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Total Synthesis of Zephycarinatines via Photocatalytic Reductive Radical *ipso*-Cyclization

Haruka Takeuchi, Shinsuke Inuki,* Kohei Nakagawa, Takaaki Kawabe, Atsuhiko Ichimura, Shinya Oishi, and Hiroaki Ohno*
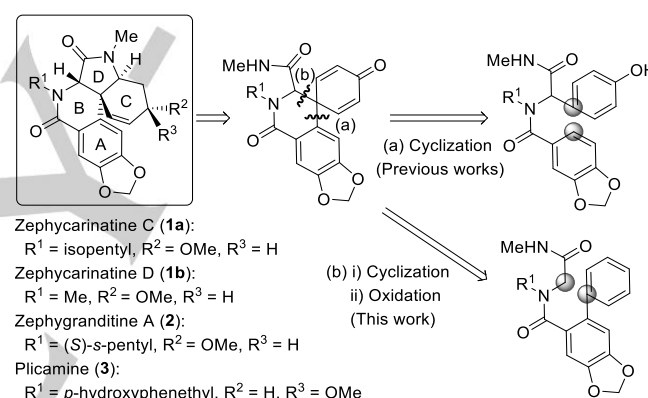
Abstract: We report herein a nonbiomimetic strategy for the total synthesis of the plicamine-type alkaloids, zephycarinatines C and D. The key feature of the synthesis was the stereoselective reductive radical *ipso*-cyclization using visible-light-mediated photoredox catalysis. This cyclization enabled the construction of a 6,6-spirocyclic core structure by the addition of the carbon-centered radical onto the aromatic ring. The biological evaluation of zephycarinatines and their derivatives revealed that the synthetic derivative having a keto group displayed moderate inhibitory activity against LPS-induced NO production. This approach would offer future opportunities to expand the chemical diversity derived from plicamine-type alkaloids as well as provide useful intermediates for their syntheses.

Introduction

Amaryllidaceae alkaloids are structurally diverse natural products possessing various biological activities.[1] Zephycarinatines (**1**) were isolated from *Zephyranthes carinata* Herbert (Amaryllidaceae) by Yao *et al.* in 2017 (Scheme 1).[2] Their structure is classified as a plicamine-type alkaloid that has a 6,6-spirocyclic core structure with multiple stereogenic centers. As a structural analog, zephygranditines including zephygranditine A (**2**) have been reported (Scheme 1). Some of the plicamine-type alkaloids and their derivatives show important biological activities. For example, zephygranditines exhibit cytotoxic properties against a variety of cancer cell lines, and anti-inflammatory activities according to the inhibitory effects on LPS-induced NO production.[3] In contrast, the detailed biological activities of zephycarinatines (**1**) have not been reported.

Owing to their biological importance and structural appeal, these alkaloids have been the target of many synthetic studies.[1a, 1c] Whereas the total syntheses of zephycarinatines (**1**) have not been accomplished, some groups have reported the total synthesis of plicamine (**3**),[4] which has a *p*-hydroxyphenethyl group on the nitrogen atom in the B-ring and a methoxy group on the C-ring with the opposite configuration to the zephycarinatines. One of the keys to the synthesis of zephycarinatines is the construction of a quaternary carbon in the center of the core scaffold. In the reported total synthesis of plicamine (**3**), its quaternary carbon center was formed by an intramolecular oxidative coupling reaction between electron-rich aromatic rings

(Scheme 1, route a),[4] which is similar to how it is formed from knowledge of its biosynthetic pathway.[1] As part of an ongoing program toward the synthesis of biologically active alkaloids,[5] we designed a nonbiomimetic synthetic strategy for zephycarinatines C (**1a**) and D (**1b**) through the creation of a quaternary carbon via a different manner from the biosynthesis (nonbiomimetic route; route b),[6] which would possibly expand their analog diversity. To achieve this purpose, we planned a photocatalytic reductive radical *ipso*-cyclization onto the aromatic rings as the key reaction, enabling direct access to the 6,6-spirocyclic core structure of the zephycarinatines (**1**).

Zephycarinatine C (**1a**):
R[1] = isopentyl, R[2] = OMe, R[3] = H
Zephycarinatine D (**1b**):
R[1] = Me, R[2] = OMe, R[3] = H
Zephygranditine A (**2**):
R[1] = (*S*)-*s*-pentyl, R[2] = OMe, R[3] = H
Plicamine (**3**):
R[1] = *p*-hydroxyphenethyl, R[2] = H, R[3] = OMe

Scheme 1. Structures of Zephycarinatine, Zephygranditine and Plicamine, and Strategy for the Synthesis of Zephycarinatines
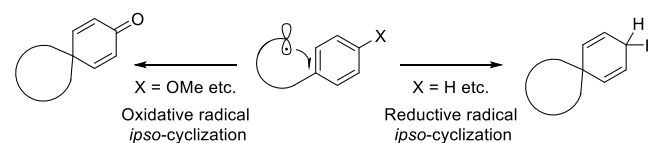

Scheme 2. Oxidative and Reductive Radical *ipso*-Cyclization

The radical *ipso*-cyclization, classfied as either an oxidative or a reductive type, has emerged as an attractive tool for the synthesis of spirocycles (Scheme 2).[7] Various useful methods have been reported for the oxidative cyclization,[7] which is represented by Curran's work involving the cyclization of an aryl radical at the *ipso*-position of a *p*-O-aryl-substituted benzamide.[8] By comparison, research into reductive radical *ipso*-cyclization is relatively limited.[9] Our group developed a samarium(II)-mediated reductive *ipso*-cyclization via an intramolecular ketyl radical addition onto aromatic rings.[9d, 9e] During the course of this study, Yoshimi *et al.* reported an intramolecular *ipso*-cyclization through photoinduced electron transfer-promoted decarboxylation of amino acid derivatives bearing an *N*-(2-phenyl)benzoyl group.[9h] More recently, Jui developed a photocatalytic dearomative

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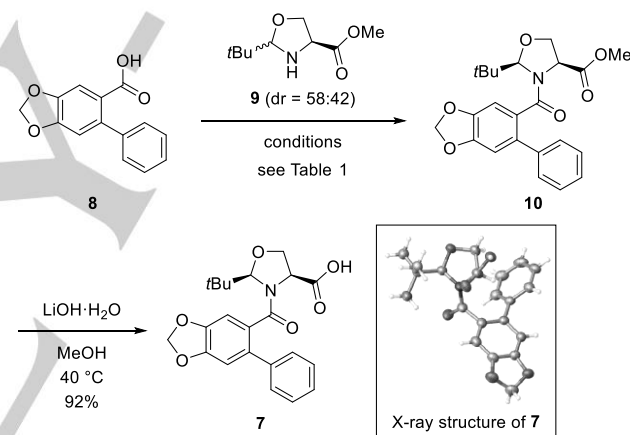
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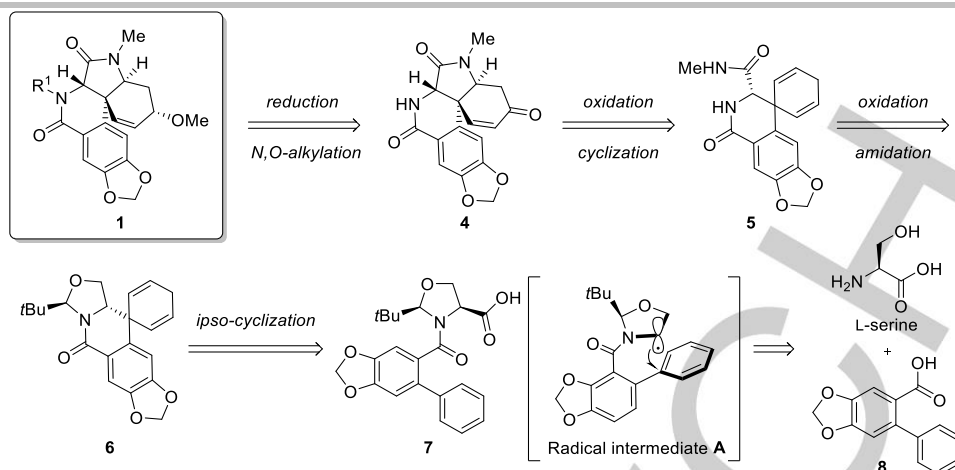
Scheme 3. Retrosynthetic Analysis of Zephycarinatines

hydroarylation triggered by an aryl halide reduction.[9j] However, despite their utility, their application to total synthesis still remains a challenge, presumably because of the difficulty in carrying out stereoselective *ipso*-cyclization using substrates congested with functional groups.

We focused on visible-light-mediated decarboxylation of amino acid derivatives for stereoselective *ipso*-cyclization. The initial carbon radical generation required for cyclization can be conducted under mild conditions, only irradiation with an LED lamp.[10] This approach should facilitate the synthesis of plicamine-type alkaloids and their analogs featuring substantial structural and/or electronic variation, because the key radical cyclization would likely not be limited only to those requiring highly electron-rich and *p*-nucleophilic species. In this paper, the total synthesis of zephycarinatines C and D via nonbiomimetic visible-light-mediated *ipso*-cyclization is described. Evaluation of their inhibitory activity against NO production is also presented.

Results and Discussion

The retrosynthetic strategy for achieving zephycarinatines (**1**) is illustrated in Scheme 3. We planned to introduce the R^1 group (nitrogen substituent) at the last stage of the synthetic route to allow synthesis of a variety of analogs having substituents on the amide nitrogen. We posited that the methoxy group would be derived from the carbonyl group of **4**. The precursor **4** was envisaged to result from the oxidation of the 1,4-diene and subsequent 1,4-addition reaction of the amide **5**. The amide **5** could be obtained by functionalization of the hemiaminal **6**, including aminal deprotection, oxidation, and amide formation with methylamine. We expected that the hemiaminal **6** could be constructed through the visible-light-mediated radical *ipso*-cyclization of carboxylic acid **7**. This disconnection represented the major synthetic challenge in this synthetic route, requiring a stereoselective *ipso*-cyclization of the α-amino carbon radical intermediate **A** generated by the CO_2-extrusion of the carboxyl radical. For this purpose, we designed the oxazolidine substrate **7** having the potential to control the chiral center at the α-position, referring to the self-regeneration of stereocenters (SRS) principle developed by Seebach *et al.*[11] The substrate **7** would be

prepared from L-serine and biphenyl carboxylic acid **8** as starting materials.

Scheme 4. Synthesis of the Key Precursor **7**.

Table 1. Investigation of the Coupling Reaction between **8** and **9**

Entry	Condition	Yield of **10** (%)[a][b]	dr[c]
1	**8**, **9**, EDC, HOBt, CH_2Cl_2, rt	ND	
2	**8**, $SOCl_2$, DMF, CH_2Cl_2 then **9**, $NaHCO_3$, THF/H_2O, 60 °C	ND	
3	**8**, Et_3N, MsCl, CH_2Cl_2 then **9**, 0 °C to rt	22	
4	**8**, **9**, Et_3N, CH_2Cl_2 then MsCl, 0 °C to rt	66	>99:1
5	**8**, **9**, Et_3N, CH_2Cl_2 then Ms_2O, 0 °C to rt	46	>99:1
6	**8**, **9**, Et_3N, CH_2Cl_2 then *i*BuOCOCl, 0 °C to rt	ND	

[a] Isolated yields. [b] ND = not detected. [c] Determined by ^1H NMR analysis.

Our preparation of the key precursor **7** for the radical *ipso*-cyclization reaction is shown in Scheme 4 and Table 1. Initially, we investigated the coupling reaction between the known oxazolidine **9**[12] derived from L-serine and the biphenyl-2-carboxylic acid derivative **8**.[13] The reaction using conventional

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coupling reagents for the amide bond formation, such as EDC, did not produce the amide **10** (Table 1, entry 1). When the corresponding acid chloride prepared from **8** was used, the desired product was not observed (entry 2). Macherla *et al.* reported the MsCl-mediated coupling reaction of the oxazolidine **9** with an aliphatic carboxylic acid derivative.[14] Following the literature procedure, the oxazolidine **9** was added to the reaction mixture of the carboxylic acid **8** and MsCl to provide the desired product **10** in low yield (22%, entry 3). After further examination, we found that the addition of MsCl to the mixture of substrates **8**, **9**, and Et_3N afforded the oxazolidine **10** in 66% yield as a single diastereomer (entry 4). The preferential production of *cis*-**10** could be rationalized by the selective acylation of the *cis*-oxazolidine **9**, resulting from the steric difference between the equiblated *cis*- and *trans*-isomers of **9** via a ring-opened intermediate.[15] The reaction under these conditions proceeded with sufficient reproducibility at a multi-gram scale. Changing MsCl to Ms_2O or *i*BuOCOCl was not effective (entries 5 and 6). Subsequently, treatment of the ester **10** with $LiOH·H_2O$ furnished the key carboxylic acid **7** (Scheme 4). The relative configuration of **7**[16] was confirmed by X-ray crystallography.

Table 2. Investigation of the Reductive Radical *ipso*-Cyclization of **7**
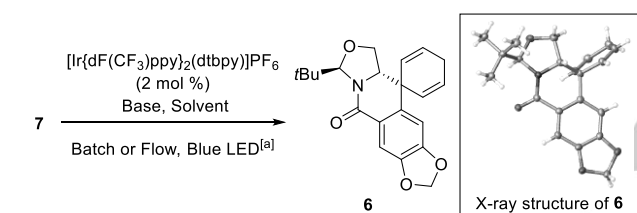
Entry	Process	Base	Solvent	Time (h)[b]	Yield (%)[c][d]
1	Batch	K_2CO_3	DMF	24	trace
2	Batch	K_2CO_3	THF	24	ND
3	Batch	K_2CO_3	CH_2Cl_2	24	ND
4	Batch	K_2CO_3	MeCN	24	32
5	Batch	Cs_2CO_3	MeCN	24	26
6	Batch	Na_2CO_3	MeCN	24	trace
7[e]	Batch	K_2CO_3	MeCN	24	58
8[e]	Batch	K_2CO_3	MeCN/H_2O (10/1)	24	31
9[e]	Batch	TMG	MeCN	24	31
10	Flow	K_2CO_3	MeCN/H_2O (10/1)	2	22
11	Flow	TMG	MeCN	2	40
12	Flow	TMG	MeCN	4	48

[a] The reaction was carried out with irradiation from a 40 W blue LED light using an EvoluChem™ PhotoRedOx Box. [b] In the cases of a flow reaction, the residence time is shown. [c] Isolated yields. [d] ND = not detected. [e] 40 W blue LED (× 2) were used instead of an EvoluChem™. dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. TMG = 1,1,3,3-tetramethylguanidine

Next, we examined the key radical *ipso*-cyclization reaction (Table 2). Reactions were carried out under irradiation with a 40

W LED bulb using an EvoluChem™ PhotoRedOx Box (Figure S1). Treatment of **7** with K_2CO_3 and [Ir{dF(CF₃)ppy}₂(dtbpy)]PF₆ as a photoredox catalyst in DMF under irradiation with visible-light (the known condition for generating a radical intermediate from a carboxylic acid)[10c] gave a trace amount of the desired product **6** (entry 1). Changing the solvent from DMF to THF or CH_2Cl_2 did not enhance the yield of **6** (entries 2 and 3). When MeCN was used as the reaction solvent, the desired spiro-compound **6** was obtained in 32% yield as a single diastereomer (entry 4). The relative configuration of **6**[16] was determined by X-ray crystallography, indicating that the *ipso*-cyclization occurred from the sterically less hindered face opposite to the *t*Bu group as expected. The use of Cs_2CO_3 or Na_2CO_3 decreased the yield of **6** (entries 5 and 6). Further optimization revealed that when the reaction was carried out using two 40 W LED bulbs directly irradiating the reaction vessel (Figure S2), the desired product **6** was afforded in 58% yield (entry 7). The reaction was amenable to operation on 300 mg scale to furnish the spiro-compound **6** in 40% isolated yield. We next focused on optimizing the reaction using a continuous flow reactor that allowed for efficient conversion, mainly by improving the irradiation efficiency of the reaction mixture compared with batch processing (Figure S3).[17] The optimized condition (entry 7) was not suitable for use in flow reactors because the inorganic base was not completely soluble in MeCN. Thus, we examined conditions that provide a homogeneous reaction mixture. When a mixed solvent of MeCN/H_2O (10:1) was used, a clear reaction mixture was formed but the yields of **6** decreased to 31% (entry 8). Using a soluble base such as TMG instead of K_2CO_3 provided the desired product **6** in 31% yield. These homogeneous conditions were applied to continuous flow chemistry (Figure S3). The flow reactions with a 2 h residence time provided **6** in low to moderate yields (entries 10 and 11), while increasing the residence time to 4 h enhanced the yield to 48% (entry 12). These results would contribute to the development of further scale-up synthesis.

With the core spiro-scaffold in hand, we turned our attention to the construction of the D-ring of zephycarinatine (Scheme 5). The hemiaminal **6** was converted to the corresponding alcohol in the presence of TsOH. The oxidation of the alcohol with AZADOL[18] gave the carboxylic acid, which was treated with methylamine and EDC to afford the *N*-methyl amide **5** in 64% yield in two steps. Our investigation into the oxidation of the 1,4-diene is summarized in Table 3. Referring to previous reports, we attempted the oxidation using several oxidants such as *t*BuOOH/PDC,[19] MnO_2[20] and DDQ,[21] which did not afford the desired product (entries 1−3). On the other hand, the oxidation with catalytic tetrapropylammonium perruthenate (TPAP)[22] provided the desired cyclic product **4** as a sole diastereomer through the oxidation of 1,4-diene followed by intramolecular 1,4-addition of the *N*-methyl amide (entry 4). When the reaction was carried out at room temperature, the imine was observed as the overoxidation side product. Several investigations revealed that the desired product **4** was produced in 70% yield by careful control of the reaction temperature (entry 5). After confirming the completion of the oxidation of the 1,4-diene at −20 °C, the reaction temperature was increased to 0 °C to furnish the 1,4-addition to the α,β-unsaturated ketone under a near-neutral condition. The relative configuration of **4**[16] was determined by X-ray crystallography. In Ley's synthesis of plicamine,[4a, 4b] the D-ring formation was accomplished via a stereoselective 1,4-addition under an acidic condition. In contrast, Miranda *et al.* reported that

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a base-mediated 1,4-addition of various related substrates proceeded with relatively low diastereoselectivity.[4c] These findings implied that the selectivity for D-ring formation through 1,4-addition could depend mainly on the reaction condition, rather than the substrate structure.
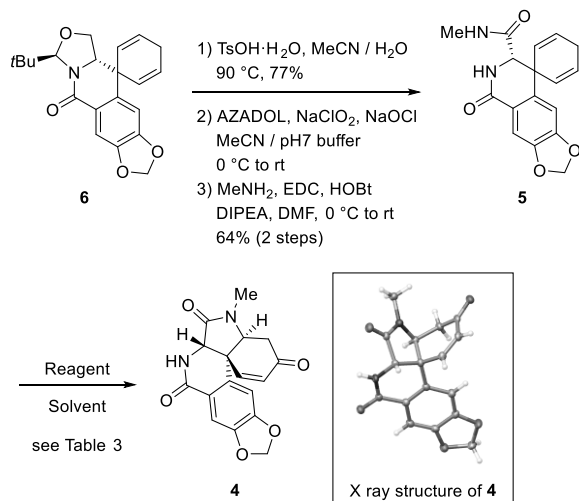
**Scheme 5.** Synthesis of the Ketone **4**

Table 3. Optimization of the Oxidation of 1,4-Diene **5**

| Entry	Reagent	Solvent	Temp. (°C)	Yield (%)[a][b]
1	tBuOOH, PDC	DMF	rt	ND
2	MnO$_2$	CH$_2$Cl$_2$	rt	ND
3	DDQ	THF	0 to rt	ND
4	NMO, TPAP	MeCN	rt	50
5	NMO, TPAP	MeCN	−20 to 0	70

[a] Isolated yield. [b] ND = not detected.

We next focused on the total syntheses of zephycarinatines C and D (Scheme 6). The synthesis commenced with the conversion of the carbonyl group to the methoxy group. Although initial attempts to reduce the carbonyl group by employing NaBH$_4$/CeCl$_3$ or DIBAL-H failed, treatment of **4** with LiAlH$_4$ allowed the 1,2-reduction of the carbonyl group to provide the alcohol **11** in 78% yield as a single diastereomer. Without determining the relative configuration, the alcohol **11** was converted into the corresponding *N,O*-dimethylated product **12** by treatment of NaH and MeI in DMF. Unfortunately, the NMR spectral data of **12** did not agree with those of natural zephycarinatine D. NOESY correlation revealed that **12** possessed the H$_3$/H$_{4a}$-syn relative stereochemistry.[23] Additionally, the observed H$_3$-H$_{4α}$ (J = 10.3 Hz) and H$_{4a}$-H$_{4α}$ (J = 12.6 Hz) coupling constants established the pseudo-axial orientation of H$_3$ and H$_{4a}$. These observations indicated that the LiAlH$_4$-reduction proceeded from the side of the benzene ring of **4** to give the precursor **11** of *epi*-zephycarinatine D (**12**). We next attempted to introduce the methoxy group to the C3 position via stereoinversion. Ley *et al.* reported that in the total synthesis of obliquine (a plicamine analog), the introduction of the methoxy group was accomplished through the nucleophilic attack of MeOH

to the mesylate prepared from the corresponding alcohol and MsCl.[24] Thus, we conducted the reaction of the alcohol **11** with MsCl and Et$_3$N. Unfortunately, the undesired chloride was obtained without producing the corresponding mesylate, probably because of the substitution of chloride derived from MsCl. Instead, mesylation of **11** with Ms$_2$O followed by treatment with MeOH was investigated, resulting in successful incorporation of the methoxy group with stereoinversion. Without purification, the subsequent *N*-alkylation with isopentyl bromide and NaH completed the total synthesis of zephycarinatine C (**1a**) in 23% in three steps from **11** with recovery of the precursor **13** in 21% (29% brsm). By changing the electrophile to MeI, the total synthesis of zephycarinatine D (**1b**) was accomplished in 52% in three steps with a small amount of removable diene **14**. All the spectroscopic data were in agreement with those of the natural zephycarinatines C and D reported in the literature[2] {zephycarinatine C: [α]$^{26}_D$ +141 (*c* 0.060, MeOH); lit. [α]$_D$ +108 (c 0.14, MeOH), zephycarinatine D: [α]$^{26}_D$ +172 (*c* 0.15, MeOH); lit. [α]$_D$ +176 (c 0.1, MeOH)}.
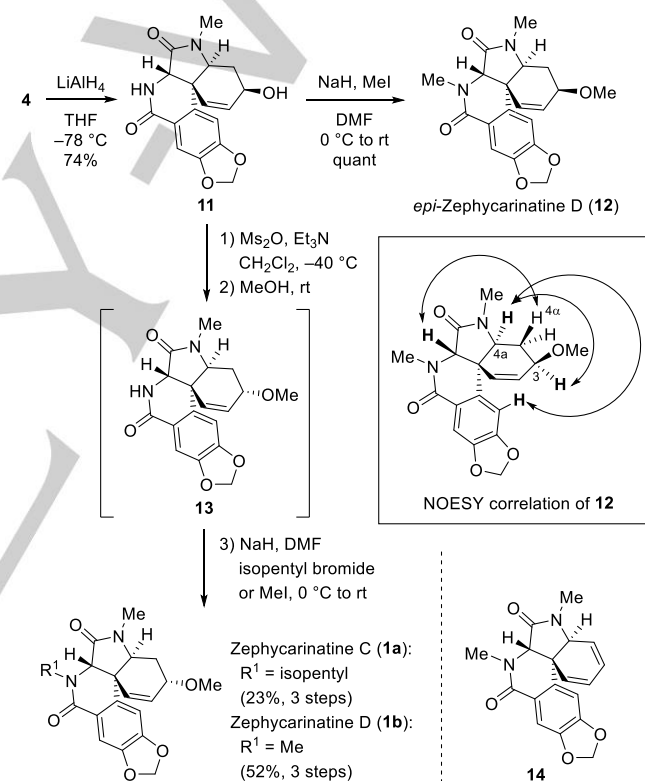
Scheme 6. Total Synthesis of Zephycarinatines (**1**)
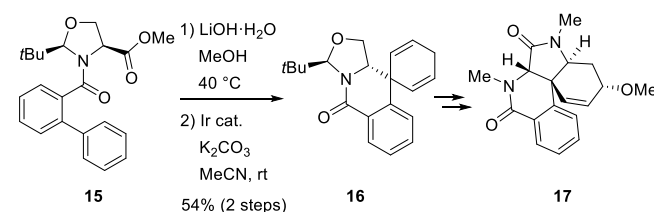
Scheme 7. Synthesis of Zephycarinatine Derivative **17**

With a facile method to synthesize the natural zephycarinatines in hand, we synthesized a derivative with a non-substituted A ring (Scheme 7 and S2). The zephycarinatine D

analog **17** lacking a methylenedioxy group was obtained in a similar manner. As expected, the key radical *ipso*-cyclization of the substrate without an electron donating group proceeded smoothly to provide the desired cyclization product **16** in 54% yield in two steps.

Finally, we evaluated the inhibitory activities of zephycarinatines C, D, and their synthetic derivatives on NO production by LPS-stimulated RAW264.7 cells (Figure 1).[3] Although the natural zephycarinatines C (**1a**) and D (**1b**) as well as their derivative **17** did not show significant inhibitory activities at 30 μM, the keto derivative **4** at 30 μM displayed a comparable level of activity to indomethacin at 100 μM (positive control). The derivative **4** exhibited dose-dependent inhibition of NO production (IC$_{50}$ = 65.3 μM, Figure 1b). No cytotoxicity was observed in the concentration range of 0.3–300 μM of **4** (data not shown).
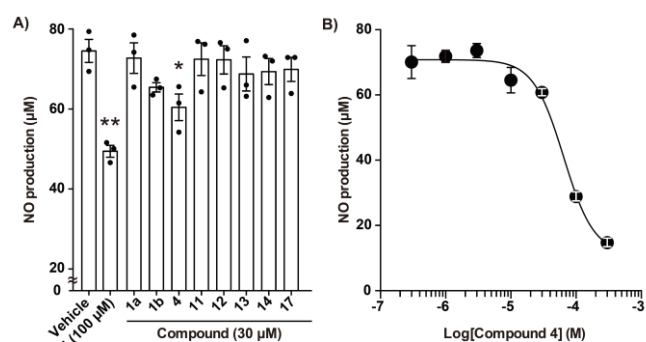

Figure 1. Inhibitory activity of eight compounds on NO production by LPS-stimulated RAW264.7 cells. A) Inhibitory activities of each compound. B) Dose-dependent inhibition of compound **4** on NO production by LPS-stimulated RAW264.7 cells. The data represent the mean ± SEM (n = 3 in each treatment, **p<0.01, *p<0.05 vs vehicle, one-way ANOVA and Dunnett's test). IM = indomethacin.

Conclusion

In conclusion, we accomplished the first total synthesis of zephycarinatines C and D starting from the known carboxylic acid **8** (2.1% and 4.7% overall yields, respectively, 11 steps). The synthesis highlights a nonbiomimetic strategy for the stereoselective construction of the B-ring based on photocatalytic reductive radical *ipso*-cyclization. The TPAP oxidation of 1,4-diene followed by intramolecular 1,4-addition allowed the construction of D-ring. We found that the keto derivative demonstrated moderate inhibitory activity against LPS-induced NO production. This strategy would contribute to expanding the chemical space of plicamine-type alkaloids that is normally inaccessible using biomimetic approaches.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloid • natural products • photocatalyst • radical *ipso*-cyclization • total synthesis

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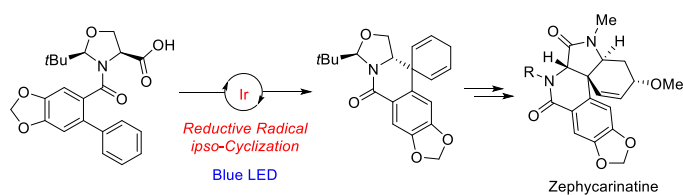
Total synthesis of the plicamine-type alkaloids, zephycarinatine C and D, has been achieved. The key feature of the synthesis was the stereoselective radical *ipso*-cyclization using visible-light-mediated photoredox catalysis. The evaluation of zephycarinatines and their derivatives revealed that a synthetic derivative displayed moderate inhibitory activity against LPS-induced NO production.