Short, Scalable Access to Pyrrovobasine

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Supporting Information Placeholder

ABSTRACT: A concise, gram-scale synthesis of pyrrovobasine (**1**) is reported. Key transformations include a 3-step decagram-scale synthesis of the tetracyclic compound without protecting groups, Mn-mediated direct radical cyclization, and introducing a naturally rare pyrraline structure. The synthesis is designed to be applicable to gram-scale synthesis using inexpensive and readily available reagents.

Pyrrovobasine (**1**) is an indole alkaloid with a pseudo-dimer structure isolated from Voacanga africana stem bark extracts, mainly in tropical Africa, by Beniddir and co-workers in 2022 (Figure 1A).[1] It is structurally characterized by a pyrraline structure on the complex linkage of tryptophan and tryptamine, which is unusual for a natural product. The total synthesis of pyrrovobasine (**1**) has not yet been reported. In this work, we report the first total synthesis of pyrrovobasine (**1**). This method features an inexpensive and efficient strategy towards pyrrovobasine (**1**) on a gram scale in a short process. It can be widely applied to synthesizing other related natural products and analogs.

The synthetic strategy of pyrrovobasine (**1**) is shown in Figure 1A. Since pyrrovobasine (**1**) has a pyrraline structure, which is relatively rare as a natural product, the key to this synthetic route is how to introduce this pyrraline structure. Considering the instability of the pyrraline skeleton, we planned to introduce a pyrraline derivative into a tryptamine derivative at the end of the total synthesis. There are several reports on the synthesis of alkyl pyrralines.[2] Alkylation of pyrrole derivatives is the simplest and most reliable reaction, although strong basic conditions are generally used. On the other hand, it has been reported that the epimerization of the methyl ester on the Vobasine skeleton proceeds readily under basic conditions.[3] Based on the above, we planned to synthesize the pyrraline skeleton using a pyranone derivative, which proceeds under weakly acidic conditions in the late stage of the synthesis. The regioselectivity and stereoselectivity of the tryptamine derivative in the Vobasine skeleton must be controlled, and we speculated that the regioselectivity of the tryptamine derivative would be C2-selective based on its electron density. Interestingly, the Me-group of methyl ester on the Vobasine skeleton shows a signal around 2.5 ppm in ^{1}H NMR.[1] This peak is shifted to a higher field than that of the normal methyl ester. This is presumably due to the shielding effect of the indole moiety of the Vobasine skeleton, which covers the methyl ester moiety, and thus shifts it to a higher magnetic field. Therefore, we speculate that the methyl ester on the Vobasine backbone acts as a steric hindrance and that the introduction of tryptamine derivatives proceeds by avoiding the methyl ester, allowing the stereoselective introduction of tryptamine derivatives.

The plausible biosynthetic pathway of pyrrovobasine (**1**) is shown in Figure 1B. After removal of the alcohol moiety of vobasinol (**2**), the C2 position of the tryptamine derivative **4** with

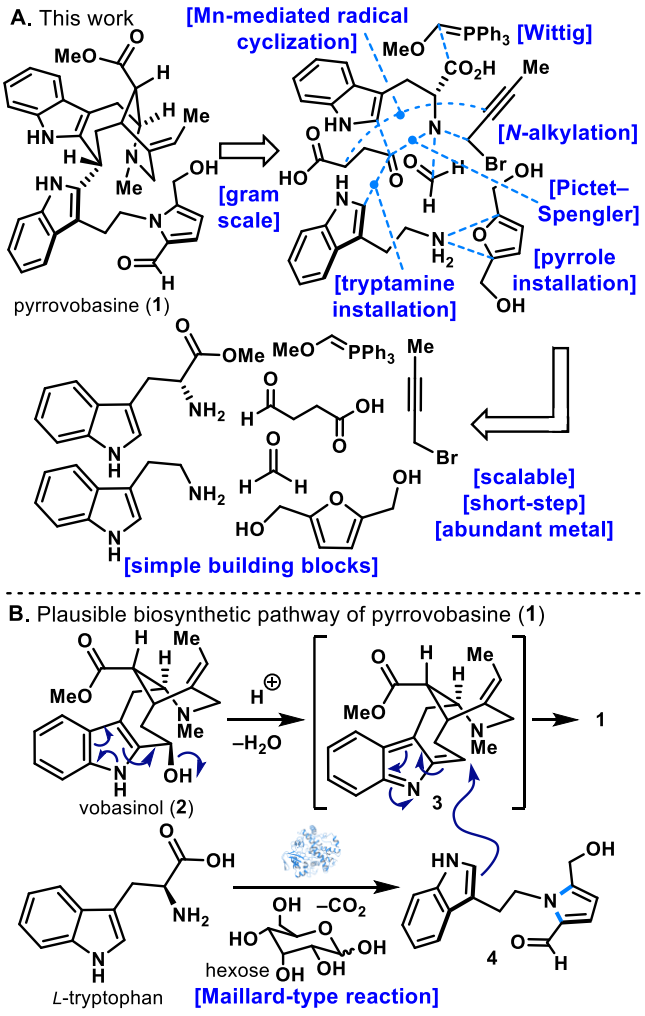
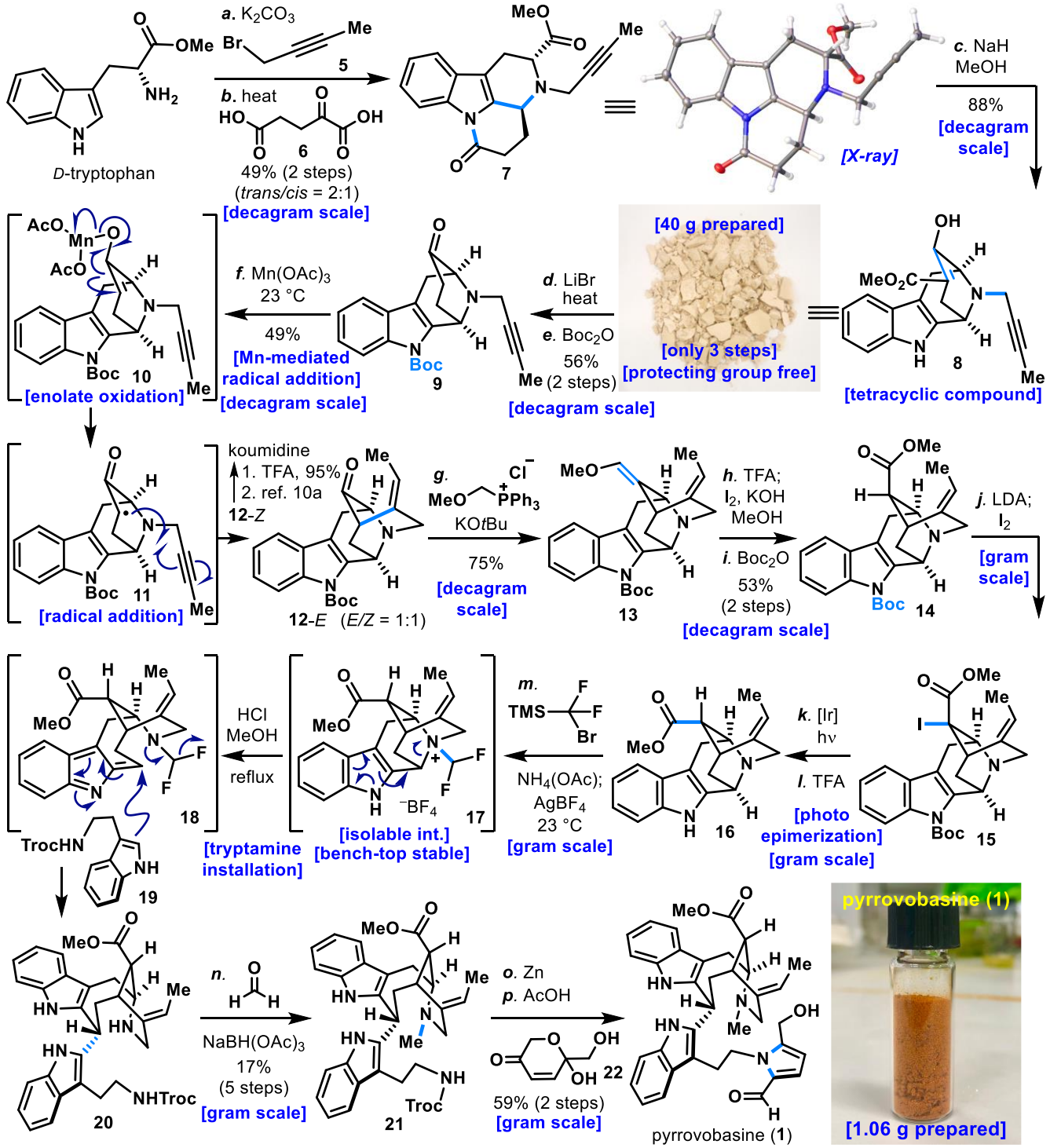


Figure 1. (A) A synthetic approach to pyrrovobasine (**1**); (B) Plausible biosynthetic pathway of pyrrovobasine (**1**).

the pyrraline structure is linked to the activated vobasinol derivative **3** to form pyrrovobasine (**1**). It is known that sugar derivatives such as hexose react with amine residues of amino acids and proteins by Maillard-type reactions.[4]

Scheme 1. Synthetic route to pyrrovobasine (**1**). [a]



[a]Reagents and conditions: **(*a*) 5** (0.95 eq.), K_2CO_3 (3.0 eq.), DMF, 23 °C, 24h; **(*b*) 6** (1.5 eq.), dioxane, reflux, 48h, 49% (2 steps, *trans/cis* = 2:1); **(*c*)** NaH (2.5 eq.), MeOH (5.0 eq.), toluene, 110 °C, 12h, 88%; **(*d*)** LiBr (5.8 eq.), DMSO, 120 °C, 24h; **(*e*)** Boc_2O (1.0 eq.), Et_3N (1.0 eq.), DCM, 23 °C, 0.5h, 56% (2 steps); **(*f*)** $Mn(OAc)_3{\cdot}2H_2O$ (1.4 eq.), AcOH, 23 °C, 5h, 49% (*E/Z* = 1:1); **(*g*)** (Methoxymethyl)triphenylphosphonium chloride (3.0 eq.), *t*-BuOK (3.0 eq.), THF, 23 °C, 2 h, 75%; **(*h*)** TFA, DCM/H_2O, 23 °C, 24h, then I_2 (1.0 eq.), KOH (4.5 eq.), MeOH, 23 °C, 2h; **(*i*)** Boc_2O (1.1 eq.), Et_3N (1.1 eq.), DMAP (0.3 eq.), DCM, 23 °C, 1h, 53% (2 steps); **(*j*)** LDA (4.0 eq.), I_2 (3.0 eq.), THF, –30 °C, 15 min; **(*k*)** $[Ir(ppy)_2(dtbbpy)]PF_6$ (1.3 mol%), DIPEA (6.5 eq.), $(TMS)_2NH$ (3.9 eq.), DMF, –60 °C, 365 nm, 7h; **(*l*)** TFA/DCM, 23 °C, 12h; **(*m*)** NH_4OAc (6.7 eq.), $TMSCF_2Br$ (6.7 eq.), then $AgBF_4$ (6.7 eq.), DCE, 23 °C, 2h, then $SOCl_2$/MeOH, reflux, 24h; **(*n*)** 37% aq. CH_2O (excess), $NaBH(OAc)_3$ (2.2 eq.), EtOAc/MeOH, 23 °C 4h, 17% (5 steps) **(*o*)** Zn (30.0 eq.), AcOH, 23 °C, 2h; **(*p*) 22** (14 eq.), THF/H_2O/AcOH, 59% (2 steps). DMSO = Dimethyl sulfoxide; DMF = *N*,*N*-dimethylformamide; DMAP = *N*,*N*-dimethyl-4-aminopyridine; LDA = lithium diisopropylamide.

Tryptamine derivative **4** is thought to be formed by the enzymatic decarboxylation of *L*-tryptophan followed by the reaction of the amino group with hexose in a Maillard-type reaction. Based on the biosynthetic pathway described above, we planned to introduce the tryptamine and pyrraline skeletons at the end of the synthesis.

The synthetic route of pyrrovobasine (**1**) is shown in Scheme 1. The key to this synthesis is the short and scalable synthesis of the vobasinol skeleton **2**, a key intermediate in the biosynthetic pathway. Therefore, the use of an inexpensive and scalable reaction that can be performed on a decagram scale is critical for the large-scale synthesis of pyrrovobasine (**1**). Therefore, we decided to perform the C-C bond formation reaction mainly in the early stage of the synthesis. In addition, we avoided using expensive transition metals such as Pd in the C-C bond formation reaction as much as possible, especially in the early stage of the large-scale synthesis. First, *D*-tryptophan was used as the starting material and *N*-propargylated by reaction with propargyl bromide **5**. The resulting compound was then reacted with α-ketoglutaric acid **6**, affording the cyclized compound **7** in 49% (2 steps) (trans/cis = 2:1).[5] Compound **7** was successfully used for the synthesis of tetracyclic compound **8** in 88% yield (40 g) via Dieckmann condensation, which proved to be very useful in the synthesis of 1,3-dicarbonyl compounds.[6] It is worth noting that the tetracyclic compound **8** can be synthesized on a 40-gram scale from the starting material *D*-tryptophan in a 3-step procedure without any protecting group using inexpensive reagents. Subsequent decarboxylation of **8** followed by Boc protection led to the synthesis of **9**.

Our next attempt was the construction of the pentacyclic compound **12**. The development of an inexpensive and scalable method for the preparation of vobasinol skeleton **2** is one of the most important aspects of this synthetic route. Several synthetic approaches for vobasinol scaffold **2** have been reported.[6b,7] However, some of them require expensive Pd catalysts, which have dramatically increased in recent years, and are not suitable for the decagram scale, or require activation of the ketone moiety of the starting material, or several derivatization steps after the cyclization reaction.[8] In view of this, we investigated various cyclization reactions of **9**. Interestingly, **12** was found to be easily synthesized by the reaction of **9** with $Mn(OAc)_3$ at room temperature in acetic acid (49%, *E/Z* = 1:1).[9] The reaction mechanism involves the coordination of **9** to $Mn(OAc)_3$ to form the Mn-enolate **10**. Subsequently, **10** undergoes enolate oxidation to form **11**, which has a radical at the α-position of the ketone. Then **11** is subjected to a radical addition with a nearby alkyne to form **12**-*Z* and **12**-*E*. This concise and short-step strategy has made it possible to prepare pentacyclic compound **12**, a common intermediate for many vobasine alkaloids, from inexpensive tryptophan on a decagram scale in only 6 steps. Notably, **12**-*Z* and **12**-*E* are separable and can be derivatized to related natural products. The obtained **12**-*Z* with Boc group was deprotected to achieve a simple formal synthesis of koumidine with antitumor activity (see Supporting Information).[10] On the other hand, **12**-*E* was converted to **13** by the Wittig reaction. The resulting **13** was hydrolyzed to the aldehyde with trifluoroacetic acid, and the thermodynamically stable stereochemistry of the methyl ester **14** was obtained using iodine, KOH, and MeOH, followed by Boc protection.

The synthetic challenge for the total synthesis of pyrrovobasine (**1**) is the epimerization of the thermodynamically stable methyl ester stereochemistry in **14** to the kinetic product methyl ester **16**. We first tried to epimerize **14** under different basic conditions, but the desired kinetic product methyl ester **16** was not observed under any of the conditions. On the other hand, Zhang and Yang *et al*. reported the epimerization of the thermodynamically stable methyl ester using Ir-catalyzed photo-epimerization.[11] Therefore, **14** was treated with LDA and iodine to give **15**, which was found to be unstable and used immediately for the next reaction without purification. Then **15** was successfully converted to **16** by UV irradiation at 365 nm in the presence of an Ir-catalyst at −50 ºC followed by deprotection of the Boc group. Although this epimerization procedure works well, the resulting kinetically dominated product **16** was difficult to separate from the thermodynamically dominated product methyl ester, which was also generated in *situ* during the photo-epimerization reaction from **15**. Therefore, the crude product **16** was used in the next reaction without further purification.

The introduction of the tryptamine derivative **4** with the pyrraline structure to **16** is the last task necessary to complete the total synthesis of **1**. Because of the possible instability of the pyrraline scaffold, we planned to introduce the pyrraline moiety step by step after the introduction of protected tryptamine **19** to **18**. The bioinspired activation of the tertiary amine moiety on **16** was inspired by the pioneering work of Han *et al*.[11] In prior studies, it was demonstrated that the activation of tertiary amine moiety followed by C-N bond cleavage could take place using (bromodifluoromethyl)trimethylsilane. When the condition using (bromodifluoromethyl)trimethylsilane[12] was applied to **16**, **17** was successfully detected in the reaction mixture by LC-MS. It is also worth noting that the BF_4 salt **17** was a stable solid and could be easily isolated by Celite® filtration followed by concentration. This stable BF_4 salt **17** is a useful intermediate that could be used for the synthesis of other related natural products. The reaction mixture of **17** was then acidified with HCl/MeOH to cleave the C-N bond and protected tryptamine **19** was added to react with intermediate **18** to give **20**. The resulting **20** was successfully subjected to *N*-methylation by reductive amination to give **21** in 17% (5 steps). Finally, **21** was deprotected with Zn to afford a primary amine and then reacted with pyranone derivative **22**[2] in AcOH at 50ºC to complete the total synthesis of 1.06 g of pyrrovobasine (**1**).

The synthesis described here was enabled by user-friendly reactions and strategies that are inexpensive and scalable. The early stages of this synthetic route focused primarily on the short steps, decagram-scale synthesis of the key intermediate, the pentacyclic compound **12**. In the process, a 3-step synthesis of the tetracyclic compound **8** without protecting groups was achieved. In addition, a direct radical coupling of ketone **9** with $Mn(OAc)_3$ was discovered and a decagram-scale synthesis of pentacyclic compound **12**, a key intermediate for many vobasine alkaloids, was achieved in only 6 steps. Finally, we developed an efficient bioinspired method for introducing tryptamine, which has a pyrraline structure that is relatively rare in natural products and achieved the first total synthesis and gram-scale supply of pyrrovobasine (**1**). This methodology is anticipated to be useful for future investigations into the biological activity and structure-activity relationships of pyrrovobasine (**1**).

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data (^{1}H and ^{13}C NMR, MS) for all new compounds as well as optimization tables. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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