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N-Acyldihydropyridones as Synthetic Intermediates. Synthesis of (±)-Septicine and (±)-Tylophorine.

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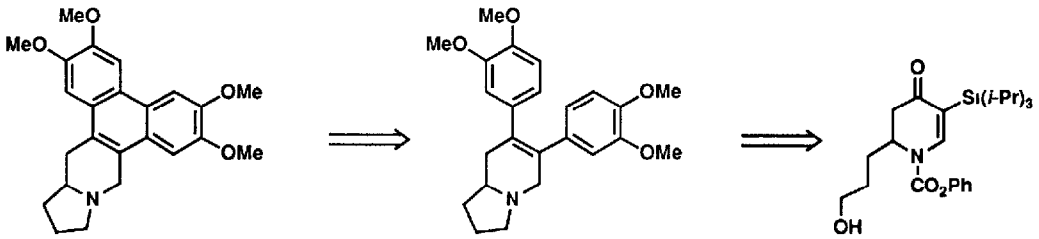
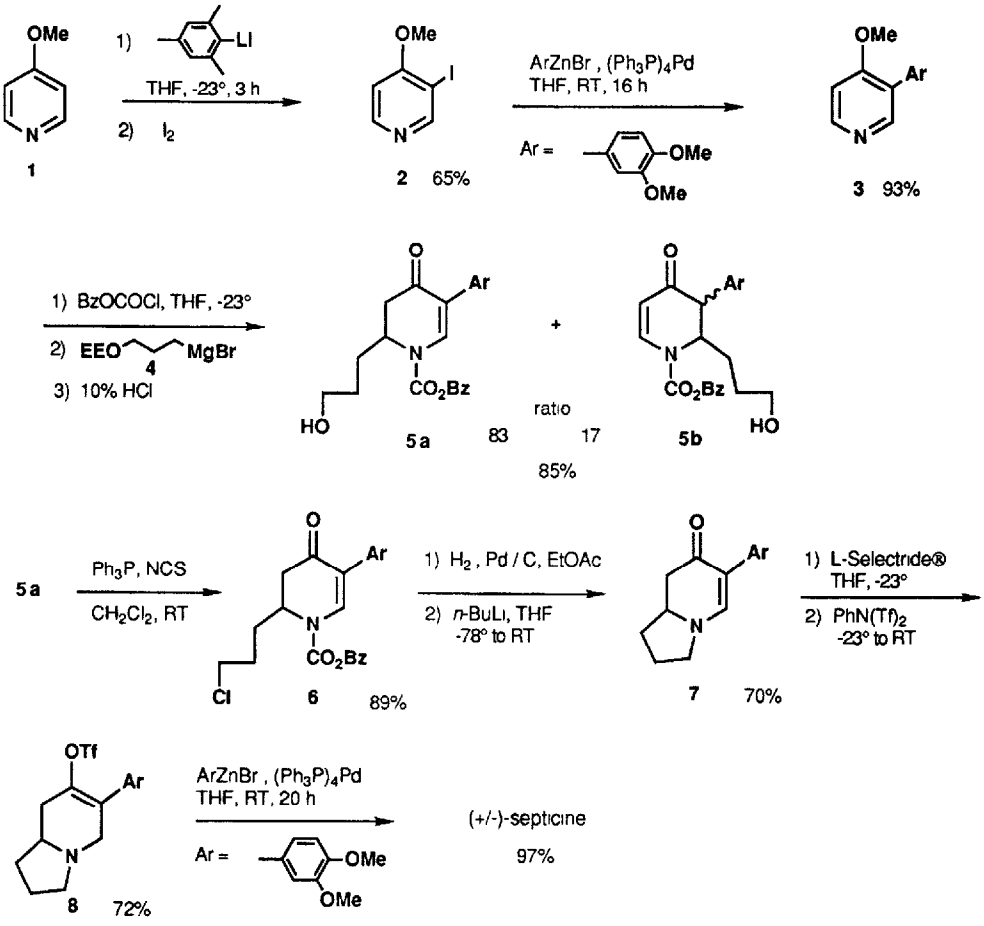
Summary *The indolizidine alkaloids (±)-septicine and (±)-tylophorine were prepared from N-acyldihydropyridone 7 in five and six steps, respectively*

Recently we have been studying the synthesis and synthetic utility of N-acyl-2,3-dihydro-4-pyridones These highly functionalized heterocycles are conveniently prepared by the addition of Grignard reagents to 1-acyl-4-methoxypyridinium salts [1] Previously, piperidine[2], quinolizidine[1,3], and *cis*-decahydroquinoline[4] alkaloids were prepared in our laboratories using N-acyldihydropyridones as synthetic intermediates We now report the conversion of N-acyldihydropyridone **7** to the indolizidine alkaloids (±)-septicine[5] and (±)-tylophorine[5] in five and six steps, respectively



Our initial approach was to prepare (±)-septicine via dihydropyridone **5a** Directed lithiation of 4-methoxypyridine (**1**) using mesityllithium as the base[6] and subsequent addition of iodine gave 3-iodo-4-methoxypyridine (**2**) in 65% yield Palladium-catalyzed cross-coupling[7] of (3,4-dimethoxyphenyl)zinc bromide (4-bromoveratrole, 2 equiv *t*-BuLi, THF, $ZnBr_2$) and **2** provided a 93% yield of 3-aryl-4-methoxypyridine **3** Treatment of **3** with benzyl chloroformate and Grignard reagent **4**,[8] followed by workup with acid, gave an 83 17 mixture of dihydropyridones **5a** and **5b** Unfortunately, the aryl group at C-3 of **3** was not of sufficient size to prevent attack by the Grignard reagent at C-2 Dihydropyridone **5a** was isolated and converted to the chloride **6** under mild conditions[9] Cleavage of the benzyl carbamate group by catalytic hydrogenolysis and subsequent cyclization using *n*-butyllithium as the base provided indolizidinone **7** in 70% yield for the two steps Reduction with L-Selectride® (Aldrich Chemical Co) and trapping of the

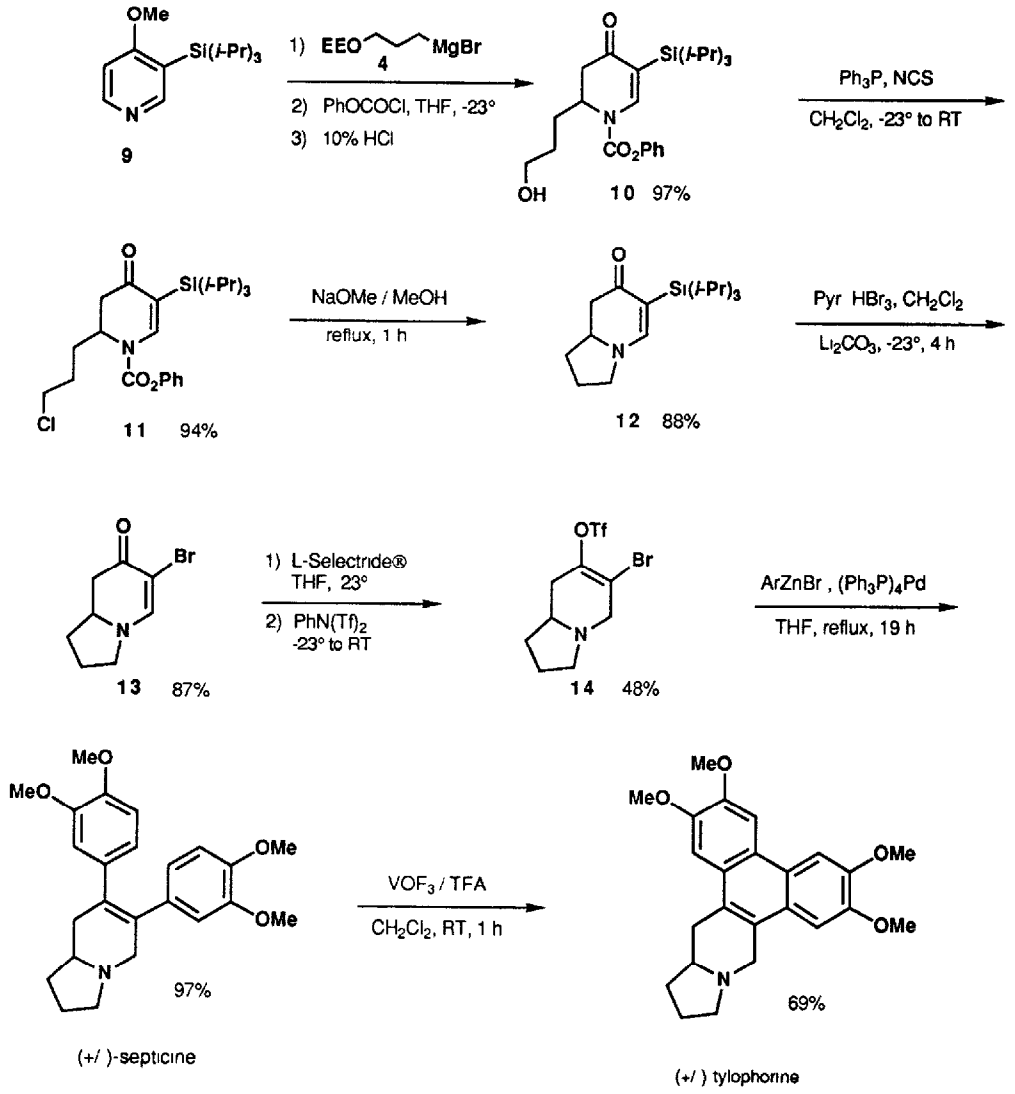
intermediate enolate in situ with N-phenyltriflimide gave vinyl triflate **8** in 72% yield Palladium-catalyzed cross-coupling[10] of (3,4-dimethoxyphenyl)zinc bromide and **8** provided a near quantitative yield of



(±)-septicine, mp 139-140°C (lit[11] mp 138-139°C), which showed spectral properties identical with those reported for authentic material[5,11] Although we were successful with this approach, we chose to explore a shorter and more regioselective route

Previous work from our laboratories has shown that a 3-triisopropylsilyl (TIPS) group can effectively block the C-2 position of a 1-acylpyridinium salt against attack by Grignard reagents[12] Treatment of 4-methoxy-3-(triisopropylsilyl)pyridine[13] (**9**) with Grignard reagent **4** and phenyl chloroformate gave alcohol **10** in near quantitative yield The alcohol **10** was converted to chloride **11** in 94% yield with triphenylphosphine and N-chlorosuccinimide[9] On treatment of **11** with sodium methoxide in methanol (4 equiv, reflux, 1 h), the N-phenoxycarbonyl group was removed and concomitant cyclization occurred to give indolizidinone **12** in 88% yield The reaction of **12** with pyridinium bromide perbromide (2 equiv, CH_2Cl_2, Li_2CO_3, -23°C) effected bromodesilylation to give bromide **13** Reduction with L-Selectride® followed by the addition of N-phenyltriflimide provided bromovinyl triflate **14** in moderate yield Palladium-catalyzed cross-coupling of excess (3,4-dimethoxyphenyl)zinc bromide (5 equiv) and **14** gave (±)-septicine in 97% yield

Reaction of our synthetic septicine with vanadium(V) trifluoride oxide (TFA, CH_2Cl_2, RT, 1 h) effected oxidative coupling[14] to provide a 69% yield of the phenanthroindolizidine alkaloid, (±)-tylophorine, mp 292-294°C (lit [15] mp 292°C), which showed spectral properties in agreement with those reported for authentic material [16-18]



Modification of the above route by incorporating our recently developed asymmetric synthesis of 2-alkyl-2,3-dihydro-4-pyridones[13] will allow for the enantioselective preparation of natural (-)-tylophorine and related alkaloids Efforts toward this goal are in progress and will be reported in due course

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