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ON THE USE OF THE IMINE-DIENE CYCLOCONDENSATION REACTION IN THE SYNTHESIS OF YOHIMBINE CONGENERS*

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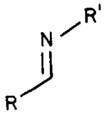
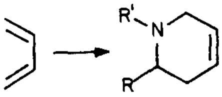
Abstract: Cycloaddition of dihydroβ-carbolines with polyoxygenated dienes is used to provide rapid access to the title compounds.

The capacity of certain highly electrophilic imines (cf. **1**, **2** or **3**) to participate as heterodienophiles in apparent cycloaddition reactions with dienes had been known for some time.[1,2] A major advance in this field was registered by J. Kerwin of these laboratories who found that with appropriately activated dienes (cf. siloxydienes) under suitable Lewis acid catalysis, conventional *non-activated* imines participate in the process.[3] A further advance was achieved at the Merck Laboratories when the process was extended to several tricyclic imines including dihydroβ-carboline[4] (**5**).

We have been investigating the possibility of applying the aldimine-diene cyclocondensation reaction to the synthesis of multifunctionalized heterocycles including alkaloids. Some very encouraging harbingers are recorded herein.



1 R = acyl
2 R' = acyl
3 R, R' = acyl



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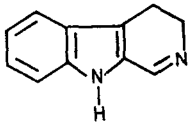

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As aldimine substitutes, we employed compound **5** used by Vacca,[4] and the analogous compound **6**, derived from L-tryptophan.[5] Reaction of diene **8**, prepared by substantially known chemistry[6] from

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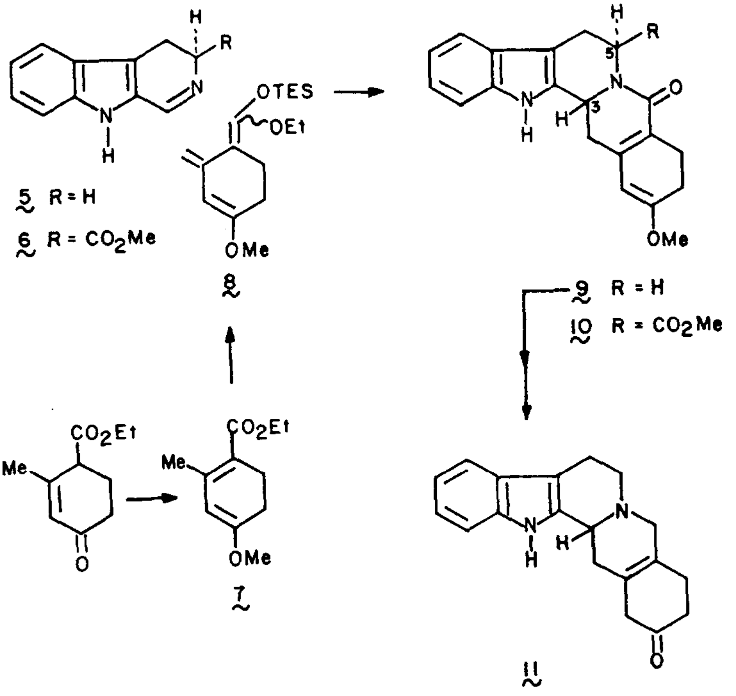
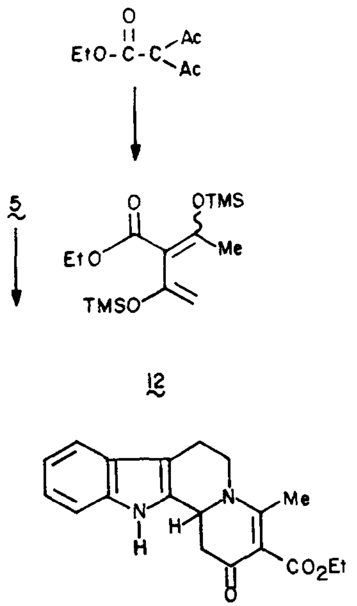
* We dedicate this paper to our friend and colleague, Professor Harry H. Wasserman on the occasion of his receipt of the Chemical Manufacturers Association Award for continuing excellence in research and teaching.

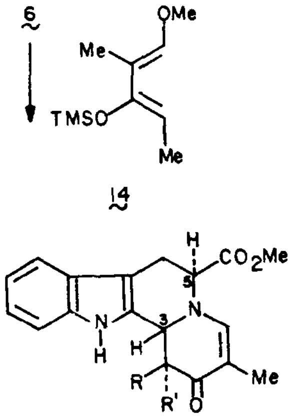
Hagemann's ester via its enol ether derivative **7**, with **5** in chloroform at rt *without catalyst*, afforded a 50% yield of the pentacyclic lactam **9**, mp 276°. Reduction of **9** with lithium aluminum hydride in THF (0°) followed by acidic hydrolysis afforded an 81% yield of the known[8] yohimbine derivative **11** mp 209°, lit.[8] 210°. Similar reaction using the optically active **6** afforded a 40% yield of **10**[7,9] mp 258° (dec). The stereospecificity of the cycloaddition reaction appears to be complete and presumably[10] involves attack of the diene anti to the carbomethoxy function. In this simple fashion, a facile entry to highly functionalized optically pure yohimbe progenitors is available.



Bis enol silylation of the commercially available ethyl diacetylacetate affords diene **12**.[7] This interesting bis silyloxydiene reacts with imine **5** (zinc chloride catalysis in acetonitrile, rt) to afford a 53% yield of the tetracyclic dihydropyridone, **13**[7] mp 241°. The successful utilization of this type of diene with other heterodienophiles holds out considerable potential for a variety of other synthetic enterprises.

Reaction of imine **6** with diene **14**[11] occurred under catalysis by zinc chloride in acetonitrile at rt, to afford a 4:1 ratio of **15** (mp 245°):**16** (mp 249°, dec) in 58% combined yield. Once again, cycloaddition is facially specific (presumably anti to the ester function)[10] but the preference for exo topography, leading to **15** is only 4:1 relative to endo mode reaction, producing **16**. The issue of endo-exo stereochemistry in this new version of the imino Diels Alder reaction is clearly of central importance to the serious application of this process to the synthesis of complex alkaloids. Accordingly, this matter is receiving careful attention. The results of these stereochemical investigations, as well as applications to the synthesis of alkaloids, will be the subjects of future reports.





15 R = Me; R' = H

16 R = H; R' = Me

15:**16** ≅ 4:1

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7. The structure of this compound is supported by high resolution NMR, IR, and mass spectral data.
8. C. Szántay, K. Honty, L. Töke, and L. Szabó. Chem. Ber. 109, 1737 (1976). We experienced difficulty in achieving a preparatively useful conversion of **11** to its α,β isomer such as previously reported: K. Okamura, S. Yamada. Chem. Pharm. Bull. 28, 2305 (1978).
9. The use of imine **6** is complicated by its oxidation to the corresponding carboline. In addition, its cyclocondensation products are less stable than their des-carbomethoxy analogs.
10. The relative configurations of carbons 3 and 5 in the products derived from imine **6** is not rigorously known. In support of our tentative formulation is the absence of an N.O.E. enhancement between C_3H and C_5H in any of these compounds.
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