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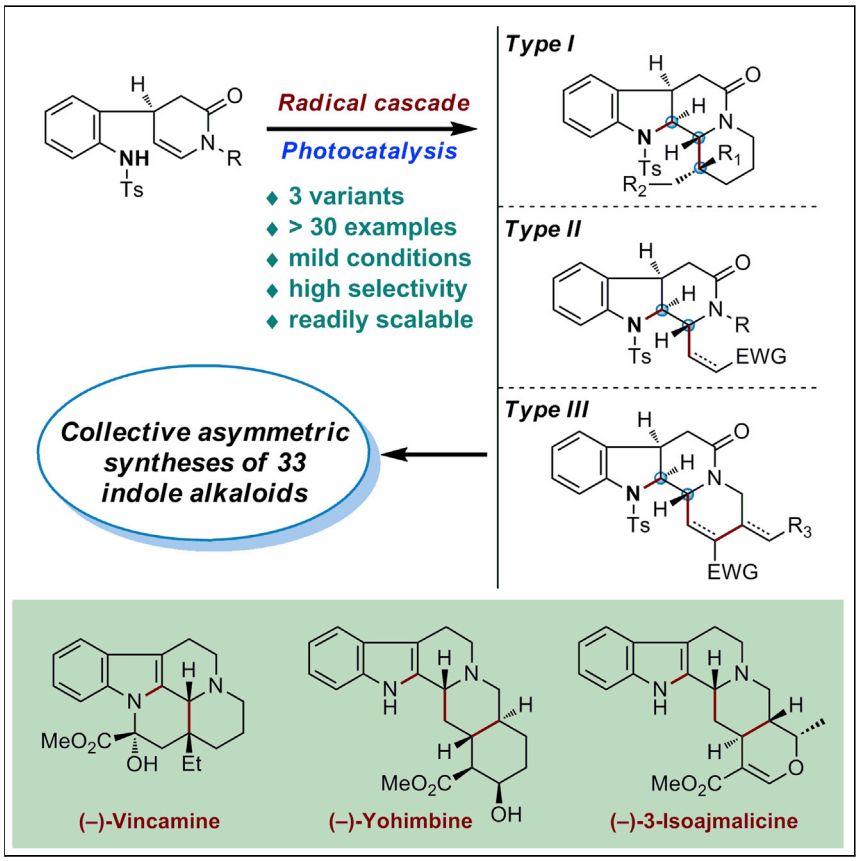

Qin and co-workers use photocatalytic conditions to generate a nitrogen-centered radical from aniline-type sulfonamide, which reverses the conventional reactivity between two electron-donating amine and enamine groups and initiates radical cascade reactions with excellent chemo-, regio-, and diastereoselectivity. The power of this distinct method has been demonstrated by the efficient syntheses of 33 monoterpenoid indole alkaloids belonging to four families.

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HIGHLIGHTS

Direct generation of nitrogen-centered radical from sulfonamide by photocatalysis

Radical cascade reactions with excellent selectivities

Efficient syntheses of 33 indole alkaloids and related analogs

Potential applications for the syntheses of other nitrogen-containing molecules

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A Radical Cascade Enabling Collective Syntheses of Natural Products

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SUMMARY

Natural products have long been important inspirations for the development of chemical methodologies, theories, and technologies, and ultimately, discoveries of new drugs and materials. Chemical syntheses have traditionally yielded individual or small groups of natural products; however, methodology development allowing the synthesis of a large collection of natural products remains scarce. Here, we report an efficient photocatalytic radical cascade method that enables access to libraries of chiral and multiple-ring-fused tetrahydrocarbolinones. The radical cascade can controllably introduce complexity and functionality into products with excellent chemo-, regio-, and diastereoselectivity. The power of this distinct method has been demonstrated by the efficient syntheses of 33 monoterpenoid indole alkaloids belonging to four families.

INTRODUCTION

Structurally complex and diverse natural products and their analogs have long been inspirations for the development of new medicines, which have greatly improved human health.[1] When access to such molecules from natural sources is uncertain or uneconomical, chemical synthesis is one of the most important alternative ways to obtain them.[2,3] Although syntheses of individual or several natural products belonging to a certain family have been achieved, a breakthrough in synthetic methods that yields diverse skeletons of natural products and that benefits the syntheses of a large collection of natural products for biological activity tests is highly anticipated. With over 15 families and more than 3,000 known members, monoterpenoid indole alkaloids represent the most stereochemically and architecturally diverse natural products.[4,5] Most of them have exhibited important biological activities, and some of them, such as vinblastine and reserpine,[6,7] have been used as clinical drugs for decades (Figure 1A). Three major types of monoterpenoid indole alkaloids, namely, corynanthe-, aspidosperma-, and iboga-type alkaloids, have been categorized on the basis of the carbon skeletons of the monoterpenoid units (bold carbon chain in Figure 1A).[4] All of these alkaloids can be roughly categorized into the non-rearranged families (shown in blue in Figure 1A) and the rearranged families (shown in black in Figure 1A), which are believed to have been biosynthesized originally from tryptamine and secologanin by strictosidine synthase- (STR1) and strictosidine glucosidase (SG)-catalyzed condensation.[8] Since the milestone syntheses of reserpine and strychnine by Woodward et al. in the 1950s,[9,10] the syntheses of complex monoterpenoid indole alkaloids has been an interesting and challenging topic because of their rich structural diversity and biological activities.[11–14]

The Bigger Picture

Today, achieving the chemical synthesis of a single natural product is rarely out of reach with sufficient manpower. However, considering the urgent demand for chemical biology studies and drug discovery, efficient preparation of a large collection of complex natural products and natural-product-like libraries with stereochemical and architectural divergence remains highly desirable. Here, we describe a visible-light-mediated radical cascade reaction that generates a nitrogen-centered radical from aniline-type sulfonamide and reverses the conventional reactivity between two electron-donating amine and enamine groups, allowing efficient syntheses of 33 complex indole alkaloids with varied architectures and divergent stereochemistry. This approach could be expanded to intermolecular reaction patterns and could be expected to facilitate the preparation of nitrogen-containing architectures, which are of great interest for the syntheses of natural products and bioactive substances.

Radical cascades are among the most powerful reactions for bond formation.[15–19] However, their application in constructing complex naturally predefined architectures, and especially in resolving the major problems—namely collective syntheses of bioactive natural products[20]—is still underexploited.[21–23] This is largely because of the high reactivity of radicals, which is difficult to control with multiple functionalities in the substrate, thus resulting in poor stereoselectivity and chemoselectivity. In addition, tedious preparation of an initiating group for the classic radical reaction further impedes its application. A design for precise control of a radical pathway is required for successful assembly of complex natural products. Recent advances in photocatalytic radical reactions[24–31] have provided great opportunities in the synthesis of natural products.[32–35] Here, we report a photocatalytic radical cascade with excellent stereo-, regio-, and chemoselectivity to prepare libraries of chiral tetrahydrocarbolinones under mild conditions. This radical cascade can be scaled up and can generate two of the three monoterpenoid indole-alkaloid skeletons, including the corynanthe-type and aspidosperma-type alkaloids, by varying easily accessible substrates. This cascade provided indoline skeletons with stereochemical divergence, which is typically difficult to achieve and which requires one-by-one synthesis using traditional synthetic methods. Rapid assembly of the core structures enabled efficient syntheses of 33 complex monoterpenoid indole alkaloids belonging to four families and also four unnatural diastereoisomers.

RESULTS AND DISCUSSION

Radical Cascade Design

Given that efficient preparation of aspidosperma-type and corynanthe-type intermediates is expected to facilitate the syntheses of diverse families of indole alkaloids,[36] we envisioned that an electron-deficient nitrogen-centered radical (**Ts-I**; Figure 1B), initiated from chiral aniline **2** (easily synthesized from the chiral compound **1**, the preparation of which[37] is described in the Supplemental Experimental Procedures; see also Figures S1–S7), would enable the formation of a C–N bond between both electron-donating aniline nitrogen and the β carbon of the enamine (**Ts-I**). The resultant heteroatom-associated carbon radical might intramolecularly attack the pre-installed double bond tethered to the enamine nitrogen to afford aspidosperma-type intermediate **3** (pathway a, via **Ts-IIa**). Similarly, the intermolecular Michael addition (**Ts-IIb**, pathway b) via **Ts-III** after radical quenching would give tetrahydrocarbolinone **4**, an important intermediate used for previous indole-alkaloid syntheses.[38–40] In addition, a further cascade reaction might occur via intramolecular addition of the resultant radical in **Ts-III** with a tethered double bond or triple bond, thus leading to the corynanthe-type intermediate **5**. Compounds **3**–**5** possess different ring systems and functionalities suitable for the syntheses of a variety of indole alkaloids. The untested aspect of the designed radical cascade was whether the stereochemistry of the adducts could be controlled by the chiral substrate **2**. Given that non-rearranged monoterpenoid indole alkaloids have been described with varying configurations at the C15 and C20 positions,[41] this concern was partly diminished.

Radical Cascade Results

The first key task in achieving the above radical cascade was the direct initiation of a nitrogen-centered radical from Ts-protected aniline by cleavage of the N–H bond in **2**. Classic generation of amide-type nitrogen-centered radicals usually requires cleavage of an N–heteroatom bond.[42,43] Direct conversion of an N–H bond of aniline-type amide to a nitrogen-centered radical via photocatalysis is promising but has proved challenging and unprecedented; there are only a few recent examples on alkyl-type amide substrates.[44–47] With the above radical cascade strategy for

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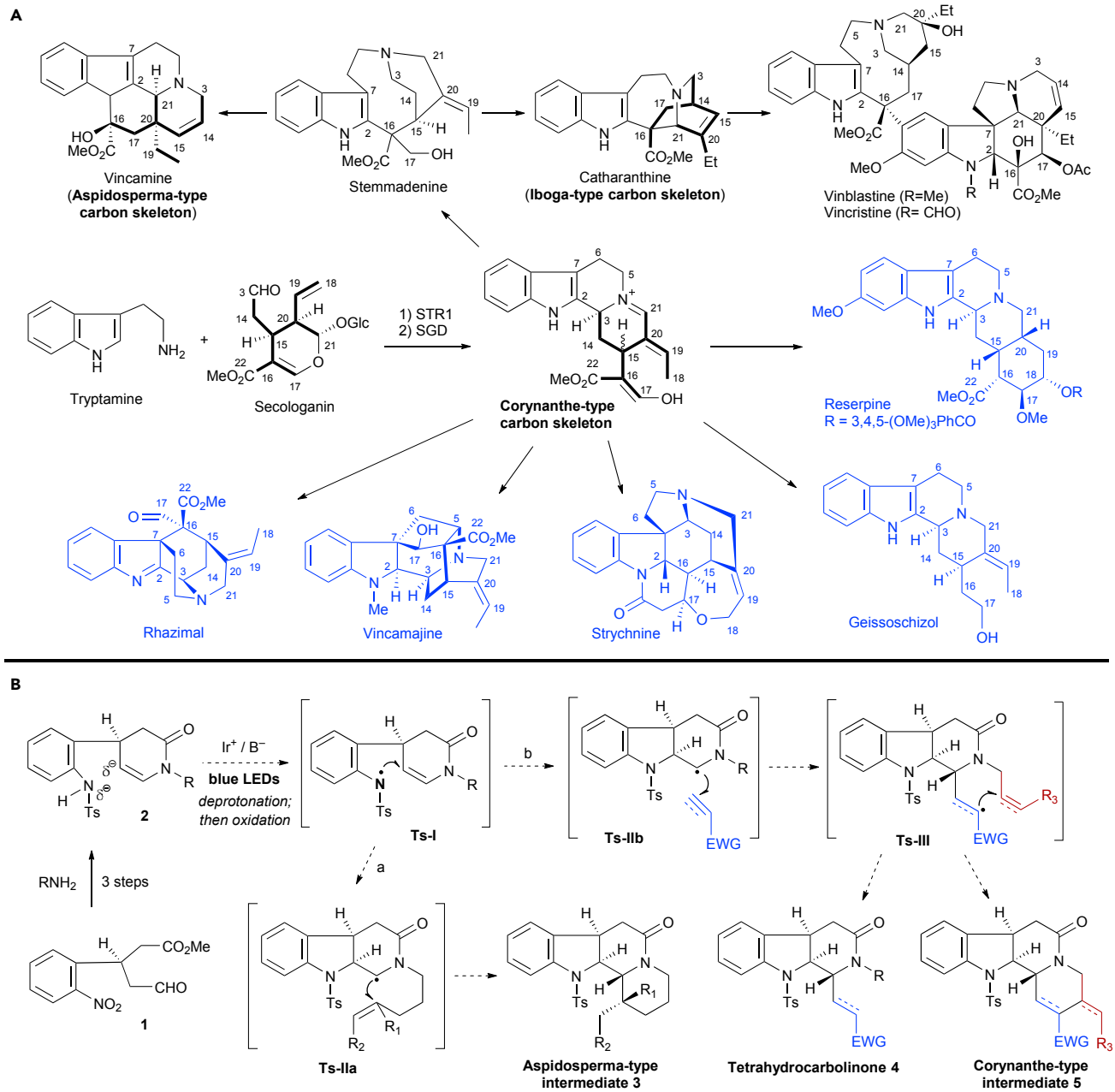


Figure 1. Background and Synthetic Plan

(A) Proposed biosynthetic pathway and structural categorization of monoterpenoid indole alkaloids.

(B) Envisioned photocatalytic radical cascade to generate aspidosperma-type intermediate **3** (path a), tetrahydrocarbolinone **4**, and corynanthe-type intermediate **5** (path b) for the syntheses of monoterpenoid indole alkaloids. Abbreviations: D-A reaction, Diels-Alder reaction; STR1, strictosidine synthase; SG, strictosidine glucosidase.

indole-alkaloid synthesis in mind, we used tosyl-protecting aniline amide **2a** (Figures S8–S11) as a substrate for generating the nitrogen-centered radical via photocatalysis in order to test the designed two-step radical cascade (pathway a; Figure 1B). After extensive screening of photocatalysts, bases, solvents, and temperature, optimal conditions (0.5 mol % Ir(dtbbpy) $(ppy)_2PF_6$, 5 equiv $KHCO_3$, degassed tetrahydrofuran [THF], 35°C, 5 W blue LEDs, Ar) were determined. Under these conditions, the radical cascade of **2a** proceeded smoothly to produce the desired **3a**

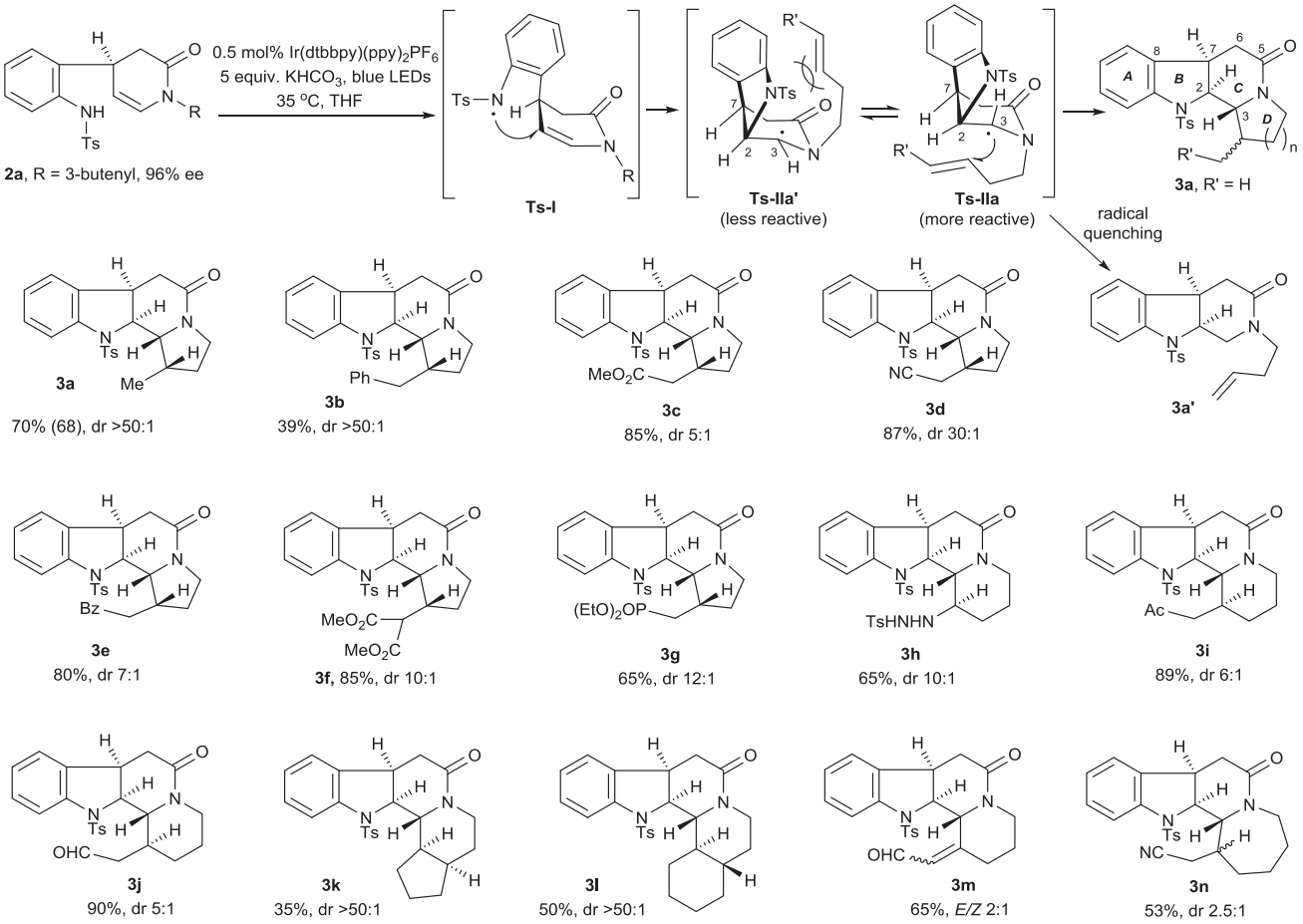


Figure 2. Preparation of Aspidosperma-Type Derivatives 3

Optimal conditions: 0.5 mol % Ir(dtbbpy) $(ppy)_2PF_6$, 5 equiv $KHCO_3$, degassed THF, 5 W blue LEDs, 35°C, Ar. The dr values were determined by LC-MS analysis. The relative carbon configurations at the C-ring and D-ring were determined by nuclear Overhauser effect experiments. **3a** and **3l**: the absolute configuration was determined by X-ray crystallography of the detosylated intermediates (see the Supplemental Information). **3a**–**3m**: the dr values or *E*/*Z* ratios were determined by LC-MS analysis. A dr > 50:1 indicated that other diastereoisomers were not detected in the LC-MS experiments. **3a**: the yield in parentheses was obtained with 50% aqueous THF as the solvent. **3n**: the dr value was determined by ^1H NMR analysis. Ir(dtbbpy) $(ppy)_2PF_6$, (4,4′-di-*tert*-butyl-2,2′-bipyridine)bis[(2-pyridinyl)phenyl] iridium(III) hexafluorophosphate. See also Figures S8–S156.

(Figures S20–S22) in 70% yield and >50:1 diastereomeric ratio (dr), along with a 2% yield of by-product **3a′** (Figure 2; see also Figures S23–S29). Notably, the reaction for production of **3a** could be performed in aqueous THF without loss of yield and diastereoselectivity. The radical reaction did not take place under the same conditions when the Ts protecting group in **2a** was replaced with Me, CO_2Me, Bz, and Boc (see the Supplemental Experimental Procedures and Figures S12–S19). Presumably, this could be due to their tendency for weaker deprotonation, which suppressed the initiation of a nitrogen-centered radical. In addition, a control experiment using a similar substrate without tosyl amide functionality was carried out under the same conditions; the starting material remained unchanged after 12 hr (Scheme S1), indicating that oxidation of the nitrogen anion to initiate a nitrogen-centered radical was crucial for the cascade reaction.

A variety of substrates (**2b–2n**; Figures S30–S87) with either an electron-rich double bond or an electron-deficient Michael acceptor linked to the enamine nitrogen were then used for the radical cascade. To our delight, all reactions afforded the

corresponding products **3b–3m** (Figures S90–S150) with a fused pyrrolidine or piperidine ring in moderate to high yields and high to excellent dr. An exceptionally low dr value (2.5:1) was observed in adduct **3n** (Figures S151 and S152), which has a more flexible azepane ring. This substrate-controlled cascade proceeded in a highly stereoselective manner to completely control the relative configurations of C2 and C3 as a *trans* relationship.

In view of the stereoselectivity for the radical cascade, the addition of the nitrogen-centered radical to the enamine double bond in the first step proceeded from the upper face (**Ts-I**; Figure 2) to give transition states **Ts-IIa′** and **Ts-IIa**, both possessing a *cis* relationship between H2 and H7. **Ts-IIa** could be more reactive than **Ts-IIa′**, considering that twisting of the amide in **Ts-IIa** would dramatically increase the donating ability of the lone electron pair of the amide nitrogen,[48] thus rendering the radical much more nucleophilic. Furthermore, because the upper face of the piperidinone in **Ts-IIa′** should be blocked by the Ts-protected indoline group, addition of a radical to the double bond (triple bond for **3m**) from the upper face of the piperidinone was unfavorable because of steric repulsion. An equilibrium shift of **Ts-IIa′** to **Ts-IIa** resulted in a dominant intramolecular attack of the radical to the double bond (or triple bond) from the bottom face of the piperidinone ring, which gave adduct **3** with a *trans* relationship between H2 and H3. Direct quenching of the radical in **Ts-IIa′** or **Ts-IIa** before the addition to the double bond (or triple bond) provided the by-product **3a′**.

Having successfully achieved the two steps of the intra- and intramolecular radical cascade for generating aspidosperma-type derivatives **3**, we then chose **2o** (Figures S157–S160) with an inert *N*-benzyl (*N*-Bn) group as a substrate to explore the planned intra- and intermolecular radical cascade (Figure 3A). Under the same conditions as above, Michael acceptors **6–9** (1.1–4.0 equiv) were then used in the radical cascade to afford the corresponding tetrahydrocarbolinones **4a–4n** (Figures S161–S198) in moderate to high yields. Although the *E*/*Z* configuration at the side chain in **4i–4l** was not controllable, the newly generated stereocenters at C2 and C3 were formed exclusively in a *trans* configuration in **4a–4n**. Using Michael acceptors **8** and **9**, we were able to isolate **4m** and **4n** with a methylene group α and β to C3, respectively. The reaction generating **4b** was also performed in aqueous THF without loss of yield and diastereoselectivity.

For the preparation of corynanthe-type derivatives **5**, we planned to use substrate **10** (Figures S199–S239) bearing a Michael acceptor or a double bond tethered to the piperidinone ring in an attempt to expand the radical chain reaction from the intermolecular radical addition (**Ts-IIb**) in the second step to the intramolecular radical addition (**Ts-III**) in the third step to give **5** (Figure 3B). In this case, the **Ts-IIb** conformer would be crucial for enabling intermolecular trapping by increasing the lifetime of the radical and disfavoring direct intramolecular 4-exo-trig cyclization with the double bond on the nitrogen side chain. According to this design, we then used alkynyl-type Michael acceptors **7a–7c** to perform the programmed radical cascade, which provided **5a–5h** (Figures S240–S278) in 36%–76% yields with excellent diastereoselectivities, as well as 7%–44% yields of by-product **11** in some cases (see the Supplemental Information). The minor diastereoisomers were the C20 epimers. The by-product **11** was produced by direct radical quenching of **Ts-III′** and **Ts-III**. With regard to the excellent stereocontrol for the D-ring formation, the transition-state **Ts-III** rather than **Ts-III′** might be responsible for generating the D ring with H20 located at the α bond in adduct **5**. The strong steric repulsion between the electron-withdrawing group (EWG) and R_2 was thus avoided in **Ts-III**.

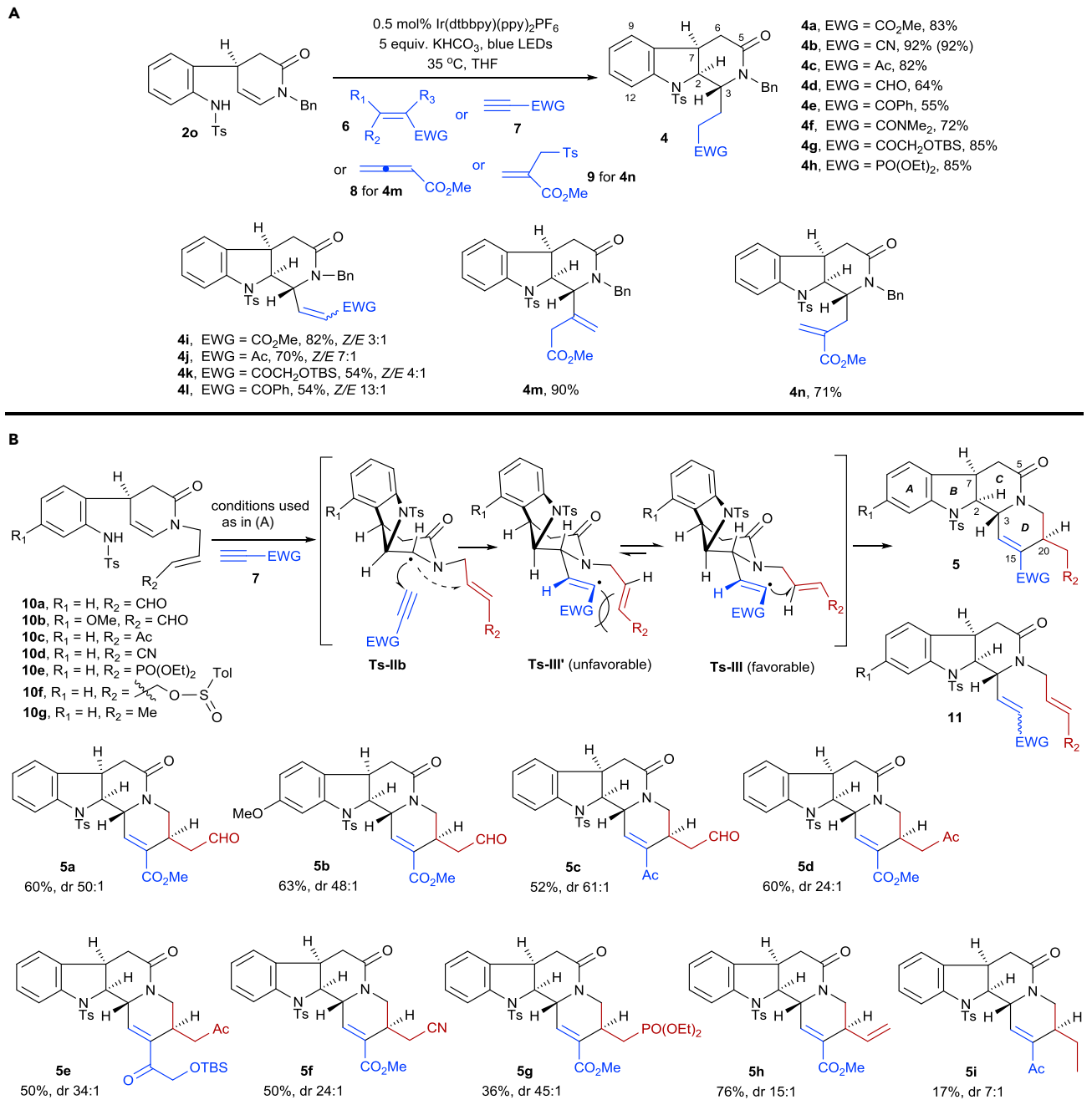
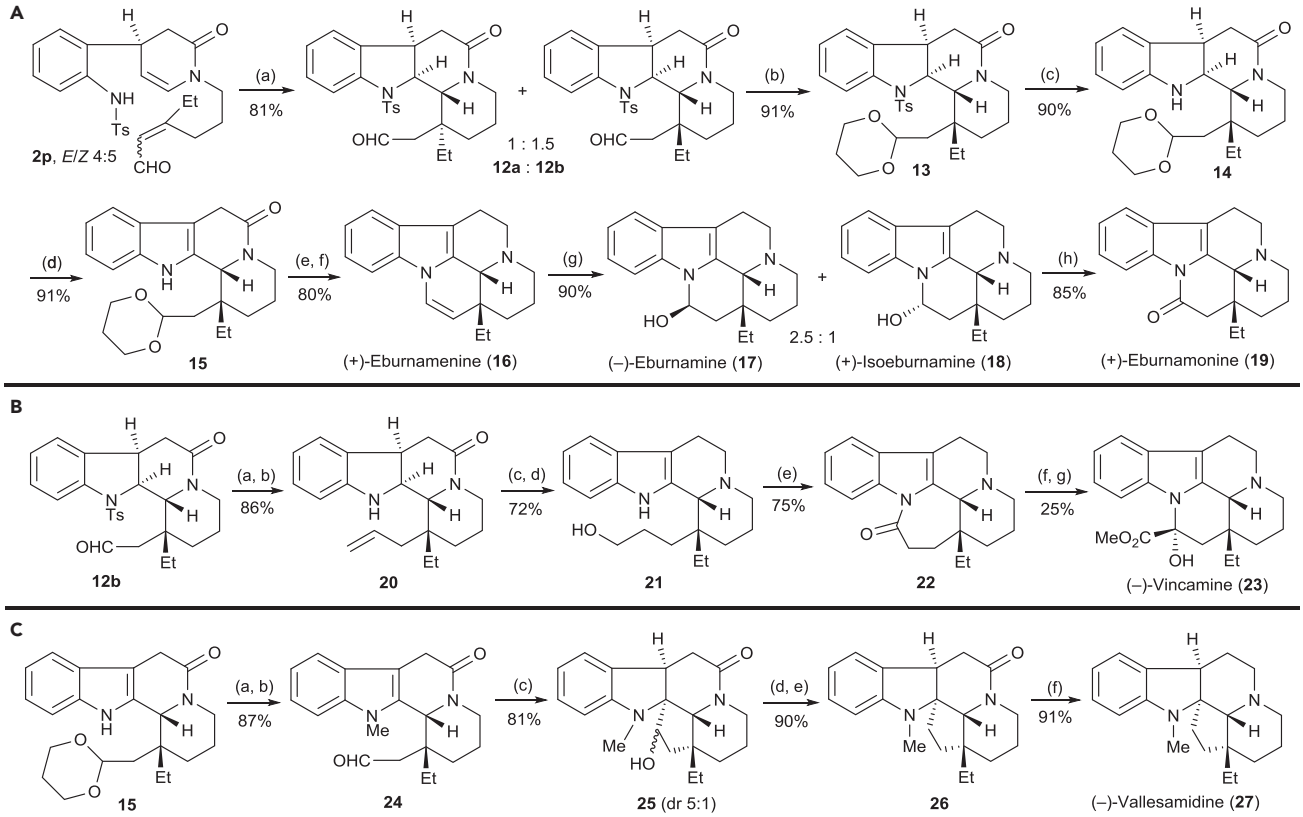


Figure 3. Preparation of Tetrahydrocarbolinones 4 and Corynanthe-Type Derivatives 5

(A) Optimal conditions: 0.5 mol % Ir(dtbbpy) $(ppy)_2PF_6$, 5 equiv $KHCO_3$, degassed THF, 5 W blue LEDs, 35°C, Ar. For the syntheses of **4a–4h**, **4m**, and **4n**, 1.1–2.5 equiv Michael acceptors **6**, **8**, and **9** were used. For the syntheses of **4i–4l**, 4 equiv Michael acceptor **7** was used. **4b**: the yield in parentheses was obtained with 50% aqueous THF as the solvent.

(B) **7**: 2.5–5 equiv was used. **5a–5i**: the dr values of **5** in (B) were determined by LC-MS analysis. The relative configurations of **5a**, **5b**, and **5d–5i** were determined by comparison of their NMR spectra with that of **5c**; the absolute configuration was confirmed by conversion of **5c** to **28a** and **29a** (see Scheme 2 and the Supplemental Information for details). **5h**: dioxane was used as the solvent. See also Figures S157–S283.



Scheme 1. Total Syntheses of the Eburnamine-Vincamine Family Alkaloids

(A) Reagents and conditions: (a) 1 mol % Ir(dtbbpy) $(ppy)_2PF_6$, 5 equiv $KHCO_3$, degassed acetonitrile, 30 W blue LEDs, 35°C, Ar; (b) *p*-TsOH, CH_2Cl_2, 1,3-propanediol, room temperature (RT); (c) sodium naphthalenide, THF, −78°C; (d) benzeneseleninic anhydride, THF, 40°C; (e) $BH_3 \cdot SMe_2$, THF, 0°C to RT; (f) trifluoroacetic acid (TFA), CH_2Cl_2, RT; (g) 0.5 M HCl (aq), RT; (h) pyridinium dichromate (PDC), CH_2Cl_2, RT.

(B) Reagents and conditions: (a) KO^{t}Bu, THF, $Ph_3P^+CH_3Br^-$, 0°C to RT; (b) sodium naphthalenide, THF, −78°C; (c) benzeneseleninic anhydride, THF, 40°C; (d) $BH_3 \cdot SMe_2$, THF, 0°C to RT, then $NaBO_3$; (e) tetrapropylammonium perruthenate, *N*-methyl morpholine-*N*-oxide, CH_2Cl_2, 4 Å molecular sieves, RT, then PDC, CH_2Cl_2, RT; (f) sodium bis(trimethylsilyl)amide (NaHMDS), ^{t}BuONO, PhMe, 50°C; (g) TsOH, paraformaldehyde, AcOH, 100°C; then KO^{t}Bu, MeOH, RT.

(C) Reagents and conditions: (a) NaH, dimethylformamide, MeI, 0°C to RT; (b) 6 M HCl (aq)/THF (1:1 v/v), RT; (c) hexamethyl phosphoryl triamide, SmI_2, THF, reflux; (d) NaH, CS_2, THF; then MeI, 0°C to RT; (e) azodiisobutyronitrile (AIBN), Bu_3SnH, PhMe, 80°C; (f) 15 mol % tris(triphenylphosphine)rhodium(I) carbonyl hydride $(Rh(H)(CO)(PPh_3)_3)$, $PhSiH_3$, THF, RT. See also Figures S284–S345.

When the R_2 group was a methyl group, reaction of **10g** with **7b** (EWG = Ac) afforded **5i** (Figures S279–S283) in a lower yield (17%) and a moderate dr value (7:1). The results were reasonable given that a simple double bond rather than a Michael acceptor in **10g** was relatively inert toward the intramolecular attack of an olefin-type radical in the third step, and the steric repulsion between the methyl group and the acetyl group in **Ts-III′** was partially alleviated.

Syntheses of the Eburnamine-Vincamine Family Alkaloids

Application of the established radical cascade to total syntheses of indole alkaloids was first demonstrated in the syntheses of eburnamine-vincamine family alkaloids. As shown in Scheme 1A, by conducting a two-step radical cascade of **2p** (Figures S284–S297) on a 14 g scale, we were able to isolate two diastereomers, **12a** and **12b** (Figures S298–S303), in 81% combined yield and 1:1.5 ratio. After masking of the aldehyde in **12b** as a dioxane, the tosyl (Ts)-protecting group in the resultant **13** was removed with sodium naphthalenide to afford amine **14** in excellent yield. Facile oxidation of the indoline moiety to indole (**14** to **15**), followed by amide

reduction and treatment with trifluoroacetic acid, gave (+)-eburnamenine (**16**; Figures S312 and S313) in 73% yield in three steps. Hydration of **16** with HCl/H_2O resulted in (−)-eburnamine (**17**; Figures S314 and S315) and (+)-isoeburnamine (**18**; Figures S316 and S317). Further oxidation of the mixture of **17** and **18** led to the formation of the alkaloid (+)-eburnamonine (**19**; Figures S318–S321).[49]

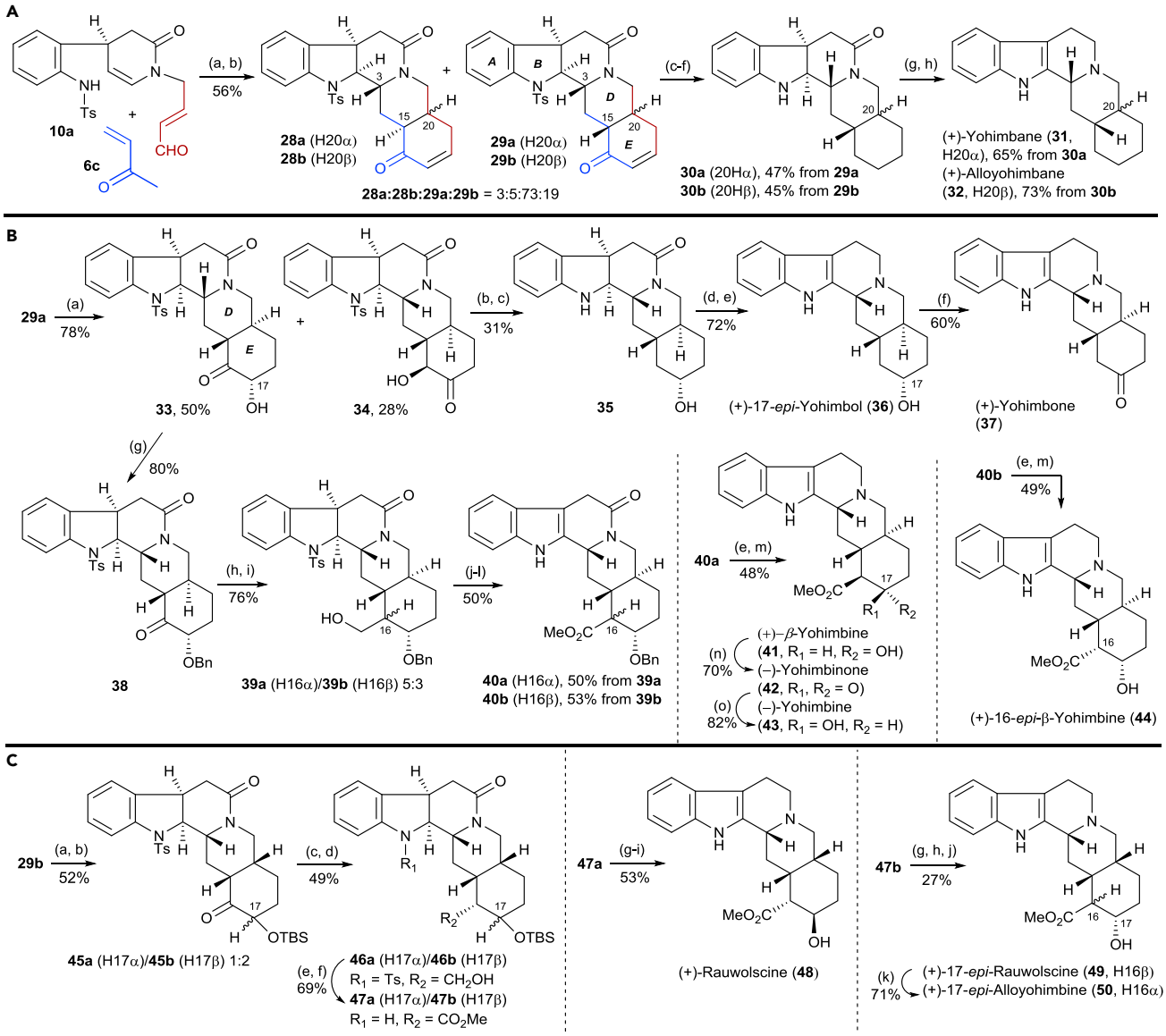
Intermediate **12b** was used for the synthesis of (−)-vincamine (**23**) in seven steps (Scheme 1B). Wittig methylenation of **12b** and removal of the Ts group afforded **20** in excellent yield. After oxidation of the indoline moiety, the double bond in **20** was then converted into a hydroxy group by hydroboration oxidation, which resulted in concomitant reduction of the amide to give alcohol **21**. Oxidation of the hydroxy group in **21** led to the formation of lactam **22**. Finally, **23** (Figures S332–S344) was synthesized from **22** according to a literature procedure.[50]

The synthesis of (−)-vallesamidine (**27**) was achieved with **15** as the starting material (Scheme 1C). After two steps of methylation and deprotection, aldehyde **24** was treated with SmI_2 to generate a ketyl radical, which was then added to the indole double bond to afford **25** as a pair of diastereomers. Removal of the hydroxy group in **25**, followed by reduction of the resulting **26** with rhodium(I) hydride,[51] provided **27** (Figures S342–S345) in excellent yield.

Syntheses of the Yohimbine Family Alkaloids

In the analysis of the radical cascade in Figure 3B, we noticed that a yohimbine-type core could be easily constructed if methyl vinyl ketone (**6c**) was used as a Michael acceptor in place of the alkynyl-type counterpart (Scheme 2A). In this context, separable diastereoisomers **28a**, **28b**, **29a**, and **29b** (Figures S346–S355) were isolated in 56% combined yield and a 3:5:73:19 ratio if compounds **10a** and **6c** (1.2 equiv) were subjected to the radical cascade conditions on a 12 g scale, followed by treatment with *p*-TsOH in toluene. The absolute configurations of **28a**, **28b**, **29a**, and **29b** were determined by X-ray crystallography (see the Supplemental Information for details). Major isomers **29a** and **29b** were then used as starting materials for the syntheses of yohimbane (**31**) and alloyohimbane (**32**) via a six-step transformation. Specifically, four steps of individual hydrogenation, reduction, and the removal of hydroxy and Ts groups in **29a** and **29b** provided the corresponding amines **30a** and **30b**, respectively. Further indoline oxidation and amide reduction afforded **31** (Figures S376–S379) and **32** (Figures S380–S383), respectively.

For the syntheses of natural 17-*epi*-yohimbol (**36**), yohimbone (**37**), β-yohimbine (**41**), yohimbine (**43**), and the unnatural yohimbinone (**42**) and 16-*epi*-β-yohimbine (**44**), intermediate **29a** with a *trans*-fused D/E ring system was used as the starting material (Scheme 2B). Mukaiyama hydration of enone **29a** led to the desired alcohol **33** as well as an unexpected by-product **34**.[52] It is clear that **34** was generated by enol rearrangement from the unstable 17-epimer of **33** under the chromatographic conditions, which were then used for the syntheses of **36** and **37**. Removal of the hydroxy group and the Ts group in **34** resulted in simultaneous stereoselective reduction of ketone to give **35** as a single diastereoisomer. The two subsequent steps of oxidation of the indoline moiety and reduction of the amide in **35** afforded **36** (Figures S394–S399). Further oxidation of **36** afforded **37** (Figures S400–S403) in 60% yield. However, after protection of the hydroxy group in **33**, Corey-Chaykovsky epoxidation of the resultant **38**, followed by opening of the epoxide ring,[53] generated two separable diastereoisomers, **39a** and **39b**. Compounds **39a** and **39b** were then individually converted to the corresponding esters **40a** and **40b** in approximately 50% yield. Further functional group transformation of **40a**, including reduction of the



Scheme 2. Total Syntheses of the Yohimbine Family Alkaloids

(A) Reagents and conditions: (a) 0.5 mol % Ir(dtbbpy) $(ppy)_2PF_6$, 5 equiv $KHCO_3$, THF, 30 W blue LEDs, 25°C; (b) *p*-TsOH, PhMe, 60°C; (c) $Pd(OH)_2$, H_2, EtOAc, RT; (d) $NaBH_4$, MeOH, RT; (e) CS_2, NaH, MeI, THF, 0°C; then AIBN, Bu_3SnH, PhMe, 80°C; (f) Mg, MeOH, RT; (g) benzeneseleninic anhydride, THF, 40°C; (h) 15 mol % $Rh(H)(CO)(PPh_3)_3$, $PhSiH_3$, THF, RT.

(B) Reagents and conditions: (a) tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) ($Mn(dpm)_3$), $PhSiH_3$, O_2, $^iPrOH/CH_2Cl_2$ (1:4 v/v), RT; then silica gel; (b) 1,1′-thiocarbonyldiimidazole, 4-dimethylaminopyridine, 1,2-dichloroethane (DCE), RT; then AIBN, Bu_3SnH, DCE, reflux; (c) Mg, MeOH, RT; (d) benzeneseleninic anhydride, THF, 40°C; (e) 15 mol % $Rh(H)(CO)(PPh_3)_3$, $PhSiH_3$, THF, RT; (f) dicyclohexylcarbodiimide, $Cl_2CHCOOH$, DMSO, 35°C; (g) BnBr, Ag_2O, PhMe, 45°C; (h) $Me_3S^+I^-$, KO^tBu, DMSO, RT; (i) Zn, Cp_2TiCl_2, 1,4-cyclohexadiene (1,4-CHD), THF, RT; (j) 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO), $PhI(OAc)_2$, $MeCN/H_2O$ (1:1 v/v); then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$ (1:1 v/v), RT; then trimethylsilyldiazomethane ($TMSCHN_2$), PhMe/MeOH (5:1 v/v), RT; (k) Mg, MeOH, RT; (l) benzeneseleninic anhydride, THF, 45°C; (m) BBr_3, CH_2Cl_2, −78°C; (n) Ac_2O, DMSO, RT; (o) lithium triisobutylhydroborate, THF, −78°C, **43**/**41** 6:1.

(C) Reagents and conditions: (a) $Mn(dpm)_3$, $PhSiH_3$, O_2, $^iPrOH/CH_2Cl_2$ (1:4 v/v), RT; (b) *tert*-butyldimethylsilyl chloride, imidazole, CH_2Cl_2, RT; (c) $Me_3S^+I^-$, ^nBuLi, THF, 0°C; (d) Zn, Cp_2TiCl_2, 1,4-CHD, THF, 50°C; (e) TEMPO, $PhI(OAc)_2$, $MeCN/H_2O$ (1:1 v/v); then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$ (1:1 v/v), RT; then $TMSCHN_2$, PhMe/MeOH (5:1 v/v), RT; (f) Mg, MeOH, RT; (g) benzeneseleninic anhydride, THF, 40°C; (h) 15 mol % $Rh(H)(CO)(PPh_3)_3$, $PhSiH_3$, THF, RT; (i) 5 M HCl/THF (1:3 v/v), 30°C; (j) pyridine hydrofluoride, THF, 40°C; (k) 1 M MeONa in MeOH, 30°C. See also Figures S346–S467.

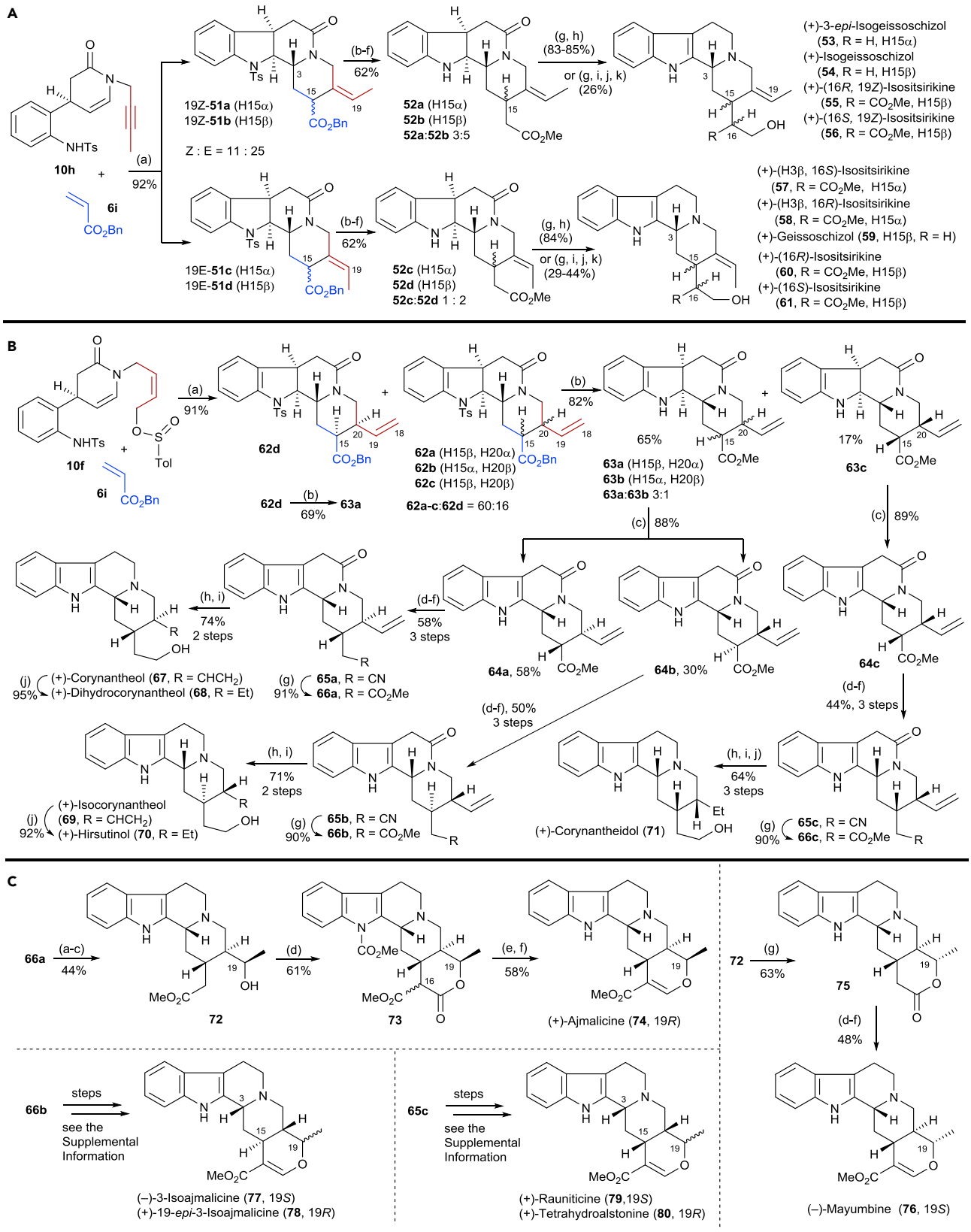
amide and O-debenzylation with BBr_3, afforded **41** (Figures S428–S431). Ultimately, a sequential oxidation-reduction of **41** via **42** (Figures S434 and S435) delivered (−)-yohimbine (**43**; Figures S436–S439).[14,54] Similarly, the diastereoisomer **44** (Figures S432 and S433) was synthesized from **40b** in 49% yield according to the same procedure as that applied for the synthesis of **41**.

Having developed a synthetic route to yohimbine (**43**) and related alkaloids from **29a**, we were able to synthesize natural rauwolscine (**48**), 17-*epi*-alloyohimbine (**50**), and the unnatural 17-*epi*-rauwolscine (**49**) from **29b**, which possessed a *cis*-fused D/E ring system (Scheme 2C). Unlike **29a**, Mukaiyama hydration of **29b** provided two inseparable diastereoisomers **45a** and **45b** in 52% yield and a 1:2 ratio after *tert*-butyldimethylsilyl (TBS) protection of the resultant hydroxy group. A mixture of **46a** and **46b** was obtained in 49% yield when Corey-Chaykovsky epoxidation, followed by opening of the epoxide ring, was performed. After oxidation of the hydroxy groups in **46a** and **46b** to esters, the Ts groups were removed to give two separable diastereoisomers, **47a** and **47b**, in 69% combined yield. Finally, three steps of indoline oxidation, amide reduction, and TBS deprotection from **47a** furnished rauwolscine (**48**; Figures S456–S459). In a similar procedure, **49** (Figures S464 and S465) was readily synthesized from **47b**, and **50** (Figures S466 and S467) was obtained by epimerization of **49** at C16.

Syntheses of the Corynanthe and Heteroyohimbine Family Alkaloids

In addition to the divergent stereochemistry at C15 and C20, the distinction among the large members of the corynanthe family alkaloids is the geometric variation of the double bond at C19. Therefore, for syntheses of alkaloids in this family, we used **6i** (5 equiv) and **10h** (Figures S469–S472) with a 2-butynyl side chain to conduct a three-step radical cascade on a 20 g scale, which afforded two mixtures of the two diastereoisomers **51a–51b** and **51c–51d** in excellent combined yield (Scheme 3A; see also Figures S468 and S473–S480). The *E*/*Z* geometric isomers were completely separated at this stage. After homologation of the ester side chain at C15 and removal of the Ts group in **51** via a five-step transformation from individual mixtures of **51a–51d**, the four separable diastereomers **52a–52d** were obtained. Starting from each isomer, we were able to synthesize eight corynanthe family alkaloids, **54–61** (Figures S513–S520 and S527–S542), and unnatural 3-*epi*-isogeissoschizol (**53**; Figures S511 and S512) via two to four steps of functionality manipulations (see Supplemental Experimental Procedures).

For further syntheses of the corynanthe family alkaloids **67–71**, a strategy that introduces a C18–C19 terminal double bond at an early stage of synthesis was designed (Scheme 3B). This strategy also enabled the formation of a dihydropyran ring by converting the terminal alkene into a hydroxy group at C19, thus facilitating the syntheses of heteroyohimbine family alkaloids **74** and **76–80** with varied stereochemistry at C15, C19, and C20 (Scheme 3C).[41] To form a C18–C19 terminal double bond, we performed the radical cascade by using **6i** (5 equiv) and **10f** to provide a mixture of **62a–62c** (Figures S543 and S544) and a single diastereomer **62d** (Figures S545 and S546) in excellent yield. Removal of the Ts group in **62d** with Mg/MeOH readily effected epimerization at C15 to give **63a**. Coincidentally, there is no corynanthe family alkaloid that possesses the same stereochemistry at C3, C15, and C20 as that of **62d**. Treatment of the mixture of the three diastereoisomers **62a–62c** with Mg/MeOH afforded a mixture of two diastereoisomers **63a** and **63b** in 65% yield and a single diastereoisomer **63c** in 17% yield. After oxidation of the indoline moiety in **63a** and **63b**, diastereoisomers **64a** and **64b** were separated. Similarly, **64c** was obtained by oxidation of **63c**. After extension of the C15 ester chain by a


A
10h
6i
(a)
92%
19Z-51a (H15α)
19Z-51b (H15β)
Z : E = 11 : 25
(b-f)
62%
52a (H15α)
52b (H15β)
52a:52b 3:5
(g, h)
(83-85%)
or (g, i, j, k)
(26%)
(+)-3-epi-Isogeissoschizol (53, R = H, H15α)
(+)-Isogeissoschizol (54, R = H, H15β)
(+)-(16R, 19Z)-Isositsirikine (55, R = CO2Me, H15β)
(+)-(16S, 19Z)-Isositsirikine (56, R = CO2Me, H15β)
19E-51c (H15α)
19E-51d (H15β)
(b-f)
62%
52c (H15α)
52d (H15β)
52c:52d 1 : 2
(g, h)
(84%)
or (g, i, j, k)
(29-44%)
(+)-(H3β, 16S)-Isositsirikine (57, R = CO2Me, H15α)
(+)-(H3β, 16R)-Isositsirikine (58, R = CO2Me, H15α)
(+)-Geissoschizol (59, H15β, R = H)
(+)-(16R)-Isositsirikine (60, R = CO2Me, H15β)
(+)-(16S)-Isositsirikine (61, R = CO2Me, H15β)
B
10f
6i
(a)
91%
62d
62d
(b)
69%
63a
62a (H15β, H20α)
62b (H15α, H20β)
62c (H15β, H20β)
62a-c:62d = 60:16
(b)
82%
65%
63a (H15β, H20α)
63b (H15α, H20β)
63a:63b 3:1
17%
63c
(c) 88%
(c) 89%
(h, i)
74%
2 steps
(d-f)
58%
3 steps
64a, 58%
64b, 30%
64c
(d-f)
44%, 3 steps
(j) 95% (+)-Corynantheol (67, R = CHCH2)
(+)-Dihydrocorynantheol (68, R = Et)
(g) 91% 65a, R = CN
66a, R = CO2Me
(d-f), 50%
3 steps
(h, i)
71%
2 steps
(h, i, j)
64%
3 steps
(j) 92% (+)-Isocorynantheol (69, R = CHCH2)
(+)-Hirsutinol (70, R = Et)
(g) 90% 65b, R = CN
66b, R = CO2Me
(+)-Corynantheidol (71)
(g) 90% 65c, R = CN
66c, R = CO2Me
C
66a
(a-c)
44%
72
(d)
61%
73
(e, f)
58%
(+)-Ajmalicine (74, 19R)
72
(g)
63%
75
(d-f)
48%
66b
steps
see the Supplemental Information
(–)-3-Isoajmalicine (77, 19S)
(+)-19-epi-3-Isoajmalicine (78, 19R)
65c
steps
see the Supplemental Information
(+)-Rauniticine (79,19S)
(+)-Tetrahydroalstonine (80, 19R)
(–)-Mayumbine (76, 19S)

Scheme 3. Total Syntheses of the Corynanthe and Heteroyohimbine Family Alkaloids

(A) Reagents and conditions: (a) 1 mol % Ir(dtbbpy) $(ppy)_2PF_6$, 5 equiv $KHCO_3$, THF, 30 W blue LEDs, 35°C, Ar; (b) $LiBH_4$, THF, 0°C to RT; (c) methanesulfonyl chloride (MsCl), Et_3N, CH_2Cl_2, RT; (d) trimethylsilyl cyanide (TMSCN), tetra-*n*-butylammonium fluoride (TBAF), THF, reflux; (e) HCl (g), MeOH, 0°C to RT; (f) Mg, MeOH, RT; (g) benzeneseleninic anhydride, THF, 40°C; (h) $LiAlH_4$, PhMe, 0°C to RT; (i) 5 mol % $Rh(H)(CO)(PPh_3)_3$, $PhSiH_3$, THF, RT; (j) lithium diisopropylamide, HCO_2Me, THF, −78°C to RT; (k) AcOH, $NaBH_4$, MeOH, 0°C.

(B) Reagents and conditions: (a) 0.5 mol % Ir(dtbbpy)$(ppy)_2PF_6$, 5 equiv $KHCO_3$, acetonitrile, 15 W blue LEDs, Ar, 37°C; (b) Mg, MeOH, RT; (c) benzeneseleninic anhydride, THF, 40°C; (d) $LiAlH_4$, THF, −30°C; (e) MsCl, Et_3N, CH_2Cl_2, RT; (f) TMSCN, TBAF, THF, reflux; (g) HCl (g), MeOH, 0°C–60°C; (h) 7 mol % $Rh(H)(CO)(PPh_3)_3$, $PhSiH_3$, THF, RT; (i) $LiAlH_4$, THF, 0°C to RT; (j) H_2, 10% PtO_2, MeOH, RT.

(C) Reagents and conditions: (a) $Pd(OAc)_2$, $HClO_4$, 1,4-benzoquinone, $MeCN/H_2O$ (7:1 v/v), RT; (b) 7 mol % $Rh(H)(CO)(PPh_3)_3$, $PhSiH_3$, THF, RT; (c) $NaBH_4$, MeOH, −30°C; (d) NaHMDS or LiHMDS, $NCCO_2Me$, THF, −78°C; (e) diisobutylaluminum hydride or $NaBH_4$; (f) *p*-TsOH, CH_2Cl_2, reflux; then K_2CO_3, MeOH, RT; (g) Ph_3P, diethyl azodicarboxylate, *p*-nitrobenzoic acid, THF, 0°C–30°C; then Cs_2CO_3, MeOH, RT. See also Figures S468–S640.

four-step transformation (**64a** to **66a**), stepwise reduction of the amide and ester and then the double bond in **66a** generated **67** (Figures S575 and S576) and then **68** (Figures S579–S582), respectively. Similarly, **69**–**71** (Figures S577, S578, and S583–S586) were synthesized from **66b** and **66c** according to the above procedure for the syntheses of **67** and **68**, respectively.

For the syntheses of heteroyohimbine family alkaloids, **66a**, **66b**, and **65c** were used as starting materials (Scheme 3C). A three-step sequence of Wacker oxidation, amide reduction, and stereoselective ketone reduction was applied to **66a** to provide the single diastereoisomer **72** in 44% overall yield. Carbonylation of **72** resulted in the formation of the lactone ring and the introduction of two methoxycarbonyl groups in one pot to yield **73**. Further reduction and hydrolysis of **73** gave rise to ajmalicine (**74**; Figures S601–S604). Lactone **75** was obtained in 63% yield from **72** by Mitsunobu inversion of the C19 hydroxy group configuration, followed by hydrolysis. Mayumbine (**76**; Figures S596–S598) was prepared according to a procedure similar to that applied for the synthesis of ajmalicine (**74**). In addition, after similar functional-group manipulations, alkaloids **77**–**80**, possessing different stereochemistry at C15 and C19, were synthesized from **66b** and **65c**, respectively (see Supplemental Experimental Procedures and Figures S605–S640).

Conclusion

We have developed an innovative photocatalytic radical cascade that reverses the conventional reactivity between two electron-donating amine and enamine groups and allows highly efficient assembly of manifold core structures of indole alkaloids with divergent stereochemistry and functionalities from simple starting materials. The power of this radical cascade has been demonstrated by easy preparation of focused libraries of natural-product-like compounds with high to excellent diastereoselectivity. By using this radical cascade as a key reaction, we synthesized 33 indole alkaloids belonging to four families and four unnatural diastereoisomers in 6–14 steps, which are difficult to achieve by traditional methods. Promisingly, the radical cascade is green, water insensitive, and readily scalable (Figure S641 and Table S1). With the current success, we anticipate that generation of a nitrogen-centered radical from direct cleavage of an aniline N–H bond can be involved in many intermolecular reaction protocols. Expansion of such ideas would provide expedient access to more nitrogen-containing architectures, such as reserpine, strychnine, and vincamajine, which are of great value. Application of this method to the syntheses of other natural products and bioactive substances is in progress and will be reported in due course.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

ACCESSION NUMBERS

The data for the X-ray crystallographic structures of detosylated derivatives of **3a** and **3l**, **28a**, **28b**, **29a**, and **29b** in this article have been deposited in the Cambridge Crystallographic Data Center under accession numbers CCDC: 1518109, 1520164, 1519507, 1519506, 1495501, and 1495500, respectively.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 641 figures, 1 table, 1 scheme, and 6 data files and can be found with this article online at http://dx.doi.org/10.1016/j.chempr.2017.04.007.

AUTHOR CONTRIBUTIONS

Y.Q. conceived and directed all aspects of the research and wrote the manuscript with the assistance of X.-Y.L. The main experiments, which included methodology development and syntheses of natural products, were performed by X.W., D.X., W.Q., R.Z., X.Z., and Q.Z. W.L., X.D., and H.W. carried out the scale-up experiments of the radical cascade. S.W. and L.T. conducted the large-scale preparation of starting materials. D.Z., H.S., and all other authors analyzed the results and commented on the manuscript.

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