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Enantiopure *N*-Acyldihydropyridones as Synthetic Intermediates. An Asymmetric Synthesis of Solenopsin A.

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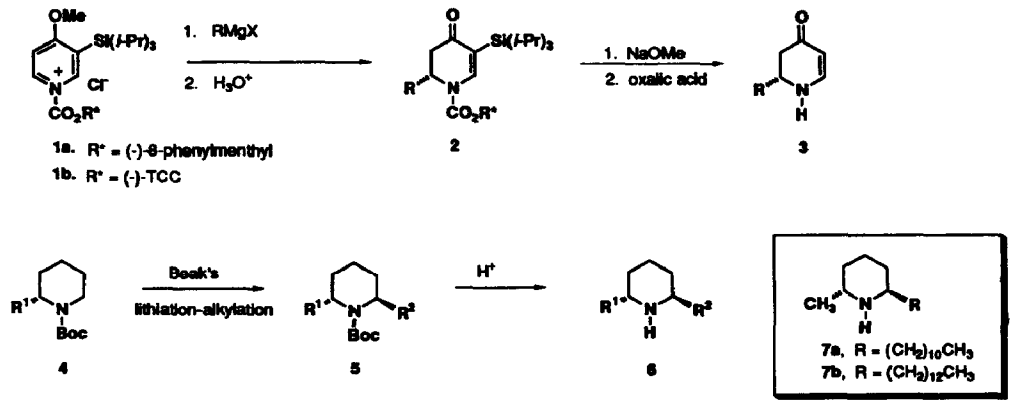
Abstract: *The trans-piperidine alkaloid, (-)-solenopsin A, was prepared in seven steps from readily available 4-methoxy-3-(triisopropylsilyl)pyridine in 43% overall yield.*

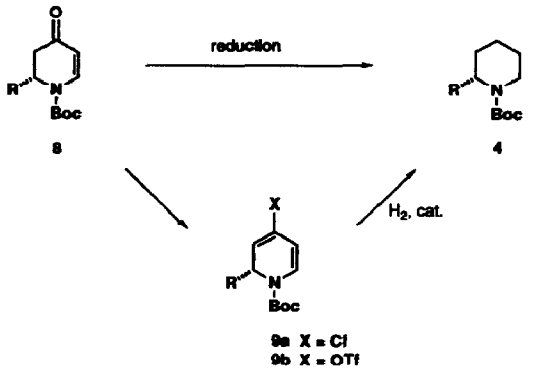
The addition of organometallics to chiral 1-acylpyridinium salt **1** gives *N*-acyl-2-alkyl-2,3-dihydro-4-pyridones **2** with high diastereoselectivity.[1,2] The dihydropyridones **3**, prepared from **2** in one step, are useful chiral building blocks for various alkaloids.[2,3] Recently, we developed a synthesis of enantiopure 2-alkylpiperidines using this methodology.[2e] With a practical asymmetric synthesis of 2-alkylpiperidines in hand, the preparation of enantiopure *trans*-2,6-dialkylpiperidines was investigated using an approach that combined our chemistry with Beak's *N*-Boc-piperidine α-lithiation methodology.[4] The plan was to prepare enantiopure *N*-Boc-piperidines **4**, which would be subjected to Beak's lithiation/alkylation to give the desired *trans*-2,6-dialkylpiperidines **5** and **6** in an asymmetric fashion. To this end, an enantioselective synthesis of solenopsin A (**7a**) was initiated.



Solenopsin A is one of several alkaloids present in the venom of the red fire ant, *Solenopsis invicta*.[5,6] The fire ant alkaloids exhibit hemolytic, insecticidal, and antibiotic activity[6], and have generated much synthetic

activity.[7,8] There have been five enantioselective syntheses of solenopsin A (**7a**) or B (**7b**) to date requiring 7 to 13 synthetic steps from readily available material.[8] We report here a 7-step, highly stereocontrolled synthesis of (-)-solenopsin A from 4-methoxy-3-(triisopropylsilyl)pyridine.

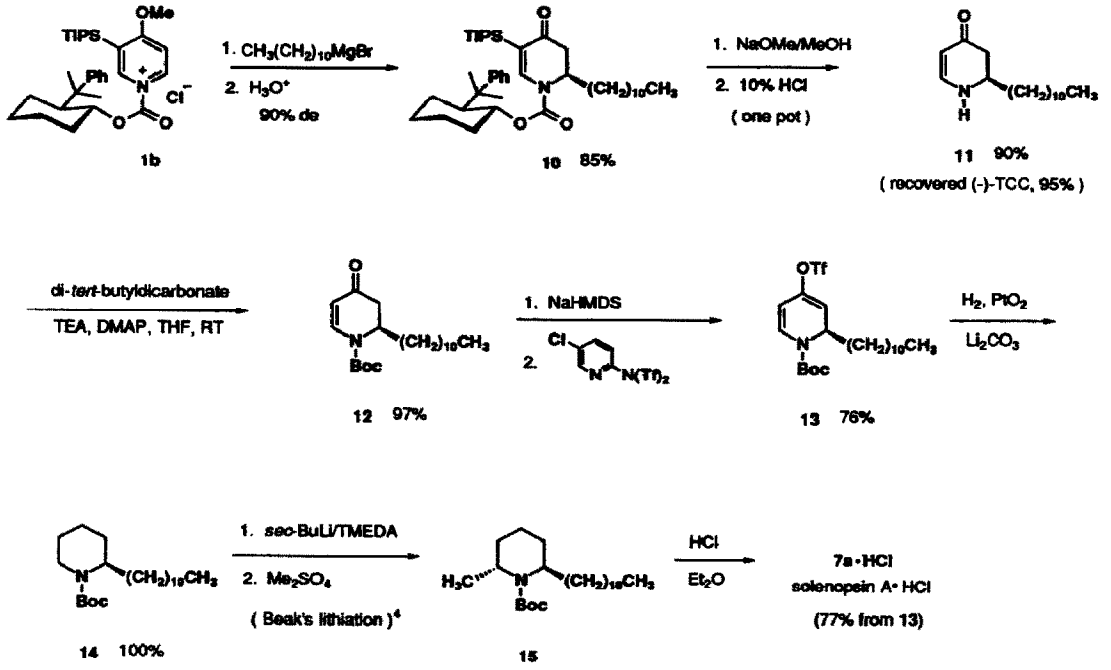
The synthetic plan called for the conversion of an *N*-Boc-2-alkyl-2,3-dihydro-4-pyridone **8** to an intermediate *N*-Boc-piperidine **4**. Multi-step reductions of *N*-acyl-2,3-dihydro-4-pyridones to *N*-acylpiperidines



have been reported in the literature. Kunz[3a] and Waldmann[9] have reported similar 3-step reductions involving L-Selectride 1,4-reduction, dithioketal formation, and Raney nickel desulfurization. We recently reported a 2-step reduction by first converting the dihydropyridone to a 4-chloro-1,2-dihydropyridine using the Vilsmeier reagent; subsequent catalytic reduction gave the piperidine derivative.[2e] This procedure generates HCl, however, and is not compatible with *N*-Boc groups. Since **9a** was not a viable intermediate, we decided to pursue a related 2-step reduction via a vinyl triflate, i.e. **9b**.

The 1-acylpyridinium salt **1b** was prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[1] and the chloroformate of readily available (-)-*trans*-2-(α-cumyl)cyclohexanol[10] ((-)-TCC). A THF solution of undecylmagnesium bromide was added dropwise (1.5 h) to the chiral salt at -78 °C in toluene to give dihydropyridone **10** on acidic workup in 95% crude yield and 90% de. Purification by radial PLC (silica gel, EtOAc/hexanes) provided an 85% yield of pure diastereomer **10**. Treatment of **10** with NaOMe/MeOH and then 10% HCl gave a 90% yield of deprotected dihydropyridone **11** [$[\alpha]_D^{25}$ + 237 (*c* 1.3, $CHCl_3$)] along with recovered (-)-TCC (95%). The *N*-Boc-dihydropyridone **12** was prepared from **11** in 97% yield using di-*tert*-butyldicarbonate, triethylamine, and DMAP in THF (RT, 14 h). The enone portion of **12** was completely reduced via the vinyl triflate **13**. Deprotonation of **12** with NaHMDS and enolate trapping with *N*-(5-chloro-2-pyridyl)triflimide[11] provided a 76% yield of **13**. Catalytic reduction[2a] of **13** (H_2, PtO_2, Li_2CO_3, EtOH) gave a quantitative yield of *N*-Boc-piperidine **14** [$[\alpha]_D^{26}$ - 25.1 (*c* 1.58, $CHCl_3$)]. Lithiation using Beak's conditions (*sec*-BuLi, TMEDA, THF, -78 °C)[4] and alkylation with Me_2SO_4 gave *trans*-piperidine **15**, which on treatment

with HCl/Et_2O at reflux (1.0 M, 7.5 h) provided a 77% yield of pure solenopsin A•HCl as white crystals, mp 141-142 °C; $[\alpha]_D^{24}$ - 7.6 (*c* 0.5, $CHCl_3$) [lit.[8a,c] mp 146 °C; $[\alpha]_D^{23}$ - 7.6 (*c* 0.7, $CHCl_3$)]. The spectral properties of our (-)-solenopsin A•HCl were in agreement with reported data.[8e,12]



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12. ^{13}C NMR data for **7a** (free base): (75 MHz, $CDCl_3$) δ 50.81, 45.80, 34.08, 32.99, 31.88, 30.79, 29.79, 29.62, 29.31, 26.44, 22.64, 21.22, 19.56, 14.06. For comparison with reported data, see reference 8e.

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