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

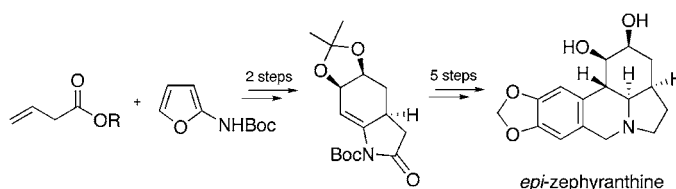Qiu Wang and Albert Padwa*

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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
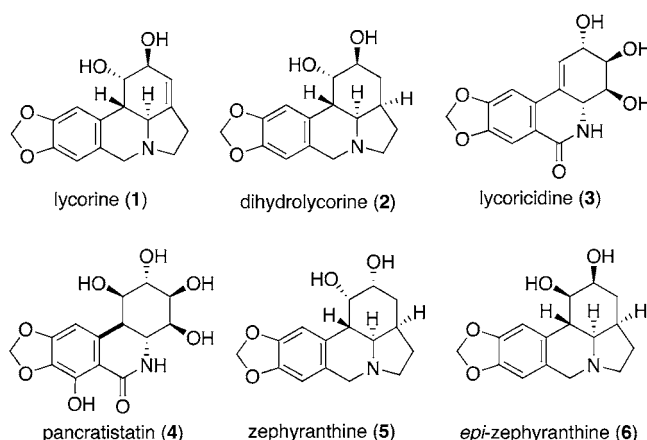

Figure 1. Lycorine-type alkaloids.

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

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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
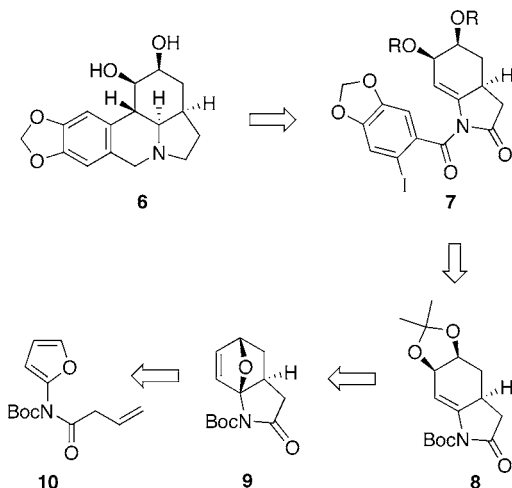
Initially, we had envisioned imidofuran **10** arising from the simple acylation of furanyl carbamate **11** with the acid chloride derived from 3-butenoic acid. However, under a variety of conditions **11** proved to be remarkably resistant toward acylation. After some experimentation, we found that 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

Scheme 2
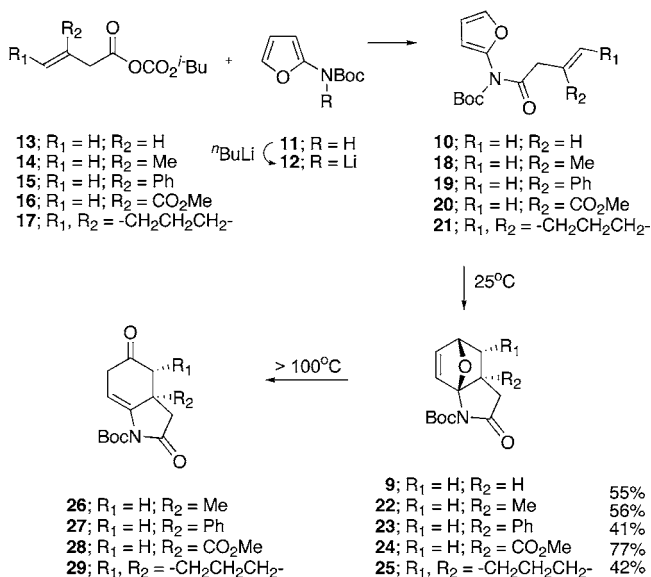
to the acylation protocol and provided the desired imidofurans **18**−**19** which also underwent cycloaddition at 25

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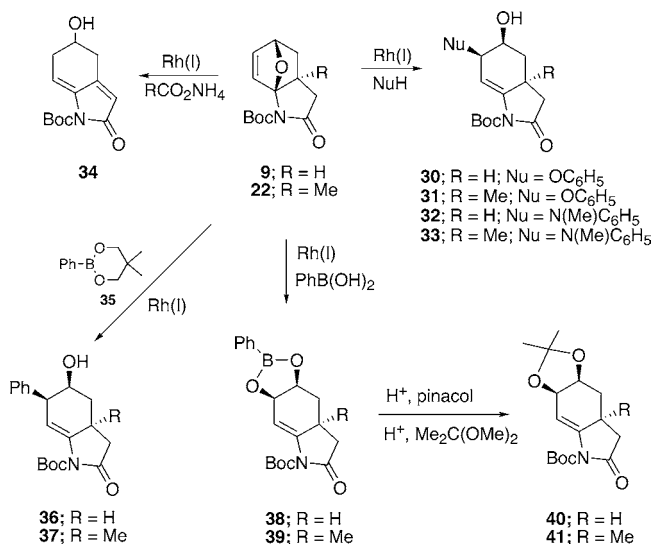
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°C (12 h) to furnish the oxabridged cycloadducts **22–23**. When the more highly activated anhydride **16** was used, imidofuran **20** could not be observed because the [4+2]-cycloaddition occurred too rapidly to preclude its detection, even at 0 °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

34

9; R = H
22; R = Me

30; R = H; Nu = OC$_6$H$_5$
31; R = Me; Nu = OC$_6$H$_5$
32; R = H; Nu = N(Me)C$_6$H$_5$
33; R = Me; Nu = N(Me)C$_6$H$_5$

35

36; R = H
37; R = Me

38; R = H
39; R = Me

40; R = H
41; R = Me

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$_2$CO$_3$ (5 M in H$_2$O) 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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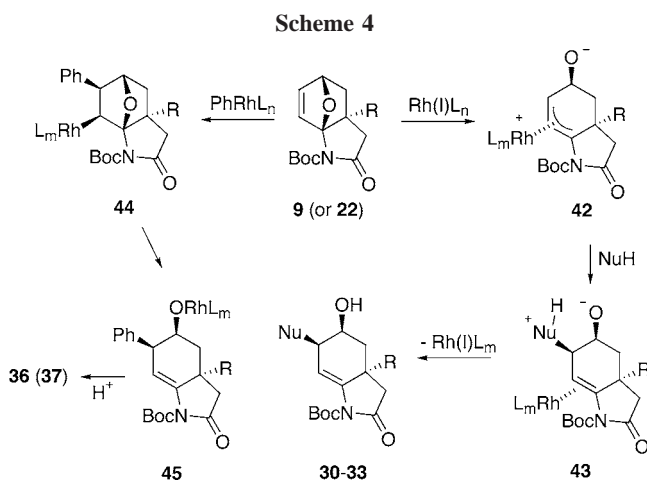
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The proposed mechanism for the Rh(I)-catalyzed reaction of the oxabicyclic adduct is outlined in Scheme 4. Coordina-

Scheme 4

Scheme 5

tion 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$_2$CO$_3$. 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**.

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$_3$CN followed by benzoylation with the acid chloride of 6-iodobenzo[1,3]-dioxazole-5-carboxylic acid (Scheme 5). Exposure of **46** to *n*-Bu$_3$SnH 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
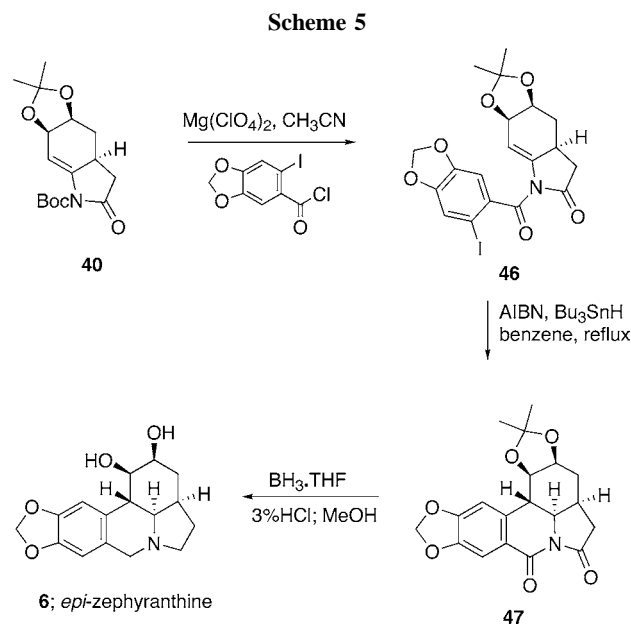
suggest that this stereochemistry corresponds to the most stable isomer, and is also in agreement with the earlier reports of Rigby[15a] and Schultz.[15b] Reduction of **47** with BH$_3$·THF followed by hydrolysis of the 1,3-dioxolane furnished (65%) *epi*-zephyranthine in an overall yield of 14.5% for 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.

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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