consin—Eau Claire for the sample of 14-ane-S_4 ligand used in this work.

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(8) The Cu(I) complex was prepared by reducing the corresponding Cu(II) complex at 0.45 V at a platinum working electrode and slowly crystallizing from a methanol–water mixture under a nitrogen atmosphere. The thin, colorless, translucent needles of Cu^{I}(14-ane-S_4)(ClO_4) are orthorhombic, Fdd2, with cell data $a = 25.514$ (4), $b = 32.356$ (7), $c = 8.067$ (1) Å, $Z = 16$, $\rho_{calcd} = 1.71$ g cm^{-3}. X-ray intensity data were collected by the θ–2θ technique with Mo Kα radiation (graphite monochromator) on a Syntex $P2_1$ diffractometer. Of a total of 1252 data examined, 985 data had $I > 3\sigma(I)$ and were used in the structure determination. The structure was solved by direct methods and refined by anisotropic least-squares refinement, with fixed contributions from hydrogen atoms, to discrepancy factors of $\Sigma(|F_o| - |F_c|)/\Sigma|F_o| = 0.042$ and $[\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2} = 0.053$.
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Thermal Isomerization and Fragmentation of 1,1-Difluoro-2,3-dimethylcyclopropane

Sir:

In recent years there has been considerable interest both experimentally and theoretically on the effect of hetero substituents on the structure and reactivity of cyclopropane compounds. Hoffmann and Günter have predicted dramatic changes in the properties of cyclopropane derivatives when electron donors or electron acceptors appear as substituents.[1,2] Richey[3] and Kirmse[4] have provided a number of examples of cases in which alkoxy substituents have been shown to accelerate sigmatropic rearrangements and geometrical isomerizations of cyclopropanes.

Fluorine is of considerable interest as a substituent on cyclopropane owing to its unique but often inscrutable potent π-donor and inductive acceptor properties. Hoffmann and Günter predicted that it would behave as a π donor in cyclopropanes with the net result of lengthening and weakening the C_2–C_3 bond.

Microwave spectra of cyanocyclopropane[5] and nitrocyclopropane[6] tend to corroborate Hoffmann's and Gunter's predictions as to the effect of π acceptors, but the microwave spectrum and a theoretical structural analysis of 1,1-difluorocyclopropane[7,8] tend to implicate fluorine as an *acceptor*.

Table I. Equilibrium Constants for the Cis-Trans Isomerization

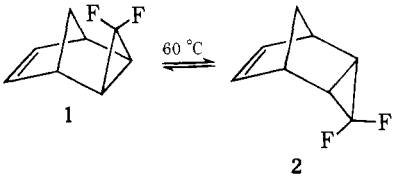
Temp, °C	297.3	306.3	314.5	325.3	336.4	344.9
K	1.917	1.911	1.890	1.871	1.847	1.828

Table II. Rate Constants for the Cis-Trans Isomerization

Temp, °C	297.3	306.3	317.0	326.3	336.3	344.9
$10^5 k_1$ (s^{-1})	3.96	8.21	16.2	33.6	68.2	116.9

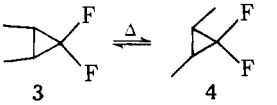
Nevertheless the lengthening and hence weakening of the C_2–C_3 bond is confirmed by these studies.

While quantitative confirmation of the enhancement of C_2–C_3 homolytic bond cleavage in *gem*-difluorocyclopropanes has not heretofore been reported, there have been qualitative corroborative reports,[9-11] perhaps the best example being the rapid thermal interconversion of exo and endo isomers **1** and **2** at 60 °C.[11]



1 **2**

As a first step in our efforts to quantify the effects of fluorine substitution on thermal homolytic processes of cyclopropanes and of hydrocarbons in general,[12] we wish to report our study of the geometrical isomerization and fragmentation of *cis*-1,1-difluoro-2,3-dimethylcyclopropane (**3**).

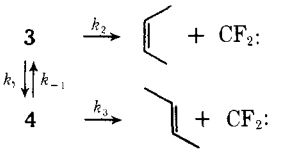


3 **4**

cis- and *trans*-1,1-difluoro-2,3-dimethylcyclopropane were synthesized using Burton's method[13] and were purified >99.5% pure by GLC. Pyrolysis at pressures varying from 4–25 mm were carried out in a well-conditioned 200-mL Pyrex vessel[14] which was heated in a fused-salt, high temperature thermostat. The reaction was found to follow good reversible first-order kinetics throughout. Equilibrium constants were obtained at six temperatures (see Table I) and a plot of ln K vs. the reciprocal of the absolute temperature yielded a ΔH for the cis–trans isomerization of -0.72 ± 0.05 kcal/mol. Rate constants were also obtained at six temperatures (see Table II), and an Arrhenius plot of this data gave a good straight line with the frequency factor and energy of activation being calculated by the method of least squares.

$$k_1 = 14.7 \pm 0.2 \exp(-49700 \pm 600/RT)\ \text{s}^{-1}$$

While the reaction was free of hydrogen-shift side reactions, such as those which complicated the pyrolysis of the analogous hydrocarbon,[15] there was observed a significantly higher energy competitive reaction which took place cleanly at a rate of $\sim 1/25$ that of the isomerization process. This process was the extrusion of CF_2 to form 2-butenes. Such an extrusion process has previously been observed for perfluoro-, tetrafluoro-, and chlorofluorocyclopropanes[16,17] and for perfluoro epoxides,[18] but to our knowledge has not heretofore been reported for simple *gem*-difluorocyclopropanes. This reaction was examined carefully at 297.3 °C and it was found to take place with high stereospecificity (>96%). Moreover it was found that **3**



and **4** extruded CF_2: at almost equal rates ($k_2/k_3 = 1.05$).

Our observed activation energy for the geometrical isomerization of **2** (49.7 kcal/mol) can be compared with that for the analogous nonfluorinated molecule (59.1 kcal/mol) which was determined by Flowers and Frey in 1960.[15] It can thus be seen that the presence of the CF_2 group *significantly* facilitates the isomerization process. However it must be emphasized that precise interpretation of these results at this time is premature. There is, as of yet, no experimental evidence as to the mechanism of the cis-trans interconversion, i.e., whether cleavage of bond C_1–C_2 or of bond C_2–C_3 is responsible for the observed isomerization. The earlier mentioned exo-endo epimerizations[10,11] do, of course, provide strong credibility for C_2–C_3 cleavage, but work is currently in progress in our laboratories to fully elucidate the mechanism of the isomerization process.

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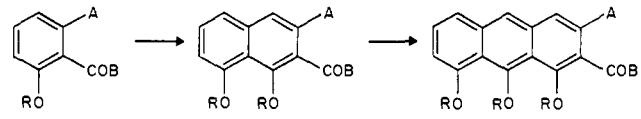
New Synthetic Strategy for the Preparation of Linear Phenolic Natural Products

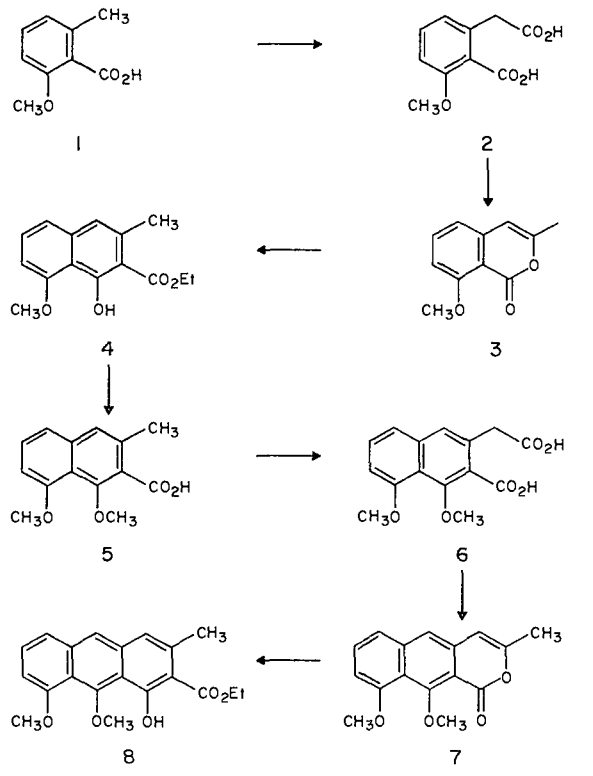
Sir:

We have developed a conceptually simple synthetic strategy which significantly facilitates the preparation of linear polynuclear phenolic systems, a structural feature present in many antiobiotics and other natural products. This strategy, shown in Scheme I, involves repetitive execution[1] of a single regioselective reaction sequence which adds a new phenolic ring to the existing aromatic system in each cycle. To illustrate the versatility of this synthetic strategy, 2-methyl-6-methoxybenzoic acid (**1**) was carried through two cycles yielding the

Scheme I



Scheme II



polyfunctionalized anthracenecarboxylic ester **8** (Scheme II).

The aglycone portion of numerous naturally occurring compounds consists of linear tri- and tetracyclic systems with two or more aromatic rings.[2] Many of the parent compounds, such as the anthracyclines adriamycin,[3] daunorubicin,[4] and carminomycin,[5] olivomycins A, B, C, and D,[6] chromomycins A 1–4,[6,7] and aureolic acid,[8] have, in addition to their antibiotic activity, significant anticancer properties. Of these, only daunorubicin[9,10] has been synthesized.

Generally, only three approaches, the use of the Friedel-Crafts acylation,[9,11] variant forms of the Diels-Alder reaction,[12-14] or cyclization of polyketides,[15,16] have been employed to construct linear polynuclear systems. Alternate synthetic methodology is much needed to permit the regioselective preparation of linear phenolic systems not achievable by these other approaches. The described repetitive synthetic strategy and the derived reaction sequence which accomplishes it should be adaptable to a broader range of these systems.

The starting material chosen for the synthesis, 2-methyl-6-methoxybenzoic acid[16] (**1**), was carboxylated on the methyl group by quenching the orange dilithium anion, formed by treatment of **1** with lithium diisopropylamide at −78 °C with dimethyl carbonate. Aqueous workup gave directly homophthalic acid **2**, mp 165–166 °C (lit.[17] mp 165–166 °C), in 90% yield.[18,19] A three-step sequence involving acylation of **2** with acetic anhydride and pyridine, followed by basic hydrolysis with concomitant decarboxylation, and, finally, ring closure of the intermediate using acetic anhydride and perchloric acid yielded isocoumarin (**3**), mp 109 °C (lit.[17] mp 109.5–110.5 °C), in 68% overall yield.[20,21] Slow addition of a dilute benzene solution of ethyl bromoacetate to a refluxing benzene solution of **3** and zinc gave naphthoate **4**, mp 59 °C,