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Efficient Synthesis of (±)-Erysotramidine Using an NBS-Promoted Cyclization Reaction of a Hexahydroindolinone Derivative

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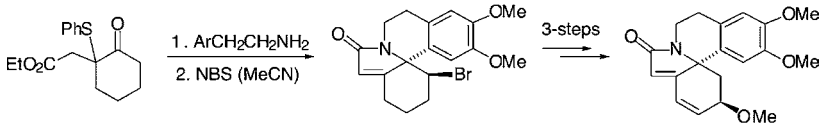
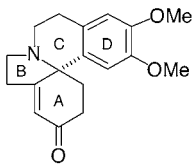
ABSTRACT



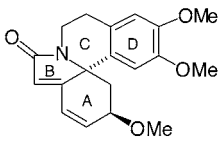
(±)-erysotramidine

An NBS-promoted intramolecular electrophilic aromatic substitution reaction of a hexahydroindolinone derivative was used to assemble the tetracyclic core of the erythrinane skeleton. The resulting cyclized product was transformed into (±)-erysotramidine in three additional steps. The cyclization reaction is also successful using variously substituted aryl and furanyl bicyclic lactams under acidic conditions.

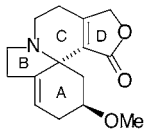
The Erythrina family of alkaloids are a well-known class of natural products that have received considerable attention over the past few decades.[1] Many members of this family possess curare-like activity, and the alkaloidal extracts have been used in indigenous medicine.[2] Erythrina alkaloids are generally classified into two groups according to their structural features;[3] those whose D-rings are aromatic (e.g., 3-demethoxyerythratidinone (**1**) and erysotramidine (**2**)) and the others whose D-rings possess an unsaturated lactone (e.g., cocculolidine (**3**)).[4] Many different approaches have been



3-demethoxy-erythratidinone (**1**)



erysotramidine (**2**)



cocculolidine (**3**)

employed for the synthesis of this class of natural products. 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;[5] (2) C-ring formation by electrophilic substitution;[6] (3) A-ring formation by an intramolecular aldol reaction;[7] (4) A-ring formation from a benzoindolizidine fragment;[8] (5) B-ring formation utilizing a C-5 spiro-isoquinoline system;[9] (6) B- and C-ring formation

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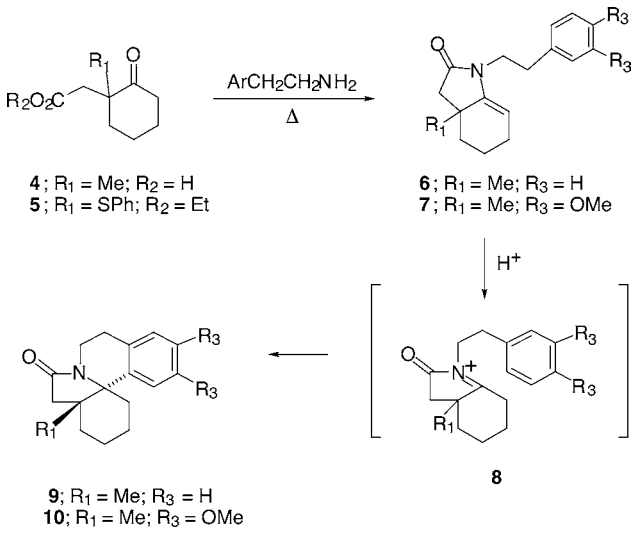
by intramolecular annulation of dibenzazonine[10] and (7) an assortment of miscellaneous methods.[11] Despite the availability of many synthetic methods for the Erythrina alkaloids, there still exists a need to develop procedures more efficient than those currently in existence. In earlier studies, our group had reported on the use of a tandem Diels−Alder/*N*-acyliminium ion cyclization cascade[12] as well as a thionium-promoted Mannich strategy[13] for assemblage of the erythrinan skeleton. In this paper, we describe an alternative approach to construct the tetracyclic core of the Erythrina family which makes use of an NBS-induced cyclization of a hexahydroindolinone derivative.

On the basis of our earlier work with the Erythrina skeleton, we reasoned that a suitably substituted hexahydroindolinone *N*-acyliminium ion precursor might allow for a facile entry to the tetracyclic core of erysotramidine (**2**) (vide infra).[14] This approach which, in the event, proved successful was initially tried using several model compounds. Our synthesis of the starting bicyclic lactam substrates followed a methodology similar to that previously described in the literature.[15] Condensation of the appropriate amine with a (1-substituted 2-oxocyclohexyl)acetic acid derivative (i.e., **4** or **5**) under Dean−Stark conditions in xylene at 160 °C for 1 h afforded the desired bicyclic lactams in high yield. The resulting aryl lactam precursors (i.e., **6** and **7**) were smoothly converted to the desired tetracyclic products in essentially quantitative yield when treated with either trifluoroacetic acid (**9**) or trifluoromethanesulfonic acid (**10**). The formation of a single lactam diastereomer is the result of the stereoelectronic preference for axial attack by the aromatic ring of the *N*-acyliminium ion (**8**) from the least hindered side (Scheme 1).[16]

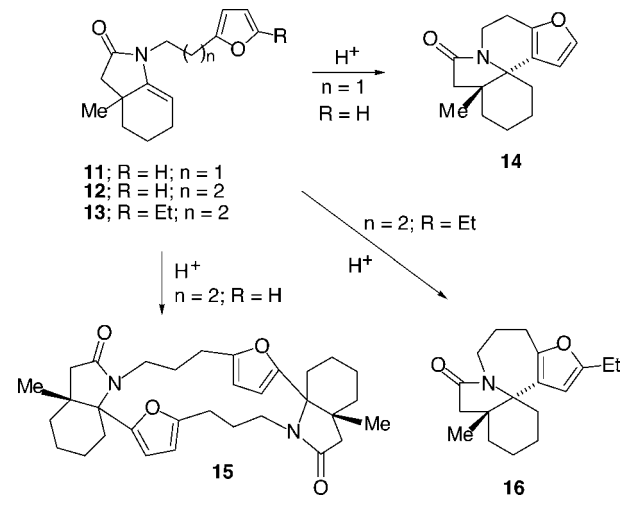
We were pleased to find that the analogous furanyl-substituted hexahydroindolinone system **11** also underwent a related acid-induced cyclization to give the tetracyclic substituted lactam **14** in 78% yield. This cyclization is especially noteworthy considering that none of the previously

Scheme 1



reported syntheses of the nonaromatic erythroidine alkaloids have employed this strategy of assemblage.[17] To demonstrate that this methodology could also be used for β-phenethylamine pharmacophores[18] possessing the homoerythrina skeleton, the homologous furan **12** ($n = 2$) was subjected to the acid-catalyzed cyclization conditions (Scheme 2). Interest-

Scheme 2



ingly, the only product isolated in 54% yield corresponded to the novel dimeric furanyl bis-lactam **15** which is derived by bimolecular trapping of the *N*-acyliminium ion at the more

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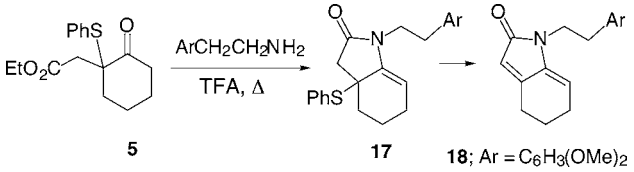
(17) The β-erythroidine skeleton has been prepared by an oxidative degradation of the aromatic ring (ring A) in erythrinans as the key step; see: Isobe, K.; Mohri, K.; Itoh, Y.; Toyokawa, Y.; Takeda, N.; Taga, J.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2632.

(18) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148.

activated 5-position of the furan ring. When this position is blocked by the incorporation of an ethyl substituent, intramolecular cyclization occurs at the 3-position of the furan ring to give tetracyclic lactam **16** in 96% yield.

We were now in a position to apply the experience gained from our model studies to the synthesis of erysotramidine (**2**) itself. To this end, bicyclic lactam **18** was prepared in 73% yield by condensation of 3,4-dimethoxyphenethylamine with ketoester **5** in the presence of TFA (Scheme 3). The

Scheme 3

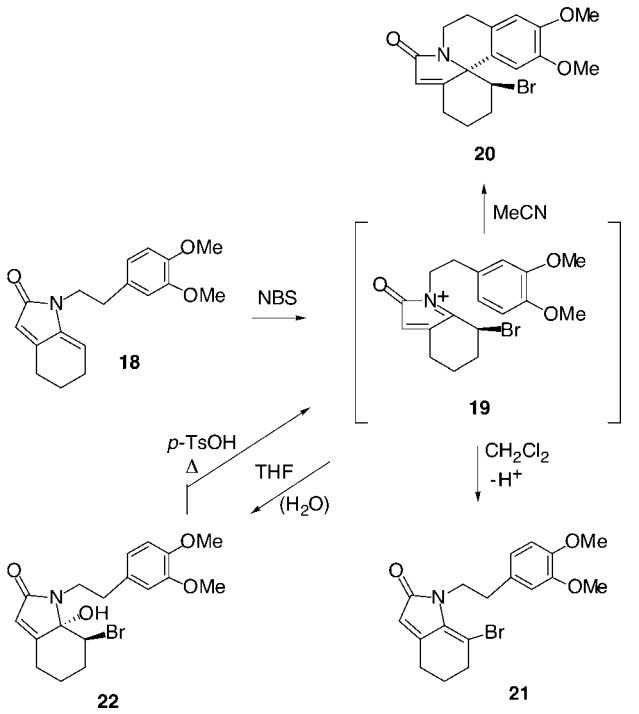


formation of the α,β-unsaturated ene-amide **18** presumably involves initial generation of the expected hexahydroindolinone **17** followed by an acid-catalyzed elimination of the phenylsulfanyl group. With **18** in hand, we attempted to induce an acid-promoted cyclization but all of our efforts failed to produce any characterizable products, perhaps as a consequence of the antiaromatic character of the resulting cationic intermediate.

We were pleased to discover, however, that bicyclic lactam **18** underwent an extremely smooth cyclization to the desired erythrinan skeleton (i.e., **20**) in 78% yield when treated with NBS in acetonitrile. It is of interest to note that this reaction is markedly dependent on the nature of the solvent and that acetonitrile is the only solvent used which favors cyclization (Scheme 4). Thus, when **18** was subjected to NBS in CH_2Cl_2, bromo ene-amide **21** was obtained in 87% yield and its formation can be attributed to a competitive deprotonation of the presumed *N*-acyliminium ion intermediate **19**. The reaction of **18** with NBS in THF furnished aminal **22** in 77% yield which, in turn, gave a 5:3 mixture of **20** and **21** when heated with a trace of *p*-TsOH in CH_3CN. These unanticipated findings can be linked to the polarity of the solvent and consequently the reactivity of the incipient *N*-acyliminium ion **19**. The more polar solvent (CH_3CN) stabilizes the *N*-acyliminium ion and allows the cyclization to proceed. The other solvents favor deprotonation (CH_2Cl_2) or trapping of the cation by some adventitious water that was present in THF.

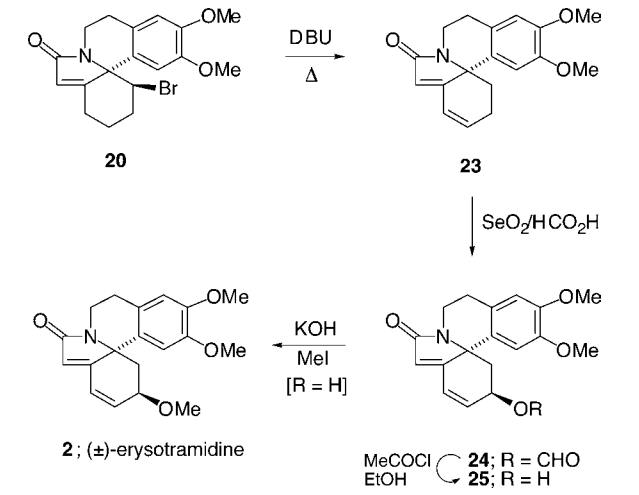
Subjection of **20** to DBU in refluxing xylene furnished the α,β,γ,δ-unsaturated diene amide **23** in 75% yield. This product is presumably formed by an initial dehydrobromination followed by isomerization of the π-bond into the thermodynamically most stable position. Stereoselective allylic oxidation with selenium dioxide in the presence of formic acid gave a 1:1-mixture of formate **24** and alcohol **25** in 60% yield (based on recovered starting material) as single diastereomers. The stereochemical outcome of the oxidation involves attack by the oxidant from the least hindered α-position. Formate **24** was quantitatively transformed

Scheme 4



into alcohol **25** by treatment with acetyl chloride in ethanol.[19] Finally, compound **25** was converted into (±)-erysotramidine (**2**) in 91% yield by *O*-methylation using KOH/MeI in THF according to Tsuda's method (Scheme 5).[14]

Scheme 5



In summary, we have shown that the intramolecular electrophilic aromatic substitution reaction of hexahydroindolinones allows for the rapid construction of the tetracyclic erythrinane skeleton. We expect that the total syntheses of other nonaromatic erythroidine alkaloids will also benefit

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from this general strategy. These investigations are currently under way.

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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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