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Electrophilic Substitution of Hydrogen in Betulin and Diacetylbetulin

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Abstract—Betulin and diacetylbetulin, which can be regarded as sterically hindered alkenes, reacted with *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimides to give products of allylic and vinylic substitution in quantitative overall yield. The contribution of allylic substitution increases in the series Cl < Br < I. Quantum chemical simulation of the reactions of diacetylbetulin with *N*-halosuccinimides showed that, regardless of the electrophile power, all reactions involve open-chain carbocationic intermediates. The direction of deprotonation of the latter with formation of allylic or vinylic substitution products is determined by preferential orientation of the vacant orbital and C–Hlg bond.

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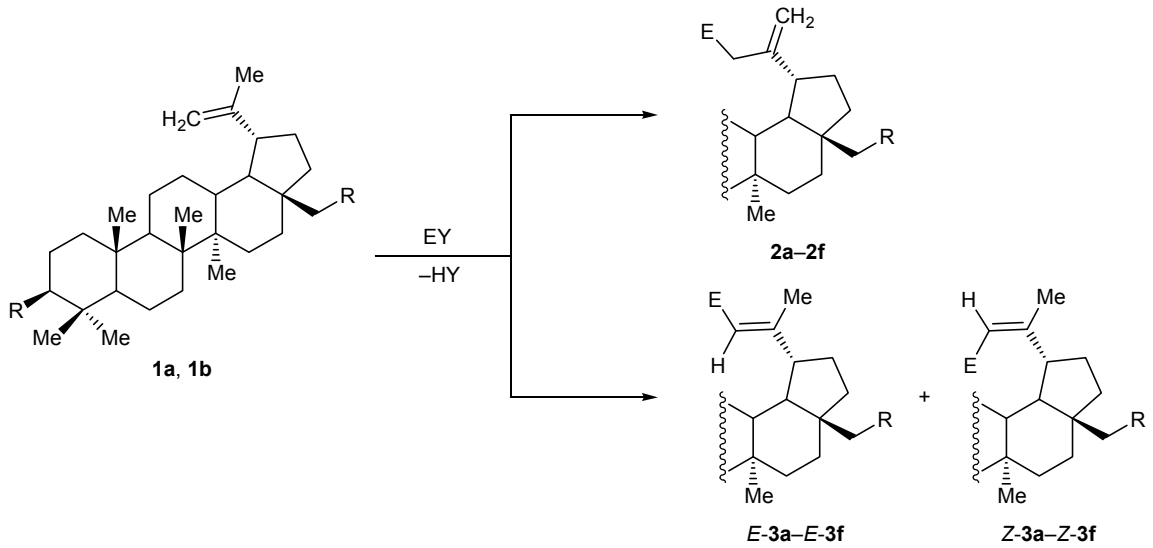
Syntheses of many organic compounds involve C=C double bonds, which constantly stimulates extension of the series of available unsaturated compounds and the scope of their transformations. In the past decades, a new field in the chemistry of unsaturated compounds has been developed, which is referred to as chemistry of sterically hindered alkenes [1]. Sterically hindered alkenes include those containing branched alkyl or polycyclic substituents in the vicinal or geminal position with respect to the double bond, polycyclanes and cage compounds with an exocyclic double bond or double bond incorporated into a rigid polycyclic system, and others.

The reactivity and reaction directions of alkenes with sterically shielded double bond radically differ from those typical of common unsaturated compounds [2]. In particular, they are subject to electrophilic substitution with the formation of vinylic or allylic derivatives [3–5]. In recent years, catalytic versions of allylic substitution have attracted attention of many chemists [6–9]. Vinylic substitution is usually accomplished as nucleophilic substitution of halogen [10] or in a catalytic way [11, 12].

We have studied reactions of alkenes with a bulky substituent in the geminal position, betulin (**1a**) and diacetylbetulin (**1b**), with electrophiles of different strengths. The choice of natural unsaturated compounds **1a** and **1b** as substrates was dictated by their diverse biological activity [13–16]; development of rational methods for their functionalization is an important problem of organic synthesis. As electrophiles we used *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimides (NCS, NBS, NIS) with the same nucleophilic moiety. Molecular bromine and iodine were also used to assess the possibility of Wohl–Ziegler radical bromination.

The reactions were carried out in acetic acid at 15–50°C, and the composition of the reaction mixtures was monitored by NMR. No mutual transformations of the substitution products were observed. Under the given conditions, the reactions of betulin and diacetylbetulin with NCS, NBS, NIS, bromine, and iodine afforded only allylic (**2**) and vinylic substitution products (**3**) (Scheme 1). The product composition and structure were reliably determined by ^{1}H and ^{13}C NMR and X-ray analysis. The ^{1}H NMR spectrum of the product obtained from betulin and NBS lacked vinylic proton signals at δ 4.5 and 4.7 ppm (Fig. 1a) typical of the initial compound, whereas signals belonging to the substitution products were present (Fig. 1b). The signals at δ 5.90 and 5.74 were assigned to the vinylic

Scheme 1.



1, R = OH (**a**), OAc (**b**); **2**, **3**, E = Cl, R = OH (**a**), OAc (**b**); E = Br, R = OH (**c**), OAc (**d**); E = I, R = OH (**e**), OAc (**f**); Y = 2.5-dioxopyrrolidin-1-yl.

proton of the *E* and *Z* bromovinyl isomers **3**, and those at δ 5.03, 5.12, and 3.99 ppm, to the H_2C=C and CH_2Br protons of allylic substitution products **2**.

The *E* and *Z* isomers of the vinylic substitution products obtained from diacetylbetulin and NCS were identified by X-ray analysis. Recrystallization of the product mixture gave crystals enriched in one isomer. The X-ray diffraction study showed that the major isomer has *Z*-configured double bond (Fig. 2). In the ^{1}H NMR spectrum, the vinylic proton signal of the

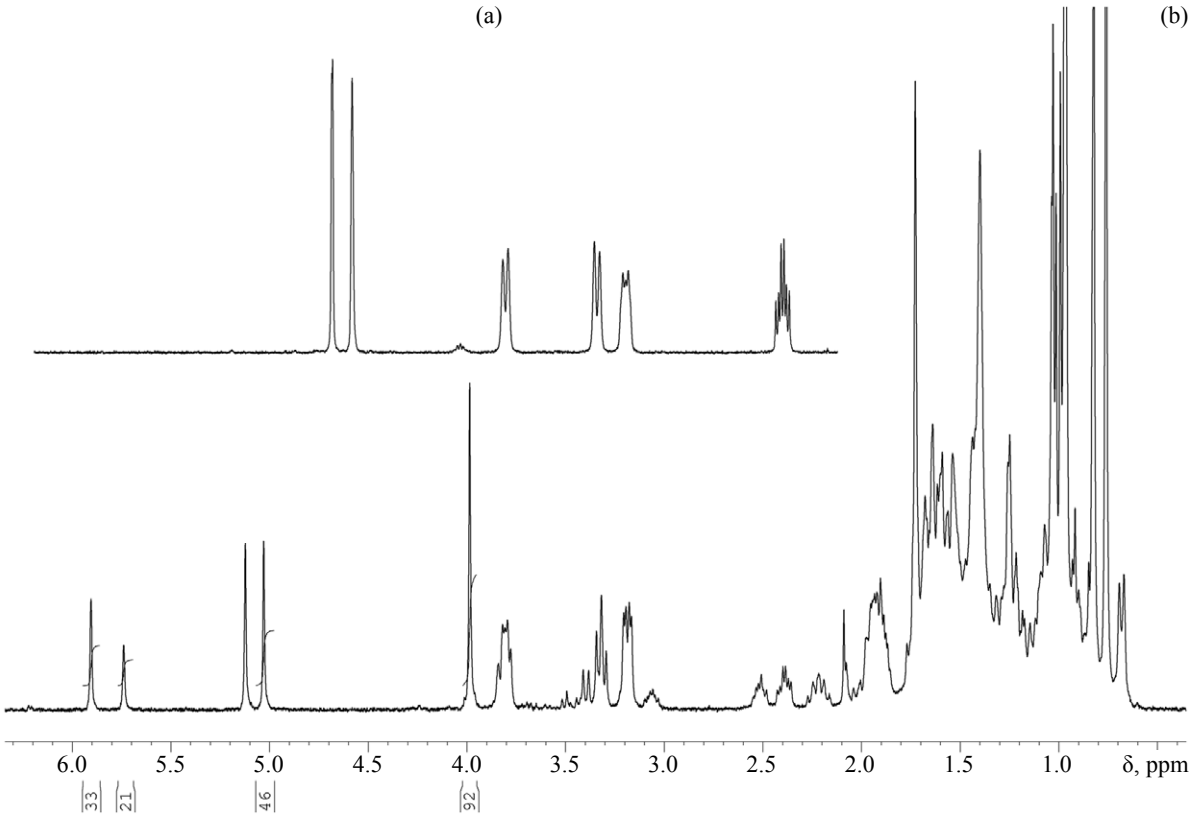


Fig. 1. ^{1}H NMR spectra of (a) betulin (fragment) and (b) products of its reaction with *N*-bromosuccinimide; 400 MHz, $CDCl_3$.

Table 1. Vinylic and allylic substitution of hydrogen in betulin and diacetylbetulin (^{1}H NMR data)

Initial compound no.	R	Reagent	Electrophile	Product composition, %	
				vinylic halogenation	allylic halogenation
1a	OH	NCS	Cl	**3a**, 40 (*E*), 32 (*Z*)	**2a**, 28
1b	OAc	NCS	Cl	**3b**, 39 (*E*), 31 (*Z*)	**2b**, 30
1a	OH	NBS	Br	**3c**, 33 (*E*), 21 (*Z*)	**2c**, 46
1b	OAc	NBS	Br	**3d**, 30 (*E*), 19 (*Z*)	**2d**, 51
1b	OAc	Br_2	Br	**3d**, 25 (*E*), 20 (*Z*)	**2d**, 55
1a	OH	NIS	I	**3e**, 6 (*E*), 3 (*Z*)	**2e**, 91
1a	OH	I_2	I	**3e**, 10 (*E*), 4 (*Z*)	**2e**, 86
1b	OAc	NIS	I	**3f**, 6 (*E*), 2 (*Z*)	**2f**, 92

major isomer (*Z*) was located in a stronger field (δ 5.64 ppm) relative to the corresponding signal of the minor *E* isomer (δ 5.80 ppm). The isomer ratios are given in Table 1.

Taking into account that in going from NBS to Br_2 and from NIS to I_2 the contribution of allylic substitution in the reactions with compounds **1a** and **1b** does not change (Table 1), we can assert that Wohl–Ziegler reaction does not occur under the given conditions. This means that in the absence of radical initiator and at a relatively low temperature NBS and NIS act as electrophilic reagents.

The structures and conformations of probable intermediates responsible for allylic and vinylic substitution in sterically hindered alkenes were determined by quantum chemical calculations. Compound **4** containing a methyl group and a bicyclic fragment with acetyloxymethyl substituent was used as model substrate which may be regarded as "truncated" diacetylbetulin.

The calculations showed that the approach of the chlorine atom of *N*-chlorosuccinimide to the double bond of **4** is accompanied by continuous increase of the energy of the system; however, this does not lead to the formation of a complex. Activation of NCS via protonation of the oxygen atom radically changes the behavior of the reacting system, and approach of the chlorine atom to the double bond leads to barrierless formation of complex **5a** (Scheme 2). Stretching of the Cl–N bond in complex **5a** leads to its rupture with formation of carbocation **6** and succinimide in the enol form (Scheme 2). The energy barrier in this step is 16 kcal/mol with subsequent decrease in energy by 1 kcal/mol.

The possibility of the transformation of **6** into a cyclic carbocation was assessed by moving the chlorine atom in **6** to the carbocationic center until a position corresponding to covalent bond is achieved; in this case, the energy of the system increased by 11 kcal/mol. However, that position of the chlorine atom does not match the maximum energy point. Thus, we have found no local energy minimum corresponding to the cyclic structure of carbocation on the potential energy surface (PES).

Approach of the bromine atom in activated NBS to the double bond of **4** gives complex **5b** (without a barrier; Scheme 2) in which the distance from the bromine atom to the methylene carbon atom is 2.4 Å and the Wiberg index of the CH_2–Br bond is 0.17. The

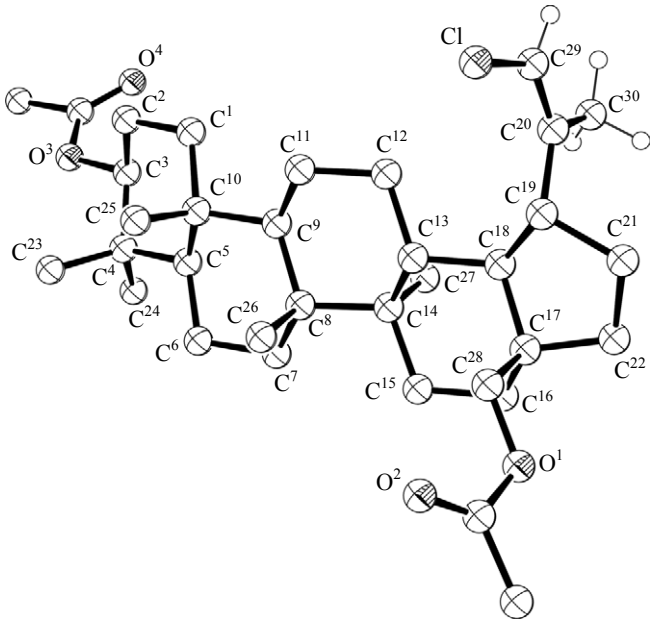
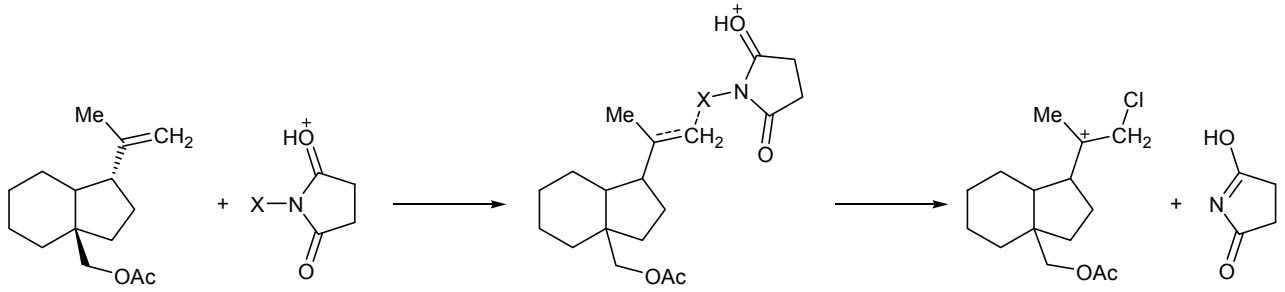


Fig. 2. Structure of the molecule of (*Z*)-29-chlorolup-20(29)-ene-3β,28-diyl diacetate (**3b**) according to the X-ray diffraction data. Shown are only hydrogen atoms on the allylic (C^{30}) and vinylic carbon atoms (C^{29}).

Scheme 2.



X = Cl (**a**), Br (**b**).

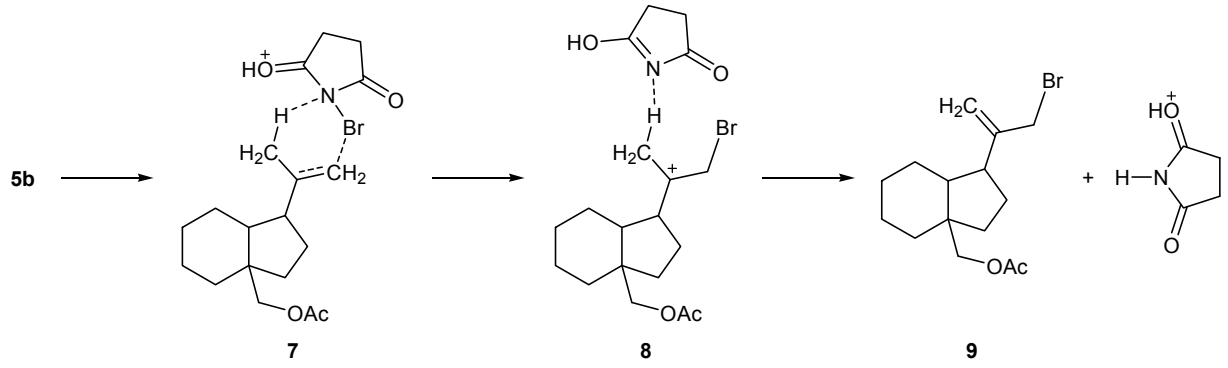
distance between the bromine atom and central carbon atom is 2.65 Å, i.e., no covalent bond is formed, and the central carbon atom retains planar bond configuration.

Elongation of the Br–N bond in **5b** to 3Å increases the energy of the system to 31 kcal/mol, but the energy barrier is higher. However, movement of the nitrogen atom of the succinimide fragment in complex **5b** toward hydrogen atom of the methyl group gives six-membered complex **7** where the distance between the central carbon atom and bromine spontaneously increases (Scheme 3). As a result, the energy of the system reaches the maximum value (30 kcal/mol) corresponding to transition state (carbocation **8**). The subsequent formation of allylic substitution product **9** reduces the energy by 33 kcal/mol.

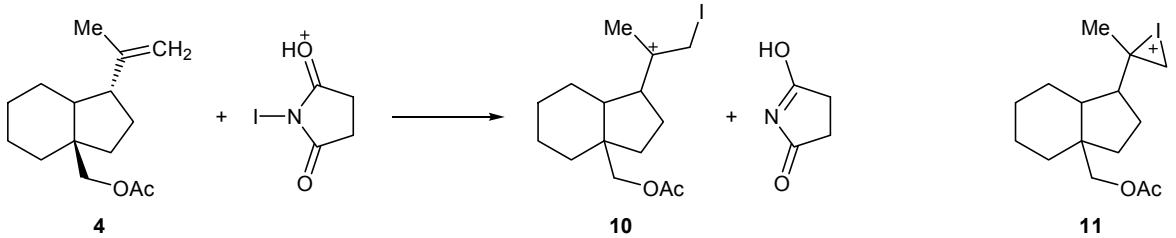
In order to estimate the possibility of the transformation of **8** to bromonium ion, the bromine atom was moved toward the central carbon atom. When the C–Br distance achieved 1.9 Å (C–Br length in a symmetrical cyclic structure), the energy of the system increased by 32 kcal/mol, but the maximum energy point was not localized. Thus, simulation of the reaction with electrophilic bromine revealed no local energy minimum on the PES corresponding to cyclic intermediate.

Approach of the iodine atom of activated *N*-iodosuccinimide to the terminal methylene group of model molecule **4** to a distance of 2.1 Å and stretching of the I–N bond until complete rupture (energy barrier 27 kcal/mol) with subsequent reduction of the energy by 3 kcal/mol led to the formation of intermediate **10**

Scheme 3.



Scheme 4.



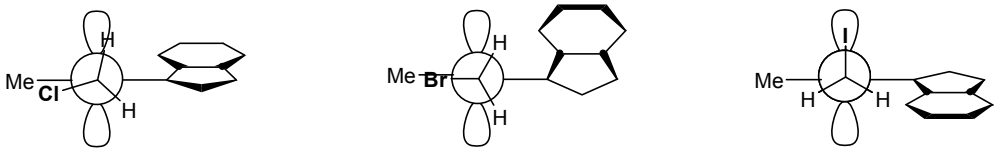


Fig. 3. Newman projections of carbocations **6**, **8**, and **10**, illustrating mutual orientation of the C–E bond and vacant orbital.

and enol tautomer of succinimide (Scheme 4). The carbocationic center in **10** has a planar bond configuration typical of sp^2-carbon atom. The iodomethyl group in this intermediate has tetrahedral structure with the Wiberg index of the H_2C–I bond equal to 0.71. The iodine atom in **10** does interact, though weakly, with the cationic carbon atom (Wiberg index 0.15).

As described above for other electrophiles, the possibility of the transformation of **10** to cyclic structure was checked by forced shortening of the distance between the iodine atom and cationic carbon atom to the length of covalent bond (2.1 Å). After surmounting the energy barrier 10 kcal/mol, subsequent reduction of the energy of the system by 1 kcal/mol gave cyclic carbocation **11** in which the C^+–I and H_2C–I distances were 2.09 and 2.04 Å, and the corresponding Wiberg indices were 0.76 and 0.9, respectively.

Thus, the results of quantum chemical calculations showed that substitution of hydrogen in model molecule **4** (and hence in betulin and diacetylbetulin) in reactions with *N*-halosuccinimides involves intermediate open-chain carbocations, regardless of the electrophile strength. We were the first to reveal the effect of the entering electrophile on the ratio of allylic and vinylic substitution paths in reactions with unsaturated compounds. As follows from the data in Table 1, reactions of the examined electrophiles with alkenes **1a** and **1b** display inversion of the direction of proton elimination paths: vinylic substitution predominate in the chlorination, whereas allylic substitution becomes almost the only reaction path in the iodination. In the bromination of **1a** and **1b**, the contributions of allylic and vinylic substitution of hydrogen are approximately similar.

It was also found that hydrogen atoms in the substituents on the cationic carbon atom in open-chain carbocations acquire a significant positive charge (Table 2) and hence become acidic.

Figure 3 shows the most populated conformations of carbocations. The low polarizability of chlorine atom hampers coplanar arrangement of the C–Cl bond and vacant orbital, so that the interaction of chlorine with the cationic center is weak (Fig. 3), and polarized C–H bonds of the chloromethyl group successfully compete with the C–Cl bond for coplanarity with the vacant orbital. This ensures prevalence of the reaction path involving elimination of one of the C–H protons to give vinylic substitution product.

Another reaction direction is realized in carbocation **10** where high polarizability of the iodine atom favors coplanar arrangement of the C–I bond and vacant orbital. The calculations showed that the iodine atom partially interacts with the carbocationic center, though carbocation **10** has open-chain structure. This prevents C–H bonds in the iodomethyl group from coplanar arrangement with respect to the vacant orbital and hence hampers proton abstraction from that fragment. Therefore, the predominant reaction path is alternative elimination of proton from the methyl group (allylic substitution) which contains no substituent preventing coplanar orientation of the C–H bond with respect to the vacant orbital.

In terms of the above considerations, the behavior of bromine-containing carbocation **8** should be intermediate between the chlorine- and iodine-containing analogs, which is well consistent with both calculation results (Fig. 3) and experimental data (Table 1).

Thus, in keeping with the character of their chemical behavior, betulin and diacetylbetulin can be

Table 2. Calculated charges on atoms in the $C^{30}H_3$, HC^{19}–C^{20}, and $C^{29}H_2E$ fragments of carbocations

Atom[a]	E = Cl	E = Br	E = I
C^{30}	–0.65	–0.65	–0.65
H^{30}	+0.25	+0.25	+0.24
C^{20}	+0.61	+0.62	+0.61
C^{19}	–0.36	–0.36	–0.37
H^{19}	+0.24	+0.25	+0.30
C^{29}	–0.45	–0.5	–0.57
H^{29}	+0.25	+0.26	+0.25
E	0	+0.05	+0.14

[a] For atom numbering, see Fig. 2.

classed as sterically hindered alkenes with a fixed planar skeleton. The developed concept is based on the conservation of planar structure of genetically related systems (alkene, classical carbocation, substitution product), which is dictated by minimization of the energy of repulsive interaction of geminal substituents with a large steric radius.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz for ^{1}H) from solutions in $CDCl_3$ (Aldrich) containing 0.03% of tetramethylsilane as internal standard. The two-dimensional ^{1}H–^{1}H and ^{13}C–^{1}H correlation spectra were recorded using COSYGPQF and HSQCETGP pulse sequences. The X-ray diffraction data for compound **3b** were obtained on a Smart APEX automated diffractometer at 100 K. The structure was solved by the direct method and was refined against F^2_{hkl} by the least-squares method in anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were placed in geometrically calculated positions and were refined according to the riding model. Quantum chemical calculations were performed using GAUSSIAN 09 package [17].

Betulin (**1a**) was preliminarily recrystallized from isopropyl alcohol, mp 251–253°C. Diacetylbetulin (**1b**) was synthesized as described in [3], mp 221–223°C. *N*-Chlorosuccinimide was prepared by passing chlorine through an alkaline solution of succinimide; the product was recrystallized from acetic acid prior to use, mp 148–150°C. *N*-Bromosuccinimide was synthesized according to [18]; the product was recrystallized from water, mp 176–178°C. *N*-Iodosuccinimide was obtained by heating a solution of equimolar amounts of NBS and iodine in carbon tetrachloride at 40–55°C [19]; mp 195–198°C.

Halogenation of betulin (1a) and diacetylbetulin (1b) (*general procedure*). A solution of 1 mmol of *N*-halosuccinimide (NHS) in 20–25 mL of acetic acid was added to a solution of 1 mmol of compound **1a** or **1b** in 25 mL of acetic acid, and the mixture was stirred for 2–12 h at 15–50°C in a reactor equipped with a thermometer and protected from light. The conversion of NHS was monitored by iodometric titration. When the reagent was consumed completely, 100–150 mL of cold water was added to the mixture, and the precipitate was filtered off, washed with water until neutral washings, and dried. In all cases, mixtures of allylic and vinylic substitution products **2** and **3** were obtained. Their yields and ratios were determined by ^{1}H NMR.

30-Chlorolup-20(29)-ene-3β,28-diol (2a). ^{1}H NMR spectrum, δ, ppm: 4.06 s (2H, $ClCH_2$), 5.02 s and 5.09 s (2H, $=CH_2$).

29-Chlorolup-20(29)-ene-3β,28-diol (3a). A mixture of isomers *E*-**3a** and *Z*-**3a** and compound **2a**. ^{1}H NMR spectrum, δ, ppm: 5.64 s and 5.80 s (ClCH=, *Z*,*E*).

30-Chlorolup-20(29)-ene-3β,28-diyl diacetate (2b). ^{1}H NMR spectrum, δ, ppm: 2.073 s [3H, $OC(O)CH_3$], 2.44 t.d (1H, 19-H, J = 11.0, 5.4 Hz), 3.84 d and 4.29 d (2H, 28-H, ^2J = 11.2 Hz), 4.05 m (2H, $ClCH_2$), 5.02 m and 5.10 m (2H, $=CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 43.3 (C^{19}), 55.41 (C^5), 62.6 (C^{28}), 80.91 (C^3), 112.6 (C^{29}), 150.4 (C^{20}), 171.02 [28-OC(O)].

(*Z*)-29-Chlorolup-20(29)-ene-3β,28-diyl diacetate (*Z*-3b). ^{1}H NMR spectrum, δ, ppm: 1.70 d (3H, $C^{30}H_3$), 2.08 s [3H, $OC(O)CH_3$], 3.16 t.d (1H, 19-H, J = 10.9, 6.0 Hz), 3.90 d and 4.29 d (2H, 28-H, ^2J = 11.4 Hz), 5.64 q (1H, =CHCl, ^4J = 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 40.9 (C^{19}), 55.43 (C^5), 62.9 (C^{28}), 80.94 (C^3), 110.7 (C^{29}), 142.1 (C^{20}), 171.00 [28-OC(O)].

Crystals of *Z*-**3b** for X-ray analysis were obtained by double crystallization from acetonitrile. Orthorhombic crystal system, space group $P2_12_12_1$; $C_{34}H_{53}ClO_4$; unit cell parameters: a = 12.6287(14), b = 15.5736(18), c = 15.7120(18) Å; Z = 4; V = 3090.1(6) Å^3; d_{calc} = 1.206 g/cm^3.

(*E*)-29-Chlorolup-20(29)-ene (*E*-3b). ^{1}H NMR spectrum, δ, ppm: 1.71 d (3H, $C^{30}H_3$), 2.069 s [3H, $OC(O)CH_3$], 2.51 t.d (1H, 19-H, J = 10.8, 6.0 Hz), 3.83 d and 4.22 d (2H, 28-H, ^2J = 10.3 Hz), 5.80 m (1H, =CHCl). ^{13}C NMR spectrum, δ_C, ppm: 55.4 (C^5), 62.7 (C^{28}), 111.8 (C^{29}), 142.1 (C^{20}).

30-Bromolup-20(29)-ene-3β,28-diol (2c). ^{1}H NMR spectrum, δ, ppm: 2.39 t.d (1H, 19-H, J = 11.0, 5.4 Hz), 3.19 d.d (1H, 3-H, J = 11.2, 4.6 Hz), 3.33 d and 3.83 d (2H, 28-H, ^2J = 9.9 Hz), 3.99 m (2H, CH_2Br), 5.03 s and 5.12 s (2H, $=CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 14.9, 15.5, 16.17, 16.24, 28.1 (CH_3), 18.4, 21.1, 25.04, 27.15, 27.5, 28.9, 29.4, 34.0, 34.34, 37.3, 37.32, 37.6 (C^{30}), 38.9, 39.0, 41.1, 42.9, 43.6 (C^{19}), 47.96, 49.06, 50.49, 55.4, 60.44 (C^{28}), 79.1 (C^3), 113.4 (C^{29}), 151.2 (C^{20}).

(*Z*)-29-Bromolup-20(29)-ene-3β,28-diol (*Z*-3c). ^{1}H NMR spectrum, δ, ppm: 1.73 s (3H, $C^{30}H_3$),

3.06 t.d (1H, 19-H, J = 10.8, 5.5 Hz), 3.19 d.d (1H, 3-H, J = 11.2, 4.6 Hz), 3.40 d and 3.80 d (2H, 28-H, ^2J = 11.2 Hz), 5.74 s (1H, =CHBr). ^{13}C NMR spectrum, δ_C, ppm: 42.8 (C^{19}), 60.54 (C^{28}), 79.1 (C^3), 100.1 (C^{29}), 145.4 (C^{20}).

(*E*)-29-Bromolup-20(29)-ene-3β,28-diol (*E*-3c). ^{1}H NMR spectrum, δ, ppm: 2.52 t.d (1H, 19-H, J = 10.6, 6.1 Hz), 3.19 d.d (1H, 3-H, J = 11.2, 4.6 Hz), 3.30 d and 3.79 d (2H, 28-H, ^2J = 9.7 Hz), 5.90 s (1H, =CHBr). ^{13}C NMR spectrum, δ_C, ppm: 48.5 (C^{19}), 60.65 (C^{28}), 79.1 (C^3), 101.1 (C^{29}), 146.4 (C^{20}).

30-Bromolup-20(29)-ene-3β,28-diyl diacetate (2d). ^{1}H NMR spectrum, δ, ppm: 2.04 s and 2.078 s [3H each, OC(O)CH_3], 2.44 t.d (1H, 19-H, J = 11.2, 5.4 Hz), 3.99 m (2H, CH_2Br, ^2J = 11.0 Hz), 5.03 s and 5.13 s (2H, $=CH_2$).

(*Z*)-29-Bromolup-20(29)-ene-3β,28-diyl diacetate (*Z*-3d). ^{1}H NMR spectrum, δ, ppm: 2.04 s and 2.084 s [3H each, OC(O)CH_3], 3.12 t.d (1H, 19-H, J = 11.0, 5.6 Hz), 5.75 s (1H, =CHBr).

(*E*)-29-Bromolup-20(29)-ene-3β,28-diyl diacetate (*E*-3d). ^{1}H NMR spectrum, δ, ppm: 2.04 s and 2.073 s [3H each, OC(O)CH_3], 2.57 t.d (1H, 19-H, J = 10.9, 5.7 Hz), 5.91 s (1H, =CHBr).

30-Iodolup-20(29)-ene-3β,28-diol (2e). ^{1}H NMR spectrum, δ, ppm: 0.68 m (1H, 5-H); 0.76 s, 0.82 s, 0.97 s, 0.99 s, and 1.03 s (3H each, CH_3), 0.84–2.05 m (1-H, 2-H, 6-H, 7-H, 9-H, 11-H, 12-H, 13-H, 15-H, 16-H, 18-H, 21-H, 22-H), 2.22–2.40 m (2H, 19-H, 21-H), 3.19 d.d (1H, 3-H, J = 11.1, 4.8 Hz), 3.33 d and 3.81 d (2H, 28-H, ^2J = 10.8 Hz), 3.94 m (2H, CH_2I, ^2J = 9.3 Hz), 4.99 s and 5.17 s (2H, $=CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 11.9 br (C^{30}), 14.9, 15.5, 16.1, 16.2, 28.1 (CH_3), 18.4, 21.0, 26.8, 27.1, 27.4, 29.3, 33.2, 33.9, 34.4, 37.26, 37.33, 38.8, 39.0, 41.1, 42.8, 43.9 br (C^{19}), 47.7, 50.5, 50.7, 55.3, 60.4 (C^{28}), 79.1 (C^3), 112.1 (C^{29}), 152.1 (C^{20}).

29-Iodolup-20(29)-ene-3β,28-diol (3e). A small amount of vinyl isomers in a mixture with **2e**. ^{1}H NMR spectrum, δ, ppm: 5.72 s and 5.90 s (=CHI, *Z*, *E*).

30-Iodolup-20(29)-ene-3β,28-diyl diacetate (2f). ^{1}H NMR spectrum, δ, ppm: 0.78 m (1H, 5-H); 0.83 s, 0.84 s, 0.85 s, 0.98 s, and 1.04 s (3H each, CH_3); 0.94–1.88 m (1-H, 2-H, 6-H, 7-H, 9-H, 11-H, 12-H, 13-H, 15-H, 16-H, 18-H, 21-H, 22-H), 2.04 s and 2.08 s [3H, OC(O)CH_3], 2.27 m (1H, 21-H), 2.40 t.d (1H, 19-H, J = 10.9, 5.3 Hz), 3.84 d and 4.87 d (2H, 28-H, ^2J = 10.8 Hz), 3.93 m (2H, CH_2I, ^2J = 9.3 Hz), 4.46 m (1H, 3-H), 4.98 s and 5.18 s (2H, $=CH_2$).

29-Iodolup-20(29)-ene-3β,28-diyl diacetate (3f). A small amount of vinyl isomers in a mixture with **2f**. ^{1}H NMR spectrum, δ, ppm: 5.74 s and 5.91 s (=CHI, *Z*, *E*).

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