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FURTHER SESTERTERPENES FROM *SALVIA HYPOLEUCA*

A. RUSTAIYAN and S. KOUSSARI

Department of Chemistry, Shahid Beheshty University, Eveen, Tehran, Iran

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Key Word Index—*Salvia hypoleuca*; Labiatea; sesterterpenes.

Abstract—The polar fractions of *Salvia hypoleuca* afforded several further sesterterpene lactones, a hydroperoxide, three isomeric epoxides and a monolactone with an additional carbocyclic ring, all derived from salvileucolide lactone, as well as several salvileucolide methyl ester derivatives with a hydroperoxide group. The structures were elucidated by high field ^{1}H NMR spectroscopic methods.

INTRODUCTION

Recently we have isolated some sesterterpenes with a new carbon skeleton from *Salvia hypoleuca* Benth [1] and from *S. syriaca* L. [2]. We have now studied the more polar fractions of *S. hypoleuca* which afforded several further sesterterpenes, the salvileucolide methyl ester derivatives **4**, **5a**, **5b** and **6** as well as the isomeric epoxides **2a**–**2c** and the hydroperoxide **1** derived from salvileucolide-6,23-lactone and a sesterterpene with a further new carbon skeleton, the ketone **3**.

RESULTS AND DISCUSSION

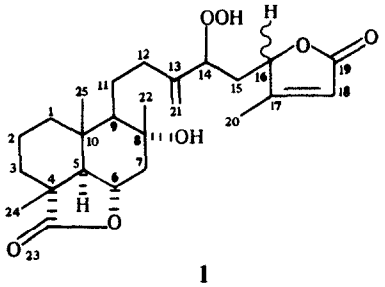
The structure of **1** followed from the ^{1}H NMR spectrum (Table 1) which was in part close to that of salvileucolide-6,23-lactone [1]. However, one of the olefinic methyl singlets was replaced by a pair of broadened singlets at δ 5.21 and 5.06, a broadened singlet at δ 9.47 and a double doublet at δ 4.73. In addition the CIMS showed the highest peak at *m/z* 449. Therefore the presence of a hydroperoxide was likely. Spin decoupling starting with H-16 confirmed this assumption. However, the relative configuration at C-8, C-14 and H-16 could not be determined.

The ^{1}H NMR spectra of **2a** and **2b** (Table 1) also were close to that of salvileucolide-6,23-lactone. Again the signals of the olefinic double bond were replaced by methyl singlets at δ 1.37 and 1.43 and doublets at δ 3.82 and 3.79 respectively. Furthermore, new olefinic signals at δ 5.09 and 5.14 respectively were visible. In agreement with the molecular formula, the presence of epimeric epoxides derived from the dehydro derivative of salvileucolide-6,23-lactone was very likely. The relative configuration at C-13 and C-14 was determined by the observed NOEs. Thus in the case of **2b** NOE between H-21 and H-14 was observed. Further NOEs established that the remaining stereochemistry was unchanged from that of salvileucolide-6,23-lactone and also allowed the assignment of the methyl signals. Thus clear effects were

Table 1. ^{1}H NMR spectral data of compounds **1**, **2a**–**2c** and **3** (400 MHZ, $CDCl_3$)

H	1	2a	2b	2c	3	H	1–3
12	2.44 *ddd* 2.19 *ddd*	1.85 *m*	1.85 *m*	1.85 *m*	2.48 *ddd* 2.17 *ddd*	5	1.52 *d*
14	4.73 *dd*	3.82 *d*	3.79 *d*	3.83 *d*	5.09 *dq*	6	4.21 *ddd*
15	2.11 *ddd* 1.49 *ddd*	5.09 *br d*	5.14 *br d*	5.10 *d*	3.18 *dd*	7α	2.45 *dd*
16	5.04 *br d*	—	—	—	—	7β	1.67 *m*
18	5.81 *dq*	6.01 *dq*	6.01 *dq*	6.01 *dq*	7.15 *dq*	9	1.20 *dd*
19	—	—	—	—	4.61 *br s*	11	1.62 *m*
20	2.06 *br s*	2.16 *d*	2.16 *d*	2.17 *d*	1.82 *dd*	11′	1.81 *m*
21	5.21 *br s* 5.06 *br s*	1.37 *s*	1.43 *s*	1.37 *s*	1.72 *d*	22	1.28 *s*
OOH	9.47 *s*	—	—	—	—	24	1.19 *s*
						25	0.92 *s*

J[Hz]: 5,6=6,7α=11; 6,7β=4; 9α, 11=5; 9α, 11′=4; 11, 11′=14; 11, 12=11′, 12′=7; compound **1**: 14, 15=10; 14, 15′=3; 15,15′=15; 15,16=1.5; 15′, 16=11; 18,20=1; compounds **2a**–**2c**: 14, 15=8; 15,18=1; 18,20=1; compound **3**: 14, 15=9; 14,21=1; 15,19=2.5; 18,19=19=18,20=19, 20=1.



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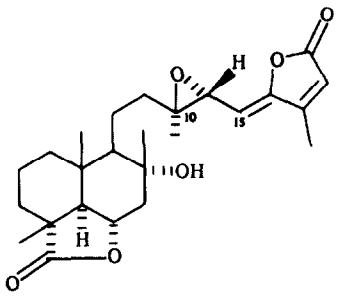
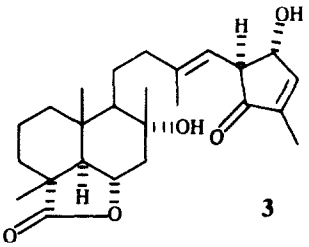


2a
2b 13 *epi*
2c 13,14 *epi*



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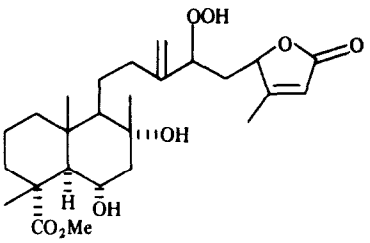

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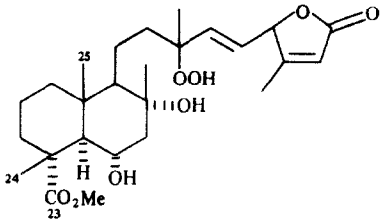
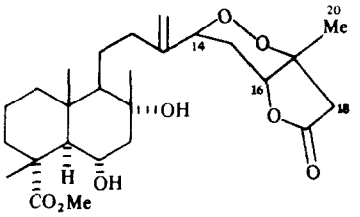


5a
5b 13 *epi*



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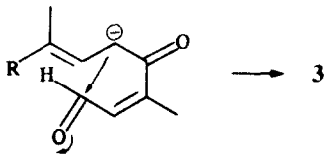

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present between H-24, H-25 and H-6 and between H-22, H-25 and H-7β in both isomers (**2a** and **2b**). The *Z*-configuration of the 15,16-double bond followed from the NOE between H-20 and H-15 which were observed in all three isomers. The ^{1}H NMR data and the optical rotation of **2c** differed slightly from those of **2a** and the NOE between H-21 and H-15 indicated a presence of a 13, 14-bis-*epi*-isomer of **2a**. The relative configuration at C-13 and C-14 in the isomers **2a**–**2c** could not be determined.

The ^{1}H NMR spectrum of **3** (Table 1) again was close to that of salvileucolide-6,23-lactone. However, the second lactone moiety was now missing. Spin decoupling led to a sequence which required a cyclopentenone group. Thus a doublet quartet at δ 5.09 was coupled with the olefinic methyl (δ 1.72 *d*) and with a double doublet at δ 3.18 which itself collapsed to a doublet (J=9 HZ) on irradiation of the broadened singlet at δ 4.61. This irradiation also made the doublet quartet at δ 7.15 collapse to a quartet. The latter signal and the singlet at δ 4.61 were both coupled with a methyl triplet at δ 1.82. The couplings together with the chemical shifts required the presence of the proposed cyclopentenone residue which most likely was formed by aldol condensation via the intermediate **7**. This latter could easily be formed from the 19,16-lactone by hydrolysis, oxidation at C-16 and reduction at C-19. The ketone **3** has been named salvileucolidone.

The ^{1}H NMR spectrum of **4** (Table 2) clearly indicated that a hydroperoxide similar to **1** was again present. However, the 6,23-lactone ring was replaced by the corresponding hydroxy ester. Accordingly, the signals were in part identical with those of salvileucolide methyl ester.

The ^{1}H NMR spectra of **5a** and **5b** (Table 2) nicely agreed with the presence of 13-epimeric hydroperoxides derived from salvileucolide methyl ester. The configuration of the Δ^{14}-double bond followed from the coupling. The relative configurations of C-8 and C-13 could not be determined. Triphenylphosphine reduction of **5a** gave the corresponding alcohol with the expected shifts in the ^{1}H NMR spectrum (see Experimental).

The last compound (**6**) was also derived from salvileucolide methyl ester as followed from the ^{1}H NMR spectrum (Table 2). However, the butenolide part was now changed as the olefinic proton (H-18) was replaced by a pair of doublets at δ 2.64 and 2.51. As the olefinic methyl

Table 2. ^{1}H NMR spectral data of compounds **4**, **5a**, **5b** and **6** (400 MHZ, $CDCl_3$)

H	4	5a	5b	6	H	4–6
12	2.37 *ddd*	2.23 *m*	2.23 *m*		5	2.07 *d*
12′	2.14 *ddd*	2.01 *m*	2.04 *m*	2.18 *m*	6	3.63 *ddd*
14	4.73 *dd*	5.89 *dd*	6.14 *br d*	5.72 *dd*	7α	1.60 *m*
15, 15′	2.16 *ddd* 1.49 *ddd*	5.44 *dd*	5.42 *dd*	2.24 *ddd* 2.07 *ddd*	7β 9	2.23 *dd* 1.15 *dd*
16	5.06 *br d*	5.16 *br d*	5.18 *br d*	4.46 *t*	11	1.64 *m*
18	5.81 *dq*	5.82 *dq*	5.82 *dq*	2.51 *d*	11′	1.85 *m*
20	2.06 *br s*	2.03 *br s*	2.03 *br s*	1.58 *s*	22	1.27*s*
21	5.18 *br s* 5.08 *br s*	1.36 *s*	1.25 *s*	5.06 *br s*	24	1.23 *s* 5.05 *br s*
OOH	9.64 *s*	0.30 *s*	9.58 *s*	—	25 OMe	0.87 *s* 3.65 *s*

J[HZ]: 5, 6=6, 7α=11; 6, 7β=4; 9, 11=5; 9, 11′=4; compound **4** as compound −1; compounds **5a/b**: 14,15 = 16; 15,16 = 8; 14,16 = 16,18 = 16,20 1; compound **6**: 14,15 = 11; 14,15′ = 3.5; 15,15′ = 13; 15,16 = 15′, 16 = 3; 18,18′ = 18.

signal was now replaced by a singlet at δ 1.58 the compound must be formed by addition of an oxygen function at the conjugated double bond. Spin decoupling indicated that the allylic proton (H-14) was coupled with a pair of threefold doublets at δ 2.24 and 2.07 which themselves were coupled further with H-16 (4.46 *t*). This data as well as the CIMS could only be rationalized by a cyclized hydroperoxide. Irradiation of H-20 gave a clear NOE with H-18 and H-16. The latter showed a NOE with H-15α while H-14 gave no NOE with H-16.

The isolation of all these sesterterpenes may be an indication that these compounds are characteristic for this genus *Salvia*. However, further investigations are needed to establish whether these compounds are widespread in this genus.

EXPERIMENTAL

The air-dried aerial parts (550 g, voucher deposited in the Herbarium of the Dept of Botany, Shahid Beheshty University, Tehran, Iran, were extracted at room temp. with MeOH–Et_2O–petrol (1:1:1). After evapn under red. pressure the residue was treated with MeOH to remove long chain saturated hydrocarbons. The extract was separated by CC (Silica). The polar fractions (Et_2O to Et_2O–MeOH, 9:1) were further separated first by medium pressure chromatography (silica gel, φ 30–60, 3 bar, Et_2O–petrol, 1:1 to Et_2O–MeOH, 4:1) and then by HPLC (RP 8, *ca* 100 bar, flow rate *ca* 2ml/min). 10 mg **2a** (R_t 13.5 min), 8 mg **2a** (R_t 16 min) and 12 mg **2b** (R_t 17 min.). HPLC of fractions 30–83 (MeOH–H_2O, 13:7) gave 6 mg **3** (R_t 12, min.). HPLC of fractions 84–112 (MeOH–H_2O, 3:2) gave 15 mg **1** (R_t 15 min), 10 mg **4** (R_t 13 min), 5 mg **6** (R_t 11 min), 10 mg **5a** (R_t 9 min) and 10 mg **5b** (R_t 7.5 min).

14-*Hydroperoxy*-13(21)-*dehydro*-13,14-*dihydrosalvileucolide*-6,23-*lactone* (**1**). Colourless gum; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3580 (OH), 1780, 1765 (γ-lactone); CIMS *m/z* (rel. int.): 449 $[M+1]^+$ (8) ($C_{25}H_{36}O_7+1$), 431 $[449-H_2O]^+$ (92), 415 $[449-H_2O_2]^+$ (64), 413 $[431-H_2O]^+$ (67), 321 (70), 303 (86), 291 (100); $[\alpha]_D^{24°}$ +13 ($CHCl_3$; *c* 0.12).

15,16-*Dehydrosalvileucolide*-6,23-*lactone-trans-epoxide* (**2a**). Colourless gum; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3580 (OH), 1780, 1765 (γ-lactone); MS *m/z* (rel. int.). 430 $[M]^+$ (0.2), 412.222 $[M-H_2O]^+$ (3) (calc. for $C_{25}H_{32}O_5$; 412.225), 394 $[412-H_2O]^+$ (2), 291 (21), 245 (31), 179 (57), 140 (100); $[\alpha]_D^{25°}$ +9 ($CHCl_3$; *c* 0.28).

cis-*Epoxide* (**2b**). Colourless gum; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3580 (OH), 1780, 1765 (γ-lactone); MS *m/z* (rel. int.). 430.235 $[M]^+$ (2) (calcd for $C_{25}H_{34}O_6$: 430.235), 412 $[M-H_2O]^+$ (5), 397 $[412-Me]^+$ (5), 370 $[412-CO_2]^+$ (6), 220 (10), 205 (24), 109 (100); $[\alpha]_D^{24°}$ +12 ($CHCl_3$; *c* 0.25).

13,14-*bis*-epi-trans-*Epoxide* (**2c**). Colourless gum; MS *m/z* (rel. int.). 430.235 $[M]^+$ (2) (calc. for $^2{}_5H_{34}O_6$: 430.235), 412 (5), 397 (4), 370 (5), 109 (100); $[\alpha]_D^{24°}$ +140 ($CHCl_3$; *c* 0.12).

Salvileucolidone (**3**). Colourless gum; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3580 (OH), 1760 (γ-lactone), 1680 (C=CC=O); CIMS *m/z* (rel. int.): 417 $[M+1]^+$ (100) ($C_{25}H_{36}O_5+1$), 399 (40), 381 (22); $[\alpha]_D^{24°}$ −42 ($CHCl_3$; *c* 0.1).

Hydroperoxide **4**. Colourless gum; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3600 (OH), 1765 (γ-lactone), 1740 (CO_2R); CIMS *m/z* (rel. int.): 481 $[M+1]^+$ (1) ($C_{26}H_{40}O_8+1$), 463 $[481-H_2O]^+$ (6), 447 $[481-H_2O_2]^+$ (5), 317 (66), 279 (71), 263 (100); $[\alpha]_D^{24°}$ +26 ($CHCl_3$; *c* 0.21).

Hydroperoxide **5a**. Colourless gum; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3600 (OH), 1760 (γ-lactone), 1735 (CO_2R); CIMS *m/z* (rel. int.): 481 $[M+1]^+$ (2), 463 (6), 447 (8), 323 (68), 305 (64), 279 (100), 263 (84); $[\alpha]_D^{24°}$ −15 ($CHCl_3$; *c* 0.1); Addition of triphenylphosphine in $CHCl_3$ afforded the corresponding carbinol; ^{1}H NMR ($CDCl_3$): δ 5.95 (*br d*, H-14), 5.42 (*dd*, H-15), 5.21 (*br d*, H-16), 1.28 (*s*, H-21) (remaining signals as in **5a**).

Hydroperoxide **5b**. Colourless gum; CIMS *m/z* (rel. int.): 481 $[M+1]^+$ (2), 463 (8), 447 (12), 323 (61), 305 (100), 279 (64), 263 (44).

Cyclic peroxide **6**. Colourless gum; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3600 (OH), 1775 (γ-lactone), 1735 (CO_2R); CIMS *m/z* (rel. int.): 481 $[M+1]^+$ (2), 463 (62), 445 (31), 427 (46), 335 (45), 317 (100), 299 (62); $[\alpha]_D^{24°}$ +18 ($CHCl_3$; *c* 0.12).

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