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Synthesis and Transformations of 20-Oxo-30-nortaraxasteryl Acetate Derivatives

V. R. Akhmetova, E. R. Shakurova, A. Z. Khalilova, L. M. Khalilov, and U. M. Dzhemilev

Institute of Petroleum Chemistry and Catalysis, Russian Academy of Sciences,
pr. Oktyabrya 141, Ufa, 450075 Bashkortostan, Russia
e-mail: ink@anrb.ru

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Abstract—20,20-Dimethoxy-, Δ^{21}-20-oxo-, and 20-oxo-30-nortaraxasteryl acetates were synthesized by selective ozonolysis of taraxasteryl acetate. Baeyer–Villiger oxidation of 20-oxo-30-nortaraxasteryl acetate with SeO_2–H_2O_2 gave 3β-acetoxytaraxa-(19,20)-ε-lactone. Mechanism of the ozonolysis of taraxasteryl acetate is discussed. The enthalpies of formation of possible intermediates were calculated by quantum-chemical methods, and most favorable paths of the ozonolysis and dehydrogenation were determined.

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Taraxast-20(30)en-3β-yl acetate (**I**) is a pentacyclic triterpenoid of the taraxastane series; it was isolated by us previously from a chloroform extract of Scotch cotton thistle *Onopordum acanthium L.* floral receptacles [1]. We found that floral receptacles of this plant contain up to 3% of compound **I** (calculated on the air-dried weight); therefore, we were able to study chemical transformations of triterpenoid **I** in more detail, as well as to search for possible ways of its application in practice.

Taraxasteryl acetate (**I**) and its derivatives exhibit antiinflammatory, antitumor, and antibacterial activity [2–4]. Data on antitumor activity of taraxasterol [**II**, taraxast-20(30)en-3β-ol] on model skin cancer in mice were reported [5]; tatraxasterol (**II**) was proposed as a component of a therapeutic composition for blocking the HIV-1 and/or HIV-2 virus replication in the CD4+ cells of the human immune system in all stages of that viral infection, and in AIDS [6]. Taking into account accessibility of taraxasteryl acetate (**I**) and biological activity of some its derivatives, we believed it to be promising to examine its chemical transformations with a view to obtain new biologically active compounds among derivatives of triterpenoid **I**.

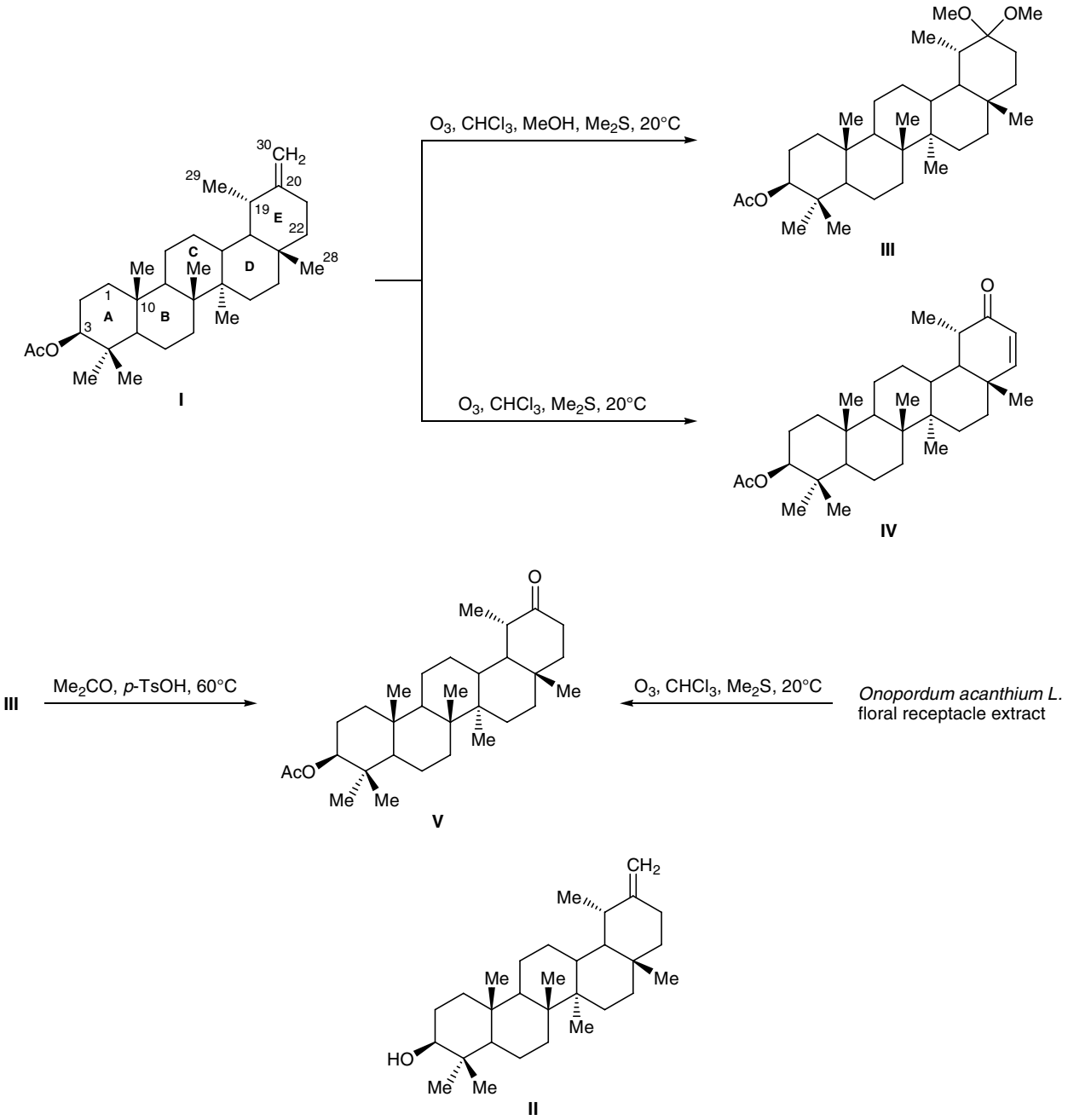
Some oxidative transformations of taraxasterol (**II**) and taraxasteryl acetate (**I**), namely epoxidation with *m*-chloroperoxybenzoic acid and oxidation with Jones' reagent, were reported in [7]. Analogous transformations were also performed with β-amyrin [8]. We have found no published data on ozonolysis of the C^{20}=C^{30} double bond in compound **I** or **II**.

20-Oxo-30-nortaraxastane is a universal synthon for the preparation of various biologically important oxygen- and nitrogen-containing triterpenoids. Taking into account disadvantages of the known methods for the preparation of 20-oxo derivatives of taraxasteryl acetate, we tried a different approach based on the oxidation of the exocyclic C^{20}=C^{30} double bond in compounds **I** and **II** with ozone.

The ozonolysis of taraxasteryl acetate (**I**) in chloroform in the presence of 4 equiv of methanol, followed by reduction of primary peroxide products with an equivalent amount of dimethyl sulfide, gave exclusively 3β-acetoxy-20,20-dimethoxy-30-nortaraxastane (**III**) in ~68% yield (Scheme 1). Compound **III** is likely to be formed through intermediate α-methoxy hydroperoxide **D** (Scheme 2) [9]. The structure of **III** is confirmed by the absence of downfield signals from double-bonded carbon atoms in its ^{13}C NMR spectrum [δ_C 154.71 (C^{20}) and 107.23 ppm (C^{30}) in the spectrum of **I**] and signals from protons on C^{30} in the ^1H NMR spectrum (δ 4.70 ppm in the spectrum of **I**). Instead, signals from two methoxy groups and C^{20} appeared in the ^{13}C NMR spectrum at δ_C 48.72 and 103.62 ppm, respectively; in the ^1H NMR spectrum of **III**, methoxy protons resonated as a singlet at δ 3.75 ppm.

When the ozonolysis of compound **I** with 1.5 equiv of O_3 was performed in chloroform in the absence of

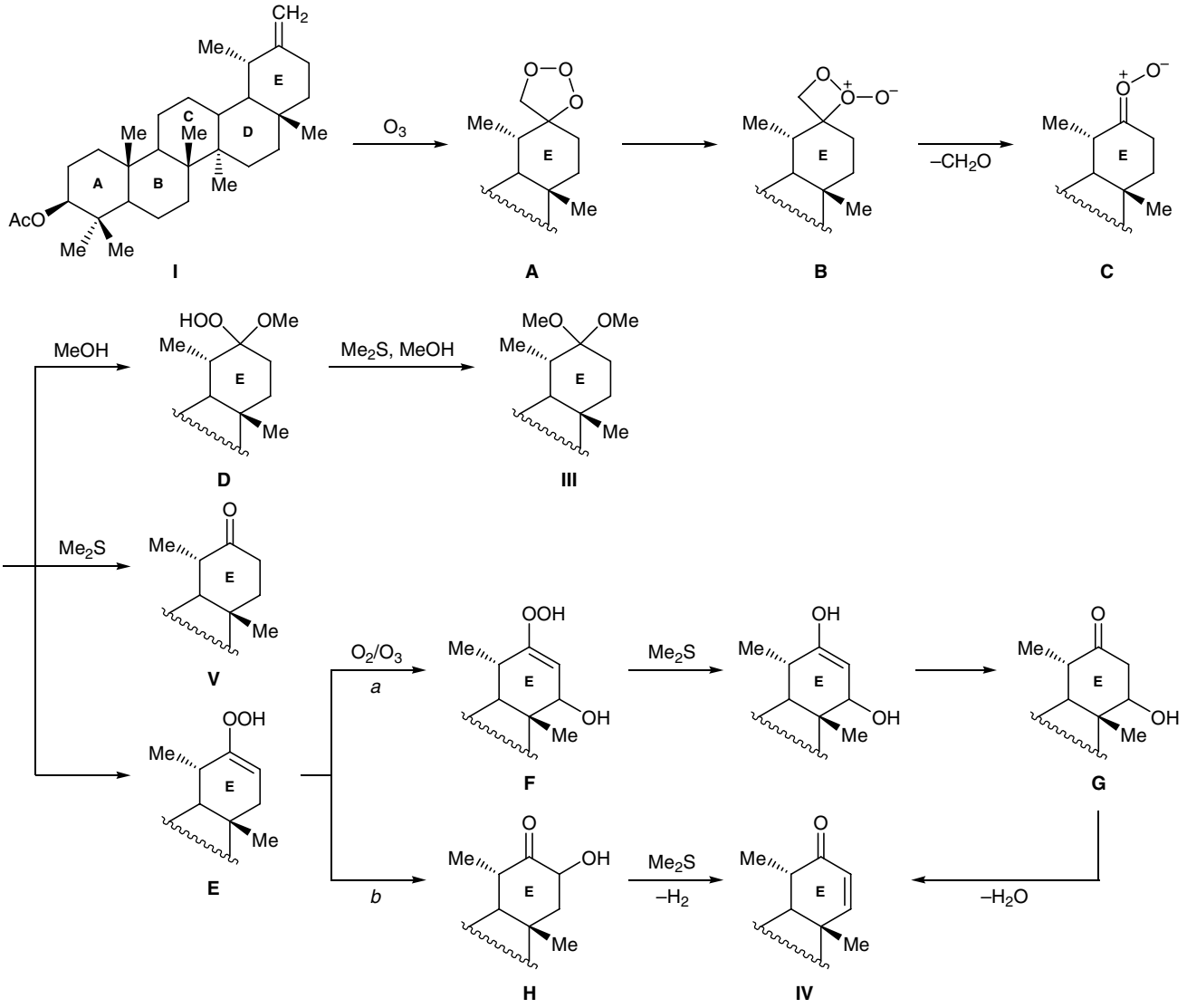
Scheme 1.



methanol, oxidative cleavage of the C^{20}=C^{30} double bond was accompanied by dehydrogenation of the C^{21}–C^{22} bond with formation of ~93% of 3β-acetoxy-20-oxo-30-nortaraxast-21-ene (**IV**). In the ^{1}H NMR spectrum of **IV**, the olefinic protons on C^{21} and C^{22} resonated at δ 5.61 and 6.75 ppm, and the ^{13}C NMR spectrum contained signals at δ_C 212.92 (C^{20}), 127.89 (C^{21}), and 166.56 ppm (C^{22}), indicating formation of α,β-unsaturated ketone. Compound **IV** showed in the UV spectrum an absorption maximum at λ 246 nm, which is typical of pentacyclic terpenoid α,β-unsaturated ketones [10]. Analogous data on dehydrogenation of steroids by the action of ozone have been reported [11, 12].

The target compound, 3β-acetoxy-20-oxo-30-nortaraxastane (**V**) was synthesized in two ways. Hydrolysis of **III** in 80% aqueous acetone in the presence of *p*-toluenesulfonic acid on heating under reflux and subsequent chromatographic separation on silica gel (eluent hexane–ethyl acetate, 15:1) afforded ketone **V**

Scheme 2.



in ~26% yield. Ketotriterpenoid **V** was also isolated in ~40% yield by chromatographic separation (silica gel, hexane–ethyl acetate, 15:1) of the product mixture obtained by ozonolysis of a chloroform extract of *Onopordum acanthium L.* floral receptacles, which is known to contain taraxasteryl acetate **I** together with other components. In the ^{13}C NMR spectrum of **V**, the C^{20}=O signal appeared at δ_C 218.45 ppm.

Under analogous conditions, ozonolysis of taraxasterol (**II**) was not selective. Presumably, cleavage of the exocyclic double bond is accompanied by oxidation of the 3β-hydroxy group in the **A** ring, leading to decomposition of the pentacyclic skeleton and formation of a complex mixture of products.

Thus the selectivity of ozonolysis of 3β-substituted taraxast-20(30)-enes depends on the nature of both substituent on C^3 and solvent. Presumably, different peroxide intermediates are formed as a result of cleavage of the exocyclic double bond in different solvents. The formation of α,β-unsaturated ketone **IV** by ozonolysis of taraxasteryl acetate (**I**) is likely to be determined by hindered access to the exocyclic π-bond in the **E** ring. In this case, the reaction mechanism includes initial formation of primary five-membered ozonide **A** which is transformed into four-membered cyclic Staudinger's molozonide **B** [13], and reduction of the latter with Me_2S yields conjugated ketone **IV** (Scheme 2). In the ^1H NMR spectrum of the ozonolysis product we observed a broadened signal at δ 4.34 ppm from protons on C^{30}, and the ^{13}C NMR spectrum of that intermediate contained two singlets corresponding to the C^{20} and C^{30} atoms linked to

oxygen (δ_C 82.57 and 78.28 ppm, respectively). The subsequent elimination of formaldehyde molecule yields carbonyl oxide **C** [14] which reacts with methanol to give α-methoxy hydroperoxide **D**, and reduction of the latter in the presence of methanol leads to exclusive formation of 20,20-dimethoxy-30-nortaraxasteryl acetate (**III**).

3β-Acetoxy-20-oxo-30-nortaraxast-21-ene (**IV**) can be formed via isomerization of dipolar ion **C** to unsaturated hydroperoxide **E**. Ozonolysis of steroids is characteristically accompanied by dehydration and hydride transfer processes [12, 15] leading to conjugated oxo systems; examples of oxidative dehydrogenation of 1,4-dihydroaromatic compounds were also reported [16]. Presumably, analogous transformations are also typical of triterpenoids, including taraxast-20(30)-ene.

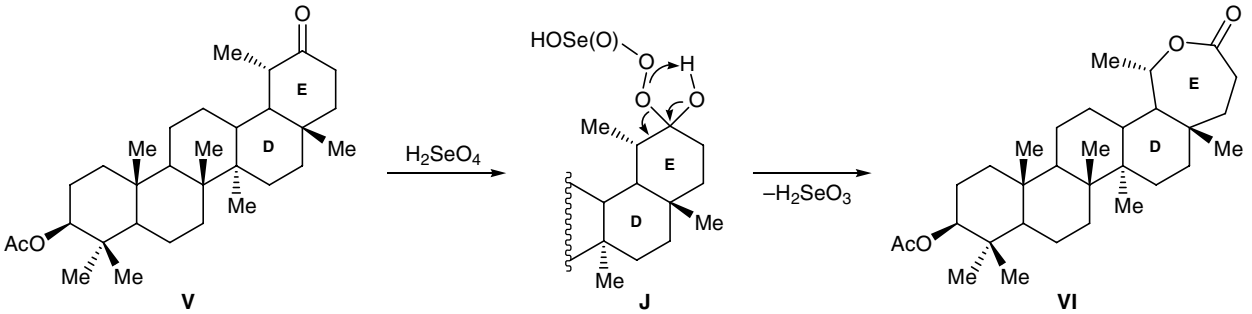
Taking into account the above stated, we believe that the ozonolysis of compound **I** can follow path *a* or *b* shown in Scheme 2. With a view to estimate which of these paths is preferential, we performed semiempirical quantum-chemical calculations (AM1, Gaussian 98) of the enthalpies of formation ΔH of intermediates **G** and **H**. Considering the difference in the conformational energies of regioisomers, $-\Delta H(\mathbf{G})$ was found to be less than $-\Delta H(\mathbf{H})$ by 6.4 kcal/mol [$\Delta H(\mathbf{G})$ = –130.63, $\Delta H(\mathbf{H})$ = –124.24 kcal/mol]. Thus the formation of enone **IV** from less stable intermediate **H** is more favorable from the viewpoint of energy; i.e., the two-step pathway (*b*) is more favorable than the four-step pathway (*a*) including oxidative dehydrogenation of enol form **E** at the allylic position to give unsaturated hydroxy hydroperoxide **F**. The ozonolysis of a chloroform extract of *Onopordum acanthium L.* floral receptacles is not accompanied by dehydrogenation of taraxasteryl acetate (**I**). Presumably, other components present in the extract affect the ozonolysis direction, so that carbonyl oxide **C** does not undergo isomerization, and its reduction with Me_2S gives ketone **V** (Scheme 2).

We also examined oxidation of ketone **V** according to Baeyer–Villiger with a view to obtain structures containing a lactone fragment. Lactones derived from triterpenoids are known as highly effective antitumor and antiinflammatory agents [17, 18]. The structure of lactone formed as a result of oxidation depends on the position and nature of substituents in the initial ketone [19]. Some oxidation processes involving pentacyclic triterpene ketones are accompanied by intramolecular rearrangements [20].

We found that the Baeyer–Villiger oxidation of compound **V** with the use of such reagents as SeO_2–H_2O_2 and *m*-$ClC_6H_4CO_3H$ gave 20-oxo-ε-lactone **VI** in ~65 and ~20% yield, respectively (Scheme 3). In the oxidation with *m*-chloroperoxybenzoic acid, the conversion of the initial ketone was fairly poor (20–25%). The product structure was confirmed by the presence in its ^{13}C NMR spectrum of an additional signal at δ_C 173.67 ppm due to lactone carbonyl carbon atom (ring **E**); the C^{19} signal appeared at 80.45 ppm due to effect of the neighboring oxygen atom. In the ^1H NMR spectrum of **VI**, the multiplet signal from 19-H was overlapped by the 3-H signal (δ 4.32–4.58 ppm, 2H). The oxidation of **V** to ε-lactone **VI** is stereoselective, and the C^{19} atom retains its *S* configuration [21, 22]. Presumably, this is the result of initial formation of adduct **J** with H_2SeO_4 (SeO_2–H_2O_2) and its subsequent rearrangement involving synchronous elimination of H_2SeO_3 and insertion of the electron-deficient oxygen atom into the C^{19}–C^{20} bond (Scheme 3).

Thus our study on the oxidation of taraxasteryl acetate (**I**) with ozone and subsequent reduction of the primary ozonolysis products with Me_2S led us to the development of selective procedures for the synthesis of 20,20-dimethoxy-, Δ^{21}-20-oxo-, and 20-oxo-30-nortaraxasteryl acetates. The oxidation of the latter with SeO_2–H_2O_2 according to Baeyer–Villiger gives the corresponding ε-lactone with high stereoselectivity and an overall yield of ~65%.

Scheme 3.



EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord 75IR spectrometer. The UV spectrum of **IV** was measured in chloroform on a Specord M-40 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX-300 instrument at 300.13 and 75 MHz, respectively, using $CDCl_3$ as solvent. The ^{13}C NMR spectra were analyzed using standard JMOD technique. The chemical shifts were measured relative to tetramethylsilane as internal reference. The melting points were determined on a Boetius melting point apparatus. The specific rotations were measured on a Perkin–Elmer 141 polarimeter. Column chromatography was performed on KSKG silica gel; Silufol plates (Czechia) were used for TLC analysis (hexane–ethyl acetate, 10:1; development by treatment with a solution of *p*-methoxybenzaldehyde in ethanol, followed by heating at 100–120°C for 2–3 min).

Taraxasteryl acetate (**I**) was isolated from a chloroform extract of *Onopordum acanthium L.* floral receptacles [23].

Peroxide ozonolysis product of taraxasteryl acetate (I). An ozone–oxygen mixture (ozonator efficiency 9.8 mmol of O_3 per hour) was passed through a solution of 0.28 g (0.59 mmol) of compound **I** in 5 ml of $CHCl_3$ under stirring at room temperature until 0.88 mmol of O_3 was absorbed. The mixture was evaporated on a rotary evaporator to obtain a peroxide ozonolysis product (test with a solution containing 2% of KI and 1% of starch). ^{1}H NMR spectrum, δ, ppm: 0.98 s (6H, 23-H, 24-H), 1.04 s (3H, 25-H), 0.928 s (3H, 26-H), 0.96 s (3H, 27-H), 0.93 s (3H, 28-H), 0.95 d (3H, 29-H), 1.11–1.86 m (20H, CH_2), 2.06 s (3H, $COCH_3$), 4.47 br.s (1H, 3-H), 4.34 s (2H, 30-H). ^{13}C NMR spectrum, δ_C, ppm: 93.04 s (C^3), 25.88 s ($CO\mathbf{C}H_3$), 172.24 s (C=O), 28.93 q and 26.08 q (C^{23}, C^{24}), 19.86 q and 20.62 q (C^{25}, C^{26}), 19.61 q (C^{27}), 22.41 q (C^{28}), 29.17 q (C^{29}), 82.57 s (C^{20}), 78.28 s (C^{30}).

20,20-Dimethoxy-3-nortaraxastan-3β-yl acetate (III). An ozone–oxygen mixture (ozonator efficiency 9.4 mmol of O_3 per hour) was passed at room temperature through a solution of 0.16 g (0.34 mmol) of compound **I** in 5 ml of $CHCl_3$ containing 0.03 ml (0.7 mmol) of methanol until 0.51 mmol of O_3 was absorbed. The resulting ozonide (test with a solution containing 2% of KI and 1% of starch) was reduced with 0.34 mmol of dimethyl sulfide at room temperature over a period of 24 h. The mixture was washed with water, dried over $CaCl_2$, and evaporated under reduced pressure. Yield 0.13 g (68%). Colorless crystalline substance, mp 210–212°C (from hexane), $[\alpha]_D^{20}$ = +97.5° (*c* = 1.06, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2910, 2830, 1235. ^{1}H NMR spectrum, δ, ppm: 0.99 s (6H, 23-H, 24-H), 1.03 s (3H, 25-H), 0.92 s (3H, 26-H), 0.95 s (3H, 27-H), 0.94 s (3H, 28-H), 0.98 d (3H, 29-H), 3.75 s (6H, OCH_3), 1.12–2.18 m (20H, CH_2), 2.04 s (3H, $COCH_3$), 4.49 br.s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 80.78 s (C^3), 21.22 s ($CO\mathbf{C}H_3$), 171.01 s (C=O), 27.82 q and 23.56 q (C^{23}, C^{24}), 15.59 q and 16.39 q (C^{25}, C^{26}), 15.48 q (C^{27}), 18.45 q (C^{28}), 27.82 q (C^{29}), 50.22 q (C^{30}, C^{31}), 101.62 s (C^{20}). Found, %: C 76.11; H 11.45. $C_{33}H_{56}O_4$. Calculated, %: C 76.69; H 10.92.

20-Oxo-30-nortaraxast-21-en-3β-yl acetate (IV). An ozone–oxygen mixture (ozonator efficiency 9.8 mmol of O_3 per hour) was passed through a solution of 0.28 g (0.59 mmol) of compound **I** in 5 ml of $CHCl_3$ under stirring at room temperature until 0.88 mmol of O_3 was absorbed. The resulting ozonide (test with a solution containing 2% of KI and 1% of starch) was reduced with 2.6 mmol of Me_2S at room temperature over a period of 24 h. The mixture was washed with water, dried over $CaCl_2$, and evaporated under reduced pressure. Yield 0.26 g (93%). Colorless crystalline substance, mp 218–220°C (from hexane), $[\alpha]_D^{20}$ = +77.5° (*c* = 1.09, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2915, 1725, 1720, 1450, 1370. UV spectrum: λ_{max} 246 nm. ^{1}H NMR spectrum, δ, ppm: 0.91 s (6H, 23-H, 24-H), 0.86 s (3H, 25-H), 1.03 s (3H, 26-H), 1.04 s (3H, 27-H), 0.96 s (3H, 28-H), 1.08 d (3H, 29-H), 0.92–1.91 m (16H, CH_2), 2.05 s (3H, $COCH_3$), 4.494 br.s (1H, 3-H), 5.61 d (2H, 21'-H, 21''-H), 6.75 d (2H, 22'-H, 22''-H). ^{13C} NMR spectrum, δ_C, ppm: 80.64 s (C^3), 21.17 s ($CO\mathbf{C}H_3$), 171.01 s (OC=O), 23.55 q and 21.63 q (C^{23}, C^{24}), 16.02 q, 16.20 q (C^{25}, C^{26}), 14.55 q (C^{27}), 19.32 q (C^{28}), 25.57 q (C^{29}), 212.92 s (C^{20}), 127.89 d (C^{21}), 166.56 d (C^{22}). Found, %: C 79.48; H 10.37. $C_{31}H_{48}O_3$. Calculated, %: C 79.44; H 10.32.

20-Oxo-30-nortaraxastan-3β-yl acetate (V). *a.* An ozone–oxygen mixture (ozonator efficiency 9.4 mmol of O_3 per hour) was passed at a flow rate of 30 l/h at room temperature through a solution of 6.8 g of a compound mixture isolated from a chloroform extract of *Onopordum acanthium L.* floral receptacles [containing ~1.7 g (4 mmol) of taraxasteryl acetate (**I**)] in 10 ml of $CHCl_3$ until 6 mmol of O_3 was absorbed. The progress of the reaction was monitored by TLC and iodine–starch test (with a solution containing 2% of KI and 1% of starch). The ozonolysis products were reduced with 40 mmol of dimethyl sulfide at room temperature over a period of 24 h, the mixture was dried over $CaCl_2$ and evaporated under reduced pres-

sure, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (15:1) as eluent. Yield 0.75 g (40%). Colorless crystalline substance, mp 250–251.5°C (from hexane), $[\alpha]_D^{22}$ = +29.3° (*c* = 1.7, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2910, 1720, 1715. ^1H NMR spectrum, δ, ppm: 0.92 s (6H, 23-H, 24-H), 0.87 s (3H, 25-H), 0.98 s (3H, 26-H), 0.96 s (3H, 27-H), 0.94 s (3H, 28-H), 1.03 d (3H, 29-H), 0.91–2.08 m (20H, CH_2), 2.03 s (3H, $COCH_3$), 4.48 br.s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 80.75 s (C^3), 21.86 s ($CO\mathbf{C}H_3$), 170.88 s (OC=O), 27.83 q and 16.40 q (C^{23}, C^{24}), 15.75 q and 16.20 q (C^{25}, C^{26}), 14.49 q (C^{27}), 18.05 q (C^{28}), 25.58 q (C^{29}), 218.56 s (C^{20}). Found, %: C 79.38; H 11.07. $C_{31}H_{50}O_3$. Calculated, %: C 79.10; H 10.71.

b. A solution of 0.13 g (0.27 mmol) of compound **III** and 0.074 g of *p*-toluenesulfonic acid in 3 ml of 80% aqueous acetone was heated for 48 h under reflux until the initial compound disappeared (TLC, hexane–ethyl acetate, 5:1). The mixture was evaporated under reduced pressure, the residue was extracted with chloroform (3×5 ml), and the extracts were washed with solutions of Na_2CO_3 and NaCl, dried over $MgSO_4$, and evaporated under reduced pressure. Yield 0.03 g (26.6%). Colorless crystalline substance. The product was identical to a sample of **V** prepared as described above in *a*.

21-Oxo-20-oxa-30-nor-22a-homotaraxastan-3-β-yl acetate (VI). *a*. Compound **V**, 0.1 g (0.21 mmol), was dissolved in 9 ml of *tert*-butyl alcohol, 0.028 g (0.25 mmol) of SeO_2 and 0.2 ml (22%) of H_2O_2 were added, and the mixture was stirred for 48 h at 90°C until the initial compound disappeared (TLC, hexane–ethyl acetate, 5:1). The mixture was concentrated under reduced pressure, the residue was dissolved in water, and the products were extracted into $CHCl_3$ (3×15 ml). The extract was dried over $CaCl_2$ and evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (1:1) as eluent. Yield 0.07 g (65.5%), colorless crystalline substance, mp 259–261°C (from hexane), $[\alpha]_D^{22}$ = +58.4° (*c* = 1.4, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2910, 1720, 1715. ^1H NMR spectrum, δ, ppm: 0.89 s (6H, 23-H, 24-H), 0.93 s (3H, 25-H), 0.97 s (3H, 26-H), 0.98 s (3H, 27-H), 0.95 s (3H, 28-H), 1.07 d (3H, 29-H), 0.94–1.96 m (18H, CH_2), 2.04 s (3H, $COCH_3$), 4.54 br.s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 80.86 d.d (C^3), 21.24 s ($CO\mathbf{C}H_3$), 171.01 s (OC=O), 27.89 q and 16.45 q (C^{23}, C^{24}), 15.84 q and 16.52 q (C^{25}, C^{26}), 14.06 q (C^{27}), 23.62 q (C^{28}), 25.64 q (C^{29}), 218.76 s (C^{20}). Found, %: C 76.23; H 10.56. $C_{32}H_{52}O_3$. Calculated, %: C 76.50; H 10.35.

b. Compound **V**, 0.1 g (0.21 mmol), was dissolved in 10 ml of chloroform, 0.109 g (0.63 mmol) of *m*-chloroperoxybenzoic acid was added, and the mixture was stirred for 7 days at 60°C until the initial compound disappeared (TLC, hexane–ethyl acetate, 5:1). The mixture was diluted with chloroform, washed with a 1 N solution of sodium hydroxide (3×20 ml) and water, dried over Na_2SO_4, and concentrated under reduced pressure. Yield 0.019 g (17.8%), mp 259–261°C (from hexane). The product was identical to a sample prepared as described above in *a*.

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