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PHOTOCYCLOADDITION-FRAGMENTATION ROUTE TO QUINANES: ALTERNATE FRAGMENTATION PATHWAYS

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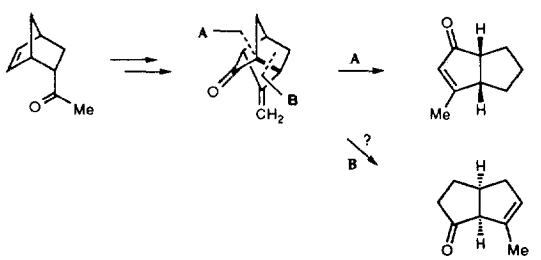
Abstract: We describe here a new type of fragmentation pathway leading to diquinane skeletons, where the normal reactivity of the systems is dramatically altered by a suitably positioned radical stabilizing groups.

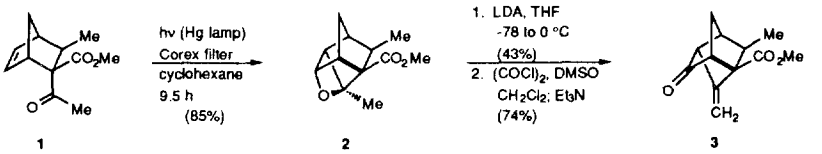
We recently reported a new strategy for the synthesis of di- and triquinanes and demonstrated its usefulness through a stereocontrolled synthesis of isocomene.[1,2] The strategy takes advantage of fragmentation of highly-strained cage compounds that are readily available from simple precursors. In all the examples tried, regardless of the position of the substituents, the key reductive fragmentation was *completely* selective, giving only products resulting from scission the "back bond" (path **A**, Scheme). Products arising from fragmentation of the front bond (**B**) were never observed. The obvious advantage of having a substrate follow the latter path is that it would produce differently substituted diquinanes (and triquinanes) and vastly increase the types of natural products accessible through the overall strategy. We describe here the results of our attempts to induce the alternate fragmentation pathway.

Scheme



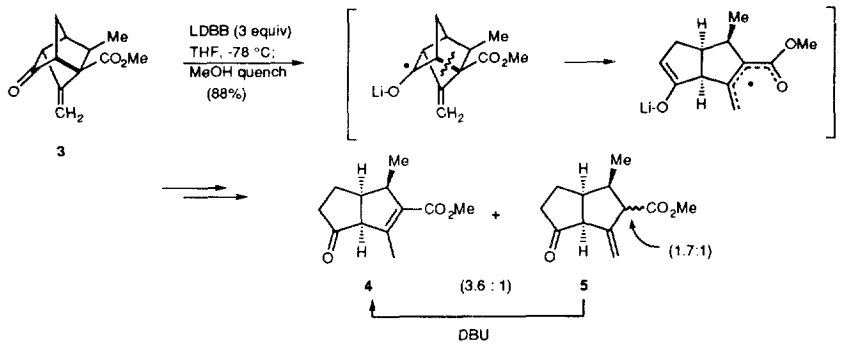
In an effort to facilitate the second path, we examined the fragmentation of three substrates, each containing an electron-stabilizing group at the α-position. For substrate **3**, the expectation was that the electronic perturbation from the withdrawing group would serve to overcome the inherent propensity for back-bond cleavage and, instead, promote cleavage of the front bond. The resulting intermediate radical would be highly stabilized, being allylic and α to

the withdrawing group. The desired fragmentation substrate (**3**, Eq. 1), with an exo-oriented methyl group, was prepared easily. Norbornene ketone **1**, the major product of the Diels-Alder reaction between cyclopentadiene and the doubly-activated dienophile, ethyl (Z)-2-acetyl-butenoate,[3, 4] was irradiated under standard Paterno-Büchi conditions,[1] yielding the expected oxetane (**2**) in high yield. Base mediated opening of the oxetane ring gave a homoallylic alcohol, which upon Swern oxidation afforded the fragmentation precursor, ketoalkene **3**.[5, 6]



(1)

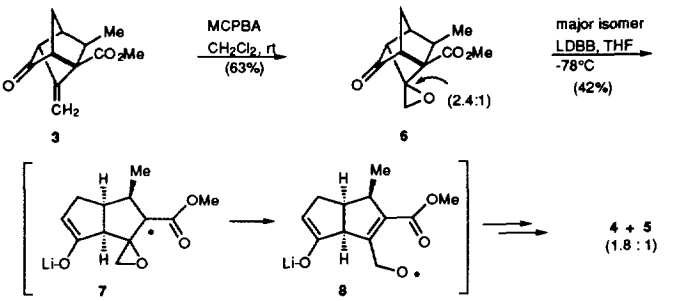
As anticipated, the electronic perturbation had a striking effect on the course of the reductive fragmentation of these strained compounds (Eq. 2). Treatment of ketoester **3** with lithium di-*t*-butyl biphenylide (LDBB)[7] resulted in *exclusive* cleavage of the front bond to afford diquinane products **4** and **5** in high yield, as a 3.6:1 mixture of the conjugated and unconjugated esters. The double bond in the latter, a 1.7:1 mixture (by NMR) of two inseparable epimers, was easily isomerized into conjugation by treatment with DBU. Clearly, diquinanes such as **4**, with extensive functionality around both rings, will prove to be of considerable use for the synthesis of di- and triquinane natural products. The consequence of cleaving the front bond is that exo-oriented substituents from the norbornene are transferred to the concave face of the diquinane.



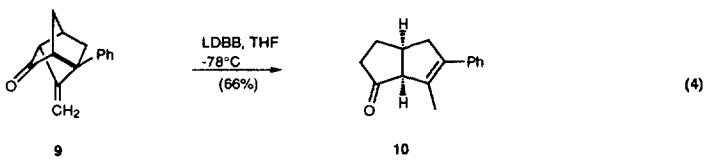
(2)

We also examined the fragmentation of the epoxide derivative of **6**, which was obtained from ketoalkene **3** (Eq. 3). The epoxidation of **3** proceeded sluggishly, but after 3 days in the presence of 3.75 equiv of MCPBA the desired epoxyketones (**6**) were obtained in 63% yield. The reductive fragmentation was carried out on the major epoxide isomer using 3 equivalents of LDBB in THF at -78 °C. The reaction was surprisingly slow and required 2h to go to completion, as compared to 2 min for the other substrates examined so far. Remarkably, the reaction gave

the same products as before, a mixture of ketoesters **4** and **5**. This outcome can be rationalized in different ways. Most likely, as with **3**, the first step probably involves reduction of the ketone to the ketyl, which rearranges via cleavage of the front bond to produce oxiranylcarbinyl radical **7**.[8, 9] Subsequent fragmentation of the epoxide would give an allyloxy radical **8**, which upon further reduction and reductive elimination of Li_2O[10] would lead to the observed products. Alternatively, the observed products could also be explained by considering the deoxygenation of **6** to **3** mediated by LDBB as the first step.



In order to probe the effect of a radical stabilizing group with electron donating capability, we prepared the phenyl substituted ketoalkene **9**.[11, 12] The reductive fragmentation of **9** was again completely selective, giving the front bond cleavage product, conjugated diquinane **10**, in 66% yield along with 12% recovered starting material.[6]



These studies establish that the pathway followed in the reductive fragmentation of strained cage compounds can be controlled by judicious placement of substituents on the substrate. The alternate fragmentation pathway described here greatly expands the types of functionalized diquinanes and triquinanes--hence the types of natural products--that can be synthesized through the Paterno-Büchi/reductive fragmentation strategy that we have developed.

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3. The dienophile was prepared according to Knovenagel's original procedure (methyl acetoacetate, acetaldehyde, 5% piperidine, 0 °C, 3h) and the desired diastereomer was separated by silica gel chromatography (see reference 4). The Diels-Alder reaction was carried out by heating this dienophile with cyclopentadiene in toluene at 40 °C overnight, which afforded the desired adduct in 56% yield.
4. (a) Knoevenagel, E. *Chem. Ber.* **1898**, *29*, 2393. (b) Knoevenagel, E. *Chem. Ber.* **1896**, *53*, 172. (c) Review: Jones, G. *Org. React.* **1967**, *15*, 204.
5. A higher yield of the ketone was obtained when the oxidation was carried out using PDC (2 equiv) in DMF, but using this protocol the reaction required two days at ambient temperature to go to completion.
6. Spectral data of key intermediates: **^{1}H NMR** (250 or 300 MHz, $CDCl_3$) **2**: δ 0.97 (d, J = 6.8 Hz, 3 H), 1.43 (m, 1 H), 1.46 (s, 3 H), 1.83 (m, 1 H), 2.08 (dd, J = 2.8, 11.2 Hz, 1 H), 2.34 (ddq, J = 0.8, 2.35, 6.8 Hz, 1 H), 3.00 (m, 1 H), 3.04 (m, 1 H), 3.71 (s, 3 H), 4.60 (dd, J = 2.3, 3.7 Hz, 1 H); **3**: δ 1.06 (d, J = 6.6 Hz, 3 H), 1.68 (br d, J = 12.3 Hz, 1 H), 2.33 (dd, J = 2.8, 12.3 Hz, 1 H), 2.51-2.61 (m, 2 H), 2.87-2.93 (m, 2 H), 3.79 (s, 3 H), 4.73 (s, 1 H), 4.92 (s, 1 H); **4**: δ 1.17 (d, J = 7.15 Hz, 3 H), 1.72-1.86 (m, 1 H), 1.90-2.04 (m, 1 H), 2.07 (br s, 3 H), 2.15-2.32 (m, 2 H), 2.95 (m, 1 H), 3.14 (br d, J = 7.8 Hz, 1 H), 3.2-3.3 (m, 1 H), 3.75 (s, 3 H); **9**: δ 1.85 (dt, J = 10.8, 2.2 Hz, 1 H), 1.96 (dd, J = 10.8, 3.2 Hz, 1 H), 2.16 (d, J = 9.7 Hz, 1 H), 2.10 (dt, J = 9.7, 2.2 Hz, 1 H), 2.65 (m, 1 H),2.86 (m, 1 H), 2.93 (dd, J = 3.2, 2.2 Hz, 1 H), 4.30 (s, 1 H), 4.56 (s, 1 H) ,7.20-7.40 (m, 5 H); **10**: δ 1.67 (m, 1 H), 1.90 (br s,3 H, Me), 2.10-2.30 (m, 3 H), 2.55 (br d, J = 12.9 Hz, 1 H), 2.95-3.30 (m, 3 H), 7.20-7.40 (m, 5 H). **^{13}C NMR** (63 MHz, $CDCl_3$) **2**: δ 12.6 (q), 17.3 (q), 36.0 (t), 40.2 (d), 47.6 (d), 48.8 (d), 51.5 (q), 61.5 (d), 63.9 (s), 85.2 (d), 100.2 (s), 172.5 (s); **3**: δ 13.1 (q), 33.9 (t), 41.2 (d), 50.3 (d), 50.9 (d), 51.7 (q), 55.4 (d), 60.5 (s), 100.1 (t), 150.0 (s), 170.2 (s), 201.4 (s); **4**: δ 12.60 (q), 13.63 (q), 21.40 (t), 38.21 (t), 40.90 (d), 41.31 (d), 50.14 (q), 62.45 (d), 132.29 (s), 147.22 (s), 165.51 (s), 215.67 (s); **9**: δ 36.5, 39.0, 44.3, 53.7, 55.1, 57.6, 99.6, 126.9, 127.7, 128.3, 137.6, 156.9, 204.8; **10**: δ 13.6(q), 28.5(t), 36.9(d), 37.9(t), 43.8(t), 64.4(d), 126.7(d), 127.7(d), 128.1(d), 130.8(s), 136.9(s), 137.6(s), 218.0(s).
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11. Ketoalkene **9** was prepared from 3-phenyl-3-buten-2-one (ref 12), by the same four step sequence used for **3**.
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