a larger HOH_aN angle could be expected in the complex. Table II emphasizes that with both isomers **1E** and **1Z** (R = H) and with both transition structures **1-TSR** and **1-TSI**, the **1E** and the **1-TSR** are found to be more stabilized by interaction with water molecule, respectively. As a consequence, it can be expected that when the solvation energy could be more fully taken into account, the solvated *E* isomer could become more stable than the solvated *Z* isomer as observed in solution[1] but the solvated rotational transition structure is still of lower energy than the solvated inversion. The nature of the counterion could also be important in determing the mechanism of interconversion, particularly in aprotic solvents. This may have been an important factor in the smaller barrier seen in solution.[1] Under these conditions experiments in the presence and absence of a complexing agent such as a crown ether would be of interest.

In conclusion, the imidate anions, $HCONR^-$ (with R = H or alkyl group) undergo *E*/*Z* interconversion by a rotation about the carbon–nitrogen partial double bond both in the gas phase and in protic solution and not by nitrogen inversion as previously claimed by Perrin, Lollo, and Hahn.[1]

Acknowledgment. We are indebted to the Department of Education (Irish Government) for financial support and the UCD computer center for computer time grant.

Registry No. $OHCNH^-$, 67131-48-0; $OHCNCH_3^-$, 58272-35-8.

Hypochlorite-Promoted Transformations of Trichothecenes. 2. Fragmentation-Rearrangement of the Primary Product from Verrucarol[1]

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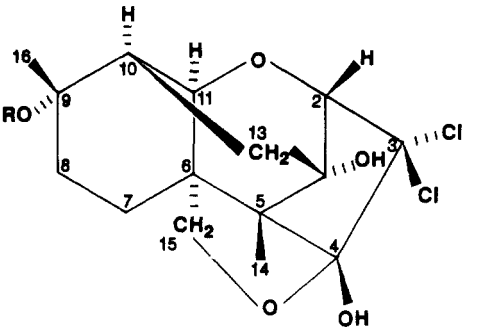
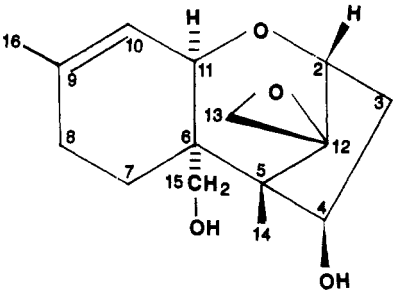
Recently we reported the isolation of two unusual pentacyclic dichlorohemiketals (**1a,b**), formed in nearly quantitative yield on treatment of verrucarol (**2**) with alkaline hypochlorite at room temperature.[2] The overall reaction involved several different processes: nucleophilic attack at C-9 resulting in opening of the epoxide and formation of the C-10,C-13 bond,[3] preferential oxidation at C-4[4] followed by α-chlorination in the manner of a haloform reaction, and cyclization to the hemiketal. These haloform/rearrangement products were thermally stable and resistant to further transformation by hypochlorite at room temperature. Since α-halo carbonyl compounds generally undergo base-promoted cleavage at elevated temperatures,[5] we sought to investigate the effect of hot



1a R=H
1b R= CH_3



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alkali on these products (**1**).

Accordingly, the predominant dichloro hemiketal **1a** ($C_{15}H_{20}Cl_2O_5$) was heated 4 h at 95 °C with 1 N aqueous sodium hydroxide containing 5–10% methanol. After neutralization, direct GC/MS analysis of the resulting mixture without derivatization showed a mixture of three products in relative ratio 1:2:1. Column chromatography on silica gel resulted in complex mixtures of secondary transformation products, in addition to the predominant primary product as a pure solid, and one of the other primary products in sufficient purity for spectral characterization. The molecular formulas of the latter two products, determined by electron impact and chemical ionization mass spectrometry (EI and CIMS), are $C_{14}H_{21}ClO_4$ and $C_{14}H_{20}O_4$, respectively. Their structures were established by ^{13}C–^1H heteronuclear and ^1H–^1H homonuclear NMR chemical shift correlation experiments. The results are summarized in Tables I and II.

Comparison of these data with the assignments documented previously for **1**[2] showed some significant differences. For the monochloro compound **3**, the signals for the two C-15 protons are not significantly changed, while the signals for the pair attached to C-13 are shifted downfield by ca. 1 ppm, to δ 2.31 and 2.85. Carbon 5 is no longer quaternary; the signal for its attached proton (a quartet due to the C-14 methyl group attached to C-5) is observed at δ 3.15. Thus, the ^{13}C singlet at δ 212.9 is assigned to a ketone carbonyl at C-12. Both the signals for C-2 (δ 100.6) and its attached proton (δ 4.99) are shifted significantly downfield in comparison to those of **1a**, and the proton is observed as a triplet. Finally, an additional methylene carbon signal appears (δ 44.4) with its attached protons as a doublet at δ 3.59. From these data, the chlorine-containing product can be assigned one of two tricyclic structures **3a,b**. The configurational assignment at C-5 was based on the observation that no long-range coupling was apparent between H-5 and H-13 under conditions where couplings smaller than 1 Hz are readily observed.[6]

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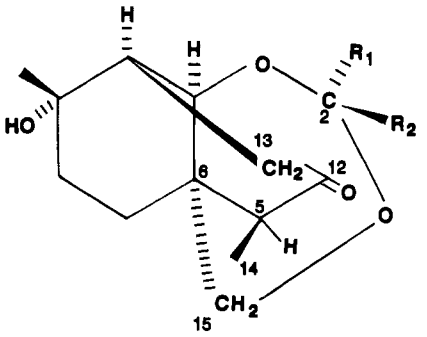
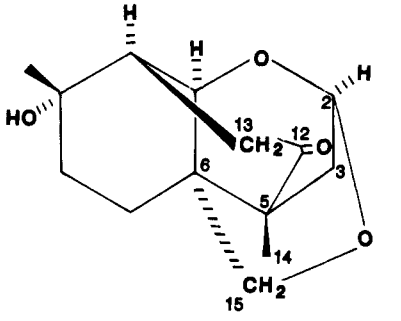


3a R_1=H, R_2= CH_2Cl
3b R_1=CH_2Cl, R_2=H

Comparison of the data for this product (Table I) with those for the chlorine-free product (Table II) in turn reveals significant differences. Carbon 5 in the latter is quaternary; consequently the C-14 protons appear as a singlet. The C-3 methylene protons, no longer equivalent, are strongly coupled to each other. Coupling of one of them to H-2 is also observed. Thus, the chlorine-free product can be assigned the unique tetracyclic stereostructure 4. Assignments of the two lowest frequency



4

quaternary signals δ 44.9 and 37.2, to C-5 and C-6, respectively, are made on the basis of analogy to **1a**[2] and are further substantiated by the observation that for **3a** the C-5 methine resonance appears at higher frequency than the C-6 quaternary signal.

The chloro compound **3** was found to cyclize quantitatively to **4** on further heating (6–7 h) with 1 N NaOH and hence is formulated as **3a**. This facile cyclization further substantiates the configurational assignment at C-5 made on the basis of the ^1H–^1H 2D experiment. Attempts to isolate the third product failed, due to its apparent instability on silica gel. Evidence from EI and CIMS indicated its probable identity as the isomeric chloromethyl compound **3b**.

In summary, hypochlorite transformation product **1a** undergoes haloform-type cleavage with oxidative decarboxylation and rearrangement to the novel tricyclic products **3**, and **3a** further cyclizes to **4**. A possible rationale for the genesis of **3** is shown in Scheme I.

Experimental Section

NMR and mass spectral instrumentation and parameters are given in ref 2. Low resolution (LR) CIMS (methane) were determined with the Hewlett Packard 5985B system at 200 eV, source temperature 100 °C.

Sodium Hydroxide Treatment of 1a. To a solution of **1a** (101 mg, 0.29 mmol) in methanol (6.5 mL) was added 1 N aqueous NaOH (100 mL). The mixture was heated 4 h under N_2 at 94–97 °C, then cooled, acidified (pH 2–3) with 6 N HCl, saturated with NaCl, and extracted with ethyl acetate (two 20-mL portions). GC/MS of an aliquot of the extract showed, in order of increasing

Table I. ^{13}C and ^1H NMR Spectra of Tricyclic Chloro Ketone 3a

assignment (carbon no.)	^{13}C chemical shift, (ppm)[a,b] (multiplicity)	^1H chemical shift, (ppm)[c,d] (multiplicity)	J (Hz)[e]
14	7.4 (q)	1.06 (d)	6.8
16	28.9 (q)	1.27 (s)	
7	23.7 (t)[f]		
8	31.7 (t)[f]	1.1–1.5 (m)[g]	
13	38.5 (t)	2.31 (m)	
		2.85 (dd)	15.9, 5.9
6	41.1 (s)		
5	43.1 (d)	3.15 (q)	6.8
3	44.4 (t)	3.59 (d)	4.2
10	46.9 (d)	2.20 (m)	
15	73.6 (t)	3.45 (d)	11.5
		3.95 (d)	11.5
9	73.7 (s)		
11	78.0 (d)	4.27 (d)	3.4
2	100.6 (d)	4.99 (t)	4.2
12	212.9 (s)		

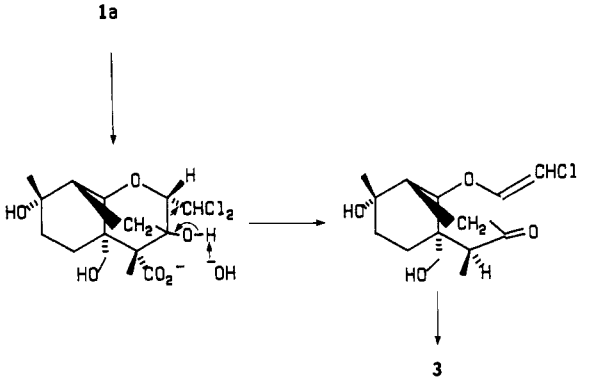
[a] 6 mg in $CDCl_3$, sweep width 12 KHz, pulse width 4 μs (~43°), repetition rate 3.75 s, multiplicity determined by an APT experiment. [b] ±0.1 ppm. [c] Sweep width 2600 Hz, pulse width 20.5 μs (90°), repetition rate 9 s. [d] ±0.01 ppm. [e] ±0.2 Hz. [f] Assigned by analogy to 1. [g] Includes O*H*.

Table II. ^{13}C and ^1H NMR Spectra of Tetracyclic Ketone 4

assignment (carbon no.)	^{13}C chemical shift, (ppm)[a,b] (multiplicity)	^1H chemical shift, (ppm)[c,d] (multiplicity)	J (Hz)[e]
14	16.5 (q)	1.22 (s)	
16	29.3 (q)	1.30 (s)	
7	23.4 (t)[f]		
8	30.7 (t)[f]	1.1–1.5 (m)[g]	
13	36.0 (t)	2.28 (m)	
		3.12 (dd)	16.9, 6.8
6	37.2 (s)		
3	41.4 (t)	1.75 (d)	14.5
		1.98 (dd)	14.5, 3.1
5	44.9 (s)		
10	45.7 (d)	2.26 (m)	
15	69.6 (t)	3.60 (d)	9.3
		4.04 (d)	9.3
9	73.0 (s)		
11	73.1 (d)	4.59 (d)	~4
2	90.0 (d)	5.07 (d)	~3
12	213.8 (s)		

[a] 15 mg in $CDCl_3$, sweep width 12 KHz, pulse width 4 μs (~43°), repetition rate 3.75 s, multiplicity determined by an APT experiment. [b] ±0.1 ppm. [c] Sweep width 2600 Hz, pulse width 20.5 μs (90°), repetition rate 9 s. [d] ±0.01 ppm. [e] ±0.2 Hz. [f] Assigned by analogy to 1. [g] Includes O*H*.

Scheme I



retention times, a mixture of **4**, **3a**, and the tentatively identified **3b**, in relative ratio 1:2:1. The residue after evaporation of the dried extract (73 mg) was combined with a similar mixture (11 mg) resulting from a smaller scale NaOH treatment, dissolved in 19:1 chloroform/acetone, and subjected to chromatography on silica gel (2.5 g, Bio-Sil A, Bio-Rad Laboratories, Richmond, CA). Elution with 9:1 chloroform acetone gave first **3a** (22 mg) as a pure solid and then 4 (14 mg) as the major constituent of a mixture. Characteristics of **3a**: mp 143–144 °C; high resolution (HR) EIMS, calcd for $C_{14}H_{21}ClO_4$ m/z 288.1128, found 288.1122.

Conversion of 3a to 4. To a solution of **3a** (19.9 mg, 0.07 mmol) in methanol (2 mL) was added 1 N aqueous NaOH (20.5 mL). The mixture was heated 7 h under N_2 at 97–98 °C, then cooled, and worked up as above, yielding **4** (17.4 mg, 91%), >96% pure by GC/MS. The material was further purified by recrystallization from acetone–ether. Characteristics of **4**: mp 134–135 °C; HREIMS, calcd for $C_{14}H_{20}O_4$, m/z 252.1362, found 252.1362.

Acknowledgment. We thank Mr. John M. Roman for the exact mass determinations. We are also grateful to one reviewer for valuable comment on the mechanism.

Registry No. **1a**, 101199-68-2; **1b**, 101199-69-3; **2**, 2198-92-7; **3a**, 104532-66-3; **3b**, 104597-40-2; **4**, 104532-67-4.

Synthesis of Tetrahydrofurans from Active Methylene Compounds via Radical Cyclization

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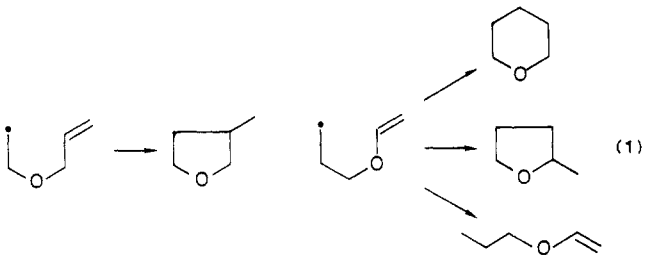
Radical Cyclization has been now variously applied as a useful method to the preparations of heterocyclic and carbocyclic compounds.[1] In view of efficient regioselectivity and rate of intramolecular radical addition, the reaction to give five-membered heterocyclic structures via analogues of 5-hexenyl radicals, which contain an allylic heteroatom such as oxygen or nitrogen in the chain, is often employed[2,3] (eq 1). Our continuous investigations on



(1)

synthetic application of the radical process have been hitherto developed along this cyclization system.[4] On the other hand, intramolecular radical addition onto a vinyl ether group has not been studied enough to utilize in organic synthesis, although this type of reaction is expected to alter some properties of radical cyclization.[5] Very recently, two works based on such cyclization process have been reported by Kuwajima[6] and Pattenden,[7] in which trimethylsiloxy-substituted carbocyclic compounds and alkoxy-substituted cyclic acetals have been prepared, respectively. We report herein a new synthetic route to tetrahydrofurans from active methylene compounds via

Scheme I

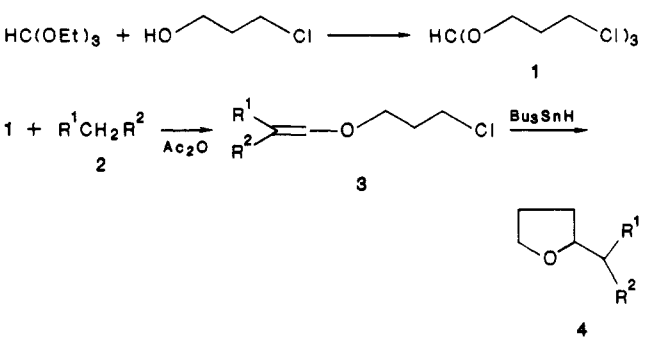


Table I. Synthesis of Vinyl Ethers 3 and Tetrahydrofurans 4

			3		4[a]	
	R^1	R^2	reacn time, h	yield, %	reacn time,[b] h	yield, %
a	CN	CO_2Et	5	59	4.5	74
b	COMe	CO_2Me	3	45	5	75
c	COMe	COPh	1	60[c]	6	54
d	CO_2Et	CO_2Et	7	43	6	81

[a] Obtained from **3**. [b] The reaction was followed by taking the IR spectrum (1810 cm^{-1}, Sn–H). [c] With a trace of impurities.

radical addition onto vinyl ether moiety, which presents a straightforward example of radical cyclization when vinylic oxygen is contained in a chain.

The preparation of the tetrahydrofurans **4** was attained via three steps shown in the Scheme I. Tris(3-chloropropyl) orthoformate (**1**) was obtained readily from triethyl orthoformate and 1-chloropropan-3-ol by a transesterification. The vinyl ethers **3**, containing two electron-withdrawing groups such as CN, COR, and CO_2R at the β-position of vinyl ether moiety, were prepared from active methylene compounds **2** and **1** by the similar procedures to those reported for the syntheses of ethyl vinyl ethers.[8] The radical cyclization of **3**, conducted with 1.1 equiv of tri-*n*-butyltin hydride (Bu_3SnH) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) in dry benzene, gave the tetrahydrofurans **4** having a mul-

† Tokyo Institute of Technology.
‡ Deceased February 27, 1985.

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