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DILACTONE FORMATION BY CHROMIC ANHYDRIDE OXIDATION OF THE GERMACRANOLIDE STIZOLICIN

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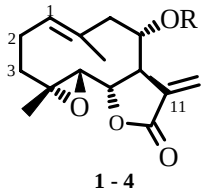
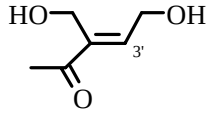
The sidechain of the germacranolide stizolicin was oxidized by CrO_3 in Py to form a lactone. The structure of the product was established as 4,5α-epoxy-7α,5,6,8β(H)-germacr-1(10),11(13)-dien-8α(3′-oxo-2′,5′-dihydrofuran-3′-carboxylyl)-12,6-olide using spectral data.

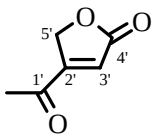
Key words: stizolicin, oxidation, dilactone, two-dimensional NMR.

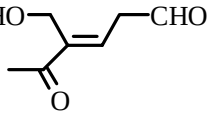
The germacranolide stizolicin (**1**) was first isolated from the aerial part of *Stizolophus coronopifolius* (Lam.)Cass. [1] and then observed in *S. balsamita* (Lam)Cass. ex. Tacht. [2] and *Saussurea elongata* DC [3]. Its structure was established [4, 5] using spectral data and chemical correlation with isospiciformin. Stizolicin has remarkable cytotoxic [5] and antiparasitic activities [6].

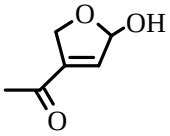


1 - 4

1: R = 

2: R = 

3: R = 

4: R = 

We prepared chemical derivatives of **1** by oxidizing it with chromic anhydride in pyridine at room temperature. According to TLC, only one product was formed, the yield of which was 53%. The low yield is explained by losses during removal of pyridine from the reaction mixture.

The ^{1}H NMR spectrum of the isolated product differs markedly from that of the starting lactone **1** in that the triplet splitting of the signal for H-3′ decreases from 5.8 to 2.2 Hz and shifts from 6.97 [5] to 6.70 ppm. Also, one slightly broadened 2H signal appears at 4.97 ppm instead of the signals for two C$\underline{H_2}$OH groups. Narrowing the lines in the ^{1}H NMR spectrum causes this signal to acquire the shape of an almost degenerate AB-system with J_{AB} = 18.5 Hz, the components of which are split into doublets with J = 2.2 Hz. The triplet splitting of the H-3′ signal is due to the presence of allyl spin—spin coupling with magnetically nonequivalent H-5′a and H-5′b. This is confirmed by a cross-peak for H-3′/2H-5′ in the two-dimensional (2D) ^{1}H-^{1}H COSY NMR spectrum of **2**. These changes in the ^{1}H NMR spectrum enable the formation process of the isolated product to be interpreted as conversion of the *bis*-hydroxymethyl group of **1** into a butenolide. The product itself has structure **2**. Its

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formation can be explained as follows. The more reactive hydroxymethyl is first oxidized to an aldehyde (**3**). Then hydroxyaldehyde **3** tautomerizes into lactol **4**. Finally, **4** is oxidized to the butenolide (**2**).

NMR spectra of **2** that were obtained using 2D ^{1}H-^{1}H (COSY) and ^{1}H-^{13}C (COSY) NMR confirmed the correctness of structure **2**. The mass spectrum lacks a peak for the molecular ion but contains peak for ions corresponding to the elemental composition of the product formed by elimination of ROH ($C_5H_4O_4$) from the sidechain of the molecular ion.

EXPERIMENTAL

IR spectra were obtained on a Vector 22 instrument. NMR spectra were recorded using $CDCl_3$ solutions on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^{1}H; 125.76 MHz for ^{13}C) using standard Bruker programs to record 2D spectra.

High-resolution mass spectra (EI, 70 eV) were obtained in a Finnigan MAT 8200 instrument. Optical rotation was measured (at 580 nm) on a Polamat A polarimeter. Column chromatography was performed over Armsorbsil 100/160 SiO_2 with elution by petroleum ether:ethylacetate mixtures with ethylacetate content increasing from 0 to 60 vol%. TLC used Silufol plates with development by saturated aqueous $KMnO_4$. Melting points were determined on a Boetius apparatus.

Starting lactone **1** with mp 180-182°C (ethanol) and $[\alpha]_{20}$ -32° (*c* 2.2, ethanol) was isolated from the aerial part of *S. balsamita* by the literature method [1].

4,5α-Epoxy-7α,5,6,8β(H)-germacr-1(10),11(13)-dien-8α-(3′-oxo-2′,5′-dihydrofuran-3′-carboxylyl)-12,6-olide (2). A weighed portion (0.20 g, 0.53 mmol) of **1** was dissolved in freshly distilled pyridine (3 mL) at room temperature and treated with CrO_3 (0.27 g). The mixture was stirred on a magnetic stirrer for 1 h, diluted with EtOAc (5 mL), washed with HCl (3%) and water, and dried over anhydrous $MgSO_4$. Solvent was removed. The solid was chromatographed using gradient elution by a hexane:ethylacetate mixture to afford **2** (0.105 g, 53%) as fine crystals with mp 180-182°C and $[\alpha]_{580}^{26}$ -36° (*c* 0.76, $CHCl_3$). Elemental analysis agreed with that calculated.

Mass spectrum (*m*/*z*, I, %): 246 (8) [M^+ - sidechain - H], 231 (2), 218 (2), 203 (9), 189 (10), 188 (31), 175 (11), 161 (13), 149 (26), 127 (18), 125 (25), 111 (81), 99 (32), 97 (57), 85 (63), 83 (93), 71 (79), 58 (8), 57 (93), 44 (17), 43 (100), 29 (17). Found *m*/*z* 246.12184. Calc. for $[C_{15}H_{18}O_3]^+$ 246.12559.

IR spectrum (KBr, ν, cm^{-1}): 3430, 3113, 2925, 2854, 1779, and 1769 (C=O in two γ-lactone rings); 1720, 1650 (C=C); 1634, 1456, 1388, 1367, 1334, 1310, 1277, 1227, 1148, 1135, 1098, 1071, 1041, 1022, 999, 941, 894, 879, 831, 818, 784, 764, 724, 695, 611.

^{13}C NMR spectrum ($CDCl_3$, 125.76 MHz): 17.14 (q, C-15), 18.25 (q, C-14), 24.25 (t, C-2), 35.72 (t, C-3), 47.02 (t, C-9), 49.39 (d, C-7), 60.87 (s, C-4), 66.31 (d, C-5), 70.26 (t, C-5′), 74.23 (d, C-8), 79.89 (d, C-6), 125.50 (t, C-13), 126.75 (d, C-3′), 128.16 (t, C-1), 128.64 (s, C-10), 133.49 (s, C-11), 171.06 (s, C-12), 153.62 (s), 160.18 (s), and 168.26 (s) (C-1′, C-2′, C-4′).

^{1}H NMR spectrum ($CDCl_3$, 500 MHz, δ, ppm, J/Hz): 6.70 (1H, t, $J_{3',5a'} = J_{3',5b'} = 2.2$, H-3′), 6.34 (1H, d, J = 3.5, H-13b), 5.63 (1H, d, J = 2.8, H-13a), 5.32 (1H, dd, J = 2.0, 12.0, H-1), 4.65 (1H, ddd, J = 1.0, 4.0, 11.0, H-8), 4.97 (1H, dd, $J_{5a',5b'} = 18.5$, $J_{3',5b'} = 2.2$, H-5b′), 4.96 (1H, dd, $J_{5a',5b'} = 18.5$, $J_{3',5a'} = 2.2$, H-5a′), 4.27 (1H, dd, J = 6.5, 9.0, H-6), 3.37 (1H, m, H-7), 2.63 (1H, d, J = 9.0, H-5), 2.62 (1H, t, J = 11.0, H-9b), 2.49 (1H, d, J = 12, H-9a), 2.43 (1H, m, H-2b), 2.25-2.30 (1H, m, H-2a), 2.18 (1H, ddd, J = 1.0, 6.0, 13.0, H-3b), 1.81 (3H, s, H-14), 1.28 (3H, s, H-15), 1.22-1.29 (1H, m, H-3a).

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