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ARTICLE

Concise syntheses of *eburnane* indole alkaloids†

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The asymmetric divergent syntheses of a group of C20 ethyl oxo-functionalized *eburnane* alkaloids, (–)-eburnaminol (**5**), (+)-larutenine (**6**), (–)-terengganensine B (**7**), (–)-strempeliopine (**8**), and (–)-terengganensine A (**9**) have been achieved. The key step in the assembly of the complex ring system of the target molecules is a photoredox catalytic nitrogen-centered radical cascade reaction, which allows the regioselective and stereoselective construction of the B, C, and D rings and the installation of the C21 chirality of the *eburnane* alkaloid skeleton in one pot.

Introduction

Eburnane indole alkaloids[1] (Figure 1, **1** — **9**) are the predominant alkaloids in plants of the genus *Kopsia*, which are mainly distributed in Southeast Asia and China. Extracts from *Kopsia* containing theses alkaloids have historically been used for detoxification and as anti-inflammatory agents in tradition Chinese medicine.[2] Although the mechanism of action is not clear, experiments using modern biological techniques have shown that the individual alkaloids possess impressive biological activities.[3] Unlike most indole alkaloids for which only one enantiomer is naturally generated by plants, it is of interesting that both enantiomers of the *eburnane* indole alkaloids have been isolated from plants of *Kopsia* growing in different geographic areas. For example, the (20*R*, 21*R*)-enantiomers of *eburnane* alkaloids were exclusively found in Malaysia *Kopsia,*[4] while the opposite enantiomers (20*S*, 21*S*) were isolated from Chinese *Kopsia.*[4a,5]

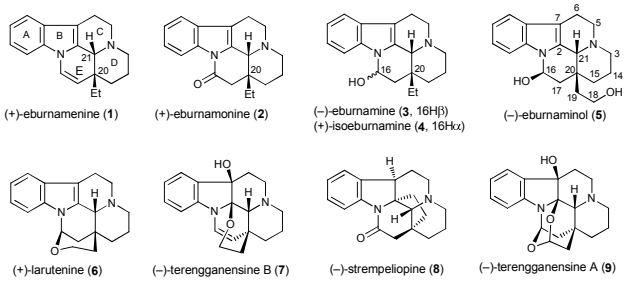

Figure 1 Structures of the *eburnane* alkaloids.

The chemical structures of *eburnane* indole alkaloids can be roughly categorized into two sub-groups: the C20 ethyl un-functionalized alkaloids (Figure 1, **1**—**4**) and the C20 ethyl oxo-functionalized alkaloids (Figure 1, **5**—**9**). The latter sub-group should be biogenetically derived from (–)-eburnaminol (**5**), making these compounds more synthetically challenge to access than their counterparts (Figure 1, **1**—**4**). Although some racemic syntheses for individual members of the later sub-group of alkaloids have been described,[6] the only asymmetric total synthesis was recently reported by Zhu's group, who described an elegant total synthesis of terenganensine A by employing Noyori's catalytic enantioselective transfer hydrogenation as a key step to set up the C21 chirality.[7] In a previous study, we reported the total syntheses of *eburnane* indole alkaloids **1**—**4** using our recently developed photoredox catalytic nitrogen-centered radical cascade reaction to regioselectively and stereoselectively construct the B, C, and D rings and install the proper C21 chirality.[8] To further expand the applicability of this radical cascade synthetic strategy, we herein report the asymmetric total synthesis of the later sub-group of structurally more complex *eburnane* alkaloids, namely, (–)-eburnaminol (**5**), (+)-larutenine (**6**), (–)-terengganensine B (**7**), and (–)-strempeliopine (**8**) as well as the asymmetric formal total synthesis of (–)-terengganensine A (**9**) (Figure 1).

Results and discussion

Our plan for the syntheses of *eburnane* alkaloids **5**—**9** is outlined in Figure 2. The precursor for nitrogen-centered radical cascade reaction (**12**) should be readily available from chiral aldehyde **10**[8] and Boc-protected amine **11**[9] by an acid-promoted condensation. Using our previously developed radical cascade protocol,[8] the B, C, and D rings and the C2 and C21 chirality could be stereoselectively installed in one step to give intermediate **13**. Generation of the C20 chirality might not be stereoselective, but because that both diastereomers **13a**

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and **13b** could be used for the syntheses of different *eburnane* alkaloids by selective modification of the nitrile group and the benzyloxy ethyl group of **13**, this drawback could be addressed at a later stage of the synthesis. Converting the indoline group in **13** into an indole group could generate a pair of diastereomers **14a** and **14b**, which could be used separately as starting materials for the syntheses of (–)-eburnaminol (**5**), (+)-larutenine (**6**), (–)-terengganensine B (**7**), and (–)-strempeliopine (**8**) by a short series of functional group transformations. Since (–)-terengganensine A (**9**) contains the same aldehyde functionality at the end of both ethyl groups on C20, both diastereomers of **13** could be used for the synthesis of intermediate **15**, which has been successfully converted to **9** by Zhu's group.[7]

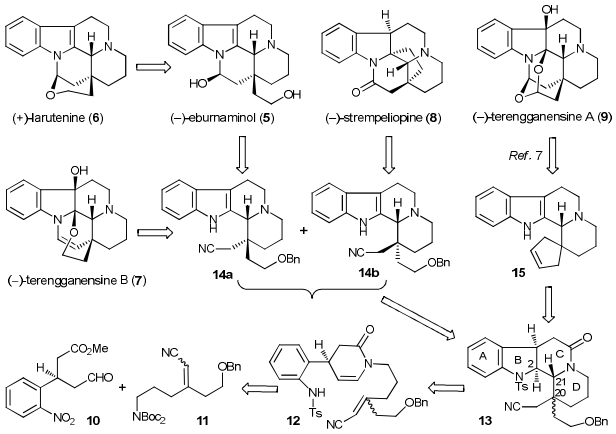
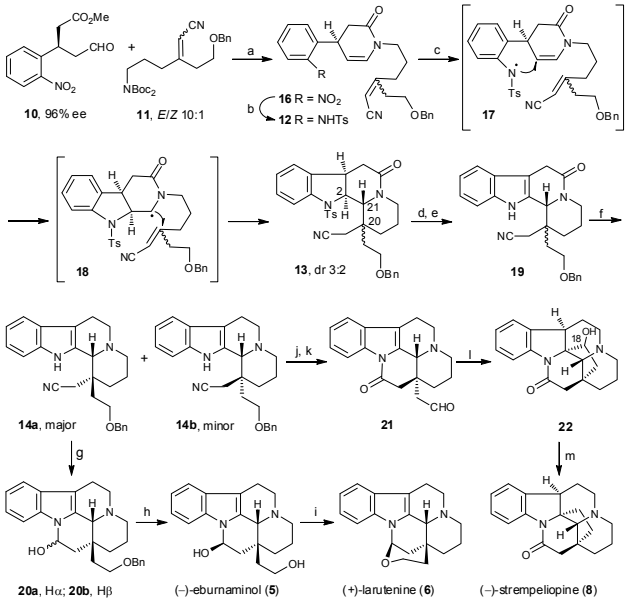


Figure 2. Retrosynthetic analysis of *eburnane* alkaloids.

We commenced the synthesis with the preparation of **12** (Scheme 1). After removing the Boc groups in **11**[9] with TFA, the resulting unstable amine was heated with readily prepared aldehyde **10**[8,10] in toluene in the presence of AcOH, and then the nitro group was reduced with Zinc dust and tosyl (Ts) protection of the resulting aniline group provided **12** in 27% overall yield. Irradiating **12** with 30 W blue LED lights in the presence of 1 mol% $Ir(dtbbpy)(ppy)_2PF_6$ and 5 equiv. of $KHCO_3$ in THF first generated nitrogen-centered radical (**17**), which subsequently attacked the enamide group to form a carbon radical (**18**). This amide nitrogen-associated carbon radical was a typical two-center, three-electron radical system and possessed stereoelectronic character, which greatly increased the radical stability, nucleophilicity, and selectivity.[11] Attack of the Michael acceptor in **18** by the radical afforded **13** as an inseparable mixture of two diastereomers in 75% yield and a 3:2 dr at C20, while the stereochemistry at C2 and C21 was fully controlled. After removal of the Ts group in **13** and oxidation of the indoline group with $(PhSeO)_2O$, a diastereomeric mixture of **19** was obtained in 80% yield. Reduction of the amide in **19** with $PhSiH_3$ catalyzed by $[Rh(H)(CO)(PPh_3)_3]$ provided **14a** in 48% yield and **14b** in 32% yield. The major isomer (**14a**) was then used to synthesize (–)-eburnaminol (**5**) and (+)-larutenine (**6**). Reduction of **14a** with DIBAL-H, followed by treatment of the resulting aldehyde with 1 M HCl afforded **20a** in 63% yield and **20b** in 13% yield. Hydrogenolysis of **20a** completed the synthesis of (–)-eburnaminol (**5**).[4c,6a] Treatment of **5** with 5% aqueous HCl at room temperature gave (+)-larutenine (**6**) in 75% yield.[4c,4d,6a] The minor isomer (**14b**) was used for the synthesis of (–)-strempeliopine (**8**). Aldehyde **21** was isolated in 64% yield by hydrolysis of **14b** in concentrated HCl solution at 70 °C, which resulted in formation of the amide bond and removal of benzyl group simultaneously, followed by oxidization of the hydroxyl group. The SmI_2-mediated radical cyclization of **21** in THF gave pentacyclic **22** as a single diastereomeric in 65% yield, leaving the configuration of the hydroxyl group at C18 unknown. Removal the hydroxyl group in **22** using Barton's protocol afforded (–)-strempeliopine (**8**) in 76% yield.[6e,6f,12]



Scheme 1 Total syntheses of (–)-eburnaminol (**5**), (+)-larutenine (**6**), and (–)-strempeliopine (**8**). Reagents and conditions: (a) 10.0 equiv. TFA, CH_2Cl_2, RT, then 2.0 equiv. AcOH, molecular sieves, PhMe, 70 °C, 45%; (b) 20.0 equiv. Zn, 20.0 equiv. NH_4Cl, MeOH, RT, then 1.5 equiv. TsCl, 20 equiv. Pyr, CH_2Cl_2, RT, 60%; (c) 1 mol% $Ir(dtbbpy)(ppy)_2PF_6$, 5.0 equiv. $KHCO_3$, THF, 30W blue LED, 35 °C, 75%; (d) 30.0 equiv. Mg, MeOH, RT; (e) 1.2 equiv. $(PhSeO)_2O$, dry THF, 40 °C, 80% over two steps; (f) 0.1 equiv. $[Rh(H)(CO)(PPh_3)_3]$, 3.0 equiv. $PhSiH_3$, dry THF, RT, 48% **14a** and 32% **14b**; (g) 2.0 equiv. DIBAL-H, PhMe, 0 °C, then 1M HCl/THF (v:v = 4:1), RT, 63% **20a** and 13% **20b**; (h) 0.1 equiv. $Pd(OH)_2/C$, MeOH, H_2, RT, 88%; (i) 5% HCl (aq), RT, overnight, 75%; (j) conc. HCl/MeOH 2:1 (v/v), reflux, 75%; (k) 2.0 equiv. Dess-Martin periodinane, CH_2Cl_2, RT, 85%; (l) 5.0 equiv. HMPA, 10.0 equiv. SmI_2, dry THF, reflux, 65%; (m) 10.0 equiv. NaH, 20.0 equiv. CS_2, 20.0 equiv. MeI, dry THF, 0 °C to RT, then 5.0 equiv. *n*-Bu_3SnH, 1.0 equiv. AIBN, dry PhMe, 60 °C, 76% for two steps.

As shown in Scheme 2, the total synthesis of (–)-terengganensine B (**7**) was carried out using **14a** as the starting material. Removal of the benzyl group using BBr_3 in CH_2Cl_2 at –78 °C gave alcohol **23** in 66% yield. Treatment of **23** with Bz_2O_2 in dry $CHCl_3$ resulted in the formation of intermediate **24** with

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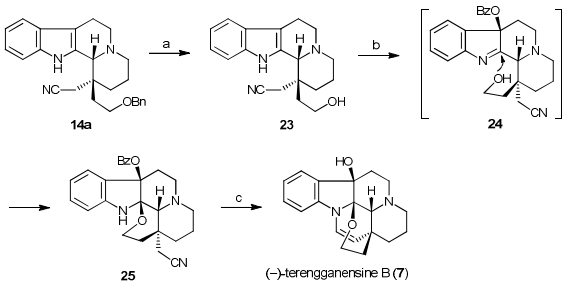
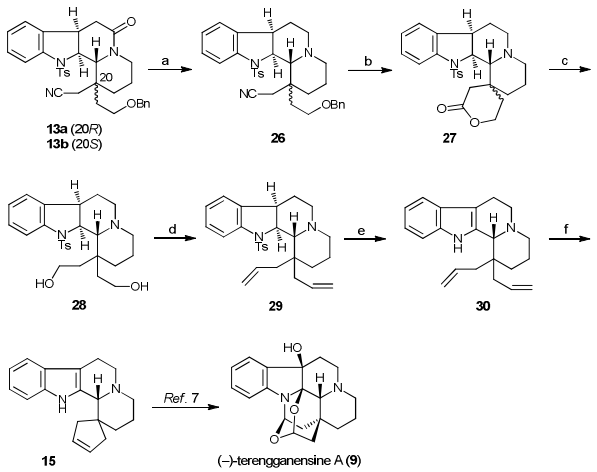
an imine functional group,[7,13] which was immediately trapped by the free hydroxyl group to give **25** in 53% yield. Reduction of the nitrile group in **25** directly formed an enamine moiety, enabling the first total synthesis of (–)-terengganensine B (**7**).[4h]



Scheme 2 Total synthesis of (–)-terengganensine B (**7**). Reagents and conditions: (a) 2.0 equiv. BBr_3, dry CH_2Cl_2, –78 °C, 66%; (b) 1.0 equiv. Bz_2O_2, dry $CHCl_3$, RT, 53% (brsm); (c) 3.0 equiv. DIBAL-H, PhMe, 0 °C, 79%.

Because the chirality at C20 in **13** would be destroyed in the conversion to known intermediate **15** (Scheme 3), both diastereomers **13a** and **13b** can be used as starting materials. Reduction of the diastereomeric mixture of **13a** and **13b** afforded inseparable diastereomers **26a** and **26b** in 82% yield. Hydrolysis of the nitrile group in **26** resulted in removal of the benzyl protecting group simultaneously and afforded a diastereomeric mixture of **27** with a lactone group in 71% yield. Reduction of **27** with $LiAlH_4$, destroyed the chirality at C20 and provided **28** as a single diastereomer in 92% yield. Oxidation of the two hydroxyl groups in **28** followed by olefination of the resulting unstable aldehyde groups afforded **29** in 64% yield. Conversion of indoline **29** to indole **30** was realized in 65% yield by a two-step procedure involving the removal of the Ts group with Na/naphthalene and oxidation with $(PhSeO)_2O$. A ring-closing metathesis reaction with Grubbs' II catalyst in CH_2Cl_2 provided the known key intermediate **15**, which has been used for the synthesis of (–)-terengganensine A (**9**) by Zhu's group,[7] completing a formal total synthesis.



Scheme 3 Formal total synthesis of (–)-terengganensine A (**9**). Reagents and conditions: (a) 0.15 equiv. $[Rh(H)(CO)(PPh_3)_3]$, 4.5 equiv. $PhSiH_3$, dry THF, 0 °C, 82%; (b) conc. HCl/MeOH 2:1(v/v), reflux, 71%; (c) 2.0 equiv. $LiAlH_4$, dry THF, 0 °C, 92%; (d) 2.5 equiv. IBX, DMSO. RT, then 3.4 equiv. *t*-BuOK, 5.0 equiv. methyltriphenylphosphonium bromide, dry THF, 0 °C to RT, 64% for two steps; (e) 5.0 equiv. Na/naphthalene, dry THF, –78 °C, then 1.2 equiv. $(PhSeO)_2O$, dry THF, 40 °C, 65% over two steps; (h) 0.05 equiv. Grubbs' II catalyst, dry DCM, 82%.

Conclusions

In summary, the first asymmetric total synthesis of a group of *eburnane* indole alkaloids, including (–)-eburnaminol (**5**), (+)-larutenine (**6**), (–)-terengganensine B (**7**), and (–)-strempeliopine (**8**), and the formal synthesis of (–)-terengganensine A (**9**) was concisely accomplished in 6 to 13 steps. Divergent syntheses of these alkaloids from common intermediate **13** was achieved using our recently developed radical cascade reaction initiated by a nitrogen-centered radical, which regioselectively and stereoselectively construct the B, C, and D rings and install the C21 chirality of the *eburnane* alkaloid skeleton in a highly efficient manner.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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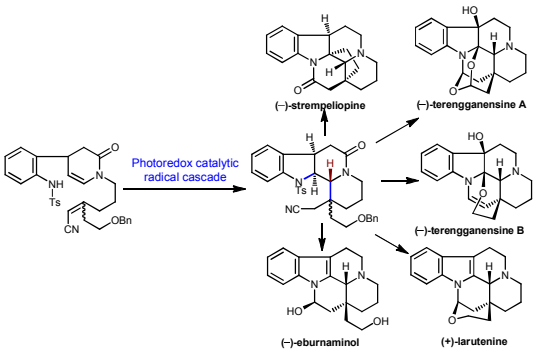

Asymmetric syntheses of a group of structurally complex *eburnane* alkaloids have been achieved employing a key photo-induced radical cascade reaction.