

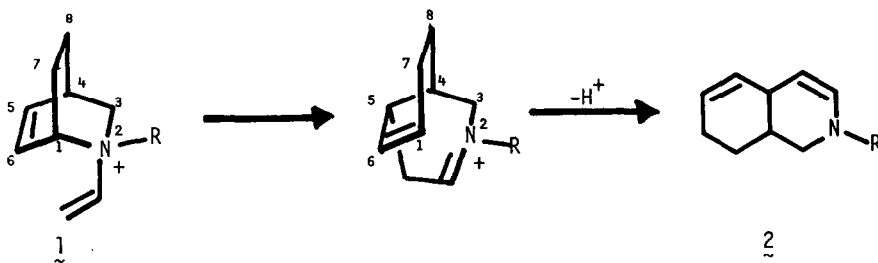
NOVEL APPROACHES TO THE SYNTHESIS OF HYDROISOQUINOLINES  
USING AZA-CLAISEN REARRANGEMENTS OF N-VINYLIISOQUINUCLIDENES.<sup>1</sup>

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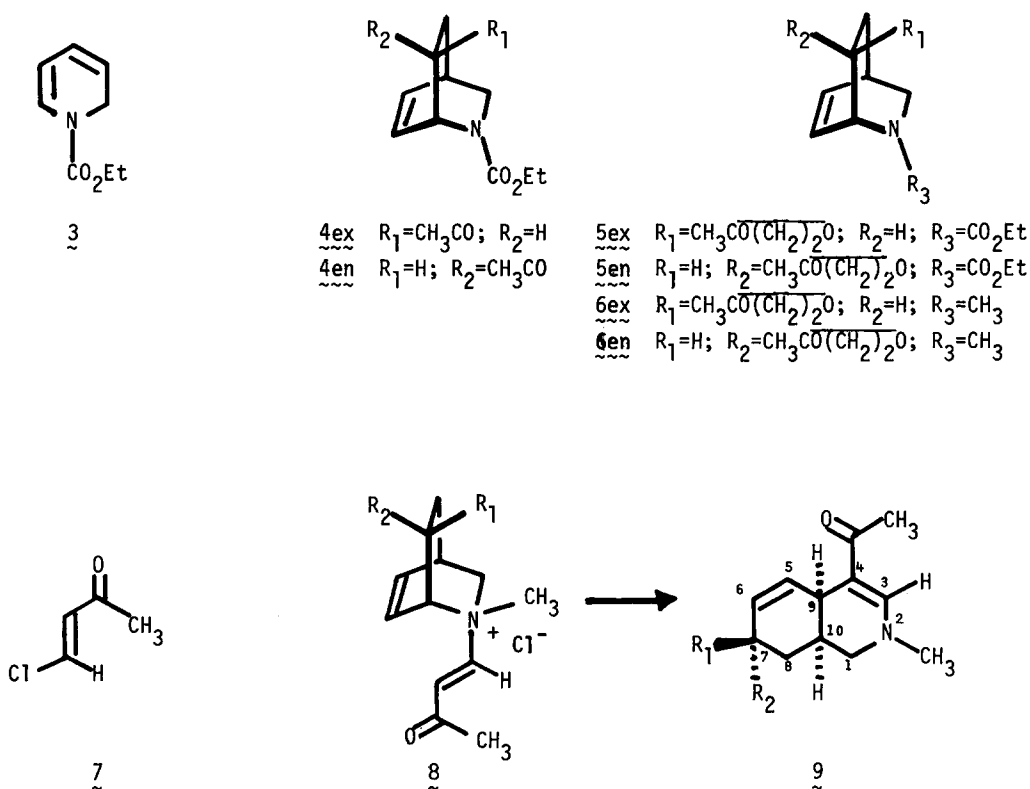
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The Claisen rearrangement of allyl vinyl ethers leading to  $\gamma,\delta$ -unsaturated carbonyl compounds has proven exceptionally useful as a general method in natural product synthesis.<sup>3</sup> Similarly, the Cope and Oxy-Cope transformations have been employed frequently to construct complex ring systems of target molecules.<sup>4</sup> Surprisingly, however, incorporation of the related aza-Claisen rearrangement,<sup>5</sup> which converts N-allyl-vinylamines or ammonium salts to their corresponding unsaturated imines or iminium salts, into preparative sequences has been much less frequent. As part of recent efforts in our laboratory aimed at the development of novel methods for isoquinoline alkaloid synthesis, we have investigated synthetic designs which employ aza-Claisen rearrangements of N-vinylisoquinuclidenes 1 in key steps to construct hydroisoquinolines 2. Our initial studies in this area using model systems have shown that transformations of this type comprise a potentially general method for isoquinoline synthesis.



The first N-vinylisoquinuclidene systems studied were the isomeric ammonium salts 8, independently prepared *in situ* by reaction of the 2-methyl-7-methyldioxolyliisoquinuclidenes 6ex and 6en<sup>6</sup> with 4-chlorobut-3-en-2-one 7.<sup>7</sup> The synthetic sequence used to prepare 6 began with Diels-Alder cycloaddition of methyl vinyl ketone to 1-ethoxycarbonyl-1,2-dihydropyridine (3)<sup>8</sup> (neat, 50°, 6 days, Fluorosil chromatography) which furnished the 7-acetyliisoquinuclidenes as a 4:3 mixture of endo (4en) and exo (4ex) isomers in an 89% yield. Reduction of a mixture of the

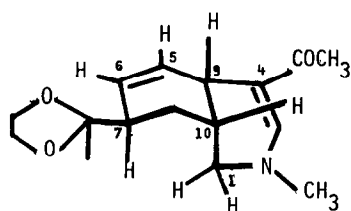
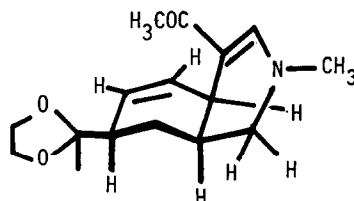
derived ethylene ketals **5** ( $\text{HOCH}_2\text{CH}_2\text{OH}$ ,  $\text{C}_6\text{H}_6$ ,  $p\text{-TsOH}$ , reflux, 81%) employing lithium aluminum hydride gave the epimeric *N*-methyl dioxolanes **6** (99%) which are separated by preparative glc. Characteristic spectroscopic data for the individual isomers were used to make regio- and stereochemical assignments.<sup>10,11</sup> Formation and rearrangement of the 7-endo-dioxolyl isoquinuclidinium salt **8** ( $\text{R}_1=\text{H}$ ;  $\text{R}_2=\text{CH}_3\text{COCH}_2\text{CH}_2\text{-O}$ ) were carried out in one step by stirring a tetrahydrofuran solution of the 7-endo epimer of **6** and chloroenone **7** containing suspended potassium carbonate (RT, 15 hr). Purification of the reaction mixture by silica gel TLC afforded the crystalline 4-acetyl-hexahydroisoquinoline **9t** ( $\text{R}_1=\text{H}$ ;  $\text{R}_2=\text{CH}_3\text{COCH}_2\text{CH}_2\text{-O}$ ) (mp 156-158°C, UV (ethanol)  $\lambda_{\text{max}}$  307 nm,  $\epsilon$  29,500) in a 60% yield.<sup>12</sup> The epimeric hexahydroisoquinoline **9c** ( $\text{R}_1=\text{CH}_3\text{COCH}_2\text{CH}_2\text{-O}$ ;  $\text{R}_2=\text{H}$ ) is derived in a similar fashion from the exo isomer, **6ex**.



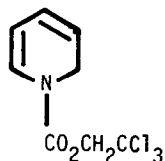
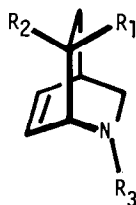
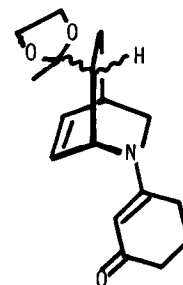
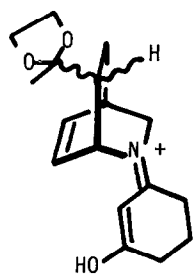
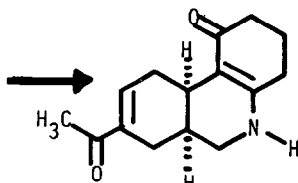
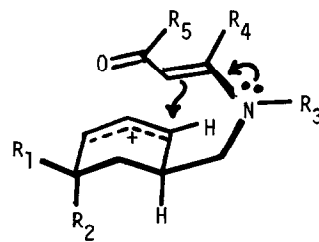
Relative configurational assignments at the three chiral centers in **9t** and **9c** can be made using characteristic  $^1\text{H-NMR}$  spectroscopic parameters in conjunction with the fact that the  $\text{C}_7$ -stereochemistry in **6** will govern relative configurations at  $\text{C}_7$  and  $\text{C}_{10}$  in **9**. In the spectrum of **9t**, vicinal coupling between  $\text{H}_5$  ( $\delta$  5.49) and  $\text{H}_9$ , and between  $\text{H}_6$  ( $\delta$  5.69) and  $\text{H}_7$  is small (2 Hz) as would be expected if both  $\text{H}_9$  and  $\text{H}_7$  are axial to the A-ring. In addition, the  $\text{H}_1\text{-H}_{10}$  coupling pattern contains a  $J_{\text{ax,ax}}$  of 12.5 Hz indirectly indicating the *cis*-relationship between  $\text{H}_9$  and  $\text{H}_{10}$ . In contrast,  $J_{5,9}$  (4 Hz) in the spectrum of **9c** is characteristic of the equatorial disposition of  $\text{H}_9$  on the A-ring. The  $\text{H}_1\text{-H}_{10}$  coupling, lacking a large axial-axial coupling constant, can be used to assign the axial orientation of  $\text{H}_{10}$  with respect to the A-ring. Lastly, the  $\text{H}_5$ -proton

resonance in  $\underline{9c}$  ( $\delta$  6.37) occurs at an exceptionally low field as models suggest should be the case since  $H_5$  lies in the plane of the acetyl carbonyl at  $C_4$ .

This method for generation of the hydroisoquinolines appears limited to utilization of chlorenones lacking  $\beta$ -alkyl substitution in light of observations which show that both isomers of  $\underline{6}$  fail to react with either 3-chlorocyclohex-2-en-1-one or 4-chloropent-3-en-2-one.<sup>13</sup> A more

 $\underline{9t}$  $\underline{9c}$ 

general approach to this problem, based upon the same strategy, has been developed. An example is found in rearrangement of the intermediate isoquinuclidene iminium salt  $\underline{15}$ , formed by protonation of the cyclohexenone derivative  $\underline{14}$ .<sup>14</sup> The preparative route adopted in this case uses  $\pi 2 + \pi 4$  cycloaddition of methyl vinyl ketone to 1-trichloroethoxycarbonyl-1,2-dihydropyridine<sup>15</sup> (neat, 53°C, 7 days, Fluorosil chromatography, 58%) to create the N-blocked isoquinuclidene  $\underline{11}$  (mixture of epimers). Ketalization produced  $\underline{12}$  (81%) which was deblocked using the reported<sup>16</sup> conditions (90%) to furnish  $\underline{13}$ . A moist benzene solution of the cyclohexenonylisoquinuclidene  $\underline{14}$ , formed

 $\underline{10}$  $\underline{11}$   $R_1, R_2 = H, COCH_3; R_3 = CO_2CH_2CCl_3$  $\underline{12}$   $R_1, R_2 = H, CH_3CO(CH_2)_2O; R_3 = CO_2CH_2CCl_3$  $\underline{13}$   $R_1, R_2 = H, CH_3CO(CH_2)_2O; R_3 = H$  $\underline{14}$  $\underline{15}$  $\underline{16}$  $\underline{17}$

from 13 and  $\beta$ -chlorocyclohexenone (60%), containing p-TsOH was refluxed for 8 h giving the tricyclic-isoquinoline derivative 16 (mp dec 200-205°C, UV (ethanol)  $\lambda_{\max}$  298 nm,  $\epsilon$  25,400) in a 60-70% yield after chromatographic purification on silica gel. Rearrangement of 15 most probably proceeds to generate the  $\Delta^{9,10}$ -unsaturated-7-dioxolyl epimers which undergo deketalization and conjugation under the reaction conditions.

It is quite likely that similar mechanisms are operating in rearrangement reactions of both intermediate isoquinuclidene salts, 8 and 15. Heterolytic cleavage of the C<sub>1</sub>-N bonds in these substances would generate the allylic cations 17 having the enamino ketone functions properly oriented for axial attack at C<sub>9</sub> on the developing cis-fused isoquinoline. It is also possible, that concerted aza-Claisen rearrangements are responsible for conversions of 8 to 9 since the same stereochemical outcome is expected.

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