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**PAPER**

# Total synthesis of (–)-indolactam V†

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The total synthesis of protein kinase C activator (–)-indolactam V (IL-V) has been successfully completed with two separate approaches: From known 4-nitrotryptophan derivative **3** in 8 steps (49% overall yield) and from L-glutamic acid in 12 steps (18% overall yield), where 4-nitrotryptophanol derivative **4** served as a key intermediate. Derivatives **3** and **4**, both incorporating indole 4-substitution and the C-9 stereocenter in IL-V, were synthesized *via* the Pd-catalyzed indole synthesis from 3-nitro-2-iodoaniline **5** with aldehydes **6** and **7**, respectively. Aldehyde 7 was, meanwhile, synthesized from L-glutamic acid in 5 steps (68% yield). Lactamization of the 9-membered ring was achieved using HATU in THF in good yield.

## Introduction

Teleocidins A and B (Fig. 1)[1] produced by actinomycetes are interesting indole alkaloids primarily because of their tumor-promoting activity, which involves binding and activating a group of kinase receptors including protein kinase C.[2] (–)-Indolactam V (IL-V)[3] (**1**), an active fragment of teleocidins, has long been considered a biosynthetic precursor to the teleocidin class.[4] Indolactam V was first synthesized and named by Shudo[5a] before its isolation from natural source *Streptoverticillium blastmyceticum*

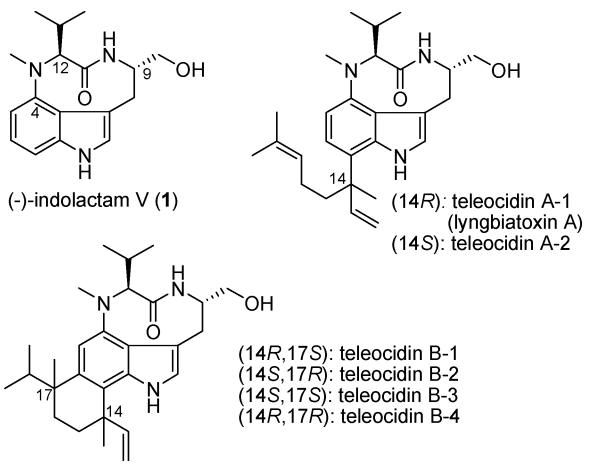


**Fig. 1** Structures of several naturally occurring teleocidins.

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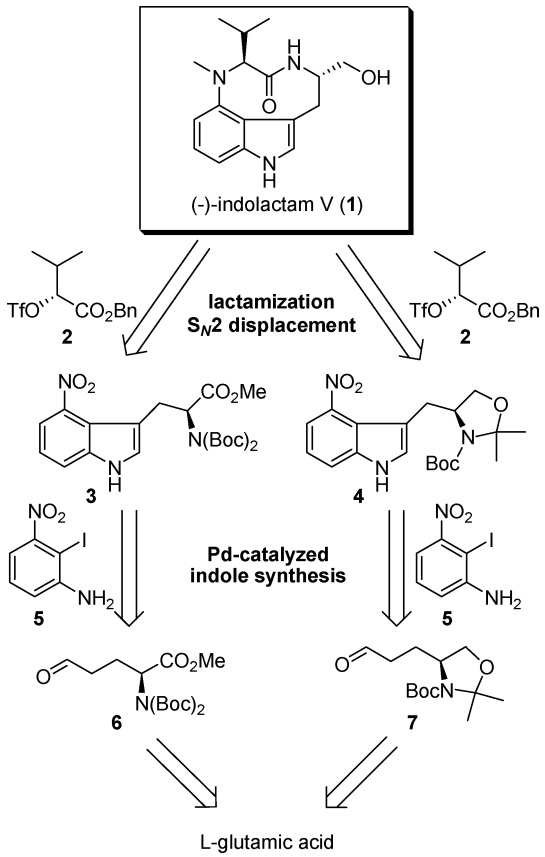
NA39-17. Due to the potent activity and peculiar structure involving a 9-membered lactam ring bridging the indole 3- and 4-positions, indolactam V has attracted much attention in the area of organic and medicinal chemistry.[5–9] Two general strategies are available in the literature for the synthesis of these 3,4-disubstituted indoles, one involves direct functionalization at the less reactive 4-position of an existing indole nucleus,[10] and the other resides in the application of a pre-existing 4-substituted indole, which is usually prepared by indole synthesis.[11] Generally, the major challenge in the synthesis of IL-V is how to construct optically pure 4-amino tryptophanol derivatives.

Recently, an appealing synthetic method for benzofunctionalized indoles, especially optically pure tryptophan derivatives, through a Pd-catalyzed reaction of *o*-haloanilines and aldehydes has been developed by Zhu and Jia, and since then it has already found applications in the synthesis of several natural products.[12–13] Taking advantage of such methodology for the assembly of 4-halotryptophan derivatives,[12i–k] we have recently reported the total synthesis of clavicipitic acid and aurantioclavine, both of which hold a 7-membered azapino[5,4,3-*cd*]-indole ring system. In order to further extend the substrate scope of the methodology and define its utilities in the total synthesis of natural products, as well as its potential applications in diversity-oriented synthesis (DOS),[14] we describe herein two separate approaches to the total synthesis of (–)-indolactam V from either known 4-nitrotryptophan derivative **3** or tryptophanol derivative **4**. Both **3** and **4** are optically pure and prepared *via* the Pd-catalyzed indole synthesis from 3-nitro-2-iodoaniline **5** and L-glutamic acid-derived aldehydes **6** and **7**, respectively.

## Results and discussion

Our retrosynthetic analysis of (–)-indolactam V is shown in Scheme 1, it was envisioned that IL-V could be achieved from either 4-nitrotryptophan derivative **3** or 4-nitrotryptophanol derivative **4** after the introduction of a valine moiety *via* $S_N2$ displacement

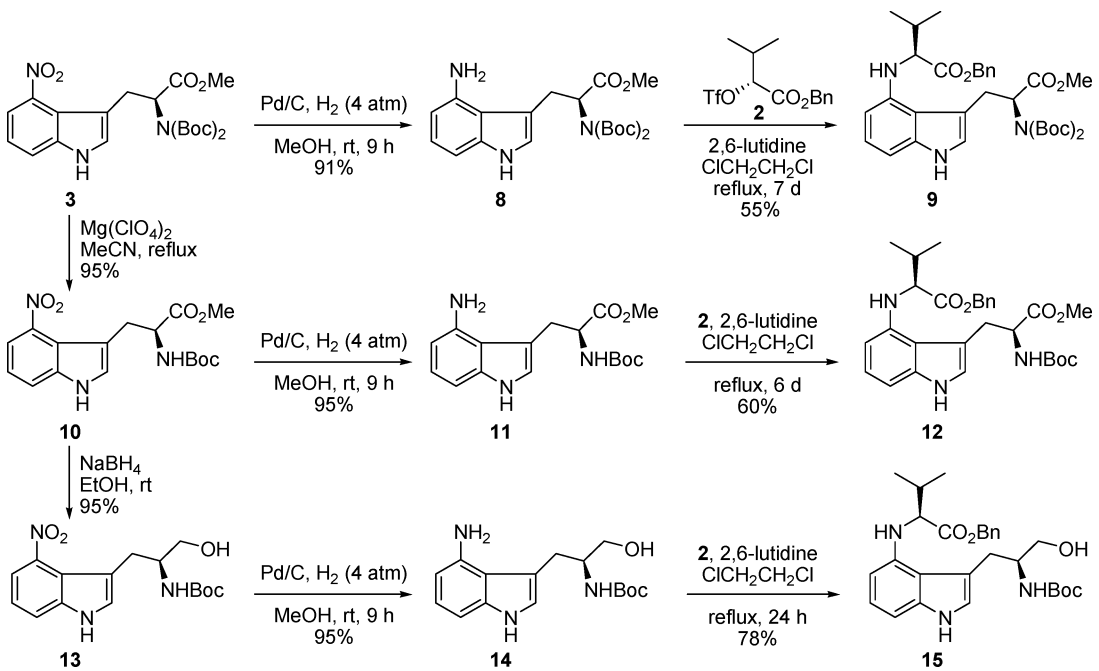
 




**Scheme 1** Retrosynthetic analysis of (–)-indolactam V.

with chiral triflate **2** based on literature precedent,[6f] followed by lactamization to form a 9-membered ring. 4-Nitrotryptophan derivative **3** has been prepared previously by our group *via* a new Pd-catalyzed indole synthesis method from 3-nitro-2-iodoaniline **5** and aldehyde **6**. Meanwhile, we envisioned that **4** could be transformed to IL-V in a more concise manner than that from **3**, by avoiding additional modifications after the indole synthesis, and **4** could also be synthesized by the same method from 3-nitro-2-iodoaniline **5** and aldehyde **7**. Chiral building block aldehydes **6** and **7** would be obtained from commercially available L-glutamic acid.

Our first-generation synthesis of (–)-indolactam V commenced with known 4-nitrotryptophan derivative **3** (Scheme 2).[12k] Attempts to reduce the nitro group with a zinc/acetic acid system only resulted in 4-aminotryptophan derivative **8** in low yield (30–40%), accompanied with a substantial amount of polymerized side products. To our delight, hydrogenation of **3** with Pd/C afforded **8** cleanly, in 91% isolated yield. However, the S$_N$2 displacement reaction of **8** with the chiral triflate **2** under the same conditions reported for a similar substrate by Kogan[6f] proceeded quite slowly, and afforded the desired product **9** in only 55% yield after refluxing for 7 days. We reasoned that the steric hindrance of the di-Boc protection at the nitrogen and methyl ester group might affect the rate of the reaction, and the relatively lower yield might be attributed to the decomposition of **8** or/and **9** under the refluxing conditions for such a long period. In order to make the S$_N$2 displacement reaction more efficient, we chose to reduce the steric hindrance of compound **3**. In this regard, selective partial deprotection of di-Boc with Mg(ClO$_4$)$_2$ afforded **10**, which upon NaBH$_4$ reduction of the methyl ester gave 4-nitrotryptophanol derivative **13**. Hydrogenation of the nitro group of **10** and **13** with Pd/C produced 4-aminotryptophan derivative **11** and 4-aminotryptophanol derivative **14**, respectively. Both **11** and **14** were subjected to the same S$_N$2 displacement reaction. The Boc group was found to have a limited effect on the reaction, as **12** could be obtained in 60% yield from **11** after refluxing for 6 days. On the other hand, 4-aminotryptophanol derivative




**Scheme 2** S$_N$2 displacement reaction for the introduction of a valine moiety.

**14** could be transformed to **15** in 78% yield after refluxing for 24 h.

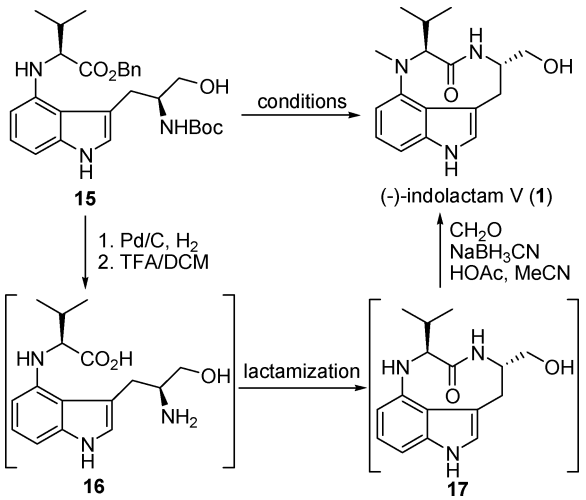
With the 4-valine substituted tryptophanol derivative **15** in hand, initial attempts to remove both the benzyl ester and Boc group in a one-pot manner by hydrogenation with Pd/C in acid solution (trifluoroacetic acid[15a] or camphorsulfonic acid[6f]) were, however, unsuccessful, and only trace amount of des-*N*-methylindolactam V **17** was detected after lactam formation with HATU in DMF. On the contrary, hydrogenation of **15** with Pd/C in ethanol followed by TFA/$CH_2Cl_2$ (1 : 5) treatment in a step-by-step manner smoothly afforded **16**, which was subsequently used in the next lactamization step after the solvent being removed without further purification. It was noteworthy that relatively dilute concentrations of both the substrate and TFA were important in the Boc-deprotection step, and the yield would otherwise be diminished after lactamization.

Lactamization of the crude known compound **16**[6f] using either HATU (Table 1, entry 1) or HBTU/HOBt (Table 1, entry 2) in DMF in the presence of the Hünig's base followed by reductive methylation using formaldehyde/cyanoborohydride in acetonitrile in the presence of acetic acid afforded IL-V in moderate 50% and 55% yield, respectively. More satisfactory results were obtained when the solvent was switched to THF (Table 1, entries 3 and 4), and the yield of IL-V could reach as high as 73% by using HATU throughout this 4-step operation. This represents one key improvement in the synthesis of IL-V.

Although the conversion of **3** to (–)-indolactam V could be successfully achieved, several functional group transformations from tryptophan derivative **3** were required. In order to streamline the synthesis and improve the efficiency of the synthesis, we envisioned that the 4-nitrotryptophanol derivative **4** could be directly synthesized *via* the Pd-catalyzed indole synthesis from 3-nitro-2-iodoaniline **5** and properly protected aldehyde **7** (Scheme 3).

The known aldehyde **7** prepared either from Garner's aldehyde[15] or L-glutamic acid[16] has been reported; however, these approaches have several disadvantages. In total 4 steps are required to convert Garner's aldehyde to **7** in less than 39% overall yield, while environmentally unfriendly Wittig reagents as well as expensive Pd/C and DIBAL-H are employed.[15b] Although the synthesis of **7** from L-glutamic acid derivative has been reported,[16] it includes a few unnecessary functional group transformations, and there is still room for improvement to streamline the synthesis in larger quantities.

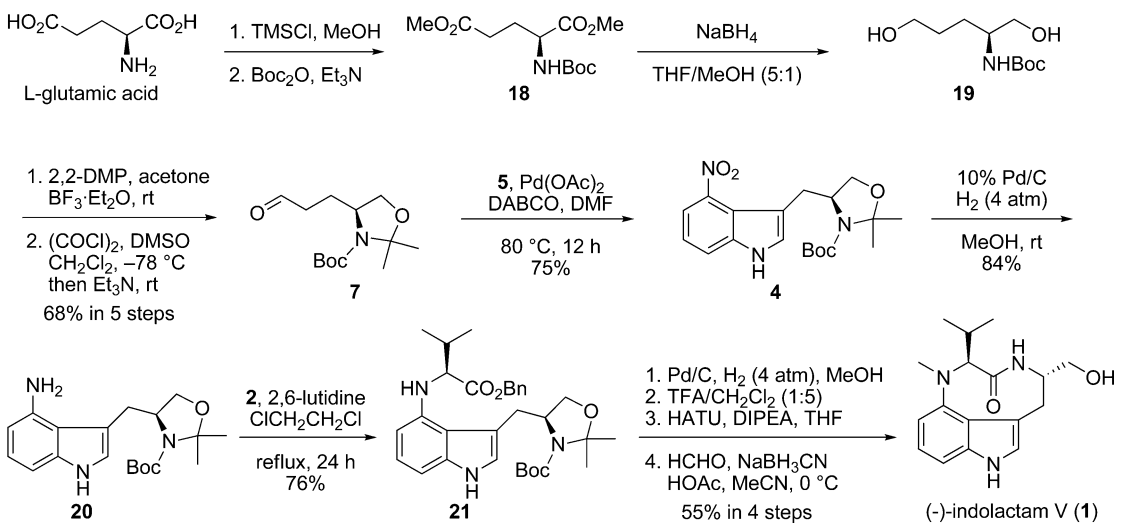
**Table 1** Reaction conditions for 9-membered lactam formation




| Entry | Conditions[a,b] | Yield[c] |
|---|---|---|
| 1 | HATU, DIPEA, DMF | 50% |
| 2 | HBTU, HOBt, DIPEA, DMF | 55% |
| 3 | HATU, DIPEA, THF | 73% |
| 4 | HBTU, HOBt, DIPEA, THF | 70% |

[a] Stirred at room temperature under argon atmosphere for 48 h in a concentration of 0.034 M (based on **15**). [b] Other conditions are identical. [c] Overall isolated yield of IL-V in 4 steps. HATU: 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. HBTU: 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. HOBt: *N*-hydroxybenzotrizole. DIPEA: *N*,*N*-diisopropylethylamine

Our modified synthetic route to **7** is summarized in Scheme 3. Treatment of L-glutamic acid with TMSCl in dry methanol, followed by Boc protection with $Boc_2O/Et_3N$ afforded *N*-Boc-glutamic dimethyl ester **18**. Reduction of the two methyl esters




**Scheme 3** Total synthesis of (–)-indolactam V from L-glutamic acid.

of **18** to give diol-**19** was effected by $NaBH_4$ in THF/MeOH (5 : 1), which is easier to manipulate compared with the $CaCl_2$-containing system.[16a] Protecting the amino alcohol **19** with 2,2-dimethoxypropane in the presence of catalytic amount of $BF_3{\cdot}Et_2O$ followed by the Swern oxidation afforded the desired aldehyde **7**. The new route for the synthesis of **7** consists merely of 5 steps (68% overall yield), and requires only two column chromatography purifications.

Reaction of **7** with 3-nitro-2-iodoaniline **5** under the same Pd-catalyzed indole synthesis conditions provided the desired 4-nitrotryptophanol derivative **4** in 75% yield. Hydrogenation of the nitro group followed by $S_N2$ displacement with chiral triflate **2** afforded 4-valine substituted tryptophanol derivative **21** smoothly, which could be transformed to (–)-IL-V following the same sequence described for **15** in 55% overall yield (not optimized). The NMR spectra and optical rotation of our synthesized (–)-IL-V are in full accord with those reported in an isolation paper.[3]

## Conclusions

In conclusion, we have successfully completed the total synthesis of (–)-indolactam V either from the known 4-nitrotryptophan derivative **3** in 8 steps (49% overall yield) or from L-glutamic acid in 12 steps (18% overall yield). Our synthesis features not only Pd-catalyzed 4-nitrotryptophan and 4-nitrotryptophanol synthesis to incorporate both indole 4-substitution and a C-9 stereocenter in IL-V, an improvement for lactamization, but also short, efficient synthesis of aldehyde **7**. The practical aspects of our synthetic strategy enables gram-scale preparation of (–)-IL-V.

## Experimental

Flash chromatography was performed using silica gel from Qingdao Mar. Chem. Ind. Co. Ltd. (200–300 mesh). Thin layer chromatography was performed with TLC plates from Merck (60 $F_{254}$) using phosphomolybdic acid solution for visualisation. Melting points are uncorrected. Infrared spectra were recorded on Thermo Nicolet Nexus-470 FT-IR spectrometers. Mass spectra were recorded on a Bruker APEX IV FT-MS (ESI spectrometer. NMR spectra were recorded on JEOL JNM-AL 300 MHz spectrometer and Bruker Avance III 400 MHz spectrometer. Chemical shifts $\delta$ are reported in ppm with the deuterated solvent as internal standard.

***N*,*N*-Di-Boc-4-aminotryptophan derivative 8.** 10% Palladium on carbon (10 mg) was added to a solution of 4-nitrotryptophan derivative **3** (156 mg) in methanol (2.0 mL), and the mixture was hydrogenolyzed at 4 atm hydrogen for 9 h, at which point TLC indicated complete reaction (PE-EtOAc, 3 : 2). Purification with FCC (PE-EtOAc, 2 : 1) afforded the desired 4-aminotryptophan derivative **8** (133 mg, 91%) as white foam. $[\alpha]_D^{23}$ –89 (*c* 2.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3355, 2979, 1782, 1738, 1366, 1281, 1139, 1094, 850, 736; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.55 (1H, br s), 6.90 (1H, t, *J* = 8.0 Hz), 6.80 (1H, s), 6.79 (1H, d, *J* = 8.0 Hz), 6.29 (1H, d, *J* = 8.0 Hz), 5.40 (1H, dd, *J* = 4.0, 10.0 Hz), 4.02 (2H, br s), 3.76 (3H, s), 3.74 (1H, dd, *J* = 4.0, 15.2 Hz), 3.37 (1H, dd, *J* = 10.0, 15.2 Hz), 1.27 (18H, s); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.1, 151.5, 140.6, 138.2, 122.7, 122.5, 116.5, 110.5, 105.4, 102.9, 83.0, 60.3, 52.1, 28.0, 27.5; HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{32}N_3O_6$: 434.2286; found: 434.2296.

**Compound 9.** A solution of 4-aminotryptophan derivative **8** (128 mg), (*R*)-2-((trifluoromethylsulfonyl)oxy)-3-methylbutanoic acid phenyl methyl ester **2** (106 mg) and 2,6-lutidine (35 mg) in 1,2-dichloroethane (2.0 mL) was stirred and heated at 70 °C for 7 days until the starting material was consumed. Purification with FCC (PE-EtOAc, 2 : 1) afforded compound **9** (101 mg, 55%) as colorless oil. $[\alpha]_D^{23}$ –61 (*c* 2.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3351, 2974, 1785, 1738, 1514, 1369, 1283, 1140, 1094, 851, 780, 731; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.56 (1H, br s), 7.31–7.38 (5H, m), 6.93 (1H, t, *J* = 7.6 Hz), 6.76–6.78 (2H, m), 6.17 (1H, d, *J* = 7.6 Hz), 5.44 (1H, dd, *J* = 2.8, 10.8 Hz), 5.21 (1H, d, *J* = 12.4 Hz), 5.10 (1H, d, *J* = 12.4 Hz), 4.89 (1H, d, *J* = 8.4 Hz), 4.05 (1H, dd, *J* = 6.0, 8.0 Hz), 3.93 (1H, dd, *J* = 2.8, 15.6 Hz), 3.76 (3H, s), 3.43 (1H, dd, *J* = 11.2, 15.6 Hz), 2.20–2.28 (1H, m), 1.22 (18H, s), 1.09 (1H, d, *J* = 6.8 Hz), 1.02 (1H, d, *J* = 6.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.6, 170.9, 151.2, 141.8, 138.1, 135.7, 128.5, 128.3, 128.2, 123.1, 122.0, 115.5, 110.5, 102.4, 100.0, 82.9, 66.4, 62.0, 59.9, 52.1, 31.6, 28.2, 27.5, 19.0, 18.7; HRMS (ESI): *m*/*z* calcd. for $C_{34}H_{46}N_3O_8$: 624.3279; found: 624.3277.

***N*-Boc-4-nitrotryptophan derivative 10.** To a stirring solution of **3** (156 mg) in acetonitrile was added $Mg(ClO_4)_2$ (4 mg), and the reaction mixture was heated at 90 °C for 20 min. After the solvent being removed *in vacuo*, the residue was purified with FCC ($CH_2Cl_2$-MeOH, 20 : 1) to give **10** (116 mg, 95%) as a yellowish foam. $[\alpha]_D^{23}$ +47.8 (*c* 1.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3368, 2978, 1693, 1518, 1366, 1323, 1166, 1055, 788, 734; $^1$H NMR (300 MHz, $CDCl_3$) showed the presence of two rotamers in a ratio of 3.3/1, major rotamer shown: $\delta$ = 9.84 (1H, br s), 7.86 (1H, d, *J* = 6.0 Hz), 7.61 (1H, d, *J* = 6.0 Hz), 7.29 (1H, br s), 7.14 (1H, br s), 5.28 (1H, br s), 4.55 (1H, br s), 3.67 (3H, s), 3.47–3.52 (1H, m), 3.33 (1H, br s), 1.34 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) major rotamer shown: $\delta$ = 173.2, 155.6, 142.5, 139.2, 129.1, 120.4, 119.1, 118.2 (2×C), 109.8, 80.0, 55.1, 52.2, 30.1, 28.0; HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{25}N_4O_6$: 381.1769; found: 381.1761.

***N*-Boc-4-aminotryptophan derivative 11.** White foam; $[\alpha]_D^{23}$ +3 (*c* 2.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3384, 2978, 1740, 1699, 1508, 1366, 1166, 738; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.36 (1H, br s), 6.97 (1H, t, *J* = 7.6 Hz), 6.81 (1H, d, *J* = 7.6 Hz), 6.80 (1H, s), 6.36 (1H, d, *J* = 7.6 Hz), 5.90 (1H, d, *J* = 7.2 Hz), 4.57 (1H, d, *J* = 6.4 Hz), 4.08 (2H, br s), 3.67 (3H, s), 3.33–3.35 (2H, m), 1.39 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.0, 155.7, 140.1, 138.0, 123.0, 121.9, 116.6, 109.7, 106.2, 103.0, 79.8, 55.7, 52.1, 29.8, 28.2; HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{23}N_3O_4K$: 372.1320; found: 372.1322.

**Compound 12.** White foam; $[\alpha]_D^{23}$ +8 (*c* 2.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3392, 2969, 1736, 1513, 1367, 1163, 733; $^1$H NMR (400 MHz, $CDCl_3$) show the presence of two rotamers, major rotamer shown: $\delta$ = 8.38 (1H, br s), 7.29–7.34 (5H, m), 6.96 (1H, t, *J* = 8.0 Hz), 6.82 (1H, d, *J* = 8.0 Hz), 6.81 (1H, s), 6.24 (1H, d, *J* = 8.0 Hz), 5.87 (1H, d, *J* = 6.8 Hz), 5.19 (1H, d, *J* = 12.4 Hz), 1.14 (1H, d, *J* = 12.4 Hz), 4.75 (1H, d, *J* = 10.0 Hz), 4.53–4.58 (1H, m), 4.06 (1H, dd, *J* = 5.6, 9.6 Hz), 3.70 (3H, s), 3.41–3.48 (1H, m), 3.27–3.33 (1H, m), 2.25–2.33 (1H, m), 1.34 (9H, s), 1.14 (1H, d, *J* = 6.8 Hz), 1.10 (1H, d, *J* = 6.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) major rotamer shown: $\delta$ = 173.8, 173.1, 155.7, 141.5, 137.7, 135.6,

128.4, 128.3, 128.2, 123.2, 121.8, 116.7, 109.8, 103.3, 101.7, 79.7, 66.5, 62.5, 55.8, 52.1, 31.5, 29.9, 28.1, 19.2, 18.9; HRMS (ESI): $m/z$ calcd. for $C_{29}H_{38}N_3O_6$: 524.2755; found: 524.2749.

***N*-Boc-4-nitrotryptophanol derivative 13.** To a stirring solution of 4-nitrotryptophan derivative **10** (1.66 g) in dry ethanol (20 mL) was added $NaBH_4$ (345 mg), and the reaction mixture was stirred at room temperature overnight until the starting material consumed. The solvent was removed under reduced pressure, and the residue was suspended in water. After being extracted with EtOAc, the combined organic layers were washed with brine and dried over $Na_2SO_4$. Purification by FCC ($CH_2Cl_2$-MeOH, 30 : 1) afforded the desired 4-nitrotryptophanol derivative **13** (1.46 g, 95%) as an amorphous yellowish powder. $[\alpha]_D^{23}$ –278.5 (*c* 1.00, MeOH); $\nu_{max}$(KBr)/cm$^{-1}$: 3560, 3368, 2983, 1682, 1515, 1318, 1294, 738; $^1$H NMR (400 MHz, $CD_3OD$) showed the presence of two rotamers in a ratio of 2.2/1: $\delta$ = 7.78 (1H, d, $J$ = 8.0 Hz, both), 7.66 (1H, d, $J$ = 8.0 Hz, both), 7.37 (1H, s, major), 7.34 (1H, s, minor), 7.16 (1H, t, $J$ = 8.0 Hz, both), 3.67–3.75 (1H, m, both), 3.57–3.60 (1H, m, both), 3.50–3.54 (1H, m, both), 3.18–3.27 (1H, m, both), 2.81 (1H, dd, $J$ = 10.0, 14.4 Hz, major), 2.64 (1H, br t, $J$ = 12.0 Hz, minor), 1.25 (9H, s, major), 0.90 (9H, s, minor); $^{13}$C NMR (100 MHz, $CD_3OD$) major rotamer shown: $\delta$ 158.1, 144.0, 141.1, 130.3, 120.7, 120.4, 118.7, 118.1, 112.5, 79.7, 65.4, 55.2, 30.4, 28.6; HRMS (ESI): $m/z$ calcd. for $C_{16}H_{22}N_3O_5$: 336.1554; found: 336.1559.

***N*-Boc-4-aminotryptophanol derivative 14.** Colorless oil; $[\alpha]_D^{23}$ –2.3 (*c* 1.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3381, 2976, 2932, 1692, 1506, 1365, 1168, 1057, 733; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.49 (1H, br s), 6.95 (1H, t, $J$ = 7.6 Hz), 6.83–6.86 (2H, m), 6.36 (1H, d, $J$ = 7.6 Hz), 5.49 (1H, d, $J$ = 6.4 Hz), 4.25 (2H, br s), 3.72 (1H, br s), 3.52 (1H, d, $J$ = 10.4 Hz), 3.43 (1H, d, $J$ = 10.4 Hz), 3.17 (1H, d, $J$ = 12.0 Hz), 2.94–3.00 (1H, m), 1.46 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 156.2, 139.4, 137.9, 122.6, 122.5, 117.4, 111.0, 107.1, 103.9, 79.4, 62.1, 54.7, 28.4, 28.2; HRMS (ESI): $m/z$ calcd. for $C_{16}H_{24}N_3O_3$: 306.1812; found: 306.1807.

**Compound 15.** White foam; $[\alpha]_D^{23}$ –47.8 (*c* 1.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3400, 2965, 1694, 1513, 1366, 1164, 731; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.43 (1H, br s), 7.33–7.34 (5H, m), 6.96 (1H, t, $J$ = 8.0 Hz), 6.88 (1H, s), 6.80 (1H, d, $J$ = 8.0 Hz), 6.23 (1H, d, $J$ = 8.0 Hz), 5.47 (1H, br s), 5.40 (1H, d, $J$ = 7.6 Hz), 5.16 (2H, s), 4.00 (1H, d, $J$ = 7.2 Hz), 3.76–3.77 (1H, m), 3.63 (1H, d, $J$ = 12.4 Hz), 3.53 (1H, d, $J$ = 12.4 Hz), 3.12–3.23 (2H, m), 2.15–2.23 (1H, m), 1.47 (9H, s), 1.13 (1H, d, $J$ = 6.8 Hz), 1.03 (1H, d, $J$ = 6.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.9, 155.9, 141.8, 137.6, 135.3, 128.6, 128.5, 128.4, 123.0, 122.2, 116.2, 111.6, 102.8, 100.6, 79.3, 66.9, 62.5, 62.0, 55.3, 31.7, 28.6, 28.4, 19.6, 19.3; HRMS (ESI): $m/z$ calcd. for $C_{28}H_{38}N_3O_5$: 496.2806; found: 496.2802.

**4-Nitrotryptophanol derivative 4.** To a degassed solution of 3-nitro-2-iodoaniline **5** (646 mg), aldehyde **7** (630 mg) and DABCO (1.62 g) in DMF (8.5 mL) was added $Pd(OAc)_2$ (55 mg), and the resultant reaction mixture was stirred at 80 °C under argon atmosphere for 12 h. Water was added to the reaction mixture after cooling, and then extracted with EtOAc. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Purification by FCC (PE-EtOAc, 3 : 1 to 2 : 1) afforded **4** (689 mg, 75%) as yellowish foam. Recrystallization from $CH_2Cl_2$ gave **4** as yellowish cube, mp 176–177 °C; $[\alpha]_D^{23}$ –71.5 (*c* 1.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3270, 2986, 1670, 1518, 1404, 1365, 1323, 788, 740; $^1$H NMR (300 MHz, $CDCl_3$) showed the presence of two rotamers in a ratio of 1/1: $\delta$ = 10.04 (1H, br s), 9.69 (1H, br s), 7.86 (1H, d, $J$ = 7.8 Hz), 7.65 (2H, br s), 7.52 (1H, d, $J$ = 7.8 Hz), 7.19 (2H, br s), 7.07 (1H, t, $J$ = 7.8 Hz), 6.90 (1H, br s), 4.26 (2H, br s), 3.95 (2H, m), 3.80 (2H, d, $J$ = 8.7 Hz), 3.08–3.24 (4H, m), 1.69 (3H, s), 1.61 (3H, s), 1.51 (15H, br s), 1.01 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) all rotamers shown: $\delta$ = 152.8, 143.0, 142.4, 139.2, 138.9, 128.5, 126.3, 120.4, 119.7, 119.0, 117.7, 117.4, 112.2, 111.6, 94.0, 93.6, 80.7, 79.3, 67.8, 66.7, 58.0, 32.0, 30.2, 28.3, 27.8, 27.4, 24.4, 23.2; HRMS (ESI): $m/z$ calcd. for $C_{19}H_{25}N_3O_5Na$: 398.1686; found: 398.1679.

**4-Aminotryptophanol derivative 20.** Yellowish foam; $[\alpha]_D^{23}$ –42.1 (*c* 1.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3380, 2980, 1678, 1399, 1171, 1106, 757; $^1$H NMR (300 MHz, $CDCl_3$) showed the presence of two rotamers in a ratio of 7.5/1, major rotamer shown: $\delta$ = 8.12 (1H, br s), 6.97 (1H, t, $J$ = 7.8 Hz), 6.78 (1H, s), 6.70 (1H, d, $J$ = 7.8 Hz), 6.31 (1H, d, $J$ = 7.8 Hz), 4.93 (2H, br s), 4.19–4.24 (1H, m), 3.91 (1H, d, $J$ = 9.0 Hz), 3.75 (1H, dd, $J$ = 5.7, 8.1 Hz), 3.52 (1H, d, $J$ = 13.8 Hz), 2.73 (1H, dd, $J$ = 11.7, 13.8 Hz), 1.68 (3H, s), 1.56 (9H, s), 1.50 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) major rotamer shown: $\delta$ = 152.6, 141.5, 138.5, 123.4, 121.4, 115.2, 111.9, 104.2, 101.1, 93.7, 80.4, 65.3, 59.0, 29.6, 28.3, 27.7, 24.2; HRMS (ESI): $m/z$ calcd. for $C_{19}H_{28}N_3O_3$: 346.2125; found: 346.2118.

**Compound 21.** Yellowish foam; $[\alpha]_D^{23}$ –54.4 (*c* 1.00, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$: 3398, 2975, 1735, 1683, 1398, 1369, 1247, 1174, 1104, 756; $^1$H NMR (300 MHz, $CDCl_3$) show the presence to two rotamers with a ratio of 3.4/1, major rotamer shown: $\delta$ = 8.23 (1H, br s), 7.26–7.32 (5H, m), 6.99 (1H, t, $J$ = 7.8 Hz), 6.75–6.81 (2H, m), 6.31 (1H, d, $J$ = 7.8 Hz), 5.46 (1H, br s), 5.19 (1H, d, $J$ = 12.3 Hz), 5.08 (1H, d, $J$ = 12.3 Hz), 4.20–4.24 (1H, m), 3.94–4.05 (2H, m), 3.62–3.74 (2H, m), 2.79 (1H, t, $J$ = 12.3 Hz), 2.54–2.61 (1H, m), 1.67 (3H, s), 1.55 (9H, s), 1.51 (3H, s), 1.19 (1H, d, $J$ = 6.3 Hz), 1.06 (1H, d, $J$ = 6.6 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) major rotamer shown: $\delta$ = 174.6, 152.1, 142.4, 138.1, 136.0, 128.3, 128.1, 127.9, 123.3, 121.7, 115.6, 111.7, 101.9, 100.7, 93.5, 80.0, 66.1, 65.3, 64.3, 59.2, 30.3, 29.3, 28.3, 27.7, 24.3, 20.7, 19.5; HRMS (ESI): $m/z$ calcd. for $C_{31}H_{41}N_3O_5Na$: 558.2938; found: 558.2930.

**(–)-Indolactam V (1).** 10% Palladium on carbon (44 mg) was added to a solution of **21** (370 mg) in methanol (12 mL), and the mixture was hydrogenolyzed with hydrogen (4 atm) for 30 min, at which point TLC indicated the complete consumption of the starting material. The reaction mixture was filtered through celite and the solvent removed by evaporation. The residue was dissolved in $CH_2Cl_2$ (15 mL) and cooled to 0 °C, TFA (3 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h, and then the solvent was removed *in vacuo* to give the residue, which was dissolved in dry THF (20 mL, 0.035 M). To this solution was added HATU (394 mg) and DIPEA (3.0 mL), and then stirred at room temperature under argon atmosphere for 48 h. Evaporation of the solvent gave a residue that was dissolved in EtOAc, washed with brine and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give crude *des-N*-methylindolactam V. To a solution of this crude product in acetonitrile (10 mL) at 0 °C was added formalin (37%, 514 μL), sodium cyanoborohydride (217 mg) and acetic acid (68 μL), and the solution was stirred at 0 °C for 1 h. The reaction mixture was diluted with water

and extracted with EtOAc. The combined organic phases were washed with brine and dried over $Na_2SO_4$. Purification by FCC ($CH_2Cl_2$-MeOH, 25 : 1) afforded (–)-Indolactam V (115 mg, 55%) as yellowish foam. $[\alpha]_D^{23}$ –196 (*c* 1.00, EtOH), [lit.[3] $[\alpha]$ –170 (*c* 0.499, EtOH)]; $^1$H NMR (400 MHz, $CDCl_3$), show the presence of two rotamers in a ration of 5.9/1, major rotamer shown: $\delta$ = 8.13 (1H, br s), 7.72 (1H, br s), 7.05 (1H, t, *J* = 8.0 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 6.89 (1H, br s), 6.49 (1H, d, *J* = 8.0 Hz), 4.40 (1H, d, *J* = 10.0 Hz), 4.31–4.33 (1H, m), 3.73 (1H, dd, *J* = 3.6, 11.6 Hz), 3.58 (1H, dd, *J* = 8.4, 11.6 Hz), 3.17 (1H, d, *J* = 17.6 Hz), 3.05 (1H, dd, *J* = 3.6, 17.6 Hz), 2.91 (3H, s), 2.54–2.63 (1H, m), 0.93 (1H, d, *J* = 6.4 Hz), 0.63 (1H, d, *J* = 6.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$), major rotamer shown: $\delta$ = 174.9, 147.8, 139.5, 122.7, 121.5, 118.0, 114.4, 106.3, 104.1, 71.0, 64.8, 55.9, 33.8, 32.9, 28.4, 21.5, 19.3; HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{24}N_3O_2$: 302.1863; found: 302.1858.

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