Full Paper

Synthesis and Biological Evaluation of Antitumor-Active Arglabin Derivatives

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Arglabin derivatives varied at the endo- or exo-cyclic double bond were synthesized and studied in a colorimetric sulforhodamine B assay for their cytotoxicity. Variations on the endocyclic double bond led to compounds of reduced cytotoxicity whereas derivatives from the reaction of the α-methylene-γ-butyrolactone moiety led to compounds of similar or only slightly reduced cytotoxicity but different, cell line-dependent selectivity. In addition, arglabin is an excellent starting material for the synthesis of the guaianolide arborescin.

Keywords: Arglabin / Arborescin / Antitumor activity / Guaianolides

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Introduction

Cancer is a leading cause of death affecting people worldwide. Chemotherapy is most often applied alone or following surgery or radiation of tumors. Chemotherapeutic agents usually affect both tumor and rapidly growing cells of normal tissue like the cells of the intestinal epithelium, hair follicles and bone marrow. Thus, developing a chemotherapeutic agent with minimal toxicity would be rewarding.

The guaianolides represent one of the largest groups of sesquiterpene lactones. Many of them have been shown to hold biological/medical activities, among them contraceptive [1, 2], antihelmintic [3], antishistosomal [4–6] and antitumor [7, 8] activity. Several years ago it has been noted that the guaianolide arglabin (**1**, Fig. 1) and several of its derivatives have a noteworthy antitumor activity and that they show less side effects than other chemotherapeutic agents. As a consequence, arglabin was approved for use in several countries for treating lung, liver and ovarian cancer [9–11].

Arglabin is a sesquiterpene-γ-lactone and can be isolated from the plants [12] of *Artemisia glabella*, a species of wormwood endemic to the Karaganda region of Kazakhstan, and from *Artemisia myriantha* – a plant [13–15] well-known in traditional Chinese medicine as a treatment for several diseases. Recently, a total synthesis of enantiomerically pure **1** has been elaborated [16].

Arglabin is assumed [17, 18] to prevent protein farnesylation without altering geranylgeranylation; thus, this compound inhibits post-translational modification of ras protein in cells. Because of limited access to **1**, only a few derivatives of arglabin have been prepared [11, 19–21] so far. In this study, we set out to synthesize some more derivatives of **1** and to evaluate their antitumor activity.

Results and discussion

Crude arglabin (by extraction from the dried plant material, purity 65–85% by HPLC) had to be purified to perform useful and reproducible reactions. Chromatography followed by repeated re-crystallizations from hexane was tedious but gave **1** of >98% purity.

Reaction of **1** with an ethanolic solution of dimethylamine [22] (Scheme 1) followed by acidic work-up (HCl) gave low yields of **2.HCl** [23]. Reaction of **1**, however, with Dimcarb [24, 25] in dry acetonitrile for one day gave 82% of isolated **2**. Its treatment with dry HCl in ethyl acetate gave 80% of the hydrochloride **2.HCl**. Yields dropped significantly, however, on scaling-up of this reaction. As an alternative, to a solution of **1** in MTBE, dry methanol and acetyl chloride [26]

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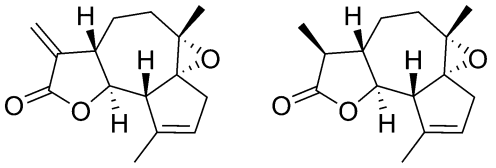


1 **13**

Figure 1. Structure of the guaianolides arglabin (**1**) and arborescin (**13**).

were slowly added at temperatures <10°C and **2.HCl** was obtained in 92% yield.

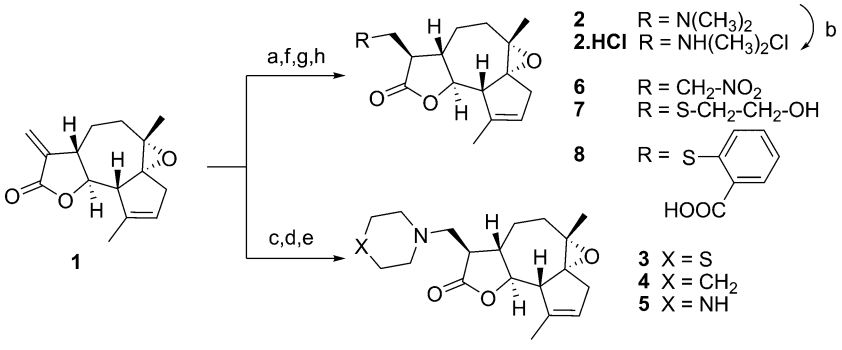
Reaction of **1** with thiomorpholine, piperidine or piperazine yielded the addition products **3–5** in 72–81% yield. Compounds **3–5** show in their ^{13}C-NMR spectra signals between δ = 54–57 ppm that matches to the methylenic carbon C-12. Addition of nitromethane to **1** in the presence of catalytic amounts of DBU [27] yielded 66% of the nitro compound **6**. From the similar reaction of **1** with 2-mercaptoethanol, compound **7** was obtained in 62.5% yield; reaction of **1** with 2-mercaptobenzoic acid gave the thioether **8**.

All of these reactions advanced smoothly at the exocyclic methylene group of the anellated α-methylene-γ-butyrolactone unit of arglabin. Interestingly enough, a cyclopropanation with ethyl diazoacetate in the presence of $[Rh(OAc)_2]_2$ (Scheme 2) did not affect this methylene group. Because of the −M effect of the adjacent lactone group this methylene group is deficient of electrons and therefore unreactive towards this reagent. Compound **9** was formed in 53% yield and is characterized in its ^{13}C NMR spectrum by the presence of extra signals at δ = 171.3 ppm (ester carbonyl) and the signals of the ethyl substituent.

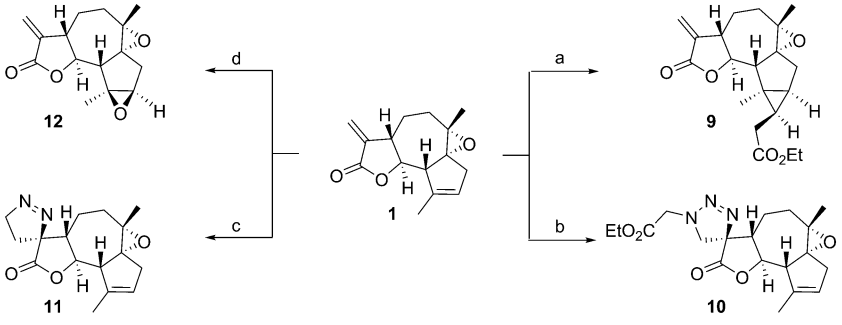
Assignments of the absolute configuration of the newly created stereogenic centers were performed by NMR: Since NOESY-NMR spectra show vicinity between H-8a and H-1 and $^3J_{H\text{-}1,H\text{-}1a}$ = 12.2 Hz (being typical for an axial/axial orientation) the abs. configuration of C-1 is (*R*) and that of C-1a is (*S*). In addition, the four possible stereoisomers were subjected to conformational search using semiempirical MOPAC-PM3 (CAChe 4.0 software from Oxford Molecular) calculations. The analysis confirmed the (1a*S*,1*R*) isomer is most easily formed and possesses the lowest heat of formation compared to the other stereoisomers.

Whereas the reaction of diazomethane with α-methylene-γ-butyrolactones is a well-known reaction [28, 29], ''Click reactions'' have scarcely been performed [30]. Thus, no reaction of the endocyclic double bond was observed on the cycloaddition of **1** with ethyl azidoacetate in the presence of CuI [31] or from its reaction with diazomethane. The corresponding 7,4'[1,2,3]triazole derivative **10** and the 7,3'-pyrazole **11** were obtained in 46% and quantitative yield, respectively.

Whereas the reaction of **1** with peracetic acid was reported [32] to give a mixture of two possible stereoisomeric epoxides,



Scheme 1. Reagents and conditions: a) MeCN, Dimcarb, 25°C, 24 h, 82%; b) MeOH/AcCl, MTBE, 10°C, 30 min, 92%; c) thiomorpholine, EtOH, 48 h, 25°C, 72%; d) piperidine, EtOH, 12 h, 25°C, 78%; e) piperazine, EtOH, 12 h, 25°C, 81%; f) $MeNO_2$, DBU (cat.), 24 h, 25°C, 66%; g) 2-mercaptoethanol, DBU (cat.), EtOH, 6 h, 25°C, 62.5%; h) 2-mercaptobenzoic acid, DBU (cat.), EtOH, 48 h, 25°C, 62.8%.



Scheme 2. Reagents and conditions: a) ethyl diazoacetate, $[(Rh(OAc)_2]_2$, 2 h, 25°C, 52.6%; b) ethyl azidoacetate, CuI, 5 d, 25°C, 46%; c) diazomethane, 2 h, 25°C, quant.; d) *m*CPBA, THF, 12 h, 10°C, 61%.

Table 1. Results of SRB-assay: The values (IC_{50} in μM) for melanoma (518A2), zervical cancer (A431), lung carcinoma (A549), ovarian cancer (A2780), colon cancer (DLD-1, HCT-8, HCT-116, HT-29), anaplastic thyroid cancer (8505C, SW-1736), mamma carcinoma (MCF-7) and liposarcoma cell lines were obtained by an SRB-assay after 96 h of treatment and are the average from at least three independent experiments; standard error 5%.

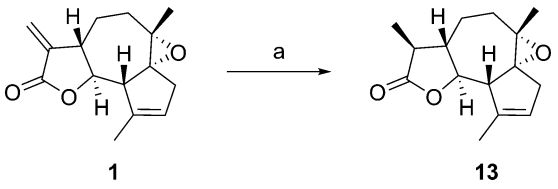
	1	2	3	4	5	6	7	8
518A2	6.72	5.54	13.21	14.30	15.02	11.51	16.94	16.87
8505C	1.68	4.57	3.85	14.46	15.07	14.83	14.07	14.85
A253	4.25	5.59	11.33	16.35	14.92	15.09	15.47	14.87
A2780	12.55	8.69	12.19	14.41	3.75	11.13	13.63	12.52
A431	4.48	5.19	16.88	18.93	4.40	14.83	12.82	13.64
A549	2.21	1.95	4.76	12.35	15.7	9.85	12.84	10.06
DLD-1	4.51	7.30	6.93	10.14	10.44	10.02	11.55	10.49
FADU	6.86	4.75	4.29	9.87	15.07	12.74	14.38	13.73
HCT-116	1.09	2.69	8.62	17.68	5.66	9.84	10.05	9.96
HCT-8	5.60	10.38	5.79	7.89	4.27	11.24	14.83	11.86
HT-29	7.00	10.76	16.20	8.13	15.07	12.72	18.61	17.82
LIPO	6.00	8.25	13.22	17.41	15.01	11.45	11.78	12.77
MCF-7	2.33	1.85	13.41	16.92	15.05	13.57	17.31	16.86
SW1736	3.85	5.58	5.01	14.24	15.87	15.62	14.53	16.84
SW480	4.46	6.52	18.22	18.11	17.48	17.12	17.85	15.51

epoxidation with *m*CPBA at 10°C advanced selectively to yield only one stereoisomer **12**.

The compounds were tested for their antitumor potential in a panel of 15 human cancer cell lines in 96 well plates using the colorimetric sulforhodamine B (SRB) [33] protocol. The calculated IC_{50} values in Table 1 were obtained from the corresponding dose-response curves; for compounds **9**–**11** IC_{50} values >30 μM were measured.

Substitution of the exocyclic double bond, however, led to compounds showing a modified selectivity for the cell lines compared to parent **1**. Of special interest seems **5** showing an $IC_{50} = 3.75$ μM with ovarian cancer cells A2780 whereas parent arglabin shows $IC_{50} = 12.55$ μM for this cell line.

Arglabin can also serve as a well accessible starting material for the synthesis of the guaianolide arborescin **13** (Fig. 1). Arborescin is guaianolide-type terpene and is structurally related to **1**; it was isolated [34] from *Artemisia arborescens*, a plant used for contraceptive purposes [1, 34] by ancient Arabs and Greeks. Hydrogenation of **1** (Scheme 3) using Pt/C or Pd/C always gave a mixture of several hydrogenation products. The *Lindlar* catalyst has widely been used for the chemoselective reduction of alkynes to alkenes, its use for the selective hydrogenation of olefins is unusual [35, 36]. Thus, hydrogenation of **1** in the presence of this catalyst gave a regioselective hydrogenation of the exocyclic double bond, and **13** was obtained in almost quantitative yields. Besides its cytotoxicity, arborescin shows significant antiplasmodial (*Plasmodium falsiparum*) activity and is – like arglabin – a tight binding substrate for the heterologously expressed human bitter receptors hTAS2R46 [37]. Our approach to arborescin provides higher yields compared to the previously published synthesis from α-santonin [38].



1 13

Scheme 3. Reagents and conditions: a) $Pd/BaSO_4$/quinoline, H_2 (20 psi), 2 h, 25°C, quant.

In summary, several arglabin derivatives were prepared exploiting the different reactivities of the endo- and exocyclic double bonds. Derivatives from the reaction of the α-methylene-γ-butyrolactone moiety led to compounds of similar or slightly reduced cytotoxicity but different, cell line-dependent selectivity whereas variations on the endocyclic double bond led to compounds of reduced cytotoxicity. In addition, arglabin can be used as an ideal starting material for the synthesis of the guaianolide arborescin.

Experimental

General

Melting points are uncorrected (*Leica* hot stage microscope), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, *J* in Hz, internal Me4Si), optical rotations were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell, 25°C), IR spectra (film or KBr pellet) on a Perkin-Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on an Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. TLC was performed on silica gel (Merck 5554, detection by UV absorption). The solvents

were dried according to usual procedures. The purity of arglabin was determined by HPLC (Merck Purosher C18e, 250 × 4 mm, 5 μm, H_2O/MeCN 1:1, 1 mL/min, 37°C, UV detection at λ = 210 nm, t_R = 8.5 min).

Cell lines and culture conditions

The cell lines 518A2, 8505C, A253, A2780, A431, A549, DLD-1, FaDu, HCT-116, HCT-8, HT-29, LIPO, MCF-7, SW1736, and SW480 were included in this study. Cultures were maintained as monolayer in RPMI 1640 (PAA Laboratories, Pasching, Germany) supplemented with 10% heat inactivated fetal bovine serum (Biochrom AG, Berlin, Germany) and penicillin/streptomycin (PAA Laboratories) at 37°C in a humidified atmosphere of 5% CO_2/ 95% air.

Cytotoxicity assay

The cytotoxicity of the compounds was evaluated using the sulforhodamine-B (SRB) (Sigma Aldrich) microculture colorimetric assay. In short, exponentially growing cells were seeded into 96-well plates on day 0 at the appropriate cell densities to prevent confluence of the cells during the period of experiment. After 24 h, the cells were treated with serial dilutions of the compounds (0–300 μM) for 96 h. The final concentration of DMSO or DMF solvent never exceeded 0.5%, which was non-toxic to the cells. The percentages of surviving cells relative to untreated controls were determined 96 h after the beginning of drug exposure. After a 96 h treatment, the supernatant medium from the 96 well plates was thrown away and the cells were fixed with 10% TCA. For a thorough fixation, the plates were allowed to rest at 4°C. After fixation, the cells were washed in a strip washer. The washing was done four times with water using alternate dispensing and aspiration procedures. The plates were then dyed with 100 μL of 0.4% SRB (sulforhodamine B) for about 20 min. After dying the plates were washed with 1% acetic acid to remove the excess of the dye and allowed to air dry overnight. 100 μL of 10 mM Tris base solution were added to each well and absorbance was measured at 570 nm (using a 96 well plate reader, Tecan Spectra, Crailsheim, Germany). The IC_{50} was estimated from the semi-logarithmic dose-response curves.

*(3aR,4aS,6aS,7R,9aS,9bR)-7-[(Dimethylamino)methyl]-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3H-oxireno[8,8a]-azuleno [4,5-b]furan-8(4aH)-on (**2**)*

A solution of arglabin (**1**) (4.0 g, 16.24 mmol) and Dimcarb (2.8 g, 20.80 mmol) in dry acetonitril (40 mL) was stirred at 24°C for 1 d. The solvent was removed and the crude product purified by chromatography (silica gel, chloroform/diethyl ether, 9:1) to yield **2** (3.88 g, 82%) as a white solid; mp 98–101°C; $[\alpha]_D = +43.2°$ (c = 1.9, $CHCl_3$); R_f = 0.42 ($CHCl_3$/Et_2O, 9:1); IR (KBr): ν = 3350 *m*, 2940 *s*, 2836 *m*, 2778 *m*, 2403 *m*, 1775 *s*, 1651 *s*, 1555 *m*, 1479 *m*, 1385 *s*, 1183 *m*, 1150 *m*, 1129 *m* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 243 nm (3.46); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.55 (*s*, 1 H, C*H* (2)), 3.95 (*dd*, 1 H, C*H* (9a), J = 10.8, 9.5 Hz), 2.81 (*d*, 1 H, C*H* (9b), J = 10.3 Hz), 2.75 (*d*, 1 H, J = 17.9 Hz, CH_a (3)), 2.59–2.41 (*m*, 1 H, C*H* (9a)), 2.28 (*m*, 2 H, CH_2 (7)), 2.25 (*s*, 6 H, 2 x CH_3 (13)), 2.13 (*d*, 2 H, J = 17.5 Hz, CH_b (3)), 2.10–2.05 (*m*, 2 H, CH_2 (5)), 1.99–1.91 (*m*, 2 H, CH_2 (12)), 1.95 (*s*, 3 H, C*H* (12)), 1.94–1.88 (*m*, 1 H, CH_b (3)), 1.61–1.40 (*m*, 2 H, CH_2 (6)), 1.31 (*s*, 3 H, CH_3 (11)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.5 (C8, C=O), 138,8 (C1, $C_{quart.}$), 125.4 (C2, *C*H), 83.3 (C9a, *C*H), 71.1 (C3a, $C_{quart.}$), 62.6 (C4a, $C_{quart.}$), 52.1 (C12, CH_2), 52.0 (C9b, *C*H), 51.8 (C6a, *C*H), 48.5 (2 × C13, CH_3), 40.9 (C7, *C*H), 39.4 (C3, CH_2), 32.9 (C5, CH_2), 21.4 (C6, CH_2), 18.2 (C11, CH_3) ppm; MS (ESI, MeOH): m/z = 292.2 ($[M+H]^+$); anal. calcd for $C_{17}H_{25}NO_3$ (291.39): C, 70.07; H, 8.65; N, 4.81; found: C, 69.82; H, 8.89; N, 4.71.

*[(3aR,4aS,6aS,7R,9aS,9bR)-1,4a-Dimethyl-8-oxo-4a,5,6,6a,7,8,9a,9b-octahydro-3H-oxireno[8,8a]azuleno-[4,5-b]furan-7-yl]-N,N dimethylmethanaminium chloride (**2.HCl**)*

To a solution of **2** (0.97 g, 3.33 mmol) in MTBE (30 mL), dry methanol (1 mL) and acetyl chloride (0.31 g, 4.1 mmol) were slowly added at 10°C. After stirring for 45 min, the precipitate was filtered off and washed with MTBE (50 mL). After drying **2.HCl** (0.995 g, 92%) was obtained as a white solid. Analytical samples were either obtained by sublimation or by re-crystallization from 2-propanol at −30°C; mp 200–202°C; $[\alpha]_D = +60.1°$ (c = 1.9, $CHCl_3$); R_f = 0.43 (CH_2Cl_2/MeOH, 7:3); IR (KBr): ν = 3347 *m*, 2979 *s*, 2894 *m*, 2765 *m*, 2399 *m*, 1773 *s*, 1650 *s*, 1567 *m*, 1379 *s*, 1182 *m*, 1159 *m*, 1119 *m* cm^{-1}; UV-vis (methanol): λ_{max} (log ε) = 239 nm (2.37); ^{1}H NMR(500 MHz, $CDCl_3$): δ = 5.52 (*s*, 1 H, C*H* (2)), 4.14 (*dd*, 1 H, C*H* (9a), J = 10.8, 9.5 Hz), 3.23 (*d*, 2 H, CH_2 (C12), J = 4,2 Hz)), 2.97–2.84 (*m*, 1 H, C*H* (7)), 2.91 (*m*, 1 H, C*H* (9b)), 2.84 (s, 6 H, 2 × CH_3 (13)), 2.70 (*d*, 2 H, CH_2 (3), J = 15.4 Hz), 1.93–2.14 (*m*, 3 H, C*H* (9a) + CH_2 (3)), 2.12 (*m*, 1 H, C*H* (5)), 1.92 (*s*, 1 H, C*H* (11)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.1 (C8, *C* = O), 139,8 (C1, $C_{quart.}$), 125.4 (C2, *C*H), 83.5 (C9a, *C*H), 72.1 (C3a, $C_{quart.}$), 62.6 (C4a, $C_{quart.}$), 54.4 (C12, CH_2), 52.0 (C9b, *C*H), 50.8 (C6a, *C*H), 43.5 (C13, CH_3), 42.9 (C7, *C*H), 39.4 (C3, CH_2), 32.9 (C5, *C*H2), 21.4 (C6, CH_2), 18.2 (C11, CH_3) ppm; MS (ESI, MeOH): m/z = 315 ($[M+Na]^+$); anal. calcd for $C_{17}H_{26}ClNO_3$ (327.85): C, 62.28; H, 8.01; Cl, 10.90; N, 4.27; found: C, 61.95; H, 8.01; Cl, 10.90; N, 4.17.

*(3aR,4aS,6aS,7R,9aS,9bR)-1,4a-Dimethyl-7-(thiomorpholin-4-ylmethyl)-5,6,6a,7,9a,9b-hexahydro-3H-oxireno[8,8a]azuleno[4,5-b]furan-8(4aH)-on (**3**)*

To a solution of arglabin (100 mg, 0.41 mmol) in ethanol (3 mL), thiomorpholine (65.01 mg, 0.63 mmol) was slowly added. The mixture was stirred for 2 days at 24°C, the solvents were removed under diminished pressure and the residue subjected to chromatography (silica gel, $CHCl_3$/Et_2O, 95:5) to yield **3** (158 mg, 72%) as a colorless solid; mp. 115–116°C; $[\alpha]_D = +62.8°$ (c = 4.4, $CHCl_3$); R_f = 0.3 ($CHCl_3$/Et_2O, 95:5); IR (KBr): ν = 3433 *m*, 2924 *m*, 2825 *m*, 1773 *s*, 1651 *s*, 1378 *s*, 1324 *m*, 1282 *m*, 1259 *m*, 1109 *m*, 1060 *m*, 1029 *m* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 222 nm (2.35) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.52 (*s*, 1 H, C*H* (2)), 3.97 (*dd*, 1 H, C*H* (9a), J = 10.2 Hz,), 2.81 (*d*, 1 H, J = 10.5 Hz, C*H* (9b)), 2.73–2.57 (*m*, 4 H, 2 × CH_2 (13)), 2.70 (*d*, 1 H, J = 17.96 Hz, CH_a (3)), 2.41 (*m*, 4 H, 2 × CH_2 (14)), 2.30 (*m*, 1 H, C*H* (7)), 2.11 (*d*, 1 H, J = 17.78 Hz, CH_b (3)), 2.08 (*dd*, 1 H, J = 15.3, 12.7 Hz, CH_a(5)), 1.95 (*ddd*, 1 H, J = 4.9, 2.7 Hz, CH_b(5)), 1.95 (*d*, 1 H, J = 2.3 Hz, CH_a (12)), 1.89 (*s*, 3 H, CH_3 (11)), 1,59 (*d*, 1 H, J = 11.85 Hz, *CH* (6a)), 1.41 (*d*, 1 H, J = 12.31 Hz, CH_b (12)), 1.31 (*s*, 3 H, CH_3 (10)), 1,23 (*m*, 2 H, C*H* (6)) ppm; ^{13}C NMR (125MHz, $CDCl_3$): δ = δ 177.6 (C8, *C* = O), 140,6 (C1, $C_{quart.}$), 124.8 (C2, *C*H), 82.8 (C9a, *C*H), 72.4 (C3a, $C_{quart.}$), 62.6 (C4a, $C_{quart.}$), 65, 8 (C13, CH_2), 56,9 (C14, CH_2), 52.4 (C9b, *C*H), 51.6 (C6a, *C*H), 44, 3 (C7, $C_{quart.}$), 39.6 (C3, CH_2), 33.6 (C5, CH_2), 22.7 (C6, CH_2), 22.8 (C12, CH_2), 22,7 (C10,

*C*H$_3$), 18.2 (C11, *C*H$_3$) ppm; MS (ESI, MeOH): $m/z = 350.4$ ([M+H]$^+$); anal. calcd for $C_{19}H_{27}NO_3S$ (349.49): C, 65.30; H, 7.79; N, 4.01; found: C, 65.18; H, 7.95; N, 3.87.

*(3aR,4aS,6aS,7R,9aS,9bR)-1,4a-Dimethyl-7-(piperidin-1-ylmethyl)-5,6,6a,7,9a,9b-hexahydro-3H-oxireno[8,8a]-azuleno[4,5-b]furan-8(4aH)-on (**4**)*

A solution of arglabin (80 mg, 0.32 mmol) in ethanol (5 mL) containing dry piperidine (40.0 mg, 0.48 mmol) was stirred at 24°C for 1 d. The solvent was removed under diminished pressure, the residue re-dissolved in dichloromethane (20 mL), extracted with water (3 × 10 mL), the organic phase was dried (Na_2SO_4) and evaporated. Chromatography (silica gel, CH_2Cl_2/MeOH, 7:3) gave **4** as a colorless solid (124 mg, 78%); mp 119–120°C; $[\alpha]_D = +66.6^\circ$ ($c = 3.7$, $CHCl_3$); $R_f = 0.49$ (CH_2Cl_2/MeOH, 7:3); IR (KBr): $\nu = 3447$ *m*, 2854 *s*, 1769 *s*, 1649 s, 1351 *m*, 1313 *m*, 1260 s, 1229 *m*, 1075 m, 1029 *m*, 1014 *m* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 225 nm (3.46); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.53 (*s*, 1 H, C*H* (2)), 3.98 (*dd*, 1 H, $J = 10.2$ Hz, C*H* (9a)), 2.80 (*d*, 1 H, $J = 10.2$ Hz, C*H* (9b)), 2.73 (*m*, 2 H, C*H* (13)), 2.70 (*d*, 1 H, C*H*$_a$ (3), 2.57 (*dd*, 2 H, *J*6.34, 13.24 Hz, C*H*$_2$ (13)), 2.40–2.30 (*m*, 4 H, C*H*$_2$ (14)), 2.34 (*m*, 1 H, C*H* (7)), 2.11 (*d*, 1 H, $J = 16.9$ Hz, C*H*$_b$ (3)), 2.07 (*ddd*, 1 H, $J = 15.3$, 12.7 Hz, C*H*$_a$(5)), 1.95 (*ddd*, 1 H, $J = 4.9$, 2.7 Hz, C*H*$_b$(5)), 1.91 (*d*, 1 H, $J = 4.8$ Hz, C*H*$_a$ (12)), 1.90 (*s*, 3 H, C*H*$_3$ (11)), 1.59 (*d*, 1 H, $J = 11.9$ Hz, *CH* (6a)), 1.40 (*d*, 1 H, $J = 12.0$ Hz, C*H*$_b$ (12)), 1.31 (*s*, 3 H, C*H*$_3$ (10)), 1,24 (*m*, 2 H, C*H*$_2$ (6)), 1.18 (*dd*, 2 H, $J = 7.1$, 14.0 Hz; C*H*$_2$ (15)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.1 (C8, *C*=O), 140,8 (C1, $C_{quart.}$), 124.6 (C2, *C*H), 82.5 (C9a, *C*H), 72.5 (C3a, $C_{quart.}$), 62.7 (C4a, $C_{quart.}$), 57.6 (C13, *C*H$_2$), 54.9 (C14, *C*H$_2$), 52.5 (C9b, *C*H), 52.2 (C6a, *C*H), 43, 9 (C7, $C_{quart.}$), 39.6 C3, *C*H$_2$), 33.7 (C5, *C*H$_2$), 25.9 (C6, *C*H$_2$), 24.2 (C15, *C*H$_2$), 22.8 (C12, *C*H$_2$), 22,7 (C10, *C*H$_3$), 18.3 (C11, *C*H$_3$) ppm; MS (ESI, MeOH): $m/z = 332.4$ ([M+H]$^+$); anal. calcd for $C_{20}H_{29}NO_3$ (331.45): C, 72.47; H, 8.82; N, 4.23; found: C, 72.31; H, 8.98; N, 4.11.

*(3aR,4aS,6aS,7R,9aS,9bR)-1,4a-Dimethyl-7-(piperazin-1-ylmethyl)-5,6,6a,7,9a,9b-hexahydro-3H-oxireno[8,8a]-azuleno[4,5-b]furan-8(4aH)-on (**5**)*

Following the procedure given for **4**, from arglabin (80 mg, 0.32 mmol), piperazine (41.4 mg, 0.48 mmol), followed by chromatography (silica gel, CH_2Cl_2/MeOH, 7:3) **5** (86 mg, 81%) was obtained as a colorless solid; 119–120°C; $[\alpha]_D = 59.8^\circ$ ($c = 3.2$, $CHCl_3$); $R_f = 0.53$ (CH_2Cl_2/MeOH, 7:3); IR (KBr): $\nu = 3447$ *m*, 1654 *s*, 1376 *m*, 1261 *m*, 1222 *m*, 1112 *m*, 1060 *m* cm^{-1}; UV-vis (methanol): λ_{max} (log ε) = 243 nm (3.46); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.24 (*s*, 1 H, C*H* (2)), 3.98 (*dd*, 1 H, $J = 10.8$ Hz, C*H* (9a)), 2.81 (*d*, 1 H, $J = 10.2$ Hz, C*H* (9b)), 2.73–2.57 (*m*, 4 H, 2 × C*H*$_2$ (13)) 2.71 (*d*, 1 H, $J = 17.9$ Hz, C*H*$_a$ (3)), 2.41 (*m*, 4 H, 2 × C*H*$_2$ (14), 2.30 (*m*, 1 H, C*H* (7)), 2.11 (*d*, 1 H, $J = 17.8$ Hz, C*H*$_b$ (3)), 2.08 (*m*, 1 H, C*H*$_a$(5)), 1.95 (*m*, 1 H, $J =$ C*H*$_b$(5)), 1.95 (*d*, 1 H, $J = 2.3$ Hz, C*H*$_a$ (12)), 1.94 (*s*, 3 H, C*H*$_3$ (11)), 1.59 (*d*, 1 H, $J = 11.9$ Hz, *CH* (6a)), 1.41 (*d*, 1 H, $J = 12.3$ Hz, C*H*$_b$ (12)), 1.31 (*s*, 3 H, C*H*$_3$ (10), 1,23 (*m*, 2 H, C*H* (6)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8 (C8, *C*=O), 140,7 (C1, $C_{quart.}$), 124.7 (C2, *C*H), 82.6 (C9a, *C*H), 72.5 (C3a, $C_{quart.}$), 62.6 (C4a, $C_{quart.}$), 56.5 (C13, *C*H$_2$), 53.5 (C14, *C*H$_2$), 52.5 (C9b, *C*H), 51.8 (C6a, *C*H), 44, 0 (C7, C_{quart}), 39.5 (C3, *C*H$_2$), 33.7 (C5, *C*H$_2$), 24.3 (C6, *C*H$_2$), 22.8 (C12, *C*H$_2$), 22,7 (C10 *C*H$_3$), 18.3 (C11, *C*H$_3$) ppm; MS (ESI, MeOH): $m/z = 333.2$ ([M+H]$^+$); anal. calcd for $C_{19}H_{28}N_2O_3$ (332.44): C, 68.65; H, 8.49; N, 8.43; found: C, 68.51; H, 8.63; N, 8.28.

*(3aR,4aS,6aS,7S,9aS,9bR)-1,4a-Dimethyl-7-(2-nitroethyl)-5,6,6a,7,9a,9b-hexahydro-3H-oxireno[8,8a]-azuleno[4,5-b]furan-8(4aH)-on (**6**)*

To a solution of arglabin (100 mg, 0.41 mmol) in dry nitromethane (5 mL), DBU (10 mg) was added and the mixture was stirred at 24°C for 1 day. The solvent was evaporated and the residue subjected to chromatography (silica gel, $CHCl_3$/Et_2O, 95:5) to afford **6** (83 mg, 66%) as a colorless solid; mp 120°C; $[\alpha]_D = +27^\circ$ ($c = 7.1$, $CHCl_3$); $R_f = 0.6$ ($CHCl_3$/Et_2O = 95:5); IR (KBr): $\nu = 3441$ *m*, 2828 *s*, 1651 *s*, 1435 *m*, 1364 *m*, 1319 *m*, 1298 *m*, 1253 *s*, 1049 *m* cm^{-1}; UV-vis (methanol): λ_{max} (log ε) = 220 nm (2.3); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.54 (*s*, 1 H, C*H* (2)), 4.76–4.70 (*m*, 2 H, CH_2 (13)); 4.04 (*dd*, 1 H, $J = 10.2$ Hz, C*H* (9a)), 2.76 (*d*, 1 H, $J = 10.1$ Hz, C*H* (9b)), 2.70 (*d*, 1 H, $J = 17.8$ Hz, C*H*$_a$ (3)), 2.34–2.31 (*m*, 1 H, C*H* (7)), 2.11 (*d*, 1 H, $J = 17.5$ Hz, CH_b (3)), 2.07–1.91 (m, 1 H, C*H* (5)), 1,93 (s, 3 H, C*H*$_3$ (11)), 1.62 (d, 1 H, $J = 12.1$ Hz, *CH* (11)), 1.46–1.42 (*m*, 2 H, C*H*$_2$ (12)), 1.31 (*s*, 3 H, C*H*$_3$ (10)), 1.24 (*m*, 2 H, C*H*$_2$ (6)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1 (C8, *C*=O), 140,2 (C1, $C_{quart.}$), 125.0 (C2, *C*H), 82.9 (C9a, *C*H), 72.3 (C3a, $C_{quart.}$), 72.2 (C13, *C*H$_2$), 62.5 (C4a, $C_{quart.}$), 52.4 (C9b, *C*H), 52.2 (C6a, *C*H), 42.7 (C7, *C*H), 39.5 (C3, *C*H$_2$), 33.3 (C5, *C*H$_2$), 25.2 (C6, *C*H$_2$), 22.6 (C12, *C*H$_2$), 22.5 (C10, *C*H$_3$), 18.2 (C11, *C*H$_3$) ppm; MS (ESI, MeOH): $m/z = 330.3$ ([M + Na]$^+$), 636.9 ([2M+Na]$^+$); anal. calcd for $C_{16}H_{21}NO_5$ (307.34): C, 62.53; H, 6.89; N, 4.56; found: C, 62.38; H, 6.99; N, 4.31.

*(3aR,4aS,6aS,7S,9aS,9bR)-7-{[(2-Hydroxyethyl)thio]-methyl}-1,4a-dimethyl 5,6,6a,7,9a,9b-hexahydro-3H-oxireno[8,8a]azuleno[4,5-b]furan-8(4aH)-on (**7**)*

To a solution of arglabin (90 mg, 0.37 mmol) in ethanol (3 mL) containing 2-mercaptoethanol (36.7 mg, 0.47 mmol), catalytical amounts of DBU (10 mg) were added and stirring at 24°C was continued for another 6 h. The solvent was removed and the residue subjected to chromatography (silica gel, $CHCl_3$/Et_2O, 7:3) to yield **7** (74 mg, 62.5%) as a colorless solid; mp 119–120°C; $[\alpha]_D = +36.5^\circ$ ($c = 4.8$, $CHCl_3$); $R_f = 0.33$ ($CHCl_3$/Et_2O, 7:3); IR (KBr): $\nu = 3448$ *m*, 2946 *s*, 1771 *m*, 1731 *m*, 1465 *m*, 1371 *m*, 1247 *m*, 1179 *m*, 1126 *m*, 1017 *m* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 212 nm (2.3); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.51 (*s*, 1 H, C*H* (2)), 4.06 (*dd*, 1 H, $J = 10.3$ Hz, C*H* (9a)), 3.77–3.67 (*m*, 2 H, C*H* (14)), 2.85–2.83 (*m*, 2 H, C*H*$_2$ (12)), 2.82–2.80 (*m*, 1 H, C*H* (9b)), 2.68–2.62 (*m*, 3 H, CH_a (3) +CH_2 (13)), 2.45–2.41 (*m*, 1 H, C*H* (7)) 2.11–2.01 (*m*, 2 H, C*H*$_b$ (3) + C*H*$_a$ (9)), 1.99–1.95 (*m*, 1 H, C*H*$_b$ (5)), 1.90 (*s*, 3 H, C*H*$_3$ (11)), 1.79–1.71 (*m*, 1 H, C*H* (6a)), 1.70–1.65 (*m*, 1 H, C*H*$_a$ (12)), 1.48–1.36 (*m*, 1 H, C*H*$_b$ (12)), 1.29 (*s*, 3 H, C*H*$_3$ (10)), 1.24 (*dd*, 2 H, $J = 14.2$, 7.1 Hz, C*H*$_2$ (6)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9 (C8, *C*=O), 140,4 (C1, $C_{quart.}$), 125.1 (C2, *C*H), 82.8 (C9a, *C*H), 72.4 (C3a, $C_{quart.}$), 65.8 (C14, *C*H$_2$), 62.6 (C4a, $C_{quart.}$), 52.3 (C9b, *C*H), 50.5 (C6a, *C*H), 46.7 (C7, *C*H), 39.5 (C3, *C*H$_2$), 36.3 (C13, *C*H$_2$), 33.3 (C5, *C*H$_2$), 28.7 (C6, *C*H$_2$), 22.6 (C12, *C*H$_2$), 22.5 (C10, *C*H$_3$), 18.2 (C11, *C*H$_3$) ppm; MS (ESI, MeOH): $m/z = 325.1$ ([M+H]$^+$); anal. calcd for $C_{17}H_{24}SO_4$ (324.44): C, 62.93; H, 7.46; S, 9.88; found: C, 62.77; H, 7.68; S, 9.61.

*2-({[(3aR,4aS,6aS,7S,9aS,9bR)-1,4a-Dimethyl-8-oxo-4a,5,6,6a,7,8,9a,9b-octahydro-3H-oxireno[8,8a]-azuleno[4,5-b]furan-7-yl]methyl}thio)benzoesäure (**8**)*

Following the procedure given for **7**, from arglabin (90 mg, 0.37 mmol), 2-mercaptobenzoic acid (72.4 mg, 0.47 mmol),

DBU (10 mg) after 48 h at 24°C and chromatographic work-up (silica gel, CH_2Cl_2/MeOH, 9:1), **8** (93 mg, 62.8%) was obtained as a colorless solid; mp 122°C; $[\alpha]_D = +31^\circ$ ($c = 4.3$, $CHCl_3$); $R_f = 0.5$ (CH_2Cl_2/MeOH, 9:1); IR (KBr): $\nu = 3445$ *m*, 2945 *s*, 1729 *m*, 1452 *m*, 1372 *m*, 1239 *m*, 1183 *m*, 1119 *m*, 1007 *m* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 215 nm (2.33); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59 (*d*, 1 H, *J* = 7.6 Hz, C*H* (18)), 7.45 (*d*, 1 H, *J* = 7.6 Hz, C*H* (15)), 7.23 (*dd*, 1 H, *J* = 8.9, 6.1 Hz, C*H* (17)), 7.15 (*dd*, 1 H, *J* = 8.5, 7.3 Hz, C*H* (16)) 5.52 (m, 1 H, C*H* (2)), 3.95(*dd*, 1 H, *J* = 10.3 Hz, C*H* (9a)), 2.85–2.83 (*m*, 2 H, CH_2 (12)), 2.82 (*d*, 1 H, *J* = 10.1 Hz, C*H* (9b)), 2.68 (*d*, 1 H, *J* = 17.9 Hz, CH_a (3)), 2.45 (*d*, 1 H, *J* = 12.5 Hz, C*H* (7)), 2.11–2.01 (*m*, 2 H, CH_b (3) +CH_a (5)), 1.99 (*dd*, 1 H, *J* = 15.4, 2.7 Hz, CH_b (5)), 1.90 (*s*, 3 H, CH_3 (11)), 1.79–1.71 (*m*, 1 H, *CH* (6a)), 1.29 (*s*, 3 H, CH_3 (10)), 1,24–1.20 (*m*, 2 H, CH_2 (6)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7 (C8, *C*=O), 170.1 (C19, *C*=O), 140,4 (C1, $C_{quart.}$), 134.9 (C13, C_{ipso}), 128.7 (C18, *CH*), 127.9 (C15, *CH*), 124.8 (C2, *CH*), 124.7 (C17, *CH*), 124.4 (C16, *CH*), 117.9 (C14, C_{ipso}), 82.9 (C9a, *CH*), 72.8 (C3a, $C_{quart.}$), 62.6 (C4a, $C_{quart.}$), 51.3 (C9b, *CH*), 50.5 (C6a, *CH*), 45.9 (C7, *CH*), 39.0 (C3, CH_2), 32.6 (C5, CH_2), 30.4 (C6, CH_2), 22.5 (C12, CH_2), 21.4 (C10, CH_3), 17.1 (C11, CH_3) ppm; MS (ESI, MeOH): *m*/*z* = 423.4 ($[M+Na]^+$); anal. calcd for $C_{22}H_{24}SO_5$ (400.49): C, 65.98; H, 6.04; S, 8.01; found: C, 65.69; H, 6.12; S, 7.85.

*Ethyl [(1R,1aS,2aR,3aS,5aS,8aS,8bR)-3a,8c-dimethyl-6-methylen-7-oxododecahydrocyclopropa[2,3]oxireno-[8,8a]azuleno[4,5-b]furan-1-yl]acetate (**9**)*

To a solution of arglabin (100 mg, 0.41 mmol) in abs. CH_2Cl_2 containing $[Rh(OAc)_2]_2$ (10 mg) within 2 h ethyl diazoacetate (55.7 mg, 0.48 mmol) is slowly added. After stirring for 30 min, the solvent was evaporated and the residue subjected to chromatography (hexane/EtOAc, 1:1) to yield **9** (74 mg, 52.6%) as a colorless solid; mp 134–136°C; $[\alpha]_D = +89^\circ$ ($c = 2.1$, MeOH); $R_f = 0.39$ (hexane/EtOAc, 1:1); IR (KBr): $\nu = 3440$ *m*, 3068 *m*, 1771 *m*, 1649 *s*, 1550 *m*, 1429 *m*, 1387 *m*, 1269 *m*, 1221 *m*, 921*s* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 210 nm (2.32); ^1H NMR (500 MHz, $CDCl_3$): δ = 6.25 (d, 1 H, *J* = 2.9 Hz, = CH_a (11)), 5.63 (d, 1 H, *J* = 3.2 Hz,=CH_b (11)), 4.51–4.40 (*m*, 2 H, CH_2 (14)), 4.90–4.81 (*m*, 1 H, C*H* (8a)), 2.80 (*d*, 1 H, *J* = 9.9 Hz, C*H* (8b)), 2.76 (*m*, 1 H, C*H* (5a)), 2.31 (*d*, 1 H, *J* = 10.0 Hz, CH_a (12)), 2.25–2.20 (*m*, 1 H, CH_b (12)), 2.11 (*ddd*, 1 H, *J* = 12.2, 4.2Hz, C*H* (1)), 2.07–1.99 (*m*, 2 H, CH_2 (4), 1.70 (*d*, 1 H, *J* = 12.1 Hz, CH_a (2)), 1.45 (*d*, 1 H, *J* = 17.0 Hz, CH_b (2)), 1.90 (*s*, 3 H, CH_3 (10)),1.45 (*m*, 1 H, C*H* (1a)), 1.39 (*t*, 3 H, *J* = 17.2 Hz, CH_3 (15)), 1.31 (*s*, 3 H, CH_3 (9)), 1.24 (*m*, 2 H, CH_2 (5)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9 (C7, *C*=O), 171.4 (C13, *C*=O), C131.5 (C6, $C_{quart.}$), 121.3 (C11,=CH_2), 82.8 (C8a, *CH*), 78.9 (C2a, $C_{quart.}$), 62.1 (C3a, $C_{quart.}$), 50.3 (C8b, *CH*), 49.2 (C5a, *CH*), 39.5 (C2, CH_2), 32.5 (C12, CH_2), 31.3 (C4, CH_2), 29.7 (C5, CH_2), 28.0 (C11, CH_2), 27.1 (C9, CH_3), 21.2 (C10, CH_3), 18.2 (C8c, $C_{quart.}$), 16.2 (C1a, *CH*), 15.9 (C1, *CH*), 13.5 (C15, CH_3) ppm; MS (ESI, MeOH): *m*/*z* = 347.9 ($[M+H]^+$); anal. calcd for $C_{20}H_{26}O_5$ (346.42): C, 69.34; H, 7.56; found: C, 69.22; H, 7.65.

*Ethyl[(3aR,4aS,6aS,7S,9aS)-1,4a-dimethyl-8-oxo-4a,5,6,6a,9a,9b-hexahydro-3H-spiro[oxireno[8,8a]-azuleno[4,5-b]furan-7,4'-[1,2,3]triazol]-1′(5′H)-yl]acetate (**10**)*

To a solution of arglabin (90mg, 0.37 mmol) in abs. THF (5 mL) containing CuI (10 mg), ethyl azidoacetate (118 mg, 0.9 mmol) was added and the mixture was stirred at 24°C for 4 d. The solvent was evaporated under diminished pressure, the residue was dissolved in CH_2Cl_2 (25 mL), washed (5 mL) and dried (Na_2SO_4). Chromatographic work-up (silica gel, hexane/ethyl acetate, 7:3) gave **10** (65 mg, 46%) as a colorless solid; mp 115–116°C; $[\alpha]_D = +169.9^\circ$ ($c = 3.5$, $CHCl_3$); $R_f = 0.6$ (hexane/ethyl acetate, 7:3); IR (KBr): $\nu = 3445$ *m*, 2931 *m*, 1648 *s*, 1451 *m*, 1376 *m*, 1246 *m*, 1219 *m*, 1163 *s*, 1137 *s*, 1115 *s*, 1081 *s*, 1027 *s*, 993*s* cm^{-1}; UV-vis (MeOH): λ_{max1} (log ε) = 219 (2.34), λ_{max2} (log ε) = 285 nm (2.45); ^1H NMR (500 MHz, $CDCl_3$): δ = 5.57 (*s*, 1 H, C*H* (2)), 4.80 (*dd*, 1 H, *J* = 10.8 Hz, C*H* (9a)), 4.70–4.51 (*m*, 2 H, CH_2 (8′)), 4.32–4.15 (*m*, 2 H, CH_2 (6′), 3.67 (*d*, 1 H, *J* = 9.7 Hz, CH_a (5′)), 3.33 (*d*, 1 H, *J* = 9.7 Hz, CH_b (5′)), 2.80 (*d*, 1 H, *J* = 10.2 Hz, C*H* (9b)), 2.70 (*d*, 1 H, *J* = 18.0 Hz, CH_a (3)), 2.34 (*m*, 1 H, C*H* (7)), 2.11 (*d*, 1 H, *J* = 16.9 Hz, CH_b (3)), 2.07 (*m*, 1 H, CH_a (5)), 1.95 (*m*, 1 H, CH_b (5)), 1.90 (*s*, 3H CH_3 (11)), 1.59 (*d*, 1 H, *J* = 11. 8 Hz, *CH* (6a)), 1.31 (*s*, 3 H, CH_3 (10)), 1.24 (*m*, 2 H, CH_2 (6)), 1.18 (*t*, 3 H, *J* = 7.1 Hz, CH_3 (9′)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9 (C8, *C*=O), 168.5 (C7′, *C*=O) 140,3 (C1, $C_{quart.}$), 125.1 (C2, *CH*), 82.5 (C9a, *CH*), 72.1 (C3a, $C_{quart.}$), 62.3 (C4a, $C_{quart.}$), 61.6 (C8′, CH_2), 56.4 (C9b, *CH*), 52.7 (C6a, *CH*), 50.2 (C6′, CH_2), 49.0 (C6, CH_2), 39.6 (C3, CH_2), 33.4 (C5, CH_2), 22.7 (C8′, CH_3), 18.2 (C5′, CH_2), 18.1 (C10, CH_3), 14.1 (C11, CH_3) ppm; MS (ESI, MeOH): *m*/*z* = 398.0 (100%, $[M+Na]^+$), 772.9 (50%, $[2M+Na]^+$); anal. calcd for $C_{19}H_{25}N_3O_5$ (375.42): C, 60.79; H, 6.71; N, 11.19; found: C, 60.51; H, 6.84; N, 11.01.

*(3aR,4aS,6aS,7R,9aS)-1,4a-Dimethyl-4′,4a,5,5′,6,6a,9a,9b-octahydro-3H-spiro[oxireno[8,8a]-azuleno[4,5-b]furan-7,3'-pyrazol]-8-on (**11**)*

To a solution of arglabin (100 mg, 0.41 mmol) in abs. THF (3 mL), diazomethane (20 mL, 20 mmol, 1 M in Et_2O) was added during 120 min; after stirring for an additional 30 min, the excess of diazomethane was destroyed by adding a few drops of acetic acid. The solvents were removed under diminished pressure and the residue was subjected to chromatography (silica gel, $CHCl_3$/Et_2O, 95:5) to yield **11** (117 mg, quant.) as a pale yellow solid; mp 119–121°C; $[\alpha]_D = +283.2^\circ$ ($c = 4.24$, MeOH); $R_f = 0.7$ ($CHCl_3$/Et_2O, 95:5); IR (KBr): $\nu = 3447$ *m*, 3051 *m*, 1776 *s*, 1651 *s*, 1559 *m*, 1431 *m*, 1375 *m*, 1277 *m*, 1223 *m*, 1172 *s*, 921 *s* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 217 nm (4.24); ^1H NMR (500 MHz, $CDCl_3$): δ = 5.55 (*s*, 1 H, CH (2)), 5.00 (*dd*, 1 H, *J* = 10.0 Hz, C*H* (9a)), 4.68–4.53 (*m*, 2 H, C*H* (5′)), 2.85 (*d*, 1 H, *J* = 10.5 Hz, C*H* (9b)), 2.72 (*d*, 1 H, *J* = 15.2 Hz, CH_a (3)), 2.12 (*dd*, 1 H, *J* = 3.8, 5.6 Hz, CH_a (4′)), 2.11–2.08 (*m*, 1 H, CH_b (3)), 2.07–2.02 (*m*, 1 H, CH_a (5)), 1.93 (*s*, 3 H, CH_3 (11)), 1.85–1.82 (*m*, 1 H, CH_b (5)), 1.82–1.79 (*m*, 1 H, C*H* (6a)), 1.35–1.42 (*m*, 1 H, CH_b (4′)), 1.42–1.36 (*ddd*, 1 H, *J* = 9.8, 13.1 Hz, CH_a (6)), 1.26 (*s*, 3 H, CH_3 (10)), 1.0–0.95 (*m*, 1 H, CH_b (6)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8 (C8, *C* = O), 140,2 (C1, $C_{quart.}$), 125.91 (C2, *CH*), 99.4 (C7, $C_{quart.}$), 83.1 (C9a, *CH*), 78.2 (C5́, CH_2), 72.6 (C3a, $C_{quart.}$), 62.2 (C4a, $C_{quart.}$), 56.3 (C6a, *CH*), 52.8 (C9b, *CH*), 39.6 (C3, CH_2), 33.5 (C5, CH_2), 22.6 (C10, CH_3), 22.5 (C4́, CH_2), 18.2 (C11, CH_3) ppm; MS (ESI, MeOH): *m*/*z* = 342.9 (100%, $[M+Na+MeOH]^+$), 289.3 (36%, $[M+H]^+$); anal. calcd for $C_{16}H_{20}N_2O_3$ (288.34): C, 66.65; H, 6.99; N, 9.72; found: C, 66.38; H, 7.14; N, 9.56.

*(1aS,2aR,3aS,5aS,8aS,8bS,8cR)-3a,8c-Dimethyl-6-methylen-octahydro-2H-bisoxireno[2,3:8,8a]azuleno[4,5-b]furan-7(3aH)-on (**12**)*

To a solution of arglabin (100 mg, 0.41 mmol) in dry THF (5 mL), *m*CPBA (346 mg, 2.0 mmol) was added and stirring at 24°C continued for 12 h. The reaction mixture was diluted with Et_2O

(20 mL), washed with an aq. solution of Na_2CO_3 (3 × 20 mL), dried (Na_2SO_4), and the solvents were evaporated. The residue was subjected to chromatography (silica gel, hexane/EtOAc, 7:3) to yield **12** (66 mg, 61%) as a colorless solid; mp 149–150°C (lit.: 149–151°C [11,32]); $[\alpha]_D = +90.9^\circ$ ($c = 1.6$, MeOH) (lit.: +94° ($CHCl_3$) [11,32]); $R_f = 0.41$ (hexane/EtOAc, 7:3); IR (KBr): ν = 3445 *m*, 3055 *m*, 1779 *m*, 1659 *s*, 1548 *m*, 1429 *m*, 1372 *m*, 1269 *m*, 1221 *m*, 1165 *s*, 921 *s* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 217 nm (2.35); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.20 (*s*, 1 H,=CH_a (12)), 5.65 (*s*, 1 H,=CH_b (12)), 4.80–4.75 (*m*, 1 H, C*H* (8a)), 2.90 (*d*, 1 H, *J* = 10.0 Hz, C*H* (8b)), 2.64 (*m*, 1 H, C*H* (5a)), 2.55 (*dd*, 1 H, *J* = 12.1, 5.2 Hz, C*H* (1)), 2.15–2.08 (*m*, 2 H, CH_2 (4), 1.76 (*m*, 2 H, CH_2 (2)), 1.94 (*s*, 3 H, CH_3 (11)), 1.25 (*s*, 3 H, CH_3 (10)), 1.24 (*m*, 2 H, CH_2 (5)), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.1 (C7, *C*=O), 139.6 (C6, =$C_{quart.}$) C121.4 (C12,=CH_2), 65.3 (C8c, $C_{quart.}$), 62.7 (C3a, $C_{quart.}$), 62.1 (C1, *C*H), 79.7 (C8a, *C*H), 72.0 (C2a, $C_{quart.}$), 52.5 (C8b, *C*H), 51.3 (C5a, *C*H), 33.2 (C4, *C*H_2), 31.5 (C2, *C*H_2),22.6 (C5, *C*H_2), 22.6 (C10, *C*H_3), 18.1 (C11, *C*H_3) ppm; MS (ESI, MeOH): m/z = 263.2 ($[M+H]^+$); anal. calcd for $C_{15}H_{18}O_4$ (262.30): C, 68.68; H, 6.92; found: C, 68.51; H, 7.04.

*Arborescin (**13**)*

A solution of arglabin (200 mg, 0.82 mmol) in EtOH (5 mL) containing Pd/$BaSO_4$ (100 mg) and quinoline (10 mg) was hydrogenated at 20 psi for 2 h. The mixture was filtered, the solvent evaporated and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 7:3) to yield **13** (203 mg, quant.) as a colorless solid; mp 140–142°C (lit.: 145°C [34], 140°C [38, 39]; $[\alpha]_D = +60^\circ$ ($c = 4.1$, $CHCl_3$) (lit.: + 63° ($CHCl_3$) [34], + 60° ($CHCl_3$) [38], + 55° (MeOH) [40]; $R_f = 0.49$ (hexane/EtOAc, 7:3); MS (ESI, MeOH): m/z = 271.2 ($[M+Na]^+$); anal. calcd for $C_{15}H_{20}O_3$ (248.32): C, 72.55; H, 8.12; found: C, 72.41; H, 8.31.

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References

[1] R. B. Bates, Z. Cekan, V. Prochazka, V. Herout, *Tetrahedron Lett.* **1963**, 1127–1130.

[2] W. Jöchle, *Angew. Chem, Int. Ed. Engl.* **1962**, *1*, 541–549.

[3] F. Sanchez-Viesca, J. Romo, *Tetrahedron* **1963**, *19*, 1285.

[4] W. Vichnewski, B. Gilbert, *Phytochemistry* **1972**, *11*, 2563.

[5] E. Rodriguez, G. H. N. Towers, J. C. Mitchel, *Phytochemistry* **1976**, *15*, 1573–1580.

[6] M. Garcia, A. J. R. Da Silva, P. M. Baker, B. Gilbert, J. A. Rabi, *Phytochemistry* **1976**, *15*, 331–332.

[7] M. Bruno, S. Roselli, A. Maggio, R. A. Ruccuglia, K. F. Bastow, K. H. Lee, *J. Nat. Prod.* **2005**, *68*, 1042–1046.

[8] M. Ando, *J. Synth. Org. Chem, Japan*, **1992**, *50*, 858–874.

[9] K. J. Musulmanbekow, WO9964003A1; *Chem. Abs.* **1999**, *132*, 30823.

[10] K. J. Musulmanbekow, WO9958148A1; *Chem. Abs.* **1999**, *131*, 332093.

[11] S. M. Adekenov, WO9848789A1; *Chem. Abs.* **1998**, *130*, 480.

[12] S. M. Adekenov, M. N. Mukhametzhanos, A. D. Kagarlitskii, Kupriyanov, *Khim. Prir. Soedin.* **1982**, 655–666.

[13] H.-F. Wong, G. D. Brown, *J. Nat. Prod.* **2002**, *65*, 481–486.

[14] C. Bottex-Gauthier, D. Vidal, F. Picot, P. Potier, F. Menichini, G. Appendino, *Biotech. Therapeut.* **1993**, *4*, 77–98.

[15] G. Appendfino, P. Gariboldi, F. Menichini, *Filoterapia* **1991**, *62*, 275–276.

[16] S. Kalidindi, W. B. Jeong, A. Schall, R. Bandichhor, B. Nosse, O. Reiser, *Angew. Chem.* **2007**, *119*, 6478–6481.

[17] T. E. Shaikenov, S. M. Adekenov, S. Basset, M. Trived, L. Wolfinbarger, *Dokl. Minist. Nauki-Akad. Nauk Resp. Kazakhstan* **1998**, *5*, 64–75; *Chem. Abs.* **1999**, *131*, 67730.

[18] T. E. Shaikenov, S. M. Adekenov, R. M. Williams, N. Prashad, F. L. Baker, T. L. Madden, R. Newman, *Oncolog. Rep.* **2001**, *8*, 173–179.

[19] R. I. Jalmahanbetova, B. B. Rakhimova, V. A. Raldugin, I. Y. Bagryanskaya, Y. V. Gatilov, M. M. Shakirov, A. T. Kulyjasov, S. M. Adekenov, G. A. Tolstikov, *Russ. Chem. Bull, Int. Ed.* **2003**, *52*, 748–751.

[20] R. I. Jalmakhanbetova, G. A. Atazhanova, V. A. Raldugin, I. Y. Bagryanskaya, Y. V. Gatilov, M. M. Shakirov, S. M. Adekenov, *Chem. Nat. Prod.* **2007**, *43*, 548–551.

[21] E. V. Tikhanova, S. M. Adekenov, N. A. Samenov, M. K. Gilmanov, *Chem. Nat. Comp.* **2001**, *37*, 69–71.

[22] A. S. Fazylova, K. I. Itzhanova, A. T. Kulyyasov, K. M. Turdybekov, S. M. Adekenov, *Chem. Nat. Prod.* **1999**, *35*, 305–307.

[23] A. Z. Abildaeva, R. N. Pak, A. T. Kulyyasov, S. M. Adekenov, *Eksperim. Klinichesk. Farmakol.* **2004**, *67*, 37–39; *Chem. Abs.* **2004**, *141*, 116748.

[24] S. M. Adekenov, M. M. Tagbergenova, WO2008035958A1; *Chem. Abs.* **2008**, *148*, 363323.

[25] K.-D. Göhler, J. Engelmann, WO2006012824A1; *Chem. Abs.* **2006**, *144*, 198708.

[26] K.-D. Göhler, J. Engelmann, WO2007079736A1; *Chem. Abs.* **2010**, *152*, 314344.

[27] R. Ballini, A. Rinaldi, *Tetrahedron Lett.* **1994**, *35*, 9247–9250.

[28] E. M. Peterson, K. Yu, K. D. Holland, A. C. McKeon, S. M. Rothman, J. A. Ferrendelli, D. F. Covey, *J. Med. Chem.* **1994**, *37*, 275–286.

[29] W. Gajewski, G. Rücker, *Arch. Pharm.* **1983**, *316*, 256–263.

[30] D. Alonso-Perarnau, P. de March, M. Figuerdo, J. Font, *Ann. Quim.* **1994**, *90*, 473–476.

[31] G. T. Shchetnikov, A. S. Pergudov, S. N. Osipov, *Synlett* **2007**, 136–140.

[32] S. M. Adekenov, K. A. Aituganov, K. Turdybekov, S. V. Lindeman, Y. T. Struchkov, I. Y. Bagryanskaya, Y. V. Gatilov, *Khim. Prir. Soedin.* **1991**, 33–42.

[33] 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.

[34] A. Meisels, A. Weizmann, *J. Org. Chem.* **1953**, *75*, 3865–3866.

[35] Y. Shi, L. F. Peng, Y. Kishi, *J. Org. Chem.* **1997**, *62*, 5666–5667.

[36] A. K. Ghosh, K. Krishnan, *Tetrahedron Lett.* **1998**, *39*, 947–948.

[37] A. Brockhoff, M. Behrens, A. Massarotti, G. Appendino, W. Meyerhof, *J. Agric. Food Chem.* **2009**, *57*, 9860–9866.

[38] M. Ando, H. Yamaoka, K. Takase, *J. Org. Chem.* **1982**, *47*, 3909–3916.

[39] M. Ando, K. Ibayashi, N. Minami, T. Nakamura, K. Uogai, *J. Nat. Prod.* **1994**, *57*, 433–445.

[40] E. Fattorusso, P. Luciano, A. Romano, O. Taglialatela-Scofati, G. Appendino, M. Borriello, C. Fattorusso, *J. Nat. Prod.* **2008**, *71*, 1988 –1992.

