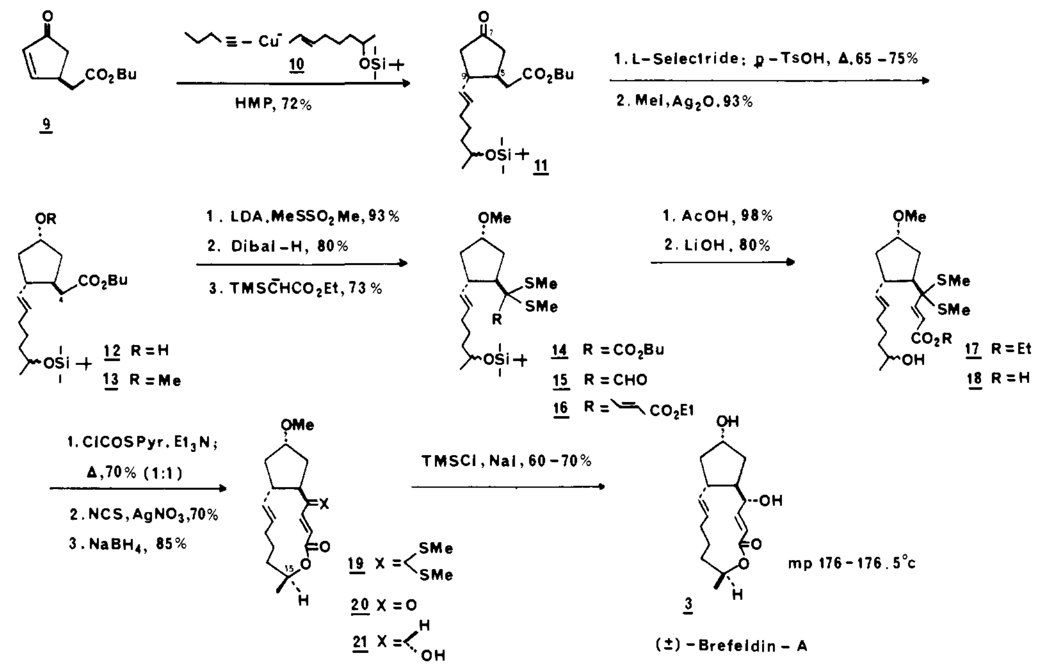
Scheme I



C-1 to C-4 γ-oxygenated crotonate unit commenced with bis(methylsulfenylation) of ester **13** (93% yield), which served to introduce directly a protected keto function at C-4, thereby avoiding the potential complications arising from the introduction of an additional center(s) of asymmetry at C-4. It is important to note that a *keto* function is ultimately "required" at C-4 in order to secure stereoselectively the C-4 α-OH of brefeldin-A (vide infra).[3a-d] Carefully controlled reduction of ester **14** with diisobutylaluminum hydride in toluene at ~−110 °C engendered aldehyde **15** directly and in high yield. As was the case with model compounds,[15] aldehyde **15** reacted only sluggishly with triethyl sodiophosphonoacetate; however, an alternative reagent, ethyl lithio(trimethylsilyl)acetate,[16] could again be employed successfully to produce the desired ketone-protected γ-oxocrotonate derivative **16**, exclusively *E*, in 73% yield. The C-15 hydroxyl group was selectively liberated by using aqueous acetic acid (98%), which was followed by saponification of the ethyl ester in aqueous ethanol to provide the hydroxy acid **18** in 80% yield.

Corey's double-activation process[17] was effective in lactonizing the hydroxy acid **18** and produced in 70% yield an ~1:1 mixture of diastereomeric lactones,[18] which were easily separated by silica gel chromatography (R_f 0.38, 0.48 using 30% Et_2O–pentane). The more polar isomer **19** was tentatively assigned the natural configuration at C-15, which proved ultimately to be correct.

The effectiveness of this particular choice for the C-4 and C-7 protecting groups can be seen by the simplicity of the conclusion of the synthesis. Treatment of **19** with silver nitrate and *N*-chlorosuccinimide in aqueous acetonitrile[19] at −10 °C afforded the fragile enone lactone **20** (70% yield), which, in the presence of sodium borohydride, was reduced at C-4 with virtually total stereoselectivity to give in high yield (±)-brefeldin-A 7-methyl ether (**21**). Exposure of this material to an excess of chlorotrimethylsilane and sodium iodide in acetonitrile[20] then concluded the synthesis, providing in 60–70% yield crystalline (±)-brefeldin-A, mp 176–176.5 °C (lit.[3c] racemic mp 175–175.5 °C), identified through spectral and chromatographic comparison with an authentic sample of the natural material. It is expected that this direct approach will prove useful for the synthesis of not only (+)-brefeldin-A (vide supra) but also various analogues of the natural product.[22]

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(17) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875 and references cited. Several other methods were examined in a closely related model system and were found to be much less effective.

(18) It is interesting to note that when this cyclization process is applied to the 4,7-bis(methoxyethoxymethyl) ethers, the derivative with the natural C-15 configuration lactonizes substantially more rapidly than that with the nonnatural configuration.[3a] In contrast, when Mukaiyama's procedure is used, the 4-dehydro compounds [7-(methoxymethyl) ethers] lactonize at roughly comparable rates,[3c] as in the present case.

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(22) **Note Added in Proof**: Another total synthesis of brefeldin-A has been reported: Köksal, Y.; Raddatz, P.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 472.

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Cyclopropane–Hydrogen Chloride Dimer: Identification and Geometry from Its Rotational Spectrum

Sir:

Recently we have reported a new method of observing the rotational spectra of weakly bound molecular complexes or otherwise transient molecules.[1] Weak molecular complexes are formed by collisional association in an adiabatic expansion of a high pressure gas through a nozzle into a vacuum. By flowing the complexes between the mirrors of a microwave Fabry–Perot cavity, the sensitive technique of pulsed Fourier transform microwave spectroscopy[2] can be used to observe the rotational

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(1) T. J. Balle, E. J. Campbell, M. R. Keenan, and W. H. Flygare, *J. Chem. Phys.*, **71**, 2723 (1979); **72**, 922 (1980).

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Table I. Spectroscopic Constants for the Cyclopropane-Hydrogen Chloride (^{35}Cl) Dimer^a

A_0 (MHz)	20004 (40)	χ_{aa} (MHz)	-54.41 (2)
B_0 (MHz)	1522.3313 (9)	χ_{bb} (MHz)	27.26 (7)
C_0 (MHz)	1454.7435 (9)	χ_{cc} (MHz)	27.15 (7)
D_J (kHz)	1.91 (3)		
D_{JK} (kHz)	29.96 (17)		

^{a} $P_b = {}^1/_2(-I_b + I_a + I_c) = 20.344$ (25) amu Å, $P_c = {}^1/_2(-I_c + I_a + I_b) = 4.920$ (25) amu Å^2.

transitions of the molecular complex. In this way, we have identified the complex formed in the gas phase between cyclopropane and hydrogen chloride. An analysis of the rotational spectrum allows us to establish several important structural properties of the dimer:

(i) The Cl atom lies in the plane of the cyclopropane ring 4.004 Å from the centroid, with the hydrogen atom in HCl between the ring and the Cl atom rather than on the far side of the latter.

(ii) At the Cl nucleus the directions perpendicular to the H–Cl bond in the dimer are electrically and mechanically equivalent.

(iii) The most reasonable interpretation of the centroid to chlorine distance is in terms of the edge-on model, involving a hydrogen bond to the center of one edge of the ring.

A gas mixture of about 4% each of cyclopropane and HCl in argon (total pressure ~2 atm) was pulsed into the evacuated cavity from a supersonic nozzle, there generating dimers in high number density by virtue of a very low (~5 K) effective temperature in the expanding gas. A suitably delayed microwave pulse then polarizes the dimer molecules when they are in collisionless expansion. The molecules subsequently emit coherent radiation at their rotational transition frequencies which is detected and, after suitable averaging, Fourier transformed to display transitions having half-widths at half-height of about 7 kHz.

The ground-state rotational spectrum so observed is characteristic of that of a nearly prolate *asymmetric* rotor ($\kappa \simeq -0.9927$). This result immediately rules out the C_{3v} face-centered form for the dimer which would be a symmetric top. Each of 12 rotational transitions observed for the ^{35}Cl species carries a nuclear quadrupole hyperfine structure indicative of the presence of a single ^{35}Cl nucleus in the molecule, the analysis of which allows the values of the coupling constants χ_{aa}, χ_{bb}, and χ_{cc} given in Table I to be determined concomitantly with unperturbed transition frequencies. The latter then lead, through a least-squares treatment, to the rotational and centrifugal distortion constants A_0, B_0, C_0, D_J, and D_{JK}, also shown in Table I. Formulation of the centrifugal distortion contribution in terms of limiting symmetric rotor constants is sufficient to allow all transition frequencies to be fitted within experimental error. The molecular geometry and identification of the inertial axes (a, b, c) are illustrated in Figure 1.

The conclusions summarized above follow from several arguments involving the spectroscopic constants given in Table I. First, the quantities A_0, P_b, and P_c (see Table I for definitions) are effectively unchanged from the corresponding values (20093 MHz, 20.179 and 4.973 amu Å,^{2} respectively) of free cyclopropane.[3] This shows clearly that the Cl atom lies in the plane (ab) of the ring and suggests that the ring geometry is unperturbed on dimer formation. If it is assumed that the acid hydrogen atom lies on the centroid to Cl line and monomer geometries[3] survive dimer formation (see Figure 1), the centroid to Cl distance of 4.004 ± 0.001 reproduces B_0 and C_0. In fact, all values of the angle of rotation ϕ of the cyclopropane molecule about its local C_3 axis yield this result which is a necessary consequence of the cyclopropane symmetry.

Secondly, the values of χ_{gg} ($g = a, b, c$) demonstrate that the acid hydrogen atom lies between the cyclopropane ring and the Cl atom. In the ground state the hydrogen atom undergoes excursions from its presumed equilibrium position on the a axis (the position of which is independent of ϕ). Then χ_{aa} is the projection of the free HCl value χ_0 on the a axis averaged over the zero point motion

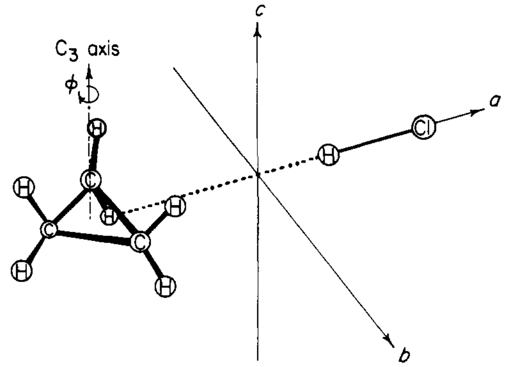

Figure 1. Moleular geometry and identification of the principal inertial axes (a, b, c) in cyclopropane–hydrogen chloride. The orientation chosen for cyclopropane defines the angle $\phi = 0$ for rotation about the local C_3 axis.

$$\chi_{aa} = {}^1\!/_2\chi_0\langle 3\cos^2\gamma - 1\rangle$$

where γ is the instantaneous value of the angle between the HCl bond direction and the a axis. Implied by the use of this equation is the assumption that the principal axis components of the electric field gradient at the Cl nucleus in HCl are unchanged in the dimer. Evidence in favor of such an assumption is the equality of χ_{bb} and χ_{cc}, which indicates that the b and c directions in the dimer are electrically and mechanically equivalent. Such a result is expected if the HCl subunit is remote from cyclopropane in the dimer. Having justified the assumption, the above equation leads to the operationally defined average value $\gamma = 21.3°$. If the H atom were uninvolved in a hydrogen bond and were to lie on the side of the Cl atom away from cyclopropane, its motion would be much less constrained, leading to a larger acute value of γ.

Finally, although all values of ϕ in the model taken with a centroid to chlorine distance of 4.004 ± 0.001 Å reproduce the observed rotational constants, only two forms, edge on ($\phi = 0°$, 120°, and 240°; C_{2v}) and corner on ($\phi = 60°$, 180°, and 300°; C_{2v}), are reasonable on grounds of symmetry. In the edge-on model, the Cl atom lies 3.57 Å from the midpoint of the C–C bond and 3.65 Å from the two nearest carbon atoms. Given that $r(\mathrm{C}\cdots\mathrm{Cl}) = 3.69$ Å and $\gamma = 23.0°$ in OC···HCl,[4] and that the sum of the van der Waals radii of C and Cl is ~3.6 Å, the edge-on model is eminently reasonable. On the other hand, the corner-on model requires the very short C···Cl distance of 3.13 Å and, moreover, places the cyclopropane and hydrogen chloride H atoms in unlikely proximity (1.57 Å). The alternative corner-on model, with Cl rather than H bound to the CH_2 group, is unlikely not only because an even shorter C···Cl distance is required but also because of the smallness of the angle γ.

In view of extensive discussion in the literature[5] concerning the relative stabilities of face-protonated, edge-protonated, and corner-protonated cyclopropane, the form of the gas-phase dimer of cyclopropane and hydrogen chloride is of value in establishing the position sought by an electrophilic reagent.

We are undertaking further isotopic investigations to elucidate further details of the dimer geometry.

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