INFORMATION TO USERS

The most advanced technology has been used to photograph and reproduce this manuscript from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book. These are also available as one exposure on a standard 35mm slide or as a 17" x 23" black and white photographic print for an additional charge.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.
Synthetic studies towards the total synthesis of renieramycin A

Tun, Min Min, M.A.
Rice University, 1988
RICE UNIVERSITY

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF RENIERAMYCIN A

by

MIN MIN TUN

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

MASTER OF ARTS

APPROVED, THESIS COMMITTEE:

T. Fukuyama, Associate Professor of Chemistry, Chairman

M. A. Ciufolini, Assistant Professor of Chemistry

R. Parry, Professor of Chemistry

Houston, Texas
March, 1988
Abstract
SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF RENIERAMYCIN A

by
Min Min Tun

Formation of intermediate 50, was achieved through sequential condensations of piperazinedione and substituted benzaldehydes. One of the key reactions of this synthesis, oxidation of benzylic position, produced hydroxylated compound 62. Further elaboration of 62 has resulted in N-methyl 65.

\[ \text{Diagram of chemical structures} \]

Renieramyic A
Acknowledgements

There are many whom I owe thanks. Not the least of whom is Dr. Tohru Fukuyama for his understanding and guidance. His patience even under stressful situations was greatly appreciated.

I would also like to express my gratitude to all of the graduate students in Dr. Fukuyama's group for sharing their ideas and providing support.

I am also grateful to Dr. Terry Marriott for providing all of the high resolution mass specs presented in this manuscript.

I am indebted to my family's unwavering support for me through the good and bad times during the school years. I would like to give special thanks to my friends, Marilyn Richnow, Mark Matney, and Sean O'Brien, for their friendship and to Larry Chang for his support and patience.

Lastly, I would like to thank the Department of Chemistry, Rice University, and the National Institutes of Health for their generous financial support.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>Synthetic Studies Towards the Total Synthesis of Renieramycin A</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>Experimental</td>
<td>24</td>
</tr>
</tbody>
</table>

References: 131
Chapter I

INTRODUCTION
In recent years there has been a lot of interest generated by the isolation and formation of a new family of isoquinolinequinone antibiotics. The most famous member of this family may be saframycin A, the most biologically active member of its series. Saframycin A is active against a number of gram-positive and a few gram-negative bacteria. It is also known to show potent antitumor activity.\(^1\) The saframycins are structurally interesting due to the presence of the functionally labile bisquinone moiety.

Attempts to synthesize the saframycins have been made by several groups. However, only two groups have reported the total synthesis of saframycin B. Recently, Kubo and his co-workers completed the total synthesis of saframycin B and its congeners.\(^2\) The earliest successful total synthesis of saframycin B was reported in 1982 by this group.\(^3\) Since then, much time and effort have been expended to improve the synthesis of saframycin B and also to synthesize saframycin A.

First isolated by Frincke and Faulkner in 1979 from a bright, blue marine sponge *Reniera* sp., the renieramycins are similar in structure to the saframycins. The structures of these antimicrobial metabolites, renieramycins (A, B, C, and D), were principally determined by analyzing the \(^1\)H NMR data.\(^4\)

![Figure 1A](image-url)
The renieramycins also contain a unique dimeric quinone structure. Although the structures of the renieramycins and the saframycins are very similar, one can see two major differences. Whereas the saframycins contain a pyruvamide side chain, the renieramycins have an angelate ester side chain. In addition the side chains of the two series are thought to possess different stereochemistry. The side chains of the saframycins are in the β-position unlike the side chains of the renieramycins which are thought to be in the α position. Another interesting feature of the renieramycins, which can also be found in saframycin C, is the presence of substitution by either a hydroxyl or an ethoxy group at the benzylic carbon-14.

Another motivating factor to synthesize renieramycins is their potential antitumor activity. Since the saframycins exhibited antitumor properties, it was highly reasonable to speculate that the renieramycins could do the same. All of the metabolites found in the sponge *Reniera* sp. have been found to be antimicrobially active against a number of microorganisms. However, since the renieramycins are only minor metabolites of the the sponge, not enough could be obtained to determine the antitumor properties of the renieramycins.

Among the renieramycins isolated from the sponge, the major dimer was found to be renieramycin A. This, in fact, was chosen to be our target molecule. Synthetic efforts towards the total synthesis of renieramycin A is described in detail in this dissertation.
Chapter II

SYNTHETIC STUDIES TOWARDS
THE TOTAL SYNTHESIS OF
RENIERAMYCIN A
Upon examining the carbon skeleton of renieramycin A, one can see that if two cleavages are made, both at the benzylic positions, the 'dimeric' nature of the molecule becomes obvious. This suggests sequential condensations of two differently substituted benzaldehydes to piperazinedione. This synthetic sequence of making the backbone of this type of molecule is described more fully in another manuscript. Following the condensations of the aldehydes with the piperazinedione, treatment with formic acid brings about the cyclization to form the fourth ring of the molecule. In order to form the B ring, a Pictet-Spengler type cyclization could be envisioned.

Scheme 1
Scheme 2

This strategy was employed for the synthesis of the model compound. Similar to saframycin A, the key intermediate in the renieramycin A synthesis was determined to be the cyclized compound 14. Scheme (2) shows the steps leading to this intermediate. Aldehyde 10 first underwent condensation with the piperazinedione using t-butoxide. In the process one of the
acetates from the nitrogens is lost. This was followed by catalytic hydrogenation of the olefin over palladium on carbon and reformation of the nitrogen as carbobenzyloxy urethane. The resulting compound 11 underwent the second condensation with another substituted benzaldehyde to afford compound 12. Following sodium borohydride reduction and formic acid cyclization, product 13 was obtained. Before the cyclized compound 13 was hydrogenated, the phenol was protected as an acetate. This allowed differentiation of the two phenols which would be present after hydrogenolysis of the benzyl ether. Upon protection, compound 13 was subjected to catalytic hydrogenation over Raney-Ni (W-2). The amine produced was once again protected as a carbobenzyloxy urethane.

This key intermediate 14 has four of the five needed rings intact. In addition all but one of the stereocenters have been established. After cyclization, the [3.3.1] bicyclic system is formed. This dictates that the geometry of the bridgehead protons be cis. In the following catalytic hydrogenation reaction over Raney-Ni (W-2) the double bond is hydrogenated from the less hindered α-side of the bicyclic system.

At this point, there were two major problems to overcome. One of the problems which needed to be addressed was how and when to effect the benzylic oxidation to introduce the hydroxyl group at C - 14. In addition, if in fact a Pictet-Spengler type cyclization was to be utilized to form the B ring, it was necessary to reduce the lactam to an amine.

In order to address the first problem oxidation was attempted on compound 15, a slightly modified version of the key intermediate. Compound 15 has its nitrogen protected as a carbomethoxy urethane and the phenol masked as a benzyl ether. Treating it with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in methanol, the methoxy group was successfully introduced at the correct position, carbon 14. However, after further reacting the product with ethanethiol and boron trifluoride ethereate, and analyzing the 1H NMR data, the conclusion was reached that a mixture of products had been obtained. Nevertheless, efforts to introduce the
hydroxyl group under similar conditions continued. Substituting acetonitrile-water for methanol, the desired product was obtained in a satisfactory manner.

Scheme 3

Having successfully effected the benzylic oxidation, attention was focused on finding an acceptable reagent to reduce the lactam. Aluminum hydride was chosen. Although this procedure did afford the desired amine, the yield for the reaction was low. Not only that, there was a concomitant reduction of the carbomethoxy urethane to methyl. Although this was not necessarily considered to be a problem, there was still a need to find a more effective method of reducing the lactam.

Concurrent with the reduction of the lactam, the N-methyl compound had been obtained. An attempt was made to perform the benzylic oxidation on the resulting compound 18. However, the desired oxidation did not occur as before. Although the oxidation was attempted on several other modified N-methyl compounds, the results were all quite disappointing. Despite this
setback, successful oxidation of the benzylic position still looked promising. The decision was made to oxidize at a later stage of the synthesis.

Therefore, efforts to reduce the lactam before attempting the oxidation were initiated. The intermediate compound 13 was used as a starting point, as shown in Scheme 5. The phenol on compound 13 was protected using ethyl bromoacetate. This time olefin 13 was subjected to hydrogenation over palladium on charcoal. The resulting amine was directly methylated with formaldehyde and sodium cyanoborohydride in methanol, yielding 22. The lactam 22 was once again subjected to aluminum hydride reduction conditions. Since the amine was present as N-methyl, not as N-urethane, it was hoped that the reaction would be cleaner than in the earlier ones. Despite the concurrent reduction of the ethyl acetate to ethyl alcohol, the reduction turned out to be fairly clean. At this point, an amine and a free phenol, requirements necessary for the Pictet-Spengler cyclization, were present. Treating the phenol-amine 23 with glycolaldehyde
benzyl ether afforded the cyclized compound 24. The formation of isomers from this reaction was not detected.

![Chemical structures and reaction mechanisms]

**Scheme 5**

The main objective was to see whether the DDQ oxidation could be performed on this molecule. Before the oxidation attempt could be made, the phenol had to be unmasked. A three step sequence involving formation of the mesylated compound followed by formation of the alkyl iodide and deprotection using zinc with acid afforded the phenol 25. This compound 25 was then treated with DDQ in acetonitrile-water mixture. Unfortunately, the reaction did not proceed...
as expected. It may be speculated that the failure to oxidize may in part be due to the nature of the protecting group on the amino group. As mentioned earlier, the initial successful attempts to effect the benzylic oxidation occurred on compounds which had the amine protected as a urethane. With this in mind, another model compound had to be synthesized.

Once again, the intermediate compound 13 was the starting point. The remaining phenol was protected as an acetate. Catalytic hydrogenation of the compound afforded the phenol-amine compound which was protected in the form of benzyl urethane. The phenol which was unmasked following hydrogenolysis of the benzyl ether was reprotected using tosyl chloride in triethylamine. Use of other reagents such as lithium aluminum hydride for the reduction of the lactam was explored. Again the results proved to be disappointing.

![Scheme 6]

Since the direct methods of reducing the lactam seemed to prove fruitless, indirect methods of reduction were explored. The new strategy involved the conversion of the lactam to a thiolactam by the Lawesson's reagent.\textsuperscript{10} Reduction of the thiolactam 28 should allow more possibilities than the direct reduction of the lactam.

Our initial attempt involved the reduction by Raney-Ni in ethanol followed by sodium borohydride. When this method failed to produce the amine, the thiolactam was converted to a thioiminoester by treating it with Meerwein's reagent.\textsuperscript{11} Despite a barrage of several different
reducing agents, the thioiminoester could not be reduced. The reagents used in these unsuccessful attempts are shown in Figure 2.

Scheme 7

REAGENTS USED FOR REDUCTION OF THIOIMINOESTER:

1) Sodium cyanoborohydride in methanol with catalytic amount of trifluoroacetic acid
2) Sodium borohydride in methanol
3) Sodium borohydride in ethanol
4) Raney-Ni in ethanol
5) Aluminum hydride in dry tetrahydrofuran
6) Super hydride
7) Palladium on charcoal with triethylsilane

Figure 2
Since the repeated efforts to reduce the thioliminoester proved unsuccessful, the thiolactam 28 was converted to an imine instead as described in Scheme 8. Upon treatment of the thiolactam with Raney-Ni in acetone, one can observe the formation of imine, the major product, and amine, the minor one. In order to obtain the desired amine, the products, without separation, were next treated with sodium cyanoborohydride in methanol at room temperature. The amine 31 obtained was then protected as a trichloroethyl urethane.

![Chemical structures](image)

**Scheme 8**

The phenol which had been earlier protected as an acetate was next removed using hydrazine. The mild condition needed for acetate removal left the tosyl group untouched on the other phenol. With the phenol now unmasked in 33, the stage was set for the benzylic oxidation. To our immense relief, treating compound 33 with DDQ in acetonitrile-water mixture provided the desired product.
Following the oxidation, compound 34 was ready for the phenolic cyclization which would form the B ring. As described in Scheme 10, the free phenol had to be methylated, the amine deprotected, and the tosyl group hydrolyzed, yielding the amine-phenol compound 36. Following experimentation with a number of different aldehydes, glycolaldehyde benzyl ether in acetonitrile was used for the cyclization. On this model compound 37, formation of the other isomer again was not detected. Upon completion of the cyclization all the necessary rings had been formed. The hydroxyl group had been introduced and a handle for the side chain attached.
The N-methyl compound 38 could be obtained, following deprotection of the nitrogen, by treating the deprotected amine with formaldehyde and sodium cyanoborohydride in methanol. Theoretically, the final product was only two steps away from this point.

![Scheme 11](image)

Despite the ease with which the monoquinone could be formed, the difficulty of forming the bisquinone 39 had been anticipated. Repeated efforts to oxidize, as shown in Scheme 12, using DDQ in various solvents and ceric ammonium nitrate (CAN) proved unsuccessful. The obstacle to the formation of quinone of the upper aromatic ring, must in part be due to the absence of a free phenol. Therefore, there was no alternative but to search once again for the 'right' aldehyde.

![Scheme 12](image)
The search for the new aldehyde involved making slight modifications on the type of protecting groups to be used. Unlike the original aldehyde, there was a need to have a protecting group that would allow the phenol to be unmasked easily. In addition, a different protecting group for the other phenol was needed. The aldehydes with which we experimented and the difficulties associated with each one are shown in Figure 3.

The original aldehyde used in earlier model studies.

The results of the second condensation with piperazinedione is unsatisfactory. Formation of major polar spot seen.

During the first hydrogenation of the olefin, the benzyl ether is lost and phenol reprotected as silyl ether. Again results from second condensation with piperazinedione are unsatisfactory.

Again, results from the second condensation with piperazinedione is messy. Very poor yield.

The aldehyde chosen for the synthesis.

Figure 3
The aldehyde 46 which was finally chosen has a methoxymethyl (MOM) protecting group and a silyl alcohol. The choice of the bulky dimethylethyl silyl group as part of the protecting group stemmed from the hope that it would survive the harsh conditions of acid-catalyzed cyclization and the catalytic hydrogenation to which it would be subjected later in the synthesis. The twelve-step synthesis of the aldehyde is outlined in Scheme 13.

As described in Scheme 15, aldehyde 46 undergoes the first condensation with the piperazinedione, followed by hydrogenation of the olefin. Protection of the amine with benzyl urethane providing 47 helps to differentiate the two nitrogens. The second condensation follows with a previously synthesized substituted benzaldehyde 6.
The two-step sequence resulting in the cyclized product 49 consists of first, a sodium borohydride reduction and second, a formic acid cyclization on compound 48. On the earlier model studies, this acid cyclization had always been a source of trouble. Frequently, the results were messy and the yield as low as 30%. During the last run careful analysis of the two major products obtained from the reaction mixture revealed that they were geometrical isomers of the olefin. The formation of isomers was not anticipated since it was thought that the steric compression present between the two aromatic rings would preclude it from forming the E isomer. Since the next reaction called for the hydrogenation of the olefin, it did not matter that the isomers had formed.

Scheme 16
Concurrent with the cyclization, the MOM protecting group and the silyl group were lost from 49 A,B. It was hoped that the silyl group would have survived both the cyclization and the hydrogenation which was to follow. Nevertheless, it was not a major disappointment. It was still possible to differentiate between the phenols and the alcohol. Another factor which needed to be considered was the polarity of the resulting compound 56. In the meantime efforts continued to obtain the key intermediate 53 as seen in Scheme 16.

Cyclized compounds 49 A,B had to be subjected to hydrogenation over Raney-Ni (W-2) in ethanol under 1100 psi for 1.5 days. In the process of the hydrogenation of the olefin from the less hindered α-face, there was a concomitant loss of benzyl ether and carbobenzoxy urethane. Although the resulting diphenol-amine-alcohol compound is highly polar, it was not too difficult to handle. Following the hydrogenation, the nitrogen was once again protected as benzyl urethane.

To effectively convert the lactam to a thiolactam using the Lawesson's reagent, the phenols and the alcohol were acetylated providing compound 53. The lactam was converted to thiolactam 54. The two-step reduction sequence of Raney-Ni and sodium cyanoborohydride provided the desired amine. Hydrolysis of the acetates yielded 56 with the phenol and the amine required for the phenolic cyclization.

Again the aldehyde used for this final cyclization was glycolaldehyde benzyl ether. The reaction resulted in formation of the isomers 57 A,B, one with the α-side chain and the other
with the \( \beta \)-side chain. Earlier reported analysis of the \( ^1 \text{H} \) NMR data indicated that the naturally occurring renieramycins had the \( \alpha \)-side chain.\(^3\) Despite this, there was reason to doubt the veracity of this conclusion. If the renieramycins were so similar in structure to the saframycins, would it not be reasonable to speculate that the two side chains were of the same conformation? In addition the \( ^1 \text{H} \) NMR spectra of the two compounds are remarkably similar. Since the data collected seemed inconclusive, it was fortunate that both isomers had been obtained. The two isomers were easily separated. Synthetic efforts continued with the less polar isomer 57 A which was thought to be the \( \beta \) isomer.

\[
\text{Scheme 18}
\]

Compound 57 A now contained all of the necessary rings. The next key reaction was the benzylic oxidation. Before proceeding with the oxidation, the free phenols had to be masked as benzyl ethers, as shown in Scheme 18. The alcohol chain had to be taken off using a three-step
deprotection sequence. First the alcohol was treated with mesyl chloride in triethylamine producing 59. Alkyl iodide was formed by treating the resulting product with sodium iodide in dimethyl formamide. The phenol 61 was then obtained when the alkyl iodide was removed using zinc in methanol with a catalytic amount of trifluoroacetic acid. Unlike earlier model compounds, this last reaction did not go to completion when a weaker acid such as acetic acid was used.

\[ \text{Scheme 19} \]

With the phenol unmasked, compound 61 was treated with DDQ in acetonitrile-water mixture to yield the desired product. The previously unmasked phenol was methylated with iodomethane and potassium carbonate in dimethyl formamide. To obtain the N-methyl compound, it was necessary to carry out hydrogenolysis of the carbobenzoxy and the benzyl ethers. This was accomplished utilizing palladium on carbon under pressure. Treatment of the diphenol amine with formaldehyde and sodium cyanoborohydride in methanol provided the desired N-methyl compound 65.

\[ \text{Scheme 20} \]
Oxidation of the N-methyl compound 65 was undertaken utilizing DDQ in acetone-water mixture. When this method proved unproductive, oxidation was attempted with ceric ammonium nitrate (CAN). The results from this reaction were inconclusive. Formation of the monoquinone was detected by analyzing $^1$H NMR spectrum. However, it was unclear whether the bisquinone was formed. It is believed that compound 65 will eventually lead to the final product. Further experimentation is necessary to search for the optimum condition to yield the desired bisquinone. When this is accomplished, then further studies must be made to establish the stereochemistry of the side chain. Successful synthesis of renieramycin will not only increase the knowledge of the formation of the elusive bisquinone system, but also provide material for testing its antitumor properties.

Through research described in this manuscript, the foundation towards the total synthesis of renieramycin A has been laid. The hydroxyl group at carbon-14 was successfully introduced and the optimum conditions for the formation of the carbon skeleton of the molecule established. Efforts continue at Rice University under the guidance of Dr. Tohru Fukuyama towards the total synthesis of renieramycin A.
Chapter III

EXPERIMENTAL
TECHNICAL NOTES

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

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1320 Infrared Spectrophotometer and are reported in wavenumbers (cm⁻¹).

Nuclear magnetic resonance (NMR) spectra were determined on an IBM AF300 instrument. Chemical shifts are reported in parts per million downfield from tetramethylsilane (δ) as the internal standard. The following abbreviations are used for spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

Mass spectra (MS) were obtained on a Finnigan 3300 quadrupole at 70 eV and 30 eV using direct probe insertion at temperatures of 25 to 300°C. High resolution mass spectra were obtained under similar conditions using a CEC 21-110B instrument.

Analytical thin layer chromatography (tlc) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. 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 PF254. Compounds were eluted from the adsorbent with 10% methanol in methylene chloride.

Column chromatography was performed on Woelm silica gel, 32 - 63 mesh, packed in Altex columns on an mpic system.

Circular chromatography was performed on a Model 7924T Chromatotron using 1 mm, 2mm, or 4mm plates prepared with Merck silica gel 60 PF254 containing gypsum.

Hydrogenations were carried out in a stainless steel Parr general purpose bomb.

Reagents and solvents were commercial grades and were used as supplied with the following exceptions:

Methylene chloride: distilled through a 24 inch Snyder column.

Tetrahydrofuran (dry): distilled from a sodium benzophenone ketyl.

Pyridine: dried over potassium hydroxide pellets.
t-Butanol: distilled from calcium hydride.

Dimethylformamide, Benzene, Acetonitrile, and Methanol (dry):

dried over 4Å molecular sieves.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
2,4-dimethoxy-3-methyl benzaldehyde (36)

A solution of 30 g (197.4 mmol) of 2,6-dimethoxytoluene in 60 ml of methylene chloride was cooled to 0°C. To this stirred solution was slowly added 43.4 ml (2 eq) of titanium tetrachloride. Following the addition of titanium tetrachloride, 21.4 ml (1.2 eq) of α, α'-dichloro methyl methyl ether was added dropwise to the reaction mixture. After 6 minutes, the reaction was complete as shown by tlc. The reaction mixture was then poured into ice water and thoroughly extracted with methylene chloride. The combined organic layer was washed with dilute sodium chloride solution. The extracts were dried over sodium sulfate and evaporated under reduced pressure to obtain crude dark purple crystals of 36. The crude crystals were pumped under reduced pressure to give 33.4 g of 36 to be used for the next reaction without purification. mp. 43-45°C (ether).

IR (CH₂Cl₂): 2940, 2845, 1680, 1590, 1460, 1150

NMR (CDCl₃): 2.16 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 6.76 (1H, dd, J = 8.5 Hz), 7.73 (1H, dd, J=8.6 Hz), 9.75 (1H, s)

MS: 180 (97, M⁺), 179 (66), 163 (100), 135 (84), 134 (75)

Exact Mass: Calculated for C₁₀H₁₂O₃ 180.0786
Found 180.0785
Compound 36 continued:
4-methoxy-3-methyl-3-phenol benzaldehyde (37)

A solution of 33.3 g (185 mmol) of 36 in 150 ml of methylene chloride was cooled to 0°C. Boron trichloride was then bubbled through the solution until the reaction was complete as shown by tlc. The product crystallizes out of the solution. It was then poured into ice water and the aqueous layer thoroughly extracted with ether. The combined organic layer was washed with saturated solution of sodium bicarbonate and sodium chloride, followed by final wash with saturated solution of sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 30.7 g of dark, brownish crystals of 37 which was used without purification. mp. 51-53°C (ether).

IR (CH₂Cl₂): 3100, 2845, 1620, 1105

NMR (CDCl₃): 2.09 (3H, s), 3.91 (3H, s), 6.56 (1H, dd, J=8.5 Hz), 7.37 (1H, dd, J = 8.6 Hz), 9.71 (1H, s), 11.45 (1H, s)

MS: 166 (100, M⁺), 148 (52), 136 (30), 109 (31)

Exact Mass: Calculated for C₉H₁₀O₃ 166.0630
            Found 166.0628
Compound 37 continued:
2-allyloxy-4-methoxy-3-methyl benzaldehyde (38)

To a stirred solution 30.6 g (184 mmol) of 37 in 150 ml of dimethyl formamide, 76 g (3eq) of potassium carbonate and 32 ml (2eq) of allyl bromide were added. The mixture was then warmed to 80°C. After 35 minutes, the reaction was complete as shown by tlc. After the reaction mixture was cooled, it was partitioned between ether, hexane and dilute solution of sodium chloride. The aqueous layer was extracted several times with ether-hexane. The combined organic layer was washed with dilute solution of sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 37.6 g of 38 as dark liquid. It was carried through without purification.

IR (CH₂Cl₂): 2860, 1675, 1580, 1100

NMR (CDCl₃): 2.16 (3H, s), 3.91 (3H, s), 4.44 (2H, d, J=5.6 Hz), 5.30 (1H, dd, J=9.9 Hz), 5.42 (1H, dd, J=17.8 Hz), 6.08 (2H, m), 6.75 (1H, dd, J=8.7 Hz), 7.75 (1H, dd, J=8.7 Hz), 10.22 (1H,s)

MS: 205 (11), 191 (14), 189 (26), 177 (77), 165 (100), 149 (52), 136 (67), 41 (44)

Exact Mass: Calculated for C₁₂H₁₄O₃ 206.0943
Found 206.0937
Compound 38 continued:
2-allyloxy-4-methoxy-3-methyl phenyl formate (39)

To a stirred solution of 37.4 g (181 mmol) of 38 in 100 ml of t-butanol, 20.1 g (1 eq) of selenium dioxide was added. The mixture was cooled occasionally with an ice bath as 17 ml (3 eq) of 30% hydrogen peroxide was added dropwise. The reaction was complete as shown by tlc. It was then poured into ice water and the aqueous layer thoroughly extracted with ether. The combined organic layer was washed three times with combined solution of saturated sodium bicarbonate and sodium sulfite. The extracts were evaporated under reduced pressure and carried through to the next reaction.

IR (CH₂Cl₂): 2920, 1760, 1740, 1590, 1105

NMR (CDCl₃): 2.17 (3H, s), 3.83 (3H, s) 4.37 (2H, m), 5.31 (1H, m), 6.02 (2H, m) 6.61 (1H, dd, J=8.9 Hz), 6.93 (1H, dd, J=8.9 Hz) 8.26 (1H, s)

MS: 222 (M⁺), 194 (86), 165 (23), 153 (100), 125 (99), 110 (41), 39 (69)

Exact Mass: Calculated for C₁₂H₁₄O₄ 222.0892
Found 222.0886
Compound 39 continued:
2-allyloxy-4-methoxy-3-methyl phenol (40)

To a solution of 39 in 35 ml of methanol, 7 ml of triethylamine was added at room temperature. After 12 minutes, the reaction was complete as shown by tlc. The reaction mixture was evaporated to dryness under reduced pressure to give 33.9 g of 40 as brown liquid.

IR (CH₂Cl₂): 3540, 3440, 1590, 1450 (br), 1140, 1100

NMR (CDCl₃): 2.17 (3H, s), 3.78 (3H, s), 4.38 (2H, d, J=6.4 Hz), 5.29 - 5.46 (1H, m) 6.10 (2H, m) 6.54 (1H, dd, J=8.8 Hz) 6.75 (1H, dd, J=8.8 Hz)

MS: 194 (13, M⁺), 167 (10) 154 (100), 139 (18), 125 (98), 110 (46), 82 (37)

Exact Mass: Calculated for C₁₁H₁₄O₃ 194.0943
Found 194.0946
Compound 40 continued:
2-allyloxy-4-methoxy-3-methyl methoxy methyl phenyl ether (41)

To a solution of 33.8 g (174 mmol) of phenol 40 in 50 ml of methylene chloride, 91 ml (3 eq) of diisopropylethylamine was added. After the solution had warmed a little, 30 ml (2.2 eq) of chloromethyl methyl ether was added. The reaction mixture was then heated at 80°C for 45 minutes. The reaction was complete as shown by tlc. It was then partitioned between ether and combined solution of 3N HCl and saturated solution of sodium chloride. The organic layer was washed several times with combined solution of 3N HCl and saturated solution of sodium chloride. The organic layer was then washed with combined solution of saturated sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 38.8 g of 41 as dark liquid.

IR (CH₂Cl₂): 2885, 1196, 1030

NMR (CDCl₃): 2.15 (3H, s), 3.52 (3H, s), 3.79 (3H, s), 4.47 (2H, d, J=2.5 Hz), 4.49 (2H, s), 5.27 (1H, m), 6.11 2H, m), 6.53 (1H, dd, J=8.9 Hz), 6.93 (1H, dd, J=8.9 Hz)

MS: 238 (100, M⁺), 197 (40), 193 (35), 167 (98), 165 (51), 153 (34), 139 (50), 123 (24), 45 (98)

Exact Mass: Calculated for C₁₃H₁₈O₄ 238.1205
Found 238.1206
Compound 41 continued:
4-allyl 3-methoxy-2-methyl-6-methoxymethoxy phenol (42)

38.6 g (162 mmol) of 41 was dissolved in 20 ml of N, N-diethylaniline and heated to 210°C under argon. After 30 minutes, the reaction was complete as shown by tlc. After cooling, the mixture was poured into ice water and partitioned between ether and combined solution of 3N HCl and saturated solution of sodium chloride. The organic layer was washed with 3N HCl and saturated solution of sodium chloride until DEA was removed. The combined extracts were then washed with saturated solution of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 10% ether in hexanes yielded 24.1 g of 42 as clear yellow oil, a (52.9%) yield over seven steps.

**IR (CH₂Cl₂):**
3540, 2900, 1595, 1080, 1035

**NMR (CDCl₃):**
2.21 (3H, s), 3.34 (2H, dd, J=6.7 Hz), 3.52 (3H, s), 3.68 (3H, s), 5.06 (1H, m, J=16.2 Hz), 5.15 (2H, s), 5.98 (1H, s), 6.74 (1H, s)

**MS:**
238 (100, M⁺), 206 (62), 193 (77), 165 (28), 161 (45), 133 (27), 105 (31), 45 (98)

**Exact Mass:**
Calculated for C₁₃H₁₈O₄: 238.1205
Found: 238.1206
Compound 42 continued:
3-methoxy-2-methyl-6-methoxymethoxy-4-propene phenol (43)

To a stirred solution of 24 g (101 mmol) of phenol 42 in 65 ml of dimethyl sulfoxide, was added excess (27.9 g) potassium hydroxide pellets. The reaction mixture was heated at 105°C overnight under argon. The reaction was complete as shown by $^1$H NMR. The reaction mixture was poured into ice water and partitioned between ether and combined solution of 3N HCl and saturated solution of sodium chloride. The pH of the aqueous layer was checked to make sure that it was acidic. The organic layer was washed with combined saturated solution of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to yield 24.3 g of 43.

IR (CH$_2$Cl$_2$): 3540, 2940, 1600, 1045

NMR (CDCl$_3$): 1.76 (1H, dd, J=1.6 Hz), 2.13 (3H, s), 3.45 (3H, s), 3.58 (3H, s), 5.08 (2H, s), 5.68 (1H, m), 5.99 (1H, s), 6.84 (1H, s)

MS: 238 (M$^+$), 206 (36), 193 (29), 165 (25), 161 (29), 45 (100)

Exact Mass: Calculated for C$_{13}$H$_{18}$O$_4$ 238.1205
Found 238.1206
Compound 43 continued:
**Ethyl Acetoxy (52)**

To a stirred solution of 24 g (101mmol) of 43 in 70 ml of dimethylformamide, was added 43 g (3eq) of pulverized potassium carbonate and 22 ml (2eq) of ethyl chloroacetate. The reaction mixture was heated at 80°C. The reaction was complete as shown by tlc. After cooling, it was partitioned between ether, hexane and dilute solution of sodium chloride. The aqueous layer was extracted several times with ether and hexane. The combined extracts were washed with saturated solution of sodium chloride. The extracts were then dried over anhydrous magnesium sulfate and evaporated under reduced pressure to yield 52 as dark yellow oil which was used without purification.

**IR (CH₂Cl₂):**

2910, 1760, 1045

**NMR (CDCl₃):**

1.32 (3H, t, J=6.6, 7.7 Hz), 1.89 (2H, D, J=6.5 Hz), 2.26 (3H, s), 3.50 (3H, s). 3.66 (3H, s), 4.27 (2H, dd, J=6.6 Hz), 4.61 (2H, s), 5.15 (2H, s), 6.15 (1H, m), 6.50 (1H, m), 7.05 (1H, s)

**MS:**

324 (100, M⁺), 279 (76), 235 (15), 207 (36), 205 (61), 193 (20), 179 (21)

**Exact Mass:**

Calculated for C₁₇H₂₄O₆ 324.1573

Found 324.1563
Compound 52 continued:
2-ethanolxy-6-methoxy-3-methoxy methylxy-5-propene toluene (44)

To 6.8 g (1.7 eq) of lithium aluminum hydride, enough anhydrous tetrahydrofuran was added to cover it. The solution of 32.8 g (101 mmol) of 52 in THF was added dropwise to the LAH solution. The reaction was complete as shown by tlc. 7 ml of water was added carefully to the reaction mixture, followed by 7 ml of 3N sodium hydroxide solution and 21 ml of water. Ether was added and the mixture then decanted. This procedure was repeated several times. To the mixture, Rochelle salt and saturated sodium chloride solution was added. The resulting mixture was filtered and the organic layer washed with saturated sodium chloride solution once again. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to yield 28.6 g of 44 as dark yellow oil.

IR (CH₂Cl₂): 3600, 3500, 2920, 1045

NMR (CDCl₃): 1.89 (3H, m), 2.22 (3H, s), 3.53 (3H, s), 3.67 (3H, s), 3.84 (2H, m), 4.07 (2H, m), 5.19 (2H, s), 6.17 (1H, m), 6.59 (1H, m), 7.07 (1H, s)

MS: 282 (80, M⁺), 250 (83), 220 (94), 205 (69), 193 (100), 165 (62), 45 (81)

Exact Mass: Calculated for C₁₅H₂₂O₅ 282.1467
          Found 282.1458
Compound 44 continued:
3-methoxy-6-methoxy methyloxy-2-methyl-4-propene dimethylthexyl silyloxy phenyl ether (45).

To a solution of 28.4 g (100 mmol) of alcohol 44 in 60 ml of dimethylformamide was added 53 ml (3 eq) of diisopropylethylamine and 29.7 ml (1.5 eq) of dimethylthexyl silylchloride. The reaction mixture was heated at 70°C under argon for 20 minutes. The reaction was complete as shown by tlc. It was then partitioned between ether, hexane and combined solution of 3N HCl and sodium chloride. The organic layer was washed with saturated solutions of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure.

IR (CH₂Cl₂): 2880, 1080, 1040

NMR (CDCl₃):
- 0.13 (6H, s), 0.88 (13H, m), 1.89 (3H, m), 2.22 (3H, s), 3.51 (3H, s), 3.66 (3H, s), 3.91 (2H, dd, J=5.2 Hz), 4.00 (2H, dd, J=5.2 Hz), 5.16 (2H, s), 6.14 (1H, m), 6.66 (1H, m), 7.04 (1H, s)

MS: 424 (24, M⁺) 267 (100), 235 (18), 223 (80), 73 (39)

Exact Mass:
- Calculated for C₂₃H₄₀O₅Si: 424.2645
- Found: 424.2649
Compound 45 continued:
2-methoxy-5-methoxy methyloxy-3-methyl-4-dimethylthexyl silyloxy benzaldehyde (46)

The solution of 42.7 g (100 mmol) of silyl ether 45 in a 2:1 mixture of methanol and methylene chloride was cooled to -78°C. After 2.5 hours of bubbling ozone through the solution, the reaction was complete as shown by tlc. The reaction was purged with argon after which 30 ml (4 eq) of dimethyl sulfide was added to the stirred reaction mixture at -78°C. It was then stirred for about 30 minutes and allowed to warm to room temperature. The mixture was then evaporated to a smaller volume under reduced pressure and partitioned between ether and saturated solution of sodium bicarbonate. The organic layer was washed once with saturated solution of sodium chloride. The ether layer was then dried over anhydrous magnesium sulfate and evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 40% ether in hexanes yielded 34.9 g of 46 as a very light yellow oil, a (75.3%) yield over five steps.

IR (CH₂Cl₂): 2920, 2860, 1680, 1590, 1110, 1050

NMR (CDCl₃):
0.12 (6H, s), 0.86 (13H, m), 2.25 (3H, s), 3.49 (3H, s), 3.83 (3H, s), 3.90 (2H, m, J=9.8 Hz), 4.17 (2H, m, J=9.8 Hz), 5.19 (2H, 3), 7.43 (1H, s), 10.26 (1H, s)

MS: 412 (1, M⁺), 337 (1), 327 (7), 281 (18), 267 (100), 223 (77), 45 (30)

Exact Mass:
Calculated for C₂₁H₃₆O₆Si: 412.2281
Found: 412.2280
Compound 46 continued:
1-acetyl-3-arylidene-piperazine-2,5-dione (71)

A solution of 16.7 g (84.3 mmol) of 1,4-diacetyl piperazine-2,5-dione 8 and 34.85 g (1 eq) of benzaldehyde 46 in 70 ml of dry tetrahydrofuran was cooled to 0°C under argon. To this stirred solution was slowly added 150 ml (1.4 eq) of 1 N potassium t-butoxide. After 55 minutes, the reaction was complete as shown by tlc. The reaction was quenched with 9.7 ml (2 eq) of acetic acid and warmed to room temperature. The mixture was poured into ice water and the aqueous layer thoroughly extracted with methylene chloride. The combined extracts were washed once with a saturated solution of sodium chloride. The extracts were dried over anhydrous sodium sulfate and then evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 80% ether in hexanes yielded 35 g (75.2%) of 71 as light yellow crystals.

IR (CH2Cl2): 2940, 2880, 1700, 1630, 1360, 1100

NMR (CDCl3): 0.14 (6H, s), 0.89 (13H, m), 2.28 (3H, s), 2.68 (3H, s), 3.52 (3H, s), 3.66 (3H, s), 3.93 (2H, m, J=5 Hz), 4.10 (2H, m, J=5 Hz), 4.49 (2H, s), 5.18 (2H, s), 6.95 (1H, s), 7.05 (1H, s)

MS: 550 (M+, 433 (25), 391 (55), 45 (100)

Exact Mass: Calculated for C27H42N2O8Si 550.2710
           Found                  550.2671
Compound 71 continued:
1-acetyl-3-aryl-piperazine-2,5-dione (72)

A solution of 34.9 g (63.5 mmol) of 71 in 80 ml of ethyl acetate was hydrogenated over 1.9 g of 10% palladium on charcoal at 1300 psi for 1.5 hours at room temperature. The solution was eluted with ethyl acetate, 10% and 20% methanol in methylene chloride through Celite and the column washed repeatedly until all of the product was eluted as evidenced by tlc. The solution was evaporated under reduced pressure to afford 38.1 g of crude 72 as light yellow oil which was used without purification.

IR (CH₂Cl₂): 3400, 2920, 2860, 1710, 1590, 1360

NMR (CDCl₃): 0.15 (6H, s), 0.89 (13H, m), 2.25 (3H, s), 2.61 (3H, s), 3.04 (2H, m), 3.30 (1H, m, J=4 Hz), 3.50 (3H, s), 3.72 (3H, s), 3.92 (2H, m, J=6.1 Hz), 4.04 (2H, m, J=6.1 Hz) 4.35 (2H, s), 5.15 (2H, s), 6.60 (1H, s), 6.83 (1H, s)

MS: 552 (S, M⁺), 467 (28), 435 (40), 393 (65), 308 (98), 223 (71), 193 (73), 45 (100)

Exact Mass: Calculated for C₂₇H₄₄N₂O₈Si 552.2867
Found 552.2848
Compound 72 continued:
Carbobenzoxyurethane (47)

A solution of 34.9 g (63.2 mmol) of 72 in 200 ml of methylene chloride was cooled to -30°C. To this stirred solution was added 28 ml (3 eq) of triethylamine and 7.7 g (1 eq) of 4-dimethylaminopyridine followed by slow addition of 24 ml (2.6 eq) of benzyl chloroformate. After 1 hour, the reaction was complete as shown by tlc and 3N HCl was added to the reaction mixture. It was poured into a solution of 3N HCl and partitioned. The aqueous layer was extracted once with methylene chloride and the combined organic layer washed with saturated solution of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 80% ether in hexanes yielded 39.6 g (91.2%) of 47 as light yellow oil.

IR (CH2Cl2): 2940, 1790, 1730, 1370

NMR (CDCl3):

0.15 (6H, s), 0.90 (13H, m), 2.17 (3H, s), 2.56 (3H, s), 2.79 (1H, d, J=19 Hz), 3.19 (2H, dd, J=4.1 Hz), 3.38 (1H, dd, J=7.6 Hz), 3.43 (3H, s), 3.49 (3H, s), 3.90 (2H, m, J=5.1 Hz), 4.00 (2H, m, J=5.1 Hz), 4.57 (1H, d, J=18.8 Hz), 5.00 (1H, d, J=6.5 Hz), 5.12 (1H, d, J=6.7 Hz), 5.35 (2H, s), 5.36 (2H, s), 6.66 (1H, s), 7.44 (5H, m)

MS: 686 (1, M+), 601 (3), 557 (3), 525 (4), 467 (14), 433 (100), 393 (41), 308 (45), 223 (85), 91 (93)

Exact Mass: Calculated for C35H50N2O10Si 686.3234
Found 686.3228
Compound 47 continued:
Diaryl piperazine dione (48)

A solution of 39.5 g (57.6 mmol) of urethane 47 and 16.5 g (1 eq) of benzaldehyde 6 in 110 ml of dry tetrahydrofuran was cooled to -78°C under argon. To this stirred solution was slowly added 57 ml (1eq) of 1N potassium t-butoxide. After 10 minutes, the starting material was shown by tlc to be gone. The reaction mixture was warmed to 0°C and 1.1 ml (0.1 eq) of 1,8-diazabicyclo [5.4.0] undec-7-ene(DBU), was added to the reaction mixture. The reaction was complete as shown by tlc. It was then quenched with 6.6 ml (2 eq) of acetic acid and warmed to room temperature. The mixture was partitioned between methylene chloride and a dilute solution of sodium chloride. After washing the organic layer, the extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 80% ether in hexanes afforded 42.5 g (85%) of 48 as light yellow foam.

IR (CH₂Cl₂):  2940, 1780, 1700, 1370

NMR (CDCl₃):  0.05 (6H, s), 8.44 (13H, m), 2.07 (3H, s), 2.22 (3H, s), 3.08 (2H, m, J=3.6 Hz), 3.36 (3H, s), 3.38 (1H, m, J=11.5 Hz), 3.45 (3H, 3H, s), 3.50 (3H, s), 3.78 (2H, m, J=5.5 Hz), 3.87 (3H, s), 3.96 (2H, m, J=5.1 Hz), 4.67 (1H, d, J=6.7 Hz), 4.79 (1H, d, J=6.5 Hz) 5.15 (2H, s), 5.33 (1H, d, J=4 Hz), 5.44 (1H, d, J=12.4 Hz), 6.47 (1H, s), 6.56 (1H, s), 6.59 (1H, s), 7.45 (10H, m), 8.98 (1H, s)

MS:  751 (5), 661 (10), 589 (9), 435 (52), 397 (36), 267 (22), 193 (43), 179 (26), 91 (100)

Exact Mass:  C₃₄H₃₇N₂O₁₀Si  661.2217
            Found  661.2330
Compound 48 continued:
Tetracyclic phenol alcohol (49 A,B)

To a solution of 42.2 g (48.3 mmol) of 48 in 270 ml of absolute ethanol at -30°C, 6.2 g (3.4 eq) of sodium borohydride was added slowly. To this stirred solution, 2.5 ml (.9 eq) of acetic acid was added very carefully. Upon completion of the reaction as evidenced by tlc, ether and 3N HCl were added to the mixture and allowed to warm to room temperature. The mixture was then partitioned with water and the aqueous layer extracted thoroughly with ether. The combined organic layer was washed with saturated solution of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure.

The residue was dissolved in formic acid and stirred at 55°C. When the ratio of the two major spots remained constant as evidence by tlc, the mixture was partitioned with saturated solution of sodium chloride and then evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 100% ether yielded 26.4 g (80%) of top and bottom isomers 49 A,B as off white foam.
Characterization for 49 A:

<table>
<thead>
<tr>
<th>IR (CH$_2$Cl$_2$):</th>
<th>1730, 1690</th>
</tr>
</thead>
</table>

NMR (CDCl$_3$):  
2.17 (3H, s), 2.22 (3H, s), 3.11 (2H, m), 3.24 (1H, m, J=10 Hz), 3.34 (3H, s), 3.49 (1H, s), 3.65 (3H, s), 3.82 (3H, s), 4.07 (2H, d), 4.48 (2H, d, J=3.5 Hz), 5.05 (2H, s), 5.18 (2H, s), 6.05 (1H, s), 6.12 (1H, s), 6.68 (1H, s), 7.40 (10H, m), 8.19 (1H, s)

MS:  
710 (7, M+1), 692 (10), 573 (7), 401 (9), 32 (10), 232 (33), 91 (100)

Exact Mass:  
Calculated for C$_{40}$H$_{42}$N$_2$O$_{10}$  
Found  
710.2787  
710.2787

Characterization for 49 B:

<table>
<thead>
<tr>
<th>IR (CH$_2$Cl$_2$):</th>
<th>3620, 3360, 2940, 1690</th>
</tr>
</thead>
</table>

NMR (CDCl$_3$):  
2.15 (3H, s), 2.19 (3H, s), 3.12 (2H, m), 3.25 (1H, m), 3.32 (3H, s), 3.49 (1H, s), 3.64 (3H, s), 3.81 (3H, s), 5.04 (2H, 3), 5.17 (2H, s), 6.07 (1H, s), 6.11 (1H, s), 6.69 (1H, s), 7.39 (10H, m), 8.25 (1H, s)

MS:  
710 (16, M+1), 401 (26), 575 (25), 396 (4), 250 (35), 91 (100)

Exact Mass:  
Calculated for C$_{40}$H$_{42}$N$_2$O$_{10}$  
Found  
710.2839  
710.2857
Compound 49 A continued:
Compound 49 B continued:
Diphenol amine alcohol (50)

A solution of 26.4 g (37.1 mmol) of 49 A,B in absolute ethanol was hydrogenated over a suspension of Raney nickel in ethanol at 1100 psi for 24 hours at 80°C. The reaction mixture was filtered through Celite and the product eluted with 50% methanol in methylene chloride. A silica gel column separation employing solvent gradient to 10% methanol in methylene chloride yielded 10.6 g (50.6%) of 50 as white crystals.

IR (CH₂Cl₂): 3340, 3280, 2940, 1640, 1110, 1050

NMR (CD₃OD): 1.89 (3H, s), 1.96 (3H, s), 3.05 (4H, m), 3.29 (3H, s), 3.39 (3H, s), 3.47 (3H, s), 6.18 (1H, s)

MS: 489 (18), 488 (15, M⁺), 458 (11), 250 (100), 191 (39)

Exact Mass: Calculated for C₂₅H₃₂N₂O₈ 488.2158
Found 488.2137
Compound 50 continued:
Carbobenzoxyurethane (51)

To a solution of 10.5 g (22.3 mmol) of 50 in 200 ml of methylene chloride was added 11.1 ml (4eq) of dimethylaniline and 10 ml of methanol at room temperature. Following this, 6.2 ml (2eq) of benzyl chloroformate was added slowly. After completion of the reaction, it was taken up in methylene chloride and neutralized with 3N HCl. The aqueous layer was extracted twice with methylene chloride and the organic layer washed with saturated solution of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous sodium sulfate and then evaporated under reduced pressure.

To obtain the mono carbobenzoxylated compound 51, the residue was dissolved in 30 ml of methanol and 10.5 ml of 3N sodium hydroxide was added to the mixture. The reaction mixture was stirred at room temperature for two hours. After completion of the reaction, dry ice was added and the pH checked. It was then evaporated under reduced pressure to a smaller volume. Ether was added and the mixture partitioned with dilute solution of sodium chloride. The aqueous layer was extracted twice and the organic layer washed with saturated solution of sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to yield crude crystals of 51 which was used without further purification. mp. 196-198°C (ether).
IR (CH₂Cl₂): 3620, 3540, 2940, 1700, 1670, 1105, 1050

NMR (CDCl₃):
2.16 (3H, s), 2.25 (3H, s), 3.14 (4H, m), 3.41 (1H, d, J=14 Hz), 3.49 (3H, s), 3.54 (2H, m), 3.66 (3H, s), 3.74 (3H, s), 3.95 (2H, m), 4.13 (1H, m), 5.13 (2H, s), 5.83 (1H, dd, J=4 Hz), 6.55 (1H, s), 7.35 (5H, m)

MS:
622 (21, M⁺), 577 (8), 487 (53), 397 (49), 340 (59), 250 (100), 188 (55), 91 (75)

Exact Mass:
Calculated for C₉H₉₈N₂O₁₀ 622.2526
Found 622.2532
Compound 51 continued:
Triacetyl carboxyurethane (53)

A solution of 13.4 g (22.1 mmol) of 51 in 28 ml of acetic anhydride and 28 ml of pyridine was stirred at 60°C for 20 minutes. Upon completion, the mixture was evaporated to dryness under reduced pressure. A silica gel column separation employing solvent gradient to 5% methanol in methylene chloride yielded 15.7 g (95%) of 53.

IR (CH2Cl2): 3380, 2940, 1770, 1740, 1700, 1680, 1180, 1110, 1040

NMR (CDCl3): 2.11 (3H, s), 2.20 (3H, s), 2.26 (3H, s), 2.30 (3H, s), 2.39 (3H, s), 3.19 (4H, m), 3.59 (2H, m), 3.64 (3H, s), 3.72 (3H, s), 3.74 (3H, s), 4.17 (1H, m), 4.33 (2H, m), 5.12 (1H, m), 5.14 (2H, s), 5.67 (1H, m), 6.68 (1H, s), 7.38 (5H, m)

MS: 748 (6, M+), 706 (58), 571 (43), 481 (45), 439 (60), 364 (53), 206 (54), 91 (51), 87 (100)

Exact Mass: Calculated for C36H38N2O13 706.2373
Found 706.2340
Compound 53 continued:
Thiolactam (54)

To a solution of 15.5 g (20.7 mmol) of 53 in 60 ml of benzene was added 5.3 g (1 eq) of Lawesson's reagent. After refluxing in benzene for about 2 hours, ether was added and the mixture partitioned with combined saturated solution of sodium bicarbonate and sodium chloride. The aqueous layer was extracted twice with ether and the combined organic layer washed with saturated solution of sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 100% ether yielded 10.2 g (64%) of thiolactam as light yellow foam.

IR (CH$_2$Cl$_2$): 3340, 2940, 1770, 1740, 1710, 1180, 1110, 1040

NMR (CDCl$_3$):

- 2.10 (3H, s), 2.23 (3H, s), 2.25 (3H, s), 2.32 (3H, s), 2.39 (3H, s), 3.21 (4H, m), 3.51 (1H, d, J=20.4 Hz), 3.61 (2H, m), 3.66 (3H, s), 3.72 (3H, s), 3.77 (3H, s), 4.14 (1H, m), 4.33 (2H, m), 5.11 (1H, dd, J=7 Hz), 5.14 (1H, dd, J=6.5 Hz), 6.72 (1H, s), 7.34 (5H, m)

MS: 764 (7, M$^+$), 722 (13), 587 (21), 497 (24), 455 (22), 334 (37), 206 (46), 91 (100)

Exact Mass: Calculated for C$_{36}$H$_{38}$N$_2$O$_{12}$S 722.2145
Found 722.2093
Compound 54 continued:
Triacetyl amine (55)

To a solution of 10.1 g (13.2 mmol) of 54 in 35 ml of acetone was added 40 ml of Raney nickel suspension in acetone. The reaction mixture was stirred at 50°C for 5 hours. Upon disappearance of the starting material, the reaction mixture was filtered through Celite and the products eluted with 50% methanol in methylene chloride. This yielded a mixture of imine and amine as white foam.

Without separation, this foam was dissolved in methanol and to this stirred solution was added sodium cyanoborohydride at room temperature. The reaction was monitored by tlc. Upon completion, it was evaporated to a smaller volume. Ether was added and the resulting mixture partitioned with a solution of 3N HCl. Immediately, a solution of saturated sodium bicarbonate and sodium chloride was added. After extracting the aqueous layer, the combined organic layer was washed with saturated solution of sodium chloride and then dried over anhydrous magnesium sulfate. Evaporation of the extracts under reduced pressure yielded 8.4 g of 55 as light yellow foam which was used without purification.
IR (CH$_2$Cl$_2$): 2930, 1770, 1740, 1690, 1370, 1190, 1110

NMR (CDCl$_3$): 2.07 (3H, s), 2.10 (3H, s), 2.19 (3H, s), 2.25 (3H, s), 2.27 (3H, s), 2.75-3.24 (7H, m), 3.59 (1H, d, J=15.2 Hz), 3.72 (6H, s), 3.73 (3H, s), 4.12 (1H, m), 5.09 (1H, m), 6.72 (1H, s), 7.34 (5H, m)

MS: 734 (<1, M$^+$), 599 (4), 557 (6), 511 (100), 206 (21), 91 (24)

Exact Mass: Calculated for C$_{39}$H$_{46}$N$_2$O$_{12}$ 734.3050
Found 734.3031
Compound 55 continued:
**Diphenol alcohol amine (56)**

To solution of 8.3 g (11.3 mmol) of 55 in methanol was added 3N sodium hydroxide. The reaction mixture was stirred at room temperature for 50 minutes. Upon completion of the hydrolysis, dry ice was added to the reaction mixture and the pH checked. It was then evaporated to a smaller volume and taken up in methylene chloride. The mixture was partitioned with saturated solution of sodium chloride. The aqueous layer was extracted and the combined organic layer washed. The extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield crude crystals of 56. The crystals were recrystallized from ether with a mixture of methanol and methylene chloride at room temperature. The crystals were dried and yielded 6.3 g of off white colored 56, a (80%) yield over two steps. mp. 110-115°C (ether).

IR (CH$_2$Cl$_2$): 3540, 3340, 2940, 1690, 1105

NMR (CD$_3$OD): 2.04 (3H, s), 2.13 (3H, s), 2.61-2.85 (7H, m), 3.19 (3H, s), 3.59 (6H, s), 3.83-3.89 (1H, m), 5.04 (2H, d), 6.38 ((1H, s), 7.17-7.21 (5H, m)

MS: 608 (2, M$^+$), 427 (100), 250 (18), 206 (11), 190 (12), 91 (32)

Exact Mass: Calculated for C$_{33}$H$_{40}$N$_2$O$_9$ 608.2733  
Found 608.2724
Compound 56 continued:
Pentacyclic benzyl ether (57 A,B)

To a solution of 1.02 g (1.68 mmol) of 56 in 4:1 mixture of acetonitrile and water, was added 573.95 mg (2.3 eq) of glycolaldehyde benzyl ether. The reaction mixture was stirred at 70°C for 4 hours. Upon formation of the two isomers, it was partitioned between methylene chloride and combined solution of saturated sodium chloride and sodium bicarbonate. After extracting the aqueous layer, the organic layer was washed. The extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. Separation on a circular preparative silica gel tlc plate (4mm) employing a solvent gradient to 80% ether in hexanes yielded 525.22 mg of the top isomer, 351.39 mg of the bottom and 104.07 mg of mixture of the two isomers for a combined yield of 980.68 mg (80%).
Characterization for 57 A:

IR (CH$_2$Cl$_2$): 3610, 3520, 2930, 1690, 1105, 1060

NMR (CDCl$_3$): 2.11 (6H, s), 2.67 (2H, m), 2.90 (1H, m), 3.13 (4H, m), 3.41 (3H, s), 3.54 (2H, d, J=6 Hz), 3.55 (3H, s), 3.46 (1H, m) 3.67 (3H, s), 4.34 (1H, dd, J=12 Hz), 5.05 (4H, m), 6.73 (1H, s), 7.15 (10H, m)

MS: 619 (100), 439 (9), 235 (11), 220 (9), 191 (6), 91 (31)

Exact Mass: Calculated for C$_{34}$H$_{39}$N$_2$O$_9$ 619.2655
Found 619.2645

Characterization for 57B:

IR (CH$_2$Cl$_2$): 3540, 2930, 1690, 1340, 1105

NMR (CDCl$_3$): 2.05 (6H, s), 2.63 (2H, m), 2.83 (1H, m), 3.13 (4H, m), 3.53 (3H, s), 3.56 (3H, s), 3.61 (3H, s), 4.07 (1H, m), 4.39 (1H, dd), 5.06 (4H, m), 5.80 (1H, s), 7.19 (10H, m)

MS: 619 (96), 439 (15), 235 (32), 220 (30), 191 (24), 91 (100)

Exact Mass: Calculated for C$_{34}$H$_{39}$N$_2$O$_9$ 619.2655
Found 619.2646
Compound 57 B continued:
Tribenzyl ether (58)

To a stirred solution of 795.4 mg (1.1 mmol) of 57 A in 6 ml of acetone was added 3 g (20 eq) of pulverized potassium carbonate and 1.9 ml (15 eq) of benzyl bromide. The reaction mixture was stirred at 70°C for 1 hour after which it was taken up in ether and partitioned with saturated solution of sodium chloride. The aqueous layer was extracted twice, the extracts dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford crude 58. Separation on a circular preparative silica gel tlc plate (4 mm) employing solvent gradient to 80% ether in hexanes yielded 892.8 mg (90%) of 58 as dark yellow oil.

IR (CH2Cl2): 2940, 1695, 1110, 1070

NMR (CDCl3): 2.08 (3H, s), 2.14 (3H, s), 2.68 (2H, m), 2.84 (1H, m), 3.09-3.21 (4H, m), 3.34 (3H, s), 3.38 (2H, m), 3.53 (2H, m), 3.56 (3H, s), 3.68 (3H, s), 4.15 (2H, m), 4.87-5.29 (8H, m), 6.99-7.59 (20H, m)

MS: 799 (3), 799 (4), 616 (2), 523 (2), 483 (6), 91 (100)

Exact Mass: Calculated for C48H51N2O9 799.3594
            Found 799.3564
Compound 58 continued:
**Tribenyl ether mesyl alcohol (59)**

To a stirred solution of 1.22 g (1.3 mmol) of 58 in methylene chloride was added 1.5 ml (8 eq) of triethylamine and 615 μl (6 eq) of mesyl chloride. After stirring at room temperature for 35 minutes, it was taken up in methylene chloride and partitioned with combined solution of 3N HCl and saturated sodium chloride. The organic layer was washed with again with 3N HCl and saturated solution of sodium chloride. The organic layer was then washed with combined solution of saturated sodium bicarbonate and sodium chloride. The extracts were dried through anhydrous sodium sulfate column and evaporated under reduced pressure to yield 59 as yellow oil.

**IR (CH₂Cl₂):**
2940, 1695, 1340, 1110

**NMR (CDCl₃):**
2.09 (3H, s), 2.11 (3H, s), 2.53-2.76 (2H, m), 2.79 (3H, s), 3.02-3.11 (4H, m), 3.39 (3H, s), 3.42 (2H, m), 3.58 (3H, s), 3.67 (2H, m), 3.69 (3H, s), 4.13-4.24 (2H, m), 4.87-5.39 (8H, m), 6.95-7.56 (20H, m)

**MS:**
691 (18), 601 (23), 485 (38), 409 (21), 322(45), 250 (100), 91 (73)

**Exact Mass:**
Calculated for C₄₁H₄₃N₂O₈ 691.3019
Found 691.3011
Compound 59 continued:
Tribenzyl ether alkyl iodide (60)

To a stirred solution of 1.3 g (1.3 mmol) of 59 in 5 ml of dimethyl formamide was added excess sodium iodide. The reaction mixture was stirred at 80°C for 2 hours. Upon completion of the reaction as shown by tlc, it was taken up in ether hexane solution and partitioned with 3N HCl and saturated solution of sodium chloride. After extracting the aqueous layer, the organic layer was washed with the combined saturated solution of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford crude 60 which was used without purification.

IR (CH$_2$Cl$_2$): 2930, 1695, 1110

NMR (CDCl$_3$): 2.08 (3H, s), 2.13 (3H, s), 2.58-2.51 (2H, m), 3.01-3.30 (4H, m), 3.41 (3H, s), 3.44 (2H, m), 3.54 (2H, m), 3.57 (3H, s), 3.69 (3H, s), 4.12-4.18 (1H, m), 4.91-5.28 (6H, m), 6.97-7.23 (20H, m)

MS: 691 (3), 601 (2), 465 (3), 218 (7), 142 (27), 91 (100)

Exact Mass: Calculated for C$_{41}$H$_{43}$N$_2$O$_8$ 691.3019

Found 691.3011
Compound 60 continued:
Triphenyl ether phenol (61)

To zinc dust under argon was added a solution of 1 g (970 mmol) of 60 in methanol and 100 μl of trifluoroacetic acid. The suspension was stirred at room temperature for 35 minutes. Upon completion of the reaction, the suspension was filtered through a fritted funnel. The remaining zinc was washed several times with 10% methanol in methylene chloride. The elutant was evaporated to a smaller volume under reduced pressure and then taken up in methylene chloride. Following this, the solution was partitioned with saturated solution of sodium chloride. After extracting the aqueous layer, the combined organic layer was washed with saturated solution of sodium chloride and the extracts evaporated under reduced pressure. A silica gel column separation employing solvent gradient to 40% ether in hexanes yielded 885.8 mg of 61, a (79%) yield over three steps.

IR (CH₂Cl₂): 3540, 2930, 1695, 1105

NMR (CDCl₃): 2.07 (3H, s), 2.09 (3H, s), 2.50-2.73 (2H, m), 2.99-3.10 (4H, m), 3.42 (3H, s), 3.47 (2H, m), 3.52 (2H, m), 3.54 (3H, s), 3.69 (3H, s), 4.16 (1H, m), 4.92-5.39 (8H, m), 6.96-7.54 (20H, m)

MS: 665 (11), 511 (14), 485 (16), 279 (32), 250 (100), 234 (57), 91 (14)

Exact Mass: Calculated for C₉₃H₄₀N₂O₈ 664.2784
Found 664.2774
Compound 61 continued:
Hydroxy carboxenzoxyurethane (62)

To a stirred solution of 865.58 mg (.988 mmol) of 61 in 15 ml of 85% acetonitrile in water, was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). After stirring at room temperature for 1.5 hours the reaction was complete as shown by tlc. The reaction mixture was partitioned with ether and combined saturated solution of sodium chloride and sodium sulfite. After thoroughly extracting the aqueous layer, the combined organic layer was washed with saturated solution of sodium bicarbonate and sodium chloride. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Separation on a circular preparative silica gel tlc plate employing a solvent gradient to 80% ether in hexanes yielded 205.58 mg (23%) of 62 as yellow foam.

IR (CH₂Cl₂): 3540, 2930, 1695, 1595, 1105

NMR (CDCl₃): 2.06 (3H, s), 2.09 (3H, s), 2.49-2.59 (2H, m), 2.95-3.22 (2H, m), 3.57 (3H, s), 3.59 (3H, s), 3.69 (3H, s), 4.12-4.15 (1H, m), 4.74-5.55 (8H, m), 6.93-7.52 (20H, m)

MS: 421 (9), 279 (40), 91 (100)

Exact Mass: Calculated for C₂₃H₂₁N₂O₆ 421.1399
                        Found          421.1328
Compound 62 continued:
Hydroxy methoxy carbobenzoxy urethane (63)

To a stirred solution of 193.72 mg (.217 mmol) of 62 in 4 ml of dimethylformamide at 80°C, was added 250 mg (8 eq) of pulverized potassium carbonate and 55 μl (4 eq) of iodomethane. After 30 minutes, the reaction was complete and the reaction mixture partitioned with ether, hexane and saturated solution of sodium chloride. Following extraction of the aqueous layer, the extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure, affording 208.24 mg of 63 as yellow oil.

IR (CH₂Cl₂): 2940, 1695, 1105

NMR (CDCl₃): 2.16 (3H, s), 2.19 (3H, s), 2.49 -2.64 (2H, m), 2.98-3.29 (3H, m), 3.69 (3H, s), 3.71 (3H, s), 3.76 (3H, s), 4.22 (1H, m), 4.92-5.56 (8H, m), 7.03-7.64 (20H, m)

MS: 785 (5), 695 (23), 605 (50), 250 (61), 234 (100), 91 (11)

Exact Mass: Calculated for C₄₇H₄₉N₂O₉ 785.3437
Found 785.3429
63
Compound 63 continued:
Diphenol amine (64)

A solution of 196.39 mg of 63 in ethyl acetate was hydrogenated over 10% palladium on charcoal at room temperature under 900 psi of hydrogen for 30 hours. The reaction mixture was filtered through Celite and the column washed thoroughly with 50% methanol in methylene chloride and evaporated under reduced pressure to afford 81.60 mg of 64.

IR (CH$_2$Cl$_2$): 3530, 2930, 2840, 1610, 1110, 1060

NMR (CDCl$_3$): 2.18 (3H, s), 2.23 (3H, s), 2.95-3.51 (6H, m), 3.59 (3H, s), 3.73 (3H, s), 3.74 (3H, s), 4.44 (1H, m), 4.69 (1H, m)

MS: 485 (6), 472 (13), 236 (100), 220 (38), 204 (32)

Exact Mass: Calculated for C$_{25}$H$_{31}$N$_2$O$_7$ 471.2131
                       Found              471.2124
Compound 64 continued:
Diphenol N-methyl (65)

To a solution of 72 mg (0.143 mmol) of 64 in 3 ml of methanol, was added formaldehyde and sodium cyanoborohydride at room temperature. After 40 minutes, it was taken up in methylene chloride and washed with saturated solution of sodium chloride and 3N HCl. Immediately following, it was washed with saturated solution of sodium bicarbonate. The aqueous layer was extracted thoroughly and the combined organic layer washed with saturated solution of sodium chloride. The extracts were dried through anhydrous sodium sulfate column and evaporated under reduced pressure. Separation on a preparative silica gel tlc employing 7% methanol in methylene chloride as solvent provided 39.72 mg of 65, a (40.5%) yield over three steps.

IR (CH₂Cl₂): 3540, 2940, 2840, 1105, 1060

NMR (CDCl₃): 2.17 (3H, s), 2.25 (3H, s), 2.49 (3H, s), 2.93-3.27 (3H, m), 3.59 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 4.29 (2H, m), 4.69 (2H, m)

MS: 485 (35), 250 (100), 236 (25)

Exact Mass:
- Calculated for C₂₆H₃₃N₂O₇: 485.2287
- Found: 485.2281
Compound 65 continued:
REFERENCES


