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Synthesis of Peraza Crown Macrocycles

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Abstract

As environmental pollution from heavy metals and transition metals continues to occur, it is important to find reliable ways to remove the contaminants from soil and water. Peraza crown macrocycles are one type of molecule that have been known to act as a ligand and trap transition metals, removing them from the environment. For this research a synthesis was proposed to create a peraza crown with four nitrogen atoms in the central binding ring, with quinoxaline groups to either side of the molecule to increase rigidity and thus the binding speed and efficiency. While the different subunits of the designed molecule have been synthesized before, the general structure of this ligand has not been shown in literature. The synthesis for this new molecule avoids using a metal ion template to build the larger structure, and the route taken allows for nonsymmetrical products to form. Molecules with different substituents have been synthesized to explore the scope and the future ion binding.

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Table of Contents

Introduction

Transition metal contamination occurs in environmental sources around the world and continues to increase on a global scale[1]. Heavy metals, such as lead and mercury, are found in soil and water from depositions of different industrial emissions, applications by farmers in fertilizers and pesticides, and even accidental spills into the environment[2]. These metals pose many dangers to humans through the risk of ingestion. Contaminated water or plants that have taken up the metals can be consumed, resulting in negative impacts to human health. These metals also have a long lifetime in soil and water, as most metals cannot be used by microbes and degraded, so their effect on the environment is pronounced[2]. With this in mind, it is crucial for scientists to take measures to reduce humanity's footprint in this area. The aim of this project was to create a synthesis pathway for a novel molecule capable of capturing transition metal contaminants from soil and water samples, and to do so using a green pathway to minimize our effect on the environment.

The molecule for this synthesis was designed based on peraza crown macrocycles, which have been proven in literature to have ligand binding properties selective towards transition metals[3]. Peraza crown macrocycles are ring systems with nitrogen atoms strategically placed around the ring, similar to the oxygen placement in crown ethers, as shown by example molecules in **Figure 1**. Crown ethers are also capable of binding metals, but they tend to favor coordination with alkali and alkaline-earth metals, so peraza compounds were chosen to increase the coordination specificity towards transition metals[4].

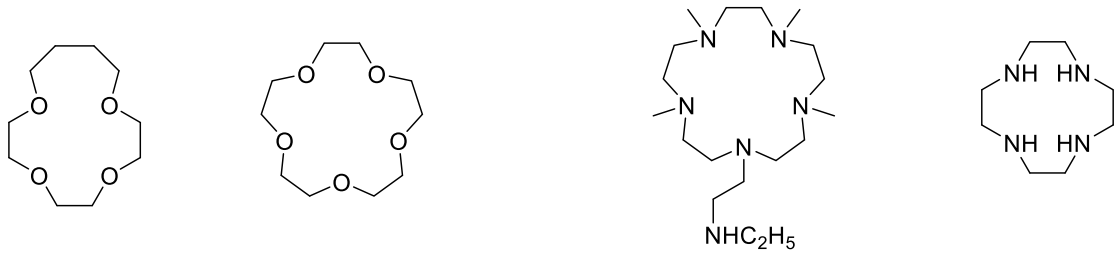


Figure 1: A Comparison between Crown Ethers and Peraza Crowns

In the design for our novel compound, a quinoxaline subunit was placed on either side of the macrocycle. Quinoxaline groups offer a rigid, planar structure to keep the peraza crown nitrogens in the ideal placement for binding as a ligand, increasing the complexing activity of the structure[5]. Quinoxaline and its derivatives have been documented in literature as DNA intercalators and even as a chelating ligand on its own, so synthetic routes of quinoxalines have been published, some of which we have incorporated into building our molecule[5,7]. The base structure, shown below in **Figure 2**, has no substituents on the benzene ring of the quinoxaline groups and has a two-carbon bridge, but other structures with variations were also created.

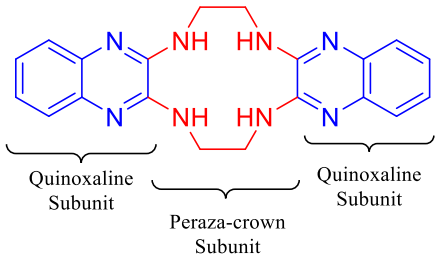


Figure 2: Base Structure for Peraza Crown Macrocycle

Usage of peraza structures have been documented in literature, including water purification, metal ion separation, and medical applications such as kidney stone treatments and usage as a contrast agent in nuclear magnetic resonance[1, 3, 6]. Despite the benefits of built-in metal selectivity, there are inherent difficulties with choosing peraza crowns as the base for our molecule that must be overcome, as current synthetic pathways are not ideal. Existing synthetic routes for peraza crown structures often are synthesized in dilute conditions, which can make it difficult to build up large quantities of the molecule or are synthesized using a metal ion to build up the structure as seen in **Figure 3**, which can later be difficult to remove and result in low yields[3].

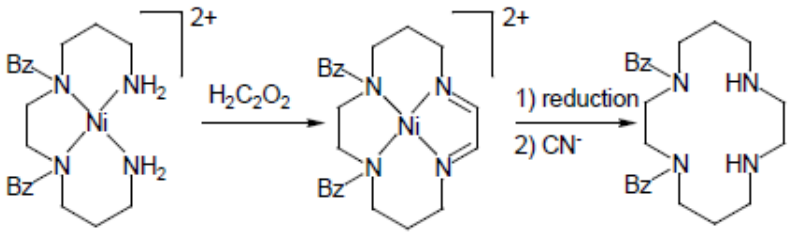


Figure 3: Scheme 10 from Denat (3). Reaction yield only 18%.

In this experiment, a synthetic route was created that could avoid both the dilute conditions and the use of a metal ion to create an overall more optimal process to produce the molecule of interest, shown in **Figure 4**. This route is also unique because it allows for the formation of a nonsymmetrical molecule, where nonequivalent quinoxaline subunits can be incorporated into the molecule.

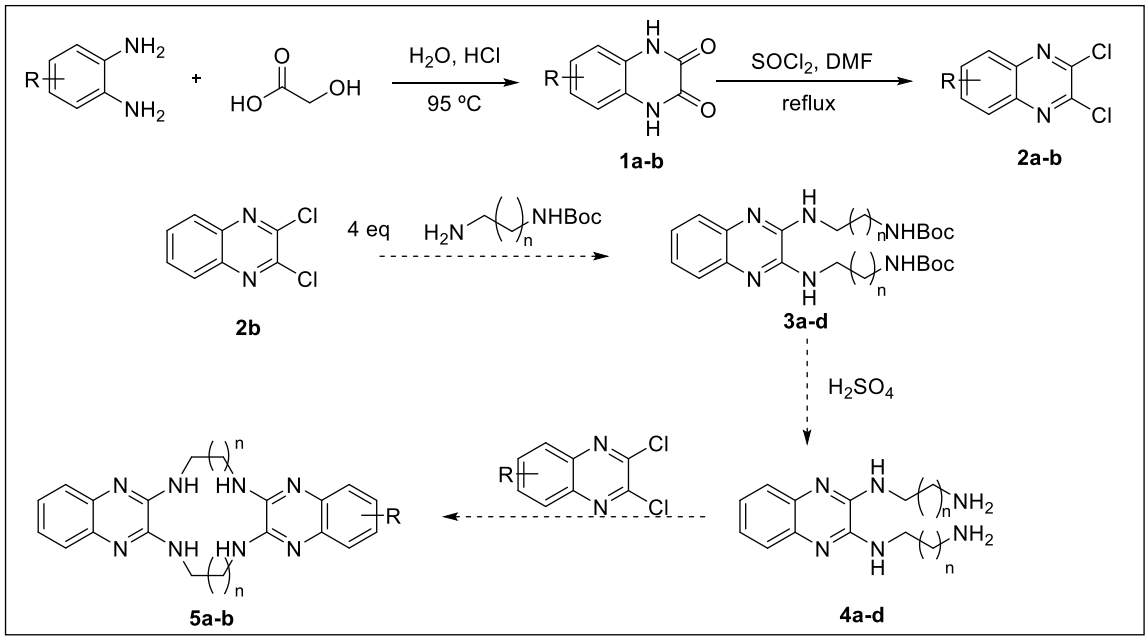


Figure 4: Proposed Scheme of Novel Peraza Crown Synthesis

Results and Discussion

Synthesis of Quinoxaline Subunit

The first portion of the reaction scheme involves synthesizing a chlorinated quinoxaline group that is reactive enough to later react with an amine. 6-nitro-1,4-dihydroquinoxaline-2,3-dione (**1a**) and 1,4-dihydroquinoxaline-2,3-dione (**1b**) were formed from 4-nitro-*o*-phenylenediamine and *o*-phenylenediamine respectively, both of which were purchased from commercial sources. These phenylenediamines were reacted with oxalic acid in the presence of acid to form the products. Both reactions showed high yields for both the nitro and hydrogen substituents.

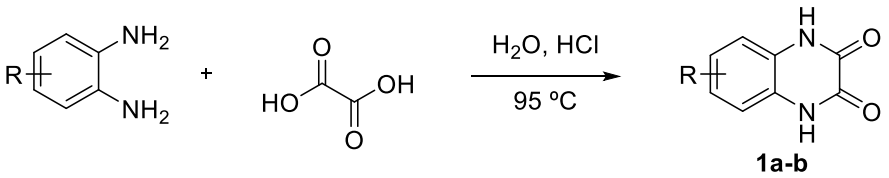


Figure 5: Synthesis of Quinoxaline Intermediate

Table 1: Yields of Quinoxaline

Compound	R-	Percent Yield
1a	NO_2	93%
1b	H	79%

After synthesizing the intermediates, the 2,3-dichloroquinoxaline was formed (**2a-b**). The quinoxaline intermediate **1a** or **1b** was combined with thionyl chloride in DMF and refluxed until the solids dissolved, and then the product was quickly crystalized on ice and filtered out. Both reactions produced high yields, from 85-96%.

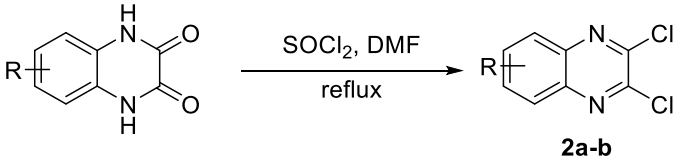


Figure 6: Synthesis of 2,3-dichloroquinoxaline

Table 2: Yields of 2,3-dichloroquinoxaline

Compound	R-	Percent Yield
2a	NO_2	85.6%
2b	H	96%

Synthesis of Protected Diamine

Before the next stage in the synthesis could be completed, a diamine first had to be protected so only one side of the molecule was reactive. This was done through the addition of a Boc protecting group, and was used to react diamines of 2, 3, or 4 carbon chain lengths to have a variety of protected diamines available. These diamines were later reacted with our synthesized intermediates to introduce further variations to our compounds. This reaction was consistently a high-yielding one, from 80-95% yield.

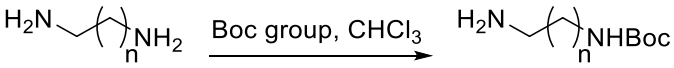


Figure 7: Synthesis of Protected Diamine

Table 3: Yields of Protected Diamines

(n) Number of Carbon Repeats	Percent Yield
0	77%
1	95.6%
2	85%

Synthesis of Intermediate 3

In this step of the synthesis, the protected diamine was combined with the synthesized 2,3-dichloroquinoxaline. This reaction was performed in a microwave reaction vessel for speed and efficiency, and resulted in the intermediate 3, shown below in **Figure 8**. Two conclusions were drawn from this data; firstly, that the reaction is low yielding when the nitro group is present on the quinoxaline subunit. Having the nitro group, an electron withdrawing group, present on the quinone structure before the amine addition could have caused instability in the reaction. From this information, **3a** was not used in further steps for this synthesis. It was also observed that the carbon chain length between the amine groups affected the yield of the reaction. Having two or three carbons in the chain resulted in enough of the product forming to be reasonable for this synthesis, but the four-carbon chain resulted in a yield low enough it was excluded from further reactions. While the exact explanation for this is unknown, it was thought that there may be some steric hinderance occurring with the longer chain as more rotation is possible between the carbon single-bonds.

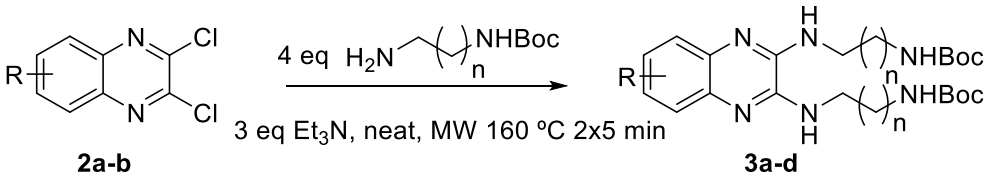


Figure 8: Synthesis of Key Intermediate 3

Table 4: Yields of Intermediate 3

Compound	R-	n	Percent Yield
3a	NO_2	1	19%
3b	H	0	50.2%
3c	H	1	75%
3d	H	2	20%

Deprotection of Intermediate 3

In the last step before synthesizing the final product, the Boc protecting group had to be removed from the compound to allow for a later reaction. This was done using concentrated sulfuric acid and resulted in a quantitative yield of compound **4**.

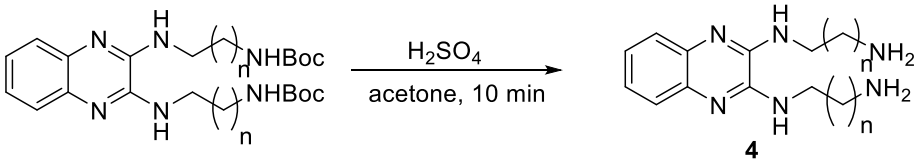
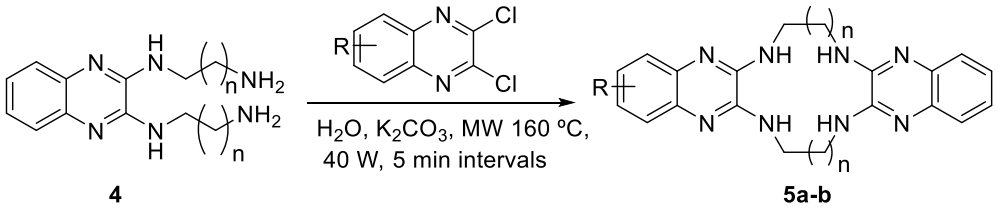


Figure 9: Deprotection of Amine on Intermediate 3

Synthesis of Product 5

The final step in this synthesis was to combine intermediate **4** with another molecule of the synthesized 2,3-dichloroquinoxaline (**2a-b**). This step allowed the formation of the peraza crown subunit in the center of the molecule, with either a two or three carbon bridge. This step also allows for asymmetry to be build into the molecule; reacting a substituted 2, 3-dichloroquinoxaline with an intermediate of a different substitution allows for specificity in the molecule created, and results in a larger variety of molecules that could be tested for transition metal ion affinity. Using the results from the synthesis of intermediate **3a**, it was decided that any nitro-substitutions should occur from the quinoxaline subunit rather than the variant of intermediate **4**, as the overall synthesis yield would be poor. The reaction of intermediate **4c** with a nitro-substituted quinoxaline (**2a**) resulted in a complex mixture where the product could not be isolated. A reaction to form product **5b** from intermediate **4b** and **2b** is still in progress, but previous steps shown are much more promising in terms of overall reaction yield and show that this compound, once created, would be a worthwhile candidate in testing for metal ion affinity.



4 5a-b

Figure 10: Synthesis of Peraza Crown Macrocycle

Table 5: Yields of Product 5

Compound	R-	n	Yield
5a	NO_2	1	Complex Mixture
5b	H	0	In Progress

Conclusion

Overall in this synthesis, it was found that compounds containing the nitro group were difficult to work with, resulting in low yields and complications in purifying. So far, the synthesis scheme shows much more favorable results using only hydrogen substitutions, from the initial reactants up to compound **4b**. The final step in this synthesis to create compound **5b** has not yet been completed but is looking to be more promising than compound **5a**. Further research is needed to continue the synthesis of analogs of this compound. Modifying the R groups and varying the lengths of the diamine carbon chain shows a difference in both the amount of product formed and the ease of purifying the compounds. With the production of different analogs of our foundational molecule, the most favorable substituent combinations can be found. Once these molecules have been created, testing can begin to determine the metal ion binding affinity of each compound. The efficiency of each molecule at successfully and selectively binding to transition metals will be observed to find a compound with the optimal combination of high synthesis yields, good purity, and binding properties that can be used as an effective contamination cleaning agent.

Experimental Methods

Microwave assisted reactions were performed in a single-mode cavity CEM Discovery Microwave Synthesizer, and reactions were purified in a Teledyne ISCO

CombiFlash® Rf+ flash chromatography system. Products were identified with Thin Layer Chromatography and NMR spectra taken with a 300 MHz Brucker spectrometer in $CDCl_3$ or DMSO-d6.

Synthesis of **1,4-dihydroquinoxaline-2,3-dione** *and* **6-nitro-1,4-dihydroquinoxaline-2,3-dione**

Oxalic acid (120 mmol) was added to 40 mL of water in a round bottom flask and was heated to 95 °C. 20 mL of concentrated hydrochloric acid was added to the flask, followed by 100 mmol of the amine (4-nitro-*o*-phenylenediamine for compound **1a** and *o*-phenylenediamine for compound **1b**). This solution was stirred for 5 minutes at a constant temperature (15 minutes for **1b**). After removing from the heat, ice was added to the solution to form a precipitate. This precipitate was filtered out, washing with water, and was dried under a high vacuum. This reaction formed 19.1168 g (92.28 mmol) of 6-nitro-1,4-dihydroquinoxalinne-2,3-dione (**1a**), giving a 92.28% yield, and a scaled-down reaction resulted in 8.3453 g (51.5 mmol) of 1,4-dihydroquinoxaline-2,3-dione (**1b**) at 79% yield.

Synthesis of **2,3-dichloroquinoxaline** *and* **2,3-dichloro-6-nitroquinoxaline**

For 2,3-dichloro-6-nitroquinoxaline (**2a**), 5.0969 (25 mmol) of 6-nitro-1,4-dihydroquinoxaline-2,3-dione was added to 12.5 mL (172 mmol) of thionyl chloride. 0.25 g of DMF acted as a catalyst for this reaction and was added and quickly placed under reflux to retain the gas formed. This solution was refluxed until the solid present dissolved, about 15 minutes. Ice was then added to the solution to cool it and form a precipitate, which was collected by filtration and washed with water. The product was placed under vacuum to dry and gave 5.2198 g (21.4 mmol) of 2,3-dichloro-6-nitroquinoxaline, an 85.6% yield. This same reaction was performed with 1,4-dihydroquinoxaline-2,3-dione at twice the scale of reactants to give a 96% yield.
2,3-dichloro-6-nitroquinoxaline spectrum:
^{1}H-NMR ($CDCl_3$) δ: 8.18 (d, J = 9 Hz, 1H), 8.45 (d, J = 9 Hz, 1H), 9.00 (s, 1H).

Synthesis of Protected Diamine

Both ethylenediamine (2 carbon chain) and 1,3-diaminopropane (3 carbon chain) were used separately in similar procedures to create mono-protected, reactive diamines. 250 mmol of the appropriate diamine was dissolved into 250 mL of chloroform in a round bottom flask while stirring. 120 mL of chloroform and 5.75 mL (25 mmol) of Boc anhydride were mixed in a mixing funnel. This solution was added dropwise into the round bottom flask with the diamine solution, and the solution was allowed to stir overnight. The product was washed with water three times, dried with sodium sulfate, and filtered. The solvent was removed to produce an oil at 95.6% for 1,3-diaminopropane and 76.8% for ethylenediamine.

*Synthesis of Compound **3***

Two synthesis pathways were found for this compound. In the first procedure, 10 mmol of the monoprotected amine were added to 2 mmol of the quinoxaline subunit in a 10 mL reaction vessel with a stir bar. These reagents were heated neat at 160 °C and 60 W for 10 minutes, and the progress of the reaction was monitored by TLC (1:1 hexanes:ethyl acetate) to show completion. Column chromatography was used to separate the product, identified by TLC and confirmed by NMR spectroscopy. The solvent was then removed and the product dried on high vacuum.

A second pathway was identified where 2 mmol of the monoprotected diamine was added to 1 mmol of the quinoxaline subunit in a 35 mL microwave vessel and with the presence of 3 mmol triethylamine. This vessel was heated at 160 °C at 60 W for 5 minutes while stirring. Another 2 mmol of diamine was added, and the heating was repeated with the same settings. After the reaction was completed, known through monitoring by TLC, the solvent was removed and the product was dried in a high vacuum. The structure was confirmed by ^{1}H NMR.

Di-tert-butyl (((6-nitroquinoxaline-2,3-diyl)bis(azanediyl))bis(propane-3,1-diyl))dicarbamate, formed by reacting the 3 carbon protected amine and 2,3-dichloro-6-nitroquinoxaline, was isolated in a 19% yield (**3a**).

^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 18H), 1.88 (t, J = 12 Hz, 7H), 3.28 (q, J = 18 Hz, 4H), 3.71 (t, J = 12 Hz, 4H), 5.34 (s, 2H), 6.36 (s, 1H), 6.62 (s, 1H), 7.57 (d, J = 9 Hz, 1H), 8.06 (q, J = 12 Hz, 1H), 8.45 (d, J = 3 Hz, 1H).

Di-tert-butyl ((quinoxaline-2,3-diylbis(azanediyl))bis(ethane-2,1-diyl))dicarbamate, formed by reacting a 2 carbon protected amine and 2,3-dichloroquinoxaline, was isolated in a 50.2% yield (**3b**).

Di-tert-butyl ((quinoxaline-2,3-diylbis(azanediyl))bis(propane-3,1-diyl))dicarbamate, formed by reacting a 3 carbon protected amine and 2,3-dichloroquinoxaline, was isolated in a 75% yield (**3c**).

^{1}H-NMR ($CDCl_3$) δ: 1.46 (d, J = 12 Hz, 18H), 1.83 (q, J = 18 Hz, 4H), 3.22 (q, J = 18 Hz, 4H), 3.67 (q, J = 18 Hz, 4H), 5.78 (s, 2H), 5.96 (s, 2H), 7.26 (quint, J = 12 Hz, 2H), 7.62 (q, J = 12 Hz, 2H).

Di-tert-butyl ((quinoxaline-2,3-diylbis(azanediyl))bis(butane-4,1-diyl))dicarbamate, formed by reacting a 4 carbon protected amine and 2,3-dichloroquinoxaline, was isolated in a 20% yield (**3d**).

*Deprotection of Compound **3** to make Compound **4***

The variant of compound 3 was dissolved in 10 mL of acetone with a large stir bar. Concentrated sulfuric acid was added dropwise to form a precipitate. This product was filtered and washed with acetone, and then was dried on a high vacuum. This reaction produced a quantitative yield and the product was confirmed with ^{1}H NMR spectroscopy.

(**4b**) ***N*^{1}, *N*$^{1'}$-(quinoxaline-2,3-diyl)bis(ethane-1,2-diamine)** was formed from compound **3b**.

(**4c**) ***N*^{1},*N*^{1}-(quinoxaline-2,3-diyl)bis(propane-1,3-diamine)** was formed from compound **3c**.

^{1}H-NMR ($CDCl_3$) δ: 2.04 (quint, J = 30 Hz, 5H), 2.99 (d, J = 6 Hz, 4H), 3.67 (t, J = 15 Hz, 4H), 7.42 (quint, J = 12 Hz, 2H), 7.72 (t, J = 6 Hz, 2H).

Synthesis of Product 5

For 2-nitro-6,7,8,9,10,17,18,19,20,21-decahydro-[1,4,8,11]tetraazacyclo tetradecino[2,3-b:9,10-b']diquinoxaline (**5a**), 0.6395 g (1 mmol) of **4c** was dissolved in 2 mL of water in a 10 mL microwave vessel. K_2CO_3 was added until the pH of the solution reached 12. In a separate container, 0.2458 g (1 mmol) of **2a** was suspended in 2 mL of

dioxane, and this was added to the main reaction vessel. The vessel was microwaved at 160 °C and 40 W for 5 minute intervals until the reaction was complete, using TLC to determine reaction progress. The solvent was removed from the product and it was dried on a high vacuum. The ^{1}H NMR spectra (taken in DMSO) showed a complex mixture, and the product could not be isolated.

The reaction of 6,7,8,9,16,17,18,19-octahydro-[1,4,7,10]tetraazacyclododecino [2,3-b:8,9-b']diquinoxaline (**5b**) has not yet been completed. The above conditions will be repeated, with **4b** and **2b** used as reagents in place of **4c** and **2a**.

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