JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

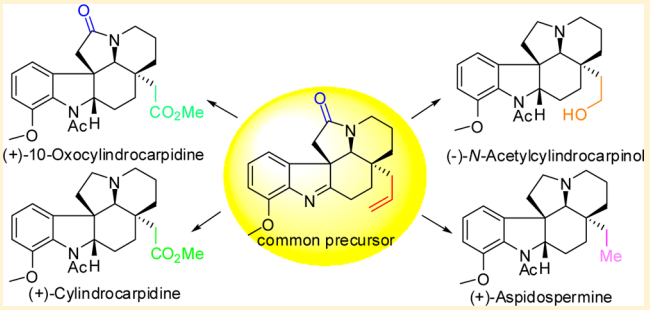
Catalytic Enantioselective and Divergent Total Synthesis of (+)-10-Oxocylindrocarpidine, (+)-Cylindrocarpidine, (−)-*N*-Acetylcylindrocarpinol, and (+)-Aspidospermine

Xiao-Lei Shen,† Rui-Rui Zhao,† Ming-Jie Mo,† Fang-Zhi Peng,* Hong-Bin Zhang, and Zhi-Hui Shao*

Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, People's Republic of China

Supporting Information

ABSTRACT: The catalytic enantioselective and divergent total syntheses of *Aspidosperma* alkaloids (+)-10-oxocylindrocarpidine **7**, (+)-cylindrocarpidine **1**, (−)-*N*-acetylcylindrocarpinol **6**, and (+)-aspidospermine **8** have been accomplished in 11 steps from a common precursor (**15**) on the basis of a highly concise route. The route features three metal-catalyzed reactions, including the key Pd-catalyzed decarboxylative asymmetric allylation of carbazolones developed in our laboratory. Our syntheses, using a combination of C−H activation, enantioselective catalysis, and collective synthesis, represent the first total synthesis of 10-oxocylindrocarpidine and the first asymmetric total synthesis of cylindrocarpidine and *N*-acetylcylindrocarpinol.



INTRODUCTION

The *Aspidosperma* alkaloids have long been the targets in the chemical synthesis community because of their complex structures and diverse biological activities.[1] To date, more than 250 members in this family have been isolated from various biological sources[2] and are composed of vastly diverse structural elements. Cylindrocarpidine **1** (Figure 1), isolated in 1960 from *Aspidosperma cylindrocarpon* Muell.-Arg. by Djerassi,[3a,b] is a representative member of a series of *Aspidosperma* alkaloids with an angular carboxymethyl group. The compounds of this series differ in the nature of their N substituents (Figure 1). From the same plant source, the same group also isolated a different alkaloid, named *N*-acetylcylindrocarpinol **6**, in which the angular carboxymethyl group was replaced by an angular 2-hydroxyethyl moiety.[3c] 10-Oxocylindrocarpidine **7** is a more highly oxidized alkaloid that was isolated from *Tabernaemontana amygdalifolia* by Achenbach.[4] Aspidospermine **8** is the prototypical member of the group. **8** was first isolated in 1878 from the bark of *Aspidosperma quebracho* by Fraude[5] and later from several other natural sources.[6] It has been shown to exhibit a variety of biological activities,[7−9] although aspidospermidine **9** with a less oxygenated indole core is not of pharmacological interest.

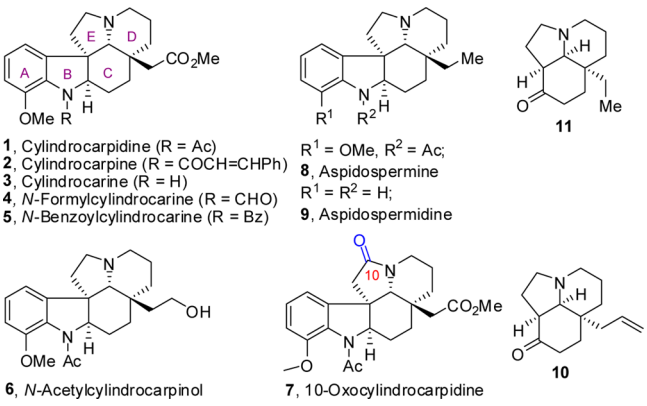


Figure 1. Natural products and intermediate ketones **10** and **11**.

The only total synthesis of cylindrocarpidine **1** and *N*-acetylcylindrocarpinol **6** disclosed to date was reported in 1975 by Saxton and co-workers, who cleverly employed a late-stage Fischer indole synthesis via the ketone **10**.[10] In this report, however, cylindrocarpidine **1** and *N*-acetylcylindrocarpinol **6** were synthesized racemically, and chiral total syntheses of these two targets have not yet been realized.[11] With regard to 10-oxocylindrocarpidine **7**, this highly oxidized alkaloid has not yet been synthesized by means of total synthesis to date.[11] This background in combination with our efforts in the catalytic enantioselective synthesis of polycyclic alkaloids[12] led us to focus our attention on the enantioselective total syntheses of these targets.

On the other hand, we noticed that, in contrast to fewer synthesis reports of the alkaloids cylindrocarpidine **1**, *N*-acetylcylindrocarpinol **6**, and 10-oxocylindrocarpidine **7**, the alkaloid aspidospermine **8** has been successfully synthesized by

Received: December 10, 2013
Published: February 21, 2014

   dx.doi.org/10.1021/jo402741g | *J. Org. Chem.* 2014, 79, 2473−2480

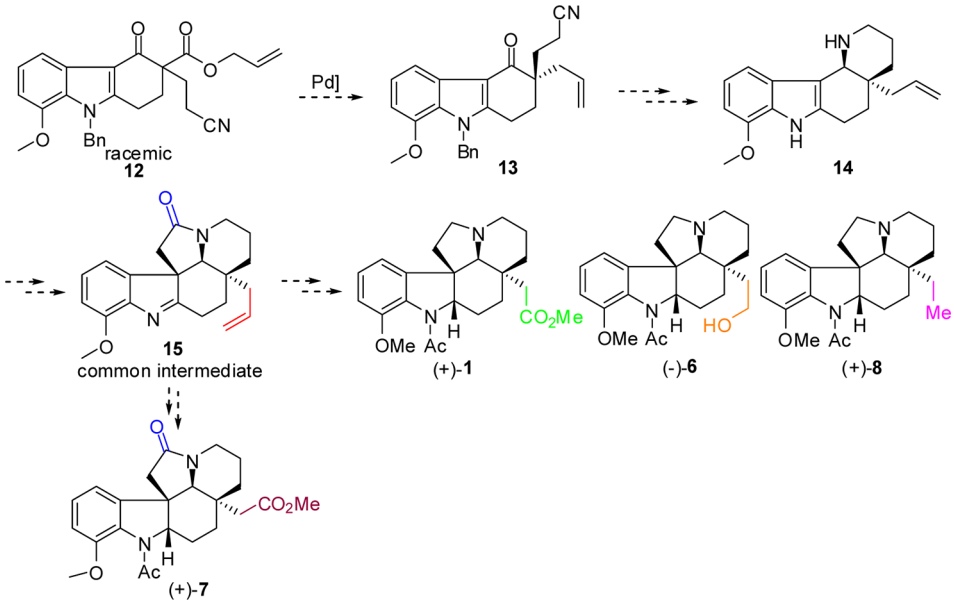
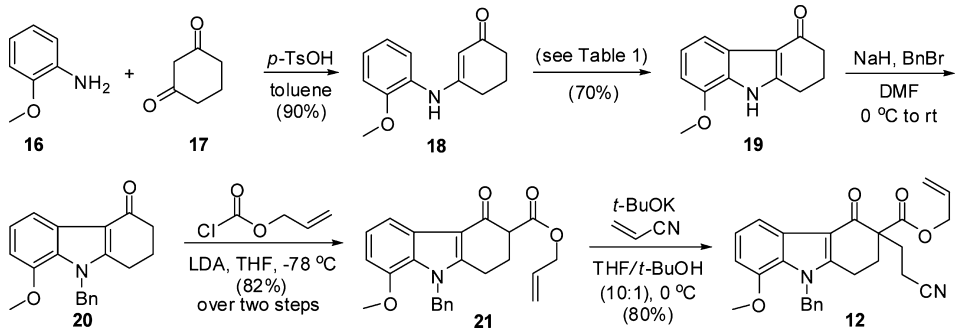


Figure 2. Working plan for the catalytic enantioselective and divergent total synthesis of (+)-7, (+)-1, (−)-6, and (+)-8.

Scheme 1. Synthesis of the Decarboxylative Allylation Precursor 12



many research groups.[13] The first synthesis of aspidospermine **8** was achieved by Stork in 1963, exploiting a Fischer indolization of the tricyclic ketone intermediate **11**.[13a] In their classic synthesis, the ketone **11** was prepared as a key intermediate in approximately 13 steps. Since then, many other syntheses or formal syntheses have been reported using various beautiful approaches.[13b−u] Recently, Boger extended his signature [4 + 2]/[3 + 2] cycloaddition methodology[14] to accomplish a nice total synthesis of aspidospermine.[13v] Resolution of the resulting racemic aspidospermine by chiral phase chromatography provided (+)-aspidospermine.[13v] Despite these elegant advances, we sought to access aspidospermine by implementation of an approach fundamentally different from all prior reports.

Recently, Lupton[15] and we[16] concurrently achieved the direct enantioselective assembly of C3-chiral carbazolones using Pd-catalyzed decarboxylative allylation of carbazolones.[17] In our previous work, we preliminarily validated the utility of this methodology by accomplishing the enantioselective total syntheses of aspidospermidine[16] and limaspermidine.[18] Pleasingly, this methodology has been very recently applied to the total synthesis of methyl chanofruticosinate alkaloids by the research group of Ma.[19] In combination with the nice use of intramolecular oxidative coupling, they achieved the first enantioselective total synthesis of (+)-methyl *N*-decarbomethoxychanofruticosinate.[19] Herein, we describe another successful example toward the catalytic enantioselective total synthesis of (+)-10-oxocylindrocarpidine **7**, (+)-cylindrocarpidine **1**, (−)-*N*-acetylcylindrocarpinol **6**, and (+)-aspidospermine **8**. Our approach is ideally suitable for (+)-10-oxocylindrocarpidine **7**, as its C10 carbonyl group can be directly installed from the enantioenriched hydrocarbazole-piperidine **14** through Heathcock-type E-ring annulation[20] (Figure 2). An added advantage of the present approach is that unlike our previous syntheses of (−)-aspidospermidine[16] and (−)-limaspermidine,[18] wherein the angular ethyl side chain and the angular 2-hydroxyethyl moiety were introduced separately before the E-ring annulation, late-stage unified installation of the angular ethyl side chain, the angular 2-hydroxyethyl moiety, and the angular carboxymethyl function through the manipulations of the allyl group of the common pentacyclic intermediate **15** also allows a concise and divergent asymmetric synthesis of (+)-cylindrocarpidine **1**, (−)-*N*-acetylcylindrocarpinol **6**, and (+)-aspidospermine **8** (Figure 2).

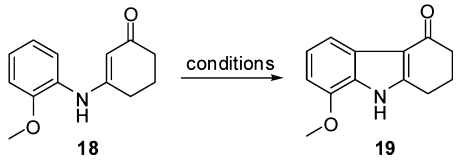
RESULTS AND DISCUSSION

Our total synthesis was initiated with the preparation of the decarboxylative allylation precursor **12** from inexpensive commercially available 2-methoxyaniline **16** and cyclohexane-1,3-dione **17** (Scheme 1), which were subject to condensation in the presence of *p*-TsOH to afford enaminone **18** in 90% yield. Cyclization of **18** into carbazolone **19** has previously been

dx.doi.org/10.1021/jo402741g | J. Org. Chem. 2014, 79, 2473−2480

reported by Kibayashi[21] using a stoichiometric amount of $Pd(OAc)_2$; however, this protocol involving electrophilic aromatic palladation gave **19** in very low yield (19%).[21] Thus, a different practical synthesis of **19** was undertaken. Fischer indole condensation[22] between (2-methoxyphenyl)hydrazine hydrochloride and cyclohexane-1,3-dione failed to give **19**. After several attempts, we found that C−H bond activation[23] was more suitable for the synthesis of carbazolone **19**. Using the procedure developed by Li and co-workers in the synthesis of carbazolones,[24a] we obtained carbazolone **19** from enaminone **18** in 42% yield (Table 1, entry 1). Pleasingly,

Table 1. Synthesis of Carbazolone 19 via C−H bond Activation

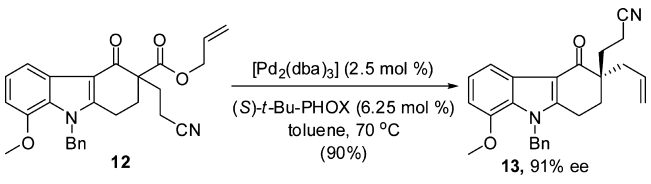


entry	conditions	yield (%)
1	$Pd(OAc)_2$ (0.15 equiv)/$Cu(OAc)_2$ (0.4 equiv), O_2, EtOH, reflux	42
2	$Pd(OAc)_2$ (0.1 equiv)/$Cu(OAc)_2$ (3 equiv)/K_2CO_3 (3 equiv), DMF, 140 °C	70
3	$Pd(OAc)_2$ (0.07 equiv) /$Cu(OAc)_2$ (3 equiv)/K_2CO_3 (3 equiv), DMF, 140 °C	70
4	$Pd(OAc)_2$ (0.05 equiv)/$Cu(OAc)_2$ (3 equiv)/K_2CO_3 (3 equiv), DMF, 140 °C	60

using Glorius's carbazolone synthesis protocol,[24b] we obtained the desired **19** from **18** in good yields (Table 1, entries 2−4). Under the optimized reaction conditions, the carbazolone **19** was obtained in 70% yield. Then protection of the indolyl nitrogen atom of **19** with BnBr gave **20**. Deprotonation of **20** with LDA and acylation of the resulting enolate with allyl chloroformate provided **21**. Subsequent Michael addition with acrylonitrile afforded the decarboxylative allylation precursor, β-keto ester **12**, in 80% yield.

Then we investigated the palladium-catalyzed enantioselective decarboxylative allylation of **12**. Pleasingly, a methoxyl group on the benzene ring was well tolerated, and the desired enantioenriched carbazolone **13** was obtained in 90% yield with 91% ee (Scheme 2).

Scheme 2. Palladium-Catalyzed Enantioselective Decarboxylative Allylation of 12



With the carbazolone **13** in hand, the synthesis of the planned pentacyclic intermediate **15** was then undertaken (Scheme 3). Hydrolysis of the nitrile group of **13** gave chiral amide **22**, which was then transformed into the tetracyclic lactam **23** in good yield without loss of enantiomeric purity. Then reduction of the amide group with $LiAlH_4$ and subsequent *N*-debenzylation with Na/NH_3 afforded the tetracyclic amine **14** in good yield (78% over two steps). The amine **14** was then ready for the installation of the E ring. Heathcock-type annulation[20] was employed, as it is ideally suited for the *direct* introduction of the carbonyl group of (+)-10-oxocylindrocarpidine **7**. At the same time, it was also suited for the *unified* synthesis of (+)-cylindrocarpidine **1**, (−)-*N*-acetylcylindrocarpinol **6**, and (+)-aspidospermine **8** via a late-stage chemical selective reduction of the amide group of the common intermediate **15**. Thus, acylation of **14** with 2-chloroacetyl chloride afforded the amide **25**. **25** was subjected to a Finkelstein reaction with NaI in acetone to produce the corresponding iodide, which was mediated by AgOTf to deliver the key pentacyclic intermediate **15**.

Having developed a catalytic enantioselective route to the key pentacyclic intermediate **15**, we converted **15** into the oxidized alkaloids 10-oxocylindrocarpidine, cylindrocarpidine, *N*-acetylcylindrocarpinol, and the prototypical alkaloid aspidospermine in a highly concise and divergent way. Reduction of the imine group of **15** with $NaBH_4$ provided **26**, which was acylated using acetic anhydride to afford **27** (Scheme 4A). Oxidation of the allyl group using the osmate−periodate procedure led to the aldehyde **28** in 85% yield. Subsequent oxidation of the aldehyde group with I_2 in the presence of KOH[25] gave the target (+)-10-oxocylindrocarpidine,[26] thus completing the total synthesis of this target. Following the same reaction sequence, the natural enantiomer (−)-10-oxocylindrocarpidine could also be synthesized in principle using (*R*)-*t*-Bu-PHOX ligand in the palladium-catalyzed decarboxylative allylation of **12**.

Reduction of the imine and the amide groups of the common intermediate **15** using $LiAlH_4$ instead of $NaBH_4$ afforded the amine **29** (Scheme 4B), which was acylated using acetic anhydride to give **30**. Similarly, oxidation of the allyl group using the osmate−periodate procedure led to the aldehyde **31**. Treatment of **31** with I_2/KOH/MeOH and $NaBH_4$, respectively, provided (+)-cylindrocarpidine and (−)-*N*-acetylcylindrocarpinol,[26] thus completing the asymmetric total synthesis of these two targets. More flexibly, using a two-step transformation involving a mercaptalation and a subsequent Raney nickel hydrogenation, the angular ethyl side chain was introduced and (+)-aspidospermine **8** was obtained. The ^1H and ^{13}C NMR spectral data obtained on this material matched those reported[13v] by Boger et al.

■ CONCLUSION

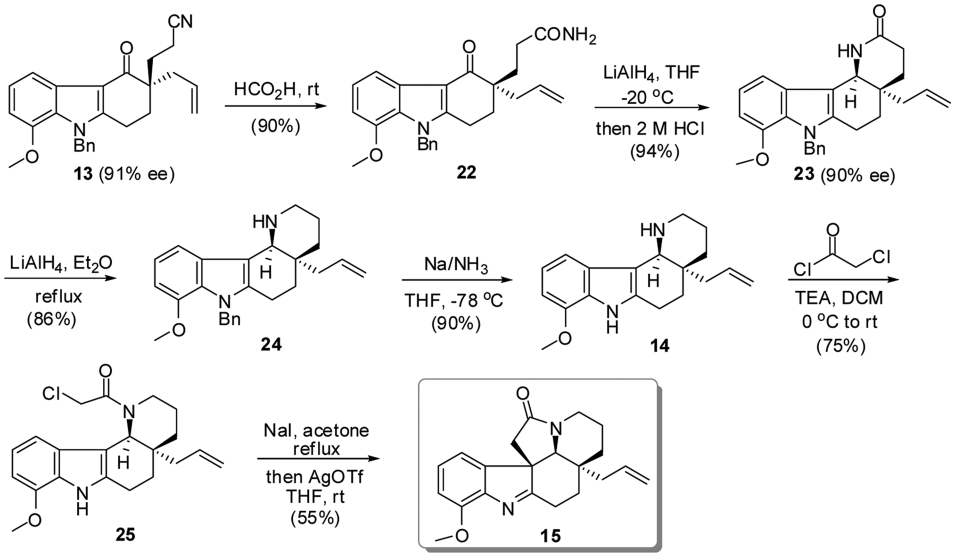
The catalytic enantioselective and divergent total syntheses of (+)-10-oxocylindrocarpidine **7**, (+)-cylindrocarpidine **1**, (−)-*N*-acetylcylindrocarpinol **6**, and (+)-aspidospermine **8** have been accomplished in 11 steps from the common precursor **15** on the basis of a highly concise route. The route features three metal-catalyzed reactions, including the key Pd-catalyzed decarboxylative asymmetric allylation developed in our laboratory. The present syntheses represent the first total synthesis of (+)-10-oxocylindrocarpidine and the first asymmetric total synthesis of (+)-cylindrocarpidine and (−)-*N*-acetylcylindrocarpinol. The present work also shows an example of combining C−H activation, enantioselective catalysis, and collective synthesis in modern natural product synthesis.

■ EXPERIMENTAL SECTION

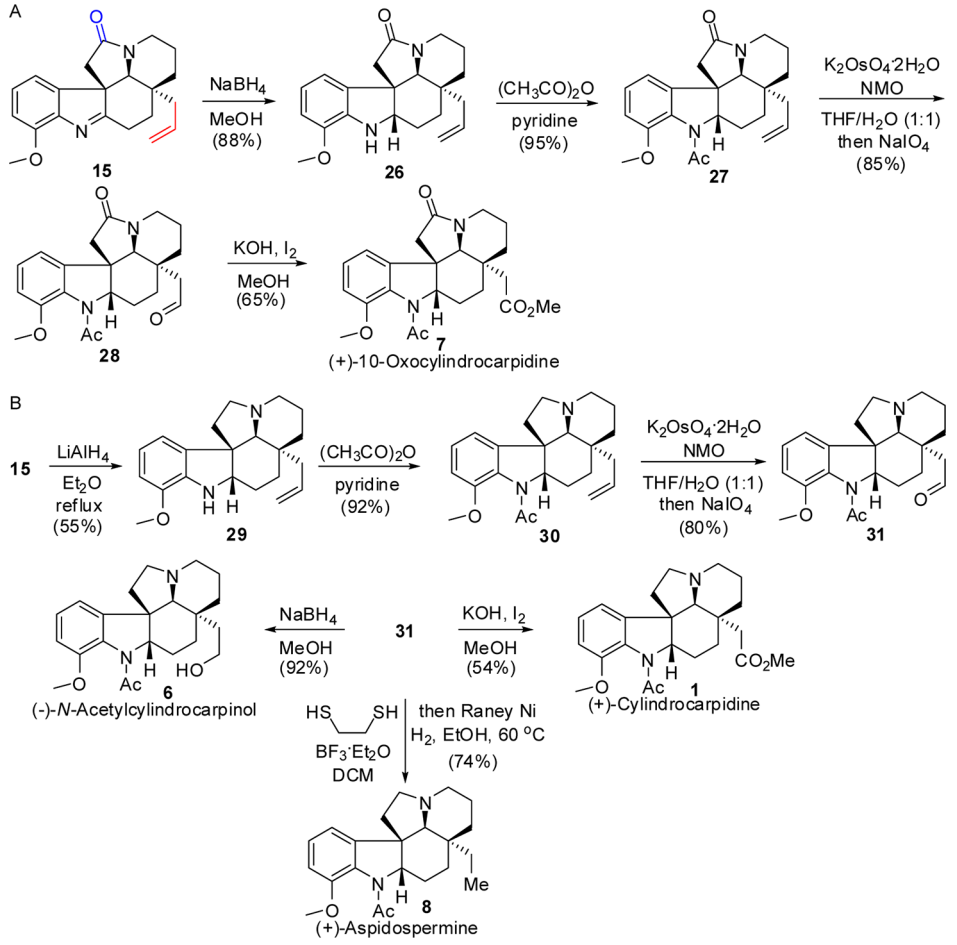
General Experimental Methods. ^1H NMR and ^{13}C NMR spectra were recorded with a 300 or 400 MHz spectrophotometer. Chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz. High-resolution mass spectrometry (HRMS) was recorded on a

dx.doi.org/10.1021/jo402741g | J. Org. Chem. 2014, 79, 2473−2480

Scheme 3. Synthesis of the Common Pentacyclic Intermediate 15



Scheme 4. End Game for the Divergent Total Synthesis of (+)-10-Oxocylindrocarpidine, (+)-Cylindrocarpidine, (−)-*N*-Acetylcylindrocarpinol, and (+)-Aspidospermine



spectrometer using a time-of-flight (TOF) analyzer. Optical rotations were measured on a polarimeter. Flash column chromatography was performed on silica gel (230−400 mesh). All palladium catalysts were purchased from Acros and Adamas. All chemicals and solvents were used as received without further purification unless otherwise stated.

Compound 19. A solution of compound **18**[21] (1.0 g, 4.6 mmol, 1 equiv), $Pd(OAc)_2$ (72.3 mg, 0.32 mmol, 0.07 equiv), $Cu(OAc)_2$ (2.7 g, 13.8 mmol, 3 equiv), and K_2CO_3 (1.9 g, 13.8 mmol, 3 equiv) in DMF (40 mL) was stirred for 3 h at 140 °C. After it was cooled to room temperature, the solution was filtered through a pad of Celite, and the residue was washed with ethyl acetate. The solution was washed with

dx.doi.org/10.1021/jo402741g | J. Org. Chem. 2014, 79, 2473−2480

aqueous ammonia (10%), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography (ethyl acetate/petroleum ether 1/2) to give compound **19** (694 mg, 70% yield) as a black solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (m, 2H), 2.59 (t, J = 6.9 Hz, 2H), 2.98 (t, J = 6.3 Hz, 2H), 3.95 (s, 3H), 6.71 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5, 23.7, 38.1, 55.4, 103.8, 113.9, 114.2,123.1, 125.7, 126.1,145.5, 150.1, 194.4; HRMS (EI) calcd for $C_{13}H_{13}NO_2$ $[M]^+$ 215.0946, found 215.0951.

Compound 21. To a solution of compound **19** (2.45 g, 11.4 mmol, 1 equiv) in DMF (50 mL) at 0 °C was slowly added NaH (328 mg, 13.6 mmol, 1.2 equiv). The resulting mixture was stirred for 2 h and then warmed to room temperature. To the solution was added BnBr (2.34 g, 13.6 mmol, 1.2 equiv), and the mixture was stirred for 2 h. The reaction was quenched with H_2O. The solution was extracted with DCM, dried over Na_2SO_4, and concentrated to dryness. The crude product **20** was used in the next step without further purification.

To a solution of the crude product **20** (334 mg, 1.1 mmol, 1 equiv) in dry THF (10 mL) at −78 °C was slowly added a solution of 2 M LDA in dry THF (0.65 mL, 1.3 mmol, 1.2 equiv) under an N_2 atmosphere, and the resulting solution was stirred for 1 h at −78 °C. Then a solution of allyl chloroformate (157 mg, 1.3 mmol, 1.2 equiv) in dry THF (8 mL) was added, and the resulting mixture was stirred for 1 h at −78 °C. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (8 mL). After removal of the solvent THF in vacuo, the resultant residue was taken up in water (10 mL) and the aqueous mixture was extracted with DCM (3 × 15 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1/4) to give pure compound **21** (500 mg, 82% yield over two steps) as a canary yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (m, 1H), 2.57 (m, 1H), 2.78 (m, 1H), 3.02 (m, 1H), 3.60 (dd, J = 4.5 Hz, J = 4.8 Hz, 1H), 3.80 (s, 3H), 4.69 (m, 2H), 5.23 (m, 1H), 5.34 (m, 1H), 5.66 (s, 2H), 5.94 (m, 1H), 6.74 (d, J = 7.5 Hz, 1H), 7.01 (m, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.27−7.34 (m, 3H), 7.92 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 26.4, 49.5, 53.4, 55.6, 65.7, 105.3, 112.4, 114.4, 118.3, 123.5, 125.9, 126.6, 127.1, 127.4, 128.8, 132.0, 137.8, 147.1, 151.4, 170.4, 187.8; HRMS (EI) calcd for $C_{24}H_{23}NO_4$ $[M]^+$ 389.1627, found 389.1633.

Compound 12. To a solution of compound **21** (500 mg, 1.3 mmol, 1 equiv) in dry THF (10 mL) and *t*-BuOH (1.0 mL) at 0 °C was added *t*-BuOK (176 mg, 1.56 mmol, 1.2 equiv), and the resulting mixture was stirred for 10 min. Then acrylonitrile (83 mg, 1.56 mmol, 1.2 equiv) was added, and the resulting solution was stirred for another 3 min. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with DCM (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1/4) to give pure compound **12** (455 mg, 80% yield) as a yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21 (m, 1H), 2.35 (m, 2H), 2.59−2.73 (m, 3H), 2.87 (m, 1H), 3.01 (m, 1H), 3.82 (s, 3H), 4.61 (m, 2H), 5.18 (m, 2H), 5.68 (s, 2H), 5.81 (m, 1H), 6.76 (d, J = 7.8 Hz, 1H), 7.01 (m, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.26−7.35 (m, 3H), 7.90 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.4, 19.7, 30.0, 31.4, 49.6, 55.6, 56.1, 66.0, 105.5, 112.3, 114.3, 118.8, 119.8, 123.7, 125.9, 126.8, 127.2, 127.5, 128.9, 131.4, 137.6, 147.2, 150.5, 171.0, 188.8; HRMS (EI) calcd for $C_{27}H_{26}N_2O_4$ $[M]^+$ 442.1893, found 442.1888.

Compound 13. A round-bottom flask (25 mL) was equipped with a magnetic stirring bar and flame-dried under vacuum. After the flask was cooled under dry nitrogen, $[Pd_2(dba)_3]$ (5.5 mg, 0.006 mmol) and (*S*)-*t*-Bu-PHOX (5.9 mg, 0.015 mmol) were added. Then dry toluene (7 mL) was added and the resulting solution was stirred at room temperature for 30 min. Compound **12** (106 mg, 0.24 mmol) was added to the resulting solution, and the mixture was stirred at 70 °C. When the reaction was complete by TLC (12 h), the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1/4) to give the allylated compound **13** (86 mg, 90% yield).: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.78 (m, 1H), 1.98−2.14 (m, 3H), 2.18−2.49 (m, 4H), 2.77 (m, 2H), 3.72 (s, 3H), 4.88−5.07 (m, 2H), 5.59 (s, 2H), 5.69 (m, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 6.6 Hz, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.16−7.23 (m, 3H), 7.82 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6, 19.0, 30.8, 31.4, 39.3, 47.0, 49.5, 55.6, 105.3, 112.0, 114.3, 119.0, 120.3, 123.5, 125.9, 126.8, 127.3, 127.5, 128.9, 133.2, 137.8, 147.1, 150.1, 195.6; HRMS (EI) calcd for $C_{26}H_{26}N_2O_2$ $[M]^+$ 398.1994, found 398.1981; $[\alpha]_D^{20}$ = −11.5° (c = 0.4 M, $CHCl_3$); HPLC (Chiralpak PA-2, 2-propanol/*n*-hexane 30/70, flow rate 0.5 mL/min, λ = 214 nm) t_{major} = 47.38 min, t_{minor} = 57.18 min.

Compound 22. Compound **13** (1 g, 2.5 mmol) was dissolved in anhydrous formic acid (15 mL), and the resulting solution was stirred at room temperature until the starting material disappeared. After removal of the solvent in vacuo, the resultant residue was taken up in water (20 mL) and the aqueous solution was extracted with DCM. The organic extract was washed with saturated aqueous $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. The solution was concentrated to dryness in vacuo to give pure compound **22** (940 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.84−1.95 (m, 1H), 1.98−2.14 (m, 3H), 2.19−2.38 (m, 3H), 2.46 (m, 1H), 2.84 (m, 2H), 3.80 (s, 3H), 4.91−5.17 (m, 2H), 5.57 (d, J = 16.2 Hz, 1H), 5.65−5.93 (m, 3H), 6.06 (s, 1H), 6.72 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 6.6 Hz, 2H), 7.18 (t, J = 7.8 Hz, 1H), 7.25−7.33 (m, 3H), 7.91 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 30.4, 31.0, 31.6, 39.7, 47.3, 49.4, 55.6, 105.1, 112.2, 114.3, 118.2, 123.3, 125.5, 125.9, 126.8, 127.4, 128.8, 134.1, 137.9, 147.1, 150.6, 176.0, 197.2; HRMS (EI) calcd for $C_{26}H_{28}N_2O_3$ $[M]^+$ 416.2100, found 416.2094; $[\alpha]_D^{20}$ = −12° (c = 0.85 M, $CHCl_3$).

Compound 23. To a solution of compound **22** (1.2 g, 3 mmol, 1 equiv) in anhydrous THF (25 mL) at −20 °C was added LAH (228 mg, 6 mmol, 2.0 equiv), and the resulting mixture was stirred at −20 °C for 5 h. The reaction mixture was quenched by addition of water (5 mL) and 2 M HCl (10 mL). The reaction mixture was extracted with DCM (3 × 10 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine. Then the organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash silica gel chromatography (DCM/MeOH 30/1) to give pure compound **23** (1.1 g, 94% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (m, 1H), 1.81−1.92 (m, 1H), 1.94−2.12 (m, 3H), 2.22 (m, 1H), 2.33−2.51 (m, 2H), 2.51−2.71 (m, 2H), 3.82 (s, 3H), 4.49 (s, 1H), 4.96 (m, 1H), 5.09 (m, 1H), 5.65 (dd, J = 16.5 Hz, J = 16.5 Hz, 2H), 5.76−5.96 (m, 2H), 6.67 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 6.9 Hz, 2H), 7.09 (m, 2H), 7.22−7.31 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.7, 25.4, 27.9, 30.5, 34.3, 40.2, 48.8, 53.3, 55.5, 103.4, 109.2, 109.8, 118.7, 120.4, 125.8, 126.5, 127.0, 128.1, 128.6, 133.4, 136.0, 139.4, 147.6, 170.9; HRMS (EI) calcd for $C_{26}H_{28}N_2O_2$ $[M]^+$ 400.2151, found 400.2157; $[\alpha]_D^{20}$ = +63.1° (c = 0.75 M, $CHCl_3$); HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane 20/80, flow rate 0.8 mL/min, λ = 254 nm) t_{major} = 17.40 min, t_{minor} = 27.92 min.

Compound 24. To a solution of compound **23** (1.0 g, 2.5 mmol, 1 equiv) in Et_2O (15 mL) was added LAH (570 mg, 15.0 mmol, 6 equiv). The reaction mixture was stirred at reflux for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with DCM, dried over Na_2SO_4 ,and concentrated to dryness. The crude product was purified by flash silica gel chromatography (DCM/MeOH 20/1) to give pure compound **24** (830 mg, 86% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (m, 1H), 1.50−1.68 (m, 3H), 1.75−1.91 (m, 3H), 2.15 (m, 1H), 2.31−2.46 (m, 1H), 2.47−2.60 (m, 1H), 2.60−2.72 (m, 1H), 2.80 (m, 1H), 3.05 (d, J = 12 Hz, 1H), 3.77 (s, 1H), 3.80 (s, 3H), 4.88 (d, J = 17.1 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 5.65 (dd, J = 16.2 Hz, J = 16.5 Hz, 2H), 5.86 (m, 1H), 6.62 (d, J = 7.8 Hz, 1H), 6.89−7.10 (m, 3H), 7.20−7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 22.9, 24.8, 34.9, 35.0, 42.0, 46.4, 48.6, 55.5, 56.5, 102.7, 110.8, 112.5, 117.2, 119.6, 126.0, 126.5, 126.7, 128.5, 129.3, 134.8, 135.9, 140.0, 147.4; HRMS (EI) calcd for $C_{26}H_{30}N_2O$ $[M]^+$ 386.2358, found 386.2354; $[\alpha]_D^{20}$ = −14° (c = 0.3 M, $CHCl_3$).

dx.doi.org/10.1021/jo402741g | J. Org. Chem. 2014, 79, 2473−2480

Compound 14. To a solution of NH_3 at −78 °C were slowly added Na (345 mg, 15 mmol, 10 equiv) and compound **24** (580 mg, 1.5 mmol, 1 equiv) in THF (15 mL). The reaction mixture was stirred at −78 °C for 0.5 h. The reaction was quenched with the addition of MeOH. After NH_3 was evaporated at room temperature, the crude product was purified by flash silica gel chromatography (DCM/MeOH 20/1) to give compound **14** (400 mg, 90% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (m, 1H), 1.45−1.60 (m, 3H), 1.76 (m, 1H), 1.82−1.98 (m, 2H), 2.18 (m, 1H), 2.32 (m, 1H), 2.63−2.79 (m, 3H), 2.98 (m, 1H), 3.70 (s, 1H), 3.90 (s, 3H), 4.88−5.07 (m, 2H), 5.85 (m, 1H), 6.57 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 8.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 22.8, 25.1, 34.7, 35.0, 41.9, 46.1, 55.3, 56.4, 101.6, 110.8, 112.6, 117.3, 119.7, 126.3, 128.8, 133.6, 134.9, 145.7; HRMS (EI) calcd for $C_{19}H_{24}N_2O$ $[M]^+$ 296.1889, found 296.1886; $[\alpha]_D^{20}$ = +20.3° (c = 0.7 M, $CHCl_3$).

Compound 25. To a solution of compound **14** (200 mg, 0.67 mmol, 1 equiv) in DCM (15 mL) was added Et_3N (108 mg, 1.0 mmol, 1.5 equiv). To the resulting solution was added 2-chloroacetyl chloride (76 mg, 0.67 mmol, 1 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with addition of H_2O (10 mL) and extracted with DCM. The solvent was removed by evaporation to dryness. The crude product was purified by flash silica gel chromatography (ethyl acetate/petroleum ether 1/3) to give compound **25** (190 mg, 75% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28−1.47 (m, 2H), 1.54−1.99 (m, 4.4H), 2.04−2.27 (m, 1H), 2.31−2.50 (m, 1H), 2.56−2.80 (m, 2.3H), 2.90 (m, 0.7H), 3.61 (m, 0.6H), 3.92 (s, 3H), 4.29 (dd, J = 11.7 Hz, J = 12 Hz, 1.3H), 4.40 (m, 0.6H), 4.54 (m, 0.3H), 4.76 (s, 0.3H), 5.13 (m, 2H), 5.74 (s, 0.6H), 5.85 (m, 1H), 6.60 (t, J = 6.3 Hz, J = 6.3 Hz, 1H), 6.79−7.00 (m, 2H), 8.31 (s, 0.6H), 8.48 (s, 0.3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.5, 20.2, 21.6, 24.6, 25.4, 32.1, 36.7, 37.2, 37.7, 40.4, 40.7, 41.7, 41.9, 42.2, 53.1, 55.3, 59.0, 101.8, 101.9, 107.4, 108.1, 111.1, 111.4, 118.3, 118.7, 120.1, 120.7, 126.4, 127.1, 127.4, 133.5, 134.0, 134.4, 134.5, 145.6, 145.7, 166.1; HRMS (EI) calcd for $C_{21}H_{25}ClN_2O_2$ $[M]^+$ 372.1605, found 372.1604; $[\alpha]_D^{20}$ = −88.9° (c = 0.82 M, $CHCl_3$).

Compound 15. To a solution of compound **25** (155 mg, 0.42 mmol, 1 equiv) in acetone (10 mL) was added NaI (623 mg, 4.2 mmol, 10 equiv). The reaction mixture was stirred under reflux for 2 h. EtOAc (10 mL) was added, and the resulting solution was washed with H_2O. The solvent was removed by evaporation to dryness. The crude product was dissolved in THF (10 mL), and AgOTf (213 mg, 0.83 mmol, 2 equiv) was added. The resulting mixture was stirred at room temperature for 0.5 h. EtOAc (10 mL) was added. The solution was washed with saturated aqueous $NaHCO_3$ and purified by flash silica gel chromatography (DCM/MeOH 40/1) to give pure compound **15** (77 mg, 55% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37−1.62 (m, 5H), 1.65−1.82 (m, 2H), 2.16 (m, 1H), 2.48 (m, 1H), 2.65−2.79 (m, 2H), 2.84−2.09 (m, 2H), 3.61 (m, 1H), 3.93 (s, 3H), 4.28 (m, 1H), 4.80 (m, 1H), 4.94 (m, 1H), 5.55 (m, 1H), 6.88 (m, 2H), 7.15 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.2, 24.1, 24.2, 34.3, 37.2, 38.7, 40.7, 41.1, 54.3, 55.9, 69.2, 111.2, 113.1, 119.1, 127.6, 132.0, 142.3, 147.3, 151.2, 170.3, 185.0; HRMS (EI) calcd for $C_{21}H_{24}N_2O_2$ $[M]^+$ 336.1838, found 336.1844; $[\alpha]_D^{20}$ = −36.8° (c = 0.62 M, $CHCl_3$).

Compound 26. To a stirred solution of compound **15** (60 mg, 0.18 mmol, 1 equiv) in MeOH (8 mL) was added $NaBH_4$ (33.7 mg, 0.9 mmol, 5 equiv) at −78 °C. After 5 min, the resulting mixture was warmed to 0 °C. After the mixture was stirred for 100 min, $NaBH_4$ (6.7 mg, 0.18 mmol, 1 equiv) was added. After the mixture was stirred for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with DCM. The organic phase was dried over Na_2SO_4 and purified by flash silica gel chromatography (DCM/MeOH 50/1) to give pure compound **26** (54 mg, 88% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (m, 1H), 1.22−1.49 (m, 3H), 1.52−1.72 (m, 6H), 2.02−2.19 (m, 2H), 2.59 (m, 1H), 2.78 (m, 1H), 3.43 (m, 1H), 3.64 (s, 1H), 3.82 (s, 3H), 4.16 (m, 1H), 4.87 (m, 1H), 4.99 (m, 1H), 5.63 (m, 1H), 6.63−6.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 23.0, 26.0, 34.7, 35.0, 40.5, 41.5, 45.3, 49.3, 55.3, 63.7, 64.6, 110.0, 114.8, 118.4, 120.0, 132.0, 132.9, 138.4, 146.0, 173.1; HRMS (EI) calcd for $C_{21}H_{26}N_2O_2$ $[M]^+$ 338.1994, found 338.2000; $[\alpha]_D^{20}$ = −14.8° (c = 0.8 M, $CHCl_3$).

Compound 27. A 25 mL flask was charged with compound **26** (54 mg), pyridine (3 mL), and acetic anhydride (3 mL). The mixture was stirred at room temperature for 3 h and concentrated. The residue was dissolved in 15 mL of DCM, washed with saturated NH_4OH/brine (1/1), dried over Na_2SO_4, and concentrated. The crude product was purified by flash silica gel chromatography (DCM/MeOH 40/1) to give pure compound **27** (57 mg, 95% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (m, 1H), 1.19−1.31 (m, 1H), 1.32−1.46 (m, 2H), 1.56−1.65 (m, 3H), 1.68−1.74 (m, 1H), 1.82−2.07 (m, 3H), 2.19 (s, 3H), 2.21−2.30 (m, 1H), 2.52 (m, 1H), 2.56−2.69 (m, 1H), 3.64 (s, 1H), 3.88 (s, 3H), 4.16 (m, 1H), 4.85 (d, J = 16.8 Hz, 1H), 5.00 (d, J = 9.9 Hz, 1H), 5.60 (m, 1H), 6.86 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9, 22.9, 23.1, 34.6, 34.9, 40.6, 41.7, 45.3, 48.2, 55.5, 63.7, 67.9, 112.3, 114.9, 118.6, 126.6, 129.4, 132.5, 139.5, 149.7, 170.7, 171.9; HRMS (EI) calcd for $C_{23}H_{28}N_2O_3$ $[M]^+$ 380.2100, found 380.2098; $[\alpha]_D^{20}$ = +33.9° (c = 0.85 M, $CHCl_3$).

Compound 28. To a solution of compound **27** (40 mg, 0.1 mmol, 1 equiv) in THF/H_2O (8 mL, 1/1) were added $K_2OsO_4{\cdot}2H_2O$ (1.94 mg, 0.005 mmol, 0.05 equiv) and NMO (58.6 mg, 0.5 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 4 h. Then $NaIO_4$ (107 mg, 0.5 mmol, 5 equiv) was added, and the resulting mixture was stirred for 2 h. Saturated aqueous $Na_2S_2O_3$ (8 mL) was added, and the resulting solution was stirred for 0.5 h. The reaction mixture was extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by flash silica gel chromatography (DCM/MeOH 40/1) to give pure compound **28** (34 mg, 85% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (m, 1H), 1.43 (m, 1H), 1.56−1.87 (m, 5H), 1.93 (m, 1H), 2.00−2.094 (m, 2H), 2.16−2.22 (m, 4H), 2.22−2.28 (m, 1H), 2.52 (m, 1H), 2.59−2.72 (m, 1H), 3.88 (s, 3H), 3.90 (s, 1H), 4.17 (m, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 9.66 (t, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 23.0, 24.3, 34.7, 35.1, 40.5, 45.0, 48.1, 49.9, 55.5, 62.3, 67.5, 112.5, 114.6, 126.7, 129.4, 138.8, 149.8, 170.9, 171.9, 200.9; HRMS (EI) calcd for $C_{22}H_{26}N_2O_4$ $[M]^+$ 382.1893, found 382.1890; $[\alpha]_D^{20}$ = +24° (c = 0.88 M, $CHCl_3$).

(+)-10-Oxocylindrocarpidine 7. To a solution of compound **28** (34 mg, 0.09 mmol, 1 equiv) in MeOH (5 mL) at 0 °C was added a solution of KOH (12.6 mg, 0.23 mmol, 2.6 equiv) in MeOH (3 mL), followed by a solution of I_2 (30 mg, 0.12 mmol, 1.3 equiv) in MeOH (3 mL). The reaction mixture was stirred for 2 h and then quenched with saturated aqueous $Na_2S_2O_3$ (3 mL). The resulting mixture was extracted with DCM (3 × 6 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash silica gel chromatography (DCM/MeOH 40/1) to give (+)-10-oxocylindrocarpidine **7** (23.8 mg, 65% yield) as a canary yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28−1.33 (m, 1H), 1.41−1.49 (m, 1H), 1.50−1.61 (m, 2H), 1.67−1.74 (m, 2H), 1.86−1.95 (m, 1H), 1.98−2.12 (m, 3H), 2.20 (s, 3H), 2.22−2.29 (m, 1H), 2.54 (d, J = 16.8 Hz, 1H), 2.65 (m, 1H), 3.61 (s, 3H), 3.89 (s, 3H), 4.04 (s, 1H), 4.15−4.21 (m, 1H), 4.47 (br s, 1H), 6.85−6.94 (m, 2H), 7.13 (t, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 23.1, 24.5, 34.3, 34.6, 40.5, 41.6, 45.1, 48.2, 51.4, 55.5, 61.9, 67.6, 112.4, 114.9, 126.6, 129.5, 139.0, 149.8, 171.5, 172.0; HRMS (EI) calcd for $C_{23}H_{28}N_2O_5$ $[M]^+$ 412.1998, found 412.1994; $[\alpha]_D^{20}$ = +21.4° (c = 0.8 M, $CHCl_3$).

Compound 29. To a solution of compound **15** (500 mg, 1.49 mmol, 1 equiv) in Et_2O (20 mL) was added $LiAlH_4$ (226 mg, 5.95 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 0.5 h, at reflux for 4 h, and at room temperature for 16 h. H_2O (60 μL), KOH (60 μL, 15% aqueous), and H_2O (180 μL) were added in sequence. The resulting slurry was filtered and rinsed with Et_2O. The solvent was removed by evaporation to dryness and then purified by flash silica gel chromatography (DCM/MeOH 40/1) to give pure compound **29** (265 mg, 55% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (d, J = 13.5 Hz, 1H), 1.21 (m, 1H), 1.35−1.54 (m, 4H), 1.54−1.84 (m, 4H), 1.90−2.04 (m, 2H), 2.15−2.40 (m, 4H), 3.08 (m, 2H), 3.58 (m, 1H), 3.82 (s, 3H), 4.81 (m, 1H), 4.92 (m, 1H), 5.66 (m, 1H),

dx.doi.org/10.1021/jo402741g | J. Org. Chem. 2014, 79, 2473−2480

6.63 (m, 1H), 6.66−6.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8, 23.9, 28.1, 35.3, 36.0, 38.2, 42.2, 52.9, 53.8, 54.1, 55.2, 65.8, 70.8, 109.1, 115.3, 117.1, 119.6, 134.3, 136.1, 138.3, 146.0; HRMS (EI) calcd for $C_{21}H_{28}N_2O$ $[M]^+$ 324.2202, found 324.2202; $[\alpha]_D^{20}$ = −15.5° (c = 0.4 M, $CHCl_3$).

Compound 30. A 50 mL flask was charged with compound **29** (150 mg), pyridine (5 mL), and acetic anhydride (5 mL). The mixture was stirred at room temperature for 3 h and concentrated. The residue was dissolved in 25 mL of DCM, washed with saturated NH_4OH/brine (1/1), dried over Na_2SO_4, and concentrated. The crude product was purified by flash silica gel chromatography (DCM/MeOH 50/1) to give pure compound **30** (156 mg, 92% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (m, 1H), 1.12 (m, 1H), 1.33−1.60 (m, 5H), 1.68 (m, 1H), 1.73−2.09 (m, 6H), 2.10−2.30 (m, 5H), 2.99 (m, 1H), 3.08 (m, 1H), 3.83 (s, 3H), 4.75 (m, 1H), 4.88 (m, 1H), 5.60 (m, 1H), 6.79 (m, 2H), 7.04 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 23.1, 23.8, 24.8, 35.1, 35.8, 37.9, 42.3, 52.4, 53.5, 55.5, 69.2, 70.6, 111.4, 115.4, 117.3, 126.2, 129.4, 133.9, 143.1, 149.8, 171.7; HRMS (EI) calcd for $C_{23}H_{30}N_2O_2$ $[M]^+$ 366.2307, found 366.2315; $[\alpha]_D^{20}$ = +19.8° (c = 0.78 M, $CHCl_3$).

Compound 31. To a solution of compound **30** (218 mg, 0.6 mmol, 1 equiv) in THF/H_2O (20 mL, 1/1) were added $K_2OsO_4\cdot 2H_2O$ (11 mg, 0.03 mmol, 0.05 equiv) and NMO (351.5 mg, 3.0 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 4 h. Then $NaIO_4$ (642 mg, 3.0 mmol, 5 equiv) was added, and the resulting mixture was stirred for 2 h. Saturated aqueous $Na_2S_2O_3$ (15 mL) was added, and the resulting solution was stirred for 0.5 h. The reaction mixture was extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash silica gel chromatography (DCM/MeOH 50/1) to give pure compound **31** (175.6 mg, 80% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15−1.27 (m, 2H), 1.34−1.71 (m, 6H), 1.80 (m, 1H), 1.97−2.11 (m, 4H), 2.12−2.24 (m, 4H), 2.25−2.32 (m, 1H), 2.42 (s, 1H), 2.96−3.23 (m, 2H), 3.88 (s, 3H), 6.80 (m, 2H), 7.08 (t, J = 8.1 Hz, 1H), 9.70 (t, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 23.0, 24.9, 35.4, 36.2, 37.4, 50.8, 52.0, 53.2, 55.4, 68.6, 69.4, 111.6, 115.1, 126.4, 129.4, 142.2, 149.8, 171.1, 202.5; HRMS (EI) calcd for $C_{22}H_{28}N_2O_3$ $[M]^+$ 368.2100, found 368.2117; $[\alpha]_D^{20}$ = +16.1° (c = 0.6 M, $CHCl_3$).

(+)-Cylindrocarpidine 1. To a solution of **31** (15 mg, 0.04 mmol, 1 equiv) in MeOH (5 mL) at 0 °C was added a solution of KOH (5.9 mg, 0.11 mmol, 2.6 equiv) in MeOH (3 mL), followed by a solution of I_2 (13.2 mg, 0.05 mmol, 1.3 equiv) in MeOH (3 mL). The reaction mixture was stirred for 2 h and then quenched with saturated aqueous $Na_2S_2O_3$ (3 mL). The resulting mixture was extracted with DCM (3 × 6 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (DCM/MeOH 50/1) to afford the pure compound (+)-cylindrocarpidine **1** (8.7 mg, 54% yield) as a canary yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16−1.26 (m, 1H), 1.33−1.44 (m, 1H), 1.47−1.62 (m, 3H), 1.69−1.80 (m, 2H), 1.84−1.91 (m, 1H), 1.95−2.08 (m, 4H), 2.15−2.23 (m, 4H), 2.25−2.33 (m, 1H), 2.43 (s, 1H), 2.99−3.09 (m, 1H), 3.09−3.20 (m, 1H), 3.56 (s, 3H), 3.87 (s, 3H), 4.62 (m, 1H), 6.82 (m, 2H), 7.07 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 23.1, 24.4, 25.0, 34.8, 35.9, 37.5, 42.4, 51.1, 52.1, 53.0, 53.3, 55.5, 68.8, 69.6, 111.7, 115.3, 126.3, 129.6, 142.5, 149.5, 170.9, 172.1; HRMS (EI) calcd for $C_{23}H_{30}N_2O_4$ $[M]^+$ 398.2206, found 398.2197; $[\alpha]_D^{20}$ = +135.0° (c = 0.92 M, $CHCl_3$).

(−)-*N*-Acetylcylindrocarpinol 6. To a solution of compound **31** (22 mg, 0.06 mmol, 1 equiv) in MeOH (5 mL) was added $NaBH_4$ (4.5 mg, 0.12 mmol, 2.0 equiv) at 0 °C, and then the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (3 mL) and was extracted with DCM (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4. The solution was concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH 40/1) to give pure (−)-*N*-acetylcylindrocarpinol **6** (20 mg, 92% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99−1.14 (m, 2H), 1.15−1.28 (m, 2H), 1.43−1.54 (m, 3H), 1.54−1.67 (m, 3H), 1.70−1.78 (m, 1H), 1.93−2.02 (m, 2H), 2.03−2.13 (m, 1H), 2.19 (s, 3H), 2.22−2.31 (m, 2H), 2.96−3.07 (m, 1H), 3.07−3.19 (m, 1H), 3.44−3.65 (bt, J = 6.3 Hz, 2H), 3.87 (s, 3H), 4.56 (q, J = 6.6 Hz, 1H), 6.82 (t, J = 8.7 Hz, 2H), 7.08 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 23.1, 24.3, 25.0, 35.2, 35.3, 37.8, 40.5, 52.3, 53.5, 55.4, 58.4, 69.2, 70.7, 111.3, 115.3, 126.3, 129.4, 143.2, 149.7, 171.8; HRMS (EI) calcd for $C_{22}H_{30}N_2O_3$ $[M]^+$ 370.2256, found 370.2266; $[\alpha]_D^{20}$ = −19.5° (c = 0.52, $CHCl_3$).

(+)-Aspidospermine 8. To a solution of **31** (50 mg, 0.135 mmol, 1 equiv) in DCM (10 mL) was added ethane-1,2-dithiol (12.7 mg, 0.135 mmol, 1 equiv) and $BF_3\cdot Et_2O$ (0.6 mL). The reaction mixture was stirred at room temperature for 0.5 h. Then Et_2O (6 mL) and saturated aqueous $NaHCO_3$ (8 mL) were added in sequence. The resulting solution was stirred for 0.5 h and extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated to dryness.

To a solution of the crude compound obtained above in EtOH (8 mL) was added Raney nickel (80 mg, 1.35 mmol, 10 equiv). The reaction mixture was stirred at reflux under an atmosphere of hydrogen for 8 h. The mixture was filtered over Celite and then washed by EtOH. The solvent was removed by evaporation to dryness. The crude product was purified by flash silica gel chromatography (DCM/MeOH 40/1) to give the pure (+)-aspidospermine **8** (35 mg, 74% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.61 (t, J = 7.5 Hz, 3H), 0.75−0.81 (m, 1H), 1.02−1.12 (m, 2H), 1.15−1.21 (m, 1H), 1.22−1.30 (m, 1H), 1.48−1.63 (m, 3H), 1.69−1.76 (m, 1H), 1.89−1.95 (m, 2H), 1.95−2.04 (m, 2H), 2.16−2.25 (m, 5H), 3.01−3.04 (m, 1H), 3.09−3.13 (m, 1H), 3.88 (s, 3H), 4.65 (br s, 1H), 6.78−6.84 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.9, 21.7, 23.2, 25.0, 30.2, 34.3, 35.7, 38.2, 52.6, 53.8, 55.6, 69.6, 71.3, 111.4, 115.6, 126.2, 129.6, 143.7, 149.8, 171.8; HRMS (EI) calcd for $C_{22}H_{30}N_2O_2$ $[M]^+$ 354.2307, found 354.2304; $[\alpha]_D^{20}$ = +88.5° (c = 0.72 M, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables and figures giving comparisons of ^{1}H NMR chemical shifts, ^{1}H NMR and ^{13}C NMR spectra of compounds **12**−**15**, **19**, **21**−**31**, 10-oxocylindrocarpidine, cylindrocarpidine, *N*-acetylcylindrocarpinol, and aspidospermine, and HPLC traces of the compounds **13** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*F.-Z.P.: e-mail, pengfangzhi@ynu.edu.cn; fax, (+86)871-65035538; tel, (+86)871-65031119.

*Z.-H.S.: e-mail, zhihui_shao@hotmail.com.

Author Contributions

†These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Program for Changjiang Scholars and Innovative Research Team in University (IRT13095), the NSFC (21162034, 21372193, 21362040), the Doctoral Fund of the Ministry of Education of China (20135301110002), and the Government of Yunnan Province (2012FB114, 2013FA026). We thank Prof. Shu-Li You at the Shanghai Institute of Organic Chemistry, CAS, for the determination of the ee value of compound **13**.

■ REFERENCES

(1) For a recent review: Lopchuk, J. M. *Prog. Heterocycl. Chem.* **2011**, *23*, 1.

(2) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. *50*, Chapter 9.
(3) (a) Djerassi, C.; Archer, A. A. P. G.; George, T.; Gilbert, B.; Shoolery, J. N.; Johnson, L. F. *Experientia* **1960**, *16*, 532. (b) Djerassi, C.; Archer, A. A. P. G.; George, T.; Gilbert, B.; Antonaccio, L. D. *Tetrahedron* **1961**, *16*, 212. (c) Milborrow, B. V.; Djerassi, C. *J. Chem. Soc. C* **1969**, 417.
(4) Achenbach, H. *Tetrahedron Lett.* **1967**, 1793.
(5) Fraude, G. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 2189.
(6) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1998; Vol. *51*, pp 2−1972.
(7) Floriani, F. *An. Farm. Bioquim.* **1931**, *2*, 215.
(8) Banerjee, J. N.; Lewis, J. J. *J. Pharm. Pharmacol.* **1955**, *7*, 46.
(9) Mitaine-Offer, A.-C.; Sauvain, M.; Valentin, A.; Callapa, J.; Mallié, M.; Zèches-Hanrot, M. *Phytomedicine* **2002**, *9*, 142.
(10) (a) Saxton, J. E.; Smith, A. J.; Lawton, G. *Tetrahedron Lett.* **1975**, 4161. (b) Lawton, G.; Saxton, J. E.; Smith, A. J. *Tetrahedron* **1977**, *33*, 1641.
(11) For a semisynthesis of (+)-*N*-acetylcylindrocarpinol starting from cylindrocarine and of (−)-10-oxocylindrocarpidine beginning from cylindrocarpidine, see: Gebreyesus, T.; Djerassi, C. *J. Chem. Soc., Perkin Trans. 1* **1972**, 849.
(12) Chen, J.-B.; Chen, J.-C.; Xie, Y.; Zhang, H.-B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1024.
(13) (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (b) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, *6*, 2261. (c) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, *7*, 1311. (d) Ban, Y.; Iijima, I.; Inoue, I.; Akagi, M.; Oishi, T. *Tetrahedron Lett.* **1969**, *10*, 2067. (e) Ban, Y.; Iijima, I. *Tetrahedron Lett.* **1969**, *10*, 2523. (f) Stevens, R. V.; Fitzpatrick, J. M.; Kaplan, M.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1971**, 857. (g) Martin, S. F.; Desai, S. R.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294. (h) Pearson, A. J. *Tetrahedron Lett.* **1981**, *22*, 4033. (i) Pearson, A. J.; Rees, D. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2467. (j) Wu, P. L.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 963. (k) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673. (l) Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625. (m) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2613. (n) Fukuda, Y.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749. (o) Gnecco, D.; Vázquez, E.; Galindo, A.; Terán, J. L.; Orea, L.; Bernés, S.; Eníquez, R. G. *ARKIVOC* **2003**, *xi*, 185. (p) Iyengar, R.; Schildknegt, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645. (q) Pearson, W. H.; Aponick, A. *Org. Lett.* **2006**, *8*, 1661. (r) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159. (s) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498. (t) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290. (u) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (v) Lajiness, J. P.; Jiang, W.; Boger, D. L. *Org. Lett.* **2012**, *14*, 2078.
(14) This remarkable methodology has been applied to the syntheses of many alkaloids. For a recent example, see: Xie, J.; Wolfe, A. L.; Boger, D. L. *Org. Lett.* **2013**, *15*, 868.
(15) Gartshore, C. J.; Lupton, D. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4113.
(16) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117.
(17) For reviews on decarboxylative allylation: (a) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246. (b) Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, *2*, 1476. (c) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (d) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745. (e) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. For pioneering contributions, see: (f) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (g) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.
(18) Zhang, S.; Shen, X.; Li, Z.; Zou, L.; Wang, F.; Zhang, H.; Shao, Z. *J. Org. Chem.* **2013**, *78*, 11444.
(19) Wei, Y.; Zhao, D.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12988.
(20) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642.
(21) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938.
(22) Robinson, B. *Chem. Rev.* **1963**, *63*, 373.
(23) For recent reviews on C−H bond activation in total synthesis: (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (b) Chen, D. Y.-K.; Youn, S. W. *Chem. Eur. J.* **2012**, *18*, 9452.
(24) (a) Weng, B.; Liu, R.; Li, J. *Synthesis* **2010**, 2926. (b) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230.
(25) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329.
(26) We are sorry that we could not obtain the natural samples for complete comparisons. For NMR data, please see the corresponding table in the Supporting Information.