JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 23 May 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Enantioselective Total Synthesis of (+)-Dihydro-β-erythroidine.

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Supporting Information Placeholder

ABSTRACT: Erythrina alkaloids represent a rich source of complex polycyclic, bioactive natural products. In addition to their sedative and hypotensive effect, their curare-like activity and structural framework have made them attractive targets for synthetic and medicinal chemists. (+)-Dihydro-β-Erythroidine (DHβE), the most potent nicotine acetylcholine receptor antagonist (nAChR) of the Erythrina family is synthesized for the first time in 13 steps from commercially available material.

The Erythrina alkaloids were first characterized at the end of the 19th century. Today, more than 100 members of the erythrinanes have been isolated from specimens collected throughout the tropical and subtropical regions of the world.[1,2] These alkaloids possess unique structural attributes, with a tetracyclic, α-tertiary spiroamine scaffold that connects the A, B and C rings in a dextrorotatory (S) fashion, see Figure 1B. Depending on the nature of the D-ring, they are categorized into aromatic and non-aromatic (lactonic) alkaloids. Further subdivision can also be made depending on the presence of a conjugated unsaturation in the A and B ring at the C-1, C-2, C-6 and C-7 carbons, or a double bond in the A ring at the C-1 and C-6 carbons (Figure 1 B).[1,3]

The structure of (+)-Dihydro-β-erythroidine (DHβE (**1**), Figure 1A) was first elucidated back in 1953 and it can be found in the seeds of the Erythrina Americana family of Mexican coral plants.[4,5] DHβE (**1**) is one of the most potent nicotine acetylcholine receptor (nAChR) antagonists described to date ($IC_{50}(\alpha4\beta2)$: 0.11μM)[6,7] and it has been used in a vast number of studies both in vitro and in vivo.[8–12] DHβE (**1**) has been demonstrated to have antidepressant-like activities in various preclinical assays, and was used as a muscle relaxant several years ago in the treatment of Parkinson's disease to relieve tetanus and spastic disorders. Importantly, DHβE (**1**) is effective when administered perorally demonstrating its excellent drug-like properties.[8,12,13] Several other Erythrina alkaloids have been shown to possess an antidepressant like neuromuscular blocking effect and many of them have been used as sedatives and hypnotics in traditional Mexican medicine.[5] Thus, the Erythrina alkaloids are an interesting source of new chemical leads for drug discovery.

The biogenesis of Erythrina alkaloids is not fully biochemically elucidated, but envisioned to be the condensation of two molecules of 3,4-dihydroxyphenylalanine to give an indoline nucleus, which then undergoes further oxidative manipulations to furnish the spiroamine skeleton (Figure 1B).[3] Given the interesting structural features and numerous applications, Erythrina alkaloids have been popular targets for total synthesis. The majority of synthetic work has been devoted to the aromatic erythrinan subclass of compounds,[2,6,14] whereas only a few synthetic approaches to the non-aromatic alkaloids have been reported.[15a-f] In 2006, the Hatakeyama group published an enantioselective synthesis of (+)-β- Erythroidine (β-E) (**2**) in 26 steps.

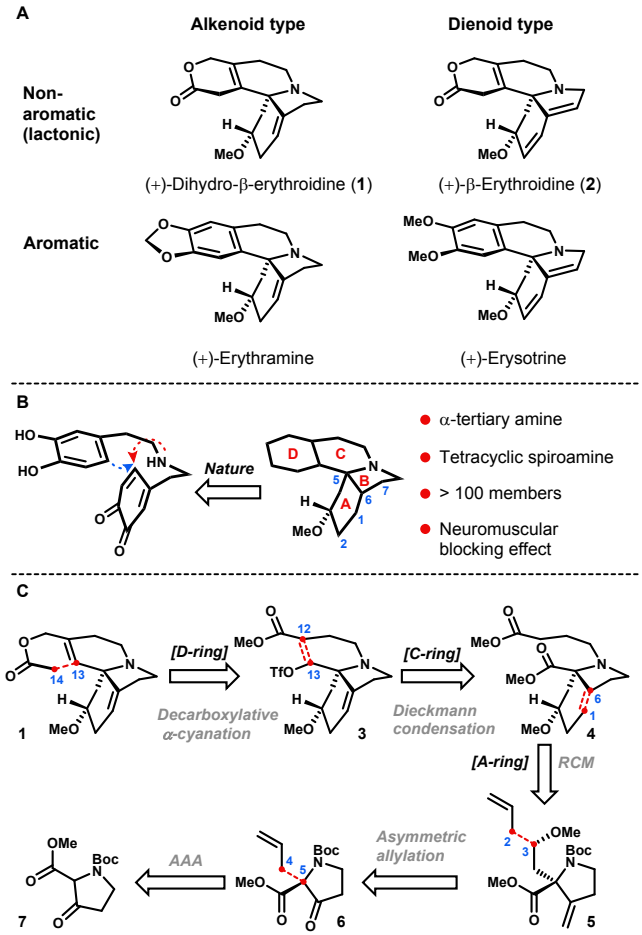
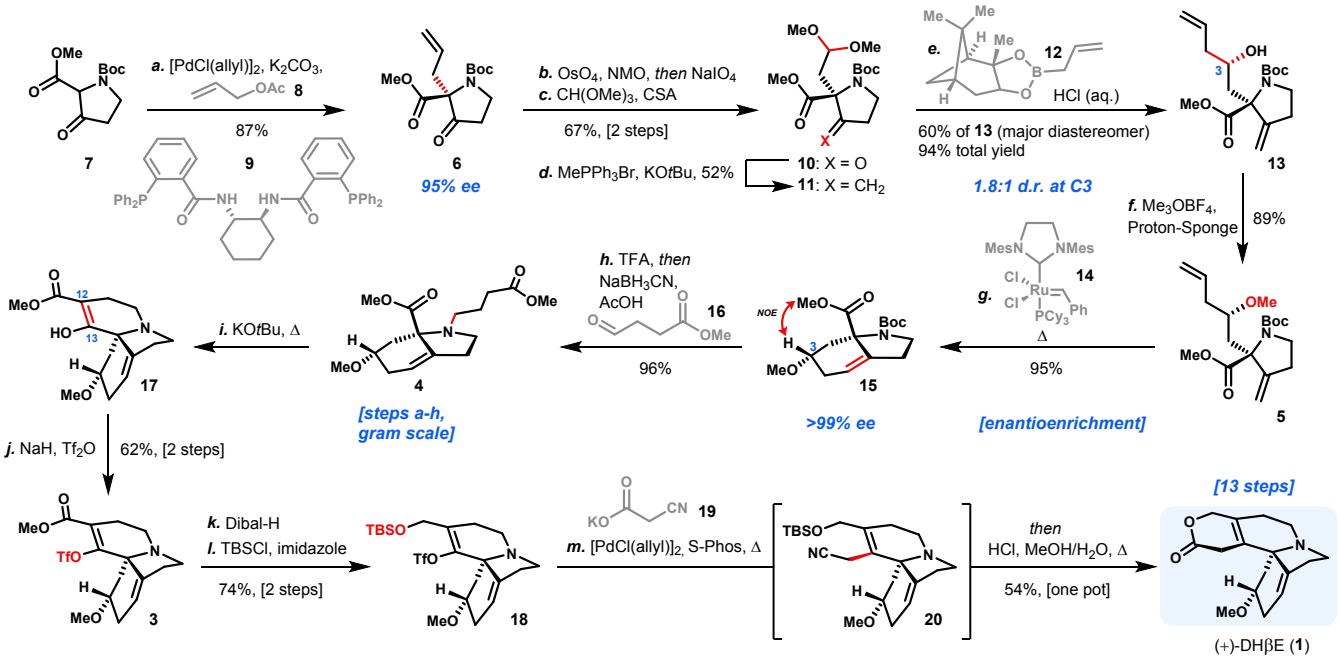


Figure 1. A) Representative members and categorization of the alkaloid family. B) Erythrina alkaloids; proposed biosynthesis and properties. C) Key transforms in the retrosynthetic analysis.

Scheme 1. 13-Step Total Synthesis of (+)-DHβE (1)[a]



[a]Reagents and conditions: a) $[PdCl(allyl)]_2$ (0.025 equiv), **9** (0.05 equiv), K_2CO_3 (1.05 equiv), **8** (1.05 equiv), DMF, -40 – 0 °C, 2.5 h, 87%, 95% ee; b) OsO_4 (0.04 equiv), NMO (1.3 equiv), THF:H_2O, room temperature, 12 h, then $NaIO_4$ (2 equiv), DCM, room temperature, 4 h; c) $CH(OMe)_3$ (1.1 equiv), CSA (0.1 equiv), toluene, room temperature, 2 h, 67% for two steps; d) $MePPh_3Br$ (2.1 equiv), KO*t*Bu (2 equiv), THF, 30 °C, 10 h, 52%; e) **12** (1.2 equiv), HCl (1 equiv), DCM: H_2O, room temperature, 8 h, 60% for **13**, 94% total yield, d.r. 1.8:1; f) Me_3OBF_4 (3 equiv), Proton-Sponge (3 equiv), DCM, room temperature, 3 h, 89%; g) **14** (0.075 equiv), toluene, 80 °C, 2 h, 95%, >99% ee; h) TFA:DCM, room temperature, 30 min, then **16** (2 equiv), AcOH (3 equiv), $NaBH_3CN$ (3 equiv), THF:MeOH, room temperature, 5 h, 96%; i) KO*t*Bu (2.3 equiv), toluene, 95 °C, 1 h; j) NaH (4 equiv), Tf_2O (2 equiv), THF:Et_2O, room temperature, 1 h, 62% for two steps; k) Dibal-H (3 equiv), DCM, -78 – 0 °C, 1.5 h; l) TBSCl (2 equiv), imidazole (3.2 equiv), DCM, room temperature, 2 h, 74% for two steps; m) **19** (3 equiv), $[PdCl(allyl)]_2$ (0.2 equiv), S-Phos (0.4 equiv), mesitylene, 110 °C, 30 min, then HCl:H_2O, 85 °C, 30 min, 54%. CSA = camphorsulfonic acid, DCM = dichloromethane, Dibal-H = diisobutylaluminium hydride, DMF = *N*,*N*-dimethylformamide, NMO = *N*-methylmorpholine *N*-oxide, S-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

Later that year the Funk group published a synthesis of the same natural product in a total of 20 steps giving access to racemic material; an approach which was used to synthesize several other congeners of β-E (**2**) with similar synthetic efficiency. Herein, we wish to report the first total synthesis of DHβE (**1**).

The first key transform in our retrosynthetic analysis of DHβE (**1**) would rely on a late-stage palladium catalyzed enolate coupling-lactonization, initiated by the construction of the C13-C14 bond, thereby forming the D-ring (see Figure 1C). The C-ring would be assembled by a Dieckmann-condensation and a reductive amination, providing the spiroamine scaffold with the desired oxidation states. A ring-closing metathesis (RCM) and an asymmetric allylation would furnish the C1-C6 double bond and the C2-C3 bond respectively, closing the A-ring and establishing the alkenoid core structure **4**. The synthesis would commence with the installment of the α-tertiary-amine stereogenic center at C5, using a Tsuji-

Trost asymmetric allylic alkylation (AAA). This approach would allow for a rapid assembly of the tetracyclic erythrinan framework.

In the forward sense, the key aza-tertiary stereocenter was installed by subjecting commercially available prolinone **7** (Scheme 1) to a Tsuji-Trost AAA[16a,b] on multigram scale. Screening of different ligands, bases and solvents (see SI Table 1) identified ligand **9** in combination with allyl acetate **8**, potassium carbonate and allylpalladium chloride dimer as an ideal combination, which delivered allyl prolinone **6** in 87% yield and 95% ee. Upjohn dihydroxylation[17] followed by periodate mediated oxidative cleavage[18a,b] of the terminal olefin gave the corresponding, unstable aldehyde that was isolated as the dimethyl acetal **10**. With acetal **10** in hand we then attempted to methenylate the sterically encumbered ketone with a wide range of titanium carbenoids,[19a-g] to no success (see SI Table 2). Peterson[20] and Grignard[21] reagents reacted selectively with the ester and Boc-group respectively. Eventually, Wittig methenylation[22] proved superior and provided the desired olefin **11** in 52% yield. Subsequently, hydrolysis followed by in situ allylation of the aldehyde with (+)-allylboronic acid pinanediol ester[23] (**12**) provided allylic alcohol 13 as the major component of a 1.8:1 mixture of diastereoisomers. Several other reagents were investigated in an attempt to improve the selectivity, however they were all inferior to the boronic ester **12** (see SI Table 3 and Figure S5).

The diastereomers of the resulting allylic alcohol **13** were, at this time, inseparable and they were thus carried through until the formation of the bicyclic system **15** in the following way: methylation of the alcohol gave methyl ether **5**, which underwent RCM[24a,b] in excellent yield, delivering the bicyclic ester **15**, bearing the A-B-alkenoid architecture of the Erythrina alkaloids. At this point, the desired diastereomer was readily separated from the unwanted diastereomer by column chromatography and it could also be further enantioenriched, using chiral chromatography. The relative configuration at C-3 was established by the noticeable presence of a through-space coupling between the methine proton at C-3 and the methyl ester (Scheme 1) in the NMR-spectra. Taking inspiration from Hatakeyama and coworkers,[15a] deprotection and reductive alkylation of the secondary amine using aldehyde **16** provided bis-ester **4**, which set the stage for the assembly of the C-ring at C12-C13 via an intramolecular Dieckmann condensation. Spiroamine **17**, which resided almost exclusively as its enol tautomer in aprotic solvents, was immediately subjected to sodium

hydride and triflic anhydride to give enol triflate **3** in 62% yield over two steps.

Moving forward, reduction of the ester and subsequent TBS-protection furnished silyl ether **18**. Silyl protection was necessary, since the corresponding alcohol was unstable. We envisioned that the final two carbons of the lactone ring would be installed via an enolate coupling, however it was quickly realized that base-dependent procedures, described by Hartwig, Buchwald and others,[25a-d] were ineffective as the coupling precursor **18**, rapidly decomposed when exposed to basic conditions under slightly elevated temperatures (see SI Table 4). We then turned to the chemistry developed by Liu and coworkers,[26] which allowed us to circumvent this issue by installing the final two carbons using a base-free decarboxylative coupling of cyanoacetate **19** to furnish α-alkenyl nitrile **20**. This is, to the best of our knowledge, the first employment of this chemistry on an alkenyl system as well as in a target-oriented synthesis. Ultimately, a process was developed in which the cross coupling was telescoped with an acid mediated hydrolysis, deprotection and lactonization-cascade, delivering (+)-DHβE (1) in 13 steps from commercially available prolinone **7**.

In summary, we have developed an enantioselective synthetic route to the alkenoid family of non-aromatic Erythrina alkaloids and the first total synthesis of (+)-DHβE (**1**). It is envisioned that several intermediates from this synthetic sequence (in particular **15** and **17**) will serve as versatile platforms from which structurally diverse DHβE-congeners can be accessed. Such endeavors, will serve to explore the structural requirements for nAChR-antagonism and probe the potential of such derivatives in drug discovery. Furthermore, the application of the current methodology to the synthesis of other lactonic Erythrina alkaloids will also be investigated.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

Experimental section including characterization (PDF)

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ACKNOWLEDGMENT

This research was financially supported by the Innovation Fund Denmark (Case no. 7038-00149B) and H. Lundbeck A/S. We thank the Medicinal Chemistry department at H. Lundbeck A/S for valuable resources and inputs. We would also like to thank Emil Märcher-Rørsted for chromatographic aid.

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