Synthesis of 6-Aza-bicyclo[3,2,1]octan-3-ones via Vinylogous Imide Photochemistry: An Approach to the Synthesis of the Hetisine Alkaloids

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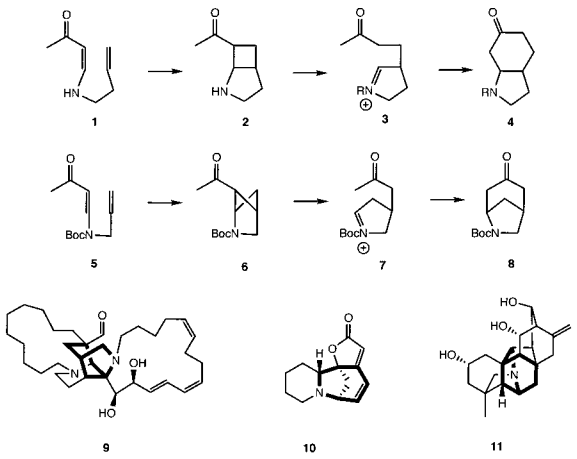
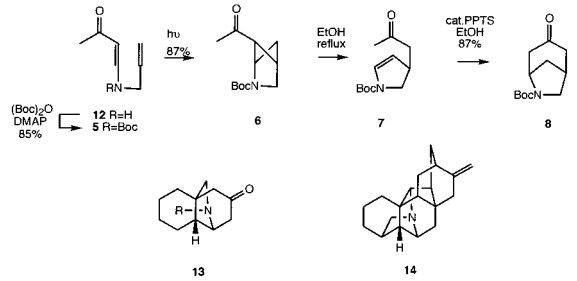
We have demonstrated that the intramolecular photocycloaddition of vinylogous amides (1,6-dienes) **1** leads, upon retro-Mannich fragmentation of **2** and isomeric Mannich closure of the derived ketoiminium **3**, to the synthesis of perhydroindoles **4**, as outlined in Scheme 1.[1] The utility of this methodology for the synthesis of nitrogen-containing ring systems is underscored by the successful application of this methodology to the syntheses of mesembrine,[2] vindorosine,[3] and manzamine A.[4] We have recently examined the photocycloaddition of the corresponding 1,5-dienes, that is, **5**, and we report herein that these substrates lead to a general synthesis of azabicyclo[3,2,1]octanones, **8**, via the "crossed" photoadduct, **6**. The widespread distribution of the azabicyclo[3,2,1]octanone ring system in molecules of nature, that is, sarain A, **9**,[5] securinine, **10**,[6] and hetisine, **11**,[7] and the importance of this ring system in medicinal chemistry for the development of analgesics[8] and muscarinic antagonists[9] suggests that the photochemistry of **5** should be of comparable utility to that of **1**.

The synthesis of **5** and its conversion to **8** is outlined in Scheme 2. Michael addition of allylamine to 3-butynone gave vinylogous amide **12**, which on reaction with di-*tert*-butyl-carbonate in the presence of DMAP gave the photosubstrate **5** in 85% yield over two steps. It is interesting to note that direct irradiation of **12** did not produce the desired photoadduct, the amine analogue of **6**, a result that is consistent with the work of Swindell.[10] This difference in photoreactivity can be attributed to the importance of sp^2 character of the nitrogen in the photocycloaddition, an indication of the subtle balance in vinylogous amide photochemistry, as nitrogen protection is not needed for the photocycloaddition of **1** (Scheme 1).

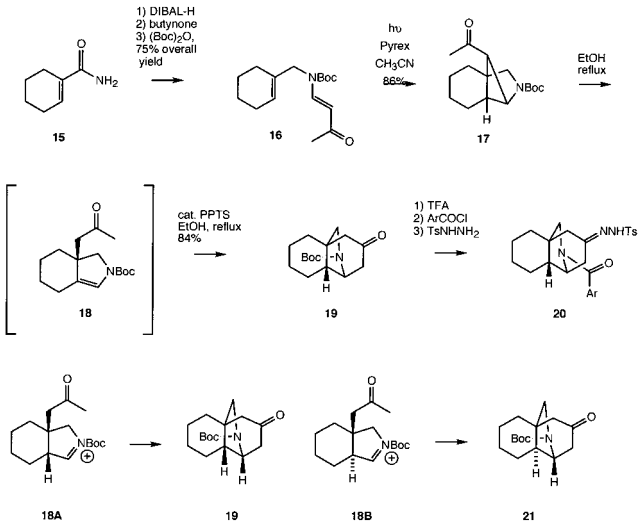
Scheme 1



Scheme 2



Scheme 3



Irradiation of **5** (0.01 M in MeCN, Pyrex filter, 450-W Hanovia medium-pressure lamp) led to the bicyclic photoadduct **6** in 87% yield. The formation of the crossed photoadduct is consistent with the "rule of five" observed in the intramolecular photocycloaddition of 1,5-dienes.[11] Exposure of **6** to refluxing ethanol led to the retro-Mannich fragmentation product **7**, which on reaction with catalytic PPTS gave the Mannich product **8** in 87% yield. Having established the viability of this approach for the construc-

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tion of the azabicyclooctane ring system, we turned our attention to the construction of **13**, the tricyclic core of **14**, the carbon skeleton of the hetisine alkaloids.

Reduction of amide **15**[12] with DIBAL-H to the corresponding amine, followed by reaction with butynone and di-*tert*-butyldicarbonate, led to the formation of photosubstrate **16** in 75% yield (one-pot reaction). Irradiation of **16** (6 μM in MeCN, Pyrex filter, 450-W Hanovia medium-pressure lamp) led to the formation of the tricyclic photoadduct **17** in 86% yield, which was obtained as a mixture of epimers, presumably at the acetyl-bearing carbon. While the presence of the Boc-protecting group complicated the ^{1}H NMR spectrum of **17**, we found that exposure of **17** to refluxing ethanol lead to formation of **18** in excellent yield, in which the relative stereochemical relationship in the photoadduct is no longer present. Exposure of **18** to catalytic PPTS gave **19** in 84% yield, which embodies the tricyclic core of the hetisine alkaloids.

The stereoselective formation of **19** can be attributed to kinetic protonation from the sterically less hindered convex face of **18**, which would lead to the formation of ketoiminium **18A** and not **18B**. Mannich closure of **18A** then leads to the observed product, **19**. The stereochemical relationships in **19** could be unambiguously established by X-ray crystallographic analysis of **20** (Ar = *p*-BrPh, mp 172 °C (dichloromethane), which was prepared from **19** via TFA-mediated Boc removal, *p*-bromobenzamide formation, and tosylhydrazone formation.

The syntheses of **8** (Scheme 2) and **19** (Scheme 3) in excellent overall yields underscore the efficiency of this new photochemical sequence. The application of this methodology to the synthesis of the hetisine alkaloids is currently underway in our laboratory, and our progress will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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