STEPS TOWARD A NEW SYNTHESIS OF HIPPADINE

by

Thomas Purgett

Submitted in partial fulfillment of the
requirements for Departmental Honors in
the Department of Chemistry
Texas Christian University
Fort Worth, Texas

May 3, 2013

STEPS TOWARD A NEW SYNTHESIS OF HIPPADINE

Project Approved:

David Minter, Ph.D.
Department of Chemistry
(Supervising Professor)

Eric Simanek, Ph.D.
Department of Chemistry

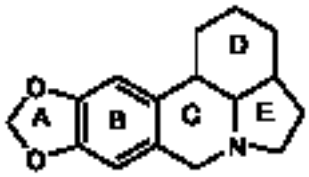
Giridhar Akkaraju, Ph.D.
Department of Biology

TABLE OF CONTENTS

INTRODUCTION

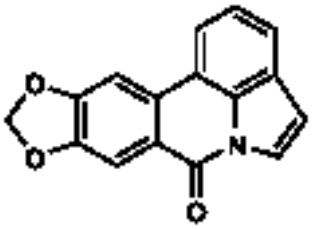
Structure and Activity of Hippadine

Hippadine is a lycorine-type alkaloid of the Amaryllidaceae family containing an interesting pentacyclic skeleton, specifically the aromatic pyrrolophenanthridinone core **(1)**. Isolated from the *Crinum* genus of tropical plants, this nitrogenous molecule shows myriad biological activity, with pharmaceutical and therapeutic applications. Hippadine has only been recently isolated from *Crinum powellii* but shows promise as one of the most interesting and potent of the Amaryllidaceae alkaloids.[1]



1

Figure 1. The Pyrrolophenanthridinone Core



2

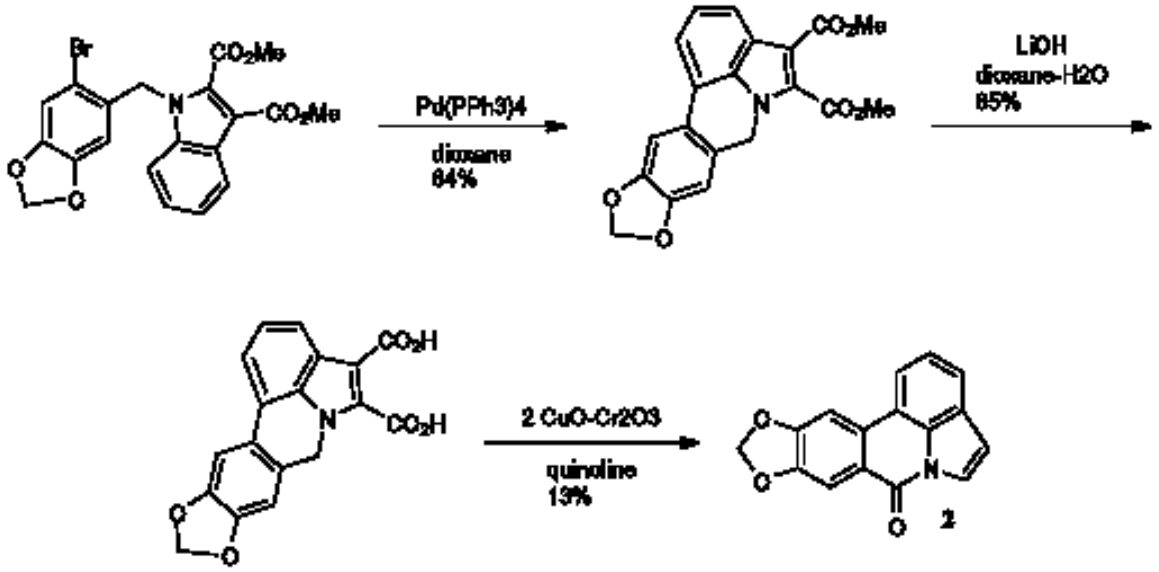
Figure 2. Structure of Hippadine

The biological importance of Hippadine relies on its ability to inhibit spermatogenesis reversibly in rats. Hippadine functions by reducing testicular weight and DNA content in these newly dividing germ cells as well as reducing their numbers.[2] Thus, Hippadine could be used as a powerful male contraceptive as defined by the compound's ability to inhibit sperm production or sperm motility, rendering the cells as non-responsive to an ovum in females.[3] Hippadine shows numerous cardiovascular effects as well by causing significant decreases in coronary flow, aortic output, cardiac output, systolic pressure and heart rate along with an increase in diastolic pressure.[4] These potential therapeutic and medicinal applications of the molecule, though, come as no surprise. Other alkaloids from the *Crinum* genus and of the lycorine variety have been used extensively in medicine as remedies, having significant pharmacological properties against diseases such as Alzheimer's.[5] Using these naturally isolated molecules as cures for ailments thus represents a neo-herbalism of sorts. Synthesis of the molecule is of paramount concern as to create suitable amounts of the alkaloid for testing and possibly for use in clinical trials and eventually as medicinal drugs.

Past Syntheses of Hippadine

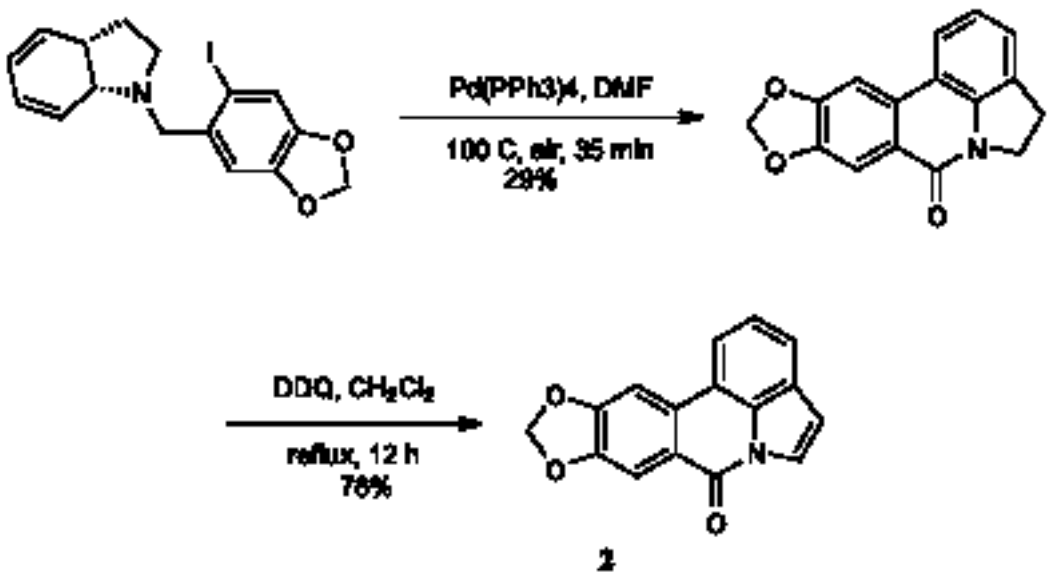
The synthesis of Hippadine is not a particularly new endeavor. The molecule has been synthesized numerous times over the past twenty years. However, several routes rely on palladium coupling to complete the synthesis. For example, Hideaki et al.'s synthesis of the alkaloid involves formation of the characteristic C-ring by the use of $Pd(PPh_3)_4$ in potassium acetate and hot dioxane. The synthesis was completed, however, in a relatively low overall yield of only 13%.[6]

Scheme 1. The Hideaki Synthesis of Hippadine



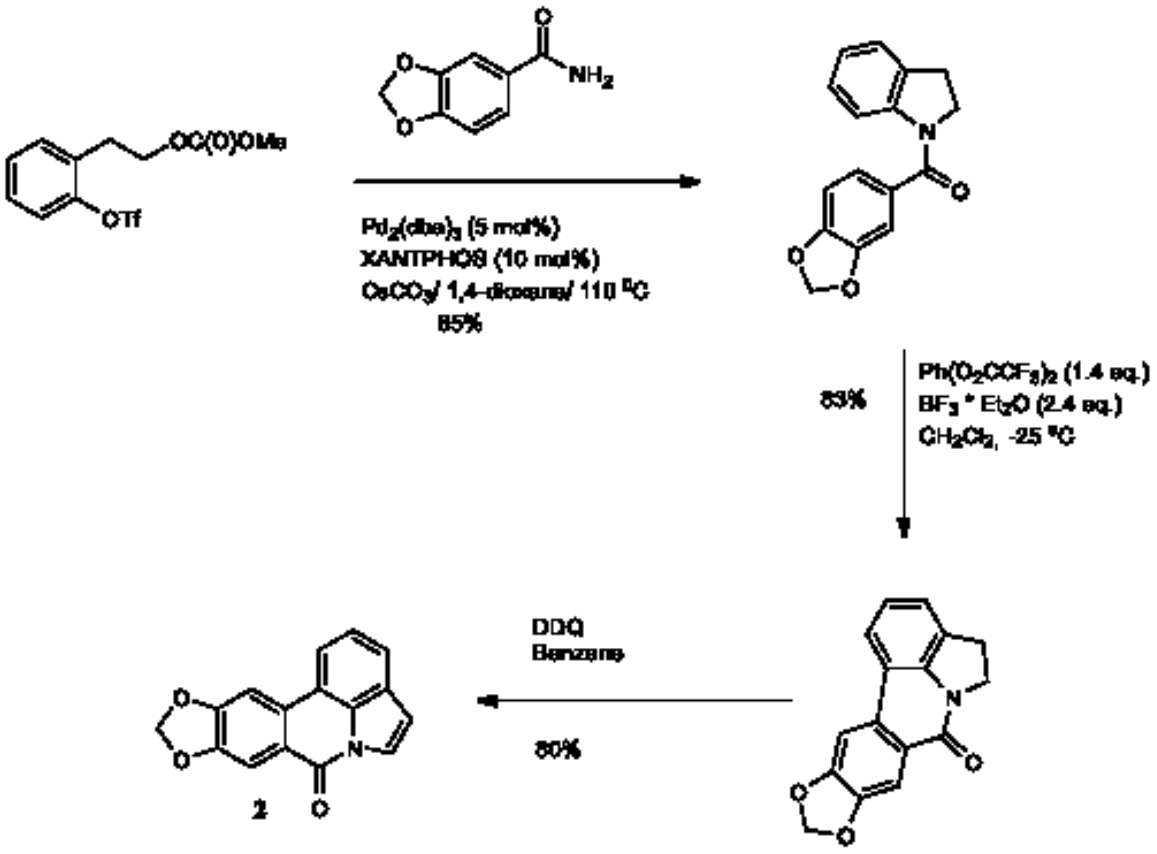
Scheme 1. The Hideaki Synthesis of Hippadine

A palladium-mediated synthesis of Hippadine was also completed by Knoelker and Filalia rather recently. The duo used a late-stage palladium coupling once again to mediate the formation of the C-ring before DDQ oxidation to the target molecule.[7]



Scheme 2. Knoelker Synthesis of Hippadine

One of the most interesting preparations of Hippadine comes from the 2005 paper reported by Ganton and Kerr. Like other approaches, their efficient three-step synthesis of the molecule uses a palladium-catalyzed aryl C-N coupling to accomplish a late-stage formation of the C-ring. However, the brevity of the sequence and its overall efficiency make it particularly atttrative.[8]



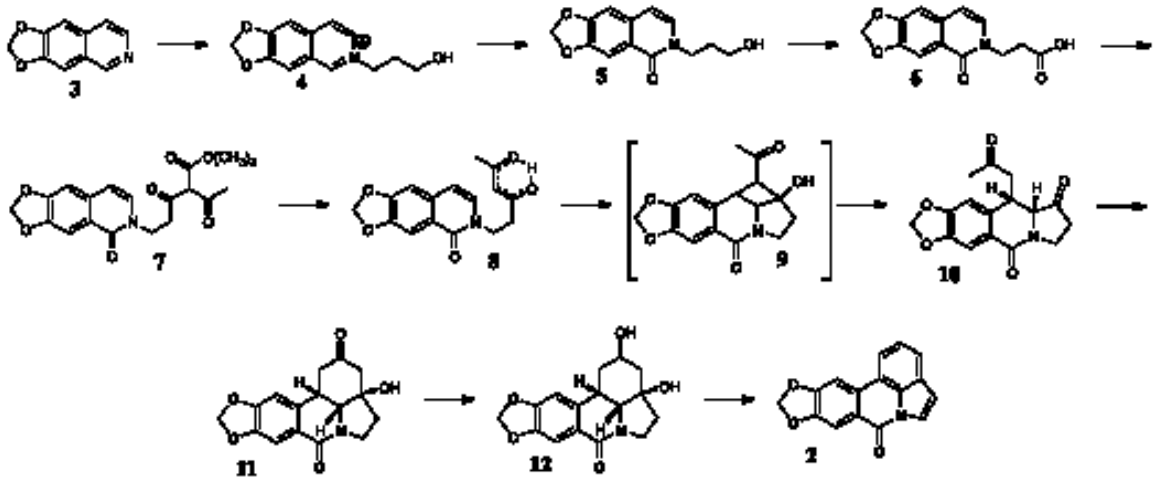
Scheme 3. Ganton and Kerr Synthesis of Hippadine

New Synthesis of Hippadine

Two motifs seem to be common in the previous syntheses of Hippadine—the use of palladium cross-coupling and the formation of the C-ring late in the synthesis. Our work, however, centers on constructing the molecule from a starting material with the A, B, and C rings already intact. Additionally, our route is free of costly reagents such as palladium and will theoretically give a higher yield than several previously completed syntheses. The first step involves the alkylation of 6,7-methylenedioxyisoquinoline (**3**) affording a compound with a functionalized tether on nitrogen. The key step of the synthesis comes from an intramolecular de Mayo reaction, in which this tether cyclizes to

form the E-ring of the molecule. A simple aldol reaction closes the D-ring to complete the pentacyclic system.

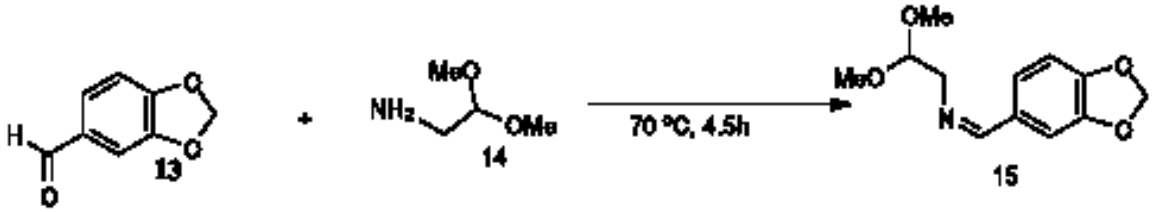
Scheme 4. Proposed New Synthesis of Hippadine



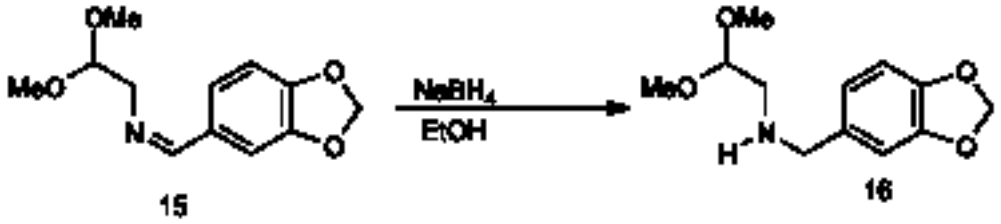
The proposed synthesis begins with an alkylation of **3** (**3→4**) followed by an oxidation of the salt to the isocarbostyril **5** (**4→5**) and finally an oxidation of the alcohol group to the acid function (**5→6**). The acid is converted to the dione **8** in two steps (**6→7→8**) thus providing the substrate for E-ring closure using the intramolecular de Mayo reaction (**8→9→10**). Finally, a simple aldol reaction creates the D ring, as shown in structure **11**. Oxidation of the D and E rings completes the total synthesis of **2.** This approach has previously been demonstrated in a model system except for the last two steps. In this model, the starting material was isoquinoline rather than compound **3** and afforded a molecule analogous to **11** but lacking the methylenedioxy function. It was assumed that the incorporation of the methylenedioxy unit (i.e. ring A in **2**) would not alter the chemistry in any of the proposed steps such that hippadine could be synthesized directly by using the procedures developed during the model study.[9]

EXPERIMENTAL SECTION

Preparation of 6,7-Methylenedioxyisoquinoline[10-12]

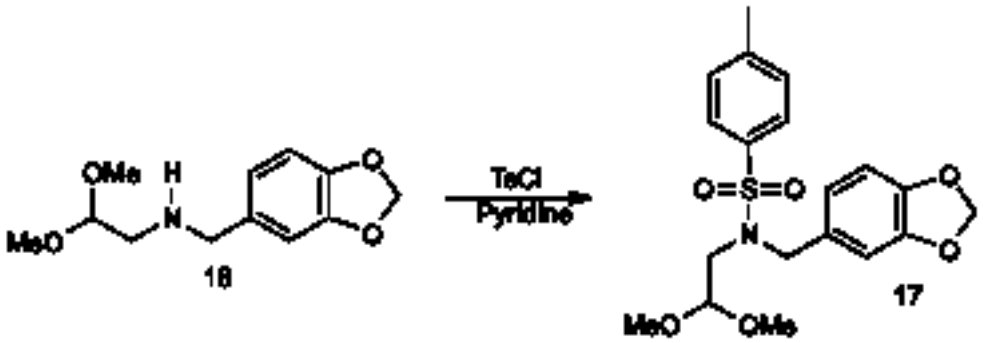


A mixture containing 45.0 g (300 mmol) of piperonal (**13**) and 37.8 g (360 mmol) of aminoacetaldehyde dimethyl acetal (**14**) was heated overnight under nitrogen at 70 °C in a 500-mL three-necked flask with an attached condenser and thermometer. After 14.5 hours, the pale yellow liquid product was cooled to room temperature and used directly in the next step without purification.



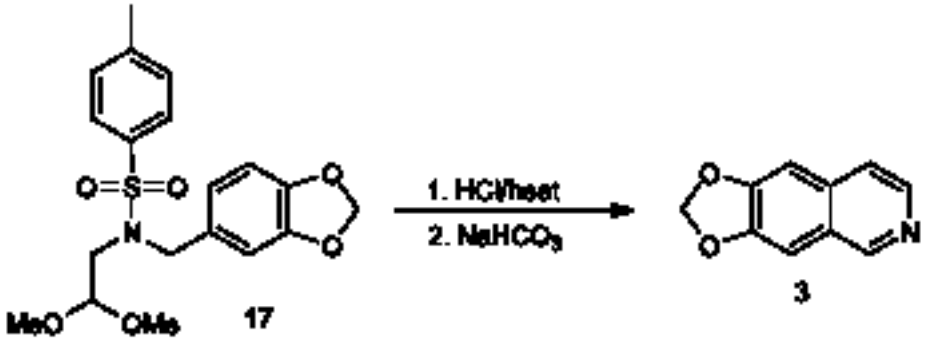
The imine **15** was then dissolved in 350 mL of 90% ethanol and cooled to 0 °C. Sodium borohydride (10.0 g, 264 mmol) was then added over a three-hour period as hydrogen gas evolved. After stirring for 16 hours under an inert atmosphere, 350 mL of water was added to the milky solution to quench the reaction. After the evolution of hydrogen gas had ceased, the reaction mixture was transferred to a 2-L separatory funnel containing 750 mL of water. The product was extracted with CH_2Cl_2 (3 x 250 mL) and the combined organic layers were dried over Na_2SO_4. Solvent was removed by rotary

evaporation before the product was placed on a vacuum pump to remove any residual volatiles. The yield was 69.82 g of **16** (97.4% over 2 steps from **13**) as a pale yellow, viscous liquid that was used in the subsequent step after determining it to be sufficiently pure by ^{1}H NMR analysis.



A solution of **16** (69.8 g, 292 mmol) in 300 mL of dry pyridine was prepared in a 1-L round-bottom flask and cooled to 0 °C in an ice bath. Tosyl chloride (63.0 g, 330 mmol) was added, causing the solution to become cloudy and dark yellow in color. The mixture was capped and allowed to stir at room temperature for 48 hours. The reaction mixture was then cooled to 0 °C and stirred rapidly during the addition of 500 mL of $NaHCO_3$. Once bubbling became less vigorous, NaOH was added causing inorganic salts to form. Water was added to dissolve the salts and the contents of the flask were transferred to a 2-L Erlenmeyer flask and stirred overnight allowing a slow neutralization to occur. As the reaction proceeded, the product became visible as a white precipitate. The reaction mixture was then transferred to a separatory funnel and extracted with CH_2Cl_2 (4 x 200 mL). The combined organic layers were subsequently washed with 5% KOH (250 mL) and brine (250 mL) before being dried over Na_2SO_4. Solvents were removed by rotary evaporation, causing a dark brown oil to form in the flask. Residual

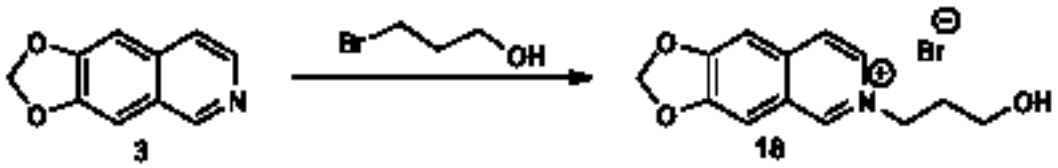
solvents and pyridine were then removed from the product using a vacuum pump to give crude **17**.



A solution containing 16.35 g (94.4 mmol) of crude **17** in 265 mL of dioxane was prepared in a 500-mL round-bottom flask and stirred while 65 mL of 6M HCl was added slowly. The mixture was heated at reflux for five hours before distillation was used to remove approximately 130 mL of dioxane.

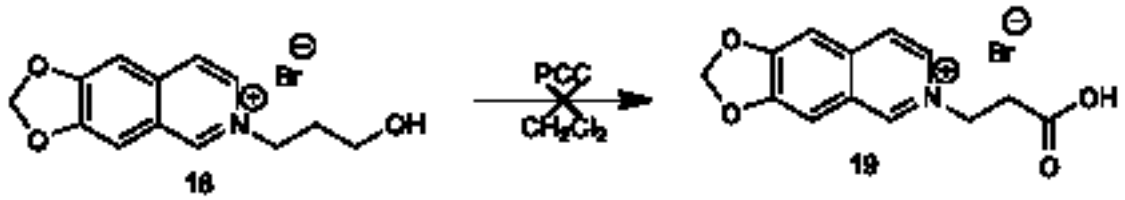
A saturated solution of $NaHCO_3$ was then added slowly, causing the solution to become brown in color and basic to red litmus paper. The reaction mixture was extracted with CH_2Cl_2 (1 x 85 mL, 2 x 65 mL), dried over $MgSO_4$, decanted into a round-bottomed flask, and concentrated by rotary evaporation. The pale yellow liquid product was placed on the vacuum line to remove residual dioxane during which time the liquid crystallized to give 8.05 g of crude **3** as confirmed by ^1H NMR analysis. The product was purified by recrystallization in 55 mL of cyclohexane to give 6.75 g (93.5%) of a powdery solid with a slight yellow tint, MP 124-125 °C.

Preparation of 6-(3-hydroxypropyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium bromide (18)



A solution containing 5.00 g (28.9 mmol) of 6,7-methylenedioxyisoquinoline (**3**) and 4.55 g (31.8 mmol) of 3-bromo-1-propanol in 13 mL of THF was prepared in a 250-mL round-bottom flask. The mixture was heated at reflux for 24 hours with a drying tube attached to the flask. The formation of a solid product was visible within only a few hours of heating. The crude product was isolated by vacuum filtration and residual THF was removed on a vacuum line. Analysis using ^{1}H NMR confirmed that the reaction was complete. The crude product was recrystallized from 50 mL of absolute ethanol to give 5.83 g (64.6% yield) of an off-yellow, powdery solid. The recrystallized product **18** was determined to be pure by ^{1}H NMR analysis.

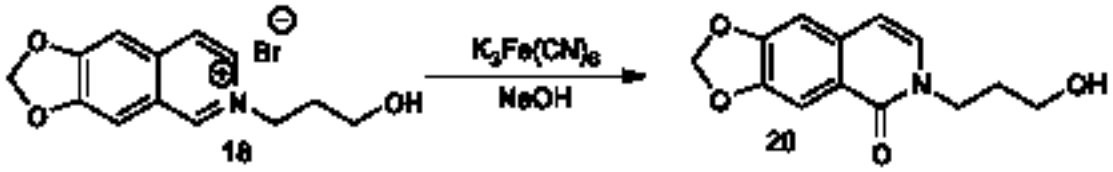
Attempted Synthesis of 6-(2-carboxyethyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium bromide (19) [13]



Pyridinium chlorochromate (PCC) (0.32 g, 1.5 mmol) was suspended in 4 mL of dry dichloromethane. A solution of the salt **18** (0.312 g, 1.00 mmol) in 4 mL of CH_2Cl_2

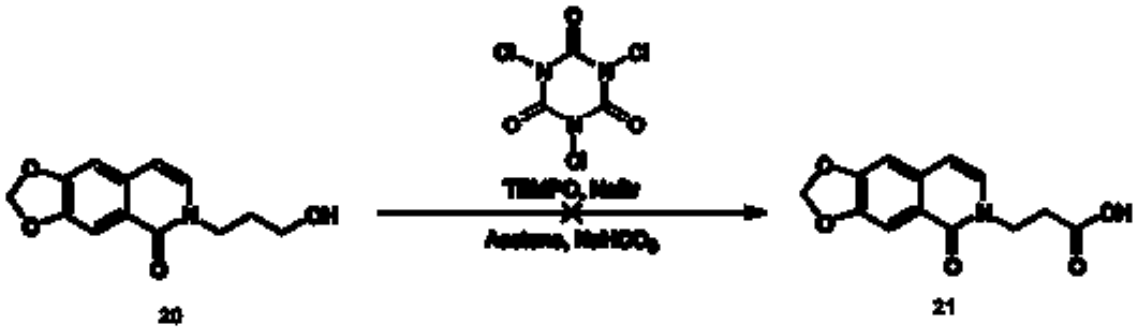
was added rapidly to the PCC suspension at room temperature with stirring. Six hours later, the solution had become brown in color with a black deposit on the bottom of the flask. The reaction mixture was diluted with 5 volumes of CH_2Cl_2 and decanted from the precipitate. After removal of solvent by rotary evaporation, an NMR analysis of the residue proved that only the starting material was present.

Preparation of 6-(3-hydroxypropyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (20)[14]



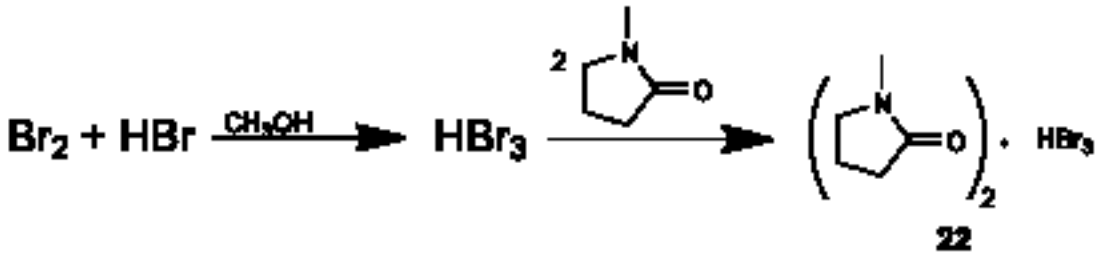
A solution containing 2.92 g (9.36 mmol) of **18** in 25 mL of DI water was cooled in a three-necked flask to 0 °C. A solution of 5.45 g (16.5 mmol) of $K_3Fe(CN)_6$ in 18.5 mL of DI water was then added all at once to the flask. A solution of NaOH (1.70 g, 42.5 mmol) in 20 mL of DI water was then added dropwise through an addition funnel at a rate sufficiently slow to assure that the temperature of the reaction mixture did not exceed 20 °C. The ice bath was then removed and the reaction mixture was allowed to stir for 18 hours. The resulting suspension was then transferred to a separatory funnel using 150 mL of DI water to rinse the flask. The product was extracted with dichloromethane (4 x 40 mL) and the combined extracts were dried over Na_2SO_4. The solvent was removed by rotary evaporation followed by pumping on a vacuum line to give 2.11 g (91.3%) of **20**, which was determined by ^{1}H NMR analysis to be adequately pure for use in subsequent reactions.

Failed Preparation of 3-(5-oxo-[1,3]dioxolo[4,5-*g*]isoquinolin-6(5*H*)-yl)propanoic acid (21) [15]



Ten milliliters of 15% aqueous $NaHCO_3$ was added to a stirred solution of **20** (1.00 g, 4.05 mmol) in 30 mL of acetone at 0 °C. Next, NaBr (0.06 g, 0.60 mmol) was added along with a catalytic amount of TEMPO (0.01 g, 0.06 mmol). Finally, TCICA (trichloroisocyanuric acid) (1.40 g, 6.0 mmol) was added slowly over a 10-minute period. The solution was then brought back to room temperature and stirred for 24 hours before addition of 2-propanol (2 mL) to destroy excess reagents. When filtered on Celite, the product was found to be a red tar that stuck to the filter paper and could not be further analyzed.

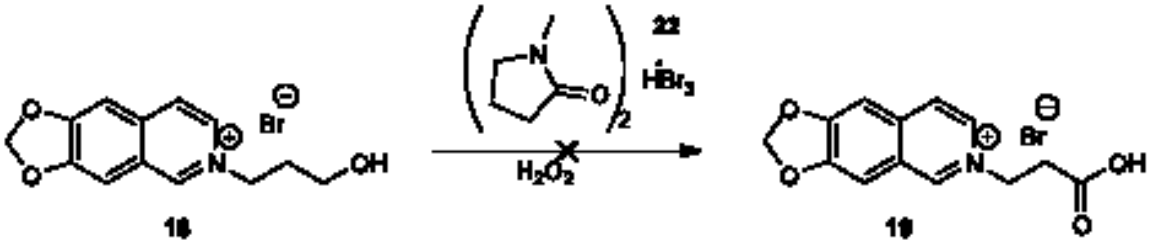
Preparation of N-Methylpyrrolidin-2-one Hydrotribromide (MPHT) (22)[16]



A 250-mL 3-necked flask equipped with a condenser and two addition funnels was cooled in an ice bath. Methanol (25 mL) was added all at once followed by the

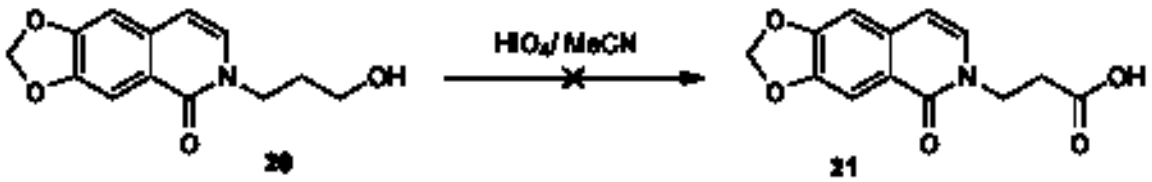
dropwise addition of 31 mL of conc. HBr. The internal temperature of the reaction mixture was maintained between 10-15 °C. Bromine (7.5 mL) was added dropwise to the mixture, and the solution was stirred for 10 minutes. Then, N-methylpyrrolidin-2-one (31 mL) was added by addition funnel at a rate of 2 drops per second. The solution was stirred for 1 hour at 10 °C after which the bright orange solid product was collected by vacuum filtration. The product was then washed with Et_2O and dried under vacuum to give 46.79 (74% yield) of MPHT.

Failed Preparation of 6-(2-carboxyethyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium bromide (19)[17]



The salt **18** (3.12 g, 1.00 mmol) was added to a solution of MPHT (0.527 g, 1.20 mmol) in acetonitrile (5 mL) and 0.22 mL (2.0 mmol) of H_2O_2 was added dropwise. The mixture was then heated at reflux for 5 hours before being cooled to room temperature and deactivating the excess hydrogen peroxide with the addition of aqueous sodium bisulfite. The solution was then filtered through a Buchner funnel. The reaction gave a black tar-like substance that could not be identified by NMR analysis.

Failed Preparation of 3-(5-oxo-[1,3]dioxolo[4,5-*g*]isoquinolin-6(5*H*)-yl)propanoic acid (21)[18]

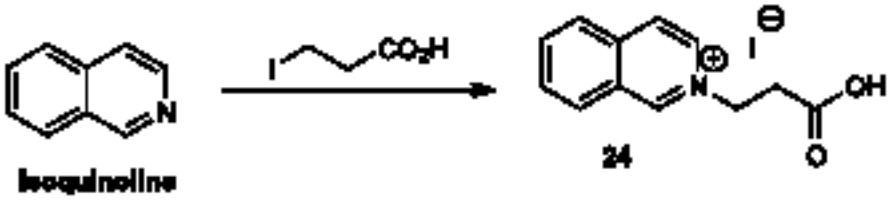


Periodic acid (1.56 g, 8.13 mmol) was dissolved in acetonitrile (16.7 mL) and the reaction mixture was stirred vigorously at room temperature for 40 minutes. The solution was cooled to 0 °C in an ice bath and a solution of the alcohol **20** (1.00 g, 4.05 mmol) in acetonitrile (25 mL) was added. The reaction mixture was stirred overnight and then concentrated by removal of half of the solvent.

The concentrated solution was then vacuum filtrated, giving a green solid on the filter paper and reddish-brown filtrate. This filtrate, thought to contain the desired product, was concentrated further under vacuum giving a dark-brown viscous liquid.

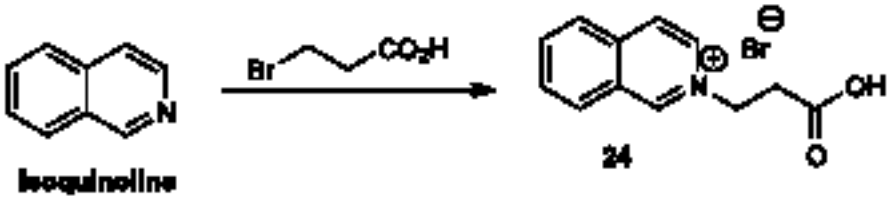
The addition of 10 mL of 5% NaOH solution caused some of the material to dissolve. The aqueous solution was separated from the residual oil and sodium bisulfite was added until a color change from red to brown was observed. Acidification of the solution using 6 M HCl caused the precipitation of a brown solid, which was isolated by vacuum filtration. The solid was dried under vacuum to remove residual solvent and water. NMR analysis, however, did not indicate the formation of the desired product.

Preparation of 2-(2-carboxyethyl)isoquinolin-2-ium iodide (23)



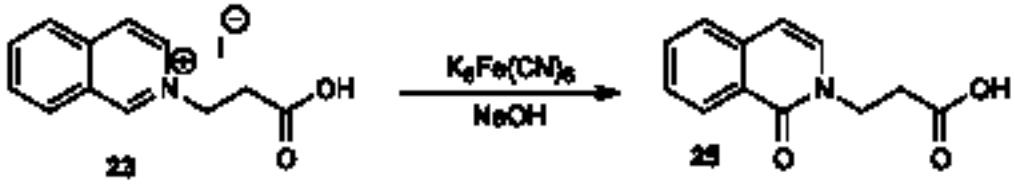
Isoquinoline (0.64 g, 4.96 mmol) and 3-iodopropionic acid (1.00 g, 5.00 mmol) were combined in a 50-mL round-bottom flask along with 4 mL of THF. The initial pale yellow solution was allowed to stir overnight. The product precipitated as a yellow solid coating the wall of the flask. The solvent, which had become brown in color, was removed by rotary evaporation, and the product was confirmed by ^{1}H NMR analysis. The reaction gave 1.48 g (90.8% yield) of product that was deemed sufficiently pure to be used in the next step of the reaction sequence.

Preparation of 2-(2-carboxyethyl)isoquinolin-2-ium bromide (24)



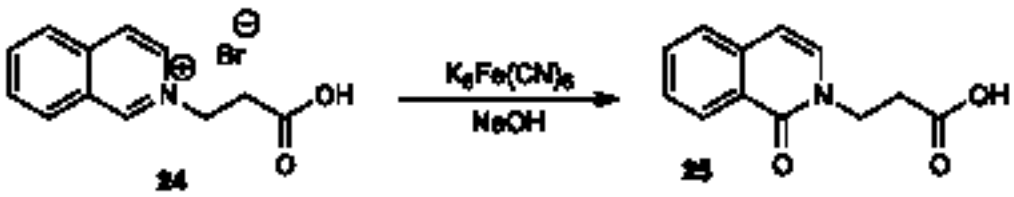
Isoquinoline (0.64 g, 4.96 mmol) and 3-bromopropionic acid (0.76 g, 4.97 mmol) were combined in a 50-mL round-bottom flask with 4 mL of THF. A white precipitate began to form almost immediately. After 24 hours, the product had coated the wall of the flask. Rotary evaporation was used to remove the THF. The product (1.25 g, 89.4% yield) was confirmed by NMR analysis and determined to be pure enough for use in the next step.

Preparation of 3-(1-oxoisoquinolin-2(1*H*)-yl)propanoic acid (25)



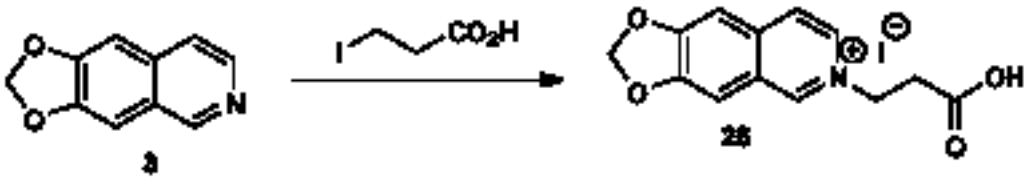
A solution of **23** (1.87 g, 5.68 mmol) in 11 mL of deionized water was prepared in a 50-mL round-bottom flask and cooled to 0 °C in an ice bath. Then a solution of 2.30 g (6.99 mmol) of $K_3Fe(CN)_6$ in 10 mL of DI water was added in a single portion to the flask. Next, a solution of 0.85 g (21.2 mmol) of NaOH in 8 mL of DI water was added dropwise over a 15 minute period with an addition funnel, making sure that the internal temperature never exceeded 20 °C. The flask was then allowed to return to room temperature and the reaction mixture was stirred for 18 hrs, open to the atmosphere, during which time the solution became red-brown in color. The mixture was acidified by the addition of 6 M HCl, causing the solution to become brown and turbid. The product was then extracted with CH_2Cl_2 (3 x 20 mL) and the organic layer was dried over Na_2SO_4 before being concentrated by rotary evaporation. After removal of residual solvent at high vacuum, the reaction gave 1.17 g of **25** (95.1 % yield). The product was determined to be adequately pure for use in further steps by NMR analysis.

Preparation of 3-(1-oxoisoquinolin-2(1*H*)-yl)propanoic acid (25)



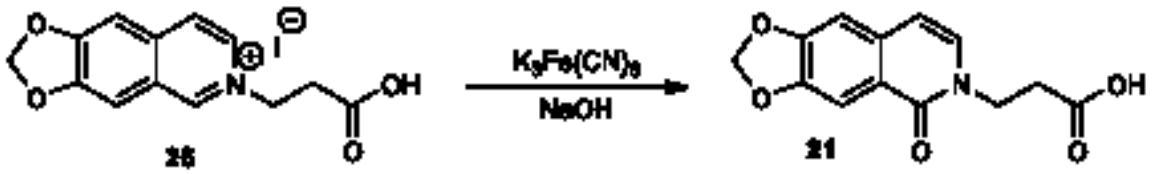
A solution of **24** (1.60 g, 5.69 mmol) in 11 mL of deionized water was prepared in a 50-mL round-bottom flask and cooled to 0 °C in an ice bath. Then a solution of 2.30 g (6.99 mmol) of $K_3Fe(CN)_6$ in 10 mL of DI water was added in a single portion to the flask. Next, a solution of 0.85 g (21.2 mmol) of NaOH in 8 mL of DI water was added dropwise over a 15 minute period with an addition funnel, making sure that the internal temperature never exceeded 20 °C. The flask was then allowed to return to room temperature and the reaction mixture was stirred for 18 hrs, open to the atmosphere, during which time the solution became red-brown in color. The mixture was acidified by the addition of 6 M HCl, causing the solution to become brown and turbid. The product was then extracted with CH_2Cl_2 (3 x 20 mL) and the organic layer was dried over Na_2SO_4 before being concentrated by rotary evaporation. After removal of residual solvent at high vacuum, the reaction gave 1.17 g of **25** (94.8% yield) that was determined to be pure enough for further use by NMR analysis.

Preparation of 6-(2-carboxyethyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium iodide (26)



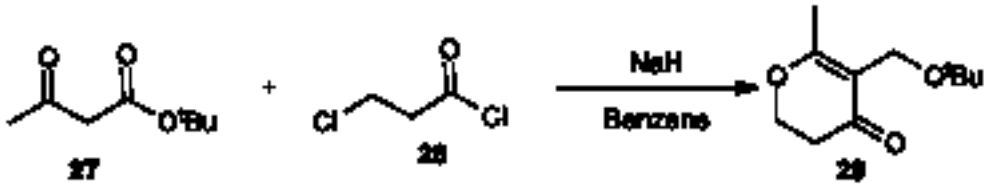
A solution of the starting material **3** (0.866 g, 5.00 mmol) and 3-iodopropionic acid (1.00 g, 5.00 mmol) in 5 mL of THF was prepared in a 50-mL round-bottom flask. The orange reaction mixture stirred overnight, giving a tan precipitate that coated the wall of the flask. The solvent was removed by rotary evaporation, and the product (1.76 g, 94.4%) was confirmed by ^{1}H NMR analysis.

Preparation of 3-(5-oxo-[1,3]dioxolo[4,5-*g*]isoquinolin-6(5*H*)-yl)propanoic acid (21)



A solution of **26** (1.87 g, 5.01 mmol) in 11 mL of deionized water was prepared in a 50-mL round-bottom flask and cooled to 0 °C in an ice bath. Then a solution of 2.30 g (6.99 mmol) of $K_3Fe(CN)_6$ in 10 mL of DI water was added all at once. Next, a solution of 0.85 g (21.2 mmol) of NaOH in 8 mL of DI water was added dropwise to the reaction mixture via an addition funnel, making sure that the solution never exceeded 20 °C. The solution was allowed to stir at room temperature overnight, open to the atmosphere, during which time the solution became bright yellow in color. The mixture was acidified by the addition of 6 M HCl, which caused the solution to become dark brown and the precipitation of a solid. This solid product was isolated by vacuum filtration, washed with CH_2Cl_2, and placed under vacuum to remove residual solvent. The reaction gave 1.15 g (87.8% yield) of **21** that was confirmed to be pure by NMR analysis.

Preparation of 5-(*tert*-butoxymethyl)-6-methyl-2*H*-pyran-4(3*H*)-one[19]



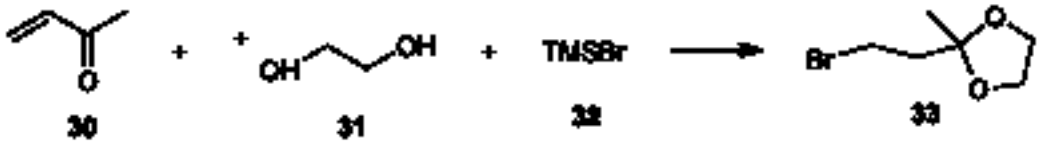
Tert-Butyl acetoacetate (6.3 mL, 6.0 g, 0.038 mol) in 50 mL benzene was added over 30 minutes to 1.65 g (0.069 mol) of oil-free sodium (prepared from 2.75 g of a 60%

dispersion of NaH in mineral oil) in 100 mL of benzene. The mixture was stirred for 2 hours under a nitrogen atmosphere. The resulting mixture was a gray slurry.

A solution of 4.0 mL of 3-chloropropionyl chloride (5.3 g, 0.042 mol) in 50 mL of benzene was added to the above mixture over a 30 minute period, causing the solution to become bright yellow and clear. The mixture was then stirred under nitrogen for 18 hours. Glacial acetic acid (2.4 mL) was added to quench the reaction and the resulting solution was washed with brine and dried over Na_2SO_4 before removal of solvent by rotary evaporation. The crude product (6.14 g of bright yellow oil) was analyzed by NMR analysis: ^{1}H NMR δ 1.53 (9H, s); 2.17 (3H, s); 2.59 (2H, t, J = 6.9 Hz); 4.48 (2H, t, J = 6.9 Hz). ^{13}C NMR δ 19.9, 28.1, 35.4, 67.6, 81.7, 114.6, 164.7, 175.3, and 187.7 ppm.

It was clear from the NMR spectra that the expected product from acylation of the anion from deprotonation of *tert*-butyl acetoacetate was not produced in this reaction.

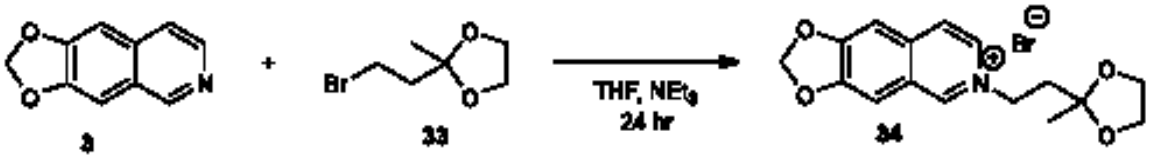
Synthesis of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (33)[20]



A solution of methyl vinyl ketone (2.03 mL, 1.75 g, 25.0 mmol) and ethylene glycol (5.6 mL, 6.33 g, 102 mmol) was cooled to 0 °C under a nitrogen atmosphere, and TMSBr (3.80 mL, 4.41 g, 28.8 mmol) was added via syringe. The reaction mixture was returned to room temperature and allowed to stir for 2 hours. The solution was then poured into a mixture of hexane (50 mL) and 5% sodium bicarbonate (25 mL) with vigorous stirring for 5 minutes. The top organic layer was then washed with 5% sodium

thiosulfate in a separatory funnel before drying over potassium carbonate. The solvent was removed by rotary evaporation and the crude product was confirmed by proton NMR analysis. Purification by vacuum line transfer at 0.05 mm Hg gave 2.80 g (57.4%) of **33** that was used in the subsequent step.

Synthesis of 6-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium bromide

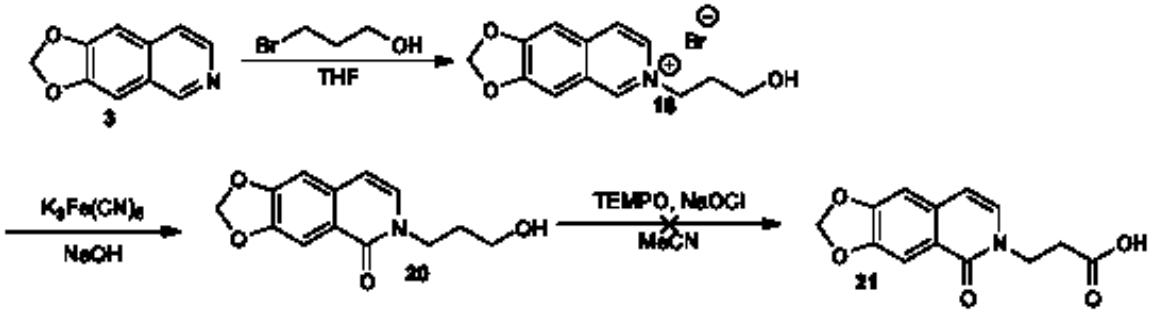


Equimolar amounts of the isoquinoline **3** (0.44 g, 2.55 mmol) and the ketal **33** (0.50 g, 2.55 mmol) were combined in a round-bottom flask with 2 mL of THF and a catalytic amount of triethylamine. The mixture was allowed to stir overnight, producing a tan precipitate that coated the flask. Rotary evaporation was used to isolate the product, and residual solvent was removed under vacuum. NMR analysis, however, showed that the desired product was not obtained, but rather a mixture of the two starting materials.

DISCUSSION AND CONCLUSION

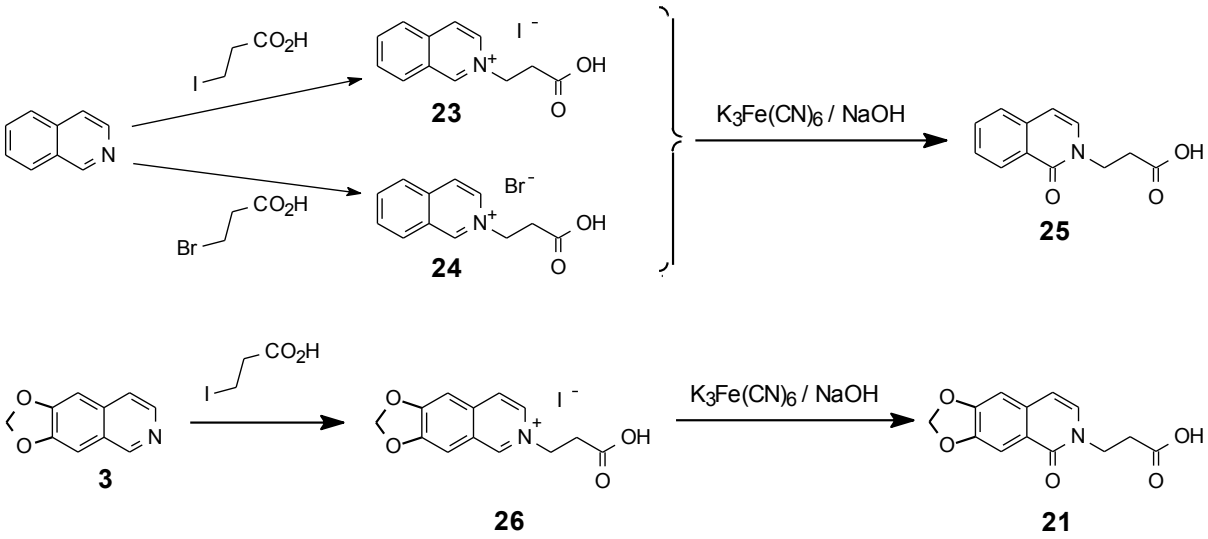
The isoquinoline **3** (Scheme 5) had previously been synthesized in our lab and was used as the starting material. This compound is also commercially available, but the procedure developed in our lab provided a reproducible route to **3** at a fraction of the cost of the commercial material.

The original synthetic plan called for the alkylation of **3** to form the salt **18** using 3-bromo-1-propanol as the alkylating agent (Scheme 5). Several attempts to oxidize the primary alcohol in **18** to the acid function failed for no apparent reason. However, the salt **18** was oxidized successfully to the isocarbostyril **20**. Unfortunately, the oxidation of **20** to the carboxylic acid **21** also failed. A number of new oxidation methods were attempted including a free radical oxidation using TEMPO, an MPHT oxidation, and two variants of the PCC oxidation. All of these resulted only in decomposition of the starting material.



Scheme 5. Attempts to prepare 21 by oxidation[21]

Since **21** was apparently unavailable via oxidation of the primary alcohol in both **18** and **20**, a new strategy to avoid this step by using 3-halopropionic acids for alkylation of **3** was explored (see Scheme 6). In a model study, both 3-iodopropionic acid and 3-bromopropionic were found to react favorably with isoquinoline to give the salts **23** and **24**, respectively. A better yield was achieved with the iodide, which has a better leaving group. Both of the alkylated isoquinolines were then oxidized to **25** using the standard reaction with NaOH and $K_3Fe(CN)_6$. This sequence was then carried out using **3** as the starting material to give **26** and **21** in 83% overall yield through 2 steps.



Scheme 6. Summary of Alkylations and Oxidations on isoquinoline and derivative

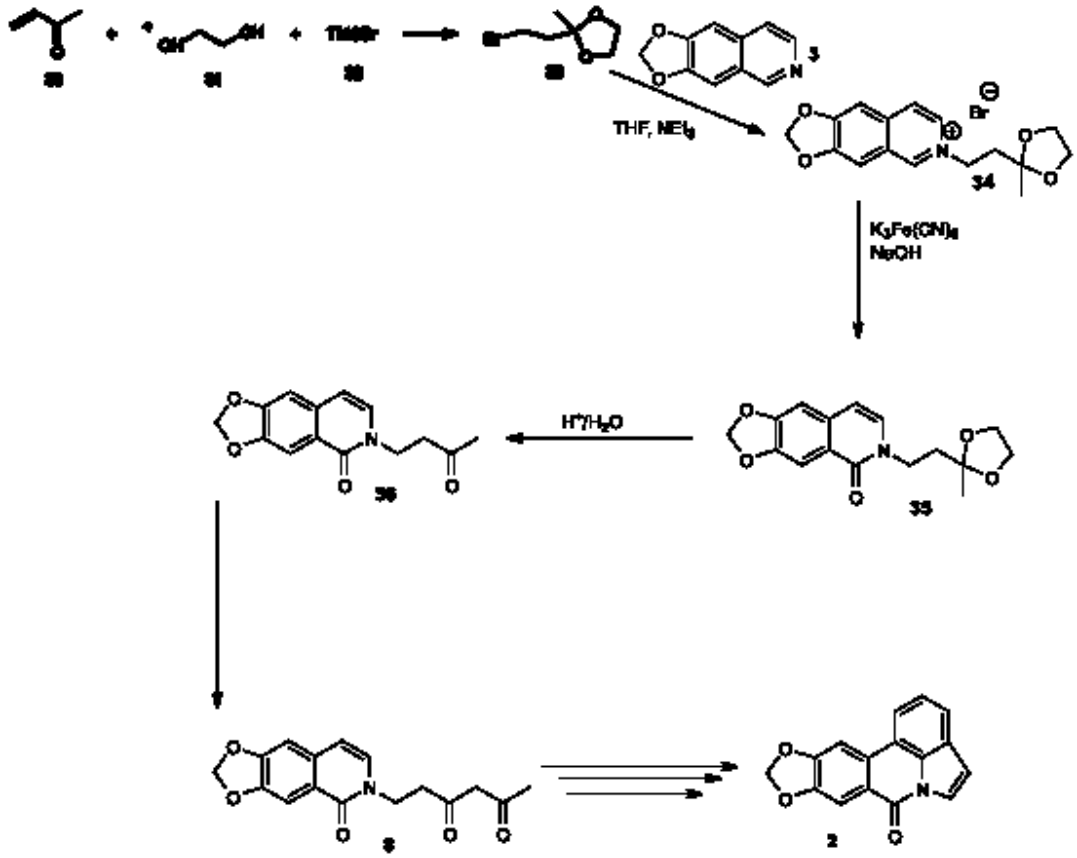
At this point, it appeared that the last obstacle in the original synthetic proposal (Scheme 4) had been overcome. However, a new problem arose in the conversion of **21** to the corresponding acid chloride which was required for the acylation of the anion from deprotonation of *t*-butyl acetoacetate. Apparently, the addition of the methylenedioxy subunit in **21** caused a substantial decrease in solubility such that none of the solvents suitable for converting acids to acid chlorides were usable. It was clear that a revised pathway was required in order to avoid the use of acid **21** altogether.

The first plan involved a convergent approach whereby the alkylating agent for converting **3** to a salt would contain the entire six-carbon nitrogen tether group with the β-diketone unit intact. Toward that end, 3-chloropropionyl chloride was allowed to react with the anion from deprotonation of t-butyl acetoacetate. However, an unexpected intramolecular cyclization reaction took place to produce **29** (see Experimental Section).

Finally, a new plan outlined in Scheme 7 was formulated to use a methyl ketone instead of the carboxylic acid to create the six-carbon nitrogen tether group in compound

8. The key intermediate in this synthesis is **36**, which may be created by using the ketal **33** as an alkylating agent. The reaction of methyl vinyl ketone with ethylene glycol and bromotrimethylsilane gave the expected ketal **33** in 57% yield. Next, **33** was used as an alkylating agent for isoquinoline **3**, which failed to produce the salt **34**.

The project rests currently at this stage. The next step in the synthesis will be to exchange the bromine on the ketal with an iodine via a Finkelstein reaction, rendering the molecule more susceptible to nucleophilic attack, forming the salt **34**. After alkylating the isoquinoline **3,** the ketal protecting group on **35** will be removed and the methyl ketone **36** will be used to synthesize **8** via one of several possible reactions involving enolate chemistry. Work on the synthesis will then proceed from **8** as planned in the original proposal (Scheme 4).



Scheme 7. Alternate Approach to Hippadine

Work will continue on the synthesis of the molecule, with possible patent applications once finished. The synthesis will hopefully provide a suitable pathway to produce Hippadine in good yield without costly reagents, allowing for more detailed study of the therapeutic applications of the alkaloid.

LIST OF REFERENCES

(1) Boger, D. L; Wolkenberg, S. E. *J. Org. Chem.* **2000**, 65, 9120-9124.

(2) Chattopadhyay, S.; Chattophadhyay, U.; Marthur, P. P.; Saini, K. S.; Ghosal, S. *Planta Med.* **1983,** 49, 252.

(3) Unny, R.; Chauhan, A.K.; Joshi, Y.C.; Dobhal, M.P.; Gupta, R.S. *Phytomedicine.* **2003,** 10, 233-260.

(4) Mugabo, P.; Obikeze, K.C.; Njagi, A.; Burger, A.P.; Green, I.; Dietrich, D.D. *Int. J. Med. Arom. Plants.* **2012,** 2, 172-177.

(5) Queckenberg, O.R.; Frahm, A.W.; Mueller-Doblies, D.; Mueller-Doblies, U. *Phytochemical Analysis.* **1996**, 7, 156-160.

(6) Umemoto, H.; Doshita, M.; Hamamoto, H.; Miki, Y. *Heterocycles.* **2011,** 83, 1111-1119.

(7) Knoelker, H.J.; Filali, S. *Synlett.* **2003,** 11, 1752-1754.

(8) Ganton, M.D.; Kerr, M.A. *Org. Lett.* **2005,** 7, 21, 4777-4779.

(9) Minter, D.; Winslow, C.D. *J. Org. Chem.* **2004,** 69, 1603-1606.

(10) Popp, F.D.; McEwen, W.E., *J. Am. Chem. Soc.* **1957**, 79, 3773.

(11) Birch, A.J.; Jackson, A.H.; Shannon, P.V.R.; Varma, P.S.P..*Tetrahedron.* **1972**, 4789.

(12) Miller, R.B.; Frincke, J.M., *J. Org. Chem.* **1980**, 45, 5312.

(13) Corey, E.J.; Suggs, W.; *Tetrahedron.* **1975,** 31, 2647-2650.

(14) Elpern, B.; Hamilton, C.S. *J. Am. Chem. Soc.* **1946**, 68, 1436.

(15) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, 68, 4999-5001.

(16) Bekaert, A.; Provot, O.; Rasolojaona, O.; Alami, M.; B, J-D. *Tet. Lett.* **2005**, 46, 4187-4191.

(17) Joseph, J.K.; Jain, S.L.; Sain, B. *Eur. J. Org. Chem.* **2006**, 590-594.

(18) Nieuwenhuizen, M. M.L.; de Greef, T. F. A.; van der Bruggen, R. L. J.; Paulusse, J. M. J.; Appel, W. P. J.; Smulders, M. M. J.; Sijbesma, R. P.; Meijer, E. W. *Chem. Eur. J.* **2010**, 16, 1601-1612.

(19) Meyer, W.L.; Clemans, G.B.; Manning, R.A. *J. Org. Chem.* **1975**, 40 (25), 3686-3694.

(20) Surendra, S.; Guiry, P.J. *J. Org. Chem.* **2009**, 74 (15), 5758-5761.

(21) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschen, D. M.; Grabowski, E. J. J.; Reider, P.J. *J. Org. Chem.* **1999**, 64, 2564- 2566.

ABSTRACT

Hippadine, a lycorine-type alkaloid isolated from several plants of the family Amaryllidaceae, contains an interesting pentacyclic skeleton, specifically the aromatic pyrrolophenanthridinone core. This molecule has shown myriad biological activity including reversible inhibition of spermatogenesis in rats and the ability to alter several cardiac functions. Previous syntheses of Hippadine have focused on a late-stage formation of the C-ring, often catalyzed by palladium. However, our synthesis begins with a molecule that already contains the A, B, and C rings intact. Alkylation of nitrogen in the starting material affords a functionalized tether on nitrogen that can be used to induce formation of the E ring via an unusual intramolecular de Mayo reaction. A simple aldol addition then closes the ring system. Our current work includes high-yielding constructions of several of the intermediates in this new synthetic pathway toward Hippadine and some potentially useful improvements and modifications designed to replace reactions that require costly organometallic materials.