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Short Note

Synthesis and Cytotoxic Potential of 3-oxo-19β-Trifluoroacetoxy-18α*H*-oleane-28-oic Acid

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Abstract: Trifluoroacetic acid-promoted Wagner-Meerwein rearrangement of betulonic acid carboxamide led to the formation of the expected 19β,28-lactam along with a new germanicane-type 3-oxo-19β-trifluoroacetoxy-18α*H*-oleane-28-oic acid. The structure of this triterpenoid was confirmed by 2D NMR analyses. A primary evaluation of biological potency revealed an anticancer activity with GI_{50} < 5 μM against leukemia, colon cancer, breast cancer, and prostate cancer cell lines, while the parent compounds were not active.

Keywords: triterpenoids; lupane; betulin; oleanane; allobetulin; germanicane; Wagner–Meerwein rearrangement; cytotoxic activity; NCI-60

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1. Introduction

Natural pentacyclic triterpenoids and their synthetic transformation products exhibit a broad spectrum of biological activity [1,2]. Allobetulin (3β-Hydroxy-19β,28-epoxy-18α-oleane) and its derivatives belong to the group of triterpenoids of the germanicane family, a very rare class of natural compounds [3]. Allobetulin and related compounds (e.g., 28-oxoallobetulone and 3β-acetoxy-18α-oleane-19β,28-lactam) can be synthesized from widely occurring natural lupane triterpenoids (e.g., betulin) by Wagner–Meerwein rearrangement in the presence of acids [4]. Allobetulone derivatives demonstrated anticancer [5,6], antidiabetic [7], and antiviral activity [8].

Cleavage of the tetrahydrofuran ring in allobetulin by nucleophilic and acidic reagent lead to oleane, germanicane (3β,19β,28-trihydroxyoleane), and ursane-type triterpenoids with biological potency. Thus, the reaction of acetoxyallobetulin with perchloric acid in acetic anhydride was proposed as an efficient method for the chemical preparation of pharmacologically important moronic and heterobetulonic acids [9]. Recently, it has been shown that 20β,28-epoxy-18α,19 β H-ursane derivatives, obtained from allobetulin and modified at A,E cycles, possess antiviral activity against HCMV, as well as anticancer and α-glucosidase inhibitory effects [10]. α,β-Unsaturated ketones of 18αH,19βH-ursane and C20 pyrazoline derivatives were also reported [11].

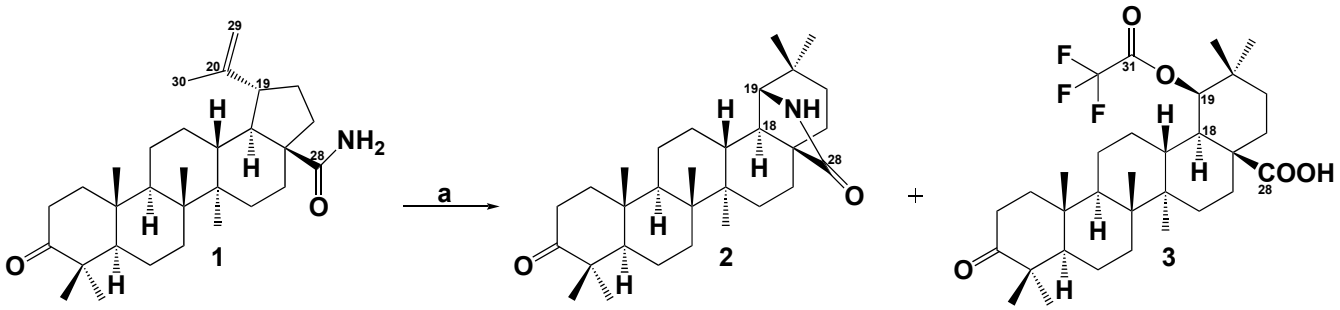
On the other hand, treatment of betulonic acid carboxamide with trifluoroacetic acid (TFA) led to E-ring lactam and its dimethylsuccinoyl ester demonstrated antiretroviral activity [12]. Interested by this type of rearrangement, we report herein our investigations, as well as the discovery of another product in this reaction.

2. Results and Discussion

In the presence of Lewis or mineral acids, the rearrangement of betulin ring E takes place, leading to allobetulin, as described for the first time by Schulze and Pieroh in 1922 and which is now known as Wagner-Meerwein rearrangement [13]. Various acidic conditions have been investigated for this rearrangement, such as hydrobromic acid in chloroform, sulfuric acid in acetic acid, concentrated hydrochloric acid in ethanol, different "solid acids", etc., and up to 2010 they are summarized in a review [3]. In a recent article,

Wagner-Meerwein rearrangement was also conducted using HCl, montmorillonite K10, and $BF_3 \cdot Et_2O$ to the synthesis of cyclopentyl units by contraction of the A-ring [14]. In this work, we tried to obtain the E-ring lactam derivative based on betulonic acid carboxamide **1** under similar rearrangement.

Reaction of betulonic acid carboxamide **1** with TFA in refluxing chloroform led to a mixture of 3-oxo-18α-oleane-19β,28-lactam **2** and a new compound **3** with yields of 65% and 32% (Scheme 1), respectively. The change of amount of TFA, temperature, or reaction time did not have any influence on the ratio of compounds **2** and **3**. The structure of compound **2** was similar to those described in [12]; the structure of compound **3** was confirmed by HSQC and HMBC spectra (Figure 1), (for NMR spectra of **3**, please see Supplementary Materials). In the ^{1}H NMR spectrum, the signal of H-19 connected with the trifluoroacetate group was observed at δ_H 4.50 ppm. In the ^{13}C NMR spectrum, the signal of C19 at δ_C 96.11 ppm and two quartet signals splited by the three ^{19}F atoms: the signal of atom C31 (δ_C 161.47 ppm, $^2J_{31\text{-}F}$ = 37.6 Hz) and signal of quaternary atom C32 (δ_C 116.25 ppm, $^1J_{32\text{-}F}$ = 290.5 Hz), were characteristic. In the ^{19}F NMR spectrum, the signal of the trifluoroacetate group is characteristic (δ_F −75.73 ppm). Based on analysis of {^{1}H, ^{1}H} NOESY spectrum, the cross peaks between H_3-30 (δ_H 0.98 ppm)/H-19 (δ_H 4.50 ppm), H_3-30 (δ_H 0.98 ppm)/H-18 (δ_H 1.94 ppm), and H-18 (δ_H 1.94 ppm)/H_3-27 (δ_H 0.91 ppm) suggests that the H-18 proton is in the α-orientation.



Scheme 1. Synthesis of compounds **2** and **3** by the reaction of betulonic amide with trifluoroacetic acid. Reagent and condition: a. TFA, $CHCl_3$, Δ, 1 h.

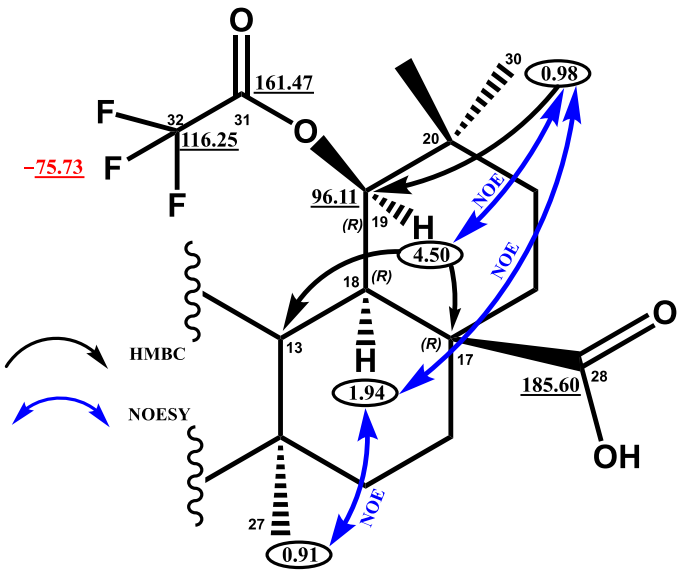


Figure 1. HMBC and NOESY correlations of compound **3**.

Therefore, according to NMR data, compound **3** is 3-oxo-19β-trifluoroacetoxy-oleane-28-oic acid. The formation of compound **2** could be explained by a Wagner-Meerwein

rearrangement of amide **1** under acidic conditions. The formation of compound **3** could be explained by the further rearrangement, including ring opening of the lactam cycle under trifluoroacetic acid condition with the following hydrolysis of amide intermediate A to 19-trifluoroacetoxy-olean-28-oic acid (Figure 2).

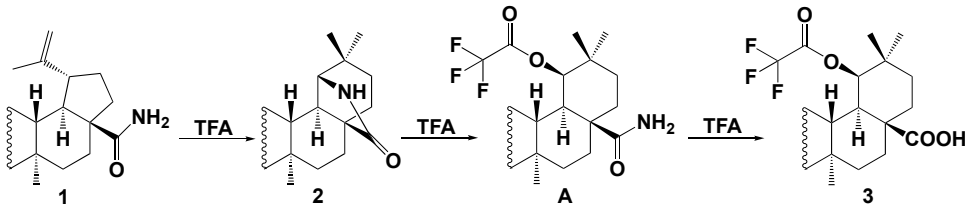


Figure 2. Plausible way of rearrangement of compound **1** to compounds **2** and **3**.

It is known that lupane-type triterpenoids betulin and betulinic acid possess a broad range of biological effects, particularly anticancer activities [15]. Betulinic acid induces the internal apoptosis pathway in cancer cells while sparing normal cells, and now is under clinical evaluation in Phase I/II clinical trials (NCT00346502) as 20% betulinic acid ointment (BA ointment) for treatment of dysplastic nevi that have potential to transform into melanoma [16,17]. Its oxidized product betulonic acid, having a carbonyl moiety at C-3 position, and which was used as a starting material for the synthesis of compound **1** in this work, possesses a better anticancer profile than betulinic acid [18]. Moreover, small structural changes of lupane type derivatives, including betulonic acid, lead to significant differences in their anticancer properties [19].

Compounds **1**–**3** were selected by the National Cancer Institute (NCI) Developmental Therapeutics Program (www.dtp.nci.nih.gov, accessed on 1 November 2018) for in vitro cell line screening to investigate their anticancer activity. As betulonic acid is a well-known compound, it was not selected by NCI. Anticancer assays were performed according to the US NCI protocol, which was described elsewhere [20,21]. The first step, during which compounds were tested at 10 μM, revealed that compounds showed cytotoxicity against cancer cells. The results of NCI screening for carboxamide of betulonic acid **1** (first assay) were presented recently [22] and revealed no cytotoxicity. The highest activity of compound **2** was against non-small cell lung cancer cell lines (HOP-92), with over 32% of cell growth, while compound **3** demonstrated cytotoxicity with lethality against leukemia cell lines (HL-60(TB)) (Table 1). Compound **3** being promising, it was further investigated in a five-dose testing mode and exhibited moderate activity with GI_{50} ranges from 3.16 to 26.40 μM against all cell lines of NCI-60 (Table 2) (please see Supplementary Materials). The highest anticancer activity (i.e., less than 5 μM) was observed against leukemia cell lines with GI_{50} values of 3.16 μM (HL-60(TB)), 3.75 μM (SR), and 3.61 μM (K-562); colon cancer cell lines with GI_{50} values of 4.80 μM (HCT-116), 4.99 μM (HCT-15), and 4.06 (HT29); breast cancer cell lines with GI_{50} values of 5.02 μM (MCF7); and against prostate cancer cell lines with GI_{50} values of 3.98 μM (PC-3).

The compounds **2** and **3** also were evaluated at the University of Queensland (Australia) using five bacterial strains, including Gram-negative *Escherichia coli, Klebsiella pneumonia*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa;* and Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA). The antifungal activity was determined against *Candida albicans* and *Cryptococcus neoformans.* The primary screening of the antimicrobial activity of compounds **2** and **3** was carried out in a single concentration of 32 mg/mL in tests of the inhibition of cell reproduction. Samples with inhibition value above 80% were classed as active. Samples with inhibition values between 50 and 80% were classed as partial actives. The techniques for testing the antimicrobial and antifungal activities of compounds are given in the website http://www.co-add.org [23], accessed on 1 November 2018. It was found that none of the tested compounds inhibited growth of the pathogenic microorganisms in the studied concentration (Table 3).

Table 1. In vitro anticancer activity in 60 human tumor cell lines for compounds **2** and **3** at 10 μM.

Compound	60 Cell Lines Assay in 1-Dose at 10 μM		
	Mean Growth, %	**Range of Growth, %**	**Most Sensitive Cell Line**
2	77.29	10.97 to 119.95	HOP-92 (Non-Small Cell Lung Cancer)
3	−62.67	−99.13 to 1.66	HL-60(TB) (Leukemia)

Table 2. In vitro anticancer activity of compound **3** against 60 human cancer cell lines in the second stage in a single concentration of 0.01–100 μM *.

Subpanel/Cell Lines (μM)	GI_{50}	Subpanel/Cell Lines (μM)	GI_{50}
Leukemia		Melanoma	
CCRF-CEM	9.51	LOX IMVI	5.91
HL-60(TB)	3.16	MALME-3M	12.90
K-562	3.61	M14	8.34
MOLT-4	4.22	MDA-B-435	10.60
RPMI-8226	4.82	SK-MEL-2	14.10
SR	3.75	SK-MEL-28	13.60
Non-Small Cell Lung Cancer		SK-MEL-5	8.11
A549/ATCC	9.66	UACC-257	10.10
EKVX	14.50	UACC-62	6.67
HOP-62	13.20	Ovarian Cancer	
HOP-92	8.08	IGROV1	18.90
NCI-H226	13.50	OVCAR-3	12.40
NCI-H23	11.00	OVCAR-4	13.10
NCI-H322M	17.80	OVCAR-5	15.70
NCI-H460	7.65	OVCAR-8	12.90
NCI-H522	12.60	NCI/ADR-RES	12.30
Colon cancer		SK-OV-3	13.40
COLO 205	6.68	Renal Cancer	
HCC-2998	10.70	786-0	14.30
HCT-116	4.80	A498	15.70
HCT-15	4.99	ACHN	13.30
HT29	4.06	CAKI-1	12.80
KM-12	10.40	RXF 393	11.10
SW-620	11.60	SN12C	11.50
CNS Cancer		TK-10	16.90
SF-268	15.30	UO-31	13.70
SF-295	14.60	Breast Cancer	
SF-539	5.34	MCF7	5.02
SNB-19	13.80	MDA-MB-231/ATCC	13.50
SNB-75	26.40	HS 578T	20.30
U251	12.40	BT-549	9.30
Prostate Cancer		T -47D	3.84
PC-3	3.98	MDA-MB-468	5.83
DU-145	14.10		

* For full data, see Supporting Information.

Table 3. % Growth inhibition of compound **2** and **3** at 32 μg/mL.

Compound	Gram–Positive Bacteria	Gram–Negative Bacteria				Fungi	
	Staphylococcus Aureus	*Escherichia coli*	*Klebsiella pneumonia*	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Candida albicans*	*Cryptococcus neoformans* var. *grubii*
	Strain ATCC43300	**Strain ATCC 25922**	**Strain ATCC 700603**	**Strain 19606**	**Strain ATCC 27853**	**Strain ATCC 90028**	**Strain H99, ATCC 208821**
2	10.58	−6.72	10.6	4.47	16.9	10.93	−8.97
3	−4.52	−6.07	−2.26	10.26	25.36	6.12	−13.08

3. Materials and Methods

The spectra were recorded at the Center for the Collective Use "Chemistry" of the UIC UFRC RAS and RCCU "Agidel" of the UFRC RAS. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer (Bruker, Billerica, MA, USA, 500, 125.5 and 470 MHz) with a Z-axis gradient unit, operated with a 5-mm broad-band multinuclear (PABBO) probe in CDCl3, using tetramethylsilane as the internal standard. A complete and unambiguous assignment of ^{1}H and ^{13}C nuclear magnetic resonance (NMR) signals is reported on the basis of two-dimensional NMR techniques (^{1}H-^{1}H COSY, ^{1}H–^{1}H NOESY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC). Melting points were detected on a micro table "Rapido PHMK05" (Nagema, Dresden, Germany). Optical rotations were measured on a polarimeter "Perkin-Elmer 241 MC" (PerkinElmer, Waltham, MA, USA) in a tube length of 1 dm. Elemental analysis was performed on a Euro EA-3000 CHNS analyzer (Euro vector, Milan, Italy); the main standard is acetanilide. Thin-layer chromatography analyses were performed on Sorbic plates (Copolymer, Krasnodar, Russian Federation), using the solvent system chloroform-ethyl acetate, 40:1. Substances were detected by a 10% solution of a sulfuric acid solution with subsequent heating at 100–120 °C for 2–3 min. Compound **1** was obtained according to the method described previously [5].

Synthesis of Compounds **2** *and* **3**

A mixture of compound **1** (0.45 g, 1 mmol) and trifluoroacetic acid (1 mL, 13.5 mmol) in $CHCl_3$ (25 mL) was stirred under reflux for 2 h. The reaction was washed with saturated $NaHCO_3$ (2 × 50 mL) and H_2O (100 mL). The organic phase was dried over $CaCl_2$ and evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 eluting with petroleum ether-chloroform (from 60:40 to 1:100) giving compounds **2** and **3**.

3-Oxo-18α-oleane-19β,28-lactam **2.** Yield 65% (295 mg) as brown powder. $[\alpha]_D^{20}$ +24 (c 0.1, CH_2Cl_2), m.p. 178–179 °C. ^{1}H-NMR (δ, ppm, $CDCl_3$, 500 MHz): 3.69 (1H, s, CONH), 2.49−1.01 (25H, m, CH and CH_2), 1.05, 1.02, 0.99, 0.98, 0.91, 0.89, 0.86 (21H, al s, 7CH_3). ^{13}C-NMR (δ, ppm, $CDCl_3$, 125.5 MHz): 218.1 (C3), 176.3 (C28), 86.2 (C19), 54.9, 50.5, 47.3, 47.0, 45.5, 40.5, 40.2, 39.8, 37.0, 35.7, 34.1, 34.1, 33.9, 33.0, 32.4, 28.8, 27.3, 26.7, 26.5, 26.4, 24.2, 21.4, 21.0, 19.5, 16.4, 15.4, 13.6. Anal. Calcd for $C_{30}H_{47}NO_2$: C, 79.42; H, 10.44; N, 3.09. Found: C, 79.41; H, 10.42; N, 3.04. MS (APCI): m/z $[M + H]^+$ 454.71.

3-Oxo-19β-trifluoroacetoxy-18α-oleane-28-oic acid **3.** Yield 32% (182 mg) as beige powder. $[\alpha]_D^{20}$ +13 (c 0.1, CH_2Cl_2), m.p. 145–146 °C. ^{1}H-NMR (δ, ppm, $CDCl_3$, 500 MHz): 4.50 (s, 1H, H-19), 2.51 (ddd, 1H, ^{2}J = 15.6, $^{3}J_{2ax\text{-}1ax}$ = 9.4, $^{3}J_{2ax\text{-}1eq}$ = 7.6, Hax-2), 2.44 (ddd, 1H, ^{2}J = 15.6, $^{3}J_{2eq\text{-}1ax}$ = 7.8, $^{3}J_{1eq\text{-}2eq}$ = 4.6, Heq-2), 2.38 (dt, 1H, ^{2}J =15.3, $^{3}J_{16eq\text{-}15ax}$ = 3.1, $^{3}J_{16eq\text{-}15eq}$ = 3.1, Heq-16), 1.94 (d, 1H, $^{3}J_{18\text{-}13}$ = 11.4, H-18), 1.94 (ddd, 1H, ^{2}J = 13.1, $^{3}J_{1eq\text{-}2ax}$ = 7.6, $^{3}J_{1eq\text{-}2eq}$ = 4.6, Heq-1), 1.79 (ddd, 1H, ^{2}J = 13.3, $^{3}J_{22eq\text{-}21ax}$ = 7.1, $^{3}J_{22eq\text{-}21eq}$ = 1.5, Heq-22), 1.74 (dt, ^{2}J = 13.3, $^{3}J_{22ax\text{-}21ax}$ = 13.3, $^{3}J_{22ax\text{-}21eq}$ = 5.6, Hax-22), 1.63 (m, 1H, Heq-12), 1.62 (m, 1H, Hax-16), 1.57 (ddt, 1H, ^{2}J = 12.3, $^{3}J_{11eq\text{-}12ax}$ = 4.3, $^{3}J_{11eq\text{-}12eq}$ = 2.3, $^{3}J_{11eq\text{-}9}$ = 2.3, Heq-11), 1.54 (ddd, 1H, ^{2}J = 13.3, $^{3}J_{21eq\text{-}22ax}$ = 5.6, $^{3}J_{21eq\text{-}22eq}$ = 1.5, Heq-21), 1.48 (m, 1H, Heq-7), 1.48 (m, 1H, Heq-6), 1.48 (m, 1H, Hax-6), 1.43 (m, 1H, Hax-1), 1.43 (m, 1H, H-9), 1.40 (m, 1H, Hax-21), 1.35 (m, 1H, Hax-7); 1.34 (m, 1H, Heq-15), 1.34 (m, 1H, Hax-15),

1.34 (m, 1H, H-5), 1.32 (m, 1H, H-13), 1.31 (m, 1H, Hax-11), 1.08 (s, 3H, H_3-24), 1.06 (s, 3H, H_3-29), 1.03 (s, 3H, H_3-23), 1.03 (qd, 1H, ^2J = 12.6, $^3J_{12ax\text{-}13}$ = 12.6, $^3J_{12ax\text{-}11ax}$ = 12.6, $^3J_{11ax\text{-}12eq}$ = 4.3, Hax-12), 0.98 (s, 3H, H_3-30), 0.94 (s, 3H, H_3-26), 0.94 (s, 3H, H_3-25), 0.91 (s, 3H, H_3-27). ^{13}C-NMR (δ, ppm, $CDCl_3$, 125.5 MHz): 217.95 (C3), 185.60 (C28), 161.47 (q, $^2J_{31\text{-}F}$ = 37.6, C31), 116.25 (q, $^1J_{32\text{-}F}$ = 290.5, C32), 96.11 (C19), 54.09 (C5), 50.56 (C17), 50.36 (C9), 47.44 (C18), 47.31 (C4), 40.46 (C8), 39.93 (C14), 39.78 (C1), 36.94 (C10), 35.95 (C13), 33.98 (C2), 33.32 (C20), 32.84 (C7), 32.48 (C22), 31.58 (C21), 28.18 (C29), 27.40 (C15), 26.67 (C24), 26.23 (C12), 24.08 (C16), 24.06 (C30), 21.16 (C11), 20.95 (C23), 19.42 (C6), 16.33 (C25), 15.20 (C26), 13.65 (C27). Spectrum ^{19}F (δ, ppm, $CDCl_3$, 470 MHz): −75.73 (s, 3F). Anal. Calcd for $C_{32}H_{47}F_3O_5$: C, 67.58; H, 8.33. Found: C, 67.56; H, 8.31. MS (APCI): m/z $[M + H]^+$ 569.34.

4. Conclusions

We have found that betulonic acid carboxamide under treatment with TFA in $CHCl_3$ undergoes a rearrangement to 3-oxo-18α-oleane-19β,28-lactam and 3-oxo-19β-trifluoroacetoxy-18α-oleane-28-oic acid. The evaluation of biological potency revealed a anticancer activity with $GI_{50} < 5$ μM against leukemia, colon cancer, breast cancer, and prostate cancer cell lines.

Supplementary Materials: NMR spectra and NCI data for compounds **2** and **3** are available online.

Author Contributions: E.F.K. conducted synthetic experiments and prepared the manuscript; A.I.P. performed the structural studies; O.B.K. brought the idea, managed the research, conducted synthetic experiments and prepared the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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