

Halogenation of Sesquiterpene γ -Lactone Molecules: New Compounds, Structure, and Biological Activity

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Physicochemical and spectral data for the synthesized compounds

1,10 β -epoxy-3.4 β -dichloromethan-5,7 α ,6 β (H)-guai-11(13)-en-6,12-olide (11).

m.p. 154-156°C, molecular formula C₁₆H₁₈O₃Cl₂, Mr 329 g/mol, R_f 0.32 (ethyl acetate/petroleum ether, 2:4). Yield: 0.007 g (5 %).

IR spectrum (KBr, ν , cm⁻¹): 3023, 2993, 2975, 2928, 2898, 2883, 1769 (C=O of γ -lactone), 1670 (C=C), 1436, 1409, 1383, 1337, 1307, 1296, 1251, 1231, 1219, 1194, 1179, 1156 (epoxy-group), 1138, 1126, 1104, 1066, 1030, 1004, 974, 958, 941, 922, 884, 873, 849, 836, 816, 711, 669 (C-Cl), 646, 629, 509, 487, 447, 433.

UV spectrum (λ , nm, log ϵ , ethanol): 206 (0.29).

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 2.64 (1H, dd, J=16.0; 6.0, H-2a), 2.10 (1H, dd, J=16.0, H-2b), 1.71 (1H, d, J=6.0; 3.0, H-3), 2.85 (1H, d, J=10.0, H-5), 4.33 (1H, t, J= 10.0; 11.0, H-6), 2.13 (1H, m, J=10.0, H-7), 1.79 (1H, m, H-8a), 1.42 (1H, m, H-8b), 2.13 (1H, m, H-9a), 1.89 (1H, m, H-9b), 6.10 (1H, d, J= 3.0, H-13a), 5.37 (1H, d, J=3.0, H-13b), 1.25 (3H, s, H-14). 1.63 (3H, br s, H-15).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 69.38 (s, C-1), 35.73 (t, C-2), 39.56 (d, C-3), 41.35 (s, C-4), 54.79 (d, C-5), 79.83 (d, C-6), 51.83 (d, C-7), 20.76 (t, C-8), 32.61 (t, C-9), 61.82 (s, C-10), 138.97 (s, C-11), 170.09 (s, C-12), 118.31 (t, C-13), 22.65 (q, C-14), 21.28 (q, C-15), 70.10 (s, C-16).

Elemental analysis: found: C-58.36, H%-5.47. Calculated: C-58.37, H%-5.51.

1,10 β -epoxy-3.4 α ,11.13 β -bis-dichloromethan-5,7 α ,6 β (H)-guai-6,12-olide (12).

m.p. 182-185°C, $[\alpha]_{580}^{18} +51^\circ$ (c 1.45; chloroform), molecular formula C₁₇H₁₈O₃Cl₄, M_r 412 g/mol, R_f 0.52 (ethyl acetate/petroleum ether, 2:4). Yield 0.1 g (61 %).

IR spectrum (KBr, ν , cm⁻¹): 3442, 3090, 3007, 2976, 2927, 1774 (C=O γ -lactone), 1636, 1457, 1431, 1419, 1377, 1335, 1243, 1163, 1150 (epoxy-group), 1108, 1045, 1026, 977, 944, 926, 900, 876, 855, 840, 819, 801, 776, 752 (C-Cl), 700, 660, 612, 558, 529.

UV spectrum (λ , nm, log ϵ , ethanol): 203 (0.45).

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 2.23 (1H, dd, J=15.5; 3.0, H-2a), 2.10 (1H, dd, J=15.5; 8.0, H-2b), 1.98 (1H, dd, J=8.0; 3.0, H-3), 2.94 (1H, d, J=11.0, H-5), 4.33 (1H, dd, J=10.0; 11.0, H-6), 2.40 (1H, br.t., J=10.0, H-7), 1.45-1.93 (1H, ddt, J=14.0; 1.2, 3.0, H-8a), 1.3 (1H, m, H-8b), 2.1 (1H, m, H-9a), 2.1 (1H, m, H-9b), 2.12 (1H, dd, J=8.2; 1.0, H-13a), 1.92 (1H, d, J=8.3, H-13b), 1.31 (3H, d, J=1.0, H-14), 1.63 (3H, br s, H-15).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 80.30 (s, C-1), 36.04 (t, C-2), 39.22 (d, C-3), 41.54 (s, C-4), 51.66 (d, C-5), 80.85 (d, C-6), 46.69 (d, C-7), 23.64 (t, C-8), 34.51 (t, C-9), 64.13 (s, C-10), 31.48 (s, C-11), 171.87 (s, C-12), 29.00 (t, C-13), 23.49 (q, C-14), 17.13 (q, C-15), 79.26 (s, C-16), 61.89 (s, C-17).

Mass spectrum (m/z, Irel (%): 410 [M⁺, Cl₃5] (0.6), 375 [M-35Cl]⁺, (3), 321 (10), 319 (6), 275 (6), 205 (3), 179 (16), 177 (18), 137 (14), 125 (12), 109 (19), 91 (21), 77 (23), 55 (28), 43 (100). Found: m/z: 375.05350 [M-35Cl]⁺. C₁₇H₁₈O₃Cl₃. Calculated: M = 375.03214.

1,10 β -epoxy-3.4 α -dichloromethano-13-trichloromethyl-7 α (H),6.11 β (H)-guai-6,12-olide (13).

m.p. 160-163°C, molecular formula C₁₇H₁₉O₃Cl₅, M_r 448.5 g/mol, R_f 0.81 (ethyl acetate/petroleum ether, 2:4). Yield 0.006 g (3 %).

IR spectrum (KBr, ν , cm⁻¹): 2996, 2926, 1782 (C=O in the γ -lactone ring), 1459, 1449, 1430, 1416, 1381, 1315, 1277, 1238, 1204, 1177 (epoxy-group), 1155, 1125, 1100, 1051, 1026, 1000, 982, 970, 930, 873, 845, 819, 798, 785, 772, 729, 700 (C-Cl), 678, 652, 626, 602, 572, 552, 500, 483, 422.

UV spectrum (λ , nm, log ϵ , ethanol): 202 (0.441).

NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 2.20 (1H, dd, J=16.0; 3.0, H-2a), 2.01 (1H, dd, J=16.0; 8.0, H-2b), 1.83 (1H, dd, J=8.0; 3.0, H-3), 2.61 (1H, d, J=11.0, H-5), 4.16

(1H, dd, J=11.0;10.0, H-6), 1.40-1.59 (1H, m, H-7), 1.85-1.93 (1H, m, H-8a), 1.40-1.59 (1H, m, H-8b), 2.12 (1H, m, H-9a), 1.85-1.93 (1H, m, H-9b), 2.64(1H, ddd, J=12.0; 5.0; 2.4, H-11), 3.40 (1H, dd, J=15.0; 6.0, H-13a), 2.72 (1H, dd, J=15.0; 3.0, H-13b), 1.29 (3H, s, H-14), 1.61 (3H, s, H-15).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 74.50 (s, C-1), 35.47 (t, C-2), 38.28 (d, C-3), 40.60 (s, C-4), 49.90 (d, C-5), 80.73 (d, C-6), 51.11 (d, C-7), 22.39 (t, C-8), 33.80 (t, C-9), 62.78 (s, C-10), 44.35 (s, C-11), 175.72 (s, C-12), 52.62 (t, C-13), 23.27 (q, C-14), 16.86 (q, C-15), 78.90 (s, C -16), 97.73 (s, C-17).

Mass spectrum (m/z, Irel (%): 448 (5), 413 (7), 411 (5), 377 (6), 375 (6), 331 (5), 311 (7), 309 (5), 283 (7), 281 (8), 259 (6), 258 (6), 256 (9), 255 (6), 253 (6), 241 (7), 233 (7), 223 (5), 207 (10), 205 (15), 203 (7), 193 (7), 191 (6), 189 (7), 187 (7), 181 (6), 179 (19), 178 (6), 177 (22), 175 (5), 171 (7), 169 (8), 165 (16), 163 (10), 161 (7), 157 (7), 155 (6), 153 (7), 151 (6), 149 (6), 145 (7), 143 (15), 141 (12), 139 (10), 137 (12), 135 (10), 131 (6), 129 (9), 128 (6), 127 (10), 125 (11), 123 (9), 119 (7), 117 (9), 115 (11), 113 (8), 111 (10), 109 (14), 107 (7), 105 (9), 103 (6), 101 (7), 99 (9), 97 (12), 93 (5), 91 (23), 89 (11), 87 (5), 83 (5), 82 (7), 81 (13), 79 (15), 77 (20), 75 (10), 71 (15), 69 (16), 68 (8), 67 (7), 65 (11), 55 (35), 53 (11), 43 (100), 41 (28), 39 (11), 27 (6).

Elemental analysis: found: C-45.48, H%-4.24. Calculated: C-45.52, H%-4.27.

The X-ray diffraction experiment was carried out on a Bruker P4 diffractometer (MoK α -radiation, graphite monochromator). Using the $\theta/2\theta$ -scanning method in zone 2 $\theta < 48^\circ$ there are 3471 reflections, of which 3152 are independent ($R_{\text{int}}=0.0281$). Using the method of integration over crystal faces, adjustments were made to absorption (transmission 0.880-0.905). The structure was determined by the direct method using the SHELXS-97 program and refined using the SHELXL-97 program using all images with an anisotropic approximation using the full matrix method.

Crystallographic data for compound (13) were deposited in the Cambridge Structural Database (deposition number CCDC 609346).

(1R,5R,6S,7R,10S,11R)-1,10-epoxy-11.13-(dibromomethane)-guai-3-en-6,12-olide (14).

m.p. 180-183°C, $[\alpha]_D^{23} +76.3^\circ$ (c 0.0002; chloroform), molecular formula C₁₆H₁₈O₃Br₂, M_r 418 g/mol, R_f 0.57 (ethyl acetate/petroleum ether, 1:4). Yield: 0.094 g (28%).

IR spectrum (KBr, ν , cm^{-1}): 2904, 2948, 2861, 1772 (C=O of γ -lactone), 1650 (C=C), 1446, 1419, 1347, 1330, 1239, 1144, 1104, 1084, 1030, 999, 946, 867, 809, 689, 661 (C-Br), 599, 506.

^1H NMR spectrum (500 MHz, CDCl_3 , δ , ppm, J/Hz): 2.77 (1H, dd, J=17.0; 3.0; H-2a), 2.06 (1H, m, H-2b), 5.58 (1H, br s, H-3), 3.02 (1H, dd, J=10.0, H-5), 4.02 (1H, t, J=10, H-6), 2.16 (1H, br s, H-7), 1.97 (m, H-8a), 1.24 (1H, m, H-8b), 2.13 (1H, dd, J=7.5;14.0, H-9a), 1.46 (1H, m, H-9b), 2.10 (1H, d, J=8.0, H-13a), 3.03 (1H, d, J=8.0, H-13b), 1.32 (3H, s, H-14), 1.94 (3H, br s, H-15).

^{13}C NMR spectrum (125.75 MHz, CDCl_3): 72.52 (s, C-1), 34.82 (t, C-2), 124.95 (d, C-3), 140.17 (s, C-4), 53.09 (d, C-5), 81.55 (d, C-6), 49.75 (d, C-7), 23.35 (t, C-8), 33.38 (t, C-9), 62.75 (s, C-10), 39.50 (s, C-11), 172.29 (s, C-12), 26.47 (t, C-13), 22.47 q, C-14), 18.15 (q, C-15), 76.89 (s, C-16).

1,10 β -epoxy-3 α ,4 β -dibromo-11 α ,13 β -(1',1'- α -dibromomethylidenyl)-5,7 α ,6 β (H)-guai-6,12-olide (15).

m.p. 141°C_{des.}, molecular formula $\text{C}_{16}\text{H}_{18}\text{O}_3\text{Br}_4$, M_r 578 g/mol, R_f 0.46 (ethyl acetate/petroleum ether, 1:5). Yield: 0.116 g (86%).

IR spectrum (KBr, ν , cm^{-1}): 2999, 2971, 2929, 1792 (C=O of γ -lactone), 1493, 1418, 1377, 1330, 1230, 1189, 1139, 1097, 1027, 962, 944, 876, 690, 659 (C-Br), 590, 534, 510.

^1H NMR spectrum (500 MHz, CDCl_3 , δ , ppm, J/Hz): 2.98 (1H, dd, J=6.4; 17.0; H-2a), 2.73 (1H, d, J=17.0, H-2b), 4.91 (1H, d, J=6.4, H-3), 2.81 (1H, d, J=10.0, H-5), 4.35 (1H, t, J=10.0 H-6), 2.18 (1H, m, H-7), 2.02 (ddd, J=18.0; 12.4; 2.4, H-8a), 1.27 (1H, m, H-8b), 2.15 (1H, dd, J=2.4, H-9a), 1.51 (1H, m, H-9b), 2.04 (1H, d, J=8.0, H-13a), 2.13 (1H, d, J=8.0, H-13b), 1.31 (3H, s, H-14), 2.22 (3H, br s, H-15).

^{13}C NMR spectrum (125.75 MHz, CDCl_3): 76.64 (s, C-1), 33.06 (t, C-2), 48.67 (d, C-3), 43.90 (d, C-4), 60.09 (d, C-5), 80.68 (d, C-6), 53.55 (d, C-7), 23.47 (t, C-8), 30.49 (t, C-9), 61.26 (s, C-10), 69.91 (s, C-11), 171.54 (s, C-12), 26.15 (t, C-13), 23.47 q, C-14), 30.84 (q, C-15), 74.84 (s, C-16).

Mass spectrum (m/z , Irel (%)): 497 [M-HBr]⁺ (6), 471 (3), 417 (4), 361 (5), 295 (7), 293 (5), 267 (5), 265 (5), 237 (9), 227 (13), 159 (6), 157 (7), 145 (6), 143 (5), 129 (5), 128 (5), 109 (7), 107 (8), 105 (11), 91 (11), 82 (100), 81 (63), 80 (97), 79 (13), 79 (67), 77 (15), 65 (12), 55 (17), 53 (11), 51 (7), 44 (47), 43 (59), 41 (10), 39 (9), 28 (24).

Found: m/z : 496.8 $[M - ^{81}\text{HBr}]^+$. Calculated: $M = 496.88798$.

X-ray diffraction study of the crystal of compound (**15**) was carried out on a Bruker P4 diffractometer at room temperature using $\text{MoK}\alpha$ radiation and a graphite monochromator. The intensity of the reflections was measured using the $\theta/2\theta$ scanning method. Absorption was taken into account by the method of integration over crystal faces.

The structure was determined by the direct method using the SHELXS-97 program and the least-squares were refined using the SHELXL-97 program with anisotropic displacement parameters for non-H atoms and isotropic parameters for H atoms using full-matrix least-squares refinement.

Crystallographic data for compound (**15**) and the parameters of the X-ray diffraction experiment were deposited in the Cambridge Structural Database (deposition number CCDC 603035).

1,4 β -dihydroxy-3,10 α -dichloro-guai-11(13)-en-6,12-olide (17**).**

Yield: 55%. m.p. 190-191 °C, $[\alpha]_D^{20}$ -90.1° (with 0.4; acetone).

IR spectrum (KBr, ν , cm^{-1}): 3465 (OH), 1750 (carbonyl γ -lactone), 1670 (C=C).

^1H NMR spectrum (500 MHz, CDCl_3 , δ , ppm, J/Hz): 4.42 (1H, dd, $J=10.0$, H-3), 4.48 (1H, t, $J=7.0$, H-6), 5.52 (1H, d, $J=3.0$, H-13a), 6.04 (1H, d, $J=3.5$, H-13b), 1.61 (3H, s, H-14).

Mass spectrum (m/z , Irel (%): 316 ($M^+ - \text{H}_2\text{O}$; 6.16), 298 ($M^+ - \text{HCl}$), 281 ($M^+ - \text{HCl} - \text{OH}$), 263 ($M^+ - \text{HCl} - \text{HCl}$), 245 ($M^+ - \text{HCl} - \text{HCl} - \text{H}_2\text{O}$), 227(21.23), 199(12.32), 171(10), 157(45.20), 131(53.42), 95(32, 87), 91(19.17), 69(17.8), 43(100).

(1*S*,3*a'R*,4*a'**R*,8*a'**R*,9*a'**R*)-2.2-Dichloro-8*a'*-methyl-3'-methylenedecahydro-2'*H*-spiro-{cyclopropan-1.5'-naphtho[2.3-*b*]furan}-2'-one (**18**).**

m.p. 164-166°C (EtOH), $[\alpha]_D^{20}$ +128.9° (c 1.3, CHCl_3).

IR spectrum (ν , cm^{-1}): 2922, 2868, 1749, 1666, 1421, 1383, 1344, 1311, 1267, 1228, 1182, 1145, 1053, 962, 893, 738, 634.

UV spectrum (EtOH, λ_{max} , nm, log ϵ): 201 (4.16), 216sh (3.80).

The X-ray diffraction experiment was carried out on a Bruker P4 diffractometer using $\text{Mo K}\alpha$ radiation and a graphite monochromator. Using the $\theta/2\theta$ scanning method over the range $2\theta < 48^\circ$, 3,471 reflections were measured, of which 3,152 were independent ($R_{\text{int}} =$

0.0281). An absorption correction was applied by integration over the crystal faces (transmission 0.880–0.905). The structure was solved by direct methods using SHELXS-97 and refined against all reflections by full-matrix least-squares refinement using SHELXL-97 with anisotropic displacement parameters for non-H atoms.

¹³C NMR spectrum (CDCl₃, δ, ppm): 18.88 (C-2), 19.21 (C-14), 26.78 (C-6), 27.71 (C-15), 31.58 (C-4), 34.13 (C-10), 35.98 (C-3), 40.69 (C-7), 41.65 (C-1), 42.38 (C-5), 42.57 (C-9), 66.51 (CCl₂), 75.89 (C-8), 120.55 (C-13), 141.62 s(C-11), 170.31 s (C-12). C₁₆H₂₀Cl₂O₂.

(3*S*,3*aR*,4*aS*,8*aR*,9*aR*)-8*a*-Methyl-5-methylen-3-(2,2,2-trichloroethyl)decahydronaphtho[2.3-*b*]furan-2(3*H*)-one (19).

Compound (19) was obtained by carrying out the reaction for 1.7 h, $[\alpha]_D^{20} +234.6^\circ$ (c 0.5, CHCl₃).

¹H NMR spectrum (CDCl₃, δ, ppm, J/Hz): 0.81 (3H, s, H-14), 1.04 (1H, ddd, J=12.7, 12.5, 12.3, H-6), 1.25 (1H, m, H-1), 1.47-1.58 (4H, m, H-1,2,2.9), 1.78 (1H, ddd, J=13.1, 5.9, 2.5, H-6), 1.82 (1H, dm, J=10.8, H-5), 1.98 (1H, ddd, J=13.0, 12.8, 7.5, H-3), 2.20 (1H, dd, J=15.5, 2.0, H-9), 2.33 (1H, dddd, J=12.9, 3.8, 2.0, 1.9, H-3), 2.76 (1H, dddd, J=12.1, 6.4, 5.8, 4.3, H-7), 3.03 (1H, dd, J=15.3, 9.6, H-13), 3.22 (1H, ddd, J=9.6, 6.4, 1.6, H-11), 3.35 (1H, dd, J=15.3, 1.6, H-13), 4.51 (1H, dd, J=2.9, 1.4, H-15), 4.59 (1H, ddd, J=4.2, 4.1, 1.9, H-8), 4.59 (1H, dd, J=2.9, 1.5, H-15). C₁₆H₂₁O₂Cl₃.

(1*S*,3*S*,3*aR*,4*aR*,8*aR*,9*aR*)-2.2-Dichloro-8*a*-methyl-3-(2,2,2-trichloroethyl)decahydro-2-*H*-spiro{cyclopropan-1.5-naphtho[2.3-*b*]furan}-2-one (20).

Compound (20) was obtained by carrying out the reaction for 5.5 hours and was isolated by recrystallization of the reaction mixture from EtOH. Yield: 60%, m.p. 202–204°C (EtOH), $[\alpha]_D^{20} +243.5^\circ$ (c 1.8, CHCl₃).

An X-ray diffraction study of a single crystal of compound (20) was carried out on a Bruker P4 diffractometer at room temperature using Mo K α radiation and a graphite monochromator. Reflection intensities were measured using the $\theta/2\theta$ scanning method. Absorption was corrected by integration over the crystal faces.

The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-squares using SHELXL-97, with anisotropic displacement parameters for non-H atoms and isotropic parameters for H atoms.

IR spectrum (ν , cm^{-1}): 2941, 1779, 1634, 1166, 738, 771, 952, 700.

UV spectrum (EtOH, λ_{max} , nm, log ϵ): 201 (3.51), 260 (1.60).

^1H NMR spectrum (CDCl_3 , δ , ppm, J/Hz): 0.66 (1H, ddd, J=12.9, 12.5, 12.4, H-6), 0.93 (3H, s, H-14), 1.17 (1H, ddd, J=12.9, 12.5, 4.3, H-1), 1.29 (1H, d, J=7.6, H-15), 1.49–1.58 (4H, m, H-1,2,2.9), 1.62 (1H, d, J=7.6, H-15), 1.67 (1H, dm, J=14.3, H-3), 1.83 (1H, dd, J=12.0, 1.8, H-5), 1.85 (1H, dddd, J=13.0, 12.9, 5.6, 0.9, H-3), 2.14 (1H, dd, J=15.5, 1.8, H-9), 2.56 (1H, ddd, J=13.3, 5.6, 2.0, H-6), 2.74 (1H, dddd, J=12.4, 6.4, 6.0, 4.3, H-7), 2.83 (1H, dd, J=15.5, 10.1, H-13), 3.16 (1H, ddd, J=10.2, 6.4, 1.6, H-11), 3.24 (1H, dd, J=15.5, 1.6, H-13), 4.51 (1H, ddd, J=4.4, 4.3, 1.8, H-8).

^{13}C NMR spectrum (CDCl_3 , δ , ppm): 18.89 (C-2), 19.05 (C-14), 20.32 (C-6), 27.74 (C-15), 31.65 (C-4), 34.68 (C-10), 36.01 (C-3), 39.49 (C-7), 41.54 (C-1), 42.44 (C-9), 42.72 (C-5), 45.86 (C-11), 49.33 (C-13), 66.39 (CCl_2), 77.44 (C-8), 98.15 (CCl_3), 175.87 (C-12). $\text{C}_{17}\text{H}_{21}\text{O}_2\text{Cl}_5$.

(4*S*,5*R*,7*R*,8*R*,10*R*,13*R*)-4(15),11(13)-bis[Spiro(2.2-dichlorocycloprop-1-yl)]-8.12-eudesmanolide (21).

Compound (21) was isolated by carrying out the reaction for 24 hours, yield - 70%, m.p. 175–177°C (EtOH), $[\alpha]_{\text{D}}^{20} +68.7^\circ$ (c 0.8, CHCl_3).

^1H NMR spectrum (CDCl_3 , δ , ppm, J/Hz): 0.99 (3H, s, H-14), 1.00 (1H, ddd, J=13.0, 12.8, 12.5, H-6), 1.20 (1H, ddd, J=12.9, 12.3, 5.0, H-1), 1.28 (1H, d, J=7.9, H-15), 1.52 (1H, d, J=7.9, H-15), 1.53–1.59 (4H, m, H-1,2,2.9), 1.63 (1H, d, J=7.8, H-13), 1.68 (1H, dm, J=13.8, H-3), 1.85 (1H, dd, J=12.5, 1.6, H-5), 1.87 (1H, m, H-3), 2.08 (1H, d, J=7.8, H-13), 2.19 (1H, dd, J=15.8, 1.3, H-9), 2.24 (1H, ddd, J=12.5, 4.2, 2.0, H-6), 2.53 (1H, ddd, J=11.2, 6.0, 5.1, H-7), 4.72 (1H, ddd, J=4.4, 4.2, 2.9, H-8).

NMR spectrum (CDCl_3 , δ , ppm): 18.88 (C-2), 19.16 (C-14), 22.73 (C-6), 26.96 (C-13), 27.70 (C-15), 31.67 (C-4), 34.48 (C-10), 36.00 (C-3), 40.34 (C-7), 41.52 (C-1), 42.34 (C-9), 42.71 (C-5), 43.29 (C-11), 60.10 (C-17), 66.51 (C-16), 77.03 (C-8), 171.52 s (C-12). $\text{C}_{17}\text{H}_{20}\text{O}_2\text{Cl}_4$.

2-oxo-8 α -chloro-5,7 α (H),6 β (H)-guaia-3(4)-en-6,12-olide (22).

An oily substance.

IR spectrum (KBr, cm^{-1}): 1786, 1733, 1690, 1643, 1619, 1442, 1386, 1315, 1209, 1002, 889, 767, 725, 687, 665, 631, 524.

UV spectrum: $\lambda_{\max}^{\text{EtOH}}$ 254 nm ($\epsilon = 17100$).

^1H NMR spectrum (CHCl_3 , δ , ppm, J/Hz): 1.23 (3H, d, $J=7.0$, H-13), 2.25 (3H, s, H-15), 2.39 (3H, s, H-14), 2.62 (1H, dd, $J=13.0$, $J_2=2.5$, H-9b), 2.73 (1H, dd, $J=13.5$, $J_2=10.5$, H-9a), 2.80 (1H, m, H-7), 2.88 (1H, q, $J_1=J_2=7.0$, H-1), 3.36 (1H, d, $J=0.5$, H-5), 3.85 (1H, t, $J=J_2=10.0$, H-6), 4.45 (1H, ddd, $J=13.0$, $J_2=11.0$, $J_3=2.5$, H-8), 6.13 (1H, s, H-3).

Mass spectrum (m/z , Irel (%): 282 (20), 280 (60), 245 (18), 244(23), 217 (9), 201 (100), 199 (30), 187 (20), 173 (49), 171 (94), 159 (39), 145 (47), 91 (88), 77 (45), 44 (38).

1 α ,10 β -dichloro-8 α -hydroxy-2-oxo-5,7,11 α ,6 β (H)guaia-3,4-en-6,12-olide (23).

Yield: 17.7%. Crystalline substance with m.p. 192-194 °C, $[\alpha]_{580}^{26} +269^\circ$ (c 1.5; chloroform).

IR spectrum (KBr, ν , cm^{-1} : 3610 (OH), 1777 (C=O γ -lactone), 1720 (C=O), 1630 (C=C), 1349, 1262, 1179, 1063, 1022, 980, 843.

UV spectrum: (λ , nm, log ϵ , ethanol) 239 (16080).

Mass spectrum (m/z , Irel (%): 280 [M-Cl] + (100), 245(23), 171 (52), 91(34). Found, m/z 280.08623; calculated for $\text{C}_{15}\text{H}_{17}\text{O}_3\text{Cl}$: 280.08661.

^1H NMR spectrum (500 MHz, CDCl_3 , δ , ppm, J/Hz): 1.39 (3H, d, $J=7.5$, $\text{H}_3\text{C}(13)$), 1.87 (3H, br s, $\text{H}_3\text{C}(14)$), 2.24 (dd, $J=15.0$; 5.0, H-9b), 2.25 (3 H, br s., $\text{H}_3\text{C}(15)$ H3, br.s.), 2.74 (d.d, $J=15.0$; 10.5, H-9a), 2.81(1H, ddd, $J=10.5$; 7.5, H-7), 2.90 (1H, q, $J=7.5$, H-11,) 3.51 (1H, br d, $J=10.5$, H-5) 4.10 (1H, ddd., $J=5.0$; 10.5, H-8), 4.88 (1H, t, $J=10.5$, H-6), 6.14 (1H, br.s, H-3).

1 α ,10 β -dichloro-2-oxo-5,7 α ,6.11 β (H)guaia-3,4-en-6,12-olide (24).

m.p. 224-226°C (chloroform). Yield: 0.24 g (75.9%).

^1H NMR spectrum (CDCl_3 , δ , ppm, J/Hz): 1.21 (3H, d, $J=7.5$, H-13), 1.79 (1H, m, H-7), 1.83 (3H, s, H-14), 1.89 (1H, m, H-8 α), 1.92 (1H, m, H-8 β), 2.22 (3H, t., $J=1.0$, H-15), 2.65 (1H, m., H-9a, H-9b), 2.68 (1H, m, H-9b, H-9a /11), 2.71 (1H, m., H-11, H-9a/9b), 3.50 (1H, br d, $J=10.0$, H-5), 4.80 (1H, t, $J=J_2=10.0$, H-6), 6.12 (1H, q, $J=1.0$, H-3).

^{13}C NMR spectrum (CHCl_3 , δ , ppm): 10.59 (C-13), 18.93 (C-15), 23.38 (C-14), 30.06 (C-11), 38.86 (C-9), 39.26 (C-8), 41.85 (C-7), 64.84 (C-5), 73.40 (C-10), 75.66 (C-1), 80.86 (C-6), 129.80 (C-3), 175.96 (C-4), 178.62 (C-12).

Mass spectrum (m/z, Irel (%): 317 (2), 315 (3) 284 (5), 283 (36), 281 (100), 245 (31), 207 (5), 199 (9), 161 (6), 125 (10), 105 (13), 91 (19), 77 (10), 69 (14), 55 (21), 43 (17), 41 (20), 29 (11).

1 α ,10 β -dichloro-2-oxo-5,7,11 α (H),6 β (H)-guaia-3(4)-en-6,12-olide (25)

m.p. 172-174°C (chloroform). Yield: 0.2 g (63.3%).

¹H NMR spectrum (CDCl₃, δ , ppm, J/Hz): 1.19 (3H, d, J=7.5, H-13), 1.83 (3H, s, H-14), 1.94 (1H, m, H-7), 1.85-1.95 (2H, m, H-8 α , H-8 β), 2.23 (3H, t., J=1.0, H-15), 2.70 (1H, m, H-9 β), 2.95-3.0 (1H, m, H-9 α), 3.16 (1H, q, J=7.6, H-11), 3.51 (1H, br d, J=10.0, H-5), 4.95-4.97 (1H, t, J=10.2, H-6), 6.13 (1H, q, J=1.0, H-3).

¹³C NMR spectrum (CHCl₃, δ , ppm): 8.18 (C-13), 18.89 (C-15), 23.28 (C-14), 28.30 (C-11), 36.93 (C-9), 38.95 (C-8), 41.33 (C-7), 61.48 (C-5), 73.34 (C-10), 75.63 (C-1), 80.07 (C-6), 129.82 (C-3), 176.03 (C-4), 179.42 (C-12).

1 α -chloro-2-oxo-5,7 α (H),6 β (H)-guaia-3(4),10(14)-dien-6,12-olide (26)

Crystals, m.p. 171 – 172°C, [α]₅₈₀²² + 261° (c 1.34; CHCl₃).

IR spectrum (KBr), ν /cm⁻¹: 3080, 1000(C=CH₂), 1780 (γ -lactone), 1710 (C=O), 1625 (C=C), 1205, 1030, 850 (C-O), 715(C-Cl).

UV spectrum (EtOH), $\lambda_{\max}$, nm: 236 nm (ϵ 10900).

Mass spectrum, m/z (Irel (%)): 280 (1.5) [M]⁺, 245(100) [M-Cl]⁺, 171(6), 105 (4), 91(6), 55(7).

Found, m/z: 280.08614; calcd for C₁₅H₁₇O₃Cl: 280.08661; found, m/z: 245.11855; calcd for C₁₅H₁₇O₃: 245.11776.

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 6.18 (3H, quint, J=1.5; 1.5, H-3), 3.36 (1H, ddd, J=10.5; 2.3; 1.5, H-5), 4.06 (1H, t, J=10.5; 10.5, H-6), 2.92 (1H, m, H-7), 1.97 (1H, dm, J=13, H-8 α), 1.43 (1H, m, H-8 β), 2.85 (1H, d.t.d.d, J=13.5; 13.5; 4.5; 4.5, H-9 α), 2.45 (1H, d.t.d.d, J=13.5; 4.3; 3.6; 0.7, H-9 β), 2.73 (1H, m, H-11), 1.16 (3H, d, J=7.8, H-13), 5.17 (1H, v.s, H-14), 2.28 (3H, t, J=1.5; 1.5, H-15).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 72.62 (s, C-1), 199.80 (s, C-2), 130.01 (d, C-3), 175.51 (s, C-4), 65.08 (d, C-5), 82.85 (d, C-6), 44.30 (d, C-7), 29.23 (t, C-8), 32.23 (t, C-9), 143.77 (s, C-10), 38.35 (d, C-11), 178.24 (s, C-12), 11.24 (q, C-13), 118.82 (t, C-14), 19.98 (q, C-15).

1 α -chloro-2-oxo-10 β -methoxy-5,7 α (H),6 β (H)-guaia-3(4)-en-6,12-olide (27)

Crystals, m.p. 169 – 171°C, $[\alpha]_{580}^{22} + 116^\circ$ (c 0.86; CHCl₃).

Found (%): Cl, 11.50. C₁₆H₂₁ClO₄. Calcd (%): Cl, 11.33.

IR spectrum (KBr), ν/cm^{-1} : 1780 (γ -lactone), 1710 (C=O), 1630 (C=C), 1216, 1190, 1033, 987, 840 (C-O), 715(C-Cl).

UV spectrum (EtOH), λ_{max} , nm: 237 nm (ϵ 11000)

Mass spectrum, m/z (Irel (%)): 277(93)[M-Cl]⁺, 276 (48)[M-HCl]⁺, 245(15), 204(35), 183(16), 109(21), 85(100), 55(33). Found, m/z: 277.14070; calcd for C₁₆H₂₁O₄: 277.14397.

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 6.05 (1H, quint, J=1.5, H-3), 3.44 (1H, ddd, J=10.5; 2.1, H-5), 4.06 (1H, t, J=9.0, H-6), 2.68 (1H, m, H-7), 1.65 (1H, dm, J=14, H-8a), 1.47 (1H, m, H-8b), 2.34 (1H, d.t.d.d, J=15.0; 13.0; 4.5, H-9a), 1.85 (1H, d.t, J=15.0; 3.8, H-9b), 2.70 (1H, m, H-11), 1.20 (3H, d, J=7.8, H-13), 1.42 (3H, s, H-14), 2.20 (3H, t, J=1.4, H-15), 3.11 (3H, s, H₃CO).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 75.17 (s, C-1), 200.28 (s, C-2), 129.65 (d, C-3), 176.14 (s, C-4), 64.23 (d, C-5), 82.51 (d, C-6), 41.71 (d, C-7), 22.41 (t, C-8), 32.55 (t, C-9), 82.39 (s, C-10), 38.99 (d, C-11), 179.09 (s, C-12), 10.73 (q, C-13), 21.31 (q, C-14), 19.03 (q, C-15), 50.50 (q, C-16).

Key cross-peaks in the 2D NMR spectrum ¹³C-¹H (COLOC): C(1)/H(14), H(5), H(9B), C(10)/H(14), OCH₃, H(8A).

1 α ,10 β -dichloro-2-oxo-14 α -methoxy-5,7 α (H),6 β (H)-guaia-3(4)-en-6,12-olide (28)

Crystals, m.p. 160 – 162°C, $[\alpha]_{580}^{22} + 207^\circ$ (c 0.511; CHCl₃).

Found (%): C, 55.55; H, 5.78; Cl, 20.20. C₁₅H₂₀Cl₂O₄. Calcd (%): C, 55.34, H, 5.80, Cl, 20.42.

IR spectrum (KBr), ν/cm^{-1} : 1780 (γ -lactone), 1710 (C=O), 1625 (C=C), 1220, 1125, 1027, 985, 840 (C-O), 712 (C-Cl).

UV spectrum (EtOH), λ_{max} , nm: 241 nm (ϵ 9500).

Mass spectrum, m/z (Irel (%)): 309(13) [M-H-HCl]⁺, 275(100) [M-Cl-HCl], 149(34), 57(21), 45(22). Found, m/z: 309.08565; calcd for C₁₅H₁₇O₄Cl: 309.08935.

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 6.14 (1H, dd, J=2.0; 1.5, H-3), 3.49 (1H, ddd, J=9.6; 2.0; 1.5, H-5), 4.85 (1H, t, J=9.5, H-6), 2.72 (1H, m, H-7), 1.83 (1H, dm, J=14, H-8a), 1.76 (1H, m, H-8b), 2.63 (1H, d.t, J=15.5; 4.0, H-9a), 2.33 (1H, ddd, J=15.5;

12.5; 3.8, H-9b), 2.72 (1H, m, H-11), 1.22 (3H, d, J=7.5, H-13), 3.86 (1H, d, J=11.0, H-14a), 3.99 (1H, d, J=11.0, H-14b), 2.25 (3H, t, J=1.4, H-15), 3.38 (3H, s, H₃CO).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 75.04 (s, C-1), 197.88 (s, C-2), 129.93 (d, C-3), 176.73 (s, C-4), 65.65 (d, C-5), 80.59 (d, C-6), 42.46 (d, C-7), 22.82 (t, C-8), 30.43 (t, C-9), 76.22 (s, C-10), 38.92 (d, C-11), 178.54 (s, C-12), 10.52 (q, C-13), 75.64 (t, C-14), 19.02 (q, C-15), 59.38 (q, C-16).

Selected cross-peaks in the 2D NMR spectrum ¹³C – ¹H (COLOC): C(1)/H(9A), H(5), H(3); C(10)/H(8A), H(9A), H(14A); C(14)/OCH₃.

1 α ,10 α -dichloro-2-oxo-14 β -methoxy-5,7 α (H),6 β (H)-guaia-3(4)-en-6,12-olide (29)

Crystals, m.p. 184 – 185°C, [α]_D²² + 182° (c 0.511; CHCl₃).

Found (%): C, 55.61; H, 5.89; Cl, 20.06. C₁₅H₂₀Cl₂O₄. Calcd (%): C, 55.34, H, 5.80, Cl, 20.42.

IR spectrum (KBr), ν /cm⁻¹: 1780 (γ -lactone), 1710 (C=O), 1625 (C=C), 1220, 1200, 1125, 1030, 985, 850 (C-O), 715 (C-Cl).

UV spectrum (EtOH), λ_{max} , nm: 238 nm (ϵ 9300).

Mass spectrum, m/z (Irel (%)): 311(1.5)[M-Cl]⁺, 275(100), [M-Cl-HCl], 55(8), 45(11).

Found, m/z: 311.10646; calcd for C₁₆H₂₀O₄Cl: 311.10500.

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 6.12 (1H, dd, J=2.4; 1.4, H-3), 3.66 (1H, ddd, J=9.0; 2.4; 1.4, H-5), 4.62 (1H, dd, J=11.0; 9.0, H-6), 2.72 (1H, m, H-7), 1.78 (1H, m, H-8a), 1.65 (1H, m, H-8b), 2.77 (1H, d.t.d.d, J=15.2; 13.0; 4.5; 1.1, H-9a), 2.29 (1H, d.t, J=15.2; 7.4, H-9b), 2.73 (1H, quint, J=7.8, H-11), 1.18 (3H, d, J=7.8, H-13), 3.50 (1H, d, J=10.6, H-14a), 3.41 (1H, dd, J=10.6; 1.1, H-14b), 2.22 (3H, t, J=1.4, H-15), 3.25 (3H, s, H₃CO).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 77.34 (s, C-1), 195.70 (s, C-2), 127.87 (d, C-3), 173.84 (s, C-4), 63.38 (d, C-5), 81.63 (d, C-6), 40.37 (d, C-7), 24.01 (t, C-8), 39.03 (t, C-9), 76.14 (s, C-10), 38.97 (d, C-11), 178.59 (s, C-12), 10.38 (q, C-13), 77.27 (t, C-14), 17.96 (q, C-15), 59.14 (q, C-16).

Selected cross-peaks in the 2D NMR spectrum ¹³C-¹H (COLOC): C(1)/H(9B), H(3), H(14A); C(10)/H(8A); C(14)/OCH₃, H(9A).

1 α ,10 α ,14-trichloro-2-oxo-5,7 α (H),6 β (H)-guaia-3(4)-en-6,12-olide (30)

Colorless crystals, m.p. 170 – 172°C (petroleum ether/ethyl acetate); $[\alpha]_{580}^{22} +181^\circ$ (c 0.44; CHCl₃).

UV spectrum: $\lambda_{\max}^{\text{EtOH}}$ 237 nm ($\epsilon = 11000$).

IR spectrum (CHCl₃) 1783 (γ -lactone), 1723 (C=O), 1626 (C=C), 1187, 1010, 990, 929, 844.

¹H NMR spectrum (CDCl₃, δ , ppm, J/Hz): 1.21 (d, 3 H, H₃C(13), J_{11,13} = 8), 1.51 (m, 1H, H(8A)), 2.76 (1H, quint, H(11), J_{7,11} = J_{7,13} = 8), 2.97 (m, 1H, H(7)), 3.61 - 3.69 (m, 3H, H(5), H(14)), 4.26 (1H, br t, H(6), J_{6,7} = J_{5,6} = 10), 6.15 (br s, 1 H, H(3)).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 69.17 (s, C-1), 195.58 (s, C-2), 129.18 (d, C-3), 177.87 (s, C-4), 63.23 (d, C-5), 81.90 (d, C-6), 39.18 (d, C-7), 23.01 (t, C-8), 29.57 (s, C-9), 73.28 (s, C-10), 38.42 (d, C-11), 178.55 (s, C-12), 10.57 (q, C-13), 76.34 (t, C-14), 18.76 (q, C-15).

1 α ,3.10 α -trichloro-2-oxo-14 β -methoxy-5,7 α (H),6 β (H)-guaia-3(4)-en-6,12-olide (31)

Colorless crystals, m.p. 210 – 212°C (petroleum ether/ethyl acetate); $[\alpha]_{580}^{22} + 195$ (c 1.18; acetone).

UV spectrum: $\lambda_{\max}^{\text{EtOH}}$ 250 nm ($\epsilon = 6055$), 254 nm ($\epsilon = 2480$).

IR spectrum (CHCl₃) 1782 (γ -lactone), 1731 (C=O), 1622 (C=C), 1160, 1098, 1037, 998, 936, 923, 735.

¹H NMR spectrum (CDCl₃, δ , ppm, J/Hz): 3.66 (ddq, H(5), J=10.5;2.0;1.5), 4.60 (dd, H(6), J=11.0; 9.0), 2.90 (m, H(7)), 1.64 (m, H(8A)), 1.80 (m, H(8B)), 2.82 (dddd, H(9A), J=15.0;13.0;5.0;1.0), 2.93 (dt, H(9B), J=15.0;7.5), 2.74 (quint., H(11), J=8.0), 1.19 (d, 3H(13), J=7.5), 3.50 (d, H(14A), J=11.0), 3.40 (dd, H(14B), J= 11.0;1.0), 2.25 (t, 3H(15), J=1.5), 3.25 (c., H₃CO).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 75.22 (s, C-1), 189.11 (s, C-2), 129.91 (s, C-3), 164.26 (s, C-4), 61.39 (d, C-5), 81.55 (d, C-6), 40.36 (d, C-7), 23.43 (t, C-8), 39.41 (t, C-9), 75.99 (s, C-10), 38.42 (d, C-11), 178.61 (s, C-12), 10.62 (q, C-13), 76.53 (t, C-14), 15.15 (q, C-15), 57.86 (q, C-16).

8β-chloroachillin (32)

Colorless crystals, m.p. 114-115 °C; $[\alpha]_{580}^{22} + 73.3^\circ$ (c 1.5; chloroform).

IR spectrum (CHCl₃, cm⁻¹): 1780 (γ-lactone), 1687 (C(2)=O), 1640, 1620 (two conjugated C=C), 1261, 1224, 1196, 1179, 1009, 867.

UV spectrum (EtOH): $\lambda_{\max}^{\text{EtOH}}$ 254 nm ($\epsilon = 17100$).

¹H NMR spectrum (CDCl₃, δ , ppm, J/Hz): 1.35 (3H, d, J_{11,13} = 7.6, H-13), 2.25 (3H, s, H-15), 2.40 (3H, s, H-14), 2.70 (1H, dd, J_{8,9a} = 6.0; J_{9a,9b} = 15.0, H-9A), 2.74 (1H, ddd, J_{7,11} = 7.6; J_{6,7} = 10.5, H-7), 2.81 (1H, quint, J_{7,11} = J_{11,13} = 7.6, H-11), 2.87 (1H, ddd, J_{9a,9b} = 15.0, H-9B), 3.32 (1H, d, J_{5,6} = 10.5, H-5), 4.30 (1H, t, J_{5,6} = J_{6,7} = 10.5, H-6), 4.53 (1H, ddd, J_{8,9a} = 6.0; J_{8,9b} ~ 1, H-8), 6.13 (1H, s, H-3).

¹³C NMR spectrum (125.75 MHz, CDCl₃): 131.21 (s, C-1), 195.20 (s, C-2), 135.72 (d, C-3), 169.49 (s, C-4), 53.85 (d, C-5), 78.17 (d, C-6), 54.72 (d, C-7), 53.99 (t, C-8), 46.07 (s, C-9), 147.33 (s, C-10), 39.36 (d, C-11), 177.07 (s, C-12), 12.29 (q, C-13), 23.37 (q, C-14), 19.27 (q, C-15).

Mass spectrum (m/z, Irel (%): 282 [M⁺(³⁷Cl)] (33), 280 [M⁺(³⁵Cl)] (100), 265 (5), 245 (26), 244 (29), 217 (13), 201 (27), 199 (21), 187 (21), 173 (33), 171 (71), 159 (27), 145 (23), 91 (39), 77 (20), 44 (22). Found (m/z): 280.08816, calcd for C₁₅H₁₇ClO₃: 280.08661.

8-β-chloro-3-oxo-1,5,7.8α,4.6β(H)-guai-11(13),10(14)-dien-6,12-olide (35).

Colorless crystalline substance (35) of composition C₁₅H₁₇O₃Cl, with m.p. 170-172 °C (ethyl acetate).

IR spectrum (KBr, ν , cm⁻¹): 3081, 2934, 1780 (C=O of γ-lactone), 1765 (C=O), 1687, 1641, 1619, 1400, 1311, 1243, 1155, 1007, 962, 913, 812 (C-Cl), 650, 497.

UV spectrum (EtOH, $\lambda_{\max}$, nm: 210 nm (lgε 3.92), 254 nm (lgε 3.42).

¹H NMR spectrum (acetone-d₆, δ , ppm, J/Hz): 2.97 (dd, 1H, H-2a, 14.0, 4.0), 2.82 (dd, 1H, H-2b, 14.0, 3.0), 2.90 (d.q., 1H, H-4, 7.0, 7.0), 4.51 (dd, 1H, H-6, 9.5, 8.5), 3.78 (m, 1H, H-7), 5.07 (ddd, 1H, H-8, 5.0, 3.0, ³J_{8,7} ~ 1.0), 2.67 (dd, 1H, H-9a, 15.5, 5.0), 2.40 (dd, 1H, H-9b, 15.0, 3.0), 6.30 (d, 1H, H-13a, 3.5), 5.83 (d, 1H, H-13b, 3.0), 5.09 (br s, 1H, H-14a), 4.87 (br s, 1H, H-14b), 1.17 (d, 3H, H-15 7.0).

Chloroacetylgrossheimin (8 α -chloroacetoxy-3-oxo-5,7 α ,4,6,8 β (H)-guai-10(14),11(13)-dien-6,12-olide) (36).

White powdery substance with m.p. 162-164 °C (ethanol), composition C₁₇H₁₉O₅Cl. R_f 0.41 (ethyl acetate:ethanol = 4:1). Yield 68%.

Elemental analysis: Found % C 60.26; H 5.6; Cl 10.5; calculated %: C 60.27; H 5.65; Cl 10.46.

IR spectrum: 1754 (C=O of γ -lactone), 1730 (C=O), 1240 (C=O of ester group), 1647 (C=C), 821 (CH₂Cl).

UV spectrum (C₂H₅OH, $\lambda_{\max}$, nm): 214 (ϵ 1.225).

The NMR spectrum of derivative (36) showed a three-proton doublet of the methyl group H-15 at 1.25 ppm with a J of 6.8 Hz, doublets of doublets of methylene protons H-2a and H-2b at 2.49 ppm with J 3.37 Hz, 19.19 Hz and 2.56 ppm with SSC 8.73 Hz, 19.19 Hz, multiplet of methine proton H-7 at 3.38 ppm, triplet of lactone proton H-6 at 4.06 ppm with a J of 9.09 Hz, doublets of the protons of the exomethylene group of the lactone ring H-13a and H-13b at 5.92 ppm with J 2.86 Hz and 6.36 ppm with a J of 3.29 Hz, as well as singlets of the protons of the exocyclic double bond H-14a and H-14b at 4.88 and 5.15 ppm, respectively.

(4R,6R,7S,13E)-13-(3-trifluoromethylphenyl)-3-oxogermacra-1(10),11 (13)-dien-6,12-olide (38a).

Yield: 22%. m.p. 175-177 °C (petroleum ether/ethyl acetate). [α]_D²⁰+221° (c 0.4; chloroform).

IR spectrum (KBr, ν , cm⁻¹): 2970, 2938, 2877, 2852, 1748 (C=O γ -lactone ring), 1705, 1661 (C=C), 1495, 1465, 1386, 1359, 1334, 1299, 1271, 1257, 1229, 1217, 1188, 1123, 1101, 1065, 1010, 974, 937, 920, 905, 886, 853, 835, 816, 800, 766, 754, 738, 713, 697, 680, 653, 633, 595, 556, 534, 520, 447, 425.

UV spectrum (ethanol), $\lambda_{\max}$, nm (log ϵ): 208 (4.28), 281 (4.11).

¹H NMR spectrum (δ , ppm, J/Hz): 1.01 (3H, d, J=7.0, Me-15), 1.23 (1H, dddd, J₁=13.2, J₂=10.6, J₃=2.8, J₄=1.6, H-5), 1.67 (3H, s, Me-14), 1.66-1.73 (1H, m, H-8), 1.87-1.96 (1H, m, H-8), 2.10 (1H, ddd, J₁=13.2, J₂=11.8, J₃=3.0, H-5), 2.30-2.45 (2H, H-9), 2.79-2.85 (1H, m, H-4), 3.03 (1H, br d, J₁=9.8, J₂=1.6, H-7), 3.07 (2H, m, H-2), 3.75 (1H, dd, J₁=9.8, J₂=2.8, H-6), 5.59 (1H, t, J=8.2, H-1), 7.50 (1H, br s, J=1.6, H-2 β), 7.60 (1H, br. d., J₁=8.2, J₂=1.6, H-

4 β), 7.62 (1H, dd, $J_1=8.4$, $J_2=8.2$, H-5 β), 7.68 (1H, br. d., $J_1=8.4$, $J_2=1.8$, H-6 β), 7.72 (1H, s, H-13).

Mass spectrum (m/z, Irel (%): 393 (0.7), 392 (3), 377 (1), 373 (2), 365 (2), 364 (8), 293 (9), 263 (3), 241 (9), 177 (8), 159 (7), 128 (6), 100 (6), 99 (100), 81 (25), 71 (18), 43 (15). Found, [M] + 392.1596. C₂₂H₂₃O₃F₃. Calculated, 392.1594.

(4R,6R,7S,13E)-13-(4-Fluorophenyl)-3-oxogermacra-1(10),11(13)-dien-6,12-olide (38b).

Yield: 32%. m.p. 154-157 °C (petroleum ether/ethyl acetate). $[\alpha]_D^{20} +249^\circ$ (*c* 0.4; chloroform).

IR spectrum (KBr, ν , cm⁻¹): 2968, 2927, 2859, 1748 (C=O of γ -lactone cycle), 1712, 1651 (C=C), 1600 (C=C), 1511, 1451, 1373, 1334, 1294, 1232, 1183, 1106, 1064, 1011, 980, 940, 889, 830, 758, 710, 671, 595, 553, 512, 413.

UV spectrum (ethanol), λ_{max} , nm (log ϵ): 207 (4.36), 221 (4.29), 286 (4.43).

¹H NMR spectrum (δ , ppm, J/Hz): 1.01 (3H, d, $J=7.0$, Me-15), 1.25 (1H, dddd, $J_1=13.0$, $J_2=10.6$, $J_3=3.2$, $J_4=1.6$, H-5), 1.67 (3H, s, Me-14), 1.64-1.71 (1H, m, H-8), 1.83-1.92 (1H, m, H-8), 2.08 (1H, ddd, $J_1=13.0$, $J_2=11.4$, $J_3=3.0$, H-5), 2.30-2.43 (2H, H-9), 2.81-2.87 (1H, m, H-4), 3.00 (1H, br d, $J_1=9.8$, $J_2=1.6$, H-7), 3.04 (1H, dd, $J_1=14.1$, $J_2=8.2$, H-2), 3.09 (1H, dd, $J_1=14.1$, $J_2=8.2$, H-2), 3.71 (1H, dd, $J_1=9.8$, $J_2=2.8$, H-6), 5.62 (1H, t, $J=8.2$, H-1), 7.14, 7.18 (both 1H, d, $J=8.0$, H-3 β , 5 β), 7.43 (2H, m, H-5 β , 6 β), 7.45 (1H, s, H-13).

Mass spectrum (m/z, Irel (%): 344 (0.2), 343 (2), 342 (7), 324 (4), 323 (9), 315 (9), 314 (48), 243 (26), 215 (69), 147 (32), 146 (39), 135 (21), 133 (37), 109 (35), 99 (100), 85 (22), 83 (34), 81 (26), 71 (31). Found: [M]+ 342.1631. C₂₁H₂₃O₃F. Calculated: [M] 342.1626.

(4R,6R,7S,13E)-13-(4-chlorophenyl)-3-oxogermacra-1(10),11(13)-dien-6,12-olide (38c).

Yield: 32% (by the method *ii*). $[\alpha]_D^{20} +231^\circ$ (*c* 0.24; chloroform). m.p. 166-169 °C (petroleum ether/ethyl acetate).

IR spectrum (KBr, ν , cm⁻¹): 3506, 3395, 3116, 2999, 2966, 2928, 2870, 2850, 2360, 1903, 1760 (C=O of γ -lactone ring), 1706, 1663 (C=C), 1455, 1443, 1427, 1404, 1387, 1359, 1342, 1325, 1278, 1269, 1241, 1222, 1201, 1182, 1128, 1107, 1093, 1028, 1009, 971, 952, 932, 883, 845, 821, 787, 763, 705, 973, 634, 602, 558, 536, 444, 409.

UV spectrum (ethanol), λ_{max} , nm (log ϵ): 206 (4.26), 223 (4.23), 290 (4.48).

^1H NMR spectrum (δ , ppm, J/Hz): 1.01 (3H, d, J=7.0, Me-15), 1.24 (1H, dddd, $J_1=13.2$, $J_2=10.8$, $J_3=3.2$, $J_4=1.6$, H-5), 1.66 (3H, s, Me-14), 1.68 (1H, m, H-8), 1.88 (1H, m, H-8), 2.09 (1H, ddd, $J_1=13.2$, $J_2=12.0$, $J_3=2.8$, H-5), 2.33-2.42 (2H, m, H-9), 2.80-2.87 (1H, m, H-4), 2.99 (1H, br d, $J_1=10.8$, $J_2=2.0$, $J_3=1.6$, H-7), 3.05 (1H, dd, $J_1=14.1$, $J_2=8.1$, H-2), 3.08 (1H, dd, $J_1=14.1$, $J_2=8.1$, H-2), 3.71 (1H, dd, $J_1=10.8$, $J_2=2.6$, H-6), 5.62 (1H, t, J=8.1, H-1), 7.38 (2H, br.d., $J_1=8.5$, $J_2=2.1$, H-2 β , 6 β), 7.42 (1H, br s, H-13), 7.45 (2H, br.d., $J_1=8.5$, $J_2=2.1$, $J_3=1.2$, H-3 β , 5 β).

Mass spectrum (m/z, Irel (%): 358 (3), 330 (19), 231 (32), 163 (11), 149 (24), 128 (35), 125 (22), 115 (19), 99 (100), 85 (31), 83 (48), 81 (24), 71 (28), 43 (18). Found: [M]⁺ 358.1327. C₂₁H₂₃O₃Cl. Calculated: [M] 358.1330.

(4R,6R,7S,13Z)-13-(2-Fluorophenyl)-3-oxogermacra-1(10),11(13)-dien-6,12-olide (39f).

White crystals, m.p. 179-181 °C, composition C₂₁H₂₃O₃F. Yield 40%.

IR spectrum (KBr, ν_{max} , cm⁻¹): 2987, 2963, 2928, 2875, 2852, 1755 (C=O of γ -lactone), 1703, 1657, 1611, 1578, 1486, 1456, 1368, 1324, 1249, 1194, 1160, 1137, 1065, 1012, 973.

UV spectrum (EtOH, λ_{max} , nm): 203, 277.

Found: m/z 342.1630 [M]⁺. Calcd: m/z 342.1626.

^1H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 1.04 (3H, d, J=6.7, Me-15), 1.29 (1H, ddd, J=12.0, 10.0, 3.5, 2.5, H-5b), 1.68-1.69 (1H, m, H-8a), 1.70 (3H, s, Me-14), 1.88-1.95 (1H, m, H-8b), 2.11 (1H, ddd, J=13.0, 12.5, 2.6, H-5a), 2.35-2.40 (2H, m, H-9a, H-9b), 2.82-2.9 (1H, m, H-4), 3.02-3.07 (1H, m, H-7), 3.07-3.12 (2H, m, H-2a, H-2b), 3.73 (1H, dd, J=2.6, 11.7, H-6), 5.62 (1H, t, J=8.4, H-1), 7.18 (1H, d, J=8.5, H-6'), 7.27 (1H, d, J=8.5, H-3'), 7.44 (2H, dd, J=8.5, 1.5, H-4', H-5'), **7.73 (1H, s, H-13)**.

NMR spectrum ^{13}C (125 MHz, CDCl₃, δ , ppm): 117.41 (d, C-1), 42.68 (t, C-2), 207.90 (s, C-3), 39.90 (d, C-4), 39.9 (t, C-5), 82.09 (d, C-6), 42.37 (d, C-7), 31.66 (t, C-8), 40.20 (t, C-9), 141.49 (s, C-10), 131.84 (d, C-11), 171.33 (s, C-12), 131.91 (d, C-13), 15.98 (q, C-14), 18.55 (q, C-15), 122.30 (s, C-1'), **122.39 (s, C-2')**, 116.65 (d, C-3'), 128.89 (d, C-4'), 129.28 (d, C-5'), 128.84 (d, C-6').

(E)-(13-(4-chlorophenyl)-8 α -hydroxy-3-oxo-5,7 α (H)-guai-10(14),11(13)-dien-6,12-olide (41a).

Yield: 11%. Colorless crystalline substance, m.p. 200-203 °C (petroleum ether/ethyl acetate). +142.8° (c 0.14; ethanol).

IR spectrum (KBr, ν , cm^{-1}): 3494 (OH group), 3078, 2925, 1737 (C=O γ -lactone cycle), 1640, 1590, 1490, 1406, 1355, 1301, 1269, 1243, 1198, 1165, 1118, 1088, 1043, 1011, 921, 839, 743, 657.

UV spectrum (ethanol), λ_{max} , nm (log ϵ): 206 (4.27), 225 (4.24), 298 (4.44).

^1H NMR spectrum (500 MHz, CDCl_3 , δ , ppm, J/Hz): 1.26 (3H, d, J=7.0, CH_3 -15), 1.36 (br s, OH), 2.38-2.25 (3H, m, H-4, 5, 9a), 2.52 (1H, dd, J=19.2, 3.15 Hz, H-2a), 2.58 (1H, dd, J=19.2, 8.5 Hz, H-2b), 2.82 (1H, dd, J=12.9, 5.0 Hz, H-9b), 3.25 (1H, t.d, J=8.5, 7.9, 3.2 Hz, H-1), 3.78 (1H, ddd, J=9.6, 6.7, 2.9 Hz, H-7), 3.88-3.84 (1H, m, H-8), 3.9 (1H, dd, J=10.3, 6.6 Hz, H-6), 4.78 (1H, s, H-14a), 5.12 (1H, s, H-14b), 7.36 (2H, br d, J=8.6 Hz, H-3',5'), 7.56 (2H, br d, J=8.6 Hz, H-2',6'), 7.82 (1H, d, J=2.9 Hz, H-13).

Elemental analysis: found (%): C 67.78, H 5.69, Cl 9.53. $\text{C}_{21}\text{H}_{21}\text{ClO}_4$. Calculated (%): C 67.65, H 5.68, Cl 9.51.

(E)-(13-(3-trifluoromethylphenyl)-8 α -hydroxy-3-oxo-5,7 α (H)-guai-10 (14),11(13)-dien-6,12-olide (41b).

Yield: 19%. Colorless crystalline substance, m.p. 131-133°C (petroleum ether/ethyl acetate).

IR spectrum (KBr, ν , cm^{-1}): 3454 (OH group), 3079, 2928, 1741 (C=O of γ -lactone ring), 1643 (C=C), 1487, 1440, 1394, 1358, 1330, 1299, 1230, 1194, 1165, 1125, 1073, 1050, 1024, 1004, 907, 836, 802, 757, 741, 695, 669, 653, 632, 562.

UV spectrum (ethanol), λ_{max} , nm (log ϵ): 205 (5.51), 284.5 (5.52).

^1H NMR spectrum (500 MHz, CDCl_3 , δ , ppm, J/Hz): 1.26 (3H, d, J=7.0, CH_3 -15), 1.62 (br s, OH), 2.40-2.26 (3H, m, H-4, 5, 9a), 2.51 (1H, dd, J=19.1, 3.2 Hz, H-2a), 2.59 (1H, dd, J=19.0, 8.5 Hz, H-2b), 2.83 (1H, dd, J=12.9, 4.8 Hz, H-9b), 3.25 (1H, ddd, J=9.0, 7.4, 3.2 Hz, H-1), 3.90-3.80 (2H, m, H-7,8), 4.02 (1H, dd, J=10.4, 6.4 Hz, H-6), 4.80 (1H, s, H-14a), 5.11 (1H, s, H-14b), 7.52 (1H, t, J=7.8 Hz, H-5'), 7.62 (1H, br d, J=7.8 Hz, H-4'), 7.77 (1H, br d, J=7.8 Hz, H-6'), 7.79 (1H, d, J=2.9 Hz, H-13), 7.88 (1H, br s, H-2').

Mass spectrum: found m/z [M]⁺ 406.1387. calculated for $\text{C}_{22}\text{H}_{21}\text{F}_3\text{O}_4$, 406.1382 [M].

(E)-13-(2-fluorophenyl)-8 α -hydroxy-3-oxo-5,7 α (H)-guai-10(14),11(13)-dien-6,12-olide (41c).

Yield: 26%. Colorless crystalline substance, m.p. 81-83 °C (petroleum ether/ethyl acetate). $[\alpha]_D^{27.1} +142.8^\circ$ (c 0.14; chloroform).

IR spectrum (KBr, ν , cm⁻¹): 3477 (OH group), 2931, 2911, 2872, 1733 (C=O of γ -lactone ring), 1648 (C=C), 1610, 1575, 1491, 1453, 1352, 1330, 1238, 1206, 1166, 1074, 1029, 996, 950, 804, 762.

UV spectrum (ethanol), $\lambda_{\max}$, nm (log ϵ): 202 (4.55), 288 (4.36).

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 1.25 (3H, d, J=7.1 Hz, CH₃-15), 1.56 (br s, OH), 2.35-2.23 (2H, m, H-4, 9a), 2.40-2.36 (1H, m, H-5), 2.50 (1H, dd, J=19.0, 3.6, H-2a), 2.58 (1H, dd, J=19.0, 8.6 Hz, H-2b), 2.74 (1H, dd, J=12.9, 5.4 Hz, H-9b), 3.15 (1H, ddd, J=8.6, 7.4, 3.6 Hz, H-1), **3.56-3.70 (1H, m, H-7)**, 3.81-3.72 (1H, m, H-8), 3.98 (1H, dd, J=10.0, 7.1, H-6), 4.75 (1H, s, H-14a), 5.08 (1H, s, H-14b), 7.10 (1H, dd, J=7.8, 7.2 Hz, H-3'), 7.16 (1H, dd, J=7.8 Hz, H-5'), 7.35 (1H, br d, J=7.8 Hz, H-6'), 7.47 (1H, br t., J=7.8 Hz, H-4'), 7.88 (1H, d, J=3.1 Hz, H-13).

Mass spectrum: found m/z [M]⁺ 356.1418. calculated for C₂₁H₂₁FO₄, 356.1417 [M].

(Z)-(13-(4-chlorophenyl)-8 α -hydroxy-3-oxo-5,7 α (H)-guai-10(14),11(13) -dien-6,12-olide (42a).

Yield: 23%. Colorless crystalline substance, m.p. 213-216 °C (petroleum ether/ethyl acetate) +71.4° (c 0.14; ethanol).

IR spectrum (KBr, ν , cm⁻¹): 3483 (OH group), 3084, 2964, 2926, 2864, 1735 (C=O of γ -lactone ring), 1640, 1592, 1490, 1400, 1352, 1330, 1249, 1204, 1167, 1119, 1089, 1089, 1075, 1060, 1013, 997, 910, 834, 785.

UV spectrum (ethanol), $\lambda_{\max}$, nm (log ϵ): 205 (4.21), 224 (4.14), 298 (4.23).

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 1.28 (3H, d, J=7.2, CH₃-15), 2.38-2.25 (2H, m, H-5, 9a), 2.52-2.41 (3H, m, H-2a, 2b, 4), 2.82 (1H, dd, J=12.8, 5.4 Hz, H-9b), 3.08 (1H, td, J=9.2, 2.7 Hz, H-7), 3.22 (1H, ddd, J=9.0, 7.9, 4.0 Hz, H-1), 4.01 (1H, m, H-8), 4.03 (1H, dd, J=10.3, 9.2 Hz, H-6), 4.98 (1H, s, H-14a), 5.08 (1H, s, H-14b), 7.32 (2H, br d, J=8.6 Hz, H-3',5'), 7.68 (2H, br d, J=8.5 Hz, H-2',6'), 7.72 (1H, d, J=2.9 Hz, H-13).

Elemental analysis: found (%): C 67.70, H 5.68, Cl 9.54. C₂₁H₂₁ClO₄. Calculated (%): C 67.65, H 5.68, Cl 9.51.

(Z)-(13-(3-trifluoromethylphenyl)-8 α -hydroxy-3-oxo-5,7 α (H)-guai-10(14),11(13)-dien-6,12-olide (42b).

Yield: 17%. Colorless crystalline substance. m.p. 119-121°C (petroleum ether/ethyl acetate). $[\alpha]_D^{27.1} +91^\circ$ (*c* 0.11; chloroform).

IR spectrum (KBr, ν , cm⁻¹): 3478 (OH group), 3082, 2966, 2932, 2897, 2857, 1736 (C=O of γ -lactone ring), 1647 (C=C), 1486, 1454, 1376, 1329, 1206, 1181, 1171, 1125, 914, 798, 694.

UV spectrum (ethanol), $\lambda_{\max}$, nm (log ϵ): 201.5 (5.32), 278 (5.15).

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 1.26 (3H, d, J=7.0, CH₃-15), 2.26 (br s, OH), 2.32 (1H, m, H-5), 2.36 (1H, dd, J=13.4, 7.0 Hz, H-9a), 2.49-2.42 (2H, m, H-2a, 4), 2.54 (1H, dd, J=18.8, 8.8 Hz, H-2b), 2.84 (1H, dd, J=13.3, 5.5 Hz, H-9b), 3.15 (1H, td, J=9.2, 3.2 Hz, H-7), 3.22 (1H, ddd, J=8.8, 7.6, 4.4 Hz, H-1), 4.06 (1H, dd, J=10.2, 9.4 Hz, H-6), 4.04 (1H, m, H-8), 4.92 (1H, s, H-14a), 5.10 (1H, s, H-14b), 7.48 (1H, t, J=7.8 Hz, H-5'), 7.58 (1H, br d, J=7.8 Hz, H-4'), 7.81 (1H, d, J=2.9 Hz, H-13), 7.89 (1H, br s, H-2'), 7.90 (1H, br d, J=7.8 Hz, H-6').

Mass spectrum: found *m/z* [M]⁺ 406.1385. calculated for C₂₂H₂₁F₃O₄ 406.1382 [M].

(Z)-(13-(2-fluorophenyl)-8 α -hydroxy-3-oxo-5,7 α (H)-guai-10(14),11(13)-dien-6,12-olide (42c).

Yield: 24 %. Colorless crystalline substance, m.p. 159-161°C (petroleum ether/ethyl acetate). $[\alpha]_D^{26.4} -266.6^\circ$ (*c* 0.075; chloroform).

IR spectrum (KBr, ν , cm⁻¹): 3475 (OH group), 3076, 2926, 1733 (C=O of γ -lactone ring), 1648 (C=C), 1610, 1576, 1490, 1454, 1352, 1269, 1238, 1206, 1190, 1074, 1029, 951, 907, 807, 762.

UV spectrum (ethanol), $\lambda_{\max}$, nm (log ϵ): 204 (4.58), 289 (4.37).

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J/Hz): 1.25 (3H, d, J=7.3 Hz, CH₃-15), 2.26 (br s, OH), 2.35-2.27 (2H, m, H-5, 9a), 2.45-2.38 (1H, m, H-4), 2.46 (1H, dd, J=19.2, 4.3, H-2a), 2.52 (1H, dd, J=18.9, 7.5 Hz, H-2b), 2.84 (1H, dd, J=13.3, 5.6 Hz, H-9b), 3.15 (1H, td, J=9.2, 3.1 Hz, H-7), 3.22 (1H, ddd, J=8.6, 7.5, 4.3 Hz, H-1), 4.04 (1H, m, H-8), 4.06 (1H, dd, J=10.2, 9.1 Hz, H-6), 4.90 (1H, s, H-14a), 5.08 (1H, s, H-14b), 7.02 (1H, dd, J=7.4, 7.2 Hz, H-3'), 7.12 (1H, dd, J=7.6, 7.8 Hz, H-5'), 7.31 (1H, dd, J=7.4, 7.8 Hz, H-4'), 7.73 (1H, br d, J=7.6 Hz, H-6'), 7.84 (1H, d, J=2.5 Hz, H-13).

Mass spectrum: found m/z $[M]^+$ 356.1416. calculated for $C_{21}H_{21}FO_4$, 356.1417 $[M]$.

X-ray diffraction studies of single crystals of compounds (41a, 41b, 42a, and 42b) were carried out at 296(2) K on a Bruker Kappa APEX II diffractometer using Mo $K\alpha$ radiation, a graphite monochromator, and a CCD detector. An absorption correction was applied using the SADABS program.

Synthesis of dichlorocyclopropane derivatives of arglabin (11-13)

A haloform (chloroform or bromoform), 2 mL of a 50% aqueous sodium hydroxide solution, and 0.03 g of dicyclohexano-18-crown-6 ether were combined. After stirring for 15 min, 0.1 g (0.4 mmol) of arglabin (5) was added. The mixture was stirred for 4 h at 15.5°C. Then, 2 mL of water was added, and the mixture was extracted as described below.

Synthesis of dibromocyclopropane derivative of arglabin (14)

To 3 mL of bromoform and 2 mL of a 50% aqueous sodium hydroxide solution, 0.06 g of dicyclohexano-18-crown-6 ether was added. With stirring, 0.2 g (0.8 mmol) of arglabin (5) was then added. The reaction mixture was stirred for 3 h at room temperature. The solution turned brown.

0.1 g (0.24 mmol) of compound (14) was dissolved in 2 mL of absolute chloroform, stirring at room temperature (20 °C), and 0.012 mL (0.24 mmol) of bromine was added dropwise. After 5 min, 2 mL of water was added to the mixture and extracted with 5 mL of chloroform (3 × 5 mL). After drying the organic layer over magnesium sulfate, the solvent was filtered and evaporated under vacuum on a rotary evaporator. The residue (190 mg) was chromatographed on a 6 g silica gel column. When eluting the column with a mixture of petroleum ether: ethyl acetate (95:5), compound (15) was isolated.

Synthesis of 1,4β-dihydroxy-3,10α-dichloro-guai-11(13)-en-6,12-olide (17)

Reaction of 3β,4β-epoxyarglabin (16) with dry hydrogen chloride in an ether–acetone medium afforded a mixture of compounds. After workup of the reaction mixture and chromatographic purification on a silica gel column using petroleum ether/diethyl ether (1:1) as the eluent, a crystalline product was obtained.

Chlorination of isoalantolactone (9)

To a solution of isoalantolactone (0.5 g, 1.57 mmol) in CHCl₃ (3 mL), triethylbenzylammonium chloride (TEBAC; 0.035 g, 0.16 mmol) was added, and the mixture was cooled to –5 °C. Under vigorous stirring, a solution of NaOH (3 g) in H₂O (3 mL) precooled to –5 °C was introduced, and stirring was continued for 3 h at the reduced temperature. The reaction mixture was evaporated and redissolved in ethanol, cooled to 0 °C, and a solution of morpholine (0.2 g, 2.35 mmol) in ethanol (1 mL) was added portionwise over 1 h; the low temperature was then maintained for 5 h. The mixture was treated with H₂O and

extracted with CHCl_3 . The Makosza reaction cycle was repeated, and the material isolated after the second cycle was again subjected to reaction with morpholine. The combined chloroform extract was washed three times with 0.5% aqueous H_2SO_4 . Individual compounds were isolated from the worked-up mixture by column chromatography, eluting with chloroform. The morpholine adduct was decomposed through quaternization with methyl iodide followed by treatment with 5% NaHCO_3 solution to afford compound **18**.

Chloro-containing lactones 19-21

To a solution of isoalantolactone (0.6 g, 1.29 mmol) in CHCl_3 (6 mL), TEBAC (0.058 g, 0.26 mmol) was added, and the mixture was cooled to $-5\text{ }^\circ\text{C}$. Under vigorous stirring, a solution of NaOH (6 g) in H_2O (6 mL) precooled to $-5\text{ }^\circ\text{C}$ was introduced, and stirring was continued for 1–24 h at the reduced temperature. The mixture was treated with H_2O (100 mL), extracted with CHCl_3 , dried over MgSO_4 , and evaporated on a rotary evaporator. Compounds **19**, **20**, and **21** were isolated from the worked-up mixture by column chromatography, eluting with chloroform.

Synthesis of 8 α -chloroachillin (22)

To a solution of 0.5 g (1.91 mmol) of grossmisin (**8**) in 15 mL of chloroform, 2 mL of pyridine was successively added and, with constant stirring, 0.3 mL (4.1 mmol) of freshly distilled thionyl chloride. After 30 min, the reaction mixture was washed with 0.5% hydrochloric acid solution, then with water until neutral. The resulting solution was dried over sodium sulfate, and the solvent was removed. Chromatography of the residue on a silica gel column, eluting with a mixture of petroleum ether-ethyl acetate (9:1), yielded 0.043 g (8%) of an oily substance (**22**).

Synthesis of 8 β -chloroachillin (32)

To a solution of grossmisin (**8**) (0.10 g) in 15 mL of chloroform, 2 mL of pyridine was added successively and, under constant stirring, 0.07 g of finely ground phosphorus pentachloride was added in small portions. After 30 min, the reaction mixture was washed with 15 mL of 5% HCl and water. The resulting reaction mixture was dried over MgSO_4 , and the solvent was removed under vacuum. Chromatographic purification of the reaction mixture, eluting with a petroleum ether–diethyl ether mixture (3:1), afforded colourless crystals of compound (**32**).

Synthesis of 1 α ,10 β -dichlorogrossmisin (23)

Dry chlorine was bubbled through a solution of 0.2 g of grossmisin (**8**) in 10 mL of absolute benzene at 20 °C for 30 min (until the initial material (**8**) completely disappeared by TLC). After evaporation of the solvent under vacuum, a crystalline mass was obtained, which was purified by flash column chromatography. When eluting the column with a hexane-ethyl acetate mixture, 0.06 g of a homogeneous substance was isolated, and its recrystallization from a hexane-ethyl acetate mixture (2:1) gave dichlorolactone (**23**).

Synthesis based on leucomisine (10)

Dry chlorine was bubbled through a solution of 0.2 g (0.81 mmol) of leucomisine (**10**) in 10 mL of absolute benzene at 20 °C for 1 h (until chlorine absorption stopped, monitored by TLC). After evaporating the solvent under vacuum on a rotary evaporator, a crystalline mass was obtained, which was purified by column chromatography. Elution of the column with a mixture of petroleum ether-ethyl acetate (95:5) yielded 0.24 g of a homogeneous substance, from which, after recrystallization from chloroform, a dichlorinated derivative (**24**) was isolated.

Syntheses based on grossheimin (7)

To a solution of grossheimin (**7**) (0.200 g) in chloroform (10 mL) at 20 °C, pyridine (5 mL) was added successively, followed by finely ground phosphorus pentachloride (0.150 g) introduced in small portions under constant stirring. After 1 h the reaction mixture was washed with 15 mL of 5% hydrochloric acid and then with water. The treated reaction mixture was dried over magnesium sulfate, and the solvent was evaporated under vacuum on a rotary evaporator. The residue was purified by column chromatography, eluting with petroleum ether-ethyl acetate mixtures of increasing ethyl acetate content (from 0 to 30%), to give a colourless crystalline substance (**35**) of composition C₁₅H₁₇O₃Cl, m.p. 170–172 °C (ethyl acetate).

General procedure for the synthesis of 13-(E)aryl-3-oxo-germacradienolides (38a-c, 39f)

A two-necked glass ampoule was filled with argon. Under an argon stream, 1.0 mmol (248 mg) of argolide (**4**), 1.1 mmol of the corresponding aryl halide (**37a-c**, **39f**), 4 mol %

palladium acetate, 16 mol % tris-(o-tolyl)phosphine, 5 mL of DMF and 1.8 mmol of triethylamine (conditions i, ii) (or Cs_2CO_3 – iii) were successively loaded into the ampoule; 3 Å molecular sieves were added, and the ampoule was sealed (under a slight excess pressure of argon). When the reaction was carried out under conditions ii, 1.0 mmol of TBAB was additionally added. The reaction mixture was heated for 12–36 h at 120–130 °C. After the ampoule had cooled, it was opened. When the reaction was carried out under conditions i, the contents were poured into a Petri dish, and the solid residue was dissolved in a minimal amount of chloroform and chromatographed on silica gel (eluent: petroleum ether/ethyl acetate with a gradual increase of the latter). Tris-(o-tolyl)phosphine, the dimerization products of the haloarenes, the arylgermacranolides and the starting lactone (**4**) were eluted successively. Water (70 ml) was added to the reaction mixture, and the products were extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with water (3×40 ml), dried over MgSO_4 and evaporated under vacuum. The oily residue was dissolved in a minimal amount of chloroform and chromatographed on silica gel. Elution of the column with a petroleum ether:ethyl acetate (19:1) solvent mixture afforded the fractions containing compounds **38a-c**, **39f**. Individual compounds were isolated by repeated chromatography of the reaction mixture on silica gel (eluent: petroleum ether–ethyl acetate, 15:1→1:1) and recrystallization from the appropriate solvent.

Heck reaction of grossheimin (7) with aryl halides (40a-c)

A two-necked glass ampoule was filled with argon. Under an argon stream, 1 mmol (262 mg) of grossheimin (**7**), 1.2 mmol of the corresponding halide (**40a-c**), 4 mol % palladium acetate, 16 mol % tris-(o-tolyl)phosphine, 1.0 mmol of TBAB, 5 mL of DMF and 1.5 mmol of triethylamine were successively loaded into the ampoule; 3 Å molecular sieves were added, and the ampoule was sealed (under a slight excess pressure of argon). The reaction mixture was heated for 24–25 h at 110–120 °C. Upon completion of the reaction, the ampoule was cooled to room temperature, opened and filtered; the filtrate was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with saturated NaCl solution (1 × 30 mL) and water (2 × 30 mL), dried over MgSO_4 and evaporated under vacuum on a rotary evaporator. The oily residue was dissolved in a minimal amount of CHCl_3 and chromatographed on a column of Silosorb SPH 600 silica gel (eluent CHCl_3 –EtOH, gradient 100:1→100:9). The starting lactone (in the case of incomplete conversion) and the aryl-

substituted grossheimin derivatives (**41a–c**) and (**42a–c**) were isolated successively. If necessary, the products were further purified by repeated column chromatography of the reaction mixture.

Table 1. Summary of the synthesized halogen-containing sesquiterpene γ -lactone derivatives: starting compound, reaction type, product, yield, characteristic $^1\text{H}/^{13}\text{C}$ NMR signals, and biological activity.

№	Starting compound	Reaction type	New compounds	Yield	Characteristic signals in the ^1H NMR and ^{13}C NMR spectra	Biological activity
1	2	3	4	5	6	7
1	Argolide (4)	Heck arylation (ArI, Pd)	13E-(3'-trifluoromethylphenyl)-argolide (38a)	26%	The absence of H-13 α and H-13 β proton signals in the ^1H NMR spectra of compounds (38a-c , 39f) confirms the introduction of aryl groups from aryl halides (37a-c) at C-13; the vinyl proton H-13 shifts downfield (7.42–7.72 ppm) relative to the protons at C-13 (5.67–6.24 ppm) in the ^1H NMR spectrum of the parent argolide (4). In the ^1H NMR spectrum of compound (39f) the H-13 signal is shifted downfield (7.73 ppm) relative to that of the E-isomer (38b) (7.45 ppm).	—
			13E-(4'-fluorophenyl)-argolide (38b)	32%		—
			13E-(4'-chlorophenyl)-argolide (38c)	28%		—
			13Z-(2'-fluorophenyl)-argolide (39f)	26%		—

Continuation of Table 1

1	2	3	4	5	6	7
2	Arglabin (5)	Synthesis of dichlorocyclopropane derivatives in chloroform (phase- transfer catalysis)	3,4 β - dichloromethano- arglabin (11)	5%	In the ¹ H NMR spectra of compounds (12–14) the H-13 α and H-13 β signals shift upfield: H-13 α (2.10–3.40 ppm), H-13 β (1.92–3.03 ppm), relative to H-13 α (5.40 ppm) and H-13 β (6.12 ppm) in the parent arglabin (5). In the ¹³ C NMR spectra of (12–14) the corresponding carbons also shift upfield: C-11 (31.48–44.35 ppm), C-13 (26.47–52.62 ppm) vs C-11 (139.15 ppm) and C-13 (118.39 ppm) in arglabin (5), indicating addition of dichloro- and dibromocarbenes across the exomethylene double bond of the γ -lactone. In the ¹ H NMR spectra of (11–13) the H-3 signal shifts upfield (1.71–1.98 ppm) vs H-3 (5.55 ppm) in arglabin (5); in their ¹³ C NMR spectra C-3 and C-4 also shift upfield (38.28–39.56 and 40.60–41.54 ppm) vs C-3 (124.98 ppm) and C-4 (140.57 ppm) in arglabin (5), indicating formation of a dichlorocyclopropane ring at C-3 and C-4.	In terms of cytotoxicity, compound (12) is 32.7 times more active against <i>Artemia salina</i> (Linnaeus, 1758) than the parent arglabin (5).
			3,4 α ,11,13b-bis- dichloromethano- arglabin (12)	61%		
			3,4 α - dichloromethano- 13 α -trichloromethyl- arglabin (13)	3%		
		Synthesis of dichlorocyclopropane derivatives in chloroform (phase- transfer catalysis)	11,13- dibromomethano- arglabin (14)	28%		–

Continuation of Table 1

1	2	3	4	5	6	7
3	Achillin (6)	Chlorination in benzene	1 α ,10 β -dichloro-achillin (25)	63.3%	In the ¹³ C NMR spectra of compounds (25–31) the C-1 signal shifts upfield (69.17–77.34 ppm) vs C-1 (131.3 ppm) in the parent achillin (6), indicating addition of chlorine at C-1. In (25, 28–31) the C-10 signal shifts upfield (73.28–76.22 ppm) vs C-10 (151.8 ppm) in achillin (6), indicating addition of chlorine at C-10. In (26–27) the C-10 signal is instead shifted downfield (143.77 and 82.39 ppm), confirming for (26) formation of the exomethylene double bond C10=C14 and for (27) addition of a methoxy radical. In (28–31) the C-14 signal shifts downfield (75.64–77.27 ppm) vs C-14 (21.0 ppm) in achillin (6), indicating addition of substituents (chlorine or methoxy) at C-14; in (26) the C-14 signal is shifted downfield (118.82 ppm), confirming the C10=C14 double bond.	–
		Chlorination in methanol at room temperature	1 α -chloro-10,14-dehydroachillin (26)	28%		Compounds (27) and (28) show comparatively high cytotoxicity against murine myeloma P3X63.Ag8.653: the cytotoxicity index at 160 μ M is 97.2% for (27) and 77% for (28), vs 67.9% for the parent achillin (6).
			1 α -chloro-10 β -methoxyachillin (27)	11%		
			1 α ,10 β -dichloro-14 α -methoxyachillin (28)	20%		
			1 α ,10 α -dichloro-14 β -methoxyachillin (29)	14%		
		Chlorination in methanol at –30 °C	1 α ,10 α ,14-trichloroachillin (30)	10%		–
			1 α ,3,10 α -trichloro-14 β -methoxyachillin (31)	20%		–

Continuation of Table 1

1	2	3	4	5	6	7
4	Grossheim in (7)	Reaction with phosphorus pentachloride in pyridine	8 α - chlorogrossheimin (35)	—	In the ¹ H NMR spectra of compounds (35–36) the H-8 signal shifts downfield (5.07–5.58 ppm) vs H-8 (3.82 ppm) in the parent grossheimin (7), indicating substitution of the C-8 hydroxyl of grossheimin (7) by halogen radicals.	—
		Reaction with chloroacetic anhydride in pyridine	8 α - chloroacetylgrosshei min (36)	68%		Compound (36) shows moderate antimicrobial activity against the Gram-positive strains <i>Staphylococcus aureus</i> and <i>Bacillus subtilis</i> and a weak anti-inflammatory effect in a model of acute exudative reaction. High cytotoxicity of (36) was established against acute monocytic leukemia in vitro and against larvae of the brine shrimp <i>Artemia</i>

Continuation of Table 1

1	2	3	4	5	6	7
						<i>salina</i> (Linnaeus, 1758).
		Heck arylation (ArI, Pd)	13E-(4'-chlorophenyl)-grossheimin (41a)	11%	The absence of H-13 α and H-13 β proton signals in the ¹ H NMR spectra of compounds (41a–c) and (42a–c) confirms the introduction of iodoarenes (40a–c) at C-13; the vinyl proton H-13 shifts downfield (7.72–7.88 ppm) vs the protons at C-13 in grossheimin (7) (6.29–6.36 ppm). In the (E)-isomers (41a–c) proton H-7 shows a downfield shift (δ = 3.56–3.90 ppm) vs the (Z)-isomers (42a–c) and grossheimin (7) (δ = 3.08–3.15 ppm). The C-13 signals of the (E)-isomers lie further downfield (δ 171.37, 171.11, 171.10 ppm) than those of the (Z)-isomers 42a–c (δ 167.94, 167.72, 167.72 ppm).	Compounds (41a), (42a) and (42b) show moderate antibacterial activity against the Gram-positive bacteria <i>Staphylococcus aureus</i> and <i>Bacillus subtilis</i> . Compounds (42a) and (42c) show moderate activity against the Gram-negative microorganism <i>Escherichia coli</i> .
			13E-(3'-trifluoromethylphenyl)-grossheimin (41b)	19%		
			13E-(2'-fluorophenyl)-grossheimin (41c)	26%		
			13Z-(4'-chlorophenyl)-grossheimin (42a)	23%		
			13Z-(3'-trifluoromethylphenyl)-grossheimin (42b)	17%		

Continuation of Table 1

1	2	3	4	5	6	7
			13Z-(2'-fluorophenyl)-grossheimin (42c)	24%		
5	Grossmisiin (8)	Reaction with thionyl chloride in pyridine	8 α -chloroachillin (22)	8%	In the ¹ H NMR spectrum of derivative (22) the H-8 signal is shifted downfield (4.45 ppm) vs the parent grossmisiin (8) (3.72 ppm), indicating substitution of the C-8 hydroxyl by chlorine.	—
		Chlorination in benzene	1 α ,10 β -dichlorogrossmisiin (23)	17.7%	In the ¹³ C NMR spectrum of compound (23) the C-1 and C-10 signals shift upfield (74.57 and 69.83 ppm) vs grossmisiin (8) – C-1 (127.78 ppm) and C-10 (137.25 ppm), indicating addition of chlorine at C-1 and C-10.	—
		Reaction with phosphorus pentachloride in pyridine	8 β -chloroachillin (32)	84%	The absence of H-8 α and H-8 β signals in the ¹ H NMR spectrum of compound (32) confirms addition of chlorine at C-8; the H-8 signal shifts downfield (4.53 ppm) vs the parent (1.29 ppm), and in the ¹³ C NMR spectrum C-8 shifts upfield (53.99 ppm) vs the parent grossmisiin (8) (64.96 ppm).	—

Continuation of Table 1

1	2	3	4	5	6	7
6	Isoalantolactone (9)	Makosza reaction with dichlorocarbene (phase-transfer catalysis)	4(15)-dichlorocyclopropyl-isoalantolactone (18)	–	In the ¹ H NMR spectra of compounds (18 , 20 – 21) the H-15 α and H-15 β signals shift upfield: H-15 α (1.25–1.29 ppm), H-15 β (1.52–1.62 ppm), vs H-15 α (4.44 ppm) and H-15 β (4.77 ppm) in the parent isoalantolactone (9); in their ¹³ C NMR spectra C-4 (31.58–31.67 ppm) and C-15 (27.70–27.74 ppm) also shift upfield vs C-4 (148.98 ppm) and C-15 (106.41 ppm), indicating addition of a cyclopropane fragment at C4–C15. In (19 – 20) the H-13 α (2.83–3.03 ppm) and H-13 β (3.24–3.35 ppm) signals shift upfield vs H-13 α (5.59 ppm) and H-13 β (6.13 ppm) in (9); in the ¹³ C NMR spectrum of (20) C-11 (45.86 ppm) and C-13 (49.33 ppm) confirm addition of a trichloroethyl radical at C-13. Cyclopropane formation at C11–C13 in (21) is confirmed by upfield H-13 α (1.63 ppm)/H-13 β (2.08 ppm) and by C-13 (26.96 ppm) vs C-13 (120.08 ppm) in isoalantolactone (9).	Compounds (18) and (19) show high cytotoxicity against three tumor cell lines: CEM-13, U-937 and MT-4.
			13 β -trichloroethyl-isoalantolactone (19)	–		
			4(15)-dichlorocyclopropyl-13 β -trichloroethyl-isoalantolactone (20)	60%		
			4(15),11(13)-dichlorocyclopropyl-isoalantolactone (21)	70%		

Continuation of Table 1

1	2	3	4	5	6	7
7	Leucomisine (10)	Chlorination in benzene	1 α ,10 β -dichloroleucomisine (24)	75.9%	In the ¹ H NMR spectrum of compound (24) the three H-14 protons shift upfield (1.83 ppm) vs the parent leucomisine (10) (2.40 ppm); in the ¹³ C NMR spectrum C-1 and C-10 shift upfield (75.66 and 73.40 ppm) vs leucomisine (10) – C-1 (131.91 ppm) and C-10 (152.31 ppm), indicating addition of chlorine at C-1 and C-10.	–
8	11,13-Dibromomethano-arglabin (14)	Bromination	3,4-dihydro-3 α ,4 β -dibromo-11,13-dibromomethano-arglabin (15)	86%	In the ¹ H NMR spectrum of compound (15) the H-3 signal shifts upfield (4.91 ppm) vs H-3 (5.58 ppm) in the parent 11,13-dibromomethano-arglabin (14); in the ¹³ C NMR spectrum C-3 and C-4 shift upfield (48.67 and 43.90 ppm) vs C-3 (124.95 ppm) and C-4 (140.17 ppm) in (14), indicating addition of bromine at C-3 and C-4.	Compound (15) inhibits the growth of Pliss lymphosarcoma, liver adenocarcinoma PC-1, and sarcomas M-1 and -45 by 70–90%. It shows antifungal activity against the dermatophyte Epidermophyton floccosum and the ascomycete Aspergillus flavus, and stimulates

Continuation of Table 1

1	2	3	4	5	6	7
						phagocytosis compared with the parent arglabin (5).
9	3 β ,4 β -Epoxyarglabin (16)	Reaction with hydrochloric acid in ether–acetone	1,4 β -dihydroxy-3,10 α -dichloroarglabin (17)	55%	In the ¹ H NMR spectrum of compound (17), relative to the parent 3 β ,4 β -epoxyarglabin (16), signals shift downfield: the three H-14 protons from 1.28 to 1.61 ppm, H-6 from 4.05 to 4.48 ppm, and H-3 from 3.31 to 4.42 ppm, indicating opening of two epoxide rings at C3–C4 and C1–C10.	Compound (17) shows comparatively high antiproliferative activity against sarcoma-45 and sarcoma M-1, including the prospidine-resistant strain of Pliss lymphosarcoma, with maximum proliferation suppression up to 71%.
10	8 β -chloroachillin (32)	Chlorination in benzene	3 α ,4 β ,8 β -trichloroachillin (33)	—	In the ¹ H NMR spectrum of compound (33) the signals of H-3 and the C-15 methyl group shift upfield by 2.00 and 0.27 ppm, respectively, vs 8 β -chloroachillin (32), indicating saturation of the C(3)=C(4) bond.	—