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Synthetic studies towards the total synthesis of the saframycins

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SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF THE SAFRAMYCINS

by

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

DOCTOR OF PHILOSOPHY

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Abstract

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF THE SAFRAMYCINS

by

Karen Lynn Ajeck

Approaches toward the total synthesis of saframycin A have resulted in formation of nitrile 79 and pyrroamide 133. Interesting features include sequential piperazinedione condensations to yield intermediate 36 and cleavage of an imidazolidine ring with concomitant introduction of cyanide.
Acknowledgments

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I would also like to thank all of my co-workers, both past and present. Special thanks go to Alison Laird for always providing encouragement and support, to Joe Nunes for his companionship during the sometimes lengthy days in the laboratory, and to Leping Li for generating a never ending supply of urethane protecting groups.

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### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter I</td>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Chapter II</td>
<td>Improved Synthesis of Saframycin B Key Intermediate</td>
<td>10</td>
</tr>
<tr>
<td>Chapter III</td>
<td>Synthetic Studies Towards the Total Synthesis of Saframycins A and S</td>
<td>23</td>
</tr>
<tr>
<td>Chapter IV</td>
<td>Experimental</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>220</td>
</tr>
</tbody>
</table>
Chapter I

INTRODUCTION
The saframycins (A, B, C, D, and E) were first isolated in 1977 as satellite antibiotics co-produced with streptothricin by *Streptomyces lavendulæ* No. 314.¹ More recently, saframycins F, G, and H were also isolated.² The structure of saframycin C was determined by X-ray crystallography and that of the B congener by comparative \(^{13}\text{C-NMR}\) data (Figure 1).³ Elucidation of the structure of saframycin A soon followed, and was accomplished by chemical degradation, isotopic labeling, and comparative \(^{13}\text{C-NMR}\) studies.⁴ Although the orientation of the nitrile group at C-21 remained unknown for quite some time, Haruyama and co-workers recently conducted a set of experiments involving spin-lattice relaxation times and nuclear Overhauser effects which determined the orientation at this position to be \(\alpha\)-axial.⁵ Finally, the structures of saframycins D, F, G, and H were also determined on the basis of spectroscopic data.²

![SAFRAMYCINS](image)

**Figure 1**

Biosynthetic studies on saframycin A were conducted by Mikami et al. (Figure 2).⁶ The dimeric quinone skeleton, common to all saframycins, was determined to be derived directly from two tyrosine molecules. This was the first example of an antibiotic being derived from the condensation of two entire tyrosine molecules without being metabolized. Feeding experiments
with \([1-^{13}\text{C}]\)glycine showed incorporation at C-1; another experiment with L-[methyl-\(^{13}\text{C}\)]\)methionine resulted in enrichment at the two O- and two C- methyls as well as the one N-methyl group. Thus these carbons arose directly from methionine. The pyruvamide carbons, C-24, C-25, and C-26, were derived from alanine.

[Safaramycin A was shown to possess the highest biological activity although it was present only as a trace component (0.01 mg/ml) in the original extracts. Arai and co-workers described a method for increased production of safaramycin A which involved addition of sodium cyanide to the culture broth and maintaining a pH lower than 5.5 after peak production of the antibiotic.\(^7\) The combined effect of these two improvements resulted in a 1,000-fold increase in safaramycin A]
production as well as isolation and identification of the saframycin A precursor. This precursor, saframycin S, was present in two forms in the culture filtrate, as iminium salt 1 and as α-carbinolamine 2 (Figure 3).

![Chemical Structures](image)

**Figure 3**

Saframycin A inhibits the growth of several gram-positive bacteria, the most sensitive being *Corynebacterium diphtheriae*. Although active against a few gram-negative bacteria, it is much less potent. The saframycins also show extreme cytotoxicity toward cultured cells, and possess potent antitumor activity against several experimental tumors. Saframycin A showed marked inhibition of Ehrlich carcinoma, both in ascites and solid forms, as well as impressive activity against mouse leukemias L1210 and P388, B16 melanomas, and even human tumor xenografts in nude mice. In addition, saframycin A showed low toxicity to immunologically competent organs and cells, particularly bone marrow.

Quite a bit has been learned about the biological activity of saframycin A. Initial studies showed RNA synthesis was most affected with L1210 leukemic cells, but the synthesis of DNA was preferentially inhibited with *Bacillus subtilis*. A reason for this discrepancy has not yet been
elucidated. Saframycin A failed to affect RNA synthesis *in vitro* until a reducing agent such as dithiothreitol was added to the medium. It was also determined that the primary mode of action of saframycin A was direct interaction with a DNA template rather than interference with replicative enzymes. Saframycin A showed preferential reactivity toward double stranded DNA and high affinity for dG-dC base pairs. No evidence of double strand scission was observed.

With this information at hand, some conclusions could be drawn about the mode of action of saframycin A. First, the quinone moiety in the A-ring of the antibiotic had to be reduced prior to interaction with DNA and this reduction triggered a simultaneous loss of the nitrile as shown below in Scheme 1.\textsuperscript{12}
This implied that saframycin S might be an active form of the antibiotic. The fact that both the hydroquinone moiety and the C-21 position played an important role in the covalent bonding of DNA was established by several experiments. For example, to determine if the presence of an iminium ion or an α-carbinolamine was the only crucial requirement, activity studies were carried out on saframycin S. Although some activity was observed, addition of dithiothreitol caused enhancement of activity to the level of the reduced form of saframycin A (5) and thus established the importance of the hydroquinone moiety. 11b This hydroquinone form alone was not enough to induce maximum activity, however, since addition of excess cyanide to the reaction mixture resulted in partially reduced activity in vivo, 11a and complete failure to form the drug-DNA complex in vitro. 11b

Having established these dual requirements, a model for the saframycin-DNA adduct was proposed (Figure 4). In this model, the active form of saframycin A was linked at C-21 to N-2 of guanine and formed hydrogen bonding between the 8-hydroxyl group of the hydroquinone and the 2-keto group of cytosine. 2 It was also suggested that this activated form of the antibiotic would fit in the minor groove of DNA. This was consistent with results that showed modification at C-14 or C-25 with bulky substituents resulted in decreased activity; these positions would have to be brought into close contact with the minor groove.

![Figure 4](image-url)
The interest the saframycins have attracted is not only due to their extensive biological activity. A unique feature of these compounds is the previously unknown system of two quinone moieties attached to a piperazine ring. This fact also makes them of interest to the synthetic chemist. A dimeric quinone system is also found in the more recently isolated renieramycins, where the pyruvamide side chain of the saframycins is replaced by an angelate ester (Figure 5). Both classes of compounds offer a formidable synthetic challenge which few chemists have taken on.

![Diagram of Renieramycins](image)

**Figure 5**

The first and, to date, only successful total synthesis has been of saframycin B, which our group reported in 1982. Presently only one other group has published work on synthetic studies of these compounds. Kurihara et al. have recently published a synthesis of the 'right half' of saframycin A. Amide 7 was obtained in good yield from phenylalanine derivative 6 (Scheme 2). Upon refluxing amide 7 in trifluoroacetic acid, the doubly cyclized product 8 formed directly. With this key reaction complete, hydrolysis followed by methylation of lactam 8 resulted in formation of methylamine 9 in 50% yield. The aminals 10 were obtained by diisobutylaluminum hydride (DIBAL) reduction carried out at -78°C. It was shown that under acidic conditions, iminium ion formation was preferred. Thus oxidation of 10 in aqueous nitric acid
resulted in formation of quinone 11 (Scheme 3). This salt was next treated with aqueous sodium bicarbonate in the presence of potassium cyanide and yielded α-aminonitriles 12 and 13. Subsequent methylation of 12 yielded the desired methoxy derivative 13. The stereochemistry of the nitrile group was determined to be α-axial. Although this route resulted in successful synthesis of the 'right half' of the target molecule, elaboration of this intermediate to saframycin A is far from being trivial.

Scheme 2
This manuscript describes in detail our intensive synthetic studies towards the total synthesis of saframycin A as well as improvements to the original saframycin B synthesis. Although these studies have not yet resulted in a successful total synthesis, a great deal of insight has been gained. Hopefully, the synthesis will be realized in the very near future.
Chapter II

IMPROVED SYNTHESIS OF
SAFRAMYCIN B
KEY INTERMEDIATE
When work in our laboratory began on the saframycins, the B congener was naturally chosen as the initial target molecule as it was the least substituted member in the series. The original synthesis pursued a convergent route dependent upon a key condensation reaction which allowed construction of the basic saframycin skeleton.\textsuperscript{14} Retrosynthetic analysis (Scheme 4) suggested two disconnections which both involved cleavage at benzylic positions, and ultimately lead to amino alcohol 18 and carboxylic acid 19.
The syntheses of 18 and 19 have been described in detail elsewhere and thus are only briefly reviewed here (Scheme 5).
Cinnamyl isocyanide 21 was synthesized from cinnamyl alcohol in 5 steps which involved Gabriel synthesis of the primary amine followed by conversion to the isonitrile. Having this as well as ethyl isocyanocetate 22\textsuperscript{18} in hand, the next step was condensation of each with the substituted benzaldehyde 20,\textsuperscript{17} which was readily synthesized in 7 steps from 2,6-dimethoxytoluene. Amino alcohol 18 and carboxylic acid 19 were readily obtained from these intermediates.

The crucial coupling reaction followed. Carboxylic acid 19 was activated with 1,3-dicyclohexylcarbodiimide (DCC) and this activated complex reacted with the amine to give the basic saframycin skeleton 25. Unfortunately, this crucial step was all but reproducible. Inconsistent yields and reaction times plagued the reaction, despite attempts to change conditions and activating agents. After considerable investigation, it appeared that the major problem was the inherent instability of amino alcohol 18,\textsuperscript{19} particularly under the conditions it was synthesized.

Quite a bit of time was spent trying to improve the reaction sequence, particularly the final hydrolysis step (Scheme 6).

![Scheme 6](image)

Various solvents and bases were employed as well as several work up procedures, but these changes brought about little improvement. Thus it was decided that protection of the alcohol function should be explored. This proved feasible via the pathway shown in Scheme 7. Selective
The hydrolysis of benzoate 26 was possible by treatment with potassium hydroxide at room temperature. The resulting alcohol 27 was protected as the tetrahydropyranyl (THP) ether using pyridinium p-toluenesulfonate (PPTS). \(^2\) Finally, amine 29 was generated under harsher hydrolysis conditions. Having conquered the instability problem associated with the amino alcohol, we could now address the more serious issue of the acid-amine condensation. While it was true that protecting the alcohol function did result in marked improvements, the yield of this key reaction (~45% - 67%) was still not as high or as consistent as we would have liked. It was clear that improvements were still necessary.

The condensation reaction yielded a complex diastereomeric mixture, due to the presence of three chiral centers. Separation was not required, however, for the sequence following would yield a single product (Scheme 8). As the oxidation-elimination-cyclization sequence did not work
on the THP ether (30), it was first necessary to replace it with acetate. Subsequent controlled ozonolysis of the double bond followed by reduction with dimethyl sulfide resulted in aldehyde formation. Elimination of acetate induced by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) yielded a complex mixture of olefinic aldehydes 31 and 32 and α-hydroxy urethanes 34.

\[
\begin{align*}
\text{31} & \xrightarrow{1} \text{PPTS, MeOH}^{100\degree C} \\
\text{32} & \xrightarrow{2} \text{Ac}_2\text{O, Py} \\
& \xrightarrow{3a} \text{O}_2 \\
& \xrightarrow{3b} \text{Me}_2\text{S} \\
& \xrightarrow{4} \text{DBU} \\
\text{33} & \xrightarrow{5} \text{HCO}_2\text{H}^{60\degree C} \\
\text{34} &
\end{align*}
\]

Scheme 8

As previously determined, cyclization of 32 to form 33 was unfavorable, presumably due to steric compression of the aromatic ring. Thus rapid acid-catalyzed equilibrium between 32 and
31 eventually lead to the single desired product 35 upon treatment with formic acid. The geometry of the olefin was tentatively assigned as Z based on the results of an independent experiment.\textsuperscript{14} The cis stereochemistry at the bridgeheads was established by requirements of the [3.3.1] bicyclic system. Catalytic hydrogenation (Scheme 9) of 35 over Raney nickel (W-2) yielded 36, with the olefin being reduced from the less hindered $\alpha$-face.

\begin{center}
\includegraphics[width=\textwidth]{scheme9.png}
\end{center}

Scheme 9

Having 4 out of 5 rings intact and 3 out of 4 stereocenters controlled, diphenol amine 36 was a key intermediate in the synthesis of saframycin B. The sequence which lead to this compound, however, was far from ideal and two major imperfections marred the route. As previously mentioned, the key acid-amine condensation still required improvement, and the overall length of the series was somewhat tedious. This is what spurred us to investigate a more efficient synthesis of key intermediate 36.

Upon reinspection of the original retrosynthetic analysis, another option became very obvious (Scheme 10). The dimeric nature of 16 coupled with results published by Gallina and Liberatore\textsuperscript{21} seemed to suggest sequential condensations of our substituted benzaldehyde 20 with a piperazinedione. Although we anticipated some difficulty in differentiating the nitrogens after condensation, we set out to test the synthetic feasibility of this route.
Actually, preliminary studies did not involve direct condensation of the aldehyde with a piperazinedione, but rather proceeded through the route shown in Scheme 11. This pathway involved use of an intermediate from the preparation of carboxylic acid 19 (see page 12). Having synthesized 41 in four steps as shown, we proceeded with a potassium t-butoxide induced piperazinedione condensation which yielded 42.
Initial studies were conducted on both 42 and the di-NH compound 43 (Scheme 12). As we suspected, selective acylation of 43 was not feasible. We did experience limited success using bromoethyl chloroformate, only to discover that the bromine was lost during a catalytic hydrogenation step that followed. Thus we turned our attention to 42, only to be disappointed here as well. Unfortunately, attempted selective reduction at the lactam carbonyl (Path A) was less favorable than reduction at the acetate carbonyl (Path B). This regioselective reduction was necessary for formation of the fourth ring as shown.
It seemed inevitable that a route be devised which allowed for protection of the appropriate nitrogen as a less reactive carbamate so that regioselective reduction would then be possible. This had to be accomplished prior to the second condensation. The new synthetic sequence developed as shown in Scheme 13.

Scheme 12
The first condensation proceeded quite smoothly with only minor modification of the original procedure. Substituted benzaldehyde 20 was condensed with 1,4-diacetyl-2,5-dione 46 using potassium t-butoxide to obtain 1-acetyl-3-arylidene-2,5-dione 47. A substantial amount of time was invested in attempting to reduce the double bond in 47 without getting hydrogenolysis of the benzyl ether. This was desirable since conditions used to replace the benzyl ether resulted in loss of the N-acetyl group. Although partial reduction was not possible, we seemed to have solved the problem by finding a protecting group for the phenol (a benzoate) which could be put on without disturbing the acetate. Actually, we succeeded only in
delaying the trouble. Although the next two reactions (described in detail below) proceeded without difficulty, selective reduction of the activated lactam carbonyl followed by formic acid cyclization was unsuccessful. This was presumably due to the electron withdrawing nature of the benzoate.

If this was indeed the problem, a likely solution would be the use of a t-butyldimethylsilyl (TBDMS) ether as the phenolic protecting group. Having protected the phenol as such, our attention turned to forming the carbamate. Little difficulty was experienced here as treatment of 49 with benzylic chloroformate (CbzCl), triethylamine (TEA), and a catalytic amount of 4-dimethylaminopyridine (DMAP) resulted in clean formation of the desired benzylic carbamate 50. A second condensation of benzaldehyde 20 with carbamate 50 proceeded well and yielded the dimeric compound 51. After investigation of several reducing agents, NaBH₄ was found to be quite effective for the regioselective reduction of the activated lactam carbonyl in 51. Subsequent formic acid cyclization proceeded without incident, yielding 52.

Catalytic hydrogenation was initially attempted on TBDMS ether 52 (Scheme 14). Despite several changes in catalysts and conditions, however, formation of both isomers was observed.

![Scheme 14](image-url)
Upon inspection of a molecular model of this compound, it was clear that the TBDMS group was blocking the α-face and thus preventing selective reduction from this side. By simply removing the TBDMS ether with tetrabutylammonium fluoride prior to the reduction, we totally eliminated formation of the undesired isomer and obtained, exclusively, key intermediate 36.

This new route to the satramycin B key intermediate allowed us to overcome both of the shortcomings of the previous pathway. First, we had reduced the total number of steps in the sequence from twenty-six to ten. Second, we had replaced the troublesome DCC acid-amine condensation with two sequential piperazinedione condensations, both of which were high yielding and consistent. In addition, this new synthesis produced several intermediates which were highly crystalline and thus dramatically simplified several purification processes. Not only had this new pathway enhanced the effectiveness of our satramycin B synthesis, it also provided a quick and efficient means of bringing up material to work on the more substituted congeners in the series.
Chapter III

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF SAFRAMYCINS A AND S
With the new and improved synthesis of our key intermediate facilitating the way, we were now ready to concentrate on the synthesis of the more substituted congeners. For nearly five years, we have been engaged in working toward modifying our saframycin B pathway to lead to a total synthesis of the most biologically active congener, saframycin A. Although we have not yet succeeded in completing the total synthesis, we have learned a great deal about the system and have generated some more recent ideas which appear to be promising. Due to the limited length of this manuscript, all of the many synthetic schemes undertaken cannot be included. Instead, three of our major approaches have been selected to be described at length both here and in the experimental chapter of this manuscript.

**Scheme 15**

---

**Strategy I**

---

**Strategy II**

---
Preliminary studies\textsuperscript{17} showed that phenolic cyclization to form the B ring was impossible with an electron withdrawing group (nitrile in the case of saframycin A) in the C-21 position. This left us with two basic strategies (Scheme 15): 1) cleavage of the C-N bond of the lactam to generate an amine for use in cyclization and an aldehyde function to introduce the nitrile, or 2) building out from the aromatic ring via hydroxymethylation so that the lactam nitrogen could be used to cyclize into an aromatic aldehyde and the lactam carbonyl could be used to introduce the nitrile. The later approach actually lead to an isomer of saframycin A and will be discussed at the end of this chapter.

Scheme 16
Synthetic studies began by employing the first option, that is, attempted cleavage of the lactam. In order to test the feasibility of this concept, we first had to protect not only the phenols of 36 but also the amine. This was done as shown in Scheme 16. The true challenge commenced as we attempted to activate the lactam of protected intermediate 58 so that cleavage would be possible. Several alkylation and acylation conditions were tried to no avail, including Grieco's procedure for formation of the N-t-butoxycarbonyl (BOC) derivative.\textsuperscript{22} Our own version of this procedure, namely the use of potassium hydride in benzene at 90°C with a large excess of 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) proved to be successful and yielded 59. With activation complete, we found once again we had two options available. If the NaBH\textsubscript{4} reduction of urethane 59 was carried out at room temperature, the fully reduced hydroxymethyl compound 62 was obtained. However, if the reaction was carried out very carefully at 0°C, partial reduction was possible yielding an equilibrium mixture of α-hydroxyurethanes 60 and the aldehyde 61.

The first of the three approaches described in this manuscript involves use of this partial reduction. The most direct method of dealing with the equilibrium mixture which resulted from the NaBH\textsubscript{4} reduction was to drive it in the desired direction by protecting the aldehyde. Initial studies involving thioacetal formation (Scheme 17) were not encouraging, however. It appeared that the actual product formed upon treatment of a mixture of 60 and 61 with methyl or ethyl mercaptan was the cyclized mono-thioether 63. Treatment of compound 63 with mercuric chloride resulted in reformation of the α-hydroxyurethanes 60 and confirmed our belief that we were dealing with the cyclized compound. As cyclization of the B ring was not possible on this type of system (see page 25), a means of keeping the aldehyde oxidation state in a latent form had to be found.
This was accomplished by treating the crude reaction mixture containing 60 and 61 with a stabilized Wittig reagent (Scheme 18). This resulted in very clean formation of the desired olefinic product 65. Following removal of BOC with trifluoroacetic acid (TFA) however, $^1$H-NMR failed to show the typical olefinic pattern. The product was then recharacterized as being the undesired ethyl ester 66, the result of an in situ Michael type addition of the newly generated amine with the $\alpha,\beta$-unsaturated ester. The easiest way around this problem was obviously to use a simpler Wittig reagent such as methylenetriphenylphosphorane. All attempts to react 60 and 61
with this reagent were unsuccessful. Apparently formation of aldehyde 61 was unfavorable under the strongly alkaline conditions associated with this reagent.

Another solution to the problem would be selective reduction of the \( \alpha, \beta \)-unsaturated ester to the allylic alcohol. This also would prevent the undesired Michael addition reaction. Several reactions were attempted using lithium aluminum hydride (LAH) and lithium triethylborohydride.
(Super H-) without success. Treatment of α,β-unsaturated ester 65 with DiBAI, however, proceeded without complication to yield the allylic alcohol 67 (Scheme 19). Due to the presence of an olefin, something other than catalytic hydrogenation was necessary to remove the two benzyl ethers. Early trials involved the use of Birch reduction, but benzyl ether cleavage was accompanied by loss of the allylic alcohol to form 68. This actually was not a problem in itself, but the reaction was exceptionally slow. Even when performed on the allylic acetate 69, the Birch reduction still was not very time efficient. Careful treatment with BCl₃ proved to be much more acceptable, provided the amine was generated first by removing the BOC group with TFA, and resulted in formation of diphenol amine 70.

Scheme 19
With both the amine and the phenols regenerated, a Pictet-Spengler type cyclization could be attempted to form the B ring. Preliminary studies with formaldehyde looked quite promising and thus the search for an appropriately substituted aldehyde began. Carbobenzoxyaminoacetaldehyde seemed to be a likely candidate as it had an appropriately protected handle with which we could later introduce the pyruvamide side chain. Although somewhat slow and with modest yields, the reaction proceeded to give two isomers 71a and 71b in a ratio of ~5:1 (Scheme 20). It was hoped that the major isomer was the desired, kinetically favored product 71a. This was the compound we carried on through the remaining sequence.

![Scheme 20](image)

Both ozonolysis and osmium tetroxide/sodium metaperiodate treatment of 71a were unsuccessful at generating aldehyde 76, presumably due to the presence of the phenols and/or amine (Scheme 21). As silyl ether formation was unrealizable, the amine was first protected as the
trifluoroacetamide by treating 71a with trifluoroacetic anhydride (TFAA) in pyridine. Subsequent acetylation of the phenols yielded the fully protected 73. Ozonolysis on this compound was still unsuccessful, but formation of the diol with osmium tetroxide followed by cleavage to the aldehyde with sodium metaperiodate went very smoothly to yield 74. As basic conditions were necessary to remove the trifluoroacetamide group the aldehyde had to be protected to circumvent any possible decomposition/epimerization. Formation of the dimethyl acetal was impossible, however dithioacetal formation proceeded well to yield 75. With the aldehyde function safe, the synthesis could proceed to the deprotection stage.

\[
\begin{align*}
71a & \xrightarrow{\text{TFAA, Py}} 72 \\
72 & \xrightarrow{\text{Ac}_2\text{O, Py}} 73 \\
73 & \xrightarrow{1) \text{OsO}_4, 2) \text{NaIO}_4} 74 \\
74 & \xrightarrow{\text{EtSH, BF}_3\text{Et}_2\text{O}} 75
\end{align*}
\]

\text{Scheme 21}
Prolonged treatment (overnight) of 75 with sodium hydroxide at 50°C resulted in formation of the diphenol amine 77 (Scheme 22). Upon regeneration of the aldehyde using mercuric chloride buffered with calcium carbonate, the amine immediately cyclized to form aminal 78. Treatment of the crude reaction mixture with trimethylsilyl cyanide (TMS-CN) and zinc chloride resulted in formation of a single compound, characterized as nitrile 79.

Scheme 22

Obviously, this first approach had lead us quite close to the target molecule. There remained only three transformations to be completed. First and most trivial would be removal of the carbobenzoxy group and formation of the pyruvamide chain. Next, the quinone functionality must be unmasked, i.e. oxidation of the phenols to the bis-quinone must take place. Finally the carboxmethoxy group must be replaced by a methyl group, which at this point in the synthesis was
a highly unlikely transformation. However, this sequence was designed as a model study case and it served its purpose well.

It seemed the problem at hand involved finding a protecting group that could survive the varied conditions of this route yet could be easily removed near the end of the sequence. A much more direct route however, would be to put the methyl group on much earlier in the synthesis. This was not initially attempted due to problems that arose during studies on saframycin B. Namely, when N-Me was present during benzyl ether formation using benzyl bromide and potassium carbonate, formation of a very polar compound was observed which turned out to be a quaternary amine salt. Thus the N-Me compound was avoided until later in the synthetic scheme. Reinvestigation of this problem proved fruitful in that we discovered an alternative method for benzyl ether formation. Reductive methylation of our key intermediate yielded 80 (Scheme 23). Upon very careful treatment of 80 with potassium t-butoxide and benzyl bromide, we could form the desired dibenzyl ether methylamine 81 without complication. Activation of the lactam using BOC-ON and potassium hydride proceeded well to give urethane 82.

![Scheme 23 Diagram]
Despite numerous attempts, we were unable to open the lactam using NaBH₄ as before to generate the aldehyde equilibrium mixture (Scheme 24). Neither were our attempts using sodium hydroxide productive. In short, the only successful method to open methylamine lactam 82 involved the use of hydrazine followed by nitrosyl chloride and then sodium borohydride. However, this resulted in formation of the fully reduced hydroxymethyl compound 84. As we were unable to generate the aldehyde equilibrium mixture (85a and 85b), our current investigation of the Wittig approach was discontinued.

**Scheme 24**
As previously mentioned, a more direct method of generating this hydroxymethyl compound existed. Treatment of activated lactam 59 with NaBH₄ at room temperature gave hydroxymethyl urethane 62 directly. As we had now discovered a means of introducing NMe at an early stage in the synthesis (see page 33), it was possible for the first time to attempt cyclization of the B ring without a carbamate protecting group on nitrogen-12. Obviously, if successful, this would be the route of choice as it required fewer steps and eliminated the need for a versatile protecting group.

The synthesis proceeded as shown in Scheme 25. Although BCl₃ treatment was not suitable for cleavage of the benzyl ethers of 84, Birch reduction using lithium in ammonia proceeded without difficulty. Subsequent reaction with TFA generated amine 86 and set the stage for phenolic cyclization. As before, carbobenzoxyaminoacetalddehyde was chosen since it would allow simple conversion to the pyruvamide side chain later in the synthesis. Despite several modifications involving solvent and temperature changes, this key cyclization reaction did not proceed in acceptable yield. At least three products were initially formed in a 1:1:1 ratio; two were determined to be isomers and the third remained uncharacterized. As the reaction proceeded, however, it appeared that the desired products decomposed to give this uncharacterized compound. Also, we no longer observed preferential formation of the less polar isomer, presumably the kinetic and thus desired product. This had not been observed in any of the
previous studies were the nitrogen was protected as a urethane. Perhaps protonation of the methyamine occurred and the conformation of the transition state was altered. Whatever the explanation, it was clear that this nitrogen should be protected at least until formation of the B ring was complete. Once again we were faced with the task of finding a versatile protecting group to fit this bill.

![Chemical Structures](image)

Scheme 25

After preliminary model studies on the carbomethoxy compound proved our hypothesis correct, i.e. phenolic cyclization did proceed much better with a urethane on nitrogen-12, the search for a removable group began. As pointed out before, this protecting group must be quite versatile. Model studies had established the sequence and thus the type of conditions that must be survived. These included 1) harsh, basic conditions (KH, 90°C) to put BOC on the lactam, 2) NaBH₄ reduction of the activated lactam, 3) catalytic hydrogenation, Birch reduction, or BCl₃ treatment to remove the benzyl ethers, and 4) acidic conditions (TFA) during deprotection of N-t-BOC. While able to withstand all of these conditions, the protecting group must also be easy to remove. We originally selected two groups that fit these criteria, 2- bromoethyl urethane and allyl urethane.
A substantial amount of time was spent investigating the effectiveness of these (as well as other) protecting groups. In an attempt to limit this manuscript to a reasonable length, detailed descriptions of these synthetic attempts will not be included. Instead, a brief description of the problems encountered with each will be summarized and is included in Table 1. Forming the allyl urethane from key intermediate 36 proceeded well, as did benzylation and lactam activation with BOC-ON. Upon treatment with NaBH₄ however, we not only succeeded in opening the lactam to the hydroxymethyl compound, but we also obtained cleavage of the allyl urethane and regenerated the amine. Hoping to solve this problem, we repeated the sequence using the less reactive homoaaiyi urethane. Indeed, NaBH₄ reduction appeared to proceed well. It was

<table>
<thead>
<tr>
<th>URETHANE</th>
<th>REASON FOR DISCONTINUED USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>came off during NaBH₄</td>
</tr>
<tr>
<td>CO₂</td>
<td>partial olefin reduction during Birch and/or NaBH₄</td>
</tr>
<tr>
<td>CO₂</td>
<td>still some possible reduction as above</td>
</tr>
<tr>
<td>CO₂</td>
<td>phenolic cyclization unsuccessful</td>
</tr>
</tbody>
</table>

Table 1
discovered some time later, however, that partial reduction of the olefin had occurred during a subsequent Birch reduction to remove the benzyl ethers. This lead us to our next candidate, 4,4-dimethylhomallyl urethane. Even with this more substituted olefin, we were apparently still getting a small amount of partially reduced compound during either the Birch or NaBH₄ reduction. This was unacceptable as it not only decreased the yield but also complicated continuation of the sequence as we were not dealing with a single compound.

Our other original protecting group choice was 2-bromoethyl urethane. This now looked even more favorable in light of the previously described problems associated with an olefin. Of course, there was a chance that bromine might be lost at some point in the sequence. Although this was not a problem, phenolic cyclization to form the B ring resulted in unacceptably poor yields.

It was at this point we decided a concession had to be made. It appeared our obstacles might be less numerous if two protecting groups were employed. Although this would add a few steps to the route, we could originally use a safer protecting group such as benzyl urethane until we had completed the NaBH₄ reduction. Catalytic reduction of the benzyl ethers would then be possible as an olefin would no longer be present, and we could regenerate the amine as well. Reprotection using one of the allyl urethanes could follow, as both of the previously troublesome reactions had been completed. This did, in fact, prove to be a workable route and is described in Scheme 26.

The amine of key intermediate 36 was protected as the benzyl urethane by treatment with CbzCl and N,N-dimethylaniline (DMA). Benzyl ether formation using benzyl bromide and potassium carbonate was followed by activation of the lactam using BOC-ON and potassium hydride. NaBH₄ opening of the lactam yielded hydroxymethyl diurethane 87. Originally the alcohol was next protected as acetate 88. It was thought this would help facilitate selective protection after cyclization of the B ring. (Selective protection will be discussed at a later point in this chapter.) We soon discovered, however, that acyl migration occurred upon deprotection of
Scheme 26
the benzyl urethane to form the undesired alcohol 89. Thus a more indirect route had to be taken. Along those lines, catalytic hydrogenation of alcohol 87 over Raney nickel followed by formation of the homoallyl urethane in a two-phase reaction with saturated sodium bicarbonate and the corresponding chloroformate yielded diphenol urethane 91. Treatment of 91 with acetic anhydride and pyridine gave the over-acylated product 92 which yielded the desired diphenol 93 upon very careful treatment with hydrazine in methanol. After generation of amine 94 with TFA, we were once again ready to attempt phenolic cyclization.

During the course of numerous cyclizations that preceded this one, we decided that our original choice of substituted aldehydes may not have been ideal. First of all, carbobenzoxyaminoacetaldehyde was fairly unstable and had to be generated just prior to use each time. Also, the cyclization reaction often required a large excess of aldehyde, a long time to complete, and/or it never quite went to completion. Another major problem with this aldehyde was it almost always happened to have an Rf identical to the desired or major isomer in the cyclization reaction. Needless to say, this endlessly complicated attempts to obtain the product in reasonably pure form. Finally, we felt the amide hydrogen on the side chain might also be complicating our efforts to selectively protect the cyclized product.

For these reasons, we chose to try the cyclization of diphenol-amine 94 on a new aldehyde which we synthesized in three steps from phthalic anhydride.25 The reaction was carried out in dry acetonitrile at 40°C with a slight excess of aldehyde 95 (Scheme 27). Formation of two products (96a and 96b) was observed and the reaction proceeded quickly and very cleanly. There was one drawback however. We no longer observed preferential formation of the less polar isomer. In fact the two isomers were produced in a ratio of ~1:1. Since we could not be sure which isomer corresponded to the desired compound (with β side chain), we actually welcomed the ready availability of both. After having completed the synthesis, we would know for sure which
compound lead to the final product and thus we could return and work on the reaction conditions to favor formation of this isomer.

\[
\begin{align*}
\text{94} + \text{CH}_2\text{CN} & \quad \rightarrow \\
\text{95} & \quad \downarrow 40^\circ\text{C} \\
\text{95 (a & b)} & 
\end{align*}
\]

\textit{Scheme 27}

As was described at the beginning of this chapter, the hydroxymethyl function was present to allow us to introduce the nitrile at C-21. In order to do this, we had to first form the aldehyde. Although cyclization product 96 had the alcohol protected as the acetate, previous studies had been done on the analogous des-acetate compound. These studies showed that oxidation of the primary alcohol in the presence of the phenols and/or the amine was unsuccessful. Therefore we knew that protection of these functional groups was necessary for continuation of this
sequence. Thus began our numerous struggles with selective protection of cyclization product 96 and related compounds.

Earlier, it was pointed out that this particular route had incorporated into it two features that hopefully would simplify selective protection. These features included an acetate on the hydroxymethyl group and the absence of an amide proton on the side chain. Unfortunately, this did little to simplify the process (Scheme 28). Treatment of 96 with benzyl bromide and potassium carbonate resulted in formation of the di-benzyl ether accompanied by N-benzylation. Attempts to use potassium t-butoxide as the base also resulted in formation of the N-benzyl compound along with further complication involving loss of acetate. Reaction of 96 with tosyl chloride was plagued once again by N-acylation, as was attempted acetylation using acetic anhydride and potassium carbonate. All attempts to control the reactions were fruitless.

The amine functionality was obviously fairly reactive. If formation of a silyl ether could be realized, this would eliminate the possibility of reaction at the nitrogen. We had experienced difficulty before, however, in efficiently forming TBDMS ethers on phenols of this type. E. J. Corey reported a procedure which involved the use of TBDMS triflate to form silyl ethers on hindered compounds.26 We hoped to obtain better results using this more reactive reagent.
Although no reaction was observed at 0°C or room temperature, (Corey’s conditions) treatment of 96 with TBDMS triflate and 2,6-lutidine at 50°C in a sealed tube finally yielded a single product after ~18 hours (Scheme 29). Characterization of this product revealed not the desired compound 97, but a mono-silyl ether which we believed was 98. Apparently the other phenol was simply too sterically crowded to allow formation of this bulky silyl ether.

Scheme 29

Obviously, selectively protecting the phenols was not as straightforward as we had originally anticipated. Therefore, we turned our attention toward protecting the amine in the presence of the phenols. In the Wittig approach previously described in detail (see pages 27-32), a method
had been established to do just that. It involved protection of the amine as the trifluoroacetamide, the phenols as acetates, and the aldehyde as a dithioacetal. We had since determined that a urethane protecting group had to be present at least until after this thioacetal formation. This was discovered during the following series of reactions described in Scheme 30. The selectively protected alcohol 100 was formed by treating diphenol alcohol amine 99 first with TFAA in pyridine, then with acetic anhydride and potassium carbonate. Swern oxidation of alcohol 100 yielded a product whose NMR showed the characteristic aldehyde peak and was identified as 101. Protection of aldehyde 101 as either the dimethyl or dithioacetal was unsuccessful however. In order to avoid protection of the aldehyde, we did attempt to remove the trifluoroacetamide group of 102 before the aldehyde and methylamine were generated. The result was isolation of a compound which we identified as 103, produced by alcohol cyclization into the urethane as shown in Scheme 31. As could be expected, removal of the trifluoroacetamide on the aldehyde (101) was unsuccessful and apparently involved air oxidation to yield a product whose NMR and MS were consistent with our assigned structure 104.
Scheme 31
In the previously discussed Wittig route, the aldehyde substrate was quite similar to aldehyde 101. In fact, the only difference was that carbomethoxy was on the nitrogen instead of methyl! Thus we established the requirement that a urethane must be present to form the acetal. In order to attempt this chemistry on the molecule at hand, some minor modifications had to be made as outlined in Scheme 32. Actually the only required transformation was regeneration of the hydroxymethyl group by removing the acetate. Unfortunately, every attempt to do this in the presence of the phthalimide resulted in decomposed reaction mixtures. Thus we first had to remove the phthalimide from 96 using hydrazine and reprotect the primary amine as the benzyl carbamate. With this completed, hydrolysis of the acetate with saturated sodium bicarbonate gave diphenol alcohol amine 106.

\[ \text{Scheme 32} \]

Treatment of 106 with TFAA in pyridine quickly and cleanly gave trifluoroacetamide 107 (Scheme 33). The phenols were protected in the presence of the alcohol by treating with two
equivalents of acetic anhydride and excess potassium carbonate. Swern oxidation of the resulting product yielded aldehyde 108. Unlike the previously described NMe case, we had no trouble whatsoever forming the dithioacetal 109 upon treatment of aldehyde 108 with excess ethanethiol and BF₃-Et₂O. We did encounter another problem however. Even after treating 109 with a large excess of aqueous sodium hydroxide at 100°C for several days, we were unable to cleanly remove the trifluoroacetamide. Although we had made some headway, it appeared that a protecting group must be found for the amine which would be easier to remove than this stubborn trifluoroacetamide. Once again we began the quest for a suitable candidate.

Scheme 33
As before, it appeared that a urethane might be the best choice, particularly if we used one that required mild deprotection conditions. This immediately brought to mind a 2,2,2-trichloroethyl urethane. It was possible to control the reaction of diphenol alcohol amine 106 with 2,2,2-trichloroethyl chloroformate by using only one equivalent in a two phase reaction with saturated sodium bicarbonate and methylene chloride. This resulted in formation of a single major product (Scheme 34). To insure that acylation was occurring on the nitrogen and not on the phenols, the crude reaction mixture was treated with aqueous sodium hydroxide in methanol. Under these conditions, the urethane should remain intact, but a carbonate, if formed, would yield the starting phenol. Although no regeneration of starting material occurred, we did observe formation of a more polar compound which we were unable to characterize. When diphenol alcohol amine 106 was treated with aqueous sodium hydroxide, formation of a polar compound

\[ \text{Scheme 34} \]
was again observed. Even though this was disturbing, it did not appear that the problem was associated with selective protection of the amine and thus we proceeded with the synthesis. With the amine successfully protected, we could continue with acetylation of the phenols using acetic anhydride and potassium carbonate to give alcohol 111. Subsequent Swern oxidation resulted in clean formation of aldehyde 112.

We were now ready to proceed with deprotection of the trichloroethyl urethane. Since typical conditions for deprotection involved mild treatment with activated zinc, we felt it would not be necessary to protect the aldehyde before attempting to regenerate the amine. Thus aldehyde 112 was dissolved in methanol and activated zinc was added to the mixture (Scheme 35). As no reaction was observed, a catalytic amount of acetic acid was added. Although the starting material eventually reacted, a major product was never formed. Treatment of this very crude reaction mixture with TMS-CN and zinc chloride resulted in an even messier reaction mixture as observed by tlc. Apparently deprotection was not as trivial as we had expected.

![Scheme 35](image-url)
The next logical approach was to protect the aldehyde before attempting to deprotect the trichloroethyl urethane. Thus aldehyde 112 was protected as the dithioacetal 114 upon treatment with excess ethanethiol and BF$_3$·Et$_2$O. Unfortunately, zinc treatment of this compound also failed to result in formation of the desired amine 115. A final attempt at deprotection, also unsuccessful, involved treatment of alcohol 111 with activated zinc and acetic acid. Efforts to improve the deprotection by varying solvents proved futile.

As was feared, selectively protecting diphenol amine 96 (or its analogue 106) was quite difficult yet necessary to allow oxidation and thus formation of the final ring and introduction of the nitrile. In addition, the extensive manipulation of protecting groups required added a considerable number of steps to an already lengthy sequence. These facts coupled with a shortage of starting material 96, convinced us that perhaps another synthetic strategy should be investigated.

At the beginning of this chapter, two basic strategies for formation of the B ring were mentioned. Although the first route involving cleavage of the C-N lactam bond did not lead to an absolute dead end, it did not prove to be exceptionally promising either. It seemed appropriate at this time to investigate the second option which involved building out from the aromatic ring. Not only would this route prove to be much shorter, but it would also incorporate a means to control the stereochemistry of the pyruvamide side chain.

A brief retrosynthetic analysis is presented in Scheme 36. As before, nitrile 116 would be formed via the corresponding aminal which might be obtained from amine lactam 117. This amine, in turn, could be generated from nitrile 118 which could be synthesized from the $\alpha$-hydroxy lactam 119. Cleavage of 119 as shown resulted in formation of intermediate 120 and suggested hydroxymethylation of the aromatic ring.

The obvious starting point was key intermediate 36. Initial studies$^{17}$ were complicated by the necessary use of allyl urethane as a protecting group for nitrogen-12. Complications arose during deprotection using tri-n-butylltin hydride; removal of the tin species was extremely difficult.
As described on page 33, we had since found a method which allowed earlier introduction of the methyl group and thus avoided these complications. Treatment of 36 with formaldehyde, sodium cyanoborohydride, and a catalytic amount of TFA in methanol gave methylamine 122 (Scheme 37). Intensive studies were carried out to determine the best conditions for hydroxymethylation of the aromatic ring. Treatment of 122 with formaldehyde and one equivalent of 0.5N standardized NaOH in n-BuOH gave the highest yield of hydroxymethyl diphenol 120. Benzylation of the two phenols using our newly established conditions followed by Swern oxidation of the primary alcohol resulted in formation of a mixture of \( \alpha \)-hydroxylactams 119. This mixture was treated with TMS-CN and BF\(_3\)-Et\(_2\)O to obtain a mixture of nitriles 123.

Scheme 36
It was at this point that we attempted to control the stereochemistry of the side chain. We discovered that the mixture of nitriles (123) could be converted exclusively to the less polar isomer if epimerization were effected using the following conditions.\textsuperscript{17} First, the mixture was treated with 3 equivalents of lithium disopropylamide (LDA) at -78°C. Protonation of the resulting anion again at -78°C, was achieved with 2,6-di-t-butylphenol. The single product isolated was assigned the structure (123a) shown in Scheme 38. This assignment was based on the assumption that protonation of the anion of 123 with a very bulky proton source should occur.
only from the less hindered α-face. This seemed a reasonable explanation as only one product was formed. To simplify matters more, we later discovered quite by accident that one of the nitrile isomers was crystalline while the other remained in solution. Thus we could easily separate the isomers so that epimerization need only be done on the undesired compound.

Scheme 38

With the stereochemistry of the side chain intact, we proceeded with the synthesis. Dibenzyl ether amine 117a was formed upon catalytic hydrogenation of nitrile 123a with Raney nickel in ethanol saturated with ammonia (Scheme 39). No hydrogenolysis of the benzyl ethers
was observed. Numerous reagents were tried before optimal conditions for partial reduction of the lactam were found. Finally, treatment of 117a with aluminum hydride generated in situ cleanly produced a single product. This product was not carbinolamine 125; apparently, the amine and newly generated aminal immediately cyclized to form imidazolidine 124. As a result, the task at hand was to cleave this C-N bond and introduce the nitrile at C-21.

Model studies were first conducted on the acetyl compound 126 (Scheme 40). Our strategy was this; hopefully a Lewis acid could be used to activate the carbonyl of the acetate. This would favor participation of the nitrogen lone pair to cleave the C-N bond as shown. With the bond broken, a nucleophile could attack the C-21 position and thus relieve the positive charge on nitrogen. With this mechanism in mind, we began what turned out to be a very lengthy investigation.

![Scheme 40](image-url)
The results from the Lewis acid cases are summarized in Table 2. Despite intensive effort on our part, we were unsuccessful in effecting cleavage of this bond using any of the acids listed. With the same general mechanism in mind, several other reagents were used as activators: 1) POCl₃, 2) 3N HCl, 3) SOCl₂, and 4) Ac₂O. These failed to induce cleavage of the desired bond as well. In hope that it might be more reactive, studies were also conducted on the
amine 124 (Scheme 41). Treatment of 124 with either phosgene, t-butyl hypochlorite, or benzene sulfonyl chloride did result in formation of an initial product. Subsequent treatment with a variety of nucleophiles, however, did not lead to further reaction.

Scheme 41

Obviously this bond cleavage was more difficult than we originally expected. Another option did exist, however, and involved use of liquid HCN. Preliminary studies on the model compound 126 looked quite promising (Scheme 42). Overnight stirring of 125 in a 2:1 solution of HCN/CH₂Cl₂ at room temperature produced a single major product, which began to regenerate starting material upon heating. Mass spec and ¹H-MNR data indicated formation of the desired nitrile 129. Hopefully the same results could be obtained on the actual molecule.

Scheme 42
Scheme 43
Although we experienced some difficulty in removing the benzyl ethers from amine 124, Birch reduction using lithium proved to be acceptable and yielded diphenol 130 which was treated with a solution of pyruvic acid and DCC in CH₂Cl₂ (Scheme 43). The reaction was complete within minutes and yielded pyruvamide 131. This set the stage for the crucial HCN reaction. After stirring 131 in a 2:1 solution of HCN/CH₂Cl₂ at room temperature overnight, we observed formation of both a major and minor product. After some confusion, we discovered that the major compound could be completely converted to the minor compound upon vigorous shaking with a saturated solution of sodium carbonate. Apparently the major product formed during the reaction was the cyanohydrin 132 which could be converted to the desired pyruvamide nitrile 133.

The current route appeared to be quite promising as only one step remained to complete the total synthesis of saframycin A. The phenols of 133 had to be oxidized to form the bisquinone system. The first attempt at oxidation involved the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aqueous acetone (Scheme 44). A subsequent attempt used a catalytic amount of sulfuric acid with manganese triacetate in aqueous acetonitrile. In both cases, a less polar compound was formed which had the characteristic yellow color on tlc of para-quinone.

\[ \text{Scheme 44} \]
systems. The $R_f$ of this product was somewhat smaller than our reference of natural saframycin A, however. $^1$H-NMR studies showed peaks typical of the bis-quinone system, so we believed we had synthesized an isomer of saframycin A.

There were two sites of questionable stereochemistry in 133. We had no absolute proof that the pyruvamide side chain possessed the proper stereochemistry, and we had no proof at all that the nitrile was in the proper orientation. With this new route in hand, it was quite simple to convert dibenzyl ether amine 124 to an intermediate in our saframycin B synthesis, which of course, had known stereochemistry at the pyruvamide side chain. This was accomplished as shown in Scheme 45. The benzyl ethers of 124 were removed using Birch reduction. The resulting compound was treated with CbzCl and DMA to form the benzyl urethane. Subsequent treatment with sodium cyanoborohydride resulted in reduction to the diphenol-amine 134.

The $^1$H-NMR of this compound was compared to those of the two isomers obtained during phenolic cyclization in the saframycin B pathway. All three NMR's are shown on the following page.
Reference: $\alpha$-side chain isomer

Reference: $\beta$-side chain isomer

Diphenol amine 134
Unfortunately, it was quite clear that the compound we had been working with possessed the wrong stereochemistry, i.e. the pyruvamide side chain was α! This implied that protonation of the nitrile anion 123 with the very bulky proton source did not occur from the least hindered α-face as was predicted. Although we are still unable to rationalize this result, we feel it must have something to do with the lone pair of electrons on the adjacent nitrogen directing delivery of the proton.

Although this certainly was distressing news, we were not yet willing to abandon this approach. As was described, two nitrile isomers (123) were formed. It just so happened that epimerization had not been performed the last few times the sequence was carried out. Thus we had available a small amount of compound with the now determined correct stereochemistry.

Upon embarking on this route, we were not without doubt that the same chemistry would work on the other isomer. The biggest question in our minds was whether partial reduction of the lactam would be possible. In the previous case (α-side chain), the aminal was intercepted by the aminomethyl group as it cyclized to from the imidazolidine ring. Molecular models seemed to suggest (Figure 6) that this cyclization would be less likely with the correct compound (β-side chain). This, no doubt, would reduce our chances of partially reducing the lactam.

```
Correct Compound
R₁ = CH₂NH₂
R₂ = H

Previously Studied Compound
R₁ = H
R₂ = CH₂NH₂
```

Figure 6
As is turned out, we never got that far. Before we could attempt partial reduction of the lactam, we had to generate the aminomethyl compound from the corresponding nitrile isomer. Although we experienced no difficulty in reducing the previous isomer 123a, numerous attempts to reduce the one at hand (123b) gave totally unacceptable results (Scheme 46). As this route was already plagued by many possible difficulties, it appeared a new method of controlling stereochemistry at this site was needed.

**Previous Case**

\[
\begin{array}{c}
\text{123a} \\
\text{117b}
\end{array}
\]

**Correct Compound**

\[
\begin{array}{c}
\text{123b}
\end{array}
\]

**Scheme 46**

Our plan involved use of the following strategy (Scheme 47). We knew from previous studies that formation of an olefin such as 135 was possible. Hopefully we could induce isomerization of this olefin. Then ozonolysis followed by reduction with dimethyl sulfide would
give an aldehyde such as 136. The stereochemistry could be controlled by formation of the enol acetate followed by catalytic hydrogenation from the less hindered \( \alpha \)-face.

![Chemical Structures](image)

**Scheme 47**

To test the feasibility of this route, the \( \alpha \)-hydroxylactams 119 were treated with allyl trimethylsilane and BF\(_3\)-Et\(_2\)O (Scheme 48). This produced olefin 138, apparently as a single isomer. Several attempts at olefin isomerization were made; reagents tried included rhodium chloride, dichlorobis(triphenylphosphine)palladium(II),\(^{28}\) and 4-phenyl-1,2,4-triazoline-3,5-dione.\(^{29}\) The unsuccessful results are summarized in Table 3, and the approach was abandoned.

Still searching for a synthetic route which would enable us to control the orientation of the pyruvamide side chain, our thoughts wandered to transition metal chemistry. Perhaps we could use palladium to effect cyclization of the B ring and if we were lucky, obtain the desired isomer.
Scheme 48

<table>
<thead>
<tr>
<th>REAGENT</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RhCl₃·3H₂O</td>
<td>apparent Tsuji type ketone synthesis</td>
</tr>
<tr>
<td>Pd(PPh₃)₂Cl₂</td>
<td>no reaction</td>
</tr>
<tr>
<td></td>
<td>very messy reaction</td>
</tr>
</tbody>
</table>

Table 3
If not, we could still try the enol acetate approach to establish proper stereochemistry. It certainly appeared to be worth investigating. We spotted a report in the literature by Waterman describing an intramolecular olefin amination which lead to formation of indoles and dihydroquinolines.\textsuperscript{30} It might be possible to obtain the same type of reaction if we could generate a system such as aminonitrile 139. Therefore our efforts were concentrated on preparation of such a compound.

139

Actually, this was relatively easy to do (Scheme 49). Beginning as usual with key intermediate 36, we protected the amine as the carbomethoxy urethane. (Since these were model studies, there was no need to introduce further complication by using one of our removable urethanes.) Formation of diallyl ether 140 resulted from treating the diphenol with allyl bromide and potassium carbonate. Claisen rearrangement of 140 was conducted in N,N-diethylaniline at 210°C and required several hours. Under these conditions, we also observed loss of the other allyl ether, resulting in formation of diphenol 141. Partial reduction of the lactam using a large excess of DI\textsubscript{BAI} gave the unstable aminal which was trapped by \textit{in situ} treatment with sodium cyanide in methanol. This resulted in formation of the desired amino nitrile 142. Using Waterman's conditions,\textsuperscript{30} we attempted Pd(II) induced cyclization. Amino nitrile 142 was treated with a solution of dichlorobis(acetonitrile)palladium(II) in tetrahydrofuran, followed by addition of TEA. Although the starting material did react, the reaction was not clean and it was impossible to characterize the major product formed.
This did not overly discourage us, however, for we realized that cyclization on an intermediate such as 155 using Pd(0) would be much more likely to proceed. Thus we set out to synthesize this compound (Scheme 50). The first approach we attempted was quite convenient in that it involved use of an intermediate from the previous pathway. Simple acetylation of diphenol 141 gave the basic starting material we required. Our plan of attack involved the use of selenium dioxide (SeO₂) chemistry, and we actually had two options starting from compound 143. If we were lucky, we might be able to obtain both rearrangement of the olefin and formation of the allylic alcohol upon direct treatment of 143 with SeO₂. As usual, we were not lucky and this
reaction was quite messy. Hopefully, we could simplify matters by first carrying out the isomerization and then attempting allylic alcohol formation with $\text{SeO}_2$. Once again we met disaster as isomerization with rhodium chloride, and dichlorobis(benzonitrile)palladium(II) failed to work on 143 as did potassium t-butoxide in dimethylsulfoxide on diphenol 141.\textsuperscript{32}
There was another way of synthesizing compound 155 that did not involve use of SeO₂. This pathway also took advantage of an old intermediate from the aromatic hydroxymethylation route, compound 120. After benzylation of the phenols, the hydroxymethyl group was protected as the 1-ethoxyethyl ether 144 (Scheme 51).
Once the alcohol was protected, formation of the N-t-butyl carbamate proceeded well to yield 145. Deprotection of the alcohol followed by Collins oxidation resulted in clean formation of aldehyde 146. We planned to obtain the cinnamyl alcohol like intermediate 155 by reaction of aldehyde 146 with a stabilized Wittig reagent followed by reduction and acetylation. Despite extensive efforts to push this reaction, we never saw formation of any product. Reaction of aldehyde 146 with the more reactive Horner-Emmons reagent also failed to produce the desired product 147.

Our original attempts to synthesize an intermediate which would allow us to test the feasibility of a Pd(0) induced cyclization were not very successful. This definitely appeared to be a route worth serious investigation, however. An alternate means of generating such an intermediate might include synthesizing a new aldehyde such as 148 to use in the second piperazinedione condensation (Scheme 52).
This would allow early incorporation of a handle with which the cinnamyl alcohol function could be derived. One possible means of doing this is shown below in Scheme 53. Swern oxidation of alcohol 150 would yield aldehyde 151. Formation of the α-phenylseleno derivative 152 might then be possible, followed by oxidation to the selenoxide and elimination to form the α-β unsaturated compound 153. Selective reduction of this α-β unsaturated aldehyde would then result in formation of alcohol 154 which could readily be converted to the desired intermediate 155 for cyclization.

Scheme 53
Synthetic studies along these lines, as well as attempts to improve the earlier lactam opening route, are currently being pursued in the laboratory of Dr. Tohru Fukuyama at William M. Rice University.
Chapter IV

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 unless otherwise noted. 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 using direct probe insertion at temperatures of 150 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 Woch silica gel, 32 - 63 mesh, packed in Altex columns on an mplic system.

Circular chromatography was performed on a Model 7924T Chromatotron using 1 mm or 2 mm 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 sodium benzophenone ketyl.
Pyridine: dried over potassium hydroxide pellets.
t-Butanol: distilled from calcium hydride.

Diisopropylamine: distilled from sodium hydride and stored over potassium hydroxide pellets.

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

dried over 4Å molecular sieves.

Lithium diisopropylamide (LDA) was prepared by dropwise addition of n-butyllithium in hexanes to a stirred solution of diisopropylamine in tetrahydrofuran at 0°C and was used after stirring for 5 minutes.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
1-acetyl-3-arylidene-piperazine-2,5-dione (47)

A solution of 10 g (50.5 mmol) of 1,4-diacetyl-piperazine-2,5-dione 46 and 14.4 g (1 eq) of the benzaldehyde 20 in 80 ml of dry tetrahydrofuran was cooled to 0°C under argon. To this stirred solution was slowly added 50 ml (1 eq) of 1 N potassium t-butoxide. After 15 minutes the reaction was complete as shown by tlc. The reaction was quenched by adding 5.7 ml (~2 eq) of acetic acid and warming to room temperature. The mixture was then poured into ice water and the aqueous layer thoroughly extracted with methylene chloride. The extracts were dried through an anhydrous sodium sulfate column and evaporated under reduced pressure to obtain crude crystals of 47. These crystals were triturated with ether at 0°C, filtered, and air dried to give 16.9 g (78.5%) of 47 as light yellow crystals. mp 178-180°C (ether).

IR (CH₂Cl₂): 1700

NMR (CDCl₃): 2.25 (3H, s), 2.66 (3H, s), 3.64 (3H, s), 3.89 (3H, s), 4.47 (2H, s), 5.09 (2H, s), 6.71 (1H, s), 6.99 (1H, s), 7.34 - 7.45 (5H, m), 9.32 (1H, s)

MS: 424 (20, M⁺), 333 (31), 291 (66), 91(100)

Exact Mass: Calcd. for C₂₃H₂₄N₂O₆ 424.1634
Found 424.1627
Compound 47 continued:
1-acetyl-3-aryl-piperazine-2,5-dione (47b)

A solution of 15.1 g (35.4 mmol) of 47 in 120 ml of ethyl acetate was hydrogenated over 1.5 g of 10% palladium on charcoal at 1000 psi of hydrogen for 30 minutes at 80°C. A solution of 75 ml of 95% ethanol in methylene chloride was added to the reaction mixture. After stirring for 30 minutes, the mixture was filtered through Celite and the column washed repeatedly until all product had been eluted as evidenced by tlc. Evaporation under reduced pressure gave 12.2 g of crude 47b as an off white foam which was used without purification.

IR (CH₂Cl₂): 3540, 1710, 1110

NMR (CDCl₃):

2.24 (3H, s), 2.60 (3H, s), 2.99 (1H, dd, J = 8.6, 13 Hz), 3.28 (1H, dd, J = 3.9, 13 Hz), 3.70 (3H, s), 3.79 (3H, s), 4.04 (1H, d, J = 17.6 Hz), 4.29 (1H, dd, J = 8.6, 3.9 Hz), 4.42 (1H, d, J = 17.6 Hz), 5.59 (1H, s), 6.58 (1H, s), 6.65 (1H, s)

MS: 336 (8, M⁺), 294 (47), 223 (100), 182 (92)

Exact Mass:

Calcd. for C₁₆H₂₀N₂O₆ 335.1321
Found 336.1326
Compound 47b continued:
t-butyldimethylsilyl ether (49)

To a solution of 41 mg (0.121 mmol) of 47b, 34 μl (2 eq) of triethylamine, and 12 mg (0.8 eq) of 4-dimethylaminopyridine in 5 ml of dry methylene chloride was added 33 mg (1.8 eq) of t-butyldimethylsilyl chloride. The reaction mixture was stirred overnight in a sealed tube at 60°C. Upon completion, the reaction mixture was poured in a solution of dilute HCl and partitioned. The methylene chloride layer was washed with a solution of saturated sodium chloride followed by a solution of saturated sodium bicarbonate. The extract was dried through an anhydrous sodium sulfate column and evaporated. Separation on a preparative silica gel tlc plate (3% methanol in methylene chloride) afforded 33 mg (60.3%) of 49 as a white foam.

IR (CH₂Cl₂):
3395, 2870, 1700, 1065

NMR (CDCl₃):
0.16 (6H, s), 0.99 (9H, s), 2.18 (3H, s), 2.58 (3H, s), 2.99 (1H, dd, J= 6, 14 Hz), 3.22 (1H, dd, J= 4, 14 Hz), 3.69 (3H, s), 3.73 (3H, s), 4.03 (1H, d, J= 17.5 Hz), 4.25 - 4.28 (1H, m), 4.33 (1H, d, J= 17.5 Hz), 6.53 (1H, s), 6.80 (1H, s)

MS:
450 (<1, M⁺), 407 (1), 393 (63), 351 (11), 295 (63), 223 (100), 193 (74)

Exact Mass:
Calcd. for C₂₂H₃₄N₂O₆Si 450.2186
Found 450.2174
Compound 49 continued:
Carbobenzoxyurethane (50)

A solution of 8.5 g (18.8 mmol) of 49 in 50 ml of dry methylene chloride was stirred at -15°C. To this solution was added 13.1 ml (2 eq) of triethylamine and 2.3 g (1 eq) of 4-dimethylaminopyridine followed by slow addition of 5.7 ml (2 eq) of benzyl chloroformate. After stirring at -15°C for 10 minutes the reaction mixture was warmed to room temperature and poured into a solution of dilute HCl and partitioned. The methylene chloride layer was washed with a solution of saturated sodium chloride followed by a solution of saturated sodium bicarbonate. The extract was dried through an anhydrous sodium sulfate column and evaporated. A silica gel column separation employing a solvent gradient to 60% ether in hexanes yielded 8.7 g (79.1%) of the urethane 50 as a light yellow oil.

IR (CH₂Cl₂): 2865, 1715, 1200, 1065

NMR (CDCl₃): 0.12 (6H, s), 0.98 (9H, s), 2.12 (3H, s), 2.52 (3H, s), 2.88 (1H, d, J= 18.7 Hz), 3.16 (1H, dd, J= 4, 14 Hz), 3.32 (1H, dd, J= 6.3, 14 Hz), 3.49 (3H, s), 3.71 (3H, s), 4.61 (1H, d, J= 18.7 Hz), 5.13 (1H, dd, J= 4, 6.3 Hz), 5.33 (2H, s), 6.38 (1H, s), 7.34 - 7.39 (5H, m)

MS: 584 (<1, M⁺), 527 (18), 455 (7), 295 (38), 223 (66), 193 (47), 73 (100)

Exact Mass: Calcd. for C₃₀H₄₀N₂O₇Si 584.2553
Found 584.2548
Compound 50 continued:

[Graphs and diagrams]
**Diaryl Piperazine Dione (51)**

A mixture of 21.1 g (36.1 mmol) of the urethane 50 and 11.4 g (1.1 eq) of the benzaldehyde 20 was dissolved in 120 ml of dry tetrahydrofuran under argon at -78°C. To this stirred solution was added 36.1 ml (1 eq) of 1 N potassium t-butoxide. Careful monitoring by tlc showed starting material was gone after 20 minutes. The reaction mixture was warmed to 0°C and an additional 3.6 ml (0.1 eq) of 1 N potassium t-butoxide was added to force the intermediate product to the desired compound 51. The reaction was quenched with 4.1 ml (~2 eq) of acetic acid, warmed to room temperature, and partitioned between methylene chloride and a dilute solution of sodium chloride. After washing the aqueous layer, the organic extracts were dried through an anhydrous sodium sulfate column and evaporated. A silica gel column separation employing a solvent gradient to 60% ether in hexanes yielded 25.5 g (87.2%) of 51 as a light yellow oil.
IR (CH$_2$Cl$_2$): 3225, 2865, 1665, 1070

NMR (CDCl$_3$):

0.096 (6H, s), 0.92 (9H, s), 2.00 (3H, s), 2.20 (3H, s), 3.09 (1H, dd, J = 3.8, 13.7 Hz), 3.29 (1H, dd, J = 5.8, 13.7 Hz), 3.45 (3H, s), 3.50 (3H, s), 3.65 (3H, s), 3.86 (3H, s), 5.07 (1H, m), 5.08 (1H, d, J = 11.8 Hz), 5.20 (1H, d, J = 11.8 Hz), 5.30 - 5.42 (2H, m), 6.31 (1H, s), 6.53 (1H, s), 6.57 (1H, s), 7.35 - 7.51 (10H, m), 9.03 (1H, s)

MS:

810 (1, M$^+$), 752 (2), 709 (39), 662 (38), 619 (36), 541 (16), 528 (29), 295 (78), 73 (100)
Compound 51 continued:
Tetracyclic tetrabutyldimethylsilyl ether (52)

A solution of 100 mg (0.123 mmol) of 51 and 7.2 μl (~2 eq) of acetic acid in 8 ml of absolute ethanol was stirred at -20°C to -30°C. Slowly and in portions, 18.6 mg (4 molar eq) of sodium borohydride was added and the reaction monitored by tlc. Upon completion, the reaction mixture was warmed to room temperature and to it was added 5 ml of ether and one drop of aqueous methyl orange solution. Acidification was effected with dilute HCl and the reaction mixture stirred at room temperature for 5 minutes then partitioned with water. After washing the aqueous layer, the ether extracts were washed with a solution of saturated sodium chloride followed by a solution of saturated sodium bicarbonate. A final sodium chloride washing was followed by drying the organic layer over anhydrous magnesium sulfate. Evaporation yielded the crude α-hydroxy urethane which was used without purification.

The residue was dissolved in 3 ml of formic acid and the resulting solution stirred at room temperature for 20 minutes. Evaporation of the reagent was conducted under reduced pressure. Separation on a preparative silica gel tlc plate (70% ether in hexanes) yielded 75 mg (76.6%) of 52 as a white foam.
IR (CH₂Cl₂): 3345, 2865, 1680, 1270 (b), 1070

NMR (CDCl₃): 0.12 - 0.37 (6H, m), 0.98 (9H, m), 2.16 (3H, s), 2.17 (3H, s), 3.05 - 3.25 (2H, m), 3.32 (3H, s), 3.48 (3H, s), 3.67 (3H, s), 3.83 (3H, s), 5.01 - 5.30 (5H, m), 5.93 - 6.19 (2H, m), 6.59 (1H, d, J= 12.5 Hz), 7.36 - 7.46 (10H, m), 8.16 (1H, s), 8.36 (1H, s)

MS: 794 (24, M⁺), 737 (24), 646 (45), 555 (27), 524 (32), 424 (35), 334 (100), 295 (53)

Exact Mass: Calcd. for C₄₅H₅₄N₂O₉Si 794.3598
             Found 794.3608
Compound 52 continued:
**Tetracyclic alcohol (53)**

To a solution of 20 mg (0.025 mmol) of 52 in 1 ml of tetrahydrofuran was added 25.7 μl (1 eq) of tetrabutylammonium fluoride. The reaction mixture was stirred at room temperature for 5 minutes then partitioned between ether and a solution of saturated sodium chloride. The ether layer was washed with a solution of saturated sodium bicarbonate followed by a solution of sodium chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated. Separation on a preparative silica gel tlc plate (60% ether in hexanes) yielded 14.3 mg (83.8%) of 53. mp 156-157°C (90% ether in hexanes).

**IR (CH₂Cl₂):**

3520, 2920, 1685, 1105, 1000

**NMR (CDCl₃):**

2.17 (3H, s), 2.22 (3H, s), 3.10 - 3.26 (2H, m), 3.34 (3H, s), 3.66 (3H, s), 3.72 (3H, s), 3.82 (3H, s), 5.05 (2H, s), 5.09 - 5.26 (1H, m), 5.68 (2H, s), 5.98 - 6.11 (2H, m), 6.62 - 6.67 (1H, m), 7.33 - 7.47 (10H, m), 8.28 (1H, s), 8.46 (1H, s)

**MS:**

680 (<1, M⁺), 545 (<1), 461 (<1), 410 (<1), 370 (3), 91(100)

**Exact Mass:**

Calcd. for C₃₉H₄₀N₂O₉  
680.2733

Found  
680.2730
Compound 53 continued:
Diphenol amine (36)

A solution of 9.1 g (13.4 mmol) of 53 in 120 ml of absolute ethanol was hydrogenated over 20 ml of a suspension of Raney nickel in ethanol at a hydrogen pressure of 1000 psi for 24 hours at 120°C. Filtration through Celite, washing with hot ethanol until all of the product had been eluted, was followed by evaporation and yielded 6g of crude 36 as light brown crystals. mp 138-141°C (hot methanol).

IR (CH2Cl2): 3680, 3520, 2920 (b), 1660, 1105, 1050, 1000

NMR (CDCl3): 2.09 (1H, dd, J= 11.7, 14 Hz), 2.21 (3H, s), 2.27 (3H, s), 3.01 (1H, dd, J= 6.8, 17.9 Hz), 3.14 (1H, d, J= 17.9 Hz), 3.39 (1H, d, J= 11.7 Hz), 3.49 (3H, s), 3.59 (3H, s), 3.69 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 3.91 (1H, d, J= 6.8 Hz), 4.17 - 4.21 (1H, m), 4.62 (1H, d, J= 4 Hz), 5.66 (1H, s), 5.72 (1H, s), 6.54 (1H, s)

MS: 458 (<1, M+), 443 (<1), 427 (2), 220 (100), 190 (19)

Exact Mass: Calculated for C24H30N2O7: 458.2053
Found: 458.2046
Compound 36 continued:

>300 x 30
**Carbomethoxy urethane (36a)**

To a solution of 2 g (4.36 mmol) of key intermediate 36 in 40 ml of methylene chloride was added a saturated solution of sodium bicarbonate until bubbling ceased. To this vigorously stirred solution was added 350 µl (1 eq) of methyl chloroformate. As the reaction proceeded, the starting material gradually went into solution and within an hour the reaction was complete. The reaction mixture was taken up in ethyl acetate and ether and partitioned with a solution of saturated sodium chloride. After extracting the aqueous layer, the organic extracts were washed with a combined solution of dilute HCl in saturated sodium chloride and dried over anhydrous magnesium sulfate. Filtration and evaporation yielded 2 g of crude 36a which was used without further purification.

**IR (CH₂Cl₂):**

3520, 3360, 2910, 1660, 1105

**NMR (CDCl₃):**

2.18 (3H, s), 2.25 (3H, s), 3.01 - 3.11 (1H, m), 3.20 (1H, d, J= 17 Hz), 3.33 - 3.40 (1H, m), 3.57 - 3.79 (15 H, m), 4.18 - 4.22 (1H, m), 4.87 and 5.01 (1H, d, J= 6.4 Hz), 5.66 - 6.14 (2H, m), 6.48 (1H, m)

**MS:**

516 (M⁺), 335 (18), 307 (98), 278 (100), 264 (59)

**Exact Mass:**

Calcd. for C₂₅H₃₂N₂O₉ 516.2107

Found 516.2105
Compound 36a continued:
Dibenzyl ether carbomethoxy urethane (58)

To a solution of 544 mg (1.05 mmol) of 36a and 727 mg (5 eq) of pulverized potassium carbonate in 6 ml of N,N-dimethylformamide was added 252 µl (2.2 eq) of benzyl bromide. The reaction mixture was stirred vigorously at 90°C for several hours until dialkylation was complete as evidenced by tlc. After cooling, the reaction mixture was taken up in ether and partitioned several times with dilute sodium chloride solution. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated. A silica gel column separation employing a solvent gradient to 80% ether in hexanes yielded 538 mg (73.3%) of 58 as a white foam.

IR (CH₂Cl₂): 3365, 2890, 1670, 1060

NMR (CDCl₃): 1.97 - 2.05 (1H, m), 2.14 (3H, s), 2.27 (3H, s), 3.09 - 3.29 (3H, m), 3.35 (3H, d, J= 8 Hz), 3.73 (3H, s), 3.77 (3H, s), 3.78 (3H, s), 3.90 (3H, s), 4.14 - 4.18 (1H, m), 4.70 - 4.80 (1H, m), 4.88 - 4.92 (1H, m), 4.96 - 4.99 (2H, m), 5.25 - 5.34 (1H, m), 5.61 - 5.79 (2H, m), 6.42 (1H, s), 7.34 - 7.61 (10H, m)

MS: 696 (2, M⁺), 605 (15), 577 (1), 514 (3), 278 (14), 91 (100)

Exact Mass:
Calcd. for C₄₀H₄₄N₂O₉ 696.3046
Found 696.3039
Compound 58 continued:

![Graph 1](image1)

>290 x 20

![Graph 2](image2)

>650 x 1
>640 x 10

![Graph 3](image3)
Dibenzyl ether N-t-BOC lactam (59)

A solution of 538 mg (0.773 mmol) of 58 in 15ml of benzene was refluxed for one hour using a Dean Stark trap to remove water. After cooling the solution, 951 mg (5 eq) of 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile followed by potassium hydride in mineral oil was added to the reaction mixture which was stirred for several hours at 90°C under argon. Additional potassium hydride was added (to the cooled solution) as necessary to push the reaction to completion. After cooling to 0°C, the reaction was quenched by addition of excess acetic acid and partitioned between methylene chloride and dilute HCl. The organic extract was washed twice with a solution of saturated sodium chloride, dried through an anhydrous sodium sulfate column, and evaporated. A silica gel column separation employing a solvent gradient to 60% ether in hexanes yielded 526 mg (85.5%) of 59 as a light yellow foam.
IR (CH₂Cl₂): 2910, 1700, 1115, 1060

NMR (CDCl₃): 1.17 (9H, d, J = 9.6 Hz), 1.71 - 2.03 (1H, m), 2.14 (3H, d, J = 9 Hz), 2.23 (3H, s), 3.09 - 3.22 (2H, m), 3.33 (3H, m), 3.74 (3H, s), 3.75 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 4.75 (1H, dd, J = 10.5, 14 Hz), 4.90 (1H, d, J = 11.6 Hz), 4.98 (1H, d, J = 11.6 Hz), 5.08 - 5.12 (1H, m), 5.16 - 5.30 (2H, m), 5.88 and 6.04 (1H, d, J = 6.5 Hz), 6.46 (1H, d, J = 15 Hz), 7.30 - 7.49 (10H, m)

MS: 696 (19), 605 (100), 278 (30), 91 (56)

Exact Mass: Calcd. for C₃₃H₅₆N₂O₉ 604.2420
           Found                  604.2420
Compound 59 continued:
α-β unsaturated ethyl ester (65)

To a stirred solution of 1.8 g (2.26 mmol) of 59 in 50 ml of dry methanol at 0°C was added 171 mg (2 molar eq) of sodium borohydride. The reaction was complete in 20 minutes and was quenched with dilute HCl. After stirring for 5 minutes, the acidic reaction mixture was neutralized with saturated sodium bicarbonate solution and evaporated to a small volume. This solution was diluted with ether and partitioned with a combination of dilute HCl and saturated sodium chloride solution. The organic extract was washed with a solution of saturated sodium bicarbonate followed by a solution of saturated sodium chloride and dried over anhydrous magnesium sulfate. Filtration and evaporation yielded a crude mixture of 60 and 61 which was used without purification.

The residue was dissolved in 25 ml of dry benzene and to this solution was added 2.36 g (3 eq) of carboethoxymethylene-triphenylphosphorane. The reaction mixture was refluxed for one hour and evaporated to dryness. A solution of 60% ether in hexanes was added to the residue and the mixture was allowed to stand at 0°C for one hour. After filtering off triphenylphosphine
oxide, the solution was again evaporated to dryness. A silica gel column separation employing a solvent gradient to 60% ether in hexanes yielded 1.7 g (86.7%) of 65 as a clear oil.

IR (CH₂Cl₂): 3420, 2885, 1690

NMR (CDCl₃): 0.91 (2H, s), 1.03 (7H, s), 1.28 (3H, t, J= 6.5 Hz), 1.66 (1H, s), 2.19 (3H, s), 2.21 (3H, s), 2.40 - 2.49 (1H, m), 3.04 - 3.14 (1H, m), 3.19 - 3.28 (1H, m), 3.62 (3H, s), 3.63 (3H, s), 3.72 (3H, s), 3.76 (3H, s), 3.87 (3H, s), 4.12 - 4.22 (2H, m), 4.52 - 4.56 (1H, m), 4.98 (4H, s), 5.71 - 6.18 (1H, m), 6.58 (1H, s), 7.14 - 7.53 (10H, m)

MS: 677 (1), 605 (1), 468 (88), 378 (15), 300 (24), 91 (100)

Exact Mass: Calcd. for C₂₆H₃₆NO₇ 468.2022
Found 468.2010
Compound 65 continued:
**Dibenzyl ether allyl alcohol (67)**

To a solution of 682 mg (0.786 mmol) of 65 in 7 ml of methylene chloride was added 1.6 ml (3 eq) of 1.5M diisobutylaluminum hydride in toluene at -78°C under argon. After stirring for 30 minutes, the reaction mixture was warmed to room temperature and quenched with a combination of dilute HCl and saturated sodium chloride solution. After thoroughly extracting the aqueous layer, the organic extracts were washed with a combined solution of saturated sodium chloride and saturated sodium bicarbonate, dried through an anhydrous sodium sulfate column, and evaporated. A silica gel column separation employing a solvent gradient to 80% ether in hexanes yielded 499 mg (76.9%) of 67 as an off-white foam.
IR (CH$_2$Cl$_2$): 3410, 2880, 1675, 1060

NMR (CDCl$_3$): 0.95 (2H, s), 1.06 (7H, s), 1.74 (1H, bs), 2.18 (3H, s), 2.21 (3H, s), 2.24 - 2.38 (1H, m), 2.96 - 3.07 (1H, m), 3.25 - 3.32 (1H, m), 3.63 (3H, s), 3.64 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.89 (3H, s), 4.15 (2H, bs), 4.36 - 4.54 (1H, m), 4.96 (4H, s), 5.94 (1H, bs), 6.60 (1H, s), 7.31 - 7.64 (10H, m)

MS: 605 (4), 468 (5), 426 (100), 335 (25), 300 (36), 91 (72)

Exact Mass: Calcd. for C$_{24}$H$_{28}$NO$_6$ 426.1916
Found 426.1913
Compound 67 continued:

Graph 1:

Graph 2:

Graph 3:

Graph 4:
Dibenzy ether allyl acetate (69)

A mixture of 290 mg (0.351 mmol) of 67, 1.5 ml of acetic anhydride, and 1.5 ml of pyridine was stirred at 45°C for 30 minutes then evaporated to dryness. A silica gel column separation using 60% ether in hexanes yielded 241 mg (79%) of 69 as a clear oil.

IR (CH2Cl2):
3420, 2870, 1685

NMR (CDCl3):
0.94 (2H, s), 1.05 (7H, s), 1.68 (1H, s), 2.05 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 2.40 - 2.44 (1H, m), 3.02 (1H, dd, J= 12, 15.6 Hz), 3.20 - 3.31 (1H, m), 3.61 (3H, s), 3.65 (3H, s), 3.72 (3H, s), 3.77 (3H, s), 3.87 (3H, s), 4.09 - 4.28 (1H, m), 4.30 - 4.57 (1H, m), 4.58 (1H, bs), 4.87 (4H, s), 5.87 - 6.06 (1H, m), 6.58 (1H, s), 7.30 - 7.61 (10H, m)

MS:
617 (1), 605 (4), 468 (100), 300 (7), 91 (42)

Exact Mass:
Calcd. for C26H30NO7 468.2022
Found 468.2010
Compound 69 continued:
Dibenzyl ether amine (69a)

A solution of 241 mg (0.278 mmol) of 69 in 3 ml of trifluoroacetic acid was stirred at room temperature for 10 minutes. Evaporation yielded the salt of 69a as an orange foam which was used without purification.

IR (CH$_2$Cl$_2$): 2865, 1685

NMR (CDCl$_3$):
- 1.26 (1H, s), 1.44 (2H, s), 2.08 (3H, s), 2.21 (3H, s), 2.32 (3H, s), 2.29 - 2.37 (1H, m), 2.65 (1H, dd, J = 12, 15.5 Hz), 3.14 (1H, t, J = 10 Hz), 3.28 (1H, d, J = 11 Hz), 3.65 (3H, s), 3.69 (3H, s), 3.70 (3H, s), 3.82 (3H, s), 3.86 (3H, s), 4.29 (1H, bs), 4.65 (1H, t, J = 4.3 Hz), 4.91 (1H, bs), 5.04 (4H, s), 5.35 - 6.06 (2H, m), 6.65 (1H, s), 7.26 - 7.58 (10H, m)

MS:
- 437 (33), 410 (100), 319 (33), 91 (88)
Compound 69a continued:
Diphenol amine (70)

A solution of 91.5 mg (0.119 mmol) of 69a in 1.5 ml of dry methylene chloride was stirred at 0°C. BCl₃ gas was bubbled through the solution until the reaction was complete as evidenced by tlc. The reaction was quenched by slow addition of a solution of saturated sodium bicarbonate and partitioned with saturated sodium chloride. After thoroughly extracting the aqueous layer, the methylene chloride extracts were dried through an anhydrous sodium sulfate column and evaporated. Separation on a preparative silica gel tlc plate (developed twice in 5% methanol in methylene chloride) afforded 56mg (79.9%) of 70 as a white foam.

IR (CH₂Cl₂): 3525, 2900, 1690

NMR (CDCl₃): 1.25 (1H, s), 2.12 (3H, s), 2.20 (3H, s), 2.22 (3H, s), 2.52 - 2.60 (1H, m), 2.75 (1H, bs), 2.96 - 3.05 (1H, m), 3.06 - 3.12 (1H, m), 3.29 (1H, dd, J= 6.8, 15.5 Hz), 3.64 (3H, s), 3.69 (3H, s), 3.74 (3H, s), 3.78 (3H, s), 3.82 (3H, s), 4.62 - 4.71 (2H, m), 5.30 - 5.66 (1H, m), 5.92 - 6.02 (1H, m), 6.58 (1H, s)

MS: 378 (20), 347 (15), 320 (40), 210 (100)

Exact Mass:  Calcd. for C₁₉H₂₄NO₇ 378.1552
               Found       378.1544
Compound 70 continued:
Tetracyclic diphenol amine (71a)

To a solution of 29 mg (0.0493 mmol) of 70 in 300 μl of dry acetonitrile was added 28.5 mg (3 eq) of carbobenzoxyaminoacetalddehyde. The reaction mixture was stirred overnight at 40°C under argon then evaporated to dryness. Separation on a preparative silica gel tic plate (ether) allowed removal of the excess reagent and repeated separation on a tic plate (3% methanol in methylene chloride) afforded 9.3 mg (24.7%) of 71a as a light orange foam.

IR (CH2Cl2): 3505, 2900, 1685

NMR (CDCl3):
1.25 (1H, s), 1.95 (3H, s), 2.20 (3H, s), 2.22 (3H, s), 2.64 - 2.68 (1H, m), 2.94 (1H, t, J= 9 Hz), 3.09 - 3.24 (2H, m), 3.47 - 3.52 (1H, m), 3.62 (3H, s), 3.63 (6H, s), 3.73 (3H, s), 3.75 (3H, s), 4.34 - 4.36 (1H, m), 4.47 (1H, d, J= 3.6 Hz), 5.09 (2H, s), 5.74 - 5.81 (2H, m), 7.32 (5H, s)

MS: 605 (15), 539 (12), 468 (50), 426 (40), 410 (30), 378 (32), 300 (44), 278 (36), 220 (26), 91 (100)

Exact Mass: Calcd. for C33H39N3O8 605.2737
Found 605.2742
71a (top isomer)
Compound 71a continued:
**Diphenol trifluoroacetamide (72)**

A solution of 7 mg (0.0091 mmol) of 71a and 12.85 µl (10 eq) of trifluoroacetic anhydride in 200 µl of pyridine was stirred at room temperature for 30 minutes. Several drops of methanol were added and the mixture stirred for 5 minutes to regenerate the diphenol. The reaction mixture was evaporated to a small volume and partitioned between methylene chloride and a combined solution of dilute HCl and saturated sodium chloride. After washing the aqueous layer, the organic extracts were dried through an anhydrous sodium sulfate column and evaporated. Separation on a preparative silica gel tlc plate (3% methanol in methylene chloride) afforded 4.75 mg (60.89%) of 72 as a beige foam.
IR (CH2Cl2): 3520, 2900, 1685

NMR (CDCl3):
1.26 (1H, s), 2.09 (3H, s), 2.21 (3H, s), 2.22 (3H, s), 2.86 - 2.99 (2H, m), 3.40 (1H, dd, J= 6.5, 15.6 Hz), 3.51 - 3.56 (1H, m), 3.61 (3H, s), 3.66 (3H, s), 3.67 (3H, s), 3.72 (3H, s), 3.74 (3H, s), 4.33 (1H, bs), 4.66 (2H, d, J= 5.7 Hz), 4.75 - 4.85 (1H, m), 5.14 (2H, s), 5.57 - 5.61 (2H, m), 5.78 - 6.11 (2H, m), 6.19 (1H, bs), 6.33 (1H, bs), 7.36 (5H, s)

MS:
539 (<1), 474 (1), 420 (<1), 378 (100)

Exact Mass:
Calcd. for C19H24NO7 378.1552
Found 378.1544
Compound 22 continued:
Triacetate trifluoroacetamide (73)

A mixture of 46.7 mg (0.0543 mmol) of 72, 350 µl of acetic anhydride, and 350 µl of pyridine was stirred at 40°C for one hour then evaporated to dryness. Separation on a preparative silica gel TLC plate (80% ether in hexanes) afforded 49 mg (95.7%) of 73 as a white foam.

IR (CH₂Cl₂): 3400, 1685, 1185

NMR (CDCl₃):
1.26 (1H, s), 2.05 (3H, s), 2.22 (6H, s), 2.30 (3H, s), 2.40 (3H, s), 2.82 (1H, dd, J= 12, 15.6 Hz), 2.95 (1H, dd, J= 12, 15.6 Hz), 3.39 - 3.58 (2H, m), 3.62 (3H, s), 3.67 (3H, s), 3.68 (3H, s), 3.69 (3H, s), 3.72 (3H, s), 4.33 - 4.37 (1H, m), 4.63 (2H, d, J= 5.7 Hz), 5.12 (2H, s), 5.35 (1H, t, J= 7 Hz), 5.60 - 5.66 (1H, m), 5.89 - 6.10 (1H, m), 7.34 (5H, s)

MS: 623 (1), 453 (7), 420 (100), 378 (52)

Exact Mass: Calcd. for C₃₂H₃₉N₂O₁₀  623.2604
Found 623.2606
Compound 73 continued:

>500 x 20

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[Graphs and data plots related to compound 73]
Trifluoroacetamide dithiocetal (75)

A solution of 20 mg (0.0212) of 73 and 5.39mg (1 eq) of osmium tetroxide in 500 μl of tetrahydrofuran containing 5 μl (3 eq) of pyridine was stirred overnight at room temperature. Hydrogen sulfide gas was bubbled through the solution and the resulting mixture was filtered through Celite and evaporated to yield a crude mixture of diols.

The residue and 45.3 mg (10 eq) of sodium metaperiodate were dissolvled in 1 ml of a 4:1 solution of methanol and water and the mixture stirred at room temperature for 2.5 hours. The reaction mixture was partitioned between methylene chloride and a saturated solution of sodium chloride. After thoroughly extracting the aqueous layer, the organic extracts were dried through an anhydrous sodium sulfate column and evaporated to yield aldehyde 74 which was used without purification.

The residue was dissolved in 500 μl of dry methylene chloride and to this was added 6.27 μl (4 eq) of ethanethiol and 3.91 μl (1.5 eq) of boron trifluoride etherate. After stirring at room temperature for 20 minutes, the reaction mixture was partitioned with a combined solution of
saturated sodium chloride and saturated sodium bicarbonate. After thoroughly extracting the aqueous layer, the organic extracts were dried through an anhydrous sodium sulfate column and evaporated. Separation on a preparative silica gel tlc plate (70% ether in hexanes) afforded 9.9 mg (47.7% - 3 steps) of 75 as a white foam.

Characterization of aldehyde 74:

IR (CH$_2$Cl$_2$): 3420, 2920, 1689, 1185

NMR (CDCl$_3$): 1.25 (1H, s), 2.19 (3H, s), 2.24 (3H, s), 2.30 (3H, s), 2.44 (3H, s), 2.79 (1H, bs), 2.96 - 3.05 (1H, m), 3.44 - 3.73 (15H, m), 4.32 (1H, dd, J= 5.3, 13.3 Hz), 5.07 - 5.16 (2H, m), 5.37 (1H, bs), 7.34 (5H, s), 9.85 (1H, bs)

MS: 677 (55), 635 (75), 392 (45), 350 (100), 308 (60), 91 (38)

Characterization of dithioacetal 75:

IR (CH$_2$Cl$_2$): 3420, 2920, 1770, 1690, 1110, 1035

NMR (CDCl$_3$): 1.26 - 1.39 (6H, m), 1.60 (1H, bs), 2.19 (3H, s), 2.22 (3H, s), 2.30 (3H, s), 2.39 (3H, s), 2.62 - 2.95 (5H, m), 3.02 - 3.11 (1H, m), 3.58 (3H, s), 3.70 (6H, s), 3.71 (3H, s), 3.74 (3H, s), 3.95 - 4.05 (1H, m), 4.66 (1H, bs), 5.12 (2H, d, J= 2 Hz), 5.29 (1H, m), 5.75 (1H, bs), 7.34 (5H, s)

MS: 845 (1), 801 (2), 699 (1), 694 (2), 652 (1), 609 (3), 456 (100)

Exact Mass:

Calcd. for $C_{21}H_{30}NO_6S_2$ 456.1514
Found 456.1510
Compound 74 continued:
Compound Z5 continued:
Diphenol amine dithiacetal (77)

To a vigorously stirred solution of 9.9 mg (0.0101 mmol) of 75 in 1.1 ml of a 10:1 mixture of methanol and water was added 23.5 µl (7 eq) of 3N sodium hydroxide. The reaction mixture was stirred for 8 hours at 50°C. After adding dry ice, the solution was evaporated to a small volume and partitioned between methylene chloride and a combined solution of dilute HCl and saturated sodium chloride. After extracting the aqueous layer thoroughly, the organic extracts were dried through an anhydrous sodium sulfate column and evaporated. Separation on a preparative silica gel TLC plate (5% methanol in methylene chloride) afforded 5.8 mg (71.9%) of 77 as a beige foam.

IR (CH₂Cl₂): 3520, 2920, 1690

NMR (CDCl₃): 1.22 (3H, t, J= 7.4 Hz), 1.33 (3H, t, J= 7.4 Hz), 2.20 (3H, s), 2.22 (3H, s), 2.46 - 2.56 (2H, m), 2.63 - 2.86 (4H, m), 3.18 - 3.35 (2H, m), 3.64 (3H, s), 3.66 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 4.12 (1H, bd, J= 9.5 Hz), 4.32 (1H, m), 4.77 (1H, bs), 5.09 (2H, d, J= 3.6 Hz), 5.41 - 5.50 (1H, m), 7.34 (5H, s)

MS: 635 (53), 573 (18), 556 (27), 414 (48), 385 (53), 277 (100)

Exact Mass: Calcd. for C₃₁H₄₅N₂O₈S₂ 635.2460
Found 635.2470
Compound "Z" continued:
Diphenol nitrile (79)

To a solution of 50 mg (0.0625 mmol) of 77 in 1.5 ml of a 4:1 mixture of acetonitrile and water was added 86 mg (5 eq) of mercuric chloride. The solution was buffered with 32 mg (5 eq) of calcium carbonate and stirred at room temperature under argon for 3 hours. After filtration through Celite, the reaction mixture was partitioned between methylene chloride and a combined solution of dilute HCl and saturated sodium chloride. After thoroughly extracting the aqueous layer, the organic extracts were dried through an anhydrous sodium sulfate column and evaporated to yield the aminal 78 as a light orange oil which was used without purification.

The residue was dissolved in 1.5 ml of dry methylene chloride and to this solution was added 10.7 µl (8 eq) of trimethylsilyl cyanide and an excess of zinc chloride. After stirring at room temperature for 10 minutes, the mixture was filtered through Celite and evaporated to dryness. Separation on a preparative silica gel tlc plate (5% methanol in methylene chloride) afforded 17 mg (38.8% - 2 steps) of 79 as a beige foam.
Characterization of aminal 78:

**IR (CH$_2$Cl$_2$):**
3520, 2920, 1700, 1410, 1230, 1105

**NMR (CDCl$_3$):**
1.26 (2H, m), 2.10 - 2.22 (5H, m), 2.68 - 2.74 (2H, m), 3.08 - 3.21 (3H, m), 3.35 - 3.49 (3H, s), 3.58 - 3.78 (15H, m), 4.46 - 4.68 (3H, m), 4.82 - 4.86 (2H, m), 5.43 - 5.63 (3H, m), 7.26 - 7.37 (5H, m)

**MS:**
537 (6), 513 (100), 395 (42), 91 (24)

Characterization of nitrile 79:

**IR (CH$_2$Cl$_2$):**
3523, 2920, 1710

**NMR (CDCl$_3$):**
1.25 (2H, s), 2.10 (3H, s), 2.18 (3H, s), 2.73 - 2.79 (1H, m), 3.16 - 3.32 (4H, m), 3.41 - 3.48 (2H, m), 3.60 (3H, s), 3.63 (3H, s) 3.67 (3H, s), 3.70 (3H, s), 3.74 (3H, s), 4.02 (1H, s), 4.14 1H, s), 4.34 (1H, bs), 4.78 - 4.93 (2H, m), 5.49 (1H, s), 5.63 1H, s), 5.77 - 5.84 (2H, m), 7.16 - 7.31 (5H, m)

**MS:**
538 (30), 513 (100), 395 (54), 278 (9), 91 (51)

**Exact Mass:**
Calcd. for C$_{29}$H$_{32}$N$_3$O$_8$ 538.2189
Found 538.2194
Compound 78 continued:
Compound 79 continued:
**Diphencarbobenzyxurethane (36b)**

To a stirred solution of 1.1 g (2.40 mmol) of 36 and 4.2 ml (10 eq) of N,N-dimethylaniline in 50 ml of chloroform was added 795 µl (1.2 eq) of benzyl chloroformate. After 10 minutes, the reaction mixture was partitioned between methylene chloride and a combined solution of dilute HCl and saturated sodium chloride. The aqueous layer was thoroughly extracted and the organic layers washed with a solution of saturated sodium chloride followed by a solution of saturated sodium bicarbonate. The methylene chloride extracts were dried through anhydrous sodium sulfate column and evaporated. A silica gel column separation employing a solvent gradient to 95% ether in hexanes yielded 1.2 g (84.5%) of 36b as a white foam.

**IR** (CH$_2$Cl$_2$): 3540, 3380, 2960, 1670, 1105

**NMR** (CDCl$_3$): 2.03 - 2.14 (2H, m), 2.19 (3H, s), 2.25 (3H, s), 3.03 (1H, dd, J= 7, 17.6 Hz), 3.10 - 3.27 (1H, m), 3.38 (1H, d, J= 13 Hz), 3.57 (3H, s), 3.66 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 4.21 (1H, bd, J= 8 Hz), 4.94 and 5.03 (1H, d, J= 6.5), 5.15 (2H, s), 5.73 - 5.89 (2H, m), 6.03 (1H, s), 6.49 (1H, s), 7.33 - 7.36 (5H, m)

**MS:** 592 (2, M$^+$), 468 (5), 457 (8), 367 (6), 339 (4), 310 (7), 220 (38), 91 (100)

**Exact Mass:**
Calcld. for C$_{32}$H$_{36}$N$_2$O$_9$ 592.2420
Found 592.2408
Compound 36b continued:
Dibenzyl ether carbobenzoxy urethane (36c)

To a solution of 1.2 g (2.03 mmol) of 36b and 2.8 g (10 eq) of pulverized potassium carbonate in 20 ml of dry N,N-dimethylformamide was added 660 µl (3 eq) of benzyl bromide. The reaction mixture was stirred vigorously at 90°C for 2 hours at which time dialkylation was complete as evidenced by tlc. After cooling, the reaction mixture was taken up in ether and partitioned several times with dilute sodium chloride solution. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated. A silica gel column separation employing a solvent gradient to 80% ether in hexanes yielded 1.4 g (89.7%) of 36c as a light yellow oil.

IR (CH$_2$Cl$_2$): 3365, 2900, 1675, 1060

NMR (CDCl$_3$): 1.86 - 2.07 (2H, m), 2.14 (3H, s), 2.27 (3H, s), 3.09 - 3.25 (3H, m), 3.31 (3H, m), 3.73 (3H, d, J= 4.6 Hz), 3.78 (3H, s), 3.90 (3H, s), 4.14 - 4.17 (1H, m), 4.48 (1H, d, J= 10 Hz), 4.82 (1H, d, J= 10 Hz), 4.93 - 5.05 (2H, m), 5.13 - 5.28 (2H, m), 5.60 - 5.81 (2H, m), 6.40 (1H, d, J= 12.7 Hz), 7.26 - 7.61 (15 H, m)

MS: 773 (<1, M$^+$ + 1), 681 (2), 637 (5), 390 (4), 310 (26), 220 (36), 91 (100)

Exact Mass: Calcd. for C$_{48}$H$_{48}$N$_2$O$_9$ 772.3359
Found 772.3339
Compound 36c continued:

>200 x 5

>340 x 40

510 550 600 650 700 750

100

10 60 100 150 200 250

100

760 800

100
**Dibenzyl ether N-t-BOC lactam (36d)**

A solution of 145 mg (0.188 mmol) of 36c in 8 ml of benzene was refluxed for 20 minutes using a Dean Stark trap to remove water. After cooling the solution, 231 mg (5 eq) of 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile followed by potassium hydride in mineral oil was added to the reaction mixture which was stirred for several hours at 90°C under argon. Additional potassium hydride was added (to the cooled solution) as necessary to push the reaction to completion. After cooling to 0°C, the reaction was quenched by addition of excess acetic acid and partitioned between methylene chloride and dilute HCl. The organic extract was washed twice with a solution of saturated sodium chloride, dried through an anhydrous sodium sulfate column, and evaporated. A silica gel column separation employing a solvent gradient to 80% ether in hexanes yielded 142 mg (86.7%) of 36d as a light yellow foam.
IR (CH₂Cl₂):  
2880, 1700, 1060

NMR (CDCl₃):  
1.16 (9H, d, J= 5.6 Hz), 1.63 - 2.06 (2H, m), 2.13 (3H, s), 2.24 (3H, s), 3.14 - 3.20 (2H, m), 3.27 (3H, d, J= 11 Hz), 3.32 - 3.38 (1H, m), 3.74 (3H, s), 3.75 (3H, s), 3.78 (3H, d, J= 2 Hz), 4.47 (1H, d, J= 10 Hz), 4.80 (1H, d, J= 10 Hz), 4.85 - 5.01 (2H, m), 5.11 - 5.27 (3H, m), 5.97 (1H, d, J= 6.7 Hz), 6.05 (1H, d, J= 6.7 Hz), 6.39 (1H, s), 6.50 (1H, s), 7.20 - 7.49 (15H, m)

MS:  
772(<1, M⁺), 681 (<1), 637 (1), 390 (<1), 310 (4), 220 (9), 91 (100)

Exact Mass:  
Calcd. for C₉₈H₄₀N₂O₇ 636.2835  
Found 636.2835
Compound 36d continued:
Hydroxymethyl dibenzyl ether (87)

To a solution of 196 mg (0.225 mmol) of 36d in 25 ml of dry methanol was added sodium borohydride until the reduction was complete as evidenced by tlc. The reaction was quenched with dilute HCl and after stirring for 5 minutes was neutralized with saturated sodium bicarbonate solution then evaporated to a small volume. This solution was diluted with ether and partitioned with a combination of dilute HCl and saturated sodium chloride solution. After extracting the aqueous layer, the organic extracts were washed with a solution of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated. A silica gel column separation employing a solvent gradient to 80% ether in hexanes yielded 175 mg (88.9%) of 87 as a white foam.
IR (CH$_2$Cl$_2$): 3420, 2900, 1680, 1060

NMR (CDCl$_3$): 0.94 (3H, s), 1.05 (6H, s), 2.17 (3H, s), 2.22 (3H, s), 3.19 (3H, bs), 3.50 (3H, s), 3.65 (3H, s), 3.77 (3H, s), 3.87 (3H, s), 3.94 - 4.41 (3H, m), 4.95 - 5.81 (5H, m), 6.54 (1H, s), 7.32 - 7.78 (15H, m)

MS: 637 (<1), 577 (<1), 476 (27), 397 (10), 342 (42), 300 (95), 91 (100)

Exact Mass: Calcld. for C$_{25}$H$_{30}$NO$_6$ 476.2073
Found 476.2073
Compound 87 continued:

[Graphs and images with labeled axes and values]
Diphenol homoallyl urethane (91)

A solution of 400 mg (0.457 mmol) of 87 in 5 ml of absolute ethanol was hydrogenated over 10 ml of a suspension of Raney nickel in ethanol at a hydrogen pressure of 1100 psi for 2 hours at 80°C. Filtration through Celite was followed by evaporation to yield diphenol 90 which was used without purification. mp 165-166°C (chloroform).

The residue was dissolved in 4 ml of methylene chloride and to this solution was added saturated sodium bicarbonate until bubbling ceased. To the vigorously stirred solution was added 184 μl (3 eq) of homoallyl chloroformate. After 20 minutes, the reaction mixture was partitioned with a combined solution of dilute HCl and saturated sodium chloride. The aqueous layer was thoroughly washed and the organic extracts were dried through an anhydrous column of sodium sulfate and evaporated. A silica gel column separation employing a solvent gradient to 95% ether in hexanes yielded 255 mg (84.6% - 2 steps) of 91 as a white foam.
Characterization of diphenol amine 90:

IR (CH₂Cl₂):
3540, 2900, 1650, 1110, 1050, 1000

NMR (CDCl₃):
1.25 (3H, s), 1.34 (6H, s), 1.89 (3H, bs), 2.16 (3H, s), 2.20 (3H, s), 2.32 - 2.48 (2H, m), 2.72 - 2.85 (2H, m), 2.96 - 3.00 (1H, m), 3.54 (3H, s), 3.63 (3H, s), 3.71 (3H, s), 3.78 (3H, s), 4.65 (2H, m), 5.36 (1H, m), 6.51 (1H, s)

MS:
489 (<1), 445 (<1), 307 (<1), 300 (<1), 252 (100), 191 (7)

Exact Mass:
Calcd. for C₁₃H₁₈NO₄
252.1236
Found
252.1231

Characterization of homoallyl urethane diphenol 91:

IR (CH₂Cl₂):
3520, 2900, 1660, 1105, 1050, 1000

NMR (CDCl₃):
0.99 (3H, s), 1.06 (6H, s), 2.20 (3H, s), 2.21 (3H, s), 2.41 - 2.54 (3H, m), 3.06 - 3.38 (3H, m), 3.60 - 3.77 (12H, m), 3.99 - 4.20 (2H, m), 5.06 - 5.16 (1H, m), 5.45 - 5.81 (1H, m), 6.70 (1H, s)

MS:
587 (<1), 489 (<1), 350 (100), 252 (39), 210 (80)

Exact Mass:
Calcd. for C₁₉H₂₄NO₆
350.1603
Found
350.1596
Compound 90 continued:
Compound 91 continued:

\[ \text{~400} \times 40 \]

\[ \text{~650} \]

\[ \text{~510} \]
Diphenol acetate (93)

A mixture of 402 mg (0.609 mmol) of 91, 2 ml of acetic anhydride, and 2 ml of pyridine was stirred at 50°C for one hour. Evaporation yielded crude 92 as a yellow foam which was used without purification.

The residue and 192 μl (10 eq) of anhydrous hydrazine were dissolved in 4 ml of dry methanol. After stirring for 15 minutes under argon, the reaction was quenched by adding a small amount of dilute HCl. The reaction mixture was partitioned between methylene chloride and a combined solution of dilute HCl and saturated sodium chloride. The aqueous layer was thoroughly extracted, and the organic extracts were dried through an anhydrous sodium sulfate column and evaporated. Separation on a circular preparative silica gel tlc plate (2 mm) employing a solvent gradient to 5% methanol in methylene chloride afforded 373 mg (87.2% - 2 steps) of 93 as a yellow foam.
Characterization of triacetate 92:

IR (CH$_2$Cl$_2$): 3425, 2900, 1685

NMR (CDCl$_3$):

1.03 - 1.09 (9H, m), 1.99 (3H, s), 2.20 (3H, s), 2.22 (3H, s), 2.26 (3H, s), 2.38 (3H, s), 2.63 (1H, dd, J= 11, 15 Hz), 3.03 - 3.20 (2H, m), 3.32 (1H, dd, J= 6.7, 16 Hz), 3.67 (3H, s), 3.70 (3H, s), 3.72 (6H, s), 4.17 (1H, bs), 4.28 - 4.34 (1H, m), 4.47 - 4.54 (1H, m), 5.08 - 5.30 (1H, m), 5.93 (1H, bs), 6.82 (1H, s)

MS: 434 (27), 392 (17), 352 (14), 252 (100)

Exact Mass: Calcd. for C$_{22}$H$_{28}$NO$_6$ 434.1814
Found 434.1805

Characterization of diphenol acetate 93:

IR (CH$_2$Cl$_2$): 3530, 2900, 1685, 1045

NMR (CDCl$_3$):

1.02 (3H, s), 1.05 (6H, s), 2.04 (3H, s), 2.20 (3H, s), 2.21 (3H, s), 2.43 (3H, bs), 2.53 - 2.72 (2H, m), 2.99 (1H, dd, J= 12.3, 15.5 Hz), 3.18 (1H, dd, J= 2.6, 14.5 Hz), 3.32 (1H, dd, J= 6.8, 15.5 Hz), 3.62 - 3.76 (12H, m), 4.03 - 4.41 (2H, m), 4.52 - 4.79 (1H, m), 5.03 - 5.14 (1H, m), 5.59 - 5.98 (1H, m), 6.73 (1H, s)

MS: 434 (47), 392 (35), 350 (57), 252 (100), 210 (29), 91 (39)

Exact Mass: Calcd. for C$_{16}$H$_{23}$NO$_6$ 349.1525
Found 349.1517
Compound 92 continued:

[Graphs and plots with no textual description]
Compound 93 continued:
Tetracyclic diphenol amine (96a and 96b)

A solution of 352 mg (0.501 mmol) of 93 in 5 ml of trifluoroacetic acid was stirred at room temperature for 15 minutes. Evaporation yielded the salt of 94 as a beige foam which was used without purification.

The residue and 188 mg (2 eq) of the phthalimide aldehyde 95 were dissolved in 5 ml of dry acetonitrile. The mixture was stirred at 40°C for 30 minutes then evaporated to dryness. Separation on a circular preparative silica gel tlc plate (2 mm) employing a solvent gradient to 4% methanol in methylene chloride resulted in crude purification. Reseparation of each isomer on a circular tlc plate (1 mm) using the same solvent system afforded 164 mg of 96a and 147 mg of 96b both as a light yellow foam. (combined yield - 80.2% over 2 steps).
Characterization of diphenol amine 94:

IR (CH$_2$Cl$_2$): 3540, 3380, 2900, 1685

NMR (CDCl$_3$): 2.14 (3H, s), 2.21 (3H, s), 2.23 (3H, s), 2.41 - 2.49 (3H, m), 2.61 - 2.78 (1H, bs), 3.03 - 3.16 (2H, m), 3.37 - 3.44 (1H, m), 3.65 (3H, s), 3.71 (3H, s), 3.77 (3H, s), 3.83 (3H, s), 4.14 - 4.30 (2H, bm), 4.57 (1H, bs), 5.08 (1H, bs), 5.31 - 5.46 (1H, m), 5.73 - 5.93 (1H, bs), 6.64 (1H, s)

MS: 602 (<1, M$^+$), 542 (2), 362 (8), 361 (100), 294 (66), 210 (70)

Exact Mass:
- Calcd. for C$_{31}$H$_{42}$N$_2$O$_{10}$ 602.2839
- Found 602.2829

Characterization of cyclization product 96a (top isomer):

IR (CH$_2$Cl$_2$): 3510, 2900, 1690, 1105, 1045, 1000

NMR (CDCl$_3$): 1.25 (1H, s), 1.81 (3H, s), 2.12 (3H, s), 2.17 (3H, s), 2.41 - 2.78 (3H, m), 2.95 - 3.01 (1H, m), 3.08 - 3.13 (1H, m), 3.36 (1H, d, J= 15.5 Hz), 3.54 (3H, s), 3.56 (3H, s), 3.59 (3H, s), 3.65 (3H, s), 3.91 (1H, dd, J= 8, 13.5 Hz), 4.19 - 4.43 (2H, bm), 4.73 (1H, s), 5.09 - 5.84 (3H, m), 7.69 - 7.80 (4H, m)

MS: 613 (<1), 553 (96), 361 (12), 220 (30), 160 (14), 55 (100)

Exact Mass:
- Calcd. for C$_{21}$H$_{21}$N$_2$O$_5$ 381.1450
- Found 381.1449

Characterization of cyclization product 96b (bottom isomer):

IR (CH$_2$Cl$_2$): 3530, 2900, 1685, 1105, 1045, 1000

NMR (CDCl$_3$): 1.24 (2H, s), 1.97 (3H, s), 1.99 (3H, s), 2.21 (3H, s), 2.38 (2H, bs), 2.61 (1H, bs), 2.93 - 3.30 (5H, m), 3.36 - 3.41 (1H, m), 3.66 (3H, s), 3.75 (6H, s), 3.76 (3H, s), 3.93 (1H, dd, J= 4.3, 14 Hz), 4.05 - 4.31 (2H, m), 4.45 (1H, bs), 4.76 (1H, dd, J= 4, 11 Hz), 4.97 - 5.78 (3H, m), 7.62 (4H, s)

MS: 613 (18), 553 (35), 392 (21), 381 (100), 294 (21), 220 (52), 160 (36)

Exact Mass:
- Calcd. for C$_{32}$H$_{41}$N$_2$O$_{10}$ 613.2761
- Found 613.2768
24
Compound 94 continued:
Compound 96a continued:
Compound 96b continued:
**Diphenol methylamine (122)**

To a solution of 1.1 g (2.40 mmol) of key intermediate 36, 360 μl (2 eq) of 37% formaldehyde solution, and 92.5 μl (0.5 eq) of trifluoroacetic acid in 40 ml of methanol was added 79.4 mg (0.5 eq) of sodium cyanoborohydride. After stirring for 10 minutes the reaction mixture was evaporated to a small volume. The solution was diluted with methylene chloride and partitioned with a combined solution of saturated sodium chloride and saturated sodium carbonate. After thoroughly extracting the aqueous layer, the organic extracts were dried through an anhydrous sodium sulfate column and evaporated. A silica gel column separation employing a solvent gradient to 10% methanol in ether yielded 1 g (88.3%) of 122 as a white foam.

**IR (CH$_2$Cl$_2$):**

3540, 3380, 2900, 1660, 1110, 1050, 1000

**NMR (CDCl$_3$):**

2.05 (1H, dd, J= 11.7, 14 Hz), 2.19 (3H, s), 2.25 (3H, s), 2.48 (3H, s), 2.94 (1H, d, J= 17.9 Hz), 3.10 (1H, dd, J= 7, 17.9 Hz), 3.32 (1H, dd, J= 2, 14 Hz), 3.56 (3H, s), 3.68 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 4.23 - 4.29 (1H, m), 4.34 (1H, d, J= 4 Hz), 5.69 (1H, s), 5.90 (1H, s), 6.49 (1H, s)

**MS:**

472 (M$^+$), 457 (10), 235 (55), 220 (100), 205 (53), 190 (26)

**Exact Mass:**

Calcd. for C$_{25}$H$_{32}$N$_2$O$_7$ 472.2209

Found 472.2217
Compound 122 continued:
**Diphenol hydroxymethy methylamine (120)**

To a solution of 900 mg (1.91 mmol) of 122 and 4.3 ml (30 eq) of 37% formaldehyde solution in 20 ml of n-butanol was added 3.8 ml (1 eq) of 0.5 N standardized sodium hydroxide solution. The reaction mixture was stirred at 100°C for one hour and then cooled to room temperature. The mixture was partitioned between ethyl acetate and a solution of dilute sodium chloride. The aqueous layer was thoroughly extracted and the organic extracts dried over anhydrous magnesium sulfate, filtered, and evaporated. A silica gel column separation employing a solvent gradient to 15% methanol in ether yielded 755 mg (78.9%) of 120 as a white foam.

**IR (CH$_2$Cl$_2$):**

3525, 3325 (b), 2940, 1645, 1110, 1050, 1000

**NMR (CDCl$_3$):**

2.13 (1H, dd, J = 7, 10.7 Hz), 2.19 (3H, s), 2.25 (3H, s), 2.42 (3H, s), 2.96 (1H, d, J = 18 Hz), 3.08 (1H, dd, J = 7, 18 Hz), 3.45 (1H, s), 3.60 (3H, s), 3.69 (3H, s), 3.75 (3H, s), 3.77 (3H, s) 4.01 - 4.06 (1H, m), 4.37 - 4.43 (2H, m), 4.69 (1H, d, J = 12 Hz), 6.43 (1H, bs), 7.17 (1H, s)

**MS:**

484 (8), 469 (6), 234 (100), 220 (40), 218 (36), 204 (30), 190 (23)
Compound 120 continued:
Dibenzyl ether hydroxymethyl methyamine (120a)

To a solution of 504 mg (1.00 mmol) of 120 and 196 μl (1.8 eq) of benzyl bromide in 7 ml of N,N-dimethylformamide was added 1.8 ml (1.8 eq) of 1 N potassium t-butoxide in t-butanol under argon. The reaction mixture was stirred at room temperature for 15 minutes, quenched with an aqueous ethanol solution of silver nitrate, and partitioned between ether and a dilute solution of sodium chloride. After filtering, the organic layer was again washed several times with a dilute sodium chloride solution, dried over magnesium sulfate, filtered, and evaporated. A silica gel column separation employing a solvent gradient to 5% methanol in ether yielded 478 mg (69.8%) of 120a as a yellow oil.
IR (CH₂Cl₂):
3595, 2900, 1665, 1055, 1000

NMR (CDCl₃):
2.12 (1H, dd, J= 11, 14 Hz), 2.18 (3H, s), 2.27 (3H, s), 2.29 (3H, s), 2.88 - 2.98 (1H, m), 3.05 (1H, dd, J= 6.6, 18 Hz), 3.39 (3H, s), 3.50 (1H, d, J= 6 Hz), 3.72 (3H, s), 3.82 (3H, s), 3.86 (3H, s), 4.01 - 4.06 (1H, m), 4.12 (1H, d, J= 4 Hz), 4.35 (2H, s), 4.75 (1H, d, J= 11 Hz), 4.99 (2H, s), 5.26 (1H, d, J= 11 Hz), 6.26 (1H, s), 7.36 - 7.47 (10 H, m)

MS:
682 (<1, M⁺), 652 (1), 637 (<1), 619 (<1), 591 (57), 326 (12), 234 (100), 218 (31), 190 (9)

Exact Mass:
Calcd. for C₄₀H₄₈N₂O₈ 682.3254
Found 682.3244
Compound **120a** continued:
Dibenzyl ether nitrile (123a and 123b)

A solution of 12.8 μl (5 eq) of oxalyl chloride and 20.8 μl (10 eq) of dimethyl sulfoxide in 300 μl of dry methylene chloride was stirred under argon at -78°C for 5 minutes. A solution of 20 mg (0.0293 mmol) of 120a in 200 μl of dry methylene chloride was then added to the above solution which again was stirred for 5 minutes. After adding 81.7 μl (20 eq) of triethylamine, the reaction mixture was slowly warmed to room temperature and partitioned with a combined solution of dilute HCl and saturated sodium chloride. The aqueous layer was thoroughly extracted and the organic layer dried through an anhydrous sodium sulfate column and evaporated to yield a crude mixture of the α-hydroxylactams 119 which were used without purification.

The residue was dissolved in 400 μl of dry methylene chloride to which 39.1 μl (10 eq) of trimethylsilyl cyanide and 5.4 μl (1.5 eq) of boron trifluoride etherate were added under argon. After stirring for one hour, the reaction mixture was partitioned with a combined solution of dilute HCl and saturated sodium chloride. The organic layer was washed with a solution of saturated sodium bicarbonate followed by a solution of saturated sodium chloride, dried through an anhydrous sodium sulfate column, and evaporated. Separation on a preparative silica gel tlc plate
(90% ether in hexanes) afforded 7.9 mg of 123b and 5 mg of 123a both as a light yellow foam.
(combined yield - 63.9% over 2 steps).

Characterization of compound 123b (top isomer):

**IR (CH$_2$Cl$_2$):**

3680, 2985, 1660, 1110, 1060, 1000

**NMR (CDCl$_3$):**

2.18 (3H, s), 2.21 (3H, s), 2.32 (3H, s), 2.83 (1H, d, J= 18 Hz),
3.10 (1H, dd, J= 8, 18 Hz), 3.30 - 3.36 (1H, m), 3.56 (3H, s),
3.67 (3H, s), 3.74 (3H, s), 3.79 (2H, m), 3.84 (3H, s), 4.25 - 4.29
(2H, m), 4.88 (1H, d, J= 11.5 Hz), 5.17 (2H, s), 5.35 (1H, d, J= 11.5 Hz),
6.36 (1H, s), 7.35 - 7.56 (10 H, m)

**MS:**

689 (4, M$^+$), 598 (17), 572 (5), 324 (50), 234 (73), 218 (41),
91 (100)

**Exact Mass:**

Calcd. for C$_{41}$H$_{43}$N$_3$O$_7$ 689.3100

Found 689.3084

Characterization of compound 123a (bottom isomer):

**IR (CH$_2$Cl$_2$):**

3680, 2900, 1655, 1110, 1060, 1005

**NMR (CDCl$_3$):**

2.06 - 2.15 (2H, m), 2.21 (3H, s), 2.23 (6H, s), 2.94 (1H, d,
J= 18 Hz), 3.08 (1H, dd, J= 6.4, 18 Hz), 3.56 (3H, s), 3.70 (3H,
s), 3.81 (3H, s), 3.85 (3H, s), 3.91 - 4.04 (1H, m), 4.84 (1H, d,
J= 11.3 Hz), 5.08 (2H, dd, J= 10.7, 17.7 Hz), 5.31 (1H, d,
J= 11.3 Hz), 6.08 (1H, s), 7.34 - 7.44 (10 H, m)

**MS:**

689 (1, M$^+$), 663 (<1), 598 (6), 572 (10), 324 (94), 234 (92),
218 (59), 91 (100)

**Exact Mass:**

Calcd. for C$_{41}$H$_{43}$N$_3$O$_7$ 689.3100

Found 689.3084
Compound 123b continued:
Compound 123a continued:
Epimerization of 123a

A solution of 210 mg (0.305 mmol) of 123a in 5 ml of tetrahydrofuran was stirred at -78°C under argon and to this was added 3 equivalents of lithium diisopropyl amide via syringe. After stirring for 5 minutes, 315.6 mg (5 eq) of 2,6-di-t-buty/phenol in 1 ml of tetrahydrofuran was added. After 5 minutes, the reaction was quenched with dilute HCl and allowed to warm to room temperature. After partitioning between ether and a saturated solution of sodium bicarbonate, the ether extract was washed with a solution of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated. A silica gel column separation employing a solvent gradient to 90% ether in hexanes yielded 165 mg (78.6%) of 123b.
Dibenzyl ether amine (117b)

To a solution of 281 mg (0.408 mmol) of 123b in 3ml of dry methylene chloride was added 7 ml of ethanol saturated with ammonia. This solution was hydrogenated over 4 ml of a suspension of Raney nickel in ethanol at 1200 psi of hydrogen for three hours at room temperature. The reaction mixture was filtered through Celite and evaporated. Separation on a preparative silica gel tlc plate (developed twice in 10% methanol in methylene chloride) afforded 228 mg (80.7%) of 117b as a yellow oil.

IR (CH₂Cl₂): 3680, 2880, 1630, 1110, 1060, 1005

NMR (CDCl₃): 1.94 (3H, s), 2.16 (3H, s), 2.18 (3H, s), 2.21 (3H, s), 2.82 (1H, d, J= 18.4 Hz), 2.90 (1H, dd, J= 9, 13.6 Hz), 3.04 (1H, dd, J= 7.6, 18.4 Hz), 3.16 - 3.30 (2H, m), 3.55 (3H, s), 3.70 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 4.26 - 4.32 (2H, m), 4.89 (1H, dd, J= 9, 11 Hz), 5.08 (1H, d, J= 11 Hz), 5.32 (2H, d, J= 11.8 Hz), 5.88 - 5.93 (2H, m), 7.33 - 7.52 (10H, m)

MS: 664 (2), 573 (3), 492 (1), 324 (63), 234 (70), 218 (50), 91 (100)

Exact Mass: Calcd. for C₄₀H₄₃N₂O₇ 663.3070
Found 663.3065
Compound 117b continued:

100

10 50 100 150 200 250

100

200 300 400 450 500

100

510 550 600 650 700

>400 x 25
Dibenzyl ether imidazolidone (124)

To generate aluminum hydride, a solution of 41.5 mg (3 eq) of aluminum chloride in 500 μl of tetrahydrofuran was added to a solution of 39.4 mg (10 molar eq) of lithium aluminum hydride in 500 μl of tetrahydrofuran at 0°C. The mixture was warmed to room temperature and stirred for 30 minutes under argon. A solution of 72 mg (0.104 mmol) of 117b in 500 μl of tetrahydrofuran was added to the aluminum hydride solution which had again been cooled to 0°C. After stirring for 15 minutes at room temperature, the reaction was carefully quenched with water and dilute HCl was added to dissolve the aluminum salts. After adjusting the pH (<8) with ammonium hydroxide, the mixture was filtered through Celite and partitioned between methylene chloride and a solution of saturated sodium chloride. The aqueous layer was thoroughly extracted and the organic layer dried through an anhydrous sodium sulfate column and evaporated. Separation on a preparative silica gel tic plate (5% methanol in methylene chloride) afforded 55 mg (78.3%) of 124 as a yellow oil.
IR (CH$_2$Cl$_2$): 3680, 2900, 1105, 1060, 1010

NMR (CDCl$_3$):
2.12 (3H, s), 2.18 (3H, s), 2.21 (3H, s), 2.55 (1H, d, J= 18 Hz), 2.89 - 2.96 (2H, m), 3.08 - 3.26 (2H, m), 3.38 - 3.44 (2H, m), 3.58 (3H, s), 3.73 (3H, s), 3.76 (3H, s), 3.80 (3H, s), 4.22 (1H, t, J= 8.6 Hz), 4.79 - 4.86 (2H, m), 5.02 (1H, d, J= 11 Hz), 5.29 (1H, dd, J= 4.5, 11 Hz), 7.33 - 7.52 (10H, m)

MS: 648 (3), 557 (8), 451 (3), 338 (9), 324 (4), 234 (20), 91 (100)

Exact Mass:
Calcd. for C$_{33}$H$_{37}$N$_2$O$_6$ 557.2651
Found 557.2646
Compound 124 continued:

~300 x 10

~600 x 20
Diphenol pyruvamide (131)

Ammonia was condensed into a solution of 39 mg (0.0576 mmol) of 124 dissolved in 500 µl of tetrahydrofuran containing 50 µl of ethanol at -33°C. Small pieces of lithium were slowly added to the solution until the reduction was complete as evidenced by tlc. After quenching the reaction with ammonium chloride, the ammonia was allowed to evaporate as the solution was slowly warmed to room temperature. The residue was taken up in methylene chloride and filtered through a column containing Celite and anhydrous sodium sulfate and evaporated to yield the diphenol 130 which was used without purification.

The residue was dissolved in 1 ml of methylene chloride and added to a solution of 35 mg (3 eq) of 1,3-dicyclohexylcarbodiimide and excess pyruvic acid in 500 µl of methylene chloride. After stirring for 5 minutes at room temperature, the reaction mixture was evaporated to small volume and diluted with ether. After filtering off the urea, separation on a preparative silica gel tlc plate (5% methanol in methylene chloride) afforded 14 mg (42.9% - 2 steps) of 131 as a light orange foam.
Characterization of diphenol amine 130:

IR (CH$_2$Cl$_2$): 3540, 2900, 1105, 1055, 1005

NMR (CDCl$_3$): 2.18 (3H, s), 2.21 (3H, s), 2.35 (3H, s), 2.60 (1H, d, J= 18 Hz), 2.96 - 3.21 (4H, m), 3.48 - 3.60 (2H, m), 3.62 (3H, s), 3.71 (3H, s), 3.72 (3H, s), 3.74 (3H, s), 3.99 - 4.07 (2H, m), 4.28 (1H, t, J= 8.5 Hz)

MS: 497 (<1, M$^+$), 468 (19), 248 (100), 234 (35), 220 (40)

Exact Mass: Calcld. for C$_{27}$H$_{35}$N$_3$O$_6$ 497.2525
Found 497.2514

Characterization of pyruvamide 131:

IR (CH$_2$Cl$_2$): 3530 (b), 2930, 1630, 1105

NMR (CDCl$_3$): 2.19 (3H, s), 2.22 (3H, s), 2.36 (3H, s), 2.49 (3H, s), 2.71 (1H, d, J= 18.6 Hz), 3.14 - 3.30 (3H, m), 3.62 (3H, s), 3.71 (3H, s), 3.72 (3H,s), 3.74 (3H, s), 4.13 - 4.24 (2H, m), 4.54 (1H, d, J= 7.7 Hz), 4.75 (1H, s), 5.45 (1H, s), 5.59 (1H, s)

MS: 567 (<1, M$^+$), 524 (<1), 496 (<1), 467 (1), 234 (100)

Exact Mass: Calcld. for C$_{30}$H$_{27}$N$_3$O$_8$ 567.2580
Found 567.2590
Compound 130 continued:

\[ \begin{array}{c}
\text{400 x 30} \\
\end{array} \]
Compound 131 continued:
**Diphenol pyruvamide nitrile (133)**

A solution of 3.9 mg (0.0068 mmol) of 131 in 1 ml of a 2:1 mixture of methylene chloride in liquid HCN was stirred at room temperature in a sealed tube overnight. A strong stream of air was passed through the reaction mixture until all of the liquid had evaporated. The residue was taken up in methylene chloride and partitioned well with a solution of saturated sodium carbonate. The aqueous layer was washed thoroughly and the organic extracts dried through an anhydrous sodium sulfate column and evaporated. Separation on a preparative silica gel tic plate (5% methanol in methylene chloride) afforded 2.8 mg (69.3%) of 133 as an orange foam.

**IR (CH₂Cl₂):**

3520, 2880, 1640, 1105, 1055

**NMR (CDCl₃):**

1.96 (3H, s), 2.06 (3H, s), 2.16 - 2.22 (2H, m), 2.25 (3H, s), 2.38 - 2.50 (5H, m), 2.76 - 2.91 (2H, m), 3.16 - 3.29 (2H, m), 3.51 (3H, s), 3.58 (6H, s), 3.60 (3H, s), 3.65 - 3.74 (3H, m), 4.04 1H, s), 4.12 (1H, d, J= 7 Hz), 4.18 (1H, s), 4.23 - 4.29 (1H, m), 5.38 (1H, s), 7.19 (1H, s)

**MS:**

567 (<1), 524 (<1), 496 (<1), 467 (1), 234 (100)

**Exact Mass**

Calcd. for C₃₀H₃₇N₅O₈ 567.2580

Found 567.2590
Compound 133 continued:
References


24) Carbobenzoxyaminoacetaldehyde was prepared as follows: allyl amine was treated with 1) CbzCl, TEA, 2) O3, and 3) Me2S. Purification was accomplished on a silica gel column employing a solvent gradient to 80% ether in hexanes.

25) Aldehyde 95 was prepared as follows: 1) a solution of phthalic anhydride and allyl amine in toluene was heated using a Dean-Stark trap to remove water, and 2) the resulting crude reaction mixture was treated with O3 followed by Me2S. The product was recrystallized with 40% ether in hexanes.


27) Note: The NMR's shown on page 60 were taken on a JEOL FX-90Q instrument.


