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Intramolecular Formal Aza-[3 + 3] Cycloaddition Approach to Indoloquinolizidine Alkaloids. A Stereoselective Total Synthesis of (±)-Tangutorine

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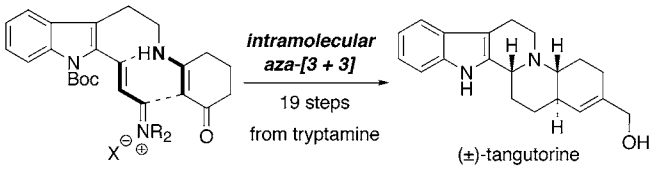
ABSTRACT



A 19-step stereoselective total synthesis of (±)-tangutorine is described here. The total synthesis features an intramolecular aza-[3 + 3] formal cycloaddition strategy and also a Heck coupling for constructing the C2–C3 bond. This work provides a novel approach toward the indoloquinolizidine family of alkaloids.

Isolation of (±)-tangutorine (**1**, Figure 1) from the leaves of *Nitraria tangutorum* was reported in 1999 by Che and coworkers.[1] It possesses a novel benz[*f*]indolo[2,3-*a*]quinolizidine skeleton and, to date, is the only known *β*-carboline natural product of this type.[2] Structurally, tangutorine (**1**) is related to well-known monoterpenoid indole alkaloids such as (+)-deplancheine (**2**)[3−5] and (+)-geissoschizine (**3**).[6,7] These natural products contain the indoloquinolizidine substructure prevalent in a large number of monoterpenoid indole alkaloids that are derived biosynthetically from tryptophan. Synthesis of these monoterpenoid indole alkaloids has often featured the classic Pictet−Spengler cyclization.[8,9] This strategy was also evident in Jokela's sole total synthesis of tangutorine (**1**).[10,11]

We became interested in tangutorine (**1**) because our intramolecular formal aza-[3 + 3] cycloaddition strategy would represent a novel approach toward the synthesis of

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(2) (a) Herbert, R. B. In *The Monoterpenoid Indole Alkaloids*; Saxon, J. E., Ed; Wiley-Interscience: New York, 1994; Supplement to Vol. 25, Part 4 of *The Chemistry of Heterocyclic Compounds*, Chapter 1. (b) Saxon, J. E. In *The Monoterpenoid Indole Alkaloids*; Saxon, J. E., Ed; Wiley-Interscience: New York, 1994; Supplement to Vol. 25, Part 4 of *The Chemistry of Heterocyclic Compounds*, Chapter 8. (c) Saxon, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vols. 50 and 51. (d) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, *15*, 327. (e) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000** *17*, 349.

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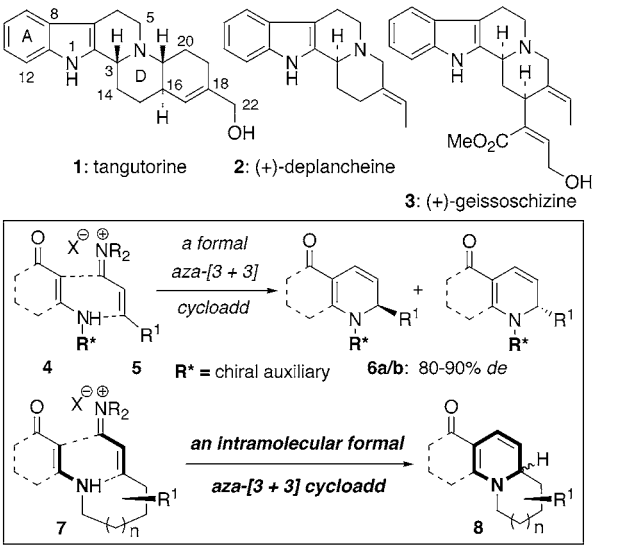
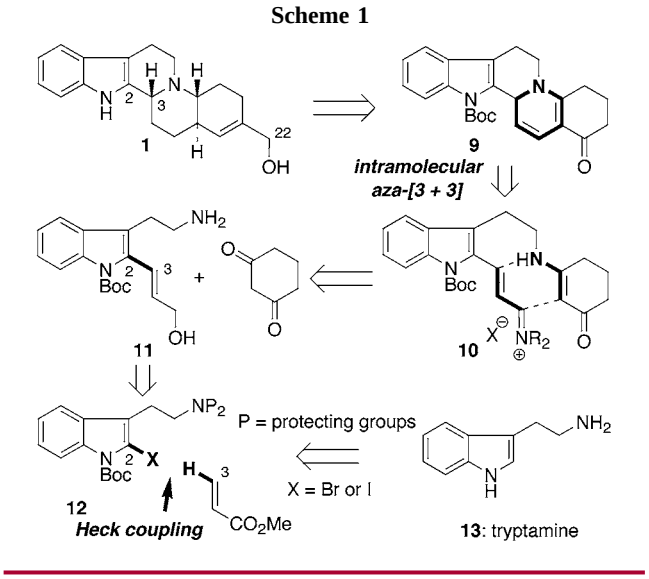


Figure 1.



indoloquinolizidine alkaloids.[12−15] Annulation of chiral vinylogous amides **4** with α,β-unsaturated iminium salts **5** provides a highly stereoselective approach to dihydropyridines **6a/b** (Figure 1).[12,13] This stepwise formal aza-[3 + 3] cycloaddition involves a tandem Knoevenagel condensation−stereoselective pericyclic ring-closure of an 1-azatriene intermediate.[16] Recently, it has also been rendered intramolecular[17] (**7** → **8**). We report here a stereoselective total synthesis of (±)-tangutorine featuring this intramolecular formal aza-[3 + 3] cycloaddition strategy.

As outlined in Scheme 1, tangutorine (**1**) was envisioned to arise from the pentacycle **9**, which lacks only the C22 hydroxymethyl group. To construct pentacycle **9**, the intramolecular aza-[3 + 3] cycloaddition would be featured using α,β-unsaturated iminium salt **10**. The key α,β-unsaturated aldehyde precursor for the iminium salt **10** could be obtained from condensation of amino alcohol **11** with 1,3-cyclohexanedione followed by oxidation of the allyl alcohol moiety. Amino alcohol **11** would be prepared via a Heck coupling of a suitably protected 2-halo-tryptamine **12**, and the ultimate starting point would be tryptamine **13**. Thus, another unique feature in the synthesis of monoterpenoid

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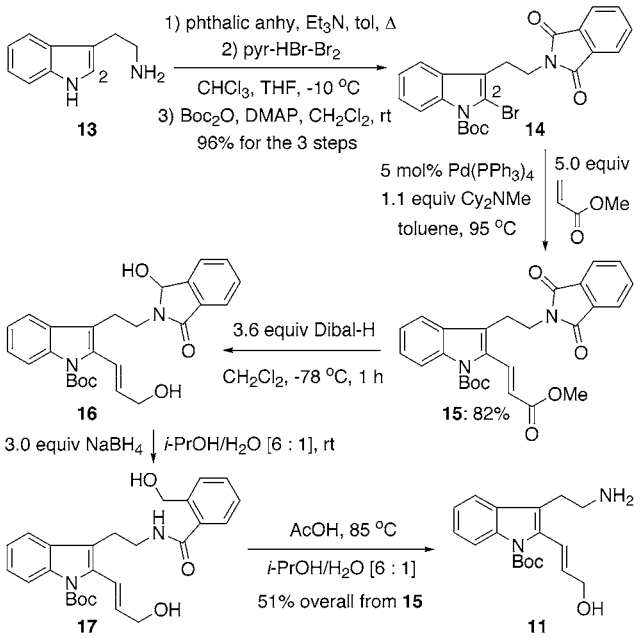
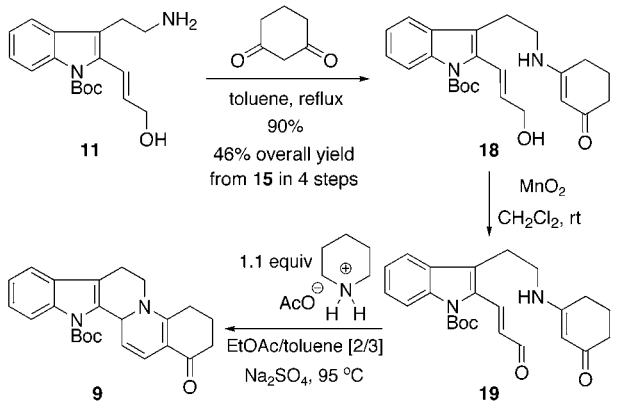
Scheme 2



Scheme 3



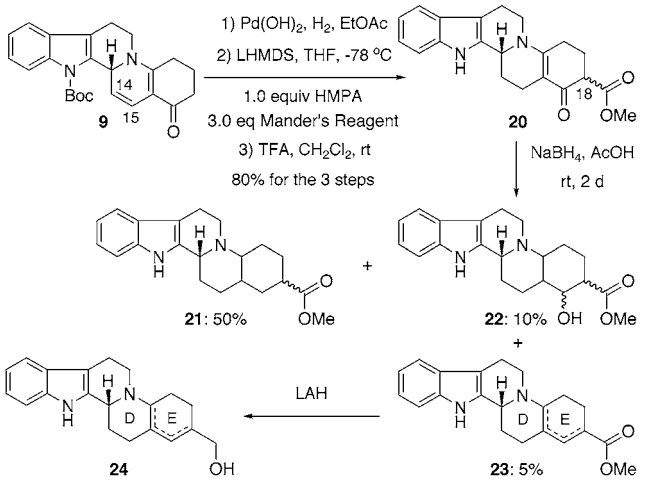
indole alkaloids would be the Heck coupling in place of the classic Pictet−Spengler cyclization for constructing the C2−C3 bond.[18]

To prepare amino alcohol **11**, tryptamine **13** was first protected as a phthalimide, and bromination at the C2 position using pyridinium hydrogen perbromide followed by Boc protection of the indole nitrogen atom led to bromide **14**[19,20a] in 96% yield over the three steps (Scheme 2). Heck coupling of bromide **14** with methyl acrylate using $Pd(PPh_3)_4$ afforded ester **15** in 82% yield, and reduction of **15** using DIBAL-H led to allyl alcohol **16** in which the phthalimido group was also partially reduced. $NaBH_4$ reduction[20b] followed by hydrolysis with HOAc was employed to afford the desired amino alcohol **11** in 51% yield overall from **15** with no purifications.

Subsequent condensation of amino alcohol **11** with 1,3-cyclohexanedione[12,13] gave vinylogous amide **18** in 90% yield (Scheme 3). MnO_2 oxidation of **18** led to the cycloaddition precursor **19**, and under the standard intramolecular formal aza-[3 + 3] cycloaddition conditions,[17] the desired pentacycle **9** was isolated. The overall yield was determined to be 56% from **18** after hydrogenating the *endo*-cyclic olefin.[21] This success establishes a viable synthetic approach to tangutorine (**1**), (+)-geissoschizine (**3**), or other tryptophan-derived monoterpenoid indole alkaloids.

The original goal was to apply this methodology in a formal total synthesis of tangutorine (**1**) with interception of an advanced intermediate reported by Jokela.[10a] To achieve this task, the C14−15 *endo*-cyclic olefin in pentacycle **9** was first hydrogenated (Scheme 4), and treatment of this hydrogenated intermediate with LHMDS at −78 °C led to a kinetic lithium enolate that was allowed to react with Mander's reagent [$NCCO_2Me$][22] in the presence of HMPA to install the methoxycarbonyl group at C18. Subsequent removal of the Boc group using TFA led to the reported[10a] β-keto ester **20** as a mixture of diastereomers in 80% overall for the three steps, thereby completing a formal total synthesis. However, because the reported spectroscopic information for **20** and subsequent intermediates including the synthetic tangutorine was limited,[10a] the remaining reported steps were pursued to complete the total synthesis.

Scheme 4



Unfortunately, in our hands $NaBH_4$ reduction of **20** in AcOH led to a mixture of **21**−**23** (assigned by LCMS) with the major product being the over-reduced product **21** (Scheme 4). The desired hydroxyester **22**[10a] was found in ≤10% LC yield. Other hydride conditions were explored,

(18) Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, 883.

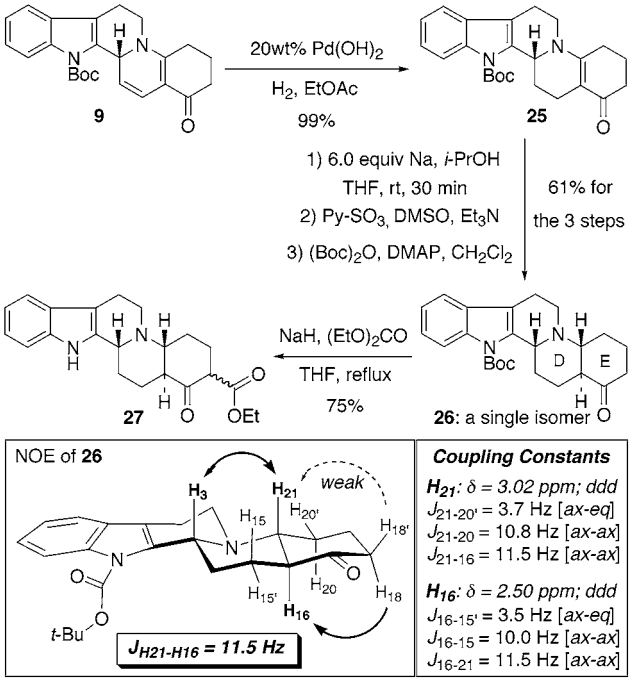
(19) All new compounds are characterized by ^1H NMR, ^{13}C NMR, FTIR, and mass spectroscopy.

(20) (a) Chu, L.; Fisher, M. H.; Goulet, M. T.; Wyvratt, M. J. *Tetrahedron Lett.* **1997**, 38, 3871. (b) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093.

(21) The desired pentacycle **9** often contained impurities but could be unambiguous assigned and fully characterized when its *endo*-cyclic olefin was hydrogenated to give **25** (see in the later scheme).

(22) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

Scheme 5



but none gave clean reductions. $NaBH_4$ and $CeCl_3$ (not shown) did afford a mixture with **23** as the major component as suggested by LCMS. Reduction of this mixture using LAH afforded **24** as an isomeric mixture that did not contain tangutorine (**1**), although each isomer possessed the right mass. This suggests that the reduction had given **23** as a mixture of alkene isomers with different relative stereochemistry with respect to the CDE-ring junctions. These difficulties convinced us to complete the total synthesis of tangutorine (**1**) via an alternate route.

As shown in Scheme 5, pentacycle **25**, obtained from hydrogenation of **9**, was reduced using a dissolving metal protocol reported by Palmieri for reduction of vinylogous amides.[23] The extent of the reduction was not easily controlled, as reduction of the carbonyl group and removal of the Boc group were observed. Thus, reoxidation using pyridine-SO_3 and DMSO,[24] as well as reprotection of the indole nitrogen using Boc anhydride, was carried out to give keto pentacycle **26** as a single diastereomer in 61% yield over three operations. NOE experiments confirmed the relative stereochemistry of H3 and H21 as *syn* (see the box in Scheme 5), and along with analysis of coupling constants, the relative stereochemistry of H16 and H21 is shown to be *trans* with $J = 11.5$ Hz. These assignments support the notion that Palmieri's dissolving metal protocol provides the thermodynamically favored stereochemical outcome.

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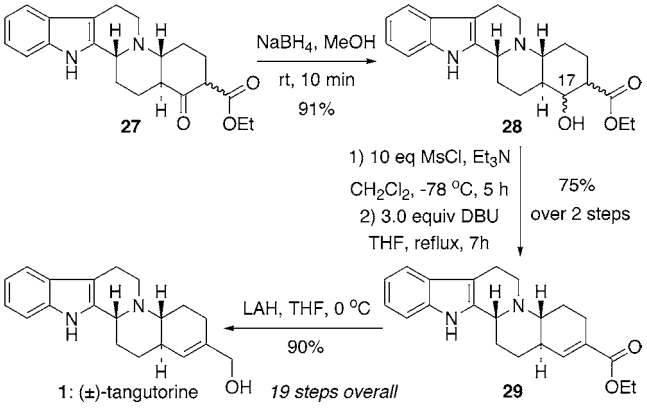
(24) Paikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5507.

Scheme 6



Intriguingly, the original LHMDS/HMPA/Mander's reagent protocol was not useful here to assemble the methoxycarbonyl group. It turned out that refluxing keto pentacycle **26** in THF in the presence of NaH and diethyl carbonate was the most suitable protocol, leading to β-ketoester **27** regioselectively as a mixture of two diastereomers.

To complete the total synthesis, β-ketoester **27** was reduced cleanly using $NaBH_4$ to give hydroxyester **28** in 91% yield (Scheme 6). Mesylation of the C17 hydroxyl group in **28** at −78 °C was slow and required 10 equiv of MsCl, presumably because the C17−OH is hindered. Subsequent elimination using 3.0 equiv of DBU led to unsaturated ester **29** in 40% overall yield but with a 53% overall conversion from **28**. The starting hydroxyester **28** could be efficiently recycled to give a combined 75% yield for the two steps. LAH reduction of **29** at 0 °C furnished tangutorine (**1**) in 90% yield. ^{13}C NMR data of the synthetic tangutorine matched completely those reported for the natural sample.[1,25]

We have described here a stereoselective total synthesis of (±)-tangutorine with an overall yield of 5.5% in 19 steps featuring an intramolecular aza-[3 + 3] formal cycloaddition strategy. The work represents a novel approach to indoloquinolizidine family of alkaloids.

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Supporting Information Available: Experimental and ^1H NMR spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) See Supporting Information for discussions on discrepancies of two ^1H NMR resonances.