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TERPENOIDS OF *PIPTOTHRIX SINALOAE*

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Key Word Index—*Piptothrix sinaloae*; Compositae; Eupatorieae; thymol derivatives; sesquiterpene lactones; diterpene.

Abstract—In addition to three known thymol esters and five known sesquiterpene lactones, two new germacrolides and a new diterpene diester were isolated from the dichloromethane extract of the aerial parts of *Piptothrix sinaloae*. Structures for the new compounds were elucidated by chemical transformations and spectral methods. The current taxonomic status of *P. sinaloae* is discussed on the basis of both morphological and secondary metabolite data.

INTRODUCTION

The little known species *Piptothrix sinaloae* Blake is part of a species complex that includes *P. palmeri* Gray and *P. pubens* Gray. *P. sinaloae* is distinguished from the latter species by its eight-flowered rather than 11 flowered heads as well as sparse pubescence on the lower surface of its leaves [1]. *P. palmeri* is essentially glabrous. Recent morphological studies of these taxa [2] indicate that all three might be better considered as elements of a single variable species. Floret numbers in both *P. pubens* and *P. palmeri* ranges from 8 to 16 per head, while in the holotype of *P. sinaloae* the range is 6–9. In addition, there appears to be clinical variation in the amount of pubescence in the members of this complex, with the nearly glabrous *P. palmeri* in the northern end of the distribution range, the densely pubescent *P. pubens* in the southern end and *P. sinaloae*, with an intermediate amount of pubescence, in the middle. Other morphological features, including small heads and an extremely fragile pappus, link these three taxa together and distinguish them from other members of the genus [2].

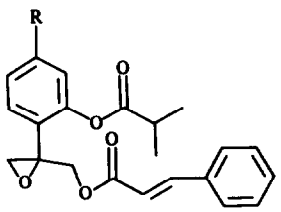
RESULTS AND DISCUSSION

Three known thymol derivatives were isolated from *P. sinaloae*. These three compounds were identified as tinifoline (**1**) [3, 4], acetyltinifoline (**2**) [5] and areolal (**3**) [5, 6] by comparison of their spectral and physical properties with those reported previously as well as by direct comparison with authentic samples.

Of the seven sesquiterpene lactones found in *P. sinaloae* five were previously isolated. The major compound in *P. sinaloae*, 8β-tigloyloxyparthenolide (**4**), was first reported from *Eupatorium serotinum* [7] and later from *Ageratina deltoidea* [8]. Of interest here is the occurrence of this compound also in one population of *Piptothrix areolare* [5]. Compound **5**, 15-hydroxy-8β-tigloyloxy costunolide, which was also recently identified from *E. serotinum* but from a different population than the one that yielded **4** [9], also co-occurs with **4** in *P. areolare*. A close analogue of **5**, cronquistic acid (**6**), was previously reported from a member of the subtribe Critoniinae *Cronquistianthus chachapoyensis* [10], as well as from *Eupatorium serotinum* [7]. The fourth known compound, the elemanolide **7**, which is the Cope rearrangement product of **6**, was also found in *C. chachapoyensis*. Finally, compound **8**, the 15-hydroxy analogue of 8β-tigloyloxyparthenolide, was isolated recently from yet another population of *E. serotinum* [11]. The previously unreported ^{13}C NMR data for **5** and **6** are listed in Table 1.

The first new compound **9**, $C_{20}H_{26}O_6$, was closely related to **4**, the major lactone of this species. The main difference in the ^{1}H NMR spectrum of **9** relative to that recorded for **4** (Table 2) was the absence of the vinyl proton signal representing H-1 and the shift of the H-14 methyl signal from δ1.73 to 1.45. Further, a new doublet of doublets not found in **4** appeared at δ2.91. These data together indicated that a 1,10 epoxy function group in **9** had replaced the 1,10 double bond of **4**.

The ^{13}C NMR spectrum of **9** (Table 1) corroborated this conclusion with two singlets at δ61.13 and 58.92 (C-4 and C-10) and two doublets at δ64.12 and 64.45 (C-1 and



R	
1	CH_2OH
2	CH_2OAc
3	CHO

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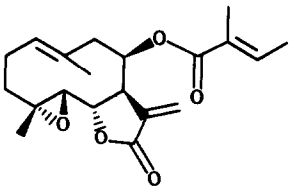

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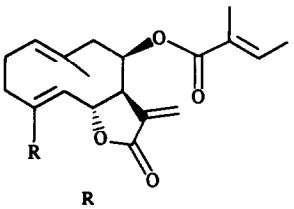
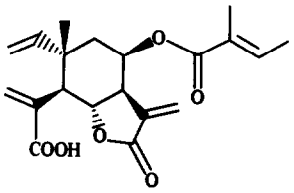


R
5 CH_2OH
6 COOH



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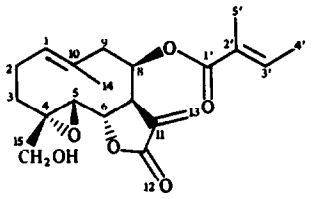
C-5), supporting the presence of both the 4,5 and 1,10 epoxy groups. The stereochemistry of the 1,10 epoxide was assumed to have a *trans* configuration, attached 1β,10α, since **9** should be biogenetically derived from **4** by enzymatic exo-epoxidation of its *trans*-1,10 double bond (as in all other known germacrolides containing this function). This configuration was also supported by the similarity of the coupling constants (*ca* 11 Hz) of the H-1 signal to those H-1 signals of 1,10 epoxidized germacrolides of X-ray crystallographically-confirmed structures [12]. Final proof of the structure was provided by the conversion of **4** with *m*-CPBA to a compound identical to **9** in all respects. Thus, **9** is 1β,10α-epoxy-8β-tigloyloxyparthenolide (= 1β,10α,4α,5β-diepoxy-8β-tigloyloxycostunolide).

The second novel lactone (**10**) ($C_{20}H_{22}O_7$) was more closely related to another known compound isolated from this species, namely, cronquistic acid (**6**) [10]. Analogous to the relationship between **4** and **9**, an epoxide function replaces the 1,10 double bond of cronquistic acid in the new compound (**10**). This was clearly indicated in the ^{1}H NMR spectrum of **10** (Table 2) by the doublet of doublets signal at δ2.78 (11.5, 2.5 Hz) in place of the vinyl



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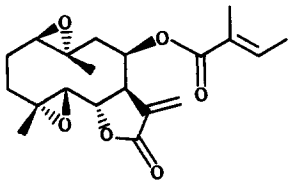

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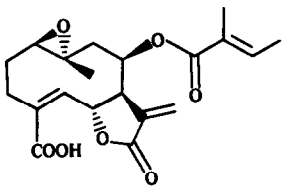

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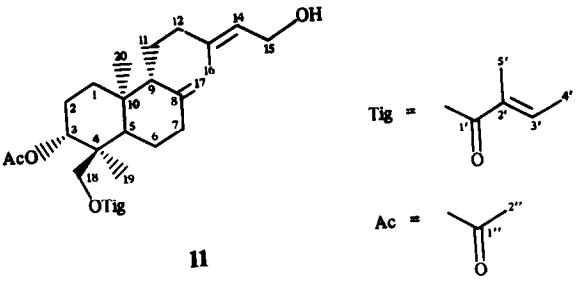
Table 1. ^{13}C NMR data for compounds **5**, **6** and **9** (δ, $CDCl_3$, TMS, 22.5 MHz)

C	5	6	9
1	128.83 *d*	129.09 *d*	64.12 *d**
2	26.86 *t*	27.38 *t*	24.39 *t*
3	35.57 *t*	35.70 *t*	34.73 *t*
4	144.24 *s*	131.70 *s*	61.13 *s*†
5	130.20 *d*	145.09 *d*	64.45 *d**
6	74.46 *d*	74.33 *d*	75.05 *d*
7	53.13 *d*	52.87 *d*	49.88 *d*
8	71.47 *d*	70.50 *d*	68.22 *d*
9	44.03 *t*	44.03 *t*	43.18 *t*
10	135.20 *s**	138.06 *s*	58.92 *s*†
11	136.63 *s**	135.59 *s*	135.91 *s*
12	169.87 *s*	169.15 *s*	168.44 *s*
13	121.48 *t*	121.94 *t*	122.72 *t*
14	18.79 *q*	18.73 *q*	20.16 *q*
15	61.21 *t*	171.43 *s*	17.04 *q*
1′	166.94 *s*	166.74 *s*	166.42 *s*
2′	128.11 *s*	127.92 *s*	127.85 *s*
3′	138.91 *d*	139.43 *d*	139.17 *d*
4′	12.22 *q*	12.03 *q*	12.23 *q*

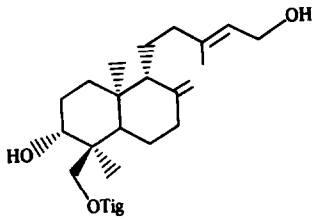
*,† Assignments interchangeable within a column.

Table 2. ^{1}H NMR data of compounds **9** and **10** (δ, J values in Hz in parenthesis, $CDCl_3$, TMS, 200 MHz)

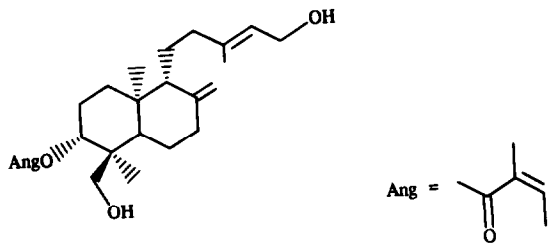
H	9 (at 55°)	10
1	2.91 *dd* (1.8, 10.4)	2.78 *dd* (2.5, 11.5)
5	2.97 *d* (9)	6.21 *d* (10)
6	5.41 *t* (9)	6.13 *t* (10)
7	3.11 *br ddd* (4, 4.4, 9)	2.93 *m*
8	5.73 *br d* (5)	5.78 *br d* (6.4)
9a	2.95 *dd* (6.4, 14.7)	2.83 *dd* (5, 14.8)
9b	2.21 *br d* (14.7)	
14	1.45 *s*	1.13 *s*
15	1.34 *s*	
3'	6.81 *dq* (1.8, 7.2)	6.88 *br q* (7)
4'	1.81 *br dt* (0.9, 7.2)	1.81 *br d* (7)
5'	1.82 *br s*	1.80 *br s*



11



11a



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proton doublet of doublets at δ5.02 in **6**. Similarly, the H-14 methyl signal shifted upfield from δ1.33 in **6** to 1.13 in **10**. Apparently, the C-15 acid function in both compounds shields the C-14 methyl relative to its chemical shift in the other C-15 methyl compounds (e.g. **4** and **9**). Although most other ^{1}H NMR signals were similar for the two compounds, one noteable difference in the spectra of cronquistic acid (**6**) and **10** is the downfield position of the H-5 vinyl signal (*ca* 0.7 ppm) in **10** compared to its chemical shift in **6**. Examination of Dreiding models indicate a 1β,10α configuration for the epoxide group in the new compound would place the oxygen atom in a position close enough to deshield the vinyl proton on C-5. Thus, **10** is 1β,10α-epoxycronquistic acid.

The final new compound (**11**) ($C_{27}H_{42}O_7$) appeared from its ^{1}H NMR spectrum (Table 3) to be a bicyclic diterpene containing two ester functions. This followed from the presence of signals for both a tiglate moiety (δ6.81, *br q*, methyls at δ1.79, *br d*; 1.80, *br s*) and an acetoxy group (methyl at δ2.08, *s*), as well as methyl singlets at δ0.76, 0.88 and 1.69. A broadened vinylic proton triplet at δ5.40 was coupled to a terminal hydroxymethylene signal (AB pair at δ3.68 and 3.86, J = 11.6 Hz) and allylically to the methyl signal at δ1.69 indicating the presence of an allyl alcohol terminated labdane side chain in **11**. In addition, two broad singlets at δ4.57 and 4.88, a two-proton doublet at δ4.18 and a broad doublet of doublets signal at δ4.89 were accounted for by an exocyclic methlene, an acyloxmethylene and an acyl geminal proton, respectively. These data are best accomodated by a labdane skeleton. Indeed, the ^{1}H NMR spectrum of **11** is quite similar to that of the labdane **12** recently isolated from *Gutierrezia sarothrae* [13] suggesting that they differ only in the esters attached to the skeleton (Table 3). Compound **12** contains only a single angeloyloxy group, In contrast to **11** which is a diester. Comparison of the ^{1}H NMR spectra of **11** and **12** clearly showed that one of the esters in **11** must be attached at C-18 since the AB pattern in **11** shifted downfield *ca* 0.6 ppm from its position in **12**. The other ester was attached, as in **12**, at C-3. The correspondence of coupling constants in both compounds suggested that the orientation of the C-3 ester was the same (i.e. α). The relative position of the two esters in **11** was determined by partial hydrolysis with 1% NaOH in ethanol at 4° for 1 hr. Under these mild conditions the acetyl moiety was preferentially removed. From this reaction a product (**11a**) was obtained which lacked the acetate methyl signal in its ^{1}H NMR spectrum (Table 3) as expected. Further, the H-3 doublet of doublets was shifted upfield to δ3.41, while the H-18 signal was not significantly altered. This clearly indicated that in **11** the acetoxy group was attached at C-3, while the tiglate ester was at C-18. Although the absolute streochemistry of **11** was not rigorously proven, the similarity of its optical rotation ($[\alpha]_D = -48°$) to that of **12** ($[\alpha]_D = -60°$) [13] indicated that **11** is most likely an *ent*-labdane. Therefore, **11** can be formulated as 3α-acetoxy-15-hydroxy-18-tigloyloxy-*ent*-labda-8(17), 13*E*-diene. The ^{13}C NMR data for **11** were in accord with this structure and are presented in Table 4.

The terpenoid chemistry of *Piptothrix sinaloae* appears to be distinct from that of *P. palmeri* and *P. pubens* [14], although the corresponding 10-benzoyloxy ester of **1** is

Table 3. ^{1}H NMR data for compounds **11**, **11a** and **12** [13] (δ, J values in Hz in parenthesis, $CDCl_3$, TMS)

H	**11** (200 MHz)	**11a** (200 MHz)	**12** (400 MHz)
3	4.89 *br dd* (4.4, 11.5)	3.41 *br dd* (5.8, 10.5)	5.00 *br dd* (4.5, 12)
7	2.41 *br ddd* (2.1, 4, 13)	2.42 *br ddd* (2.1, 4, 13)	2.39 *br d* (13)
12			2.16 *m*
14	5.40 *br t* (7)	5.40 *br t* (7)	5.39 *br t* (7)
15	4.18 *br d* (7)	4.18 *br d* (7)	4.14 *br d* (7)
16	1.69 *br s*	1.69 *br s*	1.68 *br s*
17a	4.88 *br s*	4.88 *br s*	4.85 *br s*
17b	4.57 *br s*	4.57 *br s*	4.53 *br s*
18a	3.86 *br d* (11.6)	3.86 *br d* (11.6)	3.35 *br d* (12)
18b	3.68 *br d* (11.6)	3.68 *br d* (11.6)	2.97 *br d* (12)
19	0.88 *s*	0.78 *s*	0.75 *s*
20	0.76 *s*	0.73 *s*	0.68 *s*
3′	6.81 *br q* (7)	6.89 *br q* (7)	6.01 *qq* (1, 7)
4′	1.79 *br d* (7)	1.83 *br d* (7)	1.98 *dq* (1, 7)
5′	1.80 *br s*	1.84 *br s*	1.86 *dq* (1, 1)
OAc	2.08 *s*		

Table 4. ^{13}C NMR data for compound **11** ($\delta CDCl_3$, TMS, 22.5 MHz)

C		C	
1	37.84 *t**	15	59.31 *t*
2	23.60 *t*†	16	16.23 *q*
3	74.33 *d*	17	107.24 *q*
4	41.23 *s*	18	65.75 *t*
5	47.41 *d*	19	13.27 *q*
6	23.80 *t*†	20	15.02 *q*
7	36.42 *t*	1′	167.52 *s*
8	147.89 *s*	2′	129.02 *s*
9	56.12 *d*	3′	137.09 *d*
10	39.21 *s*	4′	14.31 *q*
11	22.18 *t*	5′	12.10 *q*
12	38.42*	1″	171.10 *s*
13	139.88 *s*	2″	20.18 *q*
14	123.56 *d*		

Assignments based on correlation with spectral data of 'analogous compounds' [16, 17].
*†Assignments interchangeable.

found in *P. palmeri* (as well as in *P. jaliscensis*) [2]. This could be used to argue for the valid specific status of *P. sinaloae*. However, these data must be interpreted in the light of the chemical variation observed within *P. areolare* [5], the most closely related species to this complex. In *P. areolare* similar chemical differences are found from the northern to the southern end of its range. Moreover, analogous morphological variation is found in *P. areolare* along its range (i.e. head size and pubescence), which in the *P. palmeri–sinaloae–pubens* complex is used to justify the specific level recognition of each taxon. Infraspecific recognition of variants within *P. areolare* have not been proposed, with the exception of variety *leiocarpum* B. L. Robinson, which may be more closely related to *P. jaliscensis* rather than to *P. areolare* [2].

At the generic level the compounds isolated are again consistent with a close relationship to at least part of *Ageratina*. As was mentioned above, the thymol derivatives **1–3** are similar or identical to compounds found in several *Ageratina* species. Further, thymols esterified with cinnamic acid are not reported from other genera in the tribe [2]. The sesquiterpene lactones, on the other hand, present a more complicated picture. While at least one of the compounds (**4**) has been isolated previously from a species in the subgenus *Neogreenella*, *A. deltoidea* [8], others have been reported from a species in *Eupatorium*, *sensu stricto* [7, 9, 11, 15] and another from a taxon placed in *Cronquistianthus* [10]. These two genera in the subtribes Eupatoriinae and Critoniinae are not generally considered close to Oxylobiinae where *Ageratina* and *Piptothrix* are assigned. The occurrence of similar compounds in divergent lineages in the tribe may not be too surprising considering the nature of the compounds. All of the lactones isolated are characterized by simple oxidations around C-4, C-5 and C-15, and to a lesser extent the C-1, C-10 double bond (**9** and **10**). The basic skeleton is the biosynthetically unspecialized 8β-tigloyloxycostunolide. It is likely that similar oxidative pathways could have arisen independently several times in the tribe.

The last compound isolated, the *ent*-labdane **11**, also supports a relationship with *Ageratina*. Although such compounds are not restricted to *Ageratina*, similar compounds in both the *ent* and normal series have been reported from *Ageratina* (*cf A. mairetiana*, [2]). Labdane diterpenes have so far not been found in *Eupatorium*, *sensu stricto*, or *Cronquistianthus*.

EXPERIMENTAL

Plant material. Leaves and heads of *Piptothrix sinaloae* (210 g) were collected on 21 November 1984 in Mexico from the State of Durango 1 km north of the Durango–Sinaloa border along the Mazatlan–Durango highway, municipality of El Salto, elevation 2500 m (23°40′ N; 105°40′ W). At the time of collection the population was mostly past flowering. A voucher specimen, Barrie & Gage No. 1265, is deposited in the Herbarium of the University of Texas at Austin (TEX).

Extraction and isolation of the compounds. Unground plant material was extracted with CH_2Cl_2 for 20 min. The extract was concd to a syrup, then the concentrate was taken up in MeOH. The resulting soln was filtered through cotton and then the filtrate was diluted with H_2O until an 80%MeOH soln was obtained. This aq. soln was then partitioned against hexane (x4), concd until only H_2O remained, and then partitioned against CH_2Cl_2 (x2). The combined CH_2Cl_2 extract was dried with dry $MgSO_4$ and then concd to a golden syrup (2 g). The whole extract was dissolved in a minimum vol. of MeOH–CH_2Cl_2 (3:1) and chromatographed over Sephadex LH-20 packed in the same solvent. Fractions were examined by TLC and combined accordingly. The combined fractions from the first column were then

separately run through a second Sephadex LH-20 column packed in cyclohexane–CH_2Cl_2–MeOH (7:4:1). Compounds from the second column were further purified if necessary by prep. TLC [silica gel, 2 mm layer, CH_2Cl_2–C_6H_6–EtOAc (3:3:1, 2:2:1 and 1:1:1)]

1β,10α-Epoxy-8β-tigloyloxyparthenolide (**9**). White amorphous solid (9 mg). EIMS (direct probe) *m/z* (rel. int.): 362 $[M]^+$ (0.3), 262 $[M - \text{tiglic acid}]^+$ (2.4), 246 (15), 244 $[M - \text{tiglic acid} - H_2O]^+$ (4), 83 $[\text{tiglate}]^+$ (45); IR ν_{max}^{KBr} cm^{-1}: 1755, 1710, 1660, 1270, 1155, 897.

Epoxidation of **4**. Twenty mg of *m*-CPBA were added to a soln of compound **4** (20 mg) in 5 ml CH_2Cl_2 and stirred for 30 min at room temp. The usual work-up afforded 1β,10α-epoxy derivative of **4** (21 mg) which was identical in physical and chemical properties to **9**.

1β,10α-Epoxycronquistic acid (**10**) Colourless gum (6 mg). EIMS (direct probe) *m/z* (rel. int.) 376 $[M]^+$ (not observed), 276 $[M - \text{tiglic acid}]^+$ (0.5), 232 $[M - \text{tiglic acid} - COOH + H]^+$ (4), 83 $[\text{tiglate}]^+$ (78); IR ν_{max}^{KBr} cm^{-1}: 3500–2750, 1775, 1690, 1715, 1640, 1270.

3α-Acetoxy-15-hydroxy-18-tigloyloxy-ent-labda-8(17), 13E-diene (**11**). Colourless gum (44 mg). EIMS (direct inlet) *m/z* (rel. int.): 446 $[M]^+$ (not observed), 428 $[M - H_2O]^+$ (0.6), 368 $[M - AcOH - H_2O]^+$ (1), 328 $[M - \text{tiglic acid} - H_2O]^+$ (2.1), 268 $[M - AcOH - \text{tiglic acid} - H_2O]^+$ (7), 253 $[M - AcOH - \text{tiglic acid} - H_2O - Me]^+$ (10.4), 83 $[\text{tiglate}]^+$ (91); CIMS (CH_4, 0.5 torr, direct probe) *m/z* (rel. int.): 447 $[M + H]^+$ (0.84), 445 $[M - H]^+$ (2.32), 429 $[M + H - H_2O]^+$ (2.85), 387 $[M + H - AcOH]^+$ (1.46), 385 $[M - H - AcOH]^+$ (2.05), 347 $[M + H - \text{tiglic acid}]^+$ (11.9), 345 $[M - H - \text{tiglic acid}]^+$ (31.7), 329 $[M + H - \text{tiglic acid} - H_2O]^+$ (65.1), 287 $[M + H - \text{tiglic acid} - AcOH]^+$ (25.4), 285 $[M - H - \text{tiglic acid} - AcOH]^+$ (58.5), 269 $[M + H - \text{tiglic acid} - AcOH - H_2O]^+$ (100), 101 $[\text{tiglic acid} + H]^+$ (11.1); IR ν_{max}^{KBr} cm^{-1}: 3600, 1742, 1715, 1650, 1263, 1240, 1160, 890.

Partial hydrolysis of **11**. Twenty mg of **11** were dissolved in an ice cold 1% ethanolic NaOH soln (3 ml) and kept in a refrigerator for 1 hr. Later the mixture was poured into 20 ml of an ice-water mixture and extracted with Et_2O (2 × 15 ml). The combined Et_2O extract was dried with dry $MgSO_4$ and evapd to dryness *in vacuo*. The crude product was purified with prep. TLC to yield 6 mg **11a**. IR ν_{max}^{KBr} cm^{-1}: 1710, 1645, 1240, 1163, 893; EIMS (direct inlet) *m/z* (rel. int.): 404 $[M]^+$ (0.3), 386 $[M - H_2O]^+$ (2.3), 368 $[M - 2 \times H_2O]^+$ (5.6), 304 $[M - \text{tiglic acid}]^+$ (4.6), 286 $[M - \text{tiglic acid} - H_2O]^+$ (12.5), 268 $[M - \text{tiglic acid} - 2 \times H_2O]^+$ (14.6), 83 $[\text{tiglate}]^+$ (95).

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