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Formal Synthesis of (±)-Dendrobine: Use of the Amidofuran Cycloaddition/ Rearrangement Sequence

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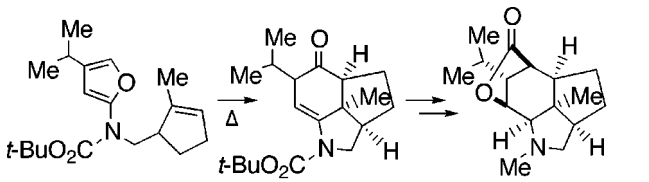
ABSTRACT



(±)-dendrobine

The formal synthesis of the alkaloid (±)-dendrobine (4) was accomplished using the IMDAF cycloaddition/rearrangement sequence of a furanyl carbamate. Conversion of the rearranged cycloadduct to Kende's advanced intermediate in eight steps completed the formal synthesis of (±)-dendrobine.

Dendrobine (**4**) is the major component of the Chinese ornamental orchid *Dendrobium nobile*[1] and exhibits antipyretic, hypotensive, and convulsant activity.[2,3] Dendrobine is a challenging synthetic target owing to the presence of seven asymmetric centers on a compact carbon skeleton and continues to represent a major challenge for efficient chemical synthesis. Total syntheses of this alkaloid were first completed by several research groups in the early 1970's.[4]

As a consequence of its intricate architecture and biological activity, it is not surprising that dendrobine has been the subject of more recent synthetic investigations. Indeed, a number of additional total and formal syntheses[5] have been reported in recent years employing a wide range of strategies.[6] In the present Letter, we present another approach to dendrobine based on our recently described *amidofuran cycloaddition−rearrangement* methodology.[7]

As part of our general interest in cascade processes,[8] we have developed the IMDAF cycloaddition of furans[9] as a

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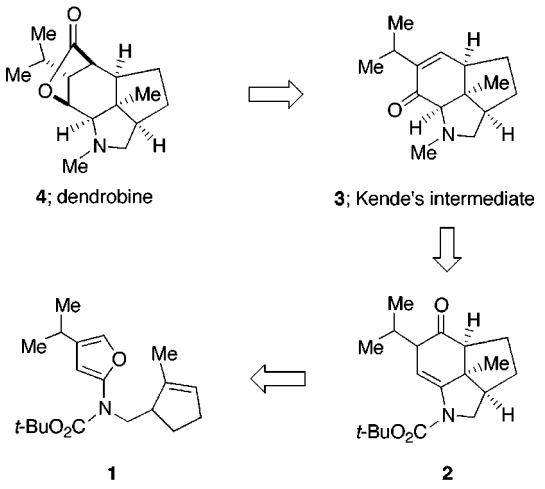
novel route to various heterocycles.[10] We came to recognize that the cycloaddition/rearrangement cascade of furanyl carbamates could be used for a concise and stereocontrolled synthesis of the tricyclic core of (±)-dendrobine. The retrosynthetic analysis is outlined in Scheme 1. The key step

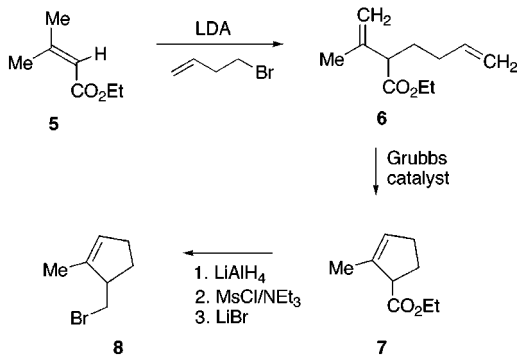
Scheme 1



in our plan involves the intramolecular Diels−Alder reaction of 2-amidofuran **1** followed by a subsequent rearrangement to give hexahydroindolinone **2**. The attractiveness of this strategem involves the possibility of establishing four of the asymmetric centers in one step. We envisioned that a few functional group manipulations would convert **2** into enone **3**, which was a key advanced intermediate in Kende's total synthesis of dendrobine.[4c]

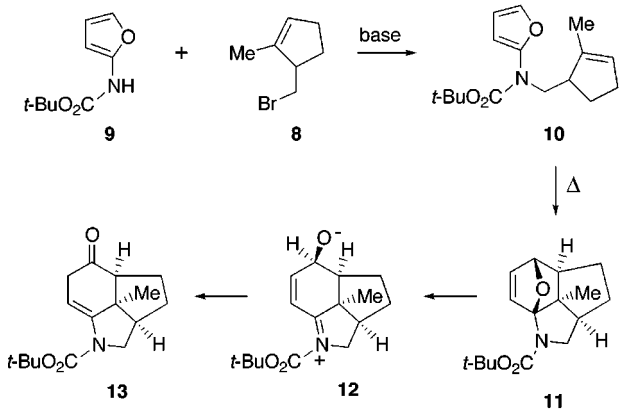
The synthetic sequence depicted above relies on a stereoselective [4 + 2]-cycloaddition of a 3-substituted amidofuran (i.e., **1**) across an unactivated cyclopentenyl π-bond. Before attempting the more challenging Diels−Alder reaction of **1**, a simpler model system (i.e. **10**) was investigated so as to test the feasibility of this approach. The desired starting material was easily synthesized by the alkylation of furan-2-yl carbamic acid *tert*-butyl ester (**9**) with 5-bromomethyl-1-methylcyclopentene (**8**). Cyclopentenyl bromide **8** was prepared by treating ethyl 3-methyl-2-butenoate (**5**) with LDA in the presence of HMPA followed by reaction with 4-bromo-1-butene to give ester **6** in 82% yield (Scheme 2). Ring-closing metathesis (RCM) is a well-established process allowing the synthesis of a wide variety of cyclic systems from the corresponding acyclic diene.[11] This reaction can be catalyzed by a number of metallocarbene complexes, among the most popular of which is the ruthenium benzylidene complex $(Cy_3P)_2Ru(=CHPh)Cl_2$.[12] When diene **6** was treated with an excess of Grubbs catalyst in dichloromethane at 30 °C for 18 h, cyclopentenyl ester **7** was formed in 63% yield. This metathesis reaction was followed by reduction of the ester group to the alcohol, conversion to the mesylate, and then bromide ion displacement to give **8** in 70% overall yield.

Scheme 2



Attachment of the cyclopentenyl tether to the furanyl carbamate was accomplished by treating **9** with potassium carbonate/sodium hydroxide/tetrabutylammonium hydrogen sulfate in benzene followed by the addition of bromide **8**, which gave **10** in 79% yield. The thermal IMDAF reaction of **10** occurred at 165 °C to furnish **13** in 78% yield as a single diastereomer (Scheme 3). The initially formed oxabridge cycloadduct **11** was not detected, as it readily underwent ring opening followed by a subsequent proton shift of the transient acyl iminium ion intermediate **12**. The ring-opened hexahydroindolinone **13** is derived from a transition state where the side arm of the tethered cyclopentenyl group is oriented *syn* (exo) with respect to the oxygen

Scheme 3



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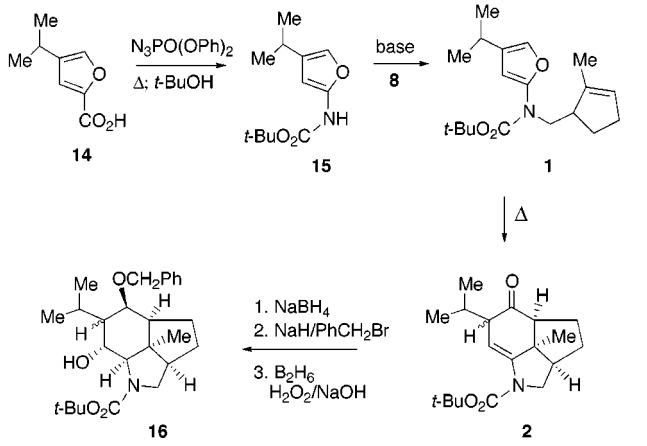
bridge. This stereochemical result is consistent with other reports in the literature involving related furanyl systems that possess short tethered alkenyl side chains.[13]

At this juncture, we turned our attention to the more complex [4 + 2]-cycloaddition of furan carbamate **1**, which bears the isopropyl group necessary for a synthesis of dendrobine. Carbamate **15** was prepared by heating a sample of the known 4-isopropylfuran-2-carboxylic acid (**14**)[14] with diphenyl phosphorylazidate[15] in *tert*-butyl alcohol which effected a Curtius rearrangement to give **15** in 83% yield. Subjection of **15** to the previously used alkylation conditions furnished **1** in 71% yield. We were gratified to find that the thermolysis of **1** proceeded in 74% yield to produce the tricyclic indolinone **2** as a 2:1 mixture of diastereomers (Scheme 4). Reduction of the keto group in **2** was effectively

Scheme 4



accomplished by treatment of the mixture with sodium borohydride in methanol. Protection of the hydroxyl group as the benzyl ether was followed by hydroboration/oxidation to deliver the tricyclic alcohol **16** as a 2:1 mixture of stereoisomers. Fortunately, the two diastereomers were easily separated by silica gel chromatography and were formed in 50 and 22% overall yields, respectively, from hexahydroindolinone **2**. Thus, the three-step sequence (reduction, protection, and oxidative hydroboration) was quite efficient, i.e., a 72% overall yield after separation. Delivery of hydride to the keto group as well as hydroboration of the enamide double bond occurred from the sterically less hindered convex face of the tricyclic core, which is on the same face as the methyl group.[5d,e]

Exposure of the major diastereomer of **16** to Dess−Martin periodinane afforded a mixture of epimers of **17**, most likely the result of epimerization at C(6) during the oxidation.

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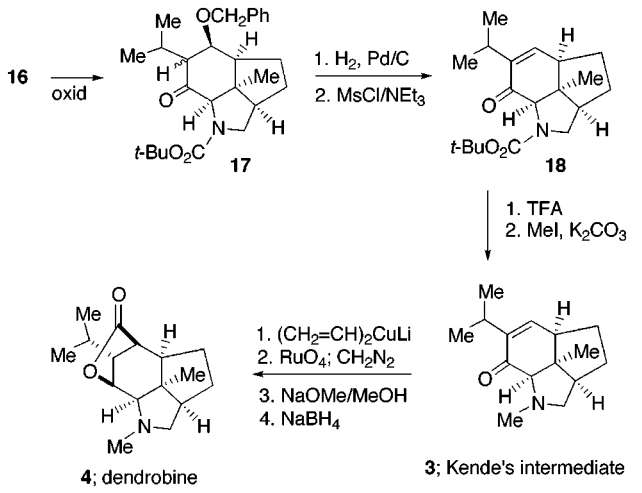
(16) Mori and co-workers report additional details for the characterization and conversion of **3** into (±)-dendrobine.[5e]

Attempts to form Kende's intermediate **3** via the elimination of benzyl alcohol directly from **17** were unsuccessful. Instead, **17** was subjected to hydrogenolysis using a Pd/C catalyst to cleave the benzylic-oxygen bond. Without purification, the resulting alcohol was treated with mesyl chloride/NEt_3 and the resulting mesylate underwent spontaneous elimination to furnish enone **18** in 62% overall yield from alcohol **16** (Scheme 5). Finally, cleavage of the BOC group in **18** with

Scheme 5



dilute trifluoroacetic acid in CH_2Cl_2 followed by methylation of the resulting secondary amine with methyl iodide furnished Kende's intermediate **3** in 65% yield for the two steps. The spectroscopic data of **3** were identical to those reported in the literature.[16]

In summary, a concise formal synthesis of (±)-dendrobine has been carried out using the IMDAF cycloaddition/rearrangement sequence of furanyl carbamates previously reported from our laboratories.[7] The synthesis of Kende's advanced intermediate **3** was accomplished in 11 steps from readily available starting materials. All synthetic steps of this sequence proceeded in good yield, and the stereogenic centers from the cycloaddition were established with high stereoselectivity. Further application of this methodology to other alkaloids is currently underway in our laboratories and will be reported in due course.

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Supporting Information Available: Full experimental and analytical data for all new compounds and compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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