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Synthesis of the *Erythrina* Alkaloid 3-Demethoxyerythratidinone. Novel Acid-Induced Rearrangements of Its Precursors

Qiu Wang and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

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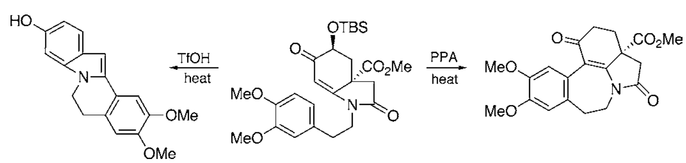
ABSTRACT



A new strategy for the synthesis of 3-demethoxyerythratidinone has been developed and is based on an extraordinarily facile intramolecular Diels–Alder reaction of a 2-imido-substituted furan. During the course of the synthesis, several novel acid-induced rearrangement reactions were encountered.

Erythrina alkaloids, a large class of natural products found in tropical and subtropical regions, represent attractive synthetic targets due to their use in indigenous medicine.[1] Members of the *Erythrina* family, as exemplified in Figure 1, display curare-like and hypnotic activity, and a variety of pharmacological effects are associated with the erythrinane skeleton, including sedative, hypotensive, neuromuscular blocking, and CNS activity.[2] Many different approaches have been employed for the synthesis of this class of natural products.[3] Taking the final step of bond formation into consideration, the methods for building up the erythrinan ring system can be loosely classified into seven different reaction types:

(1) C-ring formation with the C-5 quaternary center being constructed by intramolecular cyclization;[4] (2) C-ring formation by electrophilic substitution;[5] (3) A-ring formation by an intramolecular aldol reaction;[6] (4) A-ring formation from a benzoindolizidine fragment;[7] (5) B-ring formation utilizing a C-5 spiro-isoquinoline system;[8] (6) B- and C-ring formation by intramolecular annulation of dibenzazonine;[9] and (7) an assortment of miscellaneous methods.[10] In this paper, we

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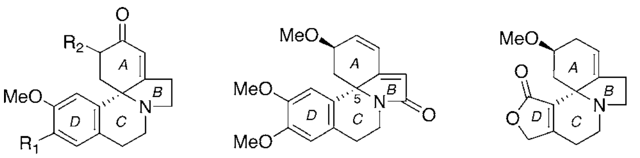


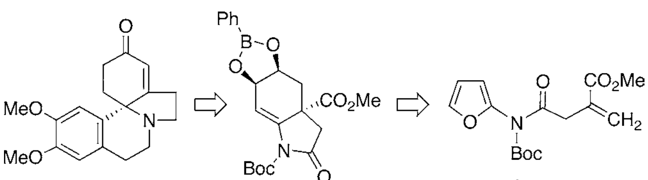
1; R_1 = OMe; R_2 = H; 3-Demethoxyerythratidinone
2; R_1 = H; R_2 = OMe; Coccudinone
3; Erysotramidine
4; Cocculolidine

Figure 1. Some representative *Erythrina* alkaloids.

report on a distinctively different strategy for the construction of the tetracyclic core of the erythrinane ring system.

Our approach toward the synthesis of a typical *Erythrina* alkaloid such as **1** derives from a program underway in our laboratory that is designed to exploit the facile Diels–Alder reaction of imidofurans for the purposes of natural product synthesis.[11] 3-Demethoxyerythratidinone (**1**) was first isolated in 1973 by Barton and his collaborators from *Erythrina lithosperma*.[12] Even though several syntheses have been reported,[6,13] we felt that this compound could serve to illustrate our methodology and provide a basis for a general cycloaddition approach toward *Erythrina* alkaloids. Our retrosynthetic analysis of **1** is shown in Scheme 1 and makes

Scheme 1



1; Demethoxy-erythratidinone
5
6

use of an IMDAF cycloaddition of imidofuran **6** followed by a Rh(I)-catalyzed reaction of the resulting cycloadduct with phenyl boronic acid[14] to give hexahydroindoline **5**. We anticipated that the erythrinane skeleton of **1** would be obtained by cyclization of a *N*-acyliminium ion[15] derived from a suitable aryl enamide precursor emanating from **5**.

The synthesis of imidofuran **6** began by coupling the known mixed anhydride of 3-carbomethoxy-3-butenoic acid (**7**) with the lithiated carbamate **9**, derived by treating furanyl-2-carbamic acid *tert*-butyl ester (**8**)[16] with *n*-BuLi at 10 °C. However, the expected imidofuran **6** was not isolated since the subsequent intramolecular [4 + 2]-cycloaddition occurred so rapidly that it was not possible to detect **6**, even at 0 °C. Our ability to isolate the somewhat labile (acid, heat) oxabicyclo adduct **10** (87%) is presumably a result of the low reaction temperatures employed as well as the presence of the carbonyl group, which diminishes the basicity of the nitrogen atom thereby retarding the ring cleavage/rearrangement reaction generally encountered with related furanyl carbamates.[17] We suspect that the facility of the cycloaddition is due to both the placement of the carbonyl center within the dienophile tether[18] as well as the presence of the carbomethoxy group which lowers the LUMO energy of the π-bond, thereby facilitating the cycloaddition.

Lautens and co-workers[14a,19] have recently demonstrated that the Rh(I)-catalyzed ring-opening reaction of unsymmetrical oxabicyclic compounds is a highly regioselective process, giving rise to products derived from the attack of the nucleophile distal to the bridgehead substituent. By taking advantage of this Rh(I)-catalyzed reaction, we were able to convert **10** into the ring-opened boronate **5** (97%), which was then converted to the corresponding diol by treatment with pinacol/acetic acid. Oxidation of the allylic hydroxyl group with MnO_2 followed by protection of the secondary OH group with TBSCl, removal of the Boc group, and a subsequent *N*-alkylation with 4-(2-bromoethyl)-1,2-dimethoxybenzene afforded enamido lactam **11** in 61% yield for the four-step sequence (Scheme 2).

Several acids were examined in our attempt to promote the planned acid-initiated Pictet–Spengler cyclization of lactam **11**. During the course of these studies, we encountered several novel rearrangement reactions. For example, when **11** was treated with polyphosphoric acid (PPA) in refluxing

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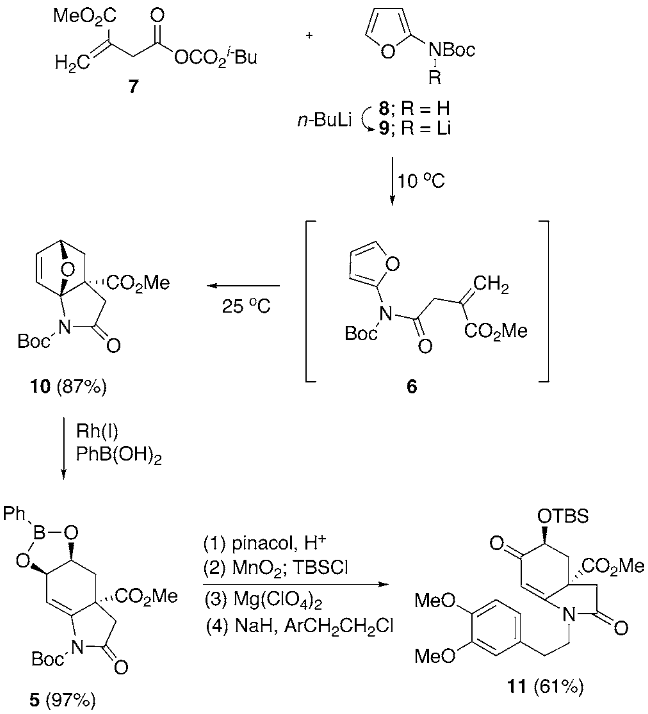
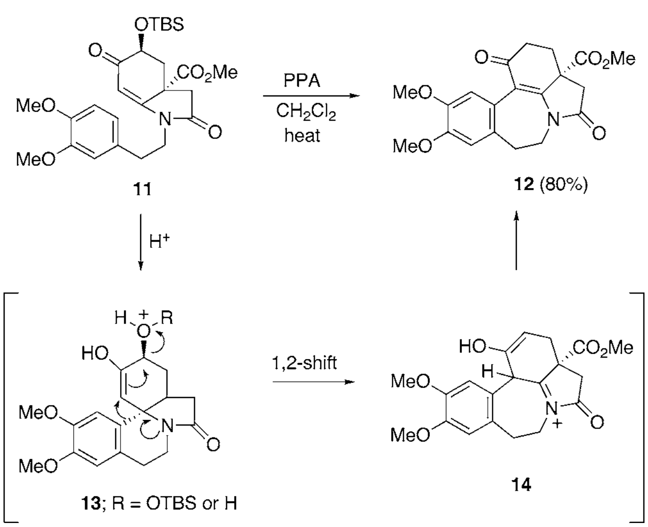
Scheme 2



CH_2Cl_2, the rearranged benzo[4,5]azepino lactam **12** was isolated in 80% yield and its structure was unequivocally established by X-ray crystallography (see the Supporting Information). This unusual reorganization can be rationalized by the pathway proposed in Scheme 3. We assume that the

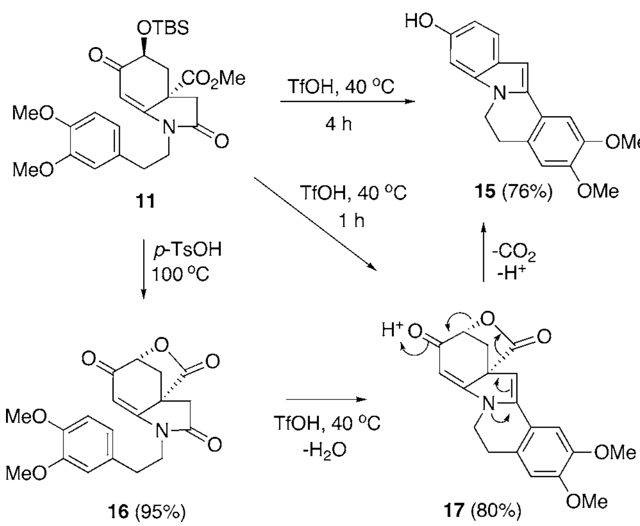
Scheme 3



first step involves generation of the tetracyclic erythrina intermediate **13**, which then undergoes a nitrogen-assisted 1,2-bond migration with simultaneous expulsion of water (or TBSOH) to produce the ring-expanded *N*-acyliminium ion **14**. Loss of a proton and subsequent enolization perfectly accounts for the formation of the observed product **12**.

In contrast to the rearrangement observed using PPA, heating a sample of **11** in CH_2Cl_2 with trifluoromethanesulfonic acid (TfOH)[20] followed by base workup afforded phenol **15** in 76% yield. Careful monitoring of the rearrangement by ^1H NMR spectroscopy revealed that the reaction proceeded via the intermediacy of lactone **17**, which could be isolated in 80% yield by terminating the thermolysis after 1 h. Further heating of **17** in the presence of TfOH afforded phenol **15** in 95% yield. When *p*-TsOH was employed as the acid promoter, a new intermediate (i.e., **16**) was now obtained in 95% yield. The isolation of **16** under these milder acidic conditions suggests that the initial step in the conversion of **11** → **15** involves formation of the γ-lactone ring. Exposure of **16** to TfOH in refluxing CH_2Cl_2 (1 h) resulted in the preferential cyclization of the activated aromatic ring onto the amido carbonyl group, producing **17** in 90% yield (Scheme 4).

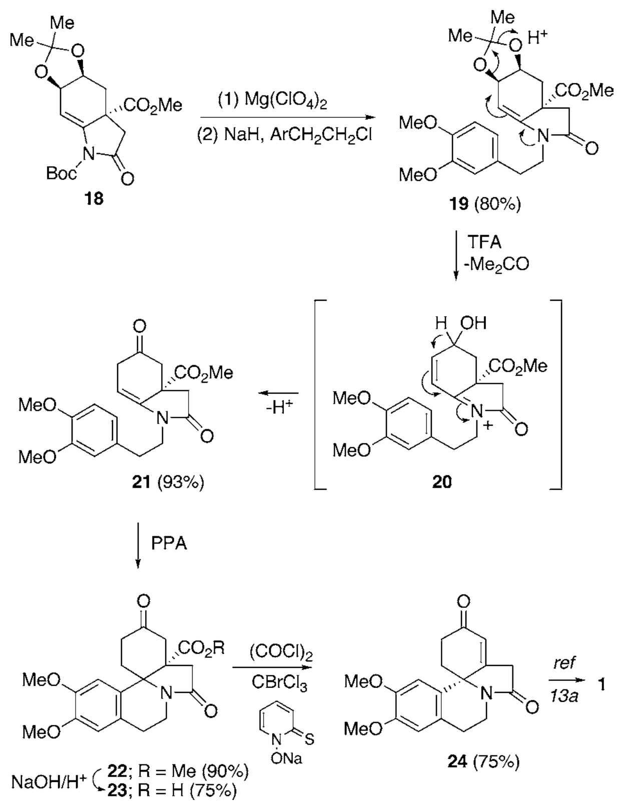
Scheme 4



Considering the difficulty we encountered with the traditional Pictet−Spengler reaction of enamido lactam **11**, we modified our approach toward 3-demethoxyerythratidinone (**1**). Boronate **5** was converted to the corresponding diol using pinacol/acetic acid, and this was followed by reaction with acetone to give acetonide **18** in 90% yield. Removal of the Boc group with $Mg(ClO_4)_2$ followed by *N*-alkylation using 4-(2-bromoethyldimethoxy)benzene gave lactam **19** (80%). On treating **19** with trifluoroacetic acid (TFA) in CH_2Cl_2 at 25 °C, we were pleased to isolate the desired hexahydroindolinone **21** (93%). As highlighted in Scheme 5, we believe that the reaction of **19** proceeds by an acid-induced loss of acetone to generate *N*-acyliminium ion **20**, which then loses the available allylic proton so as to dissipate the positive charge. Ketonization of the resulting enol produces **21**. The

(20) For an example of a TfOH-induced Pictet−Spengler cyclization, see: Nakamura, S.; Tanaka, M.; Taniguchi, T.; Uchiyama, M.; Ohwada, T. *Org. Lett.* **2003**, *5*, 2087.

Scheme 5



Pictet−Spengler reaction of **21** was carried out uneventfully with PPA to furnish the tetracyclic erythrinane **22** in 90% yield. Base hydrolysis of **22** gave carboxylic acid **23**, which was then subjected to Barton decarboxylation conditions[21] using $BrCCl_3$ as the solvent. A subsequent elimination of HBr from the labile tertiary bromide afforded the known 5*H*-indolo[7a,1a]isoquinolinedione **24**.[13a] This compound was converted to 3-demethoxyerythratidinone following the reductive method of Tsuda and co-workers.[13a]

In summary, a new strategy for the synthesis of the erythrina alkaloid family has been developed, which is based on an extraordinarily facile intramolecular Diels−Alder reaction of a 2-imido-substituted furan. By using a Rh(I)-catalyzed ring opening of the oxabicyclic adduct, it was possible to synthesize the key hexahydroindolinone necessary for a Pictet−Spengler cyclization. The application of this approach to other natural product targets is currently under investigation, the results of which will be disclosed in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds together with an ORTEP drawing for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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