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GUAIANOLIDES FROM *CALEA SUBCORDATA*

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Key Word Index—*Calea subcordata*; Asteracae; Heliantheae, sesquiterpene lactones, guaianolides

Abstract—Chemical analysis of *Calea subcordata* yielded three new guaianolides, 8-epi-isobutyrylrupicolin A, 8-epi-isobutyrylrupicolin B and subcordatolide A, which represent the first guaianolide-type sesquiterpene lactones reported in the genus *Calea*. The structures of the new compounds were established by chemical and spectroscopic methods.

INTRODUCTION

As part of our biochemical systematic study of the subtribe Galinsoginae, tribe Heliantheae [1] we have analysed *Calea subcordata* of section *Calea* from the State of Tachira, Venezuela for their sesquiterpene lactone constituents. Previous studies on the genus *Calea* have yielded germacrolides, heliangolides and eudesmanolides, but the presence of guaiolides has not yet been reported in *Calea* species. This paper describes the isolation and structure determination of three new guaianolide type sesquiterpene lactones from *Calea subcordata*.

RESULTS AND DISCUSSION

8-epi-isobutyrylrupicolin (**1**), $C_{19}H_{24}O_5$ was a gum with an IR spectrum showing the presence of a tertiary hydroxyl group (3580 and 1150 cm^{-1}), a γ-lactone (1765 cm^{-1}), saturated ester(s) (1725 cm^{-1}), and carbon–carbon unsaturation(s) (1665 cm^{-1}). The α-methylene-γ-lactone moiety was further corroborated by the ^{1}H NMR spectrum of **1** which exhibited two one-proton doublets at δ6.30 (H-13a) and 5.54 (H-13b), and a multiplet at δ3.38 (H-7). The ester substituent was assigned to an isobutyrate group on the basis of diagnostic ^{1}H NMR signals (a one-proton heptet at δ2.47, and two three-proton doublets at δ1.09 and 1.06), together with characteristic mass spectral peaks at *m/z* 71 (A^1) and 43 (A^2). The CD spectrum showed a negative Cotton effect (CE) at 250 nm, suggesting a *trans*-fused 12,6α-lactone or a *cis*-fused 12,8β-lactone [2]. Further assignments of the basic skeleton were deduced from extensive double irradiation experiments in different solvents, the results being summarized in Table 1.

Saturation of the multiplet at δ3.38 (H-7) changed the doublet of doublets at δ5.79 (H-8) to a doublet, simplified the doublet of doublets at δ4.43 (H-6) to a doublet, and collapsed the two one-proton doublets at δ6.30 (H-13a) and 5.54 (H-13b) to singlets. Irradiation of the doublet of doublets at 4.43 (H-6) changed the multiplet at δ3.38 (H-7), and collapsed the broadened doublet at δ2.78 (H-5) to a singlet. Similarly, irradiation of the doublet of doublets at δ5.79 (H-8) collapsed the broadened doublet at δ5.59 (H-9) to a singlet. On the basis of chemical shift arguments, the doublet of doublets at δ4.43 was assigned to a proton on a lactonic carbon, and the doublet of doublets at δ5.79 to a proton on a carbon carrying the ester function. The ^{1}H NMR spectrum suggested the presence of two olefinic methyl groups, which appeared as broadened three-proton singlets at δ2.00 (C-10-Me) and 1.98 (C-4-Me). Saturations of H-3 (δ5.54) and H-9 (δ5.59) sharpened the respective C-4-Me and C-10-Me signals, indicating allylic positions of H-3 and H-9 in relation to the C-4-Me and C-10-Me, respectively.

On the basis of the chemical shift of H-5 (δ2.78) and its multiplicity (doublet, $J_{5,6}$ = 12.0 Hz), as well as the multiplicity of H-6, which appeared as a doublet of a doublet with large coupling constants ($J_{5,6}$ = 12.0 and $J_{6,7}$ = 10.0 Hz), a guaianolide-type skeleton for the new compound can be postulated. Based on the above spectroscopic evidence one can formulate this new lactone as a 12,6α- *trans*-lactonized guaianolide with an isobutyrate group at C-8 and a hydroxyl group at C-1. The CD data presented above support the presence of a 12,6α-*trans* lactone since Geissman's rule [2] can be generally applied to guaianolides [3].

The configurations at C-5, C-6 and C-8 could be derived from the ^{1}H NMR coupling constants which were correlated with dihedral angles obtained from stereomodels. The large couplings $J_{5,6}$ = 12.0 Hz and $J_{6,7}$ = 10.0 Hz clearly indicated antiperiplanar arrangements of H-5, H-6 and H-7. Assuming an α-orientation of H-7 as in all sesquiterpene lactones from higher plants [3], we concluded that H-5 is α and H-6 β. The small coupling constant $J_{7,8}$ = 3.0 Hz was in accord with α-orientation of H-8, that is, a β-oriented isobutyrate group at C-8.

The configuration at C-1 was determined by *in situ* acylation of the hydroxyl group with trichloroacetyl isocyanate [4]. The ^{1}H NMR spectrum of the trichloroacetylcarbamate derivative (**4**) of **1** showed one NH signal at δ8.32, providing further evidences for the presence of a hydroxyl group in compound **1**. The paramagnetic acylation shifts of H-5 from δ2.38 in **1** to δ3.19 in **4** ($\Delta\delta$ = 0.81, C_6D_6) clearly demonstrated a relative *cis*-configuration of H-5 and the hydroxyl group at C-1 [4]. Further corroboration for a C-1α-hydroxyl was provided by the downfield shift of H-7 from δ2.76 in compound **1** to

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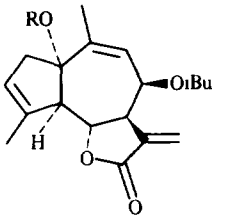

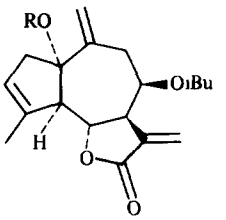

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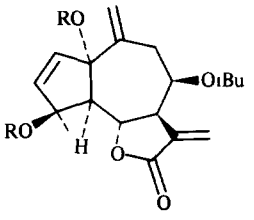
4 R = —C(=O)—NH—C(=O)—CCl_3

2 R = H

5 R = —C(=O)—NH—C(=O)—CCl_3



R

3 H

6 Ac

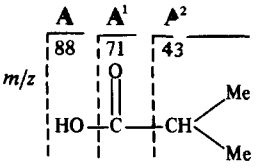


Table 1. ^{1}H NMR spectral data* of compounds **1** and **2**, **3** and **6** (200 MHz in $CDCl_3$ [C_6D_6] with TMS as internal standard)

	1	2	3	6
H-2a	2.66 –2.26] *m*	2.91 [2.53] *br d* (17.8)	5.57 [5.54] *d* (5.5)	6.34 *d* (5.5)
H-2b		2.49 [2.07] *br d* (17.8)		
H-3	5.51–5.57† [6.18–6.24]†	5.50–5.58† [5.19]‡	5.93 [5.91] *d* (5.5)	6.73 *d* (5.5)
H-5	2.78 [2.38] *br d* (12.0)	2.79 [2.41] *br d* (11.0)	2.44 [2.64] *d* (11.2)	3.06 *d* (11.2)
H-6	4.43 [4.34] *dd* (12.0; 10.0)	4.38 [4.44] *dd* (11.0; 9.8)	4.62 [4.74–4.76] *dd* (11.2; 9.0)	4.73 *dd* (11.2, 9.0)
H-7	3.38 [2.76] *dddd* (10.0; 3.0; 3.8; 3.5)	3.40 [2.96] *dddd* (9.8; 2.5; 3.8; 3.4)	3.50 [3.51] *m*	3.39 *m*
H-8	5.79 [5.61] *dd* (7.0; 3.0)	5.52–5.58† [5.29] *dt* (4.8, 2.5)	5.49 [5.45] *m*	5.49 *m*
H-9a	5.59 [5.46] *br d* (7.0)	3.08 [2.80] *dd* (15.0; 5.0)	3.13 [3.24] *dd* (14.5; 4.0)	2.58 *dd* (14.5, 2.5)
H-9b		2.37 {2.17} *dd* (15.0; 5.0)	2.36 [2.38] *dd* (14.5; 2.5)	2.41 *dd* (14.5; 4.0)
H-13a	6.30 [6.20] *d* (3.8)	6.28 [6.20] *d* (3.8)	6.24 [6.24] *d* (3.5)	6.35 *d* (3.3)
H-13b	5.54 [5.14] *d* (3.5)	5.52 [5.13] *d* (3.4)	5.56 [5.12] *d* (3.5)	5.64 *d* (3.3)
H-14a	1.98 [1.75] *br s* (3H)	5.18 *br s* [4.94] *br d* (1.3)	4.83 [4.75] *br s*	5.01 *br s*
H-14b		4.96 [4.72] *br s*	4.81 [4.75]$^+$ *br s*	4.99 *br s*
C-4-Me	2.00 [1.93] *br s*	1.89 [1.84] *br s*	1.33 [1.40] *br s*	1.61 *br s*
OiBu	2.47 [2.14] *h* (7.2)	2.46 [2.17] *h* (7.2)	2.44 [2.22] *h* (7.2)	2.55 *h* (7.0)
	1.09/1.06 [0.94/0.86] *d* (7.2)	1.12/1.09 [0.94/0.89] (7.2)	1.07/1.04 [0.95/0.93] *d* (7.2)	1.12 *d*/1.10 *d* (7.0)
OAc	—	—	—	2.10 *s*, 2.04 *s*

*Multiplets are given by the usual symbols: *s* = singlet, *d* = dobulet, *t* = triplet, *q* = quartet, *m* = multiplet, and *br* = broadened Chemical shifts are recorded in ppm relative to TMS Coupling constants (*J*) or line separations in Hz are given in parentheses.

†Obscured by other signals.

‡Narrow multiplet.

δ3.86 in the derivative **4** ($\Delta\delta$ = 1.10, C_6D_6). With H-5 and H-7 having an α-orientation, as outlined before, it can be concluded from the paramagnetic acylation shifts of these two protons that the hydroxyl group at C-1 must also be α-oriented.

8-Epi-isobutyrylrupicolin B (**2**), $C_{19}H_{24}O_5$, is a gum which exhibited in the ^{1}H NMR spectrum two one-proton doublets at δ6.28 (H-13a) and 5.52 (H-13b), and a multiplet at δ3.40 (H-7) which are characteristic of an α-methylene-γ-lactone. This was corroborated by an IR absorption at 1765 cm^{-1}. A one-proton heptet at δ2.46 and two three-proton doublets at δ1.12 and 1.09, together with strong mass spectral peaks at *m/z* 71 (A^1) and 43 (A^2) indicated the presence of an isobutyrate side chain. Furthermore, IR absorptions at 3470 and 1150, 1725 and 1660 cm^{-1} suggested the presence of tertiary hydroxyl(s), ester(s) and carbon–carbon double bond(s).

Compounds **1** and **2** showed very similar ^{1}H NMR signals for H-3, H-5, H-6, H-7, H-13 and H-15 suggesting a guaianolide skeleton for **2**. However, instead the C-10 methyl singlet at δ1.98 in **1**, in **2** two broadened one-proton singlets at δ5.18 (H-14a) and 4.96 (H-14b) appeared, suggesting an exocyclic methylene group at C-10. In addition, two H-9 protons were indicated by two one-proton doublets of doublets at δ3.08 and 2.37 with a large geminal coupling ($J_{9a,9b}$ = 15.0 Hz) and a small coupling to H-8 ($J_{8,9a} = J_{8,9b}$ = 2.5 Hz).

Following the same arguments as for guaianolide **1**, the large coupling constant $J_{5,6}$ = 11.0 Hz and $J_{6,7}$ = 9.8 Hz in compound **2**, were in accord with a *trans*-pseudoaxial disposition of these protons, allowing the stereochemical assignments H-5α and H-6β with reference to H-7α. The small coupling constant $J_{7,8}$ = 2.5 Hz indicated a β-orientation of the iso-butyrate side-chain at C-8. The CD spectrum of compound **2** exhibited a negative Cotton effect at 260 nm, which according to Geissman's rule [2] supported the presence of a *trans*-fused 12,6α-lactone.

The stereochemistry at C-1 was established as in compound **1** by *in situ* acylation with trichloroacetyl isocyanate [4]. The ^{1}H NMR spectrum of the trichloroacetylcarbamate derivative (**5**) of compound **2** showed one NH signal at δ8.55, and paramagnetic acylation shifts for H-5 ($\Delta\delta$ = 0.65, C_6D_6) and for H-7 ($\Delta\delta$ = 0.48, C_6D_6), which indicated an α-orientation for the tertiary hydroxyl group at C-1.

Subcordatolide A (**3**), $C_{19}H_{24}O_6$, was a gum with an ^{1}H NMR spectrum showing signals typical for an α-methylene-γ-lactone moiety [two one-proton doublets at δ 6.24 (H-13b) and 5.56 (H-13a), and a multiplet at δ 3.50 (H-7)]. The IR spectrum also exhibited a characteristic γ-lactone absorption at 1760 cm^{-1}. Other IR bands indicated the presence of hydroxyl groups (3580 and 3440 cm^{-1}), ester(s) (1725 cm^{-1}) and carbon–carbon unsaturation(s) (1640 cm^{-1}). The ester side-chain was identified as an iso-butyrate group on the basis of diagnostic ^{1}H NMR signals (a one-proton heptet at δ2.44, and two three-proton doublets at δ1.07 and 1.04), together with typical mass spectral peaks at *m/z* 71 (A^1) and 43 (A^2). Assignments of the ^{1}H NMR signals were derived from detailed spin decoupling experiments, the results of which are summarized in Table 1.

A distinct feature of the ^{1}H NMR spectrum of compound **3** was the appearance of two one-proton doublets at δ5.93 (H-3) and 5.57 (H-2) coupled only with each other, as shown by double irradiation. The magnitude of this coupling ($J_{2,3}$ = 5.5 Hz) suggested a double bond in a five membered ring. This feature together with the multiplicities of H-5, H-6, H-7 and H-8 suggested a guaianolide type skeleton represented by structures **3**.

Table 2. ^{13}C NMR spectral data* for compound **3**

Carbon	δ, multiplicity	Carbon	δ, multiplicity
C-1	85.7 *s*‖	C-11	144.0 *s*
C-2	140.2 *d*†	C-12	176.0 *s*
C-3	134.6 *d*†	C-13	122.1 *t*
C-4	82.0 *d*‖	C-14	116.8 *t*
C-5	66.5 *d*‡	C-15	23.9 *q*
C-6	67.3 *d*‡	C-1′	169.7 *s*
C-7	46.2 *d*	C-2′	34.0 *d*
C-8	76.8 *d*	C-3′	19.0 *q*§
C-9	35.8 *t*	C-4′	18.8 *q*§
C-10	135.0 *s*		

*The spectrum was obtained in $CDCl_3$ at ambient temperature at 50.32 MHz. Chemical shifts are given in ppm relative to TMS as determined by proton noise decoupling. Peak multiplicity was obtained by off-resonance decoupling (2.5 ppm above TMS), and are designated as usual: *s* = singlet, *d* = doublet, *t* = triplet and *q* = quartet

†‡§‖Assignments interchangeable

The ^{13}C NMR spectral data (Table 2) corroborated the ^{1}H NMR assignments for compound **3**. The analysis of the spectrum showed three primary, three secondary, seven tertiary and six quaternary carbons, accounting for 19 carbon atoms in the molecule. Moreover, the presence of two singlets at δ85.7 (C-1) and 82.0 (C-4), which correspond to quaternary carbon atoms bearing hydroxyl group, provided further confirmation of the presence of two tertiary hydroxyl groups in subcordatolide A.

Acetylation of compound **3** with acetic anhydride/4-dimethylaminopyridine [5] gave the diacetate **6**, $C_{23}H_{30}O_8$, which lacked the hydroxyl absorptions in the IR spectrum, but instead gave an additional broad carbonyl band at 1730 cm^{-1} (saturated ester groups). The ^{1}H NMR spectrum of **6** showed two three-proton singlets at δ2.10 and 2.04 indicating the presence of two acetate groups in the molecule. The paramagnetic acetylation shifts of H-5 from δ2.44 in compound **3** to 3.06 in **6**, and the C-4-Me from δ1.33 in **3** to 1.61 in the diacetate provided not only further evidence for the presence of hydroxyl groups at C-1 and C-4, but also arguments for proposing probable configurations for these centers.

The stereochemistry at C-5, C-6 and C-8 was deduced from the observed coupling constants in the ^{1}H NMR spectrum of **3**. Assuming on biogenetic grounds that H-7 is α-oriented [3], the observed value for $J_{5,6}$ = 11.2 Hz necessitated an α-orientation for H-5 and a β-orientation for H-6. Similarly, from the small coupling $J_{7,8}$ an α-orientation for H-8 was concluded, and therefore a β-configuration for isobutyrate side-chain at C-8.

The configuration of C-1 was suggested by comparison of the ^{1}H NMR spectra of **3** with **1** and **2**, and Dreiding model considerations. The appearance of the lactonic H-6 in compound **3** at the usual chemical shift position for this type of proton (δ4.62), and the absence of a paramagnetic acetylation shift for H-6 in the diacetate **6**, were a clear indication of the α-orientation of the hydroxyl group at C-1. Further confirmation of this orientation was given by the downfield shift of H-5α in **6**, which also indicated a relative *cis*-configuration of H-5 and the hydroxyl group at C-1.

On the basis of stereo model considerations and by comparison of the chemical shifts of H-5α, H-6β and the C-4-Me group in subcordatolide A and its diacetate derivative **6**, with the corresponding chemical shifts of similar guaianolides from *Athanasia* [6] and *Ursinia* species [7, 8], we tentatively suggest a β-orientation for the hydroxyl group at C-4 as the most probable configuration at this center.

EXPERIMENTAL

Calea subcordata S. F. Blake was collected on 12 September, 1979 in the State of Tachira, Venezuela, 13.3 km from Delicias along the road toward Villa Paez (L Urbatsch, No. 3427, voucher deposited at LSU, U.S.A.). The air-dried plant material (456 g) was extracted and worked up as described previously [9], providing 16.4 g of the crude syrup. The crude terpenoid syrup was chromatographed on a silica gel column with petrol–Me_2CO mixtures of increasing polarity, 64 fractions of 200 ml each being collected

Fractions 25–28 (0.8 g) were rechromatographed on silica gel with $CHCl_3$–Me_2CO mixtures with 26 fractions of 50 ml each being collected. From these, fractions 9–11 (68 mg) were further purified by prep. TLC on silica gel with Et_2O–petrol (3:1), giving 27 mg of 8-epiisobutyrylrupicolin A (**1**) and 24 mg of 8-epiisobutyrylrupicolin B (**2**).

Fractions 36–37 (2.1 g) of the first chromatographic run were rechromatographed on a silica gel column with $CHCl_3$–Me_2CO mixtures of increasing polarity, yielding 56 fractions of 100 ml each. Fractions 41–46, after further purification by prep TLC, afforded 450 mg of subcordatolide A (**3**).

8-Epi-isobutyrylrupicolin A (**1**). $C_{19}H_{24}O_5$, gum; UV λ_{max}^{MeOH} nm: 214 (ε 5.83 × 10^3), CD (MeOH; *c* 1.88 × 10^{-4}, *c'* 2.08 × 10^{-3}): $[\theta]^{c'}_{250}$ − 1.37 × 10^2, $[\theta]^{c}$ 207 − 5.30 × 10^4; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 1765 (γ-lactone), 1725 (ester), 1665 (double bond), 1150 (tertiary alcohol); EIMS (probe) *m/z* (rel. int.). 244 $[M-A]^+$ (19.3), 229 $[M-A-Me]^+$ (9.3), 227 $[M-A-OH]^+$ (4.0), 226 $[M-A-H_2O]^+$ (5.2), 216 $[M-A-CO]^+$ (4.2), 211 $[M-A-H_2O-Me]^+$ (4.5), 200 $[M-A-CO_2]^+$ (2.7), 199 $[M-A-CO-OH]^+$ (7.5), 198 $[M-A-CO-H_2O]^+$ (2.8), 71 $[A^1]^+$ (64.8), 43 $[A^2]^+$ (100.0). CIMS (methane) *m/z*: 333.2 (M + 1).

8-Epi-isobutyrylrupicolin B (**2**). $C_{19}H_{24}O_5$, gum, UV λ_{max}^{MeOH} nm: 215 (ε 6.47 × 10^3); CD (MeOH, *c* 2.08 × 10^{-4}, *c'* 1.43 × 10^{-3}): $[\theta]^{c'}_{260}$ − 6.04 × 10^2, $[\theta]^{c}_{211}$ − 8.62 × 10^3; IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3470 (OH), 1765 (γ-lactone), 1725 (ester), 1660 (double bond), 1150 (tertiary alcohol); EIMS (probe) *m/z* (rel. int.). 332 $[M]^+$ (2.1), 244 $[M-A]^+$ (40.2), 229 $[M-A-Me]^+$ (9.4), 226 $[M-A-H_2O]^+$ (12.0), 216 $[M-A-CO]^+$ (8.0), 211 $[M-A-H_2O-Me]^+$ (5.6), 201 $[M-A-CO-Me]^+$ (18.0), 200 $[M-A-CO_2]^+$ (6.0), 198 $[M-A-CO-H_2O]^+$ (7.1), 71 $[A^1]^+$ (55.6), 43 $[A^2]^+$ (100.0). (Found: (MS) 332.1622. $C_{19}H_{24}O_5$ requires: 332.1623.)

Subcordatolide A (**3**) $C_{19}H_{24}O_6$, gum; UV λ_{max}^{MeOH} nm· 206 (ε 8.74 × 10^3); CD (MeOH; *c* 2.27 × 10^{-4}): $[\theta]_{240}$ − 2.91 × 10^3, $[\theta]_{209}$ − 1.44 × 10^4; IR $\nu_{max}^{CHCl_3}$ cm^{-1}. 3580 (OH), 3440 (OH), 1760 (γ-lactone), 1725 (ester), 1640 (double bond), 1155 (tertiary alcohol); EIMS (probe) *m/z* (rel. int.): 260 $[M-A]^+$ (2.9), 243 $[M-A-OH]^+$ (5.1), 242 $[M-A-H_2O]^+$ (23.3), 227 $[M-A-H_2O-Me]^+$ (11.6), 217 $[M-A-Me-CO]^+$ (6.6), 216 $[M-A-CO_2]^+$ (1.7), 214 $[M-A-H_2O-CO]^+$ (8.6), 199 $[M-A-H_2O-CO-Me]^+$ (16.4), 71 $[A^1]^+$ (82.1), 43 $[A^2]^+$ (100.0). CIMS (methane) *m/z* 349.2 (M + 1)

Subcordatolide A diacetate (**6**). 100 mg of compound **3** were acetylated with Ac_2O (3 ml), 4-dimethylaminopyridine (2.2 mg) and NEt_3 (0.03 ml) at 60° for 3.5 hr Excess anhydride was destroyed with H_2O and the mixture extracted with $CHCl_3$. The organic layer was washed with N HCl, 10% aq. Na_2CO_3 and dried Removal of the solvent under red pres. gave 48 mg of an oily product which after purification by prep TLC ($CHCl_3$–Me_2CO, 19:1) yielded 21 mg subcordatolide A diacetate (**6**), $C_{23}H_{28}O_8$, gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3025 (double bond), 1765 (γ-lactone), 1730, 1720 (satd esters), 1665 (double bond), 1635 (double bond); EIMS (probe) *m/z* (rel. int.)· 373 $[M-AcO]^+$ (1.9), 372 $[M-AcOH]^+$ (0.2), 331 $[M-AcO-CH_2{=}CO]^+$ (1.9), 330 $[M-AcO-Ac]^+$ (7.4), 329 $[M-AcOH-Ac]^+$ (0.8), 314 $[M-2AcO]^+$ (1.4), 313 $[M-AcO-AcOH]^+$ (4.3), 312 $[M-2AcOH]^+$ (1.4), 243 $[M-AcO-CH_2{=}CO-A]^+$ (16.3), 242 $[M-AcO-Ac-A]^+$ (38.2), 228 $[M-AcO-CH_2{=}CO-A-Me]^+$ (11.8), 227 $[M-AcO-Ac-A-Me]^+$ (6.4), 226 $[M-2AcO-A]^+$ (10.2), 225 $[M-AcO-AcOH-A]^+$ (46.5), 224 $[M-2AcOH-A]^+$ (21.0), 71 $[A^1]^+$ (68.3), 43 $[Ac]^+$, $[A^2]^+$ (100.0).

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