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NEW SESQUITERPENE LACTONES FROM *INULA* SPECIES*

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Key Word Index—*Inula* species; Compositae; new eudesmanolides; new germacranolides; new guaianolides; new pseudoguaianolide, new xanthanolides.

Abstract—An investigation of *Inula* helenium, *I. royleana, I. salicina* and *I. bifrons* afforded in addition to known sesquiterpene lactones 20 new lactones, the eudesmanolides **3**, **6** and **8–12**, the germacranolides **14–18** and **20–22**, the guaianolides **23** and **25**, the pseudoguaianolide **26**, the xanthanolides **28** and **32** and the cyclopropane analogue **30**. Structures and configurations of these new compounds were established by extensive PMR studies and by some chemical transformations. Some of the investigated species contain besides the widely distributed pentaynene **33** several known thymol derivatives together with a new one (**40**).

INTRODUCTION

The genus *Inula* (tribe Inuleae) with about 80–100 species represents a badly delineated complex [1]. Chemical investigations have shown that there are two main groups, one containing sesquiterpene lactones, especially eudesmanolides, and one containing simple thymol derivatives [2]. Furthermore several triterpenes and some diterpenes are present, while the pentaynene **33** seems to be widespread [2]. Reinvestigation of 3 species together with the investigation of a further one has now led to the isolation of a considerable number of new sesquiterpene lactones.

RESULTS AND DISCUSSION

Investigation of *Inula helenium* L., *I. royleana* DC, *I. salicina* and *I. bifrons* L., all grown from seeds, afforded together with large amounts of alantolactone (**5**) and isoalantolactone (**1**) many sesquiterpene lactones, most of them not previously isolated. Scheme 1 contains the lactones isolated and some transformation products and scheme 2 the other compounds. Table 8 lists the species investigated with the isolated compounds.

The fresh plant material was extracted with mixtures of ether and petrol; the extracts were first separated by column chromatography and further by TLC, which normally had to be repeated several times as very often extremely complex mixtures were obtained. In such instances, $AgNO_3$ columns and plates were frequently useful. Besides MS data 270 MHz–PMR spectra were extremely useful in structural elucidation of the new lactones. In most cases assignment of signals was possible by double resonance experiments and application of shift reagent.

The structure of **3** could be solved easily as the spectral data of ivalin acetate (**2**) [13] were identical with those of the isolated lactone (see Table 1). Structure and configuration of **6** was elucidated by extensive decoupling experiments of the PMR spectra of both **6** and the corresponding ketone **8**, which was not only prepared by chromic acid–pyridine complex oxidation, but also isolated as a natural product (see Table 1). The *cis*-annelation of the lactone group of **6** follows from the value of $J_{7\alpha,8\alpha}$ and $J_{8\alpha,9}$. They are always smaller than those for $J_{7\alpha,8\beta}$ and $J_{8\beta,9\alpha}$ (see Tables 1 and 2). The β-orientation of the 4-methyl group follows from the couplings too. Only the equatorial position of the 2-hydroxy group is in agreement with the observed couplings ($J_{1\alpha,2} = J_{2,3\alpha} = 10$).

Similar arguments for another compound led to structure **9**, which is that of hydroxyalantolactone. The observed shifts after addition of $Eu(fod)_3$ are in good agreement with **9** (see Table 1).

The structure of **10** was elucidated by double resonance experiments which allowed assignment of most PMR signals. The 8α-H signal is a *ddd* at 4.5 with equal coupling constants, which indicates *cis*-annelation of the lactone ring. Furthermore the chemical shift of 7α-H is typical of *cis*-fused lactones whereas in *trans*-lactones the signal of 7α-H is always shifted to considerably higher fields. The position of the double bond clearly follows from the 6-H signals (see Table 2). The enantiomer of **10** has been reported as constituent of liverworts [23]. All PMR data of **11** are in good agreement with the proposed structure. They are similar to those of **10**, but due to the deshielding effect of the OH group the 9-H signals are now separated, which further establishes the β-orientation of the OH. **11** is the 8-epimer of ivangustin [3] which also follows from the chemical shift of 7α-H. **12** is an unsaturated analogue of **11**. The PMR data (Table 2) clearly show that a *trans*-fused lactone is present; the β-position of the 1-OH follows from the downfield shift of the 9β-H.

While 2α-OH costunolide (**19**) is known [5], the 9β-derivatives **14–18** are new. The 9β-position of the oxygen function can be inferred from the shifts which result after addition of $Eu(fod)_3$ as both the 10-Me and 1-H signal, are shifted downfield. If the oxygen function

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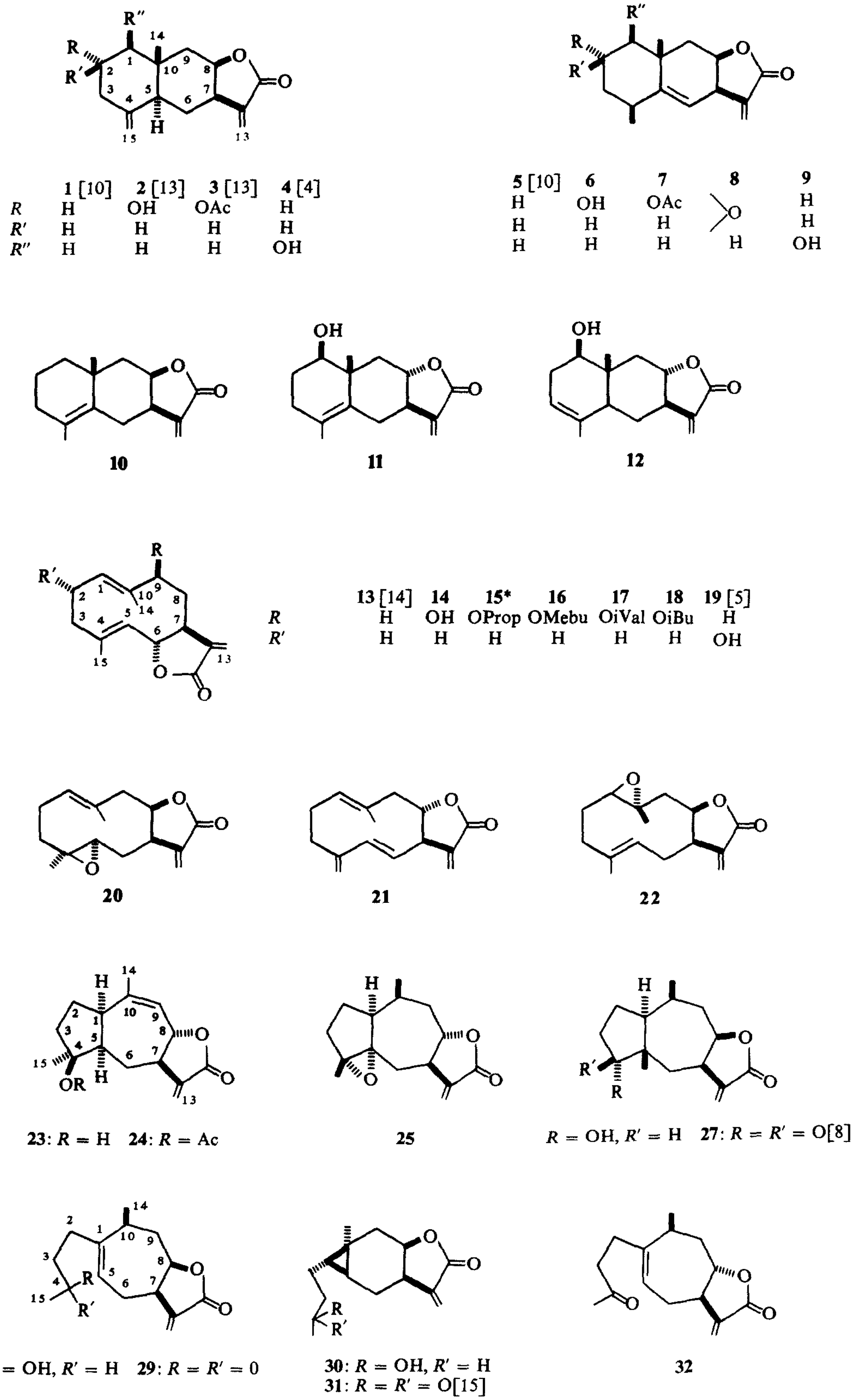
*Part 142 in the series "Naturally Occurring Terpene-Derivatives"; for part 141 see: Bohlmann, F. and Zdero, C. *Phytochemistry*. **17**, 759.



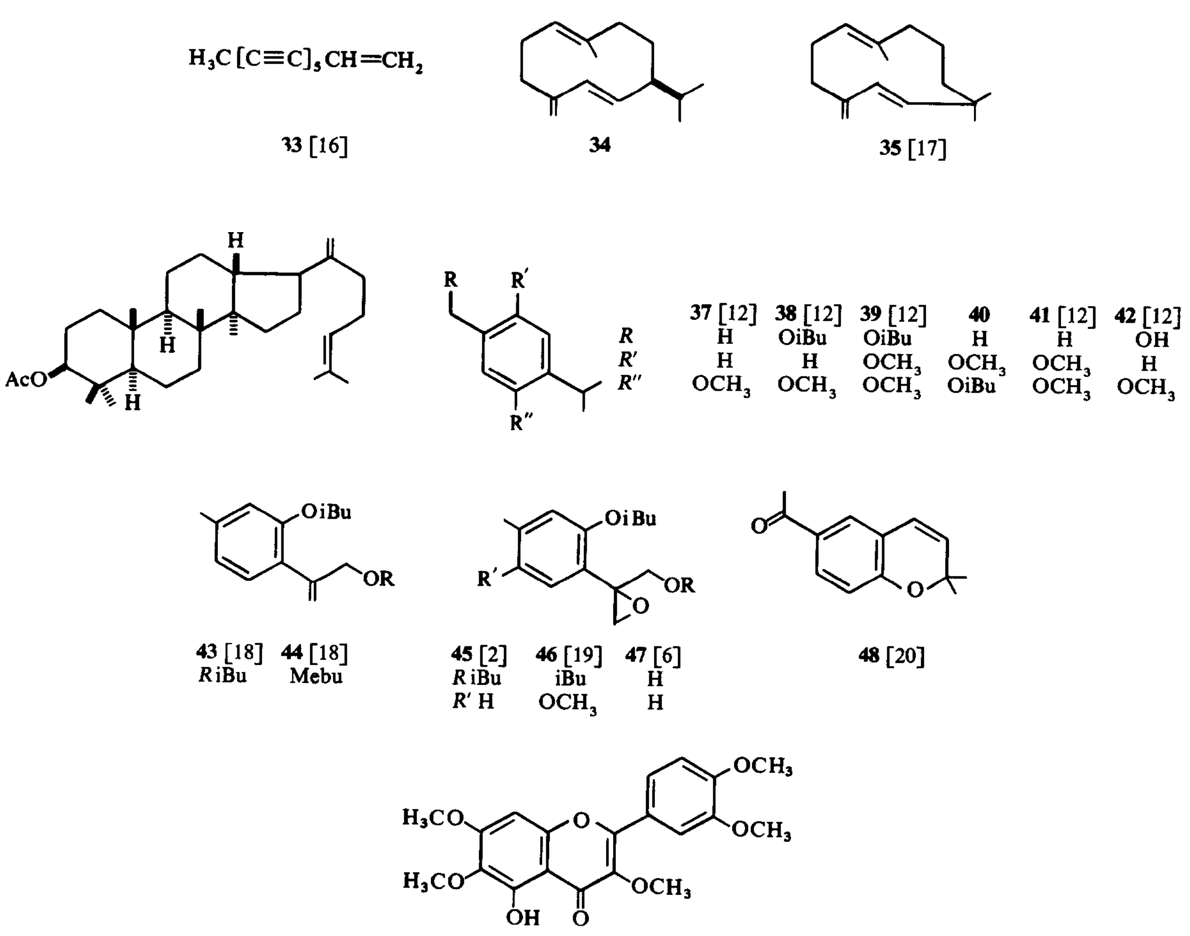
	1 [10]	**2** [13]	**3** [13]	**4** [4]
R	H	OH	OAc	H
R'	H	H	H	H
R''	H	H	H	OH

5 [10]	**6**	**7**	**8**	**9**
H	OH	OAc	>O	H
H	H	H		H
H	H	H	H	OH

	13 [14]	**14**	**15***	**16**	**17**	**18**	**19** [5]
R	H	OH	OProp	OMebu	OiVal	OiBu	H
R'	H	H	H	H	H	H	OH

Scheme 1 (literature citations in brackets).

* Prop = Co Et; Mebu = COCH(Me)Et; iVal = $COCH_2CHMe_2$; iBu = $COCHMe_2$.



Scheme 2.

were at C-3 the signal of the 4-Me group should be shifted (see Table 3). All other signals are in good agreement with the proposed structures.

Structure and configuration of **20** were confirmed by extensive decoupling experiments. All data are in good agreement with the proposed structure (see Table 4). Assignment of the signals was confirmed by using the solvent shift method. The observed coupling constants are in good agreement with those expected from the angles in a Dreiding model. The corresponding, not epoxidized lactone inunolide, without established stereochemistry, is reported from *I. racemosa* [24]. We therefore propose the name 4β,5α-epoxy-4,5-H-*cis*-inunolide for **20**. The 1β,10α-epoxide we also have isolated. The structure follows again from the PMR data (see Table 4) and decoupling experiments.

21 is a lactone derived from the widely distributed hydrocarbon germacrene D. Again the PMR signals and the results of decoupling experiments are in good agreement with the proposed structure. Comparison of the couplings of 7- and 8-H with those of **20** indicates a *trans*-lactone (see Table 4).

Structures of **23** and **25** again follow from the PMR spectra. As the spectrum of **23** was not well resolved, the substance was transformed to the acetate **24**. Addition of Eu(fod)$_3$ was again helpful in solving some of the stereochemical problems. Inspection of a Dreiding-model shows that the proposed configurations agree with the observed coupling constants (see Table 5). In the case of **25** good results were only obtained in deuteriobenzene by using different amounts of shift-reagent at elevated temperature. As shown in Table 5 all signals then can be assigned. The relative shifts of the signals of 6α- and 6β-H are in better agreement with β- than with α-orientation of the epoxide. The same argument leads to 4β-orientation of the acetoxy group in **24**. Similarly *trans*-annelation of the lactone rings agrees much better with the observed coupling constants than *cis*-annelation. Furthermore comparison of the PMR data of **23** with those of inuviscolide [6] shows that the configuration at C-4 is different, as in the latter case the signal of 5α-H is shifted downfield due to the *cis*-position of the 4-OH group. A lactone with the same structure, but without configurational assignment, has been isolated from *Helenium* species [7]. The few data given however, do not agree with those of **23**. Therefore the stereochemistry must be different; **23** is 4-*epi*-isoinuviscolide.

The only pseudoguaianolide isolated from 4 *Inula* species was **26**. Its structure and configuration follow from the PMR data (see Table 6) and from the result of

Table 1. PMR data of **1**, **3**, **6**, **8** and **9** (270 MHz, $CDCl_3$, δ-values, TMS as external standard)

	1	**3**	**6**	**8**	**9**	+ $Eu(fod)_3$
1α-H	*ddd* 1.25	*m* 1.26	*m* 1.25	*d* 2.28	*dd* 3.30	*dd* 4.86
1β-H	*ddd* 1.61	*d*(*br*) 1.86	*d*(*br*) 1.91	*dd* 2.36	—	—
2α-H	*m* 1.57	—	—	—	*m* 1.58 *m* 1.83 *m* 2.31	*d*(*br*) 2.57
2β-H		*dddd* 4.91	*dddd* 4.19	—		*dddd* 2.8
3α-H	*ddq* 2.01	*ddd* 2.74	—	*dd* 2.6		
3β-H	*dddd* 2.35	*m* 2.25	—	*ddd* 2.27		
4α-H	—		*ddq* 2.65	*ddq*(*br*) 2.93	*m* 2.43	*m* 2.7
5α-H	*d*(*br*) 0.85	*d*(*br*) 2.06	—	—	—	—
6α-H	*ddd* 1.75	*ddd* 1.94	*d* 5.25	*d* 5.52	*d* 5.24	*d* 5.5
6β-H	*ddd* 1.34	*ddd* 1.40				
7α-H	*ddd*(*br*) 2.98	*ddddd* 3.00	*dddd* 3.63	*dddd* 3.76	*dddd* 3.57	*dddd* 3.77
8α-H	*ddd* 4 51	*ddd* 4.51	*ddd* 4.82	*ddd* 4.88	*ddd* 4.86	*ddd* 5.09
9α-H	*dd* 1.5	*dd* 1.54	*m* 1.9	*dd* 1.79	*dd* 1.56	*dd* 2.24
9β-H	*dd* 2.21	*dd* 2.27	*dd* 2.19	*dd* 2.24	*dd* 2.59	*dd* 3.61
13-H	*d* 6.14	*d* 6.16	*d* 6.21	*d* 6.28	*d* 6.22	*d* 6.51
13′-H	*d* 5.59	*d* 5.61	*d* 5.66	*d* 5.71	*d* 5.64	*d* 5.77
14-H	*s* 0.84	*s* 0.92	*s* 1.29	*s* 1.16	*s* 1.19	*s* 1.99
15-H	*ddd* 4.78	*s*(*br*) 4.94	*d* 1.17	*d* 1.18	*d* 1.09	*d* 1.40
15′-H	*ddd* 4.45	*s*(*br*) 4.61				
OAc	—	*s* 2.03	—	—	—	—

J(Hz): **1**: 1α,1β = 1α,2β = 12; 1α,2α = 4; 1β,2α = 1β,2β = 3; 2α,3α = 6; 2β,3α = 12; 3α,3β = 13; 3α,15 = 1.5; 2α,3β = 2; 2β,3β = 2; 3β,15 = 1.5; 5α,6β = 12; 5α,6β = 2.5; 6α,6β = 14; 6α,7α = 6.5; 6β,7α = 11; 7α,8α = 5; 7α,13 = 1; 8α,9α = 5; 8α,9β = 2; **3**: 1α,2β = 13; 1α,2β = 12; 1β,2β = 5; 2β3α = 12; 2β,3β = 5; 5α,6β = 12; 6α,7α = 6; 6β,7α = 12; 7α,8α = 5; 7α,13 = 1; 8α,9α = 5; 8α,9β = 2; 9α,9β = 16; **6**: 1α,2β = 10; 1β,2β = 3; 2β,3α = 10; 2β,3β = 3; 3α,4α = 3β,4α = 4α,15 = 7; 6,7α = 4; 7α,8α = 5; 7α,13 = 2; 8α,9α = 4; 8α,9β = 2,5, 9α,9β = 15; **8**: 1α,1β = 15; 1β,3β = 1; 3α,3β = 16; 4α,6 = 1; 6,7α = 5, 7α,8α = 7; 7α,13 = 2.2; 7α,13′ = 1.8; 8α,9α = 2.5; 8α,9β = 3.5; 9α,9β = 16; **9**: 1α,2α = 4; 1α,2β = 2α,2β = 2β,3α = 12; 2β,3β = 4; 4α,15 = 7; 6,7 = 4; 7,8 = 6.5; 7,13 = 1.7; 8.9α = 3.

Table 2. PMR data of **10**, **11** and **12** ($CDCl_3$)

	10	**11**	**12**	+ $Eu(fod)_3$ Δ
1α-H	*m* 1.45–1.75	*dd* 3.63	*dd* 3.7	1.13
1β-H		—	—	—
2α-H		*m* 1.74	*dddq* 2.4	0.65
2β-H			*dddq* 2.01	0.8
3α-H	*m* 1.97	*m* 2	*s*(*br*) 5.34	0.21
3β-H				
5α-H	—	—	*d*(*br*) 2.17	0.36
6α-H	*dd* 2.81	*dd* 3	*ddd* 2.25	0.2
6β-H	*m* 1.97	*dd*(*br*) 1.96	*ddd* 1.42	0.29
7α-H	*ddddd* 3.05	*dddddd* 2.25	*ddddd* 2.42	0.32
8-H	*ddd* 4.50	*ddd* 4.09	*ddd* 4.05	0.4
9α-H	*d* 1.74	*dd* 1.46	*dd* 1.42	0.61
9β-H		*dd* 2.58	*dd* 2.51	0.9
13-H	*d* 6.24	*d* 6.11	*d* 6.09	0.39
13′-H	*d* 5.6	*d* 5.45	*d* 5.45	0.17
14-H	*s* 1.08	*s* 1.09	*s* 0.89	0.53
15-H	*s*(*br*) 1.66	*s*(*br*) 1.67	*s*(*br*) 1.69	0.15

J(Hz): **10**: 6α,6β = 13.5; 6α,7α = 7.5; 6β,7α = 10; 7α,8α = 7.5; 7α,13 = 2.5; 8α,9 = 7.5; **11**: 1α,2α = 6; 1α,2β = 10; 6α,6β = 13.5; 6α,7α = 3; 6β,7α = 12; 7α,8β = 11; 7α,13 = 3; 8β,9α = 11; 8β,9β = 3.5; **12**: 1,2α = 7; 1,2β = 10; 2α,2β = 12; 2α,3 = 2β,3 = 2,15 ~ 2; 3,15 = 2; 5α,6α = 3; 5α,6β = 12.5; 6α,6β = 12.5; 6α,7α = 3; 6β,7α = 12.5; 7α,13 = 3; 7α,8β = 12.5; 8β,9α = 12.5; 8β,9β = 4.

Table 3. PMR data of **14–18** (CDCl$_3$)

	14	Δ†	**16**‡
1-H	*dd*(*br*) 5.07	0.30	*dd*(*br*) 5.19
2-H	*m* 2.3		*m* 2.32
3-H			
5-H	*d*(*br*) 4.61	0.26	*d*(*br*) 4.69
6β-H	*dd* 4.54	0.33	*dd* 4.57
7α-H	*ddddd* 2.65	0.56	*ddddd* 2.75
8α-H	*m* 1.95		
8β-H			*m* 2.05
9α-H	*dd* 4.19	0.91	*dd*(*br*) 5.22
13-H	*d* 6.27	0.30	*d* 6.31
13′-H	*d* 5.57	0.18	*d* 5.56
14-H	*s*(*br*) 1.44	0.42	*s*(*br*) 1.46
15-H	*s*(*br*) 1.7	0.16	*s*(*br*) 1.74
OCOR	—	—	*tq* 2.31 *d* 1.15 *t* 0.90

† Δ-Values after addition of 0.1 equivalents of Eu(fod)$_3$.

‡ The values of the other esters are very similar.

J (*Hz*): **14**: 1,2α = 11; 1, 2β = 2.5; 5, 6 = 10; 6, 7α = 9.5; 7α, 8α ~ 2; 7α, 8β = 9; 7α, 13 = 3.5; **15**: OCOR: *q* 2.35(2) *t* 1.14(3) (*J* = 7) **17**: *d* 2.37(2) *m* 1.5(1) *d* 1.00(6) (*J* = 7); **18**: *qq* 2.54(2), *d* 1.17(3), *d* 1.16(3) (*J* = 7).

Table 4. PMR data of **20**, **21** and **22**

	20	**21**	**22**	+ Eu(fod)$_3$
1-H	*dd*(*br*) 5.27	*dd*(*br*) 5.36	*dd* 2.67	*d*(*br*) 3.58
2α-H	*m* 2.39	*m* 2.16	*m* 1.45	*m* 2
2β-H				
3α-H	*m* 2.2		*m* 2.25	*m* 2.45
3β-H	*ddd* 1.25	*d*(*br*) 2.82		
5-H	*d*(*br*) 2.65	*d*(*br*) 6.07	*dd*(*br*) 5.2	*dd*(*br*) 5.48
6α-H	*m* 2.35	*dd* 5.33	*d*(*br*) 2.51	*d*(*br*) 2.75
6β-H	*ddd* 1.45		*m* 2.25	*m* 2.45
7α-H	*m* 2.85	*dddd* 3.6	*m* 2.71	*ddddd* 3.02
8-H	*ddd* 4.1	*ddd* 4	*dd*(*br*) 4.17	*dd*(*br*) 4.66
9β-H	*m* 2.34	*dd* 2.64	*m* 1.45	*dd* 3.13
9α-H	*d*(*br*) 2.79	*d*(*br*) 2.82	*d*(*br*) 2.73	*dd* 2.02
13-H	*d* 6.34	*d* 6.14	*d* 6.29	*d* 6.62
13′-H	*d* 5.65	*d* 5.48	*d* 5.62	*d* 5.72
14-H	*s*(*br*) 1.78	*s*(*br*) 1.56	*s* 1.28	*s* 1.71
15-H	*s* 1.17	*s*(*br*) 4.96 *s*(*br*) 4.8	*dd* 1.69	*dd* 1.87

J (Hz): **20**: 1, 2α = 3; 1, 2β = 12; 2α, 3α = 7; 2β, 3α = 13; 3α, 3β = 13; 5,6 = 10; 6α,6β = 15; 6β,7α = 10; 7α,8α = 7; 8α, 9β = 11; 8α, 9α = 1.5; 9α, 9β = 13; 7, 13 = 3.5; 7, 13 = 3.0; **21**: 1, 2α = 2; 1, 2β = 10; 3α, 3β = 13; 5, 6 = 16: 6, 7α = 9; 7α, 8β = 9.5; 8β, 9α = 10; 8β, 9β = 3;7, 13 = 3.5; 7, 13 = 3.0; **22**: 1, 2α = 10; 1, 2β = 2.3; 5, 6α = 10; 5, 6β = 4; 6α, 6β = 14; 6α, 7α = 3.5; 6β, 7α = 10; 7α, 8α = 7; 7α, 13 = 3.3; 8α, 9β = 10.5; 9α, 9β = 13.5.

Table 5. PMR data of **23**, **24** and **25**

	23	**24**	+ Eu(fod)$_3$	**25** (C$_6$D$_6$)	+ Eu(fod)$_3$ (80°)
1-H	*m* 1.5–1.9	*m* 2.07	*m* 2.11	*d*(*br*) 2.15	*d*(*br*) 4.51
2α-H		*m* 1.77	*m* 1.94	*m* 1.7	*dd*(*br*) 3.36
2β-H				*dd* 1.72	*dddd* 3.52
3α-H		*m* 2.07	*m* 2.69	*dd* 0.85	*dd* 2.2
3β-H	*m* 2.5	*dd*(*br*) 2.44	*m* 2.3	*m* 1.34	*ddd* 2.81
5-H	*m* 1.95	*m* 2.07	*d*(*br*) 2.43	—	—
6α-H	*m* 2.5	*ddd* 2.75	*ddd* 3.33	*d*(*br*) 1.77	*d*(*br*) 5.29
6β-H	*ddd* 1.43	*ddd* 1.41	*ddd* 1.73	*m* 1.34	*dd*(*br*) 3.92
7α-H	*ddddd* 2.54	*ddddd* 2.56	*t*(*br*) 2.81	*ddddd* 2.36	*dddddd* 5.21
8β-H	*ddq* 4.72	*ddq* 4.72	*d*(*br*) 4.95	*ddd* 3.41	*ddd* 6.23
9α-H	*ddq* 5.84	*ddq* 5.87	*s*(*br*) 6	*ddd* 1.31	*ddd* 2.96
9β-H				*ddd* 1.89	*ddd* 3.17
10α-H	—	—	—	*m* 1.43	*m* 2.7
13-H	*d* 6.19	*d* 6.2	*d* 6.45	*d* 6.07	*d* 9.31
13′-H	*d* 5.50	*d* 5.55	*d* 5.68	*d* 4.81	*d* 6.26
14-H	*s*(*br*) 1.82	*s*(*br*) 1.79	*s*(*br*) 1.89	*d* 0.41	*d* 1.75
15-H	*s* 1.23	*s* 1.44	*s* 2.04	*s* 1.1	*s* 2.96
OAc	—	*s* 1.99	*s* 2.75	—	—

J (Hz): **24**: 5α, 6α = 6α, 7α = 3; 5α, 6β = 6α, 6β = 13; 6β, 7α = 11; 7α, 8β = 9.5; 7α, 13 = 3.5; 7α, 13′ = 3; 8β, 9 = 1.5; 8β, 14 = 1.5; 9, 14 = 1.5; **25**: 1, 2α = 8; 2α, 2β = 13; 2α, 3α = 9; 2β, 3β = 8; 2α, 3β = 10; 3α, 3β = 13; 6α, 6β = 16; 6α, 7α = 3; 6β, 7α = 10; 7α, 8β = 10; 7α, 13′ = 3.5; 7α, 13 = 3; 8β, 9α = 12; 8β, 9β = 3.5; 9α, 9β = 12; 9α, 10α = 3; 9β, 10α = 4; 10α, 14 = 7.

the chromic acid/pyridine oxidation, which leads to a ketone whose physical properties are in good agreement with those reported for confertin **27** [8].

In addition to some known xantholides 3 other lactones were isolated. **29** is probably identical with tomentosin, isolated from *Parthenium tomentosum* [9]. **29** is also present in *Inula viscosa* Ait. [6]. We now also have isolated the 8-epimer **32**, which may be identical

Table 6. PMR data of **26**

		+ Eu(fod)$_3$
3α-H	*m* 2.15	*m* 4.73
3β-H	*m* 1.45	*m* 3.61
4β-H	*dd* 3.76	*dd* 9.38
6α-H	*d(br)* 1.62	*d(br)* 6.18
6β-H	*dd* 1.87	*dd* 4.28
7α-*H*	*ddddd* 3.15	*m* 5.22
8α-H	*ddd* 4.7	*ddd* 6.39
9α-H	*d(br)* 1.86	*d(br)* 3.25
9β-H	*ddd* 2.15	*ddd* 3.43
10-H	*m* 1.45	*m* 3
13-H	*d* 6.27	*d* 8.4
13′-H	*d* 5.6	*d* 6.28
14-H	*d* 1.03	*d* 1.88
15-H	*s* 0.92	*s* 3.54

J (Hz): 3α, 4β = 8; 3β, 4β = 8; 6α, 6β = 13; 6β, 7α = 13; 7α, 8α = 8; 8α, 9α = 3; 8α, 9β = 12; 9α, 9β = 13; 9β, 10α = 13; 10α, 14 = 7

with xanthinosin, found in a *Xanthium* species [22]. Data, however, are not given. Careful PMR studies lead to the conclusion that most probably tomentosin has a *cis*-fused lactone ring and that **32** is the *trans*-isomer. As already mentioned previously the chemical shift of the 7α-H seems to be characteristic, while $J_{7,8}$ is not useful in making a distinction between *cis*- and *trans*-lactone ring fusion. Also the CD-curves of **29** and **32** are in agreement with the stereochemistry assigned.

We have also isolated the corresponding alcohol **28**, which on oxidation affords **29**. Together with carabrone (**31**) [10] we have also found the corresponding alcohol **30**, which could be oxidized to a ketone identical with **31**. The configuration at C-4 in alcohols **28** and **30** has not been established. PMR data of **28**–**30** and **32** are given in Table 7.

The compounds in scheme 2 are all known except for **40** whose structure clearly follows from the spectroscopic data (see Experimental).

In summary, it turns out that again two groups of *Inula* species can be recognized, one containing sesquiterpene lactones and one containing mainly thymol derivatives.

I. helenium L. which has been previously investigated [10] afforded a considerable number of lactones with different carbon skeletons. *I. royleana* DC, from which so far only diterpenes have been reported [11], also contained several different types of lactones. There were some differences between the constituents of plants which have grown for 2 and 5 years. *I. salicina* L. afforded a series of thymol derivatives as already reported earlier [12], together with small amounts of **1** and **5**. *I. bifrons* L. yielded only thymol derivatives.

From the chemotaxonomical point of view the isolation of very different types of sesquiterpene lactones may be of interest. However, while the main constituents are eudesmanolides, the other types are only present in relatively small amounts. Clearly further investigations are necessary to get a clearer picture about this large genus.

EXPERIMENTAL

IR: CCl_4 or $CHCl_3$ solns; PMR: 270 MHz δ-values, TMS as internal standard; optical rotation: $CHCl_3$ solns. The plant material was grown from seed and fr. material was extracted with Et_2O/petrol 1:2. The extracts were first separated by column chromatography (Si gel grade II activity) and further by

Table 7. PMR data of **28**, **29**, **30** and **32**

	28	**32**	+ Eu(fod)$_3$	**29**	**30**
1-H	—	—	—	—	*m* 0.38
2-H	*t* 2.25	*m* 2 53	*dd(br)* 3.44	*m* 2.43	
2′-H			*dd(br)* 3.33		
3-H	*t* 2.53		*dd(br)* 3.88	*m* 1 54	*dt* 1.54
3′-H			*dd(br)* 3.78		
4-H	—	—	—	*tq* 3.8	*tq* 3.48
5-H	*dd(br)* 5.45	*dd(br)* 5.53	*dd(br)* 6.09	*dd(br)* 5.5	*m* 0.47
6α-H	*m* 2.38	*m* 2.3	*dd(br)* 2.42	*ddd* 1.92	—
6β-H		*dd(br)* 2.02	*ddd* 2.88	*ddd* 2.2	*dd* 2.38
7α-*H*	*ddddd* 3.32	*m* 2.5	*ddddd* 3.13	*ddddd* 3 34	*ddddd* 3.15
8-H	*ddd* 4.65	*ddd* 4.24	*ddd* 4.85	*ddd* 4.67	*ddd* 4.8
9α-H	*ddd* 1.9	*ddd* 1.77	*ddd* 2.22		*m* 1.2
9β-H	*ddd* 2.02	*ddd* 2.28	*ddd* 2.59	*m* 2	*dd* 2.32
10-H	*m* 2.38	*m* 2.3	*ddq* 2.99		
13-H	*d* 6.26	*d* 6 16	*d* 7.08	*d* 6.27	*d* 6.25
13′-H	*d* 5.53	*d* 5.43	*d* 5.85	*d* 5.53	*d* 5.55
14-H	*d* 1.14	*d* 1.14	*d* 1.39	*d* 1.14	*s* 1.08
15-H	*s* 2.16	*s* 2.16	*s* 3.4	*d* 1.2	*d* 1.21

J (Hz): **32**: 2, 2′ = 16; 2, 3 = 7; 3, 3′ = 15; 5, 6α = 3; 5, 6β = 8.5; 6α, 6β = 15.5; 6α, 7α = 8.5; 6β, 7α = 10; 7α, 8β = 11; 8β, 9α = 12.5; 8β, 9β = 3; 9α, 10 = 4; 9β, 10 = 3; *P* (Hz): **29**: 3, 4 = 4, 15 = 7; 5, 6α = 6; 5, 6β = 9; 6α, 7α = 4; 6β, 7α = 12; 7α, 13 = 3; 7α, 8α = 8; 10, 15 = 7; **30**: 3, 4 = 4, 15 = 6; 6α, 6β = 14; 6α, 7α = 6β, 7α = 7; 7α, 8α = 11.5; 7, 13 = 3; 7, 13′ = 2 5; 8α, 9α = 6; 8α, 9β = 9; 9α, 9β = 14

Table 8. Investigated species and isolated constituents

	kg	Roots	kg	Aerial parts
Inula helenium L. (seeds Bot. Garden Budapest, voucher 77/952, 2 years grown)	3	6 g **1**, 2 g **5**, 550 mg **10***, 100 mg **21***, 20 mg **33**, 200 mg **35**, 180 mg **36**, 15 mg **45**	1.5	20 mg **1**, 10 mg **4**, 30 mg **5**, 15 mg **8**†, 4 mg **9**‡, 60 mg **12**‡, 30 mg **13**, 30 mg **14**‡, 30 mg **16**†, 3 mg **17**†, 6 mg **18**†, 50 mg **20**†, 25 mg **22**†, 10 mg **23**‡, 40 mg **25**†, 2 mg **26**‡, 40 mg **29**, 60 mg **31**‡, 25 mg **32**†
Inula royleana DC (seeds Bot. Garden Vacratot) (a) 5 years grown voucher 77/960	1.5	4 g **1**, 3 g **5** 5 mg **33**, 100 mg **36**	2	70 mg **1**, 40 mg **2**, 10 mg **3**†, 75 mg **6**, 11 mg **10**, 50 mg **11**‡, 3 mg **12**, 17 mg **14**, 20 mg **15**†, 20 mg **16**†, 8 mg **20**, 120 mg **25**, 7 mg **28**‡, 3 mg **29**, 69 mg **30**†, 4 mg **31**
(b) 2 years grown voucher 77/991	2	7 g **1**, 5 g **5**, 2 mg **33**, 20 mg **36**	2	35 mg **1**, 25 mg **5**, 10 mg **6**, 2 mg **8**, 3 mg **20**, 28 mg **23**, 8 mg **30**, 8 mg **31**
Inula salicina L. (seeds Bot. Garden Triest, voucher 77/990) (1 year grown)	0.05	0.1 mg **33**, 10 mg **34**, 2 mg **37**, 50 mg **38**, 20 mg **39**, 10 mg **41**, 15 mg **42**, 2 mg **43**, 4 mg **44**, 35 mg **45**, 60 mg **46**	0.2	20 mg **1**, 50 mg **5**, 13 mg **38**, 8 mg **39**, 7 mg **41**, 5 mg **48**
Inula bifrons L. (seeds, Bot. Garden Vacratot, voucher 77/982 (5 years grown)	0.4	12 mg **33**, 15 mg **35**, 9 mg **38**, 20 mg **40** (ether/petrol 3:1) 18 mg **43**, 120 mg **45**, 24 mg **47**	3	35 mg **34**, 15 mg **49**, 200 mg linolenic acid

* Ag–NO_3 coated plates, ether/petrol 2:1; † ether/petrol 1:1; and CH_2Cl_2/C_6H_6 2:1; ‡ ether/petrol 2:1, several times.

TLC (Si gel, GF 254), which was repeated several times. In some cases only $AgNO_3$-coated plates were successful. Known compounds were identified by comparison of IR- and PMR-spectra with those of authentic material. The results are given in Table 8.

Ivalin-acetate (**3**). Colourless oil, IR: OAc 1730, 1260, methylene lactone 1770, 1660 cm^{-1}. MS: M$^+$ *m/e* – ; (M$^+$-AcOH) 230.131 (48 %) ($C_{15}H_{18}O_2$); 230-$^{\cdot}$Me 215(8); $C_9H_{11}^+$ 119(100). **3** was identical with the acetate of ivalin (IR, PMR, TLC).

2α-Hydroxy alantolactone (**6**). Colourless oil, IR: OH 3620; methylene lactone 1770, 1660 cm^{-1}. MS: M$^+$ *m/e* 248.141 (5 %) ($C_{15}H_{20}O_3$); (M$^+$-H_2O) 230(37); 230-$^{\cdot}$Me 215(12); $C_3H_7^+$ 43(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+60.7 \quad +62.2 \quad +71.8 \quad +134.5^\circ}\,(c = 1.0).$$

20 mg **6** in 2 ml CH_2Cl_2 were stirred at room temp with 100 mg CrO_3/pyridine complex. After TLC of the reaction product 13 mg **8** were obtained, identical with the natural product. 10 mg **6** on heating with 1 ml Ac_2O at 70° for 30 min afforded 8 mg **7**, colourless oil, IR: OAc 1750, 1245, lactone 1765 cm^{-1}.

2-Oxo-alantolactone (**8**). Colourless crystals from Et_2O, mp 152–153°. IR: $>$C=O 1715; methylene lactone 1765 cm^{-1}. MS: M$^+$ *m/e* 246.157(100 %) ($C_{15}H_{18}O_3$); (M$^+$-$^{\cdot}$Me) 231(56); (M$^+$-H_2O) 228(2); (M$^+$-$H_2C{=}C{=}O$) 204(26); (228-$^{\cdot}$Me) 213(8); (204-CO) 176(82).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+301.3 \quad +316.4 \quad +366.5 \quad +700.6^\circ}\,(c = 1.3).$$

1β-Hydroxy alantolactone (**9**). Colourless oil, IR: OH 3620; methylene lactone 1790, 1675 cm^{-1}. MS: M$^+$ *m/e* 248.141(29 %) ($C_{15}H_{20}O_3$); (M$^+$-H_2O) 230(36); (230-$^{\cdot}$Me) 215(37); $C_3H_7^+$ 43(100).

1-*Desoxy*-8-*epi-ivangustin* (**10**). Colourless oil, IR: methylene lactone 1780, 1670 cm^{-1}. MS: M$^+$ *m/e* 232.146 (21 %) ($C_{15}H_{20}O_2$)

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+35.2 \quad +36.4 \quad +40.0 \quad +59.6^\circ}\,(c = 0.5)$$

8-*Epi-ivangustin* (**11**). Colourless oil, IR: OH 3620; methylene lactone 1780, 1670 cm^{-1}. MS: M$^+$ *m/e* 248.141 (72 %) ($C_{15}H_{20}O_3$); (M$^+$-H_2O) 230(67); (230-$^{\cdot}$Me) 215(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-25.4 \quad -27.4 \quad -31.6 \quad -56.9^\circ}\,(c = 3.7).$$

8-*Epi-isovangustin* (**12**). Colourless crystals, mp 135.5° (Et_2O/petrol), IR: OH 3620; methylene lactone 1775 cm^{-1}. MS: M$^+$ *m/e* 248.141 (14 %) ($C_{15}H_{20}O_3$); (M$^+$-H_2O) 230(11); (230-$^{\cdot}$Me) 215(8); $C_6H_9^+$ 81(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-50.4 \quad -52.5 \quad -59.8 \quad -102.5^\circ}\,(c = 0.48).$$

9β-Hydroxy costunolide (**14**). Colourless oil, IR: OH 3610; methylene lactone 1760, 1670 cm^{-1}. MS: M$^+$ *m/e* 248.141 (25 %) ($C_{15}H_{20}O_3$); (M$^+$-$^{\cdot}$Me) 233(5); (M$^+$-H_2O) 230(26); (230-$^{\cdot}$Me) 215(15); $C_9H_{11}^+$ 119(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546\,\text{nm}}{+38.6 \quad +42.7 \quad +61.5^\circ}\,(c = 1.0).$$

9β-Propionyloxy costunolide (**15**). Colourless oil, IR: CO_2R 1725; methylene lactone 1770, 1665 cm^{-1}. MS: M$^+$ *m/e* 304.167 (5 %) ($C_{18}H_{24}O_4$); (M$^+$-$C_2H_5CO_2H$) 230(51); (230-$^{\cdot}$Me) 215(23); $C_2H_5CO^+$ 57(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+54.3 \quad +56.4 \quad +64.3 \quad +98.8^\circ}\,(c = 0.6).$$

9β-(2-*Methyl butyryloxy*)-*costunolide* (**16**). Colourless oil, IR: CO_2R 1725; methylene lactone 1770, 1665 cm^{-1}. MS: M$^+$ *m/e* 332.199 (20 %) ($C_{20}H_{28}O_4$); (M$^+$-$C_4H_9CO_2H$) 230(100); (230-$^{\cdot}$Me) 215(41).

9β-Isovaleryloxy costunolide (**17**). Colourless oil, not free from **18**, IR: CO_2R 1725; methylene lactone 1770, 1665 cm^{-1}. MS. M^+ *m/e* 332.199 (17%) ($C_{20}H_{28}O_4$).

9β-Isobutyryloxy costunolide (**18**). Colourless crystals, mp 154° (Et_2O/petrol), IR: CO_2R 1725; methylene lactone 1770, 1660 cm^{-1}. MS: M^+ *m/e* 318.183 (6%) ($C_{19}H_{26}O_4$); (M^+-$C_3H_7CO_2H$) 230(49); (230-'Me) 215(31); $C_3H_7CO^+$ 71(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+104.8 \quad +110.6 \quad +128.3 \quad +245.2^\circ} (c = 0.48).$$

4β,5α-Epoxy-4,5-cis-inunolide (**20**). Colourless crystals from Et_2O, mp 131°. IR: methylene lactone 1775, 1665 cm^{-1}. MS: M^+ *m/e* 248.141 (17%) ($C_{15}H_{20}O_3$); (M^+-H_2O) 230(31); (230-'Me) 215(12); (M^+-C_3H_6O) 190(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-14.4 \quad -15.2 \quad -17.5 \quad -18.4^\circ} (c = 1.0).$$

Germacrene-D-lactone (**21**). Colourless crystals, mp 142° (Et_2O/petrol). IR: methylene lactone 1775; C=C 1670, 1636, 995, 950, 895 cm^{-1}. MS: M^+ *m/e* 230.131 (18%) ($C_{15}H_{18}O_2$). (M^+-'Me) 215(12); (M^+-CO) 202(10); (M^+-CHO) 201(16); $C_7H_7^+$ 91(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-200.9 \quad -213.2 \quad -255.9 \quad -590.6^\circ} (c = 1).$$

1β,10α, Epoxy-1 10-H-cis-inunolide (**22**). Colourless crystals, mp 156° (Et_2O/petrol). IR: methylene lactone 1765 cm^{-1}. MS: M^+ *m/e* 248.141 (8%) ($C_{15}H_{20}O_3$); (M^+-H_2O) 230(5); (230-'Me) 215 (4); (-$C_3H_7^+$) 43 (100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-20.0 \quad -21.5 \quad -25.5 \quad -48.0^\circ} (c = 0.2).$$

4-Epi-iso inuviscolide (**23**). Colourless crystals, mp 147°. IR: OH 3620; methylene lactone 1775 cm^{-1}. MS. M^+ *m/e* 248.141 (27%) ($C_{15}H_{20}O_3$); (M^+-H_2O) 230(9); (230-'Me) 215(8); $C_3H_7^+$ 43 (100). 20 mg **23** in 0.5 ml Ac_2O and 20 mg 4-pyrrolidinopyridine were heated for 30 min at 70°. After TLC (Et_2O/petrol 3:2) 15 mg **24** were obtained, colourless oil, IR: OAc, methylene lactone 1770 cm^{-1}. MS: M^+ *m/e* 290.152 (6%) ($C_{17}H_{22}O_4$); (M^+-AcOH) 230(70); (230-'Me) 215(21); H_3CCO^+ 43(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-112.9 \quad -117.8 \quad -135.1 \quad -241.1^\circ} (c = 1.8).$$

4α,5α,Epoxy-10α,14H-inuviscolide (**25**) Colourless oil, IR: methylene lactone 1775, 1660 cm^{-1}. MS: M^+ *m/e* 248.141 (9%) ($C_{15}H_{20}O_3$); (M^+-'Me) 233(3); (M^+-H_2O) 230(26); (230-'Me) 215(13); (M^+-C_3H_6O) 190(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+39.7 \quad +42.0 \quad +48.0 \quad +84.4^\circ} (c = 1.4).$$

4α-H-confertin (**26**). Colourless crystals, mp 147°. IR: OH 3605; methylene lactone 1760, 1660 cm^{-1}. MS: M^+ *m/e* 250.157 (4%) ($C_{15}H_{22}O_3$); (M^+-H_2O) 232(15); 108(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+83.3 \quad +88.8 \quad +101.3 \quad +178.3^\circ} (c = 0.6).$$

6 mg **26** were oxidized with CrO_3/pyridine complex as above. After TLC (Et_2O/petrol 2:1) 3 mg **27** were obtained, identical data with those of confertin.

4H-Tomentosin (**28**) Colourless oil, IR: OH 3600; methylene lactone 1770, 1650 cm^{-1}. MS: M^+ *m/e* 250.157 [illegible] (C[illegible]$H_{22}O_3$); (M^+-H_2O) 232(26); $C_9H_{13}^+$ 121(100); C_7H_9 [illegible])

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+37.0 \quad +38.8 \quad +43.7 \quad +68.6^\circ} (c = 0.9).$$

10 mg **28** were oxidized as above. After TLC 6 mg **29** were obtained, identical with authentic material.

4H-Carabrone (**30**). Colourless oil, IR: OH 3610; methylene lactone 1760, 1665 cm^{-1}. MS: M^+ *m/e* 250.157 (1%) ($C_{15}H_{22}O_3$); (M^+-H_2O) 232(2); C_5H_9O 85(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+19.4 \quad +20.4 \quad +25.5 \quad +56.0^\circ} (c = 1.0).$$

10 mg **30** on oxidation afford 6 mg **31**, identical with authentic material.

8-Epi-tomentosin (**32**) ('xanthinosin' [22]). Colourless oil, IR: >C=O 1710; methylene lactone 1775 cm^{-1}. MS: M^+ *m/e* 248.141 (20%) ($C_{15}H_{20}O_3$); (M^+-H_2O) 230(21); (230-'Me) 215(7); (M^+-CH_3COCH_3) 190(53); $C_3H_7^+$ 43(100).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-38.9 \quad -41.1 \quad -47.0 \quad -81.1^\circ} (c = 0.44).$$

2-Methoxy thymol isobutyrate (**40**) Colourless oil, IR: Ph-O-CO-R 1760; 1625, 1590 cm^{-1}. MS: M^+ *m/e* 250.157 (7%) ($C_{15}H_{22}O_3$); (M^+-Me_2C=C=O) 180(100); (180-'Me) 165(61); $C_3H_7CO^+$ 71(6); (71-CO) 43(25). PMR: *s* 6.72(3-H); *s(br)* 6.74(6-H); *s* 2.16(7-H); *qq* 2.97(8-H); *d* 1.33(9,10-H); *qq* 2.87 and *d* 1.20 (*J* = 7 Hz) ($COCHMe_2$); *s* 3.83 (OCH_3).

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