STUDIES ON THE PHENANTHRIDONE RING SYSTEM

by

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Abstract

Phenanthridone alkaloids, many of which have been studied in vitro and in vivo, have been extracted from the bulbs and petals of Amaryllidaceae plants. Due to their specific tri- and tetracyclic skeletons, these alkaloids have been shown to possess antiviral, antimitotic, and anti-tumor qualities. The specific phenanthridone alkaloids Narciclasine, Lycoricidine and Pancratistatin have been shown to exhibit potent cytotoxic activity and to inhibit cell division in E. coli and sarcoma cells. Previous syntheses of phenanthridone alkaloids have focused on a retrosynthetic approach whereby a modified hexose sugar comprises the C-ring. This is added to a starting material containing the A-ring, and the last step in these syntheses uses an expensive metal to catalyze the formation of the B-ring. Our novel synthesis, however, begins with an aromatic dicarboxylic acid that contains the A-ring. Cyclization of this compound allows the B-ring to be formed early in the synthesis without the need of expensive metals. Carbon 4 on the B-ring is then available for functionalization. The C-ring results from a ring-closing metathesis reaction and subsequent ring expansion to give the phenanthridinone ring system. Current research on a model system has shown this route to be high-yielding. If an efficient method to synthesize the phenanthridinone ring system is developed, it will provide a template to produce numerous modified alkaloids in sizable quantities sufficient for pharmacological testing.
Introduction

Structure and Medicinal Benefits of Phenanthridone Alkaloids

Located in tropical and subtropical regions, plants of the Amaryllidaceae family contain important phenanthridone alkaloids such as those shown in Figure 1. Ancient extractions of the bulbs and petals of Narcissus poetics by the Greek physician Hippocrates of Cos were used in the primitive treatment of cancer.\(^1\),\(^2\) The Narcissus genus (daffodils) primarily contains the phenanthridone alkaloid narciclasine (1a) with lycoricidine (1b) and pancratistatin (1c) in lesser amounts.\(^3\)

![Figure 1. Structures of Phenanthridone Alkaloids](image)

Narciclasine (1a, R=OH)
Lycoricidine (1b, R=H)

![Figure 2. Phenanthridone Core](image)
The phenanthridone alkaloids contain a unique and interesting tricyclic substructure (see Figure 2) whose presence gives these alkaloids antimitotic, antiviral, and anticancer activities. Narciclasine has actually been shown to possess strong antimitotic activity by inhibiting the growth of *E. coli* and sarcoma tumor cells. In eukaryotic ribosomes, narciclasine specifically inhibits peptide bond formation and binds to the 60-S ribosomal subunit. Studies with narciclasine, lycoricidine, and pancratistatin on HeLa cells showed all these phenanthridone alkaloids to possess potent cytotoxic activity. Thus, these alkaloids can be utilized in many fields of medicine including alternatives to chemotherapy and radiation for cancer patients. In fact, the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) is looking to develop effective antiviral drugs against many RNA viruses that are significant health hazards to persons traveling through endemic regions of the world.

The use of natural compounds as cures for ailments represents a neo-herbalism of sorts for Western medicine. However, the extraction of these phenanthridone alkaloids from bulbs and petals of *Amaryllidaceae* plants gives extremely small amounts of material. It is therefore imperative to create an efficient and cost-effective route to produce these alkaloids in much larger quantity sufficient for testing, clinical trials and eventually the marketplace if any of these can be developed as medicinal agents.

**Past Syntheses of Phenanthridone Alkaloids**

Due to their potent cytotoxic effects, phenanthridone alkaloids have been targets for synthetic chemists for decades. Many have used retrosynthetic approaches to these alkaloids that rely on palladium and other expensive metals as catalysts to close the B-ring late in the synthesis.
For example, McIntosh and Weinreb’s synthesis of Lycoricidine used Pd(DIPHOS)$_2$ in hot DMF. This synthesis was completed in 13 steps, but the last reaction proceeded in only 50% yield.$^7$

Scheme 1. Key steps in the McIntosh and Weinreb Synthesis of Lycoricidine$^7$

Sanghee Kim and co-workers managed to synthesize pancratistatin without the use of expensive metal catalysts in 2002.$^8$ This strategy also involved late stage B-ring formation using a Bischler-Napieralski cyclization. However, the synthesis required 16 steps and gave an overall yield of only 4.7%.
More recently, lycoridine was synthesized by Elango and Yan. Similar to other approaches, the B-ring was formed at a fairly late stage in the synthesis. These workers controlled the stereochemistry by using a camphor-based chloronitroso ester in the formation of a key cyclohexenol intermediate. The synthesis required 9 steps with an overall yield of less than 12%.

Scheme 2. Ko, E. Kim, and D. Kim Synthesis of Pancratistatin
Scheme 3. Elango and Yan Synthesis of Lycoricidine

New Synthesis of Phenanthridone Alkaloid Precursors

A review of the literature including the examples above reveals that previous syntheses of phenanthridone alkaloids have some common features: the use of modified sugars to form the functionalized C-ring and a late-stage formation of the B-ring that often uses palladium and other expensive metals. Our work, however, will construct the B-ring early as a novel way to synthesize phenanthridone alkaloid precursors. In addition, our route uses cheap, commercially
available reagents, avoids the use of highly toxic chemicals, and will give potentially higher yields than several of the previously completed syntheses. Two schemes have been investigated for synthesizing the dicarboxylic acid 5, which is necessary for an early formation of the B-ring as illustrated in Scheme 4.

Scheme 4. Proposed Synthesis of 11

The synthesis proposed in Scheme 4 begins with a cyclization reaction followed by ring opening to give the dicarboxylic acid 5 (3→4→5). Formation of the anhydride 6 with thionyl chloride followed by treatment with benzylamine gives the imide 7. Subsequent addition of two allyl groups at C-4 provides a precursor for the ring-closing metathesis reaction to generate 9 (7→8→9). Selective reduction of the carbonyl at C-3 and ring expansion affords the complete phenanthridinone system (9→10→11).
Scheme 5. Alternative Synthesis of 11

An alternative to generating the dicarboxylic acid 5 is given in Scheme 5. Piperonal (12) can be converted easily to the substituted cinnamic acid 13, which can be reduced and cyclized to the ketone 15 (13→14→15). Finally, formation of the oxime followed by a Beckmann-type rearrangement affords the diacid 5 (15→16→5). The remaining step to 11 will be the same as shown in Scheme 4.

The key steps in this strategy are the ring-closing metathesis reaction to give 9 and the ring expansion to give 11. This represents an unusual strategy for creating the phenanthridinone system.
Experimental Section

Preparation of 6-(carboxymethyl)benzo[d][1,3]dioxole-5-carboxylic acid (5)\textsuperscript{10}

\[
\begin{align*}
\text{3} & \quad \text{CO}_2\text{H} \\
\text{17} & \quad \text{H} \quad \text{O} \\
\end{align*}
\]

A mixture containing 15.0 g (83.3 mmol) of acid 3 and 7.50 g of p-formaldehyde (17) (249 mmol) was placed in a 500-mL three-necked flask with an attached reflux condenser and stirring bar. The system was placed under nitrogen after 300 mL of acetic acid and 31 mL of concentrated HCl had been added. The solution was heated to 75 °C for 1 hour. After 1 hour, the red/yellow solution was cooled to room temperature. The reaction mixture was poured into a separatory funnel containing 600 mL of DI water and extracted with ethyl ether (2 x 300 mL). The organic layers were combined and dried with magnesium sulfate. Most of the solvent was removed by rotary evaporation before the product was placed on a vacuum line to remove residual volatiles. The resulting yellow solid (8.30 g, 52% yield) was used in the following step after \textsuperscript{1}H NMR analysis determined the product to be pure. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 6.73 (s, 1H), 6.70 (s, 1H), 6.01 (s, 2H), 5.22 (s, 2H), 3.63 (s, 2H).
Lactone 4 from the previous step (4.34 g, 22.6 mmol) was added to a three-necked flask with a reflux condenser and the system was placed under nitrogen. A 7% KOH solution (51 mL) was added to the flask producing a dark yellow solution. After refluxing for 16 hours, the resulting brown solution was allowed to cool slowly to room temperature. The reaction mixture was then placed in an ice bath and a solution containing 3.57 g (22.58 mmol) of KMnO₄ in water (47.0 mL) was added dropwise to the flask being careful not to allow the temperature of the reaction mixture to rise above 5 °C. After all the KMnO₄ was added, the solution was dark brown/purple in color and was allowed to stir at room temperature for 48 hours.

After 48 hours, 25 mL of 10% NaHCO₃ solution was added, which caused the solution to become transparent and red. The solution was then acidified with concentrated HCl until the solution became cloudy, and the product was removed by extraction with ethyl acetate (2 x 25 mL). The organic layers were dried over MgSO₄. The solvent was removed by rotary evaporation yielding a green solid. Recrystallization from chloroform yielded a light brown solid (1.55 g, 31%) that decomposed at 205-207 °C. NMR analysis determined the product to be pure. ¹H NMR (DMSO, 400 MHz): δ 7.26 (s, 1H), 7.19 (s, 1H), 6.22 (s, 2H), 5.26 (s, 2H).
Isolation of 2-(6-(hydroxymethyl)benzo[d][1,3]dioxol-5-yl)acetic acid (18)

Lactone 4 (2.58 g, 13.4 mmol) was added to a three-necked flask with a reflux condenser and the system was placed under nitrogen. Roughly 45 mL of a 7% KOH solution was added and produced a yellow-colored solution. The solution was refluxed for 16 hours, after which the solution turned dark amber in color. Concentrated HCl was added until a precipitate began to form and the pH was below 3. The resulting white solid was collected by vacuum filtration to give 2.01 g (71%) of primary alcohol 18, which proved to be pure by NMR analysis. $^1$H NMR (DMSO, 400 MHz): δ 6.97 (s, 1H), 6.92 (s, 1H), 6.03 (s, 2H), 5.23 (s, 2H), 3.37 (s, 2H).

Failed Oxidation of 2-(6-(hydroxymethyl)benzo[d][1,3]dioxol-5-yl)acetic acid (5)$^{11}$

Alcohol 18 (0.21 g, 1.0 mmol) was added to a solution of MPHT (0.527 g, 1.20 mmol) in 5 mL of acetonitrile. After all the solid had dissolved, 0.22 mL of 30% $\text{H}_2\text{O}_2$ were added dropwise. The orange-colored solution was heated to reflux under nitrogen for 5 hours. After cooling the solution to room temperature the excess $\text{H}_2\text{O}_2$ was destroyed with NaHSO$_3$. The
solution was extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the solvents were removed by rotary evaporation. The recovered brown oil was placed on a vacuum line to remove volatiles. However, $^1$H NMR analysis showed only recovered alcohol 18 and no oxidation products.

**Alternative Oxidation of 2-(6-(hydroxymethyl)benzo[d][1,3]dioxol-5-yl)acetic acid (5)**

[Chemical structure image]

Alcohol 18 (3.86 g, 18.4 mmol) was placed in a 1-L three-necked flask and equipped with a stir bar and two addition funnels. Acetonitrile (92.1 mL), 0.67 M phosphate buffer (69 mL) and TEMPO (0.20 g, 1.28 mmol) were added to the reaction mixture. A reflux condenser was attached and the system was placed under nitrogen. A solution containing 3.33 g (36.8 mmol) of NaClO$_2$ in 18.4 mL of water and added to one addition funnel. To the other addition funnel, bleach (8.25% NaOCl, 0.67 mL, ca. 2.0 mol%) was diluted with 12.1 mL of water. The solution was heated to 35-38 °C at which point 20% of the total volume of each addition funnel was added. Over a period of 2 hours, equal portions of the bleach and NaClO$_2$ solutions were added simultaneously. After everything was added, the light orange-colored solution was stirred at 35-38 °C for 10 hours.

After 10 hours, the solution was cooled to room temperature and 138 mL of DI water were added. The pH was adjusted to 8.0 by addition of 2.0 N NaOH. The reaction mixture was then poured into ice-cold sodium sulfite solution (5.62 g in 92.2 mL of water) which caused a white precipitate to form. This precipitate was isolated by vacuum filtration to afford 1.53 g (37
% of white solid. $^1$H NMR analysis showed a successful oxidation to 5, which was deemed sufficiently pure to be used in the subsequent step. $^1$H NMR (DMSO, 400 MHz): $\delta$ 7.26 (s, 1H), 7.19 (s, 1H), 6.22 (s, 2H), 5.26 (s, 2H).

Attempted Synthesis of 5H-[1,3]dioxolo[4,5-g]isochromene-5,7(8H)-dione (6)$^{13}$

The diacid 5 (1.55 g, 6.91 mmol) was added to a round-bottom flask containing 1 mL of SOCl$_2$ and 20 mL of CH$_2$Cl$_2$. A reflux condenser was attached and the system was placed under nitrogen. The solution was heated at reflux for 3 days using an oil bath. After 3 days, the CH$_2$Cl$_2$ was distilled off yielding a dark brown solid. The $^1$H NMR analysis of the solid showed only the starting material and no conversion to the anhydride 6.
Alternative Route to 2-(6-(hydroxymethyl)benzo[d][1,3]dioxol-5-yl)acetic acid (5)

Synthesis of (E)-3-(benzo[d][1,3]dioxol-5-yl)acrylic acid (13)\textsuperscript{14}

A solution of piperonal (12)(13.88 g, 133.4 mmol) in 46 mL of pyridine was prepared in a three-necked round bottom flask equipped with a thermometer. Malonic acid (19)(19.06 g, 126.96 mmol) was added and a reflux condenser was attached. After most of the acid had dissolved, roughly 2 mL of piperidine was added and the system was placed under nitrogen. The addition of piperidine caused the solution to turn yellow. The solution was then refluxed for 8 hours at an internal temperature between 115-117 °C. After 8 hours, the solution was immediately poured into 200 mL of cold DI water causing a milky white suspension to form. Concentrated HCl was added until the solution turned blue litmus paper red. The white solid was collected by vacuum filtration and recrystallized from acetone to produce 12.15 g (68%) of product. Analysis by $^1$H NMR found this material to be pure (E)-3-(benzo[d][1,3]dioxol-5-yl)acrylic acid (13): $^1$H NMR (DMSO, 400 MHz): δ 12.26 (s, 1H), 7.51 (d, $J = 16$ Hz, 1H), 7.38 (d, $J = 1.6$ Hz, 1H), 7.16 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.40 (d, $J = 16$ Hz, 1H), 6.08 (s, 2H).
Attempted Reduction of \((E)-3\)-(benzo[d][1,3]dioxol-5-yl)acrylic acid (13)

A solution containing 6.94 g (36.1 mmol) of 13 in 90.3 mL of acetic acid was prepared in a three-necked round bottom flask and a catalytic amount of 5% Pd/C was added. A reflux condenser was attached, the remaining joints were capped, and the system was placed under a hydrogen atmosphere. The solution was heated and stirred vigorously at reflux for 2 days under hydrogen. The Pd/C was removed by passing the solution through a glass frit and the solvent was removed to afford a white solid. \(^1\)H NMR analysis showed partial reduction to the saturated acid 14 with an estimated conversion of 29%.

Reduction of \((E)-3\)-(benzo[d][1,3]dioxol-5-yl)acrylic acid (13)

Solubility tests with water, ethyl acetate, acetone, and acetone-ethyl acetate were performed on the unsaturated acid 13 in order to find a suitable hydrogenation solvent. It was found that acetone had the highest degree of solubility. A sample of 13 (4.0 g, 20.8 mmol) was placed in a 600 mL beaker and heated while adding acetone until all the solid dissolved. A 150 mL fraction of this solution was transferred to a hydrogenation bottle and a catalytic amount of 5% Pd/C was added. The hydrogenator was pressurized to 40 psi, the solution was warmed slightly, and the reaction was allowed to proceed for 3 days. The black solution was passed
through a glass frit to remove the Pd/C and placed on a rotary evaporator to remove acetone. A gray solid (3.31 g, 82% yield) precipitated after all the acetone was evaporated. A \(^1\)H NMR analysis showed complete reduction of \(\textbf{13}\) to the saturated acid \(\textbf{14}\): \(^1\)H NMR (DMSO, 400 MHz): 
\[\delta 12.11 \text{ (s, 1H)}, 6.82 \text{ (d, } J = 1.7 \text{, 1H)}, 6.79 \text{ (d, } J = 7.9 \text{ Hz, 1H)}, 6.67 \text{ (dd, } J = 7.9, 1.7 \text{ Hz, 1H)}, 5.96 \text{ (s, 2H)}, 2.73 \text{ (t, } J = 7.6 \text{ Hz, 2H)}, 2.48 \text{ (t, } J = 7.6 \text{ Hz, 2H)}\].

\textbf{Synthesis of 6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-one (15)}

A sample of the saturated acid \(\textbf{14}\) (3.31 g, 17.05 mmol) was placed in a 100-mL three-necked round bottom flask. All the joints were capped and the system was purged with nitrogen. Thionyl chloride (6 mL) was added to the solid immediately producing a black solution. After stirring under nitrogen for 3 hours, the black solution was placed on a water aspirator to remove the excess thionyl chloride. No solid formed, so the black oil was placed on the vacuum line overnight. To this black oil, 50 mL of CH\(_2\)Cl\(_2\) was added to re-dissolve the compound and the resulting solution was placed in a three-necked flask equipped with a 50-mL addition funnel. Dichloromethane (20 mL) was placed in the addition funnel followed by 3.6 mL of SnCl\(_4\) added to the addition funnel using a syringe. The system was capped and purged with nitrogen. The apparatus was cooled to 0 °C using an ice bath and the SnCl\(_4\)/CH\(_2\)Cl\(_2\) solution was added dropwise over 10 minutes with stirring.
After everything had been added, the solution was allowed to stir at 0 °C for 10 minutes and then an additional 30 minutes at room temperature. The solution was dark and tinted slightly blue after stirring. Crushed ice (15 g) was placed in a beaker and the dark solution was poured into the ice. After all the ice had melted, the mixture was placed in a separatory funnel and the aqueous layer was removed. The organic layer was washed with 3N HCl (2 x 60 mL) and 100 mL of DI water and then dried with MgSO₄. The resulting dark brown solution was passed through a plug of silica gel deposited on a glass frit. Removal of the solvent by rotary evaporation gave 1.63 g (54% yield) of 15 as a brown flaky solid, mp 138-140 °C, that was proven to be pure indanone 15 by ¹H NMR analysis: ¹H NMR (CDCl₃, 400 MHz): δ 7.28 (s, 1H), 7.08 (s, 1H), 6.05 (s, 2H), 3.01 (t, J = 5.2 Hz, 2H), 2.67 (t, J = 5.2 Hz, 2H).

Synthesis of (E)-6-(hydroxyimino)-6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-one (16)

A sample of indanone 15 (0.5 g, 2.8 mmol) was added to 45 mL of methanol in a three-necked round bottom flask fitted with an addition funnel. The flask was heated to 45 °C in order to dissolve the indanone. To this solution, 0.42 mL (3.11 mmol) of isoamyl nitrite was added. The joints were capped and the system was placed under a nitrogen atmosphere. Concentrated HCl (0.27 mL) was placed in the addition funnel and added dropwise over 1 minute producing a yellow precipitate in the flask. After the addition was complete, the reaction mixture was stirred for 45 minutes, after which an additional 0.2 mL each of isoamyl nitrite and concentrated HCl
were added. The suspension was allowed to stir for an additional 30 minutes. The oxime 16 was collected as a yellow solid by vacuum filtration to afford 0.28 g (48%) of material that was shown to be sufficiently pure for subsequent use by $^1$H NMR analysis: $^1$H NMR (DMSO, 400 MHz): $\delta$ 12.48 (s, 1H), 7.17 (s, 1H), 7.14 (s, 1H), 6.20 (s, 2H), 3.65 (s, 1H).

**Synthesis of 6-(carboxymethyl)benzo[d][1,3]dioxole-5-carboxylic acid (5)**

A sample of oxime 16 (0.28 g, 1.36 mmol) was placed in a three-necked round bottom flask with a reflux condenser. The joints were capped and the system was placed under nitrogen. The oxime was dissolved in 10% NaOH (0.348g of NaOH in 3.11 mL of water) to produce a tan/yellow solution, which was heated using a water bath at 40-48 °C. Solid p-toluenesulfonyl chloride (0.5 g, 2.6 mmol) was added to the solution in small portions. After the addition was complete, the solution was maintained at 40-48 °C and stirred for 40 minutes, after which the reaction mixture was light brown/amber in color. An additional 3.11 mL of 10% NaOH solution was added and the reaction mixture was heated at reflux for 10 hours. The solution was allowed to cool to room temperature and then acidified with HCl. The white solid product (0.124 g, 40%) was isolated by filtration and determined to be the pure diacid 5 by NMR analysis: $^1$H NMR (DMSO, 400 MHz): $\delta$ 7.26 (s, 1H), 7.19 (s, 1H), 6.22 (s, 2H), 5.26 (s, 2H).
Synthesis of 6-benzynaphtho[2,3-d][1,3]dioxole-5,7(6H,8H)-dione (7)

A sample of the diacid 5 (0.50 g, 2.4 mmol) was placed in a three-necked round bottom flask with an attached reflux condenser. The system was placed under nitrogen and all joints were capped. To the diacid, 0.243 mL (0.238 g, 2.22 mmol) of benzylamine (20) was added, producing a brown solution and a white gas. The mixture was heated between 140-175 °C for about 2 hours. The brown solution was allowed to cool to room temperature resulting in the formation of a brown, gummy solid (0.50 g, 76%). NMR analysis showed a successful conversion to imide 7: \( ^1\text{H NMR} \) (DMSO, 400 MHz): \( \delta 7.47-7.18 \) (m, 7H), 6.21 (s, 2H), 5.26 (s, 2H), 3.86 (s, 2H).

**Discussion & Conclusion**

Previous work on a model system (Scheme 6) used homophthalic acid (21) as the starting material and led to the phenanthridinone compound 27 in very high overall yield. While this model did not contain the methylenedioxy group that will be required for making alkaloids, it was assumed that the reactions developed in Scheme 6 could be applied directly to the synthesis of 11 as indicated in Scheme 7.

While the model system started with the commercially available diacid 21, the synthesis of 11 requires a source for the diacid 5; and that is the focus of the first part of the work.
presented here. The second part of this project carries the synthesis two additional steps forward to the imide 7 as indicated in Scheme 7. Thus, the compound 5 provides the A-ring, and the two substituents on 5 will be elaborated to give the B-ring.

Fortunately, the carboxylic acid 3 as well as piperonal (12) is commercially available and many of the reactions that were attempted could be based on literature precedents. The first attempt to generate 5 used the carboxylic acid 3 in a cyclization reaction to synthesize the lactone 4 (see Scheme 8). Paraformaldehyde was used as an electrophile and concentrated HCl served as an acid catalyst for both the hydroxylation and the cyclization processes. The yield was much lower than the literature example and suffered from difficulty in removing the acetic acid that served as solvent for the reaction. Using less acetic acid helped only marginally; and when the solvent was changed to acetone, the reaction failed altogether.
Hydrolysis of lactone 4 and subsequent oxidation with KMnO₄ afforded the diacid 5 but only in very low yield. To increase the yields, two different oxidation methods were attempted. Hydrolysis of lactone 4 with KOH afforded 18 as white crystals in high yield (71%). Oxidation of 18 with hydrogen peroxide and the catalyst MPHT failed, but better results were obtained with TEMPO and bleach.

Bleach oxidation occurs through a free-radical mechanism with the catalyst TEMPO. Although the oxidation of 18 gave only slightly higher yield than the previous procedure, the literature reported a 90-92% conversion of primary alcohols to carboxylic acids. However, these reactions were done on substrates with electron withdrawing groups (EWG) on the aromatic ring and this aided the oxidation. Electron donating groups (EDG) retarded the reaction and that is likely the cause of the problem in our system since the methylenedioxy group is an EDG.
A second attempt to produce 5 efficiently involved the generation of the cinnamic acid analog 13 and its conversion to the substituted indanone 15 (see Scheme 9). The condensation reaction between piperonal (12) and malonic acid (19) using catalytic piperidine gave 13 which could be hydrogenated to produce 14.

Initial attempts to hydrogenate 13 using ethanol as the solvent gave only partial reduction due to solubility problems. Later, it was discovered that acetone was much better. Under the best conditions, 13 was reduced to 14 in 82% yield after a 3-day reaction period. The poor solubility of 13 is most likely due to the methylenedioxy function, and the harsh conditions for the reaction are necessary due to the stability of the highly conjugated double bond.

While the first two steps of Scheme 9 proved to be high yielding, the remaining reactions leading to 5 were not as efficient. This route also required five steps and some very long reaction times. Nevertheless, the target diacid 5 was produced by the chemistry shown in both Schemes 8 and 9 using very inexpensive, readily available materials.
According to the model study shown in Scheme 6, the next step is the conversion of 5 to the anhydride 6 analogous to the conversion of 21 to 22. In the model study, this reaction was quantitative; but the diacid 5 was not converted to the anhydride 6 using the same conditions.

Scheme 9. Alternate route to 5 via indanone 15

Scheme 10. Alternate Pathway to the Phenanthridone Alkaloid Precursor 11
The cause of this failure is not clear since the presence of the methylenedioxy group should not interfere with the reaction. To avoid this issue, we investigated the possibility of converting 5 directly into 7 as shown in Scheme 10. This reaction was marginally successful although the crude material contained numerous by-products making it very difficult to purify the compound.

The project currently rests at this stage. The next step in the synthesis will be the purification of 7 followed by the addition of the allyl groups on the B-ring to give 8 as shown previously in Scheme 4. Other work currently underway includes additional research on the model system to aromatize the C-ring as shown by the conversion of 27 to 28 in Scheme 11.

![Scheme 11. Functionalizing the C-ring in the Model System](image)
References


