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ARTICLE *in* ORGANIC LETTERS · MARCH 2006

Impact Factor: 6.36 · DOI: 10.1021/ol0527330 · Source: PubMed

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Org Lett. 2006 February 16; 8(4): 601–604.

Synthesis of the Erythrina Alkaloid 3-Demethoxyerythratidinone. Novel Acid-induced Rearrangements of its Precursors

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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 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 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

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(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 coworkers[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 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 Supplemental Section). This unusual reorganization can be rationalized by the pathway proposed in Scheme 3. We assume that the 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 ^{1}H-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).

Considering the difficulty we encountered with the traditional Pictet-Spengler reaction of enamido lactam **11**, we modified our approach toward 3-demethoxyerythratidin-one (**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 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[7*a*,1*a*]isoquinoline-dione **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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We appreciate the financial support provided by the National Institutes of Health (GM 059384) and the National Science Foundation (CHE - 0450779).

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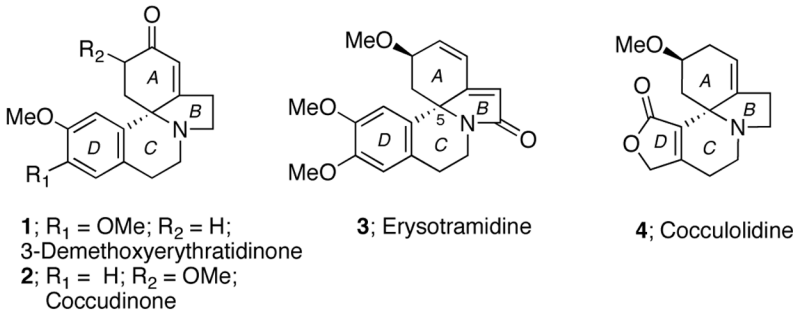
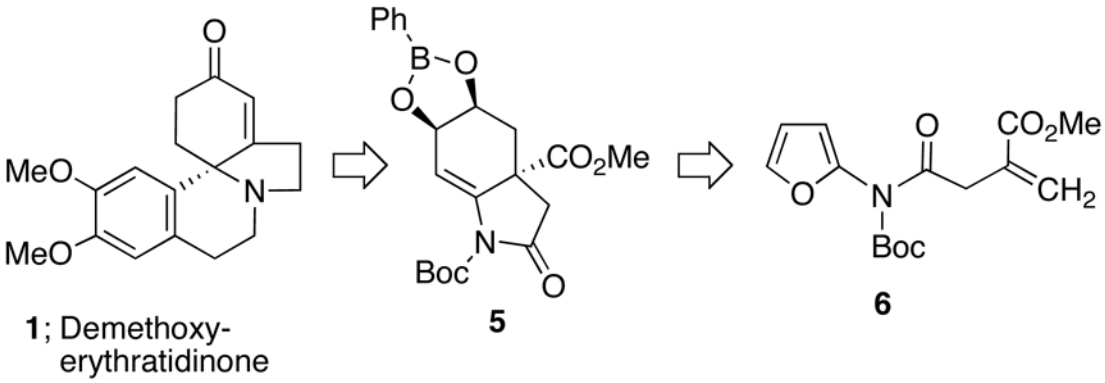


1; R_1 = OMe; R_2 = H; 3-Demethoxyerythratidinone
2; R_1 = H; R_2 = OMe; Coccudinone

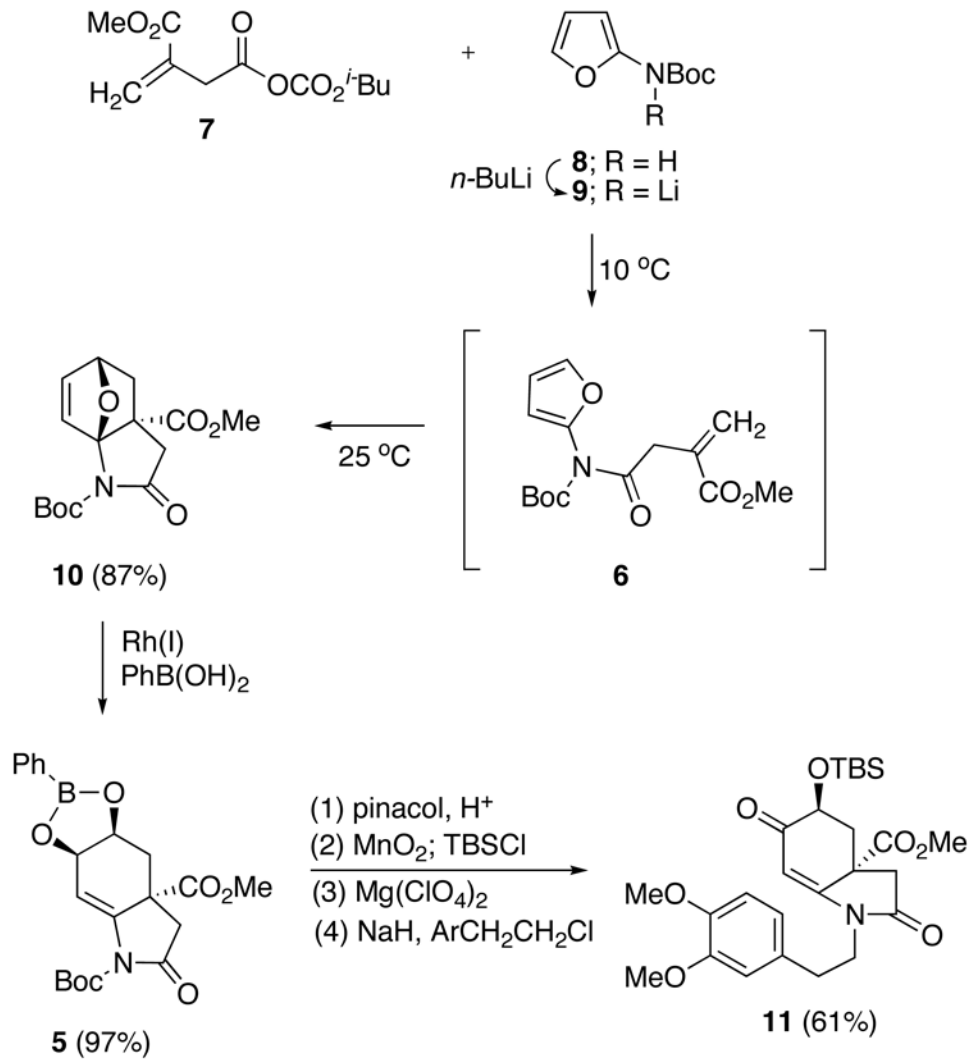
3; Erysotramidine

4; Cocculolidine

Figure 1.
Some Representative *Erythrina* Alkaloids



Scheme 1.



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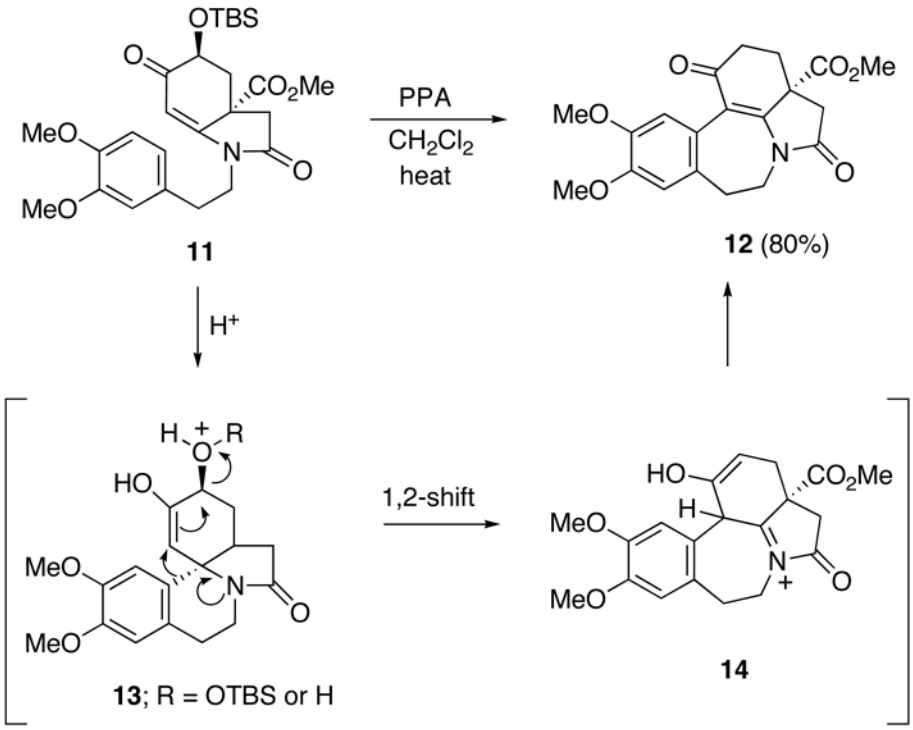

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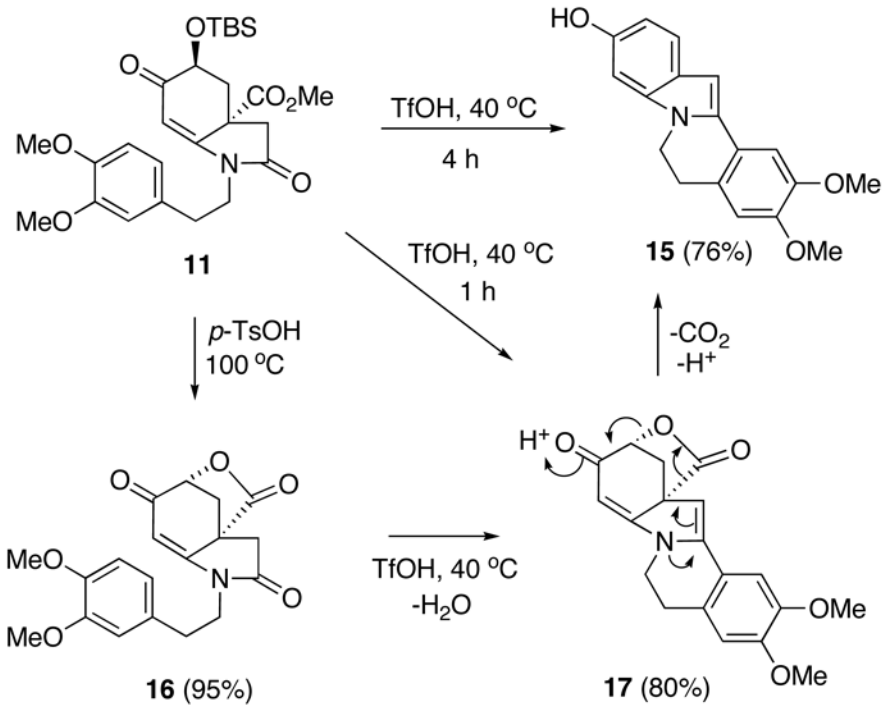
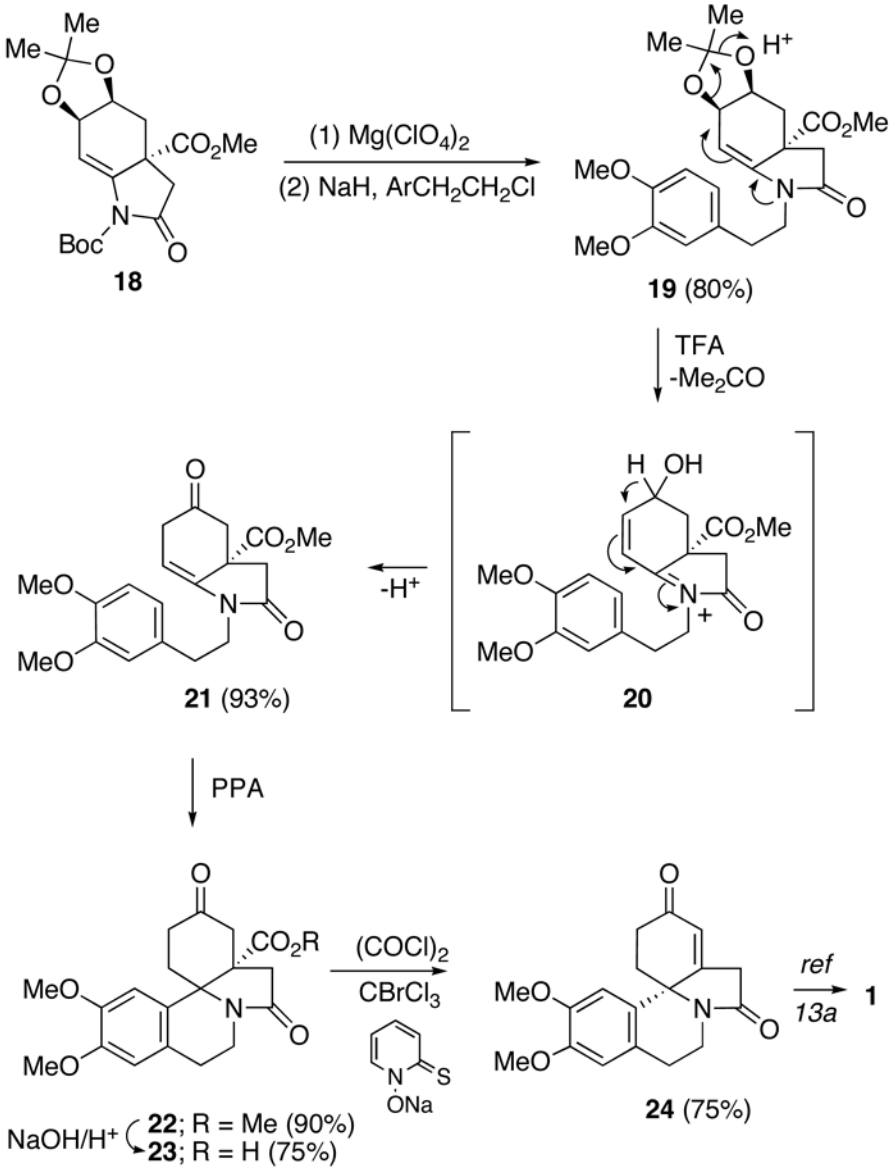


Scheme 4.



Scheme 5.