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Enantioselective total synthesis of (+)-vincamine

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ABSTRACT

A catalytic asymmetric total synthesis of (+)-vincamine is presented. Key features of the synthesis include a Pd-catalyzed enantioselective decarboxylative allylation to form the C20 quaternary stereogenic center and a stereoselective iminium reduction to install the critical *cis*-C20/C21 relative stereochemistry.

The eburnamine-vincamine monoterpenoid indole alkaloids represent a large group of natural products found from the plants of genus *Hunteria, Vinca*, and *Kopsia* [1–8]. (+)-Vincamine (**1**, Fig. 1) is a unique member in this alkaloid subfamily that displays significant pharmacological activities and has been used as a peripheral vasodilator and nootropic agent in clinic [9–13]. Additionally, other selected compounds belonging to this subfamily of alkaloids include (−)-eburnamonine (**2**), (−)-19-OH-eburnamonine (**3**), and unnatural (−)-20-*epi*-vincamine (**4**). Due to their significant pharmacological activities and limited natural abundance [14], the eburnamine-vincamine indole alkaloids became privileged synthetic targets for decades, which has resulted in a number of successful total syntheses [15–59].

Despite the numerous efforts, two critical issues remain to be addressed toward an efficient enantioselective synthesis of the eburnamine-vincamine alkaloids. On one hand, catalytic asymmetric protocols for establishing the stereogenic chiral centers in these complex target molecules have been limited [36,42,46]. The most known synthetic approaches to enantioenriched eburnamine-vincamine alkaloids relied on resolution, chiral pool or chiral auxiliary methods [23–35,37−41,43–45,52,56,57,59]. On the other hand, control of the *cis*-C20/C21 relative stereochemistry represents a key challenge in accessing the eburnamine-vincamine alkaloids [58]. Recent endeavours in this research field have been particularly focused on solving the above-mentioned two issues. For example, Zhu and co-workers reported a conformation-directed

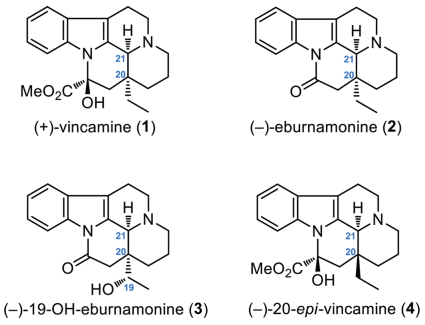

Fig. 1. The structures of (+)-vincamine and related monoterpenoid indole alkaloids.

cyclization process to selectively control the *cis*-C20/C21 stereochemistry in their total synthesis of (±)-eburnamonine [58]. In 2019, the Trost group documented an enantioselective synthesis of C19-oxo eburnane alkaloids (*e.g.*, **3**) featuring a new Pd-catalyzed asymmetric allylation reaction [57]. Recently, Chen, Tang, and colleagues developed an Ir-catalyzed asymmetric imine hydrogenation/lactamization cascade strategy to install the *trans*-C20/C21 stereocenters (dr = 7.4:1) in their synthesis of (−)-**4** [59]. During our preparation of this manuscript, Stoltz *et al.* published a catalytic asymmetric synthesis of (+)-eburnamonine ((+)-**2**) with 3.4:1 dr in the formation of the C20/C21 relative stereochemistry [46]. Our group previously described a photocatalytic radical cascade approach to (−)-vincamine ((−)-**1**) [36]. However, the key step (*i.e.*, **6** to **7**, Scheme 1) suffered from low diastereoselectivity

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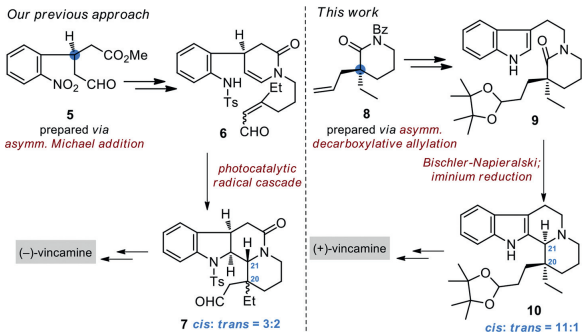
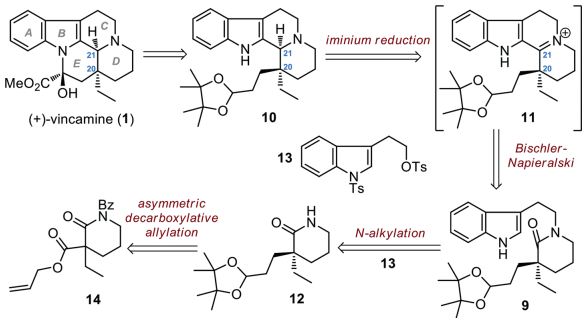


Scheme 1. Our two generations of asymmetric synthetic approaches to vincamine.

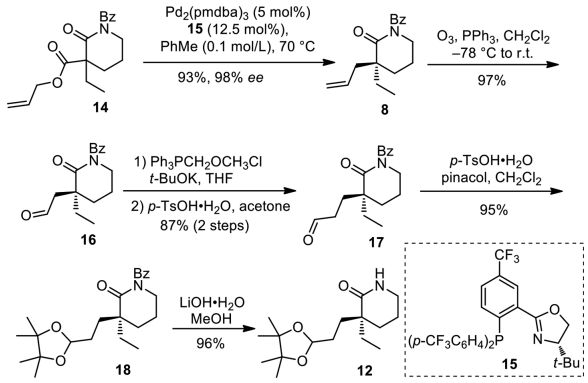


Scheme 2. Retrosynthetic analysis of (+)-vincamine (**1**).

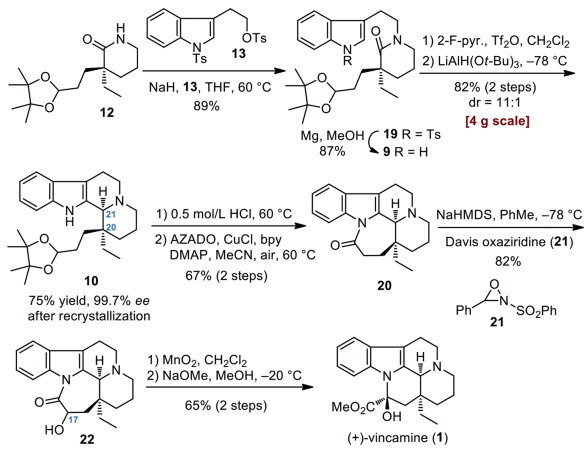
(*cis:trans* = 3:2) of the C20/C21 relative stereochemistry. As part of our long-lasting interest in the total synthesis of complex alkaloid natural products [60–62], here we disclose our second-generation synthesis of (+)-vincamine (**1**) with excellent control of both the enantioselectivity and diastereoselectivity.

Our retrosynthetic analysis of (+)-vincamine (**1**) is outlined in Scheme 2. According to known strategies, the E ring in **1** could be formed at the late stage of the synthesis through lactamization and subsequent rearrangement of **10**. Preparation of the tetracyclic compound **10** could rely on a Bischler-Napieralski cyclization/iminium reduction sequence of amide **9**, which would not only construct the C ring but also establish the configuration of the newly generated stereocenter at C21. We envisioned that introduction of a sterically hindered tetramethyl dioxolane group at the C20 side chain would greatly block the upper face of the iminium functionality in intermediate **11**, thus securing a C20/C21 *cis*-relationship after iminium reduction. In turn, amide **9** could be prepared *via* *N*-alkylation of **12** using the indole fragment **13** as the electrophile. Finally, the quaternary stereocenter in **12** could be generated by an asymmetric decarboxylative allylation of **14** based on the Stoltz protocol [63].

The first challenge in the asymmetric synthesis of vincamine was to efficiently construct the all-carbon quaternary stereocenter at C20. Over the past decade, the Pd-catalyzed enantioselective allylic alkylation reaction has been a powerful tool for the construction of all-carbon quaternary stereocenters [64–67]. Our total synthesis commenced with the Pd-catalyzed enantioselective decarboxylative allylation of racemic lactam **14** (Scheme 3). Based on the slightly modified conditions ($Pd_2(pmdba)_3$ (5 mol%), **15** (12.5 mol%), PhMe (0.1 mol/L), 70 °C) of Stoltz's report, we were able to obtain N-Bz piperidinone **8** with 93% yield and 98% *ee* on a gram scale [63]. Ozonolysis of the terminal alkene in **8** in CH_2Cl_2 at −78 °C afforded aldehyde **16** with excellent efficiency (97% yield). Olefination of aldehyde **16** by Wittig reaction using methoxymethylene phosphonium chloride, followed by hydrolysis of the resulting methyl enol ether provided **17** in 87% yield over two steps. Subsequently, condensation of aldehyde **17** and pinacol in the presence



Scheme 3. Synthesis of the chiral building block **12**.



Scheme 4. Total synthesis of (+)-vincamine (**1**).

of *p*-toluenesulfonic acid delivered acetal **18** (95% yield). Removal of the *N*-Bz group of **18** under basic conditions ($LiOH{\cdot}H_2O$, MeOH) gave the chiral lactam **12**.

With the chiral building block **12** secured, we turned our attention to the linkage of **12** with an indole motif (Scheme 4). Direct *N*-alkylation of lactam **12** with β-indolyl electrophiles proved challenging due to the instability of the latter under basic conditions. This problem was also encountered by Stoltz *et al.* in their recent synthesis of (+)-eburnamonine [46], who ultimately employed a stepwise approach to introduce the indole moiety. In our hand, after extensive experimentation, we were delighted to observe that tosylate **13** was a capable substrate to react with lactam **12** using NaH in THF at 60 °C to give the desired product **19** in 89% yield [68]. Removal of the tosyl group at the indole N-atom in **19** through treatment with Mg/MeOH yielded **9**. At this stage, the key Bischler-Napieralski cyclization/iminium reduction sequence of amide **9** was explored. Subjecting **9** to 2-F-pyridine and Tf_2O in CH_2Cl_2 smoothly generated the iminium intermediate **11** (Scheme 2) [69–72]. After screening various reduction conditions ($NaBHEt_3$, $NaBH(OAc)_3$, $NaBH_3CN$, DIBAL-H, L-selectride, LDBBA, H_2/Pd-C, *etc.*), we found that the use of $LiAlH(Ot\text{-}Bu)_3$ at −78 °C furnished the tetracyclic product **10** with the optimal diastereoselectivity (dr = 11:1) in 82% yield over two steps. The above transformation (**9** to **10**) was easily conducted on a 4 g scale, which delivered the key intermediate **10** with requisite *cis*-C20/C21 stereochemistry in gram quantity with enhanced enantiomerical purity (99.7% *ee*) after recrystallization with acetone/water (4:1). Next, removal of the acetal group in **10** followed by oxidation of the resulting hemiaminal (structure not shown) according to Iwabuchi's method [73] produced lactam **20**, a known precursor

to (+)-vincamine [32]. Davis oxidation of **20** installed the C17-OH group and delivered hydroxyl lactam **22** [59]. Finally, MnO_2-mediated oxidation of **22** and subsequent NaOMe-promoted rearrangement afforded (+)-vincamine (**1**) in 65% yield over two steps [26].

In conclusion, we have established a practical and concise approach to catalytic asymmetric total synthesis of the biologically important indole alkaloid (+)-vincamine in 14 steps and 16.2% overall yield. To a large extent, the current synthesis addressed the two major selectivity issues that have long puzzled the synthetic community by taking advantage of a Pd-catalyzed enantioselective decarboxylative allylation and a diastereoselective iminium reduction as key steps. Consequently, this synthetic strategy provides a general way to prepare other members and derivatives of the eburnamine-vincamine alkaloids possessing *cis*-C20/C21 stereocenters.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.09.032.

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