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SYNTHETIC STUDIES ON
ECTEINASCIDIN 743

by
Chung-Kuang Jow

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE

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March, 1995
Abstract

Synthetic Studies on Ecteinascidin 743

by

Chung-Kuang Jow

Synthetic studies on ecteinascidin 743 (1b), an antitumor antibiotic, are described. The key reactions include: (1) an acyliminium ion-mediated stereoselective construction of the optically pure diazobicyclo[3.3.1]nonane nucleus 26, (2) a stereocontrolled Pictet-Spengler cyclization for the formation of tetrahydroisoquinoline 92, and (3) the attempted benzylic oxidation of the pentacyclic phenol 122.
Acknowledgments

I wish to express my sincere gratitude to Professor Tohru Fukuyama for his guidance and help. His dedication, perseverance, and love for the art of organic chemistry has provided a constant inspiration to me.

I would also like to thank my coworkers, both past and present, for their support and friendship. Special thanks to Dr. Xiaoqi Chen and Dr. Lianhong Xu for their help at the beginning of my graduate career, Tangqing Li, and Mui Cheung for their friendship.

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I would like to express my sincere gratitude to my family for their moral support throughout my education years.

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To My Parents
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Chapter 1

Introduction

The ecteinascidins (Et’s) 1 (a-h) are the newest members of the growing family of isoquinolinequinones.\textsuperscript{1} Et’s were isolated from the colonial tunicate *Ecteinascidia turbinata* by Rineheart et al.\textsuperscript{2} and Wright et al.\textsuperscript{3} independently in 1990. The ecteinascidins and the safracins 2 (a, b)\textsuperscript{4} share somewhat similar structural features. The absolute and the relative configuration of the safracins was determined by X-ray crystallographic of the 4-bromo derivative of safracin A (2c).\textsuperscript{5}

![Diagram of Ecteinascidin structures](image)

Some of these isoquinolinequinones exhibit potent antitumor activities in animal models, the most notable being saframycin A (3a),\textsuperscript{6} saframycin S (3s),\textsuperscript{7} and ecteinascidin 743 (1b).\textsuperscript{2,3} The unique dimeric
bisquinone structure of these antibiotics imposes a serious challenge to synthetic chemists. To date, \(\pm\)-saframycins A-D (3a–d), (\(\pm\))-renieramycin A (4a) have been synthesized,\(^8,9,10,11\)

**safracin**

A: (2a) \(R = X = H\)
B: (2b) \(R = OH, X = H\)
(2c) \(R = H, X = Br\)

**saframycin**

D: (3d) \(R_1 = H, R_2 = R_3 = R_4 = O\)
F: (3f) \(R_1 = CN, R_2 = R_3 = R_4 = O\)
Mk1: (3y) \(R_1 = OH, R_2 = H, R_3 = OMe, R_4 = H, NH_2\)
Mk2: (3z) \(R_1 = R_2 = H, R_3 = OMe, R_4 = H, NH_2\)

**saframycin**

A: (3a) \(R_1 = CN, R_2 = H\)
B: (3b) \(R_1 = R_2 = H\)
C: (3c) \(R_1 = H, R_2 = OMe\)
G: (3g) \(R_1 = CN, R_2 = OH\)
S: (3s) \(R_1 = OH, R_2 = H\)

**Renieramycin**

A: (4a) \(R_1 = R_2 = H, R_3 = OH\)
B: (4b) \(R_1 = R_2 = H, R_3 = OEt\)
C: (4c) \(R_1 = R_2 = O, R_3 = OH\)
D: (4d) \(R_1 = R_2 = O, R_3 = OEt\)
E: (4e) \(R_1 = OH, R_2 = R_3 = H\)
F: (4f) \(R_1 = OH, R_2 = H, R_3 = OMe\)
The extracts of the colonial tunicate *Ecteinascidia turbinata* showed potent in vivo efficacy against experimental tumors. This prompted separation and elucidation of several compounds. Further testing showed that the most abundant component, ecteinascidin 743, exhibited high activities: IC$_{50}$ 0.5 ng/mL vs L1210 leukemia cells and T/C 167 at 15 µg/kg vs P388 murine leukemia. Studies on the saframycins and the safracins suggest that the mode of action of isoquinolinequinone is similar to that of the antitumor agents containing the pyrrolo[1,4]benzodiazepine skeleton. These are thought to act by binding the minor groove of DNA followed by alkylation of the 2-amino group of a guanine moiety. The key intermediate of the DNA alkylation is thought to be the iminium ion as illustrated in Scheme 1.

The antitumor activities of the safracin-type antibiotics can be amplified by reduction of one or both of the quinone rings. The reduction increases the lability of the C-21 substituents involved in the iminium ion formation. It follows that compounds incapable of alkylating DNA are less active than those that can. However, binding in the minor groove interferes with the DNA template function, resulting in retention of some antitumor activities (Figure 1).
Scheme 1

Figure 1
To date, there has been no report on the total synthesis of the ecteinascidins and/or their congeners. As for the synthesis of the safracins, Kubo and coworkers reported their model studies on the synthesis of the ABC ring of the safracins in 1992 as summarized in Scheme 2. In order to introduce the phenol functionality in the ring A, the tricyclic amine 5 was nitrated to form intermediate 6. Hydrogenation, diazotization of the resulting amine, and acid treatment of the diazonium salt gave the desired phenol 8 in low yield.

Scheme 2
Another key step for the total synthesis of the ecteinascidins was the formation of the sulfide bridge between the C-1 and the C-4 position. Our approach to this step employed oxidation of the C-4 position using mild conditions followed by cyclization of the resulting alcohol (Scheme 3). This seemed to be a reasonable strategy for the formation of the bridge.

![Scheme 3](image)

In 1990, our group published the total synthesis of renieramycin A, in which oxidation of the phenol 12 by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was performed to introduce the benzylic alcohol 13.\(^\text{11}\)
This proved to be a good methodology for oxidation of the C-4 position when a free phenol group is present at the C-7 position (Scheme 4).

![Scheme 4](image)

On the other hand, selenium dioxide proved to be effective for the preparation of the desired benzylic alcohol 18 or its methyl ether 17 (Scheme 5). Applications of this model studies to the synthesis of ecteinascidins have not yet been reported.
We became interested in the total synthesis of the ecterinasidins not only because they were isolated in minute quantities from the natural
source, but also because of their unique and challenging structural features. The remarkable characteristics of the ecteinascidins include the interesting sulfide bridge between the C-1 and the C-4 position and the unique A and E ring systems, which are considerably different from the majority of the saframycin-class of natural products. Because of similarities in the ABC ring systems of the ecteinascidins and the safracins, we began our studies on the total synthesis of safracin B (2b), which was completed in 1994.16

This thesis describes in detail our intensive synthetic studies towards the total synthesis of ecteinascidin 743 as well as preparation of the key intermediate of the total synthesis of safracin B. Although the former studies have not yet resulted in a successful total synthesis, a great deal of insight has been gained. Hopefully, the synthesis of ecteinascidin 743 will be realized in the near future.
Chapter 2

Synthetic Studies on Ecteinascidin 743

Retrosynthetic Analysis

Our initial retrosynthetic analysis is outlined in Scheme 6. A spirocondensation of the tetrahydroquinoline moiety from \( \alpha \)-keto ester 21 and amine 22 by Pictet-Spengler cyclization\(^{17}\) would be performed in the last stage of the synthesis. An acid-catalyzed cyclization of the thiol 23 could form the requisite bicyclo[6.2.2] system 21. Construction of the major pentacyclic framework was projected via either D ring closure (path A) or C ring cyclization (path B, Scheme 7). For the path A, a stereocontrolled Pictet-Spengler cyclization of amino-nitrile 24 with cinnamaldehyde is expected to give the requisite tetrahydroisoquinoline. Phenol 24 should be available by utilizing the Friedel-Crafts type formylation\(^{18}\) of lactam 25 followed by the Baeyer-Villiger oxidation\(^{19}\) of the resultant aldehyde. An efficient stereocontrolled reduction of olefin 26, developed earlier in our laboratories, would be employed in order to control the stereochemistry at the C-3 position of the lactam 25.

For the retrosynthetic approach of path B, Swern oxidation\(^{20}\) of alcohol 27 was considered for the construction of the C ring, as in the case of saframycin A synthesis (Scheme 7).\(^{8}\) The \( \beta \)-epimer of the tetrahydroisoquinoline 27 could be synthesized by a stereocontrolled Pictet-Spengler cyclization of cinnamaldehyde with amino phenol 28. Cleavage of the hindered lactam in 25 could be performed according to the procedure
developed by Grieco\textsuperscript{21} via the intermediate 29. Both paths A and B call for the an efficient synthesis of the intermediate 26.

Scheme 6
The preparation of compounds analogous to the key intermediate 26 has been extensively studied in our laboratories, in connection with work on the saframycins. Details of these efforts are discussed more fully in other manuscripts.\textsuperscript{22,23} Briefly, structures of the type 26 may be
constructed via two different pathways. One method involves two Perkin type condensations between N,N'-diacetylpiperazinedione 30 and a highly substituted benzaldehyde 31 (Scheme 8). An acylimminium ion-mediated cyclization of intermediate 33 then forms the main framework 34, which is similar to the key intermediate 26.

![Chemical structures](image)

**Scheme 8**

The second strategy rests upon coupling of amino alcohol 35 and acid 36 to provide amide 37 (Scheme 9). Acetylation of 37 followed by ozonolysis and elimination of the acetate give the same intermediate 33.
We favored the second approach for the creation of 26, because it would allow us to obtain optically active end products if an optically pure acid of the type 36 was used. Accordingly, disconnection of the B ring of key intermediate 26 revealed amide 38 (Scheme 10). This substance is available by condensation of a simple amino alcohol 39 with optically active acid 40. Amino alcohol 39 could easily be synthesized from aldehyde 41 and isonitrile 42, while 40 was eventually obtained in optically pure form from the readily available L-tyrosine derivative 43. We note that the absolute stereochemistry of 39 is immaterial for our purpose, as both stereogenic carbons in 39 will eventually be lost.
Scheme 10
Synthesis of Optically Pure Key Intermediate 26

In order to synthesize the optically pure olefin 26, our first target was the optically pure carboxylic acid 40. We initiated our model studies with the enzymatic hydrolysis of the racemic ester 44. Upon treatment with papain, the racemic ester 42 gave a mixture of L-amino acid derivative 45 and the unchanged D-ester 46 (Scheme 11). Total syntheses of the optically pure saframycins A and B would be accomplished from 45 by following our published scheme for the racemic saframycins.\(^8,9\)

![Scheme 11](image)

Replacement of the methoxy group at the C-2 position of acid 45 with a removable functional group, such as bromide or triflate, was the first step towards the intermediate 26. Treatment of dimethylhexylsilyl chloride and imidazole selectively protected the C-1 position of commercially available 3-methylcatechol 47, yielding the mono silyl ether 48 (Scheme 12). Mesylation of phenol 48 followed by bromination of mesylate 49 furnished the mono-bromo compound 50. Deprotection of silyl ether 50 with hydrochloric acid provided phenol 51.\(^{15}\)
In order to verify the position of the bromide in phenol 51, allyl ether 52 was obtained by allylation of 51 (Scheme 13). Demesylation of 52 followed by methylation yielded methyl ether 53. Upon heating at 230 °C in N,N-diethylaniline, allyl ether 53 underwent the Claisen rearrangement to give the phenol product 54, which demonstrated that the bromide was on the desired C-4 position instead of the undesired C-6 position.
Phenol 51 was protected as a benzyl ether 56. Demesylation of 56 followed by allylation of the resultant phenol in a conventional manner provided allyl ether 57 (Scheme 14). The Claisen-Cope rearrangement of 57 was achieved by heating at 230 °C to give the desired p-allyl phenol 58. After methylation of the phenol 58, the olefin was isomerized under strong alkaline condition to give the conjugated olefin 59. Ozonolysis of the olefin 59 followed by treatment with dimethyl sulfide furnished the aldehyde 60.

Scheme 14

Condensation of the aldehyde 60 with isonitrile\textsuperscript{24} 61 according to the Schölkopf's procedure\textsuperscript{25} gave an isomeric mixture of the olefins 62 (Scheme 15)\textsuperscript{26}. Upon treatment with sodium borohydride in the presence of phenanthroline and cobalt chloride, the olefin 62 underwent a smooth reduction to give the amino acid derivative 63 without hydrogenolysis of
the bromide. Acid-catalyzed hydrolysis of formamide 63 followed by protection of the resultant amine as a benzyl carbamate yielded 64. Unfortunately, an attempted enzymatic hydrolysis of ester 64 with papain failed to produce the desired L-amino acid derivative 65.

Scheme 15
Enzymatic hydrolysis also failed for the similar bromo-esters 67 and 70 (Scheme 16). Papain does not appear to have as a wide substrate specificity as we expected.

![Chemical structures](image)

**Scheme 16**

Having failed to enzymatically resolve the racemic 64, 67, and 70, we decided to employ the optically pure amino acid derivative 43 as our starting material. This substance can be prepared easily from L-tyrosine.\(^{27}\) The aldehyde in 43 could be completely reduced to a methyl group 73 by catalytic hydrogenation under the forcing conditions (Scheme 17). The Friedel-Crafts type acylation of the aromatic system 73 with \(\alpha,\alpha\)-dichloromethyl methyl ether and titanium tetrachloride furnished the aldehyde 74 in 88 % yield. Baeyer-Villiger oxidation\(^{19}\) of 74 with m-chloroperoxybenzoic acid, followed by methanolysis of the resultant formate, gave phenol 75. Fortunately, bromination of phenol 75 afforded the desired para-bromo-phenol 76 as the sole product. Acidic hydrolysis of 76 followed by workup gave amine 77, which was then protected as its \(t\)-butyl carbamate 78. Hydrolysis of ester 78 with lithium hydroxide produced the optically pure acid 40.
Scheme 17
At this point, we tried to confirm the position of the bromide and the optical purity of the acid 40. Conversion of the N-acetyl group of 76 to the corresponding carboxybenzoxyl group followed by benzylolation of the phenol gave 79. The spectroscopic properties of 79 matched those of the previously synthesized racemic ester 64 (Scheme 18).

In order to determine the optical purity of acid 40, we employed a diastereotopic method. The acid 40 was condensed with (R)-(+)-$\alpha$-methylbenzylamine 80 and subsequent deprotection of t-Boc group gave a single isomer of the amide 81. Similar manipulation converted (±)-82 to 83. This material was clearly formed as a 1:1 mixture of diastereomers ($^1$H NMR). Comparison of the $^1$H NMR spectra of 81 and 83 confirmed amide 81, and therefore acid 40, to be of ee > 98% (Scheme 19).
Addition of the anion 84, generated from cinnamyl isocyanide,\textsuperscript{24,25} to the aldehyde 41 at low temperature, followed by acidic hydrolysis of the resultant formamide at 80 °C, gave a diastereomeric mixture of the amino alcohol 39 (Scheme 20).

Condensation of 39 with the optically pure acid 40 under the influence of 1,3-dicyclohexyl carbodiimide (DCC) furnished a complex diastereomeric mixture of amides 85 (Scheme 21). The mixture consists of four diastereomers, due to the presence of two uncontrolled stereogenic centers. Separation and/or purification of these compounds was not attempted, because the subsequent steps would destroy these stereogenic centers and generate a cyclic product as a single stereoisomer. Acetylation of alcohol 85 with acetic anhydride and pyridine provided the diacetate 38 which underwent ozonolysis to yield a complex mixture of diastereomers of aldehydes 86. Treatment of the mixture with 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU) gave the elimination product 87. The phenolic acetate 87 was deprotected by alkaline hydrolysis to give phenol 88. Acyliminium ion-mediated cyclization of 88 was facilitated by heating in 5\% trifluoroacetic acid in benzene, giving the tetracyclic amine 26 in 65\% overall yield from the acid 40, with concomitant deprotection of the \( t \)-Boc group.
Scheme 21
From this key intermediate 26, we have recently completed the total synthesis of (-)-safracin B (2b) in good overall yield (Scheme 22).\textsuperscript{16}
Model Study I

Our initial model study was aimed at the stereoselective Pictet-Spengler cyclization to form the D ring of the ecteinascidins. Reduction of the lactam 90, a key intermediate for the synthesis of saframycin A, with diisobutylaluminum hydride at -78 °C and subsequent treatment of the resultant unstable aminal with sodium cyanide at room temperature furnished the amino nitrile 91 (Scheme 23). Compound 91 reacted with cinnamaldehyde in the presence of (+)-camphorsulfonic acid (CSA) to afford a mixture of pentacyclic amino nitriles, 92 and 93, and aminals, 94 and 95. After numerous attempts to maximize the yield of the thermodynamically favorable β-epimer 92, we found that prolonged heating in the presence of trimethylsilyl cyanide (TMSCN) afforded the desired tetrahydroisoquinoline 92 in 65% yield as the predominant product. Optimization of the reaction conditions is summarized in Table 1.
<table>
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<th>Reaction conditions</th>
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<td>CSA eq.</td>
<td>RCHO eq.</td>
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<tr>
<td>1</td>
<td>2</td>
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<tr>
<td>2</td>
<td>3</td>
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<td>5</td>
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**Table 1**

This exciting result has paved the way for the efficient synthesis of the main pentacyclic framework of the saframycin-family of natural products including ecteinascidins.

The phenolic hydroxyl groups of the β-epimer 92 were protected as the corresponding mesylate 96 in a conventional manner (Scheme 24). Much to our surprise, ozonolysis of 96 followed by sodium borohydride reduction did not give a trace of the desired alcohol 98. Therefore, we opted to cleave the olefin 96 in an indirect manner. Compound 96 was first converted to diol 97 by treatment with N-methylmorpholine N-oxide (NMO) and a catalytic amount of osmium tetroxide.²⁹ Cleavage of the diol 85 with sodium meta-periodate followed by reduction of the resultant unstable aldehyde with sodium borohydride furnished the alcohol 98.
Subsequent alkaline hydrolysis of the dimesylate of 98 gave the triol 99, which could serve as a key intermediate for the total synthesis of saframycin A. Biological testing of 92, 98, and 99 has revealed that the triol 99 exhibits potent antitumor activities in *vitro.*

Scheme 24
Model Study II

Having succeeded in controlling the stereochemistry of the Pictet-Spengler cyclization, we turned our attention to the benzylic oxidation of the phenol 100 to form the alcohol 101 (Scheme 25).

![Diagram](image)

Scheme 25

We first used a racemic model to investigate this key reaction. The racemic carboxylic acid 102 was generated in 70% overall yield from the readily available aldehyde 41 using the procedure developed in our laboratories (Scheme 26). Condensation of the amino alcohol 39 and acid 102 with DCC, followed by acetylation, furnished a complex diastereomeric mixture of amides 103. Ozonolysis of the olefin 103, base promoted elimination of acetic acid and alkaline hydrolysis of the phenolic acetate afforded the enal 104. Acyliminium ion-mediated cyclization of 104 was facilitated by heating in 5% trifluoroacetic acid in benzene, giving the tetracyclic amine 105 in 56% overall yield from acid 102 with concomitant deprotection of the Boc group.
Before reducing the olefin 105, the amine was protected as 2,2,2-trichloroethyl carbamate 106 (Scheme 27). In our previous synthesis of the saframycins, the reduction of the corresponding olefin was performed by catalytic hydrogenation over W-2 Raney nickel in ethanol, under high pressure (1500 psi) of hydrogen, at 120 °C for 20 hours. Since these harsh conditions gave somewhat erratic results, we decided to explore a new method for reducing the olefin under milder conditions. After numerable attempts, a facile reduction of the olefin was realized by treatment with
sodium cyanoborohydride and trifluoroacetic acid in acetic acid. The hydride was delivered to the olefin 106 from the less hindered, exo side, giving exclusively the desired endo product 107 in 99% yield. Methylation of the phenol 107 and subsequent Friedel-Crafts-type formylation with α,α-dichloromethyl methyl ether and titanium tetrachloride furnished the aldehyde 109.
Selective demethylation of 109 by treatment with boron trichloride afforded phenol 110 (Scheme 28), which was protected as a benzyl ether 111. Baeyer-Villiger oxidation of the aldehyde and subsequent methanolation of the resultant formate furnished phenol 112.

We then focused our attention to the benzylic oxidation of the tetracyclic skeleton prior to constructing of the pentacyclic framework. To this end, the model compound 114 was prepared from 112 by methylation and subsequent debenzylation using boron trichloride (Scheme 29). Gratifyingly, phenol 114 underwent smooth benzylic oxidation upon
treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ) at room temperature to provide the desired benzylic alcohol 115 in reasonable yield.

With this encouraging result in hand, we initiated an investigation of the benzylic oxidation in a more elaborate pentacyclic model system. Deprotection of the 2,2,2-trichloroethyl carbamate 112 with active zinc in acetic acid and N,N-dimethyl formamide (DMF), followed by reductive methylation of the resultant amine gave tertiary amine 116 in 95% yield (Scheme 30). Reduction of the lactam 116 with diisobutylaluminum
hydride at -78 °C and subsequent treatment of the resultant aminal with sodium cyanide at room temperature furnished amino nitrile 117. The Pictet-Spengler cyclization of amino phenol 117 was performed under the aforementioned conditions (cinnamaldehyde, CSA, TMSCN, CH₃CN, 100 °C, 6 hr), giving the desired pentacyclic β-epimer 118 in 56% yield.

![Chemical diagram showing the transformation from 112 to 118 and 116 to 117 via the Pictet-Spengler cyclization.]

**Scheme 30**

After methylation of the phenol in 118, cleavage of the olefin 119 was performed in a three-step sequence via diol 120, as discussed previously (Scheme 31). In order to avoid hydrogenation of the nitrile...
debzonylation was carried out with boron trichloride, to give the phenol 122.
Unfortunately, treatment of phenol 122 with 2,3-dichloro-5,6-dicyano-quinone (DDQ) in methanol at room temperature gave exclusively the undesired ortho quinone dimethyl acetal 124, instead of the desired benzylic methyl ether 123 (Scheme 32).

Scheme 32

In order to realize the benzylic oxidation, we reduced the electron density of the aromatic ring of phenol 122 by replacing a methoxy group with a mesylate group (Compound 125, Scheme 33). To our dismay, the attempted benzylic oxidation of phenol 125 with DDQ proved futile even after prolonged heating.
To examine if the free primary alcohol in phenol 122 might be interfering with the benzylic oxidation, we attempted DDQ oxidation of the olefinic phenol 126. Once again, the undesired ortho quinone dimethyl acetal 127 was the only isolable product (Scheme 34).

We began to suspect that the electron-rich N-methyl amino group in 126 might be a source of interference during DDQ oxidation. Accordingly, the N-methyl amine was replaced with 2,2,2-trichloroethyl urethane (Compound 128). Unfortunately, the undesired ortho-quinone 129 still emerged as the sole product, even under milder oxidative condition (Scheme 35).
Similar disappointing results were observed with mesylate 130, wherein the sulfonyl group reduces the electron density of the A ring, and should therefore favor oxidation of the E ring. Quinone 131 was still the sole product of DDQ oxidation (Scheme 36).

In addition to DDQ, several other oxidizing agents have been used to achieve this key benzylic oxidation. As observed with DDQ, both electrolysis and [bis(trifluoroacetoxy)iodo]benzene gave the undesired ortho quinone 133 (Scheme 37).
Recognizing that the electron-rich, ring-fusion nitrogen could possibly be a further source of interference during benzylic oxidation, we investigated oxidation of the phenolic lactam 134. Unfortunately, the undesired ortho quinone monoacetal 135 was the only product (Scheme 38).

Finally, we attempted to oxidize the reactive quinone 136 by means of selenium dioxide. To our dismay, we did not isolate a trace of the desired alcohol 137, after numerable attempts (Scheme 39).
On the basis of these results, we came to the conclusion that oxidation of the benzylic position would be extremely difficult, if not impossible, to perform once the main pentacyclic skeleton has been constructed. Therefore, we decided to introduce the critical benzylic hydroxyl group prior to the formation of the pentacyclic system.
Future Plan

As mentioned in the retrosynthetic analysis, another viable strategy is to oxidize the benzylic position of the tetrahydroisoquinoline such as 138 (Scheme 40). Cyclization of the C ring would then provide the pentacyclic framework.

![Chemical Structures](image)

**Scheme 40**

Model studies have been conducted that strongly support the feasibility of this alternative strategy. A simple model compound 139 was chosen to investigate the benzylic oxidation with DDQ. It was gratifying to learn that the phenol 139 underwent facile oxidation with DDQ in methanol to give the desired methyl ether 140 (Scheme 41). These highly encouraging results prompted us to concentrate on the more complicated model studies starting with compound 110.

![Chemical Structures](image)

**Scheme 41**
In order to cleave the hindered lactam of compound 110, an N-t-butoxycarbonyl group was introduced by treatment of 110 with di-tert-butyl dicarbonate and 4-dimethylaminopyridine (DMAP) to give 141 (Scheme 42). Baeyer-Villiger oxidation of the aldehyde 141, followed by methanolysis of the resultant formate, afforded phenol 142. Cleavage of the activated lactam 142 was performed by treatment with sodium borohydride to give alcohol 143. Deprotection of the t-butyl carbamate 143 with trifluoroacetic acid provided the amine 144.

![Scheme 42]
From the intermediate 144, a possible future plan is shown in Scheme 43. Stereocontrolled Pictet-Spengler cyclization of the amino phenol 144, protection of amine and phenol, and debenzylation, would give tetrahydroisoquinoline 145. Benzylic oxidation of 145 would result in the desired alcohol 146. Formation of the benzodioxolane F ring, followed by construction of the thio bridge, would afford compound 147. Swern oxidation of the primary alcohol 147 would lead to the formation of the C ring, thus forming pentacyclic framework that could be readily converted to the final target molecule 148 for our model studies.

Synthetic studies along these lines are currently underway in the laboratories of Dr. Tohru Fukuyama at the Chemistry Department of Rice University.
Scheme 43
Chapter 3

Experimental

Technical notes

Melting points (mp), determined on a Mel-Temp, were uncorrected.

Infrared (IR) spectra were recorded on Nicolet 205 Infrared Spectrophotometer and are reported in wave numbers (cm\(^{-1}\)).

Nuclear magnetic resonance (NMR) spectra were determined on a Bruker AC250 instrument, unless otherwise noted. Chemical shifts are reported in parts per million downfield from tetramethylsilane (δ = 0) as the internal standard. The following abbreviations are used for spin multiplicity:
s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet and b = broad.

Mass spectra (MS) were obtained on a Finnigan Mat95 with electron impact ion source at 70 eV, unless otherwise noted, using probe insertion at temperatures of 50 to 300 °C. High resolution mass spectra were obtained under similar conditions.

Optical rotations were measured on a Jasco DP-370 polarimeter at ambient temperature.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F\(_{254}\). Preparative TLC separations were made on 10 x 20 cm or 20 x 20 cm plates prepared with a 2 mm layer of Merck silica gel 60 PF\(_{254}\).
Compounds were eluted from the adsorbent with 10 % methanol in dichloromethane.

All evaporations were performed under reduced pressure on a rotary evaporator.

Column chromatography was performed on Woelm silica gel, 32-63 mesh.

Hydrogenations were carried out in a stainless Parr general purpose bomb unless otherwise noted.

Commercial grades reagents and solvents were used as supplied with the following exceptions:

Dichloromethane and ether: distilled through a 24 inch Snyder column.

Tetrahydrofuran (dry): distilled from sodium benzophenone ketyl.

Pyridine and triethyl amine: dried over potassium hydroxide pellets.

$\tau$-Butanol: distilled from calcium hydroxide.

$N, N'$- dimethyl formamide, benzene, toluene, acetonitrile, and methanol: dried over 4Å molecular sieves.

Methanesulfonyl chloride and thionyl chloride:

distilled over phosphorus pentoxide.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
N-acetyl-3-methyl-O-methyl-L-tyrosine methyl ester (73)

A solution of 25.35 g (90.9 mmol) of aldehyde 43 in 150 ml of acetic acid was hydrogenated over 2.5 g (10% of weight) of 10% palladium on charcoal at 1500 psi of hydrogen for 1 hour at 85 °C. The reaction was filtered through Celite and the column was washed thoroughly by ethyl acetate until all product had been eluted as evidenced by tlc. After evaporation under reduced pressure to dryness, the crude residue was thoroughly partitioned between ethyl acetate and a solution of saturated sodium bicarbonate and brine. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to provide 23.74 g (98.6 %) of 73 as yellow oil.
Characterization of 73:

IR (film): 3290, 3080, 3010, 2950, 2840, 1760, 1660, 1540, 1500, 1430, 1370, 1250, 1210, 1140, 1030

$^1$H NMR (CDCl$_3$): 1.98 (3H, s), 2.18 (3H, s), 3.03 (2H, dd, $J = 5.7$, 2.5 Hz), 3.73 (3H, s), 3.80 (3H, s), 4.82 (1H, dt, $J_d = 7.7$ Hz, $J_t = 5.7$ Hz), 5.91 (1H, d, $J = 7.7$ Hz), 6.73 (1H, d, $J = 7.9$ Hz), 6.84 (1H, s), 6.86 (1H, d, $J = 7.9$ Hz)

$^{13}$C NMR (CDCl$_3$): 16.3, 23.2, 37.0, 52.3, 53.3, 55.3, 110.0, 126.8, 127.3, 127.4, 131.6, 157.0, 169.7, 172.4

MS: 266 (1, M+1), 265 (4, M+), 207 (10), 206 (80), 175 (11), 135 (100)

$[\alpha]_{D}^{23}$: +89.0° (c = 0.685, CHCl$_3$)

Exact Mass: Calculated for C$_{14}$H$_{19}$NO$_4$ 265.1314

Found 265.1315
Compound 73 continued:
N-acetyl-3 formyl-5 methyl-O-methyl-L-tyrosine methyl ester (74)

To a stirred solution of 49.4 g (186.4 mmol) of 73 in 600 ml of methylene chloride was added 61.4 ml (3 eq.) of titanium tetrachloride slowly at 0 °C. To the stirred solution, 25.2 ml of α,α-dichloromethyl methyl ether was added dropwise. After 1 hour, the reaction was complete as shown by tlc. The reaction mixture was poured into a stirring solution of ice chips slowly until the solution appeared clear, then partitioned between dichloromethane and 3N hydrochloric acid solution. The organic layer was washed with a solution of 3N hydrochloric acid, 1N hydrochloric acid, saturated sodium bicarbonate, and brine. The aqueous layers were extracted with dichloromethane thoroughly. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield 48.0 g (87.9 %) of aldehyde 74 as yellow solid.
Characterization of 74:

mp (CH₂Cl₂): 112 °C

IR (KBr): 3300, 3070, 3000, 2960, 2860, 1740, 1680, 1660, 1540, 1470, 1430, 1370, 1300, 1250, 1130, 1010

¹H NMR (CDCl₃): 2.00 (3H, s), 2.31 (3H, s), 3.02 (1H, dd, J = 5.8, 13.9 Hz), 3.13 (1H, dd, J = 5.8, 13.9 Hz), 3.75 (3H, s), 3.87 (3H, s), 4.86 (1H, dt, Jₓ = 7.3 Hz, Jᵧ = 5.8 Hz), 6.03 (1H, d, J = 7.3 Hz), 7.21 (1H, d, J = 1.9 Hz), 7.40 (1H, d, J = 1.9 Hz), 10.34 (1H, s)

¹³C NMR (CDCl₃): 15.6, 23.2, 37.2, 52.5, 53.2, 63.2, 126.8, 139.1, 132.3, 132.6, 138.5, 161.0, 169.7, 172.0, 190.1

MS: 293 (3, M⁺), 234 (100), 216 (12), 203 (7), 192 (9), 163 (68), 149 (9), 88 (9), 43 (14)

[α]D²³: +84.4° (c = 0.655, CHCl₃)

Exact Mass: Calculated for C₁₅H₁₉NO₅ 293.1263
Found 293.1265
Compound 74 continued:
N-acetyl-3-hydroxy-5-methyl-O-methyl-L-tyrosine methyl ester (75)

To a stirred solution of 52.4 g (178.8 mmol) of aldehyde 74 in 600 ml of chloroform was slowly added 42.4g (1.1 eq.) of 80% m-chloroperoxybenzoic acid dissolved in 150 ml of chloroform at room temperature. After stirring for 3 hours, the reaction was evaporated under reduced pressure to about 200 ml. 300 ml of hexanes was added to the crude mixture to precipitate m-chlorobenzoic acid. After filtering, the filtrate was partitioned between methylene chloride and a solution of saturated sodium sulfite. The organic layer was washed by dilute sodium bicarbonate (2X) and brine. The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to afford crude products. The mixture was dissolved in 400 ml of methanol and 5.0 ml (0.2 eq.) of triethylamine was added at room temperature. After stirring overnight, the reaction mixture was concentrated to dryness under reduced pressure, then was partitioned between methylene chloride with a solution of 3N hydrochloric acid. The organic layers were washed by saturated sodium bicarbonate and brine (2X). The aqueous layers were thoroughly
extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to afford 49.6 g (98.9%) of phenol 75 as yellow oil.

Characterization of 75:

IR (film): 3330, 3080, 3010, 2950, 2830, 1750, 1650, 1600, 1540, 1440, 1370, 1210, 1010

$^1$H NMR (CDCl$_3$): 2.00 (3H, s), 2.25 (3H, s), 2.98 (2H, dd, $J = 5.6$ 2.9 Hz), 3.74 (3H, s), 3.77 (3H, s), 4.83 (1H, dt, $J_D = 7.8$ Hz, $J_I = 5.6$ Hz), 5.99 (1H, bs), 6.42 (1H, d, $J = 2.0$ Hz), 6.53 (1H, d, $J = 2.0$ Hz)

$^{13}$C NMR (CDCl$_3$): 16.0, 23.2, 37.4, 52.4, 53.2, 60.7, 114.1, 123.3, 131.0, 132.2, 144.7, 148.9, 169.9, 172.2

MS: 281 (15, M$^+$), 222 (100), 207 (15), 151 (95), 136 (10)

$[\alpha]_D^{23}$: $+86.0^\circ$ (c = 0.670, CHCl$_3$)

Exact Mass: Calculated for C$_{14}$H$_{19}$NO$_5$ 281.1263
Found 281.1261
Compound 75 continued:
**N-acetyl-2-bromo-3-hydroxy-5-methyl-O-methyl-L-tyrosine methyl ester (76)**

To a stirred solution of 21.2 g (75.2 mmol) of phenol 75 in 250 ml of dichloromethane was added 1.94 ml (0.5 eq.) of bromine slowly at room temperature. After stirring for 3 hours, 0.233 ml (0.06 eq.) of bromine was added in several portions and the reaction was monitored by tlc carefully until the starting material was consumed. The reaction mixture was washed with a solution of saturated sodium bisulfite, saturated sodium bicarbonate, and brine. The aqueous layers were thoroughly extracted with dichloro-methane. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to yield 25.6 g (94.4%) of bromophenol 76 as yellow oil. The crude product was recrystallized in methylene chloride to provide 22.4 g (82.6 %) of bromophenol 76 as pale yellow crystal and 3.2 g (11.8 %) of crude residue.
Characterization of 76:

mp: 154 °C

IR (KBr): 3320, 3080, 3000, 2950, 2850, 2690, 1750, 1630, 1550, 1410, 1330, 1250, 1160, 1010

$^1$H NMR (CDCl₃): 1.97 (3H, s), 2.35 (3H, s), 3.11 (1H, dd, $J = 14.0$, 7.9 Hz), 3.24 (1H, dd, $J = 14.0$, 5.9 Hz), 3.74 (3H, s), 3.76 (3H, s), 4.88 (1H, m), 6.14 (1H, d, $J = 7.9$ Hz), 6.72 (1H, s)

$^{13}$C NMR (CDCl₃): 17.2, 23.1, 38.2, 52.6, 52.7, 61.0, 115.5, 117.7, 132.2, 132.3, 145.3, 148.2, 170.3, 172.3

MS: 361 (6, M+2), 359 (6, M+), 302 (13), 300 (13), 280 (32), 231 (33), 229 (50), 221 (100), 206 (6), 88 (9)

$[\alpha]_D^{23}$: +37.4° (c = 0.850, CHCl₃)

Exact Mass: Calculated for C$_{14}$H$_{18}$BrNO$_5$ 359.0369

Found 359.0376
Compound 76 continued:
2-bromo-5-hydroxy-3-methyl-O-methyl-L-tyrosine methyl ester (77)

To a solution of 10.0 g (27.8 mmol) of bromophenol 76 in 200 ml of methanol was added 20.2 ml (10 eq.) of thionyl chloride at 0 °C slowly. After heating the reaction mixture at 90 °C for 12 hours, the reaction was complete as shown by tlc analysis. The reaction mixture was evaporated to dryness under reduced pressure. The crude solid was dissolved in 400 ml of methylene chloride and ammonia gas was bubbled for 30 min. The mixture was filtered through Celite and the column was washed thoroughly by methylene chloride until all product had been eluted as evidenced by tlc. Evaporation of the filtrate gave 8.80 g (99.4 %) of aminophenol 77 as light purple solid which was used without purification.
Characterization of 77:

mp (CH₂Cl₂): 109 °C

IR (KBr): 3360, 3290, 2940, 1750, 1570, 1480, 1220, 1100, 1010

¹H NMR (CDCl₃): 2.35 (3H, s), 2.81 (1H, dd, J = 13.6, 9.2 Hz), 3.20 (2H, bs), 3.26 (1H, dd, J = 13.6, 4.9 Hz), 3.73 (3H, s), 3.75 (3H, s), 3.87 (1H, dd, J = 9.2, 4.9 Hz), 6.72 (1H, s)

¹³C NMR (CDCl₃): 17.1, 41.8, 52.2, 54.4, 60.9, 116.2, 117.5, 132.1, 133.4, 145.2, 148.1, 175.3

MS: 260 (13, M+2 - CO₂CH₃), 258 (14, M - CO₂CH₃), 238 (100), 231 (69), 229 (67), 178 (7), 151 (8)

[α]D₂₃: +12.0° (c = 0.50, CHCl₃)

Exact Mass: Calculated for C₁₂H₁₆BrNO₄ 317.0263

Found 317.0237
Compound 77 continued:
2-bromo-N-\textit{tert}-butoxycarbonyl-5-hydroxy-3-methyl-O-methyl-L-tyrosine methyl ester (78)

To a solution of 9.78 g (30.7 mmol) of amine 77 in 100 ml of methylene chloride was added 8.6 ml (2.0 eq.) of triethylamine and 7.05 g (1.05 eq.) of di-\textit{tert}-butyl dicarbonate at room temperature. After stirring for 1 hour, the reaction was complete as shown by tlc. The reaction mixture was washed with a solution of 3N hydrochloric acid, 1N hydrochloric acid, saturated sodium bicarbonate, and brine. The aqueous layers were extracted thoroughly with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give 12.5 g (97.0\% ) of amide 78 as pale yellow solid.
Characterization of **78**: 

**mp** (Et$_2$O): 76-78 °C

**IR** (KBr): 3370, 2970, 1750, 1690, 1590, 1500, 1480, 1360, 1160, 1060, 1000

**$^1$H NMR** (CDCl$_3$): 1.36 (9H, m), 2.36 (3H, s), 3.00 (1H, dd, $J = 13.7$, 8.5 Hz), 3.27 (1H, dd, $J = 13.7$, 5.4 Hz), 3.74 (3H, s), 3.75 (3H, s), 4.61 (1H, m), 5.12 (1H, d, $J = 4.3$ Hz), 6.03 (1H, bs), 6.72 (1H, s)

**$^{13}$C NMR** (CDCl$_3$): 17.1, 28.3, 39.2, 52.4, 53.6, 61.0, 80.0, 115.6, 117.9, 131.9, 132.7, 145.1, 147.9, 155.1, 172.6

**MS**: 419 (3, M+2), 417 (3, M+), 363 (28), 361 (28), 346 (6), 344 (6), 302 (9), 238 (11), 231 (100), 229 (100), 221 (40), 57 (69)

**[$\alpha$]$_D^{23}$**: +4.5$^\circ$ (c = 0.465, CHCl$_3$)

**Exact Mass**: Calculated for C$_{17}$H$_{24}$BrNO$_6$ 417.0787

**Found** 417.0786
Compound 78 continued:
2-bromo-N-tert-butoxycarbonyl-5-hydroxy-3-methyl-O-methyl-L-tyrosine (40)

To a stirred solution of 11.57 g (27.7 mmol) of ester 78 in 100 ml of methanol and 30 ml of water was added 1.32 g (2.0 eq.) of lithium hydroxide. The reaction was monitored carefully by tlc and the starting material was consumed after 3 hours. The reaction mixture was quenched by adding a solution of 3N hydrochloric acid until the pH dropped below 3. The reaction mixture was partitioned between ether and a solution of 1N hydrochloric acid. The organic layer was washed by 1N hydrochloric acid solution and saturated sodium chloride (3X). The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to afford 10.87 g (97.0 %) of acid 40 as pale yellow solid.
Characterization of 40:

mp (Et₂O): 80-81 °C

IR (KBr): 3350, 2980, 2930, 1730, 1700, 1580, 1480, 1410, 1260, 1160, 1060, 1000

¹H NMR (DMSO-d₆): 1.27&1.43 (9H, br), 2.36 (3H, s), 2.52 (1H, s), 2.86 (1H, dd, J = 13.6, 10.7 Hz), 3.23 (1H, dd, J = 13.6, 4.3 Hz), 3.75 (3H, s), 4.17-4.32 (1H, m), 6.89 (1H, s), 7.03 (1H, d, J = 8.4 Hz)

¹³C NMR (DMSO-d₆): 16.6, 28.1, 37.7, 53.5, 59.6, 77.8, 115.4, 117.2, 130.9, 133.0, 145.0, 148.7, 155.3, 173.5

MS: 405 (2, M+1), 403 (3, M+1), 349 (22), 347 (23), 231 (95), 229 (100), 207 (17), 151 (7)

[α]D²³: -11.9° (c = 0.570, CHCl₃)

Exact Mass: Calculated for C₁₆H₂₂BrNO₆ 403.0631
Found 403.0635
Compound 40 continued:
Amino-alcohol (39a and 39b)

To a stirred solution of 1.92 g (13.4 mmol) of cinnamyl isonitrile in 150 ml of dry tetrahydrofuran at -78 °C was added 5.3 ml (1.0 eq.) of 2.51N n-butyl lithium in hexane, over 5 minutes. After stirring at -78 °C for 10 minutes, a solution of 2.41 g (13.4 mmol) of aldehyde 41 in 10 ml of dry tetrahydrofuran was added slowly, over 3 minutes. After stirring at -78 °C for 30 minutes, 10 ml of 3N hydrochloric acid was added and the reaction mixture was allowed to warm to room temperature over 30 minutes. The reaction mixture was heated at 85 °C for 1 hour until the resultant formamide was consumed as shown by tlc. The reaction mixture was partitioned between methylene chloride and saturated sodium bicarbonate (3X). The organic layer was washed with brine (2X). The aqueous layers were extracted thoroughly with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Chromatographic separation on silica gel, eluted with a gradient of methanol and methylene chloride, yielded 3.90 g (93%) of mixture of 39a and 39b as light yellow oil.
Characterization of 39a:

IR (film): 3350, 3280, 2940, 2840, 1610, 1490, 1450, 1270, 1110

$^1$H NMR (CDCl$_3$): 2.13 (3H, s), 3.06 (3H, bs), 3.73 (3H, s), 3.79 (3H, s), 3.89-3.96 (1H, m), 5.07 (1H, d, $J$ = 3.3 Hz), 6.24 (1H, dd, $J$ = 16.0, 7.2 Hz), 6.46 (1H, d, $J$ = 16.0 Hz), 6.60 (1H, d, $J$ = 8.6 Hz), 7.18-7.31 (6H, m)

$^{13}$C NMR (CDCl$_3$): 9.2, 55.6, 58.9, 61.1, 71.5, 106.2, 119.3, 125.1, 125.6, 126.5, 127.5, 128.2, 128.5, 132.7, 136.8, 156.7, 158.3

MS: 312 (13, M-1), 295 (25), 280 (23), 180 (43), 179 (46), 165 (100), 163 (37), 117 (27), 91 (42)

Exact Mass: Calculated for C$_{19}$H$_{23}$NO$_3$ 313.1678
             Found 313.1681
Compound 39a continued:
Characterization of 39b:

IR (film): 3350, 3280, 3010, 2940, 2840, 1600, 1490, 1460, 1270, 1110

$^1$H NMR (CDCl$_3$): 2.11 (3H, s), 3.21 (3H, bs), 3.61 (3H, s), 3.79 (3H, s), 3.91-3.99 (1H, m), 4.93 (1H, d, $J = 5.7$ Hz), 6.18 (1H, dd, $J = 15.8$, 6.5 Hz), 6.50 (1H, d, $J = 15.8$ Hz), 6.61 (1H, d, $J = 8.5$ Hz), 7.16-7.33 (6H, m)

$^{13}$C NMR (CDCl$_3$): 9.2, 55.6, 59.0, 61.2, 71.3, 106.2, 119.4, 125.1, 126.3, 126.5, 127.5, 128.4, 128.8, 132.1, 136.8, 157.0, 158.4

MS: 295 (9, M$^+$ - H$_2$O), 221 (7), 181 (100), 151 (12), 132 (31), 115 (9)

Exact Mass: Calculated for C$_{19}$H$_{23}$NO$_3$ 313.1678

Found 313.1677
Compound 39b continued:
**Amide (85)**

To a stirred solution of 6.05 g (19.3 mmol) of the mixture of amino-alcohols 39a and 39b in 50 ml of dichloromethane was added 4.78 g (1.2 eq.) of 1,3-dicyclohexylcarbodiimide at room temperature. After stirring for 10 minutes, 7.8 g (1.0 eq.) of acid 40 was added. The reaction mixture was allowed to stir for 1 hour until the starting material was consumed. 200 ml of ether was added to precipitate the urea. Filtration of the solid product through Celite and the column was washed thoroughly by ether. Evaporation of filtrate and chromatography on silica gel, eluted with a gradient of ether in hexanes, gave a combine yield of 13.2 g (98%) of 85 as a mixture of diastereomers.
Tetracyclic amine (26)

A solution of 13.2 g (18.9 mmol) of amide 85 in 20 ml of pyridine and 20 ml of acetic anhydride was stirred for 30 minutes, then evaporated to dryness under reduced pressure. The reaction mixture was dissolved in 100 ml of dichloromethane, and 100 ml of methanol was added. The solution was cooled to -78 °C. Ozone was bubbled into the solution in 3 minute portions until the starting material was gone by tlc analysis. A total of 30 minutes of ozone was required. Nitrogen was bubbled thorough the reaction mixture for 10 minutes, 10 ml of dimethyl sulfide was added, and the solution was allowed to warm to room temperature. After stirring for 2 hours, the reaction mixture was evaporated to dryness under reduced pressure. The crude mixture was dissolved in 150 ml of dichloromethane and 2.3 ml (1.2 eq.) of 1,8-diazabicyclo[5,4,0]undec-7-ene was added at room temperature. After stirring for 2 hours, the reaction mixture was partitioned between ether and a solution of 3N hydrochloric acid. The organic layer was washed with 1N hydrochloric acid and brine. The
aqueous layers were extracted thoroughly with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The mixture was added with 200 ml of benzene and heated to 85 °C in a Dean-Stark apparatus. To the refluxing solution, 6 ml of trifluoroacetic acid was added slowly. After 30 minutes, the intermediate enal was consumed as evidenced by tlc. Another 4 ml of trifluoroacetic acid was added to the reaction mixture and heated for 1 hour. The reaction mixture was poured into a solution of saturated sodium bicarbonate carefully then partitioned with ether. The organic layer was washed by dilute sodium bicarbonate solution and brine(2X). The aqueous layers were extracted with ether thoroughly. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness. Chromatography on silica gel, eluted with a gradient of methanol and dichloromethane, provided 6.0 g (65.0%) of amine 26 as pale yellow solid.
Characterization of 26:

mp (Et₂O): 190-192 °C

IR (KBr): 3420, 3310, 3000, 2940, 2840, 1740, 1660, 1450, 1410, 1280, 1220, 1100

¹H NMR (CDCl₃): 2.11 (3H, s), 2.34 (3H, s), 3.05 (1H, dd, \( J = 17.6, 6.5 \) Hz), 3.16 (1H, dd, \( J = 17.6, 1.7 \) Hz), 3.71 (3H, s), 3.81 (3H, s), 4.08 (1H, dd, \( J = 6.5, 1.7 \) Hz), 5.03 (1H, s), 6.00 (1H, s), 6.62 (1H, d, \( J = 8.5 \) Hz), 7.01 (1H, d, \( J = 8.5 \) Hz), 8.21 (1H, s)

¹³C NMR (CDCl₃): 8.8, 16.7, 34.3, 49.6, 53.1, 55.7, 60.2, 61.2, 102.5, 106.5, 118.1, 120.0, 120.5, 121.6, 127.7, 128.9, 130.4, 134.2, 144.0, 144.9, 155.9, 158.1, 170.9

MS: 490 (95, M+2), 488 (100, M⁺), 410 (7), 408 (8), 270 (88), 268 (90), 255 (21), 253 (21), 193 (37), 190 (20), 176 (28), 146 (10)

\([\alpha]_D^{23}\): +30.3° (c = 0.370, CHCl₃)

Exact Mass: Calculated for C₂₃H₂₅BrN₂O₅ 488.0947
Found 488.0945
Compound 26 continued:
2,2,2-trichloroethyl urethane (106)

A solution of 2.22 g (5.05 mmol) of amine 105 and 1.27 g (3 eq.) of sodium bicarbonate was stirred in 50 ml of methylene chloride at room temperature. To this stirred solution was added 0.70 ml (1.1 eq.) of 2,2,2-trichloroethyl chloroformate. After 30 minutes, the reaction was complete as shown by tlc and 100 ml of ether was added to the reaction mixture. The salts were filtered through Celite and washed thoroughly with ether. Evaporation and chromatography of the crude mixture on silica gel, eluted with a gradient of ether in hexanes, gave 2.91 g (93.7%) of 106 as pale yellow solid.
Characterization of 106:

Note: This material was obtained as an approximately 2 : 1 mixture of two rotamers about the TROC.

mp (Et₂O): 98-100 °C

IR (KBr): 3280, 3000, 2930, 2830, 1730, 1660, 1600, 1460, 1420, 1290, 1110

¹H NMR (CDCl₃): 2.10 (3H, s), 2.22 (3H, s), 3.10-3.22 (1H, m), 3.31 (1H, d, J = 17.0 Hz), 3.42 (3H, s), 3.67 (3H, s), 3.72 (3H, s), 3.81 (3H, s), 4.66&4.70 (1H, s), 4.91&4.97 (1H, d, J = 12.5 Hz), 5.17-5.19 (1H, m), 5.90 (1H, AB, J = 6.5 Hz), 6.09-6.13 (2H, m), 6.62 (1H, d, J = 8.6 Hz), 7.02 (1H, d, J = 8.6 Hz), 8.33&8.43 (1H, s)

¹³C NMR (CDCl₃): 8.8, 9.6, 26.8, 27.2, 49.7, 50.5, 52.4, 52.9, 55.7, 60.1, 60.2, 75.2, 76.6, 95.2, 95.4, 104.5, 104.9, 106.6, 118.0, 118.1, 119.7, 120.4, 121.2, 121.6, 123.8, 128.0, 128.1, 128.4, 130.6, 130.9, 142.1, 142.3, 144.3, 149.7, 151.7, 152.1, 155.6, 155.7, 158.3, 168.1, 168.3

MS: 618 (35, M+4), 617 (28, M+3), 616 (100, M+2), 615 (29, M+1), 614 (100, M+), 582 (8), 580 (11), 398 (14), 397 (16), 396 (31), 395 (17), 394 (23), 382 (9), 380 (15), 355 (14), 220 (25), 204 (18), 176 (18), 165 (10)

Exact Mass: Calculated for C₂₇H₂₉Cl₃N₂O₈ 614.0990
Found 614.0989
Compound 106 continued:
**Tetracyclic lactam (107)**

To a solution of 2.91 g (4.73 mmol) of olefin \textbf{106} in 2 ml of acetic acid and 6 ml of trifluoroacetic acid at 65 °C was added 550 mg (2 eq.) of sodium cyanoborohydride carefully, over 15 minutes. After stirring for 30 minutes, 275 mg (1 eq.) of sodium cyanoborohydride was added in several portions and the reaction was monitored carefully by tlc until the starting material was consumed. The reaction mixture was slowly quenched with a solution of saturated sodium bicarbonate. The mixture was partitioned between ether and saturated sodium bicarbonate (2X) and saturated brine. The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to yield 2.89 g (99.0%) of \textbf{107} as a yellow foam which was used without purification.
Characterization of 107:

Note: This material was obtained as an approximately 2:1 mixture of two rotamers about the TROC.

mp (Et2O): 94-95 °C

IR (KBr): 3370, 3000, 2940, 2830, 1660, 1600, 1460, 1420, 1260, 1110

$^1$H NMR (CDCl$_3$): 2.05-2.20 (1H, m), 2.12 (3H, s), 2.26 (3H, s), 3.11 (1H, dd, $J = 17.5$, 6.8 Hz), 3.28 (1H, dd, $J = 17.5$, 1.2 Hz), 3.47&3.48 (1H, d, $J = 14.0$ Hz), 3.60&3.66 (3H, s), 3.68 (3H, s), 3.78&3.79 (6H, s), 4.20-4.32 (1H, m), 4.67&4.68 (1H, AB $J = 12.0$ Hz), 4.85&4.92 (1H, AB, $J = 12.0$ Hz), 4.98-5.04 (1H, m), 5.75-5.85 (2H, m), 5.94&5.99 (1H, s), 6.55 (1H, d, $J = 8.4$ Hz), 6.85&6.87 (1H, d, $J = 8.4$ Hz)

$^{13}$C NMR (CDCl$_3$): 9.2, 9.7, 22.7, 27.5, 28.1, 31.6, 32.4, 32.6, 48.3, 48.9, 51.7, 52.3, 55.7, 57.9, 58.2, 60.1, 60.4, 60.5, 60.9, 75.1, 75.2, 95.1, 95.4, 106.4, 106.5, 115.6, 115.7, 120.5, 120.6, 121.2, 121.3, 123.1, 123.4, 124.1, 127.9, 128.0, 142.3, 142.6, 143.9, 144.0, 149.9, 151.9, 157.9, 158.4, 169.1, 169.3

MS: 620 (20, M+4), 619 (18, M+3), 618 (58, M+2), 617 (16, M+1), 616 (65, M$^+$), 582 (13), 453 (21), 451 (23), 425 (61), 423 (65), 398 (17), 397 (28), 396 (39), 395 (27), 394 (27), 220 (40), 204 (27), 166 (86), 165 (100)

Exact Mass: Calculated for C$_{27}$H$_{31}$Cl$_3$N$_2$O$_8$ 616.1146
Found 616.1146
Compound 107 continued:
N-Troc-penta-methyl ether (108)

To a stirred solution of 2.89 g (4.68 mmol) of phenol 107 and 3.04 g (4 eq.) of pulverized potassium carbonate in 30 ml of N,N-dimethylformamide was added 0.69 ml (2 eq) of iodomethane at room temperature. The reaction was stirred vigorously for 2 hours until methylation was complete as evidenced by tlc. The reaction mixture was partitioned several times between ether and dilute sodium chloride solution. The aqueous layers were extracted thoroughly with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give 2.71 g (91.7%) of 108 as a yellow foam which was used without purification.
Characterization of 108:

Note: This material was obtained as an approximately 2 : 1 mixture of two rotamers about the TROC.

mp (Et₂O): 82-83 °C

IR (KBr): 3370, 3000, 2940, 2830, 2370, 1720, 1680, 1600, 1460, 1260, 1110

₁H NMR (CDCl₃): 1.98-2.19 (1H, m), 2.12 (3H, s), 2.23 (3H, s), 3.07-3.16 (1H, m), 3.27 (1H, AB, J = 17.5 Hz), 3.34-3.43 (1H, m), 3.63&3.65 (3H, s), 3.68 (3H, s), 3.80 (3H, s), 3.84 (3H, s), 3.88&3.91 (3H, s), 4.18-4.32 (1H, m), 4.70&4.76 (1H, AB J = 12.0 Hz), 4.83&4.85 (1H, AB, J = 12.0 Hz), 4.98-5.03 (1H, m), 5.66-5.76 (2H, m), 6.55&6.56 (1H, d, J = 8.4 Hz), 6.86&6.88 (1H, d, J = 8.4 Hz)

₁³C NMR (CDCl₃): 9.2, 9.5, 25.0, 25.6, 27.6, 28.0, 32.1, 32.3, 34.0, 48.5, 49.0, 51.6, 52.3, 55.7, 57.7, 58.0, 59.9, 60.2, 60.3, 60.4, 60.5, 75.2, 75.3, 95.1, 95.4, 106.4, 106.5, 120.5, 120.6, 121.1, 121.2, 122.0, 122.2, 122.4, 122.7, 125.7, 125.8, 127.7, 127.8, 146.3, 146.6, 150.2, 151.5, 152.1, 152.8, 152.9, 157.7, 158.3, 169.0, 169.1

MS: 634 (20, M+4), 633 (16, M+3), 632 (58, M+2), 631 (16, M+1), 630 (62, M⁺), 597 (6), 596 (6), 467 (19), 465 (32), 441 (20), 440 (15), 439 (78), 438 (17), 437 (77), 413 (11), 412 (22), 411 (32), 410 (50), 409 (33), 408 (38), 396 (14), 394 (16), 234 (46), 204 (42), 166 (100), 165 (85)

Exact Mass: Calculated for C₂₈H₃₃Cl₃N₂O₈ 630.1302
Found 630.1304
Compound 108 continued:
**Tetracyclic benzaldehyde (109)**

To a stirred solution of 2.71 g (186.4 mmol) of crude **108** in 50 ml of methylene chloride was added 0.94 ml (2.0 eq.) of titanium tetrachloride slowly at room temperature. To the stirred solution, 0.50 ml of α,α-dichloromethyl methyl ether was added slowly. After one and half hours, the reaction was complete as shown by tlc. The reaction mixture was poured into a stirring solution of ice chips slowly until the solution appeared clear then partitioned with 3N hydrochloric acid solution. The organic layer was washed with a solution of 3N hydrochloric acid, 1N hydrochloric acid, saturated sodium bicarbonate, and brine. The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield 2.64 g (93.3 %) of aldehyde **109** as a light foam solid which was used without purification.
Characterization of 109:

Note: This material was obtained as an approximately 2:1 mixture of two rotamers about the TROC.

mp (CH₂Cl₂): 110-111 °C

IR (KBr): 3390, 3330, 3210, 2950, 1730, 1680, 1590, 1450, 1410, 1210, 1120, 720

¹H NMR (CDCl₃): 2.14-2.20 (1H, m), 2.25 (6H, s), 3.05-3.18 (1H, m), 3.25 (1H, AB, J = 17.5 Hz), 3.43 (1H, d, J = 14.0 Hz), 3.72 (3H, s), 3.84 (3H, s), 3.88 & 3.91 (6H, s), 4.22-4.34 (1H, m), 4.69-4.86 (2H, m), 4.99-5.03 (1H, m), 5.54 & 5.56 (1H, s), 5.70-5.75 (1H, m), 7.49 (1H, s), 10.26 (1H, s)

¹³C NMR (CDCl₃): 9.5, 9.6, 15.3, 27.6, 28.0, 32.3, 32.5, 48.3, 48.9, 51.6, 52.3, 57.1, 57.7, 60.0, 60.2, 60.4, 60.5, 60.6, 63.4, 75.2, 75.3, 95.1, 95.4, 121.6, 121.9, 122.4, 122.7, 125.8, 126.0, 126.1, 126.4, 126.5, 127.9, 128.1, 146.2, 146.5, 150.3, 151.5, 152.1, 152.9, 153.0, 162.8, 162.9, 163.6, 163.7, 169.0, 169.2, 189.0

MS: 662 (22, M+4), 661 (19, M+3), 660 (69, M+2), 659 (23, M+1), 658 (69, M+), 626 (10), 625 (9), 624 (15), 467 (36), 465 (48), 441 (29), 439 (100), 437 (100), 412 (36), 411 (47), 410 (68), 409 (50), 408 (59), 396 (22), 394 (17), 374 (16), 234 (55), 204 (53)

Exact Mass: Calculated for C₂₉H₃₃Cl₃N₂O₉ 658.1251
Found 658.1252
Compound 109 continued:
Tetracyclic phenol (110)

To a stirred solution of 2.64 g (4.00 mmol) of aldehyde 109 in 50 ml of methylene chloride was added 1.5 ml solution of 20% of boron trichloride in methylene chloride at room temperature. After about 30 minutes, 0.5 ml of 20% of boron trichloride solution was added in several portions and the reaction was monitored carefully by tlc until the starting material was consumed. The reaction was poured into ice chips and partitioned between dichloromethane and a solution of 3N hydrochloric acid. The organic layer was washed with 1N hydrochloric acid solution and brine (2X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Chromatography on silica gel, eluted with a gradient of methanol in methylene chloride yielded 2.49 g (94.9 %) of phenol 110 as a pale yellow foam.
Characterization of **110**: 

**Note:** This material was obtained as an approximately 2:1 mixture of two rotamers about the TROC.

**mp (CH₂Cl₂):** 129-130 °C

**IR (KBr):** 3390, 2940, 2840, 1720, 1690, 1650, 1420, 1410, 1300, 1260, 1180, 1120, 1060

**¹H NMR (CDCl₃):** 1.99-2.15 (1H, m), 2.18 (3H, s), 2.24 (3H, s), 3.05-3.18 (1H, m), 3.22-3.30 (1H, m), 3.42-3.48 (1H, m), 3.70 (3H, s), 3.75&3.76 (3H, s), 3.85 (3H, s), 3.89&3.91 (3H, s), 4.22-4.33 (1H, m), 4.69-4.90 (2H, m), 4.99-5.04 (1H, m), 5.64-5.77 (2H, m), 7.14&7.16 (1H, s), 9.73&9.74 (1H, s), 11.41&11.42 (1H, s)

**¹³C NMR (CDCl₃):** 8.8, 9.5, 27.5, 28.0, 32.2, 32.4, 48.3, 48.9, 51.6, 52.3, 57.3, 57.6, 60.0, 60.2, 60.4, 60.5, 60.6, 60.7, 75.2, 75.3, 95.1, 95.4, 117.0, 117.1, 120.4, 120.5, 121.4, 121.5, 121.7, 121.9, 122.4, 122.7, 125.9, 126.0, 132.8, 133.0, 146.3, 146.5, 150.3, 151.5, 152.2, 152.9, 153.0, 161.5, 161.6, 164.2, 169.1, 169.3, 195.3

**MS:** 648 (14, M+4), 647 (14, M+3), 646 (53, M+2), 645 (15, M+1), 644 (56, M+), 610 (9), 469 (20), 467 (41), 465 (51), 441 (32), 440 (22), 439 (98), 438 (19), 437 (100), 412 (25), 411 (39), 410 (61), 409 (45), 408 (50), 396 (19), 394 (15), 278 (11), 234 (47), 204 (45), 179 (32)

**Exact Mass:** Calculated for C₂₈H₃₁Cl₃N₂O₉ 644.1095 
Found 644.1092
Compound 110 continued:
**Tetracyclic benzyl ether (111)**

To a stirred solution of 2.49 g (3.86 mmol) of crude phenol 110 and 1.60 g (3 eq.) of pulverized potassium carbonate in 30 ml of N,N-dimethyl-formamide was added 0.50 ml (1.1 eq) of benzyl bromide at room temperature. The reaction was stirred vigorously for 2 hours at 85 °C until benzylation was complete as evidenced by tlc. The reaction mixture was partitioned several times between ether and dilute sodium chloride solution. The aqueous layers were extracted thoroughly with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give 2.69 g (94.8 %) of 111 as a pale yellow oil which was used without purification.
Characterization of 111:

Note: This material was obtained as an approximately 2:1 mixture of two rotamers about the TROC.

IR (KBr): 3380, 2940, 1720, 1680, 1600, 1470, 1310, 1240, 1110, 1070, 1000

$^1$H NMR (CDCl$_3$): 2.14-2.21 (1H, m), 2.25 (3H, s), 2.26 (3H, s), 3.08-3.18 (1H, m), 3.26 (1H, AB, $J = 17.6$ Hz), 3.45 (1H, d, $J = 13.5$ Hz), 3.72 (3H, s), 3.73 (3H, s), 3.85 (3H, s), 3.88&3.91 (3H, s), 4.26-4.35 (1H, m), 4.69-4.88 (2H, m), 4.96 (2H, s), 4.99-5.04 (1H, m), 5.58&5.60 (1H, s), 5.72-5.75 (1H, m), 7.40 (5H, m), 7.49 (1H, s), 10.13 (1H, s)

$^{13}$C NMR (CDCl$_3$): 9.5, 10.0, 27.6, 28.0, 32.4, 32.5, 48.4, 48.9, 51.6, 52.4, 57.2, 57.8, 60.0, 60.2, 60.4, 60.6, 75.2, 75.3, 78.1, 95.1, 95.4, 121.6, 121.9, 122.4, 122.7, 126.0, 126.1, 126.2, 126.5, 126.6, 126.7, 128.0, 128.1, 128.3, 128.5, 128.8, 135.7, 146.2, 146.5, 150.3, 151.5, 152.1, 152.9, 153.0, 161.3, 163.6, 163.7, 169.0, 169.2, 189.0

MS: 737 (4, M+3), 736 (6, M+2), 735 (5, M+1), 734 (9, M$^+$), 646 (8), 645 (8), 644 (5), 643 (5), 465 (9), 439 (38), 437 (36), 412 (14), 411 (18), 410 (30), 409 (20), 408 (27), 396 (12), 242 (11), 234 (35), 204 (25), 179 (15), 106 (17), 105 (18), 91 (100), 77 (19)

Exact Mass: Calculated for C$_{35}$H$_{37}$Cl$_3$N$_2$O$_9$ 734.1564
Found 734.1563
Compound 111 continued:
*o*-benzoxoxy phenol (112)

To a solution of 2.69 g (3.66 mmol) of aldehyde 111 in 30 ml of chloroform was slowly added 1.89 g (2 eq.) of 50% 3-chloroperoxybenzoic acid at room temperature. After stirring for 2 hours at 85 °C, the reaction was complete as shown by tlc. After cooling, the reaction mixture was partitioned between ether and a solution of saturated sodium sulfite. The organic layer was washed with sodium bicarbonate (2X) and brine. The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to dryness. The crude products were dissolved in 20 ml of methanol and 0.5 ml (1.0 eq.) of triethylamine was added at room temperature. After stirring for two hours, the reaction mixture was concentrated to dryness under reduced pressure, then partitioned between ether and a solution of 3N hydrochloric acid. The organic layer was washed by saturated sodium bicarbonate solution and brine (2X). The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and
evaporated under reduced pressure to afford 2.34 g (88.4%) of phenol 112 as pale yellow oil.

Characterization of 112:

Note: This material was obtained as an approximately 2:1 mixture of two rotamers about the TROC.

IR (KBr): 3370, 2950, 2240, 1730, 1670, 1590, 1470, 1410, 1290, 1240, 1110, 1070, 720

$^1$H NMR (CDCl$_3$): 2.04-2.20 (1H, m), 2.23 (3H, s), 2.25 (3H, s), 3.06-3.17 (1H, m), 3.26 (1H, AB, $J = 16.9$ Hz), 3.30-3.40 (1H, m), 3.57&3.58 (3H, s), 3.71 (3H, s), 3.83 (3H, s), 3.87&3.90 (3H, s), 4.18-4.29 (1H, m), 4.67-4.68 (2H, m), 4.96 (2H, s), 4.96-5.03 (1H, m), 5.69-5.74 (1H, m), 5.80&5.87 (1H, s), 6.53&6.54 (1H, s), 7.34-7.42 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.5, 10.3, 27.6, 28.0, 32.1, 32.3, 48.4, 49.0, 51.6, 52.3, 57.6, 58.1, 60.0, 60.2, 60.3, 60.4, 60.5, 60.6, 75.2, 75.3, 75.5, 95.1, 95.4, 114.1, 114.2, 121.9, 122.1, 122.4, 122.7, 125.5, 125.6, 125.7, 125.8, 125.9, 128.2, 128.3, 128.5, 128.6, 128.8, 136.8, 144.2, 145.9, 146.0, 146.3, 146.5, 150.2, 150.5, 151.5, 152.1, 152.8, 152.9, 169.1, 169.3

MS: 726 (6, M+4), 725 (5, M+3), 724 (11, M+2), 723 (6, M+1), 722 (23, M$^+$), 690 (8), 688 (13), 465 (15), 439 (42), 437 (38), 412 (17), 411 (15), 410 (29), 409 (14), 408 (22), 403 (26), 374 (18), 346 (10), 256 (31), 234 (49), 204 (33), 91 (100), 65 (10)

Exact Mass: Calculated for C$_{34}$H$_{37}$Cl$_3$N$_2$O$_9$: 722.1564
Found: 722.1564
Compound 112 continued:
Methoxy benzyl ether (113)

To a stirred solution of 314.5 mg (0.435 mmol) of phenol 112 and 180 mg (3.0 eq.) of pulverized potassium carbonate in 30 ml of N,N-dimethyl-formamide was added 35.0 μl (1.3 eq.) of iodomethane at room temperature. The reaction was stirred vigorously for 2 hours until methylation was complete as evidenced by tlc. The reaction mixture was partitioned several times between ether and dilute sodium chloride solution. The aqueous layers were extracted thoroughly with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give 274.1 mg (85.5%) of ether 113 as a light yellow oil which was used without purification.
Characterization of 113:

Note: This material was obtained as an approximately 2 : 1 mixture of two rotamers about the TROC.

IR (film): 3380, 2940, 2840, 2240, 1710, 1680, 1600, 1470, 1410, 1230, 1120, 1070

$^1$H NMR (CDCl$_3$): 2.11 (3H, s), 2.12-2.19 (1H, m), 2.24 (3H, s), 3.08-3.18 (1H, m), 3.25-3.41 (2H, m), 3.53&3.56 (3H, s), 3.70 (3H, s), 3.83&3.84 (6H, s), 3.89&3.91 (3H, s), 4.20-4.33 (1H, m), 4.68-4.90 (2H, m), 4.94 (2H, s), 5.00-5.05 (1H, m), 5.71-5.87 (1H, m), 6.47&6.51 (1H, s), 7.38 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.5, 10.1, 25.0, 27.6, 28.1, 32.4, 32.7, 48.5, 49.1, 51.7, 52.3, 56.2, 58.0, 58.2, 59.9, 60.1, 60.4, 60.5, 60.6, 74.5, 75.2, 75.3, 95.1, 95.4, 111.2, 121.9, 122.1, 122.5, 122.8, 124.1, 124.2, 125.8, 125.9, 126.7, 126.8, 128.0, 128.3, 128.4, 137.7, 146.2, 146.3, 146.4, 146.5, 149.6, 149.7, 150.2, 151.0, 151.1, 151.5, 152.1, 152.8, 152.9, 169.1, 169.1

MS: 740 (8, M+4), 739 (8, M+3), 738 (21, M+2), 737 (9, M+1), 736 (21, M+), 647 (4), 645 (4), 439 (14), 437 (14), 410 (13), 408 (11), 272 (11), 271 (10), 234 (16), 204 (10), 181 (100), 131 (13), 91 (43)

Exact Mass: Calculated for C$_{35}$H$_{39}$Cl$_3$N$_2$O$_9$ 736.1721

Found 736.1723
Compound 113 continued:
**Phenol (114)**

To a solution of 107.4 mg (0.146 mmol) of 1113 in 2 ml of dichloromethane was added 500 μl (large excess) of 20% of boron trichloride in dichloromethane at room temperature. After 30 minutes, the reaction was complete as shown by tlc. The reaction mixture was partitioned between dichloromethane and dilute sodium chloride solution (3X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to furnish 70.1 mg (74.5 %) of phenol 114 as light yellow oil.
Characterization of \textbf{114}:

Note: This material was obtained as an approximately 2:1 mixture of two rotamers about the TROC.

IR (film): 3330, 3010, 2930, 2830, 1720, 1660, 1600, 1490, 1470, 1410, 1290, 1260, 1120, 1070

\textbf{^1H NMR (CDCl}\textsubscript{3}): 1.94-2.08 (1H, m), 2.16 (3H, s), 2.23 (3H, s), 3.07-3.18 (1H, m), 3.25-3.43 (2H, m), 3.58&3.60 (3H, s), 3.69&3.70&3.73 (6H, s), 3.84 (3H, s), 3.89&3.91 (3H, s), 4.16-4.33 (1H, m), 4.68-4.89 (2H, m), 5.00-5.04 (1H, m), 5.71-5.76 (1H, m), 5.85&5.97 (1H, s), 6.11&6.23 (1H, bs), 6.34&6.39 (1H, s)

\textbf{^13C NMR (CDCl}\textsubscript{3}): 9.3, 9.5, 27.5, 28.0, 32.4, 32.7, 48.4, 49.0, 51.5, 52.3, 55.8, 55.9, 58.0, 58.2, 59.9, 60.0, 60.2, 60.4, 60.5, 60.6, 75.2, 75.3, 95.1, 95.4, 109.4, 118.6, 118.7, 118.9, 121.9, 122.2, 122.4, 122.7, 125.8, 125.9, 128.4, 143.1, 143.2, 144.1, 144.2, 146.4, 146.6, 150.2, 151.5, 152.1, 152.8, 152.9, 169.3, 169.6

MS: 650 (16, M+4), 649 (14, M+3), 648 (43, M+2), 647 (15, M+1), 646 (47, M+), 614 (6), 612 (9), 439 (32), 437 (31), 412 (11), 411 (15), 410 (23), 409 (15), 408 (16), 396 (9), 394 (9), 234 (32) 204 (24), 182 (100), 181 (65)

Exact Mass: Calculated for \text{C}_{28}\text{H}_{33}\text{Cl}_3\text{N}_2\text{O}_9 \quad 646.1251

Found \quad 646.1254
Compound 114 continued:
Phenolic alcohol (115)

To a solution of 225.3 mg (0.039 mmol) of phenol 114 in 0.8 ml of tetrahydrofuran and 0.2 ml of water was added 17.8 mg (2 eq.) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at room temperature. After 3 hours, the reaction was complete as shown by tlc. The reaction mixture was partitioned between dichloromethane and dilute sodium chloride solution (3X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to give 12.1 mg (46.7 %) of quinone 115 as pale yellow oil.
Characterization of 115:

Note: This material was obtained as an approximately 2 : 1 mixture of two rotamers about the TROC.

IR (film): 3370, 3000, 2940, 2830, 1720, 1670, 1600, 1450, 1410, 1290, 1250, 1110, 1070, 1000, 770

$^1$H NMR (CDCl$_3$): 2.20 (3H, s), 2.21 (3H, s), 3.14 (1H, dd, J = 17.6, 6.7 Hz), 3.29 (1H, AB, J = 17.6 Hz), 3.70 (3H, s), 3.74 & 3.75 (3H, s), 3.78 & 3.79 (3H, s), 3.82-3.91 (6H, m), 4.36 (1H, dd, J = 4.1, 3.9 Hz), 4.69 (1H, AB, J = 12.0 Hz), 4.78 (1H, d, J = 4.1 Hz), 4.85 (1H, AB, J = 12.0 Hz), 5.02 & 5.04 (1H, d, J = 6.7 Hz), 5.31 & 5.55 (1H, s), 5.78 & 5.87 (1H, d, J = 3.9 Hz), 5.92 & 6.25 (1H, s), 6.04 & 6.13 (1H, bs), 6.76 & 6.85 (1H, s)

$^{13}$C NMR (CDCl$_3$): 9.3, 9.5, 27.6, 28.2, 47.8, 48.3, 51.6, 52.5, 56.2, 56.3, 60.0, 60.3, 60.4, 60.5, 60.6, 60.7, 61.2, 62.2, 66.7, 66.8, 75.3, 75.5, 77.2, 95.1, 95.3, 104.9, 105.1, 118.3, 118.4, 123.1, 123.2, 123.4, 123.8, 126.3, 126.5, 142.9, 143.0, 144.4, 144.5, 145.8, 146.1, 149.6, 150.1, 150.3, 151.3, 152.1, 153.2, 153.3, 169.6, 170.0

MS: 648 (37, (M+4) - H$_2$O), 647 (32, (M+3) - H$_2$O), 646 (99, (M+2) - H$_2$O), 645 (32, (M+1) - H$_2$O), 644 (100, M$^+$ - H$_2$O), 610 (17), 566 (10), 497 (8), 410 (37), 408 (34), 234 (53), 204 (27), 192 (17), 181 (12)

Exact Mass: Calculated for (M$^+$ - H$_2$O)

C$_{28}$H$_{33}$Cl$_3$N$_2$O$_9$ 644.1095
Found 644.1103
Compound 115 continued:
Tetracyclic N-methylamine (116)

To a solution of 1.31 g (1.81 mmole) of urethane 112 and 1.15 g (10 eq.) of fresh active zinc in 20 ml of N,N-dimethylformamide was added 156 μl (1.5 eq.) of acetic acid dropwise at 85 °C. After 30 minutes, 104 μl (1.0 eq.) of acetic acid was added in several portions and the reaction was monitored carefully by tlc until the starting material was consumed. After cooling, the reaction mixture was added to 10 ml of saturated sodium bicarbonate solution. After stirring for 5 minutes, the reaction mixture was filtered through Celite and was washed with ether. The filtrate was partitioned between ether and saturated sodium bicarbonate. The organic layer was washed with dilute sodium bicarbonate and brine (2X). The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was dissolved in 30 ml of methanol and added 735 μl (5 eq.) of 37 % aqueous formaldehyde and 228 mg (2 eq.) of sodium cyanoborohydride, followed by 70 μl (0.5
eq.) of trifluoroacetic acid. After stirring for 20 minutes, the reaction was complete as shown by tlc. The mixture was partitioned between ether and a solution of saturated sodium bicarbonate. The organic layer was washed by dilute sodium bicarbonate and brine (2X). The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to afford 970 mg (95%) of amine 116 as clear oil which was used without purification.

Characterization of 116:

IR (KBr): 3370, 2940, 1670, 1590, 1450, 1400, 1350, 1250, 1100, 1070, 1010

$^1$H NMR (CDCl₃): 1.99 (1H, dd, $J = 13.9$, 5.7 Hz), 2.17 (3H, s), 2.22 (3H, s), 2.54 (3H, s), 3.00 (1H, AB, $J = 17.9$ Hz), 3.12 (1H, dd, $J = 17.9$, 6.6 Hz), 3.27 (1H, dd, $J = 13.9$, 1.3 Hz), 3.54 (3H, s), 3.63 (1H, d, $J = 6.0$ Hz), 3.68 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 4.25-4.30 (2H, m), 4.88 (2H, s), 5.78 (1H, s), 6.52 (1H, s), 7.33-7.45 (5H, m)

$^{13}$C NMR (CDCl₃): 9.4, 10.2, 24.1, 31.8, 40.2, 54.6, 55.1, 58.0, 59.9, 60.3, 60.5, 75.2, 77.3, 114.2, 121.9, 122.2, 125.0, 125.6, 125.9, 128.3, 128.4, 128.5, 128.7, 137.1, 144.1, 146.0, 147.2, 150.0, 150.5, 152.5, 171.7

MS: 562 (14, M⁺), 547 (4), 471 (7), 248 (100), 234 (8), 218 (13), 131 (13), 91 (8)

Exact Mass: Calculated for C$_{32}$H$_{38}$N$_2$O$_7$ 562.2679
          Found 562.2677
Compound 116 continued:
Pentacyclic amino nitrile (118)

To a stirred solution of 970 mg (1.73 mmole) of lactam 116 in 20 ml of methylene chloride at -78 °C was added 1.73 ml (1.5 eq.) of 1.5 M diisobutylaluminum hydride in toluene dropwise. After 2 hours at -78 °C, the reaction was complete as shown by tlc and 10 ml of methanol was slowly added and 425 mg (5 eq.) of sodium cyanide was added. The solution was allowed to warm to room temperature over 30 minutes. After stirring for 3 hours at room temperature, the aminal was consumed as evidenced by tlc and 10 ml of saturated sodium bicarbonate solution was added to the mixture. The reaction mixture was filtered through Celite and the filtrate was partitioned between dichloromethane and saturated sodium bicarbonate. The organic layer was washed by dilute sodium bicarbonate and brine (2X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to dryness. The crude amino nitrile was dissolved in 20 ml of acetonitrile and 651 μl (3 eq.) of
cinnamaldehyde, 1.6 g (4 eq.) of (+)-camphorsulfonic acid, and 230 µl of trimethyl-silyl cyanide (2 eq.) were added in a sealed tube. The reaction mixture was heated at 100 °C for 6 hours until the reaction was complete as shown by tlc. After cooling, the reaction mixture was partitioned between ether and saturated sodium bicarbonate solution. The organic layer was washed with dilute sodium bicarbonate and brine (2X). The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. A silica gel column separation employing a solvent gradient to 80 % ether in hexanes afforded 560.1 mg (55.7%) of 118 as white solid.
Characterization of 118:

mp (Et$_2$O): 114-116 °C

IR (KBr): 3520, 3430, 2940, 2840, 2230, 1600, 1450, 1420, 1330, 1110, 1070

$^1$H NMR (CDCl$_3$): 1.92 (1H, dd, $J$ = 15.6, 11.5 Hz), 2.22 (3H, s), 2.24 (3H, s), 2.37 (3H, s), 2.47 (1H, AB, $J$ = 18.4 Hz), 3.02 (1H, dd, $J$ = 18.4, 8.1 Hz), 3.21 (1H, dd, $J$ = 15.6, 2.4 Hz), 3.30 (1H, ddd, $J$ = 11.5, 2.6, 2.4 Hz), 3.39 (1H, dd, $J$ = 8.1, 2.5 Hz), 3.61 (3H, s), 3.63 (3H, s), 3.82 (3H, s), 3.87 (3H, s), 4.00 (1H, d, $J$ = 2.5 Hz), 4.14 (1H, d, $J$ = 2.6 Hz), 4.53 (1H, d, $J$ = 6.2 Hz), 4.82 (2H, AB, $J$ = 1.4 Hz), 5.34 (1H, s), 5.98 (1H, dd, $J$ = 15.7, 6.2 Hz), 6.40 (1H, d, $J$ = 15.7 Hz), 7.12-7.22 (5H, m), 7.33-7.40 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.4, 9.9, 21.4, 26.0, 41.9, 55.1, 56.1, 57.0, 59.2, 59.6, 59.7, 60.0, 60.3, 60.4, 75.6, 118.4, 119.5, 122.2, 123.6, 123.8, 124.0, 126.4, 127.2, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 128.9, 129.7, 136.8, 137.0, 142.0, 142.4, 147.8, 148.4, 149.3, 151.3

MS: 688 (2, M+1), 687 (4, M$^+$), 660 (4), 570 (7), 569 (8), 467 (4), 288 (24), 248 (100), 218 (15), 91 (17)

Exact Mass: Calculated for C$_{42}$H$_{45}$N$_3$O$_6$ 687.3308

Found 687.3309
Compound 118 continued:
Pentamethoxyl pentacyclic amino nitrile (119)

To a stirred solution of 250.0 mg (0.36 mmol) of phenol 118 and 151 mg (3.0 eq.) of pulverized potassium carbonate in 3.0 ml of N,N-dimethyl-formamide was added 25 µl (2 eq) of iodomethane at room temperature. The reaction was stirred vigorously for 2 hours until methylation was complete as evidenced by tlc. The reaction mixture was partitioned several times between ether and dilute sodium chloride solution. The aqueous layers were extracted thoroughly with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, evaporated, and separated on preparative tlc to give 231.4 mg (90.7%) of 119 as a white foam.
Characterization of 119:

mp (Et₂O): 90-91 °C

IR (KBr): 2940, 2830, 2230, 1590, 1460, 1400, 1340, 1100, 1080

¹H NMR (CDCl₃): 1.90 (1H, dd, J = 15.4, 11.6 Hz), 2.11 (3H, s), 2.25 (3H, s), 2.37 (3H, s), 2.47 (1H, AB, J = 18.4 Hz), 3.03 (1H, dd, J = 18.4, 8.0 Hz), 3.20 (1H, dd, J = 15.4, 2.4 Hz), 3.28 (1H, ddd, J = 11.6, 2.4, 2.4 Hz), 3.40 (1H, dd, J = 8.1, 2.3 Hz), 3.57 (1H, s), 3.58 (3H, s), 3.77 (3H, s), 3.80 (3H, s), 3.87 (3H, s), 4.03 (1H, d, J = 2.3 Hz), 4.13 (1H, d, J = 2.4 Hz), 4.59 (1H, d, J = 6.2 Hz), 4.90 (2H, AB, J = 10.9 Hz), 5.95 (1H, dd, J = 15.6, 6.2 Hz), 6.37 (1H, d, J = 15.6 Hz), 7.14-7.23 (5H, m), 7.30-7.45 (5H, m)

¹³C NMR (CDCl₃): 9.3, 9.6, 21.5, 26.0, 41.9, 55.1, 56.4, 57.0, 59.5, 59.6, 59.9, 60.0, 60.3, 60.4, 60.6, 74.4, 118.4, 123.6, 123.7, 123.8, 124.0, 124.1, 126.4, 126.5, 127.2, 128.0, 128.3, 128.4, 129.5, 130.8, 137.1, 137.6, 146.3, 147.8, 148.5, 149.3, 151.2, 151.3

MS: 702 (M+1), 701 (M), 674 (5), 610 (2), 583 (5), 481 (3), 288 (32), 248 (100), 218 (15), 91 (15)

Exact Mass: Calculated for C₄₃H₄₇N₃O₆ 701.3465
Found 701.3466
Compound 119 continued:
Pentacyclic diol (120)

To a stirred solution of 201.4 mg (0.29 mmol) of olefin 119 in 3 ml of acetone and 1 ml of water was added 1 mg of osmium tetraoxide and 41 mg (1.2 eq.) of N-methylmorpholine N-oxide at room temperature. After 2 hours, the reaction was complete as shown by tlc. The reaction mixture was partitioned between dichloromethane and a solution of saturated sodium sulfite (2X). The organic layer was washed with saturated sodium bicarbonate and brine. The aqueous layers were extracted thoroughly with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to afford 178.4 mg (84.5 %) of diol 120 as clear oil.
Characterization of 120:

IR (film): 3470, 2940, 2830, 2230, 1450, 1410, 1340, 1100, 1080

$^1$H NMR (CDCl$_3$): 1.99 (1H, dd, $J = 16.1$, 12.3 Hz), 2.13 (3H, s), 2.21 (3H, s), 2.34 (3H, s), 2.53 (1H, bs), 2.70 (1H, AB, $J = 18.6$ Hz), 3.18 (1H, dd, $J = 16.1$, 7.9 Hz), 3.21-3.30 (2H, m), 3.41 (1H, d, $J = 7.9$ Hz), 3.46-3.48 (1H, m), 3.61 (3H, s), 3.69 (1H, m), 3.78 (3H, s), 3.81 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 4.13 (1H, d, $J = 1.4$ Hz), 4.37 (1H, s), 4.49 (1H, d, $J = 4.8$ Hz), 4.75 (1H, d, $J = 2.3$ Hz), 4.79 (1H, AB, $J = 10.9$ Hz), 5.10 (1H, AB, $J = 10.9$ Hz), 6.84 (2H, dd, $J = 7.7$, 1.9 Hz), 7.14-7.22 (3H, m), 7.30-7.46 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.4, 9.7, 21.5, 26.5, 41.4, 55.1, 57.1, 58.6, 59.6, 60.1, 60.4, 60.6, 61.1, 61.4, 63.1, 71.2, 74.7, 78.9, 118.3, 123.1, 123.2, 124.4, 124.9, 125.0, 125.4, 125.5, 126.4, 127.1, 128.1, 128.3, 128.5, 137.4, 141.8, 145.9, 147.6, 148.9, 149.9, 151.7, 151.8

MS: 708 (4, M - HCN), 598 (11), 572 (10), 481 (100), 248 (47), 218 (11), 105 (17), 91 (10), 77 (16)

Exact Mass: Calculated for C$_{43}$H$_{49}$N$_3$O$_8$ 735.3519
                       Found         735.3526
Compound 120 continued:
Pentacyclic alcohol (121)

To a stirred solution of 150.4 mg (0.20 mmol) of diol 120 in 3 ml of ethanol was added 2.2 ml (1.1 eq.) of 0.1N sodium periodate in water. After stirring for 2 hours at room temperature, the reaction was complete as evidenced by tlc. The reaction mixture was filtered through Celite and 12.0 mg (1.5 eq.) of sodium borohydride was added to the filtrate. After 20 minutes, the reaction mixture was partitioned between dichloromethane and brine (3X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to furnish 110.4 mg (85.7 %) of alcohol 121 as light yellow oil.
Characterization of 121:

IR (film): 3500, 2930, 2830, 2240, 1610, 1460, 1400, 1340, 1120, 1070

$^1$H NMR (CDCl$_3$): 1.79 (1H, dd, J = 15.5, 12.0 Hz), 1.97 (1H, bs), 2.11 (3H, s), 2.20 (3H, s), 2.37 (3H, s), 2.51 (1H, AB, J = 18.5 Hz), 3.10 (1H, dd, J = 18.5, 7.8 Hz), 3.15-3.33 (3H, m), 3.42 (1H, dd, J = 7.9, 2.5 Hz), 3.56-3.61 (1H, m), 3.60 (3H, s), 3.72 (3H, s), 3.78 (3H, s), 3.86 (6H, s), 4.07-4.12 (3H, m), 4.79 (1H, AB, J = 10.9 Hz), 5.03 (1H, AB, J = 10.9 Hz), 7.31-7.45 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.4, 9.6, 21.7, 25.9, 41.8, 55.1, 56.6, 56.9, 58.5, 59.9, 60.0, 60.4, 60.5, 60.7, 60.9, 65.9, 74.5, 117.9, 122.8, 123.4, 124.1, 124.5, 124.8, 125.5, 128.0, 128.3, 128.4, 137.5, 146.0, 147.7, 148.5, 149.6, 151.2, 151.4

MS: 602 (8, M - HCN), 598 (43), 573 (6), 354 (18), 288 (23), 278 (10), 248 (100), 218 (18), 91 (18)

Exact Mass: Calculated for C$_{36}$H$_{43}$N$_3$O$_7$ 629.3101
Found 629.3110
Compound 121 continued:
Pentacyclic alcohol phenol (122)

To a solution of 50.8 mg (0.081 mmol) of benzyl ether 121 in 2 ml of dichloromethane was added 200 µl (large excess) of 20% of boron trichloride in dichloromethane at room temperature. After 30 minutes, the reaction was complete as shown by tlc. The reaction mixture was partitioned between dichloromethane and dilute sodium chloride solution (3X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to furnish 35.3 mg (81.6 %) of phenol 122 as yellow oil.
Characterization of 122:

IR (KBr): 3420, 2930, 2830, 2230, 1600, 1400, 1110, 1060, 1000

$^1$H NMR (CDCl$_3$): 1.76 (1H, dd, $J = 15.5, 11.9$ Hz), 1.93 (1H, bs), 2.15 (3H, s), 2.19 (3H, s), 2.36 (3H, s), 2.52 (1H, AB, $J = 18.5$ Hz), 3.01-3.18 (3H, m), 3.25 (1H, ddd, $J = 11.9, 2.5, 2.4$ Hz), 3.41 (1H, d, $J = 7.7$ Hz), 3.55 (1H, dd, $J = 10.7, 4.4$ Hz), 3.63 (3H, s), 3.71 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 3.86 (3H, s), 4.03 (1H, dd, $J = 4.8, 4.4$ Hz), 4.11 (2H, s), 5.47 (1H, bs)

$^{13}$C NMR (CDCl$_3$): 9.0, 9.4, 21.7, 25.9, 41.7, 55.1, 56.9, 57.2, 58.7, 59.8, 60.0, 60.4, 60.5, 61.4, 61.5, 66.5, 117.2, 118.1, 120.7, 122.7, 123.4, 124.1, 124.3, 139.6, 145.9, 147.6, 149.6, 151.4, 152.0

MS: 539 (2, M$^+$), 512 (8), 508 (34), 288 (23), 278 (10), 264 (18), 248 (100), 218 (15)

Exact Mass: Calculated for C$_{29}$H$_{37}$N$_3$O$_7$ 539.2632

Found 539.2631
Compound 122 continued:
Ortho-quinone dimethyl acetal alcohol (124)

To a solution of 23.8 mg (0.044 mmol) of phenol 122 in 1 ml of methanol was added 30.0 mg (3 eq.) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at room temperature. After 1 hour, the reaction was complete as shown by tlc. The reaction mixture was partitioned between dichloromethane and dilute sodium chloride solution (3X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to give 17.9 mg (71.2 %) of quinone 124 as yellow oil.
Characterization of 124:

IR (KBr): 3510, 2940, 2830, 2230, 1660, 1590, 1450, 1400, 1330, 1240, 1070

$^1$H NMR (CDCl$_3$): 1.56-1.67 (1H, m), 1.86 (3H, s), 2.09 (1H, bs), 2.19 (3H, s), 2.34 (3H, s), 2.45 (1H, AB, $J = 18.5$ Hz), 2.77 (1H, dd, $J = 16.7$, 2.8 Hz), 3.07 (1H, dd, $J = 18.5$, 7.8 Hz), 3.18 (3H, s), 3.24 (3H, s), 3.40 (1H, d, $J = 6.9$ Hz), 3.50-3.59 (2H, m), 3.65-3.72 (1H, m), 3.70 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 3.82 (3H, s), 4.00 (1H, d, $J = 2.5$ Hz), 4.05 (1H, d, $J = 2.5$ Hz)

$^{13}$C NMR (CDCl$_3$): 8.2, 9.3, 21.5, 26.2, 41.8, 49.8, 52.5, 54.9, 55.4, 56.5, 59.1, 59.8, 59.9, 60.0, 60.2, 60.4, 63.4, 93.8, 117.5, 117.7, 122.9, 123.0, 124.4, 134.7, 135.6, 147.5, 149.6, 151.5, 164.5, 195.0

MS: 569 (2, M$^+$), 539 (13), 538 (39), 288 (38), 249 (40), 248 (100), 218 (18)

Exact Mass: Calculated for C$_{30}$H$_{39}$N$_3$O$_8$ 569.2737
Found 569.2738
Compound 124 continued:
N-Boc-lactam benzaldehyde (141)

To a solution of 220.1 mg (0.299 mmol) of lactam 110 in 5 ml of acetonitrile was added 285 mg (3 eq.) of di-tert-butyl dicarbonate and 53 mg (1 eq.) of 4-dimethylaminopyridine. After heating for 30 minutes at 65 °C, the reaction was complete as shown by tlc. The reaction mixture was partitioned between ether and a solution of 1N hydrochloric acid. The organic layer was washed by saturated sodium bicarbonate and brine (2X). The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, evaporated under reduced pressure, and purified on preparative tlc to afford 158.4 mg (63.4 %) of 141 as pale yellow oil.
Characterization of 141:

Note: This material was obtained as an approximately 2 : 1 mixture of two rotamers about the TROC.

IR (film): 3440, 2940, 2870, 1720, 1680, 1590, 1450, 1300, 1240, 1120

$^1$H NMR (CDCl$_3$): 1.25&1.31 (9H, s), 2.20 (3H, s), 2.28 (3H, s), 2.26-2.43 (1H, m), 3.13-3.33 (3H, m), 3.58-3.73 (9H, m), 3.75&3.76 (3H, s), 4.72-4.86 (2H, m), 4.93-4.96 (2H, m), 5.12-5.21, (2H, m), 5.87-5.94 (1H, m), 7.41 (5H, bs), 7.55&7.62 (1H, s), 10.18 (1H, s)

$^{13}$C NMR (CDCl$_3$): 9.5, 9.8, 9.9, 26.5, 26.8, 27.5, 27.6, 31.7, 32.2, 47.5, 47.8, 53.4, 54.1, 58.8, 59.7, 59.8, 60.0, 60.1, 60.3, 75.2, 75.3, 77.9, 78.0, 84.1, 84.2, 95.1, 95.2, 121.7, 122.1, 122.5, 123.0, 125.4, 125.5, 125.7, 126.0, 126.1, 127.8, 128.3, 128.6, 128.7, 128.8, 129.1, 136.0, 136.1, 146.5, 146.6, 150.2, 151.3, 151.4, 151.7, 152.3, 152.9, 160.4, 160.5, 163.6, 163.7, 170.4, 170.5, 189.1, 189.2

MS: 838 (5, M+4), 837 (5, M+3), 836 (12, M+2), 835 (6, M+1), 834 (14, M$^+$), 735 (19), 733 (19), 668 (12), 647 (18), 646 (19), 645 (46), 644 (26), 643 (45), 577 (34), 565 (12), 467 (32), 465 (35), 439 (33), 437 (31), 414 (7), 413 (19), 412 (34), 411 (54), 410 (15), 409 (48), 408 (51), 396 (16), 394 (15), 330 (19), 234 (100), 204 (36), 179 (19), 91 (78)

Exact Mass: Calculated for C$_{40}$H$_{45}$Cl$_3$N$_2$O$_{11}$ 834.2089
Found 834.2089
Compound 141 continued:
N-Boc-lactam phenol (142)

To a solution of 120.1 mg (0.144 mmol) of aldehyde 141 in 5 ml of chloroform was added 46.6 mg (1.5 eq.) of 80% m-chloroperoxybenzoic acid at room temperature. After stirring for 2 hours at 80 °C, the reaction was complete as shown by tlc. After cooling, the reaction mixture was partitioned between ether and a solution of saturated sodium sulfite. The organic layer was washed with sodium bicarbonate (2X) and brine. The aqueous layers were thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness. The crude products were dissolved in 3 ml of methanol and 0.02 ml (1.0 eq.) of triethylamine was added at room temperature. After stirring for 2 hours, the reaction mixture was concentrated to dryness under reduced pressure, then partitioned between ether and a solution of 3N hydrochloric acid. The organic layer was washed by saturated sodium bicarbonate and brine (2X). The aqueous layers were extracted thoroughly with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, evaporated, and purified on
preparative tlc to afford 98.1 mg (81.5 %) of phenol 142 as pale yellow oil.

Characterization of 142:

Note: This material was obtained as an approximately 2 : 1 mixture of two rotamers about the TROC.

IR (film): 3530, 3410, 2940, 1770, 1710, 1590, 1460, 1240, 1150, 1120, 1080

$^{1}$H NMR (CDCl$_3$): 1.26&1.35 (9H, s), 2.19 (3H, s), 2.25&2.26 (3H, s), 2.23-2.31 (1H, m), 3.09-3.37 (3H, m), 3.61&3.64 (6H, s), 3.71&3.74 (3H, s), 3.75&3.76 (3H, s), 4.71-4.85 (2H, m), 4.88 (2H, s), 5.01-5.10, (1H, m), 5.17-5.21 (1H, m), 5.88-5.96 (1H, m), 6.61&6.69 (1H, s), 7.39-7.44 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.4, 10.1, 26.5, 26.7, 27.5, 27.6, 31.6, 32.2, 47.6, 47.9, 53.3, 54.1, 59.0, 59.8, 60.0, 60.1, 60.3, 75.3, 75.5, 84.0, 84.2, 95.0, 95.1, 112.1, 113.0, 121.6, 122.1, 122.7, 123.3, 124.1, 124.2, 126.0, 127.8, 128.1, 128.2, 128.6, 128.7, 128.9, 136.8, 136.9, 143.0, 143.3, 145.1, 146.6, 146.7, 150.2, 150.3, 150.4, 151.0, 151.2, 151.6, 152.3, 152.8, 170.5, 170.8

MS: 726 (4, (M+5) - Boc), 725 (4, M+4) - Boc), 724 (15, (M+3) - Boc), 723 (5, (M+2) - Boc), 722 (16, (M+1) - Boc), 465 (8), 439 (29), 437 (23), 410 (17), 408 (15), 256 (12), 234 (22), 204 (15), 91 (100)

Exact Mass: Calculated for (M+ - CO$_2$, - C$_4$H$_8$) C$_{34}$H$_{37}$Cl$_3$N$_2$O$_9$ 722.1564
Found 722.1557
Compound 142 continued:
Tricyclic alcohol (143)

To a stirred solution of 85.3 mg (0.104 mmol) of lactam 142 in 2 ml of methanol was added 11.8 mg (3 eq.) of sodium borohydride at room temperature. After 3 hours, the reaction was complete as evidenced by tlc. The reaction mixture was quenched with dilute hydrochloric acid. After 5 minutes, the reaction mixture was neutralized with saturated sodium bicarbonate and partitioned between dichloromethane and a solution of saturated sodium bicarbonate. The organic layer was washed with dilute sodium bicarbonate and brine (2X). The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to give 71.4 mg (83.3 %) of alcohol 143 as light yellow oil.
Characterization of 143:

Note:
This material was obtained as an approximately 2:1 mixture of two rotamers about the TROC.

IR (film):
3430, 2940, 2830, 1700, 1590, 1470, 1460, 1410, 1300, 1240, 1170, 1120, 1060, 1000

$^1$H NMR (CDCl$_3$):
1.00&1.05 (9H, s), 2.18 (3H, s), 2.20 (3H, s), 2.42-2.60 (1H, m), 3.11-3.38 (3H, m), 3.62&3.69 (6H, s), 3.77-3.91 (8H, m), 3.99-4.08 (1H, m), 4.18-4.26 (1H, m), 4.51-4.72 (2H, m), 4.83 (1H, s), 4.83-5.02 (1H, m), 5.54&5.58 (1H, s), 6.72 (1H, s), 7.33-7.40 (5H, m)

$^{13}$C NMR (CDCl$_3$):
9.2, 9.3, 10.2, 22.2, 27.7, 27.9, 28.0, 33.1, 33.3, 53.6, 53.8, 54.9, 55.1, 55.7, 56.6, 60.1, 60.4, 60.6, 60.7, 60.8, 60.9, 61.0, 61.2, 61.8, 64.5, 65.1, 75.3, 75.7, 78.5, 79.1, 95.3, 114.4, 123.5, 124.3, 124.4, 124.6, 126.9, 127.6, 128.2, 128.4, 128.7, 137.1, 143.5, 143.6, 145.4, 145.6, 145.7, 149.3, 149.6, 149.9, 151.4, 151.5, 155.0, 155.2

MS:
826 (<1, M$^+$), 677 (2), 578 (7), 444 (11), 442 (37), 440 (37), 406 (12), 386 (32), 321 (34), 286 (100), 234 (16), 91 (49)

Exact Mass:
Calculated for $\text{C}_{39}\text{H}_{49}\text{Cl}_3\text{N}_2\text{O}_{11}$
826.2401
Found
826.2330
Compound 143 continued:
Amino alcohol (144)

A solution of 41.3 mg (0.050 mmol) of 143 in 1 ml of trifluoroacetic acid was stirred at room temperature for 20 minutes. The reaction mixture was evaporated to dryness then partitioned between dichloromethane and a solution of saturated sodium bicarbonate. The organic layer was washed by dilute sodium bicarbonate and brine. The aqueous layers were thoroughly extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, evaporated, and purified on preparative tlc to give 24.4 mg (67.6 %) of amine 144 as light yellow oil.
Characterization of 144:

Note: This material was obtained as an approximately 2 : 1 mixture of two rotamers about the TROC.

IR (film): 3350, 3290, 3010, 2940, 1710, 1580, 1460, 1420, 1310, 1110, 1070

$^1$H NMR (CDCl$_3$): 2.11&2.16 (3H, s), 2.20 (3H, s), 2.42-2.51 (1H, m), 2.88-3.40 (3H, m), 3.45-3.59 (3H, m), 3.65 (3H, s), 3.69-3.80 (2H, m), 3.82 (3H, s), 3.88 (3H, s), 3.92-4.09 (1H, m), 4.30-4.58 (1H, m), 4.60-5.05 (4H, m), 5.62-5.67 (1H, m), 6.49&6.62 (1H, s), 7.35 (5H, bs)

$^{13}$C NMR (CDCl$_3$): 9.4, 10.2, 22.5, 22.7, 22.8, 35.0, 35.6, 55.3, 55.4, 55.5, 56.0, 56.2, 60.1, 60.8, 60.9, 64.3, 74.8, 75.0, 95.4, 114.7, 122.9, 123.1, 125.0, 125.2, 126.5, 127.9, 128.1, 128.3, 128.6, 128.7, 137.2, 137.3, 143.8, 145.8, 146.2, 149.6, 149.7, 149.9, 150.0, 151.7, 154.9, 156.1

MS: 578 (15), 547 (6), 488 (6), 457 (7), 321 (100), 289 (13), 234 (6), 167 (7), 91 (29)

Exact Mass: Calculated for (M+ - OH, - CH$_2$CCl$_3$)

C$_{32}$H$_{38}$N$_2$O$_8$ 578.2628

Found 578.2623
Compound 144 continued:
References


