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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 properties¹ 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 sources⁹ and their use as therapeutic agents¹⁰ depends on their ready availability. The principle hurdles to their 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-based¹¹ 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 of a tandem cascade sequence consisting of a Stille coupling¹⁵ 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 (ClO₄)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 coupling¹⁵ using methyl 2-tri-*n*-butylstannylacrylate¹⁸ (Scheme 2). The optimum conditions for this reaction were eventually determined to be those described by Corey which utilize a combination of CuCl/Pd(0)/LiCl for the key coupling.¹⁹ The use of DMSO with rigorous exclusion of 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 carbamates²⁰ (>150 °C) is due to both the placement of the carbonyl center within the dienophilic tether as well as 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 OsO₄ 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). Having introduced the correct *cis*-stereochemistry of the hydroxyl groups at the C₃,C₄ positions, we then proceeded to set the stereochemistry at the C_{4a} position, insert the remaining α -hydroxyl group at C₂ 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 which can be released by treatment with a Lewis acid such as TMSOTf. When the resulting ring opened iminium ion was treated with Zn(BH₄)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 C₂-hydroxyl group, remove the carbomethoxy moiety and generate a double bond between the C₁-C_{10b} position of the C-ring. To this end, compound **5** was treated with NaH followed by the addition of CS₂ 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 elimination²⁴ in 94% yield (Scheme 4). Since the 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 C₂-hydroxyl group. Indeed, when **16** was treated with OsO₄/NMO, the desired diol **17** was formed as a transient species but underwent spontaneous cyclization with the adjacent 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 C₁-hydroxyl group. The PMB group was removed by the reaction of **19** with PdCl₂ in the presence of acetic acid²⁵ to furnish the deprotected amide. Gratifyingly, the reaction of this amide with LiOH in aqueous THF induced a novel tandem hydrolysis/decarboxylation/elimination sequence²⁶ to furnish allylic alcohol **20**. Deprotection of the acetonide with TFA afforded ($\pm$)-Lycoricidine in 90% yield.

In summary, we have described here a novel and highly efficient synthesis of ($\pm$)-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 C₃, C₄ and C_{4a}, and (c) the novel introduction of the C₁-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.

Supporting Information Available

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.