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Stereospecific Route to 5,11-Methanomorphanthridine Alkaloids via Intramolecular 1,3-Dipolar Cycloaddition of Nonstabilized Azomethine Ylide: Formal Total Synthesis of (±)-Pancracine

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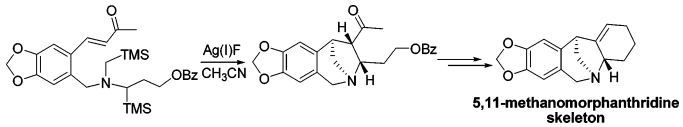
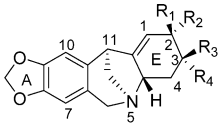
ABSTRACT



The core structure of the complex pentacyclic 5,11-methanomorphanthridine alkaloids is constructed stereospecifically in one step employing an intramolecular [3 + 2]-cycloaddition of nonstabilized azomethine ylide as the key step. The strategy is demonstrated by accomplishing the formal total synthesis of (±)-pancracine.

The 5,11-methanomorphanthridine alkaloids, belonging to the subclass *Amaryllidaceae*, were first isolated by Wildman and co-workers in 1955.[1] These natural products, produced by various plant species such as *Pancratium*, *Narcissus*, and *Brunsvigia*, have a unique pentacyclic framework. In general, alkaloids of this group, (−)-pancracine (**1**), (−)-montanine (**2**), (−)-coccinine (**3**), and (−)-brunsvigine (**4**), possess identical structural features except for the oxygen substitutions in the E-ring (methoxy vs hydroxyl)[2] and stereochemistry at C-2 and C-3. Due to unique structural features and important biological activities[3] associated with these alkaloids, considerable attention is directed from synthetic chemists toward the total syntheses of these alkaloids.



	R_1	R_2	R_3	R_4	
1	H	OH	OH	H	(-)-pancracine
2	H	OH	H	OH	(-)-brunsvigine
3	H	OMe	OH	H	(-)-montanine
4	OMe	H	OH	H	(-)-coccinine

Literature scrutiny revealed that methodologies pertaining to the construction of the core pentacyclic 5,11-methanomorphanthridine skeleton (**5**) have mainly been limited to either Pictet−Spengler reaction from **6**, intramolecular alkylation of **7**, or intramolecular radical cyclization from **8**.

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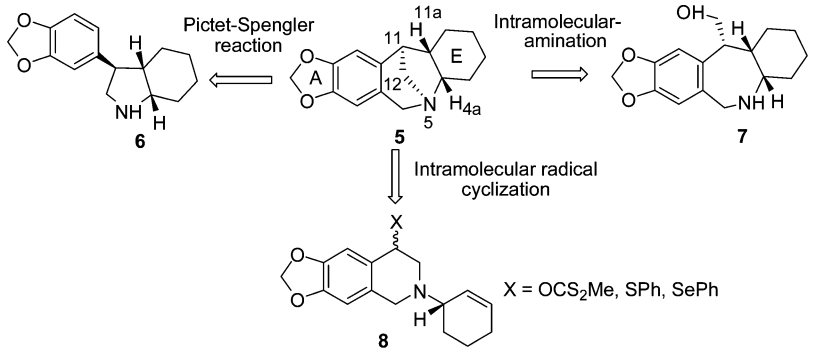
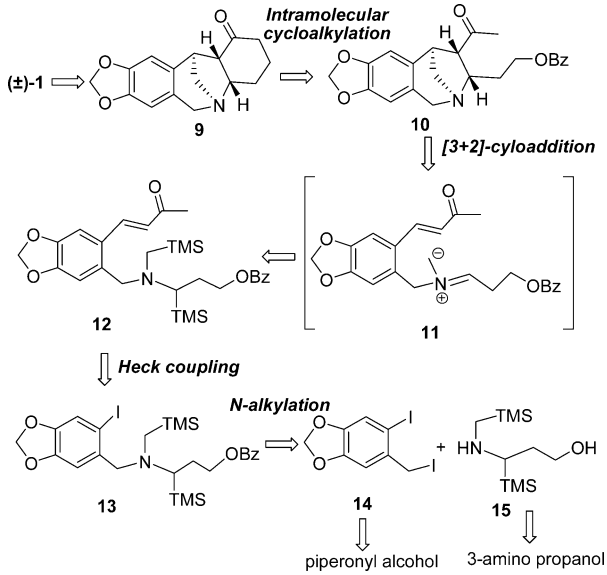


Figure 1. Summary of the reported strategies for assembling the 5,11-methanomorphanthridine class of alkaloids.

(Figure 1) However, in all these strategies, synthesis is elaborated from a precursor having the proper stereochemistry at C-4a and C-11a and a relative disposition of the C-12 methylene group of **5** that involved their construction in a stepwise manner. Hoshino and co-workers[4] have accomplished the synthesis of **1**−**4** in racemic form from a precursor of type **7**, obtained from the Pictet−Spengler reaction of a corresponding cyclohexane derivative. Weinreb and Jin[5] also utilized similar cyclization strategy from a compound of type **7** in their synthesis of (−)-pancracine (**1**) and (−)-coccinine (**4**). In another approach, Hoshino and co-workers[6] have used radical cyclization from a precursor of type **8** to construct skeleton **5**. Overman,[7] Pearson,[8] Ikeda,[9] Sha,[10] and Banwell[11] have used a precursor of type **6** in their respective elaborations of these alkaloids.

We viewed the synthesis of these alkaloids differently, as depicted retrosynthetically in Scheme 1, employing an

Scheme 1. Retrosynthetic Analysis



intramolecular 1,3-dipolar cycloaddition strategy of a non-stabilized azomethine ylide (AMY) for the construction of the core 5,11-methanomorphanthridine CD-ring system in one step. It may be mentioned that this concept originated from our ongoing research activities in the area of alkaloid syntheses[12] involving a nonstabilized azomethine ylide cycloaddition strategy, generated by sequential double desilylation of α,α′-bis(trimethylsilylmethyl)alkylamines[13] as the key step. In this communication, we explore a conceptually new route for the expedient construction of **9** toward the total synthesis of (±)-pancracine (**1**).

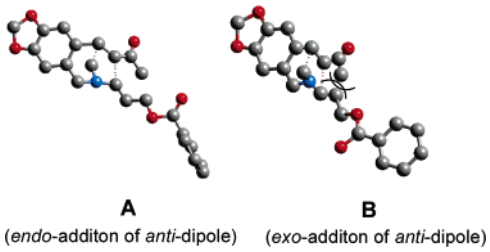


Figure 2. Empirical view of transition state **11** (hydrogens have been omitted for simplicity).

An analysis of the steric repulsion present in **A** and **B** indicated that *endo* attack (**A**) would be preferred over the more encumbered *exo* alternative (**B**) (Figure 2). Such cycloaddition was also envisaged to provide core 5,11-methanomorphanthridine skeleton **10** with the stereochemical dispositions required for assembling a suitably equipped E-ring for further elaboration by intramolecular cycloalkylation reaction.

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(6) Ishizaki, M.; Kurihara, K.-I.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101.
(7) (a) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005. (b) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662.
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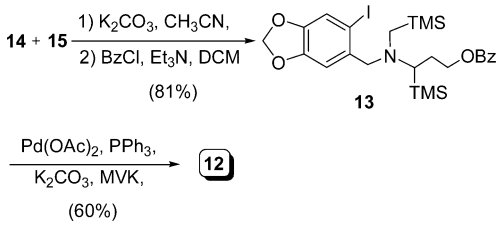
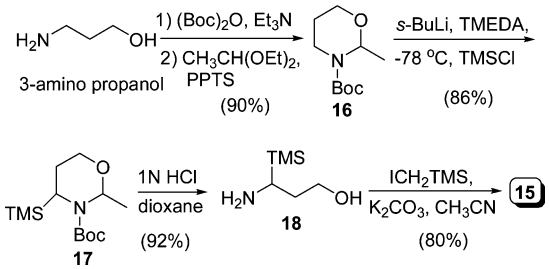
Our synthetic journey began with the preparation of principal precursor **12** in 70% yield by following the simple steps as shown in Scheme 2.

Scheme 2. Synthesis of **12**



Refluxing a mixture of **14** (1 equiv) and **15** (1.25 equiv) in CH_3CN in the presence of anhydrous K_2CO_3 gave the corresponding coupled alcohol, which upon benzoylation gave **13** in 81% yield. Our initial attempt of Heck coupling[14] between **13** and methyl vinyl ketone (MVK) by following usual reported procedures such as $PdCl_2(CH_3CN)_2$ in THF[15a] or $Pd(OAc)_2$/*n*-Bu_4NCl in DMF at room temperature,[15b] however, failed to provide **12** in satisfactory yield. Finally, with little experimentation and optimization, we succeeded in obtaining **12** in 60% yield using $Pd(OAc)_2$ as the catalyst and with an increased amount of MVK (8 equiv). One of the coupling components (**14**) used in this reaction was prepared very easily from the commercially available piperonyl alcohol in 70% yield in two steps using known procedures.[5b,16] The synthesis of another component (**15**) is shown in Scheme 3.

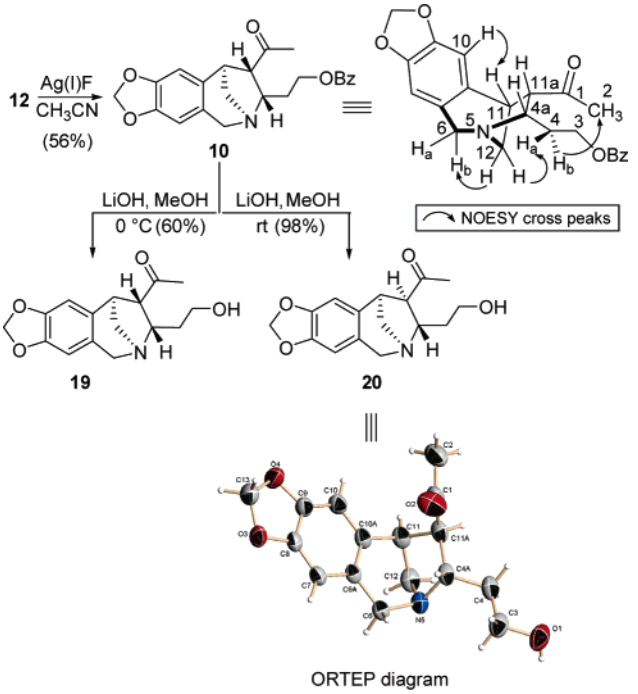
Scheme 3. Synthesis of **15**



The *N*-Boc cyclic amine **16**, synthesized easily in two steps from commercially available 3-amino propanol, upon metalation using *s*-BuLi/TMEDA in THF at −78 °C and quenching with TMSCl, gave **17** in 92% yield.[17] Deprotection of both *N*,*O*-acetal as well as *N*-Boc moieties using 1 N HCl in refluxing dioxane produced corresponding free amine **18** in 87% yield, which upon alkylation with (iodomethyl)-trimethylsilane in the presence of anhydrous K_2CO_3 in CH_3-CN gave **15** in 80% yield.

The crucial intramolecular cycloaddition reaction of the azomethine ylide generated from **12**, to our delight, gave **10** as a single diastereoisomer in 56% yield. The cycloaddition reaction was performed by slow addition of **12** (1 equiv) to a stirring heterogeneous mixture of the flame-dried Ag(I)F (2.5 equiv) in dry CH_3CN. The cycloadduct **10** was fully characterized by ^1H NMR, ^{13}C NMR, and mass spectral data. The stereochemical assignments, as shown in Scheme 4, are

Scheme 4. Cycloaddition of **11**



based on extensive COSY and NOESY NMR spectral studies.

To proceed further from **10**, we subjected it to the usual debenzoylation reaction (LiOH/MeOH, rt), which, however, provided unexpected epimerized alcohol **20** in 98% yield (confirmed by X-ray crystallography).[18] Although unepimerized alcohol **19** could be obtained from **10** by stirring with LiOH/MeOH at 0 °C (Scheme 4), we decided to continue further with **20** itself, as the C11a stereochemistry at this stage was irrelevant for final natural product synthesis. Intramolecular cycloalkylation[19] of the corresponding me-

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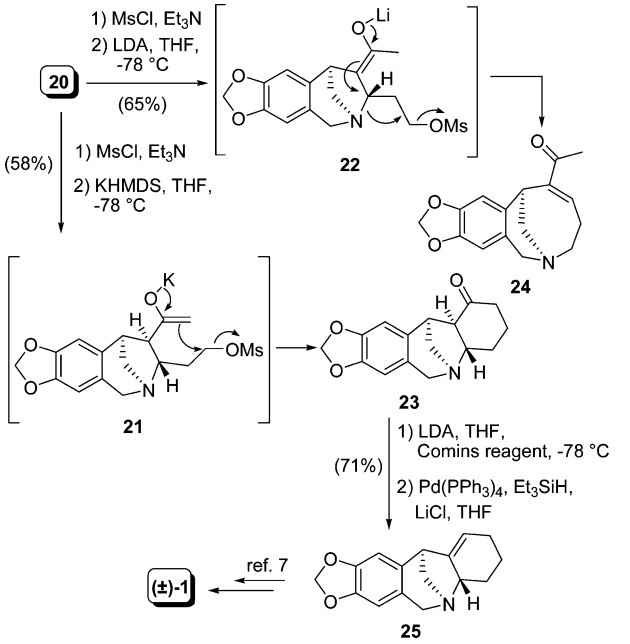
sylate derivative of **20** using LDA/THF at −78 °C very surprisingly produced **24** in 65% yield, indicating the involvement of a thermodynamic enolate **22** in this rearrangement (Scheme 5). Successful transformation of **20** to **23** (*epi*-9) was finally achieved in 58% yield involving kinetic enolate[20] **21**, generated from **20** in the presence of KHMDS/THF at −78 °C. Involvement of an azetidinium salt-type intermediate from **20** in the formation of **23** and **24**, neither can be supported nor ruled out at this stage.

To demonstrate the significance of our strategy, we decided to complete the formal total synthesis of (±)-pancracine **1**. The pivotal $\Delta^{1,11a}$ double bond from **23** leading to the formation of **25** (71% yield) was created by the reductive elimination of the corresponding enol triflate using $Pd(PPh_3)_4/Et_3SiH$ in THF.[21] The required enol triflate from **23** was generated by the reaction of the corresponding lithium enolate of **23** with the Comins reagent.[22] All spectral data of **25** matched very well with the values reported by Overman et al.,[7] who have also elaborated **25** in a couple of steps to (±)-pancracine **1**.

In conclusion, we have developed a short and conceptually new route for the stereospecific construction of the core structure of 5,11-methanomorphanthridine alkaloids in one step. The success of this strategy is demonstrated by accomplishing the formal total synthesis of (±)-pancracine **1**. The asymmetric version of this approach, along with an alternative strategy for constructing the E-ring and synthesis of some other important alkaloids of this class, is in progress and will be revealed in a full paper shortly.

Scheme 5. Formal Total Synthesis of (±)-Pancracine **1**



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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051321O

(18) X-ray analysis of **20**: $C_{16}H_{19}NO_4$, $M_r = 289.32$, crystal dimensions 0.40 × 0.38 × 0.13, *Bruker SMART APEX* CCD diffractometer, Mo Kα radiation, multiscan data acquisition, $a = 5.7666(5)$, $b = 9.7162(8)$, $c = 13.4268(11)$ Å, $\alpha = 98.029(1)$, $\beta = 100.091(1)$, $\gamma = 97.602(1)°$, $V = 723.8(1)$ Å^3, $Z = 2$, $D_c = 1.327$ mg m^{-3}, triclinic, space group *P*-1, μ (Mo Kα) = 0.095 mm^{-1}, of 7005 reflections measured, 2539 unique [$I > 2\sigma(I)$], *R* value 0.0441, wR_2 = 0.1167. All data were corrected for Lorentzian, polarization, and absorption effects. SHELX-97 was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-271169.

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