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SEMIATRIN, A NEO-CLERODANE DITERPENOID FROM *SALVIA SEMIATRATHA*

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Key Word Index—*Salvia semiatratha*; Labiatae; diterpenoid; new neo-clerodane derivative; semiatrin.

Abstract—From the aerial part of *Salvia semiatratha*, a known diterpenoid and a new neo-clerodane diterpenoid, semiatrin, were isolated. The structure of the new diterpenoid was established mainly by spectroscopic means.

INTRODUCTION

Continuing our studies on diterpenoid metabolites from mexican Salvia species [1–3] we have studied *S. semiatratha* Zucc. of S. sect. *atratae* (Epling) [4] a perennial subshrub endemic to the semi-arid parts of Oaxaca (México).

From the aerial parts of this plant we obtained two neo-clerodane diterpenoids. Product **1** was previously isolated from *Baccharis trimera*, a Compositae native to Sao Paulo [5]. The second diterpenoid, named semiatrin, was shown to have structure **2**, by chemical and spectroscopic means, and by comparison with closely related compounds.

RESULTS AND DISCUSSION

The new diterpenoid (**2**) had a molecular formula of $C_{20}H_{26}O_6$. Its IR spectrum revealed the presence of one or more hydroxyl groups (3600 and 3455 cm^{-1}) and two α,β-unsaturated γ-lactone functions (1776, 1750 and 1640 cm^{-1}). On acetylation it yielded the diacetate **3**, which did not show hydroxyl absorption in the IR.

The ^1H NMR spectrum of **2** gave most of the relevant information. A double doublet at δ5.9 (1H, J = 4 and 2 Hz) and a doublet at δ4.9 (2H, J = 2 Hz) were assigned to the vinylic H-14 and the C-16 methylene group of a terminal β substituted butenolide ring. A doublet observed at δ6.68 (1H, J = 7 Hz) was attributed to an olefinic β proton of an α,β-unsaturated lactone function. It was assigned to H-3 by comparison with the ^1H NMR spectra described for teugin [6] and articulin [7].

The C-19 methylene group was observed as an AB system at δ4.3 (1H, *d*, J = 8 Hz) and 3.9 (1H, *dd*, J = 8 and 1 Hz). The signal at δ3.9 was assigned to the pro-*S*-diasterotopic H-19, as it showed a further splitting (J = 1 Hz) due to a long-range coupling. Such a long-range coupling has been described in some clerodane 18,19-olides with a *trans* A/B ring fusion lacking a substituent at C-6 [6, 8] although salvifarin, a *cis* neo-clerodane diterpenoid [9], shows this long-range coupling [10]. Two complex signals at δ4.5 and 4.9 were assigned to two protons at the carbon atoms bearing the hydroxyl groups, as they were shifted downfield in the ^1H NMR spectrum of the diacetyl derivative **3**, where they appeared as a double triplet at δ5.35 (J = 3 and 7 Hz) and a broad triplet (J = 6 Hz) at 5.67. The complex signal observed at δ4.5 in the ^1H NMR spectrum of **2** was simplified on addition of D_2O to a double triplet (J = 7 and 3 Hz). It was assigned to H-2α as it was converted into a triplet (J = 3 Hz) on irradiation of the olefinic proton doublet at δ6.68. The coupling constants (3, 7 Hz) and the multiplicity (*d*, *t*) observed for this proton, are consistent with a β-axial orientation of the hydroxyl group at C-2 when the A/B ring fusion is *trans*. Observation of the Dreiding model of semiatrin (**2**), showed H-1β–C–C–H-2α and H-1α–C–C–H-2α dihedral angles of *ca* 60°.

A broad doublet (J = 14 Hz, $W_{1/2}$ = 4 Hz) observed at δ2.5 was ascribed to H-10. This signal was shifted to δ2.75 (Δ = 0.25) when the ^1H NMR spectrum of **2** was run in pyridine-d_5, thus suggesting for H-10 the same relative orientation as for the hydroxyl group at C-2. A series of proton decoupling experiments (in pyridine-d_5) allowed the assignment of a double triplet at δ1.3 (J = 14 and 3 Hz) to H-1α, since irradiation at δ2.75 transformed the signal at δ1.3 into a double doublet ($J_{1\alpha,2\alpha}$ = 3 Hz, $J_{1\alpha,1\beta}$ = 14 Hz) and irradiation at δ4.60 (H-2α) collapsed it into a triplet ($J_{gem} = J_{1\alpha,10\beta}$ = 14 Hz).

The second hydroxyl group must at C-12 as the chemical shifts exhibited by H-12 in **2** and **3** (see above), revealed its allylic nature. Comparison with the ^1H NMR data described for marrubiastrol [11] and olearin [12] supported this assignment.

The ^1H NMR spectrum of **2** showed a singlet (3H) and a doublet (3H, J = 6 Hz) which were assigned to the quaternary methyl group at C-9 and the secondary methyl group at C-8 respectively.

The ^{13}C NMR spectra of **2** and its diacetyl derivative **3** (Table 1), provided strong support for the structures and stereochemistry proposed. The assignments were based on application of the usual shift parameters and comparison with literature data [5, 6, 8–11]. Catalytic hydro-

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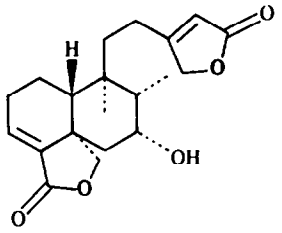

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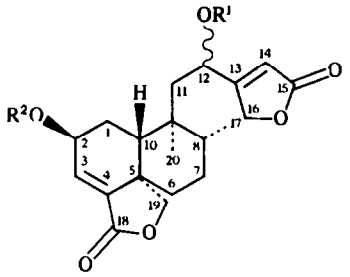
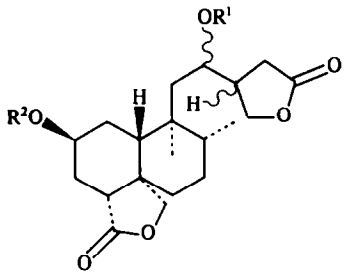


2 $R^1 = R^2 = H$
3 $R^1 = R^2 = Ac$



4a, **4b** $R^1 = R^2 = H$ C-13 epimeric mixture
5a, **5b** $R^1 = R^2 = Ac$ C-13 epimeric mixture

Table 1. ^{13}C NMR chemical shifts of compounds 2 and 3 (20 MHz, TMS as int. standard)

C	2 (DMSO-d_6)	3 ($CHCl_3$)
1	27.38 *t*	27.78 *t*
2	63.8 *d*	66.65 *d*†
3	133.1 *d*	128.57 *d*
4	140.9 *s*	143.69 *s*
5	45.4 *s*	45.56 *s*
6	33.28 *t*	33.89 *t*
7	27.38 *t*	25.38 *t*
8	37.10 *d*	38.83 *d*
9	43.8 *s*	38.9 *s*
10	40.45 *d*	42.48 *d*
11	38.26 *t*	41.22 *t*
12	62.6 *d*†	66.27 *d*†
13	173.3 *s*	170.11 *s*
14	113.3 *d*	117.41 *d*
15	175.6 *s*	172.35 *s*
16	70.9 *t*‡	70.66 *t*‡
17	15.71 *q*	15.96 *q*
18	168.7 *s*	168.01 *s*
19	70.28 *t*‡	70.39 *t*‡
20	16.4 *q*	16.63 *q*
OCOMe		168.07, 169.69 (*s*)
OCOMe		20.83, 20.83 (*q*)

*SFORD multiplicities.

†, ‡ Values in any vertical column may be interchanged.

genation of **2** gave the tetrahydroderivative as a mixture of epimers at C-13 (**4a, b**).

EXPERIMENTAL

Mps: uncorr; MS: direct inlet, 70 eV; ^1H NMR (80 MHz) and ^{13}C NMR (20 MHz): $CDCl_3$ or DMSO-d_6 solns with TMS as internal standard. Plant material was collected in Dec. 1983, 3 km North of Nochistlán (Oaxaca, México). A voucher specimen [MEXU 379088] was deposited at the Herbarium of the Instituto de Biología, UNAM.

Isolation of **1** *and* **2**. Dried and powdered aerial parts of *Salvia semiatratha* Zucc. (600 g) were extracted with Me_2CO at room temp. for 1 week. The solvent was removed under vacuum to yield 38.9 g of gummy residue, which was subjected to dry CC over silica gel (Merck silica gel 60; 500 g deactivated with 10% H_2O). From the first fractions obtained by elution with hexane–EtOAc (4:1), 157 mg **1** were isolated: mp 186–187°, $[\alpha]_D^{20} = -163$ (*c* 0.22; $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3626, 1751, 1662, 1640, 1189, 1038, 962, 889, 856, 759, 732; ^1H NMR ($CDCl_3$): δ6.9 (1H, *dd*, *J* = 3 and 8 Hz, H-3), 5.85 (1H, *t*, *J* = 1 Hz, H-14), 5.25 (1H, *d*, *J* = 8 Hz, H-19), 4.7 (2H, *d*, *J* = 1 Hz, H_2-16), 4.07 (1H, *dd*, *J* = 3 and 6 Hz, H-7), 3.85 (1H, *dd*, *J* = 8 and 1 Hz, H-19), 1.05 (3H, *d*, *J* = 7 Hz, Me-17), 0.9 (3H, *s*, Me-20); MS *m/z* (rel. int.): 346 $[M]^+$ (2.0), 329 (2.2), 316 (20), 299 (20), 233 (30), 219 (10), 201 (25), 91 (100), 77 (86), 55 (86), 41 (97). Spectroscopic data for **1** are in agreement with those described in ref. [5] for a diterpenoid isolated from *Baccharis trimera*, apart from the mp (lit. 195–196°) and $[\alpha]_D$ (lit. −97°; $CHCl_3$) value.

The following fractions gave **2** (3.5 g, 0.58% dry weight), mp 203–204° from EtOAc–hexane; $[\alpha]_D^{20}$ −133 (*c* 0.2; $CHCl_3$); UV λ_{max}^{MeOH}: 208 nm (ε37 931); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3608, 3455, 1776,

1750, 1640, 1448, 1139, 1035; ^{1}H NMR ($CDCl_3$): δ6.65 (1H, *d*, *J* = 7 Hz, H-3), 5.9 (1H, *dd*, *J* = 4 and 2 Hz, H-14), 4.9 (1H, *m*, H-12), 4.9 (2H, *d*, *J* = 2 Hz, 2H-16), 4.5 (1H, *dt*, *J* = 7 and 3 Hz, H-2), 4.3 (1H, *d*, *J* = 8 Hz, H-19), 3.9 (1H, *dd*, *J* = 8 and 1 Hz, H-19), 0.87 (3H, *d*, *J* = 6 Hz, Me-17), 0.65 (3H, *s*, Me-20); ^{13}C NMR: see Table 1; MS *m/z* (rel. int.): 362 $[M]^+$ (0.6), 344 (2.3), 326 (0.7), 296 (1), 250 (5), 232 (10), 216 (9), 187 (20), 186 (40), 158 (50), 148 (30), 91 (60), 83 (30), 79 (40), 55 (100). (Found: C, 66.42; H, 7.45. $C_{20}H_{26}O_6$ requires: C, 66.28; H, 7.23%).

Acetylation of **2**. Compound **2** (200 mg) in C_5H_5N (2 ml) was treated with 2 ml Ac_2O at room temp. for 4 hr. After usual work up, the crystalline product **3** (197 mg) was obtained, mp 191–192° from CH_2Cl_2–iso-Pr_2O; $[\alpha]_D^{20} = -198.5$ (*c* 0.2; $CHCl_3$); UV λ_{max}^{MeOH}: 208 nm (ε45 000); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1781, 1752, 1740, 1667, 1644, 1450, 1371; ^{1}H NMR ($CDCl_3$): δ6.75 (1H, *d*, *J* = 7 Hz, H-3), 6.05 (1H, *t*, *J* = 2 Hz, H-14), 5.7 (1H, *br t*, *J* = 6 Hz, H-12), 5.35 (1H, *dt*, *J* = 7 and 3 Hz, H-2), 4.85 (2H, *t*, *J* = 2 Hz, 2H-16), 4.3 (1H, *d*, *J* = 8 Hz, H-19), 3.85 (1H, *dd*, *J* = 8 and 1 Hz, H-19), 2.1 (3H, *s*, Me–CO–R), 2.07 (3H, *s*, Me–CO–R), 0.85 (3H, *d*, *J* = 6 Hz, Me-17), 0.65 (3H, *s*, Me-20); ^{13}C NMR: see Table 1; MS *m/z* (rel. int.): 446 $[M]^+$ (11.8), 404 (13.4), 386 (5), 362 (5), 344 (15), 327 (4), 326 (5), 235 (15), 234 (14), 186 (10), 185 (40), 173 (20), 159 (15), 158 (20), 105 (50), 79 (46), 77 (43), 91 (100). $C_{24}H_{30}O_8$ requires $[M]^+$ at 446.

Catalytic hydrogenation of **2**. Compound **2** (200 mg) in EtOAc (5 ml) was hydrogenated using Pd–C (10‰ 50 mg) as catalyst during 30 hr. After usual work up, products **4a** and **4b** (176.3 mg) were obtained as a crystalline mixture, mp 177–179°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3614, 3482, 1771, 1380, 1268, 1183, 1009; ^{1}H NMR ($CDCl_3$): δ0.6 (3H, *s*, Me-20), 0.85 (3H, *d*, *J* = 6 Hz, Me-17), 3.9 (*m*, H-2), 4.35 (complex and overlapped signals for H_2-19, H_2-16 and H-12); MS *m/z* (rel. int.): 366 $[M]^+$ (0.5), 365 (0.4), 348 (4), 330 (8), 265 (10), 218 (25), 173 (20), 135 (20), 119 (20), 117 (25), 115 (20), 91 (30), 79 (30), 69 (40), 57 (40), 55 (80), 43 (50), 41 (100). $C_{20}H_{26}O_6$ requires $[M]^+$ at 366.

Acetylation of **4a, b**. The above mixture (60 mg) in C_5H_5N (1 ml) were treated with Ac_2O (1 ml) during 20 hr. Usual work up afforded 55 mg of mixture of **5a, b** as a crystalline mixture, mp 183–185°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1776, 1736, 1485, 1374, 1241, 1206, 1181, 1024; ^{1}H NMR ($CDCl_3$): δ5.15 (2H, *m*, H-2 and H-12), 4.2 (4H, *m*, overlapped signals for H_2-19 and H_2-16), 2.01 (3H, *s*, AcO), 2.04 (3H, *s*, AcO), 2.05 (3H, *s*, AcO), 0.85 (3H, *d*, *J* = 6 Hz, Me-17), 0.6 (3H, *s*, Me-20); MS *m/z* (rel. int.): 408 (0.2), 407 (0.9), 391 (0.8), 390 (2.6), 372 (0.9), 330 (1), 219 (10), 173 (10), 91 (20), 43 (100). $[M]^+$ ($C_{24}H_{34}O_8$, *m/z* 450) not observed.

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