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UMI
Synthetic Approaches to Coniochaetones A & B

By

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Chemistry
University of Toronto

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Abstract

Several routes to the synthesis of coniochaetones A and B, two natural products isolated from a liquid culture of Coniochaeta saccardo,\(^1\) were explored. Two different pathways which we believe will eventually lead to the synthesis of coniochaetones A and B have been focused upon. Utilizing a model series, key intermediates for each synthetic route have been synthesized and characterized. The synthesis of 4a-bromo-1a-methoxycyclopenta-[b]-chromone 81 has been accomplished by the reaction of cyclopenta-[b]-chromone 14 with N-bromosuccinimide (NBS) in methanol. Methyl 5-chloro-6-(2’-hydroxyphenyl)-6-oxohexanoate 96 has been synthesized by the bromination of 6-(2’-hydroxyphenyl)-6-oxohexanoic acid followed by an esterification reaction involving HCl in methanol.
Dedicated to my wife.

Thanks for your patience and understanding.
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2-Carbethoxycyclopent-2-one (36)
1,3-Dimethoxy-5-methylbenzene (45)
6-Methoxy-8-methyl-5-oxocyclopenta-[b]-chromone (54) and
8-Methoxy-6-methyl-5-oxocyclopenta-[b]-chromone (55)
p-Orsellinic acid (17)
2,6-Diacetoxy-4-methylbenzoic Acid (33)
1-N-Morpholino cyclopentene (35)
Cyclopenta-[b]-chromone (14)
2'-Hydroxyphenyl 2-[(N-isobutyramino)cyclo-1-penteny1 ketone (74)
2'-Hydroxyphenyl 2-[(N-isobutyramino)-3-bromocyclo-1-penteny1 ketone (75)
4a-Bromo-1a-hydroxycyclopenta-[b]-chromanone (77)
cyclopenta-[b]-1a,4a-epoxychromanone (80)
4a-Bromo-1a-methoxycyclopenta-[b]-chromanone (81)
4a-Chloro-1a-methoxycyclopenta-[b]-chromanone (85)
Attempted preparation of (2,4-Dinitrophenyl)-(3a-methoxy-2,3,3a,9-tetrahydrocyclopenta[b]chromen-9-yl) diazene (90)
Attempted synthesis of Methyl 6-((2',6'-dihydroxy-4'-methylphenyl)-6-oxohexanoate (28)
6-(2'-Hydroxyphenyl)-6-oxohexanoic Acid (69)
5-Bromo-6-(2'-hydroxyphenyl)-6-oxohexanoic Acid (91)
5-(2'-Hydroxybenzoyl)-3-pentanolide (94)
Methyl 5-chloro-6-(2'-hydroxyphenyl)-6-oxohexanoate (96)
2-(3'-hydroxycarbonylpropyl)benzofuranone (98)
2-(3'-methoxycarbonylpropyl)benzofuranone (97)

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2-(3'-hydroxycarbonylpropyl)benzofuranone (98)
2-(3'-methoxycarbonylpropyl)benzofuranone (97)
1. INTRODUCTION

In 1995, Gloer, Malloch and co-workers reported the isolation of two new compounds from the coprophilous, or dung-colonizing, fungus *Coniochaeta saccardoi* Cain. These compounds were shown to possess antifungal activity. Upon characterization, it was shown that they contained a cyclopenta-[b]-benzopyran-4-one skeleton and were named coniochaetone A (1) and B (2). The only difference between coniochaetone A and coniochaetone B is the reduction of the carbonyl of the cyclopentane ring of 1 to the (R)-hydroxyl group of 2.

![Chemical structures of coniochaetone A and B](image)

Working independently, Yamazaki and co-workers have shown that an ethyl acetate extract from *coniochaeta tetraspora* Cain has a significant inhibition of mouse liver monoamine oxidase (MAO). Upon characterization, it was determined that the extract contained coniochaetone A (1) and coniochaetone B (2) which showed MAO activity, as well as a third structurally divergent compound that possessed no MAO activity.

Having realized the biological activity of these compounds as well as the novel structure of cyclopentane-[b]-benzopyran-4-one, we felt that this would be an interesting target for a total synthesis.
1.1 Benzopyranones and Benzopyrans

1.1.1 *Classification of Benzopyranones*

A benzopyran (e.g., 2H-chromene, 3) consists of a benzene ring fused to a pyran ring. Pyran is a six-membered cyclic ether containing two double bonds. A benzopyranone possesses a carbonyl group on the pyran ring (e.g., benzopyran-4-one or chromone, 4).

![Molecular structures of benzopyrans and benzopyranones](image)

Due to the diversity of natural products possessing the benzopyran ring system, this class of compounds has been further sub-classified. The classification is based upon the location of the ring oxygen, the placement of the carbonyl, whether the pyran ring possesses a double bond and, in the case of flavones and flavanones (7), a phenyl substituent at C-2. The trivial names for these compounds are chroman (5), 4-chromanone (6), flavanone (7), coumarin (8), and 3-chromanone (9), respectively.
1.1.2 Biosynthesis of Chromones

Labeling studies using C-1 labeled sodium acetate have produced 5-hydroxy-2-methylchromone (10) with labels at C-2, C-4, C-5, C-7, and C-8a.\(^4\) This result fits well with the established head-to-tail assembling of acetate units in the biosynthesis of natural products.

\[ \text{Na}^+ \text{O}^{-} \rightarrow \text{OH} \]

Although no work on the biosynthesis of coniochaetones A & B has been published, they appear to follow this general rule. The most notable exception is the tail to tail joining of the cyclopentane ring (C2 to C3). Another point to note is the replacement of the expected oxygen of the C7/C8 acetate unit with a carbon atom.

1.1.3 Synthesis of Chromones

The synthesis of chromones dates back to the turn of the century.\(^3\)\(^5\) These natural products, although not as prevalent as flavones, continue to interest synthetic chemists.\(^6\) There are a number of methods for preparing chromones and there are new methods still being developed.
The most common method for the direct preparation of chromones is the Claisen condensation. This involves the condensation of an ester with a 2'-hydroxyacetophenone in the presence of a base. The resulting 1,3-diketone is then cyclized into a chromone. (Scheme 1)

Scheme 1

A second common strategy for the synthesis of chromones involves the Baker-Venkatarayan rearrangement. This reaction is a modification of the Claisen condensation above in which the ester is a 2'-hydroxyacetophenone derivative. (Scheme 2) This reaction has the advantage of being intramolecular and hence a milder base can be used; the most common being potassium carbonate.
Acid catalyzed condensations have also been used to synthesis chromones. Reactions of 2'-hydroxy-substituted aryl alkyl ketones with triethyl formate and other formic acid derivatives under acid catalysis have produced a variety of chromones. \(^9,10\) (Scheme 3)

\[
\text{Scheme 3}
\]

In 1892, Nagai\(^11\) and Tahara\(^12\) independently performed what was later to become known as the Kostanecki-Robinson reaction, in which they refluxed 2'-hydroxy-4'-methoxyacetophenone in acetic anhydride and sodium acetate. (Scheme 4) The nature of the reaction was later correctly predicted by Kostanecki and co-workers\(^13,14\) and was further extended by Robinson and co-workers.\(^15,16\)
The von Pechmann condensation of a phenol with a β-ketoester in sulfuric acid produces a coumarin.\(^\text{17}\) (Scheme 5) Replacement of the sulfuric acid with \(\text{P}_2\text{O}_5\) produced what Simonis and co-workers originally thought were chromones.\(^\text{18}\) (Scheme 6) Further work carried out by numerous groups\(^\text{19,20,21}\) has shown that in fact either chromones or coumarins, or both, may be formed depending on the nature of the ring and the substitution of the ketoester. Generally, it was found that substitution pattern of the ketoester tends to favor formation of the chromone. It was also noted that phenols which give poor yields in the von Pechmann condensation tend to produce chromones when subjected to the Simonis conditions.\(^\text{3}\)

![Scheme 5 The von Pechmann Condensation](image)

![Scheme 6 The Simonis Condensation](image)

Another important method for the construction of the chromone ring system, also starting from a phenol, is the addition of the phenolate ion to an \(\alpha,\beta\)-unsaturated ester. The resulting O-alkylated phenol is then cyclized under acidic conditions.\(^\text{22}\)
Scheme 7

Chromones have also been synthesized by the oxidation of the chromanone ring. This transformation is driven in part by the formation of the aromatic benzopyranone system. One of the most common transformations is bromination/dehydrobromination. This reaction has seen the use of a variety of bromination agents, but the choice of bases is limited, due to a competing base catalyzed ring opening of the pyranone ring. The ring opening can proceed via two routes depending on which base is used. A hydroxide base opens the ring by a reverse Claisen reaction breaking the C-2/C-3 bond and resulting in a 2'-hydroxy acetophenone. When a primary or secondary amine is used, however, an enamine is produced. Both of these reactions will be explained in greater detail in the discussion.

Scheme 8
Chromanones have also been dehydrogenated with reagents such as triphenylmethyl perchlorate in acetic acid\textsuperscript{24}, H\textsubscript{2}SO\textsubscript{4}\textsuperscript{25}, DDQ, and a variety of other reagents.\textsuperscript{26,27} Another method involves the reaction of the chromanone with an alkyl nitrite to form isonitroso derivatives (oximes) (15).\textsuperscript{28} The oxime is then hydrolyzed and isomerized in mineral acids to form the 3-hydroxychromone (Scheme 9). Synthesis of 3-benzyl chromones has been produced via an aldol reaction between benzaldehyde and a chromanone, followed by isomerization of the resulting exo double bond.\textsuperscript{29}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{scheme9.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 9}

1.1.3 \textit{Synthesis of Chromanones}

With the oxidation of chromanones being an important synthetic route to chromones, the synthesis of chromanones must also be examined. The most widely used method for the synthesis of the chromanones involves the cyclization of 3-phenoxypropanoic acid derivatives. The dehydrating agents used for this reaction include P\textsubscript{2}O\textsubscript{5}, polyphosphoric acid (PPA), PCl\textsubscript{5}/ AlCl\textsubscript{3}, sulfuric acid, and HF. This list is by no means exhaustive, however it covers the most common reagents. The acid derivatives
employed include the acids themselves, acid anhydrides, acid chlorides, esters, and nitriles.\(^{30,28,31,32,33}\) (Scheme 10)

![Chemical structure](image)

**Scheme 10**

An intermolecular Friedel-Crafts reaction has also been employed in the synthesis of chromanones. This method involves the acid catalyzed acylation of a substituted anisole with an \(\alpha,\beta\)-unsaturated (activated) acid derivative. This produces a 2'-methoxyphenyl \(\alpha,\beta\)-unsaturated ketone which then undergoes a 1,4 conjugate addition of the oxygen of the methoxy group to the \(\alpha,\beta\)-unsaturated ketone to form the chromanone.\(^{34}\) (Scheme 11)

A second, related acid-catalyzed method for the formation of the chromanone ring may proceed through an intramolecular reaction of an aromatic \(\alpha,\beta\)-unsaturated ester. This reaction proceeds via an initial Fries rearrangement; followed by a 1,4 conjugate addition of the resulting phenol to the \(\alpha,\beta\)-unsaturated ketone.\(^{35}\) (Scheme 11)

![Chemical structures](image)
The acylation of α-bromo acid chlorides has also been carried out. After the acylation the α-bromo ketone is then treated with base to eliminate HBr and effect the 1,4 conjugate addition.36

Lastly, the condensation of 2'-hydroxyacetophenone with methyl formate has been found to form 2-hydroxychromanones in some cases. However, it is more common for the 2-hydroxychromanone to dehydrate to form the chromone as discussed previously. (Scheme 3)

1.2 Previous Synthesis of Coniochaetone A and Coniochaetone B

In March of 1998, Mori and co-workers published the first total synthesis of coniochaetone A and coniochaetone B.37 Their synthesis started with methyl di-O-methyl-p-orsellinate 18 which was prepared from orcinol (1,2-dihydroxy-5-methylbenzene) 16. Orcinol was converted to p-orsellinic acid 17 by a procedure published by Kalamar and co-workers38, and was subsequently methylated by refluxing with dimethyl sulfate (DMS) and K₂CO₃ in acetone to give methyl di-O-methyl-p-orsellinate 18 as reported previously by Ramaswamy and co-worker.39 (Scheme 12)
One of the ethers was subsequently demethylated with BCl₃ in CH₂Cl₂. The ester was then converted to the key intermediate 19, a β-ketosulfoxide, with an overall yield of 63% from 18.

![Diagram of the reaction](image.png)

**Scheme 13**

The key step in this synthesis is the formation of the cyclopentane ring. Using a procedure modified from the work of Casale⁴⁰, compound 19 was reacted with succinaldehyde to initiate a cascade reaction. The initial reaction probably involves an aldol condensation between the β-ketosulfoxide and the succinaldehyde. This is followed by a second (intramolecular) condensation to produce intermediate 20. Elimination of HSOCH₃ then gave compound 21.

![Diagram of the reaction](image.png)

**Scheme 14**
Compound 21 was then converted into both coniochaetone A and coniochaetone B. The synthesis of coniochaetone A was completed by an oxidation of the hydroxyl of 21 with tetrapropylammonium perruthenate (TPAP)/4-methylmorpholine N-oxide (NMO) followed by demethylation using BCl₃, with a yield of 69% for the two steps and an overall yield of 9.6% starting from the permethylated p-orsellinic acid (18). (Scheme 15)

Scheme 15

The synthesis of coniochaetone B (2) was also completed in two steps from compound 21. The free hydroxyl group was first acetylated with acetic anhydride in pyridine catalyzed by 4-dimethylaminopyridine (DMAP). Treatment of the resulting compound (23) with BCl₃ deprotected both the methylated and acetylated hydroxyls with a yield of 56% for the two steps and an overall yield of 7.8% for coniochaetone B (2). (Scheme 16)

Scheme 16
Although both coniochaetone A and coniochaetone B have thus been synthesized we felt that there was room for improvement. One of the most obvious sites of improvement is the formation of the cyclopentane ring. We felt that Mori's yield of 22% could be improved upon with a different approach. Secondly, we hoped to synthesize enantiomerically pure coniochaetone B for comparison with an authentic sample.

1.3 Retrosynthetic analysis

In the course of our attempted synthesis of coniochaetone A and coniochaetone B a number of synthetic approaches have been developed and subsequently discarded. For completeness, all synthetic approaches will be explained fully in the discussion; however, only the two routes which we felt to be the most promising will be introduced at this time.

In the first route (Scheme 17), it was envisioned that coniochaetone A could be obtained from the chromanone 24 via a simple oxidation such as a bromination/dehydrobromination. This type of reaction, as discussed previously, is well known in the literature and does not appear to present any problems. An intramolecular Claisen reaction was envisioned for the key cyclization of the cyclopentane ring, converting structure 25 into 24. Formation of the chromanone 25 from the α,β-unsaturated ketone 26 was expected to proceed via a 1,4 conjugate addition of a phenolate to the enone, a procedure well known in the literature (also discussed previously). The bromination/dehydrobromination of 28 to produce the α,β-unsaturated ketone 26 was also not expected to present any problems. The first step is the acylation of orcinol. This presented a key problem; orcinol can be acylated in one of three
positions, producing two distinct compounds. Based upon information inferred from the literature, it was concluded that the acylation of 1,3-dimethoxy-5-methylbenzene would produce the wrong isomer and that the acylation of unprotected orcinol would produce the isomer required for the synthesis, albeit in poor yields. Since both orcinol and the mono methyl ester of adipic acid are relatively inexpensive, the low yield was deemed acceptable.

Scheme 17
During the writing of this thesis, compound 27, with the substitution of a chlorine for the bromine (to be discussed later), from the first route has been synthesized and characterized. It is hoped that conditions may be found to convert compound 27 into compound 24 in one pot with the addition of the correct base, although initial attempts have not been successful.

The second route involves the oxidation of coniochaetone B to coniochaetone A, first reported by Yamazaki and co-workers\(^2\), as the final step. It was believed that coniochaetone B (2) could be synthesized from 30 by an isomerization of the exo double bond. This rearrangement was thought to be highly favored for two reasons: first, the *exo* double bond is converted to an *endo* double bond and, second, the due to aromatic stability of the chromone ring system. It was believed that compound 30 could be produced by the dehydrobromination of compound 31. 2-Methoxy-3-chlorochromanones\(^4\), similar to compound 31, have been synthesized previously and it was felt that this step would not present any difficulty. The synthesis of cyclopenta-[b]-chromones, such as 32, has been accomplished by a number of routes;\(^4\) the most promising being the condensation of the acetyl protected orsellinic mixed anhydride, formed by the reaction of the protected acid 33 with methyl chloroformate 34, with an enamine of cyclopentanone 35.\(^4\) The synthesis of the acetylated orsellinic acid 33, a new compound, was easily achieved from the reaction of *p*-orsellinic acid 17 with acetic anhydride. Orsellinic acid was obtained from orcinol via the Kolbe-Schmitt reaction.

In the second route, compound 31, and its chloro analogue, have been synthesized and characterized. The elimination of HBr/HCl has been found to be extremely
problematic under basic conditions. A possible solution to this obstacle has been devised and this will be discussed later.

Scheme 18
2 RESULTS AND DISCUSSION

2.1 First Attempted Synthesis of Coniochaetones A & B

Our initial synthetic plan involved a 1,4 conjugate addition of orcinol 16 to 2-carbethoxycyclopent-2-en-1-one 36. This was to be followed by an intramolecular Friedel-Crafts acylation and subsequent oxidation to the chromone. (Scheme 19)

Scheme 19

Compound 36, 2-carbethoxycyclopent-2-en-1-one, was not commercially available and therefore it had to be synthesized. It was felt that the simplest route to 36 was via a bromination/dehydrobromination of the readily available 2-carbethoxycyclopentanone 39. Using a modification of a procedure published by Ozols and co-workers, compound 39 was brominated with N-bromosuccinimide (NBS) in dry chloroform to produce 2-bromo-2-carbethoxycyclopentanone 40, with a crude yield of 96%. The $^1$H NMR spectrum of the product was compared with the spectral data obtained by Marx and co-workers to verify the structure as that of 40. Our attempt to
eliminate HBr under basic conditions to obtain 36, however, was unsuccessful. Marx and co-workers found that when 40 is subjected to basic conditions, 5-carbethoxycyclopent-2-enone 41 is the only isomer obtained, along with a large percentage of polymer (Scheme 20).

**Scheme 20**

Having been unsuccessful in synthesizing 36 by a bromination/dehydrobromination reaction, we decided to utilize a selenoxide elimination as an alternative. Compound 39 was deprotonated with NaH followed by treatment with benzeneselenenyl chloride to produce the α-selenide 42. The α-selenide 42 was isolated and the crude compound was oxidized to the selenoxide by the addition of H₂O₂, which was followed by the elimination of PhSeOH. (Scheme 21)
Having compound 36 in hand we proceeded to the next step of the synthesis; the mono-alkylation of orcinol 16 by a 1,4 addition to the enone 36. Orcinol 16 was dissolved in dry hexane, treated with n-butyllithium, followed by the addition of compound 36 (Scheme 22). Upon workup only orcinol 16 was isolated. The decomposition of 36 under basic conditions appeared to be faster than the addition of the phenolate. This result eliminated the possibility of a base-catalyzed coupling of the enone 36 with orcinol 16.

![Scheme 22](image)

**2.2 Polyphosphoric Acid (PPA) Condensation of Orcinol 16 and 2-Carbethoxycyclopentanone, 39**

Having been unsuccessful in alkylating orcinol by the above approach, we decided to attempt the acylation first. This would be followed by an oxidation of the ketone to an enone, intramolecular 1,4 conjugate addition, and a second oxidation to the chromone. (Scheme 23)
Although Scheme 23 shows the acylation of orcinol, it was realized that the hydroxyl groups would have to be protected and that methyl ethers would provide the most stability towards the harsh acidic conditions necessary for the acylation. The methylation of orcinol was readily accomplished by treatment with DMS/K$_2$CO$_3$ in acetone with a yield of 95%.

The methylated orcinol (1,3-dimethoxy-5-methylbenzene 45) was added to PPA and heated to \(-100\, ^\circ\text{C}\), at which point 2-carbethoxycyclopentanone 39 was added. Surprisingly, neither isomer (46 or 47) of the expected product was formed.
The $^1$H NMR of one of the two products obtained showed two aromatic protons ($\delta$ 6.78 and 6.51), three benzylic protons ($\delta$ 2.51), six aliphatic protons ($\delta$ 3.30, 2.82 and 2.10) and three methoxy protons ($\delta$ 3.87). An integration of only two protons in the aromatic region indicates that the 1,3-dimethoxy-5-methylbenzene 45 had been acylated, however, the loss of one of the methoxy signals indicates that the reaction had not ended with the acylation. The $^1$H NMR data and mass spectral data together indicated the formation of a chromone. It is known that 2'-hydroxyphenyl-\(\beta\)-diketones, such as the example given in Scheme 25, condense under acidic conditions to produce chromones but the condensation of a 2'-methoxyphenyl-\(\beta\)-diketone is, to our knowledge, unprecedented (Scheme 26).
The mechanism of the condensation of 2'-hydroxyphenyl-β-diketones, such as 48, likely proceeded via the nucleophilic attack of the phenol at the more remote carbonyl group, thus forming the (protonated) hemi-acetal 51. This mechanism is thought to be less likely for 2'-methoxyphenyl-β-diketones, such as compound 49, due to the reduced nucleophilicity of the ether as well as its increased steric bulk. A second plausible mechanism is also shown in Scheme 27. In this mechanism, the hydroxyl of the enol adds to the aromatic ring in a formal nucleophilic, sense causing a loss of aromaticity. The aromaticity of the ring is regained by the elimination of methanol from 53.
It was concluded that the reaction of 1,3-dimethoxy-5-methylbenzene 45 with 2-carbethoxycyclopentanone 39 in PPA produced two chromones. The structures of these compounds were assigned as compounds 54 and 55 and it became necessary to identify the structure with the correct compound. This became a trivial task once the difference between the chemical shifts of the respective benzylic protons was noticed and explained. The benzylic protons appear at δ 2.51 for one spectrum and δ 2.83 for the other. The downfield shift of δ 0.32 for the second isomer may be explained as a result of the deshielding effect of the carbonyl group on the neighbouring methyl group at C-6 (isomer 55). The other isomer, having a C-8 methyl group experienced no such effect from the carbonyl group. Therefore, the $^1$H NMR data given above (δ 2.51 for the C-8 methyl) is for 6-methoxy-8-methylcyclopenta-[b]-chromone 54. The total yield for the condensation reaction ranges from 35% to 50%, with isomer 55 being the favored product (over isomer 54) by approximately a 3:1 ratio. This results in a yield of only between 8% and 12% for the required isomer 54.
Although in a poor yield, compound 54 had been obtained in only two steps and it was believed that the introduction of a carbonyl group at C-4, followed by the deprotection of the methoxy group, would allow us to complete our synthesis of coniochaetone A. A literature search was conducted to gather information on the oxidation of C-3 alkyl substituents of chromone systems. It was at this point that it was realized that C-2 alkyl substituents are oxidized preferentially over C-3 substituents.49

Unfortunately, the poor yield of the chromone formation coupled with the difficulty, or even impossibility, of the direct oxidization of the C-3 alkyl substituent, convinced us that this route was not going to lead to our target.

2.3 Kolbe-Schmidt Reaction

Based upon the results obtained during the attempted acylation of the methylated orcinol 45, it seemed apparent that the regiochemistry of the acylation was going to present a larger problem than originally thought. The focus of the synthesis was therefore shifted to finding ways of introducing a carbonyl functionality between the hydroxyl groups of orcinol 16. The most convenient and reliable method of introduction of the required functionality appeared to be the Kolbe-Schmidt reaction.

The Kolbe-Schmidt reaction is a reaction that carboxylates a phenol. A number of groups have reported the synthesis of p-orsellinic acid 17 by various procedures.50,51,52 The synthesis of p-orsellinic 17 with yields of ~85% had been reported by both Hassall50 and Kalamar51, however both involved using an autoclave, with pressures of 50 atmospheres and temperatures of over 200 °C. A procedure reported by Robertson and
Robinson utilized glycerol at 110 °C as a solvent to obtain a yield of 59%. The conditions of the first procedure and the yield of the second made neither of these methods especially desirable. A procedure for the carboxylation of 3-aminophenol published by Doub and co-workers utilized boric acid (as a co-reagent) and water, under slight pressure and temperatures around 100 °C, as the solvent. This procedure was more appealing, provided it could be modified for the synthesis of p-orsellinic acid 17.

The initial conditions for the carboxylation reaction of orcinol 16 consisted of 5.0g orcinol, ~5g CO₂ (s), and 15 mL H₂O in a sealed reaction vessel. The reaction was heated to ~100 °C for 20 hrs. The reaction mixture was cooled and acidified with 6M HCl to precipitate the product with a yield of 50%. The filtrated was then extracted with ethyl ether and 45% of the unreacted orcinol 16 was recovered. The overall yield based on recovered starting material was therefore 91%. The addition of boric acid was not attempted because it was believed that any increase in the yield might be countered by an increase in the difficulty in recovering the orcinol 16.

2.4 Formation of Cyclopenta-[b]-chromone From Acetylsalicylic Acid (ASA)

The most common routes to the direct synthesis of chromones involve either the acylation of a phenol, followed by a condensation, or the condensation of a 2'-hydroxyacetophenone with an ester (Scheme 30). The first route, as shown
previously, is unsuitable. The second route is similar to the total synthesis reported by Mori and co-workers. Substituted cyclopenta-[b]-chromones have however, been synthesized by methods starting with salicylates and salicylaldehydes.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=\textwidth]{scheme30.png}};
\end{tikzpicture}
\end{center}

Scheme 30

In 1977, Watanabe and co-workers published the synthesis of cyclopenta-[b]-chromone 14 as well as the six- and seven-membered ring analogues.\textsuperscript{54} (Scheme 31) The first step of the reaction was an aldol reaction between the methoxymethyl (MOM) protected salicylaldehyde 56 and cyclopentanone. Both diastereomeric alcohols 57a and 57b were oxidized to the diketone 58 and treatment with HCl effected the cyclization to the chromone 14.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=\textwidth]{scheme31.png}};
\end{tikzpicture}
\end{center}

Scheme 31
Syntheses of cyclopenta-[b]-chromone 14 starting from acetylsalicylic acid 59 have also been reported.\textsuperscript{43,55,56,57} The syntheses published by Hall\textsuperscript{43} and Yamaguchi\textsuperscript{56} condensed the acid chloride 60a of acetylsalicylic acid 59 with an enamine of cyclopentanone, whereas the synthesis of Watanabe\textsuperscript{55} utilized a lithium enolate as the nucleophile and the acid chloride 60a as the electrophile. (Scheme 32) A third variant published by Raval and Thakor\textsuperscript{57} used a mixed anhydride (60b) as the electrophile and an enamine as the nucleophile. The mixed anhydride was formed \textit{in situ} by the reaction of methyl chloroformate and the deprotonated acetylsalicylic acid 59. The second step of the reaction was the removal of the acetyl group which was not fully understood. The final step of the sequence was the acid catalyzed cyclization of the chromone ring which has been discussed previously.

\begin{equation}
59 \quad \rightarrow \quad X=\text{a=Cl, b=OCOOMe}
\end{equation}

Scheme 32

27
Having established the availability of \( p \)-orsellinic acid 17, we decided to simplify our work at this point by employing a model compound. It was believed that salicylic acid 62 would be a suitable substitute for \( p \)-orsellinic acid 17 owing to the similarity in structure. This also allowed us to use the work of Hall\(^4\) and others for the synthesis of the key compound cyclopenta-[b]-chromone 14.

\[
\begin{align*}
\text{OH} & \quad \text{COOH} \\
\text{17} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{62} & \quad \text{COOH}
\end{align*}
\]

2.5 Attempted Indirect Oxidation of Cyclopenta-[b]-chromone

It has been reported that the direct oxidation of a 2,3-dialkyl substituted chromone proceeds preferentially at the carbon atom attached to the C-2 position.\(^49\) It was our intention therefore, to develop an indirect method for this oxidation.

\[
\begin{array}{c}
\text{\[0\]} \\
\text{\begin{array}{c}
\text{\includegraphics[width=1cm]{chromone.png}} \\
\text{\includegraphics[width=1cm]{o-alkylchromone.png}}
\end{array}}
\end{array}
\]

2.5.1 Attempted Basic Hydrolysis of Cyclopenta-[b]-chromone

The bromination of 1-phenyl-1,3-dioxoalkanes in the 2-position is a well known transformation and it can be accomplished by one of several straightforward reactions. It
was therefore our intention to transform cyclopenta-[b]-chromone 14 into the 1-phenyl-1,3-dioxoalkane 63 or more simply, to hydrolyze the chromone ring. This would allow the oxidation to the enone 64, followed by an intramolecular 1,4 addition and a second oxidation step to give 4-oxocyclopenta-[b]-chromone 65, an analogue of coniochaetone A (Scheme 33).

Scheme 33

Cyclopenta-[b]-chromone 14 was stirred in a 2M solution of NaOH for 2 days. The solution was acidified and the product was collected by filtration. The resulting product was not compound 63 as expected. The chromone had been hydrolyzed to the acid 69. This type of reaction has been previously reported by Hall. The mechanism of the reaction is depicted in Scheme 34. Hydroxide attacks at C-2, thus forming the enolate 66. The enolate is reprotonated to give the 2-hydroxychromanone 67. Deprotonation of the hydroxyl group forms a second enolate which is reprotonated to give a nine-membered lactone 68, which is then hydrolyzed to give the observed acid product 69 in near quantitative yield.
2.5.2 Formation and Attempted Oxidation of an Enamine of Cyclopenta-[b]-chromone

Having determined that the hydrolysis of cyclopenta-[b]-chromone 14 was not possible with a hydroxide base, an amine was considered. In 1966, Kostka\textsuperscript{58} reported the cleavage of chromone 4 in the presence of various primary and secondary amines, which gave a variety of enamines 70.
In 1981, Ghosh and Khan$^{59}$ showed that the same structures could be obtained from chromone-3-carboxylates 71 via the reaction with an primary or secondary amine involving the elimination of CO$_2$. More importantly, they also showed that the amination could be reversed to reform the chromone, minus the carboxylate unit.

Scheme 36

Ghosh and Khan proceeded to show that for primary amines, 70a R = alkyl R' = H, the NH $^1$H NMR signal was shifted considerably downfield, due to hydrogen bonding to the carbonyl, thus confirming the configuration of the double bond as Z. In contrast, when a secondary amine was used in this reaction, the $^1$H NMR coupling constants for the two vinylic protons of the enamine, 70a (R,R' = alkyl), were in accordance with that of an E double bond.

Having established a precedent for the formation of an enamine from a chromone and for the reconstitution of the chromone by elimination of the amine, we felt that this would be a potential route to the enone 64. It was hoped that the enamine could be brominated between the carbonyl unit and the carbon containing the nitrogen to furnish compound 73 in a manner similar to the bromination of a 1,3-dioxoalkane, in which the 2-position is usually brominated. It was felt that the elimination of HBr followed by
hydrolysis to reform the second carbonyl group would produce compound 64. Compound 64 could easily be converted into 65 as discussed previously.

Scheme 37

Cyclopenta-[b]-chromone 14 was dissolved in methanol and 5 equivalents of iso-butylamine were added. The reaction mixture was stirred for 3 days at room temperature. The enamine 74 (compound 70b R=H, R'=iso-butyl) precipitated as a bright yellow solid, with a yield of 78%. An additional 19% was recovered by concentrating the methanol. All spectral data were obtained on the initial precipitate and no impurities were detected.
Bromination of the emamine 74 did not lead to compound 73, however: instead, the regioisomer 75 was obtained. It is believed that compound 73 may have formed initially but that under the reaction conditions it rearranged to form compound 75. The initial loss of the bromide ion is believed to reduce the steric strain in the compound. This loss also allows the double bond of the emamine to be isomerized into a position of conjugation with the carbonyl group and phenyl ring. The nucleophilic attack of the bromide on the allylic cation completes the rearrangement.
2.5.3 Bromination of Cyclopenta-\([b]\)-chromone 14 to form a Bromohydrin

Opening the chromone ring to form a 1,3-diketone thus proved to be an ineffective route for synthesizing coniochaetone A and coniochaetone B. We therefore decided to take a second look at the oxidation of chromones. As was previously stated, when a chromone with both C-2 and C-3 alkyl substituents was oxidized, the C-2 alkyl substituent was oxidized exclusively.\(^{49}\) This is not the only known oxidation of chromones. The oxidation of the C-2/C-3 double bond of chromones to form bromohydrins has also been reported.\(^{60}\)

![Scheme 40](image)

This structure was compared to the 2-bromo-1,3-diketone we had been previously trying to synthesize. The only difference between these compounds is the presence of the hemi-acetal in structure 77. It was believed that the much sought after enone 64 could be synthesized from compound 76: the question was whether 64 could be synthesized from compound 77.

![Scheme 41](image)
It was believed that by subjecting compound 77 to basic conditions one of two things would happen. The route leading to compound 64 was obviously preferable to us since it would lead to the objective in the least number of steps. A second route, via compound 78, although not ideal, would still allow the completion of the synthesis. The final step in this sequence would involve an intramolecular condensation to reform the cyclopentane ring. Compound 77 was stirred in chloroform with 2.2 equivalents of triethylamine (TEA) for 3 hours. Complete conversion of the starting material to a single product was observed by TLC. This compound, however, was neither of the expected products discussed above.

Scheme 42

The previous two synthetic pathways were proposed because they lead to the desired product. As is often the case, the actual reaction pathway was obscured by excessive optimism. Bromohydrins, when reacted under basic conditions, form epoxides.
This reaction is an example of the Williamson ether synthesis. This is the reaction pathway that is actually followed when the bromohydrin 77 was treated with TEA.

![Scheme 43](image)

2.6 Synthesis of 4a-Bromo-1a-methoxycyclopenta-[b]-chromanone

One of the most promising routes to the synthesis of coniochaetones A and B involves 4a-bromo-6-hydroxy-1a-methoxy-8-methylcyclopenta-[b]-chromanone 31 (The numbering of the cyclopenta-[b]-chromone ring has been used here for consistency). The retro-synthetic pathway presented in the Introduction is shown in more detail in Scheme 44. The synthesis of p-orsellinic acid 17 has been discussed previously and is only shown here for completeness. p-Orsellinic acid 17 was acetylated with acetic anhydride to give compound 33 in 80% yield. Rather than proceeding with the condensation reaction to obtain compound 32, we switched to the model compound also discussed previously.
We had previously shown that cyclopenta-[b]-chromone 14, a model compound of 32, could be converted into the bromohydrin 77. Although we have shown that this bromohydrin undergoes a Williamson ether synthesis reaction to form the epoxide 80, it was felt that if this reaction pathway could be blocked we could still complete our synthesis of coniochaetones A and B by this route. We felt that the easiest method of blocking the Williamson ether synthesis reaction was to convert the hydroxyl group into a methoxy group by treatment with dimethyl sulfate (DMS). This conversion was expected to be straightforward for the model compound, since it had only one hydroxyl
group, but the bromohydrin formed during the synthesis of coniochaetones A and B possessed a hydroxyl group on the aromatic ring which could also be methylated. At this point we decided that it would be easier if we synthesized compound 81 directly from cyclopenta-[b]-chromone 14, thus eliminating the need to perform a regiochemically specific methylation when the methodology is transferred to the actual series.

Scheme 45

The first attempted synthesis of 4a-bromo-1a-methoxycyclopenta-[b]-chromanone 81 involved a modification of the procedure for synthesizing the corresponding bromohydrin 77. Cyclopenta-[b]-chromone 14 was dissolved in a 4:1 mixture of DMSO and methanol, NBS was added slowly and the reaction mixture was heated to 40 °C for 2 hours. Extraction of the reaction mixture resulted in the recovery of starting material. A second reaction was conducted in which the cyclopenta-[b]-chromone 14 was dissolved in pure methanol followed by the addition of the NBS and stirring overnight. The product was extracted with CH₂Cl₂ to give a crude yield of 94%. The product was purified by column chromatography using 60μ silica and CHCl₃ as eluent, Rₜ = 0.42. The yield after chromatography was only 17% indicating that the compound had probably
decomposed on the column. The explanation for this decomposition will be discussed later. An attempt to purify 4a-bromo-1a-methoxycyclopenta-[b]-chromanone 81 by a reduced pressure distillation was also unsuccessful. We decided at this point, based upon the crude $^1$H NMR, that 4a-bromo-1a-methoxycyclopenta-[b]-chromanone 81 was probably pure enough to be carried on to the next step and therefore further attempts to purify it were not carried out.

It was hoped that by subjecting 4a-bromo-1a-methoxycyclopenta-[b]-chromanone 81 to basic conditions an exo-cyclic double bond could be introduced to give the enone 82. It was felt that this compound might possess enough ring strain to undergo an allylic rearrangement reaction to produce the chromone ring and give 4-methoxycyclopenta-[b]-chromone 83 or 4-hydroxycyclopenta-[b]-chromone 84, if water was introduced.

![Scheme 46](image)

4a-Bromo-1a-methoxycyclopenta-[b]-chromanone 81 was subjected to various bases and conditions. The results are summarized in Table 1. The only product isolated from any of these reactions was cyclopenta-[b]-chromone 14, which formally makes this reaction a reduction. Reductive debromination is known to be a competing reaction in
the dehydrobromination of α-bromoketones, although in this case it accounts for all the product. Reductive debromination is most likely the reason that 4a-bromo-1a-methoxycyclopenta-[b]-chromanone 81 decomposed on the column as previously mentioned.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Sodium Acetate</td>
<td>Acetic Acid</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>14</td>
<td>Sodium Acetate</td>
<td>Acetone</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>14</td>
<td>Sodium Hydroxide</td>
<td>Methanol</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>14</td>
<td>DBU</td>
<td>Chloroform</td>
<td>1</td>
<td>Reflux</td>
</tr>
<tr>
<td>14</td>
<td>1M Sodium Hydroxide</td>
<td>Ethanol</td>
<td>1.5</td>
<td>Reflux</td>
</tr>
<tr>
<td>14</td>
<td>Silver Oxide</td>
<td>Methanol</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>14</td>
<td>Silver Nitrate</td>
<td>Methanol</td>
<td>3</td>
<td>Room Temperature</td>
</tr>
</tbody>
</table>

Having been unsuccessful in dehydrobrominating 4a-bromo-1a-methoxycyclopenta-[b]-chromanone 81 with a number of bases, including two silver salts, we decided to switch to the chloro analogue. We believed that by switching to a chlorine substituent we would reduce the propensity of the halogen to be reductively eliminated.

As with the preparation of 4a-bromo-1a-methoxycyclopenta-[b]-chromanone 81, 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85 was made by reacting cyclopenta-[b]-chromone 14 with N-chlorosuccinimide (NCS) in methanol. The chloro analogue was more crystalline and therefore was more easily purified by recrystallization from hexanes.
Having 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85 in hand we then proceeded to attempt the dehydrochlorination. As with the bromo analogue, 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85 was subjected to a variety of reaction condition which have been summarized in Table 2.

**Table 2**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Temperature</th>
<th>YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Hydroxide</td>
<td>Water</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>Water/Ethanol</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>Water</td>
<td>1</td>
<td>Reflux</td>
</tr>
<tr>
<td>Potassium Hydroxide</td>
<td>Toluene</td>
<td>1.5</td>
<td>Reflux</td>
</tr>
<tr>
<td>DBU</td>
<td>THF</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>DBU</td>
<td>THF</td>
<td>1</td>
<td>Reflux</td>
</tr>
<tr>
<td>DBU</td>
<td>Toluene</td>
<td>1.5</td>
<td>Reflux</td>
</tr>
<tr>
<td>Sodium Nitrite</td>
<td>Water/Methanol</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Potassium Hydride</td>
<td>Hexanes</td>
<td>2</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Potassium tButoxide</td>
<td>tButanol</td>
<td>1</td>
<td>Reflux</td>
</tr>
<tr>
<td>Sodium Amide</td>
<td>Hexanes</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Sodium Acetate</td>
<td>Acetic Acid</td>
<td>20</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>None</td>
<td>Water</td>
<td>48</td>
<td>Reflux</td>
</tr>
<tr>
<td>Hydrogen Chloride</td>
<td>Water</td>
<td>48</td>
<td>Room Temperature</td>
</tr>
</tbody>
</table>

* The yield of compound 14 was 20-30% with the starting material making up the remaining mass.
After so many attempts it was realized that we were not going to be able to form the required enone 85 via a base-catalyzed reaction of 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85. It was at this point that the Kendall-Mattox reaction was brought to our attention (Scheme 48).

![Scheme 48](image)

The Kendall-Mattox reaction is used to convert α-bromoketones into α,β-saturated ketones. The first step of this reaction is the formation of a phenylhydrazone 86 (a simplified example is shown in Scheme 49). The deprotonation of the phenylhydrazone causes the elimination of the bromide ion as shown, to give compound 87. After the dehydrobromination a prototropic shift reforms the phenylhydrazone 88, with the addition of the α,β-unsaturated double bond. The phenylhydrazone is then reacted with 2-oxopropanoic acid to produce the α,β-unsaturated ketone 89.
One attempt has been made to convert 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85 into the chromanone 82 by the Kendall-Mattox reaction. The first step involved reacting 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85 and 5 equivalents of sodium acetate with 2,4-dinitrophenylhydrazine in acetic acid under an atmosphere of argon (Scheme 50). Although no product was isolated, the crude $^1$H NMR showed a doublet at $\delta$ 8.4 which is thought to represent the C-6 proton of the cyclopenta-[b]-chromone ring system in compound 90. The downfield shift of this proton, from $\delta$ 7.9 for 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85, can be compared to the C-6 signal for cyclopenta-[b]-chromone 14 of $\delta$ 8.2. The downfield shift of the C-6 proton for cyclopenta-[b]-chromone 14 is a result of the deshielding cone of the C-5 carbonyl group. The upfield value of $\delta$ 7.9 for 4a-chloro-1a-methoxycyclopenta-[b]-chromanone 85 is probably due to the distortion from planarity of the chromanone ring system. The value of $\delta$ 8.4 can therefore be assigned to the C-6 proton of the phenylhydrazone 90.
2.7 The Acylation of Orcinol with Adipic Acid Derivatives

The acylation of orcinol at the site between the hydroxyl groups has been reported by a number of groups.\textsuperscript{65,66,67} It appears to be possible to acylate between the hydroxyl groups of orcinol only if the hydroxyl groups are not protected and even then the yields are not very good, as low as 17% in some cases. This having been said, we still feel that the acylation of orcinol with an adipic acid derivative such as 5-methoxycarbonylpentanoyl chloride might provide an acceptable synthetic route to coniochaetones A and B. The second step is a conceptually straightforward bromination reaction to produce compound 27. The next three steps are all base catalyzed and it is
hoped that with the correct base these transformations may be completed as a cascade reaction in one pot, to eventually give compound 24. The final step of the synthesis would involve an oxidation of chromanone 24 to coniochaetone A 1 which, as discussed previously, is not expected to present any difficulty.
The synthesis of 5-methoxycarbonylpentanoyl chloride 29 was achieved by the reaction of the mono methyl ester of adipic acid and oxalyl chloride. The acylation of orcinol 16 with 5-methoxycarbonylpentanoyl chloride 29 using aluminum chloride has been attempted. There was some indication of product formation in the crude $^1$H NMR however the product has not yet been isolated in pure form.

At this point we switched to a model compound. The reason for the use of the model compound at this point is two fold. The first reason is, as stated above, that the yield from the acylation reaction is expected to be low. The second reason is that compound 69 had been synthesized previously in an attempt to hydrolyse the chromone ring of cyclopenta-[b]-chromone 14. Our bromination of 6-(2'-hydroxyphenyl)-6-oxohexanoic acid 69 with pyridinium tribromide in chloroform proceeded in a gratifying 90% yield to give compound 91.

![Scheme 52](image)

Having obtained compound 91 in excellent yield, we proceeded to attempt the dehydrobromination to give compound 92. At this point we chose a mild and non-nucleophilic base to effect the dehydrobromination because we did not want 1,4 conjugate addition to occur and complicate the reaction. The brominated acid 91 was therefore dissolved in chloroform and 3.3 equivalents of triethylamine (TEA) were added. The reaction mixture was stirred for three hours at room temperature and was then partitioned between water and chloroform. The organic layer was dried and concentrated. The $^1$H NMR of the product showed only one signal in the vinylic region,
a triplet at $\delta$ 5.94. This did not fit either of the expected products, compounds 92, or 93. If the $\alpha,\beta$-unsaturated ketone 92 had been formed, two signals would have been detected in the vinylic region. If the phenolate had added to the $\alpha,\beta$-unsaturated ketone to produce 93, no signals would be expected between $\delta$ 5.0 – 6.5.

![Chemical structure diagram]

Scheme 53

A closer look at the mechanism of the reaction of TEA with the brominated acid led us to the structural determination of the isolated product. The most acidic proton of the brominated acid 91 is the carboxylic acid hydrogen. With the removal of this proton, the acid acted as a nucleophile and displaced the bromine ion, most likely in an intramolecular $S_N2$ fashion. The $^1H$ NMR of the resulting lactone 94 was compared to the $^1H$ NMR spectrum of parent compound 95. The previously noted peak at $\delta$ 5.94 for the methine hydrogen was observed in both spectra, with less than a $\delta$ 0.1 shift from that in the parent compound 95.
It became apparent that the pathway to the formation of the lactone had to be blocked. The most obvious way to accomplish this was to return to our original synthetic outline and synthesize the methyl ester of 91. The acid 91 was dissolved in methanol and HCl was bubbled through to saturate the solution. The reaction mixture was then refluxed overnight using a Soxhlet extractor and 3Å sieves to trap out the water as it formed. The initial calculated yield of 70% had to be recalculated to a yield of 82% when the mass spectrum surprisingly revealed that the α-bromine atom had been replaced by a α-chlorine atom.

The ester 96 was dissolved in methanol and 3.3 equivalents of sodium methoxide were added. The reaction mixture was stirred overnight at room temperature. Once again none of the desired products, the α,β-unsaturated ketone 92a, the C-2 substituted chromanone 93a, or the tricyclic chromanone 79, were formed (Scheme 56).
The product which we actually isolated, based upon the crude $^1$H NMR, is believed to be the result of an intramolecular $S_{N}2$ displacement of the chlorine by the phenoxide ion to produce the benzofuranone 97 shown in Scheme 57. This reaction was partially expected due to the previously noted lability of the $\alpha$-chlorine atom. The $^1$H NMR signal for the methine proton appears at $\delta$ 4.55. The chemical shift for the methine proton in similar benzofuranones falls within the range $\delta$ 4.45 - 4.8. Although full characterization of the product of this reaction has not yet been completed, it has been tentatively concluded that it is the benzofuranone 97. The brominated acid 91 was also reacted with 3.3 equivalents of sodium methoxide in methanol which produced what is believed to be compound 98, again based upon the $^1$H NMR signal for the methine proton. This result contrasts with the reaction of compound 91 with TEA to produce the 6 lactone 94, demonstrating the importance of the base used in determining the reaction pathway.
We have shown that the synthesis of the chlorinated ester 96 can be accomplished in four steps and an overall yield of 39\% from acetylsalicylic acid 59 (Scheme 58). It remains to be seen whether this route can be shortened to two steps by the direct acylation of orcinol 16 with an adipic acid derivative. The following three steps required for the completion of the synthesis, although at present unsuccessful, are likely to occur as a cascade reaction once the side reactions have been eliminated and the correct base has been found. The final step of this synthetic route involves the oxidation of a chromanone to a chromone, a straightforward procedure.
Scheme 58
Conclusion

Although the synthesis of coniochaetones A and B is incomplete, we have provided groundwork for what we believe to be two potential synthetic pathways to these natural products. During our attempted synthesis of coniochaetones A and B we were able to synthesize a number of novel compounds. These compounds are summarized in Scheme 59. It is believed that both compounds 81 and 96, as discussed in the body of the text, in the model series are only one to two steps away from being converted into the analogues of coniochaetones A and B.

Scheme 59
Experimental

$^1$H NMR and $^{13}$C NMR spectra were run at 200 MHz on a Varian spectrometer using TMS as the internal standard in CDCl$_3$, DMSO-$d_6$ or CD$_3$OD as stated. Infrared spectra were run as KBr disks or liquid films on either a Nicolet 5DXB FTIR or a Nicolet Avatar 360 FTIR. Mass spectra were run under electron impact conditions on a VG11-250S instrument. Melting points were determined on an Electrothermal 1A 6304 apparatus and are uncorrected. All solvents used were ACS grade. Dichloromethane was distilled prior to use. Chloroform was dried by passing it through a column of anhydrous Al$_2$O$_3$.

2-Carbethoxycyclopent-2-enone (36)

KH (0.4 g, 10 mmol), after being washed with hexanes to remove the mineral oil in which it was stored, was placed in 30 mL of dry THF. 2-Carbethoxycyclopentanone 39 (1.56 g, 10 mmol) was added dropwise. The solution was stirred for 0.5 h. Benzeneselenenyl chloride (2.11 g, 11 mmol) was then added. The reaction mixture was added slowly, with stirring, to 75 mL of a mixture of 1:1:1 ether/pentane/saturated sodium carbonate. The organic layer was washed with an ice cold saturated solution of NaCl, dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give the crude phenylselenium compound 42. The crude phenylselenenyl compound was dissolved in 30 mL CH$_2$Cl$_2$. Hydrogen peroxide (30%, 2.83 mL) was mixed with water (2.5 mL). The
H₂O₂ solution was added slowly to the CH₂Cl₂ solution. The reaction mixture was stirred for 0.5 h. The organic layer was washed with H₂O (2 x 10mL) and the water layer was back-extracted with CH₂Cl₂ (2 mL). The organic layer was dried with Na₂SO₄ and concentrated under reduced pressure to give 1.2 g (76%) of product. The 2-carbethoxycyclopent-2-enone was purified by Kugelrohr distillation.

2-Carbethoxy-2-phenylselenocyclopentanone 42: 

\[ ^1H \text{NMR (CDCl}_3): \delta 7.6 \text{ (m, 2H), 7.3 \text{ (m, 3H), 4.2 \text{ (q, 2H), 2.6-2.2 \text{ (m, 3H), 2.2-1.8 \text{ (m, 3H), 1.25 \text{ (t, 3H)}}).} \]

2-Carbethoxycyclopent-2-enone 36: 

\[ ^1H \text{NMR (CDCl}_3): \delta 8.4 \text{ (t, 1H) 4.3 \text{ (q, 2H) 2.73 \text{ (m, 2H) 2.55 \text{ (m, 2H) 1.3 \text{ (t, 3H)}}).} \]

1,3-Dimethoxy-5-methylbenzene (45)

Orcinol 16 (2 g, 16.1 mmol) was dissolved in 50 mL acetone. Potassium carbonate (6.9 g, 50 mmol) was added followed by dimethyl sulfate (6.7 mL, 71 mmol). The reaction mixture was stirred for 4 h at room temperature. 2M NaOH (25 mL) was added and the mixture was refluxed for 1 h. The reaction mixture was then stirred overnight, followed by partitioning between CH₂Cl₂ and water. The crude product was purified by reduced pressure distillation to yield 45 (2.26 g, 88%).

\[ ^1H \text{NMR (CDCl}_3): \delta 6.36 \text{ (s, 2H) 6.31 \text{ (s, 1H) 3.79 \text{ (s,6H) 2.32 \text{ (s, 3H)}}).} \]
6-Methoxy-8-methyl-5-oxocyclopenta-[b]-chromone (54) and 8-Methoxy-6-methyl-5-oxocyclopenta-[b]-chromone (55)

Approximately 10 mL of polyphosphoric acid (PPA) was heated to 110 °C. 1,3-Dimethoxy-5-methylbenzene (0.57 g, 3.75 mmol) was added with stirring. 2-Carbethoxycyclopentanone (1.44 g, 9.22 mmol) was also added. The reaction mixture was stirred at 110 °C for 0.5 h and was then allowed to cool to room temperature. Ice cold 10 % NaOH (20 mL) was added and the product was extracted with CH₂Cl₂. The two isomers were separated by column chromatography (CH₂Cl₂/silica) to give 54 mp 197-198 °C, Rᵣ = 0.52 (0.12 g, 14%) and 55 mp 158-159 °C, Rᵣ = 0.42 (0.33, 38%)

6-Methoxy-8-methyl-5-oxocyclopenta-[b]-chromone 54: ¹H NMR (CDCl₃): δ 6.78 (s, 1H) 6.51 (s, 1H) 3.87 (s, 3H) 3.30 (m, 2H) 2.82 (m, 2H) 2.41 (s, 3H) 2.14 (m, 2H); ¹³C NMR (CDCl₃): δ 110.0, 106.8, 55.7, 36.2, 29.6, 22.8, 22.0. (sample too dilute to detect quaternary signals); EIMS m/z (%): 230 (100), 202 (45), 187 (34); HR-EIMS: calculated for C₁₄H₁₄O₃, 230.09429; observed, 230.09429; Anal. Calcd. for C₁₄H₁₄O₃: C, 73.03; H, 6.13; found: C, 72.43; H, 6.08.

8-Methoxy-6-methyl-5-oxocyclopenta-[b]-chromone 55: ¹H NMR (CDCl₃): δ 6.67 (s, 2H) 3.85 (s, 3H) 2.83 (m, 7H) 2.08 (m, 2H); ¹³C NMR (CDCl₃): δ 178.0, 166.7, 161.9, 160.4, 142.7, 121.8, 116.8, 115.9, 99.0, 55.4, 31.9, 26.1, 22.9, 19.7; FTIR (KBr): 2925, 2858, 1655 cm⁻¹; EIMS m/z (%): 230 (100), 202 (16), 187 (16); HR-EIMS:
calculated for C₁₄H₁₄O₃, 230.09429; observed, 230.09407; Anal. Calcd. for C₁₄H₁₄O₃: C, 73.03; H, 6.13; found: C, 72.66; H, 6.07.

\[ \text{p-Orsellinic acid 17} \]

Orcinol 16 (2.0 g, 14 mmol) was placed in a pressure vessel. NaHCO₃ (2.94 g, 35 mmol) was added followed by H₂O (10mL) and solid CO₂ (Approx. 2.0 g). The reaction vessel was vented to allow the CO₂ to force out the remaining air. When most of the CO₂ had sublimed the pressure vessel was capped. The reaction mixture was heated to 100 °C for 18 h. The reaction mixture was filtered and the filtrate was acidified with 6 M HCl causing the p-orsellinic acid to precipitate. The precipitate was filtered giving 1.2 g (52%) of p-orsellinic acid. The filtrate was extracted with ether to recover 46% of the starting material.

\(^1\text{H NMR (CD₃OD): } \delta \text{ 6.27 (s, 2H) 4.90 (s, 2H) 2.24 (s, 3H) (note: carboxylic acid not observed).} \]
2,6-Diacetoxy-4-methylbenzoic Acid (33)

*p*-Orsellinic acid 17 (2 g, 12 mmol) was dissolved in acetic anhydride (10 mL). A catalytic amount of 4-N,N-dimethylaminopyridine (DMAP) was added and the reaction mixture was refluxed overnight. The product was partitioned between water and CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give an oil which eventually solidified to give 2.4 g (80%) of compound 33.

$^1$H NMR (CDCl$_3$): $\delta$ 6.88 (s, 2H) 2.40 (s, 3H) 2.29 (s, 6H) (note: carboxylic acid not observed).

1-N-Morpholinocyclopentene (35)

Cyclopentanone (25 g, 300 mmol), morpholine (26.26 g, 305 mmol) and toluene (200 mL) were placed in a 500 mL round-bottom flask. The flask was fitted with a Dean-Stark trap and the reaction mixture was distilled for 16 h to azetropically remove water. The reaction mixture was then concentrated under reduced pressure to remove the
toluene. The product was distilled at ~35 mmHg and 135 °C to give 34.6 g (75%) of compound 35.

$^1$H NMR (CDCl$_3$): $\delta$ 4.46 (br s, 1H) 3.73 (t, 4H, J= 5.1 Hz) 2.88 (t, 4H, J= 5.1 Hz) 2.35 (m, 4H) 1.90 (m, 2H).

**Cyclopenta[1b]chromone (14)**

Acetylsalicylic acid 59 (10.6 g, 58.8 mmol) was placed in a 300 mL round bottom flask and CHCl$_3$ (100 mL) was added, followed by triethylamine (TEA) (5.95 g, 58.8 mmol). The reaction mixture was cooled to -10 °C with an ice/salt bath. Methyl chloroformate (6.39 g, 58.8 mmol) was added dropwise. The reaction mixture was stirred for 15 min. 1-N-Morpholinocyclopentene (8.90 g, 58.8 mmol) was added dropwise and the reaction mixture was stirred for 4-8 h. Conc. HCl (35 mL) was added and the reaction mixture was refluxed for a further 4 h. The organic layer was extracted, washed twice with a conc. NaHCO$_3$ soln., dried (Na$_2$SO$_4$) and concentrated to give the crude product. The yield was found to vary between 20-55% in several attempts. The product was also very difficult to purify on a large scale. It was recrystallized from hexanes, mp 113-115 °C.

$^1$H NMR (CDCl$_3$): $\delta$ 8.25 (d, 1H, J= 9.8 Hz) 7.62 (t, 1H, J= 7.3 Hz) 7.40 (m, 2H) 2.99 (t, 2H, J= 7.3 Hz) 2.87 (t, 2H, J= 7.3 Hz) 2.13 (m, 2H).
2'-Hydroxyphenyl 2-(N-isobutylamino)cyclo-1-pentenyl ketone (74)

Cyclopenta-[b]-chromone 14 (2 g, 11 mmol) was dissolved in 25 mL methanol. Excess of iso-butylamine (7.5 g, 100 mmol) was added and the reaction mixture stirred for 3 days. The reaction mixture was filtered to give pure 2'-Hydroxyphenyl 2-(N-isobutylamino)cyclo-1-pentenyl ketone 74, 2.22 g (78%). The filtrate was concentrated to give an additional 0.54 g (19%) of product. The total yield was thus 2.76 g (97%) mp 99-100 °C (methanol).

1H NMR (CDCl3): δ 13.14 (s, 1H) 10.73 (s, 1H) 7.60 (d, 1H, J= 7.3 Hz) 7.24 (t, 1H, J= 9.5 Hz) 6.90 (d, 1H, J= 8.0 Hz) 6.76 (t, 1H, J= 8.0 Hz) 3.15 (t, 2H, J= 5.9 Hz) 2.92 (t, 2H, J= 6.6 Hz) 2.60 (t, 2H, J= 7.3 Hz) 1.87 (m, 3H) 0.99 (d, 6H, J= 6.6 Hz); 13C NMR (CDCl3): δ 188.4, 173.3, 161.9, 132.1, 128.6, 122.9, 117.6, 117.4, 104.4, 53.0, 32.5, 31.6, 29.3, 22.9, 19.9. FTIR (KBr): 2955, 2858, 1603 cm⁻¹; EIMS m/z (%): 259 (100) 242 (42) 216 (31) 202 (51) 187 (43) 121 (26) 110 (54); HR-EIMS: calculated for C16H21NO2, 259.15723; observed, 259.15752; Anal. Calcd. for C16H21NO2: C, 74.10; H, 8.16; N, 5.40; found: C, 74.87; H, 8.34; N, 5.65.
2'-Hydroxyphenyl 2-(N-isobutylamino)-3-bromocyclo-1-pentenyl ketone (75)

The 2'-hydroxyphenyl 2-(N-isobutylamino)cyclo-1-pentenyl ketone 74 (0.30 g, 1.16 mmol) was dissolved in CHCl₃ and N-bromosuccinimide (NBS) (0.247 g, 1.39 mmol) was added slowly with stirring. The reaction mixture was stirred overnight. The reaction mixture was washed with H₂O, dried (Na₂SO₄) and concentrated under reduced pressure. The product was purified by column chromatography (silica/CH₂Cl₂, R₁ = 0.67) to give 0.31 g (77%) of compound 75.

¹H NMR (CDCl₃): δ 12.0 (br s, 1H) 10.15 (br s, 1H) 7.86 (d, 1H, J = 8.0 Hz) 7.31 (t, 1H, J = 7.7) 6.94 (d, 1H, J = 8.5 Hz) 6.82 (t, 1H, J = 8.7 Hz) 4.95 (d, 1H, J = 4.8 Hz) 3.30 (m, 3H) 2.80 (m, 1H) 2.25 (m, 2H) 1.95 (m, 1H) 1.04 (d, 6H, J = 7.0 Hz); ¹³C NMR (CDCl₃): δ 191.0, 167.9, 133.0, 128.7, 122.4, 117.9, 117.7, 105.2, 52.3, 49.2, 35.1, 30.4, 30.2, 29.3, 20.0; EIMS m/z (%): 339 (36) 337 (37) 258 (99) 202 (32) 136 (80) 121 (100); HR-EIMS: calculated for C₁₆H₂₀BrNO₂, 337.06774; observed, 337.06672.
4a-Bromo-1a-hydroxycyclopenta-[b]-chromanone (77)

Cyclopenta-[b]-chromone 14 (1.00 g, 5.37 mmol) was dissolved in 40 mL 4/1 DMSO/H₂O. N-Bromosuccinimide (3.82 g, 21.48 mmol) was added with stirring. When the initial color had disappeared, the solution was poured into ice-water (200 mL). The product was extracted with ether, dried (CaCl₂) and concentrated under reduced pressure to give 1.15 g (75%) of compound 77.

* Compound 77 is believed to be trans due its reaction with base to form an epoxide. This reaction is believed to proceed via an SN₂ reaction and therefore the cis would not form the epoxide.

¹H NMR (CDCl₃): δ 7.94 (d, 1H, J= 7.6 Hz) 7.56 (t, 1H, J= 7.7 Hz) 7.05 (m, 2H) 3.78 (s, 1H) 3.02 (m, 1H) 2.5-1.5 (m, 5H); ¹³C NMR (CDCl₃): δ 136.7, 128.5, 122.2, 118.2, 33.0, 29.8, 17.9 (sample too dilute to detect quaternary carbons); FTIR (KBr): 3416, 1680 cm⁻¹; EIMS m/z (%): 284 (15) 282 (18) 202 (25) 147 (47) 121 (100); HR-EIMS: calculated for C₁₂H₁₁BrO₃, 283.98711; observed, 283.98794.
cyclopenta-[bl]-1a,4a-epoxychromanone (80)

The 4a-bromo-1a-hydroxycyclopenta-[b]-chromanone 77 (0.100 g, 0.35 mmol) was dissolved in methanol and sodium methoxide (0.57 g, 1.06 mmol) was added. The solution was stirred overnight. The reaction mixture was then partitioned between water and CHCl₃. The organic layer was dried (Na₂SO₄) and concentrated to give 40 mg (56%) of compound 80, mp 61-62 °C.

¹H NMR (CDCl₃): δ 7.96 (d, 1H, J= 7.3 Hz) 7.55 (t, 1H, J= 8.8 Hz) 7.15 (m, 2H) 2.63 (m, 1H) 2.25 (m, 3H) 1.85 (m, 1H) 1.6 (m, 1H); FTIR (KBr): 2986, 2945, 1675 cm⁻¹; EIMS m/z (%): 202 (28) 185 (7) 147 (100) 121 (23); HR-EIMS: calculated for C₁₂H₁₀O₃, 202.06299; observed, 202.06290.

4a-Bromo-1a-methoxycyclopenta-[bl]-chromanone (81)

Cyclopenta-[b]-chromone 14 (1.00 g, 5.37 mmol) was dissolved in 50 mL methanol and N-bromosuccinimide (0.80 g, 21.48 mmol) was added with stirring. The reaction mixture was allowed to stir overnight. The product was partitioned between water and CHCl₃. The organic layer was dried (Na₂SO₄) and concentrated under reduced
pressure to give 1.67 g. An attempt to purify the crude product by chromatography resulted in the isolation of only 0.30 g, mp 82-83 °C. The compound is believed to have decomposed on the column as was discussed in the body of the text.

* Compound 81 is believed to be the trans isomer because of the similarity in its formation and that of the bormohydrin 77.

\( ^{1}H \text{NMR (CDCl}_3) \): \( \delta \) 7.97 (d, 1H, J= 7.3 Hz) 7.53 (t, 1H, J= 7.7 Hz) 7.10 (m, 2H) 3.18 (s, 3H) 2.8-2.3 (m, 4H) 2.10 (m, 1H) 1.85 (m, 1H); FTIR (KBr): 2991, 1701 cm\(^{-1}\); EIMS m/z (%): 298 (6) 296 (6) 217 (73) 185 (73) 121 (100); HR-EIMS: calculated for \( C_{13}H_{13}BrO_3 \), 296.0048; observed, 296.0053.

4a-Chloro-1α-methoxy cyclopenta-[b]-chromanone (85)

Cyclopenta-[b]-chromone 14 (1.00 g, 5.37 mmol) was dissolved in 50 mL methanol and N-chlorosuccinimide (NCS) (1.50 g, 11.2 mmol) was added with stirring. The reaction mixture was allowed to stir overnight. The product was partitioned between water and CHCl\(_3\). The organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to give 1.2 g (89%) of compound 85, mp 88-89 °C (hexanes).

\( ^{1}H \text{NMR (CDCl}_3) \): \( \delta \) 7.93 (d, 1H, J= 10.2 Hz) 7.51 (t, 1H, J= 8.8 Hz) 7.08 (m, 2H) 3.17 (s, 3H) 2.6-2.3 (m, 4H) 2.1 (m, 1H) 1.85 (m, 1H); \( ^{13}C \text{NMR (CDCl}_3) \): \( \delta \) 187.3, 156.2, 135.4, 127.7, 122.3, 121.0, 117.5, 111.7, 71.9, 50.1, 30.2, 26.0, 17.5. FTIR (KBr): 2997, 2971, 1711 cm\(^{-1}\); EIMS m/z (%): 254 (8) 252 (23) 185 (48) 132 (100) 121 (82);
HR-EIMS: calculated for C$_{13}$H$_{13}$ClO$_3$, 252.05532; observed, 252.05420; Anal. Calcd. for C$_{13}$H$_{13}$ClO$_3$: C, 61.79; H, 5.19; Cl, 14.03; found: C, 61.69; H, 5.13; Cl, 14.09.

**Attempted preparation of (2, 4-Dinitrophenyl)-(3a-methoxy-2, 3, 3a, 9-tetrahydrocyclopenta[b]chromen-9-yl) diazene (90)**

The 4a-Chloro-1a-methoxycyclopenta-[b]-chromanone 85 (0.200 g, 0.79 mmol) was dissolved in 25 mL of acetic acid of sodium acetate (5 equivalents) was added. The reaction mixture was placed under an atmosphere of argon and 2,4-dinitrophenylhydrazine (0.19 g, 0.95 mmol) was added. The reaction mixture was partitioned between water and CHCl$_3$. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a crude product which appeared to contain the required product, based on $^1$H NMR.
Attempted synthesis of Methyl 6-(2',6'-dihydroxy-4'-methylphenyl)-6-oxohexanoate (28)

Orcinol 16 (1 g, 7.24 mmol) and 5-methoxycarbonylpentanoyl chloride 29 (1.3 g, 7.238 mmol) were dissolved in 5 mL of nitrobenzene. Aluminum chloride was added and the reaction mixture was stirred for 1 h. The reaction mixture was warmed to 60 °C, cooled and poured into ice-water (50 mL). The solution was extracted with ether. The ether extract was extracted twice with 2 N NaOH (50 mL). The NaOH extracts were washed with ether, acidified and extracted again with ether. The ether extracts were combined, dried and concentrated under reduced pressure. A solid product was obtained. The 1H NMR showed the resulting solid to consist of multiple products. No attempt was made to purify the product.

6-(2'-Hydroxyphenyl)-6-oxohexanoic Acid (69)

Cyclopenta-[b]-chromone 14 (100 mg, 0.54 mmol) was placed in a round bottom flask and 2 N NaOH (20 mL) was added. The reaction mixture was stirred until all the chromone had dissolved. The solution was acidified to precipitate the crude product with
a near quantitative yield. The product was recrystallized from hexanes to give 110 mg (94%) of compound 69.

\[^1\text{H NMR (CDCl}_3\text{): }\delta\ 12.30\ (s, 1\text{H}) 7.75\ (d, 1\text{H}, J= 9.8\ \text{Hz}) 7.47\ (t, 1\text{H}, J= 7.3\ \text{Hz}) 6.90\ (m, 2\text{H}) 3.04\ (t, 2\text{H}, J= 7.4\ \text{Hz}) 2.44\ (t, 2\text{H}, J= 7.4\ \text{Hz}) 1.8\ (m, 4\text{H})\ (\text{note: the carboxylic acid proton was not observed}); \ EIMS \text{ m/z (\%): 222 (37) 204 (23) 149 (35) 121 (100).}

\[
\text{5-Bromo-6-(2'-hydroxyphenyl)-6-oxohexanoic Acid (91)}
\]

6-(2'-Hydroxyphenyl)-6-oxohexanoic acid 69 (0.390 g, 1.75 mmol) was dissolved in CHCl\textsubscript{3}. Pyridinium tribromide (0.644 g, 2.11 mmol) was added and the reaction mixture was stirred overnight. The solution was washed with water, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to give 0.475 g (90%) of compound 91, mp 99-100 °C (hexanes).

\[^1\text{H NMR (CDCl}_3\text{): }\delta\ 11.89\ (s, 1\text{H}) 11.00\ (br \text{s, 1H}) 7.80\ (d, 1\text{H}, J= 6.6\ \text{Hz}) 7.76\ (t, 1\text{H}, J= 7.6\ \text{Hz}) 7.00\ (m, 2\text{H}) 5.18\ (t, 1\text{H}, J= 6.5\ \text{Hz}) 2.47\ (t, 2\text{H}, J= 7.3\ \text{Hz}) 2.23\ (m, 2\text{H}) 1.8\ (m, 2\text{H}); \ FTIR (KBr): 2500-3200, 1721, 1634 \text{ cm}^{-1}; \ EIMS \text{ m/z (\%): 302 (2), 300 (2), 220 (7), 147 (38), 121 (100); HR-EIMS: calculated for C\textsubscript{12}H\textsubscript{13}\textsuperscript{81}BrO\textsubscript{4}, 301.99767; observed, 301.99654.\]
5-(2'-Hydroxybenzoyl)-5-pentanolide (94)

5-Bromo-6-(2'-hydroxyphenyl)-6-oxohexanoic acid 91 (0.200 g, 0.664 mmol) was dissolved in CHCl₃ and triethylamine (0.222 g, 2.19 mmol) was added. The reaction was followed by TLC. The TLC showed complete conversion of the starting material after 3 h. The CHCl₃ solution was washed with water, dried (Na₂SO₄) and concentrated to give the desired lactone 94 (0.140 g, 96%).

\(^1\)H NMR (CDCl₃): δ 11.79 (s, 1H) 7.65 (d, 1H, J= 8.8 Hz) 7.55 (t, 1H, J= 8.8 Hz) 7.05 (d, 1H, J= 7.3 Hz) 6.95 (t, 1H, J= 7.3 Hz) 5.94 (t, 1H, J= 6.1 Hz) 2.70 (m, 2H) 2.2 (m, 2H) 1.85 (m, 2H).

Methyl 5-chloro-6-(2'-hydroxyphenyl)-6-oxohexanoate (96)

5-Bromo-6-(2'-hydroxyphenyl)-6-oxohexanoic Acid 91 (0.300 g, 1.0 mmol) was dissolved in methanol and HCl was bubbled through the solution to saturate it. The reaction mixture was refluxed overnight, cooled and partitioned between water and CHCl₃. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to give 0.220 g (82%) of compound 96.
\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 11.85 (s, 1H) 7.78 (d, 1H, \(J=8.8\) Hz) 7.49 (t, 1H, \(J=7.3\) Hz) 7.00 (m, 2H) 5.18 (t, 1H, \(J=8.7\) Hz) 3.68 (s, 3H) 2.43 (t, 2H, \(J=8.7\) Hz) 2.3-1.7 (m, 4H); 
\(^1^3\)C NMR (CDCl\(_3\)): \(\delta\) 198.7, 173.0, 163.8, 137.1, 129.8, 119.1, 119.0, 117.3, 56.5, 51.4, 33.3, 32.9, 21.8; FTIR (KBr): 2951, 1731, 1640 cm\(^{-1}\); EIMS m/z (%): 272 (3) 270 (9) 121 (100); HR-EIMS: calculated for C\(_{13}\)H\(_{15}\)ClO\(_4\), 270.06589; observed, 270.06535.

2-(3'-Hydroxy)carbonyl(propyl)benzofuranone

5-Bromo-6-(2'-hydroxyphenyl)-6-oxohexanoic acid 91 (100 mg, 0.33 mmol) was dissolved in methanol and sodium methoxide (60 mg, 0.1 mmol) was added. The reaction mixture was stirred overnight and then the product was partitioned between water and CHCl\(_3\). The organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to give 50 mg (70%) of crude product.

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.65 (m, 2H) 7.10 (m, 2H) 4.57 (m, 1H) 2.45 (t, 2H, \(J=7.3\) Hz) 2.10 (m, 1H) 1.85 (m, 3H) (note: the carboxylic acid proton was not observed).
2-(3'-Methoxycarbonylpropyl)benzofuranone (97)

Methyl 5-chloro-6-(2'-hydroxyphenyl)-6-oxohexanoate 96 (450 mg, 1.75 mmol) was dissolved in methanol. Sodium methoxide (324 mg, 6 mmol) was added. The reaction was stirred overnight. The product was partitioned between water and CHCl₃. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to give 300mg (73%) of crude product.

¹H NMR (CDCl₃): δ 7.65 (m, 2H) 7.10 (m, 2H) 4.55 (m, 1H) 3.70 (s, 3H) 2.45 (t, 2H, J= 7.3 Hz) 2.10-1.6 (m, 4H).
References


