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Mild and Efficient Synthesis of 2-Indole-2'-oxazolines at Room Temperature—A Simple Access to Novel IndOX Ligands

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Abstract: A simple synthesis of a totally new enantiopure compound family, the IndOX compounds, is presented. These chiral compounds can be prepared in two simple steps from commercial starting materials, using no protective groups. The motive for preparing this family is the promising ligand activity of the already known analogs and structural similarity to active pharmaceuticals.

Keywords: asymmetric catalysis, 2-indolecarboxylic acids, IndOX ligand, oxazoline

Indolyl oxazolines are of synthetic interest, both for their potential medicinal and ligand properties. A novel structural group of medically interesting target molecules, represented by the potential antineoplastic agent A-289099, has been recently reported by Abbott Laboratories.^[1] The racemate corresponding to A-289099 was found to be inactive and thus lowers the activity of A-289099.^[1]

Bidentate ligands have gained widespread attention in catalysis, mainly because of their compatibility with a variety of catalyst metals. By varying the electronic and steric properties on the coordination sites, catalytic features can be tuned. Common examples of bidentate ligands are those

with two nitrogen atoms as coordination sites, such as PyOX,^[2] PyrOX,^[3] BOX,^[4] or bipyridines (bipy),^[5] the first two of which are non-C₂-symmetric (Fig. 1). These cores have electronically different rings surrounding the coordinating nitrogens, facilitating easier tuning of the ligands.

In this article, we present an efficient synthesis of the enantiopure 2-indolyl-2'-oxazoline core (IndOX, Fig. 2). A racemic version corresponding to this structure has been reported earlier.^[7] The oxazoline ring chirality has been utilized in ligand design for only two decades.^[8–10]

IndOX compounds are not yet tested as ligands, but recent studies of pyrrolyl oxazolines (PyrOX) in metal-mediated asymmetric reactions^[11] can also be seen as an indication of IndOX-ligand activity.

We decided to investigate the synthesis of the IndOX structures with differing electronic properties. We chose to vary the substituents at the 5-position of the indole ring (Scheme 1) to obtain information on the electronic impact on substituents at a fixed position. The chosen substituents at the indole ring were the electron-donating methoxy group, the neutral unsubstituted ligand, and the withdrawing chloride group, while the oxazoline ring was kept fixed. Correspondingly, we functionalized the oxazoline ring with the *t*-butyl, benzyl, phenyl, and *i*-butyl tails in the case of unsubstituted indole derivative. In all of these cases, preparation worked in a similar manner and caused no problems. The indole nitrogen need not be protected for this synthesis. The synthesis was also performed with the phenylsulfonyl and Boc protected acids **1–3**, but the unprotected route was more efficient. The commercial 2-indolecarboxylic acids were coupled with the suitable amino alcohols using standard amide coupling, and cyclization could be achieved in a single step by mesylation under basic conditions at room temperature (Scheme 1). This contrasts with the preparation of PyOX ligands, where the cyclization had to be promoted by another base treatment of the formed mesylate at elevated temperatures.^[12] The clean reactions went into completion, and no chromatographic purification was needed. The yields varied between moderate and good. The

Figure 1. Structures of antineoplastic A-289099 and bidentate non-C₂-symmetric N,N-ligand cores: PyOX, PyrOX,^[6] and IndOX (framed).

Figure 2. Novel IndOX core and its building blocks. R_2 denotes a substituent at a chiral center.

difference in yields mainly depended on crystallization difficulties rather than reactivity (Table 1).

Formation of amido alcohols **4–9** was an efficient step, and it was completed cleanly within 2–3 h. Complete conversion could always be achieved according to thin-layer chromatographic (TLC) analysis. Furthermore, the reactions proceeded cleanly: no amido ester was formed using BOP coupling at pH = 9. The amido alcohol was then smoothly cyclized to the corresponding oxazoline (**10–15**) in a single step, without base treatment or heating. Furthermore, no racemization of the oxazoline ligand was detected. Ligand **12** was prepared from both (*R*)- and (*S*)-phenylalaninol and their purity was determined by chiral HPLC (Chiralpak OD, 10% *i*PrOH/hexane, 1.0 ml/min), $t_R((R)\text{-12})$ 16.5 min, $t_R((S)\text{-12})$ 36.7 min. The achieved yields on these clean, complete reactions remained moderate because of difficult crystallizations. Column chromatographic purification was, however, avoided in this work.

A novel, enantiopure compound family has been synthesized in two simple and clean reaction steps. This excludes the need for chromatographic purification and protective groups of these compounds. Further investigations of applications of the IndOX family are in progress in our laboratory.

Scheme 1. Preparation of IndOX ligands: i, **1–3**, amino alcohol, BOP, DIPEA, CH_2Cl_2 , rt, pH = 9; ii, **4–9**, MsCl, NEt_3 , DMAP, CH_2Cl_2 , rt.

Table 1. Isolated yields of compounds **4–15**

Compound	Yield (%)
4	42
5	65
6	50
7	40
8	84
9	49
10	68
11	47
12	65
13	57
14	41
15	59

EXPERIMENTAL

For all reactions, dried solvents were used; the dichloromethane was distilled over CaH_2 . The NMR spectra were recorded on a Bruker Avance 400 spectrometer (^1H 400.13 MHz, ^{13}C 100.61 MHz) in CDCl_3 using the signal of the solvent as the internal standard (residual CHCl_3 for ^1H : δ 7.26 ppm, or CDCl_3 ^{13}C : δ 77.0 ppm) or in DMSO (^1H : δ 2.50 ppm, ^{13}C : δ 39.5 ppm). TLC plates were Merck aluminium-based plates with silica gel 60 F_{254} (230–400 mesh). For indicating, UV light ($\lambda = 254$ nm), KMnO_4 solution (1.0 g KMnO_4 , 6.7 g K_2CO_3 , 1.7 ml 5% aq. NaOH solution, 100 ml H_2O), or ninhydrin solution (1.0 g ninhydrin, 0.2 ml glacial AcOH, 100 ml EtOH) was used. Flash chromatography was made with Merck silica gel 60 F_{254} (230–400 mesh), and the eluents for TLC and flash chromatography were of commercial quality. Elemental analyses have been provided for solid products and HRMS for oils and foams.

Typical Procedure for Formation of Amido Alcohols **4–9**

A substituted indole-2-carboxylic acid (2.58 mmol, 100 mol%) was dissolved in 7 ml of CH_2Cl_2 and 1 ml of DMF. A chiral amino alcohol (2.60 mmol, 100 mol%) in 4 ml of CH_2Cl_2 was added, followed by 2.62 mmol (100 mol%) of BOP. The acidity of the reaction was kept at pH = 9 by addition of DIPEA. As the reaction reached completion according to TLC (2–3 h), it was quenched by water and extracted three times with CH_2Cl_2 . The extracts were washed with water and dried over Na_2SO_4 . The residue was filtered through a pad of silica to yield a quantitative amount of a crude

crystalline product. It was recrystallized from the indicated solvent system to yield 1.27 mmol of product.

Typical Procedure for Formation of 10–15

An amido alcohol (1.00 mmol, 100 mol%) was dissolved in 7 ml of CH₂Cl₂. NEt₃ (6.03 mmol, 600 mol%) and 0.21 mmol (20 mol%) of DMAP were added. To this mixture was carefully added 2.83 mmol (280 mol%) MsCl. The progress was monitored by TLC, to see the formation and later the disappearance of the mesylate intermediate. After 1.5 h, the oxazoline was totally formed. The reaction was quenched with water and diluted with CH₂Cl₂, followed by extraction twice with CH₂Cl₂. The extracts were washed with water and dried over Na₂SO₄. The residue was filtered through a pad of silica to yield the crude product. It was recrystallized from the indicated solvent system to yield 0.59 mmol of a white powder.

Data on Compound 4

Yield: 215 mg (0.82 mmol, 42%); $[\alpha]_D^{20}$ –10.0 (*c* 0.5, MeOH); TLC: R_f = 0.79 (EtOAc, UV); mp = 176.5–177°C (CH₂Cl₂); ¹H NMR (400 MHz, d₆-DMSO) δ 11.49 (br s, 1H, indoleN-*H*), 7.80 (d, 1H, *J* = 9.5 Hz, -CONHR), 7.59 (d, 1H, *J* = 8.0 Hz, 4-indoleC-*H*), 7.41 (d, 1H, *J* = 8.2 Hz, 7-indoleC-*H*), 7.22 (d, 1H, *J* = 1.3 Hz, 3-indoleC-*H*), 7.17–7.13 (m, 1H, 6-indoleC-*H*), 7.03–6.99 (m, 1H, 5-indoleC-*H*), 4.49–4.46 (m, 1H, -CH₂OH), 3.93–3.87 (m, 1H, -NHCHCH₂CMe₃), 3.71–3.65 (m, 1H, -CH_aH_bOH), 3.51–3.45 (m, 1H, -CH_aH_bOH), 0.91 [s, 9H, -C(CH₃)₃]; ¹³C NMR (100 MHz, d₆-DMSO) δ 162.3, 137.2, 133.0, 128.0, 124.0, 122.2, 120.5, 113.1, 103.6, 61.2, 59.9, 35.0, 27.8. CHN: C, 68.59; H, 7.92; N, 10.66. Calculated for C₁₅H₂₀N₂O₂: C, 69.20, H, 7.74; N, 10.76.

Data on Compound 5

Yield: 653 mg (2.22 mmol, 65%); $[\alpha]_D^{20}$ –144.7 (*c* 1, MeOH); TLC: R_f = 0.31 (50% EtOAc/hexane, UV); mp = 181–181.5°C (CH₂Cl₂); ¹H NMR (400 MHz, d₆-DMSO) δ 11.47 (br s, 1H, indoleN-*H*), 8.20 (d, 1H, *J* = 8.5 Hz, -CONHR), 7.61 (d, 1H, *J* = 8.1 Hz, 4-indoleC-*H*), 7.41 (dd, 1H, *J* = 0.7 Hz, *J* = 8.2 Hz, 7-indoleC-*H*), 7.30–7.22 (m, 4H, 3-indoleC-*H*, 3*Ar-*H*), 7.18–7.12 (m, 3H, 3-indoleC-*H*, 2*Ar-*H*), 7.05–7.00 (m, 1H, 5-indoleC-*H*), 4.91 (t, 1H, *J* = 5.6 Hz, -CH₂OH), 3.55–3.45 (m, 2H, -CH_aH_bOH), 2.99 (dd, 1H, *J* = 5.0 Hz, *J* = 13.7 Hz, -CH_aH_bPh), 2.81 (dd, 1H, *J* = 9.2 Hz, *J* = 13.7 Hz, -CH_aH_bPh); ¹³C NMR (100 MHz, d₆-DMSO) δ 161.6, 140.3, 137.2, 132.7, 129.9, 129.0, 127.9, 126.8, 124.0,

122.3, 120.5, 113.1, 103.4, 63.9, 53.7, 37.4. CHN: C, 73.03; H, 6.17; N, 9.31. Calculated for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52.

Data on Compound 6

Yield: 525 mg (1.87 mmol, 50%); $[\alpha]_D^{20} + 105.5$ (*c* 1, MeOH); TLC: $R_f = 0.18$ (50% EtOAc/hexane, UV); mp = 217–218°C (CH₂Cl₂); ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.54 (br s, 1H, indoleN-*H*), 8.70 (d, 1H, *J* = 8.2 Hz, -CONHR), 7.64 (d, 1H, *J* = 7.9 Hz, 4-indoleC-*H*), 7.44–7.41 (m, 3H, 3*Ar-*H*), 7.35–7.16 (m, 5H, 3-indoleC-*H*, 6-indoleC-*H*, 7-indoleC-*H*, 2*Ar-*H*), 7.05 (td, 1H, *J* = 0.8 Hz, *J* = 7.9 Hz, 5-indoleC-*H*), 5.15–5.10 (m, 1H, -NHCHRPh), 5.00 (t, 1H, *J* = 5.7 Hz, -CH_aH_bOH), 3.78–3.68 (m, 2H, -CH_aH_bOH); ¹³C NMR (100 MHz, *d*₆-DMSO) δ 161.7, 142.1, 137.3, 132.6, 129.0, 127.9, 127.8, 127.7, 124.2, 122.3, 120.6, 113.1, 103.9, 65.4, 56.3. CHN: C, 72.30; H, 5.57; N, 9.84. Calculated for C₁₇H₁₆N₂O₂: C, 72.84; H, 5.75; N, 9.99.

Data on Compound 7

Yield: 415 mg (1.59 mmol, 40%); $[\alpha]_D^{20} - 39.6$ (*c* 0.5, CDCl₃); TLC: $R_f = 0.22$ (50% EtOAc/hexane, UV); ¹H NMR (400 MHz, CDCl₃) δ 9.68 (br s, 1H, indoleN-*H*), 7.62 (dd, 1H, *J* = 0.7 Hz, *J* = 8.0 Hz, 7-indoleC-*H*), 7.41 (dd, 1H, *J* = 0.8 Hz, *J* = 8.3 Hz, 4-indoleC-*H*), 7.28 (ddd, 1H, *J* = 1.1 Hz, *J* = 7.1 Hz, *J* = 8.2 Hz, 6-indoleC-*H*), 7.14 (ddd, 1H, *J* = 1.0 Hz, *J* = 7.1 Hz, *J* = 8.0 Hz, 5-indoleC-*H*), 6.89 (dd, 1H, *J* = 0.7 Hz, *J* = 2.0 Hz, 3-indoleC-*H*), 6.45 (d, 1H, *J* = 8.5 Hz, -CONHR), 4.38–4.31 (m, 1H, -NHCHR₂), 3.83 (dd, 1H, *J* = 3.6 Hz, *J* = 11.0 Hz, -CH_aH_bOH), 3.83 (dd, 1H, *J* = 5.5 Hz, *J* = 11.0 Hz, -CH_aH_bOH), 3.01 (br s, 1H, -CH_aH_bOH), 1.79–1.70 (m, 1H, -RCHMe₂), 1.61–1.55 (m, 1H, -RCH_aH_bCMe₂), 1.54–1.44 (m, 1H, -RCH_aH_bCMe₂), 0.98 [dd, 6H, *J* = 1.7 Hz, *J* = 6.6 Hz, -CH(CH₃)₂]; ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 136.8, 130.9, 128.0, 125.0, 122.3, 121.1, 112.4, 102.9, 66.4, 50.6, 40.8, 25.4, 23.5, 22.6; EI-HRMS *m/z* calcd. for C₁₅H₂₀N₂O₂ + Na: 283.1422; found: 283.1398 (M + Na).

Data on Compound 8

Yield: 462 mg (1.59 mmol, 84%); $[\alpha]_D^{20} - 5.2$ (*c* 0.5, MeOH); TLC: $R_f = 0.23$ (50% EtOAc/hexane, UV); mp = 136–137°C (CH₂Cl₂/hexane); ¹H NMR (400 MHz, CDCl₃) δ 9.80 (br s, 1H, indoleN-*H*), 7.17 (d, 1H, *J* = 8.6 Hz, 7-indoleC-*H*), 6.93–6.86 (m, 2H, 4- and 6-indoleC-*H*), 6.78 (d, 1H, *J* = 1.6 Hz, 3-indoleC-*H*), 6.56 (d, 1H, *J* = 1.6 Hz, -CONHR), 4.15–4.08 (m, 1H, -NHCHCH₂CMe₃), 3.98–3.92 (m, 1H, -CH_aH_bOH), 3.79 (s, 3 H, ArOCH₃), 3.74–3.66 (m, 1H, -CH_aH_bOH), 3.42 (br s, 1H, -OH), 1.03 [s, 9H,

-C(CH₃)₃]; ¹³C NMR (100 MHz, CDCl₃) δ 163.1, 155.1, 132.1, 131.3, 128.7, 128.3, 116.3, 113.2, 102.7, 63.3, 60.0, 56.1, 34.4, 27.4. CHN: C, 65.93; H, 7.81; N, 9.54. Calculated for C₁₆H₂₂N₂O₃: C, 66.18; H, 7.64; N, 9.65.

Data on Compound 9

Yield: 375 mg (1.27 mmol, 49%); [α]_D²⁰ -2.4 (c 0.5, MeOH); TLC: R_f = 0.50 (50% EtOAc/hexane, UV); mp = 171.5–172°C (CH₂Cl₂/hexane); ¹H NMR (400 MHz, d₆-DMSO) δ 11.74 (br s, 1H, indoleN-*H*), 7.93 (d, 1H, *J* = 9.5 Hz, -CONHR), 7.70 (d, 1H, *J* = 2.0 Hz, 4-indoleC-*H*), 7.44 (d, 1H, *J* = 8.7 Hz, 7-indoleC-*H*), 7.25 (d, 1H, *J* = 1.6 Hz, 3-indoleC-*H*), 7.17 (dd, 1H, *J* = 2.1 Hz, *J* = 8.7 Hz, 6-indoleC-*H*), 4.51–4.48 (m, 1H, -CH₂OH), 3.95–3.90 (m, 1H, -NHCHCH₂CMe₃), 3.72–3.67 (m, 1H, -CH_aH_bOH), 3.53–3.46 (m, 1H, -CH_aH_bOH), 0.93 [s, 9H, -C(CH₃)₃]; ¹³C NMR (100 MHz, d₆-DMSO) δ 162.0, 135.6, 134.6, 129.0, 124.9, 124.0, 121.3, 114.6, 103.2, 61.1, 60.1, 35.0, 27.8; EI-HRMS *m/z* calcd. for C₁₅H₁₉ClN₂O₂ + Na: 317.1033; found: 317.1024 (M + Na).

Data on Compound 10

Yield: 163 mg (0.67 mmol, 68%); [α]_D²⁰ -16.5 (c 0.2, MeOH); TLC: R_f = 0.30 (20% EtOAc/hexane, UV); mp = 127–128.5°C (MeOH/H₂O); ¹H NMR (400 MHz, CDCl₃) δ 10.74 (br s, 1H, indoleN-*H*), 7.70–7.67 (m, 1H, 7-indoleC-*H*), 7.36 (dd, 1H, *J* = 0.9 Hz, *J* = 8.3 Hz, 4-indoleC-*H*), 7.28 (ddd, 1H, *J* = 1.1 Hz, *J* = 7.0 Hz, *J* = 8.2 Hz, 6-indoleC-*H*), 7.14 (ddd, 1H, *J* = 1.0 Hz, *J* = 7.0 Hz, *J* = 8.0 Hz, 5-indoleC-*H*), 7.05 (dd, 1H, *J* = 0.8 Hz, *J* = 2.0 Hz, 3-indoleC-*H*), 4.51 (dd, 1H, *J* = 8.7 Hz, *J* = 10.0 Hz, 4-oxC-*H*), 4.38 (dd, 1H, *J* = 7.4 Hz, *J* = 8.6 Hz, 5-oxC-*H_a*), 4.23 (dd, 1H, *J* = 7.4 Hz, *J* = 10.0 Hz, 5-oxC-*H_b*), 0.97 [s, 9H, -C(CH₃)₃]; ¹³C NMR (100 MHz, CDCl₃) δ 159.5, 137.7, 128.2, 125.8, 124.6, 122.3, 120.6, 111.9, 106.5, 76.1, 69.6, 34.6, 26.2. CHN:C, 74.25; H, 7.43; N, 11.40. Calculated for C₁₅H₁₈N₂O: C, 74.35; H, 7.49; N, 11.56.

Data on Compound 11

Yield: 190 mg (0.69 mmol, 47%); [α]_D²⁰ +30.4 (c 0.5, CDCl₃); TLC: R_f = 0.75 (50% EtOAc/hexane, UV); ¹H NMR (400 MHz, CDCl₃) δ 9.62 (br s, 1H, indoleN-*H*), 7.69 (dd, 1H, *J* = 0.9 Hz, *J* = 8.0 Hz, 7-indoleC-*H*), 7.42–7.38 (m, 1H, 4-indoleC-*H*), 7.33–7.22 (m, 6H, 6-indoleC-*H*, 5*Ar-*H*), 7.16 (ddd, 1H, *J* = 1.0 Hz, *J* = 7.0 Hz, *J* = 8.0 Hz, 5-indoleC-*H*), 7.05 (dd, 1H, *J* = 0.9 Hz, *J* = 2.0 Hz, 3-indoleC-*H*), 4.71–4.64 (m, 1H, 4-oxC-*H*), 4.47 (dd, 1H, *J* = 8.5 Hz, *J* = 9.1 Hz, 5-oxC-*H_a*), 4.23 (dd, 1H,

$J = 7.3$ Hz, $J = 8.4$ Hz, 5-oxC- H_b), 3.19 (dd, 1H, $J = 5.8$ Hz, $J = 13.8$ Hz, -RCH_aH_bPh), 2.82 (dd, 1H, $J = 8.3$ Hz, $J = 13.8$ Hz, -RCH_aH_bPh); ¹³C NMR (100 MHz, CDCl₃) δ 159.5, 138.1, 137.5, 129.6, 129.0, 128.2, 127.0, 125.7, 124.8, 122.4, 120.8, 111.9, 106.7, 72.6, 68.0, 42.3; EI-HRMS m/z calcd for C₁₈H₁₆N₂O + H: 277.1341; found: 277.1328 (M + H).

Data on Compound 12

Yield: 240 mg (0.91 mmol, 65%); $[\alpha]_D^{20}$ -34.4 (c 0.5, CDCl₃); TLC: R_f = 0.63 (50% EtOAc/hexane, UV); mp = 145.5–146°C (MeOH); ¹H NMR (400 MHz, CDCl₃) δ 9.32 (br s, 1H, indoleN- H), 7.71 (dd, 1H, $J = 0.7$ Hz, $J = 8.0$ Hz, 7-indoleC- H), 7.41–7.29 (m, 7H, 4-indoleC- H , 6-indoleC- H , 5*Ar- H), 7.17 (ddd, 1H, $J = 1.0$ Hz, $J = 7.0$ Hz, $J = 8.0$ Hz, 6-indoleC- H), 7.14–7.13 (m, 1H, 3-indoleC- H), 5.44 (dd, 1H, $J = 8.1$ Hz, $J = 9.9$ Hz, 5-oxC- H_a), 4.87 (dd, 1H, $J = 8.4$ Hz, $J = 9.9$ Hz, 5-oxC- H_b), 4.35 (app t, 1H, $J = 8.4$ Hz, 4-oxC- H); ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 142.4, 137.4, 129.3, 128.2, 128.2, 127.1, 125.4, 125.0, 122.4, 120.9, 111.9, 107.0, 75.5, 70.2. CHN:C, 77.78; H, 5.10; N, 10.48. Calculated for C₁₇H₁₄N₂O: C, 77.84; H, 5.38; N, 10.68.

Data on Compound 13

Yield: 185 mg (0.76 mmol, 57%); $[\alpha]_D^{20}$ -20.6 (c 1, CDCl₃); TLC: R_f = 0.70 (50% EtOAc/hexane, UV); ¹H NMR (400 MHz, CDCl₃) δ 10.65 (br s, 1H, indoleN- H), 7.71 (app d, 1H, $J = 8.0$ Hz, 7-indoleC- H), 7.38 (dd, 1H, $J = 0.6$ Hz, $J = 8.2$ Hz, 4-indoleC- H), 7.32–7.27 (m, 1H, 6-indoleC- H), 7.18–7.13 (m, 1H, 5-indoleC- H), 7.09–7.08 (m, 1H, 3-indoleC- H), 4.63 (dd, 1H, $J = 8.1$ Hz, $J = 9.1$ Hz, 5-oxC- H_a), 4.53–4.44 (m, 1H, 4-oxC- H), 4.13 (app t, 1H, $J = 7.6$ Hz, 5-oxC- H_b), 1.92–1.82 [m, 1H, -RCH(CH₃)₂], 1.74–1.67 (m, 1H, -RCH_aH_bCHMe₂), 1.47–1.39 (m, 1H, -RCH_aH_bCHMe₂), 0.94 [dd, 6H, $J = 6.6$ Hz, $J = 17.8$ Hz, -CH(CH₃)₂]; ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 137.8, 128.2, 126.0, 124.6, 122.3, 120.7, 112.0, 106.5, 73.9, 64.9, 46.1, 25.7, 23.4, 22.8; EI-HRMS m/z calcd. for C₁₅H₁₈N₂O + H: 243.1497; found: 243.1485 (M + H).

Data on Compound 14

Yield: 45 mg (0.17 mmol, 41%); $[\alpha]_D^{20}$ -2.8 (c 0.4, MeOH); TLC: R_f = 0.84 (50% EtOAc/hexane, UV); ¹H NMR (400 MHz, CDCl₃) δ 13.02 (br s, 1H, indoleN- H), 7.53 (d, 1H, $J = 9.1$ Hz, 7-indoleC- H), 7.37–7.35 (m, 1H, 4-indoleC- H), 7.13 (dd, 1H, $J = 2.4$ Hz, $J = 9.1$ Hz, 6-indoleC- H), 6.97 (d, 1H, $J = 2.4$ Hz, 3-indoleC- H), 4.97 (app t, 1H, $J = 9.8$ Hz, 4-oxC- H), 4.78 (dd, 1H, $J = 3.2$ Hz, $J = 9.5$ Hz, 5-oxC- H_a), 4.41 (dd, 1H, $J = 3.2$ Hz, $J = 10.0$ Hz, 1H, 5-oxC- H_b), 3.85 (s, 3 H, ArOCH₃), 1.16 [s, 9H,

-C(CH₃)₃]; ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 154.9, 132.9, 128.5, 126.1, 116.0, 112.7, 106.2, 102.8, 76.1, 69.5, 56.1, 34.5, 26.2; EI-HRMS m/z calcd for C₁₆H₂₀N₂O₂ + H: 273.1603; found: 273.1609 (M + H).

Data on Compound 15

Yield: 164 mg (0.59 mmol, 59%); [α]_D²⁰ -9.2 (c 1, MeOH); TLC: R_f = 0.74 (50% EtOAc/hexane, UV); mp = 77–78°C (MeOH/H₂O); ¹H NMR (400 MHz, CDCl₃) δ 11.24 (br s, 1H, indoleN-*H*), 7.65 (d, 1H, *J* = 1.9 Hz, 4-indoleC-*H*), 7.28–7.26 (m, 1H, 7-indoleC-*H*), 7.22 (dd, 1H, *J* = 2.0 Hz, *J* = 8.7 Hz, 6-indoleC-*H*), 6.99–6.98 (m, 1H, 3-indoleC-*H*), 4.53 (dd, 1H, *J* = 8.8 Hz, *J* = 10.0 Hz, 4-oxC-*H*), 4.40 (dd, 1H, *J* = 7.4 Hz, *J* = 8.7 Hz, 5-oxC-*H*_a), 4.22 (dd, 1H, *J* = 7.4 Hz, *J* = 10.0 Hz, 5-oxC-*H*_b), 0.94 [s, 9H, -C(CH₃)₃]; ¹³C NMR (100 MHz, CDCl₃) δ 159.6, 136.2, 129.0, 127.0, 126.2, 125.1, 121.5, 113.0, 106.2, 76.1, 69.7, 34.6, 26.1. CHN: C, 65.06; H, 5.88; N, 9.88. Calculated for C₁₅H₁₇ClN₂O: C, 65.10; H, 6.19; N, 10.12.

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