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SYNTHESIS OF TETRACYCLIC INDOLINE AND INDOLENINE DERIVATIVES HAVING β-LACTAM USING AMPHIPHILIC REACTIVITY OF 2-METHYLINDOLENINE

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Abstract – Novel tetracyclic indoline and indolenine β-lactam derivatives were synthesized from 2-methylindolenine β-lactams using the amphiphilic nature of 2-methylindolenine.

β-Lactam is a ubiquitous framework in biologically active compounds including naturally occurring antibiotics[1] and drug candidates.[2] β-Lactam is also incorporated in indole alkaloids such as chartelline marine alkaloids,[3] whose unique structures have stimulated the development of synthetic methods for the construction of their core frameworks (Figure 1). During the course of our synthetic studies on the chartelline family,[4] we have already developed synthetic methods for the construction of β-lactams bearing oxindole[4a] and indolenine.[4b] In the latter method, indolenine β-lactam was synthesized by an intramolecular nucleophilic substitution of the nitrogen atom of *O*-sulfonylated hydroxamic acid derivative (Scheme 1).

2-Methylindolenine is known to show amphiphilic reactivity,[5] as shown in Scheme 2. Thus, 2-methylindolenine **A** could react as an imine with a nucleophilic functional group to provide 2,2-disubstituted indoline **C**. On the other hand, enamine **B**, a tautomer of **A**, could react with an electrophilic functional group to provide indolenine **D** in which the 2-methyl group can be functionalized. Because this amphiphilic reactivity is potentially useful for the construction of various indoline and indolenine compounds, we investigated the amphiphilic reactivity of 2-methylindolenine β-lactams to find two cyclizations leading to tetracyclic compounds.

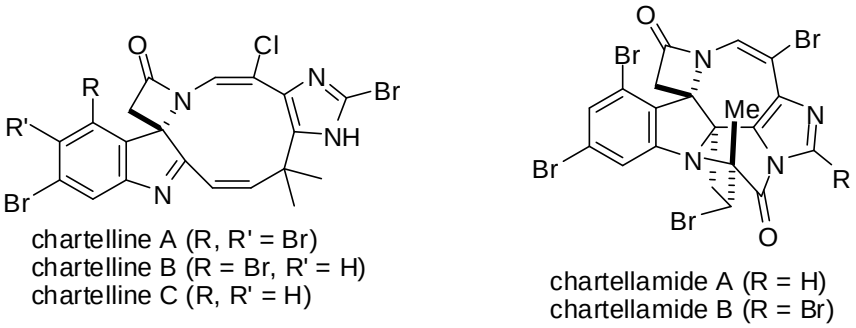
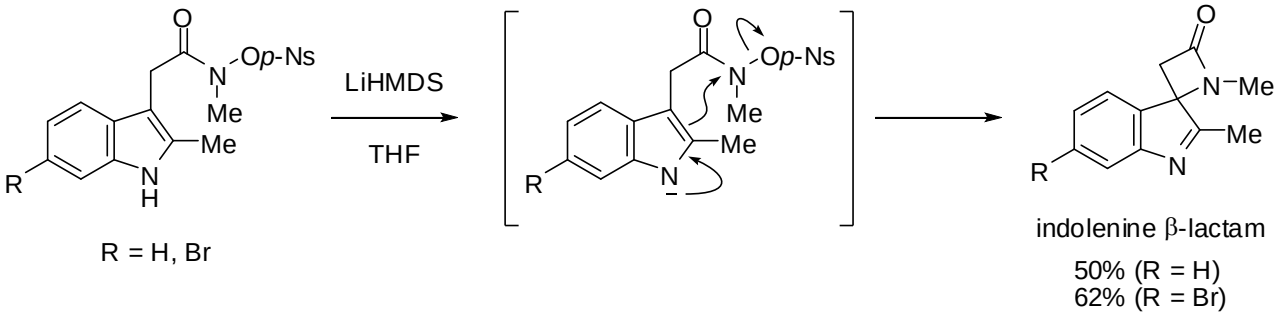
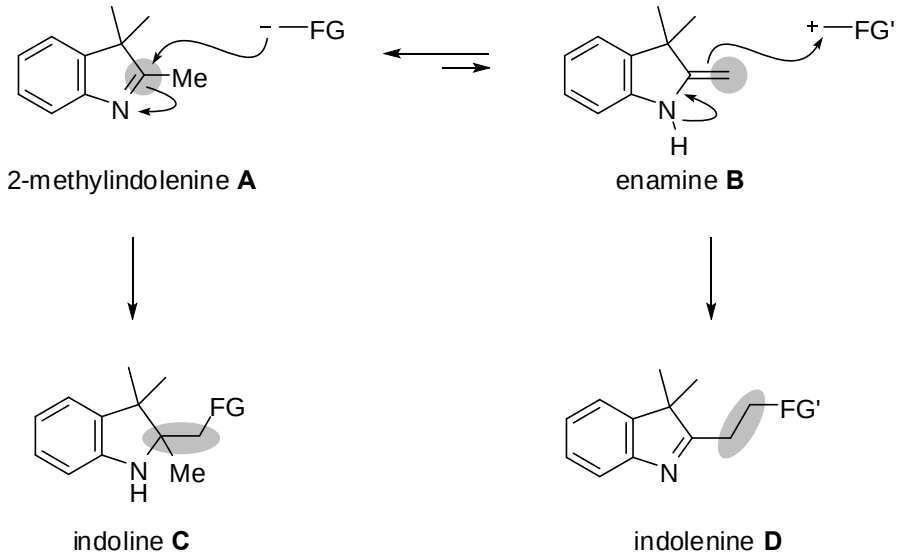


Figure 1. Structures of alkaloids containing β-lactam



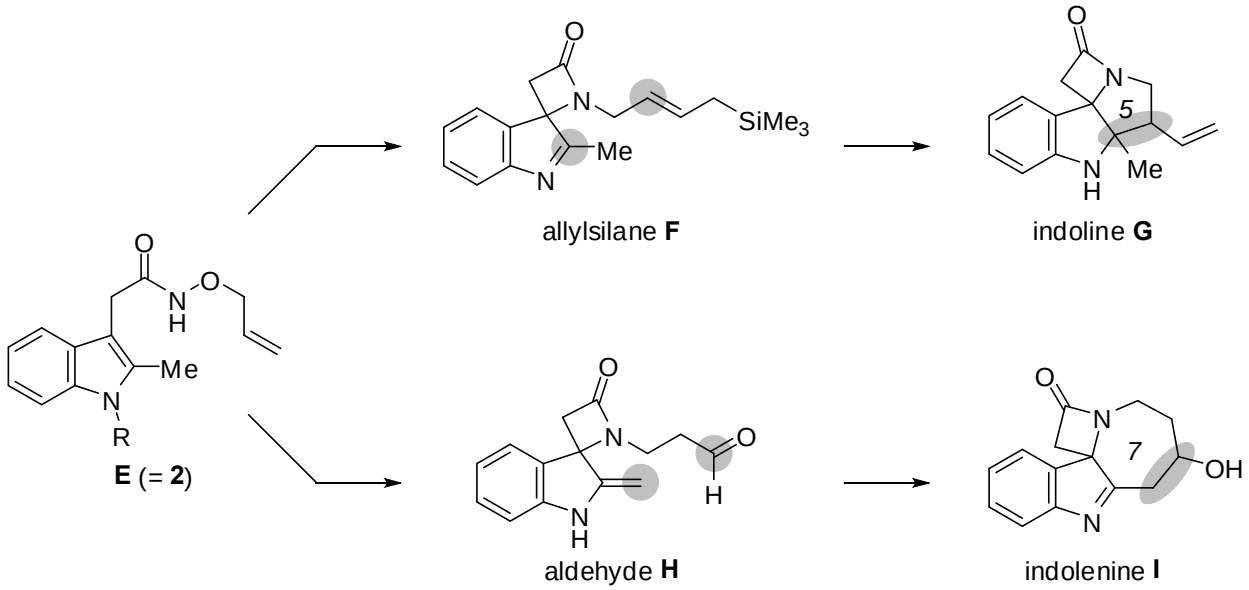
Scheme 1. β-Lactam formation through intramolecular nucleophilic substitution



Scheme 2. Amphiphilic reactivity of 2-methylindolenine **A**

In order to study the amphiphilic reactivity, we planned to investigate the cyclization of 2-methylindolenines with nucleophilic or electrophilic functionality on β-lactam (Scheme 3). Thus,

allylsilane **F** and aldehyde **H** would be derived from a common hydroxamic acid allyl ester **E**, and then cyclizations to the functionalized 5-membered indoline **G** and 7-membered indolenine **I** were examined.

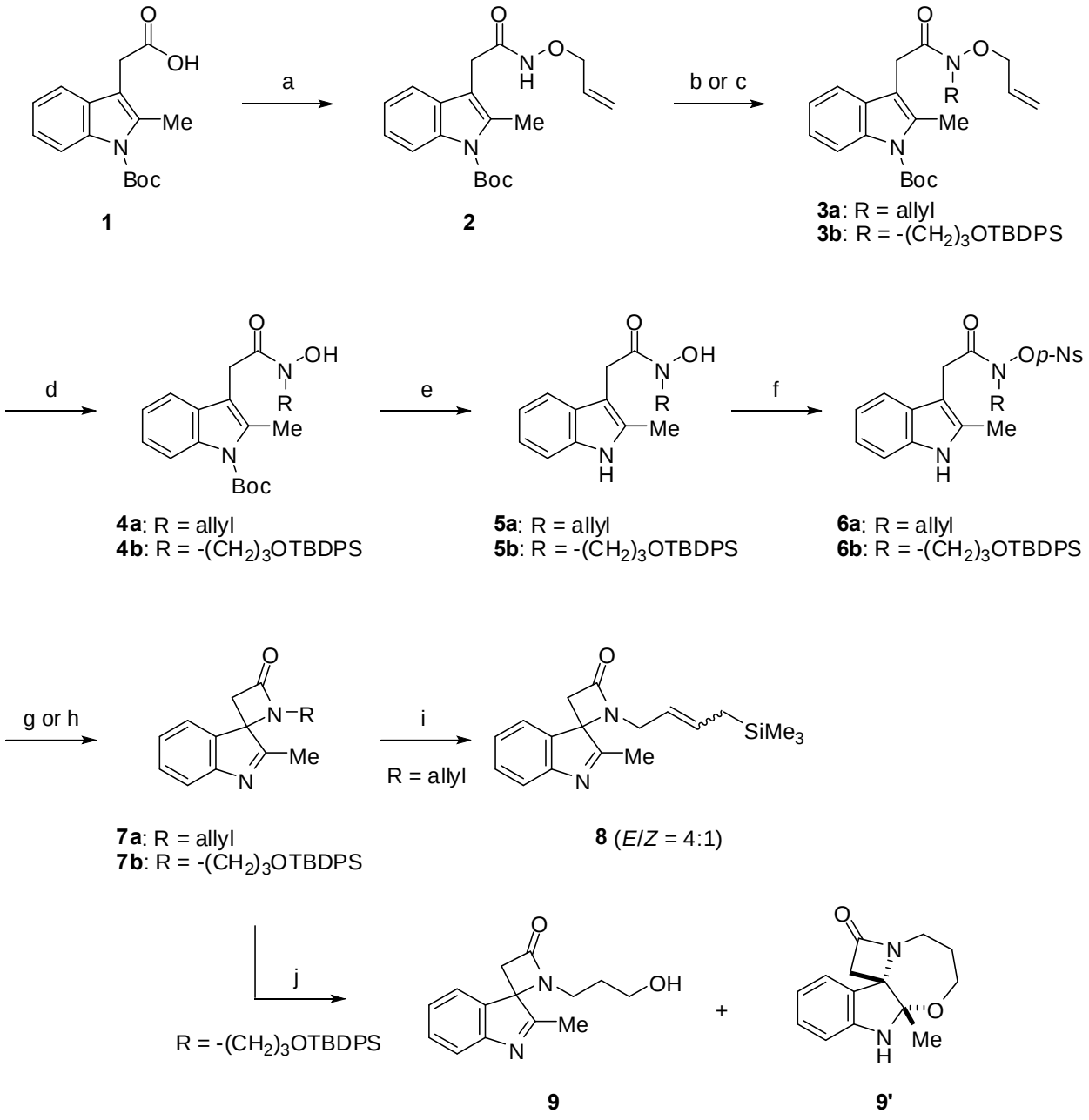


Scheme 3. Synthetic plan of tetracyclic indoline and indolenine β-lactams

The synthesis of the cyclization precursors **8** (= **F**, in Scheme 3) and **9** (an equivalent of **H**) is described in Scheme 4. To prepare substrates **6a** and **6b** for β-lactam cyclization, we modified the procedure reported by this group.[4b] *N*-Boc indoleacetic acid **1**, prepared from a commercially available 2-methylindoleacetatic acid, was converted into amide **2** using EDCI and allyloxyamine in 88% yield. *N*-Allylation of **2** was followed by the removal of *O*-allyl and Boc groups under conventional conditions to afford hydroxamic acid **5a** in good overall yield. The hydroxy group in **5a** was transformed into a *p*-nitrobenzenesulfonate (nosyl) group to yield **6a**. According to the β-lactam formation method,[4b] the cyclization of **6a** was carried out with LiHMDS as a base to afford the desired indolenine β-lactam **7a** in 27% yield.[6] Surprisingly, the cyclization of **6a** using $NaHCO_3$ at 40 °C provided **7a** in higher yield (49%).[6] Next, the cross metathesis of the obtained *N*-allyl β-lactam **7a** with allyltrimethylsilane and Grubbs 2nd generation catalyst[7] gave the corresponding allylsilane **8** in moderate yield as an inseparable mixture of *E*/*Z* isomers (*E*/*Z* = 4:1).

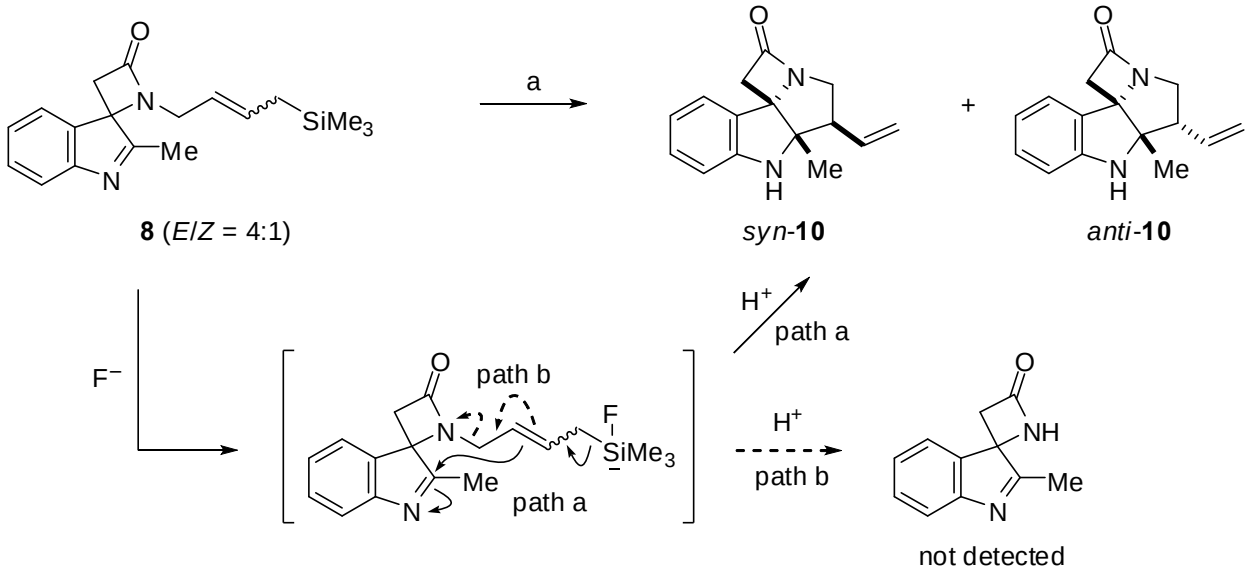
N-(3-Hydroxypropyl) β-lactam **9** was also synthesized from **2** in a manner similar to **7a** (Scheme 3). The *N*-alkylation of **2** with 3-siloxypropyl bromide gave **3b** in 77% yield. The deprotection of *O*-allyl and Boc groups followed by *O*-nosylation gave **6b**. The β-lactam cyclization of **6b** using LiHMDS was found to give the desired β-lactam **7b** in the same level of yield as that of **7a**.[6] Unfortunately, the cyclization of **6b** using $NaHCO_3$ resulted in a complex mixture, and no desired product was observed.

The TBDPS group in **7b** was removed with TBAF, leading to the cyclization precursor **9** as an inseparable mixture of its tautomer, *N*,*O*-acetal **9'**.



Scheme 4. Synthesis of cyclization precursors **8** and **9**. Reagents and conditions: (a) EDCI, allyloxyamine·HCl, Et_3N, CH_2Cl_2, rt, 88%; (b) allyl bromide, NaH, TBAI, DMF, 0 °C, 76% for **3a**; (c) K_2CO_3, KI, $Br(CH_2)_3OTBDPS$, acetone, reflux, 77% for **3b**; (d) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, CH_3CN-H_2O, 40 °C, 91% for **4a**, 83% for **4b**; (e) TFA, CH_2Cl_2, 0 °C, 87% for **5a**, 82% for **5b**; (f) *p*-NsCl, Et_3N, CH_2Cl_2, 0 °C→rt, 95% for **6a**, 94% for **6b**; (g) $NaHCO_3$, THF, 40 °C, 49% for **7a**; (h) LiHMDS, THF, –78 °C→rt, 26% for **7b**; (i) Grubbs 2nd generation catalyst, allyltrimethylsilane, CH_2Cl_2, reflux, 45%; (j) TBAF, AcOH, THF, rt, 72% (**9**:**9'** = 75:25).

With requisite precursors **8** and **9** now in hand, their cyclizations were next examined (Schemes 5 and 6). Upon the treatment of indolenine β-lactam **8** with TBAF, intramolecular allylation occurred to give a mixture of the desired tertacyclic indoline β-lactam *syn*-**10** and *anti*-**10** in 24% and in 19% yield, respectively (Scheme 5). The intramolecular imine allylation of **8** did not take place under Lewis acidic conditions ($BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to rt). These epimeric products were separable by silica gel column chromatography, and the relative stereochemistry of the diastereomers was determined by NOESY correlations (Figure 2). It revealed that the geometry of allylsilane in **8** does not appear to influence the relative stereoselectivity of products **10**. Interestingly, the elimination of the 4-(trimethylsilyl)but-2-enyl group from β-lactam in **8** was not detected, indicating that intramolecular allylation (path a, Scheme 5) was much faster than the loss of the 4-(trimethylsilyl)but-2-enyl group (path b).



Scheme 5. Reagents and conditions: (a) TBAF, THF, rt, 24% for *syn*-**10** and 19% for *anti*-**10**.

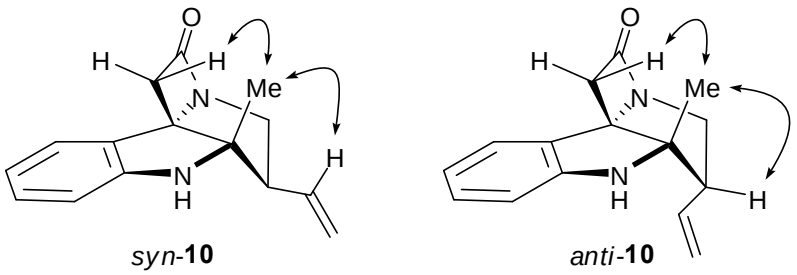
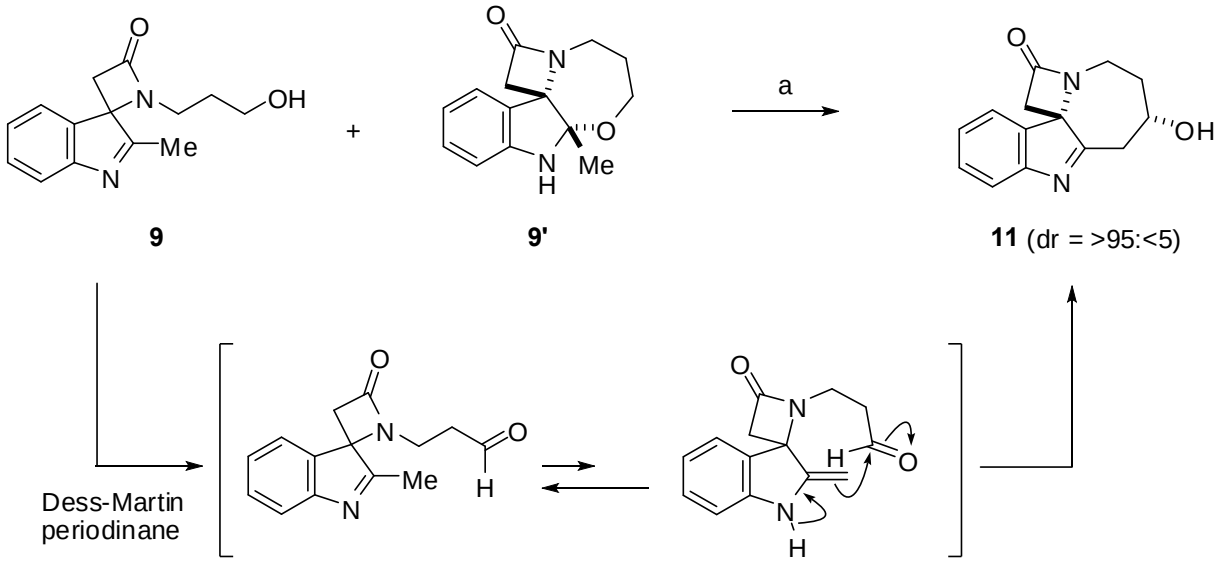


Figure 2. Selected NOESY correlations of cyclized products *syn*-**10** and *anti*-**10**

Next, the cyclization of aldehyde derived from **9** was examined to synthesize tetracyclic indolenine β-lactam **11** by using an enamine nature of 2-methylindolenine (Scheme 6). Treatment of a mixture of tautomers **9** and **9'** with 1.2 equiv of Dess-Martin periodinane in CH_2Cl_2 smoothly led to an alcohol **11** having a 7-membered ring in 31% yield as a single diastereomer. In this reaction, both of tautomers **9** and **9'** were consumed, and none of its epimer and the corresponding aldehyde and ketone derived from product **11** were observed. This transformation involves oxidation with concomitant tautomerization of the imine moiety and intramolecular enamine aldol reaction in a one-pot manner. Other oxidation conditions (TEMPO, NaClO, KBr, $NaHCO_3$ aq., CH_2Cl_2, rt; SO_3·py, Et_3N, DMSO, CH_2Cl_2, rt; IBX, EtOAc, 80 °C; PCC, MS 4A, NH_4OAc, CH_2Cl_2, rt) gave inferior results. The relative stereochemistry of **11** was determined by ^1H NMR and NOESY analyses, as depicted in Figure 3. Thus, the present process serves as a simple and mild synthetic route for obtaining the potentially useful indolenine with requisite functionality for the construction of chartellamide core scaffold (Figure 1).[8]



Scheme 6. Reagents and conditions: (a) Dess-Martin periodinane, CH_2Cl_2, rt, 31%.

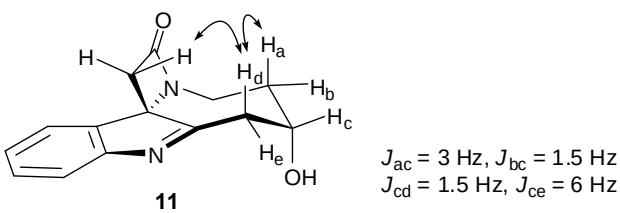


Figure 3. Selected NOESY correlations and coupling constants of cyclized product **11**

In conclusion, we have developed two synthetic approaches to the functionalized tetracyclic indoline and indolenine β-lactam derivatives using the amphiphilic reactivity of 2-methylindolenine. The results of our study should serve as a potentially useful method for the synthesis of chartelline marine alkaloids. Our study also revealed that the β-lactam formation of the nosyl *N*-allyl hydroxamic acid derivative proceeded under mild conditions ($NaHCO_3$, THF, 40 °C).

EXPERIMENTAL

General Techniques.

All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plates $60F_{254}$ (Merck, #1.05715). Preparative thin-layer chromatographic separations were carried out on 0.5 mm silica gel plates $60F_{254}$ (Merck, #1.05744). Silica gel 60N (spherical, neutral, particle size 63-210 μm, Kanto Chemical Co., Inc., #37565-84) was used for open-column chromatography. Silica gel 60N (spherical, neutral, particle size 40-50 μm, Kanto Chemical Co., Inc., #37563-84) and silica gel 60 (spherical, particle size 40-50 μm, Kanto Chemical Co., Inc., #37562-84) were used for flash column chromatography. Dehydrated THF, Et_2O and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Infrared spectra (IR) were recorded on a JASCO FT/IR-4100 type A spectrophotometer and reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-2000 (300 MHz) or a Bruker ARX-400 (400 MHz). NMR samples were dissolved in $CDCl_3$, CD_3OD, or C_6D_6, and chemical shifts were reported in ppm relative to the residual undeuterated solvent ($CDCl_3$ as δ = 7.26, CD_3OD as δ = 3.30, or C_6D_6 as δ = 7.15). ^{1}H NMR data were reported as follows: chemical shifts, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, m = multiplet), coupling constant(s), and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini-2000 (75 MHz) or a Bruker ARX-400 (100 MHz). NMR samples were dissolved in $CDCl_3$, CD_3OD, or C_6D_6, and chemical shifts were reported in ppm relative to the solvent ($CDCl_3$ as δ = 77.0, CD_3OD as δ = 49.0, or C_6D_6 as δ = 128.0). Elemental analyses were performed by the Analytical Laboratory of the Graduate School of Bioagricultural Sciences, Nagoya University. Melting points (Mp) were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. High resolution mass spectra (HRMS) were recorded on an Applied Biosystems Mariner ESI-TOF spectrometer and are reported in *m/z*.

Amide 2: To a solution of *N*-Boc indole-3-acetic acid **1** (6.15 g, 21.3 mmol) in CH_2Cl_2 (500 mL) were added AllylO-NH_2·HCl (2.83 g, 25.8 mmol), Et_3N (3.57 mL, 25.8 mmol) and EDC·HCl (3.84 g, 20.0 mmol). After being stirred at room temperature for 2 h, the reaction was quenched with H_2O (500 mL),

and the resulting mixture was extracted with CH_2Cl_2 (300 mL x 3). The combined extracts were washed with H_2O (500 mL), 0.01 M NaOH aq. (300 mL x 2) and brine (500 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:hexane = 2:3) to afford amide **2** (6.08 g, 88%) as a white solid.

Mp 101-103 °C; IR (film) ν_{max} 3186, 1731, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.69 (9H, s, -Boc), 2.56 (3H, s, -Me), 3.64 (2H, s, -C*H*$_2$-), 4.30 (2H, d, *J* = 6 Hz, -C*H*$_2$-CH=CH$_2$), 5.19 (1H, d, *J* = 17 Hz, -CH=C*H*$_A$H$_B$), 5.20 (1H, d, *J* = 11 Hz, -CH=CH$_A$*H*$_B$), 5.84 (1H, m, -C*H*=CH$_2$), 7.22 (1H, td, *J* = 8, 1 Hz, indole), 7.27 (1H, t, *J* = 8 Hz, indole), 7.42 (1H, d, *J* = 8 Hz, indole), 8.20 (1H, dd, *J* = 8, 1 Hz, indole), 8.21 (1H, brs, -NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 28.2, 30.0, 77.2, 84.1, 110.2, 115.5, 117.7, 121.0, 122.9, 124.1, 128.9, 131.8, 135.5, 135.7, 150.4, 167.6; Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.27; H, 7.02; N, 8.13. Found: C, 66.24; H, 6.90; N, 8.11.

***N*-Allylamide 3a**: A dried two-necked flask was charged with N_2, and NaH (60% dispersion in mineral oil, 0.86 g, 29.6 mmol) was added. The mineral oil was removed by washing with hexane (5 mL x 3) and DMF (300 mL) was added in the flask. After being stirred at 0 °C, to the resulting solution were added a solution of amide **2** (6.08 g, 17.7 mmol) in DMF (50 mL), allyl bromide (2.56 mL, 29.6 mmol), and TBAI (0.654 g, 1.77 mmol). After being stirred for 26 h at 4 °C, the reaction was quenched with H_2O (700 mL), and the resulting mixture was extracted with AcOEt (500 mL x 2). The combined extracts were washed with H_2O (1 L x 2) and brine (1 L), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:hexane = 1:10 to 1:9 to 1:5 to 1:4 to 1:2 to 1:1) to afford *N*-allylamide **3a** (5.20 g, 76%) as a colorless oil.

IR (film) ν_{max} 1729, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.67 (9H, s, -Boc), 2.56 (3H, s, -Me), 3.84 (2H, s, -C*H*$_2$-CO), 4.26 (2H, dt, *J* = 6, 1 Hz, -C*H*$_2$-CH=CH$_2$), 4.38 (2H, dt, *J* = 6, 1 Hz, -C*H*$_2$-CH=CH$_2$), 5.20 (1H, ddt, *J* = 10, 1.5, 1 Hz, -CH=C*H*$_2$), 5.24 (1H, ddt, *J* = 17, 1.5, 1 Hz, -CH=C*H*$_2$), 5.35 (1H, ddt, *J* = 10, 1.5, 1 Hz, -CH=C*H*$_2$), 5.38 (1H, ddt, *J* = 17, 1.5, 1 Hz, -CH=C*H*$_2$), 5.85 (1H, ddt, *J* = 17, 10, 6 Hz, -C*H*=CH$_2$), 5.98 (1H, ddt, *J* = 17, 10, 6 Hz, -C*H*=CH$_2$), 7.18 (1H, td, *J* = 7, 1.5 Hz, indole), 7.22 (1H, td, *J* = 7, 1.5 Hz, indole), 7.46 (1H, dd, *J* = 7, 1.5 Hz, indole), 8.09 (1H, dd, *J* = 7, 1.5 Hz, indole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 28.2, 28.6, 49.4, 75.8, 83.5, 111.8, 115.3, 118.0, 118.3, 120.7, 122.5, 123.4, 129.8, 131.3, 132.2, 135.0, 135.6, 150.6, 172.2; Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.76; H, 7.36; N, 7.29.

***N*-Allylhydroxamic acid 4a**: To a solution of *N*-allyl amide **3a** (5.20 g, 13.5 mmol) in MeCN (108 mL)

and H_2O (27 mL) were added $Pd(OAc)_2$ (303 mg, 1.35 mmol), PPh_3 (1.41 g, 5.41 mmol), HCO_2H (4.43 mL, 118 mmol), and Et_3N (16.3 mL, 118 mmol) and the resulting mixture was heated at 40 °C. After being stirred at 40 °C for 7 h, the reaction was diluted with AcOEt (200 mL). The resulting mixture was washed with H_2O (200 mL x 2) and brine (200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:hexane = 1:1) to afford *N*-allylhydroxamic acid **4a** (4.23 g, 91%) as a yellow solid.

Mp 152-153 °C; IR (film) ν_{max} 3171, 1729, 1611 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.67 (9H, s, -Boc), 2.53 (3H, s, -Me), 3.87 (2H, s, $-CH_2-CO$), 4.20 (2H, d, J = 6 Hz, $-CH_2-CH=CH_2$), 5.18 (1H, dd, J = 10, 1.5 Hz, $-CH=CH_AH_B$), 5.22 (1H, dd, J = 17, 1.5 Hz, $-CH=CH_AC H_B$), 5.83 (1H, ddt, J = 17, 10, 6 Hz, $-CH=CH_2$), 7.15 (1H, td, J = 7, 1.5 Hz, indole), 7.19 (1H, td, J = 7, 1.5 Hz, indole), 7.46 (1H, dd, J = 7, 1.5 Hz, indole), 8.06 (1H, dd, J = 7, 1.5 Hz, indole); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.4, 28.5, 29.1, 52.3, 84.9, 113.5, 116.2, 118.5, 119.2, 123.5, 124.4, 131.4, 133.1, 136.2, 137.1, 152.1, 173.3; Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.29; H, 7.00; N, 8.13.

Indole 5a: To a solution of *N*-allylhydroxamic acid **4a** (4.23 g, 12.3 mmol) in CH_2Cl_2 (369 mL) was added TFA (41 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 24 h. The mixture was diluted with toluene and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt:hexane = 3:2) to afford indole **5a** (2.60 g, 87%) as a colorless oil.

IR (film) ν_{max} 3401, 2917, 1622, 1464, 1241 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 2.36 (3H, s, -Me), 3.86 (2H, s, $-CH_2-$), 4.19 (2H, brd, J = 6 Hz, $-CH_2-CH=CH_2$), 5.13 (lH, brd, J = 10 Hz, $-CH=CH_AH_B$), 5.20 (lH, brd, J = 17 Hz, $-CH=CH_AH_B$), 5.72-5.90 (1H, m, $-CH=CH_2$), 6.92 (1H, t, J = 7 Hz, indole), 6.98 (lH, t, J = 7 Hz, indole), 7.21 (1H, d, J = 7 Hz, indole), 7.45 (lH, d, J = 7 Hz, indole); ^{13}C NMR (CD_3OD, 75 MHz) δ 11.5, 29.3, 52.1, 105.2, 111.3, 118.4, 118.9, 119.6, 121.4, 130.2, 133.3, 134.4, 137.1, 174.8. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.77; H, 6.70; N, 11.43.

Sulfonate 6a: To a stirred solution of hydroxamic acid **5a** (116 mg, 0.475 mmol) and Et_3N (0.131 mL, 0.952 mmol) in CH_2Cl_2 (4.8 mL) was added *p*-NsCl (106 mg, 0.476 mmol). After being stirred for 5 min, the reaction mixture was directly purified by silica gel column chromatography (AcOEt:hexane= 1:5 to 1:2) to afford sulfonate **6a** (193 mg, 95%) as a orange amorphous solid.

^1H NMR ($CDCl_3$, 400 MHz) δ 2.25 (3H, s, -Me), 3.61 (2H, s, $-CH_2-$), 4.36 (2H, brd, J = 5 Hz, $-CH_2-CH=CH_2$), 5.20 (lH, brd, J = 15 Hz, $-CH_2CH=CH_AH_B$), 5.23 (lH, brd, J = 8 Hz, $-CH_2CH=CH_AH_B$), 5.69-5.81 (lH, m, $-CH_2-CH=CH_2$), 7.04 (lH, t, J = 7 Hz, indole), 7.10 (lH, t, J = 7 Hz, indole), 7.18 (lH, d, J = 7 Hz, indole), 7.24 (lH, d, J = 7 Hz, indole), 7.86 (1H, brs, N*H* of indole), 8.02 (2H, d, J = 9 Hz, *p*-Ns),

8.12 (2H, d, *J* = 9 Hz, *p*-Ns).

***N*-Allyl β-lactam 7a:** The freshly prepared sulfonate **6a** (147 mg, 0.342 mmol) was dissolved in THF (34 mL) with $NaHCO_3$ (58 mg, 0.68 mmol). The mixture was heated at 40 °C with stirring for 24 h. The solution was allowed to cool to room temperature and diluted with AcOEt, washed with H_2O (x 2) and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:2 to 1:1) to afford *N*-allyl β-lactam **7a** (37.8 mg, 49%) as a colorless oil.

IR (film) ν_{max} 3321, 2926, 1762, 1586, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.35 (3H, s, -Me), 3.23 (lH, d, *J* = 15 Hz, -C$H_A$$H_B$-), 3.28 (1H, d, *J* = 15 Hz, -C$H_A$$H_B$-), 3.43 (1H, dd, *J* = 15, 7 Hz, -C$H_C$$H_D$-CH=$CH_2$), 3.82 (lH, dd, *J* = 15, 6 Hz, -CH_CCH_D-CH=CH_2), 4.92 (1H, dd, *J* = 17, 1 Hz, -CH_2CH=C$H_E$$H_F$), 5.00 (1H, dd, *J* = 10, 1 Hz, -CH_2CH=$CH_E$$H_F$), 5.48-5.59 (lH, m, -$CH_2$-C*H*=$CH_2$), 7.26 (lH, t, *J* = 7 Hz, indolenine), 7.38 (IH, d, *J* = 7 Hz, indolenine), 7.41 (lH, t, *J* = 7 Hz, indolenine), 7.52 (lH, d, *J* = 7 Hz, indolenine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1, 44.4, 45.9, 68.6, 120.3, 120.8, 122.2, 126.1, 130.1, 130.3, 134.1, 154.0, 165.4, 180.6; HRMS (FAB) $(M+H)^+$ ca1cd for $C_{14}H_{15}ON_2$ 227.1184, found 227.1163.

***N*-(4-Silyl-2-butenyl) β-lactam 8**: To a solution of *N*-allyl β-lactam **7a** (10.0 mg, 0.044 mmol) and allyltrimethylsilane (0.021 mL, 0.132 mmol) in CH_2Cl_2 (0.44 mL) was added Grubbs 2nd generation catalyst (2.0 mg, 2.4 μmol) and the resulting mixture was refluxed. After being stirred at that temperature for 16.5 h, the reaction was concentrated under reduced pressure. The resulting residue was purified by preparative TLC (AcOEt:hexane = 1:1) to afford *N*-(4-silyl-2-butenyl) β-lactam **8** (6.2 mg, 45%, *E*/*Z* = 4:1 determined by ^1H NMR analysis) as a yellow oil.

IR (film) ν_{max} 1764 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ –0.12 (1.8H, s, -SiC(CH_3)), –0.09 (7.2H, s, -SiC(CH_3)), 1.04-1.19 (0.4H, m, Si-CH_2-), 1.27 (1.6H, d, *J* = 8 Hz, Si-CH_2-), 2.34 (3H, s, -Me), 3.18 (0.8H, d, *J* = 15 Hz, -C$H_A$$H_B$), 3.20-3.27 (0.4H, m, -C$H_A$$H_B$), 3.23 (0.8H, d, *J* = 15 Hz, -C$H_A$$H_B$), 3.37 (0.8H, dd, *J* = 15, 8 Hz, N-C$H_C$$H_D$), 3.43-3.48 (0.2H, m, N-C$H_C$$H_D$), 3.78 (0.8H, dd, *J* = 15, 8 Hz, N-C$H_C$$H_D$), 3.81-3.87 (0.2H, m, N-C$H_C$$H_D$), 4.93-5.02 (0.2H, m, -NCH_2-C*H*=CH-), 4.96 (0.8H, ddd, *J* = 15, 8, 7 Hz, -NCH_2-C*H*=CH-), 5.26 (0.8H, dt, *J* = 15, 8 Hz, -CH=C*H*-CH_2-Si), 5.44 (0.2H, q, *J* = 9.5 Hz, -CH=C*H*-CH_2-Si), 7.25 (1H, t, *J* = 7 Hz, indolenine), 7.37 (1H, t, *J* = 7 Hz, indolenine), 7.40 (1H, d, *J* = 7 Hz, indolenine), 7.51 (1H, d, *J* = 7 Hz, indolenine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ –2.0, 15.0, 18.5, 22.7, 37.9, 43.9, 45.7, 68.6, 118.2, 120.1, 120.8, 122.2, 126.1, 130.1, 134,0, 134.6, 165.2, 180.9; HR-MS (ESI, positive): calcd. For $C_{18}H_{24}N_2ONaSi$ (M+Na), 335.1550; found, 335.1545.

***N*-Siloxypropylamide 3b**: To a solution of 3-(*tert*-butyldiphenylsiloxy)propyl bromide (2.19 g, 5.81

mmol) in acetone (19.4 mL) were added amide **2** (2.00 g, 5.81 mmol), K_2CO_3 (3.20 g, 23.2 mmol) and KI (96 mg, 0.58 mmol) at room temperature. After the reaction mixture was refluxed for 35 h, the reaction was quenched with saturated NH_4Cl aq. (40 mL), and the resulting mixture was extracted with AcOEt (30 mL x 3). The combined extracts were washed with H_2O (100 mL x 2) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:hexane = 1:12 to 1:5 to 1:3) to afford *N*-siloxypropylamide **3b** (2.86 g, 77%) as a colorless oil.

IR (film) ν_{max} 1730, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (9H, s, -SiC(C*H*$_3$)$_3$), 1.68 (9H, s, -Boc), 1.88 (2H, tt, *J* = 7, 6 Hz, -CH_2C*H*$_2$$CH_2$-), 2.55 (3H, s, -Me), 3.70 (2H, t, *J* = 6 Hz, -C*H*$_2$-), 3.80 (2H, t, *J* = 7 Hz, -C*H*$_2$-), 3.80 (2H, s, -C*H*$_2$-CO-), 4.36 (2H, dt, *J* = 6, 1 Hz, -C*H*$_2$-CH=CH_2), 5.34 (1H, dd, *J* = 10, 1 Hz, -CH=C*H*$_A$H$_B$), 5.37 (1H, dd, *J* = 17, 1 Hz, -CH=CH_A*H*$_B$), 5.98 (1H, ddt, *J* = 17, 10, 6 Hz -C*H*=CH_2), 7.17 (1H, td, *J* = 7, 2 Hz, indole), 7.23 (1H, td, *J* = 7, 2 Hz, indole), 7.34-7.46 (6H, m, TBDPS), 7.45 (1H, d, *J* = 7, 2 Hz, indole), 7.63-7.69 (4H, m, TBDPS), 8.10 (1H, dd, *J* = 7, 2 Hz, indole); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 19.1, 26.7, 28.2, 28.5, 29.8, 43.4, 61.4, 75.2, 83.5, 112.0, 115.4, 118.0, 120.7, 122.5, 123.4, 127.7, 129.7, 129.9, 131.4, 133.7, 135.1, 135.6, 135.7, 150.8, 172.1; Anal. Calcd for $C_{38}H_{48}N_2O_5Si$: C, 71.20; H, 7.55; N, 4.37. Found: C, 71.20; H, 7.45; N, 4.25.

***N*-Siloxypropylhydroxamic acid 4b**: To a solution of *N*-siloxypropylamide **3b** (2.99 g, 4.67 mmol) in MeCN (37.4 mL) and H_2O (9.3 mL) were added $Pd(OAc)_2$ (104 mg, 0.467 mmol), PPh_3 (0.489 g, 1.87 mmol), HCO_2H (1.53 mL, 40.6 mmol) and Et_3N (5.62 mL, 40.6 mmol), and the resulting mixture was heated at 40 °C. After being stirred at 40 °C for 23 h, the reaction was quenched with H_2O (20 mL), and the resulting mixture was extracted with AcOEt (30 mL x 3). The combined extracts were washed with H_2O (60 mL x 2) and brine (60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:hexane = 1:5 to 1:3 to 1:2) to afford *N*-siloxypropylhydroxamic acid **4b** (2.33 g, 83%) as an orange amorphous solid.

IR (film) ν_{max} 3177, 1730, 1608 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 1.00 (9H, s, -SiC(CH_3)$_3$), 1.67 (9H, s, -Boc), 1.88 (2H, tt, *J* = 7, 6 Hz, -CH_2C*H*$_2$$CH_2$-), 2.50 (3H, s, -Me), 3.68 (2H, t, *J* = 6 Hz, N-C*H*$_2$-), 3.76 (2H, t, *J* = 7 Hz, O-C*H*$_2$-), 3.82 (2H, s, -C*H*$_2$-CO-), 7.10 (1H, td, *J* = 7, 2 Hz, indole), 7.18 (1H, td, *J* = 7, 2 Hz, indole), 7.32-7.41 (6H, m, TBDPS), 7.42 (1H, d, *J* = 7, 2 Hz, indole), 7.61-7.66 (4H, m, TBDPS), 8.06 (1H, dd, *J* = 7, 2 Hz, indole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 19.1, 26.8, 28.3, 28.7, 30.3, 46.8, 64.1, 83.4, 112.3, 115.3, 118.3, 122.5, 123.3, 127.8, 128.0, 130.2, 132.1, 135.0, 135.4, 135.6, 150.7, 170.5; Anal. Calcd for $C_{35}H_{44}N_2O_5Si$: C, 69.97; H, 7.38; N, 4.66. Found: C, 69.99; H, 7.28; N, 4.71.

Hydroxamic acid 5b: To a solution of *N*-siloxypropylhydroxamic acid **4b** (1.00 g, 1.66 mmol) in CH_2Cl_2

(45.4 mL) was added TFA (10.0 mL) at 0 °C. After being stirred at 0 °C for 5.3 h, the reaction mixture was diluted with toluene and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:hexane = 1:3) to afford hydroxamic acid **5b** (0.679 g, 82%) as an orange amorphous solid.

IR (film) ν_{max} 3195, 1615 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.01 (9H, s, -SiC(CH_3)$_3$), 1.87 (2H, tt, J = 7, 6 Hz, -CH_2CH_2CH_2-), 2.34 (3H, s, -Me), 3.68 (2H, t, J = 6 Hz, N-CH_2-), 3.74 (2H, t, J = 7 Hz, O-CH_2-), 3.81 (2H, s, -CH_2-CO-), 6.89 (1H, td, J = 8, 1 Hz, indole), 6.97 (1H, td, J = 8, 1 Hz, indole), 7.21 (1H, dd, J = 8, 1 Hz, indole), 7.33-7.43 (6H, m, TBDPS), 7.44 (1H, dd, J = 8, 1 Hz, indole), 7.63 (4H, d, J = 7 Hz, TBDPS); ^{13}C NMR (CD_3OD, 100 MHz) δ 11.6, 20.0, 27.4, 29.4, 30.9, 46.6, 62.7, 105.3, 111.2, 118.9, 119.5, 121.3, 128.8, 130.2, 130.8, 134.3, 134.9, 136.6, 137.0, 174.6; Anal. Calcd for $C_{30}H_{36}N_2O_3Si$: C, 71.96; H, 7.25; N, 5.59. Found: C, 71.95; H, 7.11; N, 5.48.

Sulfonate 6b: To a solution of hydroxamic acid **5b** (150 mg, 0.30 mmol) and Et_3N (83 μL, 0.60 mmol) in CH_2Cl_2 (1.5 mL) was added *p*-NsCl (66.0 mg, 0.30 mmol) at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was directly purified by silica gel column chromatography (AcOEt: hexane = 1:5 to 1:2) to afford sulfonate **6b** (192 mg, 94%) as a yellow oil.

IR (film) ν_{max} 3403, 1702, 1535, 1191 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (9H, s, -SiC(CH_3)$_3$), 1.86 (2H, brs, -CH_2CH_2CH_2-), 2.23 (3H, s, -Me), 3.65 (2H, s, -CH_2-CO-), 3.65 (2H, brs, O-CH_2-), 4.00 (2H, brs, N-CH_2-), 7.04 (1H, t, J = 7 Hz, indole), 7.12 (1H, t, J = 7 Hz, indole), 7.22 (1H, d, J = 7 Hz, indole), 7.25 (1H, d, J = 7 Hz, indole), 7.37-7.47 (6H, m, TBDPS), 7.63 (4H, d, J = 7 Hz, TBDPS), 7.94 (2H, d, J = 8 Hz, *p*-Ns), 7.97 (2H, d, J = 8 Hz, *p*-Ns); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7, 19.1, 26.8, 29.4, 29.6, 50.2, 60.6, 103.1, 110.5, 117.6, 119.7, 121.5, 123.7, 127.7, 127.8, 128.0, 129.8, 130.6, 133.0, 133.3, 134.9, 135.4, 139.2, 150.8, 173.8; HR-MS (ESI, positive): calcd. For $C_{36}H_{39}N_3O_7NaSSi$ (M+Na), 708.2170; found, 708.2139.

***N*-Siloxypropyl β-lactam 7b**: To a solution of sulfonate **6b** (63.8 mg, 0.093 mmol) in THF (3.2 mL) was added LiHMDS (1.0 M in THF, 0.10 mL) at –78 °C. The mixture was stirred for 10 min, then allowed to warm to room temperature. After being stirred at room temperature for 1 h, the reaction mixture was poured into cold saturated NH_4Cl aq. (10 mL), and the resulting mixture was extracted with AcOEt (5 mL x 3). The combined extracts were washed with H_2O (20 mL x 2) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:hexane = 3:4) to afford *N*-siloxypropyl β-lactam **7b** (11.6 mg, 26%) as a yellow oil.

IR (film) ν_{max} 3314, 1764 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.07 (9H, s, -SiC(CH_3)$_3$), 1.30 (2H, tt, J = 7,

6 Hz, -$CH_2CH_2CH_2$-), 1.85 (3H, s, -Me), 2.55 (1H, d, J = 14 Hz, CH_AH_B), 2.62 (1H, d, J = 14 Hz, CH_AH_B), 2.93 (2H, td, J = 7, 4 Hz, O-CH_2-), 3.32 (2H, td, J = 6, 4 Hz, N-CH_2-), 6.75 (1H, dd, J = 8, 1 Hz, indolenine), 6.86 (1H, t, J = 8 Hz, indolenine), 7.04 (1H, td, J = 8, 1 Hz, indolenine), 7.20-7.25 (6H, m, TBDPS), 7.56 (1H, d, J = 8 Hz, indolenine), 7.63-7.66 (4H, m, TBDPS); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.5, 19.3, 27.0, 31.0, 38.8, 45.7, 61.1, 68.8, 121.1, 122.3, 126.0, 128.5, 129.96, 129.97, 130.1, 134.0, 135.4, 135.89, 135.91, 155.1, 165.0, 180.6; Anal. Calcd for $C_{30}H_{34}N_2O_2Si$: C, 74.65; H, 7.10; N, 5.80. Found: C, 74.63; H, 7.07; N, 5.75.

Alcohol 9 and *N,O*-Acetal 9': To a solution of *N*-siloxypropyl β-lactam **7b** (26.9 mg, 0.056 mmol) in THF (1.1 mL) was added a mixture of TBAF (1.0 M in THF, 0.056 mL) and AcOH (3.1 μL, 0.056 mmol). After being stirred at room temperature for 6 h, the reaction was quenched with H_2O (2 mL) and the resulting mixture was neutralized by saturated $NaHCO_3$ aq. and extracted with AcOEt (3 mL x 7). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:MeOH = 20:1) to afford alcohol **9** and *N*,*O*-acetal **9'** (9.9 mg, 72%, **9**:**9'** = 75:25) as a yellow oil.

Alcohol 9: IR (film) ν_{max} 3339, 1752 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.47 (2H, tt, J = 7, 6 Hz, -$CH_2CH_2CH_2$-), 2.38 (3H, s, -Me), 3.04 (1H, dt, J = 14, 7 Hz, NCH_AH_B), 3.12 (1H, dt, J = 14, 7 Hz, NCH_AH_B), 3.30 (1H, d, J = 15 Hz, -CH_CH_DCO), 3.42 (1H, d, J = 15 Hz, -CH_CH_DCO), 3.44 (2H, td, J = 6, 1.5 Hz, -CH_2OH), 7.31 (1H, td, J = 7, 1.5 Hz, indolenine), 7.44 (1H, td, J = 7, 1.5 Hz, indolenine), 7.47 (1H, dd, J = 7, 1.5 Hz, indolenine), 7.53 (1H, dd, J = 7, 1.5 Hz, indolenine); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.9, 31.8, 40.2, 46.3, 60.1, 70.3, 121.2, 124.0, 127.8, 131.5, 135.5, 154.5, 168.5, 183.6; HR-MS (ESI, positive): calcd. For $C_{14}H_{16}N_2O_2Na$ (M+Na), 267.1104; found, 267.1120.

***N,O*-Acetal 9'**: ^{1}H NMR (CD_3OD, 400 MHz) δ 1.50 (3H, s, Me), 1.51 (1H, ddq, J = 13, 3, 2.5 Hz, -$CH_2CH_AH_BCH_2$-), 1.81 (1H, dtdd, J = 14, 13, 5, 3 Hz, -$CH_2CH_AH_BCH_2$-), 2.46 (1H, td, J = 14, 3 Hz, -NCH_CH_D-), 3.04 (1H, d, J = 15 Hz, -CH_EH_FCO-), 3.42 (1H, d, J = 15 Hz, -CH_EH_FCO-), 3.67 (1H, dq, J = 13, 2.5 Hz, -OCH_GH_H-), 3.75 (1H, ddt, J =14, 5, 2.5 Hz, -NCH_CH_D-), 3.96 (1H, td, J = 13, 2.5 Hz, -OCH_GH_H-), 6.64 (1H, dd, J = 8, 1 Hz, aromatic), 6.76 (1H, td, J = 8, 1 Hz, aromatic), 7.11 (1H, dd, J = 8, 1 Hz, aromatic), 7.14 (1H, td, J = 8, 1 Hz, aromatic).

β-Lactam *syn*-10 and *anti*-10: To a solution of *N*-(4-silyl-2-butenyl) β-lactam **8** (16.6 mg, 0.053 mmol) in THF (5.3 mL) was added TBAF (1.0 M in THF, 0.053 mL) at 0 °C. After being stirred at 0 °C for 10 min, the reaction was quenched with H_2O (10 mL) and the resulting mixture was extracted with AcOEt (10 mL x 3). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (AcOEt:hexane = 1:3) to

afford *syn*-**10** (3.1 mg, 24%) as a colorless oil and *anti*-**10** (2.4 mg, 19%) as a colorless oil. Stereochemistries of *syn*-**10** and *anti*-**10** were determined by NOESY correlations.

***syn*-10**: IR (film) ν_{max} 3340, 1757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (3H, s, -Me), 2.98 (1H, td J = 9, 8 Hz -C*H*-CH=CH_2), 3.07 (1H, dd, J = 11, 8 Hz, -NC$H_A$$H_B$-), 3.16 (1H, d, J = 17 Hz, -C$H_C$$H_D$-CO-), 3.18 (1H, d, J = 17 Hz, -C$H_C$$H_D$-CO-), 3.37 (1H, dd, J = 11, 9 Hz, -NC$H_A$$H_B$-), 4.20 (1H, brs, -NH), 5.13 (1H, dd, J = 17, 2 Hz, -CH=C$H_E$$H_F$), 5.19 (1H, dd, J = 10, 2 Hz, -CH=C$H_E$$H_F$), 5.77 (1H, ddd, J = 17, 10, 9 Hz -C*H*=CH_2), 6.69 (1H, dd, J = 7, 1 Hz, aromatic), 6.87 (1H, td, J = 7, 1 Hz, aromatic), 7.14 (1H, td, J = 7, 1 Hz, aromatic), 7.35 (1H, dd, J = 7, 1 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.7, 44.4, 47.9, 58.4, 70.1, 72.0, 111.1, 118.8, 120.0, 124.8, 128.2, 130.1, 134.4, 148.7, 175.6; HR-MS (ESI, positive): calcd. For $C_{15}H_{16}N_2ONa$ (M+Na), 263.1154; found, 263.1164.

***anti*-10**: IR (film) ν_{max} 3354, 1759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (3H, s, -Me), 2.65 (1H, ddd J = 11, 8, 6 Hz, -C*H*-CH=CH_2), 2.73 (1H, t, J = 11 Hz, -NC$H_A$$H_B$-), 3.26 (1H, d, J = 17 Hz, -C$H_C$$H_D$-CO-), 3.60 (1H, d, J = 17 Hz, -C$H_C$$H_D$-CO-), 3.79 (1H, dd, J = 11, 6 Hz, -NC$H_A$$H_B$-), 5.22 (1H, dd, J = 18, 1 Hz, -CH=C$H_E$$H_F$), 5.25 (1H, dd, J = 10, 1 Hz, -CH=C$H_E$$H_F$), 5.77 (1H, ddd, J = 18, 10, 8 Hz -C*H*=CH_2), 6.63 (1H, dd, J = 8, 1 Hz, aromatic), 6.81 (1H, t, J = 8 Hz, aromatic), 7.17 (1H, td, J = 8, 1 Hz, aromatic), 7.31 (1H, d, J = 8 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 43.2, 50.4, 58.5, 71.8, 73.3, 109.6, 118.9, 119.4, 124.4, 126.3, 130.4, 134.5, 163.3, 177.0; HR-MS (ESI, positive): calcd. For $C_{15}H_{17}N_2O$ (M+H), 241.1335; found, 241.1347.

Indolenine 11: To a solution of **9** and **9'** (8.1 mg, 0.033 mmol) in CH_2Cl_2 (0.66 mL) was added Dess-Martin periodinane (16.9 mg, 0.040 mmol). After being stirred at room temperature for 1 h, the reaction was diluted with Et_2O (1.5 mL) and the resulting mixture was quenched with saturated $NaHCO_3$ aq. (0.5 mL) and saturated $Na_2S_2O_3$ aq. (0.5 mL). After being stirred for 30 min, H_2O (3 mL) was added and the mixture was neutralized with saturated NH_4Cl aq. The resulting mixture was extracted with AcOEt (3 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (AcOEt:MeOH = 20:3) to afford indolenine **11** (2.5 mg, 31%, dr = >95:<5 determined by ^1H NMR analysis) as a yellow oil.

IR (film) ν_{max} 3348, 1761 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.84 (1H, ddt, J = 14, 3, 1.5 Hz, -$NCH_2C$$H_A$$H_B$CH(OH)), 2.07 (1H, ddt, J = 14, 13, 3 Hz, -$NCH_2CH_A$$H_B$CH(OH)), 2.60 (1H, ddt, J = 15, 13, 1.5 Hz, -NC$H_C$$H_D$), 2.96 (1H, dd, J = 13, 1.5 Hz, -C$H_E$$H_F$CH(OH)), 3.14 (1H, ddd, J = 13, 6, 1.5 Hz, -$CH_E$$H_F$CH(OH)), 3.33 (1H, d, J = 15 Hz, -C$H_G$$H_H$CO-), 3.50 (1H, d, J = 15 Hz, -$CH_G$$H_H$CO-), 3.55 (1H, dt, J = 15, 3 Hz, -NC$H_C$$H_D$), 4.29 (1H, ddt, J = 6, 3, 1.5 Hz, C*H*-OH), 7.29 (1H, td, J = 7, 1 Hz, indolenine), 7.42 (1H, td, J = 7, 1 Hz, indolenine), 7.47 (1H, dd, J = 7, 1 Hz, indolenine), 7.52 (1H, dd, J

= 7, 1 Hz, indolenine); ^{13}C NMR (CD_3OD, 100 MHz) δ36.4, 37.6, 37.7, 47.6, 65.3, 70.6, 121.3, 123.8, 127.7, 131.3, 137.0, 154.9, 169.7, 183.5; HR-MS (ESI, positive): calcd. For $C_{14}H_{14}N_2O_2Na$ (M+Na), 265.0948; found, 265.0948.

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