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Junyi Liu April 08 2016

Synthetic Studies Towards the Total Synthesis of Myrtoidine

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

Synthetic Studies Towards the Total Synthesis of Myrtoidine

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The Malagasy alkaloids extracted from *Strychnos myrtoides* have shown potential antimalarial activity. A total synthesis of the Malagasy alkaloid malagashinine has recently been completed in our lab, and we hypothesized that we would be able to potentially access the analogous alkaloid myrtoidine via a modified synthetic route. We envisioned that we could divergently synthesize myrtoidine from a common synthetic intermediate, which requires the development of a synthetic method that provides access to a crucial 2-(5*H*)-furanone moiety. Initially, we wished to explore a strategy involving vinylic C-H halogenation at the 6-position in a 3,4-dihydro-2*H*-pyran model. Using $[RhCp^*(MeCN)_3](SbF_6)_2$ as a catalyst, various iodination, bromination, and chlorination conditions were explored using carboxylic acids or carboxamides as directing groups; however, no desired products could be efficiently isolated due to undesired background addition reaction of the halogenation reagents with our substrate. We have also explored a 6-lithiation of our 3,4-dihydro-2*H*-pyran-5-carboxylic acid model as a possible method for functionalization at this position. We deprotonated the 6-proton with kO*t*-Bu and trapped it with stannane, but were unable to proceed to obtain stable compounds. Due to lack of success of the model studies, we are working to build the core structure that is common in both malagashinine and myrtoidine, which will enable the incorporation of the moiety via Stille coupling.

Synthetic Studies Towards the Total Synthesis of Myrtoidine

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Table of Contents

Figures

Schemes

1. Background

Malaria, one of the most widespread infectious diseases nowadays, puts more than three billion people from over 90 countries at risk of infection. Although the death rate has decreased notably in the past decade thanks to increasing malaria control efforts, the disease takes lives of more than half a million people out of two million diagnosed cases annually, including over one thousand children in Africa per day. Artemisinin-based combination therapies (ACTs) and the chloroquine are commonly employed to prevent and treat malaria. However, malaria strains resistant to drugs have been identified in both Africa and Asia[1]. Faced with this problem, researchers have found that various natural products isolated from African plants show anti-malarial properties. For instance, akuammiline alkaloids have long been used by African locals for anti-pain and anti-malarial therapies[2]. The Malagasy people were found to combine chloroquine with a kind of tea derived from the local shrub *Strychnos myrtoides* as a remedy for malaria, the functional component of which is Malagashinine. Malagashanine is shown to potentiate chloroquine in resistant strains. Malagashinine belongs to a natural product family known as Malagasy alkaloids, in which many members have shown promising biological activity[2,3]. Natural products such as akuammiline alkaloids and Malagasy alkaloids are promising ethnobotanical compounds exhibiting anti-malarial, anti-pain, anti-cancer, anti-inflammatory, and antitussive quanlities. Because it is usually expensive to extract natural products from flora in large amount due to low purity, seasonal variation naturally, and large quantity of biomaterial required, the total

synthesis of anti-malarial alkaloids for phytopharmaceutical use as well as new drug development is encouraged[4].

A total synthesis of the Malagasy alkaloid malagashinine has recently been completed in our lab. In this study, various strategies towards the total synthesis of the analogous Malagasy alkaloid myrtoidine were developed and evaluated.

2. Model studies of the synthesis of the 2-(5*H*)-furanone moiety of myrtoidine

We hypothesize that we would be able to potentially access myrtoidine by a common synthetic intermediate with Malagashinine (Figure 1). Therefore, divergent synthesis from the common intermediate could significantly improve the efficiency and yield in the work.

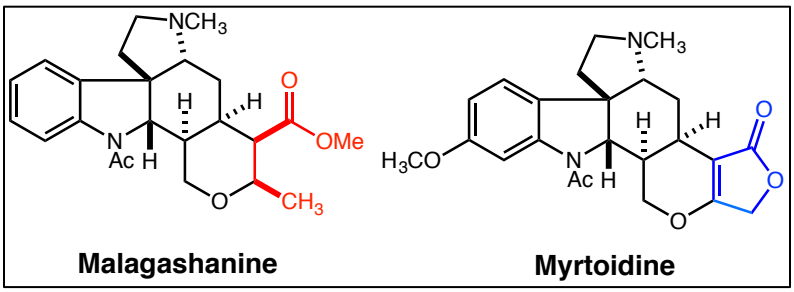
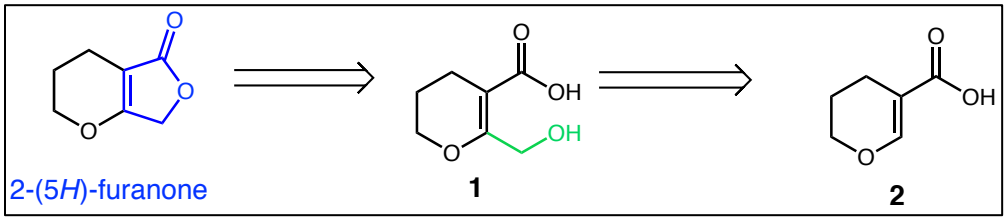


Figure 1 Structures of Malagasy alkaloids Malagashanine and myrtoidine.

In order to access myrtoidine, it is necessary to develop a synthetic method to access the crucial 2-(5*H*)-furanone moiety (Scheme 1).

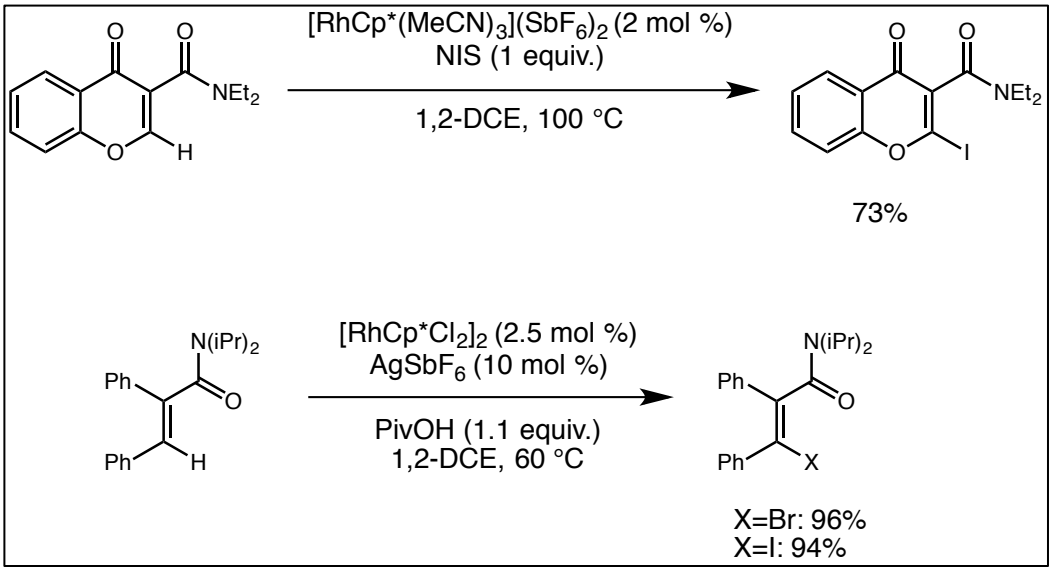


Scheme 1 Retrosynthetic analysis for the 2-(5*H*)-furanone moiety.

We envisioned that we could obtain the furanone moiety from the hydroxymethyl carboxylic acid **1** through lactonization by intramolecular transesterification. The carboxylic acid **2** can serve as a potential model system in early stage synthesis of myrtoidine. Our initial studies explored how to add the hydroxymethylene substituent to **2** in order to access **1**.

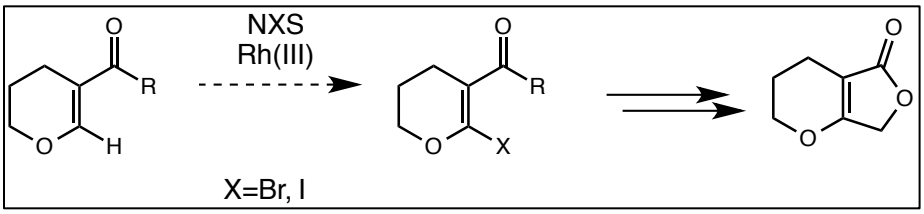
2.1 Rh(III)-catalyzed C-H halogenation strategies

Frank Glorius *et al.* managed to halogenate the β-position of α,β-unsaturated carboxamides with $[RhCp^*(MeCN)_3](SbF_6)_2$.[5a, 5b] (Scheme 2).



Scheme 2 C-H halogenation completed by the Glorius group.

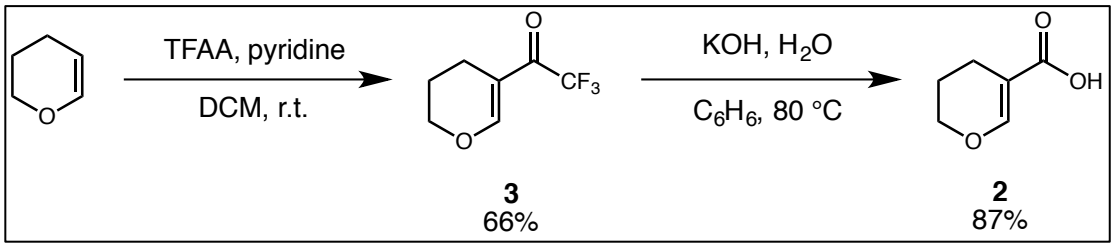
We hypothesized that this methodology could potentially functionalize the β-position of our model, such as 6-halogenation (Scheme 3).



Scheme 3 Model system for C-H halogenation.

i.Substrate synthesis

The substrate was synthesized from commercially available 3,4-Dihydro-2*H*-pyran (Scheme 4). We obtained carboxylic acid **2** via trifluoromethyl ketone **3** in high yield.



Scheme 4 Synthesis of substrate carboxylic acid 2.

We introduced various amines to serve as the directing group to halogenate the β-position, so that the halogen substituent can serve as a functional handle for further reactions. We synthesized pentafluoro carboxamides (**4a**), diisopropyl carboxamides (**4b**) and diethyl carboxamides (**4c**) from **2** as potential model substrates for these reactions (Figure 2). Pentafluoro carboxamides **4a** was synthesized because it is highly UV active, and has been used by Jin-Quan Yu et al. in Rhodium (III) catalyzed olefination of benzamides[6a]. Carboxamides **4b**, **4c** are the exactly same directing groups used by Glorius et al. Carboxylic acid itself has been used as a directing group in Palladium (II)-catalyzed C-H activation by Yu et al[6b], and therefore served as a potential substrate.

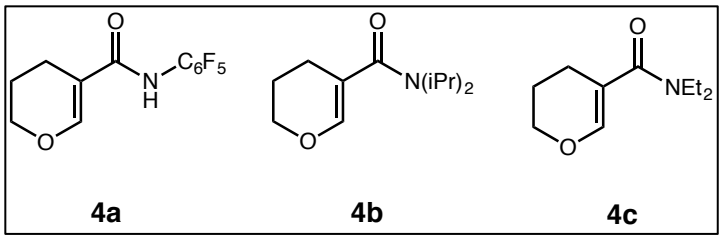
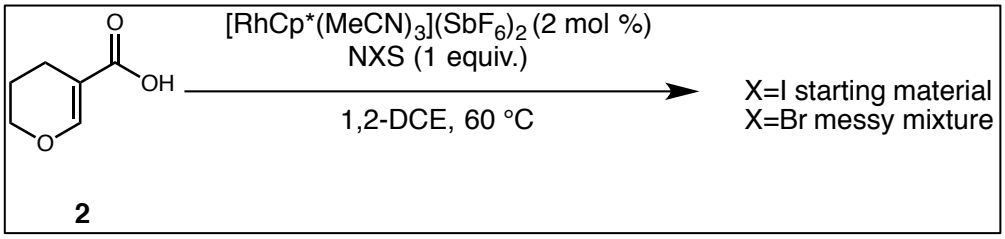


Figure 2 Synthesized carboxamide substrates.

ii. Regioselective halogenation

We first selected carboxylic acid **2** as a testing substrate because it does not need protection or deprotection and we might be able to complete the synthesis in fewer steps. Carboxylic acid **2** gave unconverted starting material with N-Iodosuccinimide (NIS) and a messy mixture with N-Bromosuccinimide (NBS) (Scheme 5). We tried to raise the reaction temperature to 100 °C, and all the reactions gave messy mixtures. Thus, all halogenation reactions were kept at 60 °C.

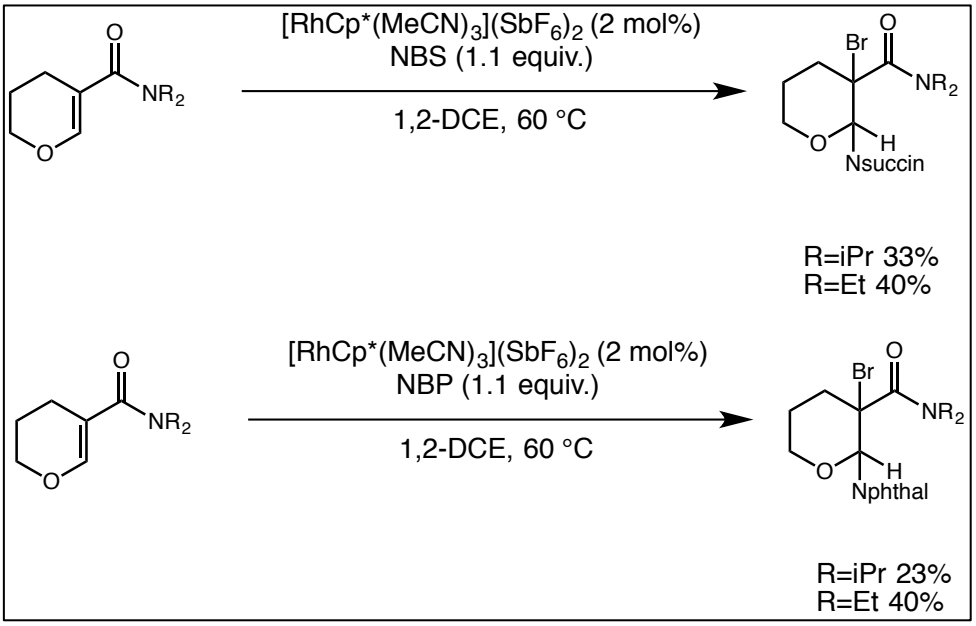


Scheme 5 Attempts of iodination and bromination of 2.

NIS did not give stable, isolatable product with **4a**, **4b**, and **4c.** Addition of 1.1 equivalents of pivalic acid in the reaction with **4a** did not change the result. In the reaction mixture with **4b** and **4c**, trace amount of compounds whose masses equaled those of expected iodination products were identified by mass spectrometry ($[M+H]^+$ calculated 338.0611, found 338.0610 for **4b**, $[M+H]^+$ calculated 310.0298, found 310.0296 for **4c**). It was unclear whether the iodination products were actually produced, but it was possible that the sp_2C-I bonds in these

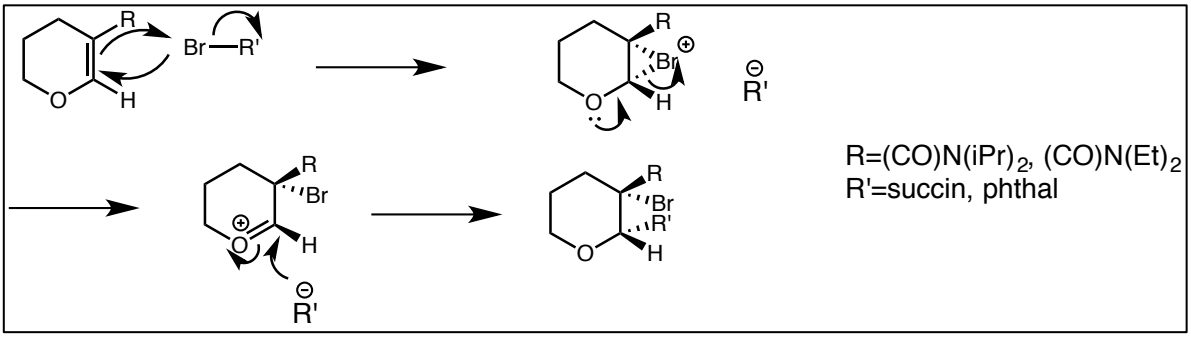
compounds were too weak to last long and to form stable products under the high energy involved in mass spectrometry.

Hoping that sp^2C-Br bond is stronger than sp^2C-I bond due to shorter bond length, we reacted **4b**, **4c** with NBS and N-bromophthalimide (NBP) (Scheme 6).



Scheme 6 Addition reactions.

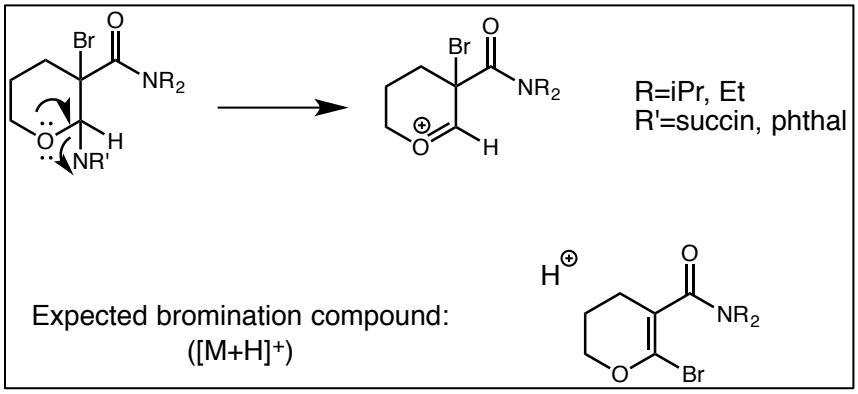
Stable products were isolated from preparatory TLC. From the spectroscopic studies, the nucleophilic N-succin of NBS and N-phthal of N-bromophthalimide added at the β-position, and bromide was picked by alkene. The mechanism is proposed in Scheme 7.



Scheme 7 Proposed mechanisms for the addition reaction.

As shown in Scheme 8, the N-succin and N-phthal parts can be eliminated in mass spectrometry, giving rise to the cation-containing structures with the same masses of the $[M+H]^+$ masses of the expected bromination products, which were also identified in the mass spectra ($[M+H]^+$ calculated 290.0750, found 290.0747 for **4b** and $[M+H]^+$ calculated 262.0437, found 262.0434 for **4c**), although a clear NMR was not available for these structures. It was unclear whether or not they were only produced in mass spectrometry or could result from decomposition. The control reaction of **4c** and NBS in absence of Rh(III) catalyst also yielded 46% N-succin addition product, suggesting that these reagents underwent background reactions with our substrates. We conclude that the addition reaction (Scheme 6, 7) dominated in our experimental conditions designed for bromination. In the mass spectrometry, the nucleophilic groups, N-succin and N-phthal, may be eliminated from the addition products under the high-energy electron beam. The remaining parts (Scheme 8) had the same masses as the expected $[M+H]^+$ masses for the bromination products and could be misleading. It can be assumed that, in the previous iodination reaction, N-succin also added to **4b**, **4c** when NIS was applied, and was eliminated from the compound in mass spectrometry. The trace amount of

compounds with the same masses of the expected iodination compound actually resulted from this addition and elimination.



Scheme 8 Proposed mechanisms for the elimination.

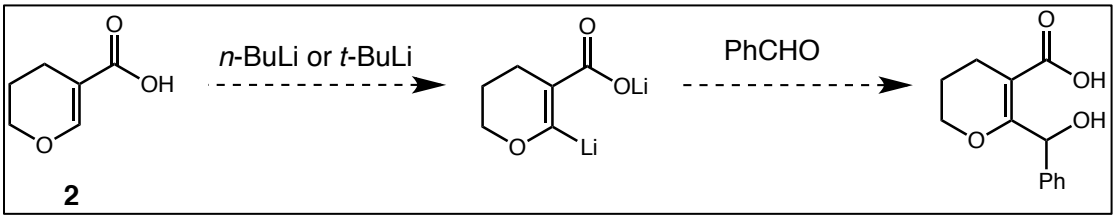
Due to lack of success of halogenation with reagents containing nucleophilic groups (NIS, NBS, NBP), we reacted **4c** with 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one. The mass spectrometry indicated the presence of a product whose mass equals the expected chlorinated product ($[M+H]^+$ calculated 218.0942, found 218.0943), but the product was messy on NMR, and we were unable to determine whether the product resulted from chlorination or other background reactions.

2.2 Lithiation and stannylation-lithiation strategies

i. Lithiation

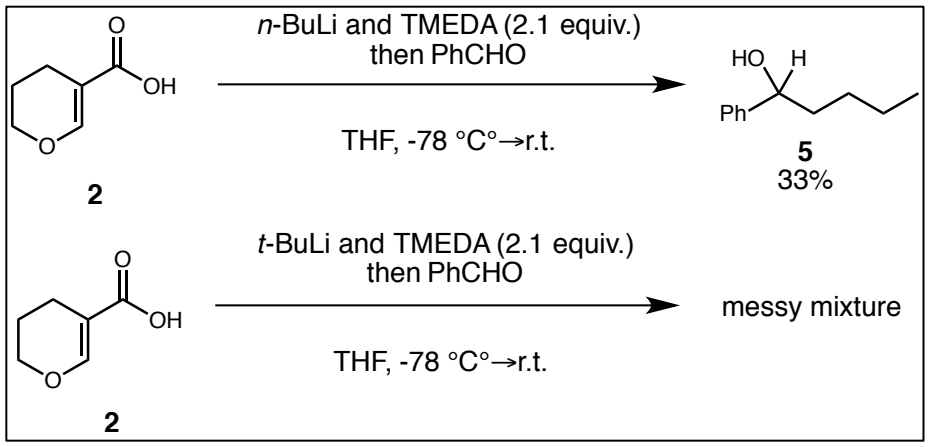
Because of lack of success with the previous C-H halogenation methodology, we turned to a more traditional way of lithiation. We proposed to directly deprotonate the β-proton with *n*-butyllithium or *t*-butyllithium. The lithiated aldehyde could then take us directly to allylic alcohol (Scheme 9), and the right choice of aldehyde could provide us with access to hydroxymethyl carboxylic acid **1**. Timothy Jamison *et al.* lithiated enol ethers and then reacted the product with

aldehydes[7]. We hoped to replicate these reactions on enol ether model **2** to obtain **1** (Scheme 9).



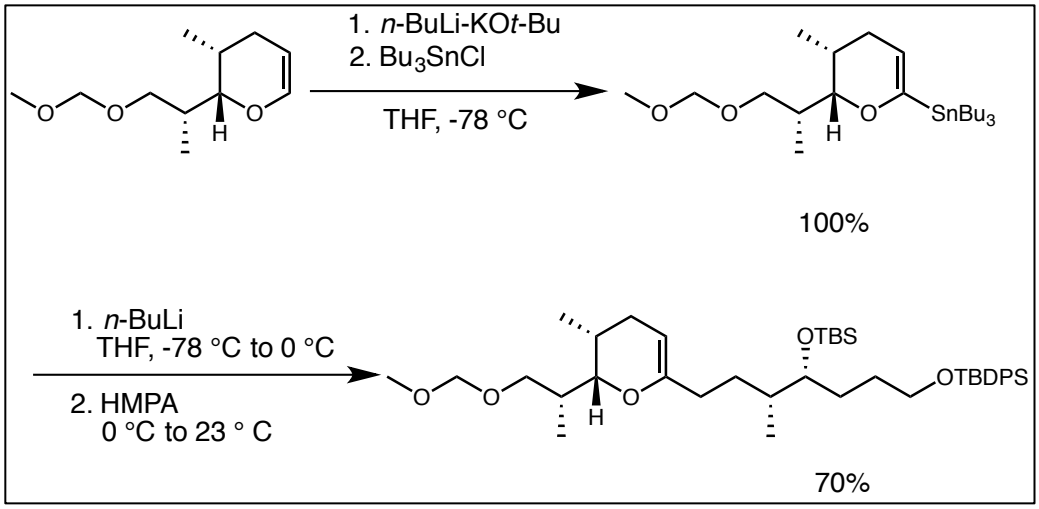
Scheme 9 Model system for lithiation.

Carboxylic acid **2** was subjected to lithiation with *n*-butyllithium and then reacted with benzaldehyde. No desired product was observed; instead, we found the nucleophilic addition of *n*-butyl to benzaldehyde in benzylic alcohol product **5** (Scheme 10). Control reactions showed that the addition of TMEDA of the same mols as *n*-butyllithium did not change the result, suggesting the lack of deprotonation did not result from the substrates clustering together. We changed the lithiation reagent to bulkier *t*-butyllithium and hoped that the bulky *t*-butyl group was less likely to nucleophilically add to benzaldehyde. A messy mixture formed from the reaction (Scheme 10). In either case, the β-proton of the substrate was intact. A better deprotonation reagent was required.



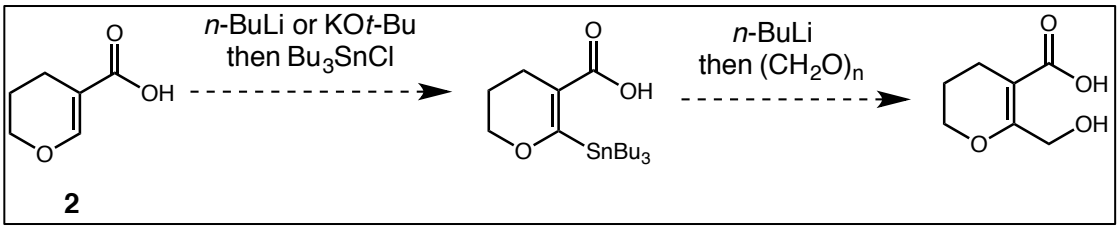
Scheme 10 Attempts to deprotonate the β-proton of 2.

ii. Stannylation-lithiation



Scheme 11 Stannylation-lithiation completed by the Johnston group.

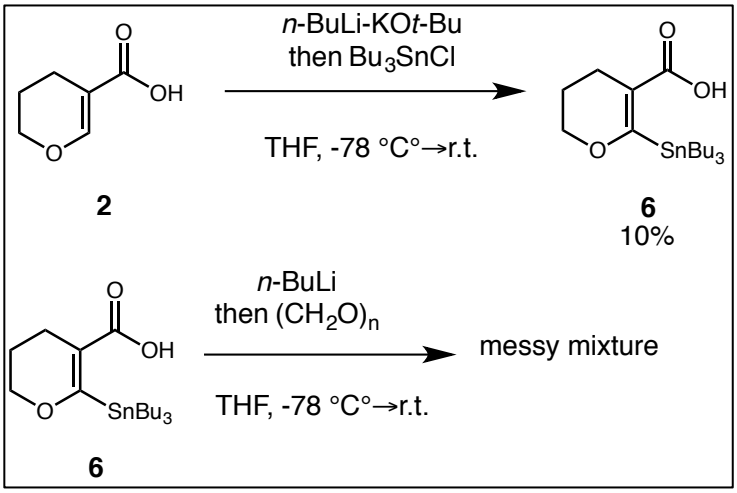
Due to lack of evidence of β-deprotonation, we decided to explore stronger bases. B. H. Johnston *et al.* deprotonated the vinylic proton of an enol ether using *n*-BuLi-KO*t*-Bu and trapped the carbanion with $SnBu_3Cl$.[8] (Scheme 11). Follwing this strategy, we proposed our experimental design in Scheme 12.



Scheme 12 Model system for stannylation-lithiation.

Carboxylic acid **2** was reacted with *n*-BuLi-KO*t*-Bu and trapped by $SnBu_3Cl$. Stannylated carboxylic acid **6** was isolated in low yields. This product was then reacted with *n*-butyllithium and paraformaldehyde. No clean product was isolated from the reaction mixture (Scheme 13). Since these reactions required strongly

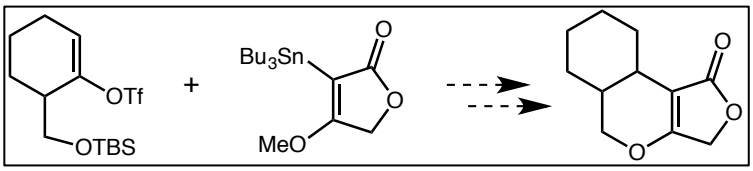
basic conditions, and since the yield of **6** is low, it is doubtful they would be found much utility in the more complex substrates used in total synthesis. Thus we turned to more traditional ways of total synthesis.



Scheme 13 Stannylation-lithiation of 2.

3. Synthesis of the core structure of myrtoidine in preparation for Stille coupling

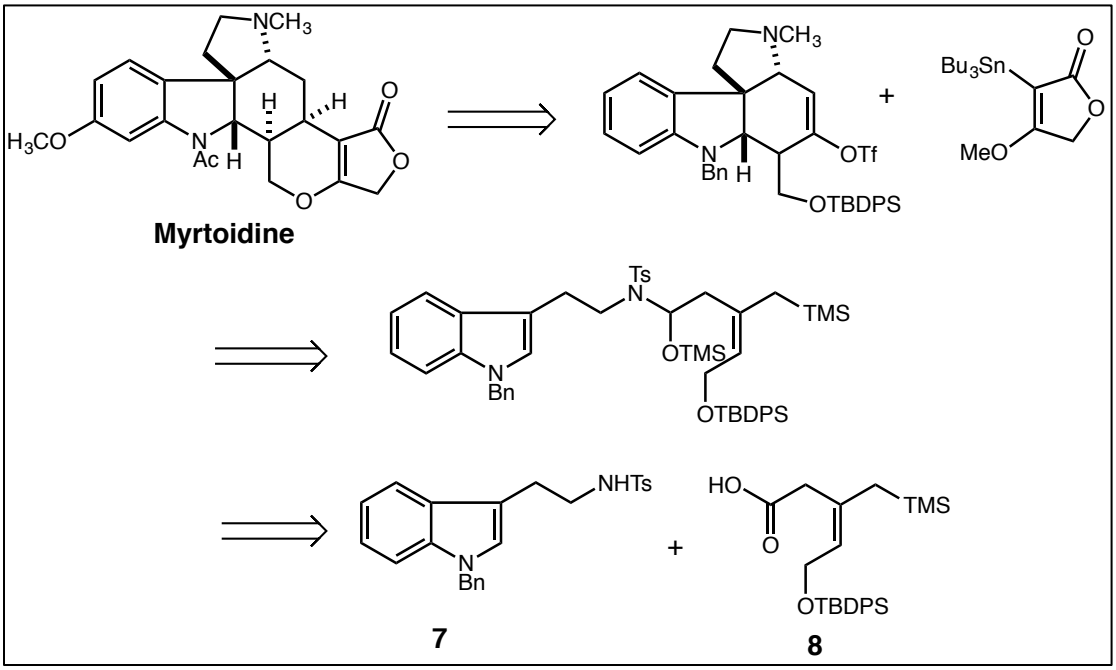
We envision that the 2-(5*H*)-furanone moiety could be incorporated onto the core structure of myrtoidine via Stille coupling as shown in Scheme 14.



Scheme 14 Stille coupling.

Previous graduate students in the Blakey lab have worked out a retrosynthetic analysis for Malagashanine[9], which can be modified for myrtoidine

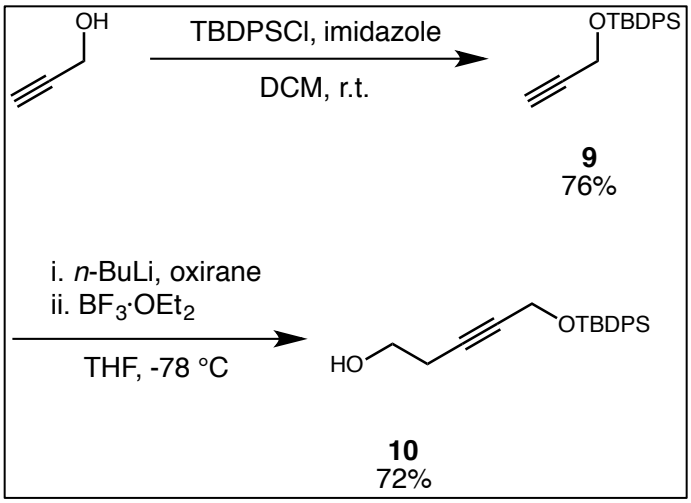
(Scheme 15) to obtain the core structure from simple pieces. From the scheme, we would like to obtain the two simple pieces, protected amine **7** and carboxylic acid **8**, in order to synthesize the core structure for later use.



Scheme 15 Retrosynthetic analysis for myrtoidine.

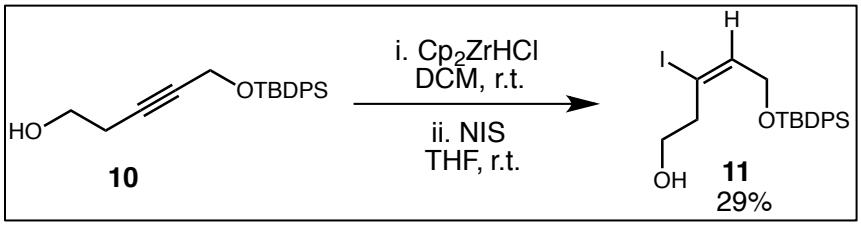
*i. Synthesis of carboxylic acid **8***

Commercially available propargyl alcohol was protected with *tert*-butyldiphenylsilyl (TBDPS) group to obtain propargyl *t*-butyldiphenylsilyl **9**. Propargyl *t*-butyldiphenylsilyl **9** was then deprotonated by *n*-butyllithium and added to oxirane to produce homopropargylic alcohol **10** (Scheme 16).



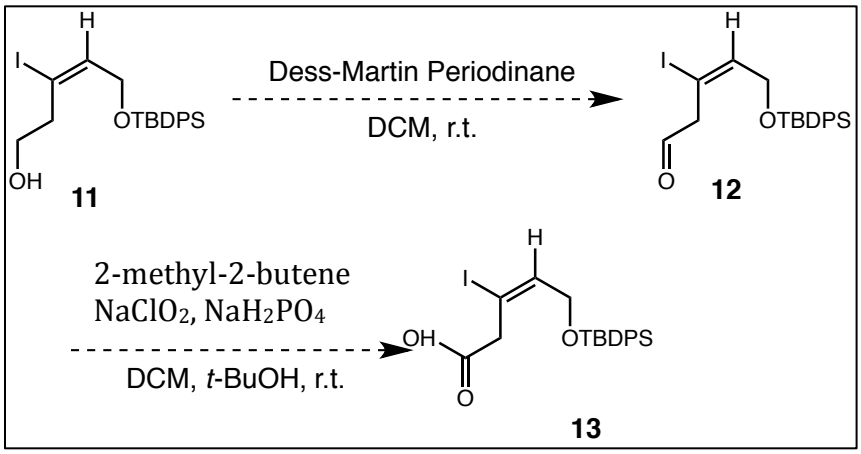
Scheme 16 Synthesis of homopropargylic alcohol 10.

Homopropargylic alcohol **10** underwent hydrozirconation using Schwartz's reagent, Cp_2ZrHCl, followed by NIS. Vinyl iodide **11** was isolated in relatively low yield (Scheme 17).



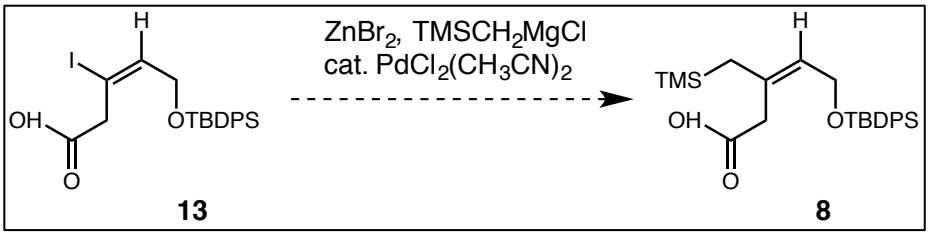
Scheme 17 Iodination of homopropargylic alcohol 10.

Right now, we are working to process **11**. In a two-step reaction, **11** will be oxidized to aldehyde **12** by Dess–Martin periodinane. Aldehyde **12** is unstable and should be rightly subjected to Pinnick oxidation to obtain carboxylic acid **13** (Scheme 18).



Scheme 18 Proposed synthesis of carboxylic acid 13.

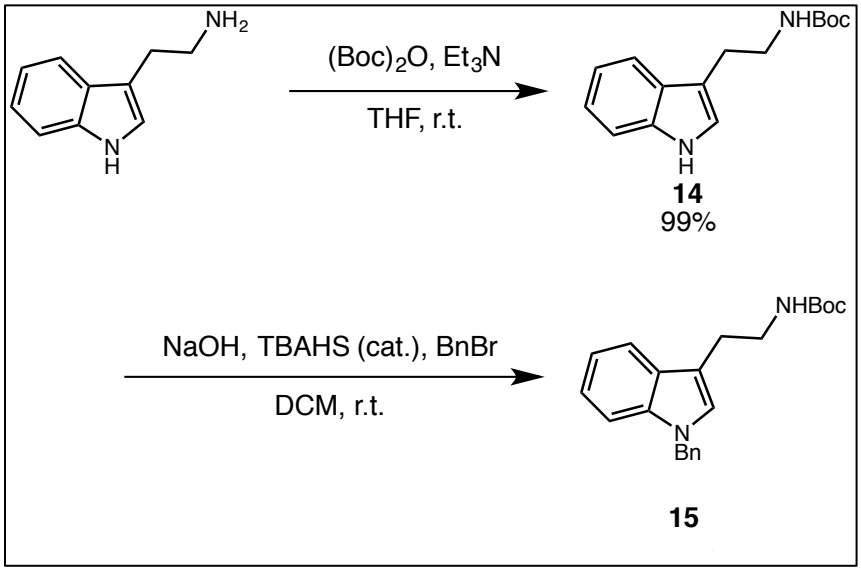
Lastly, we want to replace the iodine with the (trimethyl)silylmethyl group ($TMSCH_2$) to obtain carboxylic acid **8**, which is then ready to undergo coupling with protected amine **7**. The Grignard reagent $TMSCH_2MgCl$ will be stirred with $ZnBr_2$ and undergo transmetallation, and the reaction mixture will be mixed with **13** for the subsequent Negishi coupling to give **8** (Scheme 19).



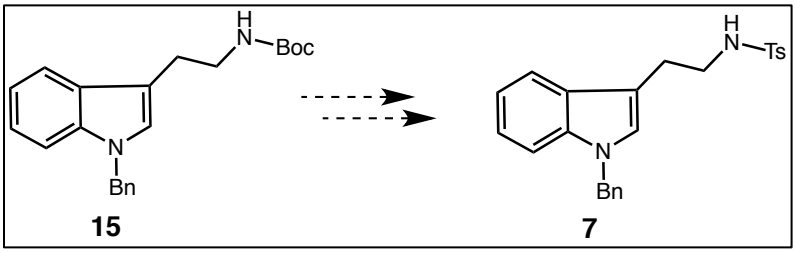
Scheme 19 Proposed synthesis of carboxylic acid 8.

*ii. Synthesis of protected amine **7***

Commercially available tryptamine was firstly protected by Boc group at the primary amine (Scheme 20) to give **14**. Protected tryptamine **14** was subsequently benzylated to give **15** (Scheme 21).

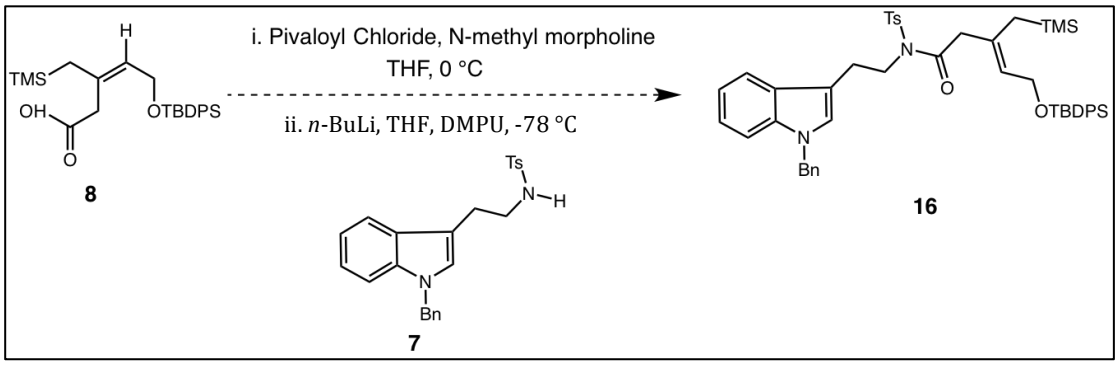


Scheme 20 Protection of tryptamine.



Scheme 21 Synthesis of protected amine 7.

We will replace the Boc protection group with tosyl group in the benzylated tryptamine **15** (Scheme 21) to obtain protected amine **7**, which will then be coupled with carboxylic acid **8** as shown in Scheme 22.



Scheme 22 Coupling of carboxylic acid 8 and protected amine 7.

4. Conclusion

This project provided important insight into the synthetic study of anti-malarial Malagasy alkaloid myrtoidine. Based on the previous total synthesis work on analogous Malagashanine, we were able to propose and evaluate several synthetic approaches to myrtoidine. Although we were unable to move forward the model system to develop new and reliable synthetic methods to incorporate the 2-(*5H*)-furanone moiety directly on the common synthetic intermediate of both myrtoidine and Malagashanine due to either incompatibility of substrates and reagents or the harsh condition required, we were able to propose the addition-elimination mechanisms in bromination and suggest future directions to apply less nucleophilic halogenation reagents. Our lab would continue working on the construction of the core structure of myrtoidine in preparation to incorporate the 2-(*5H*)-furanone moiety using Stille coupling.

5. Experimental methods

5.1 Synthesis of 5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran (**3**)

Commercially available 3,4-dihydro-2*H*-pyran (60 mmol, 5.0 g) was dissolved in 40 ml dichloromethane and pyridine (122.6 mmol, 9.7 g) was added. The solution was cooled to 0 °C over an ice bath, and trifluoroacetic anhydride (120.4 mmol, 25.3 g) was added dropwise. The mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous sodium carbonate and extracted with dichloromethane. The organic extract was washed with water, dried over sodium sulfate, and concentrated in vacuo to give an orange liquid. The liquid was purified by vaccum distillation to afford trifluoromethyl ketone **3** as a light yellow liquid (7.1 g, 66%). R_f=0.75 (7:3 hexane: ethyl acetate); ^{1}H NMR, ^{19}F NMR were confirmed by literature[10].

5.2 Synthesis of 3,4-dihydro-2*H*-pyran-5-carboxylic acid (**2**)

Trifluoromethyl ketone **3** (19.8 mmol, 3.57 g) was dissolved in 296 mL benzene. Powdered potassium hydroxide (33.7 mmol, 1.89 g) in 1.8 mL of water was added. The solution was refluxed at 88 °C with vigorous stirring overnight. The reaction mixture was extracted with water, and the aqueous layer was acidified with 6M hydrochloric acid to pH=1. The acidified solution was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and condensed in vacuo. Carboxylic acid **2** was afforded as a white solid (2.21 g, 87%), which was used without further purification. R_f=0.05 (pure ethyl acetate); ^{1}H NMR was confirmed by literature[11].

5.3 Synthesis of *N*-(perfluorophenyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (**4a**)

Carboxylic acid **2** (2.12 mmol, 271.0 mg) was dissolved in 11.1 mL dichloromethane. EDCI·HCl (2.12 mmol, 405.5 mg), 4-dimethylaminopyridine (DMAP) (4.24 mmol, 518.9 mg), and pentafluoro aniline (1.92 mmol, 352.0 mg) were added to the solution, and stirred at room temperature for 24 hours. The reaction was quenched by adding 10% citric acid aqueous solution and stirring for 15 minutes. The liquid layers were separated. The organic extract was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and condensed in vacuo to give a light yellow liquid. The liquid was subjected to silica column chromatography (7:3 hexane: ethyl acetate) to give a colorless liquid, which was condensed in vacuo to afford pentafluoro carboxamides **4a** as a white solid (34%, 186.4 mg). R_f=0.26; ^{1}H NMR (400 MHz, $CDCl_3$): 7.68 (s, 1H), 4.11 (t, J= 6.0 Hz, 2H), 2.33 (t, J =6.2 Hz, 2H), 1.97 – 1.89 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): 178.99, 162.08, 118.17, 115.27, 112.38, 111.25, 92.90, 77.00, 69.36, 67.83, 20.31, 17.92.

5.4 Synthesis of *N*,*N*-diisopropyl-3,4-dihydro-2*H*-pyran-5-carboxamide (**4b**)

Carboxylic acid **2** (2.95 mmol, 378.3 mg) and catalytic amount of DMF were dissolved in 6 mL dichloromethane. The solution was cooled to 0 °C over an ice bath, and oxalyl chloride (2.90 mmol, 368.1 mg) was added dropwise to the solution. The reaction was warmed to room temperature and stirred for 4 hours. The solution was cooled to 0 °C over an ice bath again. Diisopropylamine (7.25 mmol, 1.02 mL) was added to the solution. The reaction was warmed to room temperature and stirred for 20 hours. The solution was extracted with saturated aqueous sodium bicarbonate and washed with brine. Then the organic extract was acidified with 1M

hydrochloric acid to pH=1, and washed with brine again. The extract was dried over sodium sulfate and condensed in vacuo. The product was subjected to silica column chromatography (3:1 hexane: ethyl acetate) to give diisopropyl carboxamides **4b** as a colorless sticky liquid (405.2 mg, 65%). R_f=0.45; $[M+H]^+$ calculated: 212.1645, found: 212.1644; ^{1}H NMR (400 MHz, $CDCl_3$): 7.67 (s, 1H), 4.11 (t, J=4.0 Hz, 1H), 4.00 (t, J=5.3 Hz, 1H), 3.84 (broad, 2H), 2.32 (td, J = 6.4, 1.3 Hz, 1H), 2.24 (td, J = 6.4, 1.6 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.29 (d, J = 6.8 Hz, 12H).

5.5 Synthesis of *N*,*N*-diethyl-3,4-dihydro-2*H*-pyran-5-carboxamide (**4c**)

Carboxylic acid **2** (2.88 mmol, 368.6 mg) and catalytic amount of DMF were dissolved in 6 mL dichloromethane. The solution was cooled to 0 °C over an ice bath, and oxalyl chloride (2.82 mmol, 357.8 mg) was added dropwise to the solution. The reaction was warmed to room temperature and stirred for 4 hours. The solution was cooled to 0 °C over an ice bath again. Diethylamine (7.05 mmol, 0.73 mL) was added to the resulting solution. The reaction was warmed to room temperature and stirred for 20 hours. The solution was extracted with saturated aqueous sodium bicarbonate and washed with brine. Then the organic extract was acidified with 1M hydrochloric acid to pH=1, and washed with brine again. The extract was dried over sodium sulfate and condensed in vacuo. The product was subjected to silica column chromatography (1:1 hexane: ethyl acetate) to give diethyl carboxamides **4c** as a colorless sticky liquid (290.3 mg, 55%). R_f=0.35; $[M+H]^+$ calculated: 184. 1332, found: 184.1332.^{1}H NMR (400 MHz, $CDCl_3$): 6.67 (s, 1H), 4.00 (t, J=6.0 Hz, 2H), 3.39

(q, J = 7.1 Hz, 4H), 2.25 (td, J = 6.3, 1.6 Hz, 2H), 1.95 – 1.86 (m, 2H), 1.13 (t, J = 7.1 Hz, 6H).

5.6 General iodination procedure

Substrate (0.3 mmol, **2**, **4a**, **4b**, **4c**) was put into a pressure tube. Catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ (0.006 mmol, 5.0 mg) and NIS (0.33 mmol, 74.3 mg) were added, and dissolved in 1.5 mL of 1,2-dichloroethane. The pressure tube was sealed under nitrogen, and the reaction was stirred at 60 °C for 16 hours in the dark. The solvent was condensed in vacuo. Preparatory TLC was attempted, but ^1H NMR appeared messy and did not indicate any stable major product.

5.7 General bromination procedure

Substrate (0.3 mmol, **2**, **4a**, **4b**, **4c**) was put into a pressure tube. Catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ (0.006 mmol, 5.0 mg) along with NBS (0.33 mmol, 58.7 mg) or NBP (0.33 mmol, 82.0 mg) was added. Reagents were dissolved in 1.5 mL of 1,2-dichloroethane. The pressure tube was sealed under nitrogen, and the reaction was stirred at 60 °C for 16 hours in the dark. The solvent was condensed in vacuo. If certain reaction showed clear, stable major product on 2D TLC, it was subjected to preparatory TLC. Figure 3 shows the structures of the isolated products.

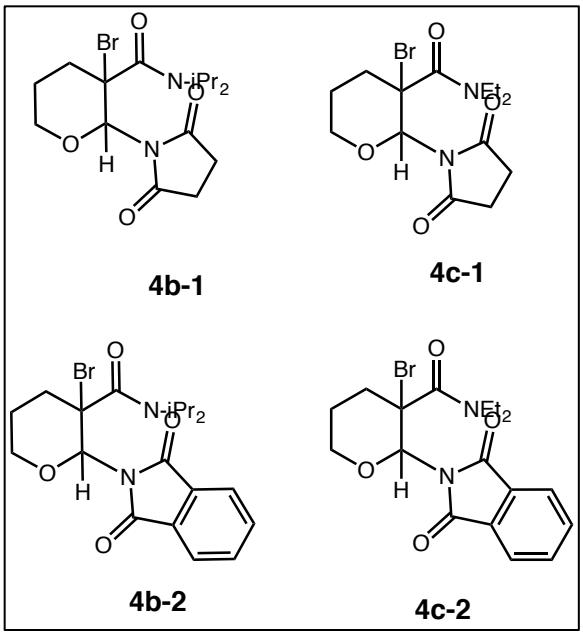


Figure 3 Structures of the addition products.

- *5.7.1*: **4b** with NBS.

Preparatory TLC (3:1 hexane: ethyl acetate) gave white powder **4b-1** (33%, 45.1 mg). R_f=0.21; $[M+H]^+$calculated: 389.1070, found: 389.1080; ^{1}H NMR (600 MHz, $CDCl_3$): 6.11 (s, 1H), 4.74 – 4.66 (m, 1H), 4.16 (ddd, J = 11.8, 8.4, 4.0 Hz, 1H), 3.80 (dt, J = 10.8, 5.1 Hz, 2H), 3.44 – 3.32 (m, 2H), 3.04 (m, 2H), 2.50 (m, 2H), 1.99 – 1.93 (m, 1H), 1.91 – 1.84 (m, 1H), 1.53 – 1.36 (m, 6H), 1.33 – 1.19 (m, 6H),

- *5.7.2* **4b** with NBP

Preparatory TLC (1:1 hexane: ethyl acetate) gave grey sticky solid **4b-2** (23%, 30.2 mg). R_f=0.37; $[M+H]^+$calculated: 437.1070, found: 437.1066; ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (ddd, J = 21.3, 5.4, 3.0 Hz, 2H), 7.73 (ddd, J = 9.8, 5.5, 3.1 Hz, 2H), 6.39 (s, 1H), 4.25 – 4.05 (m, 2H), 3.40 (h, J = 6.8 Hz, 1H), 3.34 – 3.19 (m, 1H), 2.63 (dt, J = 13.6, 4.8 Hz, 1H), 2.54 – 2.45 (m, 1H), 1.96 (m, 1H), 1.77 – 1.66 (m, 1H), 1.34 – 1.15 (m, 12H).

- *5.7.3* **4c** with NBS

Preparatory TLC (1:1 hexane: ethyl acetate) gave white solid **4c-1** (40%, 50.6 mg). R_f=0.48; $[M+H]^+$calculated: 361.0757, found: 361.0789; ^1H NMR (600 MHz, $CDCl_3$): 6.02 (s, 1H), 4.15 – 4.03 (m, 2H), 3.72 (m, 2H), 3.43 (broad, 4H), 2.92 (m, 2H), 2.46 (ddd, J = 13.8, 7.2, 4.2 Hz, 2H), 2.00 – 1.92 (m, 1H), 1.80 (m, 1H), 1.26 – 1.15 (m, 2H), 1.18 – 1.09 (m, 4H).

- *5.7.4* **4c** with NBP

Preparatory TLC (1:1 hexane: ethyl acetate) gave grey solid **4c-2** (40%, 49.1 mg). Rf = 0.41; $[M+H]^+$ calculated: 409.0757, found: 409.0775. ^1H NMR (600 MHz, $CDCl_3$): 7.93 – 7.82 (m, 2H), 7.80 – 7.70 (m, 2H), 6.36 – 6.30 (s, 1H), 4.23 (ddd, J = 12.2, 8.3, 4.3 Hz, 0H), 3.82 (ddd, J = 13.6, 9.6, 4.9 Hz, 1H), 3.77 – 3.42 (broad, 4H), 3.15 (ddd, J = 13.9, 9.1, 4.9 Hz, 1H), 2.69 (dt, J = 13.7, 5.2 Hz, 1H), 2.06 – 1.93 (m, 2H), 1.32 – 1.17 (m, 6H).

5.8 Chlorination of **4c**

Commercially available 2,3,4,5,6,6-Hexachloro-2,4-cyclohexadien-1-one (0.3 mmol, 101.4 mg), **4c** (0.3 mmol, 54.7 mg), and $[RhCp^*(MeCN)_3](SbF_6)_2$ (0.006 mmol, 5.0 mg) were charged into a pressure tube and dissolved in 1.5 mL of 1,2-dichloroethane. The pressure tube was sealed under nitrogen, and the reaction was stirred at 60 °C for 16 hours in the dark. The solvnt was condensed in vacuo, and the major spot in preparatory TLC (3:1 hexane: ethyl acetate) yields a white solid, the ^1H NMR of which appeared messy. Rf = 0.22. Expected chlorination product is shown in Figure 4. $[M+H]^+$ calculated: 218.0942. $[M+H]^+$ found for the white solid: 218.0943.

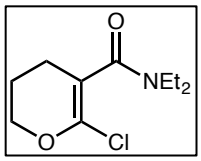


Figure 4 Expected chlorination product.

5.9 Lithiation of **2** with *n*-butyllithium

Carboxylic acid **2** (1.09 mmol, 139.8 mg) was dissolved in 1 mL tetrahydrofuran. The solution was cooled to -78 °C over a dry ice/acetone bath, and *n*-butyllithium (2.4 mmol, 153.7 mg, measured as 2.5 M in hexane solution) was added dropwise. The reaction was stirred at -78 °C for 1 hour, and then warmed to 0 °C over an ice bath and stirred for 2 hours. The reaction was cooled back to -78 °C, and a prepared solution of benzaldehyde (2.4 mmol, 254.7 mg) in 0.5 mL tetrahydrofuran was added slowly to the reaction. The reaction was warmed to room temperature and stirred for 24 hours. The reaction mixture was quenched by adding 1N hydrochloric acid dropwise and stirred for 15 minutes until the solution was acidified to pH=1. The reaction mixture was diluted with diethyl ether and liquid layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and condensed in vacuo to give a yellow liquid. The liquid was subjected to preparatory TLC (17:3 hexane: ethyl acetate) to give unexpected product benzylic alcohol **5** as a colorless liquid (33%, 58.5 mg). R_f=0.67; ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 – 8.01 (m, 2H), 7.60 – 7.50 (m, 1H), 7.49 – 7.37 (m, 2H), 4.33 (t, J = 6.6 Hz, 2H), 1.83 – 1.68 (m, 2H), 1.57 – 1.40 (m, 4H), 0.98 (t, J = 7.4 Hz, 3H).

5.10 Lithiation of **2** with *t*-butyllithium

Carboxylic acid **2** (0.90 mmol, 115.0 mg) was dissolved in 0.34 mL tetrahydrofuran. The solution was cooled to -78 °C over a dry ice/acetone bath, and *t*-butyllithium (1.89 mmol, 121.1 mg, measured as 1.7 M in pentane solution) was added dropwise. The reaction was stirred at -78 °C for 3 hours, and a prepared solution of benzaldehyde (0.99 mmol, 105.1 mg) in 0.1 mL tetrahydrofuran was added slowly. The reaction was warmed to room temperature and stirred for 24 hours. The reaction mixture was quenched by adding 1N hydrochloric acid dropwise and stirred for 15 minutes, until the solution was acidified to pH=1. The reaction mixture was diluted with diethyl ether and the liquid layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and condensed in vacuo to give a yellow liquid. Preparatory TLC was attempted but failed to deliver a stable compound in ^{1}H NMR.

5.11 Stannylation-Lithiation of **2**

Potassium *tert*-butoxide (3.42 mmol, 383.2 mg) was dissolved in 2.73 mL tetrahydrofuran at -78 °C. *n*-butyllithium (3.76 mmol, 240.7 mg, measured as 2.5 M in hexane solution) was added drop-wise. The mixture was stirred for 10 minutes. A solution of carboxylic acid **2** (0.85 mmol, 109.4 mg) in 0.61 mL tetrahydrofuran was added to the mixture. The reaction was stirred for 1 hour at -78 °C. Tributyltin chloride (2.56 mmol, 884.0 mg) was added to the reaction. The reaction was warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated aqueous ammonium chloride and diluted with diethyl

ether. The liquid layers were separated, and the organic extract was washed with brine, dried over sodium sulfate, and condensed in vacuo to give a white sticky solid. This crude product was subjected to preparatory TLC (3:1 hexane: ethyl acetate) to give *β*-stanylated carboxylic acid **6** as a white solid (10%, 34.3 mg). R_f=0.30; $[M-H]^-$ calculated: 417.1457, found: 417.1467; ^{1}H NMR (300 MHz, $CDCl_3$): 3.84 – 3.67 (m, 1H), 3.66 – 3.54 (m, 1H), 2.27 (t, J = 6.3 Hz, 1H), 1.93 – 1.72 (m, 2H), 1.73 – 1.53 (m, 6H), 1.57 – 1.08 (m, 12H), 1.05 – 0.65 (m, 9H).

Freshly synthesized *β*-stanylated carboxylic acid **6** (0.082 mmol, 34.3 mg) was dissolved in 0.03 mL tetrahydrofuran. The solution was cooled to -78 °C over a dry ice/acetone bath, and *n*-butyllithium (0.18 mmol, 11.5 mg, measured as 2.5 M in hexane solution) was added drop-wise. The reaction mixture was warmed to 0 °C over an ice bath and stirred for 1 hour. Paraformaldehyde (0.4 mmol, 12.0 mg, measured from the monomer) was added to the reaction, and the reaction was warmed to room temperature and stirred for 1 hour. The reaction was quenched with 10 equivalents of glacial acetic acid (0.10 mL). The reaction mixture was diluted with diethyl ether, and liquid layers were separated. The organic layer was washed with brine, dried over sodium sulfate, and condensed in vacuo to give a colorless sticky liquid. Preparatory TLC was attempted, but ^{1}H NMR appeared messy and did not indicate any stable major product.

5.12 Synthesis of propargyl *t*-butyldiphenylsilyl **9**

Commercially available propargyl alcohol (32.0 mmol, 1.8 g) was dissolved in 10 mL dichloromethane. *Tert*-butyl(chloro)diphenylsilane (TBDPS·Cl) (35.2 mmol, 39.7 g)

and imidazole (35.2 mmol, 2.4 g) were dissolved in 30 mL dichloromethane. The solutions were mixed and stirred for 5 hours at room temperature. The reaction was diluted with diethyl ether and extracted with water. The organic extract was washed with brine, dried over sodium sulfate, and condensed in vacuo to give a yellow solid. This crude product was subjected to silica column chromatography (95:5 hexane: ethyl acetate) to give propargyl *t*-butyldiphenylsilyl **9** as a white solid (76%, 7.2 g). R_f=0.34. The ^{1}H NMR matches the literature[9].

5.13 Synthesis of homopropargylic alcohol **10**

Propargyl *t*-butyldiphenylsilyl **9** (24.5 mmol, 7.2 g) was dissolved in 161 mL tetrahydrofuran and cooled to -78 °C over a dry ice/acetone bath. *n*-Butyllithium (31.8 mmol, 2.0 g, from freshly titrated 2.0 M in hexane solution) was added dropwise over 15 minutes, and the mixture was stirred for 1 hour. Boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) (31.8 mmol, 4.5 g, freshly distilled over calcium hydride) was added over 5 minutes and stirred for 15 minutes. Oxirane (29.4 mmol, 1.3 g) was dissolved in 1.0 mL tetrahydrofuran at -78 °C, and added to the reaction mixture via cannula. The reaction was stirred for 2 hours, and quenched with saturated aqueous ammonium chloride. The liquid layers were separated, the organic layer was kept, and the aqueous layer was extracted with diethyl ether. The combined organic extract was washed with brine, dried over sodium sulfate, and condensed in vacuo to give a grey sticky solid. This crude product was subjected to silica column chromatography (7:3 hexane: ethyl acetate) to afford homopropargylic alcohol **10** as a colorless liquid (73%, 6.0 g). R_f=0.32. The ^{1}H NMR

matches the literature[9].

5.14 Iodination of homopropargylic alcohol **10**

Schwartz's reagent Cp_2ZrHCl (53.2 mmol, 13.73 g, measured in the glove box) was dissolved in 89.2 mL dichloromethane at 0 °C over an ice bath. Homopropargylic alcohol **10** (17.7 mmol, 6.01 g) was dissolved in 89.2 mL dichloromethane at -78 °C over a dry ice/acetone bath, and transferred into the Cp_2ZrHCl solution via cannula. The mixture was stirred for 3 hours. NIS (25.9 mmol, 5.90 g) was dissolved in 89.2 mL tetrahydrofuran over an ice bath, and added to the reaction mixture. The mixture was stirred for 30 minutes in the dark. The reaction was quenched with a 1:1 aqueous mixture of saturated sodium bicarbonate and saturated sodium sulfite and stirred for 15 minutes. The mixture was filtrated through a celite pad. The filter cake was washed with diethyl ether. The organic layer was kept, and the aqueous layer was extracted with diethyl ether. The combined organic extracts was washed with brine, dried over sodium sulfate, and condensed in vacuo. The crude product was subjected to silica column chromatography (7:3 hexane: ethyl acetate) to give vinyl iodide**11** as a yellow liquid (29%, 2.40 g). R_f = 0.64. The ^1H NMR matches the literature[9].

5.15 Boc protection of tryptamine

Tryptamine (19.97 mmol, 3.2 g), di-tert-butyl dicarbonate ($(Boc)_2O$) (21.97 mmol, 4.8 g), and triethylamine (39.9 mmol, 4.0 g) were dissolved in 32 mL tetrahydrofuran. The solution was stirred at room temperature for 4 hours. The

solvent was condensed in vacuo to give a sticky yellow liquid. This crude mixture was subjected to silica column chromatography (7:3 hexane: ethyl acetate) to give Boc-protected tryptamine **14** as a white sticky liquid (99%, 5.1 g). R_f = 0.47. The ^1H NMR matches the literature[9].

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