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

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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, $\mathrm{C}-$ 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 coworkers 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 ${ }^{2 e}$ from our group had disclosed progress made to build the simpler [5-6-7] tricyclic moiety (i.e., rings $\boldsymbol{B}-\boldsymbol{C}-\boldsymbol{D}$ in structure $\mathbf{1}$ 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- $\mathrm{C}^{6}-\mathrm{H}$ orientation (Scheme 1) that is opposite to what is present in natural products. Furthermore, the attempted piperidine $\boldsymbol{A}$ ring closure via an intramolecular $\mathrm{C}^{9}-\mathrm{N}$ bond-forming nucleophilic displacement event ${ }^{5}$ was repeatedly hampered by failures in
identifying an appropriate alcohol protecting group (i.e., $\mathrm{P}_{2}$ 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., $C^{1}, C^{2}, C^{4}$, $\mathrm{C}^{5}, \mathrm{C}^{6}, \mathrm{C}^{7}$, and $\mathrm{N}^{8}$ ) 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 $\mathrm{S}_{\mathrm{N}} 2$ displacement of the $\mathrm{C}^{9}$-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 $5 .{ }^{2 e}$ 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

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

## Scheme 1. Retrosynthetic Strategies


alcohol protecting group $\mathrm{P}_{2} .{ }^{9}$ 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 shortwavelength 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 $\mathrm{CCl}_{3} \mathrm{CN}$ followed by Overman rearrangement ${ }^{12}$ under xylene refluxing conditions converted 9 into allylic trichloroacetamide $\mathbf{1 0}$. Treatment of $\mathbf{1 0}$ with MeOH and then HCHO under basic conditions yielded the hydroxymethylated carbamate 12 through the intermediacy of 11. Mannich unification of $\mathbf{1 2}$ with cyclopentanedione was found to be effected by $\mathrm{Sn}\left(\mathrm{NTf}_{2}\right)_{4}$ 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 $\mathbf{1 3}$ 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 $\mathrm{C}^{5}-\mathrm{Me}$ and $\mathrm{C}^{6}-\mathrm{H}$ 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 $\mathrm{C}^{6}$ chiral center, hints on the difficulty of reverting the inherent substrate thermodynamic bias imposed by saturating the double bond in 18 toward the requiste syn- $\mathrm{C}^{5}$ -Me-versus- $\mathrm{C}^{6}-\mathrm{H}$ stereochemistry. Hypothetically, a solution to this problem would invite consideration on crafting 18's relatively flat tricyclic skeleton into a much reinforced bowltwisted 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 $\mathrm{TMSI}^{16}$ and $\mathrm{Et}_{3} \mathrm{~N}$ was found to lead to the formation of the desired structure 21 in $80 \%$ isolated yield under very mild conditions.

Indeed, $\mathrm{PtO}_{2}$-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 $\mathrm{C}^{6}$ stereochemistry (Scheme 3). The syn-C ${ }^{5}$-Me-versus-$\mathrm{C}^{6}-\mathrm{H}$ 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 $23^{2 e}$ produced 24 only very slowly (16 h) with opposite alkene enantiofacial recognition and poor $\mathrm{C}=$ C versus $\mathrm{C}=\mathrm{O}$ 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

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

features Overman rearrangement, $[2+2]$ photochemical cycloaddition, Grob fragmentation, $\mathrm{C}-\mathrm{N}$ 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

(1S,5S)-5-((S)-1-(4-Methoxyphenoxy)propan-2-yl)-2-methyl-cyclohex-2-enol (9). To a solution of alcohol $8^{11}(4.7 \mathrm{~g}, 27.6 \mathrm{mmol})$
in $\mathrm{CHCl}_{3}(80 \mathrm{~mL})$ were added pyridine $(4.7 \mathrm{~mL}, 55.2 \mathrm{mmol})$, TsCl $(7.9 \mathrm{~g}, 41.4 \mathrm{mmol})$ and DMAP $(674 \mathrm{mg}, 5.5 \mathrm{mmol})$. The reaction mixture was stirred for 30 h at room temperature and quenched with $\mathrm{H}_{2} \mathrm{O}$. The aqueous phase was extracted three times with ethyl acetate. The combined layers were washed with brine $(2 \times 20 \mathrm{~mL})$ and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $(5.2 \mathrm{~g})$ in $58 \%$ yield as yellow oil: ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.73(\mathrm{~d}, J=8 \mathrm{~Hz}, 2 \mathrm{H}), 7.31(\mathrm{~d}, J=$ $8 \mathrm{~Hz}, 2 \mathrm{H}), 5.34(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.04(\mathrm{t}, J=6 \mathrm{~Hz}, 1 \mathrm{H}), 3.90(\mathrm{dd}, J$ $=9.6,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.84(\mathrm{dd}, J=9.4,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.45(\mathrm{~s}, 3 \mathrm{H}), 1.92$ (dd, $J=11.8,6 \mathrm{~Hz}, 1 \mathrm{H}), 1.80(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 1.75-1.57$ (m, overlapped, $3 \mathrm{H}), 1.67(\mathrm{~s}, 3 \mathrm{H}), 1.09$ (quartet, $J=12 \mathrm{~Hz}, 1 \mathrm{H}), 0.84(\mathrm{~d}, J=6.8 \mathrm{~Hz}$, $3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 144.8,136.5,132.9,129.8$, 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 $\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{O}_{4} \mathrm{SNa}\left(\mathrm{M}+\mathrm{Na}^{+}\right)$347.1293, found 347.1286.

To a solution of $p$-methoxy phenol $(4.36 \mathrm{~g}, 35 \mathrm{mmol})$ in DMF (70 $\mathrm{mL})$ at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaH}(1.76 \mathrm{~g}, 44 \mathrm{mmol})$ and the mixture

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 $(9.5 \mathrm{~g}, 29.3 \mathrm{mmol})$ 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 $\mathrm{mL})$. The aqueous phase was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 80 \mathrm{~mL})$. The combined organic layers were washed with $\mathrm{H}_{2} \mathrm{O}(3 \times 80 \mathrm{~mL})$ and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $9(6.9 \mathrm{~g})$ in $85 \%$ yield as white solid: ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 6.80(\mathrm{~s}, 4 \mathrm{H}), 5.45(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H})$, $4.20-4.10(\mathrm{~m}, 1 \mathrm{H}), 3.88-3.80(\mathrm{~m}, 1 \mathrm{H}), 3.79-3.70(\mathrm{~m}$, overlapped, $4 \mathrm{H}), 2.14(\mathrm{dd}, J=8,2 \mathrm{~Hz}, 1 \mathrm{H}), 2.0-1.70(\mathrm{~m}$, overlapped, 4 H$), 1.73$ $(\mathrm{s}, 3 \mathrm{H}), 1.54(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 1.30-1.20(\mathrm{~m}, 1 \mathrm{H}), 1.00(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 3 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 153.7,153.3,136.4,124.1,115.4$, 114.6, 71.5, 71.1, 55.7, 37.2, 36.0, 35.3, 30.0, 18.8, 13.8; HRMS calcd for $\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{NaO}_{3}\left(\mathrm{M}+\mathrm{Na}^{+}\right)$299.1623, found 299.1616; mp 58.1-58.5 ${ }^{\circ} \mathrm{C}$.

2,2,2-Trichloro- $N$-((1R,5R)-5-((S)-1-(4-methoxyphenoxy)-propan-2-yl)-2-methylcyclohex-2-enyl)acetamide (10). To a solution of allylic alcohol $9(2.89 \mathrm{~g}, 10.5 \mathrm{mmol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50$ $\mathrm{mL})$ was added DBU ( $2 \mathrm{~mL}, 15.8 \mathrm{mmol}$ ), and the solution was cooled to $0^{\circ} \mathrm{C}$. To this solution was added 2,2,2-trichloroacetonitrile $(2 \mathrm{~mL}$, 21 mmol ) over 20 min . After being stirred at $0^{\circ} \mathrm{C}$ for 1 h , the reaction mixture was quenched with satd $\mathrm{NH}_{4} \mathrm{Cl}$ solution. The organic layer was washed with satd $\mathrm{NH}_{4} \mathrm{Cl}$ solution $(\times 2)$, passed through a column packed with anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ 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 $\mathrm{K}_{2} \mathrm{CO}_{3}(2 \mathrm{~g})$, 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 $10(2.2 \mathrm{~g})$ in $50 \%$ yield as a white solid: ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 6.80(\mathrm{~s}, 4 \mathrm{H}), 6.45(\mathrm{dd}, J=9.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.62-5.58(\mathrm{~m}, 1 \mathrm{H})$, $4.62-4.50(\mathrm{~m}, 1 \mathrm{H}), 3.83(\mathrm{dd}, J=9.2,6 \mathrm{~Hz}, 1 \mathrm{H}), 3.74(\mathrm{~s}, 3 \mathrm{H}), 3.72$ (dd, $J=9.2,6 \mathrm{~Hz}, 1 \mathrm{H}), 2.13$ (dd, $J=12,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.09-1.82$ (m, overlapped, 4 H$), 1.66(\mathrm{~s}, 3 \mathrm{H}), 1.32$ (quartet, $J=12 \mathrm{~Hz}, 1 \mathrm{H}), 0.98(\mathrm{~d}, J$ $=6.8 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 161.6,153.8,153.2$, 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 $\mathrm{C}_{19} \mathrm{H}_{25} \mathrm{Cl}_{3} \mathrm{NO}_{3}\left(\mathrm{M}+\mathrm{H}^{+}\right) 420.0900$, found 420.0887; mp 88.9-89.3 ${ }^{\circ} \mathrm{C}$.

Methyl (1R,5R)-5-((S)-1-(4-Methoxyphenoxy)propan-2-yl)-2-methylcyclohex-2- enylcarbamate (11). Trimethoxymethane (1.1 mL ) and $p$-toluensulfonic acid ( $101 \mathrm{mg}, 0.58 \mathrm{mmol}$ ) were placed in a sealed tube. DMF $(27.5 \mathrm{~mL})$ and $\mathrm{MeOH}(6.4 \mathrm{~mL})$ 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 $10(2.2 \mathrm{~g}, 5.23 \mathrm{mmol})$ and $\mathrm{Na}_{2} \mathrm{CO}_{3}(1.1 \mathrm{~g}, 10.34$ $\mathrm{mol})$. Then the reaction was conducted in the sealed tube at $150{ }^{\circ} \mathrm{C}$ for 4 h and cooled to room temperature. The mixture was quenched with $\mathrm{H}_{2} \mathrm{O}(10 \mathrm{~mL})$, diluted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 20 \mathrm{~mL})$, washed with $\mathrm{H}_{2} \mathrm{O}$ $(1 \times 30 \mathrm{~mL})$ and brine $(1 \times 30 \mathrm{~mL})$, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated. The residue was purified by flash chromatography on silica gel ( $n$-hexane/ethyl acetate $=8 / 1$ ) to give $11(1.45 \mathrm{~g})$ in $82 \%$ yield as white solid: ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 6.80(\mathrm{~s}, 4 \mathrm{H}), 5.50$ $(\mathrm{s}, 1 \mathrm{H}), 4.49(\mathrm{~d}, J=9.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.27(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.86-3.79(\mathrm{~m}, 1 \mathrm{H})$, $3.74(\mathrm{~s}, 3 \mathrm{H}), 3.71-3.62(\mathrm{~m}$, overlapped, total 4 H$), 2.07(\mathrm{dd}, J=11.8$, $4.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.96(\mathrm{~d}, J=15.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.90-1.77(\mathrm{~m}, 3 \mathrm{H}), 1.64(\mathrm{~s}$, $3 \mathrm{H}), 1.25-1.15(\mathrm{~m}, 1 \mathrm{H}), 0.95(\mathrm{~d}, J=7 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (100 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 156.9,153.7,153.2,134.2,124.9,115.4,114.6,71.5$, 55.7, 52.0, 51.9, 37.2, 35.7, 35.4, 27.7, 19.4, 13.4; HRMS calcd for $\mathrm{C}_{19} \mathrm{H}_{28} \mathrm{NO}_{4}\left(\mathrm{M}+\mathrm{H}^{+}\right)$334.2018, found 334.2024; mp 128.1-128.5 ${ }^{\circ} \mathrm{C}$.

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

Methyl ((2-Hydroxy-5-oxocyclopent-1-en-1-yl)methyl)-((1R,5R)-5-((S)-1-(4-methoxyphenoxy)propan-2-yl)-2-methyl-cyclohex-2-en-1-yl)carbamate (13). To a solution of the 12 (300 $\mathrm{mg}, 0.83 \mathrm{mmol})$ in 8 mL of $\mathrm{CH}_{3} \mathrm{CN}$ were successively added under an argon atmosphere 1,3 -cyclopentanedione $(162 \mathrm{mg}, 1.65 \mathrm{mmol})$ and $\mathrm{Sn}\left(\mathrm{NTf}_{2}\right)_{4} \cdot 9 \mathrm{DMSO}(242 \mathrm{mg}, 0.12 \mathrm{mmol}, 15 \mathrm{~mol} \%)$. The reaction mixture was stirred at ambient temperature for 4 h , and then the solution was quenched with a $5 \%$ aqueous solution of $\mathrm{NaHCO}_{3}$ and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The solvent was removed under vacuum, and the resulting
residue was purified by flash chromatography on silica gel ( $n$-hexane/ ethyl acetate $=4 / 1)$ to give $13(283 \mathrm{mg})$ in $77 \%$ yield as yellow oil: ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.14(\mathrm{~s}, 1 \mathrm{H}), 6.85-6.75(\mathrm{~m}, 4 \mathrm{H}), 5.73$ $(\mathrm{s}, 1 \mathrm{H}), 4.64(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.81-3.69(\mathrm{~m}$, overlapped, 2 H$), 3.77(\mathrm{~s}, 3 \mathrm{H})$, $3.72(\mathrm{~s}, 3 \mathrm{H}), 3.69-3.59(\mathrm{~m}, 2 \mathrm{H}), 2.48(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 2.40-2.30(\mathrm{~m}, 2 \mathrm{H})$, $2.10-1.68(\mathrm{~m}$, overlapped, 6 H$), 1.49(\mathrm{~s}, 3 \mathrm{H}), 0.93(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 3 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 203.3,189.4,160.8,153.6,153.4$, 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 $\mathrm{C}_{25} \mathrm{H}_{34} \mathrm{NO}_{6}\left(\mathrm{M}+\mathrm{H}^{+}\right)$ 444.2386, found 444.2386.

2-( ( (Methoxycarbonyl) ((1R, 5R)-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 $13(324 \mathrm{mg}, 0.73 \mathrm{mmol})$ in 4 mL of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ at $0^{\circ} \mathrm{C}$ were added consecutively triethylamine ( $0.3 \mathrm{~mL}, 2.19 \mathrm{mmol}$ ) and acetyl chloride $(150 \mu \mathrm{~L}, 2.19 \mathrm{mmol})$. After being stirred at $0{ }^{\circ} \mathrm{C}$ for 1.5 h , the reaction mixture was quenched by addition of satd $\mathrm{NH}_{4} \mathrm{Cl}$, and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $14(337 \mathrm{mg})$ in $95 \%$ yield as yellow oil: ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 6.79(\mathrm{~s}, 4 \mathrm{H}), 5.62(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.88$ and 4.69 (each br s, total 1 H$), 4.12-3.95(\mathrm{~m}, 1 \mathrm{H}), 3.70-3.40(\mathrm{~m}$, overlapped, 9 H$), 2.85-2.70(\mathrm{~m}, 2 \mathrm{H}), 2.50-2.31(\mathrm{~m}, 2 \mathrm{H}), 2.15$ and 2.12 (each s, total 3 H ), 1.99-1.68 (m, overlapped, total 6 H ), 1.49 ( s , 3 H ), 0.93 (d, $J=5.6 \mathrm{~Hz}, 3 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ some peaks double due to amide conformational isomers) $\delta 205.1,176.8$, $175.8,166.8,153.7,153.3,132.9,127.7,126.4,115.3,114.6,71.5,61.9$, $57.6,57.3,55.8,52.6,37.4,36.5,35.8,34.2,34.0,32.0,31.3,28.1,27.5$, 27.1, 19.4, 13.8, 13.4; HRMS calcd for $\mathrm{C}_{27} \mathrm{H}_{36} \mathrm{NO}_{7}\left(\mathrm{M}+\mathrm{H}^{+}\right)$ 486.2492, found 486.2482 .

Synthesis of 15 and 16. A solution of $14(60 \mathrm{mg}, 0.12 \mathrm{mmol})$ in acetonitrile ( 90 mL ) in a photoreaction vessel (quartz) was degassed by bubbling $\mathrm{N}_{2}$ through the solution for 15 min . The resulting solution was then irradiated ( 10 W medium pressure lamp, 254 nm ) for 1 h at $0{ }^{\circ} \mathrm{C}$ under nitrogen atmosphere. Evaporation of volatiles and purification by flash chromatography ( $n$-hexane/ethyl acetate $=4 / 1$ ) to give $15(30 \mathrm{mg})$ in $50 \%$ yield as yellow oil and $16(15 \mathrm{mg})$ in $29 \%$ yield as yellow oil.
(2aR,2a $\left.{ }^{1} R, 4 R, 5 \mathrm{aS}, 5 \mathrm{bS}, 8 \mathrm{a} R\right)$-Methyl 5b-acetoxy-4-((S)-1-(4methoxyphenoxy) propan-2-yl)-2a1-methyl-8-oxodecahydrocyclopenta[1,4]cyclobuta[1,2,3-cd]indole-2(1H)carboxylate (15): ${ }^{1} \mathrm{H}$ NMR ( $\left.500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.79(\mathrm{~s}, 4 \mathrm{H}), 3.81$ (dd, $J=9,6 \mathrm{~Hz}, 1 \mathrm{H}), 3.76-3.69$ (m, overlapped, 2 H ), $3.73(\mathrm{~s}, 3 \mathrm{H})$, $3.645(\mathrm{~s}, 3 \mathrm{H}), 3.49(\mathrm{dd}, J=10,2 \mathrm{~Hz}, 1 \mathrm{H}), 3.42(\mathrm{~d}, J=12.5 \mathrm{~Hz}, 1 \mathrm{H})$, 2.74-2.65 (m, 1H), 2.50-2.29 (m, overlapped, 4H), 2.21 (br s, 1H), $2.06(\mathrm{~s}, 3 \mathrm{H}), 1.87-1.77(\mathrm{~m}$, overlapped, 2 H$), 1.68-1.52(\mathrm{~m}, 3 \mathrm{H})$, $1.12(\mathrm{~s}, 3 \mathrm{H}), 0.94(\mathrm{~d}, J=7 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 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 $\mathrm{C}_{27} \mathrm{H}_{36} \mathrm{NO}_{7}\left(\mathrm{M}+\mathrm{H}^{+}\right) 486.2492$, found 486.2494.
(2aR,2a $\left.{ }^{1} R, 6 \mathrm{aS}, 8 R, 9 \mathrm{a} R\right)$-Methyl 8-((S)-1-(4-methoxyphenoxy)-propan-2-yl)-2a ${ }^{1}$-methyl-3,6-dioxododecahydro-1 H -cyclohepta[cd]indole-1-carboxylate (16): ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 6.82-6.72(\mathrm{~m}, 4 \mathrm{H}), 4.15$ and 4.08 (each dd, $J=12,8.8 \mathrm{~Hz}$ and $J=11.8,9.2 \mathrm{~Hz}$, total 1 H$), 3.70-3.89(\mathrm{~m}$, overlapped, 3 H$), 3.75$ $(\mathrm{s}, 3 \mathrm{H}), 3.69$ and $3.66($ each s , total 3 H$), 3.73-3.70$ and $3.58(\mathrm{~m}$, overlapped and dd, $J=14,5.6 \mathrm{~Hz}$, total 1 H ), 3.48 and 3.44 (each dd, $J$ $=11,9.2 \mathrm{~Hz}$ and $J=11.6,8.8 \mathrm{~Hz}$, total 1 H$), 3.19(\mathrm{td}, J=13.2,4 \mathrm{~Hz}$, $1 \mathrm{H}), 2.72-2.56(\mathrm{~m}$, overlapped, 2 H$), 2.51-2.39(\mathrm{~m}, 1 \mathrm{H}), 2.34(\mathrm{dt}, J=$ $12,4 \mathrm{~Hz}, 1 \mathrm{H}), 2.23-2.15$ and $2.08-1.98$ (each m, total 1 H ), $1.97-$ $1.87(\mathrm{~m}, 1 \mathrm{H}), 1.82-1.76(\mathrm{~m}, 1 \mathrm{H}), 1.69-1.62(\mathrm{~m}$, overlapped, 2 H$)$, $1.29-1.11(\mathrm{~m}, 1 \mathrm{H}), 0.51(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}), 0.88(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ some peaks double due to amide conformational isomers) $\delta 210.7,210.6,206.3,205.9,155.1,153.9,153.0,115.5,115.4$, $114.7,71.4,71.3,66.2,66.1,60.5,55.8,52.4,51.4,50.4,43.7,43.2$, $42.9,42.2,38.3,37.3,36.2,36.1,33.5,323.0,32.2,28.5,28.2,23.5$,
23.4, 13.7, 13.6; HRMS calcd for $\mathrm{C}_{25} \mathrm{H}_{34} \mathrm{NO}_{6}\left(\mathrm{M}+\mathrm{H}^{+}\right)$444.2386, found 444.2380.
( $2 \mathrm{a} R, 2 \mathrm{a}^{1} R, 4 R, 5 \mathrm{aS}, 5 \mathrm{bS}, 8 R, 8 \mathrm{aS}$ )-Methyl 5b-Acetoxy-8-hy-droxy-4-((S)-1-(4-methoxyphenoxy)propan-2-yl)-2a ${ }^{1}$ -methyldecahydrocyclopenta[1,4]cyclobuta[1,2,3-cd]indole-2(1H)-carboxylate (17). To a solution of $15(188 \mathrm{mg}, 0.39 \mathrm{mmol})$ in $\mathrm{MeOH}(10 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaBH}_{4}(30 \mathrm{mg}, 0.77 \mathrm{mmol})$. The reaction mixture was stirred for 2 h at $0^{\circ} \mathrm{C}$ and then quenched by satd $\mathrm{NH}_{4} \mathrm{Cl}$. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $17(181 \mathrm{mg})$ in $95 \%$ yield as colorless oil: ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.79(\mathrm{~s}, 4 \mathrm{H}), 4.17(\mathrm{dd}, J=10.8,7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 3.82-3.76(\mathrm{~m}, 2 \mathrm{H}), 3.74(\mathrm{~s}, 3 \mathrm{H}), 3.71-3.68$ (m, overlapped, $1 \mathrm{H}), 3.67(\mathrm{~s}, 3 \mathrm{H}), 3.61(\mathrm{t}, J=6 \mathrm{~Hz}, 1 \mathrm{H}), 3.43(\mathrm{~d}, J=12 \mathrm{~Hz}, 1 \mathrm{H}), 2.44$ (dd, $J=14,8 \mathrm{~Hz}, 1 \mathrm{H}), 2.32(\mathrm{t}, J=9 \mathrm{~Hz}, 1 \mathrm{H}), 2.15-2.10(\mathrm{~m}, 1 \mathrm{H})$, $2.02(\mathrm{~s}, 3 \mathrm{H}), 2.02-1.70(\mathrm{~m}, 5 \mathrm{H}), 1.58-1.50(\mathrm{~m}, 1 \mathrm{H}), 1.50-1.49(\mathrm{~m}$, $1 \mathrm{H}), 1.35(\mathrm{~s}, 3 \mathrm{H}), 1.32-1.26(\mathrm{~m}, 1 \mathrm{H}), 0.91(\mathrm{~d}, J=7 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 170.1,156.4,153.8,153.5,115.6,114.7$, 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 $\mathrm{C}_{27} \mathrm{H}_{38} \mathrm{NO}_{7}(\mathrm{M}+$ $\mathrm{H}^{+}$) 488.2648, found 488.2634.
( $\left.2 \mathrm{a}^{1} R, 6 \mathrm{aS}, 8 R, 9 \mathrm{a} R\right)$-Methyl 8-((S)-1-(4-Methoxyphenoxy)-propan-2-yl)-2a ${ }^{1}$-methyl-6-oxo-2,2a ${ }^{1}, 4,5,6,6 a, 7,8,9,9 a-d e c a h y-$ dro-1H-cyclohepta[cd]indole-1-carboxylate (18). To a stirred solution of $17(181 \mathrm{mg}, 0.37 \mathrm{mmol})$ in pyridine ( 10 mL ) were added methanesulfonyl chloride ( $0.3 \mathrm{~mL}, 3.7 \mathrm{mmol}$ ) and DMAP ( 44 mg , 0.36 mmol ). The reaction mixture was stirred for 1.5 h at room temperature, diluted with ethyl acetate $(10 \mathrm{~mL})$, and washed consecutively with satd $\mathrm{NH}_{4} \mathrm{Cl}(2 \times 5 \mathrm{~mL})$ and brine $(2 \times 5 \mathrm{~mL})$. The organic layer was dried with $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated to yield mesylate which was carried on to the next step. The mesylate was dissolved in $\mathrm{MeOH}(5 \mathrm{~mL})$ and stirred with $\mathrm{K}_{2} \mathrm{CO}_{3}(305 \mathrm{mg}$, 2.2 mmol ) overnight at room temperature. The reaction mixture was filtered, evaporated, diluted with water $(5 \mathrm{~mL})$, and extracted with ethyl acetate before drying over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $18(129 \mathrm{mg})$ in $82 \%$ yield as colorless oil: ${ }^{1} \mathrm{H} \mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.80-6.71$ $(\mathrm{m}, 4 \mathrm{H}), 5.71(\mathrm{~d}, J=19.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.27$ and 4.19 (each $\mathrm{d}, J=16.5$ and 15.0 Hz , total 1 H ), $3.91(\mathrm{t}, J=15 \mathrm{~Hz}, 1 \mathrm{H}), 3.75$ and 3.74 (each s, total $3 \mathrm{H}), 3.69$ and 3.67 (each s, total 3 H ), 3.81-3,71 (m, overlapped, 2 H ), $3.70-3.63$ and 3.53 (overlapped and dd, $J=10,5.5 \mathrm{~Hz}$, total 1 H ), 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, $J=13,2.5 \mathrm{~Hz}$ and $13,2.5 \mathrm{~Hz}$, total 1 H ), $1.87-$ $1.77(\mathrm{~m}, 1 \mathrm{H}), 1.76-1.70(\mathrm{~m}, 1 \mathrm{H}), 1.70-1.55$ (overlapped, 1 H$), 1.40$ (pentet, $J=12.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.20 and 1.19 (each s, total 3 H ), 1.10-0.92 $(\mathrm{m}, 1 \mathrm{H}), 0.94(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ some peaks double due to amide conformational isomers) $\delta 213.0,155.4$, $155.1,154.0,153.9,153.3,140.8,140.0,121.4,121.2,115.6,155.6$, $114.8,71.7,71.7,65.8,65.7,60.3,55.8,52.4,52.3,50.1,49.7,45.1$, $44.5,42.3,37.5,37.3,37.3,33.2,32.4,30.5,30.2,29.7,27.0,27.0,24.0$, 13.8, 13.7; HRMS calcd for $\mathrm{C}_{25} \mathrm{H}_{34} \mathrm{NO}_{5}\left(\mathrm{M}+\mathrm{H}^{+}\right) 428.2437$, found 428.2412.
( $2 a^{1} R, 6 a S, 8 R, 9 a R$ )-Methyl 8-((S)-1-Hydroxypropan-2-yl)-2a²-methyl-6-oxo-2,2a ${ }^{1}, 4,5,6,6 a, 7,8,9,9 a-d e c a h y d r o-1 H-$ cyclohepta[cd]indole-1-carboxylate (19). To a solution of 18 $(160 \mathrm{mg}, 0.37 \mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=4: 1(2.5 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ was added CAN $(410 \mathrm{mg}, 0.75 \mathrm{mmol})$. After being stirred for 30 min , the reaction was quenched with brine $(2 \mathrm{~mL})$, and the aqueous layer was extracted with ethyl acetate $(3 \times 2 \mathrm{~mL})$. The combined organic portion was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel ( $n$ hexane/ethyl acetate $=1 / 2)$ to give $19(120 \mathrm{mg})$ in $99 \%$ yield as yellow oil: ${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.73$ and 5.70 (each $\mathrm{d}, J=$ 2.8 and $J=3 \mathrm{~Hz}$, total 1 H ), 4.23 (ddd, $J=35,28,3 \mathrm{~Hz}, 1 \mathrm{H}), 3.90(\mathrm{td}$, $J=13.2,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.68(\mathrm{~s}, 3 \mathrm{H}), 3.63$ and $3.58-3.50(\mathrm{dd}$ and overlapped, $J=10,7 \mathrm{~Hz}$, total 1 H$), 3.57-3.42(\mathrm{~m}, 2 \mathrm{H}), 2.71-2.60$ and $2.48-2.35(\mathrm{~m}$, total 2 H$), 2.49(\mathrm{td}, J=15,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.29-2.18$
$(\mathrm{m}, 1 \mathrm{H}), 2.05-1.96$ and $1.90-1.80$ (each m , total 1 H ), 1.72-1.47 (overlapped, total 4 H ), 1.36-1.27 (m, 1H), 1.19 and 1.18 (each s, total 3 H ), $1.09-0.92(\mathrm{~m}, 1 \mathrm{H}), 0.85$ and 0.84 (each $\mathrm{d}, J=8$ and 8 Hz , total 3 H ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ some peaks double due to amide conformational isomers) $\delta 213.5,213.4,155.3,155.1,140.5$, $139.7,121.4,121.2,65.7,65.7,60.2,60.2,52.5,52.4,50.0,49.7,45.0$, 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 $\mathrm{C}_{18} \mathrm{H}_{28} \mathrm{NO}_{4}\left(\mathrm{M}+\mathrm{H}^{+}\right) 322.2018$, found 322.2023.
(2a ${ }^{1} R, 6 \mathrm{aS}, 8 R, 9 \mathrm{a} R$ )-Methyl 2a1-Methyl-8-((S)-1( (methylsulfonyl)oxy)propan-2-yl)-6-oxo2,2a ${ }^{1}$,4,5,6,6a,7,8,9,9a-decahydro-1 H -cyclohepta[cd]indole-1carboxylate (20). To a solution of $19(120 \mathrm{mg}, 0.373 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ were added $\mathrm{Et}_{3} \mathrm{~N}(160 \mu \mathrm{~L})$ and methylsufonyl chloride $(60 \mu \mathrm{~L})$, and then the mixture was warmed to room temperature. After the mixture was stirred for 2 h , the reaction was quenched with brine $(4 \mathrm{~mL})$, and the aqueous layer was extracted with ethyl acetate $(3 \times 3 \mathrm{~mL})$. The combined organic portion was washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel ( $n$ hexane/ethyl acetate $=1.5 / 1)$ to give $20(142 \mathrm{mg})$ in $95 \%$ yield as yellow oil: ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.69(\mathrm{~d}, J=11.6 \mathrm{~Hz}, 1 \mathrm{H})$, 4.27-3.82 (m, overlapped, 4 H ), 3.65 and 3.64 (each s, total 3 H ), 3.59 and 3.48 (each dd, $J=11,5.2 \mathrm{~Hz}$ and $J=11,5.2 \mathrm{~Hz}$, total 1 H ), 2.96 and 2.95 (each s, total 3 H$), 2.70-2.58(\mathrm{~m}, 2 \mathrm{H}), 2.44(\mathrm{td}, J=12.6,3.2$ $\mathrm{Hz}, 1 \mathrm{H}), 2.40-2.32(\mathrm{~m}, 1 \mathrm{H}), 2.27-2.14(\mathrm{~m}, 1 \mathrm{H}), 2.02-1.93$ and 1.84 ( m and $\mathrm{dt}, J=12.8,2.4 \mathrm{~Hz}$, total 1 H ), 1.74 (pentet, $J=6 \mathrm{~Hz}, 1 \mathrm{H}$ ), $1.70-1.61(\mathrm{~m}, 1 \mathrm{H}), 1.49-1.38(\mathrm{~m}, 1 \mathrm{H}), 1.38-1.25(\mathrm{~m}, 1 \mathrm{H}), 1.56(\mathrm{~s}$, $3 \mathrm{H}), 0.98-0.92(\mathrm{~m}, 1 \mathrm{H}), 0.89(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 100 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ some peaks double due to amide conformational isomers) $\delta 212.7,212.6,155.1,154.9,140.2,139.4,121.5,121.3,72.1$, $72.0,65.3,65.3,59.9,52.3,52.2,49.9,49.5,44.8,44.2,42.2,37.2,37.2$, 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 $\mathrm{C}_{19} \mathrm{H}_{30} \mathrm{NO}_{6} \mathrm{~S}\left(\mathrm{M}+\mathrm{H}^{+}\right)$400.1794, found 400.1777.
(2R,3S, $11 \mathrm{~S}, 11 \mathrm{a} R, 11 \mathrm{~b}$ )-3,11a-Dimethyl-3,4,6,8,9,11,11a,11b-octahydro-1H-2,11-methanocyclohepta[a]indolizin-10(2H)one (21). To a solution of $20(20 \mathrm{mg}, 0.05 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(1.5$ mL ) was added TMSI ( $30 \mathrm{mg}, 0.15 \mathrm{mmol}$ ). The mixture was stirred at room temperature for 4 h , quenched with satd $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ (aq), and extracted with $\mathrm{CH}_{3} \mathrm{OH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}=1: 9(8 \times 2 \mathrm{~mL})$. The combined organic portion was washed with brine and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude product was dissolved in 1.5 mL of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and $50 \mu \mathrm{~L} \mathrm{Et}_{3} \mathrm{~N}$ added. After being stirred for 16 h , the mixture was purified by flash chromatography on silica gel $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} /\right.$ $\left.\mathrm{MeOH} / \mathrm{Et}_{3} \mathrm{~N}=100: 5: 1\right)$ to give $21(10 \mathrm{mg})$ in $80 \%$ yield as a colorless oil: ${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.19$ (ddd, $J=7.2,3.0,2.8 \mathrm{~Hz}$, $1 \mathrm{H}), 4.08(\mathrm{dt}, J=13.6,2.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.77(\mathrm{~s}, 1 \mathrm{H}), 3.37(\mathrm{~d}, J=13.6 \mathrm{~Hz}$, $1 \mathrm{H}), 3.25(\mathrm{~d}, J=13.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.17(\mathrm{dd}, J=13.4,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.71-$ $2.55(\mathrm{~m}$, overlapped, 3 H$), 2.50-2.40(\mathrm{~m}, 1 \mathrm{H}), 2.30-2.22(\mathrm{~m}, 1 \mathrm{H})$, $2.21-2.13(\mathrm{~m}, 2 \mathrm{H}), 2.15-1.90(\mathrm{~m}, 1 \mathrm{H}), 1.90-1.71(\mathrm{~m}, 1 \mathrm{H}), 1.64(\mathrm{dd}$, $J=16,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.49-1.37(\mathrm{~m}, 1 \mathrm{H}), 1.32(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H}), 1.26$ $(\mathrm{s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 210.5,139.0,129.3,66.8$, 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 $\mathrm{C}_{16} \mathrm{H}_{24} \mathrm{NO}\left(\mathrm{M}+\mathrm{H}^{+}\right) 246.1858$, found 246.1852.
(2R,3S,6aS, 11S, $11 \mathrm{aS}, 11 \mathrm{bR}$ )-3,11a-Dimethyldecahydro-1 H -2,11-methanocyclohepta[a]indolizin-10(2H)-one (22). To a solution of $21(4.5 \mathrm{mg}, 0.018 \mathrm{mmol})$ in $\mathrm{MeOH}(1 \mathrm{~mL})$ was added $\mathrm{PtO}_{2}(2 \mathrm{mg}, 0.009 \mathrm{mmol})$. 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 $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} / \mathrm{Et}_{3} \mathrm{~N}=100: 5: 1\right)$ to give $22(4.2 \mathrm{mg})$ in $94 \%$ yield as colorless oil: ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 3.42(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.21-3.12(\mathrm{~m}, 2 \mathrm{H}), 2.86(\mathrm{dd}, J=$ $14.2,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.69-2.68(\mathrm{~m}$, overlapped, 2 H$), 2.52(\mathrm{dd}, J=11.6$, $6.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.50-2.41(\mathrm{~m}, 1 \mathrm{H}), 2.40-2.30(\mathrm{~m}, 1 \mathrm{H}), 2.09-1.96(\mathrm{~m}$, $1 \mathrm{H}), 1.95-1.65$ (m, overlapped, 8 H ), 1.44 (dd, $J=15.2,3.6 \mathrm{~Hz}, 1 \mathrm{H})$, $1.44(\mathrm{~s}, 3 \mathrm{H}), 0.91(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 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 $\mathrm{C}_{16} \mathrm{H}_{26} \mathrm{NO}\left(\mathrm{M}+\mathrm{H}^{+}\right)$248.2014, found 248.2010 .
(2aR,2a1S,6aS,8R,9aR)-Methyl 8-Isopropyl-2a¹-methyl-6-ox-ododecahydro-1H-cyclohepta[cd]indole-1-carboxylate (24). To a solution of carbamate $23(42 \mathrm{mg}, 0.14 \mathrm{mmol})$ in MeOH (2 $\mathrm{mL})$ was added $\mathrm{PtO}_{2}(16 \mathrm{mg}, 0.07 \mathrm{mmol})$. 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 ( $170 \mathrm{mg}, 0.42 \mathrm{mmol}$ ) and $\mathrm{NaHCO}_{3}$ $(70 \mathrm{mg}, 0.84 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{~mL})$ for 3 h . The reaction was quenched with satd $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} / \mathrm{NaHCO}_{3}=1: 1(2 \mathrm{~mL})$, and the aqueous layer was extracted with ethyl acetate $(3 \times 2 \mathrm{~mL})$. The combined organic portion was washed with $\mathrm{H}_{2} \mathrm{O}(2 \mathrm{~mL})$ and brine $(2 \mathrm{~mL})$ and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $24(32 \mathrm{mg})$ in $74 \%$ yield as colorless oil: ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.64$ and 3.63 (each s, total 3 H ), $3.58-3.48$ and 3.38 ( m and dd, $J=11,6 \mathrm{~Hz}$, total 2 H ), 3.11 and 3.05 (each $\mathrm{t}, J=11 \mathrm{~Hz}$ and $J=10.5 \mathrm{~Hz}$, total 1 H ), 2.65 (ddd, $J=$ $19.6,6.5,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.64-2.56(\mathrm{~m}, 1 \mathrm{H}), 2.46-2.34(\mathrm{~m}, 2 \mathrm{H}), 2.12-$ 2.07 and $1.96-1.90(\mathrm{~m}$, total 1 H$), 1.87-1.60(\mathrm{~m}, 4 \mathrm{H}), 1.49-1.40(\mathrm{~m}$, 2 H ), 1.29 (ddd, $J=24.8,12.3,2 \mathrm{~Hz}, 1 \mathrm{H}), 1.23-1.12(\mathrm{~m}, 1 \mathrm{H}), 1.05-$ $0.94(\mathrm{~m}, 1 \mathrm{H}), 0.98$ and 0.97 (each s, total 3 H$), 0.86-0.82(\mathrm{~m}, 6 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ some peaks double due to amide conformational isomers) $\delta 214.2,155.4,155.1,66.6,66.5,60.3,60.2$, $52.2,52.1,50.1,49.8,42.2,42.2,41.6,41.5,40.8,39.2,38.3,32.3,32.3$, 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 $\mathrm{C}_{18} \mathrm{H}_{30} \mathrm{NO}_{3}\left(\mathrm{M}+\mathrm{H}^{+}\right)$308.2226, found 308.2220.

## ASSOCIATED CONTENT

## (5) Supporting Information

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

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## Notes

The authors declare no competing financial interest.

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