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INTRAMOLECULAR DIELS-ALDER REACTIONS OF 2-ALKENYL-1,2-DIHYDROPYRIDINES. AN APPROACH TO THE SYNTHESIS OF THE CIS-DECAHYDROQUINOLINE RING SYSTEM.

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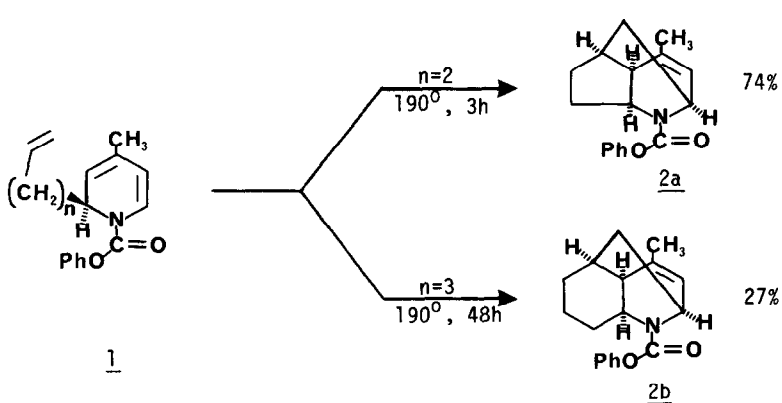
Summary: In refluxing decalin 2-alkenyl-1-alkoxycarbonyl-1,2-dihydropyridines undergo an intramolecular Diels-Alder reaction to provide novel polycyclic compounds. The cis-decahydroquinoline ring system can be prepared from the appropriate Diels-Alder product utilizing a ring-opening reverse Mannich reaction.

In recent years there has been considerable interest in the synthetic uses of the intramolecular Diels-Alder reaction.[1] This reaction has been especially useful for the synthesis of polycyclic natural products as it provides for the regioselective and stereospecific introduction of multiple chiral centers. Certain 1,2-dihydropyridines are useful dienes for the intermolecular Diels-Alder cycloaddition,[2,3] however, only a few examples of intramolecular Diels-Alder reactions of dihydropyridines have been reported.[4] It occurred to us that this reaction has potential for the synthesis of various cis-decahydroquinoline alkaloids, such as gephyrotoxin.[5] To determine the feasibility of this approach, the following model studies were carried out.

The desired 2-alkenyl-1-phenoxycarbonyl-1,2-dihydropyridines (1) were readily obtained by addition of the appropriate alkenyl Grignard reagent to the 1-phenoxycarbonyl salt of 4-picoline in THF.[6] On heating (refluxing decalin), dihydropyridines 1 underwent an intramolecular Diels-Alder reaction to provide polycyclic compounds 2.[7]

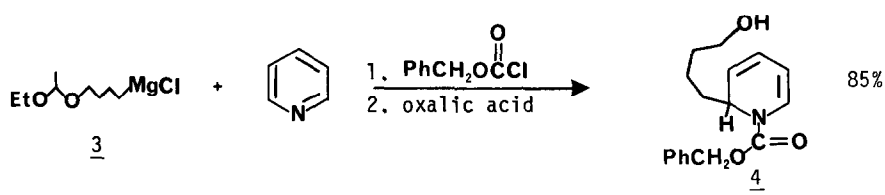


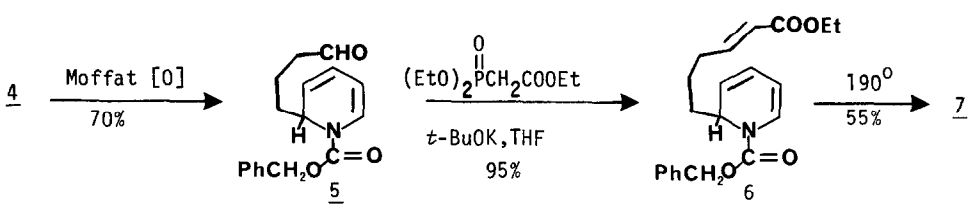
1 2a 2b

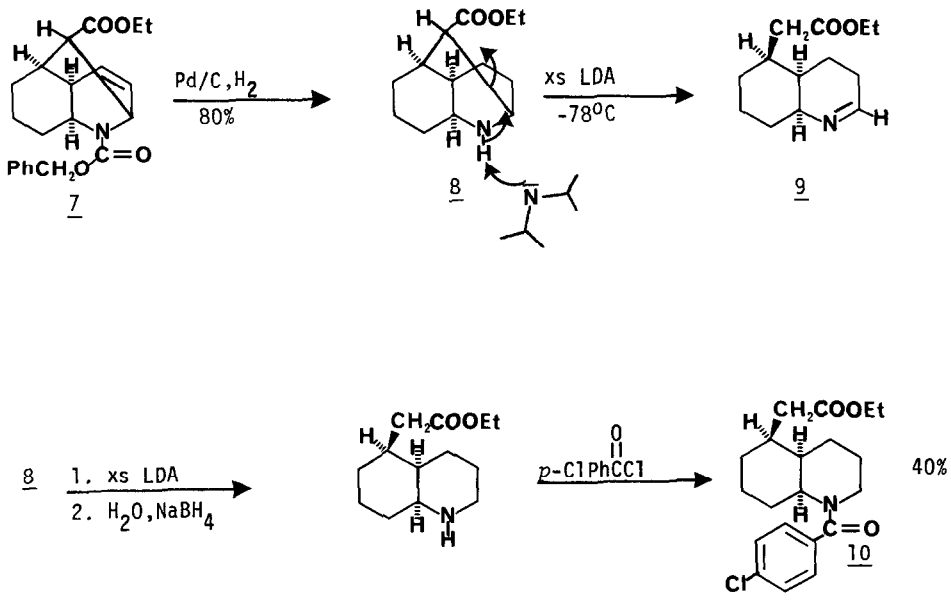
The success of the above reactions prompted us to examine an approach to the synthesis of cis-decahydroquinoline alkaloids utilizing the intramolecular Diels-Alder reaction followed by a ring-opening reverse Mannich reaction. The desired starting material was prepared by the dropwise addition of benzyl chloroformate to Grignard reagent 3 and pyridine in THF at -20°C. The resulting crude dihydropyridine was treated with aqueous oxalic acid in THF to provide alcohol 4 in 85% overall yield (SiO_2, 30% acetone-hexanes). Moffat oxidation gave aldehyde 5 (70%) which was treated with triethylphosphonoacetate(t-BuOK, THF, -78°C) to give the triene 6 (95%). Triene 6 in decalin was heated at reflux (190°C) under nitrogen for 48 h to provide the polycyclic compound 7 (55%). Reduction of the carbon-carbon double bond and removal of the CBZ group occurred in one synthetic step (H_2, Pd/C, 40 psi, RT, HOAc) to give the amine 8 (80%).

Ring-opening was achieved by adding 8 to excess LDA (6 equiv) at -78°C in THF to furnish imine 9 (~50%).[8] Imine 9 was labile and could not be purified. A stable derivative (10) was prepared by in situ reduction ($NaBH_4$, H_2O, THF) and subsequent amide formation in an overall yield of 40% from amine 8.[7] The cis-decahydroquinoline ring structure was confirmed by comparing the ^1H and ^{13}C NMR spectra of 10 with the corresponding NMR spectra of the p-chlorobenzamides of cis-[9] and trans-[10] decahydroquinoline.

This route to imine 9 will allow us to pursue the synthesis of various cis-decahydroquinoline alkaloids, e.g., gephyrotoxin,[5] and this effort is currently underway.







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7. All new compounds exhibited the expected MS, IR, ^{1}H NMR, and ^{13}C NMR spectra; satisfactory analytical data (0.4% for C,H,N) were also obtained for compounds, 2, 4, 7, 8, and 10.

8. The yield was determined from the ^{1}H NMR spectrum of the crude product. The cyclic imine hydrogen appeared as a broad multiplet at δ 7.68 (CCl_4).

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