

## 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<sub>50</sub> = 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 tradi-

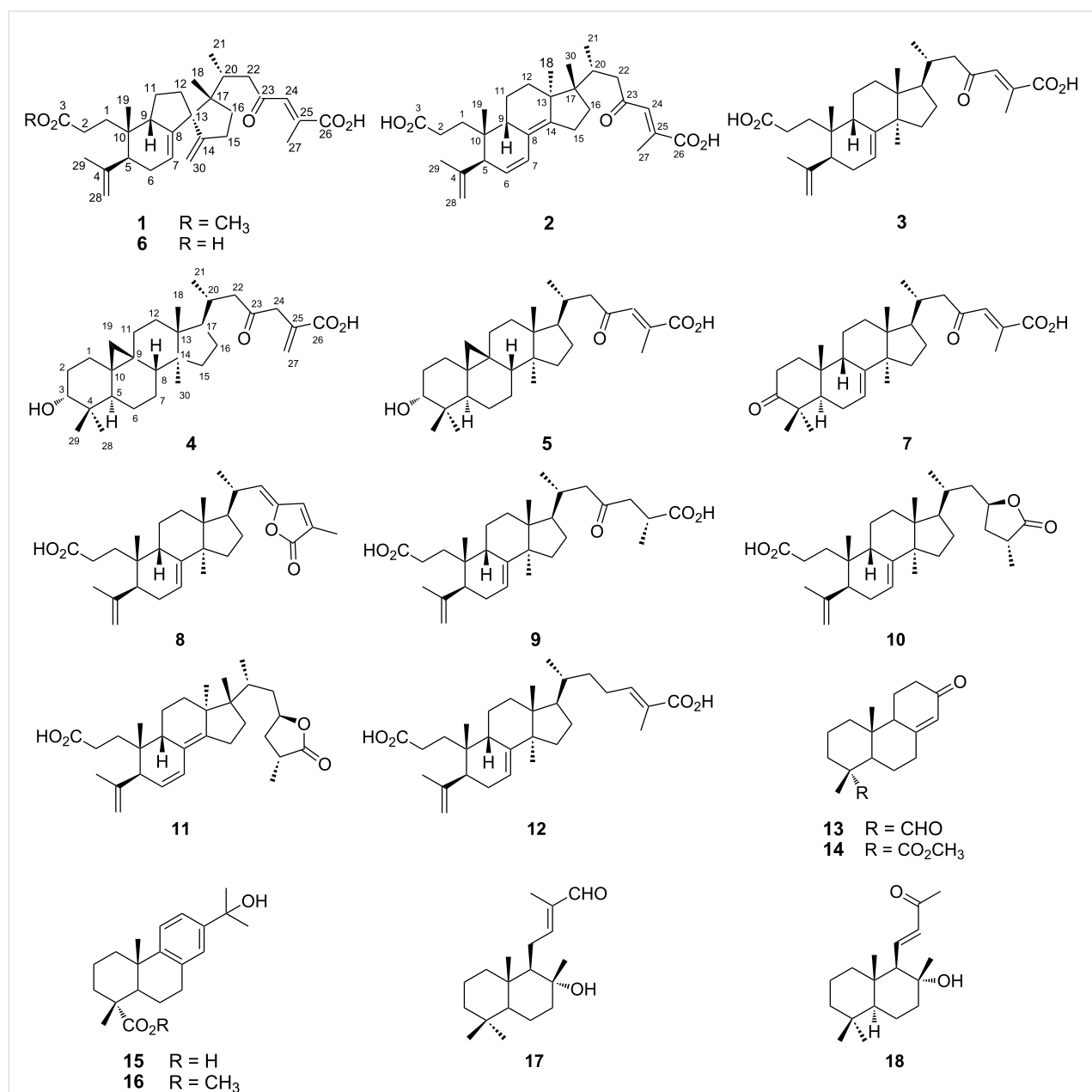
tionally by North American aboriginal people as an antiseptic, tuberculosis remedy, and venereal aid [4]. In recent years, we have become interested in studying the bioactive constituents of *A. balsamea*. Our work allowed the identification of antibacterial sesquiterpenoids, active against *S. aureus*, from balsam fir essential oil [5]. We also isolated two cytotoxic tetraterpenoids from the cortical oleoresin of the tree bark, featuring an unprecedented C<sub>40</sub> 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* (1<sup>st</sup> 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<sub>18</sub> HPLC resulted in the isolation of three new (**1–3**) and six known terpenoids (Figure 1). In another experiment, oleoresin (2<sup>nd</sup> lot) was triturated with hexanes. The precipitate was subjected to successive silica gel column chromatography followed by reversed phase C<sub>18</sub> 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). <sup>1</sup>H and <sup>13</sup>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<sub>31</sub>H<sub>44</sub>O<sub>5</sub> from the [M + H]<sup>+</sup> 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<sup>-1</sup> indicative of carboxylic acid functionalities. The <sup>13</sup>C NMR and DEPT spectroscopic data (Table 1) exhibited 31 carbons including one carbonyl carbon at δ<sub>C</sub> 202.4, and two carboxylic carbons at δ<sub>C</sub> 172.4 and 174.8. The <sup>1</sup>H NMR data (Table 2) exhibited six olefinic signals at δ<sub>H</sub> 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<sub>H</sub> 3.67 (s), four tertiary methyl at δ<sub>H</sub> 0.90 (s), 0.92 (s), 1.75 (s) and 2.18 (s) and one secondary methyl at δ<sub>H</sub> 0.85 (d, *J* = 6.4 Hz). Detail analysis of the above NMR information, together with <sup>1</sup>H–<sup>1</sup>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<sub>C</sub> 174.8 (C-3) allowed the assignment of compound **1** as (–)-*rel*-abiesonic acid 3-methyl ester.

Compound **2**, obtained as a white amorphous powder, possessed a molecular formula of C<sub>30</sub>H<sub>42</sub>O<sub>4</sub> with ten degrees of unsaturation based on the [M + H]<sup>+</sup> 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<sup>-1</sup>) and olefin (1635 cm<sup>-1</sup>) functionalities. The <sup>13</sup>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*<sup>3</sup> methylene and three *sp*<sup>3</sup> methine groups, three *sp*<sup>3</sup> quaternary carbon atoms, one *sp*<sup>2</sup> methylene and three *sp*<sup>2</sup> methine groups, and seven *sp*<sup>2</sup> quaternary carbon atoms. A <sup>1</sup>H–<sup>1</sup>H COSY experiment provided correlations from H<sub>2</sub>-1 to H<sub>2</sub>-2, H-6 to H-5 and H-7, H<sub>2</sub>-11 to H-9 and H<sub>2</sub>-12, H<sub>2</sub>-15 to

**Table 1:** <sup>13</sup>C NMR spectroscopic data (100 MHz, CDCl<sub>3</sub>) of compounds **1**–**4**.

Position	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
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	–	–	–

H<sub>2</sub>-16 and H-20 to H<sub>3</sub>-21 and H<sub>2</sub>-22 (Figure 2). Analysis of HMBC spectra indicated correlations from H<sub>3</sub>-19 to C-1, C-5, C-9 and C-10; from H<sub>3</sub>-29 to C-4, C-5 and C-28; from H-7 to C-8; from H<sub>3</sub>-18 to C-12, C-13, C-14 and C-17; from H<sub>3</sub>-30 to C-13, C-16, C-17 and C-20; from H<sub>3</sub>-21 to C-17, C-20 and C-22; from H<sub>2</sub>-22 and H-24 to C-23; and from H<sub>3</sub>-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<sub>2</sub>-2; H-28*Z* to H-9; H-22*a* (δ<sub>H</sub> 2.85) to H<sub>3</sub>-18 and H<sub>3</sub>-21; H<sub>3</sub>-18 to H-22*b* (δ<sub>H</sub> 2.16) and H-24; H-24 to H-20 and H-22*b*. These correlations indicated the α-orientation of H-5 and H<sub>3</sub>-30 and the β-orientation of H-9, H<sub>3</sub>-18 and H<sub>3</sub>-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<sub>H</sub> 6.15) was upfield of the signal for **1** (δ<sub>H</sub> 7.11), **2** (δ<sub>H</sub> 7.23), **6** (δ<sub>H</sub> 7.13) and **7** (δ<sub>H</sub> 7.07), this suggested

**Table 2:** <sup>1</sup>H NMR spectroscopic data (400 MHz, CDCl<sub>3</sub>) of compounds **1–4**.

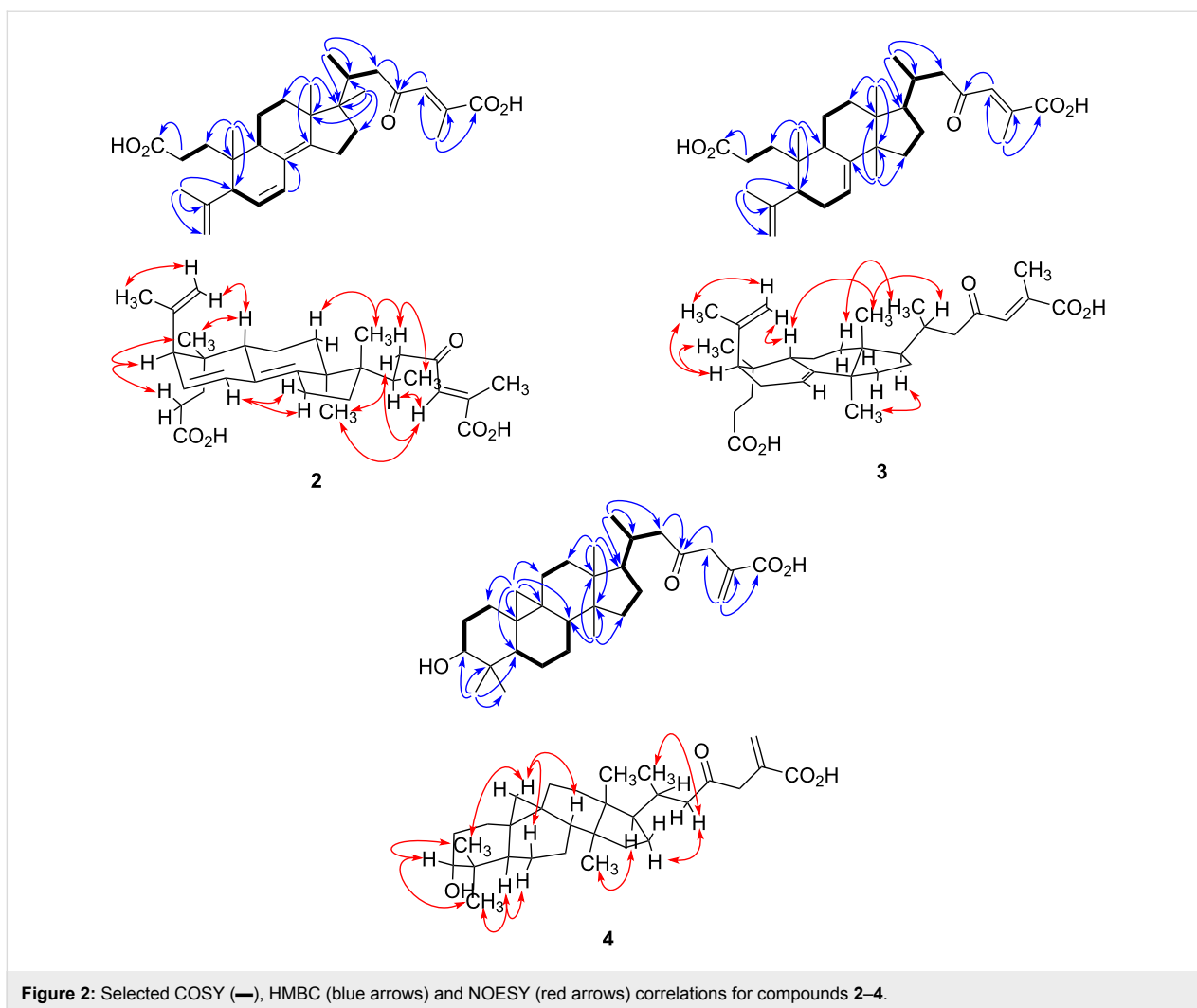
Position	$\delta_{\text{H}}$ (J in Hz)			
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
1	1.74, m, 1.62, m	1.60, m	1.73, m, 1.60, m	1.85, m, 1.01, m
2	2.30, m	2.31, m	2.32, m	1.93, m, 1.64, m
3	–	–	–	3.48, t (2.4)
5	2.08, m	2.63, d (5.4)	2.08, m	1.82, m
6	2.40, m, 2.13, m	5.39, dd (9.9, 5.5)	2.27, m, 1.99, m	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<sub>3</sub>-30, but not to H<sub>3</sub>-27. Consequently, the structure of **2** was determined as (–)-*rel*-(2*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<sub>30</sub>H<sub>44</sub>O<sub>5</sub> based on the [M + H]<sup>+</sup> 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<sup>-1</sup>) and olefin (1633 cm<sup>-1</sup>) functionalities. The <sup>13</sup>C NMR spectroscopic data of **3** resembled those of (2*E*)-3,4-*seco*-9β*H*-lanosta-4(28),7,24-triene-3,26-dioic acid (**12**) [12] except for change at  $\delta_{\text{C}}$  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  $\delta_{\text{C}}$  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<sub>3</sub>-19 and H<sub>3</sub>-29; H<sub>3</sub>-18 to H-9 and H-20; H<sub>3</sub>-30 to H-17; and H<sub>3</sub>-21 to H<sub>2</sub>-12. NOESY correlation between H-24 and H<sub>3</sub>-27 was not observed, suggesting that the geometry of the C-24,25 double bond was *E*. This was confirmed by  $\delta_{\text{H}}$  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*-(2*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]<sup>+</sup> ion peak at *m/z* 471.3463, corresponding to the formula C<sub>30</sub>H<sub>46</sub>O<sub>4</sub> (calcd. 471.3469), indicating eight degrees of insaturation. The IR absorption bands at 3416, 1708 and 1633 cm<sup>-1</sup> suggested the presence of hydroxyl, carbonyl and olefin functionalities. The <sup>13</sup>C NMR and DEPT-135 spectra of **4** showed signals for 30 carbons designated as five methyl; twelve methylene, including one alkene at  $\delta_{\text{C}}$  130.5; five methine, including one secondary alcohol at  $\delta_{\text{C}}$  77.1; and eight quaternary carbons, including those at  $\delta_{\text{C}}$  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  $^1\text{H}$  NMR spectrum showed two doublets at  $\delta_{\text{H}}$  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 triterpene family in the genus *Abies* [3]. In the  $^1\text{H}$ - $^1\text{H}$  COSY spectrum, correlations between H<sub>2</sub>-2 to H<sub>2</sub>-1 and H-3; H<sub>2</sub>-6 to H-5 and H<sub>2</sub>-7; H<sub>2</sub>-7 to H-8; H<sub>2</sub>-16 to H<sub>2</sub>-15 and H-17; and H-20 to H<sub>3</sub>-21 and H<sub>2</sub>-22 were observed (Figure 2). HMBC correlations from H<sub>2</sub>-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<sub>3</sub>-18 to C-12, C-13, C-14 and C-17; H<sub>3</sub>-21 to C-17, C-20 and C-22; H<sub>2</sub>-27 to C-24, C-25 and C-26; H<sub>3</sub>-28 and H<sub>3</sub>-29 to C-3, C-4, C-5, C-28 and C-29; H<sub>3</sub>-30 to C-8, C-13, C-14 and C-15; and H<sub>2</sub>-22 and H<sub>2</sub>-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-19 $\beta$  to H-6 $\beta$ , H-8 and H<sub>3</sub>-29; H-5 to H<sub>3</sub>-28

and H-6 $\alpha$ ; H<sub>3</sub>-30 to H-11 $\alpha$  and H-17; and H-22 $\beta$  to H-20 and H<sub>2</sub>-16 (Figure 2). The  $\alpha$ -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<sub>3</sub>-28 and H<sub>3</sub>-29. Accordingly, the structure of compound **4** was defined as (+)-*rel*-3 $\alpha$ -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  $\Delta^{22}$  was determined as *E* but it was not supported by any spectroscopic data. Since  $^1\text{H}$  and

$^{13}\text{C}$  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  $\Delta^{22}$  should be assigned to *Z* because of the clear NOESY correlation between H-22 and H-24. Interestingly, lanostane with *E* geometry at  $\Delta^{22}$  has never been isolated so far. Moreover, triterpenes with this kind of side chain bearing an *E* configuration for  $\Delta^{22}$  have only been reported by Guo et al [23,24]. During their work on *Schisandra* spp., they isolated many nortriterpenes having both  $\Delta^{22}$  configurations. A statistical analysis of the  $^1\text{H}$  chemical shift for H-22 and H-24 was conducted: for *E*-configured  $\Delta^{22}$ ,  $\delta_{\text{H}}$  are  $5.9 \pm 0.2$  and  $7.8 \pm 0.1$  while for *Z*-configured  $\Delta^{22}$ ,  $\delta_{\text{H}}$  are  $5.3 \pm 0.1$  and  $7.2 \pm 0.2$ , respectively. Since  $\delta_{\text{H}}$  measured for compound **8** was 4.98 and 6.97, it should be assigned as (22*Z*)-3,4-*seco*-9 $\beta$ *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 ( $\text{IC}_{50} \leq 1.0 \mu\text{M}$ ). None of the compounds were found to be active ( $\text{IC}_{50} > 25 \mu\text{M}$ ) with the exception of abiesonic acid (**6**), which showed a weak cytotoxic activity against A549 ( $\text{IC}_{50} = 22 \mu\text{M}$ ). 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 ( $\text{MIC} < 0.1 \mu\text{g/mL}$ ). No activity was observed for all the tested compounds ( $\text{MIC} \geq 50 \mu\text{M}$ ) except for triterpenoids **1** and **4**, which were weakly active against *S. aureus* ( $\text{MIC} = 25 \mu\text{M}$ ).

## Supporting Information

### Supporting Information File 1

Experimental procedures, product characterization and  $^1\text{H}$  and  $^{13}\text{C}$  spectra for compounds **1**–**18**.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-150-S1.pdf>]

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