PHENANTHRIDONE ALKALOIDS VIA FUNCTIONALIZATION OF 2-BENZYL-6(5*H*)-PHENANTHRIDINONE

by

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Abstract

Phenanthridone alkaloids, derived from the *Amaryllidiceae* family of tropical plants, are a group of natural products that have been shown to exhibit biological activity. In recent decades, this group of alkaloids has sparked interest due to their antibiotic, anticancer, and immunosuppressant properties. Because of their limited natural availability, pharmaceutically-active compounds require laboratory syntheses to provide sufficient quantities for testing. Previous work in this laboratory has provided a general method for constructing the phenanthridinone skeleton from homophthalic acid in high yields. In this research project, our work involves the reproduction of these results as well as establishing a general method for functionalization of the non-conjugated alkene in the phenanthridinone skeleton. This research provides the basis for future syntheses of complex alkaloids that show promise in the development of pharmaceutically-active compounds.

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Introduction

In the field of biological research, many natural products have been studied extensively for their application in animal systems as a means of treating various diseases or eliciting other physiological activity. In recent decades, there has been an increased attraction towards phenanthridone alkaloids for their pharmaceutical relevance, particularly in the area of cancer research. Phenanthridone alkaloids are a branch of natural products derived from the *Amaryllidaceae* family of tropical plants and have been shown to exhibit a wide array of biological properties. The general tricyclic skeleton shown in Figure 1 is a substructure in this group of alkaloids. All carbon centers and rings are labeled in the figure. Over the next few pages, the structures, properties and past syntheses of some notable phenanthridone alkaloids will be discussed. Following this, a research plan for synthesizing some target molecules will be introduced.

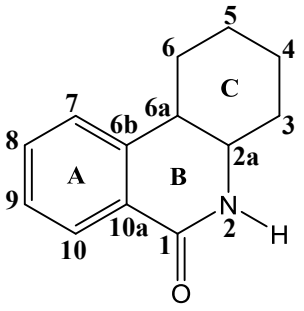

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Figure 1: The General Phenanthridinone Skeleton

Structure and Activity of Notable Phenanthridone Alkaloids

The phenanthridone alkaloid lycoricidine, which is of particular interest to this research, is a member of the *Amaryllidaceae* family of alkaloids. It was first isolated in 1968 in trace amounts from *Lycoris radiate*.[1] Its biological activity includes potent growth-inhibitory action against a variety of human cancer cell lines at nanomolar concentrations[2] and anti-flavivirus

properties.[3] Lycoricidine has the tricyclic core that is characteristic of phenanthridone alkaloids and an additional ring as illustrated in Figure 2. It also contains four carbon stereocenters of interest (C-2a, C-3, C-4, and C-5). The stereospecific hydroxyl groups located on the C-ring are of particular importance as they are found in the same configuration among other biologically-active *Amaryllidaceae* alkaloids.

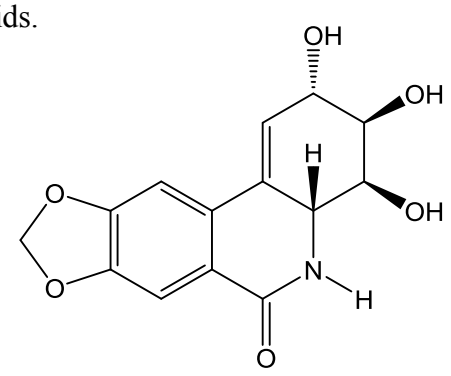

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Figure 2: Structure of Lycoricidine

An important structural analog of lycoricidine that has been studied extensively for its functionality in various biological systems is the compound narciclasine. Shown in Figure 3, it can be observed that narciclasine possesses the characteristic tricyclic phenanthridinone core as well as the same chirality in the C-ring as found in lycoricidine. However, unlike lycoricidine, narciclasine contains a hydroxyl group at C-10.

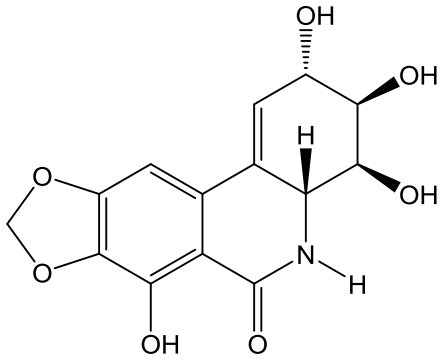

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Figure 3: Structure of Narciclasine

In terms of its biological properties, narciclasine is a potent inhibitor of the human cytochrome CYP3A4. Human cytochrome CYP3A4 is a member of the cytochrome P450 system that plays a crucial role in drug metabolism within our hepatic cells.[4] Drug-enzymatic interactions have been a popular area of pharmaceutical research in recent decades and thus highlights the relevance of narciclasine as another phenanthridone alkaloid of interest, particularly in the realm of cancer treatment as a means of potentiating drug therapy. Interestingly, certain phenanthridone analogs of narciclasine, such as *trans*-dihydronarciclasine (which lacks a double bond between C-6 and C-6a), do not have the same potent inhibitory effects.[5] This suggests that the C-ring double bond, in conjunction with the stereospecific hydroxyl groups, plays a critical role in cytochrome CYP3A4 interactions.

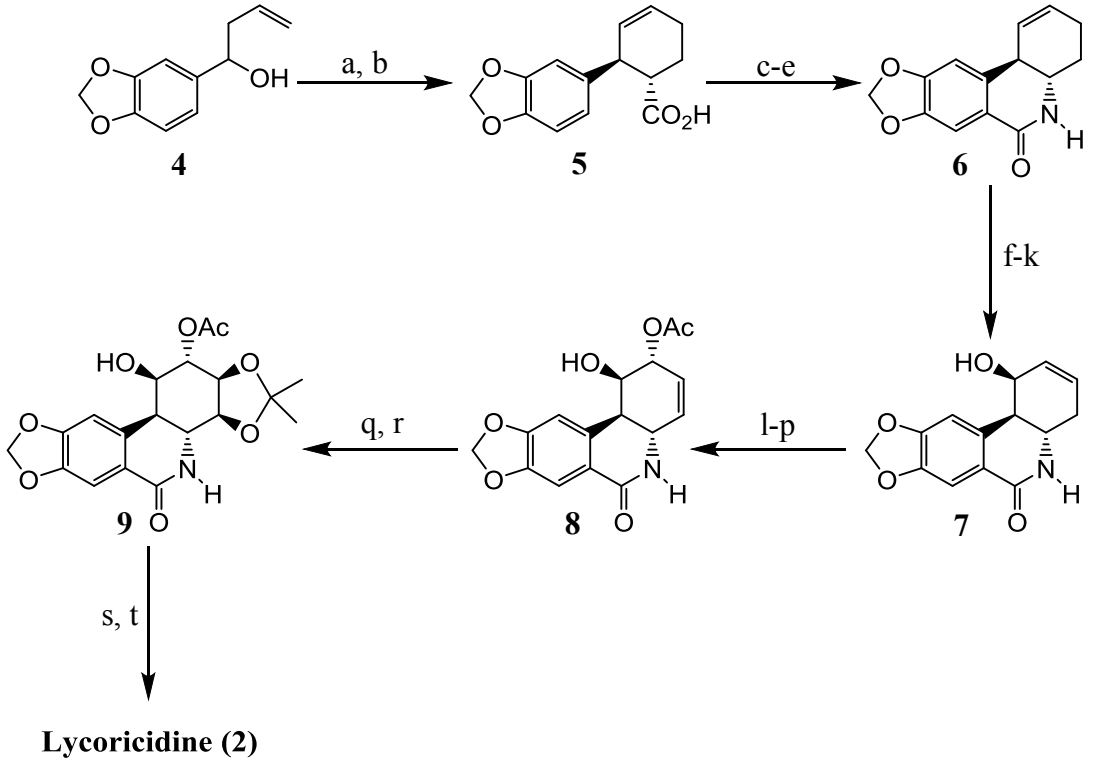
Similar to lycoricidine, narciclasine has demonstrated potent anti-cancer properties in human cell cultures as well. In an *in vitro* analysis against sixty different human cancer cell lines as well as a P338 murine leukemia cell line, Pettit et al. found similar potent cytotoxicity profiles of narciclasine and various structurally-related analogs.[6]

Previous Synthetic Approaches to Phenanthridone Alkaloids

As mentioned, phenanthridone natural products are ubiquitous among members of the *Amaryllidaceae* plant family. Unfortunately, the biosynthetic routes to these products are largely unknown. Nevertheless, laboratory syntheses provide efficient methods for obtaining these target alkaloids. In recent decades, there have been many diverse approaches to synthesizing phenanthridone compounds such as lycoricidine and narciclasine as outlined below.

a. Previous Syntheses of Lycoricidine.

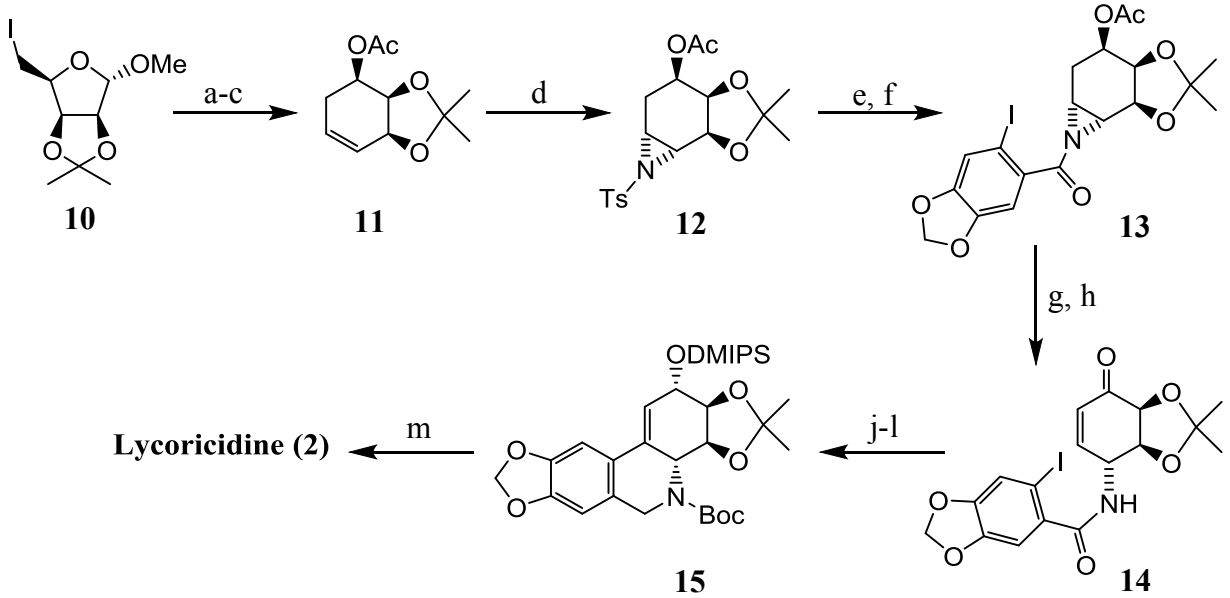
The total synthesis of lycoricidine is not a particularly new endeavor. Various attempts have been made in the past few decades at constructing the alkaloid, resulting in both racemic as well as enantioselective syntheses. The first racemic synthesis of lycoricidine was performed by Ohta and Kimoto in 1975.[7] Shown in Scheme 1, this A→C→B-ring synthesis begins with a Diels-Alder reaction between the allylic alcohol **4** and ethyl acrylate, followed by hydrolysis, to yield **5**. Following this, a Curtius rearrangement and electrophilic cyclization yielded **6**, forming the B-ring. Subsequent steps involved the functionalization of the C-ring to produce the stereospecific hydroxyl groups and successive elimination of the hydroxyl group at C-6 to produce lycoricidine.



Scheme 1: Ohta and Kimoto's Synthesis of Lycoricidine[7]

Reaction conditions: (a) ethyl acrylate, TsOH, 56%; (b) (i) NaOEt, EtOH, (ii) H_2O; 74%; (c) $ClCO_2Et$, Et_3N, acetone, H_2O, 42%; (d) (i) NaN_3, H_2O; (ii) toluene, reflux; (e) BF_3*Et_2O; 89%; (f) Ac_2O, pyridine, 83%; (g) KOH, EtOH, 68%; (h) NBS, THF, 96%; (j) DBU, pyridine, 98%; (k) NaOH, EtOH, 90%; (l) DHP, TsOH, 75%; (m) *m*CPBA, $CHCl_3$, 85%; (n) (i) $(PhSe)_2$, $NaBH_4$; (ii) H_2O_2; 63%; (o) Ac_2O, pyridine, 97%; (p) TsOH, AcOH, MeOH, 59%; (q) OsO_4, pyridine, 87%; (r) 2,2-DMP, DMF, 84%, (s) $SOCl_2$, pyridine, 58%; (t) TsOH, $CHCl_3$, CH_3OH, H_2O.

Since this original approach, many recent syntheses toward lycoricidine have been conducted from various starting materials, including the use of chemoenzymatic techniques.[8] The most recent synthesis, performed by Yadav et al. in 2009, began with the generation of the iodoglycoside **10** from D-(+)-mannose in a five-step process.[9] Following this, successive allylation, ring-closing metathesis using the 1st Generation Grubbs' catalyst, and acetylation yielded the cyclohexenol derivative **11**. From here, the aziridine **12** was generated and condensed with 6-iodopiperonylic acid to yield **13**. Subsequent Dess-Martin periodinane oxidation yielded the unexpected *α,β*-unsaturated ketone **14**. Finally, successive protection, cyclization through Heck coupling, and deprotection generated the natural lycoricidine enantiomer. The entire synthesis is outlined in Scheme 2.

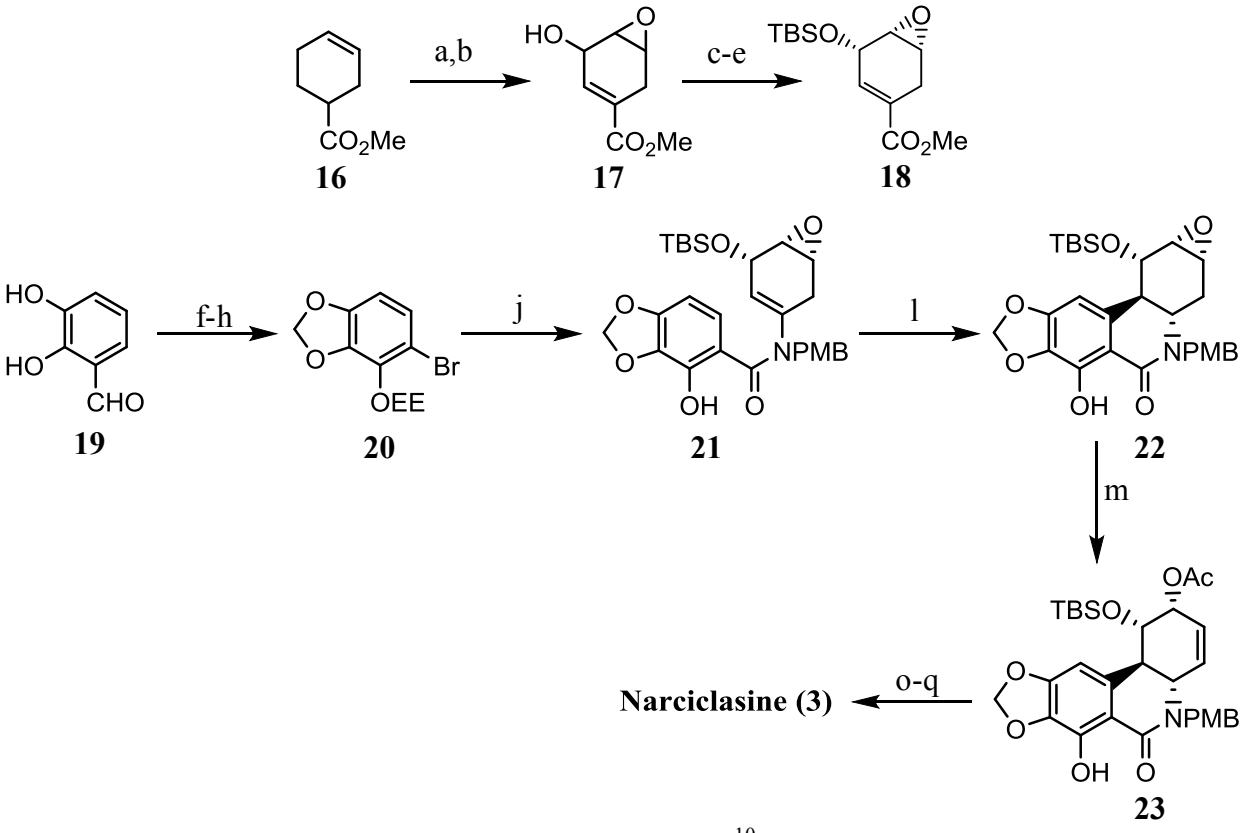


Scheme 2: Yadav's Synthesis of Lycoricidine[9]

Reaction conditions: (a) allyl bromide, Zn, THF, H_2O, 85%; (b) 1st Gen. Grubbs, CH_2Cl_2, 84%; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 92%; (d) PhINTs, $Cu(acac)_2$, MeCN, 52%; (e) Na/napthalenide, DME, 67%; (f) 6-iodopiperonylic acid, EDCl, CH_2Cl_2, Et_3N, 85%; (g) K_2CO_3, MeOH, 92%; (h) (i) DMP, CH_2Cl_2; (ii) silica gel; 82%; (j) (i) $CeCl_3$, $NaBH_4$, MeOH; (ii) imidazole, DMIPSCl, CH_2Cl_2, 90%; (k) Boc_2O, DMAP, Et_3N, MeCN, 95%; (l) $Pd(OAc)_2$, $Tl(OAc)_2$, dppe, anisole, 35%; (m) HCOOH, THF, H_2O, 95%.

b. Previous Syntheses of Narciclasine.

As is the case of lycoricidine, the synthesis of narciclasine has also been performed by various research groups in recent decades. The first reported total enantioselective synthesis was performed by Rigby and Mateo in 1997.[10] Interestingly, this procedure reports the use of a hydrogen-bond-direct aryl enamide photocyclization to construct the B-ring. The synthesis begins with the generation of the *syn*-epoxyalcohol **17** from the starting cyclohexene carboxylic acid **16**. This was subsequently protected, thus forming the necessary C-ring fragment **18**. The A-ring fragment was constructed from 2,3-dihydroxybenzaldehyde by its conversion to the protected compound **20** which, after generating the organometallic lithium intermediate, was condensed with **18** to yield **21**. Subsequent photocyclization formed the phenanthridone framework. Successive deprotection and functionalization of the C-ring produced the natural enantiomer of narciclasine. This synthesis is illustrated below in Scheme 3.



Scheme 3: Rigby and Mateo's Synthesis of Narciclasine[10]

Reaction Conditions: (a) NBS, AIBN, *n*Bu_3SnH, 75%; (b) (i) O_2. rose Bengal, hυ; (ii) $RuCl_2(PPh_3)_2$, CH_2Cl_2; (iii) NaOMe, MeOH; 42%; (c) (i) *n*PrCOCl, Et_3N; (ii) cholesterol esterase, 40%; (d) (i) TBSCl, imidazole, 52%; (ii) LiOH, MeOH, H_2O, 42%; (e) (i) DPPA, Et_3N, benzene; (ii) PhMe, reflux; (f) CH_2Br_2, K_2CO_3, DMF, 84%; (g) (i) *m*CPBA; (ii) KOH, EtOH, 63%; (h) (i) CF_3CO_2Ag, Br_2; (ii) EVE, PPTS; 85%; (j) (i) *n*BuLi, THF; (ii) **23**; 52%; (k) (i) PMBBr, NaH; (ii) PPTS, MeOH; 76%; (l) hυ, benzene, 46%; (m) (i) $(PhSe)_2$, $NaBH_4$; (ii) H_2O_2; (iii) AcCl, NaH; 48%; (o) (i) OsO_4, NMO, *t*BuOH; (ii) 2,2-DMP, TsOH; 76%; (p) (i) TBAF, THF; (ii) Burgess reagent, benzene; 64%; (q) (i) K_2CO_3, MeOH,; (ii) *n*BuLi, THF, O_2; (iii) TsOH; 37%.

In each of the syntheses used to construct the phenanthridinone skeleton, there are two common motifs worth mentioning. First, each of the above approaches as well as many other syntheses not covered in this review construct the tricyclic system using an A→C→B-ring sequence. In other words, the A and C rings are introduced into the structure first followed by late-stage formation of the B ring.

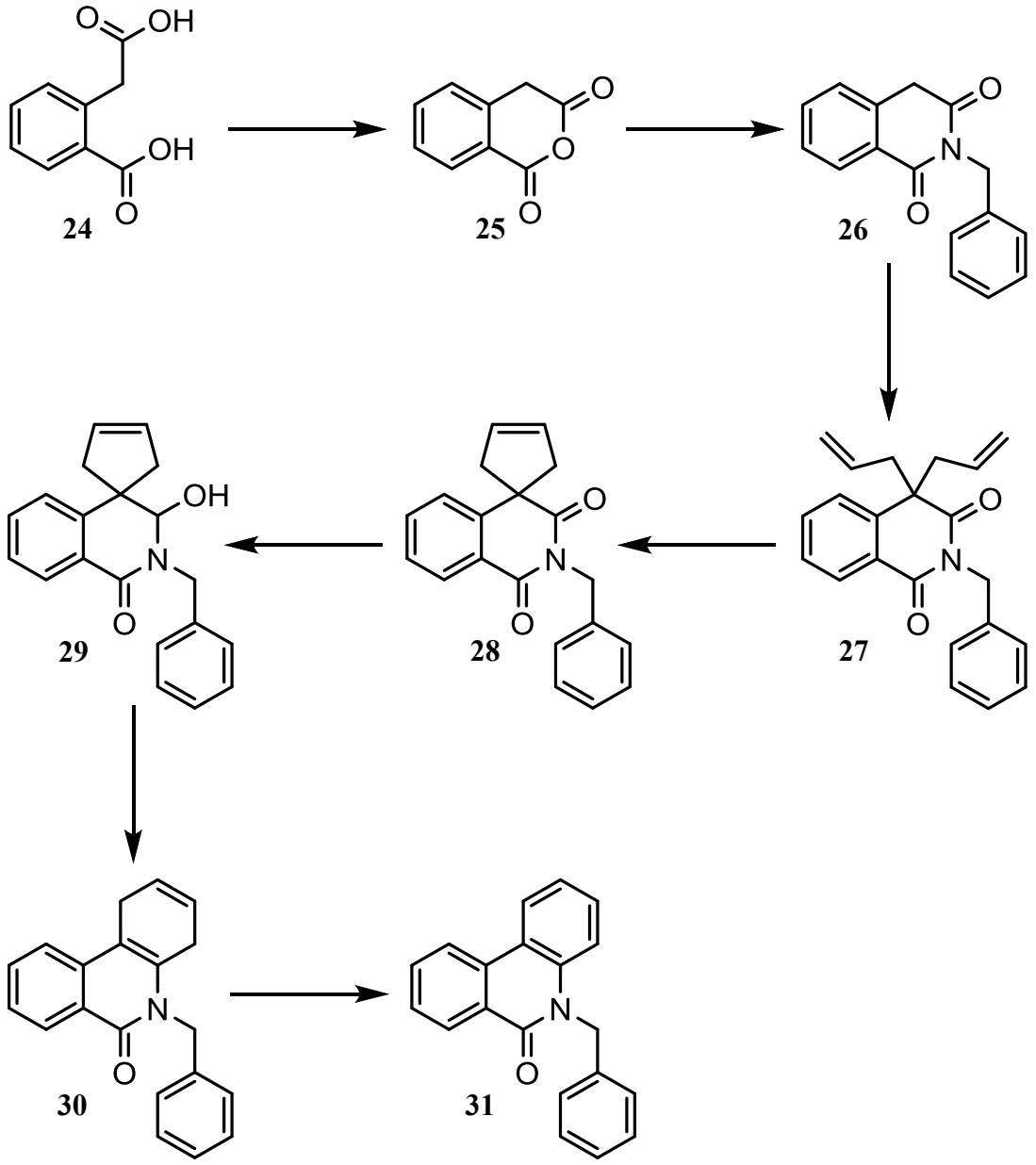
The second motif common to each of these syntheses, and perhaps even more relevant to the future of this research project, is the stereospecific functionalization of the C-ring to construct lycoricidine and its related analogs. As mentioned earlier, the importance of this specific stereochemistry in the C-ring stems from its selective biological activity within cellular environments. Furthermore, the production of unnatural phenanthridone analogs with variant C-ring substituents and chiralities will lay the basis for future pharmaceutical testing.

Current Approach to Synthesizing the Phenanthridinone Skeleton

In this research project, we propose a novel production of the phenanthridinone skeleton using a general model system. This methodology involves a fundamentally new route to the tricyclic system (Figure 1) using an A→B→C-ring sequence in which the C-ring is constructed last. This approach has the advantage of avoiding by-products during formation of the B-ring when an unsymmetrical substituent pattern is present on the A-ring.

As shown in Scheme 4, the proposed synthesis begins with generation of the B-ring by cyclization of the two carboxylic acid functional groups on homophthalic acid (**24**) to give homophthalic anhydride (**25**). Subsequent heating of **25** with benzylamine (**32**) produces the protected imide **26**. This benzyl protecting group prevents further reactivity of the nitrogen at the 2 position and enables further functionalization of the molecule. Following this, the allylation of **26** to give **27** provides the substituents required for production of the C-ring. This will be achieved by a remarkable ring-closing metathesis reaction using the 2nd Generation Grubbs' catalyst (**34**) to afford the cyclopentene ring on compound **28**. Sequential reduction of the C-4 carbonyl group and ring-expansion yields the tricyclic product **30**. Following this, aromatization

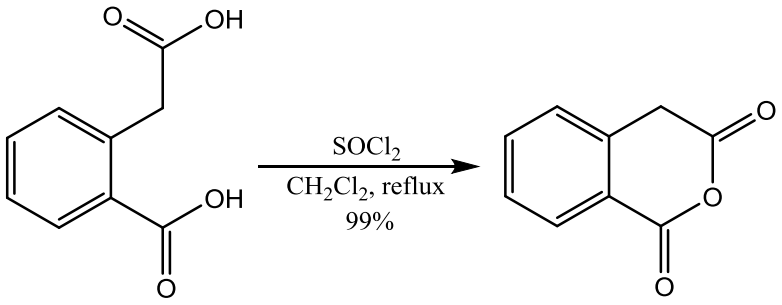
of the C-ring will yield 2-benzyl-6(5*H*)-phenanthridinone (**31**), the target model system of this research project. Through this general methodology, our aim is to develop a novel synthetic pathway that allows for versatility in producing various natural alkaloids such as lycoricidine, narciclasine and a number of other pharmaceutically-active natural compounds derived from the *Amaryllidaceae* family of plants.



Scheme 4: Proposed Novel Synthesis of the Phenanthridinone Skeleton

Experimental Section

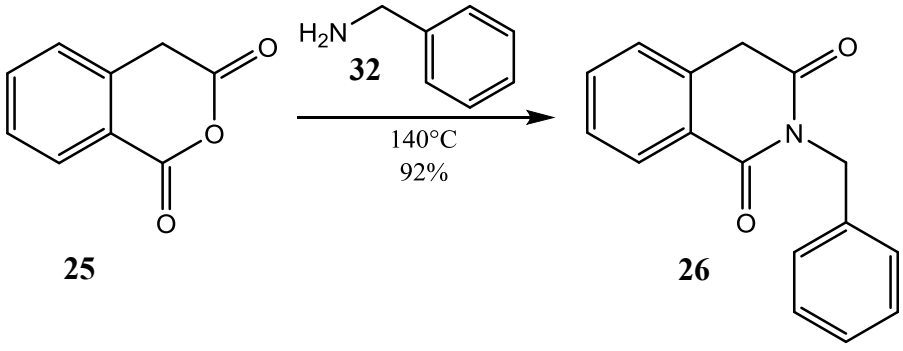
Preparation of homophthalic anhydride



24 **25**

Homophthalic acid **(**12.70 g, 70.5 mmol) was dissolved in 200 mL of dichloromethane. Thionyl chloride (10 mL, 16.4 g, 138 mmol) was added. The mixture was then heated at reflux under a nitrogen atmosphere for 3 days resulting in an amber solution. The solvents were removed by simple distillation to give a yellow-orange residue. Residual volatiles were removed by rotary evaporation to give 11.38 grams (99%) of **25** that was shown to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (dd, J = 7.9, 0.8 Hz, 1H), 7.72 (td, J = 7.6, 1.3 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 4.17 (s, 2H).

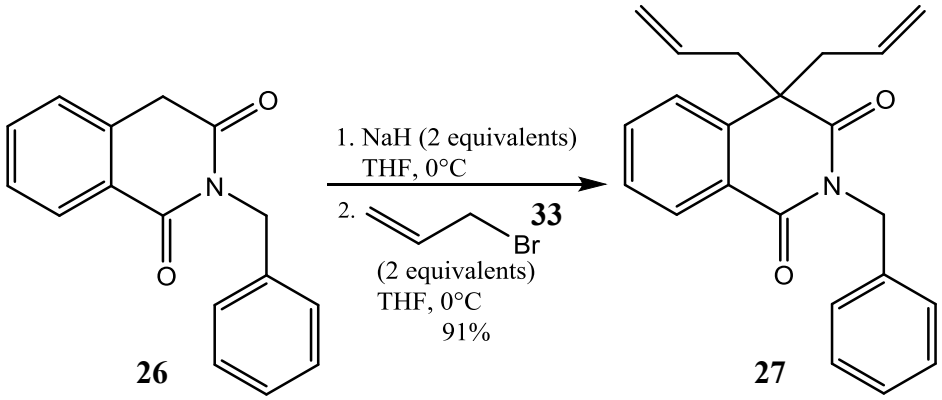
Preparation of 2-benzyl-1,3(2*H*,4*H*)-isoquinolinedione



25 **26**

Benzylamine (7.52 g, 70.2 mmol) and homophthalic anhydride (11.38 g, 70.2 mmol) were mixed in a 250-mL round-bottom flask. Upon addition of the benzylamine, gas evolution and the deposition of a white precipitate occurred. The mixture was heated at 140 °C for 50 minutes during which the mixture became a dark, brown oil. Following the heating period, a brown, gummy solid began to harden as it cooled in the flask. This solid was recrystallized in a 1:1 mixture of petroleum ether and ethyl acetate to yield 16.21 grams of orange-brown solid that proved to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (dd, J = 7.9, 1.0 Hz, 1H), 7.59 (td, J = 7.5, 1.4 Hz, 1H), 7.50-7.43 (m, 3H), 7.34-7.27 (m, 4H), 5.21 (s, 2H), 4.09 (s, 2H).

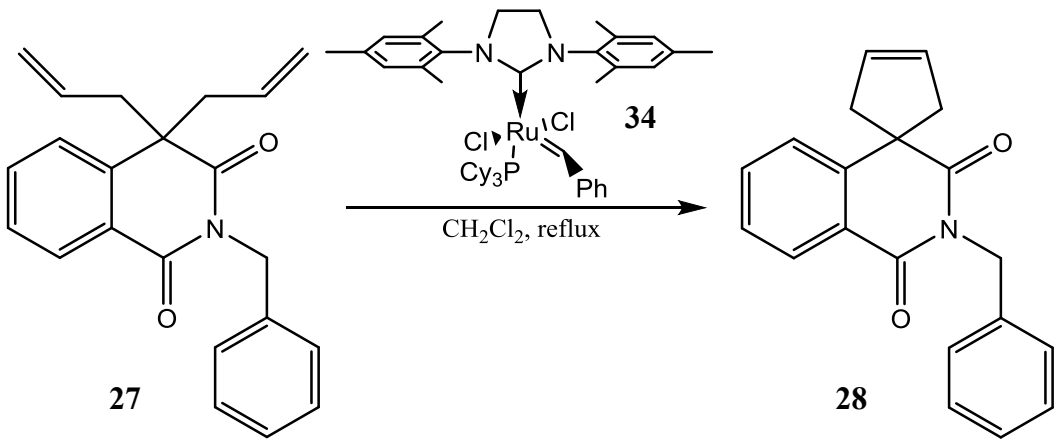
Preparation of 2-benzyl-4,4-diallyl-1,3(2*H*,4*H*)-isoquinolinedione



Sodium hydride (60% dispersion in mineral oil, 0.84 g, 21 mmol) was placed in a 50-mL three-necked flask and washed with hexanes (3 x 5 mL) to remove the mineral oil. Following this, THF (17 mL) was added and the slurry was cooled to 0 °C with stirring. The imide **26** (2.69 g, 10.7 mmol) was then added slowly. Upon addition, bubbling occurred and the solution turned yellow then dark brown. The ice bath was removed and the mixture was allowed to stir at room temperature for 20 minutes. The mixture was re-cooled to 0 °C and a solution of allyl bromide

(2.6 g, 21 mmol) in THF (17 mL) was added dropwise over 25 minutes. Following the addition, the ice bath was removed and the green solution was allowed to stir for three days at room temperature under nitrogen atmosphere. The green solution was then poured into a 250-mL separatory funnel containing 32 mL of brine and 43 mL of water. The mixture was extracted with dichloromethane (3 x 35 mL). The organic extracts were then combined, dried over sodium sulfate, and concentrated via rotary evaporation before being placed under vacuum overnight to remove trace amounts of solvent. The resulting dark green oil (3.22 grams, 91%) proved to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.69 (td, *J* = 7.9, 1.4 Hz, 1H), 7.48-7.43 (m, 4H), 7.31-7.25 (m, 3H) 5.19 (s, 2H), 5.20-5.10 (dddd, *J* =17.1, 10.1, 8.0, 6.6 Hz, 2H), 4.86 (dd, *J* = 17.1, 1.6 Hz, 2H), 4.76 (dd, *J* = 10.1, 1.6 Hz, 2H), 3.04 (dd, *J* = 13.4, 8.0 Hz, 2H), 2.67 (dd, *J* = 13.4, 6.6 Hz, 2H).

Preparation of 2-benzyl-4-cyclopentenyl-1,3(2*H*,4*H*)-isoquinolinedione; 50% completion

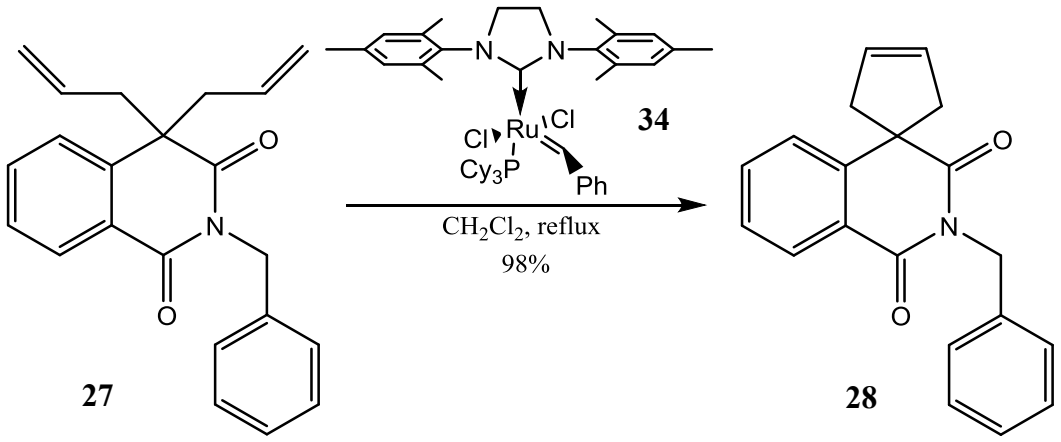


To a 250-mL round-bottom flask was added the diallyl 2-benzylimide **27** (1.3 g, 4.0 mmol). The dark green oil was dissolved in 80 mL of dichloromethane. Grubbs' catalyst, 2nd Generation (84.7 mg, 2.5 mol %) was added to the solution in one portion. The mixture was then

heated at reflux under a nitrogen atmosphere for 10 hours which yielded a dark brown mixture. The volatiles were removed via rotary evaporation and the dark oil was added to a 125-mL separatory funnel containing 40 mL of water. The mixture was extracted with ethyl ether (4 x 55 mL) in order to remove the products. The organic extracts were combined and concentrated via rotary evaporation to yield a dark brown oil before being placed under vacuum overnight.

Upon NMR analysis, it was observed that the ring cyclization had successfully occurred but only to 50% completion. The product mixture from this reaction (0.37 g) was combined with additional **27** (2.53 g, 7.6 mmol) and the reaction was repeated as described below. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (td, *J* = 7.5, 1.5 Hz, 1H), 7.49-7.39 (m, 4H), 7.34-7.27 (m, 3H), 5.83 (s, 2H), 5.24 (s, 2H), 3.33 (d, *J* = 13.8, 2H), 2.76 (d, *J* = 13.8, 2H).

Preparation of 2-benzyl-4-cyclopentenyl-1,3(2*H*,4*H*)-isoquinolinedione; 100% completion

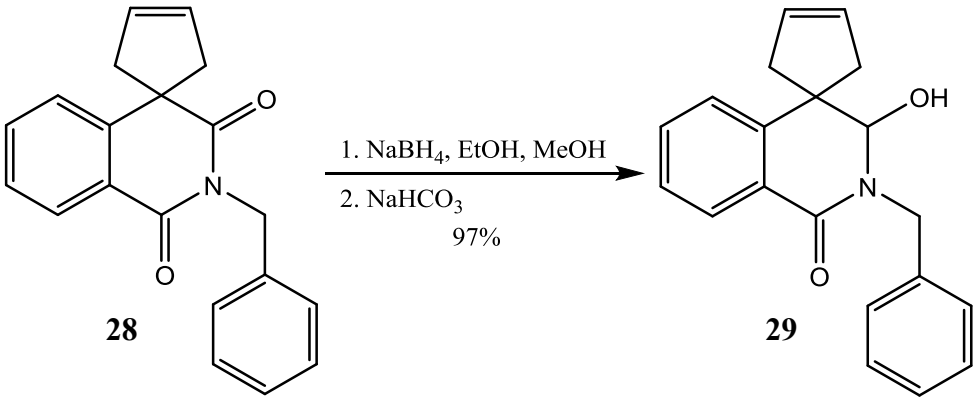


To a 500-mL round-bottom flask was added the mixture of **27** and **28** from the reaction above plus 2.53 grams of additional **27** (2.90 g total, 8.8 mmol). The dark green oil was dissolved in 240 mL of dichloromethane. An excess of 2nd Generation Grubbs' catalyst (0.5 g,

6.7 mol %) was added to the solution in one portion. The mixture was then heated at reflux under a nitrogen atmosphere for 10 hours which yielded a dark brown mixture. The volatiles were removed via rotary evaporation and the dark oil was added to a 125-mL separatory funnel containing 45 mL of water. The mixture was extracted with ethyl ether (4 x 90 mL) to remove the product. The organic extracts were then combined and concentrated via rotary evaporation to yield a dark brown oil before being placed under vacuum overnight.

Upon NMR analysis, it was observed that the ring cyclization had successfully occurred to 100% completion. Following this, the oil was dissolved in 30 mL of dichloromethane and vacuum filtered through a silica gel plug. The resulting gold oil was concentrated via rotary evaporation and placed under vacuum overnight to give 2.61 grams (98%) of **28**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (td, *J* = 7.5, 1.5 Hz, 1H), 7.49-7.39 (m, 4H), 7.34-7.27 (m, 3H), 5.83 (s, 2H), 5.24 (s, 2H), 3.33 (d, *J* = 13.8, 2H), 2.76 (d, *J* = 13.8, 2H).

Preparation of 2-benzyl-4-cyclopentenyl-3-hydro-3-hydroxy-1,3(2*H*,4*H*)-isoquinolinone

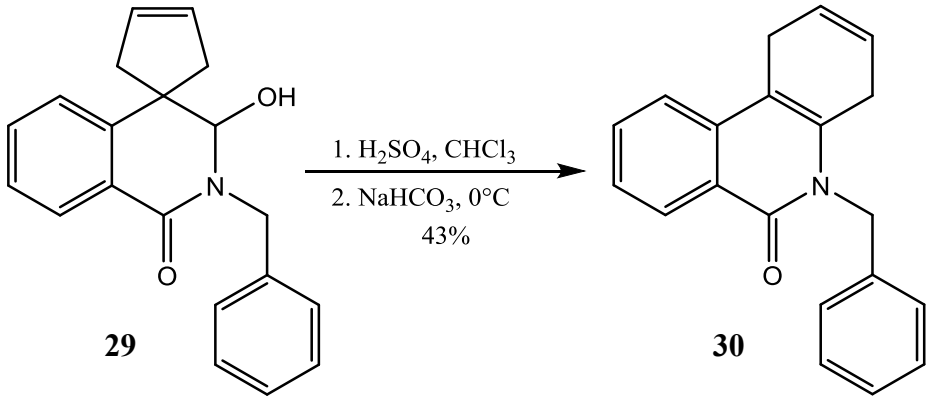


28 **29**

The imide **28** (2.16 g, 7.1 mmol) was dissolved in 95% ethanol (65 mL) and methanol (17 mL). The solution was cooled to 0 °C in ice and excess sodium borohydride (1.0 g, 27 mmol) was added cautiously, resulting in the evolution of hydrogen gas. The mixture was then warmed

to room temperature and stirred for 1.5 hours under a nitrogen atmosphere. During this time, undissolved starting material became solvated as the reaction was allowed to proceed. After the time had passed, the mixture was cooled again to 0 °C in ice and more sodium borohydride (1.0 g, 27 mmol) was added, resulting once again in gas evolution. The mixture was allowed to warm to room temperature and stir for an additional 3 hours under nitrogen. The reaction was quenched with saturated aqueous sodium bicarbonate (80 mL) which resulted in vigorous gas evolution. The mixture was allowed to stir for 30 minutes until all gas had evolved. The milky solution was then extracted with dichloromethane (3 x 100 mL), dried over sodium sulfate, and concentrated via rotary evaporation before being placed under high vacuum overnight. The flaky tan solid (2.10 grams, 97%) proved to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.50 (td, *J* = 7.6, 1.6 Hz, 1H), 7.43-7.25 (m, 7H), 5.86 (m, 1H), 5.48 (m, 1H), 5.34 (d, *J* = 14.6 Hz, 1H), 4.76 (bs, 1H), 4.45 (d, *J* = 14.6 Hz, 1H), 2.87 (m, 1H), 2.75 (m, 1H), 2.35 (m, 1H), 2.09 (m, 1H), 1.63 (bs, 1H).

Preparation of 2-Benzyl-6(5*H*)-Phenanthridinone Precursor



29 **30**

The alcohol **29** (0.29 g, 0.95 mmol) was dissolved in 6 mL of chloroform. Concentrated sulfuric acid (1 mL) was added dropwise over ten minutes while the mixture stirred at room

temperature under a nitrogen atmosphere. The mixture was allowed to stir for 10 additional minutes during which it was noted that water had begun to condense on the interior walls of the flask. In addition, it was also noted that two layers had formed (top: chloroform; bottom: sulfuric acid). The biphasic mixture was basified at 0 °C to pH 8 by slow addition of saturated aqueous sodium bicarbonate (30 mL) and allowed to stir for an additional 10 minutes. The resulting yellowish suspension was then poured into a separatory funnel containing 7 mL of water and extracted with chloroform (3 x 8 mL). The organic extracts were combined, dried over sodium sulfate, and concentrated via rotary evaporation to yield a green-yellow residue which was placed under vacuum overnight. Upon NMR analysis of the crude product (0.12 g, 43%), it was evident that the reaction had been successful. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (dd, J = 8.1, 0.9 Hz, 1H), 7.77-7.52 (m, 3H), 7.34-7.17 (m, 5H), 5.97 (m, 1H), 5.77 (m, 1H), 5.5 (bs, 2H), 3.48 (m, 2H), 3.34 (m, 2H).

Discussion and Conclusion

The reagents required for this synthesis are all commercially available and relatively inexpensive. Furthermore, this process utilizes mild reaction parameters while generating exceptional yields. Experimental shortcomings, implications, and future direction will be discussed in the remainder of this section.

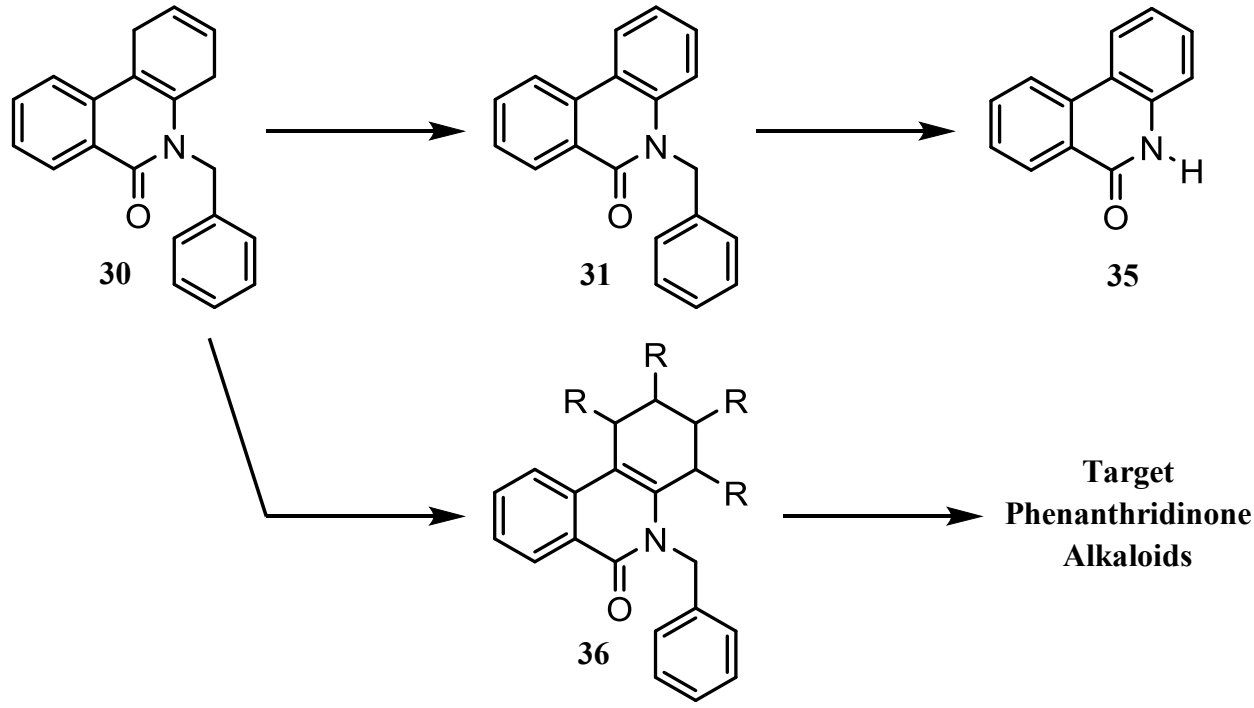
Previous work in this laboratory demonstrated an effective ring-closing metathesis of **27** to generate the cyclopentene ring in **28** using 2nd Generation Grubbs' catalyst (2.5 mol. %). However, this reaction had been performed only on milligram quantities as a means to test the effectiveness of the Grubbs' catalyst in cyclizing the ring. In the current research, the metathesis was found to be reproducible on small scales using the same 2.5 mole percent amount of catalyst. Difficulties were faced, however, when the reaction was scaled up using larger quantities of **27** while maintaining the same ratio of Grubbs' catalyst. Upon NMR analysis, it was observed that the reaction had been successful, but only proceeded to 50 percent completion. Thus, it was necessary to increase the relative amount of Grubbs' catalyst as well as the reaction time in order to force the reaction to 100 percent completion. For the larger scale reactions, a quantitative generation of **28** was obtained by utilizing 6.7 mole percent of Grubbs' catalyst and a 12-hour reflux period.

Although most of the steps in this synthesis produced yields greater than 90 percent, it was found that the ring expansion of **29** to **30** gave only a 43 percent yield. This was likely due to partial decomposition of the starting material by concentrated sulfuric acid during the reaction, thus generating by-products. Future work will focus on altering the reaction parameters in order to increase the efficiency of this step. For example, the incorporation of aluminum chloride or

another Lewis acid in a non-nucleophilic solvent instead of sulfuric acid may give the carbocation at C-3 on **29** under much milder conditions.

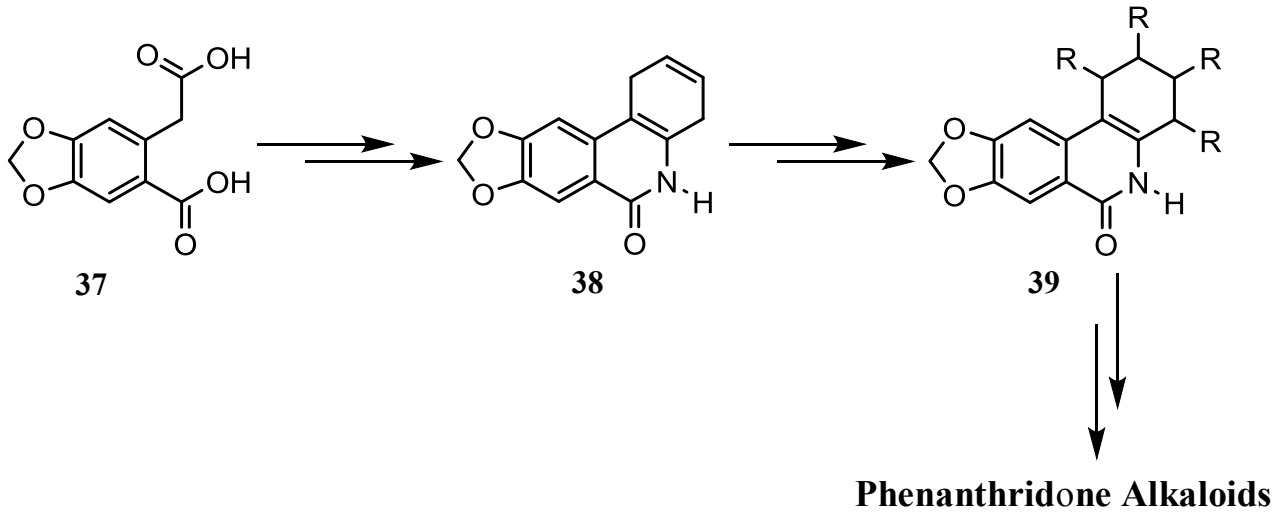
Regardless of these minor experimental shortcomings, this research provides some notable practical implications. First and foremost, our work demonstrates a novel construction of the phenanthridinone skeleton, generating the sequential A→B→C rings in exceptional yields using inexpensive reagents and mild reaction parameters. Future work will aim to functionalize the C-ring on **30** with the appropriate enantiomeric hydroxyl groups in an attempt to lay the foundation for producing biologically active phenanthridone alkaloids such as lycoricidine and narciclasine.

Alternatively, aromatization of the C-ring in **30** to generate **31** followed by the removal of the benzyl protecting group will yield 6(5*H*)-phenanthridinone (**35**). Remarkably, it has been found that **35** exhibits potent immunomodulatory activity. Specifically, it has been shown to halt lymphocyte proliferation as well as potentiate the effects of gamma radiation in murine spleen cells through the inhibition of cytosolic poly(ADP-ribose) polymerases (PARPs) at micromolar concentrations.[11] PARPs are known to modify the activities of proteins involved with cellular processes such as drug metabolism and responses to DNA damage.[12] Taken in conjunction with certain therapeutic drugs, **35** may provide immense practical benefit in the areas of cancer treatment. Regardless, this research project allows for versatility in future synthetic attempts towards producing biologically-active alkaloids. The alternative routes that may be taken by future researchers are summarized in Scheme 5.



Scheme 5: Alternate Synthetic Approaches towards Phenanthridinone Alkaloids from **30**

This synthesis provides a proof of concept for constructing the phenanthridinone core. To synthesize phenanthridone alkaloids, future work will employ the same methodology using an analog of homophthalic acid containing the methylenedioxy group (**37**). Shown in Scheme 6, this approach may become the method of choice for synthesizing these alkaloids.



Scheme 6: Future Approach towards Pharmaceutically-Active Phenanthridone Alkaloids

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