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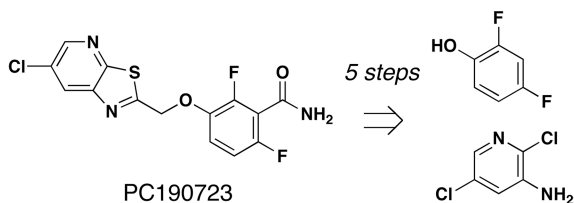
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Practical Synthesis of PC190723, An Inhibitor of the Bacterial Cell Division Protein FtsZ

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Abstract



A high-yielding and practical synthesis of the bacterial cell division inhibitor PC190723 is described. The synthesis is completed in a longest linear sequence of five steps from commercially available starting materials and can be readily executed on a multi-gram scale.

The emergence of pathogenic bacteria that are resistant to current antibiotics requires the exploration of new methods for treating infections caused by these organisms. Recent efforts have included finding new ways to modify the structures of existing antibiotics as well as discovering and developing new leads and new molecular targets. One promising area of development involves inhibiting bacterial cell division.¹ The central protein required for bacterial cytokinesis is FtsZ, a tubulin-like GTPase.² Although FtsZ and tubulin share little sequence homology, X-ray crystallography revealed a high level of structural similarity.³ Tubulin's function is effectively inhibited by a wide range of natural and synthetic inhibitors, some of which have become effective treatments for cancer (e.g. taxol). Binding sites for three potent tubulin inhibitors (colchicine, taxol, and *Vinca* alkaloids) have been elucidated by crystallography.⁴ In contrast, few selective inhibitors of FtsZ are known, and most exhibit modest potency as judged by inhibition of GTP hydrolysis.⁵ Moreover, there has been no direct elucidation (e.g. X-ray crystallography, NMR) of the binding sites for any FtsZ inhibitors.

We have initiated a program to synthesize and study naturally-occurring⁶ and synthetic inhibitors of FtsZ with a long term goal of elucidating their mechanism of inhibition. Researchers at Prolysis, Inc. recently described the activity of PC190723, a heterocyclic inhibitor of FtsZ that exhibits a high level of bacterial lethality against Gram-positive organisms and promising antimicrobial activity against *Staphylococcus aureus* infection in a mouse model.⁷ This compound represents an impressive optimization of the known cell-division inhibitor 3-methoxybenzamide (3MBA).⁸ 3MBA shows activity *in vivo* at 10 mM (10,000 μ M) and analysis of resistant mutants at the time of its discovery indicated that FtsZ

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Supporting Information Available: Experimental procedures for **3**, **5**, **13–15**, and **19**. Spectra (¹HNMR, ¹³CNMR, and ¹⁹F) for all new compounds spectra and the crystallographic information file (.cif) for **17**. In addition, complete references 7a, 7b and 10 are provided. (This material is available free of charge via the Internet at <http://pubs.acs.org>.)

was the target. Optimization of this modest lead revealed PC190723, which inhibits the GTPase activity of FtsZ with an IC₅₀ of 0.154 μM. In the absence of direct evidence, analysis of the structure of FtsZ from resistant mutants suggests that this compound interacts with FtsZ at a site outside of the GTP binding pocket.^{7a} In addition, a recent report documents stabilization of FtsZ polymers by **1**.⁹ Herein we report a practical synthesis¹⁰ of this compound that will enable more detailed studies of this compound's function and a broader understanding of the structural biology of FtsZ.

Retrosynthetic analysis reveals that PC190723 could be accessed by alkylation of phenol **3–5** with chloromethyl-substituted heterocycle **2** (Scheme 1). Phenols **3–5** are readily available from 2,4-difluorophenol by lithiation and acylation. The required chloroacetamide-substituted pyridine was prepared in two steps from commercially available 2,5-dichloro-3-aminopyridine **8**.

The phenol fragment of **1** could be introduced as either aldehyde **3**, amide **4**, or ester **5** (Scheme 2). Aldehyde **3** was prepared from difluorophenol in two steps.¹¹ Protection with ethoxymethyl chloromethyl ether (EOM-Cl) followed by regioselective lithiation, acylation with DMF and EOM group removal provided aldehyde **3** in moderate yield. Quenching aryllithium reagent¹² **10** with CO₂ yielded acid **11**, which was converted to the requisite amide **4** in two steps. Treatment of **11** with methanolic H₂SO₄ effected both esterification and deprotection to provide **5** in high yield.¹³

We initially explored several different methods for displacing the 2-chloro group of **8** with NaSH and a variety of nucleophilic sulfur sources. Ultimately this route was abandoned in favor of *N*-acylation followed by sulfurization of the amide with concomitant ring closure (Scheme 3). Acylation of 2,5-dichloro-3-aminopyridine proceeded smoothly under standard conditions. Sulfurization with Lawesson's reagent¹⁴ in toluene provided the desired thiazole **2** as well as the dechlorinated product **15** as determined by NMR spectroscopy and mass spectrometry. Further proof of the identity of **15** was provided by synthesis of a reference sample. Reaction of **2** with Lawesson's reagent did not produce **15** and the starting material was recovered unchanged, demonstrating that **2** is stable toward dechlorination. Attempts to convert **15** to **2** by radical chlorination were unsuccessful. Finally, switching from toluene to *p*-xylene for the reaction with Lawesson's reagent increased the yield of **2** and only trace amounts of **15** were observed.

We attempted to solve the problem of dehalogenation during sulfurization by changing the order of events. In an attempt to alkylate **7** directly with aldehyde **3**, an interesting cyclization occurred to produce lactam **17**. Under the reaction conditions for alkylation, subsequent ring closure by S_NAr displacement of the ortho fluorine could not be avoided.¹⁵ The structure of **17** was suspected based on the signals for diastereotopic methylene protons and confirmed by X-ray crystallographic analysis. Although alkylation of **7** with amide **4** did lead to the desired *O*-alkylation product (not shown), the subsequent sulfurization-cyclization resulted in a complex mixture of products.

The synthesis of the PC190723 from chloromethyl thiazole **2** was completed in high yield after exploring three possible routes. When alkylation of aldehyde **3** with chloromethyl heterocycle **2** was attempted (Cs₂CO₃, THF or CH₃CN), multiple products were observed. Reaction of amide **4** with **2** produced **1** in modest yield under mild conditions. Finally, we demonstrated that ester **5** underwent alkylation in higher yield (62%, unoptimized) relative to amide **4**. Unfortunately, the resultant ester could not be converted to **1** by aminolysis under a variety of conditions.¹⁶ An alternative route is the conversion of chloride **2** to iodide **20** (78% yield),¹⁷ which alkylates **4** in good yield (70%). Although the reaction via **20** is one step longer, the overall yield is slightly higher (55%) when compared to the one-step

process. Characterization data for **1**/PC190723 (^1H NMR, ^{13}C NMR, ^{19}F NMR, HRMS, IR) was consistent with published structure of PC190723.

In summary, we have demonstrated a practical synthesis of PC190723 in a longest linear sequence of five steps from 2,4-difluorophenol using a single protecting group. Although the synthesis requires metallation of an intermediate with *n*-BuLi, it is easily scaleable for the production of multi-gram quantities. A principle contrast between the previously reported route and ours is the use of low-cost starting materials, specifically avoiding 2,6-difluoro-3-methoxybenzamide and benzyloxyacetyl chloride. Access to this potent inhibitor of bacterial cell division will enable detailed studies of this essential process¹⁸ and pave the way for the development of new inhibitors that might serve as medicinal leads.

Experimental Section

1-Ethoxymethoxy-2,4-difluorobenzene (**9**)

2,4-difluorophenol (0.999 g, 7.68 mmol) was dissolved in 10 mL of dry CH_2Cl_2 . (*i*-Pr) $_2$ NEt (1.58 mL, 9.22 mmol) was added and the mixture was cooled to 0 °C. This was followed by the addition of chloromethyl ethyl ether (9.86 mL, 9.26 mmol). After 2 h of stirring at room temperature, 3M NaOH (20 mL) was added and extracted 2x with CH_2Cl_2 . The organic layers were combined and 1M HCl was added (20 mL) and extracted 2x with CH_2Cl_2 . The organic layers were combined and washed with brine and dried over K_2CO_3 . The solvent was evaporated *in vacuo* yielding a colorless oil (1.32 g, 91%): ^1H NMR (300 MHz, CDCl_3) δ 7.16 (td, $J = 9.1, 5.4$ Hz, 1H), 6.90-6.71 (m, 2H), 5.19 (s, 2H), 3.76 (q, $J = 7.1$ Hz, 2H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.4 (dd, $J = 242.7, 10.5$ Hz), 153.2 (dd, $J = 248.8, 12.1$ Hz), 141.7 (dd, $J = 10.9, 3.6$ Hz), 119.1 (dd, $J = 9.4, 2.6$ Hz), 110.6 (dd, $J = 22.5, 3.9$ Hz), 104.8 (dd, $J = 26.8, 22.6$ Hz), 95.0, 64.8, 14.9; R_f 0.851 in 30% EtOAc/hexanes; HRMS (ESI) m/z calcd for $\text{C}_9\text{H}_{10}\text{F}_2\text{O}_2$ (M - H) $^-$ 187.0574, found 187.0579.

3-Ethoxymethoxy-2,6-difluorobenzoic acid (**11**)

Compound **9** (3.93 g, 20.9 mmol) was dissolved in dry THF (80 mL) and *n*-BuLi (10 mL, 25.0 mmol, 2.5M in hexanes) was added dropwise at -78 °C. After stirring at -78 °C for 2 h, the mixture was poured onto freshly crushed CO_2 followed by the addition of another layer of freshly crushed CO_2 . The mixture was allowed to warm to room temperature overnight. Water was added to the mixture (50 mL) and extracted with EtOAc. The aqueous layer was acidified to pH 1 and extracted immediately with CH_2Cl_2 . The organic layers were combined and dried over Na_2SO_4 . The solvent was evaporated *in vacuo*, yielding a white solid (4.51 g, 93%): mp 154-154 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.37 (m, 1H), 6.91 (dd, $J = 10.1, 8.3$ Hz, 1H), 5.25 (s, 2H), 3.80 (q, $J = 7.1$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 155.5 (dd, $J = 253.5, 4.4$ Hz), 151.9 (dd, $J = 260.0, 5.9$ Hz), 142.2 (dd, $J = 11.0, 3.7$ Hz), 122.2 (dd, $J = 9.9, 3.2$ Hz), 111.6 (dd, $J = 23.1, 4.4$ Hz), 110.5 (dd, $J = 17.7, 14.5$ Hz), 95.1, 65.0, 15.1; IR (neat) 3536, 3476, 1671 cm^{-1} ; R_f 0.340 in 50% EtOAc/hexanes; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{10}\text{F}_2\text{O}_4$ (M - H) $^-$ 231.0469, found 231.0479.

3-Ethoxymethoxy-2,6-Difluoro-benzamide (**12**)

Compound **11** (1.20 g, 5.18 mmol) was dissolved in 50 mL of dry CH_2Cl_2 followed by the addition of (*i*-Pr) $_2$ NEt (0.976 mL, 5.70 mmol). Ethyl chloroformate (0.600 mL, 6.30 mmol) was added at 0 °C. After 1.5 h at 0 °C, 6 mL of 12M NH_4OH was added and stirred for an additional 30 min. The reaction was monitored by TLC. After 3 h, the solvent was evaporated *in vacuo* and then 1M HCl (30 mL) was added to the mixture and extracted 2x with ethyl acetate. The organic layers were combined, washed with brine and concentrated. The crude mixture was purified by flash chromatography (40 to 70% EtOAc/hexanes). The

solvent was evaporated *in vacuo* yielding a white solid (1.13 g, 94%): mp 87.4–87.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.27 (td, *J* = 9.4, 5.3, 1H), 6.98 – 6.80 (m, 1H), 6.33 (brs, 1H), 6.06 (brs, 1H), 5.23 (s, 2H), 3.78 (q, *J* = 7.1, 2H), 1.23 (t, *J* = 7.1, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 162.7, 154.2 (dd, *J* = 247.3, 5.2), 150.5 (dd, *J* = 253.9, 7.2), 142.0 (dd, *J* = 11.1, 3.4), 120.3 (d, *J* = 9.3), 114.4–113.8 (m), 111.3 (dd, *J* = 23.5, 3.6), 94.9, 64.9, 15.1; IR (neat) 3381, 3198, 1656 cm⁻¹; R_f 0.409 in 60% EtOAc/hexanes; HRMS (ESI) *m/z* calcd for C₁₀H₁₁F₂NO₃ (M + H)⁺ 232.0785, found 232.0765.

2,6-Difluoro-3-hydroxy-benzamide (4)

The EOM-protected amide **12** (0.875 g, 3.78 mmol) was dissolved in a 50:50 mixture of 6M HCl and MeOH (30 mL total volume). The reaction was monitored by TLC. After ~2 h, the solvent was evaporated *in vacuo* yielding an amorphous white solid (0.622 g, 95%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.96 (brs, 1H), 8.09 (brs, 1H), 7.79 (brs, 1H), 6.93 (m, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 162.5, 151.3 (dd, *J* = 238.6, 6.3), 147.6 (dd, *J* = 245.2, 8.6), 142.1 (d, *J* = 14.9), 118.1 (dd, *J* = 9.0, 3.6), 117.1 (dd, *J* = 24.6, 20.7), 111.6 (dd, *J* = 22.8, 3.4); IR (neat) 3433, 3371, 1687 cm⁻¹; R_f 0.185 in 50% EtOAc/hexanes; HRMS (ESI) *m/z* calcd for C₇H₅F₂NO₂ (M + H)⁺ 174.0366, found 174.0354. ¹H NMR spectrum was in accordance with the literature¹⁰.

2-Chloro-N-(2,5-dichloro-pyridin-3-yl)-acetamide (7)

3-amino-2,5-dichloropyridine **8** (1.02 g, 6.25 mmol) was dissolved in dry CH₂Cl₂ (50 mL). The mixture was cooled to 0 °C and chloroacetyl chloride (0.75 mL, 9.43 mmol) was added dropwise. This was followed by the addition of (*i*-Pr)₂NEt (1.6 mL, 9.35 mmol). The reaction was monitored by TLC. After 3 h, the solvent was evaporated *in vacuo* and the crude mixture was purified by flash chromatography (30 to 50% EtOAc/hexanes) yielding an off-white solid (1.44 g, 96%): mp 121–122 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.94 (s, 1H), 8.82 (d, *J* = 2.4, 1H), 8.14 (d, *J* = 2.4, 1H), 4.26 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 164.7, 143.3, 137.9, 131.6, 131.4, 128.1, 42.7; IR (neat) 3366, 2946, 1682 cm⁻¹; R_f 0.833 in 50% EtOAc/hexanes; HRMS (ESI) *m/z* calcd for C₇H₅Cl₃N₂O (M + H)⁺ 238.9545, found 238.9512.

6-Chloro-2-chloromethyl-thiazolo[5,4-*b*]pyridine (2)

Compound **7** (0.561 g, 2.34 mmol) was dissolved in dry toluene (25 mL) and Lawesson's reagent (0.946 g, 4.68 mmol) was added. The reaction mixture was refluxed for 12 h at 110 °C. The reaction was monitored by mass spectroscopy for disappearance of starting material. After ~12 h, the color of the reaction mixture turned slightly red. At this point, the reaction was stopped and cooled to room temperature. The crude mixture was passed through a plug of silica gel and washed with CH₂Cl₂. The solvent was evaporated *in vacuo* and the crude mixture purified by flash chromatography (30 to 50% EtOAc/hexanes) yielding a solid (0.307 g, 60%): mp 89–90 °C; ¹H NMR (600 MHz, CDCl₃) δ 8.58 (d, *J* = 2.1, 1H), 8.23 (d, *J* = 2.1, 1H), 4.92 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 170.4, 156.6, 146.8, 146.5, 130.3, 130.1, 42.4; IR (neat) 3038, 1736, 1682 cm⁻¹; R_f 0.833 in 50% EtOAc/hexanes; HRMS (ESI) *m/z* calcd for C₇H₄Cl₂N₂S (M + H)⁺ 218.9850, found 218.9839.

3-((6-Chloropyrido[3,2-*d*][1,3]thiazol-2-yl)methoxy)-2,6-difluoro-benzamide (1)

Compound **4** (0.250 g, 1.44 mmol) was dissolved in 20 mL of dry CH₃CN and Cs₂CO₃ (0.94 g, 2.88 mmol) was added. Compound **2** (0.211 g, 0.963 mmol) was added to the mixture and stirred at 65 °C for ~3 h. The solution was filtered, concentrated *in vacuo* and purified by flash chromatography (30 to 70% EtOAc/hexanes) yielding an off-white solid (0.135 g, 40%): m.p. 212.5–214.5 (lit¹⁰, 218 °C); R_f 0.333 in 50% EtOAc/hexanes; ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.73 (d, *J* = 2.2, 1H), 8.68 (d, *J* = 2.2, 1H), 8.18 (brs, 1H), 7.90 (brs,

2H), 7.41 (m, 2H), 7.12 (m, 2H), 5.73 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d) δ 171.5, 161.8, 156.2, 154.3–154.4 (dd, $J = 235.49, 7.0$), 152.1–152.0 (dd, $J = 239.7, 9.0$), 149.9 (d, $J = 8.3$), 147.4 (d, $J = 8.3\text{Hz}$), 142.5 (d, $J = 10.9$), 130.6, 129.9, 117.4 (dd, $J = 41.7, 17.0$), 117.0 (d, $J = 8.8$), 111.9 (d, $J = 23.1$), 69.6; ^{19}F NMR (282 MHz, DMSO-d) δ -123.4, -134.1; IR 3393, 3198, 1671 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_8\text{ClF}_2\text{N}_3\text{O}_2\text{S}$ ($\text{M} + \text{H}$) $^+$ 356.0072, found 356.0051. ^1H NMR spectrum was in accordance with the literature¹⁰.

3-((6-Chloropyrido[3,2-d][1,3]thiazol-2-yl)methoxy)-2,6-difluoro-benzamide (1)

Compound **4** (0.100 g, 0.579 mmol) was dissolved in 20 mL of dry CH_3CN and K_2CO_3 (0.241 g, 1.73 mmol) was added. Iodide **20** (0.120 g, 0.386 mmol) was added and stirred at 65 °C for ~3 h. The solution was filtered, concentrated *in vacuo* and purified by flash chromatography (30 to 70% EtOAc/hexanes) yielding an off-white solid (0.097 g, 70%). ^1H NMR spectrum was in accordance with the literature¹⁰.

4-(2,5-Dichloro-pyridin-3-yl)-6-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-5-carbaldehyde (17)

Compound **7** (0.314 g, 1.31 mmol) was dissolved in dry DMF (15 mL) and NaI (0.197 g, 1.31 mmol) was added and stirred at 45 °C for 40 min. Then compound **3** (0.249 g, 1.57 mmol) and K_2CO_3 (1.0 g, 7.23 mmol) were added and the mixture was stirred for 2–3 h. The solution was filtered, concentrated *in vacuo* and purified by flash chromatography (30 to 50% EtOAc/hexanes) yielding a white solid (0.295 g, 66%); mp 190–191 °C; R_f 0.833 in 50% EtOAc/hexanes; ^1H NMR (300 MHz, CDCl_3) δ 9.90 (s, 1H), 8.34 (d, $J = 2.4$, 1H), 7.90 (d, $J = 2.4$, 1H), 7.37 (dd, $J = 9.0, 5.1$, 1H), 7.00 (m, 1H), 4.82 (d, $J = 14.3$, 1H), 4.63 (d, $J = 14.3$, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 185.2 (d, $J = 10.6$), 164.3, 162.7, 159.3, 148.0, 145.5 (d, $J = 14.7$), 141.3, 132.9, 130.5, 129.2, 123.4 (d, $J = 10.5$), 115.9 (d, $J = 11.3$), 113.2 (d, $J = 23.8$), 68.8; ^{19}F NMR (282 MHz, CDCl_3) δ -125.0; IR (neat) 1724, 1694 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_7\text{Cl}_2\text{FN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 340.9896, found 340.9897.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

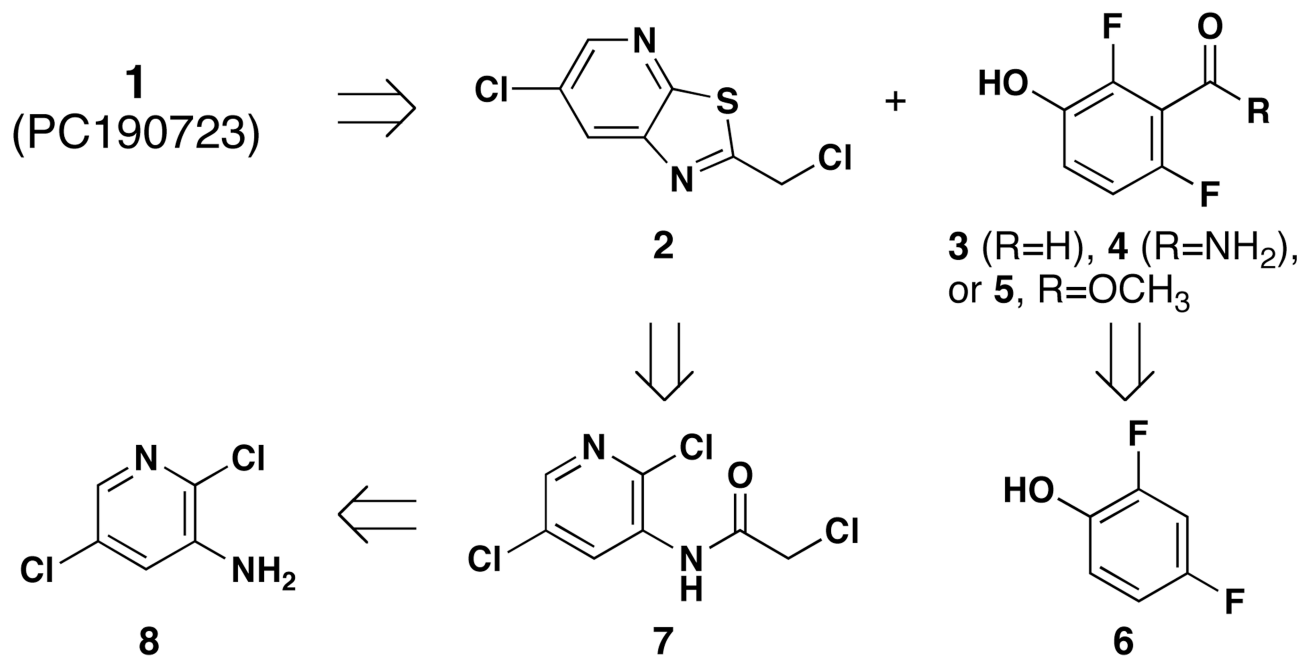
Acknowledgments

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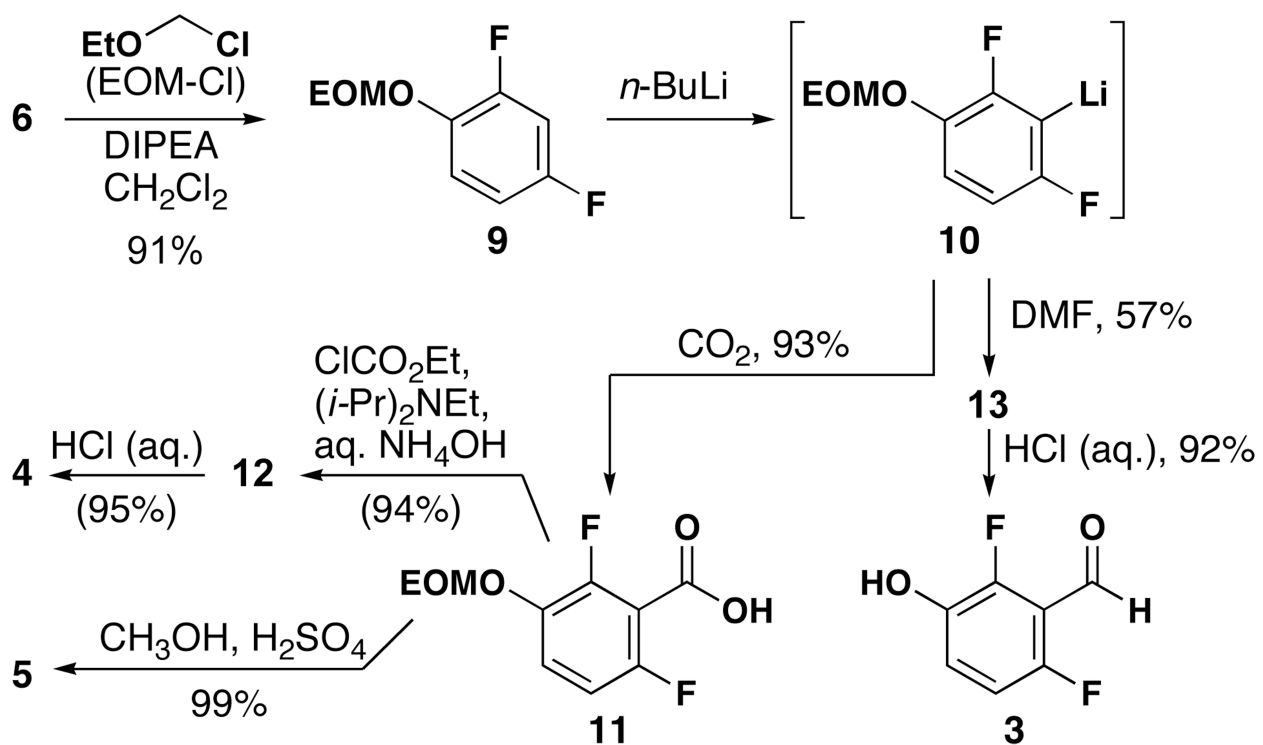
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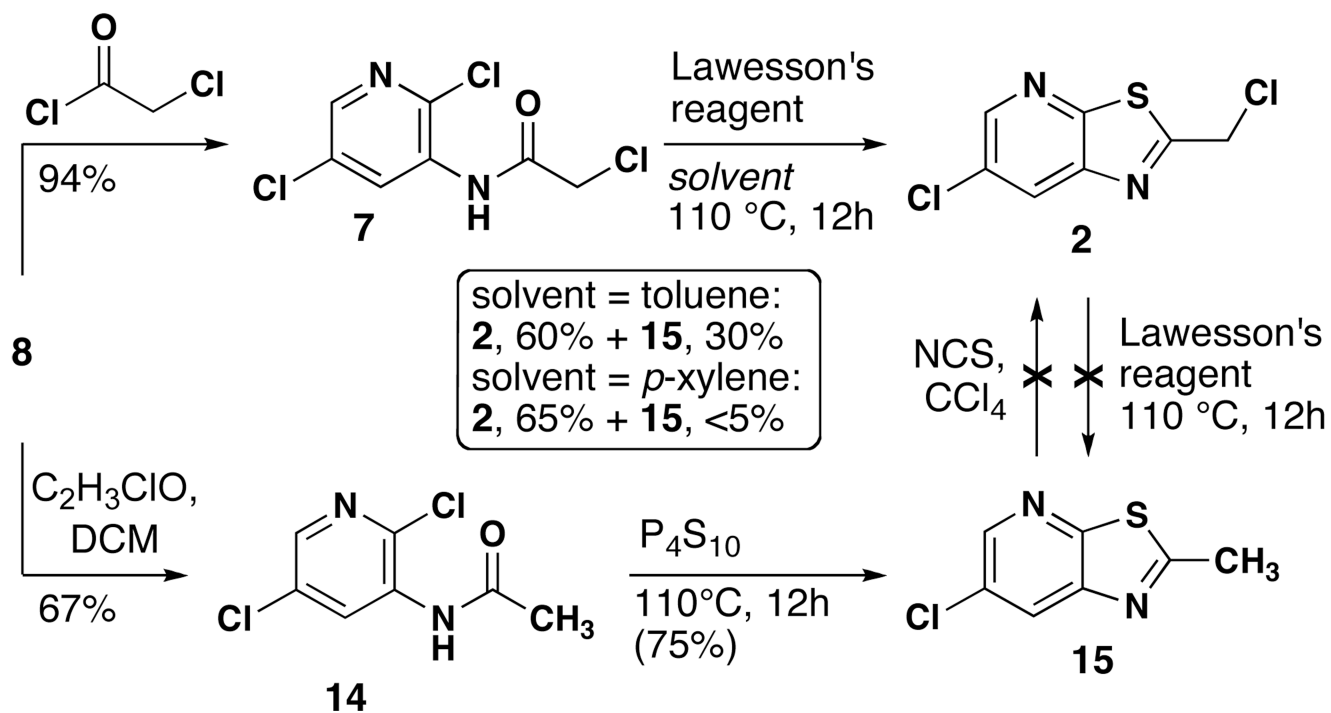
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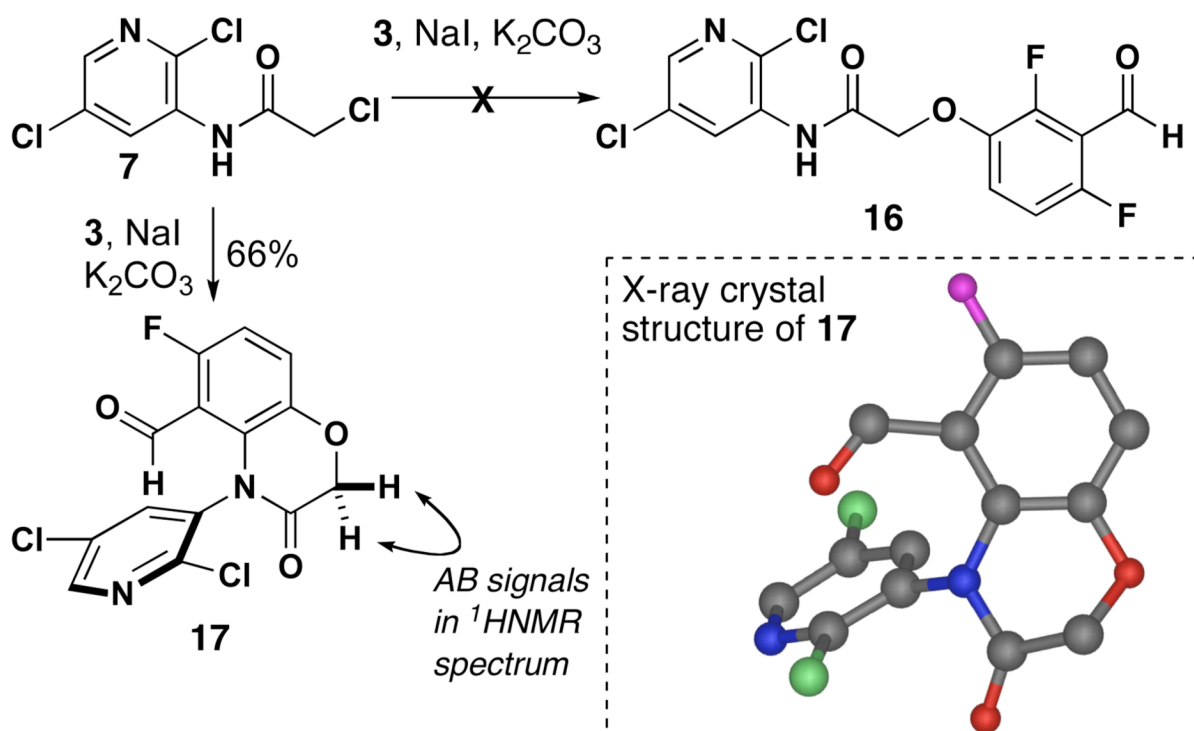
Scheme 1.
Retrosynthetic analysis of PC190723 (**1**).

**Scheme 2.**

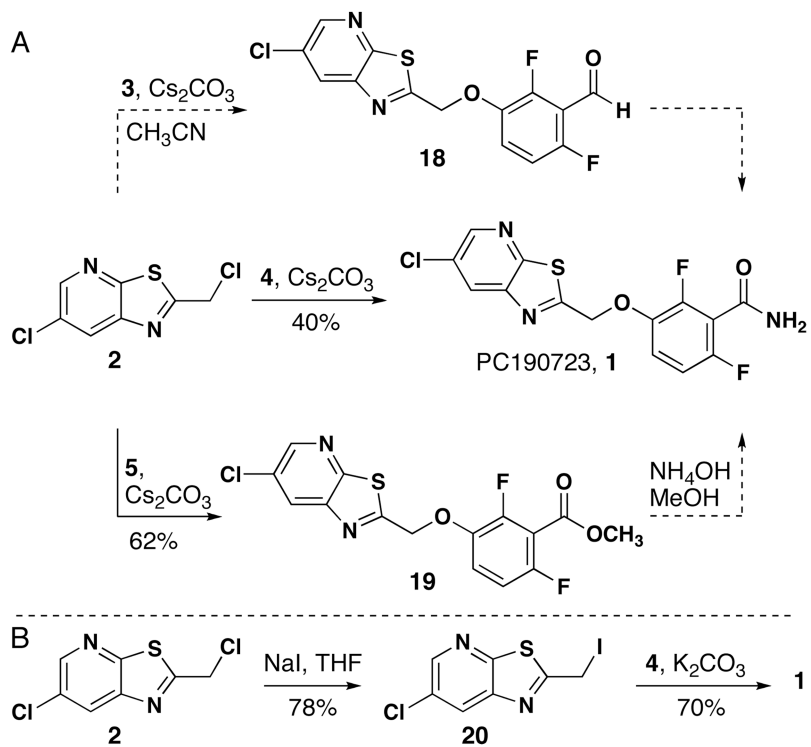
Synthesis of 2,6-difluoro-3-salicylaldehyde **3**, amide **4** and methyl ester **5**.



Scheme 3.
 Synthesis of chloromethyl thiazoline **2**.



Scheme 4.
Attempted alkylation of **7** with phenol **3**.

**Scheme 5.**

A) Final alkylation to produce **1**. B) Improved alkylation yield from conversion of chloride **2** to iodide **20**.