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TMM DIYL-INDUCED VINYLCYCLOPROPANE FRAGMENTATION AND RECOMBINATION

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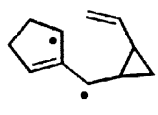
Abstract: A new reaction pathway for trimethylenemethane diradicals has been discovered. Those of general structure **1** undergo opening of the cyclopropyl unit, followed by recombination of the resulting distonic diyl (**3**), to afford either the [6.3.0] or [4.3.0] ring systems (**4**, **5**).

In our effort to expand the scope of the chemistry related to trimethylenemethane-like (TMM) diyls,[1] we have elected to examine a new set of diradicals of general structure **1**. Because they have not been generated previously, these materials are of interest mechanistically, and show promise for application to synthesis. Imbedded within this structure are three subunits whose chemistries are reasonably well defined, that of the TMM diyl,[1] a vinylcyclopropane,[2] and the cyclopropylcarbinyl radical;[3] in **1**, these subunits are *coupled*. Recent independent studies by Gajewski[4] and Adam[5] have focused on the related cyclopropyl diyls **2**.



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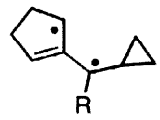
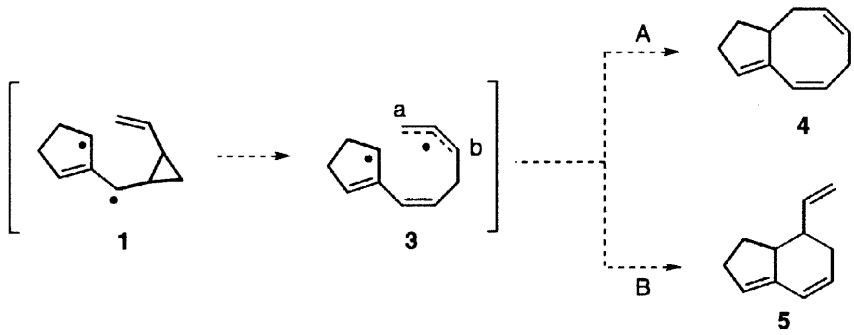


2a, R = H
2b, R = cyclopropyl

We envisaged that diyl **1** would undergo ring opening in a manner reminiscent of the cyclopropylcarbinyl radical and diyls **2**. As illustrated, this process leads to the allylic distonic diyl **3**, a system for which sigma bond formation according to reaction pathways A and B appear reasonable.



1 **3** **4** **5**

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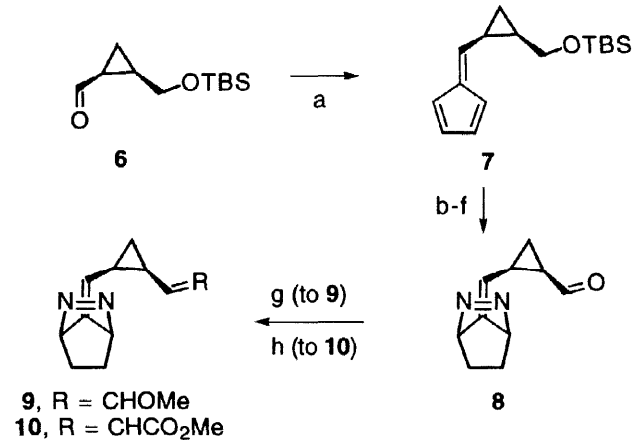
Each leads to the formation of a product with either an eight or a six membered ring fused to the original five membered ring. What is the chemistry of these systems, and if pathways A and B are operational, is it possible to select between them?

Diazenes **8-11** were synthesized to address these issues; diazenal **8** served as a common intermediate. 1,4-Dihydroxy-cis-2-butene was selected as the starting material to assure the cis relationship between the vicinal substituents appended to the cyclopropyl ring.[6] It was transformed in a 50-55% yield over three steps, to the cyclopropyl aldehyde **6** *via* monoprotection as a silyl ether, Simmons-Smith cyclopropanation, and oxidation using PCC. The sequence from **6** to diazenes **9** and **10** proved straightforward and is portrayed below.



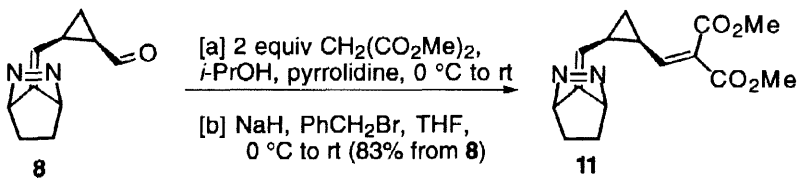
6 **7**

9, R = CHOMe
10, R = $CHCO_2Me$

8

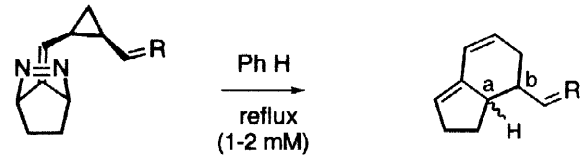
[a] CpH, pyrrolidine, *i*-PrOH; AcOH (>90%); [b] $EtO_2CN{=}NCO_2Et$; [c] $KO_2CN{=}NCO_2K$, AcOH (88-92%, b & c); [d] TBAF; [e] KOH, EtOH; $K_3Fe(CN)_6$ (69%, d-e); [f] $(COCl)_2$, DMSO (84-92%); [g] *s*-BuLi, $MeOCH_2PPh_3Cl$, THF (45%); [h] $MeO_2CCHPPh_3$, CH_2Cl_2 (85%)

The 1,1-diactivated diazene **11** presented more of a challenge in that the initially formed Knoevenagel adduct undergoes a facile Michael reaction with malonate. Fortunately, we were able to effect a reverse Michael reaction using sodium hydride in the presence of benzyl bromide to scavenge the malonyl anion as it was formed. Despite the need for these corrective measures, the sequence proved both convenient and efficient (83% from **8**).



8 **11**

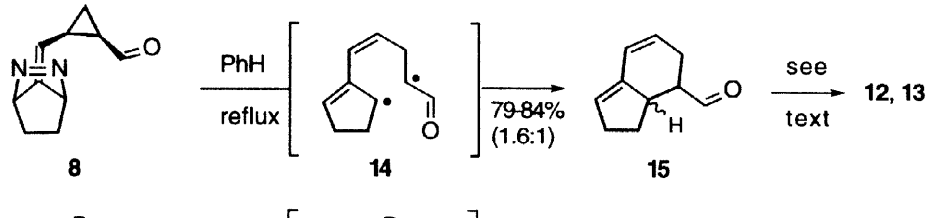
When heated, both the electron rich and the electron poor diazenyl alkenes **9** and **11** smoothly undergo conversion to [4.3.0] adducts **12** and **13**, respectively. Interestingly, no evidence for the formation of a [6.3.0] adduct was obtained in either instance.

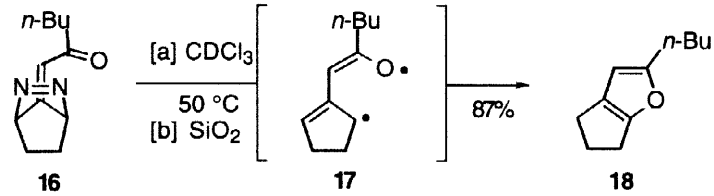


9, R = CHOMe
11, R = $C(CO_2Me)_2$

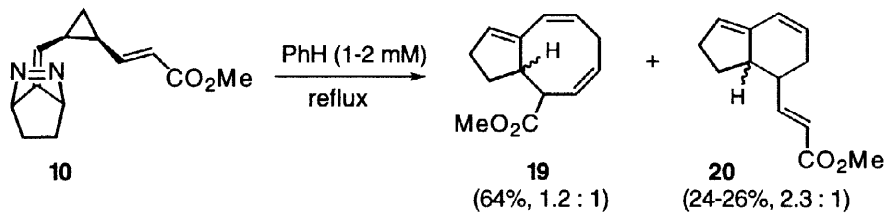
12, R = CHOMe (58-62%; 1.6 : 1 Z/E;
12E, 1.8 : 1; **12Z**, 1.2 : 1, about C_a-C_b)
13, R = $C(CO_2Me)_2$ (83%, 1.2 : 1, about C_a-C_b)

Diazenal **8** undergoes a similar conversion. This is noteworthy for two reasons. First, it is interesting to compare its behavior with that of the simple ketone **16**.[7] As illustrated, the latter undergoes a process wherein the pi portion of the carbonyl unit is utilized in the formation of a new carbon to oxygen bond. While it is perhaps not too surprising, we note that the insertion of a cyclopropyl unit between the carbonyl and the diyl closes down this pathway. Second, the [4.3.0] adduct **15** was useful in establishing unequivocally the structure of substances **12** and **13** since each could be synthesized from **15** (*s*-BuLi, $MeOCH_2PPh_3Cl$, THF, -78 °C to rt afforded **12**; $CH_2(CO_2Me)_2$, *i*-PrOH, pyrrolidine, 0 °C to rt afforded **13**).



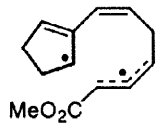


In contrast to the chemistry illustrated thus far, heating the singly activated electron deficient diazene ester **10** afforded an excellent combined yield of *both* the [6.3.0] and the [4.3.0] adducts, **19** and **20**, with the former dominant (~2.6/1). That the eight membered ring containing product was indeed



formed followed from a careful analysis of its spectral data, particularly ^1H-^1H decoupling experiments, C-APT, and HETCOR.[8]

The appearance of the [6.3.0] adduct **19** is noteworthy. It suggests that by securing a more complete understanding of the basic process, one might be able to selectively obtain these materials by design, and utilize this capability in the construction of naturally occurring substances possessing this substructure. These represent our goals with this chemistry. At this stage, we simply point out that while neither an electron rich (**9**) nor a 1,1-diactivated electron poor substrate (**11**) leads to the eight membered ring, the singly activated electron deficient ester **10** does. Clearly these observations suggest an interplay between electronics and sterics as contributing factors in determining product selectivity. For example, while the presence of an electron deficient alkene appears necessary for the formation of the [6.3.0] adduct, the presence of two electron withdrawing groups, as in structure **22**, sterically inhibits this process. Efforts to efficiently select between these pathways is ongoing and the results will be reported in due course.



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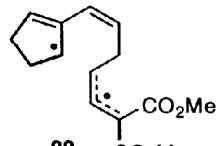

22

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References and Notes

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6. The *trans* cyclopropyl diazenes have been synthesized by Mr. Peter Mikesell, UCSB.
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8. Coupling between the proton alpha to the ester (H_b), and the adjacent bridgehead and vinylic protons (H_a and H_c, respectively) helped to confirm that bonding occurred at the alpha rather then at the gamma-position of the unsaturated ester, (J_{ab}=11 Hz, J_{bc}=6 Hz for the major isomer). For the [6.3.0] isomers: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: (isomer 1): 6.22 (1H, d, J=11 Hz), 5.80 (1H, dd, J=2 Hz), 5.83 (1H, m), 5.70 (1H, br ddd), 5.52 (1H, ddd, J=11, 6, and 1.6 Hz), 3.96 (1H, br dd, J=11 Hz), 3.73 (3H, s, OMe), 3.72 (2H, m), 3.32 (1H, dd, J=11 and 6 Hz), 2.39 (1H, m), 2.22-2.10 (2H, m), 1.57 (1H, m); (isomer 2): 6.12-5.83 (3H, m), 5.36 (1H, dd, J=2 Hz), 5.32 (1H, br ddd), 3.68 (3H, s, OMe), 3.05 (1H, m), 2.97 (1H, m), 2.83 (1H, br ddd, J~8.6 Hz), 2.72 (1H, m), 2.32 (2H, m), 2.01 (1H, m), 1.40 (1H, m).