

Development of a Divergent Route to Erythrina Alkaloids

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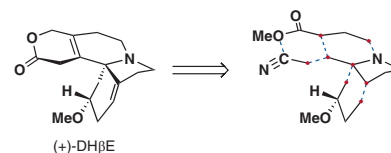
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Abstract Erythrina alkaloids were identified at the end of the 19th century and today, more than 100 members of the erythrinane family have been isolated. They are characterized by a unique tetracyclic, α -tertiary spiroamine scaffold. Herein we detail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

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Key words Erythrina alkaloids, total synthesis, asymmetric allylic alkylation, ring closing metathesis, decarboxylative cross coupling, spiroamine

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 alkaloids². 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.^{2,3} A clear majority of these approaches rely on an achiral iminium intermediate, and consequently only a handful enantioselective syntheses are known.^{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.^{3c,4a,b} An overview of the notable efforts of the Hatakeyama and the Funk group is provided in Scheme 1.^{4a,b}

In 2006 the Hatakeyama group published their landmark enantioselective synthesis of (+)- β -erythroidine (**3**) in 26 steps.^{4a} Advanced intermediate **7** readily underwent Reformatsky cyclization to furnish the lactonic D-ring of compound **8**.⁵ Subsequent elimination of the tertiary alcohol gave a mixture of the α,β - and β,γ -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 (+)- β -erythroidine (**3**). Later that same year, the Funk group published a 20-step synthesis^{4b} of racemic β -erythroidine (**3**) using an intramolecular Diels–Alder⁶ reaction as their key reaction to build up aldehyde **11** *en route* to the dienoid AB-ring system of the Erythrinanes. The aldehyde underwent facile Still–Gennari modified Horner–Wadsworth–Emmons olefination⁷ and subsequent intramolecular Heck reaction⁸ to close the C-ring and give carboxylic acid **12**, which set the

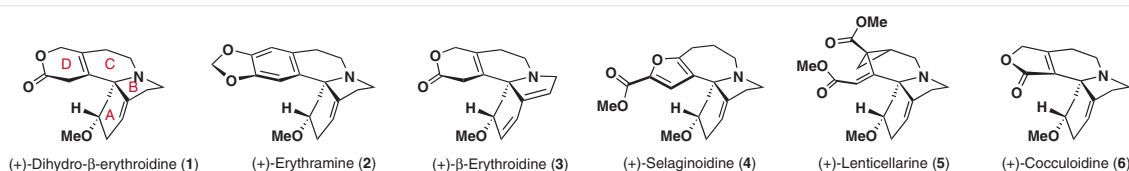


Figure 1 Representative lactonic, aromatic, and heteroaromatic Erythrina and Homoerythrina alkaloids

stage for a novel 6π -electrocyclization that closed up the tetracyclic ring system.⁹ 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 Erythrinane 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 frame-

work.^{3e,f,i,j} The promising properties of these fragments prompted us to pursue the development of a divergent synthetic route to DH β E 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 DH β E (**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 activa-

tion 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 Da-

vid 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 Co-

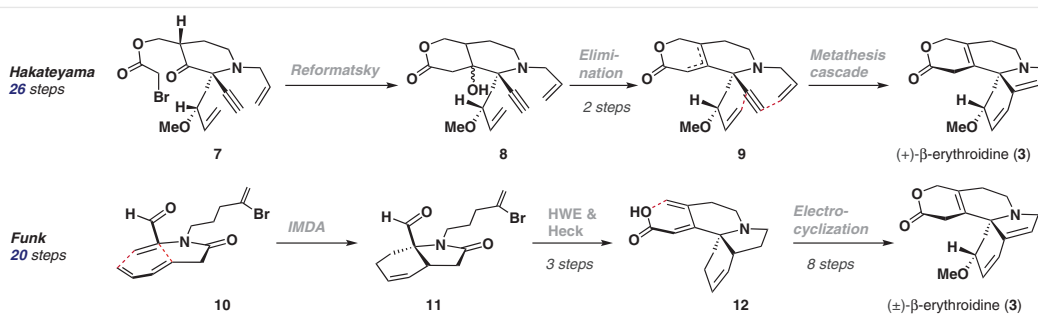
penhagen where he focused on CNS drug discovery. He is currently a medicinal chemist at Bial A/S in Porto, Portugal.



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 Medici-

nal 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.



Scheme 1 Previous total syntheses of lactonic Erythrina alkaloids

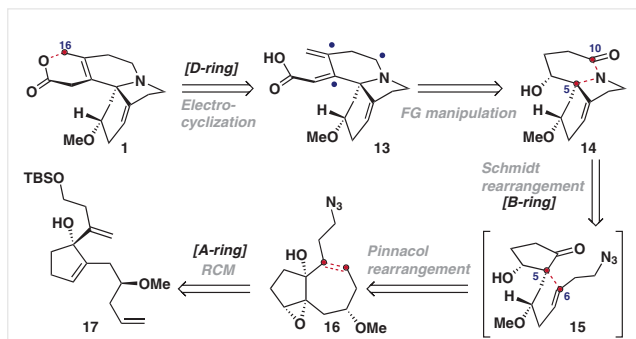
2 Synthetic Strategy

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 structur-

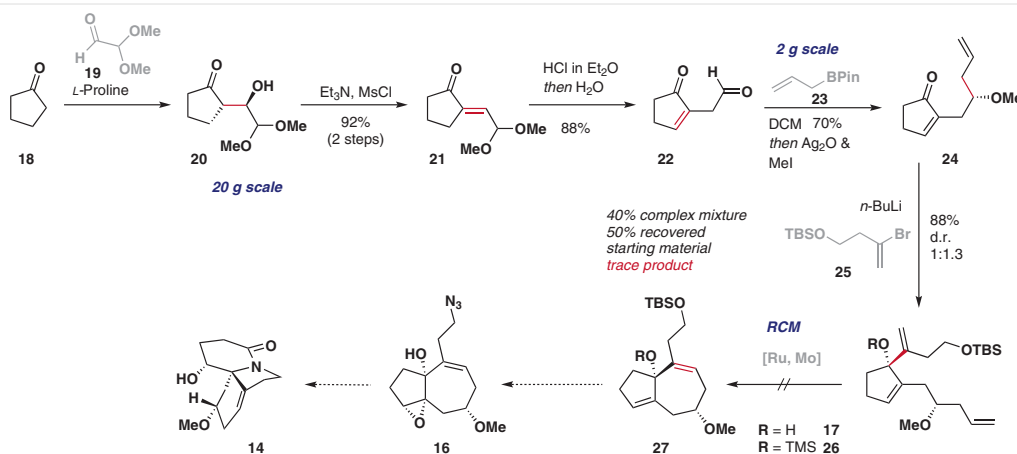
ally related and bioactive erythrina congeners, both nonaromatic, heteroaromatic, and aromatic.

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 disconnection¹¹ 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 glyoxal **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-



Scheme 2 First retrosynthetic approach

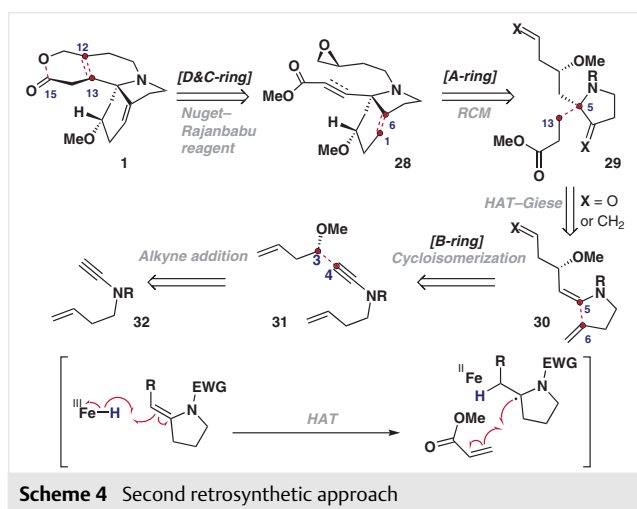


Scheme 3 First-generation approach

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 catalyst¹³ gave us, along with byproducts, trace amounts of the desired bicycle, but this low material throughput was not enough to proceed with. Consequently, we decided to explore other retrosynthetic disconnections.

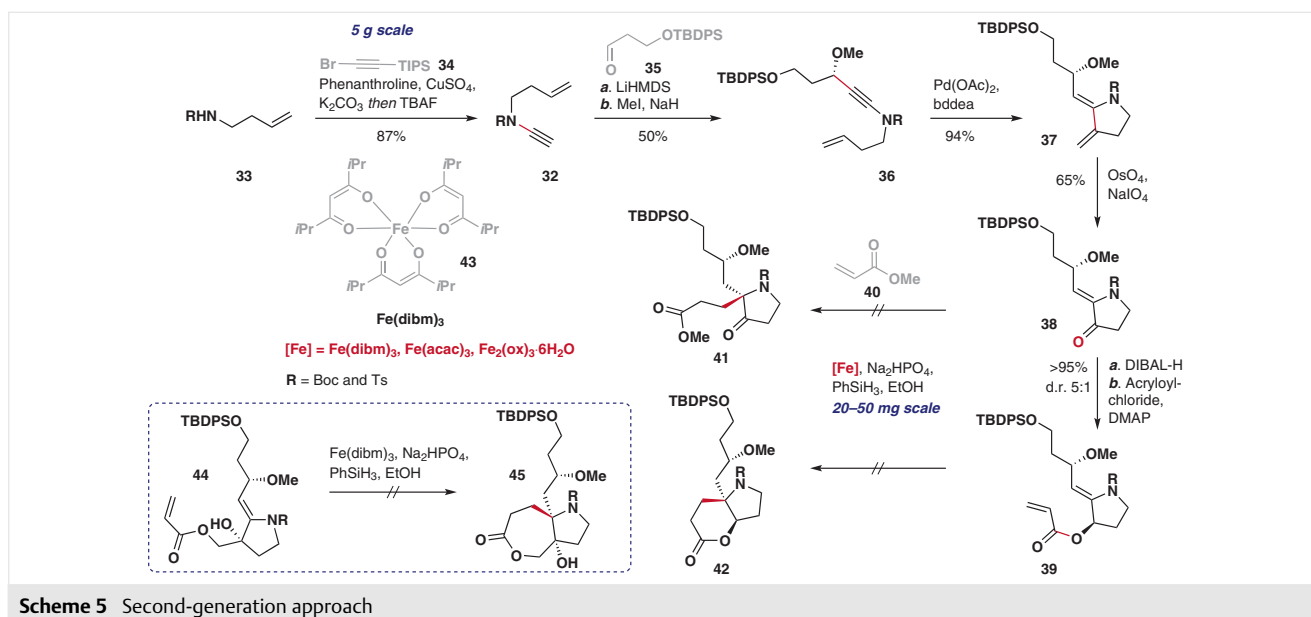
2.2 Second Generation

Our second approach (Scheme 4) was conceptionally quite different but still emphasized the formation of the D-ring at a late stage.



We postulated that the C- and D-ring of DH β E (**1**) could be synthesized in one reaction, where a radical conjugate addition^{14a,b} would furnish the C-ring and that subsequent lactone formation would occur spontaneously, from epoxide **28**. The A-ring would be stitched up using either a McMurry¹⁵ reaction or RCM from branched prolinone **29**. It was our desire to utilize the HAT-chemistry originated from the Baran lab as the key step in order to generate a radical α to the amide that could undergo a Giese reaction, thus generating the α -tertiary C5–C13 bond of **29** from enamide **30**.¹⁶ The C5–C6 diene moiety of said enamide was proposed to be formed through a cycloisomerization¹⁷ 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-coupling¹⁸ 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,¹⁷ we were able to generate the C5–C6 bond with the desired olefin geometry in a facile manner. Selective oxidative cleavage¹⁹ of the terminal, less electron-rich double bond gave us the α,β -unsaturated ketone **38**, which was also reduced and acylated to enone **39** in order to attempt an intramolecular delivery of the electrophile. However, 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 conditions 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

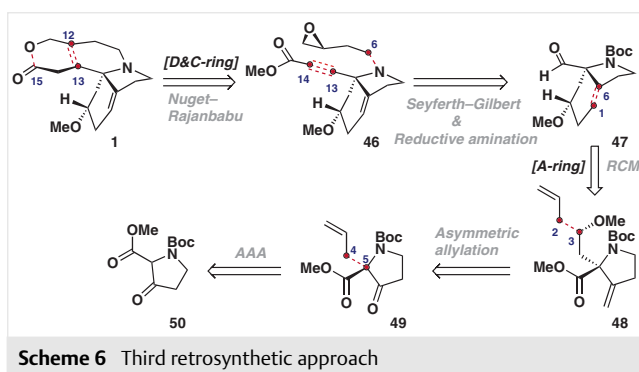
At this point we still thought that the endgame postulated for the second approach was a viable option. We envisioned that the C13–C14 and N–C6 bonds, respectively, could be introduced via a Seyferth–Gilbert homologation^{20a,b} and a reductive amination from bicyclic aldehyde **47**, thus acquiring the necessary C- and D-ring carbons (Scheme 6). Again, an RCM disconnection¹¹ 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).^{21a,b}

Subsequent oxidative cleavage¹⁹ 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 at-

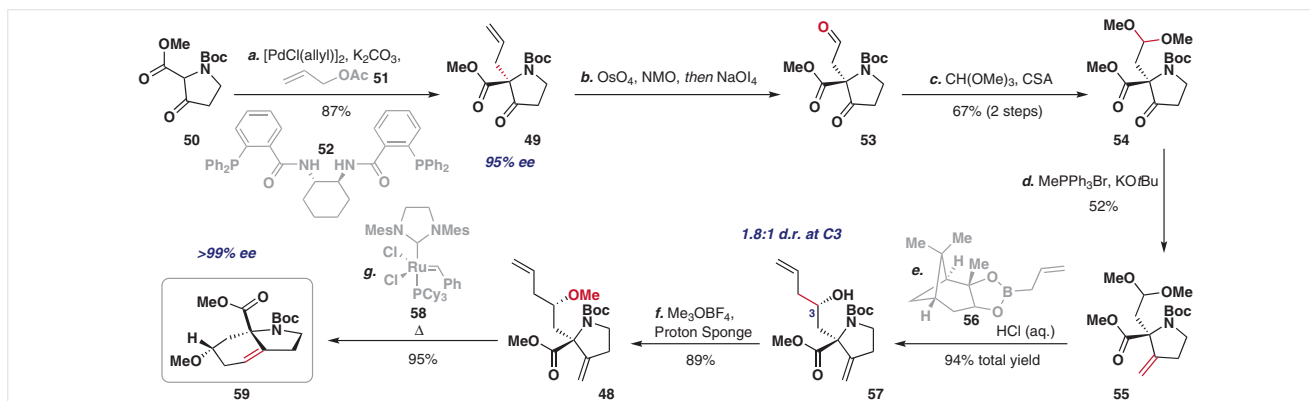
tempts and in the end a Wittig reaction under slightly elevated temperature provided the desired methenylated product **55** in acceptable yields.²² We conducted a survey of 12 different allylating reagents and found that boron species under Brønsted acidic conditions displayed significantly superior 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

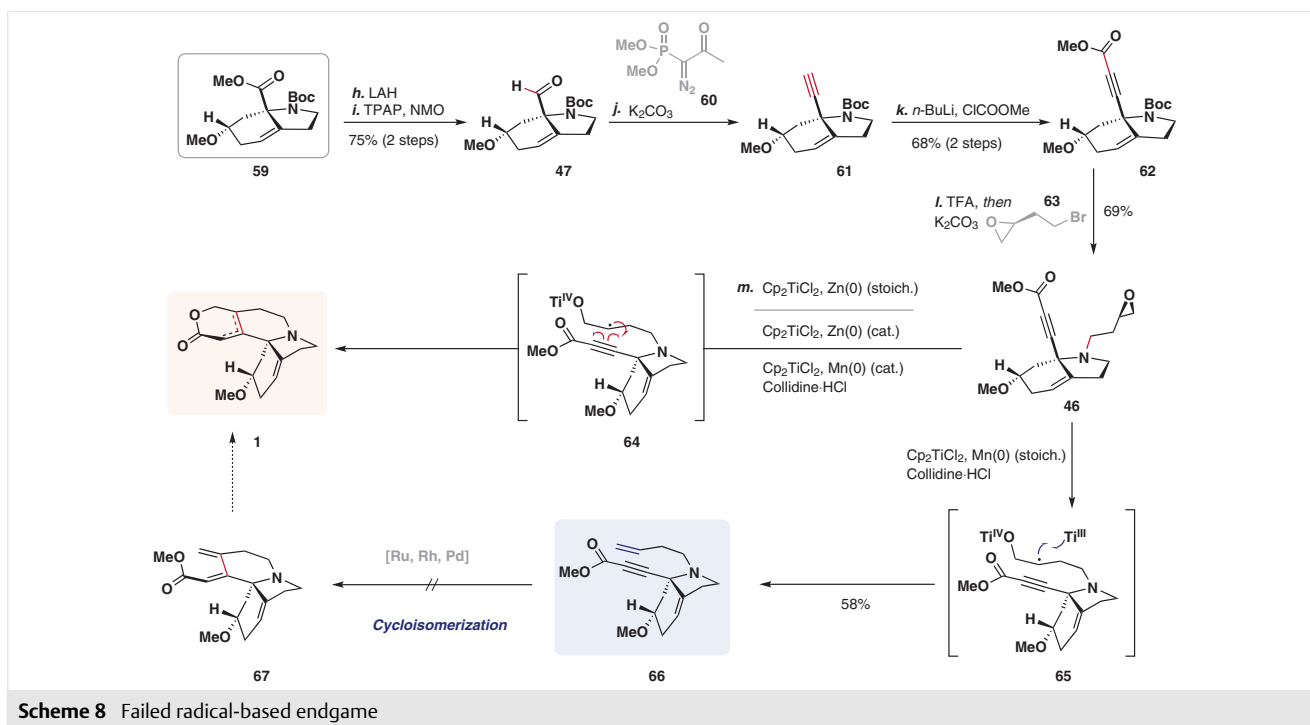
Redox manipulations to bicycle **59**, followed by Seyferth–Gilbert homologation^{20a,b} and acylation swiftly gave us access to ynone **61**, in 51% yield over 4 steps (Scheme 8). The remaining carbons were then introduced via a one-pot deprotection–alkylation to form the radical-cyclization precursor **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.



Scheme 6 Third retrosynthetic approach



Scheme 7 Third-generation approach delivering the key intermediate **59**

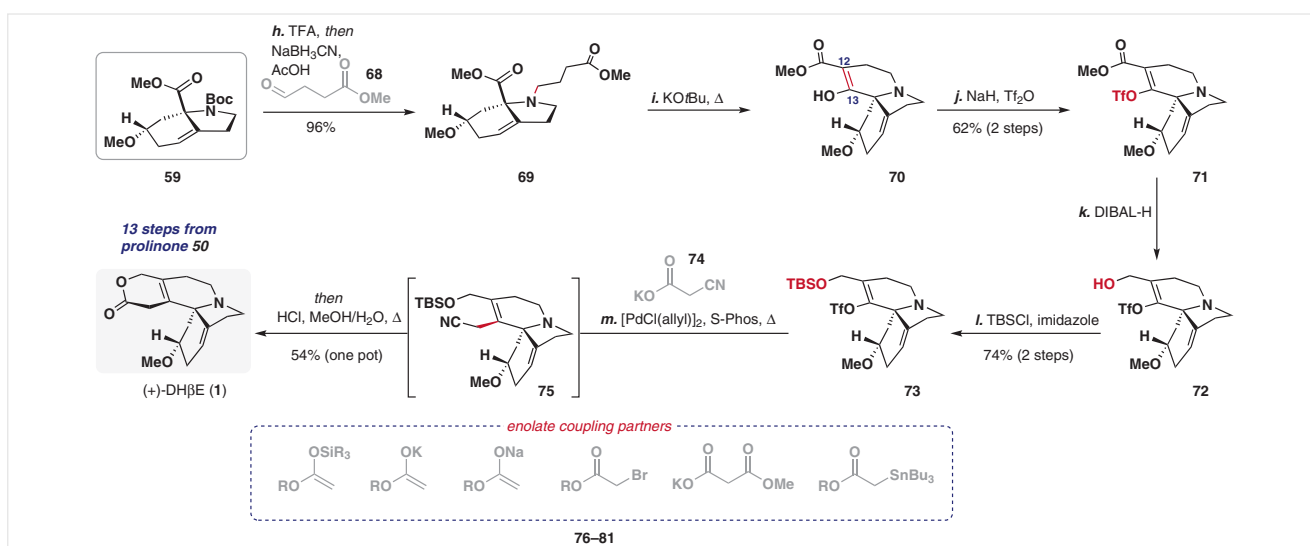


At this point we reflected upon our two failed attempts at radical cyclizations and whether it was the right way forward. We felt that our current system might be more compatible with anionic chemistry and therefore set out to try and cyclize the final two rings in such a manner.

2.3.2 Completion of the Total Synthesis

Bicyclic ester **59** underwent deprotection and subsequent reductive amination in a one-pot procedure using al-

dehyde **68** (Scheme 9). The formed bisester **69** was subject to a Dieckmann condensation and cyclized readily to the tricyclic β -keto ester **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 sp^2 - sp^3 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 partners²⁴ 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 group²⁵ and translate it to our alkenyl triflate. The formed nitrile could then be telescoped to target natural product **1**, by adding aqueous HCl in methanol.²⁶

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 (+)-DH β E (**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 (+)-DH β E (**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 DH β E and related Erythrina alkaloids.

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