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Rh(I)-Catalyzed Ring Opening of an IMDAF-Derived Oxabicyclo Cycloadduct as the Key Step in the Synthesis of (±)-*epi*-Zephyranthine

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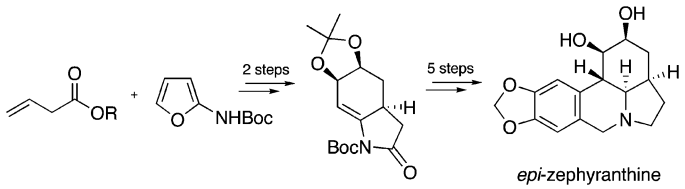
ABSTRACT



A new strategy for *epi*-zephyranthine has been developed that is based in part on an extraordinarily facile intramolecular Diels–Alder reaction of a 2-imido-substituted furan. By using a Rh(I)-catalyzed ring opening of the resulting oxabicyclic adduct, the *cis*-diol stereochemistry of *epi*-zephyranthine was established.

The alkaloids of the *Amaryllidaceae* family are composed of over 100 architecturally interesting natural bases and have been classified into various skeletally homogeneous subgroups.[1] The lycorine-type group[2] constitutes one of the eight classes within this large family of natural products and has captured the interest among a number of synthetic groups as targets for total synthesis due to the challenging tetracyclic galanthan skeleton.[3−5] The lycorine alkaloids display useful biological properties including antiviral, insect antifeedant, and antineoplastic activity, as well as other pharmacological properties.[6] Lycorine (**1**) was the first alkaloid of this group to be isolated[7] and was studied for its antitumor properties long before the more oxygenated congeners were identified.[8] The structurally related amaryllidaceae constituents dihydrolycorine (**2**),[9] lycoricidine (**3**), pancratistatin (**4**), and zephyranthine (**5**)[10] have also been isolated,[11] screened for biological activity,[12] and synthesized by several research groups.[3−5] In contrast to other members of the lycorine family, only a limited number of syntheses of zephyranthine (**5**) have been carried out[10] and there are no reports dealing with the synthesis of the stereoisomeric *epi*-zephyranthine

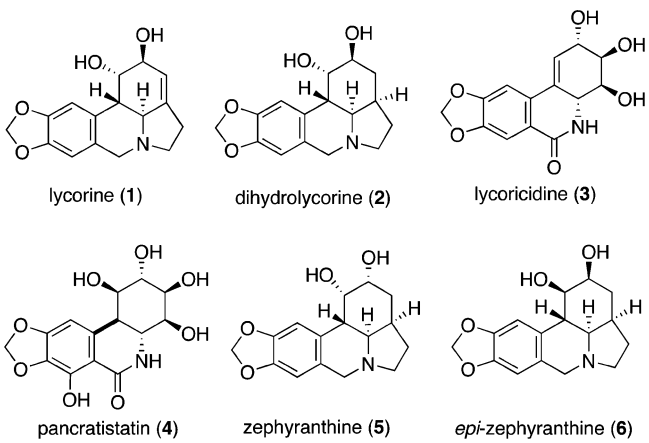


Figure 1. Lycorine-type alkaloids.

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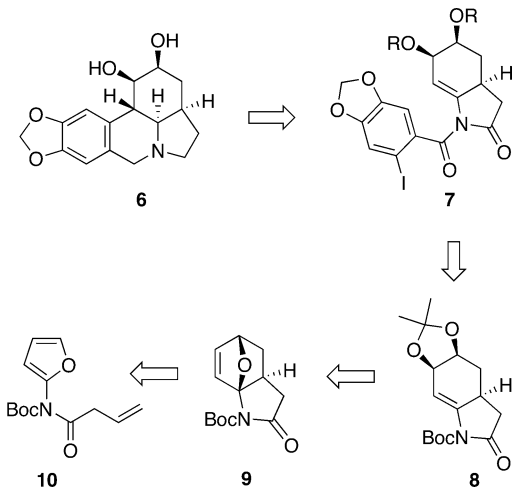
6. The work reported herein derives from a general program underway in our laboratories that is designed to exploit the [4+2]-cycloaddition chemistry of readily available 2-amidofurans for natural product synthesis.[13] Our approach toward *epi*-zephyranthine **6** employs two novel synthetic steps: (1) an imidofuran Diels−Alder reaction that occurs at room temperature and (2) a Rh(I)-catalyzed ring opening of the resulting 7-oxa-bicyclo[2.2.1]hept-2-ene cycloadduct, which sets the *cis*-diol stereochemistry of **6** with complete diastereoselectivity. The approach takes advantage of some related chemistry developed by Lautens and co-workers where an oxabicyclo[2.2.1]heptane undergoes a Rh(I)-catalyzed nucleophilic ring opening reaction.[14]

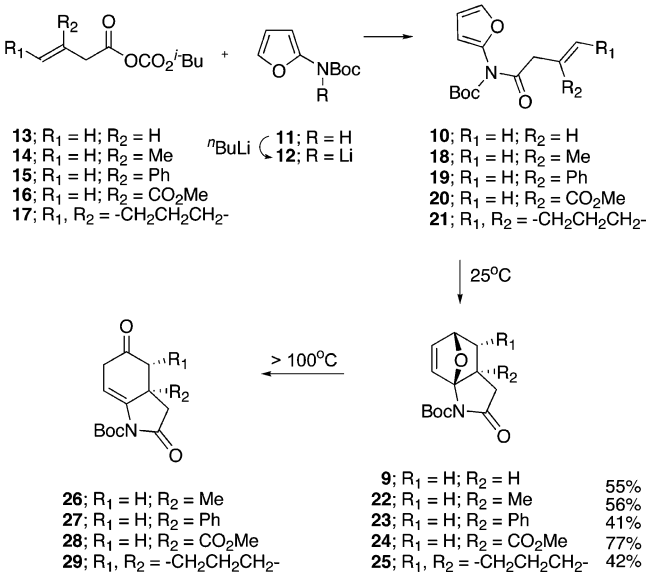
Our retrosynthetic analysis was based on our earlier report describing the intramolecular [4+2]-cycloaddition of amidofurans (IMDAF).[13] The desired tetracyclic galanthan core of **6** was envisioned to arise from a radical-induced cyclization of **7**,[15] which in turn may be derived from lactam **8**. We anticipated that the hexahydroindolinone unit of **8** would be formed by a Rh(I)-catalyzed alcoholysis of cycloadduct **9**[16] acquired by an IMDAF reaction of furan **10** (Scheme 1).

Scheme 1



Initially, we had envisioned imidofuran **10** arising from the simple acylation of furanyl carbamate **11** with the acid chloride derived from 3-butenoic acid. However, under a variety of conditions **11** proved to be remarkably resistant toward acylation. After some experimentation, we found that the addition of lithium carbamate **12**, formed by the action of *n*-BuLi on **11**, to a solution of the mixed anhydride **13** provided the expected imidofuran **10**, which rapidly reacted at room temperature to deliver the Diels−Alder cycloadduct **9** in 55% isolated yield. Intrigued by the ease with which imidofuran **10** underwent cycloaddition, we investigated several other systems containing related tethers as illustrated in Scheme 2. The mixed anhydrides **14**−**15** were subjected to the acylation protocol and provided the desired imidofurans **18**−**19** which also underwent cycloaddition at 25

Scheme 2



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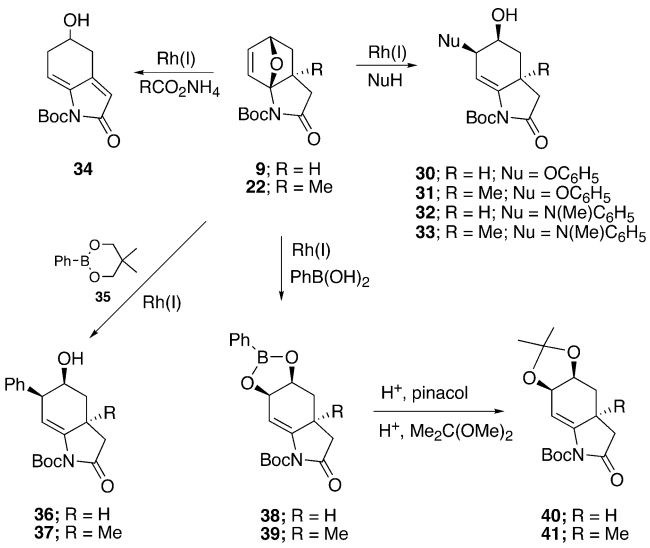
°C (12 h) to furnish the oxabridged cycloadducts **22**−**23**. When the more highly activated anhydride **16** was used, imidofuran **20** could not be observed because the [4+2]-cycloaddition occurred too rapidly to preclude its detection, even at 0 °C. In contrast, the more sterically congested anhydride **17** furnished imidofuran **21**, which required heating at 90 °C to give cycloadduct **25**. The increase in reactivity of these 2-imido-substituted furans (0−90 °C) when compared to the related furanyl carbamates[13] (>150 °C) is clearly related to the placement of the carbonyl center within the dienophilic tether. Dramatic effects on the rate of the Diels−Alder reaction were previously noted to occur when an amido group was used to anchor the diene and dienophile.[17] Our ability to isolate the highly labile oxabicyclic adducts (**9**; **22**−**25**) is presumably a result of the lower reaction temperatures employed as well as the presence of the extra carbonyl group, which diminishes the basicity of the nitrogen atom thereby retarding the ring cleavage/rearrangement reaction generally encountered with these systems.[13] When exposed to more forcing conditions (i.e., >100 °C), the oxabridged cycloadducts **22**−**25** were smoothly transformed (>90%) into the corresponding hexahydroindolinone systems **26**−**29**.

7-Oxabicyclo[2.2.1]heptanes have been employed as valuable intermediates for the synthesis of a variety of natural products.[18] The large number of selective transformations possible with the oxabicyclic system endow this nucleus with impressive versatility. A crucial synthetic transformation employing these intermediates involves cleavage of the oxygen bridge to provide functionalized cyclohexane derivatives.[19] In earlier reports, Lautens and co-workers demonstrated that the ring opening of unsymmetrical oxabicyclic compounds is highly regioselective, giving rise to products derived from the attack of the nucleophile distal to the bridgehead substituent.[16,19] Our first set of experiments were carried out with oxabicyclics **9** and **22** using Lauten's conditions[16] ([Rh(COD)Cl]$_2$, DPPF). Phenol and *N*-methylaniline were employed as the nucleophilic reagents. This led to the ring-opened alcohols **30**−**33** in excellent yield (Scheme 3). An X-ray crystal structure (i.e. **31**) of the major

Scheme 3



diastereomer formed (5:1 for **30**/**31**; 20:1 for **32**/**33**) unequivocally established the cis relationship between the nucleophile and hydroxyl groups in the ring-opened products. Interestingly, the stereochemical outcome of this reaction was exactly opposite to that reported by Lautens for the Rh(I)-catalyzed alcoholysis and aminolysis of oxabenzonorbornadiene.[16] Subsequent experiments revealed that the reaction of **9** with the Rh(I)-catalyst in the presence of various ammonium carboxylates[16c] generated the dienyl alcohol **34** in 75% isolated yield as the exclusive product. Reaction of 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**35**) with oxabicyclics **9** and **22**, using 5 mol % of the Rh(I) catalyst and 2.0 equiv of Cs_2CO_3 (5 M in H_2O) in THF at 65 °C, led to the ring-opened alcohols **36** and **37** in 70−80% yield. The *cis* isomer was formed exclusively and parallels the results observed with the alcoholysis and aminolysis experiments. When the Rh(I)-catalyzed reaction was carried out with phenyl boronic acid[16d] and without added base, the ring-opened boronates **38** and **39** were obtained in excellent yield (>95%). Both boronates were cleaved to the corresponding diols[20] which were subsequently transformed into dioxolanes **40** and **41** by reaction with 2,2-dimethoxypropane. It was also possible to prepare the same 1,3-dioxolanes (>90%) by treating oxabicyclic adducts **9** and **22** with catalytic anhydrous $SnCl_2$ in acetone.[21]

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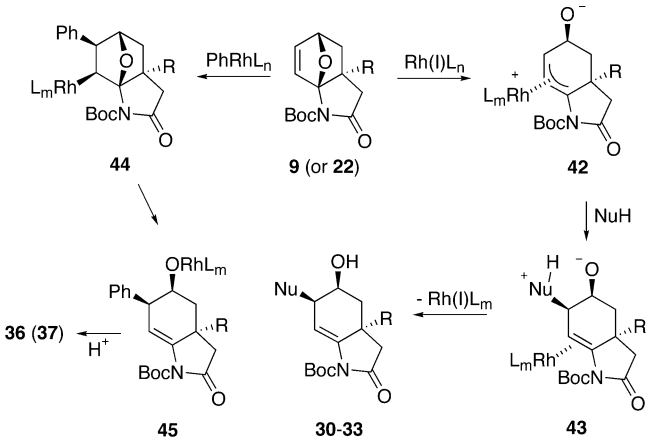
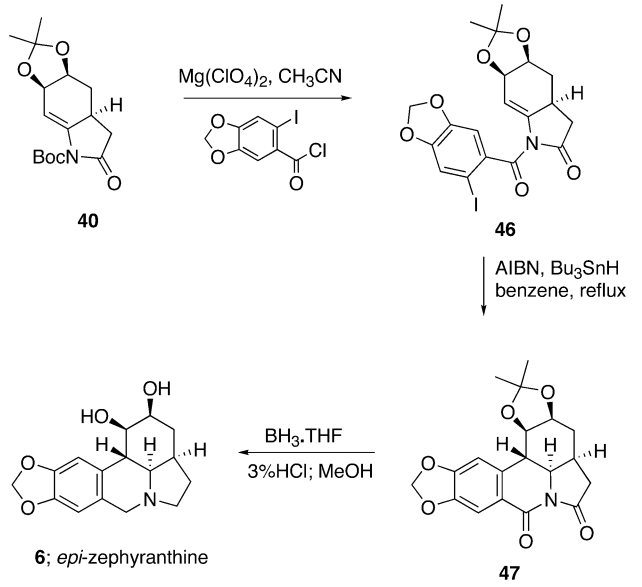
The proposed mechanism for the Rh(I)-catalyzed reaction of the oxabicyclic adduct is outlined in Scheme 4. Coordination of Rh(I) to the alkenyl π-bond followed by nitrogen-assisted cleavage of the carbon−oxygen bond occurs to furnish the π-allyl rhodium(III) species **42**. A subsequent nucleophilic addition occurs from the least hindered terminus of **42** and on the side opposite the rhodium complex. Proton exchange of intermediate **43** followed by rhodium decomplexation ultimately leads to the cis diastereomers **30**−**33**. In the presence of the basic ammonium carboxylate, intermediate **42** (R = H) undergoes preferential deprotonation and subsequent loss of Rh(I) to generate a transient diene that isomerizes to give **34**. The formation of **36** (or **37**) from the reaction with phenyl boronic ester **35** can best be rationalized as proceeding by an initial transmetalation of the boronate to rhodium(I) chloride or hydroxide in the presence of Cs_2CO_3. The resulting species will then undergo an *exo*-selective carborhodation at the oxabicyclic olefin to generate intermediate **44**. Chelation of the olefin and oxygen atom of the oxabicycle with the rhodium metal accounts for the high *exo* selectivity. β-Elimination of oxygen, assisted by the nitrogen lone pair, furnishes intermediate **45**, which eventually leads to the ring-opened alcohols **36** and **37**.

Scheme 4



We are now in a position to apply the experience gained from our model studies to the synthesis of *epi*-zephyranthine (**6**). To this end, dioxolane **40** was easily converted to the corresponding benzamide **46** in 81% yield by first removing the *t*-Boc group, using $MgClO_4$ in CH_3CN followed by benzoylation with the acid chloride of 6-iodobenzo[1,3]-dioxazole-5-carboxylic acid (Scheme 5). Exposure of **46** to *n*-Bu_3SnH in benzene at reflux in the presence of AIBN afforded the anticipated tetracyclic product **47** in 55% yield. The *trans*-B,C- and *cis*-C,D-ring fusion of the cyclized product was unambiguously assigned by an X-ray crystal structure of compound **47**. SYBYL force field calculations

Scheme 5



suggest that this stereochemistry corresponds to the most stable isomer, and is also in agreement with the earlier reports of Rigby[15a] and Schultz.[15b] Reduction of **47** with BH_3·THF followed by hydrolysis of the 1,3-dioxolane furnished (65%) *epi*-zephyranthine in an overall yield of 14.5% for the 7-step sequence starting from *tert*-butyl furanyl carbamate **11**.

In summary, a new strategy for the synthesis of the amaryllidaceae alkaloid family has been developed, which is based in part on an extraordinarily facile intramolecular Diels−Alder reaction of a 2-imido-substituted furan for construction of the hexahydroindolinone core. By using a Rh(I)-catalyzed ring opening of the oxabicyclic adduct, the *cis* diol stereochemistry of *epi*-zephyranthine was established. The application of this approach to other natural product targets is currently under investigation, the results of which will be disclosed in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds together with an Ortep drawing for compounds **31** and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

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