

Terpenoid Chemistry of *Mikania* Species[†]

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The terpene chemistry of the genus *Mikania* (Asteraceae, tribe Eupatorieae) is reviewed with emphasis on recent developments which suggest that mikanolide-type sesquiterpene dilactones, although prominent in members of the *Mikania scandens* complex, may not be chemical markers for the complex as suggested earlier.

The genus *Mikania*, the largest genus in the tribe Eupatorieae, family Asteraceae, comprises nearly 450 species and is almost entirely tropical American¹. Only a few *Mikania* species occur in the Old World; these are listed in Table 1². In Central and South America some of the more common species which go under the name 'guaco' are widely used in folk medicine, particularly against snake bite. The genus is one of the most easily recognized and most uniform genera in the tribe, hence apparently phylogenetically isolated within it, but difficulty is often encountered in species delimitation. Aside from the very large number of species the difficulty is due in large part to the existence of highly polymorphic species complexes¹.

TABLE 1—OLD WORLD *Mikania* SPECIES*

<i>M. capensis</i> DC	S. Africa north to central and eastern Africa, Madagascar
<i>M. carteri</i> Baker	Southern Nigeria and Cameroon
<i>M. chenopodifolia</i> Willd.	West and central tropical Africa south to Angola and Mozambique, Madagascar
<i>M. chevalieri</i> (C. Adams) Holmes & McDaniel	West tropical Africa
<i>M. cordata</i> (Burm. f.) Robinson	S. E. Asia, East Indies north to Taiwan
<i>M. micrantha</i> Kunth	Introduced from tropical America into S. E. Asia, East Indies etc.
<i>M. microptera</i> DC	Only disjunct <i>Mikania</i> species; Guianas, W. Venezuela, Awazan Basin; West tropical Africa/east to Uganda and south to Angola
<i>M. natalensis</i> DC	Natal
<i>M. sagittifera</i> Robinson	Zimbabwe north to Uganda, east to Angola

*Ref. 2.

One of these complexes comprises a group of taxa closely related to *M. scandens*. Table 2 is a listing of species included in a modern treatment of this so-called *M. scandens* complex by Holmes³. It is interesting that this complex includes all species listed in Table 1 except *M. microptera* about whose position within or without the complex, Holmes

TABLE 2—*Mikania scandens* AND RELATED SPECIES*

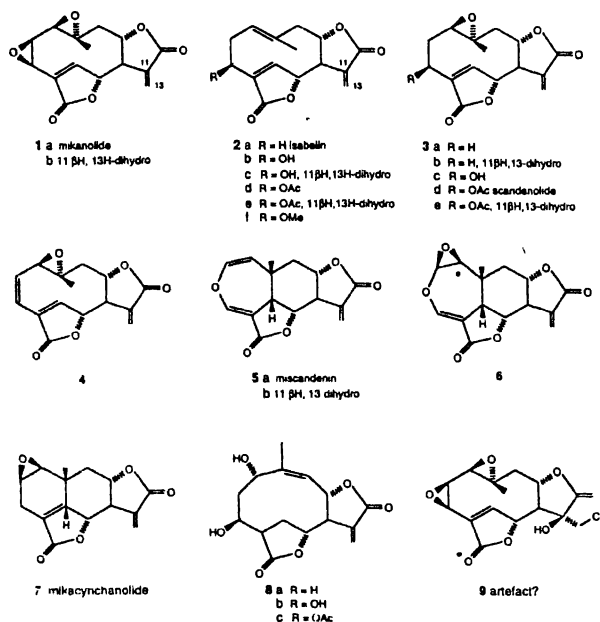
<i>M. amblyolepis</i> Robins. (= <i>M. panamensis</i> Ronins.) (Mexico, Panama, N. Colombia)
<i>M. batataefolia</i> DC** (S. Florida, Cuba, Bahamas)
<i>M. capensis</i> DC (see Table 1)
<i>M. carteri</i> , Baker (see Table 1)
<i>M. chenopodifolia</i> Willd. (See Table 1)
<i>M. chevalieri</i> (C. Adams) Holmes & McDaniel (see Table 1)
<i>M. congesta</i> DC** (Puerto Rico, Lesser Antilles, S. America to Peru, Bolivia and Brazil)
<i>M. cordata</i> (Burm. F.) Robinson** (see Table 1)
<i>M. cynanchifolia</i> Hook. & Arn.** (n.e. Argentina, Paraguay, S. Brazil, Uruguay)
<i>M. dusenii</i> Robins** (S. Brazil, E. Panama)
<i>M. ecuadoriensis</i> Holmes & McDaniel (s. coastal plain of Ecuador into N. Peru)
<i>M. mendocina</i> Phil.** (S. Brazil into Uruguay and C. Argentina)
<i>M. micrantha</i> HBK. (see Table 1)**
<i>M. minima</i> (Baker) Robinson** (Tucumán, Argentina)
<i>M. natalensis</i> DC (See Table 1)
<i>M. periplocifolia</i> Hook. & Arn.** (S. Brazil, Paraguay, S. Bolivia, Uruguay, N. Argentina)
<i>M. ranunculifolia</i> A. Rich (Cuba)
<i>M. sagittifera</i> Robins. (see Table 1)
<i>M. scandens</i> Willd.** (U.S. west coastal plain from Texas to S. Mass., interior along Mississippi embayment to Mo. and Ill.)
<i>M. ypacarayensis</i> Holmes & McDaniel** (= <i>M. trachypleura</i> Robinson) (N.E. Argentina to Rio de Janeiro)
<i>M. microptera</i> DC (see Table 1. Inclusion in complex not clear ^a)

*Ref. 3. **Chemistry reported. ^aRefs. 3, 4.

seems to be of two minds^{3,4}. In an earlier not readily accessible article⁵, I suggested that on the basis of what was then known about the chemistry of *Mikania* species dilactones of the mikanolide (1) type might be chemical markers for the *M. scandens* complex. The present review reconsiders this suggestion in the light of more recent results.

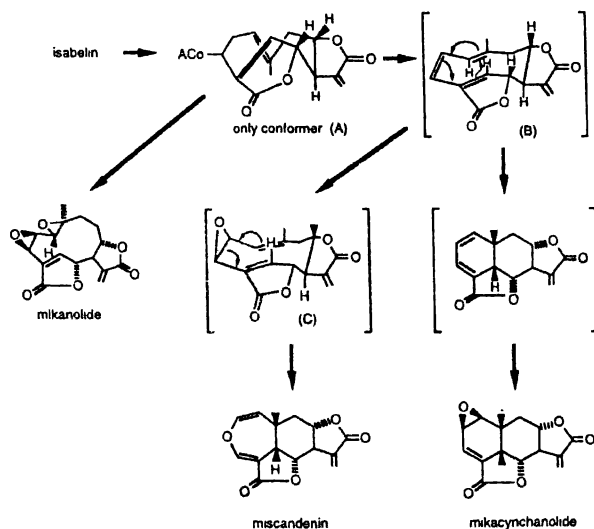
Scheme 1 lists naturally occurring mikanolide type sesquiterpene lactones, a type of lactones originally thought to be restricted to members of the *Mikania scandens* complex. Possible biogenetic relationships between various dilactones

[†]In honor of Prof. Sukh Dev's 75th. birthday.



Scheme 1. Mikanolide type sesquiterpene dilactones.

of Scheme 1 are shown in Scheme 2. A probable precursor for all of them is isabelin (2a) via 3-acetoxyisabelin (2d) whose conformation is shown as A. Biological epoxidation of A from the most accessible side would give scandenolide (3d); the same conformation is apparently also responsible for elimination of hydroxyl or acetate and eventual biological conversion to mikanolide. On the other hand, the stereochemistry of the congeners miscandenin (5a) and mikacynchanolide (7) shows that they are formed through transition states which resemble conformations B and C. Mikaperiplocolide (8a) can be thought of as having been

Scheme 2. Biogenetic type relationships among *Mikania* species dilactones.

formed from 2a by a biological version of the 'ene' reaction involving singlet oxygen.

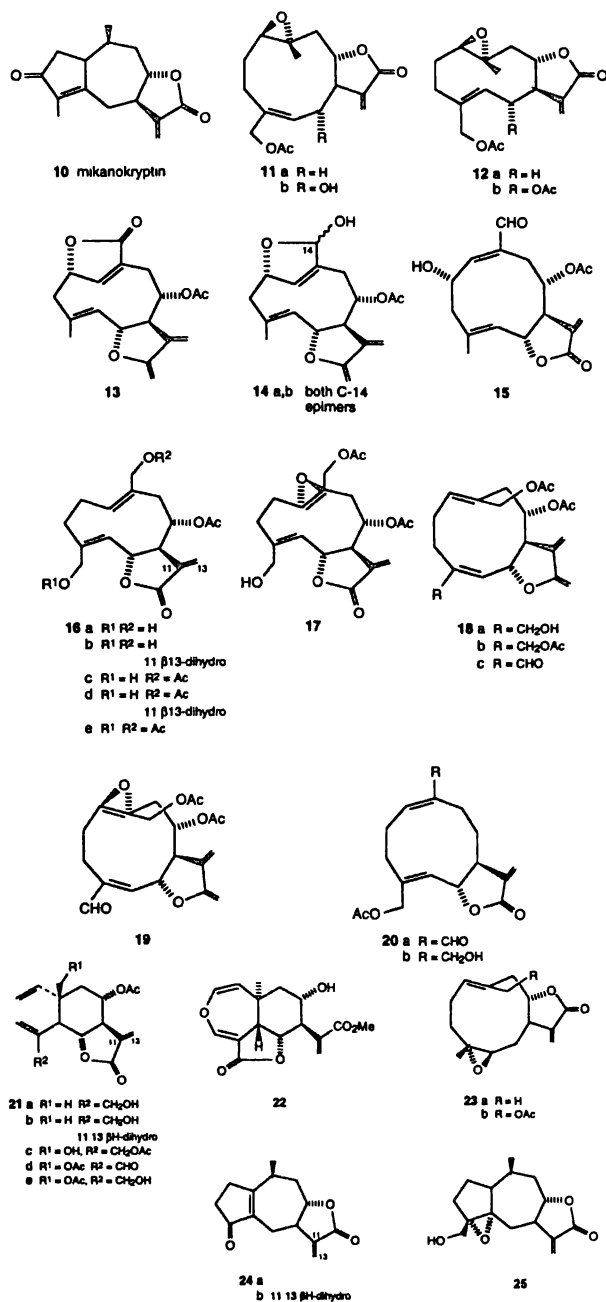
Table 3 lists those members of the *M. scandens* complex for which chemical records are currently available in the order in which they were first studied and also lists the sesquiterpene lactones isolated from them, both those of the mikanolide type (1-9, Scheme 1) and others depicted in Scheme 3. It is seen that while mikanolide type lactones have up to now been isolated from eight members of the complex three other complex members studied relatively recently, i.e. *M. congesta*²¹, *mendocina*²⁶ and *minima*^{22,23}, produce exclusively other types of lactones included in Scheme 3. Thus my original hypothesis seems to require modification. Lactone 22 is of course intimately related to mikanolide but dilactones 13 and 14a, b from *M. congesta*²¹ which is often confused with *M. micrantha* differ in type from mikanolide and its congeners and differ from some dilactones of *Elephantopus* species (Vernonieae)²⁷⁻²⁹ only in the nature of the ester function while monolactone 11a from *M. mendocina* is also found in several other members of the *M. scandens* complex.

A few other comments on Table 3 are in order. In the wide-ranging and polymorphic species *M. micrantha* au-

TABLE 3—SESQUITERPENE LACTONES FROM MEMBERS OF THE *M. scandens* COMPLEX

Species	Lactone constituents
<i>M. scandens</i> ^a	1a, b, 3a, c-e, 5a
<i>M. batataefolia</i> ^b	1a, b
<i>M. micrantha</i>	
(a) Canal Zone ^c	1a, b
(b) Canal Zone ^d	10
(c) Mexico ^e	10
(d) Paraguay ^e	1a, 3a, 5a
(e) Argentina ^f	
<i>M. cordata</i>	
(a) Malaysia ^g	1a, b
(b) Natal ^h	ent-Kaurenes
(c) Bangladesh ⁱ	1a, b, 3a, c
(d) Philippines ^j	1a, b, 3a, c, d, 9, 11a, b'
<i>M. cynanchifolia</i> ^k	2b, d, e, 5a, 6, 7
<i>M. periplocifolia</i>	1a, b, 2b, c, e, 3b, d, e, 5a, 7, 8b
<i>M. congesta</i> ^m	13, 14a, b, 15
<i>M. minima</i> ⁿ	16a-c, 17, 18a-c, 19, 20a, b, 21a-c
<i>M. dusenii</i> ^p	1a, b, 2b, 3a, c, 11a, b'
<i>M. ypacarayensis</i> ^p	1a, b, 2b, d, f, 3a, d, e, 4, 5b, 8a, c, 11a, 22
<i>M. mendocina</i> ^q	11a, 12a, 23a, b, 24a, b, 25

^aRefs. 6-8. ^bRef. 9. ^cRef. 10. ^dRefs. 10, 11. ^eRef. 12. ^fRef. 14. ^gRef. 15. ^hRef. 16; Misidentification. ⁱRef. 17. ^jRef. 18. ^kRef. 19. ^lRef. 20. ^mAlso contains geranylgeraniol derivatives. ⁿRefs. 21, 23. ^oRef. 24. ^pRef. 25. ^qRef. 26. ^rRevised from 12a, b in accordance with Ref. 26. ^{*}Also contains 12,14-dihydroxy-15-aceto-xylema-1,3,11(13)-triene.

Scheme 3 Other sesquiterpene lactones from members of the *M. scandens* complex

thenticated material from the Canal Zone gave, in accordance with the original hypothesis, dilactones **1a** and **1b**, while material from near-by, originally classified as *M. panamensis* ($\equiv$ *M. amblyolepis*) and later on as an aberrant form of *M. micrantha*, furnished a guaianolide which we named mikanokryptin^{10,11}. Mikanokryptin was subsequently obtained¹² also from a Mexican collection of '*M. micrantha*' not examined by McDaniel or Holmes which may actually have been *M. amblyolepis*, while mikanolide-type dilactones

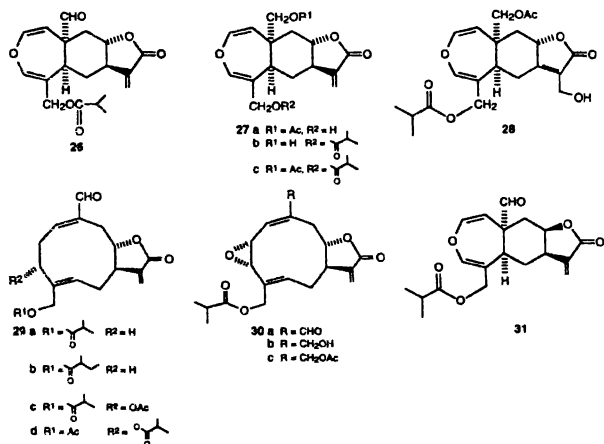
TABLE 4—REPORTS ON THE CHEMISTRY OF OTHER *Mikania* SPECIES

<i>M. alvimii</i> R. M. King & Robinson	<i>ent</i> -Labdanes ^{a,b}
<i>arrojadoti</i> Mattf	<i>ent</i> -Kauranes ^a
<i>banisteriae</i> DC	<i>ent</i> -Kauranes ^{c,d} , ozic acid ^c , 4-epiabiatic ^c acid, lactones from oxidation of furanoeudesmanes ^d , 1,6 α -dihydroxyeudesm-4(11)-ene ^d
<i>belemii</i> R. M. King & H. Robinson	<i>ent</i> -Kauranes ^e
<i>glomerata</i> Spreng	<i>ent</i> -Kauranes ^f
<i>hirsutissima</i> DC	<i>ent</i> -Kauranes ^g
<i>laevigata</i> Sch. Bip	<i>ent</i> -Kauranes ^f
<i>lindbergii</i> Baker	<i>ent</i> -Kauranes ^h
<i>luetzelbergii</i> Mattf	<i>ent</i> -Kauranes ^e
<i>oblongifolia</i> DC	<i>ent</i> -Kauranes ⁱ
<i>obtusata</i> DC	<i>ent</i> -Kauranes ⁱ
<i>officinalis</i> Marti	Geranylgeraniol derivatives ^e
<i>pyramidata</i> J. D. Smith	<i>ent</i> -Labdanes ^k
<i>saltensis</i> Hieron	Menthanes ^j
<i>sessilifolia</i> DC	Geranylgeraniol derivatives ^e , <i>ent</i> -kauranes ^e
<i>shushunensis</i> Holmes & McDaniel	Bisabolenes ^m
<i>smilacina</i> DC	Coumarin ⁿ
<i>triangularis</i> Baker	<i>ent</i> -Pimaranes ^{o,p} , <i>ent</i> -abieta-nes ^p , <i>ent</i> -kauranes ^p

^aRef 51 ^bRef 52, ^cRef 53 ^dRef 54 ^eRef 55 ^fRef 56 ^gRef 57
^hRef 58 ⁱRef 59 ^jRef 60 ^kRef 39 ^lRef 61 ^mRef 62 ⁿRef 63
^oRef 64 ^pRef 65

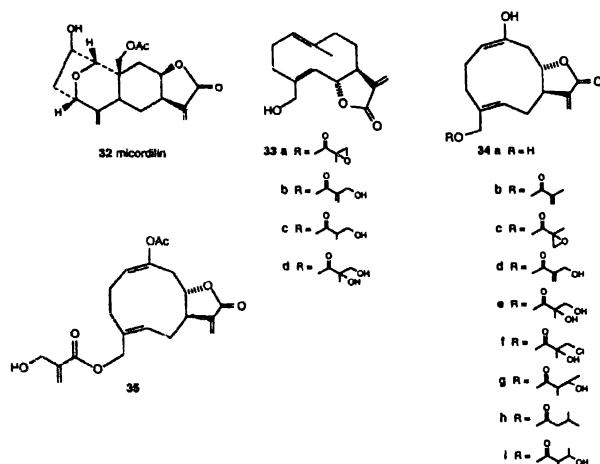
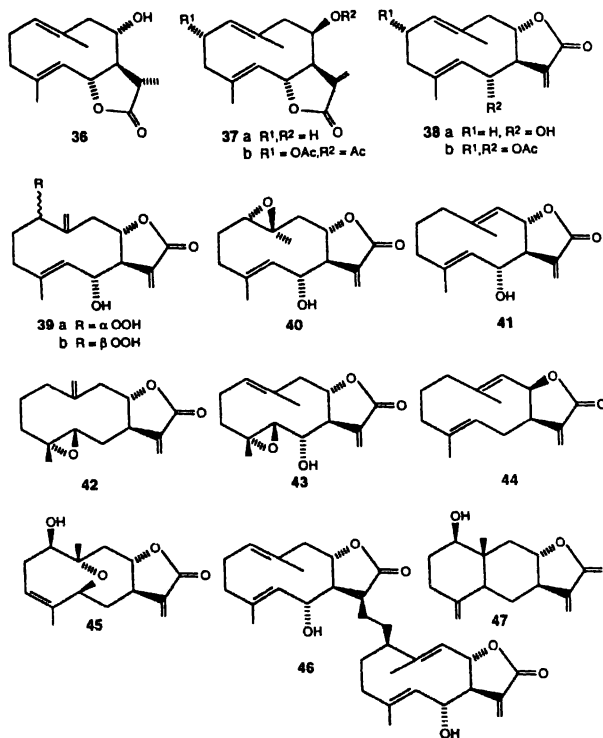
were isolated from Paraguayan¹³ and Argentinian¹⁴ *M. micrantha*. In the case of *M. cordata*, the identity of a collection from Natal which is quite outside the range of *M. cordata* but within the range of *M. capensis* and the rarely collected *M. natalensis*² is suspect, especially since three other collections from widely differing localities gave mikanolide-type dilactones. Finally, it is interesting that the only acyl ester function found in the lactones of Schemes 2 and 3 is acetate.

Also seemingly incompatible with my original hypothesis were reports^{30,31} on the Venezuelan species *M. monagasensis* Badillo, apparently a member of the *M. banisteriae* complex³³, which furnished **1a**, **1b** and an *ent*-kaurene, and our own much later work³³ on *M. urticaefolia* Hook. & Arn. which gave **1a**, **3**, **4**, **5a** and a geranylgeraniol derivative of a type also found in *M. perplotifolia* and *congesta*. *M. urticaefolia* is a species characteristic of the Chaco phytogeographical region whose distribution ranges from Southern Bolivia to the province of Córdoba, Argentina and the western region of Entre Ríos³⁴. It was not included in Holmes' original treatment³ of the *M. scandens* complex, although this exclusion may be subject to revision³⁵.

Scheme 4 Sesquiterpene lactones from *M. microptera* and *M. rimachii*.

The questionable position of *M. microptera* within or without the *M. scandens* complex^{3,4} seems to be reflected in the sesquiterpene lactone content of this species³⁶ which is shown in Scheme 4 together with a lactone **31** from *M. rimachii*,³¹ a new species from Peru closely related to *M. microptera*³⁷. Other noteworthy terpenoid constituents were nerolidol derivatives and 1 β ,6 α -dihydroeudesma-4(15), 11(13)-diene from *M. microptera* and olean-9(11),13-dien-3-one from *M. rimachii*.

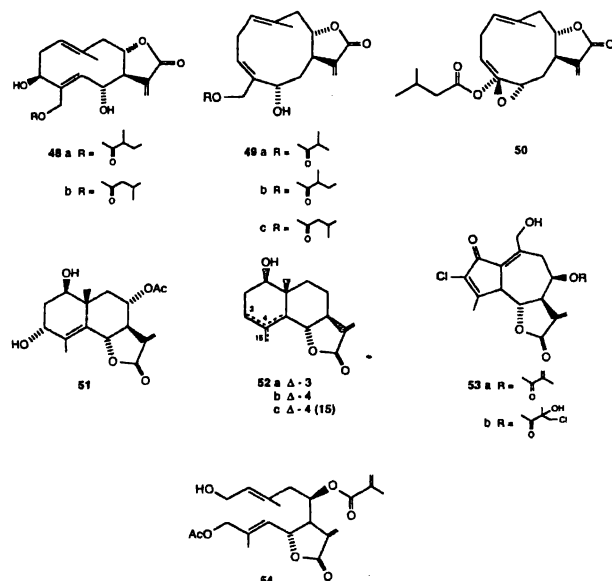
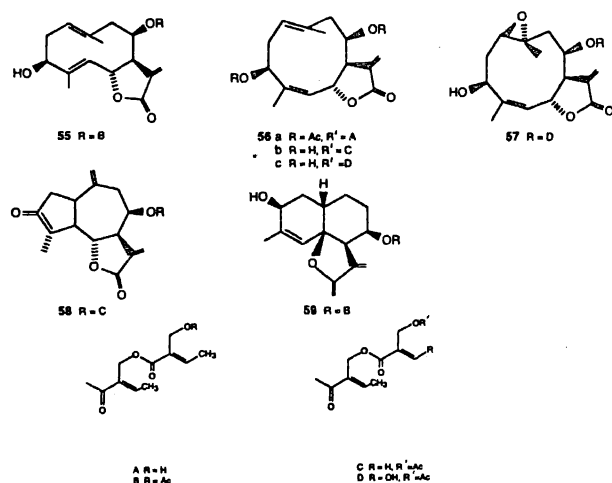
A group of species clustered around the very widespread taxon *M. cordifolia* (L.f.) A. Willd. is presumed to be close to the *M. scandens* complex¹; however, the reported chemistries of various collections of *M. cordifolia* differ significantly not only from those of most *M. scandens* complex members, but also from each other and one wonders whether the plant material was always correctly identified. Thus the earliest collection of *M. cordifolia* from Puerto Rico³⁸ gave the elemanolide micordilin **32** (Scheme 5) and a collection from Ecuador³⁹ gave the germacradienolides

Scheme 5 Sesquiterpene lactones from *Mikania cordifolia*.Scheme 6 Sesquiterpene lactones from *M. goyazensis*, *grazieleae*, *pohlii* and *purpurascens*.

33a-d. Only later collections from Argentina⁴⁰ and Costa Rica⁴¹ dovetailed, the former giving lactones **34a-h**, the latter giving lactones **34a-d, g-i** and **35**.

Scheme 6 illustrates a series of very similar germacranolides **36-46** from *M. goyazensis*⁴², *purpurascens*⁴³ and *pohlii*⁴⁴, three related taxa from Brazil, and from *M. grazieleae*, also from Brazil, which is morphologically somewhat similar to members of the *M. scandens* complex. The biogenetically related eudesmanolide **47** occurs in *M. goyazensis* and *M. pohlii*. The stereochemistries originally assigned to lactones **40**, **46** and **47** were corrected in subsequent work⁴⁵⁻⁴⁷. Six other *trans*-lactones closed to C-8, **48a, b**, and **50** (Scheme 7) have been reported from Costa Rican *M. holwayana* (the identity of the collection is in question since standard floras do not locate this taxon in Central America) which is quite unrelated to the *M. scandens* group while a collection of the wide-ranging species *M. guaco* from Costa Rica furnished a group of eudesmanolides **51** and **52a-c** closed toward C-6 and so far unique for *Mikania*⁴⁹. The somewhat polymorphic and wide ranging *M. vitifolia* from the same country gave guaianolides **53a, b**, the unusual *seco*-germacranolide **54** and *ent*-kaurenic acid⁴⁹.

Finally, *M. haenkeana* DC from Jujuy province, Argentina (this species ranges from Ecuador to northwestern Argentina) contained (Scheme 8) the germacradienolide **55**,

Scheme 7. Sesquiterpene lactones from *M. holwayana*, *guaco* and *vitifolia*.Scheme 8. Sesquiterpene lactones from *M. haenkeana*.

the heliangolides **56a-c** and **57**, the guaianolides **58a,b** and the cadinanolide **59** as well as several *ent*-kaurene derivatives⁵⁰. Among the more than 40 *Mikania* species investigated so far, this species is the only one to have yielded lactones of the type **55-59** with complex ester side-chains more typical of some genera within the subtribes Liatrineae, Oxylobinae and Critoniinae of the Eupatorieae and Peritylinae of the Heliantheae. Whether this constitutes a distinctive character of a group within *Mikania* will require further investigation.

From the preceding discussion it appears that diterpenes are not very conspicuous in extracts of *Mikania* species producing sesquiterpene lactones. Geranylgeraniol derivatives accompanied lactones in *M. periplocifolia*²⁰,

*congesta*²¹ and *urticaefolia*³³ while *ent*-kauranes were encountered in work on *M. monagasensis*³¹, *vitifolia*⁴⁹, *haenkeana*⁵⁰ and one collection presumed to be *M. cordata*. On the other hand, a very large proportion of the other *Mikania* species which have been investigated to date (Table 4) contains kauranes as major terpenoid constituents. However, since less than 10% of the known *Mikania* species have so far been studied chemically and since so far no attempts at infrageneric classification have gained acceptance, the question whether chemistry mirrors phylogeny in this large genus must remain open for the time being.

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