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BEYOND THE MEDIUM RING: A [4 + 4] CYCLOADDITION/FRAGMENTATION SYNTHESIS OF ELEVEN-MEMBERED RINGS

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Abstract: Reduction of the polycyclic product of intramolecular 2-pyridone photocycloaddition with lithium/ammonia yields a functionalized cycloundecane, via an apparent multi-step reaction sequence.
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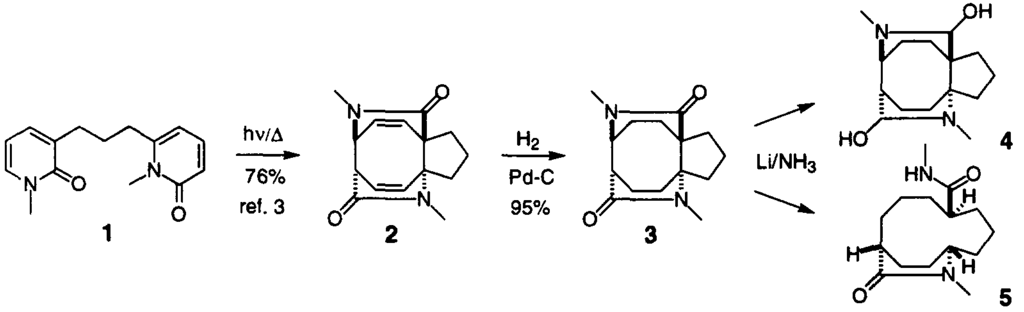
The coupling of cycloaddition and fragmentation reactions is a venerable approach to the less accessible ring sizes, particularly seven and eight-membered carbocycles;[1] the evolving methods for medium ring construction via higher order cycloadditions[2] therefore sets the stage for even larger rings. We report here the serendipitous preparation of an eleven-membered ring by fragmentation of an 8–5 ring system.



Scheme 1. Photo-[4 + 4]-cycloaddition and lithium-ammonia reduction leads to cycloundecane product **5**.

Bis-2-pyridone **1** undergoes an efficient [4 + 4] photocycloaddition to yield the trans product **2** along with its cis isomer. Isomerization of the more labile cis isomer through a simple thermal and photochemical procedure results in the isolation of **2** in 76% yield.[3] During a study of the chemistry of photoproduct **2**, with a goal of opening the amide bonds, the alkenes were hydrogenated and the resulting product **3** was subjected to lithium–ammonia reduction. These conditions have been used to reduce amides to aminals[4] (e.g., **4**), an intermediate for reduction of the carbonyls to methyl groups. In addition to a compound tentatively identified as **4**, another product could be isolated in an unoptimized yield of 25%. This product retained both amide groups but one was now a secondary amide, with a well defined amide proton coupled to an *N*-methyl group. A number of possible structures were considered, however X-ray crystallography unequivocally identified the product as **5**.

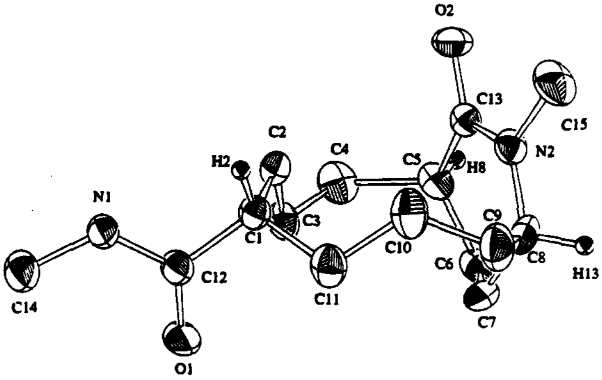
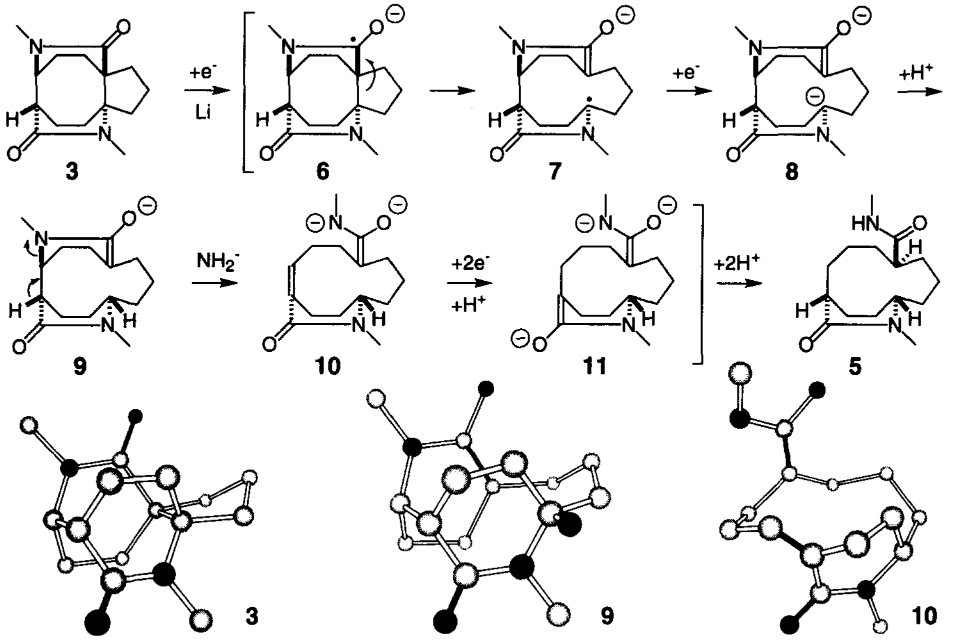


Figure 1. X-ray structure of **5**.

The X-ray structure of **5**[5] shows that the nitrogen–carbon bond originally at the bridgehead carbon of 3 is retained, and cleavage of the central carbon–carbon bond is accompanied by inversion of configuration at both of the carbons

A possible mechanism for the formation of **5** is shown in Scheme 2. Addition of an electron to one carbonyl of **3** yields radical anion **6**. A ketyl-retro-aldol reaction gives **7** and forms the eleven-membered carbocycle. The resulting radical is further reduced and protonated. Cleavage of the amide carbon-nitrogen bond is most easily explained by a deprotonation/elimination reaction to yield **10**. The conjugated system in **10** is then reduced to an enolate. Finally, protonation of the two enolates during workup leads to product **5**.



Scheme 2. Possible mechanism for the formation of 5 and molecular models of selected structures.

Several unusual features of this mechanism are notable. The ketyl-retro-aldol reaction (**6** → **7**) has little precedent. All four stereogenic centers in **3** are trigonalized or inverted during the reaction, nevertheless the sequential nature of the overall scheme and the conformation of the polycyclic system preserves the relative orientation at the three stereogenic centers remaining in **5**. Both amides are protected from reduction as the enolates (**11**). Note that the brigehead olefin in **10** is not strained (molecular mechanics).

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5 Compound **5** crystallizes from ethyl acetate in the monoclinic space group $P2_1/n$ with $a = 7.967$ (3) Å, $b = 9.346$ (1) Å, $c = 19.773$ (4) Å, $\beta = 98.27$ (1)°, $V = 1457.1$ (5) Å^3, and $Z = 4$. Final least squares refinement using 1291 unique reflections with $I > 3\sigma(I)$ gave $R(R_w) = 0.060$ (0.055).

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