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SESQUITERPENE LACTONES AND OTHER CONSTITUENTS OF *ARNICA ACAULIS*

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Key Word Index—*Arnica acaulis*; Heliantheae; Compositae; helenanolides; melampolides; *trans*-fused guaianolides; sesquiterpene lactones; flavonoids.

Abstract—Chemical investigation of the aerial parts of *Arnica acaulis* resulted in isolation of 12 known helenanolides, one new melampolide baileyin acetate and the *trans*-fused guaianolides florilenalin acetate and 11α*H*,13dihydroflorilenalin acetate as well as other relatively common plant constituents. The implications for the biogenesis of helenanolides and the chemotaxonomic situation in *Arnica* are discussed.

INTRODUCTION

Aranica (Compositae) is a circumboreal predominantly montane genus of about 32 species most of which are confined to western North America [1]. Its tribal position, traditionally within the Senecioneae, has been the subject of considerable discussion [2–4]. On morphological, serological and chemical grounds it has been argued that its affinities are with the Heliantheae rather than with the Senecioneae; thus the most recent treatment of Heliantheae [5] includes *Arnica* and its close relatives in subtribe Chaenactidinae which in turn appears to be closely related to subtribe Gaillardiinae.

The chemical evidence which has been adduced in support of this relationship [5] includes *inter alia* the discovery [6–8] in *A. foliosa* Nutt. [*A. chamissonis* Less. ssp. *foliosa* (Nutt.) Maguire] and *A. montana* L. of sesquiterpene lactones of the helenanolide type which are characteristic constituents of Gaillardiinae. Because of the role which *Arnica montana*, the only member of the genus found in Europe, plays in European popular medicine its chemistry and that of a few other *Arnica* taxa has been studied more thoroughly in recent years [9–22]. This has resulted in the isolation of an additional number of helenanolides with the biological effects of the drug being attributed primarily to helenalin (**1a**) and some of its derivatives.

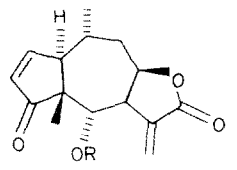
The only *Arnica* species found in North America east of the Mississippi and south of the Adirondacks is *A. acaulis* (Walt.) B.S.P. According to Maguire [1] it has no near relative in North America while its general habitat and character of pubescence strongly suggest it to be an offshoot of European *A. montana*. It was therefore of interest to compare the chemistry of the two species. In the present report we describe isolation from *A. acaulis* of the sesquiterpene lactones **1a-e**, **2a–e**, **3**,**4**,**5b**,**6b** and **7b**, the thymol derivative **9a** and the flavones pilloin (**10a**) and salvigenin (**11**).

RESULTS AND DISCUSSION

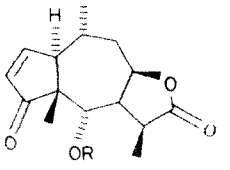
Extraction of the aerial parts of *A. acaulis* furnished a complex mixture of the known helenanolides **1a–e**, **2a–e**, **3** and **4** which were identified by comparison with authentic samples or by comparison with ^{1}H NMR spectra of esters of helenalin (**1a**) and 11α*H*,13-dihydrohelenalin(**2a**) recorded in the literature. Lactones **3** (mexicanin I) and **4** (11α*H*,13-dihydromexicanin I) have not been reported previously from *Arnica*.

A new crystalline lactone was the acetate **5b** of a C-8 lactonized melampolide baileyin (**5a**) from *Baileya pleniradiata* and *B. multiradiata* [23, 24], as shown by the ^{1}H and ^{13}C NMR spectra (Tables 1* and 2), extensive decoupling and the observation of a significant NOE between H-1 and H-14 (Table 3). The H-2β, H-8β-stereochemistry originally suggested [24] for baileyin was speculative due to uncertainty about the conformations adopted by C-8 *cis*- and C-8 *trans*-lactonized melampolides. Since then it has been shown in the case of schkuhriolide and its derivatives [25–27] that the conformation of such C-8 *cis*-lactonized melampolides is similar to C-6 *trans*-lactonized members of this class, i.e. $_1$D$_{14}$, ^{15}D$_5$ [28], and gives rise to values of $J_{7,13} < 3$ Hz, whereas C-8 *trans*-lactonized melampolides exemplified by frutescin [29, 30] assume the ^{1}D^{14}, ^{15}D$_5$ conformation. Associated with this conformation of C-8 *trans*-lactonized melampolides are values of $J_{7,13} > 3$Hz, an upfield shift of H-8 to δ3.8–4.0† and relatively large values of $J_{7,8}$[29–31]. All this is clearly the case for **5a,b** which are therefore C-8 *trans*-lactonized. Inspection of the model constructed in accordance with Fig. 1 of ref [30] then requires β-orientation of the 2-hydroxy or acetoxy group to accommodate the values of $J_{1,2}$,$J_{2,3a}$ and $J_{2,3b}$; moreover the model and the H-2α,H-8β stereochemistry deduced from it for **5a,b** are in highly satisfactory agreement with the NOE difference spectrum of **5b**

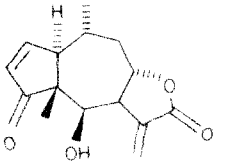
*Table 1, column 1 of ref. [24] which lists the ^{1}H NMR spectrum of baileyin contains an erroneous assignment and several misprints. For this reason the correct NMR spectrum of **5a** is reproduced in Table 1.



	R
1 (a)	H
(b)	MeAcr
(c)	Tig
(d)	Sen
(e)	2-Me Bu
(f)	Ac



	R
2 (a)	H
(b)	MeAcr
(c)	Tig
(d)	Sen
(e)	2-Me Bu
(f)	Ac



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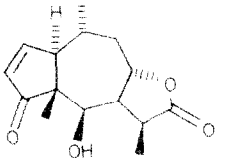

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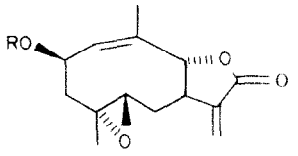
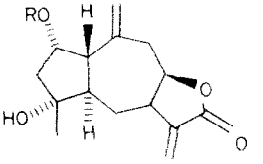
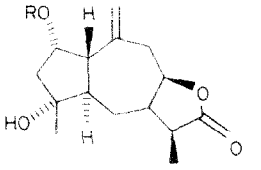


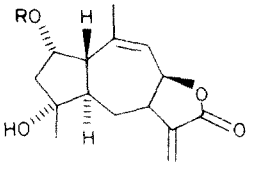
	R
5 (a)	H
(b)	Ac



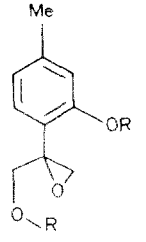
	R
6 (a)	H
(b)	Ac



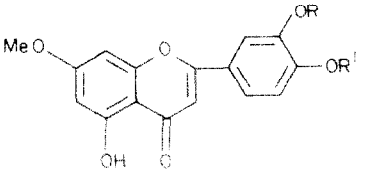
	R
7 (a)	H
(b)	Ac



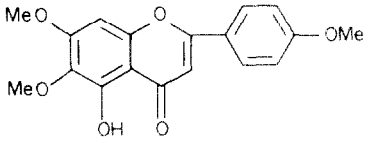
	R
8 (a)	H
(b)	Ac



	R
9 (a)	*i*-Bu
(b)	*i*-Val



	R	R'
10 (a)	H	Me
(b)	Me	H



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†A multiplet appearing at δ3.75 in the ^{1}H NMR spectrum of the C-8 *trans*-lactonized melampolide soulangianolide B has been ascribed to H-7[32]. The chemical shift of the H-8 signal was not reported. In the light of the preceding discussion it appear to us that the δ3.75 signal of soulangianolide B is associated with H-8 and that the H-7 signal is found at higher field as usual.

detailed in Table 3. The CD curves of **5a** and **5b** exhibit positive maxima for the n,π^* -transition of the α,β-unsaturated lactone chromophore, hence the formulas also represent the absolute configurations (2*R*, 4*R*, 5*R*, 7*R*, 8*S*) of these compounds.

Table 1. ^{1}H NMR data for compounds **5a**, **5b**, **6a** and **7b** (270 MHz, $CDCl_3$)

Hydrogen	5a*	5b	6b	7b‡
1	5.33 *br d* (10)	5.28 *br d* (10)	1.93 *br d* (15)	1.90 *br d* (15)
2	4.69 *m* (10, 10, 6)	5.60 *dt* (6, 10)	5.29 *br dd* (6, 2.5)	5.16 *br t* (5.5)
3α	2.62 *dd* (12, 6)	2.58 *dd* (11, 6)	2.20 *dd* (16, 6)	
3β	1.27 *dd* (12, 10)	1.33 *t* (11)	~2.06	
5	2.37 *br d* (12)	2.73 *dd* (10, 1)	~2.18	
6α	2.33 *br d* (15)	2.39 *br d* (15)	~2.10	
6β	1.4 *m*	1.46 *dt* (15, 10)	1.53 *m*	
7	2.85 *m*	2.95 *m* (10, 6.5, 3.3, 2.9)	3.24 *m*	3.06 *m*
8	4.05 *dd* (12, 9)	4.06 *ddd* (10.5, 6.5, 1.5)	4.62 *br ddd* (11, 8, 4)¶	4.55 ddd (11, 8, 3.5)
9α	2.47 *t* (12)	2.46 *dd* (13, 10.5)	2.72 *br dd* (13, 4)¶	
9β	2.79 *br d* (12)	2.79 *br d* (13)§	2.32 *tt* (13, 11)	
13a	6.37 *d* (3.5)	6.35 *d* (3.3)	6.30 *d* (2.9)	2.50 *m* (H-11)
13b	5.67 *d* (2.7)	5.67 *d* (2.9)	5.69 *d* (2)	1.19 *d* (7)†
14	1.85 *br* (1)†	1.95 *br d* (1)†	5.07 *br*	5.11 *br*
			4.89 *br*	5.01 *br*
15†	1.18	1.20 *br*	1.22 *s*	1.19 *s*
Ac†	–	2.03 *s*	2.06 *s*	2.08 *s*

°Taken from ref. [24] with corrections.
†Intensity three protons.
‡Taken from mixture with **6b**.
§Long range coupled to H-14.
‖$J_{6a,7}$ 2Hz, $J_{6b,7}$ = 12Hz.
¶Also coupled to H-14a at δ5.07.

Table 2. ^{13}C NMR data for compounds **5b** and **6b** (67.89 MHz, $CDCl_3$)

Carbon	5b	6a
1	127.87 *d*	53.34 *d*†
2	68.67 *d**	73.89 *d*
3	46.93 *t**	49.19 *t*
4	59.93 *s*	78.50 *s*
5	66.10 *d**	51.69†
6	43.23 *t*	29.64 *t**
7	46.23 *d*	39.66 *d*
8	83.61 *d**	80.33 *d**
9	30.98 *t**	29.87 *t**
10	138.94 *s*	139.94 *s*‡
11	133.03 *s*	139.27 *s*‡
12	168.63 *s*	169.68 *s*
13	121.81 *t*	122.54 *t*
14	18.18 *q**	115.58 *t*
15	17.14 *q**	25.32 *q*
Ac	170.16 *s*	170.55 *s*
	20.99 *q*	21.28 *q*

*Assignment confirmed by single frequency decouping.
†,‡Assignments may be interchangeable.

Table 3. NOE difference spectrum of compound **5b**

Saturation	Observed NOE (%)
H-1	3β (8.3)
	14 (8.3)
	15 (7)
	Ac (8.3)
H-2 and H-13b	3α (11.4)
	5 (11.4)
	6α (11.3)
	9α (11.3)
H-8	6β (8.2)
	9β (8)
	14 (12.3)
	15 (8.2)
H-14	1 (6.7)
	8 (13)
H-15	8 (8.9)

Two additional non-crystalline lactones, the second obtained only in admixture with the first, were **6b** and its 11,13-dihydro-derivative 7b. That these substances were C-8 lactonized guaianolides with a tertiary hydroxyl group on C-4 or C-10 and an exocyclic methylene group on C-10 or C-4 was evident from the ^{1}H NMR spectra (Table 1), the ^{13}C NMR spectrum of **6b** (Table 2) and extensive decoupling in the usual way, beginning with irradiation at the frequencies of H-13a,b, which established the location of the H-7 signal and eventually led to formulation of the entire sequence C-3, C-2, C-1, C-6, C-7, C-8, C-9. As H-8 under the lactone oxygen and one of the two C-9 protons were both coupled to one of the two non-conjugated vinylic protons, the exocyclic methylene group was attached to C-10. The *trans*-fusion of the bicyclo(5,3,0) system followed from the very large coupling constants involving H-1 and H-5, with the remaining features of the stereochemistry also being deduced from the coupling constants. Thus **6b** was a double bond isomer of pleniradin acetate (**8b**), a derivative

oi pleniradin 18a) from *Bailey pleniradiata* [33.1 and *multiradiata* [34], whose siructure has been deduced by X-ray analysis [24] IFor the IH NMR spectrum of 8b. scc Table 1. column 2 of ref. [24]. A search of the literalurc **then** re~ealed that 6b **and 7b,** although nea as natural products, had been prepared earlier Irom floiilenalin **(6al,** resp. dih)droflorflenalin (7a). t~o minor constituents ota *tteh'nium autumna/e* collection Iiom north } lorida u ho,~c structure had also bccn establmhed cryslaltographicall 3 [>, 3q,

Our discovery el 6b and 7b in ,*4. a~uu/i,~* is lhe second instance in which representatives of lhc tal~ laclouc t3,pes postulated to lie on the biogenetic pathway to helenanolidos [37] ha~c been isolated from the satnc collection as the presumed end producis, the first being lhc isolatiori ol 6a and 8a from *Baileya* species [24]. Indeed the ~l)"~ ~SD5 conlormation deduced lor 5a arid 5b [> cxaclly thai ,ahose c)clization would bc expected io bad loa *lfitt.5:H-t-tran>fuscd* guainolide intcrmcciiatc and thence to a ('-8 *trans-lactonlzcd* hetenanolklc cl Upe 3 or 4 Howexcr, extension oi the proposal to biogenesis ol **('-X** c/s-lactonized helenanolides nmv prcsenls dillicuhic~ since, if,xhat holds liue lo~ the conformatlon o! ~,chkuh-riolide and its relatives can bc cxlcndcd lo (-8 <l.v lactonizcd 4.5 epox}melampolidcs, c3cil~,ation o~ their, lo*~ cnergy ~D~<,. ~D~ coilli~rmei., would lead to I,~H,5~H c/s-|used guaianolides, not to compounds o~ t)pc 6 or 8. The difliculb could bc o~ercome b3' invokln~ the intcr~cntion, under cnzymatic comrol, ol higher energy ('-8 c/s-lactonizcd ~l)~;. ~[)> 4.5-epoxym¢tam-polidc oi 1[)~¢. ~SD5 4.5-cpoxygermacr-l(ltt)-cllohdc conformers* or by assuming ttiat lactone ling l\~rmalion does not necessarily precede cyclizalion, in which casc the conformational restrictions imposed on the lo-men~bered ring precursor might be less rigid.

Ihc chemistry *ot A. acau/is* is ui line wiih ihat oi ell'i;* *A rtficu* laxa (/l. *D~olltltltl, .'t. WJlODllXsOt175*:~ti bspccics aild ,4 *long(/olia)* whose lacione chemi.qry has been In~ estigatcd [6 18, 20. 2t] m that ihc t~pe> el hclenanohdc isolated lrom it seem lypical oi the genus. Minor dill)rences exist chiet among which is the presence in fl~c ~arious .~ub-species of *A, chamissonis* of 2,4-dih$ drox,, hclenanolides and their apparent absencc in *A. ,~c.l&~. 4. A,Iwi/o/ia* and 4 *montana.* Also tloleworlh} is the apparcm absence m 4 *acaulis,* although looked \or. el If and 2f which arc present in alnlost all other *.4rnicu* taxa in; c:,ngated ,~ lat tile presence, so lar unique in *,,trnl~d.* ~:~ *(-,~ trmls-*lactonized hclenanohdes, and the dctection ol mclampo-lides and n'an.~-iused guaianolides presumed lolic on thc biogenetic path~a~ to the helenanolidcs lound in mc genus. Howcxer. information on die chcm>,tCr o~ the genus available so lar seems to pro~,ide little evidence to or against the proposal that. wilhJn 4rm~ a..4. *m<mnma* ~s the species most ctosch related *to A. a~.m/iv*

EXPERIME%'I AI.

E.xtraction o/Arnica acaulis Abo~c ground paH,~ol .4 at auu,~ **(Walt.)B.Sf'..v,t** 1.5kg, coll¢ctcdb3 John B Nelson on 2 Ma;

1986 in Clarendon (_o.. S.(t~oucher~ oil deposh m the herbaria ol]hc Univer~il3 ol St;uth ('asolma and Florida Stale [Jm,,ersilyl ~,¢re extracted ~ith ('}1('1.~The u.~uat ~ork-up [40] all, rded 14g ol crude gum which v~;t>adsorbed on 40 got S~gel alld chromatographcd ovc~ a ~,dumn conhiimna)fit)g ol lhc same adborbeF!t set iB ('ll ( ].. ql)(}nil „! title;It haclion~ being ~.~,llccited ~;~ lollot~): t .4 I('tt (i.,. 5 /~ tMc2(() Ctt2t-12 t:24k]4 {7 (Me~('() ('H-('1- ~ 4-). I,s 2l iiMc2('() t'tt:('12 **~:23L** 2"~ 2~ IMc;(() (H,('I 1'~ _t~ . ~ (\1c,(t) ('H,('[, !?L ~b 35 Me:(() (H:(i 1:4~ .~ ~7 I\1c~(t) ('H:CI-4 3:"b.~ 41 MuX () ¢'1t.(i:2 :a.,42 45`lMc:('O ~,lij.'I.: iiL 46 49 **Mlc.('() ('H tl. 5** 21 ',,,i ~,; **~\1¢:((1 ( ]t-(12 4, t~.**

monm>rcd b~ TL(a~al :H NMR ~pcctromcu)

It, I S ,x.crCd~scardcd] ~, '} I~ ,~i ~ rag. contained mainly 9a ;~hlch was pulxficd b\ ((~5i ~.el - ~. cll4clH ('l{:(l 2 hexarlc 4 !)and radial cbhm~alobr,g~h), 151 gel. i into pmlc. 11o~,, late 3 nil iron. hexanc tl O 4 l)1o 7i,,c S< 1137t,t 9a a4 a 7cllo\~ o~]. **|~|,~** ~ .'D m ifH(i , _"c ~ft NMR ,;-i! Mite. t-l)(t,1(~ {;S br,~ /H-2). 734 J i t r' c t lZ| l l-·tj, " ~:~' 7~"',l l"1 ~ ~ 7 t l". } t ~(~~, 2 } 2 /~'i {fl--'). 4 55,7 l,s ;,7 ill H ,tak4 <',.,/ [-, ,tie. t!-gb). ; Ot) d (J 55tl7. H-IOal]'tx ,/1J-<" tl/. tt. ttibk 2,<2 ~c[>l Id tl/.ll-l 71 .~op ~ -tl 1t-2 ,tndtl-; ._.6,s~<m d - *HL* H-I Oaam.i , J,'<; :n ,::ach. s ib ttC: alld tt-.~ I Ihc H ~]R ;-i'ict {{till; ~,i {lll:~ LL-!llPOtlnd *,Lt~ ldCIltlcat tn d!J es~,ciltlal IOalLIFt.'S %t,~[t thtil o: [fit" cccnl],- repelled [41 i.o-xealoralo anal\ dut, ~)h [ltHY *tHh<~i "nJlminth'>,* bU{ tJlllttTC4J tl SCtCFal [c';pc~'[\ l(>, "IKtc 4[Cc I ' 1 {i/',rDtll tlCll\kIII~c' el tln',pcCIIi0d lOI~llIOn tl,l)g_J \~,db, \OIdICtt IIt~lll *Ht','i'Dtlt#k tlk'~ CtlllIitll* III lc;t~~ and ,1%~-,I~llct[Ml'clclul~. 9a i42 '~c' ar< unable io dLUOtln[ ]t)l {li['.g dl~crct-Jaltc) t tln]F~c!dIliJ l)ll t~,<lb li~*~ ik['~OllCtl lntqc fCk'c[ll , IFt'llll *hi"* ll,7:.'i ,,,',.,.,, f4t i btil n'<t oh~,!qccl] prop;rile', ;~c:C li.;leci

t :] -~ [1t2 l~,,l~ d ll]lX[UlC o -,ll~Hll{l~{ClO }.tlltl [kl l " [.~]5 [4.~ ~< %kCFCll1 t[.tli't'~ ch th it ~t[<.l 2ti t' v, tilc! Cclt/h.l be ~cpaHt[Ctl om~ pariiali3 lit)lll ca;ll o[11o! ~< 1l (!fP[t t,~ lathal chrorllatttgrapit) Ihc COll]f)tlnell{< V,ClC chu!.l,'!cll/c'd b\ N2Mp. ,'~;pecWol31Ctr} d bllla[t t~i <II];A[\ [llXIti!C~

}-rs 1(I* 767 nigl ~+crc ~:onib,ncd Radi<tl chromatography lS1 gC]. ~ l]ln] {)[~l[t.. }lt\{tllC-[)l i CliltlICn{ i]tl~A Yilt,, ~, 111] [nln alh-~rcled 2"75,nig ot , .; ' lhiX[UF.J 2C ancl 5b and 25t) lnl2 tit a n]lXltlFc cti!llttttltlnl~ 2{ tilt] |{}a bc",,zr,il IccF;s|aHlz.l[io[i~ ~ [lie 2C ~b ll~[XlUI'l, lit)n| ~2~ (() !lCktlltC l{ll l/txttk'l.l W1 111t-t"i D[lIX.' ~t]l. mp 16;>4 171"ldeC.L tR ~n~ ~ftl f ~>~,.t"~t). l(w:< tl) till;t" "(MCfTM

(hromatograph} o~ the 2~ lib lp,!\[i.!re ~Scphadcx Ilt-20, ('H(l, }lo(JH t: ~. ~hl~c (nl7 c,' Ilia. SIID *224* !McOll lll 2355 236,5 7441.2Y 241 [45j ,u :~j *14(,i.2>>* 2.m [47 ttXMR 27! M1lz tl)('i. ~i2f; ,, ;,-()ILL 7.t~ ,dd.d ~. 2Hz. }1-6 .~upcrlnlpo.-.cd on 4)I{ " 11"..; .l ? ib 11-2 . t_" a. - tiz.){ 5 LO2"~ 1{ ,i (l:',t) cacn~/.o] }[z t{-O and }I-Sf 4 1" .tpx ~', ~cach t! i I }~lt-'s [hc ~,{l'lOtl5 I11[(~ I'CCOFdCIA Ill lhc h[craHs/c l J~lt "~" IBdtiC ldc?l/[ll]C;A,i{lln ~11 tills ~;tlh>lal]CC st.,~ll]c~n<t{ OiHh_ltl 1 tilt. txllllCilO[I lit)lll \;'hi{lll 10b mp *225* 227 l.s,4j, ,<,., ~,,.,'.: ,,. i,< :c at ,c cm.m~c.d ~.h~ ~,,; H 2 and fl-h m *~a ~!In !t-6 ~,+,~ai:r,cld ,: ti,-2

I'r_~ i~ and [+l ltJ 27 t :~,crc lllIXhHC-, <', 2a.b. lOa and I I ,,k~llclt could not be separated :>{tliShlt loril HIIO illdl~ ldUai con] ()tillCI]I:~ by ('{" I hl.] prcccIIce el I] V<b; eslabii:shcd h~ c ,ff!p,trlbon "aIth liP, an[hc.tltlC sample !r!< }(,I 2{ ;l'.t= ~<C[C n]l~,tUl¢> ('(INt gel 70 ~. Cl[ICIl! (', It, i-1 { }'~,t" dtlOl<l~<l S g ,... ClHk'FpCBC acid IIIlXIUrC V~inch vt>as ~llC[!t%Itti 't' (t{ , %, Ptl[L't)hid 13OI bc' chaFactcql/cd 5d[l',l~t(.to{ 1 I ~ ,h: ~I o i["~, J~ .~ [2 ~] wllh Me,('() g-2\l o lh g . >,,~i,, ." : ill!>.ILlIC Ol . i.i i_ dih~,t[P.Jhciellatillf2a rt~4] lllC~h21r}H I ("hro:f.,at,~,Jr,iph\ el\he

*** For molecular mechanics calculations on corllormalions of C-6 and C-8 *tran.s-lacionized trans, trans-germacradmnolides see* ref. [38]. C-8 cis-lacionized germacradienolides seem io be unknown** as the result of **a revision m** the .qereochemmtr} **of** several laclones preqousl.~ Ihoughl to belong u" rhN clas~ [39]

mother liquors (hexane–Me_2CO 4:1) afforded 115 mg of a 5:1 mixture of **1a** and **3** and mixtures containing **1a, 2a, 3** and **4** in varying proportions.

Rechromatography of frs 31–33 (375 mg) (20 ml fractions, Si gel, 30 g, eluent 100 ml each of Me_2CO–CH_2Cl_2 1:19, 1:9 and 3:17) gave in frs 10–18 mainly florilenalin acetate (**6b**, 150 mg) and in frs 19–21 a 1:2 mixture of **6b** and **7b**. Rechromatography of crude **6b** gave pure florilenalin acetate as a gum (100 mg), ^1H and ^{13}C NMR in Tables 1 and 2; PCIMS *m/z* (%) 307 ($M^+ + 1$, 100), 289 ($M^+ + 1 - H_2O$, 15.8), 229 ($M^+ + 1 - H_2O - C_2H_4O_2$, 33.9). The mixture of **6b** and **7b** could not be separated satisfactorily; the structure of **7b** was evident from the ^1H NMR spectrum (Table 1) and the PCIMS which exhibited additional strong peaks at *m/z* 309 ($M^+ + 1$), 291 and 231.

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