Generation and Trapping of Methylenecyclopropene

Summary: Evidence is presented for the intermediacy of methylenecyclopropene as a reactive intermediate.

Sir: Methylenecyclopropene (1) is of considerable interest both from a preparative and theoretical standpoint. This

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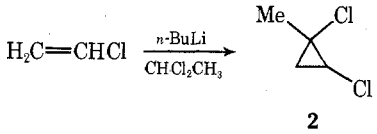
elusive hydrocarbon is predicted to possess only minor resonance stabilization,[1] and the high index of free valency at the exocyclic position is expected to facilitate polymerization, a process favored additionally by release of strain. Although numerous derivatives of the methylenecyclopropene family have been reported,[2] only two attempts to prepare the parent hydrocarbon can be found in the literature.[3] We report here the generation and trapping of this hydrocarbon.

The starting material **2** was prepared in low yield by addition of chloromethyl carbene (CH_3CHCl_2, *n*-BuLi)[4] to vinyl chloride. Compound **2** was separated from several unidentified



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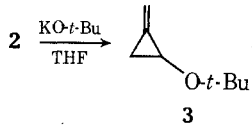
products by preparative GLC (Carbowax 20M on Chromosorb W). Preliminary results from a study of the microwave spectrum of **2** suggest that the chlorines bear a cis relationship.[5] Other spectral data follow: NMR (CCl_4) δ 1.12–1.43 (m, 2 H), 1.60 (s, 3 H), and 2.70–2.99 (m, 1 H); mass spectrum calcd for $C_4H_6Cl_2$ 123.9846, found 123.9836.

Reaction of **2** (1 equiv) with KO-*t*-Bu (8 equiv) in THF at −30–40 °C for 1 h gave **3** in 37% isolated (preparative GLC) yield. In Me_2SO at 18–20 °C **3** was produced in 33% yield.



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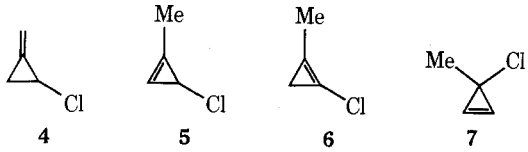
Compound **3** was characterized by its NMR spectrum which shows a multiplet at δ 1.19–1.40 overlapping a singlet at 1.20 (11 H total) with other signals at 3.35–3.62 (m, 1 H) and 5.23–5.57 (m, 2 H). Elemental composition was provided by mass spectroscopy: calcd for $C_8H_{14}O$ 126.1044, found 126.1042.

The formation of **3** is rationalized in terms of **1** as a reactive intermediate. Possible intermediates in the conversion of **2**

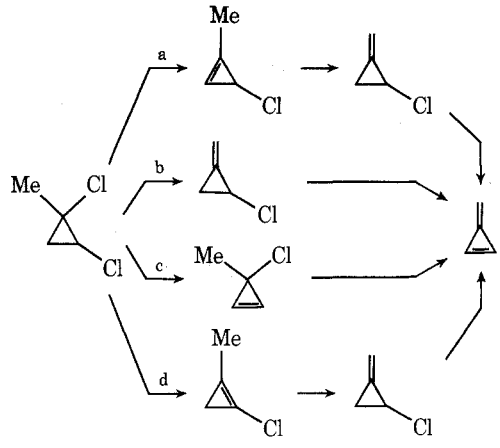


4 5 6 7

→ **1** → **3** are compounds **4–7**. Four paths (a–d) which utilize these intermediates are summarized in Scheme I.

Intermediate **4** appears in paths a, b, and d and would be expected to undergo dehydrochlorination to give **1**. One might escape postulating **4** (and thus methylenecyclopropene) by assuming addition of *t*-BuO^- to cyclopropenes **5** and **6** prior to isomerization to **4**, although the previous observation that

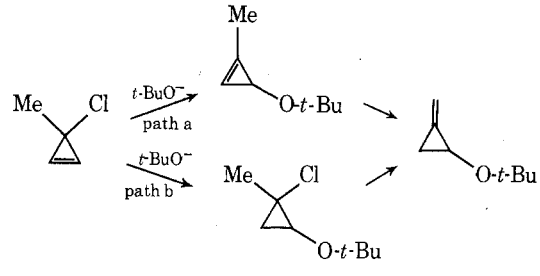
Scheme I



alkylcyclopropenes undergo double-bond isomerization to the exocyclic position rather than add *t*-BuO^- would seem to undermine this assumption.[6]

Such an option is not available for intermediate **7** (path c). While the facile conversion of **7** to **1** would be expected, nevertheless, two additional routes (paths a[7] and b) for **2** → **3** via **7** which bypass methylenecyclopropene are shown in Scheme

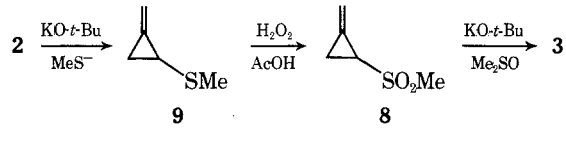
Scheme II



II. These routes cannot be eliminated on the basis of the data that are available.

Much more compelling evidence which supports the intermediacy of methylenecyclopropene is found in the reaction sequence of Scheme III. Thus, reaction of **2** with KO-*t*-Bu (6

Scheme III



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equiv) in Me_2SO in the presence of MeS^- (2 equiv) yielded, in addition to **3** (12%), the sulfide **9** in 34% yield. Spectral data: NMR (CCl_4) δ 0.93–1.73 (m, 2 H), 2.10 (s, 3 H), 2.20–2.58 (m, 1 H), and 5.27–5.53 (m, 2 H); mass spectrum calcd for C_5H_8S 100.0346, found 100.0342. When 4 equiv of MeS^- was used, **9** was produced in 51% yield. Oxidation of **9** with 30% H_2O_2 in glacial acetic acid gave the sulfone **8** in 72% yield. When **8** was treated with KO-*t*-Bu (8 equiv) in Me_2SO, **3** was produced as the only volatile product in 11% yield.

Since sulfones are well known to give alkenes via β elimination,[8] this result provides the most compelling evidence for the intermediacy of methylenecyclopropene. Another possible interpretation, e.g., SN2 displacement in **8** or **4** seems unlikely, since cyclopropyl systems normally fail to undergo SN2 reactions.

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References and Notes

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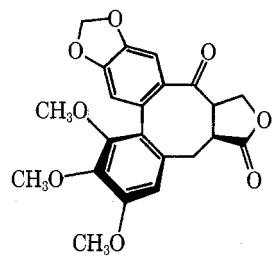
A Short Synthesis of (±)-Isostegane[1]

Summary: (±)-Isostegane has been prepared in a three-step sequence utilizing sequential substitution of the β and α positions of an electron-deficient olefin followed by nonphenolic oxidative coupling.

Sir: Kupchan and coworkers recently described an unusual and highly cytotoxic class of dibenzocyclooctadiene lactones exemplified by the ketone lactone steganone (**1**).[2] Two total syntheses of **1** have been reported and another group has described synthetic efforts in this area.[3] Our retro-synthetic analysis of **1** suggested that the dibenzocyclooctadiene skeleton might be efficiently constructed by sequential substitution of the β and α positions of an electron-deficient olefin using a conjugate addition alkylation sequence followed by nonphenolic oxidative coupling to yield a tetracyclic debenzocyclooctadiene structure.[4] Herein, we wish to describe a three-step construction of isostegane (**2**)[1] which demonstrates the validity of this strategy and which proceeds in 55% overall yield.



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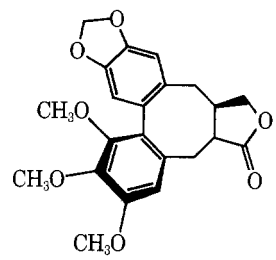

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Compound **2** was prepared in the following manner. The carbonyl anion equivalent **3** was generated from piperonal dithiomethyl acetal[5] (1 equiv, 1 M in THF, −78 °C) by treatment with *n*-butyllithium (1 equiv). After stirring for 40 min at −78°C, the butenolide **4**[6] (1 equiv, 1 M in THF) was slowly added over a period of 30 min. The resulting white suspension was stirred for 3 h at −78 °C whereupon the bromide **5**[7] (1 equiv, 1 M in THF) was rapidly added followed immediately by tetramethylethylenediamine (1 equiv).[8] The temperature of the reaction mixture was then raised to −20 °C and stirring continued for 10 to 12 h. Standard workup gave the adduct **6** as an amorphous yellow solid in 99% crude yield.[9] Without purification, adduct **6** (2.5 g) was treated with a suspension of W-4 Raney Nickel (25 g) in acetone (100 ml) at reflux for 30 min. Vacuum filtration of the crude desulfurized product through silica gel gave compound **7** as a clear oil in 85% overall yield from **3**.

Cyclization of **7** into **2** was accomplished by slowly adding (10 min) compound **7** (1 equiv, 0.02 M in methylene chloride) to VOF_3 (3 equiv.) suspended in a 2:1 mixture of methylene chloride and trifluoroacetic acid (0.16 M) at −45 °C.[10] The reaction mixture was stirred at −45 °C for 7 h and then worked up by addition of saturated sodium carbonate solution. The crude dark yellow product was purified by vacuum filtration through silica gel followed by crystallization from chloroform–methanol to give pure isostegane (mp 172–172.5 °C) as the sole reaction product in 65 to 70% yield.[11]

The spectral characteristics of compound **2** (uv, ir, NMR, and mass spectrum) clearly indicated it to be a tetracyclic dibenzocyclooctadiene lactone. However, the stereochemical configuration of **2** could not be assigned from these data. As a result, the bromide **8** was prepared[12] and an x-ray structure determination undertaken.

The crystals of compound **8** were monoclinic, space group $P2_1/a$, with a = 22.699 (9), b = 7.433 (6), c = 11.984 (5) Å; β = 95.16 (2)° and d_{calcd} = 1.574 g cm^{-1} for Z = 4. The intensity data were measured on a Hilger-Watts diffractometer (Ni filter Cu Kα radiation, θ–2θ scans,

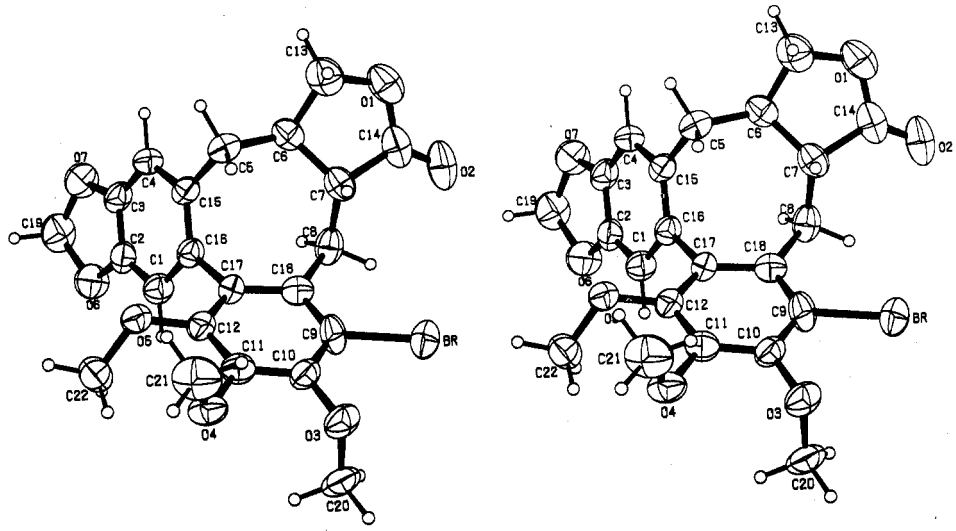

Figure 1.