JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

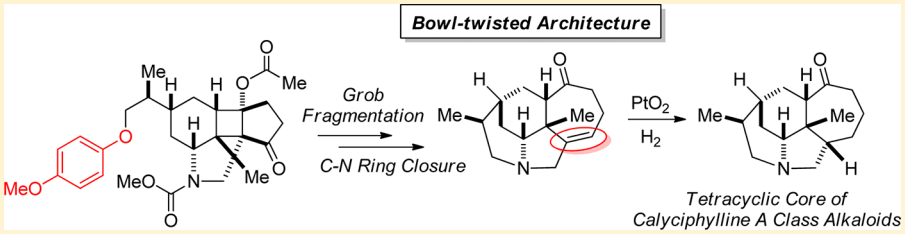
Tackling Reactivity and Selectivity within a Strained Architecture: Construction of the [6−6−5−7] Tetracyclic Core of *Calyciphylline* Alkaloids

Chen Xu,[†] Lu Wang,[†] Xiaojiang Hao,*[,‡] and David Zhigang Wang*[,†]

[†]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen University Town, Nanshan District, Shenzhen 518055, China

[‡]Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China

Supporting Information



ABSTRACT: A stereochemically controlled route to the enantiopure [6−6−5−7] tetracyclic core of *Calyciphylline* A class alkaloids was established, which involves Overman rearrangement, [2 + 2] photochemical cycloaddition, Grob fragmentation, C−N bond-forming nucleophilic displacement, and ring strain-directed hydrogenation as strategic steps.

The Daphniphyllum class alkaloids have in recent years garnered much attention due primarily to their unusual structural diversities and stereochemical complexities.[1] Driven by their aesthetical appeal as well as the desire to explore their so far poorly studied biological utilities, several laboratories have engaged in chemical synthesis of a certain member of this remarkable natual product family.[2] In this field, Carreira and co-workers have recently recorded a landmark accomplishment by completing a highly stereoselective total synthesis of (+)-daphmanidin E.[3]

Our own efforts have been focused on Calyciphylline A type compounds within this family.[4] As highlighted in blue in Figure 1, a recurring skeletal motif found among these structures is the highly stereochemically fused [6−6−5−7] tetracyclic core. It could thus be recognized that the goal of establishing a divergent synthetic approach to such diverse targets would be most economically served by defining an efficient and stereocontrolled strategy to this tetracycle. A previous communication[2e] from our group had disclosed progress made to build the simpler [5−6−7] tricyclic moiety (i.e., rings ***B*−*C*−*D*** in structure **1** of Scheme 1). Implementation of the previously uncovered key transformations in the more elaborated [6−6−5−7] setting had, however, demanded new strategic planning, as it was subsequently discovered that substrates-directed double bond hydrogenations within those tricycles surprisingly led only to an *anti*-C^5-**Me**-versus-C^6-**H** orientation (Scheme 1) that is opposite to what is present in natural products. Furthermore, the attempted piperidine ***A*** ring closure via an intramolecular C^9−N bond-forming nucleophilic displacement event[5] was repeatedly hampered by failures in identifying an appropriate alcohol protecting group (i.e., P_2 group, Scheme 1) that is both easy to manipulate and compatible with Mannich condensation[6] conditions employed earlier in the sequence for assembling the key precursor **5** for an enone−alkene [2 + 2] photochemical cycloaddition.[7] Challenged by solving these significant problems, a substantially revised synthetic plan was thus designed and further experimentally explored. We reported herein the success in execution of such plans for rapid construction of the critical [6−6−5−7] tetracycle and with all of the seven stereogenic centers densely situated on the ring junctions (i.e., C^1, C^2, C^4, C^5, C^6, C^7, and N^8) clearly defined in a way that exactly corresponds to the absolute configurations found in natural products.

As shown in Scheme 1, we envisioned that the ring closure of piperidine ***A*** of the tetracycle **1** could be in situ initiated by liberating the basic nitrogen center in **2** toward an intramolecular S_N2 displacement of the C^9-mesylate. Its immediate precursor **3** could be furnished through a Grob-type fragmentation[8] on an advanced intermediate **4**, which itself was accessible with an intramolecular [2 + 2] photochemical cycloaddition event on an allylic amine-tethered enone substrate **5**.[2e] The assembly of **5** by Mannich condensation of an appropriately functionalized iminium ion **6** and cyclopentanedione **7** had emerged as a major challenge as its success, rather unexpectedly, was found (vide infra) to be critically dependent on the nature of a seemingly remotely positioned

Received: April 23, 2012
Published: June 12, 2012

ACS Publications © 2012 American Chemical Society

dx.doi.org/10.1021/jo300776d | *J. Org. Chem.* 2012, 77, 6307−6313

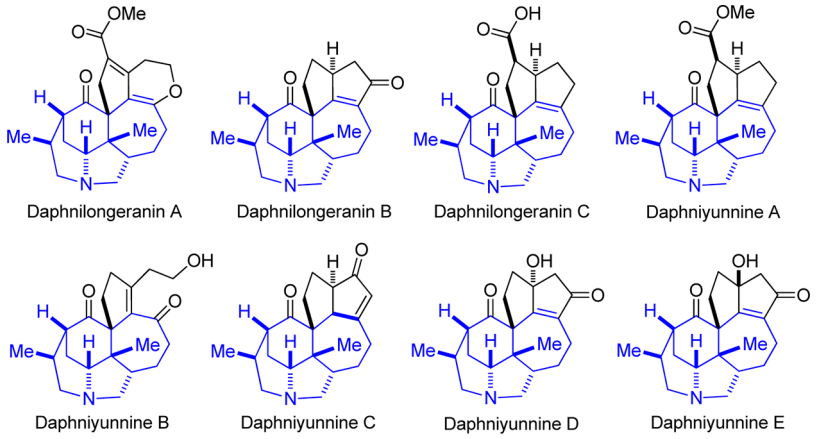
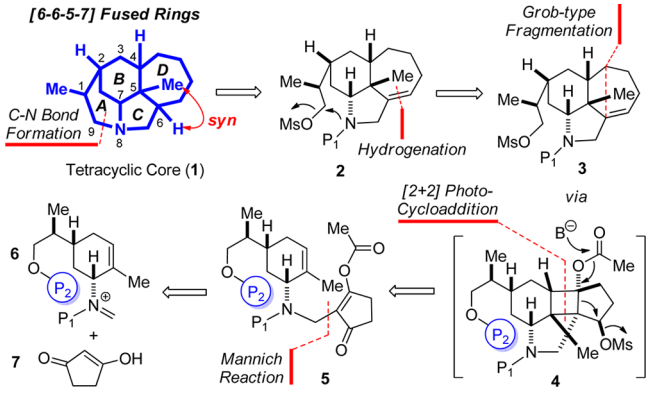


Figure 1. *Calyciphylline A* class alkaloids featuring the common [6−6−5−7] tetracyclic core structure.

Scheme 1. Retrosynthetic Strategies



alcohol protecting group P_2.[9] It was only after extensive trial-and-error efforts that we eventually determined 4-methoxyphenyl[10] to be a viable structure compatible with both the strongly Lewis acidic Mannich reaction promoter and short-wavelength light employed in subsequent photocycloadditions.

Scheme 2 summarized our experimental explorations leading to an advanced tetracyclic alkene intermediate **21**. Starting from the known enantiopure diol **8**,[11] primary alcohol-protected **9** was prepared by the action of tosylation and 4-methoxyphenoxide substitution. Imidation of the allylic alcohol with CCl_3CN followed by Overman rearrangement[12] under xylene refluxing conditions converted **9** into allylic trichloroacetamide **10**. Treatment of **10** with MeOH and then HCHO under basic conditions yielded the hydroxymethylated carbamate **12** through the intermediacy of **11**. Mannich unification of **12** with cyclopentanedione was found to be effected by $Sn(NTf_2)_4$ leading to structure **13** in 77% isolated yield.[13] A range of other Lewis acids known in the arts[6] for promoting Mannich condensations were also examined but found to be either inefficient or labile for incurring substantial substrate decomposition. Acylation of the enol in **13** with acetyl chloride produced **14** which was next subjected to photolysis with a medium-pressure Hg lamp emitting light primarily around 254 nm, yielding highly substituted and congested [2 + 2] cyclobutane product **15** with complete stereochemical control. It merits attention that this represents a very rare example of photochemical [2 + 2] cycloadditions on *N*-tethered substrates in complex synthesis setting.[14] Accompanying **15** was a diketone byproduct **16** (**15**:**16** = 50:29) whose formation could apparently be attributed to a strain-releasing-driven retro-Aldol-type collapse of the keto-ester moiety of **15**.[15] Reduction of the ketone carbonyl from its less-hindered face in **15** followed by mesylation of the resultant alcohol **17** readily sets the stage for base-triggered Grob-fragmentation to give tricyclic alkene **18**, with a remarkable 79% isolated yield over these three steps.

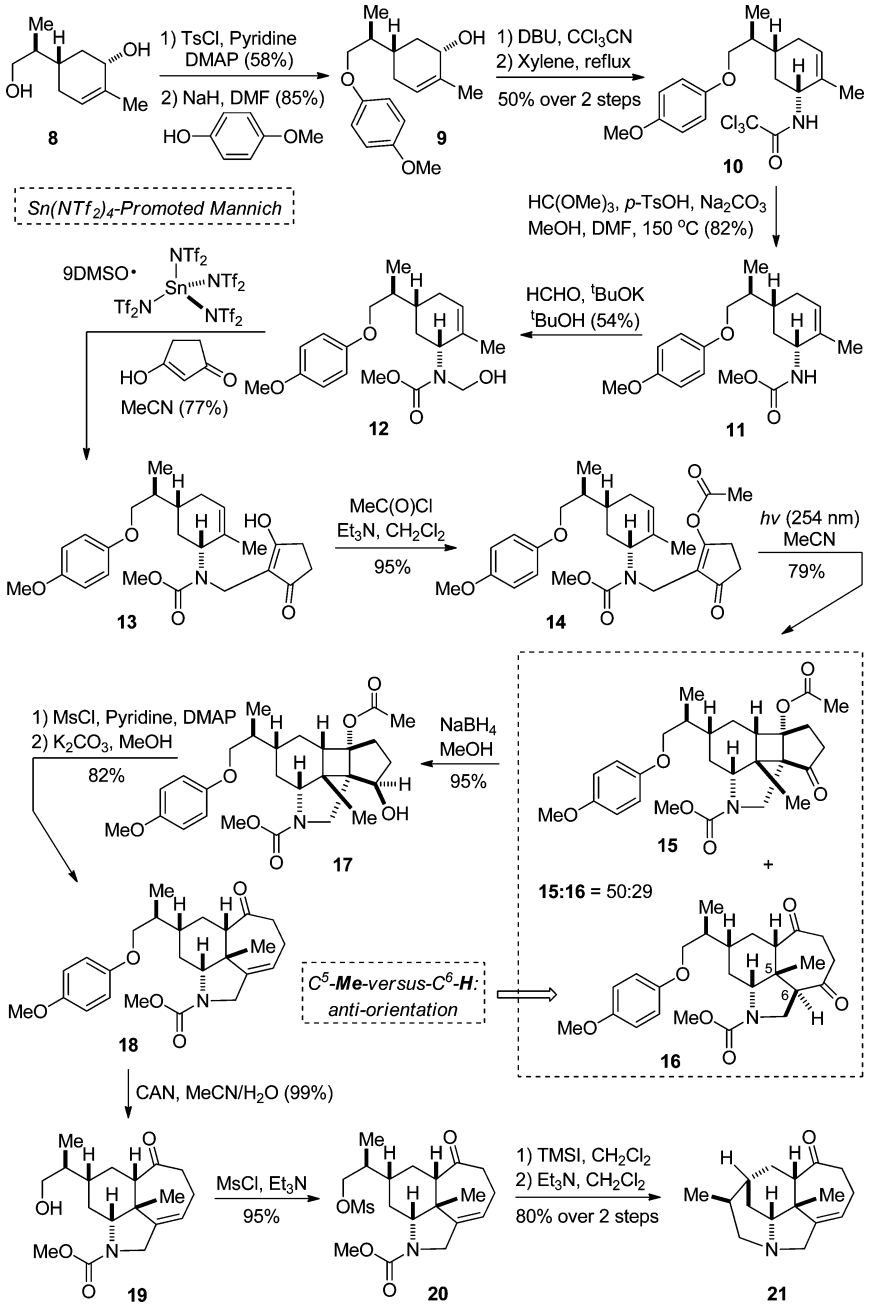
It should be noted that in **16** the C^5-**Me** and C^6-**H** displayed spatially an *anti*-orientation (NOESY), which, in conjunction with our earlier observations in tricyclic alkene model systems that catalytic hydrogenations failed to deliver the desired (*S*)-configuration at the C^6 chiral center, hints on the difficulty of reverting the inherent substrate thermodynamic bias imposed by saturating the double bond in **18** toward the requisite *syn*-C^5-**Me**-versus-C^6-**H** stereochemistry. Hypothetically, a solution to this problem would invite consideration on crafting **18**'s relatively flat tricyclic skeleton into a much reinforced bowl-twisted tetracyclic architecture as widely present in Calyciphylline A-class alkaloids. With this design concept in mind, **18** was next transformed to **20** in very high yield by sequential protecting group oxidative removal and alcohol mesylation. Delightfully, exposure of **20** to the action of TMSI[16] and Et_3N was found to lead to the formation of the desired structure **21** in 80% isolated yield under very mild conditions.

Indeed, PtO_2-promoted catalytic hydrogenation[17] of **21** was found to proceed exclusively from the exposed convex face of its bowl-twisted skeleton, leading to the target **22** with the correct C^6 stereochemistry (Scheme 3). The *syn*-C^5-**Me**-versus-C^6-**H** orientation was clearly manifested by their nuclear Overhauser effect (NOE) correlation. The reduction was remarkably facile, completing at room temperature in just 2 h and with 94% isolated yield. In marked contrast, similar action on a tricyclic structure **23**[2e] produced **24** only very slowly (16 h) with opposite alkene enantiofacial recognition and poor C=C versus C=O functionality selectivity, the combined yield of **24** after reoxidation of the alcohol byproduct was 74%. Such an intriguing discrepancy in both reactivity and stereoselectivity could most reasonably be rationalized by effects of conformational shielding as well as ring junction strain that are uniquely associated with the double bond embedded in the bowl-shaped architecture of **21**.[18]

In summary, through exploring functionality compatibility and substrate-reinforced stereoelectronic control, we were able to solve some critical problems that were, as revealed in simpler model systems, otherwise impossible to overcome. Our strategy

dx.doi.org/10.1021/jo300776d | *J. Org. Chem.* 2012, 77, 6307−6313

Scheme 2. Construction of [6−6−5−7] Tetracyclic Alkene 21



features Overman rearrangement, [2 + 2] photochemical cycloaddition, Grob fragmentation, C−N bond-forming nucleophilic displacement, and polycyclic ring strain-directed hydrogenation as key steps and culminates in construction of the common [6−6−5−7] tetracyclic core of Calyciphylline A type alkaloids in a highly efficient and stereocontrolled manner. We believed that the success disclosed here would help establish an enabling and supportive platform on which diversity-oriented syntheses of this family of fascinating natural products could be convergently tackled. Continued efforts toward total syntheses of some members in this class are currently being pursued and will be reported in due course.

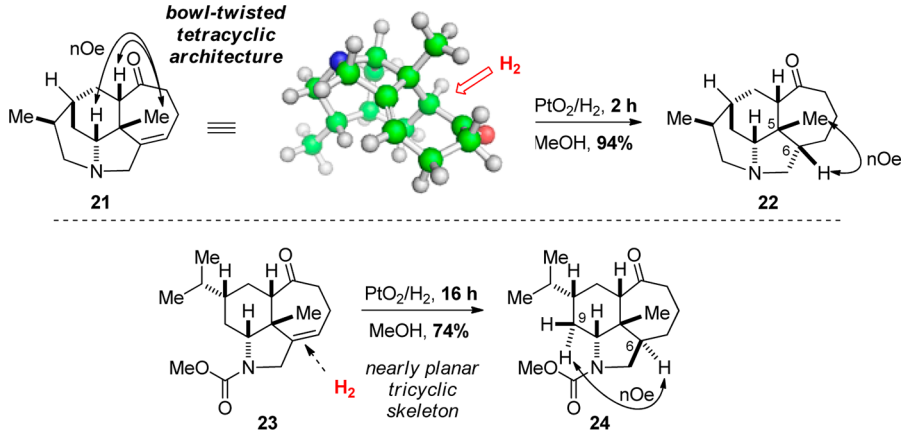
EXPERIMENTAL SECTION

(1*S*,5*S*)-5-((*S*)-1-(4-Methoxyphenoxy)propan-2-yl)-2-methylcyclohex-2-enol (9). To a solution of alcohol **8**[11] (4.7 g, 27.6 mmol) in $CHCl_3$ (80 mL) were added pyridine (4.7 mL, 55.2 mmol), TsCl (7.9 g, 41.4 mmol) and DMAP (674 mg, 5.5 mmol). The reaction mixture was stirred for 30 h at room temperature and quenched with H_2O. The aqueous phase was extracted three times with ethyl acetate. The combined layers were washed with brine (2 × 20 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 2/1) to give an intermediate (5.2 g) in 58% yield as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 5.34 (d, J = 4.4 Hz, 1H), 4.04 (t, J = 6 Hz, 1H), 3.90 (dd, J = 9.6, 5.2 Hz, 1H), 3.84 (dd, J = 9.4, 5.6 Hz, 1H), 2.45 (s, 3H), 1.92 (dd, J = 11.8, 6 Hz, 1H), 1.80 (br s, 2H), 1.75−1.57 (m, overlapped, 3H), 1.67 (s, 3H), 1.09 (quartet, J = 12 Hz, 1H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 136.5, 132.9, 129.8, 127.8, 123.3, 73.0, 70.7, 36.8, 35.5, 34.5, 29.6, 21.6, 18.7, 13.2; HRMS calcd for $C_{17}H_{24}O_4SNa$ (M + Na^+) 347.1293, found 347.1286.

To a solution of *p*-methoxy phenol (4.36 g, 35 mmol) in DMF (70 mL) at 0 °C was added NaH (1.76 g, 44 mmol) and the mixture

dx.doi.org/10.1021/jo300776d | J. Org. Chem. 2012, 77, 6307−6313

Scheme 3. Construction of [6−6−5−7] Tetracyclic Core 22: Remarkable Conformational Strain-Driven Reactivity and Stereoselectivity



stirred for 1 h. Then the solution of the above-prepared intermediate (9.5 g, 29.3 mmol) in DMF (30 mL) was added into the mixture via syringe, and the reaction was warmed to room temperature. After being stirred for 16 h, the mixture was poured into ice−water (100 mL). The aqueous phase was extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with H_2O (3 × 80 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 5/1) to give **9** (6.9 g) in 85% yield as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 4H), 5.45 (d, J = 4.4 Hz, 1H), 4.20−4.10 (m, 1H), 3.88−3.80 (m, 1H), 3.79−3.70 (m, overlapped, 4H), 2.14 (dd, J = 8, 2 Hz, 1H), 2.0−1.70 (m, overlapped, 4H), 1.73 (s, 3H), 1.54 (br s, 1H), 1.30−1.20 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 153.3, 136.4, 124.1, 115.4, 114.6, 71.5, 71.1, 55.7, 37.2, 36.0, 35.3, 30.0, 18.8, 13.8; HRMS calcd for $C_{17}H_{24}NaO_3$ (M + Na^+) 299.1623, found 299.1616; mp 58.1−58.5 °C.

2,2,2-Trichloro-*N*-((1*R*,5*R*)-5-((*S*)-1-(4-methoxyphenoxy)-propan-2-yl)-2-methylcyclohex-2-enyl)acetamide (10). To a solution of allylic alcohol **9** (2.89 g, 10.5 mmol) in dry CH_2Cl_2 (50 mL) was added DBU (2 mL, 15.8 mmol), and the solution was cooled to 0 °C. To this solution was added 2,2,2-trichloroacetonitrile (2 mL, 21 mmol) over 20 min. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with satd NH_4Cl solution. The organic layer was washed with satd NH_4Cl solution (×2), passed through a column packed with anhydrous Na_2SO_4 and silica gel (to remove polymeric products), and evaporated under reduced pressure to give crude trichloroacetimidate, which was used for the following step without any purifications. To a solution of the crude imidate in xylene (105 mL) was added powdered anhydrous K_2CO_3 (2 g), and the mixture was heated at reflux temperature for 6 h with vigorous stirring. After being cooled to room temperature, the mixture was filtered through a pad of Super-Cel, and the precipitate was washed with toluene. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (*n*-hexane/ethyl acetate = 8/1) to give **10** (2.2 g) in 50% yield as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 4H), 6.45 (dd, J = 9.6 Hz, 1H), 5.62−5.58 (m, 1H), 4.62−4.50 (m, 1H), 3.83 (dd, J = 9.2, 6 Hz, 1H), 3.74 (s, 3H), 3.72 (dd, J = 9.2, 6 Hz, 1H), 2.13 (dd, J = 12, 5.6 Hz, 1H), 2.09−1.82 (m, overlapped, 4H), 1.66 (s, 3H), 1.32 (quartet, J = 12 Hz, 1H), 0.98 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 153.8, 153.2, 132.6, 126.3, 115.4, 114.6, 92.9, 71.4, 55.7, 52.3, 37.2, 35.1, 34.4, 27.5, 19.2, 13.3; HRMS calcd for $C_{19}H_{25}Cl_3NO_3$ (M + H^+) 420.0900, found 420.0887; mp 88.9−89.3 °C.

Methyl (1*R*,5*R*)-5-((*S*)-1-(4-Methoxyphenoxy)propan-2-yl)-2-methylcyclohex-2- enylcarbamate (11). Trimethoxymethane (1.1 mL) and *p*-toluensulfonic acid (101 mg, 0.58 mmol) were placed in a sealed tube. DMF (27.5 mL) and MeOH (6.4 mL) were added, and the mixture was stirred at reflux temperature for 1 h. After being cooled to room temperature, the mixture was added with trichloroacetamide **10** (2.2 g, 5.23 mmol) and Na_2CO_3 (1.1 g, 10.34 mol). Then the reaction was conducted in the sealed tube at 150 °C for 4 h and cooled to room temperature. The mixture was quenched with H_2O (10 mL), diluted with Et_2O (3 × 20 mL), washed with H_2O (1 × 30 mL) and brine (1 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 8/1) to give **11** (1.45 g) in 82% yield as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 4H), 5.50 (s, 1H), 4.49 (d, J = 9.6 Hz, 1H), 4.27 (br s, 1H), 3.86−3.79 (m, 1H), 3.74 (s, 3H), 3.71−3.62 (m, overlapped, total 4H), 2.07 (dd, J = 11.8, 4.8 Hz, 1H), 1.96 (d, J = 15.5 Hz, 1H), 1.90−1.77 (m, 3H), 1.64 (s, 3H), 1.25−1.15 (m, 1H), 0.95 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.7, 153.2, 134.2, 124.9, 115.4, 114.6, 71.5, 55.7, 52.0, 51.9, 37.2, 35.7, 35.4, 27.7, 19.4, 13.4; HRMS calcd for $C_{19}H_{28}NO_4$ (M + H^+) 334.2018, found 334.2024; mp 128.1−128.5 °C.

Methyl (Hydroxymethyl)((1*R*,5*R*)-5-((*S*)-1-(4-methoxyphenoxy)propan-2-yl)-2-methylcyclohex-2-enyl)-carbamate (12). To a solution of **11** (390 mg, 1.2 mmol) in *t*-BuOH (12 mL) at room temperature was added *t*-BuOK (650 mg, 5.85 mmol) followed by $(HCHO)_n$ (351 mg, 11.7 mmol). The resulting yellow suspension was stirred for 1.5 h at room temperature, and then satd NH_4Cl (10 mL) was added. The resulting mixture was extracted with ethyl acetate (2 × 10 mL), and the combined organic layers were washed first with water (30 mL) and then with brine (30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography (*n*-hexane/ethyl acetate = 8/1) to give **12** (169 mg) in 54% yield as a colorless oil (based on 102 mg starting material recovered): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 and 6.79 (each s, total 4H), 5.63 (br s, 1H), 4.95−4.88 (m, 1H), 4.87 and 4.60 (each br s, total 1H), 4.25 (t, J = 10 Hz, 1H), 3.86−3.65 (m, overlapped, 8H), 3.65−3.55 and 2.86−2.75 (each m, total 1H), 2.01−1.75 (m, overlapped, 6H), 1.52 (s, 3H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ some peaks double due to amide conformational isomers) δ 157.7, 153.7, 153.7, 153.3, 132.9, 132.7, 127.2, 115.5, 114.6, 71.6, 68.6, 67.9, 57.1, 55.7, 52.9, 52.7, 37.4, 37.4, 35.7, 35.5, 33.8, 33.5, 27.7, 27.4, 19.7, 19.5, 13.4, 13.3; HRMS calcd for $C_{20}H_{29}NNaO_5$ (M + Na^+) 386.1943, found 386.1936.

Methyl ((2-Hydroxy-5-oxocyclopent-1-en-1-yl)methyl)-((1*R*,5*R*)-5-((*S*)-1-(4-methoxyphenoxy)propan-2-yl)-2-methyl-cyclohex-2-en-1-yl)carbamate (13). To a solution of the **12** (300 mg, 0.83 mmol) in 8 mL of CH_3CN were successively added under an argon atmosphere 1,3-cyclopentanedione (162 mg, 1.65 mmol) and $Sn(NTf_2)_4$·9DMSO (242 mg, 0.12 mmol, 15 mol %). The reaction mixture was stirred at ambient temperature for 4 h, and then the solution was quenched with a 5% aqueous solution of $NaHCO_3$ and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the resulting

dx.doi.org/10.1021/jo300776d | *J. Org. Chem.* 2012, 77, 6307−6313

residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 4/1) to give **13** (283 mg) in 77% yield as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 6.85−6.75 (m, 4H), 5.73 (s, 1H), 4.64 (br s, 1H), 3.81−3.69 (m, overlapped, 2H), 3.77(s, 3H), 3.72 (s, 3H), 3.69−3.59 (m, 2H), 2.48 (br s, 2H), 2.40−2.30 (m, 2H), 2.10−1.68 (m, overlapped, 6H), 1.49 (s, 3H), 0.93 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 189.4, 160.8, 153.6, 153.4, 131.4, 128.7, 115.3, 114.9, 114.6, 71.4, 58.0, 55.7, 53.8, 37.2, 35.3, 34.0, 33.7, 31.3, 26.9, 19.4, 13.2; HRMS calcd for $C_{25}H_{34}NO_6$ (M + H$^+$) 444.2386, found 444.2386.

2-(((Methoxycarbonyl)((1*R*,5*R*)-5-((*S*)-1-(4-methoxyphenoxy)propan-2-yl)-2-methylcyclohex-2-en-1-yl)-amino)methyl)-3-oxocyclopent-1-en-1-yl Acetate (14). To a solution of **13** (324 mg, 0.73 mmol) in 4 mL of CH_2Cl_2 at 0 °C were added consecutively triethylamine (0.3 mL, 2.19 mmol) and acetyl chloride (150 μL, 2.19 mmol). After being stirred at 0 °C for 1.5 h, the reaction mixture was quenched by addition of satd NH_4Cl, and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the resulting residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 2/1) to give **14** (337 mg) in 95% yield as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 4H), 5.62 (br s, 1H), 4.88 and 4.69 (each br s, total 1H), 4.12−3.95 (m, 1H), 3.70−3.40 (m, overlapped, 9H), 2.85−2.70 (m, 2H), 2.50−2.31 (m, 2H), 2.15 and 2.12 (each s, total 3H), 1.99−1.68 (m, overlapped, total 6H), 1.49 (s, 3H), 0.93 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ some peaks double due to amide conformational isomers) δ 205.1, 176.8, 175.8, 166.8, 153.7, 153.3, 132.9, 127.7, 126.4, 115.3, 114.6, 71.5, 61.9, 57.6, 57.3, 55.8, 52.6, 37.4, 36.5, 35.8, 34.2, 34.0, 32.0, 31.3, 28.1, 27.5, 27.1, 19.4, 13.8, 13.4; HRMS calcd for $C_{27}H_{36}NO_7$ (M + H$^+$) 486.2492, found 486.2482.

Synthesis of 15 and 16. A solution of **14** (60 mg, 0.12 mmol) in acetonitrile (90 mL) in a photoreaction vessel (quartz) was degassed by bubbling N_2 through the solution for 15 min. The resulting solution was then irradiated (10 W medium pressure lamp, 254 nm) for 1 h at 0 °C under nitrogen atmosphere. Evaporation of volatiles and purification by flash chromatography (*n*-hexane/ethyl acetate = 4/1) to give **15** (30 mg) in 50% yield as yellow oil and **16** (15 mg) in 29% yield as yellow oil.

(2a*R*,2a^1*R*,4*R*,5a*S*,5b*S*,8a*R*)-Methyl 5b-acetoxy-4-((*S*)-1-(4-methoxyphenoxy)propan-2-yl)-2a^1-methyl-8-oxodecahydrocyclopenta[1,4]cyclobuta[1,2,3-*cd*]indole-2(1*H*)-carboxylate (15): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 4H), 3.81 (dd, J = 9, 6 Hz, 1H), 3.76−3.69 (m, overlapped, 2H), 3.73 (s, 3H), 3.645 (s, 3H), 3.49 (dd, J = 10, 2 Hz, 1H), 3.42 (d, J = 12.5 Hz, 1H), 2.74−2.65 (m, 1H), 2.50−2.29 (m, overlapped, 4H), 2.21 (br s, 1H), 2.06 (s, 3H), 1.87−1.77 (m, overlapped, 2H), 1.68−1.52 (m, 3H), 1.12 (s, 3H), 0.94 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 170.4, 155.9, 153.8, 153.4, 115.5, 114.7, 80.5, 71.4, 64.1, 63.0, 55.8, 52.2, 50.8, 48.9, 47.3, 38.7, 38.2, 35.4, 31.1, 26.8, 21.5, 21.2, 21.0, 13.6; HRMS calcd for $C_{27}H_{36}NO_7$ (M + H$^+$) 486.2492, found 486.2494.

(2a*R*,2a^1*R*,6a*S*,8*R*,9a*R*)-Methyl 8-((*S*)-1-(4-methoxyphenoxy)propan-2-yl)-2a^1-methyl-3,6-dioxododecahydro-1*H*-cyclohepta[*cd*]indole-1-carboxylate (16): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82−6.72 (m, 4H), 4.15 and 4.08 (each dd, J = 12, 8.8 Hz and J = 11.8, 9.2 Hz, total 1H), 3.70−3.89 (m, overlapped, 3H), 3.75 (s, 3H), 3.69 and 3.66 (each s, total 3H), 3.73−3.70 and 3.58 (m, overlapped and dd, J = 14, 5.6 Hz, total 1H), 3.48 and 3.44 (each dd, J = 11, 9.2 Hz and J = 11.6, 8.8 Hz, total 1H), 3.19 (td, J = 13.2, 4 Hz, 1H), 2.72−2.56 (m, overlapped, 2H), 2.51−2.39 (m, 1H), 2.34 (dt, J = 12, 4 Hz, 1H), 2.23−2.15 and 2.08−1.98 (each m, total 1H), 1.97−1.87 (m, 1H), 1.82−1.76 (m, 1H), 1.69−1.62 (m, overlapped, 2H), 1.29−1.11 (m, 1H), 0.51 (d, J = 6.8 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ some peaks double due to amide conformational isomers) δ 210.7, 210.6, 206.3, 205.9, 155.1, 153.9, 153.0, 115.5, 115.4, 114.7, 71.4, 71.3, 66.2, 66.1, 60.5, 55.8, 52.4, 51.4, 50.4, 43.7, 43.2, 42.9, 42.2, 38.3, 37.3, 36.2, 36.1, 33.5, 323.0, 32.2, 28.5, 28.2, 23.5, 23.4, 13.7, 13.6; HRMS calcd for $C_{25}H_{34}NO_6$ (M + H$^+$) 444.2386, found 444.2380.

(2a*R*,2a^1*R*,4*R*,5a*S*,5b*S*,8*R*,8a*S*)-Methyl 5b-Acetoxy-8-hydroxy-4-((*S*)-1-(4-methoxyphenoxy)propan-2-yl)-2a^1-methyldecahydrocyclopenta[1,4]cyclobuta[1,2,3-*cd*]indole-2(1*H*)-carboxylate (17). To a solution of **15** (188 mg, 0.39 mmol) in MeOH (10 mL) at 0 °C was added $NaBH_4$ (30 mg, 0.77 mmol). The reaction mixture was stirred for 2 h at 0 °C and then quenched by satd NH_4Cl. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 2/1) to give **17** (181 mg) in 95% yield as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 4H), 4.17 (dd, J = 10.8, 7.5 Hz, 1H), 3.82−3.76 (m, 2H), 3.74 (s, 3H), 3.71−3.68 (m, overlapped, 1H), 3.67 (s, 3H), 3.61 (t, J = 6 Hz, 1H), 3.43 (d, J = 12 Hz, 1H), 2.44 (dd, J = 14, 8 Hz, 1H), 2.32 (t, J = 9 Hz, 1H), 2.15−2.10 (m, 1H), 2.02 (s, 3H), 2.02−1.70 (m, 5H), 1.58−1.50 (m, 1H), 1.50−1.49 (m, 1H), 1.35 (s, 3H), 1.32−1.26 (m, 1H), 0.91 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 156.4, 153.8, 153.5, 115.6, 114.7, 83.4, 76.7, 71.7, 64.8, 58.6, 55.8, 52.2, 50.1, 48.8, 43.3, 37.8, 36.3, 32.0, 31.1, 29.0, 23.5, 21.4, 21.2, 13.3; HRMS calcd for $C_{27}H_{38}NO_7$ (M + H$^+$) 488.2648, found 488.2634.

(2a^1*R*,6a*S*,8*R*,9a*R*)-Methyl 8-((*S*)-1-(4-Methoxyphenoxy)-propan-2-yl)-2a^1-methyl-6-oxo-2,2a^1,4,5,6,6a,7,8,9,9a-decahydro-1*H*-cyclohepta[*cd*]indole-1-carboxylate (18). To a stirred solution of **17** (181 mg, 0.37 mmol) in pyridine (10 mL) were added methanesulfonyl chloride (0.3 mL, 3.7 mmol) and DMAP (44 mg, 0.36 mmol). The reaction mixture was stirred for 1.5 h at room temperature, diluted with ethyl acetate (10 mL), and washed consecutively with satd NH_4Cl (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried with Na_2SO_4 and concentrated to yield mesylate which was carried on to the next step. The mesylate was dissolved in MeOH (5 mL) and stirred with K_2CO_3 (305 mg, 2.2 mmol) overnight at room temperature. The reaction mixture was filtered, evaporated, diluted with water (5 mL), and extracted with ethyl acetate before drying over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 4/1) to give **18** (129 mg) in 82% yield as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80−6.71 (m, 4H), 5.71 (d, J = 19.5 Hz, 1H), 4.27 and 4.19 (each d, J = 16.5 and 15.0 Hz, total 1H), 3.91 (t, J = 15 Hz, 1H), 3.75 and 3.74 (each s, total 3H), 3.69 and 3.67 (each s, total 3H), 3.81−3,71 (m, overlapped, 2H), 3.70−3.63 and 3.53 (overlapped and dd, J = 10, 5.5 Hz, total 1H), 2.71−2.61 (m, 2H), 2.53−2.39 (overlapped, 2H), 2.29−2.19 (m, 1H), 2.05 and 1.90 (each dt, J = 13, 2.5 Hz and 13, 2.5 Hz, total 1H), 1.87−1.77 (m, 1H), 1.76−1.70 (m, 1H), 1.70−1.55 (overlapped, 1H), 1.40 (pentet, J = 12.5 Hz, 1H), 1.20 and 1.19 (each s, total 3H), 1.10−0.92 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ some peaks double due to amide conformational isomers) δ 213.0, 155.4, 155.1, 154.0, 153.9, 153.3, 140.8, 140.0, 121.4, 121.2, 115.6, 155.6, 114.8, 71.7, 71.7, 65.8, 65.7, 60.3, 55.8, 52.4, 52.3, 50.1, 49.7, 45.1, 44.5, 42.3, 37.5, 37.3, 37.3, 33.2, 32.4, 30.5, 30.2, 29.7, 27.0, 27.0, 24.0, 13.8, 13.7; HRMS calcd for $C_{25}H_{34}NO_5$ (M + H$^+$) 428.2437, found 428.2412.

(2a^1*R*,6a*S*,8*R*,9a*R*)-Methyl 8-((*S*)-1-Hydroxypropan-2-yl)-2a^1-methyl-6-oxo-2,2a^1,4,5, 6,6a,7,8,9,9a-decahydro-1*H*-cyclohepta[*cd*]indole-1-carboxylate (19). To a solution of **18** (160 mg, 0.37 mmol) in CH_3CN/H_2O = 4:1 (2.5 mL) at 0 °C was added CAN (410 mg, 0.75 mmol). After being stirred for 30 min, the reaction was quenched with brine (2 mL), and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic portion was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 1/2) to give **19** (120 mg) in 99% yield as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 and 5.70 (each d, J = 2.8 and J = 3 Hz, total 1H), 4.23 (ddd, J = 35, 28, 3 Hz, 1H), 3.90 (td, J = 13.2, 1.2 Hz, 1H), 3.68 (s, 3H), 3.63 and 3.58−3.50 (dd and overlapped, J = 10, 7 Hz, total 1H), 3.57−3.42 (m, 2H), 2.71−2.60 and 2.48−2.35 (m, total 2H), 2.49 (td, J = 15, 4.5 Hz, 1H), 2.29−2.18

dx.doi.org/10.1021/jo300776d | *J. Org. Chem.* 2012, 77, 6307−6313

(m, 1H), 2.05−1.96 and 1.90−1.80 (each m, total 1H), 1.72−1.47 (overlapped, total 4H), 1.36−1.27 (m, 1H), 1.19 and 1.18 (each s, total 3H), 1.09−0.92 (m, 1H), 0.85 and 0.84 (each d, J = 8 and 8 Hz, total 3H); ^{13}C NMR (100 MHz, $CDCl_3$ some peaks double due to amide conformational isomers) δ 213.5, 213.4, 155.3, 155.1, 140.5, 139.7, 121.4, 121.2, 65.7, 65.7, 60.2, 60.2, 52.5, 52.4, 50.0, 49.7, 45.0, 44.4, 42.4, 39.98, 39.92, 36.7, 36.5, 30.2, 29.8, 27.1, 27.0, 23.7, 13.4, 13.1; HRMS calcd for $C_{18}H_{28}NO_4$ (M + H$^+$) 322.2018, found 322.2023.

(2a^1*R*,6a*S*,8*R*,9a*R*)-Methyl 2a1-Methyl-8-((*S*)-1-((methylsulfonyl)oxy)propan-2- yl)-6-oxo-2,2a^1,4,5,6,6a,7,8,9,9a-decahydro-1*H*-cyclohepta[*cd*]indole-1-carboxylate (20). To a solution of **19** (120 mg, 0.373 mmol) in CH_2Cl_2 (4 mL) at 0 °C were added Et_3N (160 μL) and methylsufonyl chloride (60 μL), and then the mixture was warmed to room temperature. After the mixture was stirred for 2 h, the reaction was quenched with brine (4 mL), and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic portion was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 1.5/1) to give **20** (142 mg) in 95% yield as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (d, J = 11.6 Hz, 1H), 4.27−3.82 (m, overlapped, 4H), 3.65 and 3.64 (each s, total 3H), 3.59 and 3.48 (each dd, J = 11, 5.2 Hz and J = 11, 5.2 Hz, total 1H), 2.96 and 2.95 (each s, total 3H), 2.70−2.58 (m, 2H), 2.44 (td, J = 12.6, 3.2 Hz, 1H), 2.40−2.32 (m, 1H), 2.27−2.14 (m, 1H), 2.02−1.93 and 1.84 (m and dt, J = 12.8, 2.4 Hz, total 1H), 1.74 (pentet, J = 6 Hz, 1H), 1.70−1.61 (m, 1H),1.49−1.38 (m, 1H), 1.38−1.25 (m, 1H), 1.56 (s, 3H), 0.98−0.92 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ some peaks double due to amide conformational isomers) δ 212.7, 212.6, 155.1, 154.9, 140.2, 139.4, 121.5, 121.3, 72.1, 72.0, 65.3, 65.3, 59.9, 52.3, 52.2, 49.9, 49.5, 44.8, 44.2, 42.2, 37.2, 37.2, 36.8, 36.5, 32.8, 31.9, 30.2, 29.8, 26.8, 26.8, 23.6, 23.5, 13.4; HRMS calcd for $C_{19}H_{30}NO_6S$ (M + H$^+$) 400.1794, found 400.1777.

(2*R*,3*S*,11*S*,11a*R*,11b*R*)-3,11a-Dimethyl-3,4,6,8,9,11,11a,11b-octahydro-1*H*-2,11-methanocyclohepta[*a*]indolizin-10(2*H*)-one (21). To a solution of **20** (20 mg, 0.05 mmol) in CH_2Cl_2 (1.5 mL) was added TMSI (30 mg, 0.15 mmol). The mixture was stirred at room temperature for 4 h, quenched with satd $Na_2S_2O_3$ (aq), and extracted with CH_3OH/CH_2Cl_2 = 1:9 (8 × 2 mL). The combined organic portion was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was dissolved in 1.5 mL of CH_2Cl_2 and 50 μL Et_3N added. After being stirred for 16 h, the mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/Et_3N = 100:5:1) to give **21** (10 mg) in 80% yield as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (ddd, J = 7.2, 3.0, 2.8 Hz, 1H), 4.08 (dt, J = 13.6, 2.8 Hz, 1H), 3.77 (s, 1H), 3.37 (d, J = 13.6 Hz, 1H), 3.25 (d, J = 13.6 Hz, 1H), 3.17 (dd, J = 13.4, 5.6 Hz, 1H), 2.71−2.55 (m, overlapped, 3H), 2.50−2.40 (m, 1H), 2.30−2.22 (m, 1H), 2.21−2.13 (m, 2H), 2.15−1.90 (m, 1H), 1.90−1.71 (m, 1H), 1.64 (dd, J = 16, 4.4 Hz, 1H), 1.49−1.37 (m, 1H), 1.32 (d, J = 7.2 Hz, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 139.0, 129.3, 66.8, 59.5, 55.7, 48.6, 41.1, 39.8, 32.5, 27.7, 26.3, 25.5, 23.6, 18.3, 16.9; HRMS calcd for $C_{16}H_{24}NO$ (M + H$^+$) 246.1858, found 246.1852.

(2*R*,3*S*,6a*S*,11*S*,11a*S*,11b*R*)-3,11a-Dimethyldecahydro-1*H*-2,11-methanocyclohepta[*a*]indolizin-10(2*H*)-one (22). To a solution of **21** (4.5 mg, 0.018 mmol) in MeOH (1 mL) was added PtO_2 (2 mg, 0.009 mmol). Then the reaction was stirred under hydrogen atmosphere (1 atm) for 2.5 h. The solvent was removed under vacuum, and the resulting residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/Et_3N = 100:5:1) to give **22** (4.2 mg) in 94% yield as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (d, J = 4.4 Hz, 1H), 3.21−3.12 (m, 2H), 2.86 (dd, J = 14.2, 7.2 Hz, 1H), 2.69−2.68 (m, overlapped, 2H), 2.52 (dd, J = 11.6, 6.4 Hz, 1H), 2.50−2.41 (m, 1H), 2.40−2.30 (m, 1H), 2.09−1.96 (m, 1H), 1.95−1.65 (m, overlapped, 8H), 1.44 (dd, J = 15.2, 3.6 Hz, 1H), 1.44 (s, 3H), 0.91 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 64.7, 56.4, 55.2, 50.2, 48.5, 43.2, 42.5, 32.1, 30.8, 28.8, 28.1, 24.7, 19.6, 19.4. 17.6; HRMS calcd for $C_{16}H_{26}NO$ (M + H$^+$) 248.2014, found 248.2010.

(2a*R*,2a1*S*,6a*S*,8*R*,9a*R*)-Methyl 8-Isopropyl-2a^1-methyl-6-oxodecahydro-1*H*-cyclohepta[*cd*]indole-1-carboxylate (24). To a solution of carbamate **23** (42 mg, 0.14 mmol) in MeOH (2 mL) was added PtO_2 (16 mg, 0.07 mmol). Then the reaction was stirred under hydrogen atmosphere (1 atm) for 16 h. The solvent was removed under vacuum, and the resulting residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 8:1) to give the mixture of compound **24** and corresponding alcohol. The crude products were treated with DMP (170 mg, 0.42 mmol) and $NaHCO_3$ (70 mg, 0.84 mmol) in CH_2Cl_2 (2 mL) for 3 h. The reaction was quenched with satd $Na_2S_2O_3/NaHCO_3$ = 1:1 (2 mL), and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic portion was washed with H_2O (2 mL) and brine (2 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the resulting residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 8:1) to give **24** (32 mg) in 74% yield as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 and 3.63 (each s, total 3H), 3.58−3.48 and 3.38 (m and dd, J = 11, 6 Hz, total 2H), 3.11 and 3.05 (each t, J = 11 Hz and J = 10.5 Hz, total 1H), 2.65 (ddd, J = 19.6, 6.5, 2.5 Hz, 1H), 2.64−2.56 (m, 1H), 2.46−2.34 (m, 2H), 2.12−2.07 and 1.96−1.90 (m, total 1H), 1.87−1.60 (m, 4H), 1.49−1.40 (m, 2H), 1.29 (ddd, J = 24.8, 12.3, 2 Hz, 1H), 1.23−1.12 (m, 1H), 1.05−0.94 (m, 1H), 0.98 and 0.97 (each s, total 3H), 0.86−0.82 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$ some peaks double due to amide conformational isomers) δ 214.2, 155.4, 155.1, 66.6, 66.5, 60.3, 60.2, 52.2, 52.1, 50.1, 49.8, 42.2, 42.2, 41.6, 41.5, 40.8, 39.2, 38.3, 32.3, 32.3, 32.0, 31.4, 29.3, 29.1, 26.2, 22.8, 22.3, 22.2, 19.6, 19.5, 19.5, 19.4; HRMS calcd for $C_{18}H_{30}NO_3$ (M + H$^+$) 308.2226, found 308.2220.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and procedures, compound characterization data, and copies of ^{1}H, ^{13}C, and 2D NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: (D.Z.W.) dzw@pkusz.edu.cn; (X.H.) haoxj@mail.kib.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation of China (Grant Nos. 20872004 and 20972008 to D.Z.W. and 20672120 to X.J.H), the National "973 Project" from the State Ministry of Science and Technology, the Shenzhen Bureau of Science, Technology and Information, and the Shenzhen "Shuang Bai Project" for generous financial support. We also thank Mr. Bo Zhang for experimental assistance and Dr. Zheng Xiang for helpful discussions.

■ REFERENCES

(1) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936−962.
(2) (a) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833−1836. (b) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658−5661. (c) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2006**, *7*, 5461−5464. (d) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267−1269. (e) Xu, C.; Liu, Z.; Wang, H. F.; Zhang, B.; Xiang, Z.; Hao, X. J.; Wang, D. Z. *Org. Lett.* **2011**, *13*, 1812−1815. (f) Sladojevich, F.; Michaelides, L. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132−5135.
(3) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501−11505.

(4) (a) Di, Y. T.; He, H. P.; Ping, Y. L.; Li, Y. L.; Wu, L.; Hao, X. J. *J. Nat. Prod.* **2006**, *69*, 1074−1076. (b) Mu, S. Z.; Li, C. S.; He, H. P.; Di, Y. T.; Wang, Y.; Wang, Y. H.; Zhang, Z.; Lü, Y.; Zhang, L.; Hao, X. J. *J. Nat. Prod.* **2007**, *70*, 1628−1631. (c) Chen, X.; Zhan, Z. J.; Yue, J. M. *Helv. Chim. Acta* **2005**, *88*, 854−860. (d) Yang, S. P.; Zhang, H.; Zhang, C. R.; Cheng, H. D.; Yue, J. M. *J. Nat. Prod.* **2006**, *69*, 79−82. (e) Zhang, H.; Yang, S. P.; Fan, C. Q.; Ding, J.; Yue, J. M. *J. Nat. Prod.* **2006**, *69*, 553−557. (f) Zhang, C. R.; Liu, H. B.; Dong, S. H.; Zhu, J. Y.; Wu, Y.; Yue, J. M. *Org. Lett.* **2009**, *11*, 4692−2695. (g) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895−2898. (h) Takatsu, H.; Morita, H.; Shen, Y. C.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 6279−6284. (i) Yahata, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2009**, *72*, 148−151. (j) Luo, D. Q.; Zhu, W. L.; Yang, X. L.; Liang, S. J.; Cao, Z. R. *Helv. Chim. Acta* **2010**, *93*, 1209−1215.

(5) (a) Nilsson, B. L.; Overman, L. E.; de Alaniz, J. R.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297−11299. (b) Chandra, A.; Pigza, J. A.; Han, J.; Mutnick, D.; Jonhston, J. N. *J. Am. Chem. Soc.* **2009**, *131*, 3470−3471.

(6) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070.

(7) (a) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052−1103. (b) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003−2020. (c) Bach, T. *Synthesis* **1998**, 683−703. (d) Crimmins, M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 123.

(8) Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741−3766.

(9) Clayden, J.; Vassiliou, N. *Org. Biomol. Chem.* **2006**, *4*, 2667−2678.

(10) (a) Fukuyama, T.; Laud, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291−6292. (b) Masaki, Y.; Yoshizawa, K.; Itoh, A. *Tetrahedron Lett.* **1996**, *37*, 9321−9324. Unsuccessful P_2 protecting groups examined included TBS, TBDPS, MOM, benzyl, acetyl, etc.

(11) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650−6652.

(12) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188−192.

(13) Othman, R. B.; Affani, R.; Tranchant, M. J.; Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 776−780.

(14) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425−6426.

(15) (a) Shinohara, T.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 7334−7336. (b) Sun, D.; Zhan, Q.; Li, C. *Org. Lett.* **2011**, *13*, 5302−5305.

(16) Lange, G. L.; Organ, M. G. *J. Org. Chem.* **1996**, *61*, 5358−5361.

(17) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025−7035.

(18) For recent references on properties and reactivities of bowl-shaped structures, see: (a) Zabula, A. V.; Spisak, S. N.; Filatov, A. S.; Rogachev, A. Y.; Petrukhina, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2971−2974. (b) Fujihara, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 1472−1476.