Total Synthesis

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Development of a Divergent Synthetic Route to the Erythrina Alkaloids: Asymmetric Syntheses of 8-Oxo-erythrinine, Crystamidine, 8-Oxo-erythraline, and Erythraline

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Dedicated to Professor Satoshi Ōmura on the occasion of his 80th birthday

Abstract: *A general synthetic methodology toward the erythrina alkaloids has been developed. Inspired by a proposed biosynthetic mechanism, the medium-sized chiral biaryl lactam was asymmetrically transformed into the common core A–D rings by a stereospecific singlet oxygen oxidation of the phenol moiety, followed by a transannular aza-Michael reaction to the dienone functionality. The late-stage manipulation of the oxidation and oxygenation states of the functional groups on the peripheral moieties enabled the flexible syntheses of the erythrina alkaloids.*

Decades of synthetic, biological, and medicinal research explorations have been devoted to the chemistry of the erythrina alkaloids. These alkaloids share a common central structure featuring diverse peripheral oxidation states, such as those present in the representative members **1**–**8**[1] (Figure 1). Curare-like paralyzing activity[2] has long been recognized as a prominent biological activity derived from antagonizing the nicotinic acetylcholine receptor (nAChR).[3] The erythrina alkaloid most commonly explored is dihydro-β-erythroidine[1a] (DHβE; **8**), bearing a lactonic D ring. This compound is commonly used in research as a moderately selective antagonist of nAChR.[4] An X-ray structural analysis of the complex formed between **8** and the acetylcholine binding protein (AChBP) suggested that the A,B ring moiety is important to the binding interaction, and the bulky C,D rings are important for site-specific repulsion.[5] These insights suggest that all the rings (A–D) are necessary for achieving the antagonist activity. Recent reports indicate that a variety of aromatic erythrina alkaloids display similar activities with different subtype selectivities.[6] A divergent synthetic approach to erythrina alkaloid analogues, having a variety of peripheral functional groups, would therefore enable the development of novel subtype-selective nAChR antagonists.[7]

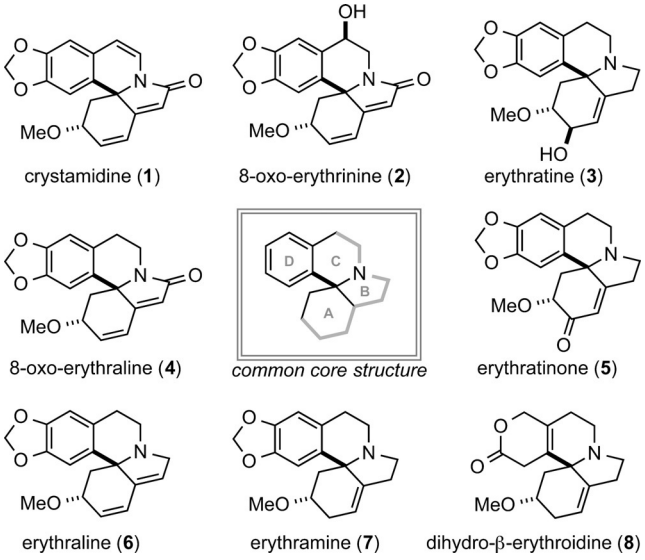

Figure 1. Representative erythrina alkaloids and their common core motif. Marked in gray is the periphery which can be differentially functionalized.

Since the first pioneering synthetic studies of the erythrina alkaloids by Belleau,[8] Mondon,[9] and Prelog et al.[10] more than half a century ago, extensive synthetic studies of these alkaloids have been pursued by numerous synthetic groups.[11,12] Among the approaches explored to date, asymmetric syntheses comprise only a small fraction.[13] This lack of asymmetric syntheses is probably due to the inherent difficulties associated with the asymmetric construction of the central tetrasubstituted stereocenter, especially with the most widely employed approach of sequential cyclizations. We thus focused upon the biosynthetic scheme of the erythrina alkaloid, as it was originally proposed by Barton[1c,14] and later revised by Zenk.[15] The nine-membered dibenz[*d*,*f*]azonine intermediate **9** undergoes an oxidation of the phenol moiety by a two-step SET mechanism (Scheme 1 a). The resulting planar cationic intermediate **10** is then subject to a transannulation from the amine to give **11**, equipped with a tetrasubstituted C5 center.[16] Subsequent adjustment of the oxidation state would give, for example, erythraline (**6**). Inspired by this biosynthetic sequence, we envisioned a novel asymmetric synthetic approach by using

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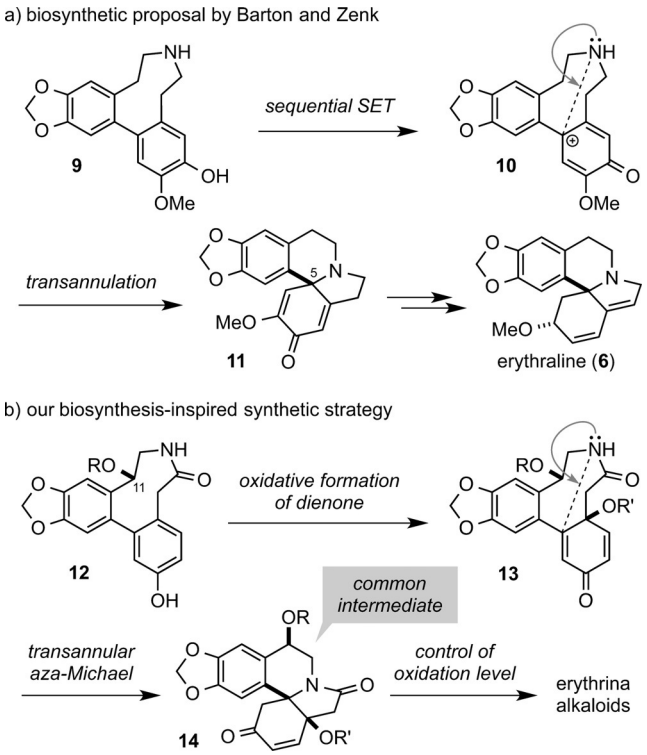
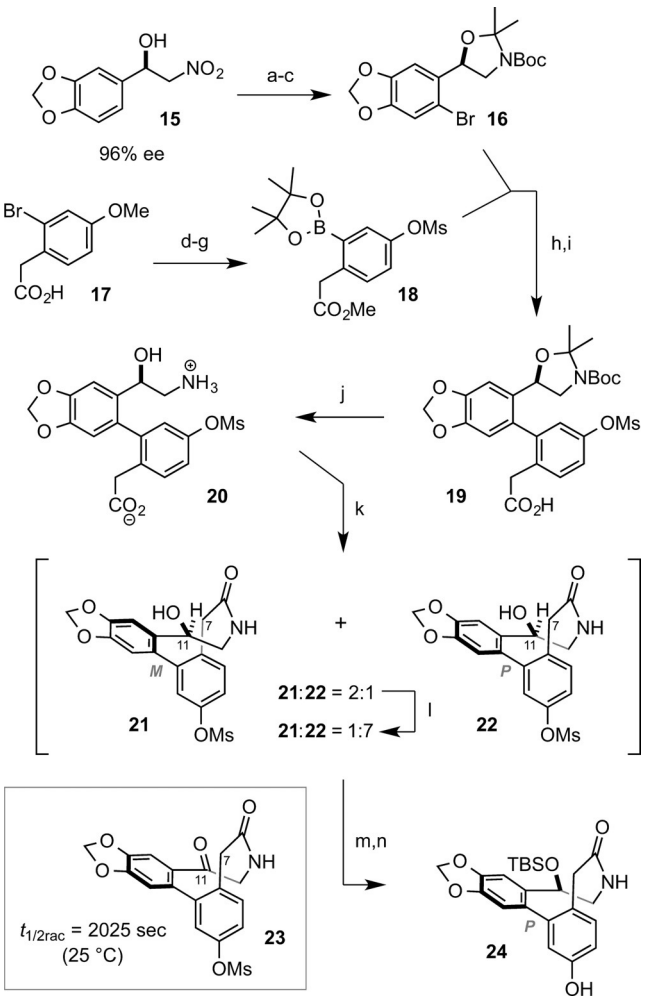


Scheme 1. Proposed biosynthesis and our synthetic strategy.

a nine-membered intermediate, which only Teetz and Ito employed in erythrina alkaloid syntheses.[17] Construction of the core structure of the tetracyclic moiety was deemed accessible through the diastereoselective oxidative transformation of **12** into the dienone **13** (Scheme 1 b). Subsequent intramolecular reaction would form the C5 tetrasubstituted chiral carbon center in **14**. The chirality at the C11 benzylic oxygen functionality was introduced with the expectation to bias the stereoinduction during the oxidation. A variety of erythrina alkaloids with a methylenedioxy moiety on the D ring could be synthetically derived from **14** through a combination of elimination, reduction, and oxidation of the oxygen functionalities. This two-phase synthetic strategy involving the initial construction of a common core structure and further functionalization of the late-stage pluripotent intermediate would facilitate the divergent syntheses of natural, as well as artificial derivatives of the erythrina alkaloids.[18]

Our synthesis commenced with the chiral nitro alcohol **15**, which was prepared by using the method reported by Gong and co-workers[19] (Scheme 2). A subsequent three-pot sequence afforded the bromoaryl compound **16** in 62% overall yield. The coupling partner, the aryl boronate **18**, was synthesized in four steps from the commercially available carboxylic acid **17**. These two substrates were subjected to Suzuki–Miyaura cross-coupling conditions to afford the biaryl intermediate **19**. Removal of the Boc and acetonide protecting groups gave the amino-acid intermediate **20**. Preferential formation of the nine-membered lactam over the eight-membered lactone was successfully achieved by means of DMT-MM[20] as the condensation reagent in methanol. Interestingly, the products proved to be a mixture of two



Scheme 2. Construction of the nine-membered lactam intermediate. Reagents and conditions: a) H_2, Pd/C, EtOH, RT; b) Boc_2O, CH_3CN, 0°C to RT; evap.; 2,2-dimethoxypropane, $BF_3{\cdot}OEt_2$, acetone, 0°C, 70% (2 steps); c) NBS, CH_3CN, 50°C, 88%; d) $SOCl_2$, CH_3OH, 0°C to RT, 95%; e) BBr_3, CH_2Cl_2, 0°C; f) MsCl, Et_3N, CH_2Cl_2, 0°C, 83% (2 steps); g) [$PdCl_2$(dppf)] (5 mol%), $(Bpin)_2$, KOAc, 1,4-dioxane, 80°C, 59%; h) [$PdCl_2$(dppf)] (10 mol%), Cs_2CO_3, DME, reflux; i) LiOH·H_2O, THF/H_2O (1:1), RT, 90% (2 steps); j) H_2O/HCO_2H (1:2), 0°C to RT; k) DMT-MM, CH_3OH (2.0 mM), RT, 62% (2 steps); l) 2-butanol, 90°C, 40 h; m) TBSCl, imidazole, $Cl(CH_2)_2Cl$, 40°C, 54% (2 steps); n) KOH, CH_3OH, 50°C, 91%. Boc = *tert*-butoxycarbonyl, DME = dimethoxyethane, DMT-MM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Ms = methanesulfonyl, NBS = *N*-bromosuccinimide, pin = pinacol, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

diastereomers comprising the stable biaryl atropisomers (*M*)-**21** and (*P*)-**22** in a ratio of 2:1. The source of the inversion barrier was attributed to the steric repulsion between the protons on C7 and C11 according to Mislow's pioneering work on the stereochemical fixation of medium-sized biaryl rings.[21] This assumption was experimentally supported by the fact that the ketone **23**, lacking a proton on C11, racemized fairly rapidly ($t_{1/2rac}$ = 2025 sec at 25 °C[22]).[23] In an attempt to improve the ratio of (*M*)-**21** and (*P*)-**22**, it was found that these were interconvertible when heated in 2-butanol at 90 °C. After 40 hours of heating, the thermodynamically more favorable (*P*)-**22** was obtained as a major isomer with good

diastereoselectivity [(*M*)-**21**/(*P*)-**22** = 1:7].[24] Selective silylation occurred only with (*P*)-**22** and the ensuing demesylation afforded **24** as a single isomer. The stereochemical configuration of the benzylic hydroxy group was thus successfully transferred to the atropisomeric stereochemistry of the biaryl moiety.

The X-ray structure of **24**[25] revealed that the silyloxy group is pointing toward the phenol moiety (Scheme 3). This peculiar configuration along with the atropisomeric stereochemistry was thus expected to influence the trajectory of the incoming reagents. Thus the oxidative transformation of the phenol moiety of **24** was performed by using singlet-oxygen oxidation,[26] which actually gave only a single diastereomer via the transition-state **25**, without even forming the undesired orthoquinone derivatives. The C5 position of the dienone **26** was spontaneously attacked by the amide nitrogen atom of the intermediate, thus creating the crucial tetrasubstituted carbon center. The in situ reduction of the hydroperoxide by PPh_3 yielded the tertiary alcohol **27** bearing the C11 oxygen functionality with the desired configuration.[27] The stereochemistry of the biaryl atropisomer was thus successfully transferred to the tetrasubstituted point chirality at C5. The intermediate **27** thus obtained is equipped with the common core helical architecture containing functional groups on the A–C rings, which are amenable to further modifications. The flexibility of **27** was showcased by the facile transformations into four members of erythrina alkaloids. Elimination of the tertiary hydroxy group by thionyl chloride gave **28**. Application of the diastereoselective Luche reduction of the enone moiety[28] led to **29**, which was converted into 8-oxo-erythrinine[1e,12h] (**2**) by methylation and treatment with TBAF. Subsequent elimination of the hydroxy group under acidic conditions afforded crystamidine (**1**).[1f] The other series without a benzylic hydroxy group was synthesized by first treating **28** with Et_3SiH under acidic conditions to afford **30**. 8-Oxo-erythraline[12h] (**4**) was obtained by a sequence involving Luche reduction and methylation. Finally, reduction of the amide moiety using a combination of $LiAlH_4$ and $AlCl_3$[28] afforded erythraline[29] (**6**). The first asymmetric total syntheses of these four alkaloids suggested that our strategy might offer an efficient route to a broad range of the erythrina alkaloids.

In conclusion, a versatile strategy for the synthesis of the erythrina alkaloids has been developed by employing the medium-membered dibenz[*d.f*]azonine intermediate **24**. The selective formation of the thermodynamically more favorable biaryl intermediate and the diastereoselective control during the singlet oxygen oxidation made it possible to construct the requisite tetrasubstituted C5 center by intramolecular 1,4-addition of an amide nitrogen atom. Throughout the transformations, the chirality of the benzylic hydroxy group was transferred to the atropisomeric stereochemistry, which in turn controlled the point chirality at C5 by exploiting the chemistry of the nine-membered ring. Manipulation of the functionalities along the peripheral moieties of the core A–C structure enabled the syntheses of four chiral erythrina alkaloids and could potentially give rise to a divergent synthetic strategy for this class of alkaloids.

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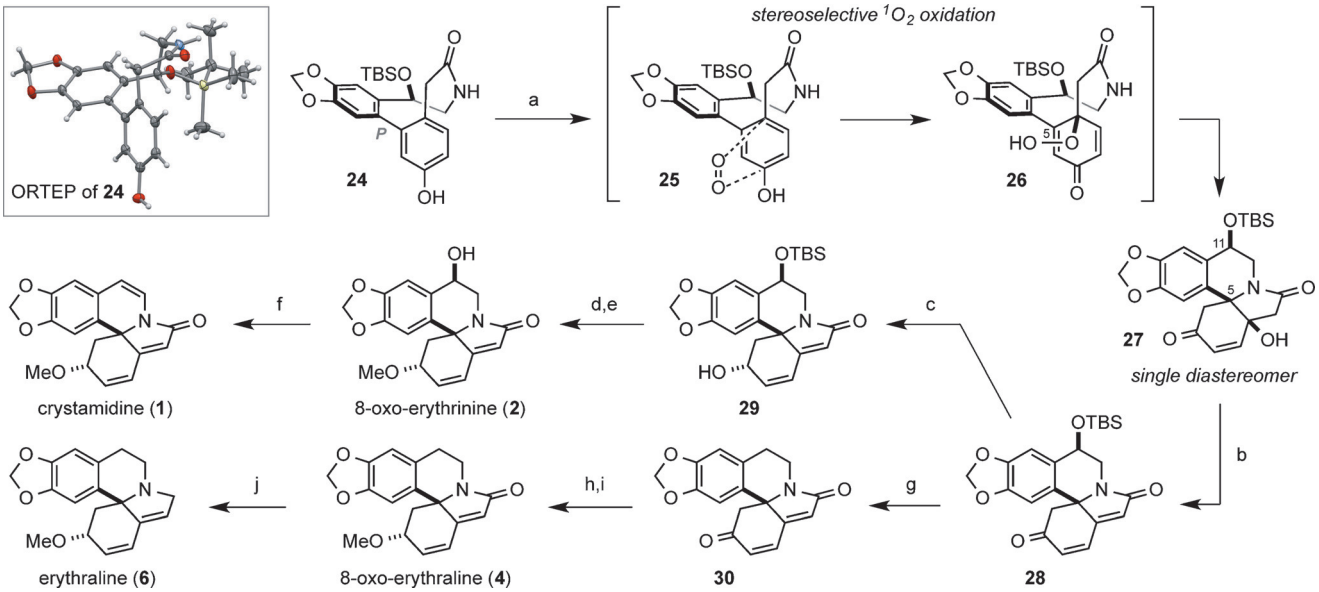

Scheme 3. Synthesis of the common intermediate and total syntheses of four erythrina alkaloids. Reagents and conditions: a) O_2, *hν*, rose bengal, PPh_3, $NaHCO_3$, CH_3CN/H_2O (1:1), RT; 77%; b) $SOCl_2$, pyridine, 0°C, 84%; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH, RT, 75%; d) CH_3I, NaH, THF, RT; e) TBAF, THF, RT, 84% (2 steps); f) $TsOH{\cdot}H_2O$ (20 mol%), toluene, reflux, 77%; g) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 74%; h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH, RT; i) CH_3I, KOH, Et_4NBr, THF, RT, 86% (2 steps); j) $LiAlH_4$, $AlCl_3$, THF/Et_2O (1:1), 0°C, 73%.

Keywords: alkaloids · annulations · atropisomerism · chirality · total synthesis

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