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Novel asymmetric total syntheses of (*R*)-(−)-pyridindolol, (*R*)-(−)-pyridindolol K1, and (*R*)-(−)-pyridindolol K2 via a mild one-pot aromatization of *N*-tosyl-tetrahydro-β-carboline with (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde as the source of chirality

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ABSTRACT

Novel total syntheses of (*R*)-(−)-pyridindolol **1**, (*R*)-(−)-pyridindolol K1 **2**, and (*R*)-(−)-pyridindolol K2 **3** are described. By using L-tryptophan methyl ester and (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde as the starting materials, (*R*)-(−)-pyridindolol **1**, (*R*)-(−)-pyridindolol K1 **2**, and (*R*)-(−)-pyridindolol K2 **3** were synthesized in 5–7 steps in 66%, 41%, and 55% overall yields, respectively. The characteristic step of the total syntheses is a mild one-pot aromatization of *N*-tosyl-1,2,3,4-tetrahydro-β-carboline (*N*-Ts-THBC), which was obtained via Pictet–Spengler reaction of L-tryptophan methyl ester with (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde, and subsequent *N*-tosylation.

1. Introduction

Pyridindolol **1** (Fig. 1) was first isolated from *Streptomyces alboverticillatus* by Umezawa et al.;[1] its structure and the (*R*)-absolute configuration were also determined via X-ray crystallographic analysis by Umezawa et al. later in the same year.[2] Pyridindolol K1 **2** and pyridindolol K2 **3**, together with pyridindolol **1**, were isolated from the culture broth of *Streptomyces* sp. K93-0711 by Omura et al. in 1997.[3] Biological studies have revealed that pyridindolol **1** is a specific inhibitor of bovine liver β-galactosidase under acidic conditions (optimal pH 4.0),[1,4] and also inhibits the activity of both bovin brain and heart PDE1's.[5,6] Pyridindolol K2 **3** has shown an activity, which inhibits the adhesion of HL-60 cells to a LPS-activated HUVES monolayer.[3]

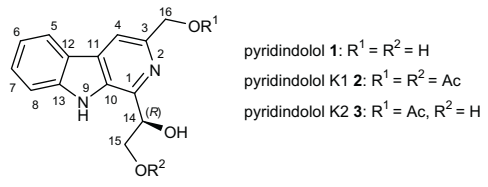

Figure 1. Structures of the three targeted β-carboline alkaloids.

Cook et al. reported the first total synthesis of racemic pyridindolol **1** and (*S*)-(+)-pyridindolol **1**.[7] Pandit et al. also reported a novel approach to racemic pyridindolol **1**.[8,9] The first total syntheses of (*R*)-(−)-pyridindolol K2 **3** and its enantiomer were performed by Hibino et al.[10] By using the same strategy, Hibino et al. also performed the total syntheses of (*R*)-(−)-pyridindolol **1**, (*R*)-(−)-pyridindolol K1 **2**, and (*R*)-(−)-pyridindolol K2 **3**.[11]

In all of the aforementioned reported syntheses[7–11] of the three pyridindolols **1**–**3**, the key point should be the strategy for constructing the β-carboline nucleus. Hibino et al. used a thermal electrocyclization reaction to build the desired β-carboline nucleus.[10,11] Cook[7] and Pandit[8] employed a two-step strategy to construct the β-carboline nucleus, which involved a Pictet–Spengler reaction to form the 1,2,3,4-tetrahydro-β-carboline (THBCs) and the subsequent aromatization of these intermediates via Pd/C-catalyzed dehydrogenation or DDQ-mediated oxidation. However, Hibino's thermal-electrocyclization-based strategy required many steps,[10,11] while Cook's and Pandit's two-step strategy[7,8] suffered from racemization of the stereogenic center of the L-acetonide moiety due to the harsh conditions of the Pd/C-catalyzed dehydrogenation of THBCs, or suffered from low yields during the DDQ-mediated oxidation of THBCs. Recently, we have developed a very mild and efficient method for constructing the β-carboline nucleus.[12] By applying this method, we were able to efficiently and practically synthesize (*R*)-(−)-pyridindolol **1**, (*R*)-(−)-pyridindolol K1 **2**, and (*R*)-(−)-pyridindolol K2 **3** starting from the readily available L-tryptophan methyl ester[13] and (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde;[14,15] herein we report our results in detail.

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2. Results and discussion

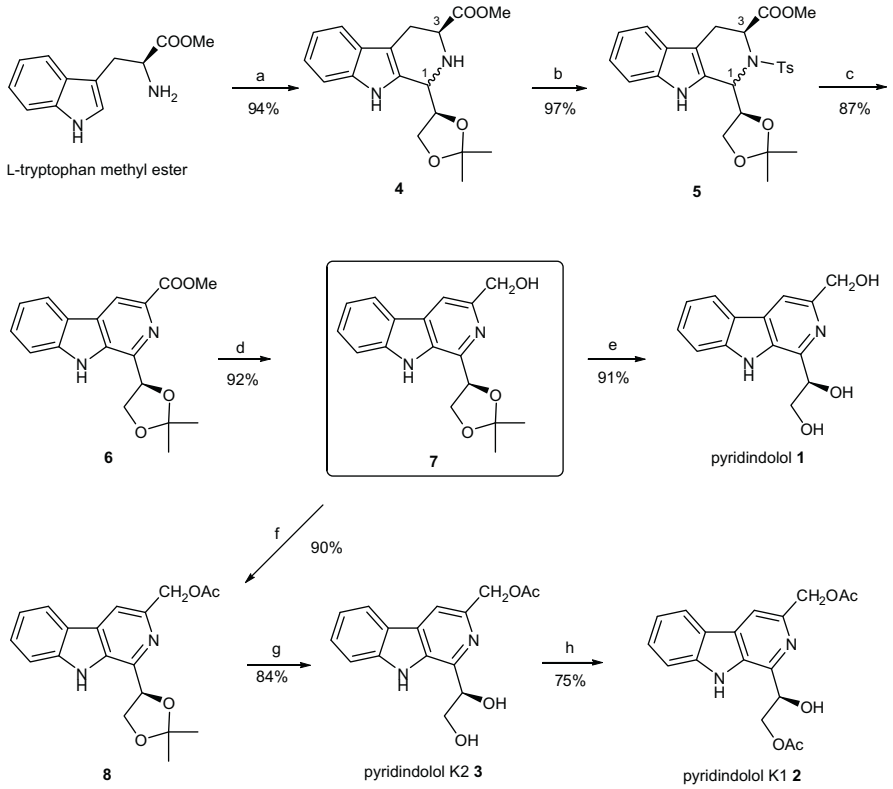
As shown in Scheme 1, our synthetic efforts began with the Pictet–Spengler reaction[16,17] of L-tryptophan methyl ester[13] with (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde, which can be prepared from L-ascorbic acid according to the literature.[14,15] When L-tryptophan methyl ester was treated with (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde (1.5 equiv.) and trifluoroacetic acid (3.0 equiv) at 0 °C in ethyl acetate, 1,2,3,4-tetrahydro-β-carboline (THBC) **4** was obtained as a diastereomeric mixture of two epimers (*cis*/*trans*, 35:65) in 94% combined yield. The epimeric mixture of compound **4** could be used as such for the next step. Compound **4** was then treated with *p*-toluenesulfonyl chloride (1.0 equiv), fine powdered potassium carbonate (3.0 equiv) and pyridine (0.3 equiv) at 0 °C to room temperature in dichloromethane, as a result, *N*-tosyl-1,2,3,4-tetrahydro-β-carboline (*N*-Ts-THBC) **5** was obtained as a diastereomeric mixture of two epimers (*cis*/*trans*, 35:65) in 97% combined yield. The epimeric mixture of *N*-Ts-THBC **5** could also be used as such for the subsequent mild one-pot aromatization. When *N*-Ts-THBC **5** was treated with powdered potassium carbonate (5.0 equiv) at room temperature in anhydrous dimethyl sulfoxide (DMSO) under an atmosphere of air, the desired β-carboline **6** was obtained in 87% yield. Although both THBC **4** and *N*-Ts-THBC **5** existed as mixtures of the corresponding epimers, isolation of the epimers was not necessary, since the stereogenic centers are lost during the conversion of *N*-Ts-THBC **5** into compound **6**.

In order to determine the optimized reaction conditions for the conversion of *N*-Ts-THBC **5** into compound **6**, we attempted the above one-pot conversion under various conditions; the results are summarized in Table 1. As can be seen from Table 1, the conversion did not occur in the absence of a base (entry 1), and fine powdered K_2CO_3 served as the best base for the reaction in DMSO (entry 8). Various solvents were also checked for this reaction (entries 9–18), when the one-pot conversion was performed in DMSO or *N*,*N*-dimethylformamide (DMF) at room temperature, the desired compound **6** could be obtained in good yields (entries

Table 1
Optimization of the reaction conditions for the one-pot conversion of *N*-Ts-THBC **5** into compound **6**

Entry	Solvent	Base (equiv)	Temperature (°C)	Time (h)	Yield[a] (%)
1	DMSO[b]	None	80	12	0
2	DMSO	$NaHCO_3$ (5)	80	12	21
3	DMSO	Et_3N (5)	80	12	41
4	DMSO	Pyridine (3)	60	10	45
5	DMSO	DMAP[c] (3)[c]	60	10	51
6	DMSO	DBU[d] (3)	25	10	80
7	DMSO	Na_2CO_3 (5)	25	10	68
8	DMSO	K_2CO_3 (5)	25	10	87
9	DMF[e]	DBU (3)	25	10	70
10	DMF	Na_2CO_3 (5)	25	10	66
11	DMF	K_2CO_3 (5)	25	10	74
12	CH_2Cl_2	K_2CO_3 (5)	25	20	<5
13	$CHCl_3$	K_2CO_3 (5)	25	20	<5
14	MeCN	K_2CO_3 (5)	25	20	42
15	THF	K_2CO_3 (5)	25	20	10
16	EtOAc	K_2CO_3 (5)	25	20	8
17	MeOH	K_2CO_3 (5)	25	20	31
18	*i*-PrOH	K_2CO_3 (5)	25	20	43

[a] Isolated yield of compound **6**.
[b] Dimethyl sulfoxide.
[c] 4-Dimethylaminopyridine.
[d] 1,8-Diazabicyclo[5,4,0]undec-7-ene.
[e] *N*,*N*-Dimethylformamide.



Scheme 1. Total syntheses of pyridindololes **1**–**3**. Reagents and conditions: (a) 1.5 equiv of (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde, 3.0 equiv of trifluoroacetic acid, 0 °C for 5 h in EtOAc; (b) 1.0 equiv of *p*-toluenesulfonyl chloride, 0.3 equiv of pyridine, 3.0 equiv of powdered K_2CO_3, 0 °C to rt for 6 h in CH_2Cl_2; (c) 5.0 equiv of powdered K_2CO_3, rt for 10 h in DMSO; (d) 5.0 equiv of diisobutylaluminum hydride (DIBAL-H), 0 °C for 6 h in CH_2Cl_2; (e) aqueous concentrated HCl (12 mol L^{-1}), 0 °C for 2 h in THF; (f) 1.5 equiv of acetyl chloride, 3.0 equiv of triethylamine, 0 °C for 0.5 h in CH_2Cl_2; (g) aqueous concentrated HCl (12 mol L^{-1}), rt for 1.5 h in THF; (h) 1.1 equiv of acetyl chloride, 2.0 equiv of diisopropylethylamine (DIPEA), 0 °C for 15 min in CH_2Cl_2.

6–11), whereas the one-pot conversion was very slow at room temperature in several other solvents such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, ethyl acetate, methanol, and isopropanol, affording the desired product **6** in only low yields (entries 12–18).

With the desired compound **6** in hand, we next attempted to convert ester **6** into the primary alcohol **7**. Several reducing agents such as potassium borohydride (KBH_4), sodium borohydride ($NaBH_4$), lithium aluminum hydride ($LiAlH_4$), and diisobutylaluminum hydride (DIBAL-H) were examined. We found that KBH_4 did not work at all in all of the tested solvents such as methanol, ethanol, THF, DMSO, and DMF. However, the ester group of compound **6** could be efficiently reduced by $NaBH_4$ in DMSO at room temperature, or $LiAlH_4$ in THF at reflux, or DIBAL-H in CH_2Cl_2 at 0 °C, affording the desired product **7** in 77%, 83%, or 92% yield, respectively.

Primary alcohol **7** is a key intermediate for the syntheses of the targeted (*R*)-(−)-pyridindolols **1**–**3**; it can be readily converted into (*R*)-(−)-pyridindolol **1**, (*R*)-(−)-pyridindolol K1 **2**, and (*R*)-(−)-pyridindolol K2 **3** as follows. When compound **7** was exposed to aqueous concentrated HCl (12 mol L^{-1}) at 0 °C in THF, the acetonide moiety was removed smoothly to afford (*R*)-(−)-pyridindolol **1** in 91% yield. When compound **7** was treated with acetyl chloride (1.5 equiv) and triethylamine (3.0 equiv) at 0 °C in dichloromethane, compound **8** was obtained efficiently in 90% yield. Compound **8** was then exposed to aqueous concentrated HCl (12 mol L^{-1}) at room temperature in THF, and (*R*)-(−)-pyridindolol K2 **3** was obtained in 84% yield. Finally, when (*R*)-(−)-pyridindolol K2 **3** was treated with acetyl chloride (1.1 equiv) and diisopropylethylamine (DIPEA, 2.0 equiv) at 0 °C in CH_2Cl_2, selective acetylation of the less hindered terminal primary hydroxyl group occurred smoothly to afford (*R*)-(−)-pyridindolol K1 **2** in 75% yield. The characterization data of the three (*R*)-(−)-pyridindolols **1**–**3** obtained from the above total syntheses were identical to those of the previously reported ones.[11]

3. Conclusion

In conclusion, novel asymmetric total syntheses of (*R*)-(−)-pyridindolol **1**, (*R*)-(−)-pyridindolol K1 **2**, and (*R*)-(−)-pyridindolol K2 **3** starting from readily available L-tryptophan methyl ester and (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde were performed. (*R*)-(−)-Pyridindolol **1** was synthesized via 5 steps in 66% overall yield, (*R*)-(−)-pyridindolol K1 **2** was synthesized via 7 steps in 41% overall yield, and (*R*)-(−)-pyridindolol K2 **3** was synthesized via 6 steps in 55% overall yield. In addition, the one-pot conversion of *N*-Ts-THBC **5** into compound **6** as the key step for the above total syntheses was studied in detail, in order to determine the optimized reaction conditions; the best yield of compound **6** could be obtained in DMSO with K_2CO_3 as the base.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were acquired on a Bruker AM-400 instrument at 400 MHz or 100 MHz. Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard by assigning the TMS resonance in the ^1H NMR spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C NMR spectrum as 77.23 ppm. All coupling constants (*J* values) are reported in Hertz (Hz). IR spectra were recorded on a Nicolet Magna IR-550 spectrometer. Mass spectra were recorded on HP5989A equipment. Optical rotations of the chiral compounds were measured on a WZZ-1S polarimeter at room temperature. Melting points were determined on a Mel-TEMP II melting point apparatus. Column chromatography was performed on silica gel (Qingdao Qcean Chemical Corp.). All reagents and solvents were analytically pure, and were used as such after being received from the commercial suppliers. The starting compound L-tryptophan methyl ester was prepared from L-tryptophan according to the literature.[13] The starting compound (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde was prepared from L-ascorbic acid according to the literature.[14,15]

4.2. Methyl (3*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-b]indole-3-carboxylate 4

L-Tryptophan methyl ester (5.010 g, 22.96 mmol) was dissolved in ethyl acetate (40 mL), and the solution was cooled to 0 °C with an ice bath. After (*S*)-2,3-*O*-isopropylidene-L-glyceraldehyde (4.480 g, 34.42 mmol) was added, trifluoroacetic acid (7.840 g, 68.76 mmol) was slowly added within 10 min. After the addition was finished, the stirring was continued for 5 h at 0 °C. After TLC showed the reaction was complete, the reaction was quenched by adding an aqueous solution of potassium carbonate until pH 9–10, after which the mixture was then transferred into a separatory funnel. Two phases were separated and the aqueous phase was extracted twice with ethyl acetate (2 × 20 mL). The organic extracts were combined and washed with brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to give a crude oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to produce compound **4** (7.130 g, 21.58 mmol) as an epimeric mixture in 94% combined yield (*cis*/*trans* = 35:65). For the *cis*-epimer: $[\alpha]_D^{20} = -23.9$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H, NH in indole ring), 7.53 (d, *J* = 7.7 Hz, 1H, H-5), 7.36 (d, *J* = 7.7 Hz, 1H, H-8), 7.20 (t, *J* = 7.7 Hz, 1H, H-7), 7.13 (t, *J* = 7.7 Hz, 1H, H-6), 4.75–4.72 (m, 1H, H-14), 4.46–4.40 (m, 1H, H-15), 4.10–4.06 (m, 1H, H-15′), 3.99 (t, *J* = 5.5 Hz, 1H, H-1), 3.75 (s, 3H, OCH_3), 3.67 (dd, J_1 = 7.2 Hz, J_2 = 7.6 Hz, 1H, H-3), 3.35 (br s, 1H, H-2), 3.20–3.14 (m, 2H, H-4 and H-4′), 1.46 (s, 3H, CH_3), 1.41 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.38, 136.13, 129.90, 126.49, 122.13, 119.48, 118.13, 111.08, 109.33, 108.29, 77.75, 66.16, 53.27, 52.38, 51.15, 26.43, 25.15, 24.13. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}N_2O_4$ $[M+H]^+$: 331.1658, found: 331.1665. IR (KBr film) 3379 (N–H), 2985, 2923, 1725 (C=O), 1688, 1460, 1434, 1360, 1246, 1218, 1159, 1087, 1007, 743 cm^{-1}. For the *trans*-epimer: $[\alpha]_D^{20} = -14.2$ (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1H, NH in indole ring), 7.50 (d, *J* = 7.8 Hz, 1H, H-5), 7.38 (d, *J* = 7.8 Hz, 1H, H-8), 7.19 (t, *J* = 7.8 Hz, 1H, H-7), 7.11 (t, *J* = 7.8 Hz, 1H, H-6), 4.23−4.13 (m, 4H, H-1, H-14 and H-15), 3.84−3.81 (m, 1H, H-3), 3.83 (s, 3H, OCH_3), 3.16 (d, *J* = 15.1 Hz, 1H, H-4), 2.84 (dd, J_1 = 15.1 Hz, J_2 = 12.4 Hz, 1H, H-4′), 2.28 (br s, 1H, H-2), 1.57 (s, 3H, CH_3), 1.45 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.41, 135.94, 133.63, 126.62, 122.01, 119.45, 118.08, 111.12, 109.97, 107.86, 78.90, 67.56, 56.16, 55.61, 52.31, 26.95, 25.62, 25.53. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}N_2O_4$ $[M+H]^+$: 331.1658, found: 331.1665. IR (KBr film) 3442 (N–H), 2984, 2955, 1747 (C=O), 1464, 1373, 1268, 1159, 1061, 857, 729 cm^{-1}.

4.3. Methyl (3*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-tosyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-b]indole-3-carboxylate 5

Compound **4** (6.930 g, 20.98 mmol) and pyridine (0.500 g, 6.321 mmol) were dissolved in dichloromethane (60 mL), and the solution was cooled to 0 °C with an ice bath. Powdered potassium carbonate (8.700 g, 62.95 mmol) was then added, after which *p*-toluenesulfonyl chloride (4.000 g, 20.98 mmol) was added in portions over 10 min. After the addition was finished, the ice-bath was removed, and the mixture was stirred at room temperature for 6 h. After the reaction was complete (checked by TLC), water

(40 mL) was added, and the mixture was transferred into a separatory funnel. Two phases were separated, and the aqueous phase was extracted twice with dichloromethane (2 × 20 mL). The organic extracts were combined, and washed successively with HCl aqueous solution (1 mol/L, 20 mL) and water (15 mL). After the organic solution was dried over anhydrous $MgSO_4$, the solvent was removed under vacuum to give a crude solid, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford compound **5** (9.870 g, 20.37 mmol) as an epimeric mixture in 97% combined yield. (*cis*/*trans* = 35:65). For the *cis*-epimer: mp 121.6–122.6 °C. $[\alpha]_D^{20} = -26.2$ (*c* 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H, NH in indole ring), 7.75 (d, *J* = 8.3 Hz, 2H, both *orth*-H in Ts), 7.45 (d, *J* = 8.2 Hz, 1H, H-5), 7.28−7.23 (m, 3H, H-8 and both *meta*-H in Ts), 7.16 (t, *J* = 8.2 Hz, 1H, H-7), 7.09 (t, *J* = 8.2 Hz, 1H, H-6), 5.39 (d, *J* = 5.0 Hz, 1H, H-1), 4.90 (dd, J_1 = 6.1, J_2 = 4.8 Hz, 1H, H-3), 4.85–4.79 (m, 1H, H-14), 3.65 (s, 3H, OCH_3), 3.47 (dd, J_1 = 12.8 Hz, J_2 = 6.5 Hz, 1H, H-15), 3.35–3.30 (m, 2H, H-15′ and H-4), 3.07 (dd, J_1 = 14.8, J_2 = 4.8 Hz, 1H, H-4′), 2.38 (s, 3H, CH_3 in Ts), 1.262 (s, 3H, CH_3), 1.265 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.13, 144.17, 137.59, 136.25, 129.66, 129.43, 127.23, 126.24, 122.30, 119.57, 118.23, 111.04, 109.72, 108.45, 76.49, 65.09, 58.17, 54.53, 52.59, 25.85, 25.18, 23.95, 21.55. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{29}N_2O_6S$ $[M+H]^+$: 485.1746, found: 485.1748. IR (KBr film) 3457 (N–H), 2984, 2925, 1742 (C=O), 1598, 1454, 1340, 1210, 1163, 1038, 847, 745, 664, 571 cm^{-1}. For the *trans*-epimer: mp 111.5–112.8 °C. $[\alpha]_D^{20} = +141.6$ (*c* 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H, NH in indole ring), 7.65 (d, *J* = 8.2 Hz, 2H, both *orth*-H in Ts), 7.40–7.34 (m, 2H, H-5 and H-8), 7.19–7.14 (m, 3H, H-7 and both *meta*-H in Ts), 7.06 (t, *J* = 7.6 Hz, 1H, H-6), 5.15 (d, *J* = 8.6 Hz, 1H, H-1), 4.97 (d, *J* = 6.0 Hz, 1H, H-3), 4.65 (dd, J_1 = 9.0, J_2 = 5.9 Hz, 1H, H-15), 4.42–4.13 (m, 2H, H-14 and H-15′), 3.65 (s, 3H, OCH_3), 3.22 (d, *J* = 15.0 Hz, 1H, H-4), 2.34 (s, 3H, CH_3 in Ts), 2.31 (dd, J_1 = 15.0, J_2 = 6.0 Hz, 1H, H-4′), 1.65 (s, 3H, CH_3), 1.42 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.10, 144.23, 136.78, 136.24, 130.46, 130.03, 126.99, 126.23, 122.39, 119.38, 118.38, 111.18, 110.25, 105.28, 78.79, 67.30, 54.81, 53.97, 52.79, 27.24, 25.84, 21.54, 20.68. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{29}N_2O_6S$ $[M+H]^+$: 485.1746, found: 485.1748. IR (KBr film) 3385 (N–H), 2984, 2929, 1733 (C=O), 1597, 1450, 1347, 1256, 1211, 1164, 1056, 894, 742, 664, 580 cm^{-1}.

4.4. Methyl (*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)-9*H*-pyrido [3,4-b]indole-3- carboxylate 6

Powdered potassium carbonate (14.07 g, 101.8 mmol) was added to a solution of compound **5** (9.870 g, 20.37 mmol) in anhydrous DMSO (40 mL). The suspension was then stirred for 10 h at room temperature. The reaction was monitored by TLC. After the reaction was complete, the mixture was diluted with ethyl acetate (200 mL), and water (200 mL) was also added. The mixture was transferred into a separatory funnel, and the two layers were separated. The aqueous solution was extracted twice with ethyl acetate (2 × 60 mL), and the extracts were then combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude oil, which was purified by flash chromatography (eluent: EtOAc/CH_2Cl_2 = 1:20) to furnish compound **6** (5.782 g, 17.72 mmol) as a pale yellow oil in 87% yield. $[\alpha]_D^{20} = -14.2$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (br s, 1H, NH in indole ring), 8.84 (s, 1H, H-4), 8.19 (d, *J* = 7.9 Hz, 1H, H-5), 7.65−7.55 (m, 2H, H-7 and H-8), 7.40−7.33 (m, 1H, H-6), 5.74 (t, *J* = 6.6 Hz, 1H, H-14), 4.68 (dd, J_1 = 8.6 Hz, J_2 = 6.6 Hz, 1H, H-15), 4.39 (dd, J_1 = 8.6 Hz, J_2 = 6.6 Hz, 1H, H-15′), 4.04 (s, 3H, OCH_3), 1.62 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.51, 142.64, 140.36, 136.78, 134.87, 129.83, 129.03, 121.79, 121.39, 120.87, 117.42, 111.98, 110.67, 78.82, 69.30, 52.65, 26.32, 25.02. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$: 327.1345, found: 327.1343. IR (neat) 3410 (N–H), 2991, 1698 (C=O), 1628, 1435, 1349, 1264, 1213, 1136, 1055, 862, 752 cm^{-1}.

4.5. (*R*)-(1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-9*H*-pyrido[3,4-b] indol-3-yl)methanol 7

Compound **6** (2.693 g, 8.252 mmol) was dissolved in dichloromethane (50 mL), and the resulting solution was cooled to 0 °C with an ice bath. A solution of DIBAL-H in toluene (2 mol L^{-1}, 20.5 mL, 41.00 mmol) was injected over 5 min with syringe. The mixture was then stirred at 0 °C for about 6 h, and monitored by TLC. After the reaction was complete, an aqueous solution of $NH_3{\cdot}H_2O$ (3 mol L^{-1}, 30 mL) was added. The mixture was then stirred vigorously for 10 min, and then transferred into a separatory funnel. Two phases were separated, and the aqueous phase was then extracted twice with dichloromethane (2 × 25 mL). The organic extracts were combined, and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum gave the crude product as a yellow solid, which was purified by flash chromatography (eluent: EtOAc/CH_2Cl_2 = 1:10) to give pure compound **7** (2.265 g, 7.592 mmol) as a pale yellow oil in 92% yield. $[\alpha]_D^{20} = -5.0$ (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H, NH in indole ring), 8.06 (d, *J* = 7.9 Hz, 1H, H-5), 7.81 (s, 1H, H-4), 7.55–7.50 (m, 2H, H-7 and H-8), 7.25 (t, *J* = 7.9 Hz, 1H, H-6), 5.58 (dd, J_1 = 6.9 Hz, J_2 = 6.7 Hz, 1H, H-14), 4.88 (s, 2H, H-16), 4.57 (dd, J_1 = 8.5 Hz, J_2 = 6.9 Hz, 1H, H-15), 4.33 (dd, J_1 = 8.5, J_2 = 6.7 Hz, 1H, H-15′), 1.56 (s, 3H, CH_3), 1.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.25, 141.92, 141.32, 133.23, 131.59, 129.29, 122.31, 121.61, 120.50, 112.22, 111.44, 111.17, 79.25, 69.87, 65.37, 26.94, 25.96. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{18}N_2O_3$ $[M]^+$: 298.1317, found: 298.1313. IR (KBr film) 3463 (N–H, O–H), 2985, 2876, 1628, 1570, 1471, 1373, 1245, 1216, 1152, 1066, 857, 787, 636, 572 cm^{-1}.

4.6. (*R*)-(−)-Pyridindolol 1

Compound **7** (0.630 g, 2.112 mmol) was dissolved in tetrahydrofuran (8 mL), and then the solution was cooled to 0 °C with an ice bath. Aqueous concentrated hydrochloric acid (12 mol L^{-1}, 0.2 mL) was then added. After the mixture was stirred at 0 °C for 2 h, the reaction was complete. The reaction solution was concentrated under vacuum to remove THF, and the residue was then partitioned between ethyl acetate (25 mL) and aqueous K_2CO_3 (10% w/w, 10 mL). The mixture was transferred into a separatory funnel, and two phases were separated. The aqueous phase was then extracted twice with ethyl acetate (2 × 10 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the crude product as a yellow solid. Recrystallization of the yellow solid from methanol afforded (*R*)-(−)-pyridindolol **1** (0.496 g, 1.920 mmol) as white solid in 91% yield. Mp 166.6–167.6 °C (lit.[11] 165–168 °C). $[\alpha]_D^{20} = -46.7$ (*c* 0.5, MeOH) {lit.[11] $[\alpha]_D^{25} = -41$ (*c* 0.1, MeOH)}. ^1H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H, NH in indole ring), 8.65 (s, 1H, H-4), 8.48 (d, *J* = 7.8 Hz, 1H, H-5), 7.85–7.74 (m, 2H, H-7 and H-8), 7.40 (t, *J* = 7.8 Hz, 1H, H-6), 5.66 (t, *J* = 5.2 Hz, 1H, H-14), 4.99 (s, 2H, both H-16), 3.99 (dd, J_1 = 11.1, J_2 = 5.2 Hz, 1H, H-15), 3.91 (dd, J_1 = 11.1, J_2 = 5.2 Hz, 1H, H-15′). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.42, 143.47, 141.95, 133.93, 131.94, 131.82, 123.70, 121.57, 119.69, 113.99, 113.49, 70.30, 65.04, 59.93. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{14}N_2O_3$ $[M]^+$: 258.1004, found: 258.1007. IR (KBr film) 3421 (N–H, O–H), 2961, 2923, 1628, 1564, 1458, 1398, 1261, 1094, 1022, 906, 801, 742, 650, 492 cm^{-1}.

4.7. (*R*)-(1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-9*H*-pyrido[3,4-b]indol-3-yl)methyl acetate 8

Compound **7** (1.270 g, 4.257 mmol) was dissolved in a dichloromethane (15 mL), and the solution was cooled to 0 °C with an ice bath. Acetyl chloride (0.500 g, 6.370 mmol) was added, and then a solution of triethylamine (1.290 g, 12.75 mmol) in dichloromethane (10 mL) was dropwise added at 0 °C over 0.5 h. After the addition was complete, the reaction was then immediately quenched by adding an aqueous solution of potassium carbonate (10% w/w, 10 mL). The organic layer was separated, washed with brine (10 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was then purified by flash chromatography (eluent: EtOAc/hexane = 1:5) to give compound **8** (1.305 g, 3.836 mmol) as a colorless oil in 90% yield. $[\alpha]_D^{20} = -9.3$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H, NH in indole ring), 8.14 (d, J = 7.9 Hz, 1H, H-5), 7.98 (s, 1H, H-4), 7.59–7.52 (m, 2H, H-7 and H-8), 7.30 (t, J = 7.9 Hz, 1H, H-6), 5.65 (t, J = 6.8 Hz, 1H, H-14), 5.38 (ab peaks, $J_{ab} = J_{ba}$ = 12.2 Hz, 2H, both H-16), 4.64 (dd, J_1 = 8.5, J_2 = 6.8 Hz, 1H, H-15), 4.41 (dd, J_1 = 8.5, J_2 = 6.8 Hz, 1H, H-15′), 2.19 (s, 3H, CH_3 in Ac), 1.61 (s, 3H, CH_3), 1,60 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.98, 143.75, 142.26, 140.46, 132.77, 130.51, 128.64, 121.72, 121.12, 120.03, 113.37, 111.69, 110.54, 78.83, 69.33, 67.75, 26.38, 25.28, 21.16. HRMS (ESI) m/z calcd for $C_{19}H_{20}N_2O_4$ $[M]^+$: 340.1423, found: 340.1418. IR (KBr film) 3403 (N–H), 2985, 2933, 1735 (C=O), 1627, 1495, 1367, 1245, 1107, 1066, 963, 858, 747, 635, 455 cm^{-1}.

4.8. (*R*)-(−)-Pyridindolol K2 3

To a solution of compound **8** (1.300 g, 3.819 mmol) in tetrahydrofuran (10 mL), aqueous concentrated hydrochloric acid (12 mol/L, 0.2 mL) was added. The resulting solution was stirred at room temperature, and the reaction then monitored by TLC. After stirring was continued at room temperature for around 1.5 h, the reaction was complete. The reaction solution was concentrated under vacuum, and the residue was partitioned between ethyl acetate (20 mL) and an aqueous solution of potassium carbonate (10% w/w, 10 mL). The two phases were separated, and the aqueous phase was extracted twice with ethyl acetate (2 × 10 mL). The organic extracts were combined, washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography (eluent: EtOAc/$CHCl_3$ = 1:4) to give (*R*)-(−)-pyridindolol K2 **3** (0.968 g, 3.213 mmol) as white crystals in 84% yield. Mp 121.3–123.3 °C (lit.[11] 123–124 °C). $[\alpha]_D^{20} = -32.5$ (*c* 0.3, MeOH) (lit.[11] $[\alpha]_D^{23} = -33$ (*c* 0.2, MeOH)). ^1H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H, NH in indole ring), 8.24 (d, J = 7.8 Hz, 1H, H-5), 8.08 (s, 1H, H-4), 7.70 (d, J = 7.8 Hz, 1H, H-8), 7.54 (t, J = 7.8 Hz, 1H, H-7), 7.23 (t, J = 7.8 Hz, 1H, H-6), 5.81 (t, J = 4.6 Hz, 1H, H-14), 5.27 (s, 2H, both H-16), 5.07 (dd, J_1 = 8.6 Hz, J_2 = 4.6 Hz, 1H, H-15), 4.81 (dd, J_1 = 8.6 Hz, J_2 = 4.6 Hz, 1H, H-15′), 2.14 (s, 3H, CH_3CO). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.81, 145.96, 142.89, 141.37, 133.34, 129.32, 128.47, 121.95, 120.77, 119.61, 112.94, 112.91, 75.27, 67.60, 65.77, 21.33. HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2O_4$ $[M]^+$: 300.1110, found: 300.1118. IR (KBr film) 3385 (N–H, O–H), 2957, 2923, 1740, 1628, 1494, 1362, 1249, 1146, 1055, 997, 868, 732, 660, 536 cm^{-1}.

4.9. (*R*)-(−)-Pyridindolol K1 2

Compound **3** (0.967 g, 3.220 mmol) was dissolved in a dichloromethane (20 mL), and the solution was cooled to 0 °C with an ice bath. Acetyl chloride (0.280 g, 3.567 mmol) was added, and then DIPEA (0.830 g, 6.422 mmol) was added dropwise at 0 °C over 15 min. TLC showed the reaction was complete immediately after the addition was finished. The reaction was then quenched by adding an aqueous solution of potassium carbonate (10% w/w, 10 mL). The organic layer was separated, and the aqueous phase was extracted twice with dichloromethane (2 × 10 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to give (*R*)-(−)-pyridindolol K1 **2** (0.830 g, 2.424 mmol) as a pale yellow solid in 75% yield. Mp 125.5–126.5 °C (lit.[11] 124–125 °C). $[\alpha]_D^{20} = -13.6$ (*c* 0.2, MeOH) {lit.[11] $[\alpha]_D^{25} = -14$ (*c* 0.2, MeOH)}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, NH in indole ring), 8.13 (d, J = 7.9 Hz, 1H, H-5), 7.99 (s, 1H, H-4), 7.61–7.57 (m, 2H, H-7 and H-8), 7.32–7.26 (m, 1H, H-6), 5.43 (dd, J_1 = 7.5, J_2 = 1.7 Hz, 1H, H-15), 5.37 (s, 2H, both H-16), 4.86 (dd, J_1 = 11.0, J_2 = 1.7 Hz, 1H, H-15′), 4.18 (dd, J_1 = 11.0, J_2 = 7.5 Hz, 1H, H-14), 2.21 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.59, 171.63, 143.82, 141.52, 140.88, 133.11, 131.10, 129.57, 122.45, 121.82, 121.00, 114.44, 112.66, 72.26, 70.91, 68.03, 21.8, 21.79. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2O_5$ $[M]^+$: 342.1216, found: 342.1210. IR (KBr film) 3373 (N–H), 3106, 2922, 1741, 1658, 1494, 1363, 1248, 1152, 1074, 988, 862, 745, 625, 480 cm^{-1}.

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