Tandem Diels−Alder *N*-Acyliminium Ion Cyclization Reactions. A New Entry into the Erythrinane Skeleton

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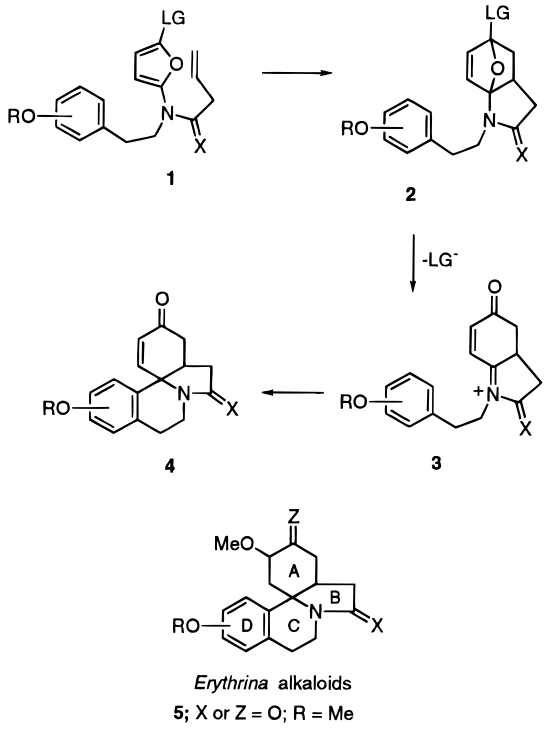
The Erythrina family of alkaloids are a well-known class of natural products that have received considerable attention over the past few decades.[1] Many members of this family possess curare-like activity, and the alkaloidal extracts have been used in indigenous medicine. The vast majority of naturally occurring Erythrina alkaloids possess the tetracyclic framework and substitution pattern shown in structure **5** (Scheme 1). Following the early pioneering studies by Mondon[2] on the assembly of the basic erythrinane skeleton, a wide array of methods have been developed for the synthesis of this class of natural products.

Tandem or cascade processes belong to a growing family of reactions that allow the regio- and stereocontrolled formation of several carbon−carbon bonds and/or ring systems in a single operation.[3] Important contributions to this area have been realized utilizing a combination of cationic, anionic, radical, carbenoid, or pericyclic processes.[4] Few reactions can compete with the Diels−Alder cycloaddition with respect to the degree of complexity that can be accomplished in a single synthetic step.[5] Carbon−carbon bond-forming reactions involving *N*-acyliminium ions play an equally important role in the synthesis of nitrogen heterocycles and alkaloidal target molecules.[6]

A sequential combination of these two powerful synthetic methods would allow for the rapid, stereocontrolled synthesis of a variety of azapolycyclic products. Of particular interest to us in this context is the possibility of using 2-amino substituted furans such as **1** containing both a suitable leaving group (LG) and an olefinic tether to allow for an intramolecular Diels−Alder reaction (Scheme 1). The resulting cycloadduct **2** is expected to readily undergo ring-opening to generate a vinylogous C-acyliminium ion of type **3**. Iminium ions such as **3** have great potential for undergoing subsequent cyclization chemistry.[6] As outlined in Scheme 1, this sequence of reactions allows for a rapid entry into the erythrinane skeleton **5**, where the key ABC ring system is assembled in a single operation (**1** → **4**), and which also allows the oxygen functionality to be placed in the appropriate position. In this paper we report on some model studies

Scheme 1



leading to the stereoselective synthesis of the 3,4-benzoerythrinane skeleton utilizing this novel triple cascade process.

Recent work in our laboratory has shown that the α-thiocarbocation generated from the Pummerer reaction of an *o*-amido-substituted sulfoxide can be intercepted by the adjacent carbonyl group to produce an α-amino isobenzofuran.[7] This transient intermediate then undergoes a subsequent bimolecular Diels−Alder cycloaddition with added dienophiles.[7] This observation led us to study the intramolecular cycloaddition reaction of sulfoxides **7** and **8** (Scheme 2). Slow addition of the sulfoxides to a refluxing mixture of *p*-xylene, acetic anhydride (10 equiv), and *p*-toluenesulfonic acid (5 mol %)[8] led to the formation of aminonaphthols **12** and **13** in 75 and 59% yield, respectively. The isolation of these oxindoles supports the proposed *cyclization−cycloaddition/ring-opening/elimination* sequence **7/8** → **9** → **10** → **11**. With these systems, the initially formed iminium ion **11** rapidly undergoes deprotonation followed by O-acetylation to afford the isolated products **12** and **13**.

Having established the facility with which the requisite *N*-acyliminium ion intermediate can be formed, we next focused our attention on the final cyclization step of the proposed cascade process. The requisite sulfoxide precursor **15**, possessing a diactivated aromatic π-tether, was readily synthesized in four steps from the known carboxylic acid **14**. Subjection of **15** to the standard Pummerer reaction conditions did not lead to the desired benzoerythrinane derivative, but gave benzoindole **21** in 78% yield (Scheme 3). An analogous process occurred with the isomeric amido sulfoxide **16**, producing indole **22** in 76% yield. In both cases, the deprotonation of the initially formed iminium ion (**20**; R = H) is much faster than spirocyclization. The driving force associated with this rapid deprotonation undoubtedly involves formation

(1) Deulofeu, V. In *Curare and Curarelike Agents;* Bovet, D., Bovet-Nitti, F., Marini-Bettolo, G. B., Eds.; Elsevier: Amsterdam, 1959; p 163.

(2) Mondon, A. *Chem. Ber.* **1959**, *92*, 1461; **1959**, *92*, 1472. Mondon, A.; Hansen, K. F. *Tetrahedron Lett.* **1960**, 5. Mondon, A.; Nestler, H. J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 588.

(3) Ho, T. L. *Tandem Organic Reactions;* Wiley: New York, 1992. Tietze, L. F. Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. Wender, P. A., Ed. Frontiers in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 1−600.

(4) For a recent classification of cascade/domino reactions, see: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(5) Roush, W. R. in *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, p 91.

(6) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082.

(7) Kappe, C. O.; Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 9285.

(8) Watanabe, M.; Nakamori, S.; Hasegawa, H.; Shirai, K.; Kumamoto, T. *Bull. Chem. Soc. Jpn.* **1981**, *57*, 817.

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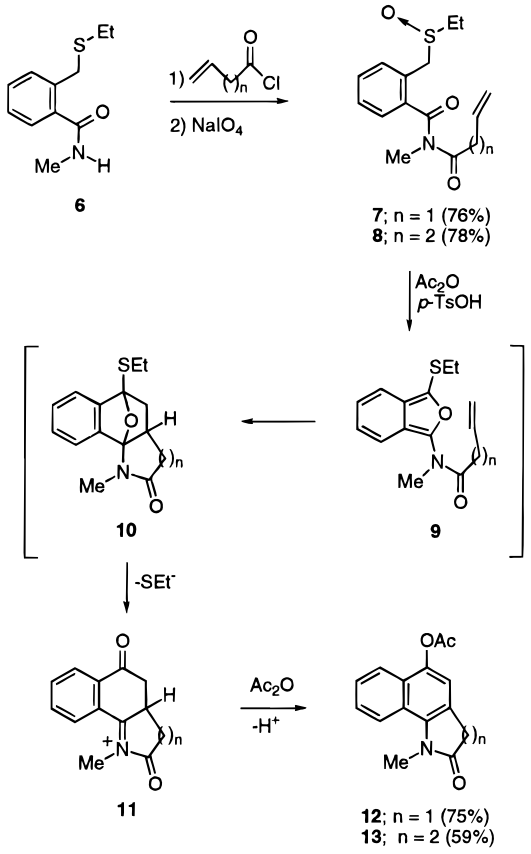
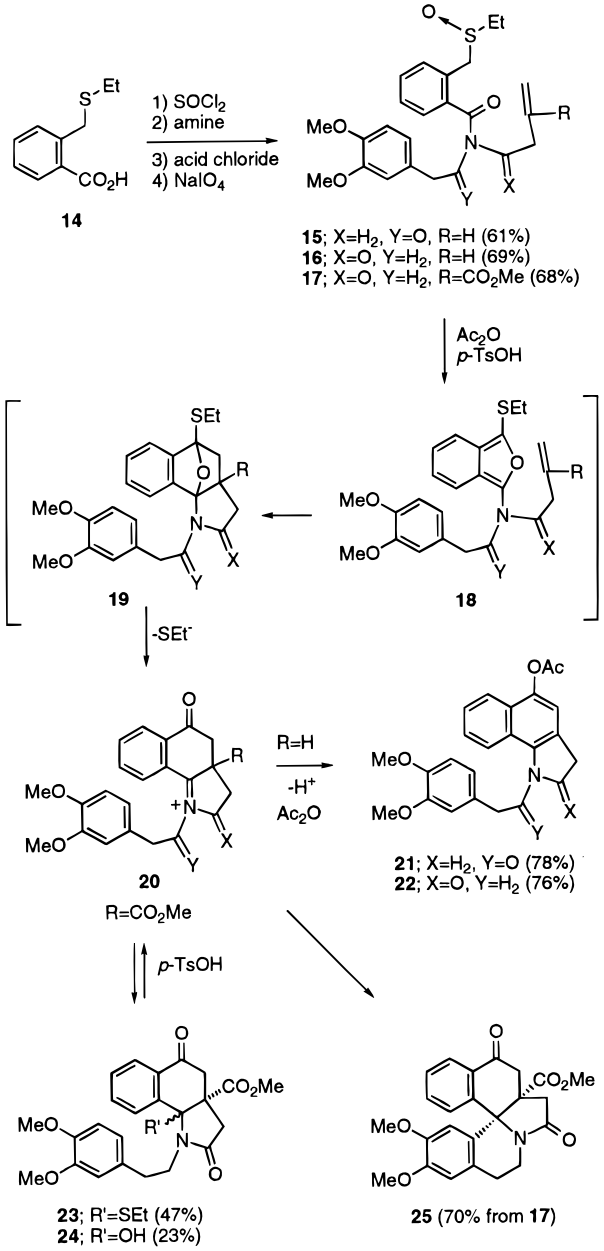
Scheme 2



Scheme 3



of the conjugated aromatic system present in products **21** and **22**.

In order to avoid the deprotonation step, we prepared sulfoxide **17** possessing a carbomethoxy group attached to the olefinic tether. Subjection of **17** to the standard Pummerer reaction conditions (toluene/Ac_2O/*p*-TsOH)[8] provided a 2:1 mixture of the *N*,*S*- and *N*,*O*-ketals **23** and **24**, respectively. These products are derived from bimolecular trapping of iminium ion **20** (R = CO_2Me) with a nucleophilic species present in the reaction medium (*i.e.*, EtS^-, AcO^-). However, both of these products can be independently converted to the desired benzoerythrinane derivative **25** by heating in toluene containing 1.1 equiv of *p*-TsOH. We found it to be more convenient, however, to carry out the triple cascade sequence (**17** → **25**) in a one-pot fashion by first subjecting sulfoxide **17** to the Ac_2O/*p*-TsOH conditions, followed by treatment of the crude reaction mixture (after evaporation of solvent and excess Ac_2O) with an additional quantity (1.1 equiv) of *p*-TsOH in refluxing toluene. By using this one-pot protocol, 3,4-benzoerythrinane **25** was obtained as a single diastereomer in 65−70% yield from sulfoxide **17**. Alternatively, the tandem sequence could also be triggered at 0 °C by utilizing the more electrophilic trifluoroacetic anhydride as the Pummerer promoter (CH_2Cl_2, 2 equiv of Et_3N).[8] In this case, cycloadduct **19** (R = CO_2-Me, X = O) was isolated and was converted to **25** (70% overall) by exposure to *p*-TsOH (1.1 equiv) in refluxing toluene. The *cis*-stereochemistry of the A/B ring system of **25** is supported by a number of related iminium ion cyclizations reported in the literature[1,9] and by the distinct ^1H-chemical shift of the methyl ester.[10]

In conclusion, the ready conversion of sulfoxide **17** into benzoerythrinane **25** represents an efficient and novel approach toward the erythrinane skeleton in which the spirocyclic ABC ring skeleton is assembled in a single operation. This triple cascade process should be applicable toward the preparation of ring homologues of the Erythrina skeleton by simply varying the tether length of the starting sulfoxides.

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Supporting Information Available: Experimental details for the preparation of, as well as spectroscopic data for, all new compounds (11 pages).

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(9) Wilkens, H. J.; Traxler, F. *Helv. Chim. Acta* **1975**, *58*, 1512.

(10) The high-field chemical shift of the methyl ester (3.21 ppm for **25** vs 3.83 for sulfoxide **17**) is due to the fact that the ester functionality present in *cis*-**25** is situated directly above the plane of the aromatic D-ring of the erythrina skeleton. This particular stereochemical relationship is only realized in the *cis*-Erythrina series and has been previously utilized to distinguish between the *cis*- and *trans*-ring fusion in Erythrina derivatives.[9]