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Sesquiterpene lactones and other constituents of *Disynaphia multicrenulata* from Argentina

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Abstract

Flowers and leaves of *Disynaphia multicrenulata* from Argentina afforded a large number of known germacradienolides and heliangolides, a new germacradienolide, a known melampolide, a new parthenolide derivative, one known and seven new cronquistiolides, a new 4Z-melampolide, three known and five new eudesmanolides, a new elemadienolide, a known grazielolide, an isoguaiaagrazielolide, two diepoxygermacran-8,12-olides, three common kauranoic acids, pinoresinol, jaceosidin and the sesquiterpene oplopanone. Structures were elucidated by high-field ¹H NMR spectrometry. The relationship to the known chemistry of other members of the Disynaphiinae is discussed. © 2001 Elsevier Science Ltd. All rights reserved.

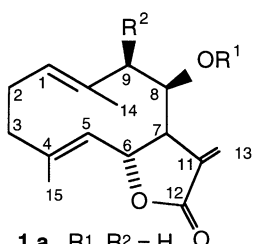
1. Introduction

Disynaphia Hook. & Arn. Ex DC. (Asteraceae, Eupatorieae, Disynaphiinae) is a genus of 16 species ranging from Southern Brazil to Uruguay westward through part of Argentina to Paraguay (King and Robinson, 1987). Previous chemical studies have dealt with *D. halimifolia* (DC) R. M. King and H. Robinson from Brazil (Bohlmann et al., 1981a) which furnished a glaucolide, an elemadienolide, an unusual modified germacranolide, a new geranylgeraniol derivative and two tremetone derivatives, and with *Disynaphia multicrenulata* from near San Lorenzo

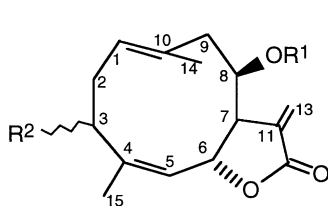
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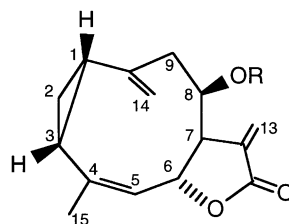
in Paraguay (Bohlmann et al., 1984) which contained the germacradienolides **1c–e**, **h**, **j**, the heliangolides **2c**, **d**, **f**, **h**, **i**, **k–n** and three well-known *ent*-kauranoic acids as well as common sesquiterpenes. In order to determine whether the chemical composition of *D. multicrenulata* varied with geography and to establish possible chemical affinities to other members of the subtribe we undertook a chemical study of *D.*



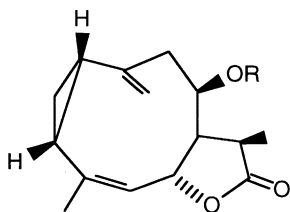
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b R¹ = A, R² = H
c R¹ = A, R² = OH
d R¹ = B, R² = H
e R¹ = D, R² = H
f R¹ = E, R² = H
g R¹ = G, R² = H
h R¹ = I, R² = H
i R¹ = J, R² = H
j R¹ = K, R² = H



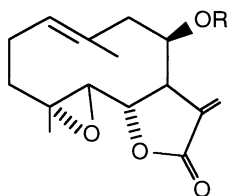
- 2 a** R¹ = A, R² = βOAc
b R¹ = C, R² = βOAc
c R¹ = D, R² = αOAc
d R¹ = D, R² = βOAc
e R¹ = E, R² = βOAc
f R¹ = E, R² = αOAc
g R¹ = F, R² = αOAc
h R¹ = F, R² = βOAc
i R¹ = I, R² = βOAc
j R¹ = G, R² = βOAc
k R¹ = B, R² = αOAc
l R¹ = B, R² = βOAc
m R¹ = H, R² = αOAc
n R¹ = H, R² = βOAc



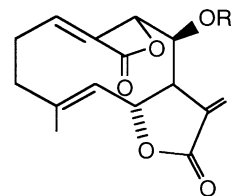
- 3 a** R = H
b R = A
c R = D
d R = E
e R = G
f R = I
g R = J



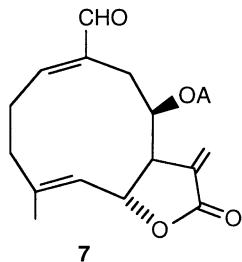
- 4 a** R = H
b R = D
c R = G



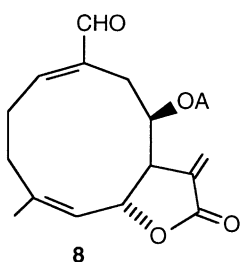
- 5 a** R = G
b R = I



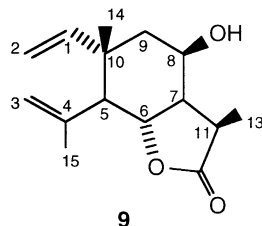
- 6 a** R = A
b R = G



7



8



9

multicrenulata from Misiones province, Argentina. The results are described in the present article.

2. Materials and methods

2.1. Plant material

Aerial parts of *Disynaphia multicrenulata* (Sch. Bip. *ex* Baker) R. M. King and H. Robinson (Asteraceae, Eupatorieae, Disynaphiinae) were collected at the flowering stage on March 14, 1996 in Misiones province in northeastern Argentina. A voucher specimen (LIL 604 022) is on deposit in the herbarium of the Fundación Miguel Lillo, Tucumán.

2.2. General procedures

For HPLC two columns were used — column A, Beckman Ultrasphere C18 (10 mm i.d. × 250 mm), column B, Beckman Ultrasphere C8 (10 mm i.d. × 250 mm). Known compounds were identified by ¹H NMR spectrometry at 500 MHz with extensive decoupling, MS. and comparison with spectra in our files.

2.3. Extraction and isolation of constituents

Flowers and leaves (802 g) of the material from Misiones province, were extracted with CHCl₃ (2 × 5 l) for 14 days to give 142 g (18%) of crude extract which was suspended in EtOH (1400 ml) at 55°, diluted with H₂O (1000 ml) and extracted successively with hexane (3 × 1000 ml) and CHCl₃ (3 × 1000 ml). The CHCl₃ extract on evaporation. at red press furnished a residue (52 g) which was subjected to CC (Si gel, CHCl₃ with increasing amounts of EtOAc [0–100%] and finally EtOAc containing 5% MeOH) to give 10 frs. (frs. I–X). Frs. I–IV were rechromatographed to give from fr. I (1.0 g, Sephadex LH-20 using CH₂Cl₂–MeOH 1:1) fr. I a (63 mg) and I b (240 mg), from fr. II (1.7 g, Si gel, CHCl₃–EtOAc mixtures of increasing polarities) frs. II a–d (396 mg), II e–i (760 mg), II j–l (428 mg) and II m (66 mg), from fr. III (640 mg, Si gel, CHCl₃–EtOAc mixtures of increasing polarities) frs. III a–e (498 mg) and frs. III f–i (250 mg), from fr. IV (900 mg, Si gel, CHCl₃–EtOAc mixtures of increasing polarity) frs. IV a–e (179 mg) and frs. IV f–k (60 mg). A portion (60 mg) of fr. Ia on HPLC (column A, [10 mm i.d. × 250 mm], MeOH–H₂O 2:1) gave new **1i** (8.6 mg) as a mixture of C-5' epimers, new **3g** (4.6 mg), **1g** (Zdero et al., 1988) admixed with **3g** (6.3 mg), new **3f** (4.7 mg) and a mixture resolved by further HPLC (Column A, MeOH–H₂O, 3:2) to give new **9** (1.5 mg), new **8** (2.0 mg) and **7** (5 mg, Bohlmann et al., 1981e, stereochemistry corrected by Bohlmann et al., 1984a). A portion (100 mg) of fr. Ib on HPLC (Column A, MeOH–H₂O, 2:1) gave more **1g** (3.3 mg) and new **3e** (1.0 mg).

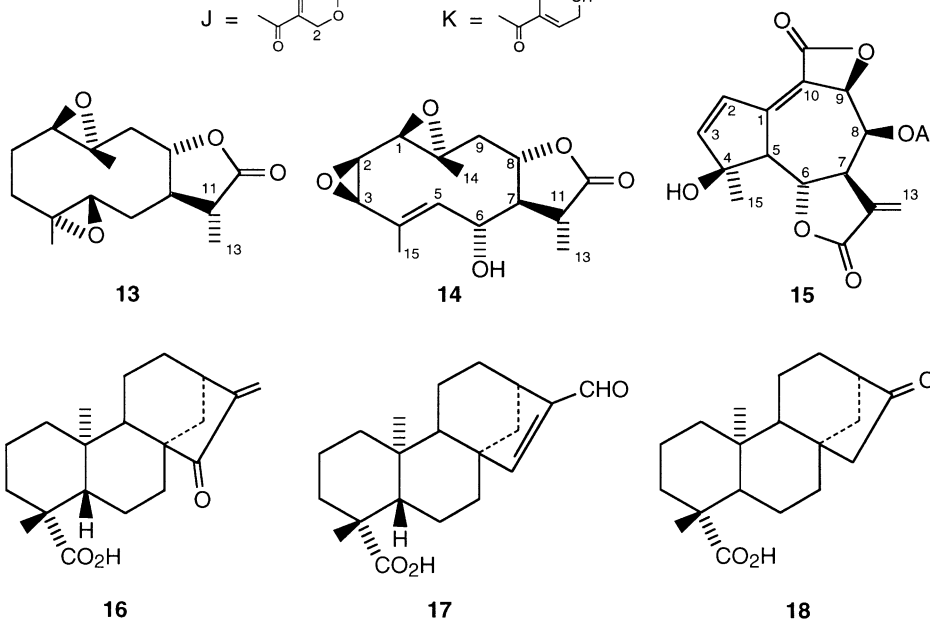
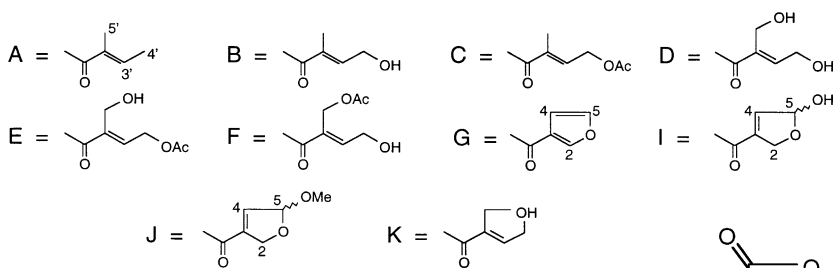
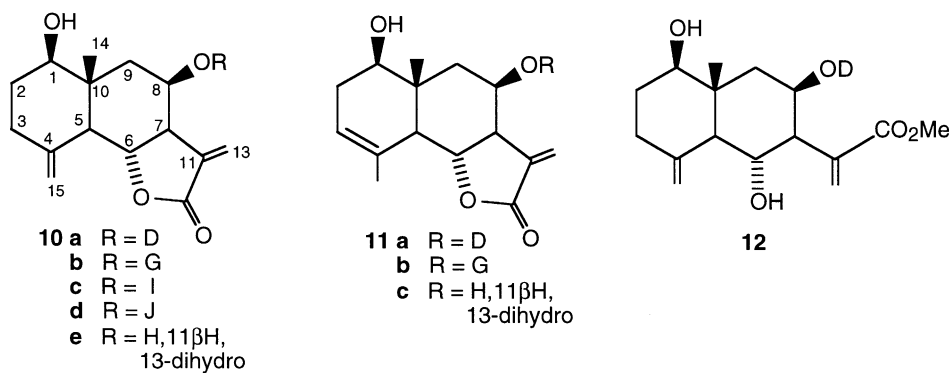
HPLC (column A, MeOH–H₂O 3:2) of a portion of frs. II a–d furnished **10b** (1 mg, Hernández et al., 1996), **1g** (8.8 mg), **3e** (5.2 mg) and new **3f** (3.1 mg, mixture

of 5'-epimers) mixed with a little **3g**. A portion of frs. II e–k on HPLC afforded only a mixture containing **1b** (Bohlmann et al., 1985), **1g** and a third ester of type **1** which decomposed before the nature of the ester group could be established. A portion of frs. II j–l on HPLC (column A) gave **6a** (8.0 mg, Bohlmann et al., 1983b) admixed with a small amount of **6b** as evidenced by the ^1H NMR spectrum, a mixture (3.1 mg) containing **1a** and subsequently 8.2 mg of the sesquiterpene oplopanone (Takeda et al., 1965) while a portion of fr. II m on HPLC gave a mixture containing **7** (16.8 mg) followed by the *ent*-kauranes **1b** (5.1 mg, Cannon et al., 1966) and **17** (5.4 mg, Bohlmann et al., 1980a). Frs. III a–e on HPLC (column A, MeOH–H₂O 2:1) gave 6 peaks which TLC showed to be mixtures and which were further purified by HPLC (column A, MeOH–H₂O 3:2). Peak 1 gave 7.1 mg of eriolin (**13**, Torrance et al., 1969) and 2.7 mg of a 2:1 mixture of new **15** and pinoresinol, peaks 3 and 4 gave **3a** (12.9 mg) and a small amount of new **4c**, new **4a** (12 mg) and new **11b** (13 mg), peak 5 gave 4 mg of a mixture of **1a** (eupatolide, Lee et al., 1972; McPhail and Onan, 1975) and **4a**, 1.7 mg of oplopanone, 5.1 mg of a mixture containing in descending order of concentration **10e** (Jeske et al., 1996), new **11b** and **11c** and subsequently 14.5 mg of **1d** (20-desoxyeupatoriopicrin, Bohlmann et al., 1984b). Frs. III f–i were combined and processed by HPLC (column A, MeOH–H₂O 2:1 and 8:2) to give lactone mixtures and jaceosidin (1.7 mg) and by column B (MeOH–H₂O 3:2) to give more jaceosidin (1 mg), new **11b** (1.5 mg), **1d** (2.5 mg) and **18** (15 mg, Herz and Kulanthaivel, 1983).

Frs. IV a–e on HPLC (column A, MeOH–H₂O 3:2) gave 16.8 mg more eriolin (**13**), a mixture (16.5 mg) of **1b** and **3a**, and new **4a** (23.2 mg), while frs. IV f–k contained mainly jaceosidin. A portion (150 mg) of fr. V (320 mg) of the original chromatogram after HPLC (column A) and rechromatography (column B, MeOH–H₂O 3:2) gave a mixture containing **1h** (major constituent, both 5'-epimers, Bohlmann et al., 1984b), **1g** and **1i** (least), followed by jaceosidin (2.5 mg), a mixture of furoyl esters of sesquiterpene lactones (25.7 mg) and a mixture (3.4 mg) of **3c** (major constituent, Zdero et al., 1991), **1b** and **3b** (least).

Fr. VI (200 mg) of the original chromatogram consisted mainly of flavonoids. Washing with Et₂O afforded 115 mg of jaceosidin. Fr. VII (1.0 g) was passed through Sephadex LH-20 using MeOH–CH₂Cl₂ (1:1) to remove chlorophyll and then subjected to CC to give several fractions. These were processed by HPLC (column A, MeOH–H₂O, 1:1) to give new **14** (5.7 mg), impure **5b** (new, 8.4 mg) which was partially converted to **5a** on keeping, a mixture (9.8 mg) containing **2i** (main constituent, Bohlmann et al., 1984b) and smaller amounts of **2a** (Jakupovic et al., 1986), **2c** (eupaformosanin, Lee et al., 1977) and **2j** (santhemoidin, Perez et al., 1984), the tiglate moiety of new **2a** being identified by the typical *qq* ($J = 7$, 1 Hz) of H-3' at δ 6.79 and the vinyl methyl signals of H-5' and H-4' at δ 1.81 *brs* and δ 1.79, new **10d** (1.9) as a mixture of 4'-epimers, **2h** (5.3 mg), **2g** (9 mg) and **2f** (6.6 mg).

A portion (60 mg) of fr. VIII on HPLC (column A, MeOH–H₂O) gave a mixture (3.3 mg) of **10b** (major constituent) and **10c** (minor constituent) followed by 1.7 mg of eucannabinolide (**2d**, Drozd et al., 1972), 2 mg of eupaformosanin (**2c**, Lee et al., 1977), 5.8 mg of **1d** (20-desoxyeupatoriopicrin, Bohlmann et al., 1984b), 3 mg of **3c** (Zdero et al., 1991) and 1 mg of new **4b**. A portion (60 mg) of fr. IX (6.3 g) was



similarly processed to give new **10c** (1.4 mg, mixture of 4'-epimers) contaminated with **10b**, **2d** (1 mg), and **2c** (5.2 mg). Finally a portion (50 mg) of fr. \times (2 g) on HPLC (column A, MeOH–H₂O–HOAc, 39 : 60 : 1) gave 1.9 mg of a 2 : 1 mixture of **10a** and **12** followed by 1 mg of **11a** (de Hernández et al., 1999).

2.4. Identification and discussion of new constituents

Lactones with ester side chains I and J were generally mixtures of hemiacetal resp. acetal epimers; thus, for example, the ^1H NMR spectra of **1i** and **5b** listed in Table 2 exhibited two signals for H-4' and four signals for H-5 of the 2,5-dihydro-5-methoxy-resp. 2,5-dihydro-5-hydroxyfuroylside chain. On standing such lactones frequently also underwent elimination to the furoyl analogs (ester side chain G) whose natural occurrence may therefore be sometimes in question.

The first and only cronquistiolid **3c** known so far was originally isolated from *Cronquistia pringlei* (Eupatorieae, subtribe Ageratinae) (Zdero et al., 1991) and later from *Asanthus soladiginifolius* (Eupatorieae, subtribe Alomiinae) (Zdero et al., 1992). In the present study cronquistiolides **3a–g** and **4a,b** were found with **3d** being contaminated with **1b** and a small amount of **3b** while one fraction containing **4a** was contaminated by a small amount of **4c**. ^1H NMR spectra of **3a, b, 3d–g** and the 11,13-dihydro analogs **4a** and **4b** are listed in Table 1. We have reversed the original assignments for H-1 and H-3 in **3b** (Zdero et al., 1991) and its relatives because of the presence of allylic coupling between H-5 and the multiplet near $\delta 1.45$. The C-11 stereochemistry assigned to **4a,b** is based on the value of $J_{7,11}$ (7.5 Hz). The co-occurrence of **2a, d, e, i, j** with **3b, d, f, g** bolsters the earlier proposal for the biogenetic route to the cronquistiolides.

Epoxygermacranolide **5b** was converted to **5a** on standing. The ^1H NMR spectra are included in Table 2 and are consonant with the assigned structures. The ^1H NMR spectrum of the β -lactone **6a** which was admixed with a small amount of the corresponding 3-furoate **6b** was identical with the spectrum of **6a** from *Grazielia serrata* (Bohlmann et al., 1983b) while the ^1H NMR spectrum of **8**, also in Table 2, was essentially identical, except for the signals of the ester side chain, with the spectra of two ester analogs from *Stevia* species (Schmeda-Hirschmann et al., 1986; Zdero et al., 1987). Elemadienolide **9** contained a *trans*-fused γ -lactone closed to C-6 ($\delta\text{H} - 6 = 3.77$, $J's = 10.5, 9.5$ Hz), a β -orientated hydroxyl group on C-8 ($J_{7,8} = 4.5$, $J_{8,9a} = 2$, $J_{8,9b} = 4.5$ Hz) and a β -orientated C-11 methyl group ($J_{7,11} = 11$ Hz); hence it is the C-11 epimer of the elemadienolide 8-epitemisin synthesized from artemisinin some time ago (Arnó et al., 1984).

Structures of the new eudesmanolides **10a**, a 2 : 1 mixture with **12** which may be an artefact, **10c**, **10d** and **11b** were obvious from the ^1H NMR spectra after extensive decoupling (Table 3) while the 11,13-dihydro derivatives **10e** (Jeske et al., 1996) and **11c** were major and minor components of a mixture with **11b**, the latter also isolated in pure form. Lactone **13** (^1H NMR spectrum listed separately) was eriolin (Torrance et al., 1969). While the stereochemistry at its epoxidic centers is known (Romo de Vivar et al., 1982, Calderon et al., 1987) that at C-11 does not seem to have been established and is now shown to be 11α -methyl from the value of $J_{7,11}$ (11 Hz).

The diepoxy-6-hydroxygermacranolide **14** with the lactone ring close to C-8 whose ^1H NMR spectrum is listed separately was closely related to dihydromikanolide (Herz et al., 1970; Cox et al., 1973). Spin decoupling established the sequences C-10 through C-3 and C-5 through C-9, while the coupling constants showed that the C-6 hydroxyl was α -orientated, the lactone ring *trans* and the methyl on C-13

Table 1
¹H NMR spectra of compounds **3a**, **d–g**, **4a** and **4b** (500 MHz, CDCl₃)

H	3a	3d ^a	3e	3f ^b	3g ^b	4a	4b
1	0.90ddd (8,6,6)	1.01m	1.03m	1.01m	1.01m	0.88brddd (8,6,6)	1.00m
2a	1.06m	1.03m	1.04m	1.01m	1.01m	1.02ddd (9,6,6)	1.01m
2b	1.09m	1.13m	1.14dt (6,5)	1.13m	1.13m	1.07ddd (8,7,5)	1.12m
3	1.42dddd (8,7,7,1.5)	1.47brdd (8,8,6)	1.49brddd (9.5,8.5,8,1.5)	1.49 approx t (7)	1.45m	1.37 dddd (9,6,6,1)	1.43brq (7)
5	5.54dq ^{int} (6.5,1.5)	5.55ddd (6,2,2)	5.57dq ^{int} (6,1.5)	5.54dq ^{int} (6,1.5)	5.54dq ^{int} (6,1)	5.57dq ^{int} (6.5,1.5)	5.61dq ^{int} (6.5,1.5)
6	5.63ddq (6.5,2.5,1)	5.71m	5.77brdd (6,2)	5.68,5.65brdd (6,2)	5.69,5.66brdd (6,2)	5.52ddd (6.5,3.5,1)	5.67brdd (6,2.5)
7	3.13q ^{tt} (2.5,2)	3.35q ^{int} (2)	3.369q ^{int} (2)	3.33q ^{int} (2)	3.38,3.33q ^{int}	2.26td (3.5,1.5)	2.52td (2.2,2)
8	4.09ddd (7.3,5.2)	5.21ddd (8,4,2)	5.25ddd (8,4,2)	5.18,5.16ddd (8,4,1.5)	5.19,5.17ddd (7,4,1.5)	4.00ddd (7.5,3.5,1)	5.19ddd (7.5,4,2)
9a	2.71ddd (14,7,1)	2.84brdd (14,7.5)	2.90ddd (14,8,1)	2.83brd (14,8)	2.85,2.84dd (14,7)	2.68brdd (14,7.5)	2.79brdd (14,7.5)
9b	2.60ddd (14,3.5,1)	2.62brdd (14,4)	2.67dd (14,4)	2.62d	2.62,2.61dd (14,3.5)	2.48brdd (14,3.5)	2.58ddd (14,4)
11	—	—	—	—	—	2.58qd (7.5,3.5)	2.43qd (7.5,2.5)
13a	6.37d (2.5)	6.33d (2)	6.32d (2)	6.30,6.34d (2)	6.34,6.33d (2)	1.33d ^c (2.5)	1.35d ^c (7.5)
13b	5.66d (2)	5.72d (2)	5.73d (2)	5.71,5.72d (2)	5.72,5.71d (2)		
14a	4.89brd (1)	4.93brs	4.95brs	4.95,4.92s	4.94,4.92s	4.87brs	4.92brs
14b	4.77brs	4.85brs	4.86brs	4.87brs	4.86,4.84s	4.75brs	4.84brs
15 ^b	1.60brd (1)	1.62brs	1.63brs	1.62brs	1.62brs	1.60brs	1.64brs
2'a	—	—	7.93dd (1.5,1)	4.78ddd (14,4.5,2.5)	4.78ddd (14,4,2.5)		
2'b	—	—		4.63,4.60ddd (14,2,1.5)	4.65,4.62ddd (14,2,1.5)		
3'		6.75t (6.5)	—	—	—		6.94t (6)
4'		4.81d ^d (6.5)	6.65dd (1.5,1)	6.50,6.56 sext (1.5)	6.55,6.52 sext (1.5)		4.43d ^d (6)
5'		4.31br ^d	7.38t (1.5)	5.87m	5.81,5.77dt (5,1.5)		4.36brd (13)
							4.33brd (13)
Ac ^c		2.08s					
OMe ^c					3.39,3.36s		

^aFrom mixture with **1b** and a little **3b** most of whose signals were slightly displaced from those of **3d** except from the signals of the tiglate moiety which appeared at δ6.74qq, (7,1.5,H-3'), 1.73dq (7,1.5,H-4'), 1.71dq (7.1,H-5').

^bMixture of 5'-epimers.

^cIntensity 3 protons.

^dIntensity 2 protons.

Table 2

¹H NMR spectra of compounds **1i**, **5a,b**, and **8** (500 MHz, CDCl₃)^d

H	1i ^a	5a ^b	5b ^a	8
1	4.89brdd (12,4)	5.32brd (12,3)	5.31brd (12,3)	6.60brddd (8.5,6.5,1.5)
2a	2.28-	2.4m	2.4m	2.75c
2b	2.38c	2.2m	2.2m	2.75c
3a	2.22brdd (12,5)	1.3m	1.3m	3.09ddd (14,11,7)
3b	2.10m	—	1.40m	2.23ddd (14,7,3)
5	4.76brd (10)	2.84d (8.5)	2.81d (8.5)	5.27dq (9.5,1)
6	5.06,5.05dd (10,8.5)	4.35t (8.5)	4.35,4.34t (8.5)	5.46dd (9.5,4.5)
7	2.93dddd (8.5,3.5,3,2)	3.18brdt (8,3,3,1)	3.17brdt (8,3,3,1)	2.61dq (4.5,2.5)
8	5.82brd (4.5)	5.78brd (5)	5.73brd (5)	5.93brd (10,7,2.5)
9a	2.82brdd (14.5,4)	2.84dd (15,5)	2.81dd (15,5)	3.01dd (14,7,1)
9b	2.35m	2.40brd (15)	2.40brd (15)	2.53ddd (14,10,1.5)
13a	6.30d (3.5)	6.39d (3.5)	6.38d (3.5)	6.29d (3.5)
13b	5.59d (3)	5.76d (3)	5.72d (3)	5.65d (2.5)
14	1.47 ^b , 1.46 ^c	1.71brs ^c	1.71brs ^c	9.39d (1.5)
15 ^c	1.74t(1)	1.36s	1.36s	1.75brs
2'a	4.83ddd (14,4,2)	7.92dd (1.5,0.5)	4.86,4.85ddd (13,4,3)	—
2'b	4.82ddd (14,4,2)	—	4.85ddd (13,4,3)	—
3'	—	—	—	6.74qq (7,1.5)
4'	6.54,6.51sext (1.5)	6.62d (2,1)	6.56,6.55sext (1.5)	1.74qq ^b (7,1.5)
5'	4.83,4.82ddd (14,4,2)	7.43dd (2.0.5)	4.86,4.85ddd (13,4,3)	1.71quint ^b (1.5)
	4.69,4.67ddd (14,3.5,1.5)		4.66,4.65ddd (13,2.5,1.5)	
OMe ^c	3.41,3.40s			

^a Mixture of 5' epimers. ^c Intensity 3 protons.^b From **5b** on standing. ^d Intensity 2 protons.

α ($J_{7,11} = 9$ Hz). Chemical shifts and coupling constants involving H-1, H-2 and H-3 were close to those of mikanolide and dihydromikanolide, hence the epoxides were β .

Finally we consider sesquiterpene dilactone **15**, obtained as a 2:1 mixture with pinoselinol. Interpretation of its ¹H NMR spectrum (listed separately) initially caused difficulties although the sequence C-5 through C-9 and the nature of the ester side chain attached to C-8 were easily established by spin decoupling, with H-8 and H-9 unusually far downfield at δ 6.16 and δ 5.02 as in **6a**. H-5 was long-range coupled (1 Hz) to H-9 indicating intervention of a double bond between C-1 and C-10 while H-9 was further long-range coupled (0.5 Hz) to one vinylic proton (later identified as H-2) at δ 6.51 which was further coupled by 5.5 Hz to a doublet at δ 6.73 (H-3). Chemical shifts and vicinal coupling constants of these two olefinic signals indicated further conjugation and inclusion in a five membered ring which because of the presence of only one methyl signal at δ 1.65 and the empirical formula C₂₀H₂₀O₇ led eventually to formula **15**. The stereochemistry C-5 through C-9 followed from the coupling constants while the stereochemistry assigned to C-4 was based on the chemical shift of H-15 at δ 1.65 which is deshielded by the lactone oxygen (Bohlmann and Knoll, 1979; Jakupovic et al., 1988) and on the absence of an NOE between H-6

Table 3
¹H NMR spectra of compounds **10a,c,d**, **11b,c** **12** (500 MHz, CDCl₃)

H	10a ^a	10c ^b	10d ^c	11b	11c ^d	12 ^a
1	3.52 <i>dd</i> (11,5)	3.52 <i>dd</i> (11,4.5)	3.51 <i>dd</i> (11,5)	3.68 <i>dd</i> (10,7)	3.60 <i>dd</i> (10,7)	3.47 <i>dd</i> (11,5)
2 α	1.83 <i>c</i>	1.83 <i>ddd</i> (12.5,5,5.2)	1.83 <i>c</i>	2.40 <i>m</i>	2.40 <i>m</i>	1.83 <i>c</i>
2 β	1.62 <i>c</i>	1.59 <i>ddd</i> (14,12.5,4)	1.58 <i>c</i>	1.59 <i>m</i>	1.95 <i>m</i>	1.62 <i>c</i>
3 α	2.35 <i>c</i>	2.39 <i>ddd</i> (14,4.5,4)	2.35 <i>m</i>	5.36 <i>c</i>	5.30 <i>m</i>	2.35 <i>c</i>
3 β	2.12 <i>c</i>	2.13 <i>ddd</i> (14,4.4)	2.13 <i>m</i>	—	—	2.12 <i>c</i>
5 α	2.25 <i>dd</i> (11,1)	2.26 <i>dd</i> (11,1)	2.25 <i>dd</i> (11,1)	2.45 <i>brd</i> (11)	2.45 <i>brd</i> (11)	1.97 <i>dd</i> (11,1)
6 β	4.25 <i>t</i> (11)	4.48 <i>t</i> (11)	4.67 <i>t</i> (11)	4.46 <i>t</i> (11)	4.42 <i>t</i> (11)	4.40 <i>t</i> (11)
7 α	2.85 <i>dq</i> (11,3)	2.86 <i>dq</i> (11,3)	2.85 <i>dq</i> (11,3)	2.83 <i>dq</i> (11,3)	1.75 <i>m</i>	3.02 <i>brdd</i> (10.5,3)
8 α	5.83 <i>q</i> (3)	5.84 <i>ddd</i> (3.5,3,2.5)	5.83 <i>ddd</i> (3,3,2)	5.90 <i>ddd</i> (3.5,3,2.5)	4.29 <i>m</i>	5.42 <i>q</i> (3)
9 α	2.42 <i>dd</i> (15,2)	2.36 <i>dd</i> (15,2)	2.39,2.37 <i>dd</i> (15,2)	2.41 <i>dd</i> (12,2.5)	2.18 <i>dd</i> (15,2.5)	2.35 <i>dd</i> (15,2)
9 β	1.62 <i>dd</i> (15,3)	1.64 <i>bdd</i> (15,3)	1.62 <i>dd</i> (15,3)	1.59 <i>dd</i> (15,3.5)	1.45 <i>dd</i> (15,4)	1.61 <i>dd</i> (15.3)
13a	6.15 <i>d</i> (3.5)	6.14 <i>d</i> (3.5)	6.15 <i>d</i> (3.5)	6.13 <i>d</i> (3.5)	1.21 <i>d</i> ^f (7)	6.41 <i>brs</i>
13b	5.44 <i>d</i> (3)	5.47 <i>d</i> (3)	5.46,5.45 <i>d</i> (3)	5.48 <i>d</i> (2.5)	—	5.78 <i>brs</i>
14 ^e	0.96 <i>s</i>	0.97 <i>s</i>	0.96,95 <i>s</i>	1.07 <i>s</i>	1.15 <i>brs</i>	0.91 <i>s</i>
15a	5.03 <i>brs</i>	5.03 <i>brs</i>	5.02 <i>brs</i>	1.89 ^e	1.83 <i>brs</i> ^e	5.08 <i>brs</i>
15b	4.96 <i>d</i> (1)	4.95 <i>brs</i>	4.94 <i>brs</i>	—	—	4.87 <i>brs</i>
2'a	—	4.89,4.88 <i>dd</i> (14,2.5)	4.83,4.82 <i>dd</i> (14,2.5)	7.96 <i>dd</i> (1,0.5)	—	—
2'b	—	4.69,4.68 <i>dd</i> (14,1.5)	4.68,4.67 <i>dd</i> (14,2.5)	—	—	—
3'	6.87 <i>t</i> (6)	—	—	—	6.84 <i>t</i>	—
4'	4.46 <i>d</i> ^f (6)	6.62 <i>q</i> (1)	6.56 <i>m</i>	6.68 <i>dd</i> (2,1)	4.43 <i>d</i> ^f (6)	—
5'	4.37 <i>s</i> ^f	6.19,6.18 <i>brs</i>	5.81 <i>m</i>	7.42 <i>dd</i> (2,0.5)	4.31 <i>s</i> ^f	—
OMe ^e	—	—	3.41,3.40 <i>s</i>	—	3.75 <i>s</i>	—

^aFrom 2 : 1 mixture of **10a** and **12**.

^dFrom mixture with **10b** and **10c**.

^b5'-epimers, from mixture with **10b** (minor).

^cIntensity three protons.

^e5'-epimers.

^fIntensity two protons.

and H-15. Dilactone **15** is related to the guaiagrazielolides from *Grazielia intermedia* (Bohlmann et al., 1981c) and *Campovassouria bupleurifolia* (Bohlmann et al., 1983a) which contain a 3,4-double bond and no hydroxyl group in the five-membered ring; consequently we have named it as a derivative of an isoguaiagrazielolide.

(6*R**,7*R**,8*R**)-8-(3-[2,5-dihydro-5-methoxy]furoyloxy)-germacra-1(10),4,11(13)-trien-6,12-olide (**1i**). Gum; Mixture of methoxy epimers; MS PCI (isobutane) *m/z* (rel. int.) 375 ([M+H]⁺ 2.5), 343 ([M+H⁺-MeOH] 8.3), 231 ([M+H⁺-C₆H₈O₄] 100); ¹H NMR spectrum in Table 2.

(6*R**,7*R**,8*R**)-8-Hydroxycronquistioidide (**3a**). Gum; MS PCI (isobutane) *m/z* (rel. int.) 247 ([M+H]⁺ 34.2) 229 ([M+H⁺-H₂O] 100); IR ν_{\max} cm⁻¹ 3400, 1765, 1720, 1650; ¹H NMR spectrum in Table 1.

(6*R**,7*R**,8*R**)-8-(3-Furoyloxy)-cronquistioidide (**3e**). Gum; MS PCI (isobutane) *m/z* (rel. int.) 341 ([M+H]⁺ 20.5), 229 ([M+H⁺-C₅H₈O₃] 100), 211 (7); IR ν_{\max} cm⁻¹ 1760, 1720; ¹H NMR spectrum in Table 1.

(6*R**,7*R**,8*R**)-8-(3-[2,5-Dihydro-5-hydroxy]furoyloxy)-cronquistioidide (**3f**). Gum; mixture of epimers; IR ν_{\max} cm⁻¹ 1765, 1720, 1660; ¹H NMR spectrum in Table 1. On standing the substance underwent conversion to **3e**.

(6*R**,7*R**,8*R**)-8-(3-[2,5-Dihydro-5-methoxy]furoyloxy)-cronquistioidide (**3g**). Gum; mixture of epimers; ¹H NMR spectrum in Table 1. On standing the substance underwent conversion to **3e**.

(6*R**,7*R**,8*R**,11*R**)-8-Hydroxy-11,13-dihydrocronquistioidide (**4a**). Gum; MS PCI (isobutane) *m/z* (rel. int.) 249 ([M+H]⁺ 19.5), 231 ([M+H⁺-H₂O] 100); IR ν_{\max} cm⁻¹ 3500, 1760, 1650; ¹H NMR spectrum in Table 1. One fraction consisting primarily of **4a** also exhibited relatively weak signals of the 3-furoyl moiety at δ 7.95, 7.42 and 6.67 due to **4c**.

(6*R**,7*R**,8*R**,11*R**)-8-(4,5-Dihydroxytiglyloxy)-11,13-dihydrocronquistioidide (**4b**). Gum; MS PCI (isobutane) *m/z* (rel. int.) 231([M+H⁺-C₅H₈O₄] 100), ¹H NMR spectrum in Table 1.

8 β -(3-[2,5-Dihydro-5-hydroxy]furoyloxy)-parthenolide (**5b**). Mixture of epimers which underwent partial dehydration to **5a** on keeping; MS PCI (isobutane) *m/z* (rel. int.) 361 ([M+H]⁺ 3.7), 343 ([M+H⁺-H₂O] 21.5), 247 ([M+H⁺-C₅H₆O₄] 100); IR ν_{\max} cm⁻¹ 3500, 1765 1720; ¹H NMR spectra of **5a** and **5b** in Table 2.

8 β -Tiglyloxygraziolide (**6a**). Gum containing a small amount of the corresponding furoate (**6b**) as an impurity; The MS PCI and the ¹NMR spectrum corresponded to the data reported for **6a**; the furoate signals of the minor constituent appeared at δ 7.92 *dd* (H-2'), 7.43 *t* (H-5') and 6.62 *dd* (H-4').

(6*R**,7*R**,8*R**)-8-Tiglyloxy-14-oxogermacra-1(10)*Z*,4*Z*,11(13)-trien-6,12-olide (**8**). Gum; MS PCI (isobutane) *m/z* (rel. int.) 345 ([M+H]⁺ 11.0), 245([M+H⁺-C₅H₈O₂] 11.3), 101 ([C₅H₈O₂+H⁺] 100); ¹H NMR spectrum in Table 2.

(5*R**,6*R**,7*R**,8*R**,11*R**)-8-Hydroxyelema-1,3-dien-6,12-olide (**9**). Gum; MS PCI (rel. int.) 251 ([M+H]⁺ 100), 233 ([M+H⁺-H₂O] 9.7); IR ν_{\max} cm⁻¹ 1770, 1725, 1660; ¹H NMR (CDCl₃, 500 MHz) δ 5.67 (*dd*, *J* = 18, 11 Hz, H-1), 4.97 (*dd*, *J* = 11, 1 Hz, H-2a), 4.93 (*brd*, *J* = 18 Hz, H-2b), 5.14 (*brs*, H-3a), 4.79 (*brs*, H-3b), 1.93 (*d*, *J* = 11 Hz, H-5), 3.77 (*dd*, *J* = 10.5, 9.5 Hz, H-6), 2.32 (*ddd*, *J* = 9, 7, 4.5 Hz, H-7), 4.95 (*ddd*, *J* = 4.5, 4.5, 2 Hz, H-8), 2.07 (*dd*, *J* = 16, 2 Hz, H-9a), 1.72 (*dd*,

$J = 16$, 4.5 Hz, H-9b), 2.89 (quint, $J = 7$ Hz, H-11) 1.37 (*d*, 3p, $J = 7.5$ Hz, H-13), 1.07 (*s*, 3p, H-14), 1.76 (*d*, $J = 1$ Hz, 3p, H-15).

(1*R**,5*S**,6*R**,7*R**,8*R**,10*R**)-1-Hydroxy-8-(4,5-dihydroxytiglyloxyeudesma-4(15), 11(13)-dien-6,12-olide (**10a**). Major component of a mixture with **12**. The PCI MS remained unsatisfactory, the only significant peak was at m/z 257 corresponding to loss of the ester side chain and water from **12**, ^1H NMR spectra of **10a** and **12** in Table 3.

(1*R**,5*S**,6*R**,7*R**,8*R**,10*R**)-1-Hydroxy-8-(3-[2,5-dihydro-5-hydroxy]-furoyloxy)-eudesma-4(15),11(13)-dien-6,12-olide (**10c**). Gum; mixture of epimers contaminated by a small amount of **10b**; MS PCI (isobutane) m/z (rel. int.) 359 ($[\text{M} + \text{H}^+ - \text{H}_2\text{O}]$ 100); ^1H NMR spectrum in Table 3.

(1*R**,5*S**,6*R**,7*R**,8*R**,10*R**)-1-Hydroxy-8-(3-[2,5-dihydro-5-methoxy]-furoyloxy)-eudesma-4(15),11(13)-dien-6,12-olide (**10d**). Gum; mixture of epimers; MS PCI (isobutane) m/z (rel. int.) 391 ($[\text{M} + \text{H}^+]$ 100), 359 ($[\text{M} + \text{H}^+ - \text{MeOH}]$ 16.3); ^1H NMR spectrum in Table 3.

(1*R**,5*S**,6*R**,7*R**,8*R**,10*R**)-1-Hydroxy-8-furoyloxy)-eudesma-3,11(13)-dien-6,12-olide (**11b**). Gum; MS PCI (isobutane) m/z (rel. int.) 359 ($[\text{M} + \text{H}^+]$ 100), 341 ($[\text{M} + \text{H}^+ - \text{H}_2\text{O}]$ 4.7), 247 ($[\text{M} + \text{H}^+ - \text{C}_5\text{H}_4\text{O}]$ 58.2), 229 ($[\text{M} + \text{H}^+ - \text{C}_5\text{H}_4\text{O} - \text{H}_2\text{O}]$ 43.2); IR ν_{max} cm^{-1} 3400, 1750, 1710; ^1H NMR spectrum in Table 3.

(1*R**,4*R**,5*S**,7*R**,8*S**,10*S**,11*R**)-1(10),5-Diepoxygermacran-8,12-olide(eriolin) (**13**). The detailed ^1H NMR spectrum of this compound (Torrance et al., 1969) has not been reported previously; MS PCI (isobutane) m/z (rel. int.) 267 ($[\text{M} + \text{H}^+]$ 100), 249 ($[\text{M} + \text{H}^+ - \text{H}_2\text{O}]$ 21.5) ^1H NMR (CDCl_3 , 500 MHz) δ 2.76 (*dd*, $J = 11$, 1.5 Hz, H-1 α), 2.13 (*ddd*, $J = 14$, 4, 1.5 Hz, H-2 α), 1.44(*c*, H-2b), 2.23 *ddd* ($J = 14$, 4, 3 Hz, H-3a), 1.26 (*c*, H-3b), 2.70 (*d*, $J = 9$ Hz, H-5 α), 2.19 *dd* ($J = 15$, 1.5 Hz, H-6a), 1.49 *ddd*, $J = 15$, 10, 9 Hz, H-6b), 1.89 (*dddd*, $J = 11$, 11, 9, 1.5 Hz, H-7 α), 4.14 (*ddd*, $J = 11$, 9, 1.5 Hz, H-8 β), 2.78 (*dd*, $J = 14$, 1.5 Hz, H-9a), 1.41 (*dd*, $J = 14$, 11 Hz, H-9b), 2.35 (*dq*, $J = 11$, 7 Hz, H-11 β), 1.28 (*d*, $J = 7$ Hz, H-13), 1.25 and 1.37 (each *s* and 3p, H-14 and H-15).

1*S**,2*R**,3*R**,6*S**,7*R**,8*S**,10*S**,11*R**)-1(10),2(3)-Diepoxy-6-hydroxygermacr-4-en-8,12-olide (**14**). Gum; MS PCI (isobutane) m/z (rel. int.) 281 ($[\text{M} + \text{H}^+]$ 100), 263 ($[\text{M} + \text{H}^+ - \text{H}_2\text{O}]$ 13.4); IR ν_{max} cm^{-1} 3500, 1760, 1660; ^1H NMR (500 MHz, CDCl_3) δ 3.21 (*ddd*, $J = 3.5$, 1.5, 0.5 Hz, H-1 α) 3.39 (*brd*, $J = 3.5$, 1 Hz, H-2 α), 2.89 (*brs*, $J = 1.5$, 1 Hz, H-3 α), 5.24 (*dq*, $J = 10.5$, 1.5 Hz, H-5), 4.40 (*dd*, $J = 10.5$, 9.5 Hz, H-6 β), 1.95 (*ddd*, $J = 9.5$, 9, 8 Hz, H-7 α), 3.97 (*ddd*, $J = 11$, 8, 1 Hz, H-8 β), 2.64 (*ddd*, $J = 13.5$, 1, 0.5 Hz, H-9 β), 1.38 *dd*, $J = 13.5$, 11 Hz, H-9 α), 2.77 (*dq*, $J = 8$, 7 Hz, H-13 β), 1.40 (*d*, $J = 7$ Hz, 3p, H-14), 1.93 (*d*, $J = 1.5$ Hz, 3p, H-15).

(4*R**,5*S**,6*S**,7*S**,8*S**,10*R**)-3-Hydroxy-8-tiglyloxyisoguiagrazielolide (**15**). Major component of a 2:1 mixture with pinoresinol; MS PCI m/z (rel. int.) 373 ($[\text{M} + \text{H}^+]$ 100), 355 ($[\text{M} + \text{H}^+ - \text{H}_2\text{O}]$ 72.6), 83 ($[\text{C}_5\text{H}_6\text{O} + \text{H}^+]$ 59.3); ^1H NMR (CDCl_3 , 500 MHz) δ 6.51 (*brd*, H-2), 6.73 (*d*, H-3), 3.01 (*dd*, H-5), 4.64 (*t*, H-6), 3.14 (*dddd*, H-7), 6.16 (*brd*, H-8), 5.02 (*brd*, H-9), 6.35 (*brd*, H-13a), 5.83 (*brd*, H-13b), 1.65 (*s*, 3p, H-15), 6.73 (*qq*, H-3'), 1.76 (*dq*, 3p, H-4'), 1.75 (*brs*, 3p, H-5'); $J_{2,3}$ 5.5 Hz,

$J_{2,9} = 0.5$ Hz, $J_{5,6} = 10$ Hz, $J_{5,9} = 1$ Hz, $J_{6,7} = 10$ Hz, $J_{7,8} = 1$ Hz, $J_{7,13a} = J_{7,13b} = 3$ Hz, $J_{8,9} = 3.5$ Hz, $J_{13a,13b} = 0.5$ Hz, $J_{3',4'} = 7$ Hz, $J_{3',5'} = 0.5$ Hz.

4. Taxonomic significance

The variety and number of sesquiterpene lactone types in our collection of Argentine *Disynaphia multicrenulata* is unprecedented but it is not clear whether the additional occurrence of conquistanolides, eudesmanolides, melampolides, elemadienolides and grazielolides, compared with the results reported earlier from the Paraguay collection of the same species, reflects a difference based on geography or derives from use of a more sensitive detection method, i.e. HPLC vs. column chromatography. *D. halimifolia*, the only other representative of the genus investigated previously (Bohlmann et al., 1981a,b) exhibited a quite different chemical profile although it too, and perhaps significantly (*vide infra*), contained sesquiterpenoid β -lactones, one of these related to **9**, the other an unusual modified germacranolide, as well as two heliangolides different in nature from those of type **2**.

There is seemingly little chemical resemblance between *D. multicrenulata* and several other members of Disynaphinae for which chemical records exist. Labdanes were the only terpenoids found in *Acanthostyles buniifolius* (Hook et Arn.) R. King and H. Robinson (as *Eupatorium buniifolium*, Caula et al., 1991, Muschietti et al., 1994, Carreras et al., 1998), one of only two members of the genus, and in *Symphiopappus ititayensis* (Vichnewski, et al., 1979) *reticulatus* and *compressus* (Bohlmann et al., 1981d) with a later article (Bohlmann et al., 1984c) also describing a guaianolide in the last mentioned representative of this genus of 11 species.

If any chemical similarities exist between *Disynaphia* and other genera of the tribe, they may be found in reports on *Campovassouria cruciata*, (as *C. bupleurifolia*, Bohlmann et al., 1980b; Bohlmann et al., 1983b), the only member of its genus, which in addition to kauranes and a guaianolide furnished germacranolides and heliangolides of types **1** and **2** and a β -lactone related to **15**, and in studies of four of the 11 recognized *Grazielia* species. One of these, *G. gaudichiana*, furnished only kauranes (Taleb et al., 1999) a second, *G. dimorpholepis*, contained kauranes and a germacradienolide of type **1** (Bohlmann et al., 1981c), a third, *G. serrata*, contained kauranes, a germacranolide of type **1** and the β -lactone analog **6a** (Bohlmann et al., 1981c, 1983b) of lactone **6b** from *Disynaphia multicrenulata*, while the fourth, *G. intermedia*, contained kauranes, the angelate analogs of **1c**, **6**, and **7** and more highly oxygenated derivatives thereof, and also a β -lactone similar to **15**. The only genus of Disynaphiinae on which no chemical information whatsoever is available is *Raulindreitzia* (three species).

The occurrence of β -lactones in the two *Disynaphia* species and in *Campovassouria* and *Grazielia* species on the one hand and their absence from *Acanthostyles* and *Symphiopappus* on the other is of some interest as it may relate to a comment by King and Robinson on p. 73 of their compendium on Eupatorieae (King

and Robinson, 1987) that “*Compovassouria* and *Grazielia* to some extent form a connecting series between the extremes of *Disynaphia* and *Symphiopappus*.” Significantly so far β -lactones have not yet been found in other species of Asteraceae.

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