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DIVERSION OF AN INTRAMOLECULAR [2 + 4] CYCLOADDITION REACTION INTO A [2 + 2] PATHWAY BY ELECTROPHILIC CATALYSIS.

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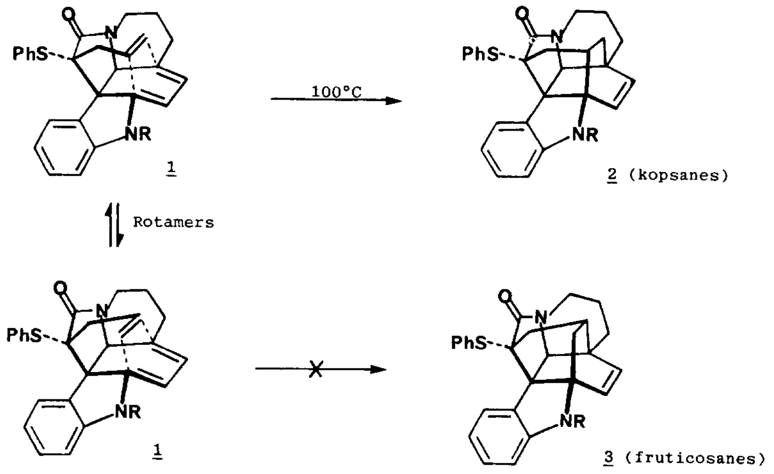
SUMMARY: The intramolecular [2 + 4] cycloaddition process 1 into 2 is diverted to a [2 + 2] process by electrophilic catalysis, 1 into 4.

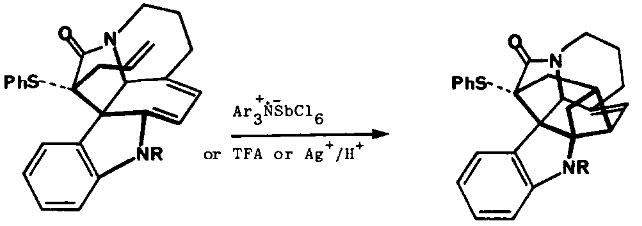
The total synthesis of the kopsane indole alkaloids was dependent upon an intramolecular [2 + 4] cycloaddition reaction that transformed the homoannular diene 1 into the basic kopsane skeleton 2.[1] *While the regiochemical mode of cyclization shown leads to the desired structure 2, the reverse mode, namely 1 into 3, would have resulted in the so-called fruticosane skeleton.*[2] *Clearly, this pathway would have to proceed through a more highly strained transition state, and as such is not observed.*



(R = $SO_2C_6H_4OMe$-p throughout)

In view of the recent exciting developments in both radical-cation[3] *and proton catalysis*[4] *of the Diels-Alder reaction, it was of some considerable interest to examine the response of 1 to these conditions to see if the "normal"* *regiochemical pathway to* $\underline{2}$ *could be changed.*

Treatment of $\underline{1}$ *with* $(p\text{-}BrC_6H_4)_3\overset{+}{N}{}^{\cdot}\,SbCl_6/CH_2Cl_2/20°C$ *for 0.5h gave the cyclobutane adduct* $\underline{4}$ *(72%), m.p. 262-263° (MeOH). The* ^1H *NMR data*[5] *enabled the structural assignment* $\underline{4}$ *to be made, but in view of its unprecedented nature it was unambiguously confirmed by single-crystal X-ray analysis.*[6] *Similarly, when* $\underline{1}$ *was treated with trifluoroacetic acid/*CH_2Cl_2*/20°C or AgOAc/*CH_2Cl_2*/20°C the cyclobutane adduct* $\underline{4}$ *was the only detectable product, uncontaminated by either* $\underline{2}$ *or* $\underline{3}$*. The cyclobutane derivative* $\underline{4}$ *was thermally stable to 300°C, and did not undergo photochemical 1,3-shifts to give the fruticosane skeleton* $\underline{3}$*. In a related series of experiments intended to examine the interaction of an acetylene suspended over the internal face of the homoannular diene moiety, we treated* $\underline{5}$[7] *with AgOAc(cat)/AcOH/*H_2SO_4*/20°C and isolated the adduct* $\underline{6}$ *(80%),*[8] *m.p. 204-205° (MeOH). The presence of the imine functionality in* $\underline{6}$ *was confirmed by treatment of* $\underline{6}$ *with TMSCN/*$ClCO_2Me/ZnI_2$*(cat) to give* $\underline{7}$ *(97%), m.p. 235-236° (Me OH),*[9] *whose structure was proven by single crystal X-ray analysis.*[10] *The adduct* $\underline{6}$ *did not undergo thermal or photochemically induced 1,3-shifts.*



$\underline{1}$ $\underline{4}$

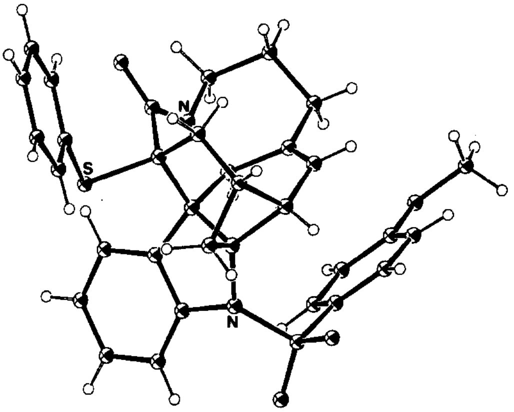
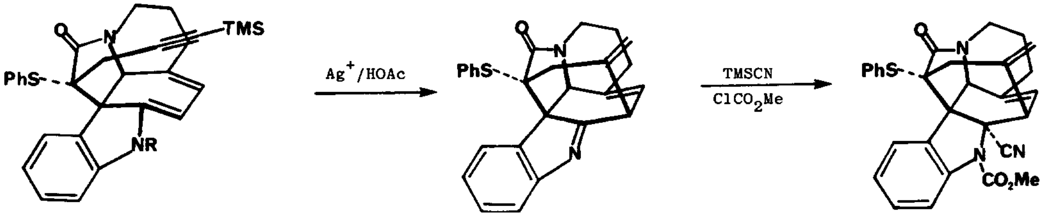


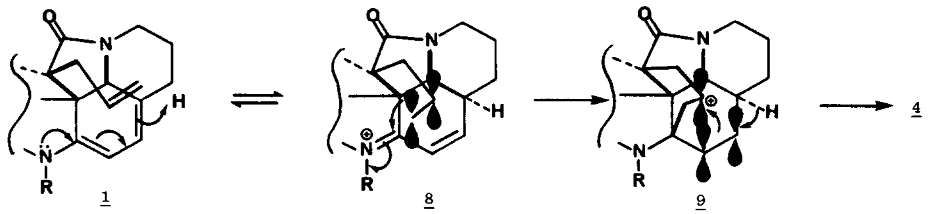
FIGURE 1



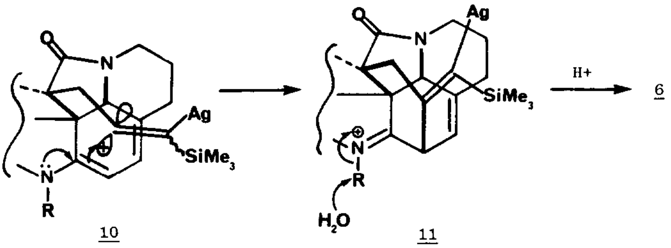
$\underline{5}$ $\underline{6}$ $\underline{7}$

The SCHEME 1 depicts a possible mechanistic explanation for the formation of the cyclobutane adduct 4. It should be noted that the aminium cation-radical often generates protons.[3,4] *Interaction of the homoannular diene 1 with an electrophile (H^+ or Ag^+) can produce an iminium ion 8, which is trapped by the pendant alkene to give 9. The secondary carbonium ion 9 is situated directly above the cyclohexenyl ring, which allows closure of the cyclobutane ring and proton loss to give 4.*

The formation of 6 is best rationalized by interaction of the acetylene with Ag^+ to give the vinylcation 10, which is trapped by the homoannular diene to give the iminium ion 11. Since 11 cannot lose a proton, nucleophile attack (presumably by H_2O) on the sulfonamide occurs, and acid catalyzed regeneration of Ag^+, and protodesilylation results in 6.



SCHEME 1



SCHEME 2

ACKNOWLEDGEMENTS:

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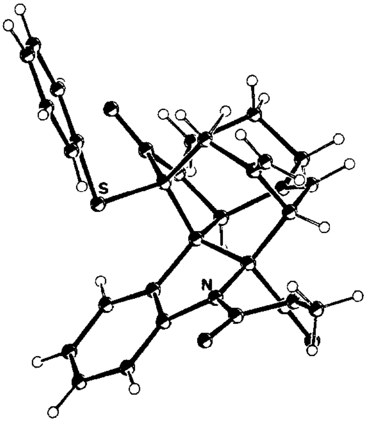
5. ^{1}H NMR (360MHz) δ 7.84(2H,m), 7.75(1H,d,J = 7Hz), 7.7(2H,d,J = 9Hz), 7.55(1H,d,J = 7Hz), 7.32(4H,m), 7.05(1H,t,J = 7Hz), 6.85(2H,d,J = 9Hz), 5.21(1H,d,J = 5.6Hz), 4.2(1H,dd,J's = 5 and 13.5Hz), 4.0(1H,t,J = 6.5Hz), 3.83(3H,s), 3.38(1H,d,J = 9.5Hz), 2.99(1H,s), 2.75(1H, d of t, J's = 3 and 12Hz), 2.25(2H,m), 2.18(1H,t,J = 7Hz), 2.00(1H,dd,J's = 4.5 and 15Hz), 1.78(1H,t, J = 14Hz), 1.65(2H,m), 1.47(1H,bm). Anal. Calcd. for $C_{33}H_{30}N_2O_4S_2$: C, 68.01; H, 5.19; N, 4.81. Found:C, 68.06; H, 5.22; N, 4.68.
6. The structure of 4 has been determined crystallographically - FIGURE 1. Details are available on microfiche, from the Indiana University Chemistry Library - request Structure Report No.85059.
7. The substrate 5 was prepared by alkylation of the corresponding C-11 proton adduct. 5 has m.p. 119-122° (MeOH). Anal. Calcd. for $C_{36}H_{36}N_2O_4S_2Si$: C, 66.23; H, 5.56; N, 4.29. Found: C, 66.10; H, 5.49; N, 4.33.
8. ^{1}H NMR (360MHz) δ 7.67(1H,d,J = 8Hz), 7.5-7.6(3H,m), 7.45(1H,t,J = 8Hz), 7.28(1H,d,J = 8Hz), 7.18-7.23(3H,m), 5.65(1H,d,J = 6.3Hz), 5.10(1H,s), 4.55(1H,s), 4.32(1H,dd,J's = 3.6 and 14Hz), 4.15(1H,d,J = 6Hz), 3.88(1H,s), 3.08(1H,d of t,J's = 3.6 and 13Hz), 2.65(2H,ABq,J = 16Hz,Δν = 100), 2.55(1H,m), 2.17(1H,d of t,J's = 4 and 13Hz), 1.9(H,bd,J = 14Hz), 1.65(1H,bm). Anal. calcd. for $C_{26}H_{22}N_2OS$: C, 76.07; H, 5.40; N, 6.82. Found: C, 76.41; H, 5.31; N, 6.74.
9. ^{1}H NMR (360MHz) δ 7.59(2H,m), 7.38(1H,t,J = 9Hz), 7.2-7.3(5H,m), 7.07(1H,t,J = 8Hz), 5.65 (1H,d,J = 6Hz), 5.18(1H,bs), 4.74(1H,s), 4.52(1H,s), 4.27(1H,d of d,J's = 5 and 14.7Hz), 4.1 (1H,bm), 4.02(3H,s), 3.19(1H,d of t,J's = 3 and 10Hz), 2.58(1H,d,J = 13Hz), 2.43(3H,m), 1.9(1H, d,J = 13Hz), 1.6(1H,m). Anal. Calcd. for $C_{29}H_{25}N_3O_3S$: C, 70.28; H, 5.08; N, 8.49. Found: C, 70.19; H, 5.07; N, 8.42.
10. The structure of 7 has been determined crystallographically - see ortep below. Details are available on microfiche, from the Indiana University Chemistry Library - request Structure Report No.85053.



Ortep of 7

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