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An Efficient Synthesis of (±)-Lycoricidine Featuring a Stille–IMDAF Cycloaddition Cascade

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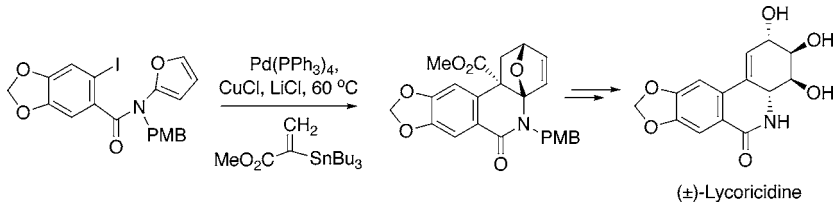
ABSTRACT



A highly efficient total synthesis of (±)-Lycoricidine is described. The synthesis features the ready preparation of the Lycoricidine skeleton by a Stille–IMDAF cycloaddition cascade. The resulting cycloadduct is then used for the stereocontrolled installation of the other functionality present in the C-ring of the target molecule.

Many of the lycorine-type *Amaryllidaceae* alkaloids display useful biological properties,[1] and as a consequence this family has captured the interest of a number of synthetic groups as targets for total synthesis.[2] The history of the hydroxylated phenanthridones of the *Amaryllidaceae* group, their biological profiles, and various syntheses have been reviewed on several occasions,[3] most recently by Hudlicky and Rinner in 2005.[4] Lycoricidine (**1**),[5] the structurally related Narciclasine (**2**),[6] as well as Pancratistatin (**3**)[7] and 7-Deoxypancratistatin (**4**)[8] are popular synthetic targets primarily because their heterocyclic framework provides a means to demonstrate the utility of new synthetic strategies.[4] In addition, the narcissus alkaloids are available only in small quantities from natural sources,[9] and their use as therapeutic agents[10] depends on their ready availability. The principle hurdles to their

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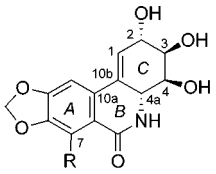
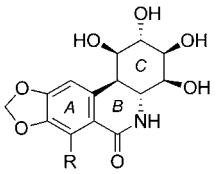
synthesis include the introduction of the aryl group and the stereocontrolled construction of the fused BC ring system.



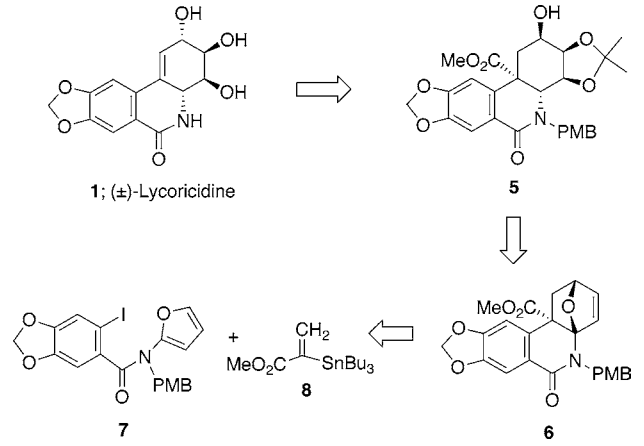
1; R = H; Lycoricidine
2; R = OH; Narciclasine



3; R = OH; Pancratistatin
4; R = H; Deoxypancratistatin

A major strategy that is routinely employed for the synthesis of the lycorine group consists of constructing two fragments representing the A and C cycles, which are then coupled together to form the B ring. This approach often involves formation of the *10a-10b* carbon−carbon bond by either a palladium-based[11] or photocyclization[6d] reaction, although other coupling methods have also been used.[3,4] An alternate synthetic route would be the formation of the C-ring from a suitable precursor in which the *10a-10b* bond of the target is already present.[12,13] It is against this background that we report a short and efficient synthesis of (±)-Lycoricidine. Our approach derives from a general program underway in our laboratory that is designed to exploit the facile Diels−Alder reaction of amidofurans for the purposes of natural product synthesis.[14] Our retrosynthetic analysis of (±)-Lycoricidine is shown in Scheme 1 and makes use

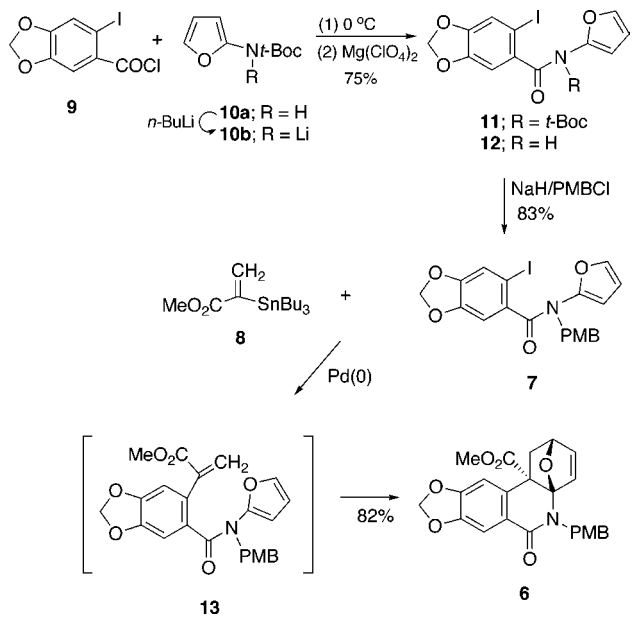
Scheme 1



of a tandem cascade sequence consisting of a Stille coupling[15] followed by a spontaneous intramolecular [4 + 2]-cycloaddition of an amidofuran (IMDAF). The resulting cycloadduct **6** is then used for the stereocontrolled installation of the other functionality present in the C-ring of Lycoricidine. The carbomethoxy substituent is utilized as a critical control element not only to facilitate the [4 + 2]-cycloaddition but also to provide a handle for the introduction of the required π-bond and to set the stereochemistry at the C_{4a}-ring juncture.

Our synthesis of amidofuran **7** began by coupling the known acid chloride **9**[16] with the lithiated carbamate **10b** derived by treating furanyl-2-ylcarbamic acid *tert*-butyl ester (**10a**) with *n*-BuLi. Removal of the *t*-Boc protecting group from the resulting carbamate **11** with $Mg(ClO_4)_2$ afforded NH amide **12** in 75% yield, and this was followed by reaction with NaH and *p*-methoxybenzyl chloride to give **7** in 83% yield.[17] The methyl acrylate moiety was introduced by means of a Stille coupling[15] using methyl 2-tri-*n*-butylstannylacrylate[18] (Scheme 2). The optimum conditions for this reaction

Scheme 2



were eventually determined to be those described by Corey that utilize a combination of CuCl/Pd(0)/LiCl for the key coupling.[19] The use of DMSO with rigorous exclusion of

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(17) Replacement of the *t*-Boc group with the PMB functionality was necessary for the subsequent Stille reaction.

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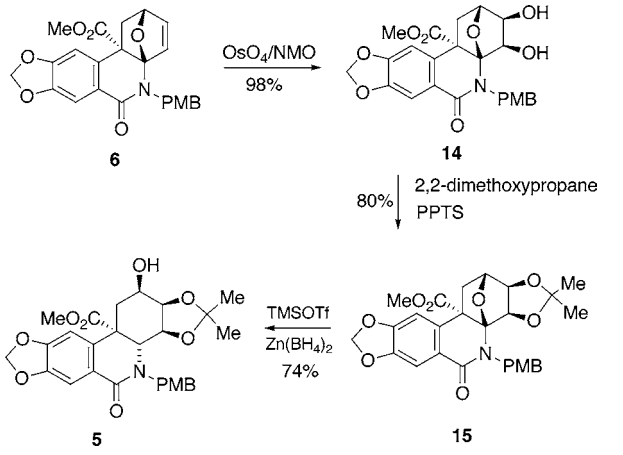
oxygen and moisture at 60 °C gave the best results. The expected cross-coupled amidofuran **13**, however, was not isolated as it spontaneously underwent an intramolecular [4 + 2]-cycloaddition to furnish cycloadduct **6** in 82% overall yield for the two-step cascade. The increase in reactivity of **13** when compared to related furanyl carbamates[20] (>150 °C) is due to both the placement of the carbonyl center within the dienophilic tether and the presence of the carbomethoxy group, which lowers the LUMO energy of the π-bond thereby facilitating the cycloaddition. 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.[21] Our ability to isolate oxabicyclic adduct **6** is presumably a result of the lower reaction temperature employed (i.e., 60 °C) as well as the presence of the amido carbonyl group, which diminishes the basicity of the nitrogen atom thereby retarding the ring cleavage/rearrangement reaction generally encountered with these systems.[20] Moreover, the IMDAF cycloaddition proceeds by a transition state where the sidearm of the tethered vinyl group is oriented *exo* with respect to the oxygen bridge.[22] As a consequence of this preferred orientation, the carbomethoxy group and oxy-bridge are disposed in an *anti* relationship in the resulting cycloadduct **6**.

With the rapid construction of the Lycoricidine framework in hand, installation of the other functional groups present on the C-ring with the correct relative stereochemistry was investigated. To continue the synthesis, cycloadduct **6** was transformed to diol **14** by reaction with catalytic OsO_4 in the presence of 4-methyl-morpholine-*N*-oxide. The dihydroxylation reaction occurred exclusively from the less hindered *exo* face, producing **14** in 98% yield (Scheme 3).

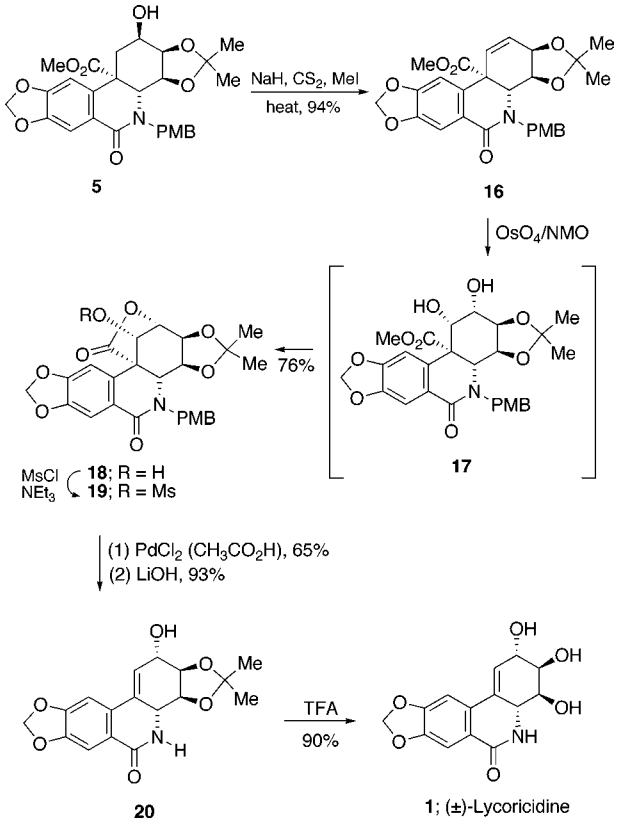
Scheme 3



Having introduced the correct *cis*-stereochemistry of the hydroxyl groups at the C_3,C_4 positions, we then proceeded to set the stereochemistry at the C_{4a} position, insert the remaining α-hydroxyl group at C_2, and ultimately introduce the required π-bond. All of these operations were facilitated by making use of the available carbomethoxy group (vide infra). First, diol **14** was converted to the corresponding acetonide **15** in 80% yield by treatment with 2,2-dimethoxypropane and catalytic pyridinium *p*-toluenesulfonate. The uniquely functionalized oxabicyclic adduct **15** contains a "masked" *N*-acyliminium ion that can be released by treatment with a Lewis acid such as TMSOTf. When the resulting ring-opened iminium ion was treated with $Zn(BH_4)_2$,[23] alcohol **5** was obtained in 74% yield.

What was required for the end game leading to Lycoricidine (**1**) was to invert the stereochemistry of the C_2-hydroxyl group, remove the carbomethoxy moiety, and generate a double bond between the C_1−C_{10b} position of the C-ring. To this end, compound **5** was treated with NaH followed by the addition of CS_2 and MeI to give the corresponding xanthate ester, which upon heating at reflux in 1,2-dichlorobenzene for 12 h afforded the expected olefin derived from a Chugaev elimination[24] in 94% yield (Scheme 4). Since the

Scheme 4



β-face of the π-bond of **16** was blocked by the bulky acetonide, a dihydroxylation reaction was expected to take place from the less hindered α-face, *syn* to the carbomethoxy group, thereby setting the correct stereochemistry of the C_2-hydroxyl group. Indeed, when **16** was treated with OsO_4/NMO, the desired diol **17** was formed as a transient species but underwent spontaneous cyclization with the adjacent

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carbomethoxy group to deliver γ-lactone **18**. A subsequent mesylation reaction afforded mesylate **19** in 76% yield for the two-step sequence starting from **16**. The γ-lactonization of **17** to **18** permits the selective activation of the C_1-hydroxyl group. The PMB group was removed by the reaction of **19** with $PdCl_2$ in the presence of acetic acid[25] to furnish the deprotected amide. Gratifyingly, the reaction of this amide with LiOH in aqueous THF induced a novel tandem hydrolysis/decarboxylation/elimination sequence[26] to furnish allylic alcohol **20**. Deprotection of the acetonide with TFA afforded (±)-Lycoricidine in 90% yield.

In summary, we have described here a novel and highly efficient synthesis of (±)-Lycoricidine, which was achieved in 14 steps with a 12.6% overall yield. The synthesis illustrates (a) the use of a one-pot Stille−IMDAF cycloaddition cascade to construct the ring skeleton, (b) a stereocontrolled dihydroxylation and *N*-acyliminium ion reduction to set the correct stereochemistry at carbon atoms C_3, C_4, and C_{4a}, and (c) the novel introduction of the C_1−C_{10b} π-bond by a one-pot hydrolysis−decarboxylation−elimination sequence. The application of this approach to other members of the lycorine family of alkaloids 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. This material is available free of charge via the Internet at http://pubs.acs.org.

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