

Combined Directed Ortho Metalation/Cross-Coupling Strategies: Synthesis of the Tetracyclic A/B/C/D Ring Core of the Antitumor Agent Camptothecin

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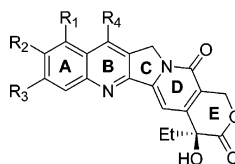
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A convergent synthesis of the A/B/C/D ring fragment **5** of camptothecin using a combination of directed ortho metalation and Negishi cross-coupling is described. The key features of the synthetic sequence are an anionic ortho-Fries rearrangement (**10** → **12**), a Negishi cross-coupling (**7** → **6**), and a terminal modified von Braun reaction (**16** → **5**) that leads to tetracyclic derivative **5** in 7 steps and 11% overall yield.

Introduction

(20S)-Camptothecin (**1a**), one of the most potent anti-tumor natural products, was first isolated in 1966 from *Camptotheca acuminata* Nyssaceae by Wall et al.^{1,2} Its unusual structure and intriguing speculative biosynthetic pathway³ stimulated immediate and intense synthetic activity worldwide,^{4,5} which subsequently precipitously declined due to the finding of discouraging biological activity data of **1a**⁵ showing serious toxic side effects. In the past 15 years, renewed synthetic interest in **1a** and analogues⁶ evolved due to findings that substituted derivatives of **1a** such as 9-aminocamptothecin (**1b**),⁷ 9-(dimethylamino)methyl-10-hydroxycamptothecin (Topotecan, **1c**),⁸ and Irinotecan (**1d**)⁹ show low overall toxicity, higher solubility, and still impressive in vivo activity against certain solid tumors. In fact, Topotecan **1c** and Irinotecan **1d** were recently approved by the FDA

for the treatment of ovarian cancer and small-cell lung cancer¹⁰ and refractory colorectal cancer, respectively.¹¹



- 1a:** R₁, R₂, R₃, R₄ = H, (20S)-Camptothecin
1b: R₁ = NH₂, R₂, R₃, R₄ = H
1c: R₁ = CH₂NMe₂·HCl, R₂ = OH, R₃ = H
 Topotecan
1d: R₁, R₃ = H, R₂ = OCON(CH₂)₄N(CH₂)₄
 R₄ = Et
 Irinotecan

Alkaloids structurally related to camptothecin (**1a**) such as homocamptothecin (**2**),^{12g,13} mappicine (**3**),^{14,15} and mappicine ketone (**4**)¹⁵ are also of clinical relevance. Homocamptothecin (**2**) and its derivatives show similar therapeutic activities to the camptothecins (**1**). The E-ring lactone in **1a** easily hydrolyzes at physiological pH leading to the biologically inactive carboxylate, an inherent deficiency of the parent compound **1a**.¹⁶ In the E-ring lactone of **2** the tertiary alcohol and the lactone carbonyl are separated by a methylene spacer. It was found in bioassays that the longevity of activity of **2** was increased compared to that of **1a**.¹⁷ Mappicine ketone (**4**) has been identified as an antiviral lead compound with selective

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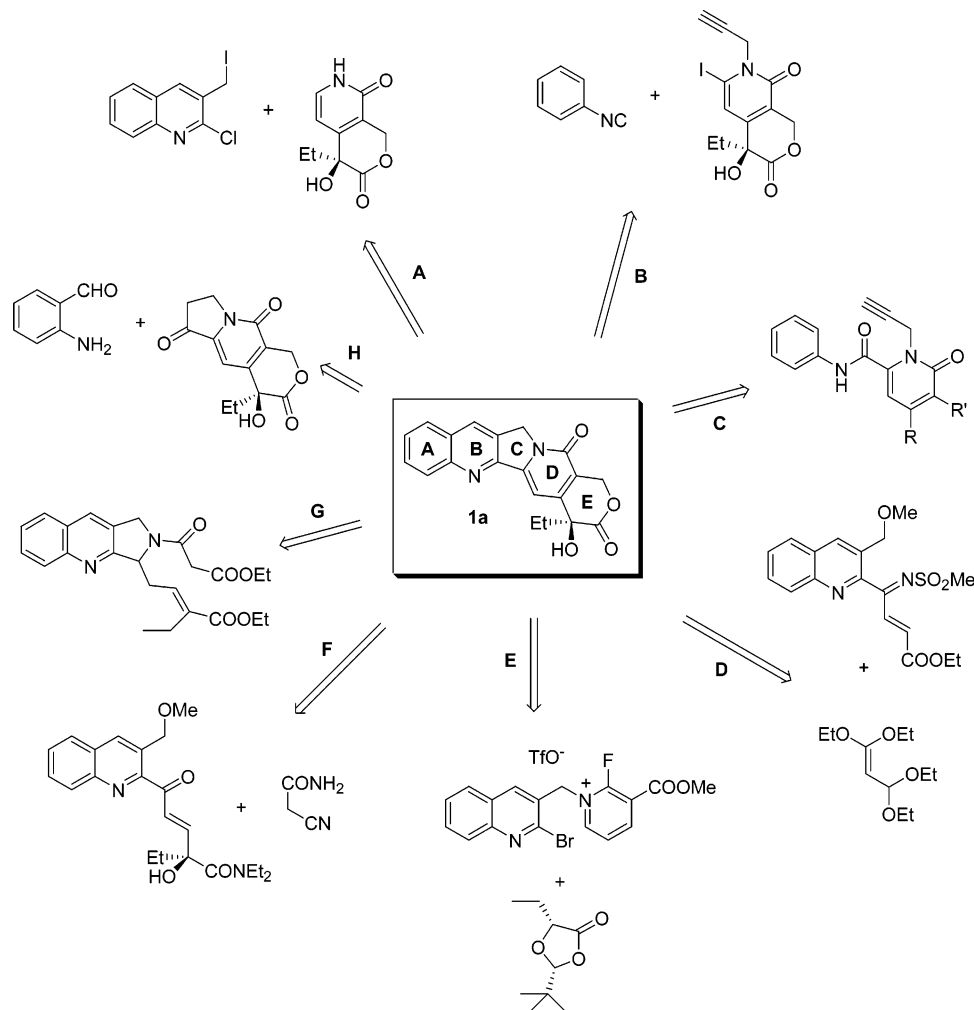
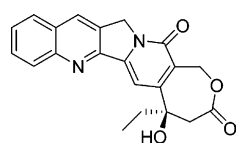
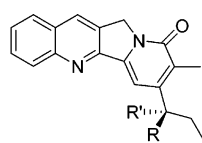


FIGURE 1. Selected strategies for the synthesis of camptothecin.

activities against herpes viruses HSV-1 and HSV-2 and human cytomegalovirus.¹⁸



2: Homocamptothecin



3: R=OH, R'=H (Mappicine)
4: R, R'=O (Mappicine ketone)

The antitumor activity of the camptothecins is now accepted to be associated with the inhibition of DNA relaxation by specific interference of the function of DNA topoisomerase I.^{19,20} Interestingly, it has been shown that the tetracyclic A/B/C/D ring core of **1a** functions as the key binding site to DNA.²¹

Camptothecin and its analogues have provided a rich playing field for development of convergent total synthesis strategies. To date, the shortest asymmetric synthesis of **1a** by Comins involves the formation of the C-ring by connecting the A/B- and D/E-fragments via an *N*-alkylation and a key intramolecular Heck ring closure reaction (Figure 1, A).²² Curran devised an imaginative strategy in which the appropriately functionalized A- and D/E-fragments (Figure 1, B) participate in a free-radical cascade leading to the formation of the B- and C-rings of **1a**.¹² A different concomitant formation of the B- and C-rings was reported by Fortunak using an efficient intramolecular Diels–Alder reaction (Figure 1, C) that is now used on an industrial scale.²³ Boger devised an approach in which a D-ring forming intermolecular Diels–Alder process precedes a C-ring cyclization (Figure 1, D).¹⁷ The key features of an inventive strategy²⁴ by Bosch consisted of an intramolecular radical cyclization to form the C-ring followed by asymmetric construction of the E-ring using enolate chemistry (Figure 1, E).

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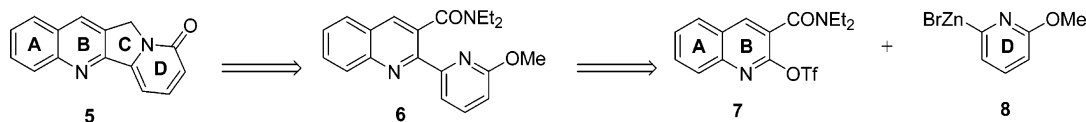
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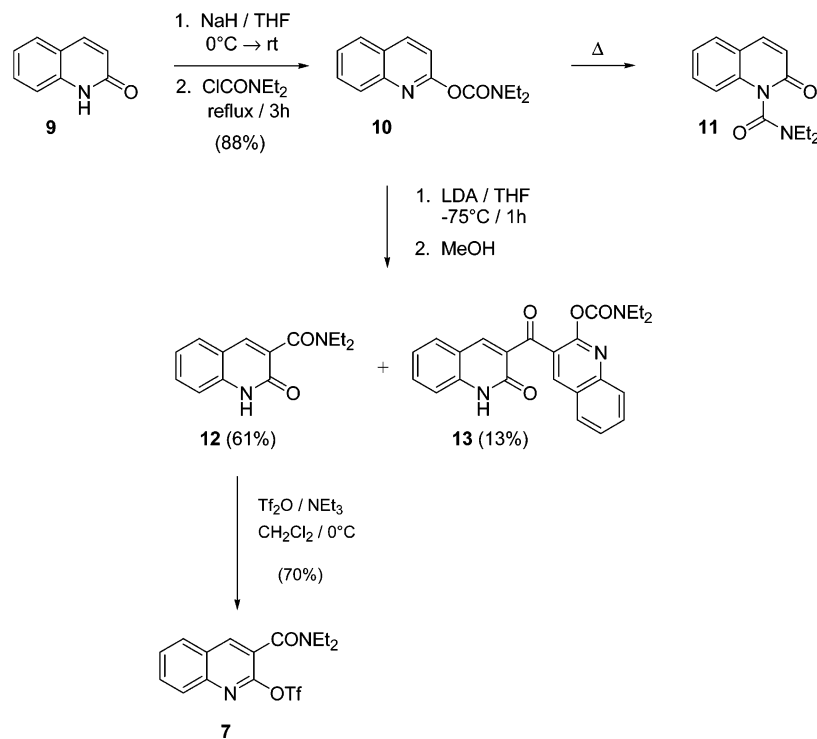
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SCHEME 1



SCHEME 2



Intermolecular²⁵ (Figure 1, F) and intramolecular²⁶ (Figure 1, G) Michael addition reactions by Ciufolini and Chavan, respectively, were utilized for the D-ring construction of **1a**. Finally, in a route that has been widely traveled from the beginning of camptothecin synthetic work, a classical Friedlander reaction of 2-aminobenzaldehyde (A-ring) with the assembled C/D/E-ring framework (Figure 1, H) was used by Henegar for B-ring annelation of **1a**.¹¹

Herein, we report a new synthesis of the A/B/C/D-ring core **5**²⁷ of **1a** using a combined directed ortho metalation (DoM)–transition metal catalyzed cross-coupling tactic.²⁸ Thus, the construction of **5** is based on the initial coupling of **7**, prepared by anionic Fries rearrangement,²⁹ with the organozinc species **8** to afford **6**, which, by simple functional group manipulation–cyclization leads to C-ring formation (Scheme 1).

Results and Discussion

As an appropriate precursor of coupling partner **7**, 2-quinolone (**9**) (Scheme 2), prepared in sizable quantities following Henze's procedure,³⁰ was converted into the O-carbamate **10** by treatment with sodium hydride and diethyl carbamoyl chloride in refluxing THF³¹ followed by purification by flash chromatography on SiO₂. In an alternative purification of carbamate **10** via short path distillation, a clean thermal 1,3-carbamoyl rearrangement was observed to form urea **11**.³² As reported by Queguiner,³¹ treatment of carbamate **10** with LDA resulted in, even at –75 °C, C-3 metalation–anionic Fries rearrangement to give the 3-amidoquinolone **12**. However, in contrast to the observations of Queguiner, apart from **12** (61%), the self-condensation product **13** was also isolated in 13% yield. When the reaction was carried out at –42 °C, compound **13** was not formed and the yield of the desired rearrangement product **12** increased to 71%. The increased selectivity favoring the intramolecular rearrangement at higher temperature may be rationalized by the difference in temperature dependence of a

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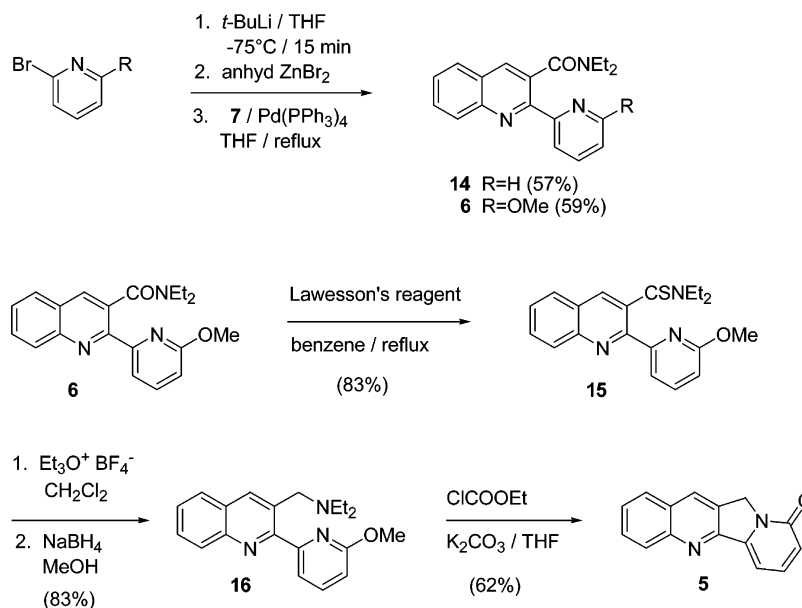
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SCHEME 3



uni- vs. bimolecular reaction. To complete the synthesis of the A/B-fragment, the quinolone **12** was transformed into the triflate **7** with use of standard conditions.

As a model reaction, the cross-coupling reaction between triflate **7** and 2-bromopyridine,³³ representing the D-ring fragment, was undertaken (Scheme 3) with use of the Negishi protocol³⁴ with Pd(PPh₃)₄ as catalyst and provided the biaryl **14** in satisfactory yield (57%). With this procedure, 2-bromo-6-methoxypyridine, prepared from 2,6-dibromopyridine (86% yield),³⁵ was sequentially treated with 2 equiv of *t*-BuLi at -78 °C and anhydrous ZnBr₂. The resulting organozinc species **8** was subjected to the Pd⁰-catalyzed cross-coupling procedure with triflate **7** to afford the biaryl **6** in 59% yield.

To avoid complications of reduction of π -deficient heterocyclic rings, the biaryl **6** was subjected to the mild reduction protocol of Raucher.³⁶ Thus, **6** was converted with use of Lawesson's reagent into the corresponding thioamide **15**, which, upon sequential ethylation with ethyl-Meerwein salt and reduction with NaBH₄, was transformed into the tertiary amine **16** in 83% yield. The final cyclization of **16** to the tetracycle **5**²⁷ was achieved in 62% yield via a modified von Braun reaction with ethyl chloroformate and potassium carbonate.³⁷ Compound **5** was found to be identical by comparison of physical and spectroscopic properties with those reported (see the Experimental Section).

Thus, the tetracyclic A/B/C/D-ring system **5** of camptothecin (**1a**) has been synthesized from quinolone **9** in 7 steps and 11% overall yield, which represents a valuable alternative to previously achieved syntheses (7 steps, 6%;^{27a} 2 steps, 27%;^{27b} and 5 steps, 17%;^{27c}). The simplicity of the steps, the ready availability of starting materials of both A/B- and D-ring fragments by DoM

chemistry, and the potential further modification of ring D in **5**, taken in sum, offer consideration of additional avenues for synthetic excursions in the camptothecin field.

Experimental Section

***N,N*-Diethyl *O*-(Quinolyl-2) Carbamate (**10**).** To a suspension of NaH (959 mg, 60% in mineral oil, 24.0 mmol) in anhydrous THF (45 mL) was added **9**³⁰ (2.88 g, 19.8 mmol) portionwise at room temperature under N₂ atmosphere. The greenish suspension was stirred at room temperature for 30 min and then ClCONEt₂ (3.75 g, 27.6 mmol) was added via syringe. The reaction mixture was refluxed for 2 h. Since TLC showed only about 50% conversion, more ClCONEt₂ (3.75 g, 27.6 mmol) was added and the mixture was stirred for an additional hour. The reaction mixture was cooled in ice and carefully treated with saturated aq NH₄Cl (20 mL). The aqueous layer was separated and extracted with Et₂O (2 × 20 mL). The combined organic phase was washed with H₂O (50 mL) and brine (50 mL) and dried (Na₂SO₄). Removal of the solvent gave the crude product as a brown oil, which was purified by flash chromatography on SiO₂ (Et₂O/hexane (1:1)) to yield **10** as a yellowish oil (4.26 g, 88%): IR (film) 3062, 2977, 2935, 1721, 1598, 1505, 1417, 1216, 1150, 1045, 978, 779, 752 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 3.43 (q, *J* = 7.1 Hz, 2H), 3.53 (q, *J* = 7.1 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.51 (td, *J* = 7.5, 1.1 Hz, 1H), 7.69 (td, *J* = 7.7, 1.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.7 Hz, 1H); MS (EI, 70 eV) *m/z* 244 (18, M⁺), 227 (17), 145 (27), 128 (30), 116 (36), 100 (100), 72 (80).

***N*-(*N,N*-Diethylaminocarbonyl)-2-quinolone (**11**).** Short path distillation (173–175 °C/0.5 Torr) of 4.26 g of **10** yielded a mixture of **10** and a new product. Flash chromatography on SiO₂ (Et₂O) gave recovered **10** (2.39 g) and a colorless crystalline material (1.81 g), which upon recrystallization from CHCl₃/Et₂O (1:3) yielded pure **11** (1.07 g, 25%): mp 108.5–110 °C; IR (KBr) 2988, 2943, 2880, 1695, 1659, 1591, 1430, 829 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.06 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 3.04–3.31 (m, 2H), 3.52–3.86 (m, 2H), 6.64 (d, *J* = 9.6 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.25 (td, *J* = 7.6, 1.0 Hz, 1H), 7.47–7.60 (m, 2H), 7.74 (d, *J* = 9.6 Hz, 1H); ¹³C NMR (50.3 MHz, CDCl₃) δ 12.6, 13.7, 41.8, 43.4, 114.4, 119.9, 121.6, 123.1, 128.6, 131.0, 137.3, 140.7, 152.0, 160.2; MS (EI,

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70 eV) m/z 244 (18, M^+), 227 (9), 145 (12), 100 (100), 72 (67). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.75; H, 6.70; N, 11.48.

***N,N*-Diethyl 1,2-Dihydro-2-oxo-3-quinolinecarboxamide (12).** To a stirred LDA solution (diisopropylamine (592 mg, 5.9 mmol) and *n*-BuLi (3.9 mL (1.6 M in hexane), 6.2 mmol)) in THF (30 mL), a solution of **10** (1.10 g, 4.5 mmol) in THF (8 mL) (precooled to -78°C) was added via cannula at -78°C under N_2 atmosphere. After the solution was stirred for 1 h, anhydrous MeOH (562 mg, 17.5 mmol) was added and the reaction mixture was stirred for an additional hour at -78°C . After quenching with saturated aq NH_4Cl (15 mL), the aqueous phase was extracted with $CHCl_3$ (3×30 mL). The combined organic phase was washed with H_2O and dried (Na_2SO_4). Removal of the solvent gave the crude product as yellow crystals (1.11 g). Flash chromatography on SiO_2 (EtOAc/MeOH (95:5)) yielded **12** as pale yellow crystals (666 mg, 61%): mp $166\text{--}167^\circ\text{C}$ (toluene) (lit.³¹ mp 167°C); IR (KBr) 3063, 2968, 2897, 1662, 1617, 1569, 1433, 1221, 946, 749 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, $J = 6.6$ Hz, 3H), 1.32 (t, $J = 6.6$ Hz, 3H), 3.34 (q, $J = 6.8$ Hz, 2H), 3.63 (q, $J = 6.7$ Hz, 2H), 7.24 (td, $J = 7.5, 1.3$ Hz, 1H), 7.41 (d, $J = 7.9$ Hz, 1H), 7.49–7.60 (m, 2H), 7.87 (s, 1H), 12.36 (s br, 1H, exchangeable with D_2O).

A second fraction was obtained and recrystallized from EtOAc/MeOH (2:1) to yield **13** as colorless crystals (122 mg, 13%): mp $>180^\circ\text{C}$ dec; IR (KBr) 3063, 2974, 2938, 2892, 2853, 1718, 1658, 1619, 1591, 1564, 1399, 1275, 1196, 1080, 754 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3/DMSO-d_6$ (2:1)) δ 0.87 (t, $J = 7.0$ Hz, 3H), 0.94 (t, $J = 7.0$ Hz, 3H), 2.98–3.06 (m, 4H), 7.22 (t, $J = 7.7$ Hz, 1H), 7.39 (d, $J = 8.2$ Hz, 1H), 7.54–7.67 (m, 2H), 7.77–7.87 (m, 2H), 7.96 (d, $J = 8.2$ Hz, 1H), 8.12 (d, $J = 7.9$ Hz, 1H), 8.35 (s, 1H), 8.70 (s, 1H), 12.10 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3/DMSO-d_6$ (2:1)) δ 11.1, 11.8, 39.3, 39.7, 113.7, 116.7, 120.7, 124.8, 125.1, 125.9, 126.7, 127.2, 127.8, 129.0, 130.0, 130.9, 138.7, 138.8, 141.2, 145.0, 150.7, 151.8, 158.5, 188.7.

***N,N*-Diethyl 2-Trifluoromethanesulfonyloxy-3-quinolinecarboxamide (7).** To a solution of **12** (441 mg, 2.0 mmol) in CH_2Cl_2 (18 mL) at 0°C was added NEt_3 (365 mg, 3.6 mmol) and Tf_2O (560 mg, 2.0 mmol) dropwise under N_2 atmosphere. The solution was stirred at 0°C for 1 h and quenched with saturated aq $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL) and the combined organic phase was washed with H_2O and dried (Na_2SO_4). Removal of the solvent gave the crude product as yellow crystals (887 mg). Flash chromatography on SiO_2 (Et_2O) afforded **7** as pale yellow crystals (478 mg, 70%): mp $89.5\text{--}91^\circ\text{C}$ ($CHCl_3$ /hexane (4:1)); IR (film) 3059, 2981, 2939, 1635, 1573, 1424, 1217, 1140, 1052, 918, 884, 847, 801, 759 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, $J = 7.1$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 3.25 (q, $J = 7.1$ Hz, 2H), 3.61 (s br, 2H), 7.67 (td, $J = 7.5, 1.2$ Hz, 1H), 7.84 (td, $J = 8.4, 1.5$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.4, 13.9, 39.5, 43.1, 118.5 (q, 321), 122.6, 127.1, 127.8, 128.3, 128.6, 131.7, 139.0, 145.4, 149.6, 163.8; MS (EI, 70 eV) m/z 376 (36, M^+), 304 (100), 227 (49), 172 (82), 143 (66); HRMS calcd for $C_{15}H_{15}F_3N_2O_4S$ 376.0705, found 376.0693.

***N,N*-Diethyl 2-(2-Pyridyl)-3-quinolinecarboxamide (14).** A solution of 2-bromopyridine (117 mg, 741 μmol) in THF (3 mL) was treated at -78°C with *t*-BuLi (1.7 M in pentane, 867 μL , 1.5 mmol) under N_2 atmosphere. After the dark red solution was stirred for 15 min at -78°C , a solution of anhydrous $ZnBr_2$ (183 mg, 813 μmol) in THF (2 mL) was added via cannula. The resulting orange solution was stirred at -78°C for 1 h and then allowed to warm to room temperature. A solution of **7** (185 mg, 492 μmol) and $Pd(PPh_3)_4$ (28 mg, 24 μmol) in THF (3 mL), which had been stirred for 15 min at room temperature, was added via cannula. The reaction mixture was refluxed (60 h) and quenched with saturated aq NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (1×20 mL, 2×10 mL) and the combined organic phase was

washed with H_2O and dried (Na_2SO_4). Evaporation to dryness in vacuo gave the crude product as a brownish oil (208 mg), which was purified by flash chromatography on SiO_2 ($CHCl_3$) to yield **14** as a yellowish oil (85 mg, 57%): IR ($CDCl_3$) 3064, 2981, 2837, 2875, 1723, 1618, 1559, 1480, 1279, 1097 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, $J = 7.1$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 3.21 (s br, 2H), 3.93 (s br, 2H), 7.28–7.34 (m, 1H), 7.58 (t, $J = 7.2$ Hz, 1H), 7.72–7.87 (m, 3H), 8.14 (s, 1H), 8.19 (d, $J = 8.5$ Hz, 1H), 8.42 (d, $J = 7.9$ Hz, 1H), 8.59 (s br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.7, 13.3, 38.7, 42.7, 123.1, 123.8, 127.0, 127.4, 127.5, 129.6, 130.1, 130.7, 134.8, 136.6, 147.3, 148.2, 153.4, 156.2, 170.3; MS (EI, 70 eV) m/z (305 ($<1, M^+$), 233 (100), 205 (19); HRMS calcd for $C_{19}H_{19}N_3O$ 305.1528, found 305.1500.

2-Bromo-6-methoxypyridine. A solution of NaOMe in MeOH (Na (1.33 g, 58 mmol) in anhydrous MeOH (14 mL)) was added to a suspension of 2,6-dibromopyridine (8.0 g, 34 mmol) in anhydrous MeOH (22 mL) and the resulting mixture was refluxed for 25 h. The reaction mixture was allowed to cool to room temperature, cold 5% aq $NaHCO_3$ (25 mL) was added, and the mixture was extracted with Et_2O (1×30 mL, 2×20 mL). The combined organic phase was concentrated, the resulting residue was taken up in Et_2O (30 mL), and the Et_2O solution was washed with brine (20 mL) and dried (K_2CO_3). Removal of the solvent gave a yellowish liquid (5.72 g). Kugelrohr distillation yielded 2-bromo-6-methoxypyridine as a colorless liquid (5.48 g, 86%): bp $87\text{--}91^\circ\text{C}/15$ Torr (lit.³⁵ bp $85\text{--}95^\circ\text{C}/15$ Torr); IR (film) 2985, 2952, 2850, 1594, 1581, 1556, 1467, 1408, 1296, 1020, 854 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.68 (d, $J = 7.7$ Hz, 1H), 7.05 (d, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.8$ Hz, 1H).

***N,N*-Diethyl 2-(2-Methoxypyridin-6-yl)-3-quinolinecarboxamide (6).** To a solution of 2-bromo-6-methoxypyridine (301 mg, 1.6 mmol) in THF (6 mL) at -78°C was added dropwise *t*-BuLi (1.7 M in pentane, 1.9 mL, 3.2 mmol) under N_2 atmosphere. The resulting pale yellow solution was stirred for 15 min at -78°C . A solution of anhydrous $ZnBr_2$ (409 mg, 1.8 mmol) in THF (4 mL) was added via cannula and the mixture was stirred for 70 min at -78°C . The reaction mixture was allowed to warm to room temperature and was added via cannula to a solution of **7** (399 mg, 1.1 mmol) and $Pd(PPh_3)_4$ (62 mg, 54 μmol) in THF (4 mL), which had been stirred for 20 min at room temperature. The resulting solution was refluxed for 45 h and the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ /MeOH (9:1) (15 mL) and washed with $Na_2EDTA \cdot 2H_2O$ (1.35 g in 15 mL of H_2O). The aqueous phase was extracted with $CHCl_3$ /MeOH (9:1) (5×12 mL) and the combined organic phase was dried (Na_2SO_4). Removal of the solvent gave a yellow gum (569 mg) that was purified by flash chromatography on SiO_2 (EtOAc/hexane (2:1)) to give **6** as a pale yellow oil (211 mg, 59%): IR (film) 3060, 2979, 2934, 2874, 1634, 1574, 1556, 1267, 1047, 921, 888, 792 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 0.84 (t, $J = 7.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 2.90–2.99 (m, 1H), 3.16–3.36 (m, 2H), 3.79–3.87 (m, 1H), 3.97 (s, 3H), 6.79 (d, $J = 8.2$ Hz, 1H), 7.56 (t, $J = 7.9$ Hz, 1H), 7.69–7.77 (m, 2H), 7.84 (d, $J = 8.1$ Hz, 1H), 7.97 (d, $J = 7.4$ Hz, 1H), 8.17 (s, 1H), 8.18 (d, $J = 5.8$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.8, 13.4, 38.9, 43.2, 53.7, 111.3, 116.3, 126.9, 127.4, 127.5, 129.5, 130.1, 130.3, 135.9, 139.2, 147.3, 153.4, 154.0, 163.4, 169.8; MS (EI, 70 eV) m/z 335 (7, M^+), 263 (100), 235 (23); HRMS calcd for $C_{20}H_{21}N_3O_2$ 335.1634, found 335.1602.

***N,N*-Diethyl 2-(2-Methoxypyridin-6-yl)-3-quinoline-thiocarboxamide (15).** A solution of **6** (120 mg, 358 μmol) and Lawesson's reagent (241 mg, 596 μmol) in anhydrous benzene (3 mL) was refluxed for 8 h under N_2 atmosphere. The reaction mixture was passed through a cotton plug and the filtrate was concentrated. The resulting orange oil was purified by flash chromatography on SiO_2 (CH_2Cl_2 / Et_2O (9:1)) to yield **15** as a yellow viscous liquid (105 mg, 83%): IR (film) 3064, 2982, 2941, 2876, 2221, 1592, 1575, 1498, 1266, 816 cm^{-1} ; 1H NMR (250 MHz, $CDCl_3$) δ 1.03 (t, $J = 7.2$ Hz, 3H),

1.27 (t, $J = 7.1$ Hz, 3H), 3.25 (dq, $J = 14.3, 7.1$ Hz, 1H), 3.66 (dq, $J = 14.3, 7.2$ Hz, 1H), 3.95 (s, 3H), 4.03–4.19 (m, 2H), 6.78 (dd, $J = 8.0, 0.6$ Hz, 1H), 7.56 (td, $J = 8.0, 1.0$ Hz, 1H), 7.68–7.76 (m, 2H), 7.82 (dd, $J = 8.1, 0.7$ Hz, 2H), 8.09 (s, 1H), 8.17 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ 11.1, 13.3, 45.9, 48.7, 53.9, 110.9, 117.3, 126.8, 127.4, 127.5, 129.2, 130.1, 134.3, 135.8, 139.1, 146.7, 152.2, 154.2, 163.2, 197.6; MS (EI, 70 eV) m/z 351 (25, M^+), 280 (47), 265 (100), 243 (12).

3-*N,N*-Diethylaminomethyl-2-(2-methoxypyridin-6-yl)-quinoline (16). To a solution of **15** (105 mg, 299 μmol) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C was added $\text{Et}_3\text{O}^+\text{BF}_4^-$ (0.5 M in CH_2Cl_2 , 0.62 mL, 310 μmol) under N_2 atmosphere. The resulting mixture was stirred for 5 min at 0 °C and then for 90 min at room temperature. The solvent was removed in vacuo and the solid residue was dissolved in anhydrous MeOH (2.5 mL). NaBH_4 (29 mg, 767 μmol) was added at 0 °C and the mixture was stirred for 5 min at 0 °C and then for 3 h at room temperature. HCl (5%, 2 mL) was added and the mixture was stirred for 5 min. After addition of aq NaOH solution to pH >10, the reaction mixture was extracted with Et_2O (1 \times 20 mL, 2 \times 15 mL). The combined organic phase was washed with H_2O (20 mL) and dried (Na_2SO_4). Removal of the solvent gave a yellow oil (101 mg) that was purified by flash chromatography on SiO_2 (EtOAc) to yield **16** as a yellow gum (80 mg, 83%): IR (CDCl_3) 3064, 2971, 2935, 2874, 2809, 1722, 1576, 1464, 1411, 1261 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.98 (t, $J = 7.1$ Hz, 6H), 2.54 (q, $J = 7.1$ Hz, 4H), 3.96 (s, 3H), 4.09 (s, 2H), 6.80 (dd, $J = 8.4, 0.6$ Hz, 1H), 7.49–7.55 (m, 2H), 7.64–7.77 (m, 2H), 7.86 (d, $J = 8.1$ Hz, 1H), 8.14 (d, $J = 8.5$ Hz, 1H), 8.53 (s, 1H); ^{13}C NMR (63 MHz, CDCl_3) δ 11.8, 47.2, 53.4, 54.9, 110.2, 117.3, 126.6, 127.4, 127.9, 129.0, 129.2, 132.3, 136.7, 139.3, 156.8, 157.2, 162.7; MS (EI, 70 eV) m/z 321 (35, M^+), 292 (100), 249 (86), 235 (50), 205 (40), 185 (53); HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}$ 321.1841, found 321.1820.

11*H*-Indolizino[1,2-*b*]quinolin-9-one (5). To a suspension of anhydrous K_2CO_3 (23 mg, 166 μmol) and ClCOOEt (25 μL ,

261 μmol) in anhydrous THF (1 mL) was added a solution of **16** (67 mg, 208 μmol) in anhydrous THF (1 mL) via cannula under N_2 atmosphere. The mixture was stirred at room temperature for 2.5 h. TLC showed a new spot with intense blue fluorescence under UV light. The reaction mixture was heated at reflux for 3 h. To the resulting orange suspension was added ClCOOEt (10 μL , 105 μmol) and the mixture was heated at reflux for 1 h. After the solution was cooled to room temperature, H_2O (10 mL) was added and the whole was extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic phase was washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent gave a yellow solid (48 mg) that was purified by flash chromatography on SiO_2 ($\text{EtOAc}/\text{NEt}_3$ (99:1)) to yield **5** as pale yellow crystals (30 mg, 62%) (lit.^{27a} mp 265 °C; lit.^{27c} mp 253–254 °C): IR (CDCl_3) 3056, 1663, 1594, 1159 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 5.25 (s, 2H), 6.73 (dd, $J = 9.0, 0.7$ Hz, 1H), 7.30 (dd, $J = 6.1, 0.8$ Hz, 1H), 7.60–7.70 (m, 2H), 7.80 (ddd, $J = 8.4, 7.0, 1.4$ Hz, 1H), 7.89 (d, $J = 8.1$ Hz, 1H), 8.20 (d, $J = 8.5$ Hz, 1H), 8.34 (s, 1H). The spectroscopic properties are identical with those reported for **5** prepared previously.²⁷

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Supporting Information Available: Spectroscopic information and reagent purification and availability. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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