Natural Product Synthesis

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Total Synthesis of the Unusual Monoterpenoid Indole Alkaloid (±)-Alstilobanine A**

*Yiqing Feng, Max M. Majireck, and Steven M. Weinreb**

The monoterpene indole alkaloids, which are usually comprised of a tryptamine moiety appended to a single C_9- or C_{10}-terpenoid unit, constitute one of the largest known classes of natural products.[1] In 2004, Kam and Choo isolated a new type of monoterpenoid indole alkaloid, angustilodine (**1**), which contains a unique rearranged skeleton, from the leaves of the Malayan plant *Alstonia angustiloba* (Figure 1).[2] The

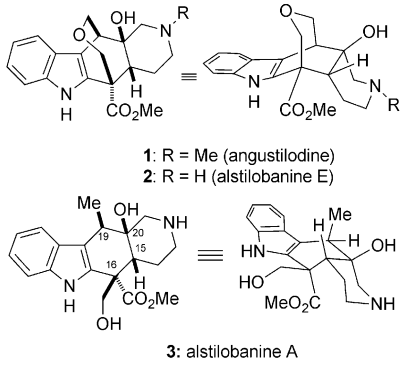
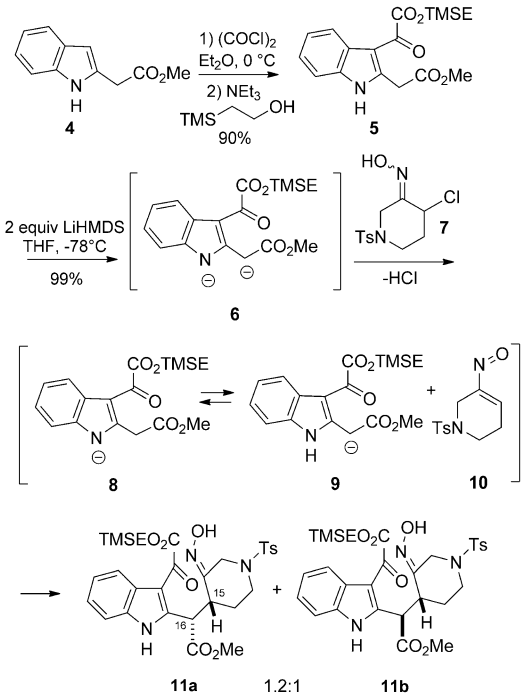


Figure 1. Structures of the alstilobanine alkaloids.

structure of **1** was determined by detailed spectroscopic analysis and found to include an indole appended to a *cis*-fused 2-azadecalin ring system bearing a seven-membered ether bridge. An interesting conformational feature of this molecule established by two-dimensional (2D) NMR studies is the observation that the piperidine ring exists as a boat. More recently, Morita and co-workers discovered the N-demethyl congener alstilobanine E (**2**), along with alstilobanine A (**3**), which lacks the bridging oxepane ring found in **1** and **2**, in the same plant.[3] Unlike alkaloids **1** and **2**, it was proposed that **3** has the piperidine ring in a chair conformation as shown in Figure 1. Alstilobanines A and E were found to possess modest relaxant activity against phenylephrine-induced contractions of thoracic rat aortic rings with endothelium. Herein we describe the first approach to these alkaloids, thus culminating in a convergent total synthesis of racemic **3**.

Our synthetic strategy was predicated upon effecting two key carbon–carbon single bond constructions. The first planned transformation involved an intermolecular conjugate addition of an indole ester enolate to a 3-piperidone-derived nitrosoalkene to form the C15–C16 bond of the alkaloid.[4] The second pivotal step was to apply the methodology of Romo et al. for intramolecular β-lactone formation[5] to generate the requisite *cis*-2-azadecalin moiety by C19–C20 bond formation, along with the necessary functionality and three contiguous stereocenters at C15, C19, and C20. The implementation of this strategy is outlined herein.[6]

Thus, the indole 2-acetic acid methyl ester **4**[7] was first acylated at C3 using oxalyl chloride with subsequent in situ treatment of the resulting α-keto acid chloride with 2-trimethylsilylethanol to afford the keto diester **5** (Scheme 1). To generate the C15–C16 bond of **3**, **5** was first converted into the dianion **6** using two equivalents of lithium hexamethyldisilazide (LiHMDS). Addition of one equivalent of the α-chlorooxime **7**, derived from *N*-tosyl-3-piperidone,[8] to the dianion led to the desired coupled product as a 1.2:1



Scheme 1. Nitrosoalkene conjugate addition. TMS = trimethylsilyl, TMSE = trimethylsilylethoxy, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

[*] Y. Feng, M. M. Majireck, Prof. Dr. S. M. Weinreb
Department of Chemistry, The Pennsylvania State University
University Park, PA 16802 (USA)
E-mail: smw@chem.psu.edu

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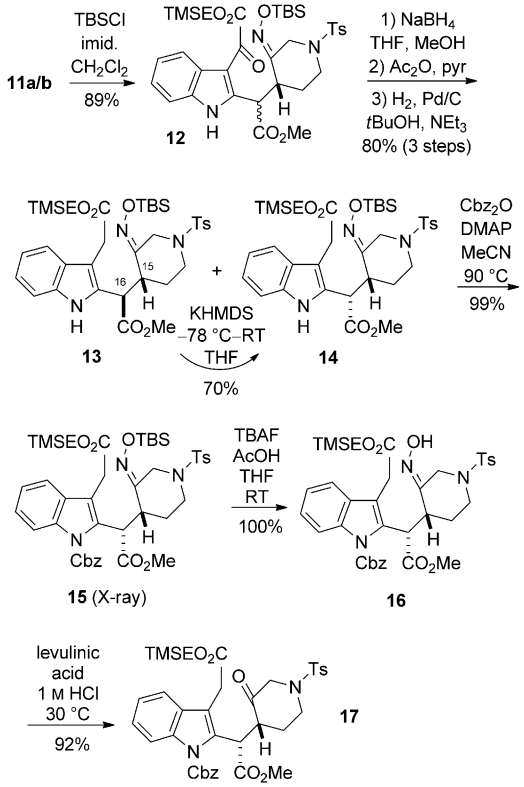
mixture of diastereomers **11a** and **11b** in high yield. The mixture could be separated and each isomer was isolated as a single oxime isomer with an *E* geometry. It should be noted that the mixture is of no consequence since it is subsequently corrected (see below).

We believe that this novel transformation involves the initial dehydrohalogenation of **7** by **6** to generate the transient nitrosoalkene **10** along with a monoanion derived from the indole ester. It seems likely that this intermediate is probably an equilibrium mixture of the resonance stabilized anions **8** and **9**, but the conjugate addition to **10** occurs exclusively through the latter.

To continue the synthesis, the mixture of **11a** and **11b** was first protected as the TBS ether **12** (Scheme 2). At this stage, **12** was deoxygenated by a modification of the method of

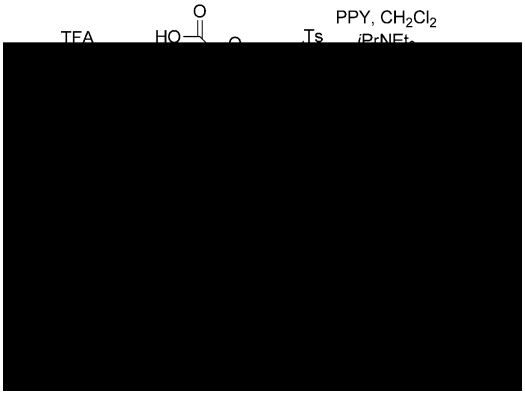


Scheme 2. Preparation of **17**. Cbz = benzyloxycarbonyl, DMAP = 4-(dimethylamino)pyridine, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

Hlasta et al.[9] Thus, the ketone was first reduced to the alcohol which was then converted into the corresponding acetate, with subsequent catalytic hydrogenation using Pd/C in *tert*-butyl alcohol/triethylamine to afford a mixture of the diastereomeric diesters **13** and **14**, which were easily separated by column chromatography.[10]

Since it was later found that these two diastereomeric systems (**13** and **14**) behave differently during the key cyclization using the protocol from Romo et al., **13** was epimerized cleanly to **14** in 70% yield upon isolation by treatment with potassium hexamethyldisilazide and subsequent quenching with aqueous ammonium chloride. The indole nitrogen atom of **14** was then protected with a Cbz group to afford **15** whose structure was established by X-ray analysis, thus confirming both the relative stereochemistry at C15 and C16 and the *E* geometry of the O-silyloxime.[11] At this point, **15** was converted into the oxime **16** with TBAF with subsequent acidic cleavage to give the corresponding ketone **17**.[12]

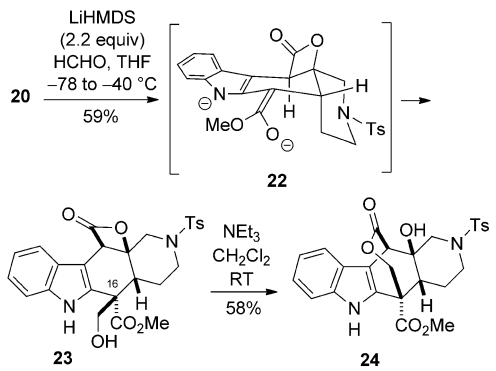
Initial attempts to convert the trimethylsilylethyl ester **17** into the corresponding carboxylic acid with fluoride sources failed,[6] but this transformation could be performed with trifluoroacetic acid in CH_2Cl_2 to afford the desired keto acid **18** in high yield without affecting the methyl ester (Scheme 3).[13] With compound **18** in hand, we were prepared to attempt the second key step, that is a formal ketene/ketone-[2+2]-intramolecular cycloaddition using the protocol by Romo et al. to generate the requisite fused β-lactone *cis*-2-azadecalin system.



Scheme 3. Cyclization of **18** to give the pentacyclic β-lactone **19**. TFA = trifluoroacetic acid.

Therefore, treatment of **18** with 2-bromo-*N*-propylpyridinium triflate, 4-pyrrolidinopyridine (PPY), and Hünig's base in CH_2Cl_2 containing 1.2 equivalents of acetic acid, to avoid epimerization of the C16 ester, led to the desired fused β-lactone system **19** needed for alstilobanine A along with a trace of the *trans*-2-azadecalin **21** (97:3 as determined by ^{1}H NMR spectroscopy) in high yield.[5b] Interestingly, when the cyclization was conducted on the C16 ester epimer of **18**, which was prepared from **13**, the major product was the undesired *trans*-2-azadecalin.

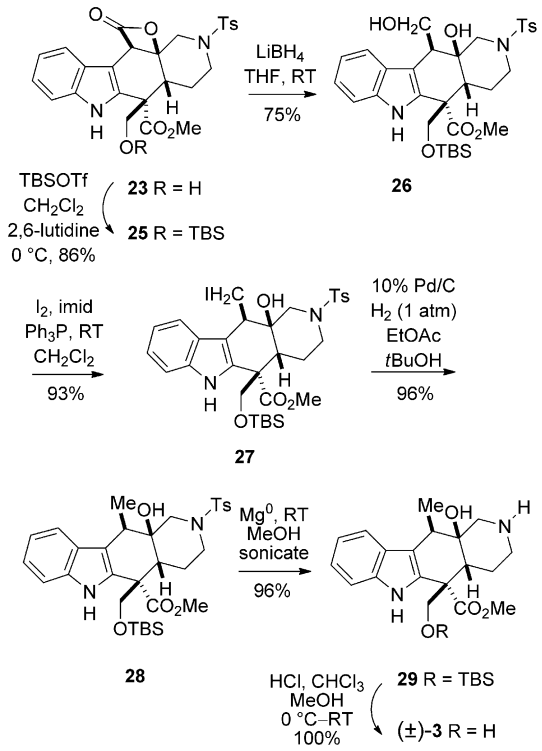
With the key intermediate **19** now in hand, we began to investigate introduction of a hydroxymethyl group at C16. Since we had found in earlier work with various other intermediates that it was not possible to generate a C16 ester enolate if a Cbz protecting group is in place on the indole nitrogen atom,[6,14] this group was removed from **19** by hydrogenolysis to afford the NH-indole ester **20**. This compound could be successfully deprotonated with two equivalents of LHMDS to generate the dianion **22**, and subsequent alkylation using monomeric formaldehyde[15] from the least hindered face produced the α-hydroxymethyl ester **23** as a single diastereomer having the configuration needed for **3** (Scheme 4).[16] The stereochemistry of **23** was



Scheme 4. Stereoselective C16 hydroxymethylation.

established by 2D NMR analysis and was also confirmed by the fact that the β lactone underwent acyl migration to afford the bridged seven-membered lactone **24** upon treatment with triethylamine in CH_2Cl_2.

Since it was observed that the hydroxymethyl group of **23** tends to be lost under a variety of reaction conditions through a retro-aldol process, this functionality was protected as the TBS ether **25** (Scheme 5). The β-lactone moiety of **25** could then be reduced selectively with $LiBH_4$ in THF to yield the diol ester **26**, which was converted into the iodo alcohol **27** by an Appel reaction.[17] Subsequent catalytic hydrogenation of this compound at atmospheric pressure using 10% Pd/C in a 1:1 mixture of ethyl acetate/*tert*-butyl alcohol cleanly led to the desired methyl compound **28**.[17] The N-tosyl protecting group of **28** was removed using magnesium metal turnings in methanol under sonication to afford **29** in good yield.[18] Once, again the structure and stereochemistry of this intermediate were confirmed by 2D NMR analysis (see the Supporting Information). Finally, removal of the TBS protecting group with HCl in methanol/chloroform afforded racemic alstilobanine A (**3**), which was isolated as its hydrochloride salt, having ^1H and ^{13}C NMR spectra as reported for the natural alkaloid.[3,19]



Scheme 5. Completion of the synthesis of racemic alstilobanine A (**3**). Tf = trifluoromethanesulfonyl.

In summary, we have devised a convergent approach to a total synthesis of the novel indole alkaloid alstilobanine A (**3**). The synthesis of **3** requires about twenty operations starting from the indole methyl ester **4**. Key steps in the route include an unprecedented conjugate addition of an indole acetate ester enolate to a nitrosoalkene, and an intramolecular Romo cyclization to generate a β-lactone fused to the requisite *cis*-2-azadecalin needed for the alkaloid. Work is currently underway using the intermediates described here for construction of the bridging oxepane ring directed towards syntheses of the congeneric alkaloids **1** and **2**.[20]

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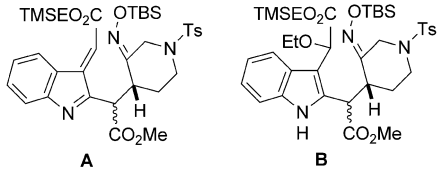
[10] This transformation presumably occurs via the azafulvene intermediate **A** derived from the indole. Evidence for this supposition is that if the hydrogenation is conducted in ethanol rather than *tert*-butyl alcohol, a significant amount of the product

B results where the acetate group is replaced by ethoxy through interception of **A** by the solvent. This compound is resistant to further catalytic reduction.[6]



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[19] We are grateful to Professor H. Morita (Hoshi University) for copies of the NMR spectra of the TFA salt of the natural alkaloid.
[20] Although alkaloids **1** and **2** in principle could be prepared by removal of the lactone oxygen atom of **24**, to date we have been unable to execute this transformation. Research is continuing on solving this problem or finding another approach to angustilodine and alstilobanine E.

