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Total syntheses of melinonine-E and strychnoxanthine: Evolution of the synthetic strategy enabled by novel method development

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Dedicated to Professor Léon Ghosez for his enormous contributions to the synthetic community.

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ABSTRACT

In this full account, the evolution of a synthetic strategy was detailed from a nitroso-ene cyclization to an aza-Wacker reaction for ring construction in the syntheses of melinonine-E and strychnoxanthine. The aza-Wacker cyclization to form the bridged ring was successfully developed and applied in the first asymmetric syntheses of melinonine-E and strychnoxanthine in 5–6 steps from a readily available chiral lactone. The proposed biogenesis of these two rare β-carbolinium alkaloids was revised based on their absolute configurations. Moreover, the substrate scope of the aza-Wacker cyclization demonstrated its potential for accessing various bridged ring skeletons. The mechanistic investigation established that the profound effect of the N-substituent on the amide was crucial to the success of the cyclization via the tunable amidopalladation pathway.

1. Introduction

Natural products have been utilized as folk medicines since ancient times for the treatment of many diseases. Traditional natural product chemistry has enabled various metabolites and their derivatives to enter the clinic use [1]. Many essential organic compounds have been used throughout human history and continue to influence society [2]. However, the challenges of limited natural resources as well as emerging drug resistance recall the sufficient supply of high valued materials, which continuously motivates synthetic chemists to develop novel approaches to meet the global demand [3]. Complex natural products in particular represent a driving force for innovation. For instance, the long-standing challenge of the construction of quaternary carbon stereocenters has attracted numerous attention for decades and is still an appealing subject [4]. On the other hand, devising an efficient syntheses of intriguing natural products as potential medicines forges the development of novel synthetic methods with modernized economic consideration [5]. Furthermore, explorations toward the broad utility of new synthetic transformations would strength the power of the chemical arsenal to access valuable chemical structures, which would greatly benefit the human society [6].

β-Carbolinium cations are a class of unique structures that display a variety of biological activities such as potent cholinesterase inhibition and protonophoric and chitinase inhibitory activities [7]. It was also reported that cryptolepine (**1**), matadine (**2**), and serpentine (**3**) could simulate the DNA cleavage by topoisomerase II as intercalating reagents, indicating their potential as candidates for antimalarial drug discovery (Fig. 1) [8,9].

The structurally related alkaloid, melinonline-E (**4**) was first disclosed in 1957 by Bächli et al. from the bark of *Strychnos melinoniana* Baillon (Loganiaceae) [10]. The chemical structure was revised in 1984 by Hesse et al. based on comprehensive spectral data, revealing an unprecedented pentacyclic monoterpene alkaloid, in which a β-carbolinium chromophore was fused with a 2-azabicyclo[3.3.1]nonane (morphan) skeleton [11]. Angenot et al. also reported a biogenetically related structure (with a C14-oxo moiety in the D ring), strychnoxanthine (**5**), from the bark of

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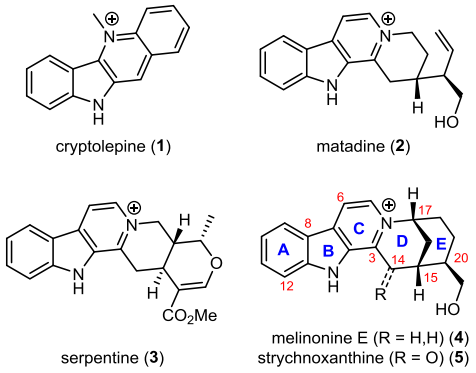
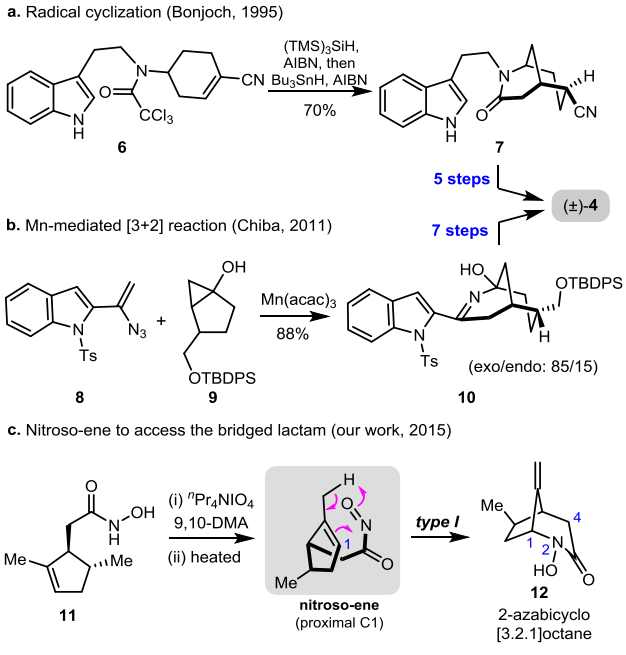


Fig. 1. Antimalarial β-carbolinium alkaloids.

Strychnos gossweileri Exell (Loganiaceae) [12]. It was also intriguing that strychnoxanthine was shown to have a moderate inhibitory activity against *Pkmodium fakiparum* (IC_{50} 8.4 μM) [8].

The unprecedented skeleton, as well as the interesting bioactivity rendered these alkaloids appealing synthetic targets. Two elegant strategies for the synthesis of melinonine-E have been reported by the Bonjoch and Chiba groups. While Bonjoch's strategy featured a radical cyclization, Chiba et al. used a Mn-mediated [3 + 2] reaction to construct the core morphan skeleton (Scheme 1, a and b) [13]. However, their routes only yielded the racemates of melinonine-E and strychnoxanthine and thus the absolute stereochemistries of these compounds remain elusive. As part of our study of the development of novel methods toward the efficient synthesis of bioactive alkaloids, we envisioned these alkaloids would be suitable synthetic targets because the nitroso-ene cyclization developed in our laboratory can effectively construct a bridged lactam ring (Scheme 1c) [14]. It is therefore reasonable to apply this ring-forming strategy to access the inherent morphan skeleton. In a recent preliminary communication [15], we reported



Scheme 1. (**a**) and (**b**): Different strategies toward syntheses of melinonine-E and strychnoxanthine; (**c**) Our previous nitroso-ene cyclization to access the bridged lactam.

the first asymmetric synthesis and absolute configuration determination of melinonine-E and strychnoxanthine. Herein, we detail the synthetic efforts on the initial nitroso-ene reaction (*detour*) and eventually led to the successful development of the aza-Wacker cyclization approach to access the bridged ring skeletons. The synthetic design behind the project reflects our principal interest of tackling unsolved problems.

2. Retro-synthesis analysis

Retrosynthetically, melinonine-E and strychnoxanthine could be derived from fragments **13** and **14** via an S_N2 coupling reaction, a Bischler-Napieralski reaction, and an oxidative aromatization (Scheme 2). To apply our recently developed ring-forming method via a nitroso-ene approach (Scheme 1c), we proposed that the bridged skeleton of the alkaloids could be constructed via an intramolecular nitroso-ene reaction [14]. It was conceivable that the ene reaction might also furnish the morphan structure, a common motif embedded in numerous biologically active alkaloids [16]. The key 6-*exo*-type cyclization would be relied on the proximal addition [17] of the alkene to the highly reactive acylnitroso moiety (highlighted in gray bracket) generated from hydroxamic acid **15** (readily prepared from *trans*-lactone **16**).

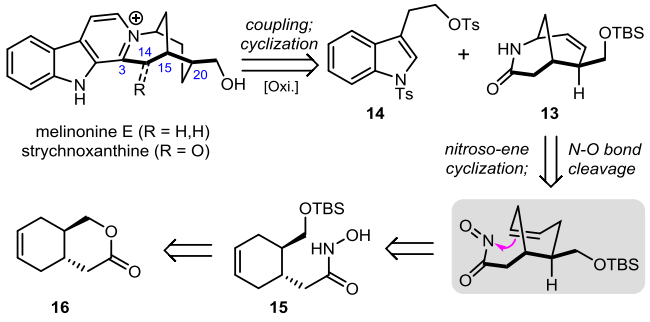
3. Attempt with the nitroso-ene cyclization

3.1. Gram-scale synthesis of lactone *16*

To quickly access hydroxamic acid **15** or its derivatives for the requisite nitroso-ene cyclization, a scalable synthesis of racemic **16** was undertaken (Scheme 3). Commercially available diester **17** was first reduced by $LiAlH_4$ on a decagram scale to afford diol **18** [18], from which mono-protection with a *tert*-butyldimethylsilyl (TBS) group and oxidation of the remaining primary alcohol by Dess-Martin periodinane (DMP) afforded aldehyde **19** in an overall yield of 77% [18]. The subsequent (*Z*)-selective Horner–Wadsworth–Emmons (HWE) olefination with Ando's phosphate (**22**) [19] and immediate lactonization by acidic work-up delivered lactone **20** in 76% yield. The following Michael addition of **20** with an allylic copper-lithium reagent gave lactone **21** in 90% in a ratio of 7:1 favoring the *trans*-configuration [20]. Ring closing metathesis (RCM) promoted by Grubbs-II catalyst resulted in *trans*-fused lactone **16** in 86% yield. The stereochemistry was further confirmed by X-ray analysis. The six-step gram-scale synthesis readily supplied a sufficient amount of lactone **16** and facilitated the key nitroso-ene reaction.

3.2. Results of the nitroso-ene reaction

With a sufficient amount of lactone **16** in hand, we then



Scheme 2. Our synthetic plan based on the nitroso-ene cyclization (an initial plan).