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Reaction of (–)-*cis*-Verbenol Epoxide with Aromatic Aldehydes over Montmorillonite K10 Clay

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Abstract—Reactions of (–)-*cis*-verbenol epoxide with a series of *para*-substituted benzaldehydes in the presence of montmorillonite K10 gave mixtures of products of intra- and intermolecular transformations, whose composition depended on the initial aldehyde.

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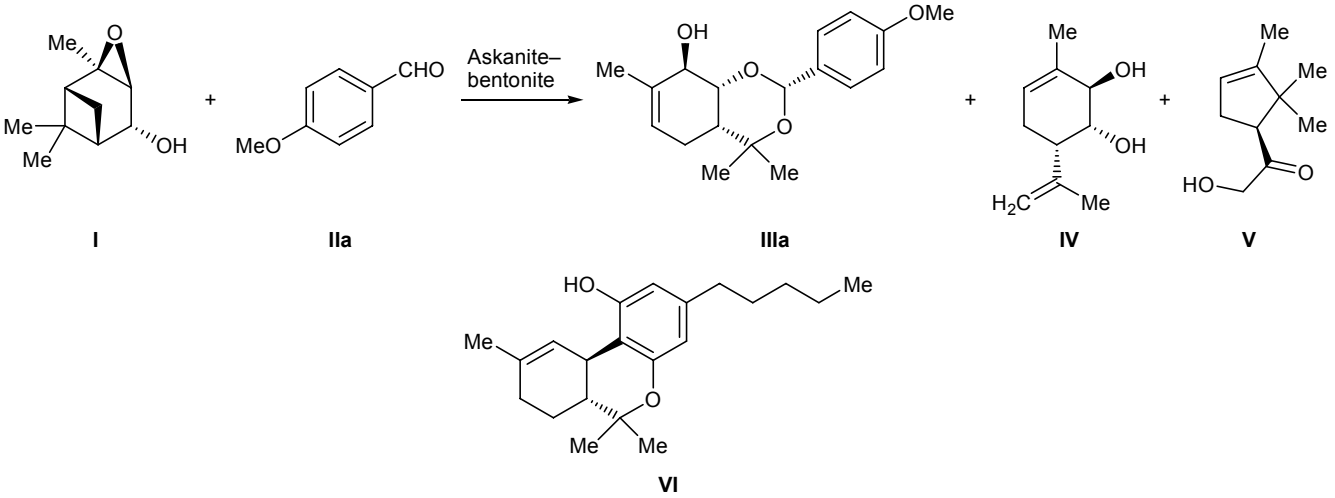
Compounds isolated from natural sources play a very important role in the design of new biologically active substances, including medical agents [1]. Among these, terpenes attract specific attention due to their accessibility (often as optically active substances), high reactivity, and the ability to undergo skeletal rearrangements. We previously [2, 3] examined reactions of some terpenoids of the *p*-menthane, carane, and pinane series with aldehydes in the presence of montmorillonite clays, which led to the formation of new polyfunctional heterocyclic compounds. For example, (–)-*cis*-verbenol epoxide (**I**) reacted with *p*-methoxybenzaldehyde (**IIa**) in the presence of natural askanite–bentonite montmorillonite clay to give heterocyclic compound **IIIa** and products of isomerization of the initial epoxide, *trans*-diol **IV** with a *p*-menthane skeleton and hydroxy ketone **V** [4] (Scheme 1). Compound **IIIa** may be regarded as a structural analog of tetrahydrocannabinol (**VI**). At present, tetrahydrocannabinol analogs and derivatives have attracted considerable interest due to their diverse biological activity [5–7].

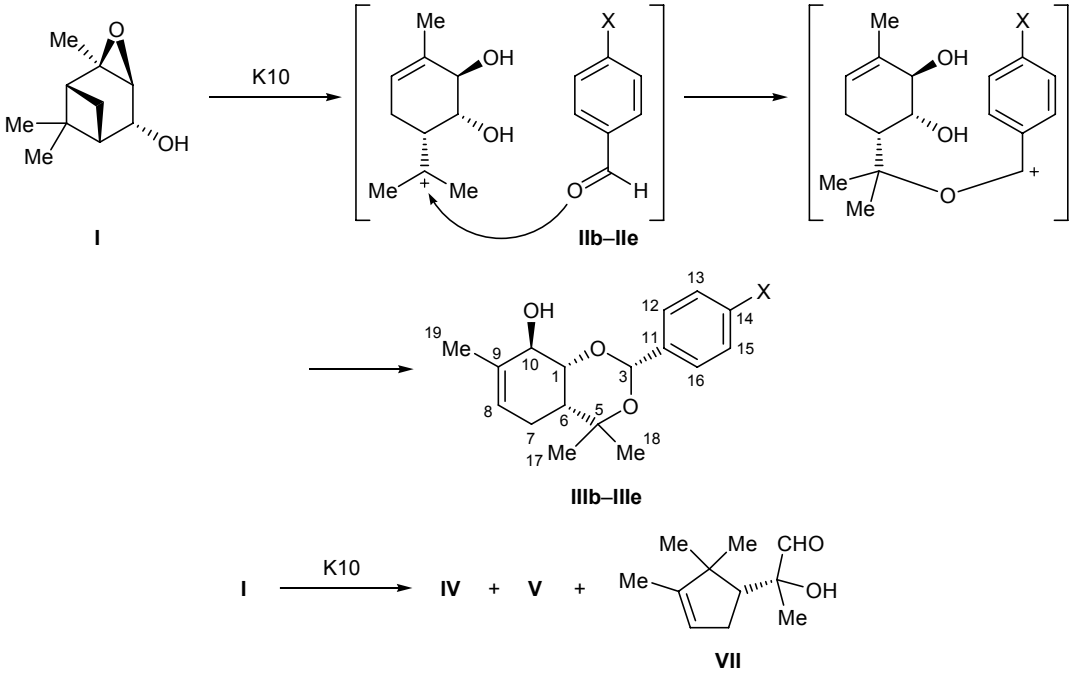
In the present work we continued our study on the above unusual reaction with a view to reveal whether variation of the initial aldehyde structure could lead to formation of new compounds. For this purpose, we examined reactions of (–)-*cis*-verbenol epoxide (**I**) with a number of *para*-substituted benzaldehydes **IIb**–**IIe** in the presence of commercially available K10 montmorillonite clay.

Scheme 1.



I **IIa** **IIIa** **IV** **V** **VI**

Scheme 2.



X = F (**b**), Cl (**c**), Br (**d**), O_2N (**e**).

The reactions of epoxy derivative **I** with halogen- and nitro-substituted benzaldehydes **IIb**–**IIe** over K10 clay gave compounds **IIIb**–**IIIe** (Scheme 2) together with isomerization products of initial epoxide **I**: *trans*-diol **IV**, hydroxy ketone **V**, and α-hydroxy aldehyde **VII**. Compounds **IV**, **V**, and **VII** were isolated previously while studying isomerization of epoxy alcohol **I** in the presence of clay [8]. The product composition is given in table. Our results showed that the yield of the intermolecular transformation products in the reactions of **I** with halogen-substituted aldehydes **IIb**–**IId** decreases from 15 to 6% in going from fluorine to chlorine and bromine. Although the reaction of (–)-*cis*-verbenol epoxide (**I**) with *p*-methoxybenzaldehyde gave 13% of compound **IIIa** [4], only traces of the corresponding product were detected by GC–MS in the reaction mixture obtained from epoxide **I** and *p*-dimethylaminobenzaldehyde (**IIf**), and we failed to isolate this product as individual substance. In the reaction of **I** with benzaldehyde **IIe** having an electron-withdrawing nitro group in the *para* position, compound **IIIe** was formed in 5% yield. Thus the reaction of verbenol epoxide (**I**) with *para*-substituted benzaldehydes is governed not only by donor–acceptor properties of the *para*-substituent but also by specificity of adsorption of the initial aldehyde on K10, as well as by the effect of the aldehyde on the active centers on the catalyst surface.

The yields of the isomerization products of epoxide **I**, i.e., compounds **IV**, **V**, and **VII**, also depend on the initial aldehyde. Diol **IV** was formed in the largest yield (45%) in the reaction of **I** with *p*-bromobenzaldehyde (**IId**), while the highest yield of α-hydroxy aldehyde **VII** (8%) was obtained in the reaction of **I** with *p*-nitrobenzaldehyde (**IIe**). High yield of compound **V** (35%) and the largest overall yield of the isomerization products (72%) were attained in the reaction with *p*-dimethylaminobenzaldehyde (**IIf**).

(–)-*cis*-Verbenol epoxide (**I**) failed to react with *o*-formylbenzonitrile, presumably for steric reasons, whereas isomerization products **IV**, **V**, and **VII** at a ratio of 5 : 10 : 1 were detected by GC–MS.

Yields (%) of compounds **III**–**V** and **VII** in the reactions of (–)-*cis*-verbenol epoxide (**I**) with *para*-substituted benzaldehydes *p*-XC_6H_4CHO (**IIa**–**IIf**)

Aldehyde	X	**III**	**IV**	**V**	**VII**
IIa [4]	OMe	13	33	7	–
IIb	F	15	26	11	2
IIc	Cl	8	27	10	4
IId	Br	6	45	14	4
IIe	NO_2	5	34	13	8
IIf	NMe_2	–	30	35	7

Compounds **IIIb**–**IIIe** were not reported previously; their structure was determined on the basis of the ^{1}H and ^{13}C NMR and high-resolution mass spectra with account taken of the data reported by us in [4] for structurally related compounds. Compounds **IIIb**–**IIIe**, as well as **IIIa** isolated previously, were formed as a single diastereoisomer.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500.13 and 125.76 MHz, respectively, from solutions in chloroform-*d*–carbon tetrachloride (~1 : 1 by volume) using the solvent signals as reference ($CHCl_3$, δ 7.24 ppm; $CDCl_3$, δ_C 76.90 ppm). The structure of the products was determined by analysis of the ^{1}H NMR spectra with the use of ^{1}H–^{1}H double resonance techniques and of the ^{13}C NMR spectra [*J*-modulation (JMOD), off-resonance decoupling from protons, two-dimensional ^{13}C–^{1}H heteronuclear correlations through direct and long-range spin–spin couplings (C–H COSY, $^1J_{CH}$ = 135 Hz; COLOC and HMBC, $^2J_{CH}$ = $^3J_{CH}$ = 10 Hz)]. The high-resolution mass spectra were obtained on a DFS Thermo Scientific instrument; a.m.u. range 0–500, electron impact, 70 eV, direct sample admission into the ion source. The optical rotations $[\alpha]_D$ were measured on a PolAAr 3005 polarimeter from solutions in chloroform.

The initial compounds and products were analyzed by GLC on a Varian Model 3700 chromatograph equipped with a 15000×0.22-mm quartz capillary column (stationary phase VC-30) and a flame ionization detector; carrier gas helium, inlet pressure 1 atm. Gas chromatographic–mass spectrometric analysis was performed on a Hewlett–Packard HP 5890 Series II gas chromatograph coupled with an HP 5971 quadrupole mass-selective detector; HP-5MS quartz capillary column, 30000×0.25 mm; carrier gas helium.

Montmorillonite K10 (Merck) was calcined for 3 h at 110°C just before use. Methylene chloride was passed through a column charged with calcined aluminum oxide. The products were separated by column chromatography on silica gel (60–200 μm, Macherey–Nagel).

(–)-*cis*-Verbenol epoxide (**I**), $[\alpha]_D^{20}$ = –44° (*c* = 1.2, $CHCl_3$), was synthesized according to the procedure described in [4].

Reaction of (–)-*cis*-verbenol epoxide (I) with *para*-substituted benzaldehydes IIb–IIe over K10 montmorillonite. A solution of 0.5 g of aldehyde **IIb**–**IIe** in 5 ml of methylene chloride was added to a suspension of 2.5 g of K10 clay in 15 ml of methylene chloride, a solution of 0.5 g of epoxide **I** in 5 ml of methylene chloride was then added dropwise, and the mixture was stirred for 1 h at room temperature. The mixture was diluted with 5 ml of diethyl ether, the catalyst was filtered off, and the solvent was distilled off from the filtrate. The residue was subjected to column chromatography on silica gel (10 g) using hexane–diethyl ether as eluent (gradient elution, 0 to 100% of diethyl ether).

(2*R*,4a*R*,8*R*,8a*R*)-2-(4-Fluorophenyl)-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4*H*-1,3-benzodioxin-8-ol (IIIb) was obtained from epoxide **I** and *p*-fluorobenzaldehyde (**IIb**). Yield 0.132 g (15%), $[\alpha]_D^{19}$ = –66° (*c* = 26, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.24 s ($C^{18}H_3$), 1.50 d.d.d (6-H_{ax}, $J_{6\text{-}ax,7\text{-}ax}$ = 10.8, $J_{6\text{-}ax,7\text{-}eq}$ = 6.0, $J_{6\text{-}ax,1}$ = 2.0 Hz), 1.51 s ($C^{17}H_3$), 1.80 m ($C^{19}H_3$), 2.04 d.d.d.q (7-H_{eq}, ^2J = 17.7, $J_{7\text{-}eq,6\text{-}ax}$ = 6.0, $J_{7\text{-}eq,8}$ = 5.3, $J_{7\text{-}eq,19}$ = 1.2 Hz), 2.42 d.d.d.q.d (7-H_{ax}, ^2J = 17.7, $J_{7\text{-}ax,6\text{-}ax}$ = 10.8, $J_{7\text{-}ax,8}$ = 2.3, $J_{7\text{-}ax,19}$ = 2.3, $J_{7\text{-}ax,10\text{-}eq}$ = 1.5 Hz), 3.82 m (10-H_{eq}), 4.29 d.d (1-H, $J_{1,10\text{-}eq}$ = 2.5, $J_{1,6\text{-}ax}$ = 2.0 Hz), 5.61 d.m (8-H, $J_{8,7\text{-}eq}$ = 5.3 Hz), 5.73 s (3-H), 6.98 d.d (13-H, 15-H, $J_{13,12}$ = $J_{15,16}$ = 8.7, $^3J_{HF}$ = 8.7 Hz), 7.39 d.d (12-H, 16-H, $J_{12,13}$ = $J_{16,15}$ = 8.7, $^4J_{HF}$ = 5.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 75.08 d (C^1), 95.21 d (C^3), 74.58 s (C^5), 34.04 d (C^6), 23.08 t (C^7), 125.26 d (C^8), 130.93 s (C^9), 70.44 d (C^{10}), 134.95 d (C^{11}, $^4J_{CF}$ = 3.1 Hz), 128.21 d (C^{12}, C^{16}, $^3J_{CF}$ = 8.0 Hz), 114.88 d (C^{13}, C^{15}, $^2J_{CF}$ = 21.2 Hz), 162.90 d (C^{14}, $^1J_{CF}$ = 247.2 Hz), 22.79 q (C^{17}), 27.30 q (C^{18}), 20.64 q (C^{19}). Found: *m*/*z* 291.1394 $[M - H]^+$. $C_{17}H_{20}O_3F$. Calculated: [*M* – H] 291.1396. Also, 0.129 g (26%) of diol **IV**, 0.055 g (11%) of compound **V**, and 0.011 g (2%) of compound **VII** were isolated.

(2*R*,4a*R*,8*R*,8a*R*)-2-(4-Chlorophenyl)-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4*H*-1,3-benzodioxin-8-ol (IIIc) was obtained from epoxide **I** and *p*-chlorobenzaldehyde (**IIc**). Yield 0.069 g (8%), $[\alpha]_D^{19}$ = –67° (*c* = 2, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.24 s ($C^{18}H_3$), 1.49 d.d.d (6-H_{ax}, $J_{6\text{-}ax,7\text{-}ax}$ = 10.6, $J_{6\text{-}ax,7\text{-}eq}$ = 6.0, $J_{6\text{-}ax,1}$ = 2.0 Hz), 1.50 s ($C^{17}H_3$), 1.79 m ($C^{19}H_3$), 2.03 d.d.d.q (7-H_{eq}, ^2J = 17.5, $J_{7\text{-}eq,6\text{-}ax}$ = 6.0, $J_{7\text{-}eq,8}$ = 5.2, $J_{7\text{-}eq,19}$ = 1.2 Hz), 2.39 d.d.d.q.d (7-H_{ax}, ^2J = 17.5, $J_{7\text{-}ax,6\text{-}ax}$ = 10.6, $J_{7\text{-}ax,8}$ = 2.5, $J_{7\text{-}ax,19}$ = 2.5, $J_{7\text{-}ax,10\text{-}eq}$ = 1.5 Hz), 3.80 m (10-H_{eq}), 4.26 d.d (1-H_{eq}, $J_{1\text{-}eq,10\text{-}eq}$ = 2.5, $J_{1\text{-}eq,6\text{-}ax}$ = 2.0 Hz), 5.60 d.m (8-H, $J_{8,7\text{-}eq}$ = 5.2 Hz), 5.71 s (3-H), 7.27 d (12-H, 16-H, $J_{12,13}$ = $J_{16,15}$ = 8.3 Hz), 7.35 d (13-H, 15-H, $J_{13,12}$ = $J_{15,16}$ = 8.3 Hz).

^{13}C NMR spectrum, δ_C, ppm: 75.07 d (C^1), 94.99 d (C^3), 74.58 s (C^5), 33.98 d (C^6), 23.00 t (C^7), 125.12 d (C^8), 130.84 s (C^9), 70.29 d (C^{10}), 137.44 s (C^{11}), 127.77 d (C^{12}, C^{16}), 128.14 d (C^{13}, C^{15}), 134.38 s (C^{14}), 22.71 q (C^{17}), 27.23 q (C^{18}), 20.61 q (C^{19}). Found: *m*/*z* 308.1174 $[M]^+$. $C_{17}H_{21}ClO_3$. Calculated: *M* 308.1174. Also, 0.133 g (27%) of diol **IV**, 0.052 g (10%) of compound **V**, and 0.018 g (4%) of compound **VII** were isolated.

(2*R*,4a*R*,8*R*,8a*R*)-2-(4-Bromophenyl)-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4*H*-1,3-benzodioxin-8-ol (IIId) was obtained from epoxide **I** and *p*-bromobenzaldehyde (**IId**). Yield 0.066 g (6%), $[\alpha]_D^{19}$ = –49° (*c* = 3.3, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.23 s ($C^{18}H_3$), 1.49 d.d.d (6-H_{ax}, $J_{6\text{-}ax,7\text{-}ax}$ = 10.6, $J_{6\text{-}ax,7\text{-}eq}$ = 6.0, $J_{6\text{-}ax,1\text{-}eq}$ = 2.0 Hz), 1.50 s ($C^{17}H_3$), 1.79 br.s ($C^{19}H_3$), 2.03 d.d.d.q (7-H_{eq}, ^2J = 17.6, $J_{7\text{-}eq,6\text{-}ax}$ = 6.0, $J_{7\text{-}eq,8}$ = 5.2, $J_{7\text{-}eq,19}$ = 1.2 Hz), 2.39 d.d.d.q.d (7-H_{ax}, ^2J = 17.6, $J_{7\text{-}ax,6\text{-}ax}$ = 10.6, $J_{7\text{-}ax,8}$ = 2.5, $J_{7\text{-}ax,19}$ = 2.5, $J_{7\text{-}ax,10\text{-}eq}$ = 1.5 Hz), 3.80 m (10-H_{eq}), 4.27 d.d (1-H_{eq}, $J_{1\text{-}eq,10\text{-}eq}$ = 2.5, $J_{1\text{-}eq,6\text{-}ax}$ = 2.0 Hz), 5.60 d.m (8-H, $J_{8,7\text{-}eq}$ = 5.2 Hz), 5.70 s (3-H), 7.29 d (12-H, 16-H, $J_{12,13}$ = $J_{16,15}$ = 8.5 Hz), 7.42 d (13-H, 15-H, $J_{13,12}$ = $J_{15,16}$ = 8.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 75.05 d (C^1), 95.05 d (C^3), 74.62 s (C^5), 33.98 d (C^6), 23.01 t (C^7), 125.18 d (C^8), 130.84 s (C^9), 70.33 d (C^{10}), 137.92 s (C^{11}), 128.11 d (C^{12}, C^{16}), 131.12 d (C^{13}, C^{15}), 122.64 s (C^{14}), 22.73 q (C^{17}), 27.24 q (C^{18}), 20.63 q (C^{19}). Found: *m*/*z* 352.0654 $[M]^+$. $C_{17}H_{21}BrO_3$. Calculated: *M* 352.0669. In addition, 0.223 g (45%) of diol **IV**, 0.072 g (14%) of compound **V**, and 0.020 g (4%) of compound **VII** were isolated.

(2*R*,4a*R*,8*R*,8a*R*)-4,4,7-Trimethyl-2-(4-nitrophenyl)-4a,5,8,8a-tetrahydro-4*H*-1,3-benzodioxin-8-ol (IIIe) was obtained from epoxide **I** and *p*-nitrobenzaldehyde (**IIe**). Yield 0.049 g (5%), $[\alpha]_D^{19}$ = –59° (*c* = 12, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.25 s ($C^{18}H_3$), 1.52 s ($C^{17}H_3$), 1.53 d.d.d (6-H_{ax}, $J_{6\text{-}ax,7\text{-}ax}$ = 10.8, $J_{6\text{-}ax,7\text{-}eq}$ = 6.0, $J_{6\text{-}ax,1}$ = 2.0 Hz), 1.79 m ($C^{19}H_3$), 2.04 d.d.d.q (7-H_{eq}, ^2J = 17.6, $J_{7\text{-}eq,6\text{-}ax}$ = 6.0, $J_{7\text{-}eq,8}$ = 5.3, $J_{7\text{-}eq,19}$ = 1.2 Hz), 2.35 d.d.d.q.d (7-H_{ax}, ^2J = 17.6, $J_{7\text{-}ax,6\text{-}ax}$ = 10.8, $J_{7\text{-}ax,8}$ = 2.5, $J_{7\text{-}ax,19}$ = 2.5, $J_{7\text{-}ax,10\text{-}eq}$ = 1.5 Hz), 3.83 m (10-H_{eq}), 4.33 d.d (1-H_{eq}, $J_{1\text{-}eq,10\text{-}eq}$ = 2.5, $J_{1\text{-}eq,6\text{-}ax}$ = 2.0 Hz), 5.59 d.d.q (8-H, $J_{8,7\text{-}eq}$ = 5.3, $J_{8,7\text{-}ax}$ = 2.5, $J_{8,19}$ = 1.3 Hz), 5.81 s (3-H), 7.58 d (12-H, 16-H, $J_{12,13}$ = $J_{16,15}$ = 8.8 Hz), 8.14 d (13-H, 15-H, $J_{13,12}$ = $J_{15,16}$ = 8.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 75.19 d (C^1), 94.25 d (C^3), 75.04 s (C^5), 34.00 d (C^6), 22.98 t (C^7), 125.11 d (C^8), 130.89 s (C^9), 70.30 d (C^{10}), 145.39 s (C^{11}), 127.34 d (C^{12}, C^{16}), 123.17 d (C^{13}, C^{15}), 148.08 s (C^{14}), 22.70 q (C^{17}), 27.17 q (C^{18}), 20.59 q (C^{19}). Found: *m*/*z* 319.1412 $[M]^+$. $C_{17}H_{21}NO_5$. Calculated: *M* 319.1414. In addition, 0.167 g (34%) of diol **IV**, 0.062 g (13%) of compound **V**, and 0.039 g (8%) of compound **VII** were isolated.

The reaction of epoxide **I** with *p*-dimethylaminobenzaldehyde (**IIf**) gave 0.152 g (30%) of diol **IV**, 0.173 g (35%) of compound **V**, and 0.035 g (7%) of compound **VII**.

REFERENCES

1. Newman, D.J., *J. Med. Chem*., 2008, vol. 51, p. 2589.
2. Il'ina, I.V., Volcho, K.P., and Salakhutdinov, N.F., *Russ. J. Org. Chem*., 2008, vol. 44, p. 1.
3. Salakhutdinov, N.F., Volcho, K.P., Il'ina, I.V., Korchagina, D.V., Tatarova, L.E., and Barkhash, V.A., *Tetrahedron*, 1998, vol. 54, p. 15619.
4. Il'ina, I.V., Volcho, K.P., Korchagina, D.V., Barkhash, V.A., and Salakhutdinov, N.F., *Helv. Chim. Acta*, 2007, vol. 90, p. 353.
5. Lopez-Rodriguez, M.L., Viso, A., Ortega-Gutierrez, S., and Diaz-Laviada, I., *Mini Rev. Med. Chem*., 2005, vol. 5, p. 97.
6. Stern, E. and Lambert, D.M., *Chem. Biodiv*., 2007, vol. 4, p. 1707.
7. Fernandez-Ruiz, J., *Br. J. Pharmacol*., 2009, vol. 156, p. 1029.
8. Ardashov, O.V., Il'ina, I.V., Korchagina, D.V., Volcho, K.P., and Salakhutdinov, N.F., *Mendeleev Commun*., 2007, vol. 17, p. 303.