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

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Keywords

alkaloids; nitrogen heterocycles; total synthesis; nitrosoalkene conjugate addition; β-lactone

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 structure of angustilodine was determined by detailed spectroscopic analysis to include an indole appended to a *cis*-fused 2-azadecalin ring system bearing a 7-membered ring ether bridge. An interesting conformational feature of this molecule established by 2D NMR studies is the observation that the piperidine ring exists as a boat. More recently, Morita and coworkers 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 alstilobanine A 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. In this communication we describe the first approach to these alkaloids, culminating in a convergent total synthesis of racemic alstilobanine A (**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 C-15,16 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 via C-19,20 bond formation, along with the necessary functionality and three contiguous stereocenters at C-15,19,20. The implementation of this strategy is outlined here.[6]

Thus, indole 2-acetic acid methyl ester (**4**)[7] was first acylated at C-3 with oxalyl chloride, followed by *in situ* treatment of the resulting α-keto acid chloride with 2-trimethylsilylethanol to afford keto diester **5** (Scheme 1). In order to generate the C-15,16 bond of **3**, indole ester **5** was first converted to the dianion **6** using two equivalents of lithium hexamethyldisilazide. Addition of one equivalent of the α-chlorooxime **7** derived

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from *N*-tosyl-3-piperidone[8] to the dianion led to the desired coupled product as a 1.2:1 mixture of diastereomers **11a** and **11b** which could be separated for characterization, each as a single oxime *E*-geometric isomer, in high total yield. It should be noted that the C-16 mixture obtained in the conjugate addition reaction is of no consequence since it is subsequently corrected (*vide infra*).

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

To continue the synthesis, the oxime moiety of the mixture of indole ester adducts **11a** and **11b** was first protected as the TBS ether **12** (Scheme 2). At this stage, the α-ketoester **12** was deoxygenated via a modification of the method of Hlasta, et al.[9] Thus, the ketone was first reduced to the alcohol which was then converted to the corresponding acetate, followed by catalytic hydrogenation using Pd/C in *t*-butanol/triethylamine to afford a mixture of diastereomeric diesters **13** and **14** which were easily separated by column chromatography.[10]

Since it was later found that these two diastereomeric C-15/16 systems behave differently during the key Romo cyclization (*vide infra*), isomer **13** was epimerized cleanly to **14** in 70% isolated yield by treatment with potassium hexamethyldisilazide, followed by quenching with aqueous ammonium chloride. The indole nitrogen of **14** was then protected with a Cbz group to afford derivative **15** whose structure was established by X-ray analysis, confirming both the C-15/16 relative stereochemistry and the *O*-silyloxime *E*-geometry.[11] At this point, *O*-silyloxime **15** was converted to oxime **16** with TBAF, followed by acidic cleavage to give the corresponding ketone **17**.[12]

Initial attempts to convert the trimethylsilylethyl ester **17** to the corresponding carboxylic acid with fluoride sources failed,[6] but this transformation could be performed with trifluoroacetic acid in methylene chloride 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, a Romo formal ketene/ketone-[2+2]-intramolecular cycloaddition to generate the requisite fused β-lactone *cis*-2-azadecalin system.

Therefore, treatment of the keto acid **18** with 2-bromo-*N*-propylpyridinium triflate, 4-pyrrolidinopyridine (PPY) and Hunig's base in CH_2Cl_2 containing 1.2 equivalents of acetic acid to avoid epimerization of the C-16 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 NMR ratio) in high yield.[5b] Interestingly, when the Romo cyclization was conducted on the C-16 ester epimer of keto acid **18** prepared from intermediate **13**, the major product was the undesired *trans*-2-azadecalin.

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

Since it was observed that the hydroxymethyl group of **23** tends to be lost under a variety of conditions via 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**, that was converted to iodo alcohol **27** via 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:*t*-butanol cleanly led to the desired methyl compound **28**.[17] The *N*-tosyl protecting group of intermediate **28** was cleaved using magnesium metal turnings in methanol under sonication to afford piperidine **29** in good yield.[18] Once, again the structure and stereochemistry of this intermediate were confirmed by 2D NMR analysis (see Supporting Information). Finally, removal of the TBS protecting group with HCl in methanol/chloroform afforded racemic alstilobanine A (**3**), isolated as its hydrochloride salt, having proton and carbon NMR spectra as reported for the natural alkaloid.[3,19]

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 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]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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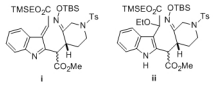
[10]. This transformation presumably occurs via an azafulvene intermediate **i** derived from the indole. Evidence for this supposition is that if the hydrogenation is conducted in ethanol rather than *t*-butanol, a significant amount of product **ii** results where the acetate group is replaced by ethoxyl via interception of azafulvene **i** by the solvent. This compound is resistant to further catalytic reduction.[6]



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[20]. Although alkaloids **1** and **2** in principle could be prepared via removal of the lactone oxygen of intermediate **24**, to date we have been unable to execute this transformation. Researchis continuing on solving this problem and/or finding another approach to angustilodine and alstilobanine E.

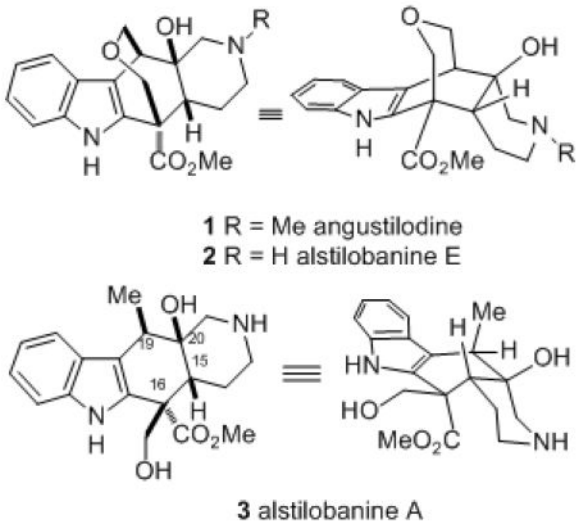
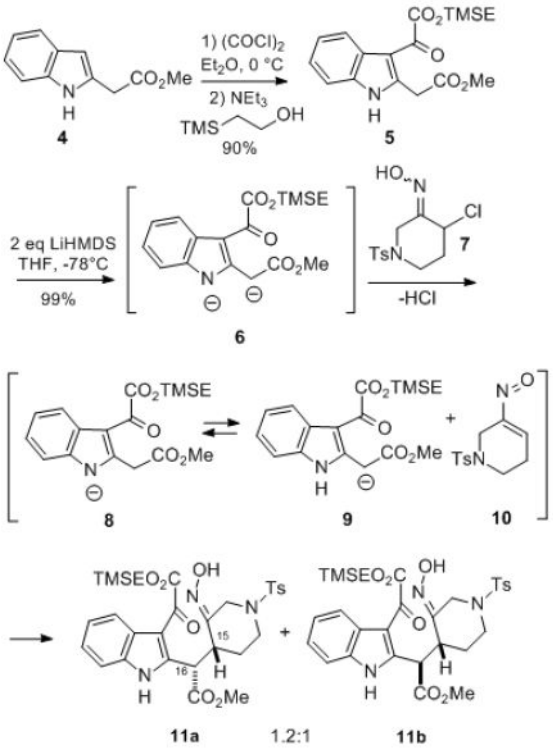
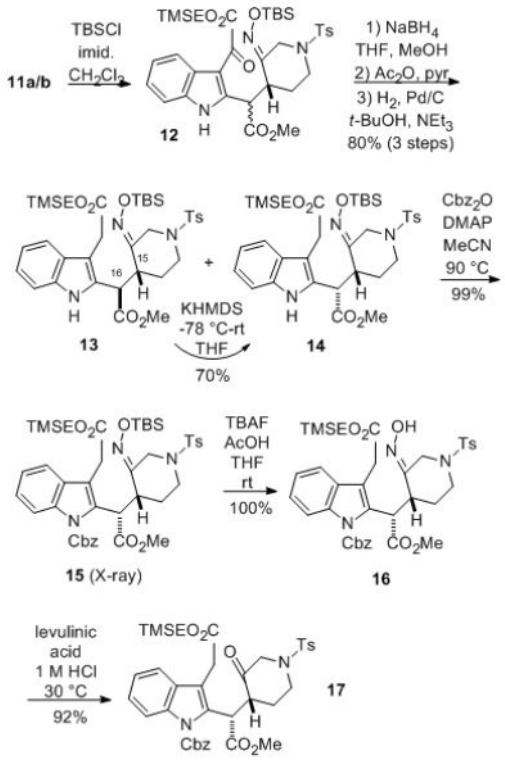


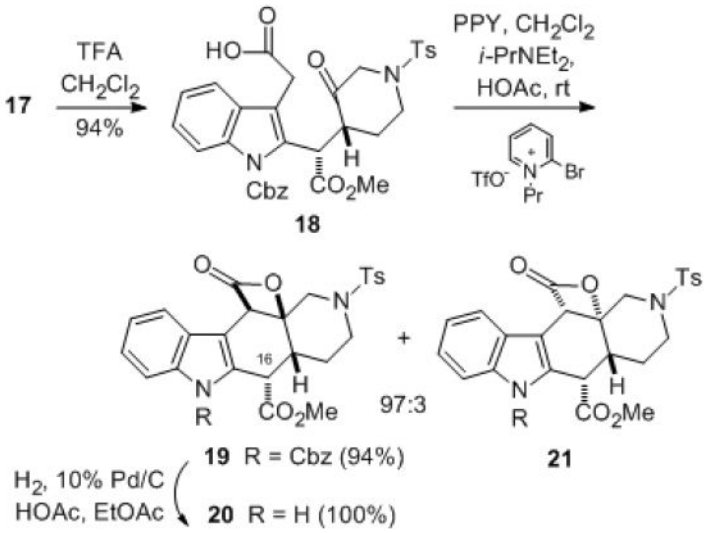
Figure 1.
Structures of the alstilobanine alkaloids.



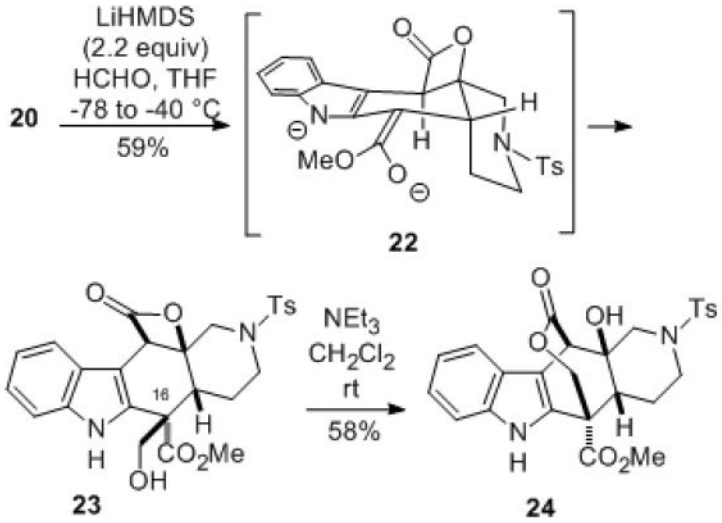
Scheme 1.
Nitrosoalkene conjugate addition.



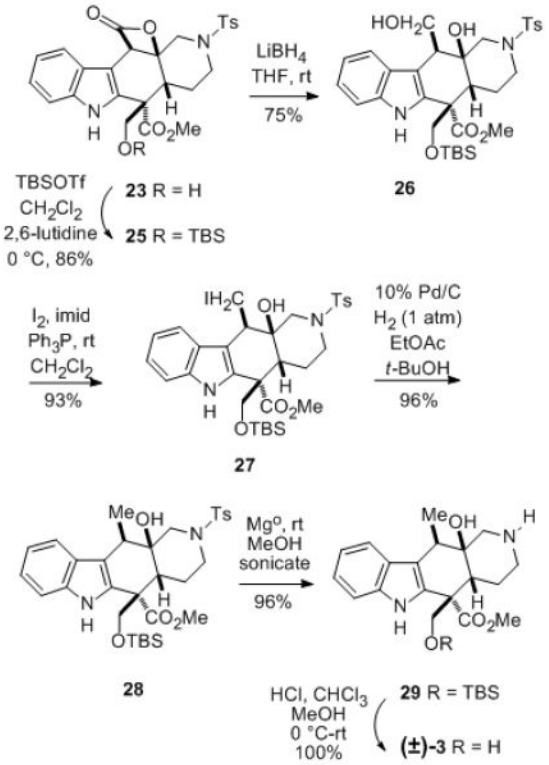
Scheme 2.
Preparation of Intermediate **17**



Scheme 3.
Romo cyclization of keto acid **18** to pentacyclic β-lactone **19**



Scheme 4.
Stereoselective C-16 hydroxymethylation



Scheme 5.
Completion of the synthesis of (±) alstilobanine A (**3**).