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**Sachleben, Richard Alan**

SYNTHETIC STUDIES ON THE SAFRAMYCINS A, B AND S: A TOTAL  
SYNTHESIS OF SAFRAMYCIN B

*Rice University*

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SYNTHETIC STUDIES ON THE SAFRAMYCINS A, B, AND S

A TOTAL SYNTHESIS OF SAFRAMYCIN B

by


RICHARD ALAN SACHLEBEN

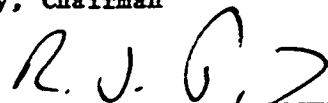
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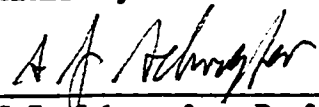
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DOCTOR OF PHILOSOPHY

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HOUSTON, TEXAS  
MAY, 1984

## Abstract

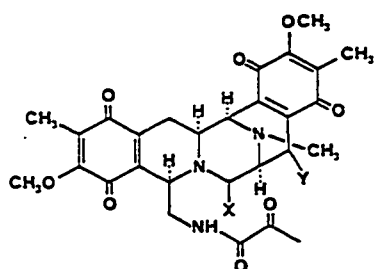
### Synthetic Studies on the Saframycins A, B and S

#### A Total Synthesis of Saframycin B

by

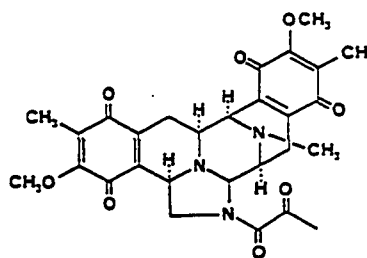
Richard Alan Sachleben

The Saframycins are naturally occurring antibiotics with an interesting bisquinone structure. The first and only synthesis of saframycin B is described herein. The interesting aspects of this synthesis are the convergent approach and the method of stereochemical control. Studies directed towards adapting the saframycin B synthesis to the synthesis of saframycins A and S are also described. These studies have resulted in the synthesis of a compound structurally related to the saframycins but so far unreported in the literature.



Saframycins

- 1) A: X= CN , Y= H
- 2) B: X= H , Y= H
- 3) C: X= H , Y= OCH<sub>3</sub>
- 4) S: X= OH , Y= H



Bis-Quinone 2  
(deshydro-saframycin S)



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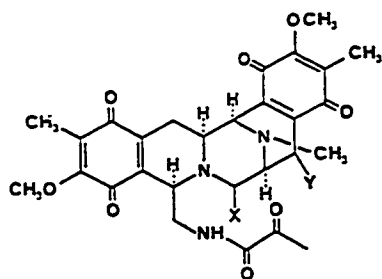
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## **Chapter I**

### **INTRODUCTION**

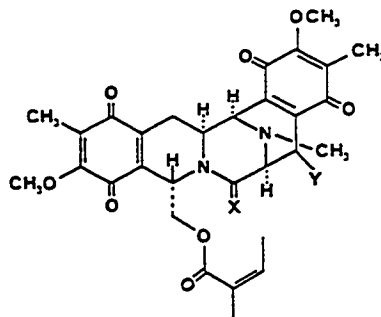
## INTRODUCTION

The Saframycins, A(1), B(2), C(3), and S(4) were isolated as satellite antibiotics from cultures of *Streptomyces lavendulae*, which is known to produce streptothricins.<sup>1,3</sup> They have been shown to be active against Gram-positive bacteria, and to exhibit anti-tumor activities.<sup>1,2</sup> Saframycins A and S are particularly active tumor inhibitors and bind preferentially to DNA.<sup>4,5</sup> The structure of saframycin C was established by X-ray crystallographic studies and the structure of saframycin B by comparison of <sup>13</sup>C NMR spectral data.<sup>6</sup> The structures of saframycins A and S were determined by comparison of <sup>13</sup>C NMR data, chemical degradation and isotopic labeling studies.<sup>7</sup> The saframycins represent a previously unknown system of two quinone moieties attached to a piperazine ring and are structurally related to the more recently isolated renieramycins,<sup>8</sup> 5, 6, 7, and 8.



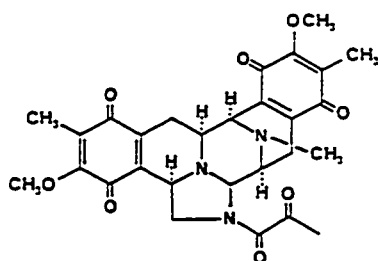
Saframycins

- 1) A: X= CN , Y= H
- 2) B: X= H , Y= H
- 3) C: X= H , Y= OCH<sub>3</sub>
- 4) S: X= OH , Y= H



Renieramycins

- 5) A: X= H, H Y= OH
- 6) B: X= H, H Y= OC<sub>2</sub>H<sub>5</sub>
- 7) C: X= O Y= OH
- 8) D: X= O Y= OC<sub>2</sub>H<sub>5</sub>



Bis-Quinone 9  
(deshydro-saframycin S)

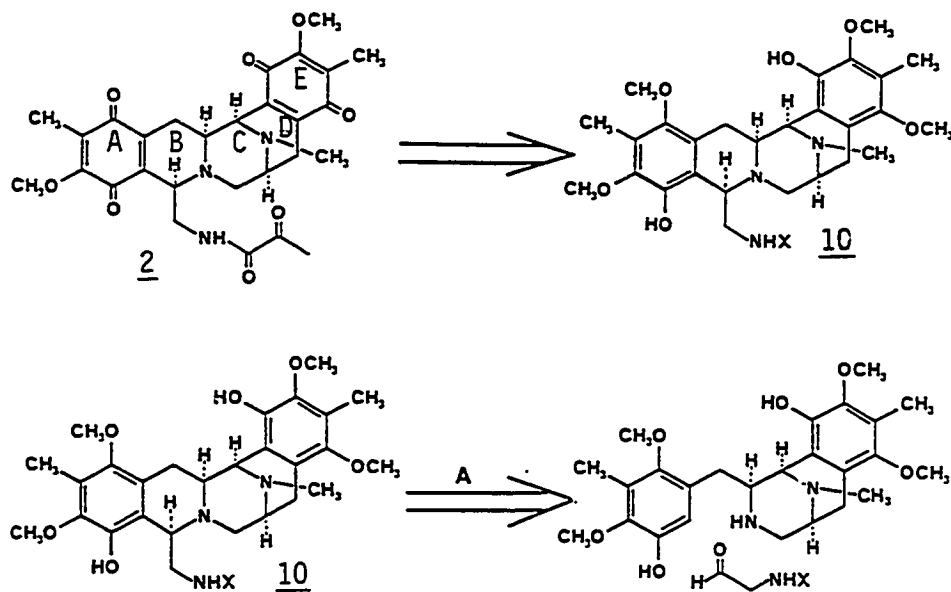
## **Chapter II**

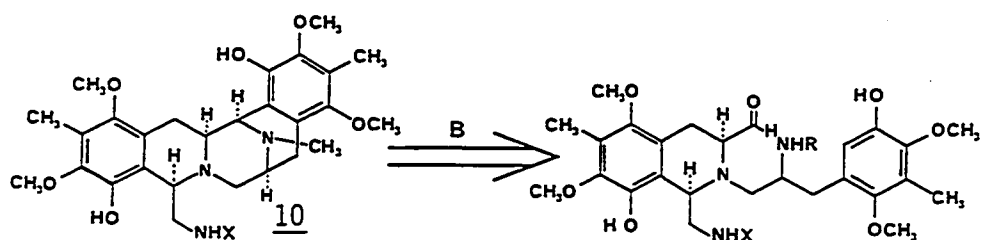
# **THE TOTAL SYNTHESIS OF SAFRAMYCIN B**

## **DISCUSSION**

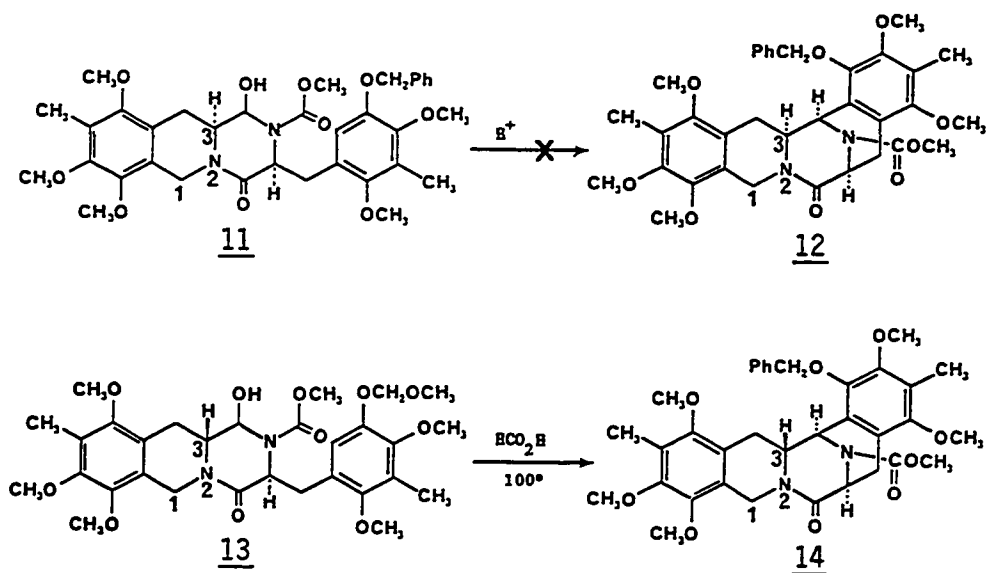
# THE TOTAL SYNTHESIS OF SAFRAMYCIN B

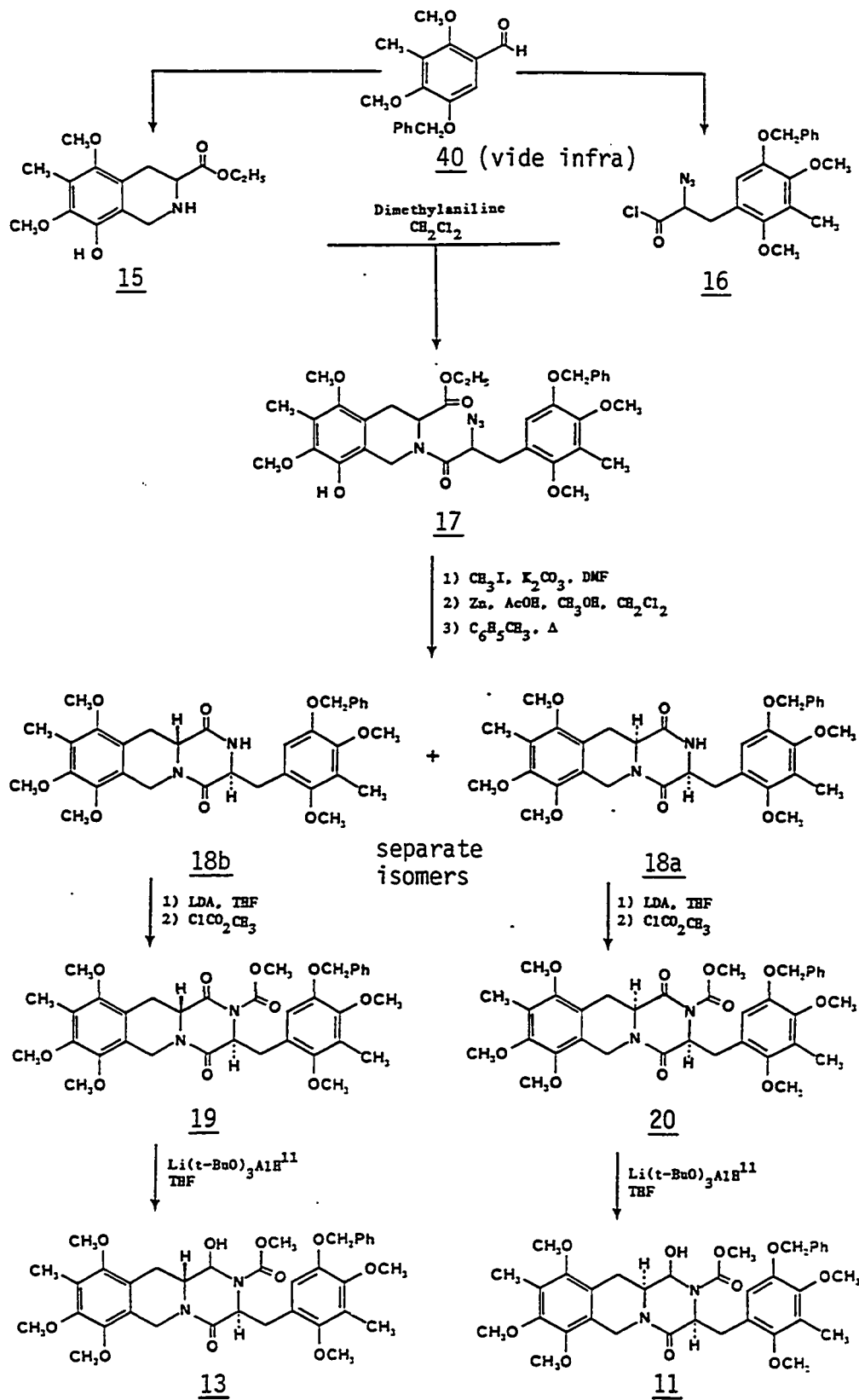
Saframycin B was chosen as the initial target molecule since it is the least substituted member of the series. The bis-quinone system may be viewed as a modified dimeric structure. This would make a convergent approach to the total synthesis appear promising. Quinone systems are sensitive to many different conditions and must be introduced in a protected form until the final step in the synthesis. With the quinones masked as substituted phenols, 10, antithetic analysis indicates two retrosynthetic disconnections, Scheme A and Scheme B, both involving cleavage to an amine, aldehyde and appropriately placed aromatic system, representing a retro-phenolic cyclization.





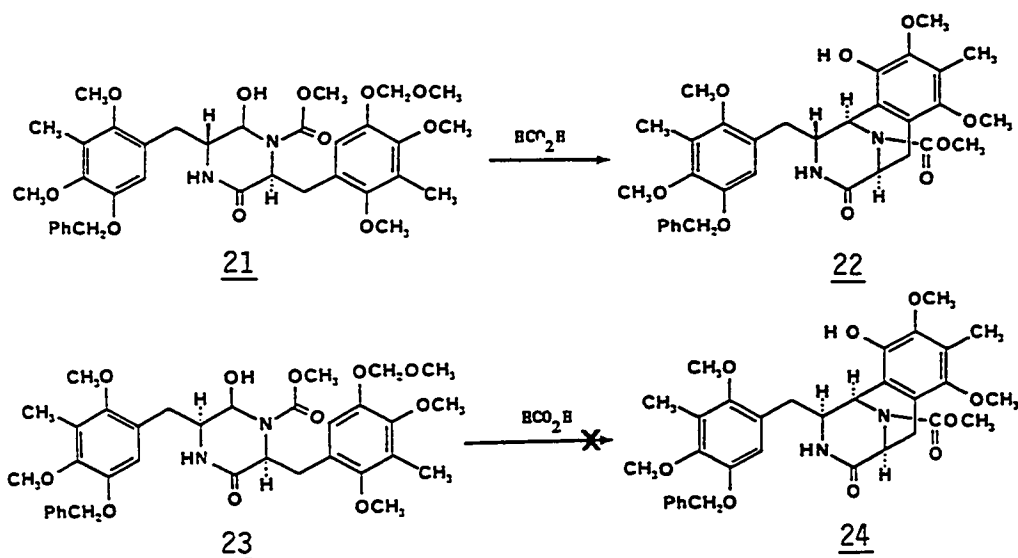
Our initial approach, as in Scheme B, was discontinued when we found that the desired cyclization of compound 11 did not proceed to give compound 12, although its isomer 13 cyclized smoothly in formic acid<sup>10</sup> to give compound 14, which would ultimately be the wrong stereochemistry at C-3. This limitation is presumably due to steric compression of the two aromatic systems in the cis system, 11. An outline of the synthesis of 11 and 13 is presented below. The stereochemical assignment of compounds 18a and 18b was based on TLC behavior.<sup>12,13</sup>



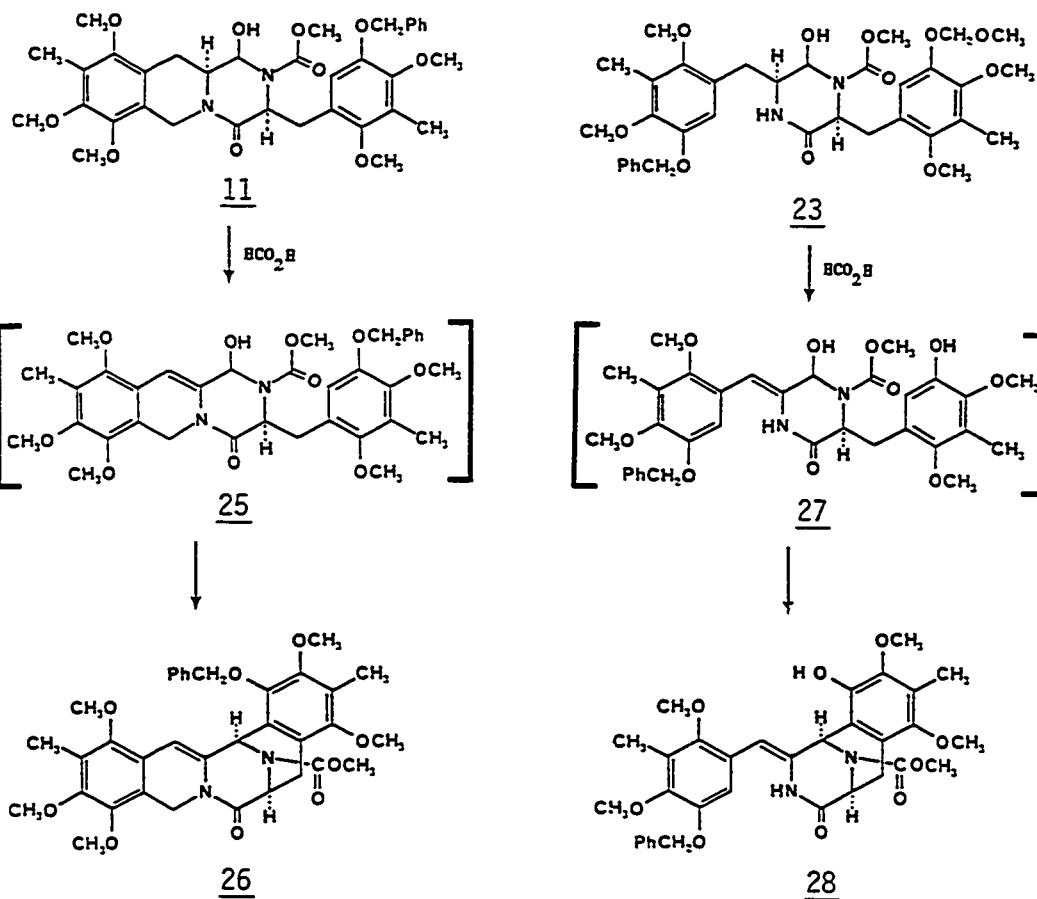




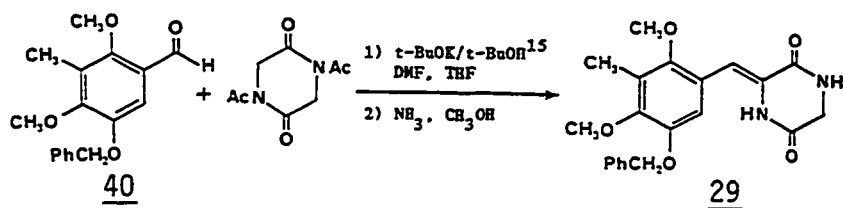
Further studies on the system where both B and D rings have been disconnected again found cyclization of the trans system, compound 21 to proceed smoothly, whereas attempted cyclization of the cis system, compound 23, gave a product inconsistent in spectral characteristics with that of the desired compound 24.<sup>14</sup>

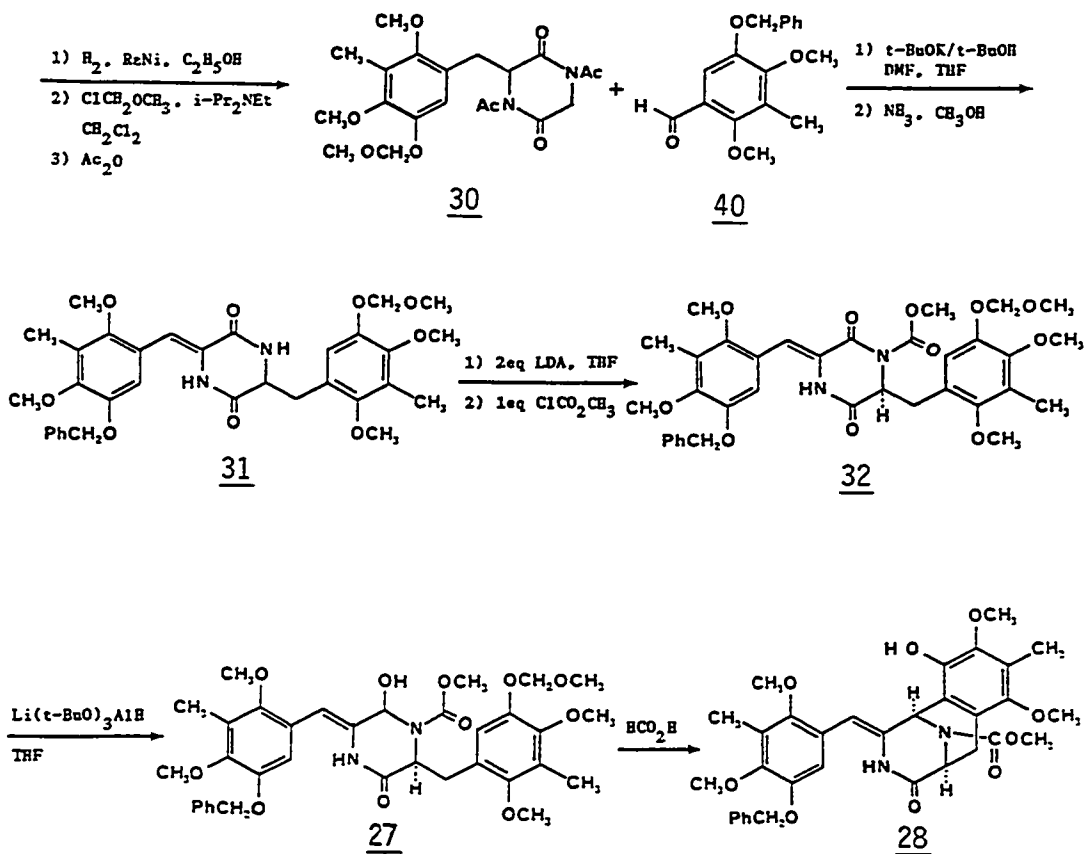


Consideration of the results of the attempted cyclizations of compounds 11 and 23 indicated the possibility of air oxidation to give compounds such as 25 and 27, respectively. This would relieve the steric compression of the two cis aromatic systems, and allow cyclization to occur, giving compounds 26 and 28.



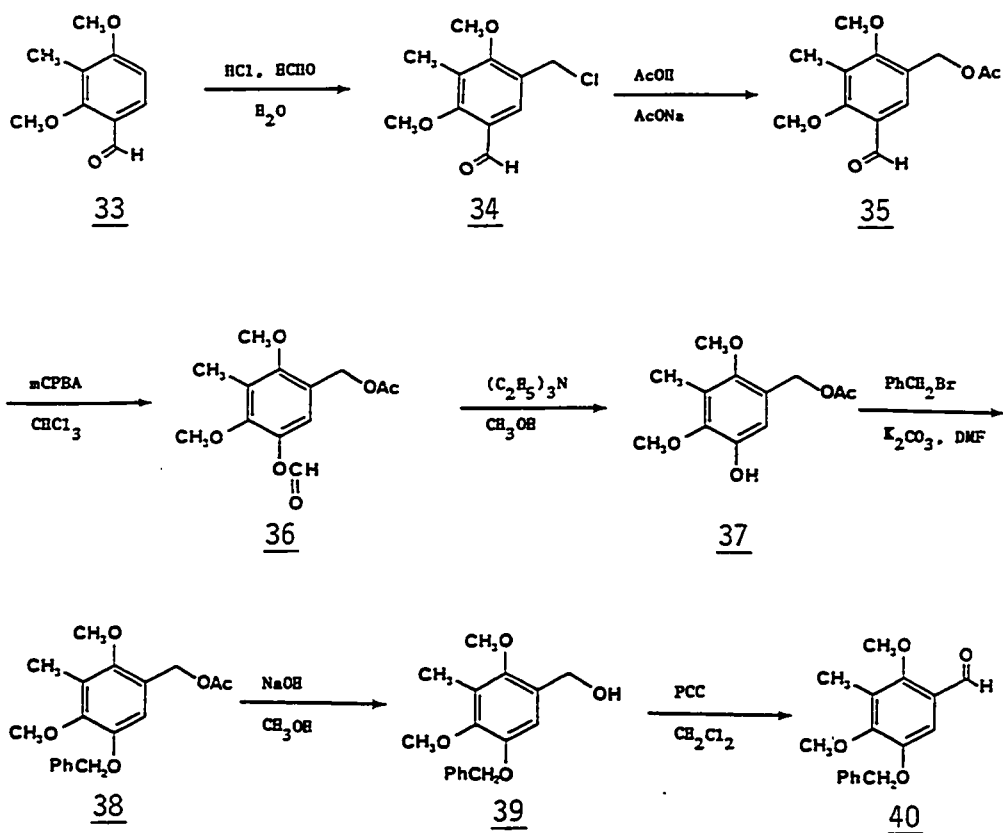
An unambiguous synthesis of compound **27** was undertaken, and cyclization shown to occur readily to give a product consistent in spectral behavior to structure **28**.



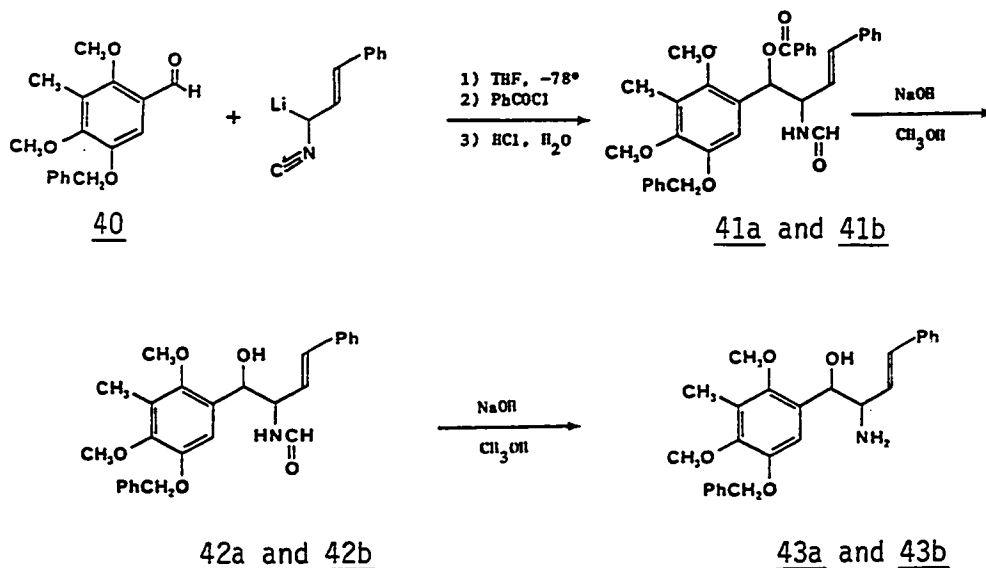


With this result in hand, a synthesis of saframycin B proceeding through an analog of compound 28 was completed as follows.

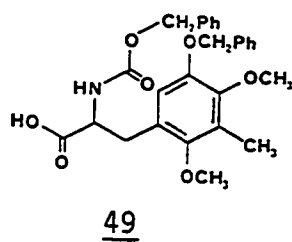
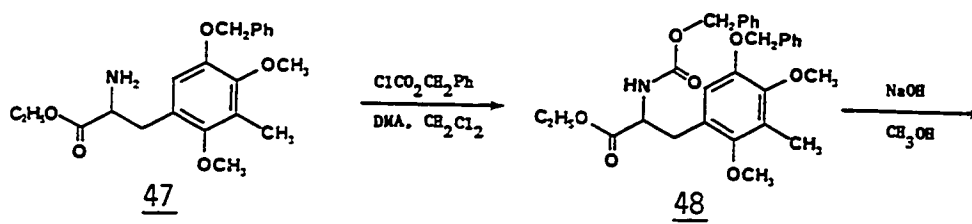
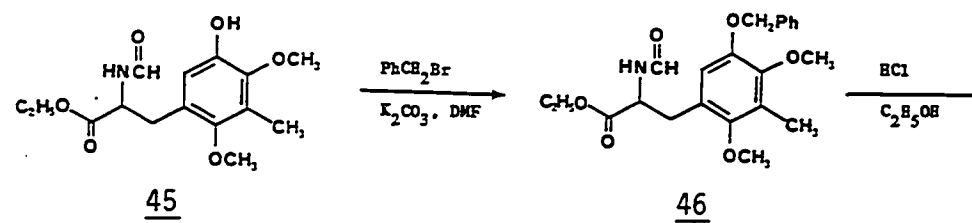
The substituted benzaldehyde 40, was synthesized in seven steps from the readily available 2,4-dimethoxy-3-methylbenzaldehyde,<sup>16</sup> 33, (74%), as outlined below. The synthesis of this compound has been previously reported,<sup>17</sup> however only partial analytical data was presented. Complete synthetic details for these compounds are included in the experimental section.



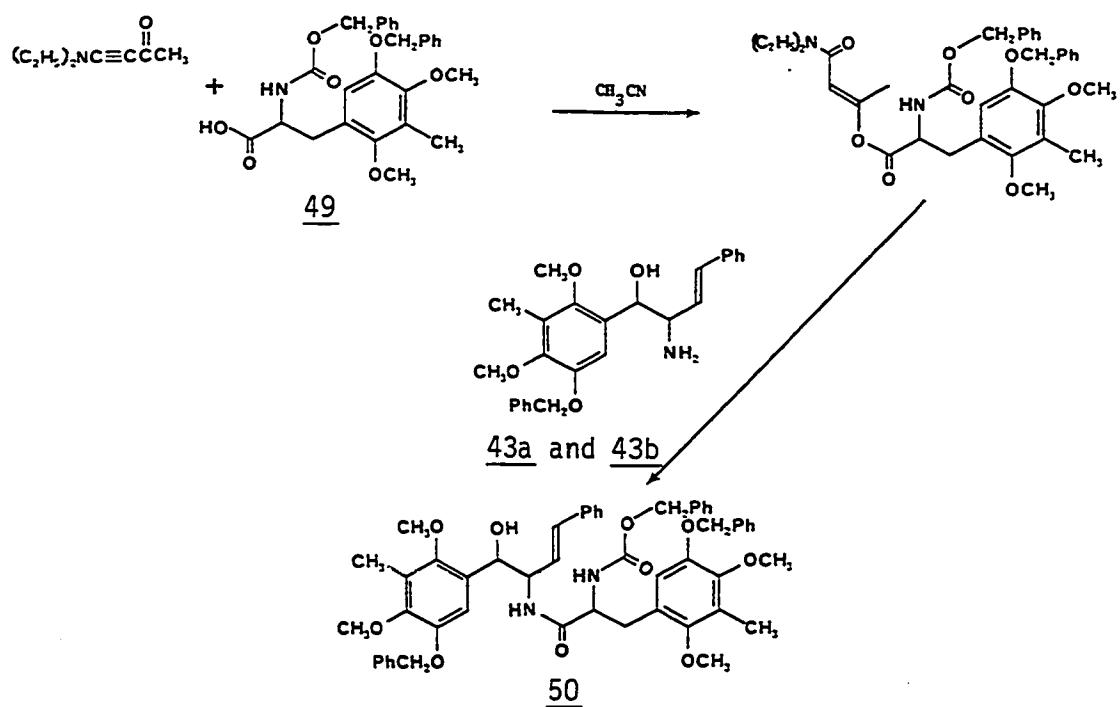
Aldehyde **40** was treated with cinnamyl isonitrile<sup>18</sup> anion<sup>19</sup> at low temperature and the alcohol product acylated in situ with benzoyl chloride. The resulting mixture of diastereomeric isonitriles was hydrolyzed with dilute hydrochloric acid to give a mixture of benzoate-formamides **41a** and **41b** in 94% yield. Basic hydrolysis of the benzoate-formamide mixture gave initially alcohol-formamides **42a** and **42b**, then more slowly, the alcohol-amines **43a** and **43b**.



When a mixture of ethyl isocyanoacetate<sup>18</sup> and aldehyde 40 was treated with potassium hydride in tetrahydrofuran, condensation<sup>19</sup> to a mixture of olefinic formamide-esters 44a and 44b occurred. This mixture was hydrogenated over Raney nickel (W-2) to give the phenol 45, which was converted to the benzyl ether 46, with benzyl bromide and potassium carbonate in dimethylformamide. Acidic hydrolysis of formamide 46 to amine 47 followed by protection as the carbobenzyloxy urethane gave ester 48. Basic hydrolysis of ester 48 gave acid 49, in 84% yield from starting aldehyde 40. This acid could be crystallized readily from ether, therefore no other purification was required in this preparation.

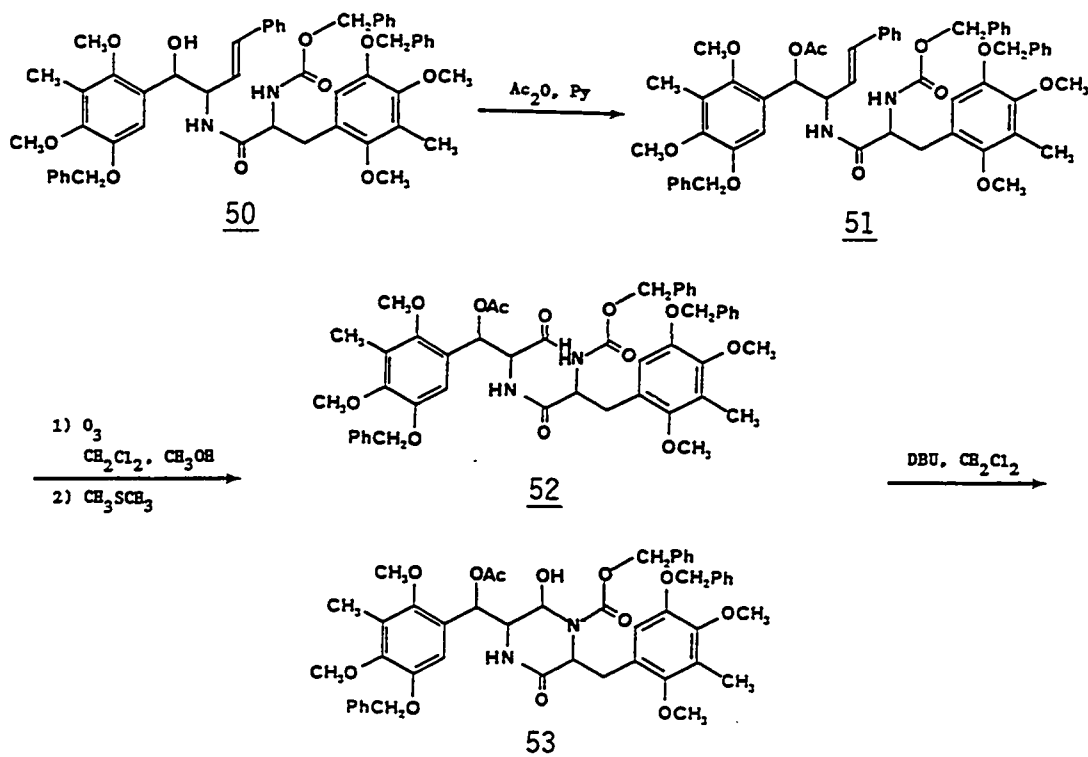


Having constructed the two halves of the desired structure, the next step was to put them together. Condensation of the amine mixture 43 and the acid 49 using DCC or, preferably, a push-pull acetylene,<sup>20,21</sup> gave a complex diastereomeric mixture, 50.

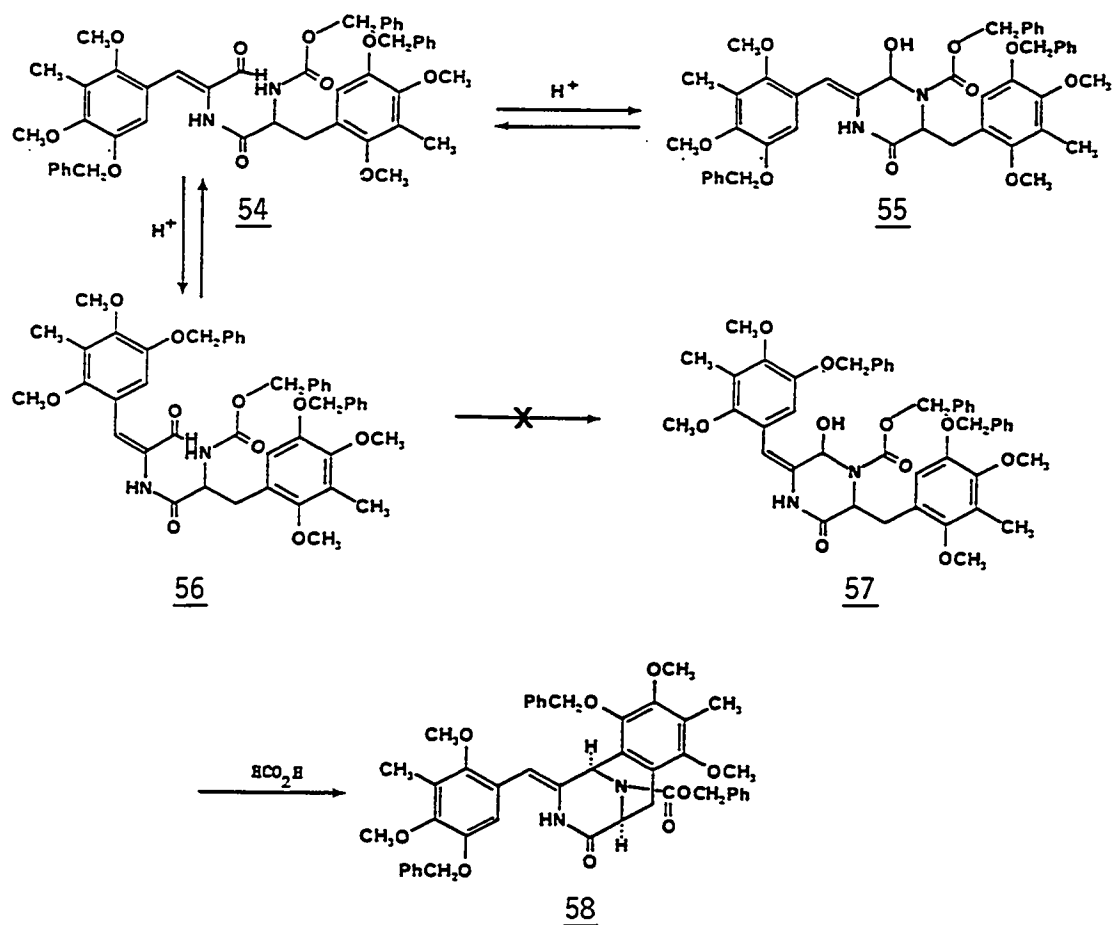


The presence of three uncontrolled chiral centers should result in four pairs of diastereomers. Separation and/or purification of these compounds was not attempted since the following steps would destroy two chiral centers and generate one new chiral center stereospecifically.

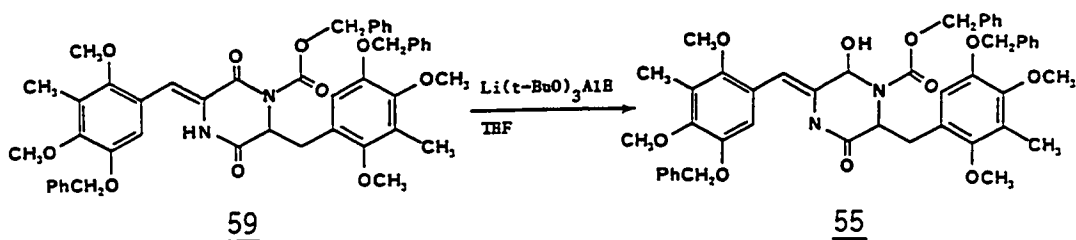
Conversion of the alcohol function of 50 to the acetates 51 with acetic anhydride and pyridine followed by careful ozonolysis gave a complex mixture of aldehydes 52 and  $\alpha$ -hydroxy urethanes 53. Treatment with base caused elimination of acetate to give the olefinic products 54, 55, and 56, which were cyclized in formic acid<sup>10</sup> to give the single product 58, in 64% overall yield from the acid 49.





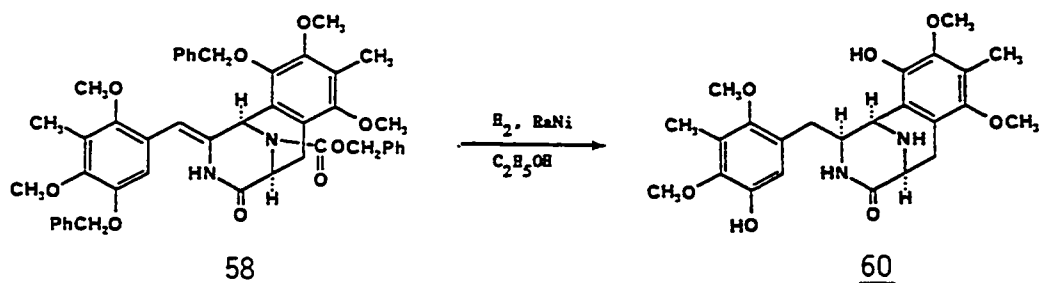


The selectivity of this cyclization is probably due to rapid isomerization of **54** and **56** through protonation-deprotonation of the enamide and the unfavorable cyclization of **56** to **57** due to steric compression of the aromatic ring. The structural assignment was based on the unambiguous synthesis of **55** via **59**, following the scheme outlined previously for compound **27**.

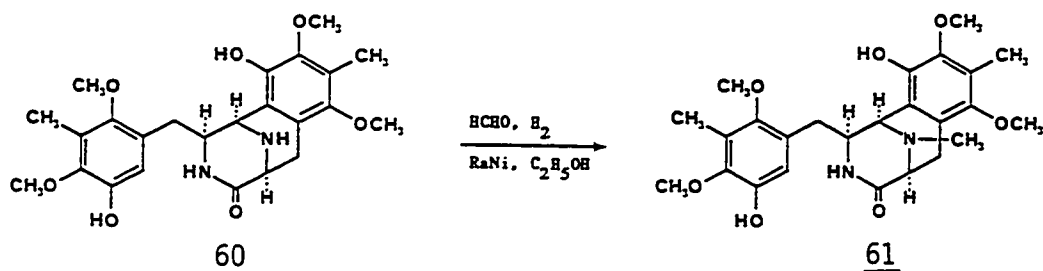


The two chiral centers of 58 must have the desired stereochemistry due to the requirements of the [3.3.1]bicyclic system.

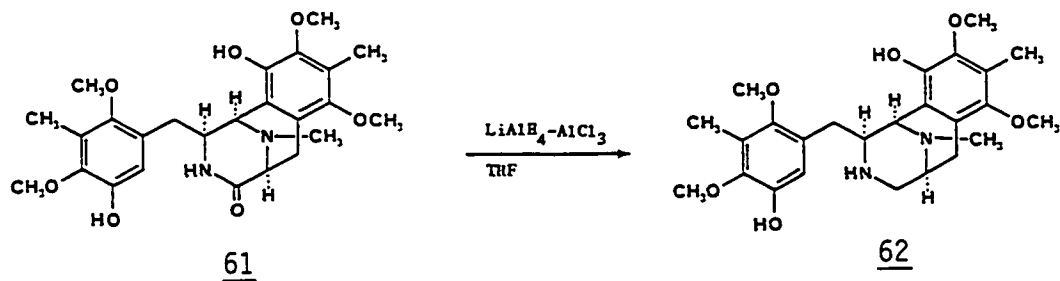
Catalytic hydrogenation of 58 over Raney nickel in ethanol resulted in hydrogenolysis of both benzyl ethers and the carbobenzyloxy group followed by reduction of the double bond from the less hindered,  $\alpha$  face. Thus, the relative configuration of three chiral centers was controlled to give a single compound 60, despite the complexity of the reaction mixture at the earlier stages.



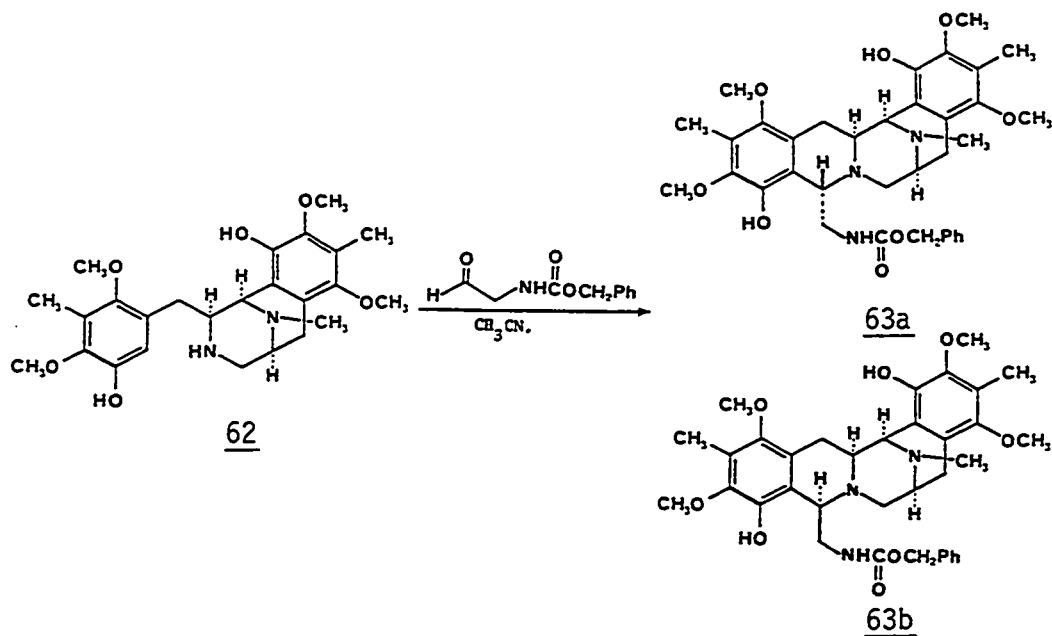
Elaboration of the intermediate 60 into saframycin B proceeded quite smoothly. Methylation of the secondary amine, by addition of formaldehyde to the reduction mixture before workup and continued hydrogenation, gave compound 61 in 75% yield.



Reduction of the lactam 61 with aluminum hydride in tetrahydrofuran gave amine 62.



Phenolic cyclization<sup>22</sup> of amine 62 with carbobenzyloxyamino-acetaldehyde gave a mixture of isomers of the pentacyclic urethanes 63a and 63b, in 75% yield.

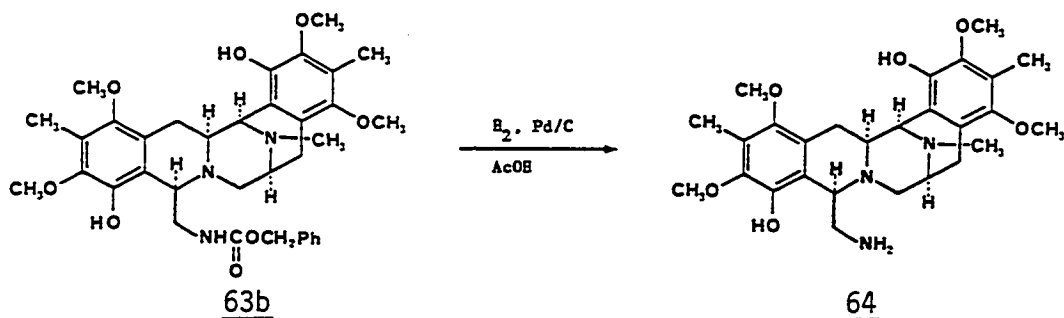


The ratio of 63a to 63b ranged from 2/3 to 1/11, depending on the solvent and temperature, as summarized in Table 1.

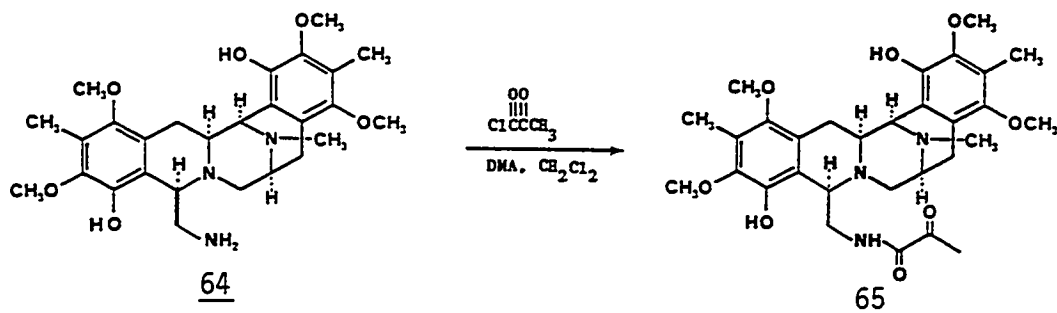
TABLE 1

<u>solvent</u>	<u>temp</u>	<u>time</u>	<u>ratio a/b</u>
tert-amyl alcohol	100°	1 hour	2/3
carbon tetrachloride	70°	.5 hour	1/3
benzene	70°	1 hour	1/4
dichloroethane	70°	1 hour	1/4
acetonitrile	70°	2 hours	1/6
acetonitrile	25°	2 days	1/11

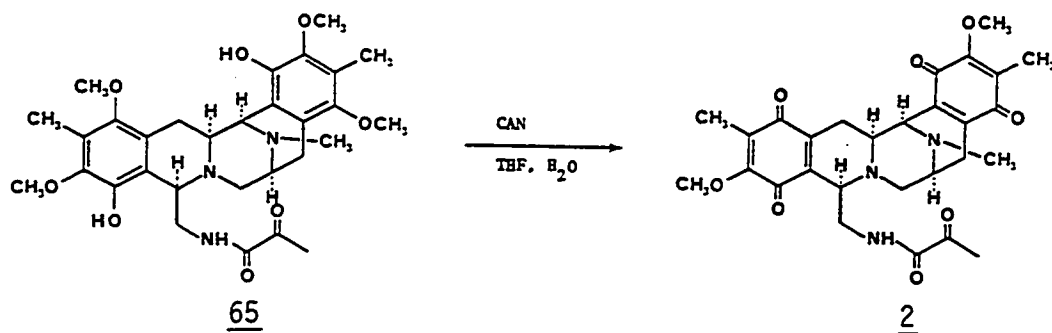
Deprotection of the carbobenzyloxy group of 63b by hydrogenolysis over palladium on carbon gave the amine 64.



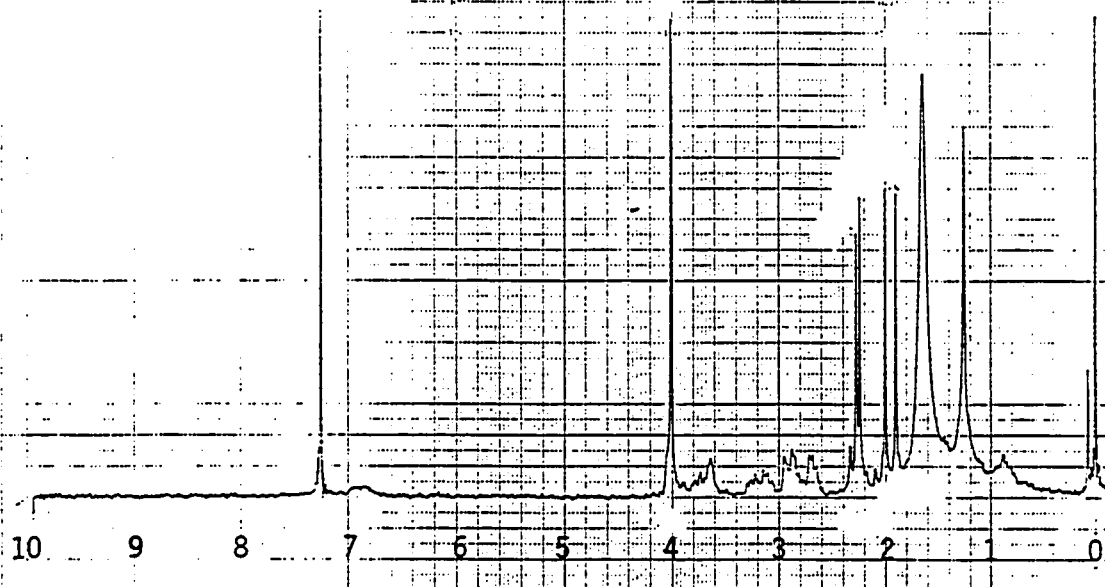
Acylation of amine 64 with pyruvyl chloride gave pyruvamide 65 in 72% yield.



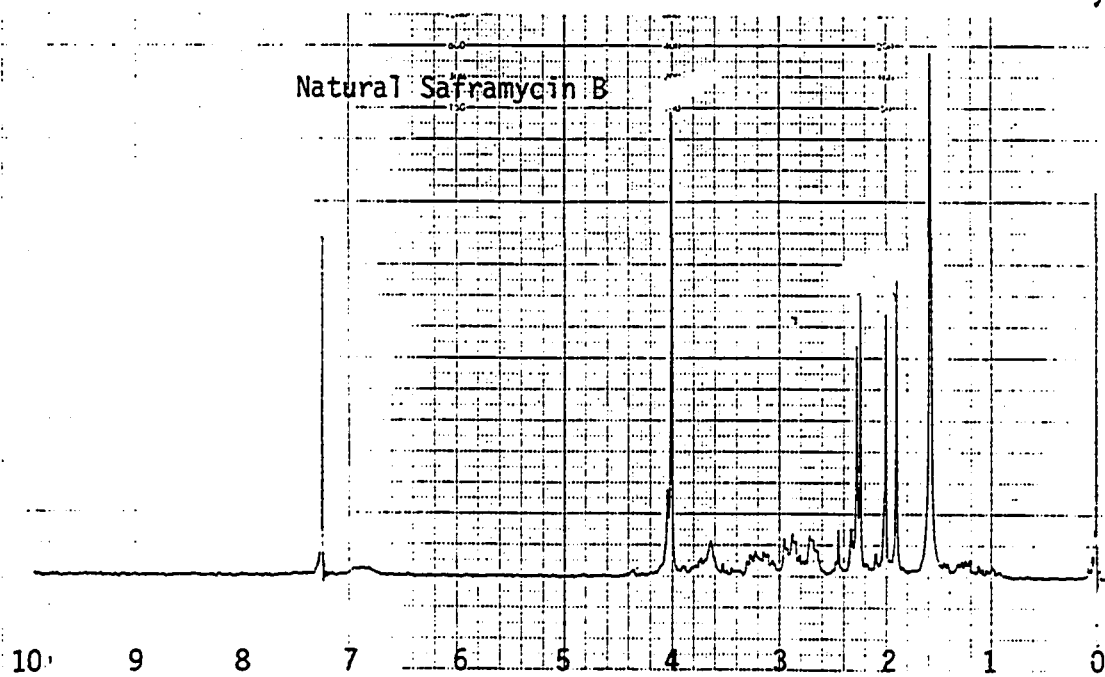
Oxidation of pyruvamide 65 with ceric ammonium nitrate<sup>23,24</sup> in tetrahydrofuran and water gave saframycin B, 2, in 37% yield, identical in TLC, MS, UV, <sup>1</sup>H and <sup>13</sup>C NMR to the authentic material<sup>25</sup>. The <sup>1</sup>H NMR of synthetic and natural saframycin B appear on the following page.



Synthetic Saframycin B



Natural Saframycin B



### **Chapter III**

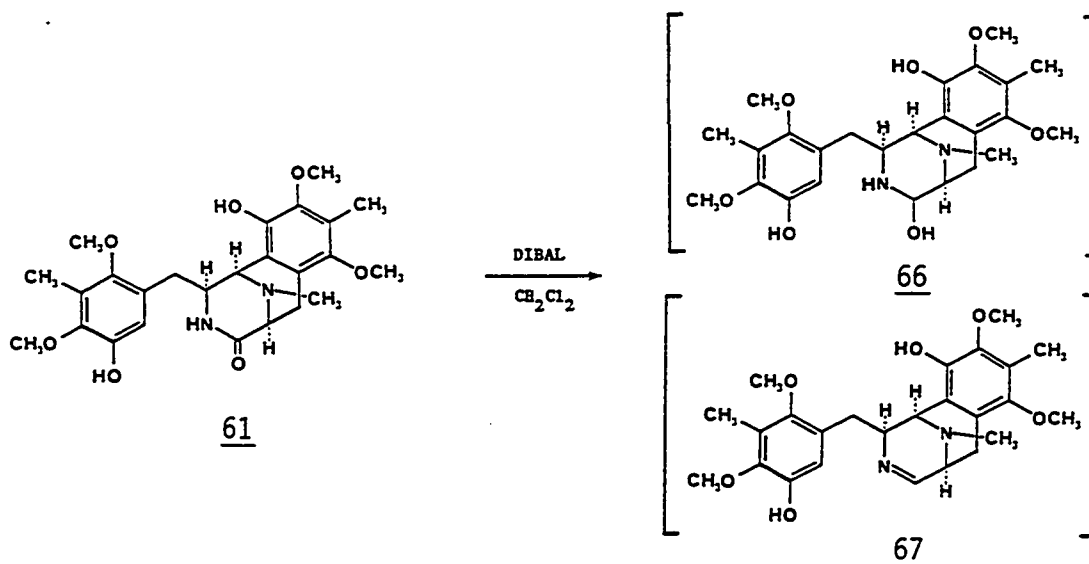
#### **SYNTHETIC STUDIES TOWARDS SAFRAMYCINS A AND S**

#### **DISCUSSION**

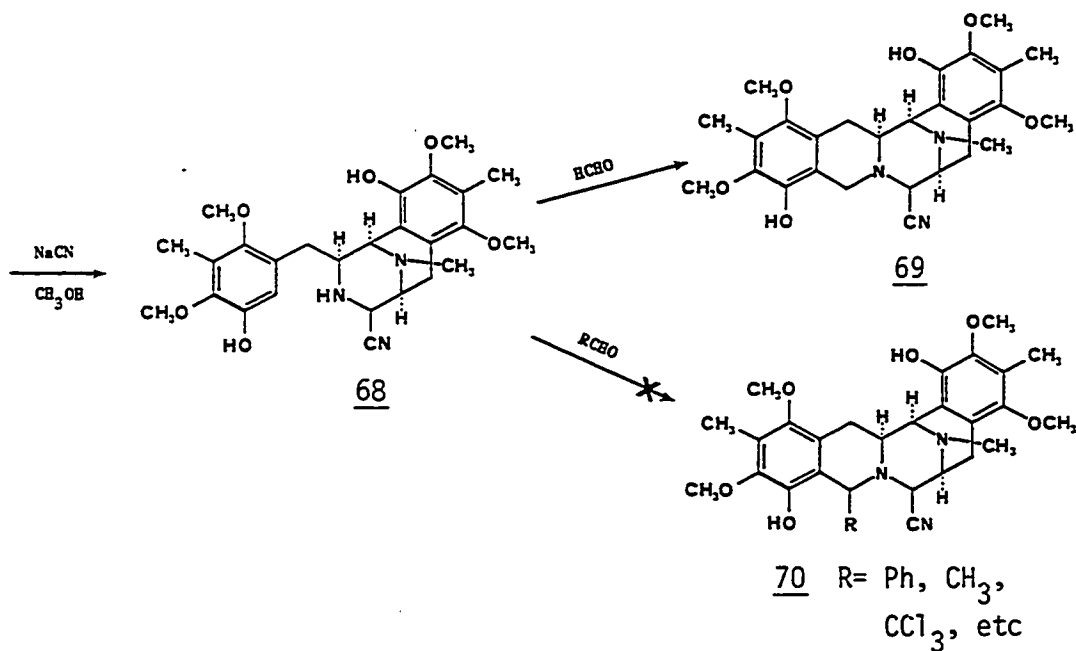
## SYNTHETIC STUDIES TOWARDS SAFRAMYCINS A AND S

With the completion of the total synthesis of saframycin B having proceeded so smoothly, modification of the procedure to the synthesis of saframycin A was undertaken.

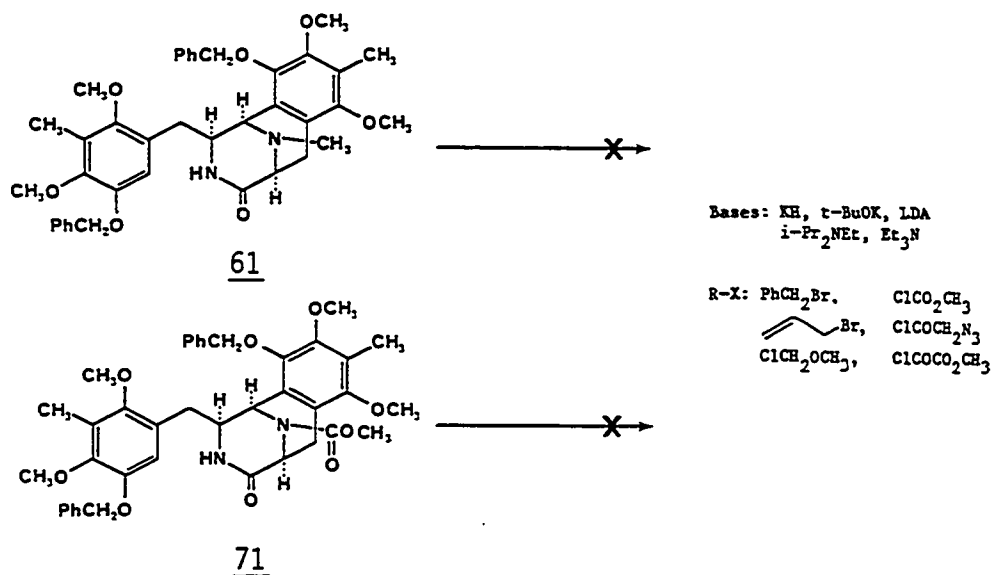
Initially, partial reduction of the lactam 61 was envisioned, followed by introduction of cyanide and phenolic cyclization as in the saframycin B synthesis. Treatment of 61 with di-isobutyl aluminum hydride (DIBAL) in dichloromethane at  $-78^{\circ}$  gave an unstable product, 66 or 67, which reacted with methanolic sodium cyanide in situ to give the amino nitrile 68. This compound reacted with formaldehyde to give the pentacyclic system 69, however, cyclization with substituted aldehydes (R= phenyl,  $\text{CH}_3$ ,  $\text{CCl}_3$ ,  $\text{CO}_2\text{CH}_3$ , etc.) was not successful.



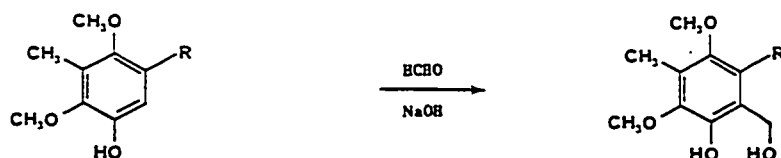




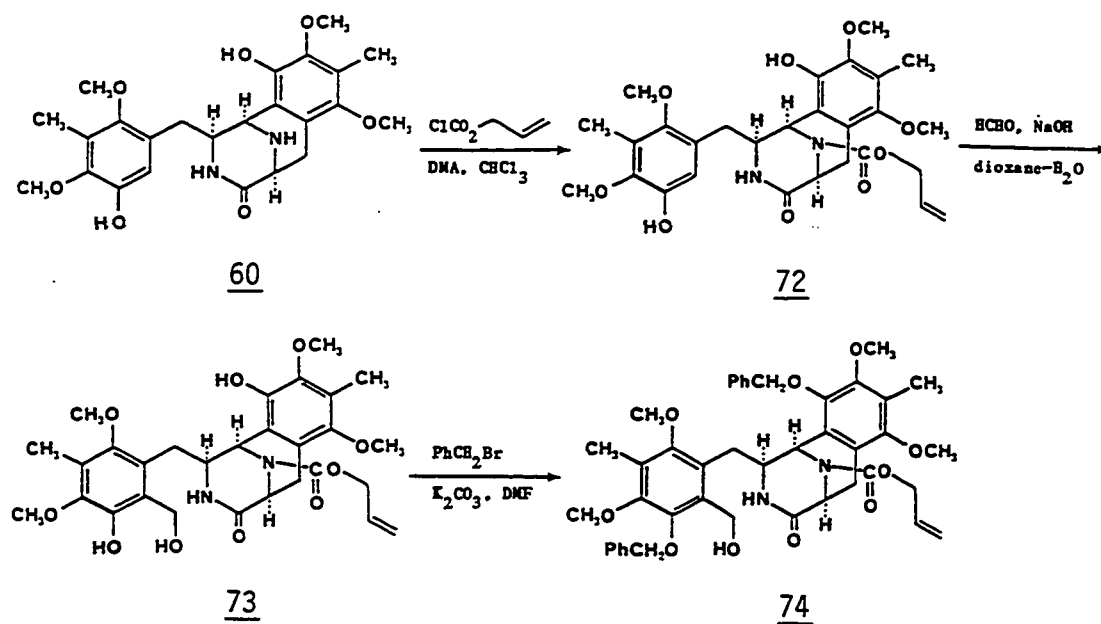
Attempts to alkylate or acylate the nitrogen of the lactams **61** or **71** either failed or resulted in unacceptably poor yields.



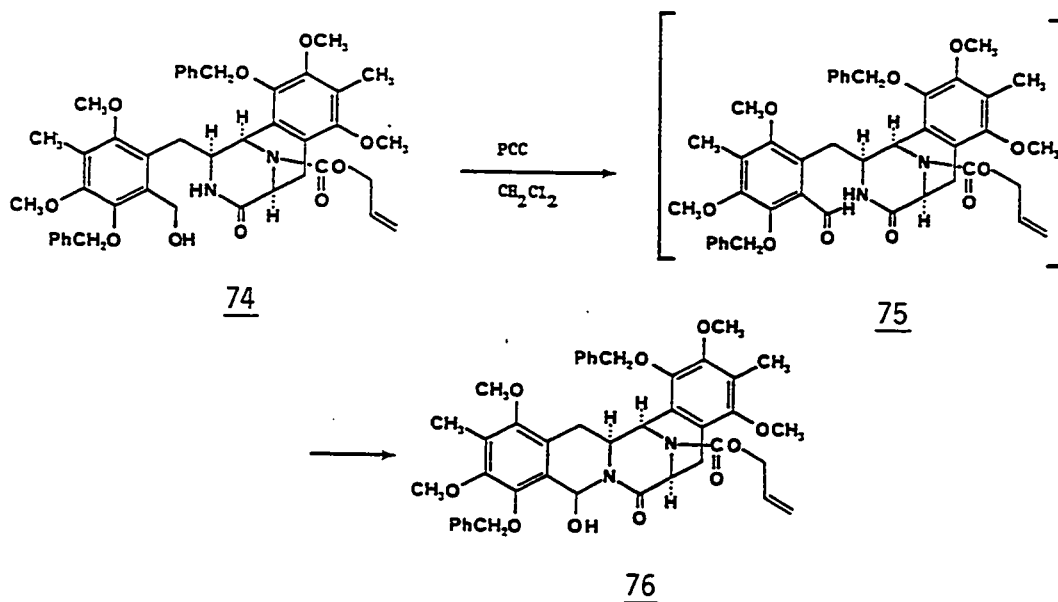
Having failed to build from the nitrogen, attempts were made to construct the necessary substitution from the aromatic ring. Hydroxymethylation of the phenol using formaldehyde under basic conditions was successful.



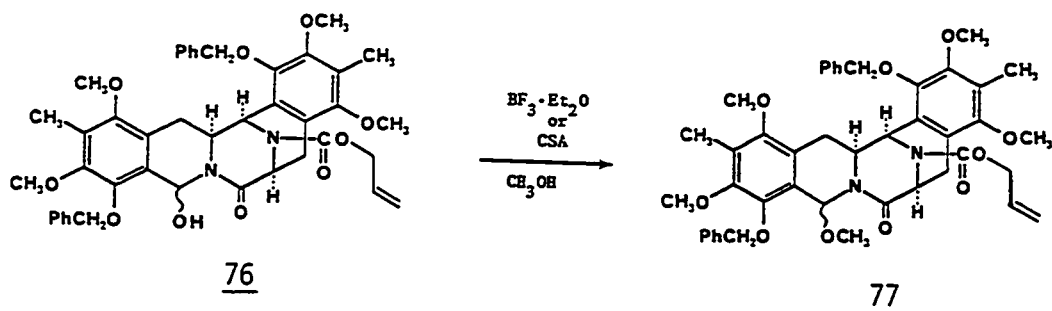
Protection of the amine 60 as the allyl urethane gave 72, followed by hydroxymethylation with formaldehyde and sodium hydroxide in dioxane to give the diphenol-alcohol 73. This was treated with benzyl bromide and potassium carbonate in dimethylformamide to give the ether-alcohol 74, in 74% overall yield including the catalytic reduction step.



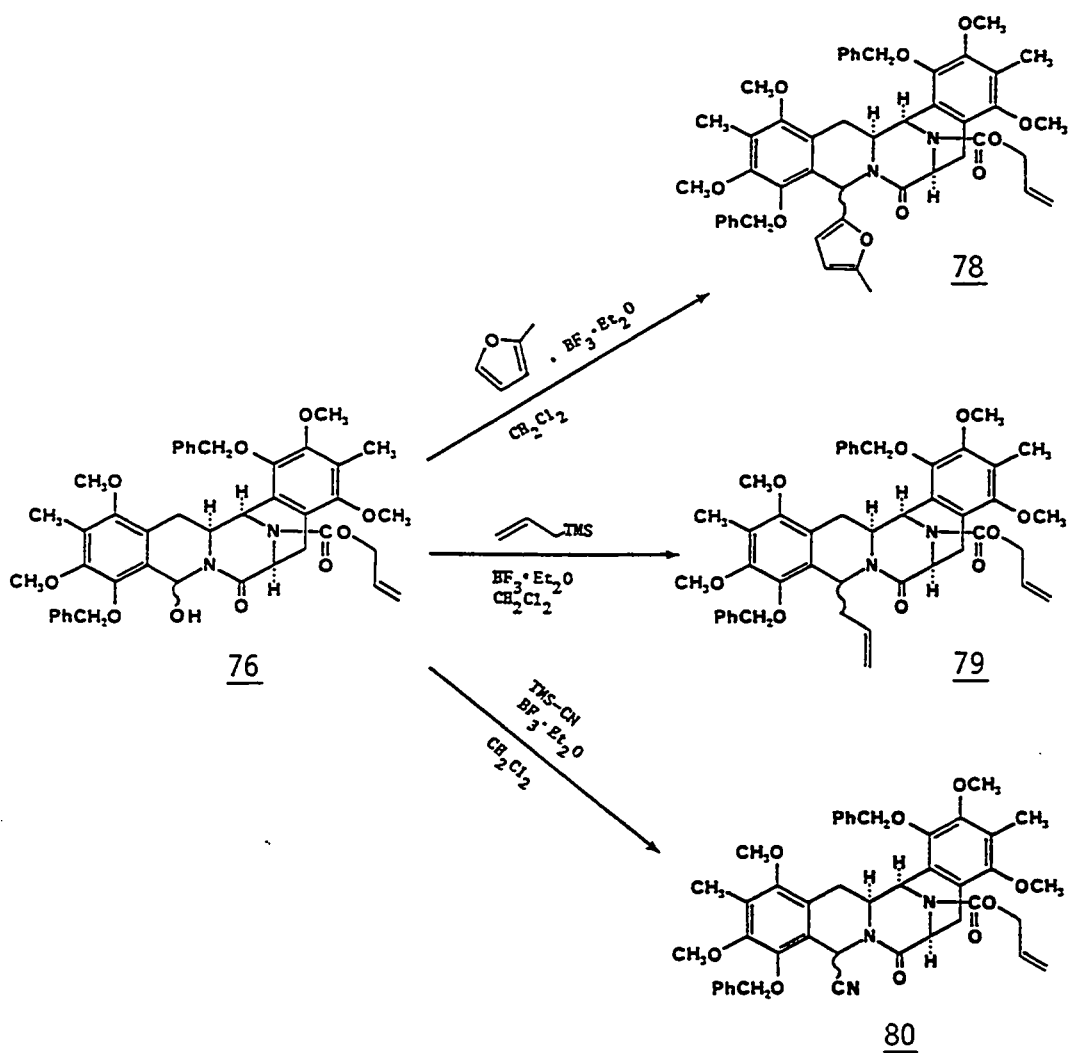
Oxidation of alcohol 74 with pyridinium chlorochromate in dichloromethane gave the benzaldehyde 75, which immediately cyclized to give a mixture of hydroxy lactams 76.



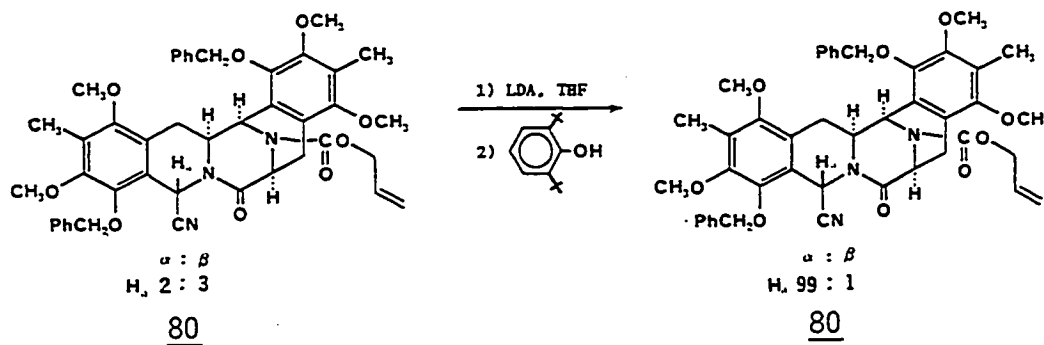
The hydroxy lactams 76 could be converted into the methoxy lactams 77 with a catalytic amount of acid in methanol.



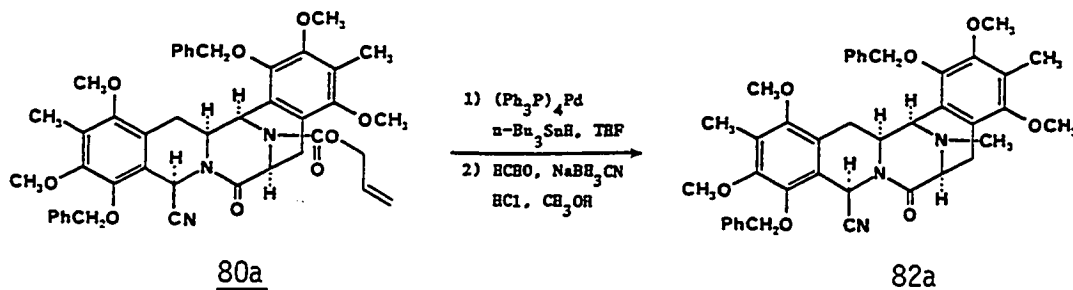
Reaction of either hydroxy- or methoxy- lactams, 76 or 77, with a variety of reagents under acidic conditions gave C-C bonds in the benzylic position. For example; methylfuran, allyltrimethylsilane, and trimethylsilyl cyanide, all gave corresponding compounds in reasonable yields.<sup>27</sup>



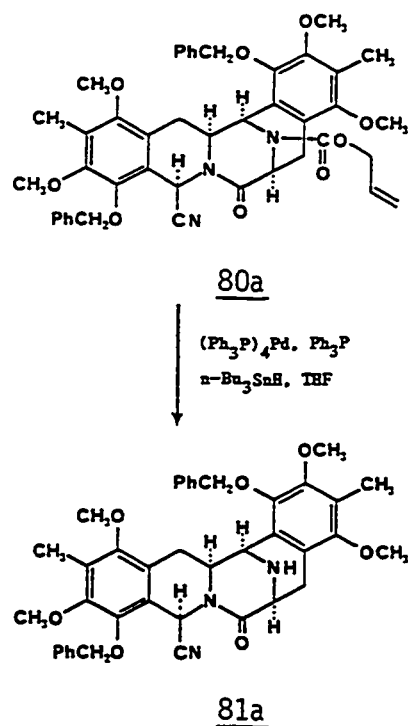
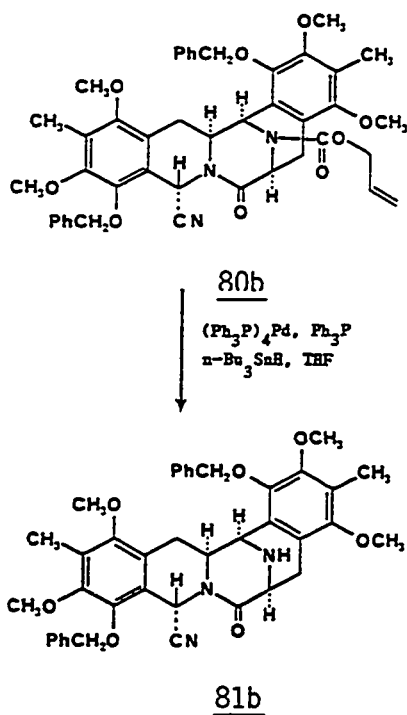
Treatment of 76 with trimethylsilyl cyanide and boron trifluoride etherate<sup>27</sup> in dichloromethane gave a 2:3 mixture of nitriles 80a and 80b in 74% yield. This mixture could be converted to a 99:1 ratio in 65% yield by treatment with lithium diisopropylamide in tetrahydrofuran, followed by quenching with a hindered proton source, such as 2,6-di-*tert*-butyl phenol. Protonation of the carbanion by a bulky proton source would be expected to result in the hydrogen being delivered from the least hindered  $\alpha$ -face of the molecule, giving the desired stereochemistry at C-1.

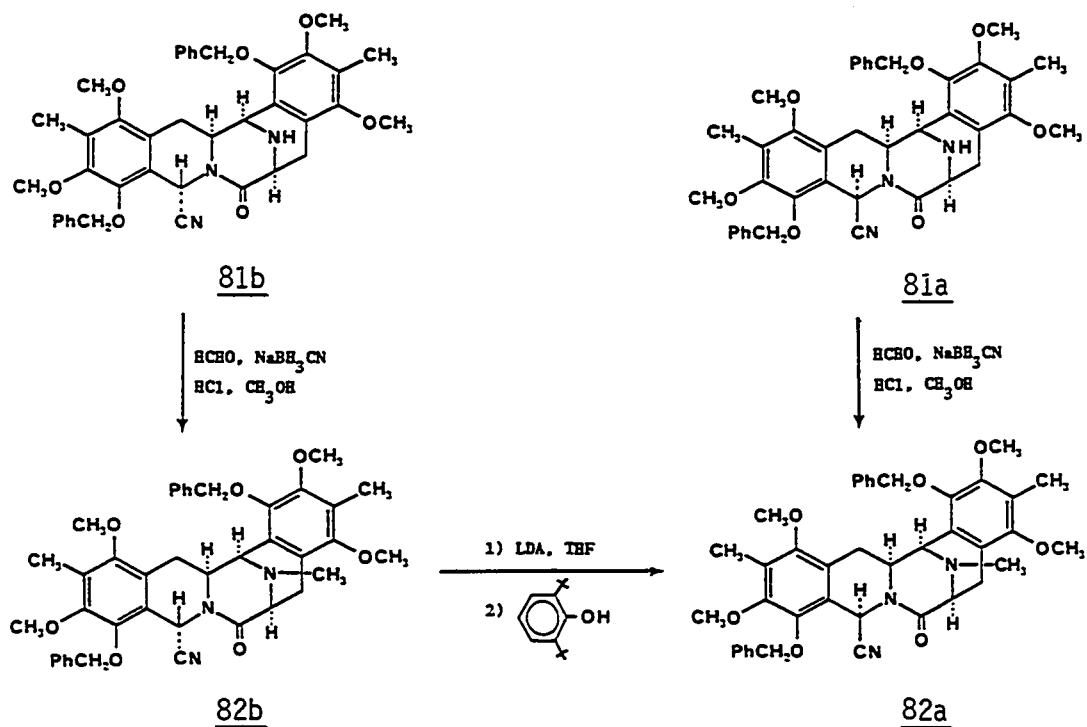


Removal of the allyl urethane using tetrakis(triphenylphosphine) palladium(0) and tri-*n*-butyltin hydride<sup>28</sup> in tetrahydrofuran followed by acidic workup and N-methylation with formaldehyde and sodium cyanoborohydride gave the methylamine 82a in 75% yield.

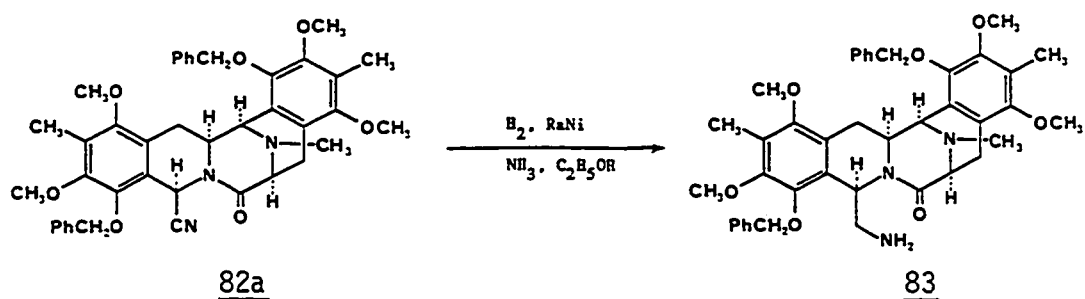


Improved yields were obtained when epimerization of the nitrile was conducted on the methylamine 82b, instead of on the urethane 80b. In fact, fractional crystallization of the urethane-nitrile mixture, 80, from methanol gave pure nitrile of the desired stereochemistry, 80a, where all of the hydrogens are cis. The undesired isomer, 80b, remained in the mother liquor. Conversion of the urethanes to the methylamines separately, allowed epimerization of only one portion, 82b, of the material to be necessary.

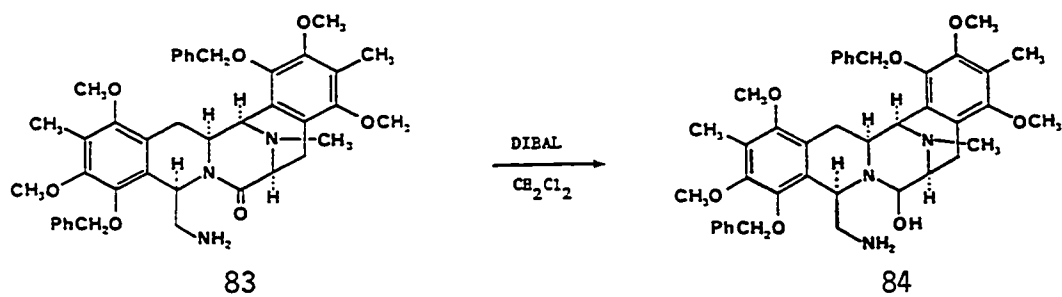




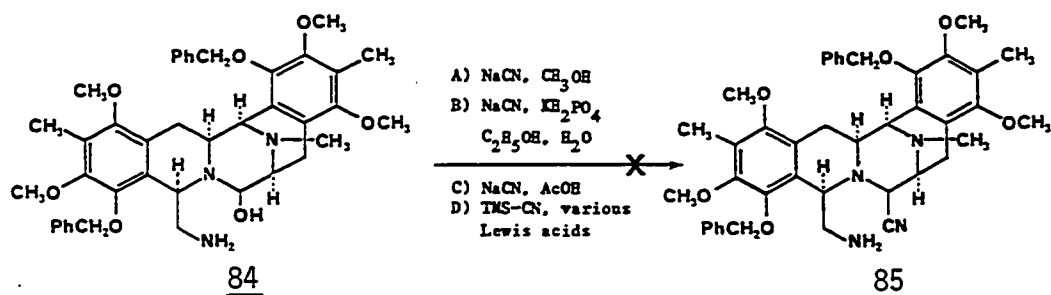
Reduction of the nitrile **82a**, with Raney nickel in ethanol saturated with ammonia, at room temperature and hydrogen pressure of 1000 psi, gave the amine **83**, without hydrogenolysis of the benzyl ethers.



Treatment of amine 83 with DIBAL in dichloromethane at  $-78^{\circ}$  gave what appeared to be the carbinolamine 84.

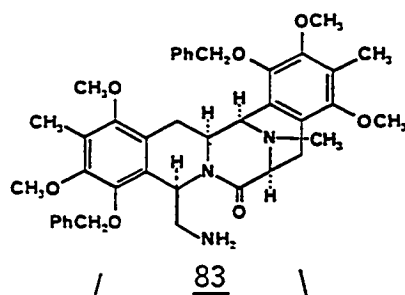


However, this compound did not react with cyanide ion under a variety of conditions; acidic, neutral or basic.



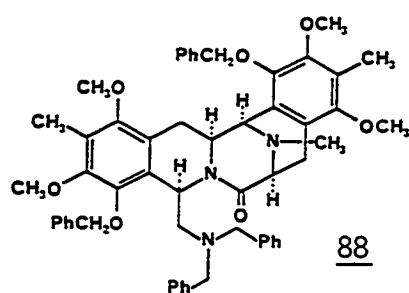
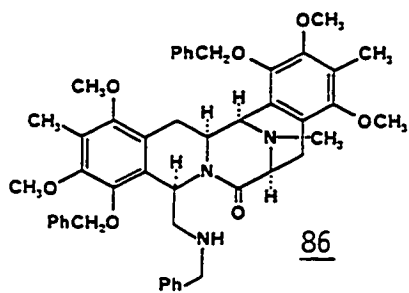
It seems naive to expect a system such as 84 to exist, in light of our later findings, but much time was spent elaborating the chemistry of this compound before the correct structure was recognized. It was found that conversion of the primary amine 83, to the secondary amine 86, by mono-alkylation, did not change the course of the DIBAL reduction. However, conversion to the dialkyl-amine 88 resulted in DIBAL reduction of the lactam to give the fully reduced compound 89.





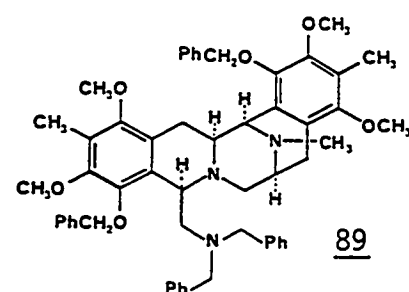
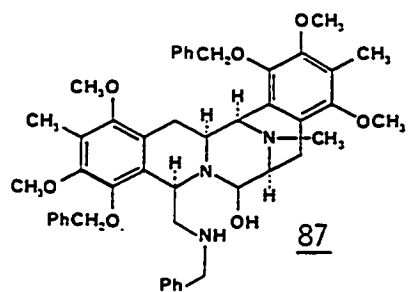
1) PhCHO, CSA  
benzene, Al<sub>2</sub>O<sub>3</sub>  
2) NaBH<sub>4</sub>, CH<sub>3</sub>OH

PhCHO, HCl  
NaBH<sub>3</sub>CN  
CH<sub>3</sub>OH

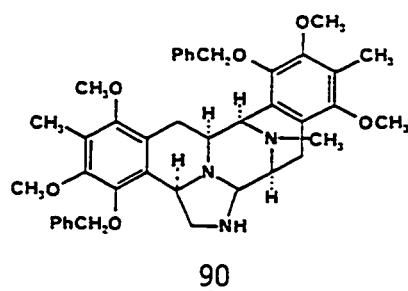


DIBAL  
CB<sub>2</sub>Cl<sub>2</sub>

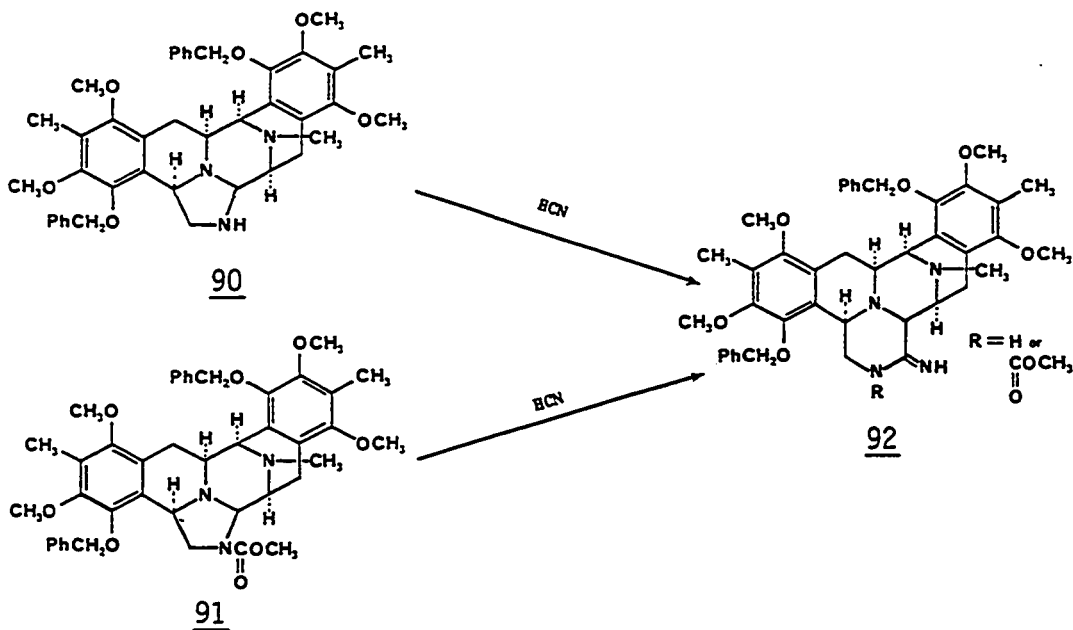
DIBAL  
CB<sub>2</sub>Cl<sub>2</sub>



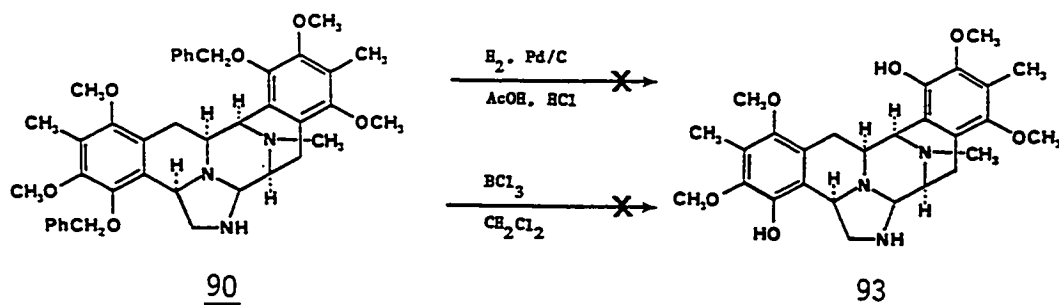
The studies on the reduction of lactam 83 indicated that an N-H bond was necessary for partial reduction to occur. Therefore, we reconsidered the structure 84. Cyclization of the primary amine into the carbinolamine to form an imidazolidine, such as 90, explains the experimental results nicely.<sup>29</sup>



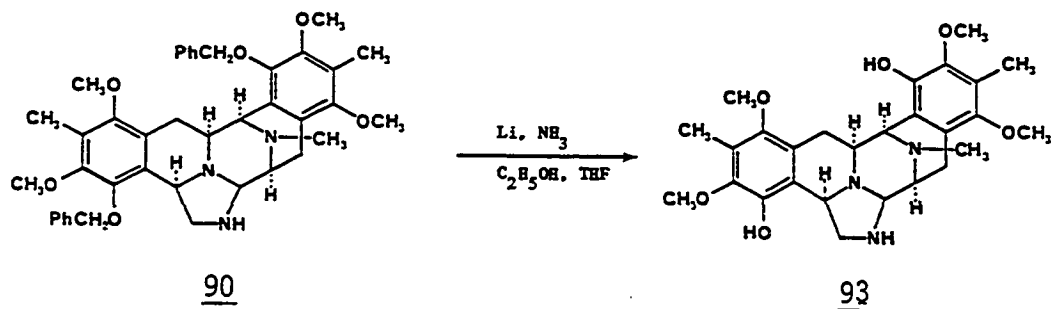
Once this structure was recognized, further progress towards saframycins A and S could be undertaken. All attempts to open the imidazolidine ring of 90 or 91 were unsuccessful or gave undesirable results.



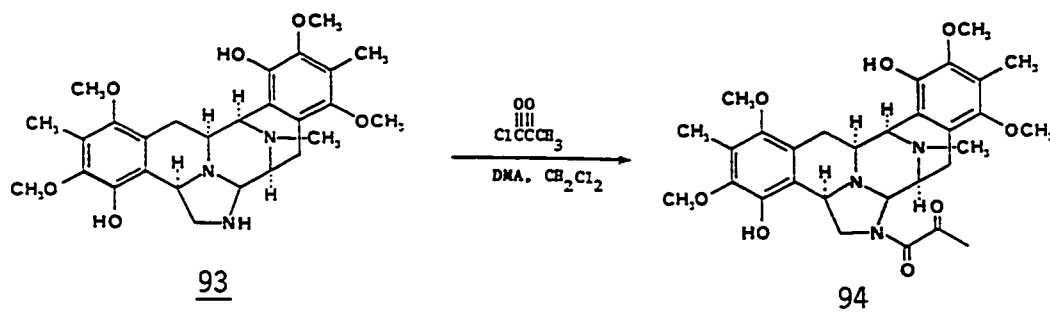
Removal of the two benzyl ethers of 90 proved surprisingly difficult. Catalytic hydrogenolysis was unsuccessful and acid cleavage with boron trichloride resulted in poor yields.



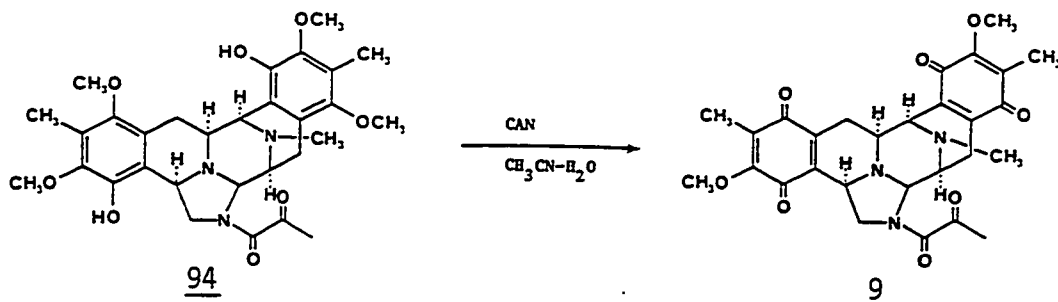
However, Birch reduction of 90 with lithium in liquid ammonia and tetrahydrofuran containing ethanol gave the diphenol-triamine 93.



The amine 93 was acylated with pyruvyl chloride to give the pyruvamide, 94.



Finally, oxidation of diphenol 94 with ceric ammonium nitrate<sup>23,24</sup> in acetonitrile-water gave the bisquinone 9 in 20% yield.



The  $^1\text{H}$  NMR of 9 appears to be consistent with that for a bisquinone with two aromatic methoxyl, two aromatic methyl, one N-methyl and one pyruvyl methyl group. The MS shows a molecular ion at  $m/e=535$ , and predictable losses of acetyl ( $-43$ ), and pyruvyl ( $-71$ ). The base peak at  $m/e$  220 is consistent with the behavior of saframycin A,<sup>1,6,7</sup> and the weakness of a  $\text{M}^+ -100$  (loss of the entire pyruvamide side chain) understandable in light of the stability of the cyclic imidizolidine structure.

Preliminary experiments on compound 9 indicate that treatment with 0.1N sulfuric acid at 100°<sup>4,5</sup> causes conversion to a more polar compound that appears similar in UV activity, on fluorescence indicating silica gel TLC, to the saframycin type quinones. Hopefully, further experiments will prove that 9 can be converted to saframycin S and therefore into saframycin A.<sup>4,5,7</sup> The activity of the saframycins A and S is postulated to involve the carbinolamine functionality.<sup>4,5</sup> If compound 9 can be shown to be a congener of the saframycins, it will be interesting to see what kind of biological activity it exhibits.

Synthetic studies on compound 9, as well as saframycin C and the renieramycins are being continued in the laboratory of Dr. T. Fukuyama at the Chemistry Department of W. M. Rice University.

**Chapter IV**

**THE TOTAL SYNTHESIS**

**OF**

**SAFRAMYCIN B**

**EXPERIMENTAL**

## EXPERIMENTAL

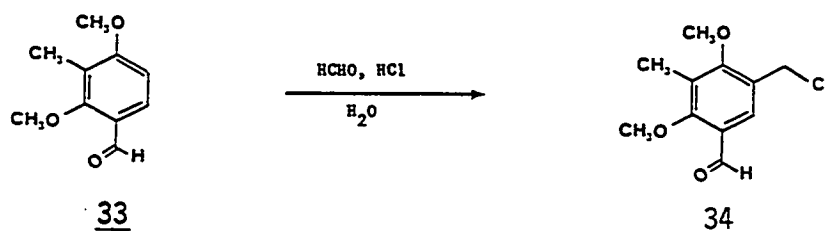
### General:

MPLC separations were done using Woelm silica gel, 32-60 mesh. TLC separations were done using Merck silica gel 60 PF-254, 1-2 mm thick, on glass plates. Analytical TLC analyses were done on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F-254.

$^1\text{H}$  spectra were run on a JEOL FX-90Q. IR spectra were run on a Beckman 4230. Low resolution mass spectra were obtained on a Finnigan 3300 quadrupole. High resolution mass spectra were obtained on a CEC 21-110B. Elemental analyses were performed by Galbraith Laboratories, Inc, Knoxville, TN.

Ether and dichloromethane were distilled through a 24 inch Snyder column. Dichloromethane was dried over  $\text{Al}_2\text{O}_3$ . Tetrahydrofuran was dried by distillation from benzophenone ketyl. Dimethyl formamide was dried over  $4\text{\AA}$  molecular sieves. Diisopropylamine was distilled from calcium hydride and stored over  $4\text{\AA}$  molecular sieves and potassium hydroxide pellets. All other reagents were of commercial quality and were used without further purification.

Melting points are uncorrected.



2,4-DIMETHOXY-5-CHLOROMETHYL-3-METHYLBENZALDEHYDE (34)

Hydrogen chloride was bubbled into a solution of 60 g (33mmol) of 2,4-dimethoxy-3-methyl benzaldehyde<sup>16</sup> 33 in 200 ml of 37% formaldehyde solution at 80° for three hours. The solution was poured over ice and the resulting crystalline mass filtered and washed with cold water. Extraction of the filtrant with ether and dichloromethane recovered a small additional amount of material. The crude product was dissolved in dichloromethane and filtered through sodium sulfate to dry. Evaporation gave 86.7 g (114%) of 34. This crude material was satisfactory for the next reaction. mp 66-67° (methanol)

IR (CH<sub>2</sub>Cl<sub>2</sub>): 1690, 1595, 1105, 995

NMR (CDCl<sub>3</sub>): 2.28 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 4.63 (2H, s), 7.78 (1H, s), 10.27 (1H, s)

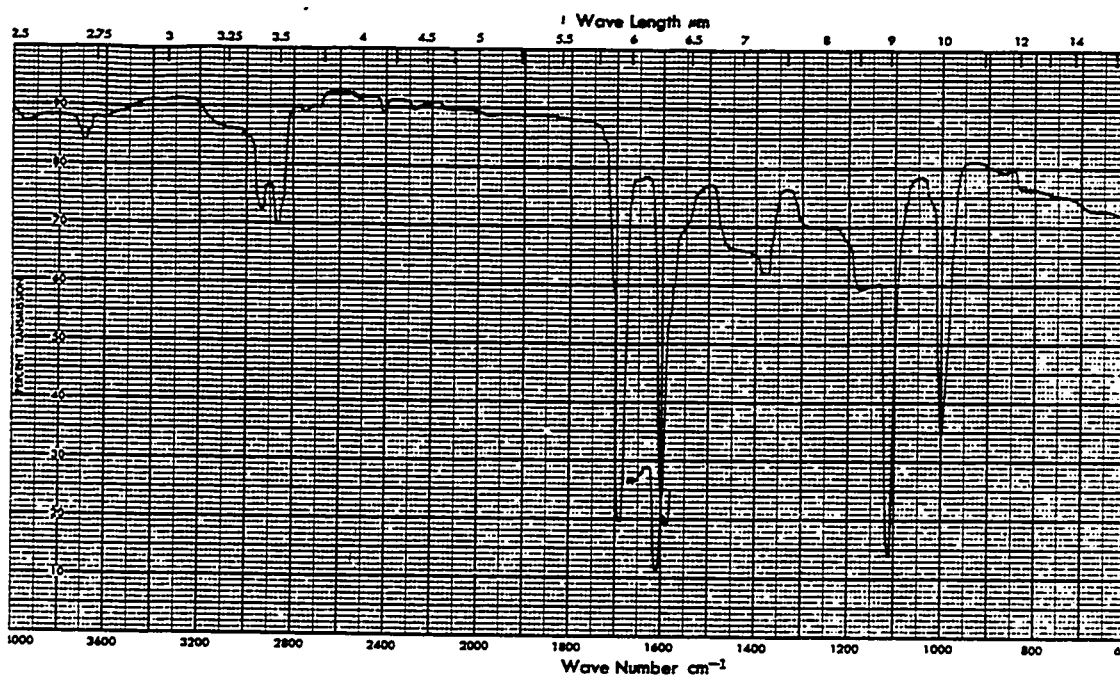
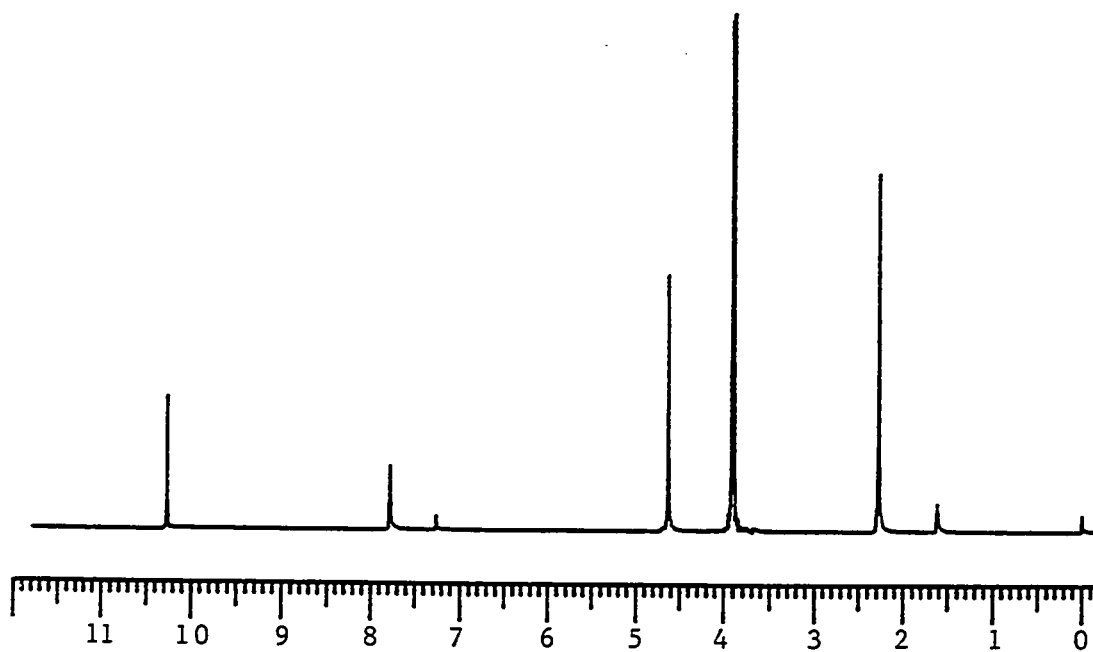
MS: 228/230 (12/4, M<sup>+</sup>), 193 (50), 18 (100)

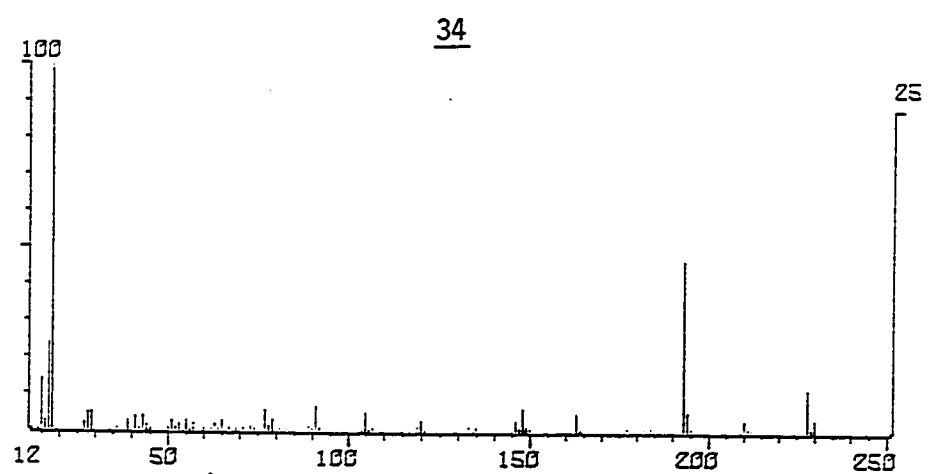
Analysis: C<sub>11</sub>H<sub>13</sub>ClO<sub>3</sub>

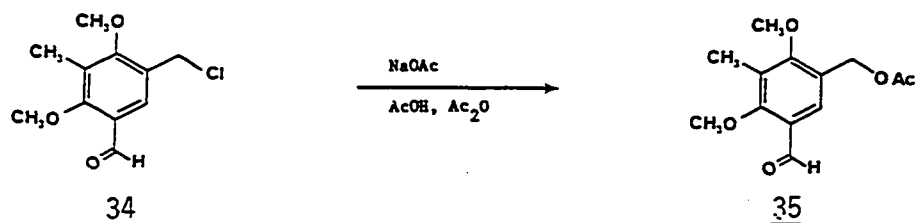
crystals from methanol

	calculated	found
C: 0.5778		0.5787
H: 0.0573		0.0584
Cl: 0.1550		0.1579



34





2,4-DIMETHOXY-5-ACETOXYMETHYL-4-METHYLBENZALDEHYDE (35)

A solution of 76.1 g (330 mmol) of 34 and 75 g (910 mmol) of sodium acetate in 300 ml of acetic acid and 20 ml of acetic anhydride was refluxed for three hours. Evaporation to a small volume was followed by partition between ether and dilute sodium chloride solution. The organic phase was extracted twice with saturated sodium chloride solution, followed by saturated sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate, and evaporated to give 78.2 g (94%) of 35. mp 37–37.5° (isopropyl ether)

IR ( $\text{CH}_2\text{Cl}_2$ ): 1785, 1680, 1595, 1360, 1100, 995

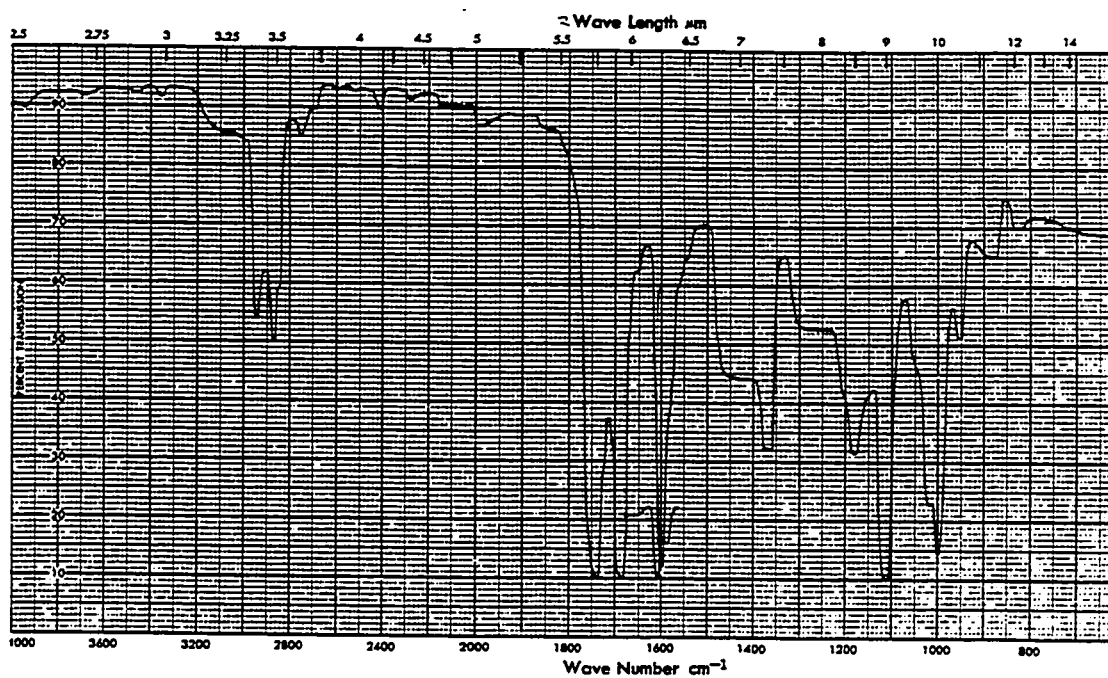
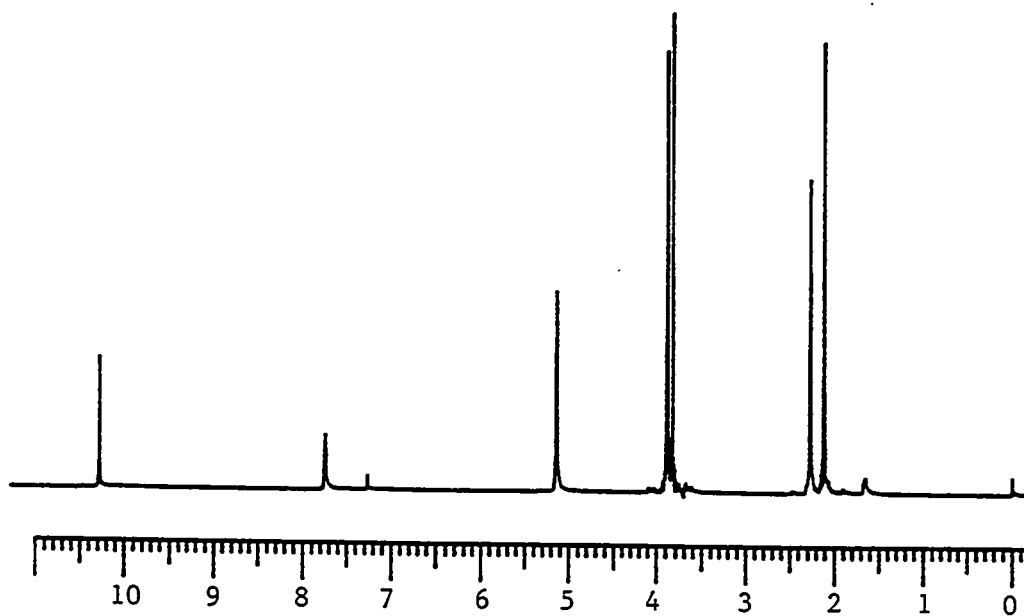
NMR ( $\text{CDCl}_3$ ): 2.11 (3H, s), 2.27 (3H, s), 3.83 (3H, s), 3.89 (3H, s), 5.14 (2H, s), 7.75 (1H, s), 10.28 (1H, 2)

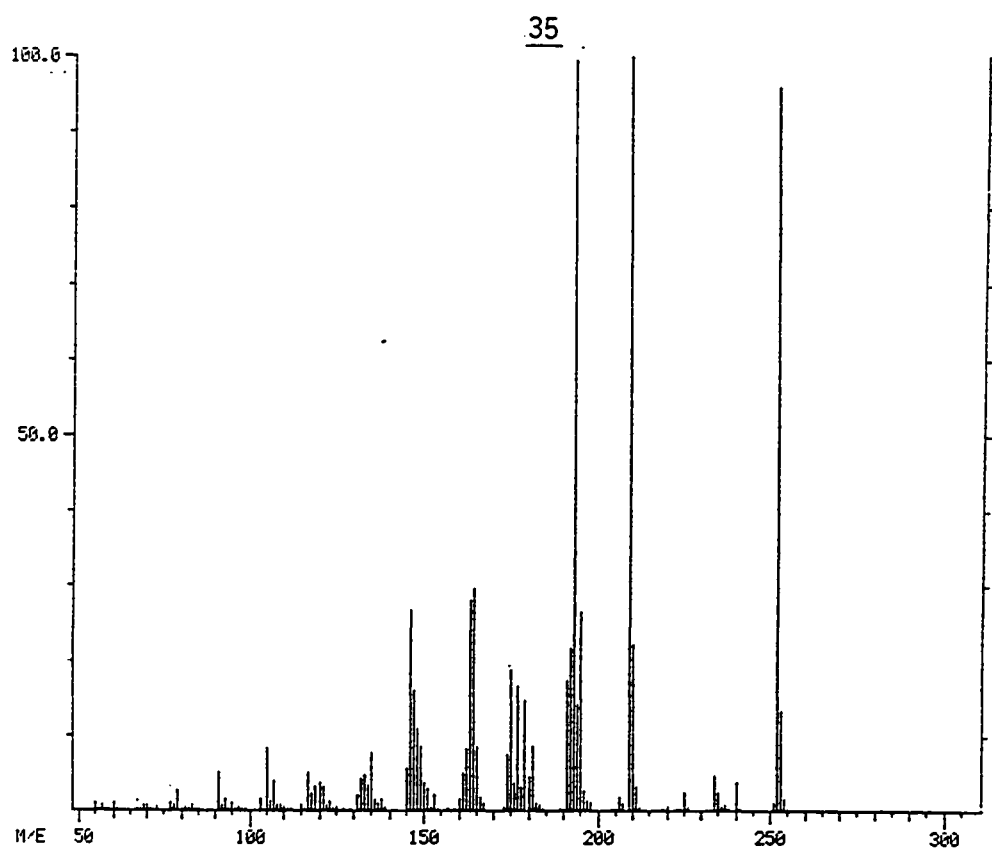
MS: 252 (97,  $\text{M}^+$ ), 209 (100), 193 (99)

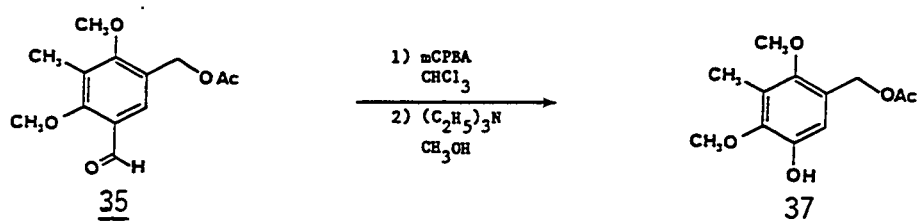
Analysis:  $\text{C}_{13}\text{H}_{16}\text{O}_5$

crystals from isopropyl ether

	calculated	found
C: 0.6190		0.6207
H: 0.0640		0.0652

35





#### 2,4-DIMETHOXY-5-ACETOXYMETHYL-3-METHYLPHENOL (37)

To a stirred suspension of 75 g (360 mmol) of 85% *m*-chloroperoxybenzoic acid in 100 ml of chloroform was added 78.2 g (310 mmol) of 35 in 200 ml of chloroform at a rate sufficient to maintain reflux. Upon completion of addition, the reaction was allowed to cool and 200 ml of hexanes added. *m*-Chlorobenzoic acid crystallized out. The suspension was filtered and the filtrant extracted twice with saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulfate and evaporated. The product 36 was dissolved in 200 ml of methanol and 10 ml of triethylamine was added. After standing for 10 minutes the solution was evaporated to give 73.6 g (99%) of 37. mp 57° (isopropyl ether).

IR ( $CH_2Cl_2$ ): 3540, 1730,

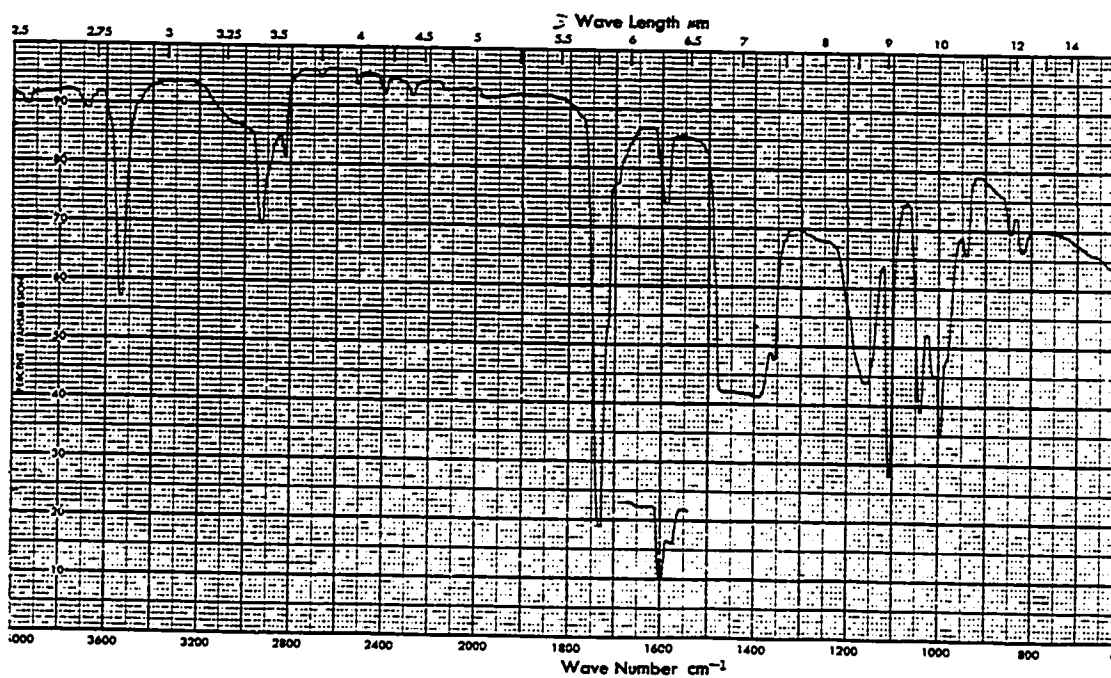
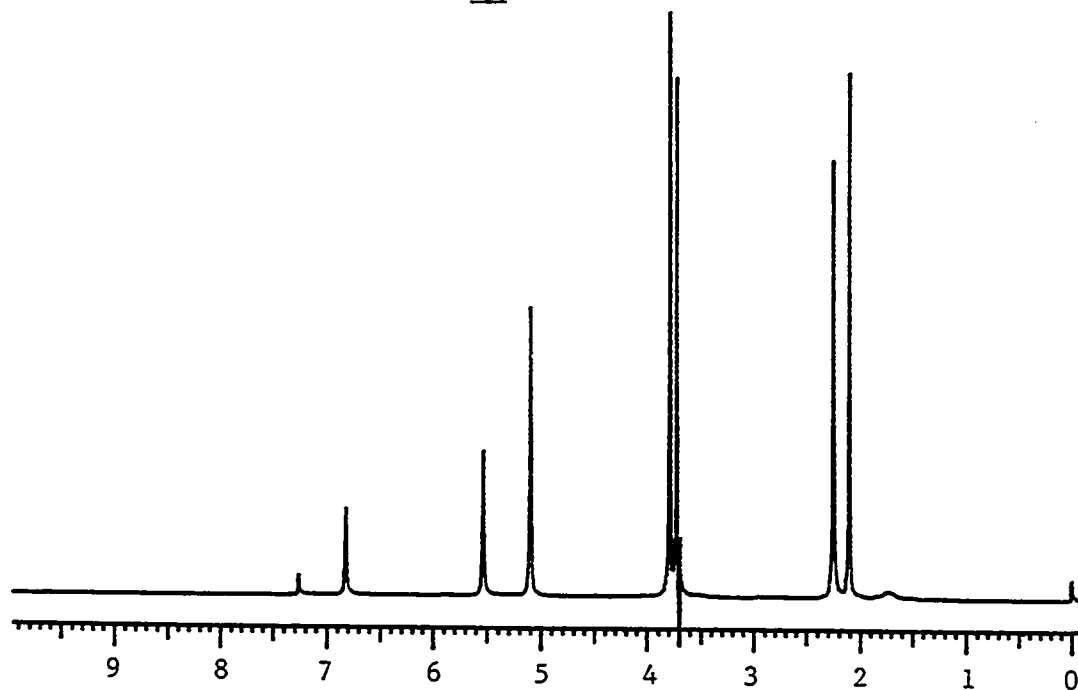
NMR ( $CDCl_3$ ): 2.11 (3H, s), 2.26 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 5.10 (2H, s), 5.54 (1H, s), 6.82 (1H, s)

MS: 240 (80,  $M^+$ ), 197 (30), 181 (45), 123 (40), 43 (80), 18 (100)

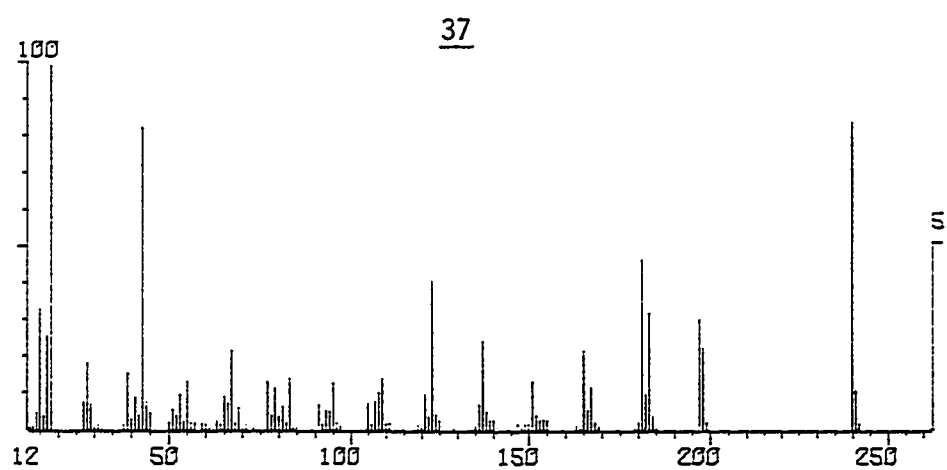
Analysis:  $C_{12}H_{16}O_5$

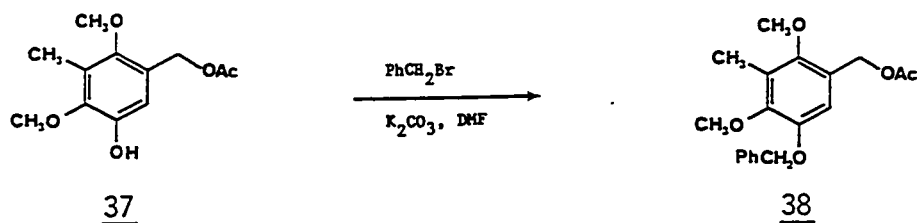
crystals from isopropyl ether

	calculated	found
C:	0.5999	0.6007
H:	0.0671	0.0697

37







2,4-DIMETHOXY-5-ACETOXYMETHYL-4-METHYLPHENOL BENZYL ETHER (38)

A mixture of 73.1 g (300 mmol) of 37, 41 ml (340 mmol) of benzyl bromide, and 130 g (940 mmol) of potassium carbonate in 200 ml of dimethylformamide was heated, with stirring, to 80° for two hours. Upon cooling, water was added to dissolve the solid, and the solution was extracted twice with ether. The organic phase was extracted with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to give 87.0 g (86%) of 38. mp 77° (methanol)

IR (CH<sub>2</sub>Cl<sub>2</sub>): 1740

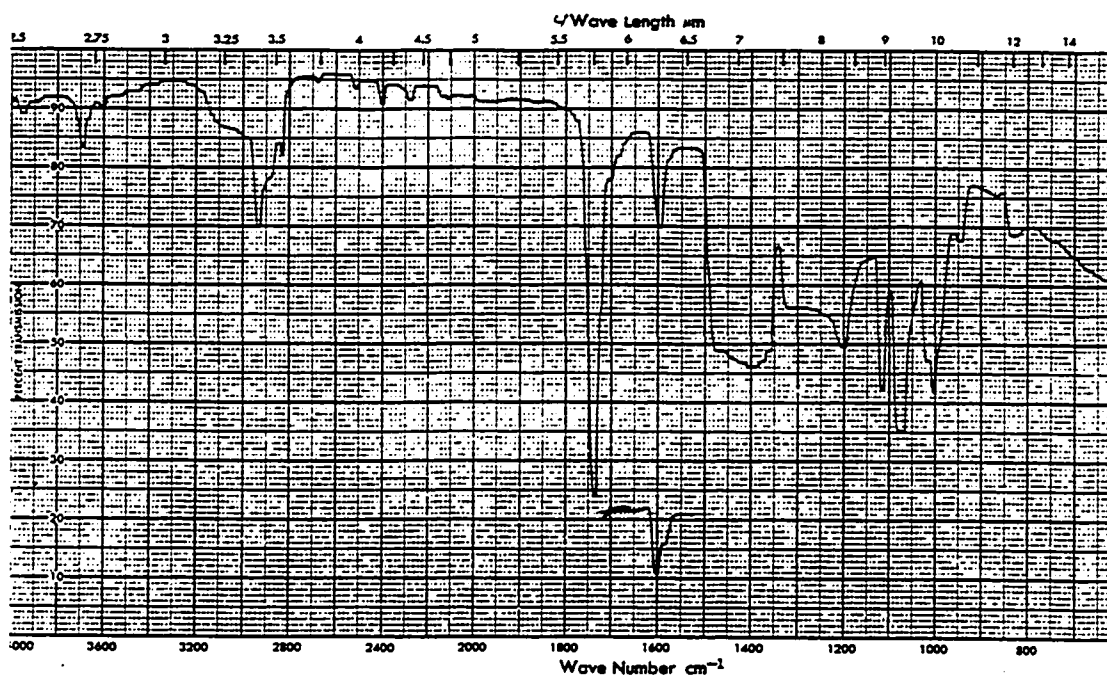
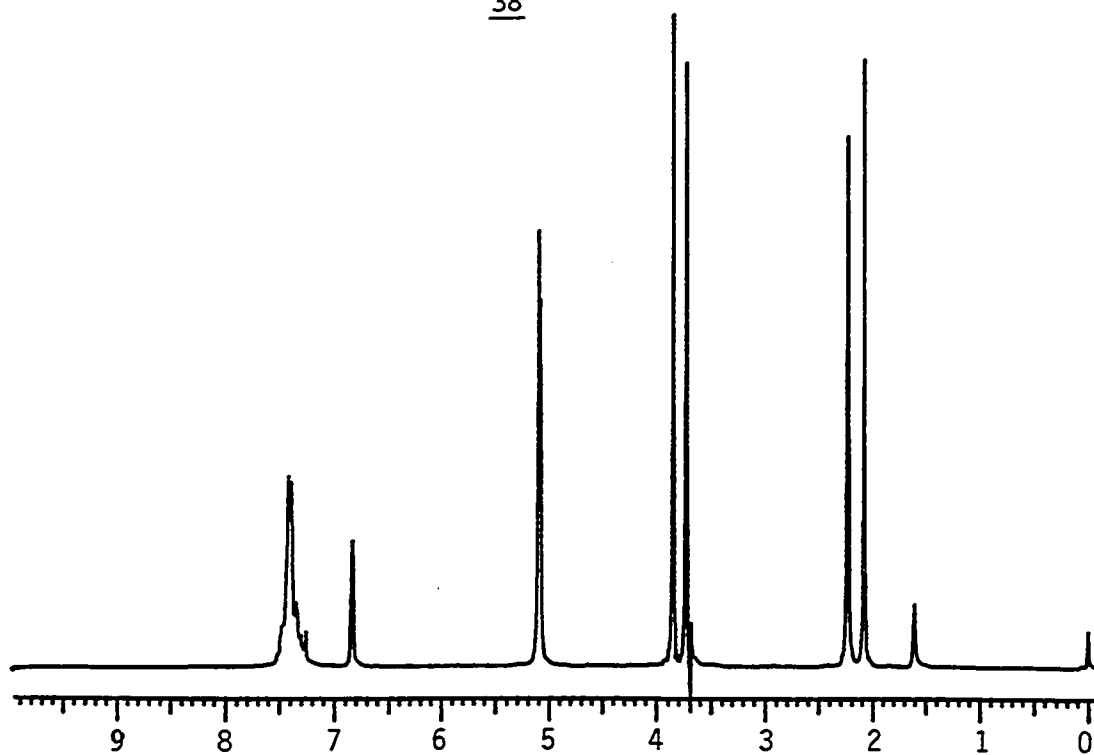
NMR (CDCl<sub>3</sub>): 2.07 (3H, s), 2.23 (3H, s), 3.72 (3H, s), 3.84 (3H, s), 5.07 (2H, s), 5.09 (2H, s), 6.83 (1H, s), 7.40 (5H, m)

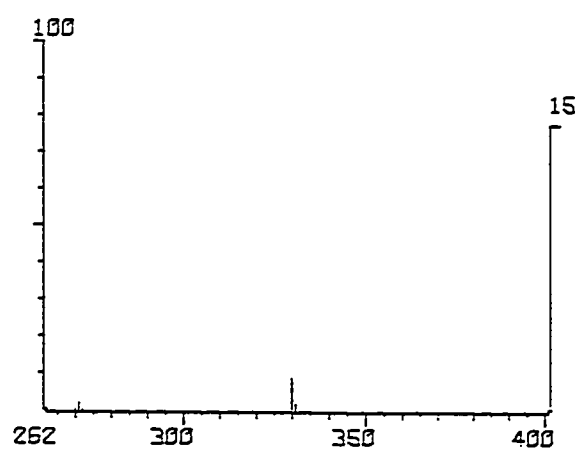
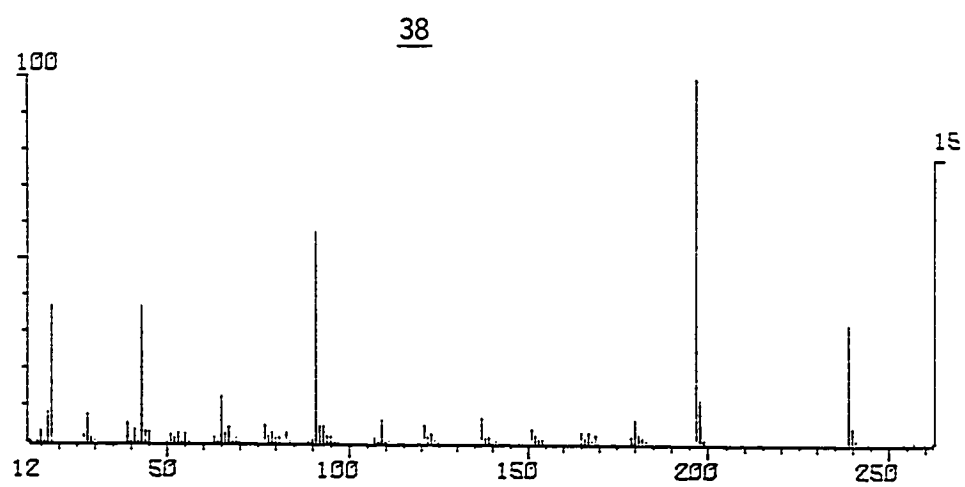
MS: 330 (10, M<sup>+</sup>), 239 (30), 197 (100), 91 (60)

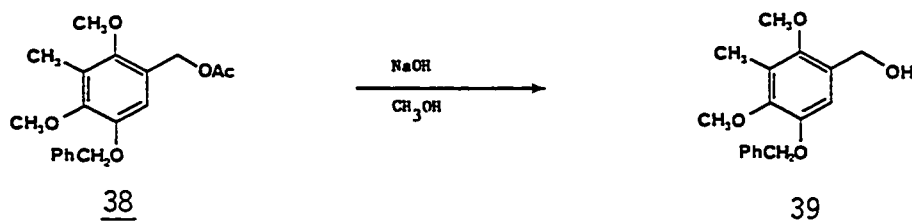
Analysis: C<sub>19</sub>H<sub>22</sub>O<sub>5</sub>

crystals from methanol

	calculated	found
C:	0.6908	0.6917
H:	0.0671	0.0670

38





2,4-DIMETHOXY-5-BENZYLOXY-3-METHYLBENZYL ALCOHOL (39)

To a solution of 87.0 g (264 mmol) of 38 in 100 ml of dichloromethane was added a solution of 11.0 g (275 mmol) of sodium hydroxide in 100 ml of methanol. The mixture heated to reflux. Upon cooling, carbon dioxide in the form of dry ice was added until the pH dropped below 10. The reaction mixture was evaporated to a small volume and partitioned between ether and saturated sodium chloride solution. The organic phase was washed twice with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to obtain 79.3 g (104%) of 39.

mp 57.5° (methanol)

IR ( $\text{CH}_2\text{Cl}_2$ ): 3605, 2935, 1400, 1115, 1070, 1005

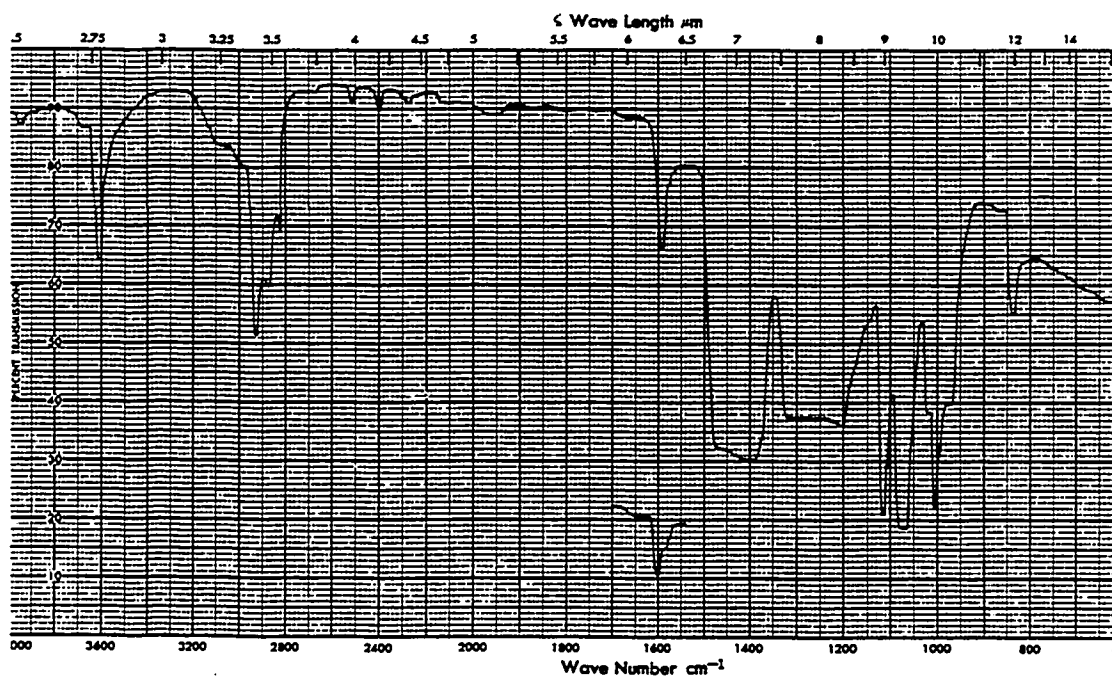
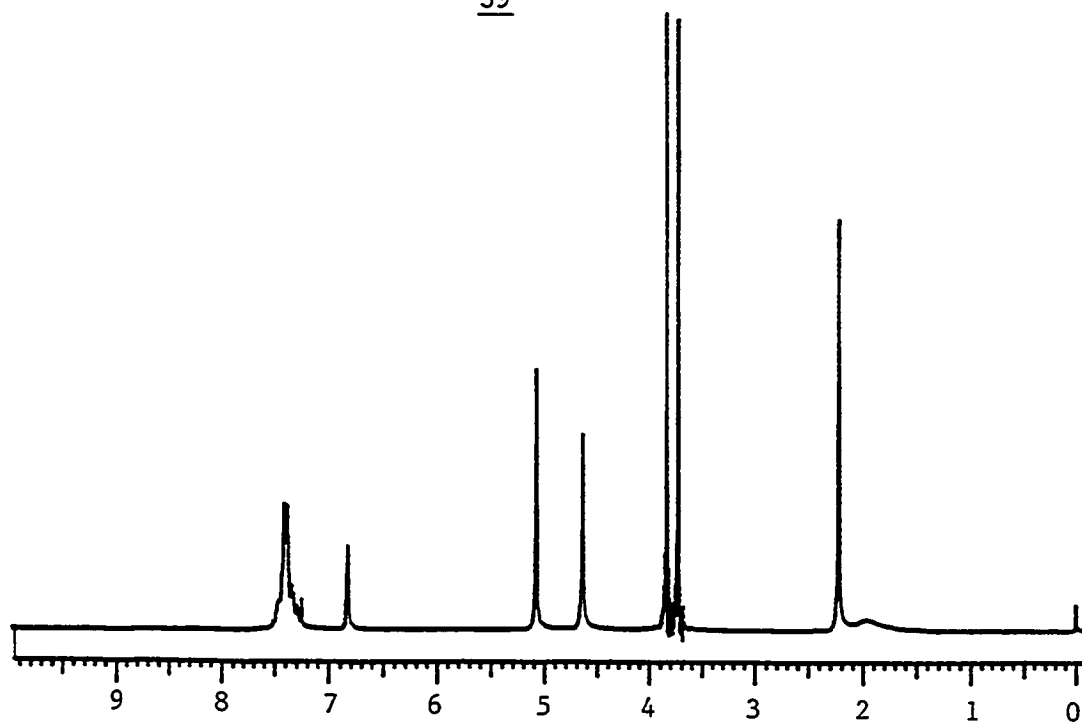
NMR ( $\text{CDCl}_3$ ): 2.22 (3H, s), 3.73 (3H, s), 3.84 (3H, s), 4.64 (2H, s),  
5.08 (2H, s), 6.83 (1H, s), 7.40 (5H, m)

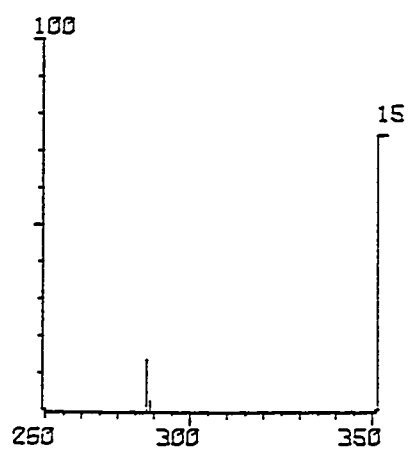
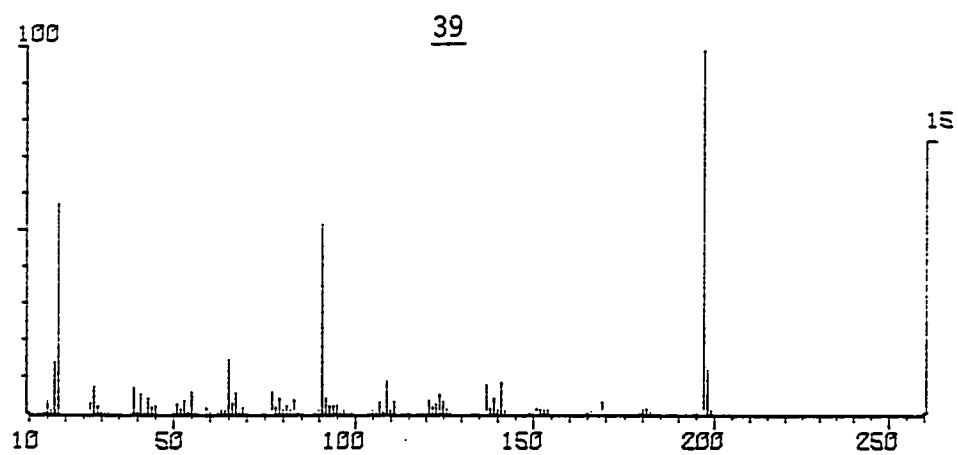
MS: 288 (15,  $\text{M}^+$ ), 198 (100), 91 (55), 18 (58)

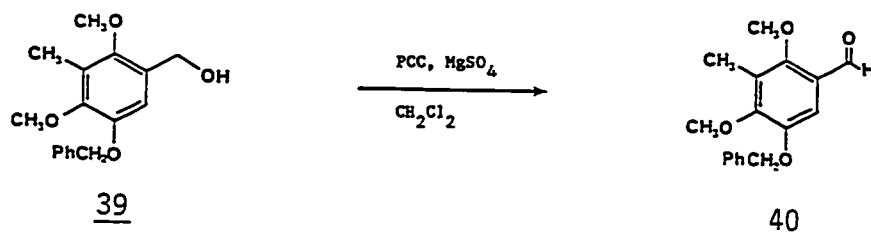
Analysis:  $\text{C}_{17}\text{H}_{20}\text{O}_4$

crystals from methanol

	calculated	found
C: 0.7081		0.7072
H: 0.0699		0.0697

39





#### 2,4-DIMETHOXY-5-PHENOXY-3-METHYLBENZALDEHYDE (40)

A solution of 79.3 g (275 mmol) of 39 in 300 ml of dichloromethane was added to a stirred suspension of 68 g (310 mmol) of pyridinium chlorochromate and 75 g of magnesium sulfate in 300 ml of dichloromethane at a rate sufficient to maintain a steady reflux. When the addition was complete, 500 ml of a solution of 60% ether in hexanes was added and stirring continued for 15 minutes. The solution was filtered through a short column containing 20 g silica gel, and the silica column washed with an additional 300 ml of 60% ether in hexanes. Evaporation of the solution and slow crystallization from 5% ethyl acetate in hexanes gave 69.0 g of 40. mp 47.5–48° (isopropyl ether)

IR ( $\text{CH}_2\text{Cl}_2$ ): 1680, 1590, 1120, 1070

NMR ( $\text{CDCl}_3$ ): 2.23 (3H, s), 3.84 (3H, s), 3.92 (3H, s), 5.10 (2H, s), 7.40 (5H, m), 10.27 (1H, s)

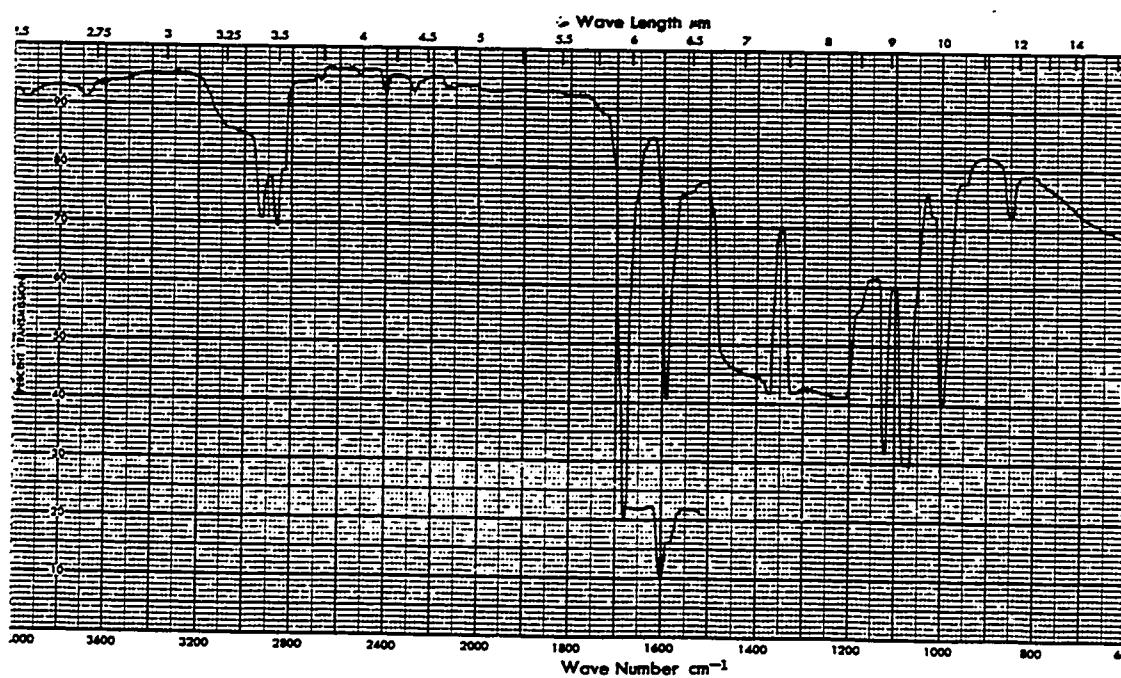
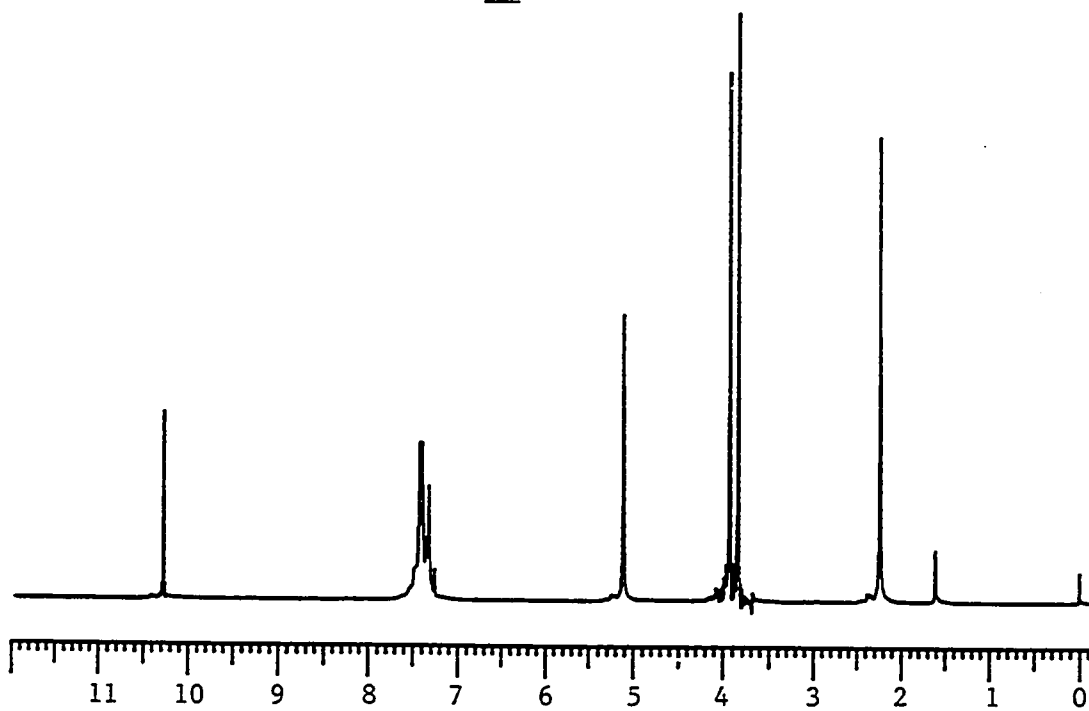
MS: 286 (15,  $\text{M}^+$ ), 195 (70), 91 (100)

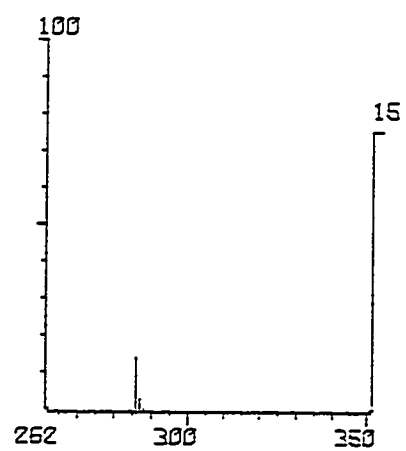
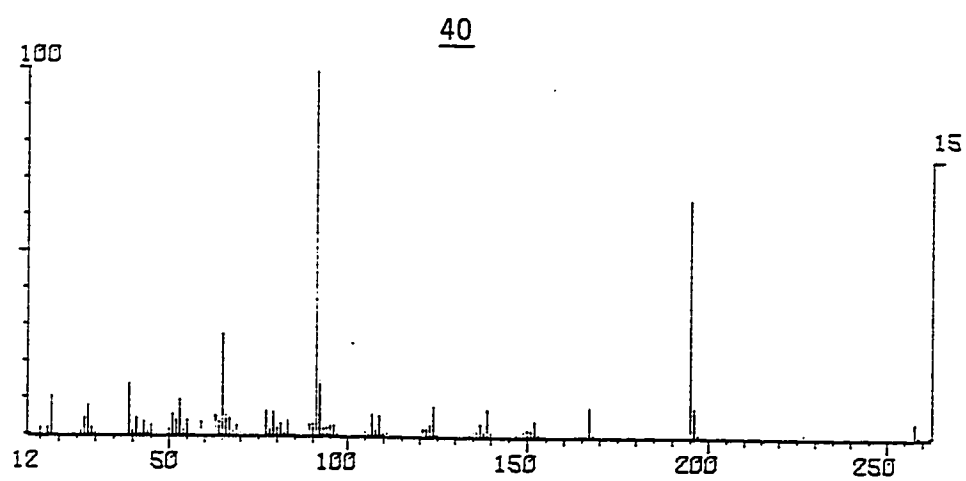
Analysis:  $\text{C}_{17}\text{H}_{18}\text{O}_4$

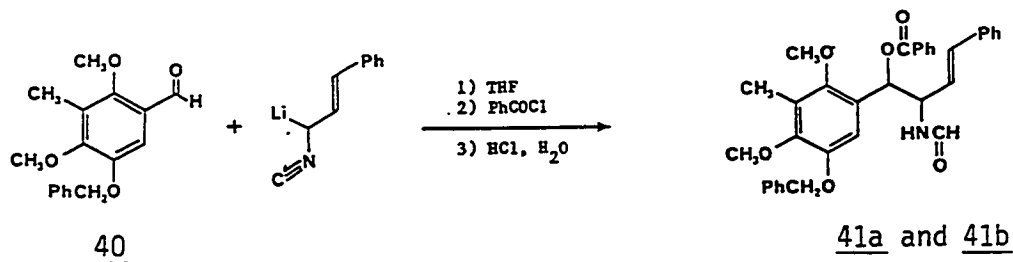
crystals from isopropyl ether

	calculated	found
C:	0.7131	0.7145
H:	0.0634	0.0652



40





#### FORMAMIDE-BENZOATE (41)

To a stirred solution of 5.50 g (38.5 mmol) of cinnamyl isonitrile in 100 ml of tetrahydrofuran at  $-78^{\circ}$  was added 18.4 ml (36.7 mmol) of 2.00 N n-butyl lithium in hexanes, over 10 minutes. After stirring at  $-78^{\circ}$  for 10 minutes, a solution of 10.0 g (35.0 mmol) 40 in 20 ml of tetrahydrofuran was added over 5 minutes. After stirring at  $-78^{\circ}$  for 10 minutes, 4.50 ml (38.5 mmol) of benzoyl chloride was added over 2 minutes and the reaction mixture allowed to warm to room temperature over 20 minutes. Approximately 3 ml of 3N hydrochloric acid solution was added and the reaction mixture stirred at room temperature for 10 minutes. The reaction mixture was partitioned between ether and saturated sodium chloride solution, followed by extraction of the organic phase with saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulfate and evaporated. Chromatographic separation on silica gel, eluted with an ether in hexanes gradient yielded 18.3 g (95%) mixture of 41a and 41b as a slightly yellow foam. Repeated chromatography on silica gel eluted with an acetone-benzene gradient gave pure samples of 41a and 41b as white foams.

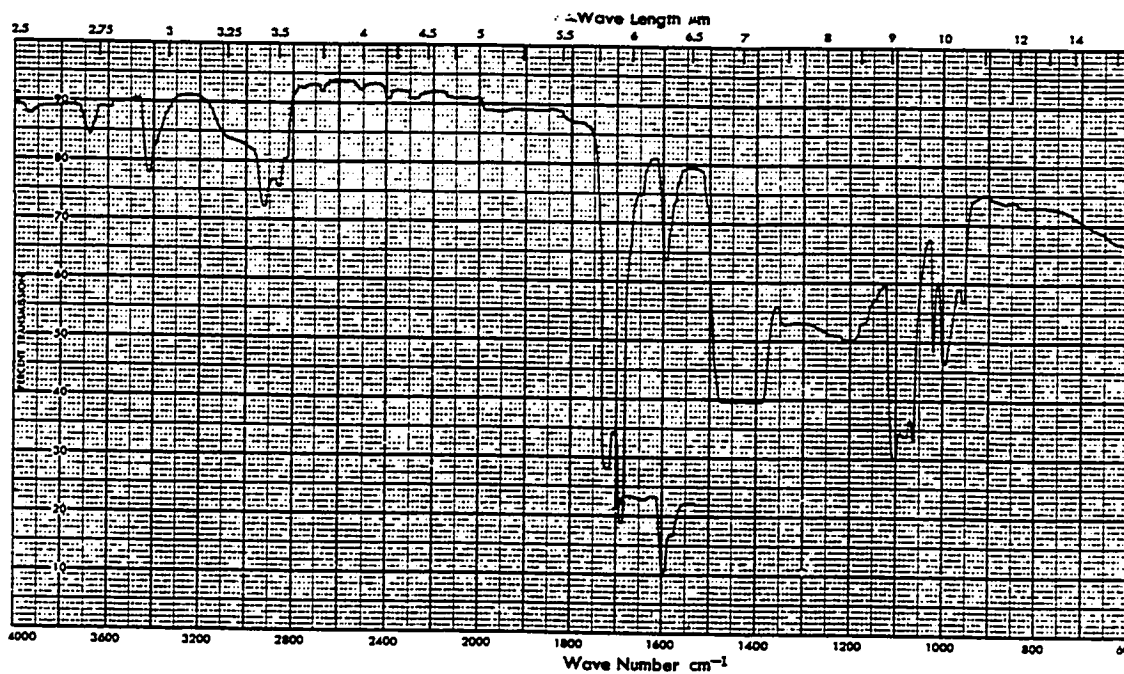
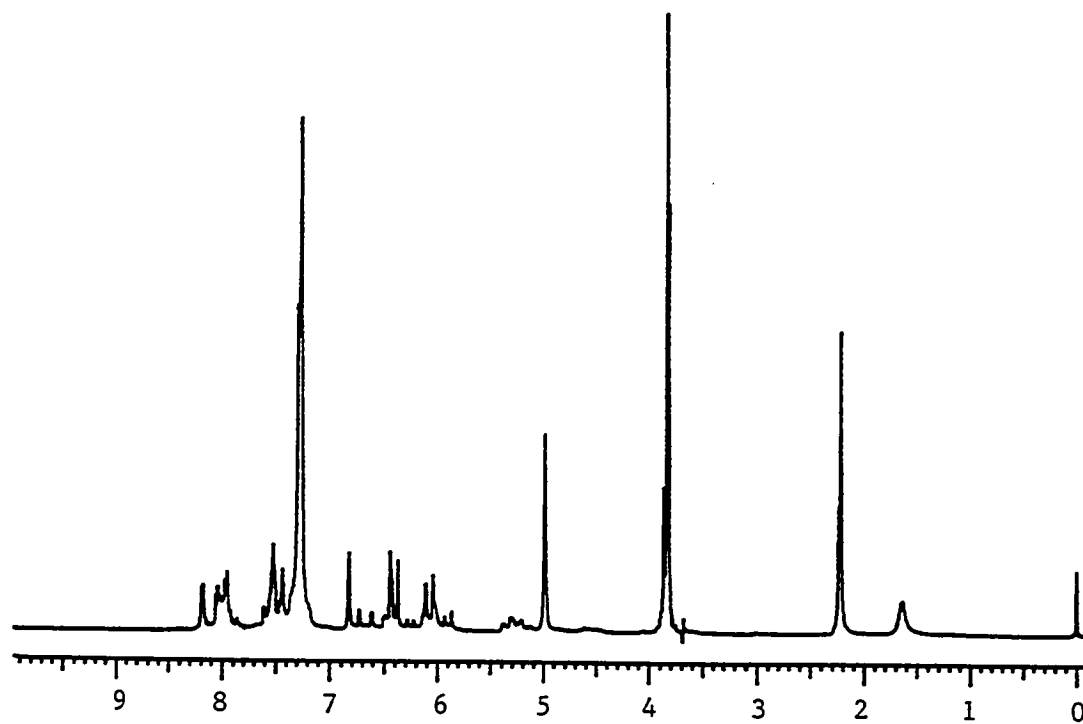
IR ( $\text{CH}_2\text{Cl}_2$ ): 1725, 1695, 1115, 1070

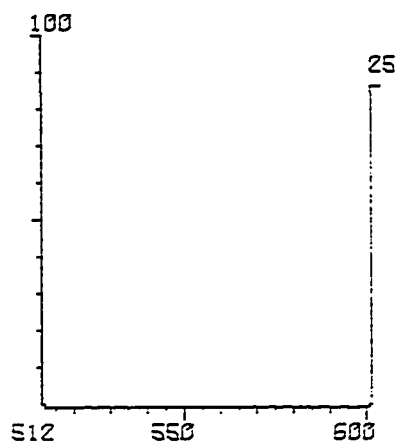
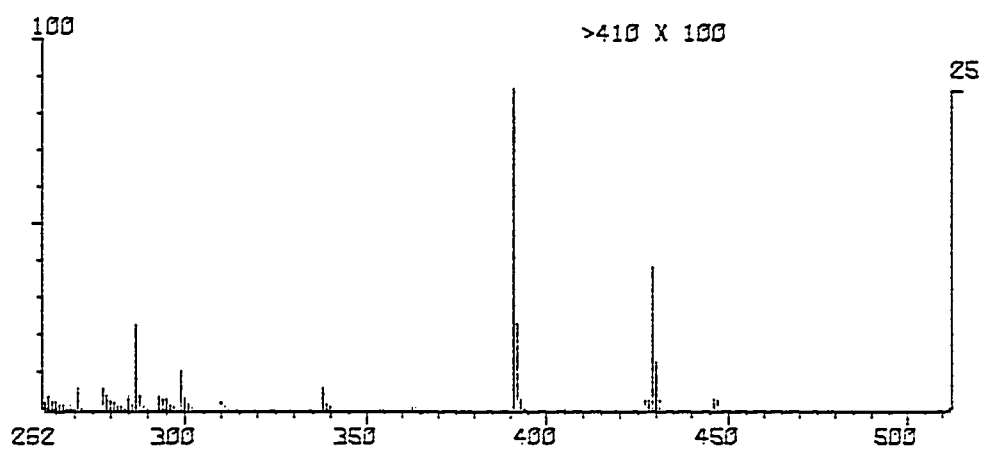
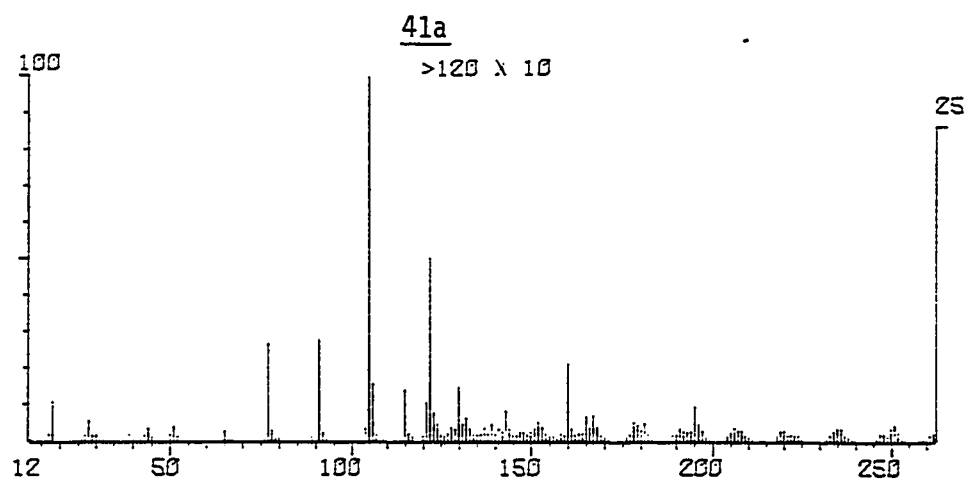
NMR ( $\text{CDCl}_3$ ): 41a 2.22 (3H, s), 3.83 (3H, s), 4.99 (2H, s),  
4.0-4.4 (1H, m), 5.8-6.8 (3H, m), 6.83 (1H, s),  
7.26 (5H, s), 7.29 (5H, s), 7.3-8.2 (6H, m)  
41b 2.24 (3H, s), 3.84 (3H, s), 3.89 (3H, s),  
4.96 (2H, s), 4.0-4.3 (1H, m), 6.0-6.8 (3H, m),  
6.75 (1H, s), 7.25 (5H, s), 7.28 (5H, s),  
7.3-8.2 (6H, m)

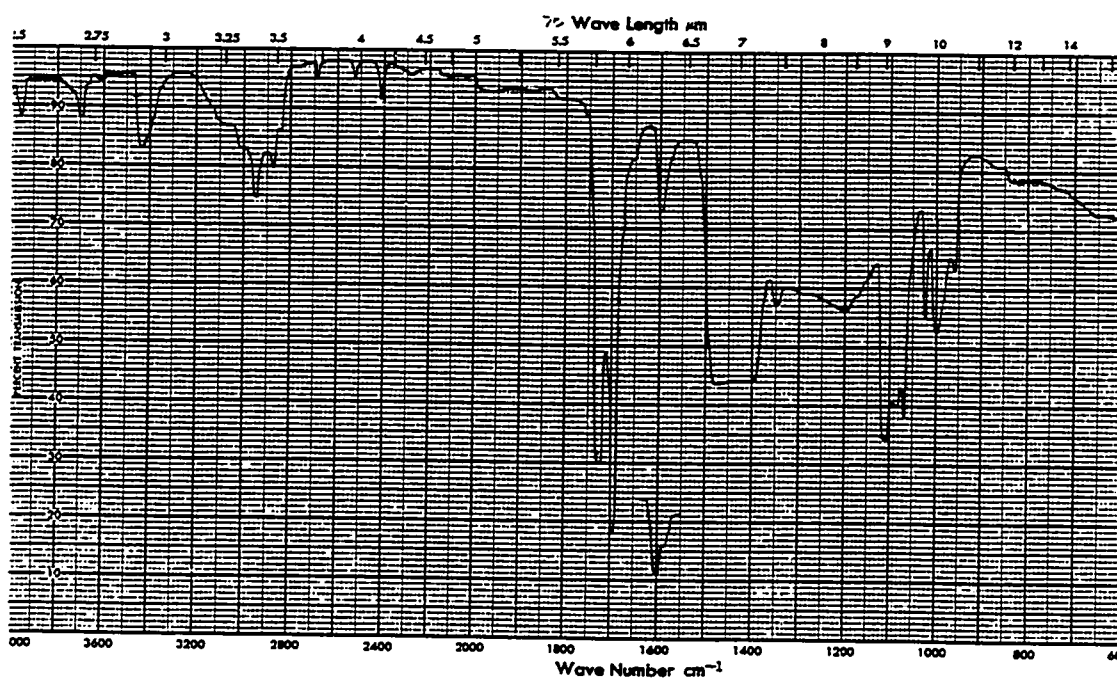
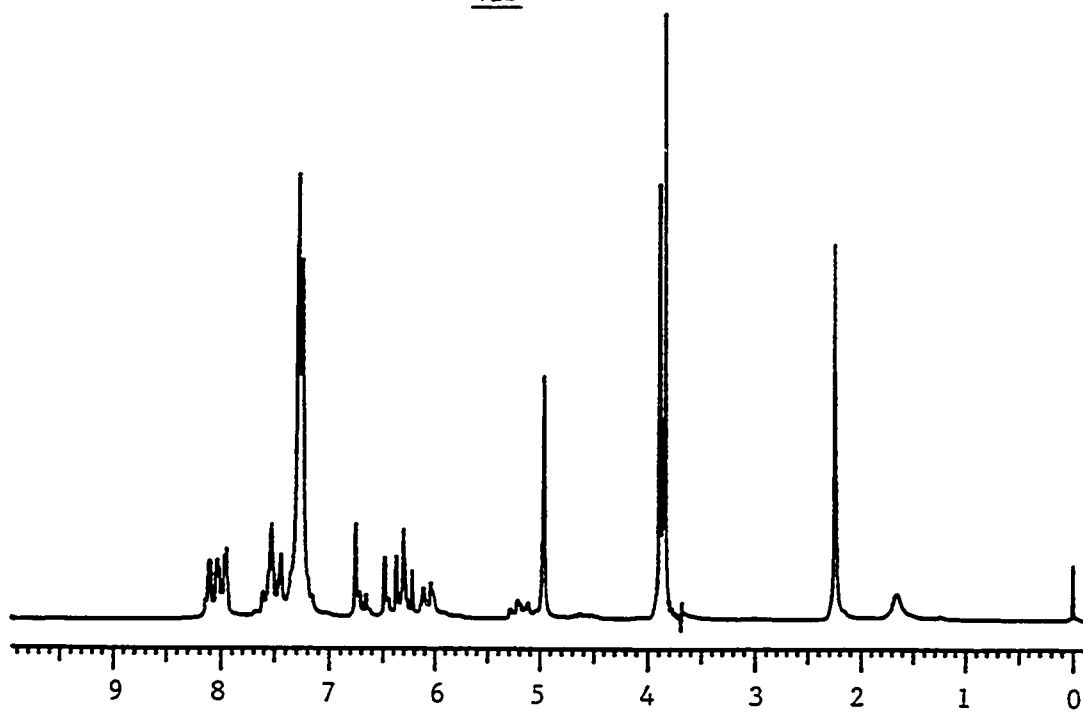
MS: 41a 429 (.4), 391 (9), 122 (5), 115 (13), 105 (100)  
41b 446 (.07), 429 (.5), 391 (22), 122 (7), 115 (38), 105 (100)

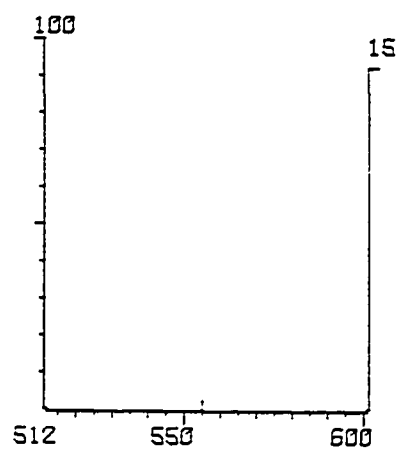
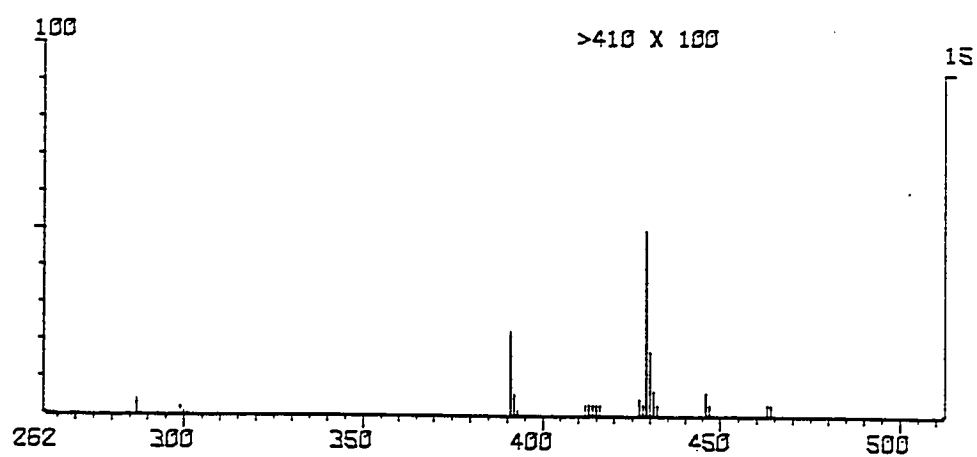
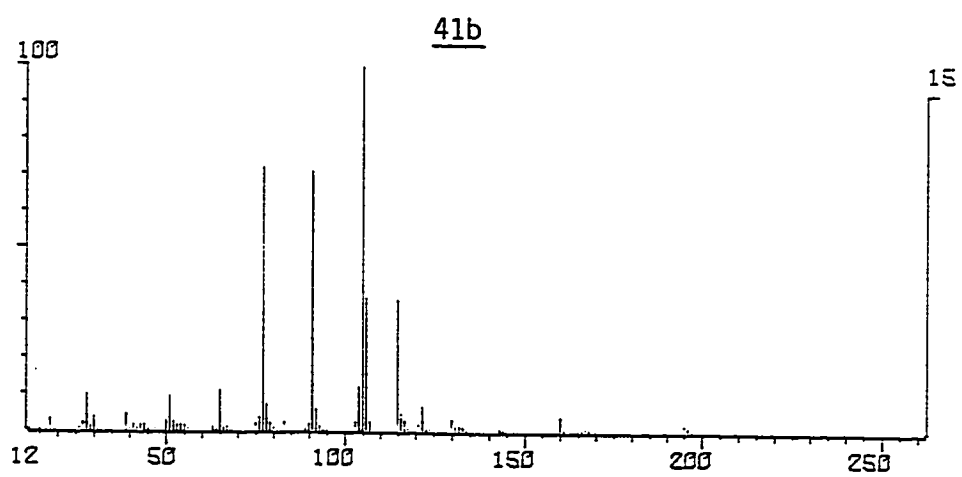
Analysis:  $\text{C}_{34}\text{H}_{33}\text{NO}_6$

<u>41a</u>		<u>41b</u>
chromatographed foam		chromatographed foam
calculated	found	found
C: 0.7403	0.7399	0.7376
H: 0.0603	0.0611	0.0620
N: 0.0254	0.0247	0.0244

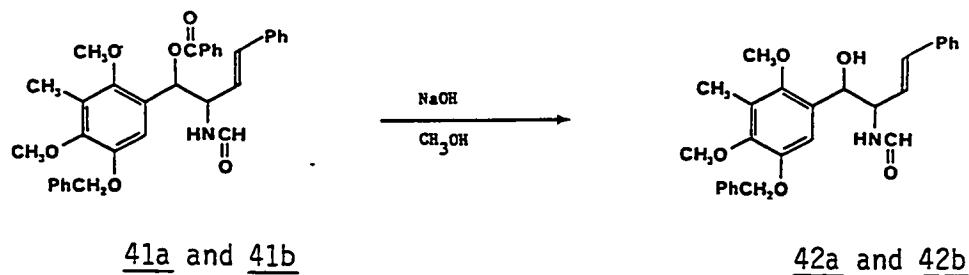
41a



41b







#### FORMAMIDE-ALCOHOL (42a and 42b)

To a solution of 1.0 g (1.8 mmol) of 42a in 10 ml of methanol was added 0.60 ml (2.0 mmol) of 3N sodium hydroxide solution. After 5 minutes, carbon dioxide in the form of dry ice was added until the pH dropped below 10. The solution was partitioned between ether and saturated sodium chloride solution. Evaporation of the organic phase gave 0.80 g (99%) 42a as off-white crystals. mp 161 (methanol)

Similar treatment of 41b gave 0.80 g (99%) 42b as a slightly yellow oil. mp 125° (isopropyl ether) Spectral data for the two diastereomers was similar.

IR ( $\text{CH}_2\text{Cl}_2$ ): 1700

NMR: 42a ( $\text{CD}_3\text{OD}-\text{CDCl}_3$ ) 2.20 (3H, s), 3.72 (3H, s), 3.83 (3H, s), 4.7–5.0<sup>3</sup> (1H, m), 5.05 (2H, s), 6.14 (1H, dd,  $J=6\text{Hz}, 15\text{Hz}$ ), 6.49 (1H, d,  $J=15\text{Hz}$ ), 6.96 (1H, s), 7.28 (5H, s), 7.1–7.5 (5H, m), 8.04 (1H, s)  
42b ( $\text{CDCl}_3$ ) 2.22 (3H, s), 3.73 (3H, s), 3.83 (3H, s), 4.7–5.0 (1H, m), 4.98 (2H, s), 5.0–5.2 (1H, t,  $J=4\text{Hz}$ ), 6.27 (1H, dd,  $J=6\text{Hz}, 16\text{Hz}$ ), 6.47 (1H, d,  $J=16\text{Hz}$ ), 6.89 (1H, s), 7.27 (5H, s), 7.34 (5H, s), 8.11 (1H, s)

MS: 42a 446 (.01,  $\text{M}^+-1$ ), 429 (.03), 338 (.12), 288 (30), 91 (100)  
42b 446 (.08,  $\text{M}^+$ ), 429 (1.5), 338 (2.2), 288 (94), 91 (100)

Analysis:  $C_{27}H_{27}NO_5$

42a

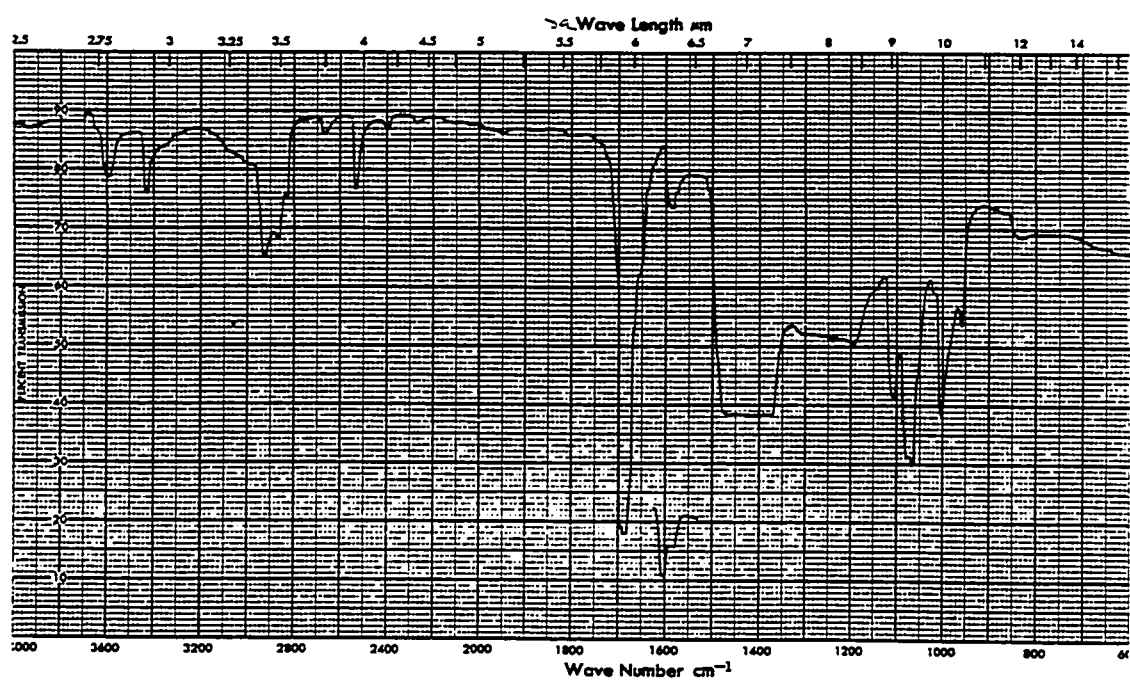
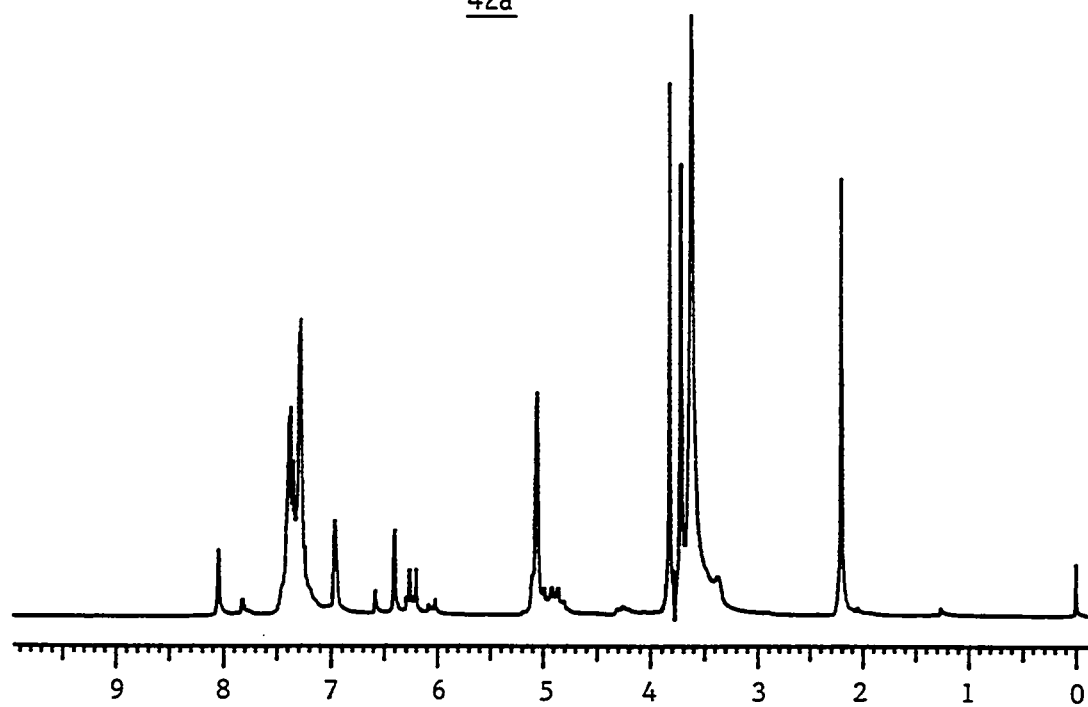
crystals from methanol

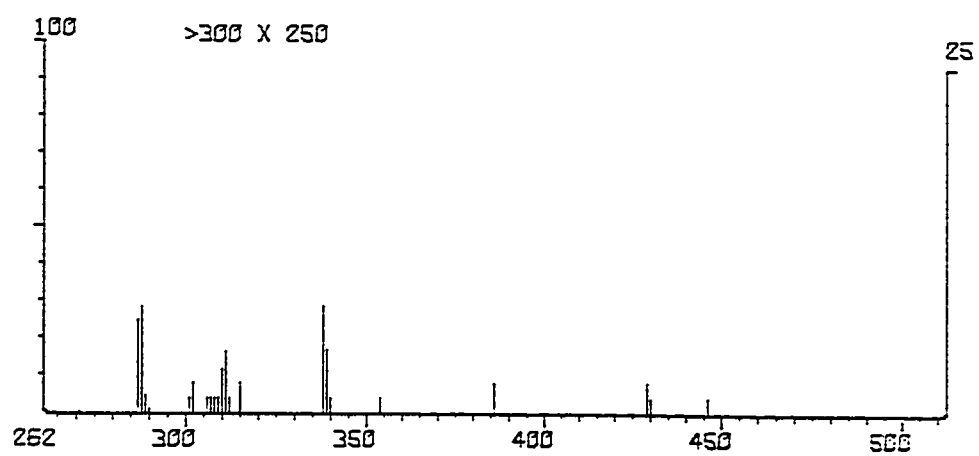
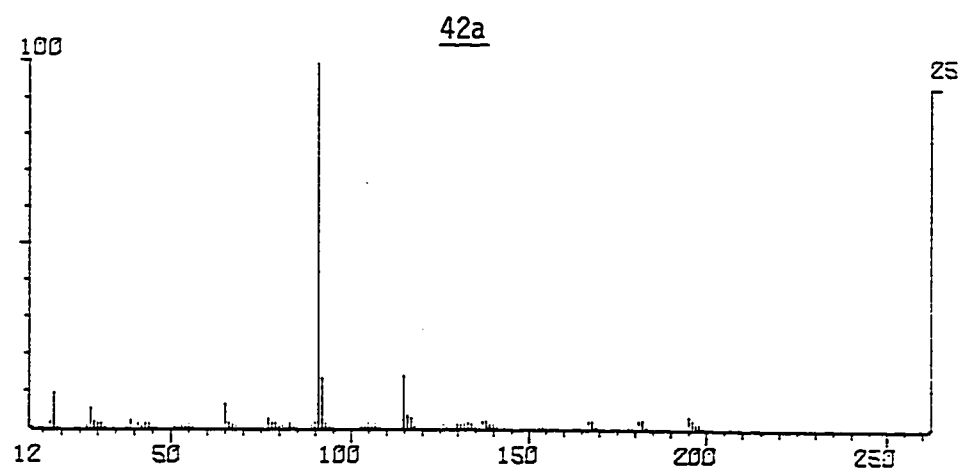
	calculated	found
C:	0.7279	0.7227
H:	0.0611	0.0681
N:	0.0314	0.0330

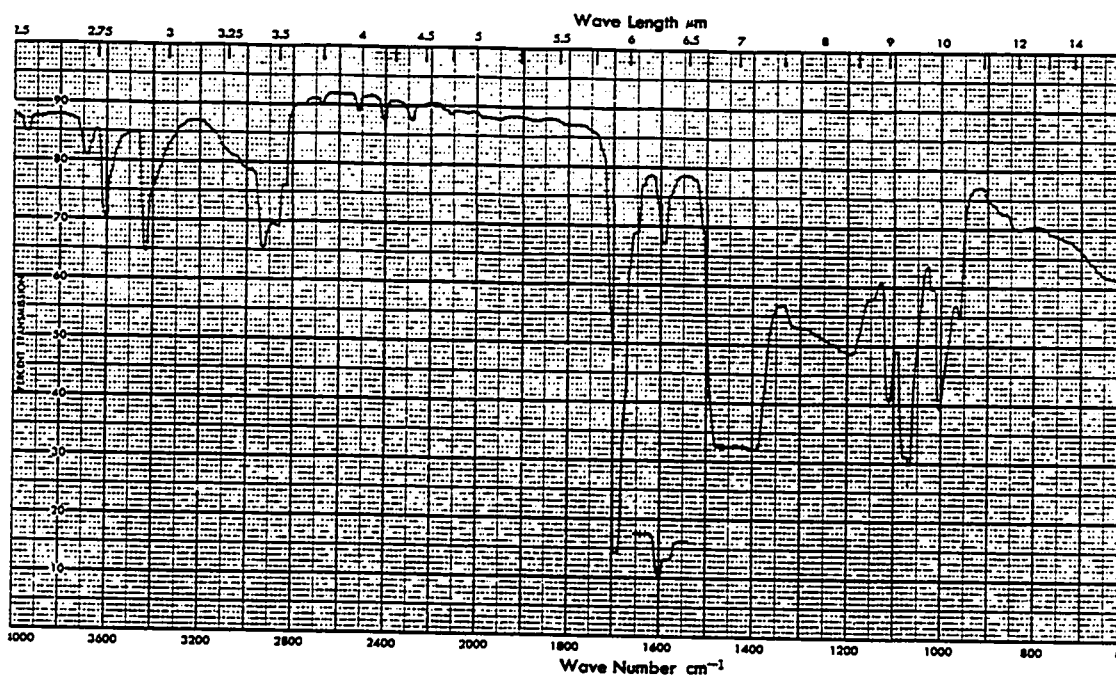
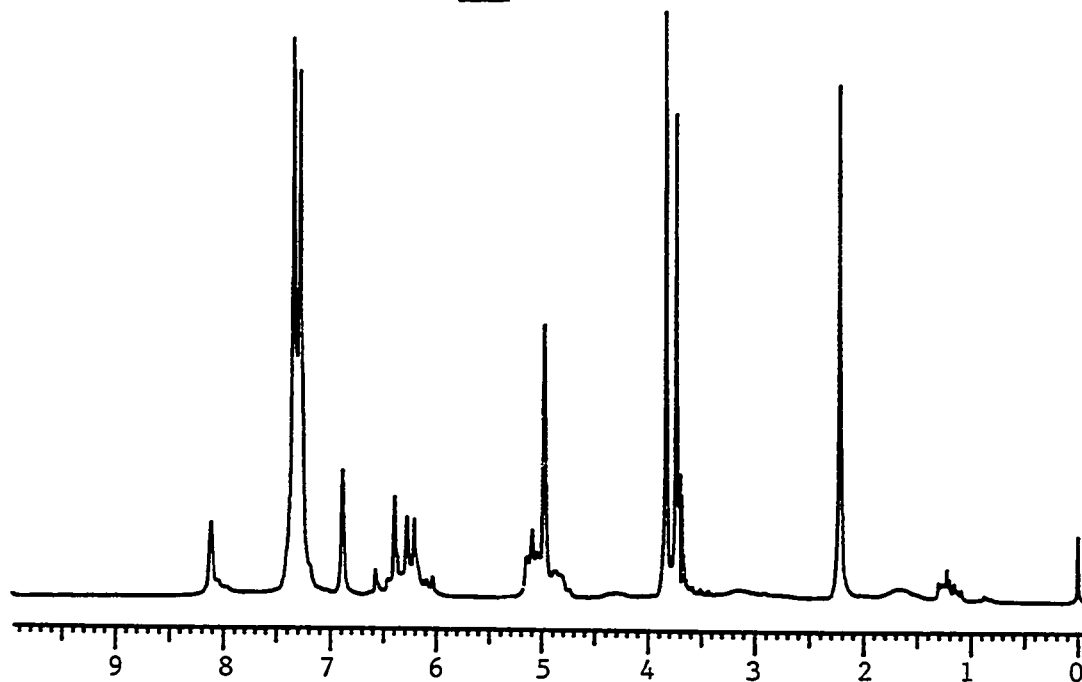
42b

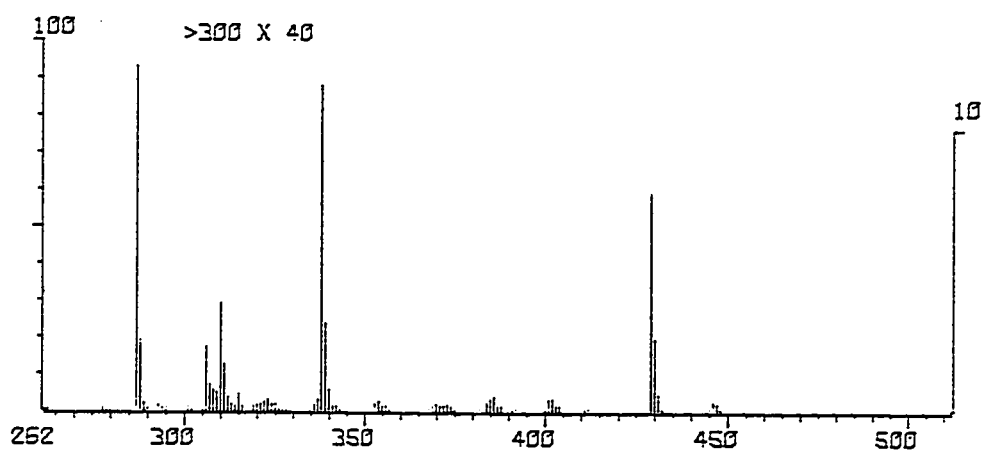
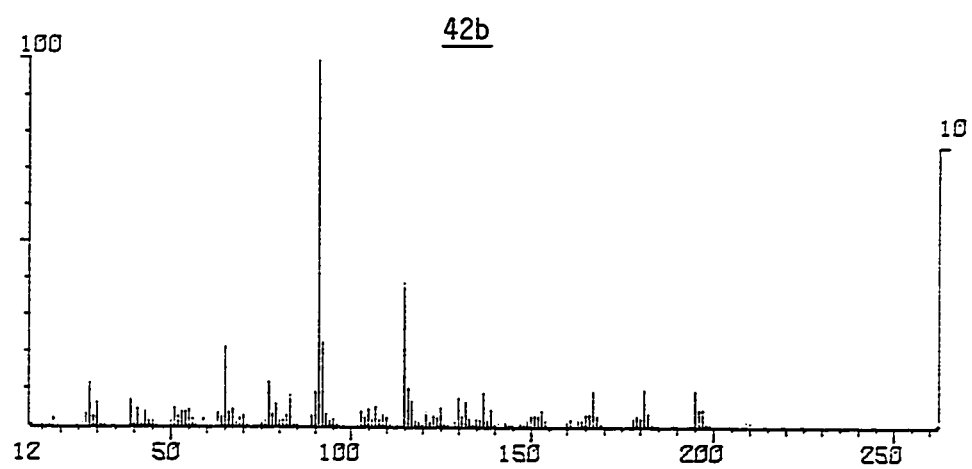
crystals from isopropyl ether

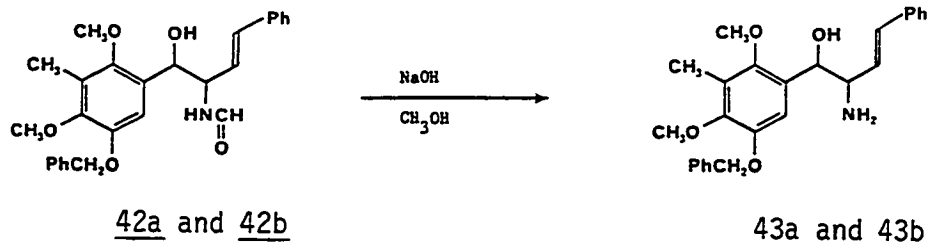
found
0.7276
0.0682
0.0307

42a



42b





#### AMINE ALCOHOL (43a and 43b)

To a solution of 1.0 g (2.2 mmol) of 42a in 20 ml of methanol was added 2.5 ml (6.7 mmol) of 3N sodium hydroxide solution. After refluxing for one hour, the reaction mixture was partitioned between ether and saturated sodium chloride solution. The organic phase was extracted with saturated sodium chloride solution and evaporated to give 0.89 g (95%) 43a as a yellow oil. Chromatography on silica gel eluted with 10% methanol in dichloromethane gave a pure foam. mp 105-106° (isopropyl ether)

Similar treatment of 42b gave 0.85 g (91%) of 43b. mp 100-110° (decomp) (isopropyl ether)

IR (CH<sub>2</sub>Cl<sub>2</sub>): 2940, 1590, 1400-1480, 1110, 1070 (d), 1005

NMR (CDCl<sub>3</sub>): 43a 2.19 (3H, s), 3.67 (3H, s), 3.83 (3H, s), 4.79 (1H, d, J=6 Hz), 5.09 (2H, s), 6.18 (1H, dd, J=6Hz,16Hz), 6.41 (1H, d, J=16Hz), 6.91 (1H, s), 7.26 (5H, s), 7.3-7.4 (5H, m)  
43b 2.20 (3H, s), 3.02 (broad), 3.71 (3H, m), 3.80 (3H, s), 4.90 (1H, AB, J=9Hz), 4.94 (1H, AB, J=9Hz), 5.0-5.3 (1H, m) 6.2-6.6 (2H, m), 6.92 (1H, s), 7.25 (5H, s), 7.31 (5H, s)

MS: 43a 287 (100), 132 (100), 91 (100)  
43b 287 (67), 132 (41), 91 (100)

Exact mass:  $C_{26}H_{29}NO_4$

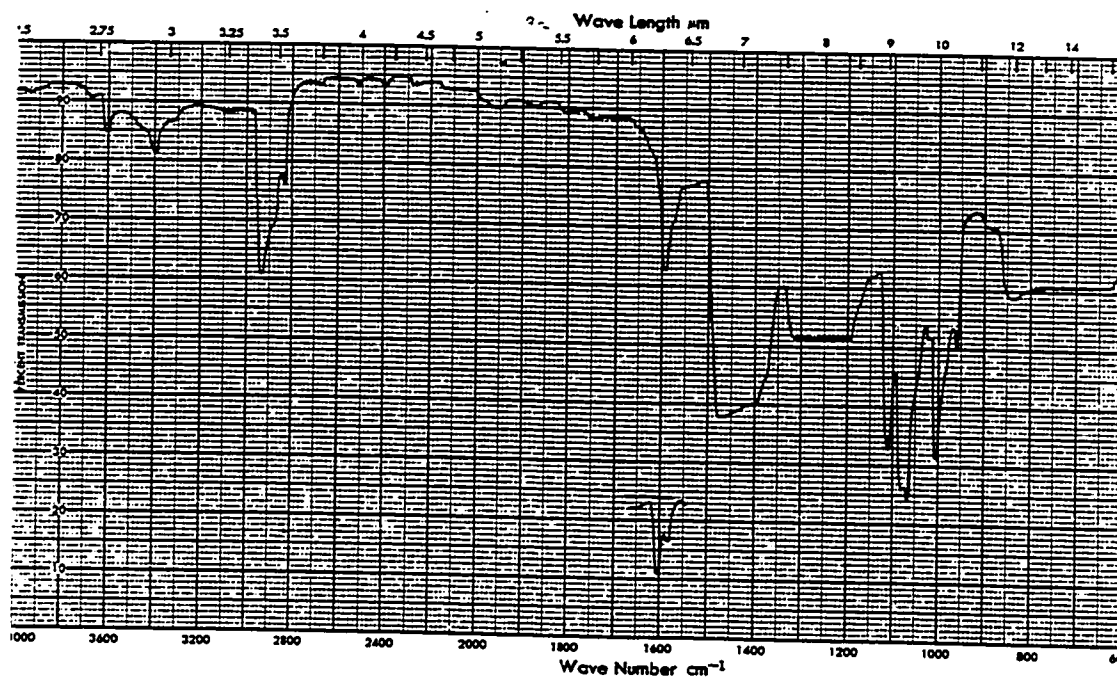
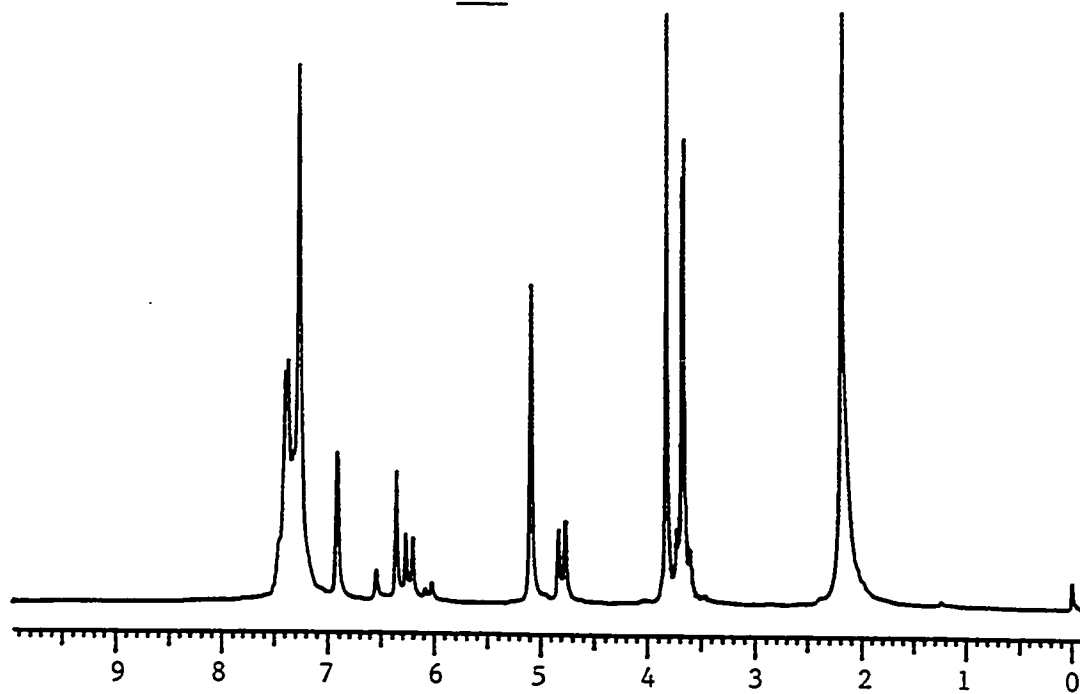
<u>43b</u>	
calculated	found
399.1682	399.1676

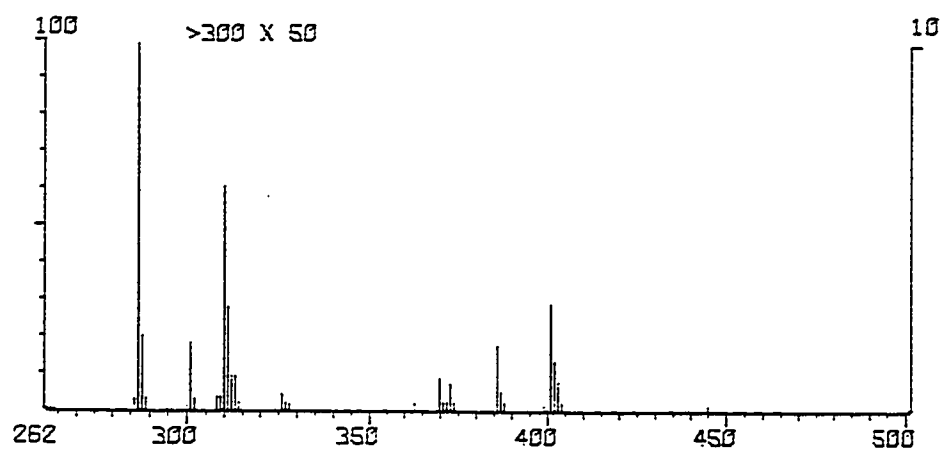
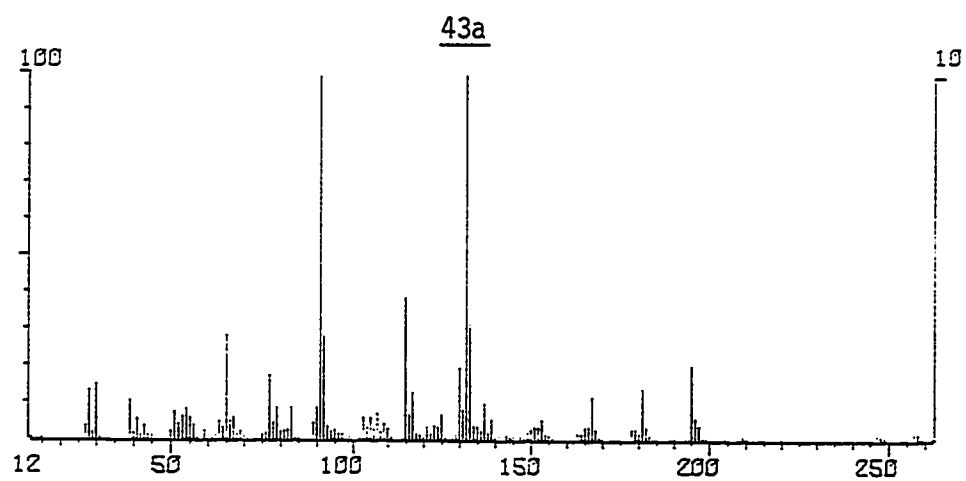
Analysis:  $C_{26}H_{29}NO_4$

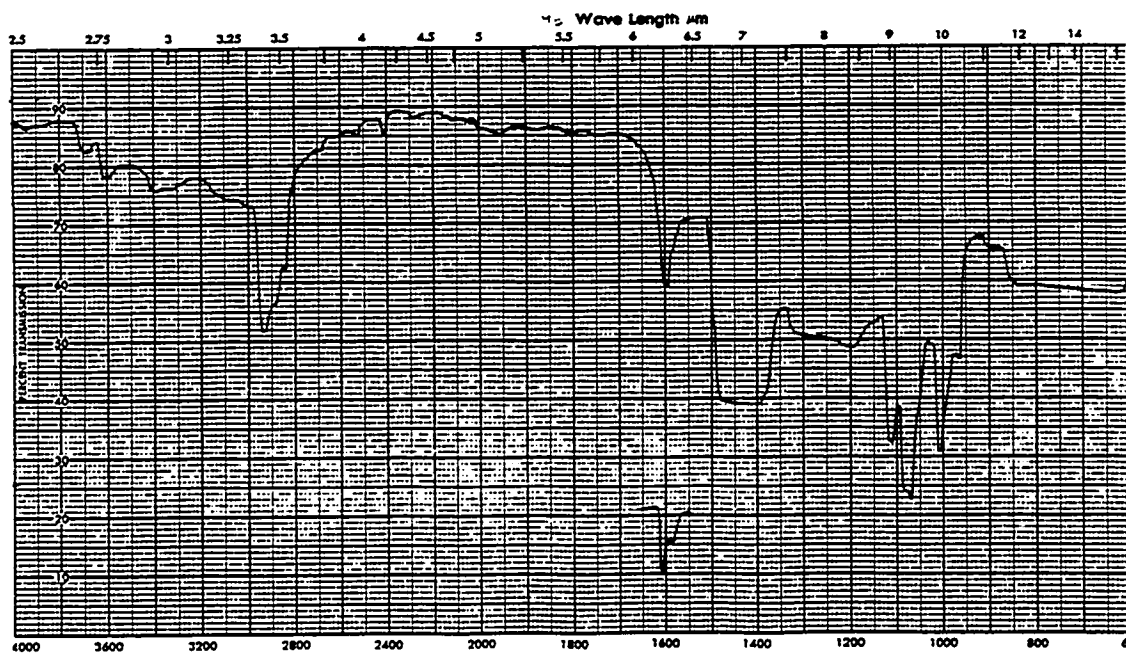
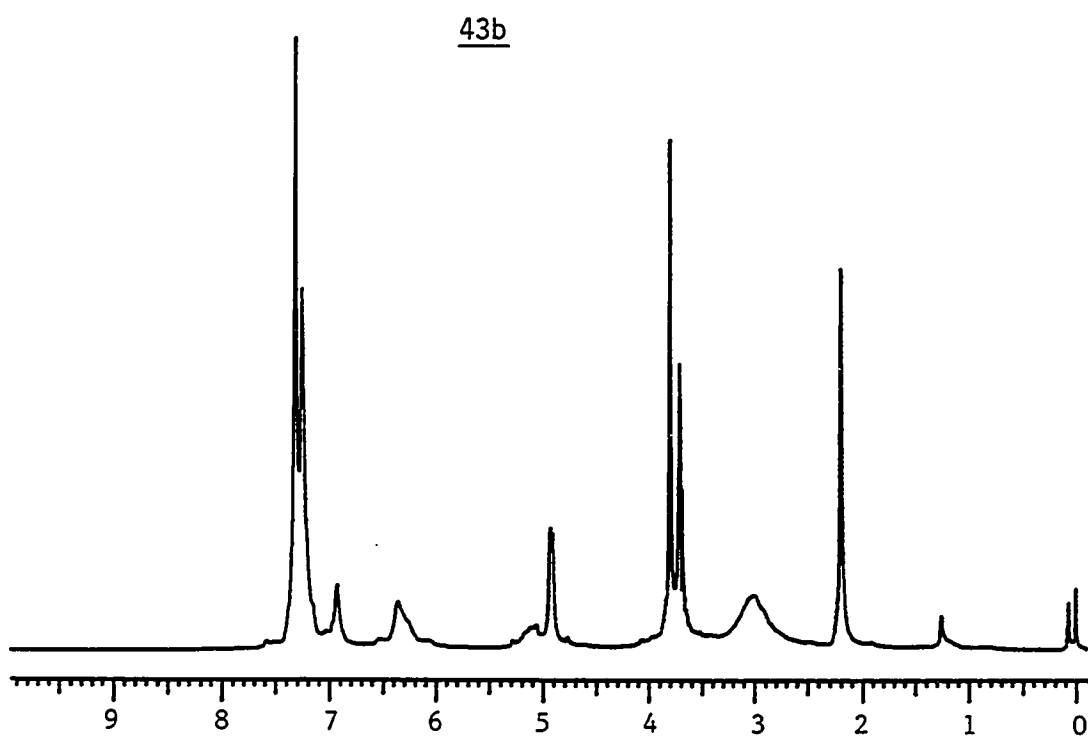
<u>43a</u>	
crystals from isopropyl ether	
calculated	found
C: 0.7444	0.7420
H: 0.0697	0.0698
N: 0.0334	0.0325

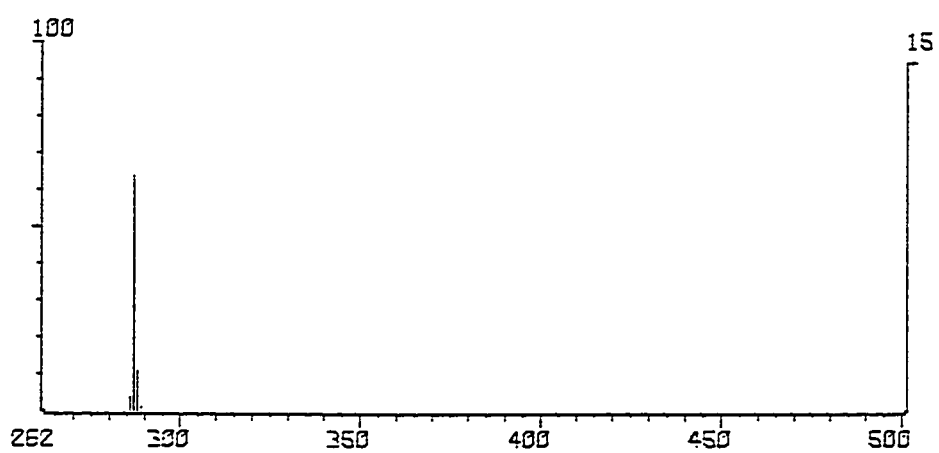
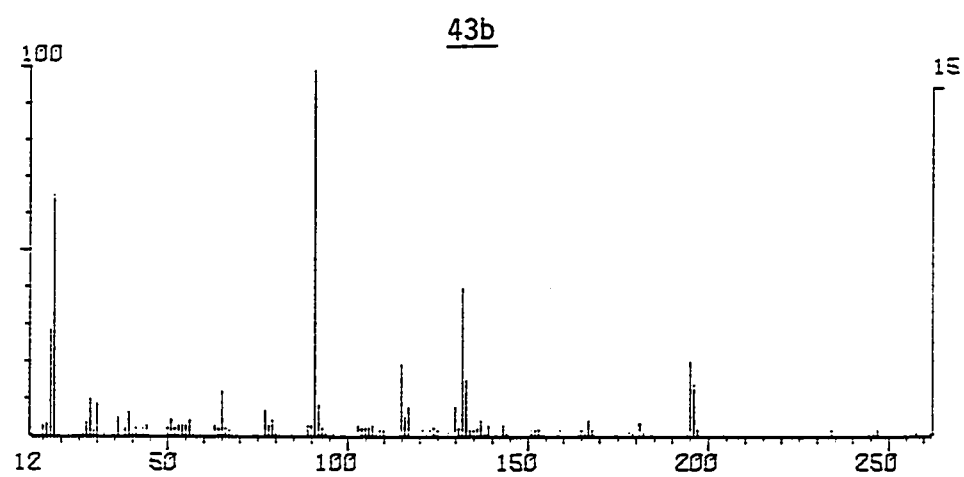
<u>43b</u>	
crystals from isopropyl ether	
found	
0.6945	
0.0677	
0.0298	

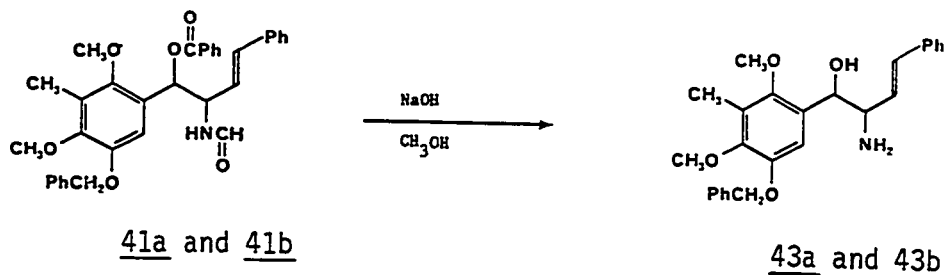


43a







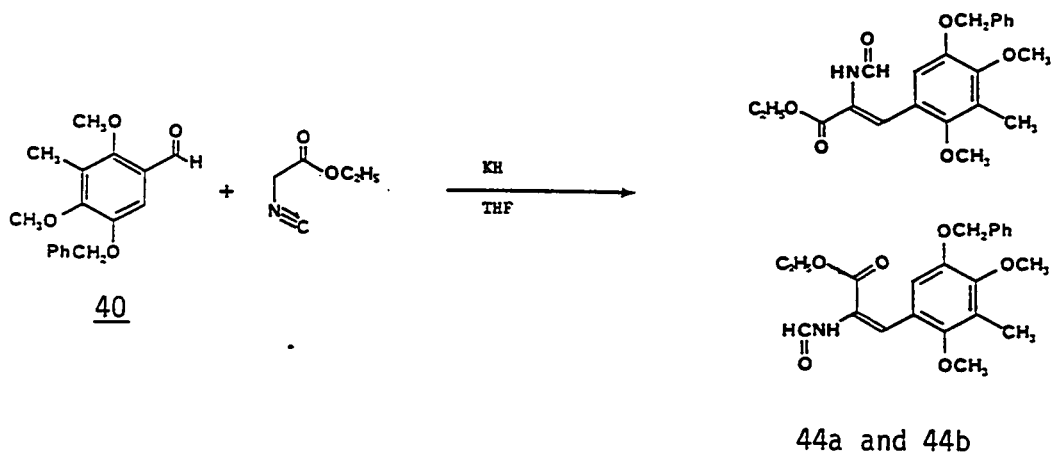


AMINE-ALCOHOL mixture. (43a and 43b)

The following procedure prepares a crude mixture adequate for the condensation with acid 49.

To a solution of 6.0 g (10.9 mmol) of the diastereomeric mixture of 41a and 41b in 150 ml of methanol was added 18 ml (54 mmol) of 3N sodium hydroxide solution. After refluxing for one hour, the reaction mixture was partitioned between 40% carbon tetrachloride in dichloromethane and dilute sodium chloride solution. The aqueous phase was extracted twice with carbon tetrachloride-dichloromethane, and the organic phases washed successively with dilute sodium chloride solution, followed by saturated sodium chloride solution. The combined organic phases were dried over sodium sulfate, and evaporated to give a crude mixture which reacted with acid 49 as if approximately 70%-80% amine 43.

Repeated experience indicated the preference for dividing the chromatographed mixture of 18 g of 41 into three 6 g portions, hydrolysis according to the above procedure, and combination of the resulting products for the condensation with 10 -12 g of acid 49.



OLEFINIC-ESTER-FORMAMIDE (44a and 44b))

To a stirred solution of 10.0 g (35.0 mmol) of 40 and 4.60 ml (38.5 mmol) of ethyl isocyanoacetate in 150 ml of tetrahydrofuran at 0° was added potassium hydride in mineral oil until further addition did not cause evolution of hydrogen, and TLC analysis on silica gel eluted with 60% ether in hexanes indicated the presence of only two highly UV active spots at  $r_f=0.3$ . TLC analysis of the incomplete reaction mixture showed a non-UV active spot slightly less polar than the desired compounds. Disappearance of this spot indicated completion of the reaction. Upon completion of the reaction, approximately 6 ml of acetic acid was added slowly and the reaction mixture allowed to warm to room temperature. After 10 minutes the reaction mixture was partitioned between ethyl acetate containing a small amount of dichloromethane and dilute sodium chloride solution. The organic phase was extracted twice with dilute sodium chloride solution and evaporated. Careful washing with hexanes removed most of the mineral oil from the oily product.

This mixture was satisfactory for the next reaction. The chromatographed yield was 12.2 g (88%) of the mixture of 44a and 44b. Crystallization from ether gave pure faster moving isomer 44a, with the slower moving isomer, 44b, remaining in the mother liquor. Repeated chromatography on silica gel gave pure 44b, as a colorless oil.

44a mp 116° (ether)

IR ( $\text{CH}_2\text{Cl}_2$ ): 44a 1700, 1080  
44b 3300, 2920, 1700, 1330, 1080

NMR ( $\text{CDCl}_3$ ): 44a 1.36 (3H, t, J=7Hz), 2.23 (3H, s), 3.67 (3H, s), 3.88 (3H, s), 4.33 (2H, q, J=7Hz), 5.05 (2H, s), 6.75-6.95 (1H, broad d, J=9Hz), 7.25-7.50 (6H, m)  
44b 0.961 (3H, t, J=7Hz), 2.20 (3H, s), 3.60 (3H, s), 3.85 (3H, s), 4.02 (2H, q, J=7Hz), 5.03 (2H, s), 6.70 (1H, s), 6.84 (1H, d, J=5Hz), 7.3-7.5 (5H, m), 7.65 (1H, broad s), 8.04 (1H, s), 8.39 (1H, s), 8.44 (1H, d, J=14Hz)

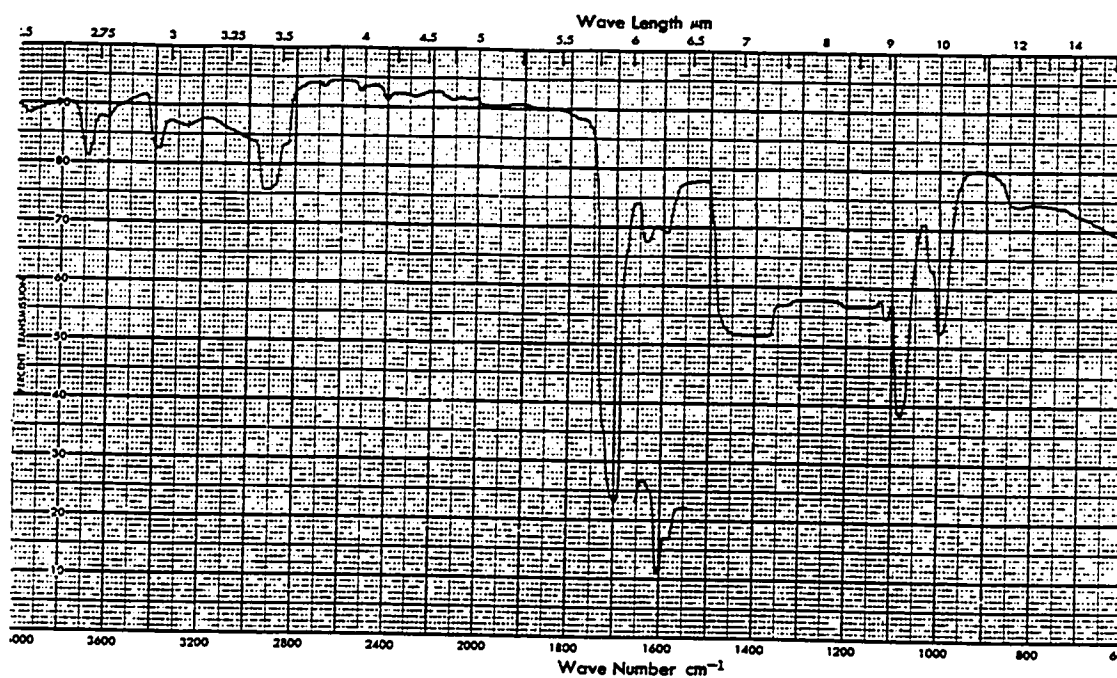
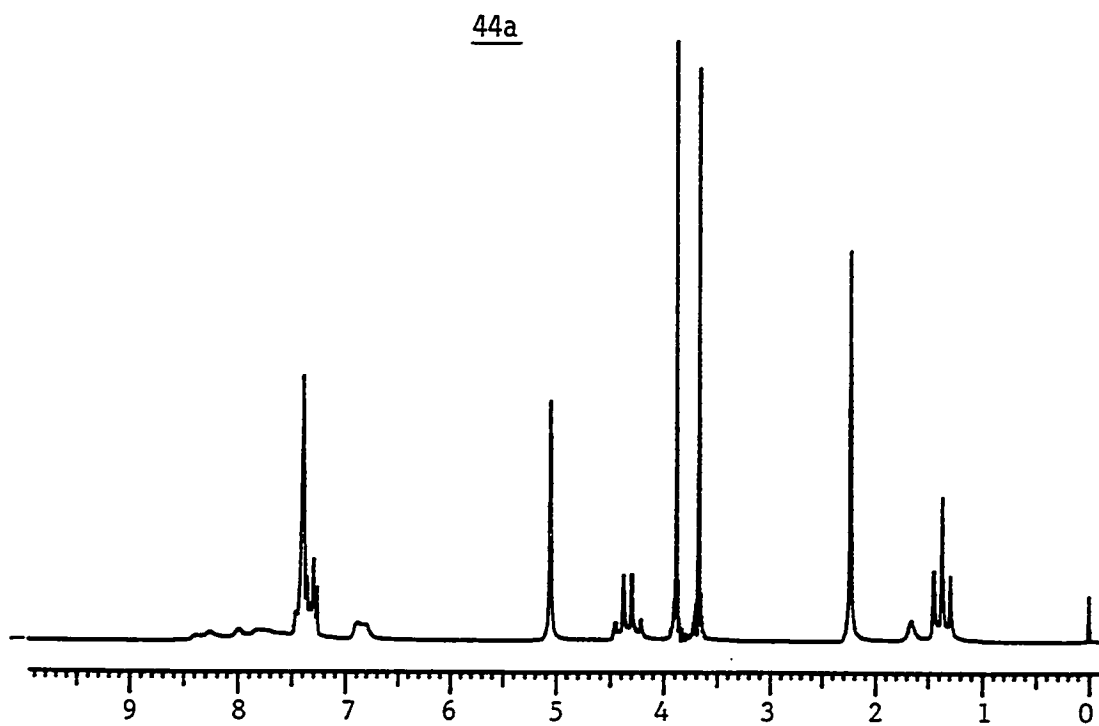
MS: 44a 399 (12,  $\text{M}^+$ ), 308 (94), 91 (100)  
44b 399 (8,  $\text{M}^+$ ), 308 (63), 91 (100)

Exact Mass:  $\text{C}_{22}\text{H}_{25}\text{NO}_6$

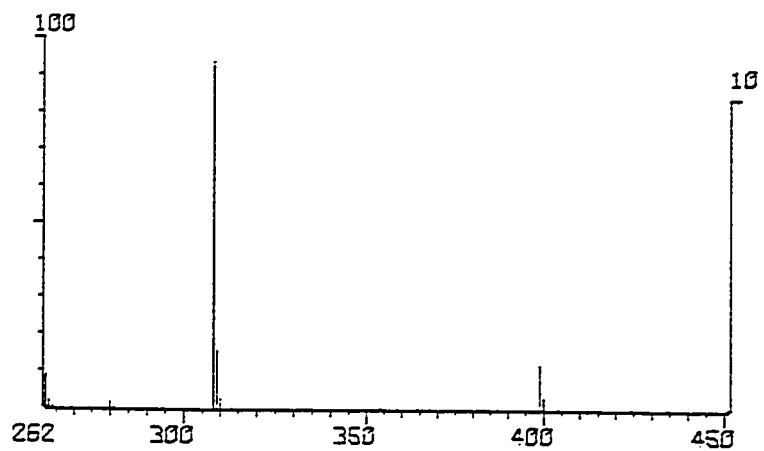
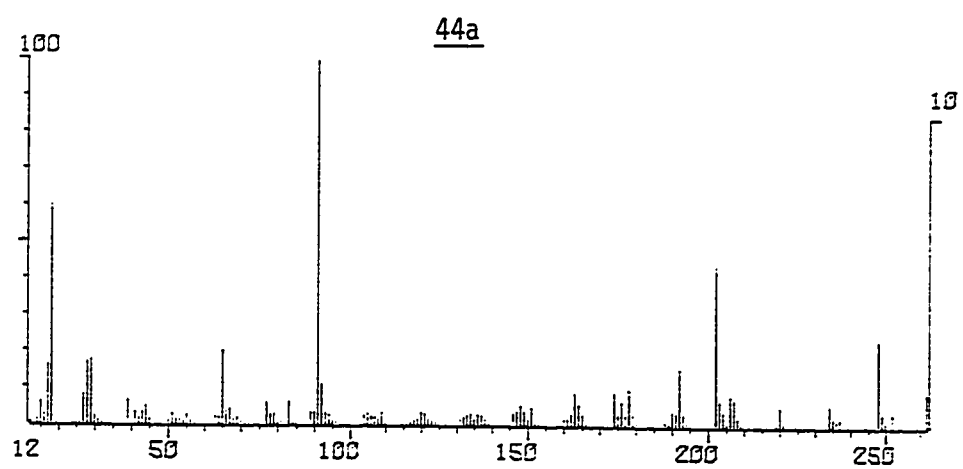
<u>44b</u>	
calculated	found
311.1369	311.1372

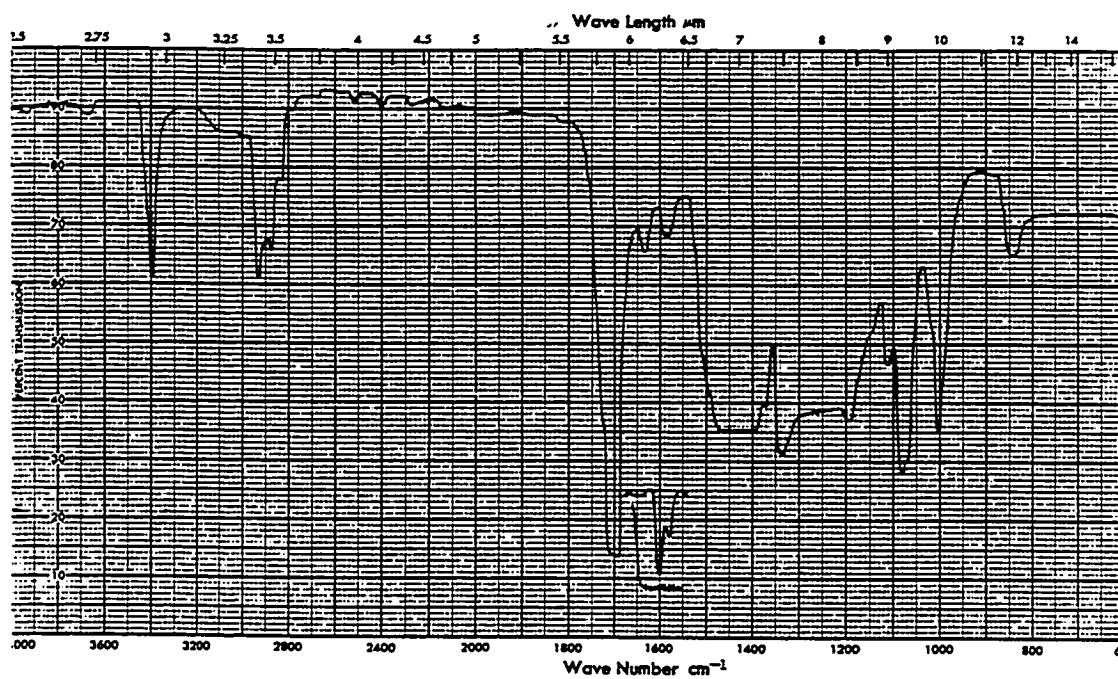
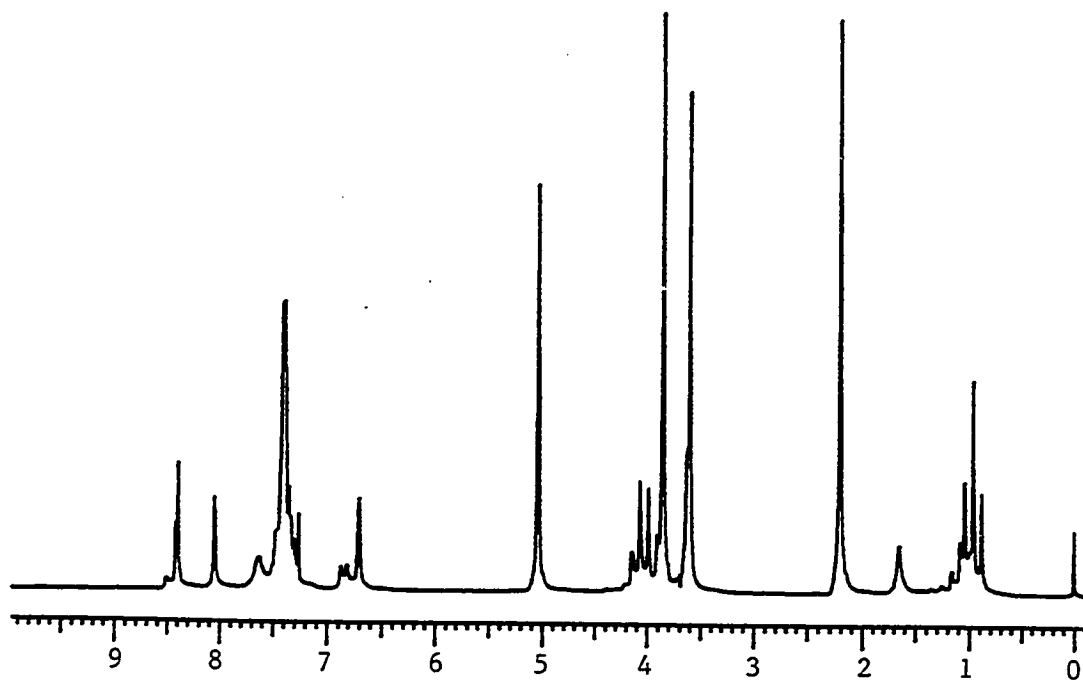
Analysis:  $\text{C}_{22}\text{H}_{25}\text{NO}_6$

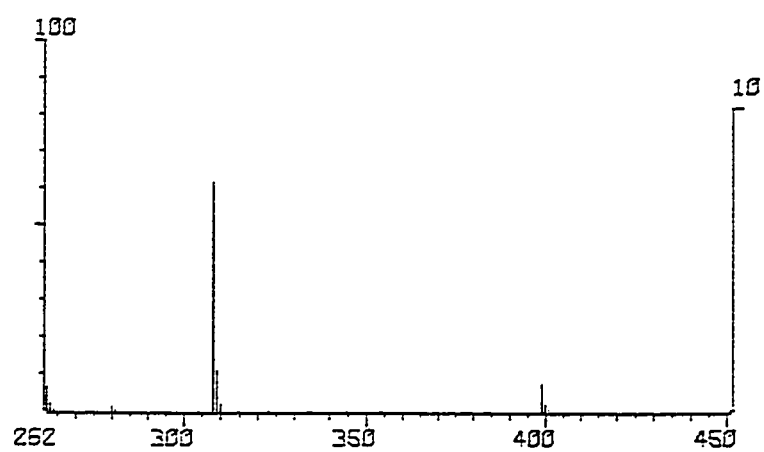
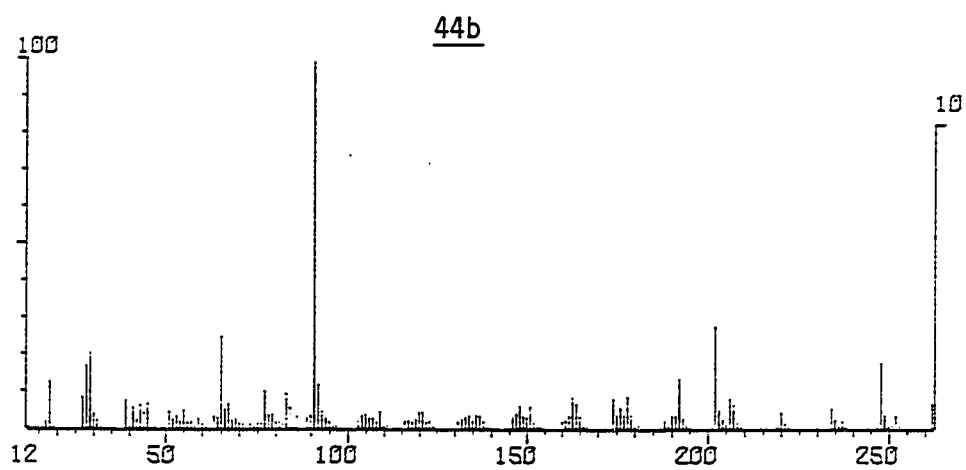
<u>44a</u>	
crystals from ether	
calculated	found
C: 0.6615	0.6626
H: 0.0631	0.0644
N: 0.0351	0.0331

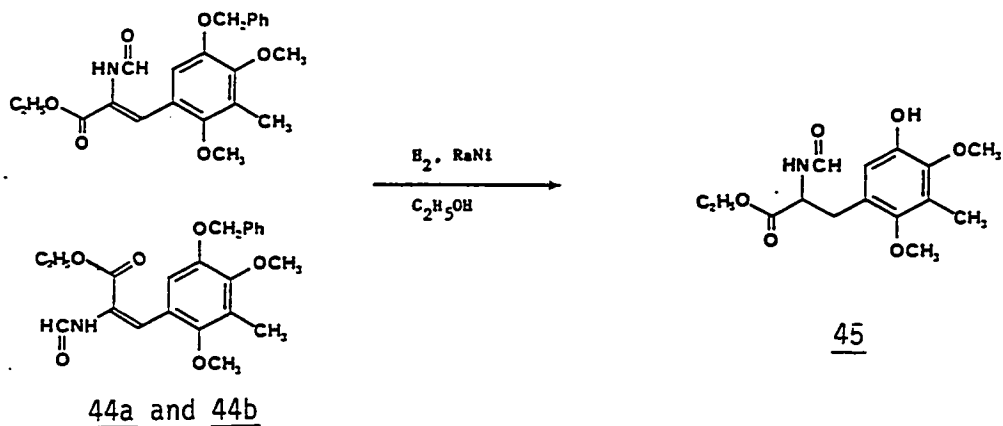






44b





### PHENOL (45)

A solution of 12.2 g (30.7 mmol) of the mixture of 44a and 44b in 125 ml of ethanol was hydrogenated over 10 ml of a suspension of Raney nickel in ethanol at 1000 psi of hydrogen for 2 hours at 80°. Filtration through Celite and evaporation gave 9.8 g (103%) 45 as a yellow oil. Repeated chromatography on silica gel gave a pale yellow oil.

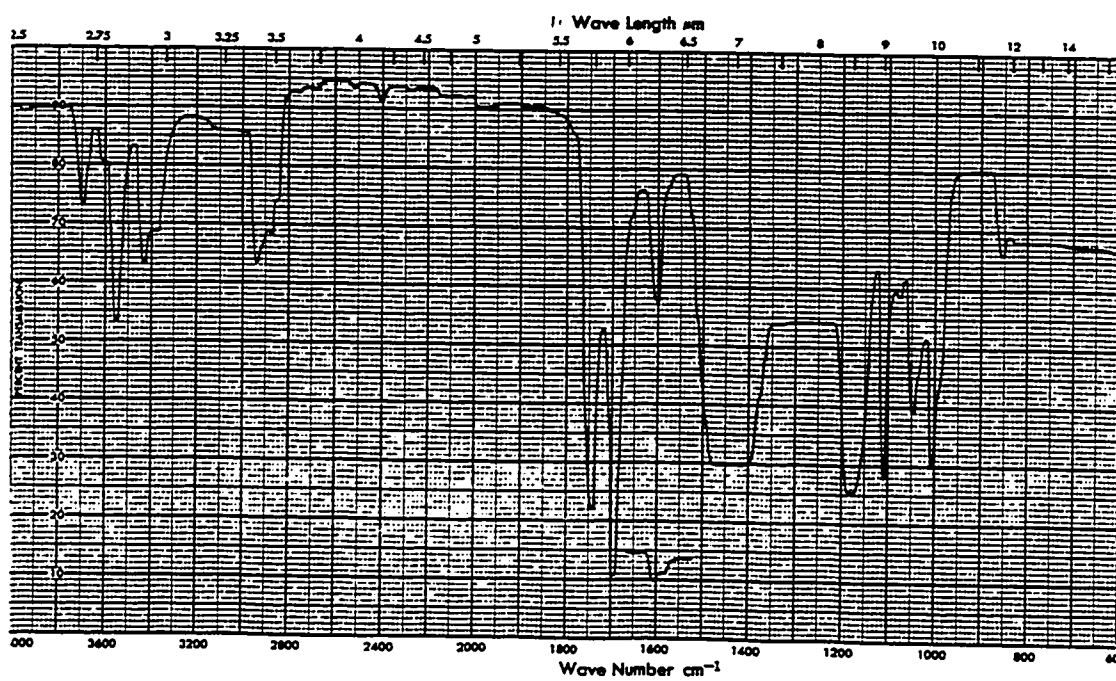
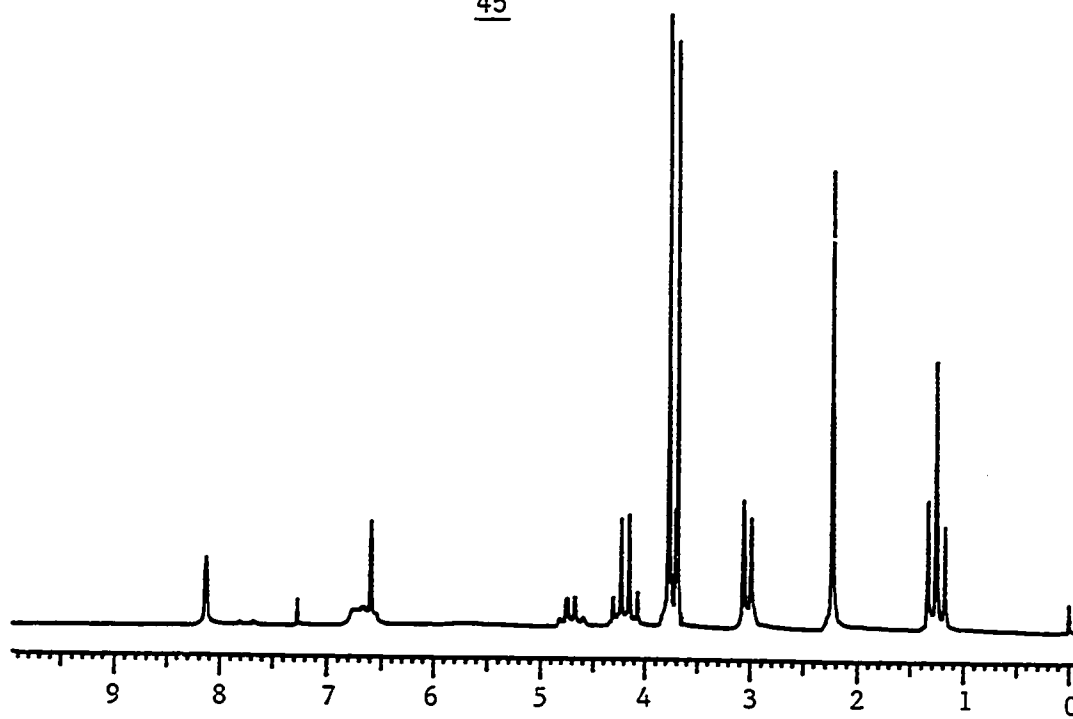
IR ( $\text{CH}_2\text{Cl}_2$ ): 3550, 1740, 1690, 1170, 1110, 1010

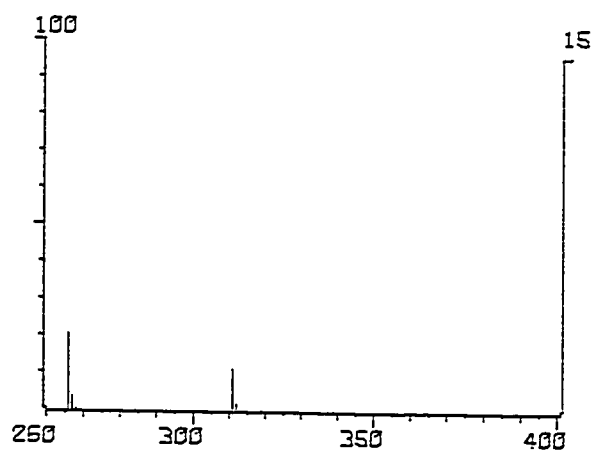
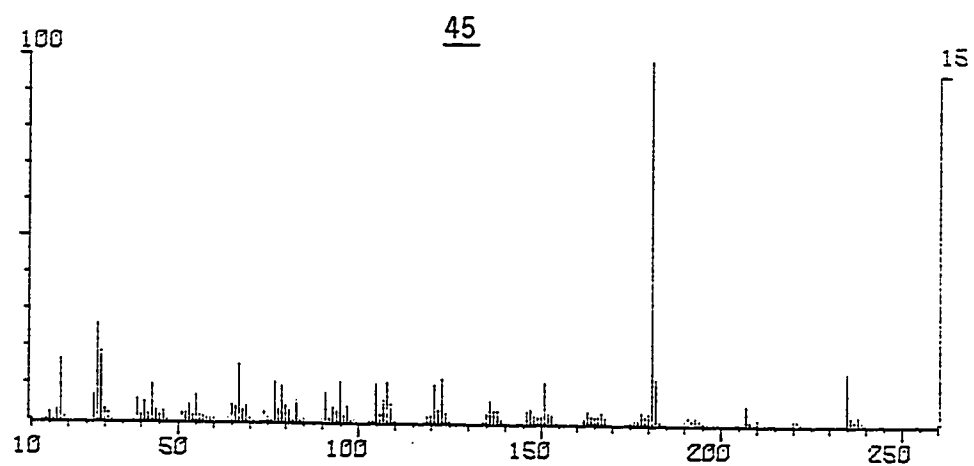
NMR ( $\text{CDCl}_3$ ): 1.26 (3H, t,  $J=7\text{Hz}$ ), 2.23 (3H, s), 3.2 (1H, d,  $J=6\text{Hz}$ ), 3.68 (3H, s), 3.77 (3H, s), 4.18 (2H, q,  $J=7\text{Hz}$ ), 4.72 (1H, d/d,  $J=6\text{Hz}, 7\text{Hz}$ ), 6.59 (1H, s), 6.5–6.8 (1H, m), 8.13 (1H, s)

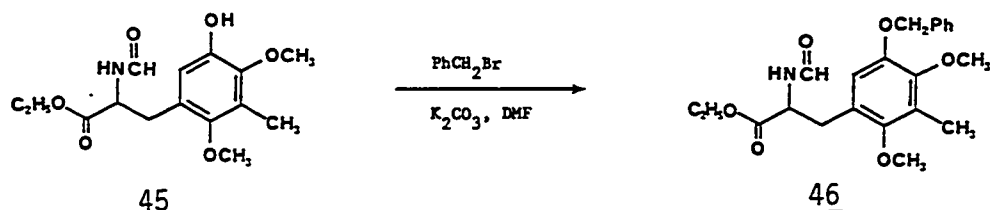
MS: 311 (11,  $\text{M}^+$ ), 266 (20), 235 (13), 181 (100)

Exact Mass:  $\text{C}_{15}\text{H}_{21}\text{NO}_6$

calculated	found
311.1369	311.1372

45





### ESTER-FORMAMIDE (46)

A mixture of 9.8 g (30 mmol) of crude 45, 3.8 ml (32 mmol) of benzyl bromide, and 20 g (145 mmol) of potassium carbonate in 50 ml of dimethyl formamide was stirred at 100° for 2 hours. After cooling, water was added to dissolve the solid, and the mixture extracted with ether. The organic phase was washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated. Chromatography on silica gel eluted with ether in hexanes gave 10.8 g (88%) 46 as amorphous solid. Alternately, washing the crude material with hexanes gave material satisfactory for the next reaction. mp 77-79° (methanol)

IR ( $\text{CH}_2\text{Cl}_2$ ): 1740, 1700

NMR ( $\text{CDCl}_3$ ): 1.24 (3H, t,  $J=7\text{Hz}$ ), 2.21 (3H, s), 3.02 (2H, d,  $J=6\text{Hz}$ ), 3.68 (3H, s), 3.84 (3H, s), 4.14 (2H, q,  $J=7\text{Hz}$ ), 4.70 (1H, dd,  $J=6\text{Hz}, 7\text{Hz}$ ), 5.05 (2H, s), 6.4-6.6 (1H, b), 6.57 (1H, s), 7.35 (5H, m), 8.05 (1H, s)

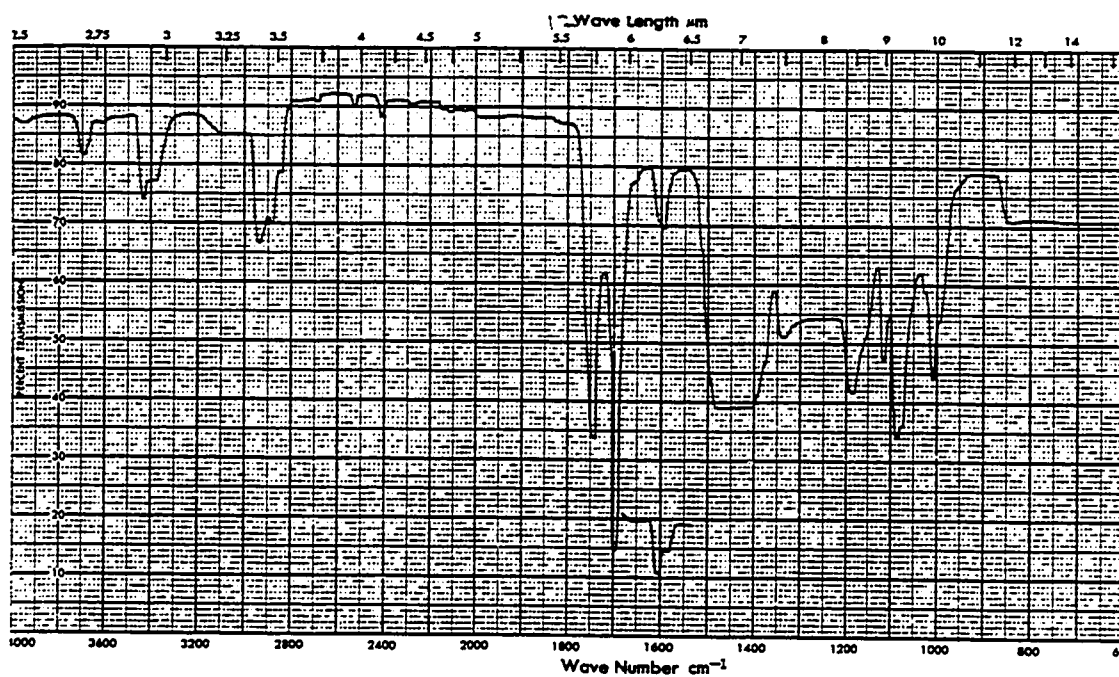
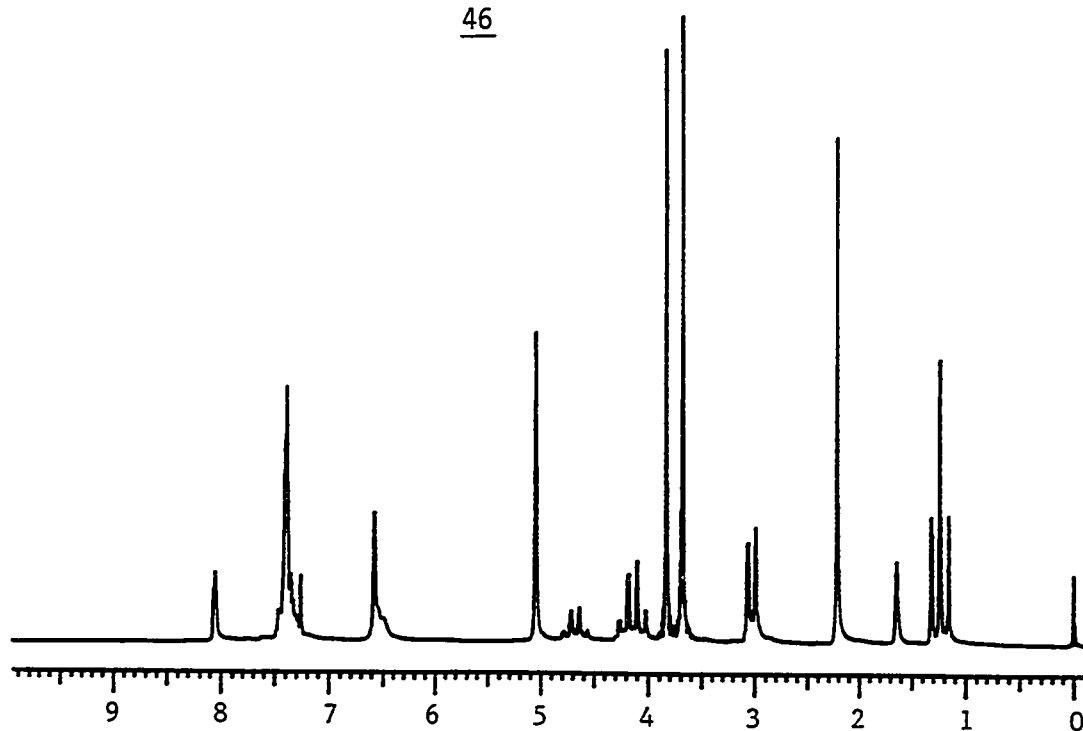
MS: 401 (8,  $\text{M}^+$ ), 271 (30), 250 (100), 176 (61), 91 (100)

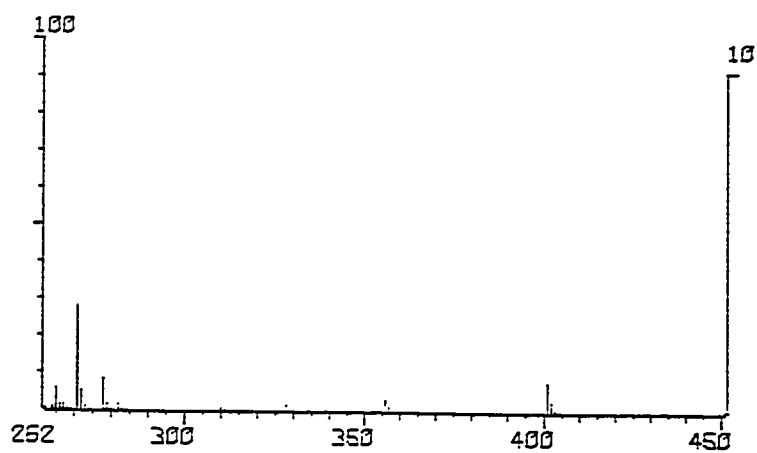
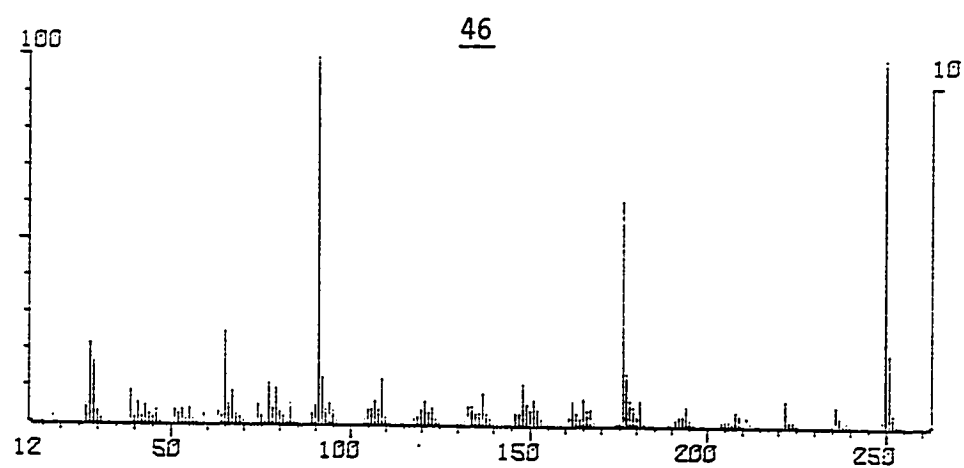
Analysis:  $C_{22}H_{27}NO_6$

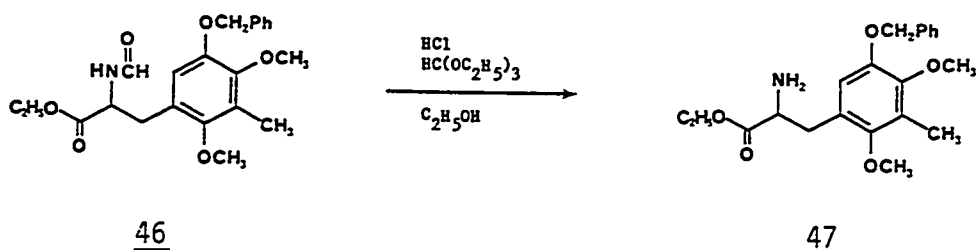
crystals from methanol

	calculated	found
C: 0.6608		0.6582
H: 0.0685		0.0678
N: 0.0349		0.0349



46



ESTER-AMINE (47)

A solution of 10.6 g (28.4 mmol) of 46 and 3 ml of triethylorthoformate in 60 ml of ethanol containing 2 equivalent of hydrochloric acid (addition of 3 ml (60 mmol) of acetyl chloride to 60 ml of ethanol) was refluxed for 2 hours, then evaporated to give 12 g (103%) of 47 hydrochloride. This mixture was used for the next reaction.

Partition between ether and saturated sodium bicarbonate, followed by drying over magnesium sulfate, evaporation, and chromatography on silica gel, eluted with ether in hexanes, gave 47 as a colorless oil.

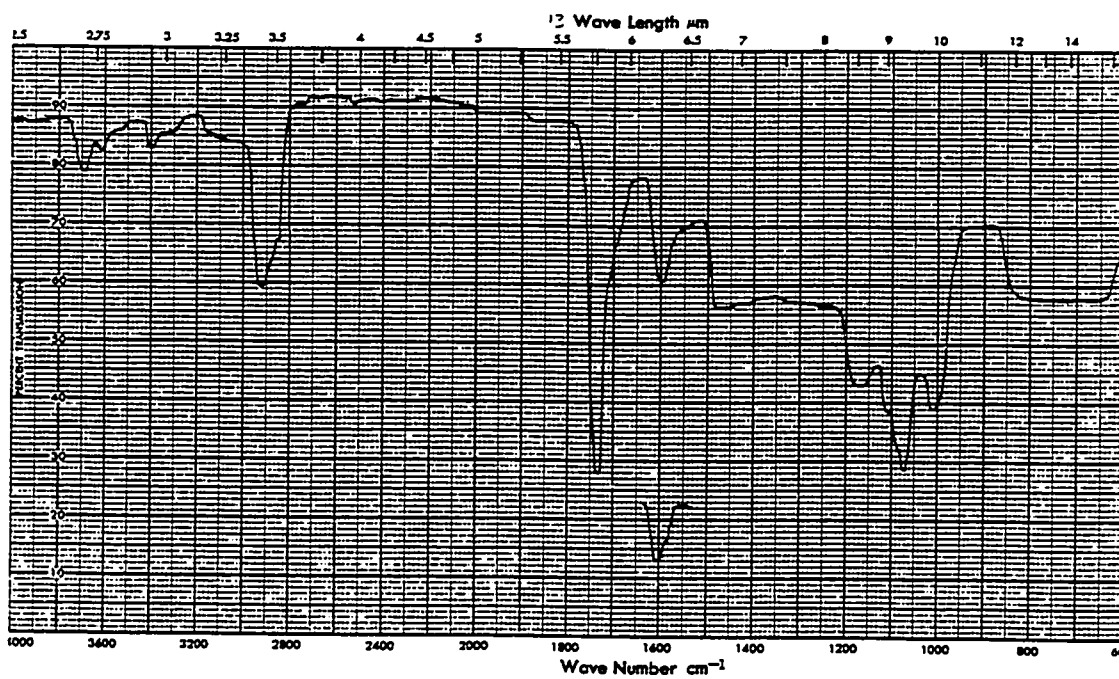
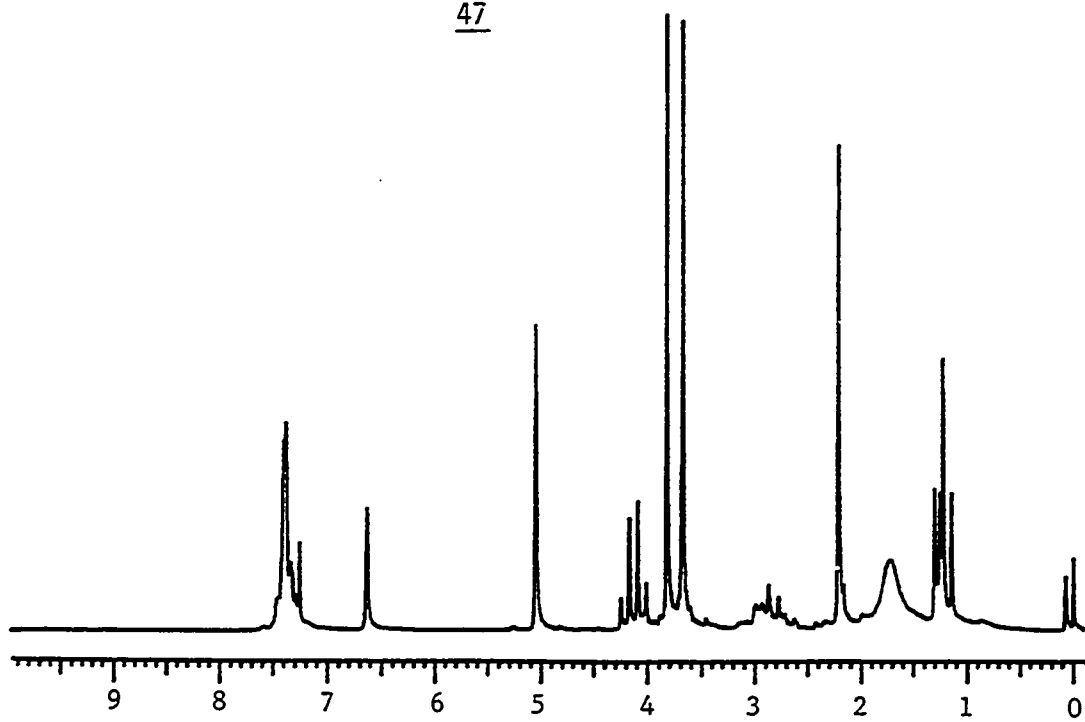
IR ( $\text{CH}_2\text{Cl}_2$ ): 1730, 1070

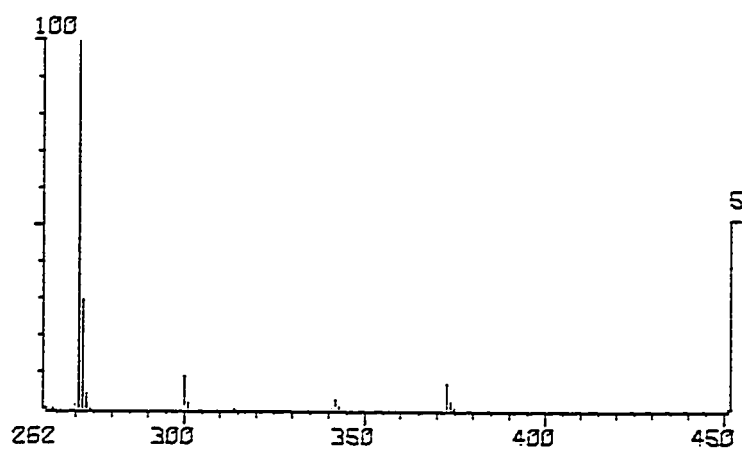
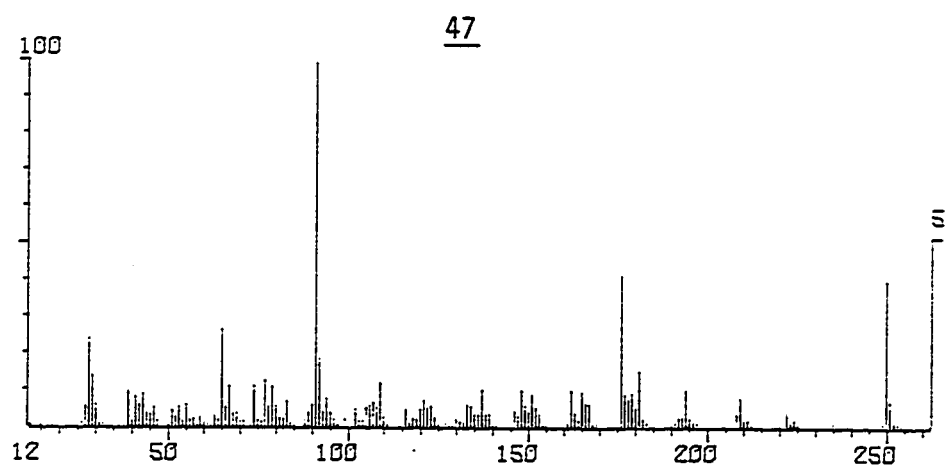
NMR ( $\text{CDCl}_3$ ): 1.22 (3H, t,  $J=7\text{Hz}$ ), 1.73 (broad), 2.22 (3H, s), 2.6–3.2 (3H, m), 3.68 (3H, s), 3.83 (3H, s), 4.13 (2H, q,  $J=7\text{Hz}$ ), 5.05 (2H, s), 6.63 (1H, s), 7.38 (5H, m)

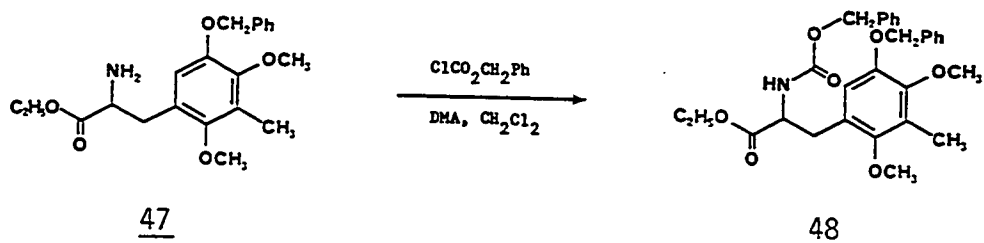
MS: 373 (7,  $\text{M}^+$ ), 271 (100), 250 (40), 176 (40), 91 (100)

Exact Mass:  $\text{C}_{21}\text{H}_{27}\text{NO}_5$

calculated	found
373.1889	373.1898

47





### ESTER-URETHANE (48)

To a stirred solution of 12 g (29.3 mmol) of crude 47 hydrochloride and 10 ml (79 mmol) of dimethylaniline in 100 ml of dichloromethane, at 0°, was added 4.5 ml (32 mmol) of benzylchloroformate. After 30 minutes the solution was partitioned between ether and saturated sodium chloride solution containing hydrochloric acid sufficient to maintain a pH below 3. The organic phase was extracted with saturated sodium chloride solution followed by saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulfate and evaporated.

Recrystallization from ether gave 12.1 g (90%) 48 as white crystals. mp 89.5–90° (ether)

IR (CH<sub>2</sub>Cl<sub>2</sub>): 1740, 1060

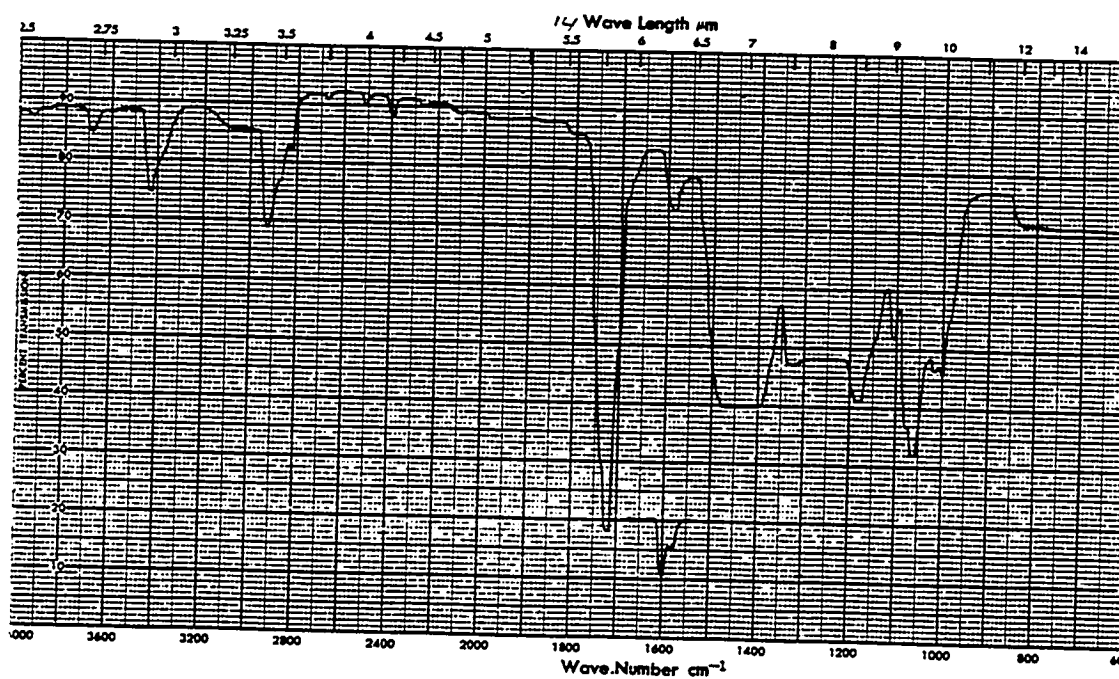
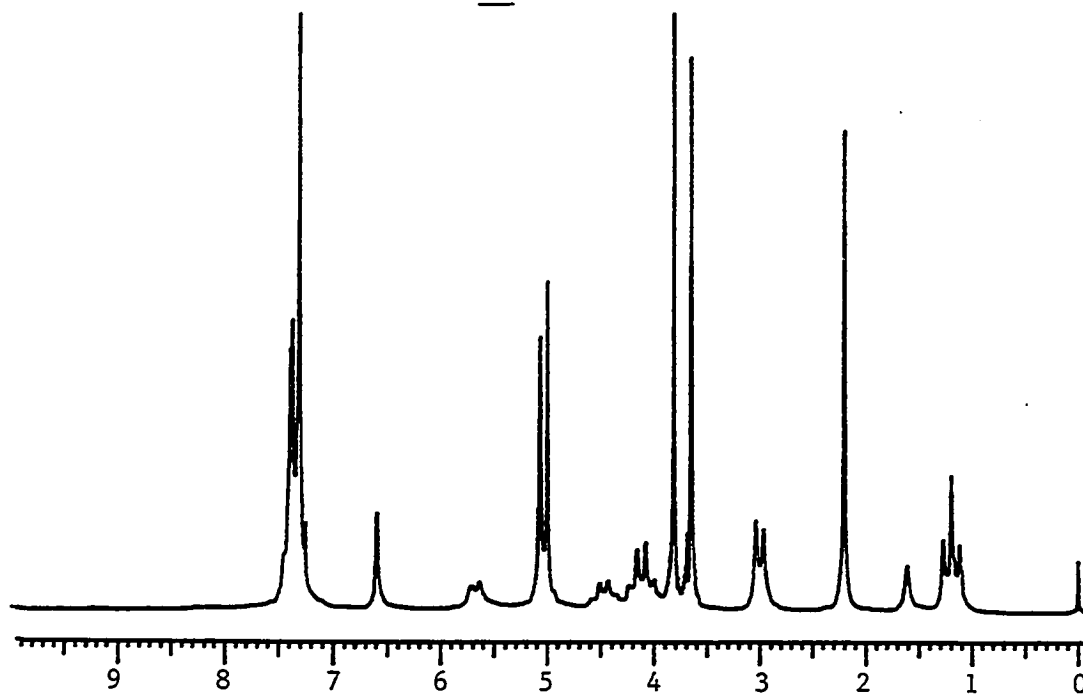
NMR (CDCl<sub>3</sub>): 1.20 (3H, t, J=7Hz), 2.20 (3H, s), 3.00 (2H, d, J=6Hz), 3.65 (3H, s), 3.82 (3H, s), 4.11 (2H, q, J=7Hz), 4.48 (1H, dd, J=6Hz, 7Hz), 5.00 (1H, s), 5.07 (1H, s), 5.6–5.8 (1H, bd), 6.59 (1H, s), 7.3–7.4 (5H, m)

MS: 507 (41, M<sup>+</sup>), 340 (18), 271 (42), 91 (100)

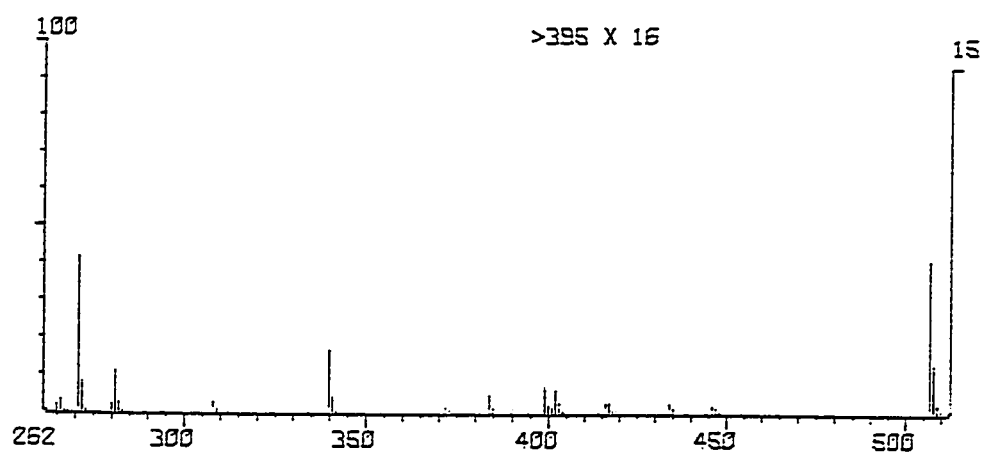
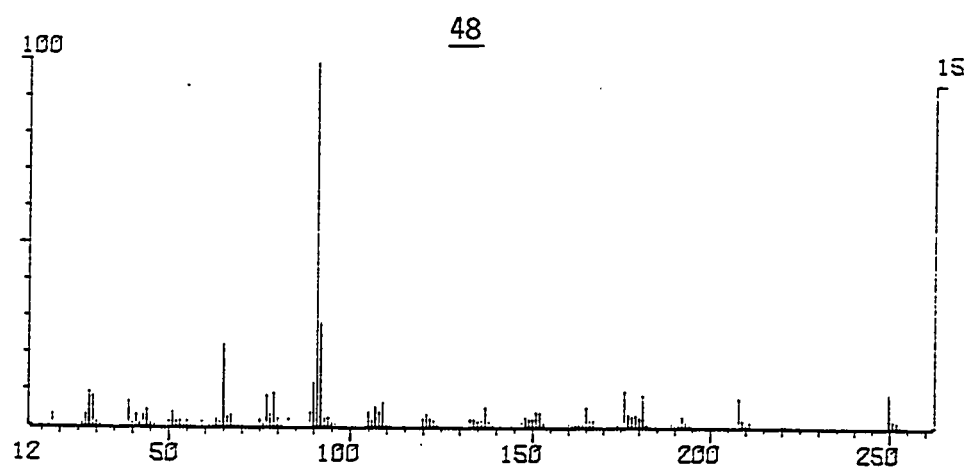
Analysis :  $C_{29}H_{33}NO_7$

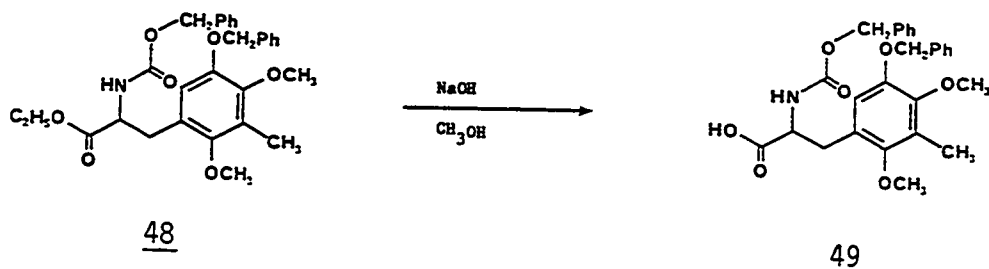
crystals from ether

	calculated	found
C:	0.6862	0.6840
H:	0.0655	0.0663
N:	0.0276	0.0265

48







### ACID-URETHANE (49)

A solution of 12.0 g (23.7 mmol) of 48 and 10 ml (30 mmol) of 3N sodium hydroxide solution in 250 ml of methanol was refluxed for 1 hour.

Carbon dioxide in the form of dry ice was added until the pH dropped below 10, and the solution was evaporated to a small volume. After partition between ethyl acetate, containing a small amount of dichloromethane, and saturated sodium chloride solution, the organic phase was dried over magnesium sulfate and evaporated. Trituration from ether gave 10.7 g (95%) of 49 as white crystals. mp 134° (ethyl acetate)

IR ( $\text{CH}_2\text{Cl}_2$ ): 1765, 1735, 1065

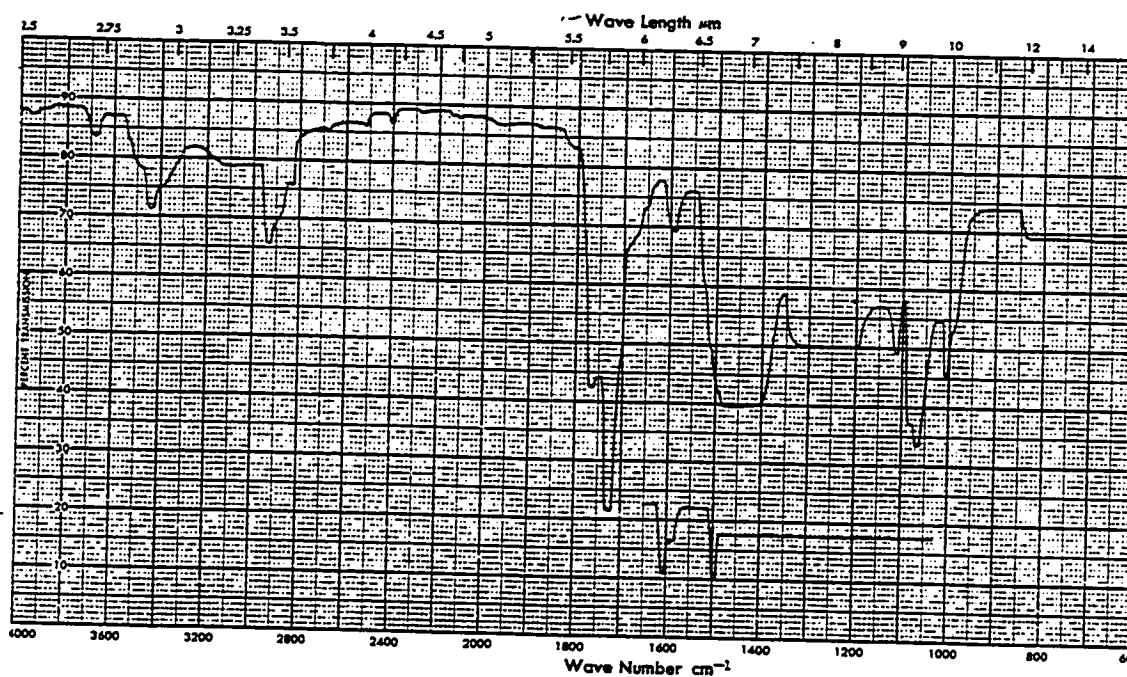
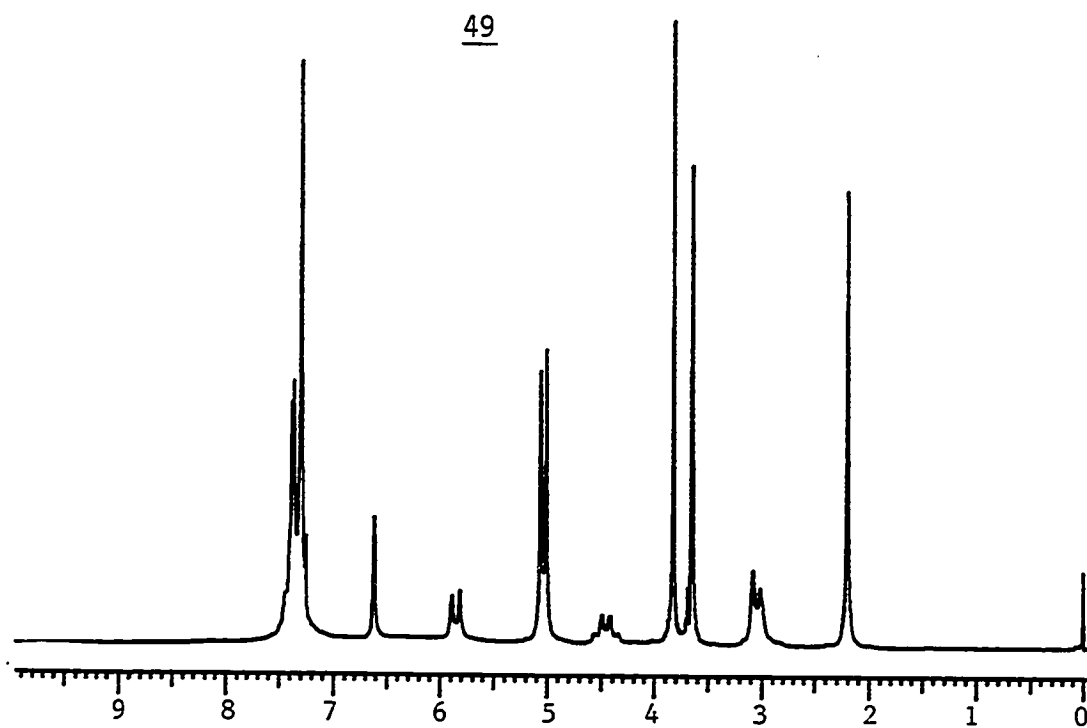
NMR ( $\text{CDCl}_3$ ): 2.20 (3H, s), 3.05 (2H, d,  $J=5\text{Hz}$ ), 3.65 (3H, s),  
3.82 (3H, s), 4.48 (1H, dd,  $J=7\text{Hz}, 7\text{Hz}$ ), 5.81 (1H, s),  
5.89 (1H, s), 5.86 (1H, d,  $J=7\text{Hz}$ ), 6.61 (1H, s),  
7.25–7.4 (5H, m)

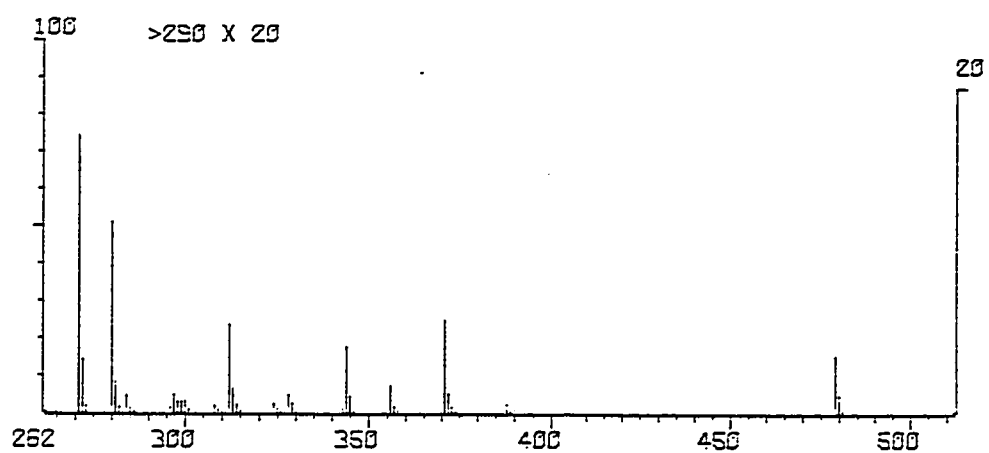
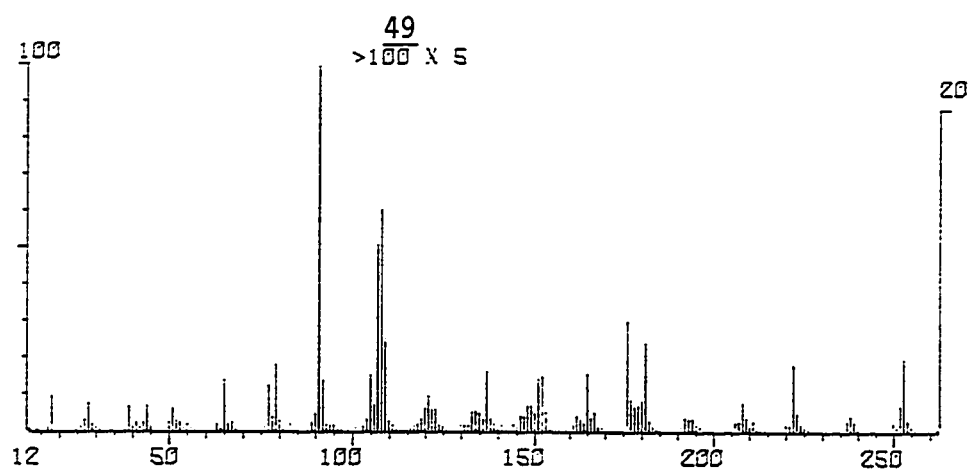
MS: 479 (3,  $\text{M}^+$ ), 371 (5), 280 (10), 271 (15), 108 (12), 91 (100)

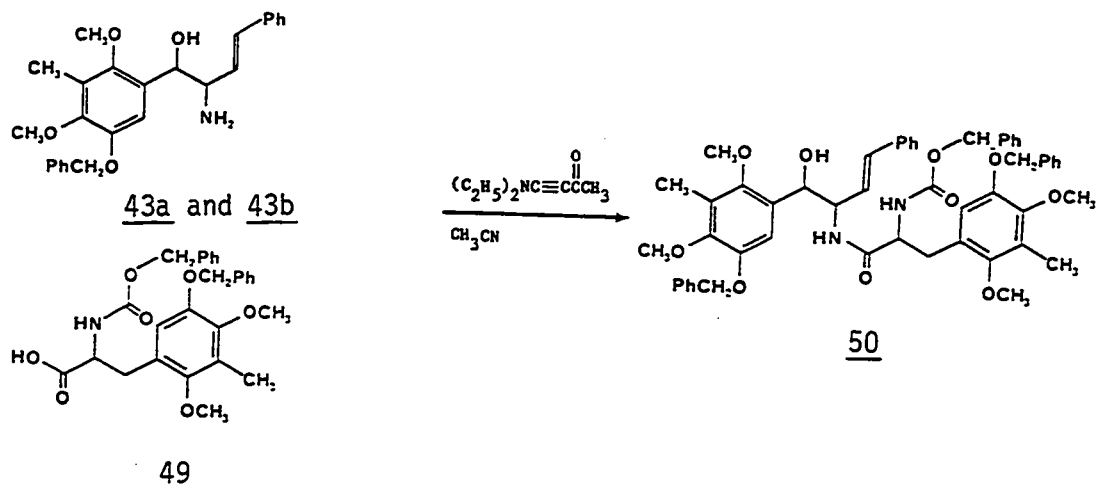
Analysis:  $\text{C}_{27}\text{H}_{29}\text{NO}_7$

crystals from ethyl acetate

	calculated	found
C: 0.6763		0.6784
H: 0.0610		0.0633
N: 0.0292		0.0281

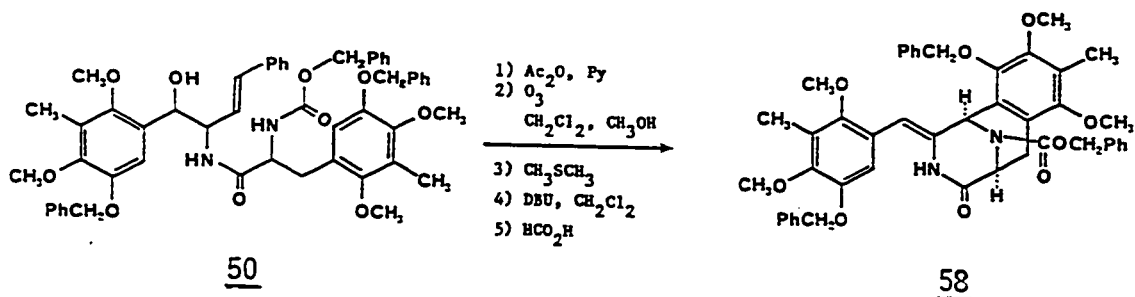






#### AMIDE (50)

To a stirred solution of 5.00 g (10.4 mmol) of acid **49** in 25 ml of acetonitrile at 0° was added 1.65 ml (10.6 mmol) of 4-N,N-diethylaminobutyn-2-one<sup>19</sup>. After 30 minutes, 6.0 g (11 mmol assuming 75% purity) of crude amino-alcohol **43** in 10 ml of acetonitrile was added and the reaction mixture allowed to warm to room temperature. Crystals begin to form after three hours and the reaction was allowed to stir overnight (total of 15 hours). Filtration of the crystalline product, evaporation and chromatography of the mother liquor on silica gel, eluted with a gradient of ether in hexanes, gave a combined yield of 8.15 g (89%) of **50** as a mixture of diastereomers. Evaporation of the crude reaction mixture gave material satisfactory for the next series of reactions.



#### 4-N-CARBOBENZZYLOXYPIPERAZIN-2-ONE (58)

A solution of 13.6 g (15.5 mmol) of amide **50** in 10 ml of pyridine and 10 ml of acetic anhydride was heated for 15 minutes at 60°, then evaporated to dryness. The mixture was dissolved in 75 ml of dichloromethane, 75 ml of methanol was added, and the solution was cooled to -78°. Ozone was bubbled into the solution in 2 minute portions until the starting material was gone by TLC analysis. The disappearance of a mixture of UV active spots of  $r_f = 0.6$  on silica gel eluted with 70% ether in hexanes indicated completion of the reaction. A total of about 20 minutes of ozone was required. Argon was bubbled through the reaction mixture for 5 minutes, 5 ml (58 mmol) of dimethyl sulfide was added and the solution allowed to warm to room temperature. After 1 hour the mixture was evaporated to dryness, dissolved in 50 ml of dichloromethane and 4.8 ml (32 mmol) of 1,8-diazabicyclo[5,4,0]undec-7-ene added at 0°. After one hour the reaction mixture was partitioned between ether and saturated sodium chloride solution containing hydrochloric acid sufficient to maintain a pH below 3. The organic layer was evaporated and dissolved in 50 ml of formic acid. After heating at 60° for one hour the solution

was evaporated, 30 ml of toluene added and evaporated to dryness.

Chromatography on silica gel eluted with an ether in hexanes gradient gave 8.61 (72%) of 57. Repeated chromatography gave an off-white foam.

IR ( $\text{CH}_2\text{Cl}_2$ ): 1690-1710, 1115, 1060, 1030, 995

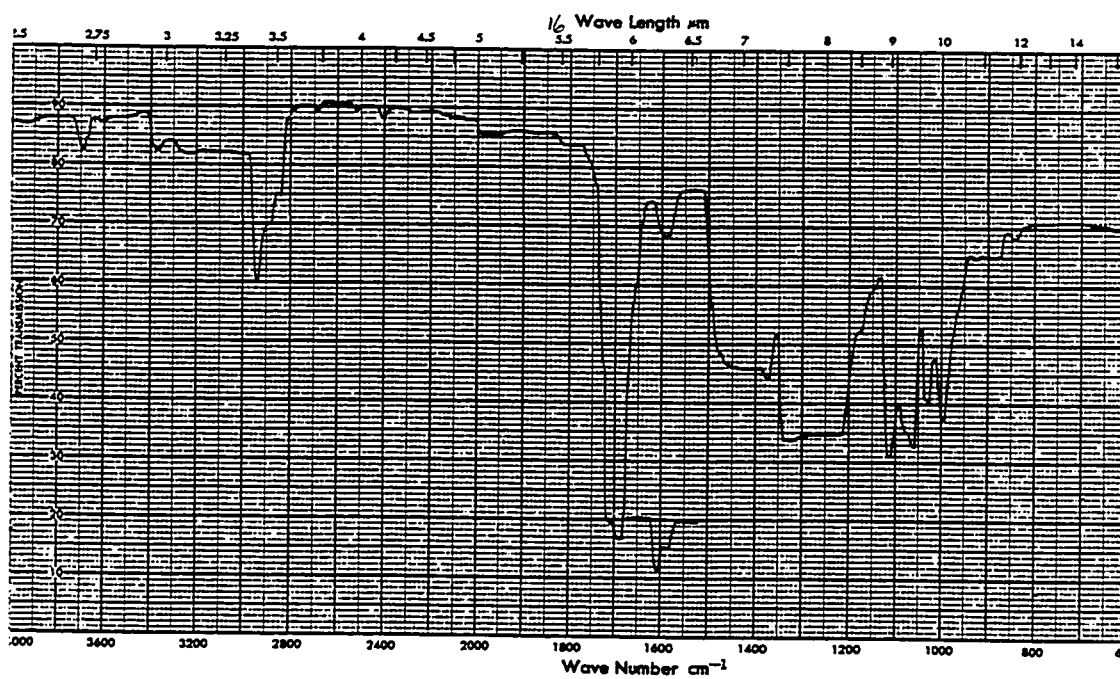
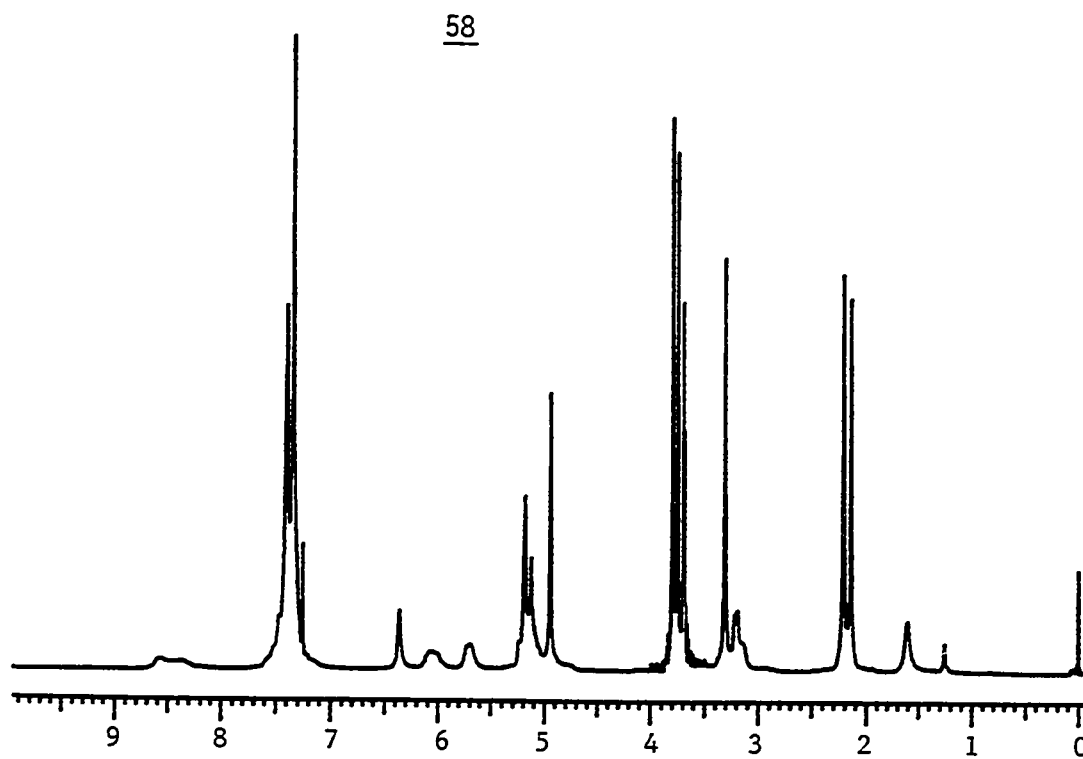
NMR ( $\text{CDCl}_3$ ): 2.14 (3H, s), 2.21 (3H, s), 3.1-3.3 (2H, m),  
3.31 (3H, s), 3.69 (3H, s), 3.75 (3H, s), 3.79 (3H, s)  
4.94 (2H, s), 5.0-5.2 (4H, m), 5.6-5.8 (1H, broad),  
5.9-6.2 (1H, broad), 6.36 (1H, s), 7.2-7.4 (15H, m)

MS: 70 EV 771 (.024,  $\text{M}^+ + 1$ ), 635 (.1), 544 (.31), 461 (46), 220 (75),  
91 (100)  
30 EV 770 (.03,  $\text{M}^+$ ), 680 (.3), 635 (.5), 544 (.7), 461 (48),  
220 (87), 91 (100)

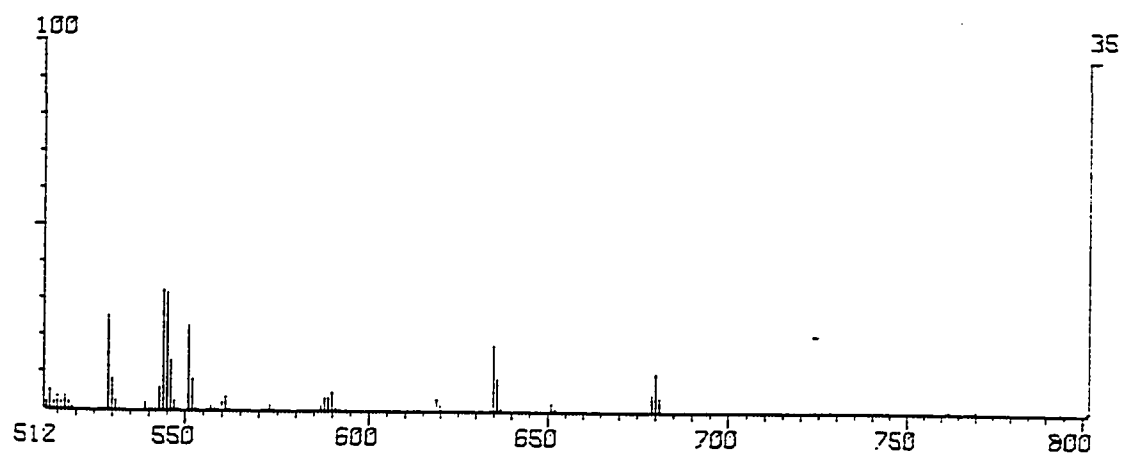
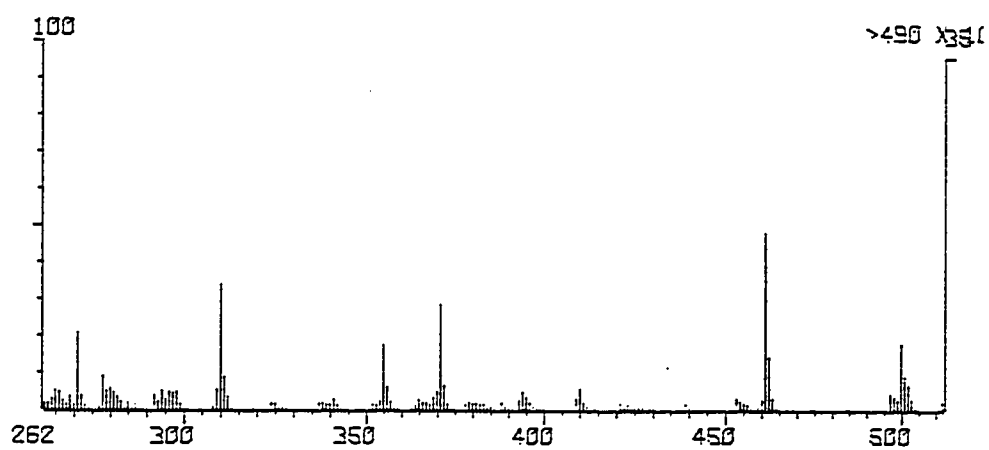
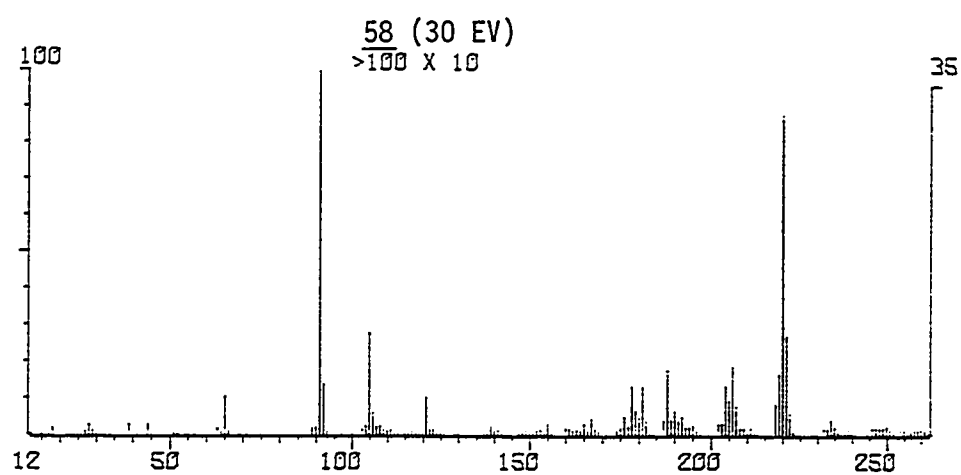
Analysis:  $\text{C}_{46}\text{H}_{46}\text{N}_2\text{O}_9$

chromatographed foam

calculated	found
C: 0.7167	0.7181
H: 0.0601	0.0617
N: 0.0363	0.0357







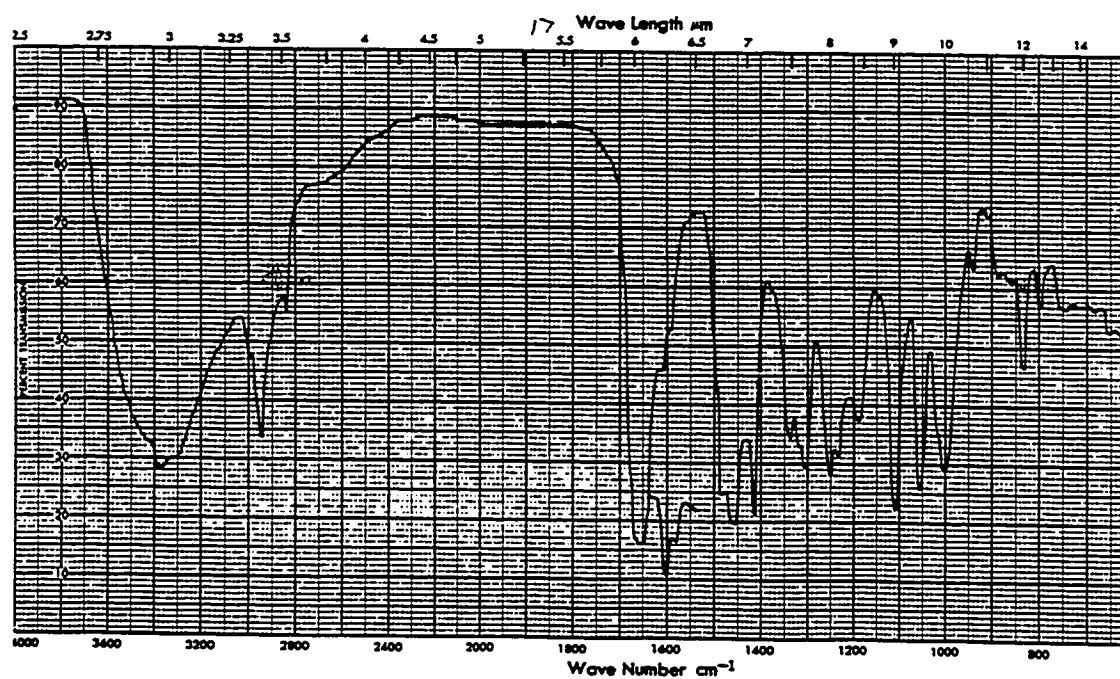
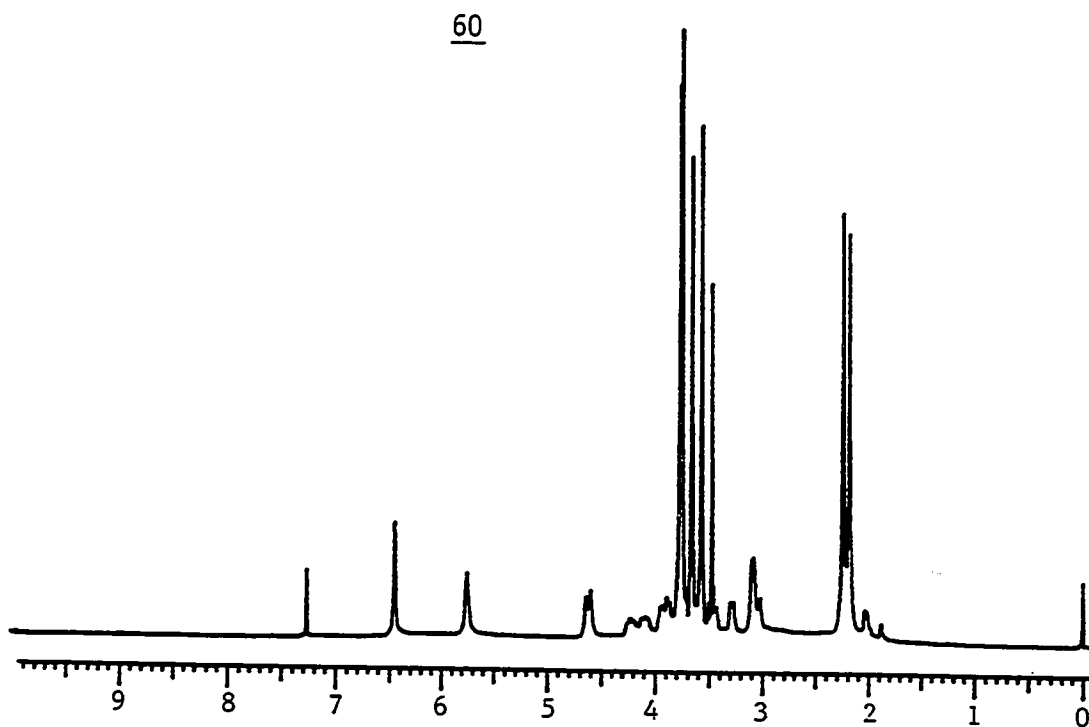
A solution of 8.61 g (11.2 mmol) of 58 in 100 ml of ethanol was hydrogenated over 10 ml of a suspension of Raney nickel in ethanol at a hydrogen pressure of 1000 psi for 2 hours at 100°. Filtration through Celite, washing with eight 50 ml portions of hot ethanol, followed by evaporation gave 4.5 g (88%) of crude 60. mp 141-150° (methanol).

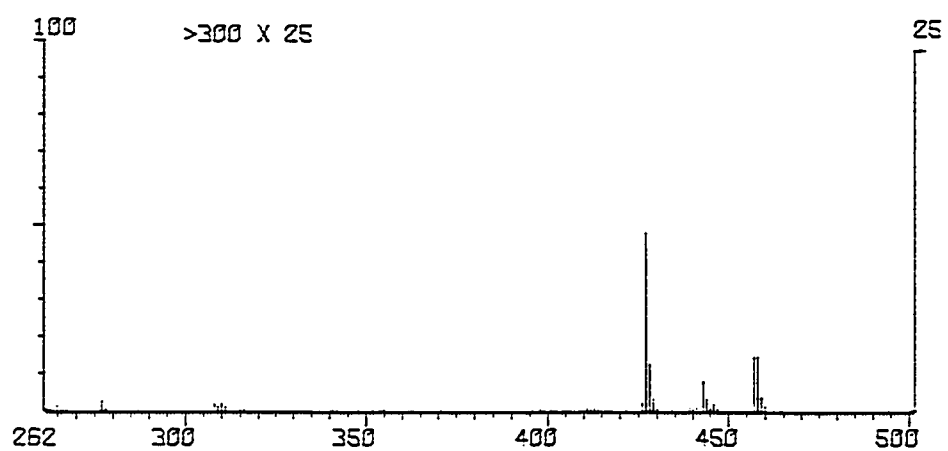
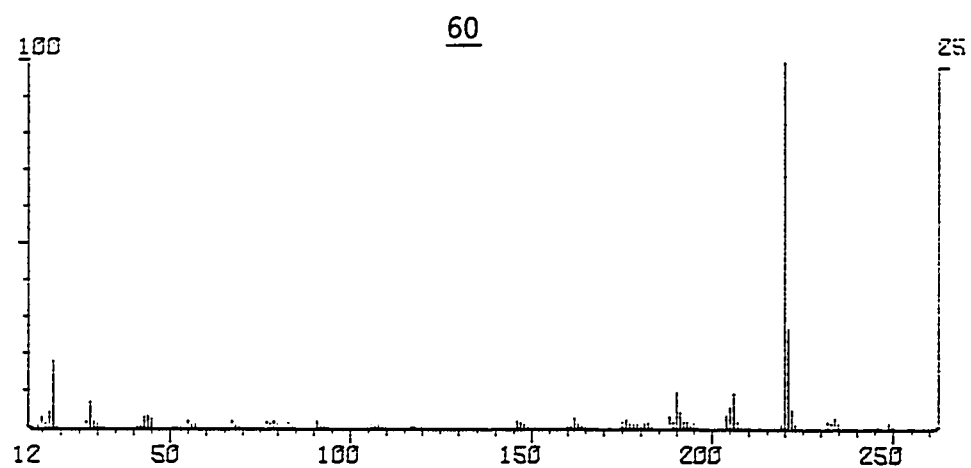
NMR (CD<sub>3</sub>OD/CDCl<sub>3</sub>): 2.18 (3H, s), 2.24 (3H, s), 3.08 (3H, s), 3.47 (3H, s), 3.57 (3H, s), 3.66 (3H, s), 3.75 (3H, s), 3.76 (3H, s), 5.75 (1H, s), 6.44 (1H, s)

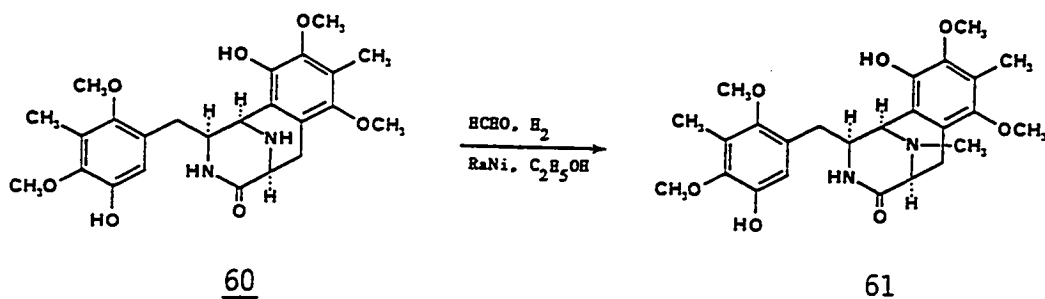
MS: 448 (15,  $M^+$ ), 447 (15), 220 (100)

Analysis :  $C_{24}H_{30}N_2O_7$

crystals from methanol	
calculated	found
C: 0.6287	0.6268
H: 0.0659	0.0680
N: 0.0611	0.0626







#### 4-N-METHYLPIPERAZIN-2-ONE (61)

Hydrogenation of a solution of 1.00 g (2.23 mmol) of 60 and 0.9 ml (12 mmol) of 37% formaldehyde solution in 10 ml of ethanol over 2 ml of a suspension of Raney nickel in ethanol at 1000 psi of hydrogen pressure for 30 minutes at room temperature followed by filtration through Celite gave 1.00 g (97%) of 61. mp 148° (ethyl acetate)

IR ( $\text{CH}_2\text{Cl}_2$ ): 3540, 3380, 2940, 1670, 1100, 1050, 1000

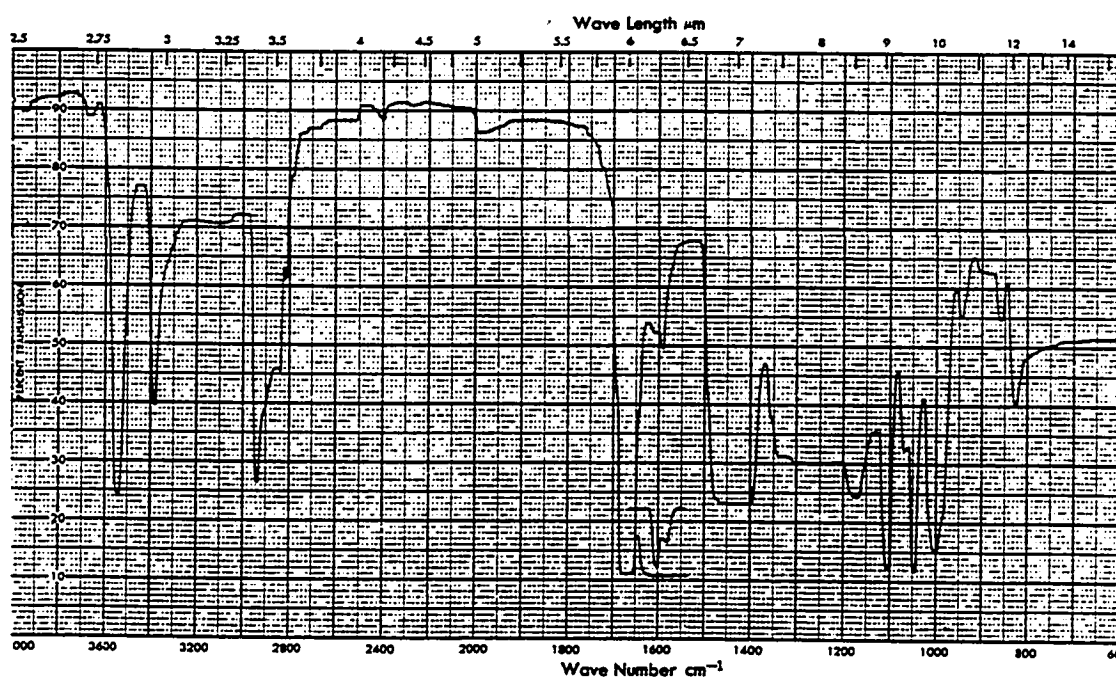
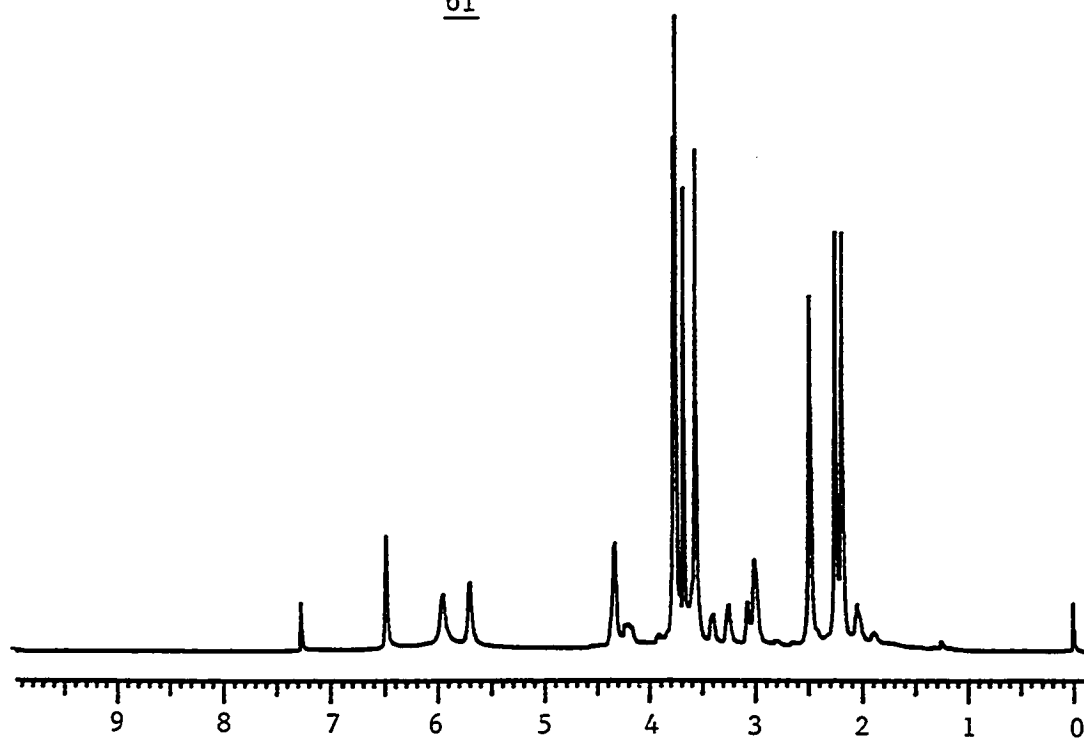
NMR ( $\text{CDCl}_3$ ): 2.19 (3H, s), 2.25 (3H, s), 2.49 (3H, s), 3.56 (3H, s), 3.68 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 4.34 (1H, s), 5.63 (1H, s), 5.98 (1H, s), 6.48 (1H, s)

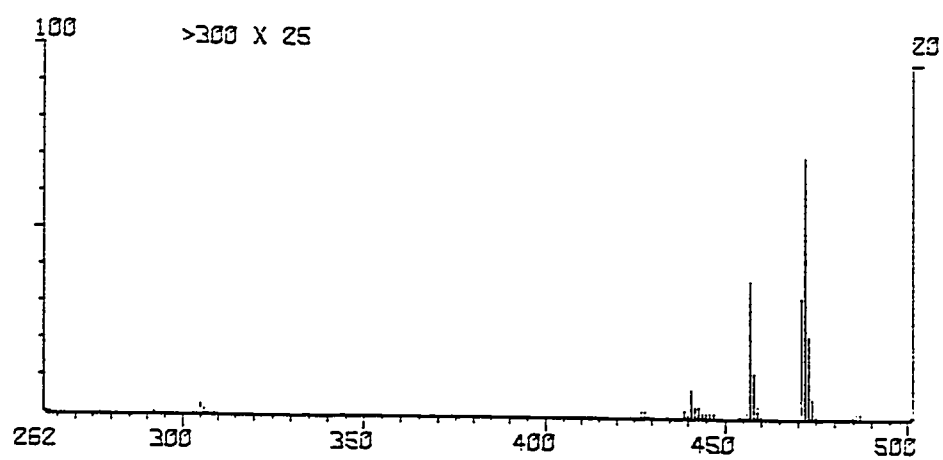
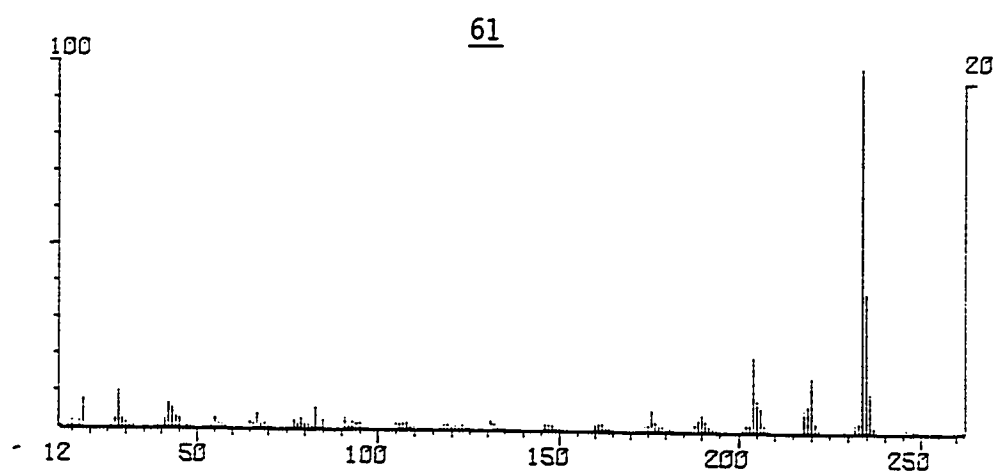
MS: 472 (2.8,  $\text{M}^+$ ), 457 (1.5), 234 (100)

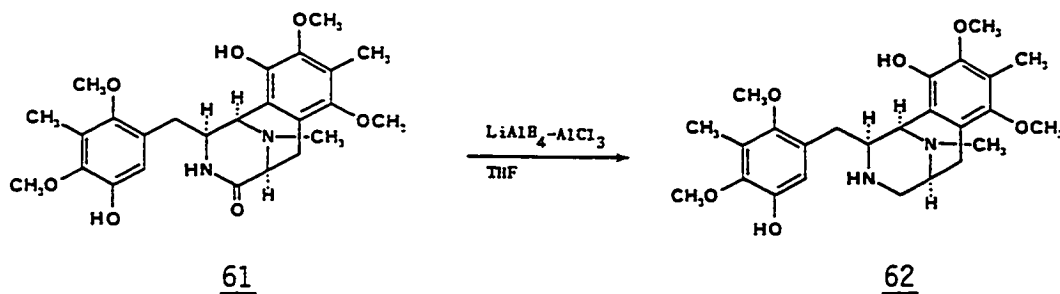
Analysis :  $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_7$

crystals from ethyl acetate

	calculated	found
C: 0.6355		0.6347
H: 0.0683		0.0710
N: 0.0593		0.0567

61





#### 4-N-METHYL-2,3,5-SUBSTITUTED-PIPERAZINE (62)

To a stirred solution of 604 mg (15.9 mmol) of lithium aluminum hydride in 25 ml of tetrahydrofuran at 0° was added a solution of 660 mg (5.00 mmol) of aluminum chloride in 7 ml of tetrahydrofuran. After warming to room temperature for 30 minutes, the mixture was cooled to 0° and 750 mg (1.59 mmol) of 61 in 10 ml of tetrahydrofuran added. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours. Water was added slowly until evolution of hydrogen ceased, then a solution of 3N hydrochloric acid was added dropwise until the solid dissolved. Dichloromethane was added to bring the volume to about 100 ml then ammonium hydroxide added until the pH was above 7. The mixture was filtered through Celite and partitioned between dichloromethane and saturated sodium chloride solution. The aqueous phase was extracted twice with dichloromethane and the organic phases dried over sodium sulfate and evaporated to give 691 mg (95%) of 62. Chromatography on silica gel eluted with 10% methanol in dichloromethane was followed by crystallization from ether. mp 198° (ether)



IR ( $\text{CH}_2\text{Cl}_2$ ): 3540, 2930, 1600, 1100, 1040, 1010

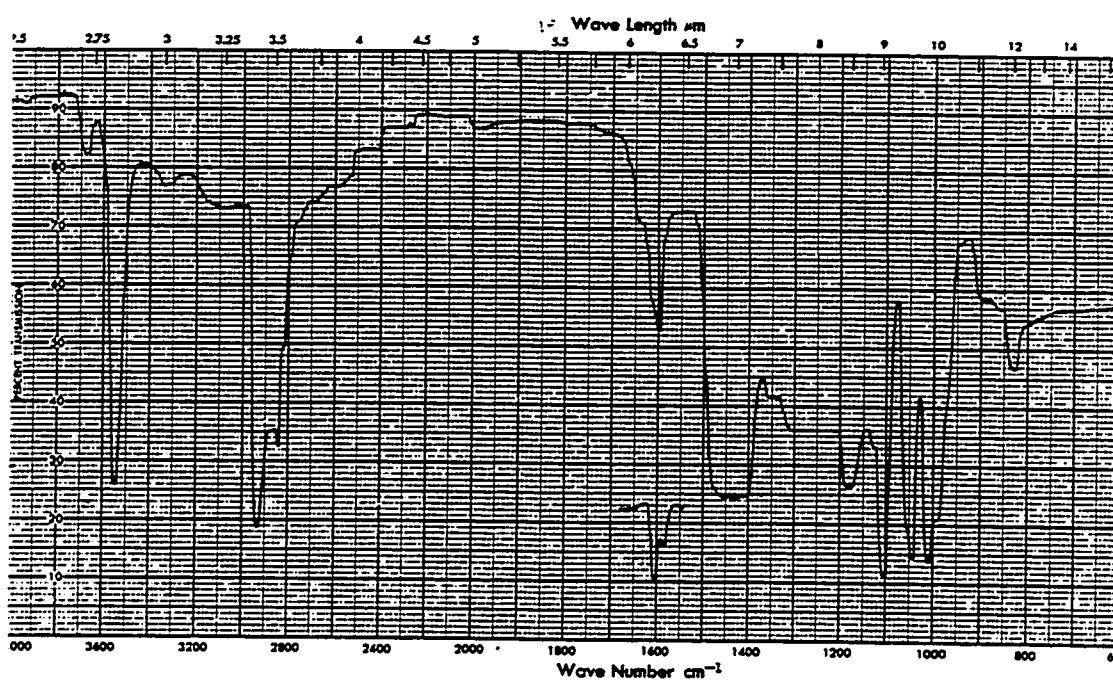
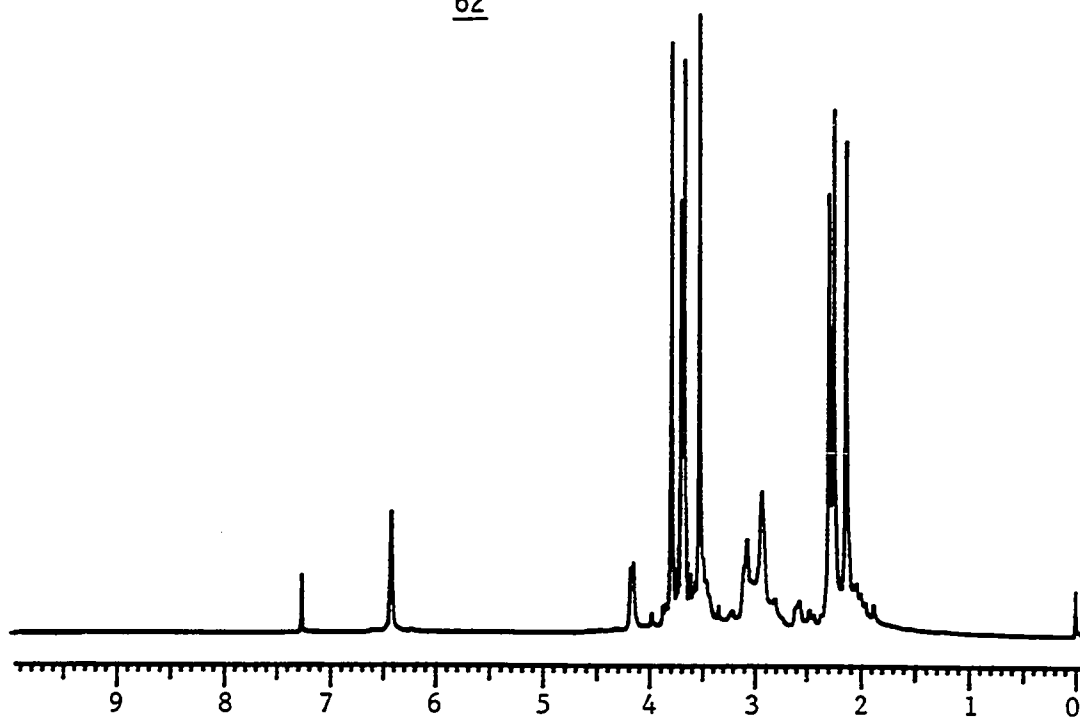
NMR ( $\text{CDCl}_3$ ): 2.13 (3H, s), 2.25 (3H, s), 2.29 (3H, s), 3.53 (3H, s)  
3.67 (3H, s), 3.69 (3H, s), 3.70 (3H, s),  
4.19 (1H, d,  $J=1\text{Hz}$ ), 6.42 (1H, s)

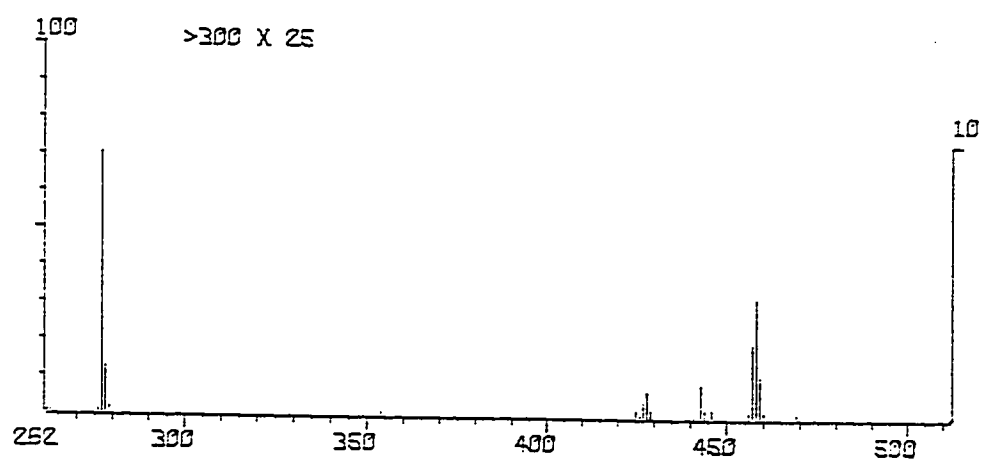
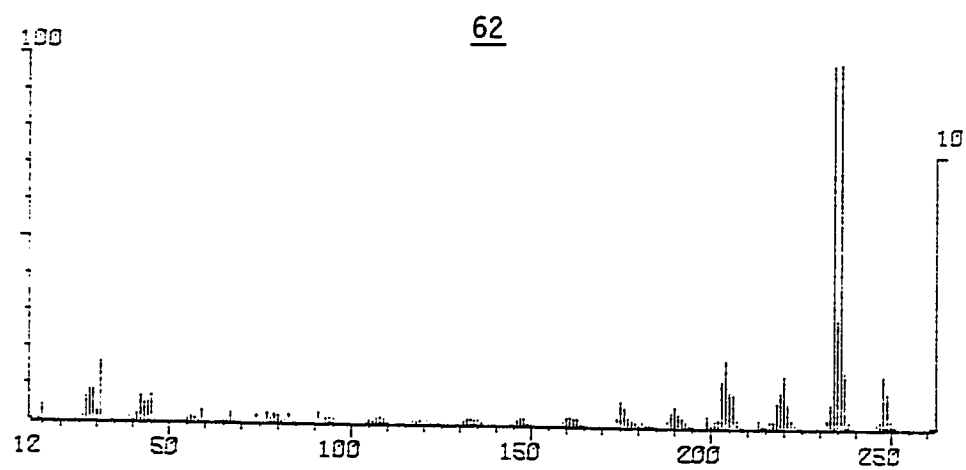
MS: 458 (1.4,  $\text{M}^+$ ), 277 (71), 236 (100), 134 (100)

Analysis :  $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_6$

crystals from ether

	calculated	found
C:	0.6548	0.6540
H:	0.0747	0.0776
N:	0.0611	0.0585

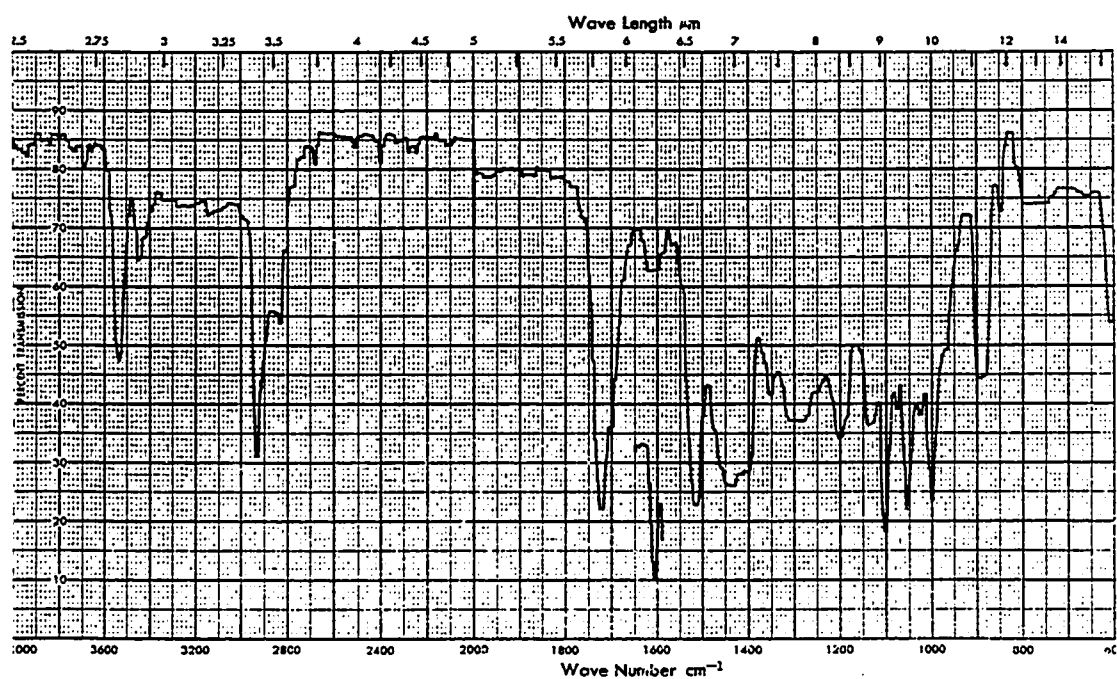
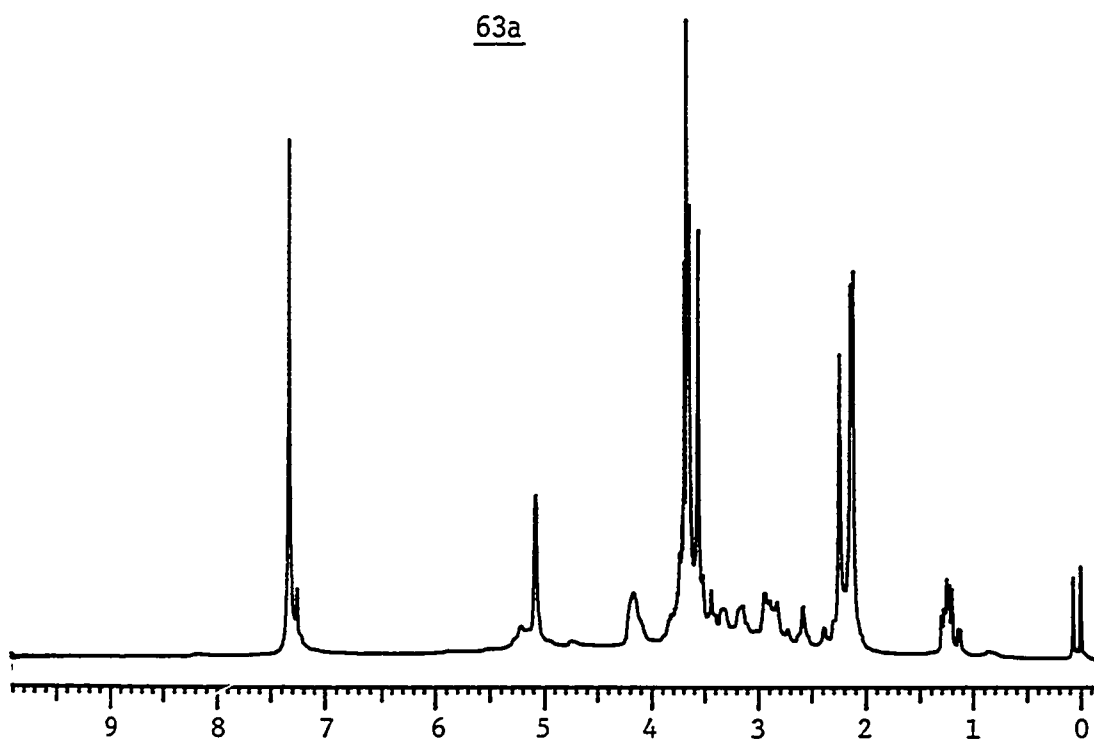
62

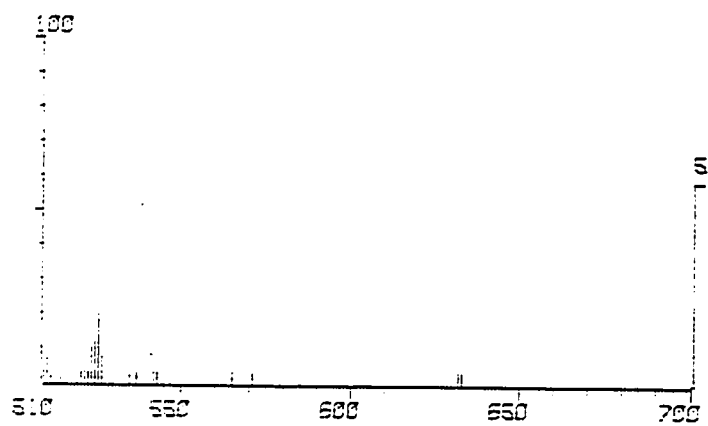
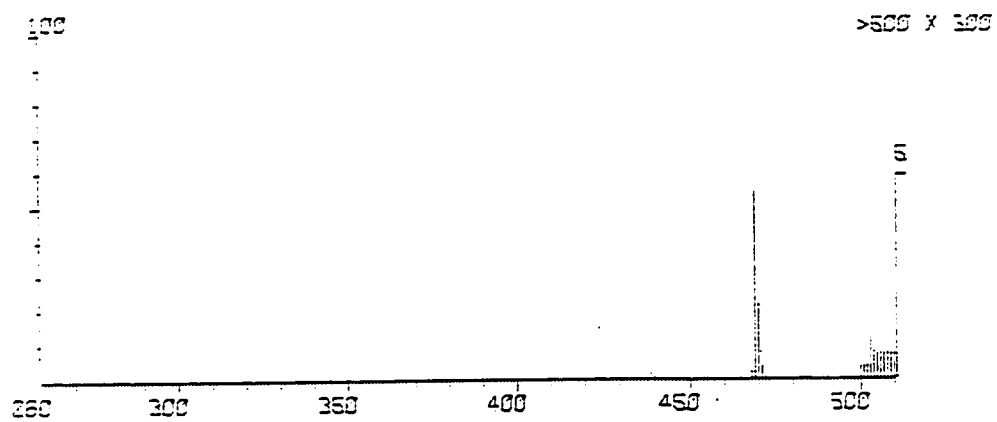
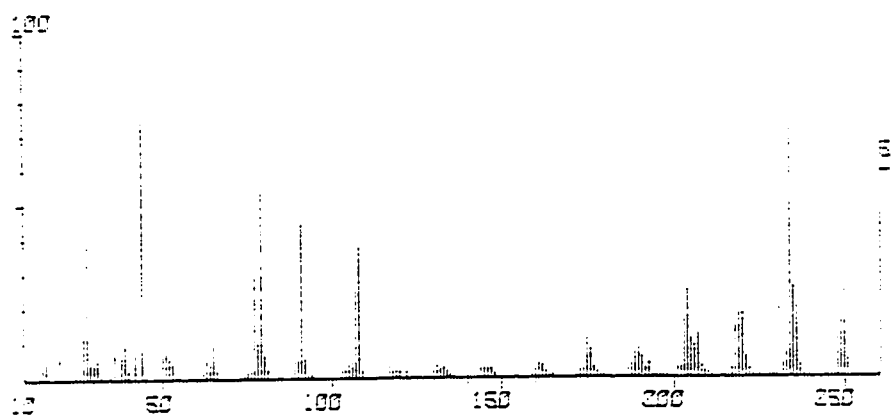


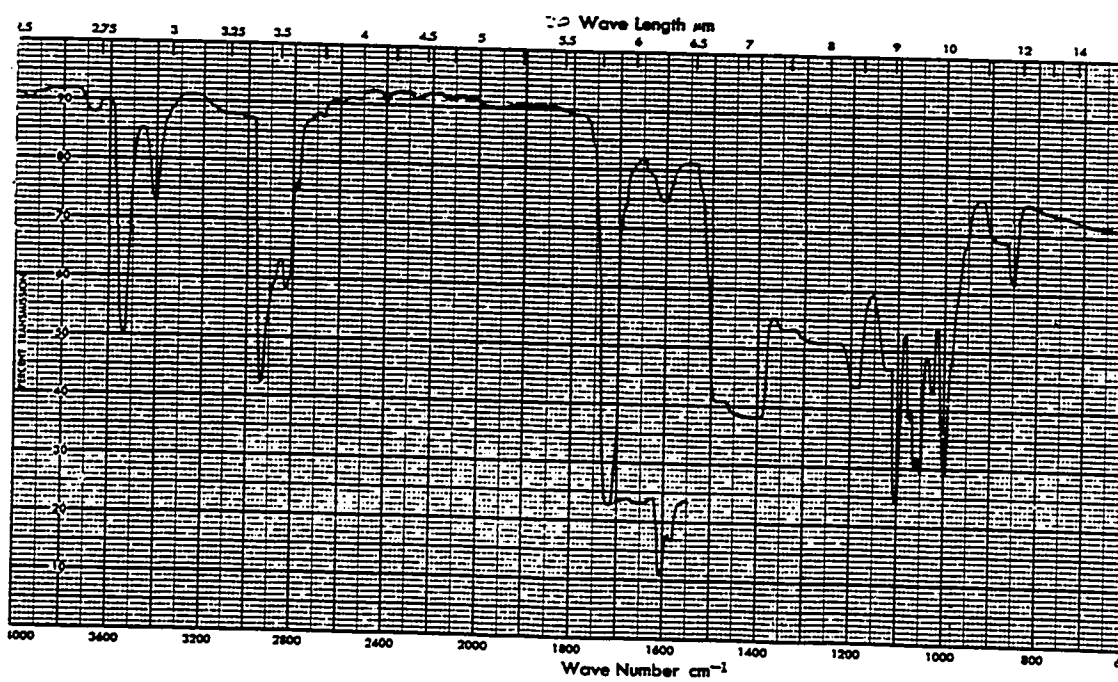
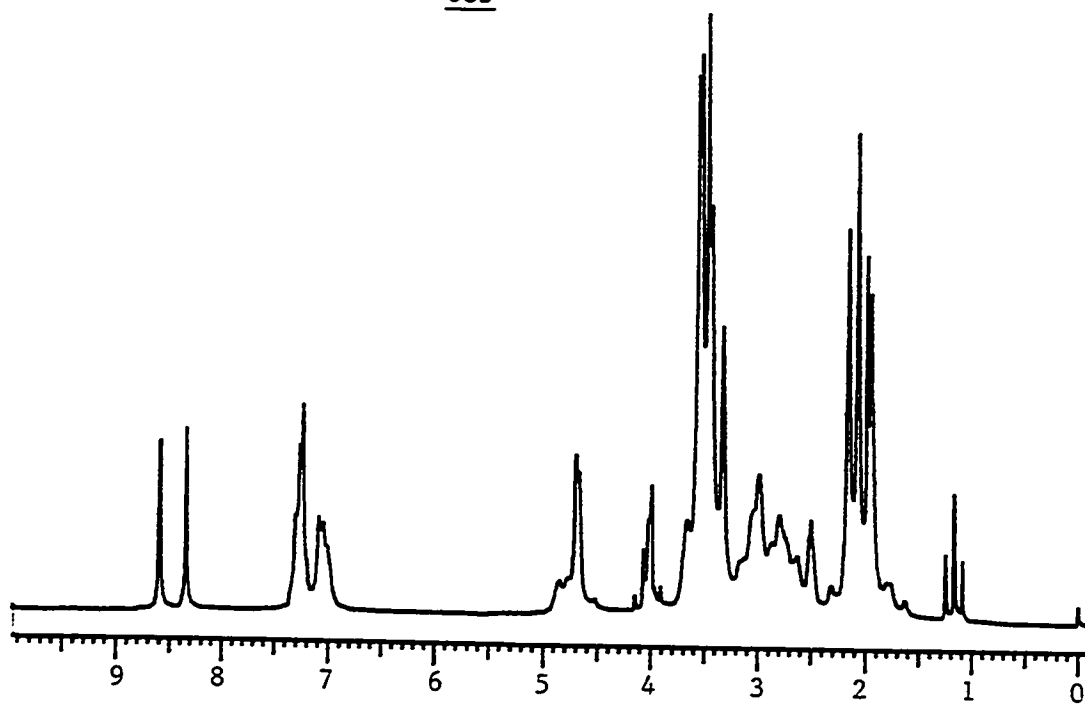
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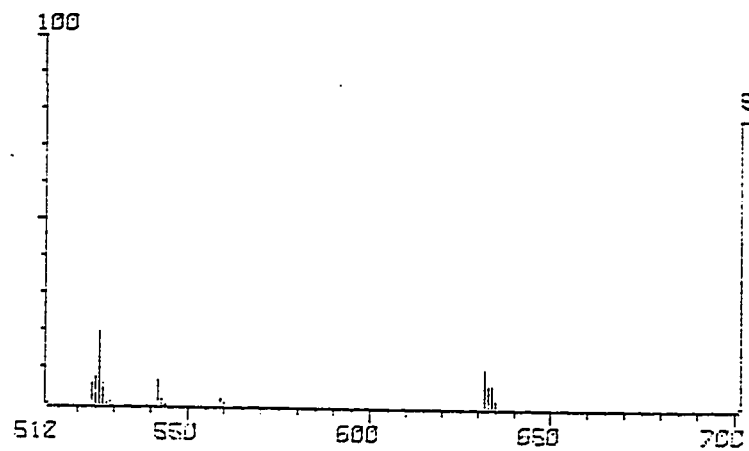
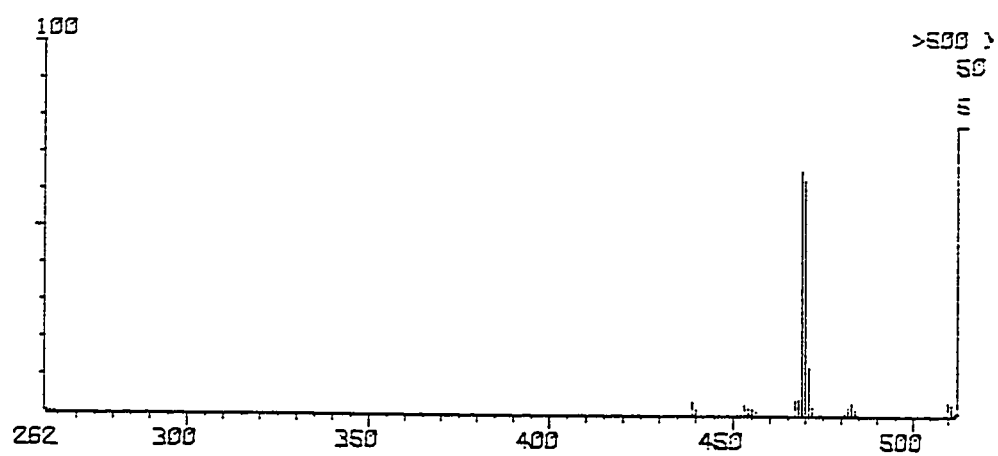
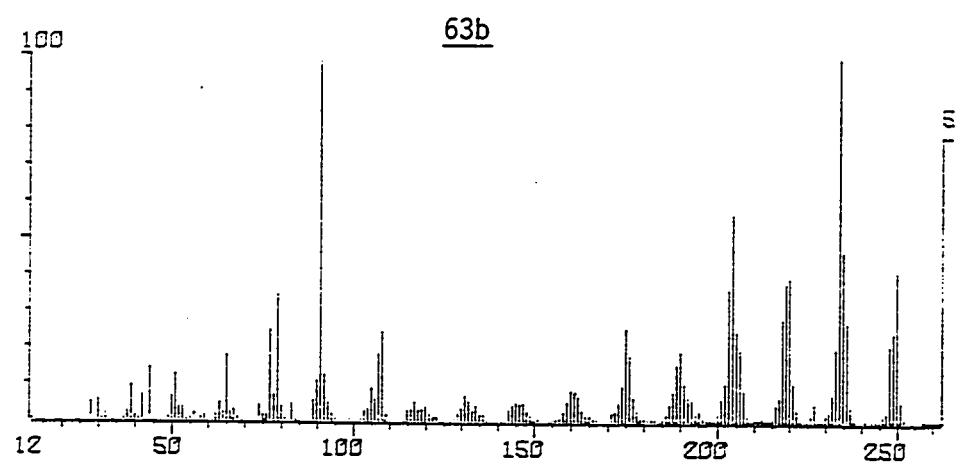
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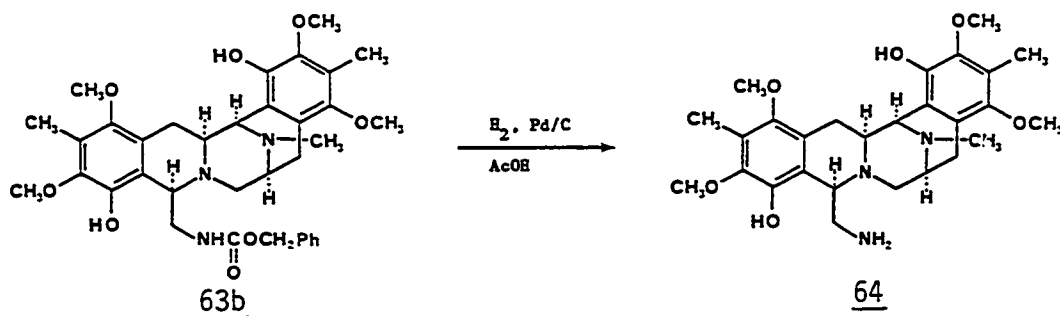


63a

63b







### DIPHENOL-TRIAMINE (64)

A solution of 759 mg (1.20 mmol) of 63b in 15 ml of acetic acid was hydrogenated over 250 mg of 10% palladium on carbon at one atmosphere of hydrogen pressure for 1 hour. Filtration through Celite and evaporation gave 610 mg (102%) of crude 64. mp 189° (ether-ethanol)

IR (KBr): 3400 (broad), 2940, 1460, 1410, 1110, 1010, 1000

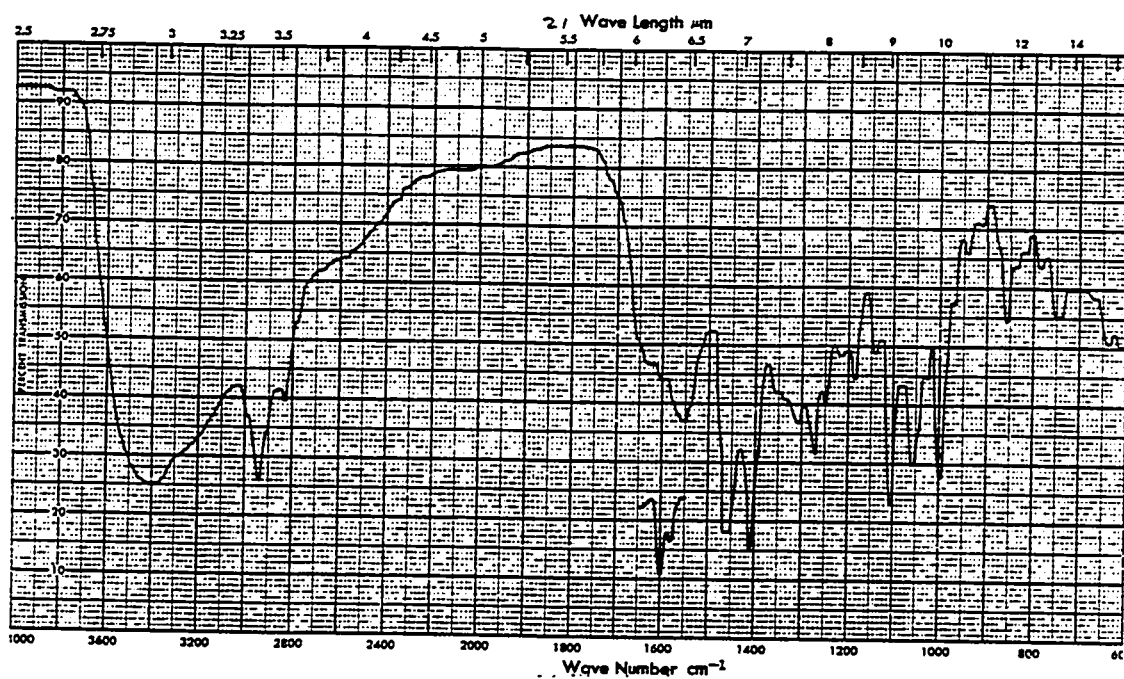
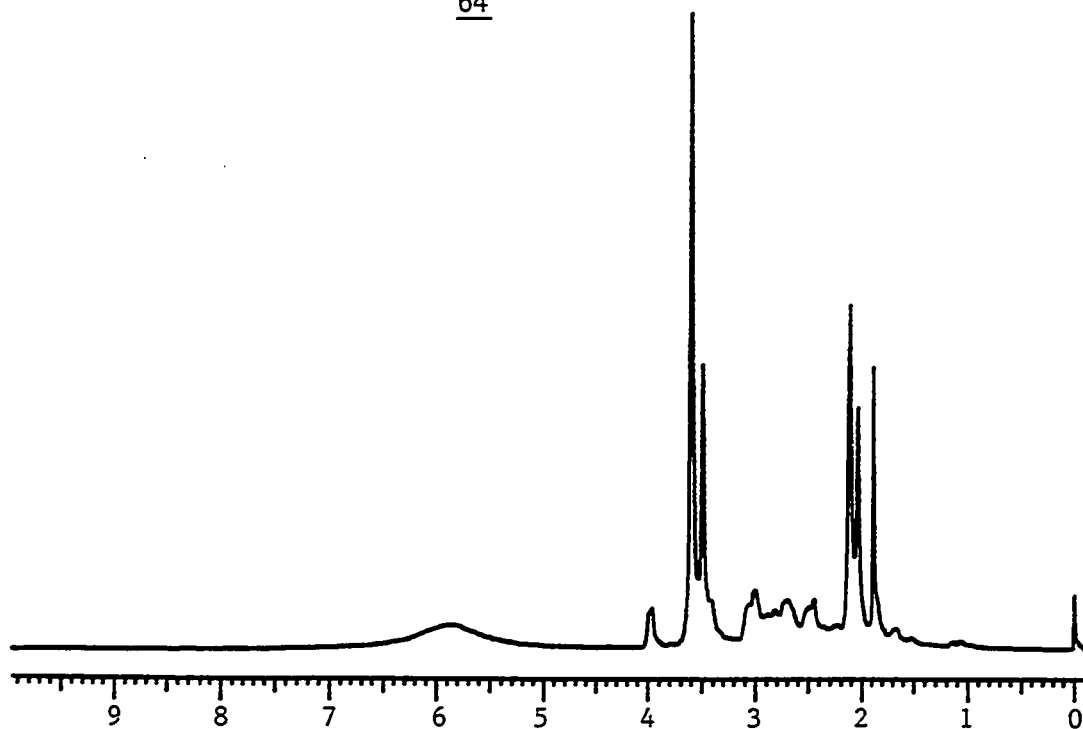
NMR ( $D_6$  DMSO): 1.88 (3H, s), 2.04 (3H, s), 2.11 (3H, s), 3.49 (3H, s), 3.60 (9H, s), 3.96 (1H, d,  $J=1\text{Hz}$ ), 5-7 (3-4, b)

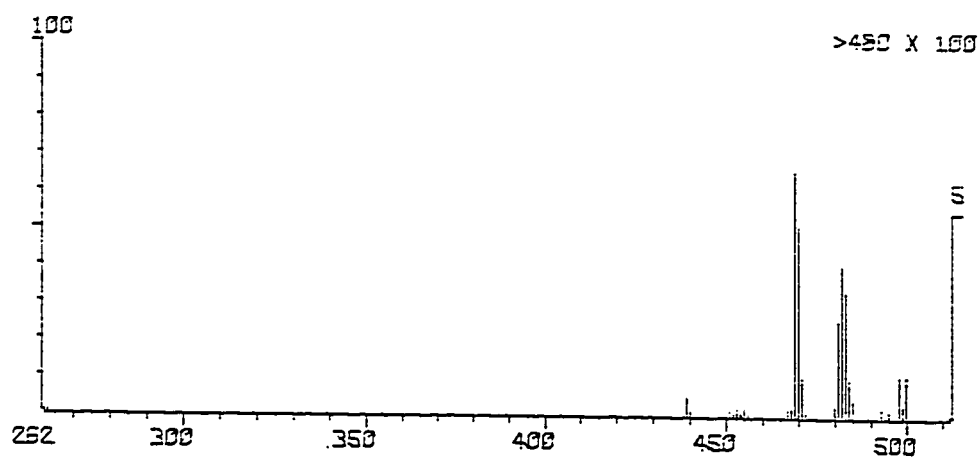
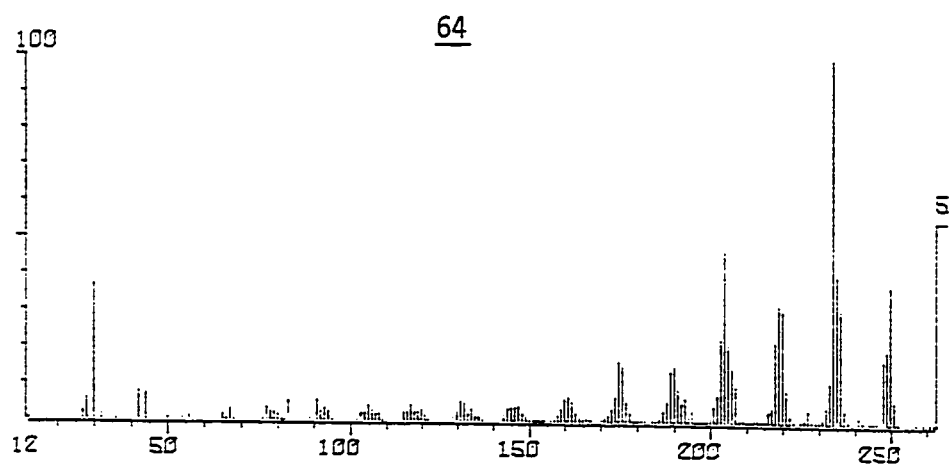
MS: 500 (0.1,  $M^++1$ ), 498 (0.1,  $M^+-1$ ), 482 (0.4), 469 (65), 234 (100)

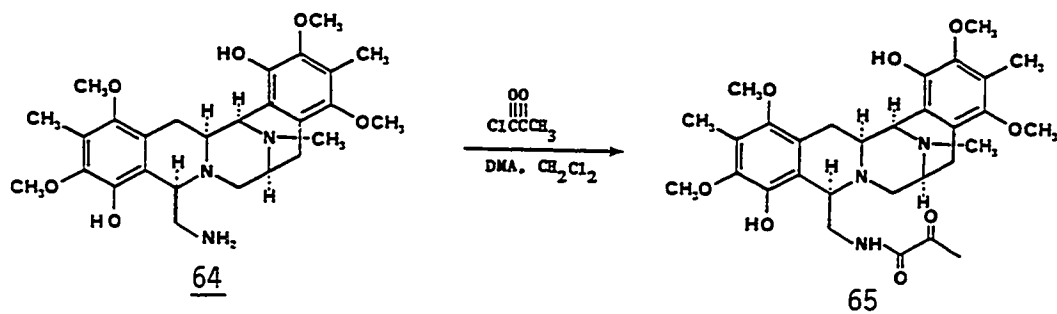
Analysis :  $C_{27}H_{37}N_3O_6$

crystals from ether-ethanol

	calculated	found
C: 0.6491		0.6235
H: 0.0746		0.0748
N: 0.0841		0.0759

64





### PYRUVAMIDE (65)

To a stirred solution of 600 mg (1.20 mmol) of 64 and 0.46 ml (3.6 mmol) of dimethylaniline in 15 ml of dichloromethane was added 0.10 ml (1.20 mmol) of pyruvyl chloride. After stirring for 15 minutes the reaction mixture was chromatographed on silica gel eluted with dichloromethane followed by a methanol in dichloromethane gradient, to give 622 mg (90%) of 65. mp 214° (ethyl acetate)

IR (KBr): 3400 (broad), 2940, 1680, 1470, 1415, 1110, 1000

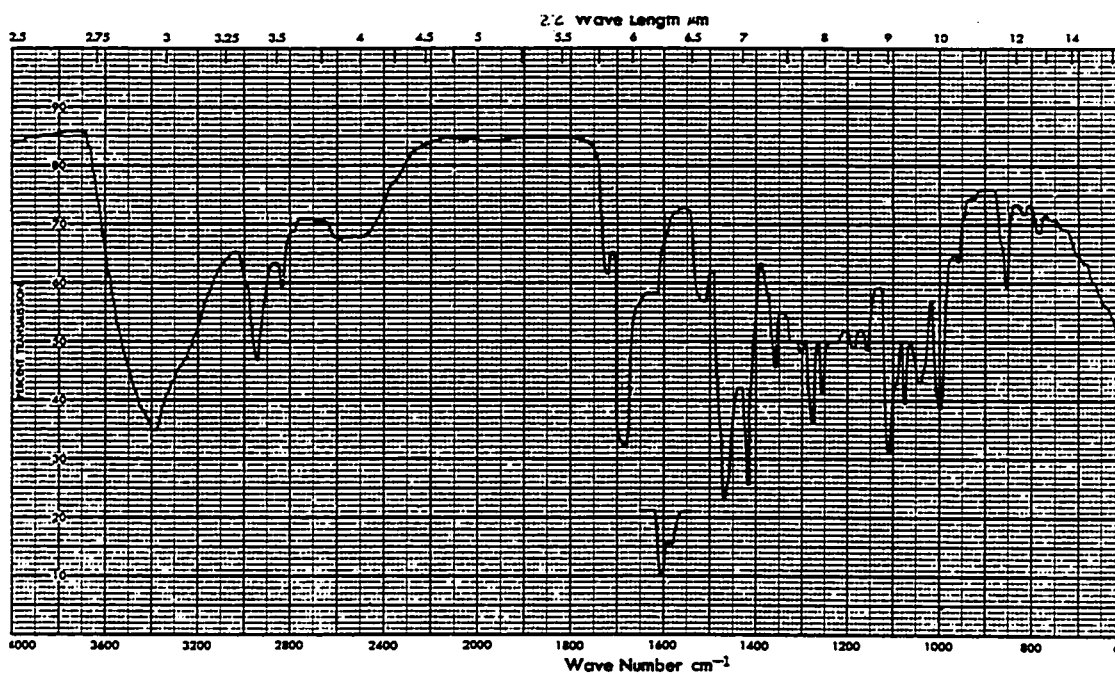
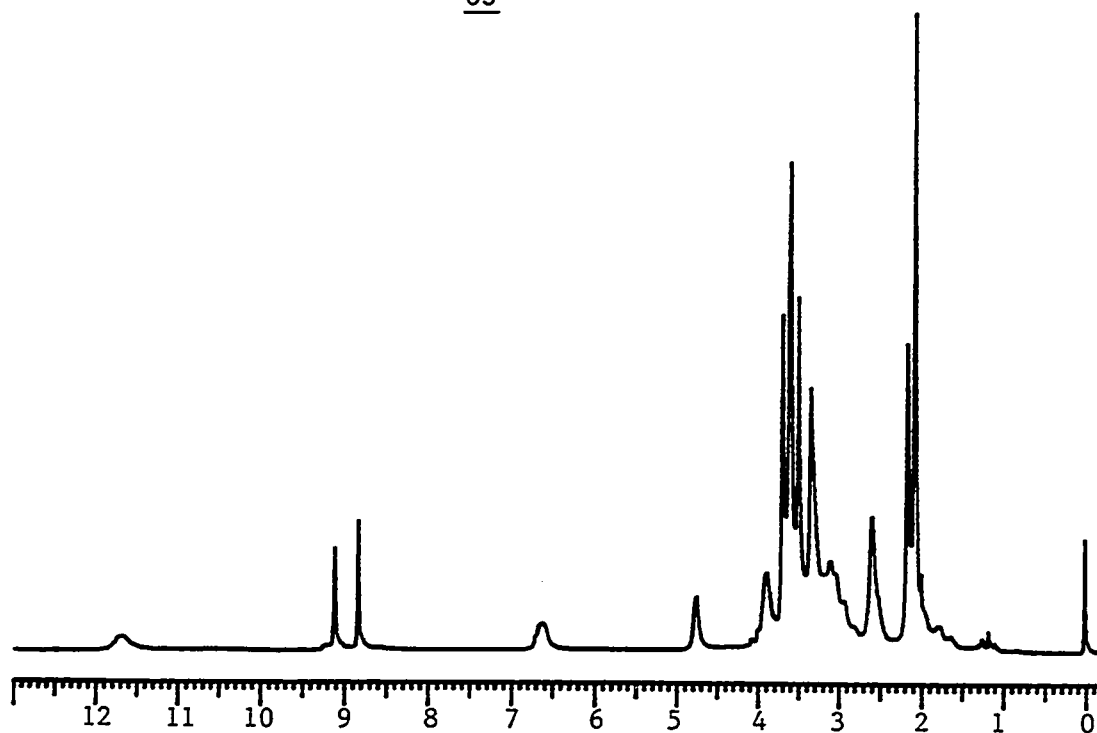
NMR ( $D_6$  DMSO): 2.06 (6H, s), 2.15 (3H, s), 3.33 (3H, s), 3.49 (3H, s), 3.58 (5H, s), 3.68 (3H, s), 4.77 (1H, s), 6.5–6.8 (1H), 8.82 (1H, s), 9.10 (1H, s), 11.6–11.9 (1H)

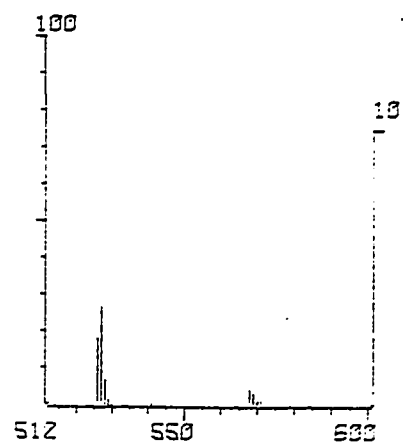
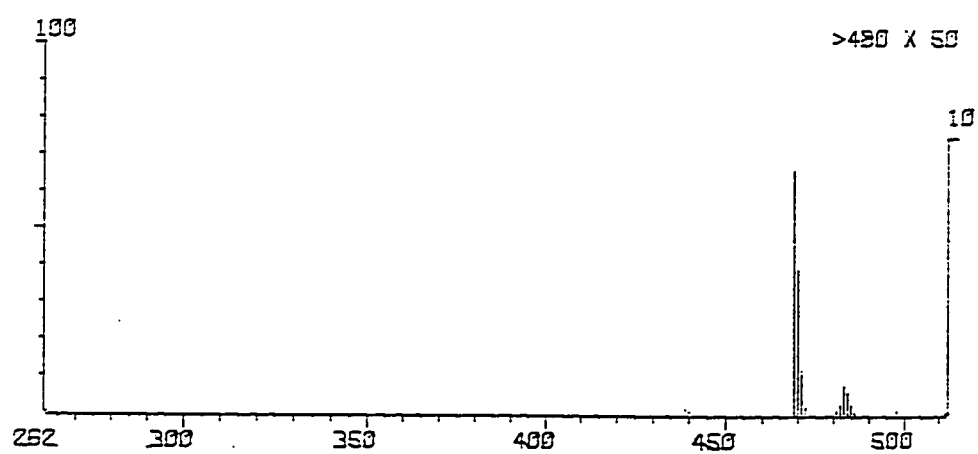
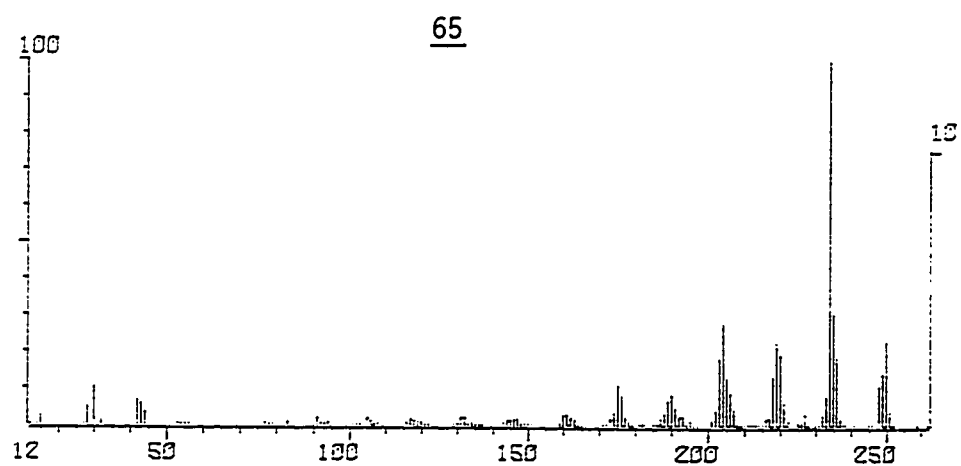
MS: 569 (0.1,  $M^+$ ), 568 (0.1), 527 (5.5), 469 (67), 234 (100)

Analysis :  $C_{30}H_{39}N_3O_8$

crystals from ethyl acetate

calculated	found
C: 0.6325	0.6258
H: 0.0690	0.0686
N: 0.0738	0.0660

65



NMR (CDCl<sub>3</sub>): Synthetic 4.01 (6H, s), 2.28 (3H, s), 2.24 (3H, s),  
2.00 (3H, s), 1.89 (3H, s)  
Natural 4.01 (6H, s), 2.28 (3H, s), 2.24 (3H, s),  
2.00 (3H, s), 1.89 (3H, s)

$^{13}\text{C}$ NMR ( $\text{CDCl}_3$ ):			
Synthetic	Natural	Synthetic	Natural
196.5	196.5	129.2	129.2
187.0	187.0	127.7	127.7
185.7	185.7	60.9	60.9
182.8	182.8	58.7	58.7
181.3	181.3	57.4	57.4
160.1	160.1	56.9	56.9
156.1	156.1	54.8	54.8
155.5	155.5	52.2	52.2
142.8	142.8	41.2	41.2
141.6	141.6	40.4	40.4
136.6	136.6	25.6	25.6
136.3	136.3	24.2	24.2
		22.7	22.7

MS: Synthetic 537 (4,  $\text{M}^+$ ), 437 (25), 234 (44), 220 (88), 30 (100)  
 Natural 537 (8,  $\text{M}^+$ ), 437 (43), 234 (29), 220 (52), 28 (100)

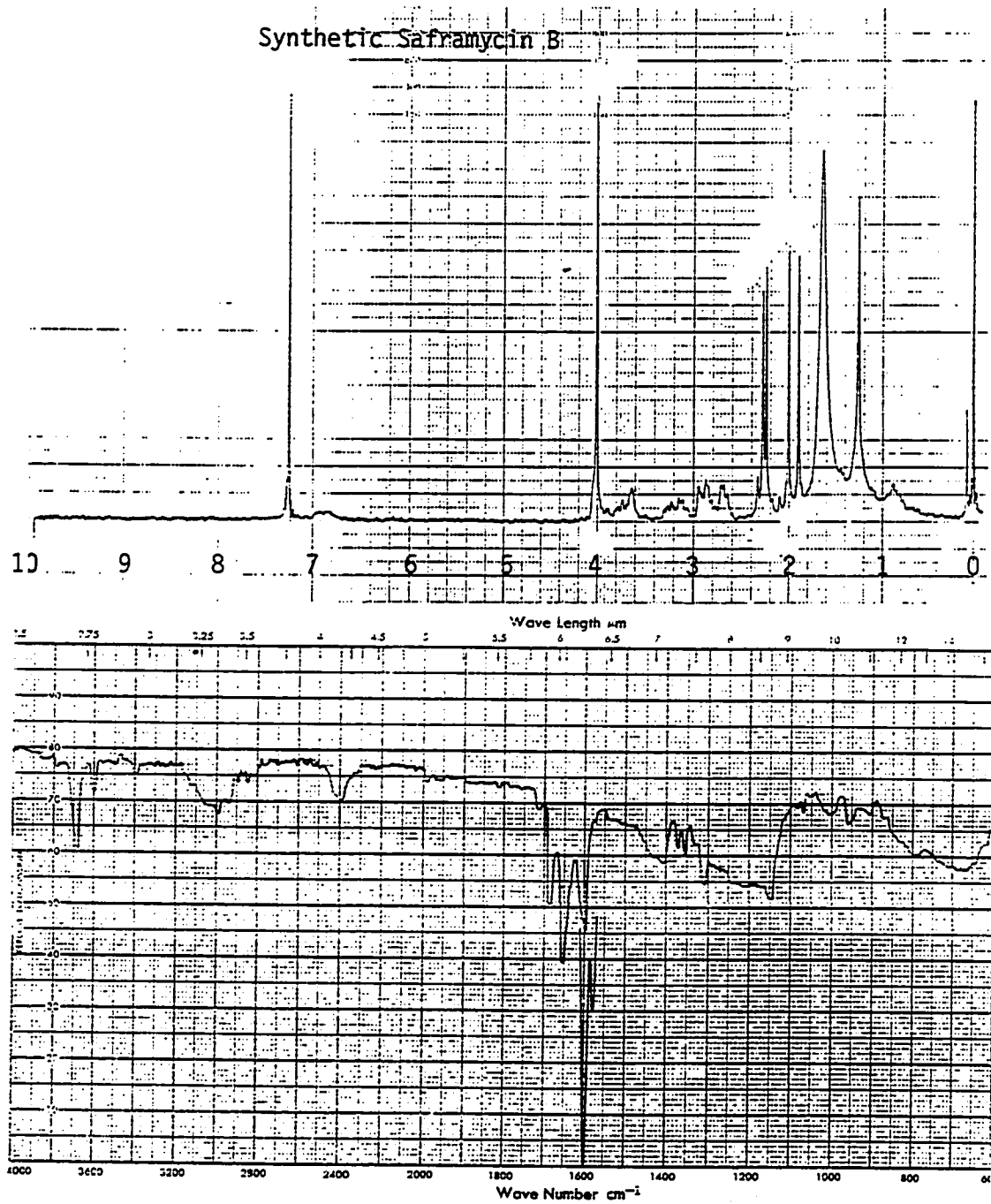
Analysis:  $\text{C}_{28}\text{H}_{31}\text{N}_3\text{O}_8$

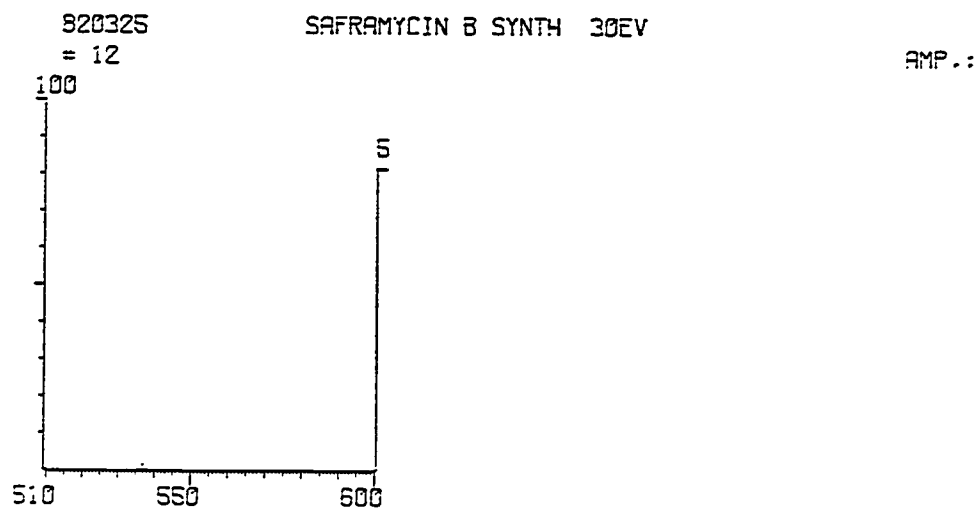
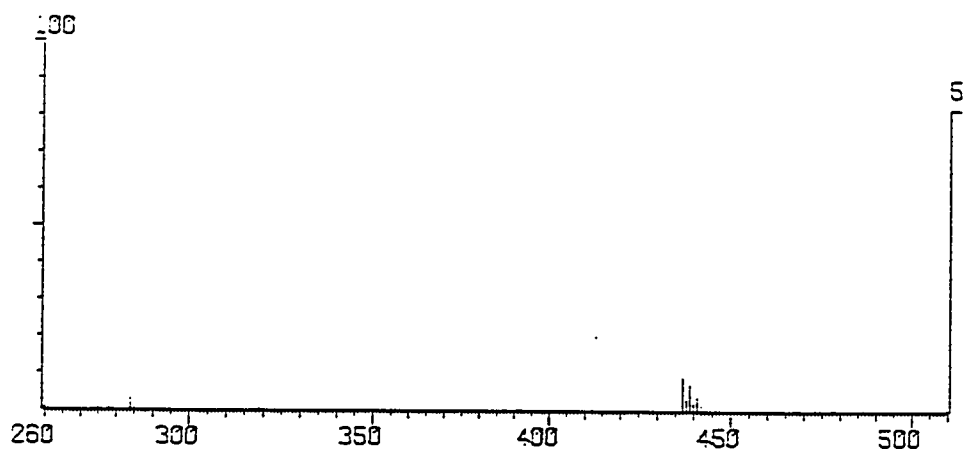
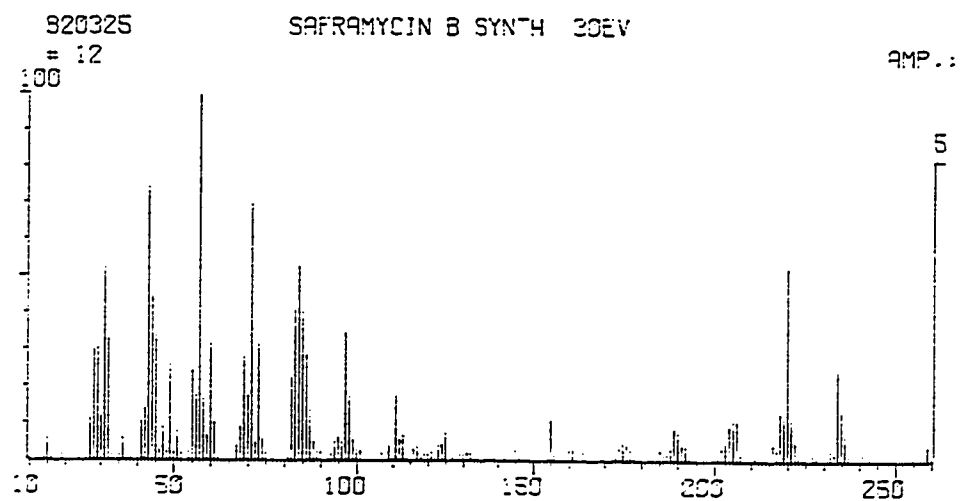
crystals from ether

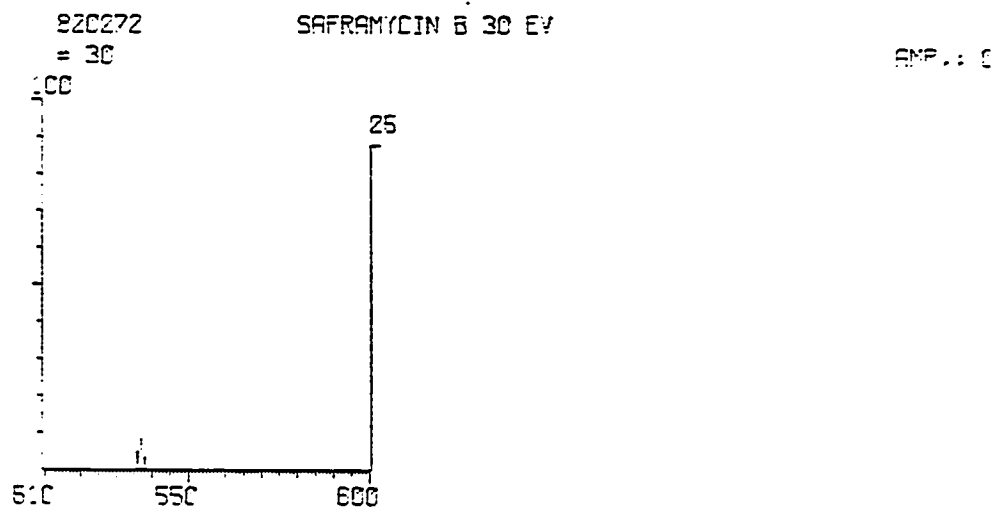
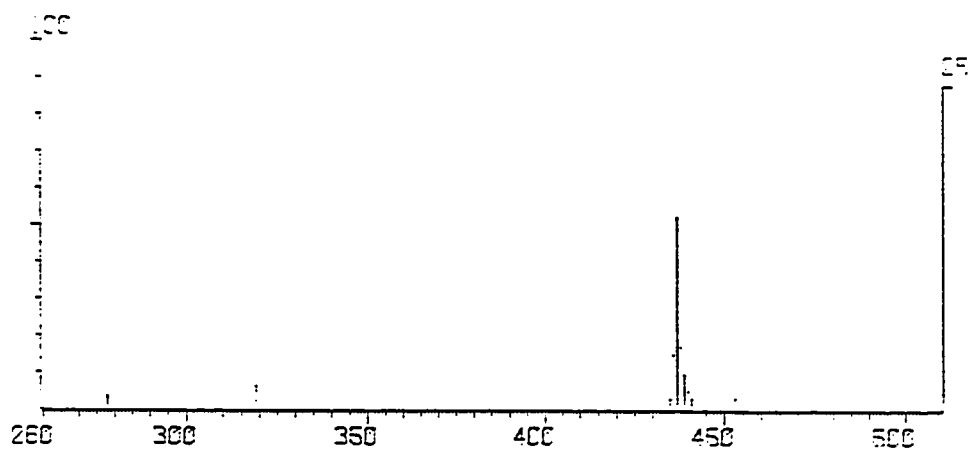
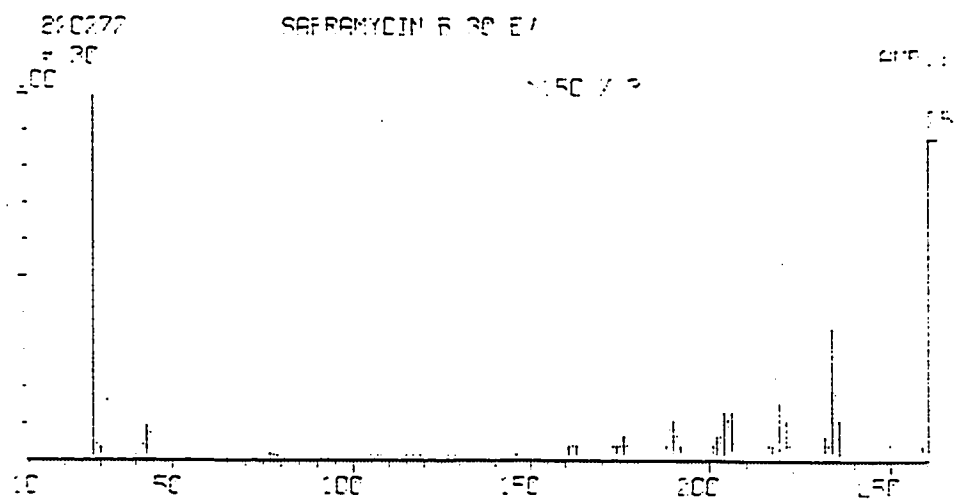
Synthetic		Natural
calculated	found	reported <sup>1</sup>
C: 0.6256	0.6265	0.6236
H: 0.0581	0.0605	0.0571
N: 0.0782	0.0787	0.0766

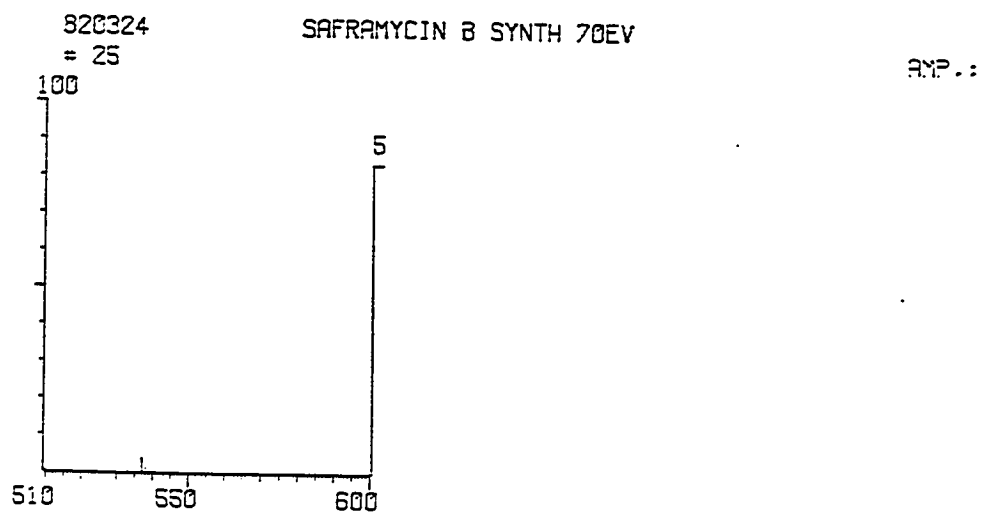
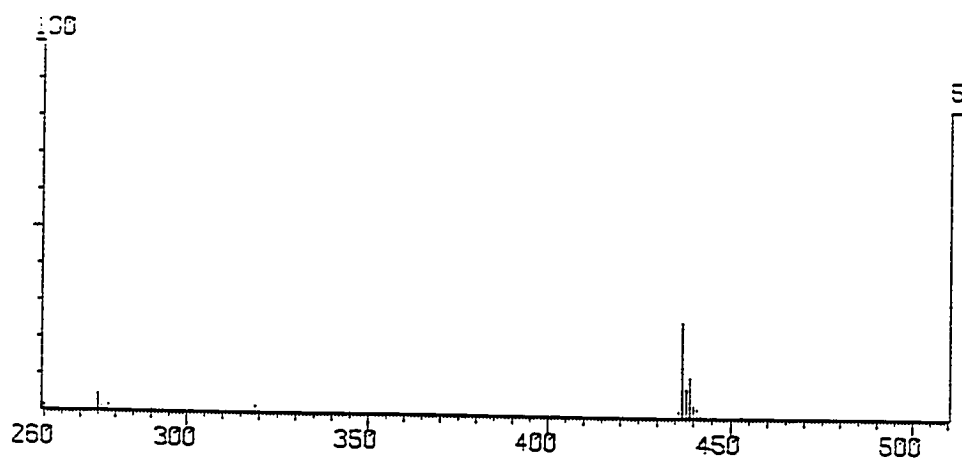
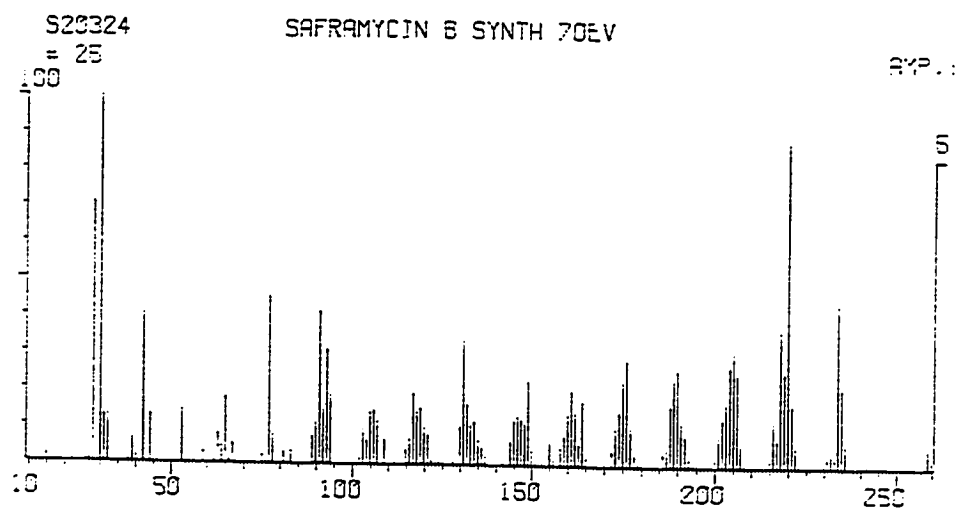


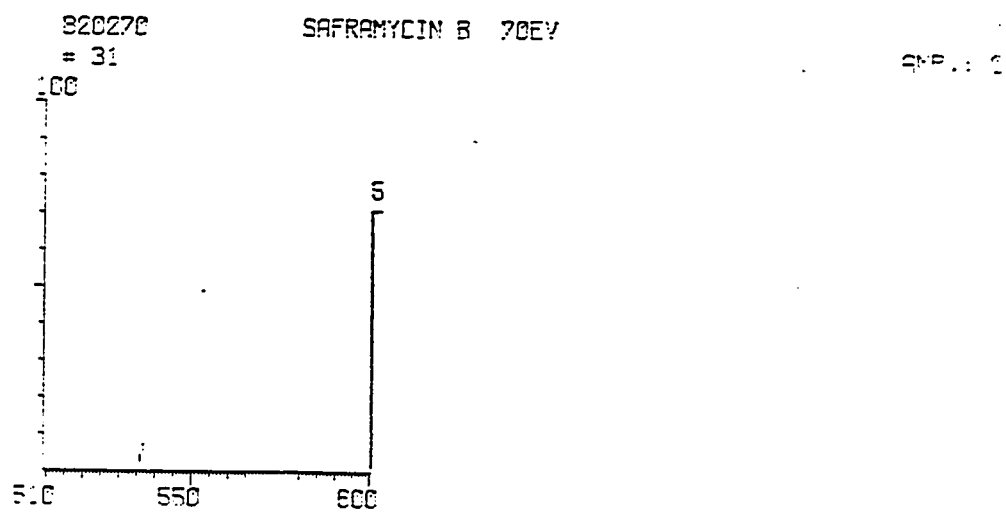
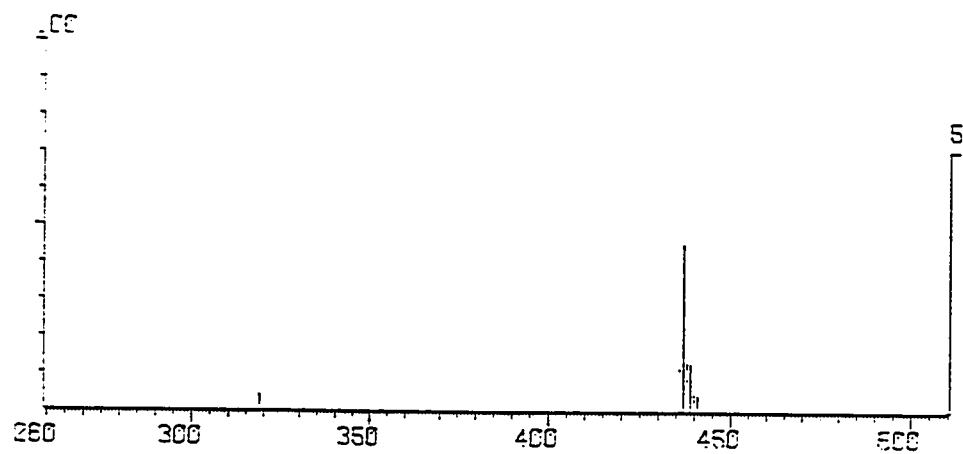
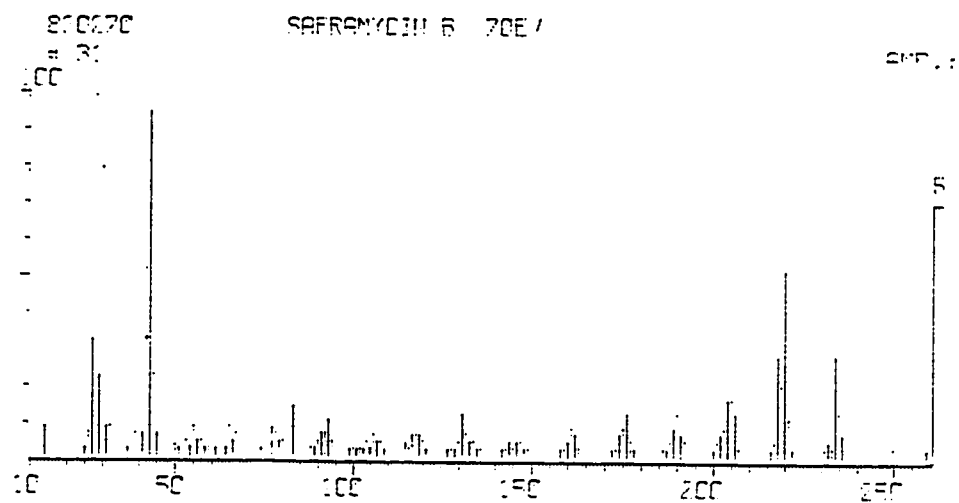
## Synthetic Safranycin B







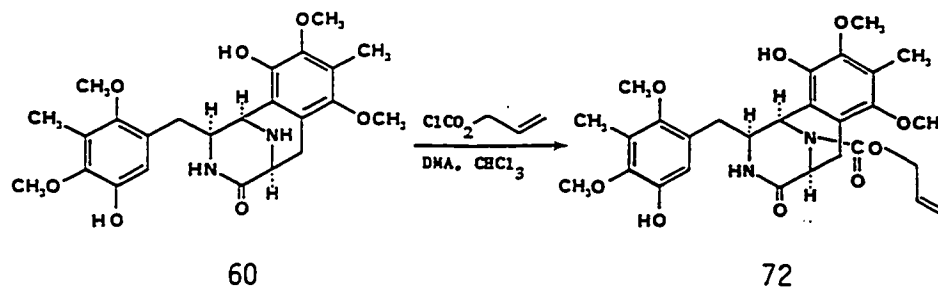




**Chapter V**

**SYNTHETIC STUDIES  
TOWARDS  
SAFRAMYCINS A AND S**

**EXPERIMENTAL**



### ALLYL-URETHANE (72)

To a stirred suspension of 1.00 g (2.18 mmol) of 60 and 0.90 ml (6.7 mmol) of dimethylaniline in 25 ml of chloroform was added 0.20 ml (2.6 mmol) of allylchloroformate. After 30 minutes the reaction mixture was partitioned between ether and saturated sodium chloride solution containing sufficient hydrochloric acid to maintain a pH below 3. The organic phase was extracted with saturated sodium chloride solution, followed by saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulfate and evaporated. Chromatography on silica gel eluted with an ether in hexanes gradient gave 1.12 g (95%) of 72. mp 125-130 (ethyl acetate)

IR ( $\text{CH}_2\text{Cl}_2$ ): 3530, 3380, 1670, 1100, 990

NMR ( $\text{CDCl}_3$ ): 2.19 (3H, s), 2.25 (3H, s), 3.0-3.6 (3H, m), 3.57 (3H, s), 3.66 (3H, s), 3.75 (3H, s), 3.79 (3H, s), 4.21 (1H, dt,  $J=3\text{hz}, 9\text{hz}$ ), 4.62 (2H, d,  $J=4\text{hz}$ ), 4.8-5.1 (1H, m), 5.1-5.4 (1H, t,  $J=7\text{hz}$ ), 5.7-6.1, (4H, m), 6.50 (1H, s)

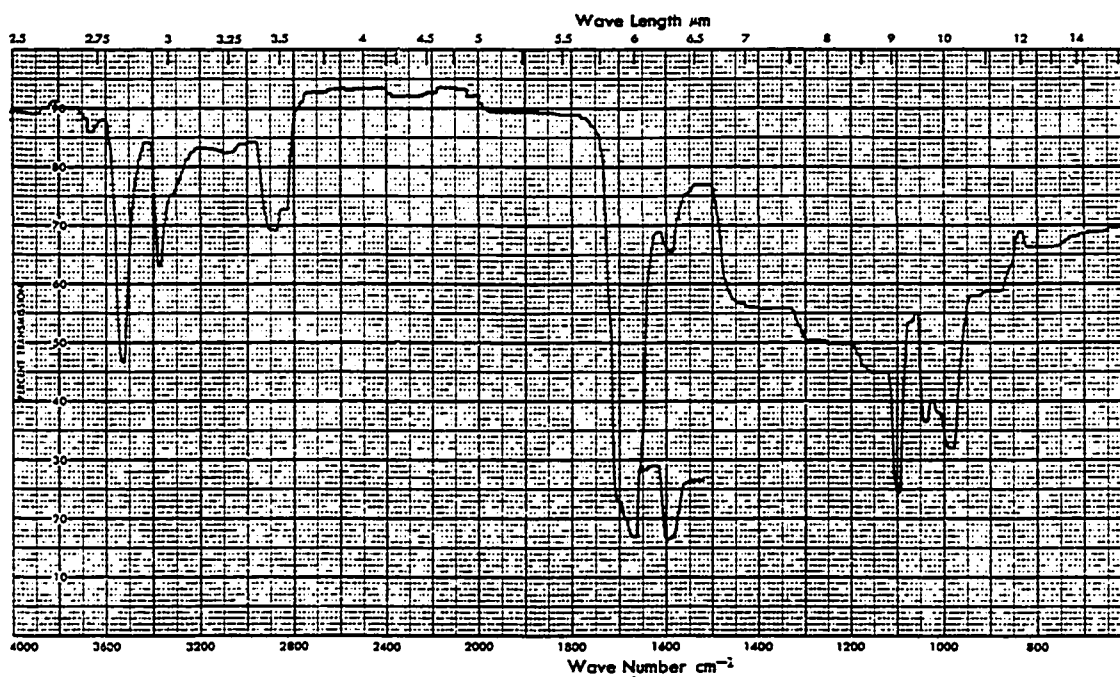
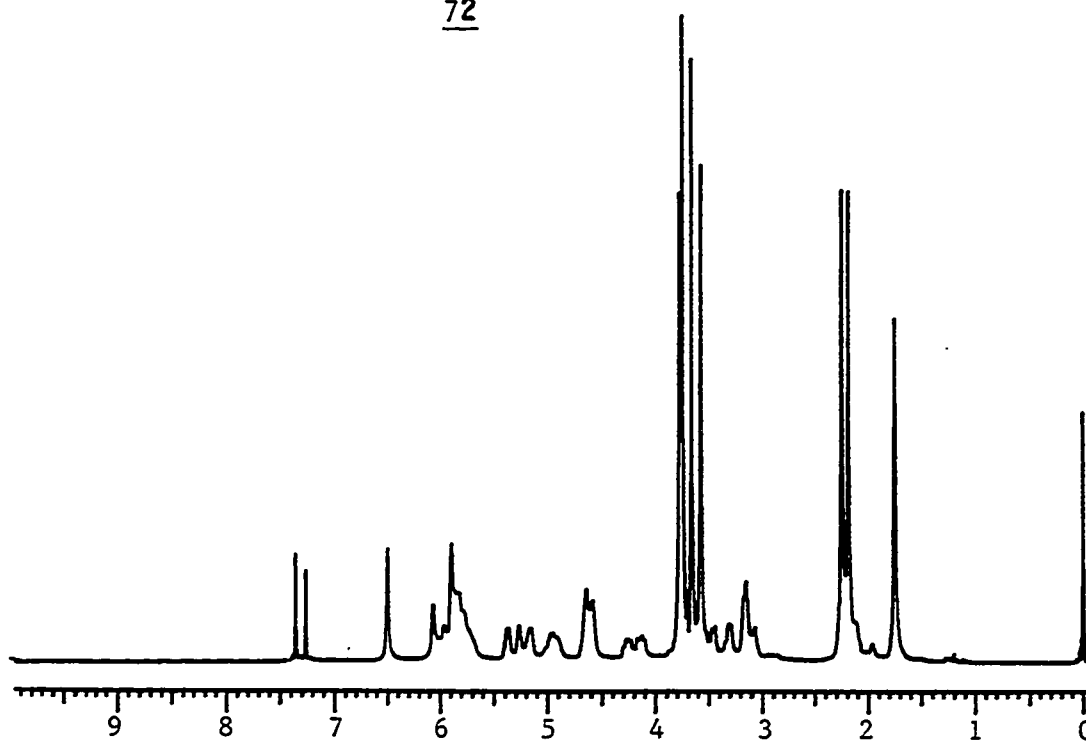
MS: 542 (8,  $\text{M}^+$ ), 361 (30), 333 (93), 220 (100), 41 (90)

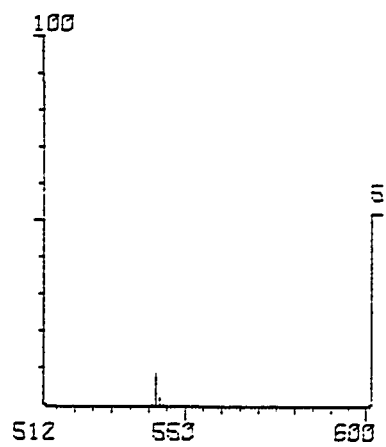
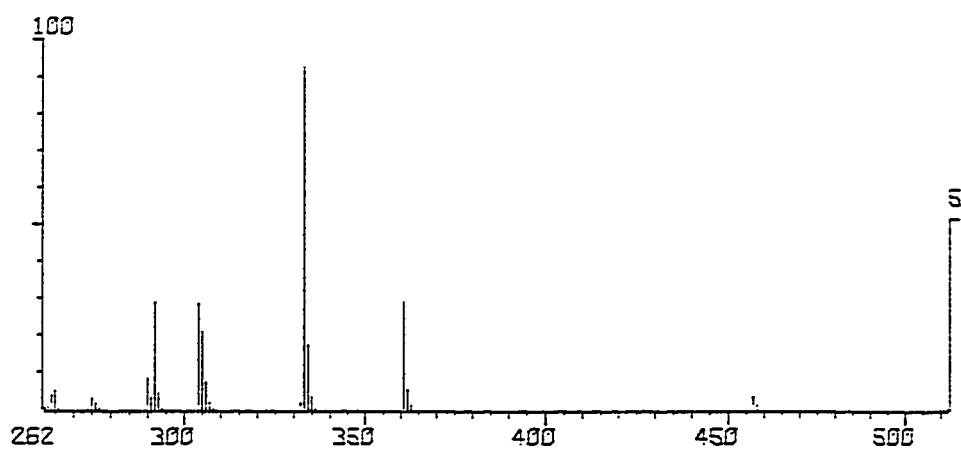
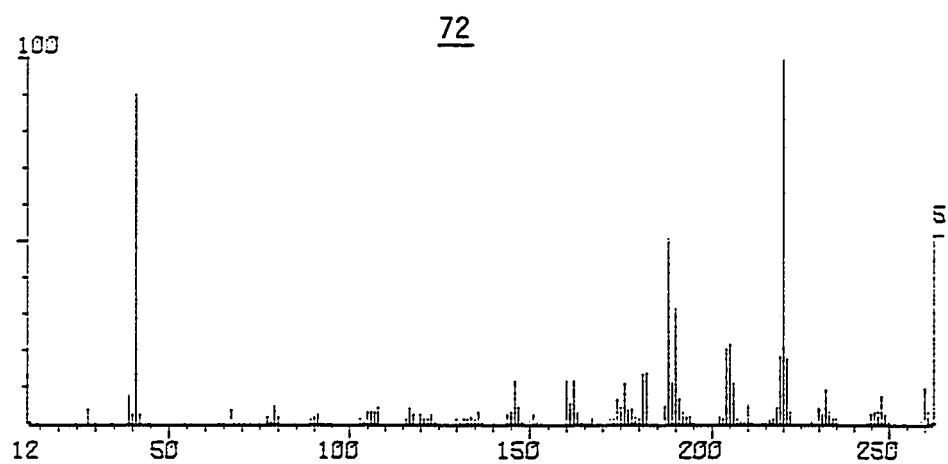
Analysis:  $C_{28}H_{34}N_2O_9$

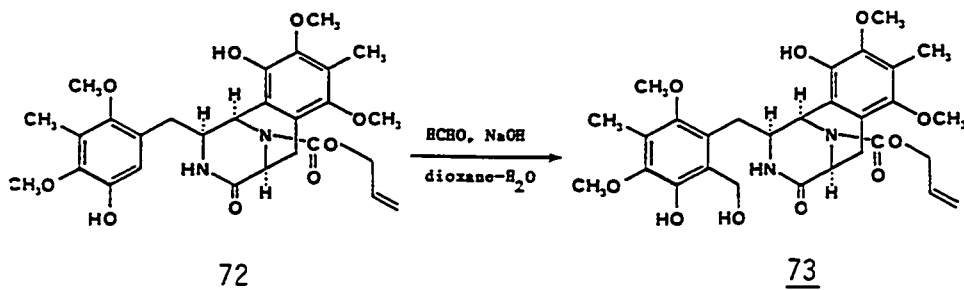
crystals from ethyl acetate

	calculated	found
C: 0.6198		0.5974
H: 0.0632		0.0631
N: 0.0516		0.0492



72





#### HYDROXYMETHYL-ALLYL-URETHANE (73)

A solution of 3.54 g (6.54 mmol) of 72, 10.6 ml (131 mmol) of 37% aqueous formaldehyde and 2.2 ml (6.6 mmol) of aqueous 3N sodium hydroxide in 50 ml of dioxane was heated for 45 minutes at 100°. After cooling, carbon dioxide in the form of dry ice was added until the pH dropped below 10 and the mixture was partitioned between ethyl acetate and dilute sodium chloride solution. The organic phase was extracted with saturated sodium chloride solution and evaporated. The mixture was dissolved in 20 ml ethanol and 3 ml (21 mmol) triethylamine was added. After 10 minutes the mixture was partitioned between ethyl acetate and saturated sodium chloride solution containing hydrochloric acid sufficient to maintain a pH below 3. The organic phase was extracted with dilute sodium chloride solution followed by saturated sodium bicarbonate solution. After drying over magnesium sulfate, the organic phase was evaporated to give 3.55 g (95%) crude 73. mp 135-136° (ethyl acetate)

IR ( $\text{CH}_2\text{Cl}_2$ ): 3530, 1720, 1100, 990

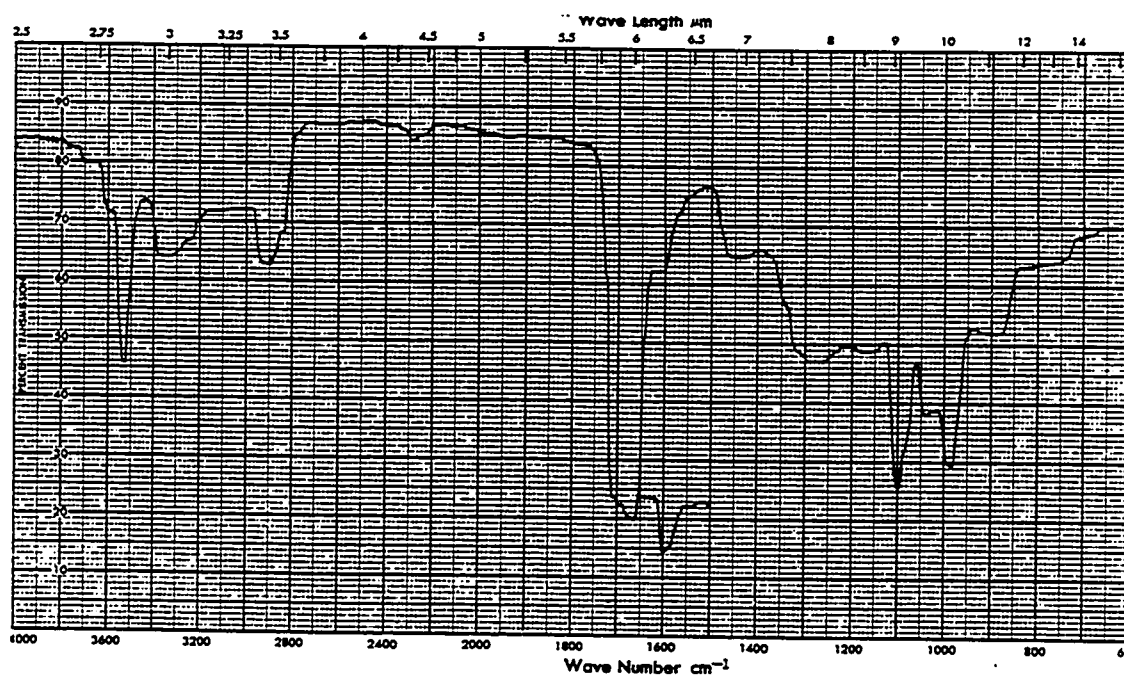
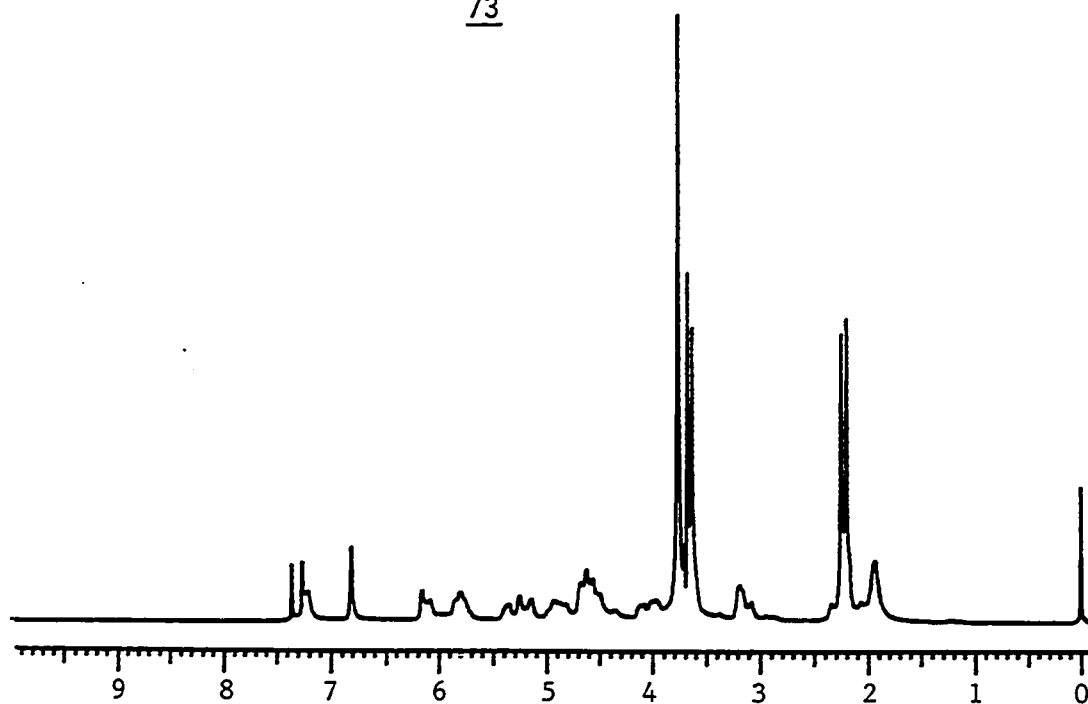
NMR ( $\text{CDCl}_3$ ): 1.92 (1H, bs), 2.20 (3H, s), 2.25 (3H, s), 3.0-3.3 (1H, m),  
3.63 (3H, s), 3.67 (3H, s), 3.70 (6H, s), 3.9-4.2 (1H, m),  
4.5-4.7 (2H, m), 4.7-5.0 (1H, m), 5.1-5.5 (1H, t,  $J=11\text{hz}$ ),  
5.7-5.9 (1H, t,  $J=3\text{hz}$ ), 6.0-6.2 (1H, d,  $J=11$ ), 6.81 (1H, s),  
7.21 (1H, d,  $J=3\text{hz}$ )

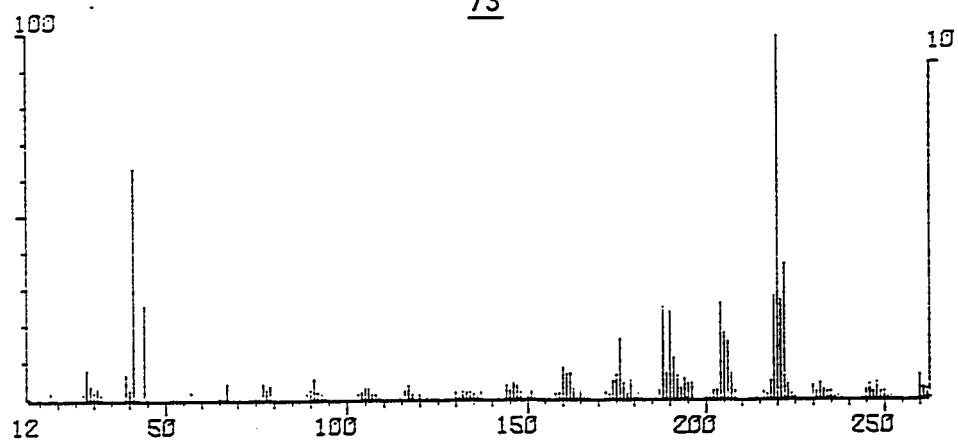
MS: 554 (1.7,  $\text{M}^+-18$ ), 469 (.8), 333 (14), 306 (20), 292 (27),  
220 (100), 41 (62)

Analysis:  $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_{10}$

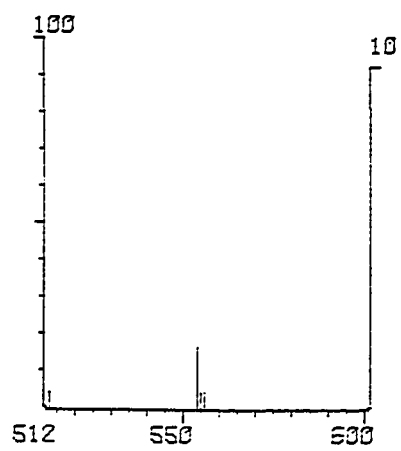
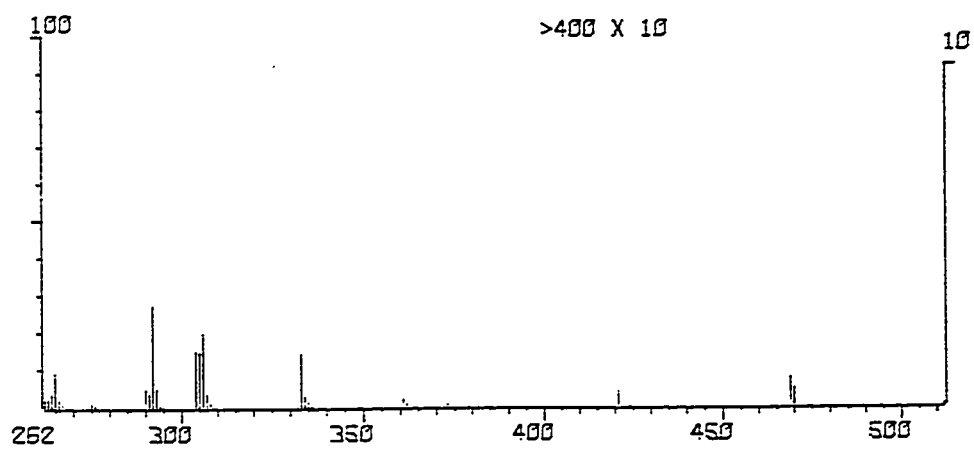
crystals from ethyl acetate

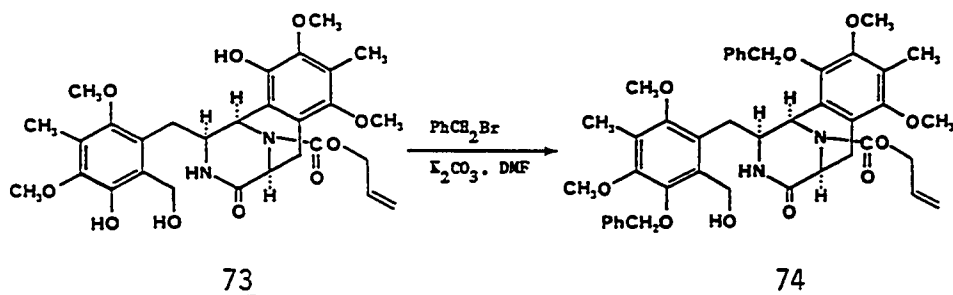
	calculated	found
C:	0.6083	0.5903
H:	0.0634	0.0631
N:	0.0489	0.0467

73

73

&gt;400 X 10





#### HYDROXYMETHYL-DIBENZYL ETHER (74)

A mixture of 3.55 g (6.21 mmol) of crude 73, 2.00 ml (16.8 mmol) of benzyl bromide, and 5.3 g (38 mmol) of potassium carbonate in 25 ml of dimethylformamide was stirred for 1 hour. Water was added to dissolve the solid and the mixture extracted with ether. The organic phase was extracted with saturated sodium chloride solution, dried over magnesium sulfate and evaporated. Chromatography on silica gel eluted with an ether in hexanes gradient gave 2.83 g (58%) of 74. mp 157° (isopropyl ether)

IR ( $\text{CH}_2\text{Cl}_2$ ): 1675, 1105, 1050, 990

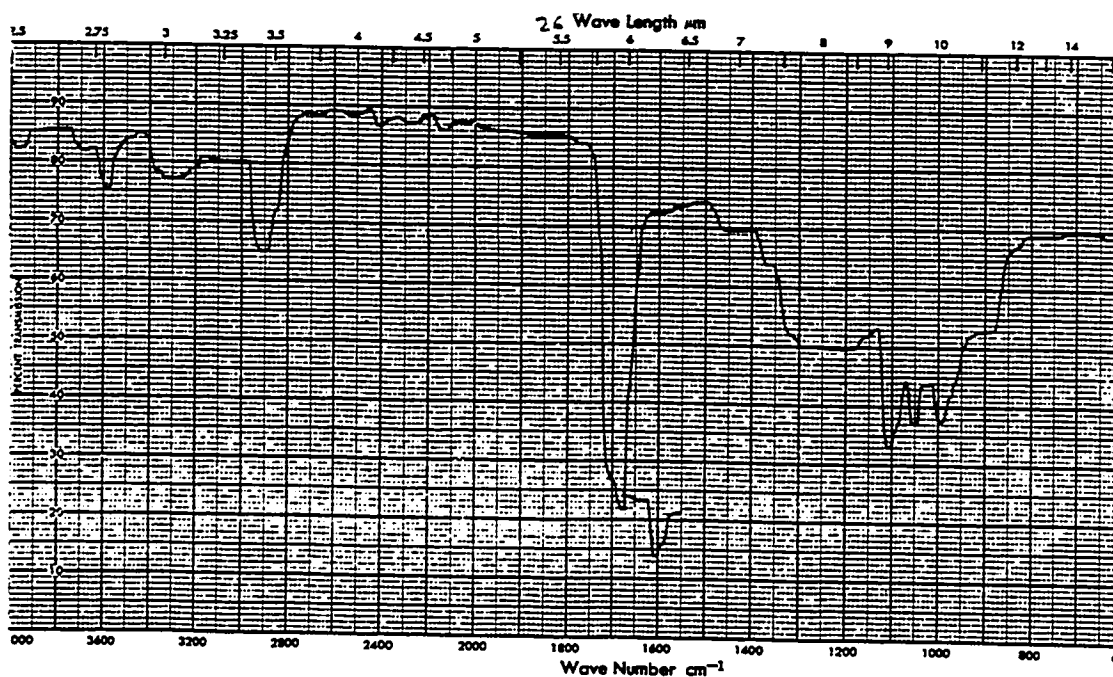
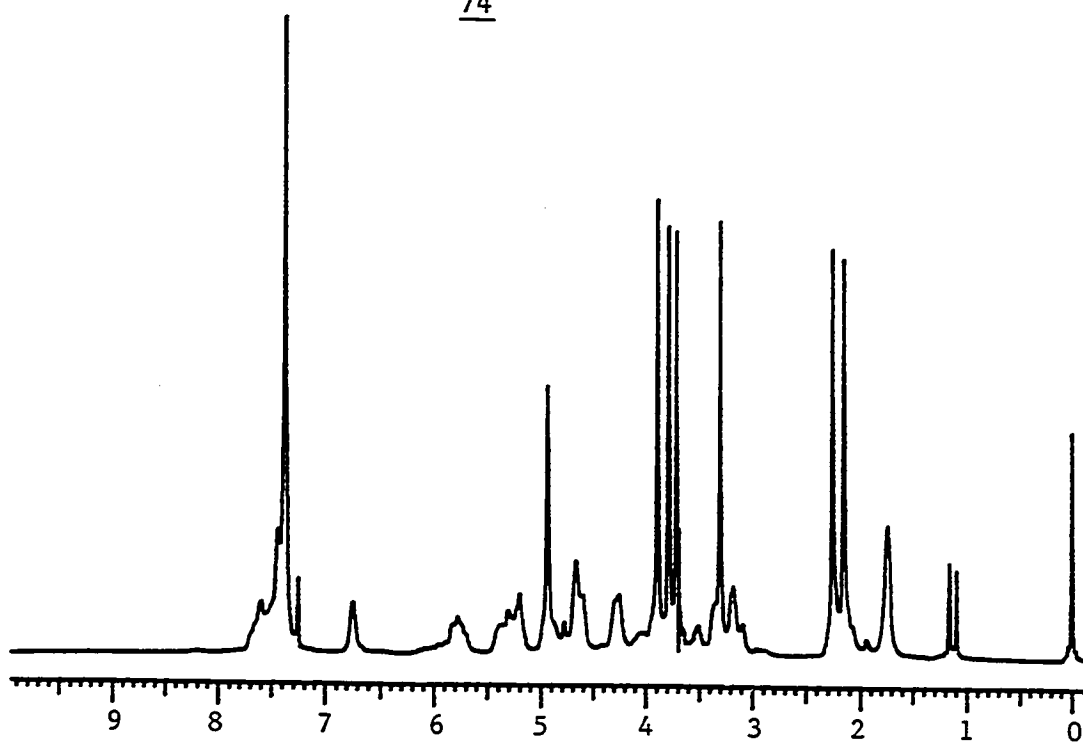
NMR ( $\text{CDCl}_3$ ): 2.15 (3H, s), 2.26 (3H, s), 3.0–3.6 (2H, m), 3.30 (3H, s), 3.71 (3H, s), 3.79 (3H, s), 3.90 (3H, s), 4.2–4.4 (1H, bd,  $J=4\text{Hz}$ ), 4.5–4.9 (2H, m), 4.94 (2H, s), 5.1–5.9 (2H, m), 5.6–6.2 (2H, m), 6.76 (1H, s), 7.3–7.8 (10H, m)

MS: 752 (.03,  $\text{M}^+$ ), 751 (.03), 721 (.07), 642 (.3), 630 (3), 91 (100)

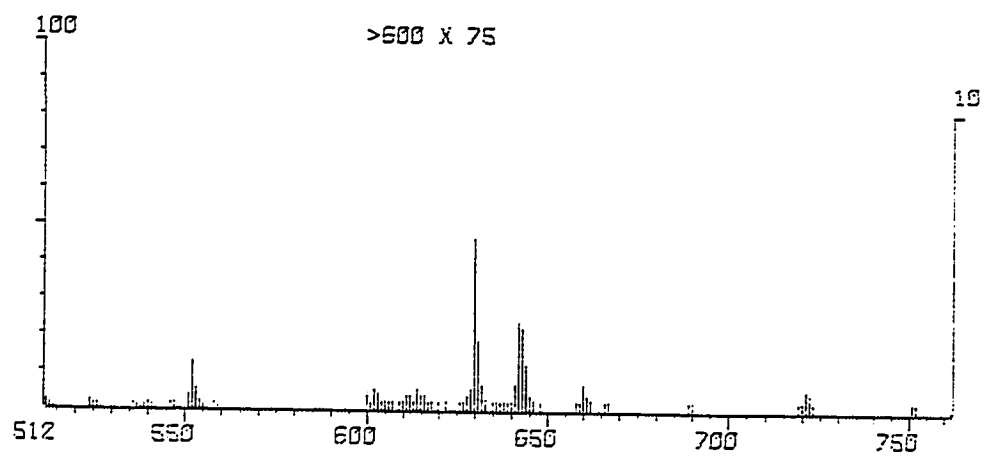
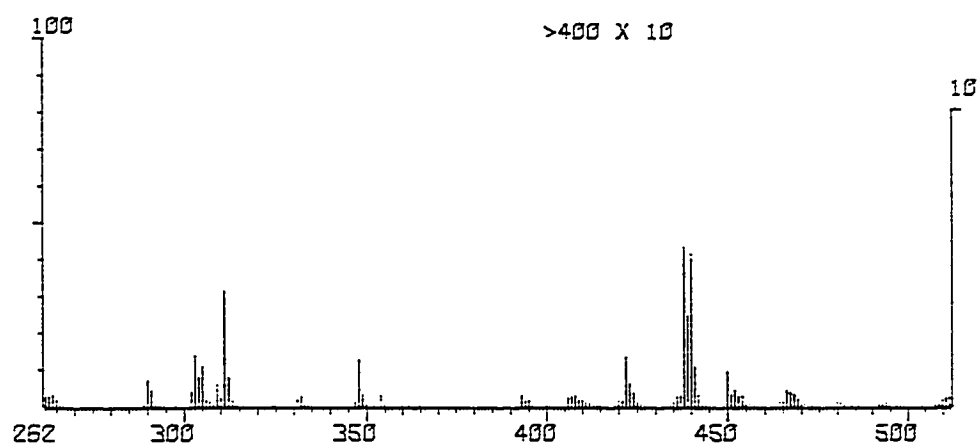
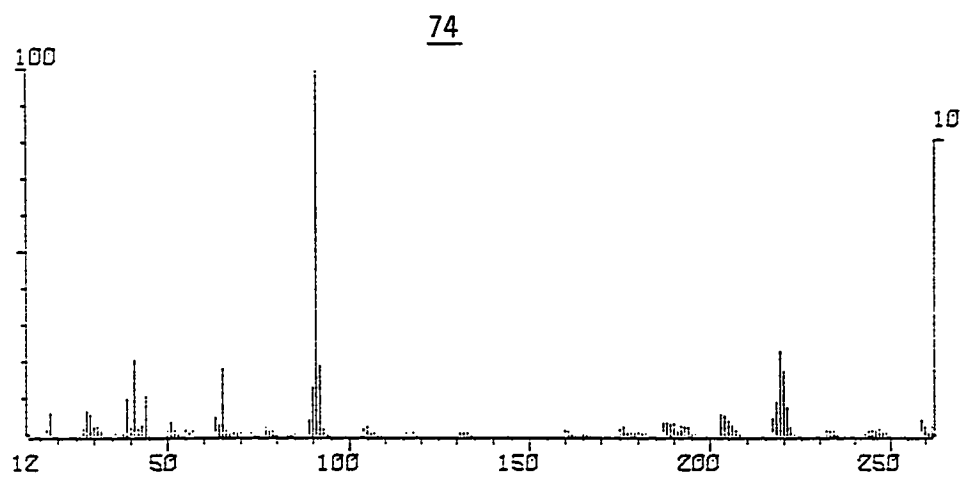
Analysis:  $\text{C}_{43}\text{H}_{48}\text{N}_2\text{O}_{10}$

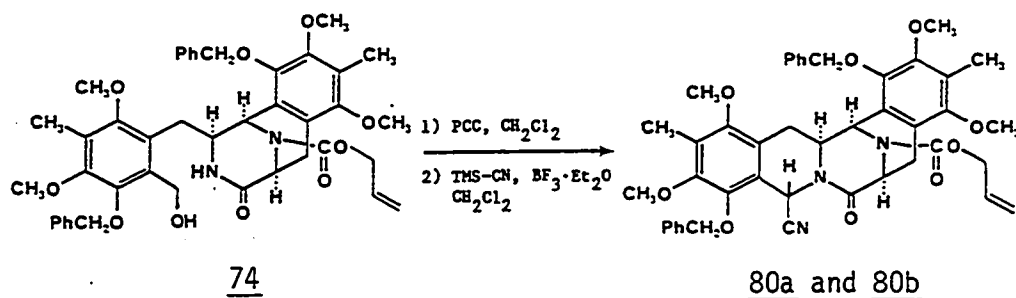
crystals from isopropyl ether

	calculated	found
C: 0.6860	0.6841	
H: 0.0643	0.0645	
N: 0.0372	0.0367	

74







#### NITRILE-URETHANE (80a and 80b)

A suspension of 2.83 g (3.76 mmol) of 74, 1.00g (4.64 mmol) of pyridinium chlorochromate, and 1.0 g of magnesium sulfate in 25 ml of dichloromethane was stirred for one hour. Addition of 100 ml of 80% ether in hexanes followed by filtration through 3 g silica gel and evaporation gave 2.5 g of crude product mixture. The mixture was dissolved in 50 ml dry dichloromethane, cooled to 0°, and 0.60 ml (4.5 mmol) trimethylsilylcyanide added with stirring. Three 0.10 ml (1.1 mmol) portions of boron trifluoride etherate were added at 20 minute intervals. The reaction mixture was partitioned between ether and saturated sodium bicarbonate. The organic phase was dried over magnesium sulfate and evaporated. Chromatography on silica gel eluted with an ether in hexanes gradient gave 1.94 g (68%) of 80 as a mixture of diastereomers. Alternately, crystallization of the crude product mixture from methanol gave pure 80a with 80b remaining in the mother liquor, which was purified by chromatography on silica gel eluted with an ether in hexanes gradient. 80a mp 180° (methanol) 80b mp 137° (isopropyl ether)

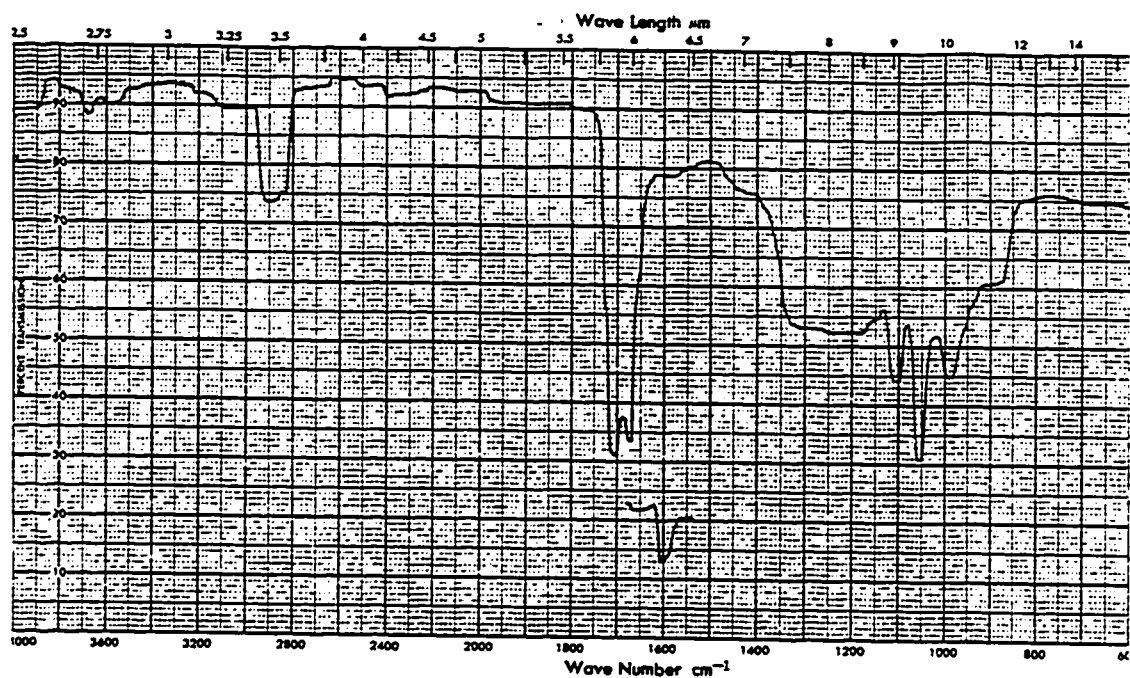
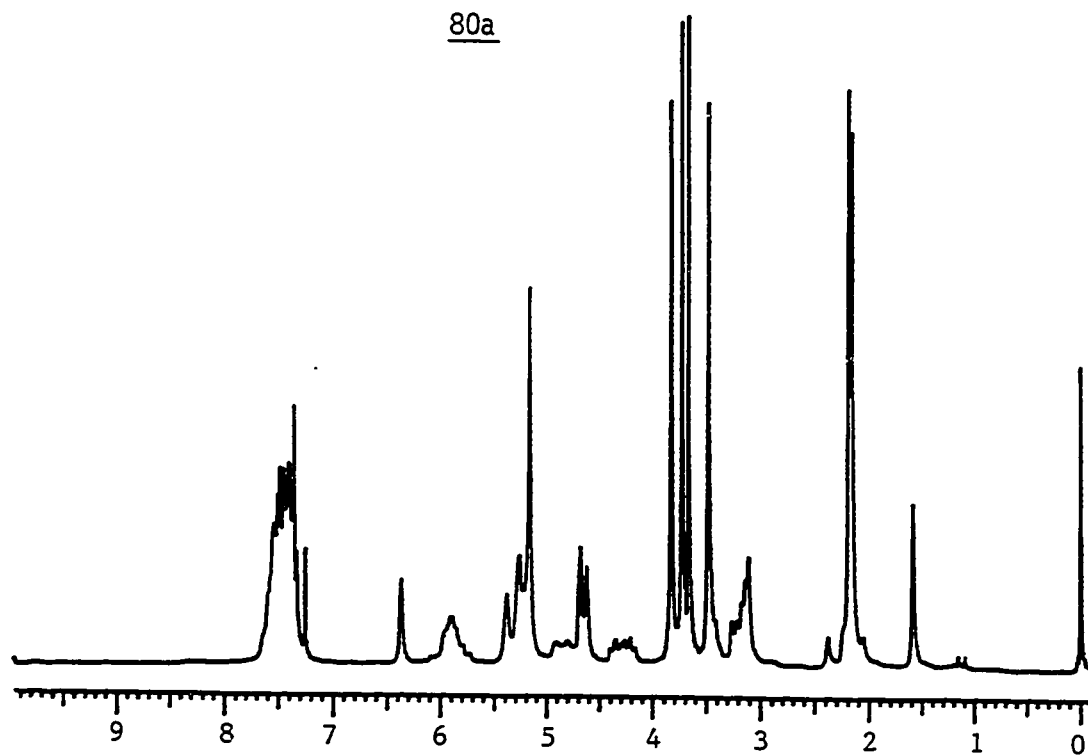
IR ( $\text{CH}_2\text{Cl}_2$ ): 80a 1700, 1670, 1100, 1050, 990  
80b 1700, 1670, 1100, 1050, 990

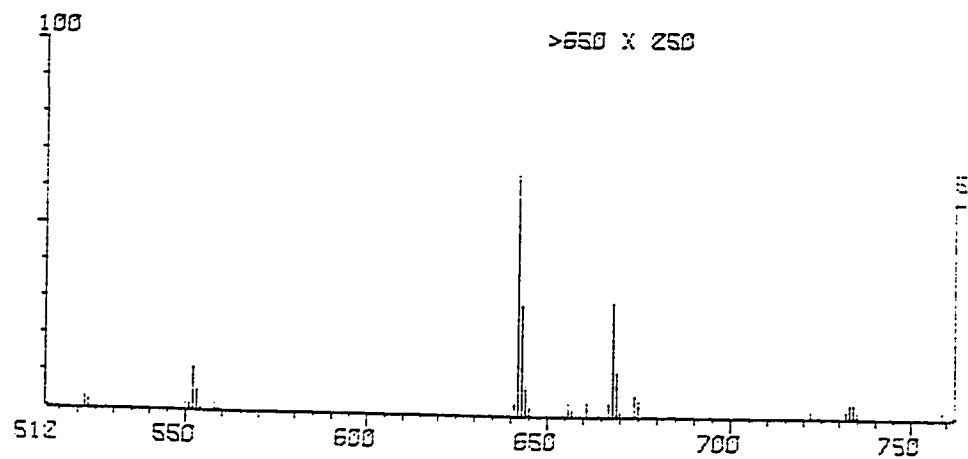
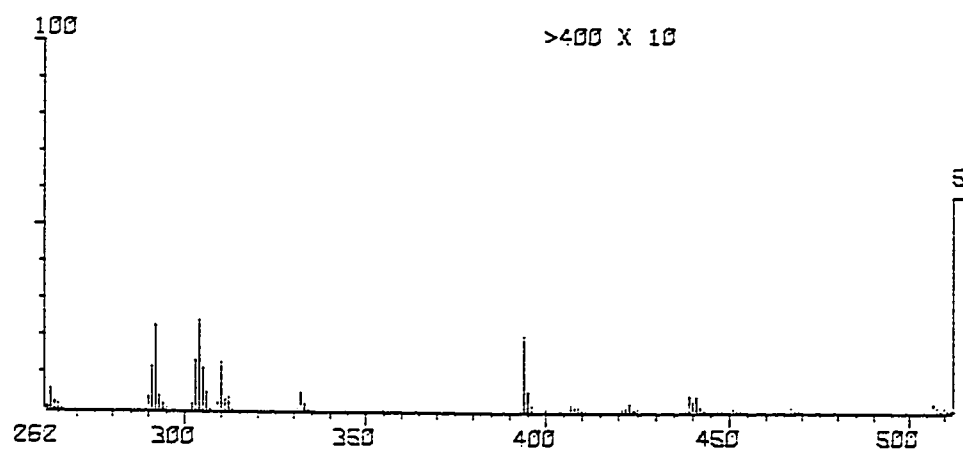
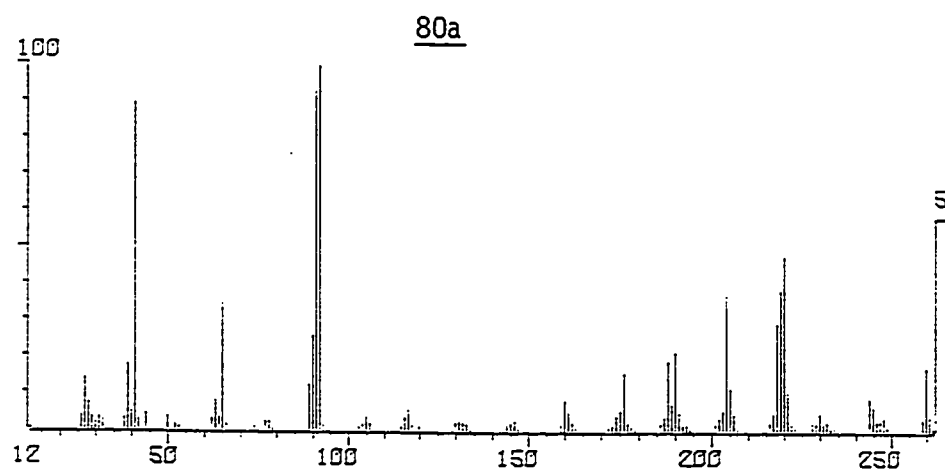
NMR ( $\text{CDCl}_3$ ): 80a 2.16 (3H, s), 2.19 (3H, s), 3.1-3.3 (3H, m),  
 3.48 (3H, s), 3.67 (3H, s), 3.73 (3H, s), 3.84 (3H, s),  
 4.2-4.4 (1H, m), 4.65 (2H, d,  $J=6\text{hz}$ ),  
 4.7-5.0 (1H, bd,  $J=9\text{hz}$ ), 5.16 (2H, s),  
 5.2-5.4 (2H, d,  $J=9\text{hz}$ ), 5.7-6.1 (2H, m), 6.36 (1H, s),  
 7.2-7.7 (10H, m)  
80b 2.20 (3H, s), 2.21 (3H, s), 3.1-3.3 (1H, m),  
 3.40 (3H, d,  $J=2\text{hz}$ ), 3.68 (3H, s), 3.82 (3H, s),  
 3.84 (3H, s), 4.63 (1H, d,  $J=5\text{hz}$ ), 4.8 (1H, d,  $J=11\text{hz}$ ),  
 5.04 (2H, s), 5.1-5.5 (2H, m), 5.5-6.2 (2H, m)

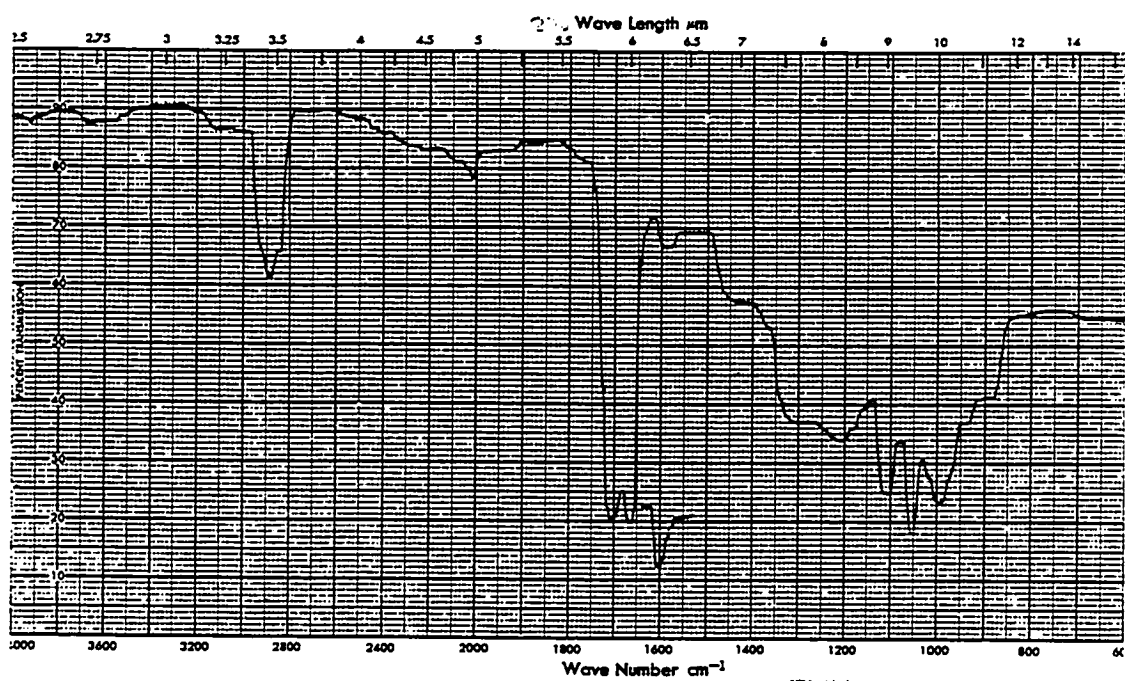
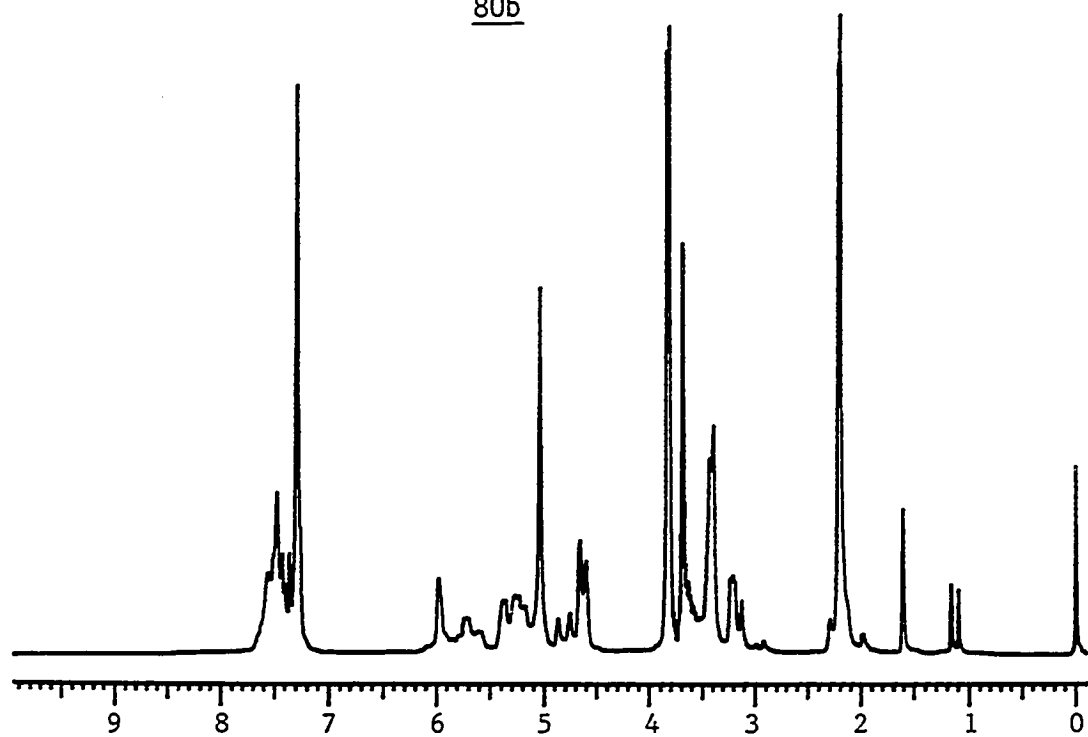
MS: 80a 759 (.01,  $\text{M}^+$ ), 733 (.02), 668 (.12), 642 (6.5),  
 220 (48), 92 (100), 91 (92), 41 (90)  
80b 759 (.01,  $\text{M}^+$ ), 733 (.01), 668 (.16), 642 (2.8), 220  
 (50), 92 (100), 91 (92), 41 (93)

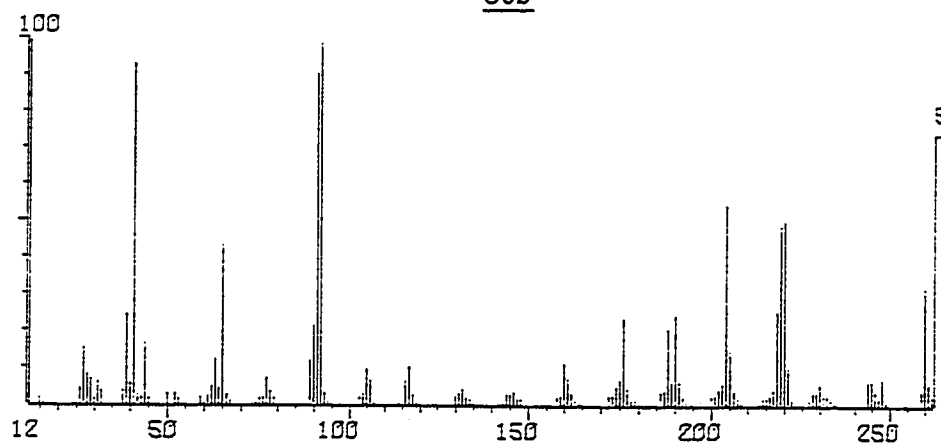
Analysis:  $\text{C}_{44}\text{H}_{45}\text{N}_3\text{O}_9$

<u>80a</u>		<u>80b</u>
crystals from methanol		crystals from isopropyl ether
Calculated	found	found
C: 0.6955	0.6956	0.6956
H: 0.0597	0.0589	0.0599
N: 0.0553	0.0542	0.0532

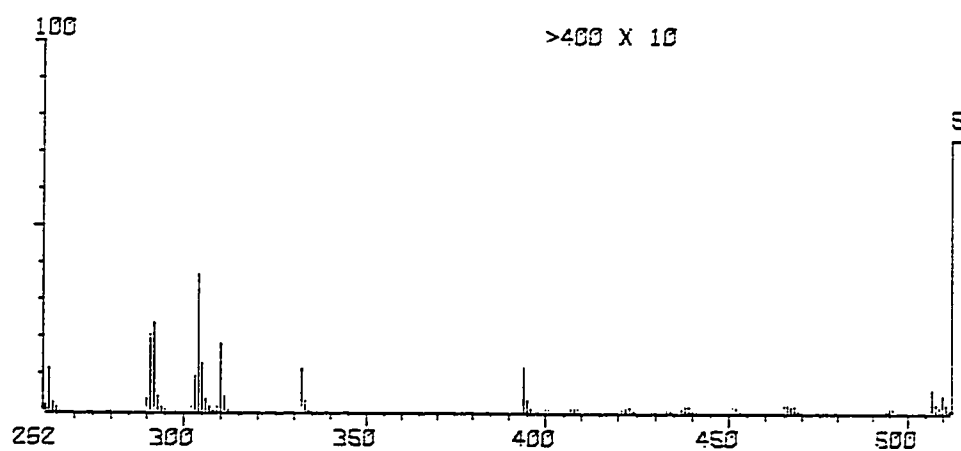
80a



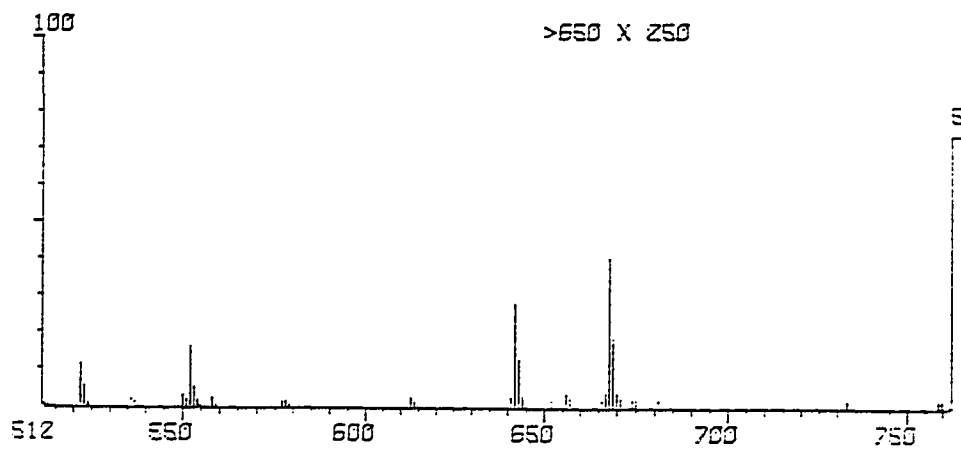
80b

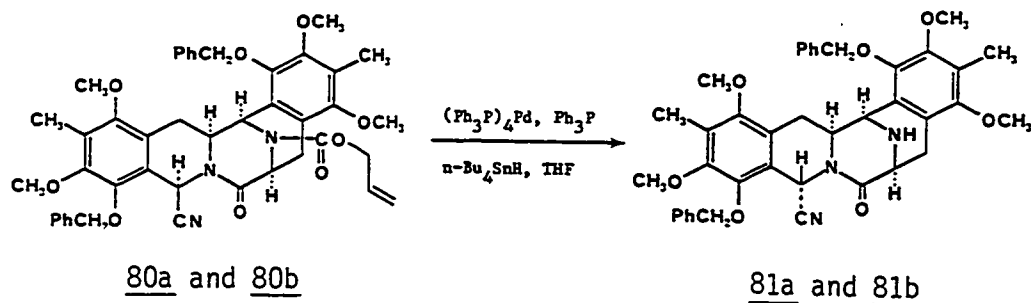
80b

&gt;400 X 10



&gt;650 X 250





### NITRILE-AMINE (81a and 81b)

To a stirred solution of 200 mg (0.263 mmol) of 80a, 0.10 ml (0.39 mmol) of tributyltin hydride, and 5 mg (0.02 mmol) of triphenylphosphine in 5 ml of tetrahydrofuran at 0° was added 3.0 mg ( $2.6 \times 10^{-3}$  mmol) tetrakis(triphenylphosphine)palladium(0). After 15 minutes, 0.15 ml of a 3N hydrochloric acid solution was added. After 5 minutes the reaction mixture was partitioned between ether and saturated sodium bicarbonate. The organic phase was dried over magnesium sulfate and evaporated. Crystallization from methanol gave 153 mg (88%) of 81a. mp 247° (methanol)

Treatment of 240 mg (0.316 mmol) of 80b according to the above procedure gave 190 mg (89%) of 81b. mp 189–190° (methanol)

IR ( $\text{CH}_2\text{Cl}_2$ ): 81a 1670, 1105, 1060, 995  
81b 1665, 1110, 1060, 1000

NMR ( $\text{CDCl}_3$ ): 81a 2.17 (3H, s), 2.20 (3H, s), 3.03 (1H, d,  $J=4\text{Hz}$ ), 3.52 (3H, s), 3.67 (3H, s), 3.74 (3H, s), 3.83 (3H, s), 4.0–4.3 (2H, m), 4.60 (1H, d,  $J=5\text{Hz}$ ), 4.85 (1H, d,  $J=7$ ), 5.17 (2H, s), 5.38 (1H, d,  $J=7\text{Hz}$ ), 5.17 (1H, s), 7.2–7.6 (10H, m)  
81b 2.22 (6H, s), 3.0–3.2 (1H, m), 3.49 (3H, s), 3.70 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 3.9–4.1 (1H, m), 4.39 (1H, d,  $J=3\text{Hz}$ ), 4.77 (1H, d,  $J=11\text{Hz}$ ), 5.07 (2H, s),

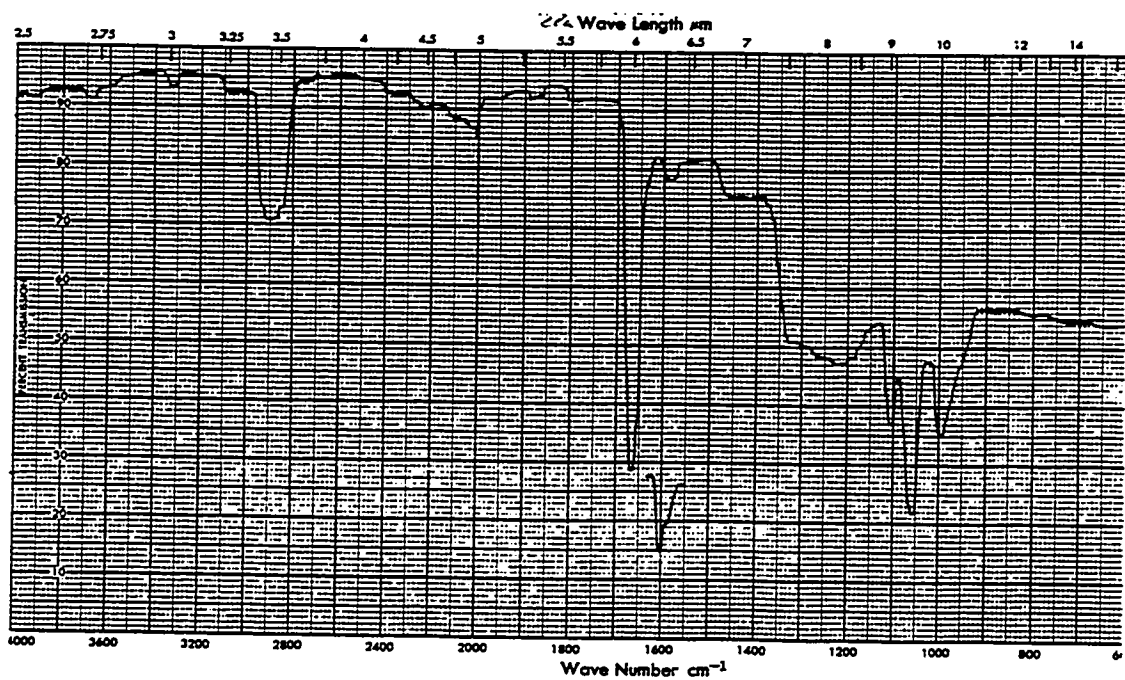
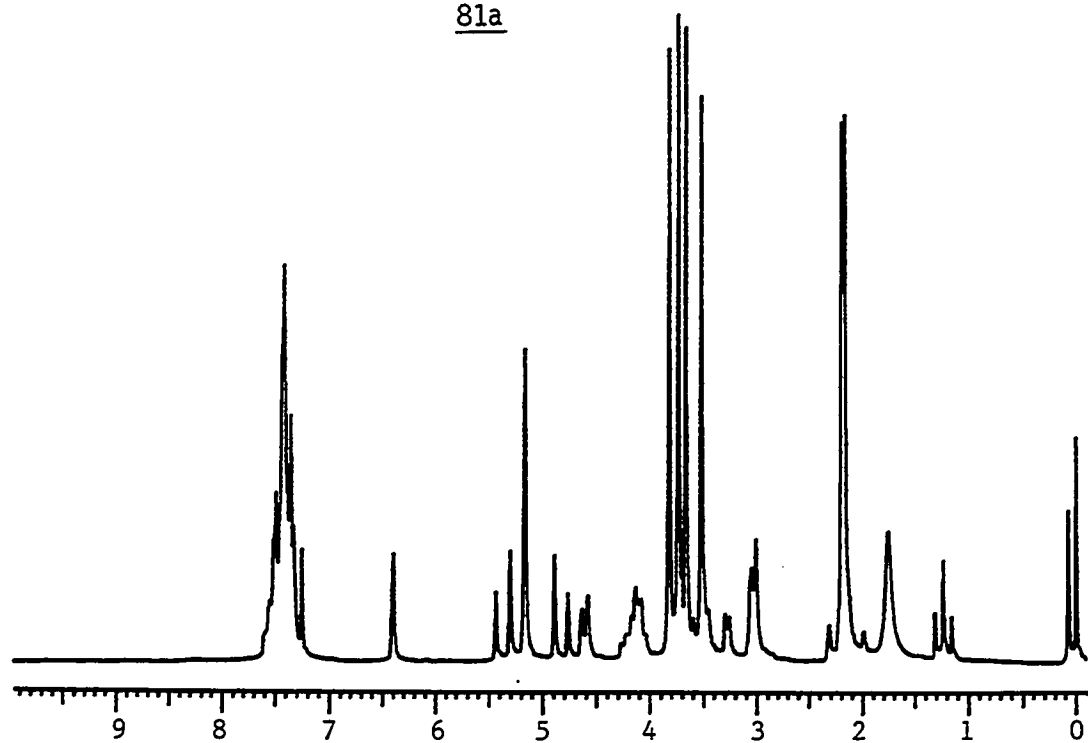


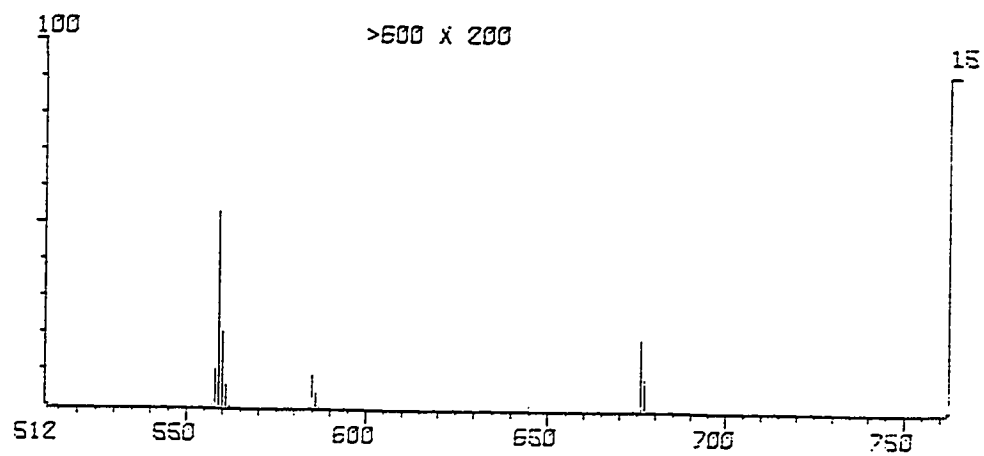
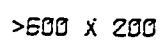
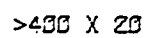
5.33 (1H, d, J=11hz), 6.10 (1H, s), 7.2-7.6 (10H, m)

MS: 81a 676 (.04, M<sup>+</sup>), 585 (.2), 558 (3), 310 (50), 220 (100), 91 (100)  
81b 676 (.07, M<sup>+</sup>), 585 (.6), 558 (3), 310 (50), 220 (100), 91 (100)

Analysis: C<sub>40</sub>H<sub>41</sub>N<sub>3</sub>O<sub>7</sub>

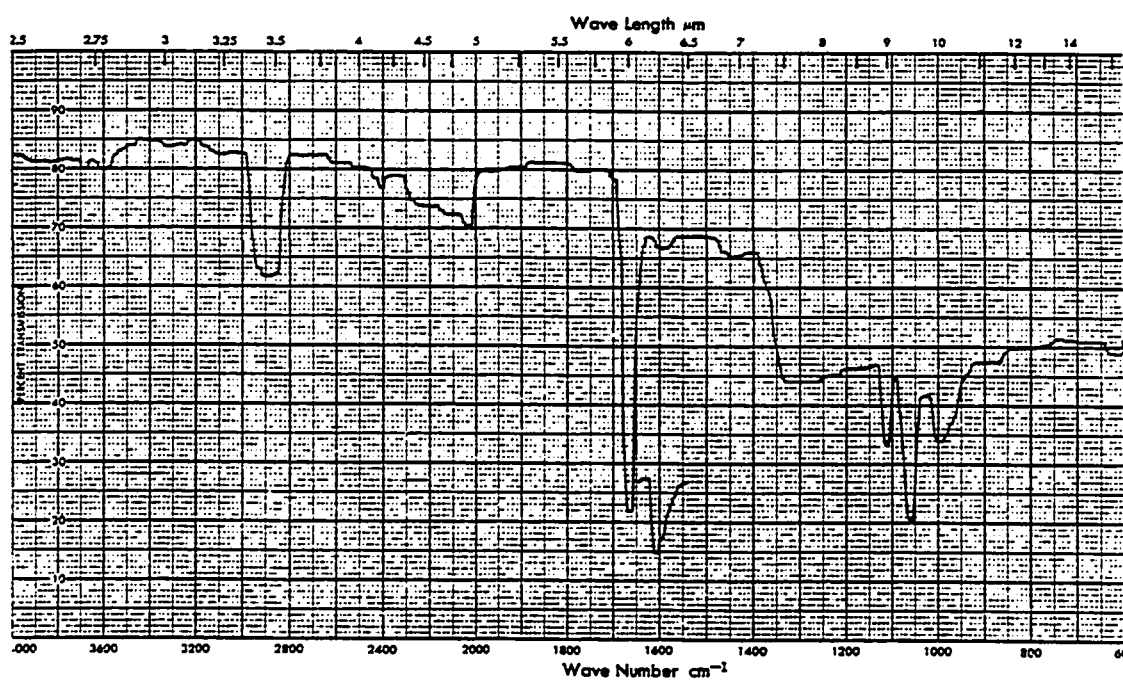
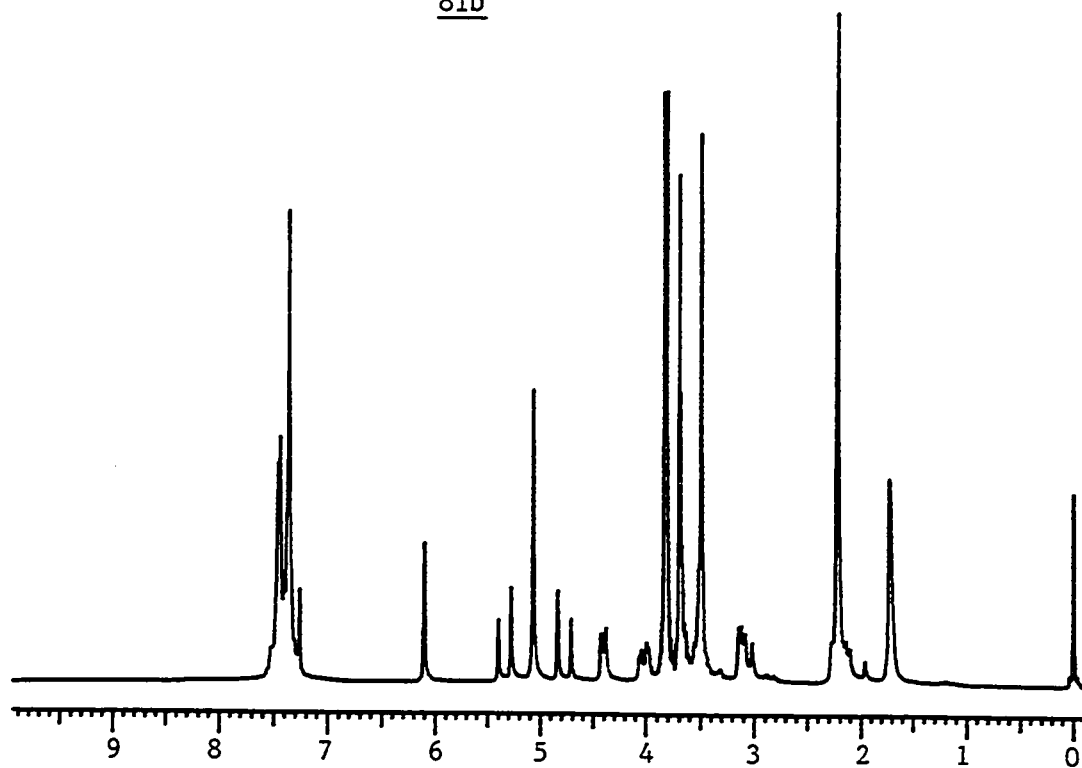
<u>81a</u>		<u>81b</u>
crystals from methanol		crystals from methanol
calculated	found	found
C: 0.7109	0.6873	0.7107
H: 0.0612	0.0625	0.0619
N: 0.0622	0.0574	0.0610

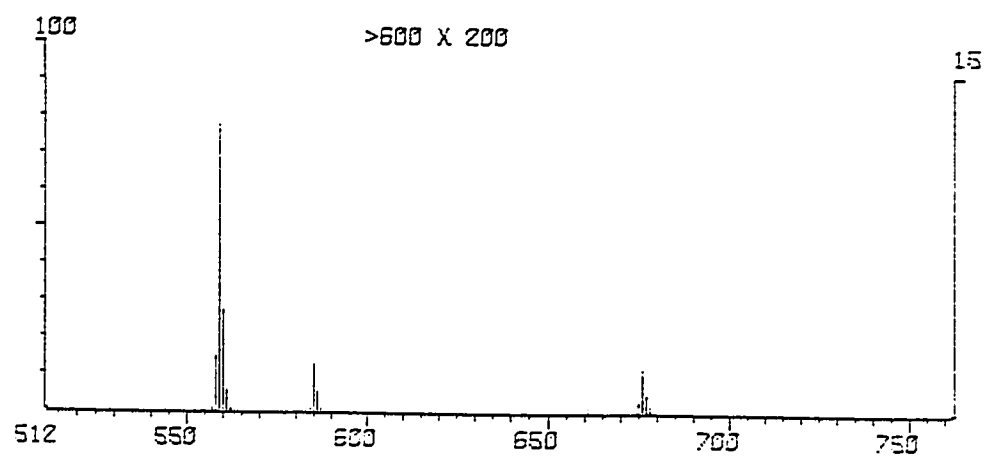
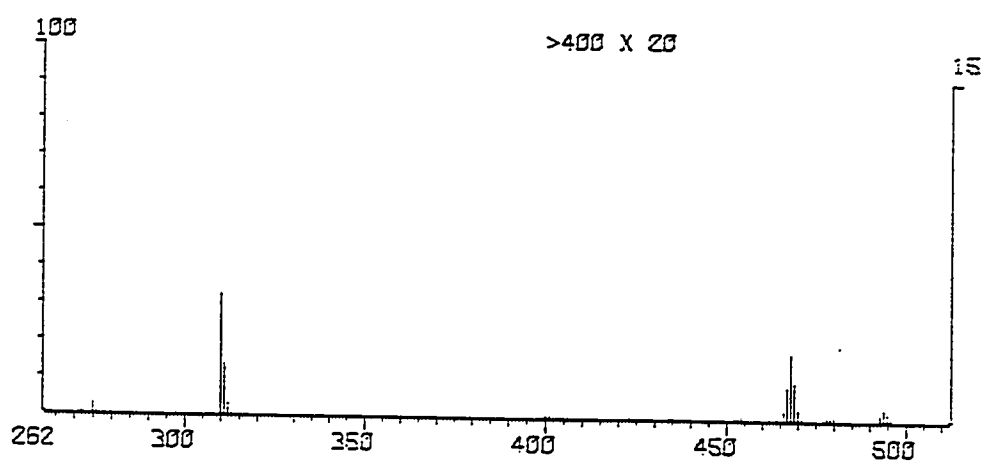
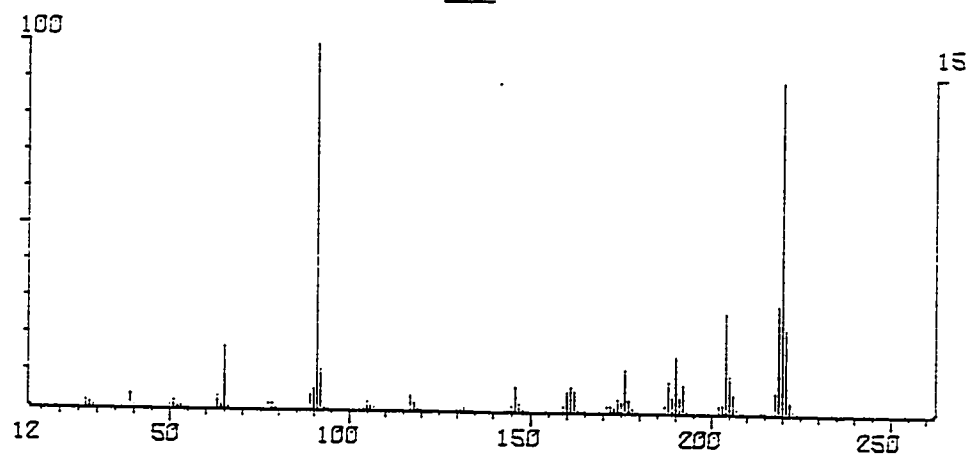
81a

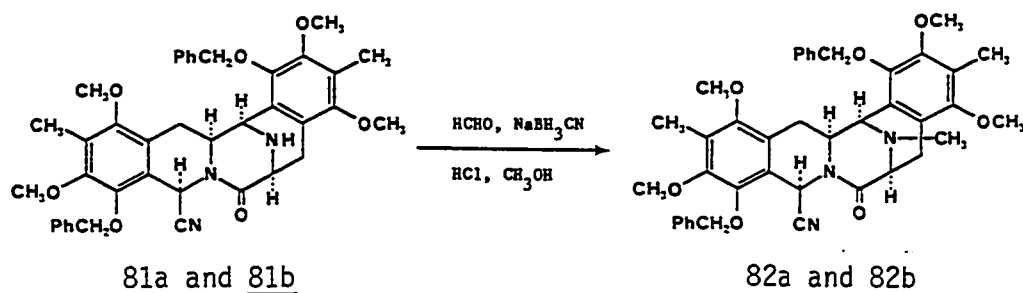


81b

155







#### NITRILE-METHYLAMINE (82a and 82b)

To a stirred solution of 153 mg (0.226 mmol) of 81a, 0.05 ml of 37% formaldehyde solution and 20 mg (0.32 mmol) of sodium cyanoborohydride in 5 ml methanol was added 3N hydrochloric acid until the pH remained below 3. The reaction mixture was partitioned between ether and saturated sodium bicarbonate. The organic phase was dried over magnesium sulfate and evaporated. Crystallization from methanol gave 145 mg (93%) of 82a. mp 220° (methanol)

Treatment of 190 mg (0.281 mmol) of 81b according to the above procedure gave 176 mg (91%) of 82b. mp 126° (methanol)

IR ( $\text{CH}_2\text{Cl}_2$ ): 1670, 1105, 1055, 1000

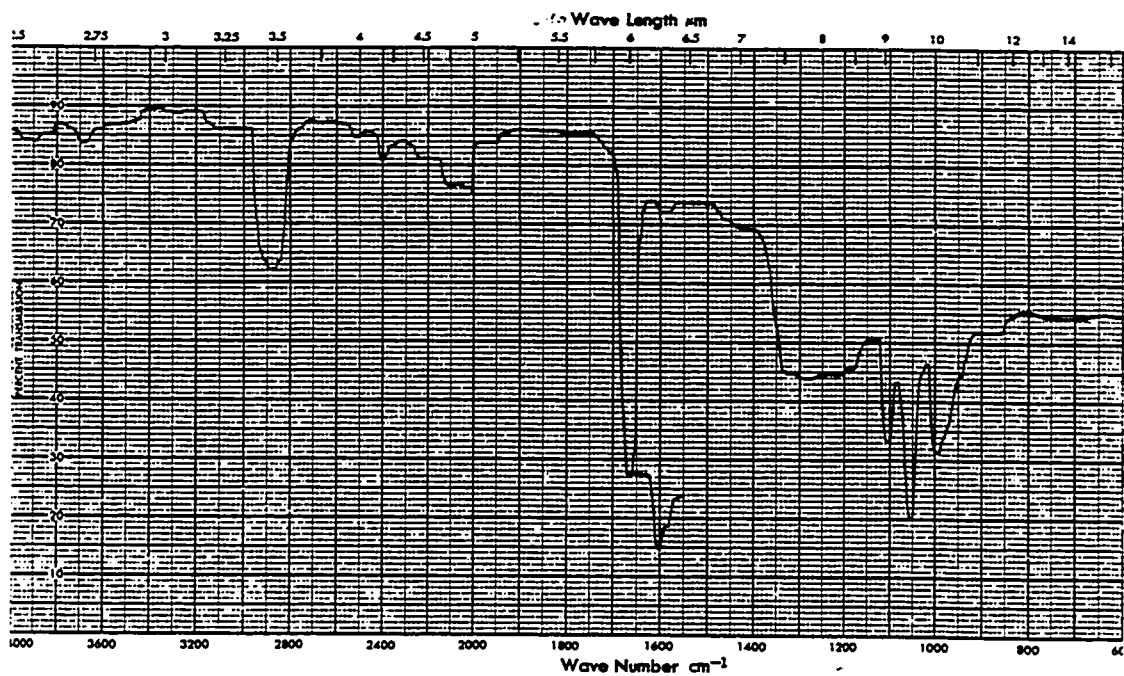
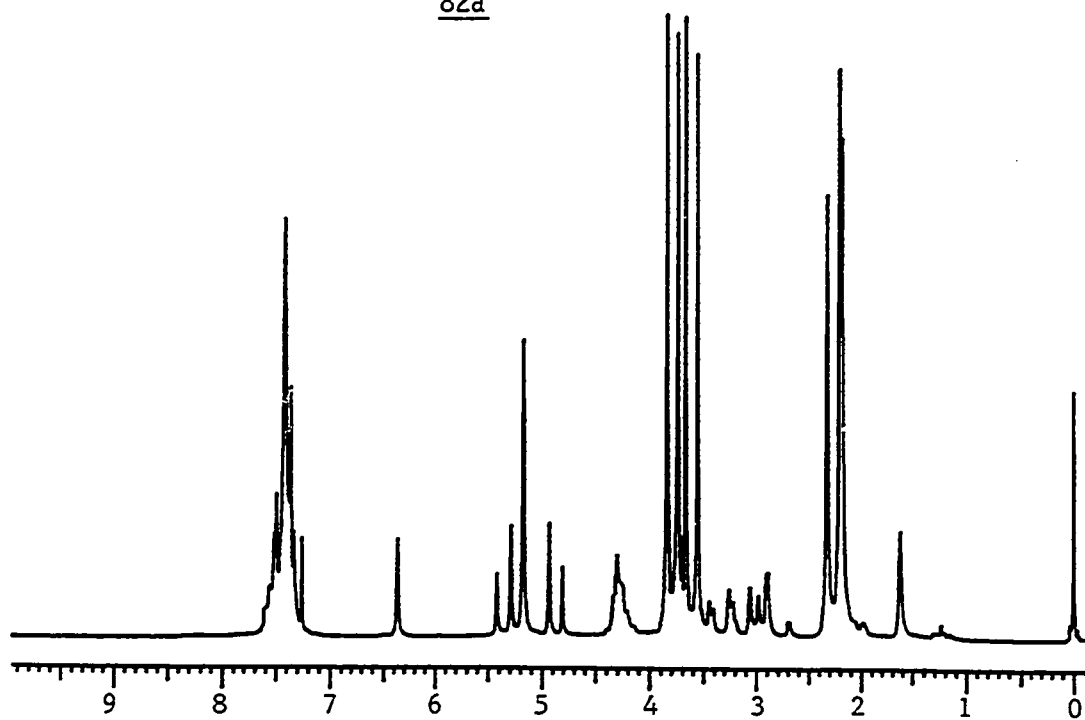
NMR ( $\text{CDCl}_3$ ): 82a 2.18 (3H, s), 2.20 (3H, s), 2.32 (3H, s), 2.6–3.5 (3H, m), 3.56 (3H, s), 3.67 (3H, s), 3.74 (3H, s), 3.84 (3H, s), 4.1–4.4 (2H, m), 4.89 (1H, d,  $J=11\text{Hz}$ ), 5.17 (2H, s), 5.37 (1H, d,  $J=11\text{Hz}$ ), 6.36 (1H, s), 7.2–7.6 (10H, s)  
82b 2.21 (3H, s), 2.23 (6H, s), 2.9–3.1 (1H, m), 3.56 (3H, s), 3.70 (3H, s), 3.81 (3H, s), 3.85 (3H, s), 4.03 (1H, d,  $J=3\text{Hz}$ ), 4.83 (1H, d,  $J=11\text{Hz}$ ), 6.08 (2H, s), 5.31 (1H, d,  $J=11\text{Hz}$ ), 6.08 (1H, s), 7.2–7.6 (10H, m)

MS: 82a 690 (.2,  $\text{M}^+$ ), 599 (1.5), 324 (62), 234 (85), 91 (100)  
82b 690 (.2,  $\text{M}^+$ ), 599 (2), 324 (50), 234 (100), 91 (100)

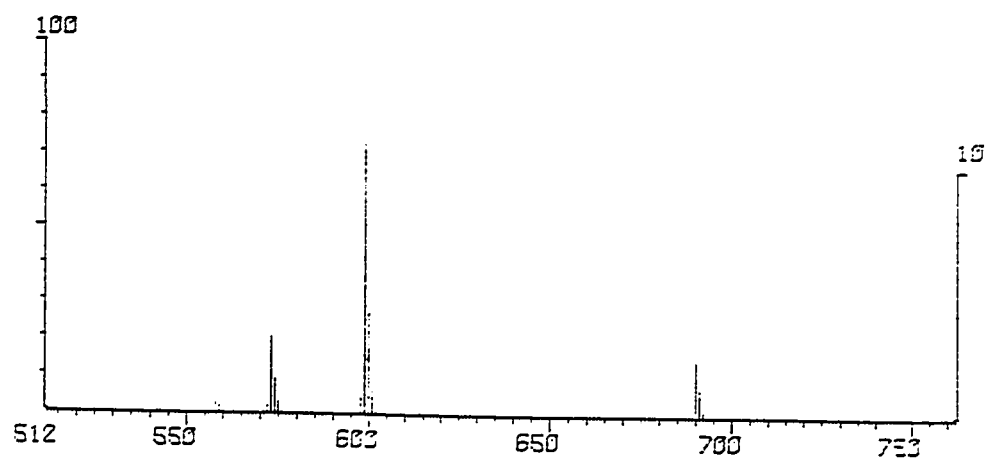
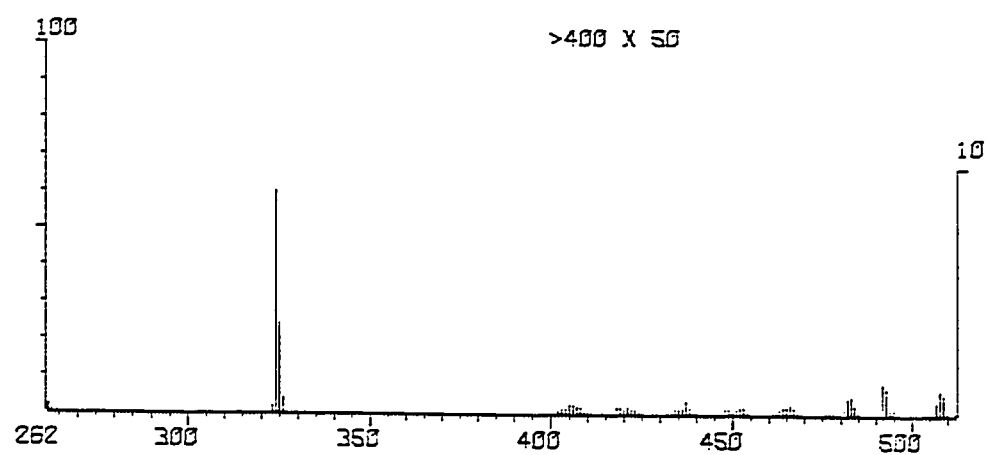
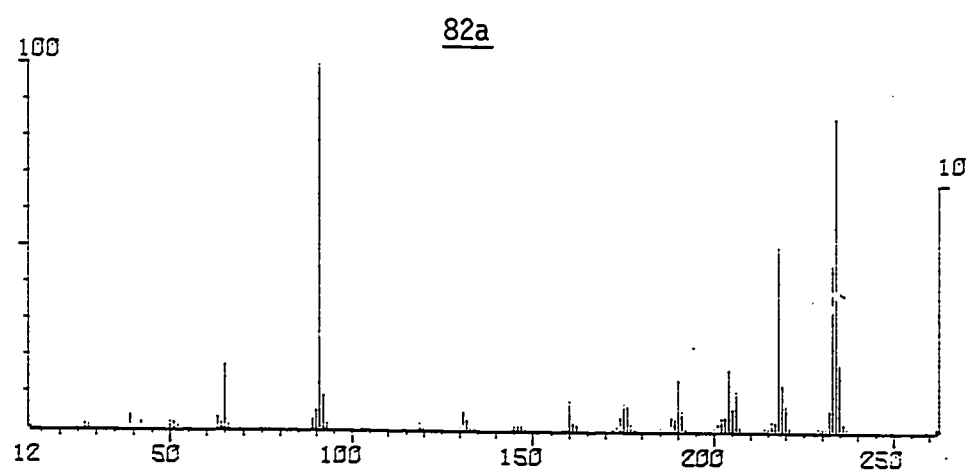
Analysis:  $C_{41}H_{43}N_3O_7$

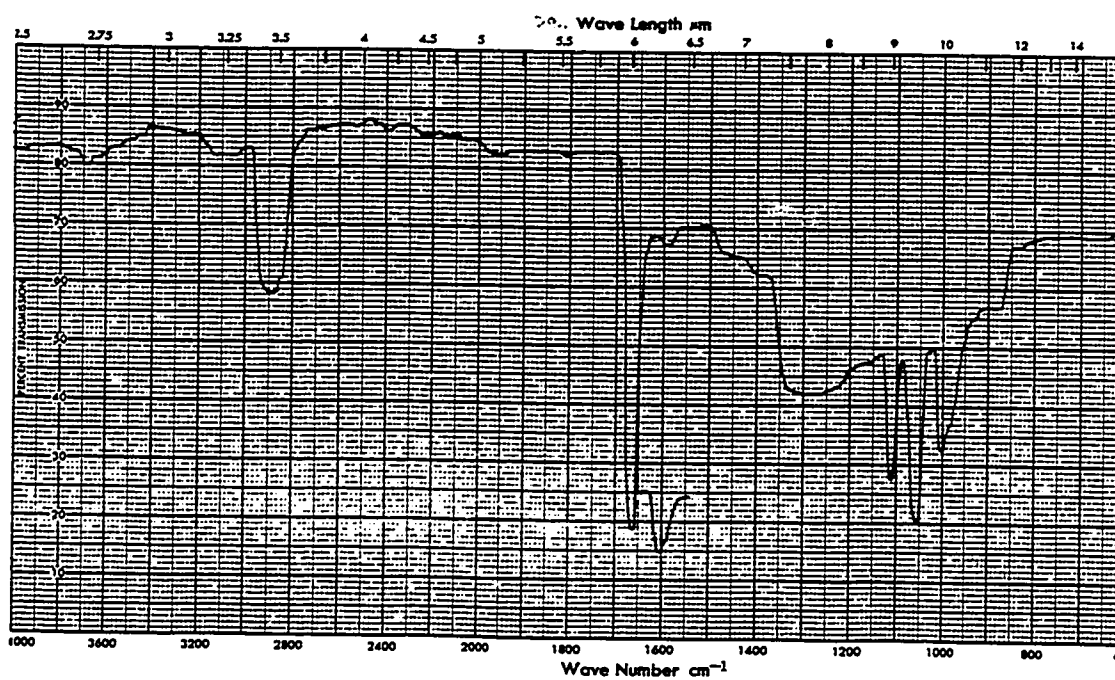
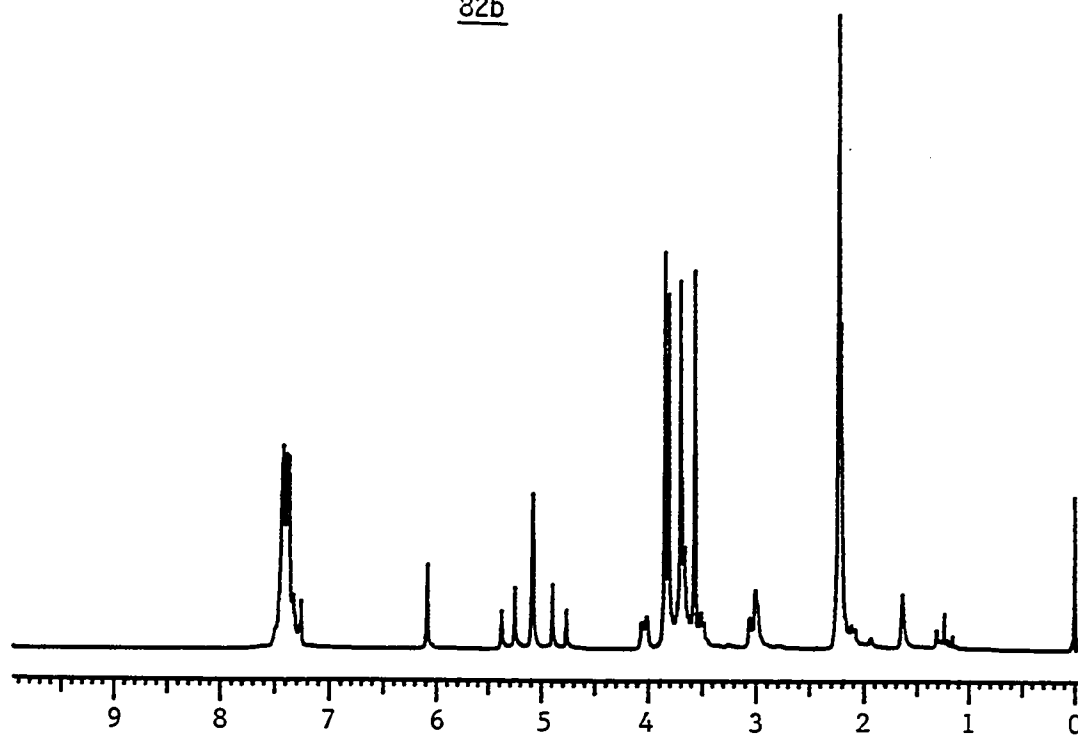
82a  
crystals from methanol  
calculated      found  
C: 0.7139      0.7122  
H: 0.0628      0.0631  
N: 0.0609      0.0591

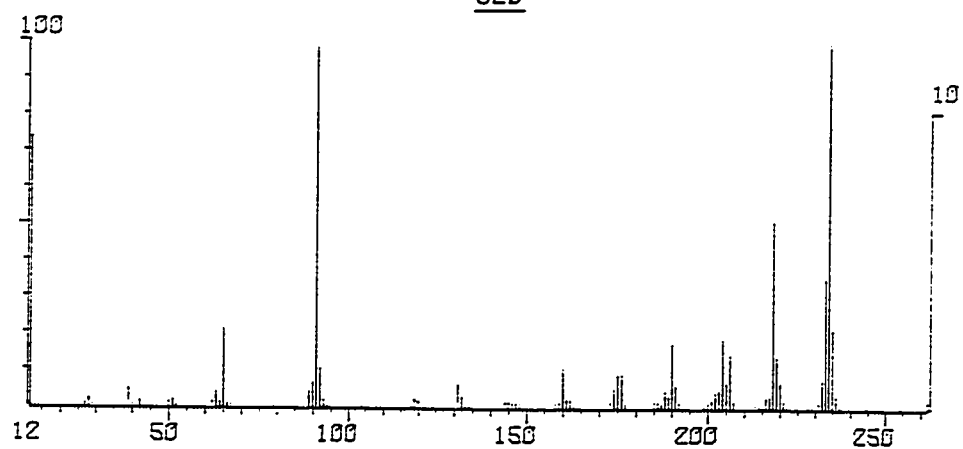
82b  
crystals from methanol  
found  
0.7147  
0.0638  
0.0611

82a

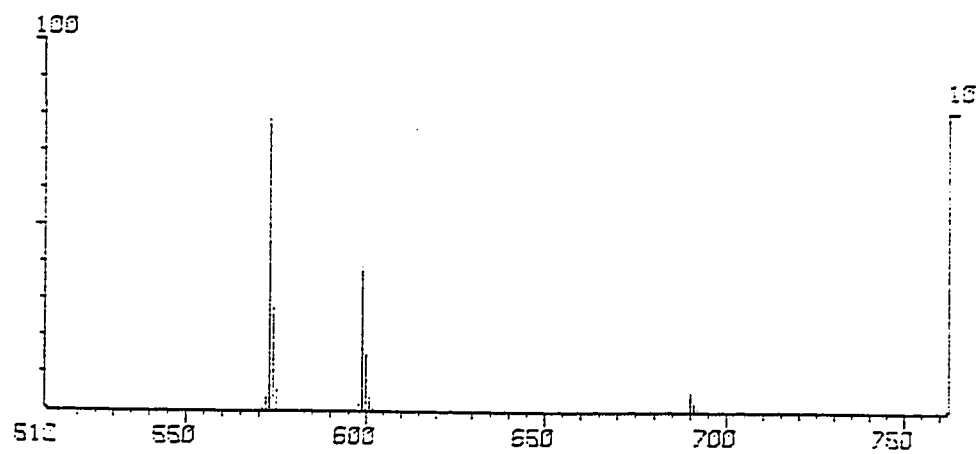
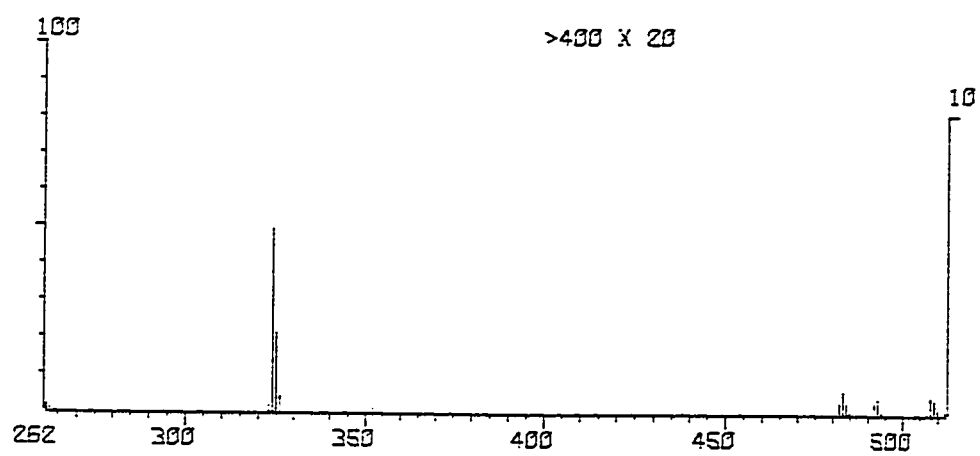


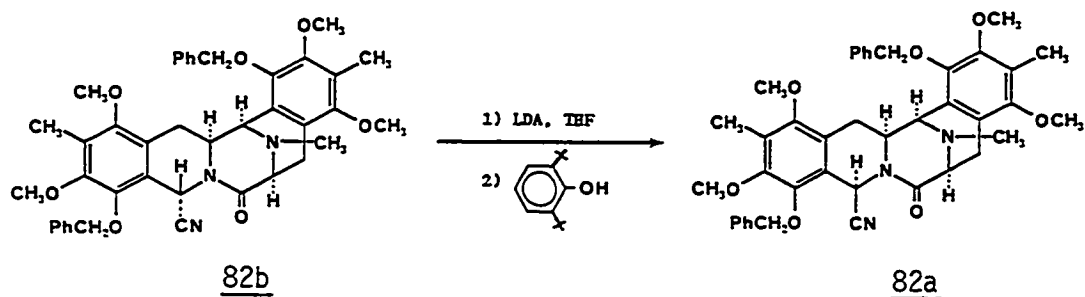


82b

82b

&gt;400 X 20

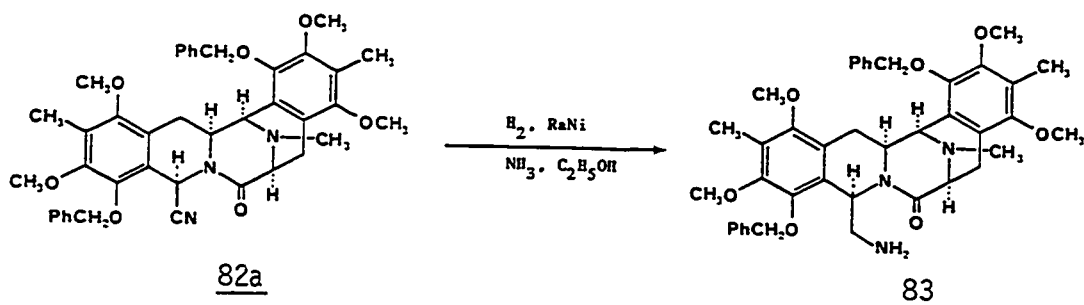




### EPIMERIZATION OF 82b

A solution of 0.17 mmol of lithium diisopropylamide in tetrahydrofuran was prepared by addition of 0.086 ml of 2.00N n-butyl lithium to a solution of 0.027 ml (0.19 mmol) of diisopropylamine in 1 ml of tetrahydrofuran. This solution was added to 100 mg (0.145 mmol) of 82b in 4 ml of tetrahydrofuran at  $-78^{\circ}$ . After stirring for 10 minutes, 45 mg (0.22 mmol) of 2,6-di-t-butylphenol in 1 ml of tetrahydrofuran was added. After 5 minutes, 0.1 ml of 3N hydrochloric acid was added and the solution was allowed to warm to room temperature. After partition between ether and saturated sodium bicarbonate, the organic phase was dried over magnesium sulfate and evaporated. Crystallization from methanol gave 91 mg (91%) of 82a.

(see previous page for spectral and analytical data)



### DIAMINE-LACTAM (83)

To a solution of 100 mg (0.145 mmol) of 82a in 0.1 ml of dichloromethane was added 5 ml of ethanol saturated with ammonia. This solution was hydrogenated over 0.3 ml of a suspension of Raney nickel in ethanol at 1000 psi of hydrogen for 1 hour at room temperature. Filtration through Celite and evaporation gave 82 mg (82%) of 83. mp 136–140° (ether)

IR ( $\text{CH}_2\text{Cl}_2$ ): 2880 (broad), 1630, 1105, 1050, 995

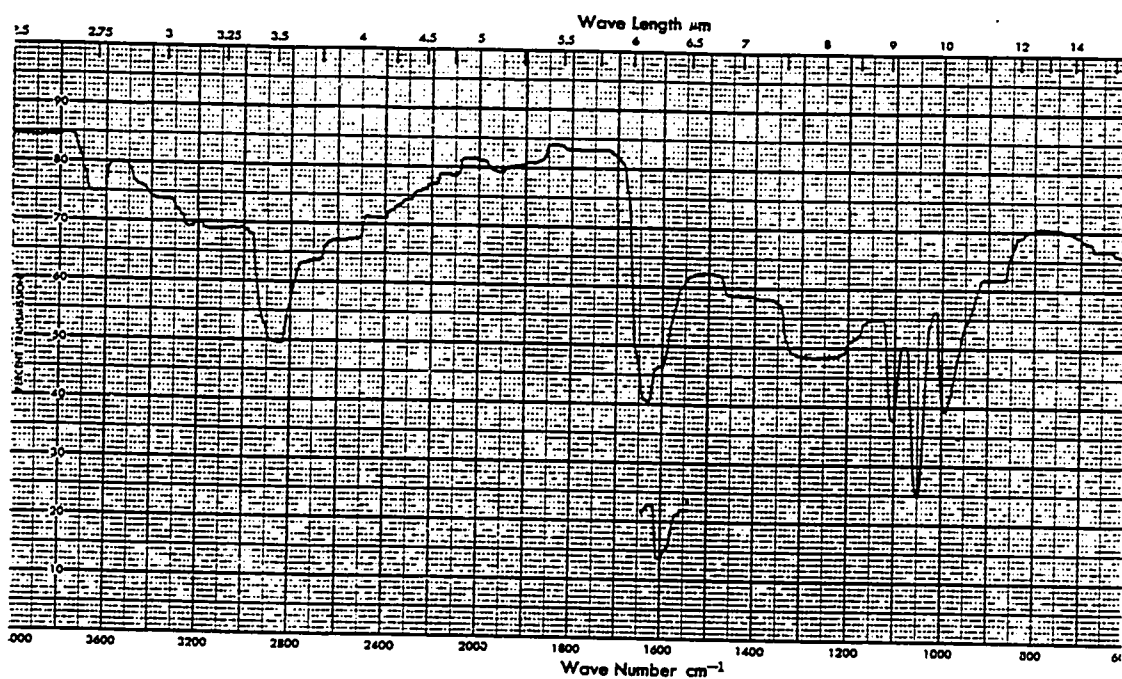
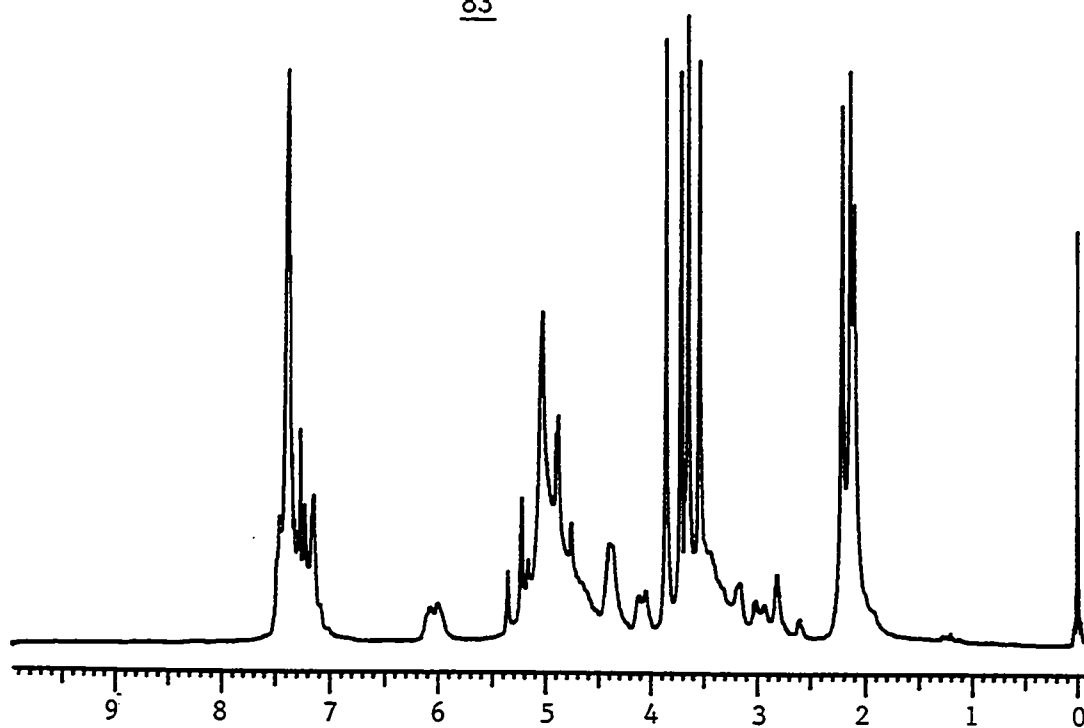
NMR ( $\text{CDCl}_3$ ): 2.10 (3H, s), 2.14 (3H, s), 2.21 (3H, s), 3.54 (3H, s), 3.65 (3H, s), 3.71 (3H, s), 3.86 (3H, s), 4.82 (1H, d,  $J=12\text{Hz}$ ), 5.02 (2H, s), 5.30 (1H, d,  $J=12\text{Hz}$ ), 5.9–6.2 (1H, m), 7.1–7.5 (10H, m)

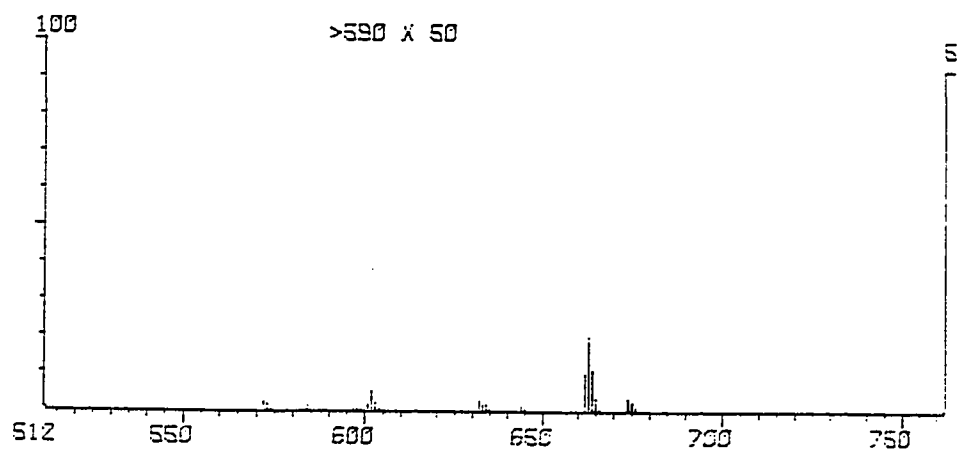
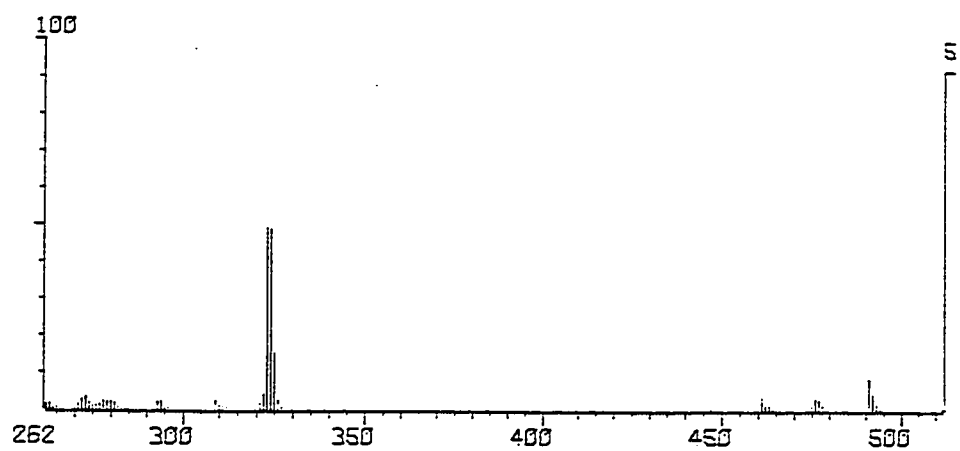
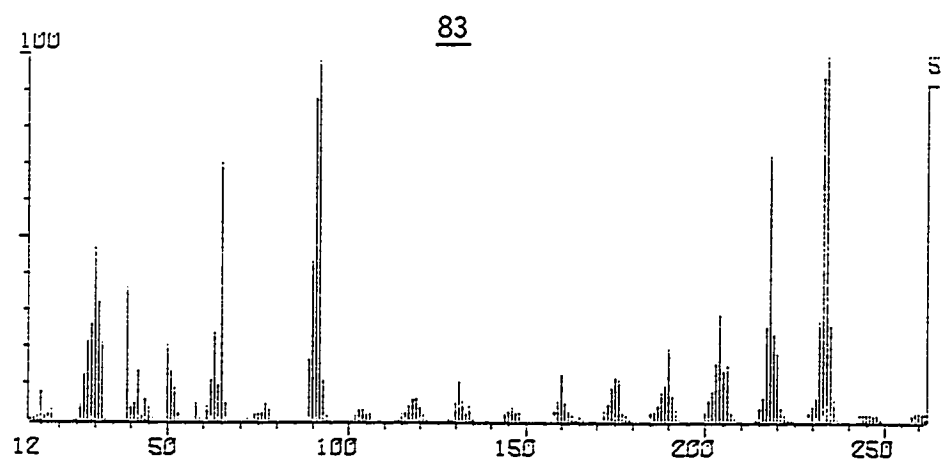
MS: 665 (1,  $\text{M}^+-29$ ), 574 (1), 324 (100), 234 (86), 91 (40)

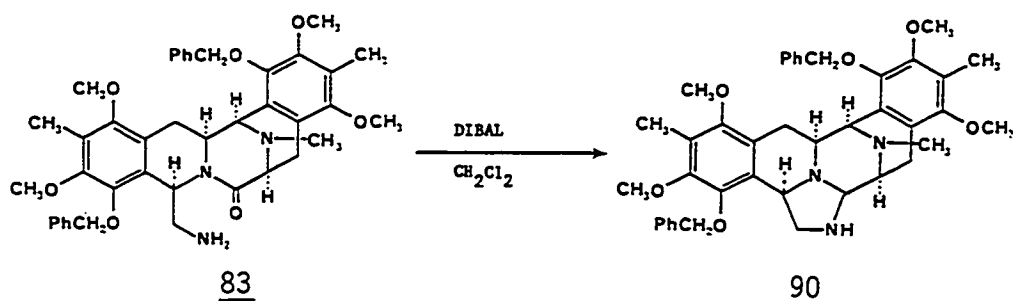
Analysis:  $\text{C}_{41}\text{H}_{47}\text{N}_3\text{O}_7$

crystals from ether

	calculated	found
C: 0.7098		0.6371
H: 0.0683		0.0687
N: 0.0606		0.0537

83





### IMIDAZOLIDINE (90)

To a stirred solution of 82 mg (0.12 mmol) of 83 in 5 ml of dichloromethane at  $-78^{\circ}$ , was added five 0.10 ml (0.1 mmol) portions of a 20% solution of diisobutyl aluminum hydride in hexanes, at 10 minute intervals. Completion of the reaction was determined by TLC analysis on silica gel eluted with a 10% solution of methanol in dichloromethane. Addition of 3N sodium hydroxide solution until the evolution of hydrogen ceased was followed by filtration through Celite and partition between dichloromethane and saturated sodium chloride solution. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried over sodium sulfate and evaporated to give 62 mg (77%) of 90. mp  $>250^{\circ}$  (decomp) (ether)

IR (CH<sub>2</sub>Cl<sub>2</sub>): 2880, 1600, 1100, 1050

NMR (CDCl<sub>3</sub>): 2.12 (3H, s), 2.18 (3H, s), 2.21 (3H, s), 2.3–3.6 (8H, m), 3.58 (3H, s), 3.73 (3H, s), 3.76 (3H, s), 3.80 (3H, s), 4.22 (1H, bt, J=9hz), 4.7–5.4 (4H, AB, AB, J<sub>1</sub>=10hz, J<sub>2</sub>=13hz), 7.2–7.6 (10H, m)

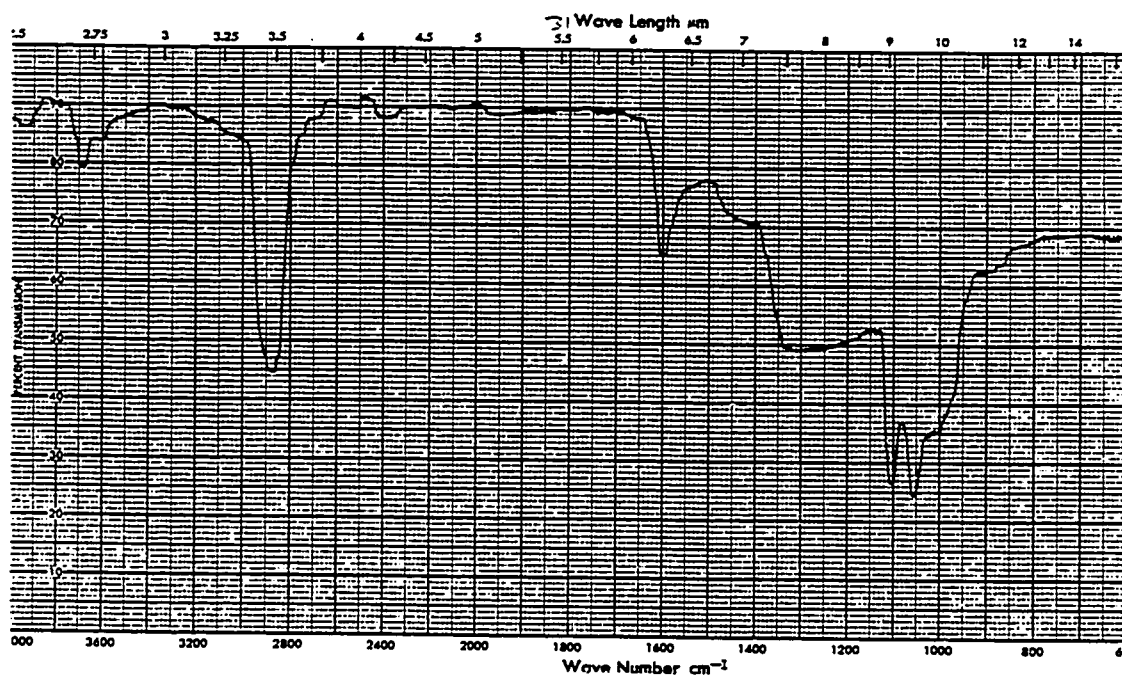
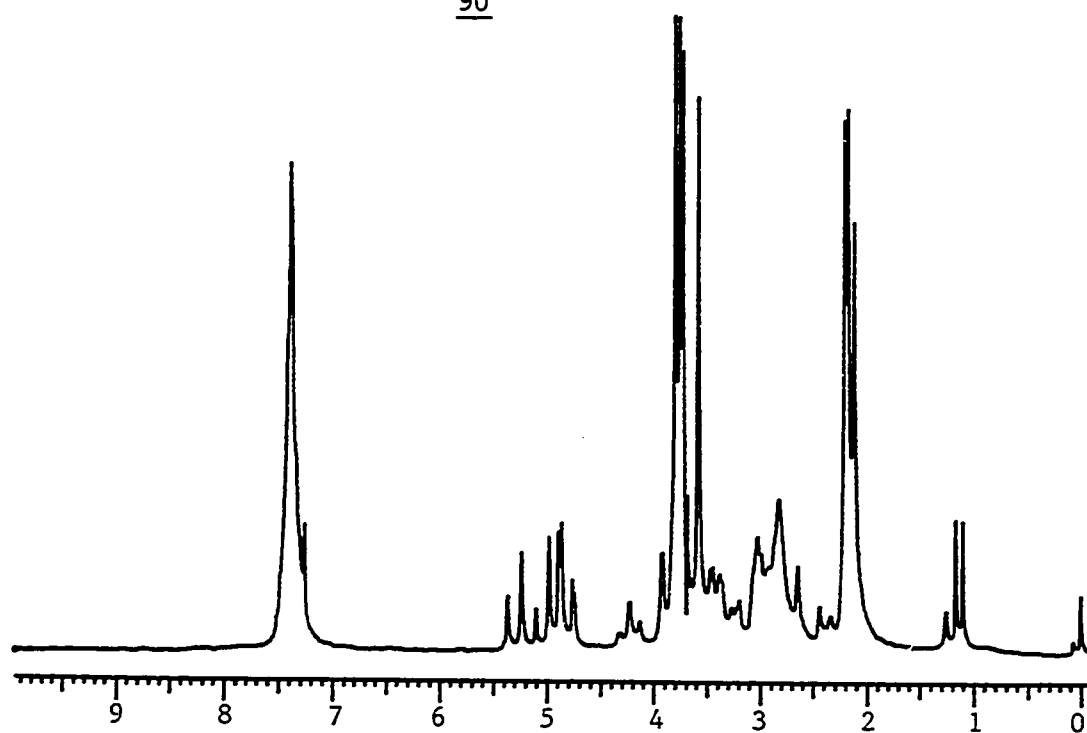
MS: 677 (.02, M<sup>+</sup>+2), 649 (1.1), 586 (.2), 91 (100)

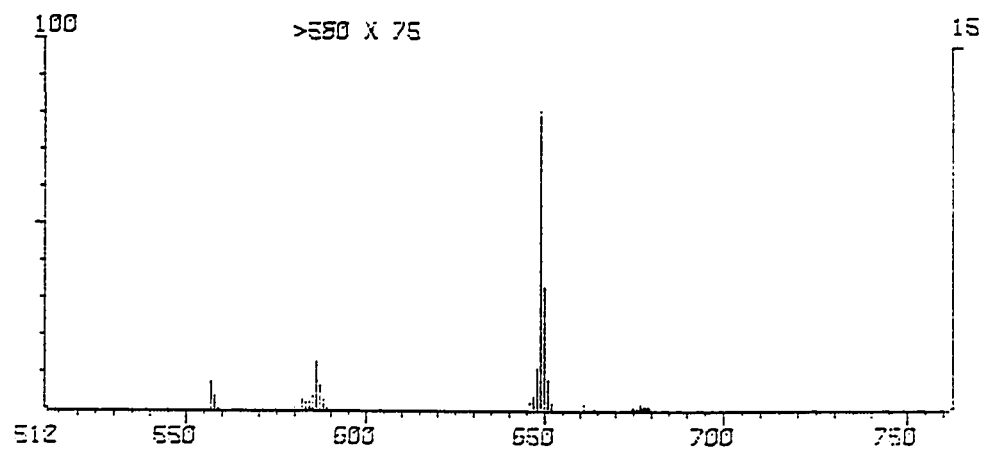
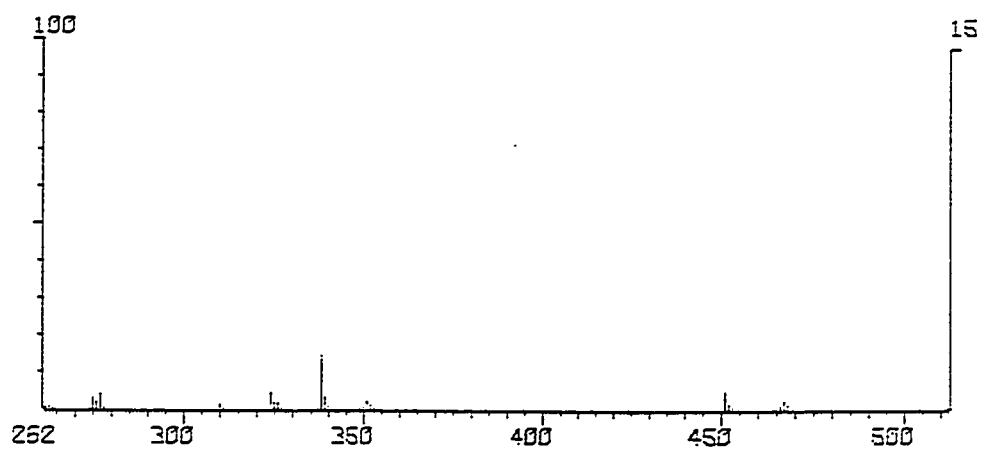
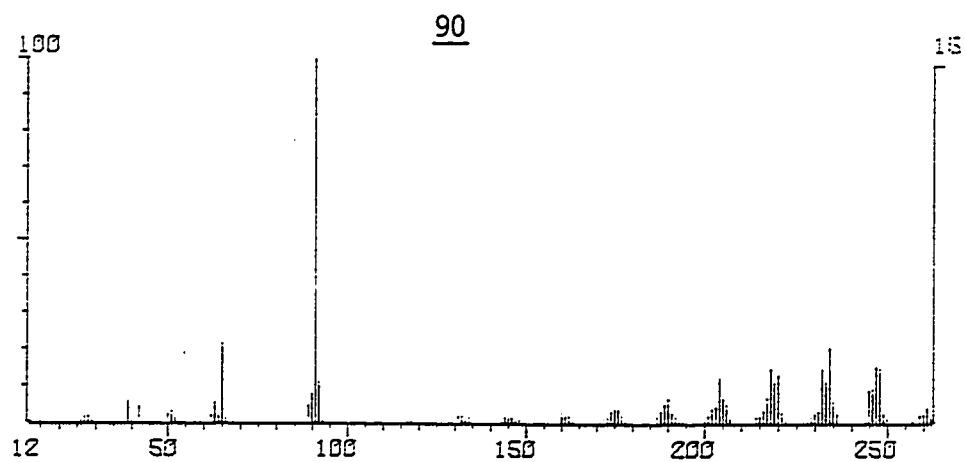


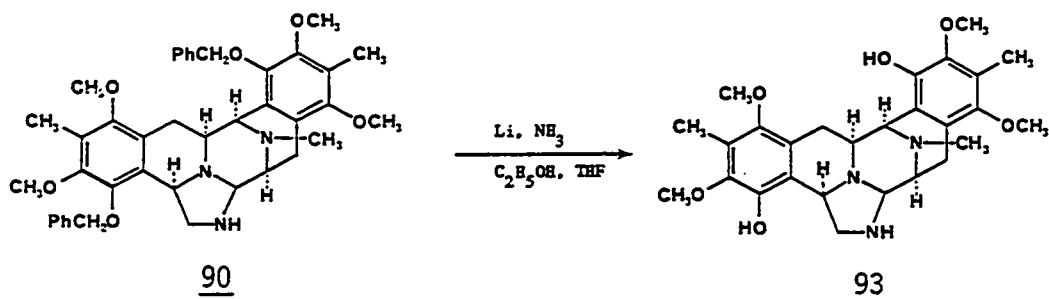
Analysis:  $C_{41}H_{47}N_3O_6$

crystals from ether

	calculated	found
C: 0.7265		0.6728
H: 0.0699		0.0676
N: 0.0620		0.0593

90





### IMIDAZOLIDINE-DIPHENOL (93)

To a solution of 62 mg (91  $\mu\text{mol}$ ) of 90 in 1 ml of ethanol, 5 ml of tetrahydrofuran, and 5 ml of liquid ammonia at  $-50^\circ$  was added small pieces of lithium until the reaction was complete by TLC analysis on silica gel eluted with a 10% solution of methanol in dichloromethane. Completion of the reaction was also indicated by the reaction mixture turning a blue color which faded slowly. Excess ammonium chloride was added and the ammonia allowed to distill off at room temperature. Dichloromethane was added and the mixture filtered through Celite. The solution was evaporated, dissolved in dichloromethane and filtered through sodium sulfate. After evaporation, chromatography on silica gel eluted with a 10% solution of methanol in dichloromethane gave 36 mg (79%) of 93 as a white solid. This compound decomposed when exposed to air. Crystallization from ethyl acetate gave off-white, air sensitive crystals.

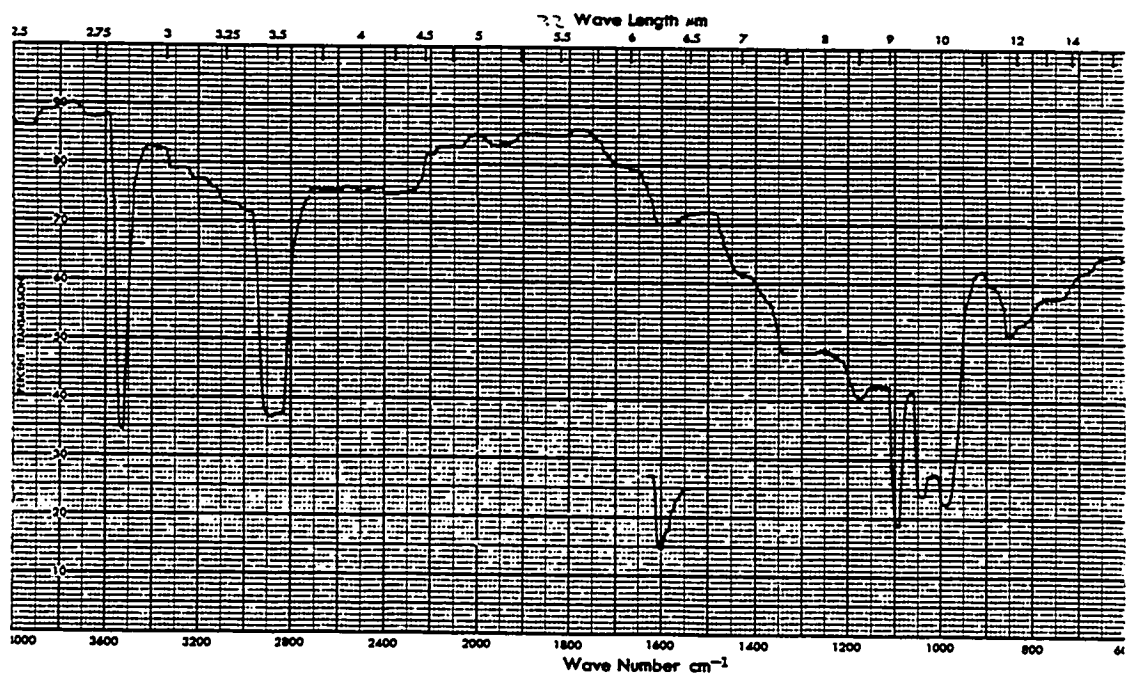
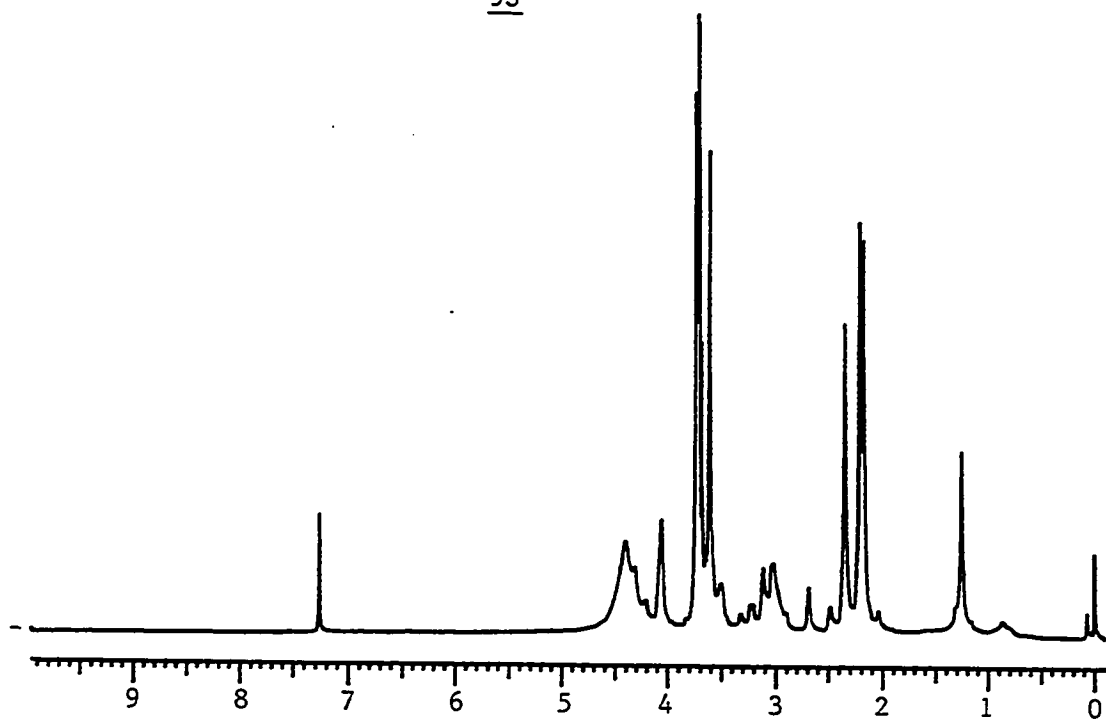
IR ( $\text{CH}_2\text{Cl}_2$ ): 3530, 2840-2880, 1095, 1040, 990

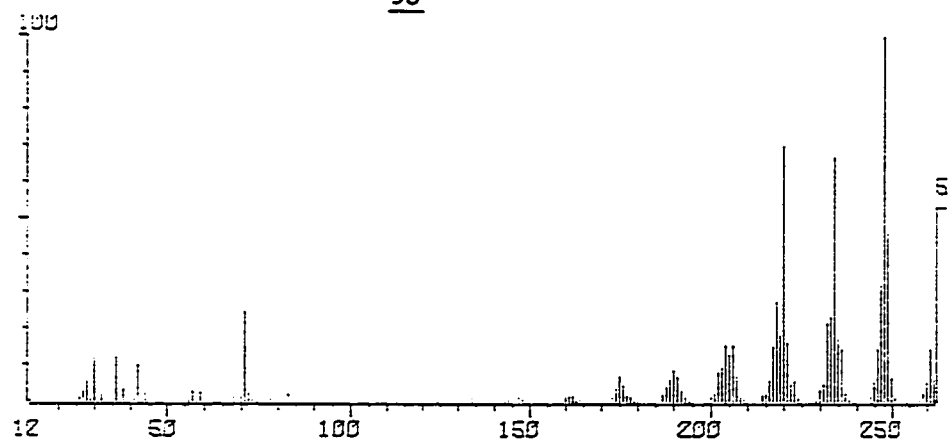
NMR ( $\text{CDCl}_3$ ): 2.19 (3H, s), 2.21 (3H, s), 2.35 (3H, s), 2.4-3.4 (4H, m),  
 3.61 (3H, s), 3.69 (3H, s), 3.70 (3H, s), 3.71 (3H, s),  
 4.06 (1H, bs), 4.2-4.6 (3H, m)

MS: 497 (.08,  $M^+$ ), 496 (.1), 495 (.1), 480 (.1), 478 (10), 248 (100),  
234 (61), 220 (64)

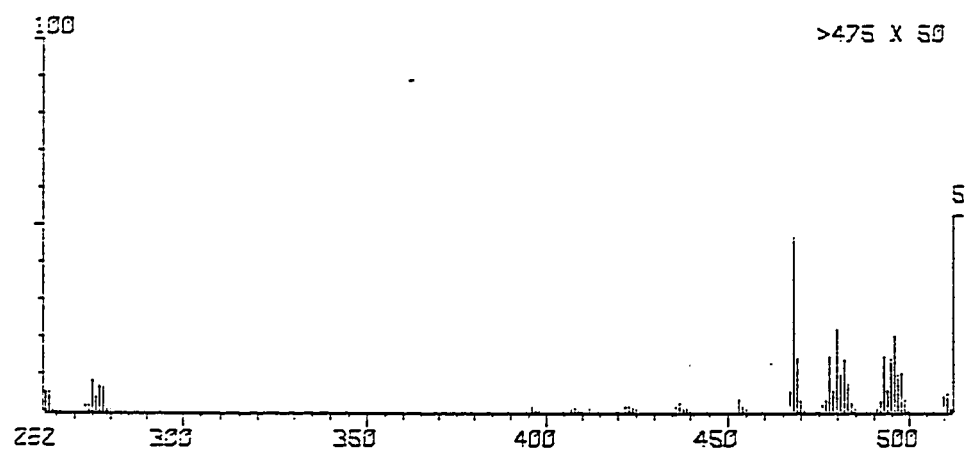
Exact Mass:  $C_{27}H_{35}N_3O_6$

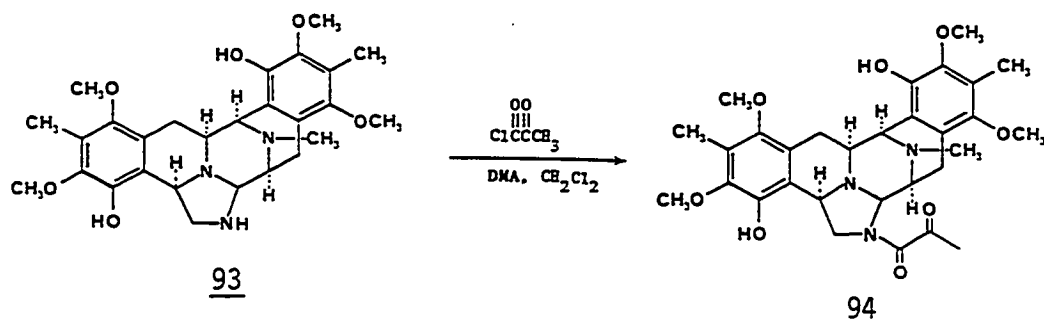
	calculated	found
$M^+$	497.2525	497.2514
$M^+-1$	496.2447	496.2451
$M^+-29$	468.2260	468.2267

93

93

&gt;475 X 50





#### PYRUVYL-IMIDIZOLIDINE (94)

To a stirred solution of 36 mg (0.072 mmol) of 93 and 27  $\mu$ l (0.22 mmol) of dimethylaniline in 5 ml of dichloromethane was added 0.12 ml (0.075 mmol) of pyruvyl chloride. After 5 minutes the reaction mixture was evaporated and crystallized from ether to obtain 22 mg (54%) of 94. mp 158° (ether)

IR ( $\text{CH}_2\text{Cl}_2$ ): 3540, 2820–2900, 1715, 1640, 1100, 1050, 990

NMR ( $\text{CDCl}_3$ ): 2.18 (3H, s), 2.22 (3H, s), 2.36 (3H, s), 2.49 (3H, s), 2.79 (1H, s), 3.0–3.6 (3H, m), 3.62 (3H, s), 3.69 (3H, s), 3.74 (3H, s), 4.1–4.3 (2H, m), 4.53 (1H, bd,  $J=6\text{Hz}$ ), 4.73 (1H, s), 5.51 (1H, bs), 5.65 (1H, s)

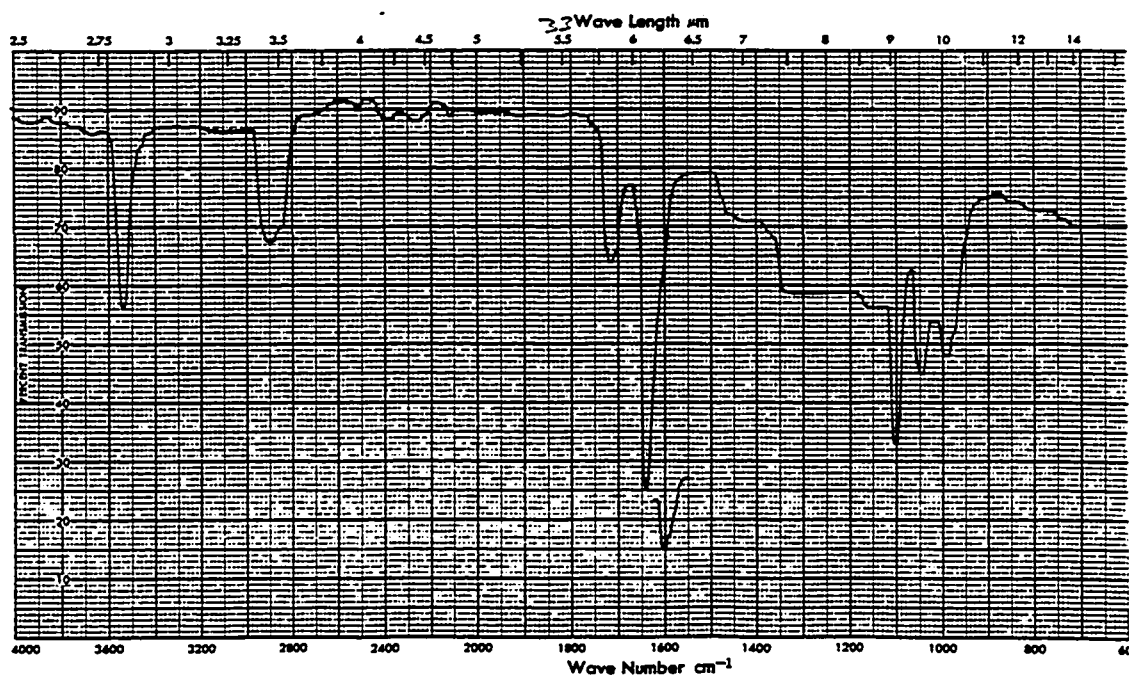
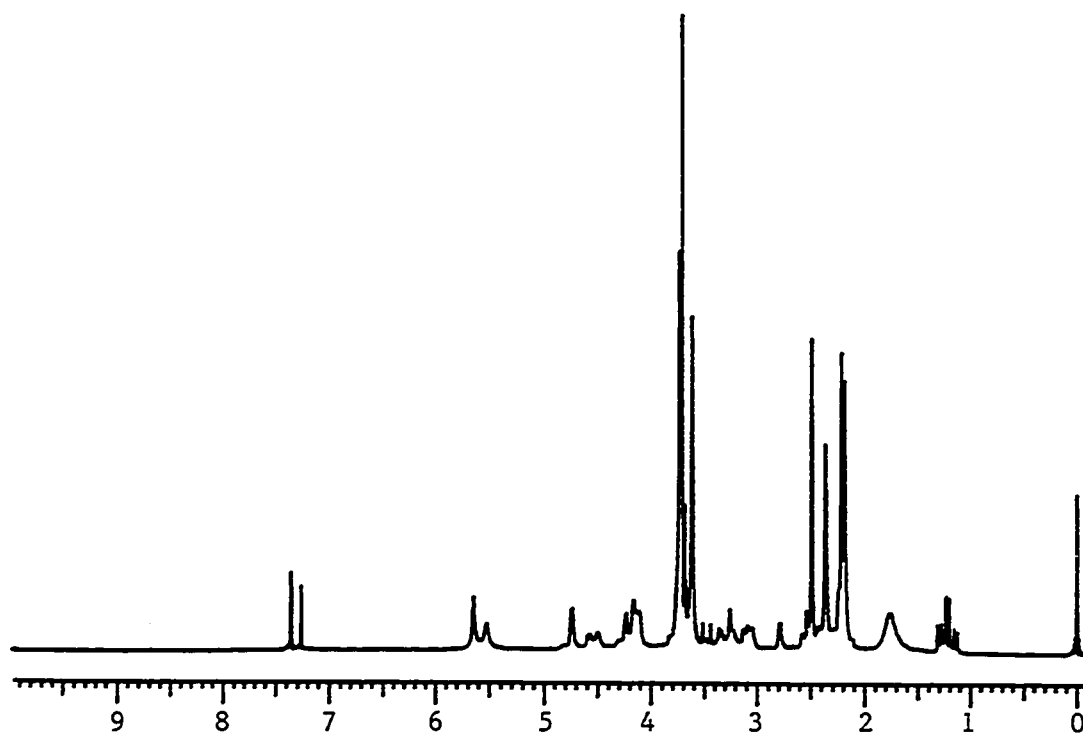
MS: 567 (.3,  $\text{M}^+$ ), 524 (.5), 496 (2), 467 (1.3), 333 (6), 234 (100)

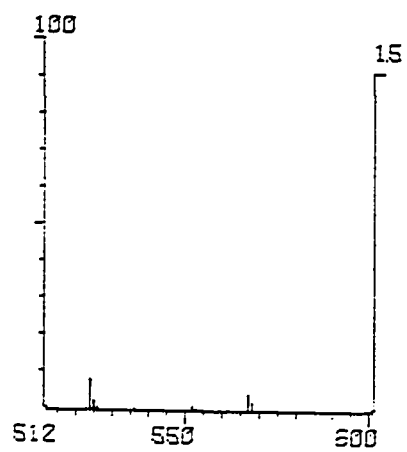
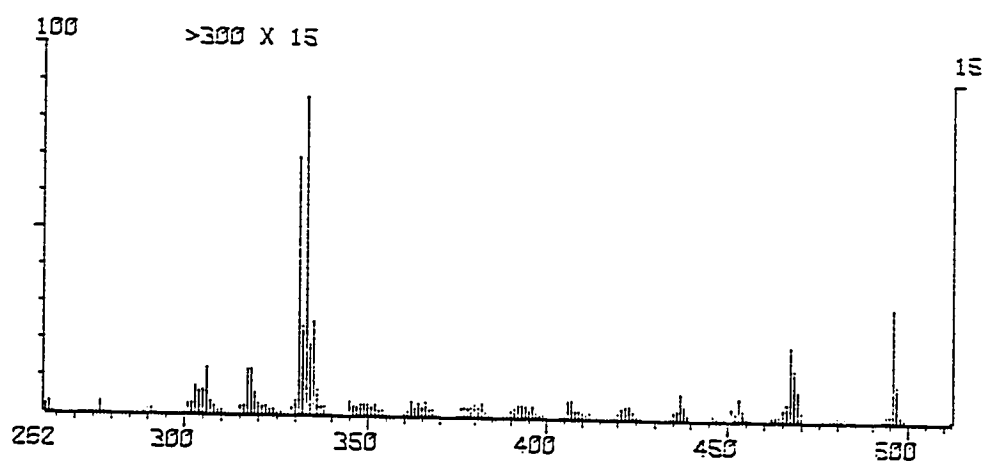
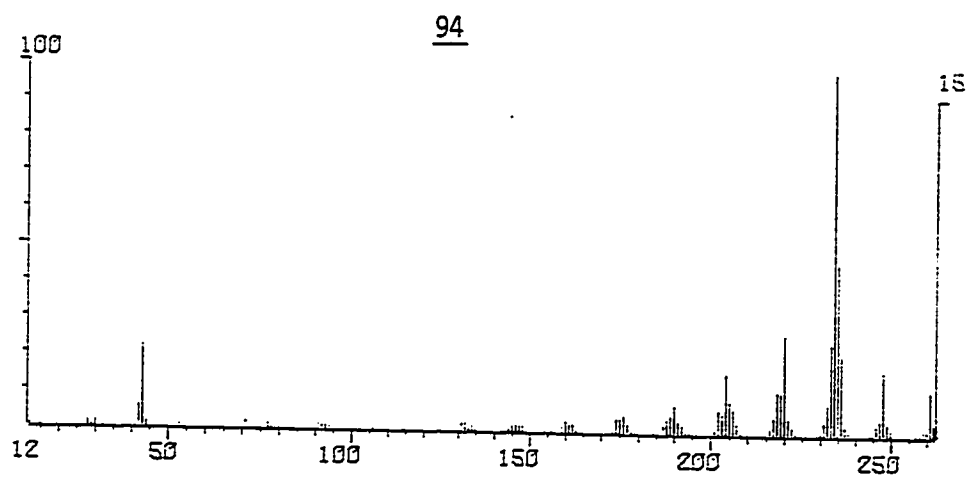
Analysis:  $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_8$

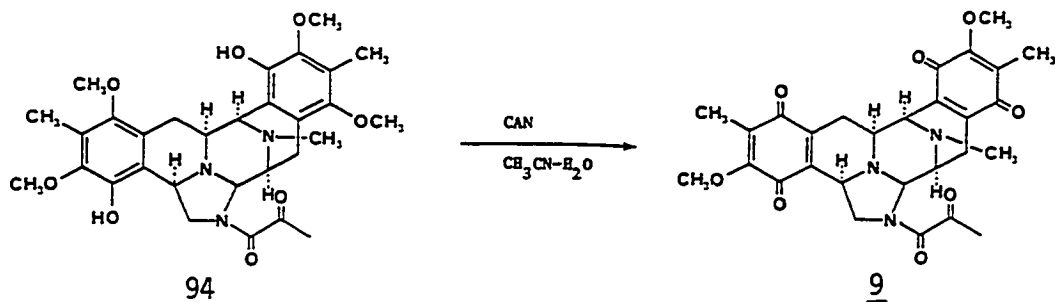
crystals from ether

	calculated	found
C: 0.6727		0.6329
H: 0.0696		0.0670
N: 0.0784		0.0717









### BIS-QUINONE (9)

To a stirred solution of 8.0 mg (0.014 mmol) of 94 in 2 ml of acetonitrile at 0° was added 40 mg (0.070 mmol) of ceric ammonium nitrate in 0.5 ml water. After 30 minutes, approximately 0.2 ml of saturated sodium bicarbonate solution was added and the mixture diluted with 20 ml dichloromethane. Filtration through Celite was followed by drying over sodium sulfate and evaporation. Chromatography on silica gel eluted with a 30% acetone in benzene solution gave 1.5 mg (20%) 9. Repeated chromatography gave 1.1 mg (14%) pure 9.

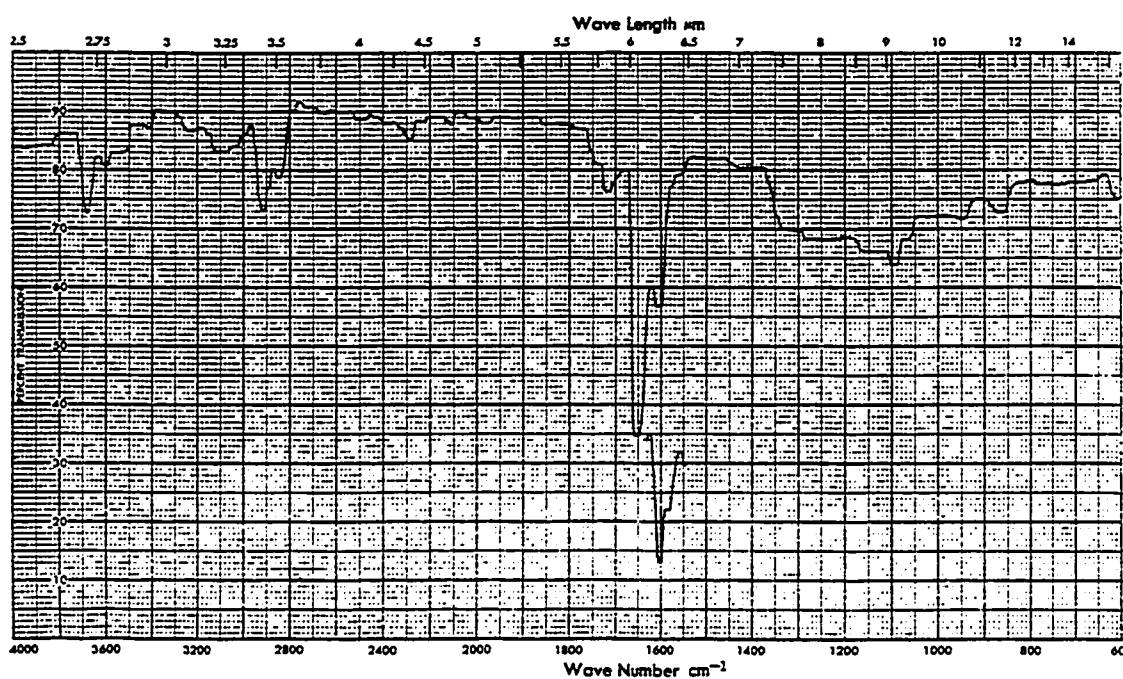
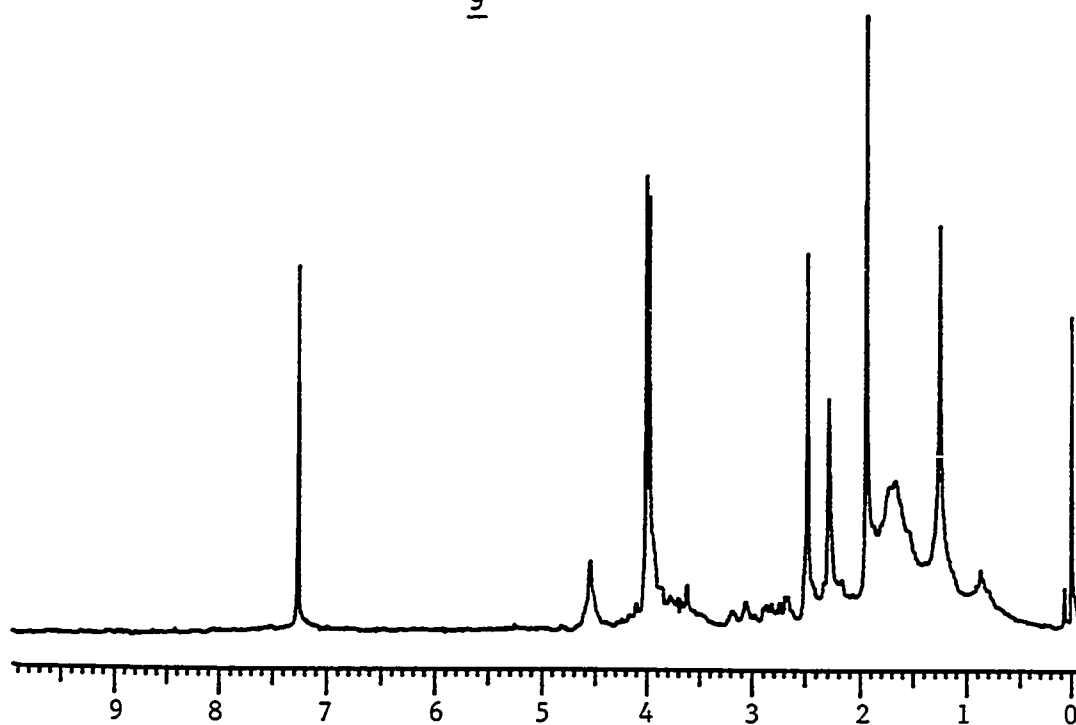
IR ( $\text{CH}_2\text{Cl}_2$ ): 3680, 3600, 2910, 1720, 1650, 1605

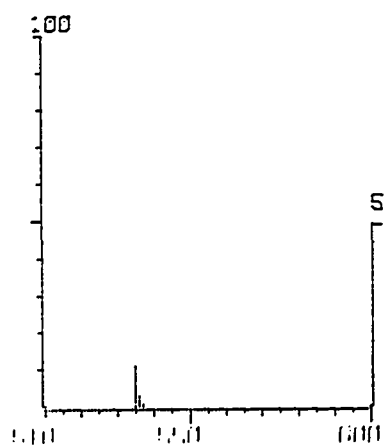
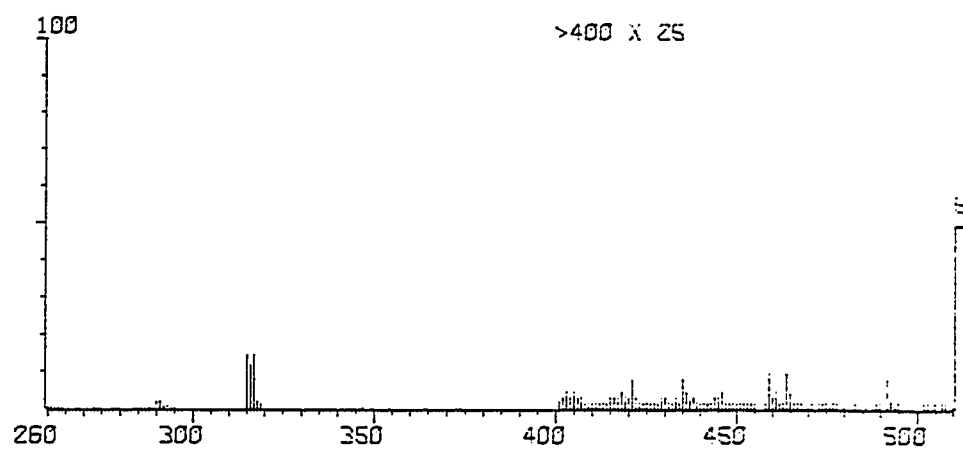
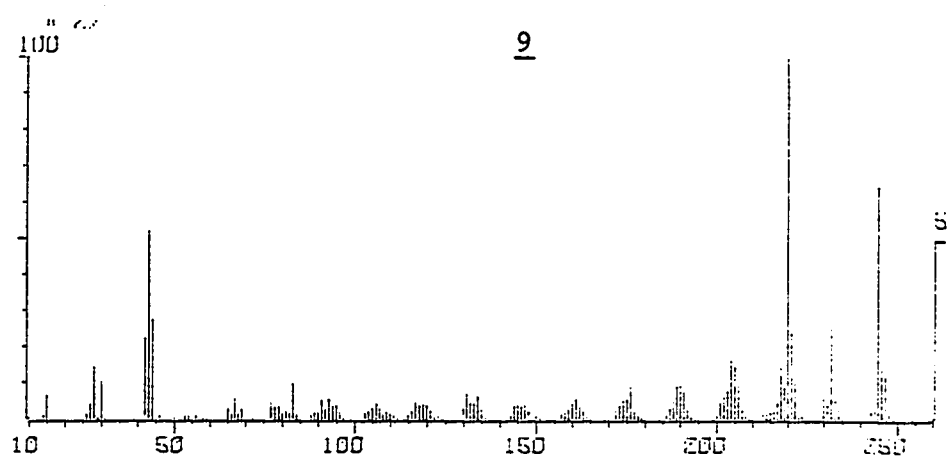
NMR ( $\text{CDCl}_3$ ): 1.94 (6H, s), 2.29 (3H, s), 2.49 (3H, s), 2.6–3.3 (2H, m), 3.4–3.9 (3H, m), 3.98 (3H, s), 4.01 (3H, s), 4.56 (2H, bs)

MS: 535 (.5,  $\text{M}^+$ ), 492 (.3), 464 (.4), 459 (.4), 435 (.3), 421 (.3), 245 (62), 220 (100)

Exact Mass:  $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_8$

	calculated	found
$\text{M}^+$	535.1954	535.1942
$\text{M}^+-43$	492.1770	492.1763

9



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13. The characteristic of cis-piperazines and piperazine-diones moving faster than the trans isomers on silica TLC (ref 11) is supported by extensive experience in our laboratory.
14. The observed strong absorption at 254 nm on fluorescence indicating silica gel TLC would not be expected for compound 24. In addition, the mass spectrum did not show  $M^+=606$ , but instead  $m/e=604$ .
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