Oxygenated germacranolides from Compositae and their taxonomic significance[†]

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The chemistry of thirtysix new oxygenated germacranolides in addition to several known sesquiterpene lactones of other types isolated from the aerial parts of *Vernonia arkansana*, *Mikania purpurascens*, *Inula cuspidata*, *Eremanthus crotonoides*, *Dicoma tomentosa*, *Dicoma anomala*, *Dicoma schinzii* and *Blainvillea acmella* have been reviewed.

The germacranolides represent a large group of sesquiterpene lactones, derived from the germacrane skeleton. The suffix "olide" in their names refers to the lactone function in the molecule.

Germacrane (**I**) is a ten membered ring compound with two methyls and an isopropyl side chain. Considerable structural variety is recognized within this class of compounds, which is mainly due to the unique configurational and conformational features and the reactivity of the cyclodecadiene skeleton. Recent recognition of configurationally isomeric germacranolides has led to their reclassification into four subgroups, shown below, which are characterized by a cyclodecadiene skeleton with double bonds in the C-1,10 and C-4,5 positions.

Among the four subgroups, the majority represent germacrolides (**IIa**), although an increasing number of melampolides (**IIb**) and heliangolides (**IIc**) have been isolated. The smallest group, lately discovered, is represented by the *cis, cis* germacranolides (**IId**). It is not clear whether the biosynthesis of the four subgroups follows independent biogenetic pathways from the four possible configurationally isomeric farnesols or whether the configurational isomers are formed from the germacrolide skeleton by double bond isomerizations at a later stage of biosynthesis. The co-occurrence of more than one skeletal types in the same

IIa Germacrolide

IIb Melampolide

IIc Heliangolide

IId *cis, cis*-Germacranolide

plant species or genus and the fact that at least in the melampolide series all presently known compounds have an oxidized C-14, found either as aldehydes or as carboxylic acid derivatives (esters or lactones), could be an indication of interconversion from one to the other skeletal system during photochemical or spontaneous double bond isomerizations.

Further structural variations among the aforesaid groups of germacranolides involve the incorporation of an epoxy, furan, hydroxyl and/or ester moieties, or the lactone ring being *cis* or *trans* fused to C₆-C₇ or C₈-C₇ positions of carbocyclic skeleton. Sesquiterpene lactones generally occur as acetates or carry other ester side chains. Acids frequently involved in esterifications are of 4 and/or 5 carbon atoms, such as methacrylic (Meacr), isobutyric (iBu), tiglic (Tigl), angelic (Ang), α -methylbutyric (α -MeBu), senecioic (Sen), isovaleric (iVal) acids or their hydroxy and/or acetoxy derivatives; the abbreviations used for the corresponding acyl groups are given within parentheses.

[†]Dedicated to Professor S. M. Mukherji.

Besides typical NMR parameters, the ester groups generally display diagnostic mass spectral peaks. Commonly, the M-RCOOH and/or M-ketene are detected as reasonably strong peaks and the peak due to the acylium ion (RCO^+) frequently represents the base peak.

The nature of these sesquiterpene lactones varies from colourless oil to crystalline solids with high melting points. These are highly bitter, relatively stable and lypophylic constituents showing wide variety of physiological activities.

In this review, we present the results of structure elucidation of a germacranolide from *Vernonia arkansana*¹, an epoxy germacranolide from *Mikania purpurascens*², five esterified germacranolides from *Inula cuspidata*³, three furanoheliangolides from *Eremanthus crotonoides*⁴, four melampolides and four germacranolides from *Dicoma tomentosa*⁵, four 7,8-germacranolides from *Dicoma anomala*⁶, three germacranolides from *Dicoma schinzii*⁶, four germacranolides and seven acanthospermolides from *Blainvillea acmella*⁷, two known germacranolides – zoapatanolides A and B from *B. latifolia*⁸ and acetylenic germacranolides from *Vernonia cotoneaster*⁹.

Vernonia arkansana DC. has been investigated previously^{10,11}. The reinvestigation of roots afforded costunolide **1** and the known guaianolides, while its aerial parts gave the glaucolide marginatin (heliangolide) **2** together with the corresponding new methacrylate **3**. The structure of **3**, $\text{C}_{21}\text{H}_{26}\text{O}_7$ (HRMS), was clearly arrived from the ^1H NMR spectral data which were very much similar to that of marginatin **2**^{11,12}.

2 R = Tigl

3 R = Meacr

The presence of methacrylate ester residue in **3** was evident by the appearance of signals at δ 5.67 (dq) and 6.12 (brs) for vinylic protons and δ 1.92 (brs) for the olefinic methyl group, respectively. It was characterized as 8-deacyl marginatin-methacrylate.

Mikania is a large genus and belongs to tribe Eupatorieae and subtribe Mikaniinae¹³. Some species of this genus afforded highly oxygenated lactones¹⁴, while others mainly give diterpenes of *ent*-kaurene types¹⁵. The aerial parts of *Mikania purpurascens* gave 5,10-epoxygermacranolide **4**.

4 R = H

5 R = Ac

The structure of **4** was arrived from its spectral studies. The presence of a γ -lactone and a hydroxyl groups was assured from its IR spectrum while its molecular formula $\text{C}_{15}\text{H}_{20}\text{O}_4$ indicated an additional oxygen function. C-5H α gave a broad doublet at δ 4.45 indicating the presence of 5,10-oxygen bridge. This compound is most probably formed via diepoxide **A**. Germacranolides with 5,10-oxygen bridge have so far only been reported from *Liatris* species¹⁶. However, these compounds are 6,12-lactones. The compound **4** was named as purpurascenolide.

So far the results of chemical investigation of *Inula* species (tribe Inuleae) indicated the presence of simple sesquiterpene lactones¹⁷. Some more complex ones have been reported from *Inula eupatorioides*¹⁸. The investigation of the aerial parts of *Inula cuspidata* C.B. Clarke afforded 1 β -hydroxy-1,10-dihydro-10,14 dehydrogermacrene **D** alongwith five new germacranolides **6-10**. These lactones were separated by HPLC (reverse phase) from polar fractions.

6 R iBu OR' iBu
7 R iBu OR' iVal, MeBu
8 R iBu OR' iBu
9 R iBu OR' iBu

Their ^1H NMR data clearly showed that all compounds were methylene lactones. The data of **6** and **10** showed the presence of 8,12-lactone moiety. Incaspitolide-A (**6**) obviously was a diisobutyrate with an additional hydroxy and a keto group. Careful spin decoupling established the sequence of protons. The stereochemistry was deduced from the couplings observed and from inspection of models. As both $J_{6,7}$ and $J_{8,9}$ were large, only a *trans*-orientation at C-6-C-9 was likely. The conformation is in agreement with the couplings of H-6-H-9, those of H-4 required a β -position of the 4-methyl group. As the ^1H NMR spectrum indicated a

relatively rigid conformation, a hydrogen bridge between 10-OH and the keto group was likely. This however, required a 10 β -hydroxy group. Therefore the stereochemistry at C-4 and C-7-C-10 was the same as that of ineupatorolide-A, where the configuration is established by X-ray¹⁸. The ¹H NMR data of the mixture of incaspitolide-B and C (**7** and **8**) clearly showed that these compounds only differed from **6** by ester residues. The typical signals of isobutyrate, isovalerate and 2-methylbutyrate clearly could be identified. However, since separation was not possible, hence no decision can be given regarding the locations of the different ester groups. As the signals of the tertiary protons of the isobutyrate moieties were different in the spectrum of **6**, more than two compounds probably were present. The ¹H NMR data of incaspitolide-D (**9**) indicated that the substitution pattern was different from that of **6**. Spin decoupling using the H-7 signal as the point of departure established the whole sequence H-2-H-9. The position of the ester groups was deduced from the chemical shifts, as the signal of H-6 was at higher field than that in the spectrum of **6** and, therefore, a free hydroxyl at C-6 was very likely. The presence of a keto group at C-1 was supported by the chemical shifts of H-2 and their couplings. The stereochemistry at C-4 and C-10 is likely to be the same as that in **6-8**. Incaspitolide-E (**10a**) on acetylation afforded the monoacetate **10c** and the diacetate **10d**. The ¹H NMR data showed that **10c** and **10d** obviously were secondary acetates with a keto group at C-5, while the data of **10a** indicated that the keto group was masked as the H-4 signal was at much higher fields. Furthermore, the H-1 signal was a sharp double doublet, unusual for a proton near a hydroxy group. Therefore the presence of a hemi-ketal was very likely, which, however, could be in equilibrium with ketone **10b**, and could be shifted by acetylation. The ¹H NMR data were in good agreement with this assumption. Those of **10c** clearly showed that the substitution at C-4-C-10 was the same as in **6**. The additional acetoxy group could be placed only at C-1 as the corresponding signal of the proton under the acetoxy group was a clear double doublet. The model showed that the hydrogen bond between

the 10-hydroxy and the keto group was likely. Then, however, only an α -orientated hydroxy would agree with the couplings observed. The dihedral angles would be in good agreement with the couplings observed for the other signals. Inspection of a model of **10a** also showed that the observed couplings would agree with the proposed stereochemistry. In the spectrum of **10d** the downfield shift of H-14 clearly indicated that the second acetoxy group was at C-10. The coupling of H-1 again was altered, indicating that the conformation was changed, probably due to the missing hydrogen bridge. At elevated temperature in the spectrum of **10c** the H-1 couplings were close to those in **10d**, showing that the hydrogen bridge may be very weak. Consequently, also the chemical shifts in the spectrum of **10c** at higher temperature were altered.

The investigation of the aerial parts of *Eremanthus crotonoides* DC. afforded, in addition to known sesquiterpene lactones **11-16**, three new furanoheliangolides **17-19**. The known sesquiterpene lactones included three eremantholides **11-13** and three furanoheliangolides **14-16**.

The structure of **17** was deduced from the ¹H NMR spectral data, which were similar to those of **14-16**^{19,20}, only the signals of the ester group being replaced by those of the isobutyrate. The other signals were slightly shifted when compared with those of the unsaturated esters. The lactones **18** and **19** again differed only in the nature of the ester groups. The molecular formula of **18** was C₁₉H₂₄O₇. All oxygen functions were deduced from the ¹H NMR spectrum. In addition to signals of a methylene lactone, of a furanone moiety and a methacrylate, a downfield double doublet was present, which was separated from a second signal only in deuteriobenzene. Spin decoupling

showed that a hydroxyl group was at C-5, since an irradiation of the corresponding signal the double doublet at δ 4.40 collapsed to a doublet and a double doublet quartet (separated from a second signal only in deuterobenzene) to a broadened quartet. The latter further showed allylic coupling with H-2, typical in cases when a 4β -proton is present²⁰. The observed couplings of H-5, therefore, required a β -position of the hydroxyl group. Further decoupling led to the assignment of H-7 through H-9. The H-7 signal was easily assigned, since its irradiation collapsed the H-13 signals to singlets and those of H-6 to a doublet. The presence of an 8,12-lactone was deduced by comparing the corresponding signals with those of similar lactones. Accordingly, **18** was the 4(15)-dihydroderivative of a goyazensanolide isolated from a *Vanillosmopsis* species²¹.

Previous investigations of *Dicoma* species (tribe Mutisieae, subtribe Gochanatiinae) have shown that 14,15-oxygenated germacranolides may be typical for this genus^{22,5}. An investigation of the aerial parts of *Dicoma tomentosa* afforded urospermal-A (**20**), four new melampolides (**21-24**) and four germacranolides (**25-28**) together with 11 β ,13-dihydroderivative (**29**)²³ of urospermal-A.

The structure of **21** followed from the ¹H NMR spectral data, which were close to those of **20**. As expected, the H-15 signals were shifted to downfield. The spectra of **27** and **28** showed that we were dealing with the mono and diacetate of albicolide. All signals in the spectrum of **28** were assigned by spin decoupling. When the spectrum of **22** was compared with that of **27**, the difference in the

configuration of the 1,10-double bond became apparent. The downfield shift of the H-1 signal in the spectrum of **22**, if compared with the H-1 shift of **27**, supported a *cis*-1,10-double bond. The same is true in the spectrum of a diacetate, isolated previously from a *Dicoma* species²². The configuration of the 1,10-double bond has to be changed to 1,10-*cis*. The spectra of **23** and **24** showed that these lactones only differed at C-15, the former being an acetate and the latter the corresponding hydroxy compound. The *cis* configuration of the 1,10-double bond followed from the chemical shift of H-14. The ¹H NMR spectrum of **25** showed that this lactone was the 1,10-*trans* isomer of **23**, as indicated by the chemical shift of H-14. The spectral data of **26** showed that this lactone was the 8 α -hydroxy derivative of **28**. As is usual in the 8 α -hydroxy germacranolides the H-13' signal was shifted downfield and a coupling $J_{13,13'}$ was visible. Also H-7 was slightly deshielded by the 8-hydroxy group. The aerial parts of *Dicoma anomala* Willd. afforded germacrene D and four new germacran-8,12-olides (**30-33**). All these lactones were 15-hydroxy-14-acetoxygermacranolides with one addi-

tional ester group. The nature of the ester functions followed from their typical signals. The lactone **33** was a 3-hydroxy-2-methyl butyrate, as could be deduced from the doublet quartets at δ 2.45 and 3.90 as well as from the two doublets at δ 1.26 and 1.18. The flexibility of the ring system and the couplings $J_{7,8}$ indicated the presence of 8,12-lactones, while the chemical shifts of H-1 and H-5 required *trans*-double bonds. The α -orientation of the ester groups followed from the couplings $J_{5,6}$ and $J_{6,7}$. The aerial parts of *Dicoma schinzii* O. Hoffm. afforded three new germacranolides (**34-36**) closely related to albicolide²⁴.

The structure of **34** followed from its ¹H NMR spectrum. Irradiation at δ 2.76 showed that the signal was that of H-7 as the typical methylene lactone doublets collapsed to singlets, the double doublet at δ 4.76 to a doublet and the three fold doublets at δ 1.75 and 2.34 to double doublets. Further spin decoupling allowed the as-

segment of all signals. The stereochemistry of C-9 followed from the couplings observed, while the relative position of the isobutyrate residue followed from the chemical shifts of H-14. The ^1H NMR spectral data of **35** were close to those of **34**. However, the signals of H-15 were shifted downfield and signals of an additional isobutyrate residue were visible. Furthermore, a small shift of the H-14 signals indicated the usual conformation of germacranolides with both C-14 and C-15 above the plane. Compound **36** was a germacranolide with an acetate group. The ^1H NMR spectral data of **36** differed from those of **34** in the chemical shift of H-9 indicating that the acetate was at C-9. Furthermore, the H-1 signal was shifted downfield by δ 0.25, which could be an indication of a 1,10-*cis*-double bond. However, acetylation of **34** afforded the diacetate **37**, where the H-1 signal showed nearly the same chemical shift, showing that the downfield shift was due to the effect of the 9β -acetoxy group. As partial saponification of **36** was not successful, the relative position of the isobutyrate group could not be established. The proposed position seemed to be likely as all the other esters had a C_4 -ester group at C-14.

The chemistry of the genus *Dicoma* showed that highly oxygenated germacranolides, especially those with O-functions at C-14 and C-15, may be typical and perhaps for the subtribe as similar lactones have been isolated from *Actinoseris*²³, *Cnicothamnus*²⁵, *Gochnatia*²⁶ and *Wunderlichia*²³, while from *Pertya*²⁷ guaianolides were reported.

The genus *Blainvillea* (tribe Heliantheae) is placed in the subtribe Ecliptinae^{28,29}. So far the chemistry of only one species has been studied³⁰. The isolation of acanthospermolides was of taxonomic interest as this type of sesquiterpene lactones had not been observed previously in any genus of the subtribe Ecliptinae. The investigation of the aerial parts of *Blainvillea acmella* L. afforded four new germacranolides **38-41** related to ovatifolin and seven new acanthospermolides **42-48** along with desacetylovatifolin (**50**), desacylgrazielic acid tiglate (**51**) and 8β -[2-methylbutyryloxy]- 9β -hydroxy-14-oxo-acanthospermolide (**52**).

The structure of **38** was deduced from its ^1H NMR spectrum which was close to that of ovatifolin (**49**)³¹. However, the presence of an additional oxygen function was obvious as the pair of double doublets (H-9) were replaced by a doublet at δ 4.40. Furthermore, the H-8 signal was shifted downfield compared to the corresponding shift in the spectrum of ovatifolin. Typical signals of a 2-methylbutyrate indicated that this was the ester at C-8. The configurations at C-8 and C-9 followed from the small

couplings which only agreed with a β -oriented oxygen function. The molecular formula of **39** ($\text{C}_{15}\text{H}_{22}\text{O}_4$) together with its IR spectrum indicated the presence of a dihydroxylactone. The ^1H NMR spectrum showed some similarities to that of desacetylovatifolin (**50**)³². However, the absence of the exomethylene double bond was conspicuous. The characteristic signals of these protons were replaced by a methyl doublet and a double quartet which could be assigned by spin decoupling to H-11. The coupling of the latter clearly showed an α -orientated C-11 methyl group. The ^1H NMR spectrum of **40** was close to that of **39**. The presence of the corresponding tiglate followed from the typical ^1H NMR signals and the observed downfield shift of the H-8 signal. Thus **40** was the 8-O-tiglate of **39**. The ^1H NMR spectrum of **41** differed somewhat from that of **39** though many signals were similar. The absence of an H-8 signal together with a new pair of doublets below δ 3 clearly indicated a carbonyl group at C-8. All this agreed with the presence of desacetoxy-11 β ,13-dihydroovatifolin-8-one. Though lactone **42** gave no molecular ion the molecular formula could be deduced

from the presence of the $[M-RCO_2H]^+$ and the acyl (m/z 85) ions in the mass spectrum and the presence of a 2-methylbutyrate group according to the 1H NMR spectrum. The other 1H NMR spectral data strongly indicated that **42** was an isomer of **52**³⁰. As could be deduced from the chemical shifts of H-8 and H-9, **42** and **52** differed only in the position of the ester residue.

The 1H NMR spectra of **43-46** were in part very similar. The compounds **44-46** differed from each other only in the nature of the ester residue, which had to be placed at C-8 on the basis of spin decoupling. The typical ester signals showed that **44** was the acetate, **45** the tiglate and **46** the 2-methylbutyrate of **43**. The signals of **43** were in part very close to those of **42**. However, the absence of an oxygen function at C-9 led to the appearance of a pair of three fold doublets at δ 2.62 and 2.00. On the other basis of models it was clear that the first signal was that of H-9 α as in **42**, a *W*-coupling was observed between that proton (H-9 α) and H-14. Of course the absence of an ester group in **43** caused a considerable upfield shift of the signal of H-8. The 1H NMR spectrum of **47** showed similarities to that of **43**. However, in addition to some shift differences, the absence of an H-8 signal and the downfield shifts of the signals of H-7 and H-9 showed that the corresponding 8-keto derivative was present. The 1H NMR spectrum of **48**, whose molecular formula had two hydrogens less than that of **47**, showed the presence of an olefinic methyl (δ 1.96d) while no signals for H-7, H-8 and H-11 were observed. As however, the remaining signals were close to those of **47**, the presence of the 7,11-dehydro derivative of the latter could be deduced.

The isolation of several acanthospermolides from *Blainvillea acmella* again indicates that these compounds may be characteristic for the genus. So far, such sesquiterpene lactones with an aldehyde group at C-10 and a 8 β -oxygen function have been reported from *Acanthospermum*^{33,34}, *Smallanthus*³⁵, *Siegesbeckia*³⁶ and *Ichthyothere*³⁷, while from *Melampodium*³⁸, *Tetragonotheca*³⁹ and *Enhydra*⁴⁰ similar lactones with an ester group at C-10 have been isolated. The co-occurrence of acanthospermolides and ovatifolin derivatives in *Blainvillea* is an indication that enzymatic oxidation of the hydroxy group of C-14 may be accompanied by isomerization of the 1(10)-double bond. If this is true *Blainvillea* may be related to *Podanthus*, which is also placed in the subtribe Ecliptinae where lactones like **38** are present.

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