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SYNTHESIS OF DIHALOCARBENE DERIVATIVES OF ARGLABIN

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Dibromocarbene and bisdichlorocarbene derivatives of the available sesquiterpene lactone arglabin were synthesized for the first time. The structures of the molecules were established by spectra methods and XSA.

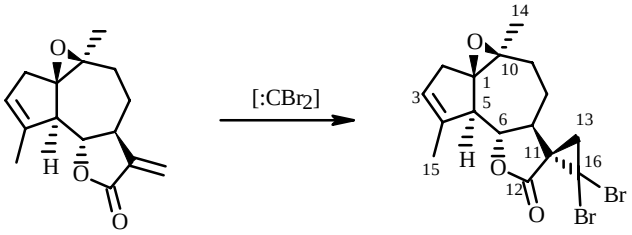
Key words: sesquiterpene lactones, arglabin, dihalocarbenes, interphase catalysis, x-ray structure analysis, NMR.

Dihalocarbene derivatives of sesquiterpene lactones were described first by Salazar and Diaz [1], who prepared a series of difluorocarbene derivatives of natural pseudoguaianolides using sodium difluoroacetate as the difluorocarbene source.

In order to broaden the range of known derivatives of the antitumor sesquiterpene lactone arglabin (**1**) [2], we examined the possibility of preparing its dihalocarbene derivatives by generating dichloro- and dibromocarbene from $CHCl_3$ and $CHBr_3$, respectively, under interphase catalysis conditions [3] using dicyclohexyl-18-crown-6. Preliminary results have been presented at scientific conferences [4, 5].

Only one product (**2**) could be isolated from the products from the reaction of **1** and dibromocarbene. Its structure and stereochemistry were established using x-ray structure analysis (XSA) (Fig. 1).

The conformation of the five-membered ring is intermediate between a 1β-envelope (ΔC_s^1 = 5.7; C-2, C-3, C-4, and C-5 are coplanar within ±0.02 Å; C-1 deviates from the plane by 0.42 Å to the β-side) and a 1β,5α-half-chair ($\Delta C_2^{5,1}$ = 6.1; C-1 and C-5 deviate from the plane passing through C-2, C-3, and C-4 by 0.32 and 0.12 Å to the β- and α-sides, respectively).



1 **2**

The seven-membered ring has the 7α,1,10β-chair conformation (ΔC_s^7 = 3.6°). The conformation of **2** is in general similar to that of previously studied arglabin molecules [6] and a dimethylamino-hydrochloride derivative of arglabin [7]. The difference in the values of the corresponding torsion angles is less than 10°.

The conformation of the lactone ring is intermediate between a 6β-envelope (C-7, C-11, C-12, and O-1 are coplanar within ±0.03 Å, C-6 deviates from the plane by 0.44 Å to the β-side) and a 6β,7α-half-chair (C-6 and C-7 deviate from the plane passing through C-11, C-12, and O-1 by 0.32 and 0.15 Å to the β- and α-sides) (ΔC_s^6 = 5.7 and $\Delta C_s^{6,7}$ = 6.7 Å, respectively).

Signals in the ^{13}C NMR spectrum of **2** were reliably assigned by first assigning those of starting **1** using 2D ^{13}C—^{1}H COSY and COLOC NMR. The resulting data were used to interpret the ^{13}C NMR spectrum of **2** (Table 1).

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TABLE 1. ^{13}C NMR Spectral Data for **1** and **2** (δ, ppm, 0 = TMS, $CDCl_3$)

Atom	**1**	**2**	Atom	**1**	**2**
1	72.23 s	72.52 s	9	33.24 d	33.38 d
2	39.53 t	34.62 t	10	62.53 s	62.75 s
3	124.76 d	124.95 d	11	138.84 s	39.50 s
4	140.23 s	140.17 s	12	170.33 s	172.29 s
5	52.51 d	53.09 d	13	118.21 t	26.47 t
6	82.72 d	81.55 d	14	22.64 q	22.47 q
7	50.81 d	49.75 d	15	18.14 q	18.15 q
8	21.24 d	23.35 d	16	-	76.89 s

TABLE 2. ^{13}C and ^{1}H Chemical Shifts and Multiplicities in NMR Spectra of **3** [δ, ppm, 0 = TMS, $(CD_3)_2CO$]

Atom	^{13}C (δ)	^{1}H (J/Hz)	Atom	^{13}C (δ)	^{1}H (J/Hz)
1	80.30 s	-	9	34.51 t	2.01-2.10* m (2H-9)
2	36.04 t	2.10 dd (H-2a, J_{gem} = 15.5; $J_{1,2a}$ = 8);	10	64.13 s	-
		2.23 dd (H-2b; $J_{1,2b}$ = 3)	11	37.48 s	-
3	39.22 d	1.98 dd (J = 3; 8)	12	171.87 s	-
4	41.54 s	-	13	29.00 t	1.92 d (H-13a; J_{gem} = 8.3);
5	51.86 d	2.94 d ($J_{5,6}$ = 11.0)			2.12 dd (H-13b; J_{gem} = 8.3; $^{4}J_{7,13}$ = 1)
6	80.85 d	4.44 dd ($J_{5,6}$ = 11.0; $J_{6,7}$ = 10.0)	14	23.49 q	1.31 d ($^{4}J_{9,14}$ = 1)
7	46.69 d	2.40 br.t ($J_{6,7}$ = $J_{7,8}$ = 10)	15	17.13 q	1.64 br.s
8	23.64 t	1.3* m (H-8a);	16	76.25 s	-
		1.45 ddt (H-8b; J_{gem} = 14.0; 3.0; 1.2)	17	61.89 s	-

*Values from 2D ^{1}H-^{1}H NMR spectra.

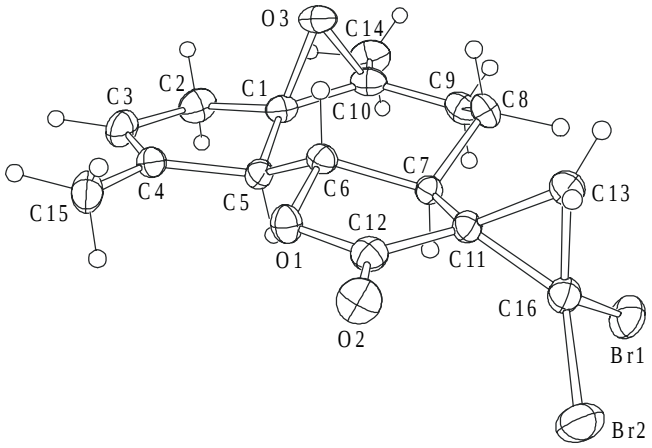
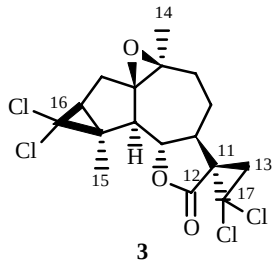


Fig. 1. Structure of **2**.

The yield of **2** (28%) was low. However, it should be noted that the yield of the dibromocarbene derivative is sometimes much less than that of the dichlorocarbene derivative under identical conditions [2].

Reaction of **1** with dichlorocarbene generated from $CHCl_3$ gave in good yield the addition product of dichlorocarbene at both double bonds, lactone **3**. Although this product was crystalline, suitable crystals for an XSA could not be obtained. Its stereochemistry is assumed to be that of **3** taking into account the known stereochemistry of electrophilic addition to **1** [7, 8]. It occurs from the β-side at the tri-substituted double bond and from the α-side at the exomethylene.



3

NMR spectra of **3** (Table 2) were interpreted using 2D ^{1}H—^{1}H and ^{13}C—^{1}H (COSY, COLOC) NMR spectra. The assumed stereochemistry of **3** at C-11 was confirmed by the presence of long-range W-type spin—spin coupling between H-13b and H-7 (J = 1 Hz); the stereochemistry at C-3 and C-4, by the lack of analogous long-range coupling between H5 and 3H-15 because a suitable mutual arrangement of the H-15, C-15, C-4, C-5, H-5 chain could not be achieved with the α-configuration of the C-4 methyl.

EXPERIMENTAL

Melting points were determined on a Boetius instrument; IR spectra, on a Vector 22 instrument in KBr; NMR spectra, on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^{1}H; 125.76 MHz for ^{13}C, δ-scale) using standard Bruker programs to record 2D COSY and COLOC (7 Hz) 2D spectra. Mass spectra were obtained in a Finnigan MAT 8200 instrument. Optical rotation was measured (at 580 nm) on a Polamat A polarimeter.

TLC used Silufol plates that were developed by spraying with aqueous $KMnO_4$ solution (1%); for column chromatography, silica gel (Armsorb). Dicyclohexyl-18-crown-6 (Reakhim) was used as received.

Starting lactone (**1**, mp 100-102°C) was isolated from the aerial part of *Artemisia glabella* Kar. et Kir. [3].

(1*R*,5*R*,6*S*,7*R*,10*S*,11*R*)-1,10-Epoxy-11,13-(dibromomethano)guai-3-en-12,6-olide (2). $CHBr_3$ (3 mL) was treated with aqueous NaOH (2 mL, 50%) and crown ether (60 mg), stirred, and treated with **1** (200 mg, 0.8 mmol). Stirring was continued at room temperature for 3 h. Then the reaction mixture was diluted with water (20 mL). The crude products were extracted with EtOAc (2×20 mL). Solvent was removed. The solid was chromatographed over a column with elution by EtOAc:petroleum ether to isolate **2** that was recrystallized from EtOAc:petroleum ether, mp 180-183°C, R_f 0.57 (EtOAc:petroleum ether, 1:4), yield 94 mg (28%).

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

PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.25 (1H, m, H-8a), 1.32 (3H, s, CH_3-10), 1.46 (1H, dm, J_{gem} = 1.38, H-8b), 1.95 (3H, br.s, Me-4), 1.96-2.16 (6H, m, H-2a, H-7, 2H-9, 2H-13), 2.76 (1H, dm, J_{gem} = 18, H-2b), 3.02 (1H, d, $J_{5,6}$ = 7.0, H-5), 4.13 (t, $J_{5,6}$ = $J_{6,7}$ = 7.0, H-6), 5.58 (1H, br.m, H-3).

For the ^{13}C NMR spectrum, see Table 1.

(1*R*,3*S*,4*R*,5*R*,6*S*,7*R*,10*S*,11*R*)-1,10-Epoxy-4,5;11,13-bis-(dichloromethano)guaian-12,6-olide (3). $CHCl_3$ (3 mL) was stirred, treated with dicyclohexyl-18-crown-6 (30 mg) and aqueous NaOH (2 mL, 50%), after 15 min treated with **1** (0.1 g, 0.04 mmol), stirred at room temperature for 4 h, diluted with water (4 mL), and extracted with $CHCl_3$ (10 mL). The organic layer was dried over Na_2SO_4 and filtered. Solvent was removed. The solid (0.22 g) was chromatographed over a column of SiO_2 (6 g) using EtOAc:petroleum ether (1:4) to elute **3**, mp 182-185°C (EtOAc:petroleum ether, 2:1), $[\alpha]_{580}^{18}$ +51° (*c* 1.45, $CHCl_3$), R_f 0.52 (EtOAc:petroleum ether, 1:2), yield 0.1 g (61%).

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

Mass spectrum (*m*/*z*, I_{rel}, %): 410 (0.6) [M,^{35}Cl]$^+$, 375 (3) [M - ^{35}Cl]$^+$, 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). $C_{17}H_{18}O_3Cl_3$.

For PMR and ^{13}C NMR spectra, see Table 2.

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