Arch. Pharm. Chem. Life Sci. 2015, *348*, 889–896

ARCH PHARM
Archiv der Pharmazie

Full Paper

First Occurrence of a Furano-glycyrrhetinoate and Its Cytotoxicity

Lucie Heller[1], Sven Sommerwerk[1]*, Felix Tzschöckell[1], Jana Wiemann[1], Stefan Schwarz[1], Bianka Siewert[1], Ahmed Al-Harrasi[2], and René Csuk[1]*

[1] Department of Organic Chemistry, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
[2] Chair of Oman's Medicinal Plants and Marine Natural Products, University of Nizwa, Birkat Al-Mauz, Nizwa, Sultanate of Oman

(18α)-Glycyrrhetinic acid (**4**) was prepared from (18β)-glycyrrhetinic acid (**1**), and the cytotoxicity of some derivatives was investigated by photometric SRB assays employing several human tumor cell lines. In summary, (18β)-**1** is slightly more cytotoxic than its (18α) epimer **4**, but its cytotoxicity is negligible. Higher cytotoxicity was observed for the esters **2** and **5** and for the 3-*O*-acetylated esters **3** and **6**. Cytotoxicity was improved dramatically when the hydroxyl group at position C-3 was replaced by an amino moiety. SeO_2 oxidations gave access to a novel furano-glycyrrhetinoate **15**. Interestingly, its seleno analog **16** is approximately five to six times less cytotoxic for the tumor cell lines tested, and tumor/non-tumor selectivity is lost upon replacement of the oxygen by a selenium substituent.

Keywords: Cytotoxicity / Furano-glycyrrhetinoate / Glycyrrhetinic acid / Selenophene / SeO_2 oxidation

Received: September 9, 2015; Revised: October 20, 2015; Accepted: October 21, 2015

DOI 10.1002/ardp.201500318

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Introduction

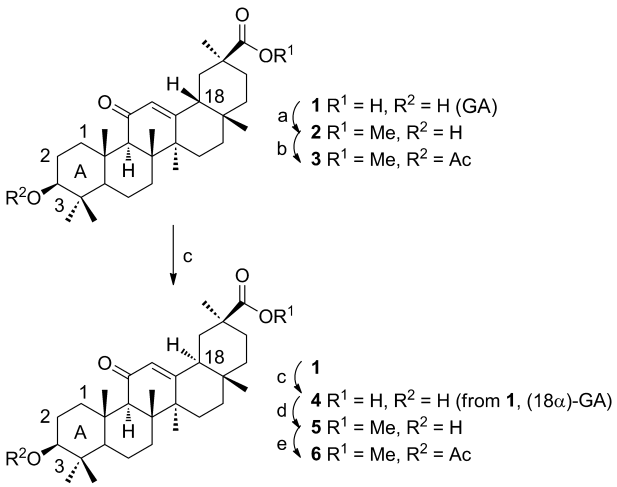
Deaths from cancer worldwide are projected to continue rising with an estimated 13.1 million deaths in 2030. Thus, cancer remains one of the leading causes of death in people from western countries, with bronchial and lung cancer still being the top killer cancer in the USA followed by rectal/colon cancer [1]. Early treatment of cancer by surgery, radiotherapy, or chemotherapy cures the disease or considerably prolongs the patient's life and improves the patient's quality of life. Plant-derived compounds have been used for the treatment or even to cure cancer for many centuries, and many interesting molecular targets have been identified by the careful analysis of "natural products" being part of recipes used in traditional medicine [2].

One of the long-known plants is *Glycyrrhiza glabra* L. (liquorice); the extracts made from the roots of this plant have been used for many indications for almost 5000 years starting with the codex Hammurabi, papyrus Eber, and some references in the traditional Chinese medicine [3]. An early use on the European continent has been documented by Plinius and later on by Paracelsus and Hildegard von Bingen [4]. Main ingredient in these extracts is glycyrrhizin, whose hydrolysis gave access to its aglycon, glycyrrhetinic acid (**1**, GA), the structure of which was established as early as in 1937 by famous Ruzicka [5]. Recently, the interest in the biological activities of **1** (Scheme 1) and derivatives led to a renaissance of these compounds, and many publications demonstrated the biological activities of derivatives of GA [6–17]. Nevertheless, the cytotoxicity of **1** is low, and was improved by altering the pattern of lipophilicity by modifications especially at position C-3 on ring A [9, 11, 13]. In the context of our work presented here, we were interested to determine the influence of the absolute configuration at carbon C-18 and the configuration/substitution pattern at C-3 on the cytotoxic activity of glycyrrhetinic acid derivatives. Recently, a (18α,18β) configuration-dependent activity of 2-cyano substituted GA derivatives as peroxisome

Correspondence: Prof. René Csuk, Bereich Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Straße 2, D-06120 Halle (Saale), Germany.
E-mail: rene.csuk@chemie.uni-halle.de
Fax: +49 345 5527030

*These two authors contributed equally to this article.

ARCH PHARM
Archiv der Pharmazie



Scheme 1. Synthesis of derivatives **2–6** from glycyrrhetinic acid (GA, **1**): (a) MeI, K_2CO_3, DMF, 25°C, 2 h, 91%; (b) AcCl, pyridine, DCM, 25°C, 2 h, 86%; (c) KOH, diethyleneglycol, 220°C, 4 h, 53%; (d) MeI, K_2CO_3, DMF, 25°C, 2 h, 86%; (e) AcCl, pyridine, DCM, 25°C, 2 h, 89%.

proliferator-activated receptor γ-agonists in colon cancer cells was established [6].

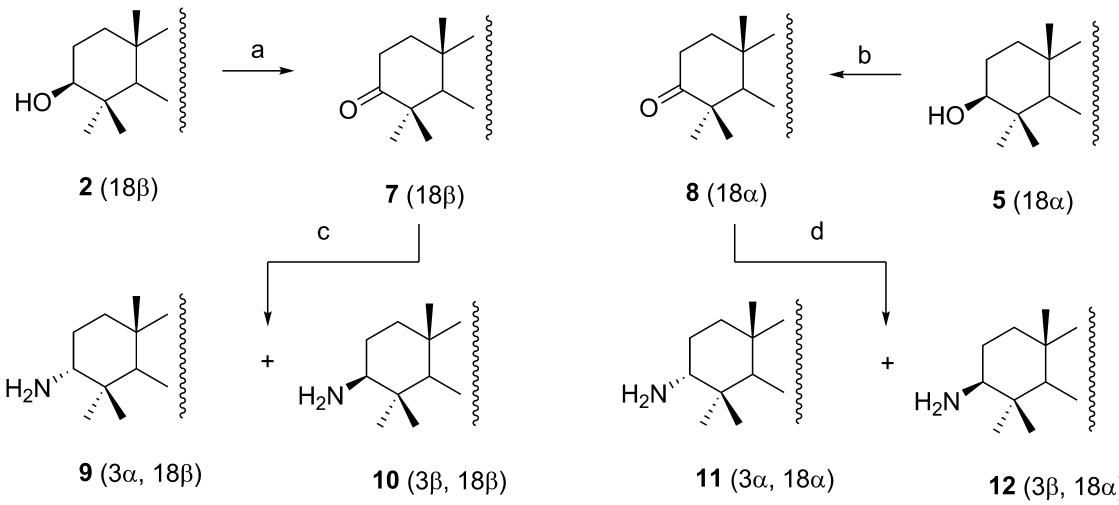
Results and discussion

Esterification of **1** with MeI in DMF in the presence of potassium carbonate [14] gave ester **2** whose acetylation [13] yielded acetate **3**. Reaction of **1** with KOH in diethylene glycol [18], however, afforded **4** [19, 20] being epimeric to **1** at position C-18. Esterification of **4** as described above for **1** gave **5** [21] that was acetylated to yield **6** [22].

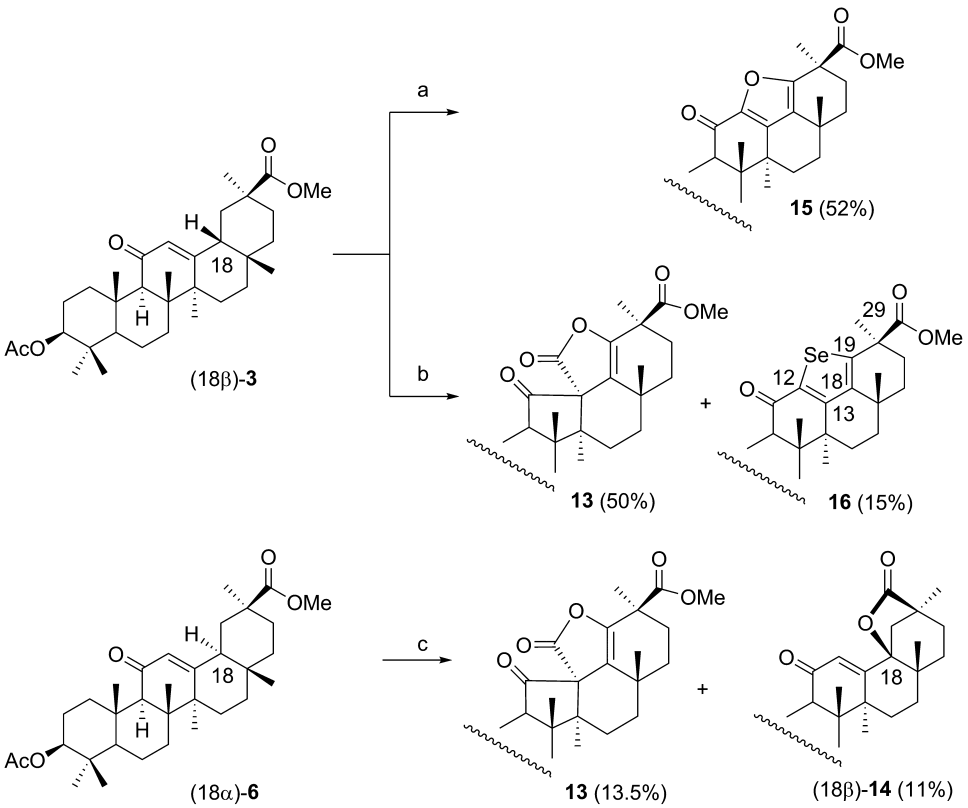
Jones oxidation of **2** (Scheme 2) [13] gave 81% yield of (18β)-configurated 3-keto-compound **7** whereas from **5** under similar conditions 79% of (18α)-configurated **8** was obtained. Reductive amination of **7** with ammonium acetate/sodium cyanoborohydride [23, 24] in methanol gave a 2:5 mixture of (3α,18β) amine **9** and (3β,18β) amine **10** [3, 11, 25]. Under the same conditions from **5**, the amines (3α,18α)-**11** and (3β,18α)-**12** [26] were obtained in a ratio **11**:**12** = 1:4. These amines were separated by column chromatography, and the assignment of the absolute configuration at carbon C-3 was deduced from the magnitude of the coupling constants $^3J_{H\text{-}2ax,\ H\text{-}3}$ and $^3J_{H2\text{-}eq,\ H\text{-}3}$ being characteristic for an axial or an equatorial orientation of H-3.

Interestingly, while from the reaction of (18β)-**3** with SeO_2 in glacial acetic acid lactone **13** (Scheme 3) was obtained [27–29], the reaction of (18α)-**6** with SeO_2 in glacial acetic acid at 145°C for 24 h also yielded **13** but as a by-product lactone **14** was formed in 11% yield. The reaction of (18β)-configurated **3** with SeO_2 in pyridine (microwave assisted, 6 h, 160°C) afforded furane **15** in 52% yield, whereas from the reaction of **3** with SeO_2 in glacial acetic acid (120°C, 24 h) selenophene **16** [30] was obtained as the main product.

Compound **13** possesses a (3β,20β) configuration, which is identical with echinolactone A [31], that had previously been isolated from a marine invertebrate, *Echinopora lamellosa* from Korolevu, Fiji. Interestingly, the same compound has been isolated as a minor constituent of liquorice by Duddeck et al. [32] several years ago, and it has also been synthesized by a photochemical Barton reaction from 3-*O*-acetyl glycyrrhetinic acid albeit in 3% yield [33]. Gayanov's route [34] to



Scheme 2. Synthesis of 3-amino-substituted methyl glycyrrhetinoates **9–12**: (a) Jones oxidation, 81%; (b) Jones oxidation, 79%; (c) $NH_4^+MeCO_2^-$, $NaBH_3CN$, MeOH, 25°C, 24 h, 20% (of **9**) and 52% (of **10**); (d) $NH_4^+MeCO_2^-$, $NaBH_3CN$, MeOH, 25°C, 24 h, 8% (of **11**) and 32% (of **12**).



Scheme 3. Synthesis of lactones **13**, **14**, furan **15**, and selenophene **16** from methyl 3-*O*-acetyl-glycyrrhetinoates **3** or **6** by SeO_2 oxidation: (a) SeO_2, pyridine, microwave, 160°C, 6 h, 52% (of **15**); (b) SeO_2, AcOH, 120°C, 24 h, 50% (of **13**) and 15% (of **16**); (c) SeO_2, AcOH, 145°C, 4 h, 36.5% (of **13**) and 11% (of **14**).

the same molecule started from 3-*O*-acetyl-glycyrrhetinic acid *N*,*N*-dimethylamine whose reaction with bromine in glacial acetic acid also resulted in the formation of **13**.

Deacetylation of **13** afforded a compound not identical with isoglabrolide that has been isolated from *Glycyrrhiza glabra* L. by Canonica et al. [35]; isoglabrolide possesses a (3β,18α,20α) configuration and is probably identical with a lactone derived from isoechinatic acid.

The formation of **13** is not unexpected, as there are some reports of oxidation reactions of steroid enones either in alkaline media (e.g., with oxygen in the presence of ^{t}BuOK or with oxygen in alkaline methanol) [36–40] or with tetrazolium salts [41]. Thus, reaction of GA isomers **1** or **4** with tetrazolium salts was reported to yield 16% (from (18α)-**4**) or 30% (from (18β)-**1**) of (3β,18β,20β) 3,18-dihydroxy-11-oxo-20-olean-12-en-29-oic acid (i.e., (18β) 18-hydroxy-glycyrrhetinic acid) [41].

Compound (18β)-**14** is formed from (18β)-**3** by an allylic oxidation followed by an intramolecular transesterification. Elimination of this primary product of an allylic oxidation of **3** affords a dienone. This dienone can undergo a [4+2] cycloaddition with SeO_2 to finally yield the selenophene **16** similar to the formation of selenophenes from the reaction of 1,3-dienes with SeO_2 at elevated temperatures [42–44]. Thermal rearrangement of an 1,2-oxaselenolane-2-oxide intermediate will result in the formation of furan **15** (along with water) similar to the synthesis of 2-acetyl-furans from conjugated dienones and SeO_2 [42, 45]. Accessing compound **15** represents the first synthesis of a 12,19 epoxy triterpenoid. Quite recently [46], the first examples of a tetrahydrofurano-substituted ursane and an oleanane-type triterpenoid have been isolated from the leaves of *Vitex negundo* var. *cannabifolia* – a small tree mainly found in tropical and subtropical regions.

Cytotoxicity screening of compounds **1**–**16** was performed using a photometric SRB assay [30, 47–50] employing two different human tumor cell lines (colorectal adenocarcinoma HT29 and lung adenocarcinoma A549) and non-malignant mouse fibroblasts (NIH 3T3). The results of these assays are displayed in Table 1.

In summary, (18β)-**1** is slightly more cytotoxic than its (18α) epimer **4**, but its cytotoxicity is negligible. Higher cytotoxicity was observed for the esters **2** and **5** and for the 3-*O*-acetylated esters **3** and **6**. Interestingly, the (18β) 3-oxo-compound **7** was inactive and showed EC_{50} values $>30\,\mu M$ whereas the corresponding (18α) epimer was twice as cytotoxic for HT29 and A549 tumor cells but showed no cytotoxicity ($EC_{50} > 30\,\mu M$) for non-malignant mouse fibroblasts.

Table 1. Cytotoxicity of glycyrrhetinic acid and several derivatives (EC_{50} values in μM from SRB assays after 96 h of treatment; the values are averaged from three independent experiments performed each in triplicate; confidence interval CI = 95%).

Compound	Cell line		
	HT29	A549	NIH 3T3
1	102.3 ± 5.4	85.0 ± 3.1	44.7 ± 1.9
2	20.4 ± 2.1	21.0 ± 1.9	23.1 ± 1.1
3	21.1 ± 1.9	22.8 ± 2.3	25.3 ± 1.7
4	>120	>120	46.2 ± 3.1
5	20.7 ± 2.0	12.9 ± 0.6	14.2 ± 0.5
6	>30	16.7 ± 1.5	17.6 ± 2.0
7	>30	>30	>30
8	18.5	18.0	> 30
9	4.7 ± 0.3	3.3 ± 0.1	5.2 ± 0.6
10	4.1 ± 0.9	2.5 ± 0.4	6.1 ± 1.0
11	4.3 ± 0.7	3.6 ± 0.3	3.5 ± 0.6
12	4.2 ± 0.9	4.3 ± 1.1	2.2 ± 0.4
13	58.7 ± 6.6	15.0 ± 0.9	38.1 ± 4.3
14	>30	>30	>30
15	11.2 ± 1.9	9.9 ± 2.4	24.2 ± 2.6
16	67.2 ± 7.8	46.9 ± 1.8	46.1 ± 4.4

The cell lines are human cancer cell lines: HT29 (colorectal adenocarcinoma), A549 (alveolar basal epithelial adenocarcinoma), and non-malignant mouse fibroblasts (NIH 3T3).

Cytotoxicity was improved dramatically when the hydroxyl group at position C-3 was replaced by an amino moiety. Thus (3α,18β) amine **9** and (3β,18β) amine **10** showed not only EC_{50} values between 2.5 and 4.7 μM for the tumor cells but also EC_{50} values between 5.2 and 6.1 μM for the non-malignant mouse fibroblasts. The cytotoxicity of (18α)-configured amines **11** and **12** was similar, albeit they were even more toxic for the non-malignant fibroblasts. Amino substituents at position C-3 seem to enhance cytotoxicity without discrimination between malignant and non-malignant cells.

Although lactones **13** and **14** showed no significant cytotoxicity for the human tumor cells, furan **15** showed a ten-times higher cytotoxicity than parent glycyrrhetinic acid, and is significantly less cytotoxic to non-malignant mouse fibroblasts than to human tumor cells. Interestingly, its seleno analog **16** is approximately five to six times less cytotoxic for the tumor cell lines than furan **15**. In addition, tumor/non-tumor selectivity is lost upon replacement of the oxygen by a selenium substituent.

In conclusion, we synthesized several derivatives of glycyrrhetinic acid differing in configuration at positions C-3 and C-18 as well as in their lipophilicity with respect to position C-3. Neither configurational inversion at position C-3 nor inversion at position C-18 led to significantly higher cytotoxicity. The introduction of an amino group, however, at position C-3 was quite promising. These compounds displayed low EC_{50} values in SRB assays but they were also rather cytotoxic for non-malignant mouse fibroblasts. SeO_2 oxidation of acetylated methyl 18α-glycyrrhetinoate (**6**) furnished a furano-glycyrrhetinoate **15**. To our knowledge, **15** represents the first example of a furano-fused glycyrrhetinoate, and its biological properties make this triterpenoid an interesting candidate for further chemical modifications and biological testing. Interestingly, compound **15** exhibited an approximately fivefold higher cytotoxicity for tumor cells than its selenophene analog **16**.

Experimental

Chemistry

General

Melting points are uncorrected (Leica hot stage microscope), NMR spectra were recorded using the Varian spectrometers Gemini 2000 or Unity 500 (δ given in ppm, *J* in Hz, internal Me_4Si; typical experiments: H-H-COSY, HMBC, HMQC, NOESY, DQF-COSY), ESI-MS spectra were taken on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.1 kV, sheath gas nitrogen) instrument. The optical rotation was measured on a Perkin–Elmer polarimeter at 20°C; TLC was performed on silica gel (Merck 5554); elemental analyses were performed on a Vario EL (CHNS). The solvents were dried according to usual procedures. The purity of the compounds was determined by HPLC and found to be >98%. Glycyrrhetinic acid (**1**) was obtained from Orgentis GmbH (Gatersleben, Germany) in bulk quantities. The SRB assay was performed as previously described [30, 47–49].

*(3β,18β) Methyl 3-hydroxy-11-oxo-olean-12-en-30-oate (**2**)*

This compound was prepared as previously described from **1** with MeI, K_2CO_3, DMF in 91% yield [14].

*(3β,18β) Methyl 3-acetoxy-11-oxo-olean-12-en-30-oate (**3**)*
From **2** by acetylation with acetyl chloride, pyridine in DCM in 86% yield as previously described [13].

*(3β,18α) 3-Hydroxy-11-oxo-olean-12-en-30-oic acid (18α-glycyrrhetinic acid, **4**)*
A solution of KOH (12.0 g, 213.88 mmol) in diethylene glycol (75 mL) was heated at 100°C for 15 min [18], and **1** (30.0 g, 63.74 mmol) was added in several portions while the temperature was raised to 220°C; heating was continued for another 4 h. Aqueous workup (water, then aq. HCl) gave a brownish precipitate that was filtered off, washed with water, and then extracted with hot acetone. The remaining white solid was filtered off and recrystallized from ethanol and **4** (15.9 g, 53%) was obtained as a colorless solid; m.p. 330–331°C (lit.: [51] 277–281°C, 331–335°C [22]); $[\alpha]_D = 152.3°$ ($c = 0.5$, $CHCl_3$) (lit.: [52] 155.9° ($CHCl_3$), 86° (EtOH) [53]); $R_f = 0.30$ (toluene/heptane/ethyl acetate/formic acid, 80:15:40:4); ESI-MS (MeOH): $m/z = 469.5$ (56%, $[M-H]^-$), 939.5 (100%, $[2M-H]^-$), 961.8 (15%, $[2M-2H+Na]^-$).

*(3β,18α) Methyl 3-hydroxy-11-oxo-olean-12-30-oate (**5**)*
Following the procedure given for the synthesis of **2**, from **4** (5.9 g, 12.54 mmol) compound **5** (5.22 g, 86%) was obtained as a colorless solid; m.p. 258–260°C (lit.: 264–266°C), $[\alpha]_D = 85.4°$ ($c = 0.30$, $CHCl_3$) (lit.: [54] 90° ($c = 0.1$, $CHCl_3$)); $R_f = 0.43$ (toluene/heptane/ethyl acetate/formic acid, 80:15:40:4); ESI-MS (MeOH): $m/z = 485.5$ (36%, $[M+H]^+$).

*(3β,18α) Methyl 3-acetoxy-11-oxo-olean-12-en-30-oate (**6**)*
Following the procedure given for the synthesis of **3**, from **5** (4.84 g, 9.98 mmol) compound **6** (4.68 g, 89%) was obtained as a colorless sold; m.p. 238–240°C (lit.: [22] 254–256°C); $[\alpha]_D = 82.3°$ ($c = 0.32$, $CHCl_3$) (lit.: [22] 87° ($c = 2.1$, $CHCl_3$)); $R_f = 0.67$ (toluene/heptane/ethyl acetate/formic acid, 80:15:40:4); ESI-MS (MeOH): $m/z = 527.4$ (47%, $[M+H]^+$).

*(18β) Methyl 3,11-dioxo-olean-12-en-30-oate (**7**)*
Jones oxidation of **2** (9.5 g, 19.60 mmol) as previously reported followed by chromatographic purification (silica gel, hexanes/ethyl acetate, 8:2) gave **7** (7.70 g, 81.4%) as a colorless solid (from methanol); m.p. 244–246°C (lit.: [13] 244–246°C, 249–250°C [55]); $[\alpha]_D = 173.0°$ ($c = 0.3$, $CHCl_3$) (lit.: [3] $[\alpha]_D = 182.1°$ ($c = 0.2$, $CHCl_3$)); $R_f = 0.60$ (hexanes/ethyl acetate, 7:3), ESI-MS (MeOH): $m/z = 483.5$ (66%, $[M+H]^+$).

*(18α) Methyl 3,11-dioxo-olean-12-en-30-oate (**8**)*
Jones oxidation of **5** (4.75 g, 9.80 mmol) as previously reported for the synthesis of **7** followed by chromatographic purification (silica gel, hexanes/ethyl acetate, 8:2) gave **8** (3.74 g, 79.1%) as a colorless solid; m.p. 235–238°C (lit.: [56] 238–240°C); $[\alpha]_D = 107.5°$ ($c = 0.4$, $CHCl_3$); $R_f = 0.37$ (toluene/heptane/ethyl acetate/formic acid, 80:15:40:4); IR (KBr): $\nu = 3432$ br, 2948s, 1726s, 1706s, 1652s, 1460m, 1387m, 1281m, 1231m, 1198w, 1118m cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 243.6 (4.05) nm; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.60$ (*s*, 1H, H-12), 3.70–3.64 (*m*, 3H, H-31), 2.86 (*ddd*, $J = 11.3$, 6.8, 3.9 Hz, 1H, H-1a), 2.63 (*ddd*, $J = 16.5$, 11.1, 7.3 Hz, 1H, H-2a), 2.34 (*s*, 1H, H-9), 2.38–2.31 (*m*, 1H, H-2a), 2.23 (*d*, $J = 12.0$ Hz, H-18), 1.98 (*dd*, $J = 13.8$, 4.8 Hz, 1H, H-15a), 1.89 (*dd*, $J = 14.5$, 4.9 Hz, 1H, H-19a), 1.72–1.66 (*m*, 1H, H-7a), 1.66 (*dd*, $J = 12.6$, 12.6 Hz, 1H, H-21a), 1.61–1.49 (*m*, 5H, H-6 + H-7b + H-21b + H-22a), 1.49–1.41 (*m*, 3H, H-16a + H-19b + H-22b), 1.37 (*m*, 2H, H-1b, H-16b), 1.34 (*s*, 3H, H-29), 1.32 (*s*, 3H, H-25), 1.31–1.23 (*m*, 2H, H-5 + H-15b), 1.21 (*s*, 3H, H-27), 1.16 (*s*, 3H, H-26), 1.09 (*s*, 3H, H-23), 1.06 (*s*, 3H, H-24), 0.72 (*s*, 3H, H-28) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 217.5$ (C-3), 179.1 (C-30), 166.5 (C-13), 124.5 (C-12), 60.3 (C-9), 55.9 (C-5), 52.3 (C-31), 48.1 (C-4), 45.4 (C-14), 44.1 (C-8), 42.9 (C-20), 40.8 (C-18), 40.1 (C-1), 38.0 (C-22), 36.9 (C-10), 36.4 (C-16), 36.0 (C-17), 34.6 (C-2), 33.6 (C-7), 32.2 (C-21), 28.9 (C-19), 27.1 (C-15), 26.8 (C-23), 21.9 (C-24), 21.2 (C-29), 21.1 (C-27), 19.3 (C-6), 18.8 (C-26), 16.4 (C-28), 16.2 (C-25) ppm; ESI-MS (MeOH): $m/z = 483.4$ (80%, $[M+H]^+$).

*(3α,18β) Methyl 3-amino-11-oxo-olean-12-en-30 oate (**9**) and (3β,18β) methyl 3-amino-11-oxo-olean-12-en-30-oate (**10**)*
As previously reported [11], these compounds were prepared from **7** (2.0 g, 4.12 mmol), ammonium acetate and sodium cyanoborohydride in methanol, and **9** (0.4 g, 20%) and **10** (1.40 g, 52%) were obtained, each as a colorless solid.

Data for **9**: m.p. 212–215°C; $[\alpha]_D = 114.3°$ ($c = 0.35$, $CHCl_3$); $R_f = 0.71$ (silica gel, $CHCl_3$/MeOH, 8:2).

Data for **10**: m.p. 206°C; $[\alpha]_D = 121.8°$ ($c = 0.57$, $CHCl_3$); $R_f = 0.64$ (silica gel, $CHCl_3$/MeOH, 8:2).

*(3α,18α) Methyl 3-amino-11-oxo-olean-12-en-30-oate (**11**) and (3β,18α) methyl 3-amino-11-oxo-olean-12-en-30-oate (**12**)*
Reductive amination of **8** (2.78 g, 56.43 mmol) with ammonium acetate (4.5 g, 58.35 mmol) in methanol (150 mL) and sodium cyanoborohydride (3.56 g, 56.43 mmol) for 24 h followed by chromatographic purification (silica gel, $CHCl_3$/MeOH, 20:1) gave **11** (222 mg, 8.1%) and **12** (864 mg, 31.6%).

Data for **11**: m.p. 204–206°C; $[\alpha]_D = 76.2°$ ($c = 0.36$, $CHCl_3$); $R_f = 0.56$ (silica gel, $CHCl_3$/MeOH, 9:1); IR (KBr): $\nu = 3445$br, 2950br, 2360w, 1727s, 1663s, 1539s, 1456s, 1384br, 1228s, 1192s, 1160m, 1115s, 1076m, 1035m, 1015m, 991m cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 246.0 (4.14) nm; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.55$ (*s*, 1H, H-12), 3.68 (*s*, 3H, H-31), 3.11 (*s*, 1H, H-3), 2.55 (*s*, 1H, H-9), 2.51 (*d*, $J = 14.4$ Hz, 1H, H-1a), 2.22 (*d*, $J = 12.2$ Hz, 1H, H-18), 2.13–2.04 (*m*, 1H, H-2a), 1.99–1.91 (*m*, 1H, H-15a), 1.90 (*dd*, $J = 13.4$, 3.6 Hz, 1H, H-19a), 1.75 (*d*, $J = 12.5$ Hz, 2H, H-2a + H-7a), 1.66 (*dd*, $J = 12.8$ Hz, 1H, H-21a), 1.59–1.52 (*m*, 2H, H-21b + H-22b), 1.52–1.45 (*m*, 1H, H-19b), 1.45–1.37 (*m*, 4H, H-6a, H-7b, H-16a, H-22b), 1.41–1.36 (*m*, 2H, H-6b + H-16b), 1.34 (*s*, 3H, H-29), 1.37–1.32 (*m*, 1H, H-5), 1.30–1.23 (*m*, 2H, H-1b + H-15b), 1.21 (*s*, 3H, H-27), 1.20 (s, 3H, H-25), 1.10 (*s*, 3H, H-26), 1.03 (*s*, 3H, H-23), 0.95 (*s*, 3H, H-24), 0.70 (*s*, 3H, H-28) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.0$ (C-11), 179.1 (C-30), 166.2 (C-13), 124.3 (C-12), 60.1 (C-9), 58.6 (C-3),

ARCH PHARM
Archiv der Pharmazie

52.3 (C-31), 47.9 (C-5), 45.4 (C-14), 44.3 (C-8), 43.0 (C-20), 40.8 (C-18), 38.1 (C-22), 37.0 (C-10), 36.4 (C-16), 35.9 (C-17), 35.8 (C-4), 33.8 (C-7), 32.8 (C-1), 32.2 (C-21), 28.9 (C-19), 28.2 (C-23), 27.1 (C-15), 23.3 (C-24), 22.2 (C-2), 21.2 (C-29), 21.0 (C-27), 18.9 (C-26), 17.9 (C-6), 17.0 (C-25), 16.4 (C-28) ppm; ESI-MS (MeOH): $m/z = 484.3$ (100%, $[M+H]^+$); analysis calcd. for $C_{31}H_{49}NO_3$ (483.73): C 76.97, H 10.21, N 2.90; found: C 76.71, H 10.44, N 2.81.

Data for **12**: m.p. 212–213°C; $[\alpha]_D = 86.5°$ ($c = 0.32$, $CHCl_3$); $R_f = 0.44$ (silica gel, $CHCl_3$/MeOH, 9:1); IR (KBr): $\nu = 3446$br, 2948br, 2361w, 1727s, 1663s, 1538s, 1456s, 1385br, 1227s, 1193s, 1158m, 1114s, 1074m, 1033m, 1016m, 992m cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 248.3 (4.07) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.60$ (*s*, 1H, H-12), 3.68 (*s*, 3H, H-31), 3.05–2.94 (*m*, 1H, H-3), 2.76 (*d*, $J = 13.6$ Hz, 1H, H-1a), 2.27 (*s*, 1H, H-9), 2.23 (*d*, $J = 11.8$ Hz, 1H, H-18), 1.98 (*dd*, $J = 13.9$, 4.7 Hz, 1H, H-15a), 1.95–1.79 (*m*, 3H, H-2 + H-19a), 1.71–1.55 (*m*, 3H, H-6a + H-7a + H-21a), 1.54–1.47 (*m*, 2H, H-21b + H-22a), 1.49–1.43 (*m*, 2H, H-7b + H-19b), 1.44–1.39 (*m*, 3H, H-6b + H-16a + H-22b), 1.39–1.33 (*m*, 1H, H-16b), 1.33 (*s*, 3H, H-29), 1.29–1.23 (*m*, 1H, H-15b), 1.21 (*s*, 3H, H-27), 1.20 (*s*, 3H, H-24), 1.13 (*s*, 3H, H-23), 1.11 (*s*, 3H, H-26), 1.03 (*dd*, $J = 14.2$, 4.0 Hz, 1H, H-1b), 0.96 (*s*, 3H, H-25), 0.79 (*d*, $J = 11.4$ Hz, 1H, H-5), 0.70 (*s*, 3H, H-28) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 199.8$ (C-11), 179.2 (C-30), 166.3 (C-13), 124.5 (C-12), 61.1 (C-3), 60.8 (C-9), 55.6 (C-5), 52.4 (C-31), 45.4 (C-14), 44.2 (C-8), 43.0 (C-20), 40.9 (C-18), 39.2 (C-1), 38.0 (C-22), 37.2 (C-10), 36.4 (C-16), 36.0 (C-17), 34.1 (C-7), 34.0 (C-4), 32.2 (C-21), 28.9 (C-19), 28.3 (C-23), 27.1 (C-15), 23.6 (C-2), 21.2 (C-29), 21.1 (C-27), 19.0 (C-26), 18.0 (C-6), 16.7 (C-25), 16.5 (C-24), 16.2 (C-28) ppm; ESI-MS (MeOH): $m/z = 484.3$ (100%, $[M+H]^+$); analysis calcd. for $C_{31}H_{49}NO_3$ (483.73): C 76.97, H 10.21, N 2.90; found: C 76.77, H 10.41, N 2.78.

*(3β) Methyl 3-acetoxy-13-carboxy-19-hydroxy-11-oxo-C-norolean-18-en-30-oate-12,19-lactone (**13**) and (3β) methyl 3-acetoxy-11-oxo-12,19-selena-olean-12,18-diene-30-oate (**16**)*

To a solution of **3** (0.8 g, 1.56 mmol) in glacial acetic acid (50 mL), freshly sublimed SeO_2 (0.8 g, 7.45 mmol) was added, and the mixture was heated for 20 h at 120°C. Another portion of SeO_2 (0.8 g, 7.45 mmol) was added, and heating was continued for another 4 h. After cooling to 25°C, the mixture was filtered, water (150 mL) was added, and the mixture was extracted with DCM (4 × 50 mL). After drying (Na_2SO_4), the solvents were removed at diminished pressure and the residue was subjected to chromatography (silica gel, hexanes/ethyl acetate, 9:1) to yield **13** (0.4 g, 50%) and **16** (141 mg, 15%) both as an off-white solid.

Data for **13**: m.p. 285–289°C (lit.: [27] 285–286°C, 288–290°C [57]); $[\alpha]_D = +2.99°$ ($c = 0.5$ $CHCl_3$) (lit.: [57] 2.4° ($c = 3.5$, $CHCl_3$)); $R_f = 0.52$ (silica gel, toluene/ethyl acetate/heptane/formic acid, 80:20:30:4); IR (KBr): $\nu = 3449$br, 3024w, 2970m, 2948m, 1778s, 1736s, 1690w, 1449m, 1382m, 1369m, 1248s, 1218m, 1197m, 1153m, 1081m, 1109m, 1081m, 1058m, 1024m, 1010m, 980m cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 232 (2.22) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.55$ (*dd*, $J = 9.2$, 7.4 Hz, H-3), 3.72 (*s*, 3H, H-31), 3.08 (*s*, 1H, H-9), 2.33 (*ddd*, $J = 13.9$, 13.9, 3.3 Hz, 1H, H-21a), 2.07 (*ddd*, $J = 14.0$, 7.0, 3.5 Hz, 1H, H-1a), 2.04 (*s*, 3H, H-33), 1.87 (*ddd*, $J = 15.0$, 14.9, 3.6 Hz, 1H, H-16a), 1.76 (*ddd*, $J = 13.9$, 6.6, 3.3 Hz, 1H, H-21b), 1.76–1.65 (*m*, 4H, H-15a + H-6a + H-2), 1.63–1.53 (*m*, 4H, H-7 + H-22a + H-6b), 1.47 (*ddd*, $J = 13.6$, 6.9, 3.4 Hz, 1H, H-22b), 1.42 (*s*, 3H, H-29), 1.45–1.38 (*m*, 1H, H-16b), 1.32–1.18 (*m*, 2H, H-15b + H-1b), 1.18 (*s*, 3H, H-26), 1.16 (*s*, 6H, H-25 + H-28), 1.11 (*s*, 3H, H-27), 0.96–0.90 (*m*, 1H, H-5), 0.88 (*s*, 6H, H-23 + H-24) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.9$ (C-11), 174.7 (C-30), 174.4 (C-12), 170.9 (C-32), 151.5 (C-19), 119.2 (C-18), 80.5 (C-3), 67.8 (C-13), 65.6 (C-9), 55.3 (C-5), 52.9 (C-31), 48.5 (C-14), 43.4 (C-20), 42.4 (C-8), 37.9 (C-4), 36.8 (C-1), 36.6 (C-16), 35.8 (C-10), 35.3 (C-22), 34.1 (C-7), 32.8 (C-15), 31.4 (C-21), 30.8 (C-17), 28.2 (C-23), 26.9 (C-28), 26.8 (C-27), 23.4 (C-26), 23.3 (C-2), 21.4 (C-33), 21.3 (C-29), 18.9 (C-6), 17.3 (C-25), 16.5 (C-24) ppm; ESI-MS (MeOH): $m/z = 555.3$ (22%, $[M+H]^+$).

Data for **16**: m.p. 199–201°C; $[\alpha]_D = 9.23°$ ($c = 0.27$, $CHCl_3$); $R_f = 0.67$ (silica gel, toluene/ethyl acetate/heptane/formic acid, 80:20:30:4); IR (KBr): $\nu = 3854$w, 3448br, 2949m, 1734s, 1641s, 1469m, 1364m, 1244s, 1121m, 1029m cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 307 (3.87) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.52$ (*dd*, $J = 11.4$, 5.1 Hz, 1H, H-3), 3.75 (*s*, 3H, H-31), 3.00 (*ddd*, $J = 13.6$, 7.3, 3.6 Hz, 1H, H-1a), 2.88–2.80 (*m*, 1H, H-21a), 2.81 (*s*, 1H, H-9), 2.07 (*dd*, $J = 14.0$, 14.0, 3.7 Hz, 1H, H-16a), 2.03 (*s*, 3H, H-33), 1.83 (*ddd*, $J = 14.3$, 6.8, 3.4 Hz, 1H, H-21b), 1.74 (*ddd*, $J = 14.0$, 14.0, 3.7 Hz, 1H, H-16a), 1.70–1.61 (*m*, 6H, H-22 + H-7a + H-2 + H6a), 1.60–1.48 (*m*, 2H, H-7b + H-16b), 1.48 (*s*, 3H, H-29), 1.42 (*ddd*, $J = 12.7$, 12.7, 3.0 Hz, 1H, H-6b), 1.32 (*s*, 3H, H-27), 1.26 (*ddd*, $J = 13.8$, 6.4, 3.3 Hz, 1H, H-15b), 1.16 (*s*, 3H, H-25), 1.15–1.10 (*m*, 1H, H-1b), 1.06 (*s*, 3H, H-28), 1.02 (*s*, 3H, H-26), 0.91–0.85 (*m*, 1H, H-5), 0.87 (*s*, 6H, H-23 + H-24) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 193.9$ (C-11), 176.1 (C-30), 171.1 (C-32), 156.7 (C-13), 153.9 (C-18), 143.2 (C-12), 139.1 (C-19), 80.7 (C-3), 63.7 (C-9), 55.8 (C-5), 52.8 (C-31), 48.6 (C-14), 48.2 (C-20), 45.4 (C-8), 39.0 (C-1), 38.4 (C-10), 38.3 (C-4), 34.8 (C-17), 34.4 (C-16), 34.1 (C-22), 33.5 (C-7), 32.3 (C-29), 30.4 (C-21), 28.3 (C-23), 28.1 (C-28), 25.4 (C-15), 24.3 (C-27), 23.8 (C-2), 21.5 (C-33), 19.2 (C-26), 17.4 (C-6), 17.0 (C-25), 16.8 (C-24) ppm; ^{77}Se NMR (95 MHz, $CDCl_3$): $\delta = 592.27$ ppm; ESI-MS (MeOH): $m/z = 603.3$ (100%, $[M+H]^+$); analysis calcd. for $C_{33}H_{46}O_5Se$ (601.68): C 65.87, H 7.71; found: C 65.69, H 7.82.

*(3β, 18β) 3-Acetoxy-18-hydroxy-11-oxo-olean-12-en-30-oic acid-30,18-lactone (**14**)*

Reaction of **6** (0.922 g, 1.75 mmol) with SeO_2 (0.92 g, 8.32 mmol) in glacial acetic acid (18 mL) for 4 h at 145°C (microwave assisted; monowave 300, Anton Parr) followed by usual work-up and chromatographic purification (hexanes/ethyl acetate, 10:2) gave **13** (354 mg, 36.5%) and **14** (100 mg, 11%); data for **14**: m.p. 347–349°C (lit.: [32] 343–345°C; 318–320°C [34]); $[\alpha]_D = 122.3°$ ($c = 0.43$, $CHCl_3$) (lit.: [34] 152.6° ($CHCl_3$)); $R_f = 0.23$ (silica gel, toluene/heptane/ethyl acetate/formic acid, 80:15:10:4); IR (KBr): $\nu = 3447$br, 2953m, 2873m,

1773s, 1736s, 1665s, 1457w, 1384m, 1326w, 1250s, 1194m, 1145m, 1051m, 1028m, 1002w, 986m, 948m cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 240.9 (4.00) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.08 (*s*, 1H, H-12), 4.50 (*dd*, *J* = 11.8, 4.7 Hz, 1H, H-3), 2.74 (*ddd*, *J* = 13.5, 3.4, 3.4 Hz, 1H, H-1a), 2.57 (*d*, *J* = 11.7 Hz, 1H, H-19a), 2.30 (*s*, 1H, H-9), 2.13 (*ddd*, *J* = 13.8, 4.8, 4.8 Hz, 1H, H-22a), 2.04 (*s*, 3H, H-33), 1.94 (*ddd*, *J* = 13.8, 5.5, 5.5 Hz, 1H, H-15a), 1.84 (*dd*, *J* = 11.7, 2.1 Hz, 1H, H-19b), 1.74–1.71 (*m*, 1H, H-21a), 1.72–1.65 (*m*, 1H, H-2a + H-21b), 1.63–1.60 (*m*, 3H, H-7a + H-16), 1.60–1.56 (*m*, 2H, H-2b + H-6a), 1.48 (*dd*, *J* = 12.3, 3.2 Hz, 1H, H-6b), 1.46–1.40 (*m*, 2H, H-7b + H-22b), 1.38 (*s*, 3H, H-27), 1.24 (*dd*, *J* = 13.1, 4.7 Hz, 1H, H-15b), 1.18 (*s*, 3H, H-29), 1.18 (*s*, 3H, H-26), 1.17 (*s*, 3H, H-25), 1.03 (*ddd*, *J* = 13.5, 3.5, 3.5 Hz, 1H, H-1b), 0.95 (*s*, 3H, H-28), 0.87 (*s*, 3H, H-23), 0.87 (*s*, 3H, H-24), 0.78 (*d*, *J* = 11.0 Hz, 1H, H-5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.4 (C-11), 179.1 (C-30), 171.1 (C-13), 162.4 (C-31), 123.1 (C-12), 87.7 (C-18), 80.6 (C-3), 61.4 (C-9), 55.1 (C-5), 50.2 (C-19), 45.7 (C-8), 44.6 (C-14), 44.0 (C-20), 39.0 (C-1), 38.2 (C-4), 37.0 (C-10), 36.6 (C-17), 35.0 (C-16), 32.9 (C-7), 32.8 (C-21), 31.4 (C-22), 28.2 (C-23), 27.1 (C-15), 23.6 (C-2), 23.2 (C-28), 22.3 (C-27), 21.4 (C-32), 20.7 (C-29), 18.7 (C-26), 17.5 (C-6), 16.8 (C-24), 16.6 (C-25) ppm; ESI-MS (MeOH): *m/z* = 511.4 (100%, $[M+H]^+$).

*(3β) Methyl 3-acetyloxy-11-oxo-12,19-olean-12,18-dien-30-oate (**15**)*

A mixture of **3** (0.3 g, 0.57 mmol) and SeO_2 (0.3 g, 2.70 mmol) in pyridine (20 mL) was heated in a microwave (Monowave 300, Anton Parr, 160°C, 3 h). The reaction mixture was filtered, and the solvent was removed. The semi-solid residue was dissolved in DCM (100 mL) and aq. HCl (0.1 M, 100 mL), the organic layer was separated, dried ($MgSO_4$), the solvent was removed, and the residue subjected to chromatography (silica gel, hexanes/ethyl acetate, 8:2) to yield **15** (160 mg, 52%) as a colorless solid; m.p. 228–230°C; $[\alpha]_D$ = 114.09° (*c* = 0.32, $CHCl_3$); R_f = 0.40 (hexanes/ethyl acetate, 8:2); IR (KBr): ν = 2930 s, 1741s, 1725s, 1660s, 1575w, 1503m, 1454m, 1371m, 1251s, 1146m, 1114m, 1030m cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 299 (4.21) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.52 (*dd*, *J* = 11.7, 4.8 Hz, 1H, H-3), 3.73 (*s*, 3H, H-31), 2.99 (*ddd*, *J* = 13.7, 3.7, 3.7 Hz, 1H, H-1a), 2.75 (*s*, 1H, H-9), 2.61 (*ddd*, *J* = 14.2, 14.2, 3.9 Hz, 1H, H-21a), 2.08–2.00 (*m*, 1H, H-15a), 2.04 (*s*, 3H, H-33), 1.86 (*ddd*, *J* = 14.4, 3.6, 3.6 Hz, 1H, H-21b), 1.83–1.55 (*m*, 7H, H-2 + H-6a + H-7a + H-16 + H-22a), 1.52–1.39 (*m*, 3H, H-6b + H-7b + H-22b), 1.38 (*s*, 3H, H-29), 1.35 (*s*, 3H, H-27), 1.31 (*ddd*, *J* = 13.6, 3.1, 3.1 Hz, 1H, H-15b), 1.21 (*s*, 3H, H-25), 1.14 (*s*, 3H, H-28), 1.10 (*ddd*, *J* = 13.4, 13.4, 3.9, 1H, H-1b), 1.01 (*s*, 3H, H-26), 0.89–0.84 (*m*, 1H, H-5), 0.88 (*s*, 6H, H-23 + H-24) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.4 (C-11), 175.0 (C-30), 174.9 (C-32), 155.4 (C-19), 145.0 (C-13), 144.1 (C-12), 126.1 (C-18), 80.7 (C-3), 63.8 (C-9), 56.2 (C-5), 52.8 (C-31), 52.1 (C-14), 45.4 (C-20), 39.2 (C-8), 38.9 (C-1), 38.4 (C-4), 38.4 (C-10), 34.6 (C-22), 34.5 (C-16), 34.1 (C-7), 33.7 (C-21), 30.1 (C-17), 28.3 (C-23), 26.5 (C-28), 26.2 (C-15), 24.1 (C-29), 23.8 (C-2), 22.9 (C-27), 21.4 (C-33), 18.6 (C-26), 17.3 (C-25), 17.2 (C-6), 16.9 (C-24) ppm; ESI-MS (MeOH): *m/z* = 539.4 (100%, $[M+H]^+$); analysis calcd. for $C_{34}H_{50}O_6$ (558.36): C 73.61, H 9.08; found: C 73.42, H 9.21.

We would like to thank Dr. R. Kluge for measuring the ESI-MS spectra, Dr. D. Ströhl for the NMR spectra, and Mrs. J. Wiese and Mr. M. Sahn for skillful experimental help in the synthesis and analysis of the compounds. The cell lines were kindly provided by Dr. Th. Müller (Dept. of Haematology/Oncology, Universität Halle-Wittenberg). Support by the "Gründerwerk-statt-Biowissenschaften" as well as by the Oman Research Council (ORG/HSS/14/004) is gratefully acknowledged.

The authors have declared no conflicts of interest.

References

[1] Available online at http://www.who.int/mediacentre/factsheets/fs297/en, accessed 10.08.2015.
[2] B. A. Chabner, T. G. Roberts, *Nat. Rev. Cancer* **2005**, *5*, 65–72.
[3] I. Beseda, L. Czollner, P. S. Shah, R. Khunt, R. Gaware, P. Kosma, C. Stanetty, M. C. del Ruiz-Ruiz, H. Amer, K. Mereiter, T. Da Cunha, A. Odermatt, D. Classen-Houben, U. Jordis, *Bioorg. Med. Chem*. **2010**, *18*, 433–454.
[4] C. Fiore, M. Eisenhut, E. Ragazzi, G. Zanchin, D. Armanini, *J. Ethnopharmacol*. **2005**, *99*, 317–324.
[5] L. Ruzicka, M. Furter, H. Leuenberger, *Helv. Chim. Acta* **1937**, *20*, 312–25.
[6] S. Chintharlapalli, S. Papineni, I. Jutooru, A. McAlees, S. Safe, *Mol. Cancer Ther*. **2007**, *6*, 1588–1598.
[7] R. Csuk, *Mini-Rev. Org. Chem*. **2014**, *11*, 253–261.
[8] S. Schwarz, S. D. Lucas, S. Sommerwerk, R. Csuk, *Bioorg. Med. Chem*. **2014**, *22*, 3370–3378.
[9] R. Csuk, S. Schwarz, B. Siewert, R. Kluge, D. Ströhl, *Z. Naturforsch. B* **2012**, *67*, 731–746.
[10] R. Csuk, S. Schwarz, B. Siewert, R. Kluge, D. Ströhl, *Arch. Pharm*. **2012**, *345*, 223–230.
[11] R. Csuk, S. Schwarz, B. Siewert, R. Kluge, D. Ströhl, *Eur. J. Med. Chem*. **2011**, *46*, 5356–5369.
[12] R. Csuk, S. Schwarz, R. Kluge, D. Ströhl, *Arch. Pharm*. **2011**, *344*, 505–513.
[13] R. Csuk, S. Schwarz, B. Siewert, R. Kluge, D. Ströhl, *Z. Naturforsch. B* **2011**, *66*, 521–532.
[14] R. Csuk, S. Schwarz, R. Kluge, D. Ströhl, *Eur. J. Med. Chem*. **2010**, *45*, 5718–5723.
[15] S. Schwarz, R. Csuk, *Bioorg. Med. Chem*. **2010**, *18*, 7458–7474.
[16] L. A. Baltina, *Curr. Med. Chem*. **2003**, *10*, 155–171.
[17] K. Kalani, V. Kushwaha, R. Verma, P. K. Murthy, S. K. Srivastava, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 2566–2570.
[18] N. Ullah, W. Seebacher, E. Haslinger, J. Jurenitsch, K. Rauchensteiner, R. Weis, *Monatsh. Chem*. **2002**, *133*, 139–150.

[19] C. H. Brieskorn, W. Wallenstätter, *Arch. Pharm*. **1967**, *300*, 717–725.
[20] H. Duddeck, M. H. A. Elgamal, G. S. Ricca, B. Danieli, G. Palmisano, *Org. Magn. Reson*. **1978**, *11*, 130–132.
[21] T. Terasawa, T. Okada, T. Hara, K. Itoh, *Eur. J. Med. Chem*. **1992**, *27*, 345–351.
[22] J. M. Beaton, F. S. Spring, *J. Chem. Soc*. **1955**, 3126–3129.
[23] T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal*. **2010**, *352*, 753–819.
[24] F. Manescalchi, A. R. Nardi, D. Savoia, *Tetrahedron Lett*. **1994**, *35*, 2775–2778.
[25] C. H. Brieskorn, H. Eschelbach, *Arch. Pharm*. **1979**, *312*, 752–762.
[26] H.-O. Kim, M. I. Goryaev, M. P. Irismetov, K. A. Alibaeva, *Izv. Akad. Nauk Kaz. SSR Ser. Khim*. **1972**, *22*, 86–87.
[27] O. Jeger, J. Norymberski, L. Ruzicka, *Helv. Chim. Acta* **1944**, *27*, 1532–1543.
[28] R. Gaware, L. Czollner, U. Jordis, K. Mereiter, *Acta Cryst. E* **2010**, *66*, O2597–U800.
[29] R. Csuk, B. Siewert, J. Wiemann, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 3542–3546.
[30] B. Siewert, J. Wiemann, A. Köwitsch, R. Csuk, *Eur. J. Med. Chem*. **2014**, *72*, 84–101.
[31] R. Sanduja, A. J. Weinheimer, M. Alam, M. B. Hossain, D. Vanderhelm, *J. Chem. Soc. Chem. Commun*. **1984**, 1091–1093.
[32] M. H. A. Elgamal, F. K. A. Hady, A. G. Hanna, G. H. Mahran, H. Duddeck, *Z. Naturforsch. C* **1990**, *45*, 937–941.
[33] Y. Hashimoto, H. Ishizone, M. Suganuma, M. Ogura, K. Nakatsu, H. Yoshioka, *Phytochemistry* **1983**, *22*, 259–264.
[34] R. K. Gayanov, K. O. Kim, M. P. Irismetov, M. I. Goryaev, *Zh. Obshch. Khim*. **1978**, *48*, 920–922.
[35] L. Canonica, B. Danieli, P. Manitto, G. Russo, *Gazz. Chim. Ital*. **1966**, *96*, 843–51.
[36] A. A. Frimer, P. Gilinskysharon, G. Aljadeff, *Tetrahedron Lett*. **1982**, *23*, 1301–1304.
[37] A. A. Frimer, P. Gilinskysharon, J. Hameiri, G. Aljadeff, *J. Org. Chem*. **1982**, *47*, 2818–281.
[38] B. Camerino, B. Patelli, R. Sciaky, *Gazz. Chim. Ital*. **1962**, *92*, 693–708.
[39] B. Camerino, B. Patelli, R. Sciaky, *Gazz. Chim. Ital*. **1962**, *92*, 676–92.
[40] R. J. Langenbach, H. W. Knoche, *Steroids* **1968**, *11*, 123.
[41] J. Jasiczak, *J. Chem. Soc. Perkin Trans*. **1988**, *1*, 2687–2692.
[42] S. Tsuboi, K. Watanabe, S. Mimura, A. Takeda, *Tetrahedron Lett*. **1986**, *27*, 2643–2644.
[43] T. M. Nguyen, I. A. Guzei, D. Lee, *J. Org. Chem*. **2002**, *67*, 6553–6556.
[44] T. M. Nguyen, D. Lee, *Org. Lett*. **2001**, *3*, 3161–3163.
[45] Z. No, Y. B. Chae, C. J. Shin, Y. Chung, *Tetrahedron Lett*. **1998**, *39*, 6191–6194.
[46] M. M. Li, X. Q. Su, J. Sun, Y. F. Gu, Z. Huang, K. W. Zeng, Q. Zhang, Y. F. Zhao, D. Ferreira, J. K. Zjawiony, J. Li, P. F. Tu, *J. Nat. Prod*. **2014**, *77*, 2248–2254.
[47] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. Mcmahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney, M. R. Boyd, *J. Nat. Cancer Inst*. **1990**, *82*, 1107–1112.
[48] B. Siewert, R. Csuk, *Eur. J. Med. Chem*. **2014**, *74*, 1–6.
[49] B. Siewert, E. Pianowski, A. Obernauer, R. Csuk, *Bioorg. Med. Chem*. **2014**, *22*, 594–615.
[50] B. Siewert, E. Pianowski, R. Csuk, *Eur. J. Med. Chem*. **2013**, *70*, 259–272.
[51] L. Canonica, G. Russo, E. Bombardelli, *Gazz. Chim. Ital*. **1966**, *96*, 833–842.
[52] N. K. Abubakirov, V. K. Yatsyn, *Med. Prom-st. SSSR* **1960**, *14*, 31–34.
[53] W. Voss, P. Klein, H. Sauer, *Ber. Dtsch. Chem. Ges. B* **1937**, *70B*, 122–132.
[54] L. R. Mikhailova, L. A. Baltina, Jr., L. A. Baltina, R. M. Kondratenko, S. A. Nepogodiev, R. A. Field, O. Kunert, M. C. Yin, *Russ. J. Bioorg. Chem*. **2009**, *35*, 619–627.
[55] X. D. Su, H. Lawrence, D. Ganeshapillai, A. Cruttenden, A. Purohit, M. J. Reed, N. Vicker, B. V. L. Potter, *Bioorg. Med. Chem*. **2004**, *12*, 4439–4457.
[56] D. V. Ignatov, Y. I. Prokof'ev, O. M. Ipatova, V. P. Timofeev, N. V. Medvedeva, A. Y. Misharin, *RussJ. Bioorg. Chem*. **2003**, *29*, 390–394.
[57] G. Brownlie, F. S. Spring, *J. Chem. Soc*. **1956**, 1949–1953.