Asymmetric Total Synthesis of (+)-21-epi-Eburnamonine Via a Photocatalytic Radical Cascade Reaction

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Abstract
An asymmetric total synthesis of (+)-21-epi-eburnamonine has been achieved. Key features of the synthesis include a visible-light photocatalytic intra-/intramolecular radical cascade reaction to assemble the tetracyclic ABCD ring system, and a highly diastereoselective Johnson-Claisen rearrangement to establish the C20 all-carbon quaternary stereocenter.

Graphic Abstract

Keywords Eburnamine-vincamine alkaloids · Photochemistry · Radical cascade reaction · Johnson-claisen rearrangement

1 Introduction
The eburnamine-vincamine indole alkaloids are a large group of natural products occurring in the plant family Apocynaceae (For selected reviews, see: [1–8]). Featuring the fused-pentacyclic skeleton with multiple continuous stereocenters, this compound class has played an important role in natural product chemistry owing to their diverse structures (For selected reviews, see: [1–8]) and medical importance in cell multiplication, cardiovascular system, and brain functions [9, 10]. During the past few decades, the continuing interests in this family regarding either the synthesis or the pharmacological activities have led to abundant research results. The prominent alkaloids (+)-vincamine (Fig. 1, 1), (−)-eburnamonine (2) and their cis D/E ring fusion congeners (Fig. 1, 3-5) exhibit significant cerebral/peripheral vasorelaxation and antihypertensive bioactivities, especially 1 and 2 have been used in the treatment of hypertension [9–12], making them among the most-studied synthetic targets in eburnamine-vincamine family (For selected examples of racemic total synthesis of 1, see: [13–20]; For selected examples of asymmetric total synthesis of 1, see: [21–32]; For selected examples of racemic total synthesis of 2, see: [33–53]; For selected examples of asymmetric total synthesis of 2, see: [54–62]). Quite a few synthetic non-natural analogues also exert bioactivities; for instance, (−)-20-epi-vincamine (6) and (−)-20-epi-eburnamonine (7) with trans D/E ring fusion show better peripheral vasodilation than (+)-vincamine (1) and (−)-eburnamonine (2) [63], and (−)-21-epi-vincamine (8) displays higher binding affinity to human serum albumin than 2 [63]. However, compared to the cis series (For selected examples of asymmetric total synthesis of 1, see: [21–32]; For selected examples of...
asymmetric total synthesis of 2, see: [32, 65–67]), the asymmetric synthesis of the above molecules (i.e., 6–8) with trans D/E ring fusion remains limited [63–67]. Among the numerous strategies developed to access eburnamine-vincamine alkaloids, stereoselective construction of the C20 and C21 stereocenters has always been the most difficult point. Particularly, the establishment of the C20/C21 trans relative stereochemistry is challenging [67].

Attracted by the fascinating structures and prominent biological activities of eburnamine-vincamine alkaloids, our group has devoted to the development of efficient strategies towards natural products belonging to this category [32, 68]. In 2017, we reported three types of nitrogen-centered photoreaction of propenal under the irradiation of blue LEDs led to the formation of 9 as a pair of separable diastereomers (d.r. = 1:1.5 at C20), of which the A/B/C/D ring of the pentacyclic eburnane skeleton was assembled in one-pot, with the C21(R) stereochemistry established in full control [32]. Tetracycle 10b with C20(R) stereocenter was further elaborated into a series of eburnamine-vincamine family alkaloids, including (+)-eburanamenine (12), (+)-isoeburnamine (4), (-)-eburnamine (3) and (+)-eburnamonine (5). However, the above-mentioned cascade reaction of 9 suffered from unsatisfactory stereocontrol at C20 (d.r. = 1:1.5), which prompted us to seek new synthetic approaches to eburnamine-vincamine alkaloids in a highly stereoselective fashion. Herein, we report our efforts in this regard that led to a stereospecific total synthesis of (+)-epi-eburnamonine (20S, 21R) (8).

2 Results, Discussion and Conclusion

Outlined in Scheme 1b is our synthetic plan of (+)-21-epi-eburnamonine (8). We envisioned that the known compound propynal 15 [32] would be an appropriate precursor for construction the A/B/C/D framework of eburnane skeleton through intra-intramolecular photocatalytic radical cascade reaction. The resultant tetracyclic product 14 bears a propenol functionality at C20, which allows us to forge the C20 all-carbon quaternary stereocenter of 13 via Johnson-Claisen rearrangement [62, 69–72]. We supposed that the substrate-controlled stereoselectivity in the rearrangement process could guarantee the desired C20(S) configuration. Furthermore, 13 could be readily transformed into the target (+)-21-epi-eburnamonine via intramolecular amidation [67] and subsequent reduction of the vinyl group.

Our synthesis began with preparation of the radical precursor 15 for the devised intra-intramolecular photocatalytic cascade reaction (Scheme 2). Following our previously reported protocols [32], amide 15 was readily obtained from aldehyde ester 16 over five steps on a decagram scale. Upon exposure to the conditions of Ir(dbbbpy)(ppy)2PF6/KHCO3/THF with blue LED irradiation, the intra-intramolecular photocatalytic cascade reaction of 15 proceeded smoothly, delivering a pair of inseparable 2:1 mixtures of E/Z isomers 17 in 57–65% yield. It is noteworthy that the above conversion allowed the assembly of the A/B/C/D ring system of eburnane-type scaffold, with stereoselectively construction.

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1. **Photocatalytic Reactions**

    of C21(R) stereochemistry. Subsequently, reduction of propynal 17 with NaBH₄ afforded the corresponding allylic alcohol 14 as a pair of inseparable geometrical isomers in 63% yield. With 14 available, the vital Johnson-Claisen rearrangement was investigated. Initially, 14 was subjected to CH₃C(OMe)₃/EtCOOH/1,2-dichlorobenzene at 135 °C. However, the reaction gave a complex mixture, and the desired product was not observed. Attempts to improve the reaction by screening different acids, solvents or temperatures were also unsuccessful. Fortunately, after changing the trialkyl orthoacetate from CH₃CH(OMe)₃ to CH₃CH(OEt)₃, the expected rearrangement took place in the presence of EtCOOH in 1,2-dichlorobenzene at 135 °C to give ethyl ester 20 in 52% yield as a single isomer, thereby constructing the C20 all-carbon quaternary stereocenter. Due to the fact that the inseparable mixture of 14 was completely consumed and only one rearrangement product was observed, we supposed that both geometrical isomers of 14 yielded the same compound 20. The high stereoselectivity of the above-mentioned reaction could be rationalized by the proposed transition-state T-18 and T-19. Presumably, the carbon–carbon bond formation of the rearrangement via T-18 was hampered by the severe steric repulsion between the ethoxy group and the hydrogen at C2 for both geometrical isomers of 14, thus the reaction would preferentially occur through transition state T-19, favoring the formation of 20 [12].

Next, we turned our attention to the last stage of the synthesis of (+)-21-epi-eburnamonine (9). To this end, conversion of indoline 20 to indole 13 through a deprotection/oxidation sequence was implemented first. Specifically, upon treatment of 20 with Mg/MeOH followed by addition of CH₃ONa, the N-Ts group was removed along with the transesterification of the methyl ester group, delivering 21 in 74% yield. Subsequent oxidation of indole 21 with (PhSeO)₂O led to the formation of indole 13 in 80% yield. Furthermore, by employing the reductive conditions of [Rh(H)CO](PPh₃)₃/PhSiH₃, amide 13 was smoothly converted into amine 22. Finally, cyclization of the E ring was realized by subjecting 22 to K₂CO₃/MeOH under reflux. The delivered pentacycle 23 was then subjected to catalytic hydrogenation in which the vinyl group was reduced to afford the target molecule in 89% yield. Notably, the NMR data of 8 had identical NMR data to (−)-20-epi-eburnamonine reported in the literature [66] but opposite optical rotation, which again confirmed the
stereochemistry of C20 established in the Johnson-Claisen rearrangement.

In summary, we have disclosed an efficient approach to the asymmetric total synthesis of (+)-21-epi-eburnamonine with trans D/E ring fusion. From a strategical perspective, the synthesis features a photocatalytic intra-intramolecular radical cascade reaction to assemble the A/B/C/D ring system and a highly diastereoselective Johnson-Claisen rearrangement to forge the C20 all-carbon quaternary stereocenter. This synthetic strategy provided alternative access towards more derivatives of eburnamine-vincamine alkaloids.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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