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# N-Acyldihydropyridones as Synthetic Intermediates. A Short Synthesis of (±)-Indolizidine 209B.

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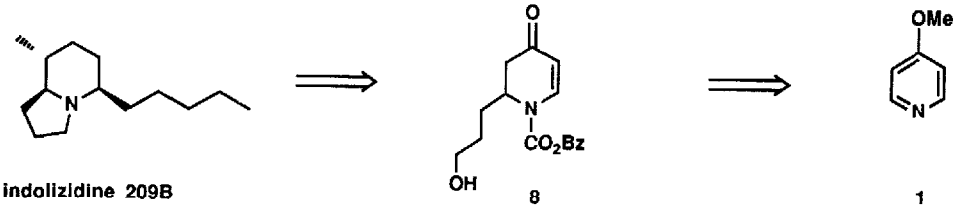
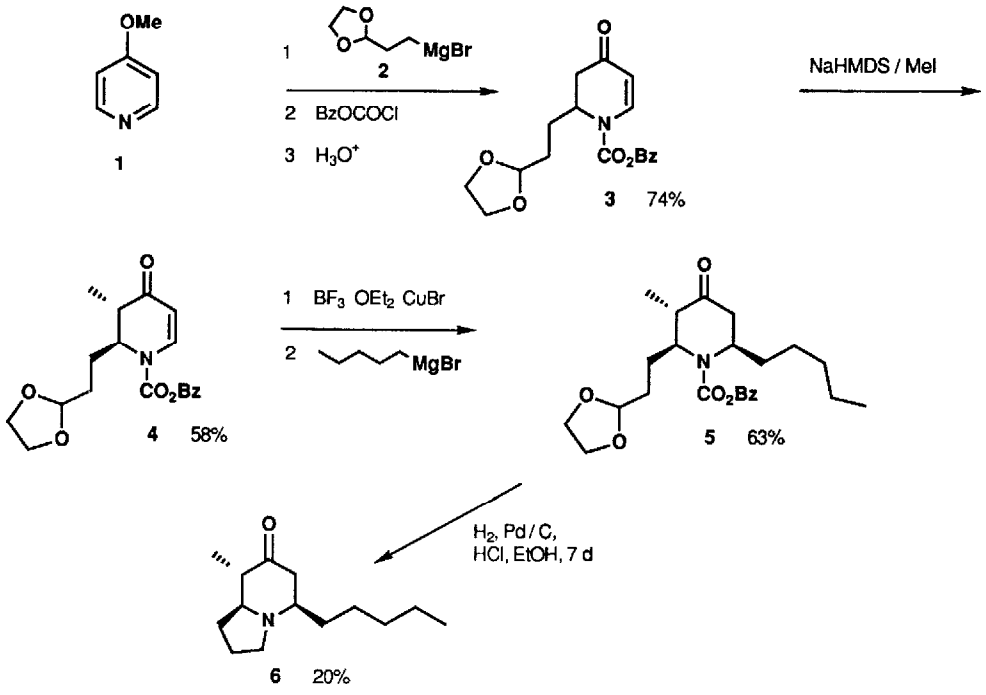
***Summary*** *The indolizidine alkaloid (±)-209B was prepared in seven steps from 4-methoxypyridine*

The alkaloids found in the skin secretions of neotropical poison-dart frogs (Dendrobatidae) have attracted wide interest in the last few years due to their promising pharmacological activity The scarcity of natural material and the biological significance of these alkaloids have stimulated considerable synthetic efforts [1,2] As part of a program directed at studying the synthesis and synthetic utility of N-acyldihydropyridones,[3] we investigated approaches to the preparation of the poison-dart frog alkaloid indolizidine 209B We now report a synthesis of (±)-indolizidine 209B in seven steps from 4-methoxypyridine via intermediate N-acyldihydropyridone **8**



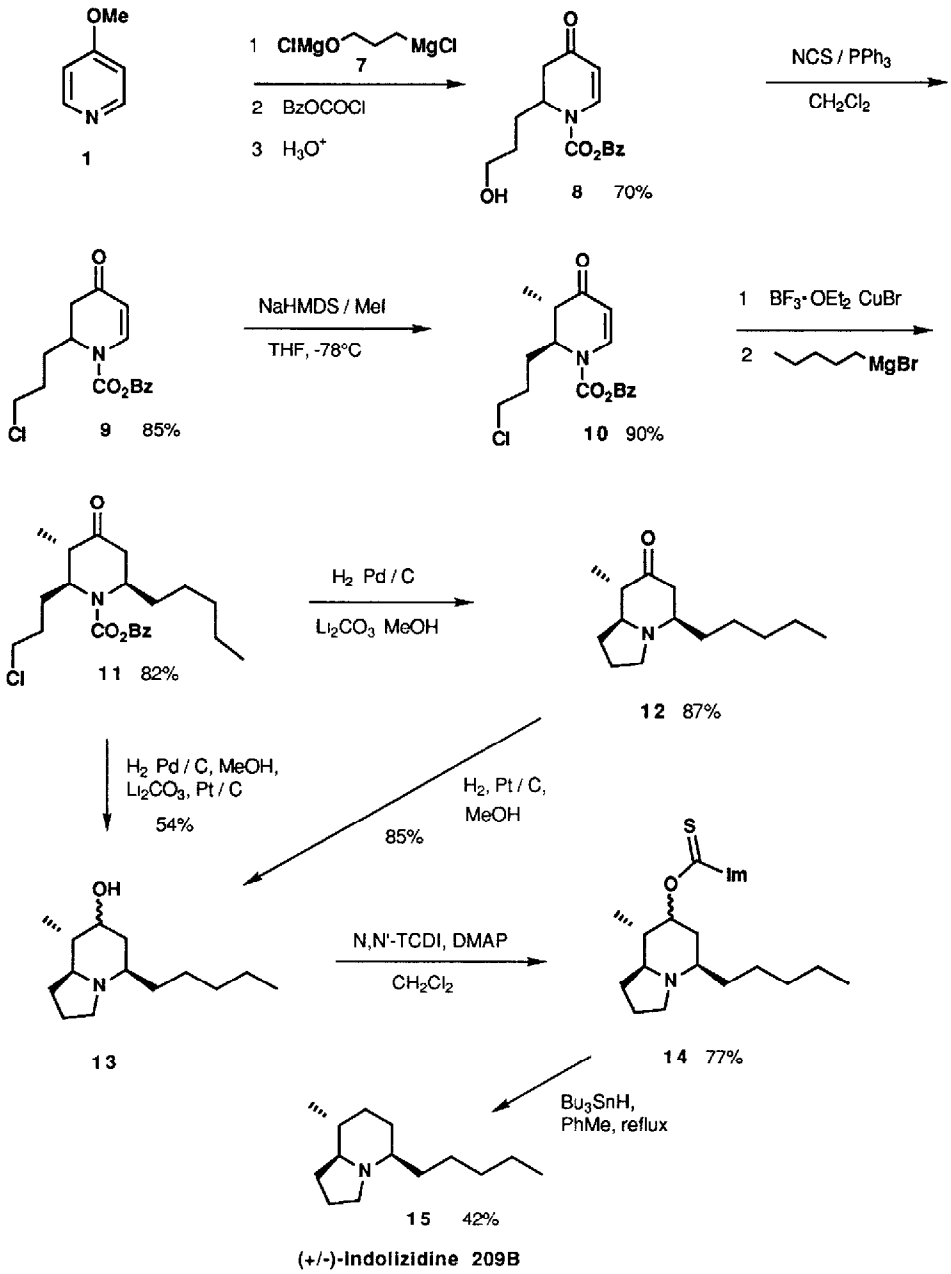

**indolizidine 209B** **8** **1**

Our first approach was to prepare indolizidine 209B via dihydropyridone **3** Treatment of 4-methoxypyridine (**1**) with benzyl chloroformate and Grignard reagent **2**,[4] followed by workup with aqueous acid, gave a 74% yield of **3** The next step in the synthetic plan called for stereoselective methylation at C-3 of dihydropyridone **3** This was accomplished by adding NaHMDS to a mixture of **3** and MeI in THF at -78°C The reaction was highly stereoselective giving only the desired *trans* diastereomer **4** in moderate yield Copper-mediated conjugate addition of *n*-pentylmagnesium bromide to **4** in the presence of boron trifluoride etherate gave *cis*-piperidone **5** in 63% yield [3b] It was established by $^1$H NMR homodecoupling studies that the 2,3-*trans* relationship in **4** had been retained during its conversion to **5** At this point our strategy required a cyclization step via an intramolecular reductive amination reaction This type of cyclization has been accomplished in one step by catalytic hydrogenation in the presence of acid over several days [5] After several attempts, the analogous hydrogenation of **5** gave only a 20% yield of the desired indolizidinone **6** Because of the poor cyclization reaction, and the moderate yields obtained in the two previous steps, this route was abandoned in favor of a new approach




The problem associated with the conversion of acetal **5** to **6** prompted us to utilize an intramolecular $S_N2$ substitution reaction to close the 5-membered ring Dihydropyridone **8** was prepared from 4-methoxypyridine (**1**), Grignard reagent **7**,[6] and benzyl chloroformate in 70% yield Conversion of **8** to the chloride **9** was carried out in 85% yield using triphenylphosphine and N-chlorosuccinimide [7] The presence of the chloroalkyl side chain did not present a problem during the next step Treatment of **9** with NaHMDS/MeI gave a 90% yield of the desired diastereomer **10** Copper-mediated conjugate addition of *n*-pentylmagnesium bromide to **10** in the presence of boron trifluoride etherate gave *cis*-piperidone **11** in 82% yield It is noteworthy that the overall yield of the last two steps is significantly higher than that observed for the analogous reactions of the previous route Cyclization of **11** was effected by a one-pot procedure involving catalytic hydrogenolysis of the benzyl carbamate group in the presence of lithium carbonate to give an 87% yield of indolizidinone **12** [8] To complete the synthesis of indolizidine 209B, reductive removal of the keto group of **12** was necessary Successive treatment of **12** with $TsNHNH_2$ and $NaBH_4$[9] gave a low yield of an unacceptable mixture of three products including indolizidines 209B and 8-epi-209B Attempts to convert the indolizidinone **12** into an enol phosphate or a vinyl triflate, to be followed by deoxygenation via catalytic hydrogenation,[10] were also unsuccessful Since there are numerous examples of Barton deoxygenations on piperidinol systems,[11] we decided to proceed by first reducing ketone **12** to alcohol **13** This was accomplished in 85% yield with catalytic hydrogenation over Pt/C Alcohol **13** could be prepared in one-step from **11** by carrying out the cyclization and ketone reduction during one hydrogenation reaction After seven hours, Pt/C was added to the hydrogenation reaction of **11** (Pd/C, $Li_2CO_3$, MeOH) and stirring under hydrogen was continued for several more hours In this manner **13** was prepared in 55% yield from **11** The alcohol **13** was converted to the thiocarbonyl derivative **14** in 77% yield with N,N′-thiocarbonyldiimidazole in the presence of a catalytic amount of DMAP [12] Deoxygenation of **14** with $Bu_3SnH$/AIBN in refluxing toluene gave a 42% yield of (±)-209B (**15**) The spectral data[13] of **15** proved to be in agreement with those reported for synthetic (-)-indolizidine 209B by Holmes and coworkers [2]

Modification of the above route by incorporating our recently developed asymmetric synthesis of 2-alkyl-2,3-dihydro-4-pyridones[14] should allow for the enantioselective preparation of natural (-)-209B and related alkaloids Studies toward this goal are in progress



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13 Satisfactory IR, $^1H$ and $^{13}C$ NMR, and HRMS or microanalyses were obtained for all new compounds NMR data for **15** $^1H$ NMR (300 MHz, $CDCl_3$) δ 0 88 (d, 3 H, J = 6 6 Hz), 0 9 (t, 3 H, J = 6 6 Hz), 1 15-2 0 (m, 22 H), 3 27 (dt, 1 H, J = 8 1 and 2 2 Hz) $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 13 9, 18 8, 20 2, 22 5, 25 4, 28 96, 31 2, 32 26, 33 7, 34 6, 36 6, 51 9, 63 6, 71 4

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