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Synthetic transformations of sesquiterpene lactones

10*. Synthesis of 13-arylguaianolides

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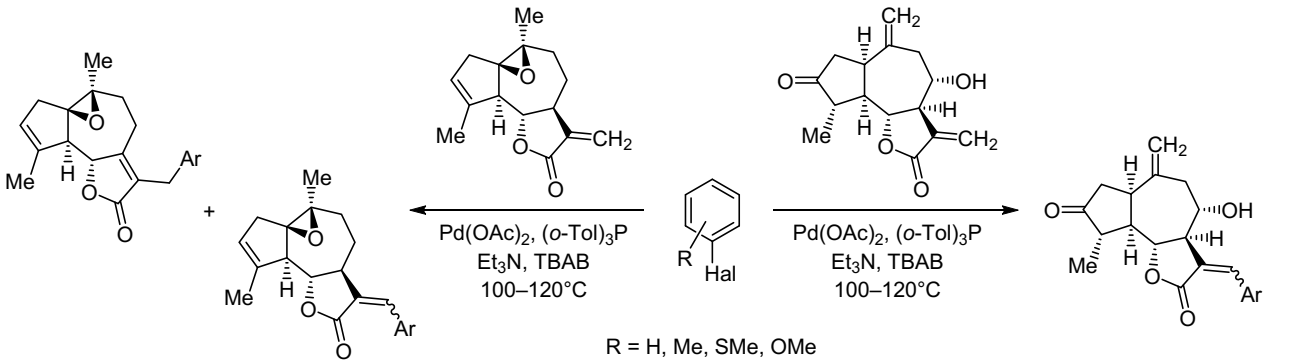


The Heck reaction of methylidene lactones of guaiane type, arglabin and ludartin, with aryl halides occurs with the formation of the respective (*E*)- and (*Z*)-13-arylidene-substituted derivatives and the respective endocyclic isomer, the ratio of which depends on the nature of methylidenelactone and the reaction conditions. The arylation of ludartin occurred with a lower yield of the target products and was accompanied by the formation of chamazulene. The interaction of grosheimin with aryl halides under Heck reaction led to the exocyclic products with (*E*)- and (*Z*)-configuration, with the latter as the major isomers. The structure of two compounds was established by X-ray structural analysis.

Keywords: arglabin, grosheimin, guaianolides, ludartin sesquiterpenoids, Heck reaction, X-ray structural analysis.

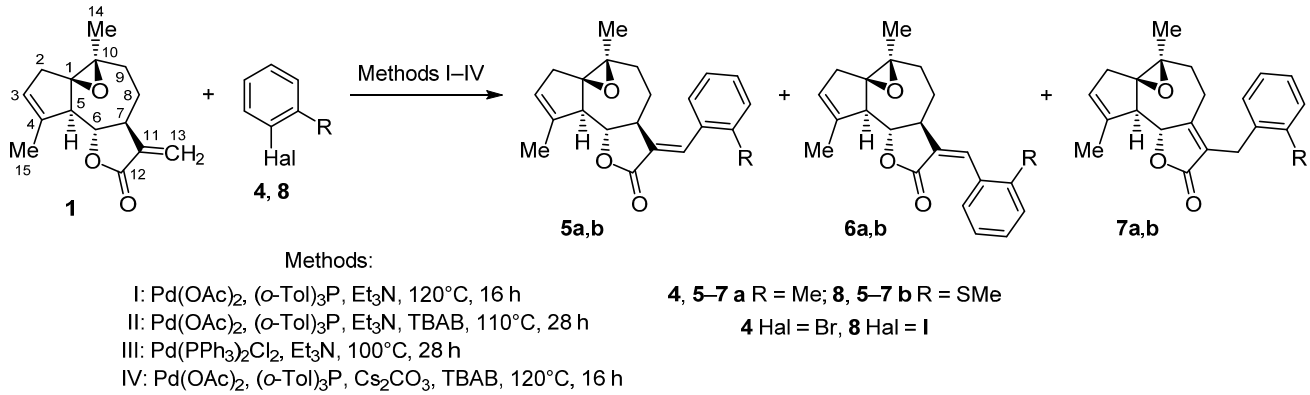
Sesquiterpene α-methylidene-γ-lactones of guaiane type represent an important group of natural compounds with a broad spectrum of biological activity, including anti-inflammatory and antitumor properties.[2] Guaianolides can serve as excellent lead compounds and reactive scaffolds in medicinal chemistry.[2] Recent studies[3] using the example of methylidenelactones of micheliolide and dehydrocostus lactone showed the prospects of synthetic modifications of guaianolides by introducing an aryl substituent at position C-13 by using Heck reaction. Semisynthetic derivatives of guaianolides exhibit significant cytotoxicity against the doxorubicin resistant tumor cells line HL-60/A, *via* the induction of tumor cell apoptosis.

Among the available methylidenelactones of guaiane type are arglabin (**1**),[4] ludartin (**2**),[5] and grosheimin (**3**),[6] isolated from various types of *Artemisia* sp. or *Cynara scolymus* L. The indicated lactones have been characterized with various types of biological activity, while an original antitumor drug (arglabin) has been developed on the basis of natural compound arglabin (**1**).[6a] Recently there has been a significant interest toward the study of synthetic transformations involving the lactones **1**,[7] **2**,[8] **3**[9].

In a continuation of our research toward directed modification of polyfunctional natural compounds of plant origin under the conditions of metal complex catalysis,[10] in the current work we have studied the possibilities for the synthesis of 13-aryl-substituted methylidenelactones **1**–**3** by Heck reaction with aryl halides. The conditions of the

* For Communication 9, see[1].

Scheme 1

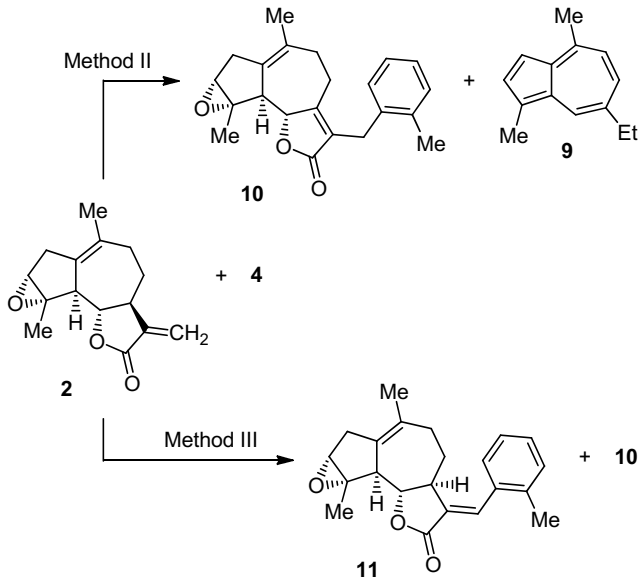


cross-coupling reaction were selected by using the example of arglabin (**1**) reaction with 2-bromotoluene (**4**) (Scheme 1). The interaction of lactone arglabin (**1**) with bromide **4** in DMF in the presence of a catalytic system consisting of $Pd(OAc)_2$–(*o*-Tol)$_3$P and Et_3N (method I) under the conditions described in the literature[1] occurred with a full conversion of the starting lactone and led to the formation of three arylation products: (*E*)- and (*Z*)-13-(2-methylphenyl)-1,10β-epoxy-5,7α(*H*),6β(*H*)-guaia-3(4),11(13)-dien-12,6β-olides **5a**, **6a**, as well as endocyclic isomer 13-(2-methylphenyl)-1,10β-epoxy-5,7α(*H*)-guaia-3(4),7(11)-dien-12,6β-olide (**7a**), which were separated by silica gel column chromatography (Scheme 1, Table 1). Increased selectivity for the formation of (*E*)-isomer **5a**, as well as an improved total yield of products were achieved by performing the reactions with added tetrabutylammonium bromide (TBAB) (Jefferey's conditions).[11] According to literature data,[11b] this additive helped to stabilize the metallic colloids formed *in situ* and prevented their aggregation into larger, inactive particles. The interaction of arglabin (**1**) with 2-bromotoluene (**4**) in the presence of TBAB additive at decreased temperature and longer reaction time (method II) provided a higher yield of the exocyclic adducts **5a**, **6a** (Table 1). Changing the palladium source to $Pd(PPh_3)_2Cl_2$ and decreasing the reaction temperature (method III) also allowed to increase the yield of (*E*)- and (*Z*)-isomers **5a**, **6a**, while the yield of the endocyclic adduct **7a** decreased (Table 1).

We have previously shown that the selectivity of Heck reaction with methylidenelactones increased when alkali metal carbonates were used as bases.[12] We have shown that the reaction of arglabin (**1**) with bromoarene **4**, catalyzed by $Pd(OAc)_2$–(*o*-Tol)$_3$P system in the presence of Cs_2CO_3 and TBAB in DMF (method IV) proceeded with full conversion and preferred formation of the exocyclic adduct **5a** (the ratio of **5a**:**6a** = 5:1, determined from ^{1}H NMR spectra of the reaction mixture); at the same time, the combined yield of the reaction products was lower than according to method II. The reaction of methylidenelactone **1** with 2-iodothioanisole (**8**) was accomplished according to the method II. Silica gel column chromatography gave 13-(2-methylthiobenzyl)-substituted guaianolides **5**–**7 b** in 64% combined yield (Table 1). Comparing the results of the reaction between lactone **1** and aryl halides, it is evident that the ratio of exocyclic adducts, (*E*)- and (*Z*)-13-arylguaianolides, depended on the aryl halide structure; a higher selectivity for the formation of (*E*)-isomer was observed in the reaction with iodoanisole.

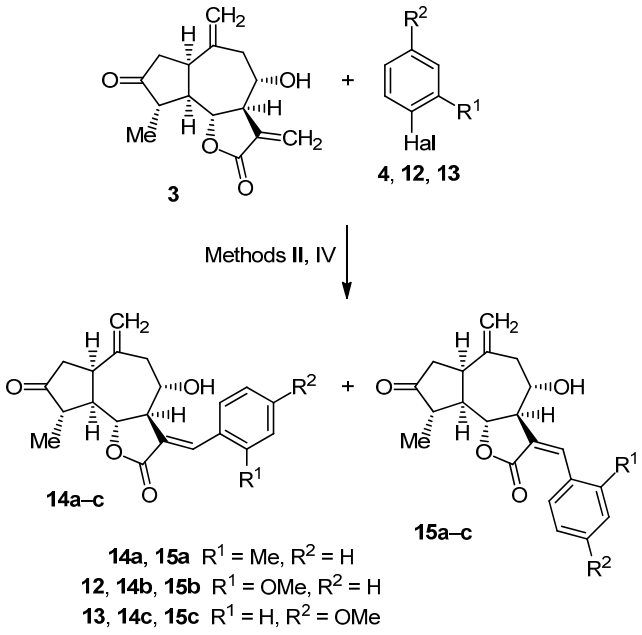
The interaction of ludartin (**2**) with 2-bromotoluene (**4**) according to method I was accompanied with significant resinification of the reaction mixture. Only chamazulene (**9**)was isolated as the reaction product by silica gel column chromatography (Scheme 2, Table 1). The reaction mixture obtained by performing Heck reaction according to the method II contained 36% of products from the arylation of lactone **2** (according to ^{1}H NMR spectrum): column chromatography yielded 13-(2-methylphenyl)-3,4α-epoxy-5,7α(*H*)-guaia-1(10),7(11)-dien-12,6β-olide (**10**) and chamazulene (**9**) as the products. The reaction of methylidenelactone **2** with bromoarene **4** according to method IV occurred with complete conversion of the starting material and led to the formation of compounds **10** and **11** in a 2:1 ratio (according to ^{1}H NMR spectral data). Silica gel column chromatography gave ludartin (*E*)-13-aryl derivative **11** in 17% yield.

Scheme 2



The reaction of grosheimin (**3**) with 2-bromotoluene (**4**) according to method II occurred with a complete conversion of the starting lactone and led to the formation of (*E*)- and (*Z*)-13-(2-methylphenyl)-substituted guaianolides **14a**, **15a** in 1:2 ratio (Scheme 3). Changing the base to Cs_2CO_3 (method IV) and lowering the reaction temperature resulted in a lower yield of compounds **14a**, **15a** (Table 1), while the starting lactone **3** was additionally isolated in 41% yield. The reaction of grosheimin (**3**) with 2-iodoanisole (**12**) or 4-iodoanisole (**13**) according to method II resulted in a complete conversion of lactone **3** and allowed to isolate products with exocyclic structure – compounds **14b**, **15b** or **14c**, **15c** (Table 1). At the same time, (*Z*)-(13-aryl)-8α-hydroxy-3-oxo-5,7α(*H*)-guaia-10(14),11(13)-dien-12,6β-olides **15a**–**c** were the main reaction products; the formation of endocyclic adducts was not observed in this reaction (by ^{1}H NMR spectra of the reaction mixture).

Scheme 3



The structures of the synthesized compounds were established by a combination of elemental analysis and spectral characteristics. ^{1}H and ^{13}C NMR spectra of the exocyclic products with (*E*)-configuration (compounds **5a**,**b**, **14a**–**c**) and (*Z*)-configuration (compounds **6a**,**b**, **15a**–**c**) were significantly different, thus enabling the assignment of these structures. The signal of 13-CH proton of (*E*)-isomers was located at a downfield position compared to the respective signal of the (*Z*)-isomer. A characteristic feature in ^{1}H NMR spectra of (*E*)-isomers **14a**–**c** was the downfield shift of 7-CH proton (3.68–3.78 ppm) compared to the position of the corresponding proton signal in the spectra of (*Z*)-isomers **15a**–**c** (3.08–3.17 ppm). The signals of C-12 carbonyl carbon atom in ^{13}C NMR spectra of (*E*)-isomers **5a**,**b**, **14a**–**c** were observed at lower field (171.6–172.2 ppm) than the corresponding signals of (*Z*)-isomer **6a**,**b**, **15a**–**c** (167.6–168.9 ppm). The (*E*)-configuration of C(11)=C(13) double bond in arylidenelactones **5a**,**b**, **11**, **14a**–**c** was additionally supported by the presence of carbon-proton *cis*-coupling constants between the olefinic proton and carbonyl carbon atom of lactone in ^{13}C NMR spectra (monoresonance mode) (^3J = 6.8–7.3 Hz); the respective ^3J-*trans*-constants for (*Z*)-isomers **6a**,**b**, **15a**–**c** were equal to 13.0–13.4 Hz. The formation of double bond isomerization products **7a**,**b**, **10** was confirmed by the presence of signals due to the 13-CH protons in ^{1}H NMR spectra (for example, at 3.57 and 3.61 ppm in the spectrum of compound **10** (both d, J = 12.0 Hz)) and the corresponding carbon atom (26.6–27.0 ppm) in ^{13}C NMR spectra.

Table 1. Reaction conditions and product yields for reactions between guaianolides **1**–**3** and aryl halides **4**, **8**, **12**, **13**

Lactone	Aryl halide	Method	Reaction conditions	TBAB, equiv	Product (yield, %)
1	**4**	I	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 120°C, 16 h	–	**5a** (15) **6a** (5) **7a** (33)
1	**4**	II	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 110°C, 28 h	1	**5a** (27) **6a** (19) **7a** (11)
1	**4**	III	$Pd(PPh_3)_2Cl_2$, Et_3N, 100°C, 28 h	–	**5a** (25) **6a** (18) **7a** (3)
1	**4**	IV	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Cs_2CO_3, 120°C, 16 h	1	**5a** (36) **6a** (5)
1	**8**	II	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 110°C, 28 h	1	**5b** (38) **6b** (7) **7b** (19)
2	**4**	I	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 120°C, 16 h	–	**9** (9)
2	**4**	II	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 110°C, 28 h	1	**9** (9) **10** (4)
2	**4**	IV	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Cs_2CO_3,120°C,16 h	1	**11** (17)
3	**4**	II	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 110°C, 28 h	1	**14a** (18) **15a** (13)
3	**4**	IV	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Cs_2CO_3,120°C,16 h	1	**14a** (7) **15a** (26)
3	**12**	II	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 110°C, 28 h	1	**14b** (11) **15b** (32)
3	**13**	II	$Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, 110°C, 28 h	1	**14c** (14) **15c** (35)

The structure of (*Z*)-isomers **15a**,**c** was confirmed by X-ray structural analysis data (Fig. 1). The bond lengths and ring conformations in molecules of compounds **15a** and **15c** were identical within the error of observation and close to the analogous parameters for grosheimin **3**.[13]

Obviously, the result of Heck reaction involving guaianolides **1**–**3** with haloarenes significantly depended on the structure of lactone. The Heck reaction of grosheimin with aryl halides occurred exclusively at the C(11)=C(13) double bond. The arylation reaction of grosheimin (**3**) gave only the exocyclic products with (*E*)- and (*Z*)-configuration (by *syn*-β-elimination of 13-CH proton, classical variant of Heck reaction). The Heck reaction of arglabin (**1**) and ludartin (**2**) with aryl halides produced a significant amount of products **7a**,**b**, **10** with exocyclic structure (non-classical variant of

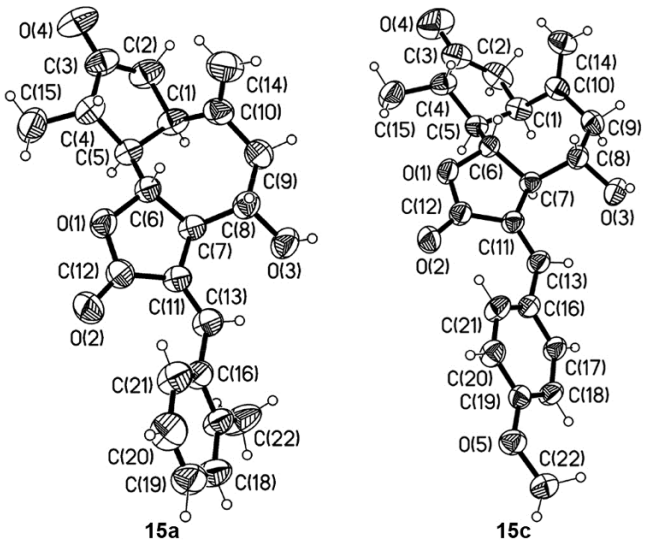


Figure 1. The molecular structure of compounds **15a**,**c** with atoms represented by thermal vibration ellipsoids of 50% probability.

Heck reaction – β-elimination of proton from C-7 position). The formation of products due to proton elimination from position C-7 was previously observed in the arylation reaction of eudesmane type lactones, isoalantolactone[14] and alantolactone.[15] The exclusive formation of exocyclic isomers with (*E*)- and (*Z*)-configuration was observed in a Heck reaction involving methylidenelactone of guaiane type, micheliolide.[3]

Thus, the palladium complex-catalyzed cross-coupling reaction of the available guaianolides, arglabin, ludartin, and grosheimin, with aryl halides allowed to synthesize derivatives containing aryl substituents at position C-13. The structure of methylidenelactone and aryl halide had a substantial effect on the yield and composition of reaction products. It was shown for the example of arglabin arylation that the variation of catalytic system composition allowed to modify the selectivity of cross-coupling reaction by increasing the yield of compounds with exocyclic methylidene double bond. The arylation of grosheimin occurred with the formation of exocyclic products.

Experimental

IR spectra were recorded on a Vector-22 FT-IR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on Bruker AV-400 (400 and 100 MHz, respectively, compounds **5a**, **6a**, **7a**, **14a**, **15a**) and Bruker AV-600 (600 and 150 MHz, respectively, the rest of the compounds) spectrometers. The solvent was $CDCl_3$, internal standard TMS. The multiplicity of signals in ^{13}C NMR spectra was determined by using standard methods for acquiring NMR spectra in monoresonance mode. Various types of proton-proton and carbon-proton correlation spectroscopy were used for the assignment of NMR signals (COSY, HMBC, COXH, NOESY – mixing time 1 s, pulse delay – 2 s). The atom numbering used for the description of ^{1}H and ^{13}C NMR spectra is shown in Scheme 1. High-resolution mass spectra were recorded on a DFS Thermo Scientific mass spectrometer (evaporator temperature 50–250°C, EI ionization, 70 eV). Elemental analysis was performed on a Carlo Erba 1106 CHN-analyzer. Melting points were determined on a Boetius apparatus and were not corrected. The specific rotation values were determined on a PolAAr 3005 polarimeter, the rotation values were expressed in (deg·ml)/(g·dm), concentration – grams in 100 ml of solution. The reaction products were isolated by column chromatography on Acros silica gel, 0.035–0.240 mm, eluents – $CHCl_3$–EtOH, 100:0→100:10; PhH–EtOAc 100:0→100:10. TLC was performed on Silufol UV-254 plates, eluent $CHCl_3$–EtOH, 9:1, or PhH–EtOAc, 3:1, visualization in iodine vapor or under UV light.

Chamazulene (**9**) was identified by comparing to a reference sample. Its quantitative content was determined by gas chromato-mass spectroscopy analysis on an Agilent 7890/5975C GC-MS instrument.

The solvents (DMF, $CHCl_3$, EtOAc) and Et_3N were purified by standard procedures and distilled under argon atmosphere immediately prior to use. The reagents 2-bromotoluene (**4**), 2-iodothioanisole (**8**), 2-iodoanisole (**12**), 4-iodoanisole (**13**), (*o*-Tol)$_3$P, Cs_2CO_3, and TBAB were purchased from Alfa Aesar. Palladium acetate and bis-(triphenylphosphine)palladium dichloride were synthesized according to published procedures.[16] The starting materials arglabin (**1**),[4a] ludartin (**2**),[5a] and grosheimin (**3**)[6a] used in this work were isolated from plants according to the respective procedures.

Heck reaction of guaianolides 1–3 with aryl halides 4, 8, 12, 13 (General method). A glass ampoule was cooled to 0–5°C under argon flow and charged with 3 Å molecular sieves (10 mg), lactone **1**–**3** (1.0 mmol), the appropriate aryl halide **4**, **8**, **12**, **13** (1.2 mmol), 4 mol % of $Pd(OAc)_2$ (methods I, II, IV) or $Pd(PPh_3)_2Cl_2$ (method III), (*o*-Tol)$_3$P (49 mg, 16 mol %) (methods I, II, IV), base (1.5 equiv of Et_3N or 1 equiv of Cs_2CO_3), DMF (8 ml), and $Bu_4N^+Br^-$ (322 mg, 1 equiv) (methods II, IV). The ampoule was sealed and heated under the conditions of methods I–IV. After the reaction was complete, the ampoule was cooled, opened, the mixture was filtered, the filtrate was poured into a saturated NaCl solution (30 ml) and extracted with EtOAc (3×30 ml). The combined organic extracts were washed with a saturated NaCl solution (30 ml), water (2×30 ml), dried over anhydrous $MgSO_4$, and evaporated under vacuum. The oily residue was dissolved in a minimum amount of $CHCl_3$ and separated by silica gel column chromatography (eluent $CHCl_3$–EtOH, gradient 100:1→100:9). The starting lactone was recovered (if the conversion was incomplete), followed by reaction products. When necessary, the products were separated by repeated column chromatography.

(1a*S*,3a*S*,6a*S*,9a*R*,*E*)-1a,7-Dimethyl-4-(2-methylbenzylidene)-2,3,3a,4,6b,9-hexahydro-1a*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-5(6a*H*)-one (5a). Yield 50 mg (15%, method I), 91 mg (27%, method II), 84 mg (25%, method III), 124 mg (36%, method IV), yellowish crystals, mp 102–104°C. $[\alpha]_D^{31}$ +21 (*c* 0.37, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3016, 2953, 2924, 2852, 1757, 1657, 1605, 1485, 1445,

1381, 1334, 1315, 1284, 1269, 1236, 1213, 1182, 1171, 1126, 1093, 1068, 1030, 1011, 960, 866, 804, 760, 721, 667, 656. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (1H, dddd, *J* = 14.0, *J* = 12.0, *J* = 10.6, *J* = 2.2) and 1.67 (1H, br. d, J_{gem} = 14.0, 8-CH$_2$); 1.25 (3H, s, 14-CH$_3$); 1.85 (1H, ddd, *J* = 14.6, *J* = 12.0, *J* = 2.7) and 1.92 (1H, ddd, *J* = 14.6, *J* = 4.9, *J* = 2.2, 9-CH$_2$); 1.98 (3H, s, 15-CH$_3$); 2.12 (1H, br. d, *J* = 16.2) and 2.74 (1H, br. d, *J* = 16.2, 2-CH$_2$); 2.43 (3H, s, ArC<u>H</u>$_3$); 2.58–2.67 (1H, m, 7-CH); 2.94 (1H, d, *J* = 10.4, 5-CH); 4.06 (1H, dd, *J* = 10.4, *J* = 9.8, 6-CH); 5.56 (1H, s, 3-CH); 7.10 (1H, d, *J* = 7.2, H-6 Ar); 7.15 (1H, t, *J* = 7.2, H-5 Ar); 7.18 (1H, d, *J* = 7.6, H-3 Ar); 7.23 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ar); 7.69 (1H, d, *J* = 2.0, 13-CH). ^{13}C NMR spectrum, δ, ppm: 18.3 (C-15); 19.7 (Ar<u>C</u>H$_3$); 20.4 (C-8); 22.4 (C-14); 34.1 (C-9); 39.4 (C-2); 50.7 (C-7); 53.1 (C-5); 62.6 (C-10); 72.4 (C-1); 82.7 (C-6); 124.1 (C-3); 125.2 (C-5'); 128.0 (C-6'); 128.8 (C-4'); 129.9 (C-2'); 130.0 (C-3'); 133.1 (C-1'); 136.2 (C-13); 136.9 (C-11); 140.5 (C-4); 171.7 (C-12). Mass spectrum, *m*/*z* (I_{rel}, %): 337 [M+H]$^+$ (21), 336 (74), 321 (33), 318 (22), 303 (29), 268 (25), 265 (36), 241 (32), 231 (62), 199 (20), 185 (24), 171 (39), 155 (26), 143 (54), 141 (56), 133 (27), 129 (65), 128 (100), 120 (32), 115 (63), 107 (48), 105 (58), 96 (45), 91 (36), 79 (23), 77 (31), 43 (26). Found, *m*/*z*: 336.1724 [M]$^+$. $C_{22}H_{24}O_3$. Calculated, *m*/*z*: 336.1725.

(1a*S*,3a*S*,6a*S*,9a*R*,*E*)-1a,7-Dimethyl-4-[2-(methylsulfanyl)benzylidene]-2,3,3a,4,6b,9-hexahydro-1a*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-5(6a*H*)-one (5b). Yield 140 mg (38%, method II), colorless crystals, mp 111–114°C (Et$_2$O). $[\alpha]_D^{26}$ +64 (*c* 0.78, CHCl$_3$). IR spectrum, ν, cm^{-1}: 3010, 2950, 2914, 1753, 1650, 1600, 1488, 1450, 1380, 1340, 1311, 1300, 1270, 1235, 1210, 1180, 1150, 1130, 1110, 1090, 1077, 1045, 1014, 1000, 955, 860, 810, 750, 720, 675, 660. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (1H, dddd, *J* = 13.8, *J* = 12.0, *J* = 10.8, *J* = 2.5) and 1.68 (1H, ddd, J_{gem} = 13.8, *J* = 2.2, *J* = 2.0, 8-CH$_2$); 1.25 (3H, s, 14-CH$_3$); 1.86 (1H, ddd, *J* = 13.6, *J* = 12.2, *J* = 2.0) and 1.93 (1H, ddd, *J* = 13.6, *J* = 5.0, *J* = 2.2, 9-CH$_2$); 1.98 (3H, s, 15-CH$_3$); 2.10 (1H, br. d, *J* = 16.2) and 2.74 (1H, br. d, *J* = 16.2, 2-CH$_2$); 2.26 (3H, s, SCH$_3$); 2.49–2.67 (1H, m, 7-CH); 2.95 (1H, d, *J* = 10.2, 5-CH); 4.07 (1H, dd, *J* = 10.2, *J* = 9.8, 6-CH); 5.56 (1H, s, 3-CH); 7.11 (1H, d, *J* = 7.2, H-6 Ar); 7.15 (1H, dd, *J* = 7.2, *J* = 7.6, H-5 Ar); 7.18 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ar); 7.23 (1H, d, *J* = 7.6, H-3 Ar); 7.68 (1H, d, *J* = 2.0, 13-CH). ^{13}C NMR spectrum, δ, ppm: 18.1 (C-15); 19.7 (SCH$_3$); 20.3 (C-8); 22.4 (C-14); 34.0 (C-9); 39.4 (C-2); 50.6 (C-7); 53.1 (C-5); 62.7 (C-10); 72.5 (C-1); 82.7 (C-6); 124.8 (C-3); 125.2 (C-5'); 128.0 (C-6'); 128.8 (C-4'); 130.0 (C-3'); 133.1 (C-2'); 136.2 (C-13); 137.1 (C-11); 137.4 (C-1'); 140.5 (C-4); 171.6 (C-12). Found, %: C 71.54; H 6.31; S 8.56. $C_{22}H_{24}O_3S$. Calculated, %: C 71.71; H 6.56; S 8.70.

(1a*S*,3a*S*,6a*S*,9a*R*,*Z*)-1a,7-Dimethyl-4-(2-methylbenzylidene)-2,3,3a,4,6b,9-hexahydro-1a*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-5(6a*H*)-one (6a). Yield 17 mg (5%, method I, IV), 65 mg (19%, method II), 62 mg (18%, method III), colorless crystals, mp 126–128°C (Et$_2$O). $[\alpha]_D^{26}$ +47 (*c* 0.43, CHCl$_3$). IR spectrum, ν, cm^{-1}: 3015, 2960, 2910, 2866, 1750, 1655, 1609, 1506, 1460, 1385, 1344, 1310, 1278, 1260, 1222, 1190, 1155, 1123, 1110, 1095, 1070, 1040, 1015, 1000, 950, 860, 845, 800, 758, 725, 685, 650. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (1H, dddd, *J* = 13.8, *J* = 11.2, *J* = 9.6, *J* = 2.5) and 1.70 (1H, br. d, J_{gem} = 13.8, 8-CH$_2$); 1.34 (3H, s, 14-CH$_3$); 1.88 (1H, ddd, *J* = 14.6, *J* = 11.2, *J* = 2.2) and 1.89–1.99 (1H, m, 9-CH$_2$); 1.95 (3H, s, 15-CH$_3$); 1.98 (1H, br. d, *J* = 16.4) and 2.86 (1H, br. d, *J* = 16.4, 2-CH$_2$); 2.42 (3H, s, ArC<u>H</u>$_3$); 2.56–2.61 (1H, m, 7-CH); 2.94 (1H, br. d, *J* = 10.4, 5-CH); 4.08 (1H, dd, *J* = 10.4, *J* = 10.0, 6-CH); 5.58 (1H, s, 3-CH); 7.11 (1H, d, *J* = 7.6, H-6 Ar); 7.16 (1H, dd, *J* = 7.6, *J* = 7.2, H-5 Ar); 7.22 (1H, d, *J* = 7.4, H-3 Ar); 7.28 (1H, dd, *J* = 7.6, *J* = 7.4, H-4 Ar); 7.58 (1H, dd, *J* = 2.2, *J* = 1.8, 13-CH). ^{13}C NMR spectrum, δ, ppm: 15.8 (Ar<u>C</u>H$_3$); 18.2 (C-15); 21.5 (C-8); 22.6 (C-14); 33.0 (C-9); 39.4 (C-2); 50.8 (C-7); 52.5 (C-5); 62.4 (C-10); 72.3 (C-1); 81.9 (C-6); 124.5 (C-3); 125.5 (C-5'); 128.5 (C-6'); 129.2 (C-4'); 130.8 (C-3'); 133.7 (C-2'); 134.7 (C-13); 137.7 (C-11); 138.6 (C-1'); 140.4 (C-4); 168.7 (C-12). Mass spectrum, *m*/*z* (I_{rel}, %): 337 [M+H]$^+$ (11), 336 (100), 320 (23), 304 (30), 269 (15), 265 (30), 231 (32), 199 (21), 185 (28), 171 (45), 156 (16), 141 (36), 129 (65), 119 (30), 105 (24), 97 (25), 79 (36), 77 (21), 43 (34). Found, *m*/*z*: 336.1722 [M]$^+$. $C_{22}H_{24}O_3$. Calculated, *m*/*z*: 336.1725.

(1a*S*,3a*S*,6a*S*,9a*R*,*Z*)-1a,7-Dimethyl-4-[2-(methylsulfanyl)benzylidene]-2,3,3a,4,6b,9-hexahydro-1a*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-5(6a*H*)-one (6b). Yield 26 mg (7%, method II), yellowish crystals, mp 118–121°C (Et$_2$O). $[\alpha]_D^{31}$ +81 (*c* 0.68, CHCl$_3$). IR spectrum, ν, cm^{-1}: 3015, 2960, 2923, 1752, 1645, 1600, 1502, 1468, 1420, 1366, 1340, 1321, 1300, 1270, 1232, 1180, 1155, 1130, 1110, 1090, 1075, 1048, 1030, 1010, 990, 945, 845, 800, 738, 714, 680, 650. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (1H, dddd, *J* = 13.8, *J* = 12.2, *J* = 10.4, *J* = 2.0) and 1.68 (1H, dm, J_{gem} = 13.8, 8-CH$_2$); 1.25 (3H, s, 14-CH$_3$); 1.86 (1H, ddd, *J* = 14.4, *J* = 12.2, *J* = 2.8) and 1.93 (1H, ddd, *J* = 14.4, *J* = 4.8, *J* = 2.5, 9-CH$_2$); 1.98 (3H, s, 15-CH$_3$); 2.10 (1H, br. d, *J* = 16.2) and 2.74 (1H, br. d, *J* = 16.2, 2-CH$_2$); 2.26 (3H, s, SCH$_3$); 2.48–2.67 (1H, m, 7-CH); 2.95 (1H, br. d, *J* = 10.4, 5-CH); 4.07 (1H, dd, *J* = 10.4, *J* = 9.8, 6-CH); 5.56 (1H, s, 3-CH); 7.11 (1H, d, *J* = 7.2, H-6 Ar); 7.15 (1H, dd, *J* = 7.6, *J* = 7.2, H-5 Ar); 7.18 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ar); 7.23 (1H, d, *J* = 7.6, H-3 Ar); 7.58 (1H, dd, *J* = 2.0, 13-CH). ^{13}C NMR spectrum, δ, ppm: 18.1 (C-15); 19.7 (SCH$_3$); 20.3 (C-8); 22.4 (C-14); 34.0 (C-9); 39.4 (C-2); 50.6 (C-7); 53.1 (C-5); 62.7 (C-10); 72.5 (C-1); 81.7 (C-6); 124.8 (C-3); 125.2 (C-5'); 128.0 (C-6'); 128.9 (C-4'); 130.0 (C-3'); 133.1 (C-2'); 136.2 (C-13); 137.0 (C-1'); 137.9 (C-11); 140.5 (C-4); 169.1 (C-12). Found, %: C 71.63; H 6.62; S 8.34. $C_{22}H_{24}O_3S$. Calculated, %: C 71.71; H 6.56; S 8.70.

(1a*S*,6a*R*,9a*R*)-1a,7-Dimethyl-4-(2-methylphenyl)-2,3,6b,9-tetrahydro-1a*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]-furan-5(6a*H*)-one (7a). Yield 111 mg (33%, method I), 50 mg (15%, method II), 10 mg (3%, method III), colorless crystals, mp 101–104°C (Et$_2$O). $[\alpha]_D^{28}$ +65 (*c* 0.55, CHCl$_3$). IR spectrum, ν, cm^{-1}: 3025, 2960, 2887, 1749, 1650, 1500, 1495, 1460, 1420, 1380, 1325, 1250, 1230, 1215, 1138,

1122, 1110, 1087, 1055, 1025, 1015, 1000, 990, 965, 950, 918, 900, 870, 830, 775, 760, 740, 702, 680, 655. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, s, 14-CH_3); 1.78 (1H, ddd, *J* = 14.2, *J* = 11.5, *J* = 2.8) and 1.96 (1H, ddd, *J* = 14.2, *J* = 5.5, *J* = 2.2, 9-CH_2); 1.98 (3H, s, 15-CH_3); 2.20 (1H, br. d, *J* = 16.4) and 2.74 (1H, br. d, *J* = 16.4, 2-CH_2); 2.27–2.35 (1H, m) and 2.51 (1H, ddd, *J* = 13.6, *J* = 5.5, *J* = 2.8, 8-CH_2); 2.32 (3H, s, ArC$\underline{H}_3$); 2.58 (1H, br. d, *J* = 9.8, 5-CH); 3.52 (1H, d, *J* = 12.8) and 3.58 (1H, d, *J* = 12.8, 13-CH_2); 4.82 (1H, br. d, *J* = 9.8, 6-CH); 5.59 (1H, br. s, 3-CH); 6.88 (1H, dd, *J* = 7.6, *J* = 2.2, H-6 Ar); 7.15 (1H, dt, *J* = 7.6, *J* = 2.0, H-5 Ar); 7.10 (1H, dd, *J* = 7.6, *J* = 2.2, H-3 Ar); 7.13 (1H, dt, *J* = 7.6, *J* = 2.0, H-4 Ar). ^{13}C NMR spectrum, δ, ppm: 18.3 (C-15); 19.7 (Ar$\underline{C}H_3$); 22.1 (C-14); 22.2 (C-8); 26.6 (C-13); 30.5 (C-9); 38.6 (C-2); 52.1 (C-5); 61.3 (C-10); 70.3 (C-1); 82.6 (C-6); 125.1 (C-11); 125.3 (C-3); 125.9 (C-5'); 126.4 (C-4'); 127.8 (C-6'); 130.2 (C-3'); 136.0 (C-2'(1')); 136.2 (C-1'(2')); 140.4 (C-4); 165.2 (C-7); 173.7 (C-12). Found, %: C 78.42; H 7.25. $C_{22}H_{24}O_3$. Calculated, %: C 78.54; H 7.19.

(1a*S*,6a*R*,9a*R*)-1a,7-Dimethyl-4-[2-(methylsulfanyl)benzyl]-2,3,6b,9-tetrahydro-1a*H*-oxireno[2',3':8,8a]azuleno-[4,5-*b*]furan-5(6a*H*)-one (7b). Yield 70 mg (19%, method II), colorless crystals, mp 113–116°C (Et_2O). $[\alpha]_D^{28}$ +52 (*c* 0.38, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3020, 2920, 2886, 1745, 1650, 1500, 1468, 1425, 1388, 1345, 1310, 1255, 1237, 1220, 1165, 1130, 1110, 1095, 1068, 1030, 1018, 1000, 980, 960, 950, 910, 900, 877, 839, 800, 768, 740, 710, 665, 640. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, s, 14-CH_3); 1.81 (1H, ddd, *J* = 14.2, *J* = 12.0, *J* = 2.7) and 1.95 (1H, ddd, *J* = 14.2, *J* = 5.8, *J* = 2.4, 9-CH_2); 1.98 (3H, s, 15-CH_3); 2.19 (1H, br. d, *J* = 16.4) and 2.72 (1H, br. d, *J* = 16.4, 2-CH_2); 2.29 (1H, ddd, *J* = 13.8, *J* = 12.0, *J* = 2.4) and 2.57 (1H, ddd, *J* = 13.8, *J* = 5.8, *J* = 2.7, 8-CH_2); 2.45 (3H, s, SCH_3); 2.59 (1H, br. d, *J* = 10.2, 5-CH); 3.66 (1H, d, *J* = 12.5) and 3.68 (1H, d, *J* = 12.5, 13-CH_2); 4.80 (1H, br. d, *J* = 10.2, 6-CH); 5.58 (1H, br. s, 3-CH); 7.07 (1H, dd, *J* = 7.6, *J* = 2.2, H-3 Ar); 7.11 (1H, dt, *J* = 7.6, *J* = 2.2, H-5 Ar); 7.18 (1H, dt, *J* = 7.6, *J* = 2.0, H-4 Ar); 7.21 (1H, dd, *J* = 7.6, *J* = 2.0, H-6 Ar). ^{13}C NMR spectrum, δ, ppm: 16.1 (C-15); 18.3 (C-14); 22.1 (SCH_3); 22.3 (C-8); 27.0 (C-13); 30.5 (C-9); 38.6 (C-2); 51.9 (C-5); 61.4 (C-10); 70.8 (C-1); 82.6 (C-6); 124.7 (C-11); 125.2 (C-3); 125.9 (C-5'); 127.1 (C-4'); 128.7 (C-6'); 129.2 (C-3'); 136.0 (C-2'); 137.0 (C-1'); 140.5 (C-4); 165.3 (C-7); 173.6 (C-12). Mass spectrum, *m*/*z* (I_{rel}, %): 368 $[M]^+$ (15), 367 (6), 366 (30), 352 (13), 337 (24), 332 (26), 309 (17), 277 (21), 250 (21), 236 (39), 205 (31), 193 (24), 171 (12), 156 (41), 141 (23), 128 (100), 119 (31), 105 (52), 91 (34), 77 (56), 65 (33), 55 (42). Found, *m*/*z*: 368.1452 $[M]^+$. Calculated, *m*/*z*: 368.1446. Found, %: C 71.44; H 6.28; S 8.52. $C_{22}H_{24}O_3S$. Calculated, %: C 71.71; H 6.56; S 8.70.

(7a*R*,8a*S*,8b*S*,8c*R*)-6,8a-Dimethyl-3-(2-methylphenyl)-4,5,7,7a,8b,8c-hexahydrooxireno[2',3':2,3]azuleno[4,5-*b*]-furan-2(8a*H*)-one (10). Yield 14 mg (4%, method II), 17 mg (5%, method IV), colorless crystals, mp 137–139°C. R_f 0.46 (petroleum ether–EtOAc, 2:1). $[\alpha]_D^{26}$ +28 (*c* 0.52, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3025, 2920, 2866, 1749, 1652, 1494, 1463, 1422, 1379, 1320, 1250, 1232, 1219, 1135, 1112, 1097, 1075, 1037, 1021, 1008, 989, 966, 946, 915, 900, 867, 829, 770, 758, 741, 722, 681, 661, 640. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.51 (3H, s, 15-CH_3); 1.69 (3H, s, 14-CH_3); 1.91 (1H, ddd, *J* = 13.0, *J* = 12.8, *J* = 2.2) and 1.99 (1H, ddd, *J* = 13.0, *J* = 5.6, *J* = 2.0, 9-CH_2); 1.95 (1H, dddd, *J* = 13.8, *J* = 12.4, *J* = 9.8, *J* = 2.0) and 2.73 (1H, ddd, *J* = 13.8, *J* = 5.6, *J* = 2.2, 8-CH_2); 2.24 (3H, s, ArC$\underline{H}_3$); 2.44 (1H, br. d, *J* = 16.2) and 2.74 (1H, br. d, *J* = 16.2, 2-CH_2); 2.78 (1H, br. d, *J* = 9.8, 5-CH); 3.57 (1H, d, *J* = 12.0) and 3.61 (1H, d, *J* = 12.0, 13-CH_2); 3.40 (1H, br. s, $J_{half\ width}$ = 6, 3-CH); 4.45 (1H, br. d, *J* = 9.8, 6-CH); 6.98 (1H, dd, *J* = 7.6, *J* = 1.8, H-3 Ar); 7.08 (1H, dt, *J* = 7.6, *J* = 2.0, H-4 Ar); 7.10 (1H, dd, *J* = 7.6, *J* = 2.0, H-6 Ar); 7.13 (1H, dt, *J* = 7.6, *J* = 2.0, H-5 Ar). ^{13}C NMR spectrum, δ, ppm: 19.1 (C-15); 19.7 (C-14); 21.4 (Ar$\underline{C}H_3$); 26.6 (C-13); 27.6 (C-8); 31.5 (C-9); 32.8 (C-2); 51.4 (C-5); 63.3 (C-3); 67.0 (C-4); 79.4 (C-6); 124.9 (C-2'); 126.0 (C-4'); 126.5 (C-6'); 127.9 (C-3'); 130.3 (C-5'); 131.9 (C-1'); 135.9 (C-11(1,10)); 136.0 (C-10(1,11)); 136.2 (C-1(10,11)); 165.5 (C-7); 173.0 (C-12). Mass spectrum, *m*/*z* (I_{rel}, %): 336 $[M]^+$ (44), 335 (12), 321 (37), 171 (27), 143 (28), 136 (49), 135 (100), 128 (47), 121 (34), 105 (93), 91 (54), 77 (34), 43 (64). Found, *m*/*z*: 336.1718 $[M]^+$. $C_{22}H_{24}O_3$. Calculated, *m*/*z*: 336.1725.

(3a*S*,7a*R*,8a*S*,8b*S*,8c*S*,*E*)-6,8a-Dimethyl-3-(2-methylbenzylidene)-3,3a,4,5,7,7a,8b,8c-octahydrooxireno-[2',3':2,3]azuleno[4,5-*b*]furan-2(8a*H*)-one (11). Yield 57 mg (17%, method IV), colorless crystals, mp 118–120°C (Et_2O). $[\alpha]_D^{26}$ +67 (*c* 0.67, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3018, 2960, 2924, 2860, 1752, 1655, 1605, 1500, 1480, 1445, 1385, 1345, 1310, 1288, 1276, 1248, 1220, 1188, 1150, 1138, 1120, 1105, 1090, 1075, 1045, 1020, 1000, 978, 880, 820, 800, 760, 732, 685, 640. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (1H, dddd, *J* = 13.8, *J* = 12.2, *J* = 9.8, *J* = 2.8, 8-CH_A); 1.55 (3H, s, 15-CH_3); 1.68 (3H, s, 14-CH_3); 1.78–1.85 (2H, m, 8-CH_B, 9-CH_A); 2.09 (1H, ddd, *J* = 13.5, *J* = 5.8, *J* = 2.8, 9-CH_B); 2.24 (3H, s, ArC$\underline{H}_3$); 2.40 (1H, br. d, *J* = 16.6) and 2.66 (1H, br. d, *J* = 16.6, 2-CH_2); 3.03 (1H, dddd, *J* = 10.0, *J* = 9.8, *J* = 2.8, *J* = 2.0, 7-CH); 3.08 (1H, dd, *J* = 10.6, *J* = 2.0, 5-CH); 3.38 (1H, s, 3-CH); 3.67 (1H, dd, *J* = 10.6, *J* = 10.0, 6-CH); 7.10 (1H, dd, *J* = 7.6, *J* = 1.6, H-3 Ar); 7.16 (1H, br. t, *J* = 7.6, H-4 Ar); 7.18 (1H, dd, *J* = 7.6, *J* = 2.0, H-6 Ar); 7.22 (1H, dt, *J* = 7.6, *J* = 2.0, H-4 Ar); 7.77 (1H, d, *J* = 2.0, 13-CH). ^{13}C NMR spectrum, δ, ppm: 19.1 (C-15); 19.8 (C-14); 22.3 (Ar$\underline{C}H_3$); 25.3 (C-8); 33.3 (C-2); 34.3 (C-9); 52.3 (C-5); 54.3 (C-7); 63.8 (C-3); 67.1 (C-4); 80.9 (C-6); 125.2 (C-4'); 128.5 (C-6'(3')); 128.7 (C-3'(6')); 129.8 (C-5'); 130.5 (C-2'); 133.2 (C-1'); 133.8 (C-1); 134.7 (C-10); 136.0 (C-13); 136.6 (C-11); 170.8 (C-12). Mass spectrum, *m*/*z* (I_{rel}, %): 337 $[M+H]^+$ (7), 336 (24), 321 (14), 268 (11), 171 (16), 155 (14), 143 (24), 141 (42), 128 (100), 115 (69), 105 (36), 91 (68), 77 (34), 43 (79). Found, *m*/*z*: 336.1721 $[M]^+$. $C_{22}H_{24}O_3$. Calculated, *m*/*z* 336.1725.

(3a*R*,4*S*,6a*R*,9*S*,9a*R*,9b*R*,*E*)-4-Hydroxy-9-methyl-3-(2-methylbenzylidene)-6-methylideneoctahydroazuleno-[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (14a). Yield 66 mg (18%, method II), 26 mg (7%, method IV), colorless crystals, mp 165–167°C ($CHCl_3$). $[\alpha]_D^{26}$ +73 (*c* 0.66, $CHCl_3$). IR

spectrum, ν, cm^{-1}: 3560, 3010, 2963, 2914, 1753, 1730, 1635, 1600, 1575, 1510, 1450, 1358, 1310, 1250, 1200, 1175, 1120, 1100, 1066, 1040, 1025, 1010, 992, 900, 828, 765, 720, 640. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, d, *J* = 6.8, 15-CH_3); 2.16 (1H, d, *J* = 7.2, OH); 2.10 (3H, s, ArC$\underline{H}_3$); 2.28 (1H, ddd, *J* = 9.8, *J* = 9.0, *J* = 2.5, 5-CH); 2.31 (1H, ddd, *J* = 13.5, *J* = 6.0, *J* = 2.6) and 2.72 (1H, dd, *J* = 13.5, *J* = 3.6, 9-CH_2); 2.38–2.58 (3H, m, 2-CH_2, 4-CH); 2.46–2.58 (3H, m, 4-CH and 2-CH_2); 3.34 (1H, ddd, *J* = 9.0, *J* = 8.2, *J* = 4.6, 1-CH); 3.76 (1H, ddd, *J* = 9.1, *J* = 7.6, *J* = 2.6, 7-CH); 3.98 (1H, dddd, *J* = 7.6, *J* = 7.2, *J* = 6.0, *J* = 3.6, 8-CH); 4.12 (1H, dd, *J* = 9.8, *J* = 9.1, 6-CH); 4.72 (1H, br. s) and 5.02 (1H, br. s, 14-CH_2); 7.14 (1H, t, *J* = 7.6, H-5 Ar); 7.18 (1H, d, *J* = 7.6, H-3 Ar); 7.21 (1H, t, *J* = 7.6, H-4 Ar); 7.43 (1H, d, *J* = 7.6, H-6 Ar); 7.96 (1H, d, *J* = 1.6, 13-CH). ^{13}C NMR spectrum, δ, ppm: 15.5 (C-15); 20.0 (Ar$\underline{C}H_3$); 39.8 (C-1); 43.1 (C-2); 45.2 (C-9); 48.5 (C-4); 49.2 (C-7); 51.6 (C-5); 74.3 (C-8); 82.8 (C-6); 113.6 (C-14); 125.2 (C-5'); 127.4 (C-2'); 129.1 (C-4'); 129.5 (C-6'(3')); 129.9 (C-3'(6')); 133.0 (C-1'); 135.9 (C-11); 141.5 (C-13); 142.9 (C-10); 171.6 (C-12); 219.1 (C-3). Found, %: C 74.76; H 6.92. $C_{22}H_{24}O_4$. Calculated, %: C 74.98; H 6.86.

(3a*R*,4*S*,6a*R*,9*S*,9a*R*,9b*R*,*E*)-4-Hydroxy-9-methyl-3-(2-methoxybenzylidene)-6-methylideneoctahydroazuleno-[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (14b). Yield 40 mg (11%, method II), colorless crystals mp 154–156°C (Et_2O). $[\alpha]_D^{28}$ +69 (*c* 0.44, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3602, 3016, 2993, 2914, 1753, 1731, 1633, 1601, 1574, 1512, 1443, 1360, 1309, 1250, 1201, 1174, 1115, 1080, 1061, 1043, 1024, 1007, 988, 920, 830, 760, 740, 660. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, d, *J* = 6.8, 15-CH_3); 2.16 (1H, br. d, *J* = 7.6, OH); 2.28 (1H, ddd, *J* =10.2, *J* = 9.0, *J* = 2.2, 5-CH); 2.31 (1H, dd, *J* = 13.6, *J* = 6.4) and 2.78 (1H, dd, *J* = 13.6, *J* = 3.2, 9-CH_2); 2.46 (1H, d, *J* = 2.2, 4-CH); 2.44 (1H, dd, *J* = 13.2, *J* = 4.6) and 2.48 (1H, dd, *J* = 13.2, *J* = 8.2, 2-CH_2); 3.20 (1H, ddd, *J* = 9.0, *J* = 8.2, *J* = 4.6, 1-CH); 3.68 (1H, dddd, *J* = 8.6, *J* = 8.0, *J* = 2.2, 7-CH); 3.87 (3H, s, OCH_3); 3.94 (1H, dddd, *J* = 8.0, *J* = 7.6, *J* = 6.4, *J* = 3.2, 8-CH); 4.08 (1H, dd, *J* = 10.2, *J* = 8.6, 6-CH); 4.74 (1H, br. s) and 5.03 (1H, br. s, 14-CH_2); 6.90 (1H, d, *J* = 7.6, H-3 Ar); 6.95 (1H, t, *J* = 7.6, H-5 Ar); 7.35 (1H, t, *J* = 7.6, H-4 Ar); 7.47 (1H, d, *J* = 7.6, H-6 Ar); 7.96 (1H, s, 13-CH). ^{13}C NMR spectrum, δ, ppm: 14.6 (C-15); 39.8 (C-1); 43.1 (C-2); 46.5 (C-4); 46.8 (C-9); 48.9 (C-7); 50.9 (C-5); 55.3 (OCH_3); 75.3 (C-8); 82.8 (C-6); 110.9 (C-3'); 115.5 (C-14); 120.6 (C-5'); 123.4 (C-1'); 126.2 (C-11); 131.0 (C-4'); 131.6 (C-6'); 137.3 (C-13); 143.7 (C-10); 157.7 (C-2'); 172.2 (C-12); 219.2 (C-3). Found, %: C 71.83; H 6.39. $C_{22}H_{24}O_5$. Calculated, %: C 71.72; H 6.57.

(3a*R*,4*S*,6a*R*,9*S*,9a*R*,9b*R*,*E*)-4-Hydroxy-9-methyl-3-(4-methoxybenzylidene)-6-methylideneoctahydroazuleno-[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (14c). Yield 49 mg (14%, method II), colorless crystals, mp 161–163°C (EtOAc). $[\alpha]_D^{26}$ +22.9 (*c* 0.42, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3545, 3020, 2983, 2914, 1753, 1731, 1633, 1601, 1574, 1512, 1443, 1360, 1309, 1250, 1201, 1174, 1115, 1080, 1061, 1043, 1024, 1007, 829, 762, 746, 628. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, d, *J* = 6.8, 15-CH_3); 2.16 (1H, br. d, *J* = 7.2, OH); 2.26 (1H, ddd, *J* =10.2, *J* = 9.2, *J* = 2.2, 5-CH); 2.31 (1H, dd, *J* = 13.8, *J* = 6.4) and 2.82 (1H, dd, *J* = 13.8, *J* = 3.4, 9-CH_2); 2.34 (1H, d, *J* = 2.2, 4-CH); 2.52 (1H, ddd, *J* = 13.5, *J* = 4.2, *J* = 2.2) and 2.57 (1H, dd, *J* = 13.5, *J* = 7.4, 2-CH_2); 3.25 (1H, ddd, *J* = 9.2, *J* = 7.4, *J* = 4.2, 1-CH); 3.78 (1H, ddd, *J* = 8.6, *J* = 8.0, *J* = 2.2, 7-CH); 3.82 (3H, s, OCH_3); 3.88 (1H, dddd, *J* = 8.0, *J* = 7.2, *J* = 6.4, *J* = 3.4, 8-CH); 3.98 (1H, dd, *J* = 10.2, *J* = 8.6, 6-CH); 4.75 (1H, br. s) and 5.09 (1H, br. s, 14-CH_2); 6.90 (2H, d, *J* = 7.6, H-3,5 Ar); 7.61 (2H, d, *J* = 7.6, H-2,6 Ar); 7.94 (1H, s, 13-CH). ^{13}C NMR spectrum, δ, ppm: 14.4 (C-15); 39.6 (C-1); 43.2 (C-2); 46.6 (C-4); 47.6 (C-9); 48.3 (C-7); 50.5 (C-5); 55.1 (OCH_3); 76.3 (C-8); 83.4 (C-6); 113.9 (C-3',5'); 115.6 (C-14); 122.2 (C-1'); 126.1 (C-11); 132.5 (C-2',6'); 141.7 (C-13); 143.9 (C-10); 161.2 (C-4'); 171.8 (C-12); 219.2 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 369 $[M+H]^+$ (27), 368 (100), 242 (22), 199 (15), 145 (31), 121 (20), 115 (15), 108 (20), 91 (19), 77 (17), 69 (17), 41 (39). Found, *m*/*z*: 368.1622 $[M]^+$. $C_{22}H_{24}O_5$. Calculated, *m*/*z*: 368.1624.

(3a*R*,4*S*,6a*R*,9*S*,9a*R*,9b*R*,*Z*)-4-Hydroxy-9-methyl-3-(2-methylbenzylidene)-6-methylideneoctahydroazuleno-[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (15a). Yield 46 mg (13%, method II), 92 mg (26%, method IV), colorless crystals, mp 145–147°C (Et_2O). $[\alpha]_D^{26}$ +103 (*c* 0.87, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3553, 3021, 2960, 2887, 1755, 1643, 1602, 1500, 1470, 1438, 1342, 1260, 1201, 1167, 1185, 1119, 1049, 997, 903, 773, 710, 660. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, d, *J* = 6.8, 15-CH_3); 2.16 (1H, br. d, *J* = 7.8, OH); 2.25 (3H, s, ArC$\underline{H}_3$); 2.30 (1H, ddd, *J* = 10.0, *J* = 8.8, *J* = 2.2, 5-CH); 2.33 (1H, ddd, *J* = 13.8, *J* = 6.8, *J* = 1.6) and 2.81 (1H, dd, *J* = 13.8, *J* = 3.6, 9-CH_2); 2.39 (1H, d, *J* = 2.2, 4-CH); 2.44 (1H, dd, *J* = 13.2, *J* = 4.6) and 2.48 (1H, dd, *J* = 13.2, *J* = 8.5, 2-CH_2); 3.17 (1H, ddd, *J* = 8.6, *J* = 6.6, *J* = 2.0, 7-CH); 3.11 (1H, ddd, *J* = 8.8, *J* = 8.5, *J* = 4.6, 1-CH); 4.02–4.10 (1H, m, 8-CH); 4.12 (1H, dd, *J* = 9.8, *J* = 8.6, 6-CH); 4.88 (1H, s) and 5.05 (1H, s, 14-CH_2); 7.14 (1H, t, *J* = 7.6, H-5 Ar); 7.16 (1H, d, *J* = 7.6, H-3 Ar); 7.22 (1H, t, *J* = 7.6, H-4 Ar); 7.43 (1H, d, *J* = 7.6, H-6 Ar); 7.89 (1H, d, *J* = 1.6, 13-CH). ^{13}C NMR spectrum, δ, ppm: 15.3 (C-15); 19.9 (Ar$\underline{C}H_3$); 40.6 (C-1); 42.6 (C-2); 46.0 (C-9); 46.7 (C-4); 50.7 (C-7); 51.6 (C-5); 73.2 (C-8); 80.2 (C-6); 115.8 (C-14); 125.1 (C-5'); 127.4 (C-2'); 128.9 (C-4'); 129.5 (C-6'); 129.7 (C-3'); 133.3 (C-1'); 136.2 (C-11); 141.5 (C-13); 142.9 (C- %): 353 $[M+H]^+$ (5), 352 (26), 334 (20), 305 (13), 268 (15), 183 (26), 165 (29), 160 (29), 143 (18), 141 (42), 131 (29), 129 (100), 128 (87), 115 (69), 105 (52), 91 (64), 77 (40), 69 (44), 41 (77). Found, *m*/*z*: 352.1666 $[M]^+$. $C_{22}H_{24}O_4$. Calculated, *m*/*z*: 352.1675.

(3a*R*,4*S*,6a*R*,9*S*,9a*R*,9b*R*,*Z*)-4-Hydroxy-9-methyl-3-(2-methoxybenzylidene)-6-methylideneoctahydroazuleno-[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (15b). Yield 112 mg (32%, method II), colorless crystals, mp 166–168°C (Et_2O). $[\alpha]_D^{26}$ +58 (*c* 0.44, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3520, 3018, 2973, 2914, 1748, 1641, 1600, 1510, 1340, 1310, 1200, 1185, 1158, 1120, 1050, 1010, 990, 910, 770, 712, 665. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, d, *J* = 6.8, 15-CH_3); 2.18 (1H, br. d, *J* = 7.5, OH); 2.27 (1H, ddd, *J* = 9.8, *J* = 9.0, *J* = 2.5, 5-CH); 2.33 (1H, dd, *J* = 13.5,

J = 6.2) and 2.78 (1H, dd, J = 13.5, J = 6.8, 9-CH_2); 2.41 (1H, d, J = 2.5, 4-CH); 2.44 (1H, dd, J = 13.1, J = 4.4) and 2.48 (1H, dd, J = 13.1, J = 7.8, 2-CH_2); 3.13 (1H, ddd, J = 8.6, J = 8.0, J = 2.0, 7-CH); 3.20 (1H, ddd, J = 9.0, J = 7.8, J = 4.4, 1-CH); 3.85 (3H, s, OCH_3); 3.98 (1H, dddd, J = 8.0, J = 7.5, J = 6.8, J = 3.2, 8-CH); 4.01 (1H, dd, J = 9.8, J = 8.6, 6-CH); 4.84 (1H, br. s) and 5.01 (1H, br. s, 14-CH_2); 6.92 (1H, d, J = 7.6, H-3 Ar); 6.98 (1H, t, J = 7.6, H-5 Ar); 7.31 (1H, t, J = 7.6, H-4 Ar); 7.48 (1H, d, J = 7.6, H-6 Ar); 7.91 (1H, s, 13-CH). ^{13}C NMR spectrum, δ, ppm: 14.3 (C-15); 40.8 (C-1); 42.6 (C-2); 45.9 (C-9); 46.5 (C-4); 51.3 (C-7); 51.9 (C-5); 55.6 (OCH_3); 73.2 (C-8); 80.2 (C-6); 110.5 (C-3'); 115.8 (C-14); 120.0 (C-5'); 123.3 (C-1'); 126.2 (C-11); 129.1 (C-4'); 131.6 (C-6'); 137.5 (C-13); 143.4 (C-10); 157.4 (C-2'); 168.1 (C-12); 218.6 (C-3). Found, %: C 71.58; H 6.72. $C_{22}H_{24}O_5$. Calculated, %: C 71.72; H 6.57.

(3a*R*,4*S*,6a*R*,9*S*,9a*R*,9b*R*,*Z*)-4-Hydroxy-9-methyl-3-(4-methoxybenzylidene)-6-methylideneoctahydroazuleno-[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (15c). Yield 123 mg (35%, method II), colorless crystals, mp 146–148°C (EtOAc). $[\alpha]_D^{26}$ +48 (*c* 0.56, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3535, 3018, 2980, 2920, 1760, 1650, 1600, 1500, 1420, 1340, 1200, 1180, 1160, 1120, 1050, 1010, 975, 910, 812, 775, 740, 700, 665. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.26 (3H, d, J = 6.8, 15-CH_3); 2.12 (1H, br. d, J = 7.0, OH); 2.27 (1H, ddd, J = 10.2, J = 9.0, J = 2.2, 5-CH); 2.33 (1H, dd, J = 13.8, J = 4.8) and 2.78 (1H, dd, J = 13.8, J = 6.8, 9-CH_2); 2.41 (1H, d, J = 2.2, 4-CH); 2.44 (1H, dd, J = 13.1, J = 4.4) and 2.48 (1H, dd, J = 13.1, J = 7.8, 2-CH_2); 3.08 (1H, ddd, J = 8.8, J = 8.0, J = 2.0, 7-CH); 3.20 (1H, ddd, J = 9.0, J = 7.8, J = 4.4, 1-CH); 3.80 (3H, s, OCH_3); 3.99 (1H, dddd, J = 8.0, J = 7.0, J = 6.8, J = 4.8, 8-CH); 4.03 (1H, dd, J = 10.2, J = 8.8, 6-CH); 4.91 (1H, br. s) and 5.06 (1H, br. s, 14-CH_2); 6.92 (2H, d, J = 7.6, H-3,5 Ar); 7.68 (1H, s, 13-CH); 7.80 (2H, d, J = 7.6, H-2,6 Ar). ^{13}C NMR spectrum, δ, ppm: 15.7 (C-15); 41.1 (C-1); 42.7 (C-2); 45.4 (C-9); 46.8 (C-4); 52.1 (C-7); 51.9 (C-5); 55.8 (OCH_3); 73.4 (C-8); 80.2 (C-6); 113.5 (C-3',5'); 115.9 (C-14); 124.1 (C-1'); 126.2 (C-11); 133.3 (C-2',6'); 142.2 (C-13); 143.4 (C-10); 160.8 (C-4'); 168.9 (C-12); 219.2 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 369 $[M+H]^+$ (8), 368 (100), 308 (18), 243 (12), 202 (11), 131 (10), 121 (14), 108 (20), 91 (18), 79 (12), 67 (16), 53 (13), 41 (28). Found, *m*/*z*: 368.1621 $[M]^+$. $C_{22}H_{24}O_5$. Calculated, *m*/*z*: 368.1624.

X-ray structural study of compounds 15a,c. Crystals of compounds **15a**,**c** suitable for X-ray structural analysis were obtained by recrystallization from EtOAc. Diffraction measurements were performed on a Bruker Kappa APEX II diffractometer (MoKα radiation, graphite monochromator, CCD-detector) at 296(2) K. The structures were solved by direct method. All calculations were performed by using SHELXTL software suite.[17] The crystallographic dataset was deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1491641 (compounds **15a**) and CCDC 1491642 (compound **15c**)).

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