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Synthesis of Novel Indole Analogues of Mycophenolic Acid as Potential Antineoplastic Agents

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Abstract—The expedient synthesis of three novel indole analogues, **2a–c**, of mycophenolic acid is described, which involved as the key steps both the $Et_2O{\cdot}BF_3$ catalyzed amino-Claisen rearrangement of *N*-allylindoline to 7-allylindoline and the ortho ester Claisen rearrangement of the allylic alcohol **12** to the methyl ester **14**. The installation of the substituents at the C-3 position in **2b** and **2c** was accomplished via Vilsmeier formylation and subsequent oxidation–aminolysis or oxidation–methoxylation. The synthetic approach described possesses general usefulness. The analogue **2b** showed significant, reproducible antitumor activity.

Introduction

Inosine monophosphate dehydrogenase (IMPD), the rate-limiting enzyme in the de novo synthesis of guanine nucleotides, catalyzes the oxidation of inosine monophosphate (IMP) to xanthosine monophosphate (XMP) with the concomitant conversion of NAD^+ to NADH.[1–3] Two isoforms of this enzyme are identified in mammalian cells. The type I isoform is expressed constitutively, while the type II is induced during cellular proliferation.[4,5] There is a markedly elevated level of the type II isoform in rapidly proliferating cells such as human tumor cells[5] and, as a result, there is an increased production of guanine nucleotides in these cells. Inhibition of IMPD has been recognized as an important chemotherapeutic approach. For example, the IMPD inhibitor tiazofuran[6] is used in the treatment of human leukemia.

Mycophenolic acid (MPA, **1**), produced by the fermentation of a number of penicillium species,[7] is a potent inhibitor of IMPD with 4.8 times greater specificity against the type II isoform (K_i=6–10 nM),[4a] and it therefore inhibits guanine nucleotide biosynthesis. This compound has been shown to have significant antineoplastic,[8] antiviral,[9] antiparasitic,[10] and immunosuppressive[11] activity. MPA is currently used in the treatment of psoriasis on a compassionate basis.[12] The morpholinoethyl ester prodrug of MPA (mycophenolate mofetil, RS-61443) has recently been approved for use as an immunosuppressant in renal allograft recipients.[13] Two attractive features of MPA are low toxicity and the reversal of toxic effects upon withdrawal. The major problem to limit the clinical utility of MPA for cancer chemotherapy, however, is that sufficient therapeutic blood levels cannot be achieved because of rapid conjugation of its C-7 phenolic group with glucuronic acid to form the inactive β-glucuronide.[14,15] As high as 90% of the drug circulates in this inactive conjugate.[15] Structure–activity studies[16] showed that methylation of the C-7 phenol of MPA eliminated activity and esters (prodrugs) were active only if they could be hydrolyzed in vivo. Replacement of the C-7 phenolic hydroxyl with a thiol produced an inactive compound. The 7-amino analogue of MPA showed less or comparable antitumor activity but was not subject to metabolic inactivation either in vitro or in vivo to form the corresponding β-glucuronide derivative.[15]

As a continuation of our efforts[17] in the development of potent, metabolically stable IMPD inhibitors for use in neoplastic disease, we designed and synthesized the indole analogues, **2a–c**, of MPA, in which the metabolically labile phenolic group was replaced by an isosteric, 'fixed-geometry' hydrogen-bonding N–H group of an indole ring, and the requisite MPA hexenoic acid side chain was retained at the C-7 position. The fixed hydrogen-bonding geometry of these indole analogues is identical to one of the two favored geometries of the MPA phenolic group.[18] For the analogues **2b** and **2c**, the carboxamide and methoxycarbonyl moieties were respectively attached at the C-3 position to prove the impact of these pharmacologically significant substituents. In this paper, we describe the

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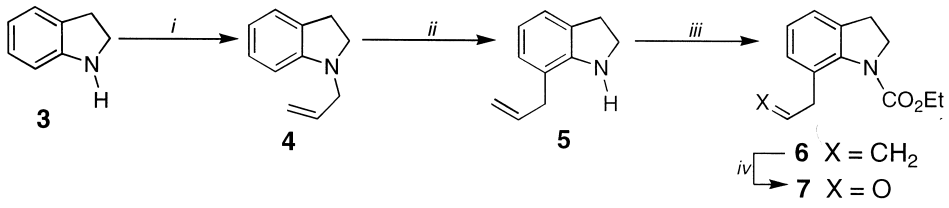
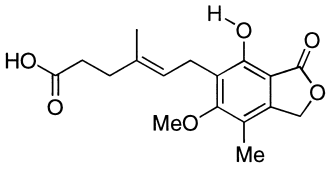
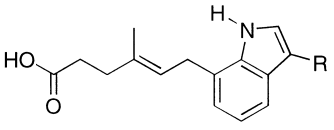


Scheme 1. (i) Allyl bromide, Et_3N, DMF; (ii) $Et_2O{\cdot}BF_3$, sulfolane, 200–210°C; (iii) $ClCO_2Et$, 2,6-lutidine, THF; (iv) OsO_4, $NaIO_4$, THF–H_2O (3:1).

expedient synthesis of these title compounds (**2a**–**c**) using our two-Claisen-rearrangement strategy.[17c]



MPA, **1**

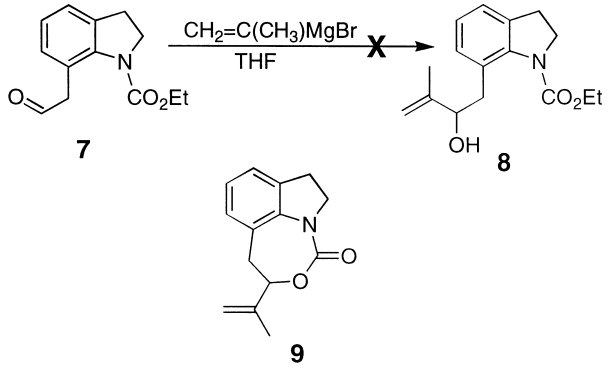


2a R = H
2b R = $CONH_2$
2c R = CO_2Me

Results and Discussion

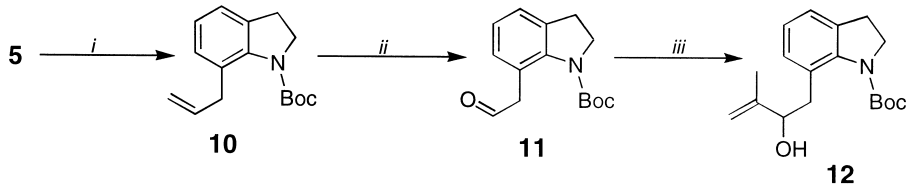
The synthesis of these new MPA analogues **2a**–**c** features both the amino-Claisen rearrangement of *N*-allylindoline (**4**), leading to the introduction of the allyl group at the C-7 position, and the ortho ester Claisen rearrangement of the allylic alcohol **12** to complete the construction of the MPA side chain in the ester form. As shown in Scheme 1, treatment of indoline with allyl bromide and triethylamine in DMF gave *N*-allylindoline (**4**) in 90% yield. After some difficulties had been experienced, we found that rearrangement of *N*-allylindoline smoothly proceeded in the presence of $Et_2O{\cdot}BF_3$ in sulfolane under argon at 200–210°C to furnish 7-allylindoline (**5**) in 47% yield.[19] Conversion of **5** to the ethoxycarbonyl derivative **6** was uneventfully accomplished by using ethyl chloroformate and 2,6-lutidine in THF. Oxidative cleavage of the double bond in the carbamate **6** with OsO_4–$NaIO_4$ in THF–H_2O (3:1)[20] provided the aldehyde **7** as a yellow liquid in 56% yield.

With the aldehyde **7** in hand, we investigated its reaction with isopropenyl magnesium bromide (prepared from isopropenyl bromide and magnesium turnings in THF[21]). Treatment of **7** with this Grignard reagent did not afford the desired allylic alcohol **8**. Instead the tricyclic compound **9** was obtained in 76% yield as a white crystalline solid (mp 79–81°C). The structure of **9** was confirmed by ^1H and ^{13}C NMR, APT, IR, and elemental analyses. Its formation may be due to the intramolecular attack of the resulting anion of Grignard reaction at the carbamate carbonyl group with the ethoxy group subsequently leaving.

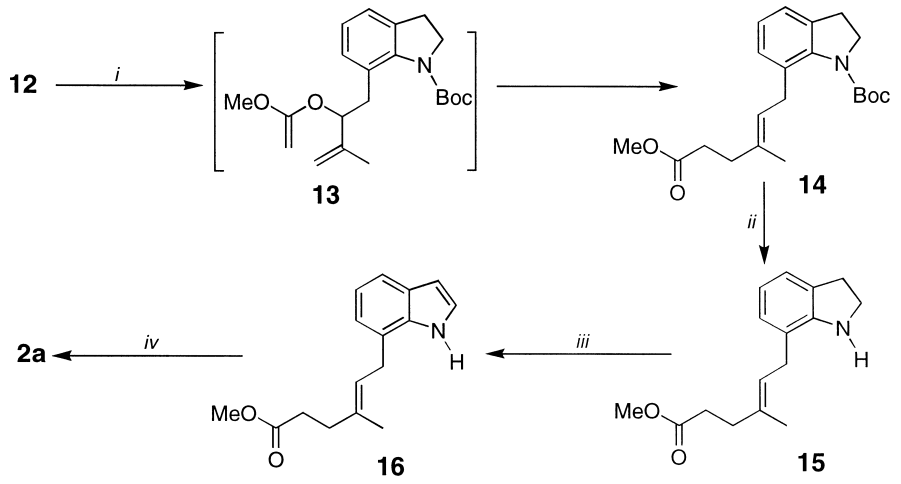


The sterically hindered, not readily leaving *tert*-butoxycarbonyl (Boc) protecting group was next tested in the hope of surmounting the formation of the undesired tricyclic compound **9**. As outlined in Scheme 2, 7-allylindoline (**5**) was converted to its Boc derivative **10** by treatment with di-*tert*-butyl dicarbonate in dioxane at 80°C.[22] Subsequent oxidation of **10** with OsO_4–$NaIO_4$[20] gave rise to the aldehyde **11** in 57% yield. Reaction of this aldehyde **11** with isopropenyl magnesium bromide in THF did indeed produce the desired allylic alcohol **12** as a white solid, without the tricyclic byproduct **9** being detected.

The synthesis of the title compound **2a** from the allylic alcohol **12** was realized in four steps (Scheme 3). Thus, under the conditions of the ortho ester Claisen rearrangement, the alcohol **12** was treated with excess trimethyl orthoacetate (10–20 equiv.) in the presence of a catalytic amount of propanoic acid (0.5–0.8 equiv.) under argon at 105–110°C overnight (ca. 12 h)[21,23] to give the corresponding methyl ester **14** in nearly quantitative yield (98%) presumably via the intermediate **13**. Removal of the Boc



Scheme 2. (i) Boc_2O, dioxane, 80°C; (ii) OsO_4, $NaIO_4$, THF–H_2O (3:1); (iii) $CH_2{=}C(CH_3)Br$, Mg, THF.



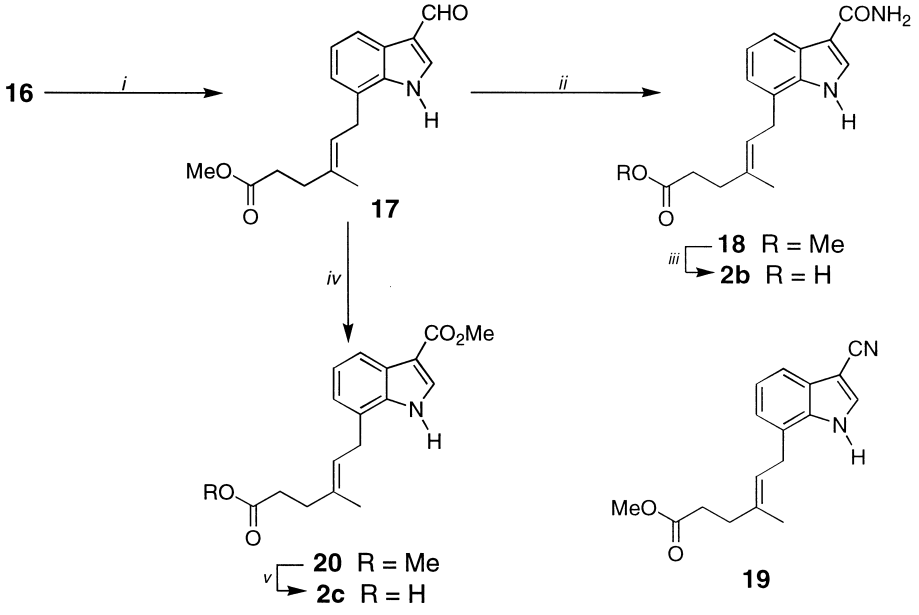
Scheme 3. (i) $CH_3C(OCH_3)_3$, $CH_3CH_2CO_2H$, 105–110°C; (ii) 4 M HCl, dioxane; or 2 M TFA, CH_2Cl_2; (iii) DDQ, xylenes, 100–110°C; (iv) KOH, EtOH, H_2O.

protecting group in **14** with 4 M HCl solution in dioxane[24] afforded the indoline **15** in 72% yield. This deprotection was also achieved in 60% yield by using 2 M TFA solution in CH_2Cl_2.[22] Dehydrogenation of **15** with DDQ in xylenes at 100–110°C[25] readily gave the indole **16** in 75% yield. Alkaline hydrolysis of the ester in **16** furnished the title compound **2a** as a white solid (mp 78–79.5°C, 92%).

The 3-substituted indole analogues **2b** and **2c** were prepared from the advanced intermediate **16**. As depicted in Scheme 4, Vilsmeier formylation of **16** with $POCl_3$ and DMF expectedly afforded the 3-formylindole **17** in satisfactory yield (77%).[26] Treatment of **17** with manganese dioxide and ammonia in 2-propanol in the presence of sodium cyanide[27] gave the desired amide **18** as a white solid in 76% yield along with a small amount of the 3-cyanoindole **19** (5%). Formation of the byproduct **19** might proceed through oxidation of the resulting aldimine from the aldehyde **17** and ammonia.[27] Alkaline hydrolysis of the ester in **18** provided the title analogue **2b** as a white solid (mp 171–172°C, 83%). Conversion of **17** to the diester **20** was accomplished by means of our modification[28] of the one-pot method reported by Corey and coworkers.[29] Selective alkaline hydrolysis of the side chain ester in **20** furnished the title analogue **2c** as a white solid (mp 92–95°C, 70%) along with the recovery of 20% of the starting diester **20**.

Preliminary biological tests showed that the carboxamide analogue **2b** possessed significant, reproducible activity in the NCI human tumor panel screen (mean $GI_{50}=3.5\times10^{-6}$ molar, for the human ovarian cancer cell line IGROV1, $GI_{50}=4.4\times10^{-7}$ molar). The two other analogues **2a** and **2c** were inactive. The analogue **2b** has been selected for advanced study against prostate cancer.

In summary, three novel indole analogues of MPA have been synthesized in 9–11 steps starting from indoline.



Scheme 4. (i) $POCl_3$, DMF; (ii) NaCN, MnO_2, NH_3, 2-propanol; (iii) KOH, EtOH, H_2O; (iv) NaCN, MnO_2, MeOH; (v) KOH, MeOH, H_2O.

This expedient route, based on both the $Et_2O{\cdot}BF_3$ catalyzed amino-Claisen rearrangement and the ortho ester Claisen rearrangement as two key steps, may be easily extended to the synthesis of other related new indole analogues of MPA.

Experimental

Melting points were determined in an open capillary with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively. IR spectra were determined with a Matteson Polaris FT-IR interferometer. Mass spectra were obtained with a VG Analytical ZG70SE spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Silica gel for flash column chromatography (230–400 mesh ASTM) was obtained from EM Science. Commercially available reagents and solvents were used without purification unless otherwise noted.

(*E*)-6-(Indol-7-yl)-4-methyl-4-hexenoic acid (2a). To a solution of **16** (280 mg, 1.09 mmol) in ethanol (4 mL) at 0°C was added 0.5 M KOH solution (13 mL, 6.5 mmol) dropwise, and the mixture was stirred at rt until the hydrolysis was complete (18 h). The mixture was cooled, acidified with cold 5% HCl solution to pH 2–3, and extracted with EtOAc (3×70 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oily residue, which was subjected to flash column chromatography (hexanes–Et_2O–HCO_2H, 150:50:1) to give 243 mg (92%) of **2a** as a white solid: mp 78–79.5°C; ^1H NMR ($CDCl_3$) δ 8.24 (s, broad, 1H, NH), 7.53 (d, J=8.0 Hz, 1H), 7.19 (t, J=2.7–3.0 Hz, 1H), 7.06 (t, J=7.5–7.7 Hz, 1H), 6.99 (d, J=6.7 Hz, 1H), 6.56 (t, J=2.5 Hz, 1H), 5.52 (t, J=6.7–7.0 Hz, 1H), 3.60 (d, J=6.7 Hz, 2H), 2.55 (t, J=6.6–8.3 Hz, 2H), 2.43 (t, J=6.7–7.6 Hz, 2H), 1.85 (s 3H); ^{13}C NMR ($CDCl_3$) δ 179.9, 135.6, 135.5, 128.5, 124.6, 124.0, 123.8, 122.1, 120.5, 119.4, 103.4, 34.7, 33.0, 31.3, 16.8; IR (KBr) 3394, 3146, 2951, 2779, 1697, 1433, 1297, 1208 cm^{-1}; EIMS *m/e* (relative intensity): 242 (M^+-1, 1), 241 (M^+-2, 8), 147 (21), 129 (100), 112 (34), 111(16), 83 (15), 71 (38), 70 (42), 57 (68), 55 (50), 43 (64), 41 (49). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 73.97; H, 7.05; N, 5.67.

(*E*)-6-(3-Carboxamidoindol-7-yl)-4-methyl-4-hexenoic acid (2b). To a solution of **18** (100 mg, 0.33 mmol) in ethanol (4 mL) at 0°C was added 0.5 M KOH solution (3 mL, 1.5 mmol) dropwise, and the mixture was stirred at rt until the hydrolysis was complete (2 h). The mixture was cooled, acidified with cold 5% HCl solution to pH 2–3, and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oily residue, which was subjected to flash column chromatography (CH_2Cl_2–EtOAc–HCO_2H, 50:50:1) to give 79 mg (83%) of **2b** as a white solid: R_f 0.42 (CH_2Cl_2–EtOAc–HCO_2H, 10:10:1); mp 171–172°C; ^1H NMR ($CDCl_3$) δ 9.35 (s, broad, 1H, NH), 8.24 (d, J=2.9 Hz, 1H), 8.05 (s, 2H, NH_2), 7.68 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.4–8.1 Hz, 1H), 7.08 (d, J=7.1 Hz, 1H), 5.59 (t, 1H), 3.70 (d, J=6.5 Hz, 2H), 2.63 (t, J=6.8–8.2 Hz, 2H), 2.47 (t, J=6.7–7.7 Hz, 2H), 1.91 (s 3H); IR (KBr) 3469, 3389, 3306, 3215, 2917, 1705, 1636, 1571, 1447, 1360, 1299, 1207 cm^{-1}; CIMS *m/e* (relative intensity): 287 (MH^+, 54), 286 (M^+, 14), 269 (54), 250 (22), 244 (68), 243 (29), 175 (100), 161 (29), 132 (15), 117 (26), 115 (66); HRMS calcd for $C_{16}H_{18}NO_3$ (M^+), 286.1317, found, 286.1317. Anal. Calcd for $C_{16}H_{18}NO_3{\cdot}0.5H_2O$: C, 65.07; H, 6.48; N, 9.49. Found: C, 64.94; H, 6.21; N, 9.28.

(*E*)-6-[3-(Methoxycarbonyl)indol-7-yl]-4-methyl-4-hexenoic acid (2c). To a solution of **20** (150 mg, 0.48 mmol) in methanol (10 mL) at 0°C was added 0.5 M KOH solution (2 mL, 1.0 mmol) dropwise, and the mixture was stirred at rt for 2 h and then diluted with EtOAc (40 mL). The mixture was cooled, acidified with cold 5% HCl solution to pH 3, and extracted with EtOAc (3×80 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give an oily residue, which was subjected to flash column chromatography (EtOAc–hexanes–HCO_2H, 100:100:1) to give 30 mg of the starting diester **20** and 80 mg (70%) of **2c** as a white solid: R_f 0.51 (EtOAc–hexanes–HCO_2H, 150:75:1); mp 92–95°C; ^1H NMR ($CDCl_3$) δ 9.08 (s, broad, 1H, NH), 8.03 (d, J=7.7 Hz, 1H), 7.93 (d, J=3.0 Hz, 1H), 7.19 (t, J=7.4–8.1 Hz, 1H), 7.05 (d, J=7.1 Hz, 1H), 5.51 (t, 1H), 3.90 (s, 3H), 3.62 (d, J=7.1 Hz, 2H), 2.57 (t, J=6.7–7.1 Hz, 2H), 2.42 (t, J=6.6 Hz, 2H), 1.83 (s 3H); ^{13}C NMR ($CDCl_3$) δ 179.1, 166.8, 136.2, 136.0, 132.1, 126.5, 124.7, 123.6, 123.4, 122.7, 120.0, 109.0, 51.7, 34.7, 32.5, 31.5, 16.8; IR (KBr) 3298, 2910, 1691, 1612, 1535, 1446, 1296, 1194, 1172, 1123 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.52; H, 6.35; N, 4.63.

7-Allyl-1-(ethoxycarbonyl)indoline (6). To a solution of 7-allylindoline[19] (3.02 g, 18.97 mmol) and 2,6-lutidine (4.4 mL, 37.78 mmol) in THF (25 mL) at 0°C was added ethyl chloroformate (3.6 mL, 37.65 mmol) dropwise. After addition, the mixture was allowed to warm to rt and stirred overnight. Ether (80 mL) was added and the mixture was then filtered. The filtrate was concentrated under reduced pressure to give a brown oily residue, which was subjected to flash column chromatography (EtOAc–hexanes, 1:10) to afford 3.87 g (88%) of **6** as a pale yellow liquid: R_f 0.20 (EtOAc–hexanes, 1:10); ^1H NMR ($CDCl_3$) δ 7.09–7.03 (m, 3H), 5.98–5.89 (m, 1H), 5.16–5.07 (m, 2H), 4.26 (q, J=7.2 Hz, 2H), 4.13 (t, J=7.6–7.7 Hz, 2H), 3.49 (d, J=6.7 Hz, 2H), 3.00 (t, J=7.7 Hz, 2H), 1.34 (t, J=7.1–7.2 Hz, 3H).

[1-(Ethoxycarbonyl)indolin-7-yl]acetaldehyde (7). A mixture of **6** (3.87 g, 16.73 mmol), OsO_4 (80 mg), THF (45 mL), and water (15 mL) was stirred for 15 min at rt. To the resulting dark brown mixture was added sodium periodate (8.95 g, 41.84 mmol) in small portions over a period of 30 min. After being stirred for 3 h at rt, the reaction was quenched with saturated ammonium chloride solution (30 mL). The mixture was extracted with EtOAc (3×140 mL). The combined organic layers were washed with water (80 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a black brown oily residue, which was subjected to flash column chromatography

(EtOAc–hexanes, 1:10) to afford 2.17 g (56%) of **7** as a yellow liquid: R_f 0.34 (EtOAc–hexanes, 1:5); ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.16 (d, J=7.2 Hz, 1H), 7.07 (t, J=7.2–7.6 Hz, 1H), 7.00 (d, J=7.1 Hz, 1H), 4.21 (q, J=7.1 Hz, 2H), 4.12 (t, J=7.9 Hz, 2H), 3.77 (s, 2H), 3.03 (t, J=7.7–8.1 Hz, 2H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.7, 156.2, 142.7, 135.5, 131.0, 125.4, 124.3, 122.9, 62.6, 50.8, 48.7, 29.9, 15.2; IR (neat) 2980, 2910, 1726, 1711, 1456, 1380, 1324 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_3 \cdot 0.25H_2O$: C, 65.67; H, 6.57; N, 5.89. Found: C, 65.96; H, 6.43; N, 5.93.

6-(Isopropenyl)-1,2,6,7-tetrahydropyrrolo[1,2,3-*cd*][1,3]-benzoxazepin-4-one (9). Into a 100 mL, three-necked, round-bottomed flask were placed magnesium turnings (200 mg, 8.23 mmol). The flask was flame dried under argon and cooled to 25°C, and anhydrous THF (30 mL) and a small crystal of iodine were added. Isopropenyl bromide (0.75 mL, 8.44 mmol) was then added dropwise with stirring. Sufficient external heat was applied to the reaction flask with oil bath (60°C). After addition, the reaction mixture was gently heated at 55–60°C for 1 h, cooled, and diluted with THF (10 mL) to give a grey solution. To this solution was added a solution of **7** (1.27 g, 5.45 mmol) in THF (10 mL) dropwise with cooling of ice-water bath. The mixture was then stirred at rt for 5 h when TLC analysis (EtOAc–hexanes, 1:3) showed the disappearance of the starting material. The mixture was poured into cold saturated ammonium chloride solution (25 mL), and extracted with ether (3×100 mL). The combined organic layers were washed with water (2×50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a brown oily residue, which was subjected to flash column chromatography (EtOAc–hexanes, 1:10) to give 950 mg (76%) of **9** as a white crystalline solid: R_f 0.20 (EtOAc–hexanes, 1:5); mp 79–81°C; ^{1}H NMR ($CDCl_3$) δ 7.10–7.07 (m, 1H), 6.95–6.90 (m, 2H), 5.10 (s, 1H), 4.98 (s, 1H), 4.87 (d, J=10.0 Hz, 1H), 4.23–4.01 (m, 2H), 3.37–3.28 (m, 1H), 3.14–3.07 (m, 1H), 3.09 (s, 1H), 2.98 (d, J=17.0 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.9, 143.0, 139.4, 133.0, 129.0, 124.4, 123.7, 123.6, 114.3, 81.2, 50.3, 38.3, 27.2, 18.7; IR (KBr) 3035, 2973, 2917, 1663, 1601, 1459, 1390, 1323, 1279, 1216 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.33; H, 6.64; N, 5.98.

7-Allyl-1-(*tert*-butoxycarbonyl)indoline (10). A mixture of 7-allylindoline[19] (1.49 g, 9.36 mmol), di-*tert*-butyl dicarbonate (3.2 mL, 13.93 mmol), and dioxane (15 mL) was stirred at 85°C for 1 h. The solvent was removed under reduced pressure to give a yellow oily residue, which was subjected to flash column chromatography (EtOAc–hexanes, 1:10) to afford 2.31 g (95%) of **10** as a pale yellow liquid: R_f 0.49 (EtOAc–hexanes, 1:10); ^{1}H NMR ($CDCl_3$) δ 7.08–6.98 (m, 3H), 5.97–5.83 (m, 1H), 5.15–5.05 (m, 2H), 4.07 (t, J=7.7–7.8 Hz, 2H), 3.51 (d, J=7.0 Hz, 2H), 2.98 (t, J=7.6–7.7 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 54.4, 141.9, 137.5, 135.2, 130.6, 129.2, 125.1, 122.8, 116.4, 81.2, 51.6, 38.3, 30.2, 29.0; IR (neat) 2979, 1811, 1709, 1370, 1120 cm^{-1}.

[1-(*tert*-Butoxycarbonyl)indolin-7-yl]acetaldehyde (11). A mixture of **10** (2.31 g, 8.91 mmol), OsO_4 (80 mg), THF (30 mL), and water (10 mL) was stirred for 15 min at rt. To the resulting dark brown mixture was added sodium periodate (6 g, 28.05 mmol) in small portions over a period of 15 min. After being stirred for 2 h at rt, the insoluble solid was filtered out, and the filtrate was extracted with ether (3×60 mL). The combined organic layers were washed with water (60 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a brown oily residue, which was subjected to flash column chromatography (EtOAc–hexanes, 1:10) to afford 1.32 g (57%) of **11** as a white solid: R_f 0.35 (EtOAc–hexanes, 1:5); mp 58–59°C; ^{1}H NMR ($CDCl_3$) δ.75 (s, 1H), 7.15 (d, J=6.6 Hz, 1H), 7.05 (t, J=7.3–7.6 Hz, 1H), 6.99 (d, J=7.6 Hz, 1H), 4.06 (t, J=7.9 Hz, 2H), 3.77 (s, 2H), 3.02 (t, J=7.7–8.1 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 00.6, 154.2, 142.7, 135.5, 130.9, 125.1, 124.2, 122.9, 81.5, 51.0, 48.9, 29.9, 28.8; IR (KBr) 2986, 2897, 2820, 2715, 1724, 1693, 1455, 1377, 1341 cm^{-1}; EIMS *m/e* (relative intensity) 261 (M^+, 5), 161 (25), 143 (100), 132 (42), 115 (30), 57 (44), 41 (48). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.35; N, 5.33.

1-[1-(*tert*-Butoxycarbonyl)indolin-7-yl]-3-methyl-3-buten-2-ol (12). Into a 100 mL, three-necked, round-bottomed flask were placed magnesium turnings (184 mg, 7.57 mmol). The flask was flame dried under argon and cooled to 25°C, and anhydrous THF (30 mL) and a small crystal of iodine were added. Isopropenyl bromide (0.75 mL, 8.44 mmol) was then added dropwise with stirring. Sufficient external heat was applied to the reaction flask with oil bath (60°C). After addition, the reaction mixture was gently heated at 55–60°C for 1 h, cooled, and diluted with THF (10 mL) to give a grey solution. To this solution was added a solution of **11** (1.32 g, 5.05 mmol) in THF (10 mL) dropwise with cooling of ice-water bath. The mixture was then stirred at rt for 5 h when TLC analysis (EtOAc–hexanes, 1:3) showed the disappearance of the starting material. The mixture was poured into cold saturated ammonium chloride solution (20 mL), and extracted with ether (3×70 mL). The combined organic layers were washed with water (2×50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a brown oily residue, which was subjected to flash column chromatography (EtOAc–hexanes, 1:3) to give 1.05 g (69%) of **12** as a white solid: R_f 0.24 (EtOAc–hexanes, 1:5); mp 79–81°C; ^{1}H NMR ($CDCl_3$) δ.19 (d, J=8.4 Hz, 1H), 7.11–7.06 (m, 2H), 5.03 (s, 1H), 4.84 (s, 1H), 4.46–4.39 (m, 1H), 4.29–4.21 (m, 1H), 3.92–3.85 (m, 1H), 3.82 (s, broad, 1H, OH), 3.18–3.07 (m, 1H), 2.96 (d, J=8.2 Hz, 2H), 2.89–2.79 (m, 1H), 1.83 (s, 3H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 54.7, 148.9, 142.3, 135.5, 129.7, 129.1, 125.5, 123.2, 110.8, 81.8, 75.9, 51.7, 39.2, 30.2, 28.9, 18.3; IR (KBr) 3407, 3072, 2966, 2913, 1678, 1451, 1390, 1243, 1156 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.33; H, 8.35; N, 4.62.

Methyl (*E*)-6-[1-(*tert*-butoxycarbonyl)indolin-7-yl]-4-methyl-4-hexenoate (14). Into a 25-mL, three-necked flask equipped with a condenser, a Dean-Stark trap, and a thermometer were charged **12** (500 mg, 1.65 mmol), trimethyl orthoacetate (4 mL, 31.43 mmol), and propanoic acid (0.1 mL, 1.34 mmol). The mixture was heated at 105–110°C under argon overnight (ca. 12 h). TLC analysis (Et_2O–hexanes, 1:3) showed no presence of the starting

material. The reaction mixture was cooled, and excess trimethyl orthoacetate was removed under reduced pressure to give a yellow liquid residue, which was subjected to flash column chromatography (Et_2O–hexanes, 1:3) to give 580 mg (98%) of **14** as a colorless liquid: R_f 0.34 (Et_2O–hexanes, 1:3); ^1H NMR ($CDCl_3$) δ 7.06–7.03 (m, 1H), 6.98 (d, J=4.6 Hz, 2H), 5.29 (t, 1H), 4.07 (t, J=7.6–7.7 Hz, 2H), 3.66 (s, 3H), 3.42 (d, J=7.2 Hz, 2H), 2.97 (t, J=7.6–7.7 Hz, 2H), 2.47–2.32 (m, 4H), 1.71 (s, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.4, 154.5, 141.9, 135.2, 135.1, 131.8, 128.7, 125.1, 124.3, 122.5, 81.2, 52.1, 51.7, 35.2, 33.6, 32.2, 30.3, 29.0, 16.7; IR (neat) 2956, 2928, 1740, 1708, 1450, 1367, 1245, 1162 cm^{-1}; CIMS *m/e* (relative intensity): 261 (17), 260 (100), 259 (37), 172 (5), 141 (10), 132 (12). Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.10; H, 8.20; N, 3.88.

Methyl (*E*)-6-(indolin-7-yl)-4-methyl-4-hexenoate (15). *Method A:* To a solution of **14** (1.5 g, 4.17 mmol) in dioxane (10 mL) was added 4 M HCl solution in dioxane (2 mL, 8 mmol) dropwise at 0°C. The mixture was stirred at rt for 4 h, diluted with EtOAc (50 mL), and made alkaline with 5% NaOH solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (50 mL), dried ($MgSO_4$), and concentrated to give a yellow oily residue, which was subjected to flash column chromatography (EtOAc–hexanes, 1:5) to afford 780 mg (72%) of **15** as a colorless liquid: R_f 0.18 (EtOAc–hexanes, 1:5); ^1H NMR ($CDCl_3$) δ 7.01 (d, J=6.6 Hz, 1H), 6.85 (d, J=7.5 Hz, 1H), 6.69 (t, J=7.3–7.4 Hz, 1H), 5.31 (t, 1H), 3.71 (s, broad, 1H, NH), 3.65 (s, 3H), 3.57 (t, J=8.4–8.5 Hz, 2H), 3.20 (d, J=7.0 Hz, 2H), 3.05 (t, J=8.4–8.6 Hz, 2H), 2.48–2.38 (m, 4H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 150.6, 135.6, 129.7, 127.6, 123.3, 123.0, 122.8, 119.4, 52.1, 47.8, 35.2, 33.4, 31.0, 30.6, 16.7; IR (neat) 3371, 2948, 2849, 1736, 1457, 1257, 1163 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.96; H, 8.05; N, 5.43.

Method B: To a solution of **14** (580 mg, 1.61 mmol) in CH_2Cl_2 (1 mL) was added 2 M TFA solution in CH_2Cl_2 (1.5 mL, 3 mmol) dropwise at 0°C. The mixture was stirred at rt until the deprotection was complete (3 h). The solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc (50 mL), followed by addition of 5% NaOH solution to neutralize the mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with water (40 mL), dried ($MgSO_4$), and concentrated to give a yellow oily residue, which was subjected to flash column chromatography (Et_2O–hexanes, 1:3) to afford 250 mg (60%) of **15** as a colorless liquid, which was identical with the product obtained by Method A.

Methyl (*E*)-6-(indol-7-yl)-4-methyl-4-hexenoate (16). To a solution of **15** (390 mg, 1.50 mmol) in dry xylenes (25 mL) was added DDQ (360 mg, 1.55 mmol) in small portions. The mixture was heated at 100–110°C for 2.5 h, cooled to rt, and filtered. The filtrate was concentrated under reduced pressure to give a brown oily residue, which was subjected to flash column chromatography (hexanes, then Et_2O–hexanes, 1:3) to give 290 mg (75%) of **16** as a pale yellow liquid: R_f 0.28 (Et_2O–hexanes, 1:3); ^1H NMR ($CDCl_3$) δ 8.42 (s, broad, 1H, NH), 7.54 (d, J=8.0 Hz, 1H), 7.23 (t, J=2.3–3.1 Hz, 1H), 7.07 (t, J=7.6 Hz, 1H), 7.00 (d, J=7.1 Hz, 1H), 6.57 (d, J=3.3 Hz, 1H), 5.50 (t, 1H), 3.62 (d, J=7.6 Hz, 2H), 3.61 (s, 3H), 2.52 (t, J=6.7–7.0 Hz, 2H), 2.43 (t, J=6.6 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 135.8, 135.6, 128.5, 124.7, 124.1, 123.9, 122.1, 120.4, 119.4, 103.3, 52.2, 35.1, 33.0, 31.6, 16.8; IR (neat) 3416, 2951, 2918, 1725, 1434, 1344 cm^{-1}. Anal. Cald for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.57; H, 7.46; N, 5.41.

Methyl (*E*)-6-(3-formylindol-7-yl)-4-methyl-4-hexenoate (17). Phosphorus oxychloride (0.14 mL, 1.49 mmol) was added dropwise with stirring to DMF (3 mL) under argon at 0–5°C. A solution of **16** (330 mg, 1.28 mmol) in DMF (3 mL) was then added dropwise with stirring, the temperature being kept at 0–5°C. After addition, the mixture was stirred at rt for 25 min when TLC analysis (EtOAc–hexanes, 1:5) showed no presence of the starting material. The mixture was diluted with EtOAc (30 mL) and made alkaline with 2% NaOH solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic layers were washed with water (2×20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oily residue, which was subjected to flash column chromatography (EtOAc–hexanes, 1:2) to give 280 mg (77%) of **17** as a pale yellow oily liquid, which became a solid after being stored in the refrigerator: R_f 0.32 (EtOAc–hexanes, 1:1); ^1H NMR ($CDCl_3$) δ 10.05 (s, 1H), 9.82 (s, broad, 1H, NH), 8.17 (d, J=8.1 Hz, 1H), 7.87 (d, J=3.2 Hz, 1H), 7.23 (t, J=7.3–7.8 Hz, 1H), 7.10 (d, J=6.7 Hz, 1H), 5.51 (t, 1H), 3.66 (d, J=7.1 Hz, 2H), 3.63 (s, 3H), 2.55 (t, J=6.2–6.8 Hz, 2H), 2.41 (t, J=6.5–7.1 Hz, 2H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 185.9, 175.0, 136.7, 136.5, 125.5, 124.9, 124.7, 123.7, 123.6, 123.5, 120.4, 120.0, 52.2, 35.1, 32.4, 31.7, 16.6; CIMS *m/e* (relative intensity): 286 (MH^+, 100), 285 (M^+, 51), 212 (17), 198 (14), 170 (10), 158 (27), 141 (12); HRMS calcd for $C_{17}H_{19}NO_3$ (MH^+), 286.1443, found, 286.1451.

Methyl (*E*)-6-(3-carboxamidoindol-7-yl)-4-methyl-4-hexenoate (18). To 10 mL of 2-propanol saturated with ammonia at 0°C was added sodium cyanide (310 mg, 6.33 mmol). After 5 min, a solution of **17** (300 mg, 1.05 mmol) in 2-propanol (2 mL) was added, followed by addition of manganese dioxide (2.2 g, 25.3 mmol) in two portions. The mixture was stirred at 0–5°C overnight, diluted with CH_2Cl_2 (80 mL), and filtered through a layer of Celite. The filtrate was concentrated under reduced pressure and the resulting crude residue was subjected to flash column chromatography (EtOAc–hexanes, 1:1, then EtOAc only) to give 15 mg (5%) of the nitrile **19** as a yellow liquid and 240 mg (76%) of **18** as a colorless oily liquid (which became a white crystalline solid after being stored in the refrigerator).

*The nitrile byproduct **19**:* R_f 0.40 (EtOAc–hexanes, 1:2); ^1H NMR ($CDCl_3$) δ 9.60 (s, broad, 1H, NH), 7.75 (d, J=3.1 Hz, 1H), 7.63 (d, J=7.8 Hz, 1H), 7.21 (t, J=7.3–7.9 Hz, 1H), 7.10 (d, J=7.1 Hz, 1H), 5.50 (t, 1H), 3.67 (d, J=6.7 Hz, 2H), 3.63 (s, 3H), 2.56 (t, J=7.0 Hz, 2H), 2.42 (t, J=7.0 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1,

136.7, 134.8, 132.9, 131.8, 128.1, 125.4, 124.4, 123.5, 122.7, 122.4, 118.2, 52.3, 35.0, 32.1, 31.9, 16.5; EIMS *m/e* (relative intensity): 282 (M^+, 45), 195 (67), 193 (48), 189 (21), 172 (25), 170 (84), 169 (60), 156 (19), 155 (100), 142 (27), 141 (44), 129 (10), 115 (46), 114 (29).

The amide product ***18****:* R_f 0.27 (EtOAc only); mp 117.5–119.5°C; ^{1}H NMR ($CDCl_3$) δ 9.29 (s, broad, 1H, NH), 7.87–7.83 (m, 2H), 7.19 (t, J=7.4–7.8 Hz, 1H), 7.06 (t, J=7.2 Hz, 1H), 5.80 (s, broad, 2H, NH_2), 5.49 (t, 1H), 3.65 (d, J=7.0 Hz, 2H), 3.61 (s, 3H), 2.53 (t, J=6.1–6.5 Hz, 2H), 2.41 (t, J=7.1 Hz, 2H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.8, 163.1, 136.4, 136.2, 129.7, 125.7, 125.2, 123.6, 123.2, 122.4, 118.7, 111.9, 52.3, 35.1, 32.6, 31.6, 16.3; IR (KBr) 3361, 3346, 3184, 2917, 1715, 1641, 1607, 1528, 1449, 1276, 1213, 1122 cm^{-1}; EIMS *m/e* (relative intensity): 301 (MH^+, 62), 300 (M^+, 14), 287 (20), 283 (100), 269 (9), 189 (31), 175 (32), 157 (21), 141 (15), 129 (51); HRMS calcd for $C_{17}H_{20}N_2O_3$ (M^+), 300.1474, found, 300.1457. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.77; H, 6.72; N, 9.25.

Methyl (*E*)-6-[3-(methoxycarbonyl)indol-7-yl]-4-methyl-4-hexenoate (20). To a solution of **17** (100 mg, 0.35 mmol) in methanol (15 mL) was added sodium cyanide (86 mg, 1.75 mmol), followed by addition of manganese dioxide (610 mg, 7.02 mmol). The mixture was stirred at rt for 24 h, diluted with CH_2Cl_2 (80 mL), and filtered through a layer of Celite. The filtrate was concentrated under reduced pressure and the resulting crude residue was subjected to flash column chromatography (EtOAc–hexanes, 1:3) to give 83 mg (75%) of **20** as a pale brown oily liquid: R_f 0.38 (EtOAc–hexanes, 1:2); ^{1}H NMR ($CDCl_3$) δ 9.16 (s, broad, 1H, NH), 8.06 (d, J=7.7 Hz, 1H), 7.95 (d, J=3.0 Hz, 1H), 7.20 (t, J=7.2–8.1 Hz, 1H), 7.06 (d, J=7.2 Hz, 1H), 5.50 (t, 1H), 3.92 (s, 3H), 3.65 (d, J=7.1 Hz, 2H), 3.62 (s, 3H), 2.54 (t, J=6.1–6.5 Hz, 2H), 2.42 (t, J=6.1–6.6 Hz, 2H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.8, 166.6, 136.3, 136.0, 132.1, 126.7, 124.9, 123.5, 123.2, 122.5, 119.9, 108.9, 52.2, 51.6, 35.1, 32.6, 31.2, 16.6; IR (neat) 3333, 2952, 1733, 1705, 1535, 1442, 1245, 1193, 1159 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.32; H, 6.70; N, 4.38.

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