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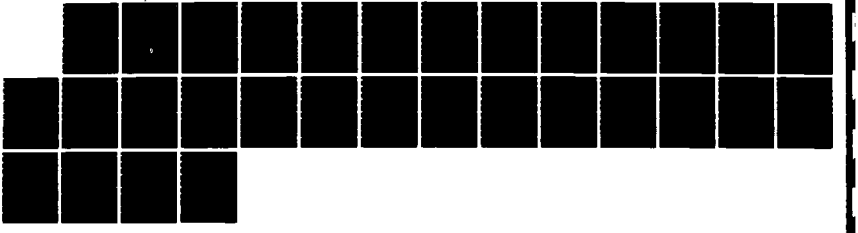

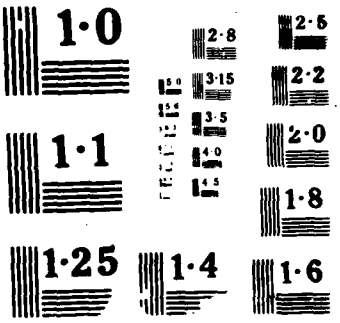
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CHEMICAL RESEARCH, DEVELOPMENT & ENGINEERING CENTER

CRDEC-TR-87013

MASS SPECTRAL INVESTIGATIONS ON TOXINS

V. DIRECT ANALYSIS OF MACROCYCLIC TRICHOTHECENES IN FERMENTATION SAMPLES BY NEGATIVE ION TANDEM MASS SPECTROMETRIC TECHNIQUES

by Thaiya Krishnamurthy, Ph.D.
Emory W. Sarver, Ph.D.
RESEARCH DIRECTORATE

February 1987

U.S. ARMY ARMAMENT MUNITIONS CHEMICAL COMMAND

Aberdeen Proving Ground, Maryland 21010-5423

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SECURITY CLASSIFICATION OF THIS PAGE

AD-A179 014

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION: UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution is unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): CRDEC-TR-87013	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: CRDEC; 6b. OFFICE SYMBOL (If applicable): SMCCR-RSL	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): Aberdeen Proving Ground, MD 21010-5423	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: CRDEC; 8b. OFFICE SYMBOL (If applicable): SMCCR-RSL	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code): Aberdeen Proving Ground, MD 21010-5423	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO.; PROJECT NO. 1L161101; TASK NO. A91A; WORK UNIT ACCESSION NO. TA 3-A

11. TITLE (Include Security Classification)
Mass Spectral Investigations on Toxins. V. Direct Analysis of Macrocyclic Trichothecenes in Fermentation Samples by Negative Ion Tandem Mass Spectrometric Techniques

12. PERSONAL AUTHOR(S)
Krishnamurthy, Thaiya, Ph.D., and Sarver, Emory W., Ph.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Technical	FROM 83 Sep TO 84 Mar	1987 February	28

16. SUPPLEMENTARY NOTATION
This work was presented at the 32nd Annual Conference on Mass Spectrometry and Allied Fields, San Antonio, TX, May 1984.

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP
15	02	

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
Toxins; Mycotoxins; Trichothecenes; Negative ions; Macrocyclic trichothecenes
(Continued on reverse)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Due to the extended conjugation in the molecules, macrocyclic trichothecenes formed negatively charged molecular (M^-) ions more effectively than positively charged quasi-molecular ions under chemical ionization (methane) conditions. These M^- ions underwent collisionally activated dissociation (CAD) (argon) yielding the daughter ions characteristic of the macrocyclic ester bridges. Structures for various specific and abundant daughter ions have been proposed; and the daughter ions and experimental conditions for selectively detecting these trichothecenes have been selected. A semisynthetic, macrocyclic trichothecene has been found to be adequate as an internal standard for quantifying macrocyclic trichothecenes under CAD conditions. Low quantities (1 to 2 ng) of Roridin H and Satratoxins have been detected under these same conditions. Preliminary results indicate that the negative ion chemical ionization-mass spectrometry/mass spectrometry method can be applied to analyzing real-life samples.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT: ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION: UNCLASSIFIED
22a. NAME OF RESPONSIBLE INDIVIDUAL: TIMOTHY E. HAMPTON	22b. TELEPHONE (Include Area Code): (301) 671-2914; 22c. OFFICE SYMBOL: SMCCR-SPS-T

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

18. SUBJECT TERMS (Continued)

Chemical ionization;
Tandem mass spectrometry;
MS/MS
Daughter mass spectra
Collisionally activated dissociation;

PREFACE

The work described in this report was authorized under Project No. 1L161101A91A, In-House Laboratory Independent Research, Technical Area 3-A. This work was started in September 1983 and completed in March 1984.

The use of trade names or manufacturers' names in this report does not constitute an official endorsement of any commercial products. This report may not be cited for purposes of advertisement.

Acknowledgments

The authors gratefully acknowledge Professor Donald F. Hunt and Dr. Jeffrey Shabanowitz of the University of Virginia (Charlottsville, VA) for generously providing their laboratory facilities for the authors' use and for their help and interest during this investigation; and Dr. Henry Fales of the National Institute of Health (Bethesda, MD) and Professor Bruce B. Jarvis of the University of Maryland (College Park, MD) for their continued interest and valuable suggestions throughout the investigation.

*This work was completed when the U.S. Army Chemical Research, Development and Engineering Center (CRDEC) was known as the U.S. Army Chemical Research and Development Center (CRDC).

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V. DIRECT ANALYSIS OF MACROCYCLIC TRICHOTHECENES IN FERMENTATION SAMPLES BY NEGATIVE ION TANDEM MASS SPECTROMETRIC TECHNIQUES

1. INTRODUCTION

For decades, trichothecene mycotoxins, products of several species of imperfect fungi, have been implicated in the loss of crops and farm animals and in human health problems caused under natural and induced circumstances.[1-7] A class of trichothecenes with large, polar, and labile ester bridges (macrocyclic trichothecenes) (Figure 1) are considered the most toxic of all trichothecenes.[1-6]

Hence, to prevent any losses or disasters, environmental and agricultural samples must be monitored to detect the presence of all trichothecenes and their fungal sources.

Several mass spectrometric (MS) methods,[7-10] including a highly sensitive and accurate negative ion chemical ionization (NICI) method (Krishnamurthy, Wasserman, and Sarver, unpublished data, October 1985), have been used for analyzing simple trichothecenes. However, despite the intensely toxic nature of the macrocyclic trichothecenes, only two methods [gas chromatography/negative ion chemical ionization mass spectrometric (GC/NICIMS)] for analyzing these molecules were reported.[11*] Both involve the alkaline hydrolysis of the molecules into their corresponding alcohols, followed by derivatization and analysis by the GC/MS technique. Even though these are sensitive and accurate methods, the procedure is time consuming and identifies only the alcohol moiety not the total structure.

During our continuing efforts to develop rapid, sensitive, and accurate analytical methods for all known trichothecenes, we found the collisionally activated dissociation (CAD) mass spectrometric (MS/MS) technique suitable for identifying and analyzing these polar, thermally labile molecules directly without lengthy sample processing and preparations. When these molecules with extended conjugation were subjected to the chemical ionization (CI) process using methane as the CI reagent gas, the negatively charged molecular (M^-) ions were formed more abundantly than the positively charged quasimolecular ions. The M^- ions were subjected to CAD using argon as the collision gas, and the recorded MS/MS spectra indicated daughter ions which were characteristic of

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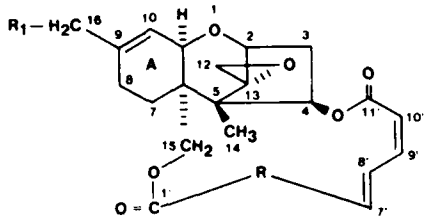
*Part of information provided was from unpublished data by Krishnamurthy, Greene, Jarvis, and Sarver (April 1986).

the ester bridges. Under these conditions, trace quantities (1 to 2 ng) of these highly polar molecules with labile, ester bridges could be detected with excellent specificity. A synthetically modified macrocyclic trichothecene was investigated and found to be adequate as an internal standard for quantifying these complex molecules by the direct MS/MS method.



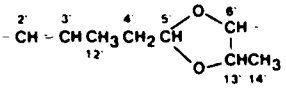
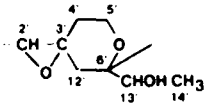
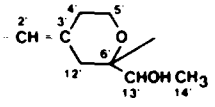
		R_1	OTHER
RORIDIN A (1)	$-CHOH\,CH\,CH_3\,CH_2\,CH_2\,OCH\,CHOH\,CH_3$	H	–
RORIDAN H (2)		H	–
SATRATOXIN G (3)		H	–
SATRATOXIN H (4)		H	–
VERRUCARIN A (5)	$-CHOH\,CH\,CH_3\,CH_2\,CH_2\,O\,C(=O)-$	H	–
9,10-EPOXYVERRUCARIN A (6)	$-CHOH\,CH\,CH_3\,CH_2\,CH_2\,O\,C(=O)-$	H	9,10-EPOXY
16-HYDROXYVERRUCARIN A (7)	$-CHOH\,CH\,CH_3\,CH_2\,CH_2\,O\,C(=O)-$	OH	–
8-KETOVERRUCARIN A (8)	$-CHOH\,CH\,CH_3\,CH_2\,CH_2\,O\,C(=O)-$	H	8-KETO
VERRUCARIN J (9)	$-CH{=}C\,CH_3\,CH_2\,CH_2\,O\,C(=O)-$	H	–

Figure 1. Macrocyclic Trichothecenes

2. EXPERIMENTAL

A Finnigan-MAT mass spectrometer with a 3000 source modified for the CAD experiments[12] was used throughout the investigation. All the CI spectra were recorded with the source temperature and pressure maintained at 100 °C and 0.5 torr, respectively. The direct exposure probe (DEP) was heated from 100 to 350 °C at 25 deg/min. The collision gas pressure and collision energy were maintained at 2.6 mtorr and 15 eV, respectively.

The macrocyclic trichothecene standards and stachybotrys fermentation samples were generously provided by Professor Bruce B. Jarvis of the University of Maryland (College Park, MD) and Dr. Robert M. Eppley of the Bureau of Foods, Food and Drug Administration (Washington, D.C.). All standard solutions were prepared in glass-distilled methanol (Burdick & Jackson, Muskegon, MI) and stored at 2 °C in reacti-vials fitted with mininert valves (Supelco, Incorporated, Supelco Park, PA).

3. RESULTS AND DISCUSSION

Relatively simple, rapid, specific, sensitive, and accurate methods for detecting trichothecenes in agricultural and environmental samples are required for public safety and prevention of economic loss. Reliable methods of analyzing the macrocyclic trichothecenes (Figure 1) are unknown. Due to their low volatility and labile ester bridges, these molecules or their derivatives cannot be passed through a GC column without substantial decomposition. Instead, these polar esters must be subjected to alkaline hydrolysis, converted into their volatile esters, and have their derivatives analyzed by the GC/MS technique.[11*] The only reported, sensitive, and applicable GC/MS method of analysis involves monitoring the negative ions (NI) of the heptafluorobutyryl (HFB) derivatives (of the hydrolysates) formed under CI conditions.* This method, although accurately quantifying alcohols and, thus, indirectly analyzing the macrocyclic trichothecenes, involved lengthy sample processing and provided only partial identity of the analytes.

Hence, we explored the possibility of applying the direct chemical ionization (DCI)-MS/MS technique to directly, specifically detect and possibly quantify these compounds. The results of our investigation led to developing an MS/MS method of analysis which met our requirements.

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* Part of information provided was from unpublished data by Krishnamurthy, Wasserman, and Sarver (October 1985) and unpublished data by Krishnamurthy, Greene, Jarvis, and Sarver (April 1986).

Producing molecular ions or other high mass ions in great abundance is essential for any successful CAD investigation.[13,14] Therefore, the efficiencies of molecular ion formation of some representative macrocyclic trichothecenes were studied under CI conditions using methane as the CI reagent gas. The samples were introduced into the CI source via the direct insertion probe which was heated from 100 °C to 350 °C at 25 deg/min. The source pressure and temperature were maintained at 0.5 torr and 100 °C, respectively. The compounds formed the M^- ions more abundantly than the positively charged protonated molecules (MH^+). The M^- ions, with the exception of Roridin A, were the base peaks in the NICI spectra, whereas the relative abundance of the $(M+1)^+$ ions was less than 5%. The preferred formation of the NI was likely due to the extended conjugation at the ester bridges between C7' and C11' atoms (Figure 1). The results of the CI experiments are presented in Table 1.

Table 1. Efficiencies of Molecular Ion Formation

	PICI		NICI		
Compound	Base peak m/z	RA of $(M+1)^+$	Base peak m/z	M^-	$M^-/(M+1)^+$
Roridin A	257	1	401	30%	12
Roridin H	513	100	512	100	17
Verrucarin A	201	--	502	100	--
Verrucarin J	485	100	484	100	158

The NICI spectra were also obtained using CH_2Cl_2/CH_4 as the CI reagent gas. The presence of methylene chloride did not enhance the production of M^- ions. The chloride adducts, $(M+Cl)^-$ of Roridin A and Verrucarin A, were formed in less than the base peaks (Table 2). Improvement in producing M^- ions was not noted when N_2O, N_2O/CH_4, and NO (discharge ionization) were used as the CI reagent gases. Hence, we conclude that the electron capture is best suited to produce the molecular ions required for the CAD studies, and methane is the most suitable reagent gas to use. To record the CAD spectra of both the ions, however, a mixture of methylene chloride (<5%) and methane was used to produce the M^- and adduct ions.

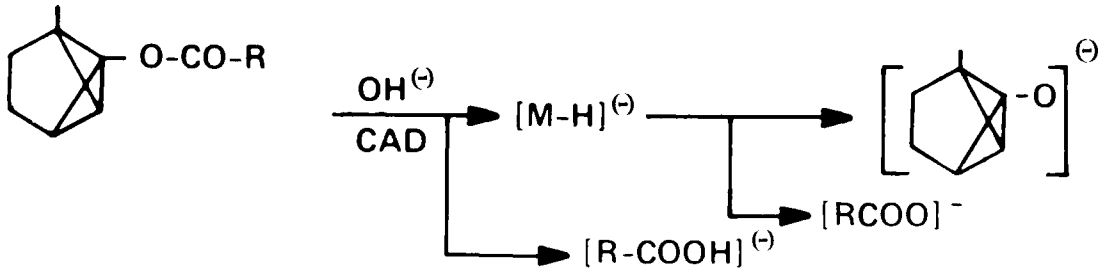
Table 2. Efficiencies of Negatively Charged Molecular Ion Formation

	Base Peak (m/z)		Relative Abundance M^- / M^-			Ratio of M^- Formation
Compound	CH_4	CH_2Cl_2/CH_4	CH_4	CH_2Cl_2	$(M+Cl)^-$	(CH_4/CH_2Cl_2)
Roridin A	401	401	30	--	25	--
Roridin H	512	512	100	100	--	9.9
Verrucarin A	502	502	100	100	49%	4.8
Verrucarin J	484	484	100	100	--	1.1

Attempts to produce the negative daughter ion (CAD) spectra of the chloride adducts using argon as the collision gas were made. The collision gas pressure and collision energy were maintained at 2.6 mtorr and 15 eV, respectively. The daughter ion mass spectra were not obtained during any of these attempts. However, the CAD mass spectra of the M^- ions recorded under the above conditions showed daughter ions in good yields from as little as 5-20 ng of the macrocyclic trichothecenes. The daughter ion spectra of the M^- ions of Roridin H and Verrucarins A and J are indicated in Figures 2 through 10.

Bambagiotti and others[15] proposed the following mode for fragmenting the NI of some of the esters under CAD conditions. (See Mechanism 1 below.)

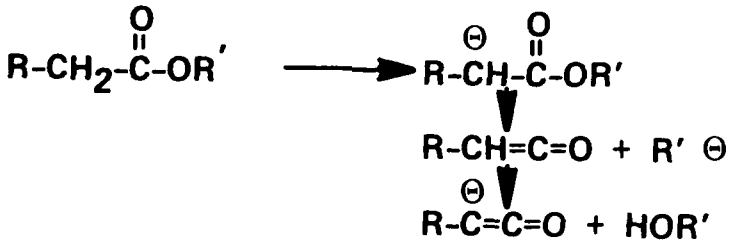
Mechanism 1



This proposed mechanism was supported by high resolution mass measurements.[15]

Hunt and co-workers[12] made the following observation about aliphatic esters:[16]

Mechanism 2



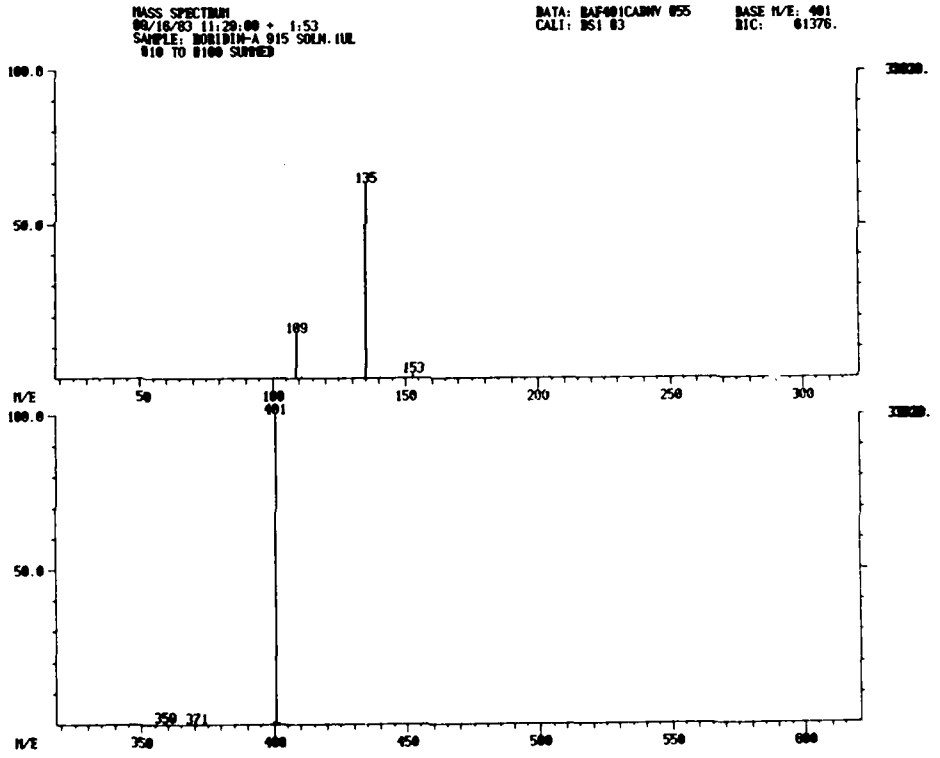


Figure 2. Negative Ion Daughter Spectrum of Roridin A (m/z 401)

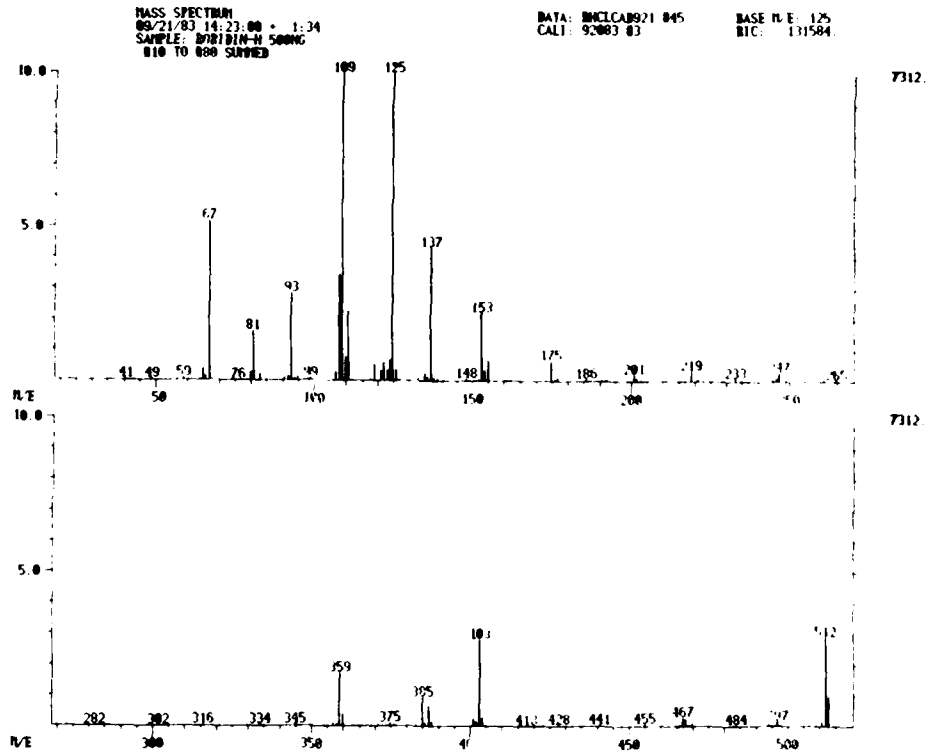


Figure 3. Negative Ion Daughter Spectrum of Roridin H (M^-, m/z 512)

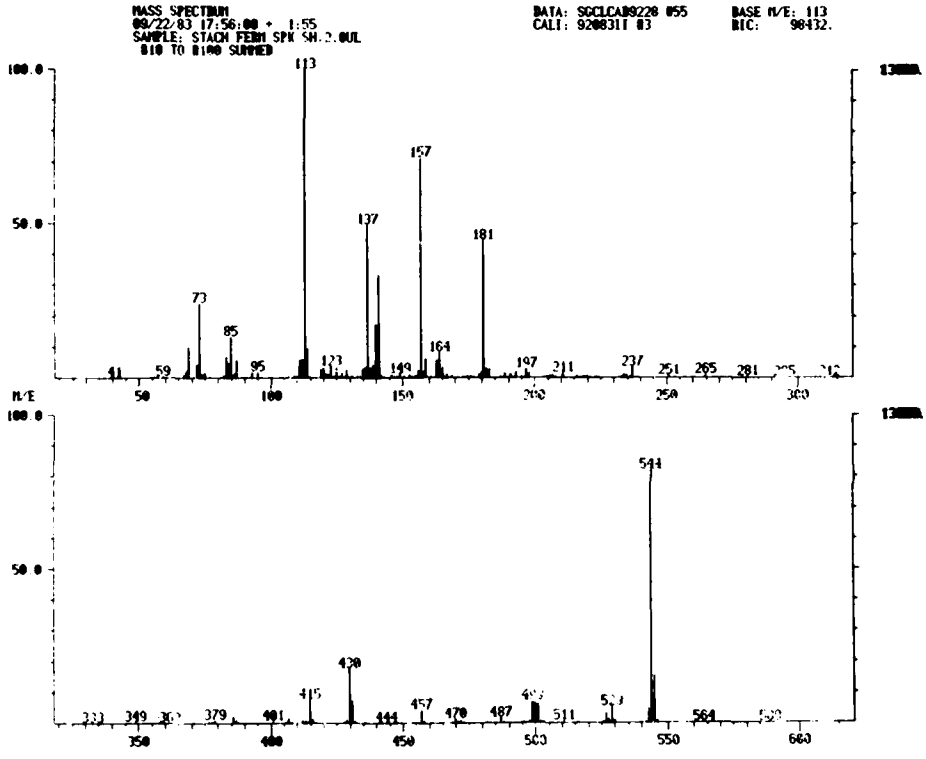


Figure 4. Negative Ion Daughter Spectrum of Satratoxin G (M^-, m/z 544)

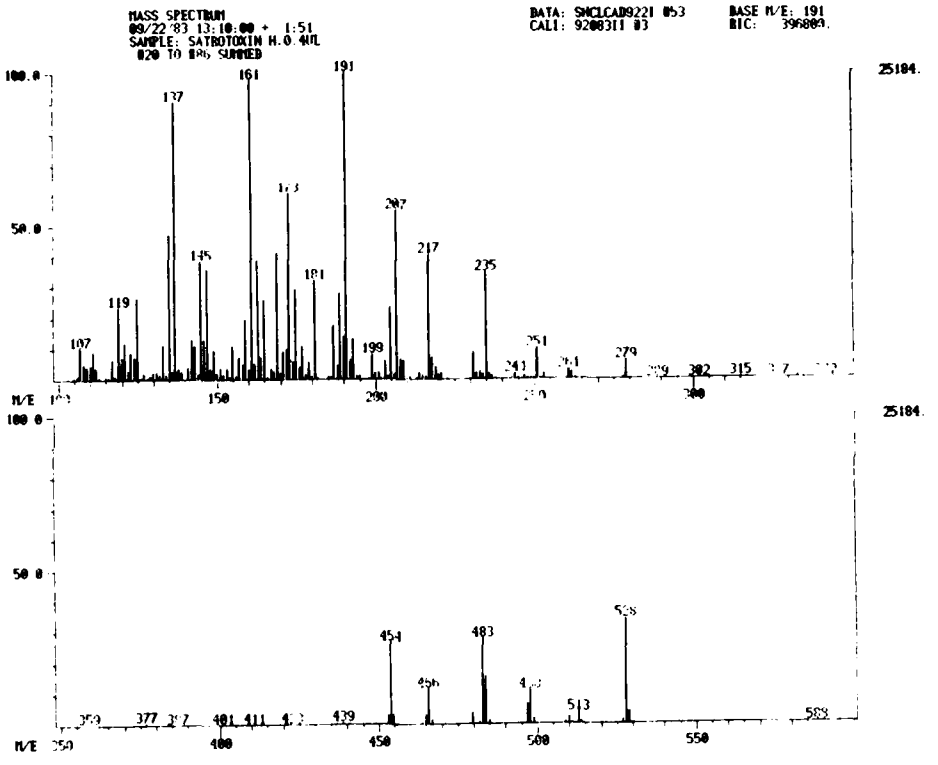


Figure 5. Negative Ion Daughter Spectrum of Satratoxin H (M^-, m/z 528)

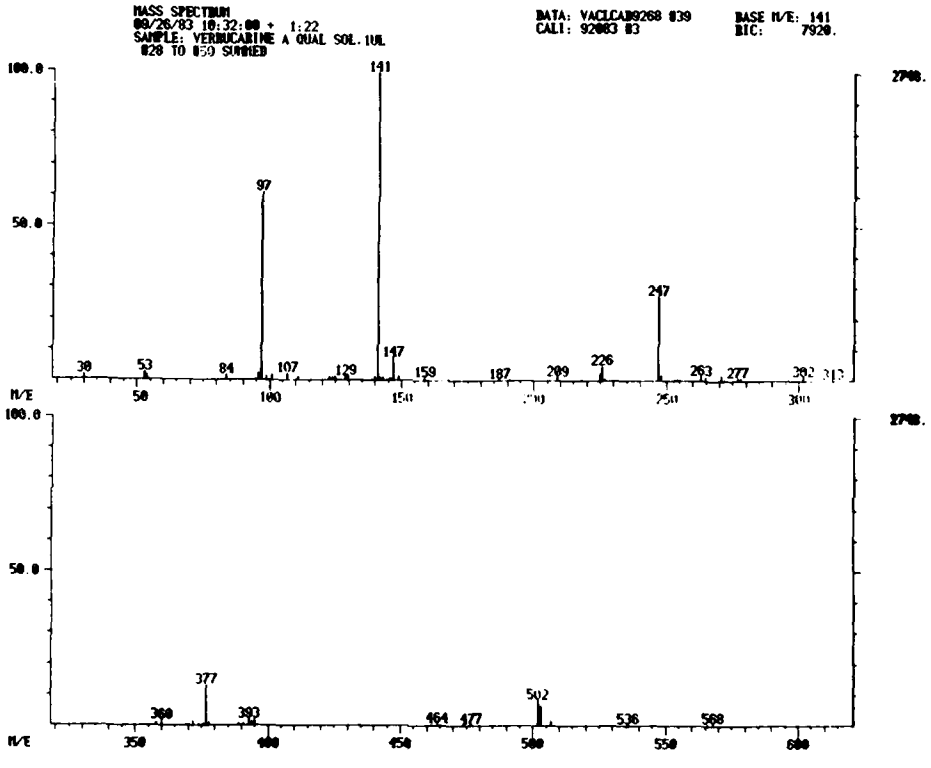


Figure 6. Negative Ion Daughter Spectrum of Verrucarin A (M^-, m/z 502)

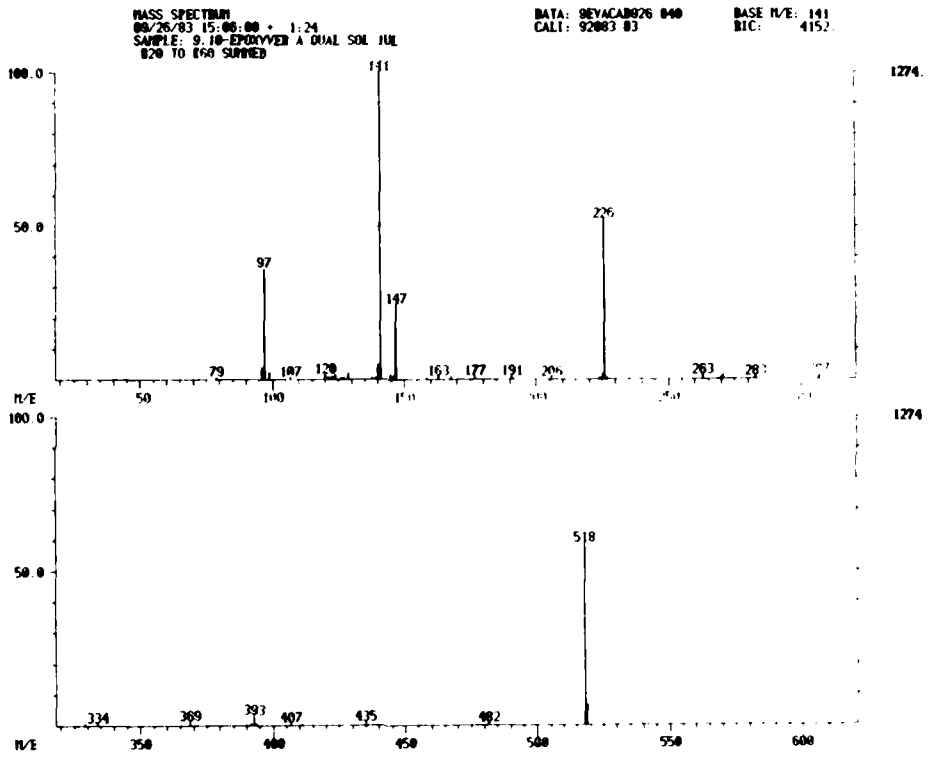


Figure 7. Negative Ion Daughter Spectrum of 9,10-Epoxyverrucarin A (M^-, m/z 518)

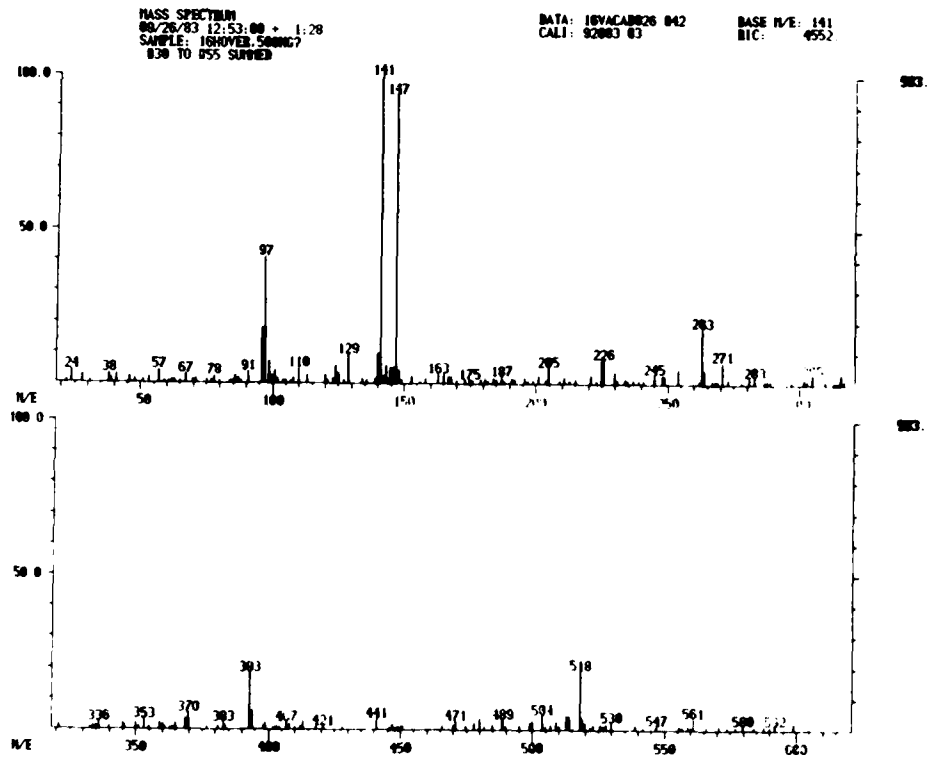


Figure 8. Negative Ion Daughter Spectrum of 16-Hydroxyverrucarin A (M^-, m/z 518)

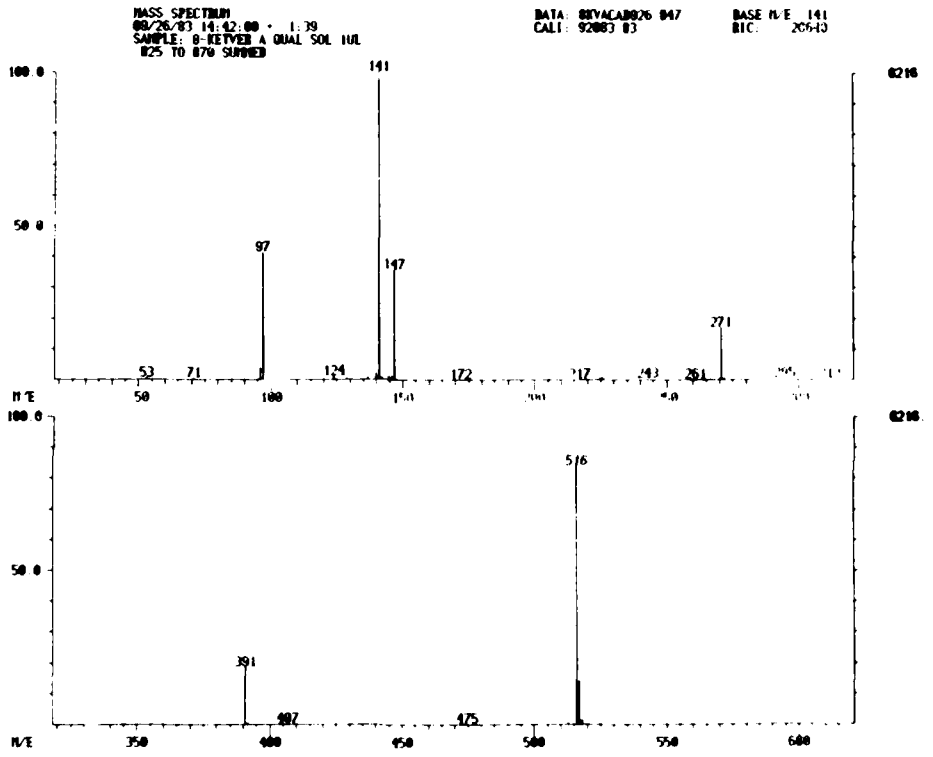


Figure 9. Negative Ion Daughter Spectrum of 8-Ketoverrucarin A (M^-, m/z 516)

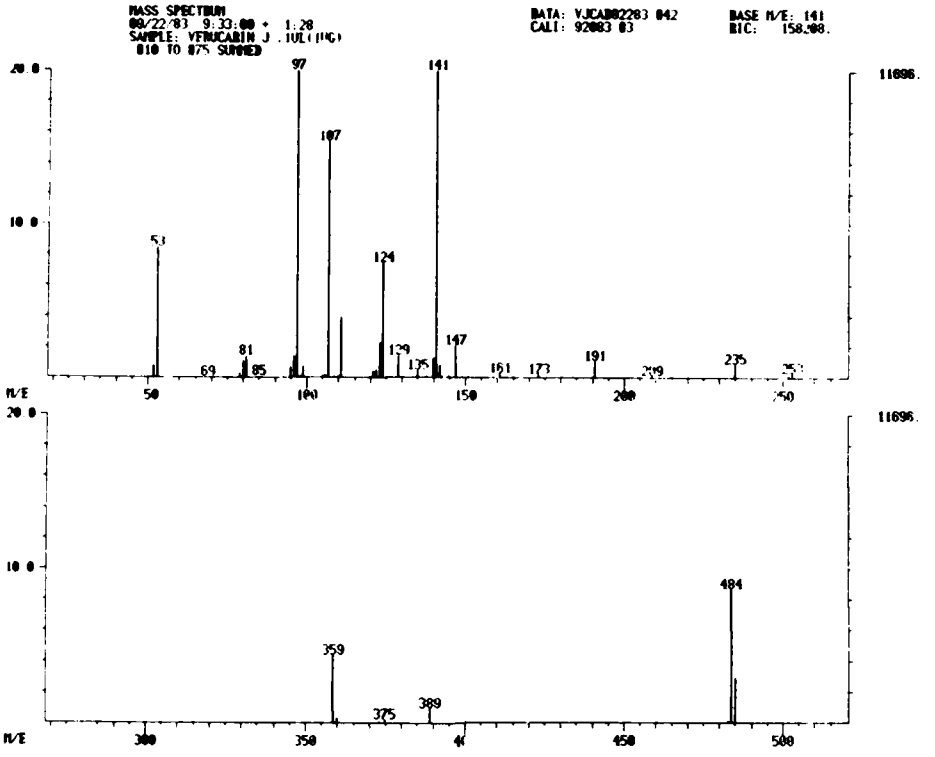


Figure 10. Negative Ion Daughter Spectrum of Verrucarin J (M^-, m/z 484)

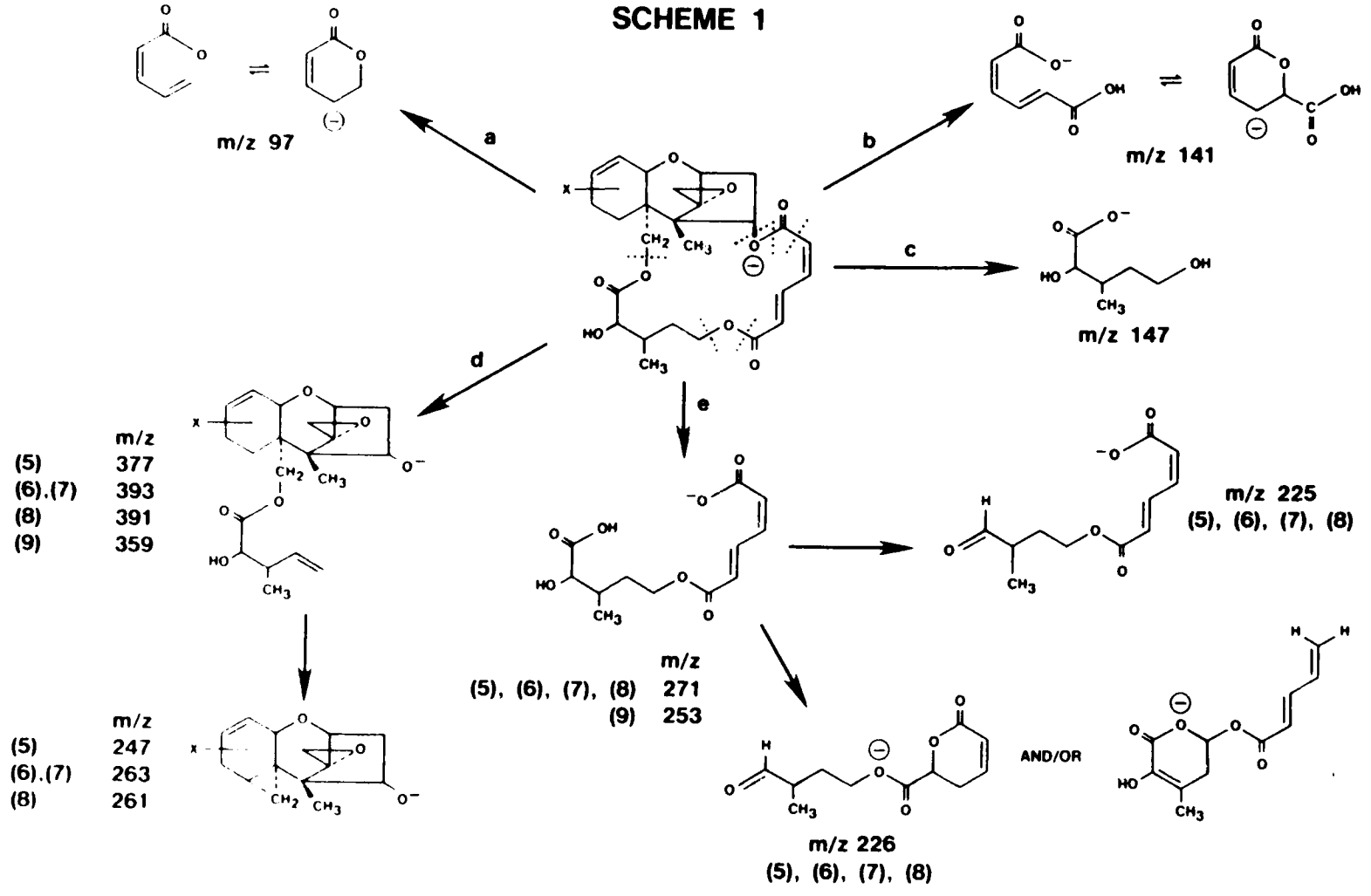
The negative daughter ion mass spectra of these macrocyclic trichothecenes show that all these cyclic triesters (verrucarins) follow a common fragmentation pattern under CAD conditions. Under CAD conditions, the M^- ions of roridins and satratoxins dissociate in a manner characteristic of their cyclic diester groups as well. Most of the CAD ions are characteristic of the ester groups and permit investigators to distinguish between molecules with common alcohol moieties but different ester bridges. The following proposed CAD fragmentation pathways and the structures of the daughter ions are based on the masses of the fragments and the stable M^- ions alone. These pathways seem logical and support the observed CAD fragments of various molecules originated from these proposed mechanisms.

For all verrucarins, the three most abundant characteristic CAD ions with m/z of 97, 141, and 147 are indicated in Scheme 1. The proposed cleavages leading to the formation of various CAD ions are also shown in this scheme. The daughter ion with m/z 97 is probably formed by the bond cleavage (a) at C5'-O and C10' to C11' followed by cyclization. However, the cleavage at C4-O and C7' to C8' for forming this ion should not be ruled out. The bond breakage (b) between C4-O and O-C6' followed by cyclization should result in the CAD ion with m/z 141. The third characteristic daughter ion (m/z 147) probably resulted from the scission (c) at C15-O and C6'-O(1). However, in the case of Verrucarin J, the formation of such a daughter ion is not clear due to the absence of a hydroxyl group in the molecule at the ester bridge. There is evidence for the bond cleavages (d) at C5'-O and C11'-O, indicated by the daughter ions formed at m/z 377 for (5), m/z 393 for (6) and (7), and m/z 391 and m/z 359 for (8) and (9), respectively. The ions at m/z 247 (5), m/z 263 (6) and (7), and m/z 261 (8) are probably formed by a further scission of bonds at C15-O. The cleavages, indicated as "e" in Scheme 1 probably resulted from the scission of C15-O and C11'-O bonds forming ions with m/z 271 for (5), (6), (7), and (8); and m/z 253 for (9). These ions were further transformed into daughter ions m/z 225 and m/z 226 as shown in Scheme 1. The proposed structures for the daughter ions of verrucarins, even without substantiation by high resolution mass measurements, seem to be logical and agree with similar results.[15,16]

The fragmentation and rearrangement of the M^- ions of roridins follow a common pathway as well. Both the molecular ions cleave at the C5'-O, C6'-O, and C11'-O as shown (a) in Scheme 2. The resulting fragment (m/z 109) could have a linear or cyclic structure as indicated in the scheme. Similarly, the other common daughter ion (m/z 153) is formed by the bond cleavage (b) at C5'-O and C11'-O carbons and the rearrangement of the lower mass fragment. The proposed pathways leading to the formation of the more abundant CAD ions characteristic of Roridin A (m/z 135 and m/z 401) and Roridin H (m/z 125 and m/z 403) are also shown in Scheme 2.

The daughter ions of satratoxins were probably formed in a manner similar to that of the bond cleavages. Both molecular ions dissociate at C14' and C13', yielding $(M-15)^-$ and $(M-45)^-$ ions, respectively; daughter ions m/z 181, m/z 157, m/z 137, and m/z 113 are common to both molecular ions. The proposed structures, as shown in Scheme 3, indicate that these ions are formed by the bond cleavage and/or rearrangement at C15-O, C6', and C7'. Even though the structures assigned to these ions are logical, the exact formation pathway is unknown at this point. There are three other daughter ions characteristic of Satratoxin H with m/z 161, m/z 191, and m/z 209. The former ions were formed by the cleavage at C5'-O, C10', and C11', followed by a rearrangement of C10' to C6', and the latter two ions were formed by the cleavage of C15-O, C10', and C11' ions.

SCHEME 1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b
m/z 141
c
m/z 147
d
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m/z
(5) 247
(6),(7) 263
(8) 261
m/z
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AND/OR
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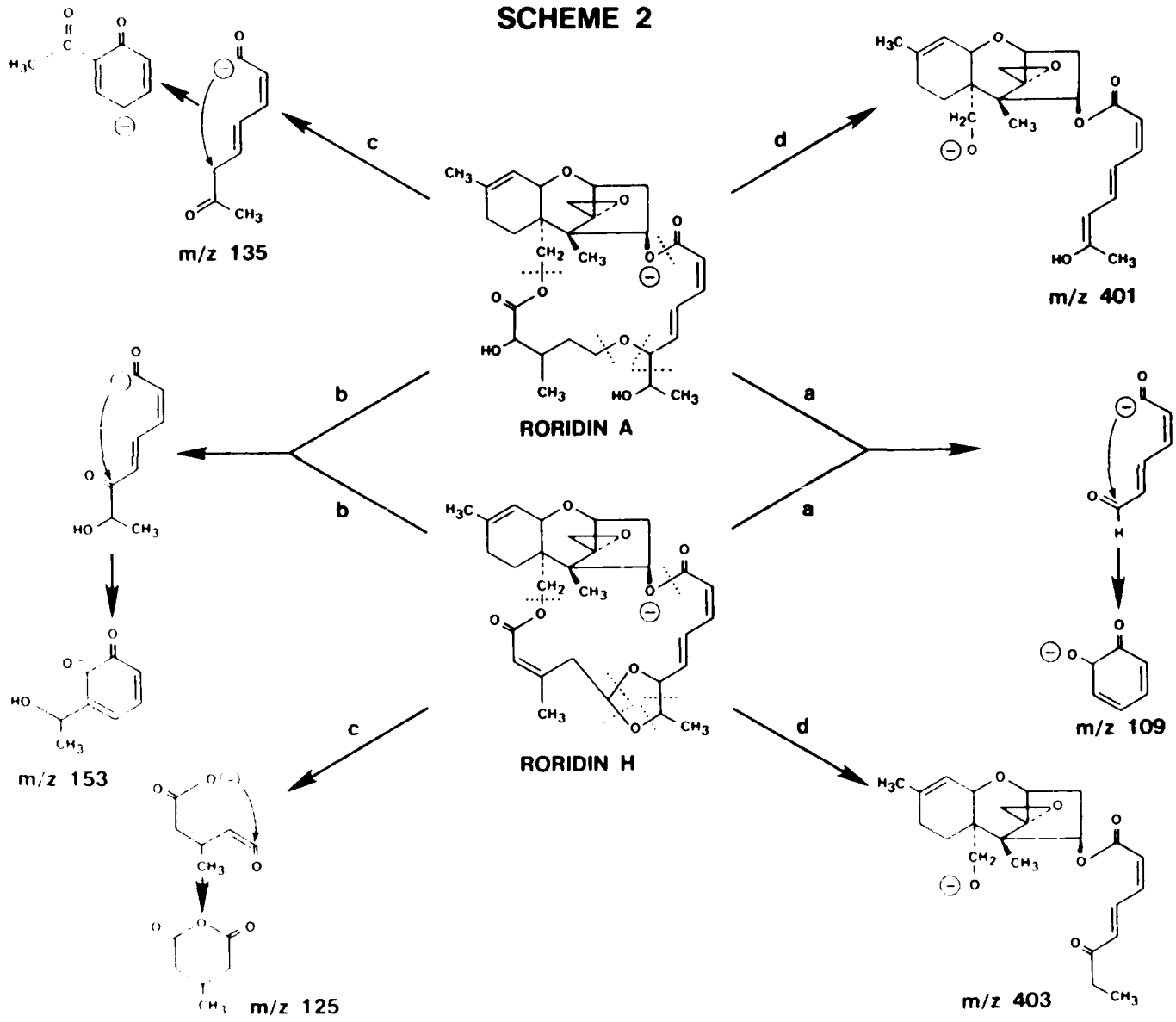
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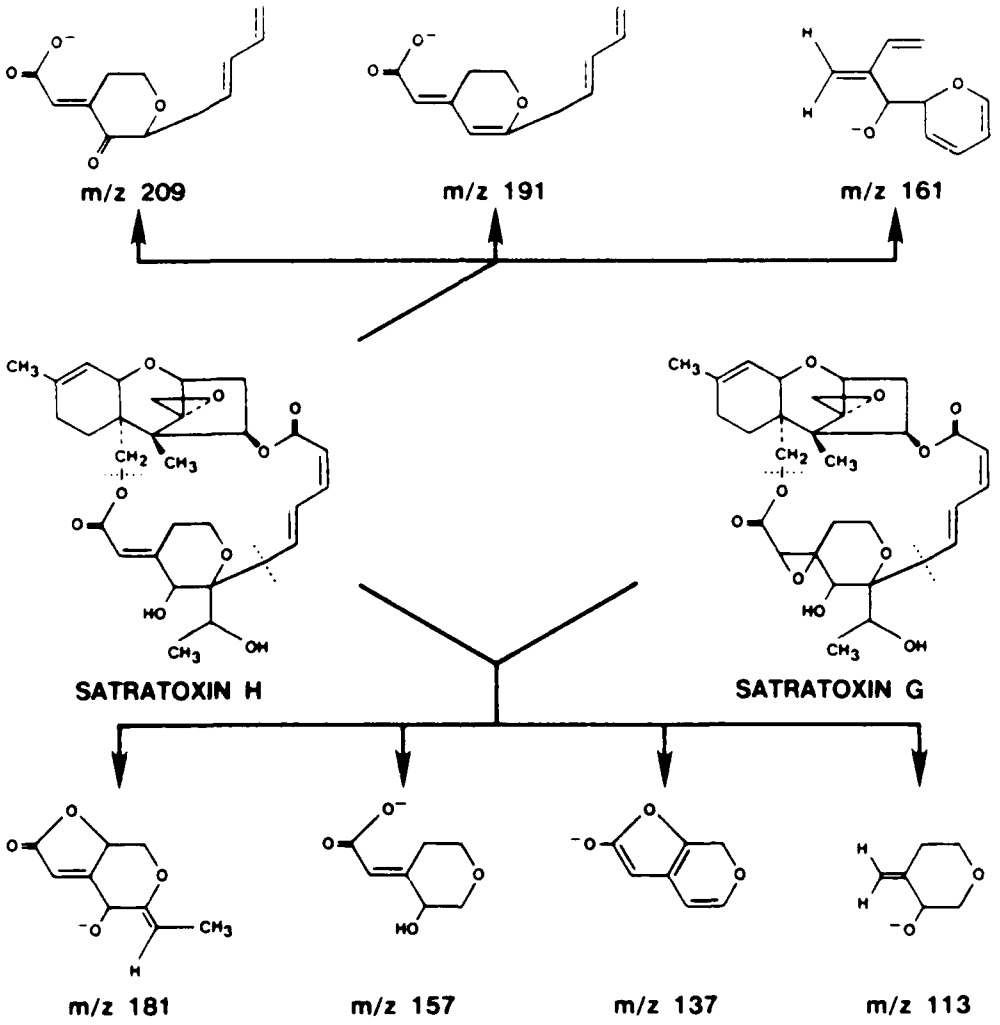
d

SCHEME 3


m/z 209
m/z 191
m/z 161
SATRATOXIN H
SATRATOXIN G
m/z 181
m/z 157
m/z 137
m/z 113

Thus, the M^- ions of these diesters and triesters seem to follow a common mode of fragmentation close to the ester groups. These observations clearly show that the macrocyclic trichothecenes may be detected with excellent specificity and analyzed by the direct NICI-CAD technique. Analysis of NI-CAD spectra of these molecules resulted in the choice of ions for detecting these molecules by obtaining their parent spectra and observing neutral loss transformations (Table 3). This observation should lead to an additional means of identifying these complex molecules.

Table 3. Characteristic Ions (m/z) for Screening the Macrocyclic Trichothecenes

Trichothecene	Daughter	Parent	Neutral Loss
Roridin A	135,153,109	153	131
Roridin H	125,153,109	153	109
Satratoxin G	113,157,181	137,181	45,114
Satratoxin H	137,161,191	137,181	45,74
Verrucarin A	97,141,247	97,141,147	125
9,10-Epoxyverrucarin A	97,141,226	97,141,147	125
16-Hydroxyverrucarin A	97,141,393	97,141,147	125
8-Ketoverrucarin A	97,141,271	97,141,147	125
Verrucarin J	97,141,359	97,141	125

Preliminary experiments indicate that these toxic substances could also be analyzed quantitatively by this method. Two synthetically modified molecules, 8-Ketoverrucarin A (KVA)[16] and 16-Hydroxyverrucarin A,[17] were investigated, and KVA was found suitable for use as an internal standard for quantifying the molecules. Low quantities (5-10 ng) of Satratoxin H were subjected to CAD experiments, and the CAD ions produced varied linearly with the amount of the analyte. Then, mixtures containing varied amounts (1-5 ng) of Roridin H, Satratoxin G, Satratoxin H, and KVA (50 ng) were analyzed by sequentially observing one CAD ion for each molecule. The relative responses of these CAD ions varied linearly with their relative amounts. The preliminary experiments indicate that this technique may prove useful for quantitatively analyzing macrocyclic trichothecenes.

When a crude fermentation broth (blank) was spiked with 50 ng of satratoxins and analyzed using methane as the CI reagent gas, good sensitivity was initially observed. However, the ion intensity was quenched suddenly and totally. This fact is probably due to electron capturing impurities in the sample and the CI

source needing to be baked for further experiments. However, when a mixture of CH_2Cl_2/CH_4 was used for the ionization, the sensitivity was improved and remained constant for a prolonged period. These data suggest that chloride ions play an important role in ionizing macrocyclic trichothecenes present in complex mixtures obtained from samples (e.g., fermentation broths, plant extracts, etc.). Further work is underway to assess the efficiency of this reagent gas in analyzing such complex mixtures.

4. CONCLUSIONS

The evaluation of these spectra indicates that the fragmentation under CAD conditions occurs at the ester bridges and that structurally similar molecules form at least one or two common daughter ions. Some common neutral losses are also observed. The results of this investigation indicate that these polar trichothecenes can be analyzed by the direct NICI-MS/MS technique by obtaining the daughter, parent, and neutral loss spectra. Using this procedure, low quantities (1-5 ng) were detected even under nonoptimum conditions. A semisynthetic macrocylic trichothecene, KVA, was found to be adequate for use as an internal standard for detecting and quantifying these molecules. The results from preliminary investigations for quantifying satratoxins and roridins are promising. Further investigations for optimizing the experimental conditions and applying the developed procedure for real-life samples are underway.

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