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An attempted oxidative coupling approach to the scholarinine A framework

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Abstract

In this manuscript, an oxidative carbon–carbon bond forming reaction to construct the framework of alkaloids such as scholarinine A is explored using a constrained substrate. Instead of the desired carbon–carbon bond formation between an indole C3 position and a malonate group, a competing carbon–nitrogen bond between the malonate and indole C3 position was observed to form. This work adds to the growing body of substrates for oxidative carbon–carbon bond formation and importantly, demonstrates that these reactions are challenging for some conformationally constrained substrates.

Keywords

Total synthesis; Scholarinine A; Oxidative coupling; Alkaloids' akuammiline; Indole

Introduction

As a part of a collaboration with Corteva Agriscience to identify small molecules with novel modes of action (MoA) for insecticidal activity, we targeted the natural product scholarinine A (**1**, Fig. 1) for total synthesis in order to obtain reasonable amounts of material as well as gain access to structurally related compounds. Scholarinine A (**1**) is an example of an akuammiline alkaloid and was first isolated in 2020 by Zhan and coworkers from the evergreen tropical tree *Alstonia scholaris* [1]. It was reported to inhibit *T*-type $Ca_v3.1$ calcium channels (IC_{50} = 4.28 μM) by binding to an allosteric site of the channel. Molecules that modulate calcium channels have been identified as potentially effective sources of

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Kerry E. Jones: Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fernando Martínez Lara:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Blane P. Zavesky:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Richmond Sarpong:** Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.154980.

new insecticidals [2,3]. Modulators of voltage-gated calcium channels such as $Ca_v3.1$ could also provide a starting point for addressing channelopathies such as absence seizures [4]. Several biosynthetic proposals have been advanced to explain the genesis of scholarinine A (**1**) either from picrinine (**3**) [1], or, according to Lim and coworkers' hypothesis, from strictamine (**4**) [5]. Biosynthetically, the akuammilines, of which **4** is representative, are also structurally related to pleiocarpamine (**6**) [6].

Among the akuammilines, a distinguishing structural feature of scholarinine A (**1**) is the presence of an imidazolidine unit in the 6/5/6/5/5/6 framework. The unusual grouping of nitrogen atoms in the polycyclic framework of **1** is likely to inspire many different synthetic approaches to the natural product. However, despite its interesting biological activity and novel structure, reports on syntheses of **1** are yet to appear. However, several natural products with closely related structures including aspidophylline A (**2**) and alstobrogaline (**5**) have been synthesized [7–10].

In our approach to **1** (outlined in retrosynthetic form in Scheme 1A), we sought to utilize an oxidative coupling reaction to convert **8** to **7** en route to **1**. This plan was inspired by Baran and coworkers' report in 2004 of an intermolecular oxidative coupling of indole and carvone derivatives to give products such as **10** [11], which was subsequently exploited in the syntheses of several natural products by the group. More recently, Ma and coworkers have expanded on the intramolecular version of this reaction, which has yielded an expedient synthesis of aspidophylline A (**2**) [10] among other indole alkaloids [12].

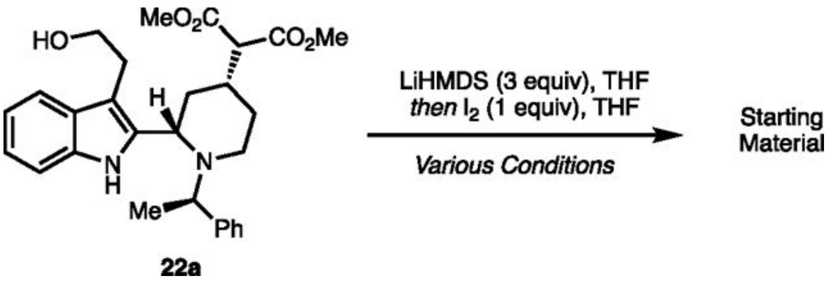
Our planned synthesis of scholarinine A (**1**) sought to incorporate opportunities for divergence to access related structures for bioactivity studies, for example, by varying the substituents on the F ring of **1** (see Fig. 1 for ring labeling) through derivatization of the piperidine unit at a late stage. To test the feasibility of the planned sequence and with an eye toward the syntheses of the related furanoindoline natural products such as aspidophylline A (**2**), we first focused on tryptophol malonate **13** (Scheme 2), which could arise from **14**. In turn, **14** would be prepared from indole *C*2-carbaldehyde derivative **15**, phenethylamine (**16**) and the Kitahara–Danishefsky diene (**17**) [13]. We commenced our studies with the preparation of vinylogous amide **14**, which was synthesized following the precedent of Kuethe and coworkers [14] from protected tryptophol aldehyde **15** [15,16] as outlined in Scheme 2. The two-step sequence from **15** involved condensation with phenethylamine (**16**) using $MgSO_4$ as a dessicant, followed by [4 + 2] cycloaddition of the resulting imine with the Kitahara–Danishefsky diene (in the presence of $ZnCl_2$) to afford ene-piperidone **14** following workup. Reasonable yields of **14** were only realized upon modification of the published protocol by adding the diene sequentially in two portions.

A two-stage reduction of ene-piperidone **14** (Scheme 3) to yield **20** was achieved using $NaBH_4$. Presumably, an iminium ion is formed under the reaction conditions which is readily reduced by the $NaBH_4$ followed by reduction of the ketone group to afford alcohol **20**. A modified Appel reaction [17] at this stage (to install a secondary iodide) followed by displacement with dimethyl malonate gave **21**. Removal of the sulfonyl and TBS groups was accomplished by treatment of **21** with Na•naphthalenide and TBAF, respectively, to give tryptophol derivative **22a**. The structure of **22a** was unambiguously confirmed by X-ray crystallographic analysis of a single crystal of the corresponding ferrocenoyl ester (see **23**).

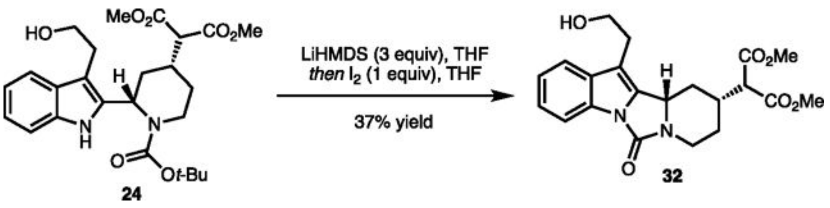
We also prepared derivatives **24** and **25** (Scheme 4A) through removal of the phenethyl group using hydrogenolysis conditions followed by derivatization of the secondary amine to give the Boc and Piv derivatives. We theorized that **24** and **25** were likely to adopt the conformations shown in Scheme 4B to minimize pseudo-$A_{1,3}$ like interactions between the *N*-substituent and indole group at *C*2, placing the malonyl group and indole C3 positions in closer proximity for bond formation as compared to **22a/b**, where all the groups would be pseudo-equatorial in the major conformer.

With tryptophol malonates **22a/b**, **24** and **25** in hand, the stage was set to test the key intramolecular oxidative coupling step. In line with the precedent of Baran,[11] and Ma,[12] we anticipated that a trianion (see **27**, Scheme 5), or possibly a ligated dianion, could form upon treatment of malonyl tryptophol **26** with base. At that stage, a single-electron oxidation would yield radical dianion **28**, which, following bond formation, would give **29**. A subsequent single-electron oxidation of **29** would yield imine **30**, which upon reaction with the alkoxide would give **31.**

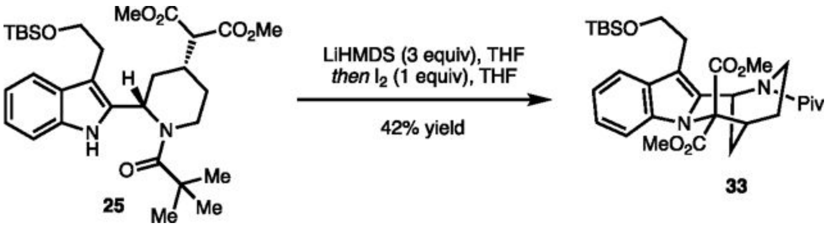
We have examined the oxidative C—C and C—O bond-forming cascade for the three different substrates as illustrated in Equations 1–3 below. With *N*-phenethylamine substrate **22a**, only starting material was observed under a variety of temperatures for trianion generation (−40 °C to 0 °C) and the ensuing oxidation upon addition of iodine (0 °C to 23 °C). The lack of productive reactivity for **22a** is likely attributable to an unproductive, major, conformer of the trianion that reflects the conformer for **22a** shown in Scheme 4B. On the other hand, treatment of *N*-Boc tryptophol malonate substrate **24** with the established conditions for the cascade simply resulted in addition of the indolide nitrogen into the carbamoyl group to give tetracycle **32** in 37 % yield following workup. Using pivalamide **25** (Eq. 3), which was anticipated to minimize the competing addition of the indolide into the piperidine nitrogen substituent as well as minimize the possible sites for deprotonation, we observed only the formation of **33**, which results from oxidative C—N bond formation. An analogous competing C—N bond formation was previously observed by Ma and coworkers en route to their synthesis of aspidophylline A [10] as well as by Poupon, Vincent, and Evanno in their preparation of 16-*epi*-pleiocarpamaine; see **6**, Fig. 1, for numbering of pleiocarpamine [18].



Eq. 1

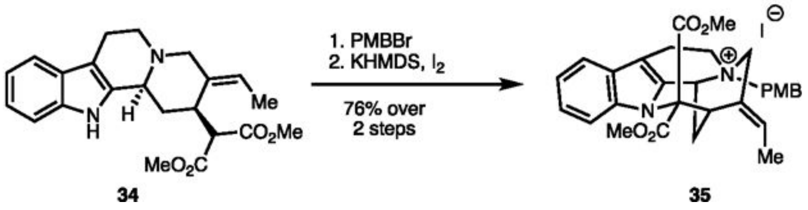


Eq. 2



Eq. 3

Poupon, Vincent, Evanno (Ref. 18, 2019)



Eq. 4

In conclusion, we report an attempted synthesis of the core framework of the akuammiline alkaloid scholarinine A (**1**) using an intramolecular oxidative indole-enolate C—C bond forming reaction. Tryptophol malonate substrates that were investigated in the key C—C bond forming reaction were synthesized by relying on a known procedure reported by Keuthe and coworkers. In the best case using a pivaloylated, TBS-protected tryptophol malonate substrate, instead of the desired C—C bond formation, an oxidative C—N bond formation was observed, which leads to a portion of the framework of the natural product pleiocarpamine (**6**). While the approach to scholarinine A (**1**) and related structures described here was ultimately unsuccessful, this work highlights the challenges of extrapolating the oxidative C—C bond forming reactions of indoles and enolates to conformationally constrained substrates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data availability

All data are contained in the Supplementary Material

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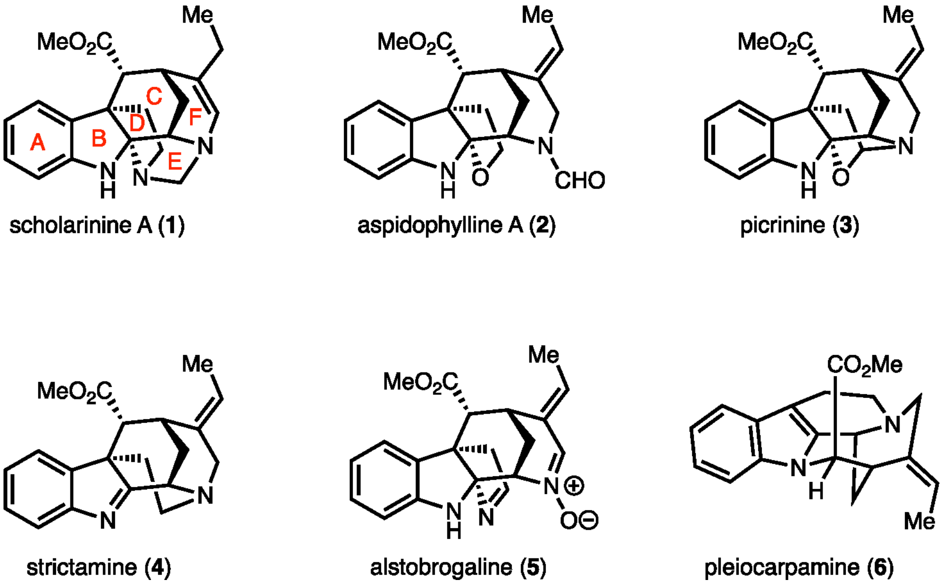
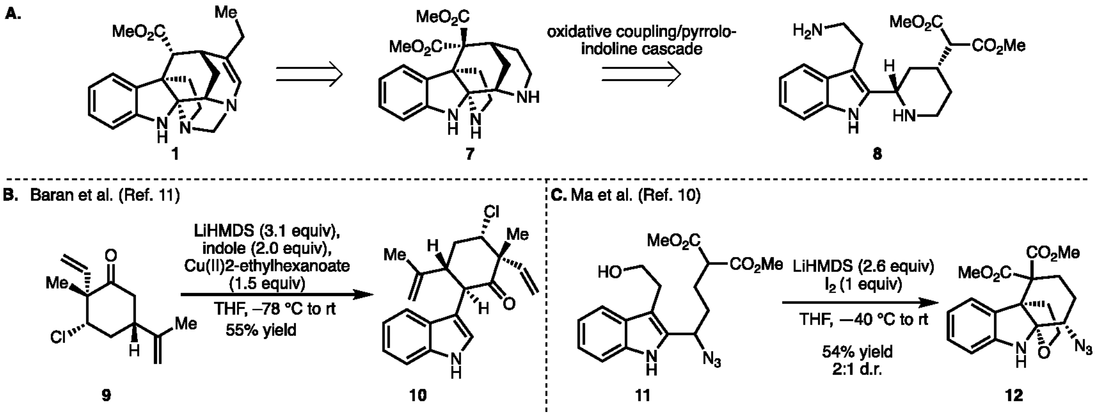


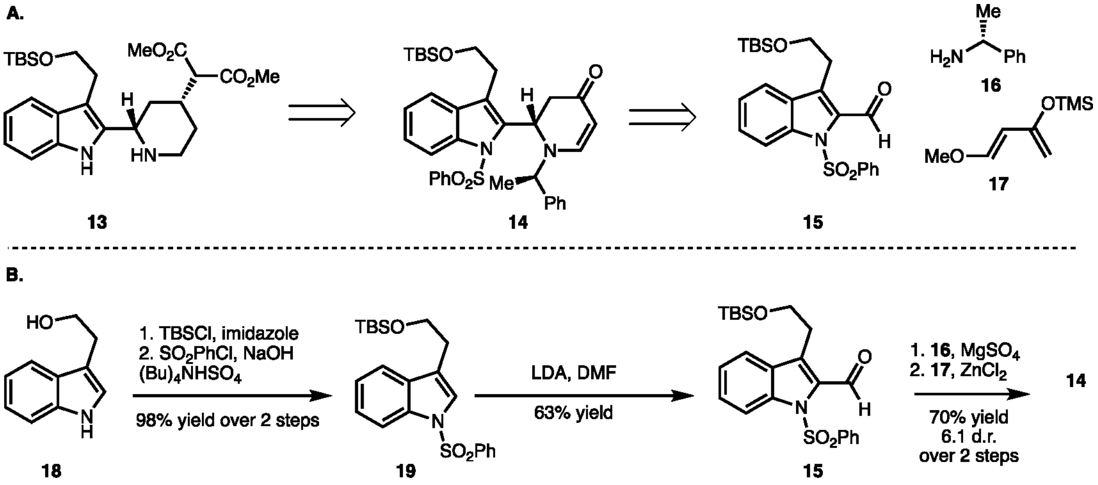
Fig. 1.

Selected akuammiline alkaloids and the structurally related **6**.



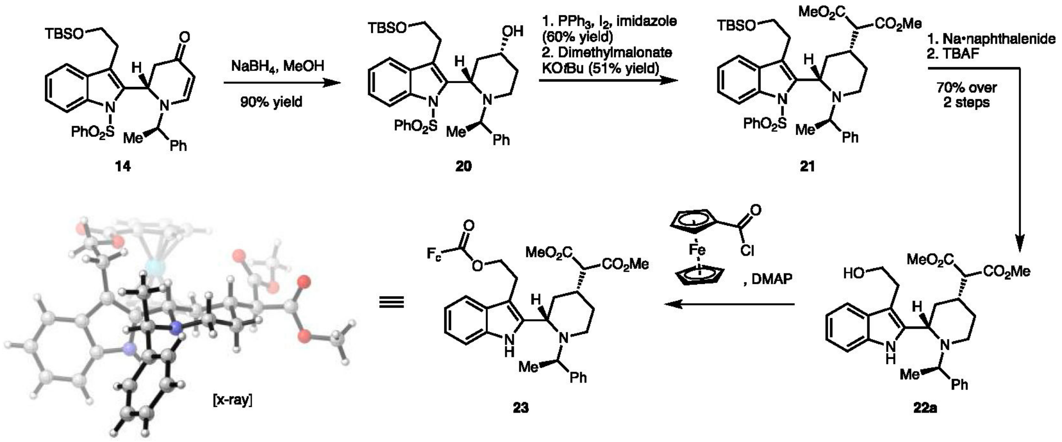
Scheme 1.

(A) Retrosynthesis plan to scholarinine A (1). (B) Precedent for oxidative enolate-indole oxidative C—C bond formation from Baran (Ref. 11) and Ma (Ref. 10).



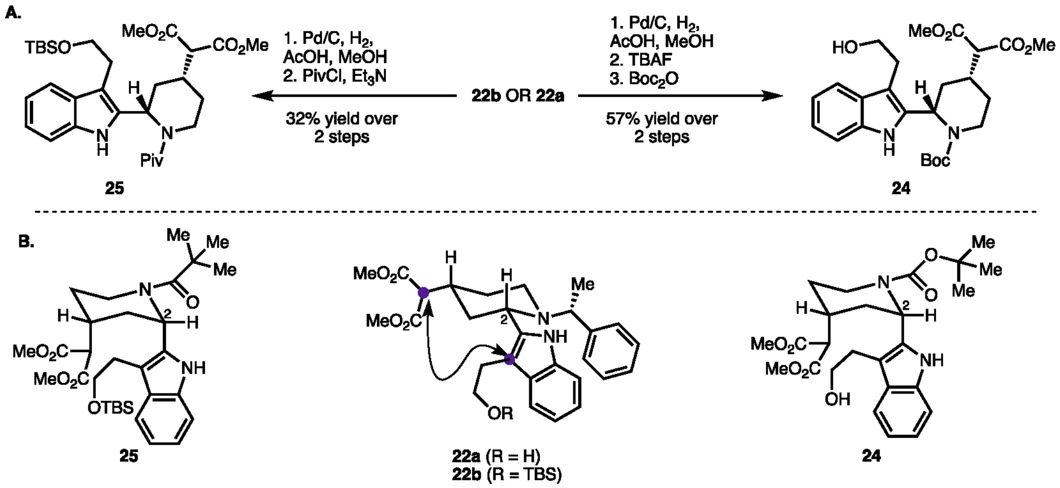
Scheme 2.

(A) Retrosynthesis plan for the preparation of tryptophol-based substrate **13**. (B) Synthesis of ene-piperidone **14**.



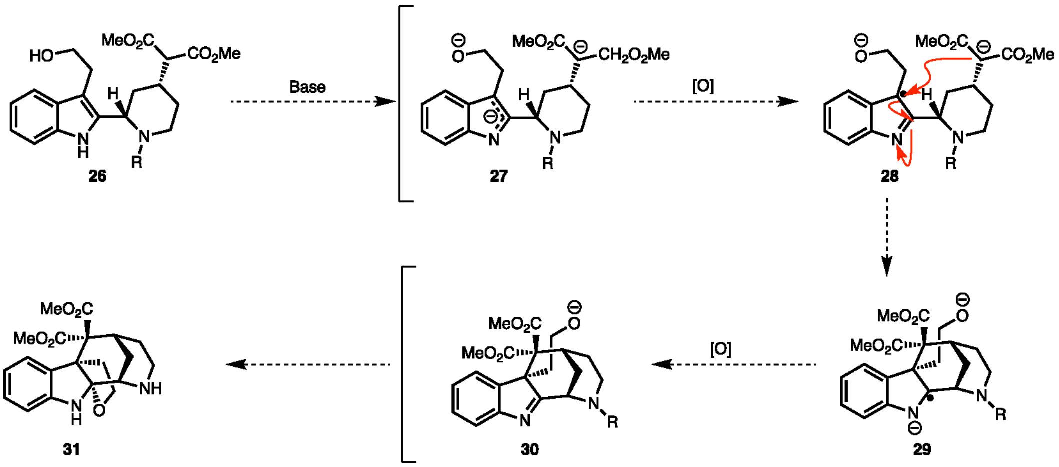
Scheme 3.

Synthesis of *N*-phenethyl tryptophol malonate substrate **22a**.



Scheme 4.

(A) Syntheses of tryptophol-derived substrates **24** and **25**. (B) Depiction of the anticipated major conformers of **22a/b**, **24**, and **25**.



Scheme 5.

Proposed mechanism for the oxidative C—C bond formation/furanoindoline formation.