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Note

Visible-Light-Promoted Biomimetic Reductive Functionalization of Quaternary Benzophenanthridine Alkaloids

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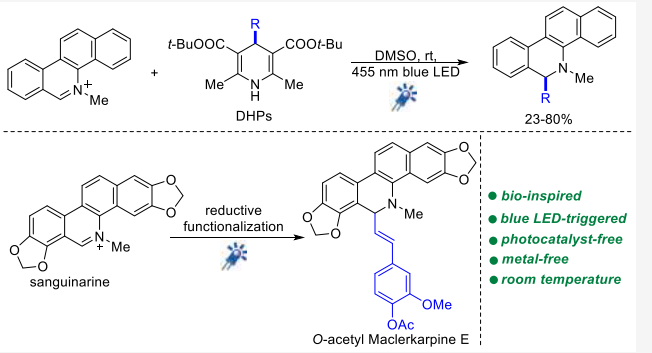
ABSTRACT: Reduction of an iminium C═N double bond is the most important phase I metabolism process associated with the cytotoxic property of quaternary benzophenanthridine alkaloids (QBAs). Inspired by the light-mediated reduction of QBAs with nicotinamide adenine dinucleotide, a visible-light-promoted reductive functionalization reaction of QBAs is reported in this study. C4-Alkyl-1,4-dihydropyridines (DHPs) enable the direct reductive alkylation of QBA independently, serving as both single-electron-transfer reductant reagents under irradiation with 455 nm blue light in the absence of photocatalysts and additional additives. Our protocol can be further applied to the semisynthesis of natural 6-substituted dihydrobenzophenanthridine derivatives such as *O*-acetyl maclekarpine E.



Iminium ions are common structural elements in natural products including quaternary benzophenanthridine-type alkaloids,[1] such as sanguinarine (**1**, Scheme 1), which exhibit interesting cytotoxic properties such as inducing oxidative DNA damage and rapid apoptosis.[2−4] The reduction of the C═N double bond represents the most important phase-I metabolic process of this kind of alkaloids in cells[5−8] and the detoxification process in sanguinarine-containing plants.[9]

Sanguinarine reductase (SR), a nicotinamide adenine dinucleotide (NADH)-dependent reductase, is a plant enzyme that prevents the cytotoxic effects of quaternary benzophenanthridine alkaloids, the main phytoalexins of Papaveraceae.[9] This enzyme catalyzes the reduction of sanguinarine (**1**) (Scheme 1 A) to dihydrosanguinarine (**2**), a toxic benzophenanthridine, which re-enters the cytoplasm after its primary accumulation in the cell wall region has reached a threshold concentration. Interestingly, it was also documented that sanguinarine could be directly reduced by NADH in the absence of protein enzymes[10] (Scheme 1B). A covalent adduct (**3**) between sanguinarine (**1**) and NADH is formed via an ene reaction and then converted slowly to NAD^+ and dihydrosanguinarine (**2**) in high yield. During our ongoing research on the reductive metabolism of sanguinarine, we were curious to find that a dihydrosanguinarine dimer (**4**) was detected as a byproduct when a mixture of sanguinarine (**1**) and NADH was stirred under the irradiation of 455 nm blue light (Scheme 1C). The generation of a dihydrosanguinarine dimer obviously points to a switch of the mechanism that differs from the ene reaction pathway.

NADH, a naturally existing 1,4-dihydropyridine derivative, primarily serves as a hydride ion or electron provider ($E(NADH^{\bullet+}/NADH)$ = 0.76 V vs SCE). When excited by light irradiation, NADH can also be employed as a potent single-electron reductant.[11] We speculated that light irradiation on the mixture of sanguinarine (**1**) and NADH probably triggers the single-electron (SET) reduction of sanguinarine (**1**), which leads to the generation of a persistent α-amino C-radical (**5**). A self-coupling reaction of radical **5** leads to the formation of dimer **4**. Meanwhile, radical **5** abstracts a hydrogen atom from the oxidized $NADH^{\bullet+}$ via a hydrogen atom transfer (HAT) procedure, thus giving dihydronsanguinarine (**2**).

The discovery of visible-light-mediated reduction of sanguinarine by NADH in the absence of photocatalysts stimulated our research interest in the exploration of Hantzsch esters, a kind of synthetic 1,4-dihydropyridine derivatives (DHPs, **6**, Scheme 2), as SET reductants ($E(DHP^{\bullet+}/DHP)$ = 1.03 V vs SCE).[11] Compared with NADH, DHPs are easily accessible from aldehydes. Especially when an alkyl group is installed on the 4-position of DHPs, the HAT process between **5** and $DHPs^{\bullet+}$ will be prevented to a certain extent. Actually,

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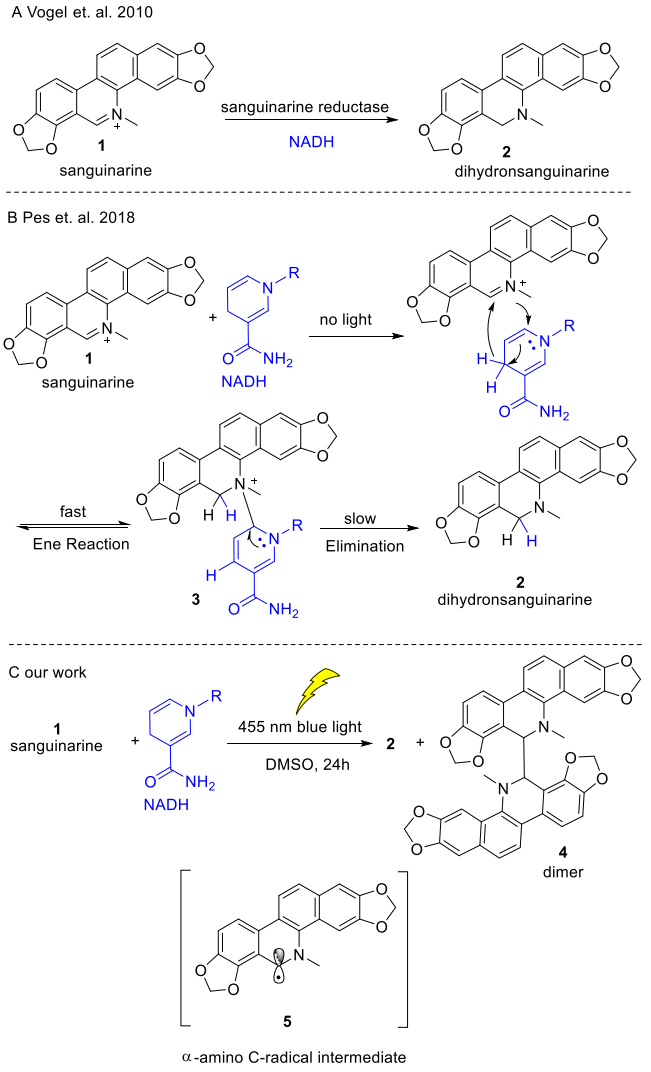
Scheme 1. Reduction of Sanguinarine to Dihydrosanguinarine without and with Blue Light Irradiation and Possible Mechanism



the radical cation DHPs$^{\bullet+}$ will fragment to pyridine and an alkyl radical R$^{\bullet}$,[12−18] which can subsequently couple with radical **5**, in line with the persistent radical effect[19] of **5**. This strategy would provide the means to achieve photoinitiated reductive alkylation of iminium cations and give 6-substituted dihydrobenzophenanthridine alkaloids (**7**, Scheme 2). Notably, 6-substituted dihydrobenzophenanthridine alkaloids are found to naturally exist in many medicinal plants such as *Macleaya cordata*,[20] *Macleaya macrocarpa*,[21] and *Zanthoxylum nitidum*.[22]

For the optimization of the reaction conditions, we chose sanguinarine (**1**) as a model substrate in combination with 4-Bn-DHP (**6a**). While poor yields were obtained using DMF or MeOH as solvent under the irradiation of a 455 nm blue LED (entries 1, 2, Table 1), DMSO furnished the desired 6-benzyldihydrosanguinarine **7a** in 57−63% yield (entries 3, 4). Interestingly, in the presence of catalytic amounts of common iridium photocatalysts Ir(ppy)$_3$ or Ir(ppy)$_2$dtbpy·PF$_6$, **7a** was obtained in 28% and 30% yields, respectively (entries 5, 6), suggesting that DHPs directly engage in the single-electron reductive process of sanguinarine. In line with this reasoning, compound **7a** could not be detected after 24 h of reaction at room temperature or 60 °C in the absence of visible light irradiation (entries 7, 8). The reaction was also carried out open to air, but a lower yield of **7a** was observed (entry 9).

With the optimized conditions in hand, we tested DHPs (**6a−6j**) with different alkyl units at the C4-position. Indeed, both sanguinarine (**1**) and chelerythrine (**8**) could be reductively benzylated using **6a−6e** as reductants, giving **7a−7e** in good yields (Table 2). The reaction was sensitive to steric effects, resulting in poor yields of compounds **7f** and **7ff** when the more bulky 1,1-diphenylmethyl radical was used as coupling partner. Next, a series of secondary alkyl radicals (**6g** and **6h**) were used in this reductive coupling reaction, affording the alkylated products in moderate to good yields. We also evaluated the reaction efficacy with primary C-radicals as coupling partners, while the desired compounds were not detected (**6i** and **6j**).

To further expand the scope of iminium substrates, *N*-methyl phenanthridine salt **9**, *N*-methyl isoquinoline salt **10**, and berberine **11** were selected as the coupling partners (Scheme 3). Under the "standard" conditions, the reductive alkylation reaction was observed only with *N*-methyl phenanthridine salt **9** as starting material, suggesting that the reduction of the iminium C=N$^+$ bond requires the phenanthridine core structure. The enamine motif of **13** and **14**, a highly reductive substructure unit, probably disrupted the desired radical reaction.

Considering that the fragmentation of 4-phenyl DHP's radical cation is obstructed, we attempted to use 4-phenyl DHP as a single reductant in combination with suitable alkenes as radical acceptors (Table 3). We were pleased to see that when a mixture of quaternary benzophenanthridine, 4-phenyl DHP (**6k**), and electron-deficient alkenes such as methyl acrylate (**15a**), 2-vinylpryridine (**15b**), or methyl 2-((phenylsulfonyl)methyl)acrylate (**15c**) was stirred at room temperature under irradiation of 455 nm blue light for 24 h, the desired addition products **16** were indeed obtained. Here, 4-phenyl DHP only serves as a SET reductant, while the electron-deficient alkenes capture the generated α-amino C-radical **5** to afford the radical type of Michael addition products.

Based on the 4-phenyl DHP-mediated reductive addition reaction, further application of the current protocol in the semisynthesis of natural 6-substituted dihydrobenzophenanthridine alkaloid maclekarpine E[21] was evaluated. As

Scheme 2. Visible-Light-Triggered Reductive Functionalization of Quaternary Benzophenanthridine Alkaloids

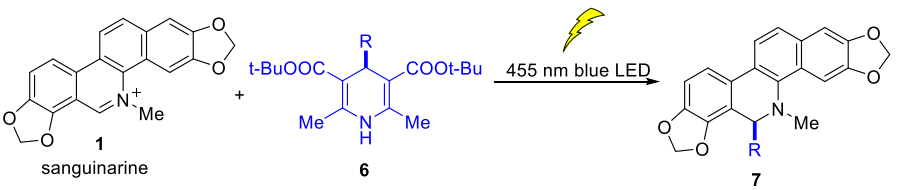


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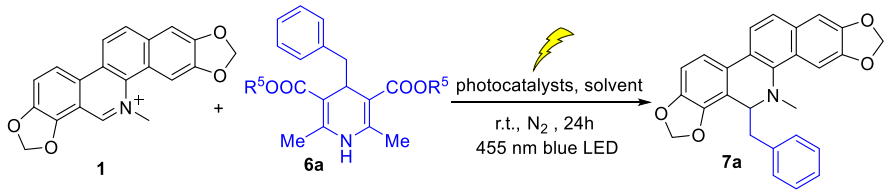
Table 1. Optimization of Reaction Parameters[a]



entry	solvents	photocatalyst	R^5 on DHP **6a**	yield[b] of **7a** (%)
1	DMF		Et	trace
2	MeOH		Et	5
3	DMSO		Et	57
4	DMSO		*t*-Bu	63
5	DMSO	$Ir(ppy)_3$	*t*-Bu	28
6	DMSO	$Ir(ppy)_2dtbpy{\cdot}PF_6$	*t*-Bu	30
7[c]	DMSO		*t*-Bu	0
8[d]	DMSO		*t*-Bu	0
9	DMSO		*t*-Bu	43

[a]Experiments were performed with **1** (0.2 mmol), **6a** (2 equiv), photocatalyst (2 mol %), and solvent (2 mL) under an atmosphere of N_2; [b]Isolated yields. [c]In the dark. [d]In the dark at 60 °C.

shown in Scheme 4, with 3-methoxy-4-hydroxybenzaldehyde (**17**) as starting material, *β*-3-methoxyl-4-acetoxyphenyl vinyl sulfone (**20**) was first synthesized as radical acceptor. Using 4-phenyl DHP (**6k**) as SET reductive reagent, a visible-light-triggered radical addition/elimination reaction occurred smoothly to give *O*-acetylmaclekarpine E (**21**) in 36% yield.

To gain the insight into the light-mediated reductive-alkylation of quaternary benzophenanthridines, we performed UV−vis spectroscopic measurements on **1**, **6a**, and the combination of **1** and **6a** in DMSO (Scheme 5A), since we suspected the formation of an electron-donor−acceptor (EDA) complex, **22** (Scheme 5B), between **6a** and quaternary salts **1**. According to the literature,[23−25] the EDA complex can enable the direct SET oxidation of donor and reduction of acceptor, respectively. Visible light irradiation could trigger the SET reduction of a quaternary benzophenanthridine salt to *α*-amino C-radical **5** under catalyst-free conditions. Under UV−vis light, we observed an absorption peak at 455 nm and tail absorption at 425 nm for sanguinarine (**1**) and DHP (**6a**), respectively. UV−vis analysis of combined **1** and **6a** showed red-shifts and increased absorbance at 455 nm compared with two substrates, indicating the suggested formation of an EDA complex (Scheme 5A). Since sanguinarine (**1**) can absorb at λ_{max} 455 nm, we also recorded the emission spectra of **1** upon excitation at 455 nm. As illustrated in Scheme 5C, there was a dominant peak with a maximum at 570 nm in the emission spectra of **1**.

Fluorescence characteristics of sanguinarine (**1**) suggested that the redox potential of sanguinatine might change when excited by 455 nm blue light. To verify this hypothesis, the cyclic voltammetry analysis of sanguinarine (**1**) was performed under the irradiation of 455 nm blue light. As illustrated in Scheme 5D, the reduction potential of **1** slightly shifted to higher potential compared with its cyclic voltammogram in the dark, which indicated that the 455 nm blue light irradiation could also facilitate the SET reduction procedure of sanguinarine (**1**).

On the basis of previous literature,[26−28] photoexcited DHP* could also act as a SET reductant independently (E_{red}*(DHP*/DHP$^{\bullet+}$) = −2.2 V vs SCE). However, 4-Bn-DHP (**6a**) only has a tail absorption at 425 nm, indicating that **6a** cannot be activated by 455 nm blue light. On the basis of our experimental results, we envision the mechanistic scenario as shown in Scheme 6. EDA complex **22** is first formed between **6a** and quaternary salt **1**. Upon excitation by 455 nm blue light, complex **22** undergoes a SET process leading to the reduction of sanguinarine (**1**) to *α*-amino C-radical **5** and the oxidation of DHP to DHP$^{\bullet+}$. Subsequently, the radical cation DHP$^{\bullet+}$ fragments to tetrasubstituted pyridine and alkyl radical $^{\bullet}R^4$. When $^{\bullet}R^4$ is secondary or benzylic, it will couple with *α*-amino C-radical **5**, giving rise to **7**. Considering the unique electrochemical properties of sanguinarine (**1**) already shown in Scheme 5D, blue light irradiation of sanguinarine also accelerates its SET reduction. It is also worth noting that dihydrosanguinarine is detected as a byproduct during the synthesis of 6-substituted dihydrobenzophenanthridines due to the HAT process between radical **5** and DHP$^{\bullet+}$. This HAT process is more obvious when $^{\bullet}R^4$ on DHP is nonbenzylic or secondary, as the fragmentation of DHP$^{\bullet+}$ is more difficult. The HAT process between DHP$^{\bullet+}$ and radical **5** finally gives rise to aromatic 4-substituted pyridine and dihydrosanguinarine (see Supporting Information).

In summary, we have described a biomimetic reductive alkylation reaction of quaternary benzophenanthridine alkaloids to prepare 6-substituted dihydrobenzophenanthridines. DHPs were demonstrated to have the ability of serving as both SET reductants and alkylation reagents in the absence of photocatalyst and additional oxidants. Importantly, DHPs, which are normally water-insensitive and easily accessible from aldehydes, eliminate the drawbacks associated with organic metal compounds as nucleophilic alkylation reagents in preparation of complex amines.[29] The mild reaction conditions developed in this study will enable the semisynthesis of complex and biologically active natural 6-substituted dihydrobenzophenanthridine alkaloids from medicinal plants.

EXPERIMENTAL SECTION

General Experimental Procedures. Column chromatography silica gel (200−300 mesh) and TLC plates were purchased from Qingdao Meijin Chemical Inc. (Qingdao; China); HRMS data were obtained in the ESI mode on an Agilent 6530 Q-TOF/MS system. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer, and chemical shifts were given in *δ* with TMS as an

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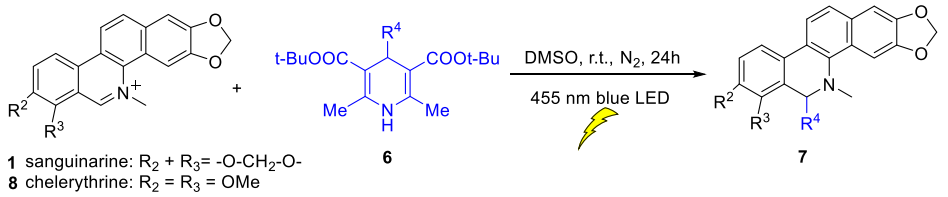
Table 2. Scope of 1,4-Dihydropyridines[a]



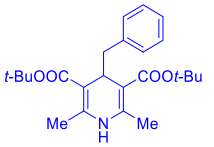
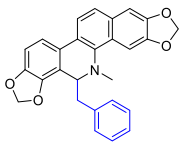
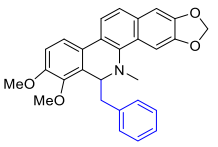
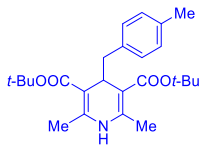
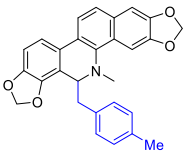
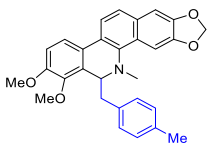
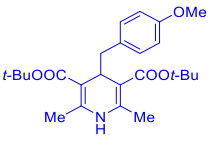
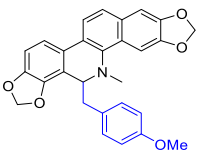
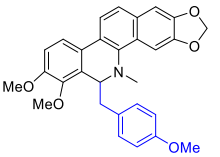
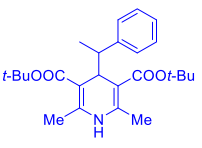
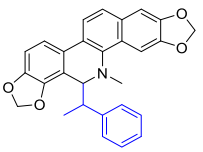
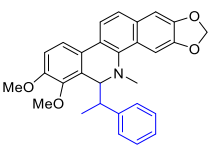
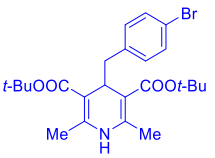
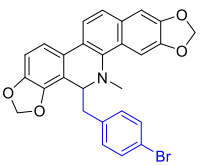
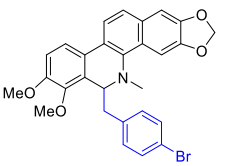
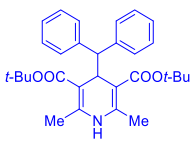
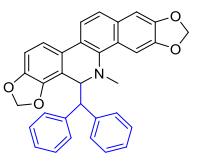
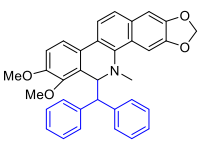
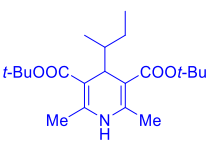
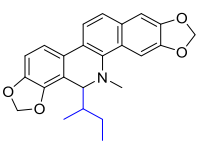
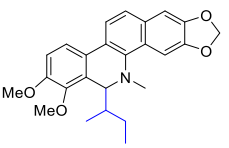
substrates **6**	products **7**[b]	
 **6a**	 **7a** 64%	 **7aa** 63%
 **6b**	 **7b** 64%	 **7bb** 67%
 **6c**	 **7c** 56%	 **7cc** 71%
 **6d**	 **7d** 67%	 **7dd** 63%
 **6e**	 **7e** 42%	 **7ee** 61%
 **6f**	 **7f** 23%	 **7ff** trace
 **6g**	 **7g** 35%	 **7gg** 80%

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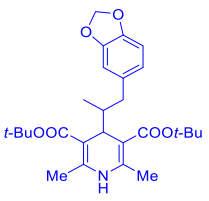
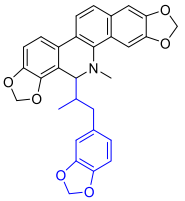
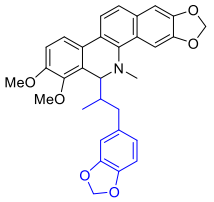
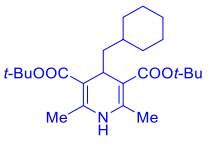
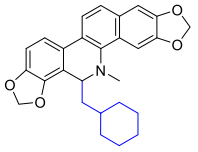
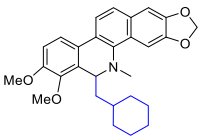
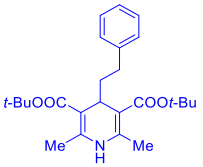
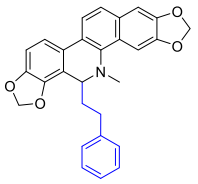
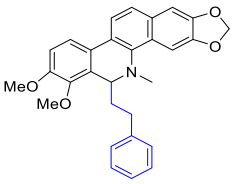
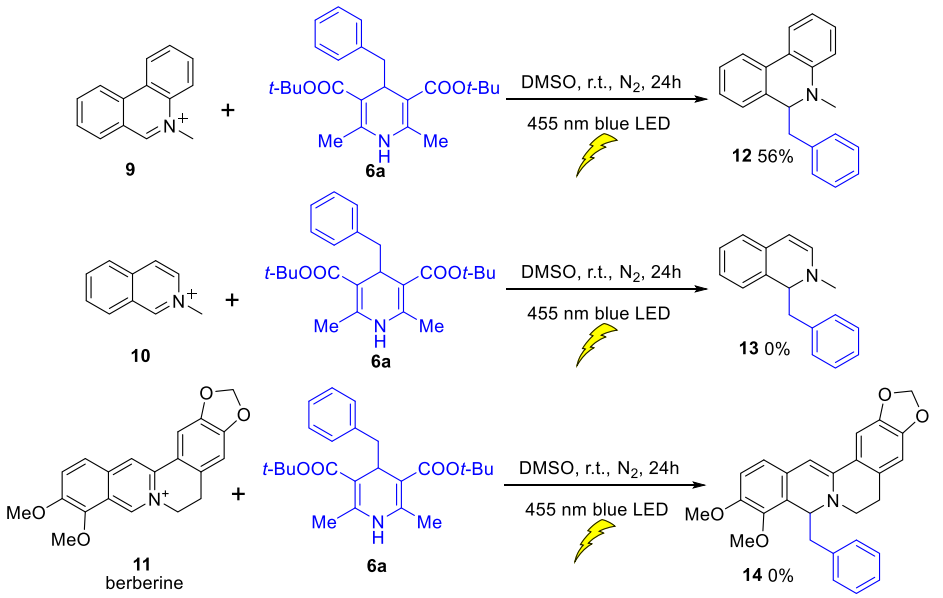
Table 2. continued

substrates **6**	products **7**[b]	
 **6h**	 **7h** 37%	 **7hh** 49%
 **6i**	 **7i** 0%	 **7ii** 0%
 **6j**	 **7j** 0%	 **7jj** 0%

[a]Experiments were performed with **1** or **8** (0.2 mmol), **6** (2.0 equiv), and DMSO (2 mL) under an atmosphere of N_2 under the irradiation of 455 nm blue light. [b]Isolated yields.

Scheme 3. Further Screening of Iminium Salts



internal reference. Sanguinarine (**1**) and chelerythrine (**8**) were isolated from *Macleaya cordata* in our lab.[30] Cyclic voltammetry measurements were done on a CHI 660E electrochemical workstation (Chenhua, Shanghai, China) using a glassy carbon electrode as working electrode and a graphite rod as counter electrode. A saturated calomel electrode (SCE) was used as reference electrode, and a 0.1 M solution of tetrabutylammonium tetrafluoroborate was applied as supporting electrolyte. The scan rate was set to 100 mV/s. The applied solvents are specified in the descriptions of the corresponding experiments. Absorption spectra were obtained on a Shimadzu UV-1280 UV/vis spectrometer. All spectra were recorded in DMSO (5 μM) in a 1 cm quartz cuvette. Fluorescence spectra were obtained with a Shimadzu RF-6000 spectrofluorophotometer in DMSO (5 μM) in 1 cm quartz cuvettes.

Procedure for Synthesis of 4-Alkyl DHPs 6. *t*-Butyl acetoacetate (3.16 g, 20 mmol) (or methyl acetoacetate and ethyl acetoacetate), aldehyde (10 mmol), ethanol (20 mL), and an ammonia aqueous solution (4.0 mL, 28%, 60 mmol) were added to a 50 mL flask equipped with a condenser. The mixture was heated at 70 °C for 8 h and then allowed to cool to room temperature. The reaction solution was concentrated under reduced pressure. A 50 mL amount of H_2O was added to the concentrated residue, and the

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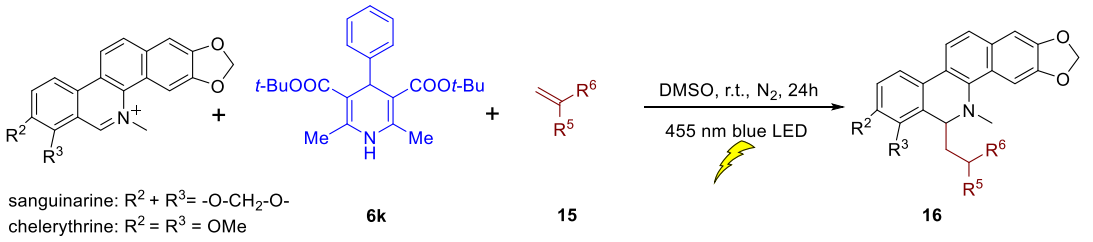
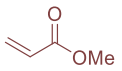
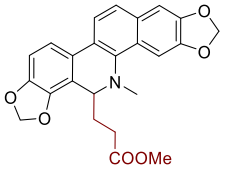
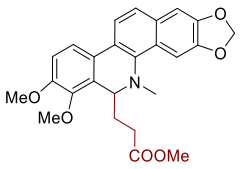
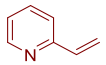
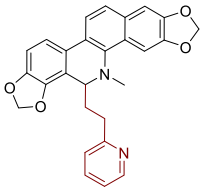
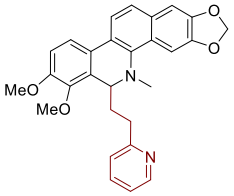
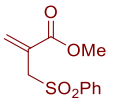
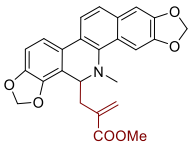
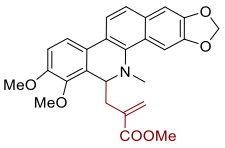
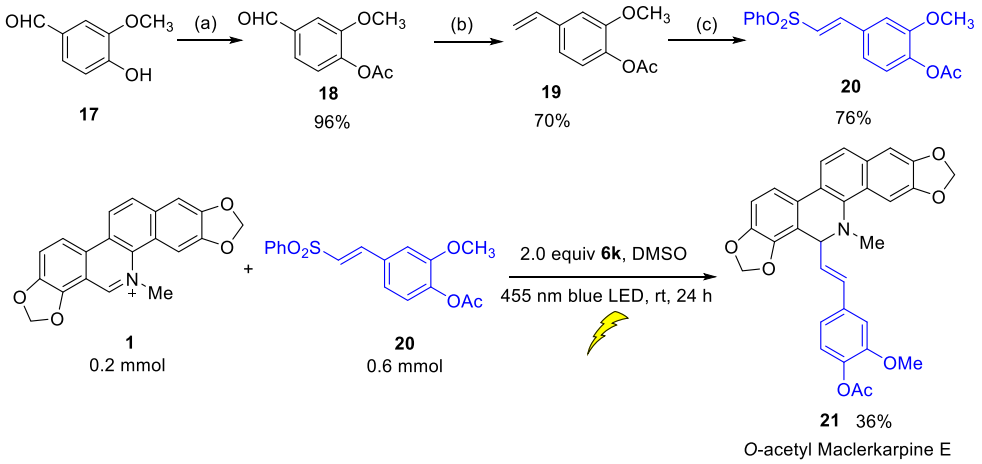
Table 3. 4-Phenyl DHP-Mediated Reductive Addition Reactions[a]



Alkenes **15**	Products **16** [b]	
 **15a**	 **16a** 55%	 **16aa** 47%
 **15b**	 **16b** 30%	 **16bb** 33%
 **15c**	 **16c** 60%	 **16cc** 62%

[a]Experiments were performed with **1** or **8** (0.2 mmol), **6k** (2 equiv), **15** (3.0 equiv), and DMSO (2 mL) under an atmosphere of N_2 under the irradiation of 455 nm blue light. [b]Isolated yields.

Scheme 4[a]



[a]Reaction conditions: (a) 6.0 equiv of Ac_2O, pyridine, rt, 12 h; (b) 1.5 equiv of CH_3PPh_3Br, 2.0 equiv of K_2CO_3, THF, reflux 4 h; (c) 3.0 equiv of $PhSO_2Na$, 1.5 equiv of NaOAc, 1.5 equiv of I_2, MeCN reflux 1 h.

aqueous layer was subsequently extracted with CH_2Cl_2 (50 mL) three times. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with PE/EA (10:1 v/v) to give 4-alkyl DHPs **6**.

Procedure for Synthesis of 6-Substituted Dihydrobenzophenanthridines 7. A Schlenk tube equipped with a magnetic stir

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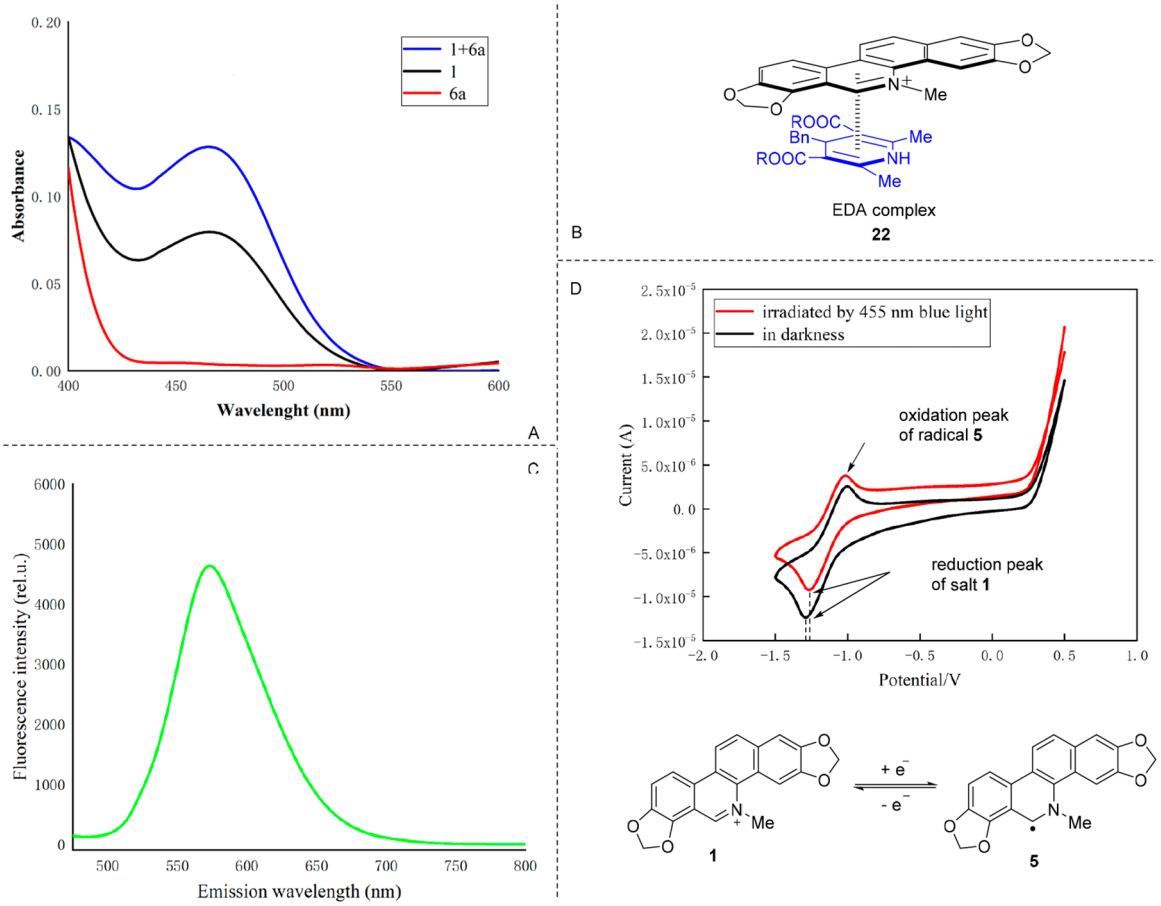
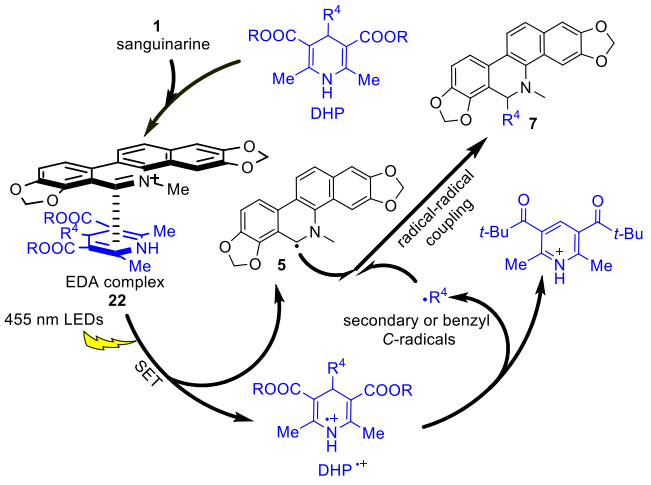
Scheme 5. (A) Optical Absorption Spectra of Sanguinarine (1), 6a, and the Combination Solution of 1 and 6a in DMSO (5 μM); (B) EDA Complex 17; (C) Emission Spectra of Sanguinarine upon Excitation at 455 nm in DMSO (5 μM); (D) Cyclic Voltammogram of Sanguinarine (1) and the Related SET Redox Procedure



Scheme 6. Putative Mechanism for Reductive Alkylation of Quaternary Benzophenanthridines



bar (Figure S3) was charged with 0.2 mmol of quaternary benzophenanthridine **1** or **8**, 2.0 equiv of a 6-substituted DHP **6**, and 2 mL of DMSO under a N_2 atmosphere. The flask was sealed by a plastic screw-cap with a Teflon-sealed inlet for a glass rod. A high-power LED (λ = 455 nm) was attached to the top of the glass rod, which then could act as an optical fiber. After irradiation at room temperature for 24 h, the LED was removed, and the solvent was poured in 20 mL of H_2O and extracted with 20 mL of EtOAc three times. The combined organic layer was then washed with 20 mL of H_2O three times and evaporated, to give a crude product, which was purified by silica gel chromatography and eluted with PE/EA to give target compounds **7**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.1c00512.

HPLC-HR-MS spectra of blue-light-promoted reduction of sanguinarine by NADH, HPLC-HR-MS spectra of blue-light-promoted reduction of sanguinarine **6j**, photoreactor and general procedure for photoreaction, and ^1H and ^{13}C NMR data and spectra of compounds **7**, **12**, and **16**−**21** (PDF)

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#L.W. and X.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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