Chemistry of Natural Compounds, Vol. 42, No. 3, 2006

CRYSTAL STRUCTURE OF A TETRABROMO DERIVATIVE OF CYCLOPROPYLDIHYDROARGLABIN AND ITS ANTIFUNGAL ACTIVITY

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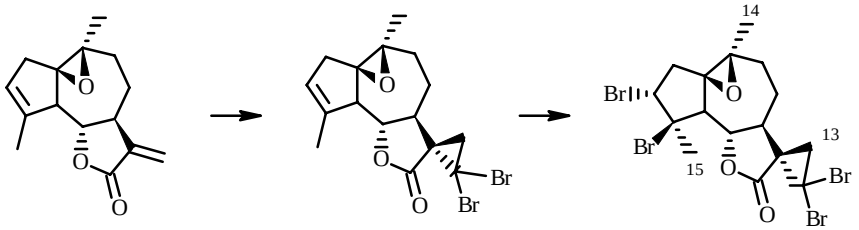
UDC 547:314+547.323

A tetrabromo derivative of arglabin was synthesized stereoselectively. The molecular structure of the new compound was established using PMR and ^{13}C NMR spectra and an x-ray structure analysis. Its antifungal activity was demonstrated.

Key words: sesquiterpene lactone, arglabin, guaianolide, NMR spectroscopy, x-ray structure analysis, biological activity.

Arglabin (**1**) is a guaiane-type sesquiterpene lactone that was isolated from *Artemisia glabella* Kar. et Kir. [1].

New derivatives of arglabin were prepared by reacting dibromocarbene derivative **2** [2] with Br_2 in $CHCl_3$ to produce in quantitative yield the colorless crystalline compound **3** of formula $C_{16}H_{18}O_3Br_4$.



1 **2** **3**

The IR spectrum of **3** contains absorption bands for γ-lactone carbonyl at 1792 cm^{-1} and C–Br at 659 cm^{-1}. An absorption band for a double bond in **3** is not observed.

The PMR spectrum of **3**, which was interpreted using two-dimensional ^1H—^1H NMR (COSY), contains a doublet for the H-3 protons at 4.91 ppm, H-5 at 2.81 ppm, and a triplet for the lactone proton at 4.35 ppm. Signals for the CH_3-14 and CH_3-15 methyls appear as a singlet and broad singlet at 1.31 and 2.22 ppm, respectively. The H-13b and H-13a protons (2.13 and 2.04 ppm) appear as an AB-system with J_{AB} = 8.0 Hz.

The molecular structure of **3** was unambiguously established by an x-ray structure analysis (Fig. 1).

The bond lengths in **3** are close to the average values [3]. The five-membered carbocycle has the E^4 envelope conformation with C4 deviating by 0.57(1) Å from the plane of the remaining atoms. The seven-membered ring has the chair conformation; the lactone ring, a $^6T_7$ twist conformation. Among the intermolecular contacts, the short Br3...H8B distance of 2.90 Å (sum of van-der-Waals radii 2.97 Å [4]) and Br4...O2, 3.309(7) Å (sum of van-der-Waals radii 3.45 Å [4]) are notable. We did not find reports of derivatives of 1,10-epoxy-11,13β-cyclopropylguai-12,6-olide in the Cambridge Structural Database [5]. One of the closest structural analogs of **3** is artefin [6], in which the conformations of the rings are practically identical to those in **3**.

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0009-3130/06/4203-0307

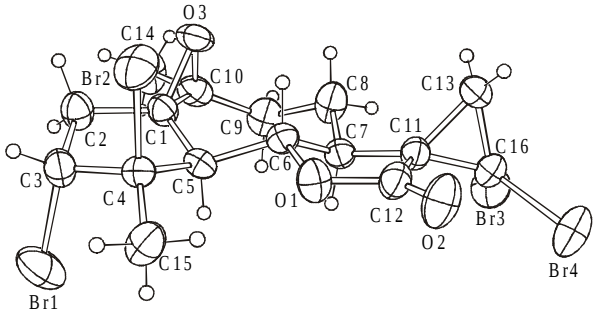

Fig. 1. Molecular structure of **3**.

The antifungal activity of **3** was studied relative to *Aspergillus niger*, *A. flavus*, *Trichophyton mentagrophytos*, *Epidermophyton floccosum*, and *Penicillium citrinum*. It was established that **3** exhibits distinct activity toward *E. floccosum* and moderate activity toward *A. flavus*.

Thus, the new arglabin derivative **3** with antifungal activity [7] was synthesized.

EXPERIMENTAL

NMR spectra of $CDCl_3$ solutions were recorded on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^1H and 125.76 MHz for ^{13}C, δ-scale) using standard Bruker programs to record two-dimensional COSY spectra. Mass spectrum (EI, 70 eV) was recorded in a Finnigan MAT 8200 instrument. Melting points were determined on a Boetius instrument. IR spectrum was recorded on a Vector 22 instrument in KBr. TLC used Silufol UV-254 plates with development by aqueous $KMnO_4$ (2%). Flash chromatography used Armsorb-grade silica gel.

Starting **2** was prepared from arglabin (**1**) by the literature method [2].

11,13-Dihydro-1,10β-epoxy-3α,4β-dibromo-11α,13α-(1′,1′-α-dibromomethylidenyl-)-5,7α,6β(H)-guai-12,6-olide (3). Compound **2** (100 mg, 0.24 mmol) was dissolved in absolute $CHCl_3$ (2 mL), stirred, and treated dropwise at room temperature (20°C) with bromine (0.012 mL, 0.24 mmol). After 5 min the reaction mixture was diluted with water (2 mL) and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried over $MgSO_4$ and filtered. The solid (190 mg) was chromatographed over a silica-gel (6 g) column with elution by petroleum ether:ethylacetate (95:5). Compound **3** was recrystallized from ethylacetate, mp 141°C (dec.), R_f 0.46, yield 116 mg (86%), $C_{16}H_{18}O_3Br_4$.

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

PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.91 (1H, d, J = 6.4, H-3), 4.35 (1H, t, J = 10.0, H-6), 2.98 (1H, dd, J = 6.4, 17.0, H-2b), 2.81 (1H, d, J = 10.0, H-5), 2.73 (1H, d, J = 17.0, H-2a), 2.22 (3H, br.s, CH_3-15), 2.18 (1H, m, H-7), 2.15 (1H, dd, H-9a), 2.13 (1H, d, J = 8.0, H-13b), 2.04 (1H, d, J = 8.0, H-13a), 2.02 (1H, ddd, J = 18.0, 12.4, 2.4, H-8a), 1.51 (1H, m, H-9b), 1.31 (3H, s, CH_3-14), 1.27 (1H, m, H-8b).

^{13}C NMR spectrum (125.76 MHz, $CDCl_3$, δ, ppm): 76.64 (s, C-1), 33.06 (t, C-2), 48.67 (d, C-3), 43.90 (s, 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). The spectrum was interpreted by comparison with the ^{13}C NMR spectrum of **2**.

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 497 (6) $[M - HBr]^+$, 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).

X-ray structure analysis of **3** was performed at room temperature on a Bruker P4 diffractometer using Mo Kα-radiation and a graphite monochromator. Intensities of reflections were measured by θ/2θ-scanning. Absorption corrections were applied by integrating over the crystal facets. The structure was solved by direct methods using the SHELXS-97 programs and refined by anisotropic (isotropic for H) full-matrix least-squares methods using the SHELXL-97 programs. Coordinates of H atoms were calculated geometrically and refined using a rocking model. Crystallographic data: $C_{16}H_{18}O_3Br_4$, MW = 577.94, orthorhombic, space group $P2_12_12_1$, a = 6.008(1), b = 16.132(3), c = 19.042(4) Å, V = 1845.5(7) $Å^3$, Z = 4,

d_{calc} = 2.080 g/cm^3, μ = 8.733 mm^{-1}, crystal size 0.25 × 0.6 × 0.8 mm, transmission 0.038-0.161, 2530 independent reflections, $2\theta_{max}$ = 56°, R_1 = 0.0461 for 1911 observed ($I > 2\sigma$) reflections, wR_2 = 0.1170 and GOF = 1.029 for all reflections, calculated absolute structure parameter 0.05(3). Crystallographic data of **3** and x-ray diffraction data were deposited in the Cambridge Structural Database (No. CCDC 603035).

ACKNOWLEDGMENT

The work was supported financially by the Ministry of Education and Science of the Republic of Kazakhstan (Basic Research Program F.0286).

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