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Total synthesis of (±)-isophellibiline

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Abstract

The total synthesis of (±)-isophellibiline is described. This represents the first synthesis of a member of the nonaromatic homoerythrinan family of alkaloids. The tetracyclic ring system of the natural product was quickly assembled by a strategy that features a retrocycloaddition/cycloaddition reaction of an amidodioxin, an intramolecular Heck reaction and a 6 π -electrocyclic ring closure of a dienoic acid.

Keywords

Isophellibiline; Homoerythrina; Amidodioxin; Diels—Alder Cycloaddition; Azepine; 6 π -Electrocyclic ring closure

The *Erythrina* alkaloids¹ are a large class of natural products that have attracted significant attention due to their biological activity and unique structures. The erythrinan alkaloids can be categorized into two groups based on their structural features: the erythrinans which possess a 6-5-6-n tetracyclic core (A-B-C-D) and the *homoerythrinans* which possess a 6-5-7-n tetracyclic core.^{1c} These can be further subdivided depending on whether the D-ring is aromatic or nonaromatic (Figure 1). A number of pharmacological effects are associated with the *Erythrina* alkaloids, including sedative, hypotensive, anticonvulsive, CNS depressive and neuromuscular blocking activity.² Members of the *homoerythrinan* alkaloids have been shown to possess cardioactivity in rat atrial preparations^{3a} and molluscicidal activity.^{3b}

The aromatic erythrinans have been the target of the majority of synthetic efforts, resulting in many successful syntheses.⁴ Commonly, syntheses have relied on the formation of the C-ring and simultaneous construction of the C(5) quaternary stereogenic center, most commonly by attack of an electron-rich aromatic D- ring upon an *N*- acyliminium ion intermediate.^{1,4} By comparison, the nonaromatic erythrinans have posed a greater challenge,⁵ and accordingly, only three members of this subclass have been synthesized: (±)-cocculolidine,^{5d} β -erythroidine^{5e,f} and (±)-8-oxo- β -erythroidine.^{5f} Although far fewer synthetic efforts towards the synthesis of the *homoerythrinan* alkaloids have been reported, Tsuda and coworkers reported the total synthesis of a number of aromatic *homoerythrinan* alkaloids, including comosine.⁶ The nonaromatic *homoerythrinans* in contrast have been less explored and to date no viable approaches have been reported.

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Surprisingly, in light of the small structural difference between the erythrinan and *homoerythrinan* alkaloids, the development of a concise, unified strategy for the preparation of both groups of natural products has proven elusive.^{7,8f} Strategies aimed at overcoming this difficult problem have thus far focused on the synthesis of the aromatic erythrinan and aromatic *homoerythrinan* alkaloids.^{6,8,9} Herein we report our synthetic studies that have culminated in the first total synthesis of a member of the nonaromatic *homoerythrinan* subclass, isophellibiline.¹⁰

Our retrosynthetic analysis draws upon our previously reported β -erythroidine^{5f} synthesis and is outlined in Scheme 1. We expected that diene **1** would permit installation of the C(3) hydroxyl substituent by an oxidation-based strategy. The diene **1** could be prepared from lactam **2** by protection of the lactone functionality as an ortho ester, introduction of a conjugated diene, and deconjugation of the diene with the lactam carbonyl via a kinetic protonation of a trienolate derivative. The β,γ -unsaturated lactone **2** could be obtained via a precedented 6π - electrocyclic ring closure¹¹ of the *E*-dienoic acid **3**, which in turn is available from a stereospecific, intramolecular Heck reaction of the *Z*-enoate **4**. Finally, an intramolecular Diels—Alder cycloaddition of the amidoacrolein **5**, followed by a Still—Gennari *Z*-enoate synthesis,¹² was expected to afford the Heck cyclization substrate **4**.¹³

The synthesis commences with the condensation of dioxanone **6** with amine **7**¹⁴ in the presence of sodium sulfate (Scheme 2). Acylation of the resulting imine with acid chloride **8**¹⁵ gave amidodioxin **9**, which upon heating underwent a smooth retrocycloaddition and concomitant cycloaddition to afford a 4.5:1 mixture of *exo*-cycloadduct **12** and *endo*-cycloadduct **11**, respectively.

Our next challenge was the completion of the synthetically challenging azacycloheptene C-ring.^{6c,7c,d,8i} As in our β -erythroidine synthesis, Still—Gennari olefination¹² of neopentyl aldehyde **13** gave the *Z*-enoate **4** (Scheme 3). However, initial attempts to effect the Heck cyclization of vinyl bromide **4** using the conditions (Pd(OAc)₂, PPh₃, K₂CO₃) employed in our previous β -erythroidine synthesis, as well as several other protocols (e.g., Pd(OAc)₂, P(*o*-tolyl)₃, K₂CO₃; Pd(OAc)₂, AsPh₃, *i*PrNEt₂; Pd(OAc)₂, dppp, Et₃N; Pd(PPh₃)₄, NaOAc), provided *E*-dienoate **13** in very low yield (< 5%) along with decomposition of the starting material. Similar difficulties in effecting a Heck cyclization to form the azacycloheptene C-ring were noted by Padwa and coworkers in their approach towards the *homoerythrina* alkaloid ($\pm$)-selaginoidine.^{8d} Eventually we found that the reductive Heck¹⁶ conditions employed in Baran's ambiguine¹⁷ synthesis gave the *E*-dienoate **13** with clean inversion of alkene stereochemistry.¹³ Saponification of ester **13** and heating the resulting dienolic acid **3** in refluxing toluene promoted a clean 6π -electrocyclic closure to lactone **2**. At this stage, all that remained to complete the synthesis of isophellibiline was the installation of the C(3) hydroxyl substituent, the C(6)—C(7) unsaturation, and reduction of the lactam. Protection of lactone **2** as the ortho ester and introduction of the C(6)—C(7) unsaturation via a selenylation, oxidative deselenylation sequence, followed by deconjugation gave diene lactam **14** (Scheme 4). The correct oxidation state at C(3) was introduced via a stereoselective cycloaddition with singlet oxygen, from the face opposite the bulky ortho ester, and a reductive workup of the crude endoperoxide with thiourea¹⁸ provided diol **15**. Selective protection of the secondary hydroxyl group at C(3) with MTBSTFA¹⁹ gave silyl ether **16**. Attempts to utilize the one-pot methylation, elimination sequence (KOH, MeI, Et₄NBr) employed in our previous synthesis of β -erythroidine were hampered by a competitive silyl transfer, resulting in the C(6) silyl ether, and subsequent methylation of the secondary hydroxyl group at C(3). Ultimately, a two step sequence involving acetylation of the tertiary hydroxyl group at C(6) and elimination with DBU reintroduced the C(6)—C(7) unsaturation present in lactam **17**. Selective 1,6-reduction of diene lactam **17** with L-Selectride gave lactam **18**. Finally, reduction of lactam **18** with alane—ethyltrimethylamine

complex, followed by hydrolysis of the ortho ester group and concomitant cleavage of the silyl ether, furnished ($\pm$)- isophellibiline. Spectral properties of synthetic ($\pm$)- isophellibiline were identical to those previously reported and authentic spectra provided by Dr. Nicole Langlois.^{10,20}

In summary, the first total synthesis of a member of the nonaromatic *homoerythrinan* class of natural products, ($\pm$)- isophellibiline, has been completed. Not unexpectedly, the seven-membered ring present in the *homoerythrina* class represented an additional challenge. This synthesis demonstrates the versatility of our strategy for the preparation of members of the nonaromatic erythrinan and nonaromatic *homoerythrinan* subclasses of natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Erythrinan and homoerythrinan alkaloids.

Scheme 1.
Retrosynthetic analysis for the synthesis of isophellibine

Scheme 2.
Preparation of cycloadduct **12**.

Scheme 3.
Preparation of azepine/lactone **2**.

Scheme 4.
Completion of the isophellibiline total synthesis.