Development of a Divergent Route to Erythrina Alkaloids

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Abstract  
Erythrina alkaloids were identified at the end of the 19th century and today, more than 100 members of the erythrinane family have been isolated. They are characterized by a unique tetracyclic, \textalpha;-tertiary spiroamine scaffold. Herein we detail our efforts towards the development of a divergent enantioselective synthesis of \textit{(+)}-dihydro-\textbeta;-erythroidine (\textit{DH} \textbeta;\textit{E}) – one of the most prominent members of this intriguing family of natural products.

1 Introduction  
During the course of the last 50 years, the synthetic community has been fascinated by the topological complexities and the potent biological activities of the Erythrina alkaloids\textsuperscript{2}. The majority of synthetic efforts have been devoted to the tetracyclic framework bearing an aromatic D-ring, and more than 30 syntheses have been reported for this subclass of Erythrinanes\textsuperscript{2,3}. A clear majority of these approaches rely on an achiral iminium intermediate, and consequently only a handful enantioselective syntheses are known\textsuperscript{2,3}.

The assembly of the nonaromatic subclass of Erythrinanes (compounds 1, 3, and 6 in Figure 1) is much less prevalent in the literature\textsuperscript{3c,4a,b}. An overview of the notable efforts of the Hatakeyama and the Funk group is provided in Scheme 1\textsuperscript{4a,b}.

In 2006 the Hatakeyama group published their landmark enantioselective synthesis of \textit{(+)}-\textbeta;-erythroidine (3) in 26 steps\textsuperscript{4a}. Advanced intermediate 7 readily underwent Reformatsky cyclization to furnish the lactonic D-ring of compound 8\textsuperscript{5}. Subsequent elimination of the tertiary alcohol gave a mixture of the \textalpha;\textbeta;- and \textbeta;\textgamma;-unsaturation and they found that it was necessary to re-open and re-close the lactone in order to achieve decent selectivity for the desired, tetrasubstituted olefin. After 25 steps a bold enyne metathesis, tandem ring-closing metathesis (RCM) cascade were then successful in stitching up the A- and the B-ring to provide the first synthetic sample \textit{(+)}-\textbeta;-erythroidine (3). Later that same year, the Funk group published a 20-step synthesis\textsuperscript{4b} of racemic \textbeta;-erythroidine (3) using an intramolecular Diels–Alder\textsuperscript{6} reaction as their key reaction to build up aldehyde 11 \textit{en route} to the dienoid AB-ring system of the Erythrinanes. The aldehyde underwent facile Still–Gennari modified Horner–Wadsworth–Emmons olefination\textsuperscript{7} and subsequent intramolecular Heck reaction\textsuperscript{8} to close the C-ring and give carboxylic acid 12, which set the

Figure 1  
Representative lactonic, aromatic, and heteroaromatic Erythrina and Homoerythrina alkaloids
stage for a novel 6π-electrocyclization that closed up the tetracyclic ring system. Another 7 steps were then required to further manipulate the scaffold into the natural product 3.

We have previously investigated the structure–activity relationships of Erythinane alkaloids as antagonists of the nAChRs and accessed a number of analogues wherein the structural complexity was reduced by the systematic delineation of one or two rings from the tetracyclic framework. The promising properties of these fragments prompted us to pursue the development of a divergent synthetic route to DHβE as a platform that would give access to further analogues of this intriguing family of natural products.

Herein we detail the different synthetic approaches that eventually lead to the development of a short, flexible enantioselective synthesis of DHβE (1).

Biographical Sketches

Sebastian Clementson received his MSc in 2016 from Lund University, Sweden where he performed research in the labs of Professor Ulf Ellervik and Professor Daniel Strand. However, most of his final year was spent working on C–N activation in the group of Professor James S. Nowick at UC Irvine (USA). After working for one year in the pharmaceutical industry he began his PhD studies as a collaboration between the Kristensen group at the University of Copenhagen (Denmark) and H. Lundbeck A/S. During 2019 he also spent 7 months in the Maimone lab at UC Berkeley (USA). His PhD research is mainly focused on the total synthesis of neuroactive natural products.

Mikkel Jessing obtained his MSc in chemistry from the University of Copenhagen (Denmark) in 2004. He then moved to the Technical University of Denmark to do his PhD under the supervision of Professor David A Tanner, in natural product synthesis, from 2005 to 2008. During his PhD he went on an external stay with Professor Phil S. Baran at The Scripps Research Institute (USA). From 2008 to 2010 he returned to the Baran group for postdoctoral work. He then returned to Denmark to take up a position at H. Lundbeck A/S, where he is now a senior research scientist.

Paulo Vital received his MSc in Chemical Engineering & Applied Chemistry from Instituto Superior Técnico (Lisbon, Portugal). He obtained his PhD from the Technical University of Denmark under the supervision of David Tanner working in total synthesis. After carrying out postdoctoral work with David A. Evans at Harvard University (USA) he joined H. Lundbeck A/S in Copenhagen where he focused on CNS drug discovery. He is currently a medicinal chemist at Bial A/S in Porto, Portugal.

Jesper L. Kristensen obtained his PhD in 2002 from the University of Copenhagen, Denmark and after a short stay in the pharmaceutical industry, he returned to academia where he is currently Professor of Medicinal Chemistry at the Department of Drug Design and Pharmacology at the University of Copenhagen. His research deals with the development of chemical probes and drugs targeting various ion channels and GPCRs within the central nervous system. The starting points for such projects are often natural products with interesting structural and pharmacological properties.
2 Synthetic Strategy

In approaching our total synthesis of the structurally related and more potent DHβE (1) we wanted, much like the Hatakeyama and Funk group, to set the challenging tertiary spiroamine stereocenter at an early stage. However, we placed significant importance in developing a shorter, divergent retrosynthetic approach that would allow for a late-stage introduction of the lactonic D-ring. Such a versatile approach would ideally open up a venue to many structurally related and bioactive erythrina congeners, both nonaromatic, heteroaromatic, and aromatic.

2.1 First Generation

In our initial approach to DHβE (Scheme 2), we envisioned the final natural product being formed through the 6π-electrocyclization of precursor 13, analogously to what Funk so elegantly described in their synthesis of β-erythroidine (3).4b We then imagined that tricyclic scaffold 14 would be furnished through a cascade of events, where the 5,7-bicycle 16 would undergo a tandem pinnacol–Schmidt rearrangement.10 A simple RCM disconnection 11 would then get us down to a simpler starting material, such as triene 17. We primarily intended to access enone 21 through the procedure described by Corey et al.12 but were unsuccessful in reproducing their synthesis. Instead we found that by simply dissolving L-proline in cyclopentenone (neat) and glycoxal 19, we could acquire the aldol product 20 (Scheme 3). E1cB elimination followed by olefin isomerization and in situ acetal deprotection gave aldehyde 22, which could readily be allylated with bispinnacol borane 23. Subsequent methylation and addition of the vinyl lithium species formed by treating 25 with n-BuLi, furnished triene 17 where the desired diastereomer was slightly un-
derrepresented. We were then poised to assemble the 5,7-ring system with a RCM. Eleven different catalyst were screened, most of which gave a complex mixture of starting material and various ring-opening-metathesis and RCM products that proved difficult to interpret. Stewart–Grubbs catalyst\(^ {13} \) gave us, along with byproducts, trace amounts of products that proved difficult to interpret. Stewart–Grubbs material and various ring-opening-metathesis and RCM screened, most of which gave a complex mixture of starting ring system with a RCM. Eleven different catalyst were represented. We were then poised to assemble the 5,7-
experiencing rings and various ring-opening-metathesis reactions or RCM from branched prolinol. It was our des-ire to utilize the HAT-chemistry originated from the Baran lab as the key step in order to generate a radical a to the amide that could undergo a Giese reaction, thus gener-at-ting the C5–C13 bond of 29 from enamide 30.\(^ {16} \) The C5–C6 diene moiety of said enamide was proposed to be formed through a cycloisomerization\(^ {17} \) from enyne 31, and an alkyne addition to an aldehyde would bring us to the known ynamide 32.

In order to probe the reactivity of the key step, we wanted to see what influence different electron-withdrawing groups on the nitrogen would have, thus the sequence was carried out for both the Boc- and tosyl-protected amine. Known copper-catalyzed cross-coupling\(^ {18} \) generated the known ynamide 32 (Scheme 5). Deprotonation of the terminal alkyne and addition to aldehyde 35 followed by methylation of the hydroxyl group gave us the cycloisomerization precursor 36. Using the conditions reported by Trost and co-workers,\(^ {11} \) we were able to generate the C5–C6 bond with the desired olefin geometry in a facile manner. Selective oxidative cleavage\(^ {19} \) of the terminal, less electron-rich double bond gave us the \( \alpha,\beta \)-unsaturated ketone 38, which was also reduced and acylated to enone 39 in order to at-tempt an intramolecular delivery of the electrophile. How-ever, all HAT attempts from the desired C5–C13 bond were unsuccessful and only decomposition of the starting material was observed, regardless of the many catalysts and con-ditions that were screened (Scheme 5). As a final attempt,
we also tried to form the seven-membered lactone 45 in the same manner but were equally unsuccessful in this effort – we therefore decided to explore other options. Notably, copper and boron hydrides were also unsuccessful in delivering the desired hydride to the β-carbon of 37 or 38.

2.3 Third Generation

At this point we still thought that the endgame postulated for the second approach was a viable option. We envisioned that the C13–C14 and N–C6 bonds, respectively, could be introduced via a Seyferth–Gilbert homologation\(^{20a,b}\) and a reductive amination from bicyclic aldehyde 47, thus acquiring the necessary C- and D-ring carbons (Scheme 6). Again, an RCM disconnection\(^ {11}\) would trace us back to branched diene 48, and a series of sequential allylations would be a good starting point for the introduction of asymmetry from commercially available prolinone 50. After extensive optimization we found that using Trost ligand 52 and allyl-chloro palladium dimer furnished the desired (+)-allyl prolinone 49, in 95% ee on a multigram scale (Scheme 7).\(^{21ab}\)

Subsequent oxidative cleavage\(^ {19}\) of the terminal double bond and immediate acetal protection allowed us to isolate dimethyl acetal 54 in 67% yield over two steps. The sterically encumbered ketone resisted most of our olefination attempts and in the end a Wittig reaction under slightly elevated temperature provided the desired methenylated product 55 in acceptable yields.\(^ {22}\) We conducted a survey of 12 different allylating reagents and found that boron species under Brønsted acidic conditions displayed significantly superior chemical yields to that of allyl silanes and stannanes under Lewis acidic conditions. Achiral allyl boronates gave the undesired diastereomer in a 3:2 ratio, but we were able to circumvent this inherent stereochemical bias by using Hoffmann reagent 56 to provide the desired diene 57 in 60% yield.\(^ {23}\) Worth noting is that performing these reactions on the isolated aldehyde retained the stereofidelity of the acetal allylation, but gave lower yields. To avoid lactonization, methylation was successfully accomplished using Meerwein’s salt, giving methyl ether 48, which then underwent facile RCM to build up the alkenoid A–B bicycle 59 of the Erythrina alkaloids.

2.3.1 Radical Endgame

Redox manipulations to bicycle 59, followed by Seyferth–Gilbert homologation\(^ {20a,b}\) and acylation swiftly gave us access to ynone 61, in 51% yield over 4 steps (Scheme 8). The remaining carbons were then introduced via a one-pot deprotection–alkylation to form the radical-cyclization precursor 46. All attempts of the radical cyclization, using chemistry developed by Gansäure and co-workers,\(^ {14}\) failed in our hands, and we could not observe any signs of the desired radical conjugate addition. However, using a stoichiometric amount of manganese gave us terminal olefin 66, presumably via intermediate 65. We then tried to use this byproduct in an effort to synthesize the desired carbon–carbon bond using transition-metal-catalyzed cycloisomerization;\(^ {17}\) 19 different catalysts were screened for this reaction, where most of which, even during forcing conditions, showed no evidence of the desired reactivity, and the starting material was recovered. Notably, all attempts of selectively accessing the α,β-unsaturated enone failed in our hands.
At this point we reflected upon our two failed attempts at radical cyclizations and whether it was the right way forward. We felt that our current system might be more compatible with anionic chemistry and therefore set out to try and cyclize the final two rings in such a manner.

### 2.3.2 Completion of the Total Synthesis

Bicyclic ester 59 underwent deprotection and subsequent reductive amination in a one-pot procedure using aldehyde 68 (Scheme 9). The formed bisester 69 was subject to a Dieckmann condensation and cyclized readily to the tricyclic ketone 70, which predominantly existed as its enol tautomer.4a With the C-ring in hand and only two carbons missing, we thought that the enol moiety could be elaborated to a handle for palladium-catalyzed sp²–sp³ couplings. The enol was thus triflated, and the ester was reduced and protected as the silyl ether 73, a necessary precaution since the free alcohol was a rather unstable compound. As displayed in Scheme 9, a versatile selection of
enolate coupling partners were surveyed, most of which necessitated strongly basic conditions and led to deterioration of the starting material. After considerable optimization, we realized that we could modify the base-free, decarboxylative α-cyanation chemistry developed by the Liu group and translate it to our alkenyl triflate. The formed nitrile could then be telescoped to target natural product, by adding aqueous HCl in methanol.

The results summarized in this Account represents our successful endeavor in the development of a divergent, enantioselective synthetic route to the alkenoid family of non-aromatic Erythrina alkaloids and the first total synthesis of (+)-DHJBE (1). Although the generalization of our approach is yet to be tested, our desire to construct the D-ring at a late stage and install the quaternary (α-tertiary amine) stereocenter at an early stage, was achieved and we aim to explore this divergency in the synthesis of more Erythrina alkaloids.

3 Conclusion

We have developed a new divergent total synthesis of (+)-DHJBE (1) that installs the quaternary stereo center via a catalytic asymmetric allylic alkylation. A key bicyclic intermediate was accessed via a ring-closing metathesis which eventually was transformed into the desired natural product via a key decarboxylative α-cyanation. Several intermediates in this sequence will serve as a flexible starting point for future explorations of the structure–activity relationships of DHJBE and related Erythrina alkaloids.

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References

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(10) Gu, P.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y.; Zhang, F. Org. Lett. 2006, 8, 5271.
(23) Hoffmann, R. W. Pure Appl. Chem. 1988, 60, 123.