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MODEL STUDIES FOR THE TOTAL SYNTHESIS OF 11-DEMETHOXYMYRTOIDINE AND MYRTOIDINE

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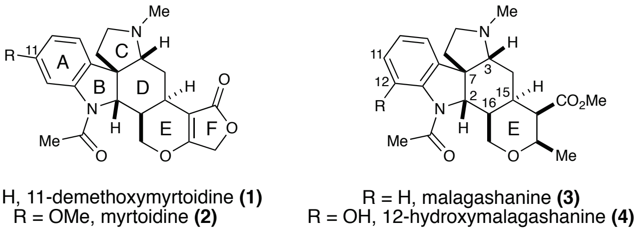
We dedicate this manuscript to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – The malagasy alkaloids, isolated in the 1990s from Madagascan shrub *Strychnos myrtoides,* are a family of strychnos alkaloids whose members have been reported to potentiate chloroquine activity against resistant strains of *Plasmodium falciparum* malaria. 11-Demethoxymyrtoidine, myrtoidine, and malagashanine were identified as the major components of the shrub used by local populations to treat malaria. Herein we report our studies on model systems to construct the EF dihydropyran lactone moiety present in 11-demethoxymyrtoidine and myrtoidine, and initial studies toward the application of these strategies to the total synthesis of these alkaloids.

INTRODUCTION

The malagasy alkaloids, a sub class of the strychnos alkaloids, were discovered and isolated in the early 1990s as part of a study to identify the major components in the stem bark of the Madagascan shrub *Strychnos myrtoides*.[1-4] The Malagasy populations used tea from this shrub, along with chloroquine, to treat malaria. The studies suggested that chloroquine activity against resistant strains of malaria, like



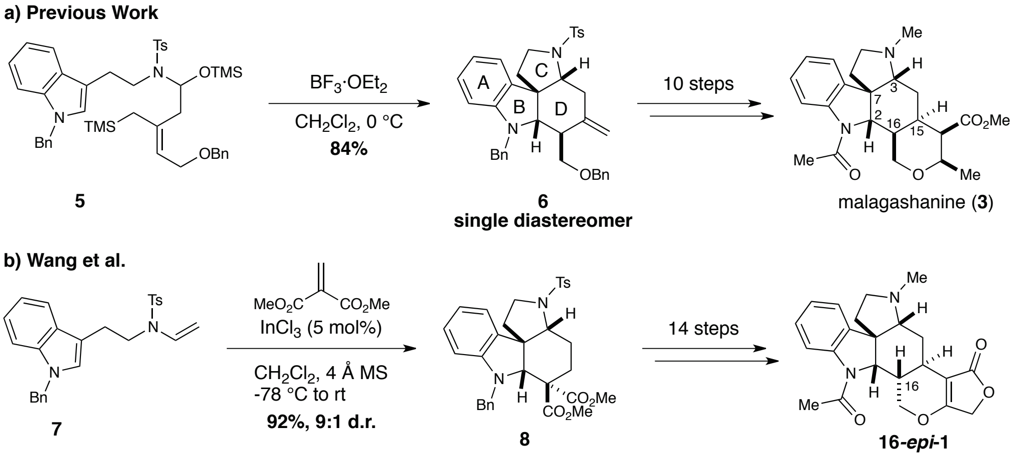
R = H, 11-demethoxymyrtoidine **(1)**
R = OMe, myrtoidine **(2)**

R = H, malagashanine **(3)**
R = OH, 12-hydroxymalagashanine **(4)**

Figure 1. Malagasy alkaloids

Plasmodium falciparum, could be enhanced by the active components in the shrub,[1] namely, 11-demethoxymyrtoidine[2] (**1**, Figure 1), myrtoidine[2,3] (**2**, Figure 1), malagashanine[4] (**3**, Figure 1), and 12-hydroxymalagashanine[2] (**4**, Figure 1).

From a structural standpoint, these natural products attracted our attention due to the synthetic challenge that they presented. In contrast to the broader family of strychnos alkaloids, the malagasy alkaloids possess an intriguing *trans* fusion between the C and D rings, owing to the inverted C3 stereochemical configuration. To address this challenge, in 2009 our group developed a powerful iminium ion cascade annulation to quickly and diastereoselectively access the ABCD core of the Malagasy alkaloids[5] (Scheme 1a), and subsequently applied this strategy to the total synthesis of malagashanine[6] (**3**). Recently, Wang and coworkers reported a formal [2+2+2] cyclization to assemble the Malagasy core **8** as a 9:1 mixture of diastereomers, which they were able to advance to the C16 epimer of 11-demethoxymyrtoidine[7] (**16-*epi*-1**, Scheme 1b). Thus far, however, our total synthesis of malagashanine (**3**) is the only published synthesis of a member of this family of indole alkaloids.



Scheme 1. Iminium ion cascades to access the Malagasy core

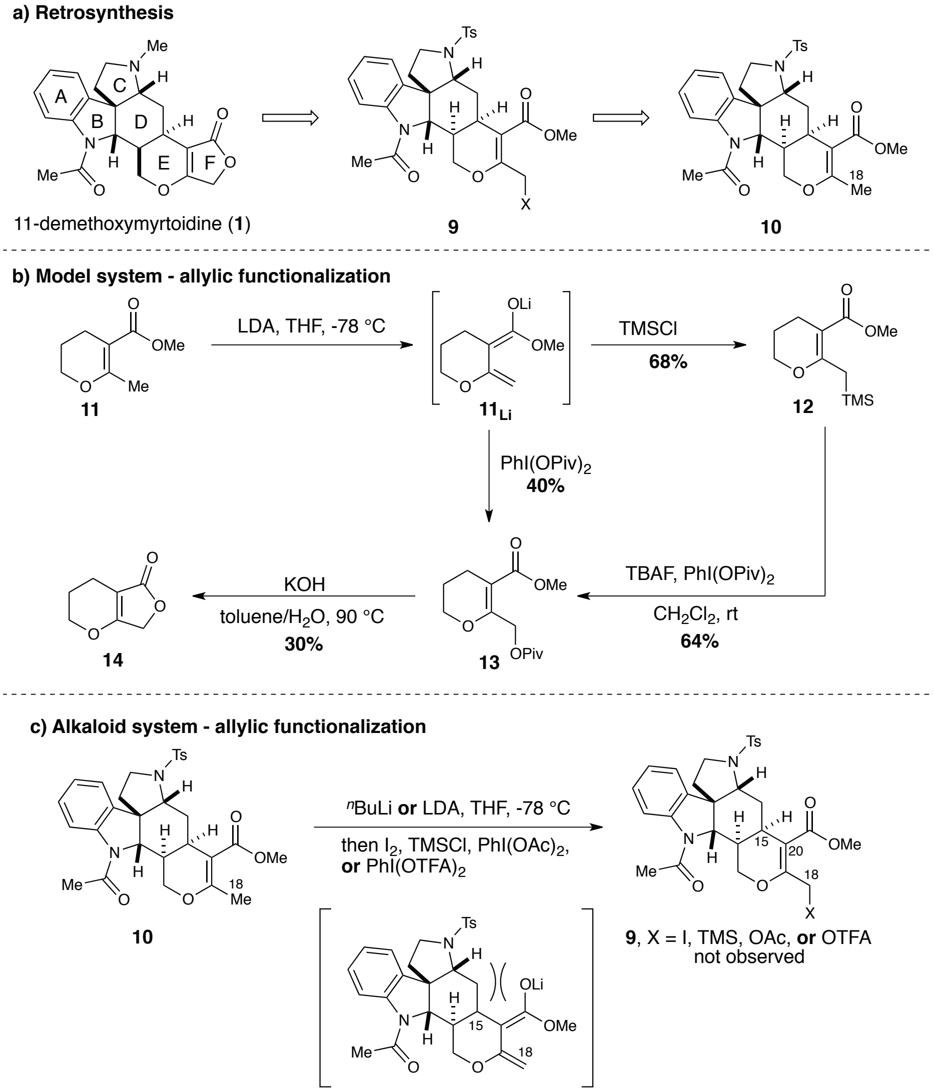
Efforts are currently ongoing in our lab to complete the total synthesis of 11-demethoxymyrtoidine (**1**) and myrtoidine (**2**). Our strategy utilizes the iminium ion cascade that our group had previously developed, as it diastereoselectively sets four of the five stereocenters present in the alkaloid at C3, C2, C7, and C16. Following the cascade annulation reaction, installation of the EF cyclic vinylogous carbonate system would complete the total synthesis. Herein we report our studies on various model systems to construct the dihydropyran lactone moiety of 11-demethoxymyrtoidine (**1**) and myrtoidine (**2**).

RESULTS AND DISCUSSION

First generation approach: Late-stage allylic functionalization

We previously reported the synthesis of methyl ester **10** (Scheme 2a) as an advanced intermediate in the total synthesis of malagashanine[6] (**3**). As our first generation approach, we envisioned that **10** could serve as an ideal divergence point to complete the synthesis of 11-demethoxymyrtoidine (**1**). The key step in this strategy would be the late-stage allylic functionalization of the C18 methyl group in **10**.

To test the feasibility of this strategy, dihydropyran methyl ester **11** was synthesized in 1 step from methyl acetoacetate and 1-bromo-3-chloropropane as a model substrate. Inspired by the two-step oxidation of the methyl group in 2-methylpyridine demonstrated by Andrews and coworkers,[8] model dihydropyran **11** was treated with LDA and the extended lithium enolate was trapped with TMSCl (Scheme 2b). Treatment of the resulting silane **12** with TBAF in the presence of $PhI(OPiv)_2$ afforded diester 13 in 64% yield. Model substrate **11** could also be directly converted to **13** by treatment of the intermediate lithium enolate with a hypervalent iodine oxidant (40% yield). Saponification of diester **13** with KOH at 90 °C provided dihydropyran lactone **14** in 30% yield, thus closing the F ring of the model system.

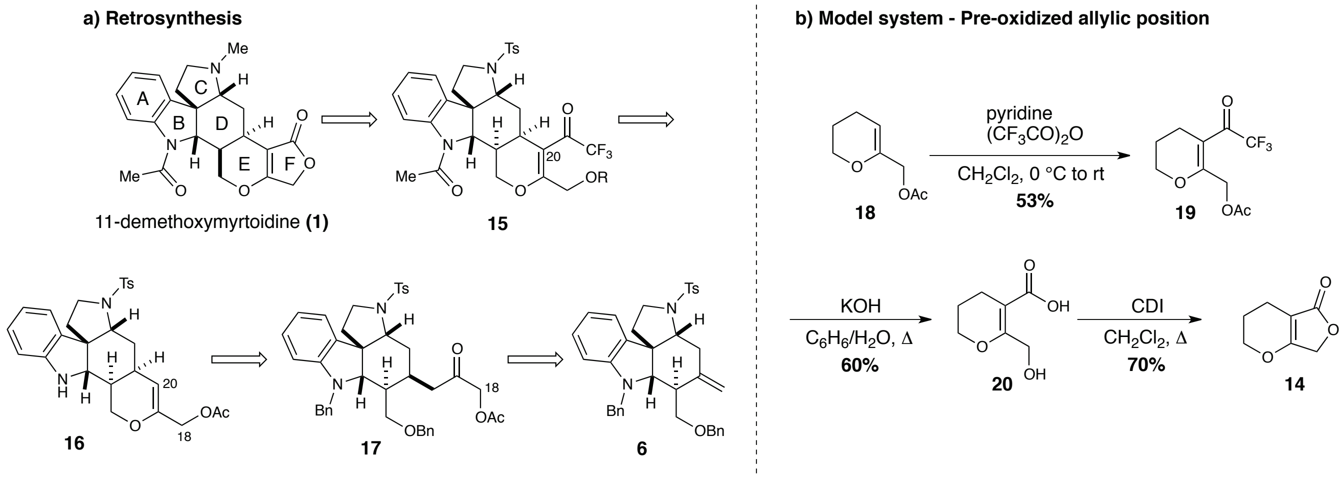


Scheme 2. First generation strategy for the synthesis of **1**

Unfortunately, treatment of late-stage methyl ester **10** with a strong lithium base (Scheme 2c), followed by quenching with various electrophiles (I_2, TMSCl, PhI(OAc)$_2$, or PhI(OTFA)$_2$) did not provide the C18 functionalized products, instead resulting in quantitative recovery of unreacted starting material in all cases. Quenching with D_2O after treatment with a strong base showed no deuterium incorporation at C18, indicating that the lithium enolate was not formed. We hypothesize that the substitution on C15 could result in a steric clash with the intended lithium enolate. Thus, while the reaction was unsucessful on methyl ester **10**, it proceeded smoothly on model methyl ester **11**, which possesses no C15 substitution. Attempts to use carboxylic acid directed functionalization, pioneered by Yu[9-12] and utilized by Martin[13] in the synthesis of benzolactones, were similarly unsuccesful, resulting in C20 decarboxylation.

Second generation approach: Pre-oxidized allylic C18

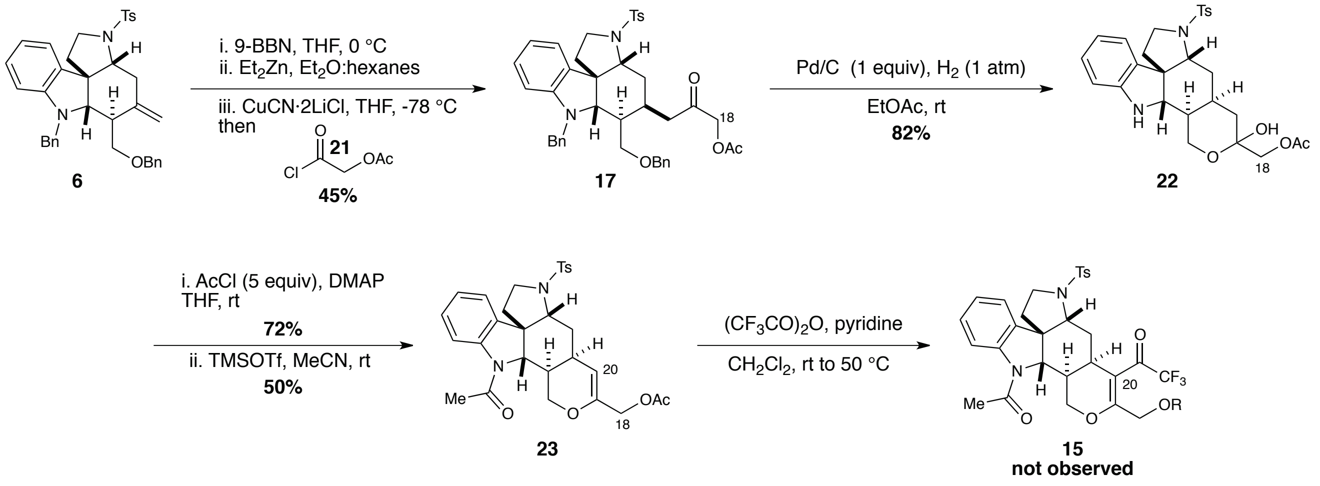
Having been unable to directly functionalize the C18 methyl group, we decided to intercept the route to malagashanine[6] (**3**) at an earlier stage and install a pre-oxidized C18 methylene group. In this revised strategy (Scheme 3a), β-acetoxyketone **17** could be synthesized from known tetracyclic core **6**, using a hydroacylation strategy similar to the one employed in the synthesis of malagashanine (**3**). This adaptation of Knochel's methodology[14,15] was identified as an ideal step to introduce the oxygen atom required for the furanone moiety.



Scheme 3. Second generation strategy for the synthesis of **1**

As before, we chose to establish a model system to validate our new strategy (Scheme 3b). Acetoxymethyl dihydropyran **18** was synthesized in two steps from dihydropyran and served as a suitable model substrate.[16,17] Treatment of **18** with $(CF_3CO)_2O$ delivered the trifluoroacetate **19** in 53% yield. **19** could further be treated with KOH at elevated temperatures to provide carboxylic acid **20** in 60% yield, which, upon treatment with 1,1'-carbonyldiimidazole (CDI) delivered dihydropyran lactone **14** in 70% yield, thus closing the lactone ring of the model system.

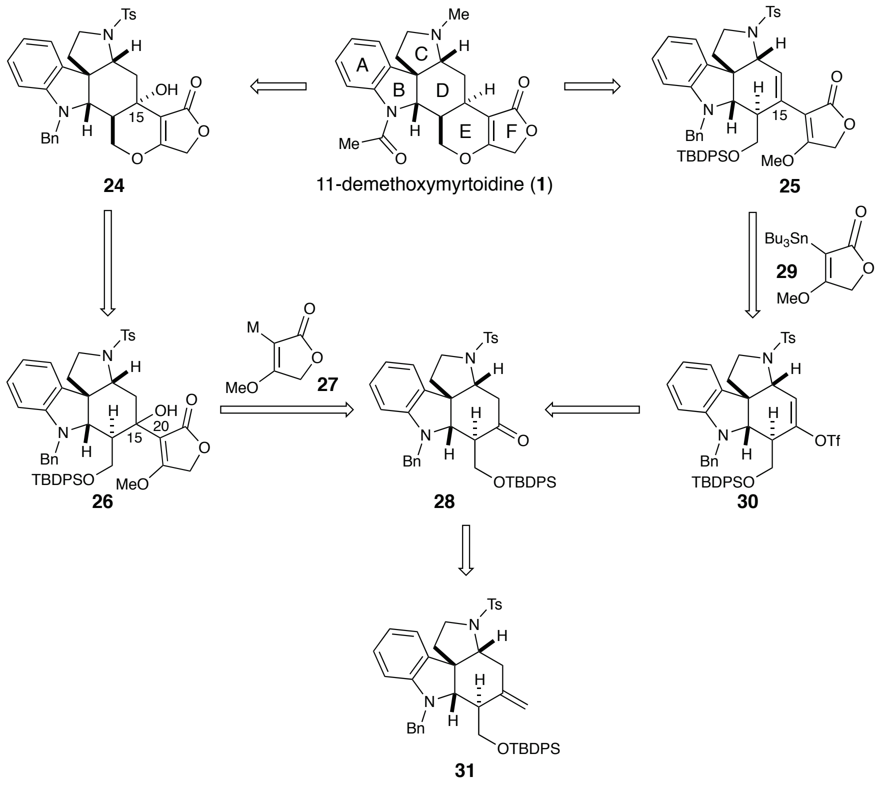
Encouraged by these results, we sought to synthesize advanced acetate intermediate **23**, on which we could attempt the key acylation step (Scheme 4). Thus, tetracyclic core **6** was hydroacylated according to Knochel's conditions; hydroboration of the exocyclic olefin produced the corresponding alkyl borane, which was sequentially transmetalated to zinc, followed by copper. Treatment of the resulting organocuprate with acetoxyacetyl chloride (**21**) delivered α-acetoxyketone **17** in 45% yield as a single stereoisomer, thus setting the final stereocenter of the alkaloid. Importantly, the oxygen atom present in the lactone of the F ring was installed at this stage, in the form of the acetoxy moiety on C18. Hydrogenolysis over Pd/C furnished hemiacetal **22** in 82% yield. Acetylation (72% yield), followed by Lewis acid mediated elimination yielded the desired acetoxymethyl dihydropyran **23**, while also installing the required acetyl group on the indoline nitrogen. Unfortunately, the previously developed conditions to acylate at C20 proved to be unsuccessful on the current system. Treatment of **23** with $(CF_3CO)_2O$ did not provide the desired trifluoroacetate **15**, instead only returning unreacted starting material even at elevated temperatures. Other electrophiles, such as Cl_3CCOCl, were likewise ineffective. We hypothesize that under reaction conditions, the C18 substituent is oriented to block the convex face of the DE ring system, rendering the olefin unreactive. A similar acylation reaction was successful in the synthesis of malagashanine (**3**), which lacks any C18 substitution.[6]



Scheme 4. Synthesis of dihydropyran acetate **23** and attempted acylation at C20

Third-generation approach: installation of pre-formed furanone moiety

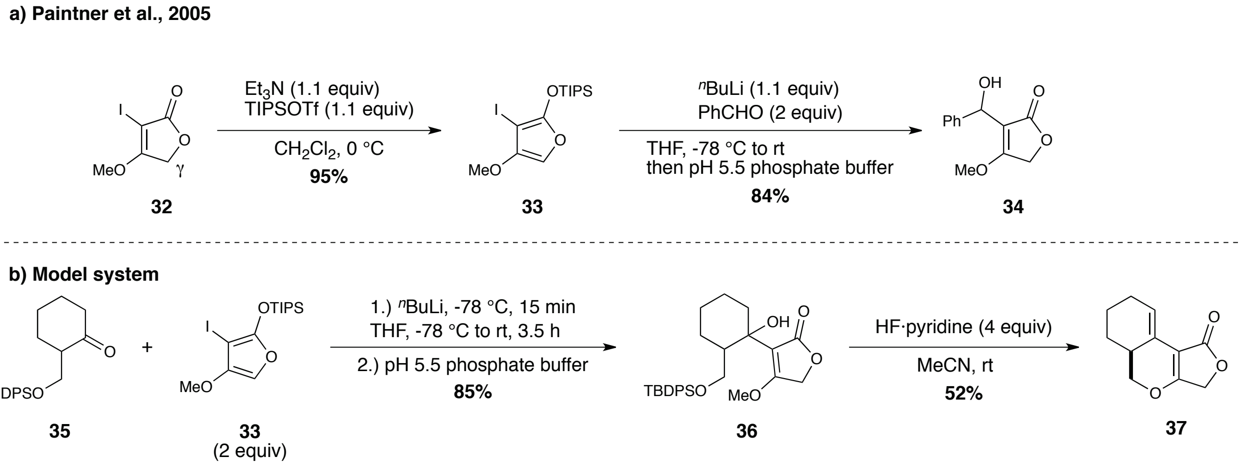
At this stage, we turned to a more convergent strategy for the synthesis 11-demethoxymyrtoidine (**1**), and chose to introduce a pre-formed furanone fragment (Scheme 5). We envisioned that **1** could be accessed by reduction of either alcohol **24** or olefin **25** to set the C15 stereocenter. Tertiary alcohol **24**, in turn, could be provided by desilylation and cyclization of primary alcohol **26**. The key step in this strategy would be the attack of organometallic nucleophile **27** on ketone **28**, to form the C15–C20 bond and introduce the F ring of **1**. Meanwhile, **25** could be accessed *via* a late-stage Stille cross coupling between kinetic enol triflate **30** and vinylstannane **29**, thus providing another possible strategy to introduce the furanone moiety. Triflate **30** could be accessed from its corresponding ketone precursor **28**, which could be provided by oxidative cleavage of tetracyclic core **31**. The tetracyclic core could be diastereoselectively assembled *via* an iminium ion cascade annulation analogous to the reaction employed in the total synthesis of malagashanine[6] (**3**). A silyl protecting group, as opposed to the benzyl group in **6** (*vide supra*), would be employed on the primary alcohol in the interest of protecting group orthogonality. We developed model systems to investigate these convergent strategies for the synthesis of 11-demethoxymyrtoidine (**1**).



Scheme 5. Third generation strategies for the synthesis of **1**

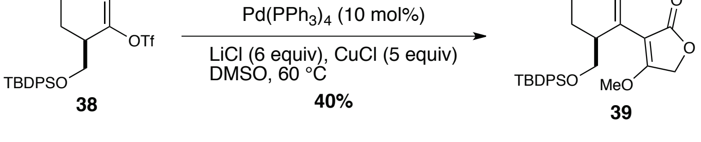
4-Alkoxy-2-furanones have been reported to be reactive at the C5-positions under strongly basic conditions, due to their tendency to aromatize upon deprotonation at the γ-position. In 2005, Paintner and coworkers reported the regioselective C3 functionalization of 4-alkoxy-2-furanones, *via* the intermediacy of 2-silyloxyfurans[18] (Scheme 6a). In this methodology, iodofuranone **32** was treated with Et_3N and TIPSOTf to provide silyloxyfuran **33** in excellent yield. These products could then smoothly undergo lithium-halogen exchange without deleterious side reactions occurring through γ-deprotonation, and the resulting organolithiates could be treated with a wide range of electrophiles. Mildly acidic work-up ensured the complete hydrolysis of the silyloxyfuran moiety back to the furanone.

Excited by these results, we prepared model substrate **35** and silyloxyfuran **33** (Scheme 6b). Gratifyingly, treatment of silyloxyfuran **33** with ^{n}BuLi at -78 °C, followed by addition of β-hydroxyketone **35** delivered tertiary alcohol **36** in 85% yield. Treatment of **36** with HF·pyridine desilylated the primary alcohol, allowing it to cyclize onto the pendant vinylogous carbonate, while also mediating the elimination of the tertiary allylic alcohol to provide dihydropyran lactone **37** in 52% yield.



Scheme 6. Model system utilizing Paintner's conditions for the selective C3 functionalization of 4-alkoxyfuranones

Concurrently, we investigated our second strategy to forge the C15-C20 bond in a convergent manner. We synthesized kinetic enol triflate **38** as a suitable model substrate to undergo a Stille coupling with vinylstannane **29**. Encouragingly, we were able to adapt Corey's[19] conditions for the Stille coupling of sterically congested systems for this purpose. Thus, treatment of triflate **38** and stannane **29** with Pd(PPh$_3$)$_4$ (10 mol%), LiCl (6 equiv), and CuCl (5 equiv) in DMSO at 60 °C delivered coupling product **39** in 40% yield (Scheme 7). Our third generation convergent strategies are currently being investigated in the synthesis of 11-demethoxymyrtoidine (**1**).



Scheme 7. Model Stille coupling

SUMMARY

We have conducted studies on various model systems to explore the construction of the EF ring system in Malagasy alkaloids, 11-demethoxymyrtoidine (**1**) and myrtoidine (**2**). Initially, we planned to intercept our synthetic route to malagashanine (**3**), a related natural product, at a suitably advanced intermediate that could be diverted towards **1** *via* an extended lithium enolate, or using late-stage C–H functionalization. Our model systems were promising, however, these strategies proved to be unsuccessful when applied to the synthesis of the furanone moiety present in 11-demethoxymyrtoidine (**1**). We then turned towards more convergent approaches, in which we could introduce a pre-formed furanone moiety as a suitable organometallic nucleophile. These model studies were likewise encouraging, and their application to the total synthesis of 1 is currently ongoing.

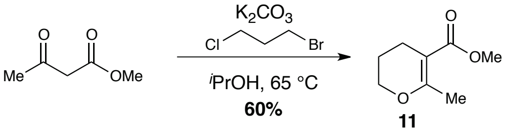
EXPERIMENTAL

General Information

All reactions were carried out under nitrogen atmospheres with anhydrous solvents in oven- or flame-dried glassware using standard Schlenk technique, unless otherwise stated. Anhydrous dimethyl sulfoxide (DMSO), obtained from EMD Millipore, was distilled over anhydrous CaH_2 and stored over activated 4Å molecular sieves. Anhydrous *N,N*-dimethylformamide (DMF), acetonitrile (MeCN), and methanol (MeOH) were obtained from EMD Millipore and were stored over activated 4Å molecular sieves. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were obtained by passage through activated alumina using a *Glass Contours* solvent purification system. Solvents for workup, extraction, and column chromatography were used as received from commercial suppliers without further purification. All other reagents were purchased from Sigma Aldrich, Strem Chemicals, Alfa Aesar, or Oakwood Chemicals and used as received without further purification. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C), a Bruker 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C), a Varian Inova 500 spectrometer (500 MHz ^{1}H, 125 MHz ^{13}C), and a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz ^{13}C) at room temperature in $CDCl_3$ (neutralized and dried over anhydrous K_2CO_3) with internal $CHCl_3$ as the reference (7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C), unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity was indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = mutiplet, br = broad. Infrared (IR) spectra were recorded using a Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra (HRMS) were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). Analytical thin layer chromatography (TLC) was performed on precoated glass backed Silicycle

SiliaPure® 0.25 mm silica gel 60 plates and visualized with UV light, ethanolic *p*-anisaldehyde, or aqueous potassium permanganate ($KMnO_4$). Flash column chromatography was performed using Silicycle SiliaFlash® F60 silica gel (40-63 μm) on a Biotage Isolera One system. Preparatory TLC was performed on precoated glass backed Silicycle SiliaPure® 1.0 mm silica gel 60 plates. We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF.

Procedures and characterization



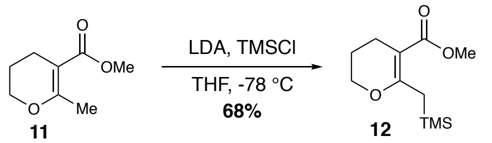
Dihydropyran methyl ester 11: K_2CO_3 (7.1 g, 100.3 mmol) and 1-bromo-3-chloropropane (4.2 mL, 40.0 mmol) were added to a solution of methyl acetoacetate (5.0 g, 43.0 mmol) in ^{i}PrOH (50.0 mL). The mixture was heated to reflux and stirred for 15 h. The reaction was allowed to cool to room temperature, and was concentrated under reduced pressure. The residue was diluted with H_2O (30.0 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 50.0 mL). The organic extracts were combined, washed with brine (20.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by Kugelrohr distillation provided dihydropyran methyl ester **11** as a colorless oil (4.2 g, 60%).

^{1}**H NMR** (CDCl3, 600 MHz) δ 4.02 (t, *J* = 5.3 Hz, 2H), 3.69 (s, 3H), 2.30 (td, *J* = 6.4, 1.4 Hz, 2H), 2.23 (s, 3H), 1.88 – 1.79 (m, 2H) ppm.

^{13}**C NMR** (CDCl3, 150 MHz) δ 169.1, 165.3, 101.2, 66.8, 51.0, 21.8, 21.7, 21.5 ppm.

IR (thin film, cm^{-1}) 2949.4, 1704.3, 1617.7, 1261.1, 1095.6, 1073.3, 786.2.

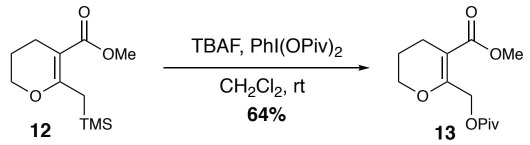
HRMS (+APCI) calculated for $C_8H_{13}O_3$ 157.0859, found 157.0857 $[M+H]^+$.



Silane 12: ^{n}BuLi (1.60 mL, 1.50 M in hexanes, 2.40 mmol) was added dropwise over 5 min to a solution of diisopropylamine (0.35 mL, 2.50 mmol) in THF (10.0 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then cooled to -78 °C. A solution of dihydropyran methyl ester **11** (0.300 mg, 1.92 mmol) in THF (9.0 mL), was added dropwise over 5 min. The resulting yellow solution was stirred at -78 °C for 40 min. TMSCl (0.3 mL, 2.40 mmol) was added dropwise over 5 min and the reaction was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (15.0 mL) and allowed to warm up to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 25.0 mL). The organic extracts were combined, washed with brine (50.0 mL), dried over anhydrous Na_2SO_4,

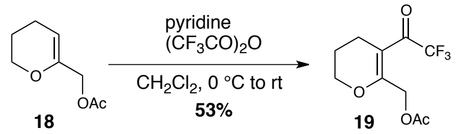
filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (9:1 Hexanes/EtOAc) provided silane **12** as a colorless oil (300 mg, 68%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.98 (t, *J* = 5.2 Hz, 2H), 3.66 (s, 3H), 2.37 (s, 2H), 2.31 (t, *J* = 6.5 Hz), 1.81 (qd, *J* = 6.6 Hz, 5.5 Hz, 2H), 0.04 (s, 9H) ppm.



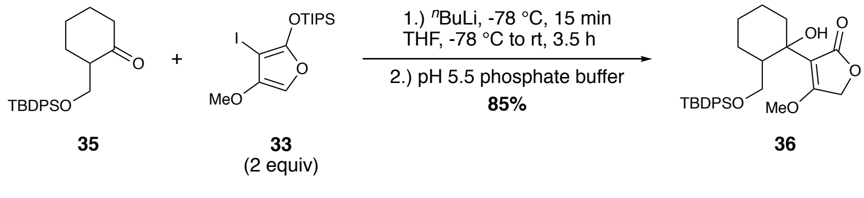
Diester 13: TBAF (0.22 mL, 1.0 M in THF, 0.22 mmol) was added to a solution of silane **12** (0.050 g, 0.22 mmol) and $PhI(OPiv)_2$ (0.233 g, 0.44 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 1 h. The reaction was quenched with pH 7.0 phosphate buffer (5.0 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (25.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (9:1 Hexanes/EtOAc) provided diester **13** (0.0362 g, 64%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.09 (s, 2H), 4.04 (t, *J* = 5.2 Hz, 2H), 3.70 (s, 3H), 2.34 (t, *J* = 6.4 Hz, 2H), 1.85 (qd, *J* = 6.4, 5.5 Hz, 2H), 1.23 (s, 9H).



Trifluoroacetate 19: $(CF_3CO)_2O$ (36.0 mL, 0.26 mmol) was added dropwise over 2 min to a solution of acetoxymethyldihydropyran **18** (0.020 g, 0.12 mmol) and pyridine (21.0 μL, 0.26 mmol) in CH_2Cl_2 (0.10 mL) at 0 °C. The mixture was stirred at 0 °C for 5 min and at room temperature overnight. The reaction was cooled to 0 °C, diluted with CH_2Cl_2 (5.0 mL), and quenched with pH 7.0 phosphate buffer (5.0 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (4:1 Hexanes/EtOAc) provided trifluoroacetate **19** (0.016 g, 53%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.05 (s, 2H), 4.21 (t, *J* = 5.3 Hz, 2H), 2.53 (t, *J* = 6.3 Hz, 2H), 2.16 (s, 3H), 1.94 (qd, *J* = 6.4, 5.2 Hz, 2H) ppm.

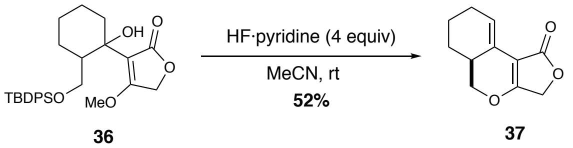


Tertiary alcohol 36: A solution of silyloxyfuran **33** (0.817 g, 2.06 mmol) in THF (10.0 mL) was cooled to -78 °C. A solution of ^{n}BuLi (1.26 mL, 1.63 M in hexanes, 2.06 mmol) was added drop-wise over 5 min to the reaction flask, and the resulting solution was allowed to stir at -78 °C for 15 min. A solution of ketone **35** (0.377 g, 1.03 mmol) in THF (5.0 mL) was added at -78 °C, and the resulting mixture was allowed to warm up to room temperature over 2 h. The reaction was quenched with pH 5.5 aqueous phosphate buffer (20.0 mL) and the resulting biphasic mixture was allowed to stir at room temperature for 15 min. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25.0 mL). The combined organic extracts were washed with brine (40.0 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (2:1 to 1:1 Hexanes/EtOAc) provided tertiary alcohol **36** (0.423 g, 85%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68 – 7.59 (m, 4H), 7.46 – 7.40 (m, 2H), 7.39 – 7.33 (m, 4H), 4.61 (s, 1H), 4.59 (s, 2H), 3.84 – 3.77 (m, 1H), 3.73 (s, 3H), 3.62 (dd, *J* = 10.5, 3.0 Hz, 1H), 2.14 (dq, *J* = 11.5, 3.5 Hz, 1H), 1.97 – 1.72 (m, 4H), 1.67 (d, *J* = 12.7 Hz, 1H), 1.60 (d, *J* = 10.3 Hz, 1H), 1.49 (dd, *J* = 9.5, 4.2 Hz, 1H), 1.35 (qt, *J* = 11.0, 2.8 Hz, 1H), 1.06 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.28, 172.16, 135.72, 135.61, 129.82, 127.75, 127.74, 108.67, 67.21, 64.20, 57.17, 43.25, 37.08, 26.89, 25.68, 24.81, 20.83, 19.28 ppm.

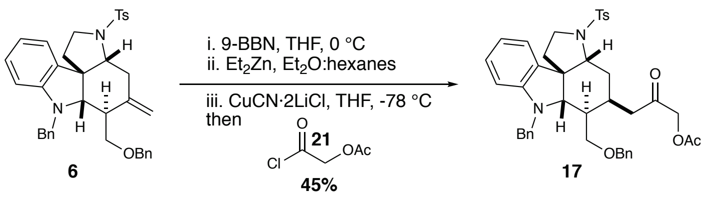
HRMS (+NSI) calculated for $C_{28}H_{36}NaO_5Si$ $[M+Na]^+$ 503.2230, found 503.2219.



Dihydropyran lactone 37: HF·pyridine (0.0165 mL) was added to a solution of tertiary alcohol **36** (0.070 g, 0.159 mmol) in MeCN (1.0 mL), and the resulting solution was allowed to stir at room temperature for 21 h. The reaction was diluted with EtOAc (5.0 mL) and quenched with saturated aqueous $NaHCO_3$ (5.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10.0 mL). The combined organic extracts were washed with brine (20.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (7:3 Hexanes/EtOAc) provided dihydropyran lactone **37** (0.015 mg, 53%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.37 (dd, *J* = 4.9, 2.5 Hz, 1H), 4.66 (d, *J* = 16.2 Hz, 1H), 4.60 (d, *J* = 16.3 Hz, 1H), 4.47 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.80 (dd, *J* = 12.3, 10.6 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.31 – 2.10 (m, 2H), 1.99 – 1.89 (m, 1H), 1.88 – 1.78 (m, 1H), 1.72 – 1.60 (m, 1H), 1.15 – 1.11 (m, 1H) ppm.

HRMS (+APCI) calculated for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0865, found 193.0856.



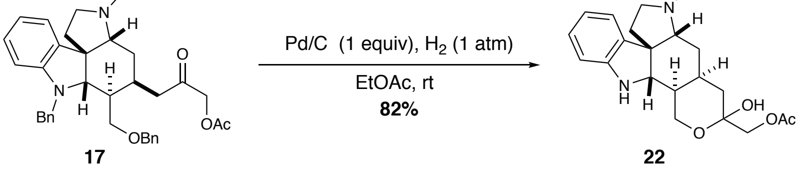
β-Acetoxyketone 17: 9-BBN (2.0 mL, 0.5 M in THF, 1.01 mmol) was added to a solution of tetracyclic core **6** (0.500 g, 0.84 mmol) in THF (2.0 mL) at 0 °C, and the resulting solution was stirred at room temperature overnight. The volatiles were removed under reduced pressure and Et_2O (4.0 mL) was added, followed by Et_2Zn (12.6 mL, 12.6 mmol, 1 M in hexanes), and the resulting solution was stirred at room temperature for 3 h. The volatiles were removed under reduced pressure, and the grey-black residue was diluted with THF (13.0 mL) and cooled to -78 °C. A freshly prepared solution CuCN·2LiCl (12.6 mL, 1 M in THF, 12.6 mmol) was added over 30 min, and the mixture was stirred at -78 °C for 30 min. Acetoxyacetyl chloride (**21**, 4.0 mL, 38.0 mmol) was added slowly over 30 min, and the resulting solution was warmed to -20 °C and stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (100.0 mL) and diluted with EtOAc (50.0 mL). The resulting biphasic mixture was stirred for 15 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50.0 mL). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (50.0 mL) and brine (50.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (4:1 to 1:1 Hexanes/EtOAc) provided β-acetoxyketone **17** as an amorphous white solid (0.260 g, 45%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.28 (m, 7H), 7.25 (d, *J* = 2.3 Hz, 3H), 7.22 (dd, *J* = 6.2, 2.6 Hz, 1H), 7.20 – 7.17 (m, 2H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.60 (t, *J* = 7.4 Hz, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 4.54 (d, *J* = 15.6 Hz, 1H), 4.47 (d, *J* = 16.8 Hz, 1H), 4.36 (d, *J* = 16.8 Hz, 1H), 4.32 (s, 2H), 4.23 (d, *J* = 15.6 Hz, 1H), 3.66 (td, *J* = 10.9, 6.9 Hz, 1H), 3.41 – 3.37 (m, 2H), 3.26 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.13 (dd, *J* = 10.7, 7.5 Hz, 1H), 3.01 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.50 (dd, *J* = 17.2, 9.8 Hz, 1H), 2.43 (s, 3H), 2.27 (ddd, *J* = 13.3, 8.8, 4.3 Hz, 1H), 2.21 (t, *J* = 4.9 Hz, 2H), 2.17 (t, *J* = 4.1 Hz, 1H), 2.13 (s, 3H), 1.84 (td, *J* = 12.6, 11.3, 7.3 Hz, 1H), 1.32 (q, *J* = 10.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 150 MHz) δ 202.6, 170.2, 150.5, 143.9, 138.3, 137.9, 138.1, 131.1, 129.9, 128.8, 128.6, 128.0, 127.9, 127.9, 127.2, 124.3, 117.0, 105.7, 73.2, 70.9, 70.1, 59.4, 53.7, 48.0, 47.8, 42.6, 39.1, 37.4, 30.9, 27.3, 21.7, 20.7 ppm.

IR (thin film, cm^{-1}) 3029.8, 2925.3, 1750.3, 1731.8, 1599.2, 1483.5, 1161.5, 1091.0, 731.4.

HRMS (+APCI) calculated for $C_{25}H_{29}N_2O_3S$ 437.1899 $[M+H]^+$, found 437.1895.



Hemiacetal 22: Palladium on carbon (0.307 g, 5% wt, 0.144 mmol) was added to a solution β-acetoxyketone **17** (0.1 g, 0.140 mmol) in EtOAc (7.0 mL). The suspension was deoxygenated by sparging with nitrogen gas for 15 min. Hydrogen gas was bubbled through the mixture for 15 min, and

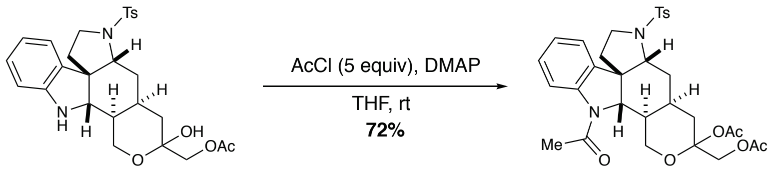
the suspension was stirred under a hydrogen atmosphere (1 atm) for 2 h. The suspension was filtered through celite and washed with EtOAc (3 x 70.0 mL). Purification by flash column chromatography on silica gel (3:2 to 1:1 Hexanes/EtOAc) provided hemiacetal **22** as an amorphous white solid (0.058 g, 82%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.50 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 6.72 (td, *J* = 7.5, 1.0 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 2H), 4.09 (d, *J* = 11.2 Hz, 1H), 4.06 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.93 (d, *J* = 11.2 Hz, 1H), 3.57 (d, *J* = 12.0 Hz, 1H), 3.56 – 3.50 (m, 1H), 3.44 (d, *J* = 9.4 Hz, 1H), 3.38 (t, *J* = 10.2 Hz, 1H), 3.03 (dd, *J* = 12.9, 3.4 Hz, 1H), 2.68 (bs, 1H), 2.49 (s, 3H), 2.35 (dt, *J* = 13.5, 3.0 Hz, 1H), 2.15 (s, 3H), 2.02 (td, *J* = 13.2, 4.9 Hz, 1H), 1.70 (dd, *J* = 10.8, 6.6 Hz, 1H), 1.54 – 1.46 (m, 2H), 1.38 (t, *J* = 13.4 Hz, 1H), 1.33 – 1.21 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.9, 149.0, 144.2, 132.5, 131.3, 130.0, 128.3, 128.1, 125.6, 120.0, 111.9, 95.0, 69.9, 62.6, 61.4, 60.6, 59.0, 55.9, 47.2, 38.2, 35.8, 31.7, 30.4, 28.3, 21.8, 21.0 ppm.

IR (thin film, cm^{-1}) 3365.0, 2933.0, 1742.6, 1604.9, 1160.7, 1090.2, 751.4.

HRMS (+APCI) calculated for $C_{27}H_{33}N_2O_6S$ 513.2054 $[M+H]^+$, found 513.2054.

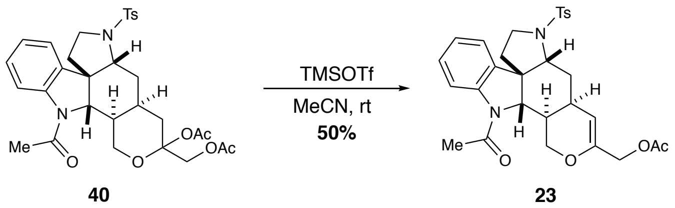


22 40

Acetamide 40: Acetyl chloride (0.021 mL, 0.29 mmol) was added dropwise to a solution of hemiacetal **22** (0.03 g, 0.059 mmol) and DMAP (0.039 g, 0.32 mmol) in THF (2.3 mL) at room temperature. The resulting mixture was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (3.0 mL) and the resulting biphasic mixture was stirred for 15 min. The layers were separated, and the aqueous was extracted with EtOAc (3 x 15.0 mL). The organic extracts were combined, washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (3:2 to 1:1 Hexanes/EtOAc) provided acetamide **40** as an amorphous white solid (0.023 g, 72%).

^{1}H NMR ($CDCl_3$, 600 MHz) (1:0.7 mixture of rotamers) δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.73 – 7.65 (m, 4.1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 3.4H), 7.28 – 7.24 (m, 0.7H), 7.15 – 7.08 (m, 2.7H), 4.87 (d, *J* = 9.8 Hz, 0.7H), 4.16 – 4.08 (m, 3.7H), 4.05 – 3.99 (m, 3.4H), 3.71 (d, *J* = 11.6, 0.7H), 3.61 (d, *J* = 11.6 Hz, 1H), 3.55 – 3.47 (m, 1.7H), 3.42 – 3.32 (m, 1.7H), 3.09 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.99 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.73 (s, 1H), 2.63 (s, 0.7H), 2.50 (s, 5.1H), 2.40 – 2.30 (m, 3.8H), 2.23 (s, 2.1H) 2.19 – 2.11 (m, 5.1H), 1.99 (m, 1.7H), 1.64 (dd, *J* = 11.0, 7.6 Hz, 0.7H), 1.58 – 1.37 (m, 3.4H) ppm.

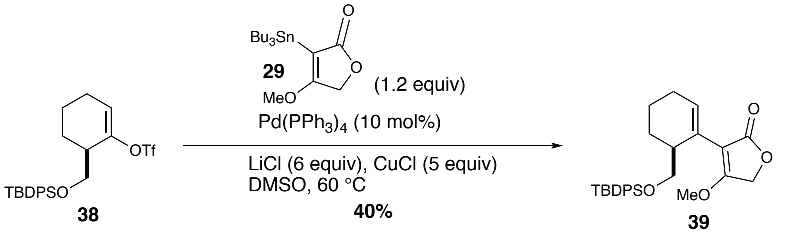
HRMS (+APCI) calculated for $C_{29}H_{34}N_2NaO_7S$ 577.1979 $[M-OAc+H_2O+Na]^+$, found 577.1980.



Acetoxymethyl dihydropyran 23: TMSOTf (0.05 mL, 0.68 mmol) was added to a solution of acetamide **40** (0.018 g, 0.03 mmol) in MeCN (0.1 mL) at room temperature. The mixture was stirred for 3 h. The reaction was quenched with K_2CO_3 and H_2O (1.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 1.5 mL). The organic extracts were combined, washed with brine (5.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1:1 Hexanes/EtOAc) provided acetamide **23** (0.008 g, 50%).

^{1}H NMR ($CDCl_3$, 400 MHz) (1:0.8 mixture of rotamers) δ 8.00 (d, J = 7.9 Hz, 1H), 7.73 (t, J = 8.1 Hz, 3.6H), 7.64 (d, J = 7.3 Hz, 1H), 7.56 (d, J = 7.4 Hz, 0.8H), 7.41 – 7.30 (m, 3.6H), 7.20 – 7.15 (m, 1.8H), 4.71 (d, J = 8.5 Hz, 0.8H), 4.68 (s, 1H), 4.62 (s, 0.8H), 4.48 – 4.35 (m, 4.6H), 4.31 (d, J = 9.5 Hz, 0.8H), 4.20 (d, J = 9.5 Hz, 1H), 4.02 (d, J = 8.6 Hz, 1.8H), 3.94 (d, J = 10.8 Hz, 1H), 3.84 (d, J = 10.8 Hz, 0.8H), 3.55 – 3.45 (m, 3.6H), 3.40 (t, J = 10.5Hz, 1.3H), 3.07 (dd, J = 9.7, 3.1 Hz, 1H), 3.01 (dd, J = 9.7, 3.1 Hz, 0.8H), 2.85 – 2.68 (m, 1.8H), 2.55 – 2.40 (m, 7.2H), 2.37 (s, 2.8H), 2.28 (s, 3H), 2.15 – 1.80 (m, 7.6H), 1.75 – 1.60 (m, 1.8H) ppm.

HRMS (+APCI) calculated for $C_{29}H_{32}Na_1N_2O_6S$ 559.1873 $[M+Na]^+$, found 533.1875.



Coupling product 39: A Schlenk flask (10 mL) containing LiCl (0.037 g, 0.86 mmol), CuCl (0.071 g, 0.72 mmol), and $Pd(PPh_3)_4$ (0.017 g, 0.014 mmol) was degassed under high vacuum and backfilled with nitrogen (x 3). A solution of vinylstannane **29** (0.070 g, 0.175 mmol) in DMSO (0.90 mL) was added to the flask, followed by a solution of enol triflate **38** (0.072 g, 0.143 mmol) in DMSO (0.90 mL). The resulting mixture was degassed by freeze-pump-thaw (-78 °C, over 4 cycles). The mixture was allowed to stir at room temperature for 40 min, and at 60 °C for 49 h. The reaction mixture was cooled down to room temperature and quenched with aqueous NH_4OH (1.0 M, 3.0 mL) and diluted with Et_2O (4 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5.0 mL). The combined organic extracts were washed with aqueous potassium fluoride (5.0 mL, 1.0 M) and brine (6.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (1:1 pentane/Et_2O) provided coupling product **39** (0.026 g, 40%).

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.67 – 7.59 (m, 4H), 7.44 – 7.32 (m, 6H), 6.08 (td, *J* = 3.9, 1.3 Hz, 1H), 4.49 (s, 2H), 3.72 (s, 3H), 3.61 (dd, *J* = 10.1, 4.2 Hz, 1H), 3.54 (dd, *J* = 10.0, 7.9 Hz, 1H), 2.93 (s, 1H), 2.14 – 2.10 (m, 2H), 1.82 – 1.60 (m, 4H), 1.03 (s, 9H) ppm.

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