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Analogs of Ecdysteroids with a Tetrasubstituted $\Delta^{8,14}$-Bond*

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Abstract—By hydrogenation of (20*R*,22*R*)-6α,14α,25-trihydroxy- and (20*R*,22*R*)-6β,14α,25-trihydroxy-2,3:20,22-bis(isopropylidenedioxy)-5α-cholest-7-enes on a catalyst (Raney nickel) the corresponding (5α,6α)- and (5β,6β)-epimers of previously unknown $\Delta^{8,14}$-6-hydroxy derivatives of ecdysteroids were synthesized.

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The unexpectedly high ecdysone activity found in the stable dimer of 7,7'-bis[20-hydroxy-14-deoxy-$\Delta^{8(14)}$-ecdysone] obtained by UV irradiation of a water solution of the most representative hormone of insects ecdysis (20-hydroxyecdysone) provoked the interest to the synthesis of the corresponding monomeric $\Delta^{8,14}$-analog or related structures [2]. In earlier publications on photochemical transformations of the same ecdysteroid the isolation of $\Delta^{8,14}$-analog of 20-hydroxyecdysone was reported [3, 4] but this information was disproved [2].

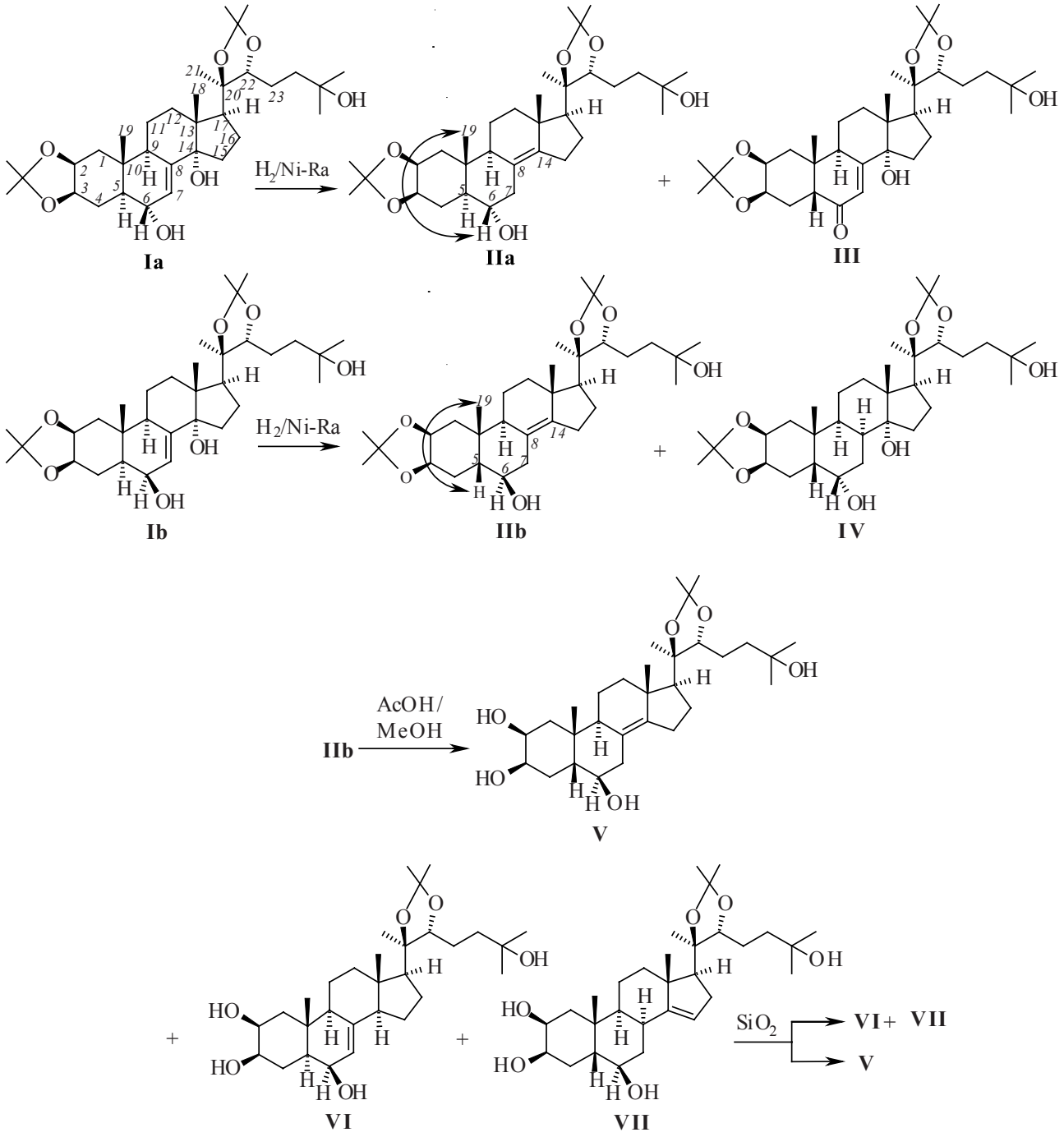
We found [1] that the hydrogenation on Raney nickel of 6α,20-dihydroxy-5α-ecdysone diacetonide led to the formation of its $\Delta^{8,14}$-6-hydroxy analog. In extension on the studies of transformations of 6-hydroxy derivatives we synthesized under the conditions of catalytic hydrogenation from 6α-Δ^{7}- (**Ia**) and 6β-Δ^{7}- (**Ib**) epimeric allyl alcohols 6α-$\Delta^{8,14}$- (**IIa**) and 6β-$\Delta^{8,14}$-(**IIb**) homoallyl alcohols respectively. The structure of compounds **IIa** and **IIb** was established from 1D and 2D ^{1}H and ^{13}C NMR spectra.

According to the data of ROESY spectrum in 6α-epimeric alcohol **IIa** the proton H^{6} is axial and has β-configuration as shows the nuclear Overhauser effect (NOE) between this atom and the protons of the group H_3C^{19}. Hydroxy group at the atom C^{6} of compound **IIa** consequently possesses the α-orientation and is equatorial. The large coupling constant $^{3}J_{5,6}$ 11 Hz indicates the axial-axial *trans*-location of protons H^{5} and H^{6} in the B ring of compound **IIa**, α-orientation of proton H^{5} and consequently the *trans*-junction of A and B rings.

In the ^{1}H NMR spectrum of 6β-alcohol **IIb** the signal of proton H^{6} was overlapped by water signal, and the lack of NOE between this atom and the protons of H_3C^{19} was unconvincing. It was presumable that the removal of the acetonide protection from the hydroxy groups at C^{2} and C^{3} would result in a shift of the H^{6} signal. Actually in the ^{1}H NMR spectrum of monoacetonide **V** obtained by the partial hydrolysis of diacetonide **IIb** the signal of H^{6} atom appeared in a weaker field (Δδ 0.18 ppm)and it was sufficient for a reliable proof of the absence of a correlation between the proton H^{6} and protons H_3C^{19} in the ROESY spectra of 6β-alcohols **IIb** and **V**. Consequently the proton H^{6} in each of these alcohols possesses the α-configuration, and the hydroxy group at the atom C^{6} in compounds **IIb** and **V** has the β-orientation. The configuration of the proton H^{5} in 6β-epimer **IIb** and its monoacetonide **V** was established with the use of ROESY spectra. The appearamce of the correlation peaks between protons H^{5} and H_3C^{19} indicated the β-orientation of the proton H^{5} and the *cis*-junction of the A and B rings in these compounds.

Thus in the course of catalytic hydrogenation of 6,20-dihydroxy-5α-ecdysones diacetonides **Ia** and **Ib** the 14α-hydroxy group was subjected to hydrogenolysis accompanied with a shift of Δ^{7}-bond into the position *8*(*14*). The formed 6α-alcohol **IIa** retained the trans-junction of the A and B rings of the initial allyl alcohol **Ia**, whereas in the hydrogenation of 6β-alcohol **IIb** an epimerization occurred at the C^{5} atom of the initial alcohol **Ib** resulting in the *cis*-junction of the A and B rings.

* For preliminary Communication, see [1]



It was also established that under the conditions of the study the α-alcohol **Ia** alongside the hydrogenolysis product **IIa** yielded compound **III** identical to the known 20-hydroxyecdysone diacetonide [5, 6]. This fact shows that dehydrogenation of compound **Ia** occurs at the C^6–O bond. Similar dehydrogenation of an allyl alcohol with the formation of a conjugated ketone was previously observed in alkaloids series [7]. In the hydrogenolysis of β-alcohol **Ib** alongside compound **IIb** formed a product of Δ^7-bond reduction in the initial compound, saturated alcohol **IV** identical to that we had formerly obtained from the 20-hydroxyecdysone 7,8-dihydroanalog [8].

From the product of acid hydrolysis of compound **IIb** (by procedure [9]) alongside the corresponding monoacetonide **V** a mixture of compounds **VI** and **VII** was isolated that we failed to separate by column chromatography. In the ^{13}C NMR spectrum of the mixture of compounds **VI** and **VII** lacked the signal at δ 84 ppm

proving the absence of the 14α-hydroxy group in these compounds. In the ^{13}C NMR spectrum of this mixture the signals of compound **VI** are similar to those characteristic of alcohol **Ib** related by its structure to compound **VI.** The second compound in the two-component mixture, monoacetonide **VII,** gave rise to signals characteristic of the corresponding diacetonide obtained before [8]. From the intensity ratio of the signals at δ 5.34 and 5.55 ppm corresponding to vinyl protons at the atoms C^{15} in compound **VII** and C^{7} in compound **VI** respectively the ratio of these compounds in the isolated mixture amounts to 2:1. The formation of $\Delta^{7,8}$- (**VI**) and $\Delta^{14,15}$- (**VII**) alkenes resulted apparently from isomerization-disproportionation in the acid medium of $\Delta^{8,14}$-alkene **V** through an intermediate carbenium ion [10].

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequencies 300.13 (^{1}H) and 75.46 (^{13}C) MHz, solvent $CDCl_3$. Homo- and heteronuclear spectra COSY, TOCSY, ROESY, HSQC, and HBMC were taken on a Bruker DRX-500 instrument [500.13 (^{1}H) and 125.76 (^{13}C) MHz, solvent DMSO-d_6]. Chemical shifts are reported in the δ scale with respect to internal reference TMS. Melting points were measured on a Boëtius heating block. The specific rotation was estimated on a polarimeter Perkin-Elmer 141. TLC monitoring was carried out on plates covered with SiO_2 (Silufol), visualization of spots with vanillin solution in ethanol acidified with sulfuric acid.

(20*R*,22*R*)-2β,3β:20,22-Bis(isopropylidenedioxy)-5α-cholest-8(14)-ene-6α,25-diol (IIa) and 2,3:20,22-20-hydroxyecdysone diacetonide (III). Through a dispersion of 0.18 g (0.32 mmol) of alcohol **Ia** (mp 134–136°C, $[\alpha]_D^{18}$ 26.5°, obtained by procedure [11]), 1.8 g of Raney nickel (obtained by procedure [12] from the powder of Ni-Al alloy purchased from Acros organics), and 5 ml of ethanol was passed hydrogen at room temperature until complete disappearance of the initial substrate (~40 h, TLC monitoring). The catalyst was filtered off, the filtrate was evaporated, and the residue was subjected to chromatography on a column packed with 8 g of SiO_2 (eluent $CHCl_3$–MeOH, 20:1). We obtained 0.071 g (40%) of compound **IIa** (R_f 0.56, $CHCl_3$–MeOH, 10:1) and 0.026 g (15%) of compound **III** (R_f 0.45, $CHCl_3$–MeOH, 10:1, mp 234–235°C, ^{1}H and ^{13}C NMR spectra identical to those previously published [5, 6]).

Compound (IIa). mp 88–90°C, $[\alpha]_D^{20}$ –2.0° (*c* 0.57, $CHCl_3$). ^{1}H (300.13 MHz, $CDCl_3$) and ^{13}C (75.46 MHz, $CDCl_3$) NMR spectra identical to those previously published [13]. ^{1}H NMR spectrum (500.13 MHz, DMSO-d_6), δ, ppm: 0.74 s (3H, H_3C^{19}), 0.91 s (3H, H_3C^{18}), 1.06 s (3H, H_3C^{27}), 1.07 s (3H, H_3C^{26}), 1.12 s (3H, H_3C^{21}), 1.18 m and 2.00 m (2H, H_2C^{12}), 1.19 m and 1.65 m (2H, H_2C^{1}), 1.23 s and 1.32 s (6H, 20,22-Me_2C), 1.24 s and 1.38 s (6H, 2,3-Me_2C), 1.34 m and 1.53 m (2H, H_2C^{24}), 1.38 m and 1.42 m (2H, H_2C^{23}), 1.41 m and 1.51 m (2H, H_2C^{11}), 1.71 m and 1.91 m (2H, H_2C^{16}), 1.73 m (1H, H^{5}), 1.78 m (1H, H^{7}), 2.24 d.d (1H, $H^{7'}$, $^{2}J_{7,7'}$ 13.5, $^{3}J_{7',6}$ 4.5 Hz), 1.83 m and 2.03 m (2H, H_2C^{4}), 2.03 m (1H, H^{9}), 2.18 m (1H, H^{17}), 2.19 m and 2.26 m (2H, H_2C^{15}), 3.72 m (1H, H^{22}), 3.84 d.d (1H, H^{6}, $J_{6,5}$ 11.0, $J_{6,7'}$ 4.5 Hz), 4.03 m (1H, H^{2}), 4.21 m (1H, H^{3}). ^{13}C NMR spectrum (125.76 MHz, DMSO-d_6), δ, ppm: 18.7 (C^{11}), 18.9 (C^{18}), 20.6 (C^{4}), 21.2 (C^{21}), 21.5 (C^{16}), 22.8 (C^{23}), 23.6 (C^{19}), 24.3 (C^{15}), 26.0 and 28.1 (2,3-$\underline{Me}_2$C), 26.1 and 28.5 (20,22-$\underline{Me}_2$C), 28.6 (C^{27}), 28.9 (C^{26}), 32.4 (C^{7}), 34.5 (C^{9}), 36.3 (C^{12}), 37.0 (C^{10}), 38.5 (C^{1}), 40.5 (C^{24}), 42.2 (C^{5}), 42.3 (C^{13}), 54.7 (C^{17}), 65.1 (C^{6}), 68.0 (C^{25}), 70.9 (C^{2}), 71.9 (C^{3}), 80.6 (C^{22}), 82.9 (C^{20}), 105.5 (2,3-$Me_2\underline{C}$), 106.0 (20,22-$Me_2\underline{C}$), 124.1 (C^{8}), 142.0 (C^{14}).

(20*R*,22*R*)-2β,3β:20,22-Bis(isopropylidenedioxy)-5β-cholest-8(14)-ene-6β,25-diol (IIb) and (20*R*,22*R*)-2β,3β:20,22-bis(isopropylidenedioxy)-5β,8α-cholestane-6α,14α,25-triol (IV). Through a dispersion of 0.18 g (0.32 mmol) of alcohol **Ib** (mp 125–127°C, $[\alpha]_D^{24}$ +8.4°, obtained by procedure [11]), 1.8 g of Raney nickel, and 5 ml of ethanol was passed hydrogen at room temperature (~40 h, TLC monitoring). The catalyst was filtered off, the filtrate was evaporated, and the residue (0.19 g) was subjected to chromatography on a column packed with 8 g of SiO_2 (eluent $CHCl_3$–MeOH, 20:1). We obtained 0.079 g (45%) of compound **IIb** (R_f 0.59, $CHCl_3$–MeOH, 10:1) and 0.030 g (17%) of compound **IV** (R_f 0.34, $CHCl_3$–MeOH, 10:1, ^{1}H and ^{13}C NMR spectra identical to those published in [8]).

Compound (IIb). mp 106–108°C, $[\alpha]_D^{20}$ 1.7° (*c* 2.5, $CHCl_3$), ^{1}H (300.13 MHz, $CDCl_3$) and ^{13}C (75.46 MHz, $CDCl_3$) NMR spectra identical to those previously published [1]. ^{1}H NMR spectrum (500.13 MHz, DMSO-d_6), δ, ppm: 0.90 s (3H, H_3C^{19}), 0.92 s (3H, H_3C^{18}), 1.06 s (3H, H_3C^{27}), 1.07 s (3H, H_3C^{26}), 1.10 s (3H, H_3C^{21}), 1.22 s and 1.37 s (6H, 2,3-Me_2C), 1.23 s and 1.32 s (6H, 20,22-Me_2C), 1.23 m and 2.01 m (2H, H_2C^{12}), 1.33 m and 1.54 m (2H, H_2C^{24}), 1.35 m (1H, H^{17}), 1.38 m and 1.47 m (2H, H_2C^{1}), 1.39 m and 1.41 m (2H, H_2C^{23}), 1.43 m (1H, H^{5}), 1.43 m and 1.47 m (2H, H_2C^{11}), 1.54 m and 1.74 m (2H, H_2C^{4}), 1.74 m and 1.95 m (2H, H_2C^{16}),

1.89 d.d (1H, H^7, $^2J_{7,7'}$ 16.0, $^3J_{7,6}$ 10.0 Hz), 2.25 d.d (1H, $H^{7'}$, $^2J_{7',7}$ 16.0, $^3J_{7',6}$ 4.0 Hz), 1.96 m (1H, H^9), 2.09 m and 2.12 m (2H, H_2C^{15}), 3.38 m (1H, H^6), 3.71 m (1H, H^{22}), 4.24 m (2H, H^2, H^3). ^{13}C NMR spectrum (125.76 MHz, DMSO-d_6), δ, ppm: 19.4 (C^{11}), 19.9 (C^{18}), 21.7 (C^{21}), 22.2 (C^{16}), 23.3 (C^{23}), 24.3 (C^{15}), 24.3 and 26.9 (2,3-$\underline{Me_2}C$), 26.3 (C^{19}), 26.6 and 29.0 (20,22-$\underline{Me_2}C$), 28.3 (C^4), 29.1 (C^{27}), 29.4 (C^{26}), 34.6 (C^7), 34.9 (C^{10}), 36.5 (C^1), 37.0 (C^{12}), 39.0 (C^9), 41.0 (C^{24}), 42.9 (C^{13}), 43.8 (C^5), 54.8 (C^{17}), 68.5 (C^{25}), 69.4 (C^6), 71.6 (C^3), 71.7 (C^2), 81.1 (C^{22}), 83.4 (C^{20}), 106.0 (20,22-$Me_2\underline{C}$), 106.2 (2,3-$Me_2\underline{C}$), 124.3 (C^8), 142.5 (C^{14}).

(20*R*,22*R*)-20,22-Isopropylidenedioxy-5β-cholest-8(14)ene-2β,3β,6β,25-tetraol (V) and a mixture of (20*R*,22*R*)-20,22-isopropylidenedioxy-5α-cholest-7-ene-2β,3β,6β,25-tetraol (VI) and (20*R*,22*R*)20,22-isopropylidenedioxy-5β,8α-cholest-14-ene-2β,3β,6β,25-tetraol (VII). To a solution of 0.15 g (0.28 mmol) of compound **IIb** in 2.7 ml of MeOH was added 4 ml of glacial AcOH, the reaction mixture was stirred at room temperature for 5 h, then it was evaporated, and the residue (0.14 g) was subjected to chromatography on a column packed 6 g of SiO_2 (eluent $CHCl_3$–MeOH, 20:1). We obtained 0.03 g (22%) of the mixture of compounds **VI** and **VII** [1:2, from the intensity ratio of broadened signals at δ 5.55 (HC^7 of compound **VI**) and 5.34 ppm (HC^{15} of compound **VII**)], R_f 0.37 ($CHCl_3$–MeOH, 5:1), and 0.07 g (51%) of compound **V**, R_f 0.30 ($CHCl_3$–MeOH, 5:1).

Compound (V). mp 189–191°C, $[\alpha]_D^{20}$ 12.4° (*c* 1.45, $CHCl_3$). ^1H NMR spectrum (300.13 MHz, $CDCl_3$), δ, ppm: 1.01 s (3H, H_3C^{19}), 1.05 s (3H, H_3C^{18}), 1.19 s (3H, H_3C^{21}), 1.23s (6H, H_3C^{26}, H_3C^{27}), 1.36 s and 1.43 s (6H, Me_2C), 1.47–2.43 m (21H, CH, CH_2), 3.74 m (3H, HC^2, H_2C^{22}, $w_{1/2}$ 37 Hz), 3.78 m (1H, HC^6, $w_{1/2}$ 14 Hz), 4.01 m (1H, HC^3, $w_{1/2}$ 7 Hz). ^{13}C NMR spectrum (75.46 MHz, $CDCl_3$), δ, ppm: 19.3 (C^{18}), 19.5 (C^{11}), 22.0 (C^{21}), 22.6 (C^{23}), 23.9 (C^{16}), 25.3 (C^{19}), 26.2 (C^{15}), 26.8 and 29.6 ($\underline{Me_2}C$), 29.0 and 29.1 (C^{26}, C^{27}), 32.4 (C^4), 33.4 (C^7), 36.6 (C^9), 37.4 (C^{12}), 37.9 (C^1), 38.2 (C^{10}), 41.4 (C^{24}), 42.5 (C^{13}), 43.5 (C^5), 55.9 (C^{17}), 67.7 (C^2), 68.9 (C^3), 70.4 (C^{25}), 73.3 (C^6), 81.8 (C^{22}), 84.1 (C^{20}), 106.9 ($Me_2\underline{C}$), 122.8 (C^8), 145.2 (C^{14}). ^1H NMR spectrum (500.13 MHz, DMSO-d_6), δ, ppm: 0.91 s (3H, H_3C^{19}), 0.93 s (3H, H_3C^{18}), 1.06 s (3H, H_3C^{27}), 1.07 C (3H, H_3C^{26}), 1.11 s (3H, H_3C^{21}), 1.16 m and 2.03 m (2H, H_2C^{12}), 1.23 s and 1.33 s (6H, Me_2C), 1.34 m and 1.55 m (2H, H_2C^{24}), 1.34 m (1H, H^{17}), 1.36 m (2H, H_2C^1), 1.39 m and 1.42 m (2H, H_2C^{23}), 1.42 m and 1.61 m (2H, H_2C^4), 1.49 m and 1.51 m (2H, H_2C^{11}), 1.70 m and 1.91 m (2H, H_2C^{16}), 1.78 d.br.s (1H, H^5, $J_{5,4a}$ 12 Hz), 1.96 m and 2.22 m (2H, H_2C^7), 2.17 m and 2.24 m (2H, H_2C^{15}), 2.19 m (1H, H^9), 3.47 m (1H, H^2), 3.56 br.s (1H, H^6, $w_{1/2}$ 8 Hz), 3.73 m (2H, H^3, H^{22}). ^{13}C NMR spectrum (125.76 MHz, DMSO-d_6), δ, ppm: 19.1 (C^{11}), 19.3 (C^{18}), 21.8 (C^{21}), 22.2 (C^{16}), 23.4 (C^{23}), 24.9 (C^{15}), 25.9 (C^{19}), 26.6 and 29.4 ($\underline{Me_2}C$), 29.0 (C^{27}), 29.1 (C^{26}), 32.7 (C^4), 33.1 (C^7), 35.9 (C^9), 37.0 (C^{12}), 37.4 (C^{10}), 38.3 (C^1), 41.0 (C^{24}), 41.6 (C^5), 42.7 (C^{13}), 55.5 (C^{17}), 66.5 (C^2), 68.2 (C^3), 68.5 (C^{25}), 71.4 (C^6), 81.2 (C^{22}), 83.4 (C^{20}), 106.0 ($Me_2\underline{C}$), 124.7 (C^8), 141.8 (C^{14}).

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REFERENCES

1. Shafikov, R.V., Afon'kina, S.R., Savchenko, R.G., Galyautdinov, I.V., and Odinokov, V.N., *Zh. Org. Khim.,* 2007, vol. 43, p. 310.
2. Harmatha, Ju., Dinan, L., and Lafont, R., *Insect Biochem. Mol. Biol*., 2002, vol. 32, p. 181.
3. Canonina, L., Danielli, B., Lesma, G., and Palmisano, G., *Chem. Commun.*, 1985, p. 1321.
4. Canonina, L., Danielli, B., Lesma, G., Palmisano, G., and Mugnoli, A., *Helv. Chim. Acta*, 1987, vol. 70, p. 701.
5. Odinokov, V.N., Galyautdinov, I.V., Nedopekin, D.V., and Khalilov, L.M., *Izv. Akad. Nauk, Ser. Khim.*, 2003, p. 220.
6. Lafont, R., Harmatha, J., Marion-Poll, F., Dinan, L., and Wilson, I.D., *Ecdybase a Free Ecdysteroid Database*, 2002, http://www. ecdybase.org.
7. Narzullaev, A.S., Yunusov, M.S., Moiseenko, A.M., and Sabirov, S.S., *Khim. Polim. Soedin*., 1989, p. 372.
8. Odinokov, V.N., Afon'kina, S.R., Shafikov, R.V., Savchenko, R.G., Galyautdinov, I.V., Khalilov, L.M., and Shashkov, A.S., *Zh. Org. Khim*., 2007, vol. 43, p. 830.
9. Suksamrarn, A. and Pattanaprateep, P., *Tetrahedron*, 1995, vol. 51, p. 10663.
10. *Comprehensive Organic Chemistry*, Barton, D. and Ollis, W.D., Eds., Oxford: Pergamon, 1979, vol. 1, p. 228.
11. Odinokov, V.N., Savchenko, R.G., Shafikov, R.V., Afon'kina, S.R., Khalilov, L.M., Kachala, V.V., and Shashkov, A.S., *Zh. Org. Khim*., 2005, vol. 41, p. 1323.
12. Fieser, L. F. and Fieser, M., *Advanced Organic Chemistry*, New York: Reinhold, 1962.
13. Galyautdinov, I.V., Ibragimova, A.Sh., Shakurova, E.R., and Odinokov, V.N., *Zh. Org. Khim*., 2007, vol. 43, p. 1566.