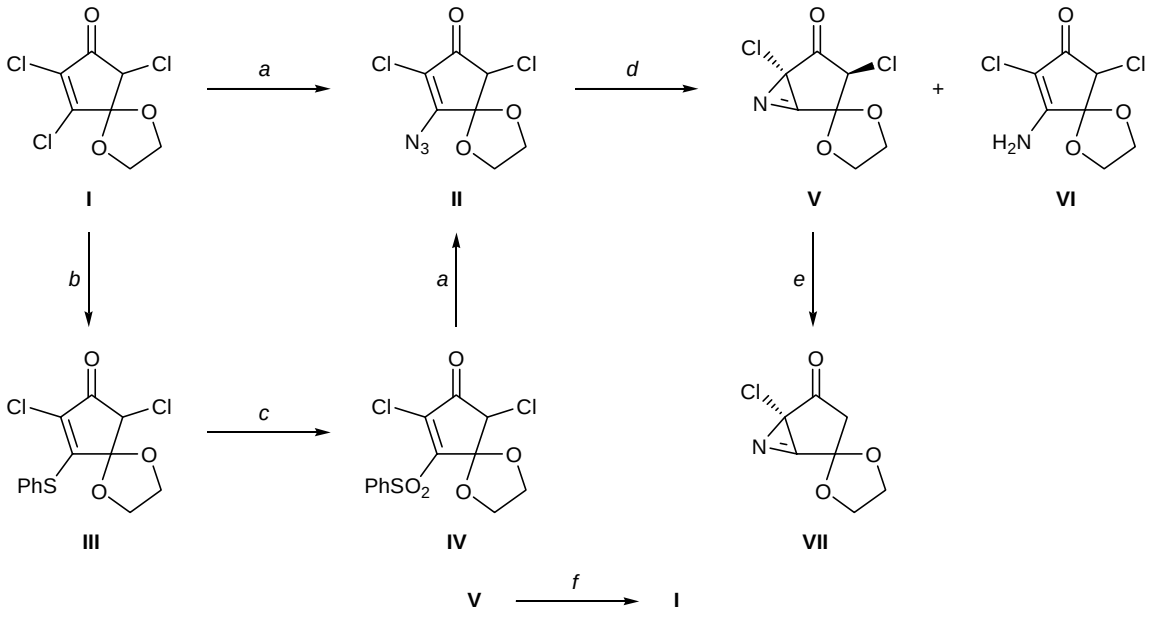
*Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia*
*fax: (3472)356066; e-mail: bioreg@anrb.ru*

Received January 17, 2004

**Abstract**—2,3,5-Trichloro-4,4-ethylenedioxy-2-cyclopentenone reacted with sodium azide in tetrahydrofuran to give the expected 3-azido derivative which was converted into 1,3-dichloro-4,4-ethylenedioxy-6-azabicyclo-[3.1.0]hex-5-en-2-one and 3-amino-2,5-dichloro-4,4-ethylenedioxy-2-cyclopentenone on heating in chloroform. The reaction of 2,3,5-trichloro-4,4-ethylenedioxy-2-cyclopentenone with potassium thiocyanate, depending on the conditions, afforded the corresponding 3-thiocyanato derivative or symmetric sulfide. Treatment of the title compound with hydroxylamine resulted in opening of the dioxolane ring with simultaneous formation of oxime via replacement of chlorine at the neighboring $sp^2$-carbon atom.

In the past decade, the synthesis and transformations of azirines have attracted persistent attention [1–10]. This interest originates from both specific chemical properties of highly strained cyclic imines and isolation of a series of natural antibiotics having an azirine structure (e.g., azirinomycin [11], enantiomeric dizidazirines [12], and antazirine [13]). The most practical and general procedures for the synthesis of azirines are based on thermal and photochemical decomposition of vinyl azides, which involve inter-

**Scheme 1.**




*a*: $NaN_3$, THF, 20°C (82% from **I**; 71% from **II**); *b*: PhSNa, THF–MeOH (85%); *c*: *m*-$ClC_6H_4CO_3H$, $CH_2Cl_2$ (79%); *d*: $CHCl_3$, Δ, (**V**, 70%; **VI**, 10%); *e*: Zn–THF–$NH_4Cl$, Δ (20%); *f*: 20% hydrochloric acid, $Me_2CO$ (60%).

1070-4280/04/4010-1521 

mediate formation of vinylnitrenes. While continuing our studies on the chemical behavior of a new series of functionalized trichlorocyclopentenones derived from hexachlorocyclopentadiene [14], we examined the reaction of 2,3,5-trichloro-4,4-ethylenedioxy-2-cyclopentenone (**I**) with azide ion with a view to obtain the corresponding vinyl azide. Here, we took into account that the chlorine atom at $C^3$ in molecule **I** can readily be replaced via reactions with heteronucleophiles according to the $Ad_NE$ pattern.

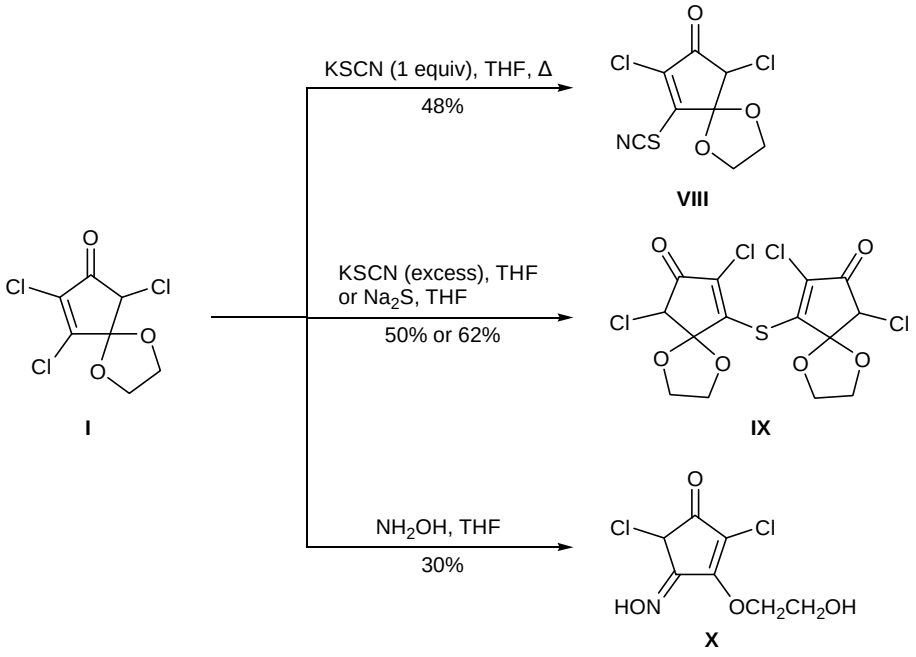
Experiments showed that trichlorocyclopentenone **I** smoothly reacted with sodium azide in tetrahydrofuran to give the corresponding vinyl azide **II** in a good yield (Scheme 1). It should be noted that analogous reaction with a stronger Michael acceptor, sulfone **IV** (which was prepared by oxidation of known sulfide **III** [15]) afforded azide **II** in a lower yield. Compound **II** was fairly stable on storage in a refrigerator, but on heating in chloroform or under UV irradiation it underwent decomposition with formation of several new products. In some experiments, by heating of azide **II** in boiling chloroform, followed by standard treatment and column chromatography on silica gel, we isolated crystalline bicyclic azirine **V** and amine **VI** (Scheme 1).

The $^{13}C$ NMR spectrum of azirine **V** revealed an appreciable upfield shift of the carbonyl carbon signal ($\delta_C$ 175.10 ppm), while the CHCl signal in the $^1H$ NMR spectrum was displaced downfield (δ 6.10 ppm), as compared to compounds **I** and **II**. The observed shifts are likely to result from the deshielding effect on 3-H of the *cis*-oriented chlorine atom at $C^1$ and anisotropic effect of the azirine ring on the carbonyl group.

We examined some reactions of compound **V**. Its decomposition (e.g., on storage in solution) leads to slow accumulation of amino derivative **VI**. Acid hydrolysis of **V** in a mixture of 20% hydrochloric acid with acetone gave initial trichloroketone **I**, and reductive dechlorination with Zn–$NH_4Cl$ in THF afforded partially dechlorinated azirine **VII** (Scheme 1).

The reaction of trichlorocyclopentenone **I** with another ambident nucleophile, potassium thiocyanate, resulted in formation of different products, depending on the reactant ratio. From equimolar amounts of enone **I** and KSCN in THF we obtained the corresponding thiocyanato derivative **VIII** as the major product, whereas treatment of **I** with excess KSCN gave sulfide **IX**. The reaction of compound **I** with hydroxylamine in the presence of sodium hydroxide was accompanied by opening of the dioxolane ring with formation of oxime **X**. The structure of sulfide **IX** was proved by independent synthesis from cyclopentenone **I** and sodium sulfide. According to the $^1H$ NMR data, symmetric sulfide **IX** is a mixture of racemic and *meso* forms at a ratio of 6:5 (or vice versa); the spectrum contained two singlets from 5-H at δ 4.60 and 4.61 ppm. In the $^{13}C$ NMR spectra, we also observed two signals at $\delta_C$ 153.66 and 153.89 ppm ($C^5$ and $C^{5'}$).

**Scheme 2.**



Undoubtedly, previously unknown bicyclic azirines **V** and **VII** attract interest from the viewpoints of their synthetic utility and potential biological activity.

## EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer from samples prepared as thin films (neat) or dispersed in Nujol. The NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 MHz for $^1$H and 75.47 MHz for $^{13}$C using $CDCl_3$ or acetone-$d_6$ (**V**, **VI**) as solvent and TMS as internal reference. The mass spectra (electron impact, 20 or 70 eV) were measured on an MKh-1306 instrument; ion source temperature 75–100°C. The progress of reactions was monitored by TLC on Silufol plates using pentane–ethyl acetate or petroleum ether–ethyl acetate as eluent; spots were visualized by treatment with an alkaline solution of $KMnO_4$ [16].

**2,5-Dichloro-4,4-ethylenedioxy-3-phenylsulfonyl-2-cyclopentenone (IV).** A solution of 1.50 g (4.73 mmol) of sulfide **III** in 15 ml of methylene chloride was added dropwise at 0°C to a suspension of 5.38 g (15.60 mmol) of 50% *m*-chloroperoxybenzoic acid in 20 ml of methylene chloride. The mixture was stirred for 1.5 h, filtered from excess *m*-chloroperoxybenzoic acid, diluted with 30 ml of methylene chloride, and washed with water. The aqueous phase was extracted with 30 ml of methylene chloride, and the extract was combined with the organic phase, washed with a solution of $NaHCO_3$ until neutral reaction, and dried over $MgSO_4$, The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethyl acetate. Yield 1.30 g (79%), colorless crystals, mp 122°C. IR spectrum, ν, cm$^{-1}$: 1765, 1600, 1040, 1335, 1160. $^1$H NMR spectrum, δ, ppm: 4.43 (2H, $CH_2O$, $J$ = 6.20 Hz), 4.50 (2H, $CH_2O$, $J$ = 6.56 Hz), 4.58 s (1H, 5-H), 7.60 t (2H, *m*-H, $J$ = 7.56 Hz), 7.72 t (1H, *p*-H, $J$ = 7.56 Hz), 8.04 t (2H, *o*-H, $J$ = 7.56 Hz). $^{13}$C NMR spectrum, $\delta_C$, ppm: 63.36 ($C^5$), 67.51 ($CH_2O$), 109.31 ($C^4$), 128.62 ($C^o$), 129.30 ($C^p$), 134.95 ($C^i$), 138.96 ($C^m$), 140.77 ($C^2$), 155.45 ($C^3$), 187.57 ($C^1$). Found, %: C 44.52; H 3.03; Cl 20.16; S 9.24. $C_{13}H_{10}Cl_2O_5S$. Calculated, %: C 44.72; H 2.89; Cl 20.31; S 9.18.

**3-Azido-2,5-dichloro-4,4-ethylenedioxy-2-cyclopentenone (II).** *a*. Sodium azide, 0.16 g (2.40 mmol), was added to a solution of 0.30 g (1.20 mmol) of ketone **I** in 6 ml of THF, and the mixture was stirred for 12 h at room temperature. The mixture was evaporated, the residue was dissolved in 10 ml of water, and the solution was extracted with chloroform (3×20 ml). The combined extracts were dried over $MgSO_4$ and concentrated, and the residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent to isolate 0.25 g (82%) of azide **II**.

*b*. Sodium azide, 0.08 g (1.15 mmol), was added at 20°C to a solution of 0.20 g (0.57 mmol) of sulfone **IV** in 5 ml of THF. The mixture was stirred for 1.5 h, diluted with water, and extracted with ethyl acetate (3×20 ml). The extract was washed with water and a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent to isolate 0.10 g (71%) of compound **II**. Colorless crystals, mp 95–97°C. IR spectrum, ν, cm$^{-1}$: 2160, 1752, 1620. $^1$H NMR spectrum, δ, ppm: 4.27–4.43 m (4H, $CH_2O$), 4.48 s (1H, 5-H). $^{13}$C NMR spectrum, $\delta_C$, ppm: 61.43 ($C^5$), 66.28 and 66.66 ($CH_2O$), 107.03 ($C^4$), 119.51 ($C^2$), 156.72 ($C^3$), 185.77 (C=O). Found, %: C 33.81; H 2.10; Cl 28.22; N 16.50. $C_7H_5Cl_2N_3O_3$. Calculated, %: C 33.63; H 2.02; Cl 28.36; N 16.61.

**Decomposition of azide II in chloroform.** A solution of 0.45 g (2.02 mmol) of azide **II** in 5 ml of chloroform was heated for 2 h under reflux. By chromatography on silica gel we isolated 0.31 g (70%) of azirine **V** and 0.04 g (10%) of amine **VI**.

**1,3-Dichloro-4,4-ethylenedioxy-6-azabicyclo-[3.1.0]hex-5-en-2-one (V).** Colorless crystals, mp 126–127°C (from ethyl acetate–petroleum ether, 7:3) IR spectrum, ν, cm$^{-1}$: 2020, 1680, 1600. $^1$H NMR spectrum (acetone-$d_6$), δ, ppm: 4.88–4.98 m (2H, $CH_2O$), 5.08–5.13 m (2H, $CH_2O$), 6.20 s (1H, 3-H). $^{13}$C NMR spectrum, $\delta_C$, ppm: 44.86 ($C^3$), 85.48 ($C^1$), 68.95 and 71.55 ($CH_2O$), 114.09 ($C^5$), 166.38 ($C^6$), 175.10 (C=O). Found, %: C 38.60; H 2.20; Cl 31.53; N 6.50. $C_7H_5Cl_2NO_3$. Calculated, %: C 38.87; H 2.27; Cl 31.94; N 6.31. Mass spectrum (EI, 70 eV), *m*/*z*: 222 $[M]^+$, 147, 103, 119, 114.

**3-Amino-2,5-dichloro-4,4-ethylenedioxy-2-cyclopentenone (VI).** Colorless crystals, mp 260°C. IR spectrum, ν, cm$^{-1}$: 3350, 1680, 1620, 1590. $^1$H NMR spectrum, δ, ppm: 3.05–3.10 m (4H, $CH_2O$), 3.14 br.s (1H, CHCl), 3.94 br.s (2H, $NH_2$). $^{13}$C NMR spectrum, $\delta_C$, ppm: 62.21 ($C^5$), 66.52 and 66.69 ($CH_2O$), 101.18 ($C^4$), 106.08 ($C^7$), 163.22 ($C^2$), 183.06 (C=O). Found, %: C 37.60; H 3.20; Cl 31.58; N 6.45. $C_7H_7Cl_2NO_3$. Calculated, %: C 37.53; H 3.15; Cl 31.65; N 6.25.

**1-Chloro-4,4-ethylenedioxy-6-azabicyclo[3.1.0]-hex-5-en-2-one (VII).** To a solution of 0.15 g (0.60 mmol) of compound **V** in 3 ml of THF we added 0.18 g (2.75 mmol) of Zn and 0.003 g (0.06 mmol) of ammonium chloride, and the mixture was heated for 2 h at the boiling point under stirring. The mixture was cooled and filtered, the filtrate was evaporated, the residue was dissolved in 5 ml of water, and the solution was extracted with methylene chloride (3×10 ml). The combined extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by column chromatography on silica gel using pentane–ethyl acetate (1:1) as eluent. Yield 0.03 g (20%), colorless oily substance, $R_f$ 0.13 (from pentane–ethyl acetate, 1:1). IR spectrum, ν, $cm^{-1}$: 2272, 1738, 1648, 1588. $^1H$ NMR spectrum (acetone-$d_6$), δ, ppm: 4.02 s (2H, 2-H), 4.81–5.01 m (4H, $CH_2O$). $^{13}C$ NMR spectrum (acetone-$d_6$), $\delta_C$, ppm: 30.15 ($C^2$), 68.47 and 70.99 ($CH_2O$), 87.49 ($C^1$), 114.82 ($C^4$), 168.85 ($C^5$), 178.39 (C=O). Found, %: C 44.80; H 3.20; Cl 18.98; N 7.50. $C_7H_6ClNO_3$. Calculated, %: C 44.82; H 3.22; Cl 18.90; N 7.47.

**2,5-Dichloro-4,4-ethylenedioxy-3-thiocyanato-2-cyclopentenone (VIII).** Potassium thiocyanate, 0.20 g (2.10 mmol), was added to a solution of 0.50 g (2.10 mmol) of trichlorocyclopentenone **I** in 5 ml of THF, and the mixture was heated for 12 h under reflux with stirring. The solvent was distilled off, the residue was dissolved in 10 ml of water, and the solution was extracted with chloroform (3×20 ml). The combined extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue was subjected to chromatography on silica gel using pentane–ethyl acetate (1:1). Yield 0.24 g (48%), colorless oily substance, $R_f$ 0.4 (pentane–ethyl acetate, 1:4). IR spectrum, ν, $cm^{-1}$: 2380, 1720, 1680, 1480, 1380. $^1H$ NMR spectrum, δ, ppm: 4.24 br.s (1H, 5-H), 4.18–4.21 m (4H, $CH_2O$). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 62.28 ($C^5$), 66.29 and 66.60 ($CH_2O$), 101.41 (CH), 106.26 ($C^4$), 150.90 ($C^2$), 163.10 ($C^3$), 182.94 (C=O). Found, %: C 36.00; H 1.80; Cl 26.52; N 5.90; S 12.15. $C_8H_5Cl_2NSO_3$. Calculated, %: C 36.11; H 1.89; Cl 26.65; N 5.60; S 12.05.

**Bis(2,4-dichloro-5,5-ethylenedioxy-3-oxo-1-cyclopentenyl) sulfide (IX).** *a.* Sodium sulfide, 0.08 g (1.05 mmol), was added to a solution of 0.50 g (2.10 mmol) of compound **I** in 5 ml of THF. The mixture was stirred for 6 h at room temperature and evaporated, the residue was dissolved in 10 ml of water, and the solution was extracted with chloroform (3×20 ml). The combined extracts were dried over $MgSO_4$, filtered, and concentrated, and the product was isolated by column chromatography on silica gel using pentane–ethyl acetate (1:4) as eluent. Yield 0.33 g (65%). Yellow oily substance, $R_f$ 0.5 (pentane–ethyl acetate, 1:4). IR spectrum, ν, $cm^{-1}$: 1740, 1610, 1580, 1470, 1270, 1200, 1003. $^1H$ NMR spectrum, δ, ppm: 4.18–4.45 m (8H, $CH_2O$), 4.61 s and 4.68 s (2H, 5-H, 5'-H). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 61.84 and 61.97 ($CH_2O$), 67.20 and 67.27 ($C^5$, $C^{5'}$), 108.77 and 108.83 ($C^4$, $C^{4'}$), 137.67 and 138.09 ($C^2$, $C^{2'}$), 153.66 and 153.89 ($C^3$, $C^{3'}$), 186.25 ($C^1$, $C^{1'}$). Found, %: C 37.52; H 2.15; Cl 31.30; S 7.20. $C_{14}H_{10}Cl_4SO_6$. Calculated, %: C 37.53; H 2.25; Cl 31.65; S 7.15.

*b*. Following the above procedure, by reaction of compound **I** with 4 equiv of potassium thiocyanate we obtained 0.25 g (50%) of sulfide **IX**.

**2,4-Dichloro-5-(2-hydroxyethoxy)-4-cyclopentene-1,3-dione 1-oxime (X).** A solution of 0.15 g (2.10 mmol) of hydroxylamine hydrochloride and 0.08 g (2.10 mmol) of sodium hydroxide in 3 ml of water was added to a solution of 0.25 g (1.05 mmol) of ketone **I** in 5 ml of THF. The mixture was stirred for 2 h and evaporated, the residue was dissolved in 10 ml of water, and the solution was extracted with methylene chloride (3×20 ml). The combined extracts were dried over $MgSO_4$, filtered, and concentrated, and the product was isolated by chromatography on silica gel using pentane–ethyl acetate (1:1) as eluent. Yield 0.07 g (30%). Colorless oily substance, $R_f$ 0.27 (pentane–ethyl acetate, 1:1). IR spectrum, ν, $cm^{-1}$: 3600, 3200, 1940, 1720, 1580. $^1H$ NMR spectrum, δ, ppm: 3.89–4.02 m (4H, $CH_2O$), 4.07 br.s (1H, CHCl), 4.11–4.40 m (1H, OH), 12.30 br.s (1H, NOH). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 42.68 ($C^2$), 60.37 ($C^{2'}$), 75.97 ($C^{1'}$), 115.08 ($C^4$), 148.09 ($C^1$), 167.88 ($C^5$), 185.26 (C=O). Found, %: C 35.10; H 2.90; Cl 29.45; N 5.80. $C_7H_7Cl_2NO_4$. Calculated, %: C 35.03; H 2.94; Cl 29.54; N 5.84.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 02-03-32594a).

## REFERENCES

1. Inui, H. and Murada, S., *Chem. Phys. Lett.*, 2002, vol. 359, p. 267.
2. Ray, C.A., Risberg, E., and Somfai, P., *Tetrahedron Lett.*, 2001, vol. 42, p. 9289.

3. Palacios, F., Aparicio, D., Ochoa de Retana, A.M., de los Santos, J.M., Gil, J.L., and de Munain, R.L., *Tetrahedron: Assymetry*, 2003, vol. 14, p. 689.
4. Alves, M.J., Ferreira, P.M.T., Maia, H.L.S., Monteiro, L.S., and Gilchrist, T.L., *Tetrahedron Lett*., 2000, vol. 41, p. 4991.
5. Alves, M.J., Gilchrist, T.L., and Sousa, J.H., *J. Chem. Soc., Perkin Trans. 1*, 1999, p. 1305.
6. Padwa, A., Woolhous, A.D., Katritzky, A.R., and Rees, C.W., *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R. and Rees, C.W.. Oxford: Pergamon, 1984, vol. 7, p. 47.
7. Bornemann, C. and Klessinger, M., *Chem. Phys*., 2000, vol. 259, p. 263.
8. Pinho e Melo, T., Cardoso, A.L., and d'A. Rocha Gonsales, A.M., *Tetrahedron*, 2003, vol. 59, p. 2345.
9. Pinho e Melo, T., Lopes, C.S.J., and d'A. Rocha Gonsales, A.M., *Tetrahedron Lett*., 2000, vol. 41, p. 7217.
10. Pinho e Melo, T., Lopes, C.S.J., Cardoso, A.L., and d'A. Rocha Gonsales, A.M., *Tetrahedron*, 2001, vol. 57, p. 6203.
11. Miller, T.W., Tristram, E.W., and Wolf, F.J., *J. Antibiot*., 1971, vol. 24, p. 48.
12. Molinski, T.F. and Ireland, C.M., *J. Org. Chem*., 1988, vol. 53, p. 2103.
13. Salomon, C.E., William, D.H., and Faulkner, D.J., *J. Nat. Prod*., 1995, vol. 58, p. 1463.
14. Akhmetvaleev, R.R., Akbutina, F.A., Ivanova, N.A., and Miftakhov, M.S., *Izv. Ross. Akad. Nauk, Ser. Khim*., 2001, p. 1417.
15. Akhmetvaleev, R.R., Ivanova, N.A., Imaeva, L.R., Belogaeva, T.A., Shainurova, A.M., and Miftakhov, M.S., *Izv. Ross. Akad. Nauk, Ser. Khim*., 1997, p. 1990.
16. Kirchner, J.G., *Thin-Layer Chromatography*, Perry, E.S., Ed., New York: Wiley, 1978, 2nd ed. Translated under the title *Tonkosloinaya khromatografiya*, Moscow: Mir, 1981, vol. 1, p. 269.