Organic LETTERS

Letter

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Synthetic Study toward the Misassigned (±)-Tronoharine

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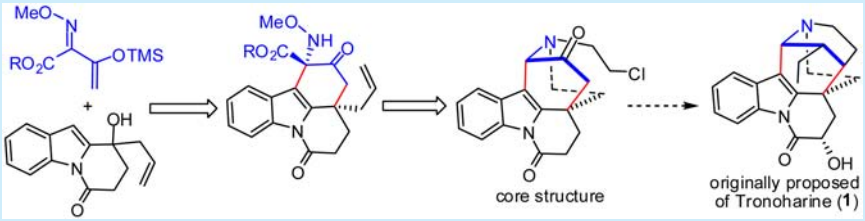
Supporting Information



ABSTRACT: The synthesis of a pentacyclic indole compound corresponding to the core structure of the misassigned indole alkaloid, tronoharine (**1**), is presented. The key reactions were a formal [3 + 3] cycloaddition of an indol-2-yl carbinol with an azadiene for the construction of the 6/5/6/6 tetracyclic system containing an all-carbon quaternary center and an intramolecular substitution reaction of an amine and a triflate for the creation of the bridged azepine ring. In addition, some other interesting transformations discovered during the synthetic studies are also discussed.

Tronoharine (Figure 1) was isolated from the stem-bark of a Malayan *Tabernaemontana* by Kam in 1999.[1] Original identification proposed that the structure of the indole alkaloid features the presence of a formidably strained 6/5/6/6/7/6 hexacycle with a cage-like architecture, and five stereocenters, one of which is an all-carbon quaternary center at the C-3 position (**1**). The biological activity of this molecule has not been evaluated due to the limited natural supply. Surprisingly, despite the intriguing structure, no synthetic effort has been directed at this novel natural product over the past 15 years.

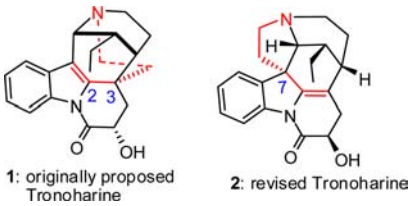


Figure 1. Originally proposed (**1**) and revised (**2**) structure of tronoharine.

As a result of our experiences in the synthesis of the polycyclic indole alkaloid, mersicarpine,[2] we initiated a study toward the synthesis of **1**. After extensive investigations of several different strategies, we have established an efficient pathway for construction of the 6/5/6/6/7 pentacyclic core of **1**. However, during the course of our efforts toward the installation of the last six-membered ring, we noted in a very recent report by the same group[3] the structure of tronoharine was corrected to **2**, in which the quaternary carbon is located at C-7 and the double bond is shifted to between C-2 and C-3. Due to the large structural revision, we have had to devise a new pathway for accessing **2**. However, the chemistries involved in our efforts toward the synthesis of the originally proposed **1** are instructive for the rapid construction of strained polycyclic indole frameworks since such structural motifs are frequently encountered in complex indole alkaloids. Herein, we present these results.

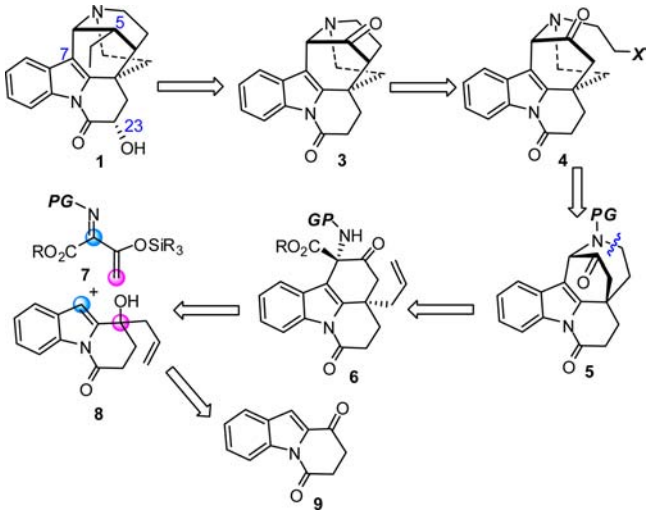
Our retrosynthetic analysis is illustrated in Scheme 1. The ethyl side chain at C-5 and the hydroxyl group at C-23 could be installed at a late stage from the hexacyclic **3**. Compound **3** was considered synthesizable through the intramolecular α-alkylation of pentacyclic ketone **4**, which was to be derived from the reductive alkylation of pentacyclic amine **5**. We planned to construct the bridged azepine in **5** through an intramolecular reaction by manipulating the olefin and amine functionalities in tetracyclic intermediate **6**. The key intermediate **6** was to be constructed through a formal [3 + 3] cycloaddition of azadiene **7** and indol-2-yl carbinol **8** developed previously by us.[4] This protocol carries with it the advantage of rapidly installing the quaternary carbon center as well as the requisite functionalities in a single transformation. Finally, the indol-2-yl carbinol **8** could be synthesized via the allylation of known ketone **9**.

We started our synthesis from the indole-lactam ketone **9** (Scheme 2), which could be prepared easily from commercially available indole and succinic anhydride via a two-step procedure.[2] Initial trials for the allylation of **9** with allylmagnesium bromide afforded the indol-2-yl carbinol **8** in poor yield (<30%). A complex mixture was obtained under various conditions presumably due to the labile nature of the

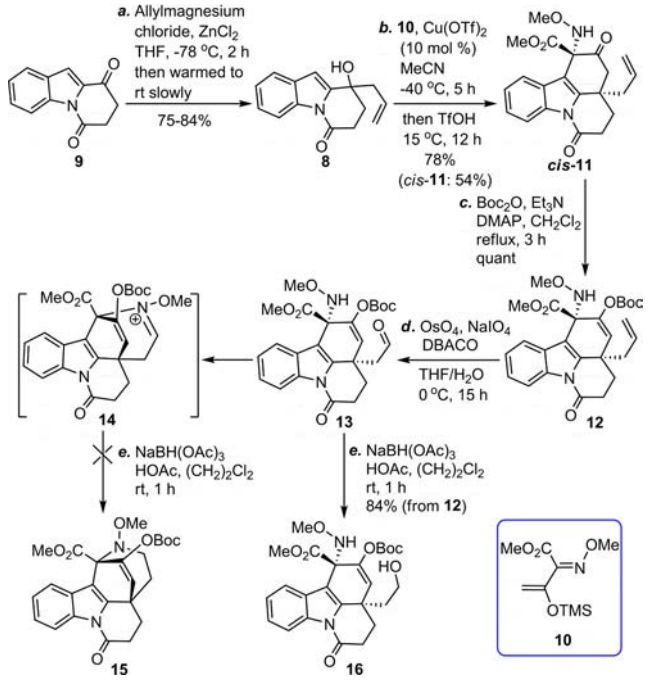
Received: December 27, 2014
Published: January 20, 2015

DOI: 10.1021/ol503734x
Org. Lett. 2015, 17, 720−723

Scheme 1. Retrosynthetic Analysis of Originally Proposed Tronoharine (1)



Scheme 2. Synthesis of Tetracyclic Intermediate 16

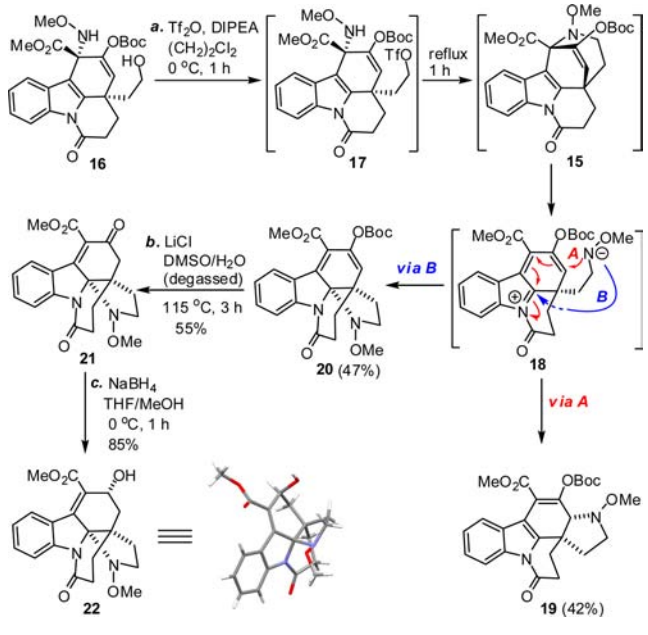


indole lactam moiety as observed by Kerr in the synthesis of mersicarpine.[5] However, these side reactions could be effectively suppressed with the presence of $ZnCl_2$ as reported by Ishihara.[6] The desired addition product **8** could be obtained in 75−84% yield on a multigram scale. Next, we tried the formal [3 + 3] cycloaddition of **8** with the azadiene **10**.[7] We found that, under our standard conditions established previously[4] [$Hf(OTf)_4$ (5 mol %) in MeCN at −40 °C; then TfOH (1.5 equiv) at 15 °C], the annulation product **11** was obtained in low yield (29%) and moderate *cis*/*trans* selectivity (ca. 3:1 by ^1H NMR analysis). The dehydrated product of **8** was observed as the major side product. This may be attributed to the relatively electron-withdrawing nature of the allyl group in **8** as compared to the alkyl group in our previously investigated carbinol substrates. After an extensive reoptimization of the conditions, the annulation could be induced to proceed smoothly to give **11** in 78% yield when $Cu(OTf)_2$ was used as a Lewis acid catalyst instead of $Hf(OTf)_4$. The *cis*-**11** (NHOMe vs allyl) could be obtained in 54% isolated yield. The reaction could be performed on a gram scale reliably.

With the key intermediate *cis*-**11** in hand, our efforts were focused on construction of the seven-membered azepine ring. Unfortunately, oxidation of the olefin in **11** to the corresponding aldehyde was extremely troublesome. Ozonolysis resulted in an intractable mixture. Alternatively, the combination use of OsO_4 with NMO, $NaIO_4$, or HIO_4 afforded a highly polar mixture. Prior literature[8] suggested that the unsuccessful oxidation with OsO_4 was possibly due to the influence of the carbonyl, methoxylamino, and ester groups in **11**. Namely, any two of these three vicinal groups may form a five- or six-membered chelate with the osmium catalyst and, ultimately, lead to the undesired oxidation. As a solution, we planned to mask the amino functionality in **11** with a bulky Boc group prior to olefin oxidation. However, the anticipated reaction did not proceed. Instead, **11** was converted into the enol carbonate **12** in almost quantitative yield. The poor reactivity of the methoxylamine is presumably due to the hindrance of the quaternary carbon adjacent to the amino group. Although the desired transformation did not proceed, we were pleased to find that carbonate **12** could be oxidized very smoothly to afford the aldehyde **13**. Attempted intramolecular azepine formation from **13** via the iminium intermediate **14** by reductive *N*-alkylation did not provide any cyclized product **15** but afforded cleanly the alcohol **16** following treatment with various reductants. This observation implied that generation of iminium **14** is difficult probably due to the highly strained ring system.

Thus, we turned to an intramolecular condensation or substitution reaction that manipulated the amino and hydroxyl functionalities in **16** for constructing the bridged azepine **15** (Scheme 3). Here, a somewhat challenging issue is to find a set of appropriate conditions that could activate selectively the hydroxyl group while keeping the amino functionality intact. Extensive trials showed that the expected transformation was

Scheme 3. Attempted Synthesis of Bridged Azepine 15



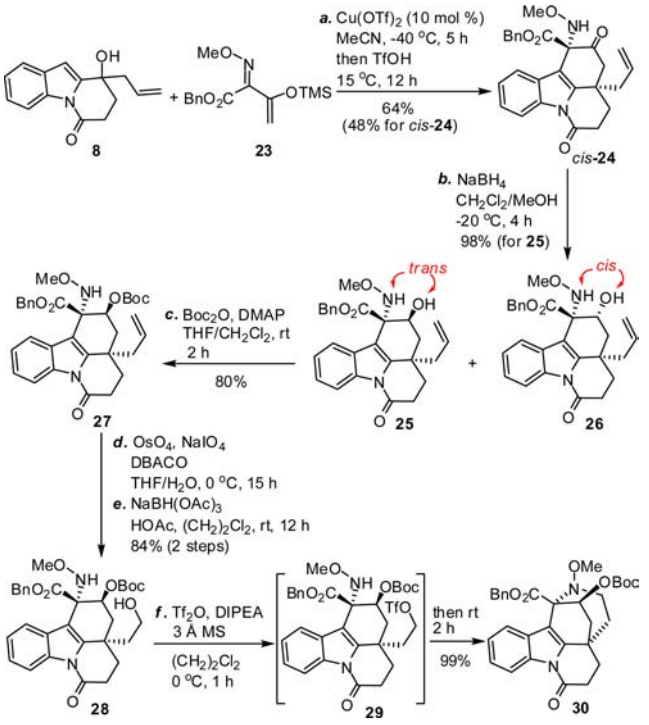
DOI: 10.1021/ol503734x
Org. Lett. 2015, 17, 720−723

complicated under Mitsunobu conditions and was sluggish when the alcohol was converted into a mesylate or halogen. However, the use of Tf_2O was efficient for promoting the reaction, affording a couple of products in ca. 1:1 ratio in high overall yield (ca. 90%). HRMS showed that the two products exhibited an identical mass. A careful analysis by the use of a combination of multi-NMR spectroscopies (see Supporting Information) suggested that one of the products was **19** generated via a Gramine-type fragmentation through path **A** from intermediate **18**. Unfortunately, we were unable to confirm confidently the structure of the other product based on the acquired NMR data. However, after the removal of the Boc in the unconfirmed compound under the effect of LiCl,[9] followed by reduction of the ketone to alcohol, we could obtain a single crystal of the derivative. Single X-ray diffraction combined with the multi-NMR spectroscopic analysis revealed that the structure of the derived compound was aminal **22**.[10] The results demonstrated that the structure of the other product was aminal **20**, a compound also formed via a Gramine-type fragmentation through path **B**.

These results indicate that the indole azepine **15** was prone to fragmentation by the cleavage of the C−N bond. Although in our later study, we could obtain sufficiently pure **15** in higher than 50% yield by performing the reaction at ca. 30 °C associated with the presence of 3 Å molecular sieves (MS), this allowed us to acquire NMR data for comparison with those of **19** and **20**. Further transformation of **15** was rather troublesome due to its lability. Based on a similar fragmentation observed in the synthesis of condylcarpine[11] by Overman and actinophyllic acid[12] by Taniguchi and Martin, the lability of **15** could result from the electron-withdrawing nature of ester and enolate groups as well as the strained ring system.

Thus, an alternative strategy was designed in which we planned to reduce the double bond of the enolate prior to construction of the bridged azepine ring. Accordingly, **24** was synthesized according to the same procedure for **11** from indol-2-yl carbinol **8** and azadiene **23** in 64% yield and a ca. 3:1 *cis*/*trans* ratio (Scheme 4). Here, the introduction of the benzyl ester group in **24** instead of the methyl ester in **11** should facilitate the late-stage removal of the ester group under mild conditions by hydrogenolysis. Reduction of ketone **24** with $NaBH_4$ at −10 °C gave **25** in 82% isolated yield whose MeONH vs OH was oriented in *trans*-form as determined by NOESY spectroscopy. The assignment of the other product was somewhat problematic due to contamination of a small amount of hard-to-separate **25** and the stereoisomers derived from *trans*-**24**. It was tentatively assigned as **26** (MeONH vs OH was *cis*) based on the crude ^1H NMR and mass analysis. In our later study, we found that **25** could be obtained in 98% yield (based on *cis*-**24** in a mixture of *cis*- and *trans*-**24**) with only a trace amount of **26** when the reaction was carried out at a temperature lower than −20 °C. The significantly improved stereoselectivity avoided much tedious work aimed at separating the stereoisomers produced from **26** in the downstream transformations. The preferred *trans*-selectivity can be attributed to a concerted coordination effect of the MeONH to the $NaBH_4$ reductant. Next, protection of the hydroxyl group of **25** by Boc-anhydride afforded **27** in 80% yield. Olefin oxidation of **27** followed by reduction of the resulting aldehyde proceeded smoothly to give alcohol **28** in 84% yield over two steps. Finally, Tf_2O mediated intramolecular substitution via the transient triflate **29** delivered the bridged azepine **30** in almost quantitative yield. Notably, the

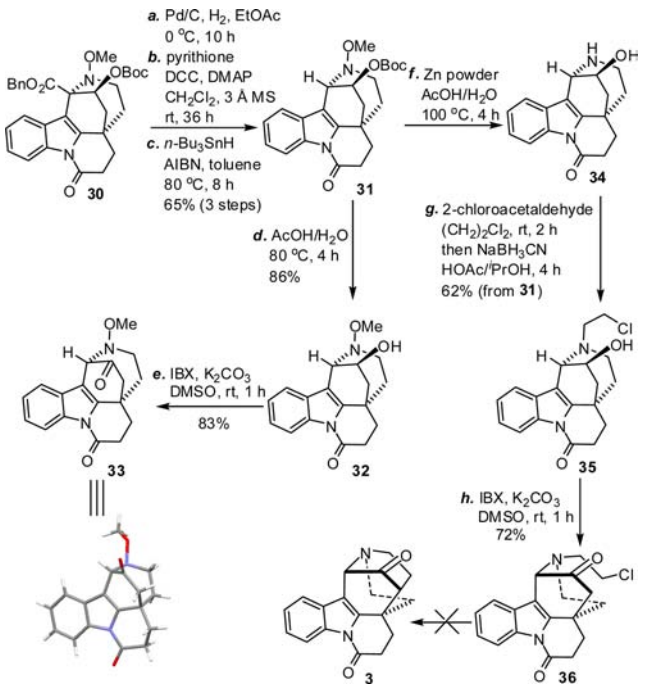
Scheme 4. Synthesis of Bridged Azepine 30



reaction could be safely performed on a gram scale. As expected, this compound exhibited fairly good stability which facilitated the following operation.

Having established an efficient pathway for construction of the 6/5/6/6/7 pentacyclic **30**, we progressed toward construction of the last six-membered ring. Toward this end, the bridgehead benzyl ester in **30** was removed by hydrogenolysis and Barton radical decarboxylation,[13] to afford **31** in 65% yield (Scheme 5). Removal of the Boc group in **31** was

Scheme 5. Attempted Synthesis of Hexacyclic 3



DOI: 10.1021/ol503734x
Org. Lett. 2015, 17, 720−723

effected by AcOH at 80 °C to give the alcohol **32** in 86% yield. The structure was confirmed by NMR analysis and X-ray single crystal diffraction of the oxidized ketone **33**. The cleavage of the N−O bond to remove the OMe of **32** was somewhat problematic due to the relatively labile nature of indole-lactam and the bridgehead amine moieties. However, an extensive screening of various conditions revealed that Zn/AcOH[14] was an effective combination which allowed for spontaneous cleavage of the Boc and OMe in **31** at 100 °C, affording cleanly the aminoalcohol **34**. Without purification, **34** was reductively *N*-alkylated with chloroacetaldehyde by adapting a known procedure[12] to furnish the chloroethyl substituent. The resulting *tertiary* amine **35** thus obtained was oxidized to ketone **36**. Finally, the base-mediated intramolecular α-alkylation of **36** aimed at construction of the last six-membered ring in **3** was examined. Unfortunately, our preliminary investigation showed that the transformation was ineffective under an array of ordinary conditions.[15] Here, although other methods remain to be investigated, we decided to terminate our efforts because, at this stage, Kam and co-workers declared that their originally proposed tronoharine **1** was misassigned and corrected the final structure to **2**[3] (Figure 1). Our attention was shifted to the synthesis of the revised structure.

As a summary, through a study toward the synthesis of the misassigned tronoharine **1**, we have established an efficient pathway for the rapid construction of highly fused 6/5/6/6/7 pentacyclic indole derivatives from the readily available indol-2-yl carbinol and azadiene. By modification of our previously established formal [3 + 3] cycloaddition, the tetracyclic system containing the quaternary carbon center was furnished via a one-pot procedure. Moreover, the protocol allowed for the spontaneous incorporation of various functional groups such as olefin, amine, and ketone functionalities, which facilitated construction of the more challenging bridged azepine very efficiently through intramolecular substitution. In addition, our observation of some unexpected transformations such as the Gramine-type fragmentation was also interesting. Finally, although our synthesis of the target molecule was not completed, the chemistries established in this study were appealing and may find practical applications or provide important hints for the efficient construction of polycyclic indole frameworks since such motifs are present in numerous indole-based complex natural products.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, ^{1}H NMR, ^{13}C NMR, and HRMS data, the copies of 1D and 2D NMR spectra, and the X-ray data for **22** and **33** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NSFC (21272225), and State Key Laboratory of Fine Chemicals (KF 1201), is acknowledged.

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(15) A free combination of K_2CO_3, Cs_2CO_3, ^{t}BuONa, ^{t}BuOLi, NaHMDS, DIPEA, or DBU base with various solvents such as DMF, THF, MeCN, 1,4-dioxane, and 2-methoxyethyl ether were examined at room temperature or by heating at 80−100 °C.

DOI: 10.1021/ol503734x
Org. Lett. 2015, 17, 720−723