JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01424 • Publication Date (Web): 21 Jul 2018

Just Accepted

ACS Publications

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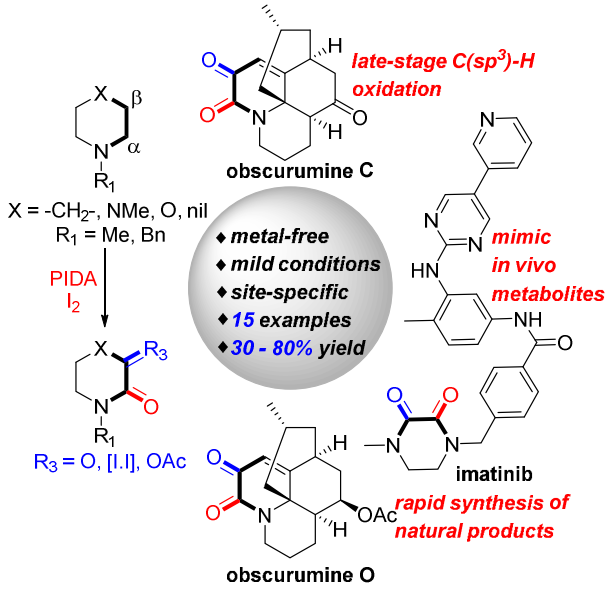
PIDA/I_2-Mediated α- and β-C(sp^3)-H Bonds Dual Functionalization of Tertiary Amines.

Yu Zhu,[†,‡,§] Li-Dong Shao,[†,§] Zhen-Tao Deng,[†,‡] Ying Bao,[†,‡] Xin Shi,[†,‡] and Qin-Shi Zhao[*,†]

[†]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, People's Republic of China

[‡]University of Chinese Academy of Sciences, Beijing 100049, People's Republic of China

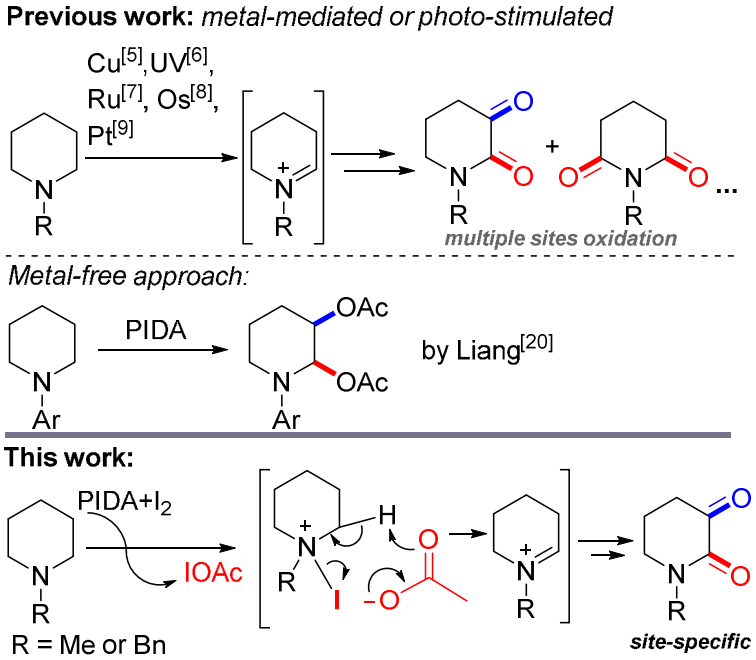

late-stage C(sp3)-H oxidation
obscurumine C
X = -CH2-, NMe, O, nil
R1 = Me, Bn
PIDA
I2
R3 = O, [I.I], OAc
♦ metal-free
♦ mild conditions
♦ site-specific
♦ 15 examples
♦ 30 - 80% yield
mimic in vivo metabolites
imatinib
rapid synthesis of natural products
obscurumine O

ABSTRACT: The α,β-C(sp^3)-H bonds dual functionalization of tertiary amines is still a challenging task for both organic and medicinal chemists. Herein, a direct, mild, metal-free, and site-specific method mediated by PIDA/I_2 was developed for α,β-C(sp^3)-H bonds dual functionalization of tertiary amines, and this method can provide facile access to α-keto lactams or rarely studied α,α-diiodo lactams. Moreover, this method was used for the effective syntheses of three natural products [obscurumine C (**13**), obscurumine O (**17**), and strychnocarpine (**18**)] and direct preparation of mimics of the *in vivo* metabolites of two FDA-approved drugs (imatinib and donepezil) in 36-60% overall yield. The method represents a promising protocol for the late-stage α,β-C(sp^3)-H bonds oxidative dual functionalization of tertiary amine-containing drugs and complex natural products.

INTRODUCTION

The functionalization of C(sp^3)-H bonds represents an important and long-standing goal in chemistry.[1] Such methods allow rapid, direct access to various C(sp^3)-functionalities from inert C(sp^3)-H bonds. In recent years, C(sp^3)-H bonds functionalization has been developed to an unprecedented level;[2] however, there are still limitations in the direct α,β-C(sp^3)-H bonds oxidative dual functionalization of tertiary amines because the nitrogen atom is more reactive than C(sp^3)-H bonds in various activated systems.[3] Tertiary amines are ubiquitous structural features in many biologically important natural alkaloids and FDA-approved drugs. The site-specific, oxidative dual functionalization of α,β-C(sp^3)-H bonds of tertiary amines is a priority for the late-stage modification of complex natural products and especially in the direct and scalable preparation of the *in vivo* metabolites of drugs that contained these moieties to further accelerate the drug development process.[4] Therefore, developing a method to oxidize C(sp^3)-H bonds of tertiary amines would be a powerful tool to facilitate the drug discovery and development process.[4a,5]

Scheme 1. α,β-C(sp^3)-H Oxidative dual functionalization of Tertiary amines..



To the best of our knowledge, photochemical conditions[6] and metal-catalyzed oxidations such as those with RuO_4,[7] OsO_4,[8] and Pt,[9] have been tested in the oxidation of the α,β-C(sp^3)-H of tertiary amines; however, most of them resulted in the formation of complex mixtures of by-products and poor yields (Scheme 1). Recently, Barry Touré and coworkers reported a Cu-mediated α,β-C(sp^3)-H oxidation of many *N*,*N*'-dialkyl piperazine-containing drugs in moderate yields.[5] Moreover, even for the simplest building block, piperidin-2,3-dione, it cannot be directly prepared from piperidine. Current routes, for

example from nicotinic acid,[10] 2,3-dihydroxypyridine,[11] enamino lactams,[12] corresponding lactams,[13] 2,2-dialkoxy-5-bromopentanoates,[14] corresponding thioacetals,[15] and (*Z*)-2-alkoxy-2- pentenoates,[16] have some shortcomings, and do not use readily available starting materials. Considering these cumbersome and multistep approaches, a more convenient, and especially a metal-free method, advance in the oxidation of *α,β*-C(sp^3)-H bonds of tertiary amines is highly desirable.

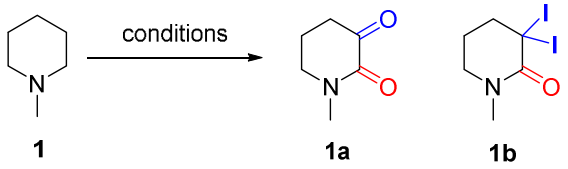
Hypervalent iodine reagents have attracted increasing attention and are a widely used promising strategy for the functionalization of C-H bond such as in the Suárez-modified Hofmann–Löffler–Freytag (HLF)[17] reaction, which uses a secondary amine to generate a cyclic amine under (diacetoxyiodo)benzene (PIDA) and I_2,[18] in the $Pd(OAc)_2$/PIDA/I_2 system reported by Yu et al.[19] for the *α*-C(sp^3)-H acetoxylation of *N*-Boc tertiary amides, and in the PIDA-promoted *α,β*-C(sp^3)-H diacetoxylation of the *N*-aryl piperidines reported by Liang et al.[20] (Scheme 1). Very recently, Antonchick and co-workers reported an effective *cis*-dihydroxylation of alkanes using the ArI/I_2/NaN_3/AcO_2H system.[21] However, PIDA/I_2-mediated *α,β*-C(sp^3)-H dual oxidations of tertiary amines have not been reported. Herein, we report a straightforward method for the *α,β*-C(sp^3)-H oxidative dual functionalization of tertiary amines using a PIDA/I_2 system.

RESULTS AND DISCUSSION

Given that cationic iodine (I^+) can promote reactions such as the Suárez-modified HLF reaction,[17,22] Pd-catalyzed *α*-C(sp^3)-H oxidations of amides,[19] electrophilic reactions of olefins,[23] and *α*-C(sp^3)-H oxidations of aromatic ketones,[24] we planned to activate the *α*-C(sp^3)-H bond of *N*-methyl piperidine (**1**) using PIDA/I_2, which could generate I^+ *in situ*.[22,23] Initially, **1** was treated with PIDA (2 equiv.) and I_2 (2 equiv.) in DCE, which provided **1b** in 15% (Table 1, entry 1). Attempts to repeat this transformation using other I^+ sources, like *N*-iodosuccinimide (NIS)，I_2/NaOH, and [bis(trifluoroacetoxy)iodo]benzene (PIFA)/I_2 or other oxidants were unsuccessful (for details, see Table S1, Supporting Information, SI). Therefore, PIDA/I_2 was selected as the final oxidant. By carefully investigating various reaction conditions (Table S2-6, SI), we found that the solvent and the amount of oxidant significantly influenced the reaction outcome (Table 1, entries 2-7). An increase in the yield of **1b** was observed using PIDA (2 equiv.) and I_2 (1 equiv.) (Table 1, entry 6). Similarly, the yield of **1a** could be improved using PIDA (3 equiv.) and I_2 (2 equiv.) (Table 1, entry 7). Most importantly, to our surprise, the type of functionalized product (*α,β*-O,O or *α,β*-O,[I,I]) could be controlled by switching the solvent from THF to DCE for simple piperidine substrates (*N*-methyl and *N*-benzyl piperidines), but failed to be compatible with other substrates. Other solvents were also screened, and among them, DCE and THF were found to be suitable for the reaction, while protic solvents like methanol and water were detrimental (Table S2, SI). In addition, inert gas protection (argon) (Table S4) and the addition of an

additive (Table S6) were not necessary. To our delight, using $Na_2S_2O_3$ (aq.) to quench the reaction provided a higher yield of the desired product (Table S5).

Table 1. Reaction Optimization



1 **1a** **1b**

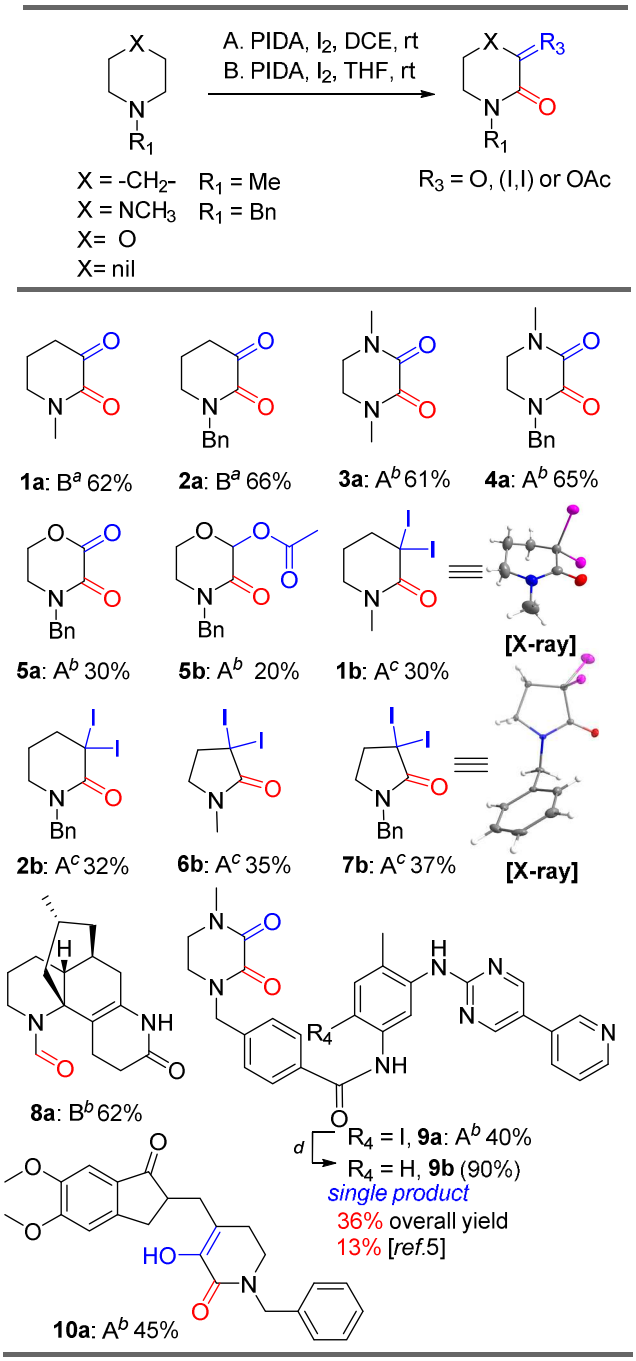
Entry	Oxidant (equiv.)	Solvent	Time (min)	product (yield)
1	PIDA+ I_2 (2:2)	DCE	180	**1b** 15%
2	PIDA+I_2 (4:2)	H_2O	180	NR [a]
3	PIDA+I_2 (4:2)	methanol	180	Complex[b]
4	PIDA+I_2 (4:2)	THF/H_2O (1:1)	180	NR [a]
5	PIDA+I_2 (2:1)	DCE	60	**1b** 20%
6	PIDA+I_2 (2:1)	DCE	30	**1b** 30%
7	PIDA+I_2 (3:2)	THF	90	**1a** 62%

[a] No reaction was detected; [b] Starting materials were decomposed.

With the optimized reaction conditions in hand, we proceeded to investigate the generality of this C-H bonds dual functionalization on different tertiary amines (Figure 1). Using *N*-benzyl piperidine (**2**), *N*,*N*'-dimethyl piperazine (**3**), and 1-benzyl-4-methyl piperazine (**4**) as substrates provided the corresponding *α*-keto lactams (**3a** and **4a**) in moderate yield; 4-benzyl morpholin (**5**) gave a mixture of the *α*-keto lactam (**5a**) and *α*-acetoxyl lactam (**5b**) in 50% yield. However, *N*-methyl or *N*-benzyl pyrroles did not give the corresponding *α*-keto lactam products probably due to the rigid pyrrole ring is hard to alleviate the high tension of the newly formed *α*-keto lactam. Notably, *N*-methyl or *N*-benzyl pyrroles and piperidines gave *α*,*α*-diiodo lactams **2b**, **6b**, and **7b**, which have not been reported before, and the structures of **1b** and **7b** were confirmed by X-ray crystallographic analysis. In addition, the reaction of *N*-benzyl piperidine (**2**) could be performed on a 0.5-g scale (0.02 M) in moderate yield (Table S7, SI). These results showed that the C-H bonds dual functionalization method can be generally applied to simple tertiary amines. We next tried to extend this method to complex molecules. Among the selected piperidine- or piperazine-containing natural products and drugs, *α*-Obscurine (**8**),[25] a *Lycopodium* alkaloid, was selectively converted to its *N*-formylated analog in 62% yield. We proposed this interesting selectivity of **8** could be resulted from the increased tension of piperidine ring by the *α*-quaternary carbon. Especially when the imine intermediate was formed, imidization of methyl group might be more easy than that of methylene group. In the case of imatinib (a medication for chronic myelogenous leukemia), the highly site-specific oxidation afforded *α*-keto lactam **9b** (36% overall yield after removal of aromatic iodine in **9a**) as the sole product, while a mixture of *N*-methyl, aromatic

methyl, and methene piperazine oxidative derivatives (13% yield) were detected from the Cu-catalyzed oxidation approach.[5] In addition, iodide **9a** could be further modified through a variety of coupling approaches to enrich the structural diversity of accessible pharmaceuticals. Moreover, the piperidine containing drug donepezil (a medication for Alzheimer's disease) was also transformed into *α*-ketolactam **10a** in 45% yield**,** which was stable at its enol form.

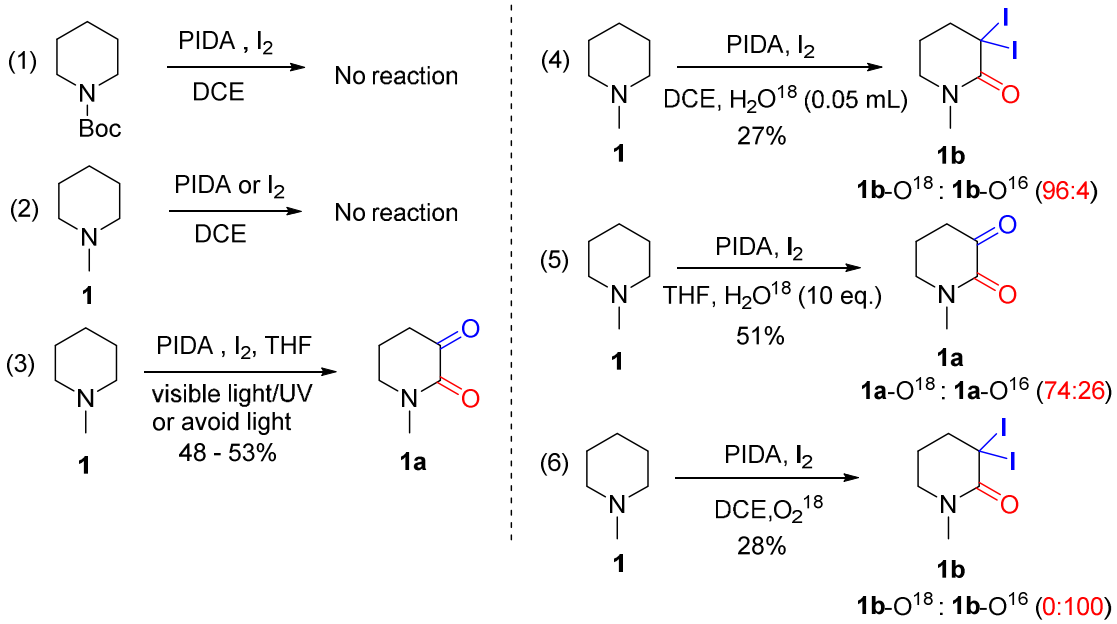
Figure 1. Substrate scope.



[a] PIDA (3 equiv.), I_2 (2 equiv.), rt; [b]PIDA (4 equiv.), I_2 (2 equiv.), rt; [c] PIDA (2 equiv.), I_2 (1 equiv.), rt; [d] Pd/C, H_2, AcOH.

To elucidate the reaction mechanism, several control experiments were conducted. First, no reaction was detected after exposure of *N*-Boc piperidine to PIDA/I_2, revealing the necessity of the free *N* lone pair of electrons (Scheme 2, equation 1). Using either PIDA or I_2 alone resulted in no reaction, which suggested an I^+-mediated pathway might be involved (Scheme 2, equation 2).[22,23] In addition, performing the oxidation under visible light (LED), under UV light or while full protected from light provided *α*-keto lactam **1a**, implying that the mechanism might not proceed through a radical approach like the HLF reaction (Scheme 2, equation 3; for details, see Table S8, SI). To determine the source of the oxygen in the products, H_2O^{18} and O_2^{18} were used (Scheme 2, equations 4-6).[26] According to the results, both **1a** and **1b** were labeled with one O^{18} atom when H_2O^{18} was used as the co-solvent[27] or to quench the reaction, and **1a** was not labled with two O^{18} atoms, and **1b** was not labeled with O^{18} when the reaction was conducted under an O_2^{18} atmosphere. The low yields of **1b** and other *α*,*α*-diiodo lactams (Figure 1, **2b**, **6b**, and **7b**) might be resulted from the high reactivity of I^+ and the instability of itself although it was detected as a single product by TLC after consumption of starting materials. These results suggested that the first oxygen on C2 might come from H_2O and the second oxygen on C3 might be from HOAc, it is clear that neither of them come from O_2 (Table S9, SI).

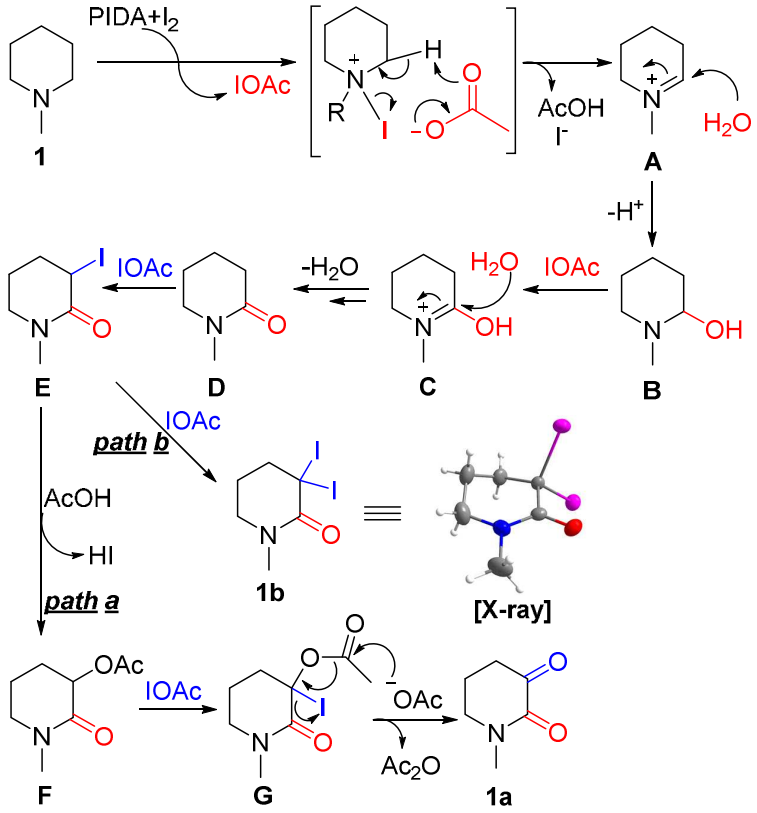
Scheme 2. Experiments for mechanism analysis.



A plausible mechanism is shown in scheme 3 using *N*-methyl piperidine (**1**) as a representative. Initially, compound **1** was transformed to iminium intermediate **A** through a dehydrogenation, which was promoted by the IOAc generated *in situ* from PIDA and I_2 (one equivalent of PIDA reacts with one equivalent of I_2 to provide two equivalent of IOAc)[22,23]. Highly reactive iminium **A** could then be attacked by H_2O (Table S9, SI) through a nucleophilic addition to provide *α*-hydroxy intermediate **B**.[26a]

These steps were repeated to form another reactive iminium **C**, which could be trapped by H_2O and then rapidly hydrolyzed to give lactam **D** (aryl iodinated lactam products were obtained with < 5% yields using 1-methyl-1,2,3,4-tetrahydroquinoline or 1-phenyl-1,2,3,4-tetrahydroquinoline as substrates, and the data was not shown). Lactam **D** was reacted with IOAc to give *α*-iodo lactam **E** (aryl iodinated *α*-iodo lactam products were obtained with < 5% yields using 1-methyl-1,2,3,4-tetrahydroquinoline or 1-phenyl-1,2,3,4-tetrahydroquinoline as substrates, and the data was not shown). From here, the reaction could proceed in two different ways. In path a, **E** could be reacted with AcOH to give *α*-acetoxyl ketolactam **F** (like compound **5b**). Similarly, **F** could be converted to *α*-iodide **G** by IOAc, which could further undergo deiodination in the presence of AcO^- to furnish **1a**. In path b, **E** likely reacted with IOAc to directly generate **1b**. The extremely obvious solvent factor of this transformation (THF *vs* DCE led to **1a** *vs* **1b**) might be resulted from the different lyolysis of **E** in THF and DCE, but we believe it is not only the solvent control but also other comprehensive factors such as substrate itself affected the reaction.

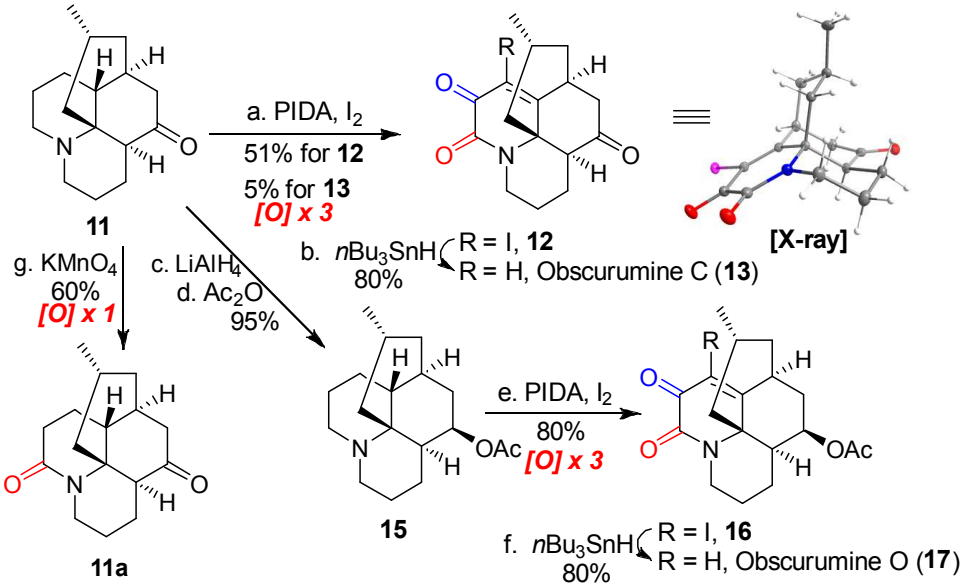
Scheme 3. Proposed mechanism.



Next, the robustness of this strategy was evaluated in the syntheses of *Lycopodium* alkaloids, obscurumine C (**13**)[28] and obscurumine O (**17**),[29] which are well-known for their unique 6/6/6/6 fused skeletons and 1,6-dihydropyridine-2,3-dione moieties. Biogenetically, these alkaloids might be derived from lycopodine (**11**) *via* the action of oxidase. Interestingly, treating **11** with PIDA/I_2 afforded iodo

ketolactam **12** in 51% yield and the natural product obscurumine C (**13**) in 5% yield, which was generated through three oxidations including *N*-α, β, γ sites in one step (Scheme 4). As a comparison, only one oxidation was achieved to form **11a** using $KMnO_4$.[30] Then, the iodine was removed using AIBN and nBu$_3$SnH to afford **13** in 80% yield (46% overall yield). A similar approach was effectively used in the synthesis of obscurumine O (**17**), which inhibits IL-2 production with an IC_{50} of 17.2 μM.[29] Consequently, starting from **11**, reduction of the carbonyl group using $LiAlH_4$ followed by acetylation (Ac_2O/DMAP, pyridine) provided **15** in 95% yield over two steps. For full consumption of starting materials, subsequent PIDA/I_2 oxidation of **15** was performed at a higher temperature (80 °C) to give product **16**, followed by removal of the iodine to yield **17** (64% in two steps). Moreover, using the developed method, we improved a facile entry to β-carboline motifs starting from commercially available *N*-methyl piperidine and *N*-benzyl piperidine. Strychnocarpine (**18**)[11] is a tetrahydro-β-carboline alkaloid first isolated from strychnos species in 1980,[31] and it is well-known for its hallucinogenic properties as it exhibits a high affinity for the peripheral type of benzodiazepine receptors in rat brain (IC_{50} = 30 μM).[32] Many synthetic approaches to **18** have been achieved.[11,33] However, these approaches require multiple steps and complicated metal-catalyzed systems. In this study, treatment of **1a** or **2a** with phenyl hydrazine in the presence of formic acid resulted in **18** or **19** (54% overall yield) *via* a Fischer indole reaction.[34] By this facile procedure, various derivatives of β-carboline alkaloids can be prepared for pharmacological screening (Scheme 5).

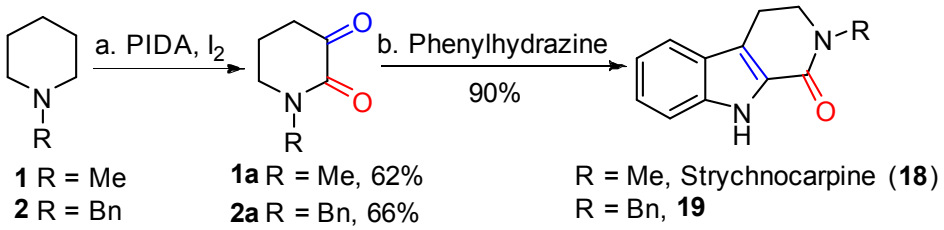
Scheme 4. Semisynthesis of obscurumine C and obscurumine O.



[a] PIDA (4 equiv.), I_2 (2 equiv.), THF, rt, 56%; [b] AIBN (0.2 equiv.), nBu$_3$SnH (2 equiv.), benzene, 50 °C, 5 h, 80%; [c] $LiAlH_4$, THF, 60 °C; [d] Ac_2O, pyridine, DMAP, 50 °C, 95% over two steps; [e] PIDA (6 equiv.), I_2 (3 equiv.), DCE, 80

°C, reflux, 3.5 h, 80%; [f] AIBN (0.2 equiv.), nBu$_3$SnH (2 equiv.), benzene, 50 °C, 5 h, 80%; [g] $KMnO_4$, acetone/H_2O (4:1), 0 °C-rt, 2h, 60%.

Scheme 5. Total synthesis of β-carboline compounds.



[a] PIDA (3 equiv.), I_2 (2 equiv.), THF, rt; [b] Phenylhydrazine, toluene, then formic acid, 80 °C, 90%.

CONCLUSION

In conclusion, we have demonstrated the PIDA/I_2-mediated C(sp^3)-H bonds oxidative dual functionalization of tertiary amines utilizing a PIDA/I_2 system. By the developed method, α-keto lactams or α,α-diiodo lactams were prepared in 30-80% yield, and the type of product could be controlled by changing the solvent in cases of *N*-methyl or *N*-benzyl piperidines. Moreover, three natural products obscurumines C (**13**) and O (**17**) and strychnocarpine (**18**) were successfully synthesized within four steps. Mimics of the *in vivo* metabolites of two clinical medications, imatinib (36% yield) and donepezil (45% yield), were directly prepared using this site-specific C(sp^3)-H oxidation. We envision this method will be highly beneficial in the total synthesis of alkaloids containing 1,6-dihydropyridine-2,3-dione units and the late-stage site-specific α,β-C(sp^3)-H oxidations of bioactive tertiary amines as well as in the drug discovery cycle.

EXPERIMENTAL SECTION

General Experimental Procedures: Lycopodine (**11**) [35] was isolated from *lycopodium obscurum*. All C-H oxidations were run under air with no precautions taken to exclude moisture. All other reactions were carried out under an atmosphere of argon in dry flask, and were monitored by analytical thin-layer chromatography (TLC), which was visualized by ultraviolet light (254 nm, if applicable), phosphomolybdic acid (50 g/L) in EtOH following heating as developing agents or by spraying improved Dragendorff's reagent if necessary. All solvents were obtained from commercial sources and were purified according to standard procedures. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted. Purification of products was accomplished by flash column chromatography using silica gel (200~300 mesh). All NMR spectra were recorded with a Bruker AVANCE III 400MHz or AVANCE III

600 MHz (^{1}H NMR) spectrometer and 100 MHz or 150 MHz (^{13}C NMR) in $CDCl_3$ or CD_3OD: chemical shifts (δ) are given in ppm, coupling constants (J) in Hz, the solvent signals were used as references ($CDCl_3$: δ_C = 77.0 ppm; CD_3OD: δ_C = 49.00 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm; residual CH_3OH in CD_3OD: δ_H = 3.31 ppm). And ^{13}C NMR spectra were obtained as proton-decoupled spectra. Infrared (IR) spectra were recorded on a BRUKER Tensor-27 Fourier-Transform Infrared spectrometer with KBr disks. Melting points were obtained on a WRX-4 apparatus (cover glass) and are uncorrected. HRMS (ESI) was taken on Agilent 6540 Q-TOF spectrometer.

General Procedure of Figure 1 (method A and method B):

To a stirring solution of tertiary amine (1.0 equiv) in solvent [DCE (method A) or THF (method B) 0.02 M, with no need for excluding H_2O] was added PIDA and I_2, and the reaction mixture was stirred at room temperature unless otherwise noted. After 30 minutes, additional PIDA were added for consumption of the starting material (if the starting material were not consumed according to TLC analysis). Then, the reaction was quenched with $Na_2S_2O_3$ (aq.) and allowed to stir until the mixture was pale yellow (few minutes). Finally, the reaction was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the entitled product.

1-Methylpiperidine-2,3-dione (1a)

According to general procedure of method B, 1-methylpiperidine (**1**) (15 mg, 0.15 mmol), PIDA (97.6 mg, 0.30 mmol, 2 equiv), iodine (75.9 mg, 0.30 mmol, 2 equiv), and THF (7.6 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (48.3 mg, 0.15 mmol, 1 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 60 minutes. Flash column chromatography on silica eluting with MeOH/DCM (1:100) yielded compound **1a** as a pale yellow oil (11.8 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (t, J = 8.0 Hz, 2H), 3.10 (s, 3H), 2.74 (t, J = 8.0 Hz, 2H), 2.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 158.1, 49.7, 38.7, 35.4, 21.7. HRMS (ESI) m/z calcd for $C_6H_9NO_2Na$ $[M + Na]^+$: 150.0525, found: 150.0525.

3,3-Diiodo-1-methylpiperidin-2-one (1b)

According to general procedure of method A, 1-methylpiperidine (**1**) (15 mg, 0.15 mmol), PIDA (97.6 mg, 0.3 mmol, 2 equiv), iodine (38.3 mg, 0.15 mmol, 1 equiv), and DCE (7.6 ml, 0.02 M) were reacted at room temperature. After 30 minutes, the reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml). Flash column chromatography on silica eluting with EtOAc/petroleum ether (1:4) yielded compound **1b** as a colorless acicular crystal (16.6 mg, 30% yield, mp 147-148 °C). IR (KBr) 3423, 2927, 1727, 1663. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (t, J = 6.25 Hz, 2H), 2.97 (m, 2H), 2.95 (s, 3H),

1.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 51.4, 50.2, 36.9, 23.7, -2.0. HRMS (ESI) *m*/*z* calcd for $C_6H_9I_2NONa$ $[M + Na]^+$: 387.8666, found: 387.8664.

1-Benzylpiperidine-2,3-dione (2a)

According to general procedure of method B, 1-benzylpiperidine (17.6 mg, 0.10 mmol), PIDA (64.8 mg, 0.20 mmol, 2 equiv), iodine (50.6 mg, 0.20 mmol, 2 equiv.), and THF (5.0 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (32.2 mg, 0.10 mmol, 1 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 60 minutes. Flash column chromatography on silica eluting with MeOH/DCM (1:100) yielded compound **2a** as a pale yellow oil (13.4 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 4.70 (s, 2H), 3.46 (t, J = 4.64 Hz, 2H), 2.74 (t, J = 4.64 Hz, 2H), 2.14 (m, 2H). (This compound was unstable in solvents like DCM, chloroform, etc, so impurities were produced during the NMR test) ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 157.8, 135.7, 128.9, 128.5, 128.1, 51.1, 46.8, 38.7, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}NO_2Na$ $[M + Na]^+$: 226.0838, found: 226.0833.

1-Benzyl-3,3-diiodopiperidin-2-one (2b)

According to general procedure of method A, 1-benzylpiperidine (17.6 mg, 0.10 mmol), PIDA (64.8 mg, 0.20 mmol, 2 equiv), iodine (25.4 mg, 0.10 mmol, 1 equiv.), and DCE (5.0 ml, 0.02 M) were reacted at room temperature. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after 45 minutes. Flash column chromatography on silica eluting with EtOAc/petroleum ether (1:4) yielded compound **2b** as a colorless acicular crystal (14.2 mg, 32% yield, mp 110.6-111.7 °C). IR (KBr) 3411, 3246, 3060, 3024, 2921, 2853, 1683, 1666, 1452, 1258, 698. (This compound was unstable in solvents like DCM, chloroform, etc, so impurities were produced during the NMR test) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 4.50 (s, 2H), 3.32 (t, J =6.24 Hz, 2H), 2.90 (m，2H), 1.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 136.4, 128.8, 128.0, 127.7, 51.8, 51.2, 47.4, 23.7, -1.5. HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}I_2NONa$ $[M + Na]^+$: 463.8979, found: 463.8978.

1,4-Dimethylpiperazine-2,3-dione (3a)

According to general procedure of method B, 1,4-dimethylpiperazine (11.4 mg, 0.10 mmol), PIDA (64.8 mg, 0.20 mmol, 2 equiv), iodine (50.6 mg, 0.20 mmol, 2 equiv.), and DCE (5.0 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (64.8 mg, 0.20 mmol, 2 equiv) were added. The reaction was quenched after by saturated aq. sodium thiosulfate solution (4 ml) another 60 minutes. Flash column chromatography on silica eluting with MeOH/DCM (1:60) yielded compound **3a** as a white amorphous powder (8.6 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 4H), 3.08 (s,

6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 46.1, 35.0. HRMS (ESI) *m*/*z* calcd for $C_6H_{10}N_2O_2Na$ [M + Na]$^+$: 165.0634, found: 165.0632.

1-Benzyl-4-methylpiperazine-2,3-dione (4a)

According to general procedure of method A, 1-benzyl-4-methylpiperazine (19.0 mg, 0.10 mmol), PIDA (64.8 mg, 0.20 mmol, 2 equiv), iodine (50.6 mg, 0.20 mmol, 2 equiv.), and DCE (5.0 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (64.8 mg, 0.20 mmol, 2 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 60 minutes. Flash column chromatography on silica eluting with MeOH/DCM (1:40) yielded compound **4a** as a white amorphous powder (14.2 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H), 4.46 (s, 2H), 3.45 (m, 2H), 3.42 (m, 2H), 3.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 157.4, 135.5, 128.9, 128.4, 128.1, 50.6, 46.4, 43.2, 35.0. HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}N_2O_2Na$ [M + Na]$^+$: 241.0953, found: 241.0950.

4-Benzylmorpholine-2,3-dione (5a) and ester (5b)

According to general procedure of method A, 4-benzylmorpholine (17.7 mg, 0.10 mmol), PIDA (64.8 mg, 0.20 mmol, 2 equiv), iodine (50.6 mg, 0.20 mmol, 2 equiv.), and DCE (5.0 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (64.8 mg, 0.20 mmol, 2 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 60 minutes. Flash column chromatography on silica eluting with EtOAc/$CHCl_3$ (1:20) yielded compound **5a** as a white amorphous powder (6.1mg, 30% yield) and ester **5b** a as colorless oil (5.0 mg, 20% yield). **5a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 4.71 (s, 2H), 4.43 (t, *J* =5.12 Hz, 2H), 3.55 (t, *J* =5.12 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 153.8, 134.6, 129.2, 128.5, 65.4, 50.6, 44.0. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{11}NO_3Na$ [M + Na]+: 228.0631, found: 228.0634. **5b:** IR (KBr) 3439, 3086, 3030, 2922, 1757, 1671, 1495, 1453, 1357, 1223, 1142, 1017, 954, 701. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 6.24 (s, 1H), 4.80 (d, *J* =14.57 Hz, 1H), 4.49 (d, *J* =14.57 Hz, 1H), 4.11 (m, 1H), 3.84 (m, 1H), 3.54 (m, 1H), 3.12 (m, 1H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 162.9, 135.5, 128.9, 128.4, 128.0, 88.4, 59.1, 49.9, 45.1, 21.0. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{15}NO_4Na$ [M + Na]$^+$: 272.0893, found: 272.0892.

3,3-Diiodo-1-methylpyrrolidin-2-one (6b)

According to general procedure of method A, 1-methylpyrrolidine (8.5 mg, 0.10 mmol), PIDA (64.8 mg, 0.20 mmol, 2 equiv), iodine (25.4 mg, 0.10 mmol, 1 equiv.), and DCE (5.0 ml, 0.02 M) were reacted at room temperature. The reaction was quenched by saturated aq. sodium thiosulfate solution (4

ml) after 45 minutes. Flash column chromatography on silica eluting with EtOAc/petroleum ether (1:4) yielded compound **6b** as a colorless acicular crystal (12.2 mg, 35% yield, mp 126-127 °C). IR (KBr) 3427, 3242, 2940, 1712, 1631, 1407, 1226, 1109, 1079. ^{1}H NMR (400 MHz, CD_3OD) δ 3.30-3.23 (m, 2H), 3.23-3.15 (m, 2H), 2.87 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 4H), 2.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 48.4, 48.2, 31.6, -13.6. HRMS (ESI) *m*/*z* calcd for $C_5H_7I_2NONa$ [M + Na]$^+$: 373.8509, found: 373.8510.

1-Benzyl-3,3-diiodopyrrolidin-2-one (7b)

According to general procedure of method A, 1-benzylpyrrolidine (16.1 mg, 0.10 mmol), PIDA (64.8 mg, 0.20 mmol, 2 equiv), iodine (25.4 mg, 0.10 mmol, 1 equiv.), and DCE (5.0 ml, 0.02 M) were reacted at room temperature. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after 45 minutes. Flash column chromatography on silica eluting with EtOAc/petroleum ether (1:4) yielded compound **7b** as a colorless acicular crystal (15.8 mg, 37% yield, mp 140.0-140.3 °C). IR (KBr) 3433, 3064, 3027, 2922, 2855, 1707, 1637, 699. (This compound has atropisomer, so the signal is complex) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 4.48 (s, 2H), 3.12 (m, 2H), 3.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.3, 167.7, 135.0, 134.9, 129.0, 128.9, 128.4, 128.3, 128.2, 128.1, 48.2, 48.1, 48.0, 46.3, 45.7, 44.6, 44.0, 43.9, -13.0. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{11}I_2NONa$ [M + Na]$^+$: 449.8822, found: 449.8824.

Formamide (8a)

According to general procedure of method A, α-obscurine **8** (20 mg, 0.07 mmol), PIDA (46.9 mg, 0.14 mmol, 2 equiv), iodine (36.9 mg, 0.14 mmol, 2 equiv.), and THF (3.5 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (46.9 mg, 0.14 mmol, 2 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 20 minutes. Flash column chromatography on silica eluting with MeOH/DCM (1:40) yielded compound formamide **8a** as a yellow oil (13.0 mg, 62% yield). IR (KBr) 3422, 3223, 3102, 2923, 2718, 1701, 1658, 1389, 1218. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.20 (s, 1H), 4.55 (d, J =13.2 Hz, 1H), 2.45 (t, J = 7.9 Hz, 2H), 2.26 (td, J = 2.5, 12.8 Hz, 1H), 2.15-1.93 (m, 5H), 1.81-1.64 (m, 4H), 1.60-1.36 (m, 4H), 1.35-1.17 (m, 2H), 0.94 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 160.2, 132.4, 109.2, 61.1, 44.2, 42.4, 41.6, 38.1, 33.1, 30.8, 29.6, 26.6, 26.5, 25.0, 22.1, 19.3. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{24}N_2O_2Na$ [M + Na]$^+$: 311.1730, found: 311.1725.

Iodo ketolactam (9a)

According to general procedure of method A, imatinib **9** (20 mg, 0.04 mmol), PIDA (51.5 mg, 0.16 mmol, 4 equiv), iodine (40.5 mg, 0.16 mmol, 2 equiv.) and DCE (2.0 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (25.7 mg, 0.08 mmol, 2 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 240 minutes. Flash column chromatography on silica eluting with MeOH/DCM (1:10) yielded compound iodo ketolactam **9a** as a yellow amorphous powder (10.4 mg, 40% yield). IR (KBr) 3397, 3246, 3031, 2954, 2923, 2852, 1667, 1571, 1516, 1497, 1446, 1398, 1258, 1099, 1019. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 9.27 (s, 1H), 8.71 (d, J = 3.7 Hz, 1H), 8.67 (d, J = 7.9 Hz, 1H), 8.54 (d, J = 5.1 Hz, 1H), 8.24 (s, 1H), 7.99 (s, 1H), 7.97 (s, 1H), 7.66 (s, 1H), 7.47 (m, 3H), 7.23 (d, J = 5.1 Hz, 1H), 7.12 (s, 1H), 4.77 (s, 2H), 3.51 (m, 4H), 3.10 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.8, 160.3, 159.1, 157.5, 151.3, 148.3, 139.9, 139.5, 138.5, 136.6, 135.7, 134.6, 132.7, 128.8, 127.8, 126.4, 123.9, 114.2, 108.7, 82.4, 50.4, 46.4, 43.6, 35.1, 17.4. HRMS (ESI) m/z calcd for $C_{29}H_{26}IN_7O_3Na$ $[M + Na]^+$: 670.1034, found: 670.1028.

Ketolactam (9b)

To a stirred solution of iodo ketolactam **9a** (5.0 mg, 0.0077 mmol, 1.0 eq.) in acetic acid (2 mL) were added Pd/C (contained 10% Pd, 0.08 mg 10% mmol) under the H_2 atmosphere (1 atm) at rt. After 12 h, the reaction was quenched by $NaHCO_3$ (aq.) and extracted with CH_2Cl_2. The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with MeOH/DCM (1:20) to give ketolactam **9b** (3.6 mg, 0.007 mmol, 90%) as a white amorphous powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.71 (s, 1H), 8.60 (s, 1H), 8.51 (m, 2H), 7.98 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.44 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 7.1 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.11 (s, 1H), 4.73 (s, 2H), 3.48 (m, 4H), 3.09 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 162.7, 160.5, 159.0, 157.5, 151.2, 148.4, 139.4, 137.8, 136.4, 135.2, 135.1, 130.8, 128.6, 127.7, 124.4, 123.8, 115.4, 113.1, 108.4, 50.3, 46.3, 43.5, 35.1, 17.7. HRMS (ESI) m/z calcd for $C_{29}H_{27}N_7O_3Na$ $[M + Na]^+$: 544.2068, found: 544.2066.

Ketolactam (10a)

According to general procedure of method A, donepezil **10** (50 mg, 0.13 mmol), PIDA (84.9 mg, 0.26 mmol, 2 equiv), iodine (66.7 mg, 0.26 mmol, 2 equiv.), and DCE (6.5 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (84.9 mg, 0.26 mmol, 2 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 20 minutes. Flash column chromatography on silica eluting with acetone/chloroform (1:40) yielded ketolactam **10a** (24.1 mg, 45% yield) as a white amorphous powder. IR (KBr) 3423, 3089, 3027, 2953, 2925, 1690,

1638, 1500, 1454, 1313, 1266, 1118, 1030, 702. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.16 (s, 1H), 6.87 (s, 1H), 6.46 (s, 1H), 4.61 (d, J = 1.5 Hz, 2H), 3.97 (s, 3H), 3.90 (s, 3H), 3.27 (m, 2H), 3.15 (m, 1H), 2.88 (m, 2H), 2.64 (m, 2H), 2.36 (m, 1H), 2.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 163.4, 155.7, 149.5, 149.4, 138.6, 136.5, 129.1, 128.7, 128.1, 127.7, 116.2, 107.5, 104.3, 56.3, 56.1, 50.5, 45.9, 44.6, 31.9, 31.5, 25.8. HRMS (ESI) m/z calcd for $C_{24}H_{25}NO_5Na$ $[M + Na]^+$: 430.1625, found: 430.1633.

Lactam (11a)

To a stirred solution of **11** (18 mg 0.073 mmol, 1.0 eq.) in acetone/H_2O(4:1) (5 mL) were added $KMnO_4$ (17.5 mg, 0.11 mmol, 1.5 eq.), the reaction was stirred at 0°C to rt. Additional $KMnO_4$ was added until the TLC analysis showed consumption of starting material. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 mL) and extracted with CH_2Cl_2. The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with MeOH/DCM (1:20) to give lactam 11a as a white amorphous powder (11.4 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (dd, J = 5.4, 13.5 Hz, 1H), 2.92 (td, J = 3.1, 13.5 Hz, 1H), 2.71-2.48 (m, 4H), 2.39-2.27 (m, 2H), 2.18 (m, 2H), 1.96 (d, J = 13.2 Hz, 1H), 1.83-1.67 (m, 5H), 1.58-1.33 (m, 3H), 1.00 (t, J = 12.9 Hz, 1H), 0.92 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 168.7, 61.6, 52.8, 43.6, 42.4, 41.7, 36.4, 35.9, 33.2, 25.2, 24.9, 22.5, 22.0, 19.1. HRMS (ESI) m/z calcd for $C_{16}H_{23}NO_2Na$ $[M + Na]^+$: 284.1621, found: 284.1624.

Iodo ketolactam (12) and obscurumine C (13)

According to general procedure of method B, lycopodine **11** (20 mg, 0.08 mmol), PIDA (51.5 mg, 0.16 mmol, 2 equiv), iodine (40.5 mg, 0.16 mmol, 2 equiv.), and THF (4.0 ml, 0.02 M) were reacted at room temperature. After 30 minutes, additional PIDA (51.5 mg, 0.16 mmol, 2 equiv) were added. The reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml) after another 120 minutes. Flash column chromatography on silica eluting with MeOH/DCM (1:120) yielded iodo ketolactam **12** as a yellow acicular crystal (16.3 mg, 51% yield, mp 273-274 °C) and obscurumine C **13** as a white powder (1.1 mg, 5% yield, mp 195-196 °C). **12**: IR (KBr) 3448, 2948, 2862, 1708, 1694, 1655, 1614, 1417, 1223, 715. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.86 (dd, J = 14.1, 5.2 Hz, 1H), 3.92 (m, 1H), 3.06 (td, J = 13.7, 3.5 Hz, 1H), 2.86 (dd, J = 16.4, 6.79 Hz, 1H), 2.82 (m, 1H), 2.67 (dd, J = 16.4, 1.4Hz, 1H), 2.47 (dd, J = 12.1, 3.3 Hz, 1H), 2.31 (m, 1H), 2.00 (m, 2H), 1.84-1.72 (m, 2H), 1.61-1.48 (m, 2H), 1.20 (t, J = 13.1 Hz, 1H), 0.95 (d, J = 8.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 172.9, 169.4, 152.3, 103.6, 65.9, 57.6, 47.3, 45.5, 44.9, 42.5, 37.7, 25.1, 24.7, 21.0, 19.8. HRMS (ESI) m/z calcd for $C_{16}H_{18}INO_3Na$ $[M + Na]^+$: 422.0224, found: 422.0228.

Obscurumine C (13)

To a stirred solution of iodo ketolactam **12** (16.0 mg, 0.04 mmol, 1.0 eq.) in benzene (4 mL) were added AIBN (1.2 mg, 0.2 mmol) and nBu_3SnH (28.0 μl, 0.06 mmol, 1.5 eq.) at rt. After 6 h, the reaction was quenched by water (4 ml) and extracted with CH_2Cl_2. The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with MeOH/DCM (1:80) to give obscurumine C **13** as a white powder (8.7 mg, 0.03 mmol, 80%, mp 195-196 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.53 (s 1H), 4.84 (dd, J = 13.8, 4.8 Hz, 1H), 3.23 (brs, 1H), 3.02 (td, J = 13.8, 3.2 Hz, 1H), 2.85 (m, 1H), 2.82 (dd, J = 16.4, 6.2 Hz, 1H), 2.66 (d, J = 16.4 Hz, 1H), 2.50 (dd, J = 12.0, 2.4 Hz, 1H), 2.27 (d, J = 13.4 Hz, 1H), 2.01 (m, 1H), 1.98 (d, J = 13.8 Hz, 1H), 1.80-1.70 (m, 2H), 1.67-1.49 (m, 2H), 1.22 (t, J = 10.7 Hz, 1H), 0.94 (d, J = 6.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.6, 177.4, 167.2, 156.3, 122.1, 63.5, 58.0, 46.5, 44.5, 43.7, 40.7, 37.1, 25.0, 24.9, 21.3, 19.4. HRMS (ESI) m/z calcd for $C_{16}H_{19}NO_3Na$ $[M + Na]^+$: 296.1257, found: 296.1258.

***β*-Dihydrolycopodine (14)**

To a suspension of $LiAlH_4$ (76.8 mg, 2.00 mmol, 10 eq.) in THF (5 ml) was added lycopodine **11** (50 mg, 0.20 mmol, 1.0 eq.) in THF (5 ml). The reaction mixture was refluxed at 60 °C until TLC analysis showed consumption of starting material. Then the reaction was quenched by addition of water (5 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (petroleum ether/acetone/diethylamine, 10:1:0.1) yielded *β*-dihydrolycopodine **14** as a white solid (47.3 mg, 95%, mp 167-168 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (td, J = 6.1, 2.5 Hz, 1H), 3.44 (td, J = 13.9, 3.6 Hz, 1H), 3.15 (td, J = 12.1, 3.2 Hz, 1H), 2.85 (m, 1H), 2.61 (dd, J = 13.2, 5.8 Hz, 1H), 2.55-2.44 (m, 2H), 2.32 (m, 1H), 2.11-2.01 (m, 1H), 2.01-1.93 (m, 1H), 1.86-1.76 (m, 1H), 1.75-1.53 (m, 4H), 1.51-1.40 (m, 4H), 1.38-1.29 (m, 2H), 1.29-1.14 (m, 2H), 0.86 (d, J = 6.41 Hz, 3H), 0.76 (t, J = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.5, 55.1, 47.2, 47.0, 45.6, 43.0, 41.8, 35.4, 33.7, 32.5, 26.5, 24.8, 24.0, 23.5, 23.4, 20.5. HRMS (ESI) m/z calcd for $C_{16}H_{28}NO$ $[M + H]^+$: 250.2165, found: 250.2159.

***β*-Acetyldihydrolycopodine (15)**

To a stirred solution of *β*-dihydrolycopodine **14** (40.0 mg, 0.16 mmol, 1.0 eq.) in pyridine (2.0 mL) were added DMAP (9.8 mg, 0.5 mmol) and Ac_2O (2 mL) at 50 °C. After 6 h, the reaction was quenched by water (4 ml) and extracted with CH_2Cl_2. The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with petroleum ether/acetone/diethylamine, 20:1:0.1, to give *β*-acetyldihydrolycopodine **15** as a white amorphous powder (46.6 mg, 0.15 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (t, J = 6. 5 Hz, 1H), 3.41 (m, 1H), 3.15 (m, 1H), 2.70-2.42 (m, 5H), 2.13-2.04

(m, 1H), 2.03 (s, 3H), 1.97-1.89 (m, 1H), 1.78-1.69 (m, 3H), 1.69-1.60 (m, 2H), 1.52-1.41 (m, 2H), 1.41-1.34 (m, 2H), 1.34-1.22 (m, 3H), 0.91 (d, J = 6. 1 Hz, 3H), 0.83 (t, J = 12. 5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 70.2, 54.7, 47.1, 46.9, 45.2, 42.8, 41.7, 34.9, 31.1, 31.0, 26.3, 24.6, 24.2, 23.5, 23.1, 21.5, 20.3. HRMS (ESI) m/z calcd for $C_{18}H_{30}NO_2$ $[M + H]^+$:292.2271, found: 292.2271.

Iodo ketolactam (16)

According to general procedure of method B, β-acetyldihydrolycopodine **15** (40 mg, 0.14 mmol), PIDA (265.4 mg, 0.82 mmol, 6 equiv), iodine (104.3 mg, 0.41 mmol, 3 equiv.) were added in DCE (7 ml, 0.02 M). And the reaction was refluxed at 80°C, after 3 h the reaction was quenched by saturated aq. sodium thiosulfate solution (4 ml). Flash column chromatography on silica eluting with MeOH/DCM (1:120) yielded iodo ketolactam **16** as a yellow oil (48.7 mg, 80% yield). IR (KBr) 3435, 2949, 1733, 1691, 1661, 1599, 1363, 1239, 1145, 1039, 1023. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, J = 6. 1 Hz, 1H), 4.82 (dd, J = 13.8, 4.9 Hz, 1H), 3.57 (brs, 1H), 3.06 (td, J = 13.6, 2.9 Hz, 1H), 2.90 (m, 2H), 2.37 (dt, J = 15.6, 6.6 Hz, 1H), 2.12 (s, 3H), 2.07-1.80 (m, 5H), 1.67-1.52 (m, 2H), 1.46 (td, J = 13.2, 4.8 Hz, 1H), 1.10 (t, J = 12.5 Hz, 1H), 0.93 (d, J = 6. 1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 173.0, 169.8, 152.5, 101.4, 68.0, 65.8, 51.7, 46.9, 44.6, 41.3, 37.9, 36.3, 25.5, 23.1, 21.9, 21.4. HRMS (ESI) m/z calcd for $C_{18}H_{22}INO_4Na$ $[M + Na]^+$: 466.0486, found: 466.0489.

Obscurumine O (17)

To a stirred solution of iodo ketolactam **16** (16.0 mg, 0.04 mmol, 1.0 eq.) in benzene (4 mL) were added AIBN (1.2 mg, 0.2 mmol) and nBu_3SnH (28.0 μl, 0.06 mmol, 1.5 eq.) at rt. After 6 h, the reaction was quenched by water (4 ml) and extracted with CH_2Cl_2. The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with MeOH/DCM (1:80) to give obscurumine O **17** as a white amorphous powder (9.2 mg, 0.03 mmol, 80%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.43 (s, 1H), 5.17 (t, J = 6.3 Hz, 1H), 4.70 (dd, J = 12.1, 3.3 Hz, 1H), 3.35 (d, J = 15.6 Hz, 1H), 3.21 (m, 1H), 3.10-2.93 (m, 2H), 2.43 (m, 1H), 2.28 (m, 1H), 2.13 (s, 3H), 2.10-1.89 (m, 3H), 1.66-1.43 (m, 3H), 1.31 (s, 1H), 1.18 (t, J = 12.3 Hz, 1H), 0.98 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.8, 175.3, 171.7, 158.4, 120.8, 69.7, 64.4, 52.6, 45.0, 43.8, 42.0, 38.6, 38.3, 26.9, 24.2, 23.7, 22.4, 21.2. HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_4Na$ $[M + Na]^+$: 340.1519, found: 340.1516. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.14 (t, J = 6.2 Hz, 1H), 4.84 (m, 1H), 3.03 (m, 1H), 2.89 (m, 3H), 2.37 (m, 1H), 2.12 (s, 3H), 2.08-1.94 (m, 3H), 1.91-1.80 (m, 2H), 1.67-1.53 (m, 2H), 1.48 (dd, J = 12.6, 4.3 Hz, 1H), 1.18 (t, J = 14.3 Hz, 1H), 0.94 (d, J = 5.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 171.6, 169.9, 156.5, 120.4, 68.0, 62.5, 51.4, 44.0, 42.7, 40.4, 37.3, 37.3, 25.8, 22.9, 22.8, 22.2, 21.4.

Strychnocarpine (18)

To a stirred solution of **1a** (10.0 mg, 0.08 mmol, 1.0 eq.) in toluene (2 mL) were added phenyhydrazine (8.5 mg, 0.08 mmol, 1 eq.), then the reaction was stirred at 80 °C. After TLC analysis showed consumption of starting material added formic acid (1 mL). The reaction was quenched by saturated aq. sodium bicarbonate solution (2 mL) after 3 h and extracted with CH_2Cl_2, the dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with MeOH/DCM (1:80) to give Strychnocarpine **18** as a white powder (14.1 mg, 0.07 mmol, 90%, 227-228 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.3 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 3.72 (t, J = 7.1 Hz, 2H), 3.17 (s, 3H), 3.09 (t, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 137.4, 127.1, 125.3, 124.7, 120.1, 120.1, 117.9, 112.5, 50.2, 34.1, 20.6. HRMS (ESI) m/z calcd for $C_{12}H_{13}N_2O$ $[M + H]^+$: 201.1022, found: 201.1021.

2,3,4,9-Tetrahydro-2-(phenylmethyl)-1H-pyrido[3,4-b]indol-1-one (19)

To a stirred solution of **2a** (50.0 mg 0.25 mmol, 1.0 eq.) in toluene (4 mL) were added phenyhydrazine (26.6 mg, 0.25 mmol, 1 eq.), then the reaction was stirred at 80°C. After TLC analysis showed consumption of starting material added formic acid (1 mL). The reaction was quenched by saturated aq. sodium bicarbonate solution (2 mL) after 4 h and extracted with CH_2Cl_2, the dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with actone/DCM (1:80) to give indol **19** as a white powder (61.1 mg, 0.22 mmol, 90%, mp 214-215 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (brs, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.47-7.21 (m, 7H), 7.11 (t, J = 7.4 Hz, 1H), 4.86 (s, 2H), 3.66 (t, J = 6.9 Hz, 2H), 3.03 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 137.8, 137.7, 128.7, 128.0, 127.5, 126.9, 125.2, 124.8, 120.0, 118.2, 112.8, 49.6, 47.5, 20.7. HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O$ $[M + H]^+$: 277.1335, found: 277.1336.

AUTHOR INFORMATION

Corresponding Author

*Q.-S. Z: phone, +86-871-65223058; fax, +86-871-65215783; E-mail, qinshizhao@mail.kib.ac.cn.

Author Contributions

§ Y.Z., and L.-D.S. contributed equally to this work.

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR for all synthetic compounds; summary of X-ray crystallographic data; condition optimization and mechanistic experiments data.

ACKNOWLEDGMENT

This work was financially supported by the National Natural Science Foundation of China (U1502223, U0932602, and 81603000), the National Basic Research Program (973 program no. 2011CB915503) of China, and the Science and Technology Program of Yunnan Province (2017FB135) and Youth Innovation Promotion Association CAS (L.-D.S).

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