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A New Entry to the Isogeissoschizoid Skeleton

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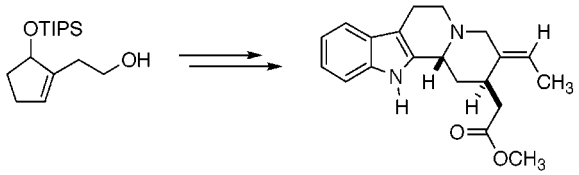
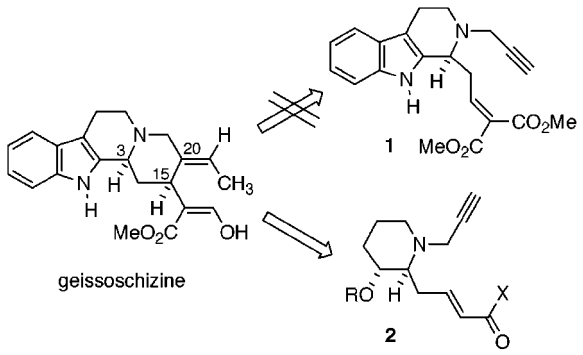
ABSTRACT



The tetracyclic isogeissoschizoid skeleton has been prepared by a novel route that involves the ozonolysis and double reductive amination of a cyclopentene, a nickel-catalyzed cyclization, and a late-stage Fischer indole synthesis.

Geissoschizine, which has been isolated from a variety of plant species, is an important biosynthetic precursor to a large number of polycyclic indole alkaloids.[1] Following the original synthesis from Van Tamelen,[2] many approaches of varying efficiency have appeared. Among the challenges to be addressed in the total synthesis of geissoschizine is the stereoselective introduction of the C-20 *E*-ethylidine unit. Successful approaches to this problem have included metal-catalyzed[3] and radical-mediated[4] cyclizations of geometrically defined alkenyl iodides, vinyl silane additions to iminium ions,[5] and stereoselective base-induced β-eliminations of β-hydroxy carbonyls[6] or hydropyrans.[7] We envisioned that nickel-catalyzed cyclization[8] of precursor **1** would directly afford the complete geissoschizine skeleton with control of the exocyclic alkene formation. However, despite the efficiency of enone alkyne cyclizations that were demonstrated with other complex heterocyclic substrates, we were unable to develop a procedure for the efficient conversion of **1** to geissoschizine due to low yields of the nickel-catalyzed cyclization process (Scheme 1).[9] Therefore,

Scheme 1



as a second generation approach, we speculated that cyclization of the structurally simpler precursor **2** would allow efficient formation of the exocyclic alkene and that the indole unit could be introduced at a late stage of the synthesis.

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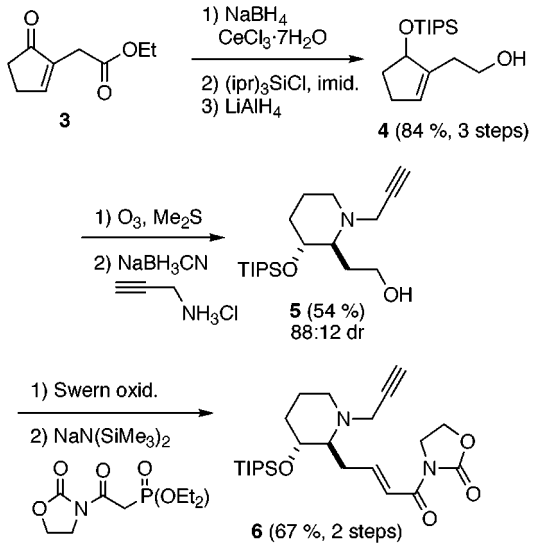
Herein, we describe our results for the latter approach. To construct the *N*-propargyl piperidine required for the strategy outlined above, we focused on a cyclopentene ozonolysis/double reductive amination approach (Scheme 2). Starting

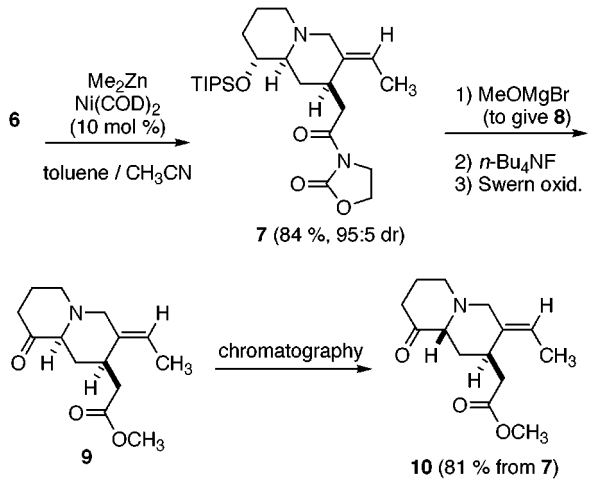
Scheme 2



from the known cyclopentenone **3**,[10] enone reduction with $NaBH_4/CeCl_3$ followed by silylation and ester reduction with $LiAlH_4$ resulted in the efficient production of protected cyclopentenol **4** in 84% yield over three steps. Ozonolysis in methanol, followed by Me_2S workup, afforded the crude keto aldehyde which was immediately treated with the hydrochloride salt of propargyl amine and $NaBH_3CN$ in methanol to afford a 54% yield of the expected piperidine **5** as an 88:12 mixture of diastereomers from which the trans isomer was isolated (47%) and carried on.[11] Swern oxidation followed by Horner−Emmons olefination[12] introduced the acyl oxazolidinone linkage of **6** in 67% yield over two steps.

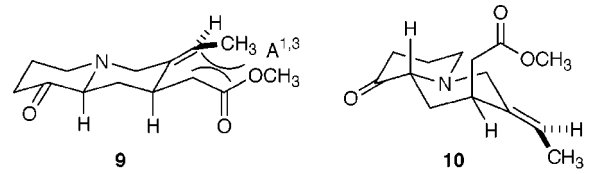
The cyclization of substrate **6** was next examined (Scheme 3). Treatment of substrate **6** with $Ni(COD)_2$ (10 mol %) and

Scheme 3



dimethylzinc (4 equiv) in 2:3 toluene:acetonitrile cleanly afforded the desired product **7** in 84% yield as a 95:5 mixture of two diastereomers. The major diastereomer possessed the cis relationship of H(3) and H(15) as determined later in the synthesis (vide infra). The acyl oxazolidinone unit of **7** was converted to the corresponding methyl ester **8** by treatment with MeOMgBr.[13] Silyl deprotection with *n*-Bu_4NF followed by Swern oxidation afforded ketone **9**. Inspection of the crude ^1H NMR spectrum revealed clean formation of the expected ketone **9** with a cis H(3)/H(15) relationship. However, all attempts to purify **9** by chromatography (Et_3N-washed SiO_2, basic alumina, or Fluorisil) led to complete isomerization of the product to the epimeric structure **10** in 81% yield from **7**.[14] This dramatic difference in reactivity and stability between epimers **9** and **10** is not surprising given the significant $A^{1,3}$ strain that is present in epimer **9** (Scheme 4). The solution structures of geissoschizine, its epimer, and

Scheme 4



numerous protected analogues have been established.[15] These studies have demonstrated that the D-ring of geissoschizine itself exists in a twist boat conformation due to the $A^{1,3}$ strain present in the natural product.[16]

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(14) Efforts to capture the cis isomer by kinetic enolization were unsuccessful. Treatment of **10** with TMSOTf and Et_3N in dichloromethane cleanly afforded the kinetic enoxysilane, whereas treatment of **9** under identical conditions prior to chromatography afforded intractable mixtures.

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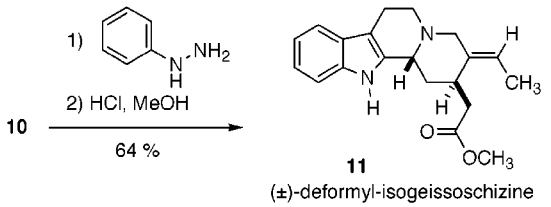
The Fischer indole synthesis is known to typically provide regioisomeric mixtures with unsymmetrically substituted ketones such as **10**.[17] However, we were pleased to find that an HCl-catalyzed Fischer indole synthesis[18] of **10** with phenyl hydrazine cleanly afforded deformyl-isogeissoschizine **11** in 64% isolated yield (from ketone **10**), which displayed NMR spectra and mp identical to that previously reported (Scheme 5).[15b,19] None of the regioisomeric indole was detected.

Scheme 5



In summary, a new entry to the isogeissoschizoid skeleton has been developed. Whereas most approaches involve functionalization of tryptamine, our strategy involves late-stage indole introduction. The requisite precursor for indole installation was prepared by a sequence involving ozonolysis/double reductive amination of a substituted cyclopentene followed by a nickel-catalyzed cyclization. The general approach should allow for preparation of a variety of polycyclic heterocycles.

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Supporting Information Available: Full experimental details and NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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