Electronic Supplementary Information

Synthesis of Tryptophan-containing 2,5-Diketopiperazines via Sequential C–H Activation: Total Syntheses of Tryprostatin A, Maremycins A and B

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Table of Contents

1. General information...........................................................................................................S1

2. Experiment Details and Characterization Data .................................................................S2

3. Comparison of NMR Data of Natural and Synthetic Compounds.................................S29

4. Copies of $^1$H and $^{13}$C NMR Spectra .........................................................................S35

5. X-ray Crystallographic Data.........................................................................................S59

6. References.......................................................................................................................S60
1. General Information

NaOCN and t-BuOH was obtained from Aladdin®, Pd(OAc)₂ was obtained from Strem®, AgBF₄ was obtained from J&K Chemical®, 1,4-Dioxane and 1,2-Dichloroethane was from Energy® without purification. The other materials and solvents were purchased from Adamas® and other commercial suppliers and used without additional purification. Nuclear magnetic resonance (NMR) spectra were recorded with BrukerAVANCE 400 MHz. ¹H and ¹³C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak as following: CDCl₃ = 7.26 (¹H NMR), (CD₃)₂CO = 2.05 (¹H NMR), (CD₃)₂SO = 2.50 (¹H NMR), CDCl₃ = 77.16 (¹³C NMR), (CD₃)₂CO = 29.84, 206.26 (¹³C NMR), (CD₃)₂SO = 39.52 (¹³C NMR). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) for new compounds were recorded on EI-TOF or ESI-TOF. Optical rotations were measured using a 1 mL cell with a 1 dm path length on Perkin Elmer 341 at 589 nm at 20 °C. Infrared spectra were recorded on a Bruker Vector 22 FT-Infrared spectrometer.
2. Experiment Details and Characterization Data

Compound 6 is a known compound prepared from alanine according to the literature procedure.\[1\]

To a stirred solution of 6-methoxyindole S1 (2.94 g, 20 mmol) in DMF (50 mL) was added KOH (2.80 g, 50 mmol). The suspension was then cooled to 0\(^\circ\)C. After 5 min, I\(_2\) (5.10 g, 20 mmol) was added by 5 portions. The mixture was stirred at 0\(^\circ\)C for 30 min under nitrogen, and poured into ice-cold saturated Na\(_2\)S\(_2\)O\(_3\) aqueous. A mass of light brown solid was separated out immediately. Filtered and resolve the residue by EtOAc, dried over MgSO\(_4\), filtered and concentrated in vacuo to afford the crude 3-iodo-6-methoxyindole S2, which was unstable under air. Dissolved the crude iodo-indole with THF (60 mL) instantly, NaOH (2.0 g, 50 mmol) was added to the stirred solution. The mixture was cooled to 0\(^\circ\)C for 10 min under N\(_2\), p-NsCl (5.5 g, 26 mmol) added by portions and the suspension was stirred at 0\(^\circ\)C for 1 hour. The reaction mixture was quenched by glacial acetic acid (5.0 mL), and the aqueous phase was extracted with EtOAc for twice. The combined organic extract was washed three times with saturated NaHCO\(_3\) aq., brine, and dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. MeOH (10 mL) was added to the brown residue, the suspension stirred under room temperature by 10 min, which was filtered to afford the 7f (7.6 g, 84% over 2 steps) as a yellow solid.

\(\text{mp} 156-157 ^\circ\text{C (decomp.)}\).  
\(\text{IR (neat, cm}^{-1}\) 2998, 2360, 1531, 1381, 1269, 1106, 1025, 755.  
\(\text{\textsuperscript{1}}\text{H NMR (400 MHz, CDCl} _3\) \(\delta 8.35 – 8.25\) (m, 2H), \(8.09 – 8.01\) (m, 2H), \(7.54\) (s, 1H), \(7.49\) (d, \(J = 2.3\) Hz, 1H), \(7.25\) (d, \(J = 8.3\) Hz, 1H), \(6.96\) (dd, \(J = 8.7, 2.3\) Hz, 1H), \(3.90\) (s, 3H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.5, 150.9, 143.1, 135.3, 128.2, 128.1, 126.6, 124.8, 123.2, 113.6, 97.9, 69.1, 56.1.

HRMS (EI-TOF) calcd. for C$_{15}$H$_{11}$IN$_2$O$_3$S (M$^+$): 457.9436, found: 457.9433.
According to the procedure reported by our group,[1] to a 50 mL-Schlenk reactor was added 6 (2.76 g, 8.0 mmol), 7f (4.76 g, 10.4 mmol, 1.3 equiv), AgBF₄ (2.34 g, 12 mmol, 1.5 equiv) and Pd(OAc)₂ (179.6 mg, 0.8 mmol), followed by t-BuOH (60 mL) and DCE (30 mL). Nitrogen was charged and the mixture was heated up to 75°C for 24 hours. The suspension was cooled to room temperature and quenched by Et₃N (10 mL). The reaction mixture was filtered through a pad of Celite, concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc/DCM = 4/1/1) to afford 10 (4.32 g, 80%) as a yellow oil.

**IR (neat, cm⁻¹):** 3115, 3064, 3019, 2942, 2780, 2701, 2369, 2334, 1776, 1715, 1531, 1378, 1270, 1110, 987, 759.

**¹H NMR (400 MHz, CDCl₃) δ 10.27 (s, 1H), 8.76 – 8.63 (m, 1H), 8.52 (dd, J = 4.2, 1.5 Hz, 1H), 8.12 (dd, J = 8.3, 1.5 Hz, 1H), 7.92 (d, J = 8.9 Hz, 2H), 7.88 – 7.81 (m, 2H), 7.82 – 7.76 (m, 2H), 7.78 – 7.70 (m, 2H), 7.58 – 7.49 (m, 3H), 7.48 (d, J = 2.2 Hz, 1H), 7.43 (s, 1H), 7.38 (dd, J = 8.3, 4.2 Hz, 1H), 6.91 (dd, J = 8.7, 2.2 Hz, 1H), 5.47 (dd, J = 9.3, 6.7 Hz, 1H), 3.91 (dd, J = 15.4, 6.6 Hz, 1H), 3.86 (s, 3H), 3.77 (dd, J = 15.3, 9.4 Hz, 1H).

**¹³C NMR (101 MHz, CDCl₃) δ 167.8, 165.8, 158.8, 150.4, 148.5, 143.2, 138.5, 136.5, 136.5, 134.6, 133.7, 131.6, 127.9, 127.8, 127.4, 124.4, 124.4, 123.8, 123.1, 122.4, 121.8, 120.5, 120.0, 116.9, 112.9, 98.6, 55.9, 54.3, 24.9.

[a]²⁰D = -9.0 (c=1.0, in CHCl₃)

**HRMS (ESI) m/z:** 698.1306 (M+Na⁺); calcd. for C₃₅H₂₅N₅NaO₈S: 698.1322.
According to the procedure reported by our group,[1] to a 50 mL-Schlenk reactor was added 10 (761 mg, 1.13 mmol), followed by MeOH (15 mL) and BF$_3$·Et$_2$O (2.84 mL, 22.5 mmol). The mixture was heated up to 100°C for 24 hours. After cooled to room temperature saturated NaHCO$_3$ aqueous was added to quench the reaction. The aqueous phase was washed by DCM three times. The combined organic layer was dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc/DCM = 5/1/1) to afford 11 (565 mg, 89%) as a yellow oil, and 8-Aminoquinoline (130 mg, 80%) was recovered.

IR (neat, cm$^{-1}$) 3011, 2944, 2860, 2362, 2336, 2200, 2154, 1715, 1614, 1533, 1382, 1271, 1108, 770, 732.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.11 – 8.05 (m, 2H), 7.92 – 7.84 (m, 2H), 7.84 – 7.74 (m, 4H), 7.48 (d, $J = 2.3$ Hz, 1H), 7.42 (d, $J = 8.7$ Hz, 1H), 7.28 (s, 1H), 6.90 (dd, $J = 8.7$, 2.3 Hz, 1H), 5.23 (dd, $J = 11.0$, 5.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.77 – 3.57 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.0, 167.4, 158.7, 150.4, 143.2, 136.3, 134.6, 131.5, 127.8, 124.4, 124.4, 123.7, 122.6, 120.2, 119.9, 112.9, 98.5, 55.9, 53.2, 51.6, 24.7.

$[\alpha]_{D}^{20} = -119.6$ (c=0.86, in CHCl$_3$).

HRMS (ESI) m/z: 586.0894 (M+Na$^+$); calcd. for C$_{27}$H$_{21}$N$_3$NaO$_9$S: 586.0896.
According to the procedure reported by Dumas,\footnote{[3]} to a stirred solution of 11 (563.5 mg, 1.0 mmol) in DMF (10 mL) was added K$_2$CO$_3$ (839.3 mg, 6.0 mmol) and mercaptoacetic acid (276.4 mg, 3.0 mmol). The suspension was stirred under nitrogen for another 1 h at ambient temperature. Acetic acid glacial (0.5 mL) was added to quench the reaction. The suspension was diluted by EtOAc and washed by NaHCO$_3$ aqueous for three times. The organic layer was dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 2/1) to afford 12 (363.3 mg, 96%) as a yellow oil.

**IR** (neat, cm$^{-1}$) 3058, 3011, 2925, 2861, 2699, 2448, 2361, 1711, 1628, 1555, 1457, 1388, 1263, 1160, 1098, 806, 750.

**$^1$H NMR** (400 MHz, CDCl$_3$) δ 7.85 (s, 1H), 7.77–7.72 (m, 2H), 7.69 – 7.60 (m, 2H), 7.44 (d, $J = 8.5$ Hz, 1H), 6.86 (d, $J = 1.5$ Hz, 1H), 6.78 – 6.65 (m, 2H), 5.25 (dd, $J = 9.7$, 6.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.74 – 3.63 (m, 2H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 169.8, 167.7, 156.6, 136.9, 134.1, 131.8, 123.5, 121.7, 121.4, 119.2, 111.2, 109.6, 94.7, 55.7, 52.9, 52.8, 24.9.

$[\alpha]^{20}_D = -38.6$ (c=1.0, in CHCl$_3$).

**HRMS (EI-TOF)** calcd. for C$_{21}$H$_{18}$N$_2$O$_5$ (M$^+$): 378.1219, found: 378.1216.
According to the procedure reported by Danishefsky,[4] to a -78°C solution of 12 (319.4 mg, 0.84 mmol) and Et₃N (140 μL, 1.0 mmol) in CH₂Cl₂ (5.0 mL) was added tert-butylhypochlorite (114 μL, 1.0 mmol) slowly via syringe. The solution was then stirred for another 30 min. Organic tin reagent 14 (1.20 g, 3.36 mmol) was added followed by rapid addition of BCl₃ (1M in hexane, 1.68 mL). After 2 hours, the solution was quenched by NaHCO₃ aqueous, and extracted with EtOAc for three times. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/ethyl acetate = 3:1) to give 13 (172.5 mg, 46%) as a yellow oil.

**IR** (neat, cm⁻¹) 3011, 2405, 2362, 1715, 1445, 1352, 1268, 1100, 756.

**¹H NMR** (400 MHz, CDCl₃) δ 7.76 – 7.70 (m, 2H), 7.67-7.61 (m, 2H), 7.62 (s, 1H), 7.33 (d, J = 8.6 Hz, 1H), 6.68 (d, J = 2.2 Hz, 1H), 6.62 (dd, J = 8.6, 2.3 Hz, 1H), 5.18 (dd, J = 10.2, 5.5 Hz, 1H), 5.14 – 5.03 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.67 – 3.56 (m, 2H), 3.41 (dd, J = 16.4, 7.4 Hz, 1H), 3.28 (dd, J = 16.4, 7.0 Hz, 1H), 1.65 (s, 6H).

**¹³C NMR** (101 MHz, CDCl₃) δ 169.8, 167.5, 155.8, 135.9, 134.6, 134.5, 134.0, 131.9, 123.4, 123.0, 120.5, 118.5, 108.8, 105.8, 94.6, 55.7, 52.8, 52.6, 25.7, 25.0, 24.1, 17.8.

[α]²⁰D = -4.0 (c=1.0, in CHCl₃).

**HRMS (ESI)** m/z: 469.1726 (M+Na⁺); calcd. for C₂₆H₂₆N₂NaO₅: 469.1739.
To a solution of 12 (378.4 mg, 1.0 mmol) in CH₂Cl₂ (2.5 mL) and MeOH (2.5 mL) was added ethylenediamine (670 μL, 10.0 mmol) in one portion. The mixture was stirred at 25°C for 2 hours. Concentrated in vacuo, and the residue was purified with flash column chromatography on silica gel (DCM/MeOH = 10:1) to give amino compound S3 (243.3 mg, 98%) as a yellow oil.

**¹H NMR** (400 MHz, CDCl₃) δ 8.11 (s, 1H), 7.47 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.79 (dd, J = 8.6, 2.2 Hz, 1H), 3.83 (s, 3H), 3.83 – 3.78 (m, 1H), 3.71 (s, 3H), 3.24 (dd, J = 14.4, 4.8 Hz, 1H), 3.02 (dd, J = 14.4, 7.6 Hz, 1H), 1.65 (s, 2H).

**¹³C NMR** (101 MHz, CDCl₃) δ 175.9, 156.7, 137.1, 122.0, 121.8, 119.4, 111.2, 109.7, 94.8, 55.7, 55.0, 52.1, 30.9.

[α]₂⁰₀ = +8.2 (c=0.96, in CHCl₃).

**HRMS (ESI) m/z**: 271.1041 (M+Na⁺); calcd. for C₁₃H₁₆N₂O₃: 271.1059.
To a solution of amino substrate S3 (243.3 mg, 0.98 mmol) in THF (10.0 mL) was added Boc₂O (320.8 mg, 1.47 mmol) in one portion. The mixture was stirred at 25 °C for 4 hours. Concentrated in vacuo, and the residue was purified with flash column chromatography on silica gel (hexane/ethyl acetate = 2:1) to give 15 (331.0 mg, 97%) as a yellow solid.

\[ \text{mp} \ 105-106 \, ^\circ \text{C}. \]

\[ \text{IR} \ (\text{neat, cm}^{-1}) \ 3016, 2929, 2853, 2771, 2697, 2370, 2338, 1703, 1630, 1506, 1454, 1365, 1163, 1026. \]

\[ \text{H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 8.03 \ (s, 1H), 7.40 \ (d, J = 8.6 \text{ Hz}, 1H), 6.88 \ (d, J = 2.3 \text{ Hz}, 1H), 6.83 \ (d, J = 2.2 \text{ Hz}, 1H), 6.78 \ (dd, J = 8.6, 2.3 \text{ Hz}, 1H), 5.09 \ (d, J = 8.2 \text{ Hz}, 1H), 4.62 \ (dt, J = 8.4, 5.5 \text{ Hz}, 1H), 3.83 \ (s, 3H), 3.67 \ (s, 3H), 3.24 \ (d, J = 5.5 \text{ Hz}, 2H), 1.43 \ (s, 9H). \]

\[ \text{C NMR} \ (101 \text{ MHz, CDCl}_3) \ \delta \ 172.9, 156.7, 155.4, 137.1, 122.1, 121.6, 119.4, 110.1, 109.8, 94.7, 79.9, 55.7, 54.2, 52.3, 28.4, 28.1. \]

\[ [\alpha]^{20}_D = +10.3 (c=0.73, \text{ in CHCl}_3). \]

\[ \text{HRMS (ESI) m/z: 371.1577 (M+Na^+); calcd. for C}_{18}\text{H}_{24}\text{N}_2\text{NaO}_5: 371.1583.} \]
### Table S1. Optimization reaction conditions of Pd-catalyzed C-H prenylation

| Entry | [Pd] (10 mol%) | PPh₃ (x mol%) | Additive (3.0 equiv) | Solvent, Temp, 24 hours | Temp /°C | yield /% |
|-------|----------------|---------------|----------------------|--------------------------|-----------|---------|
| 1     | PdCl₂          | 20            | Cs₂CO₃               | Dioxane:DMF=1:1          | 90        | 0       |
| 2     | PdCl₂          | 20            | Cs₂CO₃               | Dioxane:DMF=1:1          | 70        | 0       |
| 3     | PdCl₂          | 0             | K₂CO₃                | DMF [0.2 M], H₂O [0.5 M] | 90        | 0       |
| 4     | PdCl₂          | 0             | K₂CO₃                | Dioxane [0.2 M], H₂O [0.5 M] | 70        | 0       |
| 5     | PdCl₂          | 0             | K₂CO₃                | DMF [0.2 M], H₂O [0.5 M] | 50        | trace   |
| 6     | Pd(OAc)₂       | 20            | Cs₂CO₃               | DMF [0.1 M], H₂O [0.5 M] | 50        | 0       |
| 7     | Pd(OAc)₂       | 20            | Cs₂CO₃               | Dioxane [0.1 M], H₂O [0.5 M] | 50        | 0       |
| 8     | Pd(OAc)₂       | 20            | Cs₂CO₃               | DMSO [0.1 M], H₂O [0.5 M] | 50        | 0       |
| 9     | Pd(OAc)₂       | 20            | Cs₂CO₃               | DMAc [0.1 M], H₂O [0.5 M] | 50        | 0       |
| 10    | Pd(OAc)₂       | 20            | Cs₂CO₃               | CH₃CN [0.1 M], H₂O [0.5 M] | 50        | 68*     |
| 11    | Pd(OAc)₂       | 20            | Cs₂CO₃               | CH₃CN [0.1 M], H₂O [0.5 M] | 40        | trace   |
| 12    | Pd(OAc)₂       | 20            | Cs₂CO₃               | CH₃CN [0.1 M], H₂O [0.5 M] | 60        | 22      |

*Isolated yield and 32% of 15 was recovered

General procedure for the optimization of Pd-catalyzed C-H prenylation:

To a 10 mL-Schlenk reactor was added 15 (34.5 mg, 0.1 mmol), additive (0.3 mmol), PPh₃ (x mol%) and [Pd] (10 mol%), followed by solvents. Prenyl bromide (35.0 μl, 0.3 mmol) and norbornene (47.0 mg, 0.5 mmol) were added to the suspension finally. Nitrogen was charged and the mixture was heated up to indicated Temp for 24 hours. The suspension was cooled to room temperature and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 16.
To a 10 mL-Schlenk reactor was added 15 (69 mg, 0.2 mmol), Cs$_2$CO$_3$ (200 mg, 0.6 mmol), PPh$_3$ (10.4 mg, 0.04 mmol) and Pd(OAc)$_2$ (4.6 mg, 0.04 mmol), followed by CH$_3$CN (2.0 mL), H$_2$O (0.4 mL). Prenyl bromide (70.0 μl, 0.6 mmol) and norbornene (94.0 mg, 1 mmol) were added to the suspension finally. Nitrogen was charged and the mixture was heated up to 50°C for 24 hours. The suspension was cooled to room temperature and extracted with EtOAc. The organic layer was dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 16 (56 mg, 68%) as a colorless oil and 15 was recovered by 32%.

**IR** (neat, cm$^{-1}$) 3006, 2378, 2331, 1717, 1463, 1368, 1267, 1164, 754.

**$^1$H NMR** (400 MHz, CDCl$_3$) δ 7.74 (s, 1H), 7.30 (d, $J = 8.7$ Hz, 1H), 6.78 (d, $J = 2.0$ Hz, 1H), 6.73 (dd, $J = 8.7$, 2.0 Hz, 1H), 5.32-5.25 (m, 1H), 5.07 (d, $J = 7.9$ Hz, 1H), 4.58 (dd, $J = 13.3$, 5.5 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.42-3.36 (m, 2H), 3.22-3.17 (m, 2H), 1.79 (s, 3H), 1.76 (s, 3H), 1.41 (s, 9H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 172.8, 155.9, 155.1, 135.8, 134.7, 123.2, 120.4, 118.7, 108.9, 104.9, 94.4, 79.7, 55.7, 54.1, 52.2, 29.3, 28.3, 27.2, 25.8, 25.0, 17.8.

$[\alpha]^{20}_D = +42.0$ (c=0.39, in CHCl$_3$).

**HRMS (ESI)** m/z: 439.2188 (M+Na$^+$); calcd. for C$_{23}$H$_{32}$N$_2$NaO$_5$: 439.2209.
**Path A**: To a solution of 13 (80.0 mg, 0.18 mmol) in CH$_2$Cl$_2$ (2.5 mL) and MeOH (2.5 mL) was added ethylenediamine (120.2 µL, 1.8 mmol) in one portion. The mixture was stirred at 25°C for 2 hours. Concentrated in vacuo, brine was added and the residue was extracted with DCM for three times. The organic layer dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product dissolved in dry DCM (4.0 mL) and to the stirred solution was added N-Boc-L-Proline (42.6 mg, 0.2 mmol), DIPEA (44.6 µL, 0.27 mmol), HOBt (24.3 mg, 0.18 mmol), followed by EDCI (44.9 mg, 0.24 mmol). The reaction mixture was stirred overnight at ambient temperature. Concentrated in vacuo, the residue was purified with flash column chromatography on silica gel (hexane/ethyl acetate = 1:1) to give 17 (87.8 mg, 95% over 2 steps) as a colorless oil.

**Path B**: To a solution of 16 (41.6 mg, 0.1 mmol) in CH$_2$Cl$_2$ (3.0 mL) was added TFA (1.0 mL). The mixture was stirred under N$_2$ atmosphere for 2 hours. Na$_2$CO$_3$ aqueous was added to adjust the pH between 7.0~8.0. The solution was extracted with DCM for three times, dried over MgSO$_4$ and concentrated in vacuo. The crude product dissolved in dry DCM (4.0 mL) and to the stirred solution was added N-Boc-L-Proline (23.7 mg, 0.11 mmol), DIPEA (25.0 µL, 0.15 mmol), HOBt (13.6 mg, 0.1 mmol), followed by EDCI (25.1 mg, 0.13 mmol). The reaction mixture was stirred overnight at ambient temperature. Concentrated in vacuo, the residue was purified with flash column chromatography on silica gel (hexane/ethyl acetate = 1:1) to give 17 (50.3 mg, 98% over 2 steps) as a colorless oil.

**IR** (neat, cm$^{-1}$) 3015, 2380, 2336, 1742, 1676, 1512, 1458, 1389, 1266, 1164, 1032, 914, 752.

**$^1$H NMR** (400 MHz, CD$_3$COCD$_3$) δ 9.69 (s, 1H), 7.36 (d, $J$ = 8.6 Hz, 1H), 7.12 (s, 1H), 6.83 (d, $J$ = 2.2 Hz, 1H), 6.67 (dd, $J$ = 8.6, 2.2 Hz, 1H), 5.32 (t, $J$ = 7.2 Hz, 1H), 4.74 (s, 1H), 4.16 (s, 1H), 3.76 (s, 3H), 3.59 (s, 3H), 3.46 (d, $J$ = 7.1 Hz, 2H), 3.30 (dd, $J$ = 7.6, 6.0 Hz, 2H), 3.25-3.08 (m, 2H), 2.97-2.88 (m, 2H), 2.09 – 1.90 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.36 (s, 9H).
$^{13}$C NMR (101 MHz, Acetone) δ 173.9, 157.4, 138.2, 136.4, 1343, 124.8, 123.0, 119.7, 110.0, 106.4, 96.0, 80.6, 62.0, 56.4, 54.7, 52.9, 48.2, 32.4, 30.6, 29.2, 28.6, 26.6, 26.5, 24.8, 18.7; $[^\alpha]^{20}_D = -30.8$ (c=0.66, in CHCl$_3$).

HRMS (ESI) m/z: 536.2731 (M+Na$^+$); calcd. for C$_{28}$H$_{39}$N$_3$NaO$_6$: 536.2737.
To a solution of 17 (77.0 mg, 0.15 mmol) in CH$_2$Cl$_2$ (3.0 mL) was added TFA (1.0 mL). The mixture was stirred under N$_2$ atmosphere for 2 hours. Na$_2$CO$_3$ aqueous was added to adjust the pH between 7.0~8.0. The solution was extracted with DCM for three times, dried over MgSO$_4$ and concentrated in vacuo to afford the crude product. To a 50 mL-Schlenk reactor was added the crude dipeptide, followed by toluene (2.0 mL). Nitrogen was charged and the mixture was heated up to 120 $^\circ$C overnight. The suspension was cooled to room temperature and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/acetone = 2:3) to give 1 (39.7 mg, 69% over 2 steps) as a colorless oil.

**IR** (neat, cm$^{-1}$) 3003, 2931, 2331, 1659, 1458, 1265, 1204, 1158, 1032, 913, 811, 755.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.97 (s, 1H), 7.34 (d, $J = 8.6$ Hz, 1H), 6.83 (d, $J = 2.2$ Hz, 1H), 6.76 (dd, $J = 8.6, 2.3$ Hz, 1H), 5.66 (s, 1H), 5.32-5.25 (m, 1H), 4.34 (dd, $J = 11.2, 2.5$ Hz, 1H), 4.06 (t, $J = 7.4$ Hz, 1H), 3.82 (s, 3H), 3.72 – 3.54 (m, 3H), 3.46 (dd, $J = 16.3, 7.6$ Hz, 1H), 3.38 (dd, $J = 15.9, 6.7$ Hz, 1H), 2.91 (dd, $J = 15.0, 11.2$ Hz, 1H), 2.41 – 2.28 (m, 1H), 2.09 – 1.97 (m, 2H), 1.95 – 1.85 (m, 1H), 1.76 (s, 3H), 1.73 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.4, 165.9, 156.4, 136.4, 135.2, 135.2, 122.4, 120.1, 118.4, 109.4, 104.5, 95.0, 59.3, 55.8, 54.7, 45.5, 28.4, 25.8, 25.8, 25.2, 22.7, 18.0.

[α]$^20_D$ = -67.5 (c=0.825, CHCl$_3$). Lit: 8 [α]$^{27}_D$ = -69.7 (c 0.70, CHCl$_3$).

**HRMS (ESI)** m/z: 404.1940 (M+Na$^+$); calcd. for C$_{22}$H$_{27}$N$_3$NaO$_3$: 404.1950.
To a stirred solution of indole (2.34 g, 20 mmol) in DMF (50 mL) was added KOH (2.80 g, 50 mmol). The suspension was then cooled to 0°C. After 5 min, I₂ (5.10 g, 20 mmol) was added by 5 portions. The mixture was stirred at 0°C for 30 min under nitrogen, and poured into ice-cold saturated Na₂S₂O₃ aqueous. A mass of light brown solid was separated out immediately. Filtered and resolve the residue by EtOAc, dried over MgSO₄, filtered and concentrated in vacuo to afford the crude 3-Iodo-indole, which was unstable under air. Dissolved the crude iodo-indole with THF (60 mL) instantly, NaOH (2.0 g, 50 mmol) was added to the stirred solution. The mixture was cooled to 0°C for 10 min under N₂, p-NsCl (5.5 g, 26 mmol) added by portions and the suspension was stirred at 0°C for 1 hour. The reaction mixture was quenched by glacial acetic acid (5.0 mL), and the aqueous phase was extracted with EtOAc twice. The combined organic extract was washed three times with saturated NaHCO₃aq., brine, and dried over Na₂SO₄, filtered and concentrated in vacuo. MeOH (10 mL) was added to the brown residue, the suspension stirred under room temperature by 10 min, which was filtered to afford the 18 (7.54 g, 88% over 2 steps) as a yellow solid.

**mp** 187-190 °C (decomp.).

**IR** (neat, cm⁻¹) 2332, 1542, 1444, 1380, 1179, 1126, 748.

**¹H NMR** (400 MHz, CDCl₃) δ 8.34 – 8.25 (m, 2H), 8.12 – 8.03 (m, 3H), 7.96 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.45–7.33 (m, 3H).

**¹³C NMR** (101 MHz, CDCl₃) δ 150.9, 143.1, 134.3, 132.8, 129.4, 128.3, 126.5, 124.9, 124.8, 122.6, 113.3, 69.2.

**HRMS (EI-TOF)** calcd. for C₁₄H₉IN₂O₄S (M⁺): 427.9328, found: 427.9328.
To a 500 mL flask was added 6 (6.9 g, 20 mmol), 18 (12.8 g, 30 mmol) and Pd(OAc)$_2$ (449 mg, 2 mmol), AgBF$_4$ (5.84 g, 30 mmol), followed by t-BuOH (140 mL) and DCE (70 mL). Nitrogen was charged and the mixture was heated up to 75°C for 24 hours. The suspension was cooled to room temperature and quenched by Et$_3$N (40 mL). The reaction mixture was filtered through a pad of Celite, concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc/DCM = 4/1/1) to afford 19 (10.55 g, 82%) as a yellow oil.

IR (neat, cm$^{-1}$) 3067, 3020, 2932, 2695, 2585, 2467, 2339, 1946, 1890, 1775, 1715, 1602, 1533, 1380, 1179, 977, 783.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.33 (s, 1H), 8.78 – 8.71 (m, 1H), 8.51 (dd, $J = 4.4, 1.7$ Hz, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 7.98 – 7.94 (m, 1H), 7.94 – 7.89 (m, 2H), 7.83 (td, $J = 6.2, 2.6$ Hz, 4H), 7.79 – 7.74 (m, 2H), 7.69 (d, $J = 7.3$ Hz, 1H), 7.58 (s, 1H), 7.57 – 7.53 (m, 2H), 7.44 – 7.28 (m, 3H), 5.52 (dd, $J = 9.2, 6.7$ Hz, 1H), 3.98 (ddd, $J = 15.2, 6.7, 1.1$ Hz, 1H), 3.81 (ddd, $J = 15.2, 9.2, 1.0$ Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.8, 165.8, 150.3, 148.4, 143.1, 138.3, 136.4, 135.2, 134.6, 133.6, 131.6, 130.7, 127.9, 127.8, 127.3, 125.7, 124.4, 124.3, 124.3, 123.8, 122.3, 121.8, 119.9, 119.9, 116.8, 113.7, 54.2, 24.9.

$[\alpha]^{20}_D = -34.6$ (c=0.96, in CHCl$_3$).

HRMS (ESI) m/z: 668.1213 (M+Na$^+$); calcd. for C$_{34}$H$_{23}$N$_5$NaO$_7$S: 668.1216.
According to the procedure reported by our group \[^6\], to a 250 mL-Schlenk reactor was added 19 (2.58 g, 4 mmol), NaOCN (520 mg, 8 mmol), N-Fmoc-Glycine (356 mg, 1.2 mmol), Pd(OAc)\(_2\) (90 mg, 0.4 mmol) and Ag\(_3\)PO\(_4\) (1.67 g, 4 mmol), followed by Dioxane (70 mL) and MeI (2.5 mL, 40 mmol). Nitrogen was charged and the mixture was heated up to 70°C for 24 hours. The suspension was cooled to room temperature and quenched by Et\(_3\)N (2 mL). The reaction mixture was filtered through a pad of Celite, concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc/DCM = 4/1/1) to afford 20 (2.3 g, 84%) as a yellow oil.

IR (neat, cm\(^{-1}\)) 3107, 3063, 2929, 2694, 2625, 2443, 2336, 1718, 1607, 1531, 1377, 1179, 1126, 780, 731.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.60 (s, 1H), 8.87 (dd, \(J = 4.3, 1.7\) Hz, 1H), 8.82-8.76 (m, 1H), 8.19 (dd, \(J = 8.3, 1.6\) Hz, 1H), 7.94 (d, \(J = 8.9\) Hz, 2H), 7.91 – 7.86 (m, 1H), 7.82 (d, \(J = 8.9\) Hz, 2H), 7.78 – 7.73 (m, 1H), 7.69 – 7.64 (m, 2H), 7.64-7.59 (m, 2H), 7.59 – 7.53 (m, 2H), 7.49 (s, 1H), 7.47 (d, \(J = 4.3\) Hz, 1H), 7.30 – 7.25 (m, 2H), 5.38 (d, \(J = 11.3\) Hz, 1H), 4.77-4.67 (m, 1H), 1.63 (d, \(J = 7.0\) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.5, 165.8, 150.2, 148.7, 143.1, 138.7, 136.3, 135.1, 134.5, 134.0, 131.1, 129.8, 127.9, 127.7, 127.3, 125.7, 125.5, 124.3, 124.1, 123.6, 122.7, 122.6, 121.8, 120.5, 117.2, 113.5, 60.7, 30.2, 19.7.

\([\alpha]\)\(^{29}\)D = -62.1 (c=0.98, in CHCl\(_3\)).

HRMS (ESI) \text{m/z}: 682.1364 (M+Na\(^+\)); calcd. for C\(_{35}\)H\(_{28}\)N\(_5\)NaO\(_7\)S: 682.1372.
To a 100 mL-Schlenk reactor was added 20 (1.1 g, 1.67 mmol), followed by MeOH (40 mL) and BF$_3$·Et$_2$O (3.3 mL, 30.4 mmol). The mixture was heated up to 100 °C for 24 hours. After cooled to room temperature saturated NaHCO$_3$ aqueous was added to quench the reaction. The aqueous phase was washed by DCM three times. The combined organic layer was dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc/DCM = 5/1/1) to afford 21 (594 mg, 65%) as a yellow oil.

**IR** (neat, cm$^{-1}$) 3066, 3029, 2936, 2759, 2693, 2595, 2469, 2360, 1719, 1533, 1382, 1181, 1007, 858, 743.

**$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ 8.08-8.01 (m, 2H), 7.91-7.85 (m, 2H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.65-7.57 (m, 5H), 7.41 (s, 1H), 7.27 – 7.16 (m, 2H), 5.05 (d, $J = 10.0$ Hz, 1H), 4.28-4.16 (m, 1H), 3.73 (s, 3H), 1.63 (d, $J = 6.9$ Hz, 3H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ 168.7, 167.2, 150.4, 143.2, 134.9, 134.4, 131.2, 130.0, 128.0, 125.6, 125.5, 124.4, 124.0, 123.5, 123.2, 120.5, 113.5, 56.2, 52.9, 31.1, 19.8.

[$\alpha$]$^{20}_{D}$ = -104.2 ($c$=0.95, in CHCl$_3$).

**HRMS (ESI)** m/z: 570.0944 (M+Na$^+$); calcd. for C$_{27}$H$_{21}$N$_3$NaO$_8$S: 570.0947.
To a stirred solution of 21 (547.5 mg, 1.0 mmol) in DMF (10 mL) was added K$_2$CO$_3$ (839.3 mg, 6.0 mmol) and mercaptoacetic acid (276.4 mg, 3.0 mmol). The suspension was stirred under nitrogen for another 1 h at ambient temperature. Acetic acid glacial (0.5 mL) was added to quench the reaction. The suspension was diluted by EtOAc and washed by NaHCO$_3$ aqueous for three times. The organic layer was dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 2/1) to afford 22 (337.0 mg, 93%) as a yellow oil.

**IR** (neat, cm$^{-1}$) 3001, 2927, 2374, 2329, 1713, 1614, 1462, 1385, 1267, 1117, 1096, 1011, 755.

**$^1$H NMR** (400 MHz, CDCl$_3$) δ 8.03 (s, 1H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.60-7.54 (m, 2H), 7.54-7.47 (m, 2H), 7.16 – 7.11 (m, 1H), 7.04 – 6.93 (m, 3H), 5.09 (d, $J = 10.1$ Hz, 1H), 4.33-4.22 (m, 1H), 3.74 (s, 3H), 1.65 (d, $J = 6.9$ Hz, 3H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 169.5, 167.3, 136.0, 133.8, 131.3, 126.3, 123.1, 122.0, 121.7, 119.3, 119.2, 117.0, 111.0, 57.1, 52.5, 31.2, 20.2.

$[\alpha]_{D}^20 = -105.7$ (c=0.92, in CHCl$_3$).

**HRMS (ESI)** m/z: 385.1152 (M+Na$^+$); calcd. for C$_{21}$H$_{18}$N$_2$NaO$_4$: 385.1164.
To a 50 mL flask was added 22 (181 mg, 0.5 mmol), 4 Å molecular sieve (75.0 mg), followed by dry DMF (5 mL). The stirred mixture was charged with nitrogen and cooled to -50°C for 10 min. NaH (60% dispersion in mineral oil, 60 mg, 1.5 mmol) was added cautiously. After 10 min, MeI (187 μL, 3 mmol) was added by one portion. The reaction stirred for another 30 min, which was quenched by glacial acetic acid (0.2 mL). The mixture was extracted with EtOAc and NaHCO$_3$ aqueous. The water layer was washed by EtOAc for three times. The combined organic layer washed by brine and dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 4/1) to afford 23 (144.9 mg, 77%) as a yellow oil.

**IR** (neat, cm$^{-1}$) 3060, 2937, 2693, 2637, 2473, 2361, 1714, 1614, 1466, 1383, 1265, 1199, 1008, 735.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.66 – 7.60 (m, 3H), 7.58-7.51 (m, 2H), 7.10 (d, $J = 7.7$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 7.01 – 6.95 (m, 1H), 6.87 (s, 1H), 5.08 (d, $J = 10.0$ Hz, 1H), 4.31-4.21 (m, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 1.64 (d, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.5, 167.4, 136.7, 133.8, 131.5, 126.8, 126.6, 123.2, 121.4, 119.5, 118.8, 115.7, 109.0, 57.1, 52.5, 32.7, 31.2, 20.3.

$[\alpha]^{20}_{D} = -106.1$ (c=0.93, in CHCl$_3$).

**HRMS (ESI)** m/z: 399.1311 (M+Na$^+$); calcd. for C$_{22}$H$_{20}$N$_2$NaO$_4$: 399.1321.
According to the procedure reported by Jia[7], to a solution of 23 (682.0 mg, 1.81 mmol) in acetic acid (3.6 mL) at ambient temperature was added 12 N aq. HCl (0.5 mL), DMSO (565.7 mg, 7.2 mmol) and phenol (34.1 mg, 0.36 mmol) successively. The reaction mixture was stirred at room temperature for 24 h and then neutralized by Na₂CO₃ aqueous. The suspension extracted with EtOAc for three times. The combined organic layer dried over MgSO₄, filtered and the solvent was removed under pressure and the residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 2/1) to afford 24 as a 1:1 diastereomer mixture (703.1 mg, 99%) as a colorless oil.

A sample of pure diastereomer of 24 was obtained by preparative TLC and the spectroscopic data were as follows, the absolute configuration of C3-position of oxindole was not determined since the configuration would not be retained during the oxidation (25 →26).

**IR** (neat, cm⁻¹) 3018, 2927, 2368, 1719, 1613, 1464, 1382, 1268, 1211, 753.

One diastereomer of 24:

**¹H NMR** (400 MHz, CDCl₃) δ 7.95 – 7.84 (m, 2H), 7.77 – 7.69 (m, 2H), 7.40 (d, J = 7.4 Hz, 1H), 7.29-7.23 (m , 1H), 7.09 (t, J = 7.3 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 5.20 (d, J = 8.5 Hz, 1H), 3.73 (s, 3H), 3.69-3.66 (m, 1H), 3.63 – 3.53 (m, 1H), 3.00 (s, 3H), 0.99 (d, J = 7.0 Hz, 3H).

**¹³C NMR** (101 MHz, CDCl₃) δ 175.7, 169.8, 167.9, 144.6, 134.2, 132.1, 128.2, 128.0, 123.9, 123.7, 122.7, 107.9, 55.3, 52.8, 47.1, 35.0, 25.9, 14.2;

[α]²⁰D = -1.7 (c=0.95, in CHCl₃).

**HRMS (ESI)** m/z: 415.1259 (M+Na⁺); calcd. for C₂₂H₂₀N₂NaO₅: 415.1270.

The other diastereomer of 24:

**¹H NMR** (400 MHz, CDCl₃) δ 7.72 – 7.59 (m, 4H), 7.24 (d, J = 6.2 Hz, 1H), 6.96 – 6.78 (m, 1H), 6.39 (dd, J = 8.0, 1.6 Hz, 1H), 4.96 (d, J = 11.2 Hz, 1H), 3.75 – 3.60 (m, 4H), 3.43-3.36 (m, 1H), 3.09 (s, 3H), 1.38 (d, J = 6.8 Hz, 3H).

**¹³C NMR** (101 MHz, CDCl₃) δ 175.9, 168.9, 167.1, 143.8, 134.0, 131.5, 127.6, 126.5, 124.6, 123.4, 122.3, 107.6, 54.4, 52.7, 48.7, 33.7, 26.2.
$[\alpha]^{20}_D = -49.4 \ (c=0.98, \text{in CHCl}_3)$.

**HRMS (ESI)** m/z: 415.1265 (M+Na$^+$); calcd. for C$_{22}$H$_{20}$N$_2$NaO$_5$: 415.1270.
To a solution of 24 (703.1 mg, 1.79 mmol, d.r. = 1:1) in CH₂Cl₂ (5.0 mL) and MeOH (5.0 mL) was added ethylenediamine (1.2 ml, 17.9 mmol) in one portion. The mixture was stirred at 25 °C for 2 hours. Concentrated in vacuo, brine was added and the residue was extracted with THF (5 mL × 4). To the combined organic layer was added Boc₂O (586.0 mg, 2.7 mmol). The reaction was stirred at ambient temperature under nitrogen. After 4 hours, the mixture was concentrated in vacuo and the residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 2/1) to afford 25 as a 1:1 diastereomer mixture (441.1 mg, 68% over 2 steps, d.r. = 1:1) as a colorless oil.

A sample of pure diastereomer of 25 was obtained by preparative TLC and the spectroscopic data were as follows, the absolute configuration of C3-position of oxindole was not determined since the configuration would not be retained during the oxidation (25 → 26).

**IR**(neat, cm⁻¹) 2932, 2337, 1701, 1519, 1466, 1364, 1264, 1165, 1083, 1016, 758.

One diastereomer of 25:

**¹H NMR**(400 MHz, CDCl₃) δ 7.34-7.27 (m, 2H), 7.19 (d, J = 7.4 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 4.47 (dd, J = 8.2, 4.8 Hz, 1H), 3.78 (s, 3H), 3.48 (s, 1H), 3.21 (s, 3H), 2.95-2.84 (m, 1H), 1.46 (s, 9H), 0.86 (d, J = 7.1 Hz, 3H).

**¹³C NMR**(101 MHz, CDCl₃) δ 176.8, 173.1, 156.6, 144.4, 128.5, 127.9, 126.8, 123.4, 123.1, 108.3, 79.6, 58.4, 52.4, 48.1, 36.7, 28.6, 26.4, 12.9.

[α]²⁰D = -17.9 (c=0.85, in CHCl₃).

**HRMS (ESI)** m/z: 385.1726 (M+Na⁺); calcd. for C₁₉H₂₆N₂NaO₅: 385.1739.

The other diastereomer of 25:

**¹H NMR**(400 MHz, CDCl₃) δ 7.55 (d, J = 6.7 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 5.33 (d, J = 9.7 Hz, 1H), 4.60-4.50 (m, 1H), 3.70 (s, 3H), 3.63 (d, J = 2.4 Hz, 1H), 3.21 (s, 3H), 2.66-2.56 (m, 1H), 1.44 (s, 9H), 0.69 (d, J = 6.9 Hz, 3H).

**¹³C NMR**(101 MHz, CDCl₃) δ 177.24, 172.55, 155.41, 144.59, 128.19, 125.29, 122.76, 108.05, 80.27, 56.52, 52.15, 46.87, 38.59, 28.29, 26.25, 12.79.
$[\alpha]^{20}_{D} = -17.5 \ (c=0.53, \text{in CHCl}_3)$.

**HRMS (ESI)** m/z: 385.1718 (M+Na$^+$); calcd. for C$_{19}$H$_{26}$N$_2$NaO$_5$: 385.1739.
According to the procedure reported by Jia[7], to a solution of 25 (332.4 mg, 0.92 mmol, d.r. = 1:1) in THF/H$_2$O (5.0 mL/2.5 mL) was added NaOH (92.0 mg, 2.3 mmol) and LiOH (55.1 mg, 2.3 mmol) at 0°C. The mixture was bubbled with oxygen for 6 hours at the same temperature. P(OEt)$_3$ (631.0 μL, 3.68 mmol) was added and the resulting mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction solution was adjusted to pH 7.0 with AcOH and extracted with EtOAc. The organic layer dried over MgSO$_4$, filtered and evaporated under reduced pressure. The crude product 26 was dissolved in DCM (10.0 mL), to which was added DIPEA (304.1 μl, 1.84 mmol) and HATU (524.7 mg, 1.38 mmol). The reaction was stirred at ambient temperature overnight under nitrogen. The mixture was concentrated in vacuo and the residue was separated with flash column chromatography on silica gel (hexane/EtOAc = 3/1) to afford 27 as a 1:1 diastereomer mixture (159.3 mg, 50 % over 2 steps, d.r. = 1:1) as a colorless oil.

A sample of pure 27a and 27b were obtained by preparative TLC and the spectroscopic data were as follows. The absolute configuration of C3-position of oxindole in 27a and 27b was determined by the transformation to maremyns A and B.

**27a:**

**IR** (neat, cm$^{-1}$) 3067, 2987, 2924, 2377, 2339, 1792, 1717, 1617, 1506, 1466, 1376, 1319, 1266, 1160, 1009, 754.

**$^1$H NMR** (400 MHz, CDCl$_3$) δ 7.43 (td, $J = 7.8$, 1.0 Hz, 1H), 7.35 (d, $J = 7.2$ Hz, 1H), 7.17 (t, $J = 7.5$ Hz, 1H), 6.89 (d, $J = 7.8$ Hz, 1H), 6.22 (d, $J = 10.7$ Hz, 1H), 4.89 (dd, $J = 10.7$, 9.0 Hz, 1H), 3.22 (s, 3H), 2.90-2.80 (m, 1H), 1.47 (s, 9H), 0.88 (d, $J = 7.1$ Hz, 3H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 174.3, 173.8, 155.8, 144.5, 131.7, 124.5, 124.3, 124.2, 109.2, 86.5, 80.4, 52.3, 41.5, 28.5, 26.6, 7.6.

[$\alpha$]$_{D}^{20}$ = -8.3 (c=0.67, in CHCl$_3$).
HRMS (ESI) m/z: 369.1419 (M+Na\(^+\)); calcd. for C\(_{18}\)H\(_{22}\)N\(_2\)O\(_5\): 369.1426.

27b:

IR (neat, cm\(^{-1}\)) 3064, 3011, 2928, 2372, 2333, 1795, 1716, 1616, 1517, 1467, 1370, 1266, 1166, 1095, 994, 752.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41 (td, \(J = 7.8, 1.1\) Hz, 1H), 7.31 (d, \(J = 7.0\) Hz, 1H), 7.10 (t, \(J = 7.5\) Hz, 1H), 6.87 (d, \(J = 7.8\) Hz, 1H), 5.73 – 5.56 (m, 1H), 5.07 (d, \(J = 3.0\) Hz, 1H), 3.18 (s, 3H), 3.17 – 3.04 (m, 1H), 1.46 (s, 9H), 1.05 (d, \(J = 7.2\) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 174.8, 174.4, 155.1, 144.4, 131.2, 126.8, 123.0, 122.8, 109.0, 84.0, 80.5, 53.2, 41.1, 28.2, 26.3, 11.4.

\([\alpha]^{20}\_D = -11.9 (c=0.46, \text{ in CHCl}_3).\)

HRMS (ESI) m/z: 369.1416 (M+Na\(^+\)); calcd. for C\(_{18}\)H\(_{22}\)N\(_2\)O\(_5\): 369.1426.
To a solution of 27 (159.3 mg, 0.46 mmol, d.r.=1:1) in CH₂Cl₂ (3.0 mL) was added TFA (1.0 mL). The mixture was stirred under nitrogen for 2 hours. Na₂CO₃ aqueous was added to adjust the pH between 7.0~8.0. The solution was extracted with DCM for three times, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in DMF (3.0 mL), to which was added DIPEA (152.0 μL, 0.92 mmol) and N-Boc-S-methyl-L-cysteine 28[11] (119.1 mg, 0.51 mmol) followed by HATU (262.4 mg, 0.69 mmol). The reaction was stirred at ambient temperature under nitrogen for 4 hours. The mixture was extracted with EtOAc and the organic layer washed with 1 M HCl, Na₂CO₃ aqueous and brine in sequence. The solvent was removed under reduced pressure and the residue was transferred to a 50 mL-Schlenk reactor with p-xylene (3.0 mL), to which was added SiO₂ (240.0 mg) and charged with nitrogen. The suspension was heated up to 140°C and stirred overnight. The solvent was removed under reduced pressure and the residue was purified with flash column chromatography on silica gel (hexane/DCM/acetone = 1/1/1) to afford maremycin A 2a (60.1 mg, 36% over 3 steps) and maremycin B 2b (63.6 mg, 38% over 3 steps) separately as a white solid.

Maremycin A (2a):

mp 228-230 °C.

IR (neat, cm⁻¹) 3005, 2926, 2473, 2333, 1710, 1464, 1268, 912, 755.

¹H NMR (400 MHz, DMSO-d₆) δ 8ZJDN 7.93 (s, 1H), 7.58 (s, 1H), 7.37 (d, J= 7.3 Hz, 1H), 7.32 (t, J= 7.7 Hz, 1H), 7.05 (t, J= 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 4.89 (s, 1H), 4.31-4.22 (m, 1H), 3.10 (s, 3H), 2.98 (dd, J= 4.0, 14.0 Hz, 1H), 2.80 (dd, J= 14.0, 4.0 Hz, 1H), 2.09 (s, 3H), 2.08-2.01 (m, 1H), 1.12 (d, J= 7.2 Hz, 3H).

¹³C NMR (100 MHz, DMSO-d₆) δ 178.0, 168.0, 165.7, 143.0, 130.6, 129.2, 125.0, 121.9, 108.5, 76.4, 54.3, 53.6, 43.1, 36.4, 25.9, 16.4, 8.3.
[α]$_{20}^D$ = -111.3 (c 0.24, MeOH); Lit: $^9$ [α]$_{25}^D$ = -120.95 (c 0.21, MeOH); Lit: $^7$ [α]$_{25}^D$ = -115.5 (c 0.30, MeOH).

**HRMS (ESI)** m/z: 386.1146 (M+Na$^+$); calcd. for C$_{17}$H$_{21}$N$_3$NaO$_4$S: 386.1150.

Maremycin B (2b):

**mp** 211-214 °C

**IR** (neat, cm$^{-1}$) 3111, 3065, 3011, 2921, 2703, 2622, 2361, 1664, 1461, 1375, 1095, 783.

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.48 (d, $J = 2$ Hz, 1H), 7.70 (d, $J = 2$ Hz, 1H), 7.38-7.26 (m, 2H), 7.08 (t, $J = 7.6$ Hz, 1H), 7.02 (d, $J = 7.6$ Hz, 1H), 6.91 (s, 1H), 4.57-4.52 (m, 1H), 4.20-4.13 (m, 1H), 3.11 (s, 3H), 2.97 (dd, $J = 14.0, 4.8$ Hz, 1H), 2.83 (dd, $J = 14.0, 3.9$ Hz, 1H), 2.32 (qd, $J = 7.2, 6.8$ Hz, 1H), 2.11 (s, 3H), 0.86 (d, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 176.3, 167.4, 166.2, 143.0, 131.4, 129.2, 123.9, 122.4, 108.6, 77.2, 55.5, 54.4, 43.6, 36.9, 25.8, 16.2, 9.8.

[α]$_{20}^D$ = +69.8 (c 0.78, MeOH); Lit: $^9$ [α]$_{25}^D$ = +2.94 (c 0.21, MeOH); Lit: $^7$ [α]$_{25}^D$ = +78.3 (c 0.28, MeOH).

**HRMS (ESI)** m/z: 386.1175 (M+Na$^+$); calcd. for C$_{17}$H$_{21}$N$_3$NaO$_4$S: 386.1150.
3. Comparison of NMR Data of Natural and Synthetic Compounds

![Structure of Tryprostatin A]

Table S1. NMR data comparison of synthetic and natural\(^8\) **Tryprostatin A**\(^8\)

| \(^1\)H NMR | \(^13\)C NMR |
|----------------|----------------|
| Natural\(^8\) | This work\(^8\) | Natural\(^8\) | This work\(^8\) |
| 7.88 (brs, 1H) | 7.97 (s, 1H) | 169.35 | 169.43 |
| 7.34 (d, \(J = 8.8\) Hz, 1H) | 7.34 (d, \(J = 8.6\) Hz, 1H) | 165.82 | 165.94 |
| 6.83 (d, \(J = 2.4\) Hz, 1H) | 6.83 (d, \(J = 2.2\) Hz, 1H) | 156.37 | 156.48 |
| 6.76 (dd, \(J = 8.8, 2.4\) Hz, 1H) | 6.76 (dd, \(J = 8.6, 2.3\) Hz, 1H) | 136.28 | 136.43 |
| 5.65 (brs, 1H) | 5.66 (s, 1H) | 135.25 | 135.25 |
| 5.29 (br dd, \(J = 7.0, 6.5\) Hz, 1H) | 5.32-5.25 (m, 1H) | 135.11 | 135.25 |
| 4.34 (br dd, \(J = 11.2, 3.5\) Hz, 1H) | 4.34 (dd, \(J = 11.2, 2.5\) Hz, 1H) | 122.30 | 122.44 |
| 4.06 (br dd, \(J = 7.8, 7.3\) Hz, 1H) | 4.06 (t, \(J = 7.4\) Hz, 1H) | 119.97 | 120.14 |
| 3.83 (s, 3H) | 3.82 (s, 3H) | 118.36 | 118.45 |
| 3.67 (ddd, \(J = 12.7, 8.8, 2.9\) Hz, 1H) | 3.72 – 3.54 (m, 3H) | 109.35 | 109.43 |
| 3.63 (ddd, \(J = 15.1, 3.5\) Hz, 1H) | | 104.46 | 104.55 |
| 3.58 (ddd, \(J = 12.7, 8.8, 2.9\) Hz, 1H) | | 94.89 | 95.06 |
| 3.46 (ddd, \(J = 16.5, 7.0\) Hz, 1H) | 3.46 (dd, \(J = 16.3, 7.6\) Hz, 1H) | 59.29 | 59.39 |
| 3.40 (ddd, \(J = 16.5, 6.5\) Hz, 1H) | 3.38 (dd, \(J = 15.9, 6.7\) Hz, 1H) | 55.77 | 55.89 |
| 2.91 (ddd, \(J = 15.1, 11.2\) Hz, 1H) | 2.91 (dd, \(J = 15.0, 11.2\) Hz, 1H) | 54.57 | 54.73 |
| 2.33 (m, 1H) | 2.41 – 2.28 (m, 1H) | 45.43 | 45.52 |
| 2.08-1.97 (m, 2H) | 2.09 – 1.97 (m, 2H), | 28.38 | 28.48 |
| 1.95-1.85 (m, 1H) | 1.95 – 1.85 (m, 1H), | 25.76 | 25.83 |
| 1.78 (s, 3H) | 1.76 (s, 3H) | 25.68 | 25.80 |
| 1.75 (s, 3H) | 1.73 (s, 3H) | 25.10 | 25.23 |
|       | 22.65 | 22.75 |
|-------|-------|-------|
|       | 17.98 | 18.06 |

*All data were recorded in CDCl₃ and to the solvent signal (7.26 ppm for ¹H, 77.16 ppm for ¹³C); b Measured at 500 MHz, δ [ppm, mult, J (Hz)]; c Measured at 125 MHz, δ (ppm); d Measured at 400 MHz, δ [ppm, mult, J (Hz)]; e Measured at 101 MHz, δ (ppm).*
Table S2. NMR data comparison of synthetic and published Maremycin A

|                  | ¹H NMR                                      |                  | ¹³C NMR                                      |
|------------------|---------------------------------------------|------------------|---------------------------------------------|
|                  | Natural[b]                                  | Synthesized by Jia[c] | This work[d]                      | Natural[e]                                  | Synthesized by Jia[f] | This work[g]                      |
| 8.60 (s, br, 1H) | 8.64 (br s, 1H)                            | 8.65 (s, 1H)      | 177.9                                      | 178.0                                       | 178.0                   |
| 7.88 (s, 1H)     | 7.92 (br s, 1H)                            | 7.93 (s, 1H)      | 167.9                                      | 168.0                                       | 168.0                   |
| 7.53 (s, 1H)     | 7.59 (br s, 1H)                            | 7.58 (s, 1H)      | 165.6                                      | 165.7                                       | 165.7                   |
| 7.37 (m, 2H)     | 7.37 (d, J = 7.6 Hz, 1H)                   | 7.37 (d, J = 7.3 Hz, 1H) | 143.0                                      | 143.0                                       | 143.0                   |
|                  | 7.33 (t, J = 7.6 Hz, 1H)                   | 7.32 (t, J = 7.7 Hz, 1H) | 130.6                                      | 130.6                                       | 130.6                   |
| 7.01 (dd, J = 7.5 Hz, 1H) | 7.05 (t, J = 7.6 Hz, 1H)                   | 7.05 (t, J = 7.6 Hz, 1H) | 129.0                                      | 129.1                                       | 129.2                   |
| 6.99 (d, J = 7.5 Hz, 1H) | 7.00 (d, J = 7.6 Hz, 1H)                   | 7.00 (d, J = 7.6 Hz, 1H) | 124.9                                      | 125.0                                       | 125.0                   |
| 4.88 (s, br, 1H) | 4.89 (br s, 1H),                           | 4.89 (s, 1H)      | 121.7                                      | 121.8                                       | 121.9                   |
| 4.25 (ABX, 1H)   | 4.27 (d, J = 2.0 Hz, 1H)                   | 4.31-4.22 (m, 1H) | 108.5                                      | 108.5                                       | 108.5                   |
| 3.09 (s, 3H)     | 3.10 (s, 3H)                               | 3.10 (s, 3H)      | 76.4                                       | 76.4                                        | 76.4                    |
| 2.96 (ABX, J = 14.0, 4.0Hz, 1H) | 2.98 (dd, J = 4.0, 14.0 Hz, 1H)             | 2.98 (dd, J = 4.0, 14.0 Hz, 1H) | 54.2                                        | 54.3                                        | 54.3                    |
| 2.83 (ABX, J = 14.0, 4.0Hz, 1H) | 2.80 (dd, J = 4.0, 14.0 Hz, 1H)             | 2.80 (dd, J = 14.0, 4.0 Hz, 1H) | 53.6                                        | 53.6                                        | 53.6                    |
| 2.08 (s, 3H)     | 2.09 (s, 3H)                               | 2.09 (s, 3H)      | 43.0                                       | 43.1                                        | 43.1                    |
| 2.05 (m, 1H)     | 2.05 (m, 1H)                               | 2.08-2.01 (m, 1H) | 36.4                                       | 36.4                                        | 36.4                    |
| 1.11 (d, J = 7.0 Hz, 1H) | 1.12 (d, J = 7.2)                         | 1.12 (d, J = 7.2) | 25.8                                       | 25.9                                        | 25.9                    |
| 1H | Hz, 3H | Hz, 3H |
|----|-------|-------|
|    | 16.3  | 16.4  | 16.4  |
|    | 8.3   | 8.3   | 8.3   |

*a* All data were recorded in d6-DMSO and to the solvent signal (2.50 ppm for \(^1\)H, 39.52 ppm for \(^{13}\)C);

*b* See reference 9, Measured at 500 MHz, \(\delta\) [ppm, mult, \(J\) (Hz)];

*c* See reference 7, Measured at 400 MHz, \(\delta\) [ppm, mult, \(J\) (Hz)];

*d* Measured at 400 MHz, \(\delta\) [ppm, mult, \(J\) (Hz)];

*e* See reference 9, Measured at 125 MHz, \(\delta\) (ppm);

*f* See reference 7, Measured at 101 MHz, \(\delta\) (ppm);

*g* Measured at 101 MHz, \(\delta\) (ppm);
Table S2. NMR data comparison of synthetic and published Maremycin B \[^{[a]}\]

|                  | \(^1^H\) NMR |                       | \(^1^C\) NMR |                       | \(^1^H\) NMR |                       | \(^1^C\) NMR |                       |
|------------------|--------------|-----------------------|--------------|-----------------------|--------------|-----------------------|--------------|-----------------------|
|                  | Natural\[^{[b]}\] | Synthesized by Jia\[^{[c]}\] | This work\[^{[d]}\] | Natural\[^{[e]}\] | Synthesized by Jia\[^{[f]}\] | This work\[^{[g]}\] | Natural\[^{[h]}\] | Synthesized by Jia\[^{[i]}\] | This work\[^{[j]}\] |
| 8.42 (d, br, \(J = 2\text{Hz}, 1\text{H}) | 8.49 (br s, 1H) | 8.48 (d, \(J = 2\text{Hz}, 1\text{H}) | 176.2 | 176.3 | 176.3 |
| 7.67 (d, br, \(J = 1.5\text{Hz}, 1\text{H}) | 7.70 (br s, 1H) | 7.70 (d, \(J = 2\text{Hz}, 1\text{H}) | 167.3 | 167.4 | 167.4 |
| 7.34 (dd, \(J = 7.5, 7.5, 1\text{Hz}, 1\text{H}) | 7.36-7.31 (m, 2H) | 7.38-7.26 (m, 2H) | 166.1 | 166.2 | 166.2 |
| 7.31 (dd, \(J = 7.5, 1\text{Hz}, 1\text{H}) | | | 142.9 | 143.0 | 143.0 |
| 7.07 (dd, \(J = 7.5, 7.5, 1\text{Hz}, 1\text{H}) | 7.08 (t, \(J = 7.6 \text{Hz}, 1\text{H}) | 7.08 (t, \(J = 7.6 \text{Hz}, 1\text{H}) | 131.4 | 131.4 | 131.4 |
| 7.01 (dd, \(J = 7.5, 1\text{Hz}, 1\text{H}) | 7.02 (d, \(J = 7.6 \text{Hz}, 1\text{H}) | 7.02 (d, \(J = 7.6 \text{Hz}, 1\text{H}) | 129.2 | 129.2 | 129.2 |
| 6.88 (s, 1H) | 6.92 (br s, 1H) | 6.91 (s, 1H) | 123.7 | 123.8 | 123.9 |
| 4.52 (dd, \(J = 5.5, 1.5, 1.5\text{Hz}, 1\text{H}) | 4.54 (d, \(J = 4.0 \text{Hz}, 1\text{H}) | 4.57-4.52 (m, 1H) | 122.3 | 122.4 | 122.4 |
| 4.15 (ABX, 1H) | 4.17 (s, 1H), 4.20-4.13 (m, 1H) | | 108.5 | 108.6 | 108.6 |
| 3.10 (s, 3H) | 3.11 (s, 3H), 3.11 (s, 3H) | | 77.2 | 77.2 | 77.2 |
| 2.96 (ABX, \(J = 5.5 \text{Hz}, 1\text{H}) | 2.96 (dd, \(J = 4.8, 14.0 \text{Hz}, 1\text{H}) | 2.97 (dd, \(J = 14.0, 4.8 \text{Hz}, 1\text{H}) | 55.5 | 55.5 | 55.5 |
| 2.85 (ABX, \(J = 13.5, 4.2 \text{Hz}, 1\text{H}) | 2.83 (dd, \(J = 3.6, 14.0 \text{Hz}, 1\text{H}) | 2.83 (dd, \(J = 14.0, 3.9 \text{Hz}, 1\text{H}) | 54.3 | 54.4 | 54.4 |
| 2.33 (qd, \(J = 7, 5.5 \text{Hz}, 1\text{H}) | 2.31 (m, 1H) | 2.32 (qd, \(J = 7.2, 6.8 \text{Hz}, 1\text{H}) | 43.5 | 43.6 | 43.6 |
| 1H)       | Hz, 1H) |  |
|-----------|---------|---|
| 2.12 (s, 3H) | 2.12 (s, 3H) | 2.11 (s, 3H) | 36.9 | 36.9 | 36.9 |
| 0.83 (d, J= 7 Hz, 3H) | 0.87 (d, J= 6.8 Hz, 3H) | 0.86 (d, J= 7.1 Hz, 3H) | 25.7 | 25.8 | 25.8 |
|           |         | 16.1 | 16.2 | 16.2 |
|           |         | 9.8  | 9.8  | 9.8  |

*a All data were recorded in d6-DMSO and to the solvent signal (2.50 ppm for 1H, 39.52 ppm for 13C); b See reference 9, Measured at 500 MHz, δ [ppm, mult, J (Hz)]; c See reference 7, Measured at 400 MHz, δ [ppm, mult, J (Hz)]; d Measured at 400 MHz, δ [ppm, mult, J (Hz)]; e See reference 9, Measured at 125 MHz, δ (ppm); f See reference 7, Measured at 101 MHz, δ (ppm); g Measured at 101 MHz, δ (ppm);
4. Copies of $^1$H and $^{13}$C NMR Spectra
Tryprostatin A (1)
Maremycin A (2a)
Maremycin B (2b)

[Chemical Structure Image]

[Graphical Spectroscopic Data]

[Chemical Structure Image]
5. X-ray Crystallographic Data

Crystal Data and Structure for 20

![Chemical Structure of 20]

**Figure S1.** X-Ray crystallographic data of 20. The ellipsoids drawn at 30% probability level.

### Table S2. Crystal data and structure refinement for 20

| Property                          | Calculated | Reported |
|-----------------------------------|------------|----------|
| Bond precision: C-C               | 0.0092 A   |          |
| Wavelength                        | 1.54184    |          |
| Cell:                             |            |          |
| a=10.5548(4)                      |            |          |
| b=27.6947(9)                      |            |          |
| c=10.8041(4)                      |            |          |
| alpha=90                          |            |          |
| beta=101.966(4)                   |            |          |
| gamma=90                          |            |          |
| Temperature: 170 K                |            |          |
| Volume                            | 3089.5(2)  | 3089.5(3)|
| Space group P 21                  |            |          |
| Hall group P 2yb                  |            |          |
| Moiety formula C35 H25 N5 O7 S    |            |          |
| Sum formula C35 H25 N5 O7 S       |            |          |
| Mr                                | 659.66     | 659.66   |
| Dx,g cm-3                         | 1.418      | 1.418    |
| Z                                 | 4          | 4        |
| Mu (mm-1)                         | 1.440      | 1.440    |
| F000                              | 1368.0     | 1368.0   |
| F000’                             | 1373.63    |          |
| h,k,lmax                          | 12,33,12   | 12,32,12 |
| Nref                              | 11119[ 5684] | 10748  |
| Tmin,Tmax                         | 0.526,0.562 | 0.385,1.000 |
| Tmin’                             | 0.477      |          |
| Correction method= #              |            |          |
| Reported T Limits: Tmin=0.385     |            |          |
| Tmax=1.000                        |            |          |
| AbsCorr = MULTI-SCAN              |            |          |
| Data completeness= 1.89/0.97      |            |          |
| Theta(max)= 67.425                |            |          |
| R(reflections)= 0.0692( 9415)     |            |          |
| wR2(reflections)= 0.1795( 10748)  |            |          |
| S = 1.031                         |            |          |
| Npar= 867                         |            |          |
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