0.7-2.2 (m, 21 H), 2.68 (q, 2 H, J = 7 Hz), 4.83 (dt, 1 H, J = 5 Hz, J = 10 Hz), 6.43 (s, 1 H), 9.56 (s, 1 H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.85; H, 9.85.

(*Z*)-**1e**: ^{1}H NMR δ 10.62 (CHO).[9]

(*E*)-**1f**: $[\alpha]^{20}_D$ -37° (c 2.77, EtOH); IR (neat) ν 2875, 1725, 1700, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.7-2.2 (m, 18 H), 1.22 (d, 6 H, J = 7 Hz), 3.57 (m, 1 H, J = 7 Hz, J = 2 Hz), 4.83 (dt, 1 H, J = 5 Hz, J = 10 Hz), 6.33 (s, 1 H), 9.52 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.69; H, 10.18.

(*Z*)-**1f**: ^{1}H NMR δ 10.57 (CHO).[9]

Registry No. (*E*)-**1** (R^1 = H, R^2 = Et), 109745-69-9; (*E*)-**1a**, 40835-18-5; (*Z*)-**1a**, 96928-85-7; (*E*)-**1b**, 108044-52-6; (*Z*)-**1b**, 109745-75-7; (*E*)-**1c**, 109745-71-3; (*Z*)-**1c**, 109745-76-8; (*E*)-**1d**, 109745-72-4; (*Z*)-**1d**, 109745-78-0; (*E*)-**1e**, 109745-73-5; (*Z*)-**1e**, 109745-77-9; (*E*)-**1f**, 109745-74-6; (*Z*)-**1f**, 109764-54-7; **2a**, 20521-59-9; **2b**, 15431-03-5; **2c**, 53828-74-3; **3** (R^2 = Et, Y = OH), 109764-53-6; $Me(CH_2)_2CHO$, 123-72-8; (±)-$MeCH(OH)CO_2Me$, 109745-70-2; glyoxylic acid, 298-12-4; L-menthyl glyoxylate, 26315-61-7.

$C_4H_7O_2^+$ Ions. Thermochemistry in Sulfuric Acid Solution and CIMS Relationships

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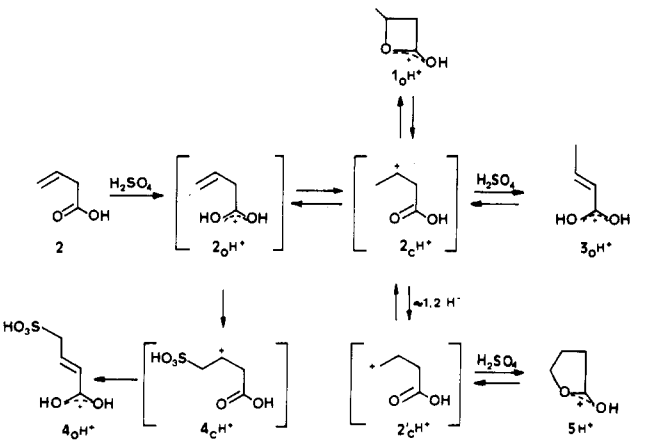
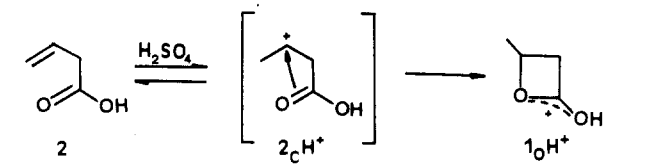
The protonation and cleavage reactions of a series of carbonyl compounds have been studied in strong acid media.[1] Independently, these processes have been also observed to take place, while their chemical ionization mass spectra (CIMS) were recorded.[2] However, no comparison has been made between the results obtained in solution (acid media) and in the gas phase (CIMS) concerning the preferential site of protonation and the further transformations of the resulting cationic species in spite of the relationship found between mass spectrometric and thermolytic reactivity.[3] The correlations between CIMS and thermochemistry in sulfuric acid solution should be meaningful since the most important source of discrepancies between fragmentation in a mass spectrometer and thermochemistry of neutrals, that is, the charge associated with the fragmenting ions, would be absent in this case.

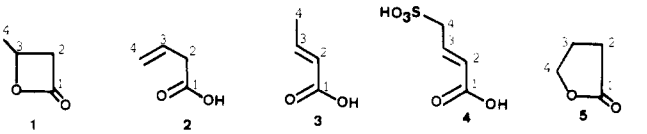
In this context it appeared to us interesting that $C_4H_7O_2^+$ ions $\mathbf{1_OH^+}$,[4] $\mathbf{3_OH^+}$,[5] and $\mathbf{5H^+}$[5] derived from vinylacetic acid (**2**), *trans*-crotonic acid (**3**), and γ-butyrolactone (**5**), respectively, had been described as stable O-protonated species in superacid medium at low temperatures, while the related methyl esters, methyl methacrylate, methyl crotonate, methyl 3-butenoate, and others had been found by CIMS[6] to undergo C-protonation and subsequent fragmentation processes.

Scheme I



Scheme II





This prompted us to study the behavior of the abovementioned $C_4H_7O_2^+$ cations in hot 96% sulfuric acid in order to minimize the difference in energy content of the cations in the acidic solution and in the CIMS experiment.

Protonations at Room Temperature. γ-Butyrolactone **5** was dissolved in 96% sulfuric acid to afford the corresponding O-protonated species $\mathbf{5H^+}$ characterized by its ^{1}H and ^{13}C NMR spectra. The chemical shift values and coupling constants found at room temperature for the ring protons agree well with those reported by Olah and Ku in magic acid at -80 °C.[5] Likewise, *trans*-crotonic acid (**3**) was treated with sulfuric acid to give the O-protonated cation $\mathbf{3_OH^+}$. The ^{1}H NMR spectral data were in concordance with the literature values.[4] The protonation of vinylacetic acid (**2**) had not been reported so far. Under our conditions it afforded O-protonated β-butyrolactone $\mathbf{1_OH^+}$. The ^{1}H NMR parameters were coincident with those reported[5] for the species resulting from direct protonation of commercially available β-butyrolactone (**1**) with Magic Acid at -80 °C. Full characterization including ^{13}C NMR data is given in Table I.

Heat-Promoted Transformations of the Protonated Species. To determine the effect of temperature, the sulfuric acid solutions of O-protonated species $\mathbf{1_OH^+}$, $\mathbf{3_OH^+}$ and $\mathbf{5H^+}$ were heated for several hours at 80, 120, or 140 °C depending on the structure. Protonated γ-butyrolactone $\mathbf{5H^+}$, previously found to be stable up to 65 °C in Magic Acid solution by Olah and Ku,[5] was then heated to 140 °C for several hours in 96% sulfuric acid. Under these conditions the formation of the sulfonated *trans*-crotonic acid derivative $\mathbf{4_OH^+}$ was observed (see Scheme I).

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(3) For a review in the relationships thermolysis/photolysis/MS, see: Dougerty, R. C. *Top. Curr. Chem.* **1974**, *45*, 93.

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(5) Olah, G. A.; Ku, A. T. *J. Org. Chem.* **1970**, *35*, 3916.

(6) Harrison, A. G.; Ichikawa, H. *Org. Mass Spectrom.* **1980**, *15*, 244.

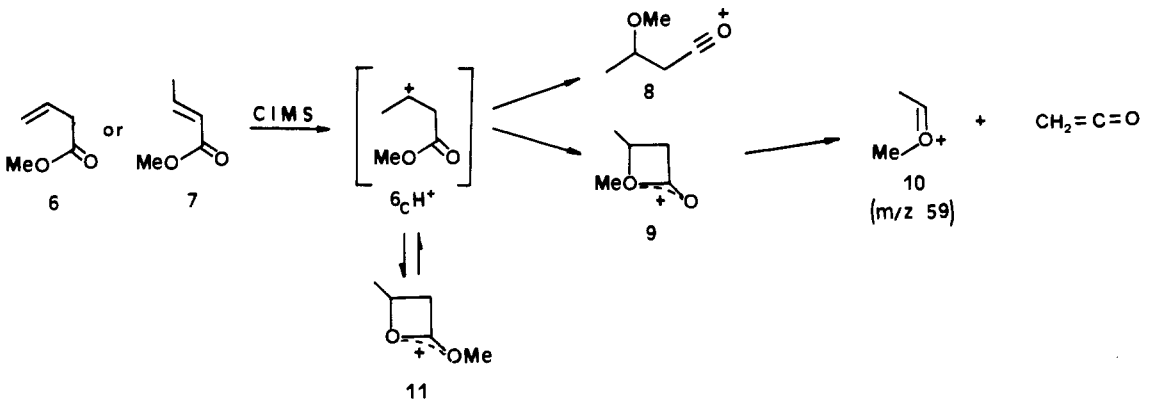
0022-3263/87/1952-4790$01.50/0

Table I. ^1H and ^{13}C NMR Spectral Data for the Cationic Species[a]

	δ_{1H}[b] for indicated H			δ_{13C}[b] and J_{C-H}[c] for indicated C			
compd	2	3	4	1	2	3	4
1_OH^+	3.2	5.4	1.7	189.4[d]	42.5[d]	81.2[d]	20.9[d]
3_OH^+	6.2	7.9	2.2	180.6(^2J = 6.0)	116.0(^1J = 170.0, ^2J = 7.0)	167.3(^1J = 158.0, ^2J = 7.0)	20.2(^1J = 130.0, ^2J = 3.5, ^3J = 2.0)
4_OH^+	6.5	7.7	4.5	178.0(^2J = 4.5, ^3J = 6.2)	124.5(^1J = 171.4)	146.1(^1J = 168.4)	54.7(^1J = 140.8)
$5H^+$	3.4	2.8	5.3	196.0	31.0(^1J = 137.0)	21.4(^1J = 137.2)	81.0(^1J = 160.0)

[a] For ^1H NMR literature data, see ref 4a (for 3_OH^+) and ref 5 (for 1_OH^+). For ^{13}C NMR, see ref 4b (for 3_OH^+). [b] ppm ± 0.1 downfield from TMS. [c] Hz ± 0.5. [d] J not measured.

Scheme III



Spectral data for ion 4_OH^+ are given in Table I.

In independent experiments, sulfuric acid solutions of *trans*-crotonic acid 3_OH^+ were heated at 120 °C, giving rise to the formation of mixtures of O-protonated γ-butyrolactone $5H^+$ and the sulfonated *trans*-crotonic acid derivative 4_OH^+ in variable relative amounts depending on the heating time (see Scheme I).

Likewise heating, under the same conditions, of the O-protonated β-butyrolactone 1_OH^+ obtained upon protonation of vinylacetic acid (**2**) afforded again a mixture of compounds 3_OH^+, $5H^+$, and 4_OH^+ in variable relative amounts depending on the reaction time. At 120 °C the transformation $1_OH^+ \rightarrow 3_OH^+$ is very fast, and hence the presence in solution of the species 1_OH^+ cannot be detected. It is noteworthy that upon heating at 80 °C the formation of protonated γ-butyrolactone $5H^+$ is not observed and then a mixture of two components 3_OH^+ and 4_OH^+ results. This is expected to occur since the formation of $5H^+$ should take place through the intermediacy of the primary carbenium ion $2'_CH^+$ for which a high activation energy must be necessary.

Results in Sulfuric Acid vs. CIMS Data. The thermochemically favored site of protonation of a carboxylic acid is the carbonyl oxygen as predicted by proton affinity–ionization energy correlations.[7] This is also supported by NMR spectroscopic data in acid solution.[1] In the case of the $C_4H_7O_2^+$ cations studied by us, this general behavior is observed at room temperature with the exception of the protonation of vinylacetic acid (**2**) whose O-protonated 2_OH^+ species cannot be observed.[8] By contrast, the formation of O-protonated β-butyrolactone 1_OH^+ is easily rationalized by assuming the C-protonation of the vinylacetic acid olefinic terminal carbon followed by intramolecular capture of the intermediate secondary carbenium ion 2_CH^+ by the carbonyl oxygen (Scheme II).

Interestingly, in the CIMS of methyl vinylacetate (**6**), loss of ketene from the protonated molecule with migration of the methoxy group to the secondary carbocationic center was observed, clearly indicating protonation of the olefinic double bond.[6] A possible reaction pathway, which also accounts for the MH^+ ion, is indicated in Scheme III.

In hot sulfuric acid, the behavior of protonated γ-butyrolactone $5H^+$ and *trans*-crotonic acid 3_OH^+ can only be understood by involvement of C-protonated intermediates as shown in the Scheme I.

In fact, the reported[6] CIMS fragmentation pattern for methyl crotonate (**7**) also implies protonation of the double bond and the subsequent reactions are confluent to those undergone by methyl vinylacetate (**6**) through a common cationic intermediate 6_CH^+ (see Scheme III). Thus, the C-protonated cations 6_CH^+ and 2_CH^+ are related intermediates in the CIMS and hot sulfuric acid promoted transformations of the unsaturated esters and carboxylic acids studied.

From this study it can be concluded that a close parallelism is expected to be found between CIMS and thermolysis in acid solution for a number of molecules that will allow, in the future, a better understanding of both types of chemical processes. A particularly interesting feature of these correlations is the possibility of spectroscopic characterization of intermediate species, ensuring the structures postulated for corresponding ions in CIMS studies.

Experimental Section

Proton spectra were recorded at 60 MHz with a Hitachi Perkin-Elmer Model R-24 B NMR spectrometer. ^{13}C spectra were recorded with a Bruker WP 80 SY NMR spectrometer using dioxane as external standard (capilar). ^1H and ^{13}C chemical shifts (δ) are reported in ppm relative to TMS.

Neutral substrates used were commercial materials. Ions were prepared by slow addition, with efficient stirring, of the cooled substrate onto concentrated sulfuric acid (96%) in an ice–water bath to give ca. 1 M solutions.

Ion solutions were heated in tightly closed NMR sample tubes by using a thermostated bath at the temperatures indicated in the text.

(7) Benoit, F. M.; Harrison, A. G. *J. Am. Chem. Soc.* **1977**, *99*, 3980.

(8) Protonation of acid **2** at −10 °C gives rise to a mixture of the O-protonated acid 2_OH^+ and 1_OH^+. 2_OH^+ was characterized by ^1H NMR (96% H_2SO_4, external standard TMS) δ: 5.1–6.2 (m, =C*H*), 5.5 (br s, CH_2=), 3.7 (d, CH_2).

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Registry No. 1, 3068-88-0; 2, 625-38-7; 3, 107-93-7; 5, 96-48-0; 6, 3724-55-8; 7, 623-43-8.

Supplementary Material Available: Reaction rates for acid-promoted transformations under heating are summarized in Figures 1-3 (4 pages). Ordering information is given on any current masthead page.

Studies on the Syntheses of Sesquiterpene Lactones. 10.[1] Improved Syntheses of (+)-Tuberiferin and the Related α-Methylene γ-Lactones and Their Biological Activities

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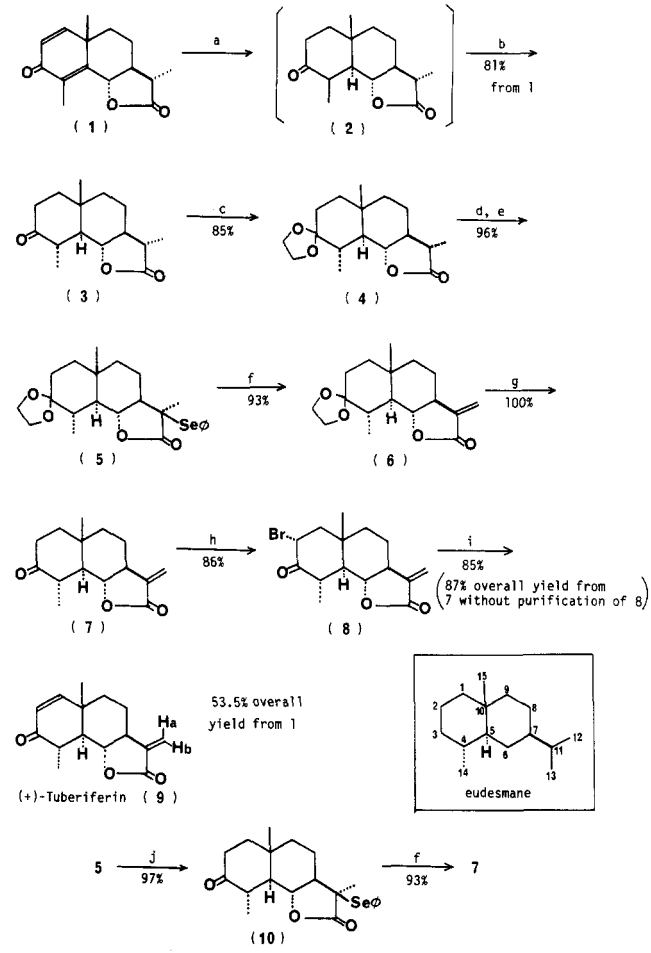
Sesquiterpene lactones with an α-methylene γ-lactone moiety fused on various skeletons are a rapidly expanding group of natural products, comprising to date more than 900 varieties.[3] Some of them have been shown to have considerable biological activities as allergenic agents, cytotoxic and antitumor agents, regulators of plant growth and antimitotic activity, and antishistosomal agents. Because of their biological activities and because they are available from natural sources often only in small quantities, their efficient syntheses are a synthetic challenge that has received much attention and many reports of such syntheses have appeared in the last decade.

In the course of our program of the study of the structure–activity relationship of α-methylene γ-lactones, we needed efficient syntheses of (+)-tuberiferin (**9**) and related α-methylene γ-lactones in gram quantities. Although total syntheses of (±)- and (+)-tuberiferin (**9**) had already appeared in the literature,[4] the reported methods were inconvenient for our purpose. In the reported total syntheses of (±)- and (+)-**9** the introduction of the α-methylene γ-lactone moiety was left to the final stage, probably because of its expected reactivity and instability.

Since we had noticed that the α-methylene γ-lactone moiety was stable under acidic and mild basic conditions and bromination by phenyltrimethylammonium perbromide (PTAB), we envisioned another approach to **9** in which, as shown in Scheme I, the introduction of the α-methylene γ-lactone moiety was at an early stage. In this note we report efficient syntheses of (+)-tuberiferin (**9**) and the related α-methylene γ-lactones **6**–**8** and their biological activities.

Scheme I[a]



[a] Reagents and conditions: (a) H_2/2% Pd-$SrCO_3$, AcOEt; (b) HCl, EtOH; (c) $HO(CH_2)_2OH$, *p*-TsOH, benzene, reflux; (d) LDA, THF; (e) $(C_6H_5Se)_2$, HMPA, THF; (f) 30% H_2O_2, AcOH, THF; (g) 20% aqueous AcOH–EtOH, reflux; (h) 1.1 equiv of PTAB, THF; (i) Li_2CO_3, LiBr, DMF, 123–131 °C; (j) 50% aqueous AcOH, reflux.

Results and Discussion

Synthesis of (+)-Tuberiferin (9). The starting material **3** was obtained from commercially available *l*-α-santonin (**1**) by modification of the known procedure[5] (Scheme I). Thus, catalytic hydrogenation of **1** over 2% palladium on strontium carbonate in ethyl acetate and epimerization of the resulting **2** possessing a β(axial)-methyl group at C_4 by 2 M hydrochloric acid in ethanol gave **3** in 81% yield. Acetalization of the C_3-carbonyl group of **3** under standard conditions gave acetal **4** in 85% yield. Phenylselenenylation of **4** by Grieco's method[6] gave the corresponding phenyl selenide (**5**) in 96% yield. Treatment of **5** with 30% hydrogen peroxide in THF in the presence of acetic acid gave an α-methylene γ-lactone (**6**) in 93% yield. Deacetalization of **6** was achieved by treatment with 20% aqueous acetic acid in ethanol at 85 °C for 4 h to give **7** in a quantitative yield. **7** was also prepared by a different procedure. Thus, deacetalization of **5** in boiling 50% aqueous acetic acid gave the corresponding keto selenide **10** in 97% yield. Successive treatment of **10** with 30% hydrogen peroxide in THF in the presence of acetic acid gave **7** in 93% yield.

The selective bromination at C_2 of **7** was achieved as follows. Treatment of **7** with 1.05 mol equiv of PTAB[7] in

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