OL Organic Letters

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Letter

Pyrroloiminoquinone Alkaloids: Total Synthesis of Makaluvamines A and K

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Cite This: *Org. Lett.* 2023, 25, 1868−1871

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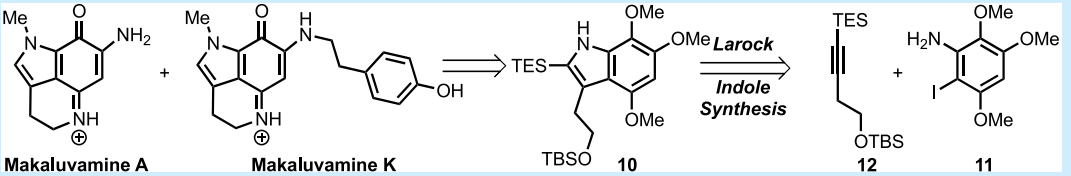


ABSTRACT: Herein, an efficient, scalable, and concise approach to an advanced pyrroloiminoquinone synthetic intermediate (**6b**) by way of a Larock indole synthesis is reported. The synthetic utility of this intermediate is demonstrated by its ready conversion to makaluvamines A (**1**) and K (**4**).

Numerous natural products containing pyrroloiminoquinone core structures have been isolated from marine sponges, and several of these, due to their potent biological activities and unique structural features, have captured the attention of the synthetic community.[1] In particular, the makaluvamines, isolated from Fijian sponges of the genus *Zyzzya*, were found to possess inhibitory activity toward topoisomerase II along with cytotoxic activity against HCT-116 human colon cancer cells.[2−4] Representative members of this family are shown in Figure 1.

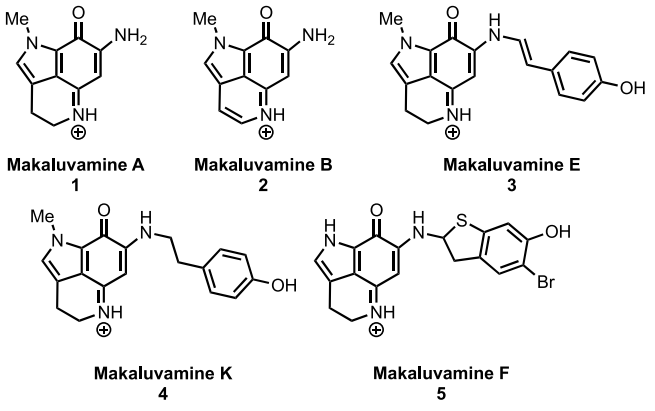
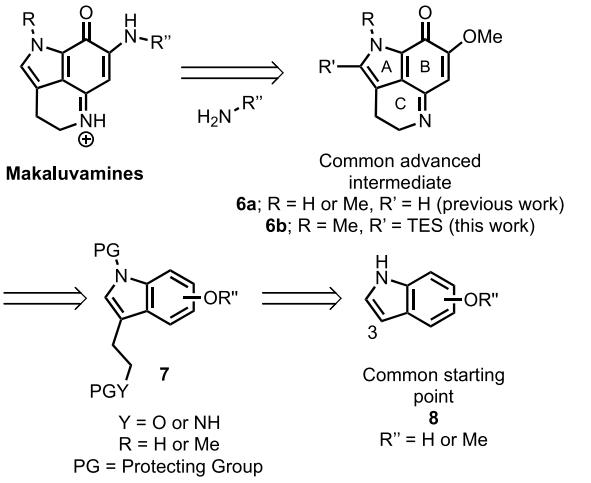


Figure 1. Members of the makaluvamine family.

To date, the synthetic approaches toward pyrroloiminioquinones have, in most cases, proceeded via aminolysis of a corresponding vinylogous imidate (e.g., **6a**, Scheme 1) with an appropriate amine.[5−10] The imidate has generally been accessed from the corresponding tryptamine (**7**, Y = NH) or tryptophol **7** (Y = O) by oxidation to an indoloquinone followed by cyclodehydration to form the C-ring. The requisite

Scheme 1. Common Synthetic Approach to Makaluvamines



3-substituted indoles (**7**) are typically prepared from the indole precursors (**8**) by regioselective electrophilic aromatic substitution at C3.

Although the previous synthetic approaches have proven effective for preparing an array of makaluvamines, they have typically required several linear steps to install the proper alkyl chain at the C3 position of the indole and oxidation pattern on the aromatic ring.[7−10] The shortest synthesis, reported to date,

Received: February 3, 2023
Published: March 13, 2023

https://doi.org/10.1021/acs.orglett.3c00350
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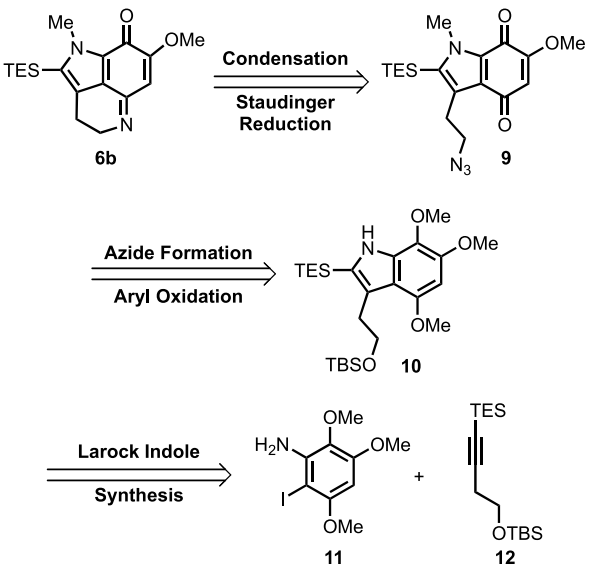
of pyrroloiminoquinones was reported by Ishibashi and coworkers starting from commercially available 6-methoxy indole (1 g/$170).[7] Although this synthetic route required only nine steps to prepare makaluvamine A and K, we were reluctant to utilize this approach due to the cost of the starting material. Therefore, as part of a program targeting the preparation of pyrroloiminoquinone-containing alkaloids of greater structural complexity, we set out to investigate alternative strategies to access **6**. Herein, we report the highly efficient preparation of a versatile pyrroloiminoquinone intermediate (**6b**) and demonstrate its synthetic utility via the total synthesis of makaluvamines A (**1**) and K (**4**).

Our approach to common advanced intermediate **6b** is illustrated retrosynthetically in Scheme 2. As illustrated, we

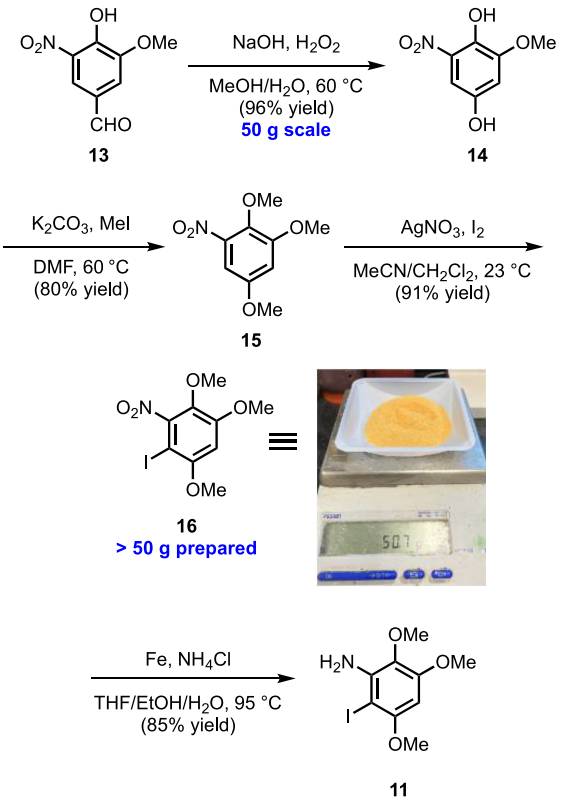
Scheme 2. Retrosynthetic Analysis of Common Advanced Intermediate 6b



envisioned accessing **6b** from azide **9** utilizing a Staudinger reduction to generate a transient primary amine, which we hoped would undergo spontaneous cyclodehydration to form the tricyclic pyrroloiminoquinone skeleton. The azide **9** would, in turn, be prepared from indole **10** by oxidation of the trimethoxy arene to the indoloquinone and subsequent azidation. We envisioned assembling indole **10**, with the desired functionality at the C3 position and oxidation pattern about the aromatic ring, in a convergent fashion by combining iodoaniline **11** and silylated internal alkyne **12** via Larock's indole synthesis. Although the Larock approach has been utilized in the synthesis of several tryptophan analogues and natural products, to the best of our knowledge it has not been employed in the preparation of pyrroloiminoquinone alkaloids.[11−15] This was surprising given the flexibility and efficiency this approach provides in accessing an array of C3-substituted indoles.

In accord with our retrosynthetic analysis, we initially turned our attention to the synthesis of iodoaniline **11**. As shown in Scheme 3, treatment of commercially available 5-nitrovanillin (**13**) under Dakin oxidation conditions provided hydroquinone **14** in excellent yield.[16] Subsequent methylation of **14** furnished **15** which, upon silver mediated iodination, produced **16** as the sole regioisomer.[17] Overall, this three-step sequence proved highly efficient and was readily performed on

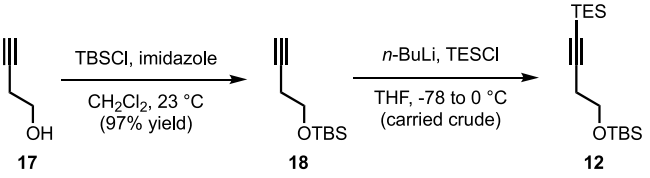
Scheme 3. Synthesis of Iodoaniline 11



multigram scale in a single pass. Reduction of **16** proceeded smoothly with iron powder in a mildly acidic medium to provide the desired aniline **11** in 85% yield.[17] Notably, this final reduction was the only step requiring chromatographic purification. All the previous intermediates were isolated and carried forward after simple aqueous workup and/or filtration.

Having developed an efficient, scalable, and operationally simple sequence to **11**, we focused our attention on the preparation of alkyne **12**. As shown in Scheme 4, **12** was

Scheme 4. Synthesis of Silylated Internal Alkyne 12

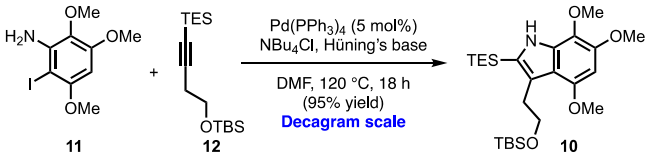


prepared from commercially available 3-butyn-1-ol (**17**) via a two-step sequence. In the event, TBS-protection of the primary alcohol of **17** was found to provide a near-quantitative yield of TBS ether **18**, which upon conversion to the lithium acetylide with *n*-BuLi, followed by quenching with TESCl, afforded **12** in sufficient purity to be used directly in the forthcoming Larock sequence.[18]

With both coupling partners in hand, we directed our attention to constructing indole **10** under Larock conditions (Scheme 5). Although a survey of the literature revealed numerous applications of the Larock chemistry, there were relatively few examples utilizing similar electron-rich anilines.[19,20] Thus, our expectations were tempered as we speculated that aniline **11** may perform poorly due to sluggish oxidative addition of the active Pd catalyst to the aryl iodide.

https://doi.org/10.1021/acs.orglett.3c00350
Org. Lett. 2023, 25, 1868−1871

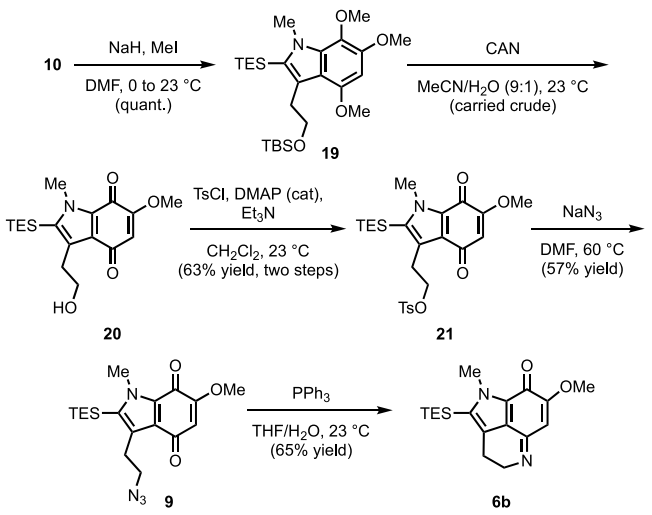
Scheme 5. Larock Indole Synthesis



In the event, we were delighted to observe that the coupling of **11** and **12**, under standard Larock conditions, proceeds smoothly to give the desired indole (**10**) in excellent yield.[19,21] Moreover, in contrast to previous reports employing electron-rich anilines, we observed that lowering the catalyst loading from 20 to 5 mol % Pd and shortening the reaction time from 24 to 18 h did not adversely affect the yield.[19] Additionally, no loss in efficiency was observed when the reaction was conducted on decagram scale.

Having accessed indole **10**, which contains all the requisite carbon atoms, the stage was set for accessing common intermediate **6b** via a series of functional group interconversions. As illustrated in Scheme 6, these efforts began with

Scheme 6. Completion of Common Advanced Intermediate 6b

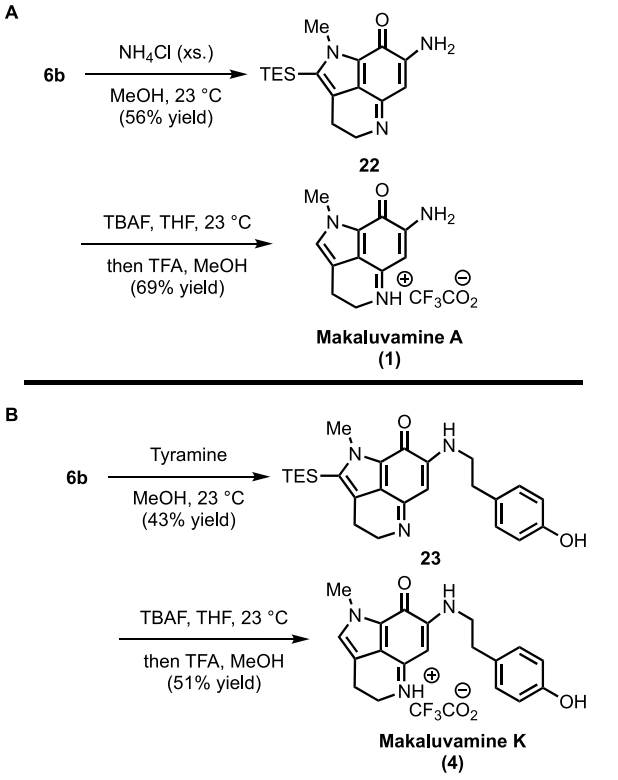


methylation of indole **10** under standard conditions to give **19** in quantitative yield.[11] Subsequent treatment of **19** with CAN induced not only oxidative demethylation of the trimethoxy arene to the corresponding methoxyquinone but also desilylation of the primary TBS-ether to deliver indoloquinone **20**.[22] Conversion of alcohol **20** to the corresponding tosylate (**21**) followed by exposure to sodium azide provided azidoindoloquinone **9**.

Much to our delight, subjection of **9** to Staudinger reduction conditions led directly to the desired vinylogous imidate **6b**.[22] This was an interesting outcome, as several literature examples of similar cyclodehydrations were conducted under either acidic or forcing conditions.[9,24−27,29]

With **6b** in hand, we turned our attention toward completing the synthesis of makaluvamines A (**1**) and K (**4**). As illustrated in Scheme 7A, aminolysis of **6b** with NH_4Cl furnished vinylogous amidine **22**. Gratifyingly, desilylation of **22** with TBAF, in contrast to **6b**, proceeded smoothly and subsequent acidification with TFA produced makaluvamine A (**1**) as a TFA salt.[2,28] A similar sequence (Scheme 7B), wherein NH_4Cl

Scheme 7. Total Synthesis of Makaluvamines A (1) and K (4)



is replaced with tyramine, was found to deliver the TFA salt of makaluvamine K (**4**).[8,30]

In conclusion, we have developed an efficient and scalable approach to access intermediate **6b** by way of the Larock indole synthesis. In addition, we have demonstrated the synthetic utility of this intermediate by advancing it to the tricyclic pyrroloiminoquinone natural products makaluvamines A (**1**) and K (**4**).

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00350.

Experimental procedures, compound characterization, and NMR spectra (PDF)

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https://doi.org/10.1021/acs.orglett.3c00350
Org. Lett. 2023, 25, 1868−1871

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from Baylor University, the Welch Foundation (Chair, AA-006), the Cancer Prevention Research Institute of Texas (CPRIT, R1309), the National Science Foundation (NSF, CHE-1764240), and the National Institute of General Medical Sciences of the National Institutes of Health (NIGMS-NIH, R01GM136759).

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