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SESQUITERPENE LACTONES FROM THE FRUITS OF *SMYRNIUM ROTUNDIFOLIUM*

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Key Word Index—*Smyrnium rotundifolium*, Umbelliferae, germacrane derivatives, secogermacrane derivatives, sesquiterpene anhydride, 8,9-epoxy-8,9-secoglechomanolide, 1*β*,10*α*-epoxy-4-methoxy-8-hydroxyglechomanolide, 8-oxo-8,9-secoglechomanolide

Abstract—In addition to known compounds an investigation of the fruits of *Smyrnium rotundifolium* afforded four new germacrane derivatives, all closely related to glechomanolide, one being a secogermacrane anhydride The new compounds were 8,9-epoxy-8,9-secoglechomanolide, 1*β*,10*α*-epoxy-4-methoxy-8-hydroxyglechomanolide and 8-oxo-8,9-secoglechomanolide The structures were assigned by spectral methods as well as by some chemical reactions

INTRODUCTION

In previous studies eremophilane and germacrane type compounds have been isolated from *Smyrnium* species [1–5] In continuation of the investigation of the genus *Smyrnium*, in addition to the known compounds *α*-selinene (**1**), germacrone (**2**) and furodiene (**3**), we report here the isolation and structure determination of two seco-glechomanolides and two glechomanolide derivatives

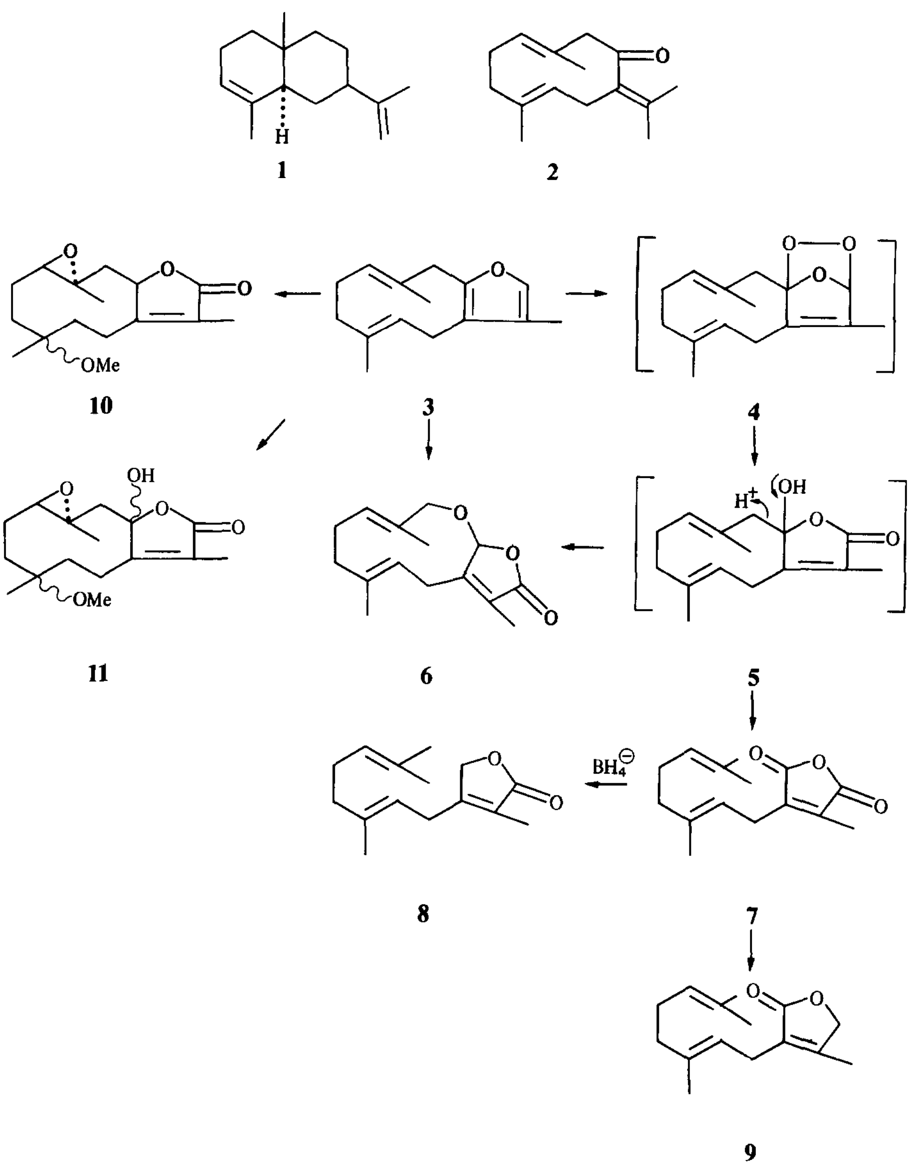
RESULTS AND DISCUSSION

Ether–petrol extracts of the fruits of *Smyrnium rotundifolium* afforded the known compounds *α*-selinene (**1**), germacrone (**2**) and furodiene (**3**) [6] as well as the new lactone (**6**), the anhydride (**7**), 1*β*,10*α*-epoxy-4-methoxy-8-hydroxyglechomanolide (**11**) and 1*β*,10*α*-epoxy-4-methoxyglechomanolide (**10**) The latter two compounds were separated by reversed phase HPLC The known compounds were identified by comparing their spectra to those of known compounds

In the mass spectrum of **6**, the molecular ion peak at *m/z* 248 indicated the molecular formula $C_{15}H_{20}O_3$ The IR spectrum (CCl_4) exhibited the presence of a *γ*-lactone (1770 cm^{-1}) and the lack of hydroxyl and carbonyl bands indicated that the third oxygen could be an ether function The structure of the compound was established by its ^1H NMR spectrum (Table 1) and by spin-decoupling experiments The presence of a methyl singlet at *δ* 1 92 and the lack of typical signals for lactone methylene indicated a methyl group at C-11 Irradiation of the olefinic methyl protons at 1 63 (*s*, H-14) sharpened both the signals of H-1 at 4 975 and H-9′ at 3 89, while irradiation of the second vinylic methyl at 1 69 (*s*, H-15) caused sharpening of the signal at 5 26 (*dd*, H-5) H-5 coupled with H-6 and H-6′, these latter protons coupled with each other as well as with H-5 forming broad double doublets at 3 035 and 2 82 respectively The signals of the geminal coupled protons at 4 15 (*d*, H-9) and 3 89 (*br d*, H-9′) indicated an isolated methylene group One proton singlet at 5 81 showed the lactone proton at H-8, the downfield shifts of the signals of the lactone proton and of H-9 together with the other data showed that the third oxygen function could only be located between C-8 and C-9 as an ether bridge The stereochemistry at C-8 could not be determined

Mass spectrum of the anhydride (**7**) exhibited the molecular ion peak at *m/z* 248 and the high resolution mass spectrum gave the molecular formula $C_{15}H_{20}O_3$ The IR spectrum (CCl_4) showed carbonyl bands at 1860, 1820, 1770 cm^{-1} typical for anhydrides and no hydroxyl band In the ^1H NMR spectrum the olefinic methyl signal at *δ*2 07 agreed with a methyl at C-11 Geranyl methyl singlets were at 1 70 (H-9), 1 58 (H-14), 1 66 (H-15), while other typical signals for the geranyl moiety were also present (Table 1) The broad doublet at 3 165 for H-6 and H-6′ indicated that the geranyl residue was attached to an unsaturated carbon The ^{13}C NMR spectrum of **7** showed two carbonyl carbons at 165 7 ppm All other signals confirmed the suggested structure (Table 3) Sodium borohydride reduction of **7** yielded a mixture of two lactones, **8** and **9**, which were separated by preparative TLC The two compounds were distinguished by their ^1H NMR spectra The triplet quartet at *δ*4 60 (H-8) and triplet triplet at 1 84 (H-13) with $J = 1$ Hz showed that in **8** the carbonyl group at C-8 was reduced On the other hand compound **9** showed broadened singlets at 2 02 (H-13) and 4 60 (H-12) indicating that the reduction occurred at C-12 Thus the structure of the anhydride part of the sesquiterpene **7** was established

IR spectrum (CCl_4) of **10** indicated an *α*,*β*-unsaturated *γ*-lactone (1750 cm^{-1}) and again the absence of the hydroxyl group The molecular formula $C_{16}H_{26}O_4$ and ^1H NMR spectrum agreed with the structure of the compound (Table 2) The signal of H-13 was at *δ* 1 78 as a doublet ($J = 1$ Hz) The other two methyl singlets proved to be non-olefinic [*δ* 1 105 (H-14) and 1 35 (H-15)] and a methoxyl signal was observed at 3 06 One hydrogen double doublet at 2 66 (H-1) showed that there should be an epoxy group instead of a double bond Spin-



Scheme 1

decoupling experiments (see Table 2) and Dreiding models proved the $1\beta,10\alpha$-positions of the epoxy group The second methyl at C-4 is situated next to the methoxy group Spin-decoupling experiments allowed the assignment of all signals Irradiation of the signal at $\delta 4\ 86$ collapsed the double doublets at 2 22 (H-9) and 2 14 (H-9′) to doublets and the methyl doublet at 1 78 (H-13) to a singlet While irradiation of H-2 signal at 1 92 collapsed the double doublet at 2 66 (H-1) to a doublet and the threefold doublet at 2 81 (H-3) to a double doublet The latter coupled with H-3′ at 1 52 and the former with H-2′ at 1 81 The ^{13}C NMR signals (Table 3) were in agreement with the proposed structure

The IR spectrum of **11** exhibited a γ-lactone absorption at 1755 cm^{-1} and a hydroxyl band at 3570 cm^{-1} The high resolution mass spectrum led to the molecular formula $C_{15}H_{26}O_5$ The ^1H NMR spectrum (Table 2) was nearly identical with that of compound **10** with the exception that the signal at $\delta 4\ 86$ was missing and the methylene protons at C-9 (Table 3) appeared as a pair of doublets in the spectrum of **11** while the same protons displayed double doublets in the ^1H NMR of **10** Therefore the hydroxyl group was at C-8 The ^{13}C NMR spectrum confirmed the proposed structure (Table 3) The stereochemistry at C-1 followed from the observed coupling constants ($J_{1\alpha\ 2\beta} = 13$ Hz, $J_{1\alpha,2\alpha} = 3\ 5$ Hz) if a Dreiding model was inspected However the configuration at C-4 in **10** and **11** could not be determined Compounds **6**, **7**, **10** and **11** obviously were formed by the oxidative degradation of **3** (Scheme 1) As the furodiene (**3**) is very sensitive to oxygen these compounds also could be artifacts

EXPERIMENTAL

Smyrnium rotundifolium mill was collected from the western area of Turkey (Izmir) A voucher (ISTE 19055) was deposited in the Herbarium of Faculty of Pharmacy, Istanbul Dried and

Table 1 ^{1}H NMR spectral data of compounds **6**–**9** (400 MHz, $CDCl_3$)

	6	**7**	**8**	**9**
H-1	4 975 *d br*	5 03 *tt*	5 04 *t br*	5 06 *t br*
H-2	2 375 *m*	2 03 *t br*	2 05 *m*	2 05 *m*
H-2′	1 91 *m*			
H-3 H-3′	2 1 *m*			
H-5	5 26 *dd br*	5 11 *tt*	5 12 *t br*	5 14 *t br*
H-6	3 035 *dd br*	3 165 *d*	3 11 *d br*	2 9 *d br*
H-6′	2 82 *dd br*			
H-8	5 81 *s br*	—	4 60 *tq*	—
H-9	4 15 *d*	1 70 *s*	1 68 *s br*	1 70 *s br*
H-9′	3 89 *d br*			
H-12	—	—	—	4 60 *s br*
H-13	1 92 *s*	2 07 *s*	1 84 *tt*	2 02 *s br*
H-14	1 63 *s*	1 58 *s*	1 59 *s br*	1 59 *s br*
H-15	1 69 *s*	1 66 *s*	1 65 *s br*	1 67 *s br*

J (Hz) **6** 1,2 = 5,6 = 11, 5,6′ = 5,6,6′ = 12, **7** 1,2 = 5,6 = 7, 1,9 = 5, 15 = 1 5, 2,3 = 5 5, **8** and **9**· 1,2 = 5,6 = 7 5, 6, 13 = 8, 13 = 1

Table 2 ^{1}H NMR spectral data of the compounds **10** and **11** (400 MHz, $CDCl_3$, C_6D_6)

	10 ($CDCl_3$)	**11** ($CDCl_3$)	**11** (C_6D_6)
H-1α	2 66 *dd*	2 54 *dd*	2 24 *dd*
H-2α	1 92 *ddd*	1 95 *m*	1 86 *ddd*
H-2β	1 81 *dd*	1 85 *m*	1 75 *dd*
H-3α	2 81 *ddd*	2 83 *ddd*	2 81 *ddd br*
H-3β	1 52 *ddd*	1 60 *m*	1 52 *ddd*
H-5 H-6	1 80 *m*	1 80 *m*	1 50 *m*
H-8β	4 86 *ddq*	—	—
H-9β	2 22 *dd*	2 54 *d*	2 54 *d br*
H-9α	2 14 *dd*	2 22 *d*	2 14 *d*
H-13	1 78 *d*	1 79 *s*	1 79 *s*
H-14	1 11 *s*	1 14 *s*	0 82 *s*
H-15	1 35 *s*	1 38 *s*	1 07 *s*
OMe	3 06 *s*	3 06 *s*	3 09 *s*
OH	—	3 46 *s*	3 01 *s*

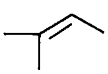
J (Hz) **10** 1α, 2β = 2α, 2β = 3α, 3β = 3α, 2β = 13, 1α, 2α = 3 5, 3α, 2α = 5, 3β, 2β = 6, 9α, 9β = 16, 9β, 8β = 2 5, 9α, 9β = 7, **11** 1α, 2β = 2α, 2β = 3α, 3β = 3α, 2β = 13, 1α, 2α = 3 5, 2α, 3α = 5 5, 3β, 2β = 7, 3β, 2β = 7, 3α, 2α = 6, 9α, 9β = 16

powdered fruits of *Smyrnium rotundifolium* (310 g) were extracted with Et_2O–petrol (1 2) and the extract was treated with MeOH to remove long chain saturated hydrocarbons The residue was roughly separated by CC (silica gel), then the fractions were further separated by preparative TLC and by HPLC (MeOH–H_2O, 1 1) Thus 5 mg **1**, 6 mg **2**, 710 mg **3**, 5 mg **6**, 5 mg **7**, 50 mg **10**, and 25 mg **11** were obtained

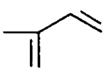
8,9-*Epoxy*-8,9-*seco-glechomanolide* (**6**) Colorless crystals, mp 138°, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1770 ^{1}H NMR given in Table 1 MS *m/z* (rel int) 248 1412 $[M]^+$ ($C_{15}H_{20}O_3$), (4), 230 $[M-H_2O]^+$ (2), 204 $[M-CO_2]^+$ (10), 189 $[204-Me]^+$ (7), 123 $[C_9H_{13}]^+$ (13), 107 [**c**]$^+$ (44), 68 $[C_5H_8]^+$ (100)

Table 3 ^{13}C NMR spectral data of the compounds **7**, **10** and **11** (100 6 MHz, $CDCl_3$)

	7	**10**	**11**
C-1	116 2 *d*	50 8 *d*	51 6 *d*
C-2	25 6 *t*	25 0 *t*	24 5 *t*
C-3	39 6 *t*	37 3 *t*	38 4 *t*
C-4	140 1 *s*	81 6 *s*	82 0 *s*
C-5	123 7 *d*	32 6 *t*	37 0 *t*
C-6	26 4 *t*	24 5 *t*	24 1 *t*
C-7	131 9 *s*	160 6 *s*	160 1 *s*
C-8	165 7 *s*	80 5 *d*	105 6 *s*
C-9	23 5 *q*	49 6 *t*	49 8 *t*
C-10	143 4 *s*	77 3 *s*	77 1 *s*
C-11	139 9 *s*	122 1 *s*	122 9 *s*
C-12	165 7 *s*	175 1 *s*	173 3 *s*
C-13	9 5 *q*	8 0 *q*	7 8 *q*
C-14	17 7 *q*	25 4 *q*	25 7 *q*
C-15	16 3 *q*	25 3 *q*	25 3 *q*



a



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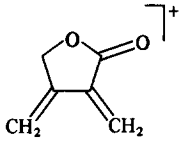
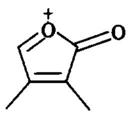


c



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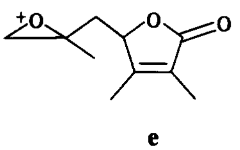

e

Seco-germacrane anhydride (**7**) Amorphous, colorless compound IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1860, 1820, 1770, 1670, 1440, 1380, 1275, 1115, 915, 730 ^{1}H NMR given in Table 1 ^{13}C NMR given in Table 3 MS *m/z* (rel int) 248 1412 $[M]^+$ ($C_{15}H_{20}O_3$) (1), 220 $[M-CO]^+$ (1), 219 $[M-CHO]^+$ (3), 205 $[220-Me]^+$ (4), 180 $[219-CHO]^+$ (3), 69 [**a**]$^+$ (100) Compound **7** (5 mg) was treated with 10 mg $NaBH_4$ in 2 ml MeOH for 5 min After addition of dil H_2SO_4 the reaction mixture was separated by preparative TLC (silica gel) in Et_2O–petrol (1 1)

Seco-germacrane lactone (**8**) Colorless oil IR $\nu_{max}^{CCl_4}$ cm^{-1} 1770 ^{1}H NMR given in Table 1 MS *m/z* (rel int) 234 162 $[M]^+$ ($C_{15}H_{22}O_2$) (10), 219 $[M-Me]^+$ (3), 191 $[219-CO]^+$ (30), 151 [219 − **b**]$^+$ (52), 69 [**a**]$^+$ (100)

Seco-germacrane lactone (**9**) Colorless oil IR $\nu_{max}^{CCl_4}$ cm^{-1} 1765 ^{1}H NMR given in Table 1 MS *m/z* (rel int) 234 162 ($C_{15}H_{22}O_2$) (% 10), 219 $[M-CH_3]^+$ (% 3), 191 [219 − CO] (% 30), 151 [219 − b] (% 52), 69 [**a**] (% 100)

1β,10α-*Epoxy-4-methoxyglechomanolide* (**10**) Colorless crystals, mp 147° IR $\nu_{max}^{CCl_4}$ cm^{-1} 1750, 1680, 1455, 1000 ^{1}H NMR given in Table 2 ^{13}C NMR given in Table 3 MS *m/z* (rel int) 280 183 $[M]^+$ ($C_{16}H_{26}O_4$) (1 5), 265 $[M-Me]^+$ (1 5), 248 [M

$-\mathrm{MeOH}]^+$ (8), 247 $[265-\mathrm{H_2O}]^+$ (8), 230 $[248-\mathrm{H_2O}]^+$ (7), 180 $[\mathbf{e}]^+$ (100), 110 $[\mathbf{d}]^+$ (37)

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436}{+23 \quad +24 \quad +28 \quad +51} (c\ 4\ 86,\ \mathrm{CHCl_3})$$

1β,10α-Epoxy-4-methoxy-8-hydroxyglechomanolide (**11**) Colorless oil IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1} 3570, 1755, 1690, 1455, 1380, 1140, 1115, 1070, 915 ^{1}H NMR given in Table 2 ^{13}C NMR given in Table 3 MS *m/z* (rel int) 296 178 $[\mathrm{M}]^+$ ($\mathrm{C_{16}H_{26}O_5}$) (0 5), 278 $[\mathrm{M}-\mathrm{H_2O}]^+$ (2), 263 $[278-\mathrm{Me}]^+$ (4 5), 246 $[278-\mathrm{MeOH}]^+$ (11), 206 (31), 81 (92), 73 (100)

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436}{+36 \quad +38 \quad +44 \quad +82} (c\ 2\ 45,\ \mathrm{CHCl_3})$$

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