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SYNTHETIC TRANSFORMATIONS OF SESQUITERPENE LACTONES. IV.* SYNTHESIS AND TRANSFORMATIONS OF *gem*-DICHLOROCYCLOPROPYL-SUBSTITUTED ISOALANTOLACTONE DERIVATIVES

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Chloro-containing compounds, the ratio of which depended on the reaction time, were formed via reaction of isoalantolactone and $CHCl_3$ through the action of a phase-transfer catalyst. 4,15-(2,2-Dichlorocycloprop-1-yl)isoalantolactone exhibited high activity and selectivity in the Heck reaction with arylhalides. Data for the cytotoxicity of the synthesized chloro-derivatives of isoalantolactone in CEM-13, MT-4, and U-937 cell tumor models were obtained. The doses of the most active compounds inhibiting the viability of tumor cells by 50% ($CCID_{50}$) were 3.2–11.1 μM.

Keywords: isoalantolactone, (gem-dichlorocyclopropyl)eudesmanolides, Heck reaction, tumor cells, XSA.

Isoalantolactone (**1**) is an available metabolite of *Inula helenium* L. and was used as an example in our previous reports for the synthesis of various 13-substituted derivatives [2, 3]. Promising anti-ulcer agents were found among the synthesized 13-aryleudesmanolides [4]. Herein we present results from a study of the reaction of **1** with dichlorocarbene generated from $CHCl_3$ in the presence of triethylbenzylammonium chloride (TEBAC) and the behavior of 4,15-(2,2-dichlorocycloprop-1-yl)isoalantolactone (**2**) in the Heck reaction.

The cycloaddition reaction of various olefins to dihalocarbenes generated under phase-transfer catalysis conditions is a convenient method for preparing dihalocyclopropanes [5]. The sesquiterpene lactones arglabin [6] and estafiatin [7] were also used earlier in this reaction. Use of the Makoshi dichlorocyclopropanation reaction enabled a complicated transformation of **1** to be carried out. It was found that four chloro-containing compounds were formed during the course of the reaction. These were 4(15)-(dichloromethylene)isoalantolactone (**2**), 13-trichloromethylisoalantolactone (**3**), a pentachloride (**4**), and a *bis*-(dichlorocyclopropyl) derivative (**5**), the yield of which depended on the reaction time (Table 1). It can be seen that the reaction occurs through two pathways. Pathway I involves addition of dichlorocarbene to the methylene in ring A according to the Makoshi method [5] to form **2**. The second direction II begins with attack of the $^{-}CCl_3$ anion at the activated double bond of the methylenelactone and proceeds with the addition of a $CHCl_3$ molecule to form **3** (Scheme 1). Then, pentachloro-adduct **4** forms. The reaction can be stopped (2-6 h) with a high yield of **4**. Intramolecular dehydrochlorination and cyclization in **4** gives tetrachloride **5**.

It can be seen that the yield of **2** was <37–38%. An alternate approach to **2** consisted of carrying out the dichlorocyclopropanation of the morpholinyllactone (**6**). Morpholine adduct **6** under the reaction conditions underwent elimination with regeneration of the α-methylene-γ-lactone (transformation half-life ~2–2.5 h, –5°C). With this, the formation rate of the product of alkylation by the trichloromethanide anion decreased. This enabled the yield of 4,15-(dichloromethylene)isoalantolactone (**2**) to be slightly increased. Use of the two-step approach, which consisted of dichlorocyclopropanation of **6**, subsequent reaction of the resulting methylenelactone with morpholine, and hydrolysis of morpholine adduct **7**, enabled **2** to be produced in yields up to 55% (Scheme 2).

*For No. III, see Ref. [1].

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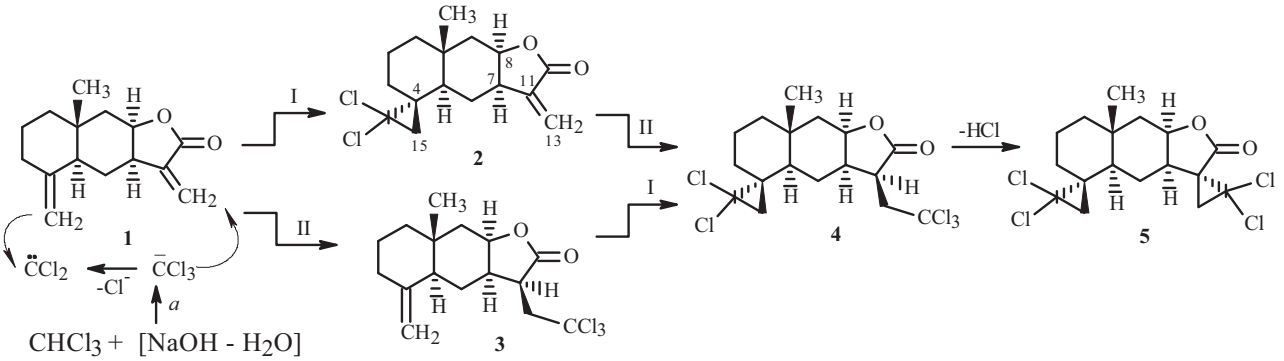
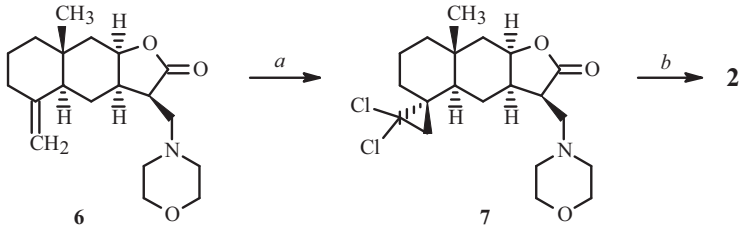
TABLE 1. Yields of Isoalantolactone (**1**) Transformation Products as a Function of Reaction Time (**1**:TEBAC, 1:0.1)

Time, h	Content, %				
	2	**3**	**4**	**5**	**1**
1.1	28	7	4	–	55
1.7	38	10	19	0.01	25
1.9	37	13	28	0.02	20
2	30	2	55	7	0.01
3	28	–	64	7	–
6	4	–	58	32	–
7.5	2	–	51	38	–
10	–	–	44	50	–
20	–	–	30	70	–

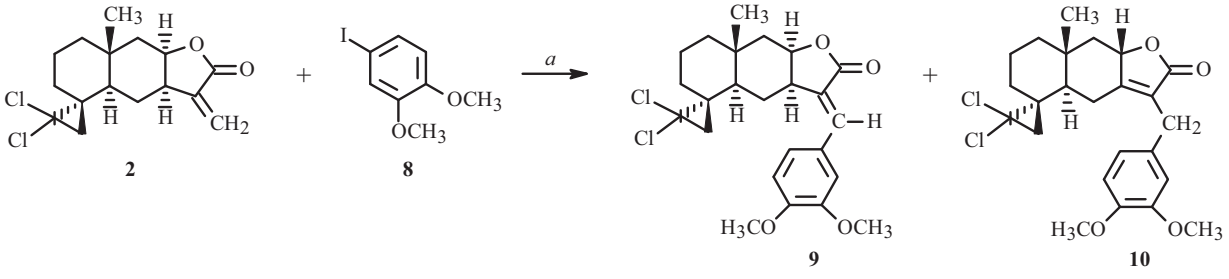


Scheme 1



Scheme 2

The availability of **2** was responsible for our interest in studying its arylation. The reaction of **2** with 4-iodoveratrol (**8**) was carried out in the catalytic system of Pd/*tris*-(*o*-tolylphosphine) (4/16 mol%) in DMF solution in the presence of Et_3N. Like in previously described experiments of arylhalides with **1** [1, 2], the reaction formed a mixture of the 11-arylidene derivative of the lactone (**9**) and the product of a double-bond shift and configuration inversion at the C(8) position (**10**) (overall yield 60%, 5:1 ratio according to GC–MS data) (Scheme 3). The reaction was sensitive to the base. Use of Cs_2CO_3 increased the yields of **9** and **10** to 68 and 16%, respectively.



Scheme 3

TABLE 2. Cytotoxicity of Isoalantolactone **1** and Its Chloro-Containing Derivatives

Compound	CEM-13 tumor cells, $CCID_{50}$, μM	U-937 tumor cells, $CCID_{50}$, μM	MT-4 tumor cells, $CCID_{50}$, μM
1	21.1	18.5	2.4
2	10.6	11.1	3.2
4	12.7	>100	39.1
5	65.8	>100	55.3

$\overline{CCID_{50}}$ is the dose inhibiting viability of tumor cells by 50%.

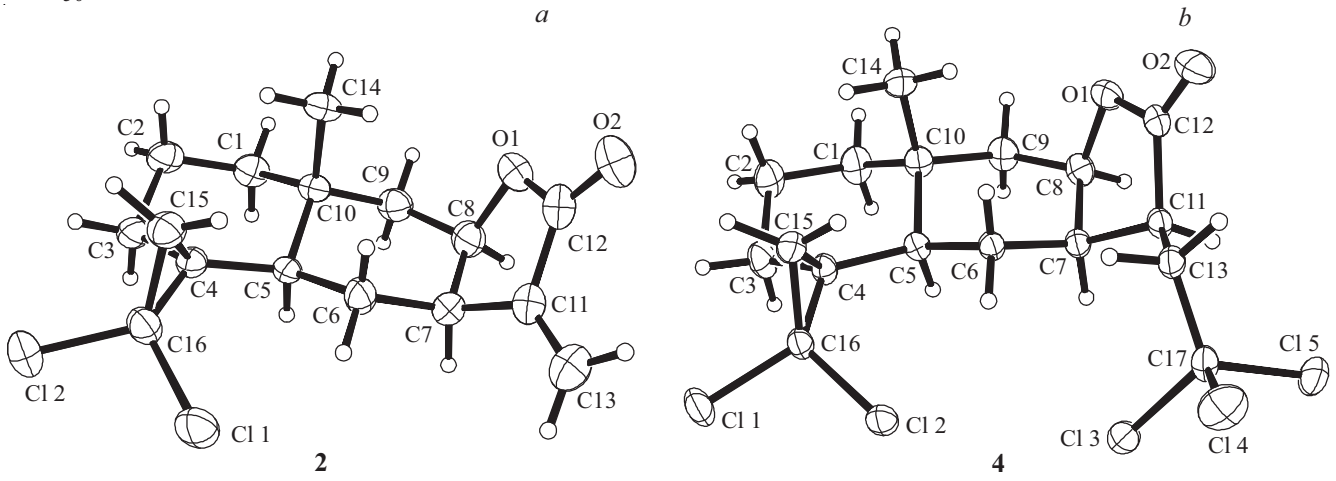


Fig. 1. Molecular structure of **2** (*a*) and **4** (*b*) from an XSA.

The structures of the synthesized compounds were established based on elemental analyses and spectral properties. X-ray crystal structure analyses (XSA) were performed for chloro-containing lactones **2** and **4** (Fig. 1).

The six-membered rings in the studied compounds had the chair conformation. The conformations of the lactone ring were slightly different, i.e., a half-chair with C7 and C8 deviating by –0.336 and +0.189 Å for **2** and an envelope with C7 deviating by 0.605 Å from the plane of the other atoms for **4**. The half-chair conformation of a lactone ring has been observed, e.g., in 4,15-epoxyisoalantolactone [8]; the envelope conformation with C7 deviating by 0.605 Å, in dibromocyclopertilide [9]. The bond lengths in **2** and **4** were similar to the literature values [10]. Layers formed by weak interactions C^8–H^{8A}…O^2 (H…O2 2.50 Å, C–H…O 151°), C^7–H^{7A}…O^2 (2.57, 140), C^3–H^{3B}…Cl^2 (2.92, 138) could be found in the crystal packing of **2**. A 3D architecture with interactions C^8–H^{8A}…O^2 (2.45 Å, 141°), C^3–H^{3B}…Cl^3 (2.81, 144), C^1–H^{1A}…Cl^2 (2.89, 140), and C^{15}–H^{15B}…Cl^2 (2.90, 147) was formed for **4**. A slightly shortened Cl^2…Cl^5 contact of 3.4862(6) Å was also noteworthy.

The XSA data were consistent with the α-position of the dichlorocyclopropane group in **2** and **4** and the 11*S*-configuration of the C(11) chiral center of **4**. It can be seen that cycloaddition of dichlorocarbene to isoalantolactone occurred with high stereoselectivity. The configuration of the product corresponded to attack of the reagent from the α-side.

A characteristic feature of the PMR spectra of **2–5**, **9**, and **10** was a strong-field shift of axial H-6 (δ 0.66–1.04 ppm) as a result of the deshielding effect of the cyclopropane group. Methylene protons H-13 in **4** and **5** resonated at 2.83/3.24 and 1.63/2.08 ppm, respectively. The multiplicity of these resonances in **4** indicated that a vicinal H atom was present. The 11*R*-configuration in **5** was assigned based on NOESY spectral data in which cross-peaks between methylene protons of C-6 and C-13 were detected.

The (*E*)-configuration of the C^{11}–C^{13} double bond of aryllactone **9** was inferred from the presence in the ^{13}C NMR spectrum (single-resonance mode) of a C–H ^3J-*cis* coupling constant between the olefinic proton and the lactone carbonyl C (^3J = 7.2 Hz). A characteristic feature of the PMR spectrum of **9** was a weak-field shift of H-7 (δ 3.36 ppm) compared with the location of the corresponding proton in the spectrum of **1** (δ 2.87 ppm). Formation of **10** was confirmed by the presence in the PMR spectrum of resonances for the C-13 methylene protons [δ 3.57 and 3.66 ppm (2H, J_{gem} = 11.5 Hz, H-13)] and a significant increase of the difference in the chemical shifts of the H-9 protons (Δδ 1.04 ppm). The strong-field proton H-9 (δ 1.06 ppm) had an axial–axial coupling constant with H-8 (J = 11.9 Hz). The 8-(*S*)-configuration of **10** was confirmed by NOESY spectral data in which cross-peaks between resonances of methyl protons $C^{14}H_3$ and H-8 were detected.

Table 2 lists the cytotoxicity of **1** and chloro-containing lactones **2**, **3**, and **5**. Methylenelactones **1** and **2**, which contained an exocyclic double bond in the lactone ring, exhibited the greatest cytotoxicity against three types of tumor cells. These data agreed with results [11, 12] obtained during a study of the properties of other types of sesquiterpene lactones. The results were indicative of the potential of modifying lactones using the Heck reaction because such transformations enable the lactones to be modified while retaining the methylene structure. Introducing *gem*-dichlorocyclopropyl substituents into the lactone ring reduced significantly the cytotoxicity of the compounds.

Thus, a synthetic method for chloro-containing derivatives of **1** was developed based on the availability of this plant metabolite. The ability to modify **2** using the Heck reaction was demonstrated. Significant cytotoxicity was found for the chloro-containing eudesmane-type methylenelactones.

EXPERIMENTAL

NMR spectra of $CDCl_3$ or CD_3OD solutions were taken on Bruker AV-300 (operating frequency 300.13 for ^1H and 75.47 MHz for ^{13}C), AV-400 (operating frequency 400.13 and 100.78 MHz, respectively), and AV-600 (operating frequency 600.30 and 150.96 MHz, respectively) spectrometers. Various types of H–H and C–H shift correlation spectroscopy (COSY, COXH, COLOC, NOESY) were used to assign resonances in NMR spectra. The multiplicity of resonances in ^{13}C NMR spectra was determined by recording spectra in J-mode. A DFS Thermo Scientific high-resolution mass spectrometer (ionizing electron energy 70 eV, vaporizer temperature 230-280°C) was used to record mass spectra and determine molecular weights and elemental compositions. Melting points were determined on a Stuart SMF-38 stage.

Reaction mixtures of **2–5**, **9**, and **10** were studied by GC–MS on a Hewlett–Packard 5890/II MSD GC with an HP MSD 5971 quadrupole mass spectrometer as a detector. We used a quartz column (30 m × 0.25 mm) with HP-5MS (copolymer of 5% diphenyl and 95% dimethylsiloxane) stationary phase as a thin film (0.25 μm) at 50–280°C at 4°C/min and 280°C for 15 min. The percent composition of the compounds was calculated from the GC peak areas without using correction factors.

IR spectra were recorded in KBr pellets on a Vector-22 instrument. UV absorption spectra were recorded in EtOH on an HP 8453 UV—Vis spectrometer. Specific rotations $[\alpha]_D^{20}$ were measured on a PolAAr3005 polarimeter. X-ray diffraction experiments were performed on a Bruker P4 diffractometer [graphite monochromator, λ (Mo Kα) = 0.71073 Å, 298 K, θ/2θ-scanning, 2θ < 54°, crystal size 0.16 × 0.20 × 0.26 mm] for **2** and on a Bruker Kappa APEX II diffractometer [graphite monochromator, λ (Mo Kα) = 0.71073 Å, 173 K, φ–ω-scanning, 2θ < 56.4°, crystal size 0.38 × 0.31 × 0.05 mm] for **4**.

Reaction products were isolated using column chromatography over silica gel (Acros, 0.035–0.070 mm) or Al_2O_3 and, if necessary, additional preparative TLC on a loose layer of silica gel containing K-35 luminophore (1%) on plates (20 × 20 cm) with a thin layer of sorbent (1 mm) and elution by benzene:EtOAc and $CHCl_3$:EtOH.

$Pd(OAc)_2$ was synthesized by the literature method [13]. Isoalantolactone (**1**) was extracted from roots of *I. helenium* with subsequent separation of the morpholine adducts as before [14].

(1*S*,3a′*R*,4a′*R*,8a′*R*,9a′*R*)-2,2-Dichloro-8a′-methyl-3′-methylenedecahydro-2′*H*-spiro-{cyclopropan-1,5′-naphtho[2,3-*b*]furan}-2′-one (2). The morpholine adduct of isoalantolactone (**6**, 500 mg, 1.57 mmol) was dissolved in freshly distilled $CHCl_3$ (3 mL), treated with TEBAC (35 mg, 0.16 mmol), cooled to –5°C, stirred vigorously, treated with a previously cooled (–5°C) solution of NaOH (3 g) in H_2O (3 mL), and stirred for 3 h at –5°C. The dry solid obtained after extraction was dissolved in EtOH, cooled to 0°C, treated in portions over 1 h with a solution of morpholine (200 mg, 2.35 mmol) in EtOH (1 mL), and held at that temperature for 5 h. The excess of morpholine was removed by H_2O. The product was extracted by $CHCl_3$. The Makoshi reaction cycle was repeated. The reaction product after the second cycle was again treated with morpholine solution. The organic layer after removal of the excess of morpholine was washed with aqueous H_2SO_4 (3×, 0.5%). The mixture of morpholine adducts **6** and **7** in the acidic layer was neutralized and extracted by $CHCl_3$. The products were separated by chromatography over Al_2O_3 ($CHCl_3$ eluent). Morpholine adduct **7** was decomposed through the ammonium salt obtained by alkylation with methyliodide and subsequent work up with $NaHCO_3$ solution (5%) to afford **2**, 55% yield, mp 164–166°C (EtOH), $[\alpha]_D$ +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).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.97 (3H, s, H-14), 1.02 (1H, ddd, J = 13.9, 12.3, 12.2, H-6), 1.18 (1H, ddd, J = 12.6, 12.5, 5.0, H-1), 1.25 (1H, d, J = 7.9, H-15), 1.50 (1H, dd, J = 14.8, 4.6, H-9), 1.52 (1H, d, J = 7.9, H-15), 1.53-1.62 (3H, m, H-1, 2, 2), 1.67 (1H, dm, J = 13.8, H-3), 1.83 (1H, dd, J = 12.3, 2.0, H-5), 1.88 (1H, ddd, J = 13.9, 13.6, 6.4, H-3), 2.14

(1H, dd, J = 15.6, 1.2, H-9), 2.35 (1H, ddd, J = 14.0, 6.7, 2.0, H-6), 2.94 (1H, ddd, J = 11.6, 6.2, 5.7, H-7), 4.44 (1H, ddd, J = 5.0, 4.8, 1.2, H-8), 5.53 (1H, d, J = 1.6, H-13), 6.09 (1H, d, J = 1.6, H-13).

^{13}C NMR spectrum ($CDCl_3$, 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 (CCl_2), 75.89 (C-8), 120.55 (C-13), 141.62 s (C-11), 170.31 s (C-12). $C_{16}H_{20}Cl_2O_2$.

Chloro-Containing Lactones 3–5. Isoalantolactone (**1**, 600 mg, 1.29 mmol) was dissolved in freshly distilled $CHCl_3$ (6 mL), treated with TEBAC (58 mg, 0.13 mmol), cooled to –5°C, stirred vigorously, treated with a previously cooled solution of NaOH (6 g) in H_2O (6 mL), held for 1–24 h at –5°C, treated with H_2O (100 mL), and extracted with $CHCl_3$. The dry solid obtained after standard drying over $MgSO_4$ and removal of solvent at reduced pressure was chromatographed over silica gel ($CHCl_3$ eluent) to isolate **3**, **4**, and **5**.

(3*S*,3a*R*,4a*S*,8a*R*,9a*R*)-8a-Methyl-5-methylen-3-(2,2,2-trichloroethyl)decahydronaphtho[2,3-*b*]furan-2(3*H*)-one (3) was obtained by carrying out the reaction for 1.7 h, $[\alpha]_D$ +234.6° (*c* 0.5, $CHCl_3$).

PMR spectrum ($CDCl_3$, 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). $C_{16}H_{21}O_2Cl_3$.

(1*S*,3′*S*,3a′*R*,4a′*R*,8a′*R*,9a′*R*)-2,2-Dichloro-8a′-methyl-3′-(2,2,2-trichloroethyl)decahydro-2′*H*-spiro{cyclpropan-1,5′-naphtho[2,3-*b*]furan}-2′-one (4) was obtained by carrying out the reaction for 5.5 h and was isolated by recrystallization of the reaction mixture from EtOH. Yield 60%, mp 202–204°C (EtOH), $[\alpha]_D$ +243.5° (*c* 1.8, $CHCl_3$). IR spectrum (ν, cm^{-1}): 2941. 1779, 1634w, 1166, 738, 771, 952, 700. UV spectrum (EtOH, λ_{max}, nm, log ε): 201 (3.51), 260 (1.60).

PMR 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). $C_{17}H_{21}O_2Cl_5$.

(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 (5) was isolated by carrying out the reaction for 24 h, yield 70%, mp 175–177°C (EtOH), $[\alpha]_D$ +68.7° (*c* 0.8, $CHCl_3$). IR specrum (ν, cm^{-1}): 2912, 1776, 1633, 1419, 1352, 1248, 1221, 1182, 1144, 1115, 1066, 964, 762. UV spectrum (EtOH, λ_{max}, nm, log ε): 201 (3.90).

PMR 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).

^{13}C 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). $C_{17}H_{20}O_2Cl_4$.

Heck Reaction. A two-necked glass ampul was filled with Ar, in a stream of which the ampul was charged sequentially with **2** (315 mg, 1.0 mmol), **8** (290 mg, 1.1 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), *tris*-(*o*-tolyl)phosphine (49 mg, 0.16 mmol), DMF (5 mL), and Et_3N (172 mg, 1.7 mmol). Molecular sieves (3 Å) were added. The ampul was sealed (with a slight excess of Ar pressure), heated for 8 h at 120°C, cooled, and opened. The contents were poured into a Petri dish. The solid precipitate was dissolved in the minimal amount of $CHCl_3$ and chromatographed over silica gel ($CHCl_3$:EtOH eluent, 100:0→10:1). *tris*-(*o*-Tolyl)phosphine, starting lactone, a mixture of lactone and reaction products, and a mixture of two reaction products ($CHCl_3$ eluent) eluted successively. Pure compounds were isolated using repeated chromatography and recrystallization from an appropriate solvent. Analytical samples were purified using preparative TLC. Yield 180 mg (40%) of

(1*S*,3a′*R*,4a′*R*,8a′*R*,9a′*R*,*E*)-2,2-dichloro-3′-(3,4-dimethoxybenzylidene)-8a′-methyldecahydro-2′*H*-spiro{cyclopropan-1,5′-naphtho[2,3-*b*]furan}-2′-one (9) and 68 mg (10%) of a mixture of **9** and **10** (content of **10**, ~75%). Carrying out an analogous reaction with Et_3N replaced by Cs_2CO_3 (488 mg, 1.5 mmol) afforded 280 mg (63%) of **9** and 41 mg (9%) of **(1*S*,4a′*R*,8a′*R*,9a′*S*)-2,2-dichloro-3′-(3,4-dimethoxybenzyl)-8a′-methyl-4′,4a′,6′,7′,8′,8a′,9′,9a′-octahydro-2′*H*-spiro{cyclopropan-1,5′-naphtho[2,3-*b*]furan}-2′-one (10)**.

Compound 9, mp 192–194°C (EtOH), $[\alpha]_D$ +322.5° (*c* 1.6, $CHCl_3$). UV spectrum (EtOH, λ_{max}, nm, log ε): 220 (3.06), 235 (3.63), 300 (3.65), 313 (3.51).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.01 (3H, s, H-14), 1.02 (1H, ddd, J = 14.3, 12.2, 11.9, H-6), 1.20 (1H, dd, J = 7.2, 6.4, H-1), 1.24 (1H, d, J = 7.5, H-15), 1.47 (1H, d, J = 7.5, H-15), 1.52-1.60 (4H, m, H-1,2,2,9), 1.66 (1H, dm, J = 13.3, H-3), 1.87 (2H, m, H-3,5), 2.20 (1H, dd, J = 15.9, 1.2, H-9), 2.65 (1H, ddd, J = 14.3, 6.4, 1.6, H-6), 3.36 (1H, ddd, J = 12.2, 6.4, 4.8, H-7), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.43 (1H, ddd, J = 4.8, 4.7, 1.1, H-8), 6.81 (1H, d, J = 8.2, H-5′), 6.94 (1H, d, J = 2.0, H-2′), 7.06 (1H, dd, J = 8.2, 2.0, H-6′), 7.30 (1H, s, H-13).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 18.84 (C-2), 19.26 (C-14), 23.60 (C-6), 27.63 (C-15), 31.47 (C-4), 34.36 (C-10), 35.91 (C-3), 40.03 (C-7), 41.68 (C-1), 42.44 (C-5), 42.53 (C-9), 55.83 (OCH_3), 55.99 (OCH_3), 66.67 (CCl_2), 75.93 (C-8), 111.08 (C-6′), 112.84 (C-2′), 123.46 (C-5′), 126.77 (C-1′), 129.11 (C-11), 135.36 (C-13), 149.02 (C-3′), 150.66 (C-4′), 172.36 (C-12). $C_{24}H_{28}Cl_2O_4$.

Compound 10, mp 101–105°C (EtOH), $[\alpha]_D$ –26.1° (*c* 0.9, $CHCl_3$). UV spectrum (EtOH, λ_{max}, nm, log ε): 218 (3.85), 280 (2.62).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.96 (3H, s, H-14), 1.03 (1H, ddd, J = 14.3, 12.2, 11.9, H-6), 1.09 (1H, dd, J = 11.9, 10.8, H-9), 1.19 (1H, m, H-1), 1.22 (1H, d, J = 7.2, H-15), 1.49 (1H, d, J = 7.2, H-15), 1.52–1.70 (4H, m, H-1,2,2,3), 1.79 (1H, dm, J = 12.0, H-5), 1.90 (1H, m, H-3), 2.13 (1H, dd, J = 11.9, 6.1, H-9), 2.64 (1H, dd, J = 13.9, 4.2, H-6), 3.57 (1H, d, J = 11.5, H-13), 3.66 (1H, dd, J = 11.5, 1.4, H-13), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.68 (1H, m, H-8), 6.71 (2H, m, H-5′,6′), 6.84 (1H, d, J = 2.0, H-2′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 18.83 (C-2), 19.43 (C-14), 21.69 (C-6), 26.13 (C-15), 28.44 (C-13), 31.67 (C-4), 34.75 (C-3), 36.88 s (C-10), 40.26 (C-1), 46.83 (C-5), 46.56 (C-9), 65.48 (CCl_2), 77.89 (C-8), 110.92 (C-6′), 112.22 (C-2′), 123.29 (C-11), 124.22 (C-5′), 128.93 (C-1′), 149.44 (C-3′), 151.17 (C-4′), 162.63 s (C-7), 173.44 s (C-12). $C_{24}H_{28}Cl_2O_4$.

X-ray Crystal Structure Analysis of 2 and 4. Crystallographic data for **2**: $C_{16}H_{20}Cl_2O_2$, MW 315.22, monoclinic system, space group $P2_1$, a = 7.617(2), b = 6.2795(10), c = 16.307(2) Å, β = 90.568(15)°, V = 779.9(3) Å^3, Z = 2, d_{calcd} = 1.342 g/cm^3, μ = 0.415 mm^{-1}, 1991 measured reflections, 1855 independent (R_{int} = 0.0333), 1087 reflections with $I \geq 2\sigma(I)$, 183 refined parameters, R_1 [$I \geq 2\sigma(I)$] = 0.0456, wR_2 = 0.1156, GOF = 0.986 (over all reflections), absolute structure parameter (Flack) –0.12(13). Crystallographic data for **4**: $C_{17}H_{21}Cl_5O_2$, MW 434.59, monoclinic system, space group $P2_1$, a = 9.0527(4), b = 9.9431(3), c = 10.9375(4) Å, β = 106.722(1)°, V = 942.87(6) Å^3, Z = 2, d_{calcd} = 1.531 g/cm^3, μ = 0.777 cm^{-1}, 8294 measured reflections, 4240 independent (R_{int} = 0.0351), 4073 reflections with $I \geq 2\sigma(I)$, 218 refined parameters, R_1 [$I \geq 2\sigma(I)$] = 0.0260, wR_2 = 0.0685, GOF = 1.191 (over all reflections), absolute structure parameter (Flack) –0.03(4).

Absorption for **2** was taken from experimental azimuthal scanning curves (T_{min}/T_{max} = 0.825/0.857); for **4**, from the SADABS program (T_{min}/T_{max} = 0.699/0.888). The structures were solved by direct methods. Positions and thermal factors of atoms were refined by full-matrix anisotropic least-squares methods. Positions of H atoms were calculated geometrically and refined using a rider model. All calculations were performed using the SHELX-97 program; geometric analysis, the PLATON program. The crystallographic data were deposited in the Cambridge Crystallographic Data Centre (CCDC 833094 for **2**; 833095, for **4**) and can be obtained by request to http://www.ccdc.cam.ac.uk/products/csd/request/.

Cell Culture. We used human tumor cell lines MT-4, CEM (human T-cell leukosis), and U-937 (human monocytes). Cells were cultivated in RPMI-1640 medium containing fetal calf serum (10%), L-glutamine (2 mmol/L), gentamicin (80 μg/mL), and lincomycin (30 mg/mL) at 37°C in a CO_2 incubator. Test compounds were dissolved in DMSO and added to cell culture at the required concentrations. We used three wells for each concentration. Cells incubated without added compounds were used as the control.

MTT Test. The standard MTT test as described before [15, 16] was used to determine the $CCID_{50}$ (doses inhibiting cell viability by 50%) values.

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