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GERMACRANOLIDES FROM *INULA CAPPA*

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Key Word Index—*Inula cappa*; Compositae; Inuleae; sesquiterpene lactones; germacranolides.

Abstract—Authentic *Inula cappa* DC afforded a known and four unknown germacranolides related to the ineupatorolides as well as a new 2,3-dihydroxy-9-angeloxygermacra-4-en-6,12-olide. A collection previously described as *Inula cappa* which yielded only flavones was identified as *Blumea balsamifera* DC.

INTRODUCTION

In an earlier article [1], we reported on the isolation of a number of unusual flavones from what was thought to be *Inula cappa* DC. The observed chemistry, particularly the absence of sesquiterpene lactones, raised some doubts about the authenticity of this collection and indeed, submission of the material to the Botanical Survey of India, Shillong, revealed that we had been dealing with *Blumea balsamifera* DC. rather than with *Inula cappa*. We now describe the isolation from authentic *Inula cappa* DC of several germacranolides which are identical with or closely related to lactones previously found in some other Indian representatives of this genus [3–5]*.

RESULTS AND DISCUSSION

The various lactones were obtained in rather small amounts and were difficult to purify. One of the lactones, **1a** or its mirror image **2a** (for a discussion of the absolute stereochemistry of such compounds see [2, 3]) was found earlier as a minor constituent of *I. eupatorioides* [3]. Examination of its previously unreported 270 MHz ^{1}H NMR spectrum (Table 1) showed that the frequencies of the two angelyl moieties differed. Conversion to a monoacetate produced the characteristic spectral changes commented upon earlier [2] in connection with the acetylation of ineupatolide (**1c** or **2c**) but instead of a mixture of acetates as in the case of **1c**, only one acetate, **1b**, was produced. The location of the acetate shown in formula **1b** was confirmed by the ^{1}H NMR spectrum of **1b** in the presence of trichloroacetylisocyanate (TAI) [7] which exhibited no significant changes except for the paramagnetic shifts of H-14 and H-1a as a result of acylation of the remaining hydroxyl group on C-10.

A related lactone **3a** (or its mirror image **4a**) contained an extra hydroxyl group. Again the two angellate esters exhibited different ^{1}H and ^{13}C NMR frequencies (Tables 1 and 4). Acetylation with acetic anhydride–pyridine gave a monoacetate **3b**; use of acetic anhydride–boron trifluoride furnished a diacetate **3c** in which one of the two angelates had been isomerized to a tiglate†. The NMR spectra of **3a–c** contained no methyl doublet, hence C-4 was hydroxylated. This was confirmed by the ^{13}C NMR spectrum. The downfield shift of the H-3 and H-15 signals on conversion of **3a** to the monoacetate **3b** and the further downfield shift of the H-14 and H-1a signals on conversion to the diacetate **3c** indicated that, in contrast to the behaviour of **1a**, acetylation of **3a** initially esterifies the C-4 hydroxyl, probably for steric reasons, and subsequently the C-10 hydroxyl. Treatment of **3c** with TAI finally results in acylation of the C-5 hydroxyl as evidenced by further significant paramagnetic shifts of the H-6 and H-15 signals (Table 1) and the absence of an NOE between H-6β and H-15. The effect on H-15 indicates that the C-4 methyl group is α-orientated.

The ^{1}H NMR spectra of a third lactone and its monoacetate (Table 2) and extensive spin decoupling experiments which will not be detailed showed that it was an analogue (**5a** or the mirror image **6a**) of a diisobutyrate (**5c** or **6c** incaspitolide D) previously [5] isolated from *I. cuspidata*. The placement of the angelate residue at C-5 followed from the downfield shift (0.1 ppm) of the H-9 signal relative to its shift in **5c** (or **6c**). The CD curve exhibited a negative Cotton effect ($[\theta]_{308} - 3750$) due to the n, π^* transition of the ketone which obscured the lactone Cotton effect and was opposite in sign to the CD curve of ineupatorolide B (**7b**), of established absolute stereochemistry [3] but offered no immediate clue to the absolute stereochemistry of this lactone owing to the

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*Bohlmann and coworkers [6] recently found only thymol and isothymol derivatives, β-farnesene, squalene, caryophyllene oxide and four inositol tetraangelates in the aerial parts of *I. cappa*. In the light of our results, this collection may also have been misidentified.

†As far as we are aware isomerization of an angelate to a tiglate under such mild conditions has not been observed previously in a sesquiterpene lactone. Isomerization of angelic acid to tiglic acid accompanying the base-catalysed hydrolysis of an angelate has been reported [8].

Table 1. ^{1}H NMR data for **1a**, **b** and **3a–c** (270 MHz, $CDCl_3$, TMS as int. standard)*

H	**1a**	**1b**	**1b** + TAI	**3a**	**3b**	**3c**	**3c** + TAI
1a	obsc.	1.53 *m*	2.71 *m*	obsc.	obsc.	obsc.	2.68 *dd* (15, 3.5)
1b	obsc.	obsc.	1.51 *m*	obsc.	obsc.	obsc.	2.37 *ddbr* (15, 12)
2	4.37 *m*	4.51 *m*	4.54 *m*	4.41 *m*	4.34 *m*	4.33 *m*	4.64 *dddd* (12, 8, 4.5, 3.5)
3a	2.56 *m*	2.70 *m*	2.71 *m*	2.53 *dd*	3.40 *dd* (*br*)	3.39 *dd* (*br*)	3.23 *dd* (*br*) (14.5, 8)
3b	1.86 *m*	1.73 *m*	1.73 *m*	obsc.	obsc.	obsc.	2.22 *d* (14.5, 4.5)
4	2.34 *m*	3.28 *m*	3.30 *m*	—	—	—	—
6	5.11 *d* (8)	5.21 *d*	5.21 *d*	5.04 *d*	5.06 *d*	5.01 *d*	5.52 *d* (9.5)
7	3.94 *m*	4.05 *m*	4.04 *m*	4.06 *m*	4.09 *m*	4.13 *m*	4.24 *dddd* (9.5, 5.5, 3, 2.5)
8	4.76 *dd* (6.5)	4.72 *dd*	4.86 *dd*	4.77 *dd*	4.78 *dd*	4.86 *dd*	4.75 *dd* (5.5, 3.5)
9	5.24 *d* (5)	5.13 *d*	5.23 *dd*	5.30 *d*	5.30 *d*	5.38 *d*	5.13 *d* (3.5)
13a	6.22 *d* (3)	6.24 *d*	6.24 *d*	6.23 *d*	6.24 *d*	6.22 *d*	6.24 *d* (*br*) (3)
13b	5.58 *d* (3)	5.60 *d*	5.60 *d*	5.64 *d*	5.62 *d*	5.62 *d*	5.66 *d* (*br*) (2.5)
14†	1.40 *br*	1.41 *br*	1.79 *br*	1.42 *br*	1.42 *br*	1.73 *br*	1.72 *br*
15†	1.04 *d* (7)	1.11 *d*	1.10 *d*	1.28 *br*	1.53 *br*	1.48 *br*	1.87 *br*
3′	6.20 *q* (*br*) (7)	6.22 *q* (*br*)	6.24 *q* (*br*)	6.22 *q* (*br*) (7)	6.22 *q* (*br*)	6.96 *q* (*br*)	7.00 *q* (*br*)
4′†	1.99 *d* (*br*) (7)	2.02 *d* (*br*)	2.03 *d* (*br*)	2.00 *d* (*br*) (7)	2.01 *d* (*br*)	1.86 *d* (*br*)	1.86 *d* (*br*)
5′†	1.94 *br* (7)	1.95 *br*	1.92 *br*	1.92 *br*	1.92 *br*	1.84 *br*	1.87 *br*
3″	6.09 *q* (*br*) (7)	6.11 *q* (*br*)	6.13 *q* (*br*)	6.11 *q* (*br*) (7)	6.11 *q* (*br*)	6.13 *q* (*br*)	6.15 *q* (*br*)
4″†	1.93 *d* (*br*)	1.95 *br*	1.97 *d* (*br*)	1.96	1.96	1.99 *d* (*br*)	1.99 *d* (*br*)
5″†	1.93 *br*	1.92 *br*	1.90 *br*	1.96	1.96	1.93 *br*	1.91 *br*
Misc.		2.1 (Ac)	2.1 (Ac) 8.49 (NH)		2.13 (Ac)	2.13, 2.04 (Ac)	2.07, 2.01 (Ac) 8.42 (NH)

*Unmarked signals are singlets. Figures in parentheses are coupling constants.

†Intensity ≡ three protons.

different placement of the ketone function on the ten-membered ring.

Two more highly functionalized derivatives of **5a** (or **6a**) were the lactones **8a,b** (or **9a,b**) which differed from each other only in the nature of one of the esters. The distribution of functional groups on the ten-membered ring was clear from the ^{1}H NMR spectra (run in $CDCl_3$ and C_6D_6 to separate superimposed signals) and spin decoupling in the usual way (Table 2); the coupling constants also showed that the relative stereochemistry was as shown. A comparison of the chemical shifts of H-6 and H-8 in **8a** and **8b** shows that the angelate moiety of **8b** should be placed at C-8. The CD curve of **8a** was similar to that of **5a**, but exhibited a definite positive lactone Cotton effect. Hence we conclude that the absolute stereochemistry of these two compounds is like that of the ineupatorolides, i.e. as depicted in **8a,b**, and assume by analogy that the absolute stereochemistry of the non-hydroxylated lactone discussed in the previous paragraph is **5a**. The stereochemistry of the C-2 hydroxyl group could not be inferred from the coupling constants. In an attempt to shed light on this, **8a** was treated with TAI; surprisingly this resulted only in acylation of the tertiary hydroxyl group (see Table 1), possibly because of strong hydrogen bonding involving the hydroxyl at C-2 or hemiacetal formation between the ketone and the hydroxyl at C-9.

^{1}H and ^{13}C NMR spectra (Tables 3 and 4) of another fraction and extensive decoupling experiments showed that it was an inseparable mixture of two ineupatorolide-like lactones whose distribution of functional groups is shown in structures **10a,b** or **11a,b** or their mirror images. As the chemical shifts and coupling constants were generally similar to those found for the ineupatorolides (**7a–d**) [2, 3] and 8α-acyloxyineupatorolides of type **12** from *Dittrichia viscosa* [9], if allowance is made for the presence of the extra oxirane function, it was logical to assume the relative stereochemistry shown in **10a,b** with the oxirane ring fused *trans* due to the coupling constant of the oxirane protons*. On the other hand, reaction of the lactone mixture with TAI produced, in addition to the expected downfield shift of the H-15 signal, significant paramagnetic shifts of H-2, H-5, H-7, H-8 and H-14 (see Table 3) from which one might draw the inference that these protons are all situated on the same face of the 10-membered rings as the C-4 hydroxyl group. Since H-7 is α,

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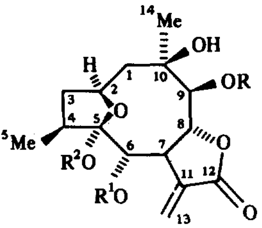
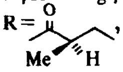
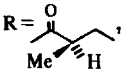
*Formulas ascribed to the lactones from *Dittrichia viscosa* [9] have been rewritten to conform to the absolute stereochemistry established for the ineupatorolides (**7**). In general, coupling constants of **7a–d** and **12** tally except for $J_{6,7}$ which is ~ 3 Hz for the ineupatorolides [2, 3] and 6.5 Hz for lactones of type **12** [9]. Whether this arises from a small difference in conformation or a more basic difference in stereochemistry is unclear. In lactone mixture **10a,b**, or **11a,b**, $J_{6,7}$ is 2 Hz comparable to the values in **7a,d**, $J_{7,13}$ is 1 Hz indicating a slight difference in lactone ring conformations from **7a–d** where $J_{7,13}$ is 2–2.5 Hz.

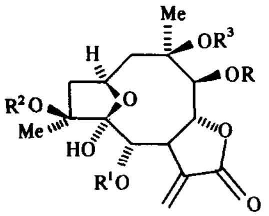


1a $R, R^1 = Ang, R^2 = H$

1b $R, R^1 = Ang, R^2 = Ac$

1c R =  , $R^1 = Ang, R^2 = H$

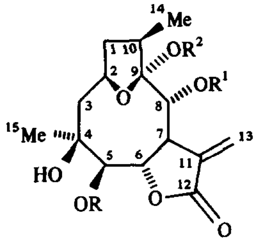
1d R =  , $R^1 = Ang, R^2 = Ac$



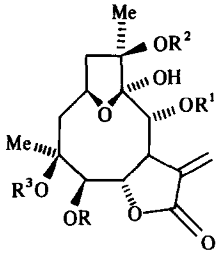
3a $R, R^1 = Ang, R^2 R^3 = H$

3b $R, R^1 = Ang, R^2 = Ac, R^3 = H$

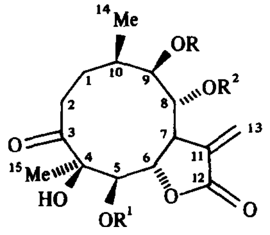
3c $R, R^1 = Ang, R^2, R^3 = Ac$



2a - d R, R^1, R^2 same as in **1a - d**



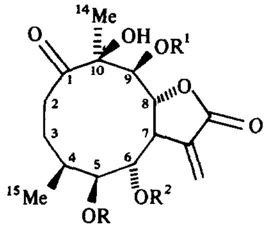
4a - c R, R^1, R^2, R^3 same as in **3a - c**



5a $R = 2-MeBu, R^1 = Ang, R^2 = H$

5b $R = 2-MeBu, R^1 = Ang, R^2 = Ac$

5c $R, R^1 = iBu, R^2 = H$



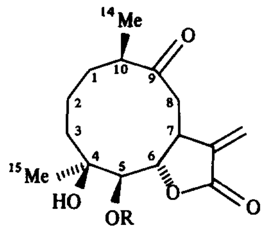
6a - c R, R^1, R^2 same as in **5a - c**

this would lead to the relative stereochemistry shown in **11a,b** which, while antithetical to previous experience in this genus, permits construction of a model which conforms equally well to the observed coupling constants. A better-informed decision between these two possibilities will have to await the acquisition of larger amounts of compounds of this type. The CD curve of the lactone mixture (see Experimental) exhibits in the ketone n,π^* region a positive Cotton effect which corresponds to that of ineupatorolide B [2]. This suggests that the absolute as well as the relative stereochemistry is that shown in **11a, b**; the lactone Cotton effect may also be positive but is obscured by a rapidly ascending curve rather than descending one as is the case for **7a**, possibly because of the presence of the angelyl moiety.

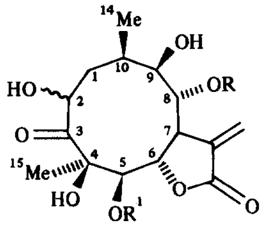
^1H and ^{13}C NMR spectra (Tables 3 and 4) of the last lactone isolated in very small amount only established formula **13a**, with the 4,5-double bond *trans* ($J_{6,7} = 10$ Hz, no NOE between H-15 and H-5) and the lactone ring fusion also *trans* ($J_{7,8} = 10$ Hz). If the molecule assumes the crown conformation characteristic of 1(10),4-germacradien-6βH,12-olides, the observed coupling constants conform with the proposed stereochemistry at C-2, C-3, C-9 and C-10 depicted in the formula. The negative lactone Cotton effect ($[\theta]_{260} - 2800$) is in accordance with the empirical rule [10] applicable to such compounds. The stereochemistry of the 2,3-diol function is opposite to that found in euperfolitin [11] and 3β-hydroxyeupaserrin [12].

EXPERIMENTAL

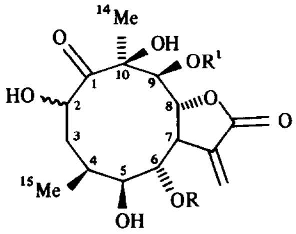
Aerial parts of *Inula* cappa DC (1.5 kg) collected in the Khasi Hills, Meghalaya, India, and identified by the Botanical Survey of



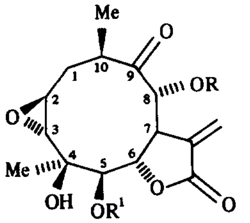
	R
7a	2-MeBu
7b	Ang
7c	iBu
7d	Sen



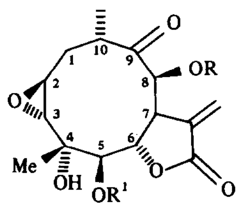
8a R = Ang, R^1 = 2-MeBu
8b R, R^1 = Ang



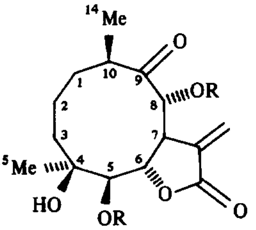
9a, b R, R^1 same as in **8a, b**



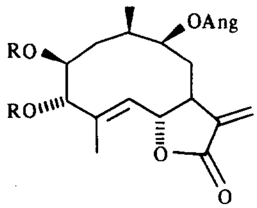
10a R = Ang, R^1 = 2-MeBu
10b R, R^1 = Ang



11a R = Ang, R^1 = 2-MeBu
11b R, R^1 = Ang



12



	R
13a	H
13b	Ac

India, Shillong, Meghalaya, were extracted with $CHCl_3$ in a Soxhlet apparatus until the extract was colourless. After removal of $CHCl_3$ at red. pres. the residue was dissolved in 300 ml MeOH containing 10% H_2O, allowed to stand overnight and filtered. The filtrate was washed with petrol (bp 60–80°, 5 × 250 ml), the MeOH portion was concd at red. pres. and the residue was thoroughly extracted with $CHCl_3$ (6 × 200 ml). The washed and dried extract was evaporated at red. pres. and the residue (15 g of 20 g total) was chromatographed over 500 g of silica gel (60–120 mesh, B.D.H., India), 200 ml fractions being collected as follows: Fractions 1–33 (C_6H_6), 34–60 (C_6H_6-EtOAc, 15:1), 61–104 (C_6H_6-EtOAc, 9:1), 105–139 (C_6H_6-EtOAc, 5:1), 140–156 (C_6H_6-EtOAc, 3:1), 157–182 (C_6H_6-EtOAc, 2:1), 183–210 (C_6H_6-EtOAc, 1:1), 211–232 (C_6H_6-EtOAc, 1:2), 233–240 (EtOAc), 241–250 (EtOAc–MeOH, 49:1), 251–255 (EtOAc–MeOH, 19:1), 256–260 (EtOAc–MeOH, 9:1), 261–262 (EtOAc–MeOH, 4:1), 263–264 (EtOAc–MeOH, 3:2), 265–266 (EtOAc–MeOH, 1:1) and 267–268 (MeOH).

Table 2. ^{1}H NMR data of **5a** and **8a, b** (270 MHz, $CDCl_3$, TMS as int. standard)*

H	**5a** (60°)	**8a**	**8a** (C_6D_6)	**8b**	**8b** (C_6D_6)	**8b** + TAI
1a	1.82 *m*	2.73 *dd*	2.41 *dd* (12, 7.5)	2.73 *dd* (*br*)	2.42 *dd*	2.81 *dd*
1b		obsc.	obsc.	obsc.	1.11 *m*	obsc.
2a	3.73 *ddd* (18, 11, 5.5)	5.01 *m*	4.53 *d* (7)	4.99 *m*	4.55 *d*	4.86 *d*
2b	2.27 *td* (5, 18)	—	—	—	—	—
5	5.42 *d* (*br*) (9)	5.01 *m*	5.34 d (10)	4.99 *m*	5.34 *d*	5.02 *d*
6	4.76 *dd* (9, 6)	5.01 *m*	4.71 *d* (*br*) (10)	4.99 *m*	4.71 *d*	5.22 *d* (*br*)
7	3.02 *ddd* (*br*) (6, 3, 3)	2.67 *d* (*br*)	2.56 *d* (*br*) (10.5)	2.66 *d* (*br*)	2.58 *d* (*br*)	2.63 *d* (*br*)
8	4.31 *d* (*br*) (10)	5.39 *dd*	5.31 *dd* (10.5, 5.5)	5.28 *dd*	5.20 *dd*	5.30 *dd*
9	5.04 *dd* (10, 1.5)	4.17 *dd*	3.74 *dd* (8.5, 5.5)	4.11 *dd*	3.75 *dd*	4.09 *dd*
10	2.22 *m*	2.37 *m*	2.11 *m* (9.5, 7.5, 6)	2.33 *m*	2.12 *m*	2.30 *m*
13a	6.44 *d* (3)	6.33 *br*	6.10 *br*	6.37 *br*	6.17 *br*	6.37 *br*
13b	5.63 *d* (3)	5.61 *br*	4.91 *br*	5.64 *br*	4.99 *br*	5.68 *br*
14†	1.01 *d* (7)	1.16 *d*	0.77 *d* (6)	1.18 *d*	0.81 *d*	1.16 *d*
15†	1.32 *br*	1.38 *br*	1.32 *br*	1.38 *br*	1.33 *br*	1.79 *br*
3′	6.15 *q* (*br*) (7)	6.16 *q* (*br*)	5.76 *q* (*br*) (7)	6.16 *q* (*br*)	5.76 *q* (*br*)	6.19 *q* (*br*)
4′†	2.00 *d* (*br*) (7)	2.01 *d* (*br*)	2.03 *d* (*br*)	2.01 *d* (*br*)	2.04 *d* (*br*)	2.01 *d* (*br*)
5′†	1.95 *br*	1.97 *br*	1.94 *br*	1.97 *br*	1.95 *br*	1.95 *br*
2″	2.48 *sext* (7)	—	—	2.27 *sext* (7)	1.88 *sext*	2.30 *m*
3″	1.73 *m*, 1.53 *m*	6.13 *q* (*br*)	5.61 *q* (*br*) (7)	1.87–1.44 *c*	1.46, 1.11 *m*	1.87–1.48 *c*
4″†	0.96 *t* (7)	1.95 *d* (*br*)	1.83 *d* (*br*) (7)	0.84 *t* (7)	0.64 *t*	0.84 *t*
5″†	1.20 *d* (7)	1.85 *br*	1.52 *br*	1.11 *d*	0.87 *d*	1.12 *d*

*Unmarked signals are singlets.

†Intensity three protons.

Table 3. ^{1}H NMR data for **11a, b** and **13a, b** (270 MHz, $CDCl_3$, TMS as int. standard)

H	**11a**	**11b**	**11a** (C_6D_6)	**11b** (C_6D_6)	**11a, b** + TAI	**13a**	**13b**
1a	2.32 *m*	2.32 *m*	1.96 *m*	1.96 *m*	2.33 *m*	1.68 *dd* (*br*) (14, 3.5)	1.73 *dd* (*br*) (14, 3.5)
1b	1.88–1.44 *c*	1.88–1.4 c	obsc.	obsc.	obsc.	1.44 *m*	1.62 *m*
2	3.30 *m*	3.30 *m*	3.37 *m*	3.37 *m*	3.61 *m*	4.03 *ddd* (7.5, 3.5, 3.5)	5.35 *ddd* (7.5, 3.5, 3.5)
3	2.71 *d* (2)	2.74 *d*	2.12 *d*	2.07 *d*	2.84, 2.81 *d*	4.27 *d* (7.5)	5.50 *d* (7.5)
5	4.86 *m*	4.86 *m*	4.90 *d* (8)	4.88 *d*	5.12 *m*	5.51 *d* (*br*) (10)	5.74 *d* (*br*) (10)
6	4.63 *d* (*br*) (8)	4.66 *d* (*br*)	4.80 *dd* (8, 2)	4.78 *dd*	4.73 *m*	4.59 *t* (10)	4.56 *t* (10)
7	3.30 *m*	3.30 *m*	3.07 *d* (*br*) (9)	3.11 *d* (*br*)	3.61 *m*	2.42 *m*	2.42 *m*
8	4.86 *m*	4.86 *m*	5.08 *d* (9)	5.15 *d*	5.12 *m*	2.10 *c*, 1.51 *m*	2.14 *c*, 1.44 *ddd* (14, 11, 5)
9	—	—	—	—	—	4.72 *dd* (*br*) (11, 3)	4.74 *dd* (*br*) (11, 3)
10	3.13 *m*	3.13 *m*	2.65 *m*	2.65 *m*	3.17 *m*	2.10 *c*	2.14 *c*
13a	6.45 *br*	6.45 *br*	6.39 *d* (1.5)	6.35 *d*	6.42 *br*	6.26 *d* (3)	6.28 *d* (3)
13b	5.90 *d* (1)	5.92 *d*	5.51 *br*	5.51 *br*	5.91 *br*	5.68 *d* (3)	5.67 *d* (3)
14*	1.23 *d* (7)	1.23 *d*	0.93 *d* (7)	0.91 *d*	1.47 *d*, 1.47 *d*	1.18 *d* (7)	1.09 *d* (7)
15*	1.34 *br*	1.34 *br*	1.15 *br*	1.15 *br*	1.91 *br*	1.86 *d* (1.5)	1.87 *d* (1.5)
3′	6.25 *q* (*br*) (7)	6.18 *q* (*br*)	†	†	6.23 *q* (*br*)	6.09 *q* (*br*) (7)	6.08 *q* (*br*) (7)
4′*	1.98 *d* (*br*) (7)	1.98 *d* (*br*)			2.01 *d* (*br*)	1.97 *d* (*br*) (7)	1.97 *d* (*br*) (7)
5′*	1.94 *br*	1.94 *br*			1.91 *br*	1.87 *br*	1.86 *br*
2′	2.45 *sext* (7)		2.11 *m*		2.47 *sext*		
3′	1.84–1.44 c	6.18 *q* (*br*) (7)	1.49, 1.25 *m*		1.80–1.45 *m*		
4″*	0.90 *t* (7)	1.98 *d* (*br*) (7)	0.70 *t* (7)		0.91 *t*		
5″*	1.19 *d* (7)	1.94 *br*	0.96 *d* (7)		1.19 *d*		
Misc.					8.56 (NH)		2.06 (Ac)

*Intensity = three protons.

†Signals of three angelyl residues at 6.21 *q* (*br*), 1.99 *d* (*br*) and 1.91 *br*, 5.67 *q* (*br*), 2.01 *d* (*br*) and 1.90 *br*, 5.70 *q* (*br*), 1.85 *d* (*br*) and 1.90 *br*.

Table 4. ^{13}C NMR data for **3a**, **11a**, **b** and **13a** (67.89 MHz, $CDCl_3$, TMS as int. standard)

C	**3a**	**11a**	**11b**	**13a**
1	47.88 *t*	33.67 *t*	33.67 *t*	31.67 *t*‡
2	69.90 *d*	60.26 *d*	60.61 *d*	74.65 *d*‡
3	46.58 *t*	53.04 *d*	52.89 *d*	82.57 *d*‡
4	79.22	70.79	70.79	141.18
5	105.59	76.91 *d*	76.76 *d*	126.53 *d*
6	74.93 *d*	75.34 *d*	75.46 *d*	79.02 *d*‡
7	46.04 *d*	45.94 *d*	45.99 *d*	45.71 *d*
8	77.21 *d*	72.27 *d*	72.32 *d*	28.74 *t*
9	80.31 *d*	208.66	208.66	80.30 *d*‡
10	73.04	38.69 *d*	38.69 *d*	28.88 *d*
11	134.06	132.79	132.88	138.48
12	169.34	167.88	167.88	169.83
13	125.86 *t*	127.13 *t*	126.99 *t*	120.01 *t*
14	25.34 *q*	18.27 *q*	18.04 *q*	12.24 *q*
15	21.62 *q*	23.95 *q*	23.84 *q*	20.85 *q**
1′	167.62	175.27		167.53
2′	127.06	40.72 *d*		127.86
3′	139.02 *d*	26.50 *t*		138.39 *d*
4′	15.83 *q*	11.57 *q*		15.92 *q*
5″	20.60 *q*	16.38 *q*		20.62 *q**
1″	166.45	167.10	165.88†	
2″	126.62	126.70	125.82 *d*†	
3″	141.50 *d*	140.30 *d*	142.82 *d*†	
4″	15.93 *q*	15.89 *q*	15.98 *q*†	
5″	20.32 *q*	20.42 *q*	20.42 *q*†	

*Assignments may be interchanged.

†Intensity reflects presence of two angelates.

‡Assignments confirmed by selective spin decoupling.

Fractions 93–104 (0.37 g) were combined and purified by prep. TLC (C_6H_6–EtOAc, 9:1, two developments, thickness of plate 0.5 mm). The most polar spot had mp 154–156° (EtOAc); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575, 1775, 1725 (*br*), 1650 and 1125 was a 4:3 mixture of **11a** and **11b**. ^{1}H and ^{13}C NMR: Tables 3 and 4; CD (MeOH): $[\theta]_{330}+2200$ (sh), $[\theta]_{315}+4470$ (max), $[\theta]_{313}+4420$ (min), $[\theta]_{310}+4560$ (max), $[\theta]_{300}+3800$ (sh), $[\theta]_{279}+1750$ (min), $[\theta]_{230}+7900$ (last reading). [Calc. for $C_{25}H_{34}O_9$ (**11a**): MW, 478.2203. Found: MW(MS) 478.2204. Calc. for $C_{25}H_{32}O_9$ (**11b**): MW, 476.2046. Found: MW(MS), 476.2045]. In the low resolution MS, significant peaks were observed for **11a** at *m/z* (rel. int.) 378 (0.2), 85 (25) and 57 (55), for **11b** at *m/z* (rel. int.): 376 (1), 276 (0.5) and 83 (100). A second slightly less polar material from fractions 93–104 (20 mg) was also a mixture of **11a** and **11b** in somewhat different proportions and remained a gum.

Fractions 118–123 (0.40 g) were combined and purified by prep. TLC (C_6H_6–EtOAc, 4:1) to give 0.10 g **5a** as a gum, CD (MeOH): $[\theta]_{308}$–3750 (neg. max) $[\theta]_{272}$ 0, $[\theta]_{259}+860$ (max); ^{1}H NMR: Table 2. [Calc. for $C_{25}H_{36}O_9$: MW, 480.2359. Found: MW(MS), 480.2359]. Other significant ions in the NCI MS were at *m/z* (rel. int.): 462 (1.5), 380 (20), 378 (22), 362 (5), 360 (2), 278 (100) and 260 (16). Acetylation of 25 mg **5a** with Ac_2O–pyridine in the usual fashion gave 25 mg **5b** as a gum.

Prep. TLC of fractions 124–131 (0.35 g, C_6H_6–EtOAc, 2:1, 5 developments) gave as the more polar substance **8b** (20 mg), mp 1749178° (EtOAc); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1775, 1725–1700 (*br*); ^{1}H NMR: Table 2. MS *m/z* (rel. int): no $[M]^+$, 478 (4), 396 (0.1), 394 (0.1), 378 (0.1), 294 (0.2), 85 (35), 83 (100), 57 (72) and 55 (38).

The less polar material **8a** from fractions 124–131 appeared to undergo partial conversion to a hemiacetal on standing and was repurified by TLC (C_6H_6–EtOAc, 4:1). Crystallization from EtOAc afforded solid **8a** (40 mg), mp 137–139°, CD (MeOH) $[\theta]_{315}-3590$ (neg max), $[\theta]_{278}$ 0, $[\theta]_{255}+3206$ (sh), $[\theta]_{240}$ approx. +6000 (last reading). ^{1}H NMR: Table 2; CIMS *m/z* (rel. int.): 495 $[M+1]^+$, (6), 477 (84), 395 (8), 377 (6), 295 (2), 277 (6) and 101 (100).

Prep. TLC of fractions 132–148 (0.45 g) (C_6H_6–EtOAc, 2:1) gave 0.20 g **1a**, mp 178° (EtOAc), identical in all respects (TLC, IR, NMR, MS) with **1a** from *I. eupatorioides* [3]. The monoacetate was identical with acetate **1b** described earlier. The previously unreported 270 MHz ^{1}H NMR spectra of these compounds are listed in Table 1.

Fractions 169–174 (0.20 g) were purified by prep. TLC (C_6H_6–EtOAc, 1:1) to give 100 mg of gummy **13a**, IR ν_{max}^{film} cm^{-1}: 3500, 1770, 1700, 1650, 1225, 1150, 1075, 1050, 975 and 750; $\nu_{max}^{CHCl_3}$ 3400, 1765 and 1705; CD (MeOH) $[\theta]_{260}-2790$ (neg max); ^{1}H and ^{13}C NMR: Tables 3 and 4; CIMS *m/z* (rel. int.): 365 $[M+1]^+$ (2.4), 347 (3), 265 (47), 247 (23) and 101 (100). Acetylation of 5 mg **13a** with Ac_2O–pyridine followed by the usual work-up gave 5 mg of diacetate **13b**: IR bands at 1765 and 1735 cm^{-1} (very strong); ^{1}H NMR: Table 3.

Purification of fraction 183–192 (0.45 g) by prep. TLC ($CHCl_3$–MeOH 19:1) furnished 0.25 g of non-crystalline **3a**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575, 1760, 1710 (*br*) 1650, 1125 and 900; CD (MeOH) $[\theta]_{265}+564$ (max); CIMS *m/z* (rel. int.) 495 $[M+1]^+$ (6.4), 477 (20), 395 (95), 377 (22), 295 (11), 277 (10) and 101 (100); ^{1}H and ^{13}C NMR: Tables 1 and 4. Acetylation of 30 mg **3a** with Ac_2O–pyridine followed by the usual work-up gave 30 mg of gummy **3b**; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 1765, 1725 and 1645; ^{1}H NMR: Table 1; MS *m/z* (rel. int.): 536 $[M]^+$, 518 (0.2), 476 (0.5), 436 (0.9), 376 (0.9), 276 (0.9) and 83 (10). Acetylation with Ac_2O–BF_3 afforded **3c** : ^{1}H NMR: Table 1; MS *m/z* (rel. int.): no $[M]^+$, 560 $[M-18]^+$ (0.1), 518 (0.4), 478 (1.4), 458 (0.2), 418 (0.5), 358 (0.7), 258 (1.1) and 83 (100).

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