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Part I. The total synthesis of two human urinary metabolites of delta-9-THC. Part II. The total synthesis of (d,1)-morphine

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PART I: THE TOTAL SYNTHESIS OF TWO HUMAN URINARY METABOLITES OF DELTA-9-THC

PART II: THE TOTAL SYNTHESIS OF (d,l)-MORPHINE

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAII IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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By

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To Jean, Tim and Andy Kerr and

to the memory of David Kerr

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ABSTRACT

Part 1: A synthesis of two human urinary metabolites of delta-9-THC is described. The target compounds, 11-nor-delta-9-THC-9-carbinol and 11-nor-delta-9-THC-9-carboxylic acid, were prepared as their naturally occurring antipodes by the acid catalyzed condensation of olivetol with a terpenoid fragment derived from R-(+)-perillaldehyde. The first preparation of this aldehyde is also described.

Part 2: A unique approach to the preparation of morphinan alkaloids has resulted in a total synthesis of thebainone and beta-thebainone in racemic form. This constitutes a total synthesis of morphine by the virtue of previously reported work. The aromatic moiety of the morphine skeleton is prepared via a novel rearrangment from a nonaromatic precursor. While the disconnection of an aromatic compound to a alicyclic starting material is not normally considered advantageous, it has been shown herein that this is indeed a practical approach. The nonaromatic carbon skeleton of morphine was prepared efficiently using a Diels-Alder reaction. In addition to a formal total synthesis of morphine, several heretofore unknown morphinan structural analogues were prepared whose skeletal connectivity differ only in the position of attachment of the aminoethyl bridge.

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LIST OF ABBREVIATIONS

A	Angstrom
Ac	acetyl
Ar	aryl
br	broad
C	Celsius
c	concentration
COSY	correlated spectroscopy
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
DNP	dinitrophenyl hydrazone
dt	doublet of triplets
EE	ethoxyethyl
eq	equation
equiv	equivalent
Et	ethyl
eV	electron volt
EVE	ethyl vinyl ether

LIST OF ABBREVIATIONS (CONT'D)

g	gram
h	hour
[H]	reduction conditions
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrum
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m	multiplet
M	molar
MCPBA	meta-chloroperoxybenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mL	millilitre
mmol	millimole
n-Bu	normal butyl
NBS	N-bromo succinimide
NMR	nuclear magnetic resonance

LIST OF ABBREVIATIONS (CONT'D)

[O]	oxidation conditions
Ph	phenyl
PPTS	pyridinium p-toluene sulphonate
q	quartet
R_f	retention factor
s	singlet
sat'd	saturated
salcomine	N,N'-bis(salicylidene)ethylenediamino cobalt(II)
t	triplet
t-Bu	tertiary butyl
TBDMS	tertiary-butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	toluenesulphonyl

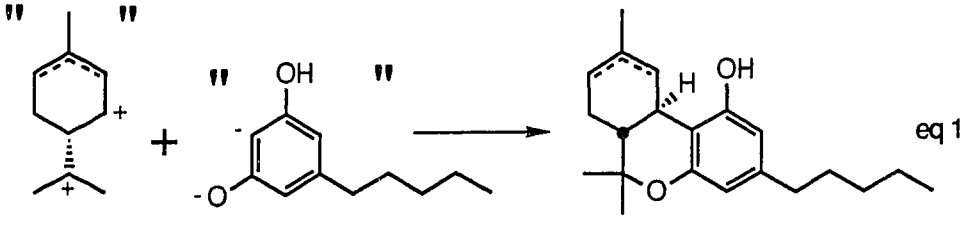
PART I:

THE TOTAL SYNTHESIS OF TWO HUMAN URINARY METABOLITES OF DELTA-9-THC

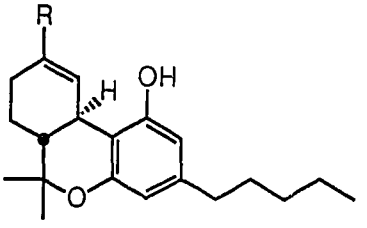
INTRODUCTION

There are essentially two main goals for studies related to cannabinoid synthesis: 1) to satisfy the demand for these compounds as analytical standards for use in drug testing[1] and 2) to understand how they affect the human body, thereby arriving at some potentially thereputic drugs. Promising activities of cannabinoids are associated with their antiemetic, antiglaucomic and analgesic effects.[2]

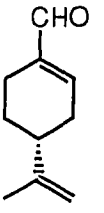
The most successful syntheses of cannabinoids to date usually involve the coupling of an aromatic fragment derived from olivetol with a menthane derived terpenoid[3] (eq 1) although there have been other approaches.[4] In the past, the coupling reactions have been hampered by side reactions and the lack of suitable terpenoid intermediates.



When delta-9-tetrahydrocannabinol (delta-9-THC) **3** is ingested by the human body as smoke, it is metabolized to, among other products, 11-nor-delta-9-THC-9-carbinol **2** and 11-nor-delta-9-THC-9-carboxylic acid **1**. These products are useful as standards for the analysis of human urine by GC-MS. The acid is commercially available in 500 ug quantities.[10] Presented herein is a convenient preparation of **1** and **2**.[5] Included in this synthetic route is the first preparation of the naturally occurring terpenoid, R-(+)-perillaldehyde **4**.[6]



1 R = COOH
2 R = CH_2OH
3 R = CH_3

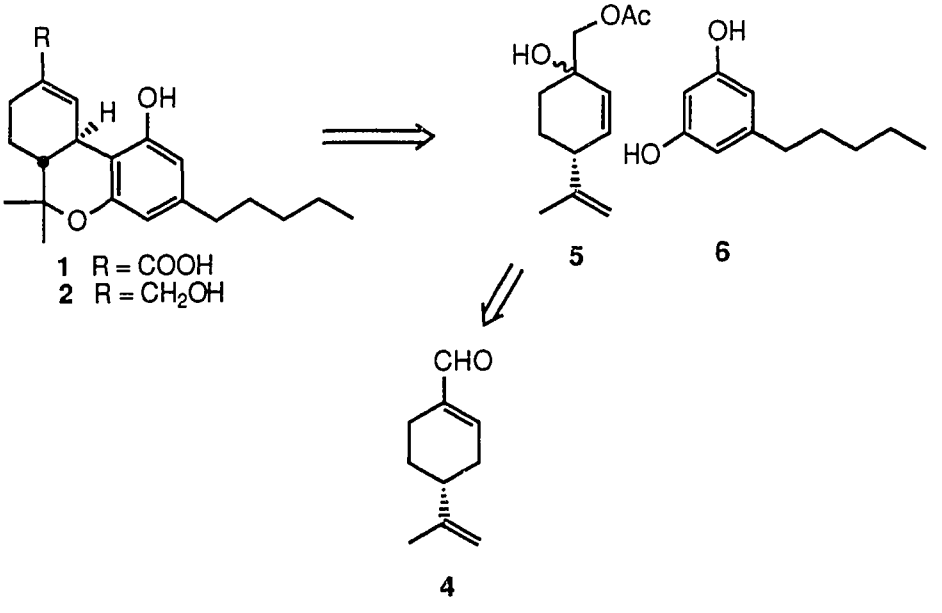


4

Although S-(-)-perillaldehyde is commericially available,[7] the R isomer, apparently, is not. The R isomer occurs naturally in false camphor wood.[8] Although syntheses of the S-antipode have been described,[9] none were suitable for the large scale preparation of the R enantiomer. The following chapter describes the preparation of R-(+)-perillaldehyde on a multigram scale.

The synthetic route described in the following chapter has been used to prepare about useful quantities of **1** and **2**. The retrosynthesis of **1** and **2** is shown in scheme 1. The monoacetate **5** was prepared from perillaldehyde **4** and was coupled with olivetol **6** to form the cannabinoid skeleton. Several functional group manipulations led to the target molecules.

SCHEME 1



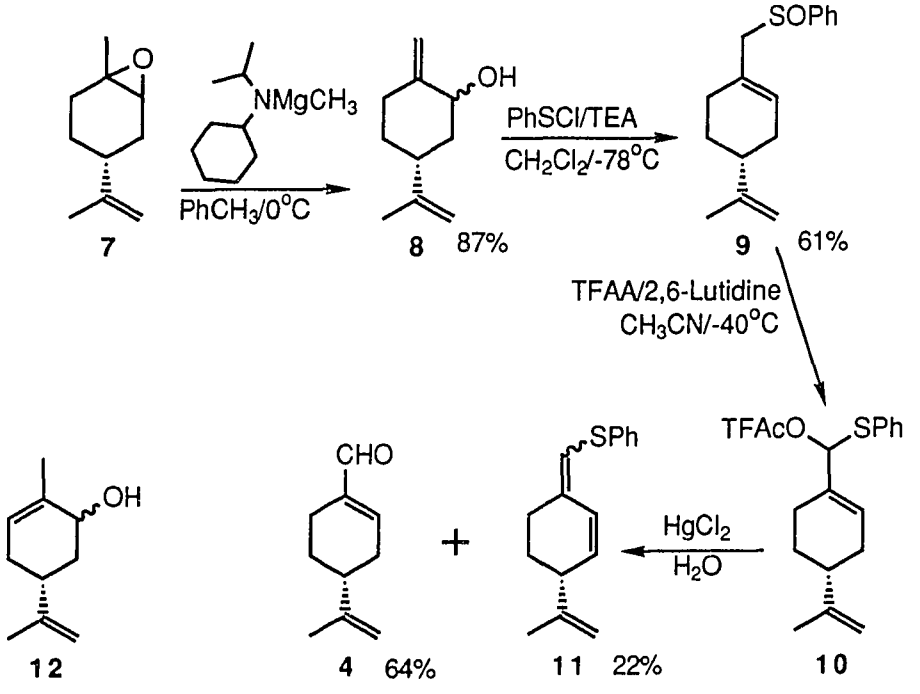
DISCUSSION

A. The Synthesis of R-(+)-Perillaldehyde[6]

The synthetic scheme for the preparation of R-(+)-perillaldehyde **4** is illustrated in scheme 2. The starting material for this synthesis is (+)-limonene oxide **7**. Since both enantiomers of limonene oxide are avaialable and inexpensive,[7] this route can be used to prepare either enantiomer of perillaldehyde. Rearrangement of (+)-limonene oxide **7** with methylmagnesium cyclohexylisopropyl-amide[11] gave the exocyclic allylic alcohol **8** in 87% yield. It is interesting to note that while no endocyclic alkene was seen under these conditions, use of dicyclohexylamine in place of cyclohexylisopropylamine gave about 25% of the endocyclic alkene **12**. Treatment of alcohol **8** with phenylsulphenyl chloride and triethylamine in methylene chloride at -78°C gave sulphoxide **9** in 61% yield.[12] This reaction was complicated somewhat by the formation of a byproduct resulting from the reaction of the reagent with the isopropenyl double bond. Pummerer rearrangement of **9** with acetic anydride gave a complicated mixture but the use of trifluoroacetic anhydride and 2,6-lutidine in acetonitrile[13] at -40°C gave intermediate **10** which was hydrolized with aqueous mercuric chloride to give a 64% yield of perillaldehyde and a 22% yield of the vinyl

sulphide **11**. If the reaction mixture was left to stand at ambient temperature overnight, **11** was the only product. E1' elimination of **10** presumably leads to the formation of **11**. Several attempts to hydrolyze the vinyl sulphide to **4** were unsuccessful.

SCHEME 2



B. The Synthesis of 11-Nor-Delta-9-THC-9-Carboxylic Acid and 11-Nor-Delta-9-THC-9-Carbinol[5]

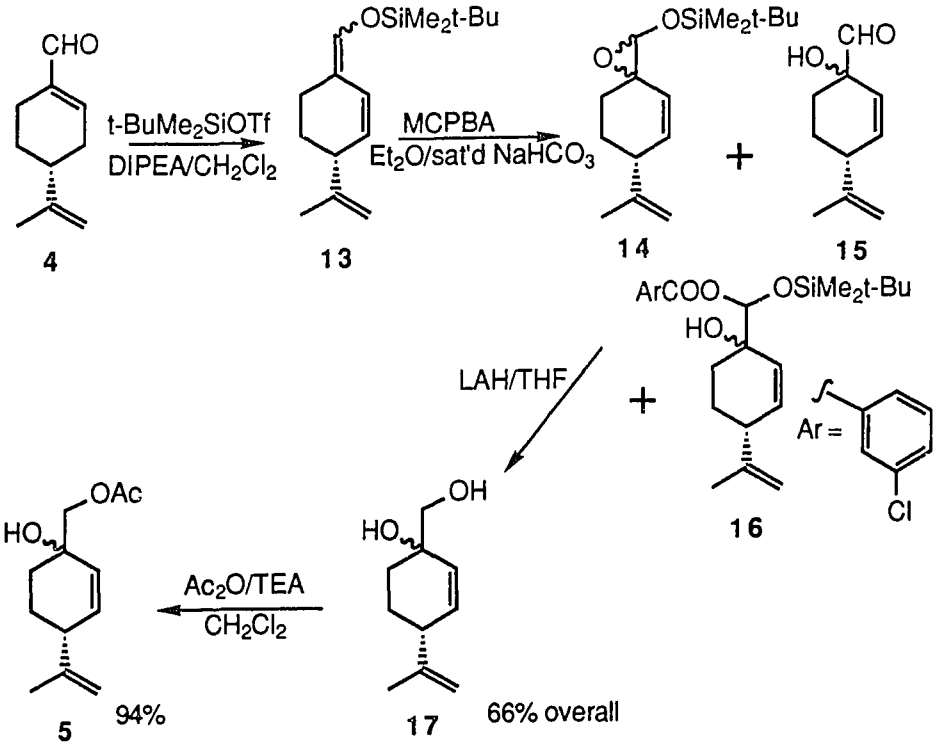
1. Synthesis of the Terpenoid Fragment

The preparation of a suitable intermediate for condensation with olivetol is shown in scheme 3. The extended t-butyldimethylsilyl enol ether of perillaldehyde was prepared by treating **4** with t-butyldimethylsilyl trifluormethane sulphonate[14] and diisopropylethylamine in methylene chloride. Treatment of crude **13** with meta-chloroperoxybenzoic acid in ether buffered with saturated aqueous sodium bicarbonate resulted in the consumption of the starting material. The identity of the product was not determined, but it may be a mixture of **14**, **15** and **16**. Treatment of the crude epoxidation product with lithium aluminum hydride gave diol **17** in a yield of 66% from perillaldehyde. Monoacetylation of **17** to produce **5** proceeded smoothly with acetic anhydride and triethylamine in methylene chloride (94% yield).

2. Synthesis of 11-Nor-Delta-9-THC-9-Carbinol

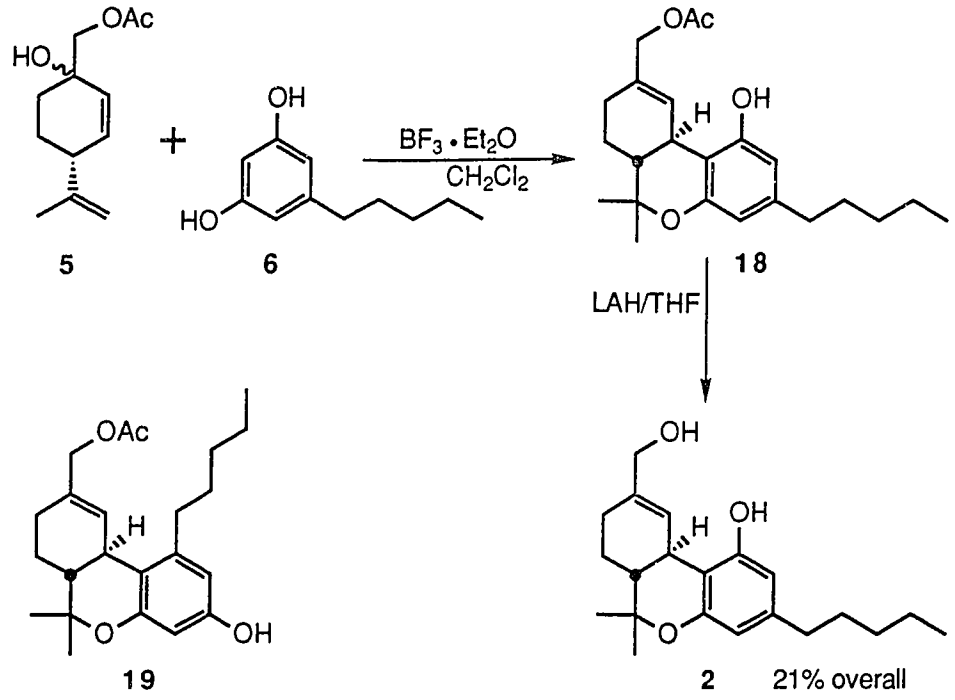
Scheme 4 illustrates the condensation of **5** with olivetol **6** and the elaboration of the product to the title compound **2**. Treatment of an equimolar mixture of **5** and **6** in methylene chloride with borontrifluoride etherate gave

SCHEME 3



in methylene chloride with borontrifluoride etherate gave a 33% yield of a mixture which was predominantly the desired condensation product **18**. Reduction of **18** with lithium aluminum hydride gave the natural metabolite **2** in 63% yield. This low yield reflects the impurity of the starting material. The overall yield of **2** from monoacetate **5** was about 21%. The modest yield of the condensation product is due in part to the formation of a significant amount of the regioisomer **19**.

SCHEME 4

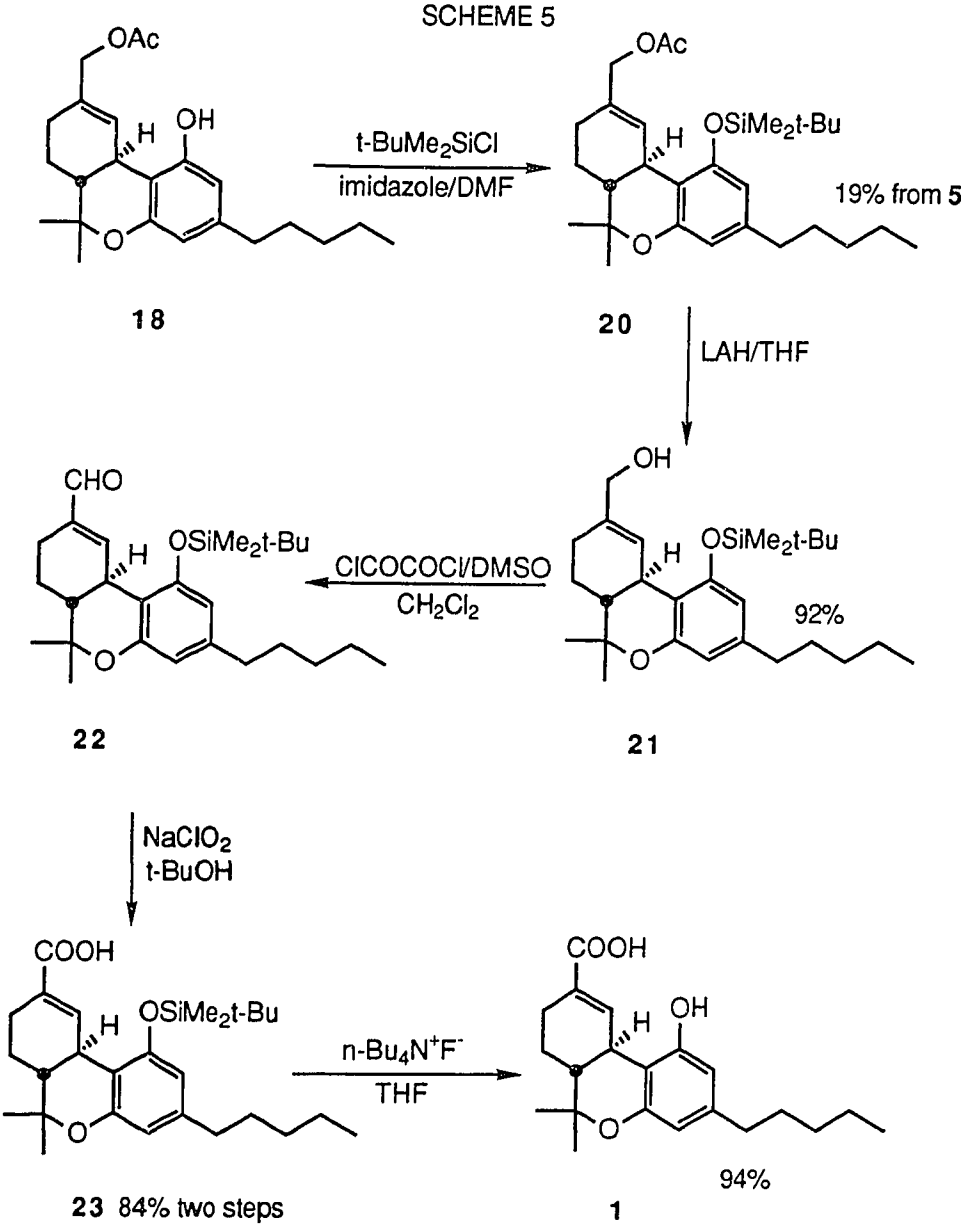


3. The Synthesis of 11-Nor-Delta-9-THC-9-Carboxylic Acid

The conversion of condensation product **18** to the title compound **1** is shown in scheme 5. Silylation of **18** (t-butyldimethylsilyl chloride/imidazole/DMF) gave **20** (19% overall yield from monoacetate **5**) which when treated with lithium aluminum hydride gave primary alcohol **21** in 92% yield. Because of the sensitivity of the aromatic moiety to oxidation, a mild two-step sequence was used to convert the hydroxyl group to the carboxylic acid. Swern oxidation[15] of **21** gave aldehyde **22** which was not purified

but oxidized with sodium chlorite[16] in tert-butanol to produce acid **23** in an overall yield of 84%. Removal of the protecting group gave the natural metabolite **1** in 94% yield.

SCHEME 5



CONCLUSION

An efficient and practical synthesis of two primary human metabolites of delta-9-THC **3** has been described. As part of this work, the first synthesis of a naturally occurring but previously unavailable terpenoid, R-(+)-perillaldehyde **4**, has been developed. The synthesis of the cannabinoids reported herein appears to be the most practical reported to date and has been used preparatively to make useful quantities of material in optically active form. The overall yield for alcohol **2** is 5% from limonene oxide. The overall yield of **1** from the same material is about 3%.

EXPERIMENTAL SECTION

General:

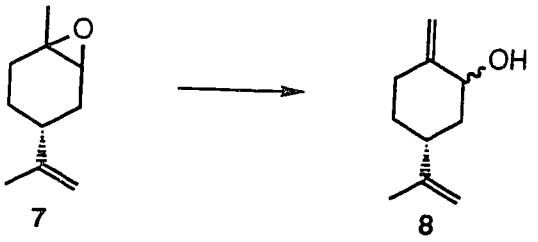
All moisture sensitive reactions were run in flame dried glassware under a positive pressure of nitrogen or argon.

Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorous pentoxide. Reagents and other solvents were purified by standard procedures outlined in references 17 and 18 or in the literature cited for the particular reaction.

Melting points were determined using a Mel-Temp apparatus and are uncorrected.

Infrared spectra were measured using a Perkin-Elmer 710B, a Perkin-Elmer 1430, or a Nicolet 740 FT-IR. Mass spectra were measured using a Varian MAT 311 or a Varian VG-70SE spectrometer and were all electron impact spectra. Nuclear Magnetic Resonance spectra were recorded using a Nicolet NT-300, a General Electric QE-300, or a General Electric QE-500 spectrometer (residual $CHCl_3$ as internal standard).

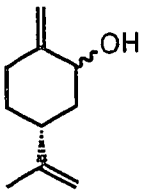
Flash chromatograpy was performed using 230-400 mesh silica gel. Thin layer chromatography was performed on EM Reagents precoated silica gel 60 F_{254} analytical plates (0.25mm thickness).



7 8

Preparation of 2(R,S)-4(R)-1(7),8-p-Menthadien-2-ol 8.

In a three necked flask equipped with a septum inlet and a overhead mechanical stirrer was dissolved 43.2 mL (263.2 mmol) isopropylcyclohexylamine in 300 mL toluene under dry nitrogen. The mixture was cooled to 0°C in an ice bath and 111.5 mL of a 2.36 M solution of n-butyllithium in hexane (263.2 mmol) was added dropwise. Stirring was continued at 0°C for 45 min during which time a white precipitate formed. A solution of 10 g (+)-limonene oxide (65.8 mmol) in 100 mL toluene was added and the mixture kept at 0°C for 24 h or until tlc indicated the complete disappearance of epoxide. The reaction mixture was neutralized using 3% aqueous HCl and was washed three times with 3% aqueous HCl, and once each with saturated aqueous $NaHCO_3$ and water. The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to yield the crude product as an oil. Flash chromatograpy on silica gel (elution with 10% EtOAc in hexanes) gave the pure product as an inseparable mixture of diastereomers. The yield was 8.75 g (87.5%).



8

tlc: R_f = 0.18 (10% EtOAc/hexanes)

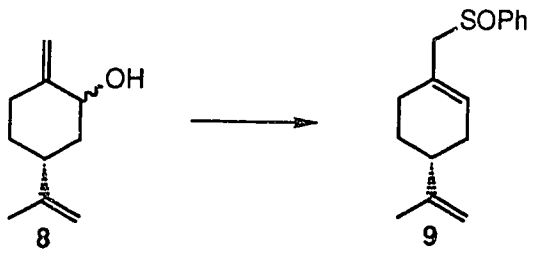
^1H NMR (300 MHz, $CDCl_3$, mixture of diastereomers):
4.95, 4.86, 4.80, 4.77 (br d, br s, br d, br t, 2H)
4.71 (br s, 2 H), 4.37, 4.13-4.09 (br s, m, 1 H),
2.54-1.75 (m, 4H), 1.73 (s, 3 H), 1.69-0.97 (m, 4 H).

IR (neat): 3410, 3140, 2990, 2910, 1675, 1475, 1405, 1110 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 152(m^+,11.3),
150(9.4), 137(11.9), 135(24.1), 134(m-H_2O,80.9),
119(45.9), 109(100).

HRMS: for $C_{10}H_{16}O$ calculated 152.1202
found 152.1203.

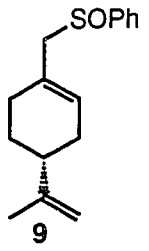
Specific rotation: $[\alpha]_D^{18}$ = +34.0° (CH_2Cl_2).



8 9

Preparation of perillyl phenyl sulphoxide 9.

A solution of 8.15 g (53.6 mmol) of the allylic alcohol **8** and 18.6 mL (134 mmol) of triethylamine in 200 mL dry methylene chloride was cooled to -78°C under an atmosphere of dry nitrogen. A solution of 7.75 g (53.6 mmol) of phenylsulphenyl chloride in 10 mL of methylene chloride was added dropwise. More phenylsulphenyl chloride in methylene chloride was added in small portions until tlc indicated that the starting material had been consumed. The reaction mixture was quenched with water, washed three times with 3% aqueous HCl, once with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by flash chromatography on silica gel (elution with 20% EtOAc/hexanes) gave 8.48 g of the pure product (61% yield) as a white solid.



9

tlc: R_f = 0.31 (20% EtOAc/hexanes)

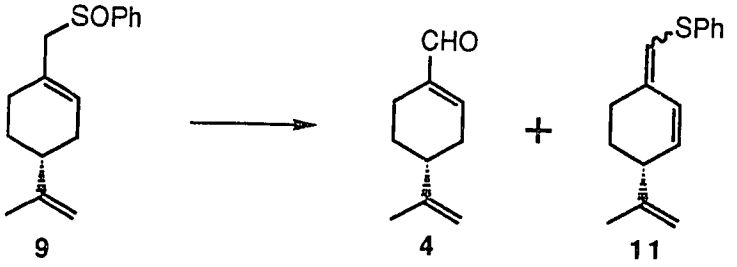
^1H NMR (300 MHz, $CDCl_3$, sulphoxide diastereomers):
7.62-7.57 (m, 2 H), 7.54-7.48 (m, 3 H),
5.57, 5.52 (br s, br s, 1 H), 4.72 (s, 1 H),
4.68 (s, 1 H), 3.50 (d, J = 12.5 Hz, 1 H),
3.32 (d, J = 12.5 Hz, 1 H), 2.16-1.89 (m, 4 H)
1.84-1.74 (m, 1 H), 1.71 (s, 3 H), 1.49-1.41 (m, 2 H).

IR (CH_2Cl_2): 3100, 3040, 2960, 1670, 1450, 1275, 1070, cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 260(m^+,0.1), 135(m-SOPh,85.0), 107(57.4), 93(100).

HRMS: for $C_{16}H_{20}SO$ calculated 260.1236
found 260.1235.

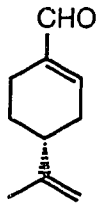
Specific rotation: $[\alpha]_D^{18}$ = +63.1° (CH_2Cl_2).



9 4 11

Preparation of (R)-(+)-Perillaldehyde 4 and sulphide 11.

To a stirred solution of 10.0 g (38.5 mmol) of the sulphoxide **9** and 13.4 mL of 2,6-lutidine (115.4 mmol) in 300 mL dry acetonitrile at -40°C was added dropwise a solution of 16.3 mL (115.4 mmol) of trifluoroacetic anhydride in dry acetonitrile. The mixture was stirred at - 40°C for 1 h. A solution of 15.6 g (57.5 mmol) of mercuric chloride in 300 mL water was added and the stirring was continued at 25°C for 2 h. The reaction mixture was diluted with 1.5 L of hexane and was washed three times each with 3% aqueous HCl, saturated aqueous $NaHCO_3$ and water. Drying over anhydrous $MgSO_4$ followed by solvent evaporation produced the crude product mixture. Flash chromatography on silica gel (elution with 10% EtOAc/hexane) gave 3.69 g (64% yield) of (R)-(+)-perillaldehyde and 1.96 g (21% yield) of vinyl sulphide **11**.



4

tlc: R_f = 0.22 (5% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

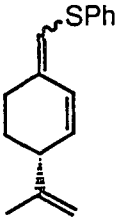
9.44 (s, 1 H), 6.84 (m, 1 H), 4.78 (s, 1 H),
4.74 (s, 1 H), 2.48-2.43 (m, 2 H), 2.31-2.03 (m, 3 H),
1.99-1.89 (m, 1 H), 1.77 (s, 3 H), 1.52-1.40 (m, 1 H).

IR (neat): 3125, 2975, 2860, 2760, 1705, 1670, 1450, 1405,
1190, 915 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 150(m^+(42.6),
135(26.5), 122(32.5), 121(25.2), 107(70.0), 93(55.0),
79(89.4), 68(100).

HRMS: for $C_{10}H_{14}O$ calculated 150.1045
found 150.0999.

Specific rotation: $[\alpha]_D^{18}$ = +128.6° ($CHCl_3$)



11

tlc: R_f = 0.57 (10% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

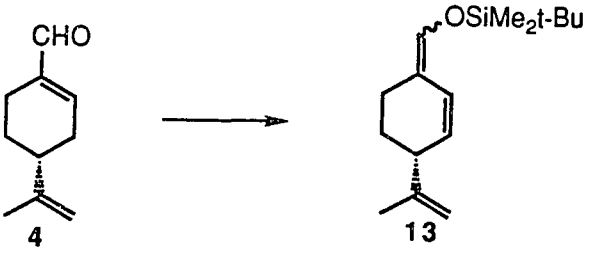
7.40-7.17 (m, 5 H), 6.19 (dd, J = 9.9, 2.2 Hz, 1 H), 6.07 (br s, 1 H), 5.70 (dd, J = 9.8, 3.3 Hz, 1 H), 4.82 (m, 1 H), 4.75 (m, 1 H), 2.91-2.88 (m, 1 H), 2.66-2.58 (m, 1 H), 2.39-2.29 (m, 1 H), 1.94-1.85 (m, 1 H), 1.76 (s, 3 H), 1.71-1.54 (m, 1 H).

IR (neat): 3120, 2990, 2905, 1610, 1510, 1470, 1110, 915, 765 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 242(m^+,28.6), 218(92.8), 133(m-SPh,28.6), 110(47.1), 109(100), 69(94.9).

HRMS: for $C_{16}H_{18}S$ calculated 242.1130

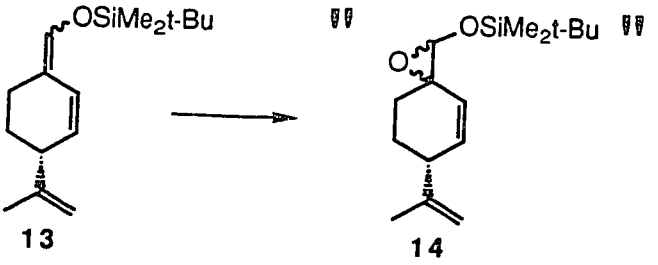
found 242.1130.



Preparation of the tert-butyldimethylsilyl enol ether 13 of (R)-(+)-perillaldehyde.

A solution of 7.00 g (46.7 mmol) of the aldehyde in 70 mL dry methylene chloride under an atmosphere of dry nitrogen was treated with 13.0 mL (93.4 mmol) triethylamine. The mixture was cooled to 0°C in an ice bath and 16.1 mL (70.0 mmol) tert-butyldimethylsilyl trifluoromethane-sulphonate was added slowly with good stirring. The ice bath was removed and the mixture allowed to warm to room temperature. When tlc indicated that no starting material remained, the mixture was diluted with hexanes and the lower density phase was removed from the oily triethylammonium triflate. This residue was washed several times with hexanes and the combined hexane portions were passed through a short pad of silica gel to remove the remaining triflate. Evaporation of the solvent in vacuo yielded essentially pure enol ether (by tlc analysis) which was used without further purification in the next reaction. The product was not characterized except by crude NMR and tlc.

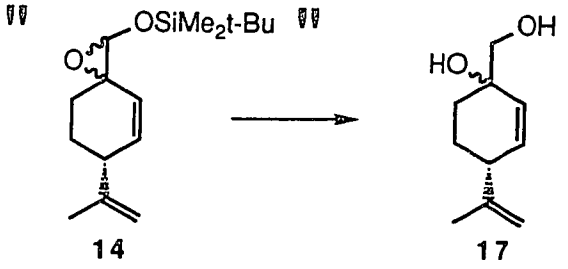
tlc: R_f = 0.39 (hexanes)



13 14

Epoxidation of enol ether 13.

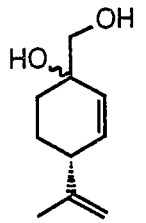
The enol ether **13** derived from perillaldehyde (assumed to be approximately 46.7 mmol) was taken up in 150 mL diethyl ether. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was stirred vigorously. A suspension of meta-chloroperoxybenzoic acid (11.0 g of approximately 80% pure, about 51 mmol) in diethyl ether was slowly added to the reaction mixture. The addition was stopped when tlc indicated the complete disappearance of the enol ether. The ether layer was washed twice each with saturated aqueous $NaHCO_3$ and Na_2SO_3 before drying over anhydrous $MgSO_4$. Evaporation of the ether gave the crude product which was not analyzed in any way, but was used directly in the next reaction.



14 17

Preparation of diol 17.

A solution of lithium aluminum hydride (70 mL of a 1 M solution in tetrahydrofuran, 70 mmol) in 100 mL dry tetrahydrofuran was cooled to 0°C under an atmosphere of nitrogen. A solution of the crude epoxidation product from the previous reaction in 50 mL dry tetrahydrofuran was added slowly via cannula and the ice bath was removed. The mixture was allowed to warm to room temperature and stirring was continued for 1 h. The reaction was worked up by addition of 12.0 g (280 mmol) sodium fluoride followed by slow addition of 3.80 mL (210 mmol) water. The mixture was stirred for 2 h after which time it was diluted with ether (500 mL) and washed twice with 3% aqueous HCl, once with brine, and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give the crude diol which was purified by flash chromatography on silica gel (elution with 20% EtOAc/hexanes). The yield was 5.17 g (66% from perillaldehyde) of pure diol as an inseparable mixture of diastereomers.



17

tlc: R_f = 0.25 (30% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$, mixture of diastereomers):
5.77-5.62 (m, 2 H), 4.72-4.58 (m, 2 H),
3.46-3.37 (m, 2 H), 2.70 (br s, 1 H),
2.62 (br m, 1 H), 2.70-2.55 (obscurred signal, 1 H),
1.83-1.42 (m, 4 H), 1.67,1.66 (s,s, 3 H).

IR (neat): 3380, 3095, 3040, 2950, 2870, 1640, 1450, 1370,
1215, 1080, 1040, 890 cm^{-1}.

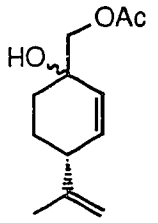
Mass spectrum (70 ev, m/e(intensity)): 168(m^+,0.7),
165(2.9), 150(m-H_2O,22.5), 138(19.3), 137(m-
CH_2OH,100), 119(21.5), 109(100).

HRMS: for $C_{10}H_{16}O_2$ calculated 168.1150
found 168.1134.
For $C_{10}H_{14}O$ calculated 150.1045
found 150.1032

17 5

Preparation of monoacetate 5 from diol 17.

The diol **17** (1.834 g, 10.92 mmol) was taken up in 20 mL dry methylene chloride under an atmosphere of nitrogen. Triethylamine (3.04 mL, 21.8 mL) was added followed by 1.23 mL (13.1 mmol) acetic anhydride dropwise. The mixture was stirred at room temperature for 24 h after which time tlc indicated that the starting material had been consumed. The reaction mixture was diluted with 50 mL methylene chloride and washed three times each with 3% aqueous HCl and saturated aqueous $NaHCO_3$ and once with distilled water. Drying over anhydrous $MgSO_4$ followed by removal of the solvent in vacuo yielded the crude monoacetate **5** which could be purified by flash chromatography (elution with 10% EtOAc/hexane). The yield was 2.165 g (94%) as a mixture of diastereomers which were not, in practice, separated except for analytical purposes.



5

tlc: Less polar diastereomer R_f = 0.32 (30% EtOAc/hexanes)

More polar diastereomer R_f = 0.25 (30% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$, less polar diastereomer):

5.83 (dd, J = 10.2, 2.3 Hz, 1 H),

5.72 (dd, J = 10.2, 1.3 Hz, 1 H), 4.81 (m, 1 H),

4.76 (s, 1 H), 4.04 (AB, 2 H), 2.73-2.68 (m, 1 H),

2.12 (s, 3 H), 2.00 (br s, 1 H), 1.86-1.60 (m, 4 H),

1.75 (s, 3 H).

^1H NMR (300 MHz, $CDCl_3$, more polar diasteromer):

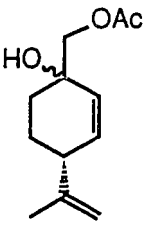
5.84 (dd, J = 10.1, 3.4 Hz, 1 H),

5.70 (dd, J = 10.1, 1.9 Hz, 1 H), 4.81 (m, 1 H),

4.67 (s, 1 H), 4.04 (AB, 2 H), 2.80-2.79 (m, 1 H),

2.12 (s, 3 H), 2.03 (br s, 1 H), 1.98-1.52 (m, 4 H),

1.75 (s, 3 H).



5

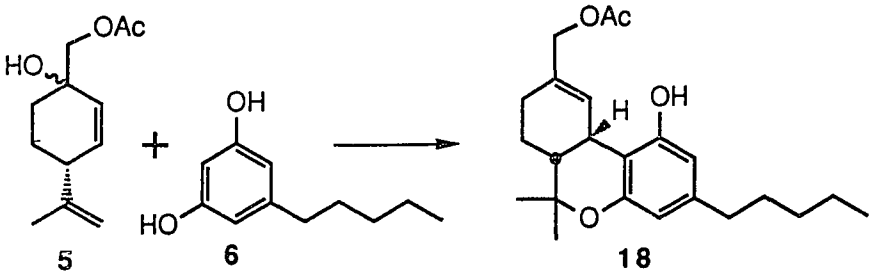
IR (neat, mixture of diastereomers): 3450, 3080, 3015, 2950, 2870, 1750, 1730, 1650, 1455, 1375, 1245, 1040 cm^{-1}.

Mass spectrum (70 ev, m/e, mixture of diastereomers): 210(m^+), 193(m-OH), 192(m-H_2O), 150, 137, 132, 117, 109(100).

HRMS (mixture of diastereomers):

for $C_{12}H_{18}O_3$ calculated 210.1256
found 210.1243.

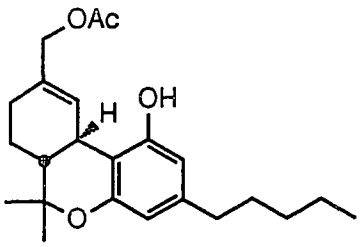
for $C_{12}H_{17}O_2$ calculated 193.1229
found 193.1202.



5 6 18

Preparation of (-)-11-nor-delta-9-THC-carbinol acetate 18.

A solution of the hydroxy acetate **5** (1.922 g, 10.98 mmol) and olivetol **6** (1.976 g, 10.98 mmol) in 10 mL dry methylene chloride was prepared and kept under an atmosphere of dry nitrogen. Anhydrous $MgSO_4$ (1.20 g, 10.0 mmol) was added portionwise and the mixture cooled to 0°C. To the stirring mixture was added borontrifluoride etherate (0.35 mL, 2.85 mmol) and the mixture stirred at 0°C for 2 h. Anhydrous $NaHCO_3$ (2.89 g) was added and the stirring continued for 0.5 h. The reaction mixture was filtered through a medium porosity glass frit and the solid washed with ether. The solvent was evaporated in vacuo and the resulting residue was purified by flash chromatography on silica gel (elution with 20% EtOAc/hexanes). The yield was 1.11 g (33%) of an oil which was predominantly the desired product.



18

tlc: R_f = 0.51 (50% EtOAc/hexanes)

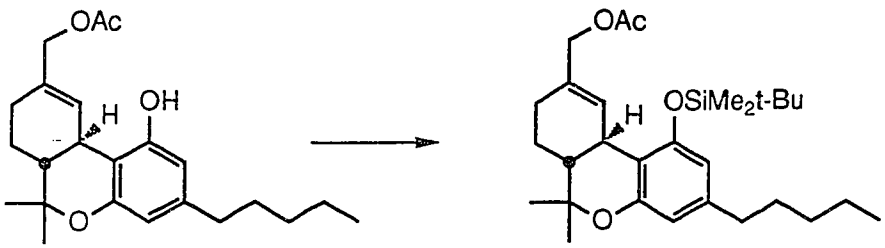
^1H NMR (300 MHz, $CDCl_3$):

6.76 (s, 1 H), 6.27 (d, J = 1.1 Hz, 1 H),
6.12 (d, J = 1.2 Hz, 1 H), 4.97 (s, 1 H),
4.48 (s, 2 H), 3.27 (br d, J = 10.9 Hz, 1 H),
2.40 (t, J = 7.7 Hz, 2 H), 2.27-2.21 (m, 2 H),
2.07 (s, 3 H), 2.00-1.94 (m, 1 H),
1.72 (dt, J = 10.8, 1.8 Hz, 1 H), 1.60-1.50 (m, 2 H),
1.42 (s, 3 H), 1.32-1.24 (m, 5 H), 1.10 (s, 3 H),
0.88 (t, J = 6.7 Hz, 3 H).

IR (neat): 3460, 3070, 2960, 2940, 2860, 1745, 1715, 1625, 1585, 1435, 1380, 1270, 1245 cm^{-1}.

Mass spectrum (70 ev, m/e): 373(m+1), 372(m^+), 313(m-OAc), 312, 297, 284, 269, 256, 244, 225, 208, 193, 150, 137.

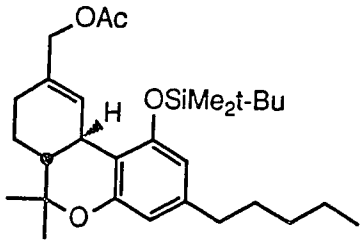
HRMS: for $C_{23}H_{32}O_4$ calculated 372.2301
found 372.2280.



18 **20**

Preparation of tert-butyldimethylsilyl ether 20.

To a solution of the monoacetate **18** (1.11 g, 2.98 mmol) and tert-butyldimethylsilyl chloride (1.35 g, 8.94 mmol) in dry N,N-dimethyl formamide was added 1.22 g imidazole (17.9 mmol) portionwise. The mixture was stirred at ambient temperature for 24 h and followed by tlc. When tlc indicated that the starting material had been consumed, the mixture was diluted with hexane and washed with three times with brine before drying over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave the crude silyl ether which was purified by flash chromatography on silica gel (elution with 5% EtOAc/hexanes) to give 822 mg of the pure product (19 % yield from hydroxy acetate **5**).



20

tlc: R_f = 0.44 (10% EtOAc/hexanes)

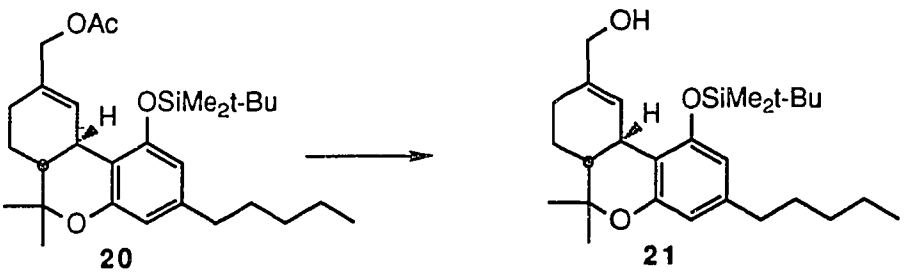
^1H NMR (300 MHz, $CDCl_3$):

6.71 (s, 1 H), 6.29 (d, J = 1.2 Hz, 1 H),
6.20 (d, J = 1.3 Hz, 1 H), 4.44 (AB q, 2 H),
3.16 (br d, J = 10.7 Hz, 1 H),
2.43 (t, J = 7.6 Hz, 2 H), 2.25-2.22 (m, 2 H),
2.05 (s, 3 H), 2.00-1.93 (m, 1 H),
1.69 (dt, J = 11.0, 1.7 Hz, 1 H), 1.58-1.53 (m, 2 H),
1.41 (s, 3 H), 1.35-1.25 (m, 5 H), 1.08 (s, 3 H),
0.99 (s, 9 H), 0.88 (t, J = 6.6 Hz, 3 H),
0.26 (s, 3 H), 0.15 (s, 3 H).

IR (neat): 2960, 2930, 2860, 1745, 1615, 1570, 1450, 1425, 1250, 1225, 845 cm^{-1}.

Mass spectrum (70 ev, m/e): 487(m+1), 486(m^+), 427, 426, 413, 369, 265, 207, 125, 123.

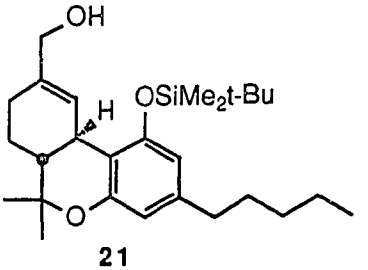
HRMS: for $C_{29}H_{46}SiO_4$ calculated 486.3165
found 486.3155.



20 21

Preparation of alcohol 21 from acetate 20.

To dry tetrahydrofuran (50 mL) under an atmosphere of nitrogen was added lithium aluminum hydride (1.69 mL of a 1 M solution in tetrahydrofuran, 1.69 mmol). The substrate (822 mg, 1.69 mmol) was added as a solution in tetrahydrofuran (10 mL) at 0°C and the ice bath removed. The mixture was stirred at ambient temperature for 1 h. The mixture was quenched carefully with brine and diluted with ether (200 mL). The organic layer was washed three times with 3% HCl and once with brine before drying over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave the crude alcohol which was purified by flash chromatography on silica gel (elution with 20% EtOAc/hexanes). The yield was 689 mg (92%).



21

tlc: R_f = 0.35 (30% EtOAc/hexanes)

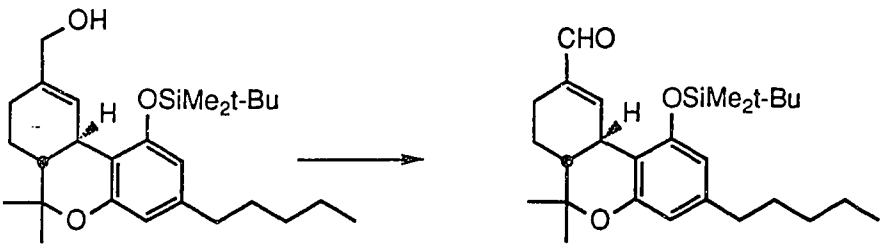
^1H NMR (300 MHz, $CDCl_3$):

6.67 (s, 1 H), 6.29 (d, 1.3 Hz, 1 H),
6.20 (d, J = 1.4 Hz, 1 H), 4.01 (s, 1 H),
3.99 (s, 1 H), 3.13 (br d, J = 10.5 Hz, 1 H),
2.44 (dd, J = 7.8, 6.8 Hz, 2 H), 2.31-2.28 (m, 2 H),
2.00-1.93 (m, 1 H), 1.67 (dt, J = 11.0, 1.8 Hz, 1 H),
1.60-1.50 (m, 3 H), 1.41 (s, 3 H), 1.35-1.25 (m, 5 H),
1.09 (s, 3 H), 1.00 (s, 9 H),
0.88 (t, J = 6.9 Hz, 3 H), 0.27 (s, 3 H),
0.15 (s, 3 H).

IR (neat): 3320, 2945, 2920, 2845, 1610, 1565, 1420, 1250, 1060, 840 cm^{-1}.

Mass spectrum (70 ev, m/e): 445(m+1), 444(m^+), 442, 426, 413, 387, 256, 149.

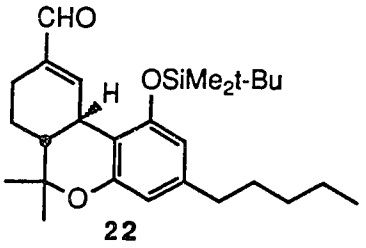
HRMS: for $C_{27}H_{44}SiO_3$ calculated 444.3060
found 444.3046.



21 22

Swern oxidation of alcohol 21 to aldehyde 22.

A solution of 0.85 mL (9.77 mmol) oxalyl chloride in 35 mL dry methylene chloride was cooled to -60°C under an atmosphere of dry nitrogen. A solution of 1.38 mL dimethyl sulphoxide (19.5 mmol) in 10 mL methylene chloride was added slowly via cannula and the mixture stirred for 5 min. The alcohol **21** (2.17 g, 4.89 mmol) dissolved in 10 mL methylene chloride was added slowly and the mixture stirred for 15 minutes. Triethylamine (5.44 mL, 39.1 mmol) was slowly added and the mixture stirred at -60°C for 5 min and at ambient temperature for 1 h. Water was added and the aqueous layer separated and reextracted with a small portion of methylene chloride. The combined organic extracts were washed twice each with 1% HCl, 5% Na_2CO_3, and once with distilled water before drying over anhydrous $MgSO_4$. The solvent was removed in vacuo to give the crude aldehyde which was almost pure and was used immediately in the next reaction.



22

tlc: R_f = 0.68 (20% EtOAc/hexanes)

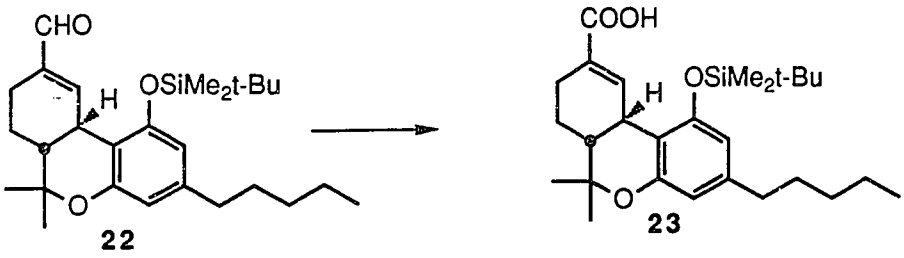
^1H NMR (300 MHz, $CDCl_3$):

9.44 (s, 1 H), 7.79 (s, 1 H), 6.32 (s, 1 H),
6.25 (s, 1 H), 3.37 (br d, J = 11.2 Hz, 1 H),
2.56-2.28 (m, 2 H), 2.46 (t, J = 7.2 Hz, 2 H),
2.08-2.01 (m, 1 H), 1.72 (t, J = 11.2 Hz, 1 H),
1.62-1.52 (m, 2 H), 1.44 (s, 3 H),
1.32-1.20 (m, 5 H), 1.12 (s, 3 H), 1.00 (s, 9 H),
0.89 (t, J = 6.4 Hz, 3 H), 0.31 (s, 3 H),
0.18 (s, 3 H).

IR (neat): 2960, 2940, 2860, 1690, 1620, 1570, 1425, 840 cm^{-1}.

Mass spectrum (70 ev, m/e): 443(m+1), 442(m^+), 439, 438, 423, 365, 350.

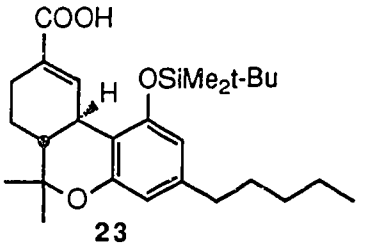
HRMS: for $C_{27}H_{42}SiO_3$ calculated 442.2903
found 442 2903.



22 **23**

Oxidation of aldehyde 22 to carboxylic acid 23.

To a mixture of the crude aldehyde **22** (assumed to be 4.89 mmol), 2-methyl-2-butene (11.1 mL, 105 mmol), saturated aqueous NaH_2PO_4 (6.7 mL), and tert-butanol (110 mL), was added 2.44 g (21.6 mmol) $NaClO_2$ portionwise with vigorous stirring. The reaction was stirred for several hours at ambient temperature after which time the mixture was extracted three times with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude acid as an oil. The crude material was subjected to flash chromatography on silica gel (elution with 10% EtOAc/hexanes). The yield of pure acid was 1.87 g (84% from alcohol **21**).



23

tlc: R_f = 0.32 (10% EtOAc/hexanes)

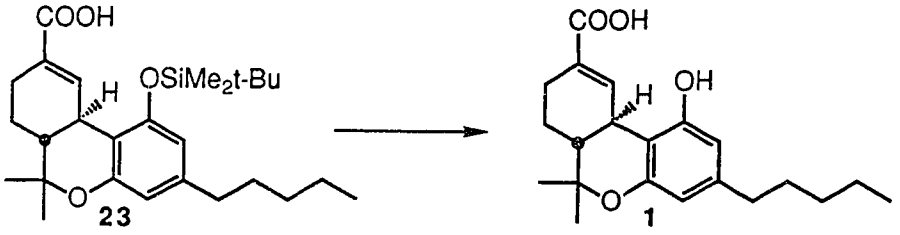
^1H NMR (300 MHz, $CDCl_3$):

8.04 (s, 1 H), 6.29 (s, 1 H), 6.23 (s, 1 H),
3.57 (br d, J = 10.0 Hz, 1 H), 2.56-2.38 (m, 2 H),
2.45 (t, J = 7.2 Hz, 2 H), 2.05-1.99 (m, 1 H),
1.70 (t, J = 11.5 Hz, 1 H), 1.61-1.48 (m, 2 H),
1.43 (s, 3 H), 1.35-1.23 (m, 5 H), 1.10 (s, 3 H),
0.99 (s, 9 H), 0.88 (t, J = 6.5 Hz, 3 H),
0.30 (s, 3 H), 0.17 (s, 3 H).

IR (neat): 3500-2500 (broad band), 2965, 2940, 2870, 1690, 1640, 1620, 1575, 1430, 845 cm^{-1}.

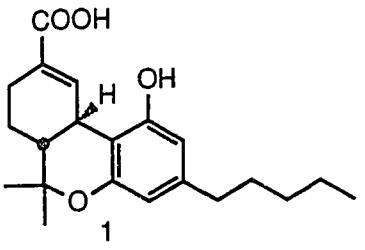
Mass spectrum (70 ev, m/e): 459(m+1), 458(m^+), 413, 402, 401, 373, 371, 249.

HRMS: for $C_{27}H_{42}SiO_4$ calculated 458.2853
found 458.2851



Preparation of (-)-11-nor-delta-9-THC-carboxylic acid 1.

To a solution of 93 mg (0.20 mmol) of silyl ether **23** in 5 mL dry tetrahydrofuran under an atmosphere of nitrogen was added tetra-n-butylammonium fluoride (0.4 mL of a 1 M solution in tetrahydrofuran, 0.4 mmol). The mixture was stirred at ambient temperature for 0.5 h after which time it was diluted with ether (25 mL), washed twice with brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave the crude hydroxy acid which was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexane). The yield was 66 mg (94%). The product could be further purified by recrystalization from ether/hexane.



1

tlc: R_f = 0.27 (30% EtOAc/hexane)

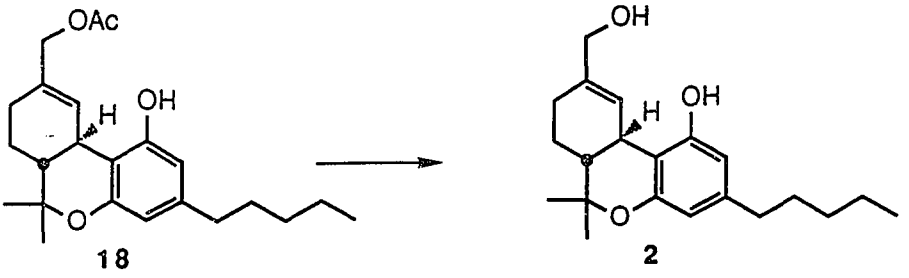
^1H NMR (300 MHz, $CDCl_3$):

8.10 (d, J = 1.8 Hz, 1 H), 6.29 (d, J = 0.9 Hz, 1 H),
6.13 (d, J = 1.2 Hz, 1 H), 4.83 (br s, 1 H),
3.39 (br d, J = 10.7 Hz, 1 H),
2.61-2.42 (m, 2 H), 2.45 (t, J = 8.8 Hz, 2 H),
2.07-1.97 (m, 1 H), 1.74 (dt, J = 11.2, 1.8 Hz, 1 H),
1.61-1.50 (m, 2 H), 1.44 (s, 3 H), 1.36-1.24 (m, 5 H),
1.12 (s, 3 H), 0.88 (t, J = 3.0 Hz, 3 H).

IR (neat): 3500-2500(broad band), 2955, 2930, 2850, 1685,
1625, 1580, 1425, 1260 cm^{-1}.

Mass spectrum (70 ev, m/e): 345(m+1), 344(m^+), 333, 312,
299, 297, 269, 244, 192.

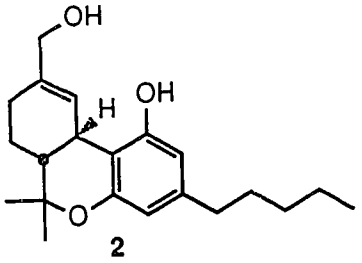
HRMS: for $C_{21}H_{28}O_4$ calculated 344.1988
found 344.1965.



18 2

Preparation of (-)-11-nor-delta-9-THC-carbinol 2.

A solution of lithium aluminum hydride (0.5 mL of a 1 M solution in tetrahydrofuran, 0.5 mmol) in 5 mL tetrahydrofuran was prepared under an atmosphere of dry nitrogen. The acetate **18** (123 mg, 0.33 mmol) in tetrahydrofuran (5 mL) was added slowly and the mixture stirred for one hour at ambient temperature. Sodium fluoride (84 mg, 2 mmol) was added followed by water (27 uL, 1.5 mmol) and the mixture was stirred for 2 h after which time it was filtered through a pad of celite. The filtrate was evaporated to give the crude alcohol which was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexanes). The yield was 69 mg (63%).



2

tlc: R_f = 0.37 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.69 (s, 1 H), 6.26 (s, 1 H), 6.13 (s, 1 H),
5.40-5.38 (br m, 1 H), 4.03 (s, 2 H),
3.25 (br d, J = 11.3 Hz, 1 H),
2.42 (t, J = 7.6 Hz, 2 H), 2.32-2.20 (br m, 2 H),
2.00-1.94 (m, 1 H), 1.74-1.62 (m, 2 H),
1.60-1.50 (m, 2 H), 1.42 (s, 3 H), 1.34-1.24 (m, 5 H),
1.10 (s, 3 H), 0.88 (t, J = 6.9 Hz, 3 H).

IR (neat): 3360, 3080, 2930, 2880, 2720, 1625, 1580,
1430, 995 cm^{-1}.

Mass spectrum (70 ev, m/e): 331(m+1), 330(m^+), 313, 312,
299, 297, 269.

HRMS: for $C_{21}H_{30}O_3$ calculated 330.2195
found 330.2190.

Specific rotation: $[\alpha]_D^{22}$ = -162.0 (c = 0.0027 g/mL).

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PART II:

THE TOTAL SYNTHESIS OF (d,l)-MORPHINE

INTRODUCTION

A. History of Opium and Morphine Development[1]

Since ancient times man has sought to control and lessen pain. The development of the first analgesic drug, opium, may have occurred over 4000 years ago. Indeed, seed capsules from the species Papaver somniferum L. (the poppy which is the principal source of morphine today) were found in the south of Spain and were dated at about 2500 B.C. A portrayal of a plant, with seed capsule, at the palace of Knossos in Crete (ca. 1600 B.C.) is the first indication of the use of opium in the eastern Mediterranian. Also in Crete is a figure of a goddess adorned with three incised poppy seed capsules (ca. 1400-1350 B.C.). It is thought that opium was used for religious and also medicinal purposes during this era. Ancient Egyptian prescriptions (ca. 1600 B.C.) are thought to make reference to the poppy. Translations of ancient Persian inscriptions, too, make reference to the use of opium.

Incision of the unripe seed capsule of the poppy species Papaver somniferum L. results in the emission of a milky fluid. When this fluid is air dried, it hardens to a

sticky dark mass known as opium. Long before any one alkaloid was isolated from opium, the analgesic used was an alcoholic solution (tincture) known as laudanum. In 1680, Thomas Sydenham, who is considered by many to be the father of modern English medicine, wrote that "among the remedies which it has pleased Almighty God to give man to relieve his sufferings, none is so universal and efficacious as opium."[2] A better drug for the general treatment of severe pain has yet to be developed.

The isolation of an opium constituent in crystalline form was first achieved by Parisian pharmacist Derosne in 1803.[3] By dilution of a syrupy opium extract with water and addition of potassium carbonate, he precipitated what he termed "the salt of opium." In 1804 Seguin presented a paper to the Institute of France describing the isolation of morphine. This work, however, was not published until ten years later.[4] It is Friedrich Wilhelm Serturner who is generally credited with the discovery of morphine in 1805.[5] Serturner understood that this new substance was basic and postulated that in addition to carbon, hydrogen and oxygen, this molecule contained nitrogen. He named his new compound morphium after the Greek god of dreams. This was the birth of alkaloid chemistry.

William Gregory[6] treated an extract of opium with a concentrated solution of calcium chloride, precipitating

calcium meconate, lactate and sulphate. The filtrate which was predominantly a solution of morphine and codeine hydrochlorides, was evaporated to give "Gregory Salt." Recrystallization and basification with ammonia precipitated morphine. This became a commercial process in 1833 and was used until a more efficient process was developed in 1960.

It soon became apparent that the analgesic quality of opium was due principally to morphine. In 1847, the correct composition of morphine was determined. The fact that morphine contains two hydroxyl groups was proven by preparation of its diacetyl derivative, heroin. By conversion to its methyl ether, codeine, morphine was shown to be a phenol. Most of the degradative work done toward elucidating the structure of morphine was in fact done using codeine due to its increased stability to the sometimes harsh degradation conditions.

Amazingly, in view of the limited analytical tools available, the correct gross structure of morphine was postulated in 1925 by Sir Robert Robinson.[7] The absolute configuration was not determined until the mid 1950s shortly before the full report of its total synthesis by Gates and Tschudi in 1956.[8] Thus the first total synthesis of morphine was accomplished about 150 years after its isolation from opium. It has been said that "the progress

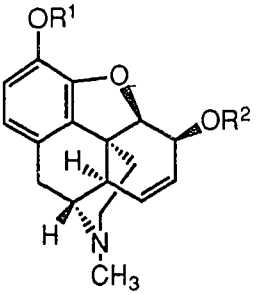
of this structural problem, culminating in the successful synthesis of morphine in 1952, represents in many ways a history in miniature of organic chemistry."[1b]

Finally it should be mentioned that Gates' impressive synthetic effort solved conclusively the structure of morphine which until that time was still in doubt. Gates apparently did not heed the words of Holmes who said, "Until such time as the constitution of morphine is settled, it is obviously impractical to attempt the complete synthesis of these alkaloids or to embark on a study of the stereochemical problem."[1e]

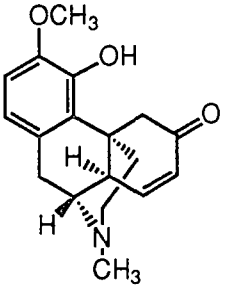
B. Some Common Opiates and Their Sources

Figure 1 shows the structures of several common opiate alkaloids. The opium from *Papaver somniferum L.* contains at least 50 alkaloids, the major constituent being morphine. The dried latex from another species of poppy, *Papaver bracteatum*, which does not contain morphine, contains 55% thebaine, a highly toxic opiate. Thebaine is in demand, however, as a starting material for many potent semisynthetic opiates. It is also convertable to codeine avoiding morphine as an intermediate, thus making conversion of this extract to heroin difficult. This species of poppy is attractive also because it may be grown

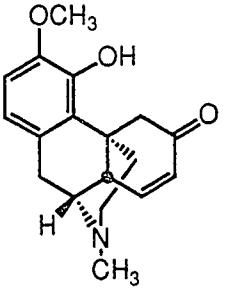
SOME COMMON MORPHINE-LIKE OPIATES



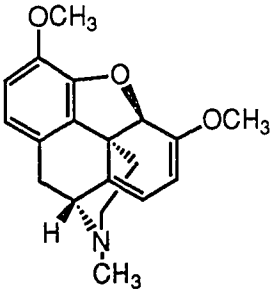
1 $R^1 = R^2 = H$: (-) - MORPHINE
2 $R^1 = CH_3$, $R^2 = H$: (-) - CODEINE
3 $R^1 = R^2 =$ ACETYL: (-) - HEROIN



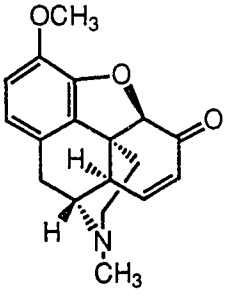
4 (-) - THEBAINONE



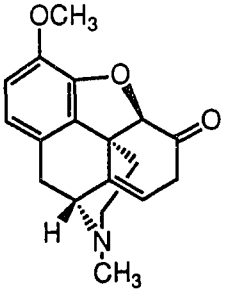
5 (-) - β - THEBAINONE



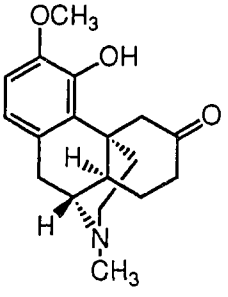
6 THEBAINE



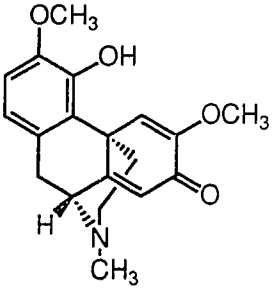
7 CODEINONE



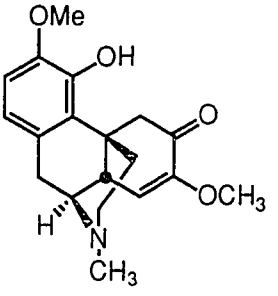
8 NEOPINONE



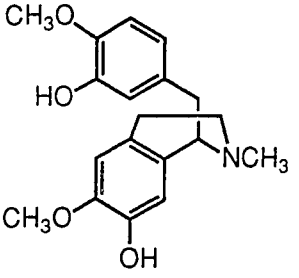
9 DIHYDROTHEBAINONE



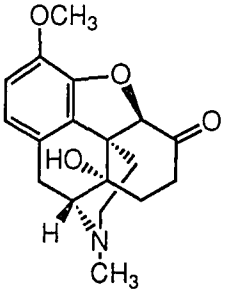
10 (+) - SALUTARIDINE



11 (-) - SINOMENINE



12 (+) - RETICULINE



13 OXYCODONE

FIGURE 1

in North America. For political reasons, however, this has been avoided.

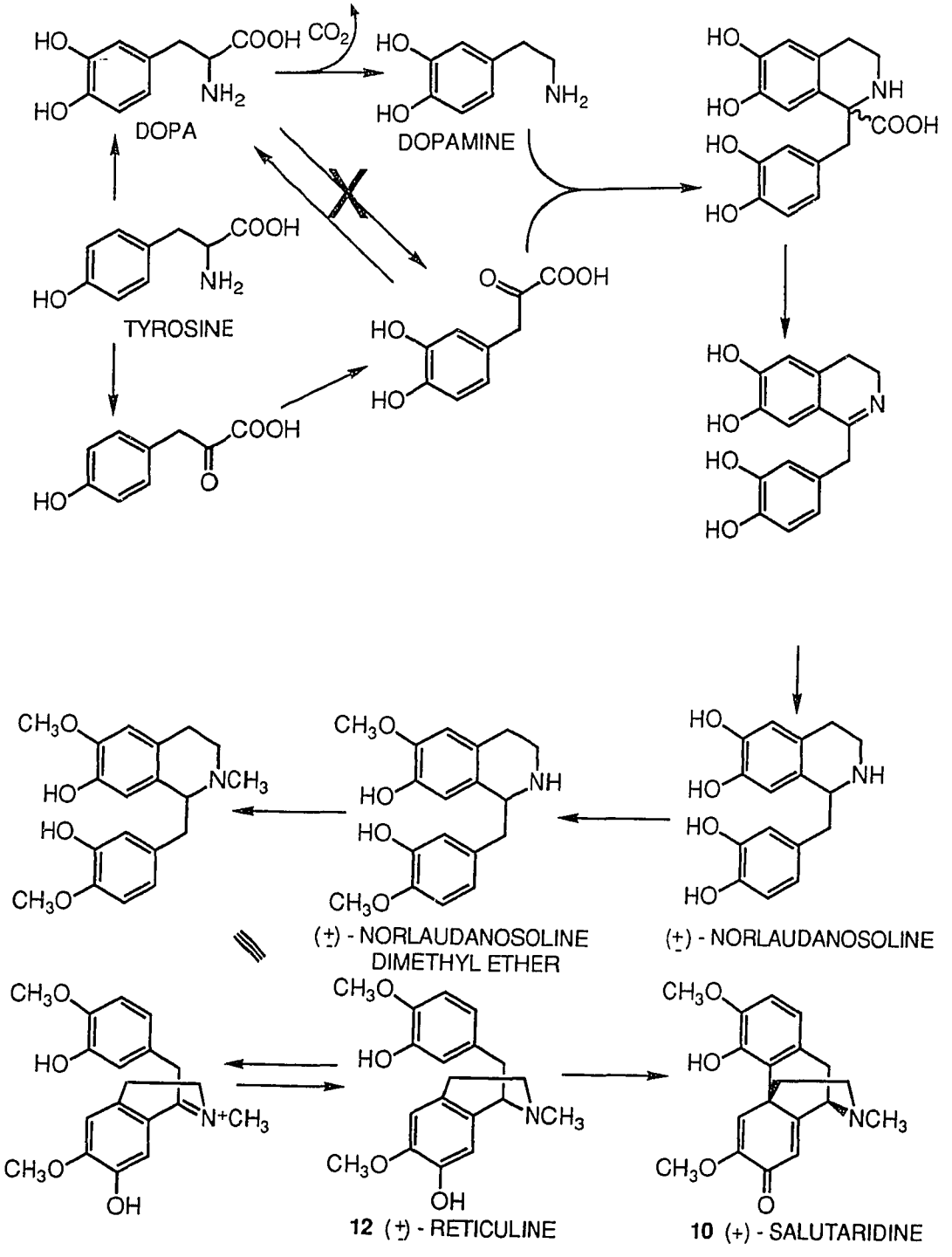
C. Use of Opiates

Codeine accounts for about 90% of U.S. opiate consumption. India and to a lesser extent Turkey provide most of the opium used in the world. The Soviet Union produces a significant crop of opium, but it is consumed domestically. In 1970, the United States consumed 23 metric tons of codeine. In 1980 that figure rose to approximately 50 metric tons. A partial crop failure in India, a Turkish ban on poppy growth (encouraged by the U.S.), and the U.S.S.R. becoming a net importer of opium, caused a near crisis in 1972-1973. This forced the U.S. to release portions of its strategic opium stockpile and to set production quotas. In 1985 the U.S. Drug Enforcement Agency quota for domestic import and production of codeine was 54 million grams and for morphine was 59 million grams (most of which was for conversion to other products).

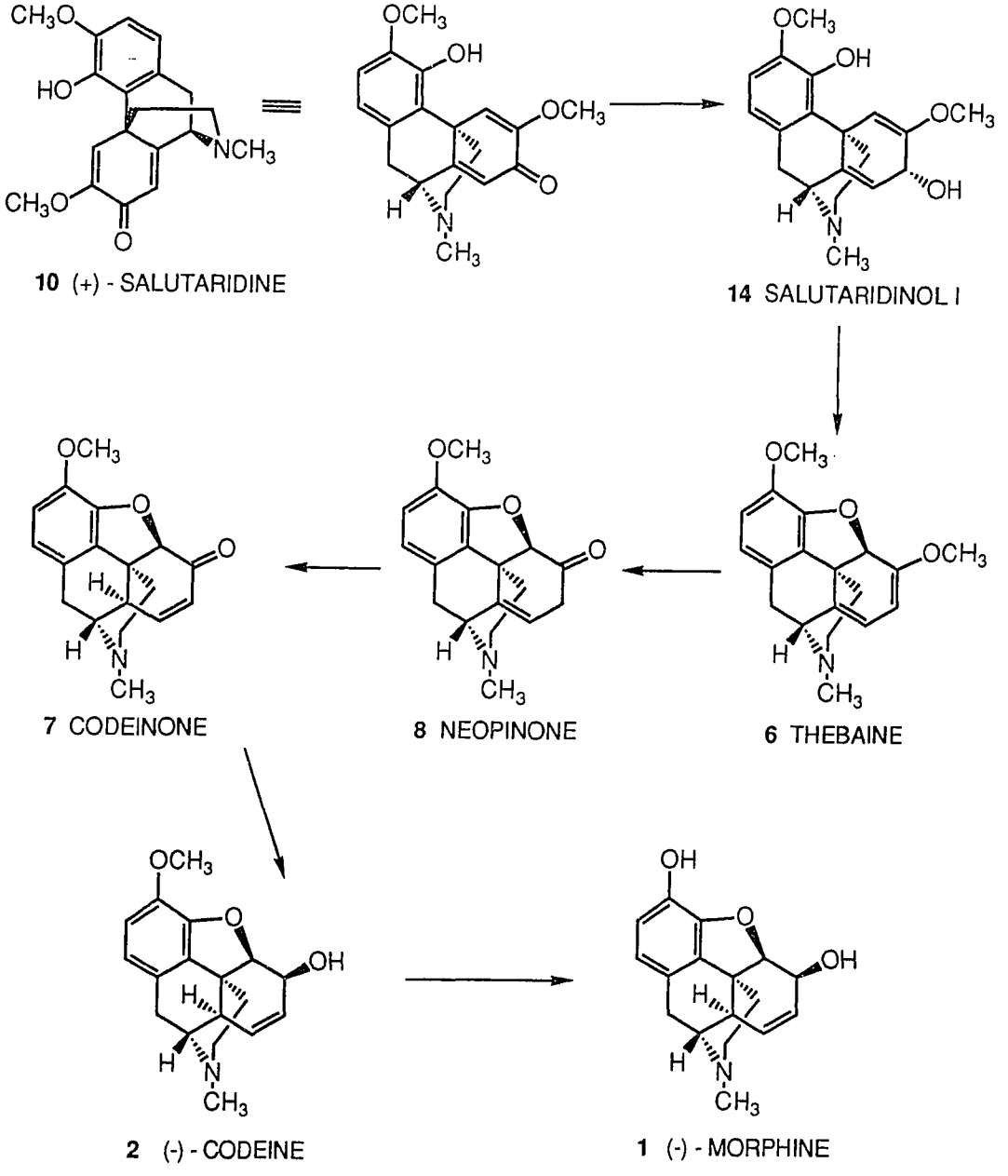
D. The Biosynthesis of Morphine

The biosynthesis of morphine will not be discussed in detail, however Scheme 1 illustrates morphine biosynthesis

SCHEME 1: BIOSYNTHESIS OF MORPHINE



BIOSYNTHESIS OF MORPHINE (CONT'D)



from tyrosine precursors.[1a] The disconnection of Salutaridine **10** to Reticuline **12** forms the basis for many of the wholly synthetic approaches.

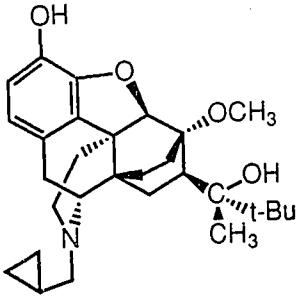
E. Opiate Research Today

Although morphine is unequalled as a general analgesic, it is not without its drawbacks. Side effects include respiratory depression, constipation, nausea and vomiting, and a lowering of the blood pressure. Death by overdose is usually attributed to respiratory arrest. The most serious drawback is, of course, the well known addictive quality of morphine. This, coupled with a developing tolerance for the drug, makes morphine a dangerous drug of abuse. As chronic use continues, more of the drug is necessary to acheive the euphoric effect which accompanies the analgesia. In the non-tolerant patient, however, 10 - 15 mg is sufficient in the treatment of all but the most severe pain. The goal of today's opiate research is to find a drug which possesses the desirable qualities of morphine but which lacks the deleterious side effects.

The volume of research related to morphine (and opiates in general) is enormous and rapidly expanding. The areas include medicinal chemistry, pharmacology, drug design, and synthetic chemistry.

The field of synthetic chemistry as it relates to opiate research may be divided into two main areas: semisynthetic approaches and totally synthetic approaches.

In a semisynthetic approach one starts with a naturally occurring material closely related in structure to the target molecule and modifies it through a series of chemical transformations. This approach has yielded much information in terms of structure-activity relationships as well as providing some useful and some potentially useful drugs. Probably the biggest success to date is the development of buprenorphine **15**[1b].

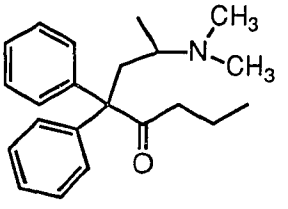


15

Buprenorphine is one of many analogues arising from a Diels-Alder reaction with a thebaine derived material participating as the diene. It shows promise as a useful drug for several reasons: It is about 50 times more potent than morphine as an agonist, it shows strong antagonist activity, and the effects are long lasting. An interesting feature of this drug is its bell shaped dose-response curve. This effect is particularly important with respect to respiratory depression. For very high doses of buprenorphine the amount of respiratory depression (the

cause of death in the case of morphine overdose) is lower than at some lower doses. This gives this drug a high level of safety.

In a totally synthetic effort, one is concerned with devising a new strategy for assembling the morphine molecule (or potentially useful fragments thereof) from commercially available and relatively inexpensive starting materials. A total synthesis of morphine or a related opiate may yield important analogues since the minimum structural requirements for opiate activity seem to be relatively simple. This is evidenced by the high analgesic potency (twice that of morphine) of methadone **16**. In addition, as one carries out a total synthesis of morphine



16

it is inevitable that more will be learned about the chemical reactivity of these systems. New synthetic strategies and methodologies may be developed which could be useful not only for the synthesis of morphine-like alkaloids but for other, structurally unrelated natural products as well.

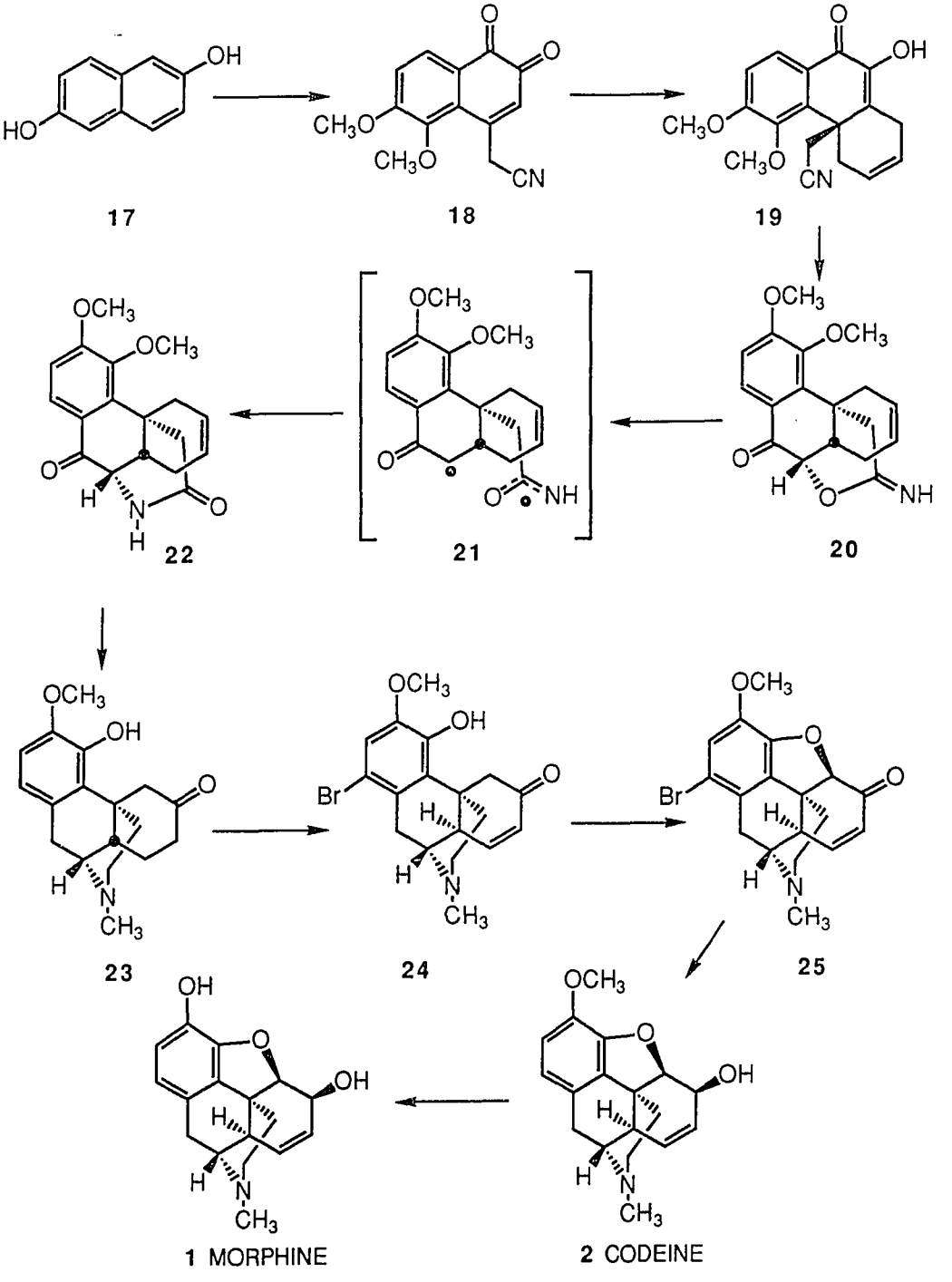
F. Previous Synthetic Efforts

There is a huge body of published research that concerns synthetic efforts directed toward the synthesis of morphine and related alkaloids. In reviewing the past synthetic work in this area, it will, of course be necessary to pass over some valuable contributions to this field. What follows is meant to illustrate the synthetic strategies used to prepare the morphine like alkaloids. Entire synthetic schemes will not be shown; only the key disconnections will be shown. The arrows shown in the schemes do not necessarily represent a single synthetic operation and reagents will not be discussed except where pertinent to the discussion.

1. Gates and Tschudi (1952)

Scheme 2 illustrates the pioneering synthesis of morphine by Marshall Gates and Gilg Tschudi.[8] The A and B rings were obtained by the elaboration of dihydroxy naphthalene **17**. The resulting intermediate **18** underwent a Diels-Alder reaction with 1,3-butadiene to give **19** thus adding the C ring. The nitrogen heterocycle was formed by treating **19** with hydrogen gas and copper chromite. This reaction presumably proceeds by saturation of the enolic double bond, formation of imino lactone **20** and a free

SCHEME 2: THE FIRST SYNTHESIS OF MORPHINE
GATES (1952)

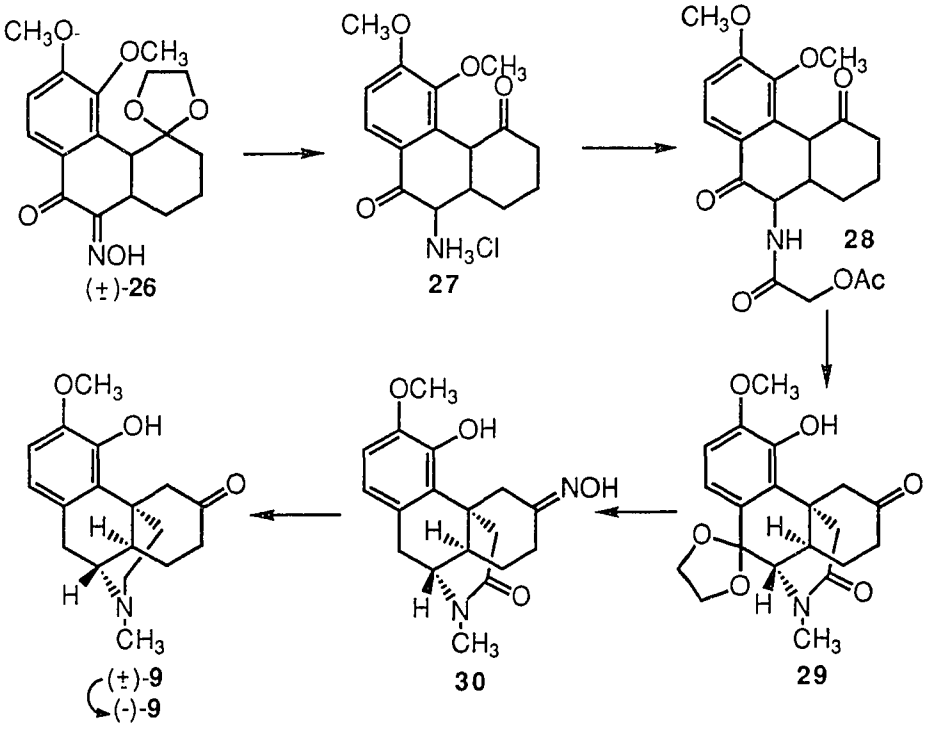


radical rearrangment (via **21**) to give lactam **22**. The required cis ring fusion was obtained by converting ketone **23** (optically active via resolution) to **24** thus labilizing the C-13 hydrogen (see figure 2 for morphine numbering). The oxide bridge was formed by resaturation of the enone, formation of the dibromoketone 2,4-DNP and reforming the ketone functionality yielding **25**. Conversion of **25** to morphine was straightforward. The overall yield for this synthesis was 0.0035%.

2. Ginsburg and Elad (1954)

Two years after Gates' initial report of his morphine synthesis, Ginsburg reported a somewhat different approach[9] which resulted in the synthesis of dihydrothebainone and a formal total synthesis of morphine. Phenanthrene based intermediate **26** (Scheme 3) was prepared in a straightforward manner. Conversion of the oxime to an amino functionality gave **27** and acylation gave alpha-acetoxy amide **28**. During a ketalization reaction, **28** unexpectedly, but serendipitously lost a molecule of acetic acid and formed **29**. Oximation, hydrolysis of the ketal and reductive removal of the two free carbonyl groups gave **30**. The conversion of **30** to dihydrothebainone **9** which was resolved to the natural antipode was uncomplicated. Ginsburg stopped at this point and Gates was cited for the final conversion to morphine.

SCHEME 3: GINSBURG (1954)



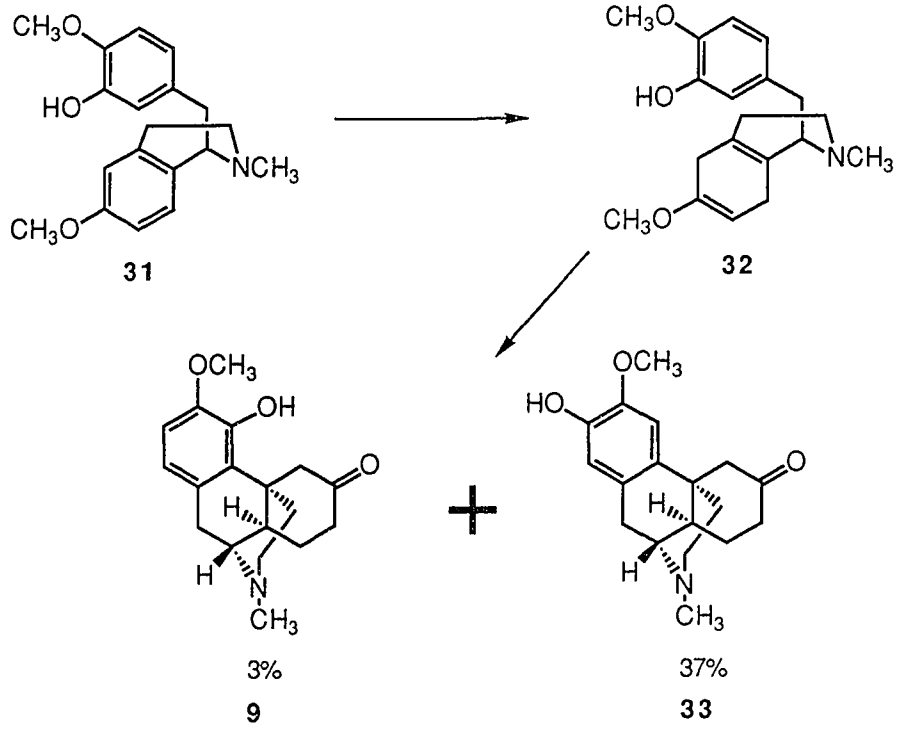
3. Morrison et. al. (1967)

Although Morrison and co-workers are generally credited with a formal total synthesis of morphine,[10] essentially the same work was published by Grewe,[11] also in 1967. In fact, Morrison uses Grewe's method to arrive at key precursor **31**. Scheme 4 shows the conversion of **31** to dihydrothebainone by Morrison and co-workers. Birch reduction of **31** yields cyclohexadiene **32** which, under the conditions of hydrolysis of the enol ether, cyclizes to give only 3% of the desired dihydrothebainone **9** along with 37% of the structural isomer **33**. The only difference in

the work published by Grewe is that 85% phosphoric acid was used to effect the cyclization. Grewe obtained both the same yield and ratio of products as Morrison. Grewe also found that changing the substituents on nitrogen prior to cyclization resulted in the production of the undesired structural isomer (similar to **33**) as the sole product. Gates is cited for the conversion of **9** to morphine.

The above cyclization reaction is generally referred to as a Grewe cyclization and provides the basis for the impressive efforts of Rice (discussed later in this section).

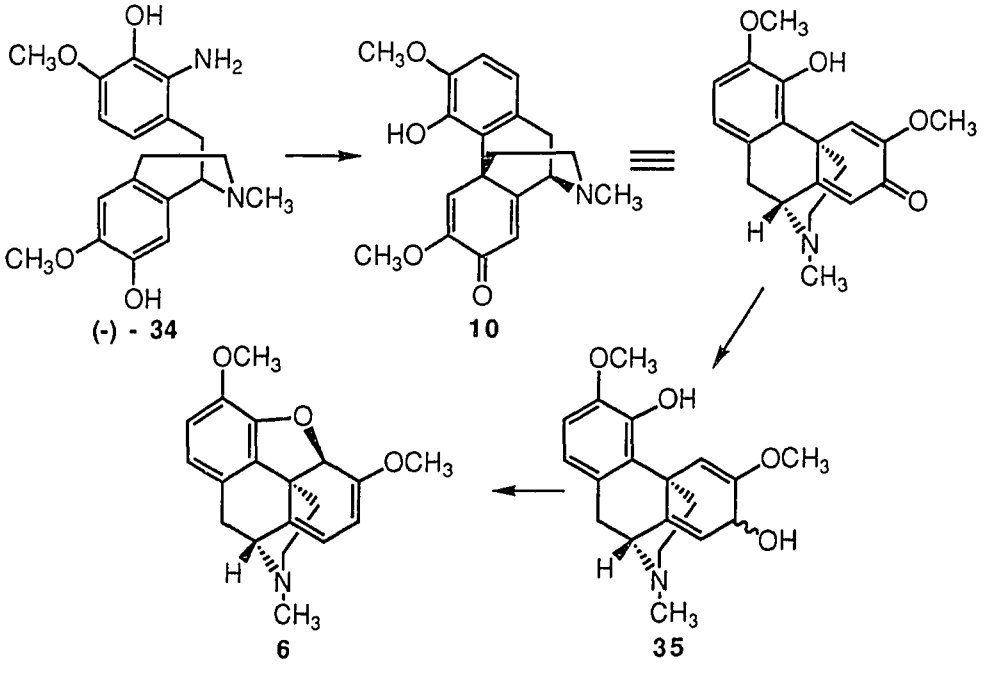
SCHEME 4: MORRISON (1967)



4. Kametani et. al. (1969)

In a strategy which makes use of a disconnection similar to that of Morrison, the Pschorr ring closure is employed to assemble the morphinan skeleton (Scheme 5).[12] The known aminoreticuline derivative **34** (the racemic mixture of this compound was resolved to give the (-) antipode) was diazotized and decomposed thermally to give salutaridine **10** in 1.1% yield. Reduction gave a mixture of salutaridinols I and II **35** which was treated with acid to produce optically active thebaine. Since the conversion of thebaine to morphine was known,[8a] this resulted in a formal total synthesis.

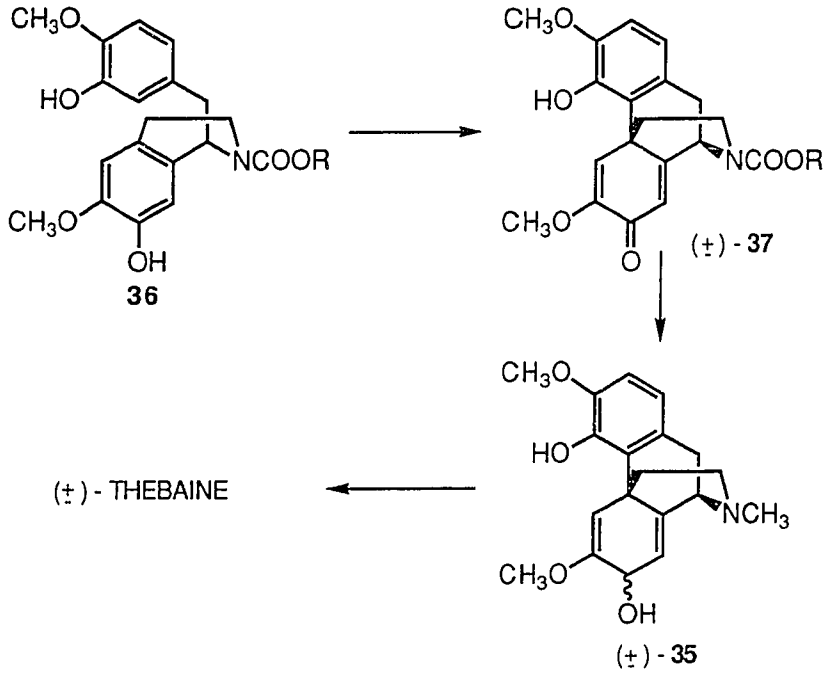
SCHEME 5: KAMETANI (1969)



5. Schwartz et. al. (1975)

A biomimetic approach similar in principle to that of Kametani was employed by Schwartz and co-workers.[13] In this route (Scheme 6), a suitably protected reticuline **36** was directly oxidized with thallium trifluoroacetate to give the protected salutaridine **37** in 23% yield. Reduction led to a mixture of salutaridinols I and II **35** which was converted to thebaine, resulting in a formal total synthesis of morphine. Barton had earlier explored a similar method[14] but was able to achieve only an 0.03% yield of salutaridine **10** by direct oxidation of reticuline. This approach also forms the basis of a total synthesis of codeine by White.[15]

SCHEME 6: SCHWARTZ (1975)



6. Rice (1980)

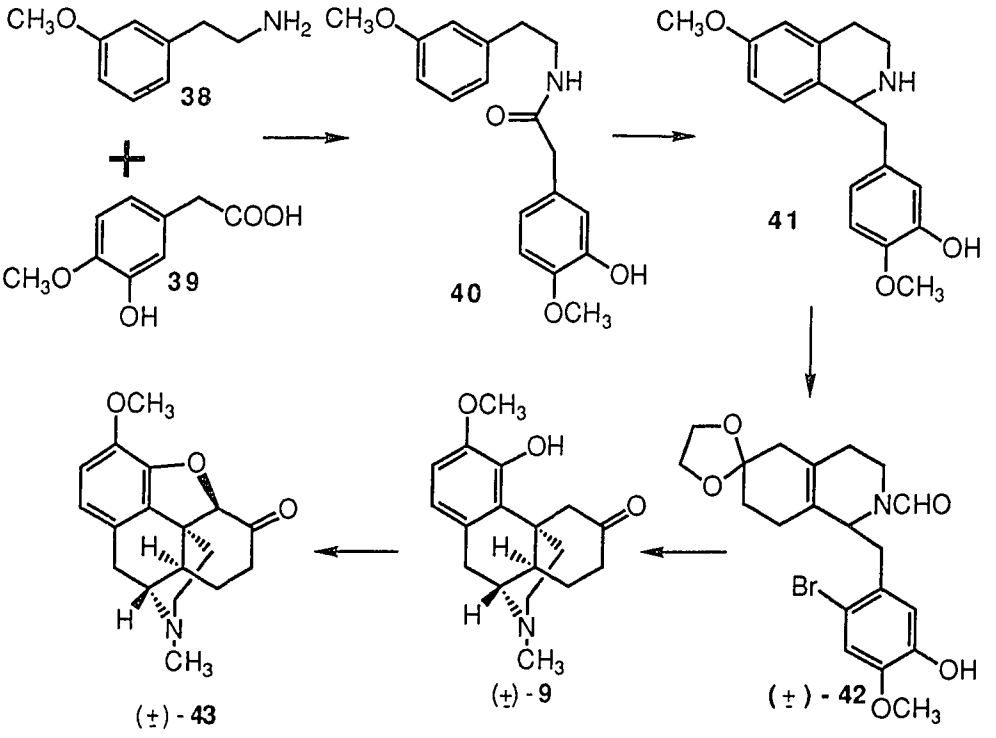
An approach which made use of a Grewe cyclization was reported by Rice (Scheme 7).[16] Although this work is similar in principle to the routes of Morrison and Grewe (Scheme 4), key modifications make this synthetic scheme an impressive accomplishment and a valuable contribution.

Condensation of phenethyl amine **38** with acid **39** yielded amide **40**. An aromatic substitution reaction with a reductive workup yielded a nor-reticuline type compound **41**. Birch reduction, protection of the carbonyl and amino groups, and bromination of the dioxygenated aromatic ring gave **42**. Bromination was necessary in order to direct Grewe cycliztion to the desired position of the aromatic ring. Indeed, cyclization took place in 60% yield to produce the desired morphinan. Subsequent classical transformations led to dihydrothebainone **9** and dihydrocodeinone **43**. The overall yields of **9** and **43** were 37% and 29% respectively. This, then, has the potential of becoming a commercial process as only six intermediates were isolated.

7. Evans et. al. (1982)

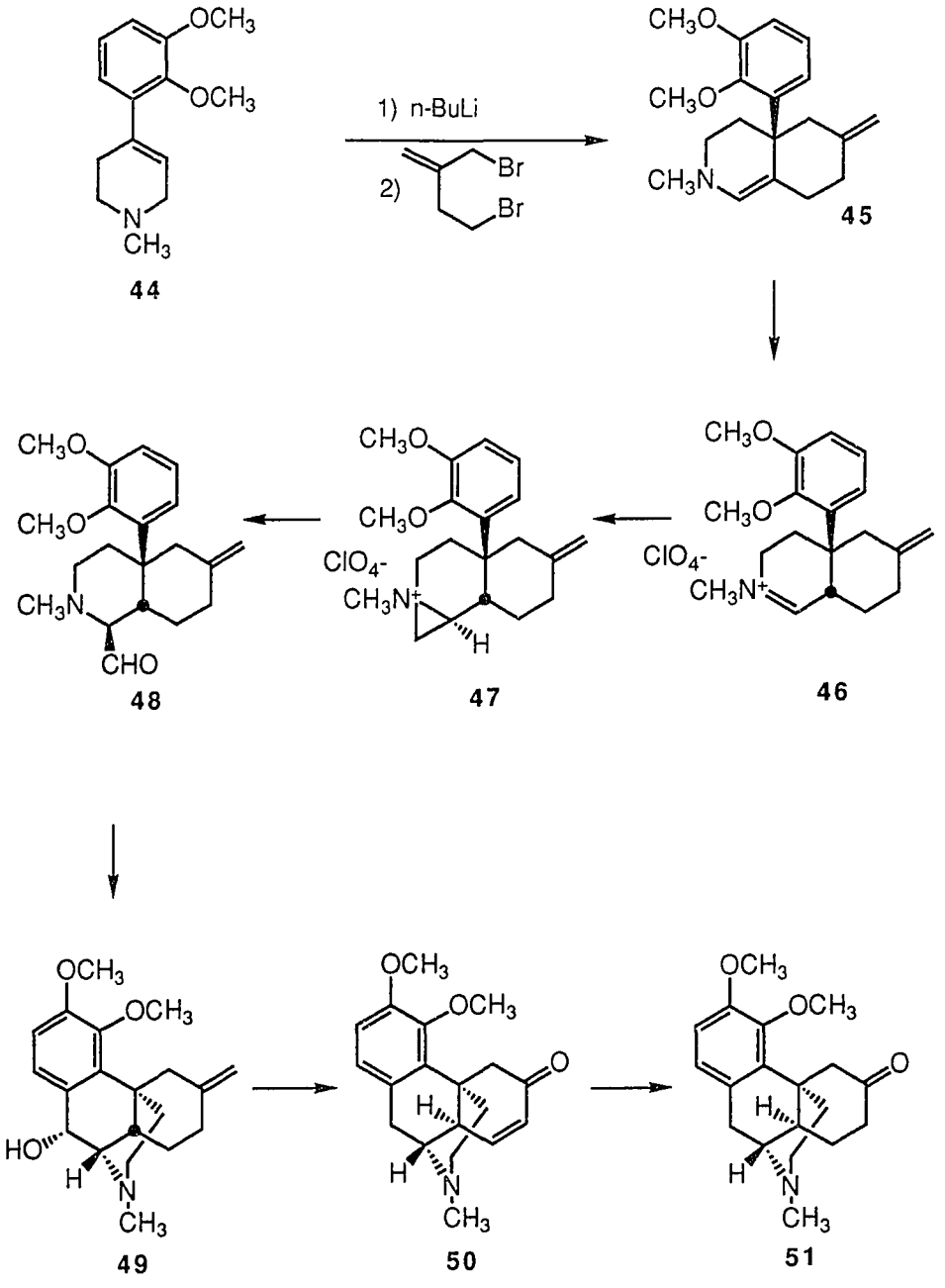
In a completely novel strategy, Evans and co-workers made use of a metallated enamine methodology developed by them (Scheme 8).[17] Metallation of **44** followed by reaction

SCHEME 7: RICE (1980)



with a suitable dibromide gave amine **45**. Conversion to imminium perchlorate **46** followed by treatment with diazomethane gave the cyclopropyl ammonium salt **47**. Reaction with DMSO yielded aldehyde **48** which underwent an electrophilic substitution reaction to produce morphinan **49**. Subsequent classical transformations produced thebainone methyl ether **50** and dihydrothebainone methyl ether **51** which had been converted to morphine by Gates. This represents a formal total synthesis of racemic morphine. Rapoport, in his codeine synthesis[18] and McMurry, in his synthetic efforts[19] used approaches resembling this one.

SCHEME 8: EVANS (1982)

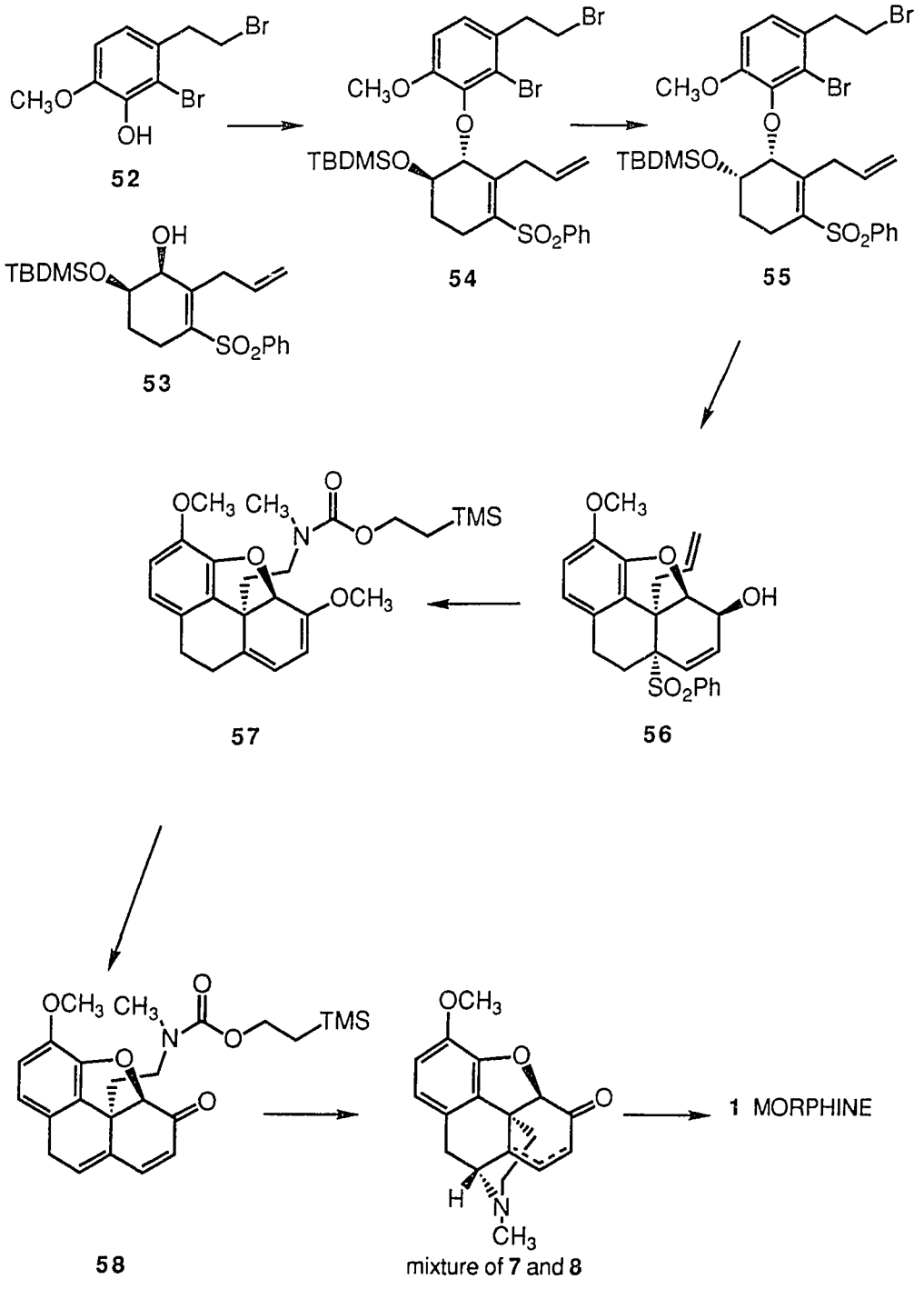


8. Fuchs et. al. (1987)

An interesting route to the morphine alkaloids was reported by Fuchs and co-workers.[20] This approach (Scheme 9) exploits the ability of vinyl sulphoxides to act as Michael acceptors. The result is an elegant one-pot formation of the A, B, and C rings of the morphine skeleton, including the 4,5-oxide bridge.

Phenol **52** was prepared from iso-vanillin while alcohol **53** was derived from 2-allylcyclohexane-1,3-dione. Mitsunobu coupling of **52** and **53** gave a good yield of ether **54**. The stereochemistry of the silyloxy group was inverted to give **55**. Treatment of **55** with n-butyllithium resulted in a halogen-metal exchange on the aromatic ring followed by conjugate addition to the vinyl sulphone. The resulting sulphur stabilized anion then displaced the primary bromide, yielding **56** in 63% yield. The terminal alkene was converted to an aminoethyl appendage and the delta-hydroxy sulphone was converted to an extended enol ether resulting in **57**. DDQ oxidation of **57** gave dienone **58** which upon removal of the carbamate protecting group underwent 1,6-addition to yield a mixture of neopinone **8** and codeinone **7**. Conversion of this mixture to morphine was accomplished using known methods.

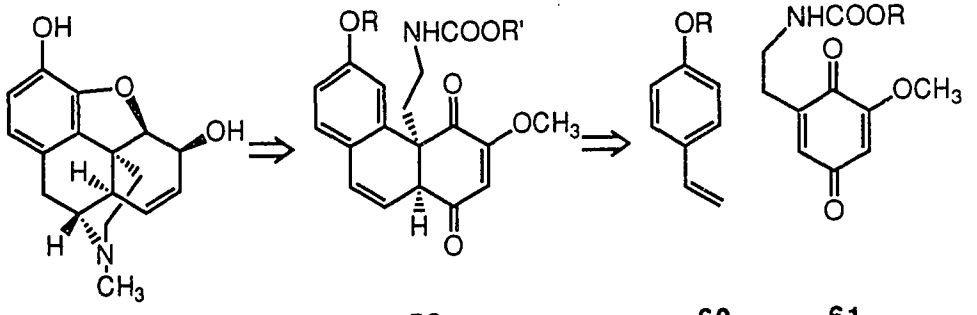
SCHEME 9: FUCHS (1987)



G. A Diels-Alder Synthesis of Morphinan Alkaloids

1. Original Retrosynthetic Analysis

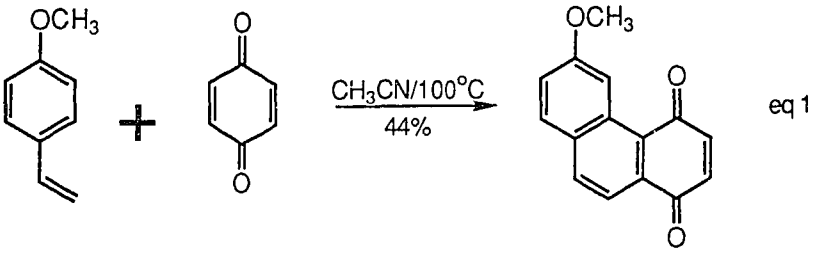
Disconnection of the two heterocyclic rings of morphine can lead to an intermediate such as **59**. This may be thought of as arising from the Diels-Alder reaction of a quinone **61** with a styrene **60** acting as a diene. These types of reactions do have precedent in the case in which the quinone is unsubstituted.



1 **59** **60** **61**

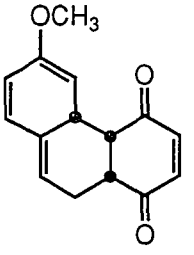
2. Model Study

Phenanthroquinone **64** was prepared in 44% yield by heating styrene **62** with a threefold excess of 1,4-p-benzoquinone **63** (eq 1). Presumably, the excess quinone is responsible for the further oxidation of putative intermediate adduct **65**. The exact mechanism of this type of reaction is unclear. In any event, when applied to **60** and **61**, no products resembling **59** were recovered. Instead



62 63 64

only starting materials were recovered with some decomposition material appearing after heating for prolonged periods.

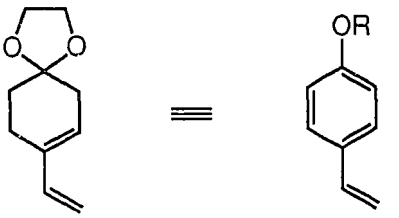


65

3. Reevaluation of the Retrosynthesis

The failure to obtain even small amounts of a desired adduct caused us to rethink our retrosynthetic strategy. A diene was needed which could serve as an equivalent to the styrene. A likely candidate appeared to be diene **66**,

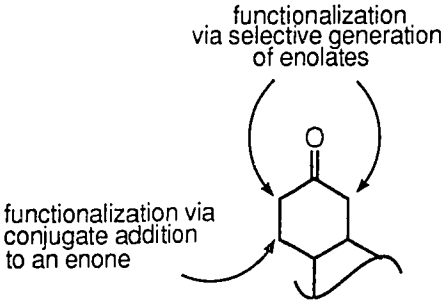
available in two steps from the commercially available 1,4-cyclohexanedione-mono-ethylene ketal. Of course, after the cycloaddition reaction, the future A ring of morphine would have to be aromatized.



66 60

It is perhaps not surprising that all of the previous synthetic efforts directed toward the synthesis of morphine and related alkaloids have used aromatic precursors. The disconnection of an aromatic ring to an alicyclic precursor is not normally considered advantageous. It occurred to us that there might be some advantages to exploring a route in which the A-ring was aromatized at an intermediate stage in the synthetic sequence. Although there are many ways to functionalize an aromatic moiety, the methods are sometimes incompatible with sensitive functionality. On the other hand, there exists a plethora of methods for mildly functionalizing carbocyclic ketones. Subsequent aromatization of variously functionalized ketones could lead to opiate analogues which possess a variety of

aromatic substituents. Since the aromatic moiety is important in binding to the opiate receptor, aromatic substitution could prove interesting.

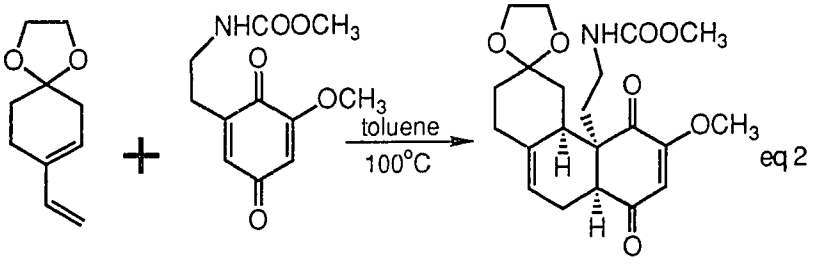


Any new route to morphine opens the door to a series of heretofore unknown analogues. In this route, one might envision the preparation of polyhydro morphinans (non-aromatic analogues). The activity of these types of compounds (not necessarily as opiates since the aromatic ring is thought to be important for this activity) could be explored.

4. A Novel Total Synthesis of Thebainone and Beta-Thebainone: A Formal Total Synthesis of Morphine

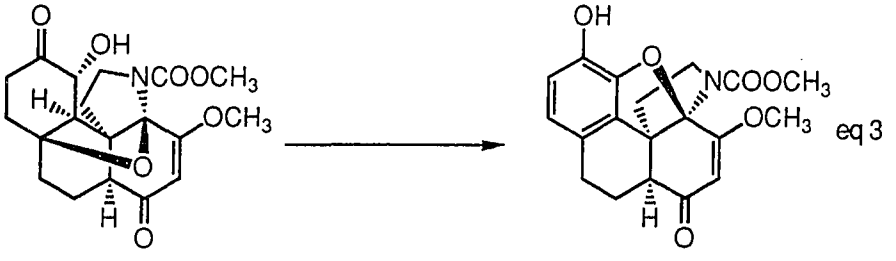
The next chapter details the preparation of racemic thebainone and beta-thebainone which constitutes a formal total synthesis of morphine.

Diels-Alder adduct **68** was prepared by the thermal reaction of diene **66** with quinone **67** (eq 2). This reaction was highly regio- and diastereofacially selective. Note that **68** contains all of the carbon atoms of morphine.



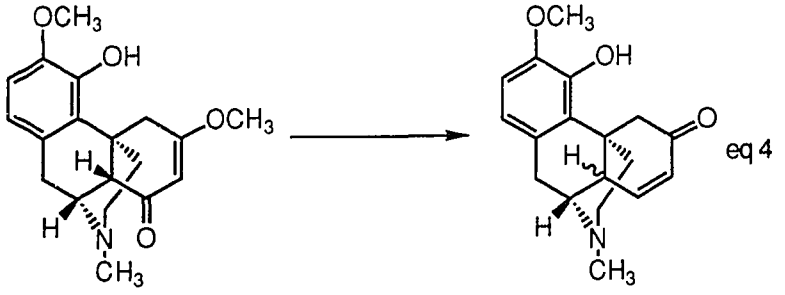
66 **67** **68**

Through a series of reactions, acyloin **69** was prepared from adduct **68**. Oxidation to the corresponding diketone and treatment with a Lewis acid resulted in the rearrangement to the aromatic compound **70** (eq 3).



69 **70**

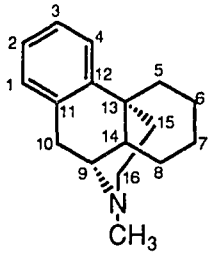
Several functional group manipulations converted **70** to morphinan **71** which was converted to beta-thebainone and thebainone in a straightforward manner (eq 4). As mentioned, Gates has converted both of these morphinans to morphine in his pioneering effort.[8]



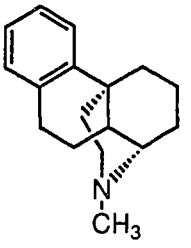
71 **4** H = α **5** H = β eq 4

An interesting feature of this work is that in addition to the morphinan skeleton **I** (figure 2), two previously unknown classes structural analogues were prepared. Structures **II** and **III** differ from the morphinan system only in the attachment of the nitrogen bridge. In structure **II** the amino group is attached to C-8 while in **III** it is attached to C-5. The activity of these types of compounds appears to be unknown.

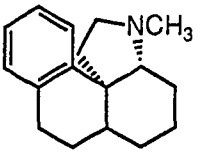
MORPHINAN ISOMERS



I



II



III

FIGURE 2

While working toward this total synthesis, new and important methodology has been developed which could be useful for the synthesis of other morphinan alkaloids as well as targets which are structurally unrelated. In addition, information about the chemical reactivity of structures closely related to the morphinan system has been obtained. Given the considerable activity in the area of opiate chemistry, this information should be very useful.

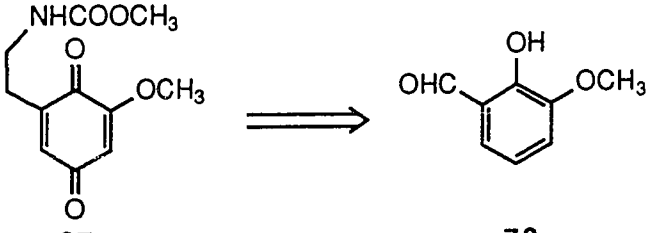
We have approached the synthesis of morphine from a strategic angle unlike any reported. What has resulted, is a first generation synthesis. With some modifications this could become a useful approach to many alkaloids of the morphinan class as well as analogues thereof.

DISCUSSION

A. Assembly of the Carbon Skeleton via a Diels-Alder Reaction

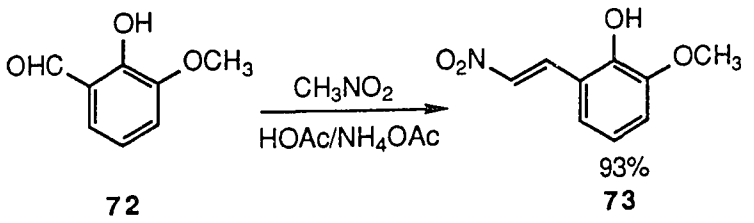
1. Synthesis of the Dienophile

The target dienophile was a quinone bearing an aminoethyl side chain (or an equivalent thereof). Retrosynthesis of quinone **67** can lead to ortho-vanillin **72**.[22] This quinone was chosen because it seemed to possess an oxygenation pattern suitable for the formation of the C-ring of the



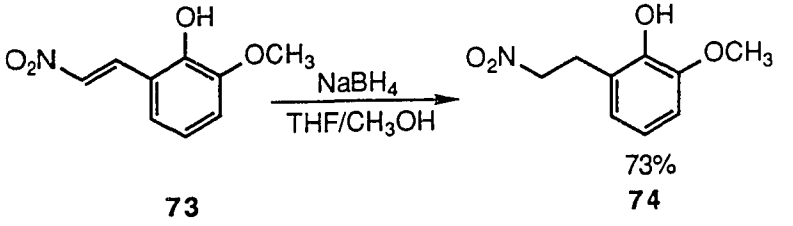
67 **72**

morphine molecule. The putative aminoethyl appendage was attached via an acid catalyzed condensation[23] of nitromethane with ortho-vanillin (eq 5). Nitrostyrene **73** was obtained in 93% yield. The crude product appeared to be a single compound by ^{1}H NMR.



72 73 eq5

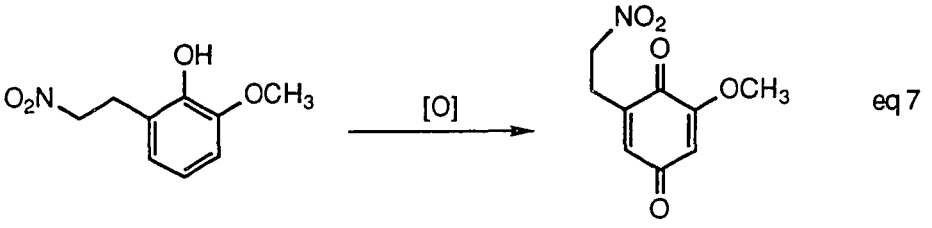
Direct reduction of the nitroalkene to an alkylamino moiety was unsuccessful under a variety of reaction conditions which included lithium aluminum hydride,[24] nickel boride catalyzed sodium borohydride,[25] and borane-tetrahydrofuran.[26] The phenolic hydroxyl group of **73** appeared to be participating in the reaction, forming what was thought to be some kind of cyclized material. This compound was not characterized. When **73** was treated with sodium borohydride in methanolic THF,[27] reduction to the



73 **74** eq6

nitroalkane **74** took place in 73% yield (eq 6). Again, reduction of the nitro group of **75** to an amino group was troublesome in the presence of the unprotected phenolic hydroxyl group.

In light of this difficulty, it was felt that oxidation of **74** to the corresponding quinone **75** (eq 7) would yield a dienophile which would be suitable for the construction of the carbocyclic framework of morphine. The nitroethyl group present in the Diels-Alder adduct could be elaborated into the required aminoethyl appendage at a later stage in the synthetic sequence.



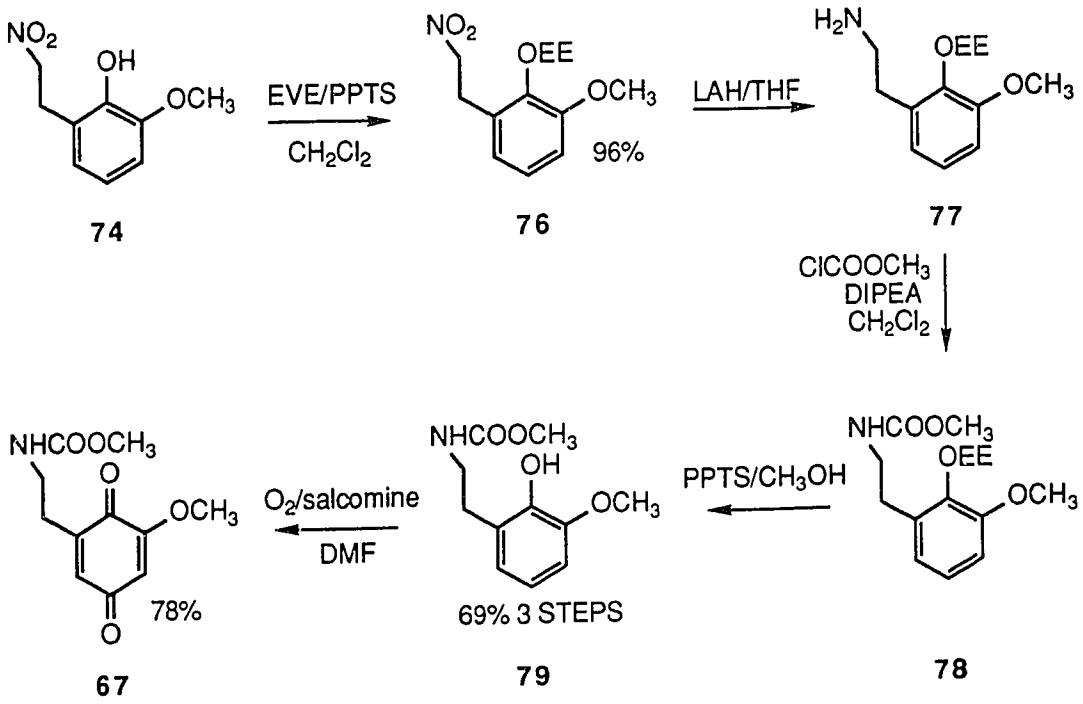
74 **75** eq 7

A variety of reaction conditions were employed in an attempt to effect the oxidation shown in eq 7. Such methods included: 1) Jones' reagent[28] 2) chromium trioxide/ acetic acid[29] 3) ruthenium trichloride/hydrogen peroxide[30] and 4) molecular oxygen/salcomine[22,31] in a variety of solvents. The yields ranged from 0 to 26%. It seemed odd

that the use of molecular oxygen and salcomine failed to produce a reasonable yield of this seemingly simple quinone since these conditions have enjoyed considerable success in reports by others.[22] A search of the literature revealed that salcomine (N,N'-bis(salicylidene)ethylenediamino cobalt(II)) binds oxides of nitrogen irreversibly.[31a] It seemed that our substrate was, in fact, poisoning the catalyst. The nitroethyl sidechain of **75** was not a suitable equivalent of the aminoethyl appendage.

Scheme 10 shows the conversion of phenol **74** to quinone **67**, a suitable dienophile for our purposes.[22] Protection of the phenolic hydroxyl group as the ethoxyethyl ether gave **76** in 96% yield. Reduction of the nitro group of **76** with lithium aluminum hydride,[32] protection of the resulting primary amine **77** as its carbomethoxy derivative **78**, and hydrolysis of the ketal protecting group gave phenol **79** in a yield of 69% over three steps. Generally, amine **77** and carbamate **78** were not purified prior to the next synthetic step. Oxidation of phenol **79** to the desired quinone **67** with molecular oxygen and salcomine[31,22] was straightforward and proceeded in 78% yield. The overall yield of **67** from ortho-vanillin was 35%. The high yield of each step and the relatively uncomplicated chemistry involved allowed for the preparation of large quantities of **67**.

SCHEME 10

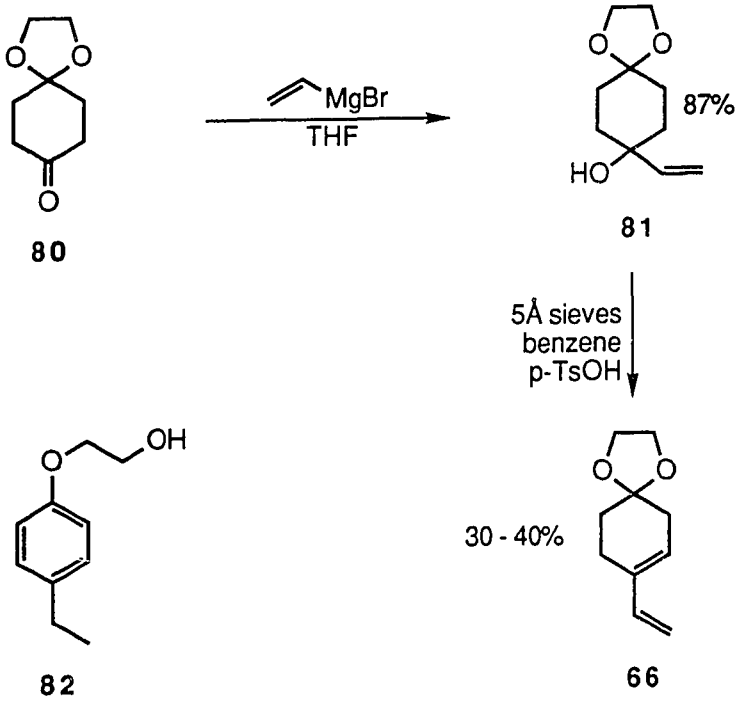


2. Synthesis of Diene

Scheme 11 illustrates the preparation of a suitable diene for Diels-Alder reaction with quinone **67**. 1,4-Cyclohexanedione-mono-ethylene ketal **80** is an article of commerce. Treatment of **80** with vinylmagnesium bromide gave allylic alcohol **81** in 87% yield. Dehydration gave a disappointing but synthetically useful yield of the desired diene **66**. A variety of reaction conditions were employed including: 1) methanesulphonyl chloride/triethylamine 2) phosphorous oxychloride/pyridine[33] 3) trifluoromethanesul-

phonic acid anhydride/triethylamine 4) pyrolysis of the trifluoroacetate and 5) 5 A molecular sieves/benzene.[34] The decision of which method to use was based on convenience. Dehydration with molecular sieves and catalytic p-toluenesulphonic acid in benzene gave yields ranging from 30 to 40% on a synthetically useful scale. On a small scale the yields were much better. The unexpectedly low yields were attributed to participation of the of the ketal moiety in cationic rearrangements. Similar alcohols

SCHEME 11



80 81 82 66

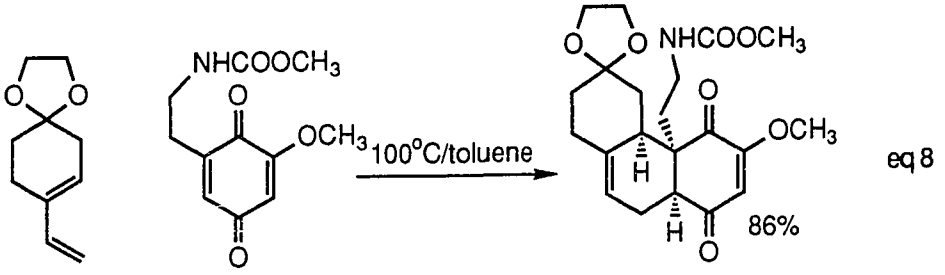
lacking the ketal moiety have been dehydrated cleanly.[34] An indication that the ketal protecting group may be the

source of the disappointing yields was given by the isolation of byproduct **82** when phosphorous oxychloride and pyridine were used.

Although the overall yield of the diene was low, the short synthetic route and the ease of the reactions allowed for the preparation of useful quantities of material.

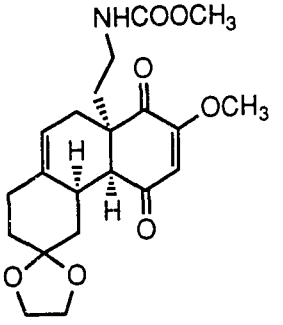
3. Diels-Alder Reaction

The Diels-Alder reaction between quinone **67** and diene **66** was uncomplicated. When the two were heated at 100°C in toluene (eq 8), a single compound, **68**, was isolated in 86%



66 **67** **68** eq 8

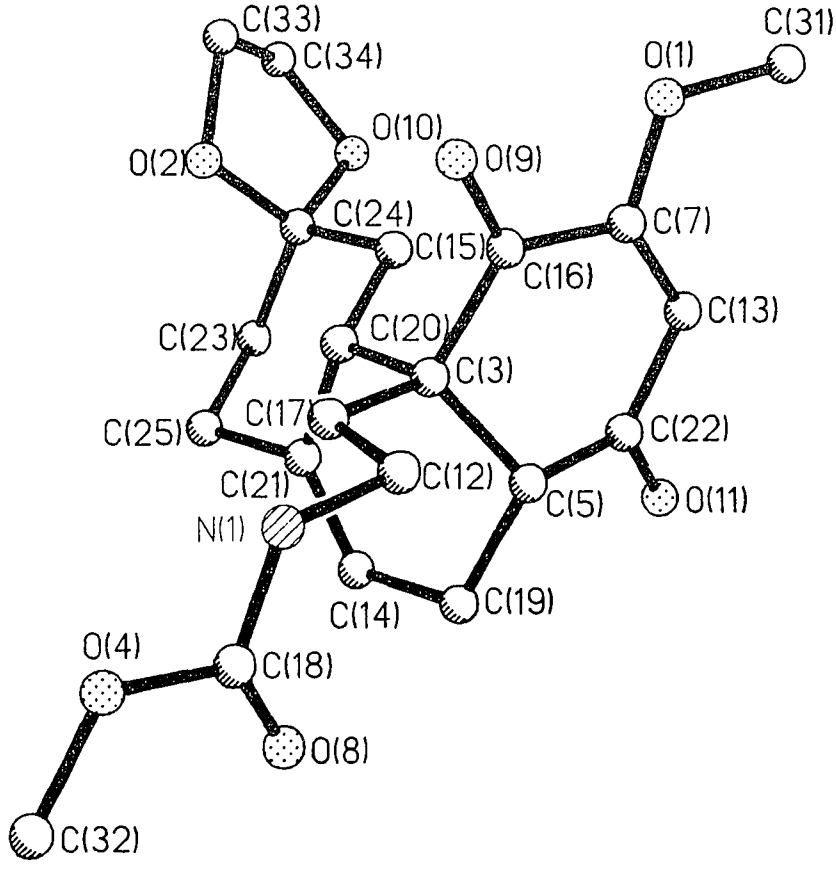
yield. Note that **68** is the reaction product resulting from endo addition. No detectable amount of regioisomer **83** was formed. Although this reaction was expected to be be chemoselective for the non-oxygenated double bond of **67**, the high degree of regio- and diastereoselectivity was



83

unexpected. There is, however, precedence[22] for this type of reactivity in closely related systems. The identity of the product was confirmed by single crystal X-RAY diffraction. A three dimensional representation of the adduct is shown in figure 3. This molecule possesses the carbon framework of the morphine alkaloids.

X-RAY STRUCTURE OF 68



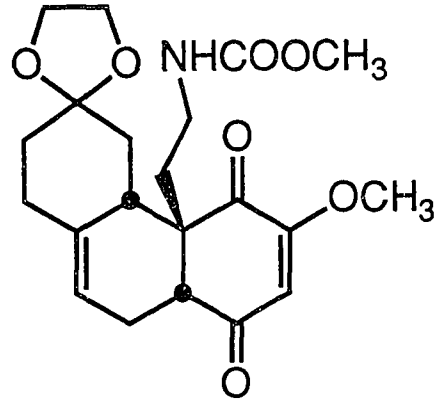
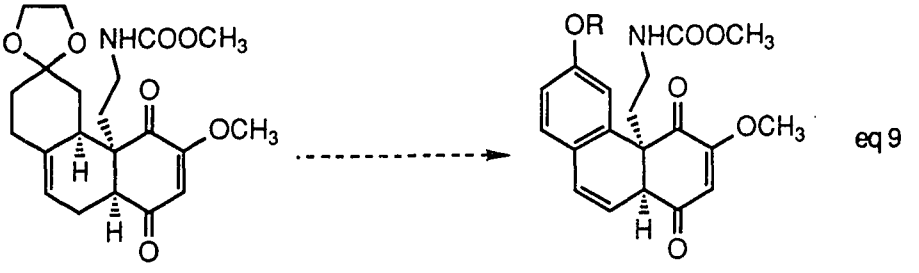


FIGURE 3

B. Aromatization of the A-Ring

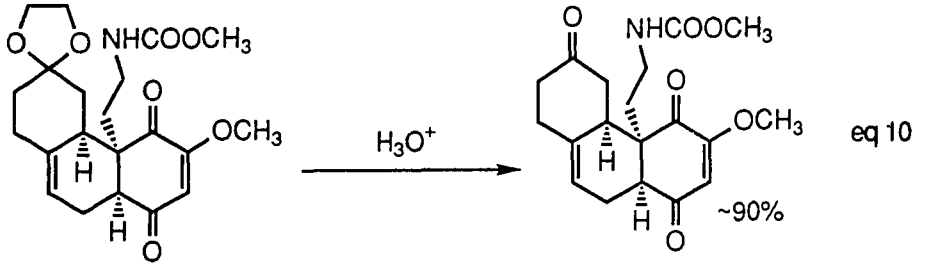
1. Attempted Aromatization of the Diels-Alder Adduct

Having assembled the carbon skeleton of morphine, the task at hand was to convert the alicyclic A-ring of adduct **68** to an aromatic moiety (eq 9).



68 eq 9

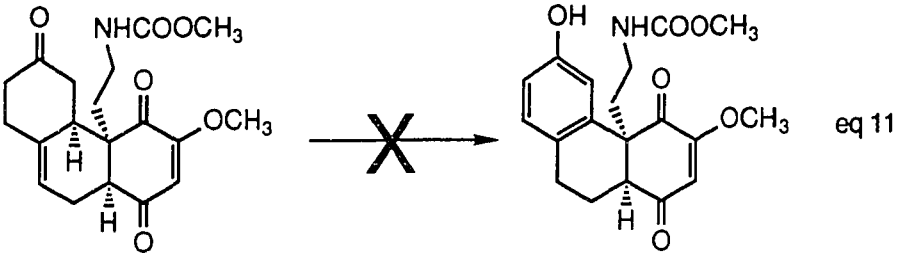
Hydrolysis of the ketal protecting group of Diels-Alder adduct **68** gave ketone **84** in good yield (eq 10).



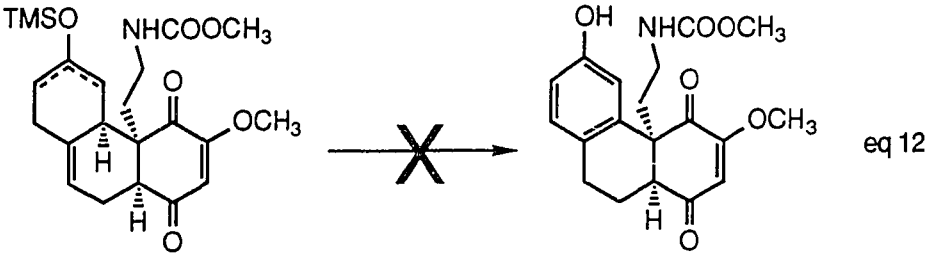
68 **84** eq 10

It was felt that aromatization of the A-ring could be done in two ways: 1) direct dehydrogenation of ketone **84** or 2) introduction of functional groups to **84** which upon elimination would give the required additional degrees of unsaturation.

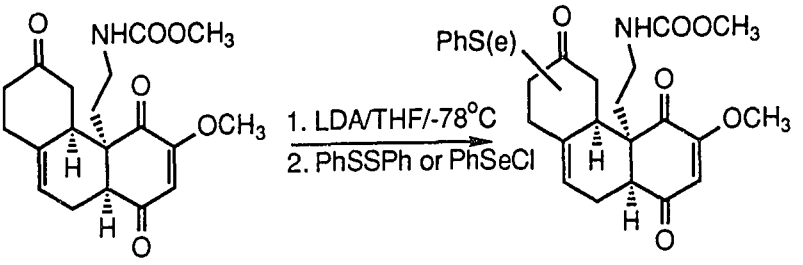
The ketone was treated with DDQ[35] in benzene (eq 11) but no aromatic product was isolated. The trimethylsilyl enol ethers **85** were treated with palladium acetate and diallyl carbonate[36] (eq 12) with no success. Attempts to selenate[37] or sulphenylate[38] **84** (eq 13) led to complicated mixtures. There appeared to be some desired products from this reaction, however attempted elimination of the thio- or selenophenyl moieties gave unrecognizable material.



84 eq 11

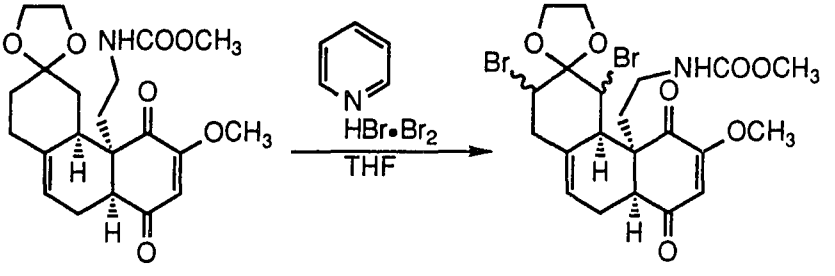


85 eq 12



84 eq 13

Bromination of the Diels-Alder adduct **68** directly with pyridinium bromide perbromide[39] gave what appeared to be dibromo ketal **86** (eq 14). This reaction was relatively clean but attempts to introduce unsaturation by HBr elimination failed, causing us to abandon this approach.

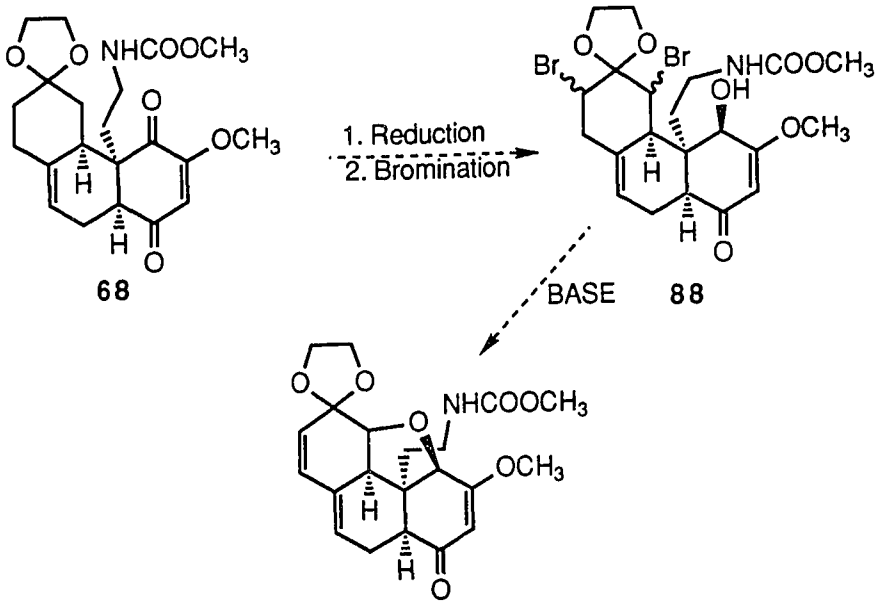


68 86 eq 14

2. Attempted Formation of the Furan and Piperidine Rings

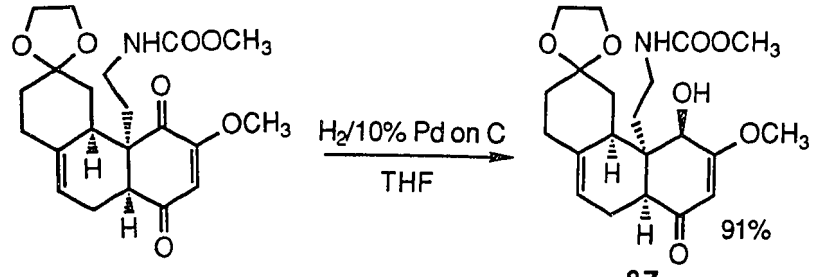
The apparent success of the bromination reaction in eq 14 led us to investigate this as a possible method for the introduction of the 4,5-oxide bridge of morphine (scheme 12). The idea was that **88** would be a suitable substrate for ether formation via an intramolecular displacement of bromide by the hydroxyl group.

SCHEME 12



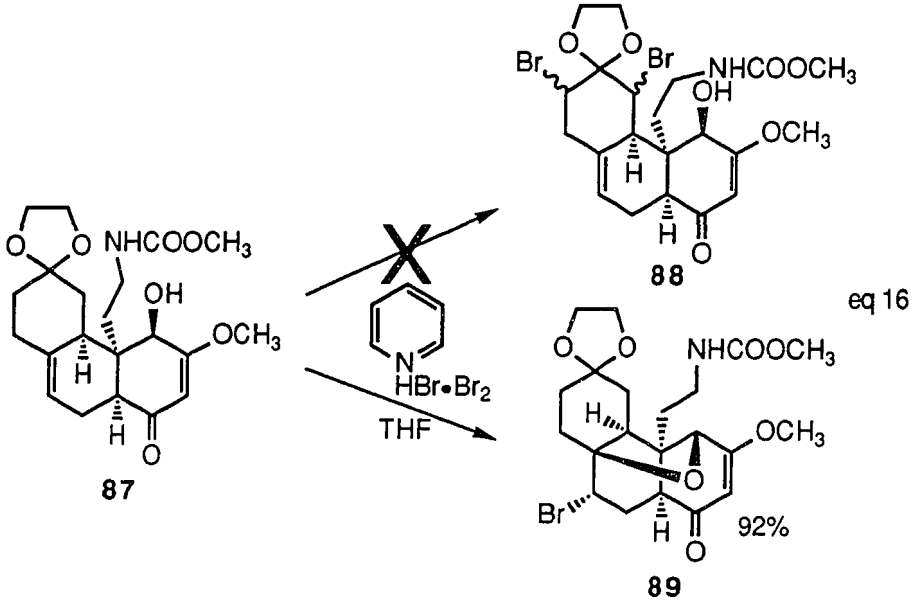
68 **88**

The ketone functionality at the 5 position of **68** (morphine numbering, figure 2) was selectively reduced with hydrogen gas in the presence of catalytic palladium on charcoal to produce **87** (eq 15). This reaction took place



68 87 eq 15

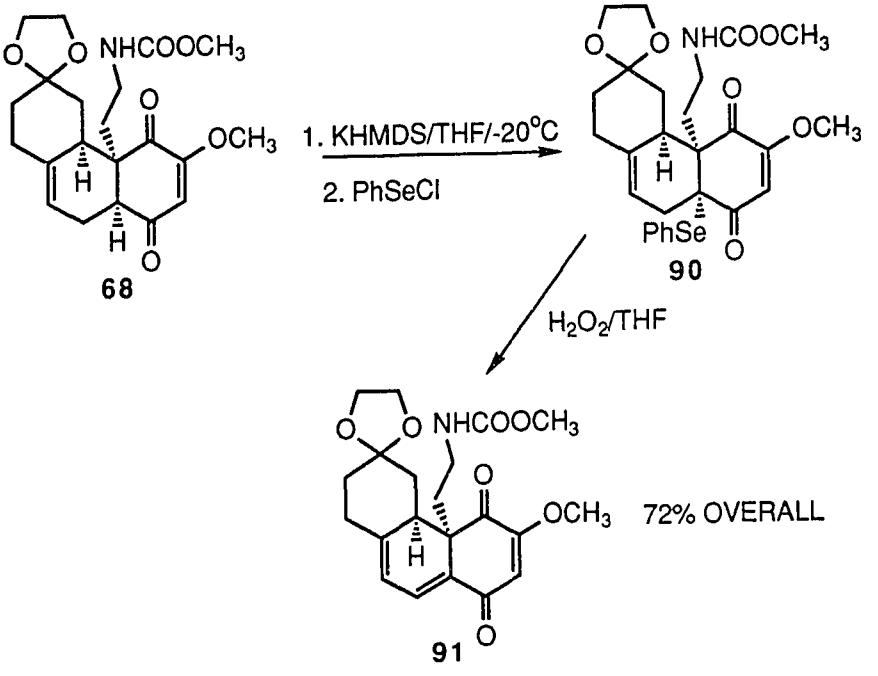
in 91% yield in approximately 5 minutes. When **87** was treated with pyridinium bromide perbromide (eq 16) in the hopes of brominating the ketal at the alpha positions to give **88**, a bromoetherification reaction took place instead producing **89** in 92% yield.



87 88 89 eq 16

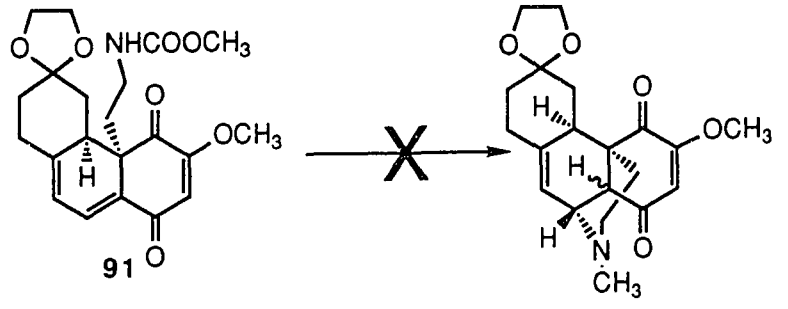
At this time attention was turned to the formation of the piperidine ring needed for the formation of the morphine skeleton. Treatment of Diels-Alder adduct **68** with potassium bis(trimethylsilyl)amide at -20°C followed by treatment of the enolate with phenylselenium chloride[37] (scheme 13) gave selenide **90**. Oxidation with hydrogen peroxide in THF followed by spontaneous elimination of the selenoxide gave dienone **91** in 72% overall yield. At lower temperatures (-78°C) enolate formation did not take place. At higher temperatures (0°C) there was extensive decomposition.

SCHEME 13



68 **90** **91**

There is precedent for the conjugate addition of secondary carbamates to unsaturated carbonyl compounds to form six membered nitrogen heterocycles.[40] The reactions normally proceed by deprotonation on nitrogen with a strong base such as potassium tert-butoxide. Unfortunately dienone **91** was inert to treatment with several bases (eq 17) including potassium tert-butoxide in THF and potassium carbonate in methanol. During the course of the reaction



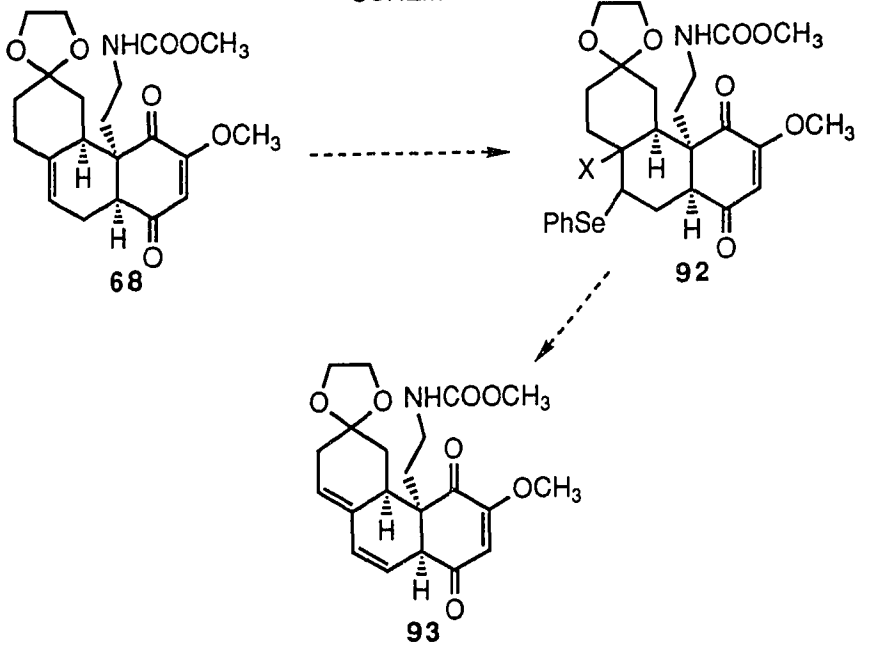
91 eq 17

a new product was observed by thin layer chromatography. Upon workup this material reverted to the starting material. One possible explanation is that 1,4-addition did indeed take place but re-elimination occurred upon workup. It was thought that the stability of the highly conjugated dienone system may have been responsible.

3. Tandem Seleno-Cyclization

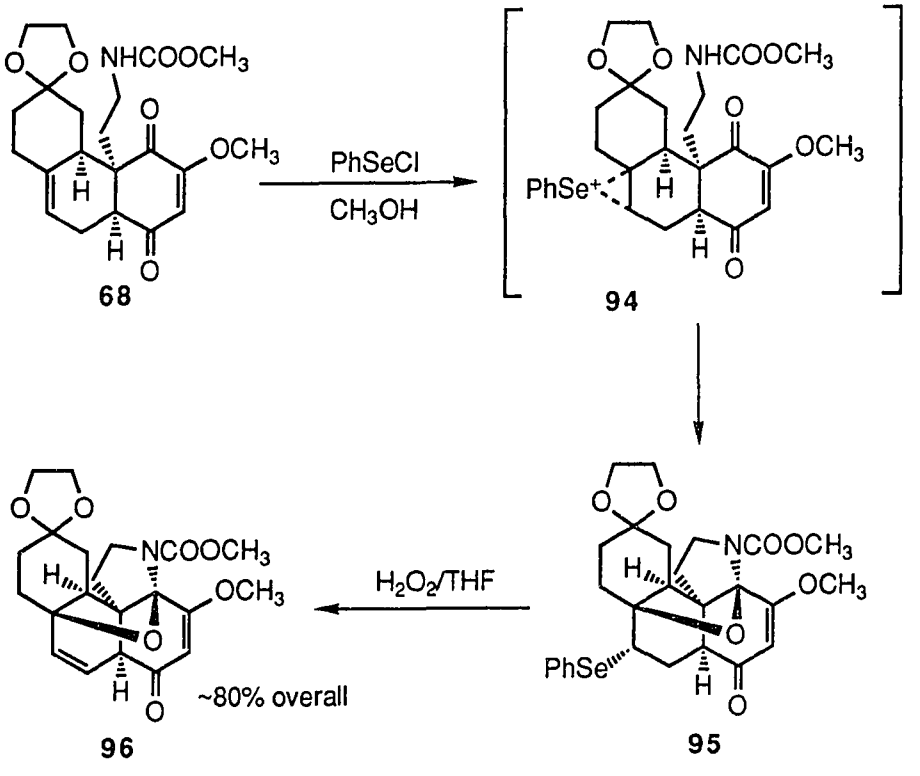
It was felt that additional unsaturation could be introduced into the Diels-Alder adduct by adding a phenylselenium halide across the trisubstituted double bond to give **92**[41] (scheme 14). Elimination of the halide and selenophenyl group to give **93** would add one unit of unsaturation. When **68** was treated with phenylselenium chloride or bromide in methylene chloride only starting material was recovered. This appeared odd to us since this reaction is very general. An explanation may be that trans attack of the halide is prohibited from the hindered endo face of the molecule. Adduct **68** was then treated with phenylselenium bromide in methanol[42] in the hopes of adding

SCHEME 14



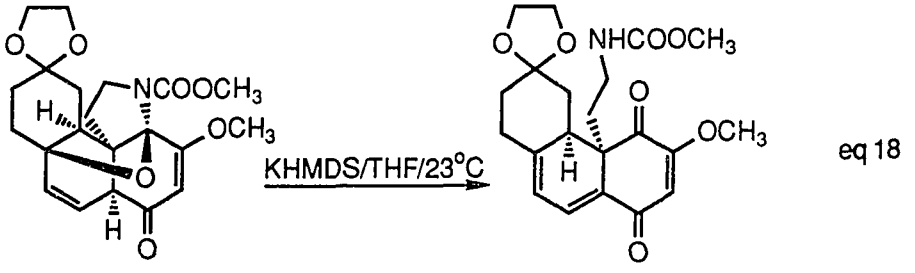
phenyl selenium methoxide across the double bond (scheme 15). Instead, a tandem seleno-cyclization took place giving cleanly selenide **95**. Better results were obtained when phenylselenium chloride was used. Oxidation of the selenide followed by elimination gave the olefin **96** in an overall yield of 80%. The structure of **96** was determined unambiguously by single crystal X-RAY diffraction. A three dimensional representation of **96** is shown in figure 4. Several aspects of this reaction are worthy of note. The reaction did not take place at all in methylene chloride

SCHEME 15



but proceeded cleanly and relatively quickly (several hours) in methanol. Also, even if the solvent is a good nucleophile (such as methanol) interception of the putative intermediate selenonium ion **94** in a tandem fashion is more favourable than interception by the solvent.

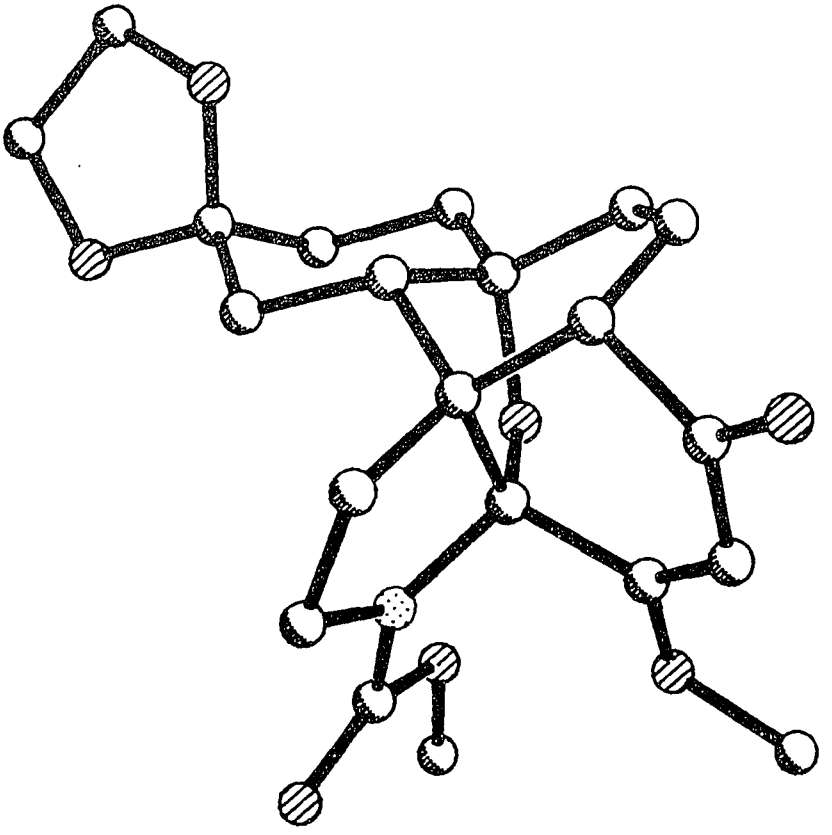
Although at first this reaction was deemed a curiosity, it soon became apparent that **96** could be a useful intermediate for the addition of a unit of unsaturation to the molecule. Indeed, treatment of **96** with a strong base (such as potassium bis(trimethylsilyl)amide) gave dienone **91** albeit in poor yield (eq. 18).



96 **91** eq 18

The synthetic plan at this juncture was to functionalize the A-ring of **96**, then to aromatize it via the elimination of the oxide bridge.

X-RAY STRUCTURE OF 96



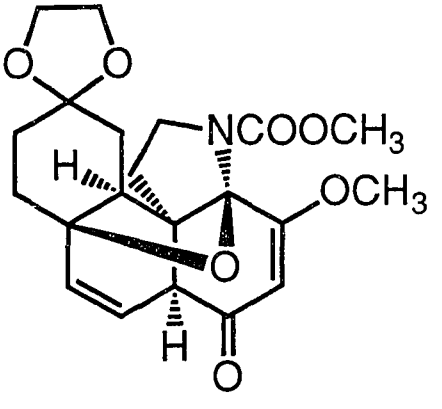
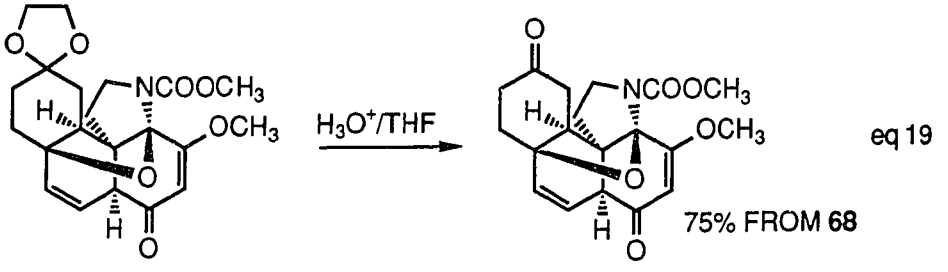


FIGURE 4

4. Introduction of the C-4 Oxygen

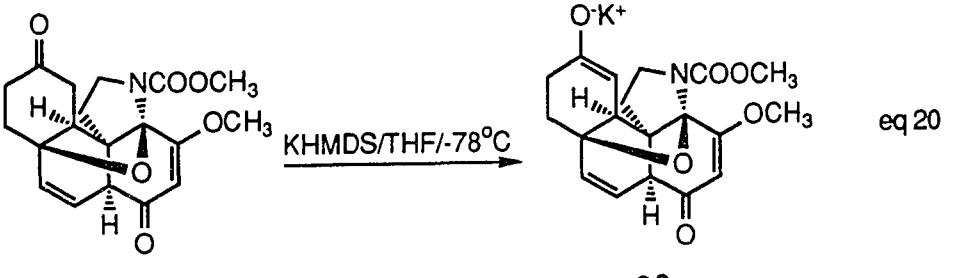
Hydrolysis of **96** with aqueous HCl in THF gave ketone **97** (eq 19). The overall yield of **97** from **68** was 75%. In practice neither selenide **95** nor olefin **96** were purified.



eq 19

96 **97**

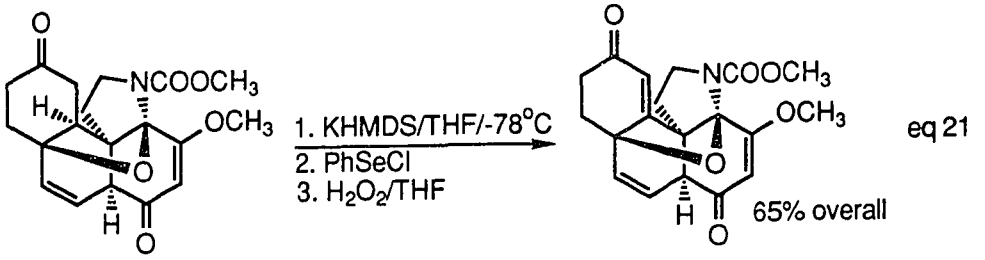
It soon became apparent that kinetic deprotonation of **97** gave the enolate shown in eq 20. The potassium enolate



eq 20

97 **98**

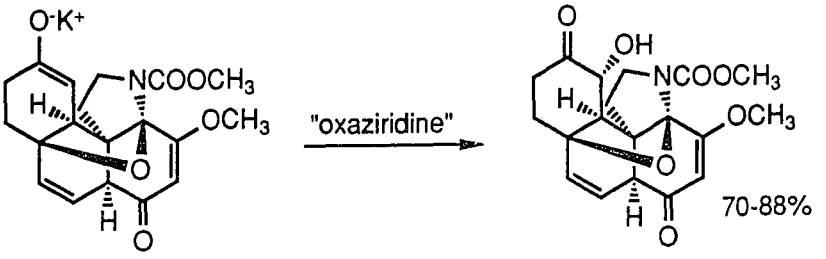
(generated with potassium bis(trimethylsilyl)amide at -78°C in THF) could be trapped with a variety of electrophiles. For example, treatment with phenylselenium chloride[37] gave, after oxidation, enone **99** in 65% yield (eq 21). Aromatization of **99** was unsuccessful.



97 **99** eq 21

Treatment of enolate **98** with 2-p-toluenesulphonyl-3-phenyl oxaziridine[43] gave acyloin **100** in good yield (eq 22). This reaction initially proved troublesome. If the substrate was added to a solution of the base and the resulting mixture treated with a solution of the oxaziridine, the yield was about 40%. A model system gave 90% yield using the identical procedure. In addition to the product, a byproduct was obtained which decomposed upon chromatography, was very water soluble, and had a ^{1}H NMR spectrum very similar to the desired product. The identity

of this product remains unknown, but since many alpha-hydroxy ketones are known to dimerize, a dimeric species is a distinct possibility.



98 **100** eq 22

If the reaction was done by adding exactly one equivalent of the base to a solution of the substrate at -78°C, followed by treatment of the resulting enolate with the oxaziridine, variable yields of 70-88% could be realized. While excellent selectivity for the desired enolate was seen at -78°C, generation of the enolate at -20°C resulted in the formation of a 1:1 mixture of the two possible enolates. Because of the need for rigorous control of the temperature, this reaction was never scaled up beyond 500 mg. It is interesting to speculate on the selectivity of enolate generation that might be observed under thermodynamic control. Should there be selectivity for the alternative enolate derived from **97**, this could

allow access to morphinan analogues which have a variety of substituents on the aromatic moiety.

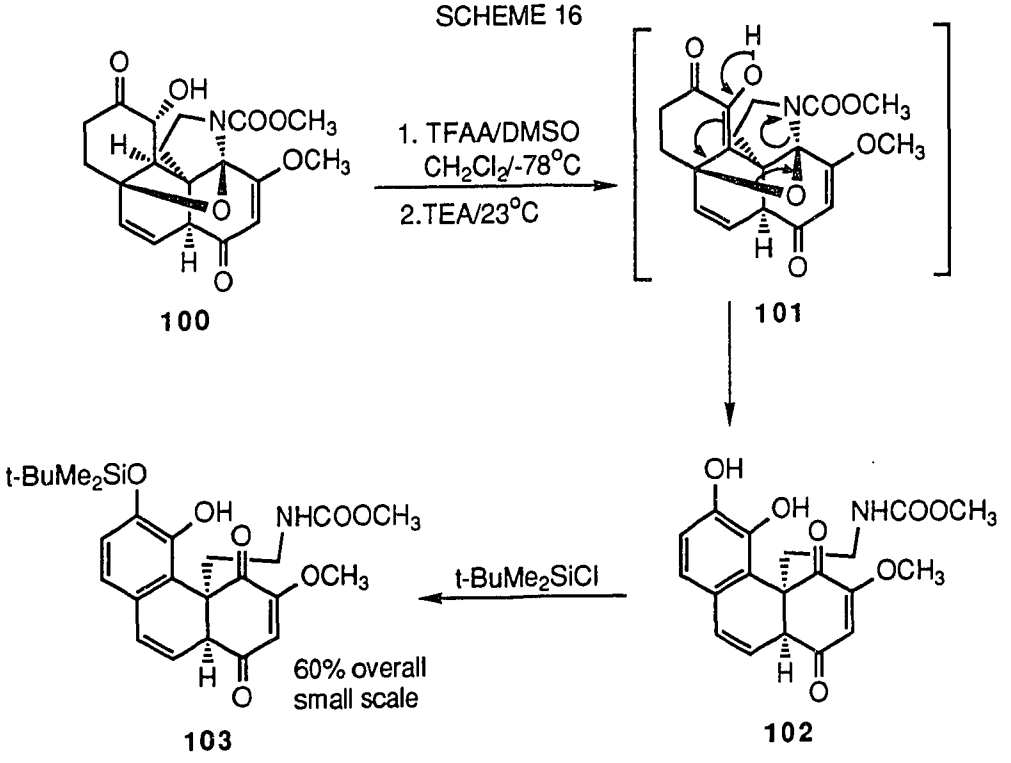
It is worthy of note at this juncture that the C-4 oxygen required for morphine had been selectively installed.

5. Aromatization of the A-Ring

The synthetic strategy at this point called for the oxidation of the acyloin **100** to an alpha-diketone. The oxide bridge would then be beta to the newly formed carbonyl and should therefore be labile to elimination with base. Scheme 16 shows the realization of this strategy. Acyloin **100** was oxidized under Swern's conditions[44]. The alpha-diketone **101** was never isolated but spontaneously eliminated the beta-oxide bridge to give catechol **102**. This product was unstable (presumably to air oxidation) and was isolated as the mono-tert-butyldimethylsilyl ether **103**. Other oxidation conditions were used for this reaction with much less success. The overall yield for the monosilyl catechol was 60%. When this reaction was scaled up to 100 mg, the yield dropped to a disappointing 30%. It is important to note, however, that the early objectives of the original synthetic strategy had been met with the formation of **103**; the carbon framework had been efficiently prepared and the A-ring had been aromatized with the proper

oxygenation pattern for morphine.

SCHEME 16

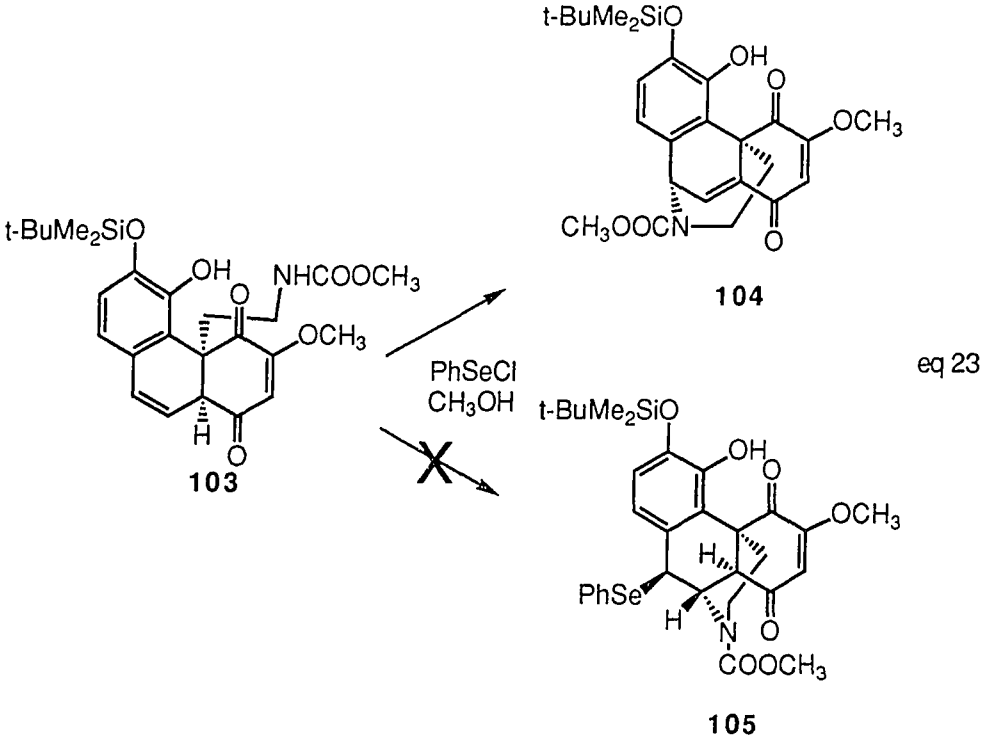


100 101 102 103

Since a selenium mediated cyclization had worked so well previously, it was felt that the piperidine ring of the morphinan alkaloids could be formed in this manner. Treatment of **103** with phenylselenium chloride in methanol gave the seven membered nitrogen heterocycle **104** rather than the desired piperidine **105** (eq 23).

It had been hoped that preference for formation of a six membered ring over a seven membered ring would dictate the course of the reaction. Electronic control was clearly

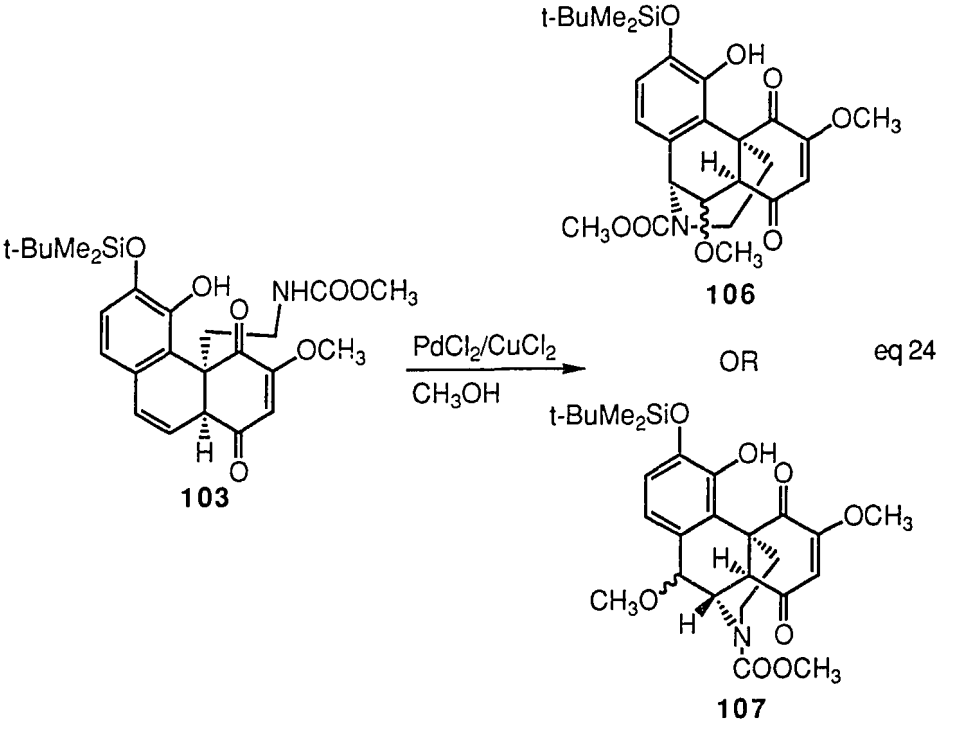
the determining factor. Note that no oxidation step was necessary for formation of the enone since the selenophenyl moiety was beta to a carbonyl group. Similar results were obtained if methylene chloride was used as the solvent and also when N-phenylseleniumphthalimide[45] was used to activate the styrene double bond.



eq 23

Palladium catalyzed amination of double bonds is known.[46] There was a reasonable probability that the piperidine ring of morphine could be formed in this manner. Treatment of the styrene **103** with palladium dichloride and

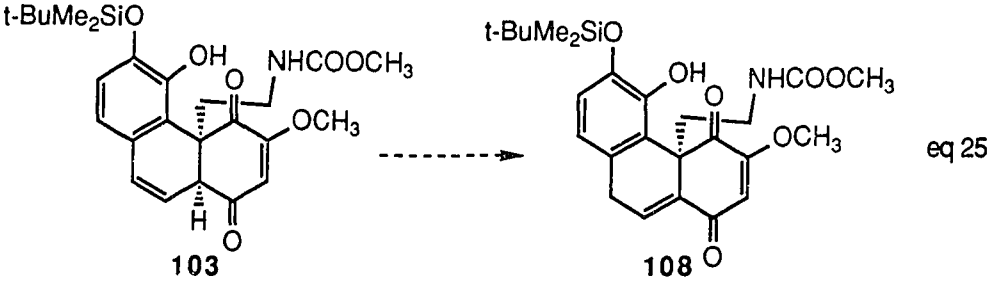
cupric chloride in methanol[46] gave a product which looked promising by ^{1}H NMR. Without resorting to two dimensional NMR experiments, we were not able to determine whether **107** was formed or its seven membered ring isomer **106** (eq 24). The ^{1}H NMR spectrum was complicated by multiple signals due to either diastereomeric products or hindered rotation about the C-N bond of the carbamate. The lack of an efficient route to the styrene **103** led us to abandon this approach although it did show some promise.



eq 24

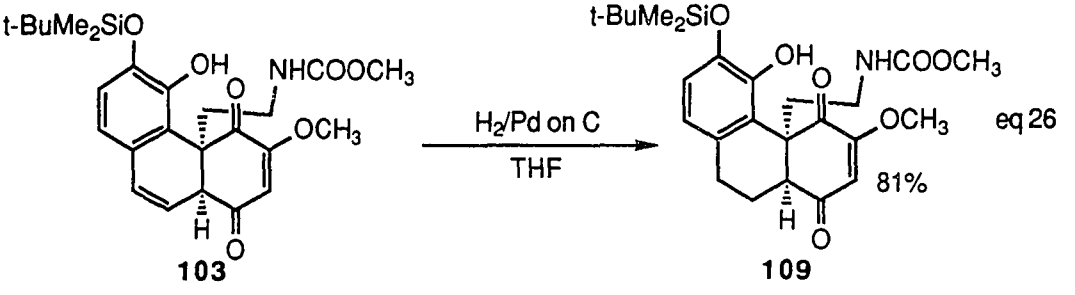
Isomerization of the styrene double bond of **103** into conjugation to produce **108** (eq 25) was unsuccessful. Treatment of **103** with base led to decomposition while

treatment with acid left the starting material unchanged, with some decomposition occurring after time. It was decided that a more promising approach, albeit a longer



eq 25

one, would be to saturate the double bond and reintroduce it in conjugation with the ketone via known methods.

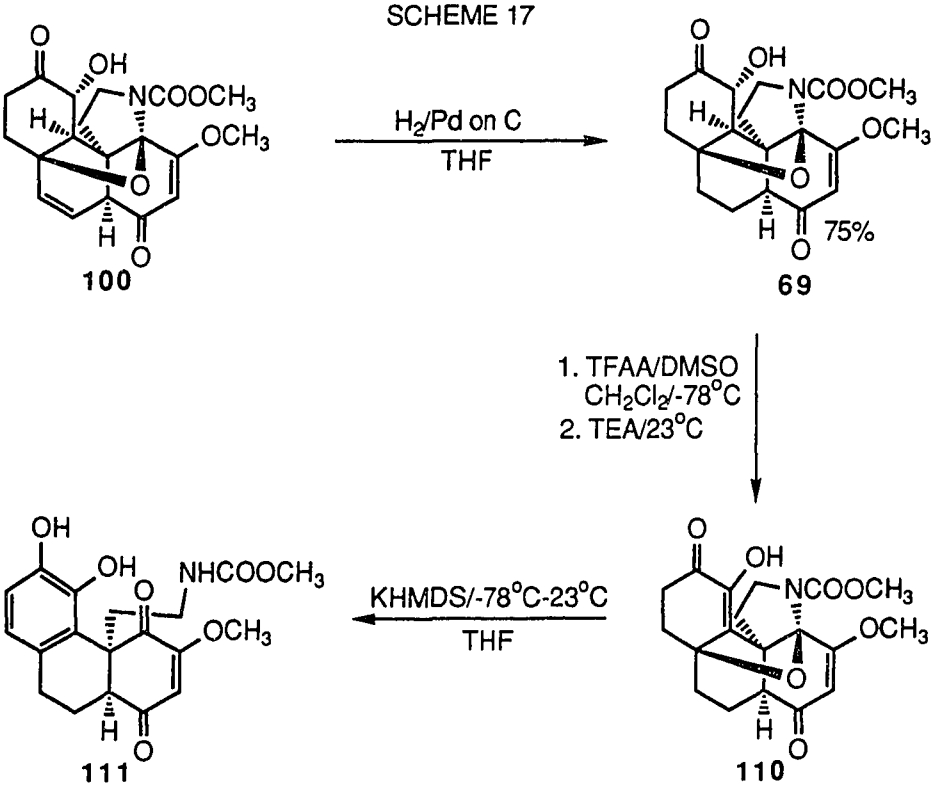


eq 26

Hydrogenation of **103** proceeded smoothly to give **109** in 81% yield (eq 26). Unfortunately, under both acidic and basic conditions, electrophilic attack on the aromatic ring

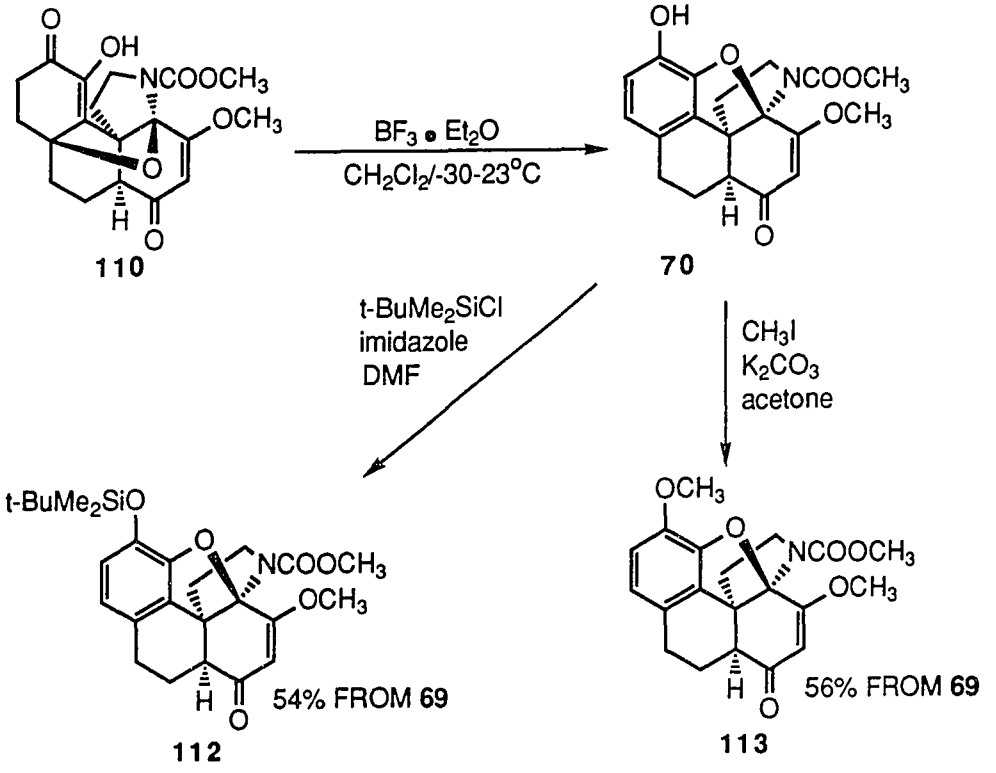
was always competitive with functionalization alpha to the carbonyl. It was obvious from the hydrogenation reaction that the electron rich styrene double bond was, to a large extent, responsible for the instability of the aromatization product; the hydrogenated product **109** was much more stable to storage than **103**. This led us to believe that the yield of aromatized product would be improved if the double bond of the styrene were removed prior to the aromatization sequence. To this end, **69** was prepared in 75% yield by hydrogenation of acyloin **100** (scheme 17).

SCHEME 17



Oxidation of **69** under Swern's conditions[44] gave the suprisingly stable diketone **110**. Recall that oxidation of **100** under the same conditions caused a spontaneous rearrangement (see scheme 16). Treatment of **110** with a strong base led to the formation of catechol **111** in low yield. The low yield was thought to be due to the susceptibility of the product to oxidation in the basic medium. Athough oxygen could have been rigorously excluded

SCHEME 18

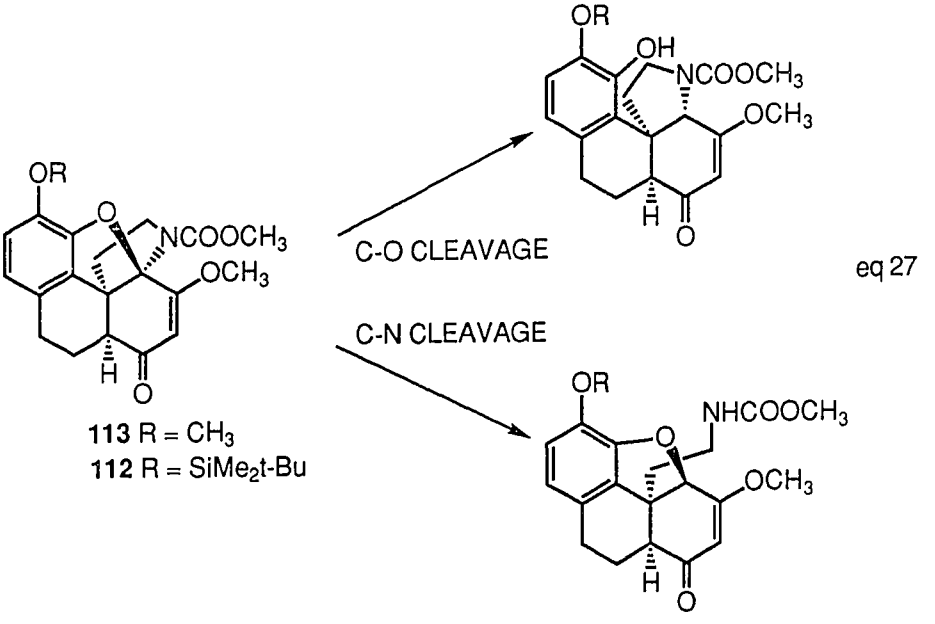


from the reaction mixture, a more efficacious method for the aromatization proved to be the treatment of **110** with boron trifluoride etherate (scheme 18). This led to rearrangement product **70** which could be protected as the silyl ether **112** (tert-butyldimethylsilyl chloride/imidazole in DMF) or the methyl ether **113** (methyl iodide/potassium carbonate in acetone). The yield of these very stable compounds was excellent (56% overall from acyloin **69** for the methyl ether **113** and 54% for the silyl ether **112**). At this juncture, the phenanthrene portion of morphine had been assembled.

C. Preparation of Thebainone and Beta-Thebainone: A Total Synthesis of Morphine

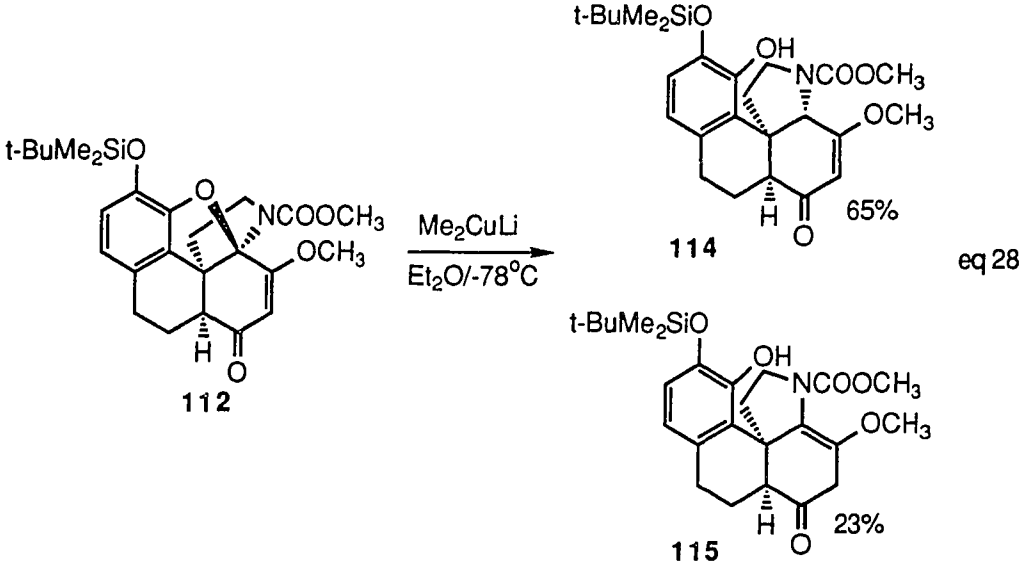
1. Attempted Cleavage of the C-N Bond

It seemed a fortunate turn of events that the dihydrofuran ring of morphine was formed during the aromatization rearrangement. Unfortunately, this left the task of selectively cleaving the C-N bond in **112** or **113** (eq 27). Reductive cleavage of alpha-amino ketones is known,[47] as is the reductive cleavage of alpha-alkoxy ketones.[48] The selective reductive cleavage of the C-N bond was worthy of investigation.



eq 27

Treatment of **112** (eq 28) with lithium dimethyl cuprate at -78°C in ether[48a] gave cleanly C-O bond cleavage. The reaction mixture consisted of two products, **114** (65%) and the deconjugated **115** (23%). The reaction was complete in 5 min.

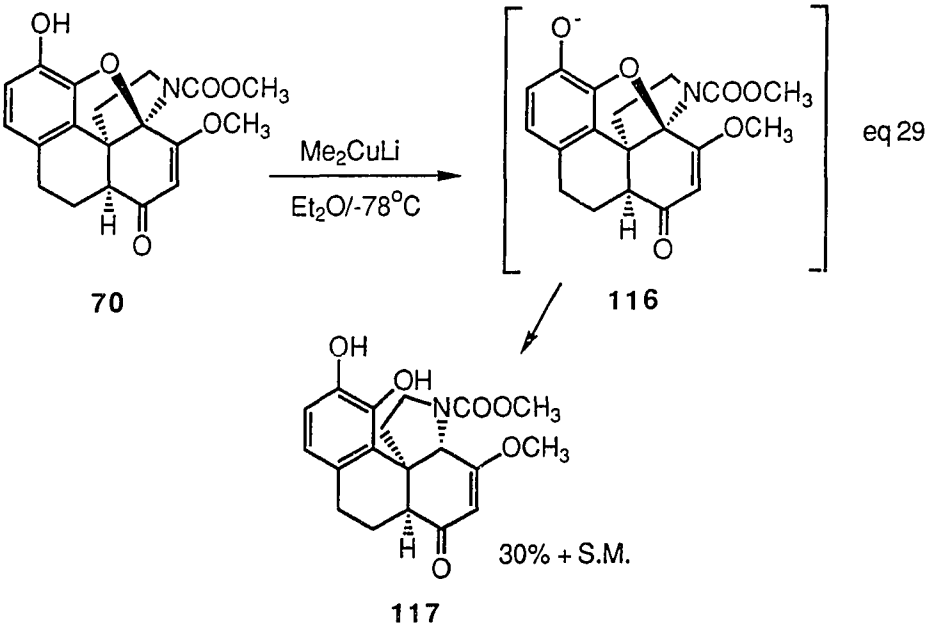


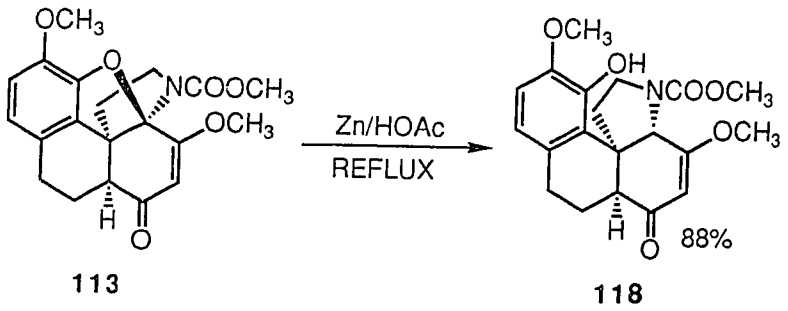
eq 28

Since the C-O bond cleavage of **112** was so facile, the obvious strategy was to attempt to slow it down so that C-N bond reduction might compete. To this end, **70** was subjected to the same conditions (eq 29), the idea being that reductive cleavage of the C-O bond in phenoxide **116** would be much slower than in phenolic ether **112**. This reasoning was partially borne out by the fact that after 8

hours a modest amount of C-O bond cleavage had occurred to form **117** (30%) with the balance of the reaction mixture consisting predominantly of starting material. Although C-O bond reduction had been made more difficult, C-N bond reduction did not compete.

When the methyl ether **113** was treated with zinc dust in refluxing acetic acid[48b] (eq 30), **118** was formed in 88% yield. The same reaction of silyl ether **112** gave a similar yield of **114**. Interestingly, no desilyation occurred.



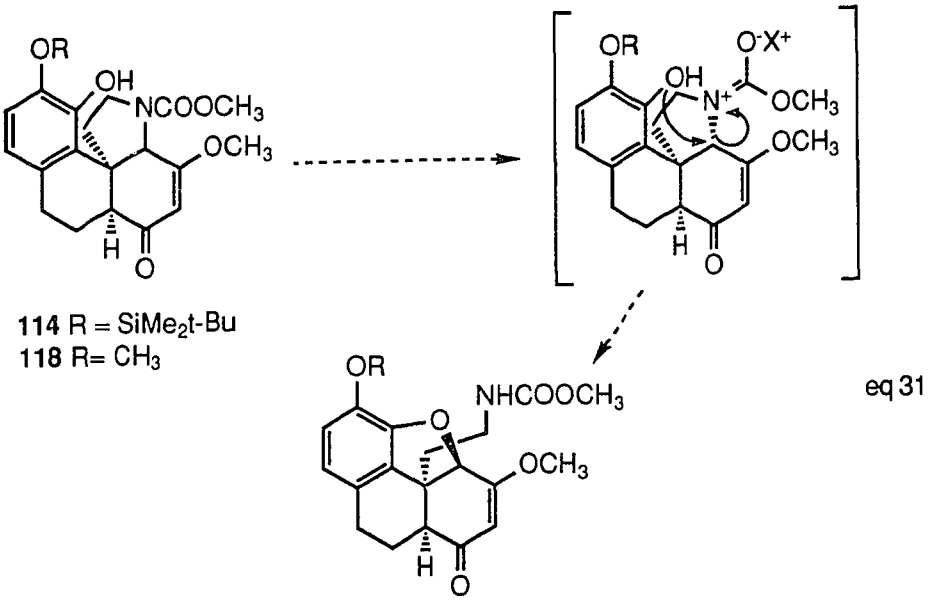


113 118 eq 30

Treatment of **112** with samarium diiodide[48c] gave a complex mixture.

2. Attempted Intramolecular Displacement to Form the Dihydrofuran Ring

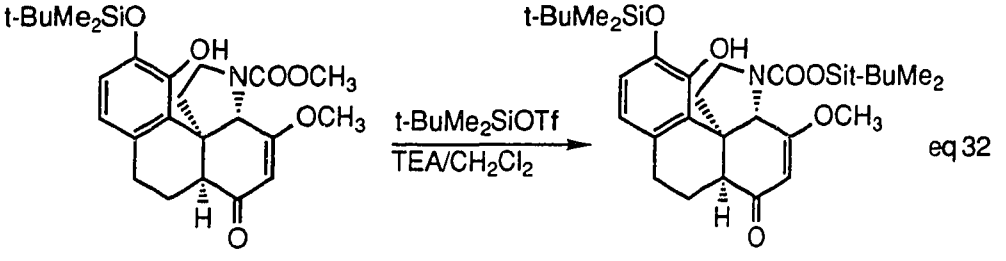
Several attempts were made to utilize the selective C-O bond reduction to form the dihydrofuran ring of morphine. The synthetic strategy was to activate the C-N bond of **114** or **118** such that an intramolecular displacement might take place, thus forming the 4,5-oxide bridge and freeing the aminoethyl appendage for the formation of the piperidine ring (eq 31).



114 R = $SiMe_2$t-Bu
118 R= CH_3

eq 31

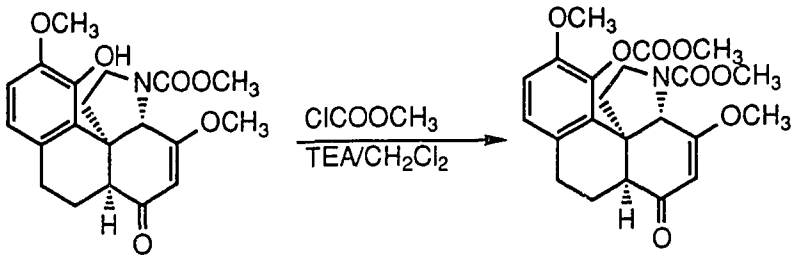
When **114** was treated with tert-butyldimethylsilyl triflate and triethylamine in methylene chloride, only the silyl carbamate **119** was formed (eq 32).



114 **119**

eq 32

When a similar reaction (eq 33) was attempted with methyl chlorofromate, only the carbonate **120** was formed.



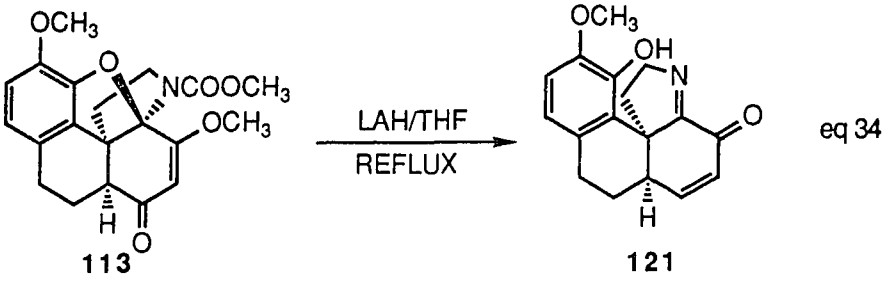
118 **120** eq 33

Finally a brute force approach was employed. Phenol **118** was heated with potassium carbonate in DMF at 120°C only to recover starting materials. When the temperature was raised to 240°C (sealed tube), some type of formylation reaction took place as evidenced by an aldehyde signal in the ^{1}H NMR. The product was not completely characterized.

In light of the failure to selectively reduce the alpha C-N bond of **112** or **113**, it was felt that conversion of the carbamate to a methylamine might lead to better results in this regard.

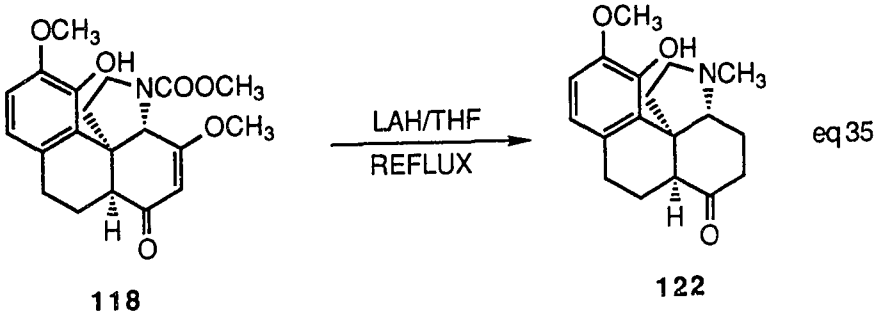
3. Conversion of the Carbamate to an N-Methyl Amine

The direct reduction of the methyl carbamate to an N-methylamino group (a classical method)[49] proved to be unsuccessful due to side reactions. Reduction of **113** with lithium aluminum hydride in refluxing THF gave imine



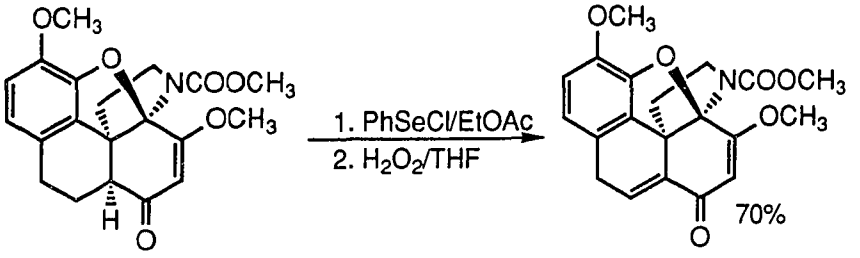
113 **121** eq 34

121 (eq 34). Reduction of **118** under the same conditions gave methyl amine **122** in which over-reduction of the vinylogous methyl ester had taken place. At ambient temperature, incomplete reduction occurred resulting the formation of a secondary amine after hydrolysis.



118 **122** eq 35

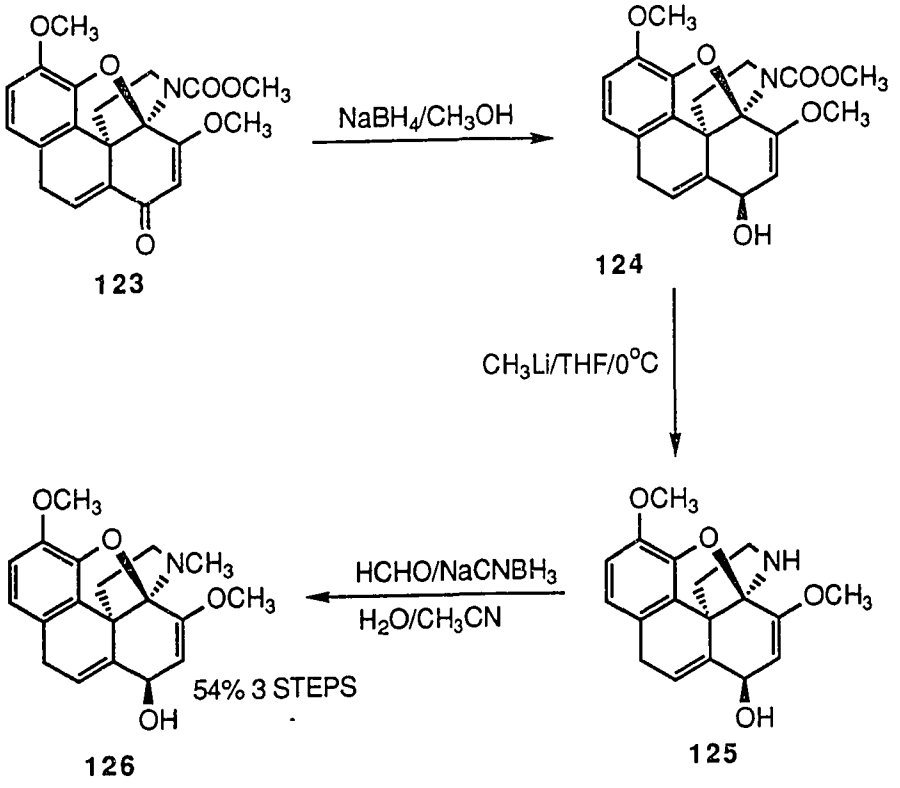
As a result of the failure to directly reduce the carbamate to the desired amine, a two step method was employed. Prior to this, however, an additional unit of unsaturation was introduced in conjugation with the ketone carbonyl of **113** (eq 36). Treatment of **113** with phenylselenium chloride in ethyl acetate[50] followed by the oxidation of the crude selenide gave enone **123** in 70% yield.



113 **123** eq 36

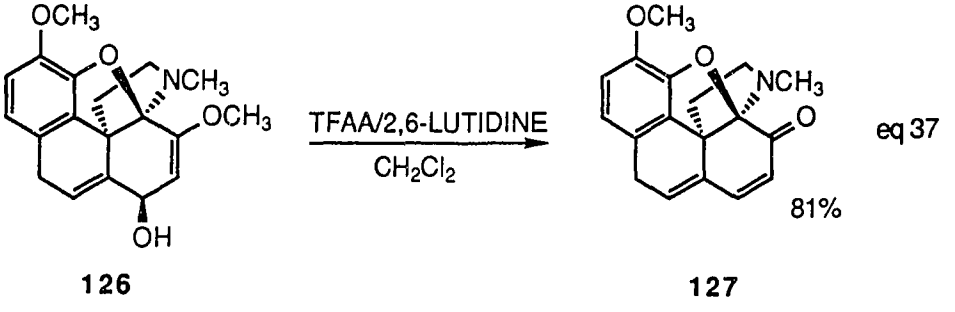
The ketone **123** (scheme 19) was reduced with diisobutylaluminum hydride to the bis-allylic alcohol **124**. Subsequent to the development of this scheme, it was found to be more convenient to perform this reduction with sodium borohydride in methanol. Initial fears that conjugate reduction might occur were not borne out. Removal of the carbomethoxy protecting group of crude **124** with

SCHEME 19



methyllithium in THF yielded **125** which without purification was treated with aqueous formaldehyde and sodium cyanoborohydride[51] to give the methyl amine **126**. The overall yield of **126** was 54% from enone **123**. It should be noted that methylation of the lithium amide produced during the carbomethoxy group removal with an excess of methyl iodide was unsuccessful.

The synthetic strategy was to convert the alcohol **126** to a dienone moiety. This, then, would provide a substrate which would be suitable for 1,6-addition of the methylamino sidechain. Alcohol **126** was treated with trifluoroacetic anhydride and 2,6-lutidine to give dienone **127** in 81% yield (eq 37).

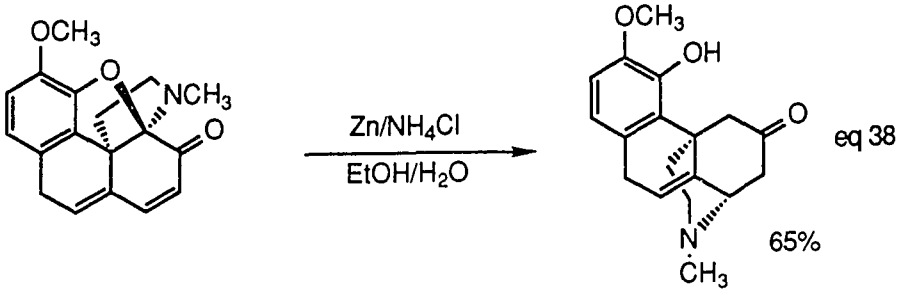


126 **127**

4. Synthesis of a Morphinan Structural Isomer

It was hoped that amine **127** would serve as a better substrate than carbamate **113** for the selective cleavage of the C-N bond alpha to the pi system. Unfortunately this was not the case. Treatment of **127** with zinc dust and aqueous ammonium chloride in ethanol[48d] gave 1,4-addition product **128** (eq 38) in 65% yield. Even if the reaction

was stopped prior to the complete consumption of the starting material, no material was isolated in which selective C-N bond cleavage had occurred. The reason that

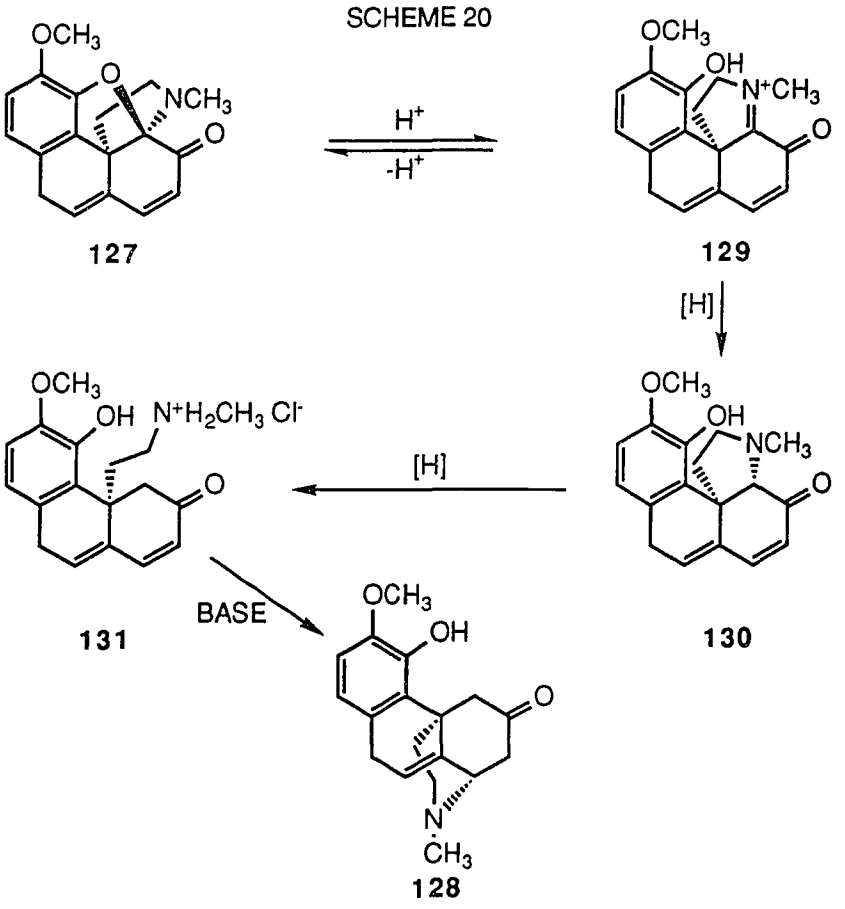


eq 38

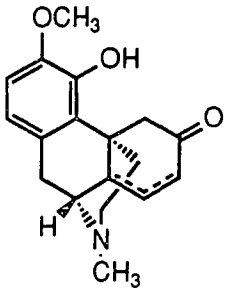
127 **128**

the C-O bond reduction is so facile may be explained by postulating the equilibrium shown in scheme 20. Acid catalyzed equilibration of **127** to an imminium species **129** may occur. The reduction of **129** with zinc should be very fast, resulting in the formation of alpha-amino ketone **130**, which in turn may be reduced to ammonium salt **131**. The conjugate addition of **131** to form **128** presumably happens upon basification.

SCHEME 20

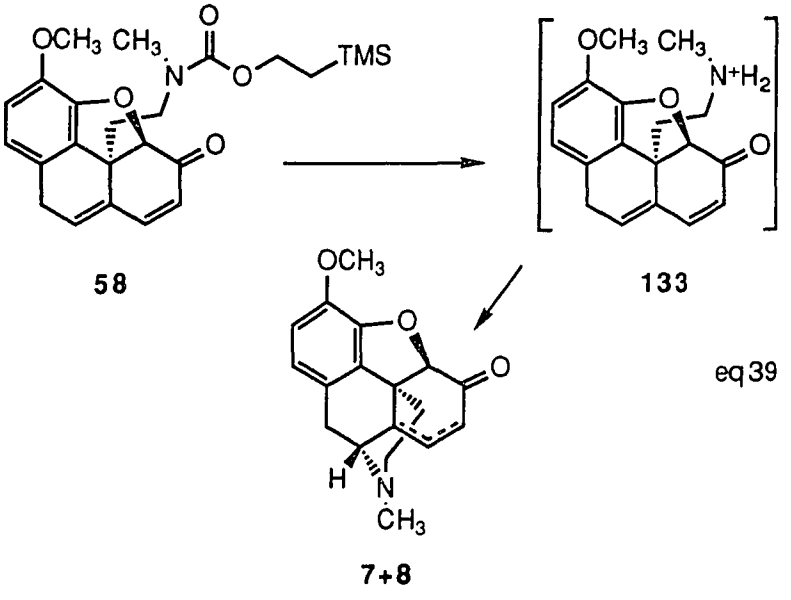


The fact that **127** produced the 1,4-addition product **128** and not the 1,6-addition product **132** was disappointing and puzzling. Fuchs and coworkers have reported[52] that **58** (eq 39), upon removal of the carbamate protecting group, gives the ammonium salt **133** which undergoes 1,6-addition selectively to produce **7**. The ammonium salt **131** differs



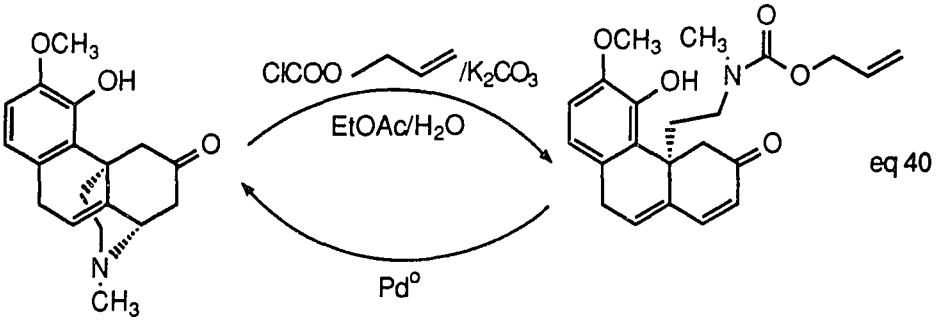
132

from **133** only by the absence of the 4,5-oxide bridge yet gives only the 1,4-addition product. This implies that the oxide bridge imposes steric constraints which favour 1,6-addition.



58 **133** **7+8**

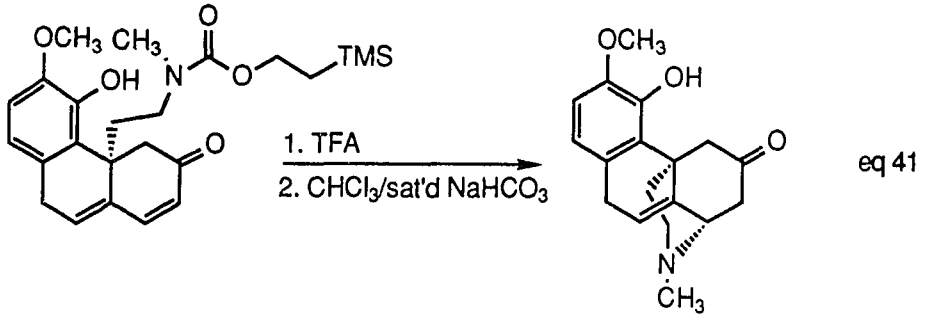
eq 39



eq 40

128 **134**

Treatment of **128** with allyl chloroformate and potassium carbonate in ethyl acetate and water[52,53] gave the carbamate **134** cleanly (eq 40). This carbamate was chosen since it can be removed mildly under palladium catalysis.[54] Removal of the protecting group under these conditions gave back the 1,4-addition product **128**. Carbamate **135**, when

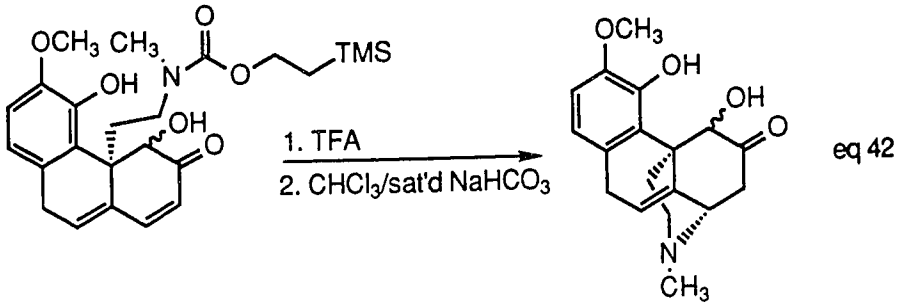


eq 41

135 **128**

treated with neat trifluoroacetic acid (eq 41), also gave **128**. Carbamate **135** differs from Fuchs' intermediate **58** only by the absence of the oxide bridge.

It is worthy of note that the acyloin **136** (eq 42), the preparation of which will be discussed, also underwent 1,4-addition to yield **137** upon removal of the carbamate protecting group.



eq 42

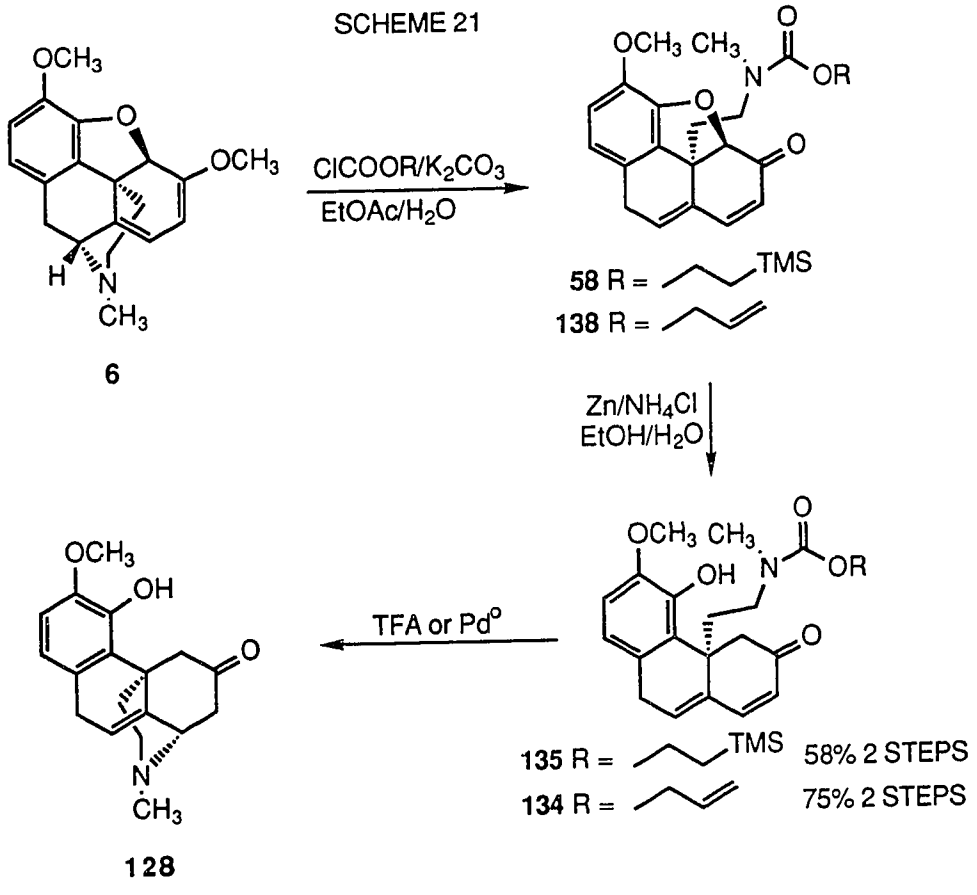
136 **137**

5. Degradation of Thebaine to a Synthetic Intermediate

Scheme 21 outlines the conversion of the naturally occurring opiate thebaine to synthetic intermediates **134** and **135**. This degradation served two purposes. It was done to confirm the structure we had assigned to **128** and **134**, but more importantly it provided large quantities of material that would have taken twenty-one steps to prepare via the totally synthetic sequence.

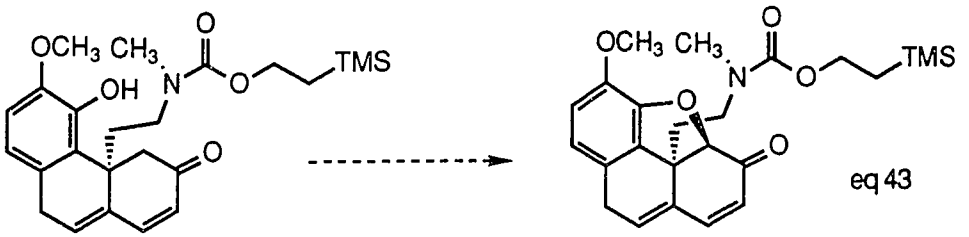
Treatment of thebaine **6** with allyl chloroformate and potassium carbonate gave **138** which upon exposure to zinc dust and aqueous ammonium chloride gave the synthetic intermediate **134**. Removal of the carboallyloxy protecting group gave **128**. The same sequence of reactions was done using trimethylsilyl chloroformate, this being the chloroformate[55] of choice since its removal was cleaner. The overall yield of trimethylsilylethyl carbamate **135** from thebaine was 58% on a scale of approximately one gram.

SCHEME 21



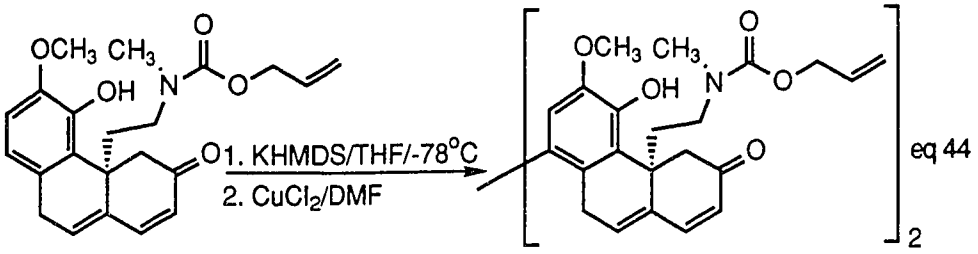
6. Attempted Formation of the 4,5-Oxide Bridge

The conversion of **135** to **58** (eq 43) would result in a formal total synthesis of morphine since **58** was an advanced intermediate in the route of Fuchs and co-workers.[20]



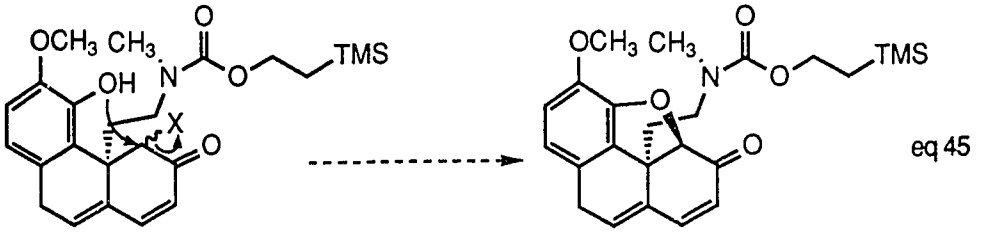
135 **58** eq 43

The first method employed in attempting to form the dihydrofuran ring was direct oxidation. Since the oxidative homo-coupling of both phenols and enolates is known,[56] it was felt that the coupling of an enolate with the oxygen atom of a phenolate as a method for the required ether formation was worthy of investigation. Treatment of **134** with 2 equivalents of potassium bis(trimethylsilyl)amide followed by 2 equivalents of cupric chloride[56a,b] gave only the dimeric compound **139** (eq 44) via the well precedented oxidative coupling of phenolic radicals.[12-15,56] Similar results were obtained when potassium ferricyanide[56c] was used as the oxidant. Use of iodine as an oxidant[56d] led to small amounts of the alpha-iodoketone.



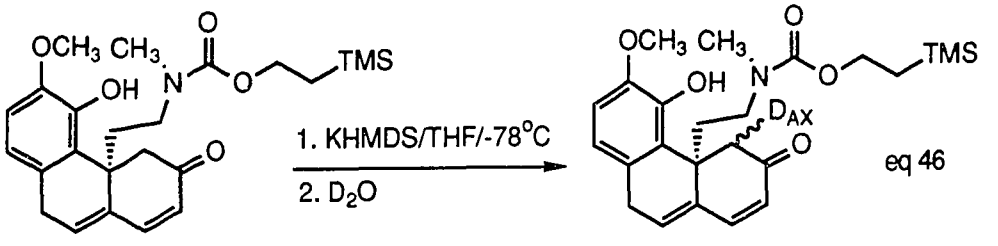
134 **139**

An approach that seemed to have a better chance of success was to introduce a substituent alpha to the carbonyl group in **135** (eq 45) that could act as a leaving group for an intramolecular displacement by the phenolic hydroxyl group. Candidates for such leaving groups included halides and oxygen based leaving groups such as tosylates and mesylates.



58

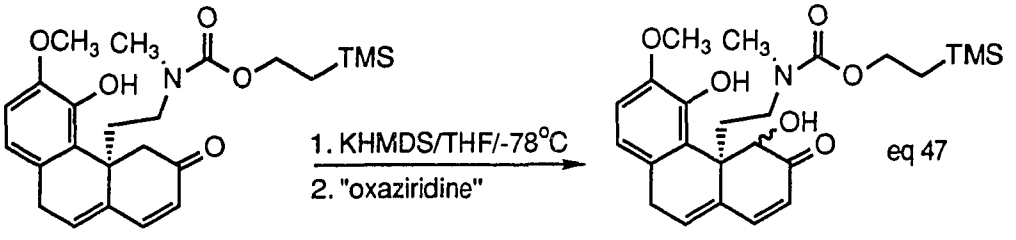
Prior to the introduction of a leaving group alpha to the carbonyl in **135**, it was important to investigate the stereochemistry of such an addition. The signals for the methylene group alpha to the carbonyl in **135** consisted of an 18 Hz doublet at 4.1 ppm and another 18 Hz doublet at 2.5 ppm. It was assumed that the 4.1 signal represented an equatorial proton and was shifted downfield due to the anisotropic effect of being in what amounts to a "bay region." The axial proton uninfluenced by such an effect was at the chemical shift that calculations would predict. When the enolate of **135** (eq 46) generated with potassium bis(trimethylsilyl)amide was quenched with D_2O, the 2.5 doublet disappeared while the 4.1 signal collapsed to a singlet. This indicated that the deuterium incorporation was stereospecific for the axial position. Unfortunately because the C-ring of this molecule may undergo a ring



135 eq 46

flip, it was not possible to assign the relative stereochemistry based on examination of Dreiding models.

When the potassium enolate derived from **135** was treated with 2-p-toluenesulphonyl-3-phenyl-oxaziridine[43] (eq 47), a poor yield (50% at best) of the acyloin **136** was produced. From observations made with other electrophiles, it was felt that the reactivity of the phenolate moiety (generated along with the enolate) toward electrophiles was competitive with the enolate. This may have been the source of the poor yields of this reaction. Mesylation of **136** in the presence of triethylamine gave a product which had many signals in the aromatic region of the ^{1}H NMR. It was thought that some sort of fragmentation took place to give a phenanthrene based material. The exact identity of the product remains unknown. Tosylation of the hydroxyl

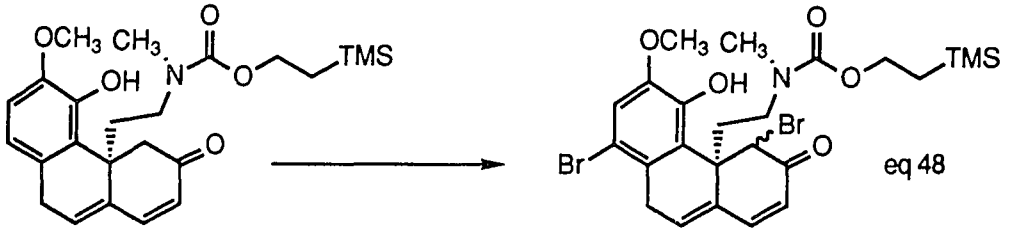


eq 47

135 **136**

group of **136** was unsuccessful as was etherification under Mitsunobu conditions.[57]

The preparation of alpha-bromo ketones by the treatment of enolates with elemental bromine is well known.[58] Attempts to brominate **135** in this fashion met with only limited success due to the reactivity of the phenolate with the bromine. The use of a deficiency of bromine led to the production of dibromo ketone **140** as the only brominated product (eq 48). The use of **140** as a synthetic intermediate was avoided since this would require the removal of the aromatic bromine atom at a later stage.

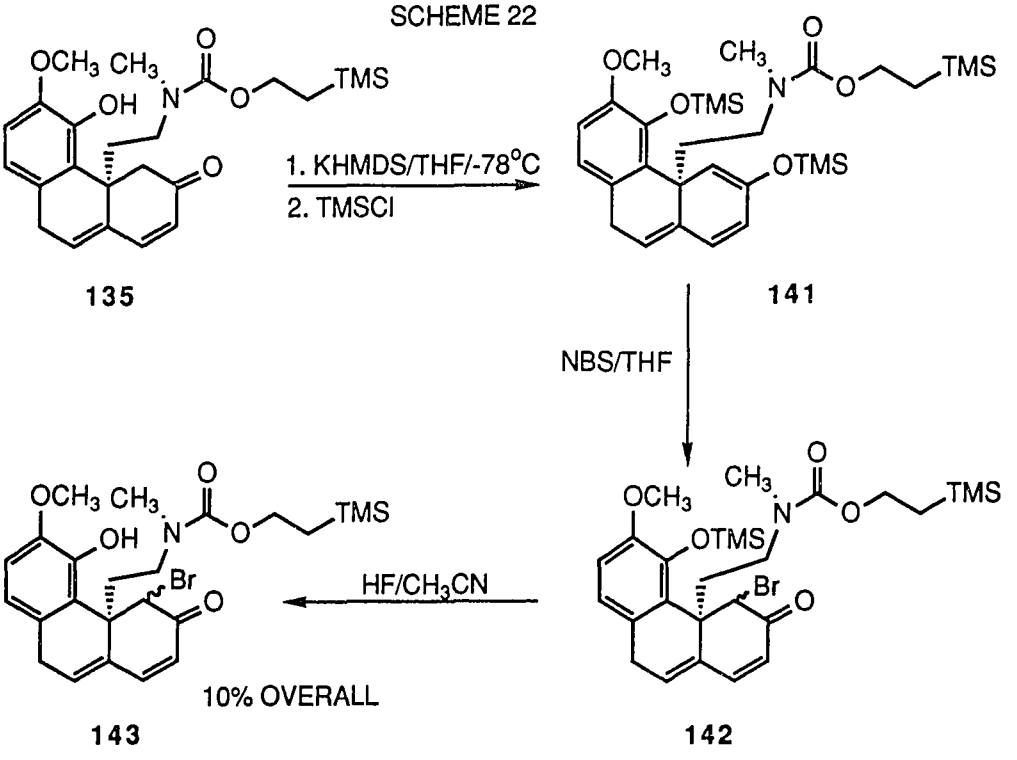


135 **140**

Similar results were obtained when iodine was used although it was possible to obtain a small yield of the desired alpha-iodo ketone. Attempts to form the oxide bridge using this material under basic conditions led to fragmentation of the molecule.

A circuitous route to the alpha-bromo ketone **143** is outlined in scheme 22. Generation of the tris(trimethylsilyl) compound **141** was accomplished by treating **135** with

SCHEME 22



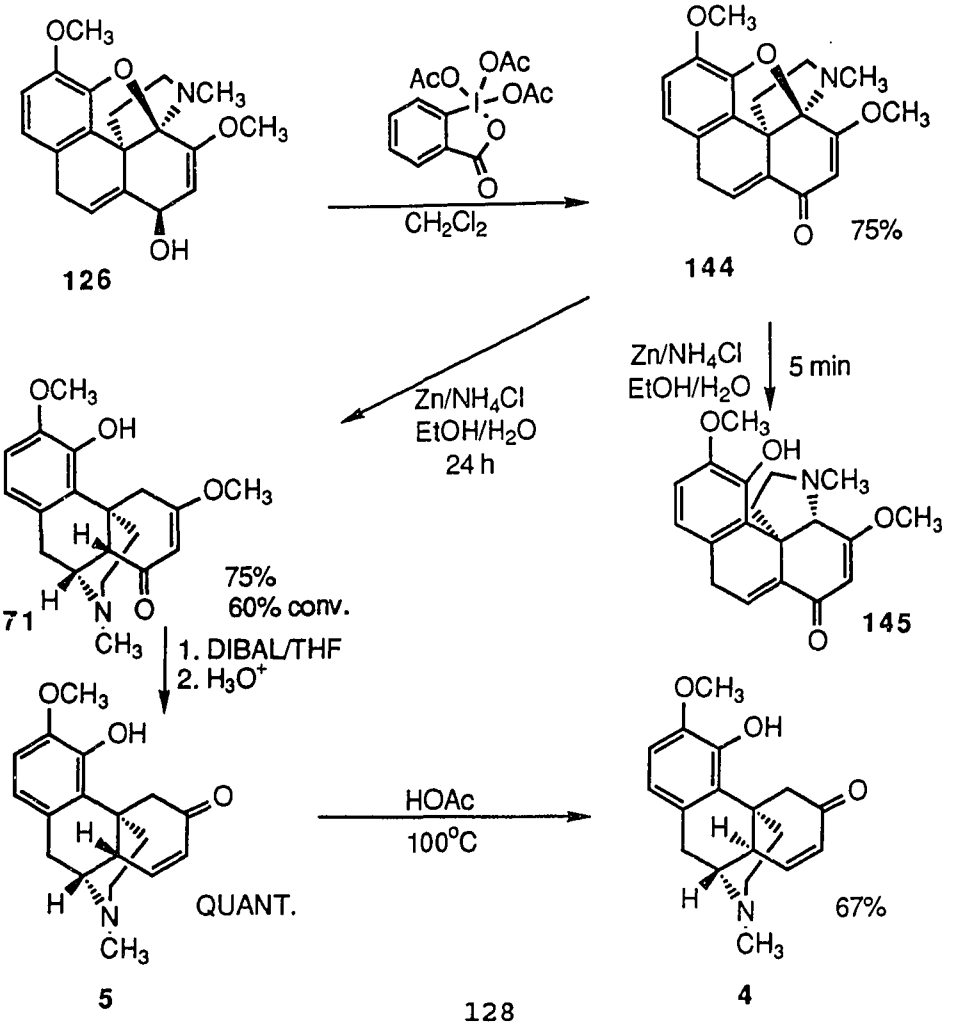
potassium bis(trimethylsilyl)amide followed by trimethylsilyl chloride. This sensitive material was treated with N-bromosuccinimide in THF[59] to yield the alpha-bromoketone **142**. Removal of the phenolic trimethylsilyl group gave the desired **143**. The overall yield of **143** from **135** was 10%. This route to the bromo ketone was unacceptable and was abandoned.

In summary, attempts to install a leaving group in the desired position of **135** were hampered by the competitive reactivity of the phenol moiety. Treatment of compounds which did have a leaving group alpha to the carbonyl led only to fragmentation products.

7. Preparation of Thebainone and Beta-Thebainone

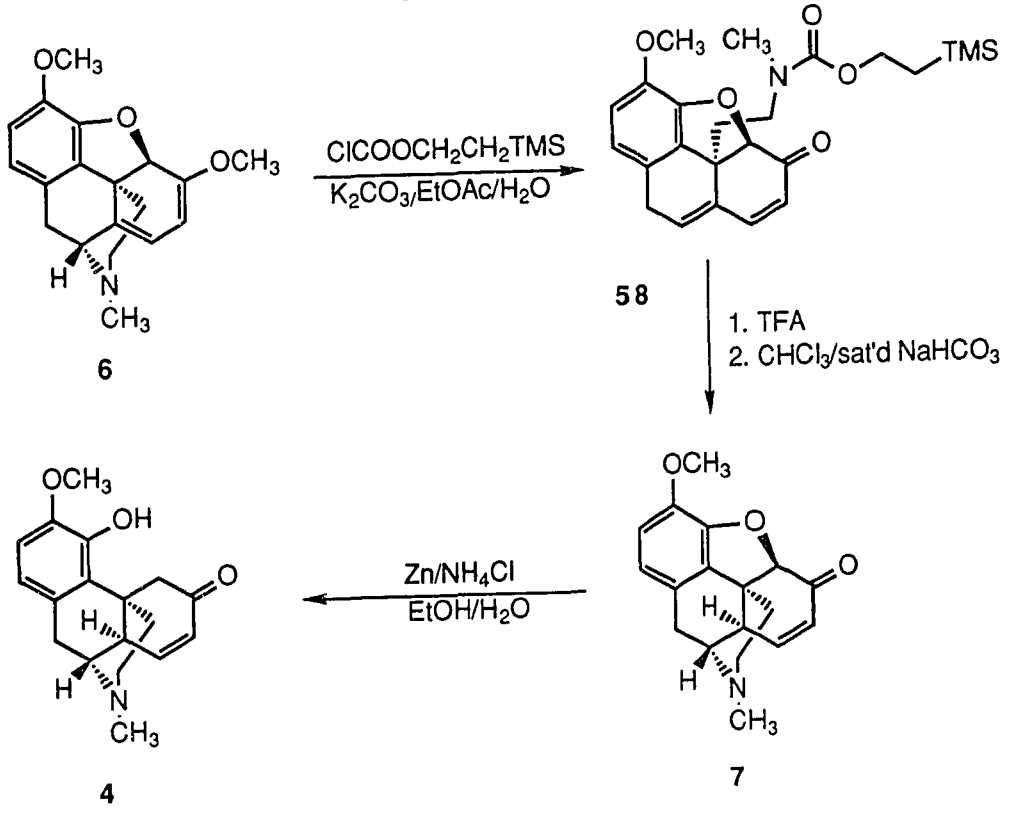
The fact that **127** underwent 1,4-addition (eq 38) to

SCHEME 23



the dienone moiety led us to develop an alternate strategy which is illustrated in scheme 23. Alcohol **126** was oxidized with the Dess-Martin periodinane[60] to give enone **144** in 75% yield. Treatment of **144** with zinc dust and aqueous ammonium chloride[48d] gave **145** in 85% yield after 5 min. If the reaction was left for 24 h, <u>trans</u>-morphinan **71** was produced in 75% yield (based on 60% conversion). DIBAL reduction of **71** followed by immediate hydrolysis gave beta-thebainone **5** quantitatively. Heating **5** in glacial acetic acid[61] gave thebainone **4** in 67% yield.

SCHEME 24



The structure of **4** was proven by comparison with a sample of thebainone derived from thebaine. Scheme 24 shows the synthesis of thebainone from thebaine. Treatment of thebaine with trimethylsilyl chloroformate and potassium carbonate gave dienone **58**[52] which upon removal of the protecting group gave a mixture of codeinone **7** and neopinone **8**. Zinc reduction of **7** gave thebainone **4**, the ^1H NMR of which was superimposable on the spectrum recorded of the totally synthetic material.

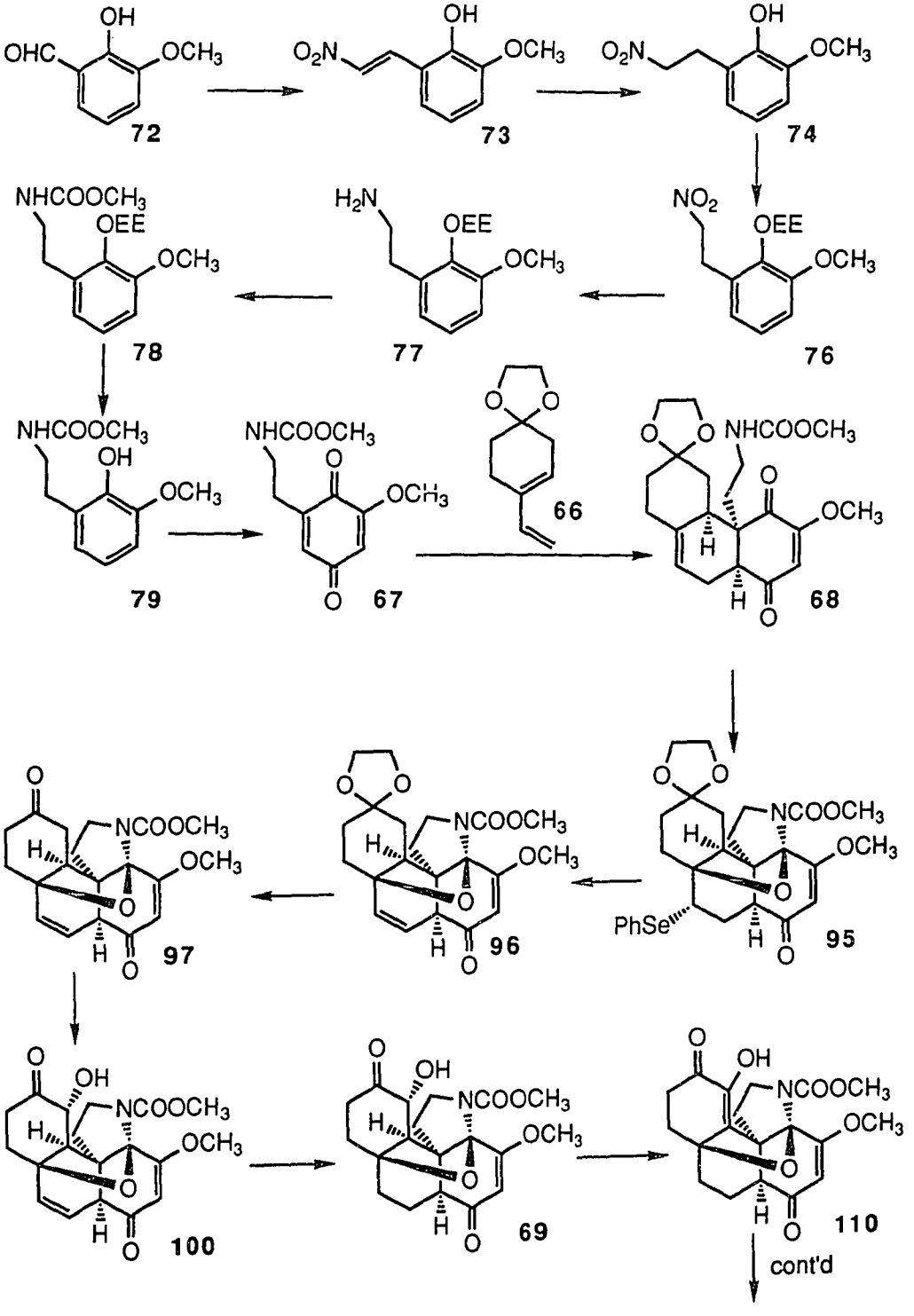
CONCLUSION

A unique synthesis of morphinan alkaloids has been discussed. By virtue of the fact that thebainone and beta-thebainone have been converted to morphine by Gates, the work described herein represents a total synthesis of racemic morphine. This work represents a departure from the standard way of thinking about the preparation of morphinans and fulfills one of the primary goals of synthetic organic chemistry; to design interesting and useful approaches to the problem of assembling complex molecules.

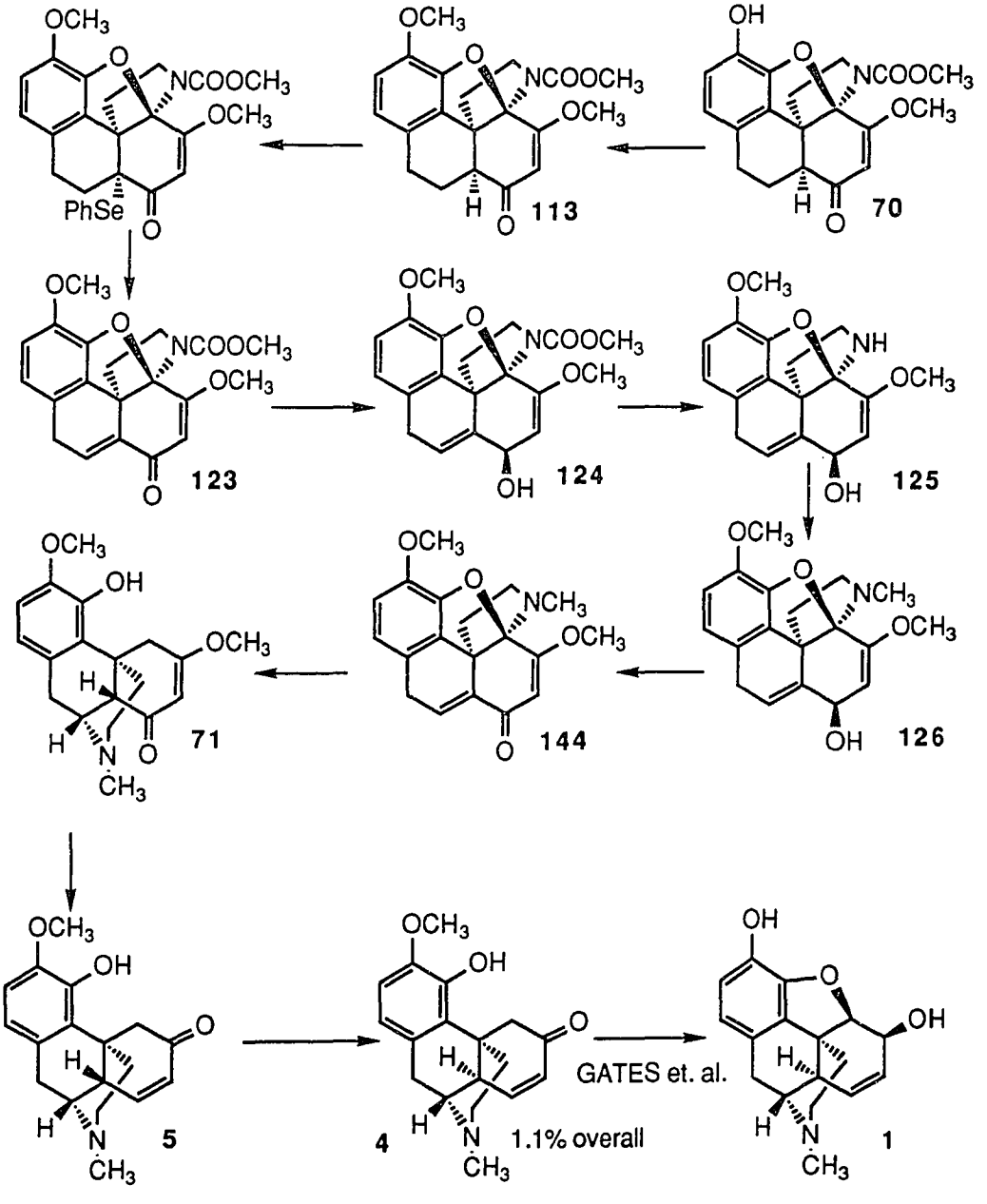
Scheme 25 shows the complete synthesis of thebainone in 24 steps and in 1.1% overall yield. Important features of the sequence include the rapid construction of the carbon skeleton of morphine, the highly regioselective oxygenation of the A-ring, the aromatization rearrangement, and the formation of the piperidine ring via the reductive cleavage of the alpha-amino ketone.

It is worthy of note that **128** and **145** represent two structural isomers of the morphinan ring system. Based on what is known of the minimum requirements for opiate activity, these compounds should exhibit opiate activity.

SCHEME 25

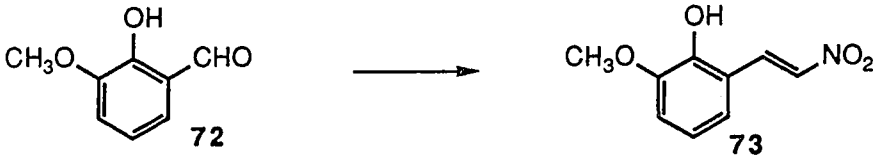

OH
OHC
OCH3
72
O2N
73
74
NHCOOCH3
OEE
78
H2N
77
NO2
76
79
67
66
68
NCOOCH3
PhSe
95
96
97
100
69
110
cont'd

SCHEME 25 (cont'd)



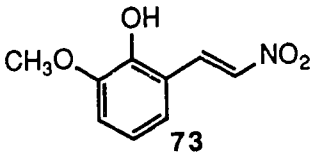
EXPERIMENTAL

For general considerations see page 12



Condensation of o-vanillin with nitromethane to prepare nitrostyrene 73.

To a solution of 30 g (0.390 mol) ammonium acetate in 200 mL glacial acetic acid was added 51 g o-vanillin (0.336 mol) and 70 mL (1.29 mol) nitromethane. The mixture was heated under gentle reflux for several hours and the progress of the reaction was monitored by tlc. If the temperature of the reaction exceeded 110-120°C, there was significant loss of material due to polymerization. When no starting material remained, the mixture was cooled to ambient temperature and poured onto crushed ice. The orangish-brown crystals were collected by filtration. The crude product was air dried first then dried further under high vacuum. The purity of the nitrostyrene was sufficient (> 95%) for use in the next reaction but material could be recrystalized from ethanol if so desired. The yield of crude product was 60.7 g (93%).



73

tlc: R_f = 0.38 (30% EtOAc/hexanes)

mp: 115-118°C

^1H NMR (300 MHz, $CDCl_3$):

8.14 (d, J = 13.6 Hz, 1 H),

8.09 (d, J = 13.6 Hz, 1 H), 7.04-6.91 (m, 3 H),

6.47 (br s, 1 H), 3.95 (s, 3 H).

IR (CH_2Cl_2): 3570, 2960, 2890, 1640, 1610, 1530, 1490,

1360, 1110, 1090, 990 cm^{-1}.

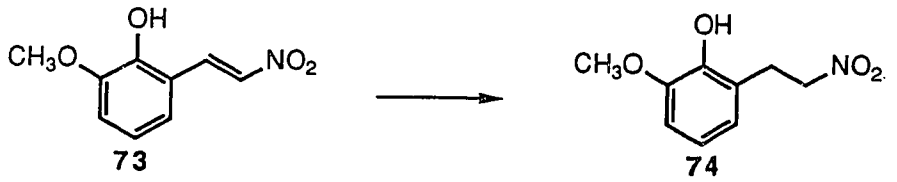
Mass spectrum (70 ev, m/e(intensity)): 196(m+1,10.3),

195(m^+,100.0), 178(6.2), 163(5.5), 148(83.4),

134(32.7), 133(35.5), 121(10.3), 105(25.1).

HRMS: for $C_9H_9NO_4$ calculated 195.0532

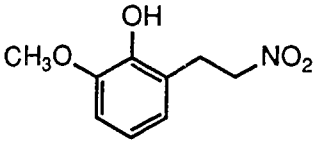
found 195.0535.



73 74

Reduction of nitrostyrene 73 to nitroalkane 74.

To a stirring solution of the nitrostyrene **73** (21.50 g, 110 mmol) in 350 mL tetrahydrofuran and 50 mL methanol was added in small portions 11.30 g (299 mmol) $NaBH_4$ (frothing occurs). The reaction took several hours and was followed by tlc. When no styrene remained, water 200 mL was added and the volatile solvents removed in vacuo. The remaining aqueous layer was brought to pH 8 by careful addition of 3% aqueous HCl and extracted three times with ether. The etheral extracts were combined, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to produce the crude nitroalkane as a dark oil. Flash chromatography on silica gel (15 % EtOAc/hexanes) yielded 15.77 g (73 %) of the pure product as an oil which sometimes solidified to a waxy solid.



74

tlc: R_f = 0.45 (30% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.79-6.71 (m, 3 H), 5.76 (s, 1 H),

4.64 (t, J = 7.3 Hz, 2 H), 3.87 (s, 3 H),

3.32 (t, J = 7.4 Hz, 2 H).

IR (neat): 3500, 3050, 3010, 2960, 2940, 2920, 2840, 1620, 1595, 1550, 1485, 1440, 1380, 1355, 1270, 1220, 1085 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 198(m+1,10.4), 197(m^+,93.6), 151(m-NO_2,69.3), 150(m-HNO2,100.0), 149(87.5), 137(25.6), 136(76.7), 135(51.9), 121(47.6), 119(44.9), 107(81.4).

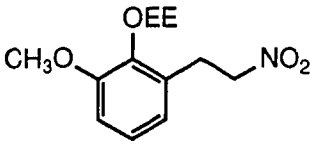
HRMS: for $C_9H_{11}NO_4$ calculated 197.0688

found 197.0677.

74 76

Preparation of the ethoxyethyl ether 76 of phenol 74.

To a solution of the phenol **74** (15.0 g, 0.076 mol) in 200 mL dry methylene chloride was added ethyl vinyl ether (14.5 mL, 0.152 mol) followed by 1 g pyridinium p-toluenesulphonate. The mixture was stirred at room temperature until tlc indicated that the starting material had been consumed (several hours). The mixture was washed twice each with 10% NaOH and distilled water before drying the organic layer over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude product as a yellow oil. Flash chromatography on silica gel (elution with 10% EtOAc/hexanes) yielded 19.74 g (96%) of the pure product.



76

tlc: R_f = 0.40 (20% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.99 (t, J = 7.9 Hz, 1 H), 6.85-6.76 (m, 2 H),

5.47 (q, J = 5.2Hz, 1 H),

4.67 (dt, J = 7.8, 1.8 Hz, 2 H), 3.85 (s, 3 H),

3.62-3.28 (m, 4 H), 1.47 (d, J = 5.1 Hz, 3 H),

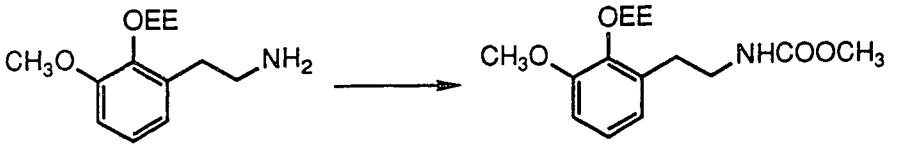
1.10 (t, J = 7.0 Hz, 3 H).

IR (neat): 3010, 2980, 2930, 1585, 1495, 1400, 1285, 1100 cm^{-1}.

76 77

Reduction of nitro alkane 76 to amine 77.

A solution of lithium aluminum hydride was prepared by adding 200 mL of a 1 M lithium aluminum hydride solution in tetrahydrofuran to 50 mL tetrahydrofuran. To this stirring solution at ambient temperature was added (via cannula) a solution of nitro alkane **76** (21.0 g, 78.1 mmol) in 50 mL tetrahydrofuran. The addition was done slowly in order to avoid an exothermic eruption. The reaction mixture was stirred at ambient temperature for 1 h after which time sodium fluoride (33.6 g, 0.80 mol) and water (10.8 mL, 0.60 mol) were carefully added. The mixture was stirred for several hours until an easily filterable precipitate was formed. The mixture was diluted with ether (200 mL) and filtered. The solid was washed with ether and the combined filtrates were concentrated in vacuo to give 14.56 g of the crude amine which was neither purified nor characterized but used directly in the next reaction.

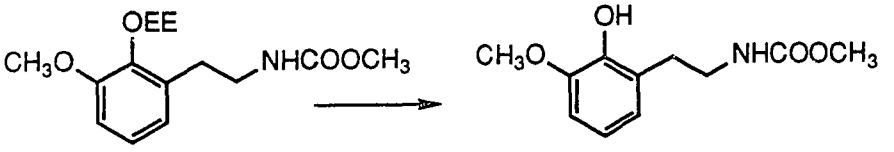


77 78

Preparation of carbamate 78 from amine 77.

To a solution of the crude amine from the previous reaction (14.56 g, about 62 mmol) in dry methylene chloride (200 mL) was added 30.0 mL (172 mmol) diisopropylethyl amine. Methyl chloroformate (9.6 mL, 124 mmol) was added slowly and the mixture was stirred at ambient temperature for 3 h. The reaction mixture was washed with water, three times with 3 % HCl, and once each with saturated aqueous $NaHCO_3$, and brine before drying over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude carbamate **78** which was neither purified nor characterized but used directly in the next reaction.

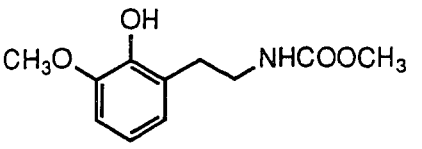
tlc: R_f = 0.57 (50 % EtOAc/hexanes)



78 79

Preparation of phenol 79 from acetal 78.

The crude product from the previous reaction (assumed to be 62 mmol) was taken up in 200 mL methanol. Pyridinium p-toluenesulphonate (0.50 g) was added and the mixture stirred at ambient temperature for 2 h until tlc indicated that the starting material had been consumed. The bulk of the methanol was removed in vacuo and this mixture was diluted with water and extracted with 100 mL ether six times. The combined etheral extracts were washed with brine and dried over $MgSO_4$. Revoval of the solvent gave the crude phenol which was purified by flash chromatography on silica gel (elution with 30 % EtOAc/hexanes). The yield was 9.68 g (69 % over three steps from nitroalkane **76**).



tlc: R_f = 0.42 (50% EtOAc/hexanes)

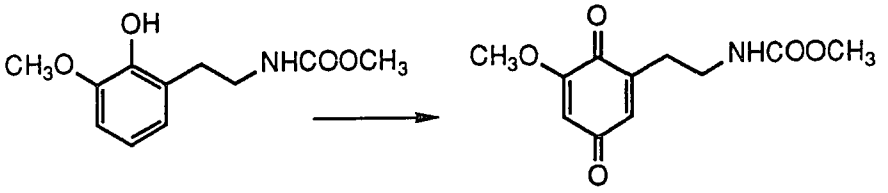
^1H NMR (300 MHz, $CDCl_3$):

6.81-6.71 (m, 3 H), 5.93 (s, 1 H), 5.02 (br s, 1 H), 3.86 (s, 3 H), 3.64 (br s, 3 H), 3.44 (br m, 2 H), 2.84 (br t, J = 6.7 Hz, 2 H).

IR (neat): 3400, 2990, 2880, 1780, 1720, 1540, 1500, 1460, 1360, 1280, 1220, 1100 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 226(m+1,1.7), 225(m^+,14.1), 193(12.9), 150(75.8), 137(m-$CH_2NHCOOCH_3$,54.6), 122(10.8), 107(12.6), 88($CH_2NHCOOCH_3$,100).

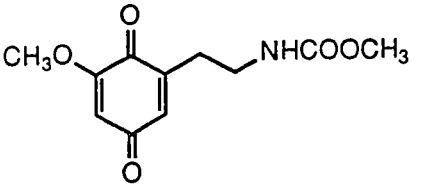
HRMS: for $C_{11}H_{15}NO_4$ calculated 225.1002
found 225.1006.



79 67

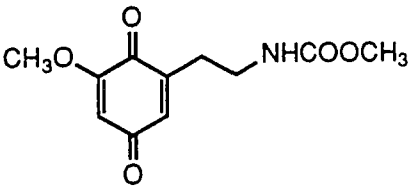
Preparation of quinone 67 from phenol 79.

The phenol **67** (9.60 g, 42.7 mmol) was taken up in 50 mL dry N,N-dimethyl formamide in a 250 mL sidearmed flask. The neck of the flask was equipped with a bubbler and the sidearm was fitted with a rubber septum. A 9" disposable pipet was pushed through the septum and this pipet was connected via a rubber hose to a balloon containing oxygen. The hose was fitted with a pinchcock to regulate the flow of oxygen. The oxygen was bubbled vigorously through the solution for several minutes after which time 1.39 g (4.27 mmol) N,N-bis(salicylidene)ethylenediaminocobalt(II) (also known as salcomine) was added portionwise. The mixture was stirred and oxygen was continuously bubbled through the suspension until tlc indicated that no starting material remained. The time of the reaction is dependent on the amount of substrate and the oxygen flow rate. The flow rate was adjusted such that one balloon lasted approximately 12 h. Upon completion of the reaction Celite was added and the solvent removed under high vacuum leaving a solid which was crushed and placed into a sohxlet



67

apparatus. This powdery solid was extracted with ether until the tlc of the extraction solvent showed no quinone remaining (anywhere from 3 days to 1 week). The ether was removed in vacuo to give the crude quinone as a orangish brown solid. It was possible use the quinone without further purification but better results were obtained when it was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes). It was important not to overload the column since doing so resulted in the product crystallizing on the column. The yield of pure quinone was 7.60 g (78%).



67

tlc: R_f = 0.20 (50% EtOAc/hexanes)

Melting point: 133-134°C

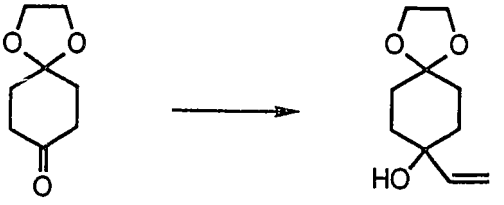
^{1}H NMR (300 MHz, $CDCl_3$):

6.54-6.53 (m, 1 H), 5.90 (d, J = 2.1 Hz, 1 H),
4.87 (br s, 1 H), 3.83 (s, 3 H), 3.64 (br s, 3 H),
3.41-3.35 (br m, 2 H), 2.66 (t, J = 6.5 Hz, 2 H).

IR (CH_2Cl_2): 3500, 3110, 3080, 2990, 2900, 1740, 1710,
1670, 1630, 1530, 1460, 1340, 1250, 1065 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 239(m^+,6.3),
207(3.0), 165(10.0), 164(28.9), 152.1(100),
88($CH_2NHCOOCH_3$,54.9).

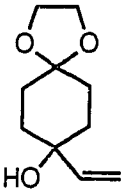
HRMS: for $C_{11}H_{13}NO_5$ calculated 239.0794
found 239.0798.



80 81

Preparation of allylic alcohol 81.

A solution of the Grignard reagent was prepared by diluting 200 mL of a 1 M tetrahydrofuran solution of vinylmagnesium bromide (200 mmol) with an additional 50 mL tetrahydrofuran. To this solution at ambient temperature was added 20 g (128 mmol) of the ketone **80** as a solution in 100 mL tetrahydrofuran. The addition was carried out by slow addition from a dropping funnel. After addition was complete, the mixture was stirred for several hours and the progress of the reaction was monitored by tlc. When the starting material had been consumed, the reaction was quenched by slow addition of 3% HCl, bringing the reaction to about pH 7. The majority of the tetrhydrofuran was removed in vacuo and the resulting mixture was diluted with ether. The organic layer was separated and the aqueous phase was extracted twice with ether. The combined etheral extracts were washed once each with 3% aqueous HCl,



81

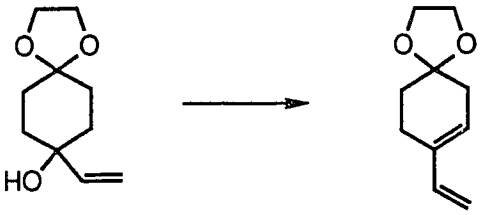
saturated aqueous $NaHCO_3$, and brine before drying over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude alcohol (20.55 g, 87%) which was of high purity and was used directly in the next reaction. Flash chromatography (elution with 50% EtOAc/hexanes) yielded pure samples for analytical purposes.

tlc: R_f = 0.42 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

5.98 (dd, J = 17.4, 10.8 Hz, 1 H),
5.28 (d, J = 17.1 Hz, 1 H),
5.06 (d, J = 10.5 Hz, 1 H), 3.99-3.91 (m, 4 H),
3.76-3.72 (m, 1 H), 2.01-1.76 (m, 4 H),
1.67-1.60 (m, 4 H).

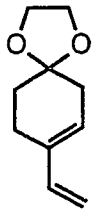
IR (neat): 3450, 3080, 2930, 2880, 1640, 1440, 1360, 1250, 1100, 1030, 990, 970, 925 cm^{-1}.



81 66

Preparation of diene 66 by dehydration of alcohol 81.

To a solution of the alcohol (7.68 g, 41.7 mmol) in dry benzene was added 100 g of 5 A molecular sieves and about 1 g p-toluenesulphonic acid. The mixture was stirred until the starting material had disappeared as determined by tlc. The reaction time was several days and it was necessary to add more acid several times per day. The mixture was filtered and the sieves washed with ether. The combined filtrates were washed with saturated aqueous $NaHCO_3$ and brine before drying over $MgSO_4$. Evaporation of the solvent gave the crude diene which was quickly purified by flash chromatography on silica gel (elution with 5-10% EtOAc/hexanes containing 1% triethyl amine). The yield of pure product was 2.34 g (34%).



66

tlc: R_f = 0.36 (10% EtOAc/hexanes)

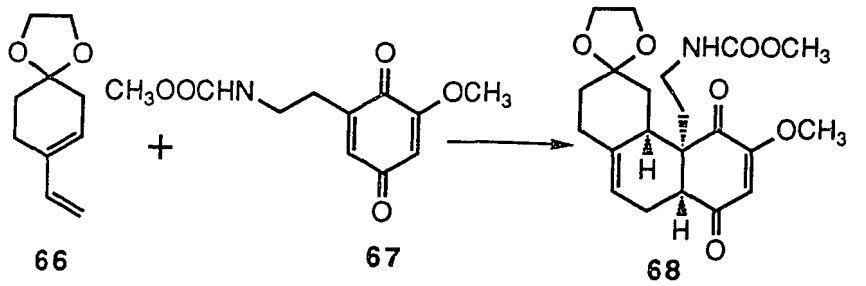
^1H NMR (300 MHz, $CDCl_3$):

6.37 (dd, J = 17.5, 10.7 Hz, 1 H), 5.66 (br s, 1 H),
5.10 (d, H = 17.5 Hz, 1 H),
4.96 (d, J = 10.7 Hz, 1 H), 4.00 (s, 4 H),
2.39 (br m, 4 H), 1.83 (t, J = 6.8 Hz, 2 H).

IR (neat): 3080, 3020, 2950, 2930, 2880, 1640, 1600, 1360, 1250, 1120, 1060, 1040, 870 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 167(m+1,2.6), 166(m^+,19.5), 155(2.2), 151(2.1), 138(4.0), 99(8.9), 86(100).

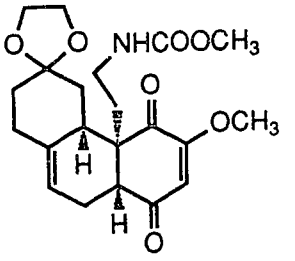
HRMS: for $C_{10}H_{14}O_2$ calculated 166.0994
found 166.1040.



66 67 68

Preparation of Diels-Alder adduct 68.

The diene (2.94 g, 17.7 mmol) and the quinone (2.82 g, 11.8 mmol) were taken up in 50 mL toluene in a 200 mL flask equipped with a reflux condenser. The suspension was heated in a sand bath to 100°C during which time the quinone completely dissolved. The progress of the reaction was monitored by tlc. Upon complete disappearance of the quinone (usually several days), the reaction was cooled and the solvent removed in vacuo. The resulting brown solid was purified by flash chromatography on silica gel (elution with 70% EtOAc/hexanes) to yield 4.30 g (86%) of the pure adduct **68** as a white or off-white solid. A small sample was recrystalized from ethyl acetate and hexanes for melting point determination, crystallographic analysis and combustion analysis.



68

tlc: R_f = 0.21 (70% EtOAc/hexanes)

Melting point: 190-191°C

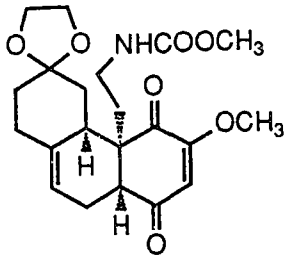
Combustion analysis: For $C_{21}H_{27}NO_7$

calculated: %C = 62.21, %H = 6.71, %N = 3.45

found: %C = 62.17, %H = 6.74, %N = 3.31

^1H NMR (300 MHz, $CDCl_3$):

6.01 (s, 1 H), 5.49 (d, J = 4.7 Hz, 1 H),
4.74 (br s, 1 H), 3.89-3.82 (m, 4 H), 3.78 (s, 3 H),
3.62 (s, 3 H), 3.30-3.14 (br m, 3 H),
2.94 (dd, J = 17.9, 5.1 Hz, 1 H),
2.43 (dt, J = 14.1, 8.1 Hz, 1 H), 2.24-2.05 (m, 4 H),
1.93-1.81 (m, 1 H), 1.72 (br d, J = 12.6 Hz, 1 H),
1.47 (dt, J = 12.9, 5.9 Hz, 1 H),
1.32 (d, J = 9.3 Hz, 2 H).



68

^{13}C NMR (75 MHz, $CDCl_3$): 197.6, 197.1, 161.3, 156.9, 136.0, 117.2, 112.7, 108.5, 64.2(two signals), 56.3, 52.0, 51.7, 44.6, 44.3, 40.7, 37.2, 36.5, 35.6, 32.6, 19.6.

IR (CH_2Cl_2): 3500, 2980, 2935, 1740, 1695, 1625, 1530, 1375, 1220, 1090 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 405(m+,9.9), 377(10.0), 373(20.6), 345(30.3), 303(m-$CH_2CH_2NHCOOCH_3$,100), 241(42.8), 166(43.3).

HRMS: for $C_{21}H_{27}NO_7$ calculated 405.1788
found 405.1802.

X-RAY CRYSTALLOGRAPHIC DATA FOR **68**

Formula: $C_{21}H_{27}NO_7$ Formula wt.: 405

Crystal System: triclinic

a(A): 9.235(4)

b(A): 9.752(4)

c(A): 11.987(7)

alpha(deg): 80.07(4)

beta(deg): 79.54(4)

gamma(deg): 86.35(4)

V(A^3): 1045.1(9)

Space Group: $P\bar{1}$

Z: 2

d_{calcd}(g/cm^3): 1.288

Radiation: MoK(alpha)

wavelength(A): 0.71073

absorption coefficient(cm-1): 0.58

temp(^oC): 20

Data Collection Instrument: Nicolet R3m/V

Scan type: 2theta-theta

Data Collection Range(2theta,deg): 4-50

No. of reflections collected: 2177

No. of unique reflections: 2006

No. of reflections with F_o>2(sigma)(F_o): 1323

No. of parameters refined: 262

X-RAY CRYSTALLOGRAPHIC DATA FOR **68** (CONT'D)

Largest delta/sigma,final cycle: 1.23

Largest residual peak: 0.55

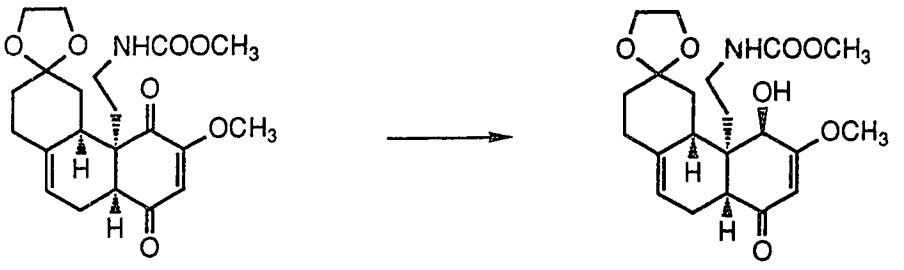
R: 0.1425

R_w: 0.1237

Goodness of fit indicator: 1.52

System used: Nicolet SHELXTL PLUS (microVAX II)

Solution: Direct Methods

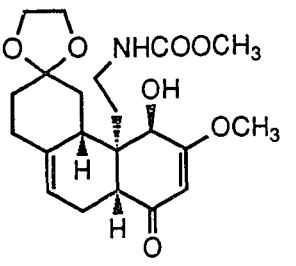


68 87

Reduction of enedione 68 to hydroxy enone 87.

A small unmeasured amount of 10% palladium on carbon (approximately 0.5 eq.) was placed in a dry 25 mL sidearmed flask equipped with a septum inlet and a three way stopcock. The flask was evacuated and purged several times with nitrogen. This procedure was repeated with hydrogen. Dry tetrahydrofuran (3 mL) was introduced followed by the substrate (35 mg, 0.086 mmol) in 3 mL tetrahydrofuran. The mixture was stirred until tlc indicated that no starting material remained (5-10 min). The mixture was filtered through a pad of Celite and the solid residue washed with EtOAc. Evaporation of the solvent in vacuo gave the crude product which could be purified by flash chromatography on silica gel (elution with EtOAc). The yield was 32 mg (91%).

tlc: R_f = 0.24 (EtOAc)



87

^{1}H NMR (300 MHz, $CDCl_3$):

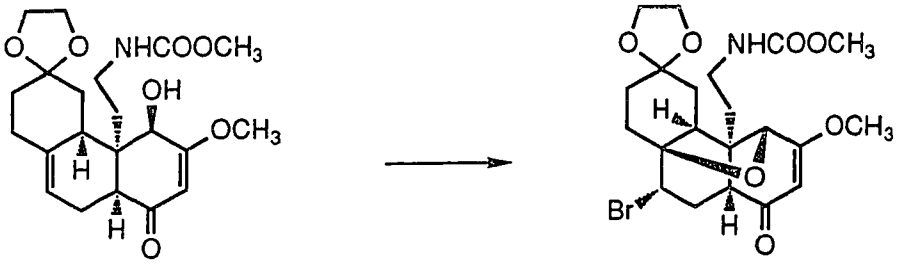
5.39 (br d, J = 4.6 Hz, 1 H), 5.36 (s, 1 H),
4.89 (br s, 1 H), 4.79 (br s, 1 H),
4.00-3.85 (m, 5 H), 3.76 (s, 3 H), 3.66 (s, 3 H),
3.34 (br m, 2 H), 3.00-2.93 (m, 2 H),
2.35-2.26 (m, 2 H), 2.13-1.97 (m, 4 H),
1.87-1.72 (m, 2 H), 1.49-1.28 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): 197.7, 174.4, 157.8, 138.0, 117.7,
109.8, 102.7, 71.2, 65.0, 64.8, 64.7, 57.1, 52.8,
45.9, 45.4, 42.2, 40.9, 38.0, 37.6, 37.0, 33.7.

IR (neat): 3360, 3060, 2950, 2895, 2860, 1725, 1710, 1700,
1645, 1610, 1535, 1445, 1355, 1255, 1200 cm^{-1}.

Mass spectrum (70 ev, m/e) 407(m^+,1.2), 389(0.3), 375(0.8),
357(0.4), 349(2.2), 305(1.6), 287(11.1), 243(8.6),
224(9.4), 197(19.1), 150(31.4), 73(100).

HRMS: for $C_{21}H_{29}NO_7$ calculated 407.1944
found 407.1936.



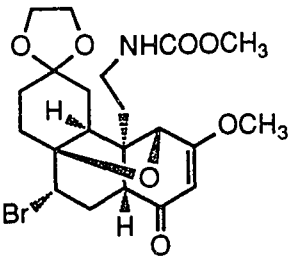
87 89

Bromoetherification of alcohol 87 to produce 89.

The olefin **87** (30 mg, 0.74 mmol) was taken up in dry tetrahydrofuran (5 mL) under an atmosphere of dry nitrogen. Dry pyridine (0.03 mL, 0.369 mmol) was added followed by pyridinium bromide perbromide (118 mg, 0.369 mmol) portionwise. The mixture was stirred for several hours until tlc indicated that the starting material had been consumed. Ethyl acetate was added and the resulting solution was washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The resulting crude product was purified by flash chromatography on silica gel (elution with 65% EtOAc/hexanes). The yield of pure bromoether **89**, obtained as a white solid, was 33 mg (92%).

tlc: R_f = 0.29 (70% EtOAc/hexanes)

IR (neat): 3340, 2940, 2880, 1725, 1710, 1655, 1605, 1525, 1450, 1430, 1210 cm^{-1}.



89

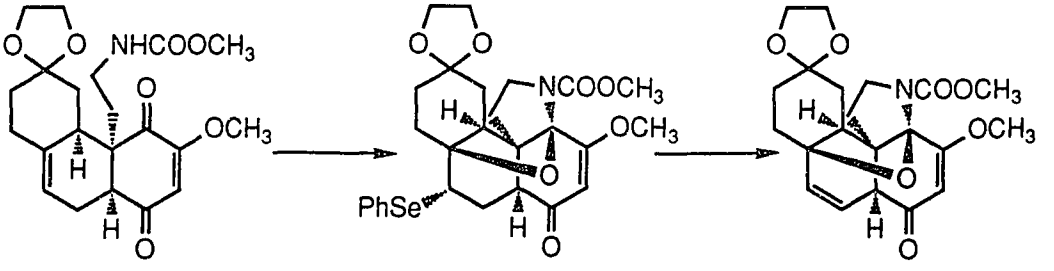
^{1}H NMR (300 MHz, $CDCl_3$):

5.19 (s, 1 H), 4.75 (br s, 1 H), 4.26 (s, 1 H),
4.06 (d, J = 5.6 Hz, 1 H), 4.07-3.95 (m, 5 H),
3.75 (s, 3 H), 3.63 (s, 3 H),
3.32-3.29 (m, 1 H), 3.16-3.12 (m, 1 H),
3.00 (dd, J = 12.1, 6.7 Hz, 1 H), 2.85-2.65 (m, 2 H),
2.54-2.43 (m, 1 H), 2.32 (dd, J = 15.1, 6.8 Hz, 1 H),
2.03-1.97 (m, 1 H), 1.87-1.74 (m, 3 H),
1.65-1.59 (m, 2 H), 1.51-1.40 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): 201.5, 169.2, 156.8, 108.0, 99.3,
85.3, 79.8, 64.7, 64.4, 56.5, 53.7, 52.1, 50.1, 45.9,
40.4, 36.8, 35.6, 30.2, 30.1, 29.5, 29.2.

Mass spectrum (70 ev, m/e(intensity)): 487(m+2,34.0),
485(m^+,33.1), 455(16.0), 453(14.4), 407(21.0),
406(m-Br,100), 374(38.8), 331(14.5), 303(7.2),
260(8.3), 216(11.2), 181(18.8), 99(89.9).

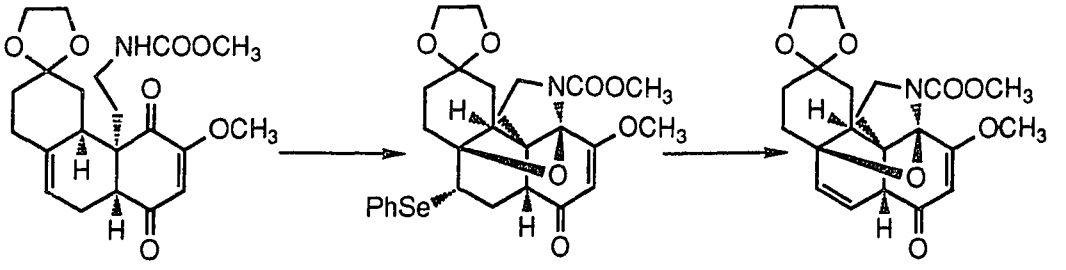
HRMS: for $C_{21}H_{28}NO_7Br$ calculated 485.1050
found 485.1051.



68 95 96

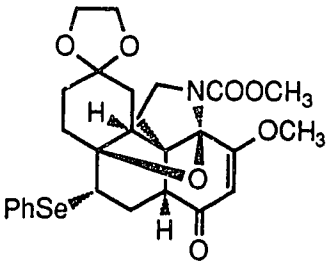
Tandem selenocyclization of adduct 68 to give selenide 95 followed by oxidation to olefin 96.

A suspension of Diels-Alder adduct **68** (1.88 g, 4.65 mmol) in 150 mL methanol was stirred vigorously under an atmosphere of nitrogen. The suspension was cooled to 0°C in an ice bath. In a separate flask, a solution of phenylselenium chloride in 25 mL methanol was prepared. This solution was added to the suspension over about 5 min via cannula. The progress of the reaction was monitored by tlc. After several hours, when the reaction was complete, 10% Na_2CO_3 was added to the reaction. After stirring for several minutes, the reaction mixture was diluted with ethyl acetate and the organic layer separated. The aqueous portion was extracted several times with ethyl acetate and the organic extracts were combined and washed twice with 10% Na_2CO_3 and once with brine. Evaporation of the solvent in vacuo gave the crude selenide which was not purified but taken up in 50 mL tetrahydrofuran and cooled to 0°C in an ice bath. Hydrogen peroxide was added (20 mL of a 30% aqueous solution) and the ice bath removed. The reaction



68 **95** **96**

mixture was stirred at ambient temperature for 2 h after which time it was poured into a separatory funnel containing 300 mL ethyl acetate. The resulting solution was washed twice each with 10% Na_2CO_3 and 10% Na_2SO_3 and once with brine. The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo to yield the crude olefin. In general the product was carried on without purification to the next reaction but could be purified for analytical purposes by flash chromatography on silica gel. For the purposes of melting point determination, combustion analysis, and crystalographic analysis, samples were recrystalized from ethyl acetate and hexanes.



95

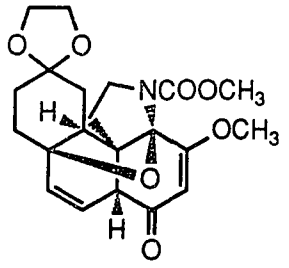
Selenide **95:**

tlc: R_f = 0.25 (70% EtOAc/hexanes)

IR (neat): 3080, 2950, 2900, 1735, 1700, 1685, 1605, 1450, 1365, 1220, 1085 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 564(m+3,0.47), 563(m+2,1.04), 562(m+1,1.60), 561(m^+,5.06), 560(m-1,0.86), 559(m-2,2.69), 558(m-3,0.89), 405(4.1), 404(5.7), 303(12.2), 248(11.3), 185(23.2), 129(28.7).

HRMS: for $C_{27}H_{31}SeNO_7$ calculated 561.1266
found 561.1208.



96

Olefin **96:**

Melting point: 237-238°C

tlc: R_f = 0.21 (EtOAc)

^1H NMR (300 MHz, $CDCl_3$):

5.74 (dd, J = 9.1, 1.4 Hz, 1 H),

5.48 (dd, J = 9.1, 2.4 Hz, 1 H), 5.14 (s, 1 H),

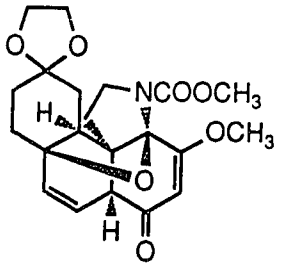
3.98-3.88 (m, 4 H), 3.74 (br s, 3 H), 3.70 (s, 3 H),

3.74-3.70 (1 H, obscured by other signals but observed from a COSY experiment),

3.43 (dt, J = 11.0, 3.6 Hz, 1 H), 3.30 (br t, 1 H),

2.29-2.23 (m, 2 H), 2.16-2.07 (m, 1 H),

1.89-1.57 (m, 6 H).



96

^{13}C NMR (75 MHz, $CDCl_3$): 197.7, 171.3, 155.5, 135.6, 127.3, 108.6, 98.2, 95.6, 84.4, 64.3, 64.2, 59.6, 57.3, 56.8, 52.7, 48.5, 47.5, 32.1, 30.3, 29.2, 24.6.

IR (neat): 3060, 2950, 2940, 2890, 1730, 1700, 1670, 1605, 1450, 1370, 1360, 1080.

Mass spectrum (70 ev, m/e): 404(m+1), 403(m^+), 388, 385, 373, 371, 359, 358, 356, 344, 326, 297, 282, 216, 173.

HRMS: for $C_{21}H_{25}NO_7$ calculated 403.1631
found 403.1636.

Combustion analysis: for $C_{21}H_{25}NO_7$
calculated: %C = 62.52, %H = 6.25, %N = 3.47
found: %C = 62.46, %H = 6.32, %N = 3.31.

X-RAY CRYSTALLOGRAPHIC DATA FOR **96**

Formula: $C_{21}H_{25}NO_7$ Formula wt.: 403

Crystal System: triclinic

a(A): 9.769(6)

b(A): 10.492(9)

c(A): 12.866(12)

alpha(deg): 72.22(7)

beta(deg): 72.13(7)

gamma(deg): 83.09(7)

V(A^3): 950.0(14)

Space Group: $P^{-}1$

Z: 2

d_{calcd}(g/cm^3): 1.410

Radiation: MoK(alpha)

wavelength(A): 0.71073

absorption coefficient(cm-1): 0.99

temp(^oC): 23

Data Collection Instrument: Nicolet R3m/V

Scan type:2theta-theta

Data Collection Range(2theta,deg): 4-45

No. of reflections collected: 2766

No. of unique reflections: 2471

No. of reflections with F_o>2(sigma)(F_o): 2081

No. of parameters refined: 285

X-RAY CRYSTALLOGRAPHIC DATA FOR **96** (CONT'D)

Largest delta/sigma,final cycle: 0.046

Largest residual peak(e/A^3): 0.29

R: 0.0652

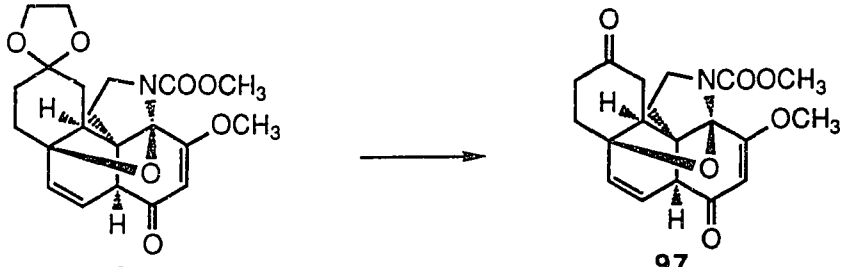
R_w: 0.0575

Goodness of fit indicator: 1.34

System Used: Nicolet SHELXTL PLUS (MicroVAX II)

Solution: Direct Methods

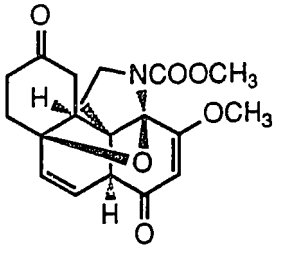
Scan time(deg/min): 1.50-14.65



96 **97**

Hydrolysis of ketal 96 to ketone 97.

The ketal **96** (the crude product from the previous reaction - assumed to be about 4.65 mmol) was taken up in 50 mL tetrahydrofuran. Aqueous HCl (50 mL of a 3% solution) was added and the mixture was stirred at room temperature until tlc indicated that no starting material remained (1-2 days). Most of the solvent was removed in vacuo and the resulting mixture was extracted with methylene chloride until tlc of the extraction solvent showed no product present (usually about 7 extractions totalling 500 mL). The combined extracts were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to yield the crude ketone **97** as a foam. Purification by flash chromatography (elution with EtOAc) on silica gel gave the pure product (1.210 g, 73% from Diels-Alder adduct **68**) as a white solid. A small sample was recrystallized from ethyl acetate and hexanes for melting point determination and combustion analysis.



97

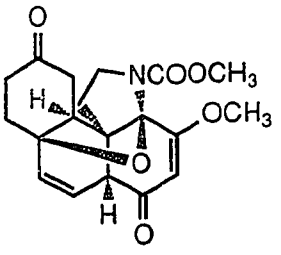
Melting point: 209-210°C

tlc: R_f = 0.15 (EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$):

5.86 (dd, J = 9.2, 2.1 Hz, 1 H),
5.57 (dd, J = 9.1, 2.8 Hz, 1 H), 5.21 (s, 1 H),
3.75 (br s, 3 H), 3.74 (s, 3 H),
3.79-3.71 (m, 1 H, partially obscurred by other signals), 3.45 (dt, J = 7.8, 4.3 Hz, 1 H),
3.36 (t, J = 2.3 Hz, 1 H), 2.81-2.47 (m, 5 H),
2.26-2.21 (m, 1 H),
2.11 (ddd, J = 14.4, 10.0, 4.3 Hz, 1 H),
1.96 (ddd, J = 14.8, 13.2, 5.3 Hz, 1 H),
1.88-1.69 (m, 1 H).

IR (CCl_4): 3020, 2985, 2940, 2895, 2840, 1745, 1730, 1700, 1680, 1610, 1450, 1360, 1230 cm^{-1}.

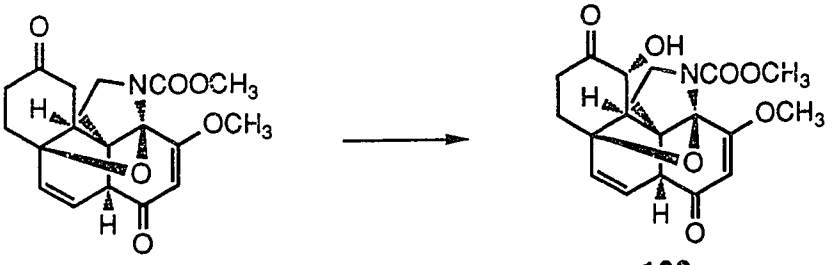


97

Mass spectrum (70 ev, m/e(intensity)): 359(m^+,8.9), 344(m-CH_3,10.4), 312(9.5), 282(20.4), 258(13.7), 257(22.5), 216(20.6), 173(31.9), 172(49.9).

HRMS: for $C_{19}H_{21}NO_6$ calculated 359.1369
found 359.1364.

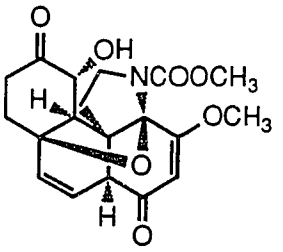
Combustion analysis: for $C_{19}H_{21}NO_6$
calculated %C = 63.50, %H = 5.89, %N = 3.90
found %C = 63.38, %H = 5.99, %N = 3.88.



97 100

Hydroxylation of ketone 97 to yield acyloin 100.

The ketone **97** (500 mg, 1.39 mmol) was taken up in dry tetrahydrofuran (90 mL) under an atmosphere of dry nitrogen. The solution was cooled to -78°C and potassium bis-trimethylsilylamide (2.78 mL of a 0.5 M solution in toluene, 1.39 mmol) was added dropwise. The solution was stirred for 1 h at -78°C after which time p-toluene-2-phenylsulphonyl oxaziridine (383 mg, 1.39 mmol) was added (as a solution in 10 mL tetrahydrofuran) via cannula. The mixture was stirred for 1 h after which time the reaction was quenched at -78°C with saturated aqueous NH_4Cl. The mixture was allowed to warm to room temperature and partitioned between water and methylene chloride. The aqueous phase was saturated with NaCl and extracted three times with methylene chloride and the combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude hydroxy ketone **100** which was subjected to flash chromatography on silica gel (elution with 70% EtOAc/ hexanes). The yield was 428 mg (82%).



100

tlc: R_f = 0.26 (EtOAc)

^1H NMR (300 MHz, $CDCl_3$):

5.79 (dd, J = 9.2, 2.0 Hz, 1 H),

5.59 (dd, J = 9.2, 2.7 Hz, 1 H), 5.23 (s, 1 H),

4.47 (br dd, J = 8.9, 2.6 Hz, 1 H),

3.99-3.86 (m, 1 H), 3.77 (s, 6 H, two signals),

3.66 (d, J = 3.3 Hz, 1 H, exchangable),

3.55 (dt, J = 11.2, 3.8 Hz, 1 H),

3.42 (br t, J = 2.4 Hz, 1 H), 2.92-2.77 (m, 2 H),

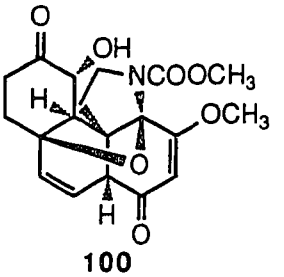
2.65 (ddd, J = 15.0, 5.8, 2.3 Hz, 1 H),

2.44 (ddd, J = 13.0, 4.4, 2.4 Hz, 1 H),

2.26 (d, J = 9.2 Hz, 1 H),

1.90 (dt, J = 14.7, 4.5 Hz, 1 H),

1.76 (ddd, J = 18.5, 11.1, 2.4 Hz, 1 H).

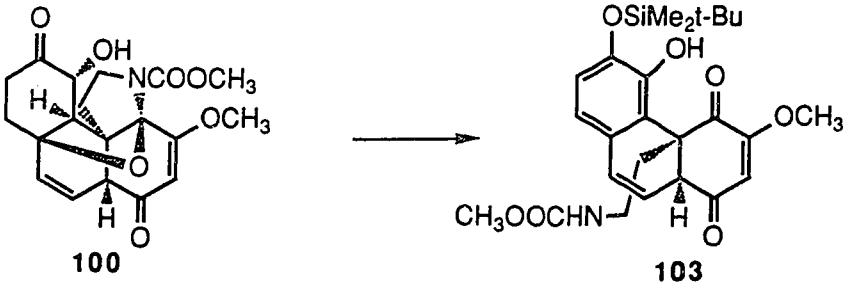


100

IR (neat): 3450, 3060, 3025, 2950, 2850, 1730, 1715, 1695, 1680, 1670, 1660, 1605, 1450, 1370, 1360, 1230, 1080 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 375(m^+,0.5), 373(0.7), 359(1.3), 357(0.6), 344(m-OCH_3,3.2), 282(7.6), 257(6.6), 216(5.9), 172(23.5), 149(15.3), 117(17.6), 57(100).

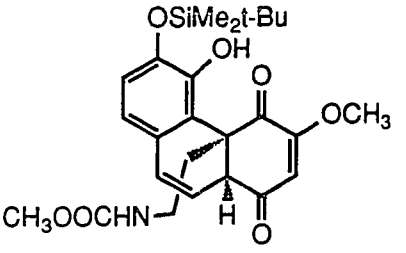
HRMS: for $C_{19}H_{21}NO_7$ calculated 375.1318
found 375.1304.



100 103

Conversion of acyloin 100 to monosilyl catechol 103.

Dimethyl sulphoxide (0.055 mL, 0.78 mmol) was taken up in dry methylene chloride (3 mL) and cooled to -78°C. Trifluoroacetic anhydride (0.055 mL, 0.39 mmol) was added slowly in 3 mL methylene chloride. After 15 min, the acyloin **100** (49 mg, 0.131 mmol) was added in methylene chloride (4 mL) and the mixture was stirred for 1 h. Triethylamine (0.5 mL, 3.6 mmol) was added and the mixture stirred at -78°C for 5 min after which time the dry ice bath was removed. After one hour, tert-butyldimethylsilyl chloride (excess - about one mmol) was added in 3 mL methylene chloride. The mixture was stirred until the appearance some bis-silylated material as determined by tlc (about 15 min). At this time the mixture was poured into water and the organic layer washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave the crude monosilyl catechol **103**. Purification by flash chromatography on silica gel (elution with 30% EtOAc/hexanes) yielded 38 mg (60%) of the monosilyl catechol and 15 mg (19%) of the bis silyl catechol.



103

tlc: R_f = 0.28 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.68 (d, J = 8.1 Hz, 1 H),

6.58 (two overlapping d, J = approx. 9 Hz, 2 H),

6.09 (dd, J = 9.4, 6.9 Hz, 1 H), 5.86 (s, 1 H),

5.68 (s, 1 H), 4.84 (br s, 1 H), 3.75 (s, 3 H),

3.58 (s, 3 H), 3.31 (d, J = 6.9 Hz, 1 H),

3.32-3.23 (m, 1 H), 3.09-3.03 (m, 1 H),

2.36-2.32 (m, 1 H), 2.05-2.01 (m, 1 H),

0.95 (s, 9 H), 0.23 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): 198.1, 196.7, 164.9, 156.8,

144.1, 142.3, 128.7, 126.9, 122.5, 120.4, 120.0,

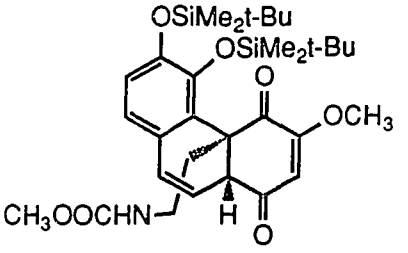
117.1, 112.2, 56.5, 54.3, 52.1, 51.9, 38.0, 32.2,

25.6, 18.2, - 4.39, -4.31.

IR (neat): 3510, 3410, 3350, 3050, 2960, 2940, 2900, 2860,

1730, 1720, 1670, 1615, 1525, 1495, 1290, 1260, 1200,

835 cm^{-1}.



tlc: R_f = 0.66 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.62 (d, J = 8.1 Hz, 1 H), 6.56 (d, J = 8.1 Hz, 1 H),

6.48 (d, J = 9.5 Hz, 1 H),

6.13 (dd, J = 9.4, 6.7 Hz, 1 H), 5.52 (s, 1 H),

4.19 (br s, 1 H), 3.62 (s, 3 H), 3.58 (s, 3 H),

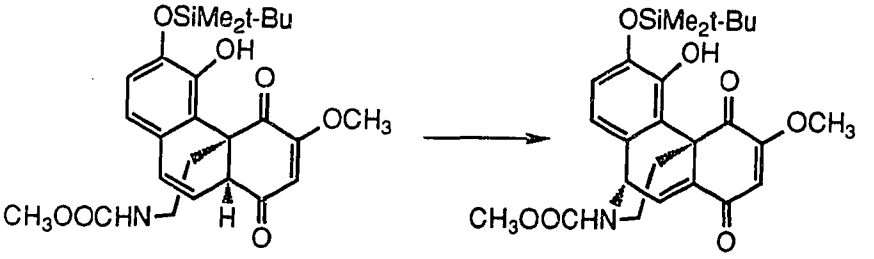
3.35-3.25 (m, 1 H), 3.15 (d, J = 6.7 Hz, 1 H),

3.15-3.07 (m, 1 H),

2.15-1.96 (two overlapping m, 2 H), 0.99 (s, 9 H),

0.93 (s, 9 H), 0.32 (s, 3 H), 0.22 (s, 3 H),

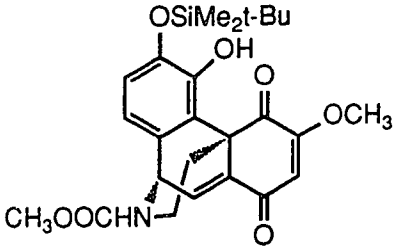
0.17 (s, 3 H), 0.15 (s, 3 H).



103 **104**

Selenocyclization of styrene 103 to 104.

The styrene **103** (a small unmeasured amount - about 10 mg) was taken up in dry methylene chloride (about 1 mL) in a 5 mL pear shaped flask. An excess of phenylselenium chloride was added portionwise and the progress of the reaction was followed by tlc. After a short time when all of the starting material had disappeared, the reaction mixture was diluted with methylene chloride and washed with 10% Na_2CO_3, 10% Na_2SO_3 and brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude product which was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexanes). The yield was not measured as this reaction was done only to characterize the product. The reaction produced almost a single compound as determined by tlc.



104

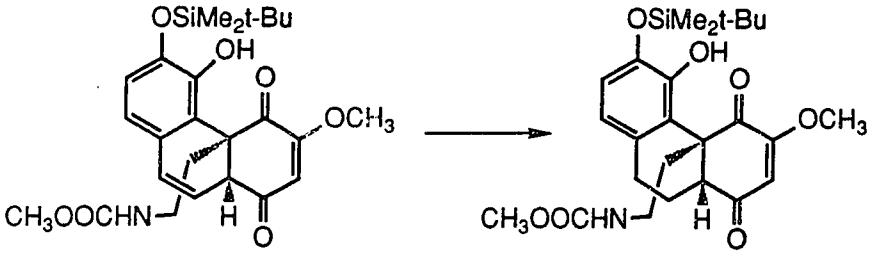
tlc: R_f = 0.33 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.72 (d, J = 8.1 Hz, 1 H), 6.59 (d, J = 8.1 Hz, 1 H),
6.50 (d, J = 9.6 Hz, 1 H),
5.97 (br s, two overlapping signals 2 H),
5.92 (s, 1 H), 3.79 (s, 3 H), 3.65 (s, 3 H),
3.67-3.57 (1 H obscurred by the 2 methoxy signals),
3.40-3.33 (m, 1 H), 2.92-2.86 (m, 1 H),
2.77-2.70 (m, 1 H), 0.99 (s, 9 H), 0.28 (s, 3 H),
0.26 (s, 3 H).

Mass spectrum (70 ev, m/e(intensity)): 486(m+1,2.9),
485(m^+,9.5), 427(9.0), 374(17.1), 373(61.5),
358(11.8), 357(46.1), 316(38.8), 315(100), 256(32.0),
207(18.5).

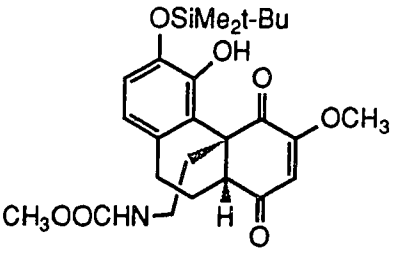
HRMS: for $C_{25}H_{31}SiNO_7$ calculated 485.1870
found 485.1872.



103 **109**

Hydrogenation of styrene 103 to 109.

A small (unmeasured) amount of 10% palladium on charcoal was placed in a 25 mL sidearmed flask equipped with a septum inlet and a three-way stopcock. The flask was evacuated and purged several times first with nitrogen and then with hydrogen via a balloon attached to the three-way stopcock. tetrahydrofuran (3 mL) was added via syringe. The substrate (27 mg, 0.055 mmol) was introduced to the stirring suspension as a solution in tetrahydrofuran (2 mL). The mixture was stirred vigorously until tlc indicated that the starting material had been consumed (about 2 days). The balloon of hydrogen was changed daily. When the reaction was complete, the mixture was filtered through a pad of Celite. The solid residue was washed with ethyl acetate. Evaporation of the filtrate gave the crude product which was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes). The yield was 22 mg (81%).



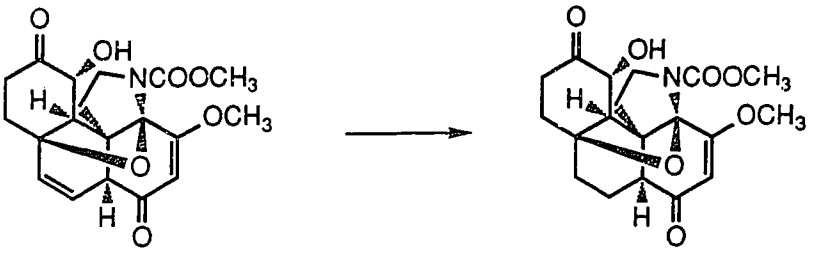
109

tlc: R_f = 0.32 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.65 (d, J = 8.3 Hz, 1 H), 6.51 (d, J = 8.3 Hz, 1 H),
5.60 (s, 2 overlapping signals 2 H),
4.93 (br s, 1 H), 3.70 (s, 3 H),
3.61 (s, 3 H), 3.42-3.30 (m, 1 H),
3.27-3.16 (m, 1 H), 2.96 (t, J = 3.8 Hz, 1 H),
2.88 (t, J = 8.8 Hz, 1 H),
2.74 (ddd, J = 15.8, 8.3, 1.9 Hz, 1 H),
2.61-2.53 (m, 1 H), 2.42-2.32 (m, 1 H),
2.18-2.04 (m, 2 H), 0.95 (s, 9 H), 0.20 (s, 3 H),
0.19 (s, 3 H).

IR (CCl_4): 3520, 3400, 3050, 2960, 2940, 2860, 1730, 1715, 1660, 1610, 1060 cm^{-1}.



100 **69**

Preparation of 69 by hydrogenation of 100.

This procedure is identical to the procedure for the hydrogenation of styrene **103** to **109** (previous experimental). The amounts were as follows:

olefin **100** - 439 mg (1.17 mmol)

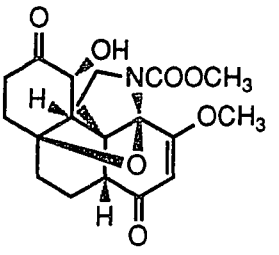
10% palladium on charcoal - 311 mg (0.239 mmol)

tetrahydrofuran - 60 mL

The crude product was purified by flash chromatography on silica gel (elution with EtOAc). The yield was 332 mg (75 %) as a white solid.

tlc: R_f = 0.20 (EtOAc)

IR (neat): 3440, 3050, 2940, 2920, 2840, 1725, 1710, 1690, 1665, 1600, 1445, 1365, 1220, 1085.



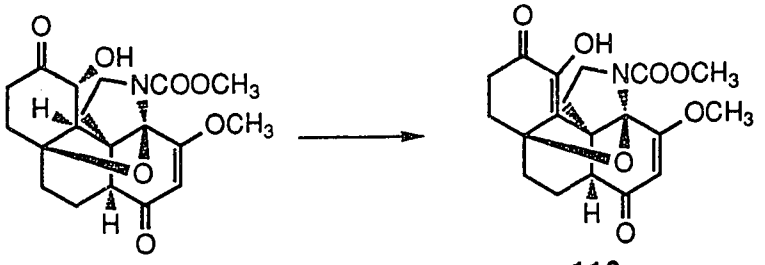
69

^{1}H NMR (300 MHz, $CDCl_3$):

5.31 (s, 1 H), 4.41 (br d, J = 7.8 Hz, 1 H),
3.79 (s, 2 signals, 6 H), 3.68 (d, J = 2.8 Hz, 1 H),
3.42 (dt, J = 11.3, 4.2 Hz, 1 H), 2.92-2.81 (m, 1 H),
2.80 (dd, J = 8.6, 6.1 Hz, 1 H),
2.69 (ddd, J = 14.2, 10.0, 4.2 Hz, 1 H),
2.59 (dt, J = 9.6, 3.6 Hz, 1 H),
2.37 (dt, J = 13.1, 3.7 Hz, 1 H),
2.08 (d, J = 8.5 Hz, 1 H), 2.12-1.95 (m, 2 H),
1.92-1.81 (m, 2 H), 1.78-1.61 (m, 3 H).

Mass spectrum (70 ev, m/e): 377(m^+), 359(m-H_2O), 345, 302,
275, 236, 209, 166.

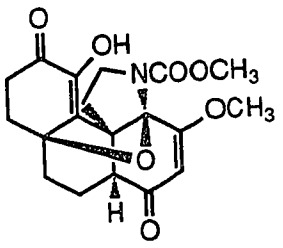
HRMS: for $C_{19}H_{23}NO_7$ calculated 377.1474
found 377.1486.
for $C_{19}H_{21}NO_6$ calculated 359.1369
found 359.1379.



69 110

Swern oxidation of acyloin 69 to yield diketone 110.

Dimethyl sulphoxide (0.43 mL, 6.05 mmol) was taken up in 15 mL dry methylene chloride under an atmosphere of dry nitrogen and cooled to -78°C. Trifluoroacetic anhydride (0.43 mL, 3.02 mmol) was added in 15 mL methylene chloride dropwise. The mixture was stirred for 15 min after which time the substrate **69** (380 mg, 1.01 mmol) was added as a solution in 15 mL methylene chloride. After 1 h, triethylamine (about 1 mL) was added and the mixture was warmed to ambient temperature. Two products were observed by tlc which after about 8 h had been converted to the less polar of the two. The mixture was poured into 3% aqueous HCl and the organic phase separated. The aqueous phase was extracted several times with methylene chloride and the combined extracts were washed successively with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine before drying over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude product which was used directly in the next reaction.



110

The diketone was mildly unstable to silica gel chromatography but could be purified by this method for characterization purposes (elution with EtOAc).

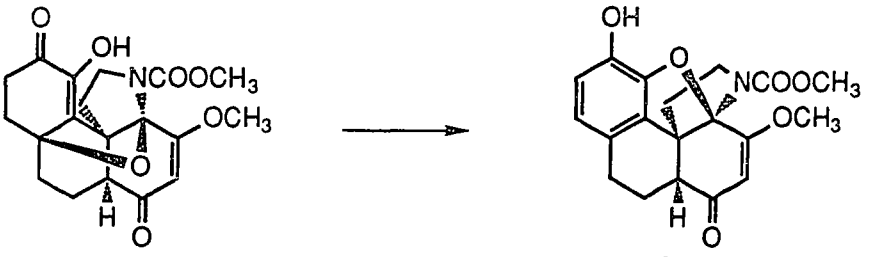
tlc: R_f = 0.28 (EtOAc)

^1H NMR (300 MHz, $CDCl_3$):

6.31 (s, exchangeable, 1 H), 5.21 (s, 1 H),
3.77 (s, 3 H), 3.76 (s, 3 H), 3.77-3.61 (m, partially obscurred by 3.77 and 3.76 s, 1 H),
3.54-3.44 (m, 1 H), 2.92-2.86 (m, 2 H),
2.72 (ddd, J = 17.7, 5.1, 2.1 Hz, 1 H),
2.49-2.04 (m, 7 H), 1.81-1.71 (m, 1 H).

Mass spectrum (70 ev, m/e): 376(m+1), 375(m^+), 357, 347, 288, 236.

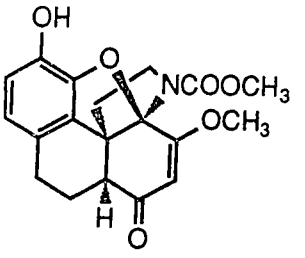
HRMS: for $C_{19}H_{21}NO_7$ calculated 375.1318
found 375.1315.



110 70

Aromatization of diketone 69 to yield 70.

The crude diketone **69** from the previous reaction (assumed to be about 1.01 mmol) was taken up in 25 mL dry methylene chloride under an atmosphere of nitrogen. The mixture was cooled to -30°C and borontrifluoride etherate (0.62 mL, 5.00 mmol) was added dropwise. The reaction mixture was warmed to ambient temperature and stirred until tlc indicated the complete disappearance of starting material (several hours). Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture stirred for about 0.5 h after which time the mixture was poured into a separatory funnel. The organic layer was separated and the aqueous layer was extracted several times with methylene chloride. The combined organic extracts were washed once each with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude product which was not purified but used directly in the next reaction. This material was characterized by tlc and ^1H NMR only.

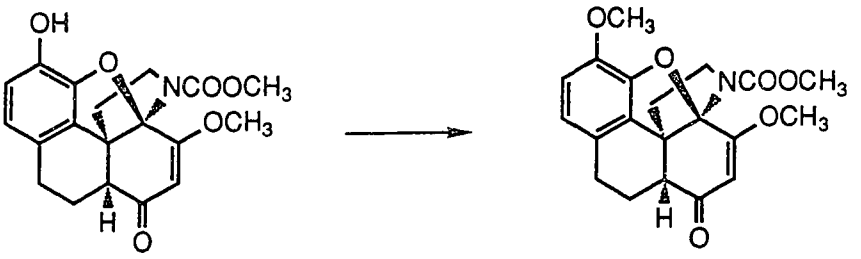


70

tlc: R_f = 0.60 (EtOAc)

^1H NMR (300 MHz, $CDCl_3$):

6.72 (d, J = 8.2 Hz, 1 H), 6.56 (d, J = 8.3 Hz, 1 H),
6.09 (br s, 1 H), 5.36 (s, 1 H), 4.13-4.06 (m, 1 H),
3.88-3.80 (m, 1 H), 3.78 (s, 3 H), 3.69 (s, 3 H),
2.72-2.47 (m, 4 H), 2.39-2.24 (m, 1 H),
2.16-2.09 (m, 1 H), 2.01-1.91 (m, 1 H).

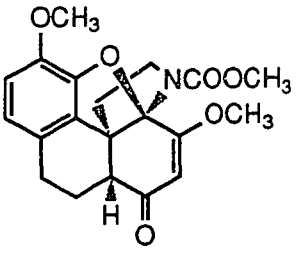


70 113

Preparation of methyl ether 113 from phenol 70.

The crude material from the previous reaction (assumed to be about 1.01 mmol) was taken up in 5 mL acetone. Anhydrous K_2CO_3 (1.4 g, 10.1 mmol) was added followed by methyl iodide (0.31 mL, 5.0 mmol). The reaction flask was stoppered and the mixture stirred vigorously for several hours. When tlc showed the complete disappearance of starting material, the liquid was decanted into a separatory funnel. The remaining solid residue was washed several times with methylene chloride and the washings poured into the separatory funnel. The mixture was washed once each with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine before drying over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude product which was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes). The yield was 209 mg (56% from hydroxy ketone **69**).

tlc: Rf = 0.52 (70% EtOAc/hexanes)



113

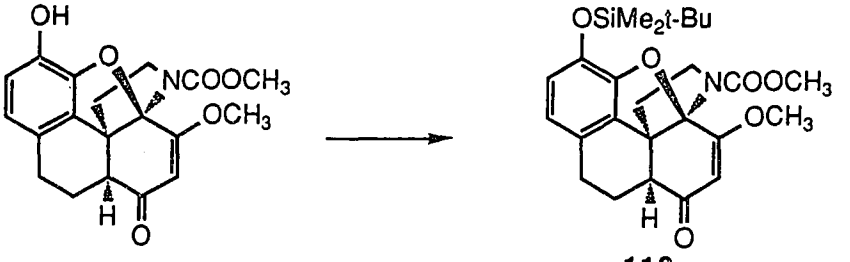
^{1}H NMR (300 MHz, $CDCl_3$):

6.72 (d, J = 8.3 Hz, 1 H), 6.60 (d, J = 8.3 Hz, 1 H), 5.39 (s, 1 H), 4.06 (ddd, J = 11.3, 9.2, 2.8 Hz, 1 H), 3.88 (dt, J = 10.8, 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 2.70-2.54 (m, 4 H), 2.36-2.26 (m, 1 H), 2.12 (ddd, J = 12.9, 7.2, 2.5 Hz, 1 H), 2.04-1.92 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): 195.7, 167.6, 154.2, 142.9, 142.5, 129.9, 126.2, 121.1, 115.0, 105.1, 104.9, 56.6, 56.4, 55.9, 53.0, 49.5, 43.7, 36.2, 21.6, 21.4.

Mass spectrum (70 ev, m/e): 372(m+1), 371(m^+), 356(m-CH_3), 312(m-$COOCH_3$), 296.

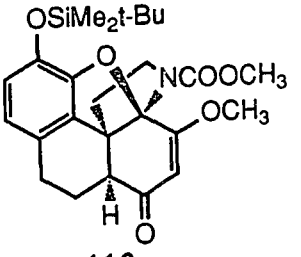
HRMS: for $C_{20}H_{21}NO_6$ calculated 371.1368
found 371.1360.
for $C_{19}H_{18}NO_6$ calculated 356.1135
found 356.1122.



70 **112**

Preparation of silyl ether 112 from phenol 70.

The crude phenol **70** (assumed to be about 228 mg, 0.639 mmol) was taken up in 8 mL dry N,N - dimethylformamide. To this stirring solution was added imidazole (435 mg, 6.40 mmol) followed by tert-butyldimethylsilyl chloride (481 mg, 3.20 mmol). The mixture was stirred for several hours after which time it was diluted with methylene chloride. This solution was washed three times with 3% HCl, and once each with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous $MgSO_4$. The solvent was removed in vacuo to yield the crude silyl ether **112** which was purified by flash chromatography on silica gel (30% EtOAc/hexanes). The yield of pure product was 164 mg (54% yield over three steps from hydroxy ketone **69**).



112

tlc: R_f = 0.47 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.64 (d, J = 8.4 Hz, 1 H), 6.50 (d, J = 8.4 Hz, 1 H), 5.35 (s, 1 H), 4.13-4.04 (m, 1 H), 3.90-3.80 (m, 1 H), 3.76 (s, 3 H), 3.65 (s, 3 H), 2.70-2.48 (m, 4 H), 2.32-2.21 (m, 1 H), 2.14-2.06 (m, 1 H), 2.02-1.89 (m, 1 H), 0.97 (s, 9 H), 0.21 (s, 3 H), 0.09 (s, 3 H).

IR (neat): 2955, 2930, 2890, 2855, 1740, 1730, 1725, 1705, 1660, 1605, 1575, 1490, 1445, 1360, 850 cm^{-1}.

Mass spectrum (70 ev, m/e): 471(m^+), 414(m-tBu), 317, 267, 195, 162, 126.

HRMS: for $C_{25}H_{33}SiNO_6$ calculated 471.2078

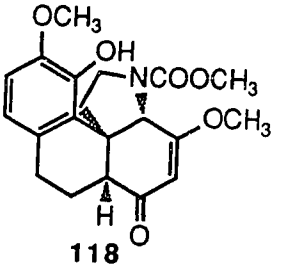
found 471.2052.

113 118

C-O bond reduction of 113 to yield phenol 118.

The substrate (208 mg, 0.561 mmol) was weighed into a 25 mL round bottomed flask equipped with a reflux condenser. Glacial acetic acid (4 mL) was added followed by zinc dust (2.7 g, 42.0 mmol). The mixture was heated to 90°C for 3 h after which time it was cooled and filtered. The zinc residue was washed with ethyl acetate and the combined filtrates were concentrated in vacuo to yield the crude product as a foam. Purification by flash chromatography on silica gel (elution with 30% EtOAc/hexanes) yielded the pure product as a white foam (183 mg, 88% yield).

Note: The above procedure was also done using the silyl ether **112**. The yield of **114** was similar and there was no detectable loss of the silyl group.



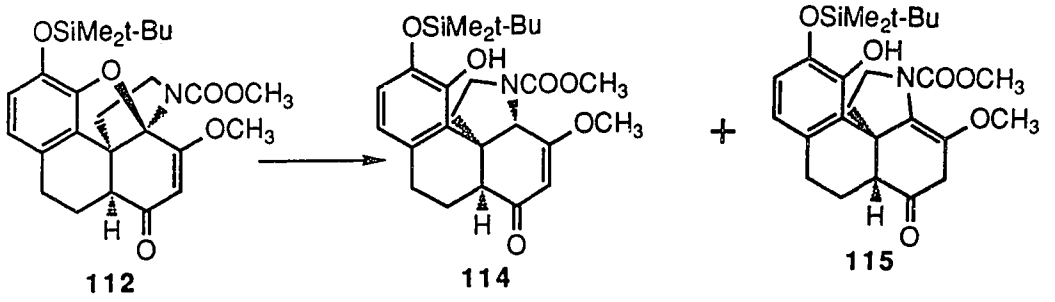
118

tlc: Rf = 0.41 (50% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$):

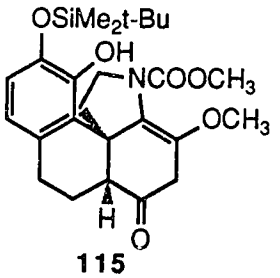
6.72 (d, J = 8.3 Hz, 1 H), 6.59 (d, J = 8.3 Hz, 1 H), 6.18 (s, 1 H), 5.45 (s, 1 H), 3.86 (s, 3 H), 3.81-3.44 (2 m, partially obscurred, 2 H), 3.68 (s, 3 H), 3.65 (s, 3 H), 2.93-2.82 (m, 1 H), 2.75-2.52 (m, 3 H), 1.93 (dd, J = 12.6, 7.7 Hz, 1 H), 1.80-1.67 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): 199.1, 174.5, 155.5, 144.6, 144.0, 132.2, 121.5, 120.0, 109.4, 102.5, 59.6, 56.1, 55.0, 52.3, 50.3, 45.8 (two coincident signals), 34.2, 26.6, 21.9.



Reduction of C-O bond of 112 with lithium dimethyl cuprate.

The CuI (251 mg, 1.32 mmol) was placed in a dry sidearmed flask under an atmosphere of nitrogen. Diethyl ether (2 mL) was added and the mixture was cooled to 0°C. MeLi (1.80 mL of a 1.47 M solution in ether, 2.64 mmol) was added slowly and the mixture stirred for 5 min at 0°C and cooled to -78°C. The substrate was added in 3 mL ether slowly and the mixture left to stir for 20 min. The reaction was then quenched at -78°C with 10% conc NH_4OH in saturated aqueous NH_4Cl. This mixture was poured into into a separatory funnel and diluted with methylene chloride. The organic layer was washed three times with 10% NH_4OH/NH_4Cl and once with brine before drying over anhydrous $MgSO_4$. The solvent was removed in vacuo to yield the crude phenols **114** and **115** which were separated by flash chromatography on silica gel (elution with 30-50% EtOAc/hexanes). The yield was 20 mg (65%) of **114** and 7 mg (23%) of **115**.



115

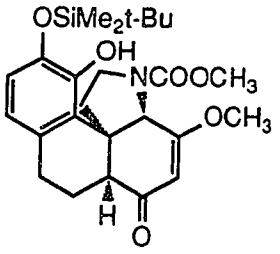
Deconjugated compound 115.

tlc: R_f = 0.52 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.62 (d, J = 8.1 Hz, 1 H), 6.44 (d, J = 8.4 Hz, 1 H),
5.68 (s, exchangable, 1 H), 4.13-4.04 (m, 1 H),
3.80 (s, 3 H), 3.57-3.49 (m, 1 H), 3.55 (s, 1 H),
2.88 (s, 2 H), 2.85-2.76 (m, 1 H),
2.65-2.57 (m, 1 H),
2.51 (t, J = 3.9 Hz, 1 H), 2.46-2.38 (m, 1 H),
2.36-2.26 (m, 1 H), 2.16-2.06 (m, 1 H),
1.94-1.82 (m, 1 H), 0.97 (s, 9 H), 0.22 (s, 6 H).

IR (neat): 3520, 2955, 2930, 2890, 2860, 1715, 1695, 1580,
1490, 1450, 1385, 1290, 1260, 845 cm^{-1}.



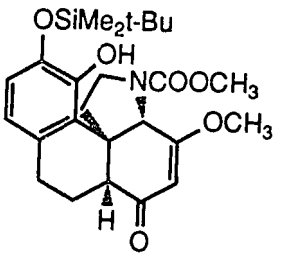
114

Conjugated compound 114.

tlc: R_f = 0.30 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.66 (d, J = 8.1 Hz, 1 H), 6.48 (d, J = 8.4 Hz, 1 H),
6.07 (s, exchangable, 1 H), 5.43 (s, 1 H),
5.37 (s, 1 H), 3.80-3.52 (m, 2 H), 3.67 (s, 3 H),
3.65 (s, 3 H), 2.87 (dt, J = 12.6, 9.9 Hz, 1 H),
2.72-2.50 (m, 4 H),
1.98-1.91 (dd, J = 12.6, 7.5 Hz, 1 H),
1.79-1.70 (m, 1 H), 0.99 (s, 9 H), 0.24 (s, 6 H),

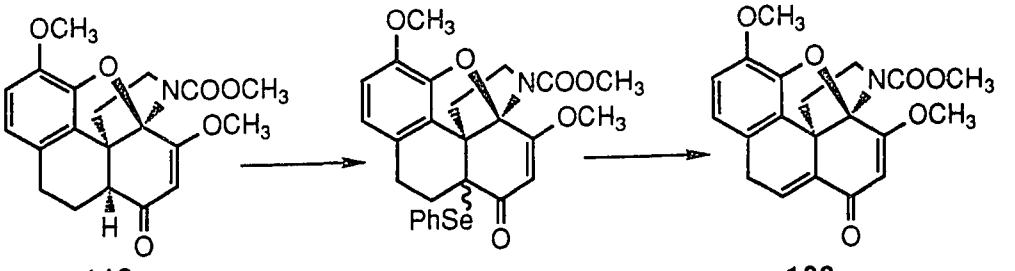


114

IR (neat): 3480, 3350, 2940, 2920, 2880, 2840, 1705, 1690, 1640, 1625, 1480, 1450, 1365, 1280, 1215, 835 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 473(m^+,8.8), 416(m-tBu,31.5), 384(14.8), 356(22.7), 329(13.3), 243(21.2), 171(26.8).

HRMS: for $C_{25}H_{35}SiNO_6$ calculated 473.2234
found 473.2197.
for $C_{21}H_{26}SiNO_6$ calculated 416.1529
found 416.1569.

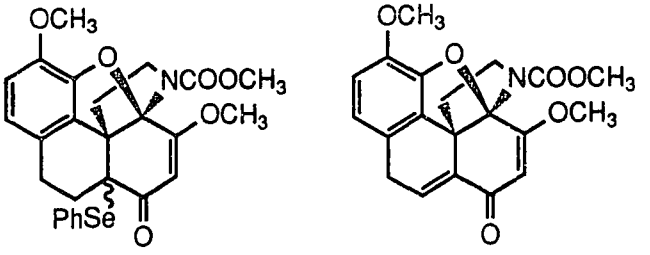


113 123

Preparation of enone 123 from ketone 113.

The ketone **113** (280 mg, 0.75 mmol) was taken up in 10 mL ethyl acetate in a round bottomed flask. Phenyl selenium chloride was added and the mixture stirred at ambient temperature. The reaction was monitored by tlc. When the starting material had been consumed, the mixture was diluted with ethyl acetate and washed twice with 10% Na_2CO_3 and once with brine. The solvent was evaporated to give the crude selenide which was not characterized in any way except by tlc.

The selenide was taken up in 20 mL tetrahydrofuran and 30% H_2O_2 (about 5 mL) was added. The mixture was stirred for about one hour at ambient temperature after which time it was poured into ethyl acetate and washed twice each with 10% Na_2CO_3 and 10% Na_2SO_3 and once with brine. The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to yield the crude enone **123**. Purification by flash chromatography on silica gel gave 194 mg (70% yield) of the enone as a white foam.



123

Selenide:

tlc : R_f = 0.50 (50% EtOAc/hexanes)

Enone 123:

tlc : R_f = 0.24 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.90 (dd, J = 5.4, 3.3 Hz, 1 H),

6.79 (d, J = 8.0 Hz, 1 H), 6.71 (d, J = 8.1 Hz, 1 H),

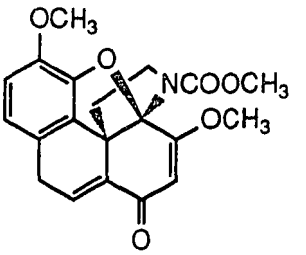
5.50 (s, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H),

3.77 (s, 3 H),

3.88-3.61 (2 m, partially obscurred, 2 H),

3.45-3.43 (br m, 2 H), 2.25-2.17 (m, 1 H),

2.08-1.98 (m, 1 H).

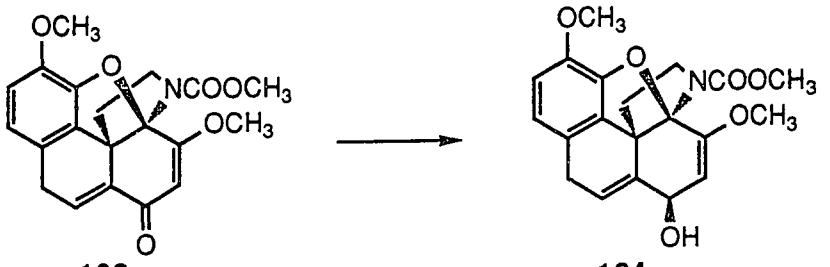


123

IR (neat): 2950, 2840, 1740, 1730, 1710, 1650, 1640, 1630, 1590, 1500, 1440, 1370, 1225 cm^{-1}.

Mass spectrum (70 ev, m/e): 370(m+1), 369(m^+), 354(m-CH_3), 326, 310(m-$COOCH_3$), 294, 266, 200.

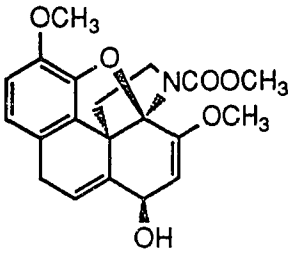
HRMS: for $C_{20}H_{19}NO_6$ calculated 369.1213
found 369.1220.
for $C_{18}H_{16}NO_4$ calculated 310.1079
found 310.1065.



123 124

Reduction of enone 123 to alcohol 124.

The substrate (50 mg, 0.136 mmol) was taken up in 10 mL methanol in a 25 mL round bottom flask. To this suspension was added sodium borohydride (11 mg, 0.136 mmol) and the mixture was stirred at ambient temperature while monitoring the progress of the reaction by tlc. After about 15 min, when the reaction was seen to be complete, several mL of water was added. The resulting solution was poured into a separatory funnel and extracted with 20 mL ethyl acetate. The aqueous phase was extracted three more times with a total of 20 mL ethyl acetate and the extracts were combined and washed with brine. Drying of the solvent over anydrous K_2CO_3 followed by removal of the solvent in vacuo gave the crude product which was, in practice, not purified but carried on to the next reaction. For characterization purposes, the material could be purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes).



124

tlc: R_f = 0.39 (70% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

6.70 (AB, 2 H), 5.97 (m, 1 H),

5.06 (br d, J = 6.6 Hz, 1 H),

4.82 (d, J = 1.3 Hz, 1 H), 3.96-3.88 (m, 1 H),

3.84 (s, 3 H), 3.74 (s, 3 H), 3.64-3.54 (m, 1 H),

3.57 (s, 3 H), 3.29-3.25 (m, 2 H),

2.06-2.01 (m, 2 H), O<u>H</u> signal not located.

IR (neat): 3500, 3040, 2990, 2970, 1750, 1730, 1725, 1715,

1650, 1525, 1465, 1390, 1380 cm^{-1}.

Mass spectrum (70 ev, m/e): 371(m^+), 353(m-H_2O),

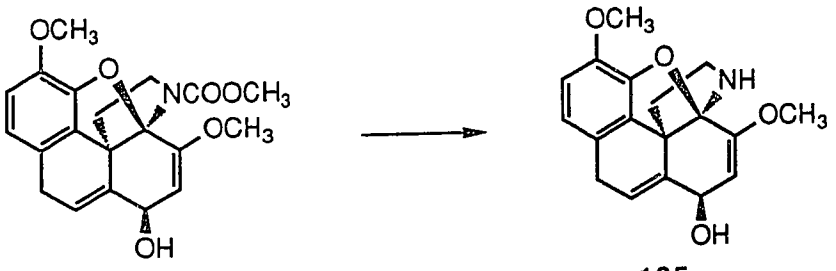
339(m-CH_3OH), 311, 119, 84(100).

HRMS: for $C_{20}H_{21}NO_6$ calculated 371.1369

found 371.1381.

for $C_{19}H_{17}NO_5$ calculated 339.1107

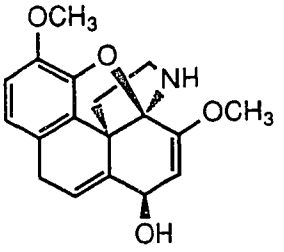
found 339.1104.



124 **125**

Conversion of carbamate 124 to secondary amine 125.

The crude carbamate **124** from the previous reaction (assumed to be 0.136 mmol) was taken up in 10 mL dry tetrahydrofuran under an atmosphere of nitrogen and cooled to 0°C. To this stirring solution was added methyllithium (1 mL of a 1.4 M solution in ether, 1.4 mmol) and the solution was stirred until tlc indicated that the starting material had been consumed (0.5-1 h). Water was carefully added and the mixture extracted 4 times with a total of 40 mL methylene chloride. The organic extracts were washed once each with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous K_2CO_3. Removal of the solvent in vacuo gave the crude secondary amine **125** which was, in practice, not purified but carried on to the next reaction. For characterization purposes the crude product could be purified by flash chromatography on silica gel (elution with 70% EtOAc/hexanes).



125

tlc: R_f = 0.41 (EtOAC)

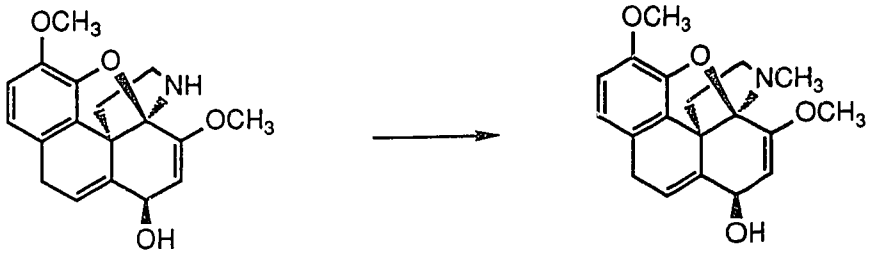
^1H NMR (300 MHz, $CDCl_3$):

6.67 (AB, 2 H), 6.18-6.15 (m, 1 H), 5.11 (br s, 1 H),
4.75 (d, J = 0.7 Hz, 1 H), 3.83 (s, 3 H),
3.60 (s, 3 H), 3.32-3.25 (m, 2 H),
3.23-3.15 (m, 2 H), 2.09-1.87 (m, 2 H),
O<u>H</u> signal not observed.

IR (neat) 3380, 3000, 2920, 2830, 1645, 1630, 1505, 1450,
1440 cm^{-1}.

Mass spectrum (70 ev, m/e): 313(m^+), 295(m-H_2O),
281(m-CH_3OH), 149, 119, 84, 69(100).

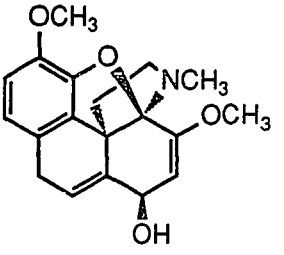
HRMS: for $C_{19}H_{21}NO_4$ calculated 313.1314
found 313.1299.
for $C_{18}H_{15}NO_3$ calculated 281.1052
found 281.1062.



125 **126**

Preparation of N-methyl amine 126 from secondary amine 125.

The crude material from the previous reaction (assumed to be 0.136 mmol) was taken up in 4 mL acetonitrile. Aqueous formaldehyde solution was added (2 mL) followed by sodium cyanoborohydride (100 mg, 1.59 mmol) and the mixture stirred at room temperature until tlc indicated the disappearance of the starting material (about 15 min). To the reaction mixture was added 10% aqueous acetic acid until the pH reached about 6 and stirring was continued for about 5 min. The mixture was poured into $NaHCO_3$ and the resulting solution was extracted four times with methylene chloride (total volume of 40 mL). The combined extracts were washed once each with saturated aqueous $NaHCO_3$ and brine and the solvent removed in vacuo. The resulting crude product was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes) to give 25 mg (54% three steps) of the pure N-methyl amine **126**.



126

tlc: R_f = 0.53 (EtOAc)

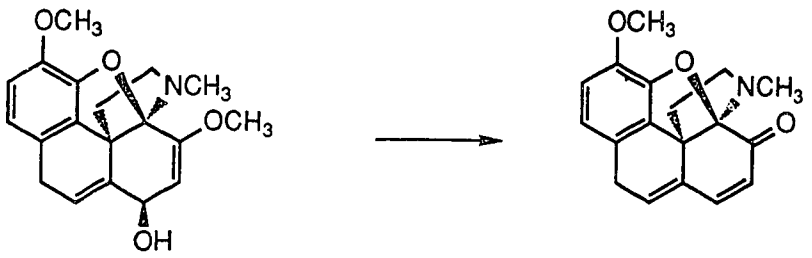
^1H NMR (300 MHz, $CDCl_3$):

6.67 (AB, 2 H), 6.06-6.05 (m, 1 H), 5.11 (br s, 1 H),
4.75 (s, 1 H), 3.84 (s, 3 H), 3.58 (s, 3 H),
3.35-3.26 (m, 2 H), 3.00-2.94 (m, 1 H)
2.90-2.82 (m, 1 H), 2.78 (s, 3 H),
2.98-2.93 (m, 2 H), O<u>H</u> signal not observed).

IR (neat): 3280, 3050, 3020, 2950, 2930, 2825, 1640, 1630,
1595, 1500, 1460, 1450, 1440, 1355 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 328(m+1,27.0),
327(m^+,100), 312(m-CH_3,28.5), 311(12.0), 310(20.0),
309(m-H_2O,52.7), 307(52.3), 295(m-CH_3OH,82.0),
266(27.2), 252(32.3), 240(40.9).

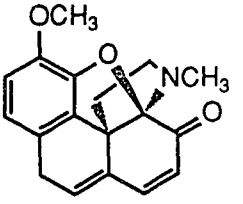
HRMS: for $C_{19}H_{21}NO_4$ calculated 327.1471
found 327.1452.
for $C_{18}H_{17}NO_3$ calculated 295.1208
found 295.1185.



126 127

Conversion of alcohol 126 to dienone 127.

The alcohol **126** (63 mg, 0.193 mmol) was taken up in dry methylene chloride and cooled to -30°C. To this stirring solution was added 2,6-Lutidine (0.44 mL, 3.8 mmol) followed by trifluoroacetic anhydride (0.27 mL, 1.9 mmol). The mixture was allowed to warm to ambient temperature and the progress of the reaction was followed by tlc. The reaction time was from 12 to 24 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and the organic layer separated. The aqueous phase was extracted twice with methylene chloride and the extracts were combined and washed once each with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous K_2CO_3. Removal of the solvent in vacuo gave the crude dienone **127** which was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes). The yield was 46 mg (81%).



127

tlc: R_f = 0.58(70% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

7.06 (d, J = 10.0 Hz, 1 H), 6.67 (AB, 2 H),

6.31 (dd, J = 6.4, 2.1 Hz, 1 H),

5.95 (d, J = 10.2 Hz, 1 H), 3.86 (s, 3 H),

3.53 (br d, J = 19.1 Hz, 1 H),

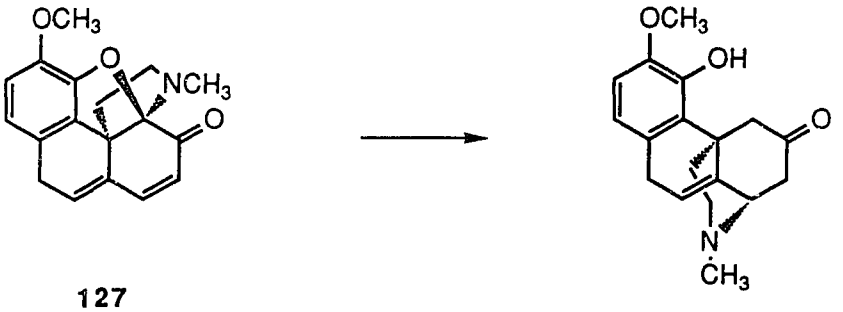
3.36 (dd, J = 19.4, 6.5 Hz, 1 H),

3.05 (dd, J = 8.6, 7.3 Hz, 1 H),

2.91-2.82 (ddd, 12.2, 8.9, 5.3 Hz, 1 H),

2.71 (s, 3 H),2.23 (dd, J = 12.0, 5.2 Hz, 1 H),

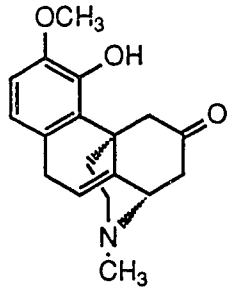
2.07-1.96 (m, 1 H).



127 128

Reduction and conjugate addition of 127 to produce ketone 128.

To a solution of the dienone **127** (12 mg, 0.041 mmol) in 2 mL ethanol was added 0.81 mL of a 1 M aqueous solution of NH_4Cl (0.81 mmol) and 27 mg zinc dust (0.41 mmol). The solution was stirred until tlc indicated that the starting material had been consumed (several hours). The mixture was filtered into a separatory funnel containing saturated aqueous $NaHCO_3$. The solid residue was washed with methylene chloride. The organic phase was separated and the aqueous phase was extracted three times with methylene chloride. The combined organic extracts were washed once each with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the crude amine which was purified by flash chromatography on silica gel (deactivated by passing acetone through the packed column prior to the elution solvent. The product was eluted with 5% MeOH/$CHCl_3$. The yield was 8 mg (ca. 65%).



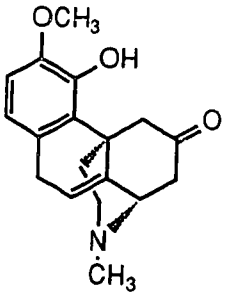
128

tlc: R_f = 0.28 (5% MeOH/$CHCl_3$)

^1H NMR (300 MHz/$CDCl_3$):

6.77 (d, J = 8.3 Hz, 1 H), 6.64 (d, J = 8.3 Hz, 1 H),
6.05 (br s, 1 H), 5.90 (t, J = 3.4 Hz, 1 H),
3.87 (s, 3 H), 3.79 (dd, J = 17.0, 1.8 Hz, 1 H),
3.65 (br d, J = 5.0 Hz, 1 H), 3.49-3.47 (m, 2 H),
3.03 (d, J = 7.1 Hz, 1 H),
2.89 (dt, J = 13.3, 2.3 Hz, 1 H), 2.73-2.68 (m, 2 H),
2.41 (s, 3 H), 2.43-2.33 (m, obscurred by N-Me, 2 H),
1.88 (dt, J = 12.0, 7.1 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): 210.9, 145.0, 143.7, 136.8,
126.1, 125.3, 119.4, 117.7, 109.4, 64.0, 56.2, 50.8,
47.8, 42.1, 41.5, 39.2, 35.5, 29.2.

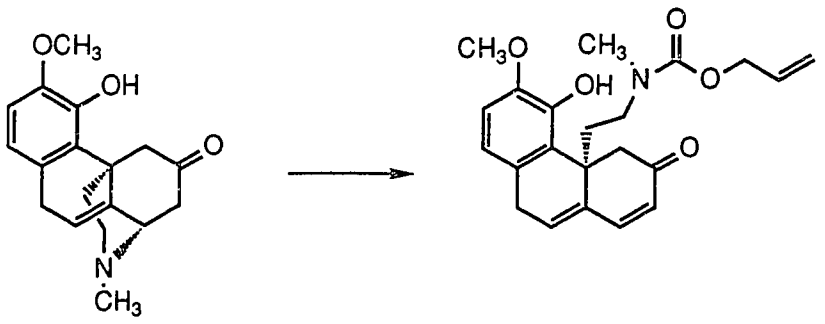


128

IR (neat): 3500, 3360, 2920, 1680, 1610, 1485, 1445, 1280 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 299(m^+,0.5), 256(0.4), 242(6.7), 226(2.0), 88(14.4), 86(82.8), 84(100).

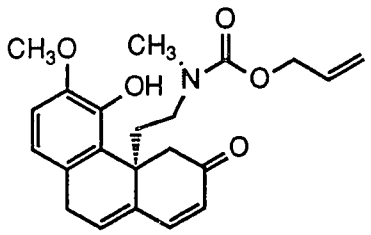
HRMS: for $C_{18}H_{21}NO_3$ calculated 299.1521
found 299.1527.



128 134

Preparation of dienone 134 from 1,4-addition product 128.

To a vigorously stirring mixture of the substrate **128** (about 4 mg) in 1 mL ethyl acetate and 1 mL water was added an excess (unmeasured amount) of K_2CO_3 followed by an excess of allyl chloroformate (unmeasured but such that the amount of K_2CO_3 exceeded the amount of allyl chloroformate). The mixture was stirred for about one hour after which time tlc indicated that the starting material had been consumed. The reaction mixture was poured into a separatory funnel and diluted with EtOAc. The organic layer was washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$ and brine before drying over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave the crude carbamate **134** which was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes). The yield was not determined as this reaction was done on a small scale only to characterize the product.

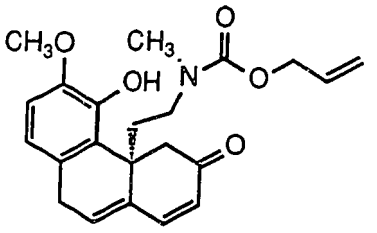


134

tlc: R_f = 0.47 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$, many signals are broadened or doubled due to hindered rotation of carbamate)

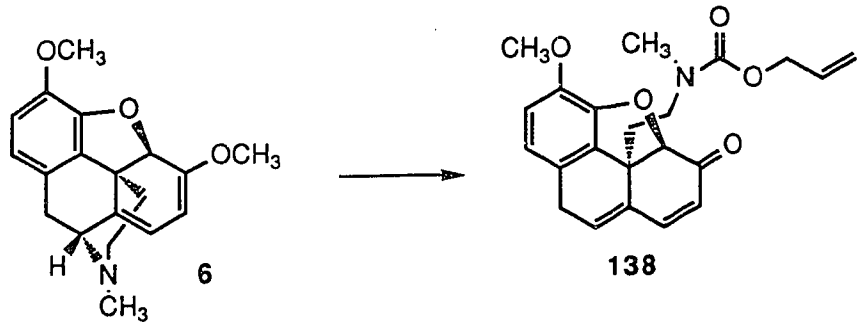
7.12-7.05 (2 d, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 8.1 Hz, 1 H), 6.37 (br s, 1 H), 6.19 (br s, 1 H), 5.96 (d, J = 9.6 Hz, 1 H), 5.92-5.71 (m, 1 H), 5.25-5.10 (m, 2 H), 4.45-4.30 (2 d, 2 H), 4.05 (d, J = 16.5 Hz, 1 H), 3.89 (s, 3 H), 3.58 (br d, 2 H), 3.25-2.98 (2 br m, 1 H), 2.68,2.67 (2 s, 3 H), 2.62 (d, J = 16.5 Hz, 1 H), 2.68-2.51 (partially obscurred m, 2 H), 2.10-2.01 (m, 1 H).



134

Mass spectrum (70 ev, m/e): 383(m^+), 326(m-O-allyl), 295, 266, 240(elimination of carbamate sidechain), 225(elimination of carbamate sidechain and Me), 209(100).

HRMS: for $C_{22}H_{25}NO_5$ calculated 383.1733
found 383.1771.
for $C_{15}H_{12}O_3$ calculated 240.0787
found 240.0796.
for $C_{14}H_9O_3$ calculated 225.0552
found 225.0566.



Preparation of dienone 138 from thebaine 6.

This procedure is identical to the previous experimental which prepared dienone **134** from **128**. The amounts were as follows:

thebaine - 500 mg, 1.61 mmol

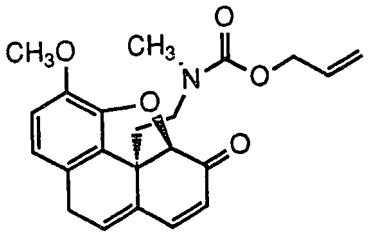
allyl chloroformate - 0.34 mL, 3.22 mmol

K_2CO_3 - 1.33 g, 9.66 mmol

EtOAc - 20 mL

H_2O - 10 mL

The crude material was purified by flash chromatography on silica gel (elution with 35-50% EtOAc/hexanes). The yield was not measured as the material was carried on directly to the next reaction.

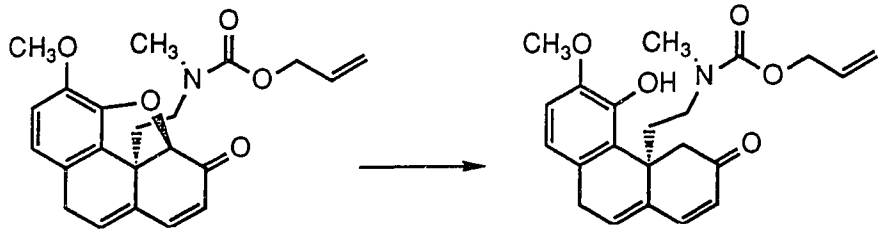


138

tlc: R_f = 0.13 (30% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

7.22 (d, J = 10.1 Hz, 1 H), 6.69 (AB, 2 H),
6.35 (dd, J = 6.4, 1.4 Hz, 1 H),
5.95 (d, J = 10.1 Hz, 1 H), 5.95-5.83 (m, 1 H),
5.29-5.05 (m, 3 H), 4.54 (d, J = 5.5 Hz, 2 H),
3.88 (s, 3 H), 3.60 (br d, J = 20.4 Hz, 1 H),
3.38 (dd, J = 19.9, 6.7 Hz, 1 H), one H signal
obscurred by dd at 3.38, 3.23-3.16 (m, 1 H),
2.85 (s, 3 H), 2.10-1.97 (m, 2 H).



138 134

Reduction of C-O bond of dihydrofuran 138 to yield phenol 134.

This procedure is identical to that which was used to prepare 1,4 adduct **128** from dienone **127**. The reagents and amounts are as follows:

dihydrofuran **138** - assumed to be about 1.6 mmol

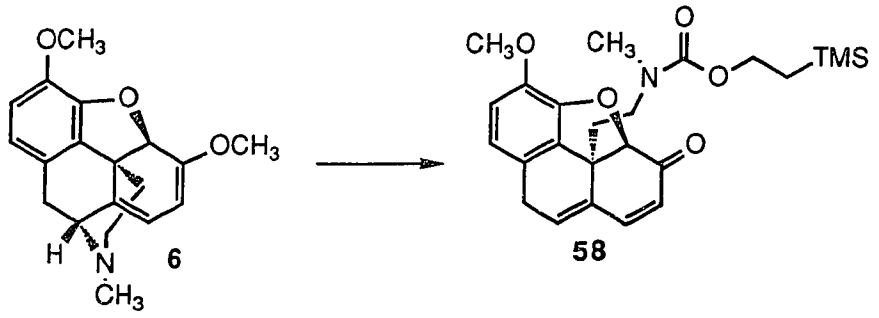
Zn dust - 520 mg, 32.2 mmol

NH_4Cl - 16.1 mL of a 1 M aqueous solution, 16.1 mmol

EtOH - 50 mL

The crude product was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes). The yield was 468 mg (75% overall yield from thebaine).

This material was identical by tlc and ^1H NMR to the product **134** produced by treatment of 1,4 adduct **128** with allyl chloroformate.



Preparation of dienone 58 from thebaine 6.

This procedure is identical a the previous experimental which prepared dienone **138** from thebaine. The reagents and amounts are as follows:

thebaine - 500 mg, 1.61 mmol

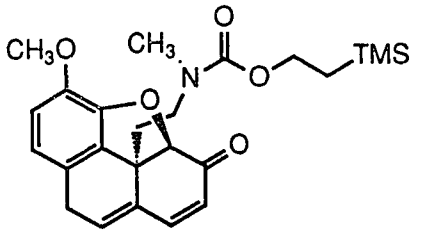
trimethylsilylethylchloroformate - about 5 mL of an approximately 1 M solution in toluene

K_2CO_3 - 1.33 g, 9.66 mmol

EtOAc - 20 mL

H_2O - 10 mL

The crude material was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexanes). The yield was 632 mg (89%). In many cases the crude material could be carried on to the next reaction.

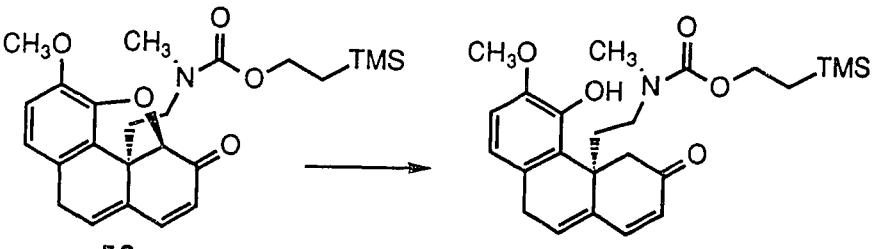


58

tlc: R_f = 0.18 (30% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

7.22 (d, J = 9.9 Hz, 1 H), 6.69 (AB, 2 H),
6.35 (d, J = 5.1 Hz, 1 H), 5.95 (d, J = 9.9 Hz, 1 H),
5.11 (br s, 1 H), 4.12 (dd, J = 9.3, 8.1 Hz, 2 H),
3.88 (s, 3 H), 3.60 (d, J = 18.9 Hz, 1 H),
3.38 (dd, J = 19.5, 6.3 Hz, 1 H),
1 H signal partially obscurred by 3.38 dd,
3.20-3.15 (m, 1 H), 2.82 (s, 3 H),
2.07-1.96 (m, 2 H), 0.97 (t, J = 9.3 Hz, 2 H),
0.26 (s, 9 H).



58 135

Reduction of C-O bond of dihydrofuran 58 to yield phenol 135.

This procedure is identical to a previous experimental used to prepare dienone **134** from 1,4 adduct **128**. The reagents and amounts are as follows:

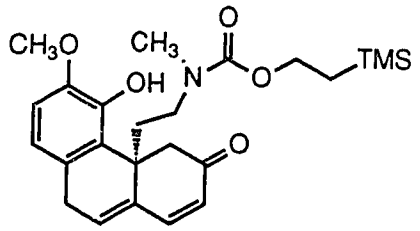
dihydrofuran **58** - 600 mg, 1.36 mmol

Zn dust - 1.78 g, 27.2 mmol

NH_4Cl - 13.6 mL of a 1 M aqueous solution, 13.6 mmol

EtOH - 30 mL

The crude material was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexanes). The yield was 370 mg (61%). The overall yield of the two steps starting with 1 g of thebaine was 58 %.

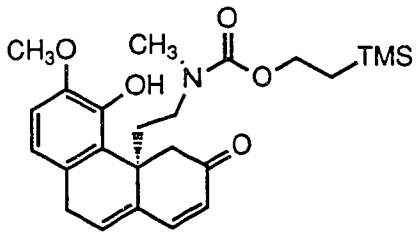


135

tlc: R_f = 0.18 (30% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$, many signals are broadened or doubled due to hindered rotation about carbamate C-N bond):

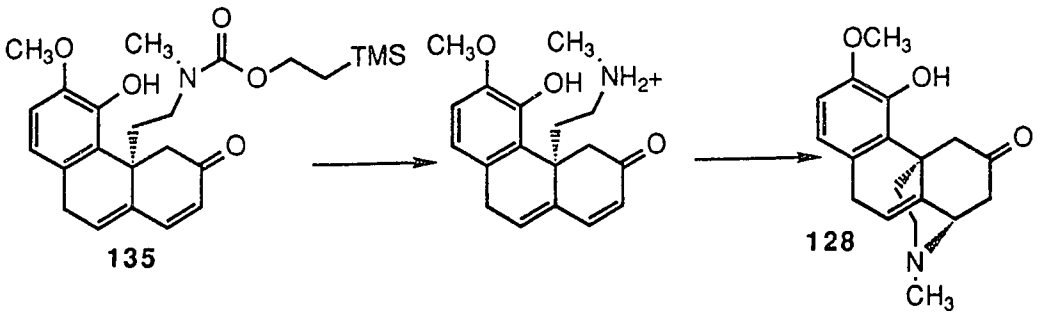
7.13-7.08 (br m, 1 H), 6.80 (d, J = 8.3 Hz, 1 H),
6.64 (d, J = 8.2 Hz, 1 H), 6.38 (br s, 1 H),
6.12 (s, exch, 1 H), 5.96 (d, J = 9.8 Hz, 1 H),
4.05 (d, J = 16.4 Hz, 1 H),
4.13-3.95 (m, partially obscurred by d at 4.05, 2 H)
3.89 (s, 3 H), 3.59-3.57 (m, 2 H),
3.28-2.90 (2 br m, 1 H), 2.65 (s, 3 H),
2.63 (d, J = 16.4 Hz, 1 H),
2,65-2.46 (m, partially obscurred, 2 H),
2.09-2.01 (m, 1 H), 0.95-0.71 (m, 2 H),
0.00 (s, 9 H).



135

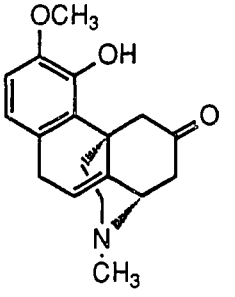
Mass spectrum (70 ev, m/e(intensity): 443(0.9,m^+),
429(1.1), 414(3.9), 400(1.6), 356(3.0), 314(17.7),
313(67.5), 209(73.5), 181(26.8, 160(37.1), 73(100).

HRMS: for $C_{24}H_{33}SiNO_5$ calculated 443.2129
found 443.2121.



Preparation of 1,4-addition product 128 from carbamate 135.

The carbamate **135** (23 mg, 0.052 mmol) was taken up in trifluoroacetic acid (0.5 mL) and stirred for several minutes. The bulk of the trifluoroacetic acid was removed in vacuo, the final amount being removed under high vacuum. The crude ammonium salt was taken up in 2 mL chloroform and treated with 2 mL saturated aqueous $NaHCO_3$. The biphasic mixture was stirred for several hours after which time the mixture was partitioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic phase was separated and the aqueous phase was reextracted several times with methylene chloride. The combined organic portions were washed with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the crude amine **128** which could be purified by flash chromatography on acetone deactivated silica gel (5% $MeOH/CHCl_3$). The yield was 13 mg (84%). The spectral data for this product were identical with those for the compound obtained by zinc reduction of dienone **127**. Proton NMR data for the ammonium salt are given on the following page.



128

^{1}H NMR (300 MHz, $CDCl_3$):

9.50 (br s, 2 H), 8.44 (br s, 1 H), 8.00 (br s, 1 H),

7.15 (d, J = 9.9 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H),

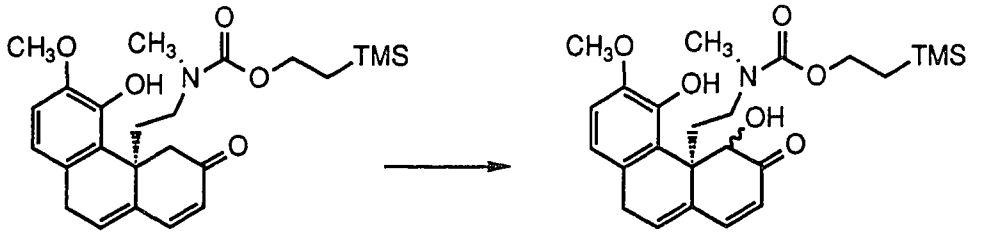
6.67 (d, J = 8.4 Hz, 1 H), 6.48 (t, J = 3.6 Hz, 1 H),

5.99 (d, J = 9.6 Hz, 1 H),

4.14 (d, J = 16.8 Hz, 1 H), 3.90 (s, 3 H),

3.62 (br t, 2 H), 2.78-2.45 (several m, 4 H),

2.57 (s, 3 H), 2.24-2.18 (m, 1 H).



135 136

Preparation of acyloin 136 by hydroxylation of dienone 135.

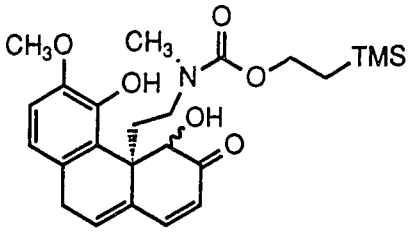
This procedure is identical to that used to prepare hydroxy ketone **100** from ketone **98** except that the enolate was generated for 15 min and was left to stir with the oxaziridine for only 15 min before workup. The reagents and their amounts are as follows:

dienone **135** - 25 mg, 0.056 mmol in 3 mL tetrahydrofuran

p-tol-2-phenylsulphonyl oxaziridine - 78 mg, 0.28 mmol in 2 mL tetrahydrofuran

potassium bis(trimethylsilyl)amide - 0.56 mL of 0.5 M toluene solution, 0.28 mmol

The crude product was purified by flash chromatography on silica gel (elution with 30-50% EtOAc/hexanes). The yield of the pure product was 15 mg (58%).



136

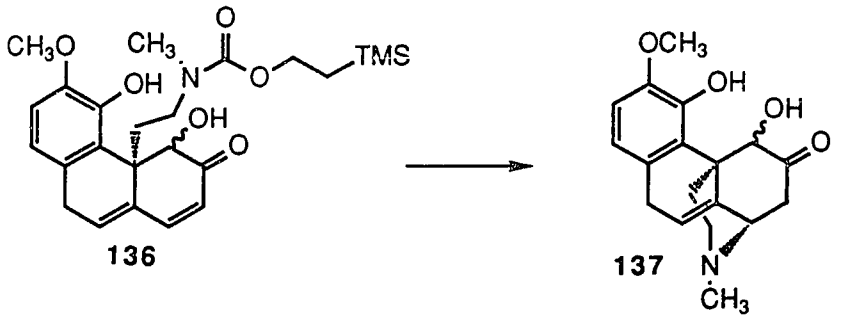
tlc: R_f = 0.17 (50% EtOAc/hexanes)

^1H NMR (300MHz, $CDCl_3$ many signals are broadened or doubled due to hindered rotation about C-N bond):

7.18-7.14 (br m, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.68 (d, J = 8.1 Hz, 1 H), 6.56 (br t, 1 H), 6.24 (s, 1 H), 5.95 (d, J = 9.8 Hz, 1 H), 5.24 (s, 1 H), 4.08-3.93 (m, 2 H), 3.90 (s, 3 H), 3.61 (br s, 2 H), 3.32-2.92 (2 br m, 1 H), 2.71-2.39 (m, 2 H), 2.64 (br s, 3 H), 2.21 (br s, 1 H), 1.85-1.75 (m, 1 H), 0.91-0.81 (m, 2 H), 0.00 (s, 9 H).

Mass spectrum (70 ev, m/e): 459(m^+), 441(m-H_2O), 277, 239, 211, 108(100).

HRMS: for $C_{24}H_{33}SiNO_6$ calculated 459.2077
found 459.2066.
for $C_{24}H_{31}SiNO_5$ calculated 441.1972
found 441.1956.



Preparation of 1,4-addition product 137 from carbamate 136.

This procedure is identical to that used to prepare 1,4-addition product **128** from carbamate **135**. The reagents and amounts are as follows:

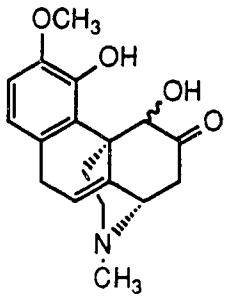
carbamate **136** - 14 mg, 0.038 mmol

trifluoroacetic acid - 0.5 mL

chloroform - 2 mL

saturated aqueous $NaHCO_3$ - 2 mL

The product was purified as for compound **128** using 5-10% MeOH/$CHCl_3$ as the elution solvent. The yield was not measured for this reaction as it was done only to characterize the product. The reaction gave **137** as the major product.



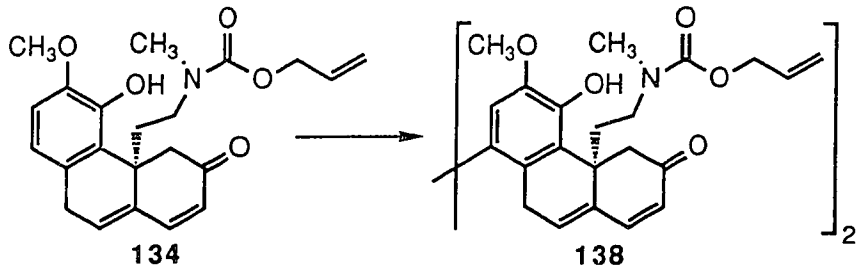
137

tlc: R_f = 0.39 (15% MeOH/$CHCl_3$)

^1H NMR (300 MHz, $CDCl_3$):

6.81 (d, J = 8.3 Hz, 1 H), 6.67 (d, J = 8.3 Hz, 1 H),
6.11 (t, J = 3.3 Hz, 1 H), 4.90 (s, 1 H),
3.89 (s, 3 H), 3.65 (dd, J = 5.0, 1.3 Hz, 1 H),
3.51 (d, J = 3.3 Hz, 2 H),
2.98 (dt, J = 13.7, 2.7 Hz, 1 H),
2.92 (d, J = 15.8 Hz, 1 H),
2.76 (dd, J = 16.3, 5.3 Hz, 1 H),
2.68 (dd, J = 9.8, 2.6 Hz, 2 H), 2.42 (s, 3 H),
1.99 (dt, J = 13.8, 9.8 Hz, 1 H).
2 O<u>H</u> signals not observed.

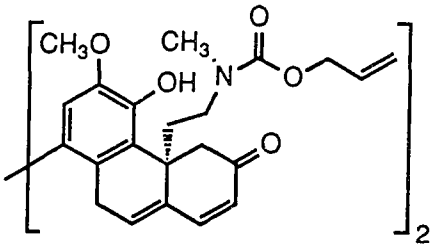
IR (neat): 3500-2500 broad band, 3380, 3050, 2940, 2840, 2810, 1715, 1610, 1490, 1450, 1380, cm^{-1}.



134 138

Attempted dihydrofuran ring formation by direct oxidation of 134.

The dienone **134** (25 mg, 0.065 mmol) was taken up in 3 mL dry tetrahydrofuran under an atmosphere of nitrogen. After cooling the solution to -78°C, potassium bis(trimethylsilyl)amide (0.26 mL of a 0.5 M solution in toluene, 0.13 mmol). After 15 min $CuCl_2$ (18 mg, 0.13 mmol) dissolved in 0.5 mL dry N,N-dimethylformamide was added and the dry ice bath removed. When the mixture reached ambient temperature, saturated aqueous NH_4Cl was added and the mixture partitioned between ethyl acetate and water. The aqueous layer was extracted several times with ethyl acetate and the combined extracts washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$ and brine before drying over anhydrous $MgSO_4$. The solvent was removed in vacuo to yield the crude product which was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexanes). Although the yield was not measured the crude material appeared to be nearly a single compound **139** by tlc.



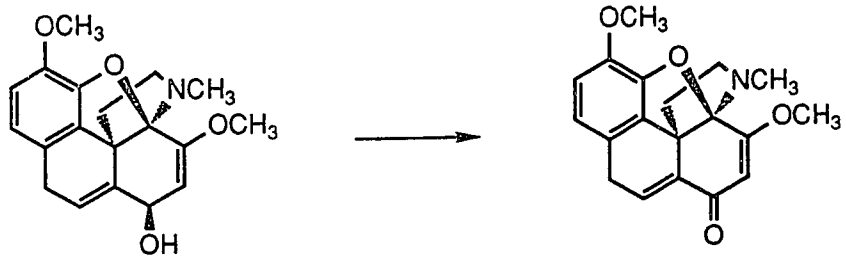
138

tlc: R_f = 0.21 (50% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$, most signals appear as broadened or as multiple signals due to several possible rotational isomers):

7.09-7.03 (m, 1 H), 6.64 (s, 1 H), 6.27-6.22 (m, 2 H), 5.97 (d, J = 9.3 Hz, 1 H), 5.88-5.72 (m, 1 H), 5.27-5.11 (m, 2 H), 4.47 (br s, 2 H), 4.18-4.11 (2 d, J = 15.5 Hz, 1 H), 3.89,3.88 (2 s, 3 H), 3.26-2.55 (m, 5 H), 2.73 (s, 3 H), 2.68 (d, J = 15.8 Hz, 1 H), 2.15-2.03 (m, 1 H).

Mass spectrum: 70 ev, m/e): 622(m-carbamate side chain, 478(100,m-(2 x carbamate side chain and H))

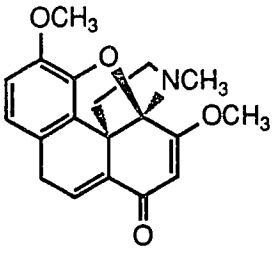


126 144

Oxidation of alcohol 126 to ketone 144.

The allylic alcohol **126** (19 mg, 0.058 mmol) was taken up in dry methylene chloride (2 mL) at ambient temperature. It was not necessary to use inert atmosphere conditions. An excess of the Dess-Martin periodinane reagent (about 3 equivalents) was added portionwise and the progress of the reaction followed by tlc. The reaction was complete within minutes. A 1:1 mixture of saturated aqueous $NaHCO_3$ and 10% Na_2SO_3 was added and the mixture stirred for about 5 min. This mixture was partitioned between methylene chloride and additional sulfite/bicarbonate solution. The aqueous phase was separated and reextracted several times with methylene chloride. The combined organic extracts were washed once each with saturated aqueous $NaHCO_3$, 10% Na_2SO_3 and brine before drying over anhydrous K_2CO_3. The solvent was removed in vacuo to yield the crude ketone which was purified by flash chromatography on silica gel (elution with 70% EtOAc/hexanes). The yield was 14 mg (74%).

tlc: R_f = 0.35 (70% EtOAc/hexanes)



144

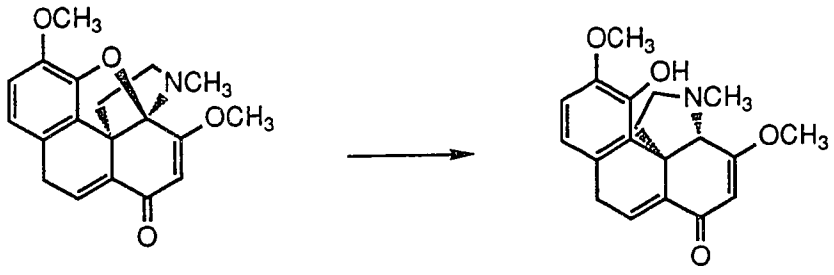
^{1}H NMR (300 MHz, $CDCl_3$):

6.99 (t, J = 4.6 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H),
6.66 (d, J = 8.1 Hz, 1 H), 5.41 (s, 1 H),
3.87 (s, 3 H), 3.79 (s, 3 H),
3.43 (d, J = 4.5 Hz, 2 H), 3.06-3.01 (m, 1 H),
2.86 (s, 3 H),
2.86-2.78 (m, partially obscurred by 2.86 s, 1 H),
2.16-1.95 (m, 2 H).

IR (neat): 3030, 3015, 3000, 2960, 2925, 2860, 2815, 2800, 1645, 1630, 1600, 1500, 1450, 1435, 1370, 1220, 850 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 326(1.5,m+1), 325(7.9,m^+), 310(1.9,m-CH_3), 248(3.4), 231(1.8).

HRMS: for $C_{19}H_{19}NO_4$ calculated 325.1304
found 325.1287.
for $C_{18}H_{16}NO_4$ calculated 310.1079
found 310.1034.



144 145

C-O bond reduction of 144 to yield phenol 145.

This procedure is identical to that used to prepare 1,4-addition product **128** from dienone **127** except that the reaction was allowed to proceed for 5-10 min before workup. The reagents and amounts are as follows:

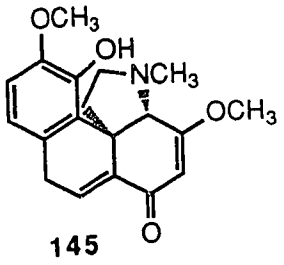
amine **144** - 14 mg, 0.043 mmol

ammonium chloride - 1 mL of a 1 M aqueous solution, 1 mmol

zinc dust - 100 mg, 1.53 mmol

ethanol - 4 mL

The crude product was purified by flash chromatography on silica gel (elution with EtOAc). The yield was 12 mg (85%).



145

tlc: R_f = 0.18 (70% EtOAc/hexanes)

^1H NMR (300 MHz, $CDCl_3$):

14.11 (br s, 1 H),

6.80 (d, J = 8.3 Hz, 1 H), 6.68 (t, J = 3.9 Hz, 1 H),

6.57 (d, J = 8.3 Hz, 1 H), 5.78 (s, 1 H),

4.11 (s, 1 H), 3.89 (s, 3 H), 3.75 (s, 3 H),

3.54 (d, J = 3.7 Hz, 2 H), 3.17 (t, J = 8.9 Hz, 1 H),

2.71-2.61 (m, 1 H), 2.61 (s, 3 H),

2.54-2.43 (m, 1 H), 2.01-1.94 (m, 1 H).

IR (neat): 3393-2322(2 broad bands), 3055, 2925, 2852,

1729, 1675, 1615, 1572, 1459, 1219 cm^{-1}.

Mass spectrum (70 ev, m/e): 327(m^+), 312(m-CH_3), 284, 269,

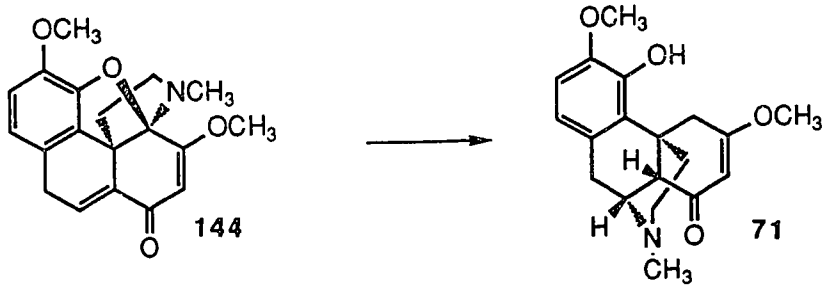
242, 149, 84.

HRMS: for $C_{19}H_{21}NO_4$ calculated 327.1470

found 327.1467.

for $C_{18}H_{18}NO_4$ calculated 312.1235

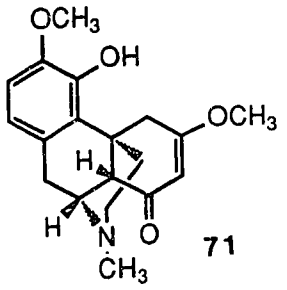
found 312.1237.



Preparation of morphinan 71 from enone 144.

The enone **144** (10 mg, 0.031 mmol) was disolved in ethanol (2 mL) in a 10 mL flask equipped with a stirring bar. To this solution was added 1 M aqueous ammonium chloride (1 mL, 1 mmol) followed by 100 mg zinc dust (1.54 mmol). The suspension was stirred for 10 h after which time about 50 mg additional zinc dust was added. The mixture was stirred over night for a total time of about 24 h. Dilute ammonium hydroxide was added to adjust the pH of the reaction mixture to about 9. The resulting mixture was partitioned between methylene chloride and dilute ammonium hydroxide. The aqueous phase was extracted three times with methylene chloride (total volume 25 mL) and the organic extracts combined. These extracts were washed with

saturated aqueous $NaHCO_3$, and brine before drying over anhydrous Na_2SO_4. Evaporation of solvent in vacuo gave the crude material which was purified by flash chromatography on acetone deactivated silica gel (elution with 5-15% $MeOH/CHCl_3$). The yield of morphinan **71** was 4.5 mg (44%). Also recovered from the reaction was 4 mg of **145** which can be used as starting material for this reaction. The yield of morphinan **71** based on recovered **145** was 73%.



71

tlc: R_f = 0.23 (5% MeOH/$CHCl_3$)

^1H NMR (300 MHz, $CDCl_3$):

6.74 (d, J = 8.3 Hz, 1 H), 6.67 (d, J = 8.2 Hz, 1 H),

5.97 (s, exchangeable, 1 H),

5.55 (d, J = 1.5 Hz, 1 H),

3.90 (1H signal obscurred by 3.88 s),

3.88 (s, 3 H), 3.83 (d, J = 18.1 Hz, 1 H),

3.73 (s, 3 H), 3.17 (d, J = 18.1 Hz, 1 H),

2.85 (dd, J = 18.2, 1.5 Hz, 1 H),

2.74 (dd, J = 18.2, 5.3 Hz, 1 H),

2.43 (br s, 1 H),

2.40 (m, partially obscurred by 2.43 s, 1H),

2.34 (s, 3 H), 2.18 (dt, J = 12.3, 5.3 Hz, 1 H),

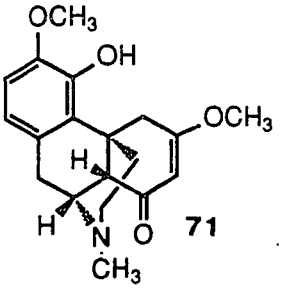
2.03 (dt, J = 11.5, 2.3 Hz, 1 H),

1.63 (d, obscurred by H_2O signal, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): 197.1, 176.7, 144.6, 143.6,

132.0, 127.5, 118.8, 108.9, 101.4, 56.2, 55.7, 50.9,

50.8, 47.0, 42.7, 39.1, 36.9, 30.1, 27.2.

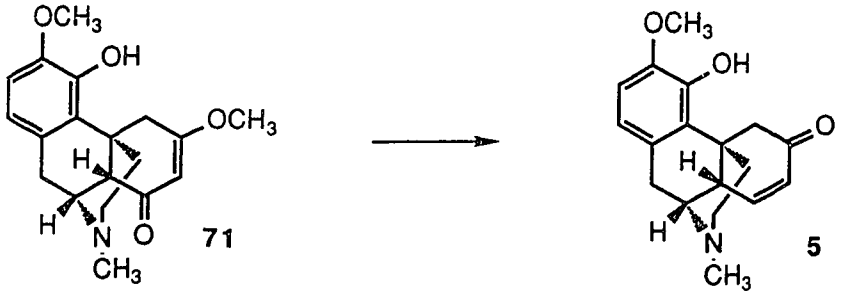


71

IR (85:15 mixture of trans and cis isomers, neat): 3400, 3010, 2933, 2845, 2804, 1725, 1651, 1616, 1484, 1458, 1440, 1380, 1280, 1222, 1204 cm^{-1}.

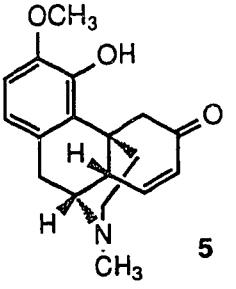
Mass spectrum (70 ev, m/e(intensity)): 330(16.7,m+1), 329(73.7,m^+), 314(47.3,m-CH_3), 271(32.9), 245(41.8), 192(100), 169(33.5).

HRMS: for $C_{19}H_{23}NO_4$ calculated 329.1627
found 329.1648.
for $C_{18}H_{20}NO_4$ calculated 314.1392
found 314.1393.



Preparation of beta-thebainone 5 from trans-morphinan 71.

The morphinan **71** (3mg, 0.009 mmol) was taken up in dry tetrahydrofuran (2 mL) underan atmosphere of nitrogen. Diisobutylaluminum hydride (0.10 mL of a 1 M solution in hexanes, 0.10 mmol) was added and the mixture stirred at ambient temperature for 0.5-1 h. The reaction was quenched carefully with water and 3% aqueous HCl (2 mL) was added. The resulting solution was stirred for several hours after which time 5% aqueous NaOH was added such that the mixture became slightly basic. This solution was extracted four times with methylene chloride (total volume 20 mL). The combined extracts were washed with brine and dried over anhydrous K_2CO_3 before removal of the solvent in vacuo. The crude mixture was purified by flash chromatography on acetone deactivated silica gel (elution with 15% MeOH/$CHCl_3$). The yield was about 3 mg (approximately 100%) of beta-thebainone. A trace of thebainone was also detected.



5

tlc: R_f = 0.39 (15% MeOH/$CHCl_3$)

^1H NMR (300 MHz, $CDCl_3$):

6.96 (dd, J = 9.9, 1.8 Hz, 1 H),

6.74 (d, J = 8.4 Hz, 1 H), 6.67 (d, J = 8.4 Hz, 1 H),

6.19 (ddd, J = 9.8, 2.8, 0.6 Hz, 1 H),

5.96 (s, exchangeable, 1 H),

4.02 (d, J = 17.5 Hz, 1 H), 3.87 (s, 3 H),

3.20 (m, 1 H, partially obscurred by 3.15 d)

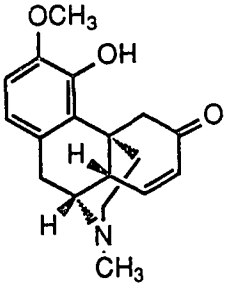
3.15 (d, J = 18.1 Hz, 1 H),

2.86 (dd, J = 18.1, 5.9 Hz, 1 H), 2.82 (s, 1 H),

2.61 (d, J = 17.5 Hz, 1 H),

2.40 (m, 1 H), 2.37 (s, 3 H), 2.19-2.00 (m, 2 H),

1.60 (br d, 1 H, partially obscurred by H_2O signal).

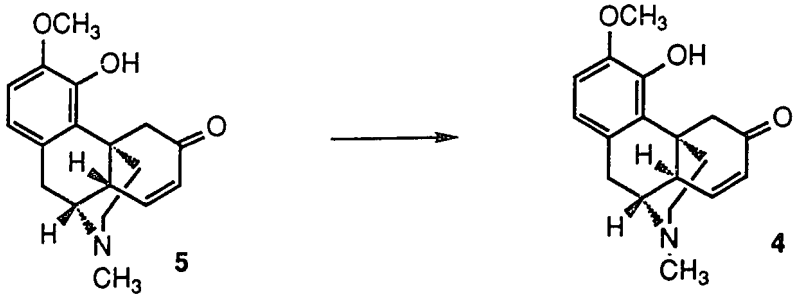


5

IR (neat): 3380, 2905, 2840, 1660, 1480, 1435, 1275, 1145, 1090, 1055 cm^{-1}.

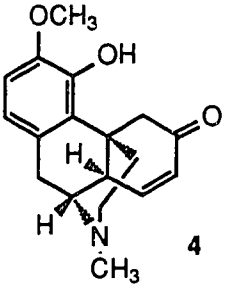
Mass spectrum (70 ev, m/e(intensity)): 300(10.8,m+1), 299(52.2,m^+), 284(3.2,m-CH_3), 256(6.5), 242(8.0), 204(9.3), 190(11.1), 162(98.6).

HRMS: for $C_{18}H_{21}NO_3$ calculated 299.1521
found 299.1550.



Preparation of thebainone 4 from beta-thebainone 5.

A solution of beta-thebainone **5** (3 mg, 0.010 mmol) in glacial acetic acid (0.5 h) was heated to 100°C under an atmosphere of dry nitrogen. The heating was continued for 1 h after which time the mixture was basified with dilute ammonium hydroxide. The resulting solution was extracted with methylene chloride several times (total volume of 20 mL). The combined organic extracts were washed once each with water and brine before drying over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the crude product (3 mg) which was essentially pure thebainone. Purification by flash chromatography gave 2 mg of pure thebainone.



4

tlc: R_f = 0.21 (15% MeOH/$CHCl_3$)

^1H NMR (300 MHz, $CDCl_3$):

6.67 (dd, J = 9.9, 1.5 Hz, 1 H),

6.64 (d, J = 8.1 Hz, 1 H), 6.54 (d, J = 8.1 Hz, 1 H),

6.05 (br s, 1 H), 5.88 (dd, J = 9.9, 2.7 Hz, 1 H),

4.26 (d, J = 15.6 Hz, 1 H), 3.80 (s, 3 H),

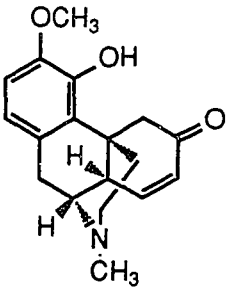
3.23 (t, J = 4.3 Hz, 1 H), 3.01 (d, J = 18.4 Hz, 1 H),

2.91 (br s, 1 H), 2.65 (dd, J = 18.3, 5.3 Hz, 1 H),

2.55 (ddd, J = 11.9, 4.0, 2.0 Hz, 1 H),

2.43 (s, 3 H), 2.38 (d, J = 15.6 Hz, 1 H),

2.07 (dt, J = 11.9, 3.7 Hz, 1 H), 1.97-1.83 (m, 2 H).

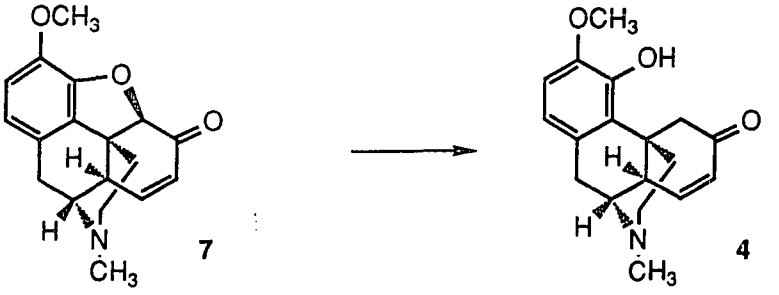


4

IR (neat): 3360, 3050, 2920, 2840, 1675, 1580, 1480, 1430, 1275, 1145, 1095, 1050 cm^{-1}.

Mass spectrum (70 ev, m/e(intensity)): 300(17.6,m+1), 299(60.9,m^+), 284(9.4,m-CH_3), 271(21.4), 178(50.4), 162(100).

HRMS: for $C_{18}H_{21}NO_3$ calculated 299.1522
found 299.1550.



Preparation of thebainone 4 from codeinone 7.

A 2:1 mixture of codeinone **7** and neopinone **8** (prepared as in reference 52) was subjected to the same reaction conditions used to prepare 1,4-addition product **128** from dienone **127**. As this reaction was done only to characterize the product, exact amounts of reagents were not determined. The desired product was the major product and was purified by flash chromatography on acetone deactivated silica gel (elution with 15% MeOH/$CHCl_3$). The ^1H NMR for this material was superimposable on that for the material prepared from **71**.

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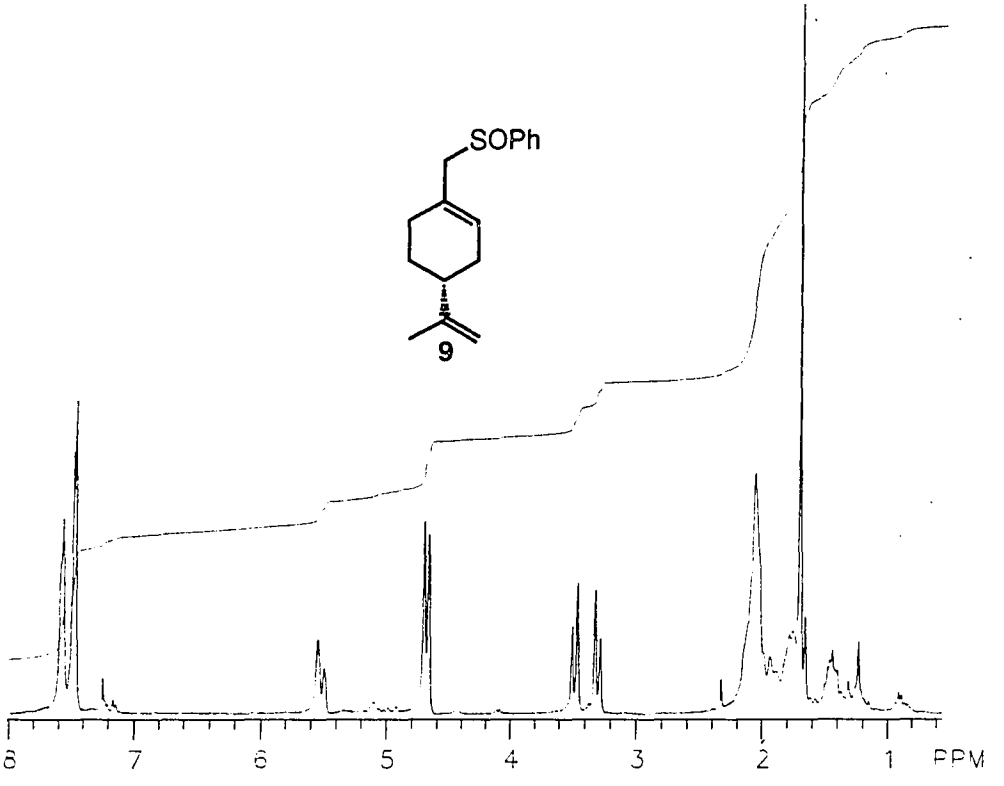
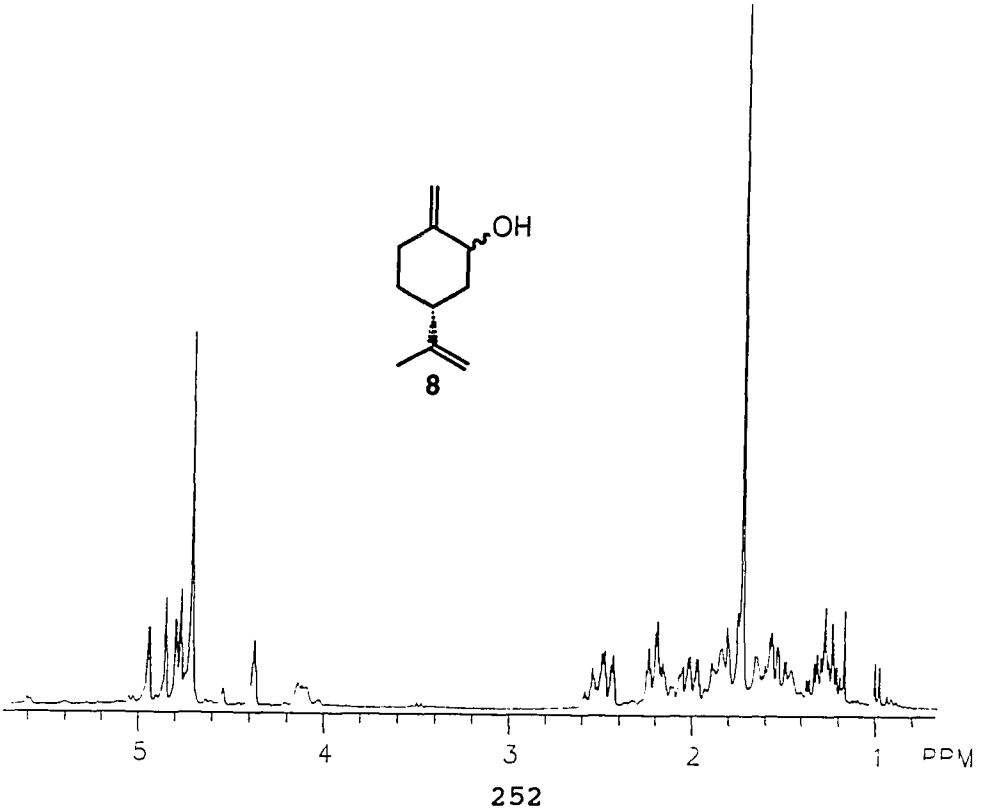
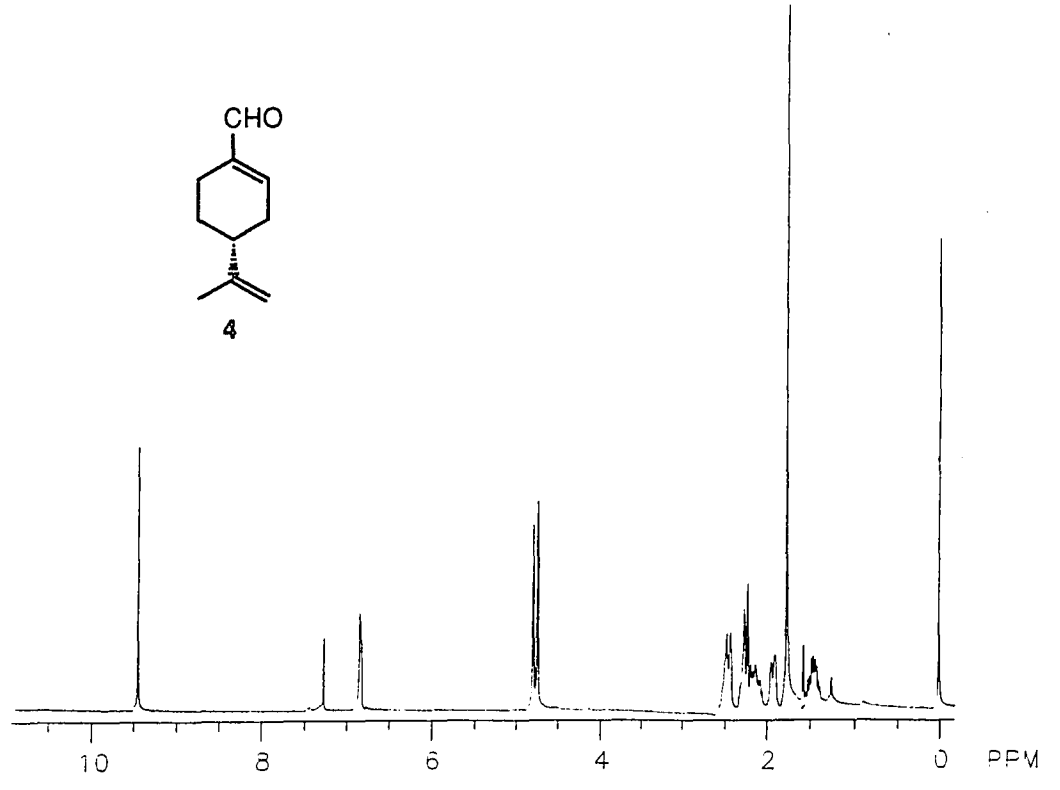
APPENDIX 1:

^{1}H NMR SPECTRA FOR SELECTED COMPOUNDS


SOPh
9
8
7
6
5
4
3
2
1
PPM


OH
8
5
4
3
2
1
PPM



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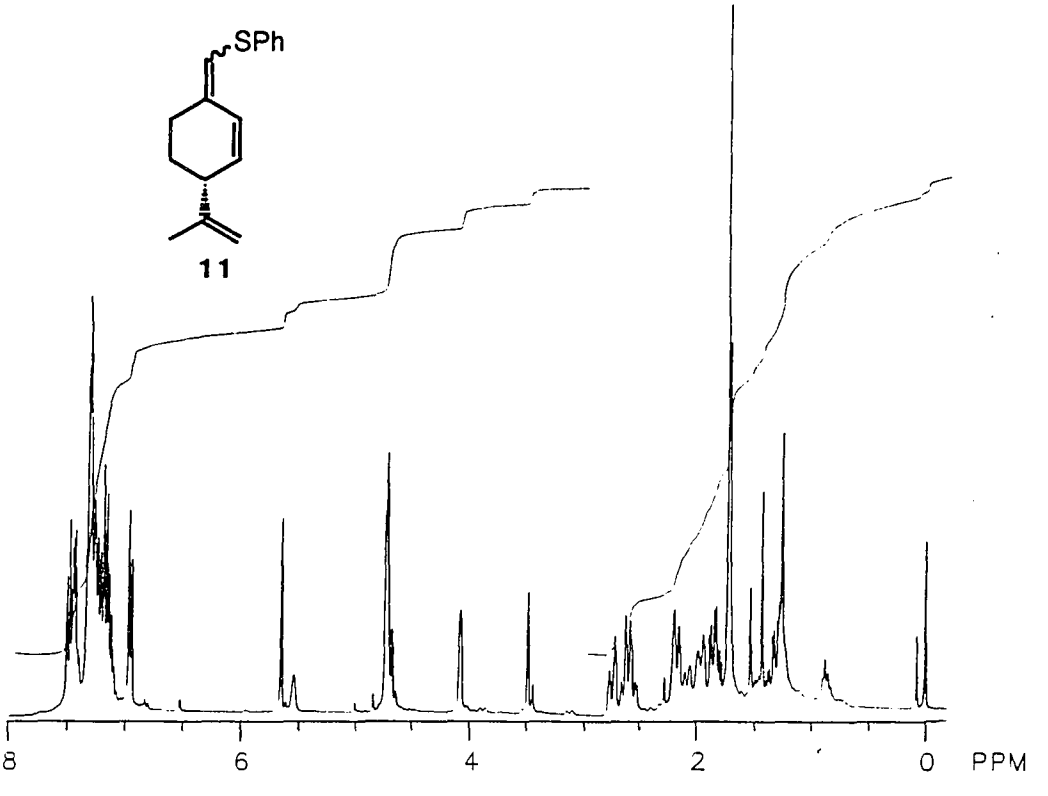
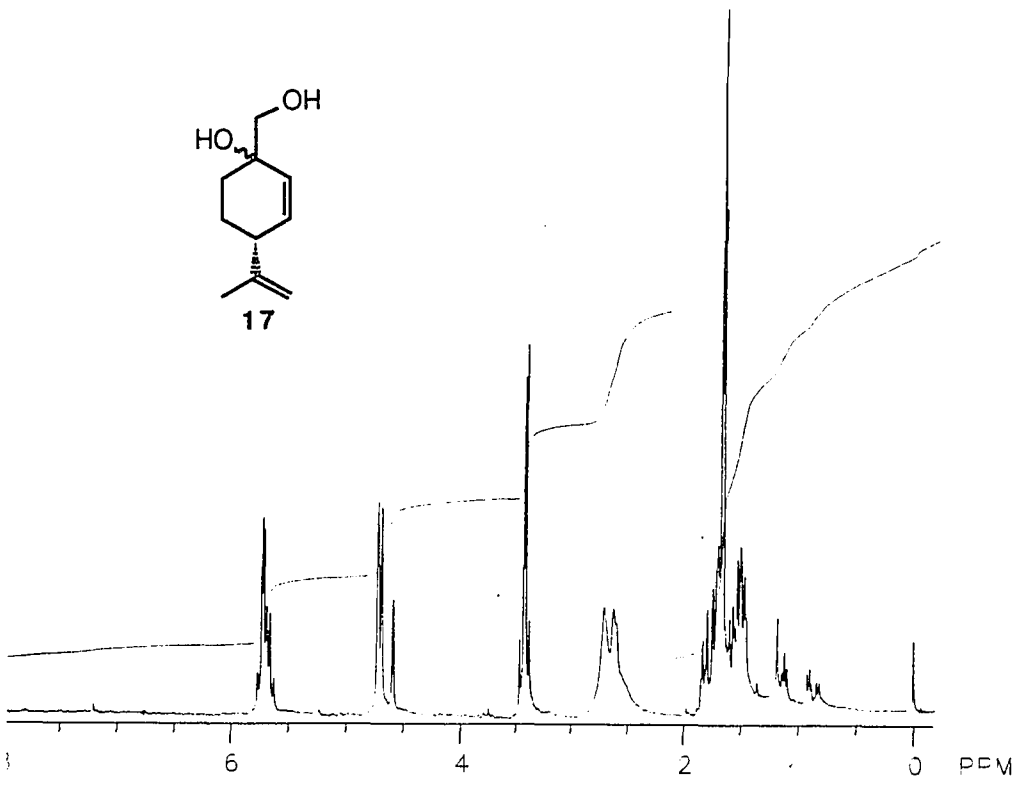
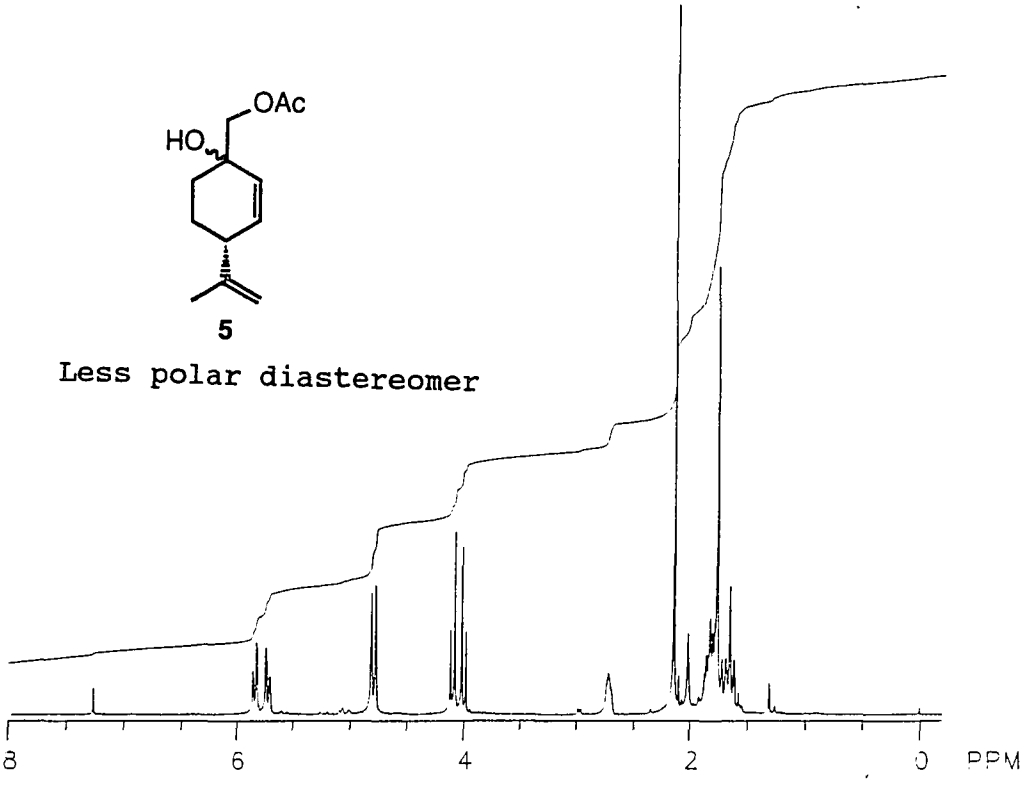


11

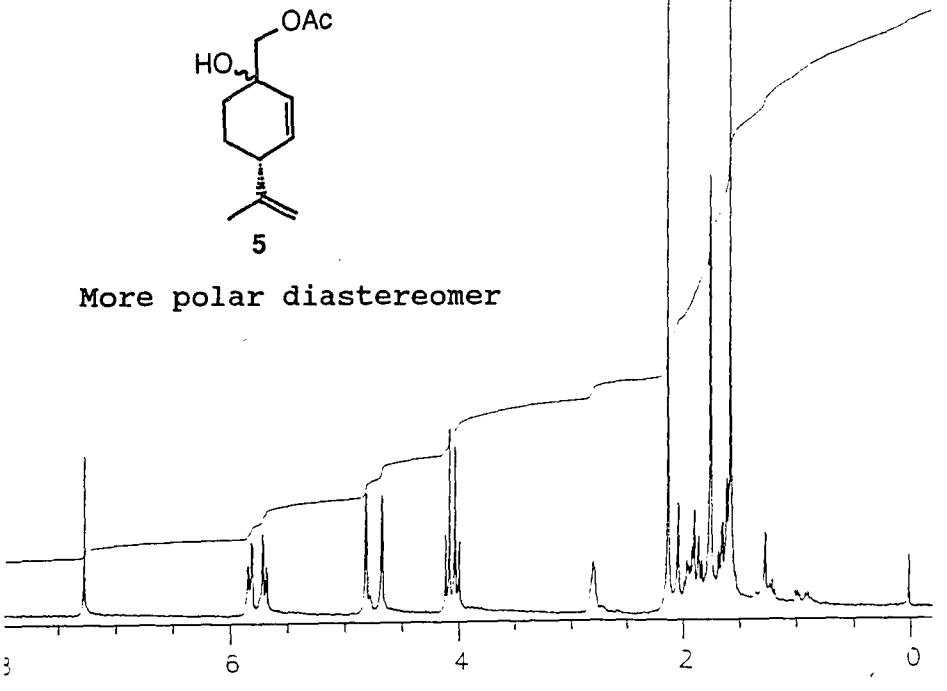


17



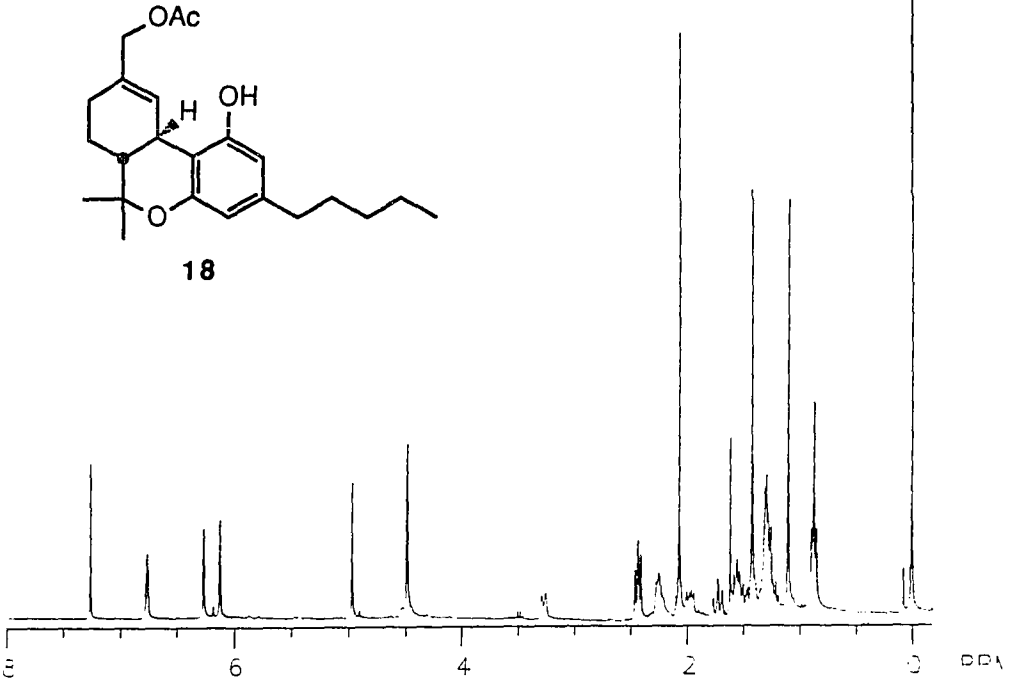
5

Less polar diastereomer



5

More polar diastereomer



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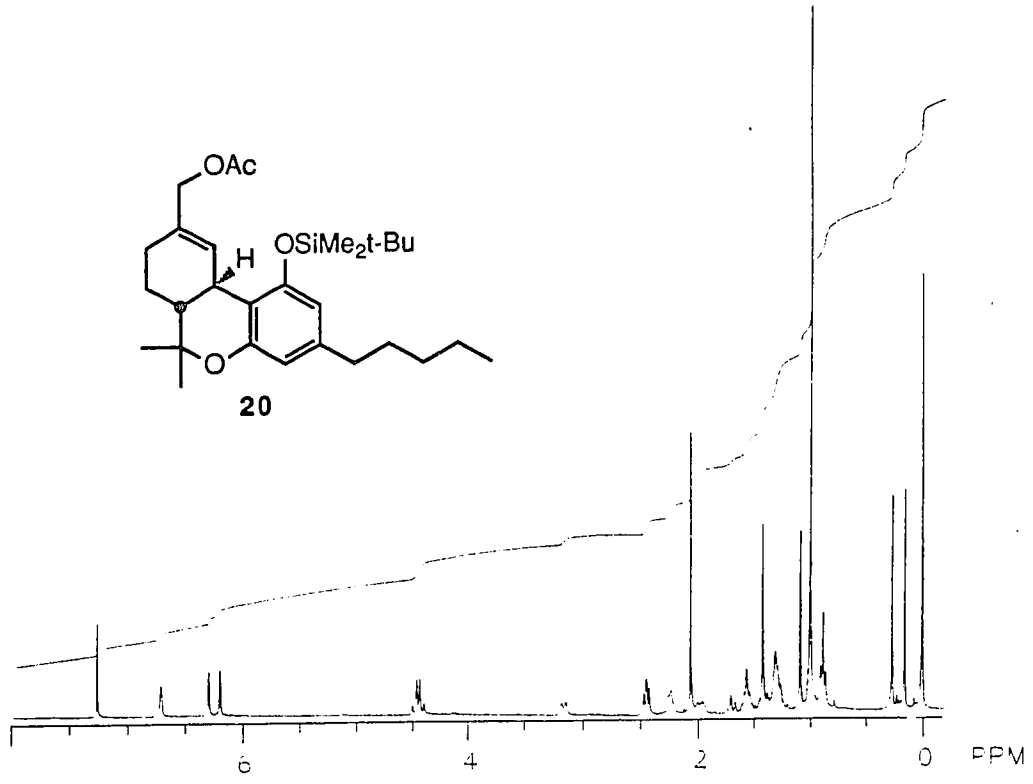

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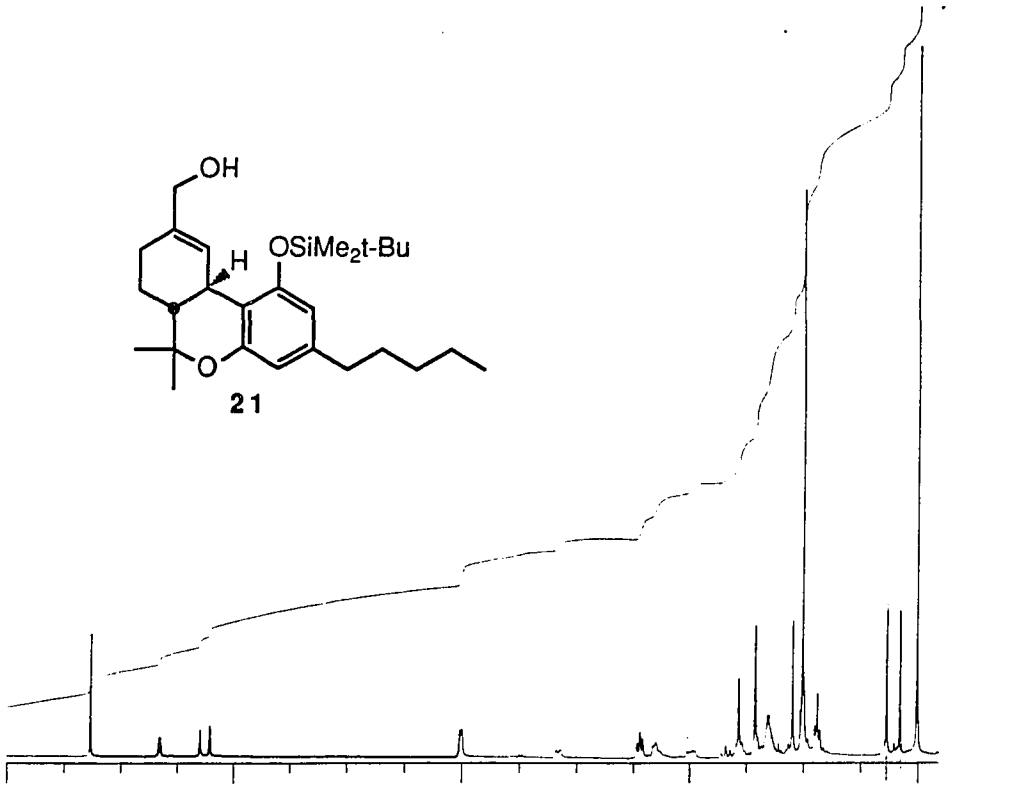

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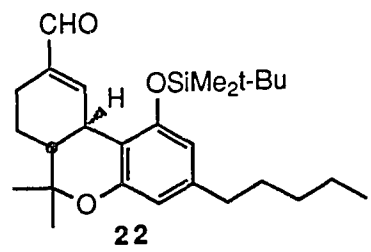
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OSiMe2t-Bu
O

22

10
8
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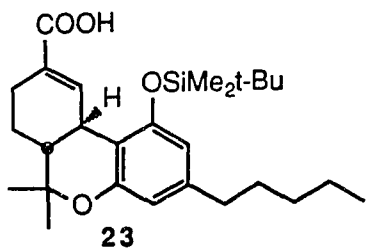
4
2
0
PPM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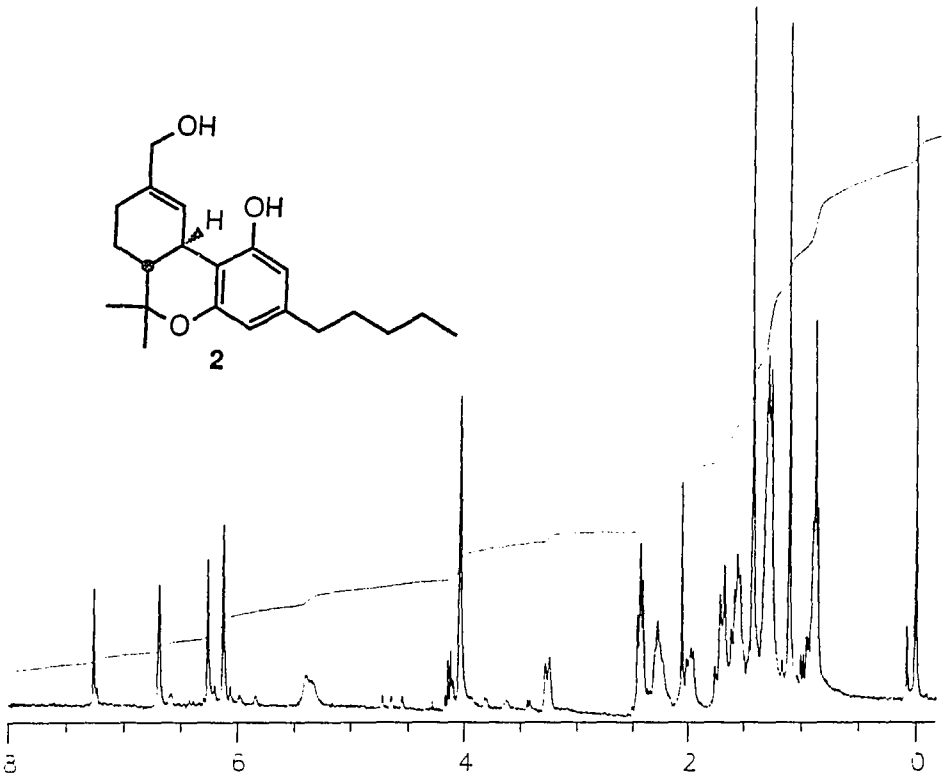
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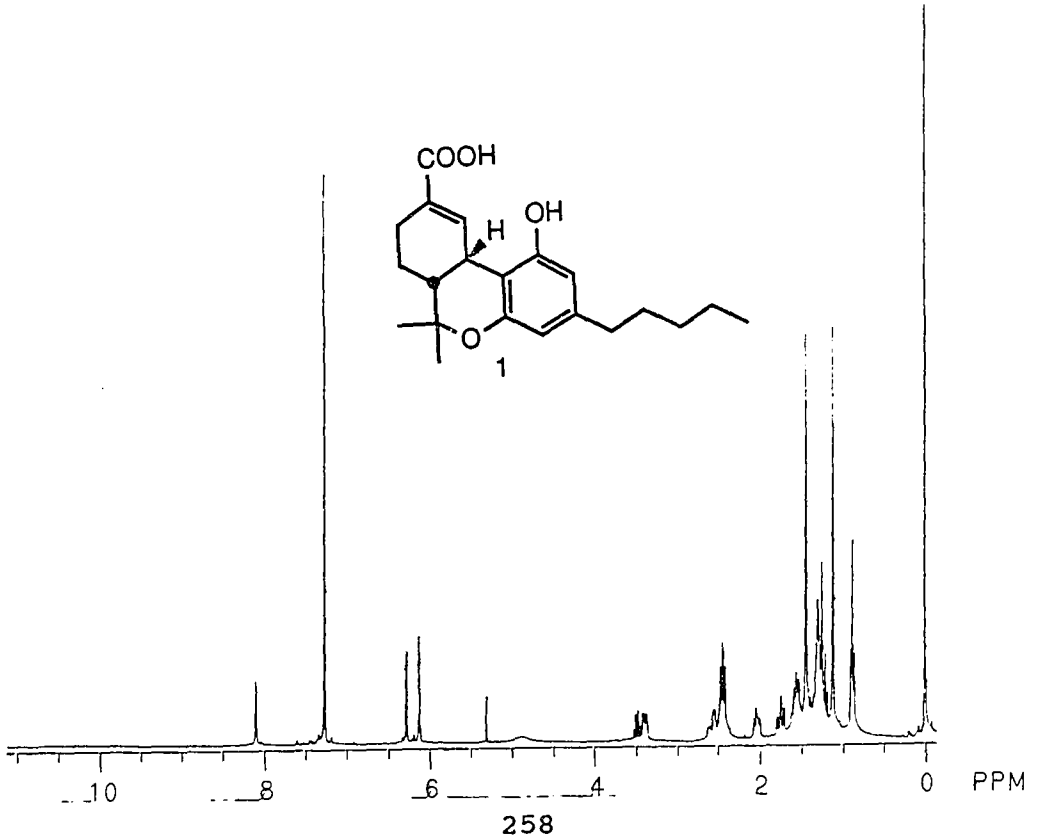
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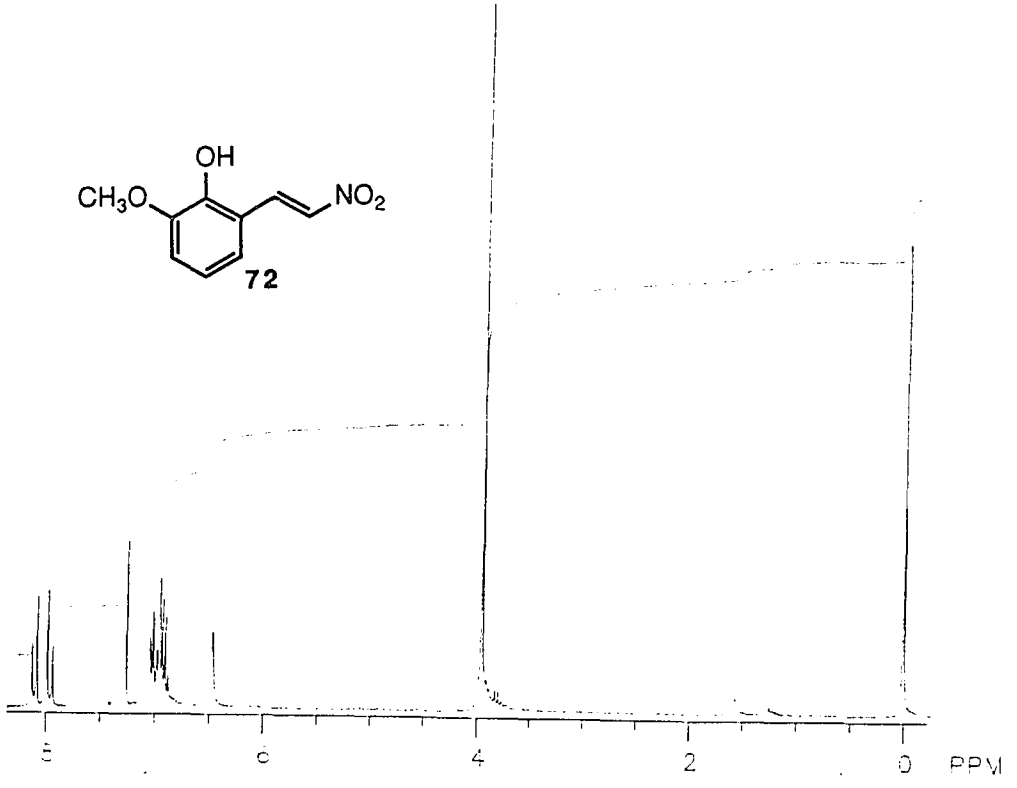
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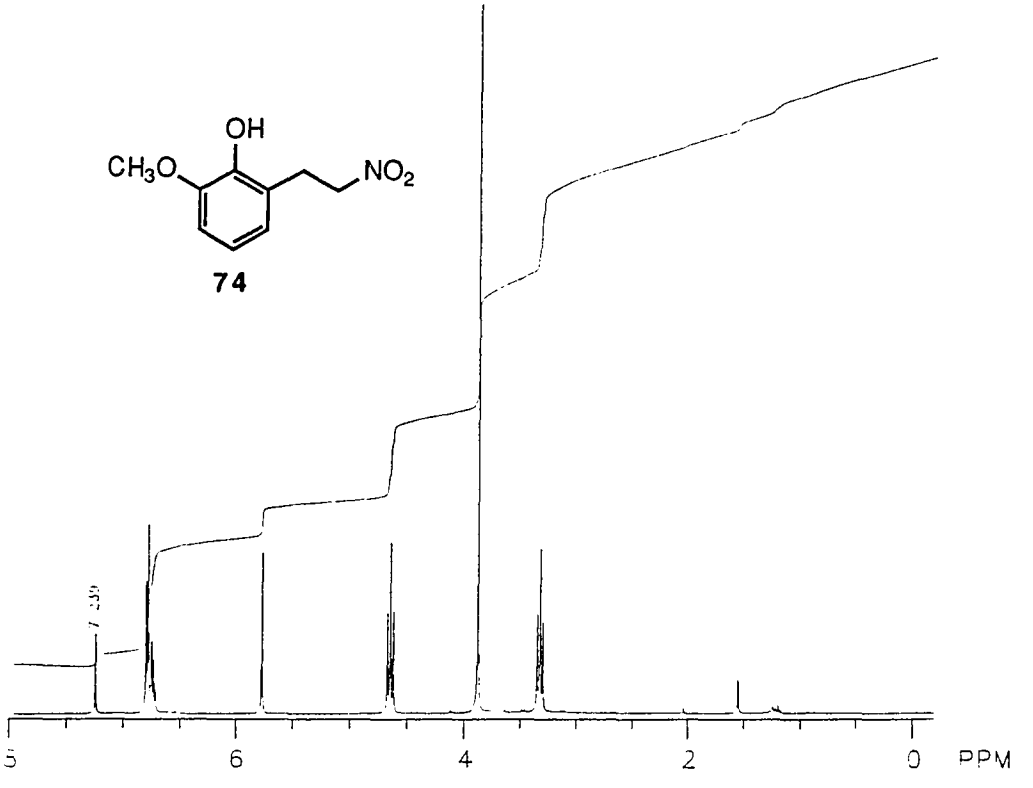
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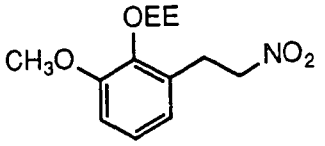

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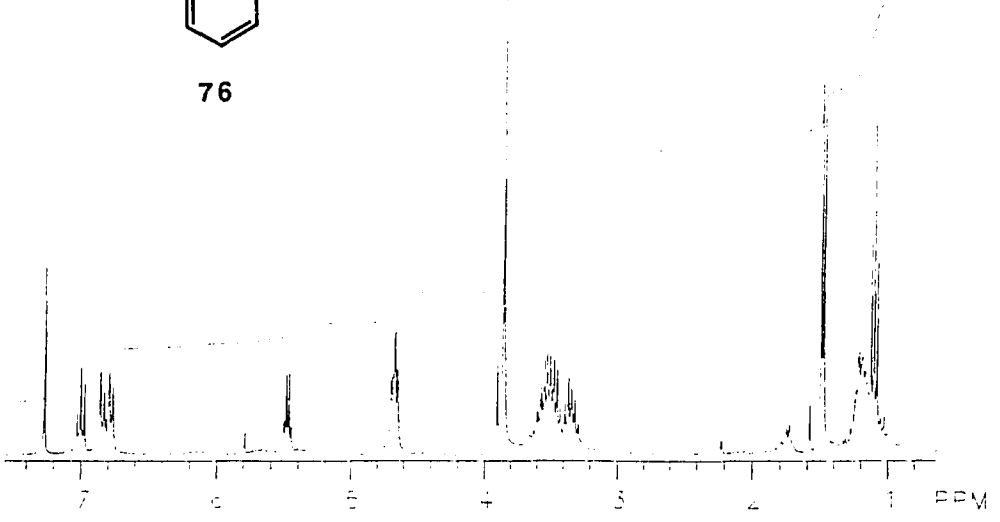

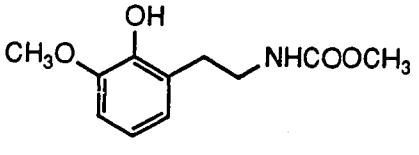

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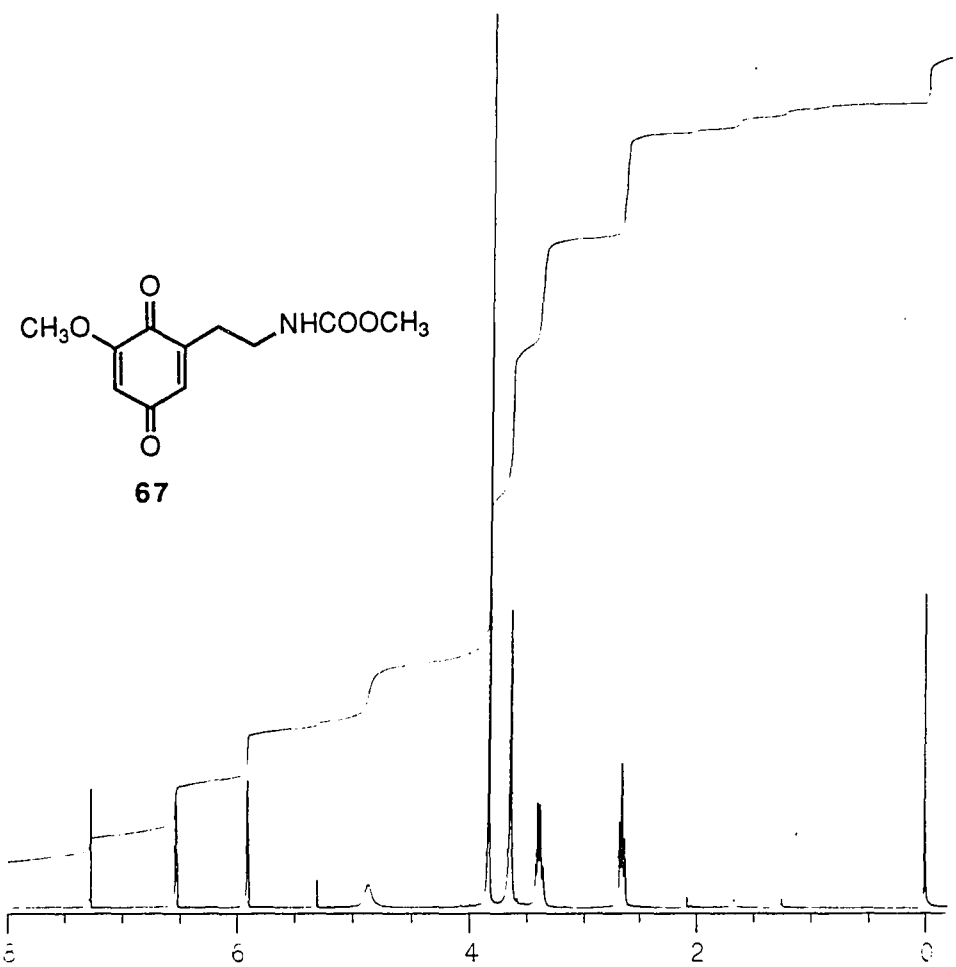

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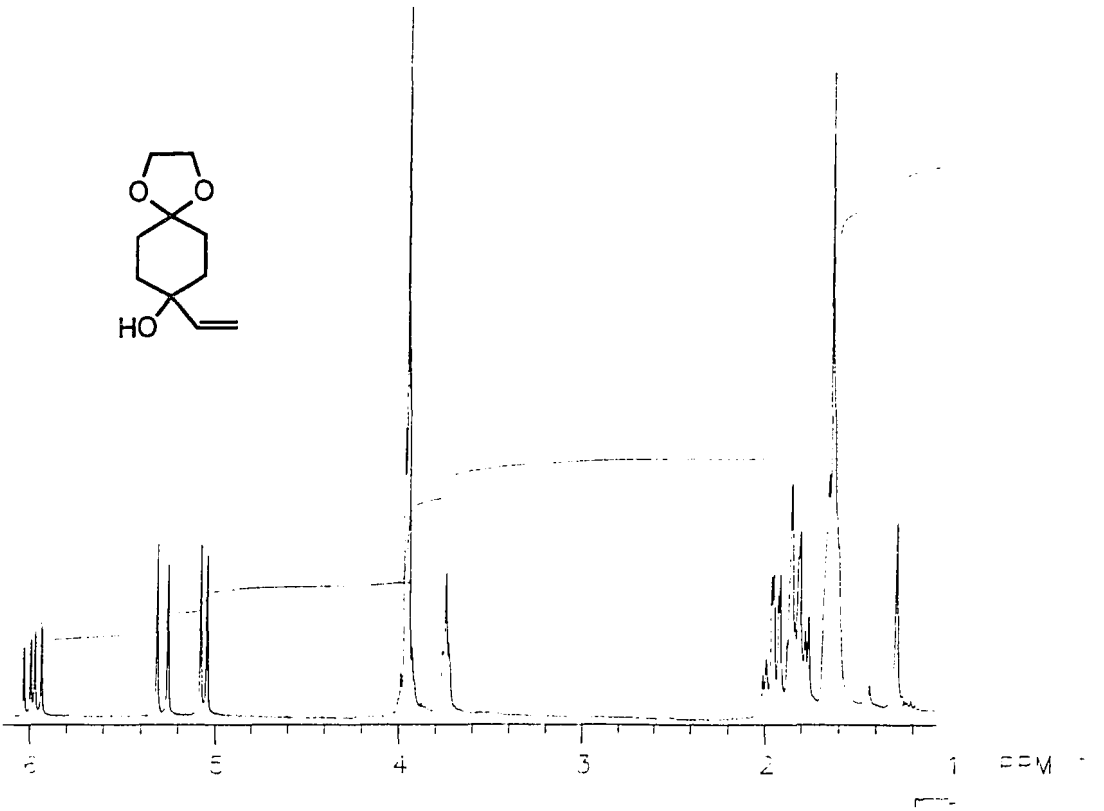
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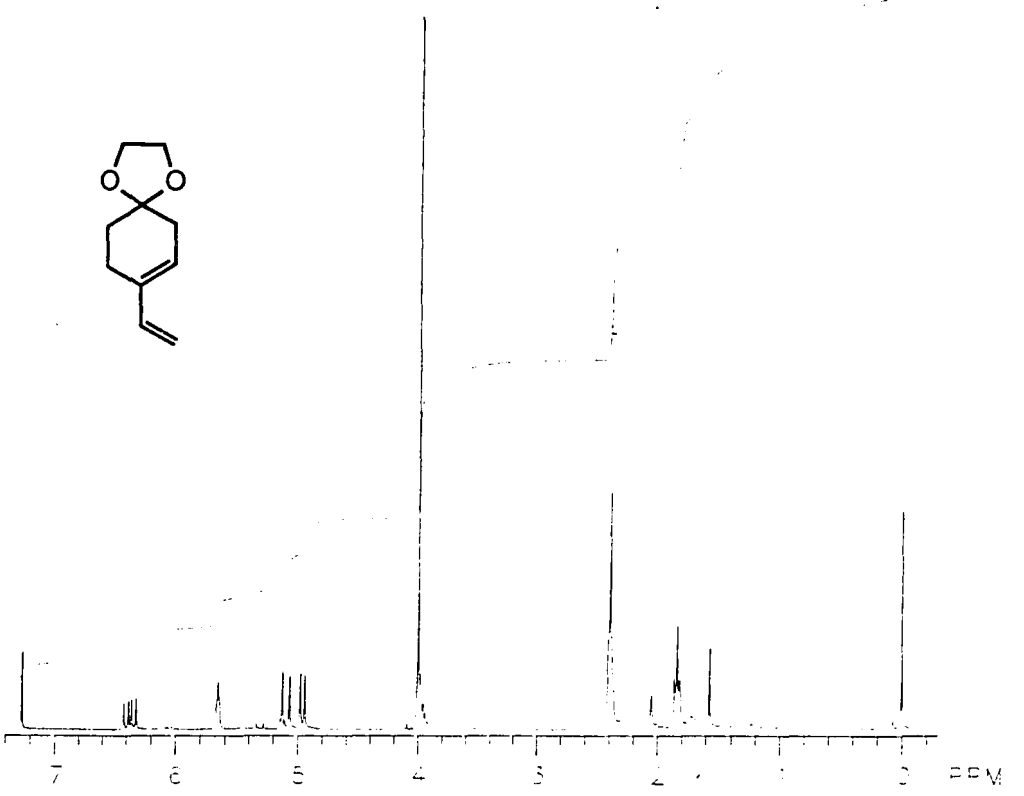
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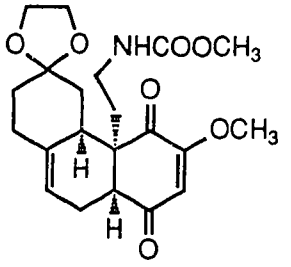

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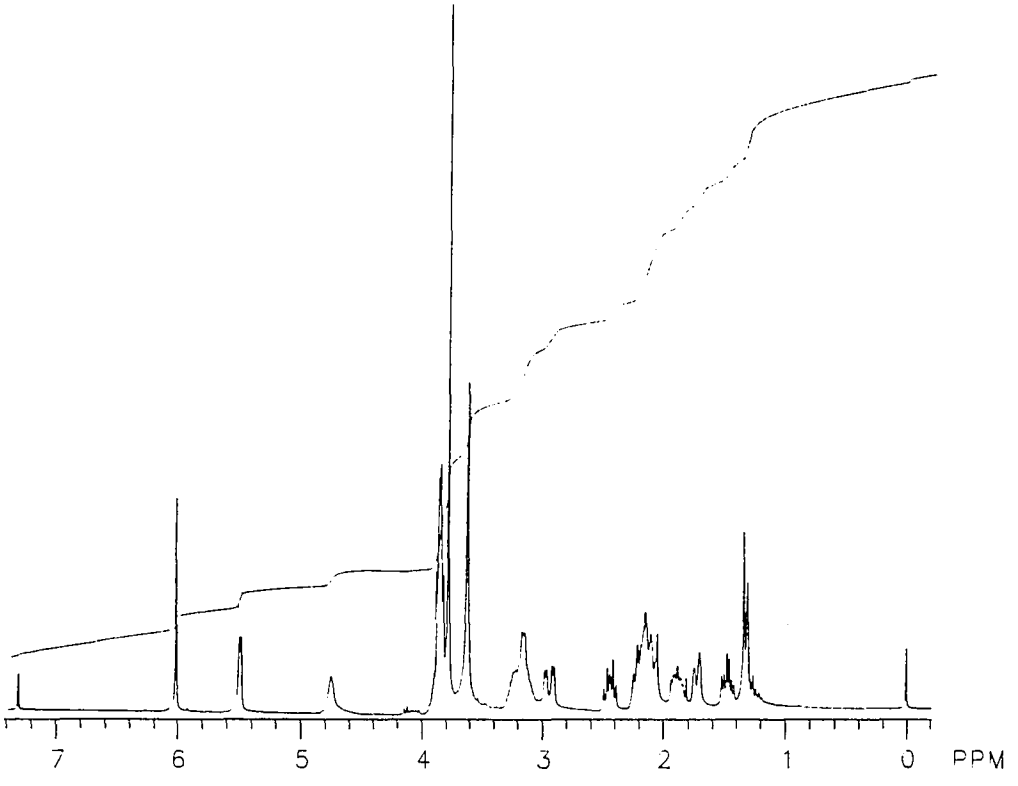

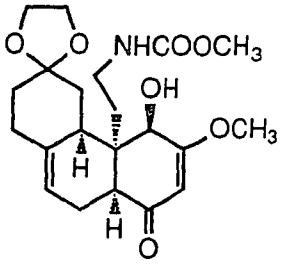

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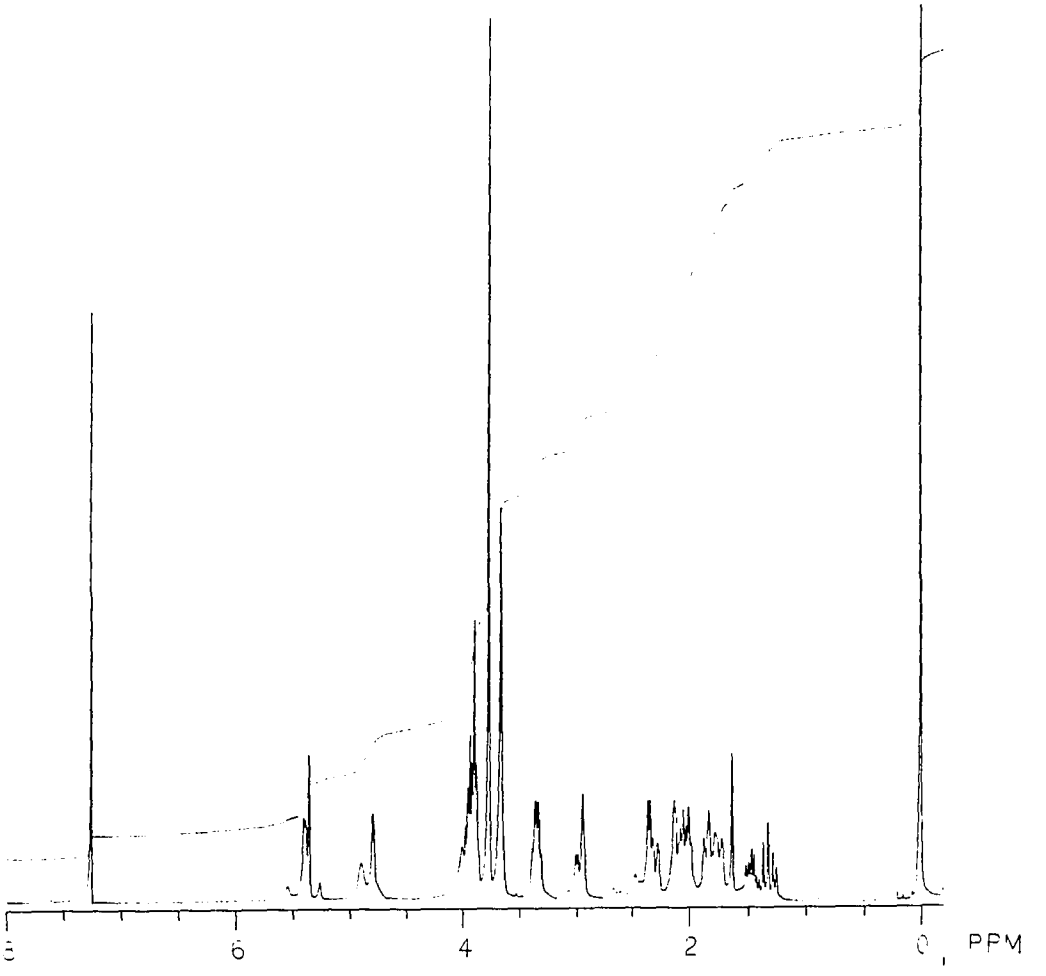

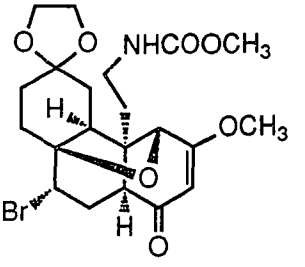

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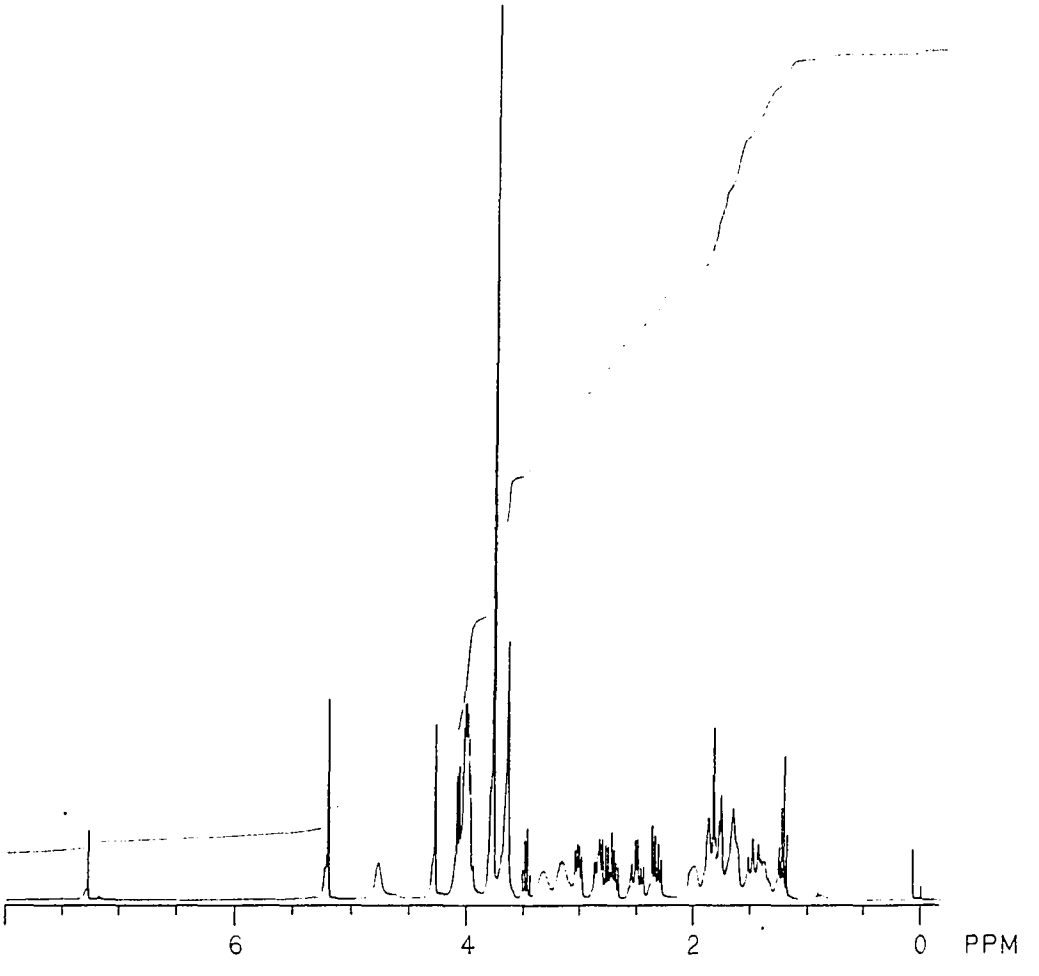

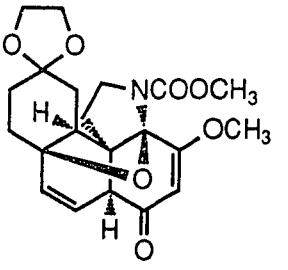

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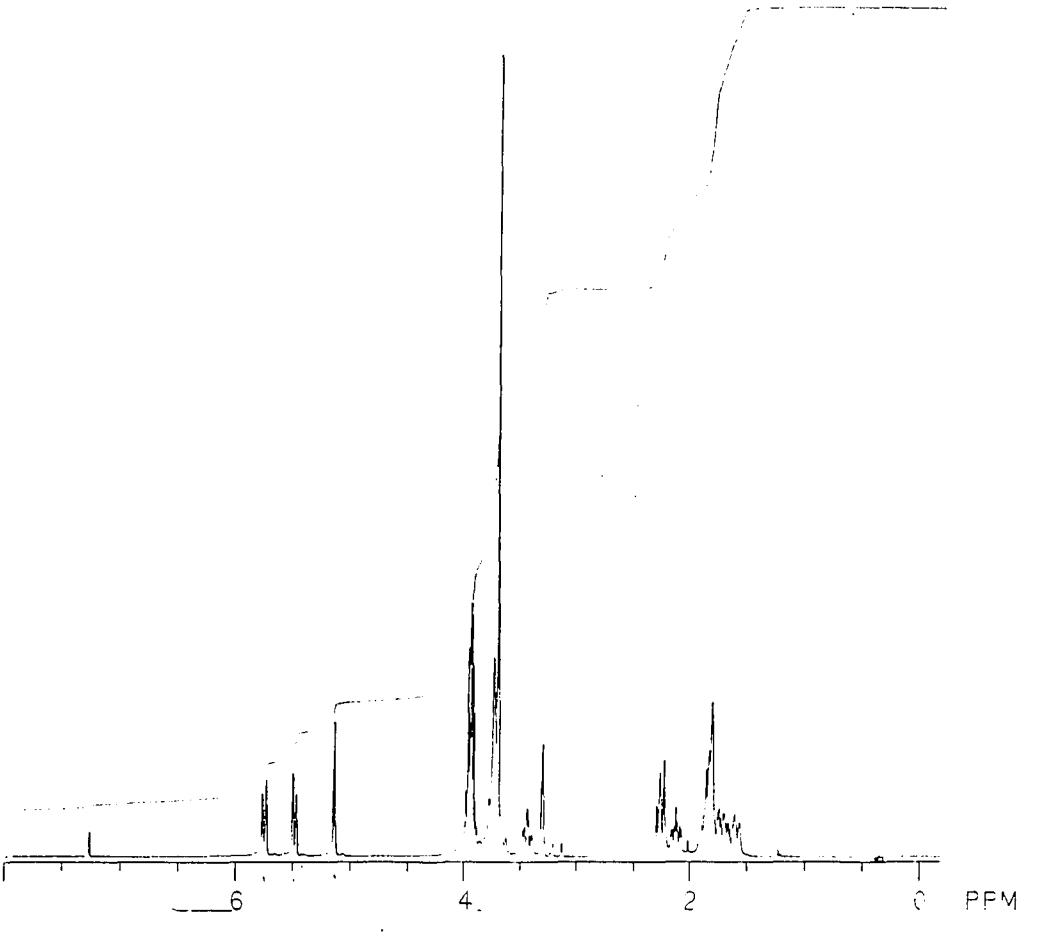

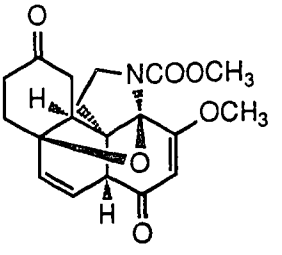

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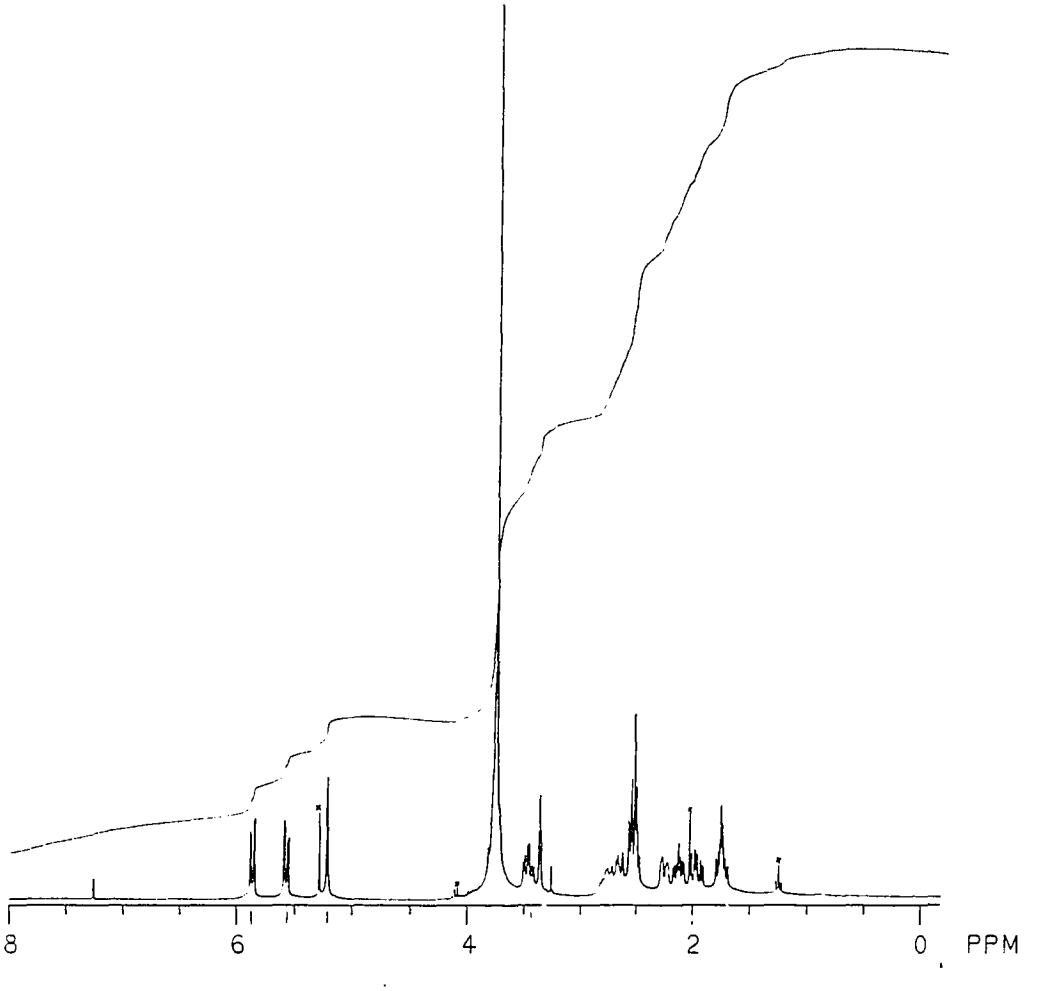

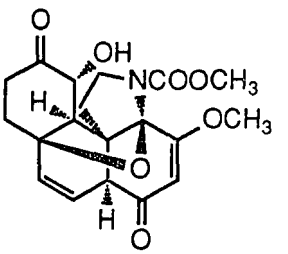

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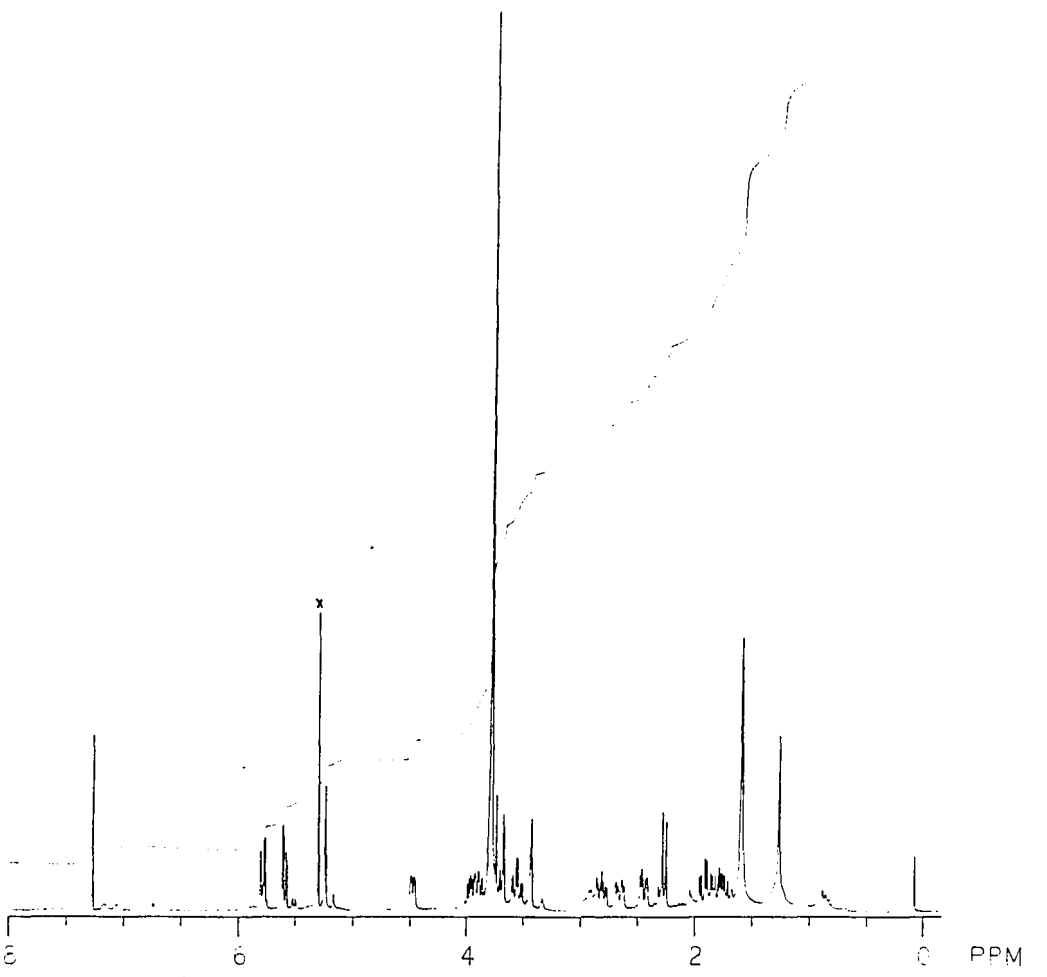

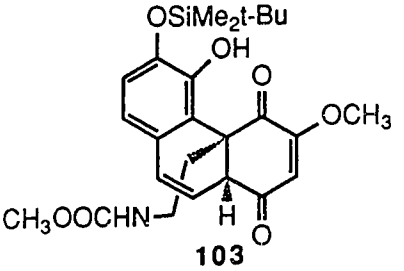

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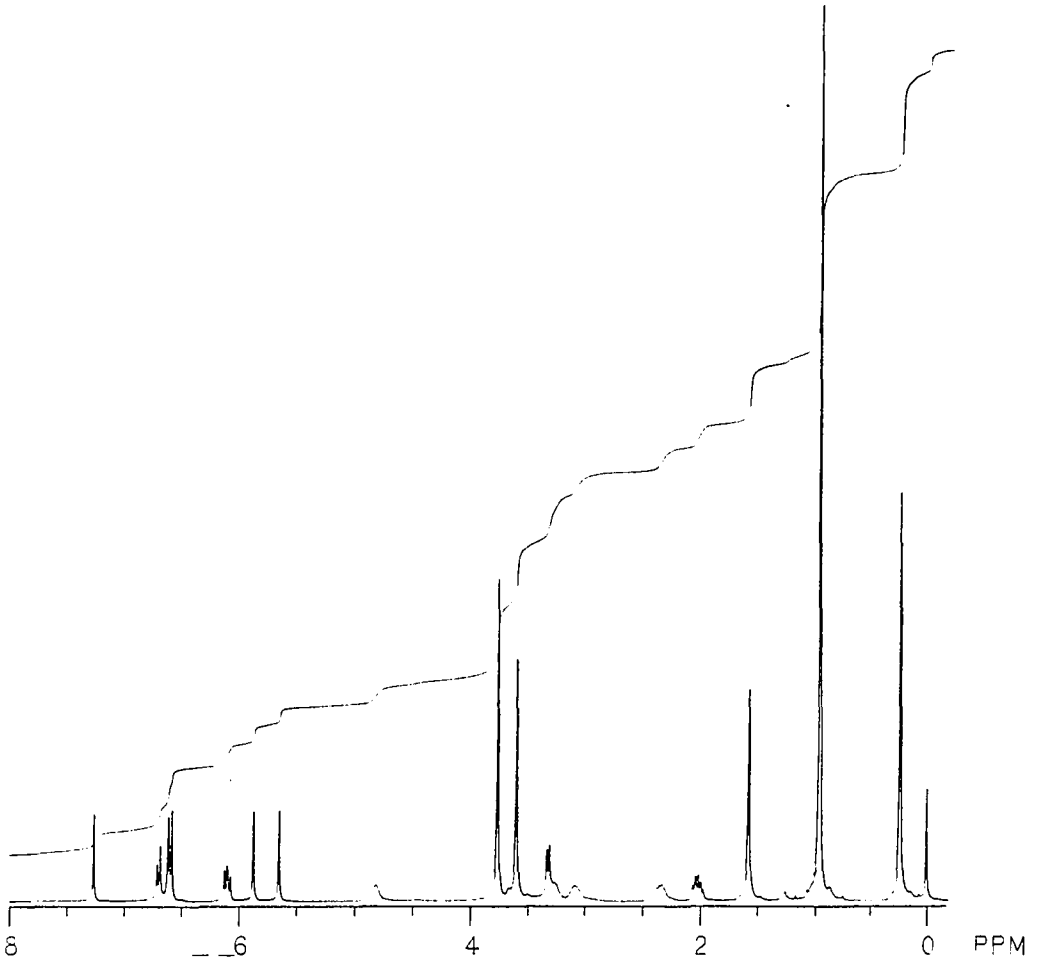

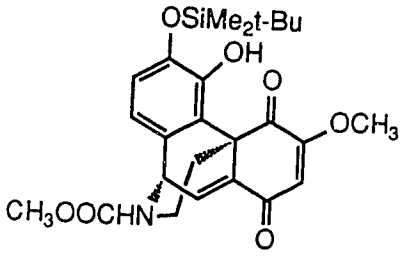

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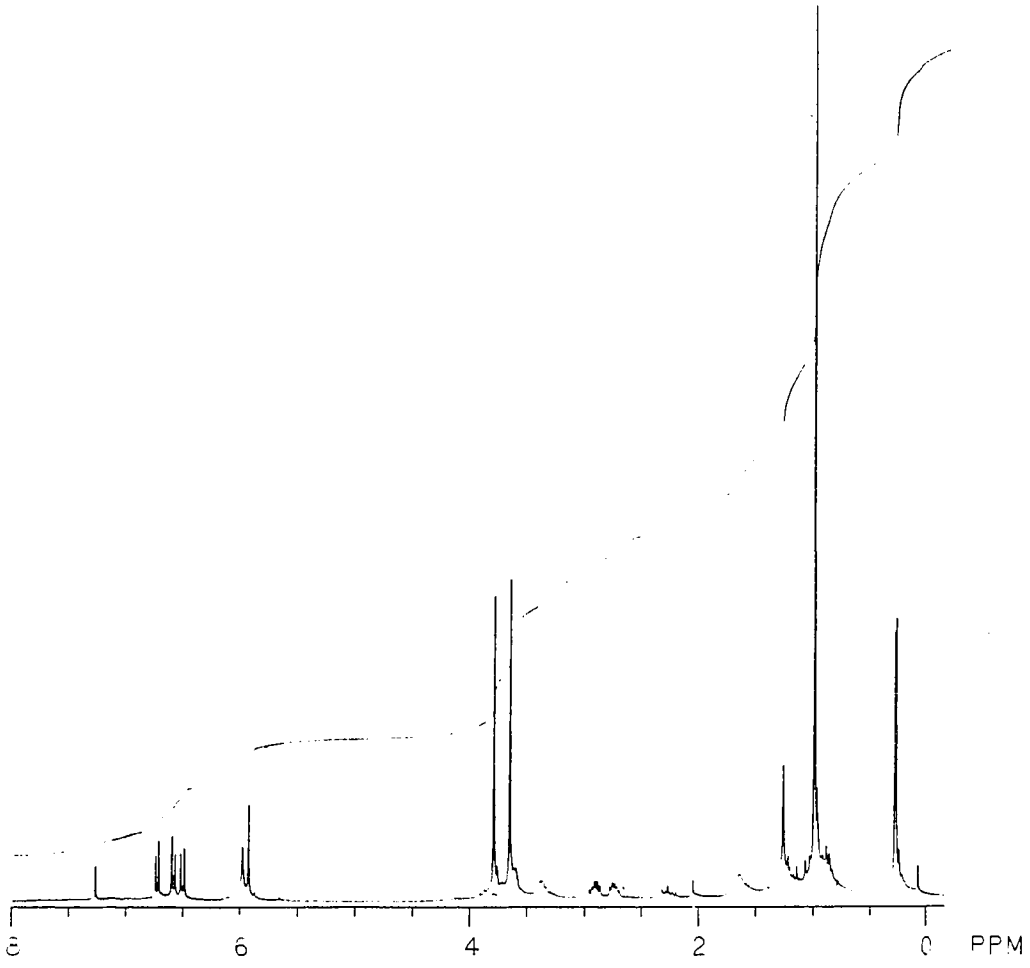

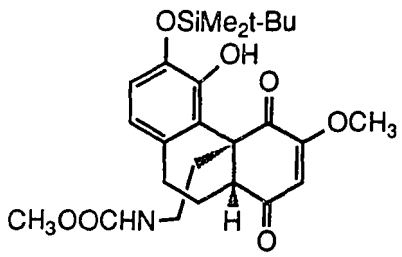

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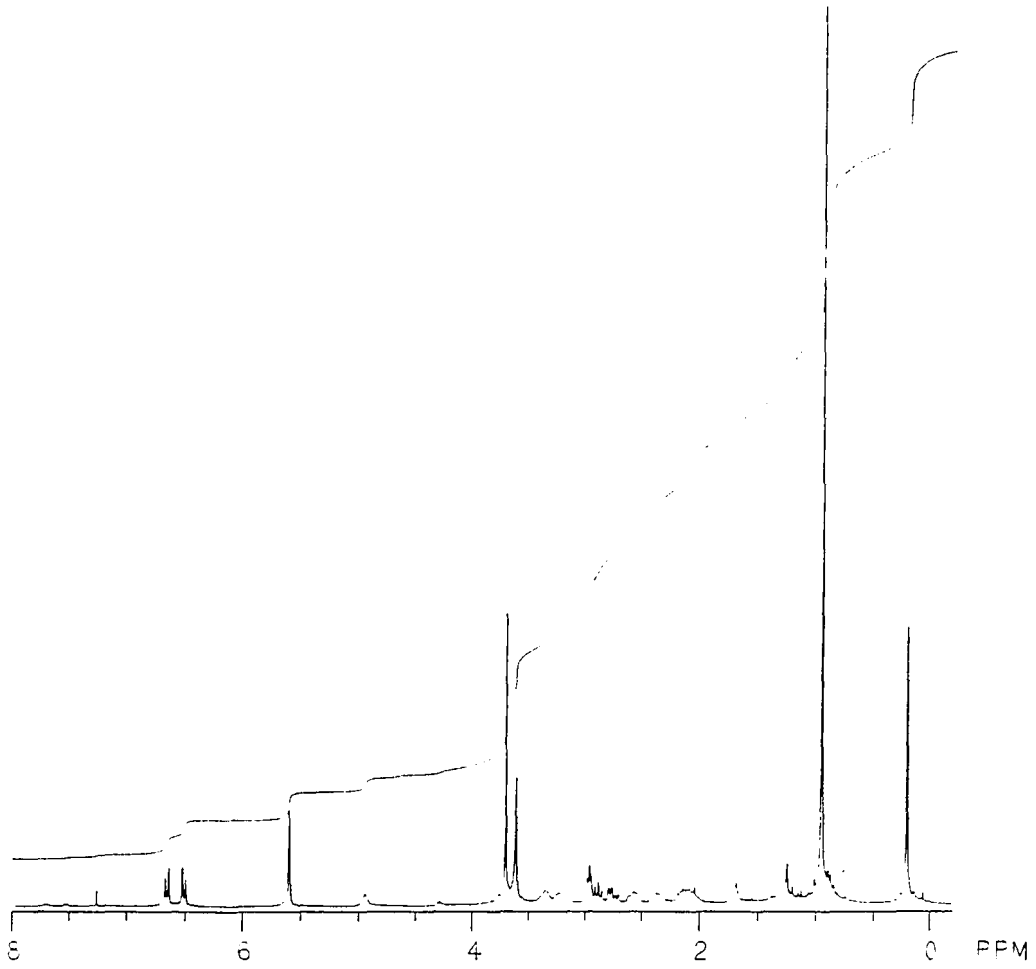

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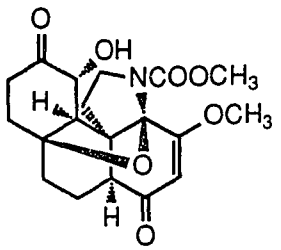

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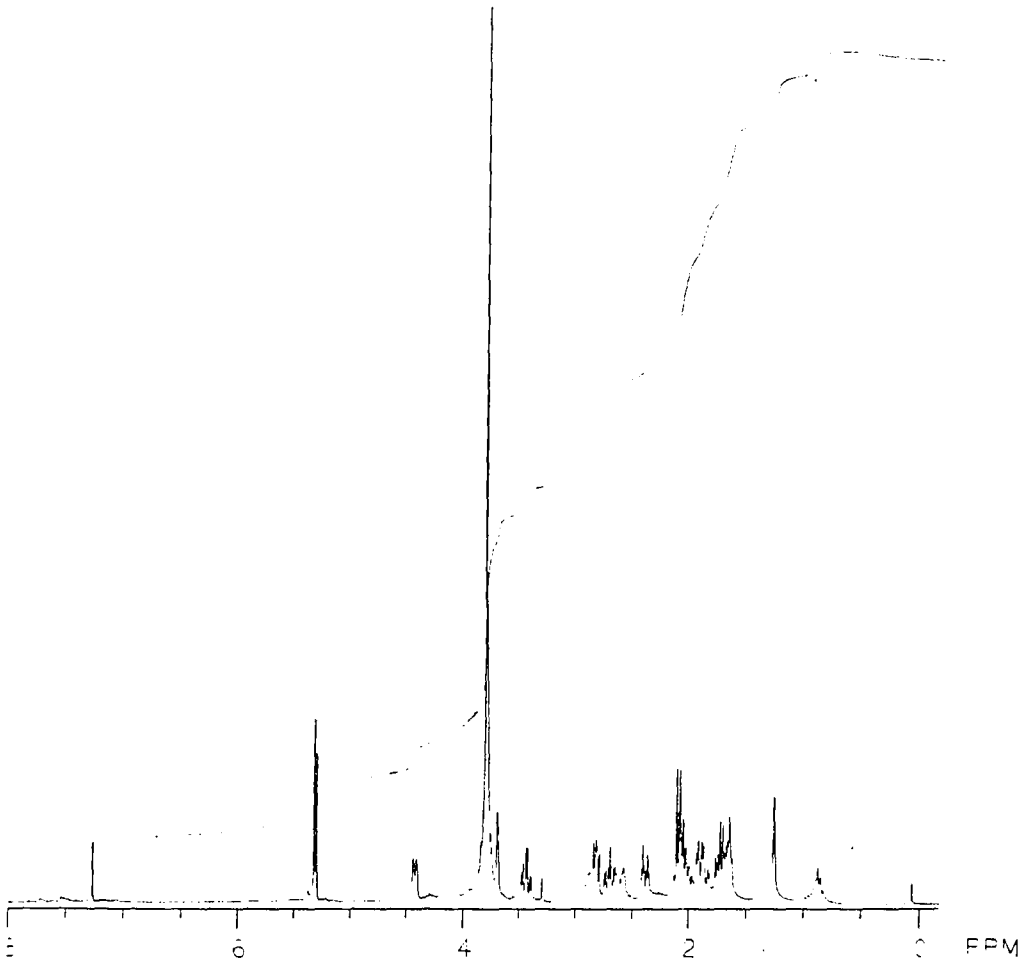

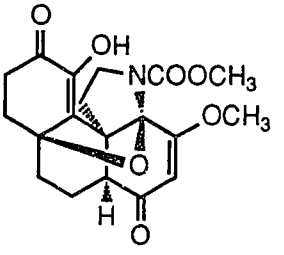

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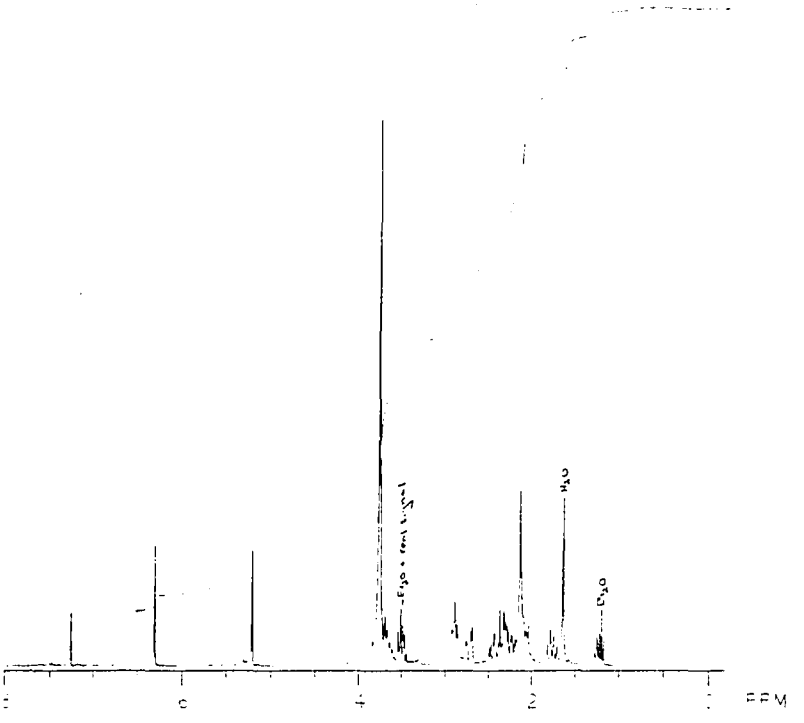

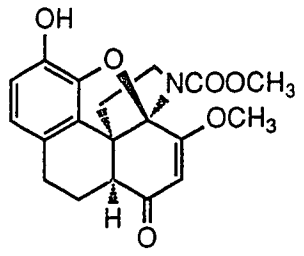

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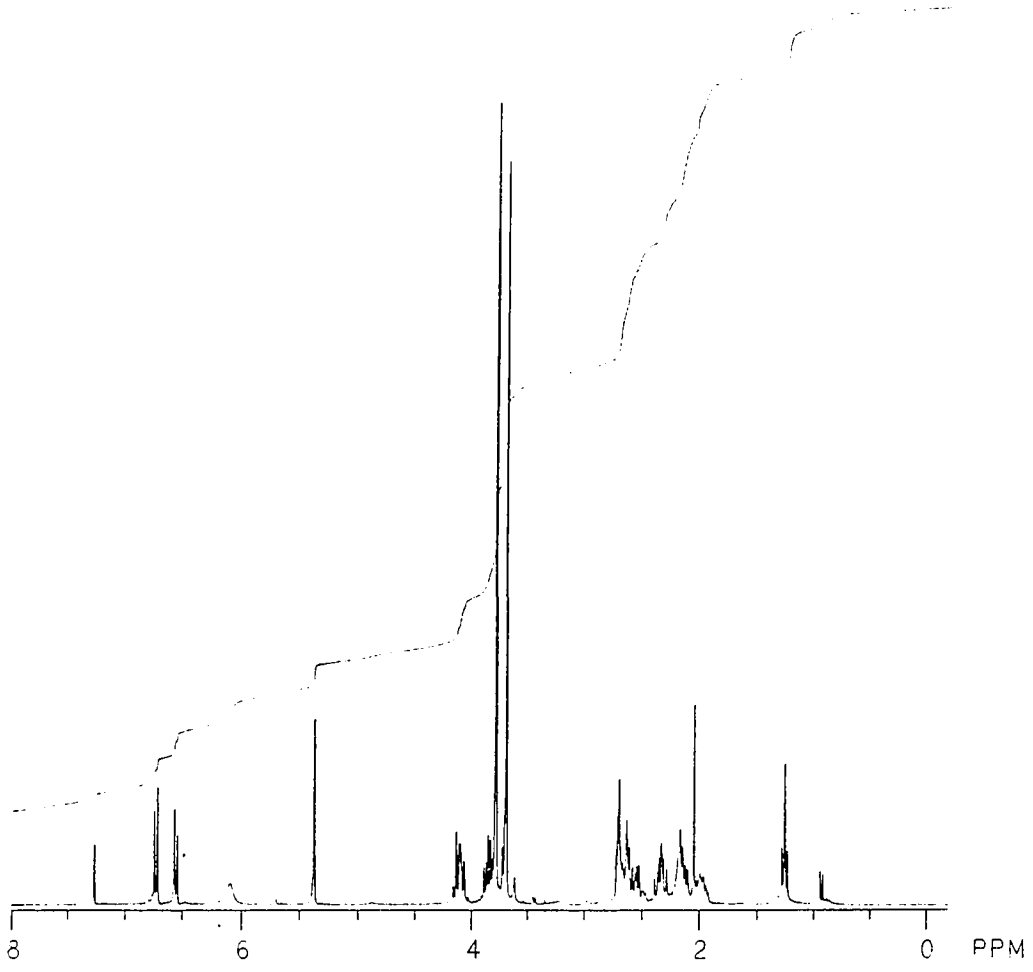

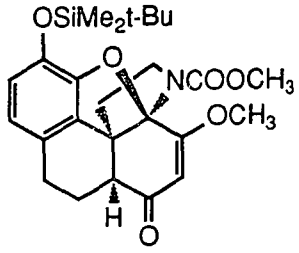

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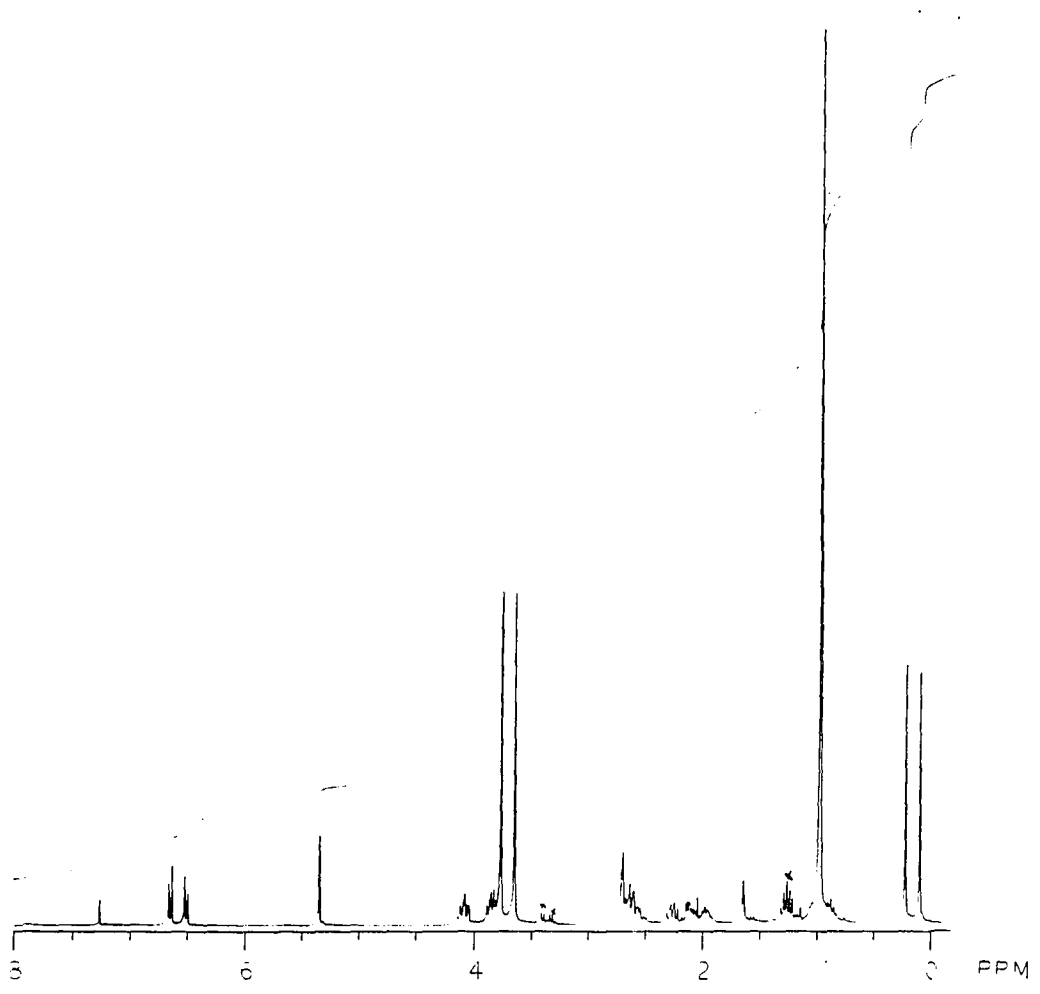

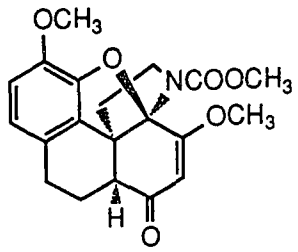

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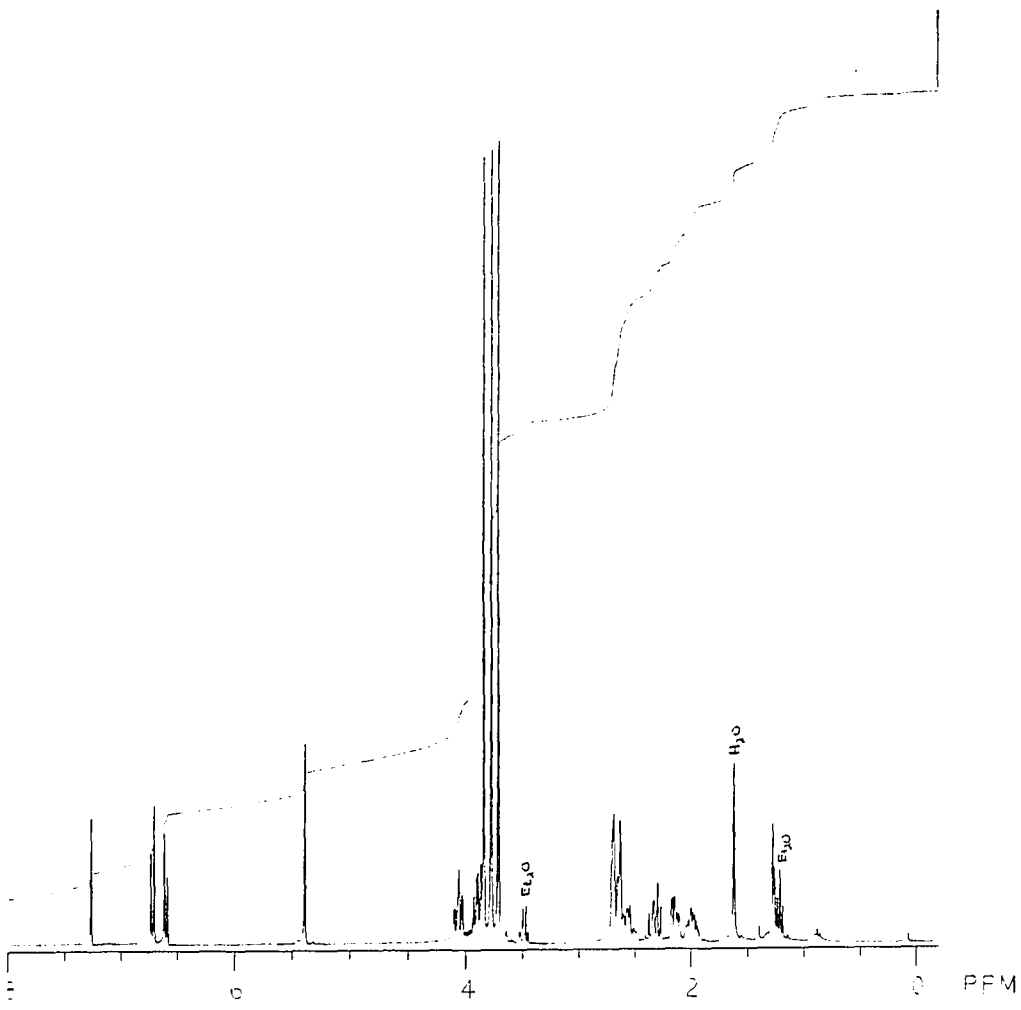

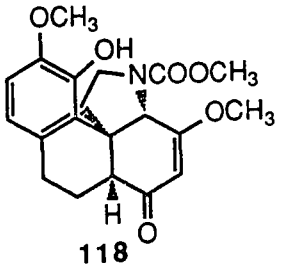

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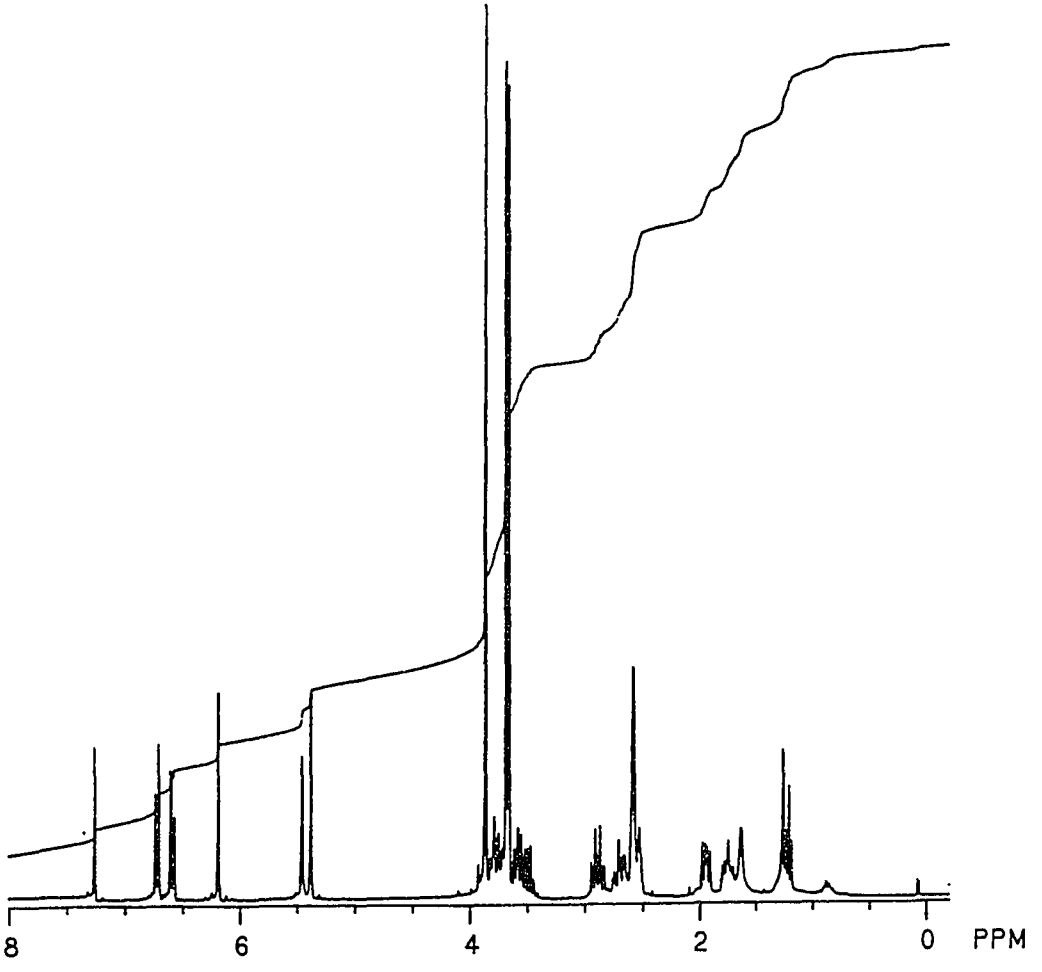

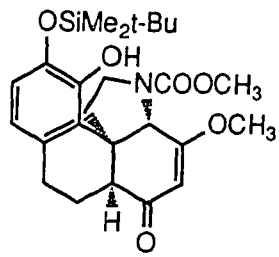

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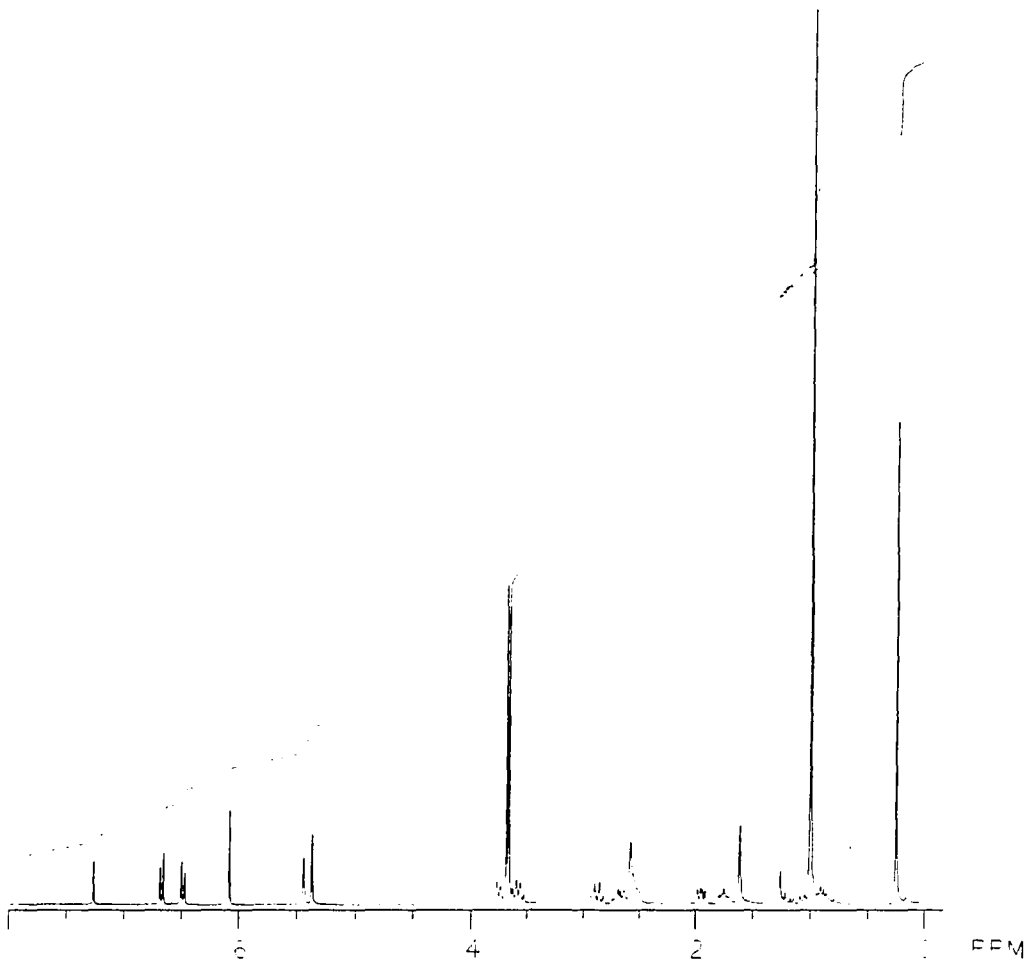

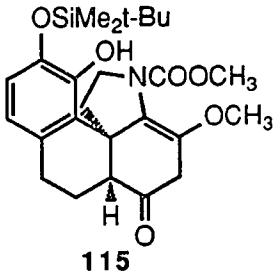

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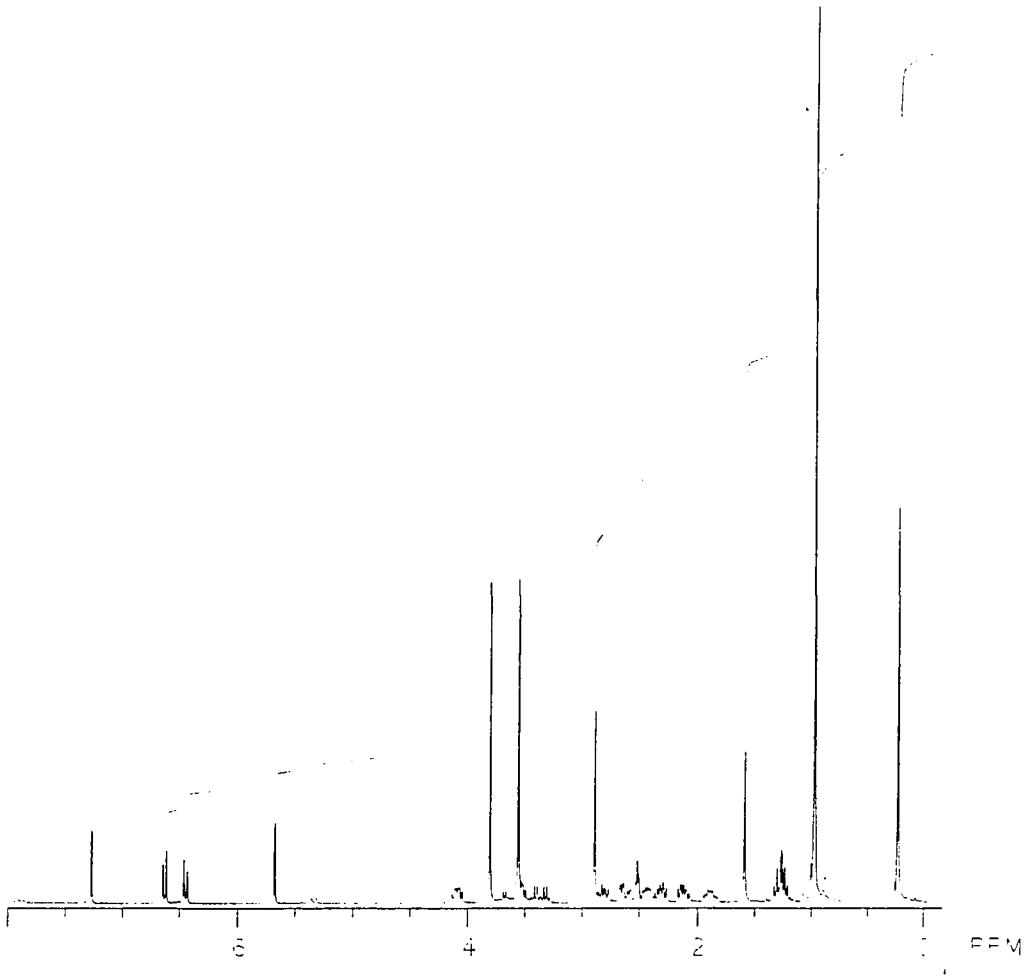

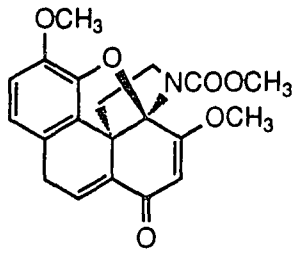

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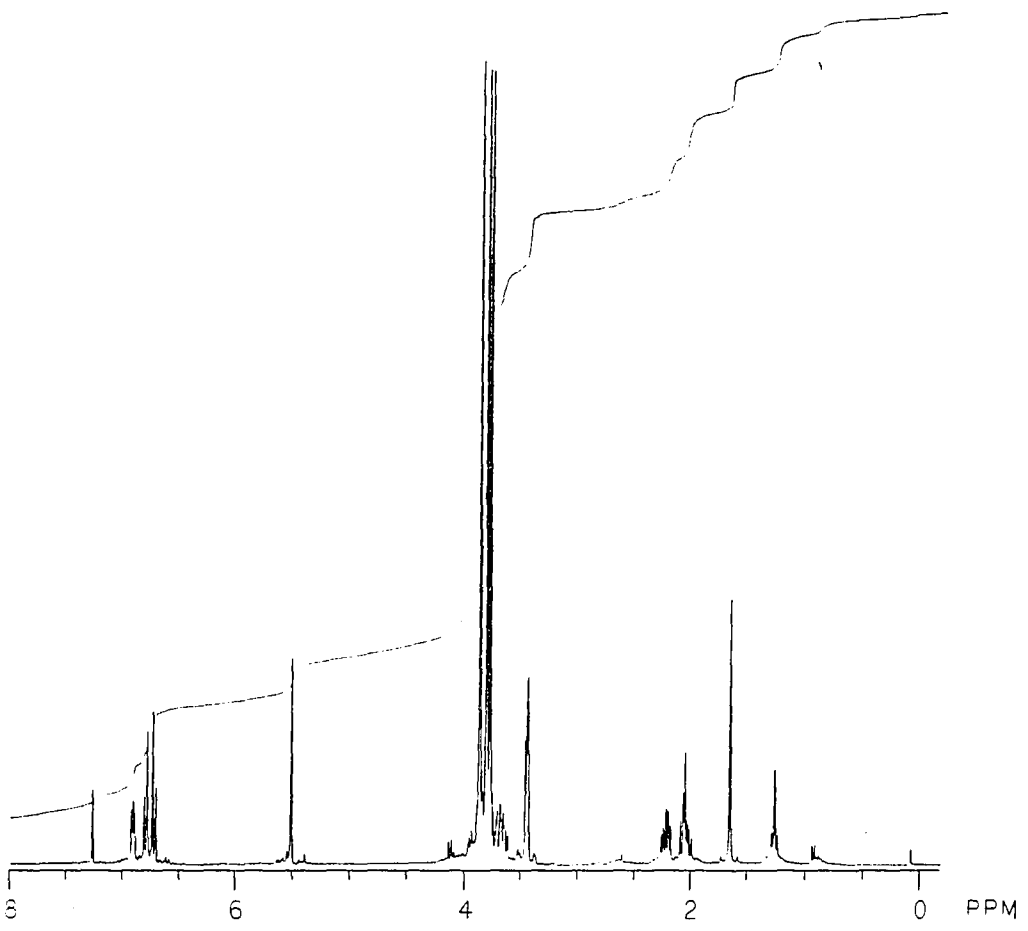

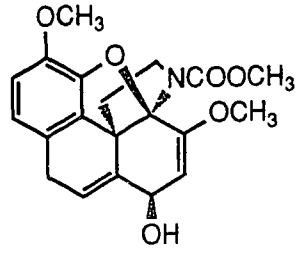

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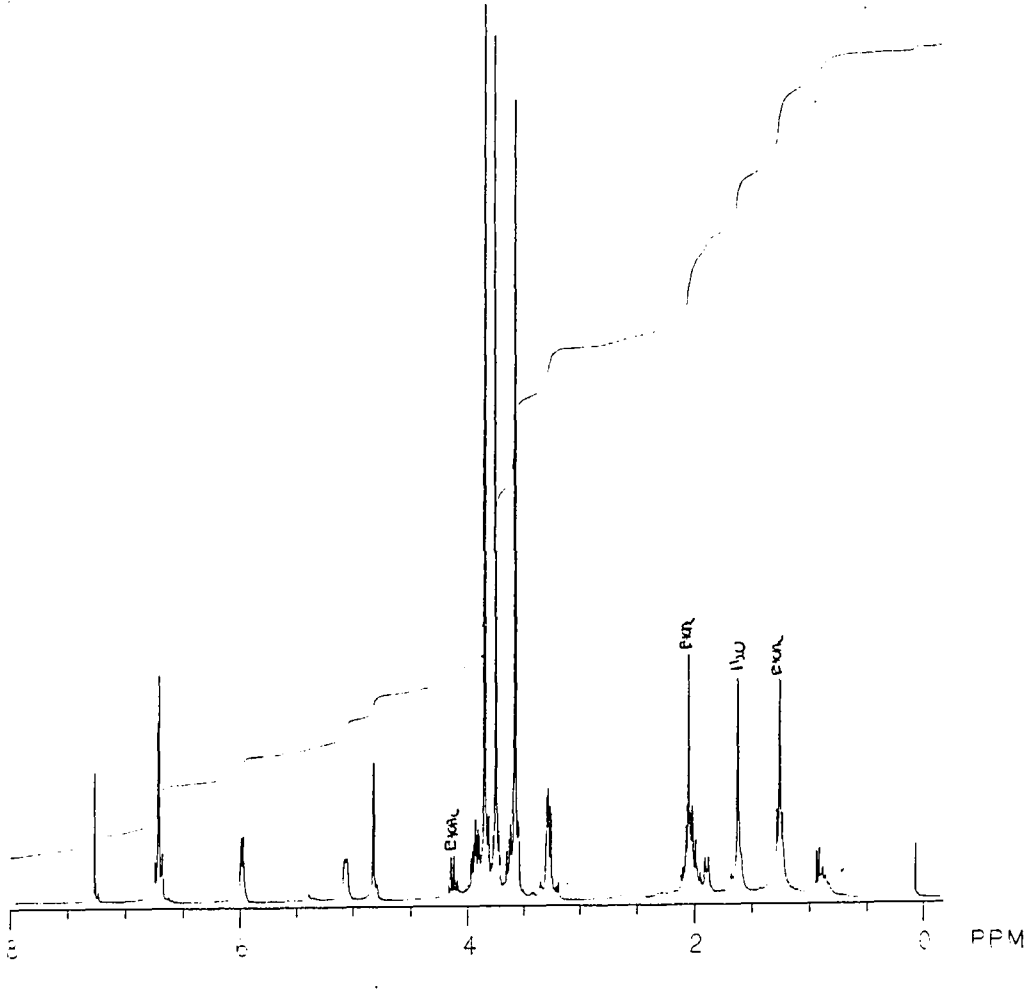

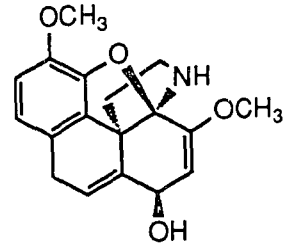

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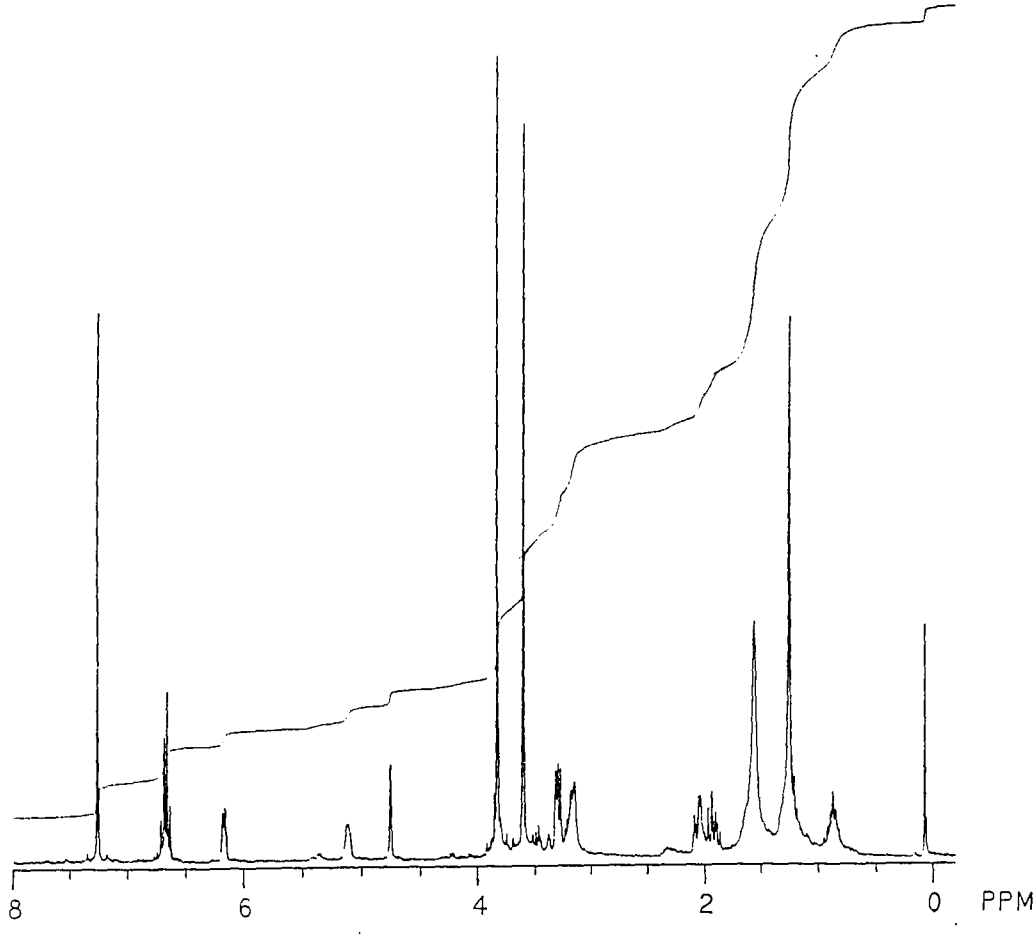

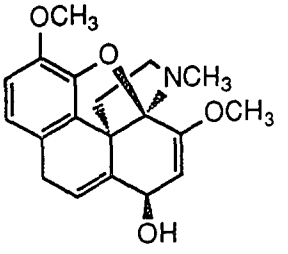

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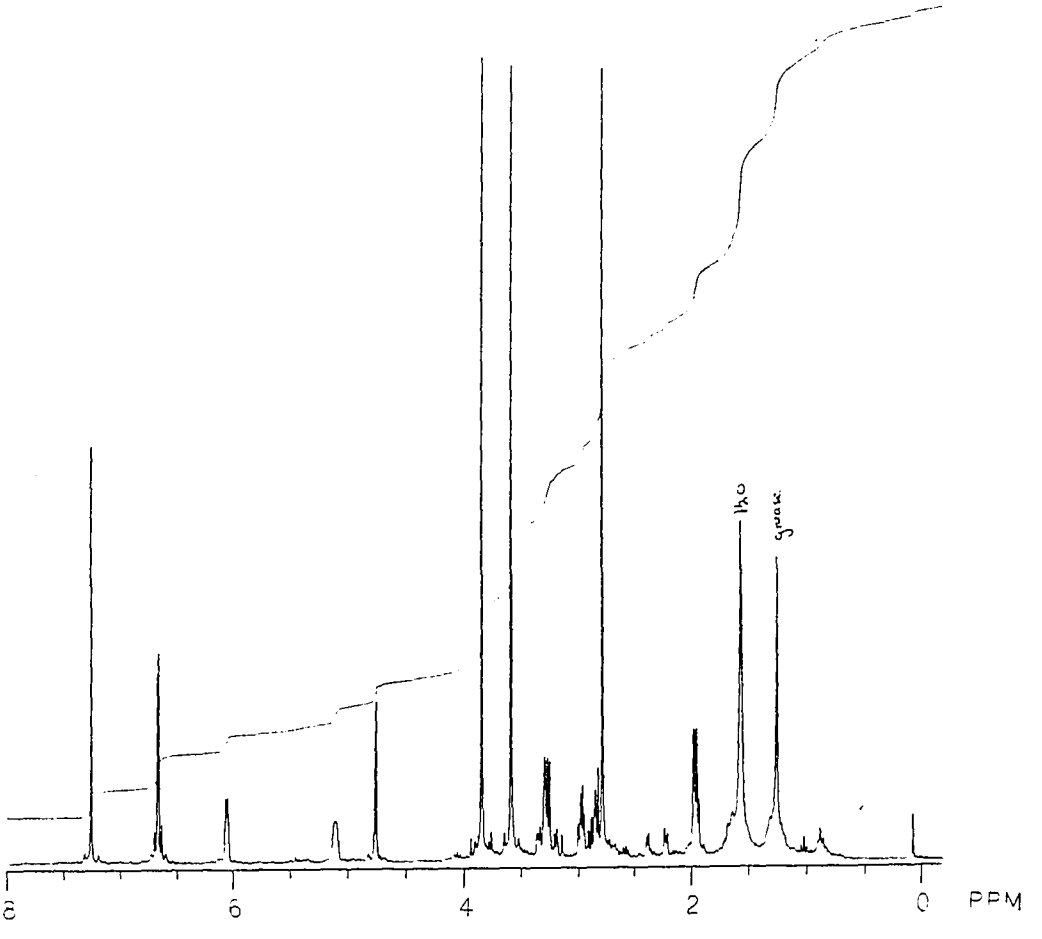

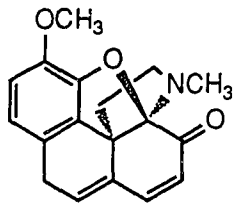

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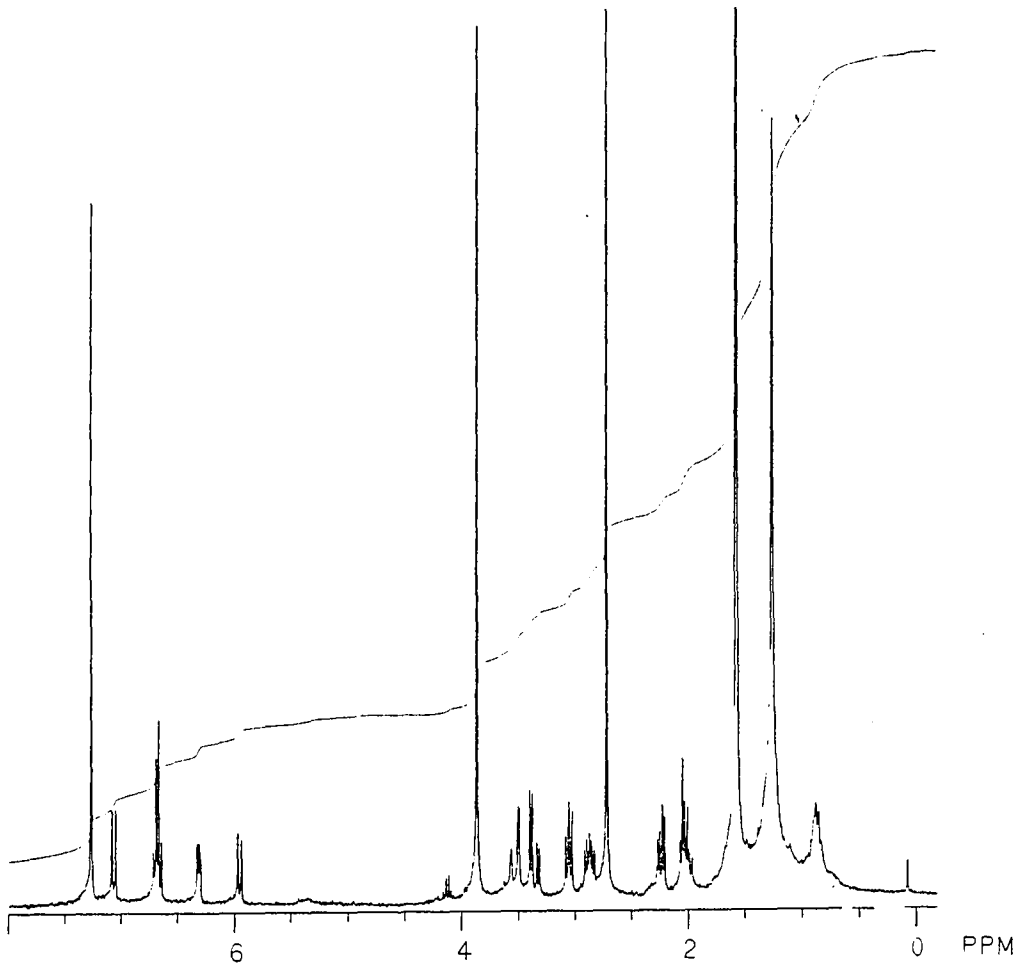

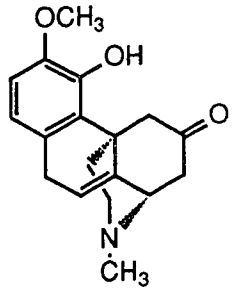

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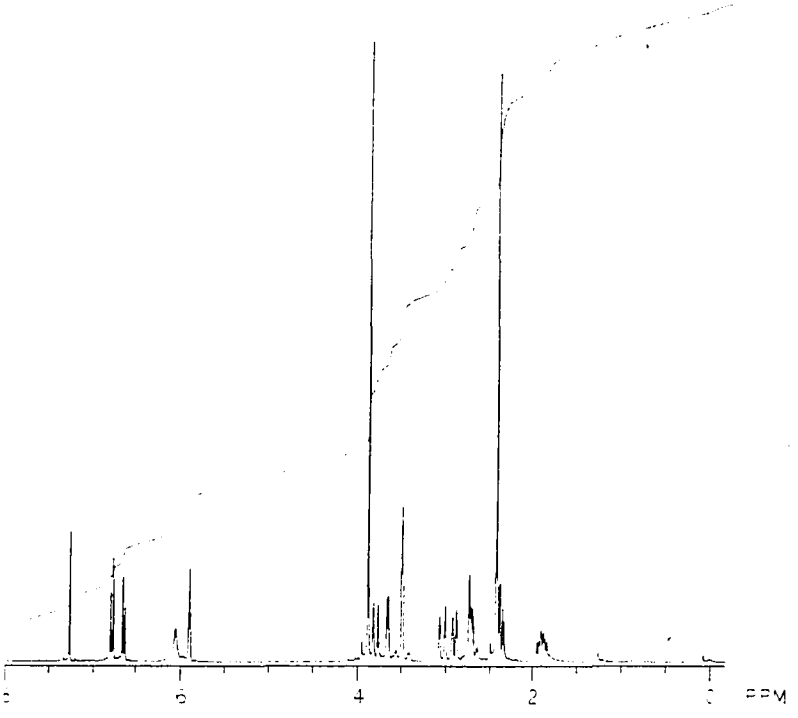

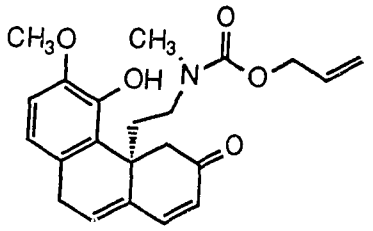

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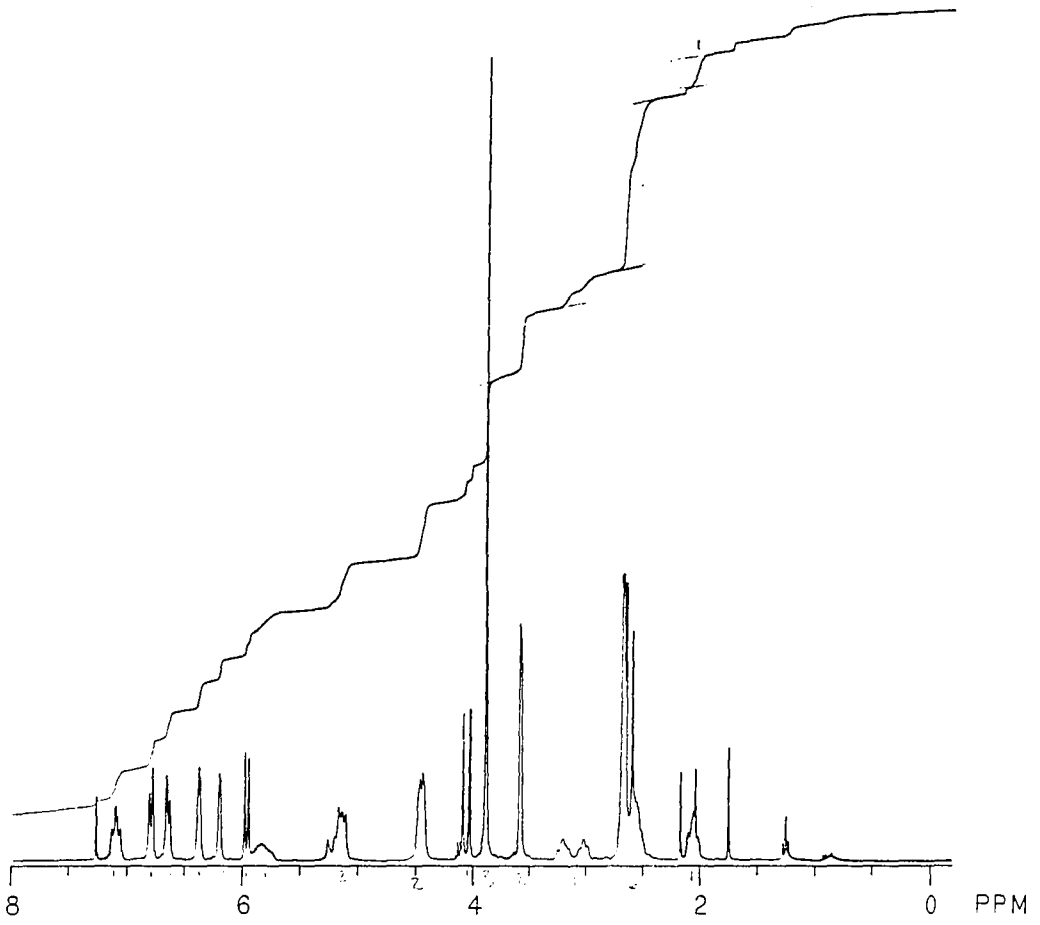

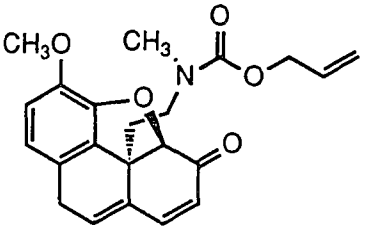

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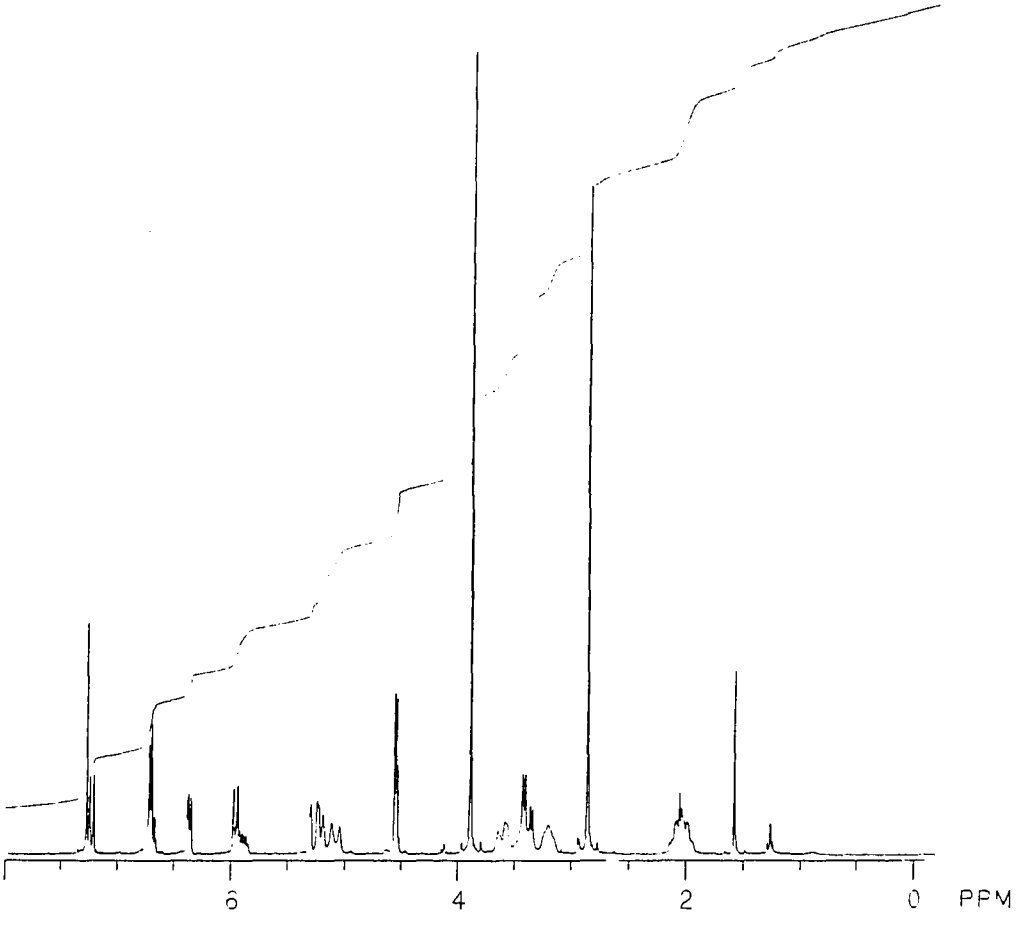

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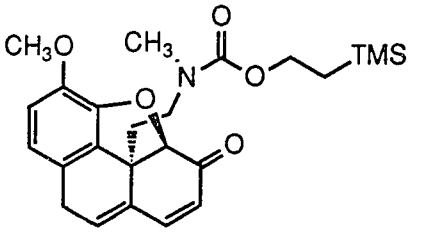

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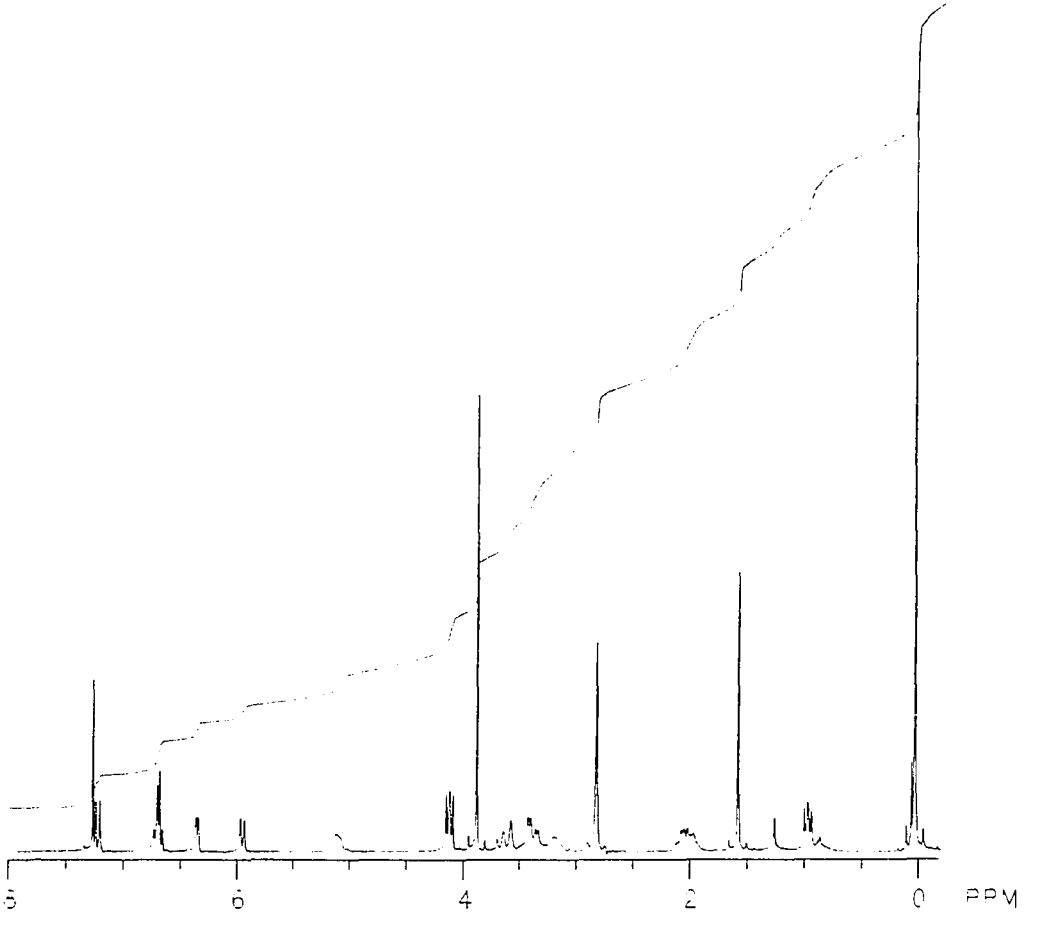

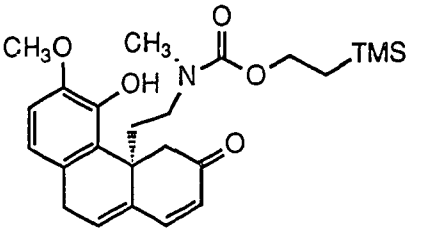

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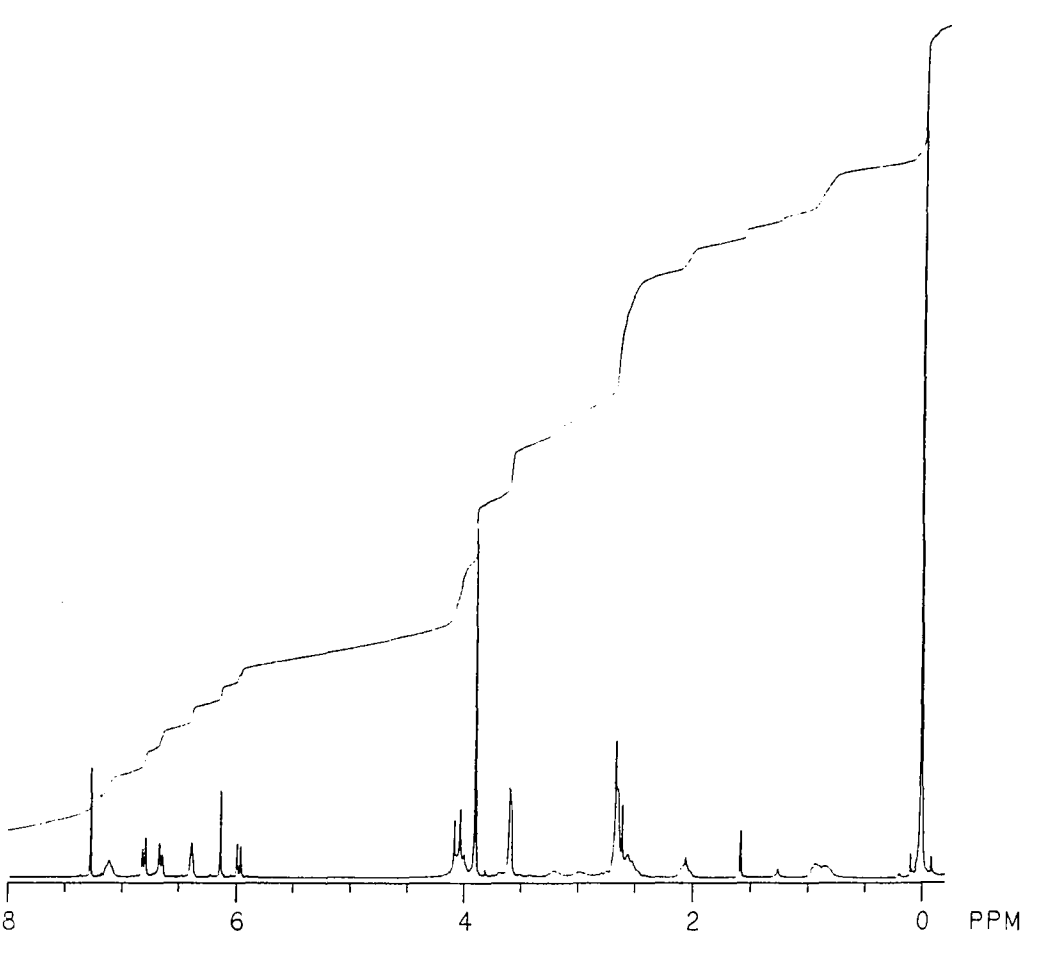

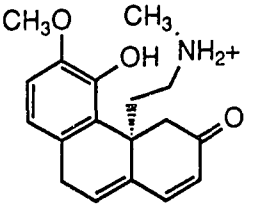
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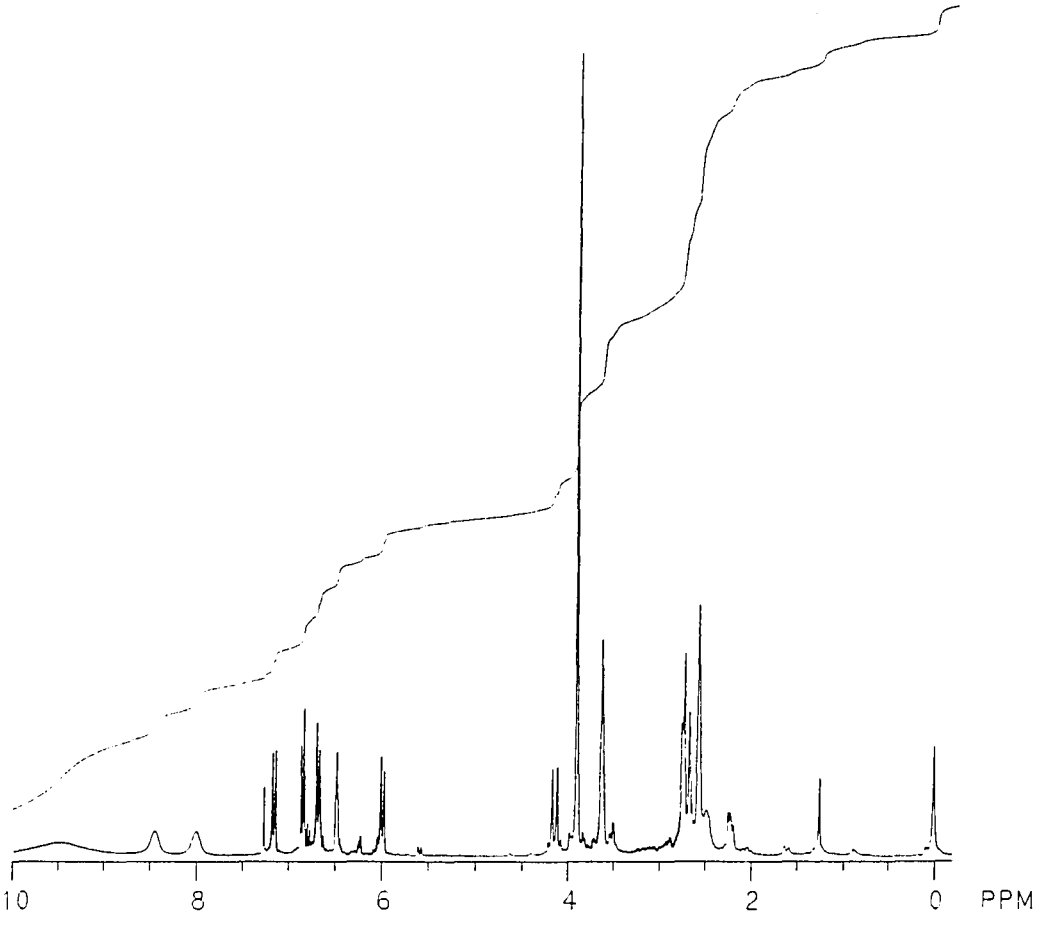
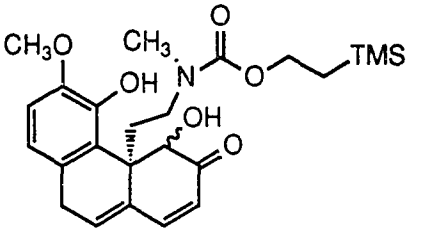
CH3
OH
NH2+
O


10
8
6
4
2
0
PPM



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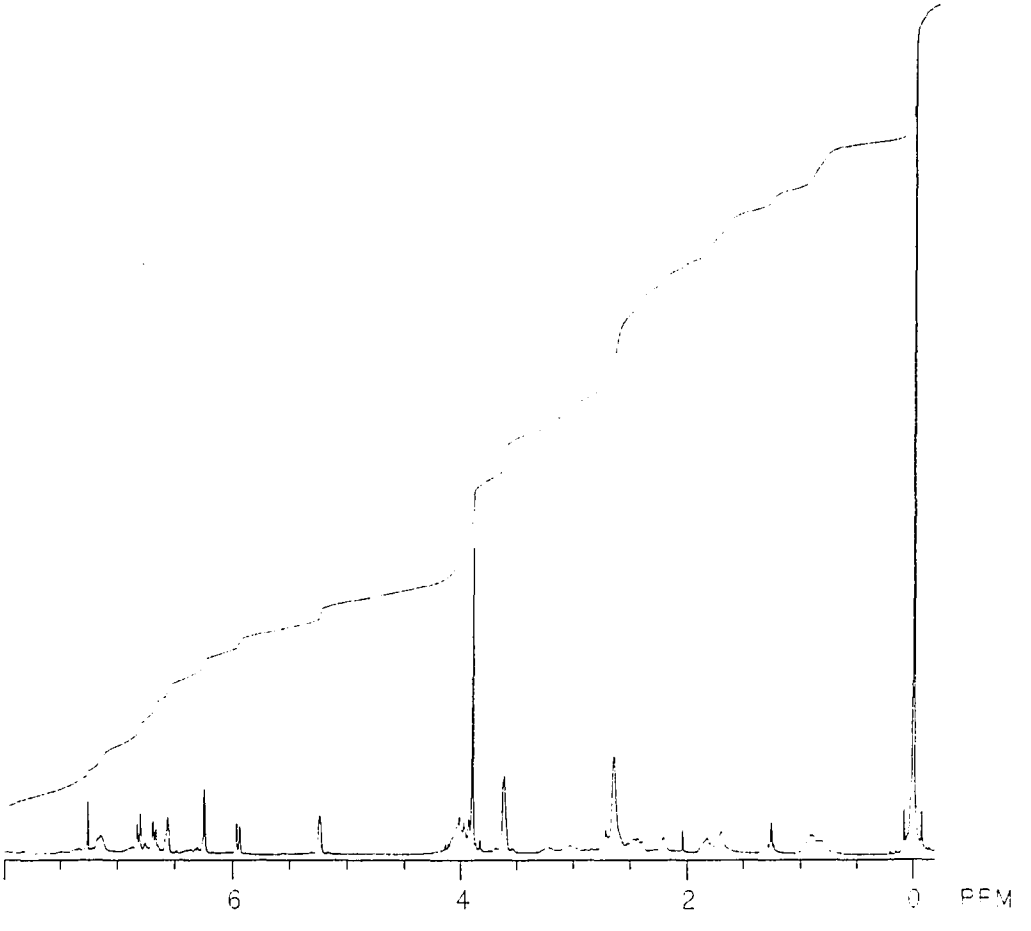

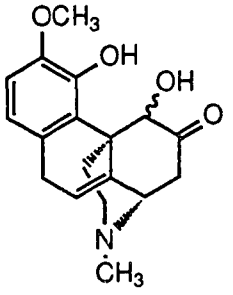

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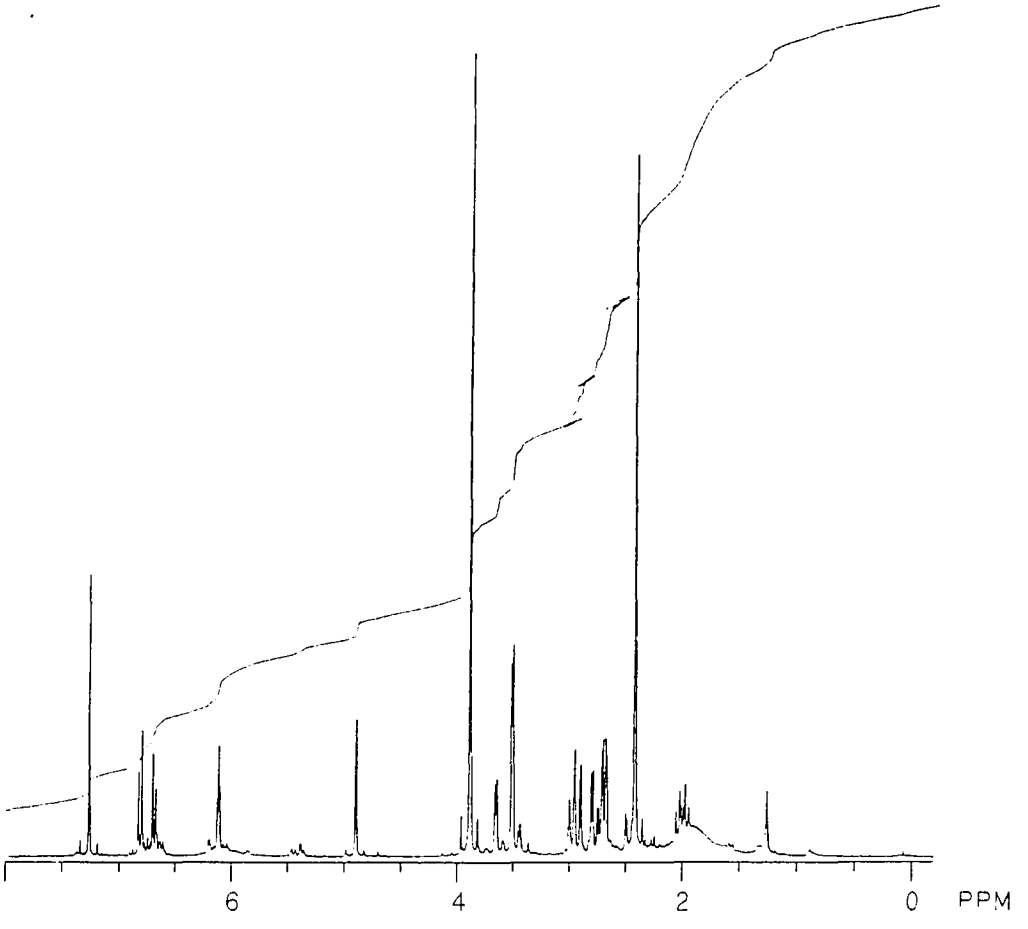

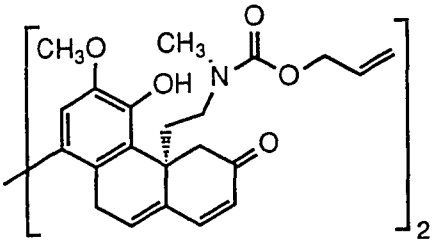

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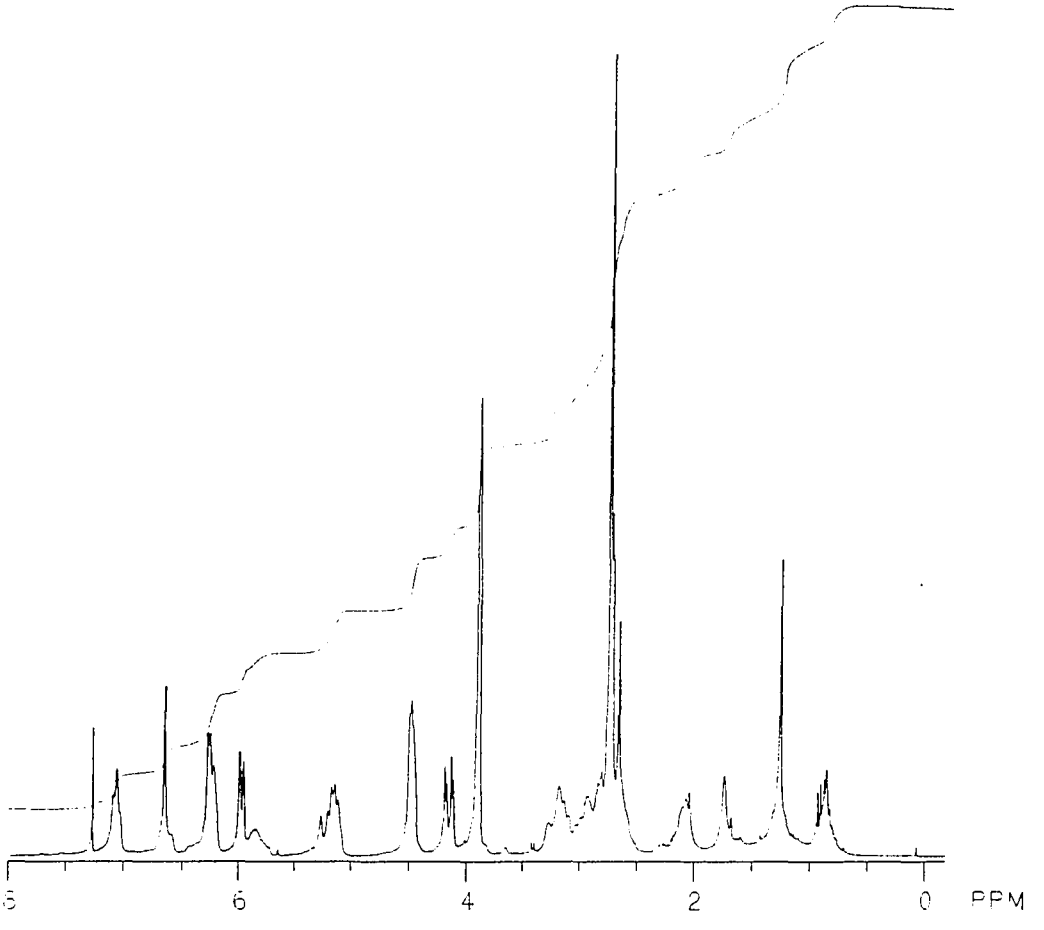

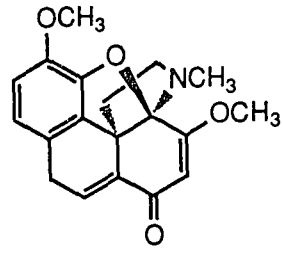

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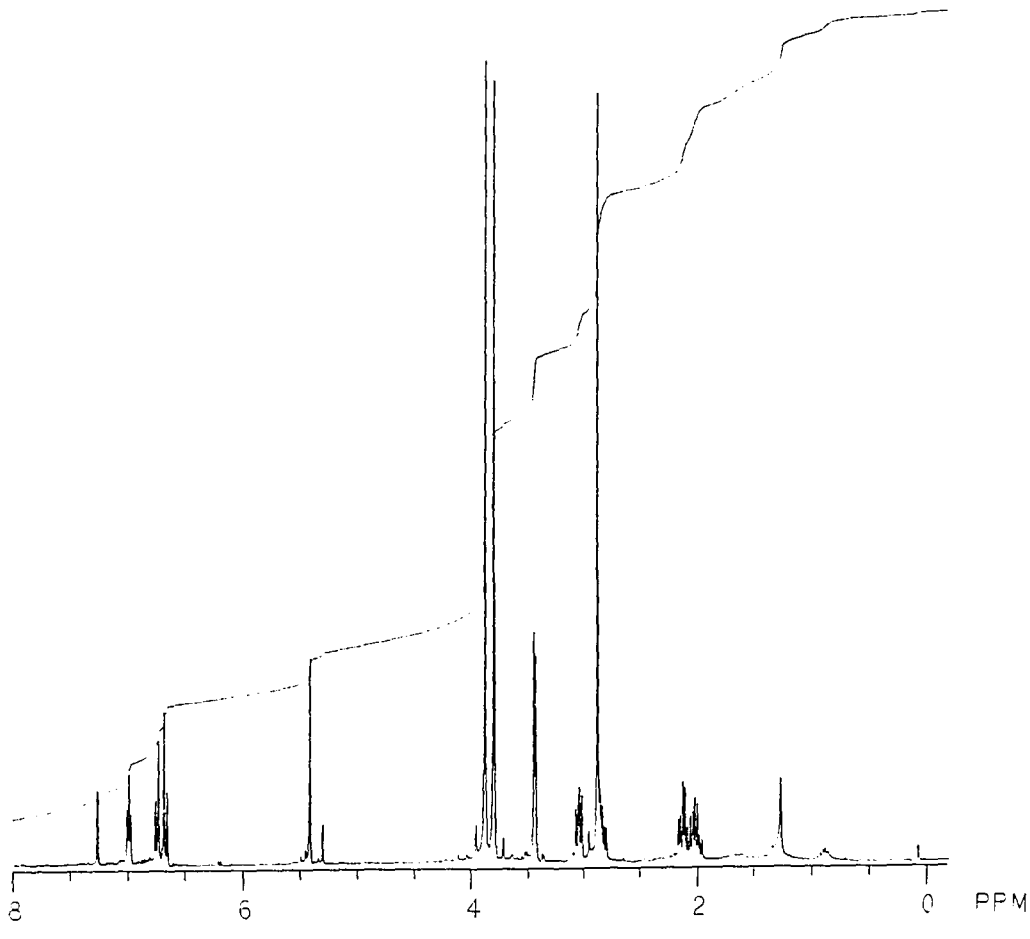

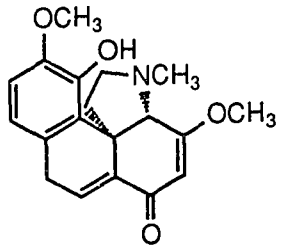

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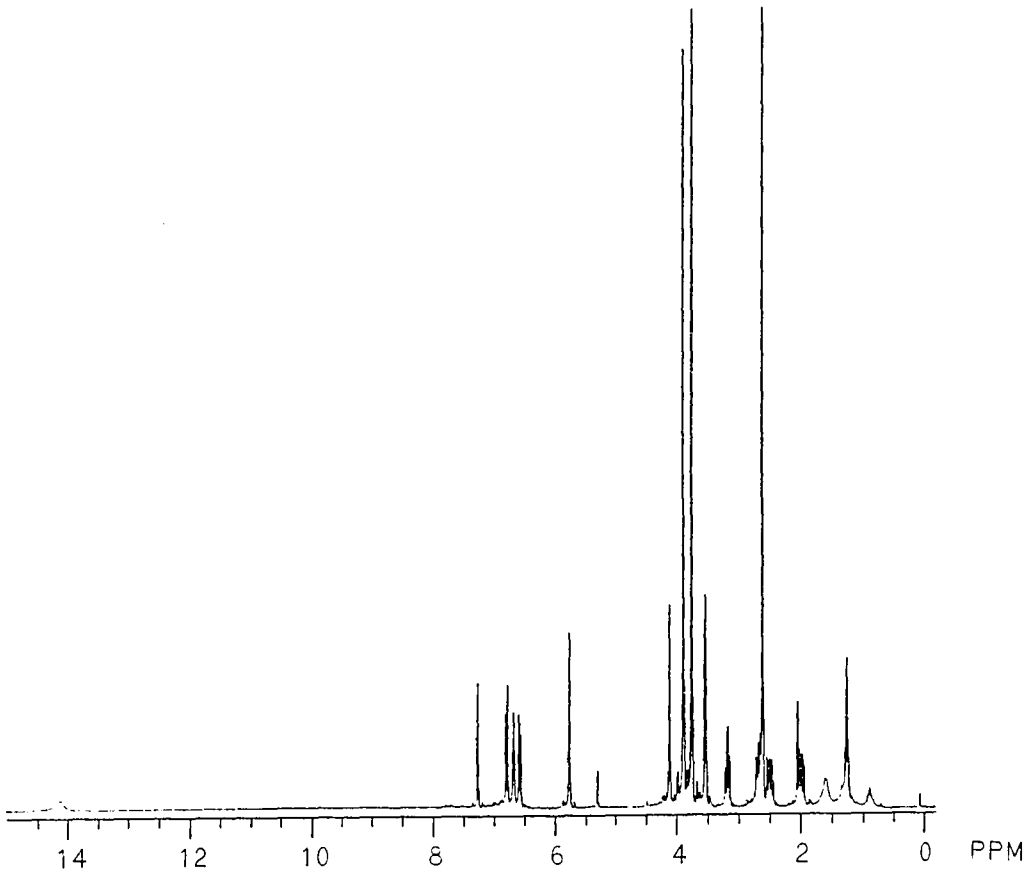

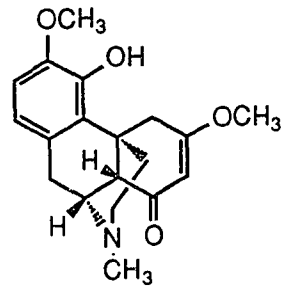

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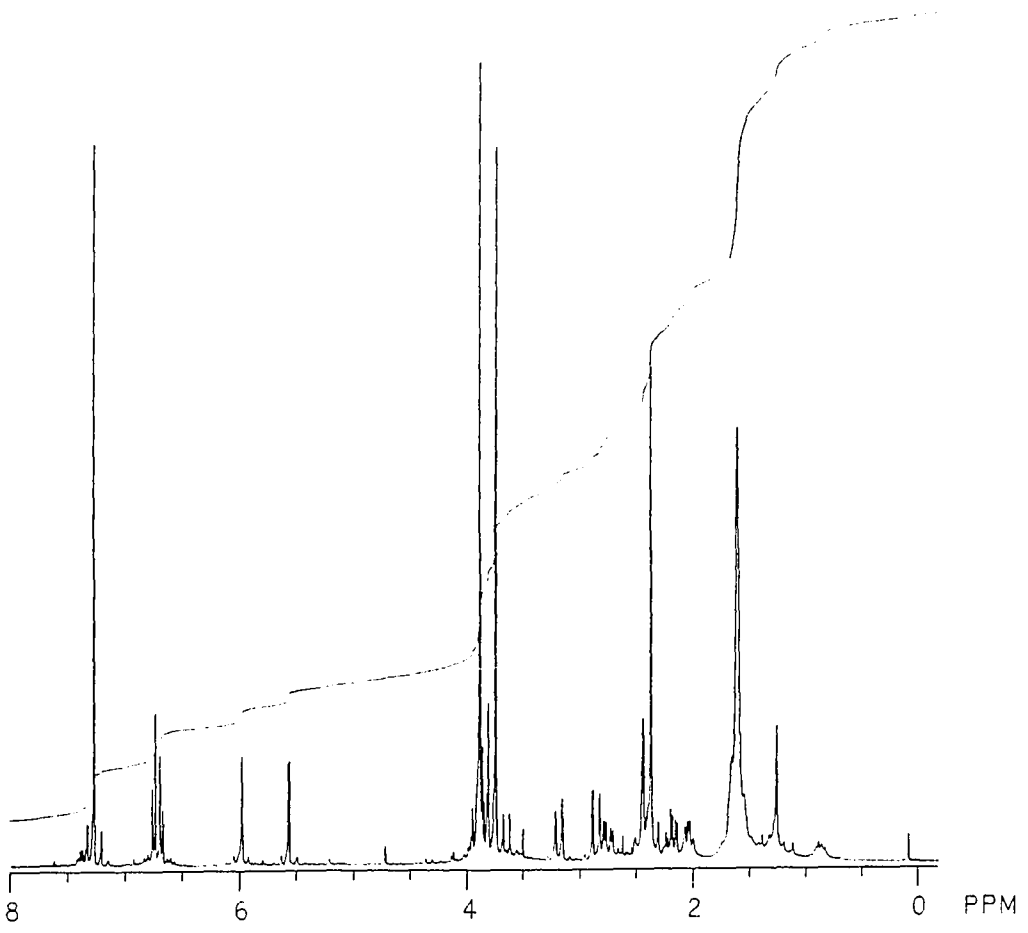

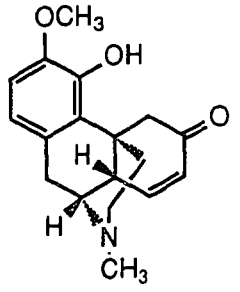

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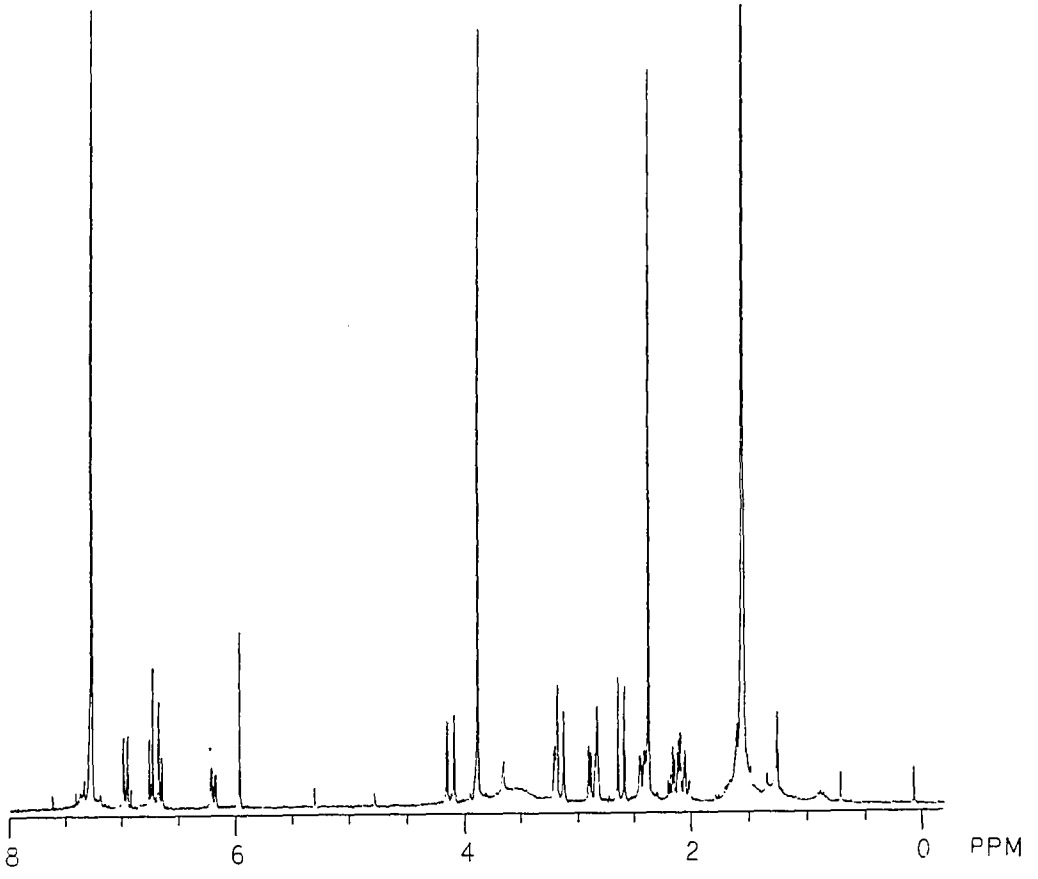
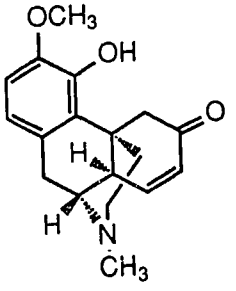
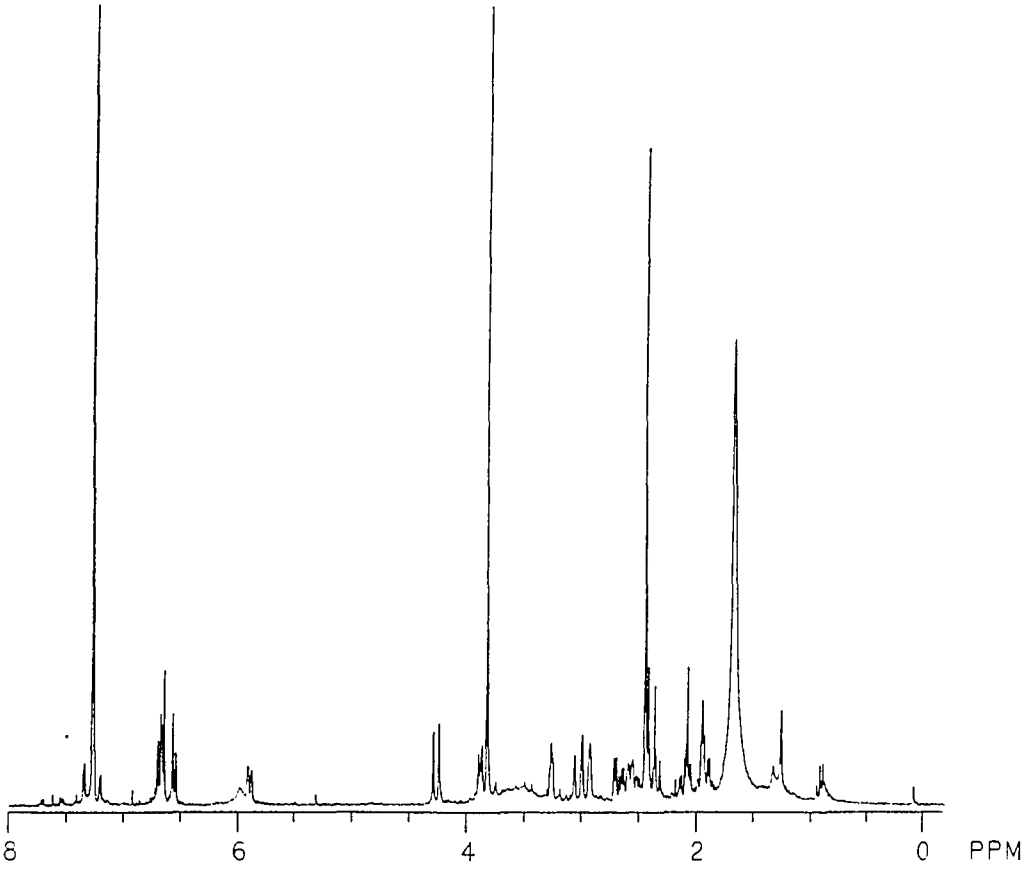
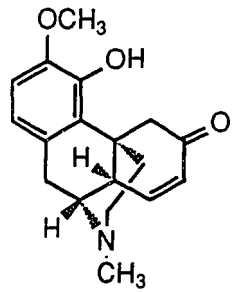




4

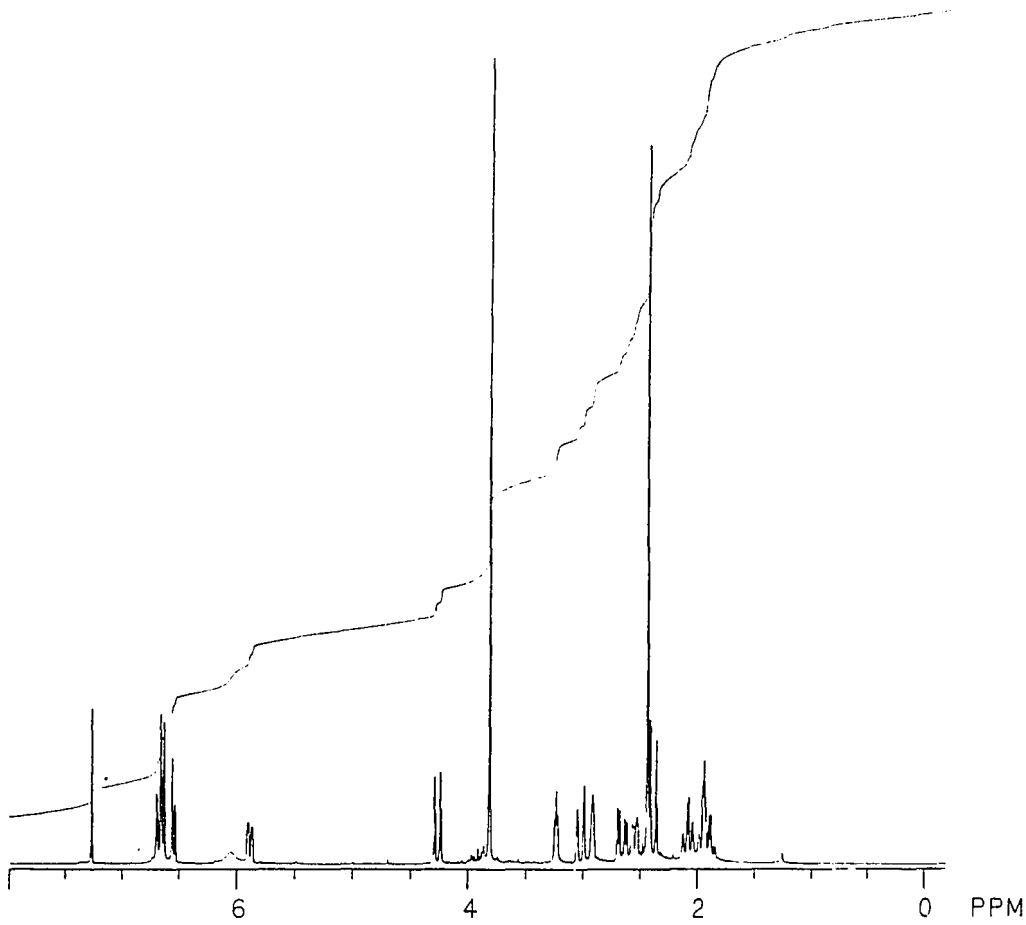
synthetic





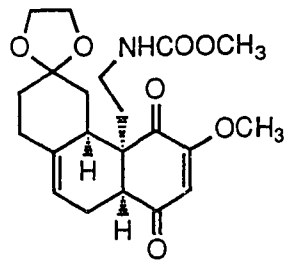
4

from thebaine

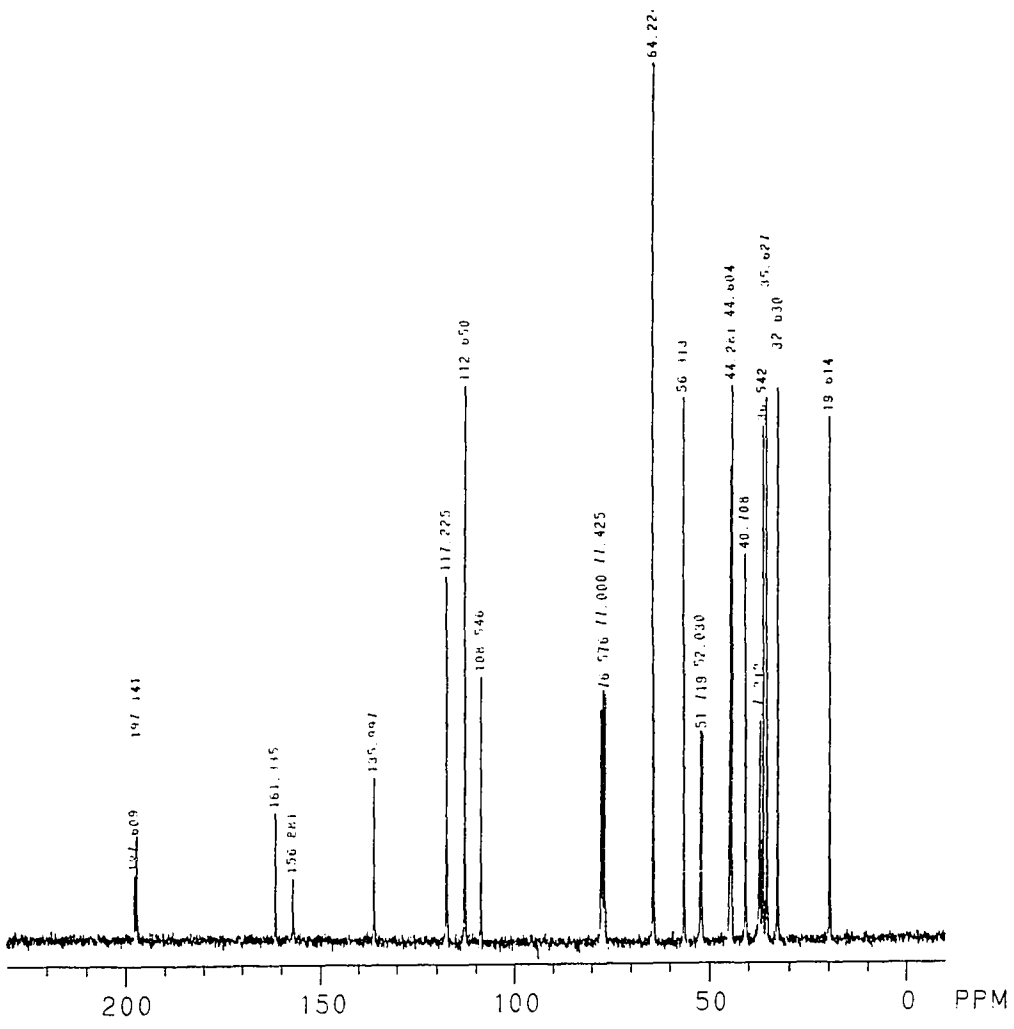


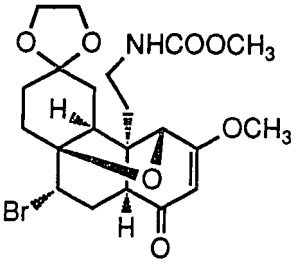
APPENDIX 2:

^{13}C NMR SPECTRA FOR SELECTED COMPOUNDS


O
O
NHCOOCH3
O
OCH3
H
H
O

68


64.22
56.113
44.264
44.004
40.708
32.030
19.614
117.225
112.050
76.576
77.000
77.425
51.119
52.030
200
150
100
50
0
PPM



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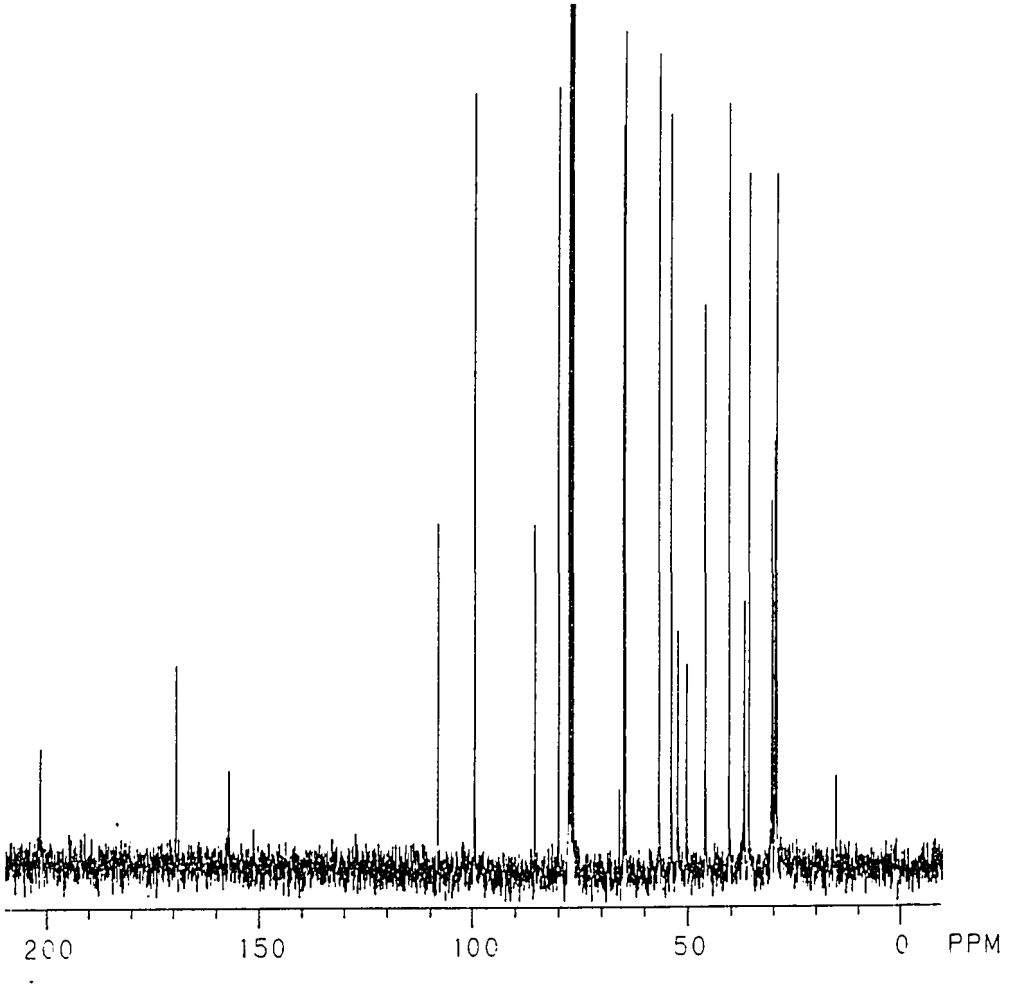
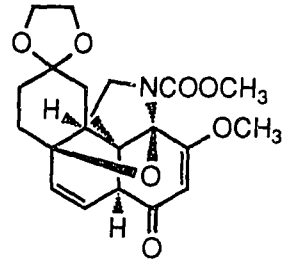
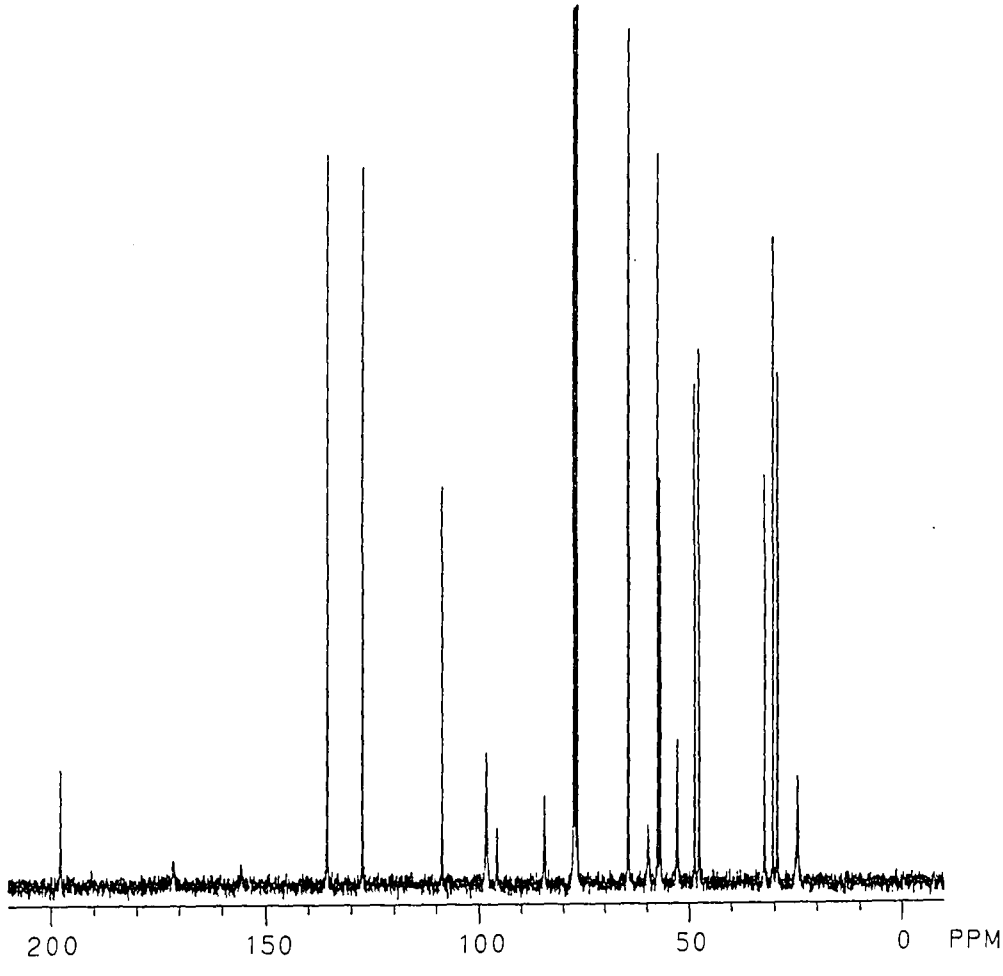
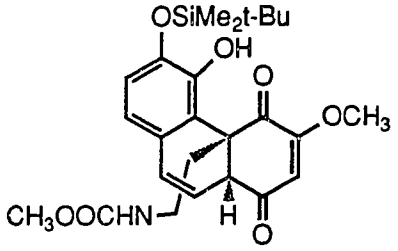


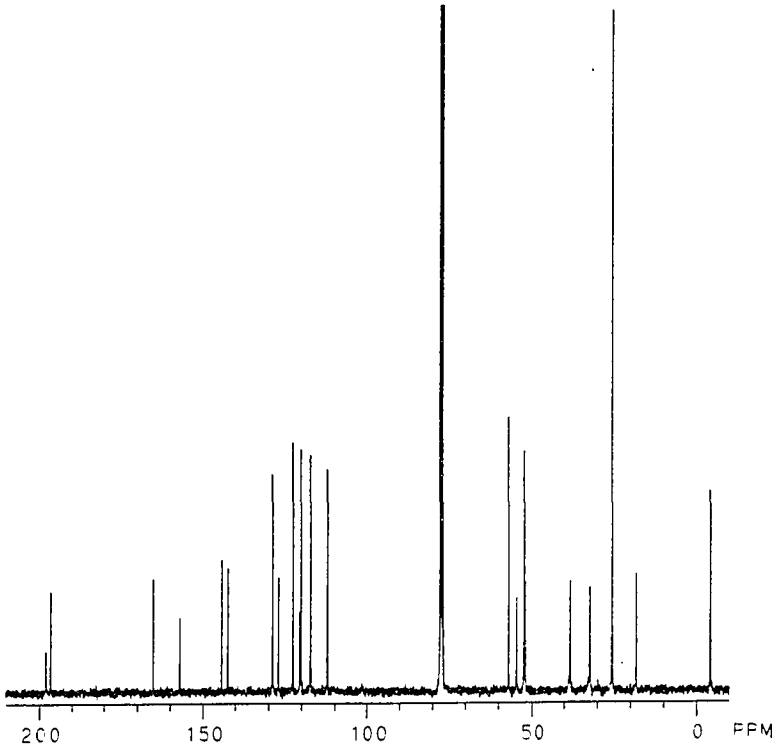


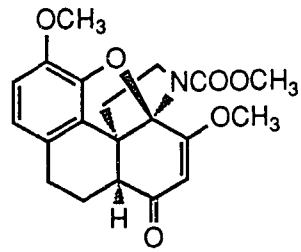
96





103





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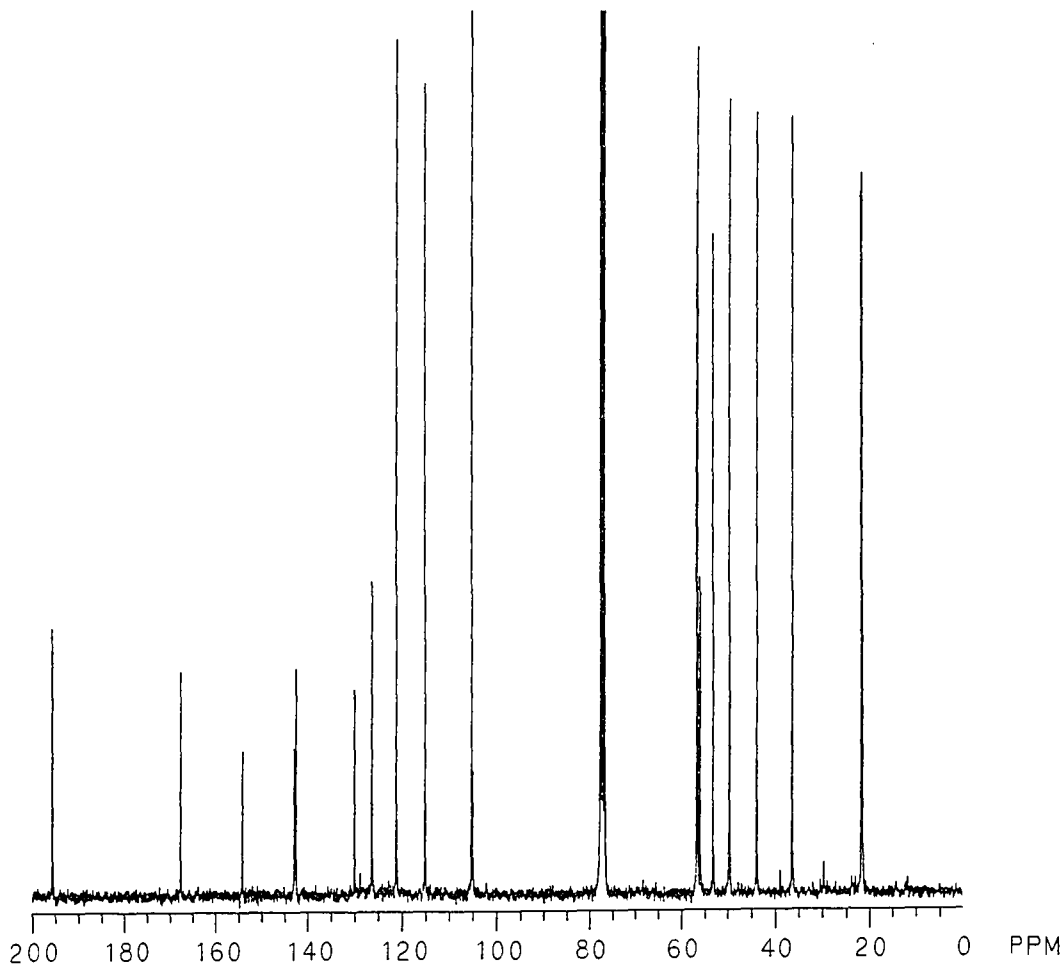

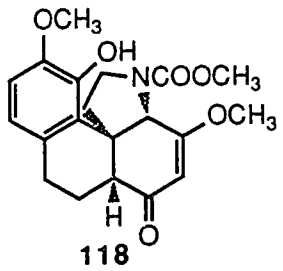

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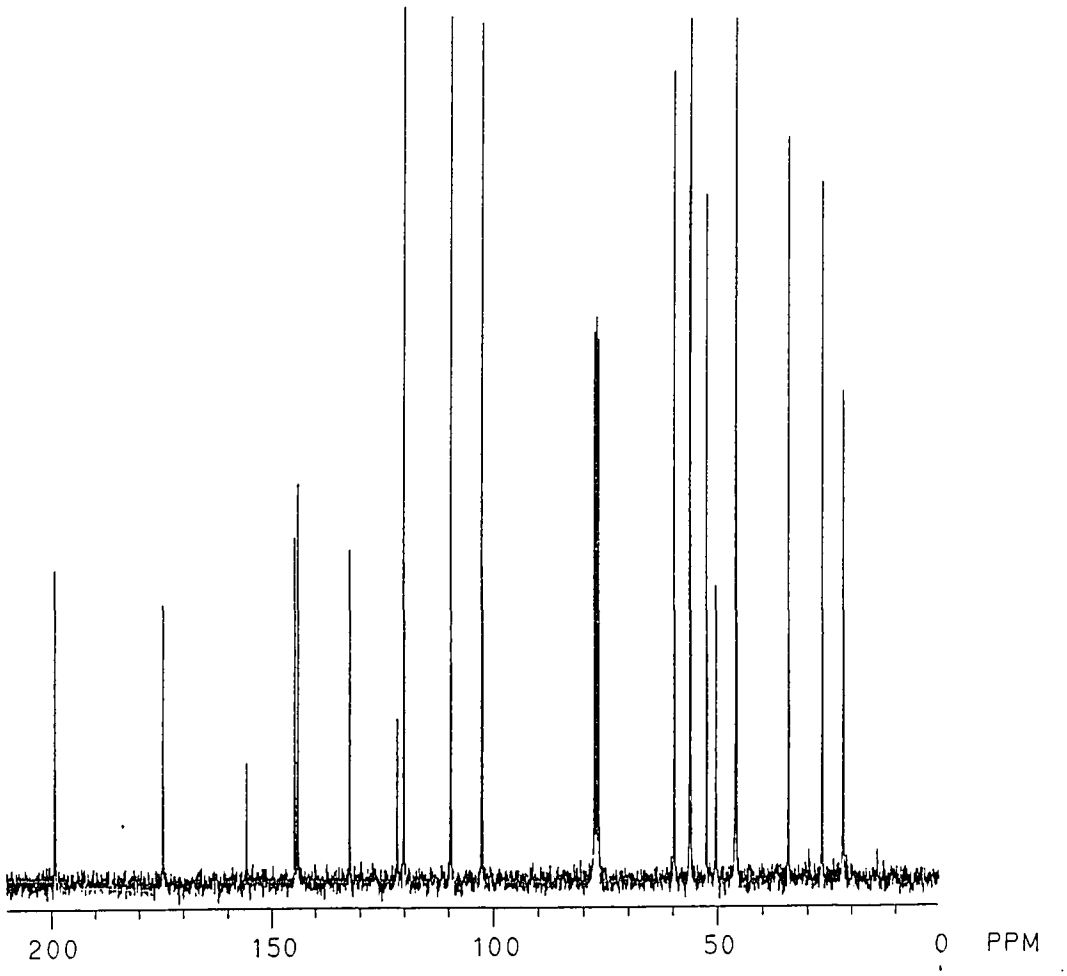

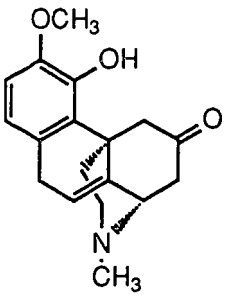

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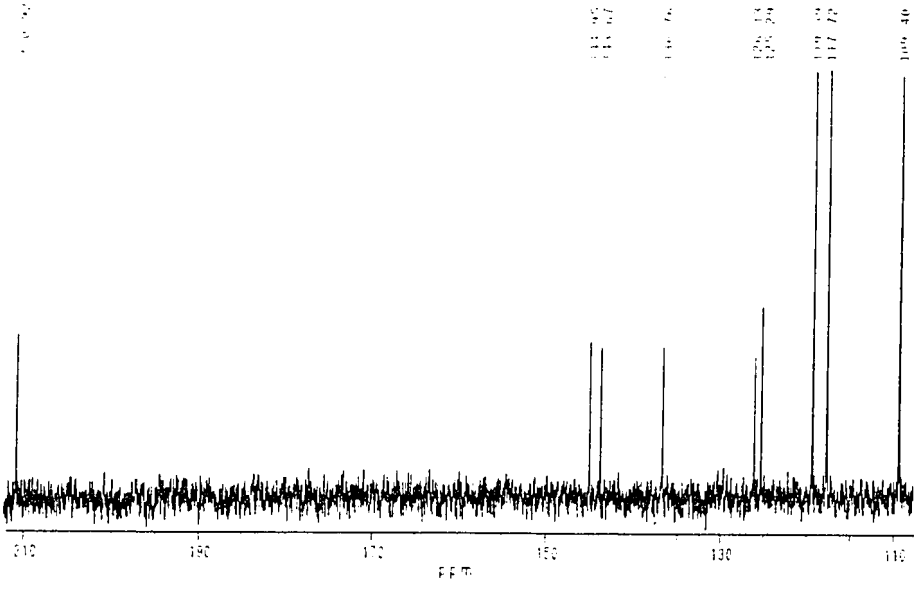
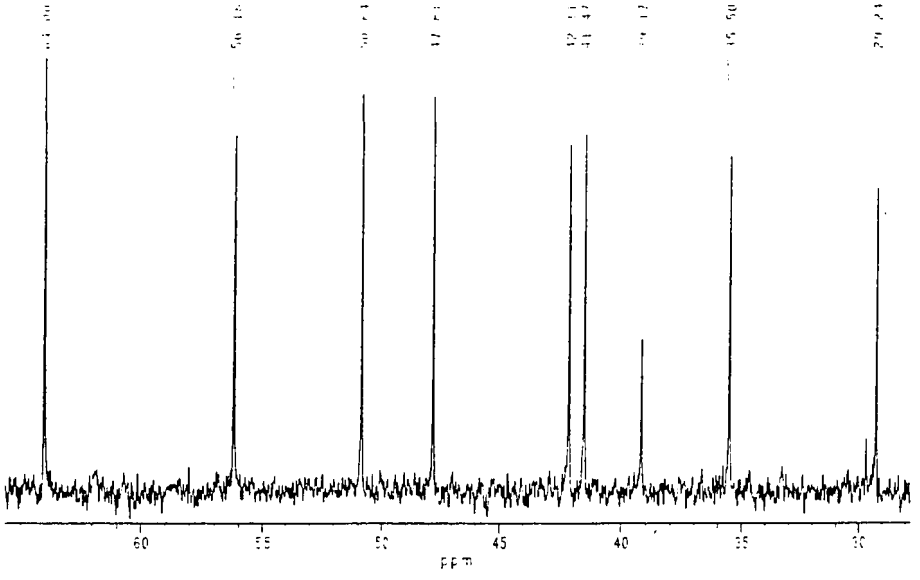
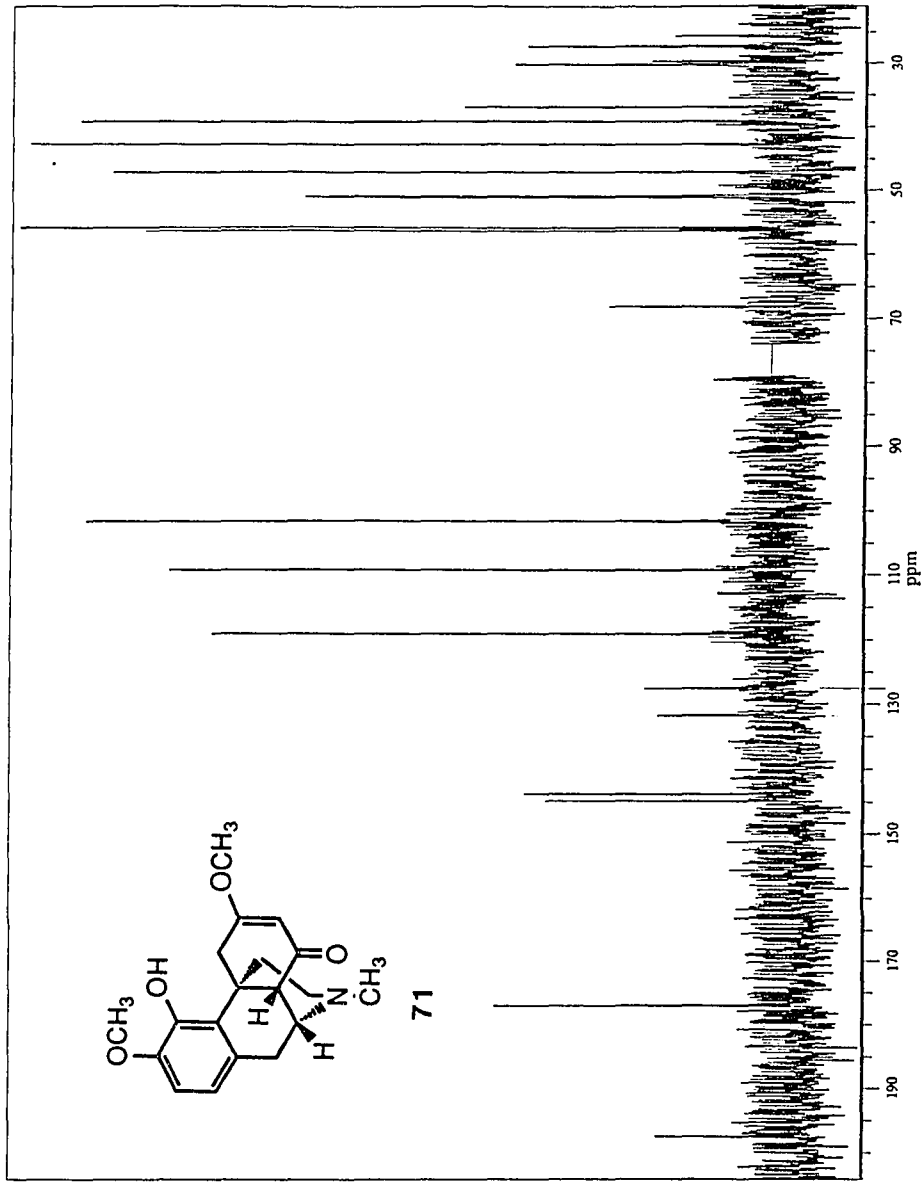
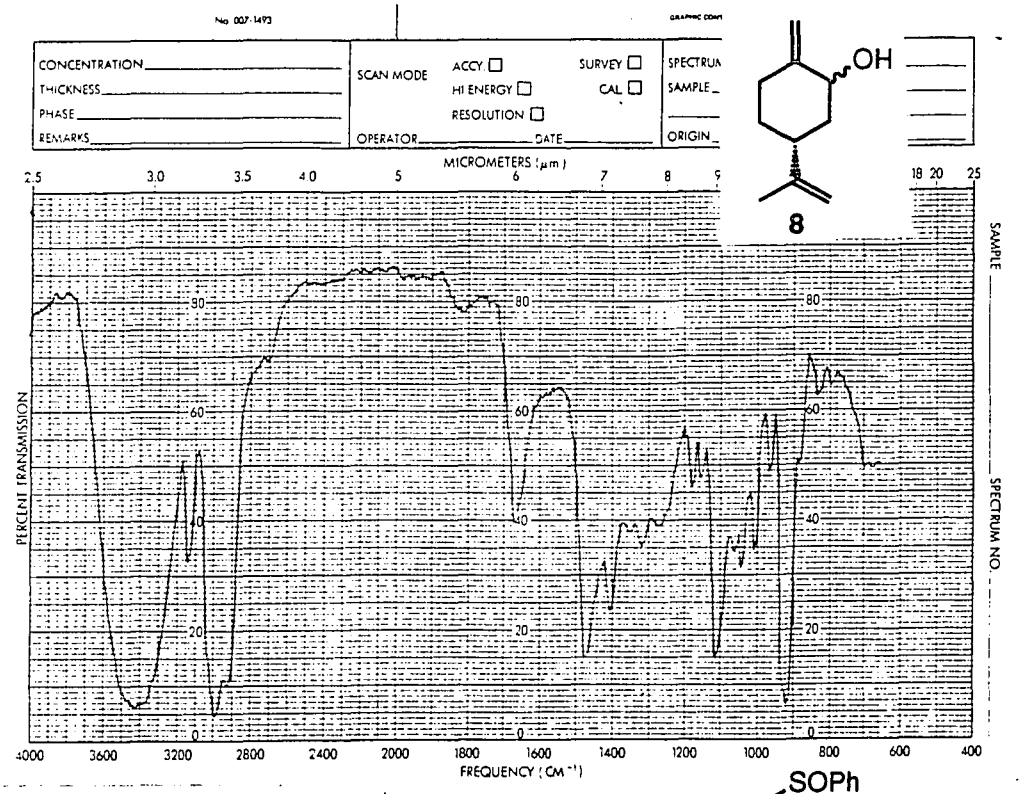


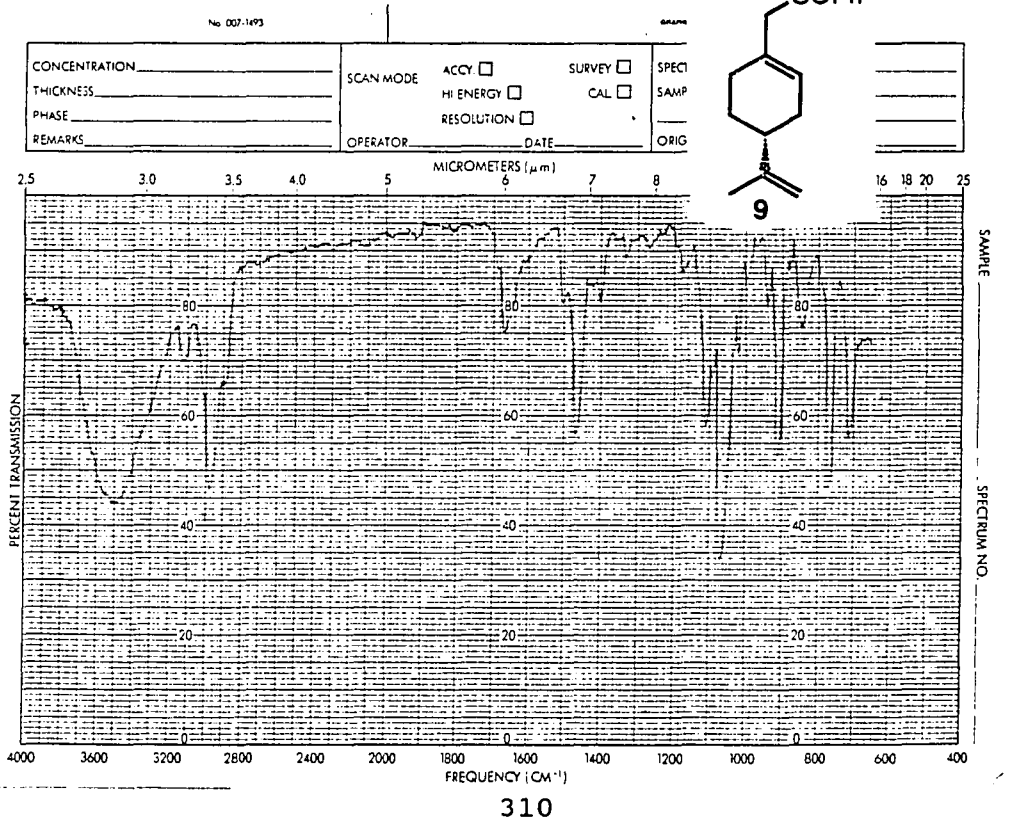



OCH3
OH
OCH3
H
H
N
O
CH3
71
30
50
70
90
110
ppm
130
150
170
190

APPENDIX 3:

INFRARED SPECTRA FOR SELECTED COMPOUNDS


No. 007-1493
CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY ☐
HI ENERGY ☐
RESOLUTION ☐
SURVEY ☐
CAL ☐
OPERATOR
DATE
SPECTRUM
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 16 18 20 25
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)
OH
8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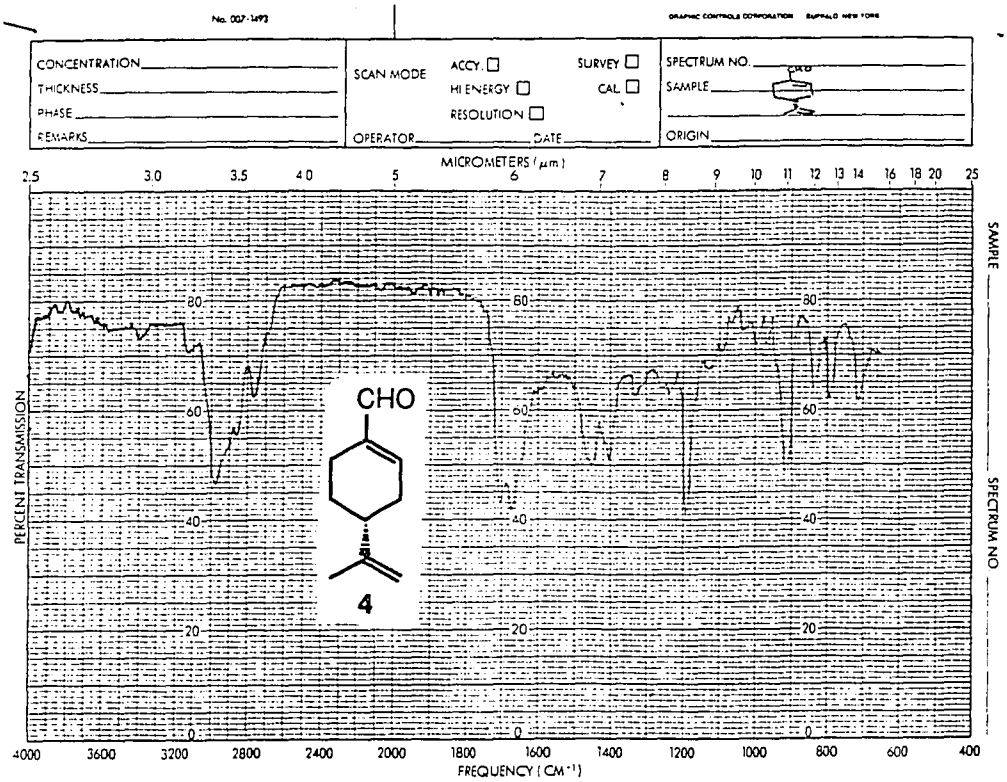
CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY ☐
HI ENERGY ☐
RESOLUTION ☐
SURVEY ☐
CAL ☐
OPERATOR
DATE
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 16 18 20 25
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)
SOPh
9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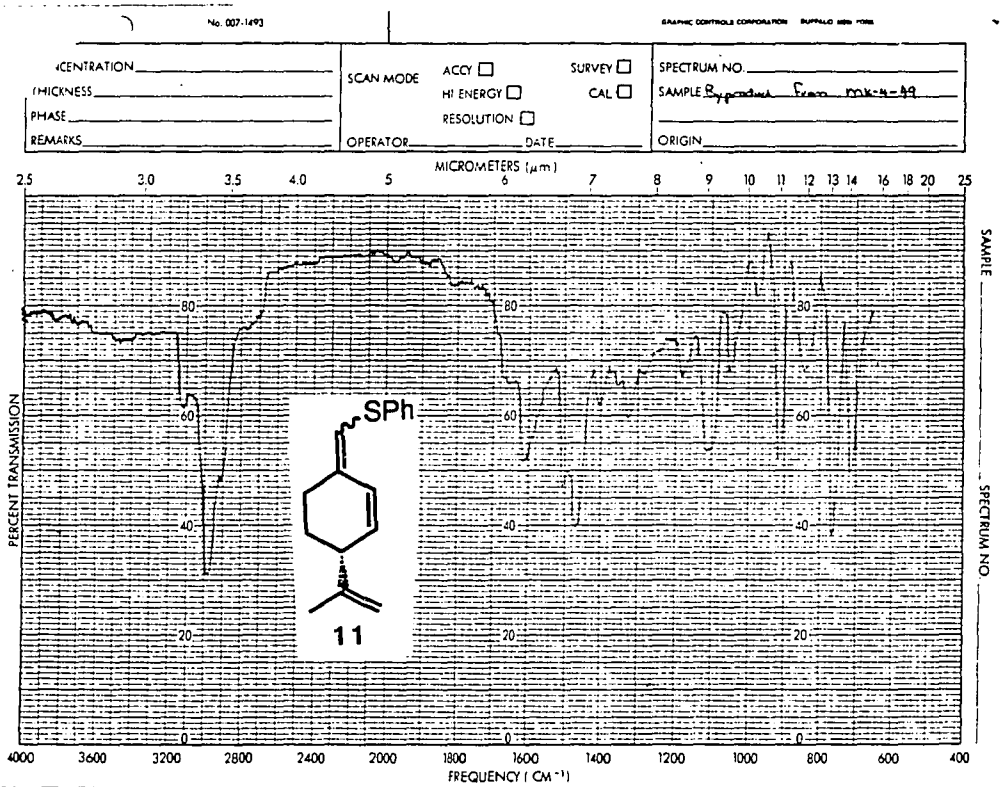
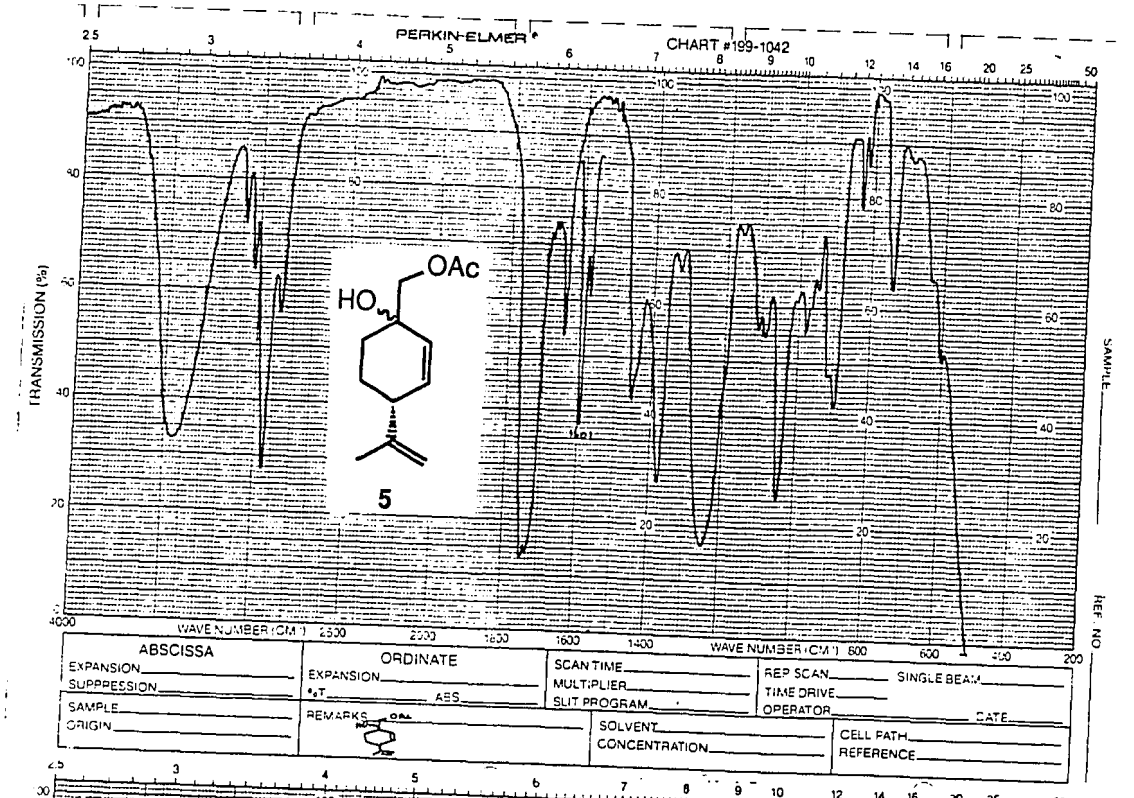
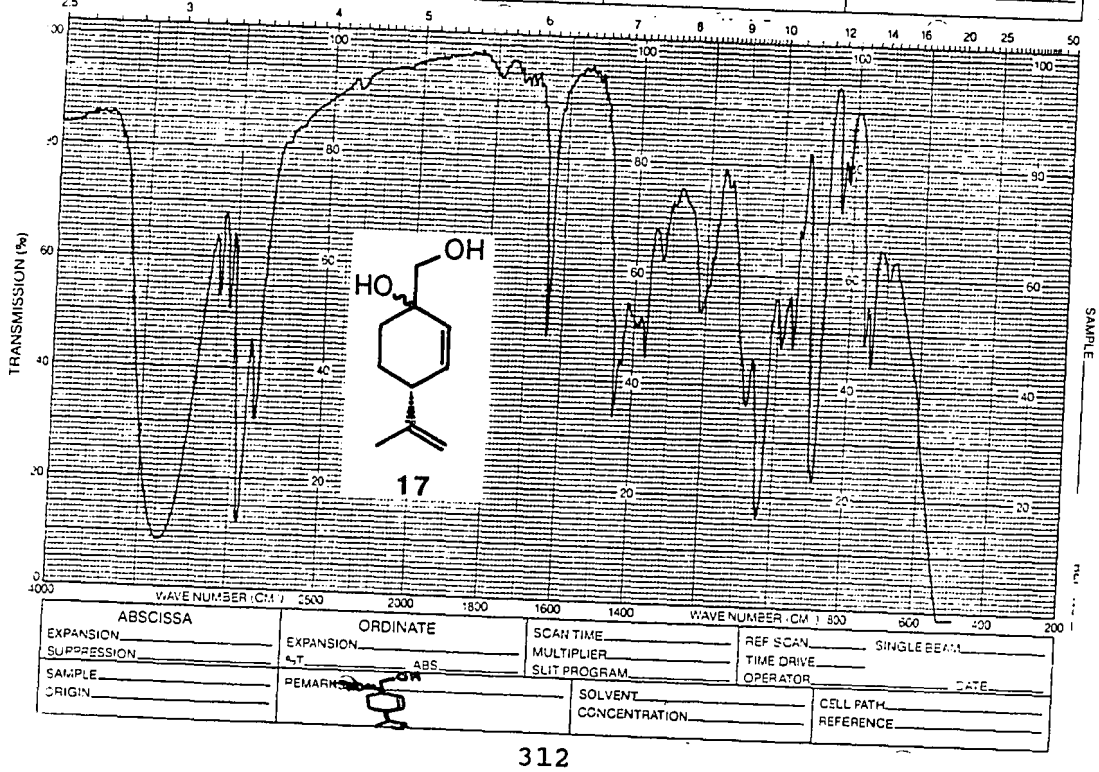
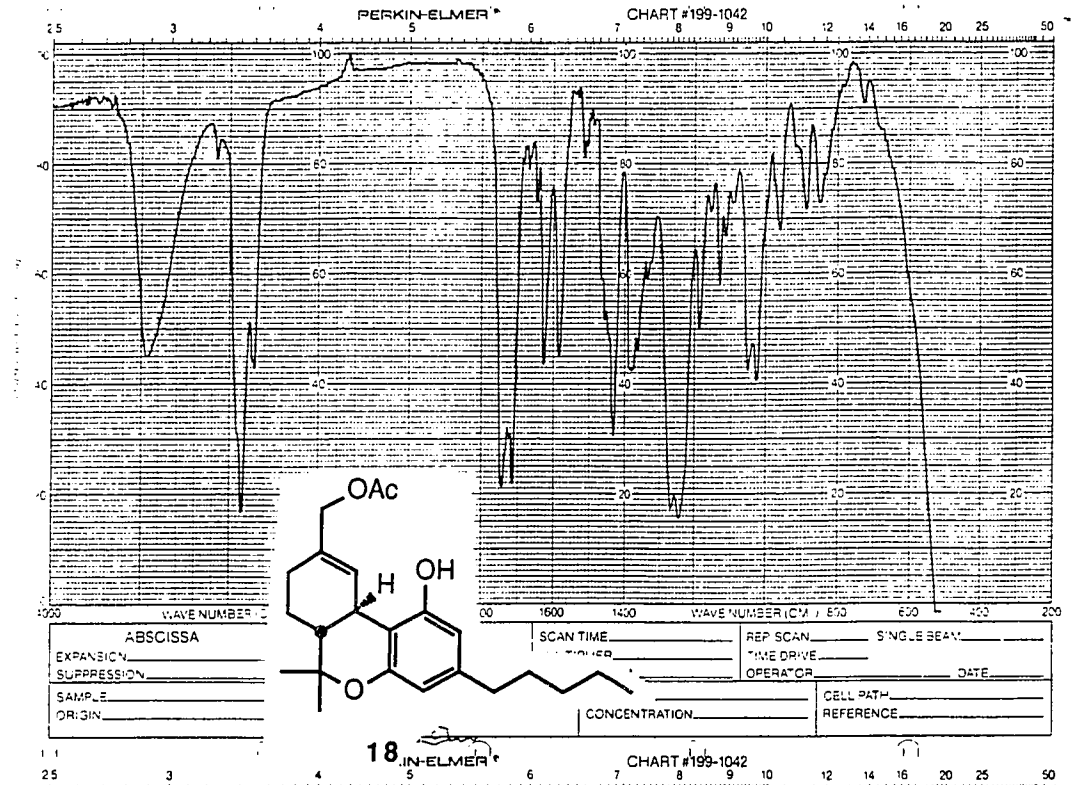
GRAPHIC CONTROLS CORPORATION BUFFALO NEW YORK
CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY. ☐
SURVEY ☐
HI ENERGY ☐
CAL ☐
RESOLUTION ☐
OPERATOR
DATE
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.
CHO
4
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)

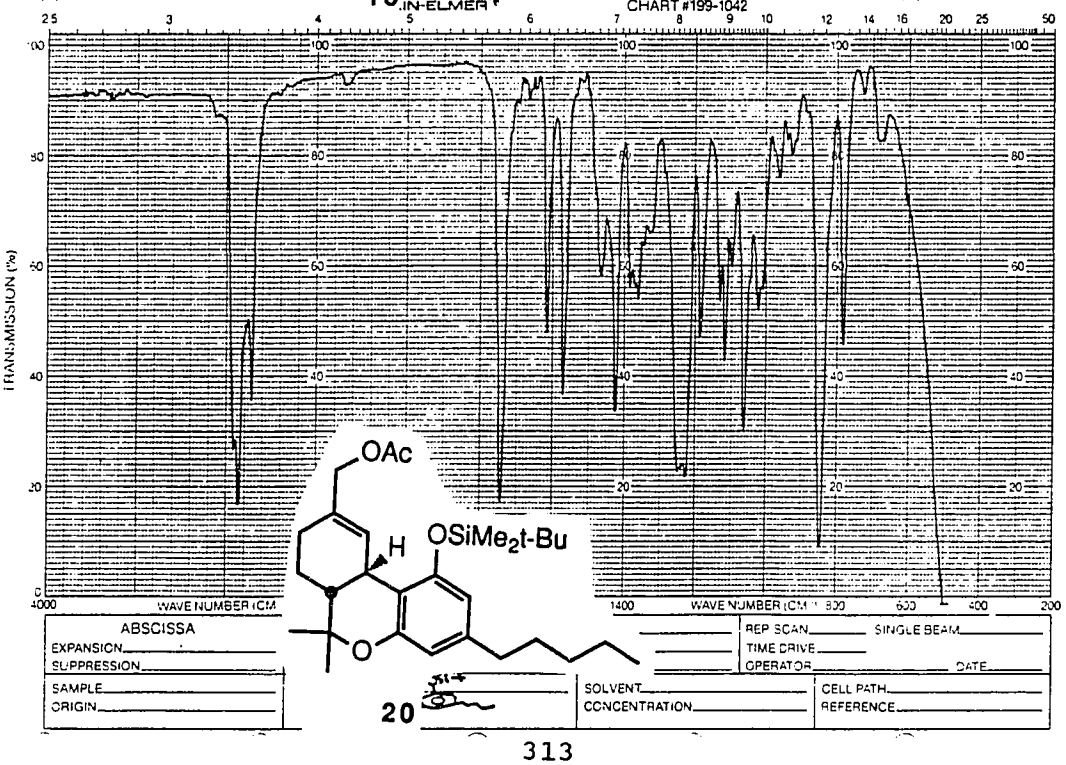

No. 007-1493
GRAPHIC CONTROLS CORPORATION BUFFALO NEW YORK
CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY ☐
SURVEY ☐
HI ENERGY ☐
CAL ☐
RESOLUTION ☐
OPERATOR
DATE
SPECTRUM NO.
SAMPLE Byproduct from mk-4-49
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.
SPh
11
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)


PERKIN-ELMER
CHART #199-1042
TRANSMISSION (%)
WAVE NUMBER (CM⁻¹)
OAc
HO
5
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
ORDINATE
EXPANSION
%T
ABS
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
REMARKS
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
SAMPLE
REF NO

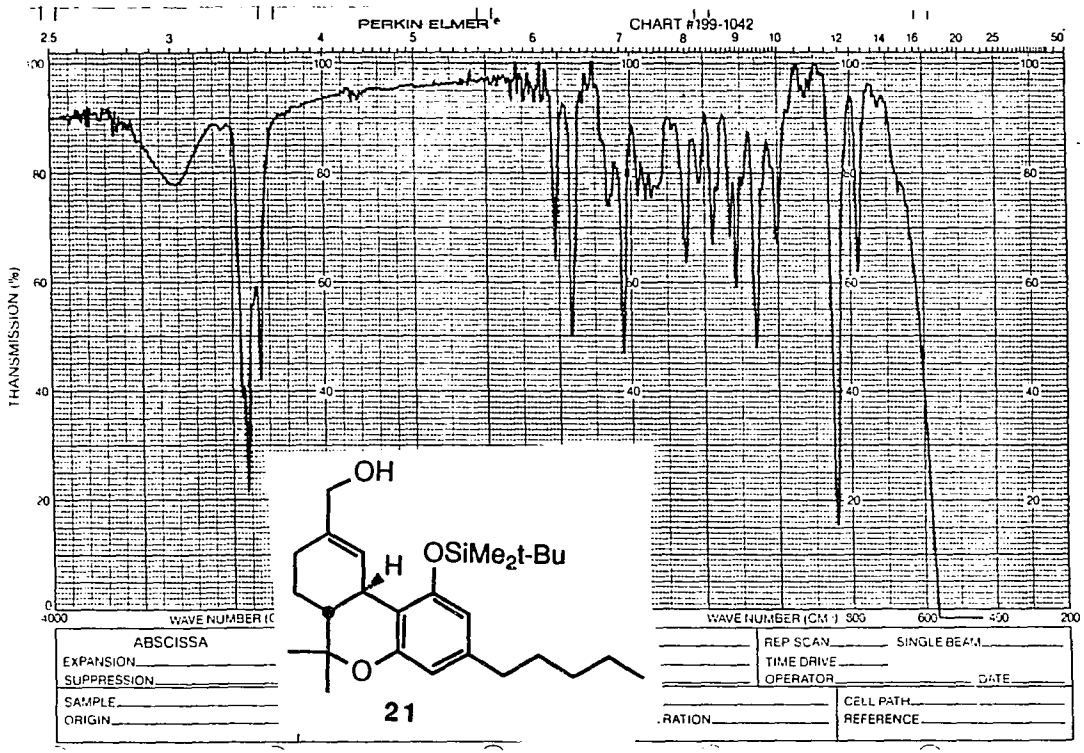

TRANSMISSION (%)
WAVE NUMBER (CM⁻¹)
OH
HO
17
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
ORDINATE
EXPANSION
%T
ABS
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
REMARKS
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
SAMPLE


PERKIN-ELMER
CHART #199-1042
OAc
H
OH
O
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
SCAN TIME
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
CONCENTRATION
CELL PATH
REFERENCE

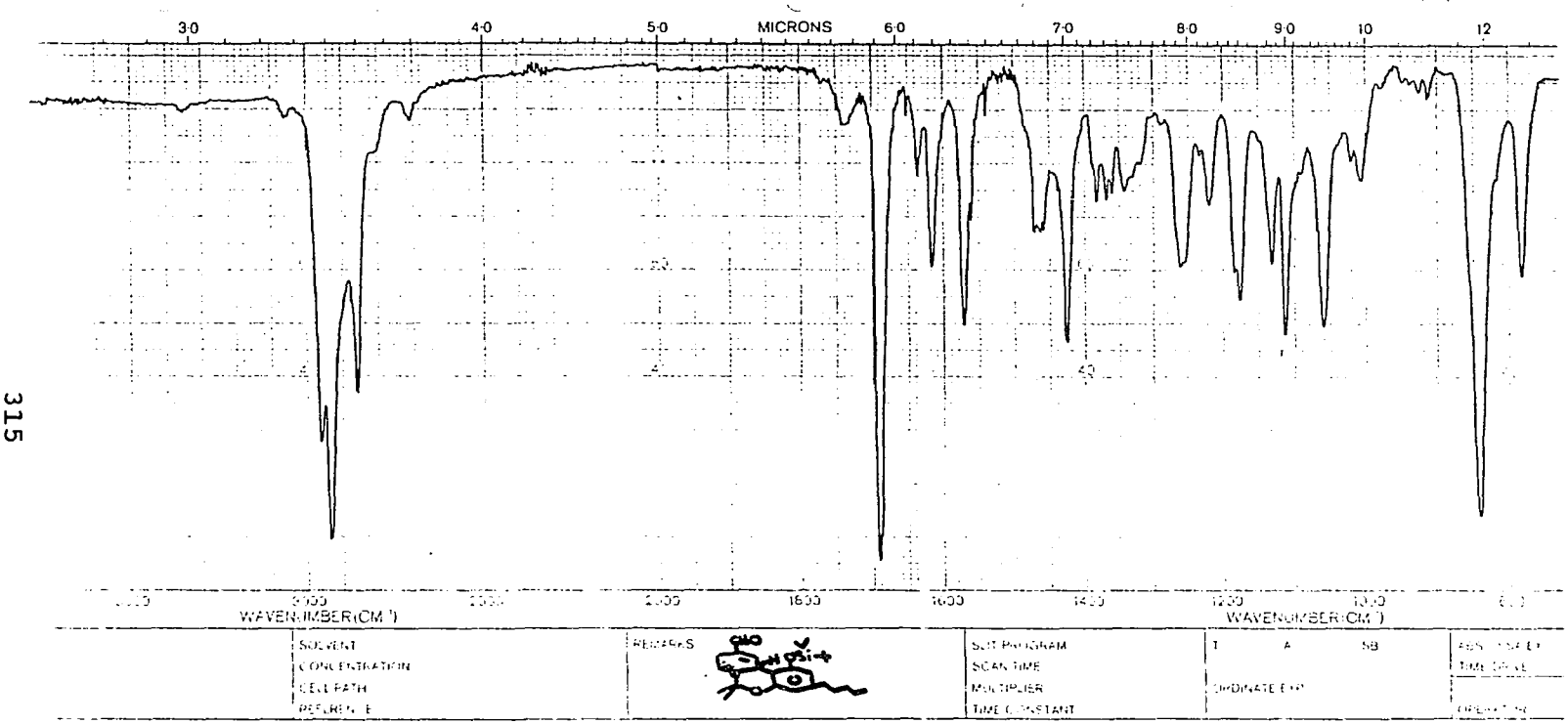
18

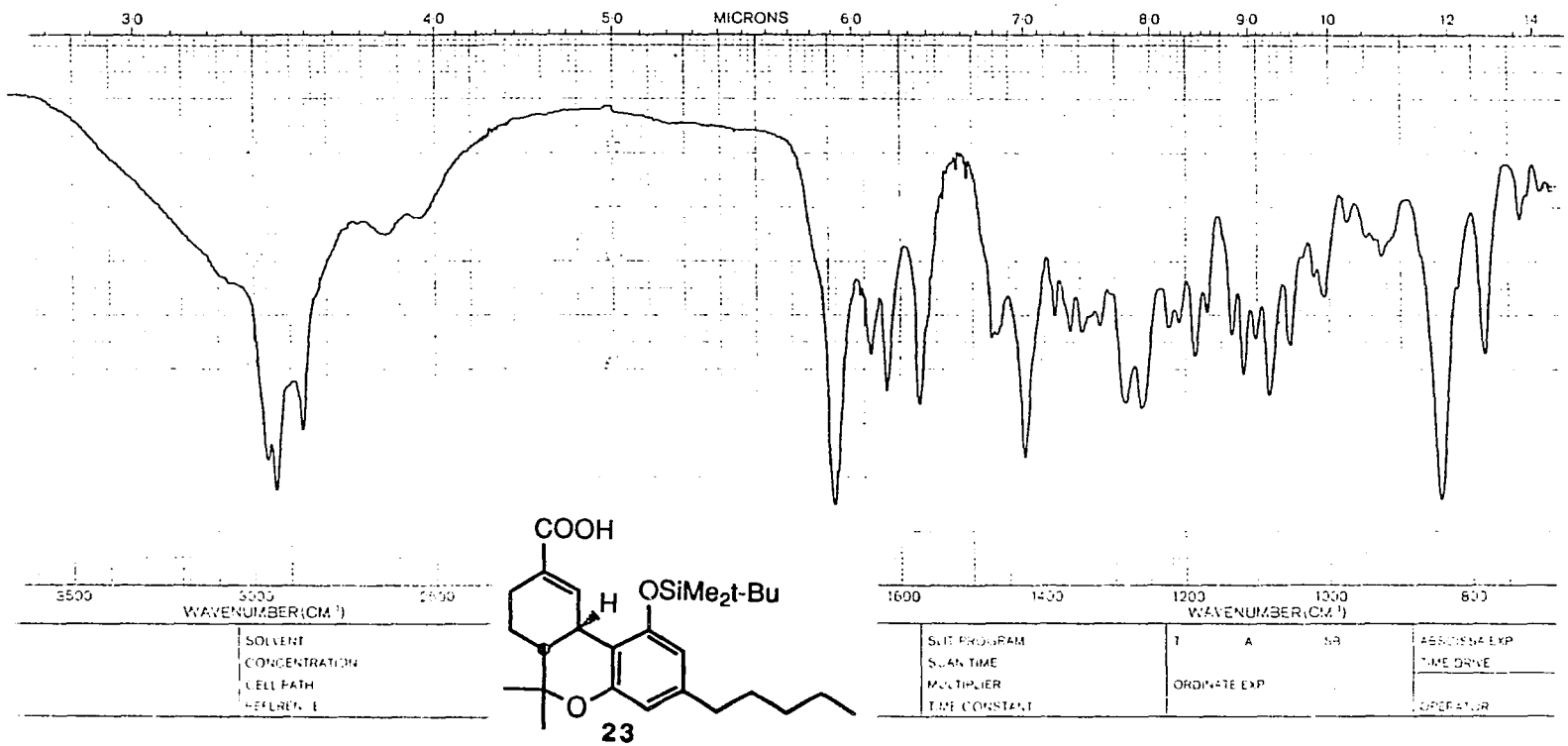

PERKIN-ELMER
CHART #199-1042
TRANSMISSION (%)
OAc
H
OSiMe2t-Bu
O
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

20

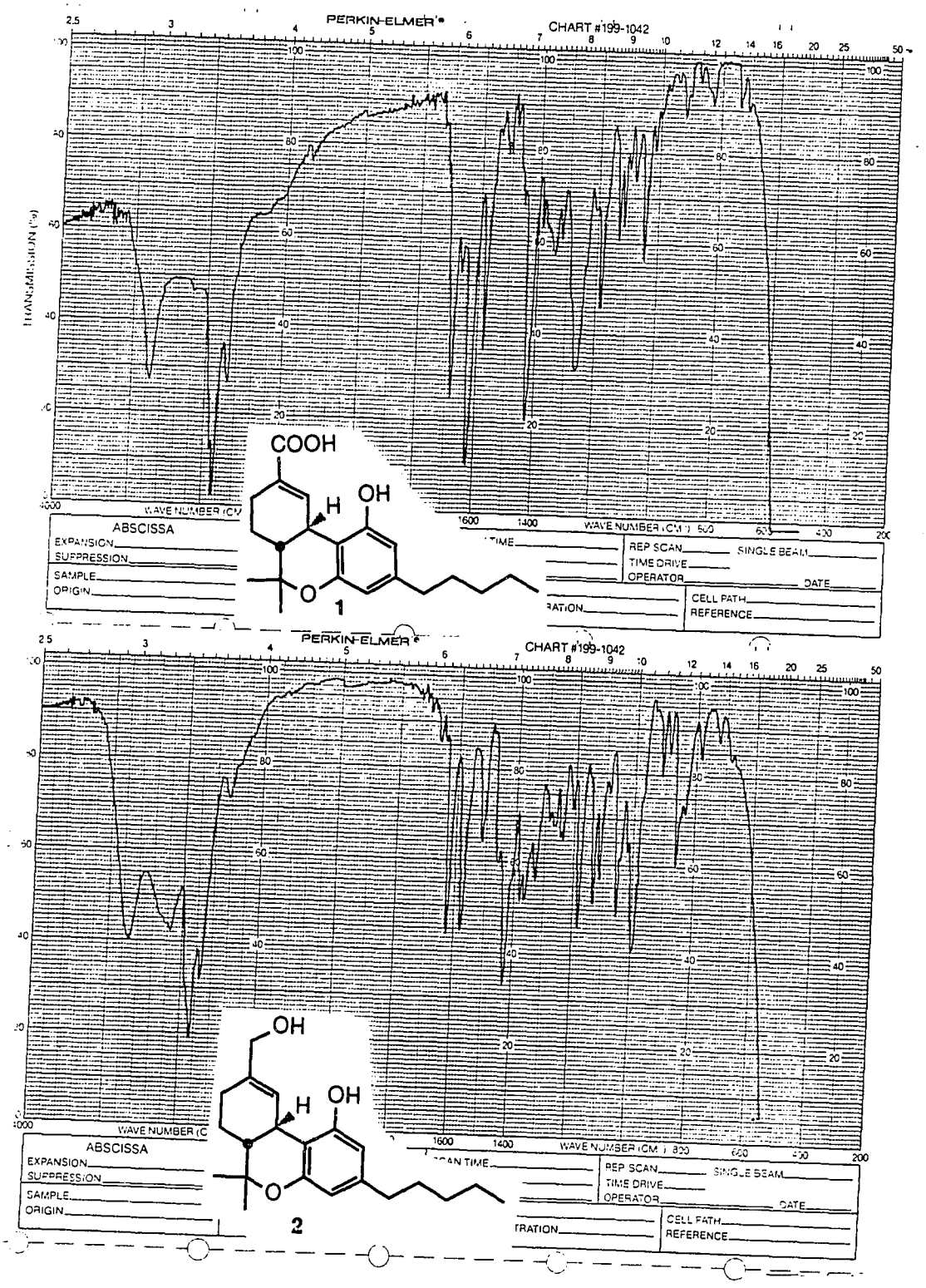

PERKIN ELMER
CHART #199-1042
TRANSMISSION (%)
WAVE NUMBER (CM⁻¹)
OH
H
OSiMe2t-Bu
O
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
CELL PATH
REFERENCE

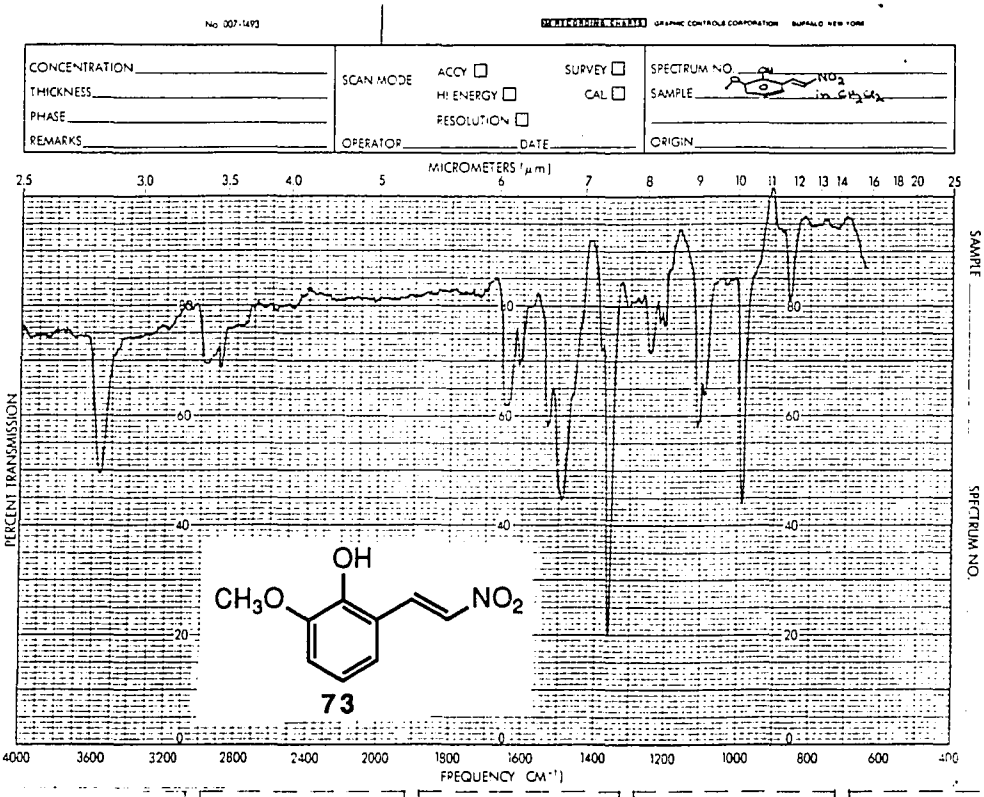
21

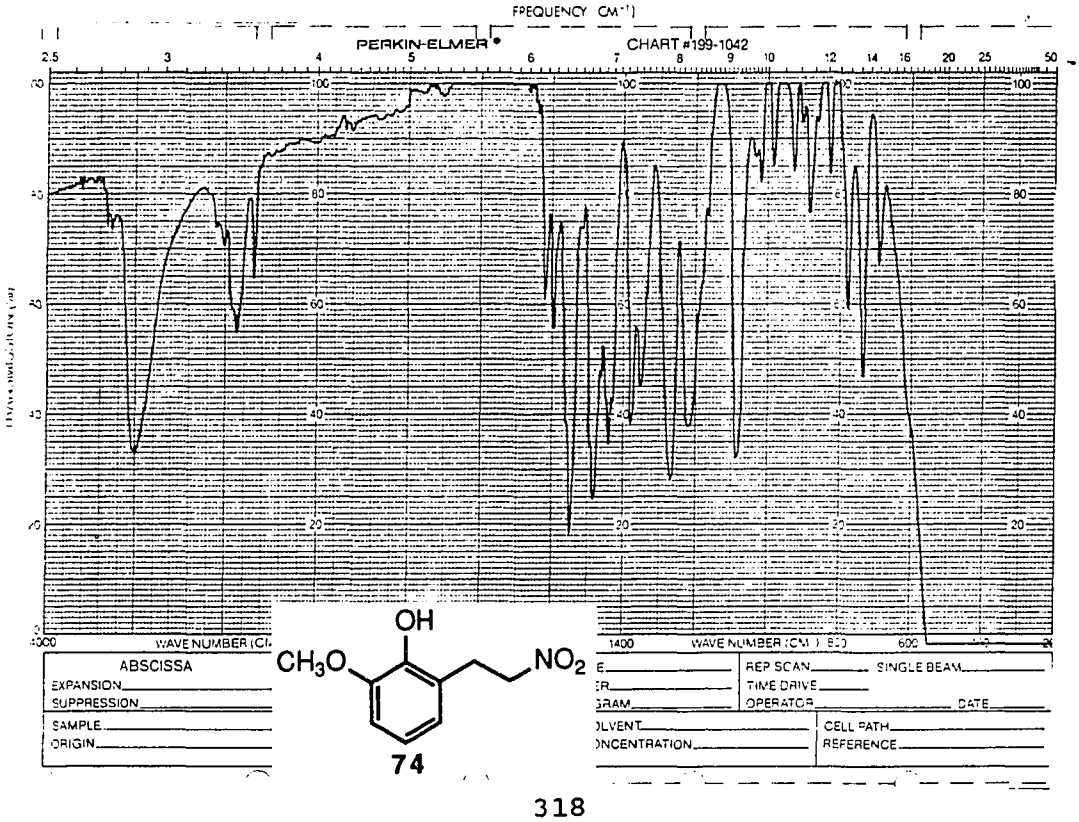

3·0
4·0
5·0
MICRONS
6·0
7·0
8·0
9·0
10
12
WAVENUMBER(CM⁻¹)
WAVENUMBER(CM⁻¹)
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
REFERENCE
SLIT PROGRAM
SCAN TIME
MULTIPLIER
TIME CONSTANT
T
A
SB
ORDINATE EXP

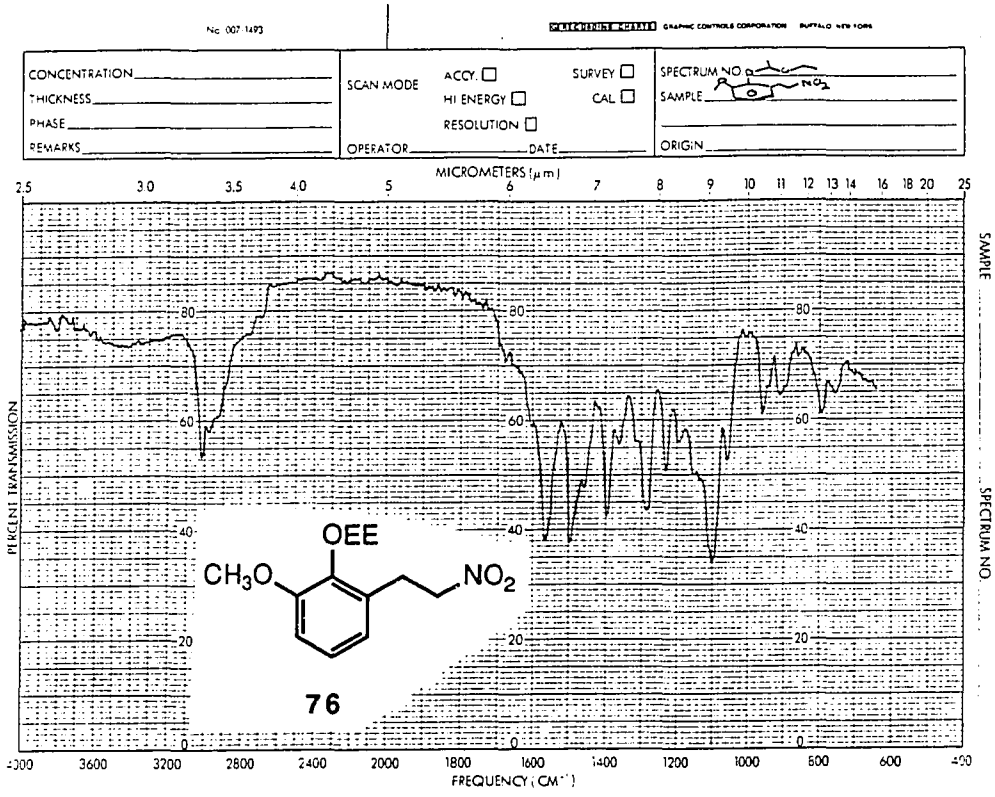

3.0
4.0
5.0
MICRONS
6.0
7.0
8.0
9.0
10
12
14
3500
3000
WAVENUMBER(CM⁻¹)
1600
1400
1200
1000
800
WAVENUMBER(CM⁻¹)
SOLVENT
CONCENTRATION
CELL PATH
SLIT PROGRAM
SCAN TIME
MULTIPLIER
TIME CONSTANT
ORDINATE EXP
TIME DRIVE
OPERATOR
COOH
H
OSiMe2t-Bu
O

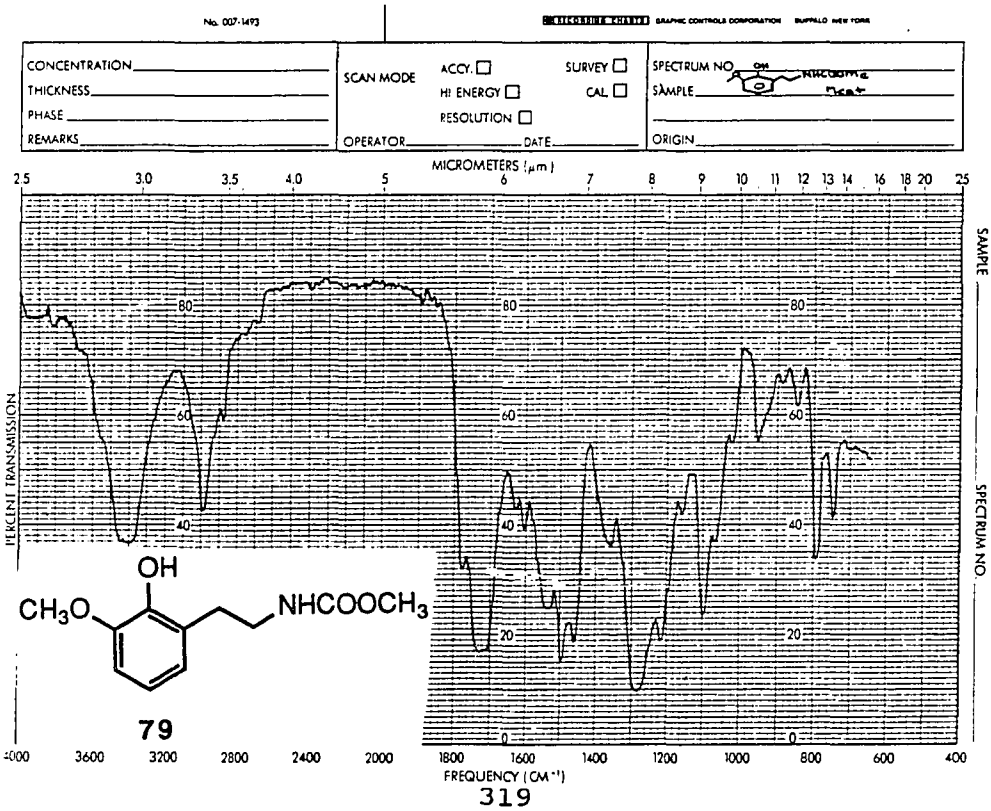
23

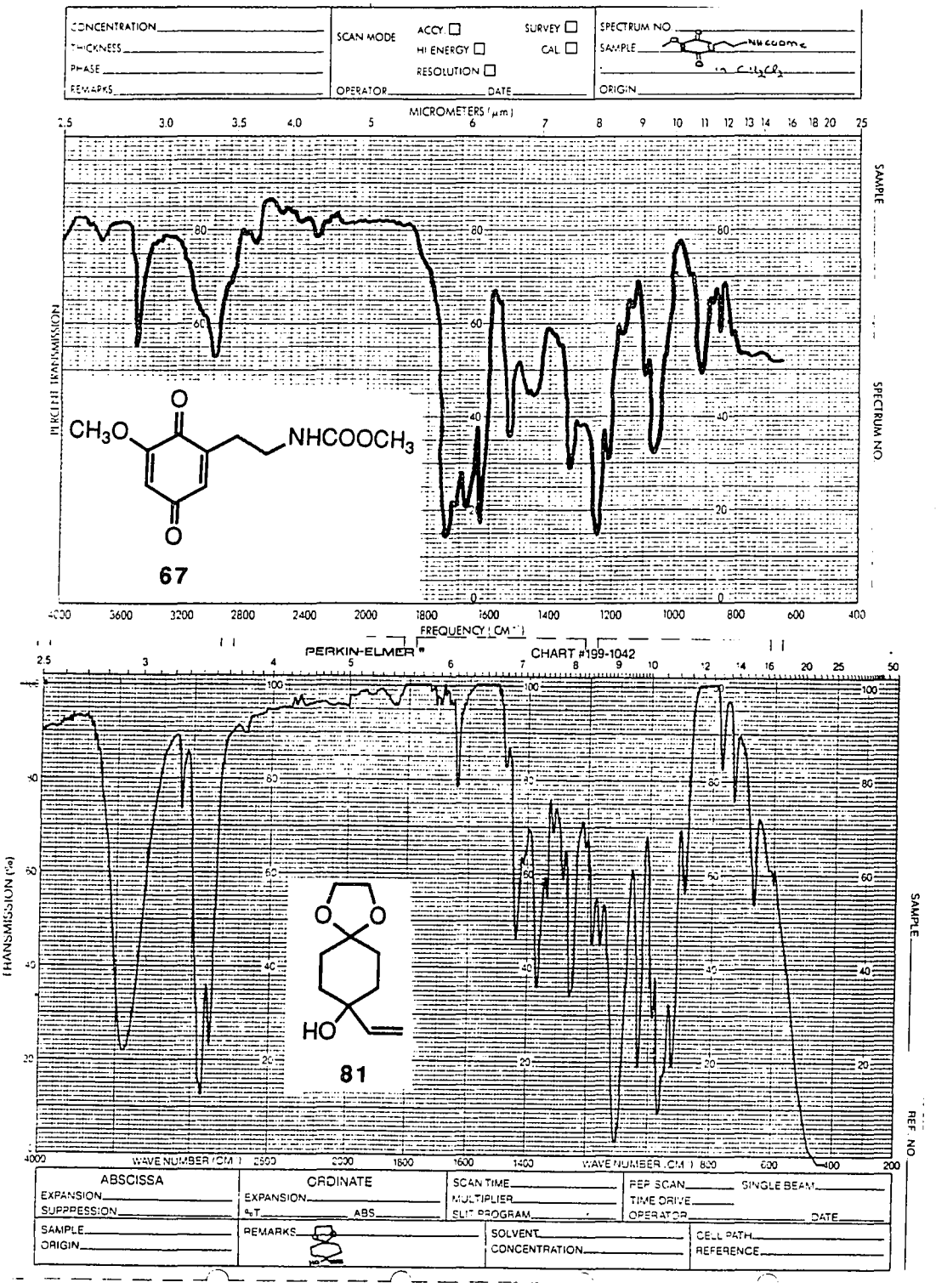

PERKIN-ELMER
CHART #199-1042
COOH
OH
H
O
1
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
CELL PATH
REFERENCE
PERKIN-ELMER
CHART #199-1042
OH
H
OH
O
2
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
CELL PATH
REFERENCE

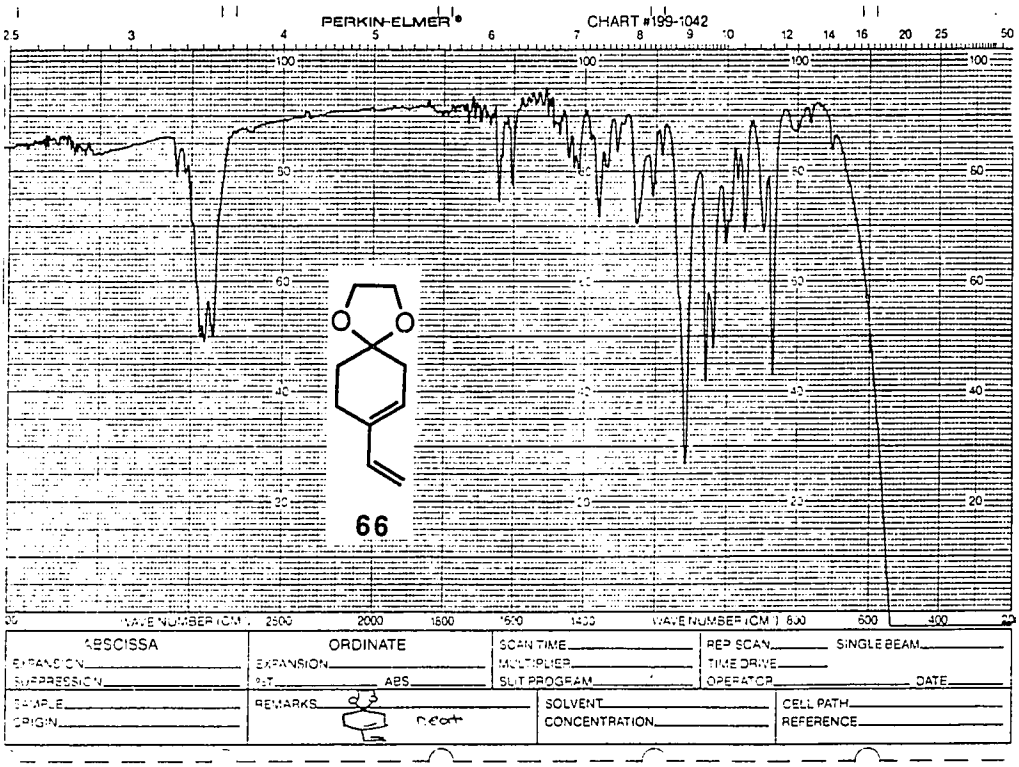

CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY
SURVEY
HI ENERGY
CAL
RESOLUTION
OPERATOR
DATE
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.
FREQUENCY (CM⁻¹)
OH
CH3O
NO2
73

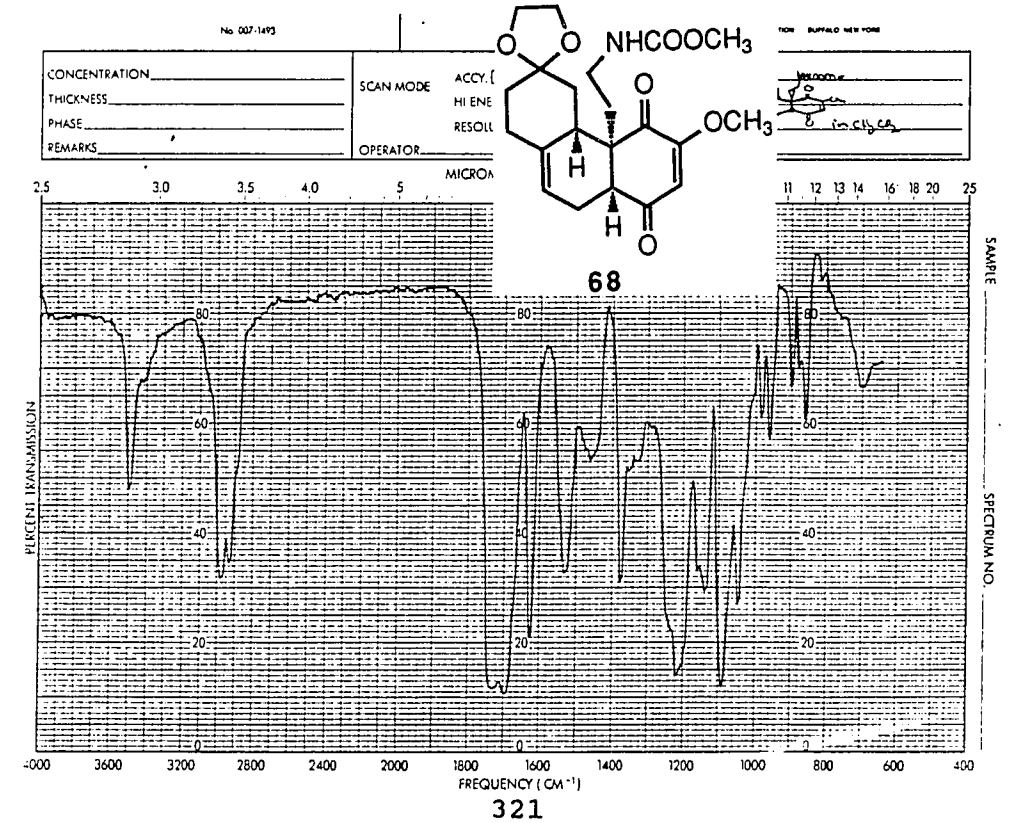

PERKIN-ELMER
CHART #199-1042
WAVE NUMBER (CM⁻¹)
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
OH
CH3O
NO2
74

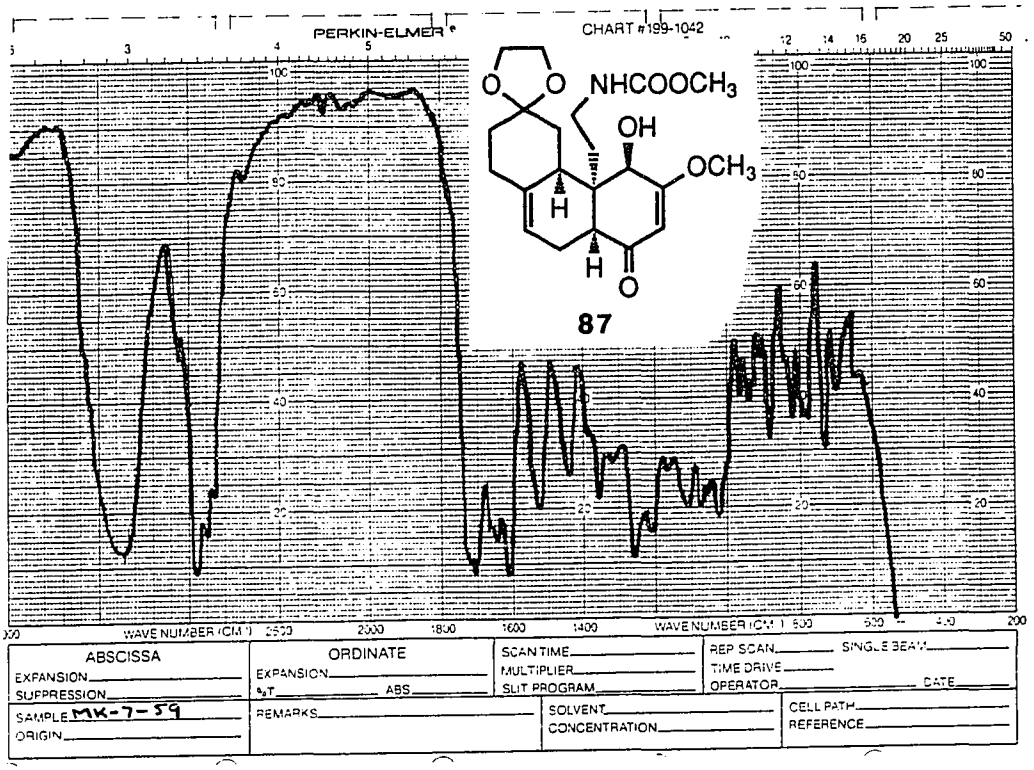

No. 007-1493
CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL
OPERATOR
DATE
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
SAMPLE
SPECTRUM NO.
OEE
CH3O
NO2
76

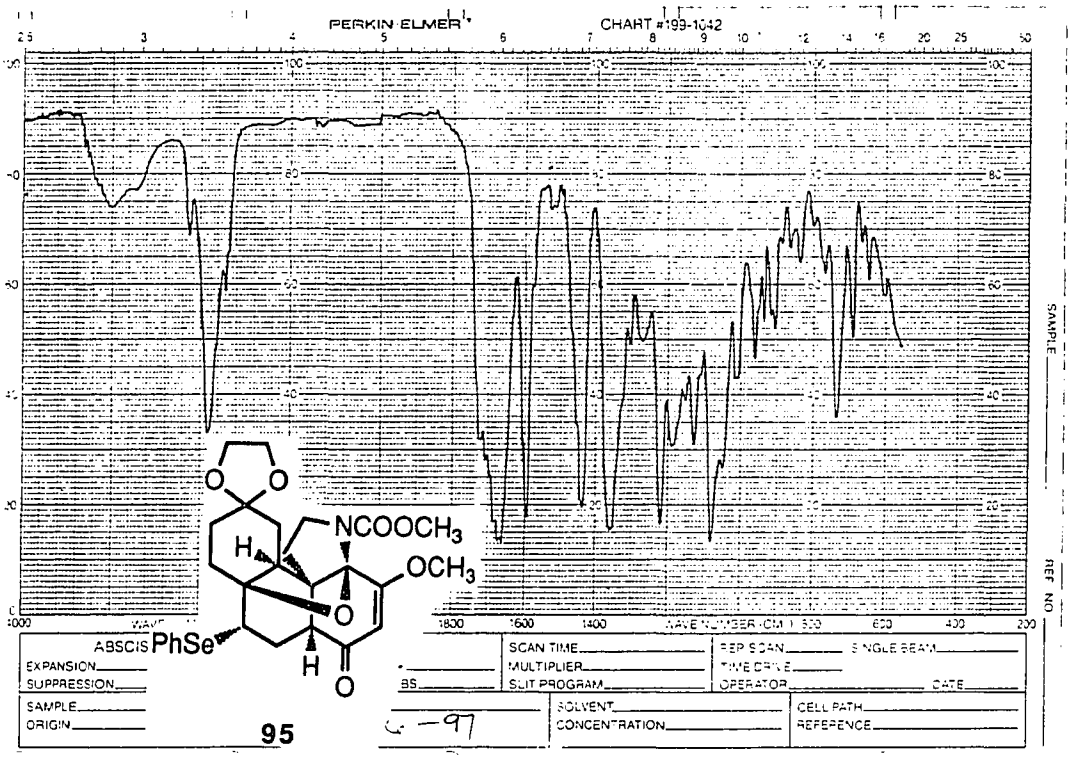

No. 007-1493
CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL
OPERATOR
DATE
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
SAMPLE
SPECTRUM NO.
OH
CH3O
NHCOOCH3
79

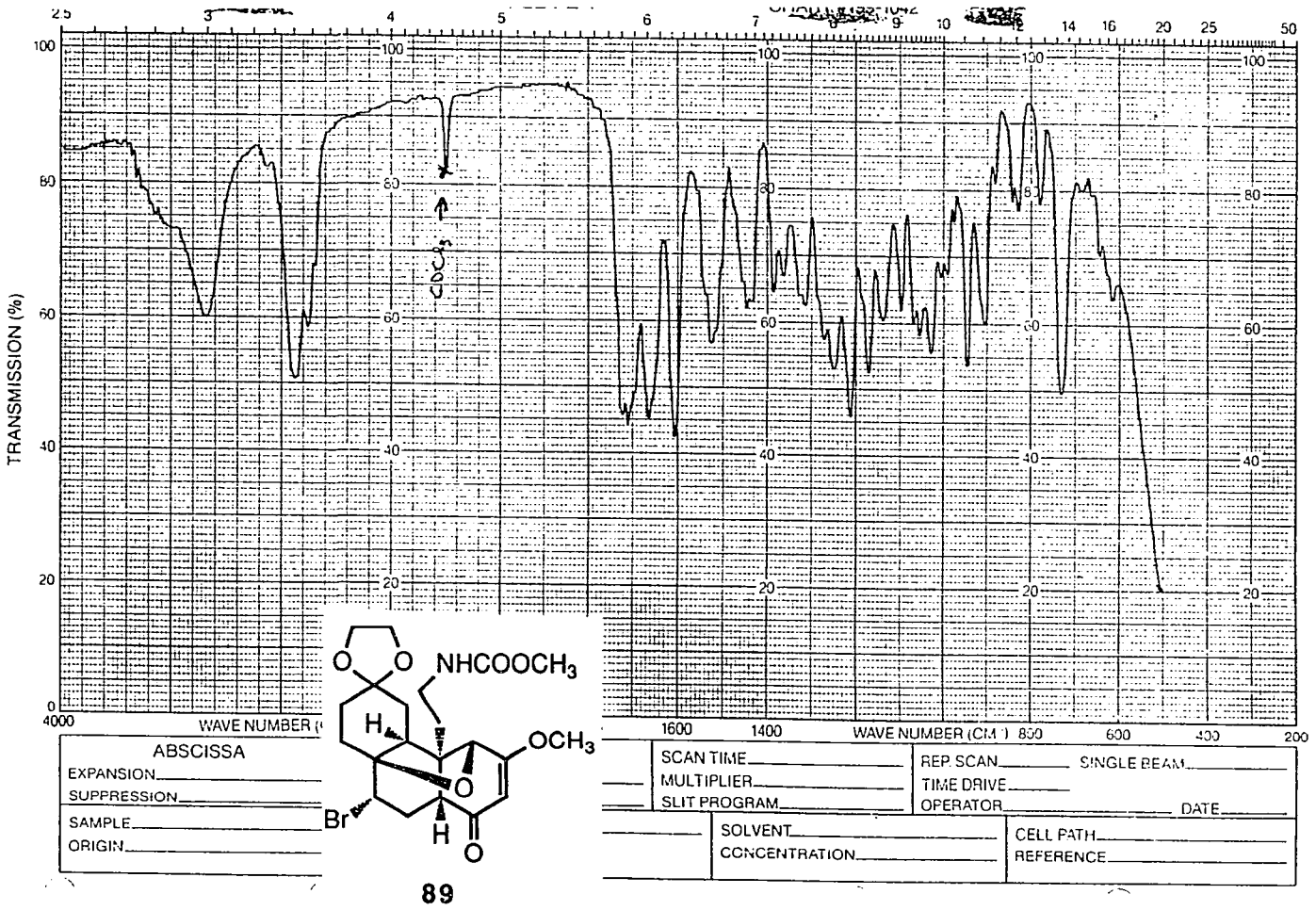

CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL
OPERATOR
DATE
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.
67
FREQUENCY (CM⁻¹)
PERKIN-ELMER
CHART #199-1042
TRANSMISSION (%)
81
WAVE NUMBER (CM⁻¹)
ABSCISSA
EXPANSION
SUPPRESSION
ORDINATE
EXPANSION
%T
ABS
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SAMPLE
ORIGIN
REMARKS
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
REF. NO.


PERKIN-ELMER
CHART #199-1042
WAVE NUMBER (CM⁻¹)
ABSCISSA
ORDINATE
SCAN TIME
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
REMARKS
66


CONCENTRATION
THICKNESS
PHASE
REMARKS
SCAN MODE
OPERATOR
NHCOOCH3
OCH3
68
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
SAMPLE
SPECTRUM NO.

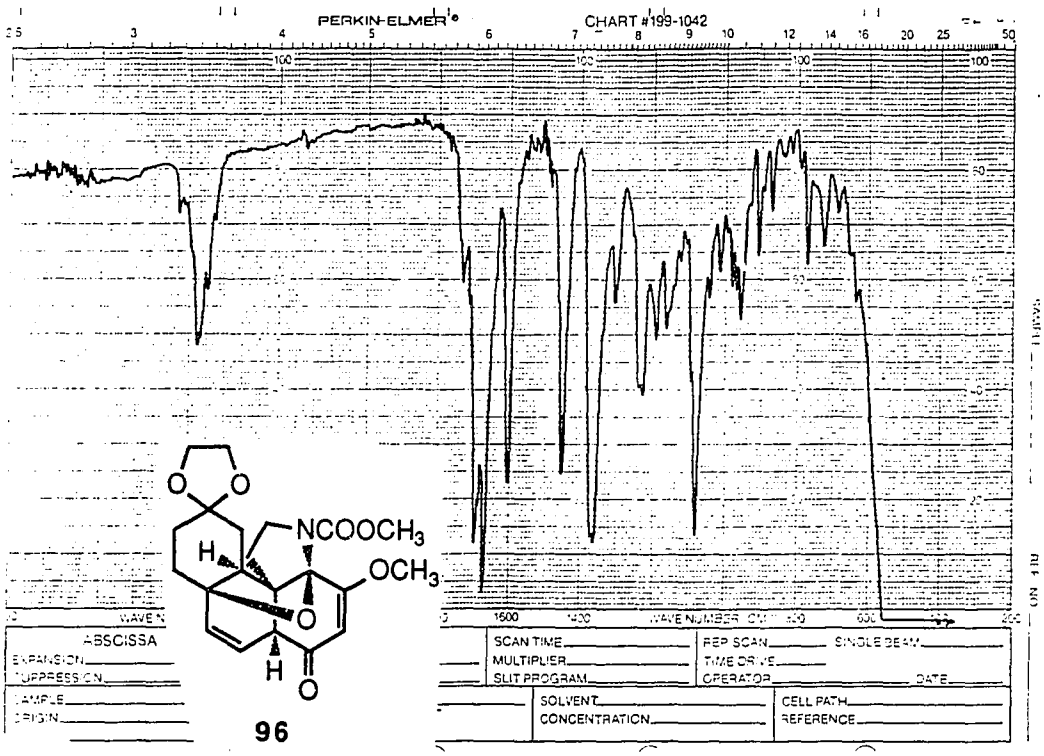

PERKIN-ELMER
CHART #199-1042
NHCOOCH3
OH
OCH3
H
H
O
O
O
87
WAVE NUMBER (CM-1)
ABSCISSA
EXPANSION
SUPPRESSION
ORDINATE
EXPANSION
%T
ABS
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SAMPLE MK-7-59
ORIGIN
REMARKS
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE


PERKIN-ELMER
CHART #199-1042
NCOOCH3
H
OCH3
O
O
O
H
ABSCIS PhSe
EXPANSION
SUPPRESSION
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SAMPLE
ORIGIN
95
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
SAMPLE
REF NO

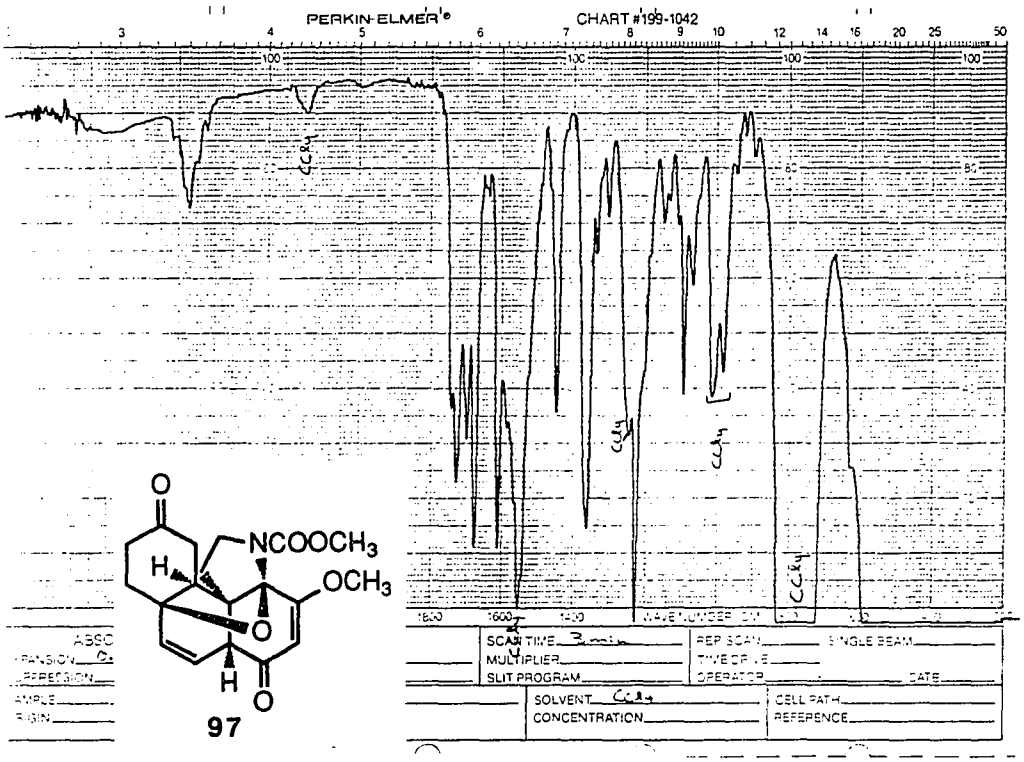

TRANSMISSION (%)
WAVE NUMBER (CM⁻¹)
CDCl3
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP. SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

NHCOOCH3
OCH3
Br
H
O

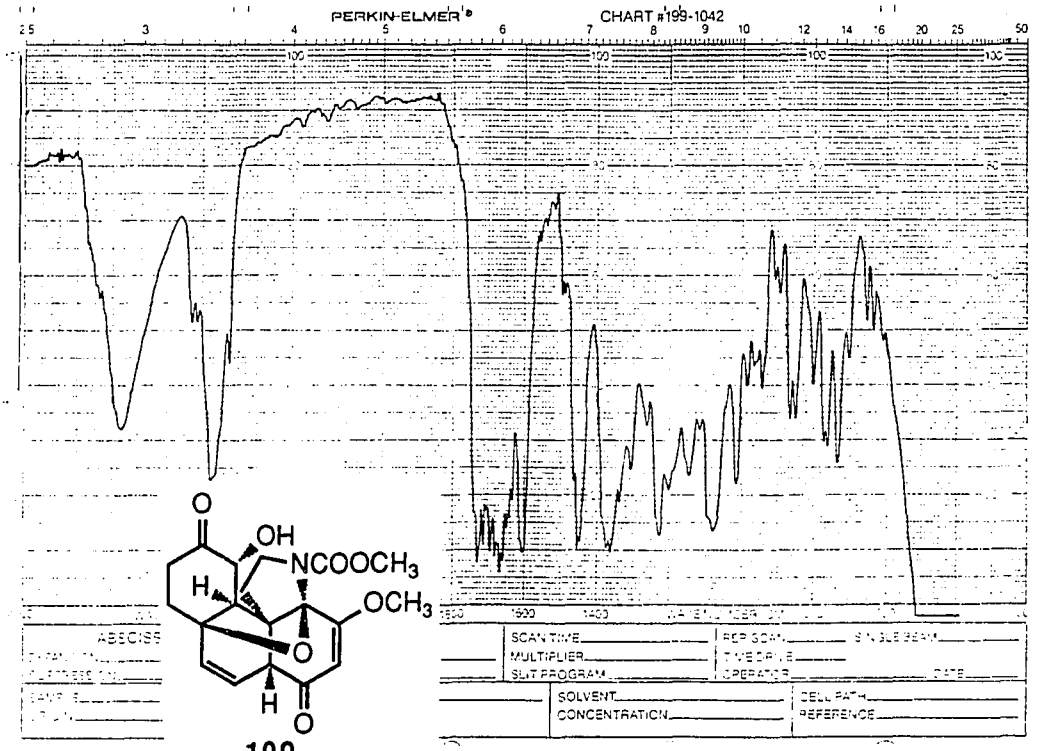
89


PERKIN-ELMER
CHART #199-1042
ABSCISSA
SCAN TIME
REP SCAN
SINGLE BEAM
MULTIPLIER
TIME DRIVE
SLIT PROGRAM
OPERATOR
DATE
SOLVENT
CELL PATH
CONCENTRATION
REFERENCE
NCOOCH3
OCH3
H
O

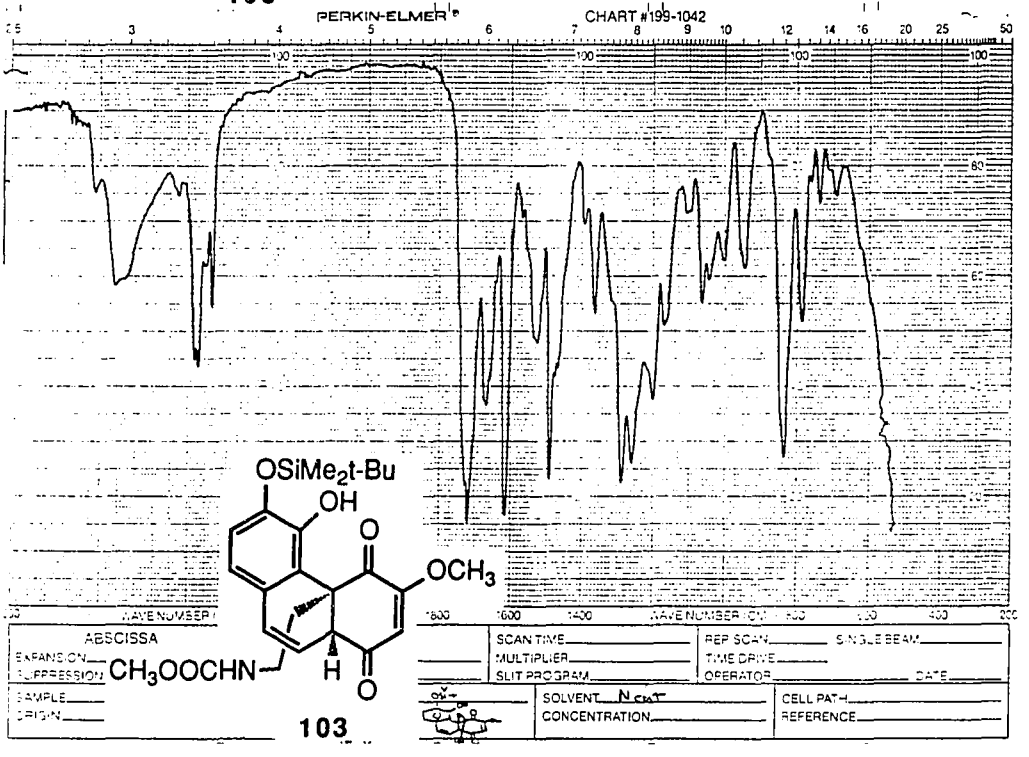
96


PERKIN-ELMER
CHART #199-1042
SCAN TIME
REP SCAN
SINGLE BEAM
MULTIPLIER
TIME DRIVE
SLIT PROGRAM
OPERATOR
DATE
SOLVENT
CELL PATH
CONCENTRATION
REFERENCE
NCOOCH3
OCH3
H
O

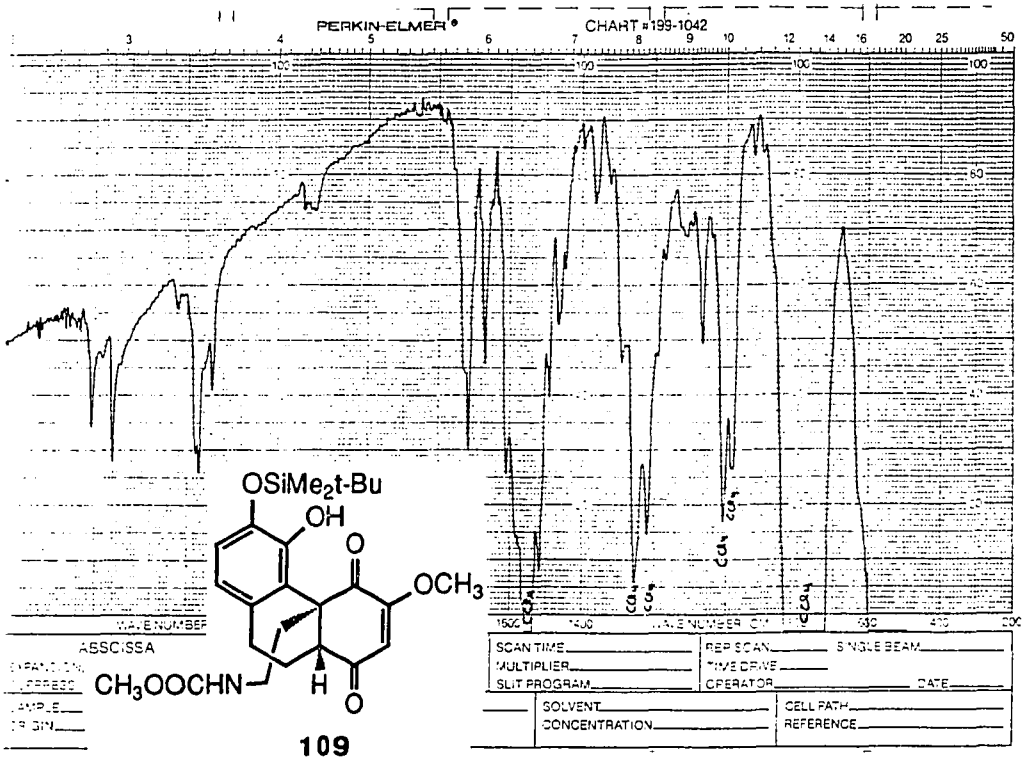
97


PERKIN-ELMER
CHART #199-1042
OH
NCOOCH3
OCH3
H
O
H
O
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

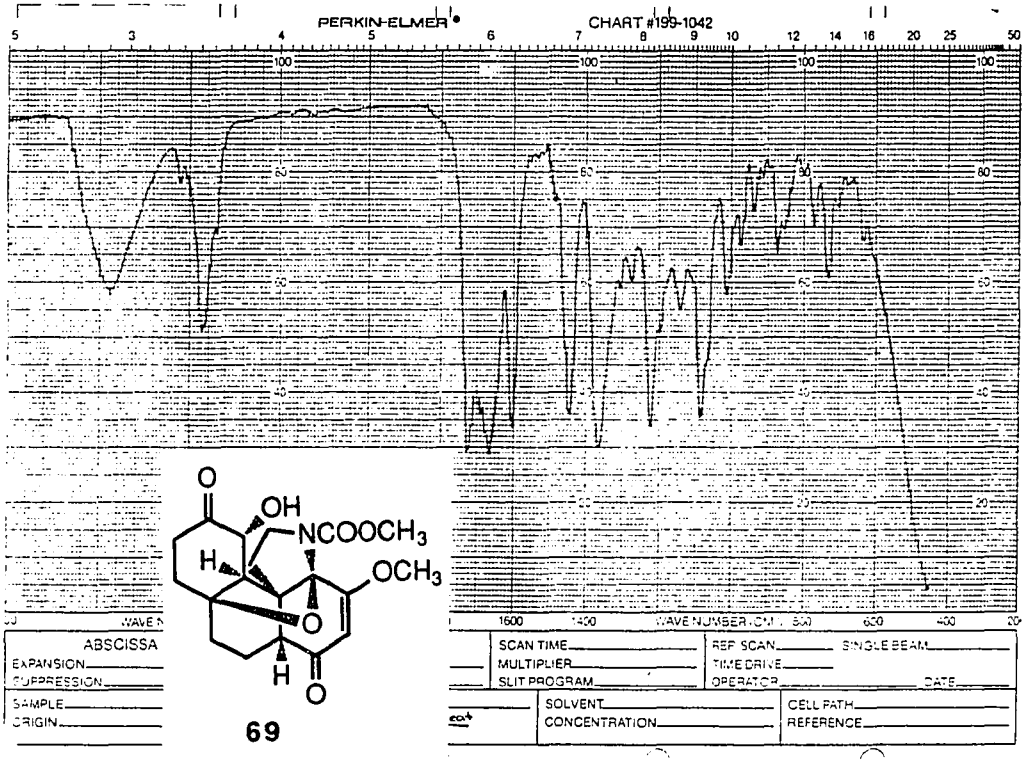
100


PERKIN-ELMER
CHART #199-1042
OSiMe2t-Bu
OH
O
OCH3
CH3OOCHN
H
O
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
TIME DRIVE
OPERATOR
DATE
SOLVENT Neat
CONCENTRATION
CELL PATH
REFERENCE

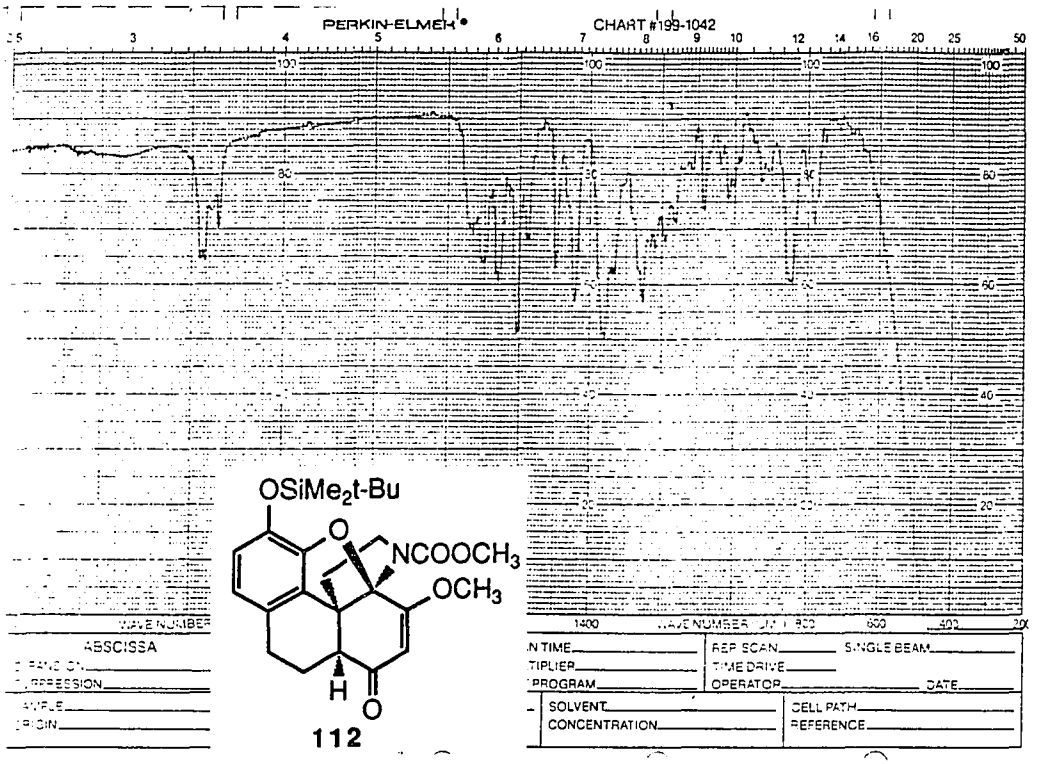
103

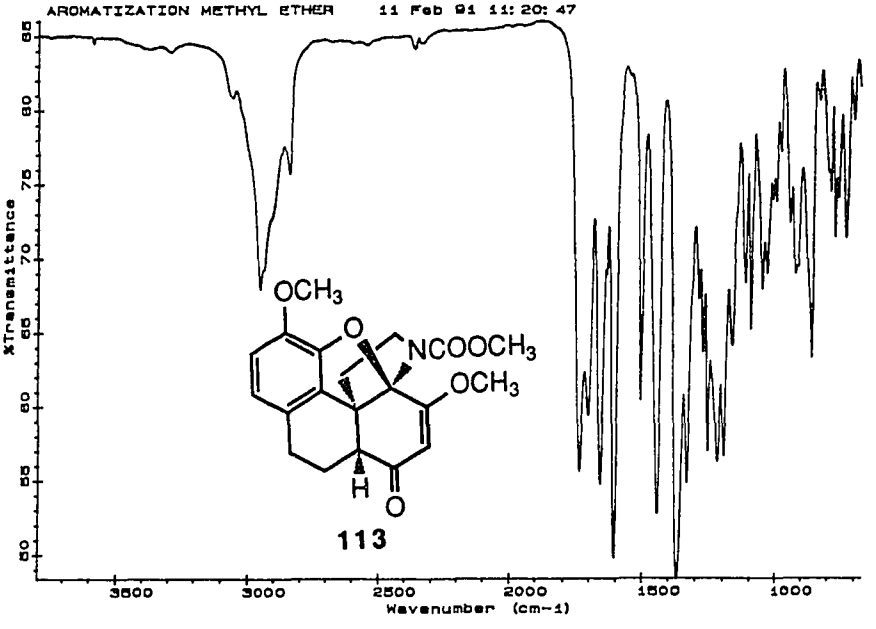

PERKIN-ELMER
CHART #199-1042
OSiMe2t-Bu
OH
O
OCH3
CH3OOCHN
H
O
ABSCISSA
SCAN TIME
REP SCAN
SINGLE BEAM
MULTIPLIER
TIME DRIVE
SLIT PROGRAM
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

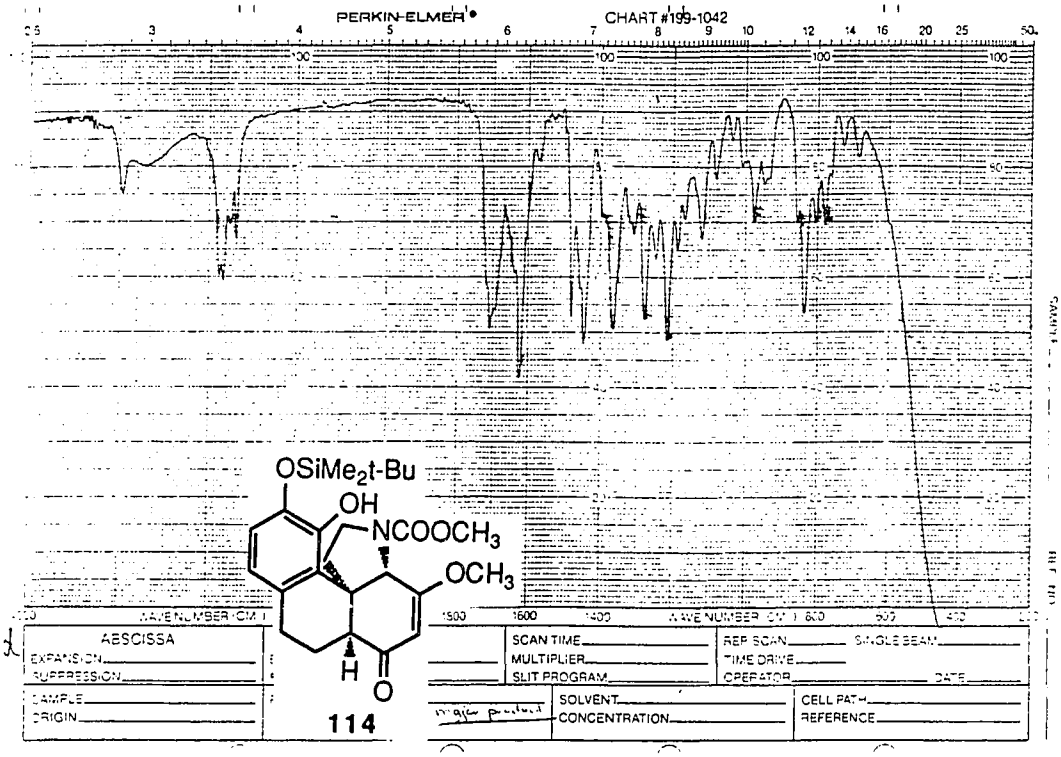
109

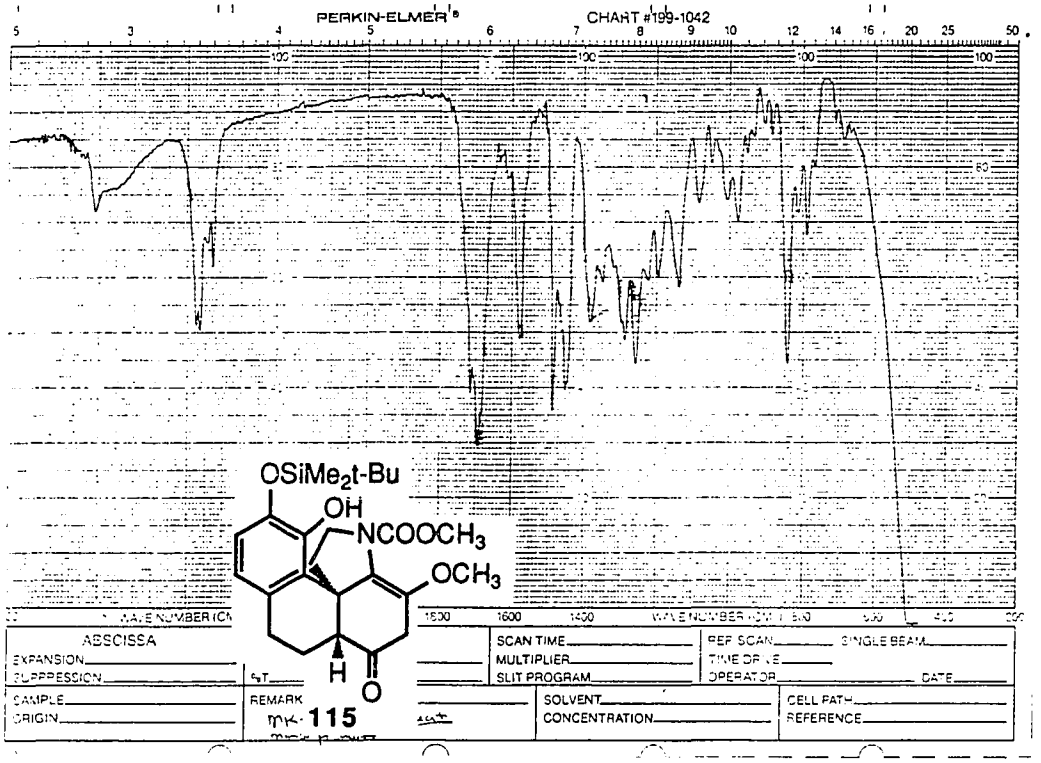

PERKIN-ELMER
CHART #199-1042
O
OH
NCOOCH3
H
OCH3
O
H
O
ABSCISSA
SCAN TIME
REP SCAN
SINGLE BEAM
MULTIPLIER
TIME DRIVE
SLIT PROGRAM
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

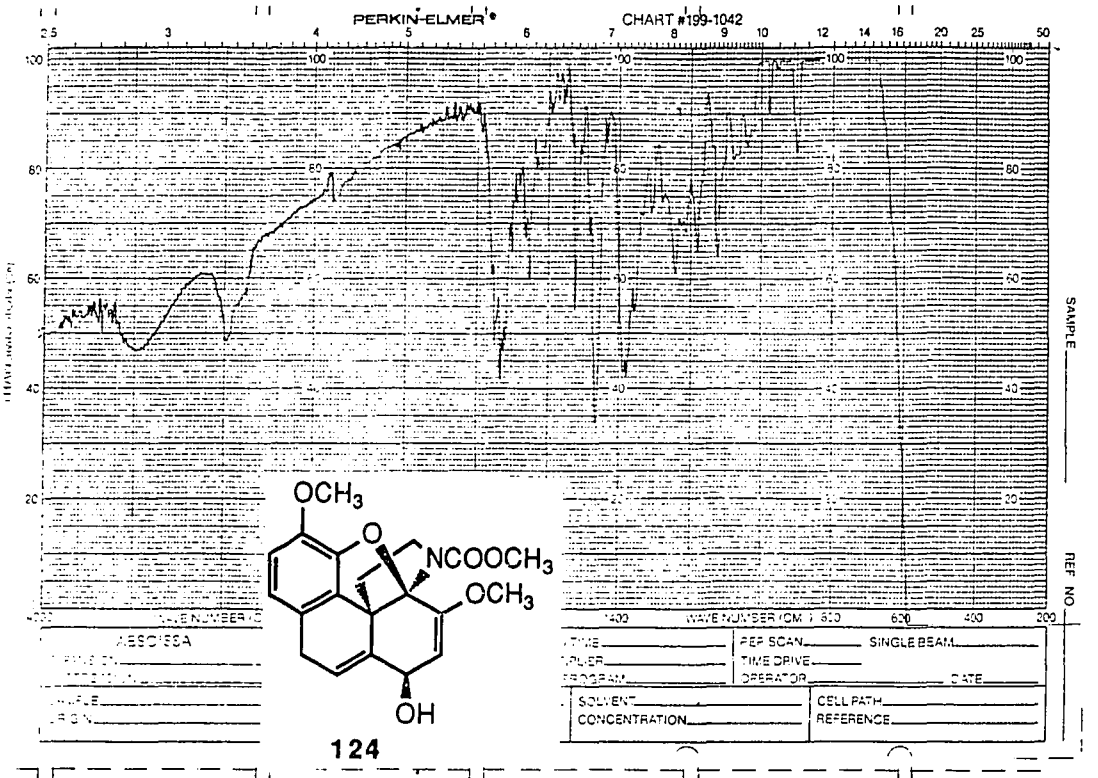
69


PERKIN-ELMER
CHART #199-1042
OSiMe2t-Bu
NCOOCH3
OCH3
H
O
112
ABSCISSA
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
SINGLE BEAM
DATE

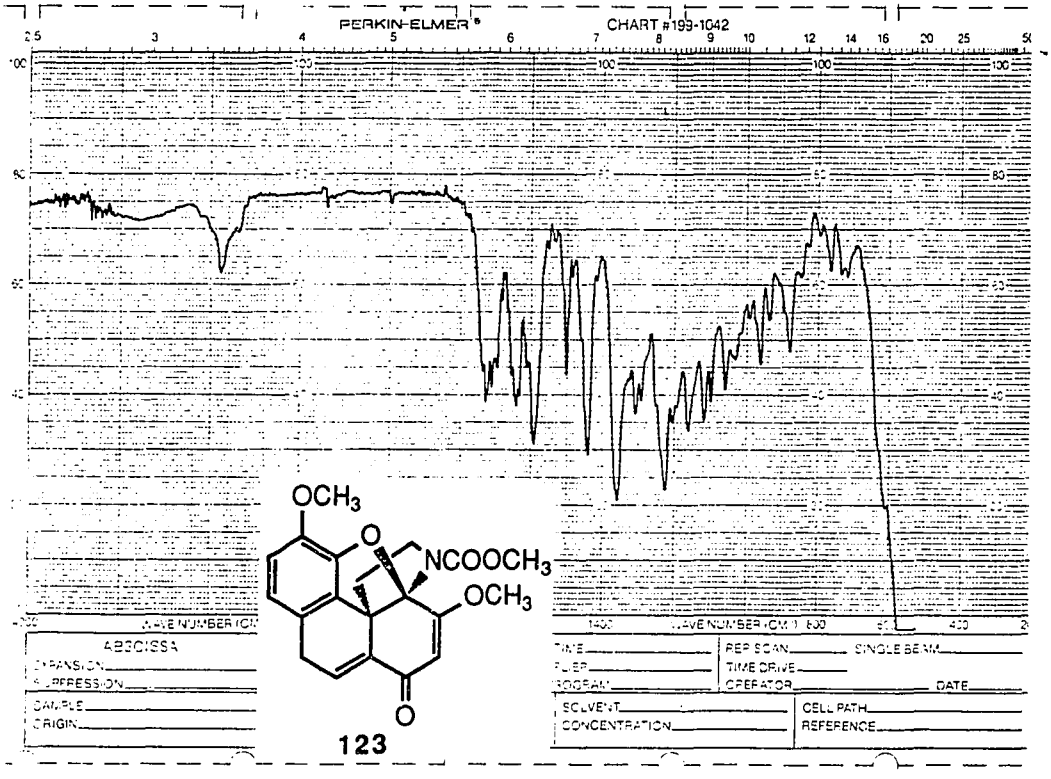

AROMATIZATION METHYL ETHER 11 Feb 91 11:20:47
%Transmittance
Wavenumber (cm-1)
3500
3000
2500
2000
1500
1000
OCH3
NCOOCH3
OCH3
H
O
113


PERKIN-ELMER
CHART #199-1042
OSiMe2t-Bu
OH
NCOOCH3
OCH3
H
O
114
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

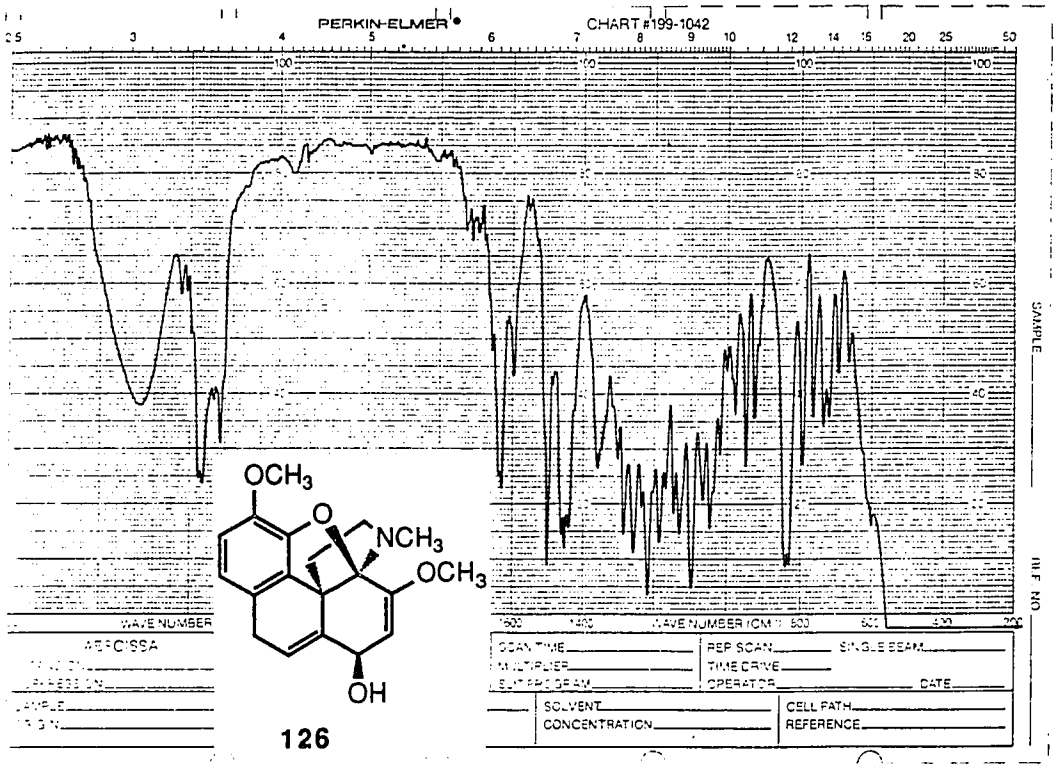

PERKIN-ELMER
CHART #199-1042
OSiMe2t-Bu
OH
NCOOCH3
OCH3
H
O
MK-115
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
REMARK
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

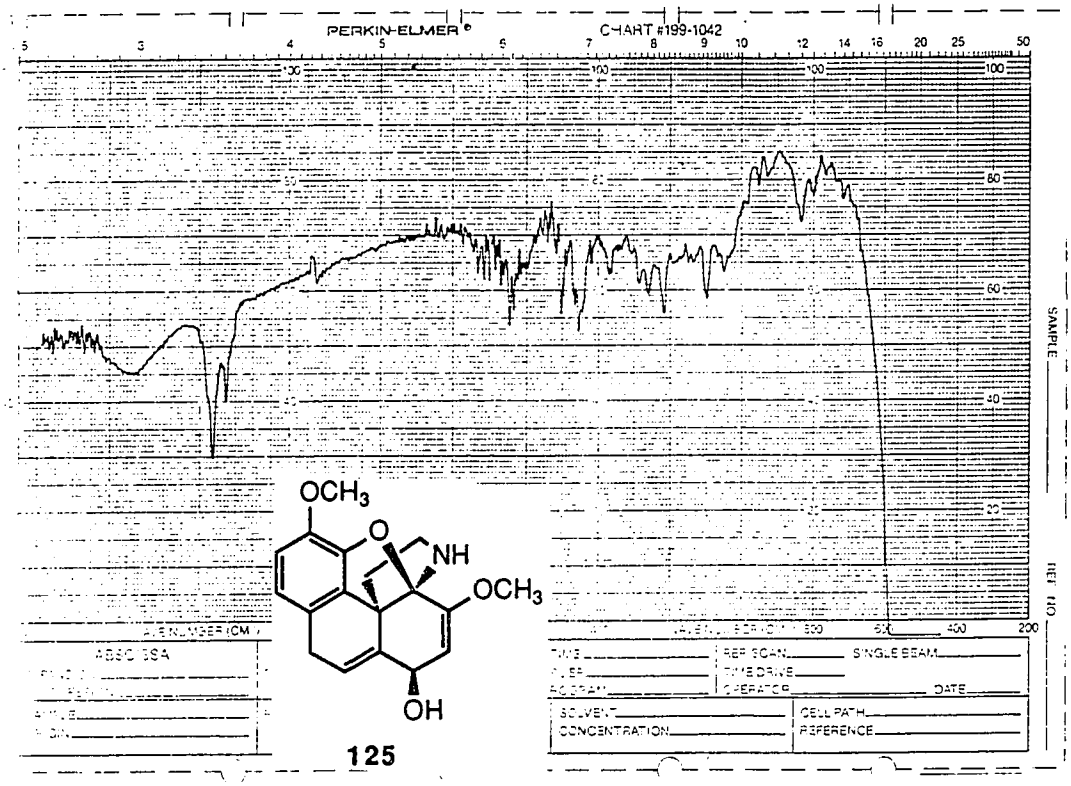

PERKIN-ELMER
CHART #199-1042
SAMPLE
REF NO.
ABSCISSA
SINGLE BEAM
PER SCAN
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
OCH3
O
NCOOCH3
OCH3
OH

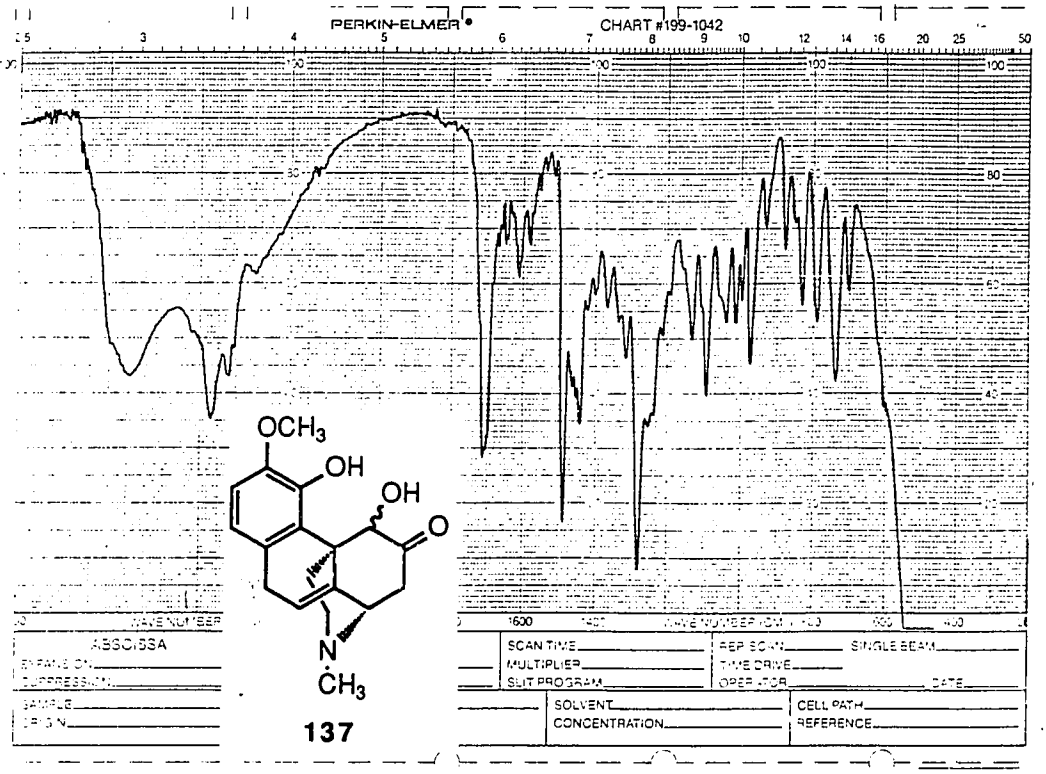
124


PERKIN-ELMER
CHART #199-1042
ABSCISSA
PER SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
OCH3
O
NCOOCH3
OCH3
O

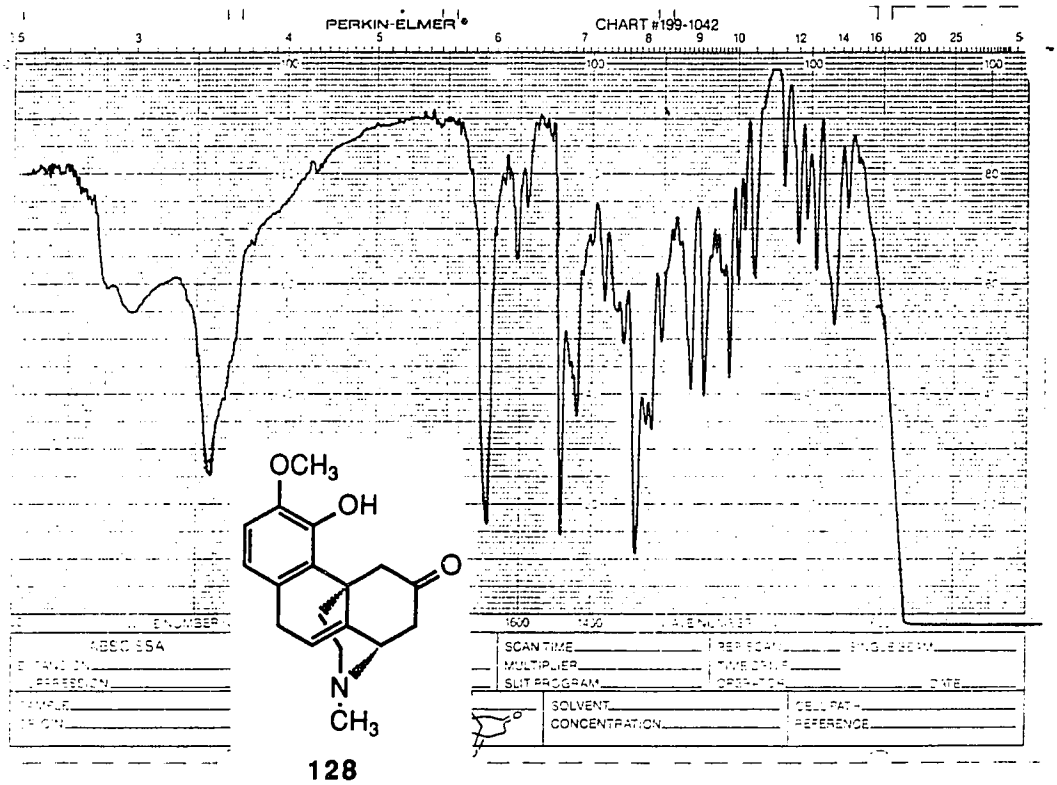
123


PERKIN-ELMER
CHART #199-1042
OCH3
NCH3
OCH3
OH
126

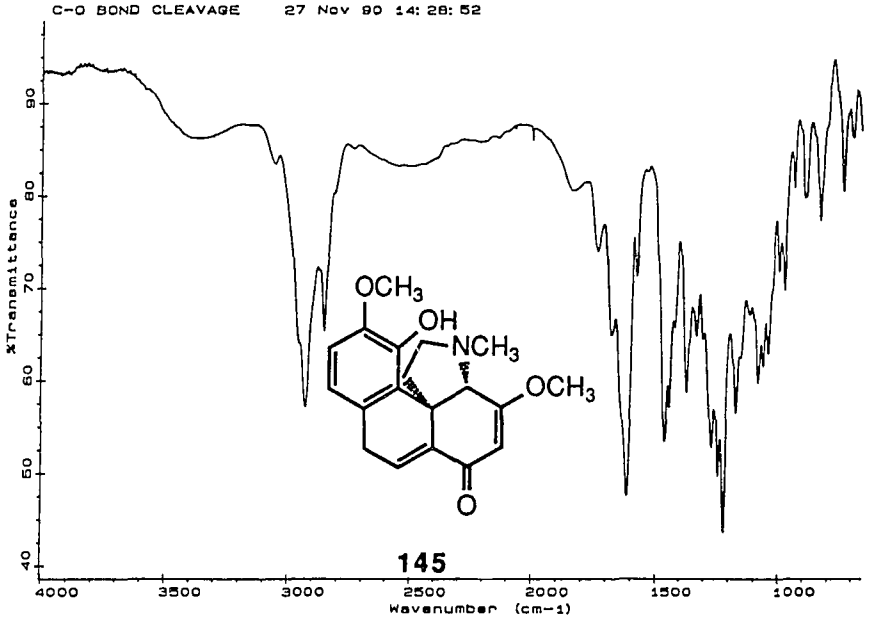

PERKIN-ELMER
CHART #199-1042
OCH3
NH
OCH3
OH
125


PERKIN-ELMER
CHART #199-1042
OCH3
OH
OH
O
N
CH3
ABSORBANCE
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
TIME DRIVE
OPERATOR
SINGLE BEAM
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

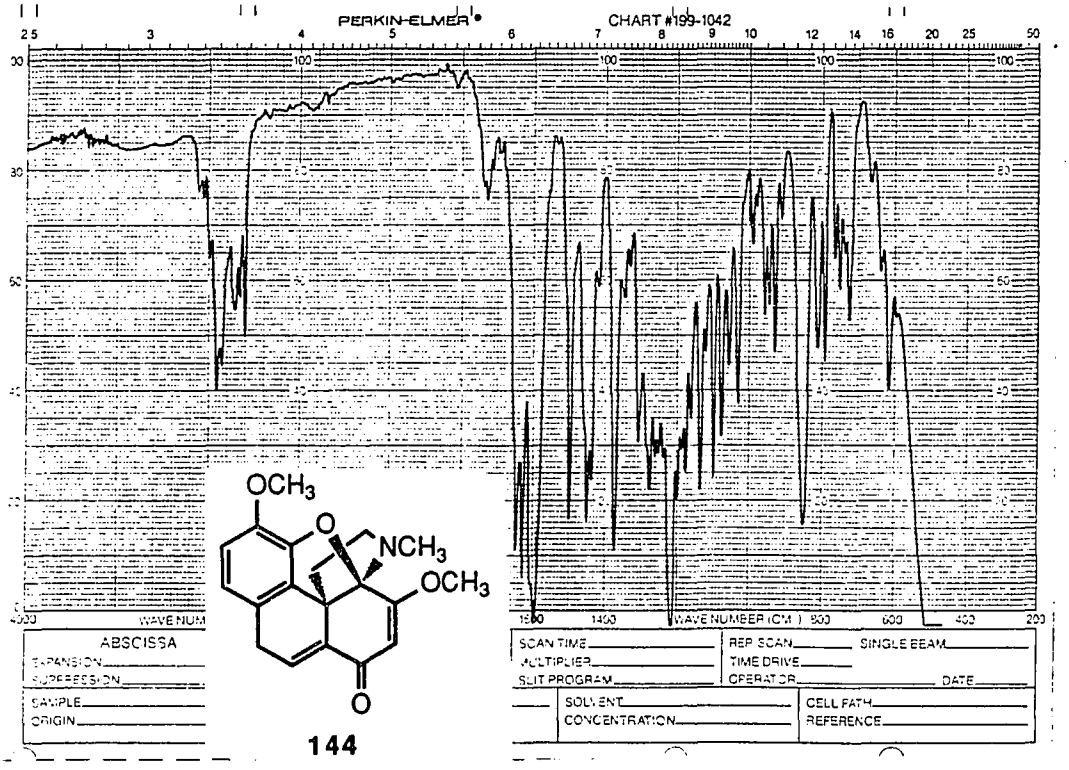
137


PERKIN-ELMER
CHART #199-1042
OCH3
OH
O
N
CH3
SCAN TIME
MULTIPLIER
SLIT PROGRAM
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

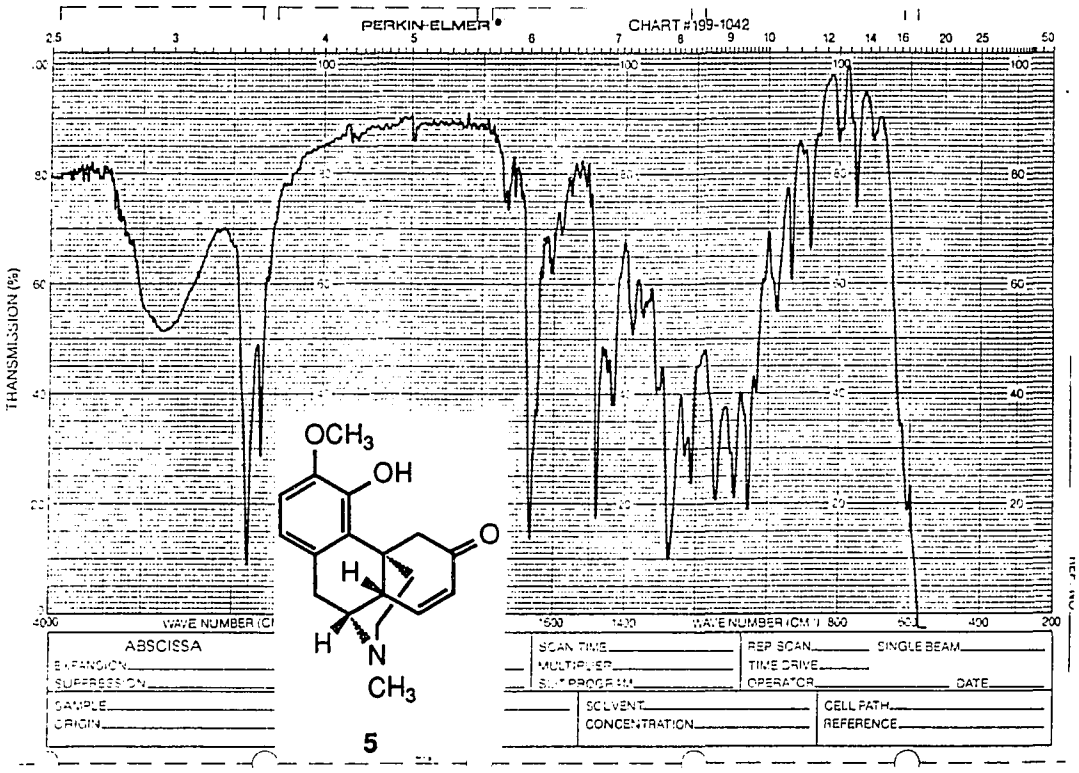
128


C-O BOND CLEAVAGE 27 Nov 90 14: 28: 52
%Transmittance
90
80
70
60
50
40
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
OCH3
OH
NCH3
OCH3
O

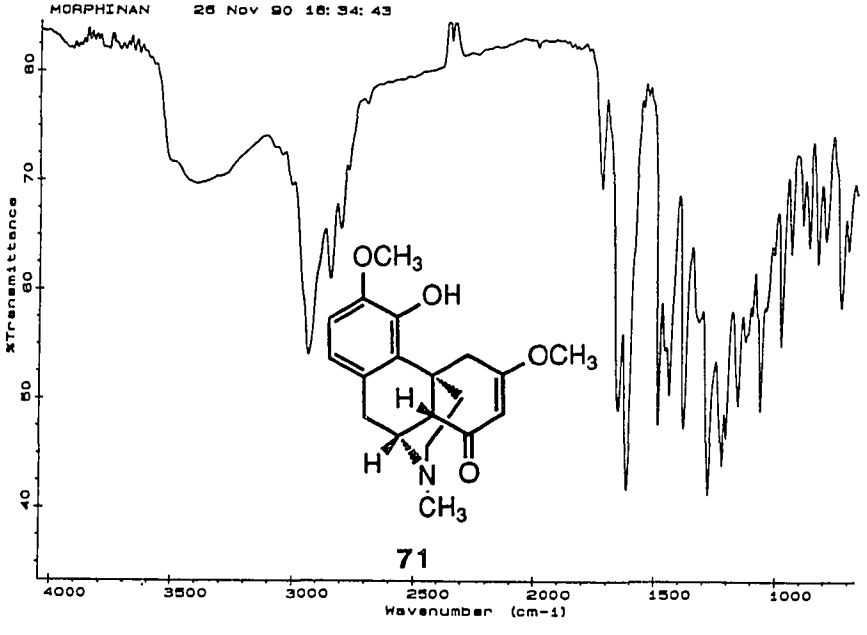
145


PERKIN-ELMER
CHART #199-1042
OCH3
O
NCH3
OCH3
O
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
SCAN TIME
MULTIPLIER
SLIT PROGRAM
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

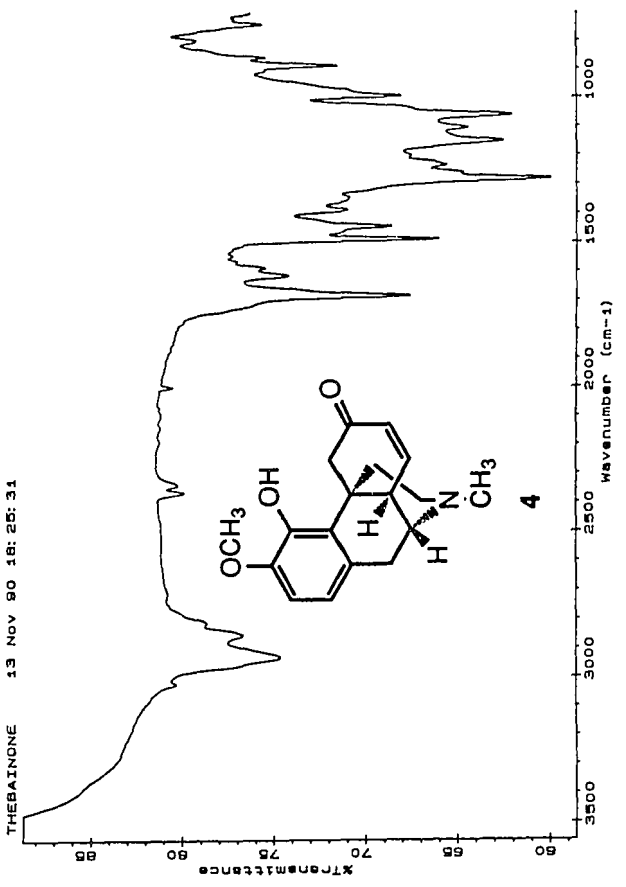
144


PERKIN-ELMER
CHART #199-1042
TRANSMISSION (%)
WAVE NUMBER (CM-1)
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
SCAN TIME
MULTIPLIER
REP SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
OCH3
OH
O
H
N
CH3

5

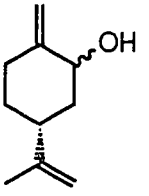

MORPHINAN
26 Nov 90 16:34:43
%Transmittance
Wavenumber (cm-1)
OCH3
OH
OCH3
H
H
N
O
CH3

71

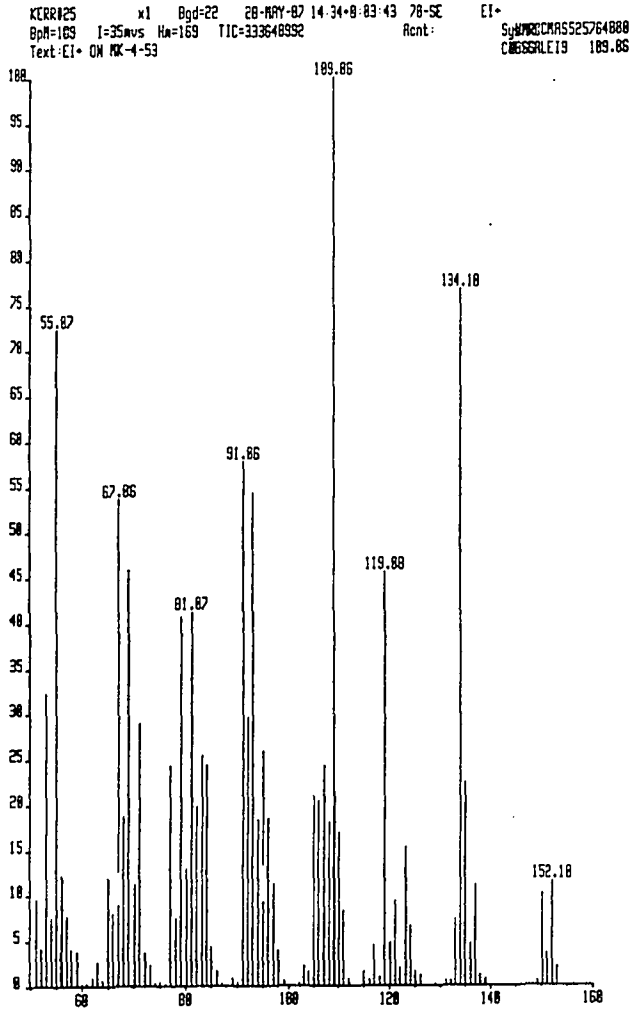

THEBAINONE 13 Nov 90 18:25:31
%Transmittance
85
80
75
70
65
60
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
OCH3
OH
O
H
H
N
CH3
4

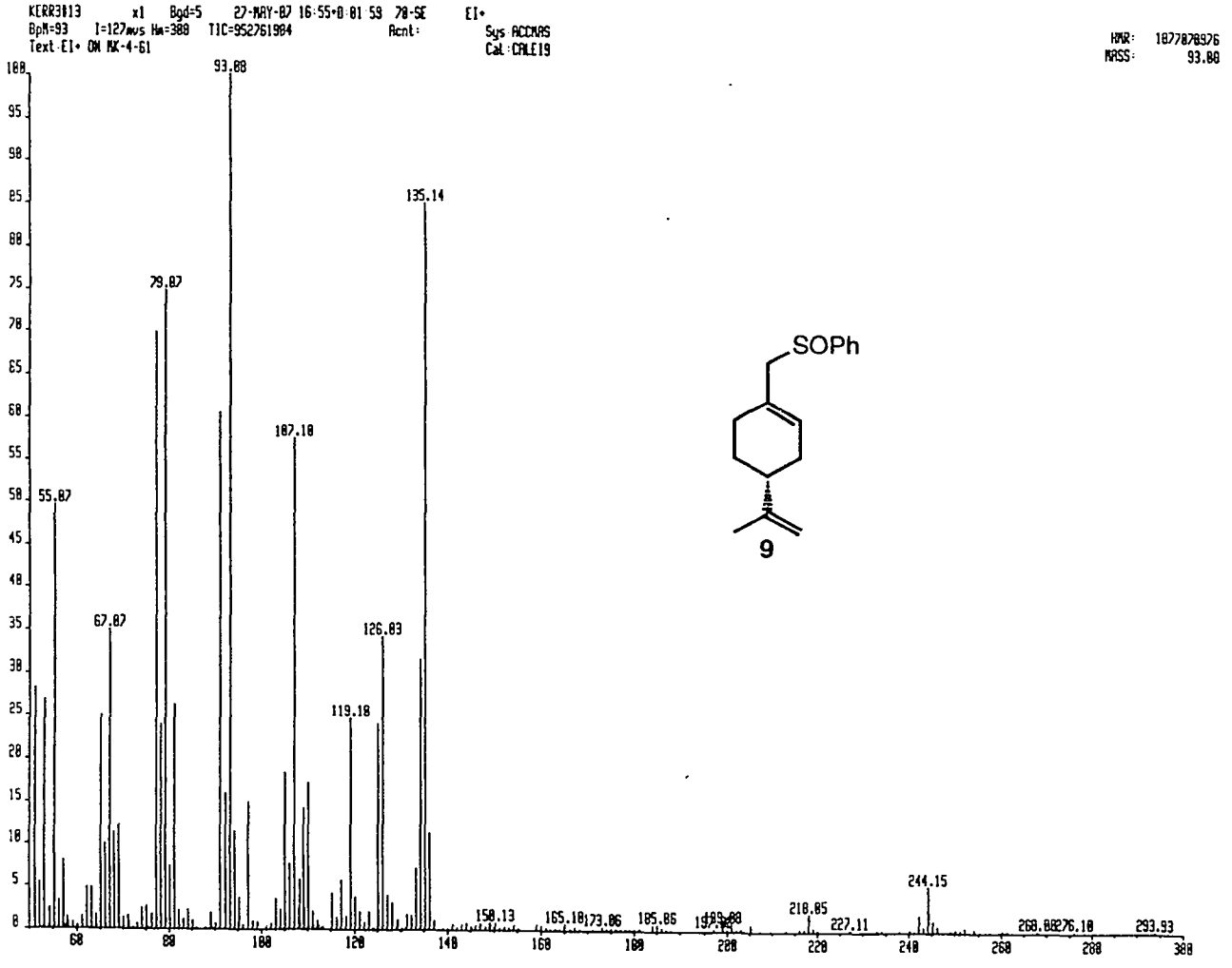
APPENDIX 4:

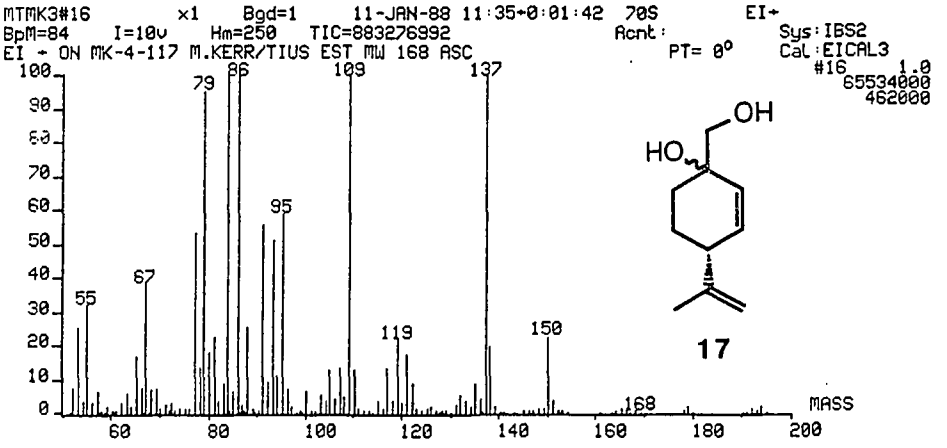
MASS SPECTRA FOR SELECTED COMPOUNDS

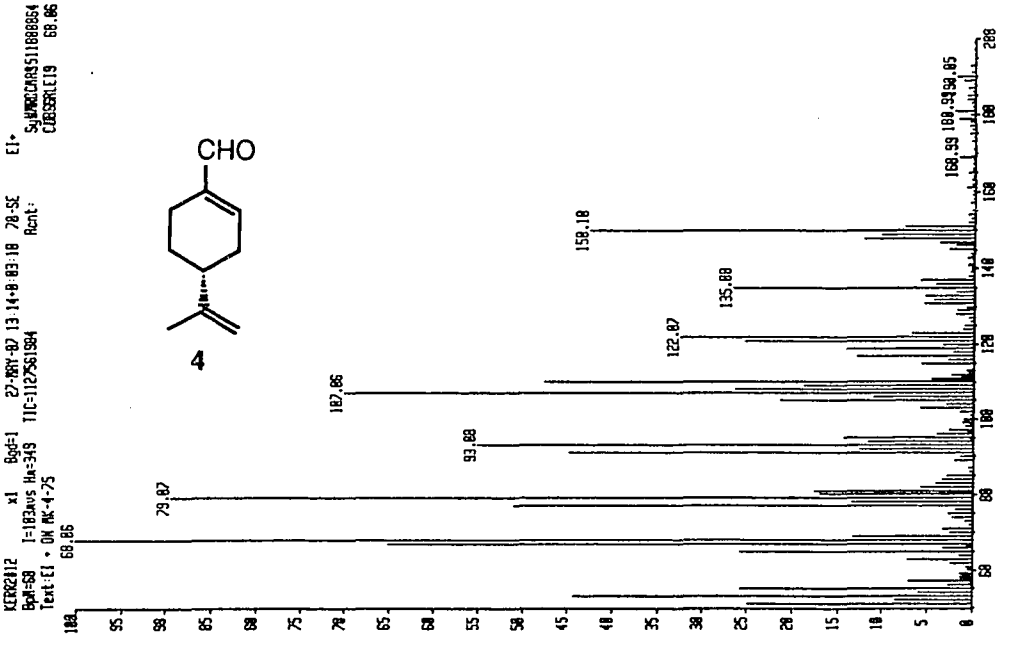


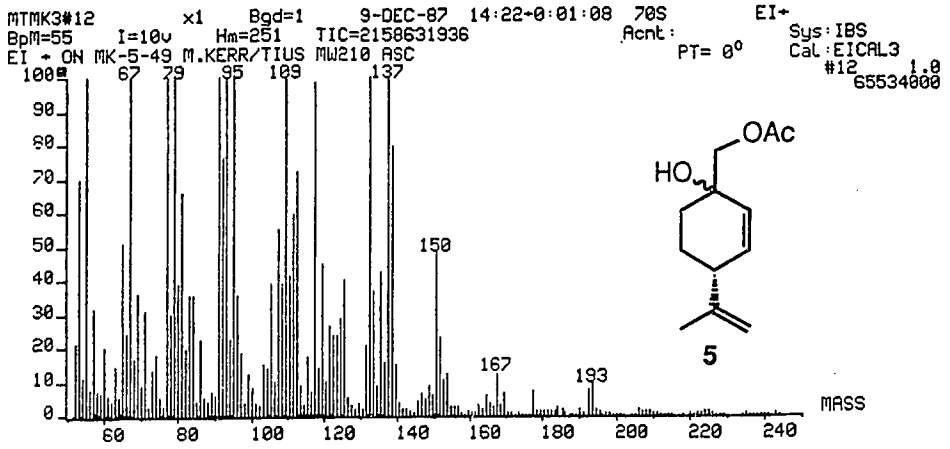
8

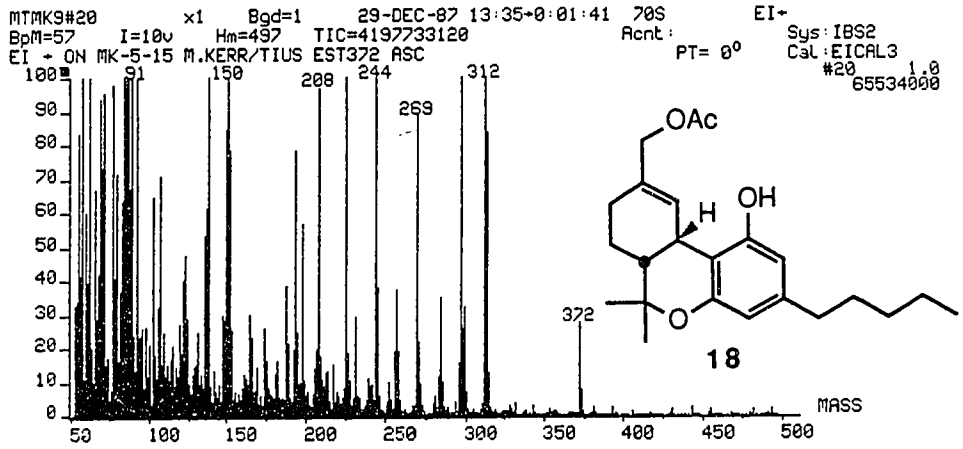


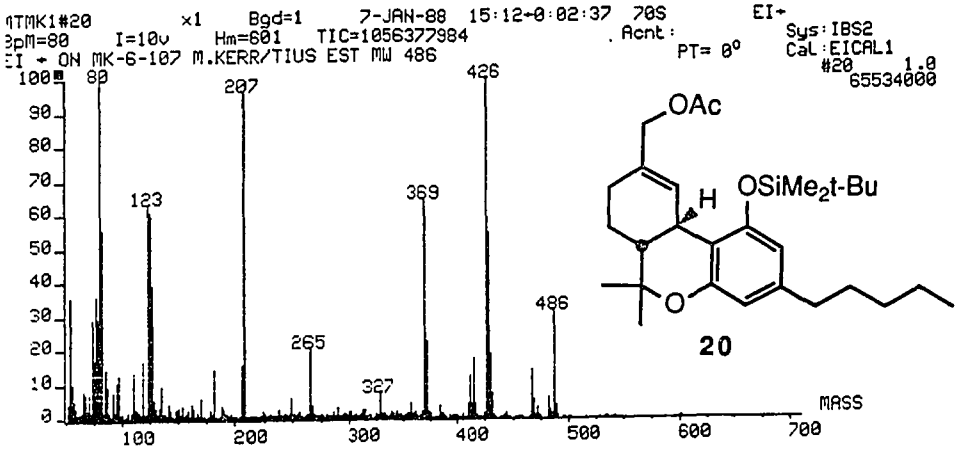

KERR3813 x1 Bgd=5 27-MAY-87 16:55+0:01 53 70-SE EI+
BpM=93 I=127mvs Hm=388 TIC=952761984 Acnt: Sys:ACCMAS
Text:EI+ ON MX-4-61 Cal:CALE19
MMR: 187878976
MASS: 93.00
93.00
135.14
79.07
107.10
55.07
67.07
126.03
119.10
244.15
218.05
227.11
158.13
165.10
173.06
185.06
SOPh
9

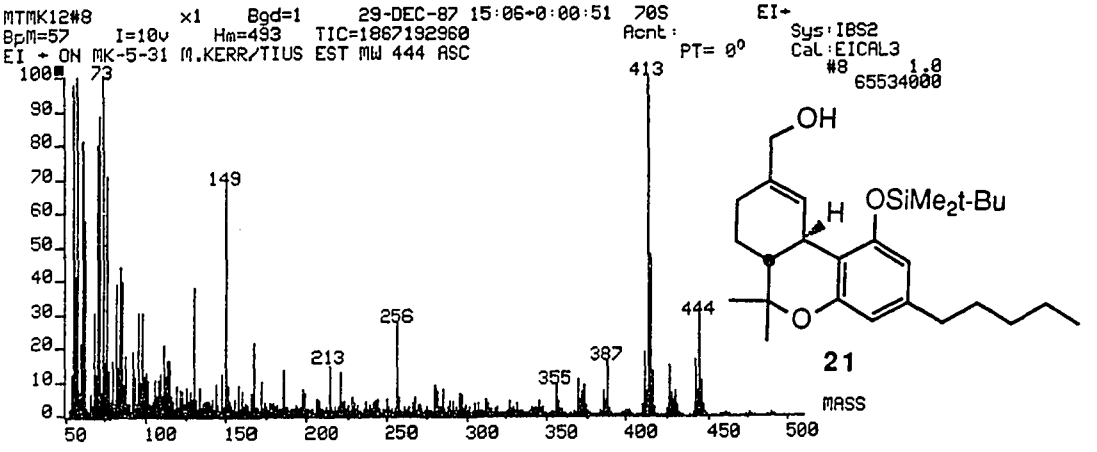

MTMK3#16 x1 Bgd=1 11-JAN-88 11:35+0:01:42 70S EI+
BpM=84 I=10v Hm=250 TIC=883276992 Rcnt: Sys:IBS2
EI + ON MK-4-117 M.KERR/TIUS EST MW 168 ASC PT= 0° Cal:EICAL3
#16 1.0
65534000
462000
OH
HO
17
MASS

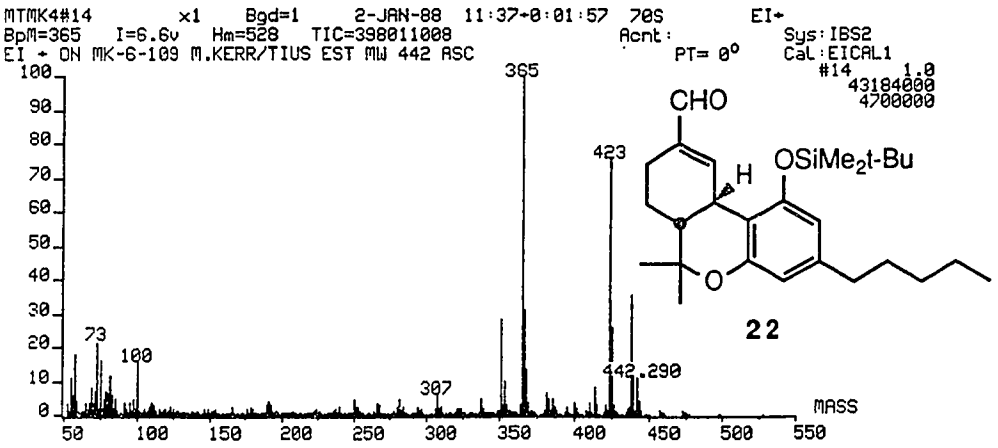

CHO
4

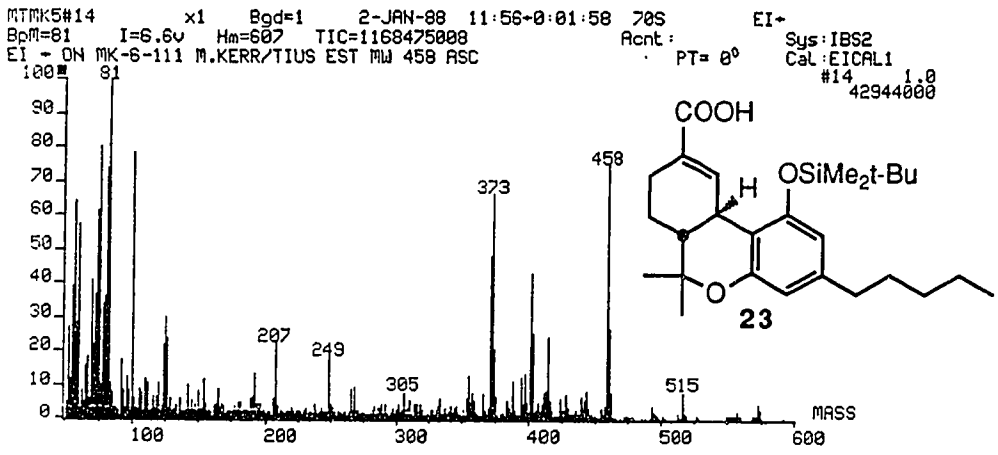

MTMK3#12 x1 Bgd=1 9-DEC-87 14:22+0:01:08 70S EI+
BpM=55 I=10v Hm=251 TIC=2158631936 Acnt: Sys:IBS
EI + ON MK-5-49 M.KERR/TIUS MW210 ASC PT= 0° Cal:EICAL3
#12 1.0
65534000
OAc
HO
5
MASS

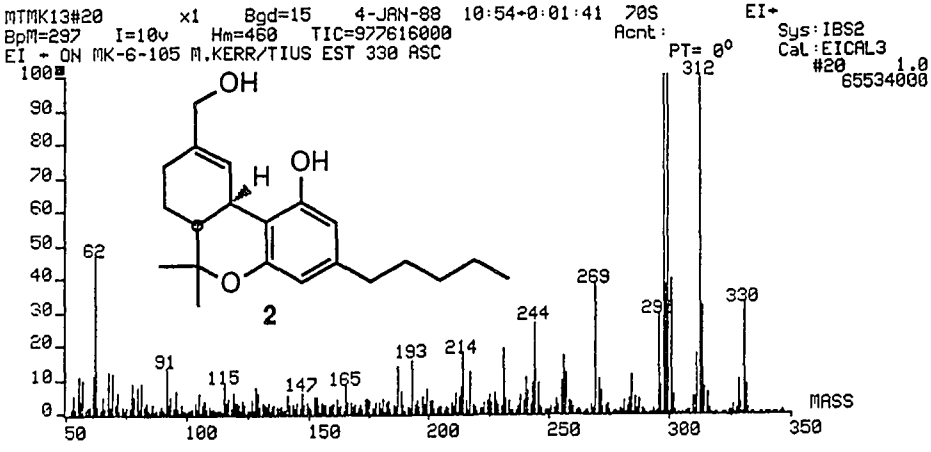

MTMK9#20 x1 Bgd=1 29-DEC-87 13:35+0:01:41 70S EI+
BpM=57 I=10v Hm=497 TIC=4197733120 Acnt: Sys:IBS2
EI + ON MK-5-15 M.KERR/TIUS EST372 ASC PT= 0° Cal:EICAL3
#20 1.0
65534000
OAc
H
OH
O
372
18
MASS

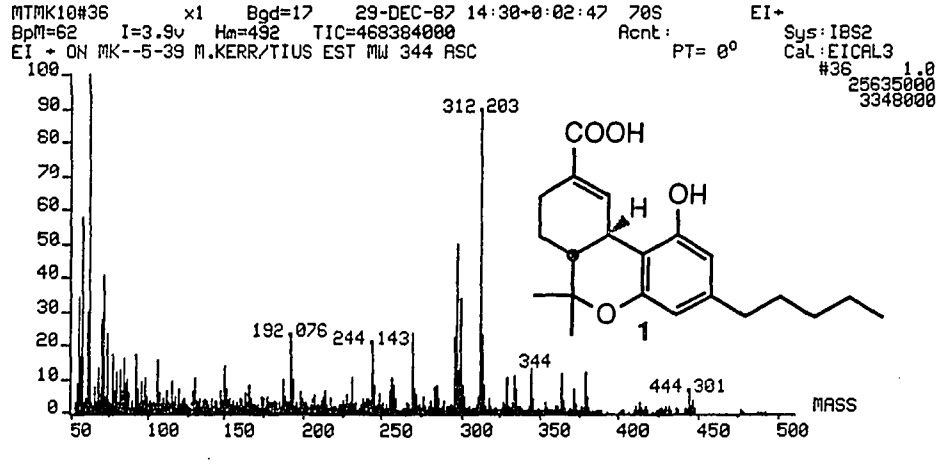

MTMK1#20 x1 Bgd=1 7-JAN-88 15:12+0:02:37 70S EI+
BpM=80 I=10v Hm=601 TIC=1056377984 Acnt: Sys:IBS2
EI + ON MK-6-107 M.KERR/TIUS EST MW 486 PT= 0° Cal:EICAL1
#20 1.0
65534000
OAc
H
OSiMe2t-Bu
O
20
MASS

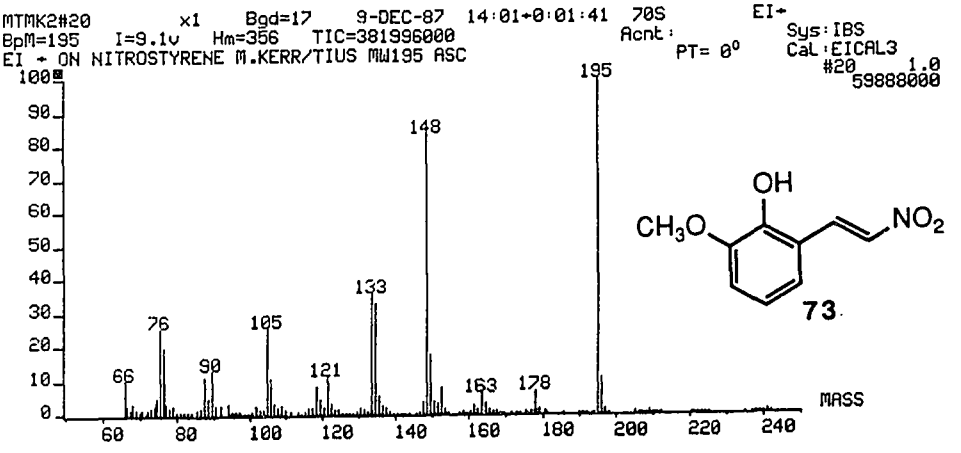

MTMK12#8 x1 Bgd=1 29-DEC-87 15:06+0:00:51 70S EI+
BpM=57 I=10v Hm=493 TIC=1867192960 Acnt: Sys:IBS2
EI + ON MK-5-31 M.KERR/TIUS EST MW 444 ASC PT= 0° Cal:EICAL3
#8 1.0
65534000
OH
H
OSiMe2t-Bu
O
21
MASS

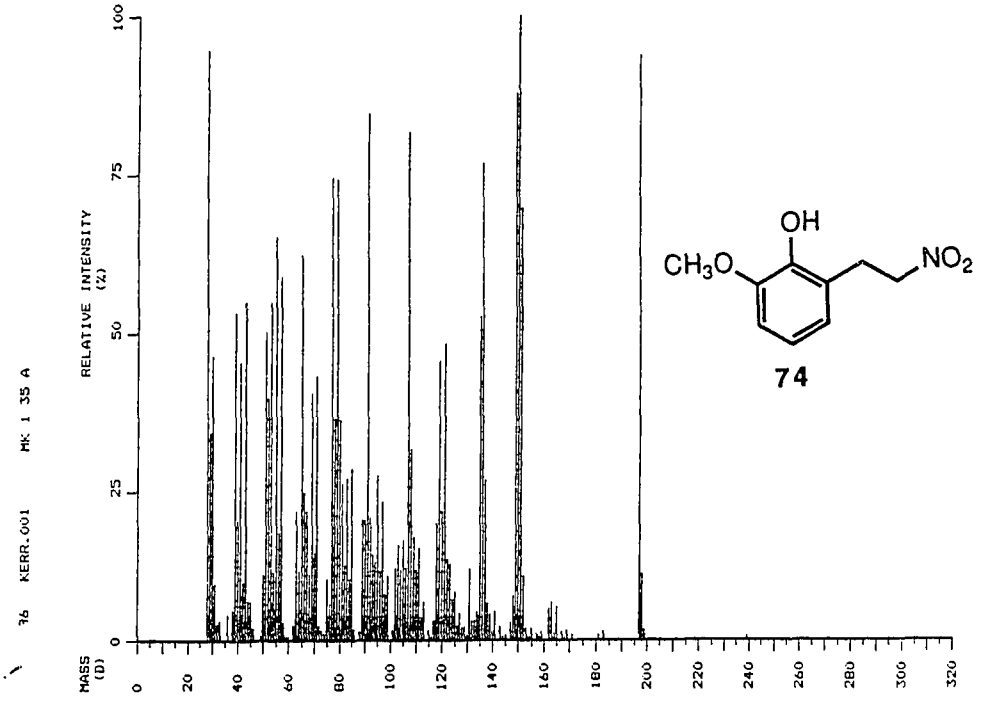

MTMK4#14 x1 Bgd=1 2-JAN-88 11:37+0:01:57 70S EI+
BpM=365 I=6.6v Hm=528 TIC=398011008 Acnt: Sys:IBS2
EI + ON MK-6-109 M.KERR/TIUS EST MW 442 ASC PT= 0° Cal:EICAL1
#14 1.0
43184000
4700000
365
423
73
100
307
442.290
MASS
CHO
H
OSiMe2t-Bu
O
22

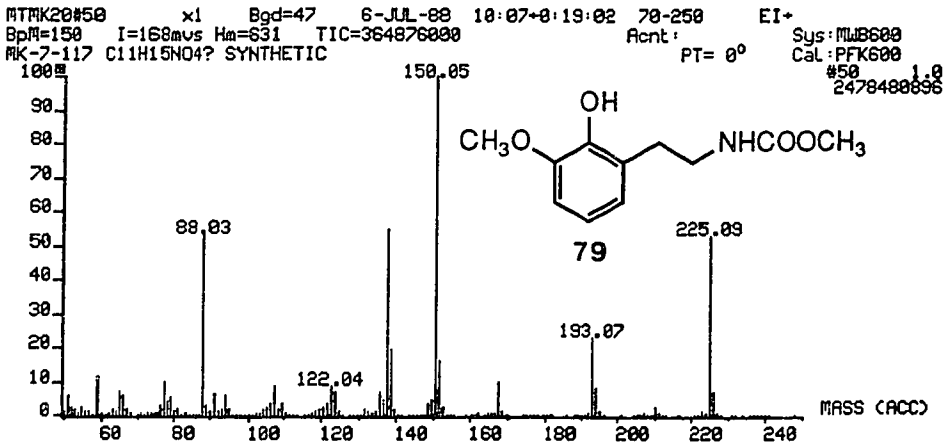

MTMK5#14 x1 Bgd=1 2-JAN-88 11:56+0:01:58 70S EI+
BpM=81 I=6.6v Hm=607 TIC=1168475008 Acnt: Sys:IBS2
EI + ON MK-6-111 M.KERR/TIUS EST MW 458 ASC PT= 0° Cal:EICAL1
#14 1.0
42944000
81
458
373
207
249
305
515
MASS
COOH
H
OSiMe2t-Bu
O
23

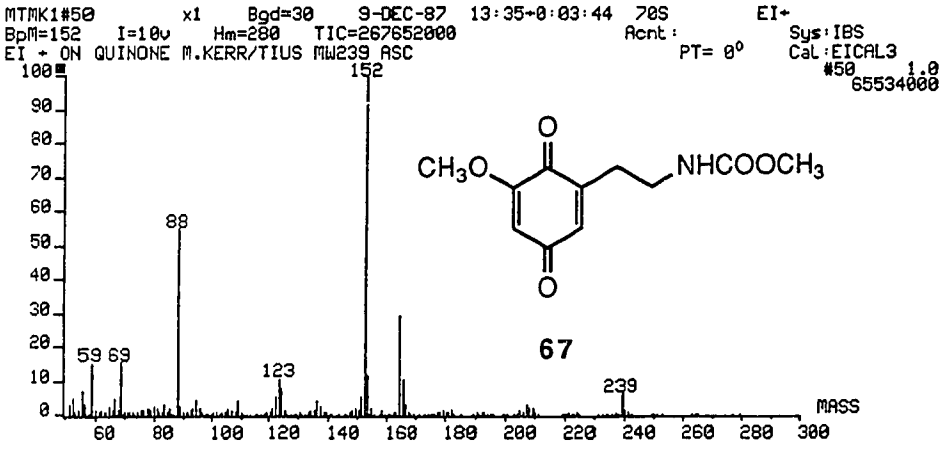

MTMK13#20 x1 Bgd=15 4-JAN-88 10:54+0:01:41 70S EI+
BpM=297 I=10v Hm=460 TIC=977616000 Acnt: Sys:IBS2
EI + ON MK-6-105 M.KERR/TIUS EST 330 ASC PT= 0° Cal:EICAL3
#20 1.0
65534000
OH
H
OH
O
2
62
91
115
147
165
193
214
244
269
298
312
330
MASS

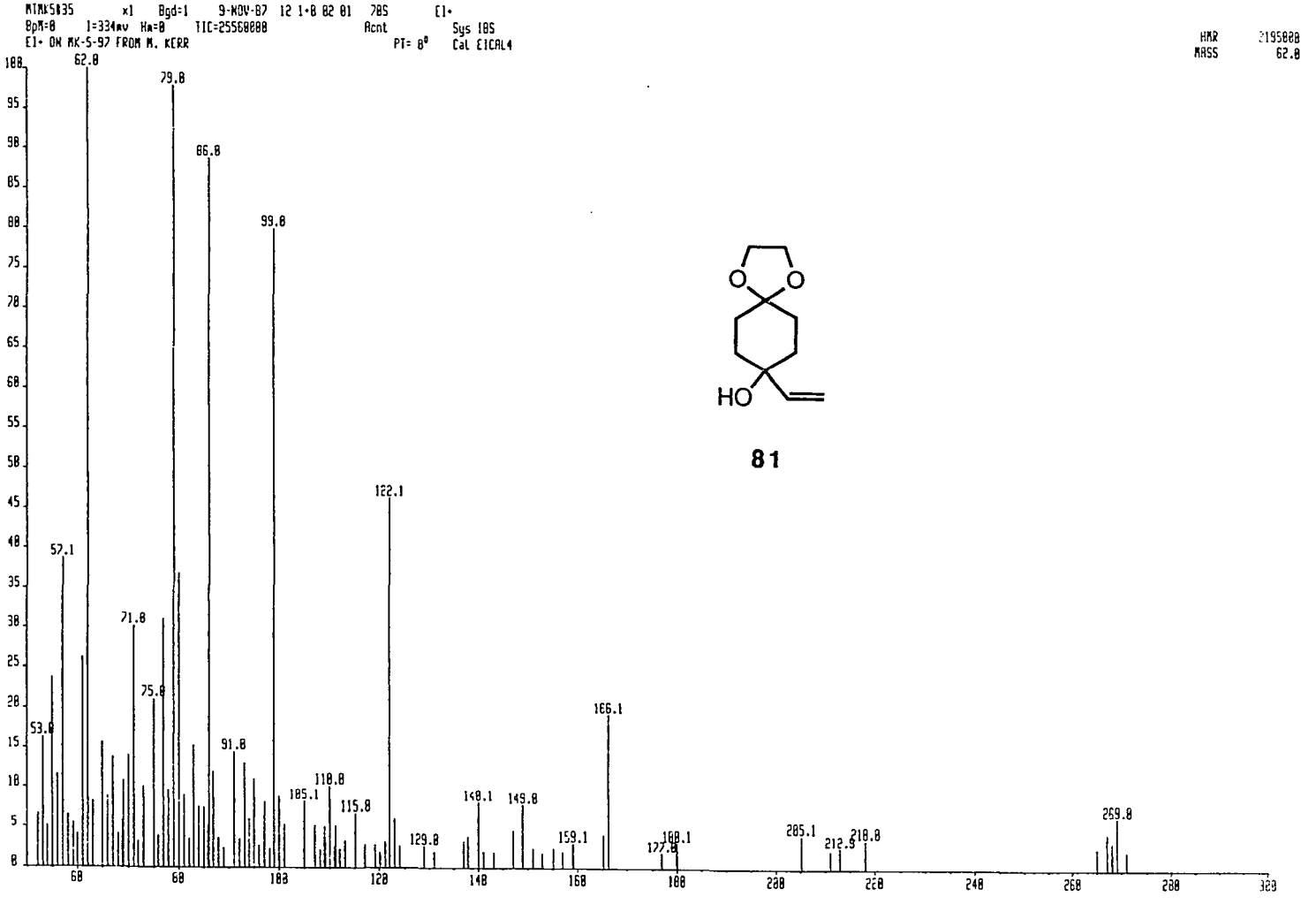

MTMK10#36 x1 Bgd=17 29-DEC-87 14:30+0:02:47 70S EI+
BpM=62 I=3.9v Hm=492 TIC=468384000 Acnt: Sys:IBS2
EI + ON MK--5-39 M.KERR/TIUS EST MW 344 ASC PT= 0° Cal:EICAL3
#36 1.0
25635000
3348000
COOH
H
OH
O
1
192.076
244
143
312.203
344
444.301
MASS

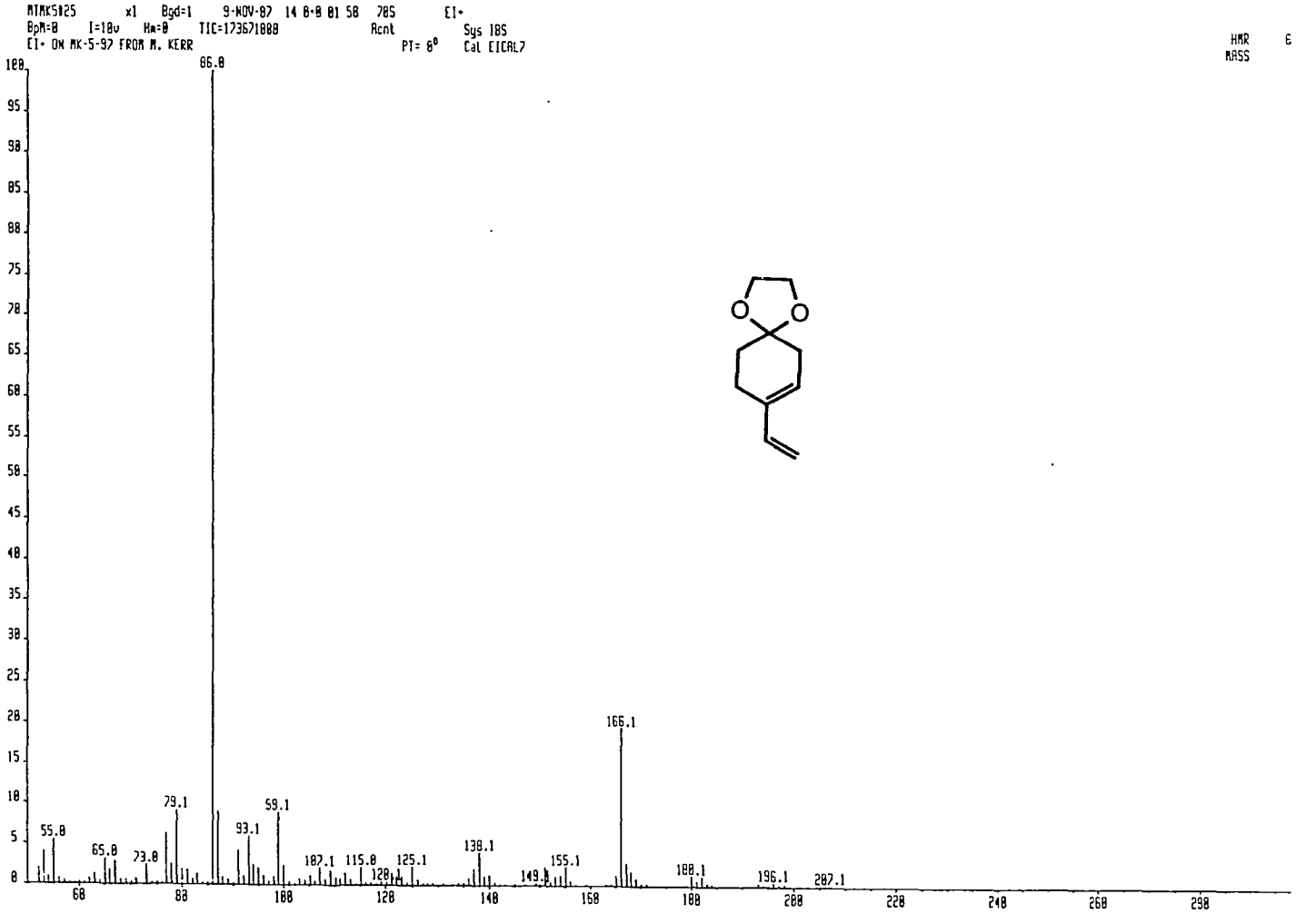

MTMK2#20 x1 Bgd=17 9-DEC-87 14:01→0:01:41 70S EI→
BpM=195 I=9.1v Hm=356 TIC=381996000 Acnt: Sys:IBS
EI + ON NITROSTYRENE M.KERR/TIUS MW195 ASC PT= 0° CaL:EICAL3
#20 1.0
59888000
195
148
133
76
105
90
66
121
163
178
MASS
OH
CH3O
NO2
73

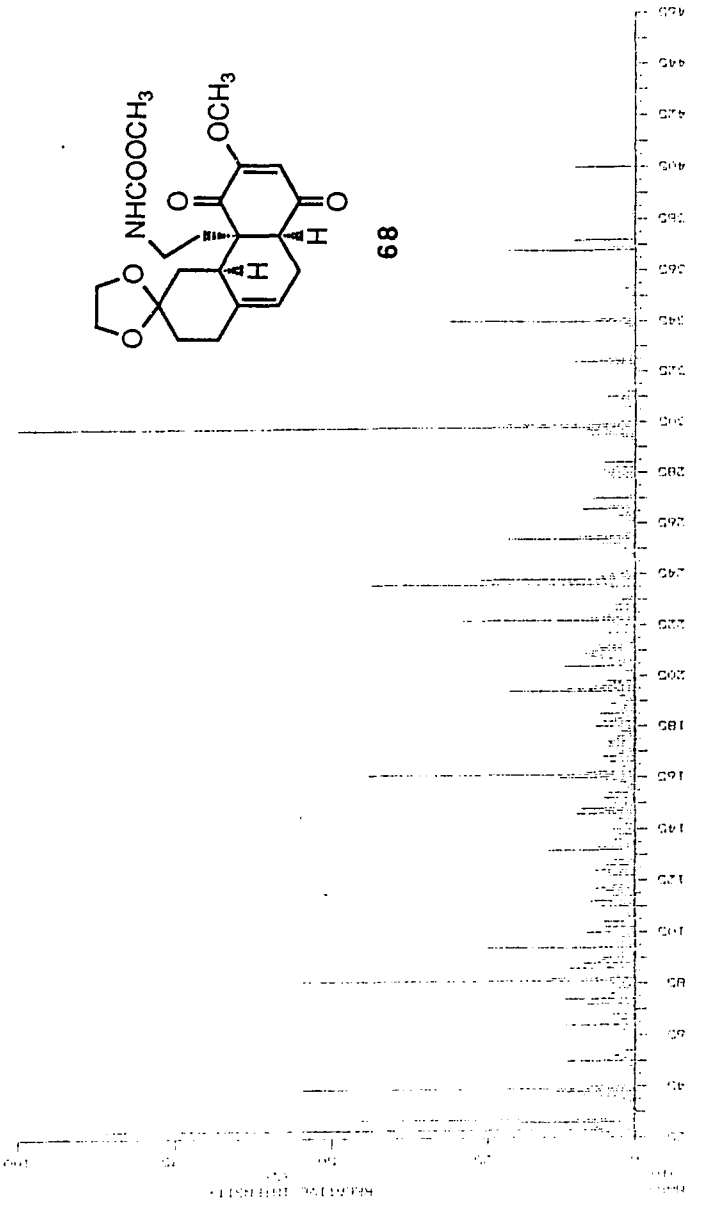

RELATIVE INTENSITY (%)
MASS (D)
OH
CH3O
NO2
74


MTMK20#50 x1 Bgd=47 6-JUL-88 10:07+0:19:02 70-250 EI+
BpM=150 I=168mvs Hm=631 TIC=364876000 Acnt: Sys:MWB600
MK-7-117 C11H15NO4? SYNTHETIC PT= 0° Cal:PFK600
#50 1.0
2478480896
150.05
88.03
225.09
193.07
122.04
OH
CH3O
NHCOOCH3
79
MASS (ACC)

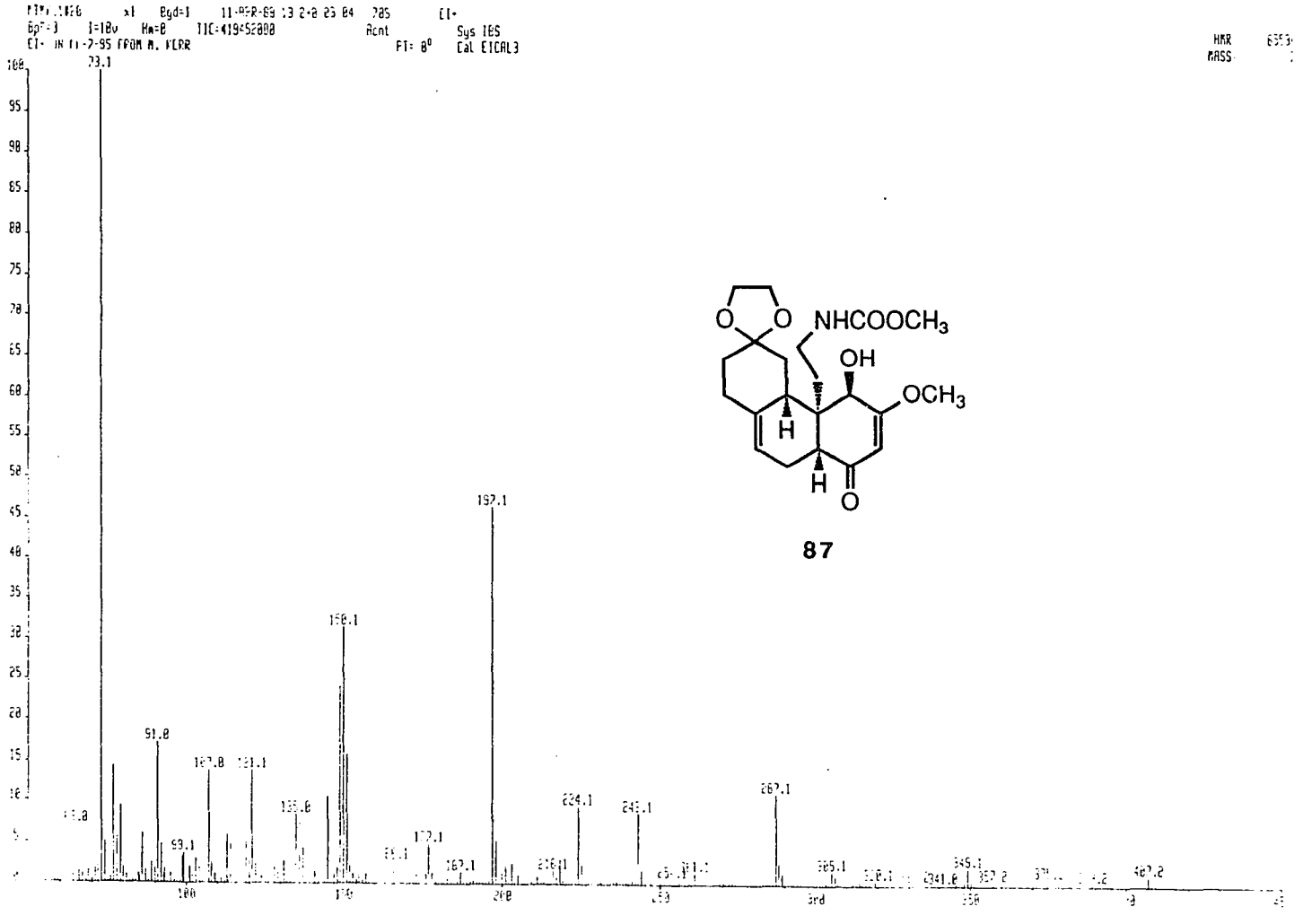

MTMK1#50 x1 Bgd=30 9-DEC-87 13:35+0:03:44 70S EI+
BpM=152 I=10v Hm=280 TIC=267652000 Acnt: Sys:IBS
EI + ON QUINONE M.KERR/TIUS MW239 ASC PT= 0° Cal:EICAL3
#50 1.0
65534000
152
88
59 69
123
239
O
CH3O
NHCOOCH3
O
67
MASS


MTMK5835 x1 Bgd=1 9-NOV-87 12 1:8 82 81 78S EI+
BpM=8 I=334mv Ma=8 TIC=25560888 Acnt Sys 18S
EI+ ON MK-5-97 FROM M. KERR PT= 8° Cal EICAL4
HMR 2195888
MASS 62.8
62.8
79.8
86.8
99.8
122.1
57.1
71.8
75.8
53.8
91.8
118.8
105.1
115.8
129.8
140.1
149.8
159.1
166.1
177.8
180.1
205.1
212.9
218.8
269.8
HO
81

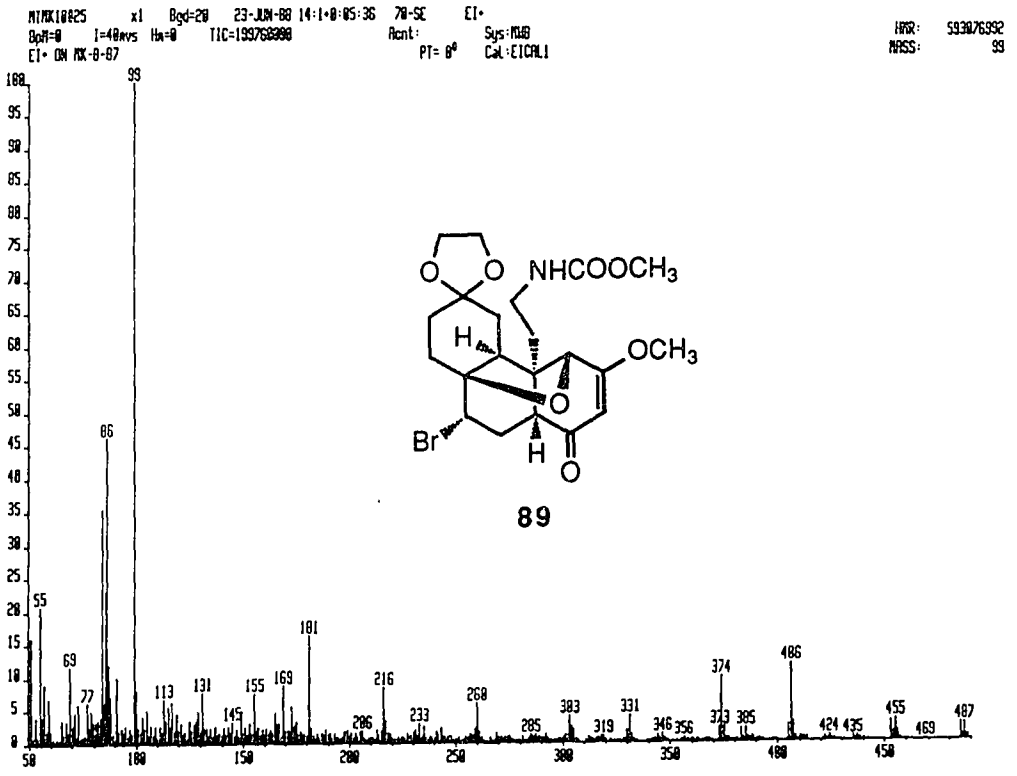

MTMK5025 x1 Bgd=1 9-NOV-87 14 8:8 01 58 705 EI+
BpM=8 I=18u Hm=8 TIC=173671888 Acnt Sys 185
EI+ ON MX-5-97 FROM M. KERR PT= 8° Cal EICAL7
HMR 6
MASS
86.8
166.1
79.1
59.1
55.8
93.1
65.8
73.8
107.1
115.8
125.1
120.1
138.1
149.1
155.1
188.1
196.1
207.1

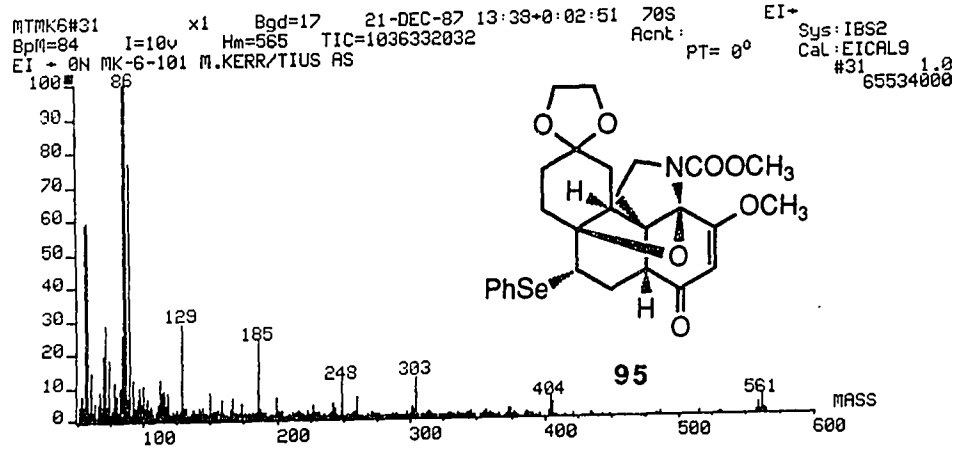


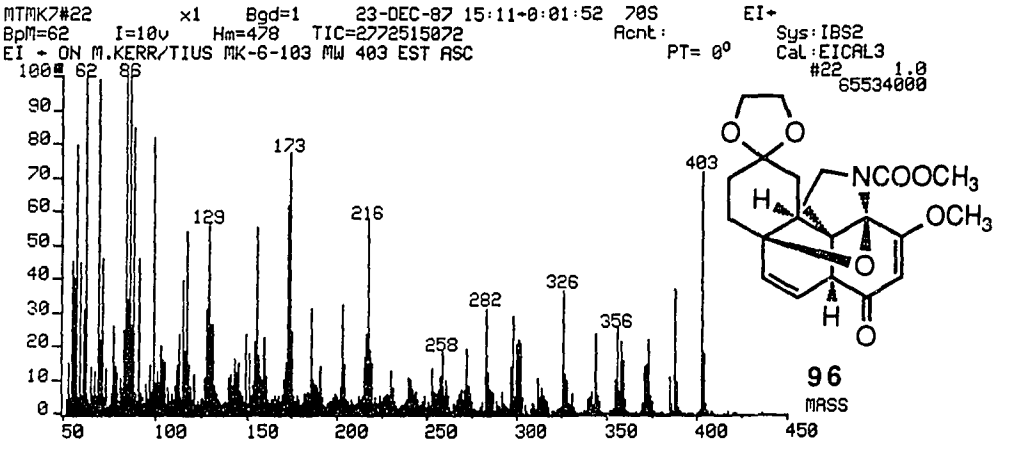
68

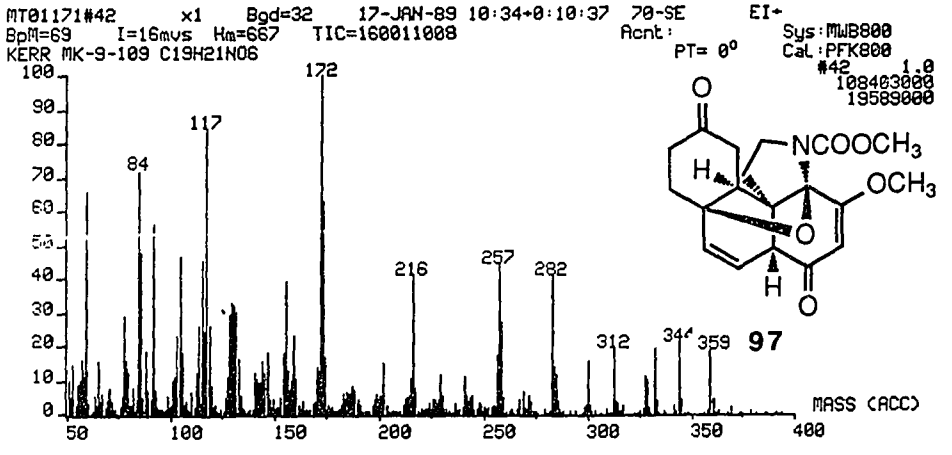


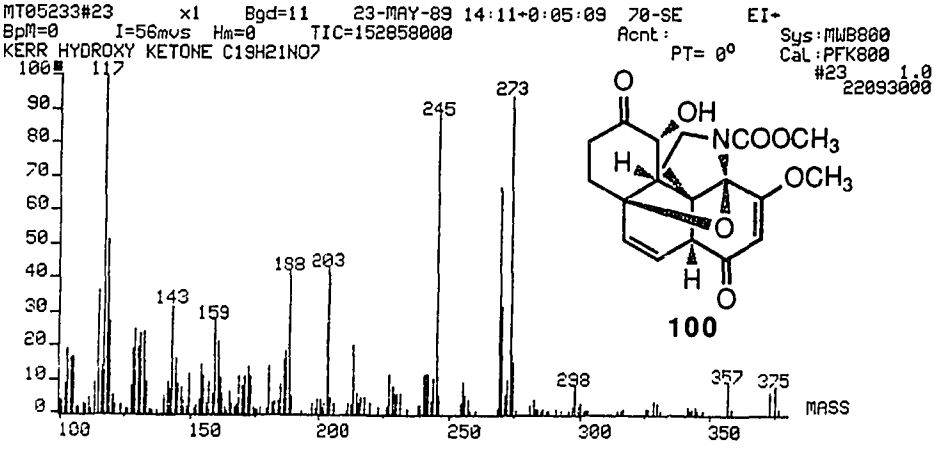
87

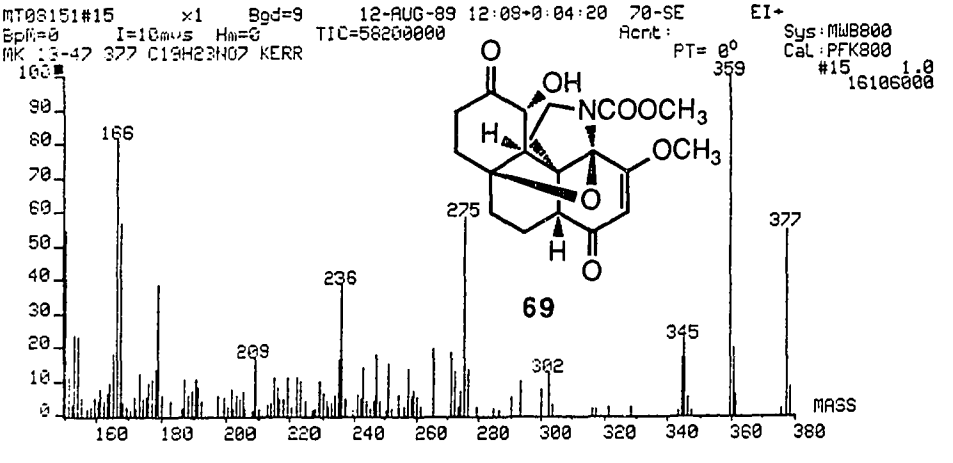

NHCOOCH3
OCH3
Br
H
O
89

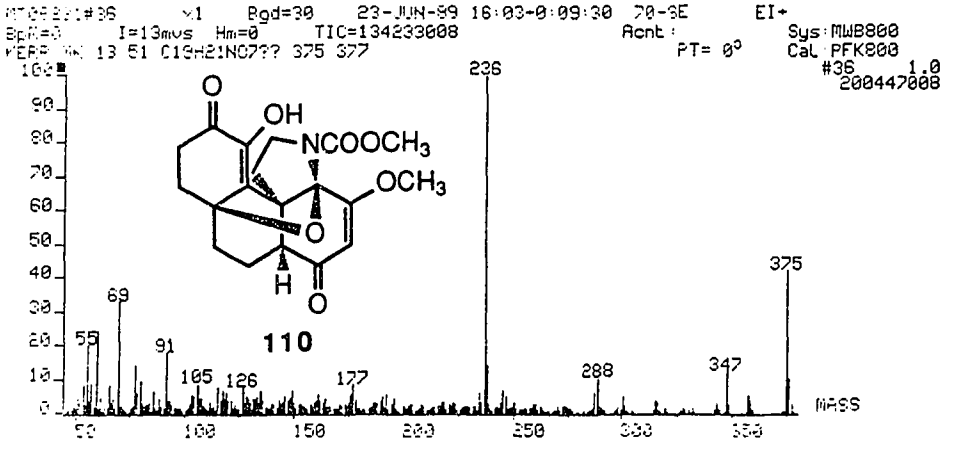

NCOOCH3
OCH3
PhSe
H
O
95
MASS

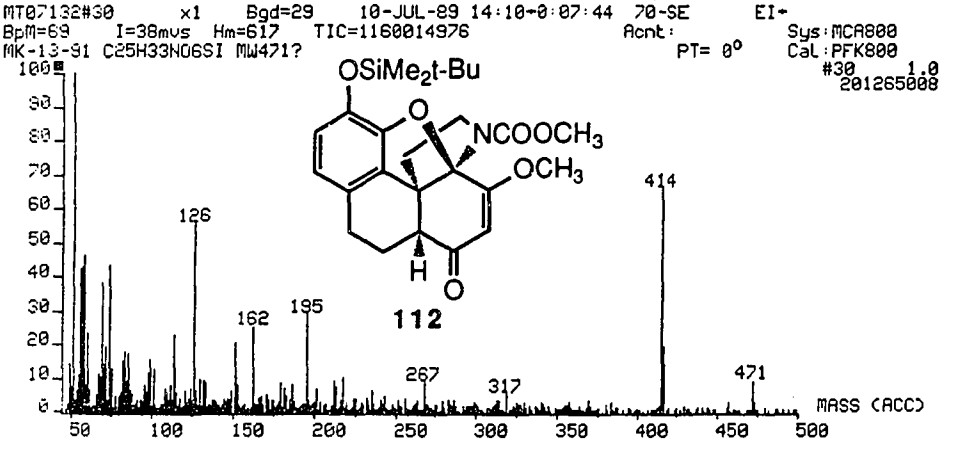

MTMK7#22 x1 Bgd=1 23-DEC-87 15:11+0:01:52 70S EI+
BpM=62 I=10v Hm=478 TIC=272515072 Acnt: Sys:IBS2
EI + ON M.KERR/TIUS MK-6-103 MW 403 EST ASC PT= 0° Cal:EICAL3
#22 1.0
65534000
62
86
173
129
216
403
282
326
356
258
NCOOCH3
OCH3
96
MASS

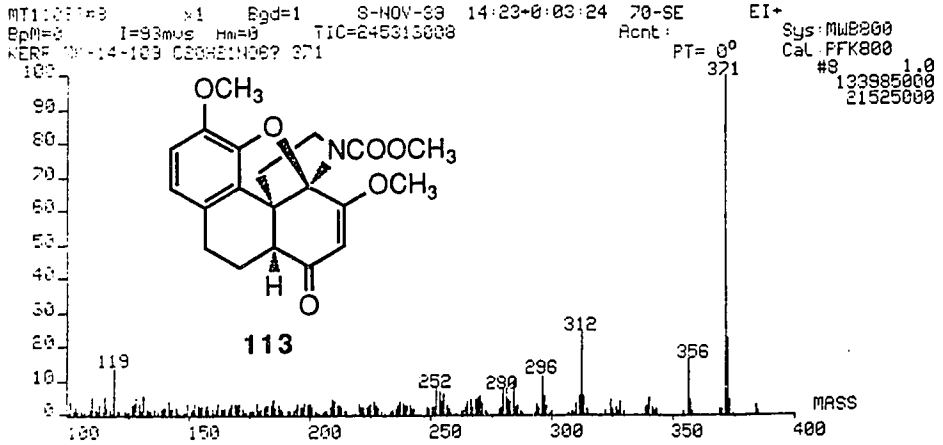

MT01171#42 x1 Bgd=32 17-JAN-89 10:34+0:10:37 70-SE EI+
BpM=69 I=16mvs Hm=667 TIC=160011008 Acnt: Sys:MWB800
KERR MK-9-109 C19H21NO6 PT= 0° Cal:PFK800
#42 1.0
108403000
19589000
172
117
84
216
257
282
312
344
359
NCOOCH3
OCH3
97
MASS (ACC)

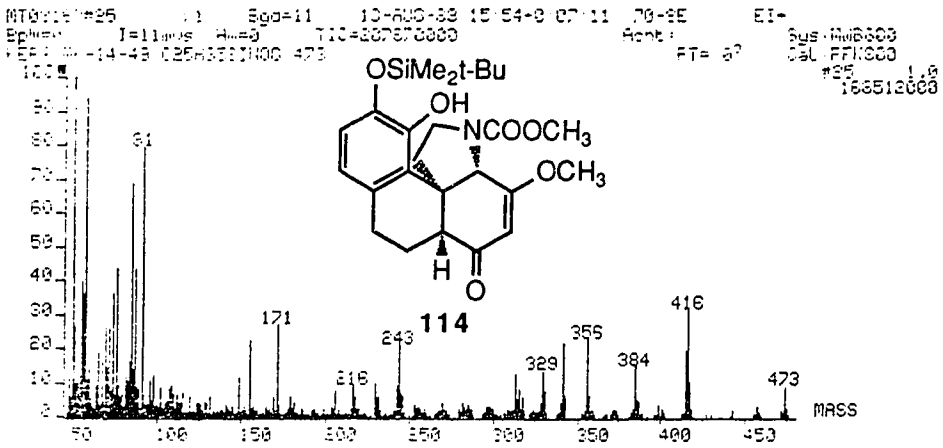

MT05233#23 x1 Bgd=11 23-MAY-89 14:11+0:05:09 70-SE EI+
BpM=0 I=56mvs Hm=0 TIC=152858000 Acnt: Sys:MWB800
KERR HYDROXY KETONE C19H21NO7 PT= 0° Cal:PFK800
#23 1.0
22093000
117
273
245
198 203
143
159
298
357 375
MASS
100
100 150 200 250 300 350
OH
NCOOCH3
OCH3
H
O

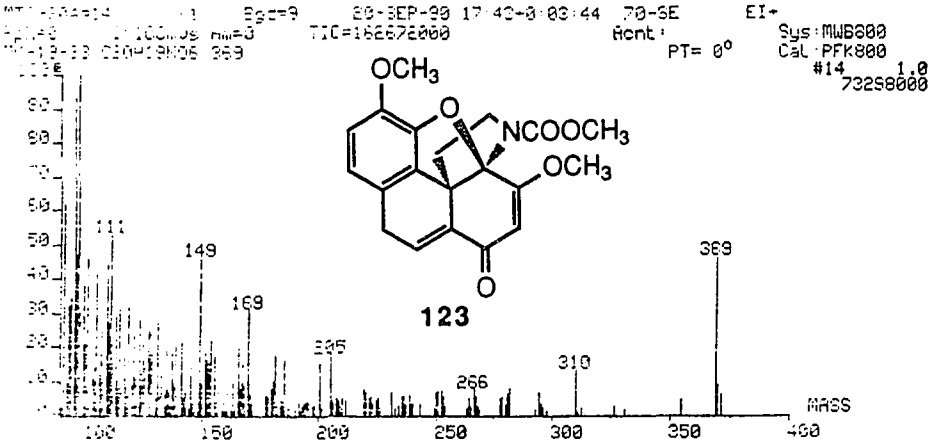

MT08151#15 x1 Bgd=9 12-AUG-89 12:08+0:04:20 70-SE EI+
BpM=0 I=10mvs Hm=0 TIC=58200000 Acnt: Sys:MWB800
MK 13-47 377 C19H23NO7 KERR PT= 0° Cal:PFK800
#15 1.0
16106000
166
359
377
275
236
345
209
302
MASS
160 180 200 220 240 260 280 300 320 340 360 380
OH
NCOOCH3
OCH3
H
O
69

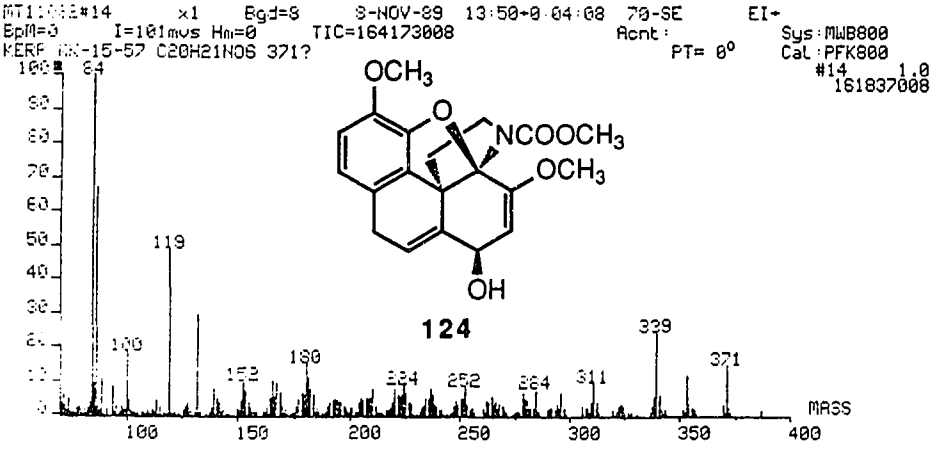

Bgd=30 23-JUN-89 16:03-0:09:30 70-SE EI+
I=13mvs Hm=0 TIC=134233008
Sys:MWB800
PT= 0°
Cal:PFK800
#36 1.0
200447008
OH
NCOOCH3
OCH3
O
H
O
110
236
375
69
55
91
105
126
177
288
347
MASS

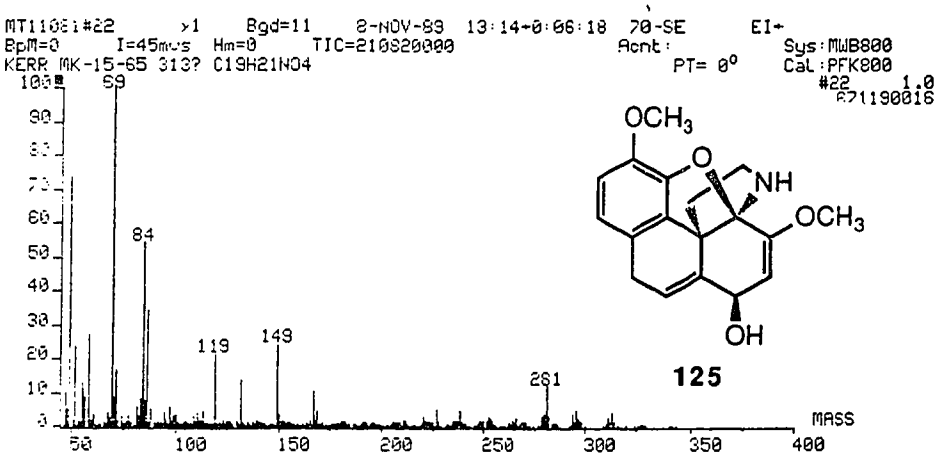

MT07132#30 x1 Bgd=29 10-JUL-89 14:10-0:07:44 70-SE EI+
BpM=69 I=38mvs Hm=617 TIC=1160014976
Sys:MCA800
MK-13-91 C25H33NO6SI MW471?
PT= 0°
Cal:PFK800
#30 1.0
201265008
OSiMe2t-Bu
O
NCOOCH3
OCH3
H
O
112
126
162
195
267
317
414
471
MASS (ACC)

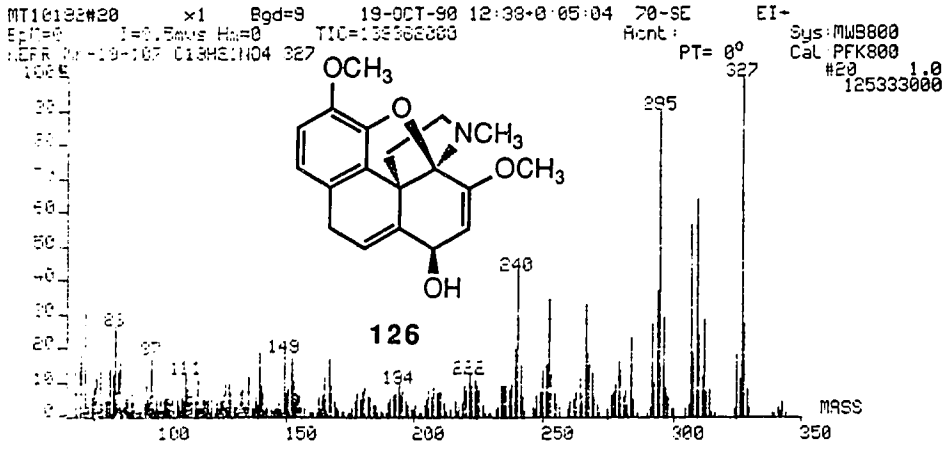

OCH3
O
NCOOCH3
OCH3
H
O
113
371
312
356
296
252
290
119
MASS
100
150
200
250
300
350
400

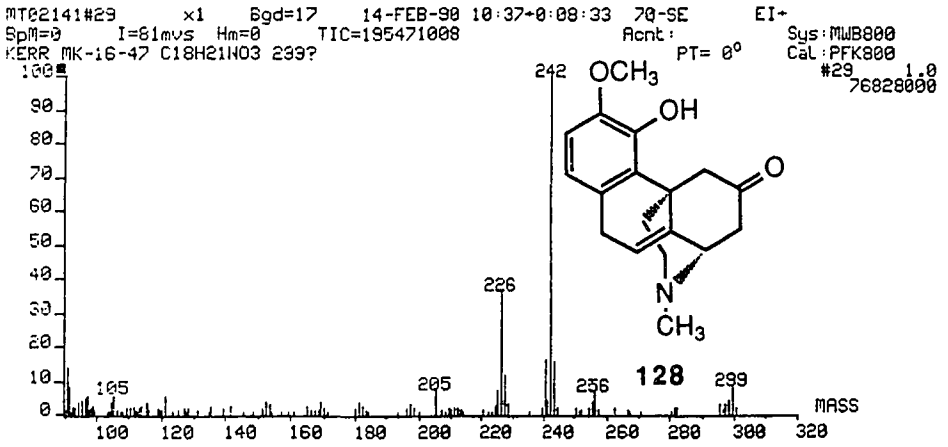

OSiMe2t-Bu
OH
NCOOCH3
OCH3
H
O
114
416
356
384
329
243
171
316
473
MASS
50
100
150
200
250
300
350
400
450

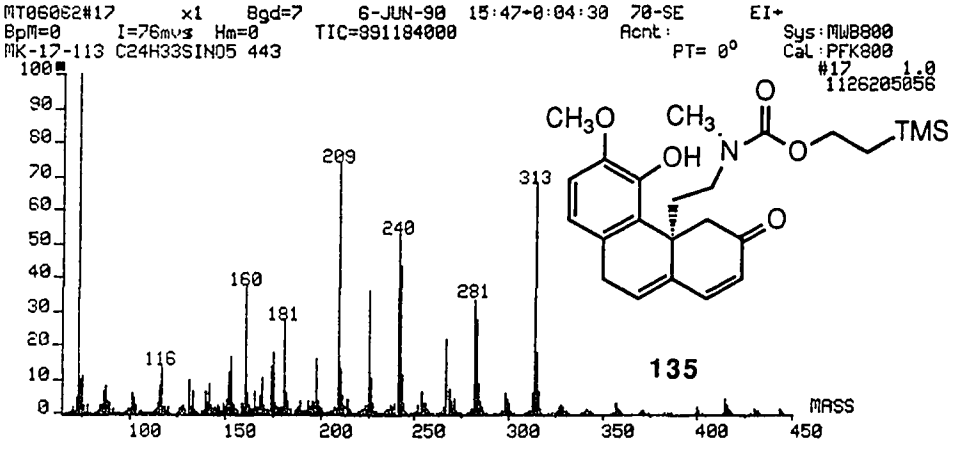

OCH3
O
NCOOCH3
OCH3
O
123
111
149
169
205
266
310
369
MASS
100
150
200
250
300
350
400

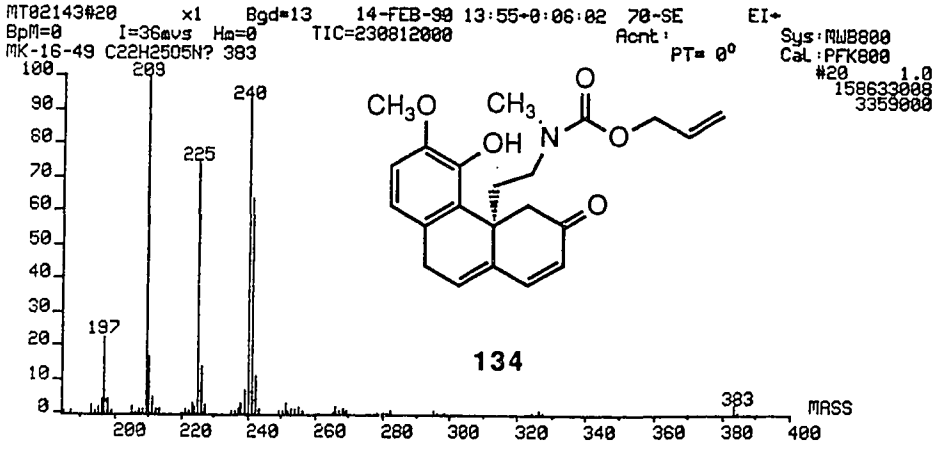

OCH3
O
NCOOCH3
OCH3
OH
124
84
119
100
152
180
224
252
264
311
339
371
MASS
100
150
200
250
300
350
400

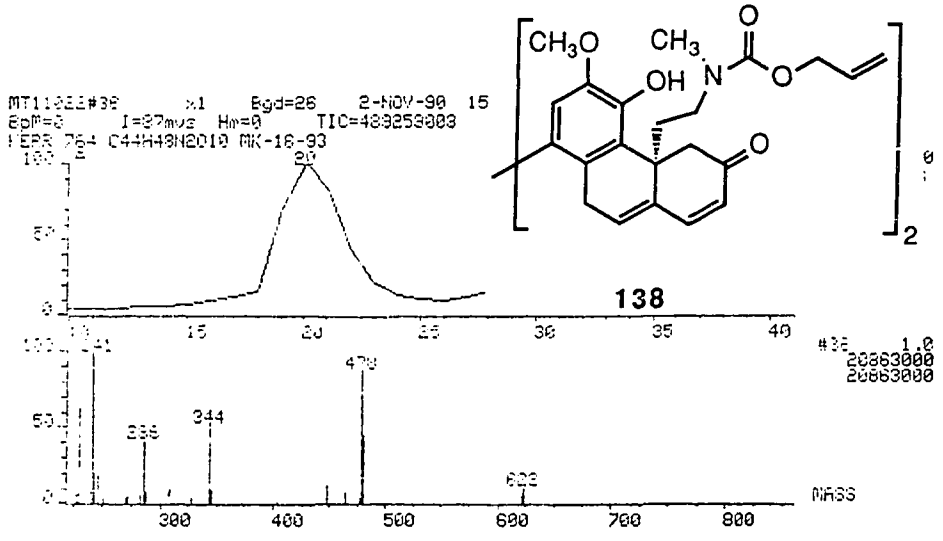

MT110E1#22 ×1 Bgd=11 8-NOV-89 13:14+0:06:18 70-SE EI+
BpM=0 I=45mVs Hm=0 TIC=210820000 Acnt: Sys:MWB800
KERR MK-15-65 313? C19H21NO4 PT= 0° Cal:PFK800
#22 1.0
84
119
149
281
MASS
50 100 150 200 250 300 350 400
OCH3
O
NH
OCH3
OH
125

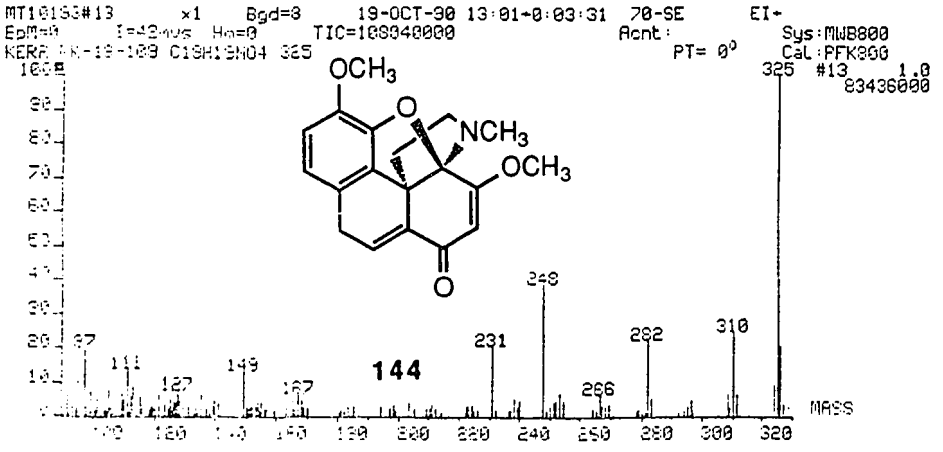

MT10102#20 ×1 Bgd=9 19-OCT-90 12:38+0:05:04 70-SE EI+
Sys:MWB800
Cal PFK800
#20 1.0
125333000
327
295
240
149
194
232
MASS
100 150 200 250 300 350
OCH3
O
NCH3
OCH3
OH
126

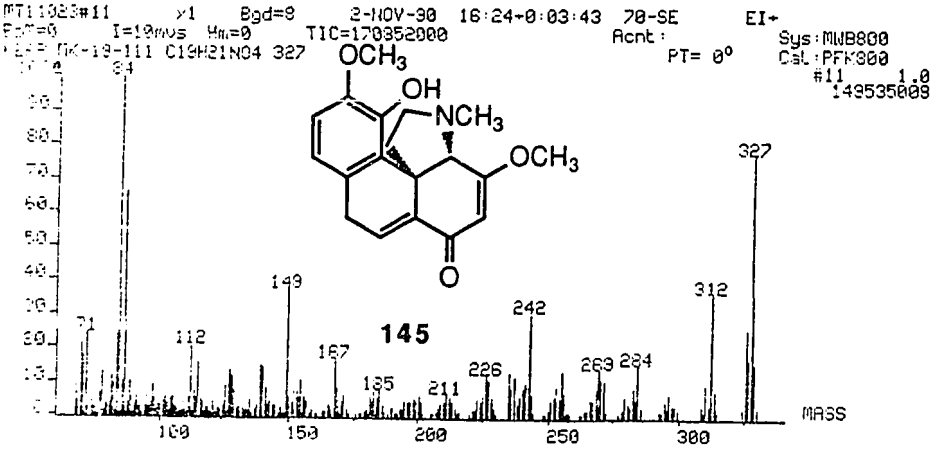

MT02141#29 x1 Bgd=17 14-FEB-90 10:37+0:08:33 70-SE EI+
BpM=0 I=81mvs Hm=0 TIC=195471008 Acnt: Sys:MWB800
KERR MK-16-47 C18H21NO3 299? PT= 0° Cal:PFK800
#29 1.0
76828000
242
OCH3
OH
O
226
N
CH3
128
105
205
256
299
MASS
100 120 140 160 180 200 220 240 260 280 300 320

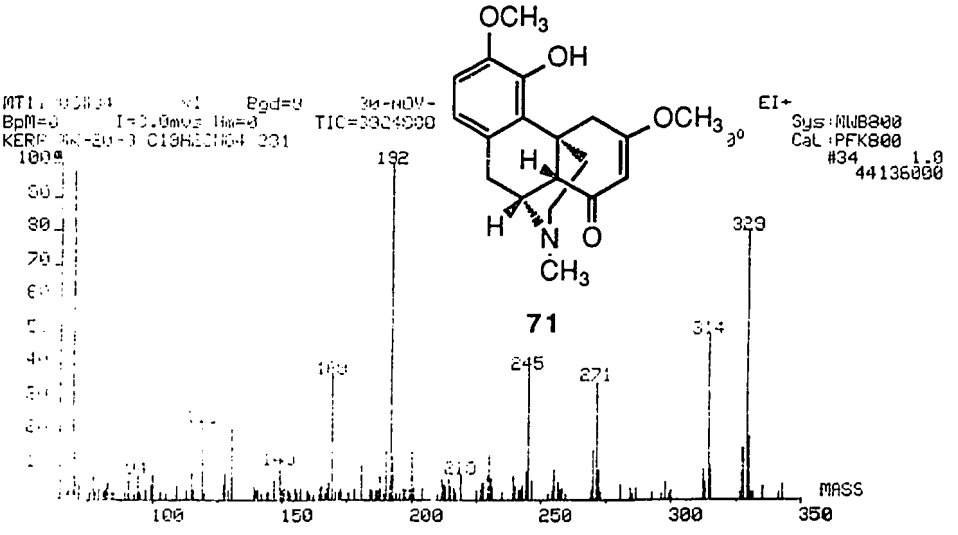

MT06082#17 x1 Bgd=7 6-JUN-90 15:47+0:04:30 70-SE EI+
BpM=0 I=76mvs Hm=0 TIC=991184000 Acnt: Sys:MWB800
MK-17-113 C24H33SINO5 443 PT= 0° Cal:PFK800
#17 1.0
1126205056
O
CH3O
CH3
N
O
TMS
OH
313
209
240
281
160
181
116
O
135
MASS
100 150 200 250 300 350 400 450

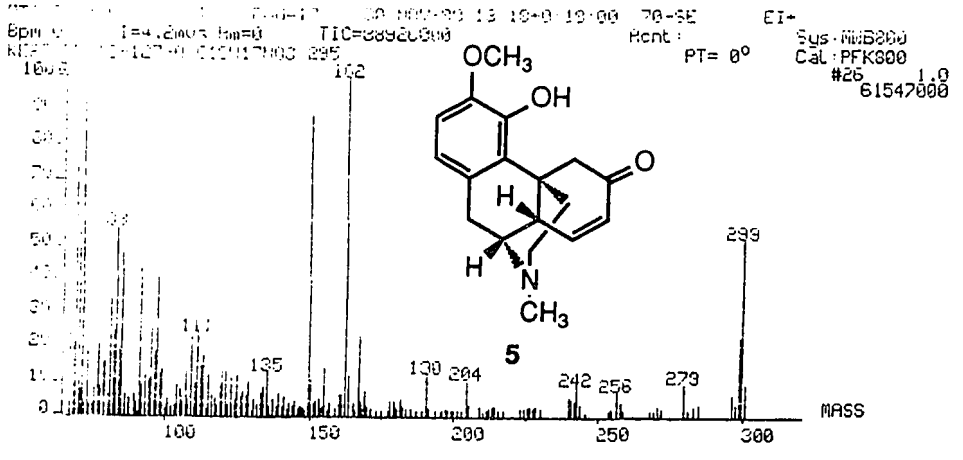

MT02143#20 x1 Bgd=13 14-FEB-90 13:55-0:06:02 70-SE EI+
BpM=0 I=36mvs Hm=0 TIC=230812000 Acnt: Sys:MWB800
MK-16-49 C22H2505N? 383 PT= 0° Cal:PFK800
#20 1.0
158633008
3359000
203
240
225
197
383
MASS
134

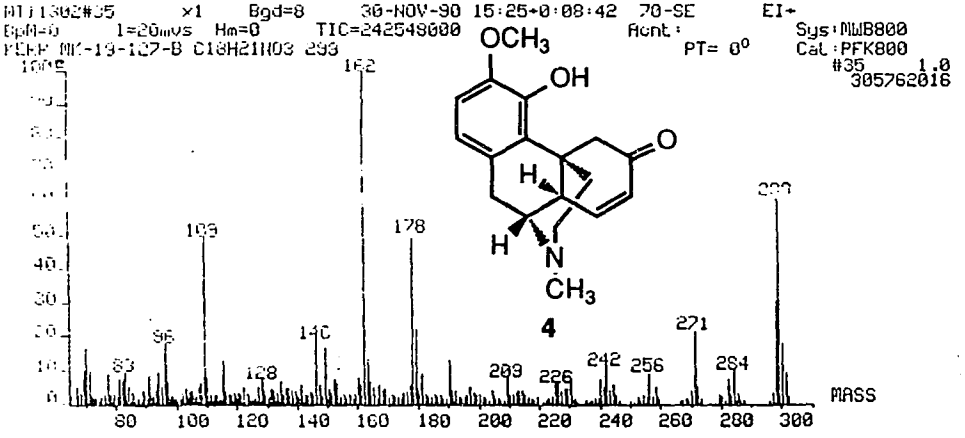

MT11022#38 x1 Bgd=26 2-NOV-90 15
BpM=0 I=87mvs Hm=0 TIC=489259003
HERB 784 C44H48N2O10 MK-16-93
20
138
#38 1.0
20863000
20863000
341
478
344
338
603
MASS


OCH3
O
NCH3
OCH3
O
144
MASS


OCH3
OH
NCH3
OCH3
O
145
MASS

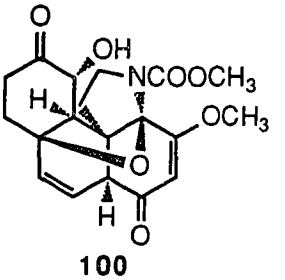

OCH3
OH
OCH3
3°
H
H
N
O
CH3
71
EI+
Sys:MWB800
CaL:PFK800
#34
44136000
192
329
314
245
271
169
MASS
100
150
200
250
300
350


OCH3
OH
O
H
H
N
CH3
5
EI+
PT= 0°
Sys:MWB800
CaL:PFK800
#26
61547000
102
299
135
130
204
242
256
279
MASS
100
150
200
250
300


OCH3
OH
O
H
H
N
CH3
4
MASS
80
100
120
140
160
180
200
220
240
260
280
300

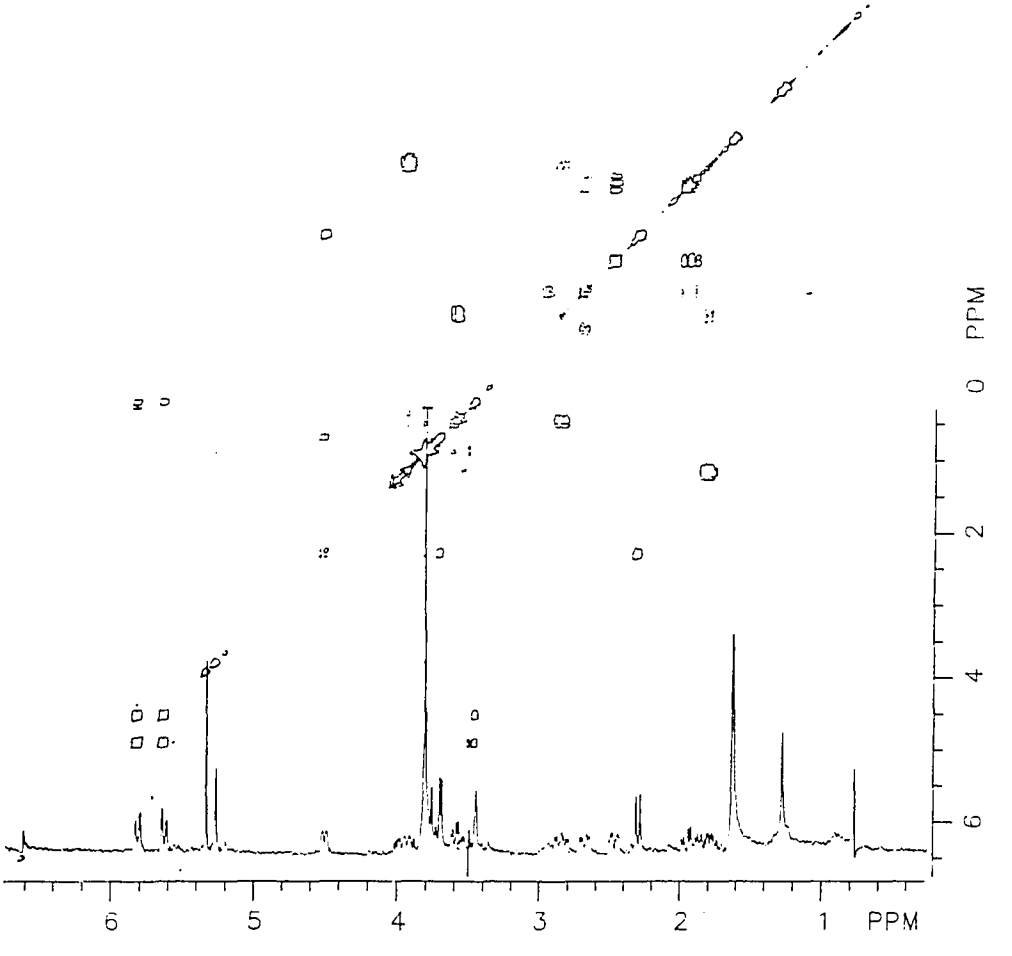
APPENDIX 5:

2D NMR SPECTRA FOR SELECTED COMPOUNDS

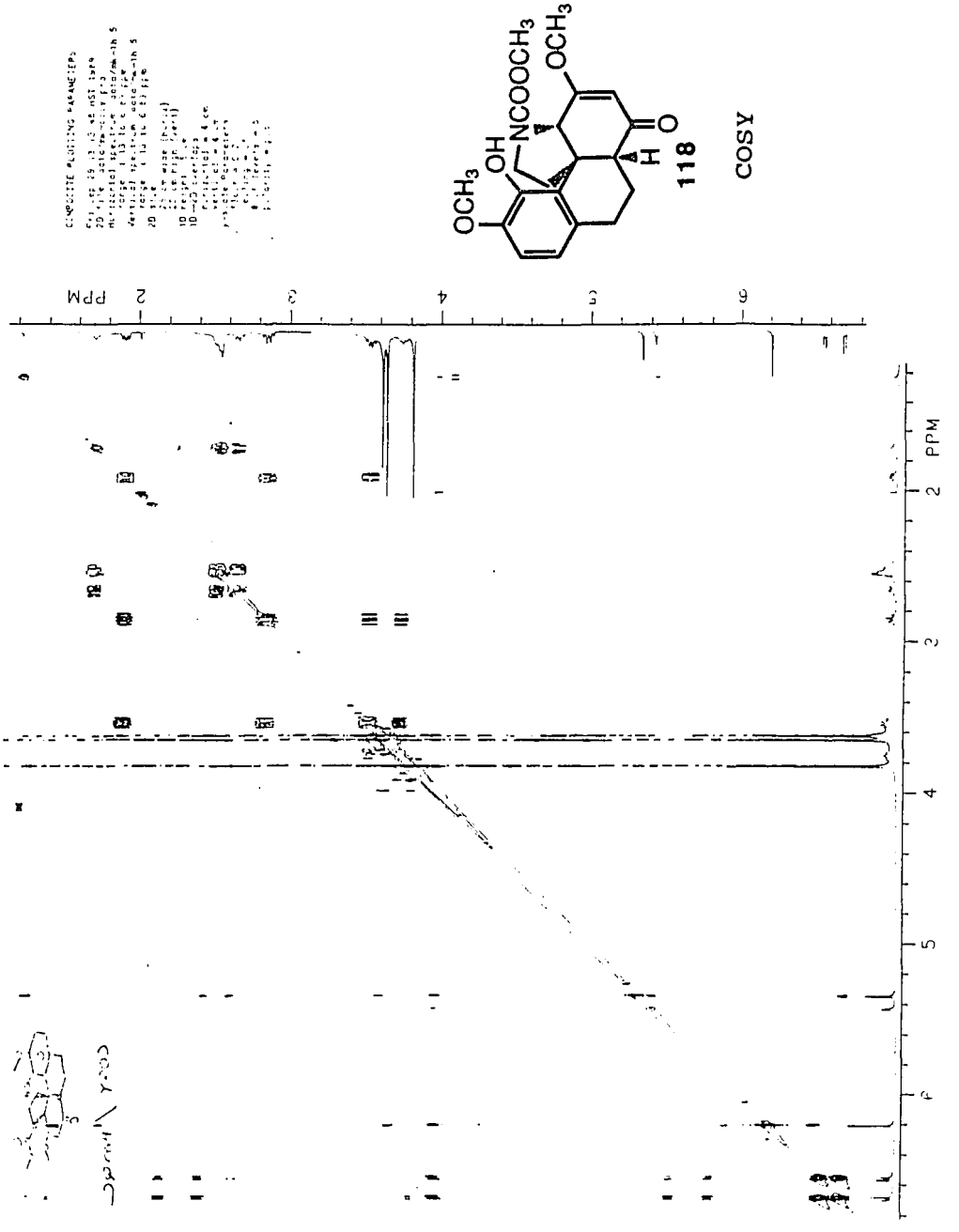


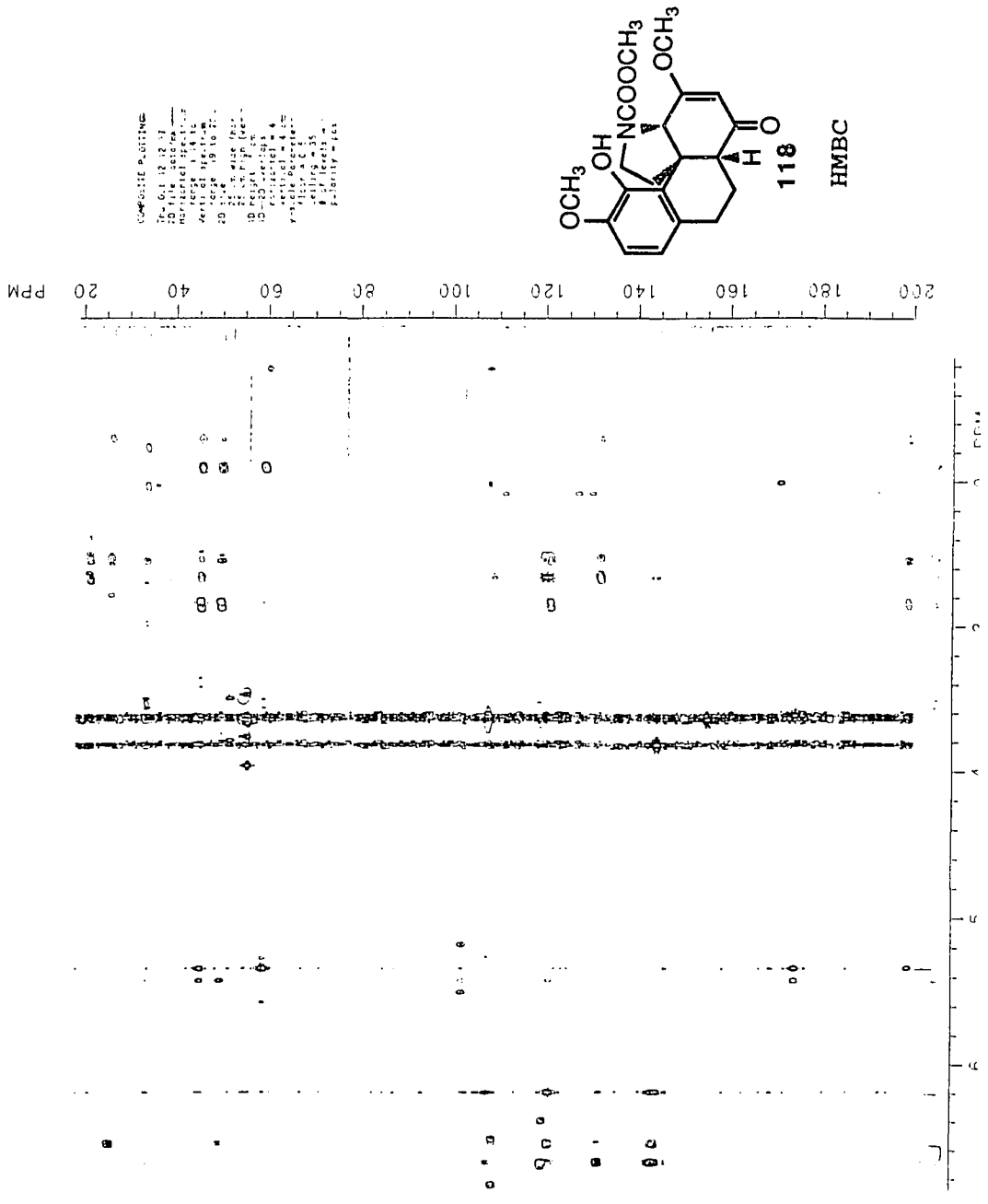
100

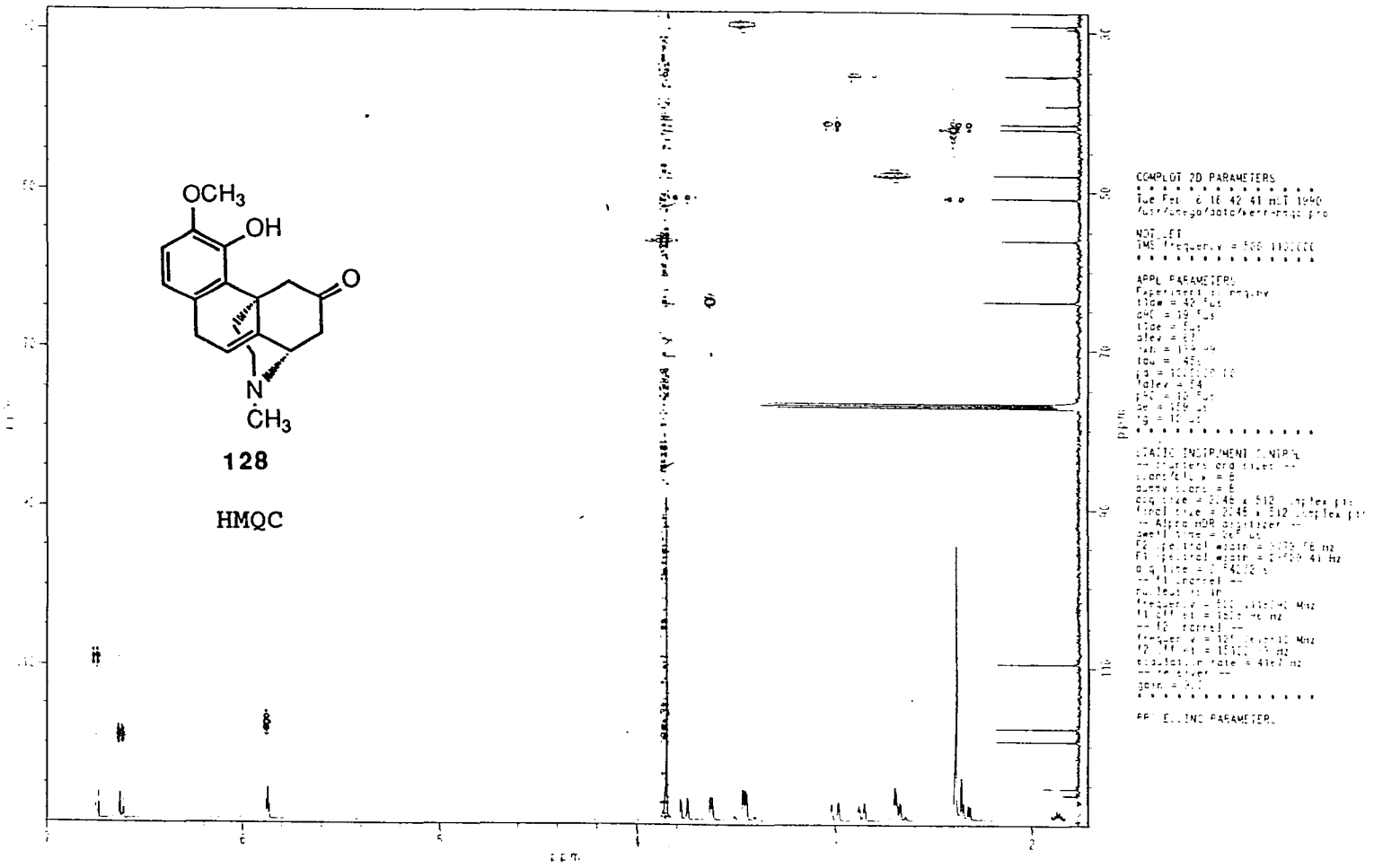
COSY

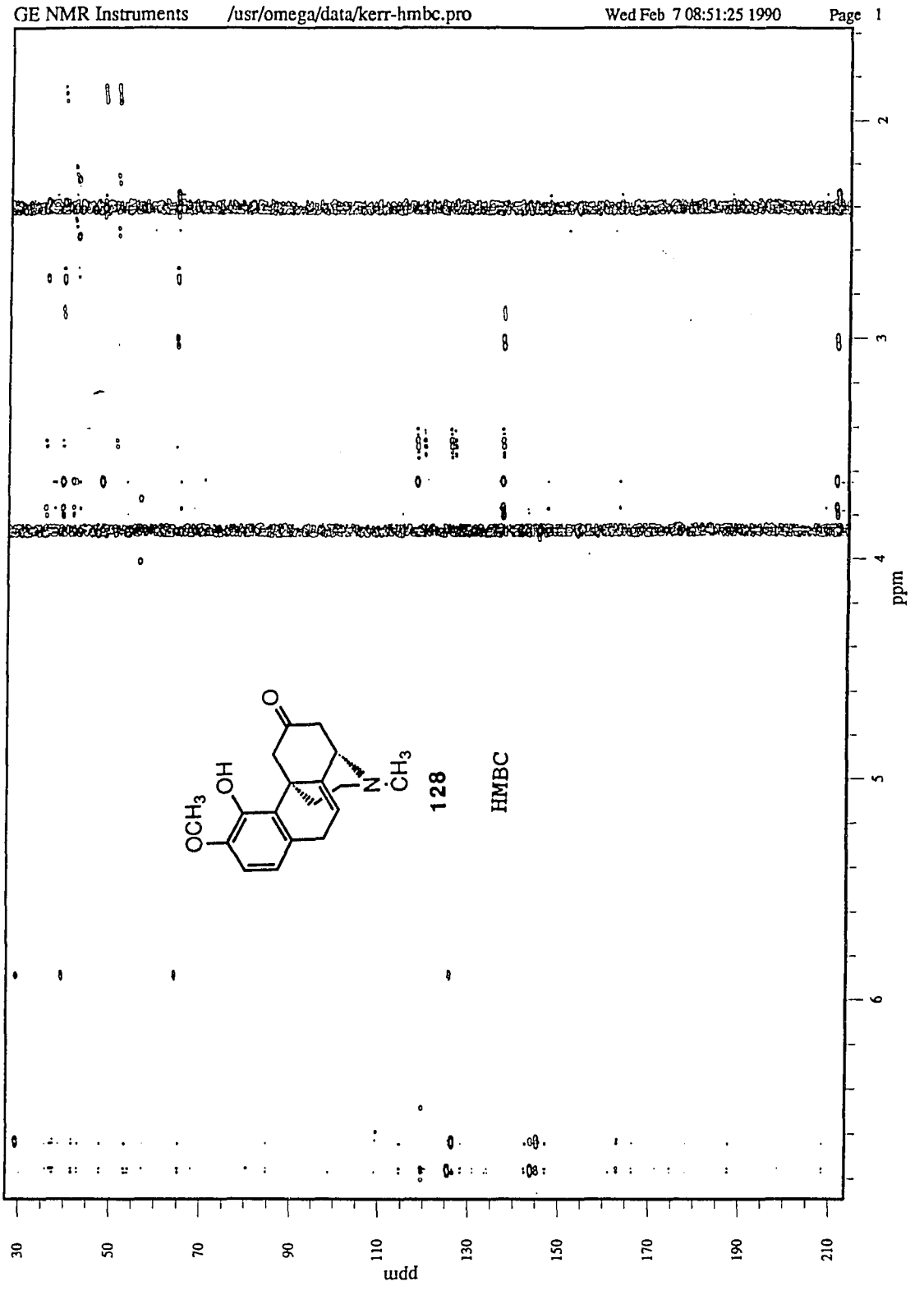


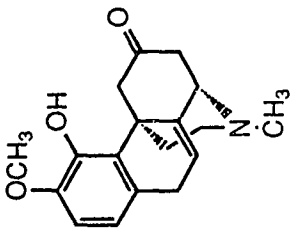
OCH3
OH
NCOOCH3
OCH3
H
O
118
HMQC
120
PPM
PPM


OCH3
OH
NCOOCH3
OCH3
H
O
118
COSY
PPM
2
3
4
5
6
2 PPM

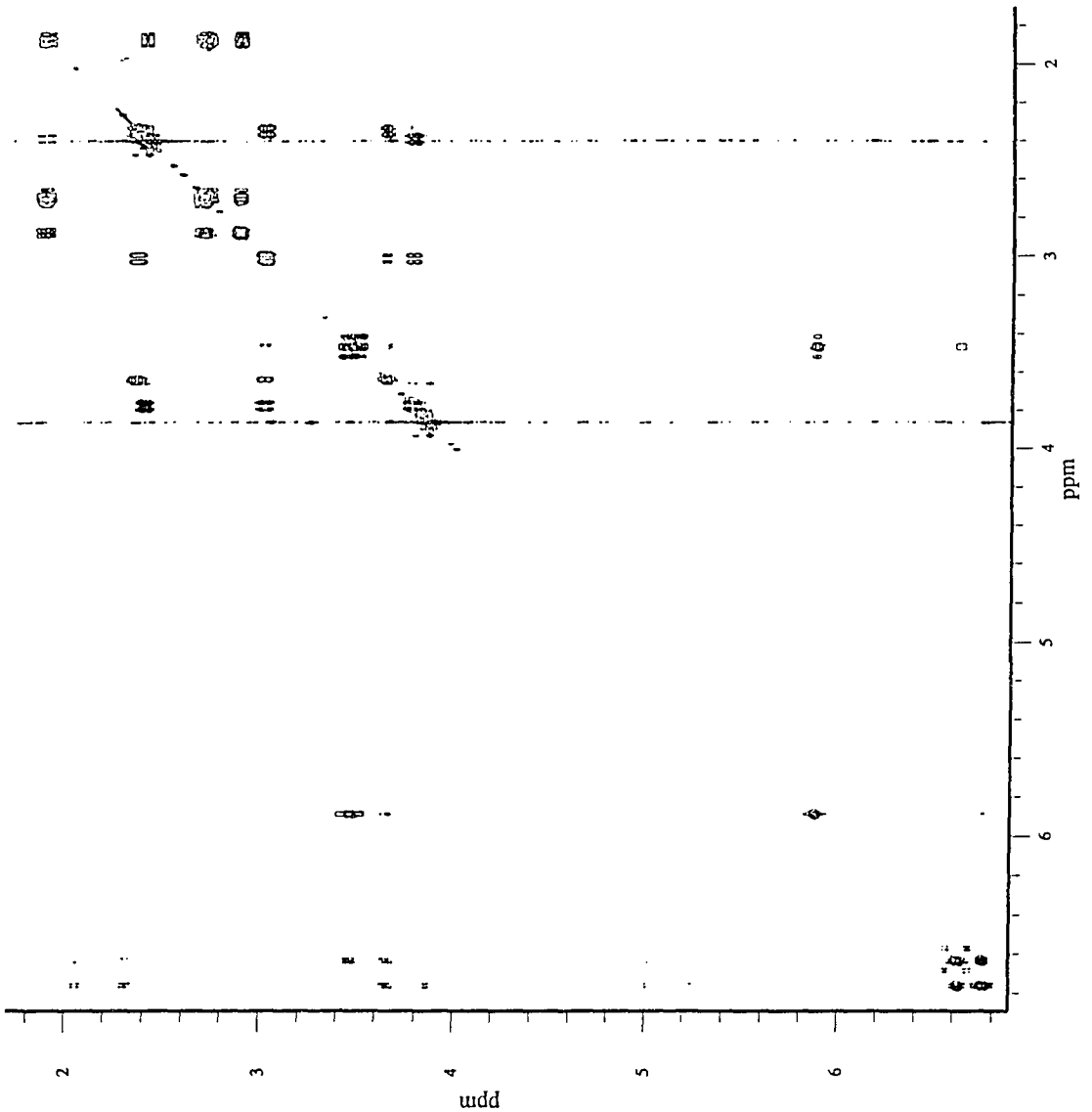

OCH3
OH
NCOOCH3
OCH3
H
O
118
HMBC
PPM
20
40
60
80
100
120
140
160
180
200

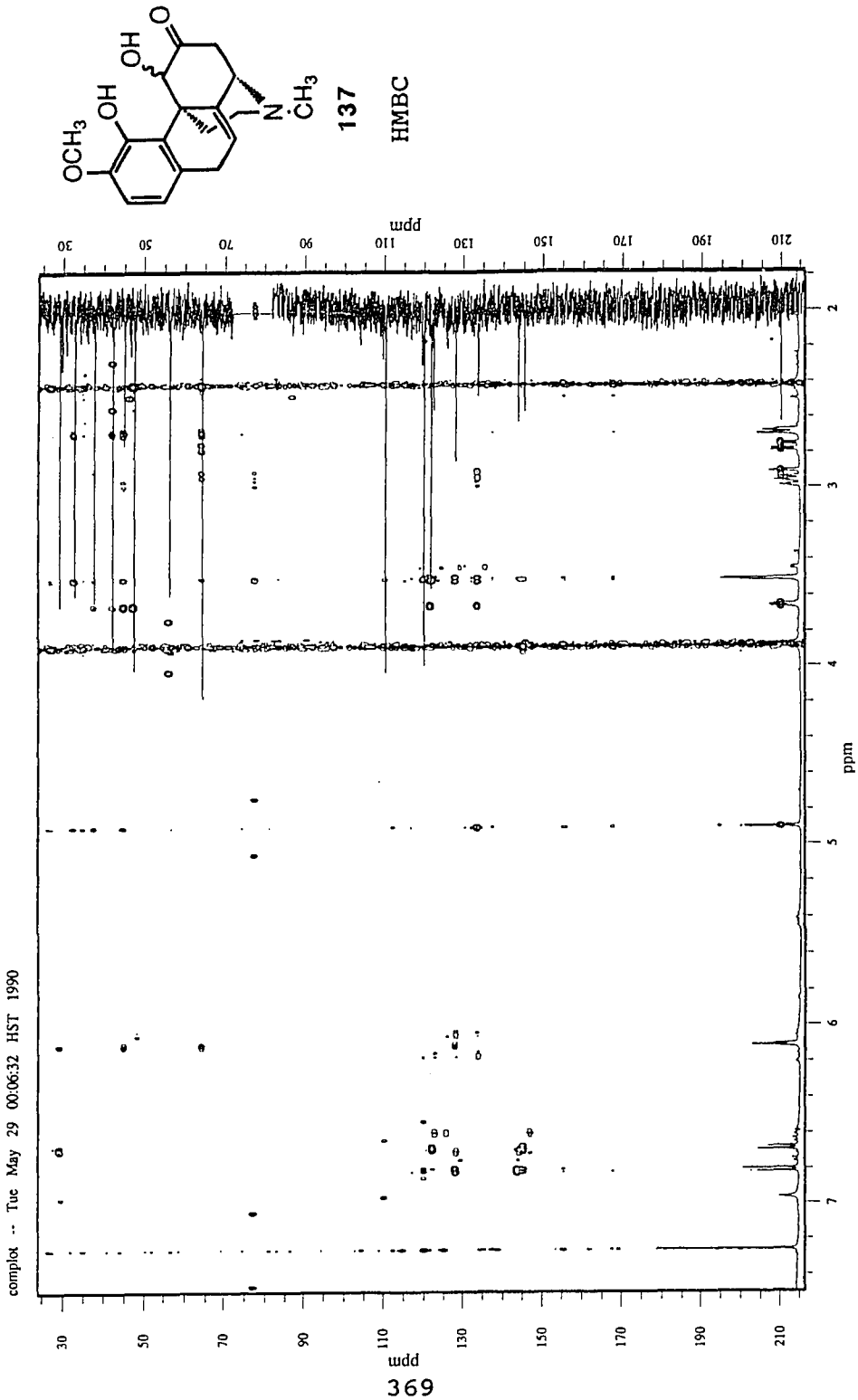

OCH3
OH
O
N
CH3
128
HMQC

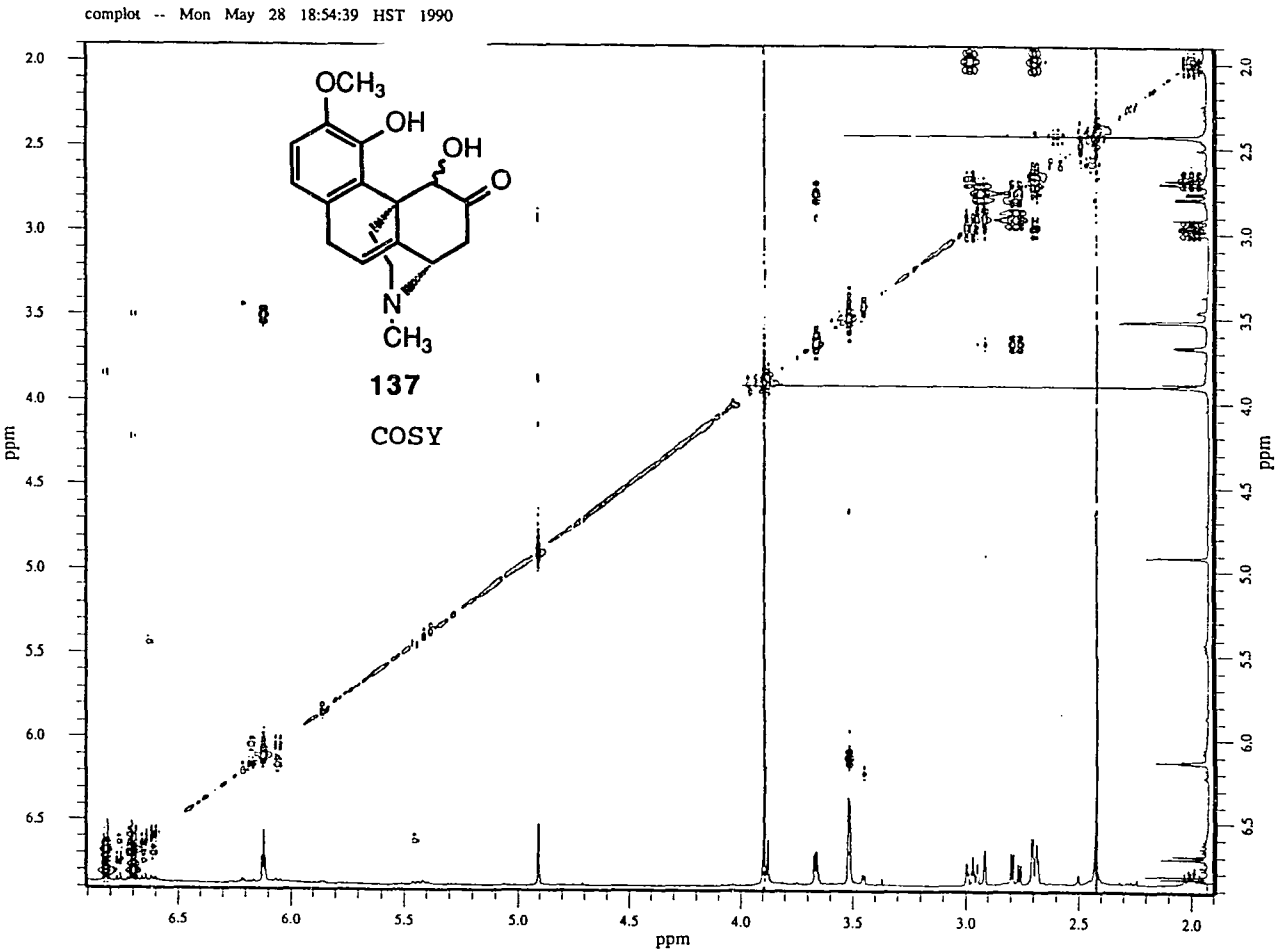

GE NMR Instruments /usr/omega/data/kerr-hmbc.pro Wed Feb 7 08:51:25 1990 Page 1
ppm
ppm
OCH3
OH
N
CH3
O
128
HMBC

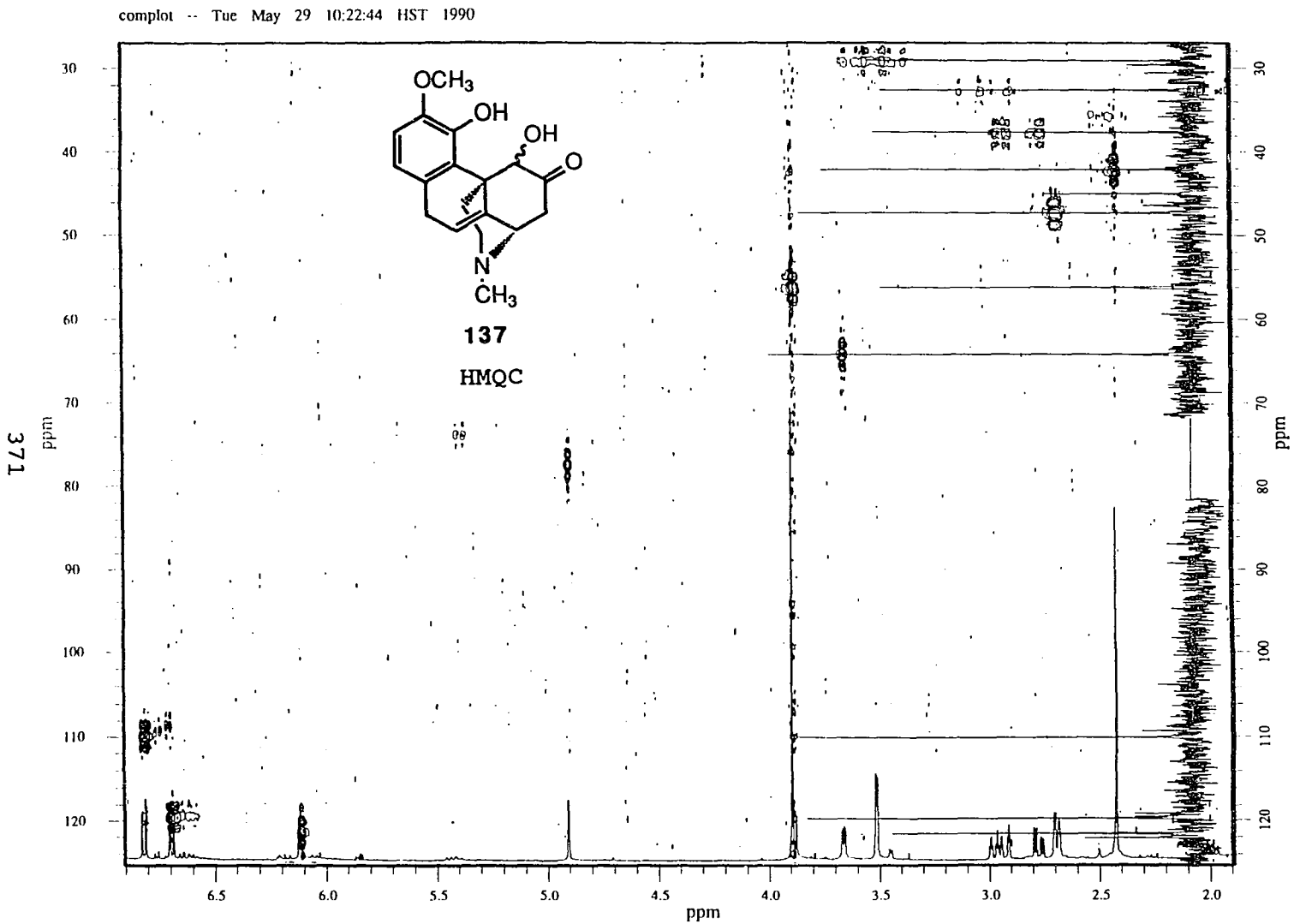


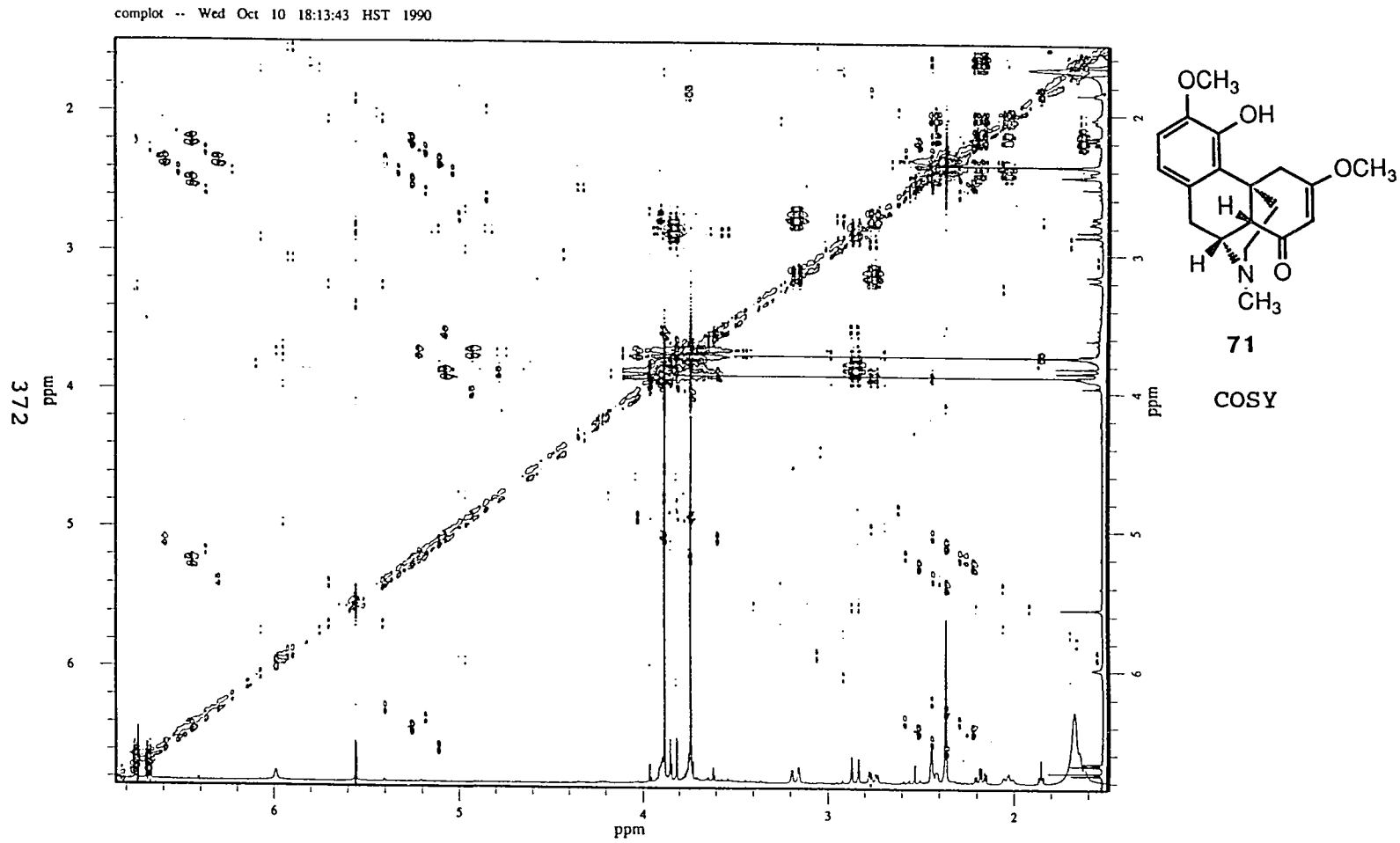
128 COSY




137
HMBC
complot -- Tue May 29 00:06:32 HST 1990
ppm
ppm

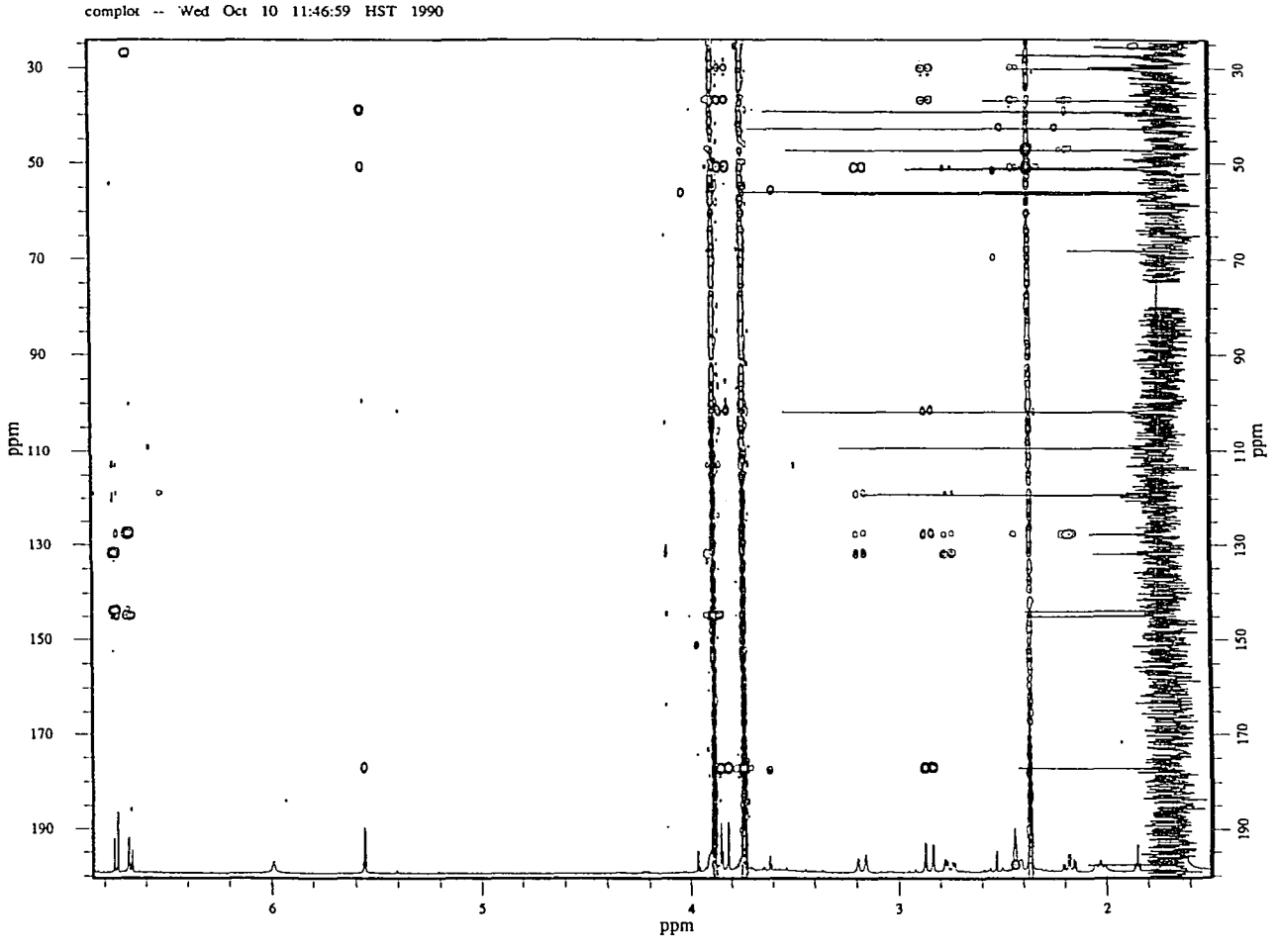

complot -- Mon May 28 18:54:39 HST 1990
OCH3
OH
OH
O
N
CH3
137
COSY
ppm
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5

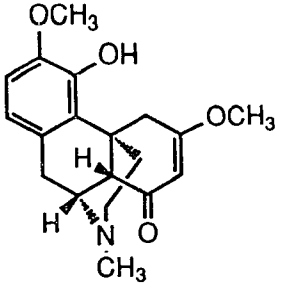

complot -- Tue May 29 10:22:44 HST 1990
OCH3
OH
OH
O
N
CH3
137
HMQC
ppm
ppm
ppm
30
40
50
60
70
80
90
100
110
120
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


complot -- Wed Oct 10 18:13:43 HST 1990
ppm
ppm
ppm
ppm
2
3
4
5
6
OCH3
OH
OCH3
H
H
N
O
CH3

71

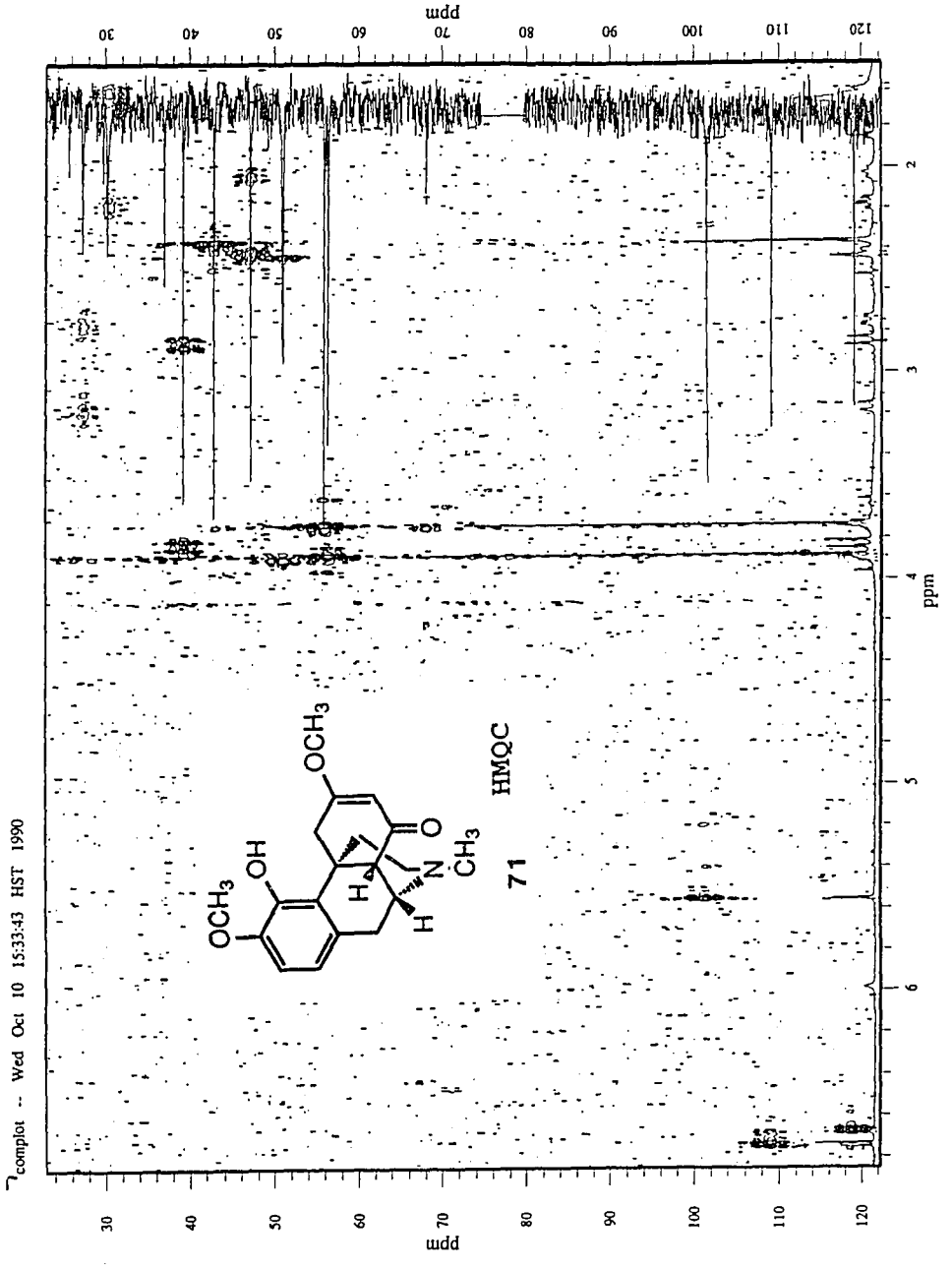
COSY


complot -- Wed Oct 10 11:46:59 HST 1990
ppm
ppm
ppm
30
50
70
90
110
130
150
170
190
6
5
4
3
2


OCH3
OH
OCH3
H
H
N
O
CH3

71

HMBC


ppm
ppm
ppm
HMQC
71
OCH3
OH
OCH3
CH3
O
N
H
H
complot -- Wed Oct 10 15:33:43 HST 1990