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Lanostane- and cycloartane-type triterpenoids from *Abies balsamea* oleoresin

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Full Research Paper

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Abstract

Phytochemical analysis of *A. balsamea* oleoresin led to the isolation of three new 3,4-*seco*-lanostane triterpenoids **1**–**3**, one new cycloartane triterpenoid **4** along with fourteen known terpenoids. Structure determinations were based on extensive 1D/2D NMR, IR and MS spectroscopic analyses, and comparison with literature data. The isolated compounds were evaluated in vitro for their cytotoxicity against human cell lines (A549, DLD-1, WS1) and their antibacterial activity against *E. coli* and *S. aureus*. Abiesonic acid (**6**) exhibited weak cytotoxic activity against A549 (IC_{50} = 22 μM) while compounds **1** and **4** were weakly active against *S. aureus* (MIC = 25 μM).

Introduction

The genus *Abies* (Pinaceae) comprises 46 species of evergreen conifers [1]. Most of them are found in temperate and boreal regions of the northern hemisphere. The first phytochemical investigation of *Abies* species was undertaken 75 years ago by Takahashi [2]. Since then, more than 277 secondary metabolites have been isolated, and mainly identified as terpenoids, flavonoids and lignans [3]. Balsam fir *Abies balsamea* (L.) Mill., a popular Christmas tree in Canada, has been used traditionally by North American aboriginal people as an antiseptic, tuberculosis remedy, and venereal aid [4]. In recent years, we have become interested in studying the bioactive constituents of *A. balsamea*. Our work allowed the identification of antibacterial sesquiterpenoids, active against *S. aureus*, from balsam fir essential oil [5]. We also isolated two cytotoxic tetraterpenoids from the cortical oleoresin of the tree bark, featuring an unprecedented C_{40} scaffold [6]. Herein, we describe the further phytochemical study of *A. balsamea* oleoresin, which led to the isolation and structure elucidation of three 3,4-*seco*-lanostane-type triterpenoids **1**–**3**, one cycloartane-type triterpenoid **4** and fourteen known terpenoids. The antibacterial (*E. coli* and *S. aureus*) and cytotoxic (A549, DLD-1 and WS1) activities of the isolated compounds are also reported.

Results and Discussion

The oleoresin of *A. balsamea* (1st lot) was fractionated by silica gel column chromatography with hexanes/EtOAc (100:0 → 93:7) and MeOH as eluent. Both hexanes/EtOAc 93:7 and MeOH fractions were combined and concentrated under reduced pressure. Purification of this extract using a combination of silica gel or polyamide column chromatography and reversed phase C_{18} HPLC resulted in the isolation of three new (**1**–**3**) and six known terpenoids (Figure 1). In another experiment, oleoresin (2nd lot) was triturated with hexanes. The precipitate was subjected to successive silica gel column chromatography followed by reversed phase C_{18} HPLC to give one new (**4**) as well as three known terpenoids. Similarly, purification of the filtrate afforded five known terpenoids. Based on their spectroscopic data (IR, MS and NMR) and comparison

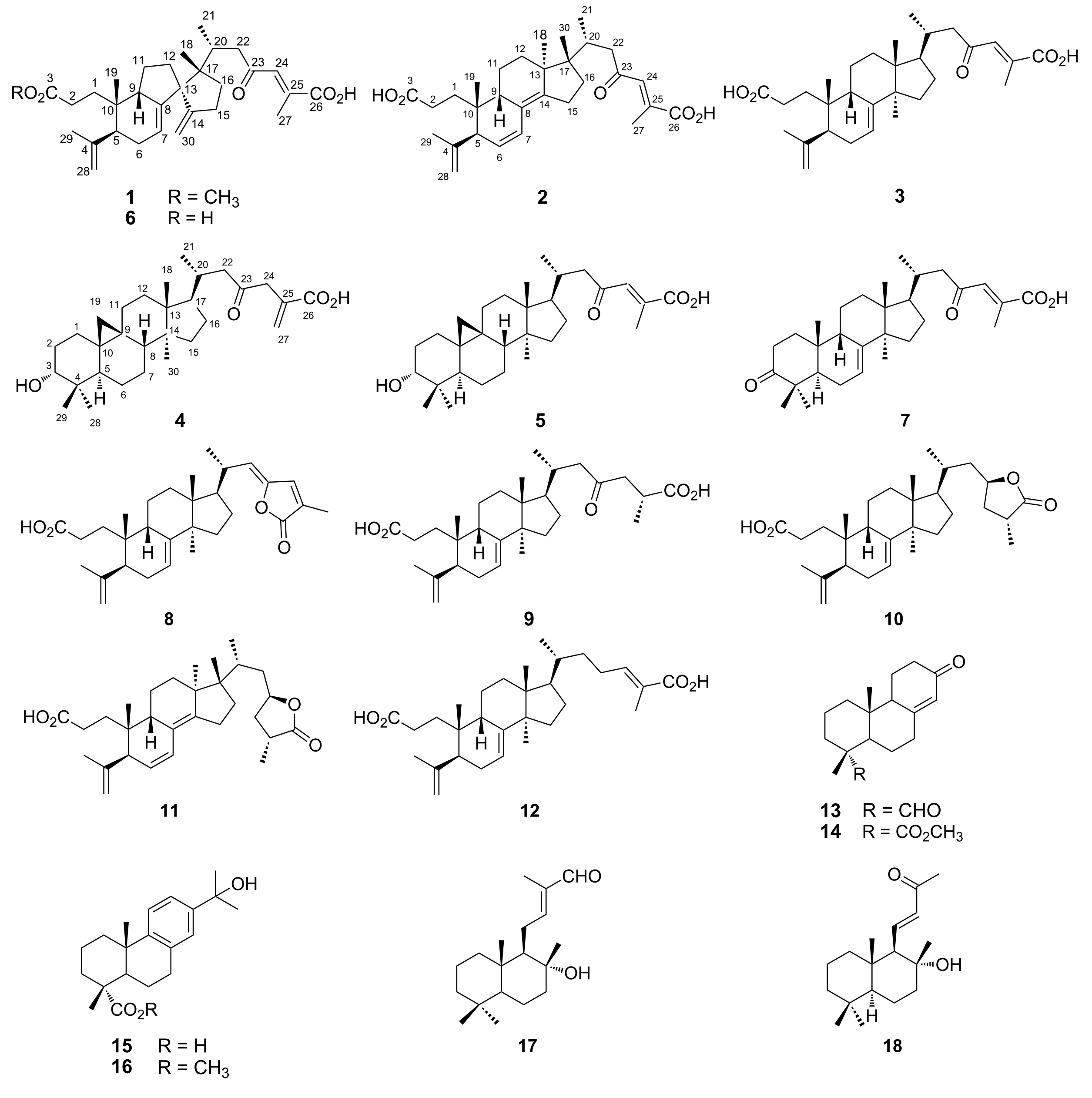

Figure 1: Structures of isolated compounds **1**–**18**.

with literature values, the structures of the known compounds were elucidated as awashishinic acid (**5**) [7], abiesonic acid (**6**) [6], firmanoic acid (**7**) [8], (22*Z*)-3,4-*seco*-9β*H*-lanosta-4(28),7,22,24-tetraen-23,26-olid-3-oic acid (**8**) [9], (25*R*)-3,4-*seco*-9β*H*-lanosta-4(28),7-diene-3,26-dioic acid (**9**) [10], abiesolidic acid (**10**) [10,11], (23*R*,25*R*)-3,4-*seco*-17,14-*friedo*-9β*H*-lanosta-4(28),6,8(14)-trien-26,23-olid-3-oic acid (**11**) [10], (24*E*)-3,4-*seco*-9β*H*-lanosta-4(28),7,24-triene-3,26-dioic acid (**12**) [12], abiesanordine C (**13**) [13], methyl 13-oxo-podocarp-8(14)-en-15-oate (**14**) [14], 15-hydroxydehydroabietic acid (**15**) [15], methyl 15-hydroxydehydroabietate (**16**) [16], (12*E*)-8-hydroxy-15-nor-12-labden-14-al (**17**) [17] and 8-hydroxy-14,15-dinor-11-labden-13-one (**18**) [13,18] (Figure 1). ^{1}H and ^{13}C NMR spectroscopic data of known compounds (**5**–**18**) are given in Supporting Information File 1.

Compound **1** was isolated as a white amorphous powder. Its molecular formula was established as $C_{31}H_{44}O_5$ from the $[M + H]^+$ peak at *m*/*z* 497.3261 (calcd 497.3262) in the positive HRESIMS, indicating ten degrees of unsaturation. The IR spectrum displayed strong absorption bands at 1692 and 1736 cm^{-1} indicative of carboxylic acid functionalities. The ^{13}C NMR and DEPT spectroscopic data (Table 1) exhibited 31 carbons including one carbonyl carbon at δ_C 202.4, and two carboxylic carbons at δ_C 172.4 and 174.8. The ^{1}H NMR data (Table 2) exhibited six olefinic signals at δ_H 4.73 (s), 4.77 (s), 4.78 (s), 4.86 (s), 5.48 (dd, *J* = 6.2, 3.1 Hz) and 7.11 (br s), one methoxy methyl at δ_H 3.67 (s), four tertiary methyl at δ_H 0.90 (s), 0.92 (s), 1.75 (s) and 2.18 (s) and one secondary methyl at δ_H 0.85 (d, *J* = 6.4 Hz). Detail analysis of the above NMR information, together with ^{1}H–^{1}H COSY, HSQC and HMBC analyses indicated that **1** shares the same structure with abiesonic acid (**6**), previously isolated from *A. balsamea* [6], but with an additional methoxy group. An HMBC cross-peak between this methyl signal and the carbon at δ_C 174.8 (C-3) allowed the assignment of compound **1** as (−)-*rel*-abiesonic acid 3-methyl ester.

Table 1: ^{13}C NMR spectroscopic data (100 MHz, $CDCl_3$) of compounds **1–4**.

Position	1	2	3	4
1	30.5	28.3	28.8	27.5
2	29.2	29.8	29.2	28.5
3	174.8	181.6	180.8	77.1
4	149.2	145.6	149.7	39.5
5	44.0	50.6	45.3	41.1
6	30.9	127.0	29.7	21.1
7	122.4	125.2	118.0	25.6
8	143.4	125.4	146.3	48.0
9	49.5	39.4	38.6	19.7
10	36.9	37.0	36.3	26.5
11	22.5	19.6	18.5	26.2
12	31.2	32.0	33.8	32.8
13	63.5	47.4	43.8	45.4
14	160.9	146.2	51.7	49.0
15	27.8	23.9	34.0	35.4
16	36.1	36.3	28.5	28.3
17	50.2	49.1	53.1	52.2
18	17.7	21.9	21.7	18.1
19	24.7	21.8	24.1	29.8
20	33.8	35.1	33.3	32.9
21	16.4	15.9	19.5	19.3
22	48.3	48.9	51.9	50.0
23	202.4	202.5	202.4	207.6
24	134.9	133.0	134.4	46.1
25	138.7	140.4	139.3	133.9
26	172.4	173.4	172.8	170.8
27	14.0	14.0	13.9	130.5
28	111.9	115.6	112.0	25.8
29	26.1	24.8	26.0	21.2
30	106.9	15.8	27.5	19.3
OMe	51.7	–	–	–

Compound **2**, obtained as a white amorphous powder, possessed a molecular formula of $C_{30}H_{42}O_4$ with ten degrees of unsaturation based on the $[M + H]^+$ peak at *m*/*z* 483.3087 (calcd 483.3105) in the positive HRESIMS. The IR absorption bands showed the presence of carboxylic acid (1702 cm^{-1}) and olefin (1635 cm^{-1}) functionalities. The ^{13}C NMR spectroscopic data of **2** (Table 1) displayed 30 carbon signals, which by the assistance of a DEPT experiment, were identified as six methyl, seven *sp*^{3} methylene and three *sp*^{3} methine groups, three *sp*^{3} quaternary carbon atoms, one *sp*^{2} methylene and three *sp*^{2} methine groups, and seven *sp*^{2} quaternary carbon atoms. A ^{1}H–^{1}H COSY experiment provided correlations from H_2-1 to H_2-2, H-6 to H-5 and H-7, H_2-11 to H-9 and H_2-12, H_2-15 to H_2-16 and H-20 to H_3-21 and H_2-22 (Figure 2). Analysis of HMBC spectra indicated correlations from H_3-19 to C-1, C-5, C-9 and C-10; from H_3-29 to C-4, C-5 and C-28; from H-7 to C-8; from H_3-18 to C-12, C-13, C-14 and C-17; from H_3-30 to C-13, C-16, C-17 and C-20; from H_3-21 to C-17, C-20 and C-22; from H_2-22 and H-24 to C-23; and from H_3-27 to C-24, C-25 and C-26. The relative configuration of **2** was determined by analysis of a NOESY experiment, which provided correlations (Figure 2) of H-5 to H_2-2; H-28Z to H-9; H-22a (δ_H 2.85) to H_3-18 and H_3-21; H_3-18 to H-22b (δ_H 2.16) and H-24; H-24 to H-20 and H-22b. These correlations indicated the α-orientation of H-5 and H_3-30 and the β-orientation of H-9, H_3-18 and H_3-19. All these facts suggested that compound **2** was strongly similar to *cis*-sibiric acid [19]. Since the chemical shift of H-24 in *cis*-sibiric acid (δ_H 6.15) was upfield of the signal for **1** (δ_H 7.11), **2** (δ_H 7.23), **6** (δ_H 7.13) and **7** (δ_H 7.07), this suggested

Table 2: ^{1}H NMR spectroscopic data (400 MHz, $CDCl_3$) of compounds **1–4**.

Position	δ_H (*J* in Hz)			
	1	**2**	**3**	**4**
1	1.74, m, 1.62, m	1.60, m	1.73, m, 1.60, m	1.85, m, 1.01, m
2	2.30, m	2.31, m	2.32, m	1.93, m, 1.64, m
3	–	–	–	3.48, t (2.4)
5	2.08, m	2.63, d (5.4)	2.08, m	1.82, m
6	2.40, m, 2.13, m	5.39, dd (9.9, 5.5)	2.27, m, 1.99, m	1.48, m, 0.77, m
7	5.48, dd (6.2, 3.1)	6.22, d (10.0)	5.33, br s	1.30, m, 1.11, m
8	–	–	–	1.54, m
9	2.06, m	2.43, m	2.59, m	–
11	1.59, m, 1.40, m	1.62, m	1.60, m	2.00, m, 1.13, m
12	1.77, m, 1.32, m	1.65, m	1.83, m, 1.67, m	1.62, m
15	2.48, m, 2.37, m	2.41, m, 2.32, m	1.52, m	1.31, m
16	1.55, m	1.73, m, 1.54, m	1.92, m, 1.26, m	1.87, m, 1.27, m
17	–	–	1.54, m	1.61, m
18	0.90, s	1.16, s	0.80, s	1.00, s
19	0.92, s	0.87, s	0.86, s	0.52, d (3.9), 0.35, d (3.9)
20	2.39, m	2.24, m	2.03, m	2.02, m
21	0.85, d (6.4)	0.80, d (6.5)	0.91, d (6.2)	0.88, d (6.8)
22	2.49, m, 2.25, m	2.85, m 2.16, br d (12.3)	2.64, m 2.32, m	2.56, dd (16.0, 2.1), 2.24, dd (16.1, 10.2)
24	7.11, br s	7.23, br s	7.15, s	3.42, d (17.0) 3.36, d (17.1)
27	2.18, s	2.22, d (1.0)	2.21, s	6.45, br s 5.73, br s
28	4.86, s, 4.78, s	4.98, br s, 4.76, d (2.4)	4.88, s, 4.82, s	0.95, s
29	1.75, s	1.79, s	1.80, s	0.88, s
30	4.77, s, 4.73, s	0.69, s	1.04, s	0.90, s
OMe	3.67, s	–	–	–

that the *trans*-stereoisomer was isolated instead of the *cis*-one (See Table 2 and Supporting Information File 1). This was further confirmed by NOESY correlation of H-24 to H-20 and H_3-30, but not to H_3-27. Consequently, the structure of **2** was determined as (−)-*rel*-(24*E*)-23-oxo-3,4-*seco*-9β*H*-lanosta-4(28),6,8(14),24-tetraen-3,26-dioic acid.

Compound **3**, a white amorphous powder, possessed a molecular formula of $C_{30}H_{44}O_5$ based on the $[M + H]^+$ peak at *m*/*z* 485.3250 (calcd 485.3262) in the positive HRESIMS, suggesting nine degrees of unsaturation. The IR spectrum implied the existence of carboxylic acid (1703 cm^{-1}) and olefin (1633 cm^{-1}) functionalities. The ^{13}C NMR spectroscopic data of **3** resembled those of (24*E*)-3,4-*seco*-9β*H*-lanosta-4(28),7,24-triene-3,26-dioic acid (**12**) [12] except for change at δ_C 33.3 (C-20), 19.5 (C-21), 51.9 (C-22), 202.4 (C-23), 134.4 (C-24), 139.3 (C-25), 172.8 (C-26) and 13.9 (C-27) (See Table 1 and Supporting Information File 1). The HMBC correlations from H-24 to C-23 indicated the presence of a ketone group at C-23 (Figure 2). This conclusion was confirmed from the downfield δ_C of C-22 (+16.4) in comparison with **12**. The relative configuration was established with the NOESY spectrum (Figure 2). Briefly, the configuration at C-5, C-9, C-10, C-13 and C-17 was determined by cross-peaks from H-28Z to H-9; H-5 to H_3-19 and H_3-29; H_3-18 to H-9 and H-20; H_3-30 to H-17; and H_3-21 to H_2-12. NOESY correlation between H-24 and H_3-27 was not observed, suggesting that the geometry of the C-24,25 double bond was *E*. This was confirmed by δ_H comparison of H-24 with that of **1**, **2**, **6** and **7** (See Table 2 and Supporting Information File 1). On the basis of these spectroscopic evidences, the structure of **3** was assigned as (−)-*rel*-(24*E*)-23-oxo-3,4-*seco*-9β*H*-lanosta-4(28),7,24-triene-3,26-dioic acid.

The HRESIMS of **4**, isolated as a white amorphous powder, showed a pseudomolecular $[M + H]^+$ ion peak at *m*/*z* 471.3463, corresponding to the formula $C_{30}H_{46}O_4$ (calcd. 471.3469), indicating eight degrees of insaturation. The IR absorption bands at 3416, 1708 and 1633 cm^{-1} suggested the presence of hydroxyl, carbonyl and olefin functionalities. The ^{13}C NMR and DEPT-135 spectra of **4** showed signals for 30 carbons designated as five methyl; twelve methylene, including one alkene at δ_C 130.5; five methine, including one secondary alcohol at δ_C 77.1; and eight quaternary carbons, including those at δ_C 170.8 and

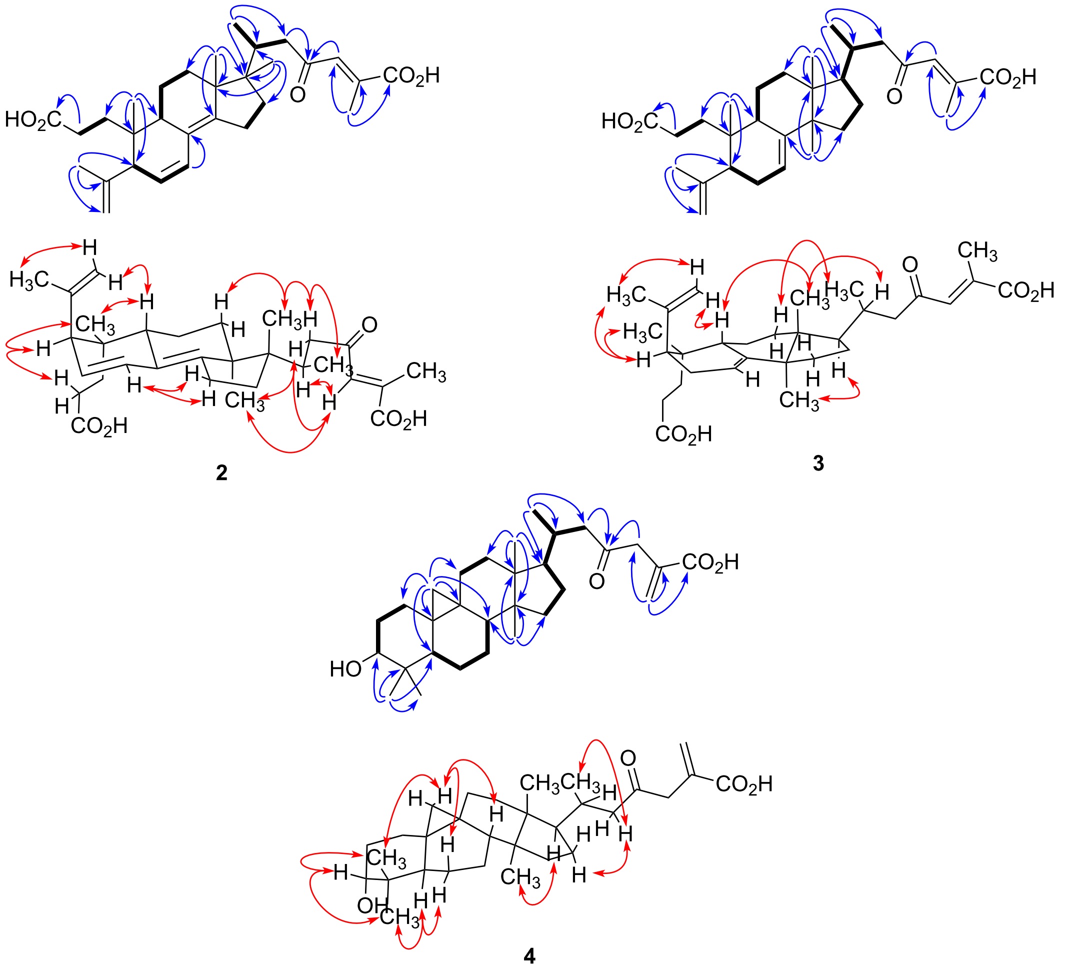

Figure 2: Selected COSY (**—**), HMBC (blue arrows) and NOESY (red arrows) correlations for compounds **2**–**4**.

207.6 representing carboxylic and ketone carbonyls, respectively (Table 1). The ^{1}H NMR spectrum showed two doublets at δ_H 0.35 (J = 3.9 Hz) and 0.52 (J = 3.9 Hz) characteristic of a cyclopropane ring (Table 2), suggesting that **4** is a member of the cycloartanes, which is an important triterpenic family in the genus *Abies* [3]. In the ^{1}H–^{1}H COSY spectrum, correlations between H_2-2 to H_2-1 and H-3; H_2-6 to H-5 and H_2-7; H_2-7 to H-8; H_2-16 to H_2-15 and H-17; and H-20 to H_3-21 and H_2-22 were observed (Figure 2). HMBC correlations from H_2-19 to C-1, C-5, C-8, C-9, C-10 and C-11 connected together three different fragments in the vicinity of the cyclopropyl group. Other correlations between H_3-18 to C-12, C-13, C-14 and C-17; H_3-21 to C-17, C-20 and C-22; H_2-27 to C-24, C-25 and C-26; H_3-28 and H_3-29 to C-3, C-4, C-5, C-28 and C-29; H_3-30 to C-8, C-13, C-14 and C-15; and H_2-22 and H_2-24 to C-23 were observed and completely assigned the carbon skeleton of the molecule (Figure 2). The relative configuration was determined with the help of a 2D NOESY experiment showing correlations from H-19β to H-6β, H-8 and H_3-29; H-5 to H_3-28 and H-6α; H_3-30 to H-11α and H-17; and H-22b to H-20 and H_2-16 (Figure 2). The α-orientation of the hydroxy group at C-3 was deduced from the small coupling constant of H-3 (J = 2.4 Hz), and from the NOESY correlations with both H_3-28 and H_3-29. Accordingly, the structure of compound **4** was defined as (+)-*rel*-3α-hydroxy-23-oxocycloart-25(27)-en-26-oic acid.

The absolute stereochemistry of the new compounds (**1**–**4**) has not been determined experimentally. However, the previously described compounds **7**, **9**, **10** and **11** have been shown to possess the usual configuration for triterpenes [8,10,11]. The structures of many other triterpenes isolated from the genus *Abies* were also reported with this absolute configuration according to their X-ray crystallographic data [20-22].

The structure of compound **8** was reported by Xia et al [9]. In their paper, the configuration at Δ^{22} was determined as E but it was not supported by any spectroscopic data. Since ^{1}H and

^{13}C NMR data obtained for **8** were identical to those reported by Xia within 0.01 and 0.1 ppm respectively (see Supporting Information File 1), we supposed that both molecules were the same. However, the geometry at Δ^{22} should be assigned to *Z* because of the clear NOESY correlation between H-22 and H-24. Interestingly, lanostane with *E* geometry at Δ^{22} has never been isolated so far. Moreover, triterpenes with this kind of side chain bearing an *E* configuration for Δ^{22} have only been reported by Guo et al [23,24]. During their work on *Schisandra* spp., they isolated many nortriterpenes having both Δ^{22} configurations. A statistical analysis of the ^{1}H chemical shift for H-22 and H-24 was conducted: for *E*-configured Δ^{22}, δ_H are 5.9 ± 0.2 and 7.8 ± 0.1 while for *Z*-configured Δ^{22}, δ_H are 5.3 ± 0.1 and 7.2 ± 0.2, respectively. Since δ_H measured for compound **8** was 4.98 and 6.97, it should be assigned as (22*Z*)-3,4-*seco*-9β*H*-lanosta-4(28),7,22,24-tetraen-23,26-olid-3-oic acid.

The isolates were evaluated in vitro for their cytotoxic activities against two human cancer cell lines, namely lung carcinoma (A549) and colon adenocarcinoma (DLD-1), as well as against one healthy cell line (WS1) using the resazurin reduction test [25]. Etoposide was used as a positive control ($IC_{50} \leq 1.0$ μM). None of the compounds were found to be active ($IC_{50} > 25$ μM) with the exception of abiesonic acid (**6**), which showed a weak cytotoxic activity against A549 ($IC_{50} = 22$ μM). The antibacterial activity of isolated compounds was also evaluated in vitro against *E. coli* and *S. aureus* using the microdilution assay [26] with gentamycin as a positive control (MIC < 0.1 μg/mL). No activity was observed for all the tested compounds (MIC ≥ 50 μM) except for triterpenoids **1** and **4**, which were weakly active against *S. aureus* (MIC = 25 μM).

Supporting Information

Supporting Information File 1

Experimental procedures, product characterization and ^{1}H and ^{13}C spectra for compounds **1**–**18**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-150-S1.pdf]

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