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A novel total synthesis of isocryptolepine based on a microwave-assisted tandem Curtius rearrangement and aza-electrocyclic reaction

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ABSTRACT

A new entry to the total synthesis of isocryptolepine (cryptosanguinolentine), isolated from *Cryptolepis sanguinolenta*, was achieved by constructing a tetracyclic ring system through a microwave-assisted tandem Curtius rearrangement and electrocyclic reaction of an aza 6π-electron system. The tetracyclic lactam was converted to isocryptolepine in a four-step sequence.

1. Introduction

Isocryptolepine (**1a**: cryptosanguinolentine) is an important indolo[3,2-*c*]quinoline alkaloid, isolated from *Cryptolepis sanguinolenta*, and used in folk medicine as an antimalarial agent.[1] Isomeric indoloquinoline alkaloids of cryptolepine (**1b**) and neocryptolepine (**1c**) displaying similar activity were also found in the same plant (Fig. 1).[1] Isoneocryptolepine (**1d**), though not yet found in nature, has potent antiplasmodial activity comparable to that of **1a**, **1b**, and **1c**.[2] All of these compounds function as DNA-intercalating agents and strongly inhibit human topoisomerase II.[3]

A linear indolo[3,2-*c*]quinoline, isocryptolepine (**1a**), was synthesized using various strategies. In 1997, the Timari group[4a] reported the first total synthesis of isocryptolepine (**1a**) by a Pd-catalyzed cross-coupling reaction of 3-bromoquinoline and *o*-substituted phenylboronic acid, followed by the formation of an indole part using the nitrene insertion reaction. In 1999 and 2001, the Molina group[4b,c] reported the synthesis of **1a** by the application of cyclization of *o*-vinylsubstituted arylheterocumulene under microwave irradiation, followed by the nitrene procedure. The Kraus group[4d] in 2010, reported the synthesis of **1a** by an intramolecular Wittig reaction, followed by the nitrene process. The Mohan group[4e,f] provided two oxidative photochemical routes to **1a** by the formation of a quinoline part using a Schiff base between aniline and indole-4-carbaldehyde, and by the formation of an indole part from 4-(2-chloroanilino)quinoline in 2002 and 2006, respectively. The Maes group[4g] in 2003 also reported a total synthesis of **1a** by consecutive Pd-catalyzed amination and arylation of the resulting 4-(2-chloroanilino)quinoline. The Mohan group[4h] in 2005 and Kumar group[4i] in 2009 groups independently reported a short-step synthesis of **1a** in a high yield by the Fischer indole procedure. In 2007, the Miki group[4j] reported the total synthesis of **1a** by an interesting intermolecular decarboxylative Heck-type reaction. The Joule group[4k] in 1998, Kundu group[4l] in 2009, and Kraus group[4m] in 2010 reported the synthesis of **1a** by a modified Pictet-Spengler

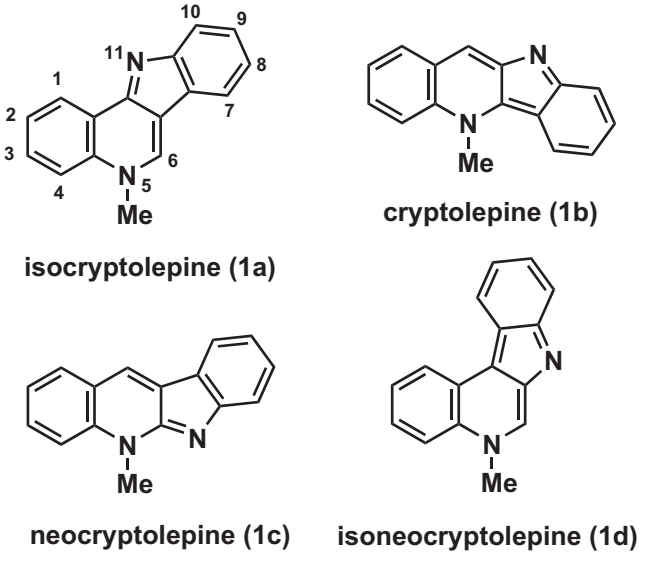

Fig. 1.

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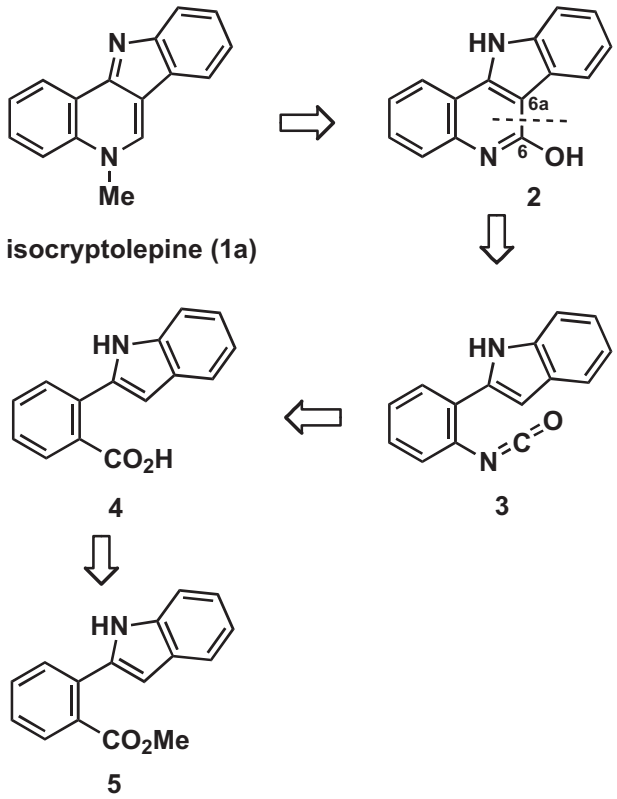
reaction for synthesis of the quinoline part. Recently, the Kusurkar group[4n] reported the synthesis of **1a** by the construction of γ-carboline based on an intramolecular thermal electrocyclization using our reported strategy.[5]

We are currently interested in the synthesis of fused pyridine ring systems based on a thermal electrocyclic reaction of an aza 6π-electron system.[6] In this context, we developed the synthesis of PhIP and DMIP having an imidazo[4,5-*b*]pyridine,[6,7a] grossularines having an α-carboline,[6,7b] and imiquimod having an imidazo[4,5-*c*]quinoline[6,7c] by a thermal electrocyclic reaction of a 2-aza 6π-electron system using an isocyanate, according to a modified Eloy's pyrido-annulation.[8] In addition, we have recently reported the construction of several fused pyridine ring systems, such as furo[3,2-*h*]isoquinoline,[9a,b] phenanthridine,[9c] benzo[*c*]phenanthridine,[9d,e] azaanthraquinone,[9f] and β-carboline[9g] alkaloids, using a microwave-assisted thermal electrocyclic reaction of a 1-aza 6π-electron system.[6] In the present work, we describe the total synthesis of isocryptolepine (**1a**) by new construction of an indolo[3,2-*c*]quinoline ring system based on a microwave-assisted tandem Curtius rearrangement followed by a thermal electrocyclic reaction of a 2-aza 6π-electron system.

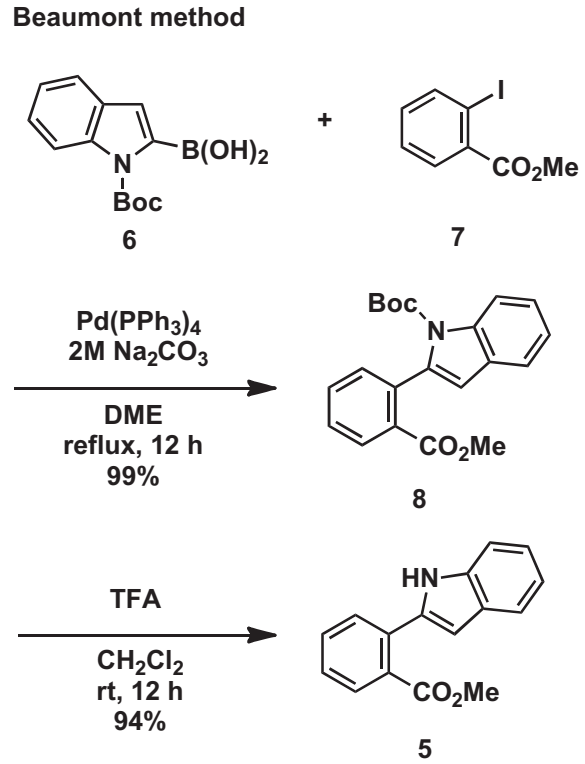
2. Results and discussion

We planned to form the indolo[3,2-*c*]quinoline nucleus **2** using a microwave-assisted thermal electrocyclic reaction of a 2-aza 6π-electron system of a 2-(indol-2-yl)phenylisocyanate **3**, derived from cleavage at a position of a C6–C6a bond of **2**. An isocyanate **3** would be prepared by Curtius rearrangement of an 2-(indol-2-yl)benzoic acid (**4**), which is easily obtained from the known methyl 2-(indol-2-yl)benzoate **5**[10] as illustrated in the retrosynthetic analysis (Scheme 1).



Scheme 1.

Known compound **5** was obtained in excellent yield from a Suzuki–Miyaura coupling reaction between the indole-2-boronic acid **6** and methyl 2-iodobenzoate (**7**), followed by deprotection of the *N*-Boc group of **8** in two steps according to the reported procedure[10] (Scheme 2).

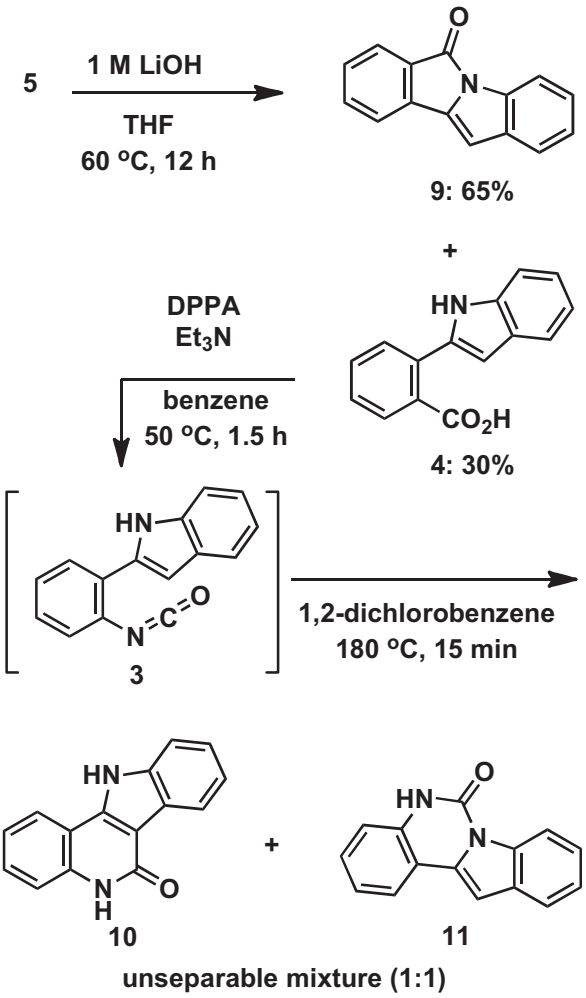


Scheme 2.

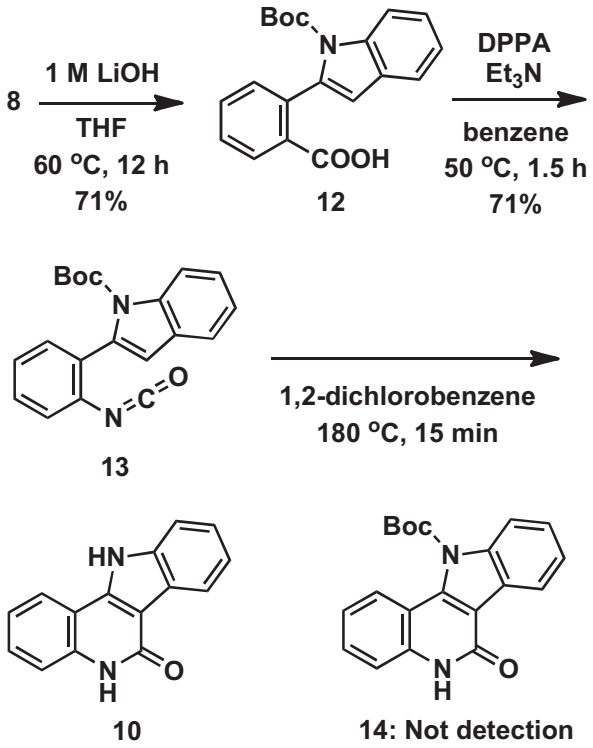
For synthesis of the indolo[3,2-*c*]quinoline ring, treatment of the known ester **5** with an aqueous 1 M LiOH in THF afforded the benzoic acid **4**[11] in 30% yield along with tetracyclic lactam **9**[11,12] as a major product (65%). The carboxylic acid **4** was treated with diphenylphosphoryl azide (DPPA)[13] at 60 °C in the presence of triethylamine to give the unstable isocyanate **3**. After replacing the benzene with 1,2-dichlorobenzene without isolation, the mixture was heated at 180 °C for 15 min to produce the indolo[3,2-*c*]quinoline **10** together with isomeric lactam **11** as an inseparable mixture (1:1, 59% yield) (Scheme 3).

Based on these experimental results, the starting material was changed to *N*-Boc-2-indolylbenzoic acid **12** to prevent intramolecular amide formation (Scheme 4). Methyl *N*-Boc-indolylcarboxylate **8** with aqueous LiOH gave the carboxylic acid **12** (71% yield), which was treated with DPPA at 50 °C to yield the isocyanate **13** (71%). When **13** was heated in 1,2-dichlorobenzene at 180 °C for 15 min, an *N*-Boc-indolo[3,2-*c*]quinoline **14** was not detected at all, but the indolo[3,2-*c*]quinoline **10**, along with elimination of the *N*-Boc group, was obtained in only low yield (6%) (Scheme 4).

We then selected a methoxymethyl (MOM) group of a less sterically-hindered protecting group (Scheme 5). For the synthesis of *N*-MOM-indolylbenzoate **15**, treatment of **5** with MOMCl in the presence of NaH afforded *N*-MOM-indolylbenzoate **15** in excellent yield (91%). Subsequent hydrolysis of the ester **15** with 1 M LiOH gave the *N*-MOM-carboxylic acid **16** (98%). Surprisingly, treatment of the carboxylic acid **16** with DPPA in benzene at 60 °C for 1.5 h provided the *N*-MOM-indolo[3,2-*c*]quinoline **18** (41%) without the isolation of isocyanate **17** (Table 1, run 1). It was considered that this result



Scheme 3.



Scheme 4.

proceeded by Curtius rearrangement followed by a thermal electrocyclic reaction in one pot. As shown in Table 1, this tandem reaction was investigated in further detail. Reaction time, temperature, solvent, and microwave parameters were examined. First, when the reaction time under the same conditions as run 1 was increased from 1.5 h to 3 h, the yield improved from 41% to 83% (run 2). The use of toluene instead of benzene provided the more promising result at the same temperature (runs 3 and 4). When the reaction was performed in toluene at 60 °C under microwave irradiation, product **18** was obtained in excellent yield and the reaction time was decreased (runs 4 and 5). The microwave-assisted condition of run 7 was more effective than the conventional condition (run 6) in terms of the yield, which increased from 89% to 99%.

To complete the total synthesis (Scheme 6), treatment of the lactam **18** with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine afforded the triflate **19**, which was subjected to a reductive cleavage of the trifluoromethanesulfonyloxy group of **20** with palladium(II) acetate and 1,3-bis(diphenylphosphino)propane in the presence of triethylsilane in DMF at 60 °C according to Katsuki's procedure[14] to produce the *N*-MOM-indoloquinoline **20**. Subsequently, treatment of **20** with MeOH, trimethyl orthoformate, and trifluoromethanesulfonic acid in nitromethane according to our previously reported method[15] gave the indolo[3.2-*c*]quinoline **21** in 96% yield. Finally, methylation of **21** with methyl iodide in toluene according to Kundu's procedure[4l] afforded isocryptolepine (**1a**). The physical and spectroscopic data of our synthetic isocryptolepine (**1a**) were identical with those of the previously reported data.[1,4n]

3. Conclusion

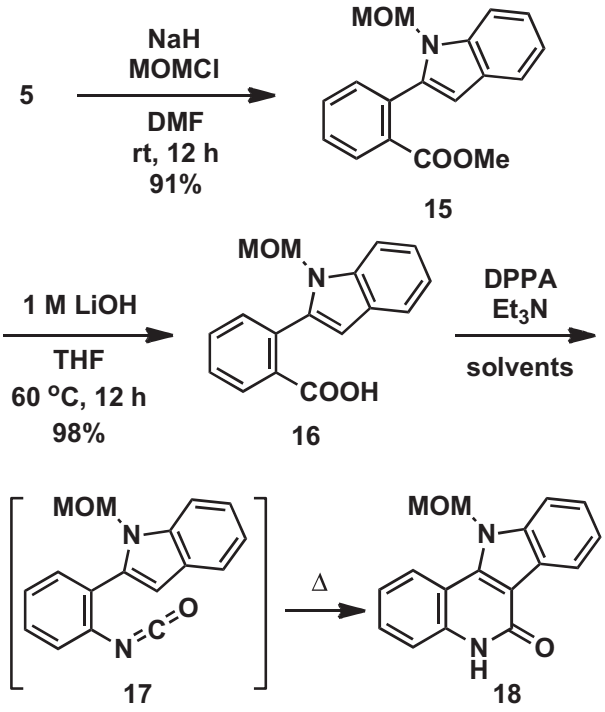
We established a new and efficient total synthesis of isocryptolepine **1a** (cryptosanguinolentine) in 57.6% overall yield in seven steps from the readily accessible known starting material **5**. The key novel step described here is the microwave-assisted tandem Curtius rearrangement with DPPA and electrocyclic ring closure of an aza 6π-electron system. Further application of this tandem methodology to various types of alkaloids including a fused pyridine ring system is under investigation in our laboratory.

4. Experimental section

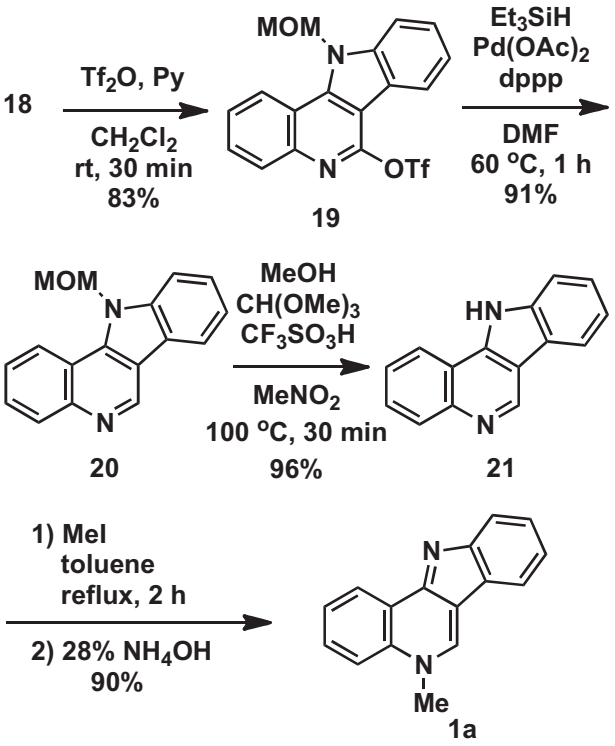
4.1. General

All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel $60PF_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60 (70–230 mesh, Merck). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). NMR spectra was measured with $CDCl_3$ unless otherwise noted. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.7). Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and technologies DuraScop. Low and high resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system.

*4.1.1. 2-(1H-Indol-2-yl)benzoic acid **4** and 6H-Isoindolo[2,1-a]indol-6-one **9**.* A mixture of *N*-Boc–indolylbenzoate **5**[10] (620 mg,



Scheme 5.



Scheme 6.

Table 1
Synthesis of Indolo[3,2-*c*]quinolin-6-one (**18**) by Microwave-assisted Tandem Reaction

Run	Solvents	MW[a]	Temp (°C)	Time (h)	Yield (%)
1	Benzene	—	60	1.5	41
2	Benzene	—	60	3	83
3	Toluene	—	60	0.5	68
4	Toluene	—	60	3	89
5	Toluene	+	60	0.5	94
6	Toluene	—	100	10 min	89
7	Toluene	+	100	10 min	99

[a] Discover (CEM corp.).

2.5 mmol) and 1 M LiOH (12.5 mL) in THF (10 mL) was heated at 60 °C for 12 h. After cooling to an ambient temperature, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, derived over Na_2SO_4 and concentrated in vacuo to give the lactam **9** (356 mg, 65%). The water layer was acidified with a 10% HCl solution, and then the resulting mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the benzoic acid **4** (180 mg, 30%). **4**: mp 155–156 °C (EtOAc–hexane) (lit.[11] mp 155–157 °C). IR (ATR) ν: 3361, 1718 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 6.73 (1H,s), 7.12 (1H, t, J=6.2 Hz), 7.21 (1H, t, J=6.7 Hz), 7.40 (1H, d, J=7.7 Hz), 7.45 (1H, d, J=6.4 Hz) 7.59 (1H, d, J=6.2 Hz), 7.64 (1H, d, J=7.7 Hz), 7.74 (1H, d, J=6.7 Hz),7.97 (1H, d, J=6.4 Hz), 9.30 (1H, br s). MS (EI) m/z: 237 (M^+); HRMS (EI) Calcd for $C_{15}H_{11}NO_2$: 237.0790. Found: 237.0800. **9**: mp 146–148 °C (EtOAc–hexane) (lit.[12] mp 150–151 °C). IR (ATR) ν: 1722 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 6.63 (1H,s), 7.16 (1H, t, J=6.0 Hz), 7.29–7.38 (2H, m), 7.46 (1H, d, J=7.2 Hz), 7.49–7.54 (2H, m), 7.77 (1H, d, J=6.0 Hz), 7.90 (1H, d, J=7.2 Hz). MS (EI) m/z: 219 (M^+); HRMS (EI) Calcd for $C_{15}H_9NO$: 219.0684. Found: 219.0709.

*4.1.2. 2-[N-(tert-Butoxycarbonyl)-1H-indol-2-yl]benzoic acid **12**.* A mixture of *N*-MOM indolylbenzoate **5** (60 mg, 0.17 mmol) and 1 M LiOH (0.85 mL) in THF (10 mL) was heated at 60 °C for 12 h. After cooling to an ambient temperature, the mixture was acidified with a 10% HCl solution, and then the resulting mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the benzoic acid **12** (41 mg, 71%), mp 145–148 °C (EtOAc–hexane). IR (ATR) ν: 3059, 1701 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 1.24 (9H, s), 6.45 (1H, s), 7.24 (1H, t, J=6.2 Hz), 7.33 (1H, t, J=6.2 Hz), 7.44 (1H, t, J=6.2 Hz), 7.49 (1H, d, J=6.2 Hz), 7.54 (1H, d, J=8.0 Hz), 7.59 (1H, t, J=6.2 Hz), 8.09 (1H, d, J=6.2 Hz), 8.25 (1H, d, J=8.0 Hz). MS (EI) m/z: 337 (M^+); HRMS (EI) Calcd for $C_{20}H_{19}NO_4$: 337.1314. Found: 337.1319.

*4.1.3. 2-[N-(tert-Butoxycarbonyl)-1H-indol-2-yl]phenylisocyanate **13**.* A solution of benzoic acid **12** (100 mg, 0.30 mmol), DPPA (194 μL, 0.90 mmol), and Et_3N (127 μL, 0.90 mmol) in toluene (3 mL) were stirred under microwave irradiation at 100 °C for 1.5 h. After cooling to an ambient temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the gummy isocyanate **13** (71 mg, 71%), which was used without any further purification, but the following data were obtained. IR (ATR) ν: 2277, 1727 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 1.25 (9H, s), 6.59 (1H, s), 6.84 (1H, br.s), 7.19 (1H, d, J=6.4 Hz), 7.27 (1H, d, J=8.4 Hz), 7.32 (1H, d, J=6.4 Hz), 7.37–7.46 (1H, m), 7.60 (1H, d, J=8.0 Hz), 8.20 (1H, d, J=8.0 Hz), 8.30 (1H, d, J=8.4 Hz). MS (EI) m/z: 334 (M^+).

*4.1.4. 5,7-Dihydroindolo[3,2-c]quinolin-6-one **10**.* A solution of isocyanate **10** (50 mg, 0.15 mmol) in 1,2-dichlorobenzene (2 mL) was heated at 180 °C for 15 min. After cooling to an ambient temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1:1 v/v) as an eluent to give the indoloquinone **10** (2 mg, 6%), mp 337–339 °C (EtOAc–hexane). IR (ATR) ν: 1637 cm^{-1} ^1H NMR (300 MHz DMSO-d_6) δ: 7.23–7.31 (2H, m), 7.36 (1H, t, J=6.4 Hz), 7.44–7.53 (2H, m), 7.60 (1H, d, J=8.0 Hz), 8.19 (1H, d,

J=8.0 Hz), 11.41 (1H, s), 12.55 (1H, s). MS (EI) m/z: 234 (M^+). HRMS (EI) Calcd for $C_{15}H_{10}N_2O$: 234.0793. Found: 234.0778.

*4.1.5. Methyl 2-[(N-methoxymethyl)indol-2-yl]benzoate **15**.* A solution of methyl indolylbenzoate **5** (964 mg, 3.8 mmol) in DMF (10 mL) was added to a suspension of NaH (456 mg, 11.4 mmol) in DMF (10 mL) under cooling with ice. After stirring at rt for 30 min, chloromethyl methyl ether (866 μL, 11.4 mmol) was added dropwise to the reaction mixture under cooling with ice, and stirred at rt for 12 h. The reaction mixture was quenched with an aqueous NH_4Cl (saturated) solution, and then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:10 v/v) as an eluent to give the oily *N*-MOM indolylbenzoate **15** (1.02 g, 91%). IR (ATR) ν: 1724 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 3.14 (3H, s), 3.63 (3H, s), 5.26 (2H, s), 6.46 (1H, s), 7.16 (1H, t, J=7.7 Hz), 7.45–7.63 (6H, m), 7.96 (1H, d, J=7.7 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ: 52.2, 55.7, 75.0, 103.2, 110.1, 120.6, 122.1, 128.2, 128.7, 129.9, 130.2, 131.4, 132.1, 132.7, 137.3, 139.6, 139.7, 167.5. MS (EI) m/z: 295 (M^+); HRMS (EI) Calcd for $C_{18}H_{17}NO_3$: 295.1208. Found: 295.1231.

*4.1.6. 2-[(N-Methoxymethyl)indol-2-yl]benzoic acid **16**.* A mixture of *N*-MOM indolylbenzoate **15** (1.02 g, 3.5 mmol) and 1 M LiOH (17 mL) in THF (20 mL) was heated at 60 °C for 12 h. After cooling to an ambient temperature, the mixture was acidified with a 10% HCl solution, and then the resulting mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the benzoic acid **16** (965 mg, 98%), mp 126–128 °C (EtOAc–hexane). IR (ATR) ν: 3047, 1685 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 3.12 (3H, s), 5.23 (2H, s), 6.51 (1H, s), 7.18 (1H, t, J=7.7 Hz), 7.27 (1H, t, J=5.8 Hz), 7.47–7.65 (5H, m), 8.03 (1H, d, J=5.8 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ: 55.7, 74.9, 103.7, 110.0, 120.5, 120.6, 122.3, 128.2, 129.0, 130.7, 131.1, 132.1, 132.8, 132.9, 137.4, 139.2, 170.8. MS (EI) m/z: 281 (M^+); HRMS (EI) Calcd for $C_{17}H_{15}NO_3$: 281.1052. Found: 281.1033.

*4.1.7. N-(Methoxymethyl)indolo[3,2-c]quinolin-6-one **18**.* A solution of benzoic acid **16** (50 mg, 0.18 mmol), DPPA (97 μL, 0.45 mmol), and Et_3N (64 μL, 0.45 mmol) in toluene (3 mL) were stirred under microwave irradiation at 100 °C for 10 min. After cooling to an ambient temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1:3 v/v) as an eluent to give the indoloquinolone **18** (49 mg, 99%), mp 272–274 °C ($CHCl_3$–hexane). IR (ATR) ν: 1643 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 3.51 (3H, s), 5.95 (2H, s), 7.32–7.57 (5H, m), 7.65 (1H, d, J=8.4 Hz), 8.41 (1H, d, J=8.4 Hz), 8.59 (1H, d, J=8.4 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ: 56.3, 75.3, 109.0, 109.4, 112.8, 117.0, 122.5, 122.5, 122.6, 123.7, 124.3, 125.0, 129.3, 138.0, 140.1, 141.3, 161.1. MS (EI) m/z: 278 (M^+); HRMS (EI) Calcd for $C_{17}H_{14}N_2O_2$: 278.1055. Found: 278.1071.

*4.1.8. N-(Methoxymethyl)-6-(trifluoromethanesulfonyloxy)indolo[3,2-c]quinoline **19**.* Tf_2O (86 μL, 0.51 mmol) was added to a solution of methyl indoloquinolone **18** (95 mg, 0.34 mmol) and pyridine (82 μL, 1.02 mmol) in CH_2Cl_2 (5 mL) under cooling with ice. After stirring at rt for 30 min, the reaction mixture was quenched with water, and then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the triflate **19** (116 mg, 83%), mp 154–156 °C (EtOAc–hexane). IR (ATR) ν: 1404, 1199 cm^{-1} ^1H NMR (300 MHz $CDCl_3$) δ: 3.52 (3H, s), 6.06 (2H, s), 7.51 (1H, t, J=7.7 Hz), 7.63 (1H, t, J=7.7 Hz), 7.69–7.82 (3H, m), 8.19 (1H, d, J=7.7 Hz), 8.31 (1H, d, J=7.7 Hz), 8.67 (1H, d, J=7.7 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ: 56.5, 75.6, 109.6, 112.3, 117.8, 119.7, 120.9, 122.1, 122.9, 123.0, 126.8, 127.0, 129.2, 129.9, 140.9, 144.1, 144.1, 149.6. MS (EI) m/z: 410 (M^+); HRMS (EI) Calcd for $C_{18}H_{13}F_3N_2O_4S$: 410.0548. Found: 410.0557.

*4.1.9. N-(Methoxymethyl)indolo[3,2-c]quinoline **20**.* A mixture of triflate **19** (50 mg, 0.12 mmol), triethylsilane (191 μL, 1.2 mmol), $Pd(OAc)_2$ (0.45 mg, 2 μmol), and dppp (0.8 mg, 2 μmol) in DMF (3 mL) were heated at 60 °C for 1 h. After cooling to an ambient temperature, the reaction mixture was quenched with water, and then extracted with EtOAc. The EtOAc layer was washed with an aqueous $NaHCO_3$ (saturated) solution and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1:1 v/v) as an eluent to give the indoloquinoline **20** (29 mg, 91%), mp 151–153 °C (EtOAc–hexane). ^1H NMR (300 MHz $CDCl_3$) δ: 3.50 (3H, s), 6.04 (2H, s), 7.44 (1H, t, J=7.7 Hz), 7.58 (1H, t, J=7.7 Hz), 7.65–7.79 (3H, m), 8.27 (1H, d, J=7.7 Hz), 8.31 (1H, d, J=7.7 Hz), 8.65 (1H, d, J=7.7 Hz), 9.59 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 56.2, 75.6, 109.5, 116.0, 117.9, 120.0, 121.9, 122.2, 122.9, 126.1, 126.3, 128.0, 130.5, 140.1, 140.9, 144.4, 147.0. MS (EI) m/z: 262 (M^+); HRMS (EI) Calcd for $C_{17}H_{14}N_2O$: 262.1106. Found: 262.1091.

*4.1.10. 11H-Indolo[3,2-c]quinoline **21**.* CF_3SO_3H (26 μL, 0.30 mmol) was added to a solution of indoloquinoline **20** (25 mg, 0.10 mmol), MeOH (43 μL, 1.0 mmol) and $CH(OMe)_3$ (109 μL, 1.0 mmol) in $MeNO_2$ (2 mL) under cooling with ice, and then was heated at 100 °C for 1 h. After cooling to an ambient temperature, the reaction mixture was quenched with an aqueous Na_2CO_3 (saturated) solution, and then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc–hexane (1:1 v/v) as an eluent to give the indoloquinoline **21** (20 mg, 96%), mp 333–334 °C ($CHCl_3$–hexane). ^1H NMR (300 MHz DMSO-d_6) δ: 7.34 (1H, d, J=7.2 Hz), 7.49 (1H, d, J=7.2 Hz), 7.62–7.76 (3H, m), 8.13 (1H, d, J=7.2 Hz), 8.31 (1H, d, J=7.9 Hz), 8.50 (1H, d, J=7.9 Hz), 9.58 (1H, s), 12.72 (1H, s). ^{13}C NMR (75 MHz DMSO-d_6) δ: 111.9, 114.3, 117.1, 120.5, 120.7, 121.9, 122.1, 125.6, 125.7, 128.1, 129.6, 138.8, 139.8, 144.9, 145.4. MS (EI) m/z: 218 (M^+); HRMS (EI) Calcd for $C_{15}H_{10}N_2$: 218.0844. Found: 218.0826.

*4.1.11. Isocryptolepine **1a**.* A mixture of indoloquinoline **21** (20 mg, 0.092 mmol) and MeI (1.1 mL, 18 mmol) in toluene (3 mL) were refluxed for 2 h. After cooling to an ambient temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 5 g) using MeOH–$CHCl_3$ (3:97 v/v) as an eluent to give isocryptolepine hydroiodide (**1a**-HI). To obtain the free base, 28% ammonia (20 mL) was added to a solution of **1a**-HI in CH_2Cl_2 (30 mL), and then stirred for 10 min. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give isocryptolepine (**1a**) (19 mg, 90%) as yellow powder, mp 191–193 °C ($CHCl_3$-hexane) (lit.,[4n] mp 192–193 °C). ^1H NMR (300 MHz DMSO-d_6) δ: 4.27 (3H, s), 7.24 (1H, t, J=7.1 Hz), 7.43 (1H, t, J=7.9 Hz), 7.69 (1H, d, J=7.9 Hz), 7.77–7.87 (2H, m), 8.06 (1H, d, J=8.0 Hz), 8.12 (1H, d, J=7.1 Hz), 8.78 (1H, d, J=8.0 Hz), 9.36 (1H, s). ^{13}C NMR (75 MHz DMSO-d_6) δ: 41.7, 116.4, 116.9, 117.0, 119.2, 120.2, 120.5, 123.9, 124.9, 125.3, 125.9, 129.6, 135.7, 137.9, 152.1, 152.4. MS (EI) m/z: 232 (M^+); HRMS (EI) Calcd for $C_{16}H_{12}N_2$: 232.1000. Found: 232.1008.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2012.03.055. These data include MOL files and InChIKeys of the most important compounds described in this article.

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