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Total Synthesis of (+)-3-Demethoxyerythratidinone and (+)-Erysotramidine via the Oxidative Amidation of a Phenol

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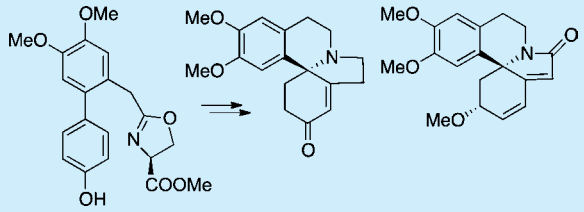
Supporting Information

ABSTRACT: Oxidative amidation chemistry provides a unified route to aromatic *Erythrina* alkaloids through a sequence that illustrates new principles and improved conditions to effect a crucial eliminative Curtius–Schmidt rearrangement.



An impressive diversity of techniques exist for the asymmetric synthesis of chiral amines, in which the N atom is bound to a secondary carbon atom.[1] By contrast, the enantiocontrolled creation of amines in which the N atom is bound to a *tertiary* carbon center remains an interesting synthetic challenge.[2] Such entities are found, for example, at the level of the spiro carbon of aromatic *Erythrina* alkaloids[3] such as (+)-3-demethoxyerythridatinone, **1**,[4] and (+)-erysotramidine, **2**[5] (Figure 1). Past syntheses of these alkaloids have addressed

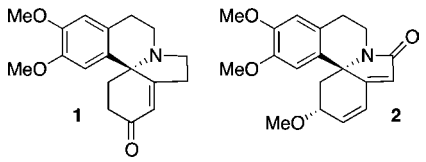


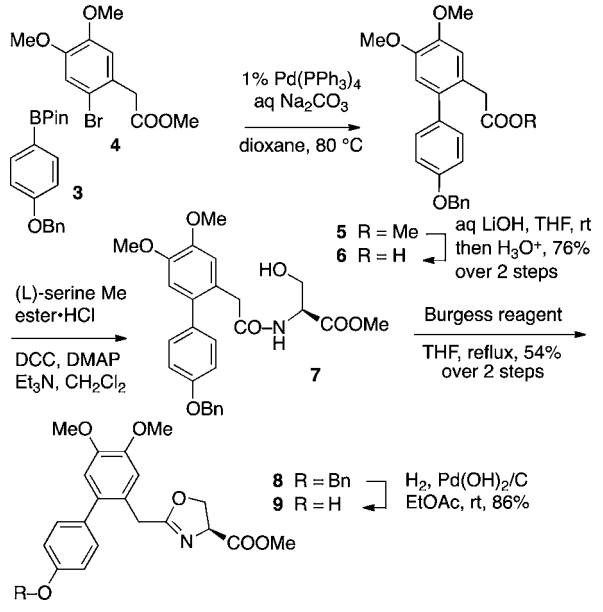
Figure 1. Structure of (+)-3-demethoxy-erythratidinone (**1**) and (+)-erysotramidine (**2**).

the problem by deriving key portions of the targets from chiral educts (L-DOPA,[6] malic acid,[7] certain lactams,[8] tartaric acid,[9] or other materials obtained by resolution[10]); by desymmetrization of a *meso*-imide with a chiral base;[11] by relaying axial chirality to the spiro center;[12] or by nucleophilic addition of organometallic agents to Ellman sulfinylimines derived from quinone monoketals.[13]

This paper describes a route to (+)-**1** and (+)-**2** from a common intermediate obtained by oxidative cyclization of a phenolic oxazoline.[14] A highly diastereoselective Michael-type cyclization of the product desymmetrizes a "locally symmetrical" dienone,[15] thus securing the correct configuration of the spirocenter. An efficient formation of spiropiperidines via oxidative amidation chemistry (heretofore a problematic objective) by the use of conformationally constrained substrates is also demonstrated.

The first subtarget of the synthesis, oxazoline **9** (Scheme 1), was prepared starting with Suzuki coupling of commercial **3** and **4** and hydrolysis of the resultant ester **5** to acid **6**. The union of the latter with methyl serinate•HCl furnished **7**, which

Scheme 1. Preparation of Oxazoline 9



upon cyclization[16] and catalytic debenzylation provided **9**. The oxidative cyclization of this oxazoline (Scheme 2)[17] was best accomplished with [bis(trifluoroacetoxy)iodo]benzene in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), producing **10** in 62% yield. Spiropiperidine-forming oxidative cyclizations of conformationally unbiased substrates afford generally mediocre yields.[17] The efficiency of the present reaction is attributable to conformational constraints imposed by the dimethoxyphenyl unit, which predisposes the oxazoline to capture the electrophilic intermediate arising through oxidative activation of the phenol. Michael cyclization of **10** occurred upon treatment with TsOH, and furnished enone **11** as a single diastereomer,[18] thus

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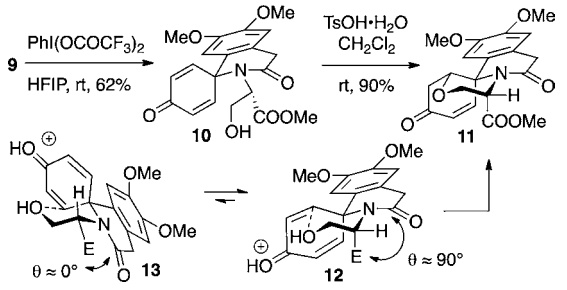
Scheme 2. Oxidative Cyclization of 9 and Stereoselective Formation of 11



securing the correct (*R*)-configuration of the spiro carbon (confirmed by X-ray diffractometry, Figure 2).[19] Stereorelay

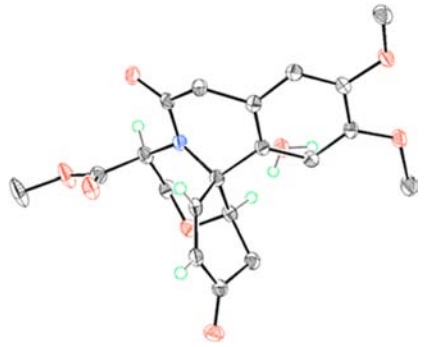
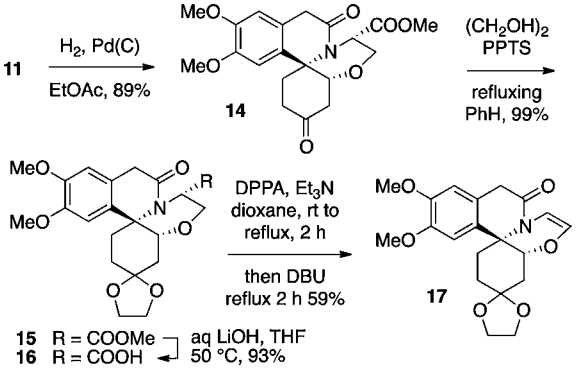


Figure 2. X-ray structure of lactam **11** (·H_2O).

from the serine fragment to the spirocenter thus occurred with perfect fidelity. The stereochemical outcome of this step may be understood by recognizing that groups adjacent to the N atom in the *N*-acylmorpholine unit of **11** favor an axial position, so as to minimize nonbonding interactions with the *N*-acyl group.[20] Assuming that cyclization occurs via a chairlike transition state, then **11** forms via conformer **12**, where the COOMe (depicted in **12** and **13** as E) is pseudoaxial in the developing morpholine. The diastereomer of **11** would result via **13**, wherein the pseudoequatorial COOMe is compressed against the *N*-acyl group.

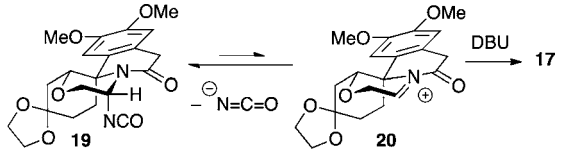
Catalytic reduction of **11** (Scheme 3) returned **14** and denied the molecule any opportunity for loss of configuration at the spiro center. In principle, the five-membered ring of the target alkaloids could be created from two of the serine carbons in **14**. However, numerous difficulties arose during attempts in

Scheme 3. Preparation of Enamide 17



that sense, leading to the conclusion that it was best to excise the serine portion altogether. Compound **14** was thus advanced to acid **16**, in preparation for an eliminative Curtius–Schmidt rearrangement *à la* Bermejo–Gonzalez (**16** → **17**).[21] However, the reaction of **16** with diphenyl phosphorazidate (DPPA)[22] under the reported conditions (toluene, Et_3N, 90 °C)[21] afforded only some of the desired **17**, the major product being isocyanate **19** (Scheme 4). VanNieuwenhze et al., also observed low yields of enamide under such conditions.[23]

Scheme 4. Likely Mechanism for the Formation of 17

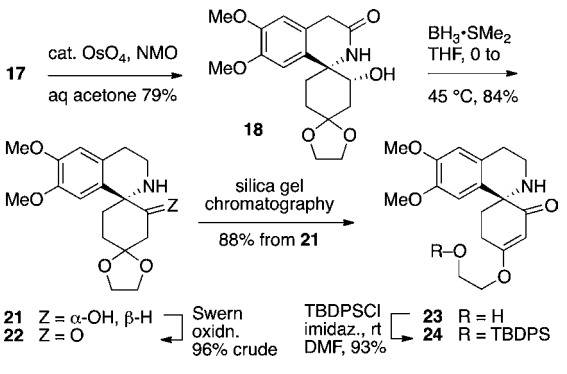


It should be noted that the DPPA protocol is more attractive than alternative methods that effect the same transformation, in that it delivers the enamide in one step and avoids the use of transition- or heavy metals. Indeed, such alternatives require two steps from the acid and involve oxidative decarboxylation by electrochemical means,[24] by reaction with Pb(IV)[25] or I(III)[26] reagents, or by photolysis of *N*-nitroso derivatives,[27] as well as Ni- or Pd-mediated dehydrocarbonylation of thioesters.[28,29] We thus sought to improve the published DPPA procedure.

In accord with VanNieuwenhze,[23] operation in dioxane, instead of toluene, afforded a slightly greater amount of **17**, although the major product remained **19**. The addition of DBU to a mixture of **19** and **17** thus obtained, and continued refluxing, induced conversion of **19** into **17** (reaction monitored by ^1H NMR).[19b] Thus, enamide **17** forms from **19**. It is unlikely that isocyanate ion acts as a leaving group in E2 reactions.[30] We presume that thermal activation of **19** reversibly forms acyliminium ion **20**, deprotonation of which then gives **17**. Notice that the axial N=C=O group can depart with assistance from the lactam N atom. Furthermore, the use of more polar dioxane in lieu of toluene is likely to favor this dissociative step. On the basis of the foregoing, acid **16** was elaborated to **17** in 59% yield by reaction with DDPA and Et_3N in dioxane (rt to reflux, 2 h), followed by the addition of DBU and further refluxing for 2 h.

Upjohn[31] dihydroxylation of **17** produced lactam **18** (Scheme 5), probably through release of the etheno bridge as glyoxal.[32] The amide carbonyl in **18** should facilitate access to

Scheme 5. Preparation of Ketones 22 and 24



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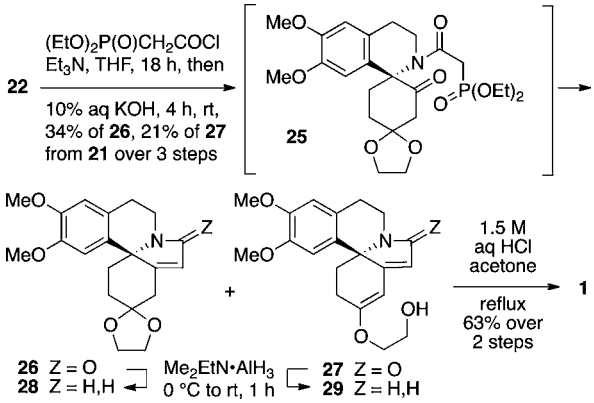
Erythrina alkaloids in which additional oxygen functionalities, or a double bond, are present on the piperidine ring.[33] Therefore, lactam **18** may be regarded as a "universal" precursor of such alkaloids.[34] However, the C=O group is not required for **1**–**2**; therefore, **18** was reduced to **21**. Interestingly, the N atom in **21** was found to be completely devoid of nucleophilic reactivity.[35] The reasons for this are unclear, but one may speculate that the sterically hinderered nature of that N atom, and the probable existence of a strong H-bond between it and the neighboring OH group, combine to suppress nucleophilic character completely. However, lack of *N*-nucleophilic reactivity enabled Swern oxidation of **21** to **22**,[36] which served as the forerunner of **1**. Ketone **22** was not amenable to chromatographic purification and was best used in crude form. Indeed, contact with silica gel caused quantitative conversion into **23**, which in turn proved to be a good precursor of **2**. Yet, compound **23** tended to cyclize back to **22** under acidic conditions. Such a proclivity was suppressed by protection of the OH group (**23** → **24**).

Unlike **21**, ketones **22** and **24** readily underwent *N*-acylation. The synthesis of (+)-**1** was thus completed by reaction of crude **22** with $(EtO)_2P(O)CH_2COCl$ and *in situ* treatment of the resultant **25** with aq KOH[37] (Scheme 6). A mixture of readily

Scheme 6. Completion of the Synthesis of (+)-3-Demethoxyerythratidinone 1

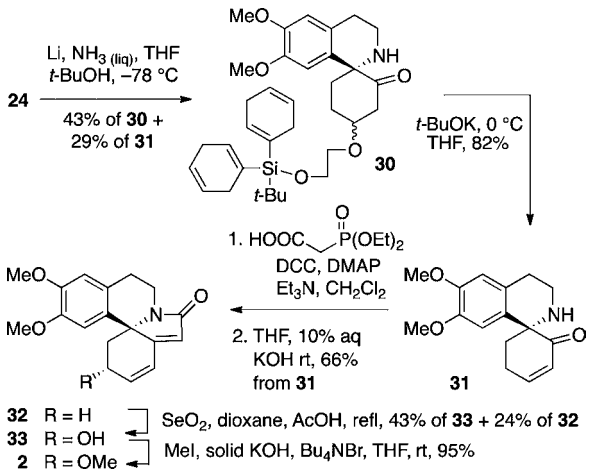


separable lactams **26** and **27** resulted. Separation of the two, however, was unnecessary: reduction of the mixture (AlH_3•$NEtMe_2$) afforded **28** and **29**, acidic hydrolysis of which delivered (+)-**1**.

The conversion of **24** into (+)-**2** (Scheme 7) started with conjugate reduction ($Li/NH_{3(liq)}$).[38] Concomitant, but inconsequential, Birch reduction of the TBDPS phenyl groups occurred during this step, leading to a mixture of diastereomers of **30** (43%), plus a significant amount of the actual desired product: enone **31** (29%). The two ketones were readily separated, and **30** was converted into **31** by treatment with *tert*-BuOK. The overall yield of **31** was 64%. Acylation of **31** (diethyl phosphonoacetic acid, DCC) and cyclization of the resultant phosphonamide gave the known erysotramidine precursor **32**,[4n] which was uneventfully advanced to (+)-**2** by a literature method.[4n,6a]

In summary, a unified approach to aromatic *Erythrina* alkaloids has been established through lactam **18**, bringing the above natural products within the scope of oxidative amidation chemistry.

Scheme 7. Completion of the Synthesis of (+)-Erysotramidine



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^1H and ^{13}C NMR spectra of new compounds, and X-ray crystal data of compound **11**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01423.

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Notes

The authors declare no competing financial interest.

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