JOC The Journal of Organic Chemistry

Article

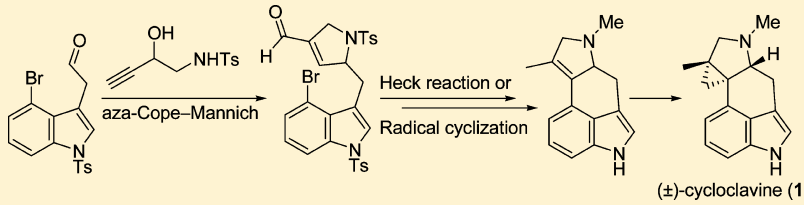
pubs.acs.org/joc

Formal Synthesis of (±)-Cycloclavine

Wei Wang, Jia-Tian Lu, Hao-Li Zhang, Zi-Fa Shi, Jing Wen, and Xiao-Ping Cao*

State Key Laboratory of Applied Organic Chemistry & College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, 730000, P. R. China

Supporting Information



ABSTRACT: An efficient formal synthesis of (±)-cycloclavine is achieved in seven steps and 27% overall yield from the known 2-(4-bromo-1-tosyl-1*H*-indol-3-yl)acetaldehyde. Key features include an iron(III)-catalyzed aza-Cope–Mannich cyclization and an intramolecular Heck reaction or a self-terminating *6-exo-trig* aryl radical–alkene cyclization.

INTRODUCTION

The *Ergot* family represents a significant class of indole alkaloids of broad pharmacological activity,[1] whose 3,4-fused polycyclic molecular architectures have been considered as attractive synthetic targets for decades.[2−10] As one of the clavine-type alkaloids, cycloclavine (**1**, Scheme 1) was first isolated in 1969 from the seeds of the African morning glory (*Ipomea hildebrandtii*) by Hoffman and co-workers.[11] Cycloclavine demonstrates appealing structure containing the same 3,4-fused indole skeleton as lysergic acid and a pithy cyclopropane ring on three contiguous stereocenters. Its striking compact but highly congested structure poses considerable challenges for synthesis.

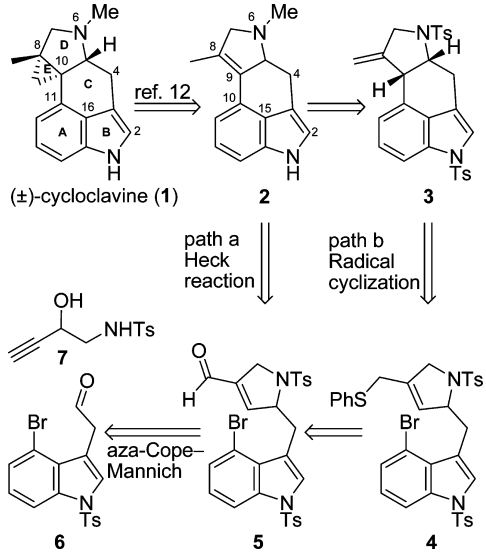
Although over 40 years has passed after the isolation of cycloclavine, only two racemic syntheses have been reported recently: (1) Szántay's first synthesis in 2008 involving intramolecular aldol condensation of Uhle's ketone derivative in 14 steps and 0.2% overall yield[12] and (2) Wipf's synthesis in 2011 employing intramolecular Diels–Alder cycloaddition of furan (IMDAF) reaction in 14 steps and 1.2% overall yield for (±)-cycloclavine and in 17 steps and 2.3% overall yield for (±)-5-*epi*-cycloclavine.[13] Clearly, an efficient and novel strategy for the synthesis of this alkaloid is needed.

Inspired by robust tandem and step-economical synthetic strategies,[14−16] herein we reported a more efficient route for the synthesis of (±)-cycloclavine (**1**) based on aza-Cope–Mannich cyclization for the construction of the D ring within it and rapid assembly of its 3,4-fused indole structure by Heck reaction or radical cycloaddition. The aza-Cope–Mannich tandem reaction, which is initiated by a cationic 2-aza-Cope rearrangement (2-azonia-[3,3]-sigmatropic rearrangement) followed by Mannich reaction,[17,18] has been applied successfully into numerous alkaloid syntheses[19−24] since it was discovered by Overman and co-workers in 1979.[25−29] In 2010, Padrón's group first reported an iron(III)-catalyzed alkyne aza-Cope–Mannich reaction between 2-hydroxy homopropargyl tosylamine and aldehydes to obtain 3-formyl-α,β-unsaturated pyrrolidines,[30] which inspired us to use the aza-Cope–Mannich reaction as a potential tool for construction of the functionalized pyrrolidine of cycloclavine.

RESULTS AND DISCUSSION

With the above considerations, the retrosynthetic analysis of (±)-cycloclavine (**1**) is outlined in Scheme 1. We envisioned that (±)-cycloclavine could be accessed via a late-stage cyclopropanation of the Szántay's intermediate **2**.[12] The crucial compound **2** could be reached by intramolecular Heck reaction

Scheme 1. Retrosynthetic Analysis of (±)-Cycloclavine (1)



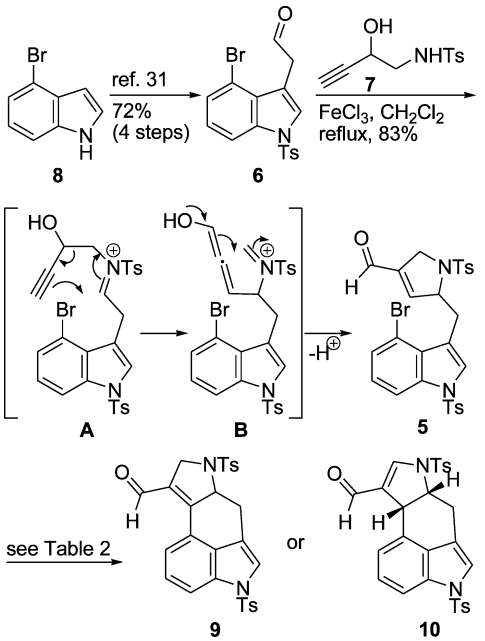
Received: October 23, 2013
Published: November 27, 2013

dx.doi.org/10.1021/jo4023588 | *J. Org. Chem.* 2014, 79, 122–127

of aldehyde **5** followed by deoxygenation (path a) or 6-*exo*-*trig* aryl radical−alkene cyclization of sulfide **4** resulting in tetracyclic compound **3** and then followed by isomerization (path b). The sulfide **4** could be obtained from aldehyde **5** through Luche reduction and thioetherfication. The aldehyde **5** could be constructed by the aza-Cope−Mannich reaction from the known aldehyde **6**[31] and alkyne **7**.[30]

The synthesis commenced with the known 2-(4-bromo-1-tosyl-1*H*-indol-3-yl)acetaldehyde (**6**), which was prepared from the commercially available 4-bromoindole (**8**) in 4 steps and 72% overall yield (Scheme 2).[31] Aldehyde **6** was then subjected to different aza-Cope−Mannich conditions with 2-hydroxy homopropargyl tosylamine (**7**) to afford the tricyclic aldehyde **5** (Table 1). Unexpectedly, a serious setback was encountered when the reaction was carried out under the standard conditions, i.e., $FeCl_3$ (1.2 equiv) and TMSCl (1.3 equiv) in CH_2Cl_2 at room temperature, established by Padrón (Table 1, entry 1), which gave only complex mixture instead of the desired pyrrolidine compound.[30] However, aldehyde **5** could be achieved in moderate yields when the reactants were treated with an excessive or catalytic amounts of TMSCl at reflux temperature (Table 1, entries 2 and 3). Eventually, desired aldehyde **5** could be obtained in excellent yield (83%) in the presence of $FeCl_3$ (1.3 equiv) without TMSCl in the preheated oil bath (45 °C) for 0.2 h (Table 1, entry 4). The plausible mechanism is based on a consecutive generation of γ-unsaturated iminium ion **A**, 2-azonia[3,3]-sigmatropic rearrangement intermediate **B** and further intramolecular Mannich reaction (Scheme 2).[30]

Scheme 2. Synthesis of Aldehydes 9 and 10



We then paid attention to the assembly of the C ring of (±)-cycloclavine by intramolecular Heck reaction between the aryl bromide and the double bond in the dihydropyrrole ring (Scheme 2 and Table 2). The first assay was discouraging with only recovery of the starting material in the presence of $Pd_2(dba)_3$ and t-$Bu_3P{\cdot}HBF_4$ with DABCO as base in dioxane (Table 2, entry 1).[32] When $Pd(OAc)_2$ combined with different ligands (PPh_3 or dppp) and base (Ag_2CO_3, $Ag_2CO_3/CaCO_3$, or K_2CO_3) with or without additive (TBAB) in various solvents (CH_3CN, DMF, CH_3CN/H_2O) was used, only Heck product **10** could be obtained (Table 2, entries 2−4).[33−35] In contrast, we found that the outcome of the cyclization changed completely on exposure of aryl bromide **5** to $Pd(OAc)_2/PPh_3$ and Ag_2CO_3 in toluene/Et_3N (1:1, v/v) at 80 °C to afford tetracyclic aldehyde **9** in 28% yield (Table 2, entry 5),[36] which would be directly transformed to target molecule **2** by deoxygenation. Unfortunately, only compound **10** was still obtained when investigating other ligands such as xantphos and dppp (Table 2, entries 6 and 7). In addition, attempts to isomerize aldehyde **10** to **9** under various conditions (*p*-TsOH, $h\nu$, K_2CO_3, DBU) failed.

Table 1. Optimization of Iron-Catalyzed Aza-Cope−Mannich Cyclization of Aldehyde 6 with 2-Hydroxy Homopropargyl Tosylamine (7) Resulting in Aldehyde 5[a]

entry	$FeCl_3$ (equiv)	TMSCl (equiv)	temp (°C)	time (h)	yield[c] (%)
1	1.2	1.3	rt	3	complex
2	1.2	1.3	reflux	4	53
3	1.2	0.2	reflux	2	69
4	1.3	0	reflux[b]	0.2	83

[a]Reaction conditions: **6** (102 mg, 0.26 mmol), **7** (62 mg, 0.26 mmol), $FeCl_3$, and TMSCl in CH_2Cl_2 (2.6 mL). [b]The oil bath was preheated to 45 °C. [c]Isolated yield.

Since the yield and scale (less than 0.2 mmol scale) of the desired tetracyclic aldehyde **9** could not be improved, we hoped that compound **10** could be deoxygenized and then isomerized to compound **2** (Scheme 3). Under the typical experimental conditions developed by Meleties, i.e., $NaBH_3CN$ (6.0 equiv) and TMSCl (6.0 equiv) in CH_3CN at rt for 24 h,[37] the desired product **3** was obtained in only 12% yield. Furthermore, after several optimizations, the compound **3** could be achieved in 22% yield under the modified procedure: $NaBH_3CN$ (10.0 equiv) and TMSCl (15.0 equiv) and powdered molecular sieves (3 Å) in CH_3CN at rt for 24 h. Subsequently, isomerization of **3** by the treatment with p-TsOH·H_2O in refluxing benzene for 24 h furnished the intermediate **11** in 63% yield.[38] Removal of the tosyl group with sodium naphthalenide and subsequent *N*-methylation led to the Szántay's intermediate **2** in 71% yield,[31] which had been converted to (±)-cycloclavine (**1**) by cyclopropanation by Szántay and co-workers.[12] All of the spectroscopic data of compound **2** were in agreement with those reported previously. This result showed that path a is a concise route (six steps from the known aldehyde **6**, 6% yield) for the synthesis of (±)-cycloclavine (**1**).

To the best of our knowledge, the radical cyclization, an efficient method for synthesis of natural products,[39−43] had not yet been applied to the construction of the C/D ring system of the ergot alkaloids. Herein, the stage was now set for our path b, which was an efficient method for the transformation of compound **5** to **3** (Scheme 4). Thus, the Luche reduction of aldehyde **5** ($NaBH_4$, $CeCl_3{\cdot}7H_2O$ in MeOH) followed by the treatment of the corresponding alcohol under the modified condition developed by Hata (phenyl disulfide, tri-*n*-butylphosphine in benzene) provided the desired sulfide **4** in 81% yield.[44] Then the self-terminating 6-*exo*-*trig* aryl radical−alkene cyclization of sulfide **4** was effected by treatment with tri-*n*-butyltin hydride (n-Bu_3SnH, 2.2 equiv) and a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.3 equiv) in refluxing benzene for 18 h to result in the common intermediate **3** in 91% yield.[42] Thus, the tetracyclic compound

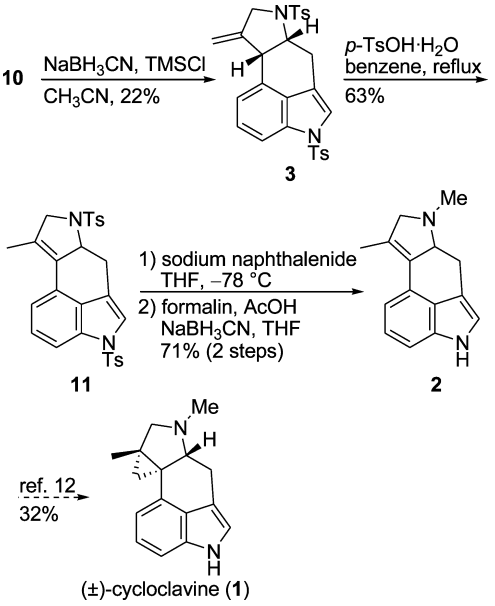
dx.doi.org/10.1021/jo4023588 | J. Org. Chem. 2014, 79, 122−127

Table 2. Optimization of the Intramolecular Heck Reaction of Aldehyde 5 Resulting in Tetracyclic Aldehyde 9 or 10

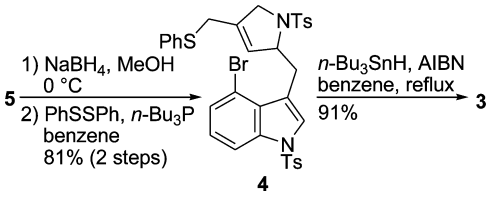
entry	catalyst (equiv)	ligand (equiv)	base (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	product	yield[f] (%)
1	$Pd_2(dba)_3$[a] (0.05)	t-$Bu_3P{\cdot}HBF_4$ (0.2)	DBACO[d] (3.0)	none	dioxane	60	60	NR	
2	$Pd(OAc)_2$ (0.3)	PPh_3 (0.6)	Ag_2CO_3 (1.1)	none	CH_3CN	80	12	**10**	54
3	$Pd(OAc)_2$ (0.3)	dppp[b] (0.6)	$Ag_2CO_3/CaCO_3$ (1.1/1.1)	none	DMF	100	5	**10**	28
4	$Pd(OAc)_2$ (0.05)	PPh_3 (0.1)	K_2CO_3 (2.5)	TBAB[e] (1.0)	CH_3CN/H_2O (10:1, v/v)	85	8	**10**	69
5	$Pd(OAc)_2$ (0.2)	PPh_3 (0.6)	Ag_2CO_3 (2.0)	none	toluene/Et_3N (1:1, v/v)	80	18	**9**	28
6	$Pd(OAc)_2$ (0.1)	xantphos[c] (0.6)	Ag_2CO_3 (2.0)	none	toluene/Et_3N (1:1, v/v)	80	18	**10**	63
7	$Pd(OAc)_2$ (0.2)	dppp (0.4)	Ag_2CO_3 (2.0)	none	toluene/Et_3N (1:1, v/v)	80	18	**10**	12

[a]dba = dibenzylideneacetone. [b]dppp = 1,3-bis(diphenylphosphino)propane. [c]xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. [d]DABCO = 1,4-diazabicyclo[2.2.2]octane. [e]TBAB = tetra-*n*-butylammonium bromide. [f]Isolated yield.

Scheme 3. Synthesis of Compound 2



Scheme 4. Transformation of Compound 5 to 3



3 was achieved in 3 steps with 74% overall yield from aldehyde **5**, which showed that path b is more efficient than path a (15% yield from **5**).

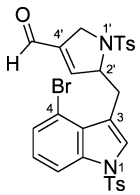
CONCLUSIONS

In summary, we have developed an efficient and concise formal synthesis of (±)-cyclocla vine (**1**) in seven steps and 27% overall yield from the known 2-(4-bromo-1-tosyl-1*H*-indol-3-yl)acetaldehyde (**6**) (path b). Namely, (±)-cyclocla vine could be achieved in 12 steps and 6% overall yield from commercially available 4-bromoindole (**8**). Key features of the synthesis include rapid construction of the C/D ring system of (±)-cyclocla vine (**1**) by using an iron(III)-catalyzed consecutive aza-Cope–Mannich cyclization and an intramolecular Heck reaction or a self-terminating 6-*exo*-*trig* aryl radical–alkene cyclization. Further use of this strategy in the total synthesis of alkaloids is in progress, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Information. All reactions that required anhydrous conditions were carried by standard procedures under argon. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying reagents. Petroleum ether (PE) used had a boiling range of 60–90 °C. Reactions were monitored by TLC on silica gel GF 254 plates. Column chromatography was generally performed through silica gel (200–300 mesh). IR spectra were recorded on a FT-IR spectrophotometer and reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer, as were the DEPT 135 experiments. Chemical shift values are given in ppm and coupling constants (J) in hertz. Residual solvent signals in the ^1H and ^{13}C NMR spectra were used as an internal reference ($CDCl_3$: δ_H = 7.26, δ_C = 77.0 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), ddd (doublet of doublet of doublets). High resolution mass spectra (HRMS) were obtained on a 4G mass spectrometer by using electrospray ionization (ESI) analyzed by quadrupole time-of-flight (QTof).

4-Bromo-3-(2,5-dihydro-4-formyl-1-tosylpyrrol-2-yl)methyl-1-tosylindole (5).

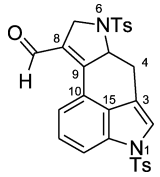


To a solution of 2-hydroxy homopropargyl tosylamine (**7**, 62 mg, 0.26 mmol) in dry CH_2Cl_2 (2.6 mL) was added a mixture of aldehyde **6** (102 mg, 0.26 mmol) and anhydrous $FeCl_3$ (55 mg, 0.34 mmol) in one portion at room temprature. The resultant mixture was stirred in a preheated oil bath (45 °C) for 12 min and then quenched by addition of H_2O (5 mL) with stirring and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography of the residue on silica gel column (PE/EtOAc = 2/1) afforded the aldehyde **5** (132 mg, 83%) as a yellow foam. R_f = 0.40 (silica gel, PE/EtOAc = 2/1). ^1H NMR (400 MHz, $CDCl_3$, δ): 9.41 (1H, s), 8.00 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 4H), 7.55 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.14 (t, J = 8.4 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 5.07 (dd, J = 5.2, 2.4 Hz, 1H), 4.21 (d, J = 14.8 Hz, 1H), 4.03 (ddd, J = 15.2, 5.2, 1.6, 1H), 3.88 (dd, J = 14.8, 5.2 Hz, 1H), 3.33 (dd, J = 14.8, 7.6 Hz, 1H), 2.40 (s, 3H), 2.34

dx.doi.org/10.1021/jo4023588 | J. Org. Chem. 2014, 79, 122–127

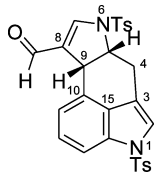
(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 186.5 (CH), 145.9 (CH), 145.5 (C), 144.0 (C), 140.6 (C), 136.1 (C), 134.6 (C), 134.0 (C), 130.0 (CH), 129.9 (CH), 128.2 (C), 128.0 (CH), 127.4 (CH), 127.1 (CH), 126.7 (CH), 125.5 (CH), 117.0 (C), 114.0 (C), 113.0 (CH), 68.2 (CH), 52.5 (CH_2), 31.8 (CH_2), 21.5 (CH_3), 21.4 (CH_3). IR (KBr) $\overline{\nu}_{max}$: 3291, 2925, 1684, 1349, 1172, 705, 668 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{26}BrN_2O_5S_2$ 613.0461, found 613.0461.

1,6-Ditosyl-8-formyl-4,5,6,7-tetrahydroindolo[4,3-*ef*]indole (9).



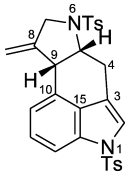
To a solution of aldehyde **5** (122 mg, 0.20 mmol) in toluene/Et_3N (1:1, 20 mL) were added $Pd(OAc)_2$ (9 mg, 0.040 mmol), triphenylphosphine (31 mg, 0.12 mmol), and Ag_2CO_3 (111 mg, 0.40 mmol) under argon. The resultant mixture was heated at 80 °C for 18 h. The solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 (10 mL) and a saturated aqueous $NaHCO_3$ (10 mL) solution. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel column (PE/EtOAc = 2/1) afforded the tetracyclic aldehyde **9** (30 mg, 28%) as a white foam. R_f = 0.37 (silica gel, PE/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.21 (s, 1H), 8.00 (dd, J = 6.0, 2.8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.37−7.29 (m, 7H), 4.78−4.72 (m, 1H), 4.56 (dd, J = 14.4, 4.8 Hz, 1H), 4.38 (dd, J = 14.4, 2.8 Hz, 1H), 3.88 (dd, J = 15.6, 6.4 Hz, 1H), 3.06 (ddd, J = 15.2, 11.2, 1.6 Hz, 1H), 2.40 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 186.3 (CH), 148.9 (C), 145.3 (C), 144.2 (C), 135.1 (C), 133.3 (C), 132.8 (C), 131.1 (C), 130.7 (C), 130.1 (CH), 130.0 (CH), 127.8 (CH), 126.8 (CH), 125.9 (CH), 122.2 (C), 121.9 (CH), 121.8 (CH), 116.4 (C), 116.3 (CH), 67.0 (CH), 54.8 (CH_2), 31.4 (CH_2), 21.6 (CH_3), 21.5 (CH_3). IR (KBr) $\overline{\nu}_{max}$: 2925, 2856, 1663, 1352, 1166, 756, 669 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_5S_2$ 533.1199, found 533.1207.

1,6-Ditosyl-8-formyl-4,5,6,9-tetrahydroindolo[4,3-*ef*]indole (10).



To a solution of aldehyde **5** (98 mg, 0.16 mmol) in CH_3CN (2.0 mL) was added triphenylphosphine (4 mg, 0.015 mmol), and the resulting solution well stirred for 10 min under argon. $Pd(OAc)_2$ (1.8 mg, 0.008 mmol) was then added and the suspension stirred for another 15 min before addition of K_2CO_3 (55 mg, 0.40 mmol), tetra-*n*-butylammonium bromide (52 mg, 0.16 mmol), and H_2O (0.2 mL). The resultant mixture was heated at 85 °C for 8 h and then worked up according to the procedure given above for compound **9** to afford the tetracyclic aldehyde **10** (59 mg, 69%) as a white foam. R_f = 0.18 (silica gel, PE/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.62 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.71−7.69 (m, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 8.4 Hz, 4H), 6.90 (s, 1H), 4.49 (d, J = 7.2 Hz, 1H), 4.45−4.42 (m, 1H), 3.66 (dd, J = 17.6, 2.8 Hz, 1H), 2.97 (dd, J = 17.6, 2.8 Hz, 1H), 2.50 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 185.9 (CH), 149.4 (CH), 145.6 (C), 144.8 (C), 135.4 (C), 134.0 (C), 133.0 (C), 130.1 (CH), 129.9 (CH), 128.6 (C), 128.4 (C), 128.1 (C), 127.2 (CH), 126.7 (CH), 126.2 (CH), 121.7 (CH), 120.1 (CH), 113.7 (C), 111.9 (CH), 65.2 (CH), 41.3 (CH), 21.9 (CH_2), 21.7 (CH_3), 21.6 (CH_3). IR (KBr) $\overline{\nu}_{max}$: 3296, 2927, 1658, 1372, 1172, 774, 671 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{24}N_2O_5S_2Na$ 555.1019, found 555.1021.

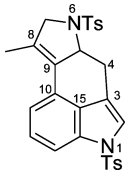
1,6-Ditosyl-8-methylene-4,5,6,7,9-pentahydroindolo[4,3-*ef*]indole (3).



Method 1. According to the procedure in Scheme 3 (path a), to a cold (ice bath) solution of aldehyde **10** (106 mg, 0.20 mmol) and TMSCl (0.38 mL, 3.0 mmol) in dry CH_3CN (4 mL), containing powdered molecular sieves (3 Å), was added $NaBH_3CN$ (126 mg, 2.0 mmol) under argon. After the suspension was stirred at room temperature for 24 h, it was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. The filtrate was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (PE/EtOAc = 5/1) afforded the tetracyclic compound **3** (23 mg, 22%) as a white foam. R_f = 0.41 (silica gel, PE/EtOAc = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.80−7.72 (m, 5H), 7.32−7.19 (m, 6H), 6.94 (d, J = 7.6 Hz, 1H), 5.04 (d, J = 1.2 Hz, 1H), 4.64 (d, J = 2.0 Hz, 1H), 4.30−4.24 (m, 1H), 4.17−4.08 (m, 2H), 3.43 (d, J = 6.8 Hz, 1H), 3.22 (dd, J = 15.6, 6.0 Hz, 1H), 2.59 (ddd, J = 15.6, 10.8, 2.0 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.1 (C), 144.8 (C), 143.7 (C), 135.53 (C), 135.46 (C), 133.4 (C), 129.92 (CH), 129.86 (CH), 128.3 (C), 127.2 (CH), 126.8 (CH), 125.4 (CH), 122.0 (CH), 120.2 (CH), 116.7 (C), 112.3 (CH), 109.5 (CH_2), 59.1 (CH), 51.2 (CH_2), 45.8 (CH), 25.8 (CH_2), 21.54 (CH_3), 21.52 (CH_3), one quaternary carbon overlapped. IR (KBr) $\overline{\nu}_{max}$: 3027, 2925, 1598, 1376, 1176, 764, 670 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_4S_2$ 519.1407, found 519.1419.

Method 2. According to the procedure in Scheme 4 (path b), to a solution of sulfide **4** (268 mg, 0.38 mmol) in dry benzene (10 mL) were added tri-*n*-butyltin hydride (244 mg, 0.84 mmol) and a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (AIBN, 18 mg, 0.11 mmol). The resultant mixture was refluxed for 18 h under under argon and then concentrated under reduced pressure. Flash chromatography of the residue on silica gel (PE/EtOAc = 5/1) afforded the tetracyclic compund **3** (179 mg, 91%). All of the spectrospic data of it were in agreement with those obtained via method 1. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.80−7.73 (m, 5H), 7.32−7.19 (m, 6H), 6.94 (d, J = 7.6 Hz, 1H), 5.04 (s, 1H), 4.65 (d, J = 2.0 Hz, 1H), 4.30−4.24 (m, 1H), 4.16−4.08 (m, 2H), 3.43 (d, J = 6.8 Hz, 1H), 3.22 (dd, J = 15.6, 6.0 Hz, 1H), 2.59 (ddd, J = 15.6, 10.8, 2.0 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 3H).

1,6-Ditosyl-8-methyl-4,5,6,7-tetrahydroindolo[4,3-*ef*]indole (11).

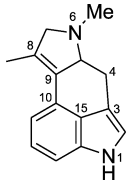


To a solution of tetracyclic compound **3** (119 mg, 0.23 mmol) in benzene (4 mL) was added *p*-TsOH·H_2O (65 mg, 0.34 mmol). The resultant mixture was refluxed for 24 h and then diluted with CH_2Cl_2 (10 mL), quenched with saturated $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (PE/EtOAc = 5/1) afforded tetracyclic compound **11** as a white foam (75 mg, 63%). R_f = 0.36 (silica gel, PE/EtOAc = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.79 (dd, J = 8.0, 5.6 Hz, 3H), 7.72 (d, J = 8.4 Hz, 2H), 7.30−7.17 (m, 7H), 4.50 (dd, J = 3.6, 2.0 Hz, 1H), 4.28−4.16 (m, 2H), 3.73 (dd, J = 15.2, 5.6 Hz, 1H), 2.87 (ddd, J = 15.2, 11.2, 2.0 Hz, 1H), 2.39 (s, 3H), 2.35 (s, 3H), 1.95 (d, 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.9 (C), 143.7 (C), 135.4 (C), 133.6 (C), 133.3 (C), 129.9 (CH), 129.8 (CH), 129.5 (C), 128.8 (C),

dx.doi.org/10.1021/jo4023588 | J. Org. Chem. 2014, 79, 122−127

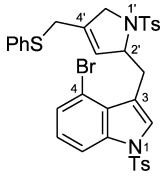
127.72 (CH), 127.67 (C), 126.8 (CH), 125.47 (CH), 125.45 (C), 120.5 (CH), 118.8 (CH), 117.8 (C), 112.7 (CH), 66.2 (CH), 60.8 (CH_2), 31.5 (CH_2), 21.52 (CH_3), 21.48 (CH_3), 12.6 (CH_3). IR (KBr) $\overline{\nu}_{max}$: 3028, 2924, 1596, 1349, 1164, 757, 670 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_4S_2$ 519.1407, found 519.1413.

6,8-Dimethyl-4,5,6,7-tetrahydro-1*H*-indolo[4,3-*ef*]indole (2).



To a stirred solution of compound **11** (78 mg, 0.15 mmol) in THF (4 mL) was added sodium naphthalenide (0.67 M solution in THF; 2.2 mL, 1.47 mmol) at −78 °C under argon. The resultant mixture was stirred for 6 min at this temperature and quenched with saturated NH_4Cl (5 mL). The mixture was made basic with saturated $NaHCO_3$ (10 mL) and then extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a crude amine, which was used without further purification. To a stirred solution of this amine in MeOH (7 mL) were added AcOH (0.16 mL), $NaBH_3CN$ (68 mg, 1.08 mmol), and formalin (0.091 mL, 1.21 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ (5 mL), concentrated under reduced pressure, and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (MeOH/$CHCl_3$ = 1/5) afforded target compound **2** as a brown foam (24 mg, 71% yield). R_f = 0.34 (silica gel, MeOH/$CHCl_3$ = 1/4). All spectral data were in agreement with those of previous report. ^1H NMR (400 MHz, $CDCl_3$, δ): 8.14 (s, 1H), 7.27−7.19 (m, 3H), 6.88 (s, 1H), 3.91 (dd, *J* = 14.0, 3.6 Hz, 1H), 3.72−3.66 (m, 1H), 3.51 (ddd, *J* = 13.6, 4.8, 1.6 Hz, 1H), 3.34 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.69 (ddd, *J* = 14.0, 10.8, 1.6 Hz, 1H), 2.59 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 134.1 (C), 130.6 (C), 130.2 (C), 127.3 (C), 125.9 (C), 123.0 (CH), 118.3 (CH), 114.7 (CH). 112.2 (C), 109.2 (CH), 72.3 (CH), 68.3 (CH_2), 40.5 (CH_3), 29.4 (CH_2), 13.6 (CH_3). IR (KBr) $\overline{\nu}_{max}$: 3209, 2927, 1607, 1445, 1116, 912, 740 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{17}N_2$ 225.1386, found 225.1392.

4-Bromo-3-[2,5-dihydro-4-(phenylthio)methyl-1-tosylpyrrol-2-yl]methyl-1-tosylindole (4).



To a solution of aldehyde **5** (245 mg, 0.40 mmol) in MeOH (6 mL) and THF (1 mL) were added $CeCl_3 \cdot 7H_2O$ (164 mg, 0.44 mmol) and $NaBH_4$ (19 mg, 0.50 mmol) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with ether (10 mL), quenched with saturated $NaHCO_3$ (10 mL), and extracted with EtOAc (15 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (PE/EtOAc = 1/2) gave the crude alcohol as a white solid, which was then dissolved in benzene (14 mL). To this solution were added diphenyl disulfide (873 mg, 4.00 mmol) and tri-*n*-butylphosphine (809 mg, 4.00 mmol) at room temperature. The resultant mixture was stirred for 30 min and then concentrated under reduced pressure. Flash chromatography of the residue on silica gel (PE/EtOAc = 4/1) afforded the sulfide **4** as a white foam (229 mg, 81% for two steps). R_f = 0.45 (silica gel, PE/EtOAc = 5/1). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.96 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 8.4, 4.0 Hz, 4H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 3H), 7.20−7.19 (m, 5H), 7.12−7.06 (m, 3H), 5.15 (s, 1H), 4.73 (d, *J* = 1.6 Hz, 1H), 4.19−4.07 (m, 2H), 3.74 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.33 (d, *J* = 14.4 Hz, 1H), 3.26 (d, *J* = 14.4 Hz, 1H), 2.93 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.39 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.2 (C), 143.4 (C), 136.2 (C), 135.3 (C), 134.8 (C), 134.7 (C), 134.5 (C), 130.8 (CH), 129.9 (CH), 129.7 (CH), 128.9 (CH), 128.8 (C), 127.9 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 126.0 (CH), 125.3 (CH), 118.4 (C), 114.4 (C), 112.8 (CH), 67.4 (CH), 56.2 (CH_2), 33.1 (CH_2), 32.9 (CH_2), 21.49 (CH_3), 21.46 (CH_3). IR (KBr) $\overline{\nu}_{max}$: 3025, 2925, 1597, 1375, 1172, 756, 670 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{34}H_{31}BrN_2O_4S_3Na$ 729.0522, found 729.0545.

■ ASSOCIATED CONTENT

Supporting Information

^1H, ^{13}C NMR (DEPT 135) spectra of compounds **5**, **9**, **10**, **3**, **11**, **2**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: caoxplzu@163.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Basic Research Program (973 program) of China (Grant No. 2010CB833203), the National Natural Science Foundation of China (Grant Nos. 21272098, 21190034, 21061160494, and J1103307), the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1138), the Fundamental Research Funds for the Central University (FRFCU: lzujbky-2013-ct02), and the 111 Project for financial support.

■ REFERENCES

(1) Somei, M.; Yokoyama, Y.; Murakami, Y.; Ninomiya, I.; Kiguchi, T.; Naito, T. Recent Synthetic Studies on the Ergot Alkaloids and Related Compounds. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 2000; Vol. *54*, pp 191−257.
(2) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.
(3) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946.
(4) Park, I.-K.; Park, J.; Cho, C.-G. *Angew. Chem.* **2012**, *124*, 2546.
(5) Rafferty, R. J.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 519.
(6) Schönherr, H.; Leighton, J. L. *Org. Lett.* **2012**, *14*, 2610.
(7) Shan, D.; Gao, Y.; Jia, Y. X. *Angew. Chem., Int. Ed.* **2013**, *52*, 4902.
(8) Trost, B. M.; McDougall, P. J. *Org. Lett.* **2009**, *11*, 3782.
(9) Xu, Q. L.; Dai, L. X.; You, S. L. *Chem. Sci.* **2013**, *4*, 97.
(10) Yonemitsu, O.; Cerutti, P.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 3941.
(11) Stauffacher, D.; Niklaus, P.; Tscherter, H.; Weber, H. P.; Hofmann, A. *Tetrahedron* **1969**, *25*, 5879.
(12) Incze, M.; Dörnyei, G.; Moldvai, I.; Temesvári-Major, E.; Egyed, O.; Szántay, C. *Tetrahedron* **2008**, *64*, 2924.
(13) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704.
(14) Lu, L. Q.; Chen, J. R.; Xiao, W. J. *Acc. Chem. Res.* **2012**, *45*, 1278.
(15) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.
(16) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.
(17) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.
(18) Overman, L. E. *Aldrichimica Acta* **1995**, *28*, 107.
(19) Brüggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284.
(20) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658.

(21) Earley, W. G.; Jacobsen, J. E.; Madin, A.; Meier, G. P.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18046.
(22) Martin, C. L.; Nakamura, S.; Otte, R.; Overman, L. E. *Org. Lett.* **2011**, *13*, 138.
(23) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568.
(24) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894.
(25) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.
(26) Overman, L. E.; Kakimoto, M.-A. *J. Am. Chem. Soc.* **1979**, *101*, 1310.
(27) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579.
(28) Overman, L. E.; Mendelson, L. T.; Flippin, L. A. *Tetrahedron Lett.* **1982**, *23*, 2733.
(29) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041.
(30) Carballo, R. M.; Purino, M.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2010**, *12*, 5334.
(31) Inuki, S.; Iwata, A.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 2072.
(32) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, *5*, 3679.
(33) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
(34) Liu, Q.; Jia, Y. *Org. Lett.* **2011**, *13*, 4810.
(35) Yokoyama, Y.; Kondo, K.; Mitsuhashi, M.; Murakami, Y. *Tetrahedron Lett.* **1996**, *37*, 9309.
(36) Bennasar, M. L.; Zulaica, E.; Solé, D.; Roca, T.; García-Díaz, D.; Alonso, S. *J. Org. Chem.* **2009**, *74*, 8359.
(37) Box, V. G. S.; Meleties, P. C. *Tetrahedron Lett.* **1998**, *39*, 7059.
(38) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *130*, 300.
(39) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1988**, *53*, 695.
(40) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796.
(41) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 1321.
(42) Boger, D. L.; Wysocki, R. J., Jr. *J. Org. Chem.* **1989**, *54*, 1238.
(43) Boger, D. L.; Wysocki, R. J., Jr.; Ishizaki, T. *J. Am. Chem. Soc.* **1990**, *112*, 5230.
(44) Hata, T.; Sekine, M. *Chem. Lett.* **1974**, 837.