

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

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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 $\text{SeO}_2\text{--H}_2\text{O}_2$ gave 3 β -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-3 β -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-3 β -ol] on model skin cancer in mice were reported [5]; taraxasterol (**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

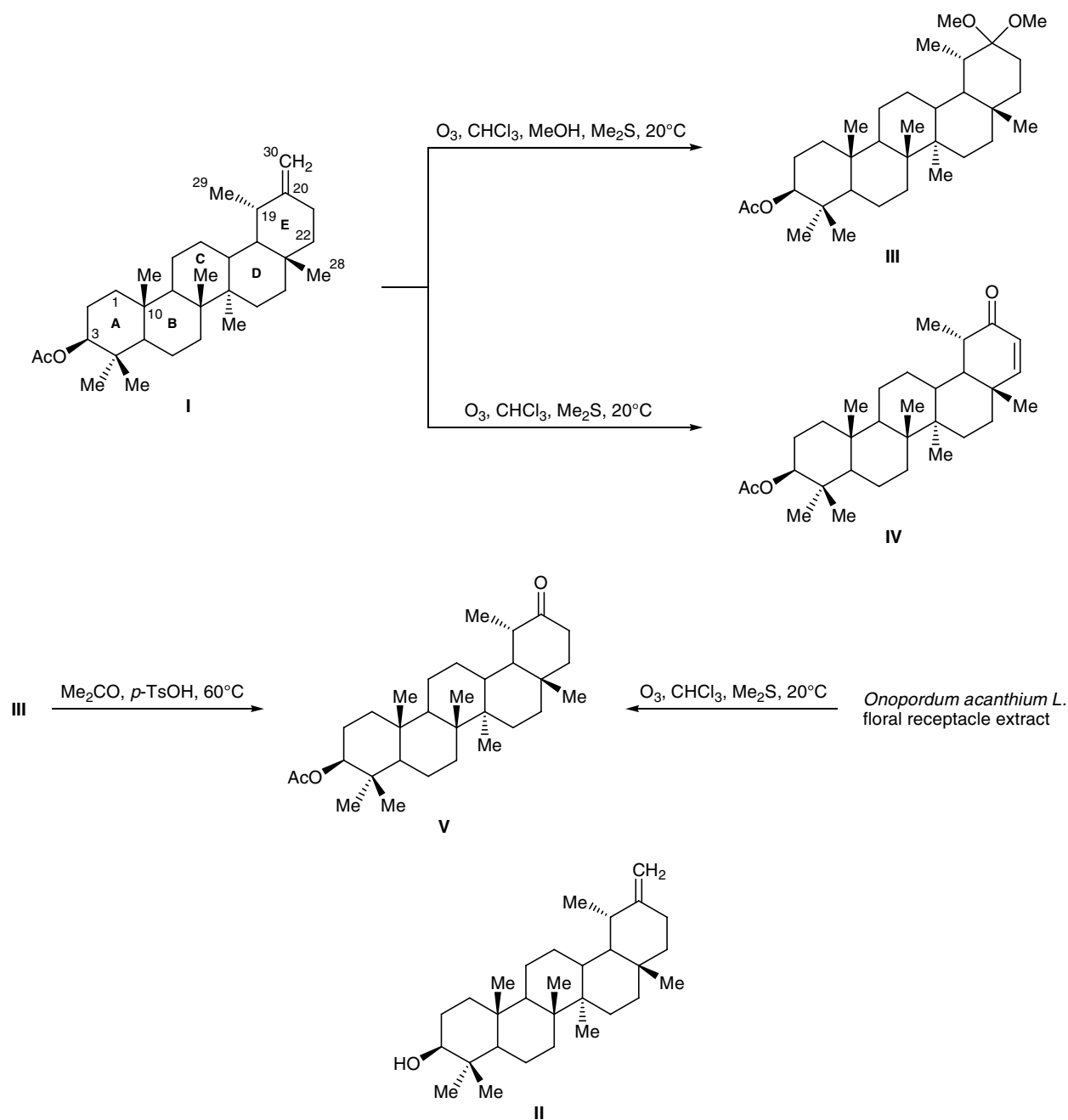
found no published data on ozonolysis of the $\text{C}^{20}=\text{C}^{30}$ double bond in compound **I** or **II**.

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 $\text{C}^{20}=\text{C}^{30}$ 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 3 β -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.

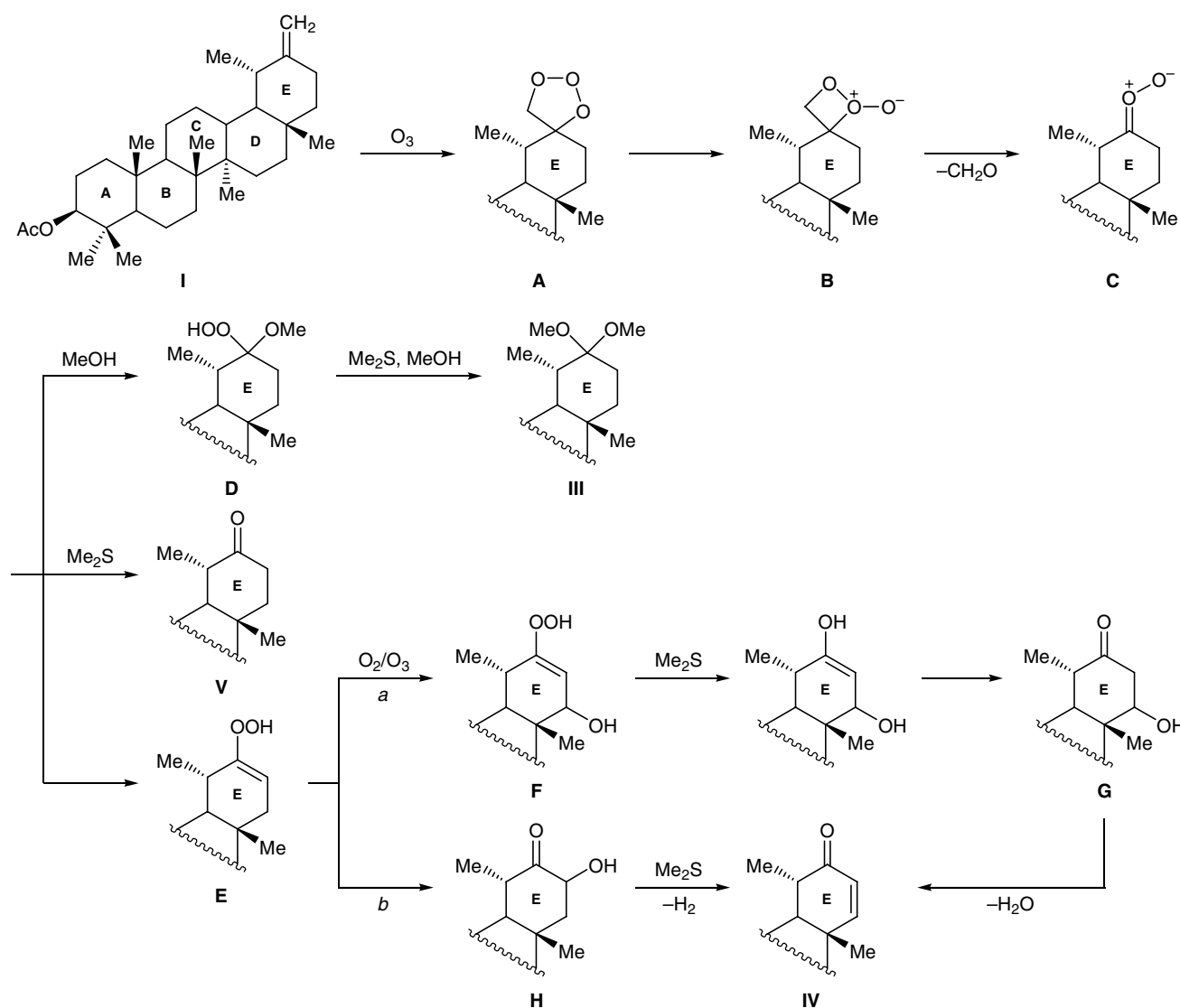


methanol, oxidative cleavage of the C²⁰=C³⁰ double bond was accompanied by dehydrogenation of the C²¹-C²² bond with formation of ~93% of 3β-acetoxy-20-oxo-30-nortaraxast-21-ene (IV). In the ¹H NMR spectrum of IV, the olefinic protons on C²¹ and C²² resonated at δ 5.61 and 6.75 ppm, and the ¹³C NMR spectrum contained signals at δ_C 212.92 (C²⁰), 127.89 (C²¹), and 166.56 ppm (C²²), 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 $\text{C}^{20}=\text{O}$ 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 moolozonide **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**).

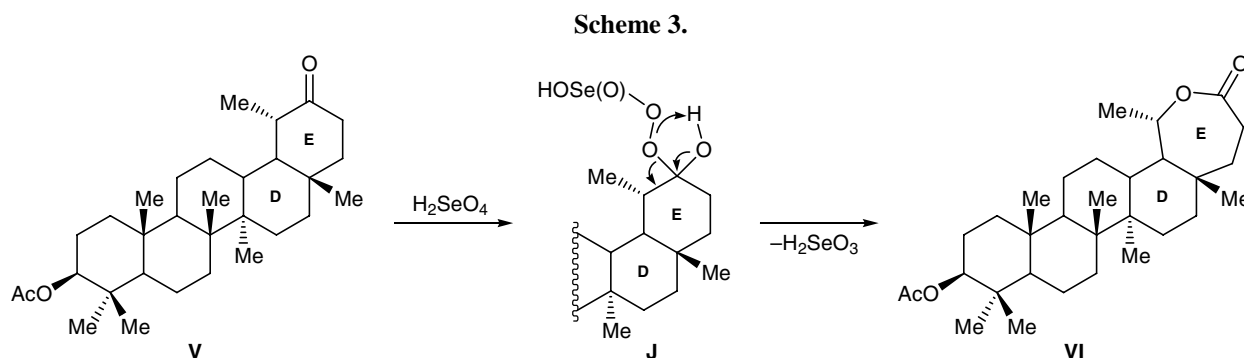
3β -Acetoxy-20-oxo-30-nortaraxast-21-ene (**IV**) can be formed via isomerization of dipolar ion **C** to unsaturated hydroperoxide **E**. Ozonolysis of steroids is characteristically accompanied by dehydration and hydride transfer processes [12, 15] leading to conjugated oxo systems; examples of oxidative 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 $\text{SeO}_2\text{--H}_2\text{O}_2$ and *m*- $\text{ClC}_6\text{H}_4\text{CO}_3\text{H}$ 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 ($\text{SeO}_2\text{--H}_2\text{O}_2$) and its subsequent rearrangement involving synchronous elimination of H_2SeO_3 and insertion of the electron-deficient oxygen atom into the $\text{C}^{19}\text{--C}^{20}$ 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 $\text{SeO}_2\text{--H}_2\text{O}_2$ according to Baeyer–Villiger gives the corresponding ϵ -lactone with high stereoselectivity and an overall yield of ~65%.



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 ^1H 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). ^1H 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 (COCH_3), 172.24 s ($\text{C}=\text{O}$), 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-3 β -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), $[\alpha]_{\text{D}}^{20} = +97.5^\circ$ ($c = 1.06$, CHCl_3). IR spectrum, ν , cm^{-1} : 2910, 2830, 1235. ^1H 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 (COCH_3), 171.01 s ($\text{C}=\text{O}$), 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. $\text{C}_{33}\text{H}_{56}\text{O}_4$. Calculated, %: C 76.69; H 10.92.

20-Oxo-30-nortaraxast-21-en-3 β -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), $[\alpha]_{\text{D}}^{20} = +77.5^\circ$ ($c = 1.09$, CHCl_3). IR spectrum, ν , cm^{-1} : 2915, 1725, 1720, 1450, 1370. UV spectrum: λ_{max} 246 nm. ^1H 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). ^{13}C NMR spectrum, δ_{C} , ppm: 80.64 s (C^3), 21.17 s (COCH_3), 171.01 s ($\text{OC}=\text{O}$), 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. $\text{C}_{31}\text{H}_{48}\text{O}_3$. Calculated, %: C 79.44; H 10.32.

20-Oxo-30-nortaraxastan-3 β -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), $[\alpha]_D^{22} = +29.3^\circ$ ($c = 1.7$, 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 (COCH_3), 170.88 s ($\text{OC}=\text{O}$), 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. $\text{C}_{31}\text{H}_{50}\text{O}_3$. 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), $[\alpha]_D^{22} = +58.4^\circ$ ($c = 1.4$, 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 (COCH_3), 171.01 s ($\text{OC}=\text{O}$), 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. $\text{C}_{32}\text{H}_{52}\text{O}_3$. 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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