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Chemical Transformations of Betulonic Aldehyde

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Abstract—Chemical transformations of 3-oxolup-20(29)-en-28-al in oxidation, reduction, reductive amination, aldol crotonic condensation, cyclopropanation, Grignard, and Wittig reactions were investigated. The structure of reaction products was established by X-ray diffraction (XRD) analysis.

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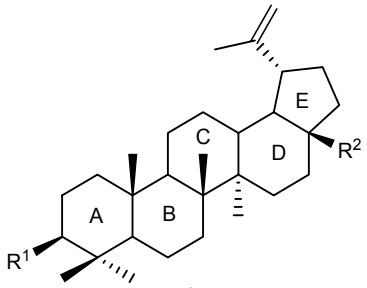
Natural molecular platforms with a complex carbon scaffold, like triterpenoids of lupane, oleanane, or ursane series, are important chirality sources for designing new optically active substances for medical chemistry and materials science. The enantiomeric purity and the rigid scaffold make them attractive objects for the synthesis of molecules of definite configuration ensuring the high affinity to stereospecific sites for fixing biotargets and are also significant for inducing helicoid supramolecular texture in liquid crystals utilized in electro optical devices [1–5]. The usefulness from the practical viewpoint of the search for the ways of such substances modification depends both on the availability and reproducibility of the raw material sources and on the functional groups present in the structure. Triterpenoids of lupane series [betulin (**1**), betulinic (**2**) and betulonic (**3**) acids, betulinic (**4**) and betulonic (**5**) aldehydes] fit to these requirements. They are present everywhere in trees' bark, especially, in the birch bark. The content of diol **1** in the latter reaches 10–35% of the dry mass [3, 5].

The presence in the structure of compounds **1**–**5** of several reactive groups provides multiple ways of the chemical transformation. Betulinic acid **2** [5–10] is the best studied among these compounds. The possibility of conversion of diol **1** in aldehydes **4** and **5** opens the way to their wider utilization in the organic synthesis yet the properties of betulonic aldehyde **5** are poorly investigated.

We attempted to extend the synthetic potential of 3-oxolup-20(29)-en-28-al **5** mainly at the expense of the transformations of carbonyl groups and the active methylene fragment in the ring **A**.



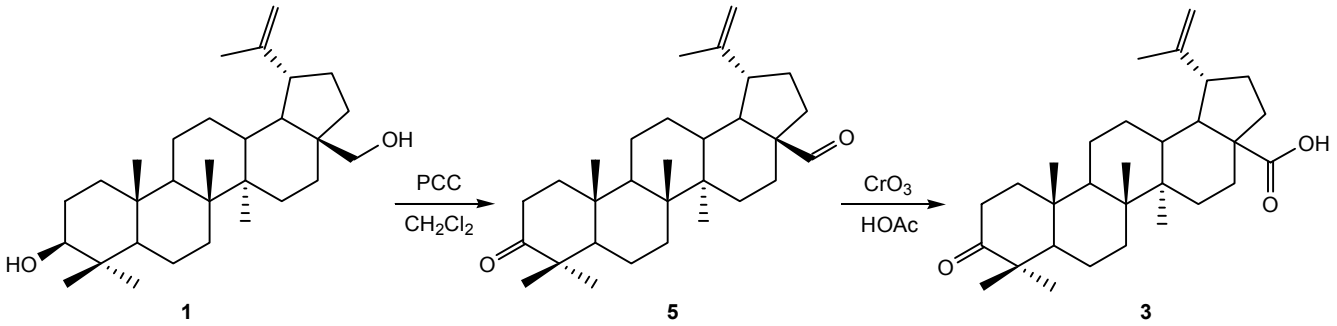
1–5

R^1 = OH, R^2 = CH_2OH (**1**), COOH (**2**), R^1 = O=, R^2 = COOH (**3**), CHO (**5**), R^1 = OH, R^2 = CHO (**4**).

Several procedures of betulin **1** oxidation into aldehyde **5** and acid **3** are described in papers and patents. We prepared betulonic aldehyde **5** in 75% yield using pyridinium chlorochromate in dichloromethane (Scheme 1). The subsequent oxidation of compound **5** with chromic anhydride in acetic acid affords acid **3**. The physicochemical characteristics of compounds **3** and **5** coincide with the published data [5–13].

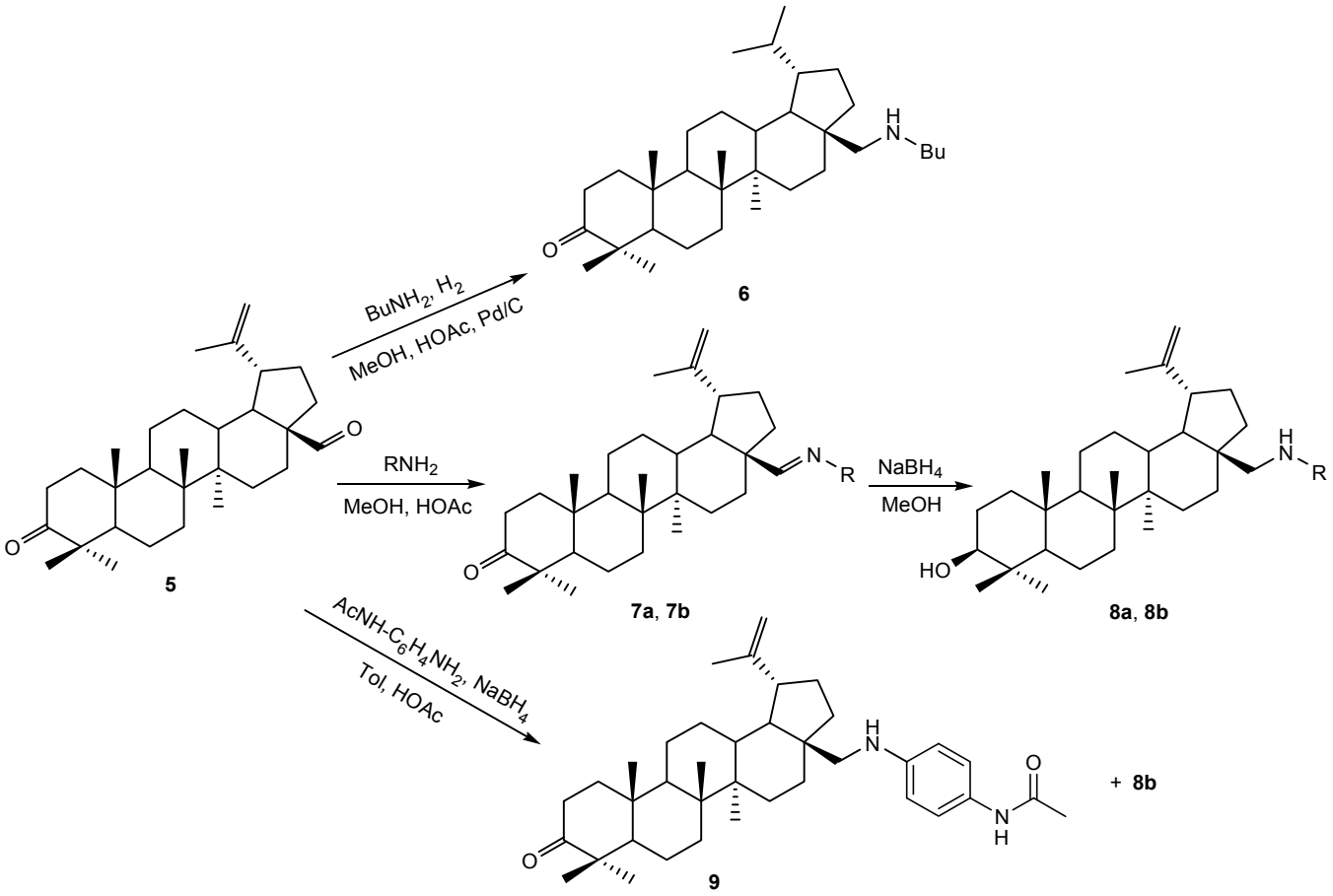
The reductive amination involving aldehyde **5** and aromatic amines was not described in the literature. Only some examples are published on the preparation

Scheme 1.



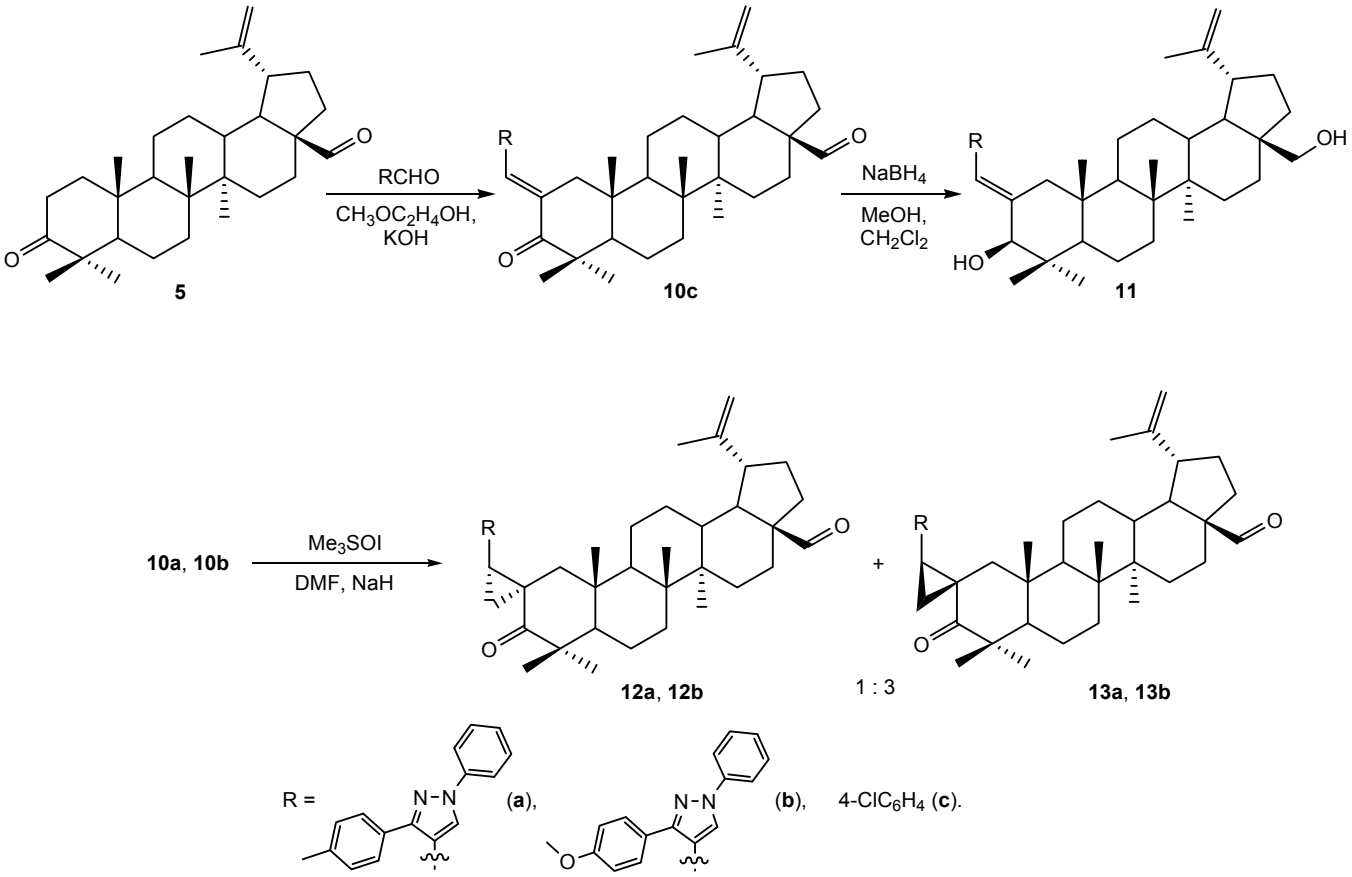
of secondary amines by reactions of betulonic aldehyde **5** with ethanolamine, hydrochlorides of methyl glycinate and 2-chloroethylamine in the presence of $NaCNBH_3$. The reduction occurred not only at the exocyclic imino group but also at the keto group in the ring **A** [14]. We synthesized secondary amines **6**–**9** under various conditions (Scheme 2) and established that hydrogen in the presence of Pd/C catalyst reduced the C=N bond and the isopropenyl fragment leaving intact the C=O group in the **A** ring. Azomethines **7a** and **7b** were reduced with $NaBH_4$–MeOH into amino alcohols **8a** and **8b**. At treating the azomethines with $NaBH_4$–HOAc in toluene we obtained a mixture of amino ketone **9** and amino alcohol **8** in the ratio 3 : 1 that was successfully separated by column chromatography.

Scheme 2.



R = C_6H_5 (**a**), C_6H_4(NHAc)-4 (**b**).

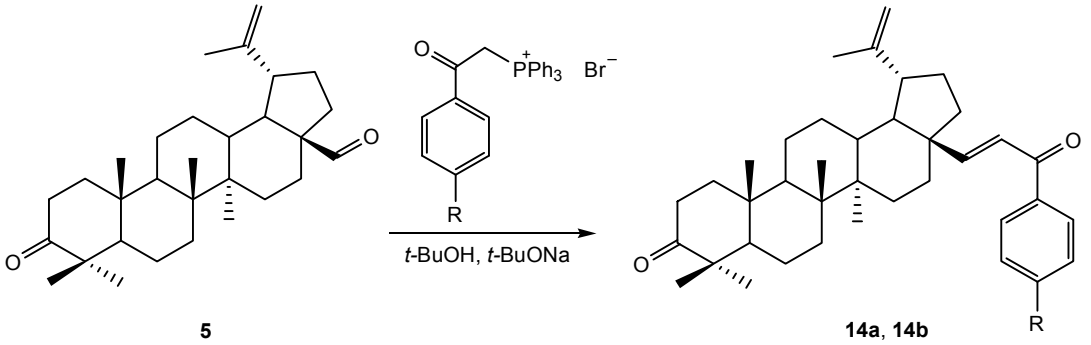
Scheme 3.



The structure of compounds **6–9** was confirmed by IR and ^{1}H NMR spectra. IR spectra of compounds **6**, **7a**, 7**b**, and **9** contain strong bands of methyl and methylene groups of lupane scaffold in the region 2977–2855, a broadened band of the associated NH group at 3403–3342 (characteristic of amino ketones **6** and **9**), and a band of stretching vibrations of the carbonyl group in the range 1707–1688 cm^{-1}. In the spectra of amino alcohols **8a** and **8b** a broad band is observed in the region 3403–3342 cm^{-1} formed by overlapping of absorption bands of hydrogen-bonded NH and OH groups. The ^{1}H NMR spectra of secondary amines **6**, **8a**, **8b**, and **9** differ from the spectrum of the initial aldehyde **5**, first of all, in the resonance region of the aromatic protons. Although the hydroxy group signal was not observed in the spectra registered in $CDCl_3$ the reduction of the carbonyl group was confirmed by the appearance of a multiplet of H^3 proton in the range δ 3.13–3.81 ppm. The signal of the methine proton H^{28} in the spectra of imines **7a** and **7b** appears as a downfield singlet at δ 7.88 ppm. The reduction of the imino group in compounds **6**, **8a**, **8b**, and **9** gives rise to two doublets of methylene group protons $C^{28}H_2$, δ 2.55–2.74, 3.01–3.24 ppm. The reduction of the isopropenyl fragment in amino ketone **6** is confirmed by the absence of the doublet of the methylene protons at 4.66 ppm.

The presence in the structure of compound **5** of an aldehyde and a keto groups makes it possible to prepare from it α,β-unsaturated ketones. We formerly synthesized such compounds by aldol crotonic condensation using pyrazole-4-carbaldehydes as carbonyl component and ketoaldehyde **5** as the methylene component of the reaction [15]. In this study we obtained by the condensation of 4-chlorobenzaldehyde with betulonic aldehyde **5** in basic medium 2-ylidene derivative **10c** (Scheme 3). Its reduction with $NaBH_4$ in the mixture of MeOH–CH_2Cl_2, 1 : 1, led to the formation of 2-[(4-chlorophenyl)methylidene]lup-20(29)-en-3,28-diol **11**. From the previously synthesized α,β-unsaturated ketones **10a** and **10b** [15] and trimethylsulfoxonium methylide in the presence of NaH in DMF a mixture was obtained of isomeric spirocyclopropanes **12a**, **12b**, **13a**, and **13b**

Scheme 4.



5 **14a**, **14b**

R= Cl (**a**), OMe (**b**).

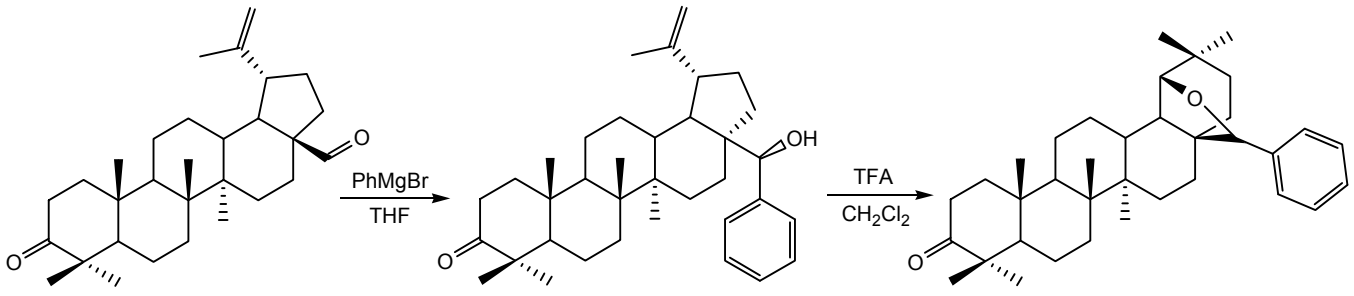
in the ratio 3 : 1, as showed the ^{1}H NMR data. We failed to separate the mixture into individual compounds both by chromatography and fractional crystallization.

In the IR spectrum of α,β-unsaturated ketones **10a**–**10c** the maximum of the absorption band of the stretching vibrations of the keto group shifts from 1705 (in ketoaldehyde **5**) to 1670–1683 cm^{-1} due to the conjugation of this group with the double bond. The band of the formyl group retains its position [ν(C=O) 1723–1717 cm^{-1}]. The IR spectrum of diol **11** lacks the absorption band of the carbonyl group, a wide band is observed in the region 3461–3435 cm^{-1} corresponding to the vibrations of the associated OH groups. The position of the absorption band of the keto group in the spectra of spirocyclopropanes **12a**, **12b**, **13a**, and **13b** does not change as compared to the spectra of the initial ketones **10a** and **10b** [15] due to the specific distribution of the electron density in the cyclopropane fragment.

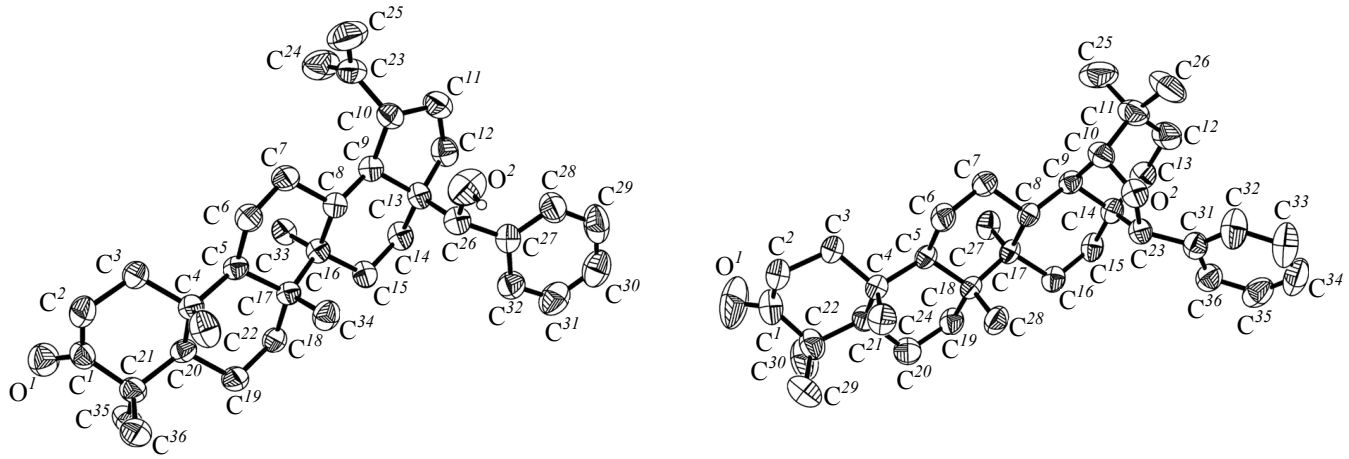
The ^{1}H NMR spectrum of compound **10c** contains a singlet of the formyl proton (δ 9.65) and a multiplet of the protons of the aryl ring in the range 7.28–7.92 ppm. The singlet corresponding to the vinyl proton is observed at 7.25–7.26 ppm. The multiplets of methine and methylene protons of the lupane scaffold are observed at 1.01–1.74 ppm, and the singlets of five methyl groups appear in the range of 0.76–1.13 ppm. The isopropylidene fragment is present as a singlet of the CH_3 group (δ 1.71–1.73) and a doublet of vinyl protons of the CH_2 group (4.70–4.72 ppm). The ^{1}H NMR spectrum of diol **11** is distinguished from the spectrum of the α,β-unsaturated ketone **10c** by the signal of the proton at the C^3 atom of the lupane scaffold (δ 3.83–3.88 ppm) and by the absence of the signal from the formyl proton, and the singlet of the vinyl proton is shifted upfield (δ 6.45–6.55 ppm). The protons of the $C^{28}H_2$ group form the *AB* system, δ 3.32–3.77 ppm, J ~11 Hz. In the ^{1}H NMR spectra of the mixture of spirocyclopropanes **12a**, **12b**, **13a**, and **13b** the singlet of the formyl proton is conserved, and the triplets appeared from the $H^{2'}$ protons of the cyclopropane fragment (δ 2.74–3.15 ppm).

Recently a vinylog of ethyl betulonate was prepared by the reaction of aldehyde **5** with triethylphosphonium acetate in the presence of NaH in toluene [16]. We synthesized α,β-unsaturated ketones**14a** and **14b** by Wittig reaction (Scheme 4).

Scheme 5.



5 **15a**, **15b** **16**



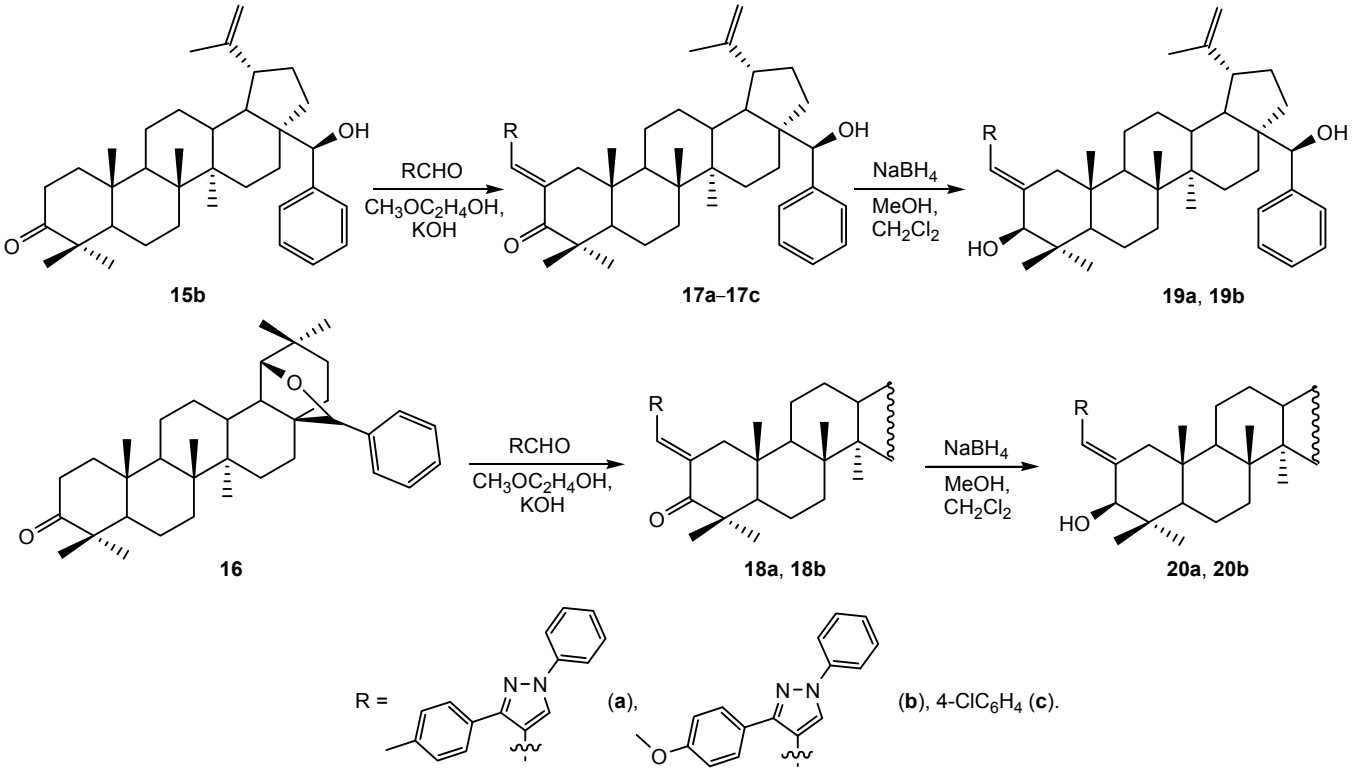
15b **16**

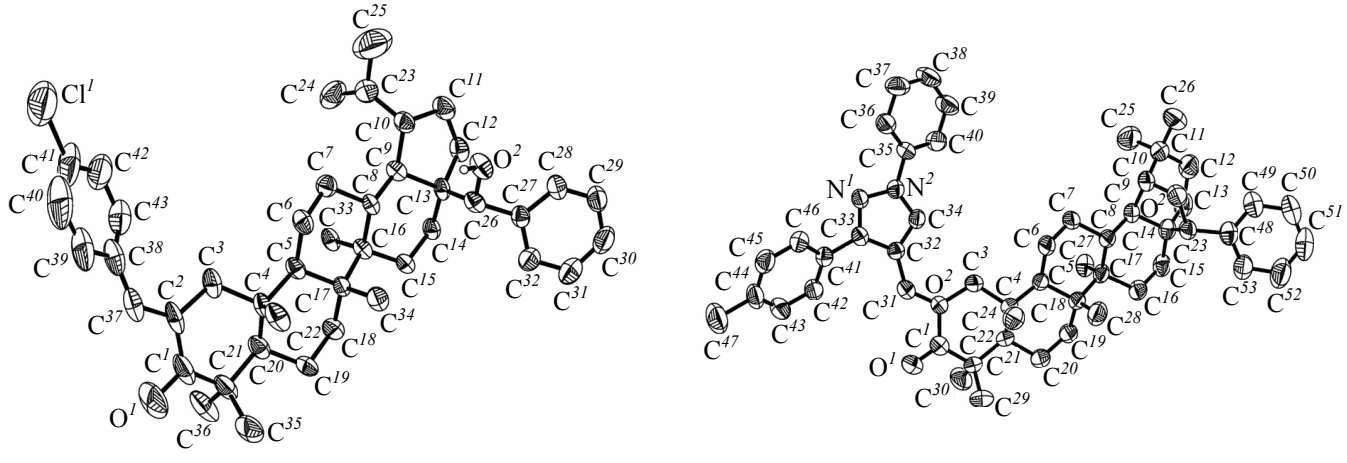
Fig. 1. Molecular structure of 28-hydroxy-28-phenyllup-20(29)-en-3-one **15b** and 28-phenylallobetulone **16** by XRD data.

In the IR spectra of compounds **14a** and **14b** absorption bands of two C=O groups at 1706–1664 cm^{-1} are observed, and the ^1H NMR spectra contain the signals of the protons of the aromatic ring and two doublets of vinyl protons, δ 6.92–6.97 and 7.34–7.37 ppm, J ~16 Hz.

The information on betulonic aldehyde reaction with Grignard reagents is very limited. The reaction of aldehyde **5** with ethynylmagnesium bromide was shown to afford 28-hydroxy-28-ethynyllup-20(29)-en-3-one [17]. We obtained 28-hydroxy-28-phenyllup-20(29)-en-3-one **15** applying phenylmagnesium bromide (Scheme 5). The

Scheme 6.





17c **18a**

Fig. 2. Molecular structure of (*E*)-28-hydroxy-2-[(4-chlorophenyl)methylidene]-28-phenyllup-20(29)-en-3-one **17c** and (*E*)-2-{[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenylallobetulone **18a** by XRD data.

compound isolated directly from the reaction mixture is a mixture of *R*,*S*-enantiomers **15a** and **15b** in the ratio 1 : 5 as indicated by the ^{1}H NMR spectrum of uncrystallized sample. The major isomer **15b** was isolated by recrystallization. The secondary alcohol **15b** in acid environment suffers Wagner–Meerwein rearrangement into 28-phenylallobetulone **16**.

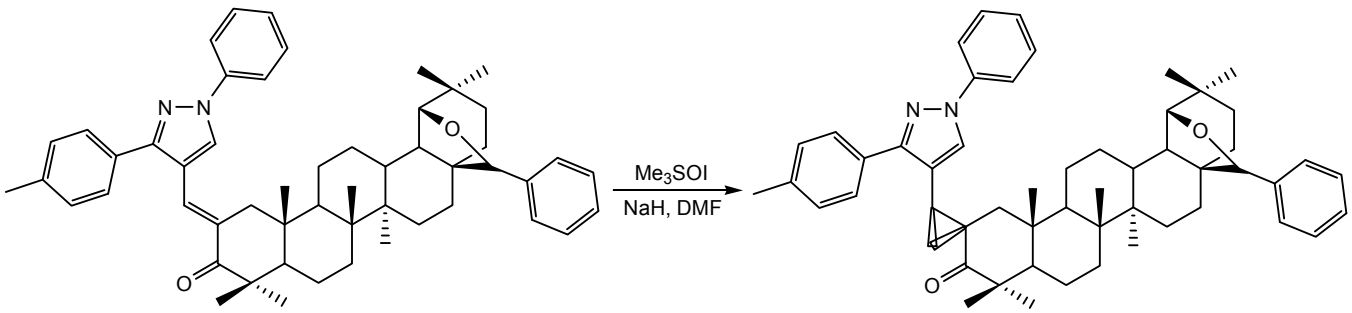
The structure of compounds **15b** and **16** was established from the data of IR, ^{1}H NMR spectra, and XRD analysis of the corresponding single crystals. IR spectra of compounds **15b** and **16** in contrast to the spectrum of initial ketoaldehyde **5** lack the absorption bands of the formyl fragment in the region 1726–1714 cm^{-1}, and in the spectrum of alcohol **15b** a wide band is present of the associated OH group in the range 3475–3447 cm^{-1}. The ^{1}H NMR spectra of compounds **15b** and **16** contain the signals of the protons of the phenyl ring and the singlet of the proton H^{28} (δ 5.22 ppm), and the spectrum of allobetulone **16** contains additionally a singlet of the methine proton H^{19} (δ 3.68 ppm).

The structure of compounds **15b** and **16** was unambiguously established by XRD analysis (Fig. 1).

Ketones **15b** and **16** were converted into 2-ylidene derivatives **17a–17c**, **18a**, and **18b**, and the latter were subjected to reduction with $NaBH_4$ in the mixture MeOH–CH_2Cl_2, 1 : 1, to obtain alcohols **19a**, **19b** and **20a**, **20b** (Scheme 6).

In the IR spectra of α,β-unsaturated ketones **17a–17c** the most characteristic absorption bands are those of the keto (1673–1670 cm^{-1}) and hydroxy groups (3467–3447 cm^{-1}). The absorption of the C=O group is absent from the spectra of alcohols **19a** and **19b**, and the vibrations of the associated OH groups give rise to a wide band in the region 3500–3440 cm^{-1}. In the IR spectra of 2-ylidene compounds **18a** and **18b** the characteristic bands are those of the stretching

Scheme 7.



18a **21**, **22**

Crystallographic data and parameters of compounds **15**–**18**

Parameter	**15**	**16**	**17c**	**18a**
a, Å	12.0066(4)	11.4738(4)	11.020(1)	6.9308(4)
b, Å	15.4935(5)	15.7914(7)	13.395(1)	12.6941(9)
c, Å	16.2139(6)	16.9884(8)	15.912(1)	49.230(3)
α, deg	90.0	90.0	69.971(8)	90.0
β, deg	90.0	90.0	89.860(7)	90.0
γ, deg	90.0	90.0	83.946(8)	90.0
V, Å^3	3016.2(2)	3078.1(2)	2193.1(3)	4331.3(5)
F(000)	1136	1136	692	1648
Crystal system	Rhombic	Rhombic	Triclinic	Rhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P1$	$P2_12_12_1$
Z	4	4	2	4
T, K	293	293	293	293
μ, mm^{-1}	0.068	0.066	0.116	0.070
D_{calc}, g/cm^3	1.138	1.115	0.968	1.167
$2\theta_{max}$, deg	60	60	50	60
Reflections measured	30371	18728	15140	48388
Independent reflections	8753	8921	10260	12583
R_{int}	0.060	0.031	0.055	0.156
Reflections with $F > 4\sigma(F)$	4588	5253	5312	4272
Number of refined parameters	356	350	840	522
R_1	0.070	0.062	0.107	0.073
wR_2	0.177	0.145	0.296	0.129
S	0.932	0.975	0.955	0.847
CCDC	1432950	1432951	1432952	1432953

vibrations of the keto group at 1670 cm^{-1} and of the fragment C–O–C (1035–1026 cm^{-1}) of the tetrahydrofuran ring. No absorption of the carbonyl group is observed in the spectra of compounds **20a** and **20b**, and a wide band appears at 3480–3445 cm^{-1}, characteristic of OH groups involved in the hydrogen bonds. The band corresponding to the vibrations of the bonds in the fragment C–O–C retains its position in the spectrum in going from ketones **18a** and **18b** to alcohols **20a** and **20b**.

The ^{1}H NMR spectra of 2-ylidene derivatives **17a**–**17c**, **18a**, and **18b** are distinguished from the spectra of their precursors **15** and **16** respectively by a singlet of vinyl proton and a multiplet of the aromatic protons, δ 7.16–7.80 ppm. The reduction of the keto group into the alcohol in compounds **19a**, **19b** and **20a**, **20b** is confirmed by the singlets of the methine proton H^3 (δ 3.88) and of vinyl proton (δ 6.63–6.45 ppm).

The structure of compounds **17c** and **18a** was unambiguously established by XRD analysis (Fig. 2).

The conversion of α,β-unsaturated ketone **18a** in a mixture of isomers **21** and **22** in a ratio 2 : 1 according to ^{1}H NMR data was performed by treating with trimethylsulfoxonium iodide in the presence of NaH in DMF (Scheme 7). We failed to isolate individual compounds **21** and **22** by chromatography or recrystallization.

IR spectra of compounds **21** and **22** possess low information since they differ from the spectrum of its precursor **18a** only in the "fingerprint" region. The signal of vinyl proton is absent from the ^{1}H NMR spectra of compounds **21** and **22**. The cyclopropane fragment gives rise to the triplet of the proton H$^{2'}$, δ 2.77–3.14 ppm, and the signals of the methylene group of the three-membered ring overlapped with the resonances of the methylene protons of the lupane scaffold.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Perkin Elmer Spectrum One FTIR from pellets with KBr. ^{1}H NMR spectra were registered on spectrometers Varian Mercury VX 200 (200 MHz) and Varian MR-400 (400 MHz) in $CDCl_3$, internal reference TMS. Elemental analysis was carried out on an analyzer EA 3000 Eurovektor (CHNS–analysis). Melting points were measured on a Koeffler heating block. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Alugram® Xtra SIL G/UV_{254} plates in the systems dichloromethane, hexane–ethyl acetate, 10 : 1, dichloromethane–methanol, 100 : 1.

3-Oxolup-20(29)-en-28-al (1). In 0.6 L of dichloromethane was dissolved at heating 10 g (0.023 mol) of betulin, and to the warm solution was added at vigorous stirring 11 g (0.05 mol) of pyridinium chlorochromate. The reaction proceeded for 25–35 min (TLC monitoring). On completion of the reaction 2/3 of dichloromethane volume was removed on a rotary evaporator, and the residue was passed through a 5–8 cm bed of silica gel. The column was washed with 500 mL of dichloromethane. The solution was evaporated on a rotary evaporator till oily state, and 10–15 mL of methanol was added. The white needle crystals of aldehyde formed almost immediately, they were filtered off, washed with methanol, and dried in air. Yield 7.63 g (76%), mp 129–131°C [11].

Betulonic acid (3). In a mixture of 20 mL of glacial acetic acid and 3 mL of water was dissolved 0.1 g of chromic anhydride. The solution was cooled, and at stirring 0.2 g (0.46 mmol) of betulonic aldehyde was added (TLC monitoring). After 45–60 min the reaction product was precipitated by adding 10% water solution of sodium chloride, the precipitate was filtered off, washed with water solution of sodium chloride, and dried. The dry residue was dissolved in a mixture of 20 mL of methanol and 5 mL of dichloromethane and 0.1 g of potassium hydroxide was added. The separated precipitate was filtered off, the filtrate was evaporated by half, to the residue 10 mL of acetic acid and water was added till an amorphous precipitate formed. The latter was filtered off and dried in air. Yield 0.16 g (80%). White amorphous powder, mp 243–245°C [7].

28-(Butylamino)lupan-3-one (6). In 15 mL of methanol was dissolved 0.25 g (0.57 mmol) of betulonic aldehyde, 0.05 g (0.62 mmol) of butylamine, 0.1 mL of acetic acid, and 10 wt % Pd/C was added. The reaction mixture was saturated with hydrogen and stirred for 12 h. On completion of the reaction the solvent was evaporated, the residue was subjected to chromatography on silica gel, eluting with a mixture dichloromethane–methanol, 10 : 1. Yield 0.20 g (71%). White amorphous powder, mp 230–232°C (decomp.). IR spectrum, ν, cm^{-1}: 3403 (NH), 2956–2782 (CH_3, CH_2), 1707 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.73 s, 0.75 s, 0.81 s, 0.83 s, 0.91 s, 0.93 s, 1.00 s, 1.05 s (24H, 8CH_3), 2.55 d (1H, H^{28A}, *J* 12.2 Hz), 3.01 d (1H, H^{28B}, *J* 12.9 Hz). Found, %: C 82.15; H 11.83; N 2.70. $C_{34}H_{59}NO$. Calculated, %: C 82.03; H 11.95; N 2.81.

28-(Phenylimino)lup-20(29)-en-3-one (7a). In 25 mL of methanol was dissolved at heating 0.50 g (1.14 mmol) of betulonic aldehyde, 0.12 g (1.20 mmol) of aniline and 0.1 mL of acetic acid was added. The reaction was carried out at 40°C. After 10 h the reaction product was precipitated with water, filtered off, and dried in air. Yield 0.48 g (81%). Yellow amorphous powder, mp 84–86°C. IR spectrum, ν, cm^{-1}: 2943–2866 (CH_3, CH_2), 1706 (C=O), 1641 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.91 s, 1.01 s, 1.06 s, 1.71 s (18H, 6CH_3), 4.67 d (2H, $C^{29}H_2$, *J* 22.1 Hz), 6.86–7.45 m (5H_{arom}), 7.88 s (1H, H^{28}). Found, %: C 84.22; H 10.14; N 2.67. $C_{36}H_{51}NO$. Calculated, %: C 84.16; H 10.00; N 2.73.

***N*-[4-(3-Oxolup-20(29)-en-28-ylideneamino)phenyl]acetamide (7b)** was synthesized similarly. Yield 0.55 g (84%). Light-brown amorphous powder, mp 101–103°C. IR spectrum, ν, cm^{-1}: 3335 br (NH), 2944–2860 (CH_3, CH_2), 1704 (C^3=O), 1688 (C=O), 1672 (NHCO, amide I), 1642 (N=C), 1533 (NHCO, amide II). ^{1}H NMR spectrum, δ, ppm: 0.90 s, 1.00 s, 1.05 s, 1.70 s (18H, 6CH_3), 2.16 s (3H, CH_3CO), 4.66 d (2H, $C^{29}H_2$, *J* 44.7 Hz), 6.94 d (2H, $H^{3',5'}$, *J* 7.7 Hz), 7.35 s (1H, H_{amide}), 7.45 d (2H, $H^{2',6'}$, *J* 7.6 Hz), 7.87 s (1H, H^{28}). Found, %: C 79.83; H 9.59; N 4.88. $C_{38}H_{54}N_2O_2$. Calculated, %: C 79.95; H 9.53; N 4.91.

28-(Phenylamino)lup-20(29)-en-3-ol (8a). 0.25 g (0.49 mmol) of imine **7a** was dissolved in methanol, and a 5-fold excess of $NaBH_4$ was added at stirring. The reaction product was precipitated with water, filtered off, and dried in air. Yield 0.23 g (92%). White amorphous powder, mp 101–103°C. IR spectrum, ν, cm^{-1}: 3422 br (NH, OH), 2942–2868 (CH_3, CH_2). ^{1}H NMR spectrum, δ, ppm: 0.74 s, 0.82 s, 0.95 s, 0.98 s, 1.02 s, 1.68 s (18H, 6CH_3), 2.45–2.56 m (1H, H^{19}),

2.74 d (1H, H^{28A}, *J* 11.6 Hz), 3.13–3.21 m (1H, H^{3}), 3.24 d (1H, H^{28B}, *J* 11.6 Hz), 4.65 d (2H, $C^{29}H_2$, *J* 45.3 Hz), 6.57–6.71 m (2H, $H^{3',5'}$), 7.12–7.20 m (3H, $H^{2',4',6'}$). Found, %: C 83.35; H 10.63; N 2.52. $C_{36}H_{55}NO$. Calculated, %: C 83.50; H 10.71; N 2.70.

***N*-[4-(3-Hydroxylup-20(29)-en-28-ylamino)phenyl]acetamide (8b)** was similarly prepared. Yield 0.24 g (95%). Light-brown amorphous powder, mp 146–148°C. IR spectrum, ν, cm^{-1}: 3435 br (OH), 3332 br (NH), 2943–2866 (CH_3, CH_2), 1666 (NHCO, amide I), 1552 (NHCO, amide II). ^{1}H NMR spectrum, δ, ppm: 0.93 s, 0.99 s, 1.01 s, 1.06 s, 1.69 s (18H, $6CH_3$), 2.13 s (3H, CH_3CO), 2.74 d (1H, H^{28A}, *J* 11.4 Hz), 3.23 d (1H, H^{28B}, *J* 11.6 Hz), 3.58–3.81 m (1H, H^{3}), 4.66 d (2H, $C^{29}H_2$, *J* 22.2 Hz), 6.60 d (2H, $H^{3',5'}$, *J* 8.5 Hz), 7.26 d (2H, $H^{2',6'}$, *J* 8.4 Hz). Found, %: C 79.18; H 10.10; N 4.72. $C_{38}H_{58}N_2O_2$. Calculated, %: C 79.39; H 10.17; N 4.87.

***N*-[4-(3-Oxolup-20(29)-en-28-ylamino)phenyl]acetamide (9).** A mixture of 0.5 g (1.14 mmol) of aldehyde **5** and 0.19 g (1.27 mmol) of amine with a catalytic quantity of acetic acid was boiled in toluene for 4 h, cooled, and excess $NaBH_4$ was added. The reaction was continued at room temperature, 2 h later the reaction mixture was filtered, excess of $NaBH_4$ was quenched with water, the organic layer was separated, and the solvent was removed. The dry residue was dissolved in dichloromethane and chromatographed on silica gel eluting with a mixture dichloromethane–methanol, 10 : 1. Yield 0.39 g (60%). Light-brown amorphous powder, mp 138–140°C. IR spectrum, ν, cm^{-1}: 3369–3342 (NH), 2944–2868 (CH_3, CH_2), 1704 (C=O), 1667 (NHCO, amide I), 1536 (NHCO, amide II). ^{1}H NMR spectrum, δ, ppm: 0.87 s, 0.93 s, 0.95 s, 1.00 s, 1.63 s (18H, $6CH_3$), 2.06 s (3H, CH_3CO), 2.68 d (1H, H^{28A}, *J* 11.2 Hz), 3.17 d (1H, H^{28B}, *J* 11.8 Hz), 4.60 d (2H, $C^{29}H_2$, *J* 21.9 Hz), 6.53 d (2H, $H^{3',5'}$, *J* 8.7 Hz), 7.02–7.30 m (3H, $H^{2',6'}$, NH_{amide}). Found, %: C 79.52; H 9.68; N 4.81. $C_{38}H_{56}N_2O_2$. Calculated, %: C 79.67; H 9.85; N 4.89.

(*E*)-3-Oxo-2-[(4-chlorophenyl)methylidene]lup-20(29)-en-28-al (10c). A mixture of 0.50 g (1.14 mmol) of betulonic aldehyde **5** and 0.18 g (1.20 mmol) of 4-chlorobenzaldehyde in 10–15 mL of ethyleneglycol monomethyl ether was boiled for 6–8 h in the presence of a catalytic quantity of KOH. On cooling the separated precipitate was filtered off and washed with alcohol. Yield 0.51 g (79%). White amorphous powder, mp 195–197°C. IR spectrum, ν, cm^{-1}: 2943–2796 (CH_3, CH_2), 1723 (CHO), 1684 (C=O), 1639 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.76 s, 0.94 s, 1.01 s, 1.10 s, 1.13 s, 1.72 s (18H, $6CH_3$), 2.15 d (1H, H^{1a}, *J* 15.7 Hz), 2.81–2.92 m (1H, H^{19}), 2.97 d (1H, H^{1e}, *J* 16.2 Hz), 4.71 d (2H, $C^{29}H_2$, *J* 43.2 Hz), 7.25 s ($1H_{vinyl}$), 7.28–7.92 m (4H, C_6H_4), 9.64 s (1H, H^{28}). Found, %: C 79.31; H 8.89; Cl 6.45. $C_{37}H_{49}ClO_2$. Calculated, %: C 79.18; H 8.80; Cl 6.32.

(*E*)-2-[(4-Chlorophenyl)methylidene]lup-20(29)-en-3,28-diol (11). In 6–8 mL of a mixture of 2-propanol and dichloromethane, 1 : 1, was dissolved 0.1 g (0.18 mmol) of α,β-unsaturated ketone **10c**, and to the solution was added at stirring a 5-fold excess of $NaBH_4$. The reaction proceeded for 2–3 h. The excess of $NaBH_4$ was quenched with water at heating to 50–60°C. The separated precipitate was filtered off and dried in air. Yield 0.09 g (90%). White amorphous powder, mp 150–152°C. IR spectrum, ν, cm^{-1}: 3435 br (OH), 2942–2868 (CH_3, CH_2), 1641 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.65 s, 0.73 s, 0.97 s, 0.98 s, 1.12 s, 1.66 s (18H, $6CH_3$), 2.35 s (1H, H^{19}), 2.89 d (1H, H^{1e}, *J* 12.8 Hz), 3.32 d (1H, H^{28A}, *J* 10.6 Hz), 3.77 d (1H, H^{28B}, *J* 10.9 Hz), 3.83 s (1H, H^{3}), 4.62 d (2H, $C^{29}H_2$, *J* 18.9 Hz), 6.63 s ($1H_{vinyl}$), 7.10 d (2H, $H^{3',5'}$, *J* 8.3 Hz), 7.25 d (2H, $H^{2',6'}$, *J* 8.0 Hz). Found, %: C 78.73; H 9.34; Cl 6.22. $C_{37}H_{53}ClO_2$. Calculated, %: C 78.62; H 9.45; Cl 6.27.

(*E*)-28-[2-Oxo-2-(4-chlorophenyl)ethylidene]lup-20(29)-en-3-one (14a). Betulonic aldehyde **5** (1 g, 2.28 mmol) was dissolved in 35 mL of a solution of *t*-BuONa. To the solution a mixture was added of 0.6 g (2.5 mmol) of ω-bromoacetophenone and 0.68 g (2.6 mmol) of triphenylphosphine in *tert*-butyl alcohol. The reaction proceeded at room temperature for 24 h. The separated precipitate was filtered off, the reaction product was precipitated from the filtrate with water, the formed oily substance was extracted with ethyl acetate. The organic layer was separated, dried with Na_2SO_4, filtered, the solvent was removed at a reduced pressure. The residue was dissolved in dichloromethane and chromatographed on silica gel eluting with dichloromethane–ethyl acetate, 10 : 1. Yield 0.27 g (21%). Light-brown amorphous powder, mp 97–99°C. IR spectrum, ν, cm^{-1}: 2943–2869 (CH_3, CH_2), 1706 (C^{3}=O), 1664 (C=O), 1258 (O–CH_3). ^{1}H NMR spectrum, δ, ppm: 0.90 s, 0.97 s, 0.99 s, 1.00 s, 1.09 s, 1.70 s (18H, $6CH_3$), 3.88 s (3H, CH_3O), 4.68 d (2H, $C^{29}H_2$, *J* 23.1 Hz), 6.91–7.05 m (3H, $H^{3',5'}$, H_{vinyl}), 7.34 d (1H, H^{28}, *J* 15.7 Hz), 7.96 d (2H, $H^{2',6'}$, *J* 8.7 Hz). Found, %: C 81.91; H 9.44. $C_{39}H_{54}O_3$. Calculated, %: C 82.06; H 9.53.

(*E*)-28-[2-Oxo-2-(4-methoxyphenyl)ethylidene]-lup-20(29)-en-3-one (14b) was obtained similarly. Yield 0.30 g (23%). Slightly colored amorphous powder, mp 88–90°C. IR spectrum, ν, cm^{-1}: 2945–2868 (CH_3, CH_2), 1704 (C^3=O), 1667 (C=O). ^1H NMR spectrum, δ, ppm: 0.90 s, 0.96 s, 1.00 s, 1.05 s, 1.69 s (18H, $6CH_3$), 4.67 d (2H, $C^{29}H_2$, *J* 22.2 Hz), 6.92 d (1H, H_{vinyl}, *J* 15.9 Hz), 7.37 d (1H, H^{28}, *J* 16.2 Hz), 7.45 d (2H, $H^{3',5'}$, *J* 8.6 Hz), 7.88 d (2H, $H^{2',6'}$, *J* 8.4 Hz). Found, %: C 79.24; H 8.78; Cl 6.05. $C_{38}H_{51}ClO_2$. Calculated, %: C 79.34; H 8.94; Cl 6.16.

28-Hydroxy-28-phenyllup-20(29)-en-3-one (15a and 15b). To a solution of 6 g (13.67 mmol) of betulonic aldehyde **5** in THF was added at stirring an excess of freshly prepared Grignard reagent. The solvent was removed at a reduced pressure from the formed gel-like mass, the dry residue was mixed with 150 mL of 20% acetic acid. The mixture was stirred for 10–12 h at room temperature. The white precipitate was filtered off, washed with water, dried in air, and recrystallized from ethanol. Yield of compound **15b** 4.84 g (69%). White amorphous powder, mp 188–190°C. IR spectrum, ν, cm^{-1}: 3475 br (OH), 2937–2600 (CH_3, CH_2), 1694 (C=O). ^1H NMR spectrum, δ, ppm: 0.97 s, 1.04 s, 1.08 s, 1.72 s (18H, $6CH_3$), 4.67 d (2H, $C^{29}H_2$, *J* 28.2 Hz), 5.26 s (1H, H^{28}), 7.19–7.48 m (5H, C_6H_5). Found, %: C 83.55; H 10.12. $C_{36}H_{52}O_2$. Calculated, %: C 83.67; H 10.14. A single crystal for XRD experiment was grown from methanol.

28-Phenylallobetulone (16). In 40 mL of dichloromethane was dissolved 2.2 g (4.26 mmol) of compound **15b** and at cooling was added dropwise 10 mL of trifluoroacetic acid. After the addition of the acid the reaction proceeded for 4 h (TLC monitoring). The solution was thrice washed with water, once with sodium hydrogen carbonate and once more with water. The organic layer was separated, dried with Na_2SO_4, and evaporated. Yield 2.13 g (97%). White amorphous powder, mp 206–208°C. IR spectrum, ν, cm^{-1}: 2942–2790 (CH_3, CH_2), 1702 (C=O), 1027 (C–O–C). ^1H NMR spectrum, δ, ppm: 0.84 s, 0.95 s, 1.00 s, 1.03 s, 1.04 s, 1.08 s (21H, $7CH_3$), 3.68 s (1H, H^{19}), 5.22 s (1H, H^{28}), 7.14–7.60 m (5H, C_6H_5). Found, %: C 83.74; H 10.23. $C_{36}H_{52}O_2$. Calculated, %: C 83.67; H 10.14. A single crystal for XRD experiment was grown from ethyl acetate.

Compounds **17a–17c** and **18a**, **18b** were prepared analogously to compound **10c** from compounds **15b** and **16** respectively.

(*E*)-28-Hydroxy-2-{[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenyllup-20(29)-en-3-one (17a). Yield 0.5 g (85%). White amorphous powder, mp 126–128°C. IR spectrum, ν, cm^{-1}: 3447 (OH), 2937–2860 (CH_3, CH_2), 1670 (C=O), 1640 (C=C). ^1H NMR spectrum, δ, ppm: 0.88 s, 1.11 s, 1.19 s, 1.23 s, 1.76 s (18H, $6CH_3$), 2.40 s (3H, 4'-CH_3), 2.94 d (1H, H^{1e}, *J* 14.8 Hz), 3.02–3.20 m (1H, H^{19}), 4.71 d (2H, $C^{29}H_2$, *J* 27.4 Hz), 5.28 s (1H, H^{28}), 7.20–7.62 m (13H, $2H^{3',5'}$, $2C_6H_5$, H_{vinyl}), 7.80 d (2H, $2H^{2',6'}$, *J* 8.0 Hz), 8.06 s (1H, $H_{pyrazole}$). Found, %: C 83.73; H 8.55; N 3.73. $C_{53}H_{64}N_2O_2$. Calculated, %: C 83.64; H 8.48; N 3.68.

(*E*)-28-Hydroxy-2-{[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenyllup-20(29)-en-3-one (17b). Yield 0.48 g (81%). White amorphous powder, mp 158–160°C. IR spectrum, ν, cm^{-1}: 3467 (OH), 2939–2867 (CH_3, CH_2), 1673 (C=O), 1639 (C=C), 1250 (O–CH_3). ^1H NMR spectrum, δ, ppm: 0.89 s, 1.12 s, 1.19 s, 1.23 s, 1.76 s (18H, $6CH_3$), 2.96 d (1H, H^{1e}, *J* 16.4 Hz), 3.11 s (1H, H^{19}), 3.86 s (3H, 4'-OCH_3), 4.71 d (2H, $C^{29}H_2$, *J* 27.8 Hz), 5.28 s (1H, H^{28}), 7.01 d (2H, $2H^{3',5'}$, *J* 8.8 Hz), 7.21–7.68 m (11H, $2C_6H_5$, H_{vinyl}), 7.80 d (2H, $2H^{2',6'}$, *J* 8.3 Hz), 8.05 s (1H, $H_{pyrazole}$). Found, %: C 82.02; H 8.39; N 3.66. $C_{53}H_{64}N_2O_3$. Calculated, %: C 81.92; H 8.30; N 3.60.

(*E*)-28-Hydroxy-2-[(4-chlorophenyl)methylidene]-28-phenyllup-20(29)-en-3-one (17c). Yield 0.30 g (81%). White amorphous powder, mp 121–123°C. IR spectrum, ν, cm^{-1}: 3515 br (OH), 2948–2867 (CH_3, CH_2), 1680 (C=O), 1639 (C=C). ^1H NMR spectrum, δ, ppm: 0.72 s, 1.03 s, 1.05 s, 1.07 s, 1.67 s (18H, $6CH_3$), 2.34 d (1H, H^{1a}, *J* 17.2 Hz), 2.92 d (1H, H^{1e}, *J* 17.2 Hz), 3.09–3.22 m (1H, H^{19}), 4.61 d (2H, $C^{29}H_2$, *J* 46.7 Hz), 4.98 s (1H, OH^{28}), 5.07 s (1H, H^{28}), 7.03–7.62 m (10H, C_6H_4, C_6H_5, H_{vinyl}). Found, %: C 80.86; H 8.79; Cl 5.50. $C_{53}H_{64}N_2O_3$. Calculated, %: C 80.78; H 8.67; Cl 5.54. A single crystal for XRD experiment was grown from ethyl acetate.

(*E*)-2-{[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenylallobetulone (18a). Yield 0.55 g (93%). White amorphous powder, mp 230–232°C. IR spectrum, ν, cm^{-1}: 2971–2860 (CH_3, CH_2), 1670 (C=O), 1024 (C–O–C). ^1H NMR spectrum, δ, ppm: 0.88 s, 0.89 s, 1.06 s, 1.08 s, 1.10 s, 1.12 s, 1.18 s (21H, 7 CH_3), 2.14 d (1H, H^{1a}, *J* 16.9 Hz), 2.41 s (3H, 4'-CH_3), 2.99 d (1H, H^{1e}, *J* 16.1 Hz), 3.72 s (1H, H^{19}), 5.25 s (1H, H^{28}), 7.20–7.65 m (13H, 2H, $2H^{3,5}$, 2 C_6H_5, H_{vinyl}), 7.78 d (2H, $2H^{2,6}$, *J* 7.8 Hz), 8.05 s (1H,

$H_{pyrazole}$). Found, %: C 83.75; H 8.45; N 3.65. $C_{53}H_{64}N_2O_2$. Calculated, %: C 83.64; H 8.48; N 3.68. A single crystal for XRD experiment was grown from a mixture dichloromethane–ethanol, 1 : 3.

(*E*)-2-{[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenylallobetulone (18b). Yield 0.52 g (88%). White amorphous powder, mp 270–272°C. IR spectrum, ν, cm^{-1}: 2946–2832 (CH_3, CH_2), 1671 (C=O), 1610 (C=C), 1248 (O–CH_3), 1035 (C–O–C). ^1H NMR spectrum, δ, ppm: 0.88 s, 0.89 s, 1.06 s, 1.08 s, 1.10 s, 1.12 s, 1.18 s (21H, 7CH_3), 2.14 d (1H, H^{1a}, *J* 16.0 Hz), 2.99 d (1H, H^{1e}, *J* 16.1 Hz), 3.72 s (1H, H^{19}), 3.86 s (3H, 4'-OCH_3), 5.25 s (1H, H^{28}), 7.01 d (2H, $2H^{3',5'}$, *J* 8.6 Hz), 7.16–7.70 m (11H, $2C_6H_5$, H_{vinyl}), 7.78 d (2H, $2H^{2',6'}$, *J* 8.0 Hz), 8.04 s (1H, $H_{pyrazole}$). Found, %: C 81.81; H 8.24; N 3.51. $C_{53}H_{64}N_2O_3$. Calculated, %: C 81.92; H 8.30; N 3.60.

Compounds **19a**, **19b** and **20a**, **20b** were prepared analogously to compound **11** from compounds **17** and **18** respectively.

(*E*)-2-{[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenyllup-20(29)-en-3,28-diol (19a). Yield 0.18 g (90%). Light-brown amorphous powder, mp 133–135°C. IR spectrum, ν, cm^{-1}: 3458 br (OH), 2932–2865 (CH_3, CH_2), 1668 (C=C). ^1H NMR spectrum, δ, ppm: 0.72 s, 0.73 s, 1.02 s, 1.05 s, 1.65 s (18H, 6CH_3), 2.83–3.03 m (2H, H^{1e}, H^{19}), 2.43 s (3H, 4'-CH_3), 3.81 s (1H, H^3), 4.62 d (2H, $C^{29}H_2$, *J* 28.2 Hz), 5.16 s (1H, H^{28}), 6.41 s (1H, H_{vinyl}), 6.93 d (2H, $2H^{3',5'}$, *J* 8.7 Hz), 7.03–7.86 m (12H, $2H^{2',6'}$, $2C_6H_5$), 7.81 s (1H, $H_{pyrazole}$). Found, %: C 83.31; H 8.62; N 3.56. $C_{53}H_{66}N_2O_2$. Calculated, %: C 83.42; H 8.72; N 3.67.

(*E*)-2-{[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenyllup-20(29)-en-3,28-diol (19b). Yield 0.19 g (95%). Light-brown amorphous powder, mp 152–154°C. IR spectrum, ν, cm^{-1}: 3461 br (OH), 2938–2867 (CH_3, CH_2), 1670 (C=C), 1248 (O–CH_3). ^1H NMR spectrum, δ, ppm: 0.70 s, 0.74 s, 1.00 s, 1.07 s, 1.64 s (18H, 6CH_3), 2.85–3.11 m (2H, H^{1e}, H^{19}), 3.77 s (4H, 4'-OCH_3, H^3), 4.59 d (2H, $C^{29}H_2$, *J* 28.4 Hz), 5.18 s (1H, H^{28}), 6.45 s (1H, H_{vinyl}), 6.88 d (2H, $2H^{3',5'}$, *J* 8.7 Hz), 7.11–7.74 m (12H, $2H^{2',6'}$, $2C_6H_5$), 7.77 s (1H, $H_{pyrazole}$). Found, %: C 81.88; H 8.46; N 3.54. $C_{53}H_{66}N_2O_3$. Calculated, %: C 81.71; H 8.54; N 3.60.

(*E*)-2-{[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenylallobetulin (20a). Yield 0.18 g (90%). White amorphous powder, mp 168–170°C. IR spectrum, ν, cm^{-1}: 3445 br (OH), 2925–2864 (CH_3, CH_2), 1670 (C=C), 1027 (C–O–C). ^1H NMR spectrum, δ, ppm: 0.77 s, 0.83 s, 1.02 s, 1.08 s, 1.15 s (21H, 7CH_3), 2.39 s (3H, 4'-CH_3), 3.09 d (1H, H^{1e}, *J* 12.8 Hz), 3.67 s (1H, H^{19}), 3.88 s (1H, H^3), 5.22 s (1H, H^{28}), 6.55 s (1H, H_{vinyl}), 7.15–7.80 m (14H, C_6H_4, $2C_6H_5$), 7.87 s (1H, $H_{pyrazole}$). Found, %: C 83.56; H 8.87; N 3.72. $C_{53}H_{66}N_2O_2$. Calculated, %: C 83.42; H 8.72; N 3.67.

(*E*)-2-{[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylidene}-28-phenylallobetulin (20b). Yield 0.18 g (90%). White amorphous powder, mp 166–168°C. IR spectrum, ν, cm^{-1}: 3480 br (OH), 2943–2864 (CH_3, CH_2), 1247 (O–CH_3), 1027 (C–O–C). ^1H NMR spectrum, δ, ppm: 0.76 s, 0.82 s, 0.83 s, 1.01 s, 1.08 s, 1.14 s (21H, 7 CH_3), 3.08 d (1H, H^{1e}, *J* 12.8 Hz), 3.67 s (1H, H^{19}), 3.85 s (3H, 4'-OCH_3), 3.88 s (1H, H^3), 5.22 s (1H, H^{28}), 6.54 s (1H, H_{vinyl}), 6.96 d (2H, $2H^{3',5'}$, *J* 8.2 Hz), 7.19–7.80 m (12H $2H^{2',6'}$, $2C_6H_5$), 7.86 s (1H, $H_{pyrazole}$). Found, %: C 81.63; H 8.47; N 3.49. $C_{53}H_{66}N_2O_3$. Calculated, %: C 81.71; H 8.54; N 3.60.

(2*S*,2'*S*)- and (2*R*,2'*R*)-2'-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl]-3-oxospiro[lup-20(29)-en-2,1'-cyclopropan]-28-al (12a and 13a). Unsaturated ketone **10a** (0.20 g, 0.29 mmol) was added by portions to a solution of excess trimethylsulfoxonium iodide and NaH in anhydrous DMF. The reaction was carried out at room temperature. On completion of the process (TLC monitoring) the reaction product was precipitated with water, filtered off, and dried in air. Yield 0.15 g (75%). White amorphous powder, mp 210–212°C. IR spectrum, ν, cm^{-1}: 2944–2866 (CH_3, CH_2), 1716 (CHO), 1673 (C=O). ^1H NMR spectrum, δ, ppm: 0.39 s, 0.84 s, 0.89 d, 0.95 s, 0.98 s, 1.00 s, 1.10 s, 1.15 s, 1.64 s, 1.67 s (12 CH_3), 2.38 d (4.5H, 1.5 4'-OCH_3), 2.77–3.09 m (1.5H, $H^{2''}$), 4.45–4.81 m (3H, $C^{29}H_2$), 7.03–7.98 m (~13H, C_6H_4, C_6H_5, $H_{pyrazole}$), 9.65 s (1.2H, H_{formyl}).

Compounds **12b**, **13b**, **21**, and **22** were obtained similarly.

(2*S*,2'*S*)- and (2*R*,2'*R*)-2'-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3-oxospiro[lup-20(29)-en-2,1'-cyclopropan]-28-al (12b and 13b). Yield 0.18 g (90%). White amorphous powder, mp 122–124°C. IR spectrum, ν, cm^{-1}: 2939–2830 (CH_3, CH_2), 1722 (CHO), 1674 (C=O), 1250 (O–CH_3). ^1H NMR spectrum, δ, ppm: 0.37 s, 0.84 s, 0.88 d, 0.95 s, 1.00 s, 1.14 s, 1.66 d (12 CH_3), 2.74–3.15 m (4H, $H^{2''}$, H^{19}),

3.87 d (4.7H, 1.5 4'-OCH_3), 4.51–4.89 m (3.7H, $C^{29}H_2$), 6.80–8.13 m (~16H, C_6H_4, C_6H_5, $H_{pyrazole}$), 9.67 d (1.6H, H_{formyl}).

(2*S*,2'*S*)- and (2*R*,2'*R*)-2'-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-28-phenylspiro[deoxyallobetulin-2,1'-cyclopropan]-3-one (21 and 22). Yield 0.09 g (93%). White amorphous powder, mp 173–175°C. IR spectrum, ν, cm^{-1}: 2925–2863 (CH_3, CH_2), 1674 (C=O), 1027 (C–O–C). ^1H NMR spectrum, δ, ppm: 0.43 s, 0.76 d, 0.88 s, 0.92 d, 1.00 s, 1.02 s, 1.09 s, 1.13 s, 1.23 d (14 CH_3), 2.37 d (4.42H, 1.5 4'-CH_3), 2.77–2.88 t (1.23H, $H^{2'}$), 3.04–3.14 t (1.26H, $H^{2'}$), 3.59 d (1.58H, H^{19}), 5.16 d (1.59H, H^{28}), 7.09–7.86 m (~22H, C_6H_4, $2C_6H_5$, $H_{pyrazole}$).

X-ray diffraction investigation of compounds 15b, 16, 17c, and 18a. XRD experiments were performed on a diffractometer Xcalibur-3 (MoK_α-radiation, CCD-detector, graphite monochromator, ω-scanning). Structures were solved by the direct method applying SHELXTL software [18]. Crystals of all the compounds belong to non-centrosymmetric space groups indicating the presence of a single enantiomer. The studied compounds (save compound **17c**) contain no heavy atoms preventing establishing the configuretion of the chiral centers by Flack parameter, therefore for compounds **15b**, **16**, and **18a** only the relative configuration has been established. For compound **17c** the configuration of the chiral centers was established basing on the Flack parameter [0.0(2)]. The positions of hydrogen atoms were found from the difference synthesis of the electron density and were refined by the *rider* model (n = 1.5 for methyl and hydroxy groups and n = 1.2 for the other hydrogen atoms). The crystallographic data and experimental parameters are collected in the table. The atomic coordinates and complete data on bond lengths and bond angles are deposited in the Cambridge Crystallographic Data Center (e-mail: deposit@ccdc.cam.ac.uk), the respective CCDC numbers are listed in the table.

REFERENCES

1. Connolly, J.D. and Hill, R.A., *Nat. Prod. Rep*., 2010, vol. 27, p. 79.
2. Ge, R., Huang, Y., Liang, G., and Li, X., *Curr. Med. Chem*., 2010, vol. 17, p. 412.
3. Tolstikov, G.A., Flekhter, O.B., Shul'ts, E.E., Baltina, L.A., and Tolstikov, A.G., *Khimiya v interesakh ustoichivogo razvitiya* (Chemistry for Sustainable Development), 2005, vol. 13, p. 1.
4. Yogeeswari, P. and Sriram, D., *Curr. Med. Chem*., 2005, vol. 12, p. 657.
5. Dehaen, W., Mashentseva, A.A., and Seitembetov, T.S., *Molecules*, 2011, vol. 16, p. 2443.
6. Swidorski, J., Meanwell, N.A., Regueiro-Ren, A., Sit Sing-Yuen, Chen, J., and Chen, Y., US Patent no. 210787, 2013; *Chem. Abstr*., 2013, vol. 159, no. 371389.
7. Barthel, A., Stark, S., and Csuk, R., *Tetrahedron*, 2008, vol. 64, p. 9225.
8. Ruzicka, L., Häusermann, H., and Rey, Ed., *Helv. Chim. Acta*, 1942, vol. 25, p. 171.
9. Saxena, B.B., Rathnam, P., and Bomshteyn, A., WO Patent no. 112929, 2005; *Chem. Abstr*., 2005, vol. 144, no. 572.
10. Tulisalo, J., Pirttimaa, M., Alakurtti, S., Yli-Kauhaluoma, J., and Koskimies, S., WO Patent no. 38314, 2012; *Chem. Abstr*., 2013, vol. 158, no. 474940.
11. Wei, Y., Maa, Ch., and Hattor, M., *Eur. J. Med. Chem*., 2009, vol. 44, p. 4112.
12. Flekhter, O.B., Ashavina, O.Y., Boreko, E.I., Karachurina, L.T., Pavlova, N.I., Kabal'nova, N.N., and Tolstikov, G.A., *Pharm. Chem. J*., 2002, vol. 36, p. 303.
13. Melnikova, N., Burlova, I., Kiseleva, T., Klabukova, I., Gulenova, M., Kislitsin, A., Vasin, V., and Tanaseichuk, B., *Molecules*, 2012, vol. 17, p. 11849.
14. Ze-Qi, X., Koohang, A., Mar, A.A., Majewski, N.D., Eiznhamer, D.A., and Flavin, M.T., US Patent no. 232577, 2007; *Chem. Abstr*., 2007, vol. 147, no. 406972.
15. Babak, N.L., Semenenko, A.N., Gella, I.M., Musatov, V.I., Shishkina, S.V., Novikova, N.B., Sofronov, D.S., Morina, D.A., and Lipson, V.V., *Russ. J. Org. Chem*., 2015, vol. 51, p. 715.
16. Durst, T., Merali, Z., Cayer, C., Arnason, J.T., and Baker, J.D., WO Patent no. 71506, 2013; *Chem. Abstr*., 2014, vol. 160, no. 716590.
17. Csuk, R., Sczepek, R., Siewert, B., and Nitsche, C., *Bioorg. Med. Chem*., 2013, vol. 21, p. 425.
18. Sheldrick, G.M., *Acta Cryst., Sect. A*, 2008, vol. 64, p. 112.