Intramolecular [4+2]-Cycloaddition of 5-Amino-Substituted Oxazoles as an Approach toward the Left-Hand Segment of Haplophytine

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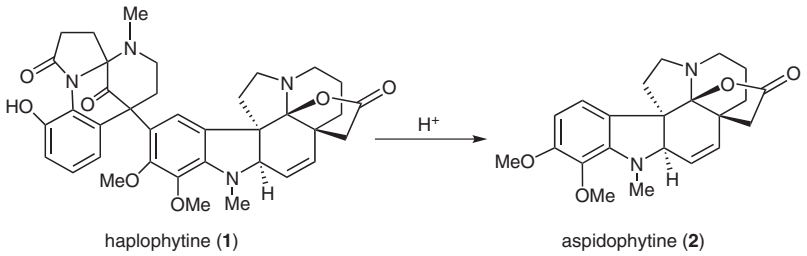
Dedicated to Alberto Brandi on the occasion of his 60th birthday

Abstract: The [4+2]-cycloaddition chemistry of several 5-amino-substituted oxazoles has been examined as an approach toward the construction of the left-half segment of the aspidosperma alkaloid haplophytine.

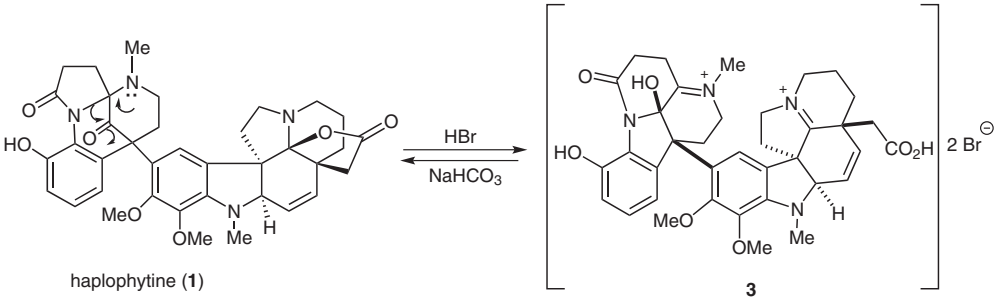
Key words: 5-aminooxazoles, intramolecular, Diels–Alder reaction, pyridines, haplophytine

Construction of azapolyheterocycles through [4+2]-cycloaddition chemistry has been a particularly fruitful area of exploration, and the synthesis of various types of alkaloids by this approach has been carried out by numerous investigators.[1] During the course of our research dealing with the cycloaddition chemistry of push-pull dipoles[2] and 2-amidofurans,[3] we began studies geared toward a synthesis of several aspidosperma alkaloids.[4] This family of indole alkaloids contains over 250 members that share in their molecular structure a common pentacyclic ABCDE framework, with the C-ring being of critical importance because all six stereocenters and most of the functionalities are located in this ring.[5] One of the more architecturally intriguing and synthetically demanding aspidosperma alkaloids is haplophytine (**1**).[6] The haplophytine molecule consists of a central indole moiety onto which two tetracyclic heterocycles are attached. Acid cleavage of haplophytine (**1**) led to aspidophytine (**2**; Scheme 1), a lactonic aspidospermine-type of alkaloid which has been suggested to be not only a biosynthetic precursor of **1** but also a possible intermediate to be used in its synthesis.[7] Because of its novel structure, aspidophytine (**2**) has attracted the attention of several major research groups,[7] including our own.[8] Prompted by our initial work dealing with aspidophytine (**2**),[8] we decided to initiate a synthetic project employing the cycloaddition chemistry of 5-amino oxazoles as an approach toward the construction of the left-half segment of haplophytine (**1**).

The recently completed synthesis of haplophytine (**1**) carried out by the Fukuyama[9] and Nicolaou[10] groups made use of a novel oxidative rearrangement of a tetracyclic β-carboline derivative to furnish the left-hand portion of the alkaloid.[11] These authors took advantage of an inherent skeletal rearrangement of haplophytine (**1**) that occurred



Scheme 1 Acid degradation of haplophytine



Scheme 2 Skeletal rearrangement of haplophytine using HBr

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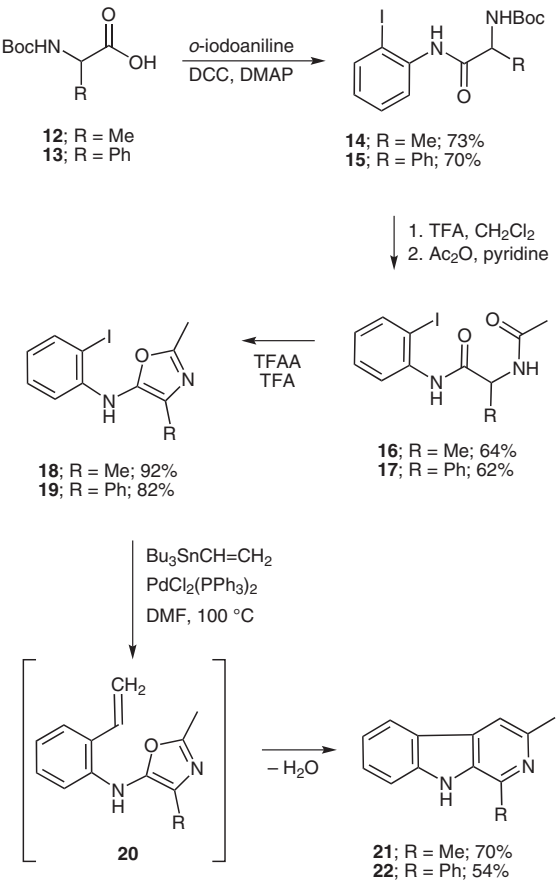
upon treatment with HBr. The rearranged isomer **3** that formed was converted back into haplophytine under basic conditions by means of a semipinacol-type rearrangement (Scheme 2).

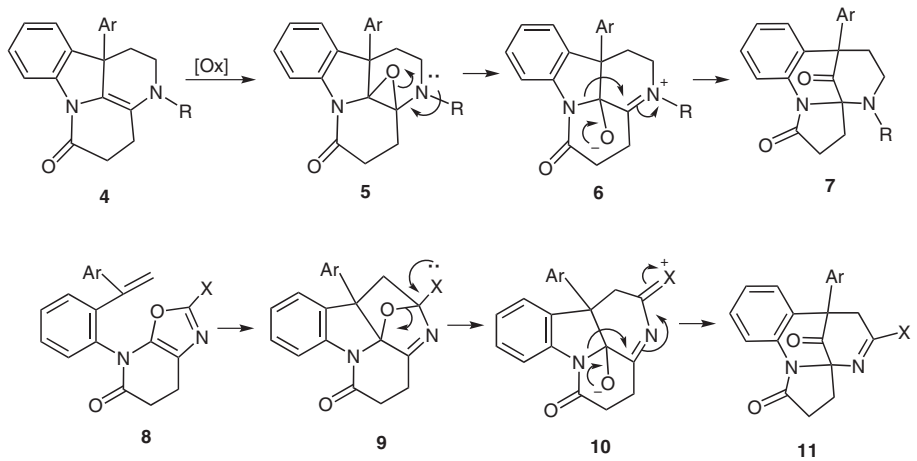
Based on this observation, both teams found that the characteristic left-hand segment (i.e. **7**) could be formed by the epoxidation of a tetrahydro-β-carboline derivative (i.e. **4**). The resulting diamino epoxide intermediate **5** underwent a facile epoxide ring opening to give iminium ion **6**. A subsequent 1,2-shift of the C–N bond furnished the desired left-hand skeleton (i.e. **7**) of haplophytine (Scheme 3). Our synthetic approach to the left-hand portion of haplophytine is also shown in Scheme 3. We planned to construct the related tetracyclic structure **11** (X = halo, SiR_3, SnR_3, etc.), a possible precursor to haplophytine, by an intramolecular Diels–Alder cycloaddition of 5-amido oxazole **8**. We envisaged that the resulting [4+2]-cycloadduct **9** would undergo ready ring opening to give zwitterion **10**. An ensuing semipinacol-type rearrangement analogous to the conversion of **6** to **7** could furnish the desired tetracycle **11**.

The Diels–Alder reaction of oxazoles with olefins has become a useful tool for the preparation of nitrogen-containing heterocycles,[12] since the first example of this cycloaddition reaction was reported by Kondratèva in 1957.[13] Although numerous studies have described the utility of oxazoles for the construction of pyridines,[14] there have been few reports exploiting the intramolecular Diels–Alder reactions of oxazole-olefins for the synthesis of natural products.[15] The feasibility of our approach toward haplophytine that is outlined in Scheme 3 clearly hinged upon a 5-amido oxazole undergoing an intramolecular [4+2]-cycloaddition with a tethered styrene derivative. Since this tactic was the focal point of our plan, we opted to first verify the viability of this reaction using simpler model substrates.

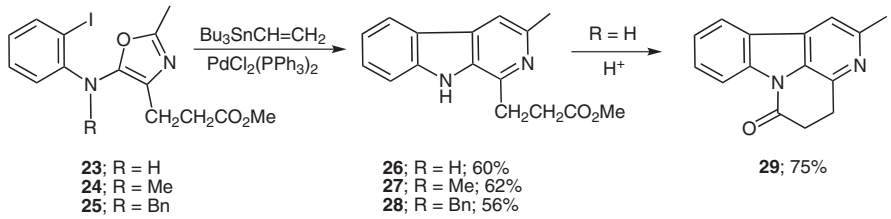
The pioneering work of Fleury and co-workers[16] showed that α-acyl amino acids readily undergo cyclization upon treatment with acid anhydrides in the presence of strong acids to furnish 5-(acetamido)oxazoles. In subsequent work, Lipshutz demonstrated that a variety of appendages on oxazole precursors can be tolerated during the cyclization step.[17] Following the Lipshutz procedure, the preparation of our model oxazole **18** commenced with the coupling of *N*-*tert*-butoxycarbonylalanine (**12**) with *o*-iodoaniline to give **14** in 73% yield. The *N*-Boc group was removed with TFA and then acetylated with acetic anhydride to afford **16** in 64% yield (Scheme 4). Although the path to **16** may seem a bit round-about, we found that an initial protection of alanine's nitrogen with acetic anhydride greatly inhibited the peptide coupling. With **16** in



Scheme 4 Synthesis and [4+2]-cycloaddition chemistry of 5-aza oxazoles



Scheme 3 Semipinacol-type rearrangement for synthesis of the left-half segment of haplophytine



Scheme 5 A linked Stille cross-coupling–cycloaddition cascade

hand, cyclodehydration using the Lipshutz protocol gave 5-anilino oxazole **18** in 92% yield. Stille coupling of **18** with *n*-tributylvinylstannane did not produce the expected cross-coupled styryl oxazole **20**. Instead, the initially formed oxazole **20** spontaneously underwent an intramolecular [4+2]-cycloaddition followed by ring opening and loss of water to give the 9*H*-pyrido[3,4-*b*] indole system **21** in 70% yield (Scheme 4). A corresponding set of reactions also occurred when the closely related 5-anilinooxazole **19** (R = Ph) was treated with *n*-tributylvinylstannane in the presence of a palladium catalyst at 100 °C in DMF affording 9*H*-pyridoindole **22** in 54% yield.

Somewhat more relevant examples of the 5-amido oxazole cycloaddition reaction concern those systems possessing a $CH_2CH_2CO_2Me$ appendage at the C-4 position of the heterocyclic ring. We expected that N-acylation at the anilino nitrogen would eventually lead to a 6,7-dihydrooxazolo[5,4-*b*]pyridin-5(4*H*)-one such as structure **8** in Scheme 3. To establish the viability of this approach, oxazoles **23**–**25** were prepared using standard synthetic reactions similar to those outlined in Scheme 4. After some experimentation, we found that a linked Stille coupling–thermolysis cascade provided 9*H*-pyrido[3,4-*b*]indoles **26**–**28** in good yield (ca. 60%). In the case of **26**, treatment with *p*-TsOH at 120 °C gave rise to 4*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6(5*H*)-one **29** in 75% yield (Scheme 5).

With reaction conditions established for both the formation of the 5-amido oxazole system and the subsequent intramolecular [4+2]-cycloaddition, the reaction scope of this annulation reaction was further explored and the results obtained are outlined in Scheme 6. The two-step synthesis of oxazole **32** from the known amide **30** worked well furnishing **32** in 80% overall yield. Acylation of **32** with but-3-enoyl chloride gave **33** in 57% yield. The thermolysis of **33** at 120 °C in toluene afforded pyridine **34** in 61% yield. This product is formed by an intramolecular Diels–Alder cycloaddition followed by the ready loss of water.

In summary, we have developed a cycloaddition protocol to construct various substituted pyridines by an intramolecular Diels–Alder reaction of a 5-amino-substituted oxazole. The potential value of this approach toward a total synthesis of haplophytine is under active investigation and will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and ^{1}H NMR, ^{13}C NMR, HRMS, and IR spectral data for all compounds.

Acknowledgment

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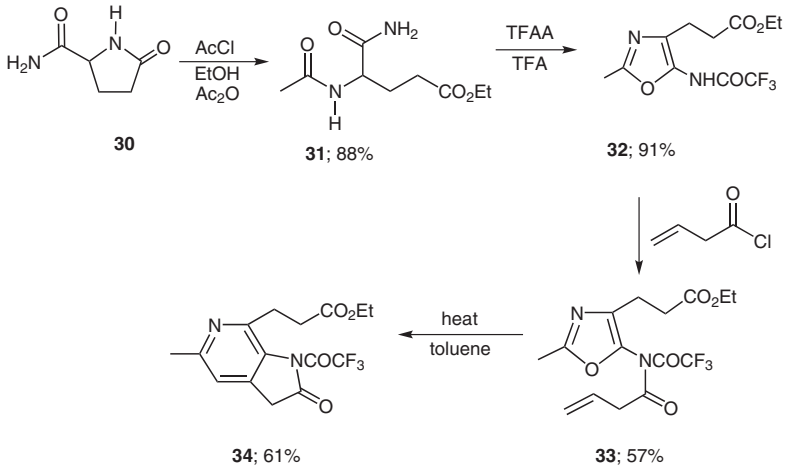

Scheme 6 Intramolecular Diels–Alder–ring opening–dehydration cascade for the synthesis of substituted pyridines

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