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Total synthesis of (±)-3-demethoxyerythratidinone *via* Tf₂O-promoted cascade reaction of enaminone†

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The tetracyclic rings with chiral quaternary center represent a formidable synthetic challenge for *Erythrina* alkaloids. We present a 6-step synthesis of the *Erythrina* alkaloid 3-demethoxyerythratidinone with a 16% overall yield. Our synthesis highlights a cascade reaction initiated by Tf₂O-induced activation of an enaminone substrate, yielding an iminium species and an enol triflate, followed by a Pictet–Spengler reaction. This method efficiently constructs the tetracyclic core skeleton, featuring an N-substituted quaternary center. It exhibits versatility across diverse (hetero)arenes and enaminone structures, providing a general strategy for the rapid synthesis of fused or spiro ring systems including the core structure of homoerythrina alkaloids.

Erythrina and homoerythrina alkaloids represent a diverse class of natural products possessing a broad range of biological activities including hypotensive, sedative, hypnotic, and CNS effects.[1] Structurally, these alkaloids are characterized by a tetracyclic ring system comprising a hydroindole moiety with an N-substituted quaternary stereocenter (Fig. 1a). As a representative member of the *Erythrina* alkaloids, 3-demethoxy-erythratidinone (**3**) frequently serves as a model compound for innovative synthetic strategies aimed at constructing complex tetracyclic ring systems.[2]

Enaminones are versatile intermediates in chemical synthesis,[3] and functionalization of enaminones *via* Tf₂O-induced activation to form iminiums **10** followed by nucleophilic attacks at C3 has been extensively studied (Fig. 1c).[4] However, unlike the use of Tf₂O for amide activation (Fig. 1b),[5] wherein *in situ* generated iminiums **7** are intra- and intermolecularly trapped to construct pivotal building blocks and

intricate ring systems, the trapping of Tf₂O-induced enaminone-derived iminiums at C1 remains less developed.[4a–c] Furthermore, to the best of our knowledge, there is no report on the Tf₂O-induced activation of enaminones followed by a Pictet–Spengler cascade reaction for construction of complex ring systems (Fig. 1c).

Our sustained interest in synthesizing natural products featuring hydroindole skeletons *via* an indole-hydrogenation strategy[6] led us to envisage construction of the tetracyclic ring system of *Erythrina* alkaloids from amide **17a**, which encompassed the A, B, and D rings in **1** (Scheme 1). Commencing with the chemoselective hydrogenation of 4-hydroxyindole **14**,[6a] we obtained enaminone **15**, which, upon condensation with 2-(3,4-dimethoxyphenyl)acetic acid **16**, yielded **17a**. We envisioned that the enaminone motif within **17a** could be activated by Tf₂O to give iminium **18**, which is further converted to the tetracyclic compound **19a** *via* an intramolecular Pictet–Spengler reaction. There are several salient features of this designed cascade reaction to be noted: (1) a tetracyclic ring system with an N-substituted quaternary center (C5) can be constructed in a single step; (2) the enol triflate can not only serve as versatile handles for further modification *via* transition metal-catalyzed cross-coupling reactions but also facilitate the construction of an alkene characteristic of *Erythrina* alkaloids that is hard to install regioselectively as demonstrated in previous studies;[6a,7] (3) variation of the enaminone, the arene ring, or the linker between them can lead to a variety of ring systems, for example, the core skeleton of homoerythrina alkaloids (**2**).

Herein, we describe the development of a cascade reaction leveraging Tf₂O-promoted activation of enaminones followed by intramolecular Pictet–Spengler reactions to construct complex ring systems and the successful application of this method to the total synthesis of the *Erythrina* alkaloid 3-demethoxyerythratidinone (**3**).

The investigation commenced by subjecting enaminone **17a** to Tf₂O (2.0 equiv.) in DCM (0.2 M) at room temperature for 24 h. Encouragingly, while residual **17a** remained, the isolated yield of the desired product **19a** reached 62% (Table 1, entry 1).

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Fig. 1 Representative *Erythrina* and homoerythrina alkaloids and our reaction design.

Scheme 1 Our strategy for construction of the tetracyclic core skeleton.

Table 1 Optimization of the reaction conditions[a]

Entry	Solvent	T (°C)	Yield (%)[b]
1	DCM	25	62
2	DCM	35	73
3	DCM	45	67
4	1,2-DCE	35	62
5	Toluene	70	54
6	CH$_3$CN	35	50
7	CH$_3$NO$_2$	35	19
8	DCM	35	40[c]
9	DCM	35	25[d]
10	DCM	35	<10[e]
11	DCM	−78–35	66
12	DCM	35	66[f]

[a] Reaction conditions: **17a** (0.2 mmol, 1.0 equiv.), Tf$_2$O (2.0 equiv.), DCM (0.2 M), sealed tube, r.t. for 0.5 h then 35 °C for 24 h. [b] Isolated yields. [c] 2-Chloropyridine (1.05 equiv.) was added. [d] *N,N*-Diisopropylethylamine (1.05 equiv.) was added. [e] 2,6-Di-*tert*-butyl pyridine (1.05 equiv.) was added. [f] Gram-scale reaction.

to a gram-scale did not significantly impact the yield (entry 12). Notably, attempts to employ Comins' reagent, *N*-phenyl-bis(trifluoromethanesulfonimide), trifluoroacetic anhydride, or acetic anhydride in place of Tf$_2$O did not yield corresponding products.

With the optimized reaction conditions established (Table 1, entry 2), we proceeded to investigate the substrate scope of this cascade reaction (Fig. 2). Arene substrates bearing electron-donating groups exhibited notable compatibility (**19a–19c**), whereas those with electron-withdrawing groups, such as Br and I, demonstrated limited suitability. And a higher reaction temperature was required for less electron-rich arenes (**19c**). Moreover, the reaction displayed compatibility with various electron-rich heteroarenes (**19d–19g**). Employing a substrate containing an N-Me-protected indole ring required an initial stirring at −78 °C for 1 h followed by stirring at −20 °C for an additional 24 h to achieve an improved yield of **19f**. We speculated that the enaminone could be activated by Tf$_2$O at −78 °C and the subsequent Pictet–Spengler reaction took place at −20 °C to give **19f**. If the substrate was initially treated with Tf$_2$O at a relatively high temperature, the electron-rich indole ring with high nucleophilicity may interrupt the enaminone activation process thus leading to undesired results.

Our pursuit of synthesizing indole alkaloids led us to synthesize a diverse array of substrates featuring indole rings with varied substitution patterns,[6] all yielding the desired products in moderate yields (**19h–19m**). To our delight, this method proved versatile not only for constructing six-membered rings as observed in **19a–19m** but also for synthesizing five (**19n**) and seven-membered (**19o**) rings. Notably, compound **19o** embodies the tetracyclic skeleton **2** characteristic of homoerythrina alkaloids. Furthermore, beyond enaminone

Raising the reaction temperature to 35 °C resulted in the complete consumption of **17a** and an increased yield of 73% (entry 2). However, further elevation of the temperature did not enhance the yield (entry 3). Alternative solvents explored instead of DCM did not give satisfactory results (entries 4–7). Unlike prior studies on Tf$_2$O-induced activation of amides and enones,[5a–d,8] the introduction of bases adversely affected the yield (entries 8–10). Additionally, subjecting **17a** to Tf$_2$O at −78 °C for 1 h followed by heating at 35 °C for 24 h did not increase the yield (entry 11). Remarkably, scaling the reaction
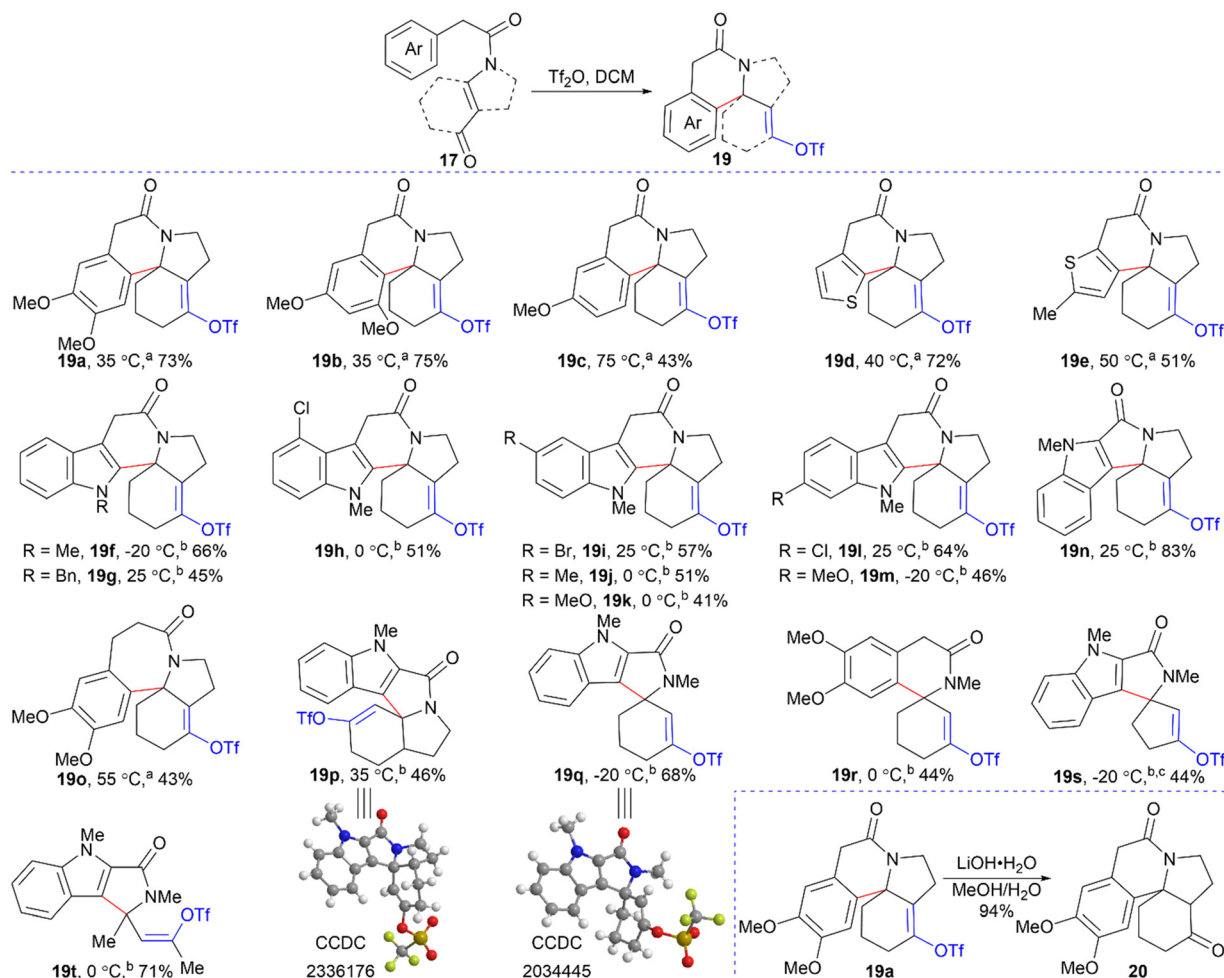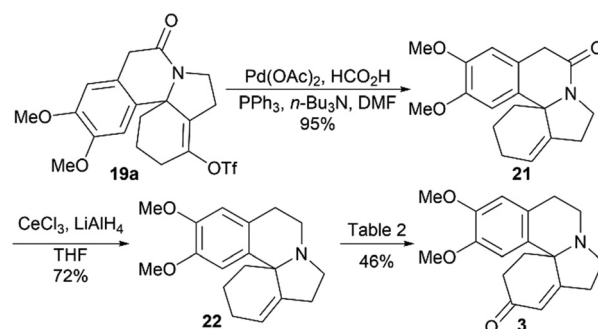
Fig. 2 Substrate scope. Isolated yields are given. [a] Reaction mixture in a sealed tube was stirred at r.t. for 0.5 h before being stirred at corresponding temperature for 24 h. [b] Reaction mixture in a sealed tube was stirred at -78 °C for 1 h before being stirred at corresponding temperature for 24 h. [c] The reaction time was 48 h.

15-derived compounds, substrates featuring diverse enaminone structures were amenable to this cascade reaction, yielding compounds **19p–19t**, with the structural elucidation of **19p** (CCDC 2336176) and **19q** (CCDC 2034445) being accomplished through X-ray diffraction analysis. Notably, compound **19a** could be smoothly hydrolysed to give compound **20**, with establishment of another stereocenter.[9]

To demonstrate the synthetic potential of this cascade reaction, we carried out the total synthesis of 3-demethoxy-erythratidinone (**3**). Removal of the OTf group in **19a** under palladium-catalyzed reductive conditions yielded **21** (Scheme 2).[10] Subsequent reduction of lactam **21** with LiAlH₄/CeCl₃ afforded **22**, a potential precursor for allylic oxidation to give **3**. However, SeO₂ mediated Riley oxidation selectively produced α-ketone lactam **23** (Table 2, entry 1), possibly arising from **22** through benzylic oxidation followed by further oxidation of the α methylene of the newly generated ketone. Palladium-catalyzed oxidation conditions gave unidentified mixtures (entry 2).[11] Copper-catalyzed oxidation conditions led to overoxidized product **24** (entry 3),[12] which holds promise
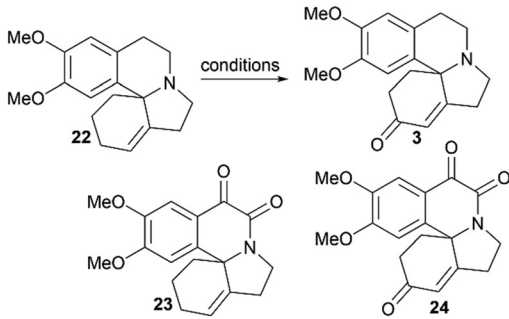
as an intermediate for synthesizing natural product 10,11-dioxoerythratidinone (**4**). Under the PDC/TBHP condition, both **23** and **24** were observed (entry 4).[13] Finally, employing the CrO₃/3,5-dimethylpyrazole oxidation condition at −20 °C yielded **3** (entry 5), whereas raising the temperature to room temperature furnished **24** (entry 6).[14] The spectroscopic data of

Scheme 2 Total synthesis of 3-demethoxyerythratidinone **3**.

Table 2 Optimization of the allylic oxidation conditions

Entry	Conditions	Products[a]
1	SeO$_2$, 100 °C	**23**
2	Pd/C, TBHP, 0 °C	—[b]
3	CuI/TBHP, r.t. or 50 °C	**24**
4	PDC/TBHP, 0 °C to r.t.	**23** and **24**
5	CrO$_3$/3,5-dimethylpyrazole, −20 °C	**3**
6	CrO$_3$/3,5-dimethylpyrazole, −20 °C–r.t.	**24**

[a] Major products detected by ^{1}H NMR and UPLC-MS are given.
[b] Reaction was messy. TBHP, *tert*-butyl hydroperoxide; PDC, pyridinium dichromate.

3 were identical to the reported data.[2p] Therefore, we completed the total synthesis of **3** in 6 steps with an overall yield of 16% from commercially available 4-hydroxyindole.

In conclusion, we have developed a cascade reaction involving Tf$_2$O-promoted activation of enaminones followed by intramolecular trapping of the iminium intermediates with (hetero)arenes. Combinations of a wide range of enaminones and (hetero)arenes can lead to products with complex fused or spiro ring systems. This method was successfully applied to the total synthesis of the *Erythrina* alkaloid 3-demethoxyerythratidinone (**3**). Further applications of this method to the total synthesis of other natural products are currently being explored in our group.

Conflicts of interest

There are no conflicts to declare.

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