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Total Syntheses of (±)-β-Erythroidine and (±)-8-oxo-β-Erythroidine by an Intramolecular Diels–Alder Cycloaddition of a 2-Amidoacrolein

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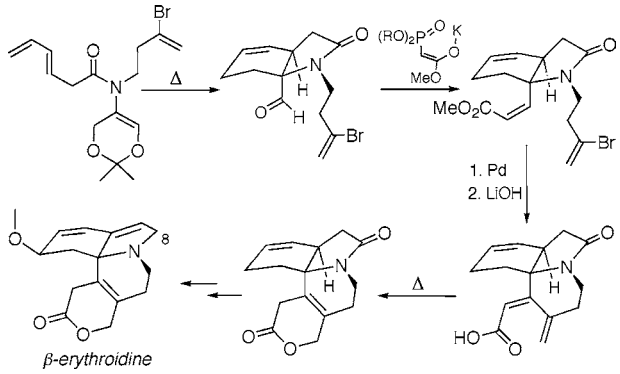
ABSTRACT



The total syntheses of (±)-β-erythroidine and (±)-8-oxo-β-erythroidine are described. The tetracyclic ring system of the natural products was quickly assembled by a strategy that features a retrocycloaddition/cycloaddition reaction of an amidodioxin, an intramolecular Heck reaction, and a 6π-electrocyclic ring closure of a dienoic acid.

The erythrinan and homoerythrinan alkaloids are a class of nearly 200 compounds isolated from 70 different species of the *Erythrina* genus.[1] They possess an interesting tetracyclic ring system and can be further categorized according to whether the D-ring is aromatic or nonaromatic (Figure 1). In addition, the C-ring is found as either a six-membered ring or a seven-membered ring. Thus, erythraline is an example of an aromatic erythrinan alkaloid and isophellibiline is a member of the nonaromatic homoerythrinan subclass. The majority of synthetic work has been devoted to the aromatic erythrinan subclass of compounds, and a number of syntheses have been recorded.[1,2] Most of the syntheses take advantage of a facile C(5)−C(13) ring closure, most commonly by attack of an electron-rich aromatic ring upon an *N*-acyliminium ion intermediate.[1,2] Consequently, the synthesis of the nonaromatic erythrinan subclass can be viewed as significantly more challenging,[3] and accordingly, only two of these natural products, cocculolidine[3d] and β-erythroidine,[3e] have been synthesized. In addition, the erythrina alkaloids exhibit an interesting pharmacology, including sedative, hypotensive, neuromuscular blocking, and CNS activity.[4] In particular, the dihydro derivative of

(1) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1996; Vol. 48, p 249.

(2) For very recent work, see: (a) Wang, Q.; Padwa, A. *Org. Lett.* **2006**, *8*, 601. (b) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185. (c) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373 and references therein.

(3) (a) Tsuda, Y.; Ishiura, A.; Hosoi, S.; Isobe, K. *Chem. Pharm. Bull.* **1992**, *40*, 1697. (b) Sano, T.; Toda, J.; Shoda, M.; Yamamoto, R.; Ando, H.; Isobe, K.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 3145. (c) Mohri, K.; Isobe, K.; Maeda, M.; Takeda, T.; Ohkubo, R.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1872. (d) Kawasaki, T.; Onoda, N.; Watanabe, H.; Kitihara, T. *Tetrahedron Lett.* **2001**, *42*, 8003. (e) Fukumoto, H.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2731.

(4) Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, p 1.

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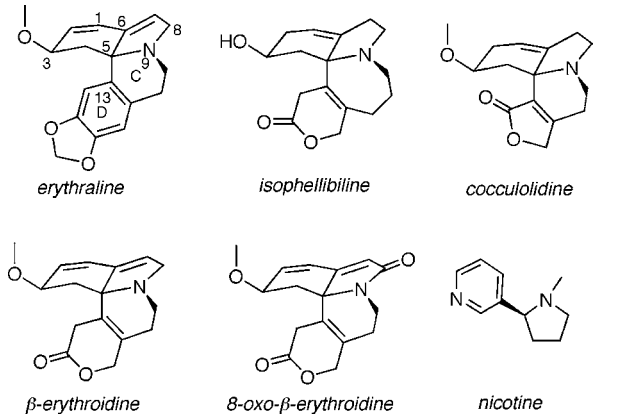
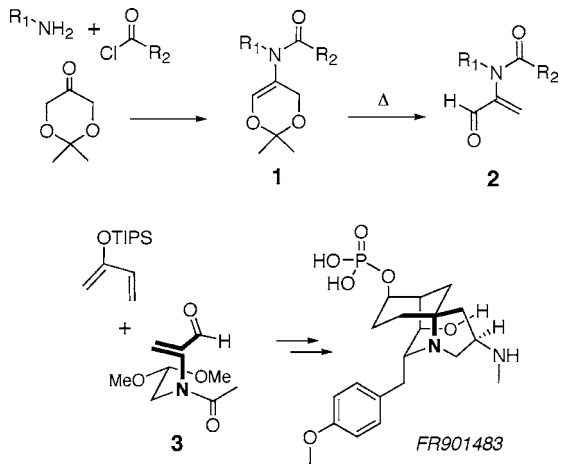


Figure 1. Erythrinan and homoerythrinan alkaloids.

β-erythroidine, 2,7-dihydro-β-erythroidine, is used extensively as a tool for understanding the biological consequence of nicotinic receptor stimulation because it is a potent neuronal nicotinic acetylcholine receptor antagonist (IC_{50} = 30 to 370 nM) but is not subtype-selective.[5] Subtype-selective nicotinic receptor antagonists would be useful for establishing the role of specific nAChR subtypes, may be useful for the treatment of neurological diseases[5,6] as well as smoking cessation,[7] and provide additional impetus for the development of a concise and flexible route to the nonaromatic erythrina alkaloids.

We have developed methodology that is particularly well-suited for the construction of the various nonaromatic erythrinan ring systems.[8] Thus, we have reported the total syntheses of several tricyclic alkaloids that initiate with a three-component assembly of 2,2-dimethyl-1,3-dioxan-5-one, a primary amine, and an acylating agent. The resulting amidodioxins **1** (Scheme 1) readily undergo bis-hetero

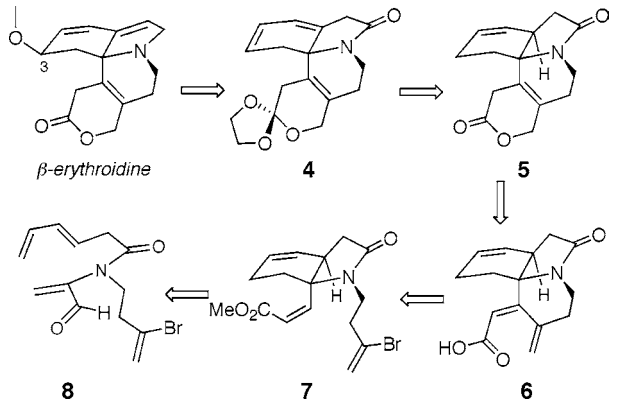
Scheme 1



retrocycloadditions upon heating in refluxing toluene to afford amidoacroleins **2** and acetone. The full potential of the amidoacrolein methodology was realized in our FR901483 total synthesis.[8a] Specifically, the trifunctional array of the 2-amidoacrolein **3** was completely incorporated into the natural product ring system, wherein each nitrogen substituent participated in a cyclization event (sequential Diels–Alder, aldol, and aldol reactions). We report herein the equally efficient application of this methodology in the concise total syntheses of β-erythroidine and 8-oxo-β-erythroidine.

Our retrosynthetic analysis is outlined in Scheme 2. Thus,

Scheme 2



we hoped that diene **4** would permit the installation of the C(3) methoxy substituent by one of several oxidation-based strategies. The diene **4** could be prepared from lactam **5** 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 kinetic protonation of a trienolate derivative. The β,γ-unsaturated lactone **5** could be obtained via a precedented 6π-electrocyclic ring closure[9] of the *E*-dienoic acid **6**, in turn, available from a stereospecific, intramolecular Heck reaction of the *Z*-enoate **7**. Finally, an *intramolecular* Diels–Alder cycloaddition of the amidoacrolein **8**, followed by a Still–Gennari *Z*-enoate synthesis,[10] was expected to afford the Heck cyclization substrate **7**.[11]

The synthesis began with the preparation of amidodioxin **12**, following the standard protocol for the formation of enamides (Scheme 3). Thus, the imine obtained by condens-

(5) (a) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169. (b) Dwoskin, L. P.; Crooks, P. A. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 395. (c) Jensen, A. A.; Frølund, B.; Liljefors, T.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2005**, *48*, 4704.

(6) Lippiello, P. M. *Med. Hypotheses* **2006**, *66*, 985.

(7) Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Wirtz, M. C.; Arnold, E. P.; Huang, J.; Sands, S. B.; Davis, T. I.; Lebel, L. A.; Fox, C. B.; Shrikhande, A.; Heym, J. H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R. S.; Chambers, L. K.; Rovetti, C. C.; Schulz, D. W.; Tingley, F. D.; O'Neill, B. T. *J. Med. Chem.* **2005**, *48*, 3474.

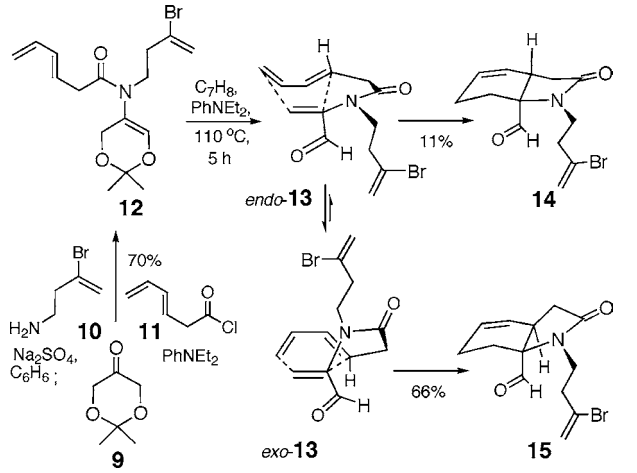
(8) (a) Maeng, J. H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125. (b) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3349. (c) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511. (d) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923. (e) Maeng, J. H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331.

(9) Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1982**, *23*, 5151.

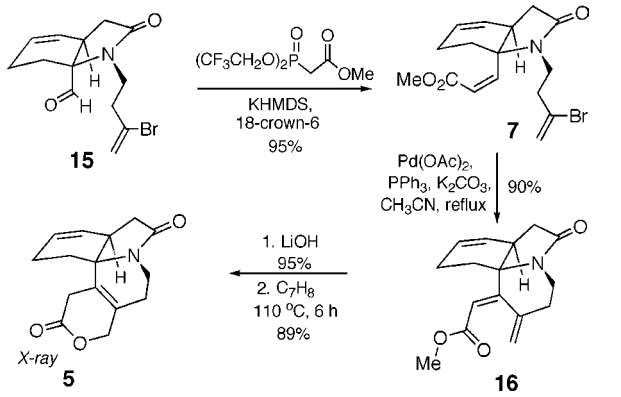
(10) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(11) This reaction sequence (Still *Z*-enoate synthesis, Heck reaction) has been previously employed in a vitamin D_3 synthesis, see: Nagasawa, K.; Ishihara, H.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523.

Scheme 3



Scheme 4



ing dioxanone **9** with amine **10**[12] in the presence of sodium sulfate was acylated with acid chloride **11**[13] to afford the appropriately functionalized amidodioxin **12**. Heating the dioxin **12** in the presence of the mild acid scavenger *N*,*N*-diethylaniline effected a smooth retrocycloaddition and concomitant cycloaddition to afford a 6:1 mixture of cycloadducts **15** and **14**, respectively. The stereochemistry for the major isomer **15** was assigned on the basis of a NOE between the aldehyde and the bridgehead proton NMR resonances, and the stereochemistry for the minor isomer **14** was based on X-ray crystallographic analysis of the corresponding 2,4-dinitrophenylhydrazone derivative. Presumably, the significant strain energy difference between *cis*-cycloadduct **15** and *trans*-cycloadduct **14** (∼5 kcal/mol, PCMODEL-MMX) is also present, to some extent, in the respective *exo*-**13** and *endo*-**13** transition states and, thereby, offsets any putative stabilization derived from a secondary orbital interaction in *endo*-**13**. In an attempt to render this total synthesis enantioselective, we subjected dioxin **12** to 0.05 equiv $SnCl_4$ in methylene chloride (0 °C, 30 min) and obtained amidoacrolein **8**. However, we were unable to catalyze the intramolecular cycloaddition of amidoacrolein **8** using either the Corey oxazaborolidine[14] or the MacMillan imidazolidinone catalysts.[15]

Our attention was now directed to the completion of the erythroidine ring system, following a route that went exceptionally well (Scheme 4). We were pleased to discover that the transformation of the neopentyl aldehyde **15** to the *Z*-enoate **7** proceeded quite smoothly in excellent yield using the Still−Gennari protocol.[10] Subjection of vinyl bromide **7** to Heck cyclization conditions was also uneventful (CH_3CN, reflux, 16 h) and furnished the *E*-dienoate **16** with clean inversion of alkene stereochemistry.[11] Finally, saponification of ester **16** and heating the resulting dienoic acid **6** in refluxing toluene (6 h) promoted a clean 6π-electrocyclic closure to lactone **5**, whose structure was secured by X-ray crystallographic analysis (Figure 2).

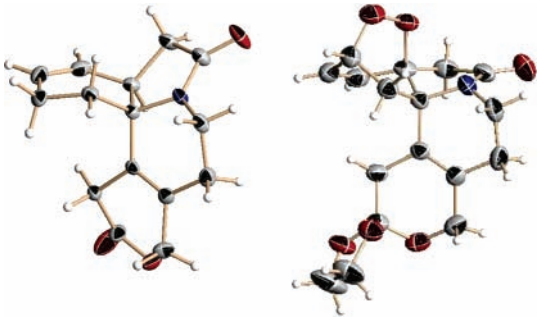


Figure 2. X-ray structures of **5** and endoperoxide derived from **4**.

To complete the total synthesis, the installation of the C(3) methoxy substituent[16] and the C(6)−C(7) unsaturation were required. All attempts to directly introduce the C(3) oxygen substituent into lactone **5** using selenium dioxide or chromium trioxide−pyrazole reagents failed. We were able to chemo- and stereoselectively brominate lactone **5** to produce the corresponding 1α,2β-dibromide (Br_2, $CHCl_3$, −60 °C), but attempts to effect double dehydrobromination to a diene led to intractable material. A solution to this problematic regiospecific oxidation problem was finally uncovered upon protection of lactone **5** as the corresponding ortho ester and introduction of the C(6)−C(7) unsaturation by the standard

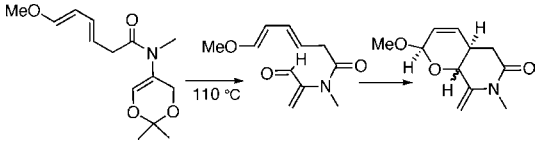
(12) Amine **10** was prepared in four steps and 56% overall yield from 3-butyn-1-ol, see: (a) Cousseau, J. *Synthesis* **1980**, 805. (b) Padwa, A.; Waterson, A. G. *Tetrahedron* **2000**, *56*, 10159.

(13) (*E*)-3,5-Hexadienoyl chloride was prepared in two steps from sorbic acid, see: Martin, S. F.; Tu, C.-Y.; Chou, T.-S. *J. Am. Chem. Soc.* **1980**, *102*, 5274.

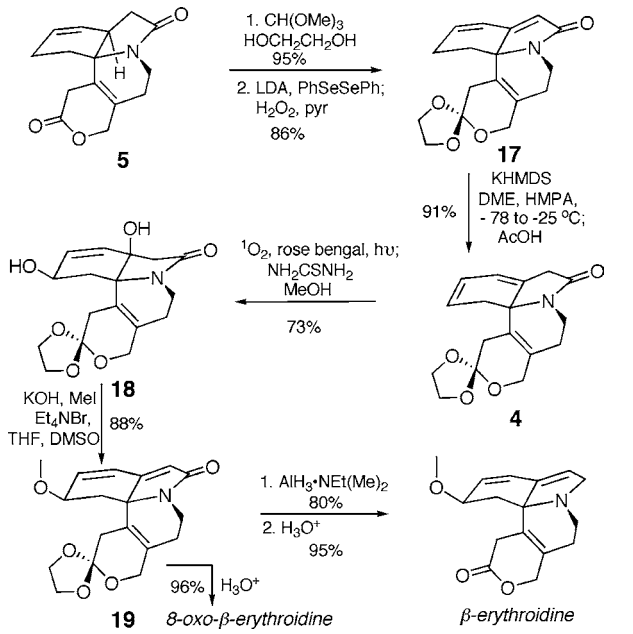
(14) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.

(15) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

(16) In an initial investigation, we had found that the methoxy substituent could not be introduced at the outset of the total synthesis due, in part, to a competitive hetero Diels−Alder cycloaddition reaction.



Scheme 5



selenylation, oxidative deselenylation procedure (Scheme 5). The resulting diene lactam **17** was then deconjugated to diene lactam **4**, which underwent a stereoselective cycloaddition with singlet oxygen from the face away from the bulky ortho ester substituent (0 °C, 2 h) to provide a single endoperoxide whose structure was confirmed by X-ray crystallographic analysis (Figure 2). Alternatively, a reductive workup of the reaction mixture using thiourea[17] provided the diol **18**, which now possesses the correct oxidation state at C(3). Subjection of diol **18** to potassium hydroxide in the presence of methyl iodide and a phase transfer reagent[18] effected simultaneous methylation of the C(3) hydroxyl and an E_{cb} reaction to reintroduce the C(6)−C(7) unsaturation present in lactam **7**. Hydrolysis of the ortho ester functionality of lactam **19** delivered 8-oxo-β-erythroidine, whose spectral properties were identical to those previously reported.[19] Finally, reduction of lactam **19** with alane−ethyldimethylamine complex, followed by hydrolysis of the ortho ester group, furnished β-erythroidine, whose spectral properties were identical to those previously reported.[19,20]

In conclusion, we have further demonstrated that the trifunctional domains of 5-amido-1,3-dioxins can be exploited in the rapid assembly of the polycyclic ring systems of natural products that embody an 1-azaspirocyclic substructure. In this specific application, an intramolecular amidoacrolein Diels−Alder cycloaddition, an intramolecular Heck reaction, and an electrocyclic closure of a dienoic acid are featured in the concise construction of the tetracyclic ring system of 8-oxo-β-erythroidine and β-erythroidine, the latter of which was prepared in 13 steps from dioxanone **9** in 13% overall yield. Moreover, this efficient strategy can be easily adapted for the preparation of other members of the nonaromatic erythrinan and homoerythrinan subclasses of natural products, as well as analogues of 2,7-dihydro-β-erythroidine, for the eventual discovery of subtype-selective nicotinic receptor antagonists. The studies are underway.

Acknowledgment. We thank Jim Fuchs (Pennsylvania State University) for the preliminary investigation of the retrocycloaddition/cycloaddition reaction of the *N*-methyl analogue of dioxin **12** and the dioxin shown in ref 16. We appreciate the financial support provided by the National Institutes of Health (GM28663).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087.
(19) Chawla, A. S.; Jackson, A. H.; Ludgate, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2903.
(20) Aguilar, M. I.; Giral, F.; Espejo, O. *Phytochemistry* **1981**, *20*, 2061.