Communications

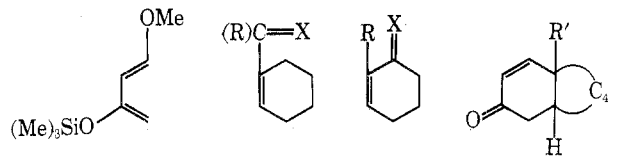
A Diels–Alder Route to Cis-Fused Δ^1-3-Octalones

Summary: Cycloaddition of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene with cyclohexene-type nucleophiles leads to *cis*-fused Δ^1-3-octalones.

Sir: Applications of the Diels–Alder reaction to the synthesis of octalones and decalones using dienophiles such as **2** and **3** (X = O, etc.) have, on the whole, proven disappointing.[1-4] High temperatures have been necessary to effect reaction, and low yields have resulted.

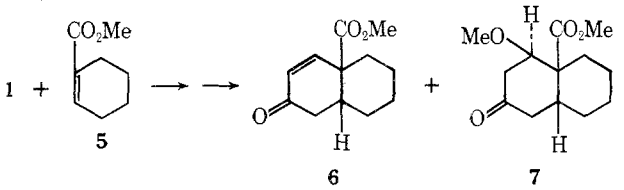
In connection with synthetic objectives directed toward vernolepin,[5,6] we sought to prepare cis-fused octalone derivatives of the type **4**. It will be recognized that such systems are not readily prepared from the corresponding *cis*-fused decalones.[7] The tendency of such decalones to undergo enolization-induced functionalizations preferentially[8] at the 4 position, or competitively at the 2 and 4 positions,[9] is well known. A recent solution to this problem in the steroid series[10] has not yet been extended to simpler systems.[11]

Recently we described[12] the preparation of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**). The smooth cycloadditions[12] of **1** with conventional electron-withdrawing dienophiles suggested that it might be sufficiently reactive to undergo Diels–Alder reactions with systems of the type **2** and **3** under milder conditions than have thus far been possible. The cycloadducts would be expected to suffer ready conversion to the target system, **4**.



1 **2** **3** **4**

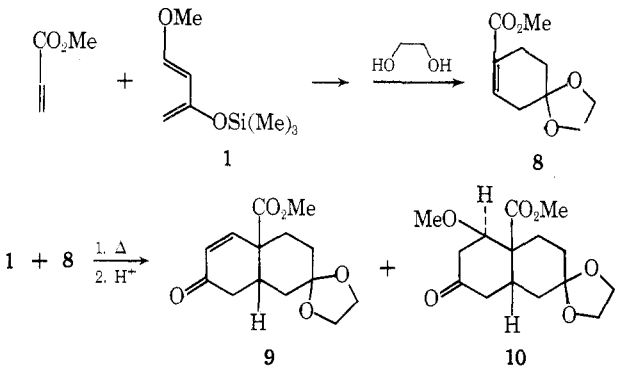
Compounds **1** and **5** were heated in a sealed tube at 190° for 30 hr. The total reaction product was added to a solution of 3:1 THF:0.005 *N* HCl at −5 to 0°. After work-up, the reaction mixture was chromatographed on silica gel. Subsequent to elution of traces of **5**, a 53% yield of enone **6** [$\bar{\nu}_{max}$ ($CHCl_3$) 1720, 1669, 1645 (sh) cm^{-1}; λ_{max} (EtOH) 229 nm (ϵ 22,500); δ ($CDCl_3$) 3.75 (s, 3 H, CO_2Me), 6.01 (d, J = 10 Hz, 1 H, O=CC**H**=CH–), 6.63 (dd, J = 10 Hz, O=C-CH=C**H**–) ppm] was obtained. Further elution afforded a 2% yield of the β-methoxy ketone **7** [$\bar{\nu}$ ($CHCl_3$) 1720 (sh), 1710 cm^{-1}; δ ($CDCl_3$) 3.24 (s, 3 H, OCH_3), 3.5–3.8 (m, containing s at δ 3.75, 4 H, OCHR + CO_2CH_3) ppm].



5 **6** **7**

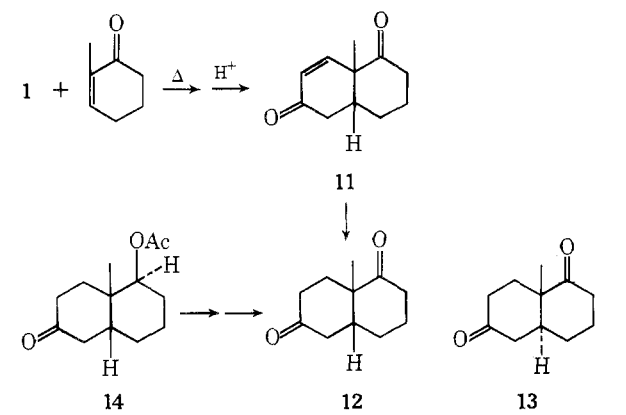
The possibilities of conducting sequential Diels–Alder reactions with diene **1** are seen in the three-step assemblage of enone ketal **9**. A solution of methyl acrylate (20 mmol) and diene **1** (23 mmol) in benzene (5 ml) was heated under reflux for 24 hr. Ethylene glycol (2 g), *p*-toluenesulfonic acid (200 mg), and additional benzene (15 ml) were added. Reflux was continued for an additional 6 hr with azeotropic removal of water. Work-up and chromatography on silica gel gave an 85% yield of ketal ester **8**, mp 40–41°. *Compound* **8**, *itself, functions as a dienophile in another Diels–Alder reaction with* **1**. The conditions required for this reaction are more severe (1 equiv of **8**, 5 equiv of **1** in xylene; sealed tube; 175–185°; 40 hr). Treatment of the total reaction mixture with 3:1 THF:0.005 *N* aqueous HCl at −5 to 0° for 10 min allowed for maintenance of the ketal while the β-methoxysilyl enol ether was unraveled to the desired enone. Chromatography on silica gel gave 11% recovered **8** and a 73% yield (65% efficiency) of enone ketal ester **9**, whose spectral properties [$\bar{\nu}_{max}$ ($CHCl_3$) 1724, 1675, 1650 (sh) cm^{-1}; λ_{max} (EtOH) 226 nm (ϵ 13,000); δ ($CDCl_3$) (3.71, s, 3 H CO_2CH_3), 3.90 (s, 4 H, dioxolane), 6.01 (d, J = 10 Hz, O=CC**H**=CH–), 6.60 (dd, J = 10 Hz, J = 1.5 Hz, 1 H, O=CCH=C**H**–)] confirm its structure. A 2% yield of the β-methoxy ketone **10** [$\bar{\nu}_{max}$ ($CHCl_3$) 1730 (sh), 1710 cm^{-1}; δ ($CDCl_3$) 3.22 (s, 3 H, OCH_3), 3.7 ~3.85 (m, containing s at δ 3.75, 4 H, OCHR + CO_2CH_3), 3.88 (s, 4 H, dioxolane) ppm] was obtained on further elution.

Compound **9** is a potentially valuable synthetic intermediate since it contains differentiated carbonyl systems and angular functionality.[13]



1 **8** **9** **10**

The cycloaddition of **1** with cyclohexene dienophiles of the type **3** was demonstrated with 2-methylcyclohexenone.[14] A solution of compound **1** (3.5 equiv) and the enone (1 equiv) in xylene was heated in a sealed tube at 200° for 20 hr. The total reaction mixture was treated with 3:1 THF:0.005 *N* aqueous HCl. Work-up and chromatography gave 11% recovered enone and 47% (42% efficiency) enedione **11**: mp 54–55°; $\bar{\nu}_{max}$ ($CHCl_3$) 1700, 1680, 1655 cm^{-1}; λ_{max} (EtOH) 227 nm (ϵ 7,000); δ ($CDCl_3$) 1.45 (s, 3 H, angular CH_3), 5.98 (d, J = 10 Hz, 1 H, O=CC**H**=CH–), 6.58 (d, J = 10 Hz, 1 H) ppm].



11 **14** **12** **13**

In view of the rather harsh reaction conditions used in the cycloaddition, the stereochemistry of the product was confirmed in a chemical fashion. Catalytic hydrogenation of **11** gave the dihydro compound **12**, mp 65–66°. The spectral properties and melting point of **12** were different from those of the authentic trans compound, **13**, mp 57.5–59°.[15,16] A positive comparison was made starting with the ketoacetate **14**.[16] Hydrolysis and Jones oxidation of **14** gave an authentic sample of **12**[17] undistinguishable with that prepared from the Diels–Alder route.

Studies of further applications of this active diene in Diels–Alder reactions as well as utilization of the octalones are in progress.

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References and Notes

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(3) For successful reactions with corresponding cyclopentenoid dienophiles, see R. L. Kronenthal and E. I. Becker, *J. Amer. Chem. Soc.,* **79,** 1095 (1957).

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(7) For entries to the corresponding trans-fused Δ^1-3-decalones by bromination–dehydrobromination, see (a) R. Rinker, J. Kalvoda, D. Arigoni, A. Furst, O. Jeger, A. M. Gold, and R. B. Woodward, *J. Amer. Chem. Soc.,* **76,** 312 (1954); (b) M. Los, U. S. Patent 3,592,855 (1971) [*Chem. Abstr.,* **75,** 140371 (1971)].

(8) For a general review of the direction of functionalization of steroidal coprostanone systems where enolization in the $\Delta^{3(4)}$ sense is strongly favored, see (a) A. J. Liston, *J. Org. Chem.,* **31,** 2105 (1966), and references. For the corresponding reactions in the tricyclic (abietane) series, see (b) M. E. Kuehna, *J. Amer. Chem. Soc.,* **83,** 1492 (1961).

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(11) For another example of functionalization (oxalylation under thermodynamic control), see G. Stork and R. K. Hill, *J. Amer. Chem. Soc.,* **79,** 497 (1957).

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(16) We thank Professor Clayton Heathcock, Department of Chemistry, University of California at Berkeley, for generous samples of **13** and **14.**

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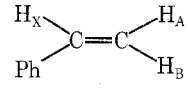
Hofmann Elimination with Diazomethane on Quaternary Curare Bases[1]

Summary: Treatment of (+)-tubocurarine, (+)-isotubocurarine, and (+)-chondocurarine at room temperature with an excess of diazomethane leads to Hofmann elimination type methine bases resulting from unique stereochemical pathways.

Sir: When O-methylating (+)-tubocurarine chloride (I) with excess diazomethane in the usual way to produce the O,O-dimethyl derivative, we observed that the crude reaction product, when examined by thin layer chromatography (tlc), showed anomalous spots which could logically be ascribed to unexpected tertiary bases on the basis of their R_f values. Additional experimentation indicated that the apparent intensities of the spots were enhanced with larger amounts of diazomethane. The same experiment repeated on (+)-isotubocurarine (II)[2] and chondocurarine chloride (III) reinforced the conclusion that a Hofmann elimination reaction had taken place to generate tertiary methine bases by the action of diazomethane on I, II, and III. This stimulated a more informative inquiry into the anomaly.[3]

The general aspects of the presently reported reaction were that the respective quaternary bases were treated in methanolic solution with a tenfold molar excess of ethereal diazomethane[4] added incrementally over a 24-hr period. The work-up of the products was essentially a separation on 1-mm precoated silica gel plates developed with a solvent system composed of 2.5% ammonia:ethyl acetate:2-propanol:methanol (0.7:3:3:4). The appropriate bands were removed and extracted with a suitable solvent mixture of methanol and ethyl acetate to yield the respective products.[5]

Examination of the nuclear magnetic resonance (nmr) spectra ($CDCl_3$, δ) of the methine bases obtained from I, II, and III provides an interesting comparison of steric factors directing the course of the Hofmann elimination (see Figure 1). The major elimination product of I isolated was the stilbene derivative (IV): 2.32 [s, 6, $N(CH_3)_2$], 2.46 (s, 3, NCH_3), 3.76 (d, 6, 2 OCH_3), 3.87 (d, 6, 2 OCH_3), 5.82–7.08 [m, 12, 10 aromatic and 2 vinyl (*i.e.,* stilbene)]. In the case of II, the methine base was exclusively a styrene derivative (V): 2.10 (s, 3, NCH_3), 2.25 [s, 6, $N(CH_3)_2$], 3.67 (d, 6, 2 OCH_3), 3.83 (d, 6, 2 OCH_3), 5.16–5.56 (4d, 2, the AB styrene protons in



J_{AX} = 9, J_{BX} = 17, J_{AB} = 1.5 Hz), 5.80–6.95 (m, 11, 10 aromatic and the X proton of the styrene product). III behaved in the expected manner to fom a monostilbene–monostyrene derivative (VI): 2.22 [s, 6, $N(CH_3)_2$], 2.34 [s, 6, $N(CH_3)_2$], 3.75 (d, 6, 2 OCH_3), 3.82 (d, 6, 2 OCH_3), 5.16–5.56 [4d, 2, the AB styrene protons (as in V)], 5.80–7.05 [m, 13, 10 aromatic, 3 vinyl (*i.e.,* 2 stilbene protons and the X proton of the styrene moiety)].

These unique stereochemical pathways become explicable by examining Dreiding models of the compounds. By orienting the molecules in their preferred conformations,[6,7] several observations account for the pathways that I, II, and III undergo in this Hofmann elimination reaction.

(1) Assuming that the eliminations proceed mostly by an E2 mechanism[8] wherein the groups must be anti-periplanar, it will be noticed that in the case of I the β hydrogens on C-4′ leading to a styrene product and those on C-a′ leading to a stilbene product can be oriented anti to the leaving quaternary group with equal ease. Thus, in I, since