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Graphical Abstract

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Asymmetric Approach towards the Total Synthesis of (+)-Actinopyllic Acid

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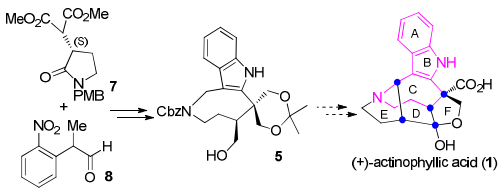

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ABSTRACT

This paper describes our efforts towards the asymmetric total synthesis of (+)-actinophyllic acid. Starting from the chiral oxazolidinone **9**, an azocino[4,3-*b*]indolyl intermediate (**5**) possessing the A/B/C ring system and the C16 quaternary stereogenic center of actinophyllic acid has been synthesized. Key steps include a LHMDS-promoted condensation to establish the critical C2–C16 bond and a successive four-step transformation to assemble the eight-membered C-ring of the target molecule.

1. Introduction

In 2005, Carroll and coworkers reported a unique monoterpernoid indole alkaloid (–)-actinophyllic acid **1** (Figure 1) to be the active component of the leave extracts of *Alstonia actinophylla* from Cape York Peninsula of Australia, with potent carboxypeptidase U inhibitory activity (IC50 of 0.84 μM).[1] Architecturally, actinophyllic acid possesses a highly compact hexacyclic skeleton that is unprecedented among the known monoterpernoid alkaloids. Specifically, its structure is characterized by an azocino[4,3-*b*]indole moiety (A/B/C-ring), an 1-azabicyclo[4.2.1]nonane unit (D/E-ring), and a highly functionalized hemi-ketal F-ring, as well as five contiguous stereogenic centers including one all-carbon quaternary center (C16).

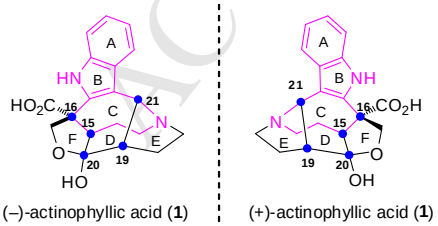
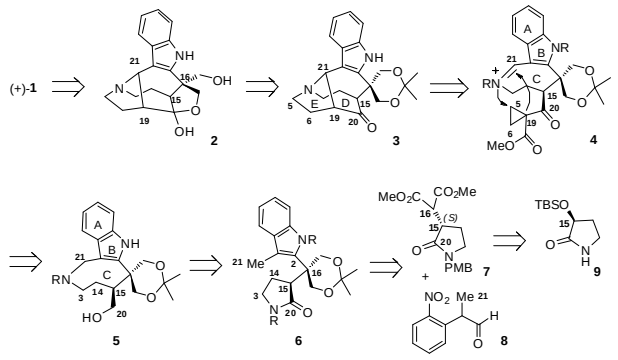


Figure 1. Structures of (–)- and (+)-actinophyllic acid.

The above-mentioned architectural features combined with its potential medicinal applications make actinophyllic acid a particularly attractive target for total synthesis.[2–5] To date, three synthetic groups have finished the total synthesis of actinophyllic acid. The first racemic (2008) and asymmetric (2010) total syntheses of actinophyllic acid were achieved by Overman *et al* through a highly efficient aza-Cope-Mannich cascade strategy.[2] Martin and coworkers documented a concise and elegant synthesis of (±)-actinophyllic acid via a carbocation/π-nucleophile cascade in 2013.[3] Recently, a creative asymmetric total synthesis of (–)-actinophyllic acid was reported by the group of Kwon using a chiral phosphine-catalyzed [3+2] annulation and subsequent novel ring formation sequance.[4] Herein, we report our efforts towards the asymmetric total synthesis of actinopyllic acid, leading to preparation of the key azocino[4,3-*b*]indolyl intermediate **5** that contains the A/B/C ring system and C15/C16 stereogenic centers of the target molecule.

Cyclopropane-based strategy has proven to be a highly versatile methodology in synthetic organic chemistry.[6] Our group previously developed a copper-catalyzed cyclopropanation/ring-opening/iminium cyclization cascade (CRI reaction) on tryptamine derivatives, which has allowed successful total syntheses of several structurally intriguing indoline alkaloids such as N-acetylardeemin, minfiensine, vincorine, and communesin F.[7] By analysis of the structure of actinophyllic acid, we envisioned a cyclopropane-based [3+2] cycloaddition strategy to construct the core of (+)-**1**. Retrosynthetically, the target molecule could be accessed from intermediate **2** according to Martin's protocol,[3] and **2** could be generated by deprotection and hemi-ketalizaiton of acetonide **3** (Scheme 1). Acetonide **3** was expected to be synthesized by an intramolecular [3+2] cycloaddition of cyclopropane derivative **4**, allowing efficient construction of the D/E rings in a single step. Preparation of **4** could be realized by introducing the cyclopropyl side chain at C20 from azocino[4,3-*b*]indolyl intermediate **5**, which would

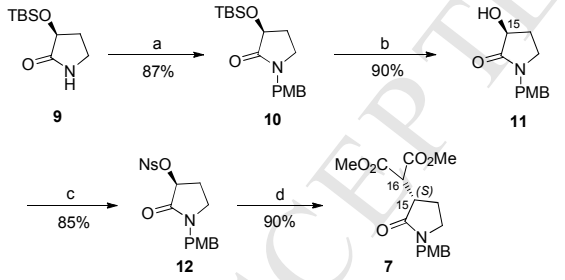
arise from intermediate **6** by ring-opening of the oxazolidinone ring and formation of the eight-membered C-ring. Since direct formation of a congested indole-C2–quaternary-carbon bond is challenging,[8] we envisioned to firstly establish the C2–C16 bond using malonate **7** and the known aldehyde **8**,[9] prior to constructing the indole core. In turn, **7** could be prepared from the known chiral oxazolidinone **9**.[10,11]



Scheme 1. Retrosynthetic analysis of actinophyllic acid

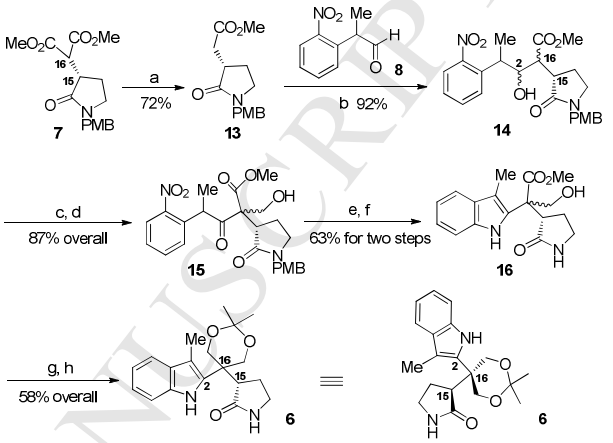
2. Results and discussion

Our synthesis commenced with the preparation of the substituted manolate intermediate **7** (Scheme 2). First of all, using a modified literature protocol,[10] the known chiral oxazolidinone **9** was prepared in decagram scales from commercially available (*S*)-4-amino-2-hydroxybutanoic acid over 3 steps (80% overall yield).[11] Protection of the free amine using PMB group, followed by desilylation of the resulting intermediate **10** with TBAF, afforded alcohol **11** in 78% yield over two steps. We next sought to install a leaving group at C15 in **11** for the further malonate displacement. Investigations on various leaving groups including I, OTs, OTf, and ONs revealed that the Ns-protected intermediate **12** gave the best results. Specifically, treatment of **12** with dimethyl malonate and *t*-BuOK delivered **7** smoothly with inverted C15 chirality in 90% yield and 98.3% ee.[12]



Scheme 2. Reagents and conditions: (a) NaH, PMBCl, DMF, 0 °C → rt, 87%; (b) TBAF, THF, 0 °C → rt, 90%; (c) NsCl, Et_3N, DCM, 0 °C, 85%; (d) dimethyl malonate, *t*-BuOK, THF, 0 °C → rt, 90%. (PMBCl, 4-methoxybenzyl chloride; TBAF, tetrabutylammonium fluoride; NsCl, *p*-nitrobenzenesulfonyl chloride).

Successful preparation of the chiral building block **7** enabled us to further investigate the synthesis of indole derivative **6** through C2–C16 bond formation and indolization (Scheme 3). Considering the steric hindrance of the diester group at C16 may impede the subsequent transformation, removal of one ester group of diester **7** was manipulated under Krapcho condition, delivering **13** in 72% yield. The desired C2–C16 bond formation was then initiated by LHMDS-promoted condensation of chiral oxazolidinone **13** with 2-(2-nitrophenyl) propanal **8**,[9] affording alcohol **14** as a mixture of diastereomers in 92% combined yield. Without separation of each diastereomer, **14** was subjected to a two-step transformation including Dess-Martin oxidation and hydroxymethylation[13] with formaldehyde to give nitrobenzene ketone derivative **15** in 87% overall yield. We found that deprotection of the PMB group met with failure after the indole ring was formed. Thus, removal of PMB protection was performed at this stage using CAN in a mixed solvent of CH_3CN/H_2O (v/v 1:1) at 0 °C, this was followed by indolization under the hydrogenation conditions to furnish **16** in 63% yield for two steps. DIBAL-H reduction of the ester functionality in **16** followed by treating the resultant diol with 2,2-dimethoxypropane yielded the desired acetonide **6**.

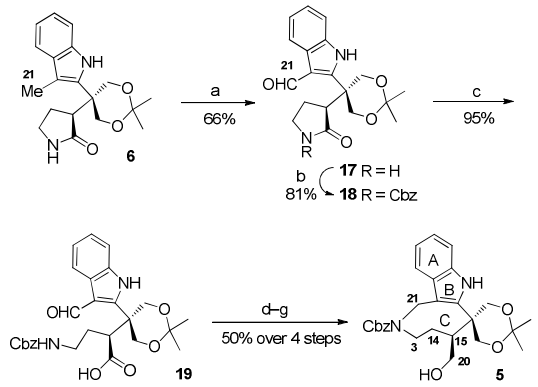


Scheme 3. Reagents and conditions: (a) LiCl, DMSO/H_2O (v/v 100:1), reflux, 72%; (b) LHMDS, THF, –78 °C, 92%; (c) Dess-Martin periodinane, DCM, 0 °C, 95%; (d) DBU, HCHO (aq 37%), THF, 0 °C, 92%; (e) CAN, CH_3CN/H_2O (v/v 1:1), 0 °C → rt; (f) 20% $Pd(OH)_2/C$, H_2, 250 psi, MeOH, rt, 63% for two steps; (g) DIBAL-H, DCM, 0 °C, 65% (88% brsm); (h) 2,2-dimethoxypropane, THF, reflux, 89%. (LHMDS, lithium bis(trimethylsilyl)amide; CAN, ceric ammonium nitrate; DIBAL-H, diisobutylaluminium hydride).

With a key C2–C16 bond formation and the indole core secured, we next turned to assemble the eight-membered C-ring of actinophyllic acid (Scheme 4). Converting the C21 methyl group in **6** into an aldehyde was conducted by DDQ oxidation to give **17** in 66% yield.[14] The latter was subjected to Cbz-protection of the oxazolidinone nitrogen atom to provide lactam **18** smoothly. Subsequent treatment of **18** with 1M NaOH in THF at room temperature gave the ring-opening product **19** in excellent yield (95%). Finally, a successive four-step transformation including Cbz deprotection, reductive amination, Cbz re-protection, and carboxylic acid reduction was carried out to secure the C-ring formation, thus giving rise to the stable intermediate **5** in 50% overall yield.

3. Conclusion

In summary, a synthesis of the optically pure azocino[4,3-*b*]indolyl intermediate **5** has been achieved using a LHMDS-promoted condensation to establish the critical C2–C16 bond and a successive four-step transformation to assemble the eight-membered C-ring. Successful synthesis of this key intermediate that possesses the A/B/C ring system and C15/C16 stereogenic centers of (+)-actinophyllic acid will pave the way for exploring our proposed cyclopropane-based [3+2] cycloaddition strategy.



Scheme 4. Reagents and conditions: (a) DDQ, DCM/H_2O (v/v 20:1), 0 °C → rt, 66%; (b) NaH, CbzCl, THF, 0 °C → rt, 81%; (c) 1M NaOH (aq), THF, rt, 95%; (d) Pd/C, H_2, MeOH, 1 atm, rt; (e) 3 Å MS, MeOH, reflux; (f) $NaBH_4$, MeOH, 0 °C; then DIPEA, CbzCl, MeOH, 0 °C; (g) BH_3 • Me_2S, THF, 30 °C. (DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; CbzCl, benzyl chloroformate; MS, molecular sieves; DIPEA, N,N-diisopropylethylamine).

4. Experimental section

4.1. General procedure

All commercially available reagents were used without further purification. All solvents were dried and distilled before use: tetrahydrofuran was dried over sodium-benzophenone; dichloromethane was distilled from calcium hydride; dimethyl sulfoxide and dimethylformamide was distilled under reduced pressure after drying over calcium hydride. Chromatography was conducted by using 200-300 mesh silica gel. All new compounds gave satisfactory spectroscopic analyses (IR, ^{1}H NMR, ^{13}C NMR, HRMS). IR spectra were recorded on a FT IR spectrometer. NMR spectra were recorded on a 400 and 600 MHz NMR spectrometer. HRMS spectra were obtained by the FAB method.

4.2. (S)-3-((tert-butyldimethylsilyl)oxy)-1-(4-methoxybenzyl)-pyrrolidin-2-one (**10**)

Compound **9** (50.00 g, 0.23 mol) was dissolved in dry DMF (400 mL) and cooled to °C. Sodium hydride (18.50 g, 0.46 mol, 60% in mineral oil) was added in small portions and the solution was stirred at °C for 30 minutes followed by slow addition of 4-methoxybenzyl chloride (40.90 mL, 0.30 mol).The reaction mixture was then stirred at rt for 2 h before it was quenched with a saturated aqueous solution of NH_4Cl (200 mL) at °C and diluted with EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with water (2 × 100 mL), brine (100 mL), dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 8:1) to give compound **10** as pale yellow foam; $[\alpha]^{20}_D$ = – 26.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 M, $CDCl_3$) δ 7.15 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 4.35 (s, 2H), 4.32 (t, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 3.20 – 3.17 (m, 1H), 3.07 – 3.05 (m, 1H), 2.26 – 2.23 (m, 1H), 1.87 – 1.84 (m, 1H), 0.90 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (150 M, $CDCl_3$): δ 173.0, 159.0, 129.4, 128.2, 113.9, 71.1, 55.1, 46.2, 29.1, 25.7, –4.5, –5.2; IR (KBr) 3473, 2930, 2856, 1705, 1612, 1586, 1513, 1462, 1439, 1299, 1249, 1175, 1144, 838, 780 cm^{-1} ; HRMS m/z ($M+Na^+$) calcd for $C_{18}H_{29}NNaO_3Si$ 358.1809, found 358.1813.

4.3. (S)-3-hydroxy-1-(4-methoxybenzyl)pyrrolidin-2-one (**11**).

Tetrabutylammonium fluoride (98.05 g, 0.37 mol) was added to a solution of compound **10** (50.00 g, 0.15 mol) in THF (400 mL) at °C. The reaction was warmed to room temperature and stirred until consumption of **10**. This mixture was then quenched with a solution of saturated aqueous solution of NH_4Cl (200 mL) at °C and diluted with EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 1:1) to give compound **11** (29.80 g, 90%) as white solid: mp 106 – 110 °C; $[\alpha]^{20}_D$ = – 59.4 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 M, $CDCl_3$) δ 7.16 (d, *J* = 9.0 Hz, 2H), 6.87-6.85 (m, 2H), 4.43 – 4.37 (m, 3H), 4.20 – 4.19 (m, 1H), 3.79 (s, 3H), 3.25 – 3.21 (m, 1H), 3.17 – 3.13 (m, 1H), 2.41 – 2.38 (m, 1H), 1.95 – 1.91 (m, 1H); ^{13}C NMR (150 M, $CDCl_3$) δ 174.7, 159.2, 129.5, 127.7, 114.1, 70.1, 55.2, 46.4, 42.8, 27.7; IR (KBr) 3416, 3322, 1669, 1442, 1317, 1247, 1111, 1032, 818, 729, 641 cm^{-1}; HRMS m/z ($M+Na)^+$ calcd for $C_{12}H_{15}NNaO_3$ 244.0944, found 244.0946.

4.4. (S)-1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl 4-nitrobenzene sulfonate (**12**)

Et_3N (25.20 mL, 0.18 mol), DMAP (387.0 mg, 3.16 mmol) and *p*-nitrobenzenesulfonyl chloride (26.05 g, 0.12 mol) were successively added to a solution of compound **11** (20.00 g, 0.09 mol) in anhydrous CH_2Cl_2 (300 mL) at °C under N_2. The reaction mixture was then warmed to room temperature and stirred for 30 minutes before it was quenched with a solution of saturated aqueous solution of NH_4Cl (100 mL) at °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 1:1) to give compound **12** (27.13 g, 85%) as pale yellow solid: mp 102 – 106 °C; $[\alpha]^{20}_D$ = – 20.9 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 M, $CDCl_3$) δ 8.42 – 8.40 (m, 2H), 8.25 – 8.23 (m, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.85 – 6.84 (m, 2H), 5.18 – 5.15 (m, 1H), 4.37 – 4.31 (m, 2H), 3.79 (s, 3H), 3.79 – 3.31 (m, 1H), 3.21 – 3.17 (m ,1H), 2.58 – 2.55 (m, 1H), 2.28 – 2.24 (m, 1H); ^{13}C NMR (150 M, $CDCl_3$) δ 167.0, 159.4, 150.8, 142.3, 129.6, 129.5, 126.9, 124.3, 114.2, 78.4, 55.3, 46.6, 42.8, 26.2; IR (KBr) 3449, 1709, 1610, 1533, 1513, 1460, 1352, 1304, 1247, 1186, 1095, 1032m 988, 958, 842, 741, 618, 554 cm^{-1}; HRMS m/z ($2M+Na)^+$ calcd for $C_{36}H_{36}N_4NaO_{14}S_2$ 835.1562, found 835.1550.

4.5. Dimethyl (S)-2-(1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl) malonate (**7**)

Potassium *tert*-butoxide (8.90 g, 0.079 mol) was added in small portions to a solution of dimethyl malonate (9.80 mL, 0.085 mol) in anhydrous THF (200 mL) at °C under N_2. The resulting suspension was stirred at this temperature for 1h before a solution of compound **12** (20.00 g, 0.057 mol) in anhydrous THF (100 mL) was added slowly over 0.5 h. The reaction was then warmed to room temperature and stirred for 24 h. This mixture was quenched with a solution of saturated aqueous solution of NH_4Cl (100 mL) at °C and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 1:1) to give compound **7** (15.19 g, 80%) as pale yellow oil: $[\alpha]^{20}_D$ = + 12.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.46 (d, *J* = 14.8 Hz, 1H), 4.33 (d, *J* = 14.8 Hz, 1H), 3.92 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 3.23 – 3.13 (m, 3H), 2.26 – 2.05 (m, 1H), 2.04 – 1.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 168.9,

168.2, 159.0, 129.4, 128.1, 113.9, 55.2, 52.7, 51.6, 46.2, 44.5, 41.7, 22.0; IR (KBr) 2965, 2871, 1738, 1676, 1513, 1462, 1438, 1247, 1176, 1088, 1048, 881, 810, 756 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{17}H_{21}NNaO_6$ 358.1261, found 358.1262. The ee value (98%) was determined by HPLC (AS-H, isopropanol : *n*-hexane = 40 : 60, flow rate 1.0 mL/min, λ = 254 nm), t_{major} = 8.89 min, t_{minor} = 11.65 min.

4.6. Methyl (S)-2-(1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl) acetate (**13**)

LiCl (1.38 g, 0.33 mol), H_2O (2 mL) was added to a solution of compound **7** (52.00 g, 0.155 mol) in DMSO (200 mL). The resulting mixture was refluxed for 2 h. This mixture was then cooled to room temperature and diluted with H_2O (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), brine (100 mL), dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 4:1) to give compound **13** (30. 98 g, 72%) as pale yellow oil: $[\alpha]^{20}_D$ = – 3.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.44 – 4.35 (m, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.21 – 3.17 (m, 2H), 2.96 – 2.86 (m, 2H), 2.44 (dd, *J* = 8.8 Hz, 16.0 Hz, 1H), 2.31 – 2.38 (m, 1H), 1.72 – 1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 172.5, 159.1, 129.5, 128.5, 114.0, 55.3, 51.7, 46.3, 44.6, 38.7, 35.5, 25.0; IR (KBr) 3454, 1736, 1681, 1513, 1439, 1247, 1175, 1111, 1031, 821, 579 cm^{-1} ; HRMS m/z $(M+Na)^+$ calcd for $C_{15}H_{19}NNaO_4$ 300.1206, found 300.1204.

4.7. 2-(2-nitrophenyl)propanal (**8**)

Methyl 2-(2-nitrophenyl)propanoate (18.00 g, 0.086 mol), which was prepared according to Hanna's procedure,[15] was dissolved in anhydrous toluene (200 mL) and cooled to –78 °C. A 1.5 M solution of DIBAL-H (57.10 mL, 0.086 mol) in toluene was dropwise added under N_2. The resulting solution was stirred at –78 °C for 2 h. Then the reaction was quenched with MeOH (20 mL) and saturated aqueous potassium sodium tartrate (50 mL) at –78 °C. This resulting suspension was warmed to room temperature, stirred for 0.5 h, diluted with EtOAc (100 mL) and filtered through Celite. The filtrate was extracted with with EtOAc (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 4:1) to give compound **8** (10.00 g, 65%) as pale yellow oil: ^{1}H NMR ($CDCl_3$, 400Hz) δ 9.77 (s, 1H), 7.99 – 8.01 (d, *J* = 8 Hz, 1H), 7.63 – 7.67 (m, 1H), 7.46 – 7.50 (m, 1H), 7.32-7.34 (d, *J* = 8.0 Hz, 1H), 4.27 – 4.29 (dd, *J* = 14.4 Hz, 7.2 Hz, 1H), 1.59 – 1.61 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 194.4, 128.6, 128.3, 125.4, 123.5, 120.2, 43.3, 9.5; IR (neat) 2950，1730，1521，1346，1206，1061，851，786，744，704，674，591 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_9H_9NNaO_3$ 202.0475, found 202.0475.

4.8. Methyl 3-hydroxy-2-((S)-1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl)-4-(2-nitrophenyl)pentanoate (**14**)

Compound **13** (20.00 g, 0.072 mol) was dissolved in anhydrous THF (200 mL) and cooled to –78 °C. A 1M solution of LHMDS in THF (76.0 mL, 0.076 mol) was added dropwise under N_2 and the resulting mixture was maintained at –78 °C for 1 h. Then a solution of aldehyde **8** (14.21 g, 0.792 mol) in anhydrous THF (100 mL) was slowly added. After stirring for 3 h, the reaction was quenched with a solution of a saturated aqueous NH_4Cl (200 mL) at –78 °C and warmed to room temperature. This mixture was diluted with EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 3:1) to give **14** (30.29 g, 92%) as pale yellow oil, which was a mixture of isomers. The mixture of isomers were used in next step directly without further separation. Analytical samples of these isomers were obtained by preparative thin-layer chromatography. Isomer **14a**: pale yellow oil; $[\alpha]^{20}_D$ = – 29.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.36 – 7.33 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2 H), 6.10 (d, *J* = 8.4 Hz, 1H), 4.49 (d, *J* = 15.0 Hz, 1H), 4.46 – 4.43 (m, 1H), 4.38 (d, *J* = 14.4 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.37 – 3.35 (m, 1H), 3.24 – 3.22 (m, 2H), 2.93 (td, *J* = 9.0 Hz, 3.0 Hz, 1H), 2.62 (t, *J* = 3.6 Hz, 1H), 2.01 – 1.96 (m, 1H), 1.77 – 1.70 (m, 1H), 1.48 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 172.1, 158.1, 138.3, 132.6, 129.5, 128.9, 127.9, 127.2, 114.1, 74.9, 55.3, 52.1, 49.9, 46.5, 45.4, 39.8, 38.2, 23.3, 18.7; IR (neat) 3200, 2952, 1732, 1651, 1523, 1512, 1461, 1435, 1355, 1242, 1172, 1031, 853, 732 cm^{-1} ; HRMS m/z $(M+Na)^+$ calcd for $C_{24}H_{28}N_2NaO_7$ 479.1789, found 479.1793. Isomer **14b**: pale yellow oil; $[\alpha]^{20}_D$ = – 24.0 (*c* 0.05, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.68 (d, *J* = 4.8 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 4.34 (d, *J* = 14.4 Hz, 1H), 4.08 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.60 – 3.57 (m, 1H), 3.20 – 3.14 (m, 2H), 2.73 – 2.69 (m ,1H), 2.33 (d, *J* = 5.4 Hz, 1H), 2.01 – 1.99 (m, 1H), 1.64 – 1.60 (m, 1H), 1.50 (d, *J* = 7.2 Hz, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 171.7, 159.1, 150.4, 139.2, 132.7, 129.5, 128.2, 128.0, 127.1, 124.5, 114.0, 55.2, 51.6, 49.2, 46.4, 44.8, 44.6, 38.8, 23.5, 20.0; IR (neat) 3200, 2952, 1732, 1651, 1523, 1512, 1461, 1435, 1355, 1242, 1172, 1031, 853, 732 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{24}H_{28}N_2NaO_7$ 479.1789, found 479.1786.

*4.9. Methyl 2-(hydroxymethyl)-2-((S)-1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl)-4-(2-nitrophenyl)-3-oxopentanoate (**15**)*

The aforementioned mixture (**14**, 30.00 g, 0.066 mol) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. Dess-Martin periodinane (41.81 g, 0.098 mol) was added in small portions and the suspension was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL).The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 2:1) to give *β*-ketoester (28.47 g, 95%) as pale yellow foam, which was a mixture of inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 – 7.79 (m, 1H), 7.54 – 7.48 (m, 1H), 7.38 – 7.33 (m, 1.5H), 7.26 – 7.24 (m, 0.3 H), 7.09 – 7.07 (m, 2H), 6.79 – 6.75 (m, 2H), 4.68 – 4.61 (m, 0.5 H), 4.53 – 4.50 (m, 0.4 H), 4.35 – 4.19 (m, 2H), 4.09 – 4.01 (m, 0.4 H), 3.96 (d, *J* = 12.0 Hz, 0.3 H), 3.85 (d, *J* = 10.8 Hz, 0.3 H), 3.69 – 3.62 (m, 4H), 3.55 (s, 0.6 H), 3.52 (s, 0.4 H), 3.36 (s, 1H), 3.29 – 3.26 (m, 0.3 H), 3.14 – 3.04 (m, 2.5H), 2.10 – 2.07 (m, 1H), 1.74 – 1.72 (m, 1H), 1.52 – 1.46 (m, 2H), 1.39 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.9, 202.8, 202.6, 202.0, 173.3, 173.2, 168.9, 168.5, 167.9, 159.1, 159.0, 149.6, 149.3, 149.2, 134.2, 134.1, 133.9, 133.8, 133.4, 133.0, 132.9, 130.5, 130.4, 130.2, 130.1, 129.4, 129.3, 128.5, 128.4, 128.3, 128.2, 128.1, 124.9, 124.8, 124.7, 124.6, 114.0, 113.9, 60.3, 57.3, 57.2, 56.1, 55.2, 53.6, 52.6, 52.4, 52.1, 48.3, 47.3, 47.2, 46.6, 46.1, 44.7, 44.6, 44.5, 43.2, 42.2, 41.8, 41.3, 25.7, 22.8, 22.4, 22.3, 21.7, 20.9, 17.9, 17.6, 17.5, 14.1; IR (neat) 2953, 1720, 1678, 1523, 1511, 1435, 1344, 1242, 1173,

1032, 788, 724, 701, 525 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{24}H_{26}N_2NaO_7$ 477.1632, found 477.1631.

The above *β*-ketoester (20.00 g, 0.044 mol) was dissolved in THF (200 mL) and cooled to 0 °C. DBU (1.32 mL, 8.81 mmol) was added and the resulting solution was stirred at 0 °C for 15 minutes before a solution of 37% aqueous HCHO (37.00 mL, 0.44 mol) was added. After 1h, this reaction mixture was quenched with saturated aqueous $CuSO_4$ (100 mL) and diluted with EtOAc (100 mL).The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 1:1) to give **15** (19.61 g, 92%) as pale yellow oil, which was a mixture of isomers. The mixture of isomers were used in next step directly without further separation. Analytical samples of the major isomers was obtained by preparative thin-layer chromatography. **Inseparable isomers A**: pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 – 7.89 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.53 (m, 3H), 7.46 – 7.41 (m, 4H), 7.37 – 7.30 (m, 2H), 7.26 – 7.23 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 4H) , 6.91 – 6.84 (m, 6H), 6.11 (d, *J* = 9.6 Hz, 1H), 4.84 (q, *J* = 6.8 Hz, 1H), 4.75 (q, *J* = 6.8 Hz, 1H), 4.60 (q, *J* = 6.8 Hz, 1H), 4.48 – 4.36 (m, 8H), 4.32 – 4.28 (m, 2H), 4.22 – 4.19 (m, 1H), 4.04 (d, *J* = 8.8 Hz, 1H), 3.94 (d, *J* = 6.8 Hz), 3.82 (s, 3H), 3.79 (s, 6H), 3.76 (s, 3H), 3.45 (s, 3H), 3.40 (s, 3H), 3.36 – 3.29 (m, 2H), 3.23-3.08 (m, 6H), 2.97 (t, *J* = 9.6 Hz, 1H), 2.24 – 2.11 (m, 2H), 1.86 – 1.72 (m, 4H), 1.60 – 1.56 (m, 6H), 1.47 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.0, 202.8, 202.2, 174.6, 173.3, 173.3, 169.8, 169.1, 167.9, 159.2, 159.1, 159.0, 149.6, 149.3, 149.0, 135.9, 134.2, 133.9, 133.4, 132.9, 132.5, 130.6, 130.2, 129.5, 129.4, 129.3, 128.4, 128.2, 128.1, 127.8, 127.2, 114.1, 114.0, 67.5, 66.7, 57.3, 56.8, 55.3, 52.8, 52.4, 52.3, 48.6, 48.2, 46.6, 46.2, 45.1, 44.7, 44.6, 43.2, 42.0, 41.8, 29.7, 22.8, 22.3, 22.1, 21.4, 18.0, 17.7; IR (neat) 2952, 1683, 1524, 1512, 1458, 1351, 1243, 1175, 1030, 732, 701 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{25}H_{28}N_2NaO_8$ 507.1738, found 507.1739. **Inseparable isomers B**: pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H), 7.54 – 7.53 (m, 4H), 7.39 – 7.34 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.91 – 4.84 (m, 2H), 4.53 – 4.48 (m, 2H), 4.40 – 4.37 (m, 1H), 4.29 – 4.21 (m, 3H), 3.99 – 3.89 (m, 4H), 3.81 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 3.41 (m, 1H), 3.37 (s, 3H), 3.33 – 3.13 (m, 6H), 2.01 – 1.85 (m, 4H), 1.58 – 1.54 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.2, 205.8, 173.9, 173.8, 170.8, 169.7, 159.1, 149.0, 148.9, 134.2, 132.8, 132.6, 129.6, 129.5, 129.4, 129.3, 128.0, 127.9, 127.6, 124.8, 124.6, 114.0, 67.6, 66.8, 65.3, 64.4, 55.3, 52.7, 52.5, 48.1, 56.3, 46.2, 46.0, 44.9, 44.8, 44.2, 43.5, 21.7, 21.6, 20.8, 20.6; IR (neat) 2953, 1683, 1524, 1512, 1458, 1351, 1300, 1243, 1175, 1059, 1030, 786, 730, , 700 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{25}H_{28}N_2NaO_8$ 507.1738, found 507.1736.

4.10. Methyl 3-hydroxy-2-(3-methyl-1H-indol-2-yl)-2-((S)-2-oxopyrrolidin-3-yl)propanoate (**16**)

Ceric ammonium nitrate (36.18 g, 0.066 mmol) was added in small portions to a solution of compound **15** (16.00 g, 0.033 mol) in CH_3CN/H_2O (200 mL, v/v = 3:1) at 0 °C. The resulting solution was stirred at 0 °C for 3 h. This reaction mixture was then quenched by saturated aqueous $Na_2S_2O_3$ (100 mL) and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered through a silica gel pad, and concentrated *in vacuo*. The residue was directly dissolved in MeOH (200 mL) and $Pd(OH)_2/C$ (2.00 g, 20% Pd on carbon, wet) was added. The reaction mixture was stirred in a pressure vessel under hydrogen (250 psi) for 36 h at room temperature. Then the mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 1:1) to give **16** (6.75 g, 63% from **15**) as a pair of diastereomers, which were used directly in next step without further separation. The analytical samples of the two isomers **16a** and **16b** were obtained by preparative thin-layer chromatography. **Minor isomer 16a**: pale yellow foam. $[\alpha]^{20}_D$ = –51.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.66 (brs, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 7.8 Hz, 1H), 7.09 (t, *J* = 8.4 Hz, 7.2 Hz, 1H), 5.85 (brs, 1H), 4.35 (q, *J* = 6.0 Hz, 1H), 4.27 (brs, 1H), 4.27 – 4.23 (m, 1H), 3.81 (s, 3H), 3.59 – 3.56 (m, 1H), 3.37 – 3.32 (m, 2H), 2.30 – 2.26 (m, 1H), 2.24 (s, 3H), 2.11 – 2.04 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) 178.2, 173.0, 135.1, 132.3, 128.8, 122.1, 119.1, 118.3, 111.0, 107.4, 66.8, 55.1, 52.6, 45.5, 40.6, 24.7, 9.1; IR (KBr) 3385, 2952, 1732, 1678, 1460, 1435, 1385, 1333, 1238, 1047, 742 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{17}H_{20}N_2NaO_4$ 339.1315, found 339.1317. **Major isomer 16b**: pale yellow foam. $[\alpha]^{20}_D$ = +23.0 (*c* 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (brs, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 7.2 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 7.6 Hz, 1H), 5.59 (brs, 1H), 5.23 (brs, 1H), 4.66 – 4.63 (m, 1H), 4.30 – 4.27 (m, 1H), 3.81 (s, 3H), 3.64 (t, *J* = 8.8 Hz, 1H), 3.29 – 3.26 (m, 1H), 3.04 – 3.02 (m, 1H), 2.53 – 2.50 (m, 1H), 2.24 (s, 3H), 2.08 – 2.02 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 173.4, 134.9, 129.9, 128.7, 122.2, 119.1, 118.3, 111.1, 109.3, 66.8, 54.0, 52.8, 46.1, 40.5, 24.8, 9.7; IR (KBr) 3385, 2952, 1732, 1678, 1460, 1435, 1385, 1333, 1238, 1047, 742 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{17}H_{20}N_2NaO_4$ 339.1315, found 339.1317.

*4.11. (S)-3-(2,2-dimethyl-5-(3-methyl-1H-indol-2-yl)-1,3-dioxan-5-yl)pyrrolidin-2-one (**6**)*

The mixture (6.00 g, 0.019 mol) of **16a** and **16b** was dissolved in anhydrous CH_2Cl_2 (300 mL) and cooled to 0 °C. A solution of 1.5 M DIBAL-H (75 mL, 0.11 mol) in toluene was dropwise added under N_2. The resulting solution was stirred at 0 °C for 4h. Then the reaction was quenched with MeOH (30 mL) and saturated aqueous potassium sodium tartrate (100 mL) at 0 °C. This resulting suspension was stirred for 0.5 h, diluted with CH_2Cl_2 (100 mL) and filtered through Celite. The filtrate was extracted with with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2 to give diol (2.50 g) as white solid. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 1:3) to give diol (1.50 g) and the starting material (1.00 g). The two portions of diol (4.00 g, 65%, brsm 88%) was combined. Diol: mp 185 – 189 °C; $[\alpha]^{20}_D$ = –57.3 (*c* 0.3, $CHCl_3$) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (brs, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.31 (*J* = 7.6 Hz, 1H), 7.16 (t, *J* = 6.8 Hz, 8.0 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 7.2 Hz, 1H), 5.87 (brs, 1H), 4.99 – 4.98 (m, 1H), 4.40 (d, *J* = 4.4 Hz, 1H), 4.25 – 4.18 (m, 2H), 4.10 – 4.05 (m, 1H), 3.43 – 3.25 (m, 4H), 2.39 (s, 3H), 2.18 – 2.05 (m ,1H), 1.94 – 1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1679.4, 135.0, 134.4, 129.4, 121.8, 119.0, 117.9, 110.9, 107.2, 67.3, 63.9, 48.2, 46.8, 40.9, 24.7, 10.2; IR (KBr) 3374, 2950, 1667,1462, 1332, 1294, 1050, 743 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{16}H_{20}N_2NaO_3$ 311.1366, found 339.1366.

The above diol (2.50 g, 8.67 mmol) was dissolved in anhydrous THF (100 mL). 2, 2-dimethyoxypropane (8.51 mL, 69.36 mmol) and *p*-TsOH (149.3 mg, 0.87 mmol) was added successively. The resulting mixture was heated to reflux for 5 h and quenched with saturated aqueous $NaHCO_3$ (100 mL) at 0 °C.

The suspension was diluted with H_2O (5 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 2:1) give compound **6** (2.53 g, 89%) as white foam: $[\alpha]^{20}_D$ = –32.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (brs, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.4Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 5.48 (brs, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 4.39 (s, 2H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.58 (dd, *J* = 11.8 Hz, 8.4 Hz, 1H), 3.30 – 3.28 (m, 1H), 3.10 (t, *J* = 9.2 Hz, 1H), 2.37 – 2.34 (m, 4H), 1.88 – 1.83 (m, 1H), 1.50 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 180.1, 135.2, 131.6. 128.9, 121.7, 118.7, 117.8, 110.8, 108.3, 98.1, 65.9, 64.3, 41.8, 41.7, 39.6, 27.3, 23.6, 20.2, 10.0; IR (neat) 3300, 2923, 1676, 1459, 1372, 1257, 1197, 1091, 834, 732, 701, 522 cm^{-1} ; HRMS m/z $(M+Na)^+$ calcd for $C_{19}H_{24}N_2NaO_3$ 351,1679, found 351.1678.

4.12. (S)-2-(2,2-dimethyl-5-(2-oxopyrrolidin-3-yl)-1,3-dioxan-5-yl)-1H-indole-3-carbaldehyde (**17**)

DDQ (64.0 mg, 2.80 mmol) was added in small portions to a solution of compound **6** (460.0 mg, 1.40 mmol) in DCM/H_2O (42 mL, v/v = 20 : 1) at 0 °C. The resulting dark green solution was warmed to room temperature and stirred for 5h. This reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), bine (30 mL)), dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 1:1) give compound **17** (316.0 mg, 66%) as pale yellow foam. $[\alpha]^{20}_D$ = –77.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 10.08 (brs, 1H), 8.22 – 8.20 (m, 1H), 7.42 – 7.40 (m, 1H), 7.36 – 7.27 (m, 2H), 5.88 (brs, 1H), 4.84 – 4.81 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 3.89 – 3.84 (m, 1H), 3.31 – 3.24 (m, 1H), 3.17 (t, *J* = 9.6 Hz, 1H), 2.21 – 2.14 (m, 1H), 1.80 – 1.72 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 178.1, 147.4, 134,7, 127.8, 123.6, 122.7, 120.0, 115.0, 111.5, 99.0, 65.3, 63.9, 42.0, 41.8, 39.6, 25.3, 24.1, 22.5; IR (neat) 3285, 2924, 1683，1636，1455, 1374，1264, 1198，830, 734, 667 cm^{-1}; HRMS m/z $(M+Na)^+$ calcd for $C_{19}H_{22}N_2NaO_4$ 365.1472, found 365.1471.

4.16. Benzyl (S)-3-(5-(3-formyl-1H-indol-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl)-2-oxopyrrolidine-1-carboxylate (**18**).

NaH (47.0 mg, 0.17 mmol, 60% in mineral oil) was added in small portions to a solution of compound xx in anhydrous THF (15 mL) at 0 °C. The resulting suspension was stirred at this temperature for 1h before CbzCl (0.2 mL, 1.40 mmol) was added dropwise. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 4:1) to give compound **18** (181.0 mg, 81%) as pale yellow oil: $[\alpha]^{20}_D$ = –37.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.3 (s, 1H), 9.95 (brs, 1H), 8.09 – 8.07 (m, 1H), 7.43 – 7.39 (m, 1H), 7.38 – 7.26 (m, 8H), 5.28 – 5.21 (m, 2H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.6 Hz, 1H), 4.35 – 4.26 (m, 3H), 3.74 (t, *J* = 10.2 Hz, 1H), 3.59 – 3.55 (m, 1H), 2.04 – 2.02 (m, 1H), 1.68 – 1.63 (m, 1H), 1.58 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.8, 173.7， 151.0, 147.2，135.0, 134.4，128.6， 128.5， 128.4， 128.3， 123.6， 122.7，118.8，113.6，111.7，64.1，63.1，43.9，43.8，41.3，26.5，21.2，20.8；IR (neat) 3280，2920，1779，1718，1646，1444，1374，1285，1197，829，728，697 cm^{-1} ; HRMS m/z $(M+Na)^+$ calcd for $C_{27}H_{28}N_2NaO_6$ 499.1840, found 499.1836.

4.17. (S)-4-(((benzyloxy)carbonyl)amino)-2-(5-(3-formyl-1H-indol-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl)butanoic acid (**19**).

A 1M solution of aqueous NaOH (0.57 mL, 0.57 mmol) was added to a solution of compound 24 (136.0 mg, 0.29 mmol) in THF (10 mL). After stirring at room temperature for 1 h, the reaction was cooled to 0 °C, and a 10% aqueous solution of citric acid was added to adjust the pH value to 6. This mixture was diluted with H_2O (3 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH = 10:1) to give compound **19** as colorless oil. $[\alpha]^{20}_D$ = –2.5 (*c* 0.2, CH_3OH);^{1}H NMR(600 M, CD_3OD): δ 10.33 (s, 1H), 7.18 (d, *J* = 5.6 Hz, 1H), 7.29 – 7.28 (m, 1H), 7.26 – 7.17 (m, 7H), 4.96 (s, 2H), 4.64 (d, *J* = 12.8 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.42 – 4.36 (m, 2H), 3.13 – 2.95 (m, 2H), 2.93 – 2.92 (m, 1H), 2.07 – 2.02 (m, 1H), 1.68 – 1.59 (m, 2H), 1.48 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) 187.0，176.3，158.7，150.9，138.3，136.6, 129.4, 128.9, 128.7, 124.3, 123.6, 120.8, 115.0, 112.9, 100.1, 67.4, 66.6, 64.7, 44.6, 40.3, 28.9, 27.4, 20.7; IR (neat) 3343, 2486, 1699, 1634, 1455, 1396, 1199, 1115, 970 cm^{-1} ; HRMS m/z $(M+Na)^+$ calcd for $C_{27}H_{30}N_2NaO_7$ 517.1945, found 517.1942.

4.18. Benzyl (S)-5-(hydroxymethyl)-2',2'-dimethyl-1,4,5,7-tetrahydrospiro[azocino[4,3-b]indole-6,5'-[1,3]dioxane]-2(3H)-carboxylate (**5**).

A mixture of compound **19** (90.0 mg, 0.18 mmol)) and Pd/C (10% Pd on carbon, wet, 50 mg) in MeOH (5 mL) was stirred at room temperature under 1.0 atm pressure of H_2 for 0.5 h. Then the mixture was filtered through Celite and the filtrate was concentrated *in vacuo.* The residue was dissolved in MeOH (10 mL), and 3 Å molecular sieves (200 mg) was added. The resulting suspension was heated to reflux overnight before it was cooled to room temperature and filtered. Then this filtrate was cooled to 0 °C. $NaBH_4$ (7.0 mg, 0.18 mmol) was added slowly. After stirring at 0 °C for 0.5 h, DIPEA (95.0 μL, 0.55 mol), CbzCl (62.0 μL, 0.44 mol) was added successively. The resulting mixture was stirred for 1 h and concentrated *in vacuo.* This residue was diluted with H_2O (5 mL) and EtOAc (5mL). Then a 10% aqueous solution of citric acid was added to adjust the pH value to 6. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The resulting crude acid was directly dissolved in anhydrous THF (10 mL), borane dimethyl sulfide complex (0.10 mL, 1.09 mmol) was added dropwise under N_2 at room temperature. The resulting mixture was stirred at 35 °C for 10 h before it was quenched with saturated aqueous NH_4Cl (5 mL) at °C. This suspension was diluted with H_2O (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 2:1) to give compound **5** (42.0 mg, 50% from **19**) as pale yellow foam: $[\alpha]^{20}_D$ = +152.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, two rotamers) δ 9.31 (s, 1H), 9.29 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.31 (m, 10 H), 7.19 – 7.13 (m,

3H), 7.03 (m, 1H), 5.23 – 5.19 (m, 2H), 5.15 – 5.12 (m, 2H), 5.06 (d, *J* = 15.6 Hz, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.63 (d, *J* = 15.0 Hz, 1H), 4.33 – 4.28 (m, 2H), 4.17 –4.09 (m, 5H), 3.97 – 3.90 (m, 4H), 3.70 (m, 2H), 3.58 – 3.55 (m, 2H), 3.30 (m, 1H), 3.10 (m, 1H), 2.49 (m, 2H), 2.40 (m, 1H), 2.20 (m, 1H), 1.86 (m, 2H), 1.57 (m, 2H), 1.49 (d, *J* = 3.6 Hz, 6H), 1.46 (d, *J* = 3.6 Hz, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 155.9, 139.7, 139.5, 136.9, 136.8, 134.8, 134.7, 128.5, 128.2, 128.0, 127.9, 122.2, 122.1, 121.9, 119.7, 119.5, 118.9, 118.3, 118.0, 110.9, 110.6, 106.9, 106.4, 100.2, 100.1, 67.8, 67.7, 67.3, 67.1, 66.0, 65.2, 64.7, 64.5, 64.4, 64.3, 43.2, 43.1, 43.0, 42.1, 41.7, 41.6, 39.5, 29.7, 28.4, 27.7, 25.3, 24.9, 22.5, 22.1 ppm. IR (neat) 3396， 2938， 1668， 1456， 1418， 1372， 1254， 1196， 1167， 1027， 832， 731， 697， 609， 522 cm^{-1} ; HRMS m/z $(M+Na)^+$ calcd for $C_{27}H_{32}N_2NaO_5$ 487.2203, found 487.2200.

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