Third International Electronic Conference on Synthetic Organic Chemistry (ECSOC-3), www.mdpi.org/ecsoc-3.htm, September 1-30, 1999

[A0019]

Synthesis of Heterocycles Using Tandem Cyclization Processes

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Received: 10 July 1999 / Uploaded: 12 August 1999

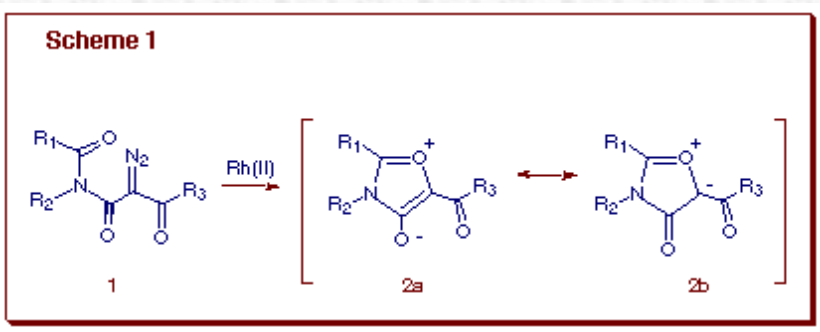
Various applications of the cycloaddition/N-acyliminium ion tandem cyclization cascade are outlined in this electronic symposium on synthetic organic chemistry. The key step in the process involves the generation of a reactive *N*-acyliminium ion by fragmentation of an amino substituted [4+2]-cycloadduct. The successful synthesis of a number of alkaloids by this sequence of reactions reveals the usefulness and importance of this unique domino cascade.

Introduction

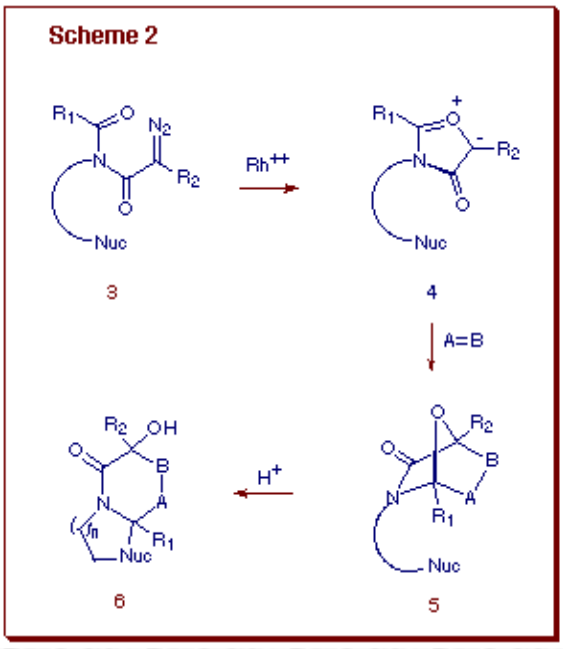
In recent years, consecutive pericyclic reactions involving at least one cycloaddition have been utilized for the synthesis of complex polycyclic ring systems [1]. In the realm of synthesis in which a premium is put on the rapid construction of polyfunctional, highly bridged carbon and heteroatom networks, the [4+2]-cycloaddition has emerged as one of the foremost synthetic methods [2]. Well known and extensively studied for many decades, the Diels-Alder reaction is frequently employed for the construction of six-membered ring systems. The high regio- and stereoselectivity typically displayed by this pericyclic process and the ease of execution have contributed toward its popularity. Carbon-carbon bond-forming reactions involving *N*-acyliminium ions play an extremely important role in the synthesis of nitrogen heterocycles [3]. A combination of these two powerful synthetic methods would allow for the rapid, stereocontrolled synthesis of a variety of azapolycyclic products. This article describes some of our work in this area.

Cycloaddition of 1,3-Oxazolium-4-oxides

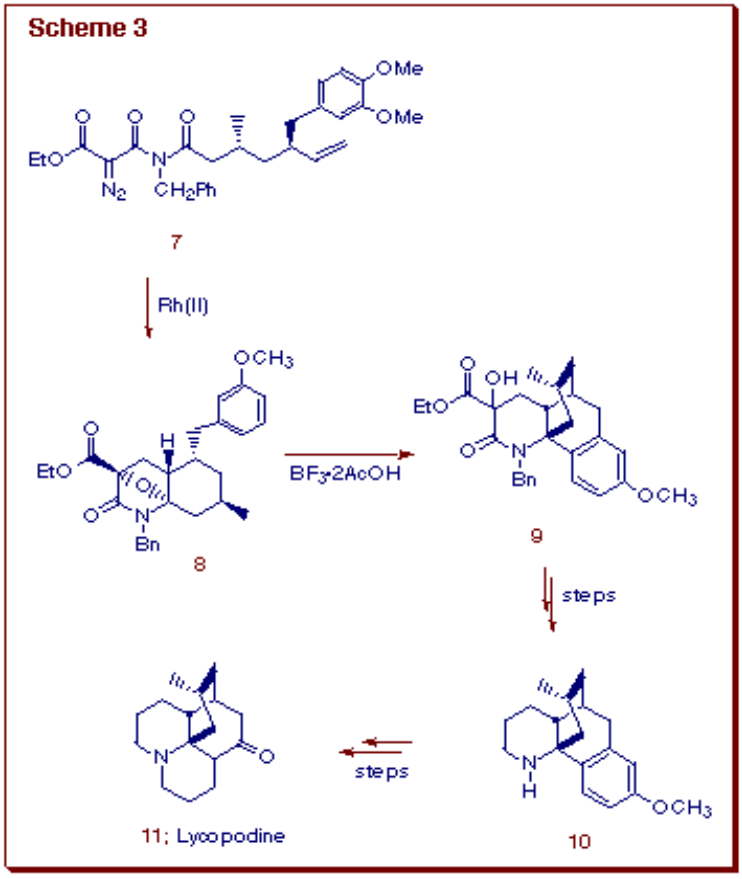
In 1994 we started work in our laboratory to synthesize ring-fused poly-heterocycles based on a *sequential cycloaddition-N-acyliminium ion cyclization process* [4]. These two types of reaction provide an opportunity for linking two disparate ring forming reactions in a novel sequential manner. We believed that such a protocol would provide one-pot access to target molecules possessing a high degree of complexity which would otherwise require technically demanding multi-step syntheses. Our early studies showed that 1,3-oxazolium-4-oxides (isom  nchnones) **2** can be generated by the rhodium(II)-catalyzed cyclization of a suitable diazo imide **1** (Scheme 1) [5]. This type of mesoionic ylide corresponds to the cyclic equivalent of a carbonyl ylide and was found to readily undergo [4+2]-cycloaddition with suitable dipolarophiles [5].



Formation of the isom&#65533;nchnone ring proceeds by initial generation of a rhodium carbenoid species, followed by an intramolecular cyclization onto the neighboring carbonyl oxygen to form the mesoionic ylide **2**. The resultant isom&#65533;nchnone may be trapped with electron rich or electron deficient dipolarophiles to give the cycloadducts in high yield. These uniquely functionalized cycloadducts (*i.e.*, **5**) contain a *masked N*-acyliminium ion which is generated by its treatment with a Lewis acid [6]. By incorporating an internal nucleophile on the tether, annulation of the original cycloadduct **5** allows for the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologues of the erythrinane family of alkaloids. Starting from simple acyclic diazo imides **3**, we established a *domino carbenoid cyclization-[4+2]-cycloaddition-cationic pi-cyclization* protocol as a method for the construction of complex nitrogen polyheterocycles of type **6** (Scheme 2). This sequence represents the first example where a [4+2]-cycloaddition and *N*-acyliminium ion cyclization are coupled in a one-pot sequence. The novelty of the process lies in the method of *N*-acyliminium ion generation, which to our knowledge, is unprecedented. *N*-Acyliminium ions are traditionally generated from the *N*-acylation of imines, *N*-protonation and oxidation of amides, electrophilic additions to enamides, and the heterolysis of amides bearing a leaving group adjacent to nitrogen [7]. These reactive intermediates readily react with a wide assortment of nucleophiles to effect an overall alpha-amido alkylation.

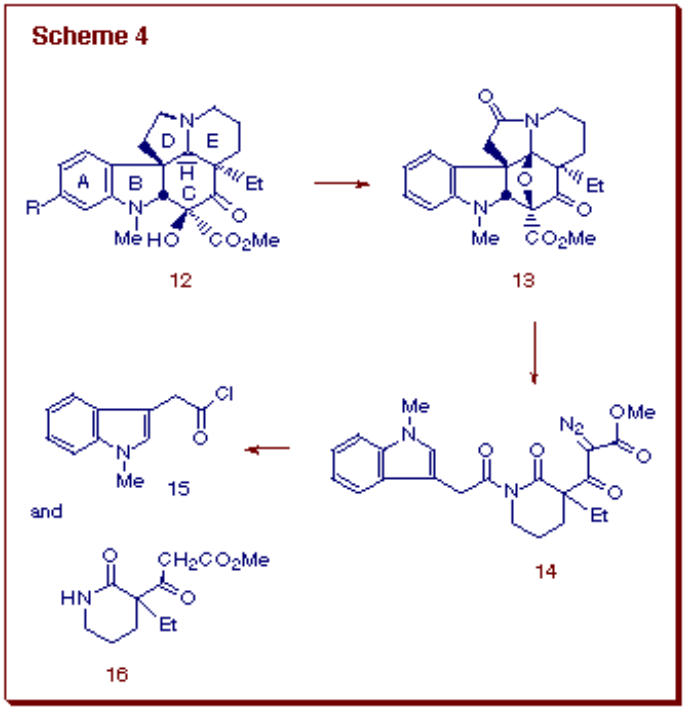


An early application of the domino cascade process toward the construction of alkaloids involved the synthesis of (&#65533;)-lycopodine (**11**) (Scheme 3) [8]. The isom&#65533;nchnone cycloadduct **8** was formed from the Rh(II)-catalyzed reaction of diazo imide **7** and was found to be the precursor of the key Stork intermediate **10** (*via* **9**) [9] which was ultimately converted into (&#65533;)-lycopodine **11** [9].



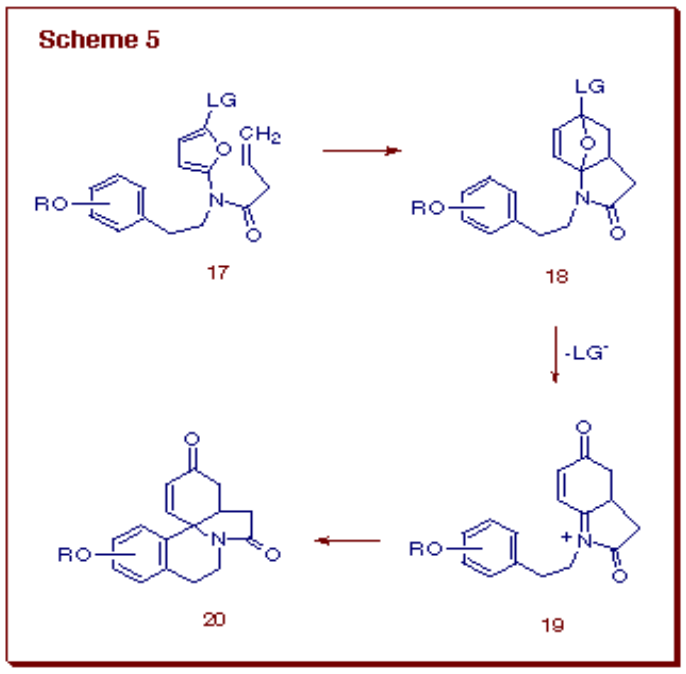
Application of the Domino Cyclization-Cycloaddition Sequence to the Pentacyclic Skeleton of the Aspidosperma Ring System

As an extension of these studies, we developed a fundamentally new approach to the construction of the pentacyclic skeleton of the aspidosperma ring system which involves a related domino cascade sequence [10]. This strategy was successfully applied to the synthesis of desacetoxy-4-oxo-6,7-dihydrovindorosine (**12**). The approach used is outlined in Scheme 4 and is centered on the construction of the key oxabicyclic intermediate **13**. We reasoned that **12** should be accessible by reduction of the *N*-acyliminium ion derived from **13**, which, by analogy with our previous work, should be available by the *tandem rhodium(II)-catalyzed cyclization cycloaddition* of alpha-diazoimide **14**. Cycloaddition of the initially formed dipole across the pendant indole pi-system [11] would be expected to result in the simultaneous generation of the CD-rings of the aspidosperma skeleton [12]. The stereospecific nature of the internal cycloaddition reaction should results in the correct relative stereochemistry of the 4 chiral centers about the C-ring.



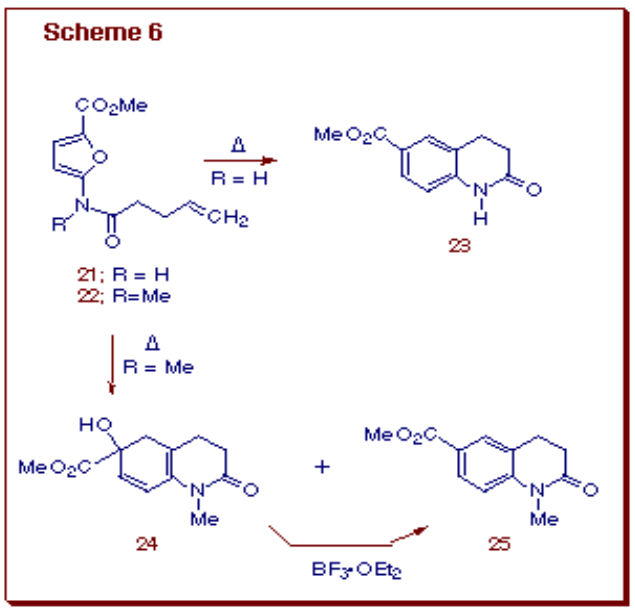
The 2-Aminofuran Diels-Alder Strategy

During the course of our work in this area, it occurred to us that we could also utilize a series of 2-amino substituted furans for the critical [4+2]-cycloaddition step rather than the highly reactive 1,3-dipole. Our long-range goal involved using 2-amino-substituted furans such as **17** that contain both a suitable leaving group (LG) and an olefinic tether to allow for an intramolecular Diels-Alder reaction (Scheme 5). The resultant cycloadduct was expected to undergo ring opening to generate a vinylogous C-acyliminium ion of type **19**. Our intention was to use this sequence of reactions for a rapid entry into the erythrinane family of alkaloids. With this goal in mind, some model studies were undertaken to determine the facility with which 2-aminofurans would undergo internal Diels-Alder cycloadditions.

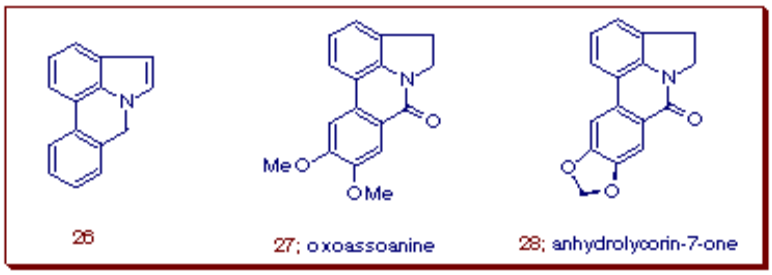


The intramolecular Diels-Alder reaction of furans, often designated as *IMDAF*, helps to overcome the sluggishness of this heteroaromatic ring system toward [4+2]-cycloaddition [13]. Not only do *IMDAF* reactions allow for the preparation of complex oxygenated polycyclic compounds, they often proceed at

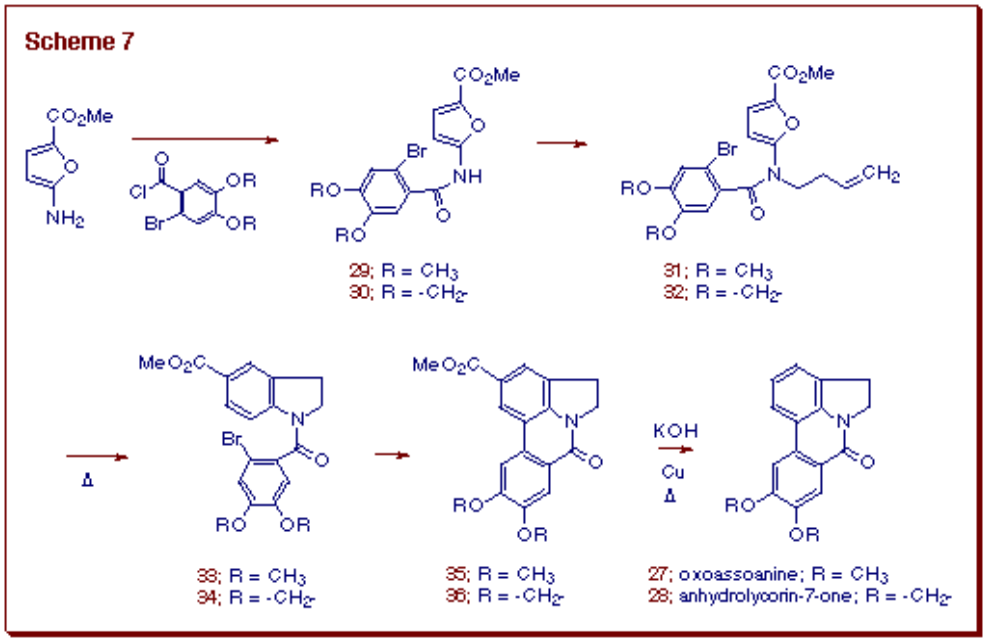
lower temperatures than their intermolecular counterparts. Even more significantly, unactivated pi-bonds are often suitable dienophiles for the internal cycloaddition. In an effort to investigate the scope of these reactions, a number of new furan substrates were prepared in our laboratory and tested for the *cycloaddition-cyclization* cascade. Tethered amidofurans **21** and **22** were easily synthesized. The thermal reaction of **21** at 200^{o}C for 24 h afforded tetrahydroquinolinone **23** in 66% yield. Likewise, heating a sample of the *N*-methylated analog **22** at 160^{o}C furnished a 6:1-mixture of cyclohexadienol **24** (77%) and tetrahydroquinoline **25** (13%), the former being easily converted to **25** by treatment with BF_3OEt_2. In both cases, the initial cycloadducts were not isolated, as they readily underwent ring opening, assisted by the lone pair of electrons on the adjacent nitrogen (Scheme 6).



Having established the suitability of 2-amido furans to generate dihydroindoles, we turned our attention to the application of the method toward the synthesis of oxoassoanine [14] (**27**) and anhydrolycorin-7-one (**28**) [15]. These compounds are members of the pyrrolophenanthridine class of alkaloids which have been isolated from various species of amaryllidaceae [16]. The 1*H*-pyrrolo[3,2,1-de]phenanthridine ring system (**26**) constitutes the core structural framework of the pyrrolophenanthridine alkaloids. Although a number of synthetic routes are available for this ring system, many of these suffer from low yields and lack generality [17].

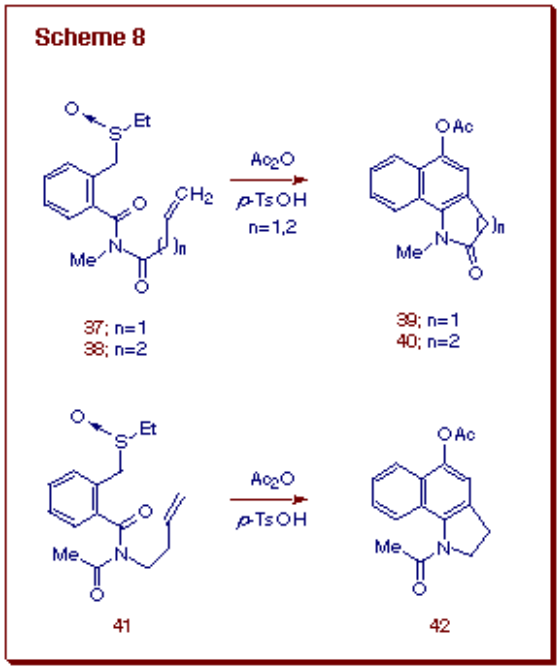


A short synthesis of **27** and **28** was carried out as depicted in Scheme 7. This approach is centered on the construction of the key dihydroindoles **33** and **34** which are formed by a *IMDAF* cycloaddition followed by subsequent nitrogen atom lone pair assisted ring opening of the initially formed oxabridged cycloadducts. After some experimentation, it was found that using *bis*(tributyltin) under photochemical conditions afforded the aryl-coupled products **35** and **36** in high yield from the corresponding dihydroindoles **33** and **34**. Both compounds were converted to the natural products by a saponification-decarboxylation protocol.



The Domino Pummerer Diels-Alder Sequence

Much of the chemistry utilized in the preceding section relied on our ability to synthesize the requisite 2-aminofurans. One limitation of the method is that sometimes the 2-aminofuran system is not easily accessible. In the context of our studies dealing with *domino cycloaddition-Mannich cyclizations*, we discovered that the Pummerer reaction can be effectively utilized to prepare the required furans. We focused our attention on an intramolecular variation of the *domino amido-Pummerer-Diels-Alder reaction sequence*. The one-pot intramolecular cascade process occurred smoothly when the olefin tether was activated by an ester or when a carbonyl group was located adjacent to the nitrogen atom of the 2-amino substituted isobenzofuran (Scheme 8) [18]. The intramolecular cycloaddition behavior of the incipient isobenzofurans in response to the presence of a C=O group is striking. Five and six ring-membered precursors **37** and **38** delivered cyclized products bearing a carbonyl within the newly formed rings in good to excellent yields.

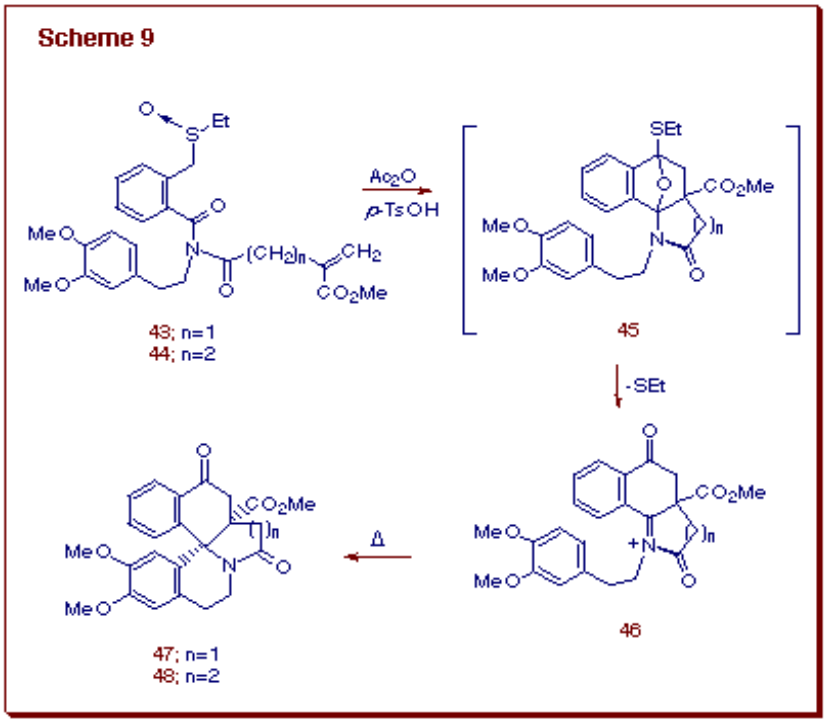


Triple Cascade Sequence for Construction of the Erythrinane Alkaloid Skeleton

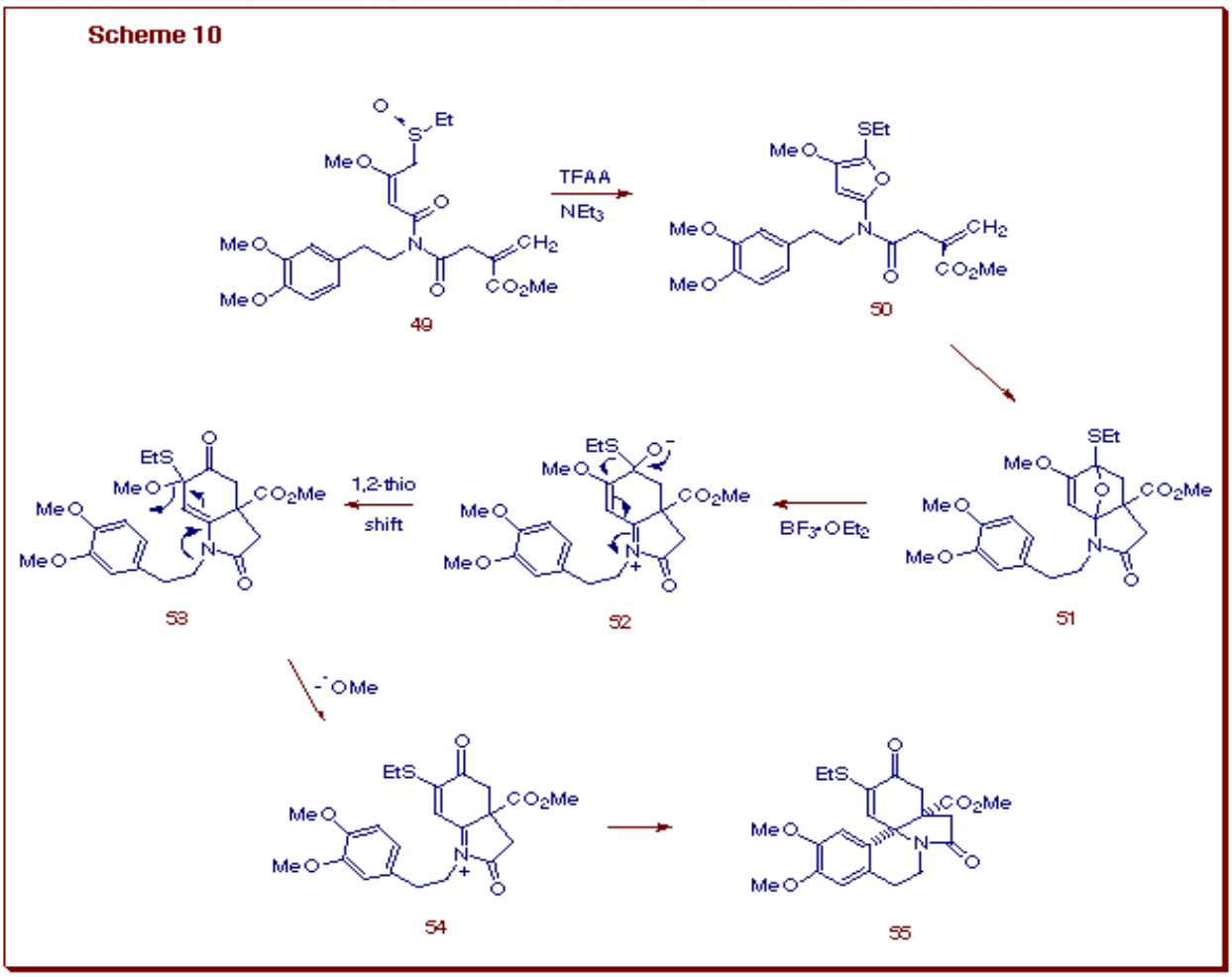
Having established the facility with which *N*-acyliminium ions can be formed from the Pummerer reaction of

o-amido substituted sulfoxides, we next focused our attention on the final cyclization step of the proposed cascade process (*i.e.*, **19 -> 20** in Scheme 5) [19]. In order to avoid the deprotonation (aromatization) step, we prepared sulfoxides **43** and **44**, each possessing a carbomethoxy group attached to the olefin tether. This substituent was selected not only to prevent deprotonation, but also because the presence of an electron withdrawing group on the double bond enhances [4+2]-cycloaddition based on FMO considerations. *N*-Acyliminium ion **46** derived from the internal cycloadduct **45** underwent stereoselective spirocyclization to furnish the *cis*-3,4-benzoerythrinane **47** or homoerythrinane derivative **48** in good yield (Scheme 9). The overall triple cascade sequence represents an efficient one-pot approach towards the erythrinane alkaloid skeleton in which the spirocyclic ABC skeleton is assembled in a single operation.

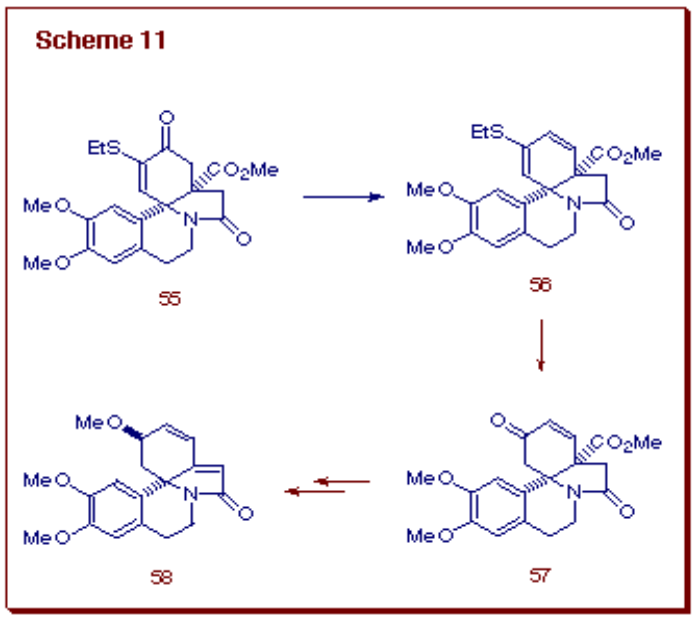
Scheme 9



At this point, we decided to undertake a synthesis of (**?**)-erysotraamidine (**58**) in order to further test the viability of the triple cascade process as an entry into the erythrinane skeleton. The requisite starting imidosulfoxide **49**, possessing both a dienophilic and diactivated aromatic pi-tether, was efficiently synthesized from known starting materials. Subjection of **49** to the Pummerer conditions gave compound **55** as a single diastereomer in 83% yield. The *cis* A/B ring fusion present in **55** was unequivocally established by an X-ray crystallographic analysis and is identical to the stereochemical relationship found in the naturally occurring Erythrina alkaloids. The conversion of **49** into **55** is believed to follow the pathway outlined below (Scheme 10). The initially formed alpha-thiocarbocation intermediate generated from the Pummerer reaction of **49** is intercepted by the adjacent imido carbonyl to producethe alpha-amido substituted furan **50**.



This transient intermediate undergoes a subsequent intramolecular Diels-Alder cycloaddition across the tethered pi-bond to furnish cycloadduct **51**. Nitrogen-assisted ring opening of the oxabicyclic bridge results in the formation of zwitterionic intermediate **52** which undergoes a 1,2-thioethyl shift followed by methoxide ion ejection. Cyclization of the diactivated aromatic tether onto *N*-acyliminium ion **54** ultimately provides the tetracyclic amide **55**. With a supply of **55** in hand, this enone was converted into the corresponding vinyl triflate which, in turn, was subjected to a palladium catalyzed formate reduction to give **56**. The resulting thio-substituted diene was subsequently transformed into ketone **57** *via* a titanium mediated hydrolysis. The present sequence constitutes a formal synthesis of (±)-erysotramidine (**58**) based on the successful conversion of **57** into **58** by Tsuda and coworkers (Scheme 11) [20].



Concluding Remarks

Over the past several years we have shown that many structurally diverse heterocyclic compounds can be readily accessed *via* the *domino cycloaddition/N-acyliminium ion cyclization cascade*. The key step in this process involves the generation of a reactive *N*-acyliminium ion by fragmentation of an amino substituted [4+2]-cycloadduct. This triple cascade is applicable toward the preparation of a broad range of alkaloids. It is a reasonable expectation that future years will see a continued evolution of this unique domino cascade toward other synthetic targets.

Acknowledgment

I thank my enthusiastic and gifted coworkers whose names appear in the appropriate references and the National Institute of Health for financial support.

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