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SYNTHETIC STUDIES ON PLAKINIDINES

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This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – Synthetic studies on plakinidines are described. As a model study for the construction of the dihydropyridone ring at the final stage of the synthesis, we investigated a Meyer–Schuster rearrangement/aza-Michael cyclization cascade. The B,C,D,E ring system possessing a pyrrolo[2,3,4-*kl*]acridine structure was constructed via a benzyne-mediated cyclization/functionalization sequence that involved the formation of a β,β-diarylethylamine derivative and a palladium-catalyzed double aryl amination of a 3-arylindoline intermediate as key processes.

INTRODUCTION

The plakinidine alkaloid family, including plakinidines A (**1**), B (**2**), C (**3**), and D (**4**) having a highly functionalized pyrrolo[2,3,4-*kl*]acridine skeleton[1] (Figure 1), exhibit a potent cytotoxicity against HCT-116 murine leukemia cells.[2b] In addition, plakinidines A (**1**) and B (**2**) exhibit antiparasitic activity against *Nippostrongylus brasiliensis*.[2a] Due to their biological activities and their densely fused pentacyclic structure, which includes the fully substituted B ring, this family of compounds have attracted a great deal of attention as synthetic targets. To date, two synthetic studies on plakinidines have been reported. Kitahara[3] described the synthesis of a pentacyclic core lacking the amino group at the 12-position of the B ring via formation of the acridine skeleton at the early stage of the synthesis and subsequent cyclization of a ketene intermediate that was thermally generated from a Meldrum's acid derivative, affording the pyridone ring.[5] Meanwhile, Fukuyama et al.[4] successfully synthesized the fully functionalized pentacyclic core by a well-designed late stage aromatization strategy for the construction

of the B ring, whereas they failed to set up the required oxidation state of the pyrroloacridine system at the final stage of the synthesis.[4] In spite of these significant efforts toward the synthesis of plakinidines, a total synthesis has not been reported to date. Herein, we report the construction of the tetracyclic core of plakinidines by utilizing our previously reported benzyne-mediated cyclization/functionalization sequence[6] and a model study for the construction of the pyridone ring[7] through a Meyer–Schuster rearrangement/aza-Michael cyclization cascade.[8]

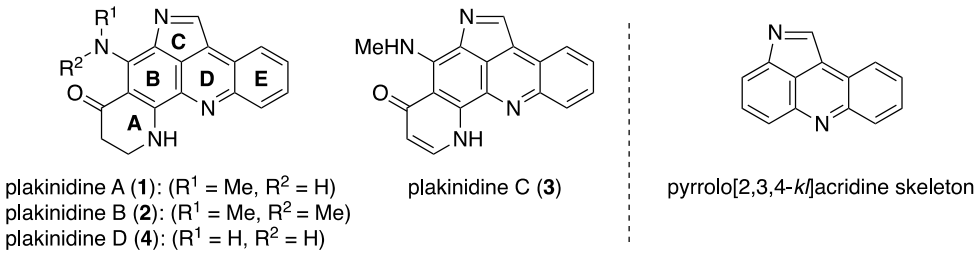
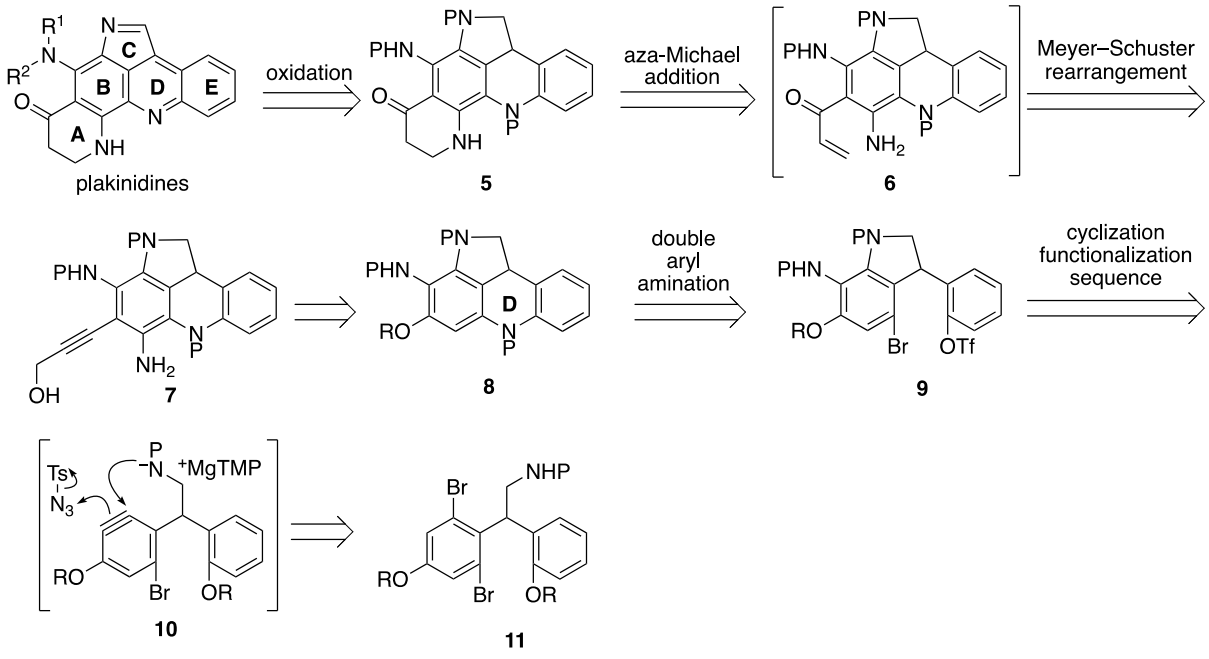


Figure 1. Plakinidine alkaloids

RESULTS AND DISCUSSIONS

Our retrosynthetic analysis of plakinidines is shown in Scheme 1. There were two key issues to be addressed in the synthesis of plakinidines. One was the construction of the pyrroloacridine core at the appropriate synthetic stage; the formation of the fully conjugated acridine skeleton at an early stage of the synthesis can be disadvantageous because its poor solubility and reactivity could hinder the subsequent

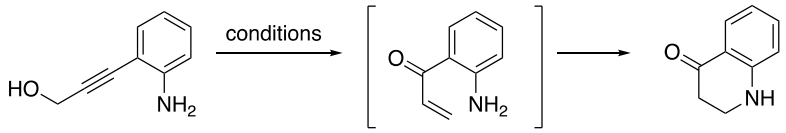


Scheme 1. Retrosynthetic analysis of plakinidines

transformations.[3] The other issue was the construction of the hexasubstituted B ring bearing the amino group and the fused pyridone ring. To circumvent the solubility issue, we selected tetrahydro derivative **5** as a precursor, which would afford the desired plakinidines upon oxidation at the final stage of the synthesis.For the crucial construction of the pyridone ring at the hindered position, we planned a cascade reaction starting with a Meyer–Schuster rearrangement and a subsequent aza-Michael addition from the *ortho*-aminophenyl propargylic alcohol derivative **7**. The tetrahydropyrroloacridine framework **8** would be easily assembled from β,β-diarylethylamine derivative **11** by performing a benzyne-mediated cyclization/functionalization strategy previously developed in our group,[6] followed by a double aryl amination reaction[9] of the as-generated indoline **9** according to Nozaki's protocol.[9a]

At the outset of the research, we examined the Meyer–Schuster rearrangement/aza-Michael addition cascade using 3-(2-aminophenyl)propyn-1-ol **12**[10] as a model substrate (Table 1). First, **12** was heated with Brønsted acids such as hydrochloric acid[8a] and *p*-TsOH,[8b] following the seminal work reported by Pisaneschi and Politanskaya (entries 1 and 2). The desired pyridone derivative **14** was obtained, albeit in a low yield. We then examined various Lewis acids to find milder conditions. Thus, π-philic Lewis acids such as PtCl[8c] or AuCl[8d] were inefficient (entries 3 and 4). On the other hand, the reaction of **12** with $Bi(OTf)_3$[8e] or $Sc(OTf)_3$[8f] provided pyridone **14** in moderate yields (entries 5 and 6). Eventually, we found that $SnCl_2$[8g] provided the most effective conditions, affording pyridone **14** in 66% yield (entry 7).

Table 1. Model study of Meyer–Schuster rearrangement/aza-Michael addition cascade

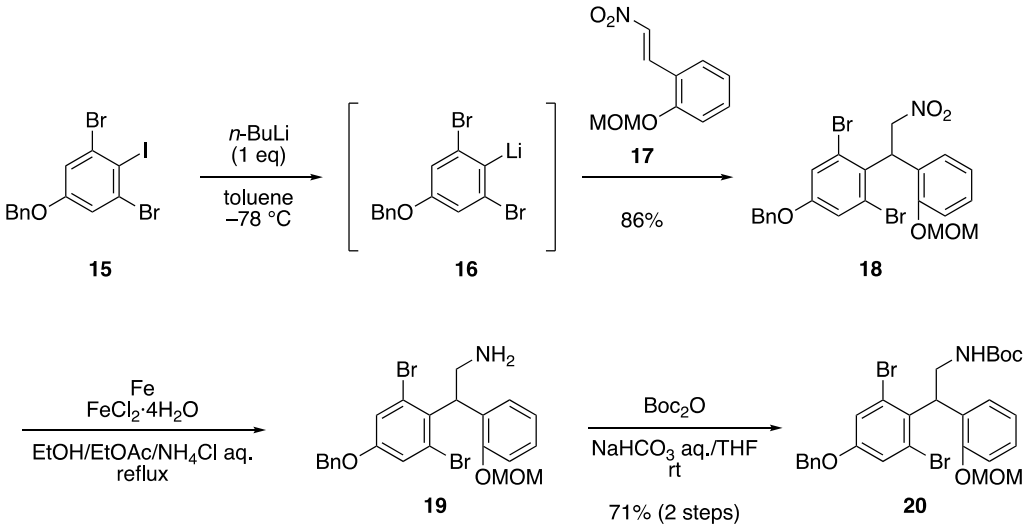


12 **13** **14**

entry	condition	yield (%)
1	conc. HCl, H_2O, reflux	18
2	*p*-TsOH·H_2O, EtOH, reflux	14
3	$PtCl_2$, *t*-BuOH, 60 °C	0
4	AuCl, $AgSbF_6$, MeOH/H_2O, 60 °C	10
5	$Bi(OTf)_3$, EtOH/1,2-DCE, 70 °C	34
6	$Sc(OTf)_3$, CH_2Cl_2/EtOH, 60 °C	44
7	$SnCl_2$, *t*-BuOH/H_2O, reflux	66

Having established the optimal conditions for the Meyer–Schuster rearrangement/aza-Michael addition cascade, we next initiated the synthetic studies on the key tetrahydropyrroloacridine intermediate. The

preparation of β,β-diarylethylamine derivative **20** commenced with the conjugate addition of the lithiated 2,6-dibromoiodobenzene derivative **15**[11] to nitroalkene **17**[12] (Scheme 2), in which the selective lithium–iodine exchange[11a,13] at **15** was promoted by treatment with *n*-BuLi (1 eq.) in toluene at –78 °C. Upon addition of nitroalkene **17**, the desired conjugate addition proceeded smoothly to give nitroalkane **18**. Reduction of the nitro group of **18** using a combination of Fe/$FeCl_2$[11a] and the subsequent protection of the resultant primary amine **19** as the corresponding Boc carbamate gave **20**.

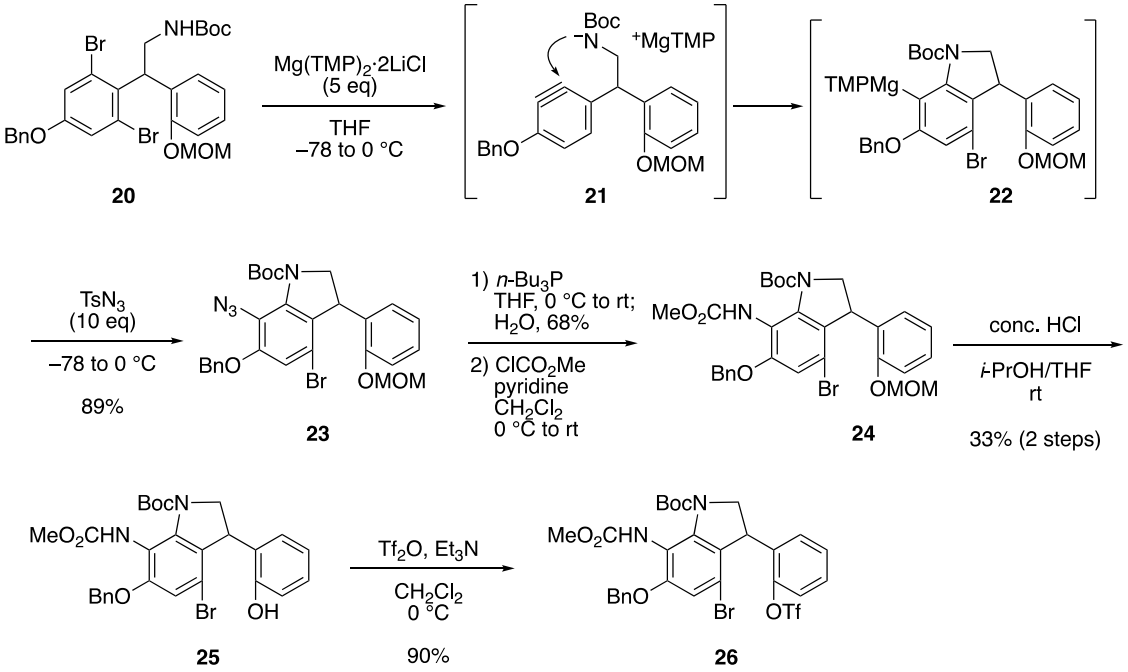


Scheme 2. Preparation of β,β-diarylethylamine derivative **20**

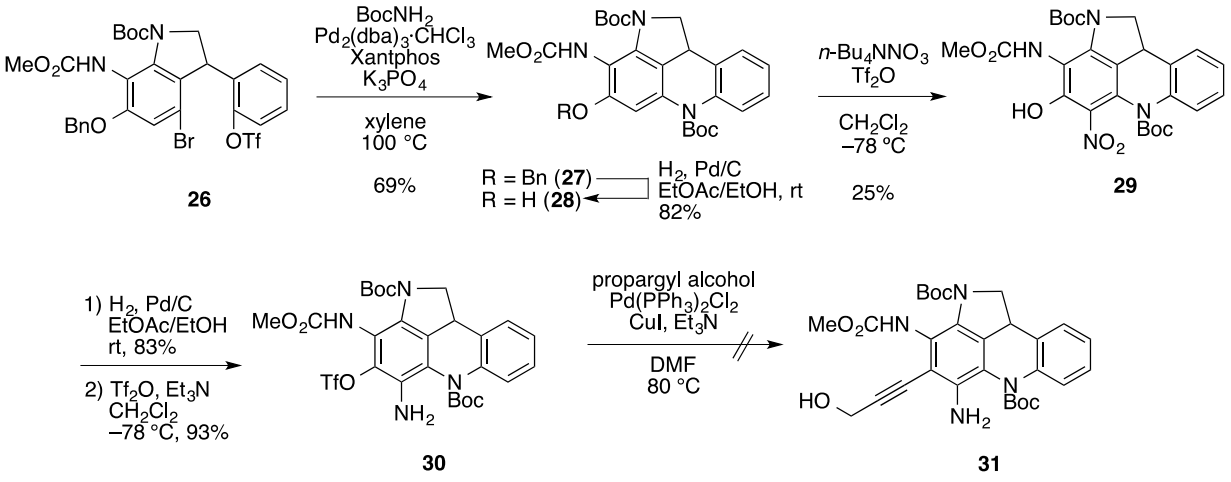
With β,β-diarylethylamine derivative **20** in hand, we conducted the key benzyne-mediated cyclization/functionalization sequence[6] (Scheme 3). Upon treatment of **20** with $Mg(TMP)_2 \cdot 2LiCl$ (TMP: 2,2,6,6-tetramethylpiperidyl) at –78 °C, followed by rising the reaction temperature to 0 °C, the intramolecular cyclization of the amide anion with the generated benzyne provided 7-magnesioindoline **22**, which was then trapped by tosyl azide to furnish 7-azidoindoline **23** in excellent yield. Reduction of the azide by Staudinger's condition and subsequent protection of the resulting primary amine as the corresponding methyl carbamate afforded **24**. Finally, the desired compound **26** was obtained by conversion of the MOM ether to triflate.

Our attention was then turned to the construction of the C and D rings (Scheme 4). The planned double amination reaction of bromo triflate **26** using Nozaki's protocol[9a] proceeded nicely to give tetracyclic compound **27** in good yield. After removal of the benzyl group, the nitro group was introduced by using a combination of *n*-Bu_4NNO_3 and Tf_2O[14] to provide **29**. Reduction of the nitro group, followed by treatment of the resulting phenol with Tf_2O afforded triflate **30**. For the introduction of the propargyl alcohol unit, we examined Sonogashira coupling reaction; however, all attempts including other coupling reactions

were unsuccessful.[15] These disappointing results could be attributed to the steric hindrance around the reaction site or to the electron-donating properties exerted by the four nitrogen atoms on the B ring.



Scheme 3. Benzyne-mediated cyclization/functionalization sequence



Scheme 4. Construction of tetracyclic core structure and attempt to introduce propargyl alcohol unit

In conclusion, we have established a novel synthetic approach to construct the tetracyclic core of plakinidine. The most salient feature of our synthesis includes the efficient introduction of three nitrogen atoms in the highly fused core skeleton of plakinidine through two cyclization processes, i.e., a benzyne-mediated cyclization/functionalization sequence and a palladium-catalyzed double amination reaction. Further investigation toward the total synthesis of plakinidine alkaloids is currently ongoing in our laboratory.

EXPERIMENTAL

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. Anhydrous THF and CH_2Cl_2 were purchased from Kanto Chemical Co. Inc. Anhydrous toluene, Et_3N, pyridine, xylene, and DMF were dried and distilled according to the standard protocols. 2,2,6,6-Tetramethylpiperidine was distilled from CaH_2 and stored over KOH. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm) using the indicated eluent. Preparative TLC and analytical TLC were performed on Merck 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. IR spectra were measured on a SHIMADZU FTIR–8300 spectrometer. NMR spectra were recorded on a JNM-AL400 spectrometer with tetramethylsilane (0 ppm) and chloroform (7.26 ppm) as internal standards. Chemical shifts were expressed in δ (ppm) values, and coupling constants were expressed in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Mass spectra were recorded on a JMS-700 (EI) or a Brucker micrOTOF II (ESI).

2,3-Dihydroquinolin-4(1*H*)-one (**14**)

A sealed tube equipped with a magnetic stirring bar and a screw cap was charged with aniline **12**[10] (10.6 mg, 72.0 μmol), $SnCl_2$ (12.7 mg, 67.0 μmol), *t*-BuOH (340 μL), and H_2O (340 μL). The reaction mixture was stirred and heated at reflux for 1 h. The reaction was quenched with 1 M aqueous NaOH and aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes-EtOAc = 1:1) to afford quinolinone **14** (7.0 mg, 48 μmol, 66%) as an orange solid. Spectroscopic data were identical with those previously reported.[16]

5-(Benzyloxy)-1,3-dibromo-2-(1-(2-(methoxymethoxy)phenyl)-2-nitroethyl)benzene (**18**)

A flame-dried 200-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with aryl iodide **15**[11] (4.16 g, 8.89 mmol) and toluene (45.0 mL). The mixture was cooled in a dry ice-acetone bath, and to the solution was added *n*-BuLi (1.55 M in hexanes, 5.80 mL, 8.99 mmol) dropwise over 5 min. After stirring for 10 min, a solution of nitro-olefin **17**[12] (1.86 g, 8.89 mmol) in toluene (20.0 mL) was added dropwise to the suspension at –78 °C over 5 min. After stirring for 10 min, the reaction was quenched with sat. aqueous ammonium chloride, and then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 7:1) to afford nitro alkane **18** (4.19 g, 7.60 mmol, 86%) as a colorless oil. R_f = 0.30 (hexanes-CH_2Cl_2 = 3:1); IR (neat, cm^{-1}): 1591, 1556, 1456, 1375,

1238, 1001; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.36 (m, 5H), 7.31–7.17 (m, 3H), 7.13–7.05 (m, 2H), 6.93 (ddd, 1H, *J* = 7.6, 6.8, 1.6 Hz), 6.04 (dd, 1H, *J* = 7.6, 6.8 Hz), 5.40 (dd, 1H, *J* = 13.6, 7.6 Hz), 5.15 (d, 1H, *J* = 7.6 Hz), 5.09 (dd, 1H, *J* = 13.6, 6.8 Hz), 5.07 (d, 1H, *J* = 7.6 Hz), 5.02 (s, 2H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 154.7, 135.6, 129.7, 129.0, 128.7, 128.6, 128.4, 127.5, 125.5, 120.9, 113.6, 93.5, 70.5, 60.4, 56.0, 44.1, 21.0, 14.2; HRMS (EI) *m/z*: calcd. for $C_{23}H_{21}{}^{79}Br_2NO_5$ [M^+] 548.9786, found 548.9777.

tert-Butyl (2-(4-(benzyloxy)-2,6-dibromophenyl)-2-(2-(methoxymethoxy)phenyl)ethyl)-carbamate (20)

A 500-mL, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with **18** (4.19 g, 7.60 mmol), Fe (4.24 g, 75.9 mmol), $FeCl_2 \cdot 4H_2O$ (963 mg, 7.60 mmol), saturated aqueous ammonium chloride (14.0 mL), EtOAc (14.0 mL), and EtOH (42.0 mL). The reaction mixture was stirred and heated at reflux for 2 h. The resulting solid was removed by filtration through a pad of Celite®, and the filter cake was washed thoroughly with MeOH. Then, the filtrate was concentrated under reduced pressure. The residue was basified with 4 M NaOH to pH = 14 and filtered through a pad of Celite®, and the filter cake was washed thoroughly with MeOH. Then, the filtrate was concentrated under reduced pressure to give a crude amine, which was used to the next reaction without further purification.

To the residue was added sat. aqueous $NaHCO_3$ (35.0 mL), THF (70.0 mL), and Boc_2O (2.49 g, 11.4 mmol). The reaction mixture was stirred at room temperature for 11 h. The reaction mixture was diluted with EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 6:1) to afford the carbamate **20** (3.35 g, 5.39 mmol, 71% over 2 steps from **18**) as a white powder. R_f = 0.19 (hexanes-EtOAc = 5:1); IR (neat, cm^{-1}): 1684, 1592, 1237, 1163, 1011, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–6.92 (m, 11H), 5.13 (dd, 1H, *J* = 8.4, 7.2 Hz), 5.02–4.97 (m, 3H), 4.92 (d, 1H, *J* = 6.8 Hz), 4.60 (brs, 1H), 4.20–3.96 (m, 2H), 3.09 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 155.7, 155.0, 135.8, 131.8, 130.0, 128.7, 128.3, 128.2, 127.7, 127.5, 120.4, 113.0, 93.3, 79.1, 70.4, 55.6, 45.75, 45.70, 40.8, 28.4, 14.2; HRMS (ESI) *m/z*: calcd. for $C_{28}H_{31}{}^{79}Br_2NNaO_5$ [M+Na^+] 642.0461, found 642.0441.

Preparation of $Mg(TMP)_2 \cdot 2LiCl$.[6]

A 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with Mg turnings (703 mg, 28.9 mmol). The flask was evacuated under

heating for 30 min and then backfilled with argon. After addition of dry THF (72.0 mL), 1,2-dichloroethane (2.27 mL, 28.9 mmol) was added dropwise to the flask at room temperature. The reaction mixture was stirred for approximately an hour until all magnesium was consumed. Another flame-dried 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with 2,2,6,6-tetramethylpiperidine (9.80 mL, 58.0 mmol) and dry THF (35.0 mL). The solution was cooled in dry ice-acetone bath, and to the solution was added *n*-BuLi (1.55 M in *n*-hexane, 37.0 mL, 57.8 mmol) dropwise at –78 °C. The resulting suspension was allowed to warm to 0 °C and stirred at the same temperature for 30 min. To the resulting pale yellow solution was transferred the $MgCl_2$-THF solution *via* cannula, and the mixture was stirred for another an hour to afford a pale yellow solution of $Mg(TMP)_2 \cdot 2LiCl$ (0.180 M in *n*-hexane-THF). The reagent was titrated prior to use at 0 °C against benzoic acid using 4-(phenylazo)diphenylamine as indicator.

tert-Butyl 7-azido-6-(benzyloxy)-4-bromo-3-(2-(methoxymethoxy)phenyl)indoline-1-carboxylate (23)

A flame-dried 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the carbamate **20** (3.35 g, 5.39 mmol), and THF (20.0 mL). The mixture was cooled in a dry ice-acetone bath, and to the solution was added $Mg(TMP)_2 \cdot 2LiCl$ (0.180 M in THF, 150 mL, 27.0 mmol) at –78 °C dropwise over 5 min. The reaction mixture was allowed to warm to 0 °C and stirred for 1 h. Then, TsN_3 (8.20 mL, 53.6 mmol) was added to the reaction mixture at –78 °C, and the resulting mixture was allowed to warm to 0 °C and stirred for 1 h. The reaction was quenched with sat. aqueous ammonium chloride, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-CH_2Cl_2 = 1:1 to hexanes-EtOAc = 5:1) to afford azide **23** (2.80 g, 4.82 mmol, 89%) as a pale yellow oil. R_f = 0.27 (hexanes-EtOAc = 5:1); IR (neat, cm^{-1}): 2120, 1712, 1336, 1154, 1001, 754; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.15 (m, 6H), 7.10 (d, 1H, *J* = 8.4 Hz), 6.86–6.82 (m, 2H), 6.67 (d, 1H, *J* = 7.2 Hz), 5.26 (d, 1H, *J* = 6.4 Hz), 5.21 (d, 1H, *J* = 6.4 Hz), 5.12 (s, 2H), 4.54 (dd, 1H, *J* = 8.0, 2.0 Hz), 4.21 (dd, 1H, *J* = 11.2, 8.0 Hz), 4.08 (dd, 1H, *J* = 11.2, 2.0 Hz), 3.44 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 153.7, 153.1, 138.3, 135.7, 130.8, 129.6, 128.7, 128.3, 128.2, 128.0, 127.5, 121.7, 119.3, 114.6, 113.8, 112.9, 94.1, 81.4, 71.9, 59.2, 56.0, 42.3, 28.0; HRMS (EI) *m/z*: calcd. for $C_{28}H_{29}{}^{79}BrN_4O_5$ [M^+] 580.1321, found 580.1306.

tert-Butyl 7-amino-6-(benzyloxy)-4-bromo-3-(2-(methoxymethoxy)phenyl)indoline-1-carboxylate

A 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with azide **23** (2.30 g, 3.96 mmol), and THF (10.0 mL). To the mixture was added tri-*n*-butylphosphine (1.48 mL, 5.94 mmol) dropwise at 0 ºC. Nitrogen gas started to evolve within 5 min. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. To the iminophosphorane generated *in situ* was added H_2O (5.00 mL), and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with EtOAc and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 6:1) to afford the aniline (1.49 g, 2.68 mmol, 68%) as a white powder. R_f = 0.27 (hexanes-EtOAc = 5:1); IR (neat, cm^{-1}): 1685, 1489, 1370, 1155, 1003, 753; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.32 (m, 5H), 7.18 (ddd, 1H, *J* = 8.4, 6.8, 1.6 Hz), 7.11 (d, 1H, *J* = 8.4 Hz), 6.85 (dd, 1H, *J* = 7.6, 6.8 Hz), 6.78 (s, 1H), 6.75 (d, 1H, *J* = 7.6 Hz), 5.28 (d, 1H, *J* = 6.8 Hz), 5.21 (d, 1H, *J* = 6.8 Hz), 5.08 (d, 1H, *J* = 11.2 Hz), 5.04 (d, 1H, *J* = 11.2 Hz), 4.90 (brs, 2H), 4.55 (dd, 1H, *J* = 8.4, 2.0 Hz), 4.21 (dd, 1H, *J* = 11.2, 8.4 Hz), 4.04 (dd, 1H, *J* = 11.2, 2.0 Hz), 3.46 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 153.8, 148.1, 136.6, 130.9, 130.6, 129.2, 128.6, 128.21, 128.16, 127.9, 127.6, 126.9, 121.7, 113.7, 111.7, 105.8, 94.2, 81.3, 71.3, 58.5, 56.0, 41.6, 28.1; HRMS (ESI) *m/z*: calcd. for $C_{28}H_{32}{}^{79}Br_2N_2O_5$ $[M+H^+]$ 555.1489, found 555.1463.

tert-Butyl 6-(benzyloxy)-4-bromo-3-(2-hydroxyphenyl)-7-((methoxycarbonyl)amino)-indoline-1-carboxylate (25)

A 30-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the aniline (1.49 g, 2.68 mmol), and CH_2Cl_2 (13.0 mL). The mixture was cooled in ice-water bath, and to the solution was added pyridine (325 μL, 4.02 mmol) and methyl chloroformate (249 μL, 3.22 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 10 min. The reaction was quenched with 1 M aqueous HCl and aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude carbamate, which was used to the next reaction without further purification.

A 100-mL, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the crude carbamate, *i*-PrOH (65.0 mL), and THF (65.0 mL). To the mixture was added conc. HCl (16.8 mL, 201 mmol) at room temperature and the reaction mixture was stirred at room temperature for 40 h. The reaction mixture was diluted with EtOAc and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column

chromatography on silica gel (hexanes-EtOAc = 4:1 to 2:1) to afford the phenol **25** (499 mg, 877 μmol, 33% over 2 steps from aniline) as a pink powder. R_f = 0.16 (hexanes-EtOAc = 3:1); IR (neat, cm^{-1}): 1699, 1684, 1507, 1457; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (brs, 1H), 7.44–7.33 (m, 5H), 7.10 (ddd, 1H, *J* = 8.0, 8.0, 1.2 Hz), 6.90 (s, 1H), 6.80 (dd, 1H, *J* = 8.0, 6.8 Hz), 6.76 (d, 1H, *J* = 8.0 Hz), 6.71 (d, 1H, *J* = 6.8 Hz), 5.10 (s, 2H), 4.97 (brs, 1H), 4.54 (dd, 1H, *J* = 8.8, 2.4 Hz), 4.30 (dd, 1H, *J* = 11.6, 8.8 Hz), 4.09 (dd, 1H, *J* = 11.6, 2.4 Hz), 3.69 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 154.5, 154.2, 153.4, 139.6, 136.5, 129.2, 128.4, 128.1, 127.9, 127.6, 127.2, 120.2, 116.5, 115.7, 115.2, 113.2, 82.1, 71.3, 71.2, 58.6, 52.6, 41.6, 28.0; HRMS (ESI) *m/z*: calcd. for $C_{28}H_{29}{}^{79}BrN_2NaO_6$ [M+Na^+] 591.1101, found 591.1074.

tert-Butyl 6-(benzyloxy)-4-bromo-7-((methoxycarbonyl)amino)-3-(2-(((trifluoromethyl)-sulfonyl)oxy)phenyl)indoline-1-carboxylate (26)

A 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with the phenol **25** (499 mg, 877 μmol), and CH_2Cl_2 (9.00 mL). The mixture was cooled in ice-water bath, and to the solution was added Et_3N (184 μL, 1.32 mmol) and Tf_2O (148 μL, 880 μmol). The solution was then stirred at same temperature for 5 min. The reaction was quenched with sat. aqueous ammonium chloride and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 6:1) to afford the triflate **26** (551 mg, 785 μmol, 90%) as a white foam. R_f = 0.35 (hexanes-EtOAc = 3:1); IR (neat, cm^{-1}): 1734, 1698, 1506, 1418, 1218, 1141; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (brs, 1H), 7.45 (d, 2H, *J* = 7.6 Hz), 7.37 (dd, 2H, *J* = 7.6, 7.6 Hz), 7.36–7.20 (m, 4H), 6.90 (s, 1H), 6.83 (d, 1H, *J* = 7.6 Hz), 5.10 (s, 2H), 4.60 (dd, 1H, *J* = 8.8, 2.4 Hz), 4.36 (dd, 1H, *J* = 11.6, 8.8 Hz), 4.06 (dd, 1H, *J* = 11.6, 2.4 Hz), 3.69 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 154.1, 153.7, 146.7, 139.2, 136.3, 134.5, 128.9, 128.8, 128.4, 127.9, 127.2, 123.3, 121.4, 120.1, 116.9, 116.4, 116.0, 113.3, 82.5, 71.3, 58.2, 52.3, 40.8, 27.9; HRMS (ESI) *m/z*: calcd. for $C_{29}H_{28}{}^{79}BrF_3N_2NaO_8S$ [M+Na^+] 723.0594, found 723.0568.

Di-*tert*-butyl 4-(benzyloxy)-3-((methoxycarbonyl)amino)-1,10b-dihydropyrrolo-[2,3,4-*kl*]acridine-2,6-dicarboxylate (27)

A 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (163 mg, 157 μmol), Xantphos (182 mg, 314 μmol), and xylene (2.60 mL). Triflate **26** (551 mg, 785 μmol), $BocNH_2$ (139 mg, 1.18 mmol), and K_3PO_4 (500 mg, 2.36 mmol) were added to the reaction mixture. The reaction mixture was stirred and heated at 100

ºC for 5 h. The reaction was quenched with sat. aqueous ammonium chloride and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 3:1) to afford the dihydroacridine **27** (320 mg, 545 μmol, 69%) as a red foam. R_f = 0.28 (hexanes-EtOAc = 3:1); IR (neat, cm^{-1}): 1714, 1349, 1153, 732; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84–7.60 (m, 3H), 7.50–7.22 (m, 4H), 7.17 (dd, 1H, *J* = 8.0, 6.4 Hz), 7.07 (s, 1H), 7.03 (d, 1H, *J* = 8.0 Hz), 5.11 (s, 2H), 4.87 (dd, 1H, *J* = 9.6, 9.6 Hz), 4.44 (dd, 1H, *J* = 9.6, 9.6 Hz), 4.03 (dd, 1H, *J* = 9.6, 9.6 Hz), 3.66 (s, 3H), 1.58 (s, 9H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 154.3, 153.7, 153.0, 152.1, 138.3, 136.9, 134.5, 133.0, 132.7, 128.7, 128.2, 128.1, 127.5, 126.9, 126.1, 125.3, 125.2, 125.0, 121.4, 114.2, 105.9, 82.0, 81.8, 71.4, 60.0, 57.0, 52.0, 36.4, 28.0, 27.8, 20.7, 13.9 (a mixture of two rotamer); HRMS (ESI) *m/z*: calcd. for $C_{33}H_{38}N_3O_7$ [M+H^+] 588.2704, found 588.2682.

Di-*tert*-butyl 4-hydroxy-3-((methoxycarbonyl)amino)-1,10b-dihydropyrrolo[2,3,4-*kl*]-acridine-2,6-dicarboxylate (28)

A 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with benzyl ether **27** (311 mg, 530 mmol), 10% palladium on activated carbon (56.4 mg, 53.0 μmol), EtOAc (2.50 mL), and EtOH (2.50 mL). The mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 10 h. The reaction mixture was filtered through a pad of Celite®, and the filter cake was washed thoroughly with EtOAc. Then, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 7:1) to afford the phenol **28** (216 mg, 434 μmol, 82%) as a pale yellow oil. R_f = 0.39 (hexanes-EtOAc = 3:1); IR (neat, cm^{-1}): 3155, 1714, 1351, 1155, 733; ^1H NMR (400 MHz, $CDCl_3$): δ 9.96 (brs, 1H), 8.28 (brs, 1H), 7.74 (dd, 1H, *J* = 8.4, 1.2 Hz), 7.31–7.24 (m, 1H), 7.16 (ddd, 1H, *J* = 7.6, 7.2, 1.2 Hz), 7.09 (s, 1H), 7.01 (d, 1H, *J* = 7.6 Hz), 4.90 (dd, 1H, *J* = 10.0, 9.2 Hz), 4.40 (dd, 1H, *J* = 10.0, 8.8 Hz), 3.97 (dd, 1H, *J* = 9.2, 8.8 Hz), 3.79 (s, 3H), 1.60 (s, 9H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 156.5, 152.2, 149.8, 138.5, 133.5, 132.6, 132.3, 126.5, 125.4, 121.5, 114.3, 112.8, 82.9, 82.4, 60.3, 57.7, 53.2, 36.6, 28.2, 21.0, 14.1; HRMS (ESI) *m/z*: calcd. for $C_{26}H_{31}N_3NaO_7$ [M+Na^+] 520.2054, found 520.2043.

Di-*tert*-butyl 4-hydroxy-3-((methoxycarbonyl)amino)-5-nitro-1,10b-dihydropyrrolo-[2,3,4-*kl*]acridine-2,6-dicarboxylate (29)

A 20-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with Tf_2O (73.0 μL, 434 μmol), *n*-Bu_4NNO_3 (132 mg, 434 μmol), and CH_2Cl_2 (2.00 mL). The mixture was cooled in dry ice-acetone bath, and to the reaction mixture was

added phenol **28** (216 mg, 434 μmol) in CH_2Cl_2 (2.50 mL). The reaction mixture was stirred for at same temperature for 10 min. The reaction was quenched with sat. aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 3:1) to afford the nitrophenol **29** (59.0 mg, 109 μmol, 25%) as a red oil. R_f = 0.1 (hexanes-EtOAc = 3:1); IR (neat, cm^{-1}): 2979, 1723, 1540, 1349, 1152, 732; ^1H NMR (400 MHz, $CDCl_3$): δ 10.9 (s, 1H), 8.27 (brs, 1H), 7.87 (d, 1H, *J* = 7.2 Hz), 7.36 (dd, 1H, *J* = 8.4, 7.2 Hz), 7.33–7.20 (m, 1H), 7.08 (d, 1H, *J* = 8.0 Hz), 4.87 (dd, 1H, *J* = 10.8, 9.6 Hz), 4.46 (dd, 1H, *J* = 10.0, 9.6 Hz), 4.11 (dd, 1H, *J* = 10.8, 10.0 Hz), 3.74 (s, 3H), 1.60 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 152.7, 151.3, 151.1, 138.4, 138.1, 132.7, 128.3, 127.1, 126.3, 126.2, 124.6, 122.9, 113.6, 83.7, 83.6, 56.6, 52.9, 37.4, 28.1, 27.8, 14.1; HRMS (ESI) *m/z*: calcd. for $C_{26}H_{30}N_4NaO_9$ [M+Na^+] 565.1905, found 565.1901.

Di-*tert*-butyl 5-amino-4-hydroxy-3-((methoxycarbonyl)amino)-1,10b-dihydropyrrolo-[2,3,4-*kl*]acridine-2,6-dicarboxylate

A 10-mL, Schlenk tube equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with nitrophenol **29** (55.7 mg, 103 μmol), 10% palladium on activated carbon (11.0 mg, 10.3 μmol), EtOAc (500 μL), and EtOH (500 μL). The mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite®, and the filter cake was washed thoroughly with EtOAc. Then, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 3:1) to afford aminophenol (43.6 mg, 85.1 μmol, 83%) as a pale yellow solid. R_f = 0.31 (hexanes-EtOAc = 3:1); IR (neat, cm^{-1}): 2979, 1697, 1471, 1370, 1258, 1161, 732; ^1H NMR (400 MHz, $CDCl_3$): δ 10.1 (brs, 1H), 8.45 (brs, 1H), 7.56 (d, 1H, *J* = 8.4 Hz), 7.23 (dd, 1H, *J* = 8.4, 7.6 Hz), 7.17 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.02 (d, 1H, *J* = 7.6 Hz), 4.85 (dd, 1H, *J* = 9.2, 9.2 Hz), 4.46 (dd, 1H, *J* = 9.2, 9.2 Hz), 3.89 (dd, 1H, *J* = 9.2, 9.2 Hz), 3.78 (s, 3H), 1.59 (s, 9H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 154.6, 152.6, 139.3, 137.3, 134.3, 131.4, 126.7, 126.2, 125.8, 124.9, 123.6, 122.5, 121.1, 115.6, 82.6, 82.3, 56.8, 53.2, 37.6, 28.3, 28.2; HRMS (ESI) *m/z*: calcd. for $C_{26}H_{33}N_4O_7$ [M+H^+] 513.2344, found 513.2377.

Di-*tert*-butyl 5-amino-3-((methoxycarbonyl)amino)-4-(((trifluoromethyl)sulfonyl)oxy)-1,10b-dihydropyrrolo[2,3,4-*kl*]acridine-2,6-dicarboxylate (30)

A 30-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon gas inlet, and a rubber septum was charged with aminophenol (43.0 mg, 83.9 μmol), and CH_2Cl_2 (800 μL). The mixture was cooled in a dry ice-acetone bath, to the solution was added Et_3N (14.0 μL, 100 μmol) and Tf_2O (14.0

μL, 84.0 μmol). The solution was then stirred at same temperature for 15 min. The reaction was quenched with sat. aqueous ammonium chloride and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 M aqueous HCl and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes-EtOAc = 3:1) to afford triflate **30** (50.8 mg, 78.8 μmol, 93%) as a white powder. R_f = 0.17 (hexanes-EtOAc = 3:1); IR (neat, cm^{-1}): 3166, 2980, 1691, 1356, 1146, 912, 733; ^1H NMR (400 MHz, $CDCl_3$): δ 10.1 (brs, 1H), 7.54–7.42 (m, 1H), 7.34–7.19 (m, 2H), 7.05 (d, 1H, *J* = 8.0 Hz), 4.88 (dd, 1H, *J* = 9.8, 8.8 Hz), 4.49 (dd, 1H, *J* = 9.8, 9.6 Hz), 4.00 (dd, 1H, *J* = 9.6, 8.8 Hz), 3.80 (s, 3H), 1.60 (s, 9H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 154.2, 152.9, 148.2, 138.3, 133.2, 132.3, 130.8, 126.7, 126.4, 126.3, 125.0, 123.3, 121.4, 117.0, 116.3, 84.0, 83.5, 57.3, 53.5, 37.3, 28.2, 28.0; HRMS (ESI) *m/z*: calcd. for $C_{27}H_{31}N_4NaO_9S$ [M+Na^+] 667.1656, found 667.1624.

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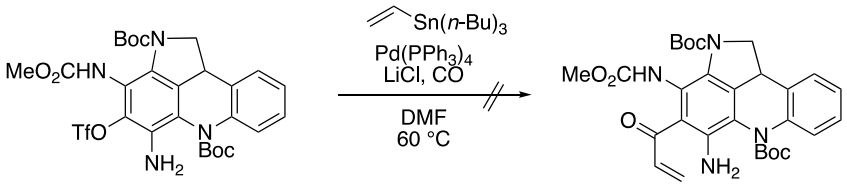

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