# Progress Towards the Total Synthesis of a Spermine-conjugated Dynemicin Analog

Thesis by

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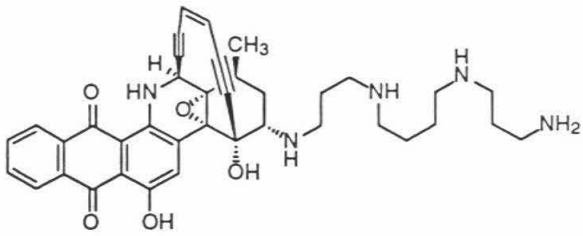
## Abstract

Progress towards the synthesis of the spermine-conjugated Dynemicin analog **4** is described. The synthetic route starts with the Michael addition of menthyl acetoacetate to *trans*-ethyl crotonate followed by a Dieckman condensation to form the cyclohexanedione **14** which, through a series of chemical reactions, is transformed into the quinone imine **6**. Key features in the route include the Suzuki coupling reaction of the aryl boronic acid **11** and the enol triflate **12**, thermal deprotection/internal amidation of the biaryl **19**, cis addition of the (Z)-enediyne **33** to the quinoline **25**, intramolecular acetylide addition to a carbonyl within the ketone **29**, and an addition/elimination of the cyanophthalide to the quinone imine **6** to form the anthraquinone **36** utilizing the Kraus and Sugimoto methodology.



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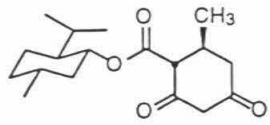

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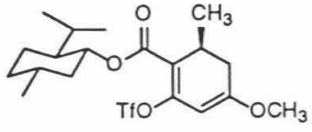

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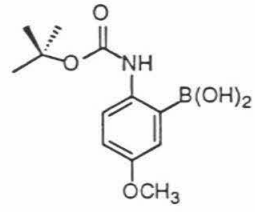

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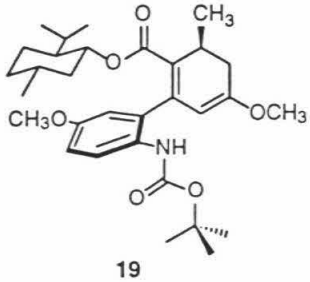

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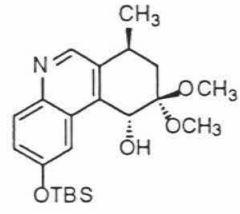

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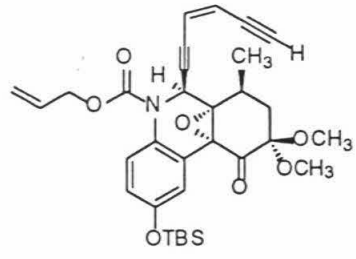
33



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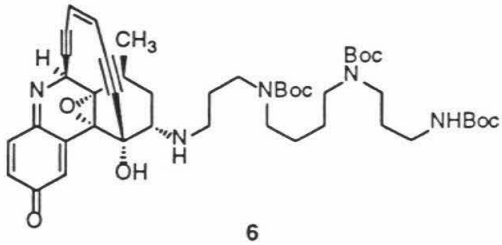

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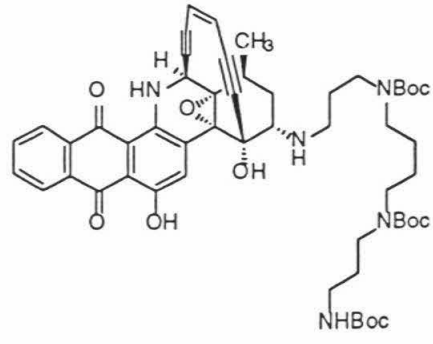

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# List of Schemes

## List of Abbreviations

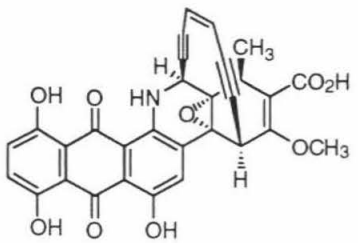
| | |
|---|---|
| Alloc | allyl carbamate |
| Boc | *t*-butyloxy carbonyl |
| ℃ | degrees Celsius |
| $CH_2Cl_2$ | dichloromethane |
| $cm^{-1}$ | reciprocal centimeters |
| CSA | 10-camphorsulfonic acid |
| δ | chemical shift |
| DMF | N,N-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| equiv | equivalent |
| EtOAc | ethyl acetate |
| g | gram |
| GSH | glutathione |
| h | hour |
| Hz | Hertz |
| IR | infrared |
| *J* | coupling constant |
| $KN(TMS)_2$ | potassium bis(trimethylsilyl)amide |
| KO-*t*Bu | potassium *t*-butoxide |
| *m* | meta |
| M | molar |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| MeOH | methyl alcohol |

| | |
|---|---|
| mg | milligram |
| MHz | megahertz |
| min | minute |
| Men | menthyl |
| mL | mililiter |
| mmol | millimole |
| mol | mole |
| µl | microliter |
| N | normal (concentration) |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| NMR | nuclear magnetic resonance |
| *o* | ortho |
| *p* | para |
| $Pd(PPh_3)_4$ | tetrakis(triphenylphosphine)palladium (0) |
| $Pd(PPh_3)_2Cl_2$ | dichlorobis(triphenylphosphine)-palladium (II) |
| pH | hydrogen ion concentration (log scale) |
| ppm | parts per million |
| $R_f$ | retention factor |
| s | seconds |
| *t* | tertiary |
| TBAF | tetrabutylammonium flouride |
| TBS | *tert*-butyldimethylsilyl |
| Tf | triflouromethylsulfonyl (triflate) |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |

| | |
|---|---|
| p-TsOH | *p*-toluenesulfonic acid |
| v/v | volune-to-volume ratio |
| w/v | weight-to-volume ratio |

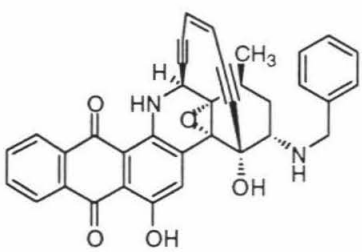
# Progress Towards the Total Synthesis of a Spermine-conjugated Dynemicin Analog

## Introduction

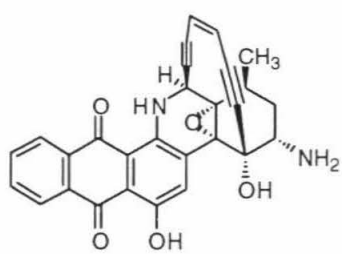



Dynemicin A (**1**)

Isolated from the soil bacterium *Micromonospora chersina* in 1989 by Konishi and co-workers[1], Dynemicin A (**1**) is an important antitumor antibiotic because it has shown in vitro and in vivo cytotoxicity against a variety of murine and human tumor cell lines.[1] As a member of the enediyne family, Dynemicin A is unique, for it possesses the anthraquinone functionality which is a feature of the anthracycline antibiotics.[2] The anthraquinone is believed to act as an intercalating agent in the DNA-cleaving mechanism shown in **Scheme 1**.[3] In the presence of a reducing cofactor such as glutathione (GSH) or NADPH the anthraquinone is reduced, followed by a cascade of reactions leading to the Bergman cycloaromatization[4] to form the reactive 1,4-phenylene diradical which abstracts hydrogen atoms from the base pairs of DNA.




**2**

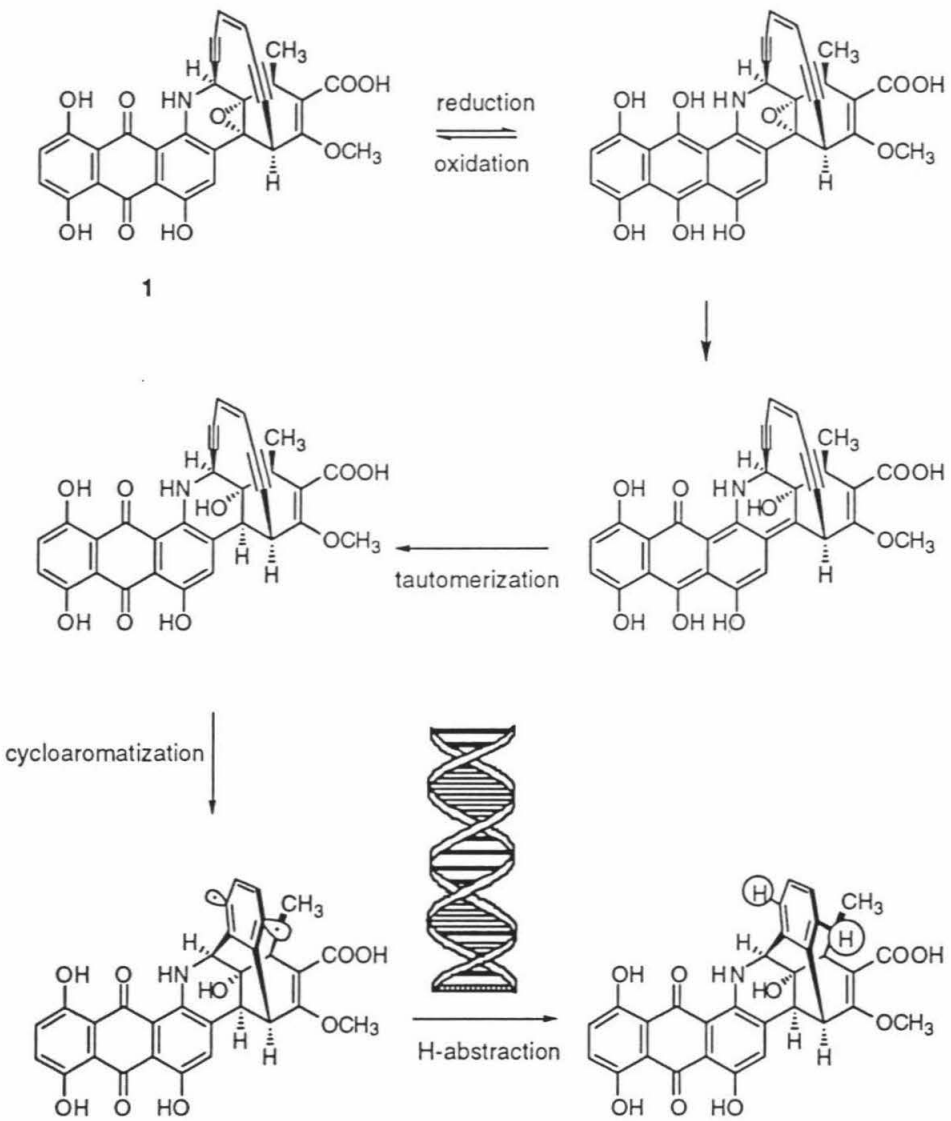



**3**

The synthesis of Dynemicin A and several of its analogs were completed[5] and tested[12] for their biological activities in this laboratory recently. After screening a variety of Dynemicin

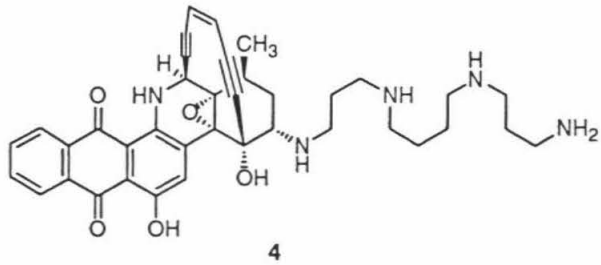
analogs, Dr. Norma J. Tom found that analogs **2** and **3** exhibit interesting DNA cleaving properties.[12] Analog **2** cleaved DNA less effectively than Dynemicin A. However, it displayed phenomenal sequence selectivity for G residues. Analog **3** cleaved DNA more effectively than Dynemicin A in the presence of GSH as the reducing cofactor. By far, it is the most powerful DNA cleaving agent in the Dynemicin family known to date.

**Scheme 1**




With these preliminary results, it is of great interest to access the spermine-conjugated analog **4**. With the four amino groups inherent within the spermine side chain, analog **4** should bind more tightly to DNA due to the electrostatic interaction between the

positively charged amino groups (at physiological pH) and the negatively charged phosphate groups of DNA. Analog **4**, in a way, is a structural compromise between analogs **2** and **3**. In this thesis progress towards the total synthesis of this spermine-conjugated Dynemicin analog **4** is described.

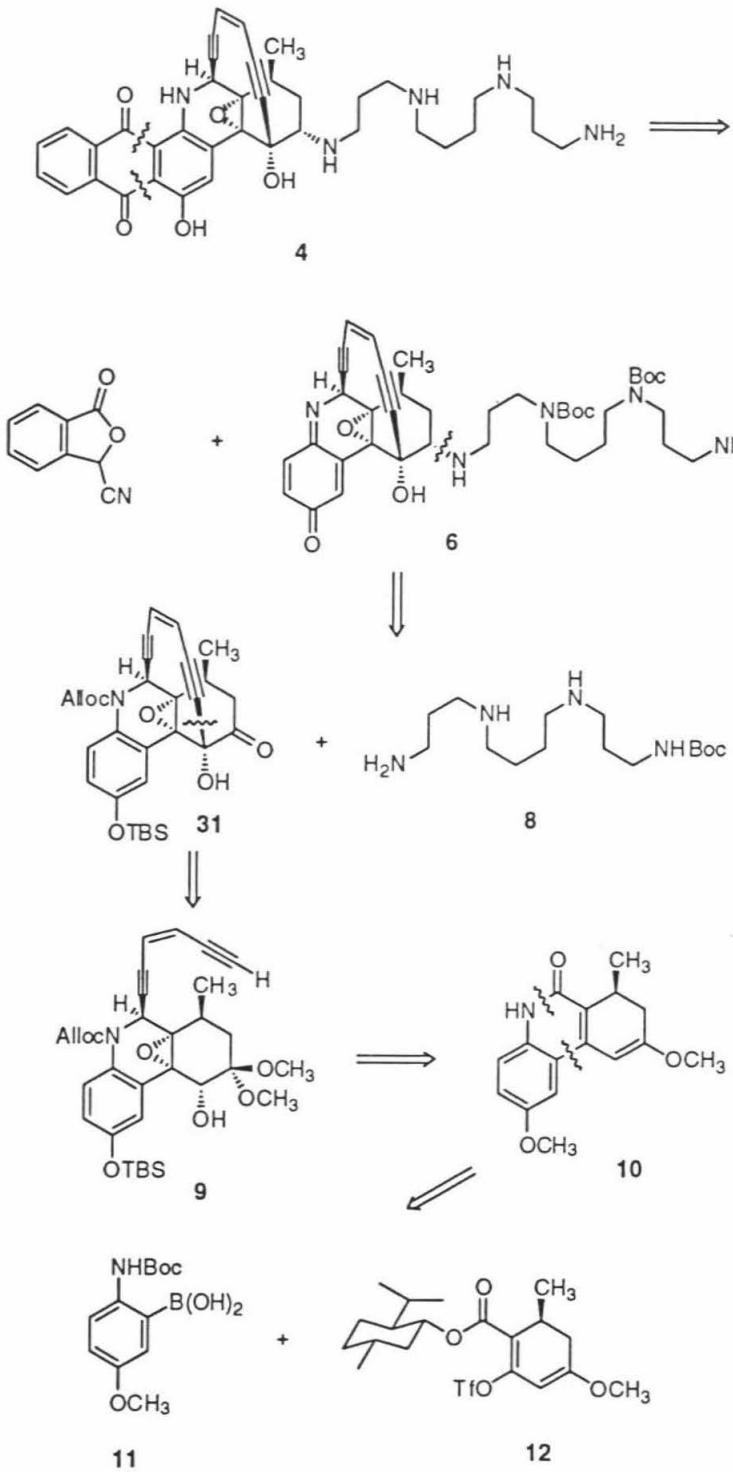



**4**

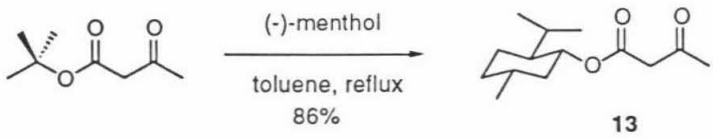
### Retrosynthetic analysis

In order to pursue a successful synthesis of the Dynemicin analog **4**, manipulations of a few difficult functional groups within the molecule need to be considered. From past experiences the anthraquinone functionality should be introduced at a very late stage in the synthesis due to its reactive nature.[6] It was decided to handle the spermine side chain in protected form. The anthraquinone is envisioned to be derived from an addition/elimination reaction of a cyanophthalide anion to the quinone imine **6** by the method of Kraus and Sugimoto (**Scheme 2**).[7] The quinone imine **6** can then be assembled from the ketone **31** and the mono-Boc-protected spermine **8** by reductive amination. Within the ketone **31** lies the strained endiyne bridge of which the key bond disconnection is from an acetylide addition to a carbonyl. Having defined a strategy for bridging the A ring and the B ring, the epoxide **9** can be a viable precursor to the ketone **31**. Through a series of chemical transformations, the complexities of the epoxide **9** can be simplified to the quinolone **10** with just one stereogenic center. Finally coupling of the boronic acid **11** and the enol triflate **12** should furnish the quinolone **10**.

## Scheme 2

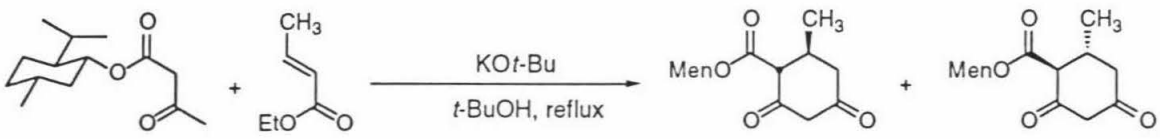

CH3
H
HN
O
O
OH
O
OH
NH
N
H
NH2
4
CN
+
CH3
N
NBoc
Boc
N
NHBoc
6
AllocN
CH3
O
OH
OTBS
31
+
H2N
NH
NHBoc
8
AllocN
CH3
H
OCH3
OCH3
OH
OTBS
9
HN
CH3
OCH3
OCH3
10
NHBoc
B(OH)2
OCH3
11
+
TfO
CH3
OCH3
12

## Synthesis




13

The synthesis of the target molecule commenced with the construction of the A ring of the analog. Towards this end, thermal transesterification of *tert*-butyl acetoacetate with (-)-menthol afforded the menthyl acetoacetate **13** in 86% yield after distillation. This transformation was proposed to proceed through an unusual acyl ketene intermediate.[8]




13 → 14 + 15

14 : 15 = 1 : 1

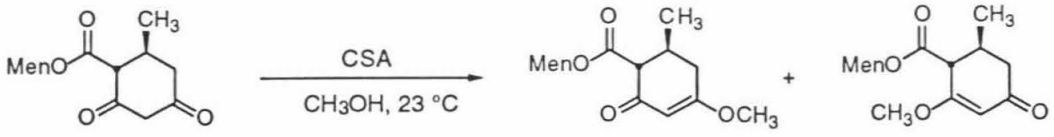
30% yield after recrystallization

Men = menthyl

A Michael addition[9] followed by a Dieckman condensation[10] of the menthyl acetoacetate **13** with *trans*-ethyl crotonate furnished a 1:1 mixture of the diastereomers **14** (30% after recrystallization) and **15**. This methodology of constructing 1,3-cyclohexanedione was first described by von Schilling and Vorlunder in 1899.[11] Despite its low yield for the desired diastereomer **14**, this reaction proved to be very practical for large scale synthesis. Through several chiral alcohol experimentation,[12] menthol proved to be the ideal chiral auxiliary for this reaction due to its virtue of crystallinity of the reaction products.

The cyclohexanedione **14** was transformed into the enol methyl ethers **16** and **17** in a 4 : 1 ratio, respectively by stirring in an acidic methanolic solution. $^1$H NMR analysis of the product **16** showed that it contained ≥95% trans (menthyl ester and methyl groups) and ≤5% cis stereoisomers. The cis contaminant was inconsequential for both the cis and trans isomers converged to the same product in the next reaction. The undesired

regioisomer **17** could be separated and could be converted to **16** in the above apparently equilibrium ratio by resubjection to the reaction condition.

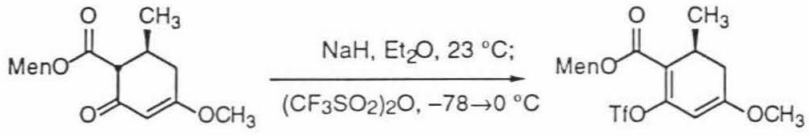



**14** **16** : **17**

4 : 1

65%

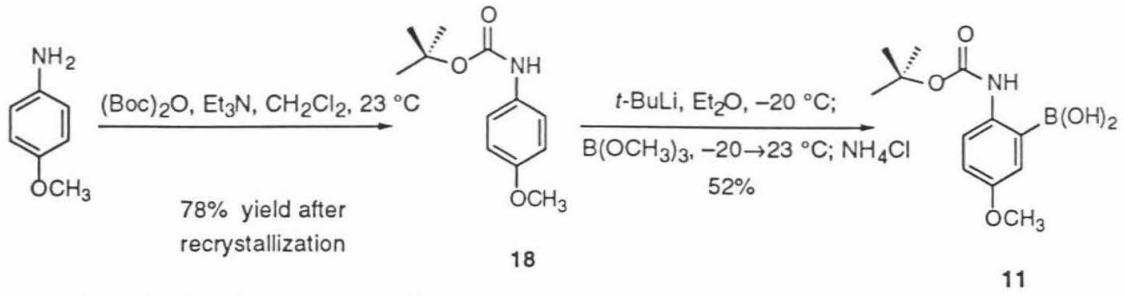
Deprotonation of the ether **16** with sodium hydride, followed by trapping the resulting anion with trflouromethanesulfonic anhydride afforded the enol triflate **12**, which was apparently the A ring of the molecule. Due to its instability to storage the enol triflate **12** was usually prepared prior to use in the following coupling reaction. On large scale synthesis, the enol triflate **12** was typically carried on to the next step without purification.




**16** **12**

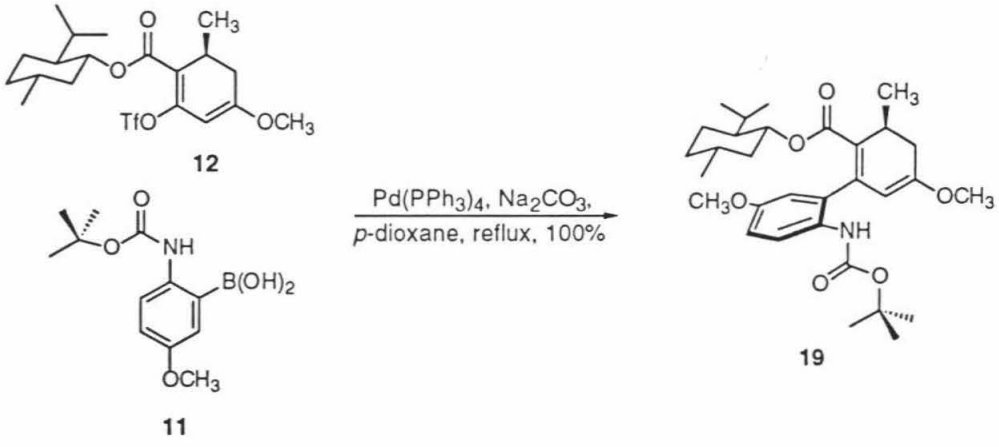
Followed the completion of the A ring was the construction of the C ring, which was started with a protection of the amino group in *p*-anisidine with di-*tert*-butyl dicarbonate and triethylamine in dichloromethane to form the *tert*-butyloxy carbamate **18** (**Scheme 3**). Upon treatment with a solution of *t*-butyllithium in pentane (2 equiv) at –20 °C, the clear solution of the needle-like aryl carbamate **18** turned cloudy almost instantaneously as the sign of deprotonation. The resulting lithio di-anion slurry was quenched with trimethyl borate, followed by hydrolysis to furnish the boronic acid **11** (**Scheme 3**) as a light yellow foam. This reaction completed the synthesis of the C ring.

Scheme 3

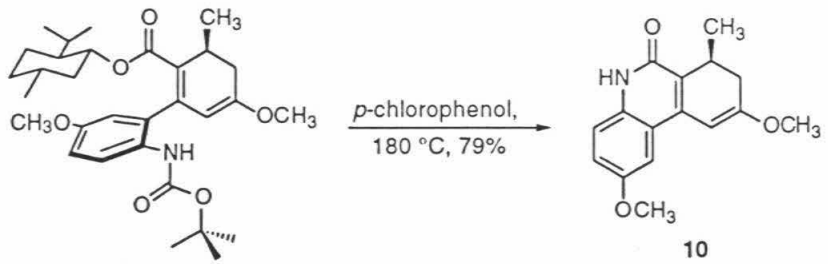



$(Boc)_2O$ = di-*tert*-butyl dicarbonate

Having both coupling components, the enol triflate **12** and the aryl boronic acid **11**, in hand the next stage in the synthetic route was to join these two pieces together to form the C ring. Utilizing the Suzuki coupling protocol[13] the heterogeneous mixture of the boronic acid **11**, the enol triflate **12**, $Pd(PPh_3)_4$, and aqueous sodium carbonate in refluxing benzene proceeded smoothly to yield the biaryl adduct **19** in quantitative yield as a 1:1 mixture of atropisomers (based on $^1H$ NMR analysis). The atropisomers were inconsequential in the synthetic route since they converged to the same product in the next reaction.

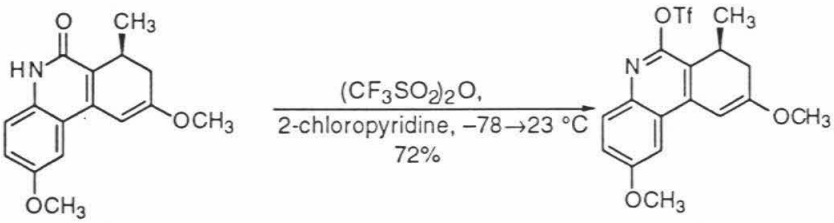



Thermal deprotection[14] of the *tert*-butyl carbamate group in the biaryl **19**, followed by internal amidation in the weakly acidic solvent *p*-chlorophenol at 180 ℃ afforded the quinolone **20** in 79% yield. Through excessive experimentation[12], *p*-chlorophenol proved to be the ideal solvent of choice. It not only provided the solvent medium but also acted as a weak Bronsted acid in the deprotection step.



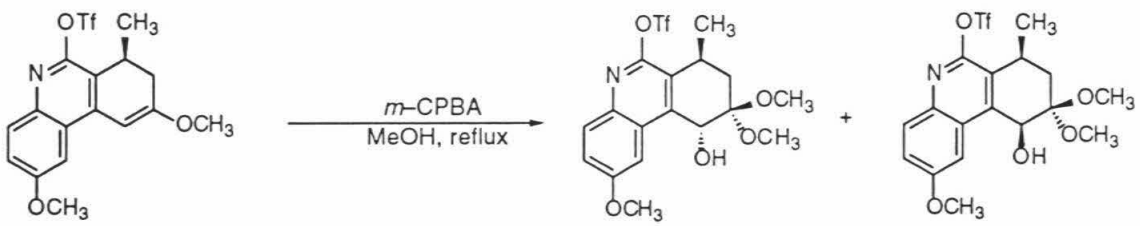

19 10

Completion of the quinolone **10** advanced to next stage in the synthesis which called for the introduction of the (Z)-enediyne bridge cis to the methyl group in the quinolone **10**. Towards this end, the quinolone **10** was transformed into the quinolyl triflate **20** in 72% yield upon treatment with 2-chloropyridine and triflouromethanesulfonic anhydride




10 20

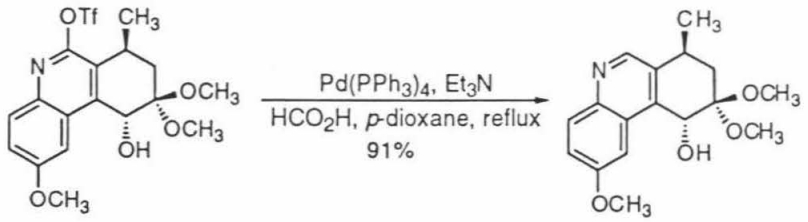
Heating a solution of the quinolyl triflate **20** and *m*-CPBA in methanol at reflux provided a mixture of diastereomers **21** and **22** in 75% and 10% yield, respectively.




20 21 22

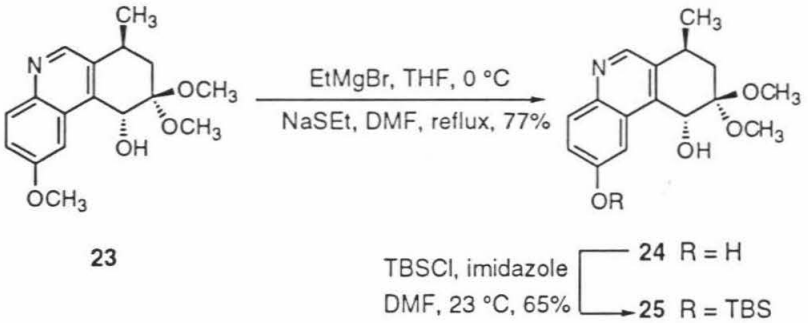
75% 10%

Reductive cleavage of the triflate group in the dimethyl ketal **21** with tetrakis(triphenylphosphine)palladium(0), formic acid, and triethylamine in refluxing *p*-dioxane[15] yielded the quinoline **23** in 91% yield.




21 23

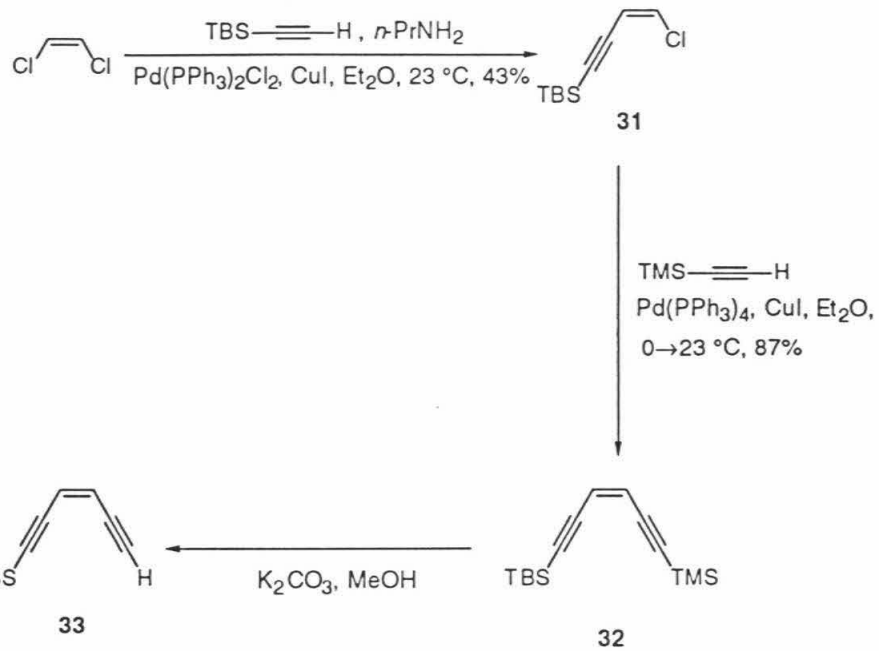
The aryl methyl ether group in **23** was not an ideal protecting group due to its harsh deprotecting conditions. A silyl ether was realized to be a more suitable one[12]. To bring about this transformation, selective demethylation of the aryl methyl ether in **23** was accomplished with the following protocol: the dimethyl ketal **23** was initially treated with a solution of ethylmagnesium bromide (1.1 equiv) in THF at 0 °C. Treatment of the resultant magnesium alkoxide solution with sodium ethylmercaptide afforded phenol **24** (77%), which was protected with *tert*-butyldimethylsilyl chloride and imidazole in THF at 23 °C to yield the aryl silyl ether **25** in 65% yield.



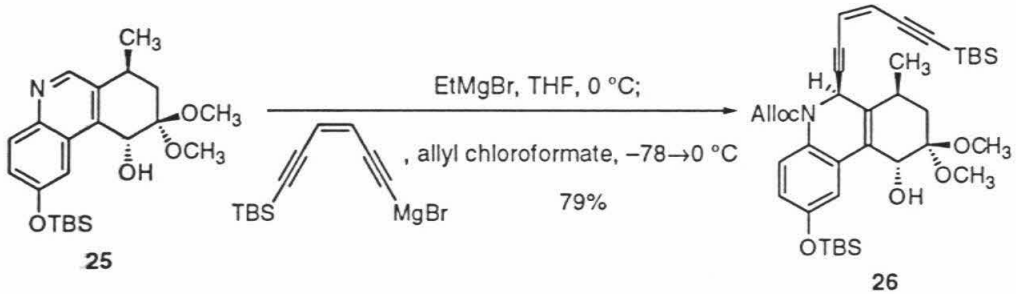

23

At this point substrate **25** was ready for the introduction of the enediyne bridge. Prior to this crucial incorporation, the mono-protected (Z)-enediyne fragment **33** was prepared according to the literature procedures.[16] Sequential palladium and copper catalyzed coupling reactions of the *cis*-1,2-dichloroethylene with (*t*-butyldimethylsilyl)acetylene and (trimethylsilyl)acetylene furnished **31** and **32**, respectively. Selective desilylation of the trimethylsilyl group with potassium carbonate in methanol yielded **33** (**Scheme 4**). Due to its instability to storage, the (Z)-enediyne fragment **33** was typically carried on to the next step without purification.

## Scheme 4

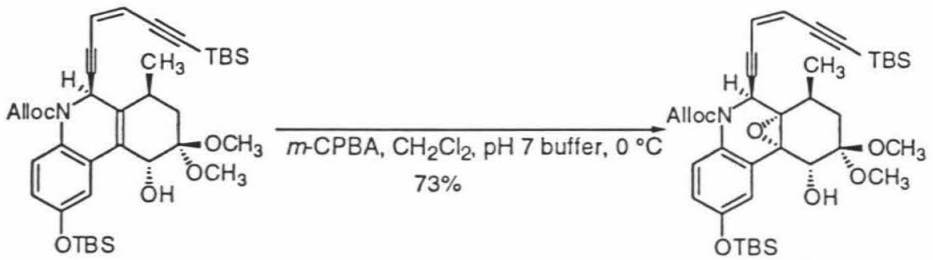



Incorporation of the mono-protected enediyne **33** into the quinoline **25** was accomplished using the Yamaguchi protocol.[17] Upon treatment with ethylmagnesium bromide (0.90 equiv), the hydroxyl group in quinoline **25** was deprotonated to form the magnesium alkoxide, which was combined with the magnesium acetylide derived from **33** and allyl chloroformate to yield the cis adduct **26** in 79% yield. In previous studies, Dr. Mark Fraley determined that the free hydroxyl group in **25** was crucial for the cis addition of the magnesium acetylide. The reactive conformation in the stereoselective Yamaguchi addition reaction was proposed to involve magnesium chelation to the face trans to the methyl group.[6]



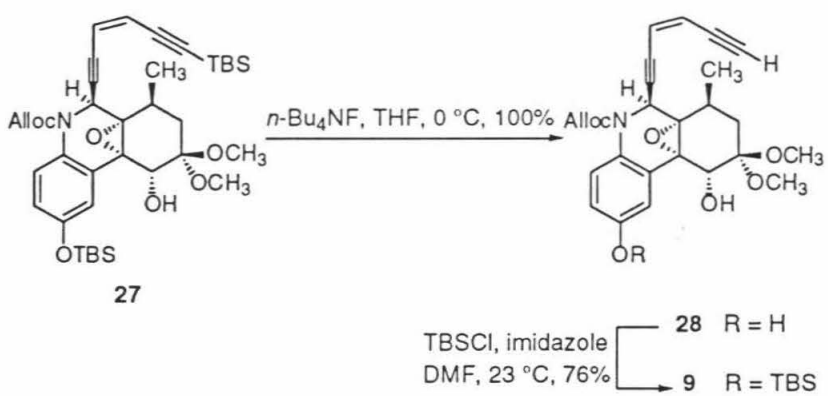

Alloc = allyl carbamate

Selective epoxidation of the tetrasubstituted olefin within the silyl ether **26** with *m*-CPBA in a biphasic mixture of dichloromethane/water at 0 °C furnished the epoxide **27** in 73% yield. It was important to conduct this reaction at low temperature, for warming the reaction would result in competitive epoxidation of the allyl carbamate.




**26** **27**

Treatment of the silyl ether **27** with 2 equivalents of TBAF resulted in cleavage of both silyl groups to yield the phenol **28** (quantitative yield), which was protected as an aryl silyl ether **9** with *tert*-butyldimethylsilyl chloride and imidazole in DMF at 23 °C.

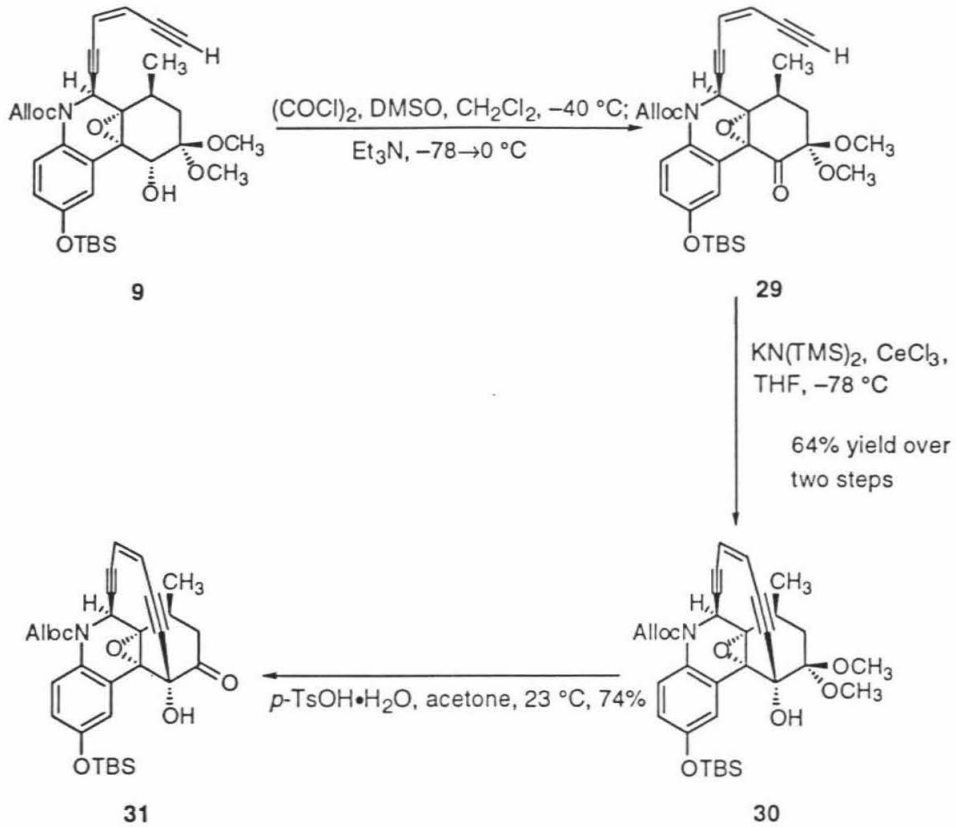



**27**

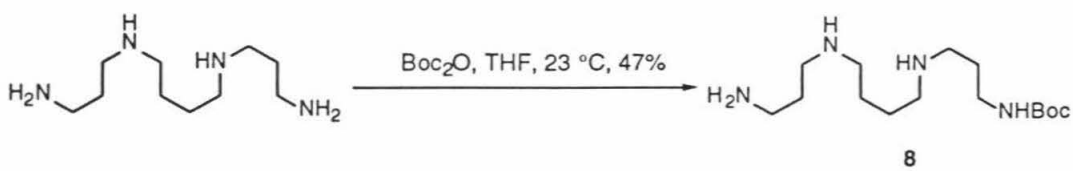
Under the Swern oxidation protocol[18], the alcohol **9** was oxidized to the ketone **30**, which was subsequently treated with potassium bis(trimethylsilyl)amide and anhydrous cesium (III) chloride in THF at –78 °C to yield the cyclization product **30** in 64% yield over 2 steps. Hydrolysis of the dimethyl ketal **30** with *p*-toluenesulfonic acid monohydrate in acetone at 23 °C gave the ketone **31** in 74% yield (**Scheme 5**).

Completion of the synthesis of the ketone **31** paved the way for the incorporation of the spermine side chain. Towards this end, mono-Boc-protection of the spermine (3 equiv) was accomplished by slow addition of a solution of di-*tert*-butyl dicarbonate in THF

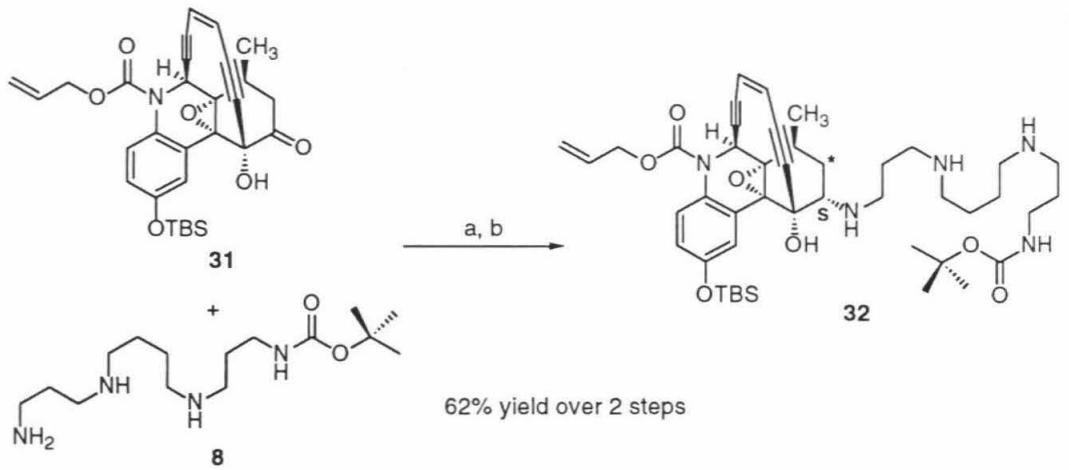
Scheme 5




to a solution of spermine in THF over 3.5 h at 23 °C to afford the carbamate **8** in 47% yield. It was important for the slow addition of the di-*tert*-butyl dicarbonate solution, for fast addition would result in low yield of the desired product due to competitive reaction with the secondary amines.



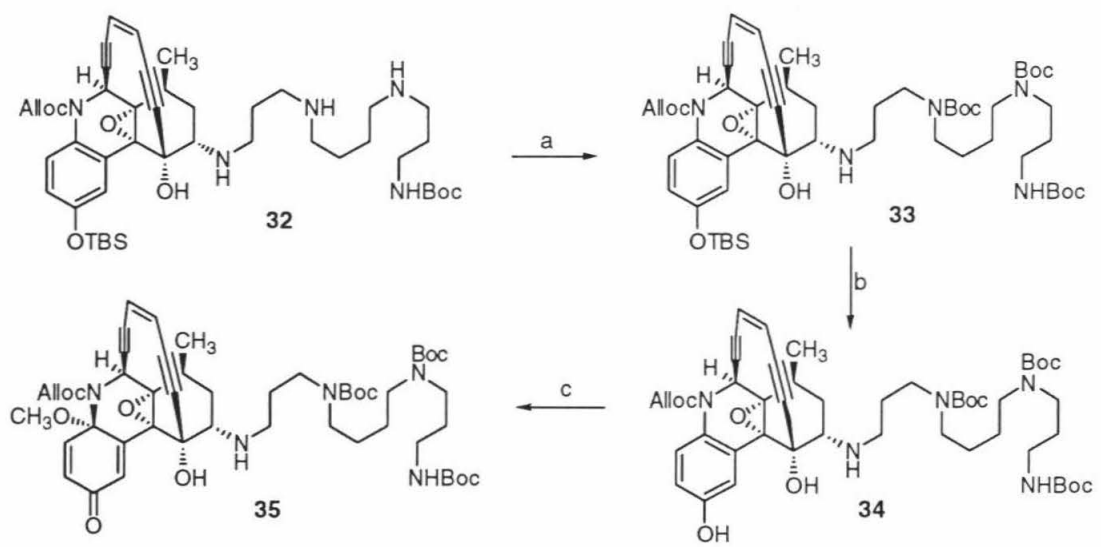

The solution of the ketone **31**, the carbamate **8**, and CSA in benzene was heated at reflux under Dean–Stark conditions to afford the condensation product imine. Due to its instability to chromatography, the intermediate imine was typically carried on to the next step without purification.




a. CSA, benzene, ruflux under Dean–Stark. b. $NaBH_3CN$, MeOH, pH 4.

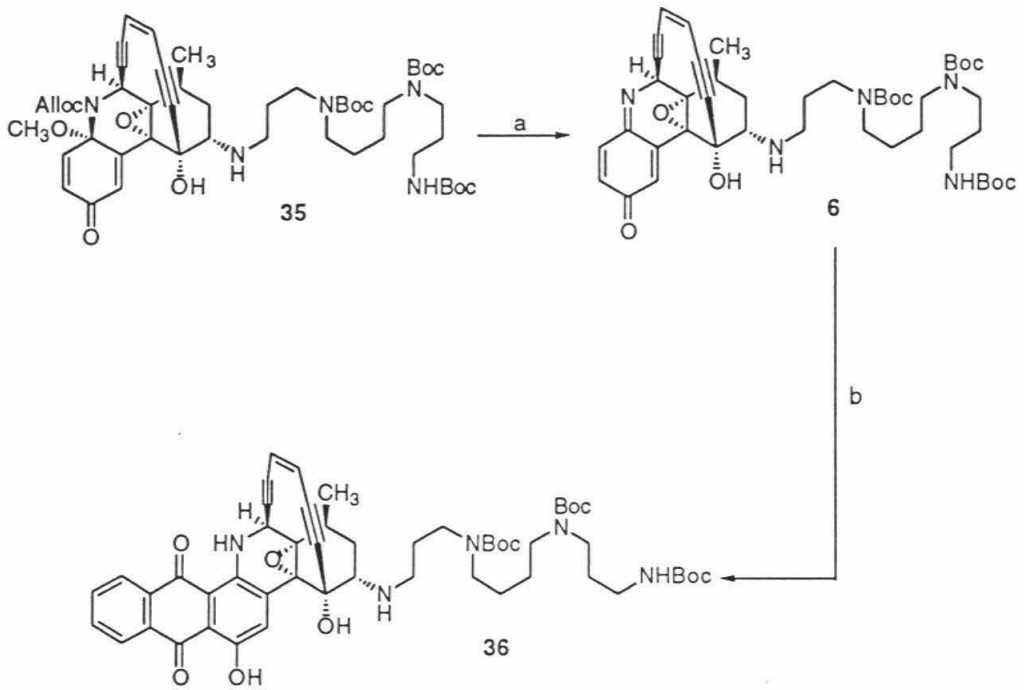
Reduction of the crude imine with sodium cyanoborohydride in acidic methanol (pH 4) gave the polyamine **32** in 62% yield over 2 steps. The starred methylene group in **32** had similar coupling constants and splitting patterns (based on $^1H$ NMR analysis) as that in analog **2**.[12] By analogy, hydride attack of the intermediate iminium ion in the reductive amination must have occurred from the β-face to result in the S-stereochemistry at the carbon indicated in compound **32**.

**Scheme 6**




a. $Boc_2O$, pyridine, THF, 23 °C. b. triethylamine trihydroflouride, $CH_3CN$, 23 °C. 75% yield over 2 steps
c. $PhI(OAc)_2$, MeOH, 23 °C, 63%.

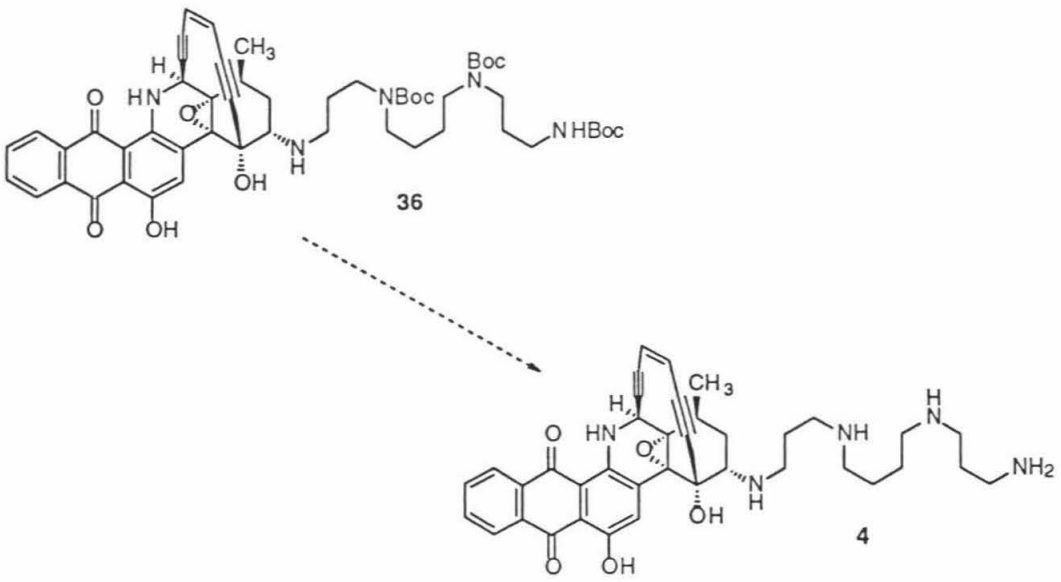
The polyamine **32** was protected as a tri-*tert*-butyloxy carbamate **33** with di-*tert*-butyl dicarbonate in THF. Desilylation of the aryl silyl ether group in the tricarbamate **33** with triethylamine trihydroflouride in acetonitrile furnished the phenol **34** (75% yield over 2 steps), which was oxidized to the enone **35** with iodobenzene diacetate[19] in methanol in 63% yield (**Scheme 6**).




a. $Bu_3SnH$, $Pd(PPh_3)_2Cl_2$, $CH_2Cl_2/H_2O$, 23 °C. b. lithio cyanophthalide, THF, −78→0 °C.

The allyl carbamate group in the enone **35** was deprotected with tributyltin hydride and palladium (II) chloride in wet dichloromethane[20] to yield the quinone imine **6**, which proved to be unstable to chromatography. Condensation of the quinone imine **6** with the lithium salt of cyanophthalide[21,22] anion formed the magenta anthraquinone **36** in 14% yield over 2 steps.

The anthraquinone **36** is one step away from the desired product. Deprotection of the Boc groups in **36** would afford the spermine-conjugated analog **4**. This seemingly simple transformation proved to be quite problematic. Thus far, efforts towards this deprotection have not been successful.


CH3
H
HN
O
O
OH
O
OH
NBoc
Boc
N
NHBoc
N
H
36
CH3
H
HN
O
O
OH
O
OH
NH
N
H
NH2
4

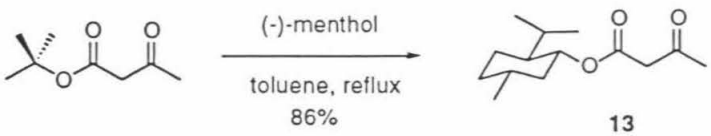
## Experimental Section

**General Procedure.** All reactions were performed in flame-dried round-bottomed or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation for 10-15 seconds and flushing with argon (≥5 iterations). Organic solutions were concentrated by rotary evaporations below 30 ℃ at ca.25 Torr (water aspirator). Analytical thin-layered chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by immersion in an acidic staining solution (*p*-anisaldehyde or ceric ammonium molybdinate) followed by heating on a hot-plate. Flash column chromatography was performed employing 230-400 mesh silica gel.

**Materials.** Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl. Methanol was distilled from magnesium turnings. Dichloromethane, triethylamine, benzene, and acetonitrile were distilled from calcium hydride. Trimethylsilyl trifluoromethane-sulfonate was stored in the glove-box in round-bottomed flasks fitted with polycarbonate or glass stoppers. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

**Instrumentation.** Infrared spectra are referenced to a polystyrene standard. Data is presented as follows: frequency of adsorption ($cm^{-1}$), intensity of adsorption (s = strong, m = medium, w = weak, br = broad) and assignment. Proton magnetic resonance ($^1H$ NMR) spectra were recorded at 400 or 300 MHz; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual

protium in the NMR solvent ($CHCl_3$: δ 7.26, $C_6HD_5$: δ 7.15). Data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet and/or multiple resonances, br = broad), integration, coupling constant in Hertz (Hz), and assignment.




13

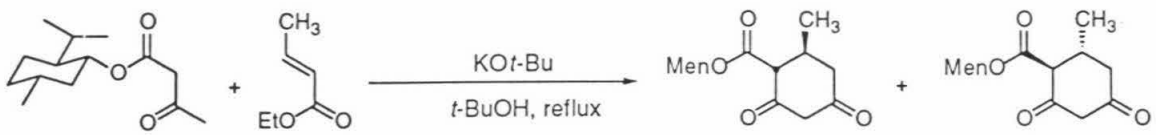
**Menthyl acetoacetate (13)**

A solution of *tert*-butyl acetoacetate (250 mL, 1.51 mol, 1 equiv) and (-)-menthol (247g, 1.58 mol, 1.1 equiv) in toluene (360 mL) was heated at reflux for 23 h, then was cooled to 23 °C. The solvent was removed *in vacuo*, and toluene (300 mL) was added to the residue. The resulting solution was heated at reflux for another 24 h, then was cooled to 23 °C, and the solvent was removed *in vacuo*. The residue was purified by distillation under reduced pressure to afford the menthyl acetoacetate **13** as a yellow viscous oil (313g, 86%).

$^1$H NMR (300 MHz, $CDCl_3$) δ: 12.25 (s, 1H, enol OH), 4.95 (s, 1H, enol CH), 4.75 (td, 1H, $J$ = 10.9, 4.4 Hz, menthyl CHO), 3.43 (s, 2H, $COCH_2CO$), 2.26 (s, 3H, $COCH_3$), 2.02 (m, 1H, menthyl $CH_2$), 1.87 (m, 1H, menthyl CH), 1.69 (m, 2H, menthyl $CH_2$), 1.42 (m, 2H, menthyl CH), 1.05 (m, 2H, menthyl $CH_2$), 0.91 (d, 3H, $J$ = 4.9 Hz, menthyl $CH_3$), 0.89 (d, 3H, $J$ = 5.4 Hz, menthyl $CH_3$), 0.83 (m, 1H, menthyl $CH_2$), 0.76 (d, 3H, $J$ = 7.0 Hz, menthyl $CH_3$).

FTIR (neat), $cm^{-1}$: 1716 (s, C=O).

TLC (40% EtOAc–hexanes), $R_f$: 0.66




13 14 15

1 : 1

**Diketone 14**

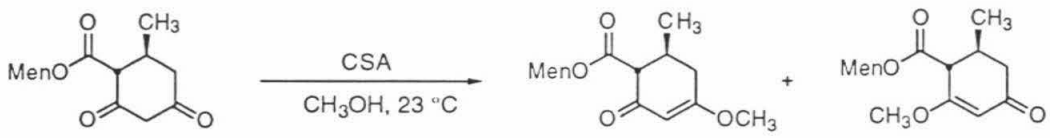
A 250-mL, 3-necked, round-bottomed flask, fitted with a condenser, a mechanical stirrer, and a rubber septum, was charged with *t*-butanol (40 mL) and potassium *t*-butoxide (6.60 g, 58.8 mmol, 1.1 equiv). The resulting mixture was heated at reflux for 15 minutes. A solution of menthyl acetoacetate (14.4 g, 59.7 mmol, 1.1 equiv) in *t*-butanol (4 mL) was then added via a syringe, and the resulting heterogeneous mixture was held at reflux for 0.5 h until the enolate salt had dissolved partially. A solution of *trans*-ethyl crotonate (7.00 mL, 56.0 mmol, 1 equiv) in *t*-butanol (4 mL) was transferred via a cannula over 20 minutes into the above reaction mixture. The resulting heterogeneous mixture was heated at reflux for another 0.5 h (from *trans*-ethyl crotonate addition), then was cooled to 23 °C. The viscous reaction mixture was partitioned between aqueous sulfuric acid solution (5% v/v, 150 mL) and dichloromethane (170 mL). The aqueous layer was separated and was further extracted with dichloromethane (2 × 170 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by recrystallization (2 ×) from boiling benzene (400 mL) to afford the diketone **14** (5.25g, 30%) as a white solid. To isolate the diastereromeric diketone product **15**, the mother liquor was concentrated *in vacuo*, and the residue was purified by recrystallization from boiling solution of ethyl acetate (130 mL) and hexanes (30 mL) to yield the ketone **15** (4.48g, 26%).

**14**

| | |
|---|---|
| $^1$H NMR (300 MHz, $CDCl_3$) δ: | 4.79 (1H, td, *J* = 10.9, 4.2 Hz, menthyl C**H**O), 3.63 (1H, d, *J* = 17.2 Hz, COC**H**$_2$CO), 3.40 (1H, d, *J* = 17.2 Hz, COC**H**$_2$CO), 3.30 (1H, d, *J* = 7.6 Hz, COC**H**CO), 2.80 (1H, dd, *J* = 15.5, 4.4 Hz, C**H**$_2$CO), 2.60 (1H, m, C**H**CH$_3$), 2.39 (1H, dd, *J* = 15.5, 10.4 Hz, C**H**$_2$CO), 2.05 (1H, m, menthyl C**H**$_2$), 1.90 (1H, m, menthyl C**H**), 1.70 (2H, m, menthyl C**H**$_2$), 1.50 (1H, m, menthyl C**H**), 1.40 (1H, m, menthyl C**H**), 1.10 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$), 1.00 (2H, m, menthyl C**H**$_2$), 0.92 (3H, d, *J* = 5.9 Hz, menthyl C**H**$_3$), 0.90 (3H, d, *J* = 6.2 Hz, menthyl C**H**$_3$), 0.85 (1H, m, menthyl C**H**$_2$), 0.78 (3H, d, *J* = 7.0 Hz, menthyl C**H**$_3$). |
| FTIR ($CH_2Cl_2$, $cm^{-1}$): | 727 (w, ester C=O, 1605 (w, C=O), 1421 (m), 1270 (s), 757 (m), 703 (s). |
| TLC (5% MeOH–$CH_2Cl_2$), $R_f$: | 0.19 |
| melting point: | 179 °C |

**15**

| | |
|---|---|
| $^1$H NMR (300 MHz, $CDCl_3$) δ: | 4.79 (1H, td, *J* = 10.9, 4.4 Hz, menthyl CHO), 3.66 (1H, d, *J* = 17.2 Hz, $COCH_2CO$), 3.40 (1H, d, *J* = 17.2 Hz, $COCH_2CO$), 3.30 (1H, d, *J* = 7.6 Hz, COCHCO), 2.80 (1H, dd, *J* = 15.5, 4.4 Hz, $CH_2CO$), 2.61 (1H, m, $CHCH_3$), 2.40 (1H, dd, *J* = 15.5, 10.4 Hz, $CH_2CO$), 2.02 (1H, m, menthyl $CH_2$), 1.85 (1H, m, menthyl CH), 1.68 (2H, m, menthyl $CH_2$), 1.51 (1H, m, menthyl CH), 1.41 (1H, m, menthyl CH), 1.10 (3H, d, *J* = 6.7 Hz, $CHCH_3$), 1.05 (2H, m, menthyl $CH_2$), 0.93 (3H, d, *J* = 5.9 Hz, menthyl $CH_3$), 0.89 (3H, d, *J* = 6.2 Hz, menthyl $CH_3$), 0.86 (1H, m, menthyl $CH_2$), 0.75 (3H, d, *J* = 7.0 Hz, menthyl $CH_3$). |
| TLC (5% MeOH–$CH_2Cl_2$), $R_f$: | 0.19 |
| melting point | 128 °C |




14 16 17

4 : 1

**Methyl enol ether 16**

Camphorsulfonic acid (129 mg, 0.550 mmol, 0.050 equiv) was added to a solution of the diketone **14** (3.41g, 11.0 mmol, 1 equiv) in methanol (50 mL). The resulting reaction solution was stirred at 23 °C for 19 h. It was neutralized by the addition of solid potassium carbonate (152 mg, 1.10 mmol, 0.10 equiv). The reaction mixture was then filtered, and the filtrate was concentrated *in vacuo*. The residue was concentrated from toluene (2 × 3 mL), and was purified by flash column chromatography (20% EtOAc–hexanes) to afford the desired methyl enol ether **16** as a white solid (2.32 g, 65%) and the regioisomeric product **17**.

**16**

$^1$H NMR (400 MHz, $CDCl_3$) δ: 5.36 (d, 1H, *J* = 1.1 Hz, C=C**H**), 4.74 (td, 1H, *J* = 11.0, 4.4 Hz, menthyl C**H**O), 3.70 (s, 3H, OC**H**$_3$), 2.96 (d, 1H, *J* = 11.0 Hz, COC**H**CO), 2.57 (m, 1H, C**H**CH$_3$), 2.47 (dd, 1H, *J* = 17.2, 4.8 Hz, CHC**H**$_2$), 2.18 (ddd, 1H, *J* = 17.6, 11.0, 1.5 Hz, CHC**H**$_2$), 2.03 (m, 2H, menthyl C**H**$_2$, menthyl C**H**), 1.65 (m, 2H, menthyl C**H**$_2$),

1.47 (m, 1H, menthyl C**H**), 1.40 (m, 1H, menthyl C**H**), 1.06 (d, 3H, $J$ = 6.2 Hz, CHC**H**$_3$), 0.96 (m, 2H, menthyl C**H**$_2$), 0.88 (d, 3H, $J$ = 6.6 Hz, menthyl C**H**$_3$), 0.87 (d, 3H, $J$ = 7.3 Hz, menthyl C**H**$_3$), 0.85 (m, 1H, menthyl C**H**$_2$), 0.76 (d, 3H, $J$ = 7.0 Hz, menthyl C**H**$_3$).

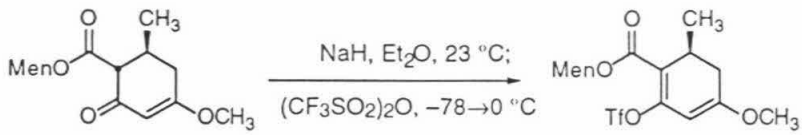
FTIR (thin film, cm$^{-1}$): 1732 (s, C=O), 1657 (s, α,β-unsaturated C=O), 1611 (s, C=C).

TLC (5% MeOH–$CH_2Cl_2$), $R_f$: 0.74

**17**

$^1$H NMR (300 MHz, $CDCl_3$) δ: 5.42 (d, 1H, $J$ = 1.2 Hz, C=C**H**), 4.74 (td, 1H, $J$ = 10.9, 4.2 Hz, menthyl C**H**O), 3.68 (s, 3H, OC**H**$_3$), 3.16 (dd, 1H, $J$ = 9.0, 1.2 Hz, COCHCO), 2.55 (m, 1H, C**H**CH$_3$), 2.50 (dd, 1H, $J$ = 15.6, 4.5 Hz, CHC**H**$_2$), 2.08 (d, 1H, $J$ = 5.4 Hz, CHC**H**$_2$), 1.97 (m, 1H, menthyl C**H**$_2$), 1.86 (m, 1H, menthyl C**H**), 1.65 (m, 2H, menthyl C**H**$_2$), 1.50 (m, 1H, menthyl C**H**), 1.40 (m, 1H, menthyl C**H**), 1.07 (d, 3H, $J$ = 6.3 Hz, CHC**H**$_3$), 0.95 (m, 2H, menthyl C**H**$_2$), 0.90 (d, 3H, $J$ = 6.6 Hz, menthyl C**H**$_3$), 0.89 (d, 3H, $J$ = 6.9 Hz, menthyl C**H**$_3$),

| | |
|---|---|
| | 0.81 (m, 1H, menthyl C**H**$_2$), 0.76 (d, 3H, *J* = 6.9 Hz, menthyl C**H**$_3$). |
| FTIR (thin film, cm$^{-1}$): | 1731 (s, C=O, 1660 (s, α,β-unsaturated C=O), 1613 (s, C=C). |
| TLC (5% MeOH–$CH_2Cl_2$), $R_f$: | 0.58 |



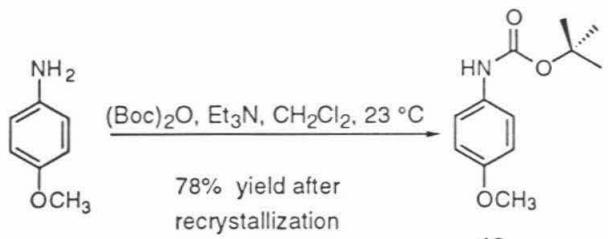

16 12

**Enol triflate 12**

A solution of the methyl enol ether **16** (1.06 g, 3.28 mmol, 1 equiv) in ether (8.5 mL) was transferred by cannula to a stirring suspension of sodium hydride (0.112 g, 4.65 mmol, 1.4 equiv) in ether (2.8 mL) at 0 °C. The resulting reaction mixture was slowly warmed to 23 °C over 10 min and was held at that temperature for 5 h. 10-μL portions of water were added every 30 min to initiate the sodium hydride until the reaction mixture turned bright yellow. The yellow reaction mixture was cooled to −78 °C, and triflic anhydride (0.830 mL, 4.96 mmol, 1.5 equiv) was added. The resulting solution mixture was warmed to 0 °C and was held at that temperature for 0.5 h. The reaction solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 11 mL) and ether (11 mL). The aqueous layer was separated and was extracted further with ether (2 × 11 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. Purification of the product by flash column chromatography (10% EtOAc–hexanes) afforded the enol triflate **12** as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ: 4.87 (br s, 1H, C=C**H**), 4.82 (td, 1H, *J* = 10.9, 4.4 Hz, menthyl C**H**O), 3.66 (s, 3H, $OCH_3$), 3.03 (m, 1H, $CHCH_3$, 2.75 (ddd,

| | |
|---|---|
| | 1H, $J$ = 17.2, 8.1, 2.1 Hz, CHC**H**$_2$), 2.03 (m, 2H, CHC**H**$_2$, menthyl C**H**$_2$), 1.89 (m, 1H, menthyl C**H**), 1.65 (m, 2H, menthyl C**H**$_2$), 1.50 (m, 2H, menthyl C**H**), 1.06 (d, 3H, $J$ = 7.0 Hz, CHC**H**$_3$), 1.02 (m, 2H, menthyl C**H**$_2$), 0.88 (d, 3H, $J$ = 4.6 Hz, menthyl C**H**$_3$), 0.87 (m, 1H, menthyl C**H**$_2$), 0.85 (d, 3H, $J$ = 5.1 Hz, menthyl CH$_3$), 0.72 (d, 3H, $J$ = 7.0 Hz, menthyl C**H**$_3$). |
| $^{13}$C NMR (75 MHz, $CDCl_3$) δ: | 166.7, 163.6, 150.5, 120.5, 114.7, 90.3, 75.0, 55.8, 46.4, 40.6, 34.1, 34.0, 31.4, 28.9, 25.8, 23.1, 21.9, 20.7, 17.1, 15.9 |
| FTIR (thin film, cm$^{-1}$): | 2957 (s), 2871 (m), 1703 (s, C=O), 1644, 1586 |
| TLC (15% EtOAc–hexanes), $R_f$: | 0.50 |



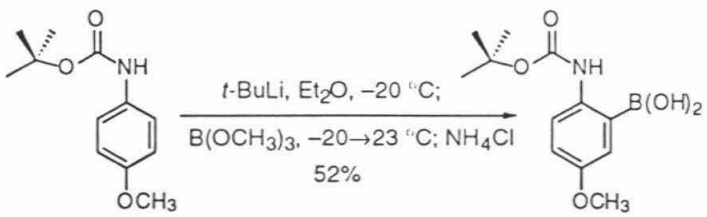

**18**

**Aryl carbamate 18**

Di-*tert*-butyl dicarbonate (134 mL, 0.585 mol, 1.2 equiv) was added to a stirring solution of *p*-anisidine (60.0 g, 0.487 mol, 1 equiv) and triethylamine (68.0 mL, 0.487 mol, 1 equiv) in dichloromethane (800 mL) at 0 °C. The resulting reaction solution was warmed to 23 °C and was held at that temperature for 6 h. As the reaction proceeded, solids were observed to crash out of the solution. The reaction mixture was filtered, and the filtrate was extracted with saturated aqueous ammonium chloride solution (2 × 500 mL). The organic layer was concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc–hexanes). Appropriate fractions were pooled and were concentrated *in vacuo*. The residue was purified by recrystallization from hot ethyl acetate (30 mL) and hexanes (6 mL) to afford the aryl carbamate **18** as clear needles (84.4 g, 78%).

| | |
|---|---|
| $^1$H NMR (400 MHz, $CDCl_3$) δ: | 7.26 (br d, 2H, $J$ = 8.6 Hz, *o*-aryl), 6.82 (d, 2H, $J$ = 8.6 Hz, *m*-aryl), 6.43 (br s, 1H, NH), 3.80 (s, 3H, $OCH_3$), 1.53 (s, 9H, *t*-butyl $CH_3$) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) δ: | 155.7, 153.2, 131.4, 120.6, 114.2, 80.2, |

| | |
|---|---|
| | 55.5, 28.4 |
| FTIR (thin film, $cm^{-1}$): | 1694 (m, C=O), 1523 (s), 1412 (m) |
| TLC (20% EtOAc–hexanes), $R_f$: | 0.39 |



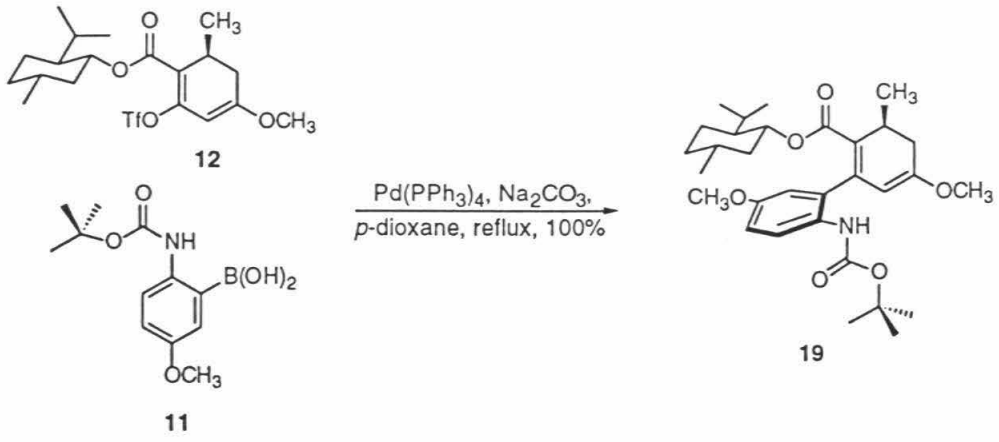

18 11

**Boronic acid 11**

A solution of *t*-butyllithium in pentane (1.42 M, 24.0 mL, 0.0335 mol, 2.5 equiv) was added to a stirring solution of the aryl carbamate **18** (3.00 g, 0.0134 mol, 1 equiv) in ether (48 mL) at –20 °C, causing the reaction solution to turn cloudy after 5 min. The reaction was held stirring for 6 h at that temperature, and then it was quenched with trimethyl borate (4.50 mL, 0.0402 mol, 3.0 equiv). Upon the addition of trimethyl borate the reaction turned viscous almost instantaneously. It was manually shaken vigorously for 5 min, was warmed to 23 °C, and was held at that temperature for 12 h. The reaction mixture was partitioned between a saturated aqueous ammonium chloride solution (45 mL) and ethyl acetate (45 mL). The aqueous layer was separated and was extracted further with ethyl acetate (45 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The yellow solid residue was purified by flash column chromatography (2.5% MeOH–$CH_2Cl_2$ gradient to 10% MeOH–$CH_2Cl_2$) to afford the aryl boronic acid **11** as a yellow foam (1.86 g, 52%).

$^1$H NMR (300 MHz, $CDCl_3$) δ: 8.85 (br s, 1H, N**H**), 7.61 (br d, 1H, *J* = 8.8 Hz, *o*-aryl), 7.38 (dd, 1H, *J* = 3.1, 0.47 Hz, *m*-aryl), 6.93 (dd, 1H, *J* = 8.8,

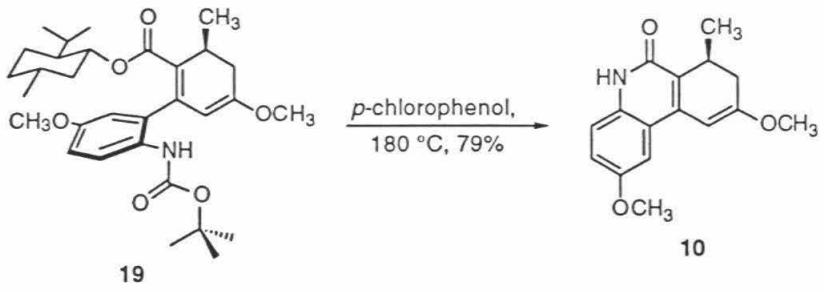
| | |
|---|---|
| | 3.1 Hz, *m*-aryl), 3.80 (s, 3H, $OCH_3$), 3.50 (s, 2H, OH), 1.47 (s, 9H, *t*-butyl $CH_3$) |
| FTIR (thin film, $cm^{-1}$): | 3331 (br, m, OH), 1722 (m, C=O), 1694 (m), 1633 (m), 1592 (m) |
| TLC (10% MeOH–$CH_2Cl_2$), $R_f$: | 0.40 |




**Bi-aryl adduct 19**

Tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0156 mmol, 0.039 equiv) was added to a deoxygenated mixture of the enol triflate **12** (180 mg, 0.395 mmol, 1 equiv), an aqueous solution of sodium carbonate (2 M, 0.290 mL, 0.573 mmol, 1.5 equiv), and the aryl boronic acid **11** (116 mg, 0.435 mmol, 1.1 equiv) in *p*-dioxane (2.5 mL). After further deoxygenation by alternate vacuum/argon purge cycles (6 ×), the resulting reaction mixture was heated at reflux for 1.5 h, was then cooled to 23 ℃ , and was concentrated to half the original volume *in vacuo*. The reaction suspension was partitioned between water (5 mL) and ethyl acetate (5 mL). The aqueous layer was separated and was further extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc–hexanes) to afford the biaryl adduct **19** as a solid in 1:1 mixture of atropisomers (276 mg, quantitative yield).

| | |
|---|---|
| $^1$H NMR (400 MHz, $CDCl_3$, 1:1 mixture of atropisomers) δ: | 7.76 (br s, 1H, *o*-aryl), 6.80 (m, 1H, *m*-aryl), 6.53, 6.47 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 6.27, 6.18 (br s, 1H, NH), 4.87, 4.86 (s, 1H, C=CH), 4.50 (m, 1H, menthyl CHO), 3.75, 3.74 (s, 3H, aryl $OCH_3$), 3.62 (s, 3H, enol $OCH_3$), 3.15, 2.99 (m, 1H, $CHCH_3$), 2.82 (m, 1H, $CHCH_2$), 2.09, 2.08 (d, 1H, *J* = 16.8 Hz, $CHCH_2$), 1.84, 1.83 (br s, 1H, menthyl $CH_2$), 1.73, 1.71 (br s, 1H, menthyl CH), 1.51 (m, 2H, menthyl $CH_2$), 1.46, 1.44 (s, 9H, $C(CH_3)_3$), 1.35 (m, 2H, menthyl CH), 1.18, 1.16 (d, 3H, *J* = 7.0 Hz, $CHCH_3$), 0.87 (m, 2H, menthyl $CH_2$), 0.82 (d, 3H, *J* = 6.6 Hz, menthyl $CH_3$), 0.78, 0.77 (d, 3H, *J* = 6.2 Hz, menthyl $CH_3$), 0.68, 0.64 (d, 3H, *J* = 7.0 Hz, menthyl $CH_3$). |
| FTIR (thin film, $cm^{-1}$): | 3427 (w), 3340 (br, w, NH), 1727 (s, C=O), 1681 (m), 1519 (s) |
| TLC (15% EtOAc–hexanes), $R_f$: | 0.32 |



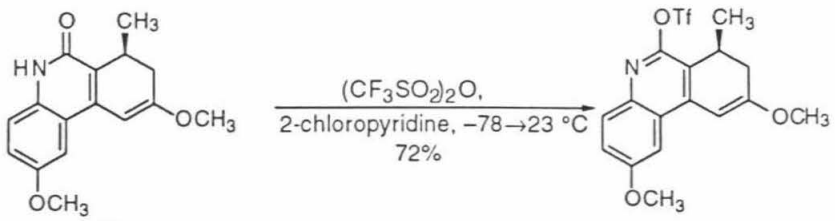

**Quinolone 10**

A deoxygenated solid mixture of the biaryl **19** (11.2 g, 21.1 mmol, 1 equiv) and *p*-chlorophenol (190 g) was heated at 180 °C for 30 min. *p*-Chlorophenol was removed by distillation under reduced pressure, and the residue was purified by flash column chromatography ($CH_2Cl_2$ gradient to 10% MeOH–$CH_2Cl_2$) to yield the quinolone **10** as a yellow solid (4.50 g, 79%).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 11.19 (br s, 1H, N**H**), 7.30 (d, 1H, $J$ = 9.0 Hz, *o*-aryl), 7.19 (d, 1H, $J$ = 2.6 Hz, *m*-aryl), 7.13 (dd, 1H, $J$ = 9.0, 2.6 Hz, *m*-aryl), 5.87 (s, 1H, C=C**H**), 3.93 (s, 3H, aryl OC**H**$_3$), 3.89 (s, 3H, enol OC**H**$_3$), 3.52 (quin, 1H, $J$ = 6.6 Hz, C**H**CH$_3$), 2.84 (ddd, 1H, $J$ = 16.5, 8.1, 1.6 Hz, CHC**H**$_2$), 2.21 (d, 1H, $J$ = 16.8, CHC**H**$_2$), 1.15 (d, 3H, $J$ = 7.0 Hz, CHC**H**$_3$)

FTIR (thin film, cm$^{-1}$): 1651 (m, C=O), 1620 (s), 1583 (s), 1505

| | (m) |
|---|---|
| TLC (EtOAc), $R_f$: | 0.34 |



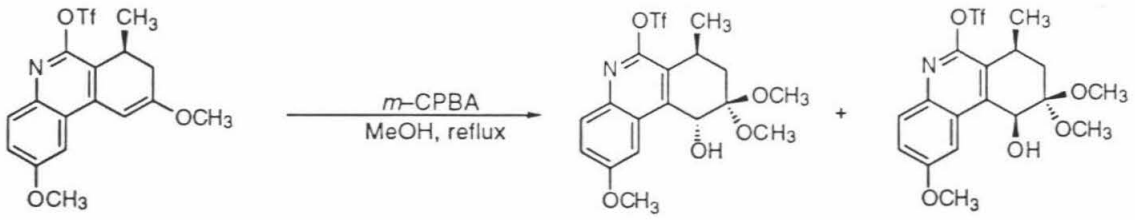

10 20

**Quinolyl triflate 20**

Triflic anhydride (226 μL, 1.34 mmol, 2.0 equiv) was added to a stirring cloudy mixture of the quinolone **10** (182 mg, 0.672 mmol, 1 equiv) and 2-chloropyridine (254 μL, 2.69 mmol, 4.0 equiv) in dichloromethane (7 mL) at –78 °C. The resulting reaction solution was warmed to 23 °C over 30 min and was held at that temperature for 15 min. As the reaction proceeded, solids were observed to dissolve in solution. The reaction solution was poured into aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 4.5 mL). The aqueous layer was separated and was extracted further with dichloromethane (2 × 5 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (30% $CH_2Cl_2$–hexanes) to furnish the quinolyl triflate **20** as a white solid (195 mg, 72%).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, 1H, $J$ = 9.5 Hz, *o*-aryl), 7.35 (dd, 1H, $J$ = 9.2, 2.6 Hz, *m*-aryl), 7.20 (d, 1H, $J$ = 2.9 Hz, *m*-aryl), 6.09 (s, 1H, C=C**H**), 3.96 (s, 3H, aryl O**CH**$_3$), 3.91 (s, 3H, enol O**CH**$_3$), 3.39 (quin, 1H, $J$ = 6.2 Hz,

| | |
|---|---|
| | C**H**CH$_3$), 2.91 (ddd, 1H, $J$ = 16.8, 7.7, 1.8 Hz, CHC**H**$_2$), 2.28 (d, 1H, $J$ = 16.8 Hz, CHC**H**$_2$), 1.21 (d, 3H, $J$ = 7.0 Hz, CHC**H**$_3$) |
| FTIR (thin film, cm$^{-1}$): | 1621 (m), 1551 (m), 1513 (m), 1411 (m), 1224 (s), 1200 (s) |
| TLC (40% $CH_2Cl_2$–hexanes), $R_f$: | 0.30 |




**20** **21** **22**

75% 10%

**Dimethyl ketal 21**

A solution of the quinolyl triflate **20** (195 mg, 0.483 mmol, 1 equiv) and *meta*-chloroperoxybenzoic acid (70% w/w, 237 mg, 0.961 mmol, 2.0 equiv) in methanol (6.6 mL) was heated at reflux for 45 min. The reaction solution was cooled to 23 °C and was partitioned between a 1:1 mixture of saturated aqueous sodium bicarbonate and sodium thiosulfate (6 mL) and dichloromethane (6 mL). The aqueous layer was separated and was further extracted with dichloromethane (2 × 6 mL). The combined organic layers were dried over sodium sulfate, and were concentrated *in vacuo*. The yellow oil residue was purified by flash column chromatography (20% EtOAc–hexanes gradient to 60% EtOAc–hexanes) to yield the dimethyl ketal **21** as a white foam (162 mg, 75%) and its diastereomer **22** as a yellow foam (21.2 mg, 10%).

**21**

$^1$H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, 1H, $J$ = 9.2 Hz, *o*-aryl), 7.44 (d, 1H, $J$ = 2.6 Hz, *m*-aryl), 7.37 (dd, 1H, $J$ = 9.2, 2.6 Hz, *m*-aryl), 5.2 (s, 1H, allylic CHOH), 3.97 (s, 3H, aryl $OCH_3$), 3.49 (s,

3H, $OCH_3$), 3.34 (m, 1H, $CHCH_3$), 3.30 (s, 3H, $OCH_3$), 2.71 (br s, 1H, OH), 2.26 (dd, 1H, $J$ = 14.3, 7.0 Hz, $CHCH_2$), 2.08 (app td, 1H, $J$ = 14.3, 1.5 Hz, $CHCH_2$), 1.44 (d, 3H, $J$ = 7.3 Hz, $CHCH_3$)

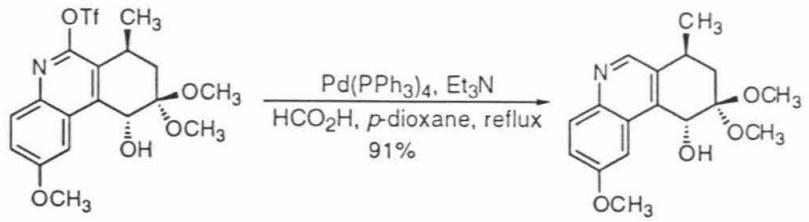
FTIR (thin film, $cm^{-1}$): 3672 (br, w, OH), 1621 (m), 1513 (m), 1415 (s), 1227 (s)

TLC (40% EtOAc–hexanes), $R_f$: 0.26

**22**

$^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.87 (d, 1H, $J$ = 9.3 Hz, *o*-aryl), 7.45 (d, 1H, $J$ = 2.7 Hz, *m*-aryl), 7.37 (dd, 1H, $J$ = 9.0, 2.7 Hz, *m*-aryl), 5.12 (d, 1H, $J$ = 1.8 Hz, CHOH), 4.0 (s, 3H, aryl $OCH_3$), 3.45 (s, 3H, $OCH_3$), 3.23 (quin, 1H, $J$ = 6.9 Hz, $CHCH_3$), 3.21 (s, 3H, $OCH_3$), 2.7 (br s, 1H, OH), 2.37 (ddd, 1H, $J$ = 14.4, 7.2, 2.1 Hz, $CHCH_2$), 1.93 (dd, 1H, $J$ = 14.1, 9.9 Hz, $CHCH_2$), 1.43 (d, 3H, $J$ = 6.6 Hz, $CHCH_3$).

TLC (40% EtOAc–hexanes), $R_f$: 0.21



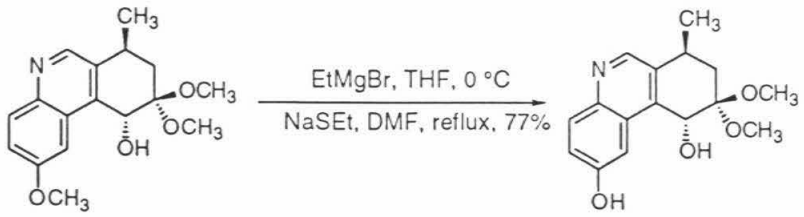

21 23

**Quinoline 23**

Tetrakis(triphenylphosphine)palladium (0) (21.3 mg, 0.00184 mmol, 0.050 equiv) was added to a deoxygenated solution of the dimethyl ketal **21** (162 mg, 0.360 mmol, 1 equiv) and triethylamine (0.200 mL, 1.44 mmol, 4.0 equiv) in *p*-dioxane (6.4 mL). The resulting yellow reaction mixture was further deoxygenated by alternate vacuum/argon purge cycles (6 ×). Formic acid (35.3 μL, 0.936 mmol, 2.6 equiv) was added, followed by further deoxygenation (3 ×), and the reaction mixture was heated at reflux for 20 min. It was subsequently cooled to 23 °C and was partitioned between saturated aqueous sodium chloride solution (6 mL) and ethyl acetate (6 mL). The aqueous layer was separated and was further extracted with ethyl acetate (2 × 6 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The yellow residue was purified by flash column chromatography (ether) to afford the quinoline **23** as yellow solids (98.8 mg, 91%).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 8.64 (s, 1H, CN**H**), 7.97 (d, 1H, $J$ = 9.2 Hz, *o*-aryl), 7.49 (d, 1H, $J$ = 2.6 Hz, *m*-aryl), 7.31 (dd, 1H, $J$ = 9.2, 2.6 Hz, *m*-aryl), 5.24 (s, 1H, C**H**OH), 3.96 (s, 3H,

| | |
|---|---|
| | aryl $OCH_3$), 3.50 (s, 3H, $OCH_3$), 3.35 (s, 3H, $OCH_3$), 3.26 (m, 1H, $CHCH_3$), 2.95 (br s, 1H, OH), 2.29 (dd, 1H, $J$ = 14.3, 6.6 Hz, $CHCH_2$), 1.90 (dd, 1H, $J$ = 14.3, 4.0 Hz, $CHCH_2$), 1.46 (d, 3H, $J$ = 7.3 Hz, $CHCH_3$) |
| FTIR (thin film, $cm^{-1}$): | 3222 (br, w, OH), 1620 (s), 1508 (s), 1227 (s), 1129 (s) |
| TLC (50% EtOAc–hexanes), $R_f$: | 0.15 |

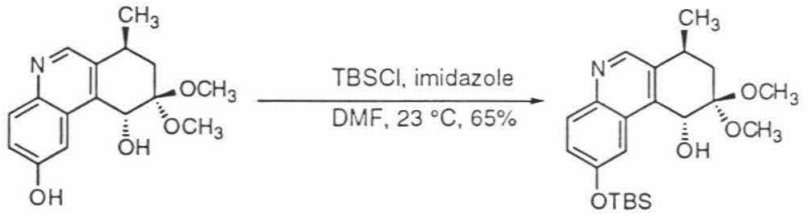



23 24

**Phenol 24**

A solution of ethylmagnesium bromide in tetrahydrofuran (1 M, 360 μL, 0.359 mmol, 1.1 equiv) was added to a stirring solution of the aryl methyl ether **23** (98.8 mg, 0.326 mmol, 1 equiv) in tetrahydrofuran (200 μL) at –78 °C. The resulting reaction solution was warmed to 0 °C and was held at that temperature for 10 min. It was then cooled to –78 °C. In a separate flask, ethanethiol (72.4 μL, 0.928 mmol, 3.0 equiv) was added to a slurry of sodium hydride (470 mg, 1.96 mmol, 6.0 equiv) in DMF (800 μL) at 0 °C. The resulting ethanethiolate anion was warmed to 23 °C and was held at that temperature for 10 min. The previously prepared magnesium alkoxide solution was transferred via a cannula into this ethanethiolate slurry. After removal of the more volatile solvent THF, the resulting reaction mixture was heated at reflux for 1.5 h and was cooled to 23 °C. It was partitioned between saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL). The aqueous layer was separated and was extracted sequentially with ethyl acetate (5 mL) and 20% methanol in dichloromethane (5 mL). The aqueous layer was separated, was acidified with 1 N hydrochloric acid solution (2 mL), and was extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (2.5% MeOH–$CH_2Cl_2$ gradient to 5% MeOH–$CH_2Cl_2$) to afford the quinoline **24** as yellow solids (77%).

| | |
|---|---|
| $^1$H NMR (400 MHz, $CDCl_3$), δ: | 8.61 (s, 1H, CN**H**), 7.93 (d, 1H, *J* = 9.15 Hz, *o*-aryl), 7.54 (d, 1H, *J* = 2.56 Hz, *m*-aryl), 7.23 (dd, 1H, *J* = 9.15, 2.56 Hz, *m*-aryl), 5.15 (s, 1H, **CH**OH), 3.44 (s, 3H, OC**H**$_3$), 3.29 (s, 3H, OC**H**$_3$), 3.24 (m, 1H, C**H**CH$_3$), 2.28 (dd, 1H, *J* = 14.27, 6.59 Hz, C**H**$_2$), 1.89 (dd, 1H, *J* = 14.27, 3.66 Hz), 1.44 (d, 3H, *J* = 7.32 Hz, CHC**H**$_3$). |
| FTIR (thin film, $cm^{-1}$): | 3198 (br, m, OH), 2961 (m), 1620 (s), 1513 (m), 1227 (s). |
| TLC (5% MeOH–$CH_2Cl_2$), $R_f$: | 0.11 |



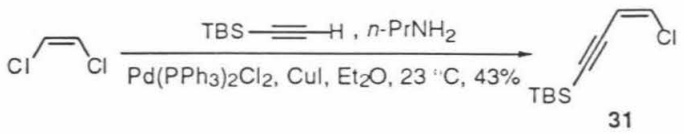

**24** **25**

**Aryl silyl ether 25**

*Tert*-butyldimethylsilyl chloride was added to a stirring solution of the phenol **24** (730 mg, 0.252 mmol, 1 equiv) and imidazole (45.5 mg, 0.668 mmol, 2.7 equiv) in DMF (500 μL) at 23 °C. The resulting reaction solution was held stirring at that temperature for 1.25 h, and it was partitioned between water (5 mL) and ethyl acetate (5 mL). The aqueous layer was separated and was extracted further with ethyl acetate (3 × 5 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc–hexanes) to yield the aryl silyl ether **25** as yellow solids (65%).

$^1$H NMR (400 MHz, $CDCl_3$), δ: 8.64 (s, 1H, CN**H**), 7.93 (d, 1H, *J* = 9.2 Hz, *o*-aryl), 7.57 (d, 1H, *J* = 2.6 Hz, *m*-aryl), 7.23 (dd, 1H, *J* = 9.2, 2.6 Hz, *m*-aryl), 5.17 (br d, 1H, *J* = 3.3 Hz, C**H**OH), 3.46 (s, 3H, OC**H**$_3$), 3.26 (s, 3H, OC**H**$_3$), 3.25 (m, 1H, C**H**CH$_3$), 2.89 (br d, 1H, *J* = 4.00 Hz, O**H**), 2.30 (dd, 1H, *J* = 14.27, 6.59 Hz, CHC**H**$_2$), 1.90 (dd, 1H, *J* =

| | |
|---|---|
| | 14.27, 4.03 Hz, $CHCH_2$), 1.47 (d, 3H, $J$ = 7.32 Hz, $CHCH_3$), 1.01 (s, 9H, $SiC(CH_3)_3$), 0.27 (s, 3H, $Si(CH_3)_2$), 0.26 (s, 3H, $Si(CH_3)_2$). |
| FTIR (thin film, $cm^{-1}$): | 3177 (br, w, OH), 2955 (m), 1617 (m), 1505 (s) |
| TLC (40% EtOAc–hexanes), $R_f$: | 0.31 |




31

**Vinyl chloride 31**

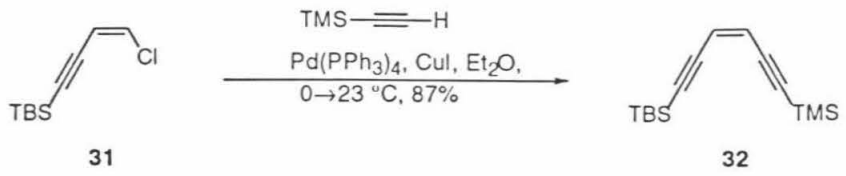
A solution of (*t*-butyldimethylsilyl)acetylene (1.30 mL, 7.13 mmol, 1 equiv), *n*-propylamine (2.90 mL, 35.7 mmol, 5.0 equiv), and 1,2-*cis*-dichloroethylene (2.20 mL, 28.5 mmol, 4.0 equiv) in ether (10.3 mL) was deoxygenated at –78 °C by alternate vacuum/argon purge cycles (8 ×). It was warmed to 0 °C, and copper iodide (204 mg, 1.07 mmol, 0.15 equiv) was added, resulting in a bluish color. The resulting bluish reaction mixture was again cooled to –78 °C for further deoxygenation (8 ×), then was warmed to 0 °C , and bis(triphenylphosphine)palladium (II) chloride (256 mg, 0.357 mmol, 0.050 equiv) was added. After further deoxygenation (10 ×) at –78 °C, the reaction mixture was warmed to 23 °C, and was held at that temperature for 4 h. As the reaction progressed it turned to greenish, to dark blue, to whitish, and eventually to yellowish green. The reaction suspension was poured into a 1:1 mixture of saturated aqueous ammonium chloride solution and saturated aqueous potassium carbonate solution (10 mL). The separated organic layer was extracted further with the above aqueous solution (2 × 10 mL), was dried over sodium sulfate, and was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes) to afford the vinyl chloride **31** as a colorless oil (43%).

$^1$H NMR (400 MHz, $CDCl_3$), δ: 6.41 (d, 1H, *J* = 7.7 Hz, CH=C**H**Cl), 5.89 (d, 1H, *J* = 7.7 Hz, CH=C**H**C≡C), 0.96 (s,

9H, $SiC(CH_3)_3$), 0.16 (s, 6H, $Si(CH_3)_2$).

FTIR (thin film, $cm^{-1}$): 2966 (s), 2946 (s), 2856 (s), 2361 (s).

TLC (hexanes), $R_f$: 0.51.

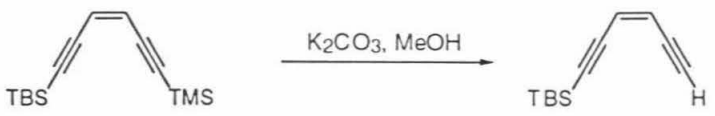



31 32

**Bis-protected enediyne 32**

To a deoxygenated solution of the vinyl chloride **31** (613 mg, 3.05 mmol, 1 equiv) in ether (6 mL) at –78 °C was added tetrakis(triphenylphosphine)palladium (0) (195 mg, 0.169 mmol, 0.060 equiv). The resulting mixture was further deoxygenated by alternate vacuum/argon purge cycles (8 ×) and was warmed to 23 °C. In a separate flask, copper iodide (93.5 mg, 0.491 mmol, 0.16 equiv) was added to a solution of (trimethylsilyl)acetylene (600 μL, 4.27 mmol, 1.4 equiv) and *n*-propylamine (1.00 mL, 11.9 mmol, 3.9 equiv) in ether (4 mL) at –78 °C. The resulting reaction mixture was deoxygenated (8 ×), was warmed to 0 °C, and was held at that temperature for 15 min. As the reaction progressed, it changed from bluish to greenish, then to reddish brown. This reddish brown reaction mixture was cooled to –78 °C and was transferred via a cannula into the previously prepared palladium slurry. The transfer was quantitated by ether (3 mL). After further deoxygenation by alternate vacuum/argon purge cycles (10 ×) at –78 °C, the reaction mixture was warmed to 0 °C and was held at that temperature for 3 h. It was further warmed to 23 °C and was held at that temperature for another 1.5 h. The resulting yellowish green reaction mixture was partitioned between saturated aqueous ammonium chloride solution (8 mL) and hexanes (16 mL). The aqueous layer was separated and was extracted further with hexanes (2 × 16 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes) to provide **32** as a yellow oil (87%).

| | |
|---|---|
| $^1$H NMR (400 MHz, $CDCl_3$), δ: | 5.84 (s, 2H, C**H**=C**H**), 0.96 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 9H, $Si(CH_3)_3$), 0.16 (s, 6H, $Si(CH_3)_2$). |
| FTIR (thin film, $cm^{-1}$): | 2955 (s), 2359 (m), 2154 (m), 1250 (s). |
| TLC (hexanes), $R_f$: | 0.37. |

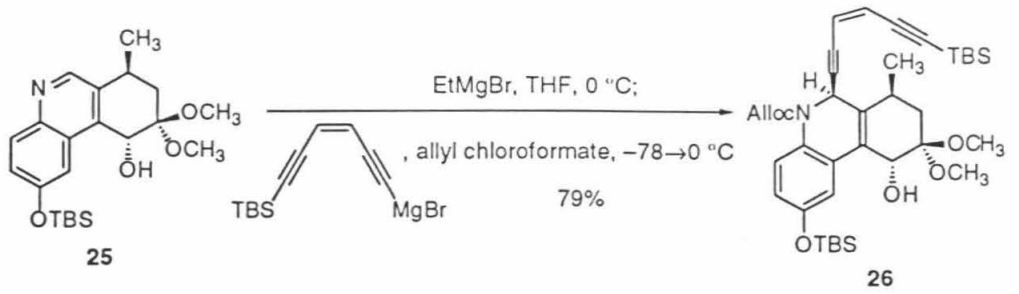



32 33

**Mono-protected enediyne 33**

Solid potassium carbonate (203 mg, 1.47 mmol, 1.1 equiv) was added to a solution the bis-protected enediyne **32** (347 mg, 1.32 mmol, 1 equiv) in methanol (4 mL). The resulting reaction mixture was held stirring at 23 ℃ for 1.25 h. It was then partitioned between brine (8 mL) and hexanes (8 mL). The aqueous layer was separated and was extracted further hexanes (8 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes) to afford **33** as a yellow oil.

| | |
|---|---|
| $^1$H NMR (300 MHz, $C_6D_6$), δ: | 5.50 (dd, 1H, $J$ = 11.1, 0.9 Hz, SiC≡CC**H**=CH), 5.37 (dd, 1H, $J$ = 11.1, 2.4 Hz, CH=C**H**C≡CH), 2.96 (d, 1H, $J$ = 0.9 Hz, C≡C**H**), 1.03 (s, 9H, SiC(C**H**$_3$)$_3$), 0.14 (s, 6H, Si(C**H**$_3$)$_2$). |
| TLC ( hexanes), $R_f$: | 0.34. |



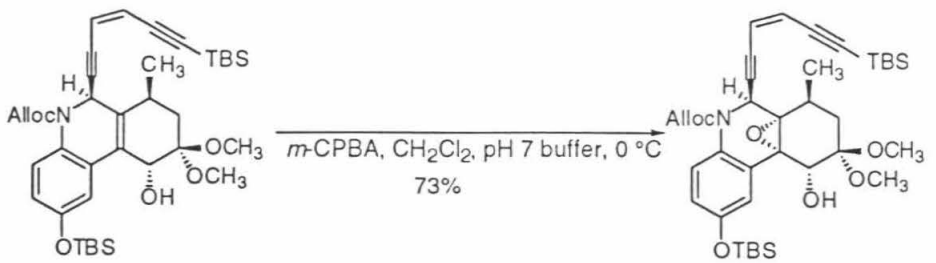

Alloc = allyl carbamate

**Alcohol 26**

A solution of ethylmagnesium bromide in tetrahydrofuran (1 M, 6.50 mL, 6.51 mmol, 0.90 equiv) was added to a solution of the quinoline **25** (2.92 g, 7.23 mmol, 1 equiv) in tetrahydrofuran (14 mL) at –78 °C. The resulting alkoxide solution was warmed to 0 °C, was held at that temperature for 10 min, and was cooled to –78 °C. In another flask, a solution of ethylmagnesium bromide in tetrahydrofuran (1 M, 10.8 mL, 11.0 mmol, 1.5 equiv) was added dropwise to a solution of the mono-protected enediyne **33** in tetrahydrofuran (9 mL) at 0 °C. The resulting solution was warmed to 23 °C and was held at that temperature for 10 min, and was brought briefly to reflux with a heat gun. After being cooled to 23 °C, the acetylide solution was transferred via a cannula into the previously prepared alkoxide solution. Allyl chloroformate (1.20 mL, 11.5 mmol, 1.6 equiv) was added, and the resulting reaction solution was warmed to 0 °C and was held at that temperature for 4 h. The reaction solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 70 mL) and ethyl acetate (70 mL). The aqueous layer was separated and was extracted further with ethyl acetate (2 × 70 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc–hexanes initially gradient to 20% EtOAc–hexanes). Appropriate fractions were pooled and were concentrated. The residue

was flash column chromatographed again (15% EtOAc-hexanes) to afford the alcohol **26** as a yellow oil (3.85 g, 79%).

| | |
|---|---|
| $^1$H NMR (400 MHz, $CDCl_3$), δ: | 7.35 (br s, 1H, *o*-aryl), 6.93 (d, 1H, *J* = 2.6 Hz, *m*-aryl), 6.71 (br d, 1H, *J* = 8.9 Hz, *m*-aryl), 5.97 (m, 2H, C**H**N, $CH_2$=C**H**), 5.71 (d, 1H, *J* = 11.3 Hz, CH=C**H**C≡CSi), 5.61 (dd, 1H, *J* = 11.0, 1.8 Hz, C**H**=CHC≡CSi), 5.31 (br d, 1H, *J* = 17.2 Hz, $CH_2$=CH), 5.23 (br d, 1H, *J* = 10.6, $CH_2$=CH), 4.73 (m, 2H, $CH_2O$, CHOH), 4.61 (m, 1H, $CH_2O$), 3.43 (s, 3H, $OCH_3$), 3.34 (s, 3H, $OCH_3$), 2.58 (m, 1H, $CH_3CH$), 2.39 (m, 1H, OH), 2.13 (dd, 1H, *J* = 14.3, 5.1 Hz, $CHCH_2$), 1.61 (dd, 1H, *J* = 14.3, 9.2 Hz, $CHCH_2$), 1.31 (d, 3H, *J* = 7.3 Hz, $CH_3CH$), 0.99 (s, 9H, $OSiC(CH_3)_3$), 0.96 (s, 9H, $C{\equiv}CSi(CH_3)_3$), 0.22 (s, 3H, $OSi(CH_3)_2$), 0.21 (s, 3H, $OSi(CH_3)_2$), 0.13 (s, 6H, $C{\equiv}CSi(CH_3)_2$). |
| FTIR (thin film, $cm^{-1}$): | 3469 (br, w, OH), 2954 (s), 2930 (s), 2143 (w), 1703 (s, C=O), 1495 (s). |
| TLC (20% EtOAc–hexanes), $R_f$: | 0.26. |

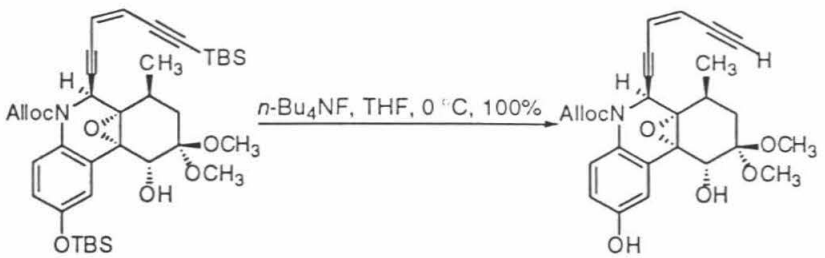



26 27

**Epoxide 27**

*m*-Chloroperoxybenzoic acid (70% w/w, 2.13 g, 8.52 mmol, 1.5 equiv) was added to a biphasic mixture of the alcohol **26** (3.85 g, 5.68 mmol, 1 equiv) in dichloromethane (87 mL) and aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 87 mL) at 0 °C. The resulting reaction mixture was stirred at that temperature for 12 h. A second portion of *m*-chloroperoxybenzoic acid (70 % w/w, 2.13 g, 8.52 mmol, 1.5 equiv) was added and the reaction mixture was stirred at 0 °C for another 7 h. A third portion of *m*-chloroperoxybenzoic acid (70 % w/w, 1.55 g, 6.29 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 0 °C for another 12 h. The reaction mixture was then poured into a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (130 mL). The aqueous layer was separated and was extracted further with dichloromethane (2 × 130 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc-hexanes) to afford the epoxide **27** as a light yellow foam (2.87 g, 73 %)

| | |
|---|---|
| $^1$H NMR (400 MHz, $CDCl_3$), δ: | 7.23 (d, 1H, $J$ = 2.6 Hz, *m*-aryl), 7.13 (br d, 1H, $J$ = 8.9 Hz, *o*-aryl), 6.76 (br d, 1H, $J$ = 8.4 Hz, *m*-aryl), 5.86 (m, 2H, CHN, $CH_2$=CH), 5.73 (d, 1H, $J$ = 11.0 Hz, CH=CHC≡CSi), 5.52 (br d, 1H, $J$ = 11.0 Hz, CH=CHC≡CSi), 5.18 (m, 2H, $CH_2$=CH), 4.63 (m, 1H, $CH_2O$), 4.62 (d, 1H, $J$ = 10.6, Hz, CHOH), 4.50 (m, 1H, $CH_2O$), 3.40 (s, 3H, $OCH_3$), 3.27 (s, 3H, $OCH_3$), 2.92 (br d, 1H, $J$ = 10.6 Hz, OH), 2.34 (m, 1H, $CH_3CH$), 1.96 (dd, 1H, $J$ = 14.7, 4.4 Hz, $CHCH_2$), 1.49 (dd, 1H, $J$ = 14.6, 11.0 Hz, $CHCH_2$), 1.46 (d, 3H, $J$ = 7.7 Hz, $CH_3CH$), 0.98 (s, 9H, $OSiC(CH_3)_3$), 0.96 (s, 9H, $C{\equiv}CSiC(CH_3)_3$), 0.23 (s, 3H, $OSi(CH_3)_2$), 0.22 (s, 3H, $OSi(CH_3)_2$), 0.13 (s, 6H, $C{\equiv}CSi(CH_3)_2$) |
| TLC (20% EtOAc–hexanes), $R_f$: | 0.26. |




27 28

**Phenol 28**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 8.30 mL, 8.26 mmol, 2.0 equiv) was added to a yellow solution of the epoxide **27** (2.87 g, 4.13 mmol, 1 equiv) in tetrahydrofuran (85 mL) at 0 °C. The resulting reddish orange reaction solution was stirred at 0 °C for 10 min. It was then poured into an aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 130 mL) and was extracted with dichloromethane (3 × 130 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (60% EtOAc–hexanes) to afford the phenol **28** in quantitative yield.

$^1$H NMR (400 MHz, $CDCl_3$), δ: 7.24 (d, 1H, $J$ = 2.9 Hz, *m*-aryl), 7.17 (br d, 1H, $J$ = 8.4 Hz, *o*-aryl), 6.78 (dd, 1H, $J$ = 8.4, 2.6 Hz, *m*-aryl), 5.85 (m, 2H, CHN, $CH{=}CH_2$), 5.69 (br s, 2H, CH=CH), 5.22 (br d, 1H, $J$ = 16.5 Hz, $CH{=}CH_2$), 5.16 (br d, 1H, $J$ = 11.0 Hz,

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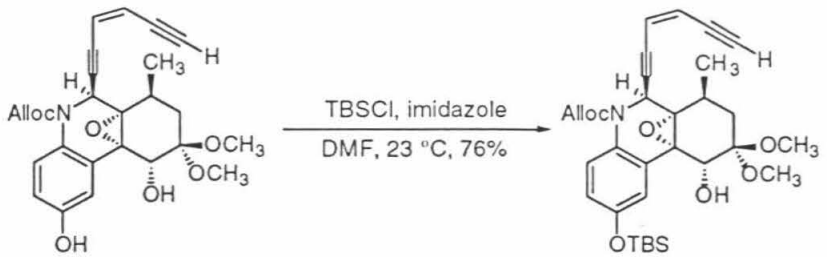
| | $CH{=}CH_2$), 5.05 (br s, 1H, OH), 4.67 (m, 2H, $CH_2O$, CHOH), 4.52 (m, 1H, $CH_2O$), 3.41 (s, 3H, $OCH_3$), 3.27 (s, 3H, $OCH_3$), 3.16 (d, 1H, $J$ = 1.5 Hz, C≡CH), 3.04 (br d, 1H, OH), 2.33 (m, 1H, $CH_3CH$), 1.97 (dd, 1H, $J$ = 14.6, 4.4 Hz, $CHCH_2$), 1.57 (dd, 1H, $J$ = 15.4, 12.4 Hz, $CHCH_2$), 1.47 (d, 3H, $J$ = 7.7 Hz, $CH_3CH$) |
| FTIR (thin film, $cm^{-1}$): | 3389 (br, m, OH), 3292 (m), 2946 (m), 1681 (s, C=O), 1505 (s), 1456 (m) |
| TLC (40% EtOAc–hexanes), $R_f$: | 0.48. |




28 9

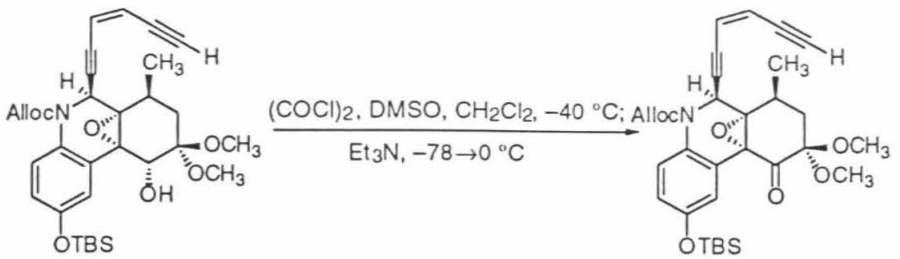
**Aryl silyl ether 9**

A solution of the phenol **28** (1.92 g, 4.10 mmol, 1 equiv) in DMF (25 mL) was treated sequentially with imidazole (739 mg, 11.0 mmol, 2.6 equiv) and *tert*-butyldimethylsilyl chloride (813 mg, 5.40 mmol, 1.3 equiv). The resulting reaction solution was stirred at 23 °C for 1.3 h. Imidazole (114 mg, 1.70 mmol, 0.40 equiv) and *tert*-butyldimethylsilyl chloride (122 mg, 0.810 mmol, 0.20 equiv) were added, and the reaction solution was stirred at 23 °C for another 2.5 h. It was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was separated and was extracted further with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulfate, and were concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc-hexanes) to yield the silyl ether **9** as a desired product (1.83 g, 76%).

$^1$H NMR (300 MHz, $CDCl_3$) δ: 7.24 (d, 1H, $J$ = 2.7 Hz, *m*-aryl), 7.15 (br d, 1H, $J$ = 8.1 Hz, *o*-aryl), 6.76 (dd, 1H, $J$ = 8.7, 2.4 Hz, *m*-aryl), 5.83 (m, 2H, NC**H**, $CH_2$=C**H**), 5.67 (m, 2H, C**H**=C**H**),

5.20 (m, 2H, $CH_2$=CH), 4.70 (m, 1H, $CH_2O$), 4.64 (d, 1H, $J$ = 11.1 Hz, CHOH), 4.50 (m, 1H, $CH_2O$), 3.42 (s, 3H, $OCH_3$), 3.28 (s, 3H, $OCH_3$), 3.16 (d, 1H, $J$ = 1.8 Hz, C≡CH), 2.94 (br d, 1H, $J$ = 10.5 Hz, OH), 2.35 (m, 1H, $CHCH_3$), 1.95 (dd, 1H, $J$ = 14.7, 4.5 Hz, $CHCH_2$), 1.60 (dd, 1H, $J$ = 14.7, 11.3 Hz, $CHCH_2$), 1.47 (d, 3H, $J$ = 7.8 Hz, $CHCH_3$), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.24 (s, 3H, $Si(CH_3)_2$), 0.22 (s, 3H, $Si(CH_3)_2$).

TLC (50% EtOAc–hexanes), $R_f$: 0.64




9 29

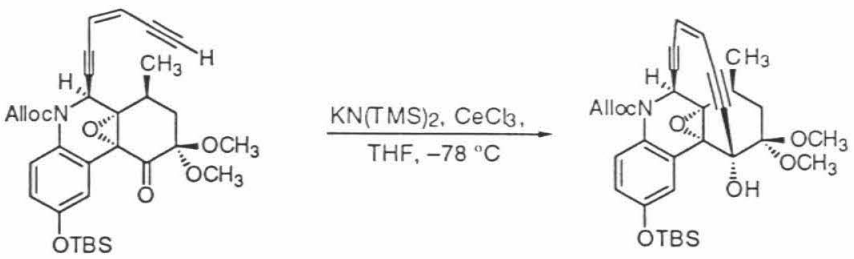
**Ketone 29**

After being stirred at –78 °C for 20 min, a solution of dimethyl sulfoxide (3.40 mL, 48.0 mmol, 15 equiv) and oxalyl chloride (2.80 mL, 32.0 mmol, 10 equiv) in dichloromethane (60 mL) was treated with a solution of the alcohol **9** (1.83 g, 3.2 mmol, 1 equiv) in dichloromethane (60 mL). The resulting reaction solution was warmed to –40 °C, was held at that temperature for 10 h, and was cooled to –78 °C. Triethylamine (13.2 mL, 95.0 mmol, 30 equiv) was added, and the resulting reaction solution was warmed to 0 °C and was held at that temperature for 30 min. It was then poured into an aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 180 mL). The aqueous layer was separated and was extracted further with dichloromethane (2 × 180 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (2% EtOAc-hexanes) to afford the desired product **29**.

$^1$H NMR (300 MHz, $CDCl_3$) δ: 7.66 (d, 1H, $J$ = 2.7 Hz, *m*-aryl), 7.18 (br d, 1H, $J$ = 9.0 Hz, *o*-aryl), 6.81 (dd, 1H, $J$ = 8.7, 2.7 Hz, *m*-aryl), 5.83 (m, 2H,

CNH, $CH_2$=CH), 5.69 (m, 2H, CH=CH), 5.19 (m, 2H, $CH_2$=CH), 4.69 (m, 1H, $CH_2O$), 4.57 (m, 1H, $CH_2O$), 3.30 (s, 3H, $OCH_3$), 3.28 (s, 3H, $OCH_3$), 3.15 (d, 1H, $J$ = 1.5 Hz, C≡CH), 2.78 (m, 1H, $CHCH_3$), 2.20 (dd, 1H, $J$ = 14.1, 6.0 Hz, $CHCH_2$), 1.99 (dd, 1H, $J$ = 14.1, 3.3 Hz, $CHCH_2$), 1.52 (d, 3H, $J$ = 7.5 Hz, $CHCH_3$), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.23 (s, 3H, $Si(CH_3)_2$), 0.22 (s, 3H, $Si(CH_3)_2$).

TLC (5% EtOAc–hexanes), $R_f$: 0.62.




29 30

**Dimethyl Ketal 30**

A slurry of the ketone **29** (1.42 g, 2.46 mmol, 1 equiv) and anhydrous cesium (III) chloride (3.04 g, 12.3 mmol, 5.0 equiv) in tetrahydrofuran (53 mL) was stirred at 23 °C for 30 min. The reaction mixture was then cooled to –78 °C, and a solution of potassium N,N-bis(trimethylsilyl)amide in toluene (0.5 M, 7.90 mL, 3.94 mmol, 1.6 equiv) was added, causing it to turn dark brown. This dark brown reaction mixture was warmed to 0 °C, and a saturated aqueous solution of ammonium chloride (250 mL) was then added. The biphasic mixture was extracted with ethyl acetate (150 mL). The aqueous layer was separated and was extracted further with ethyl acetate (2 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc–hexanes) to afford the cyclization product **30** as a yellow foam (1.16 g, 64% over two steps).

$^1$H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, 1H, $J$ = 2.7 Hz, *m*-aryl), 7.12 (br s, 1H, *o*-aryl), 6.74 (dd, 1H, $J$ = 8.7, 2.7 Hz, *m*-aryl), 5.90 (m, 1H, $CH_2$=C**H**), 5.78 (d, 1H, $J$ = 10.2 Hz, HCC≡CCH=C**H**),

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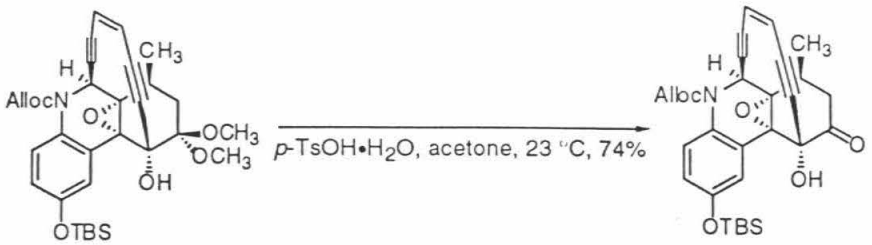
| | 5.70 (br s, 1H, NC**H**), 5.65 (dd, 1H, $J$ = 9.9, 1.8 Hz, HCC≡CC**H**=CH), 5.19 (m, 2H, C**H**$_2$=CH), 4.69 (br dd, 1H, $J$ = 13.5, 5.1 Hz, C**H**$_2$O), 4.58 (m, 1H, C**H**$_2$O), 3.51 (s, 3H, OC**H**$_3$), 3.49 (s, 1H, O**H**), 3.36 (s, 3H, OC**H**$_3$), 2.50 (m, 1H, C**H**CH$_3$), 2.07 (m, 2H, CHC**H**$_2$), 1.39 (d, 3H, $J$ = 7.5 Hz, CHC**H**$_3$), 0.98 (s, 9H, SiC(C**H**$_3$)$_3$), 0.21 (s, 3H, Si(C**H**$_3$)$_2$), 0.20 (s, 3H, Si(C**H**$_3$)$_2$). |
| FTIR (thin film, cm$^{-1}$): | 3483 (br, w, OH), 2343 (w, C≡C), 1704 (s, C=O) |
| TLC (20% EtOAc–hexanes), $R_f$: | 0.14. |



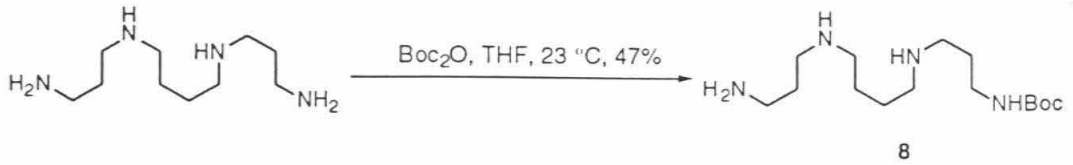

30 31

**Ketone 31**

*p*-Toluenesulfonic acid monohydrate (275 mg, 1.44 mmol, 4.1 equiv) was added to a yellow solution of the dimethyl ketal **30** (204 mg, 0.353 mmol, 1 equiv) in acetone (11 mL) at 23 °C, causing the resulting reaction to turn reddish orange. This reddish orange reaction solution was stirred at 23 °C for 2 h and was partitioned between the aqueous saturated solution of sodium bicarbonate (11 mL) and ethyl acetate (11 mL). The aqueous layer was separated and was extracted further with ethyl acetate (2 × 11 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (initially 15% ethyl acetate in hexanes, grading to 20% ethyl acetate in hexanes, and finally 40% ethyl acetate in hexanes) to yield the ketone **31** as a light yellow foam (0.140 g, 74%).

$^1$H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, 1H, $J$ = 3.0 Hz, *m*-aryl), 7.16 (br d, 1H, $J$ = 7.2 Hz, *o*-aryl), 6.80 (dd, 1H, $J$ = 8.7, 2.7 Hz, *m*-aryl), 5.90 (m, 1H, $CH_2$=C**H**), 5.86 (d, 1H, $J$ = 9.9 Hz, HCC≡CCH=C**H**), 5.79 (br s, 1H, NC**H**),

| | |
|---|---|
| | 5.78 (dd, 1H, $J$ = 10.2, 1.5 Hz, HCC≡CC**H**=CH), 5.19 (m, 2H, C**H**$_2$=CH), 4.68 (m, 1H, C**H**$_2$O), 4.60 (br m, 1H, C**H**$_2$O), 2.99 (m, 1H, CH$_3$C**H**), 2.90 (m, 2H, CHC**H**$_2$), 1.53 (d, 3H, $J$ = 6.9 Hz, CHC**H**$_3$), 0.96 (s, 9H, OSiC(C**H**$_3$)$_3$), 0.21 (s, 3H, OSi(C**H**$_3$)$_2$), 0.20 (s, 3H, OSi(C**H**$_3$)$_2$). |
| FTIR (thin film), cm$^{-1}$: | 3422(br, m, OH), 2955(m), 2930 (m), 1709 (s, C=O) |
| TLC (40% ethyl acetate in hexanes), $R_f$: | 0.52 |




8

**Spermine derivative 8**

A solution of di-*tert*-butyl dicarbonate (1.50 mL, 6.56 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added slowly to a stirring solution of spermine (4.00 g, 19.7 mmol, 3.0 equiv) in tetrahydrofuran (30 mL) over 205 min at 23 °C with a syringe pump, causing the resulting reaction to turn cloudy with white precipitates. The reaction suspension was then stirred for another 12.8 h, and the volatiles were removed *in vacuo*. The white residue was purified by flash column chromatography (20:5:1 $CH_2Cl_2$:MeOH:conc. $NH_4OH$ gradient to 25:12:5 $CH_2Cl_2$:MeOH:conc. $NH_4OH$) to afford the desired product **4** as a colorless oil (0.937 g, 47%).

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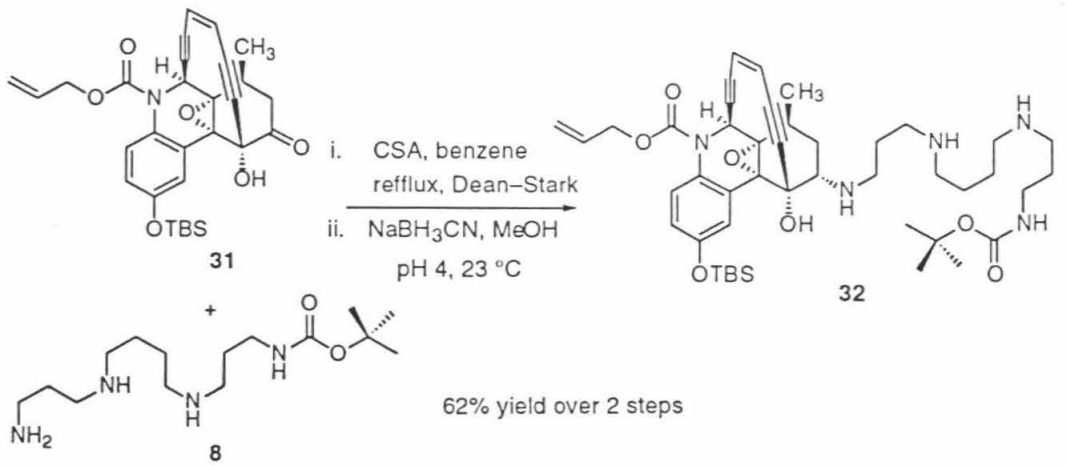
|---|---|
| $^1$H NMR (300 MHz, $CDCl_3$) δ: | 3.15 (m, 2H, $CH_2NHC=O$), 2.60 (m, 10H, $CH_2N$), 1.62 (m, 4H, $NCH_2CH_2CH_2N$), 1.50 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.40 (br s, 9H, $C(CH_3)_3$) |
| FTIR (thin film), cm$^{-1}$: | 3354 (br, s, NH), 3295 (br, s, NH), 2932 (s), 1690 (s, C=O) |
| TLC (25:12:5 $CH_2Cl_2$:MeOH:$NH_4OH$), $R_f$: | 0.40 |



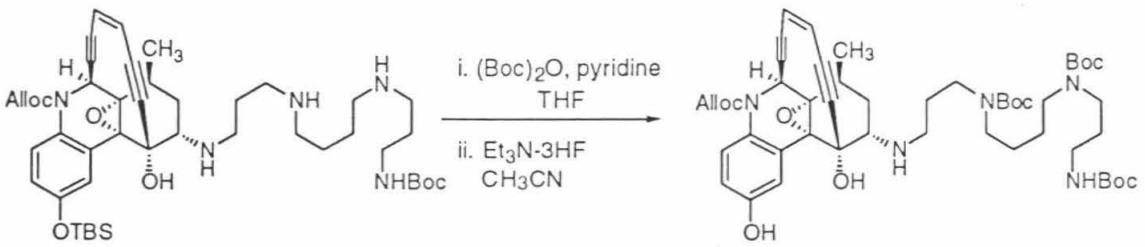

**Amine 32**

A solution of ketone **31** (150 mg, 0.280 mmol, 1 equiv), mono-Boc-protected spermine **8** (821 mg, 2.80 mmol, 9.7 equiv), and camphorsulfonic acid (71.9 mg, 0.31 mmol, 1.1 equiv) in benzene (60 mL) was heated at reflux under Dean–Stark conditions for 22 h. It was then cooled to 23 °C and was partitioned between a saturated aqueous solution of sodium bicarbonate (160 mL) and ethyl acetate (160 mL). The aqueous layer was separated and was extracted further with ethyl acetate (2 × 160 mL). The combined organic layers were dried over sodium sulfate and were concentrated to yield the crude imine as a yellow oil. Due to its instability to chromatography, the intermediate imine was typically taken on to the next step without purification. Sodium cyanoborohydride (91.8 mg, 1.46 mmol, 5.2 equiv) was added to a solution of the crude imine in methanol (40 mL). Bromocresol green (10 mg) was added, resulting in a deep blue solution. Concentrated hydrochloric acid was added dropwise via a 50 μL syringe until the reaction turned yellow. The resulting yellow solution was stirred at 23 °C for 13 h, and concentrated hydrochloric acid was added periodically to keep the reaction in yellow. The reaction solution was partitioned between saturated aqueous solution of sodium bicarbonate (150 mL) and methylene chloride (150 mL). The aqueous layer was separated and was

extracted further with methylene chloride (2 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (20:5:0.5 $CH_2Cl_2$:MeOH:conc. $NH_4OH$) to yield the amine **32** as a green oil (142 mg, 62%).

$^1$H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, 1H, $J$ = 2.6 Hz, *m*-aryl), 7.11 (br s, 1H, *o*-aryl), 6.75 (dd, 1H, $J$ = 8.8, 2.6 Hz, *m*-aryl), 5.88 (m, 1H, $CH_2$=C**H**), 5.78 (d, 1H, $J$ = 9.9 Hz, HCC≡CCH=C**H**), 5.70 (br s, 1H, NC**H**), 5.64 (dd, 1H, $J$ = 9.9, 1.5 Hz, HCC≡CC**H**=CH), 5.22 (m, 2H, C**H**$_2$=CH), 4.70 (dd, 1H, $J$ = 13.9, 4.8 Hz, C**H**$_2$O), 4.55 (m, 1H, C**H**$_2$O), 3.18 (m, 2H, C**H**$_2$NHC=O), 2.99 (m, 1H, CH$_2$C**H**NH), 2.90 (m, 1H, C**H**$_2$NHCH), 2.62 (m, 10H, C**H**$_2$NH, CH$_3$C**H**), 2.12 (ddd, 1H, $J$ = 14.6, 6.2, 2.9 Hz, CHC**H**$_2$), 1.97 (app td, 1H, $J$ = 15.0, 3.3 Hz, CHC**H**$_2$), 1.63 (m, 4H, NHCH$_2$C**H**$_2$CH$_2$NH), 1.49 (m, 4H, NHCH$_2$C**H**$_2$C**H**$_2$CH$_2$NH), 1.43 (br s, 9H, C(C**H**$_3$)$_3$), 1.40 (d, 3H, $J$ = 7.3 Hz, C**H**$_3$CH), 0.96 (s, 9H, OSiC(C**H**$_3$)$_3$), 0.22 (s, 3H, OSi(C**H**$_3$)$_2$), 0.20 (s, 3H, OSi(C**H**$_3$)$_2$).

| | |
|---|---|
| FTIR (thin film), $cm^{-1}$: | 3332 (br, m, OH), 1704 (s, C=O) |
| TLC (20:5:1 $CH_2Cl_2$:MeOH:$NH_4OH$), $R_f$: | 0.59 |




32 34

**Phenol 33**

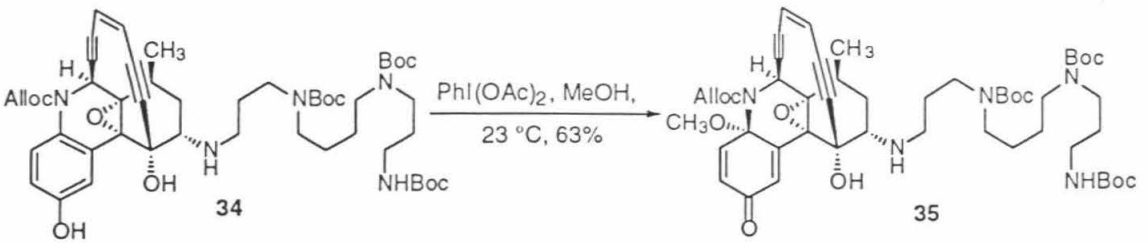
A solution of di-*tert*-butyl dicarbonate (80.0 µL, 0.348 mmol, 4.0 equiv) and the alcohol **32** (71.2 mg, 0.0870 mmol, 1 equiv) in tetrahydrofuran (20 mL) was stirred at 23 °C. As the reaction progressed, different amounts of di-*tert*-butyl dicarbonate was added at the following time intervals: 105 min - 400 µL (1.74 mmol, 20 equiv); 12.7 h - 1 mL (4.35 mmol, 50 equiv). After 13 h stirring at 23 °C, pyridine (200 µL, 2.61 mmol, 30 equiv) was added, and the resulting reaction solution was stirred for an additional 5 min. An aqueous saturated solution of sodium bicarbonate (40 mL) was added and the biphasic mixture was extracted with ethyl acetate (40 mL). The aqueous layer was separated and was further extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (5% MeOH–$CH_2Cl_2$). Appropriate fractions were collected and were concentrated to afford the tri-Boc-protected polyamine as a colorless oil, which was dissolved in acetonitrile (25 mL) in a polypropylene test tube. Triethylamine trihydroflouride (280 µL, 1.74 mmol, 20 equiv) was added, and the resulting solution was stirred for 140 min at 23 °C. It was then partitioned between saturated aqueous solution of sodium bicarbonate (100 mL) and dichloromethane (100 mL). The aqueous layer was separated and was extracted further with dichloromethane (2 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue

was purified by flash column chromatography (5% MeOH–$CH_2Cl_2$) to afford the desired phenol **34** (63.0 mg, 75%).

$^1$H NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, 1H, $J$ = 2.4 Hz, *m*-aryl), 7.09 (br s, 1H, *o*-aryl), 6.77 (dd, 1H, $J$ = 8.4, 2.4 Hz, *m*-aryl), 5.85 (m, 1H, $CH_2$=C**H**), 5.77 (d, 1H, $J$ = 9.9 Hz, HCC≡CCH=C**H**), 5.70 (br s, 1H, NC**H**), 5.64 (dd, 1H, $J$ = 9.9, 1.2 Hz, HCC≡CC**H**=CH), 5.21 (m, 2H, $CH_2$=CH), 4.68 (m, 1H, $CH_2O$), 4.54 (m, 1H, $CH_2O$), 3.20 (m, 10H, $CH_2N$), 2.95 (m, 1H, $CH_2$C**H**NH), 2.88 (m, 1H, $CH_2$NCH), 2.53 (m, 1H, $CH_3$C**H**), 2.33 (m, 1H, $CH_2$NCH), 2.11 (ddd, 1H, $J$ = 16.0, 6.0, 2.0 Hz, CHC$H_2$CH), 1.95 (m, 1H, CHC$H_2$CH), 1.65 (m, 4H, NC$H_2$C$H_2$C$H_2$N), 1.48 (m, 4H, NC$H_2$C$H_2$C$H_2$C$H_2$N), 1.45 (s, 9H, C(C$H_3$)$_3$), 1.44 (s, 18H, C(C$H_3$)$_3$), 1.40 (d, 3H, $J$ = 7.3 Hz, C$H_3$CH).

FTIR (thin film), $cm^{-1}$: 3333 (br, m, OH), 2977 (m), 2934 (m), 2249 (w, C≡C), 1693 (s, C=O).

TLC (10% MeOH–$CH_2Cl_2$): 0.43




**Enone 35**

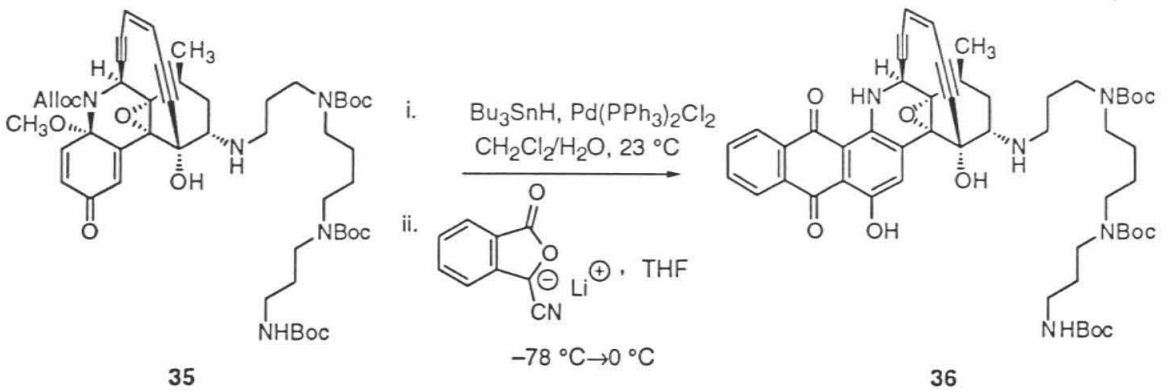
A solution of iodobenzene diacetate (29.4 mg, 0.0913 mmol, 1.5 equiv) and phenol **34** (63.0 mg, 0.0627 mmol, 1 equiv) in methanol (4 mL) was stirred at 23 °C for 35 min. It was then partitioned between a 1:1 mixture of saturated aqueous solution of sodium bicarbonate and and saturated aqueous sodium thiosulfate solution (30 mL) and ethyl acetate (30 mL). The aqueous layer was separated and was further extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was purified by flash column chromatography (3% MeOH in $CH_2Cl_2$) to furnish the enone **35** (40.9 mg, 63%).

$^1$H NMR (400 MHz, $CDCl_3$, 40 °C) δ: 7.45 (br s, 1H, β-enone), 7.27 (d, 1H, *J* = 1.83 Hz, α-enone), 6.29 (dd, 1H, *J* = 10.25, 1.83 Hz, α-enone), 5.94 (m, 1H, $CH_2$=C**H**), 5.88 (d, 1H, *J* = 9.88 Hz, HCC≡CCH=C**H**), 5.78 (br s, 1H, NC**H**), 5.75 (dd, 1H, *J* = 9.88, 1.48 Hz, HCC≡CC**H**=CH), 5.35 (dd, 1H, *J* = 17.20, 1.10 Hz, C**H**$_2$=CH), 5.25 (dd, 1H,

$J$ = 10.61, 1.10 Hz, $CH_2$=CH), 4.68 (m, 2H, $CH_2O$), 3.15 (m, 10H, $CH_2N$), 3.10 (s, 3H, $OCH_3$), 2.91 (m, 1H, $CH_2CHN$), 2.84 (m, 1H, $CH_2NCH$), 2.58 (m, 1H, $CH_3CH$), 2.33 (m, 1H, $CH_2NCH$), 2.18 (ddd, 1H, $J$ = 14.64, 7.32, 2.56 Hz, $CHCH_2CH$), 1.92 (m, 1H, $CHCH_2CH$), 1.65 (m, 4H, $NCH_2CH_2CH_2N$), 1.48 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 1.45 (s, 9H, $C(CH_3)_3$), 1.43 (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 1.28 (d, 3H, $J$ = 7.0 Hz, $CH_3CH$).

FTIR (thin film), $cm^{-1}$: 3357 (br, m, OH), 2975 (m), 2360 (m, C≡C), 1682 (s, C=O).

TLC (5% MeOH in $CH_2Cl_2$), $R_f$: 0.30




14% yield over 2 steps

**Anthraquinone 36**

Tributyltin hydride (5.00 μL, 0.0190 mmol, 1.1 equiv) was added to a deoxygenated biphasic mixture of the enone **35** (17.4 mg, 0.0170 mmol, 1 equiv) and bis(triphenylphosphine)palladium(II) chloride (10.6 mg, 0.0150 mmol, 0.90 equiv) in dichloromethane (2 mL) and water (50 μL). The resulting reaction mixture was stirred at 23 °C for 15 min. As it progressed the reaction turned orange and eventually back to yellow. The volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography (2% MeOH–$CH_2Cl_2$) to yield the corresponding quinone imine **6**, which was dissolved in tetrahydrofuran (1.5 mL). In a separate flask, a solution of *tert*-butyllithium in pentane (1.5 M, 15.0 mL, 0.0230 mmol, 2.0 equiv) was added to a solution of cyanophthalide[18,20] (3.70 mg, 0.0230 mmol, 2.0 equiv) in tetrahydrofuran (0.5 mL) at –78 °C causing the reaction solution to turn bright yellow. The yellow lithio cyanophthalide anion solution was stirred at –78 °C for 15 min, and the previously prepared quinone imine **6** solution was added via a syringe dropwise over 5 min. The resulting slightly yellowish green reaction mixture was stirred at –78 °C for 15 min. It was then slowly warmed to 0 °C over 30 min and was held at that temperature for 5 min, resulting in a color change to deep forest green and finally to a bluish mixture, which was partitioned between a saturated aqueous solution of sodium bicarbonate (10 mL) and ethyl

acetate (10 mL). The aqueous layer was separated and was extracted further with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate and were concentrated *in vacuo*. The residue was loaded on a Sephadex LH-20 column and was eluted with 10% $CH_3CN$–MeOH. Fractions contained the desired product **36** were pooled and were concentrated *in vacuo*. The residue was purified by flash column chromatography ($CH_2Cl_2$ initially gradient to 2% MeOH–$CH_2Cl_2$). Appropriate fractions were collected for another purification by flash column chromatography (40% EtOAc–hexanes) to afford the desired anthraquinone product **36** as magenta solids (2.40 mg, 14%).

$^1$H NMR (400 MHz, $C_6D_6$) δ: 13.73 (br s, 1H, aryl O**H**), 10.45 (br d, 1H, $J$ = 3.7 Hz, aryl N**H**), 9.43 (br s, 1H, aryl **H**), 8.31 (d, 1H, $J$ = 7.5 Hz, aryl **H**), 8.10 (d, 1H, $J$ = 7.5 Hz, aryl **H**), 7.11 (td, 1H, $J$ = 8.0, 1.2 Hz, aryl **H**), 7.02 (td, 1H, $J$ = 8.0, 1.2 Hz, aryl **H**), 5.24 (d, 1H, $J$ = 10.0 Hz, HCC≡CCH=C**H**), 5.19 (dd, 1H, $J$ = 10.0, 1.2 Hz, HCC≡CC**H**=CH), 3.88 (d, 1H, $J$ = 4.00 Hz, NC**H**), 3.07 (m, 11H, $CH_2N$, $CH_2CHN$), 2.50 (m, 1H, $CH_2NCH$), 2.20 (m, 1H, $CH_3CH$), 1.89 (m, 1H, $CHCH_2CH$), 1.75 (m, 1H, $CHCH_2CH$), 1.45 (m, 30H, $C(CH_3)_3$, $CH_3CH$), 1.30 (m, 4H, $NCH_2CH_2CH_2N$), 1.10 (m, 4H, $NCH_2CH_2CH_2CH_2N$).

| | |
|---|---|
| FTIR (thin film, $cm^{-1}$): | 3354 (br, w. OH), 2363 (m, C≡C), 1684 (s, C=O). |
| TLC (5% MeOH–$CH_2Cl_2$), $R_f$: | 0.22 |

## References and Notes


1. (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, 42, 1449. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, 112, 3715. (c) Shiomi, K.; Iinuma, H.; Naganawa, H.; Hamada, M.; Hattori, S.; Nakamura, H.; Takeuchi, T.; Iitaka, Y. *J. Antibiot.* **1990**, 43, 1000. (d) Konishi, M.; Ohkuma, H.; Matsumoto, K.; saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1991**, 44, 1300. (e) Kamei, H.; Nishiyama, Y.; Takahashi, A.; Yumiko, O.; Oki, T. *J. Antibiot.* **1991**, 44, 1036. (f) Miyoshi-Saitoh, M.; Morisaki, N.; Tokiwa, Y.; Iwasaki, S.; Konishi, M.; Saitoh, K.; Oki, T. *J. Antibiot.* **1991**, 44, 1037.
2. (a) *Anthracycline Antibiotics*; El Khadem, H. S.; Ed.; Academic: New York, 1982. (b) *Recent Aspects in Anthracyclinone Chemistry (Tetrahedron Symposia-in-Print)*; Kelly, T. R.; Ed.; *Tetrahedron* **1984**, 40, 4357. (c) *Anthracycline and Anthracenedione-Based Anticancer Agents*; Lown, J. W.; Ed.; Elsevier: Amsterdam, 1988. (d) Fisher, J. F.; Aristoff, P. A. *Prog. Drug Res.* **1988**, 32, 411.
3. Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T.; *Proc. Nat. Acad. Sci. U.S.A.* **1990**, 87, 3831. (b) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, 31, 1521. (c) Snyder, J. P.; Tipsword, G. E. *J. Am. Chem. Soc.* **1990**, 112, 4040. (d) Shiraki, T.; Sugiura, Y. *Biochemistry* **1990**, 29, 9795. (e) Sugiura, Y.; Arakawa, T.; Uesugi, M.; Shiraki, T.; Ohkuma, H.; Konishi, M. *Biochemistry* **1991**, 30, 2989. (f) Langley, D. R.; Doyle, T. W.; Beveridge, D. L. *J. Am. Chem. Soc.* **1991**, 113, 4395. (g) Cordozo, M. G.; Hopfinger, A. J.

*Mol. Pharmacol.* **1991**, 40, 1023. (h) Wender, P. A.; Kelly, R. C.; Beckham, S.; Miller, B. L. *Proc. Nat. Acad. Sci. U.S.A.* **1991**, 88, 8835.

4. (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, 94, 660. (b) Bergman, R. G. *Accounts Chem. Res.* **1973**, 6, 25. (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, 103, 4082. (d) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, 103, 4091.

5. (a) Myers, A. G.; Cohen, S. B.; Tom, N. J.; Madar, D. J.; Fraley, M. E.; *J. Am. Chem. Soc.* **1994**, 117, 7574. (b) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, 119, 6072. (c) Myers, A. G.; Fraley, M. E.; Tom, N. J.; Cohen, S. B.; Madar, K. *J. Chem. Biol.* **1995**, 2, 33.

6. Fraley, M. E. Ph.D. Thesis, California Institute of Technology, 1995.

7. Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263.

8. (a) Witzeman, J. S. *Tetrahedron Lett.* **1990**, 31, 1401. (b) Cohn, P. *Monatsh.* **1900**, 21, 200. (c) Lapworth, A.; Hann, A. C. O. *J. Chem. Soc.* **1902**, 81, 1499. (d) Carroll, M. F. *Proc. XIth Intern. Congr. Pure and Applied Chem.* **1947**, 2, 39. (e) Bader, A. R.; Cummings, L. O.; Vogel, H. A. *J. Am. Chem. Soc.* **1951**, 73, 4195.

9. Michael, A. *J. prakt. Chem.* **1887**, 35, 349.

10. Dieckmann, W. *Ber.* **1894**, 27, 102.

11. von Schilling, R.; Vorlunder, D. *Ann.* **1899**, 308, 184.

12. Tom, N. J. Ph.D. Thesis, California Institute of Technology, 1998.

13. (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, 11, 513. (b) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, 56, 3763. (c) Yasuda, N.; Xavier, L.; Rieger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U. H. *Tetrahedron Lett.* **1993**, 34, 3211.

14. (a) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, 23, 465. (b) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, 52, 19.

15. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, 27, 5541.

16. (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, 28, 3313. (b) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, 26, 3811. (c) Volhardt, K. P. C.; Winn, L. S. *Tetrahedron Lett.* **1985**, 26, 709. (d) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, 29, 4217. (e) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, 110, 631.

17. Yamaguchi, R.; Nakazone, Y.; Kawanisi, M. *Tetrahedron Lett.* **1983**, 24, 1801.

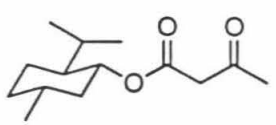
18. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

19. (a) Shair, M. D.; Yoon, T.-Y.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1721. (b) Shair, M. D.; Yoon, T.-Y.; Danishefsky, S. J. *J. Org. Chem.* **1994**, 59, 3755. (c) Shair, M. D..; Yoon, T.-Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, 118, 9509.

20. (a) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, 23, 1825. (b) Guibe, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986**, 27, 2365. (c) Dangles, O.; Guibe, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, 52, 4984.

21. (a) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, 50, 805. (b) Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, 52, 713. (c) Okazaki, K.; Nomura, K.; Yoshii, E. *Synth. Commun.* **1987**, 17, 1021.

22. Cyanophthallide prepared by Dr. David J. Madar.



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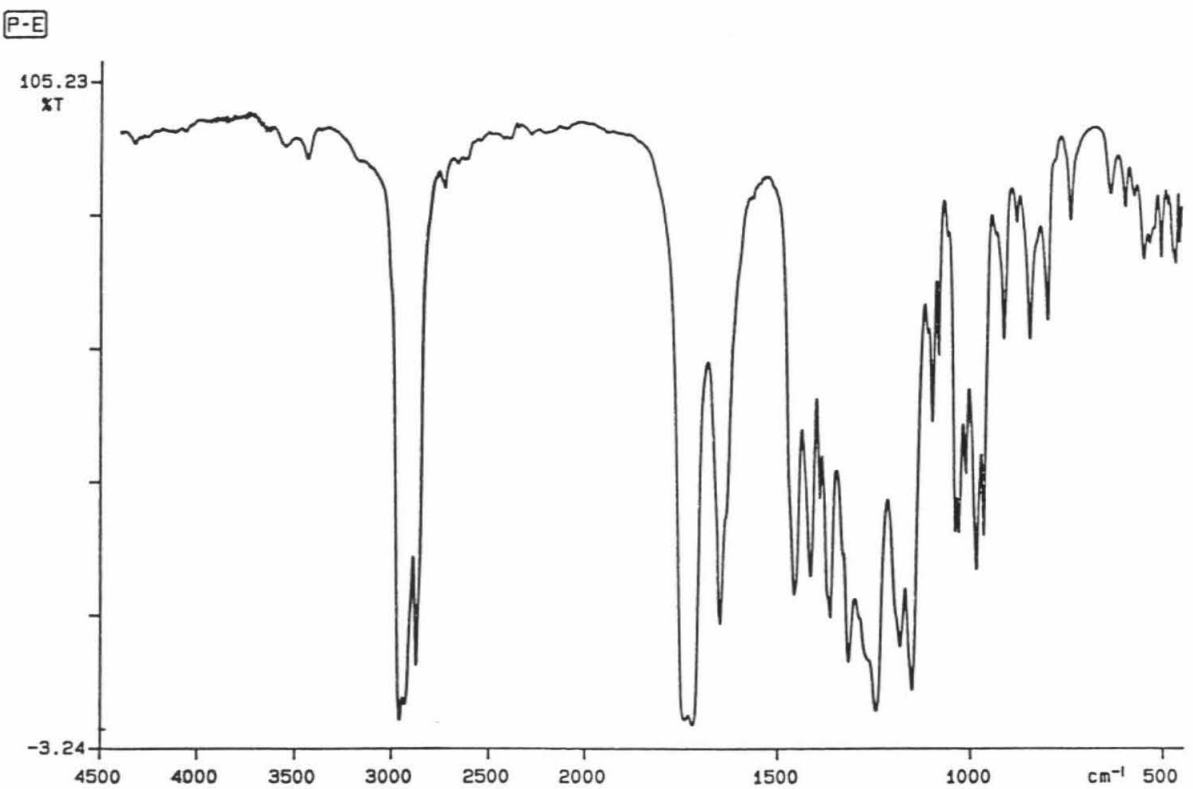
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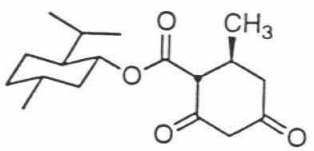
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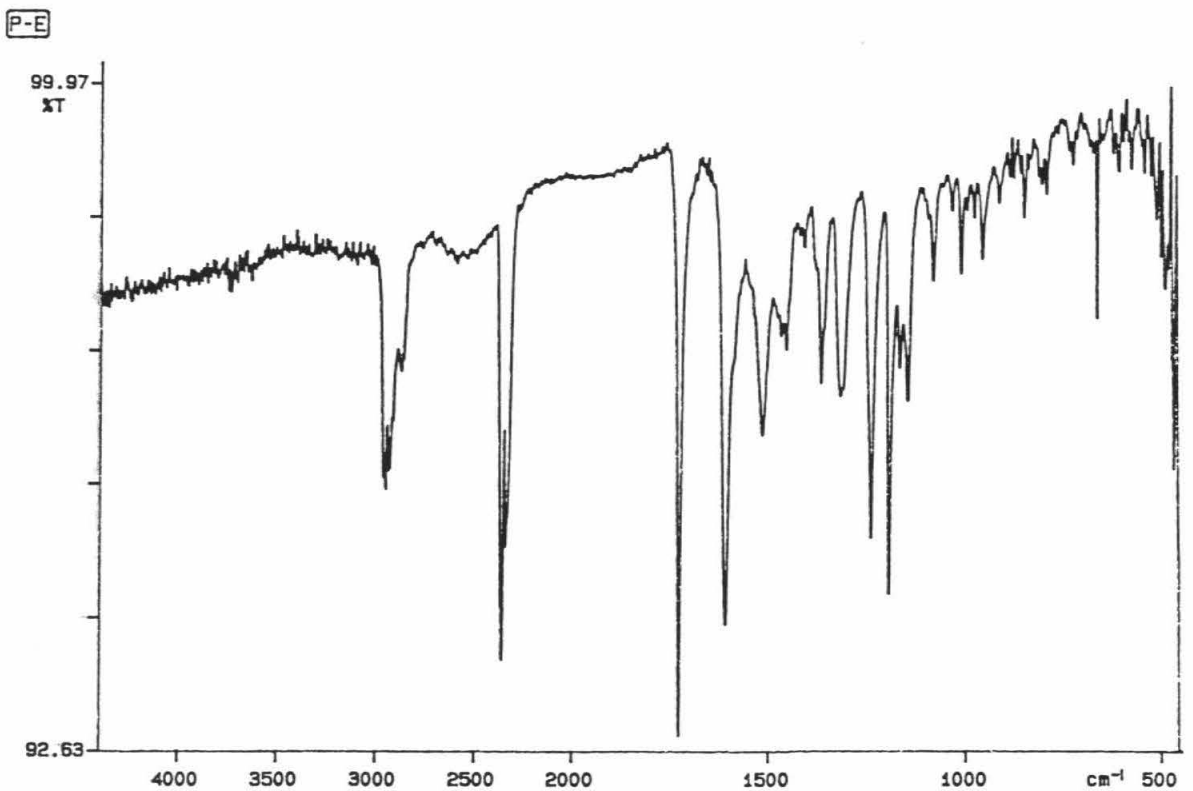
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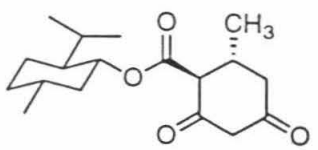
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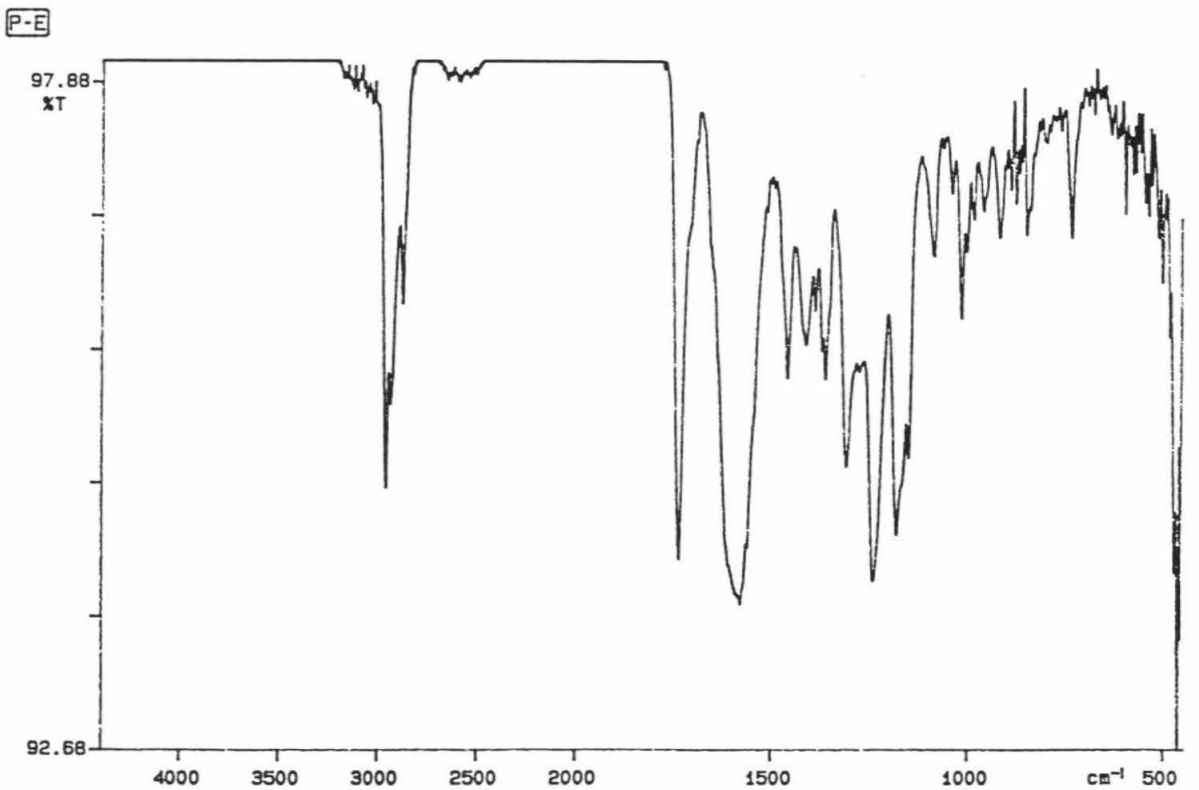
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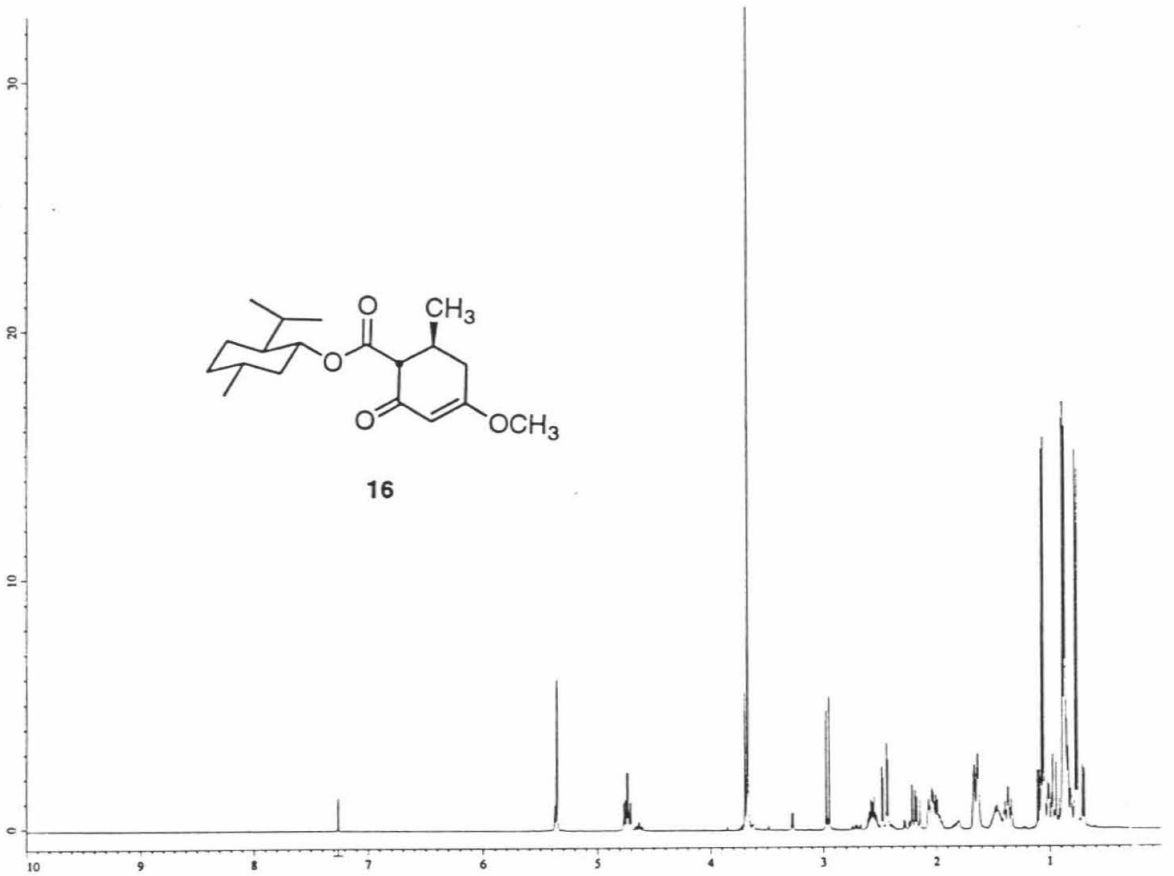
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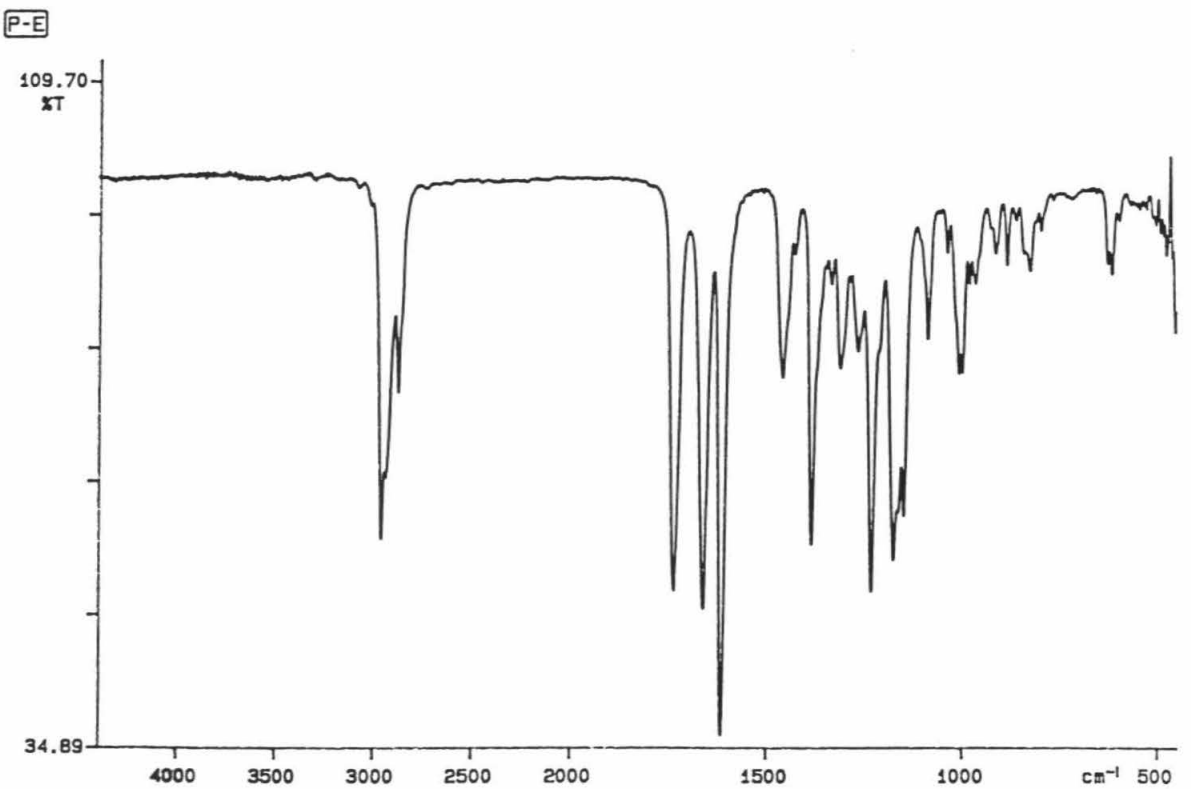
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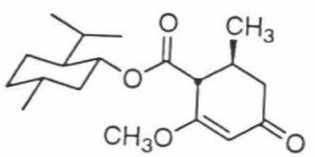
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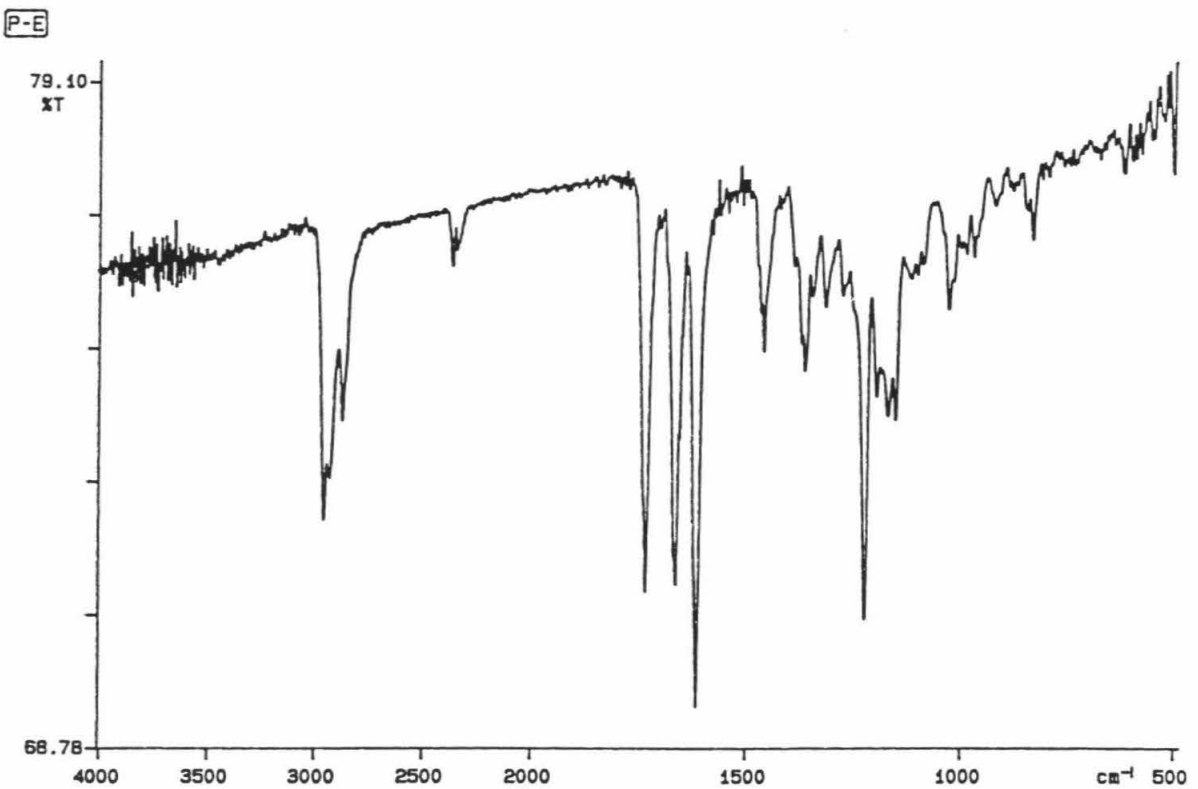
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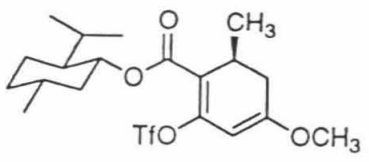
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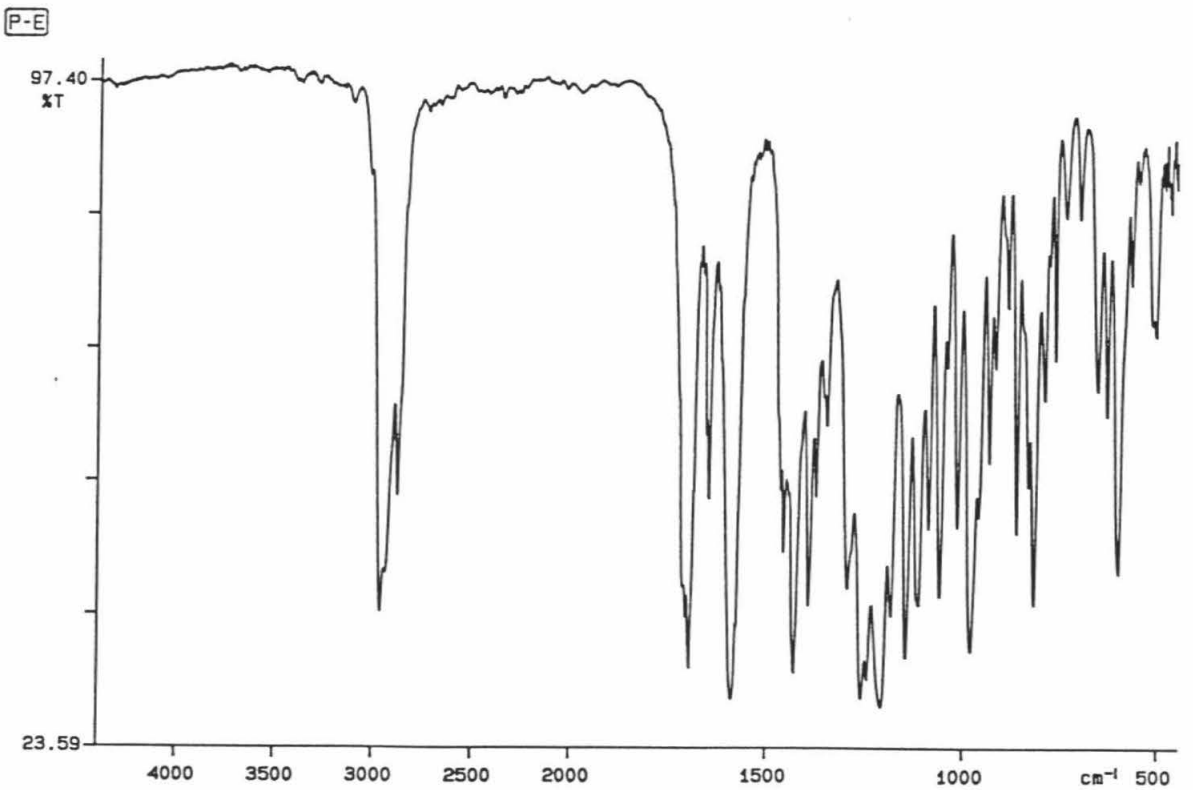
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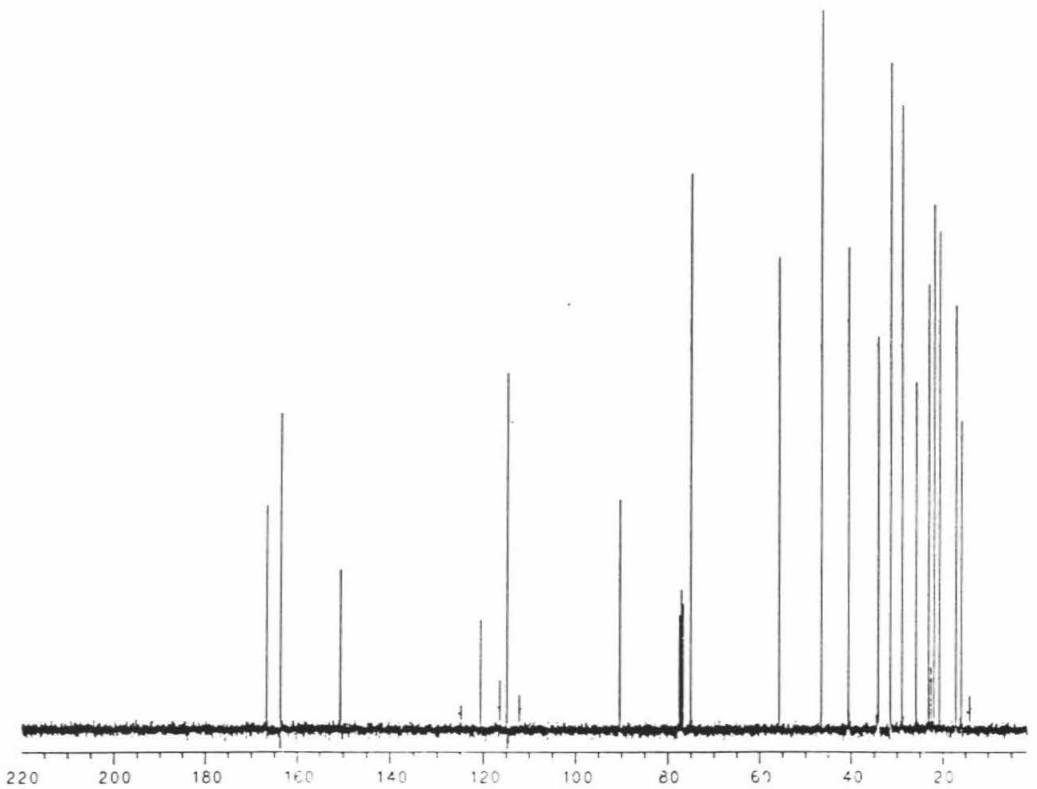
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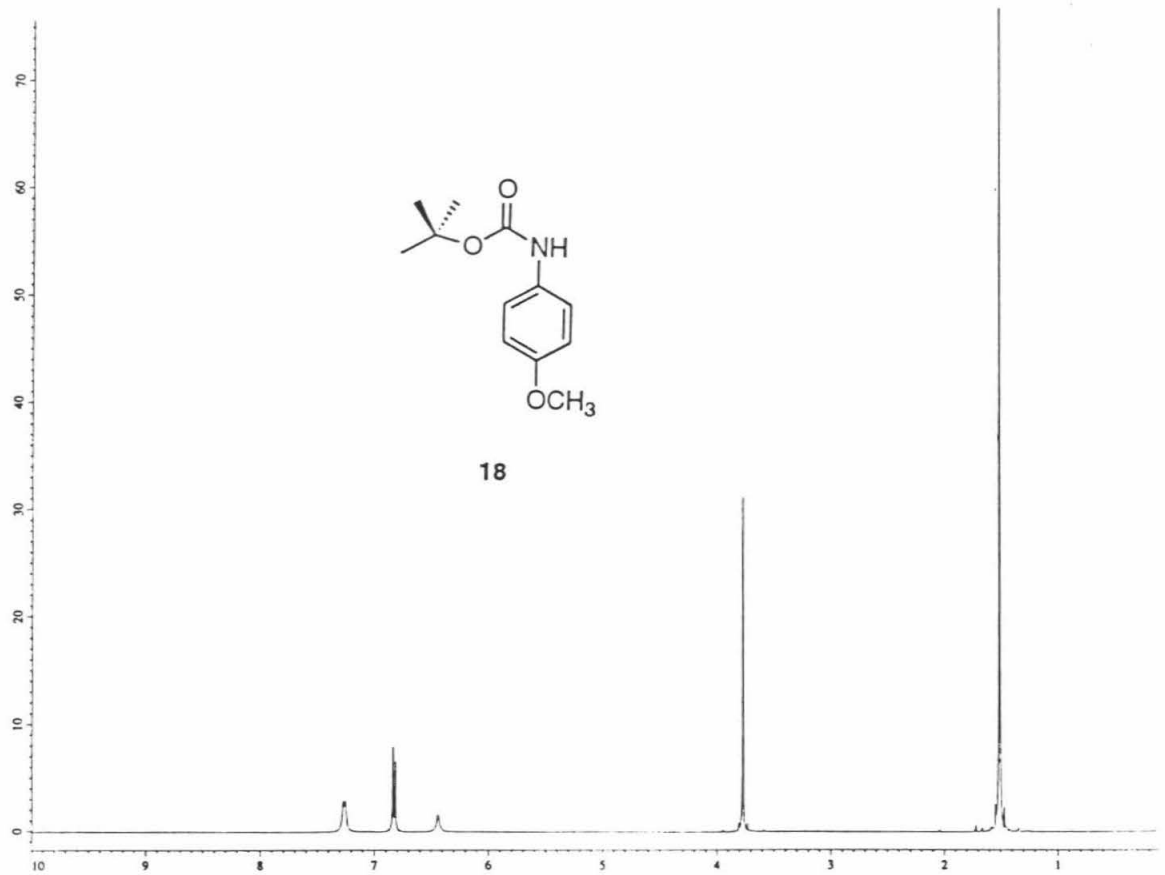
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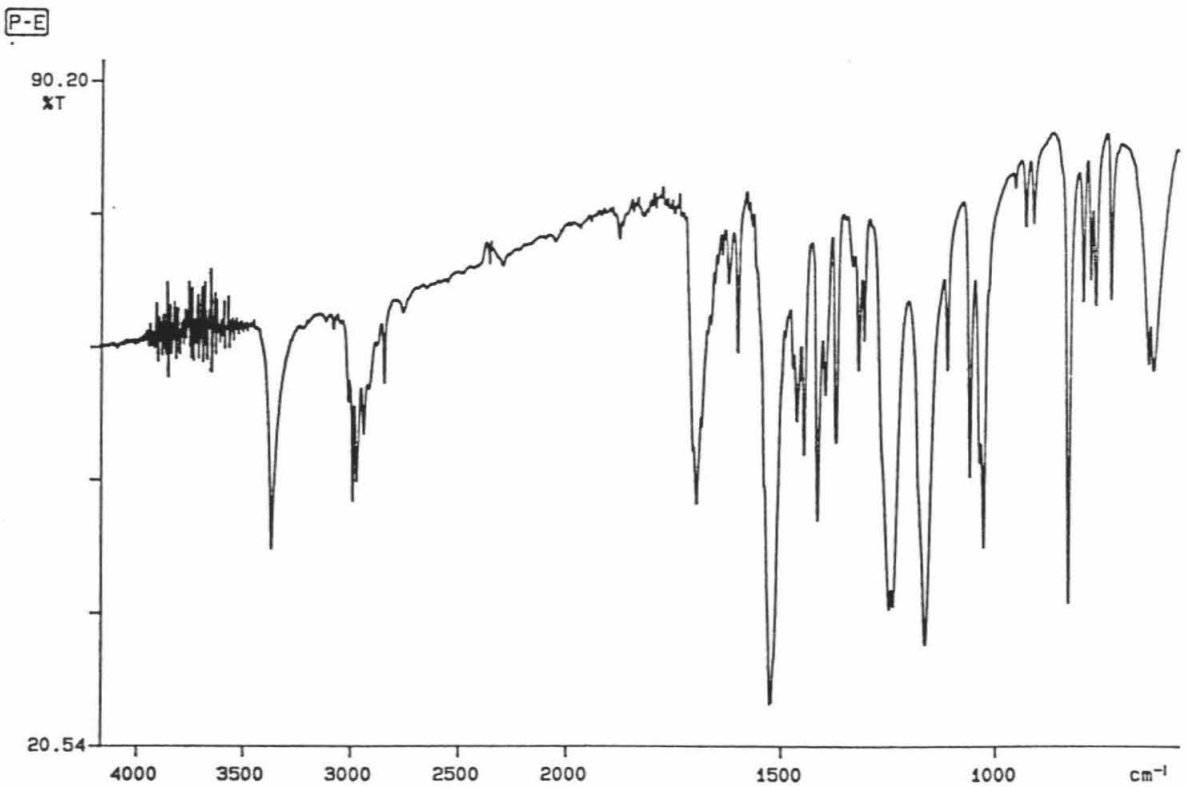
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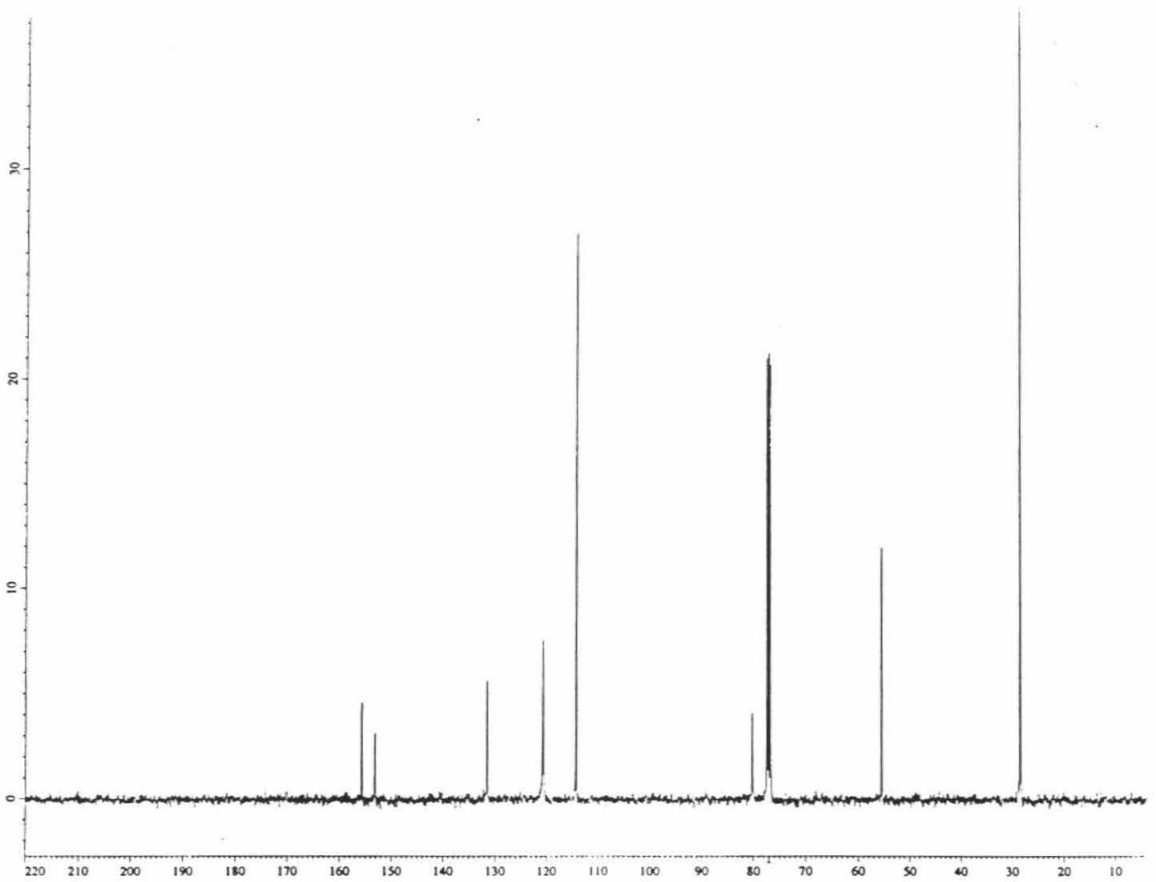
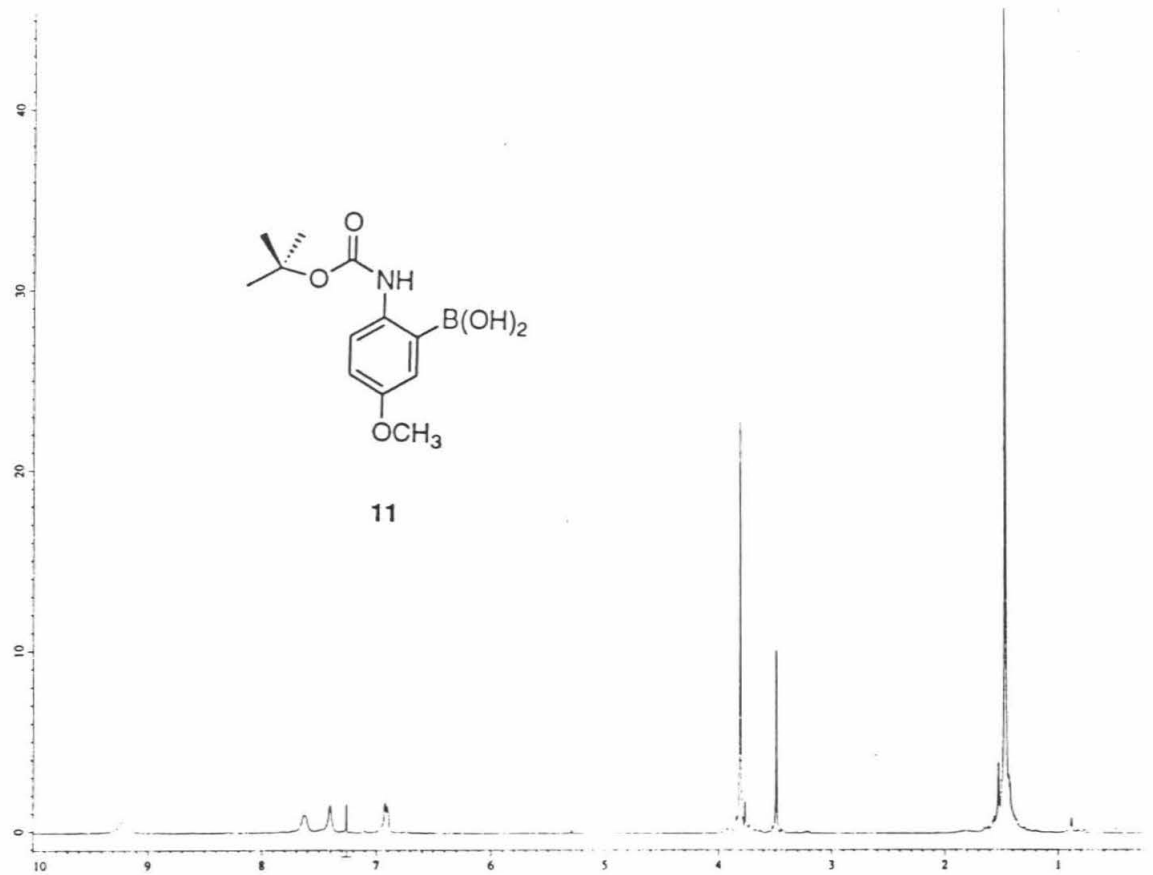
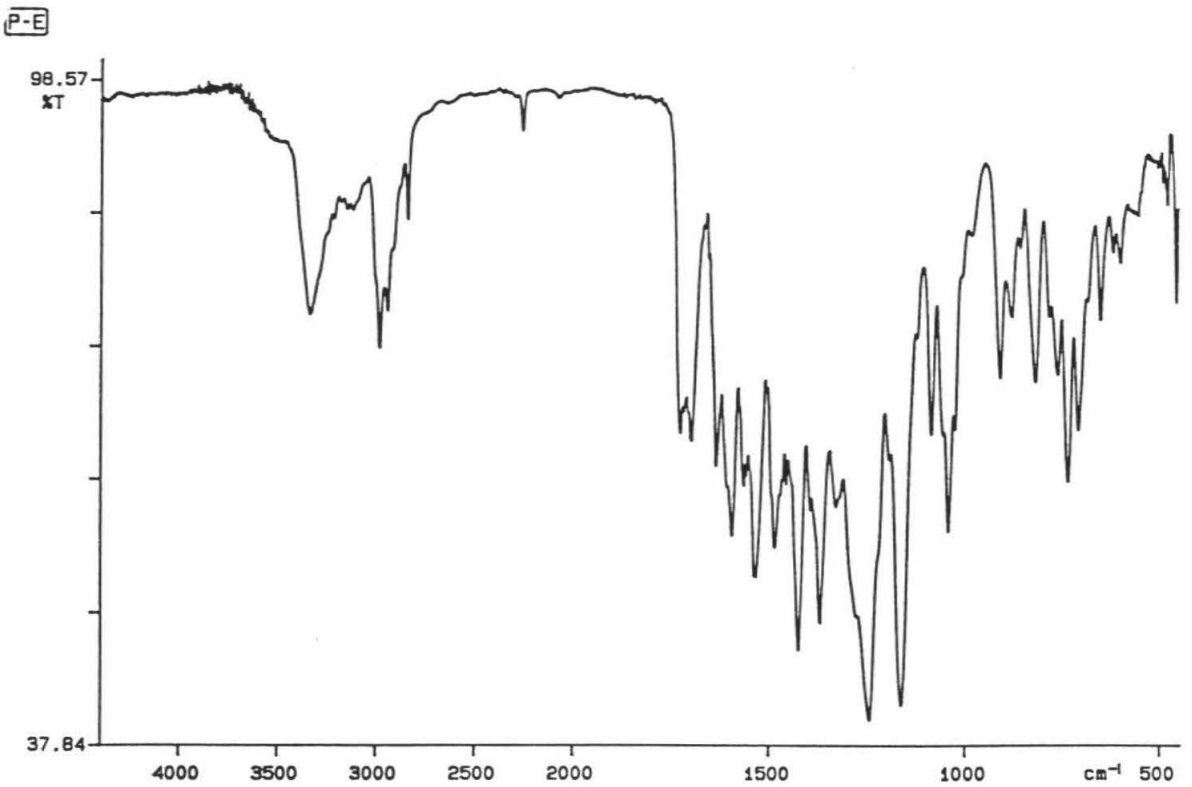
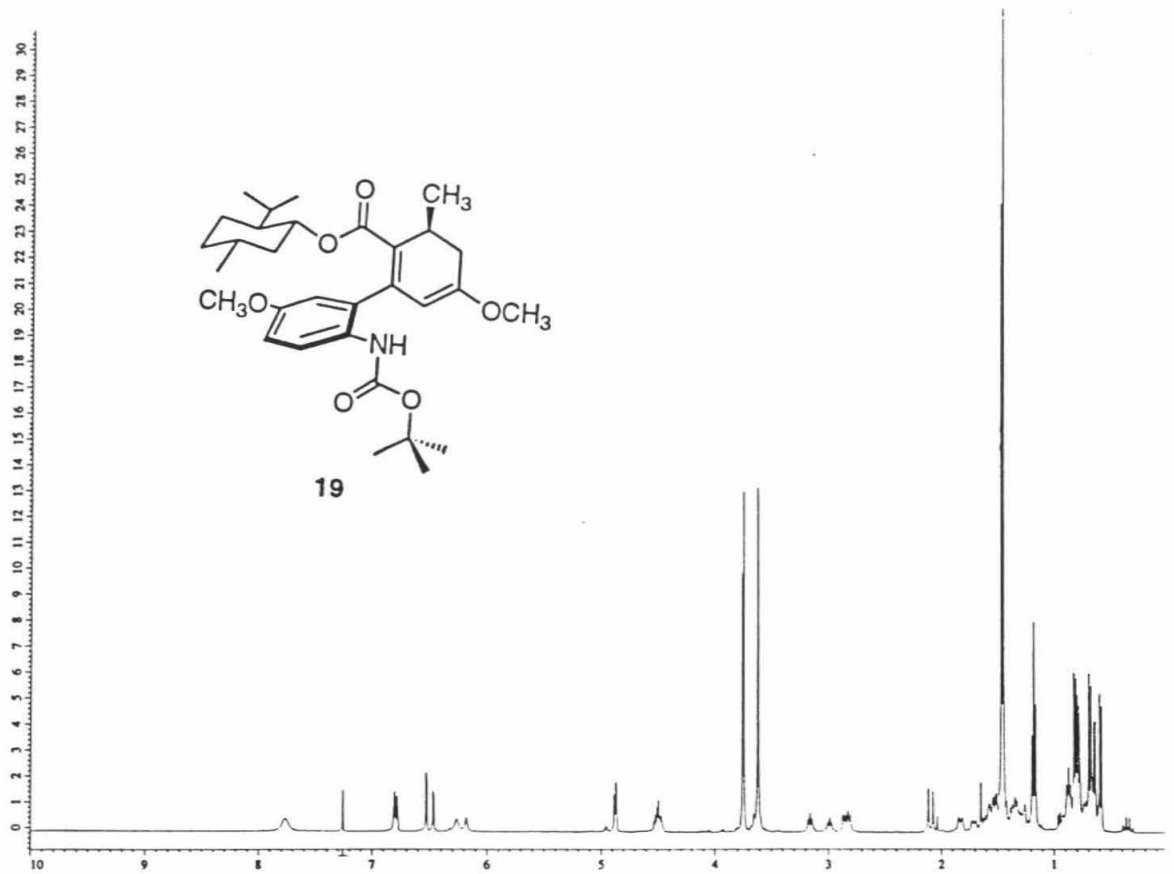
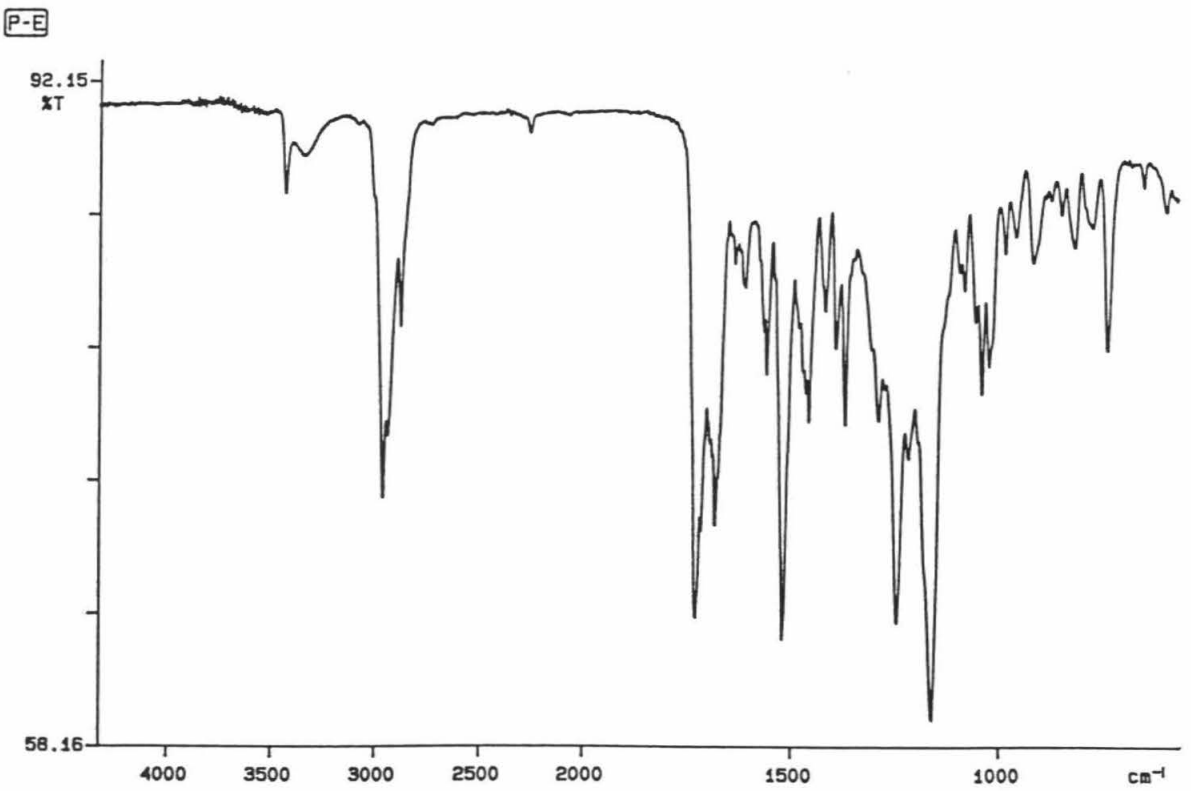

30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

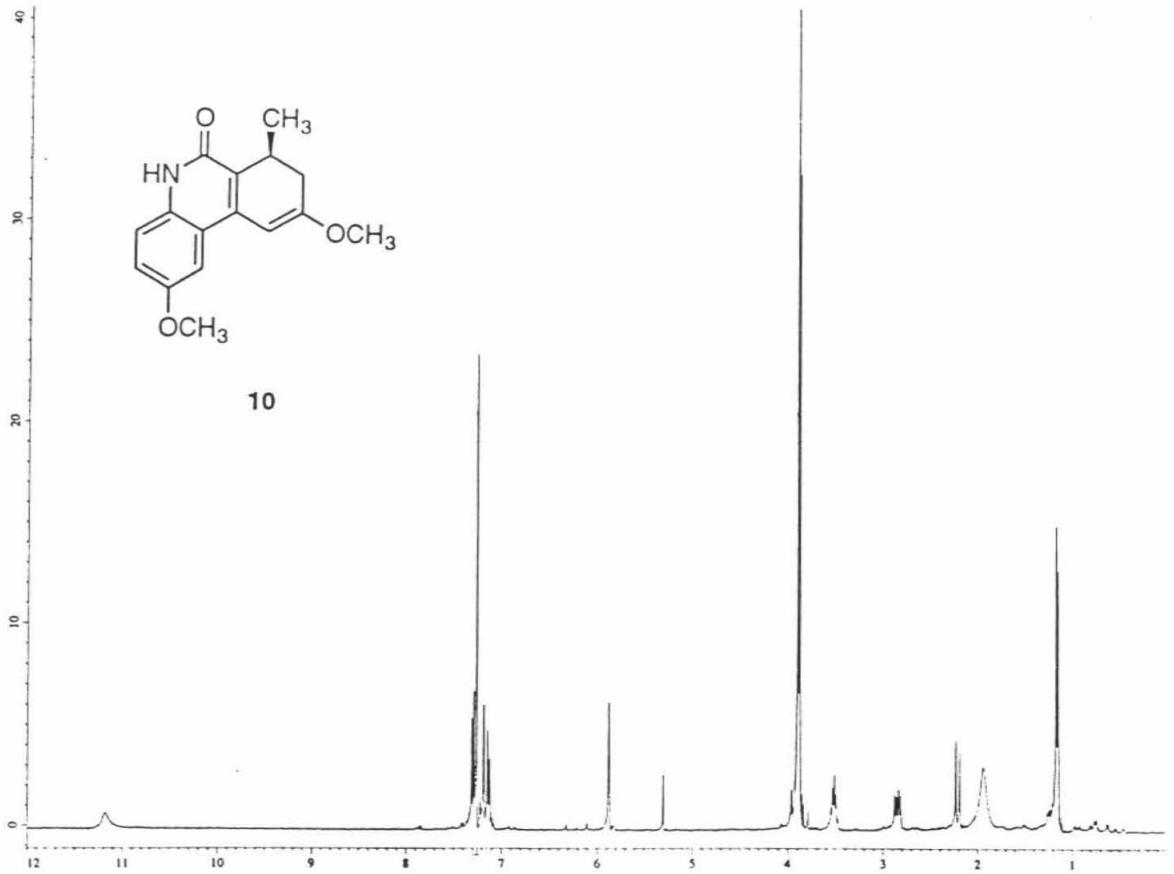

O
NH
B(OH)2
OCH3
11


P-E
98.57
%T
37.84
4000
3500
3000
2500
2000
1500
1000
cm-1
500

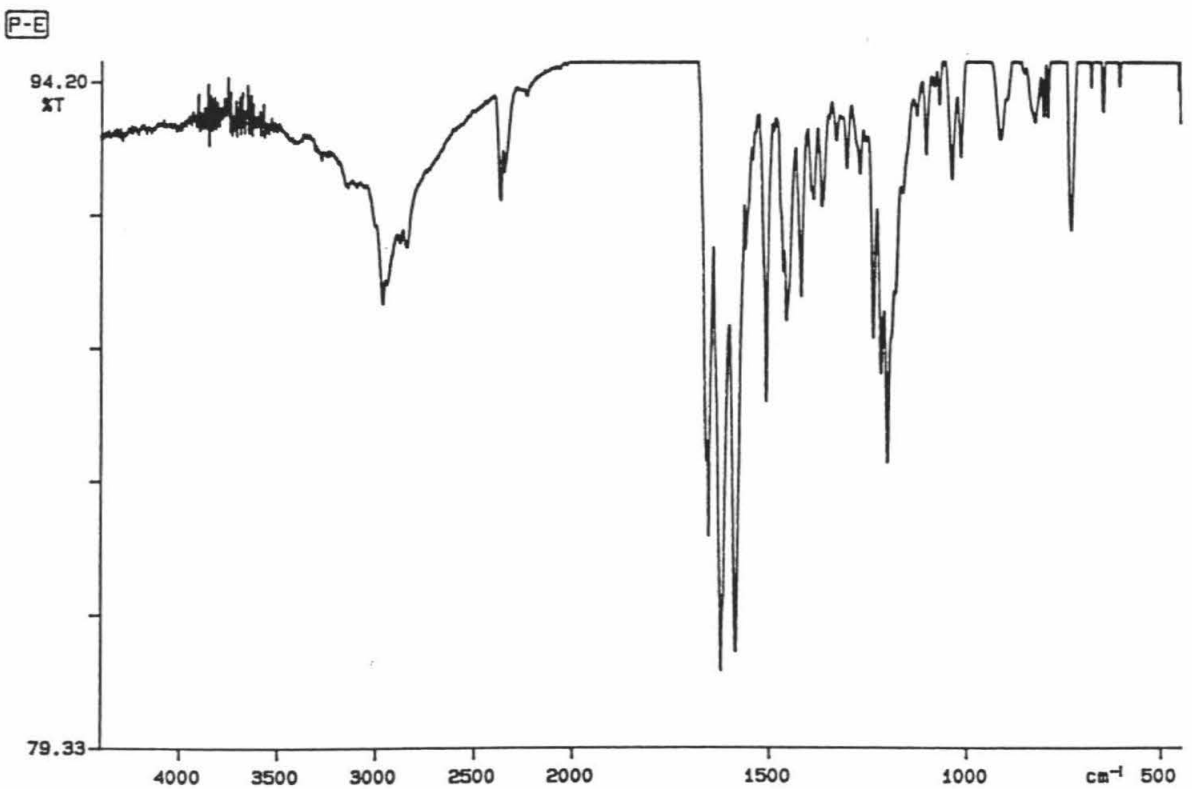

O
CH3
O
CH3O
OCH3
NH
O
O

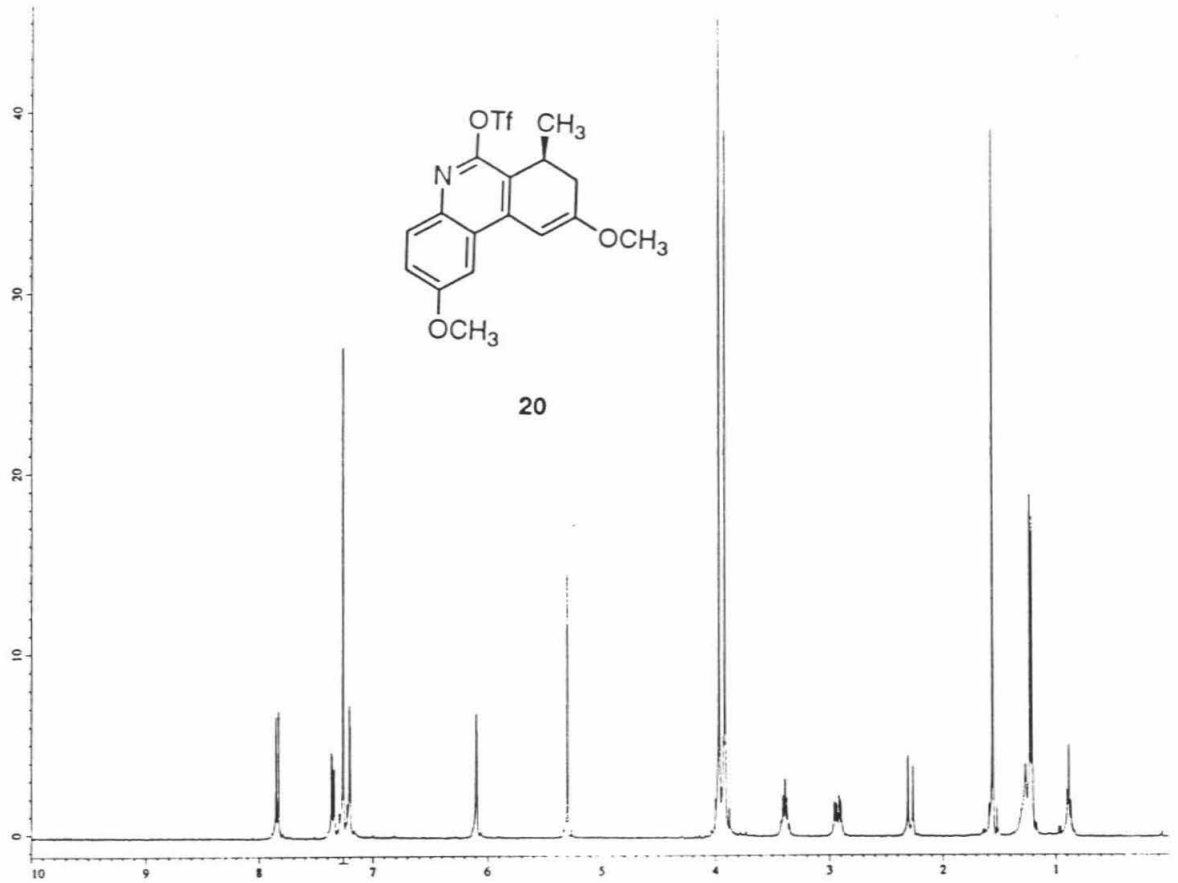
19


P-E
92.15
%T
58.16
4000
3500
3000
2500
2000
1500
1000
cm-1

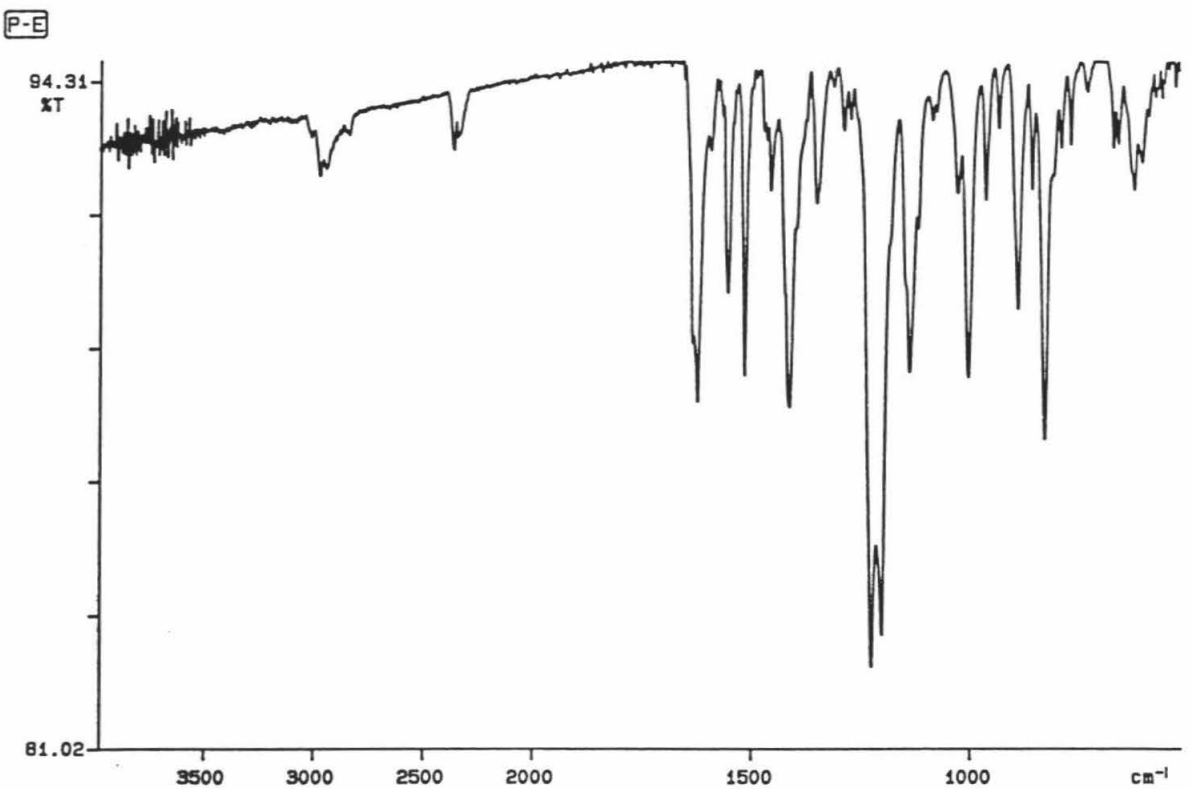

O
CH3
HN
OCH3
OCH3

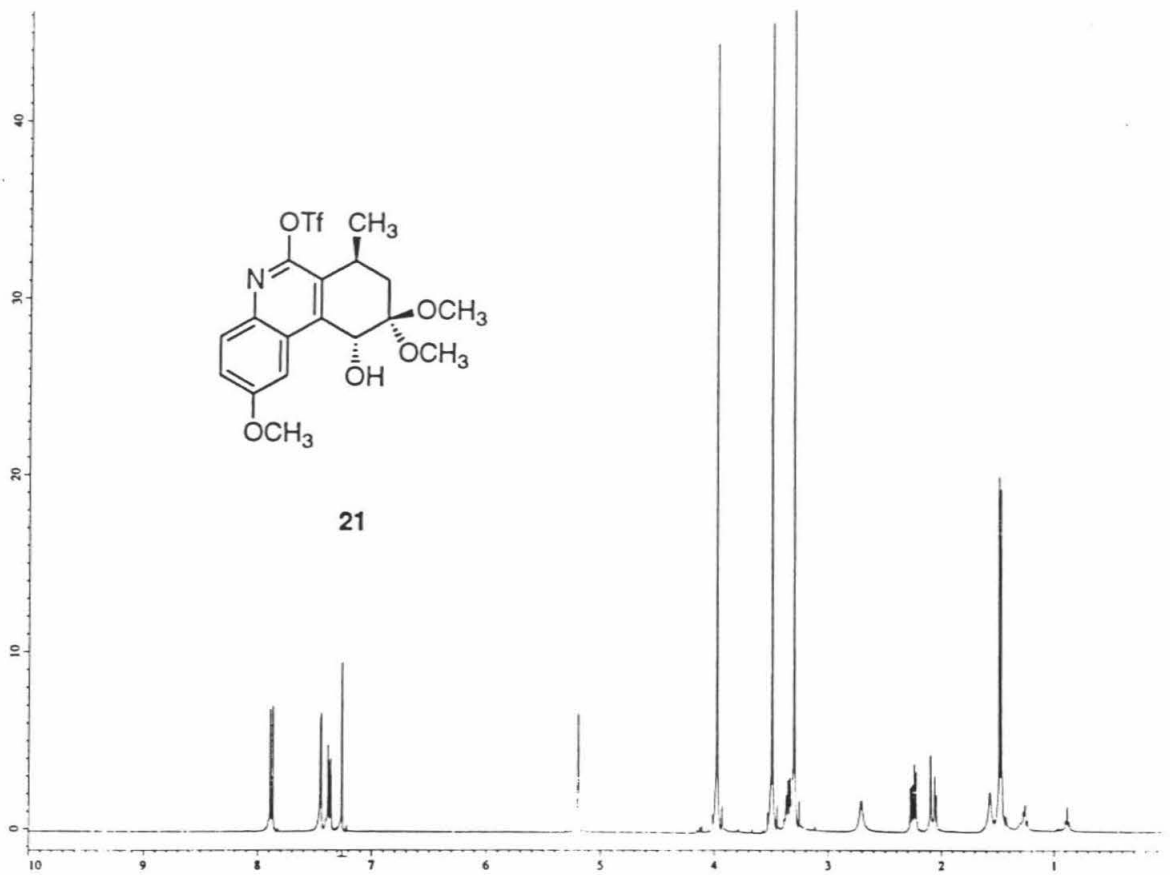
10


P-E
94.20
%T
79.33
4000
3500
3000
2500
2000
1500
1000
cm-1
500

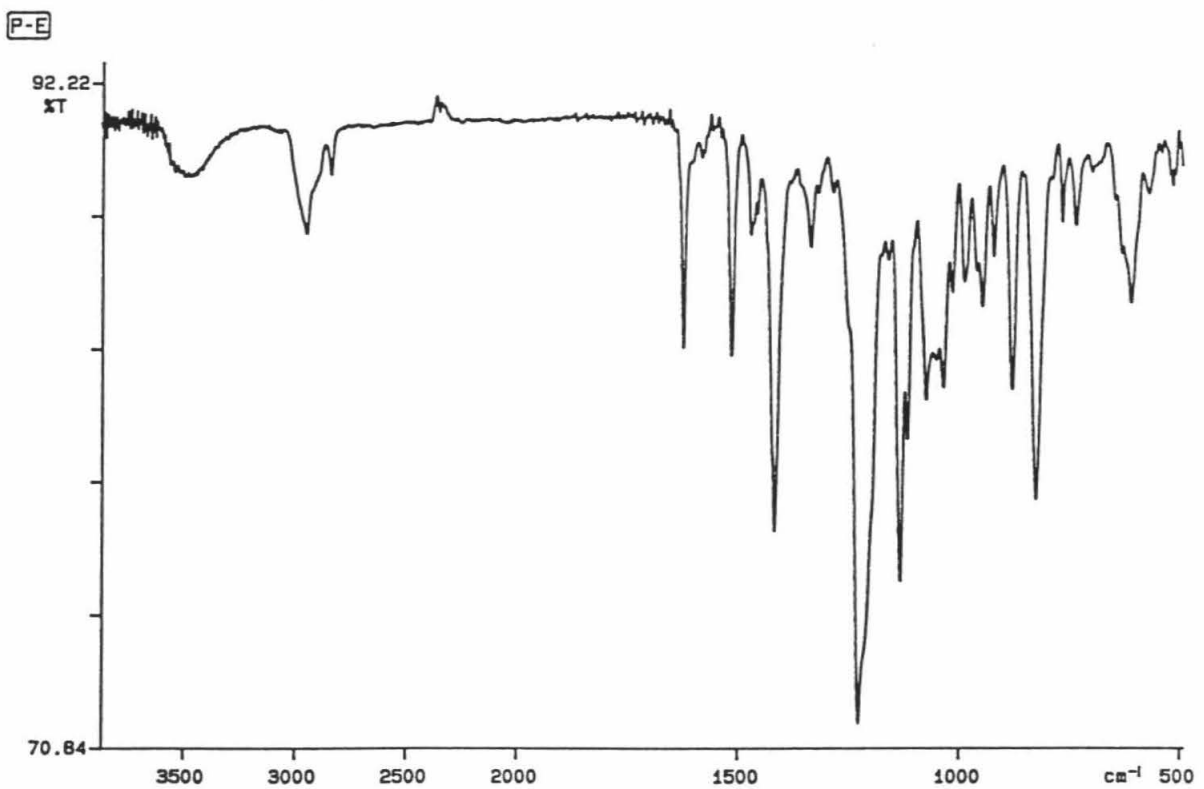

OTf
CH3
N
OCH3
OCH3

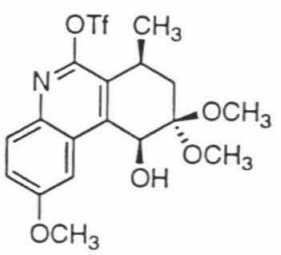
20


P-E
94.31
%T
81.02
3500
3000
2500
2000
1500
1000
cm-1

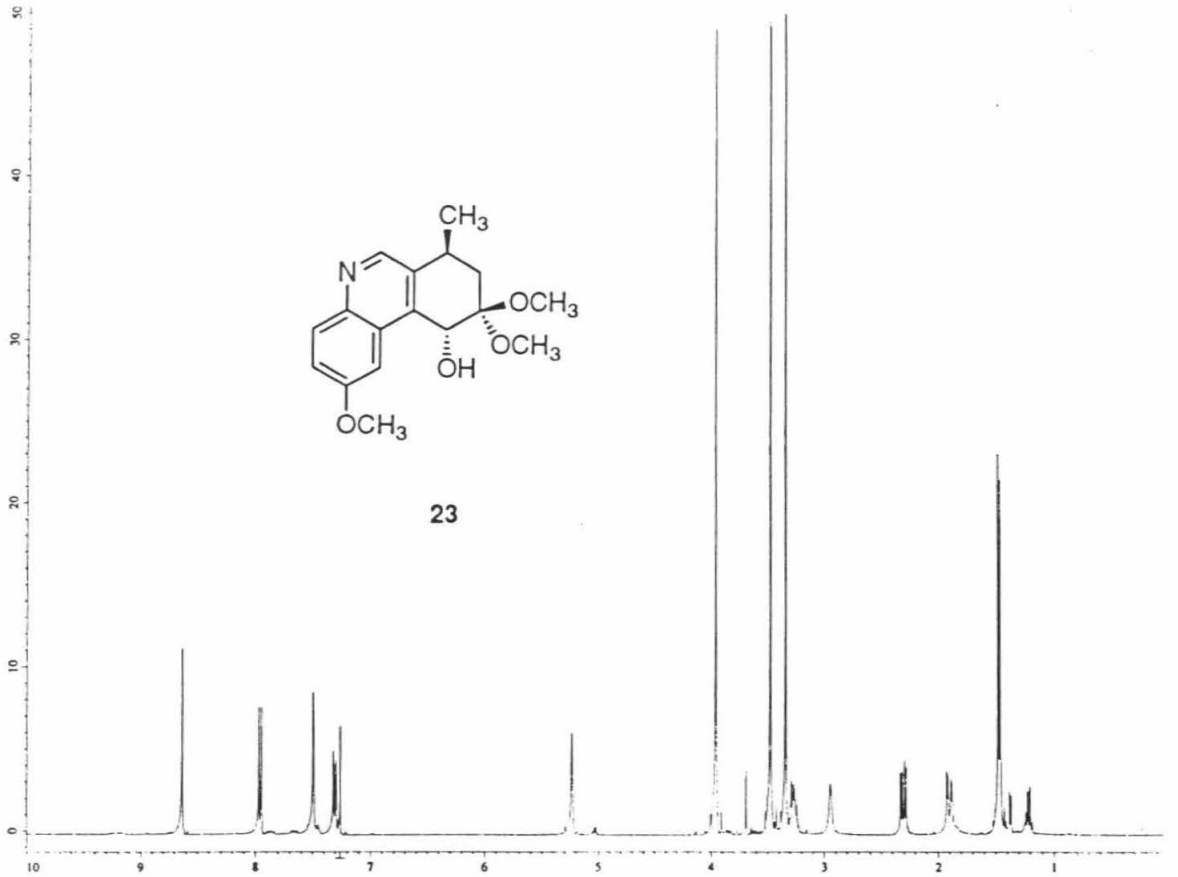

OTf
CH3
N
OCH3
OCH3
OH
OCH3

**21**

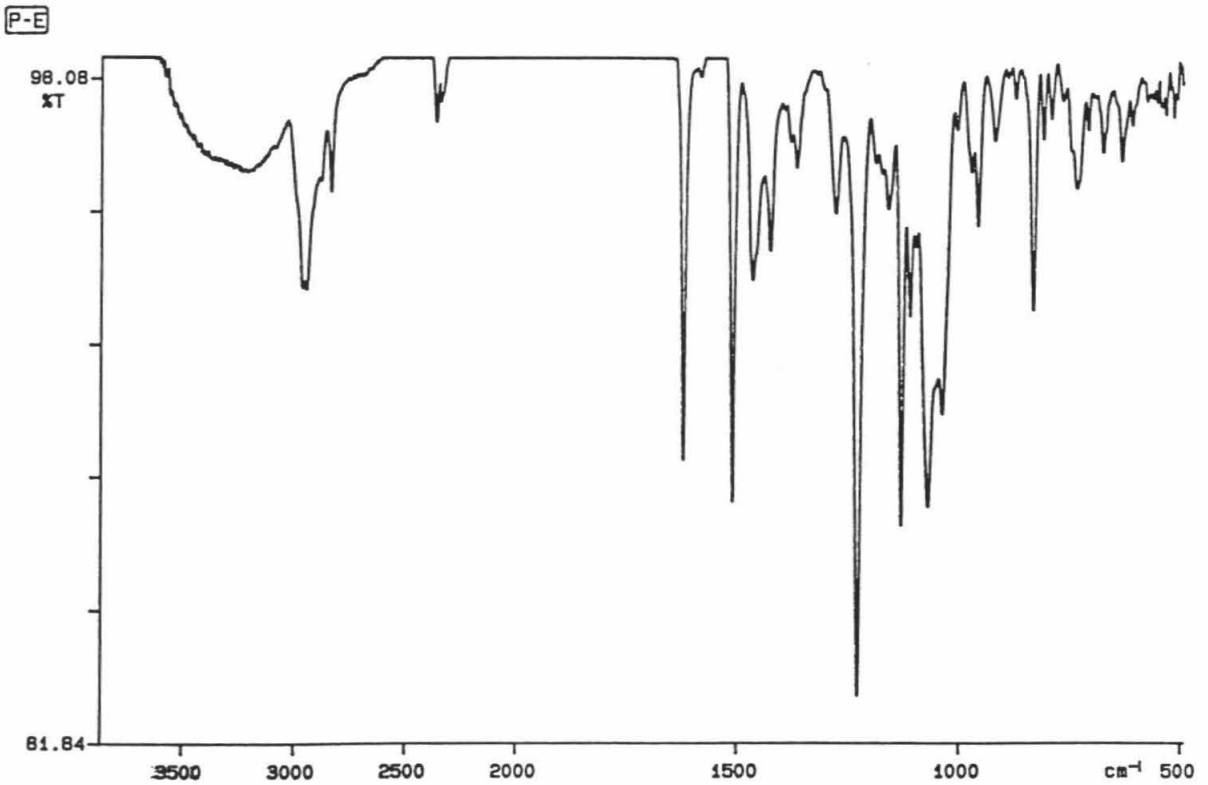

P-E
92.22
%T
70.84
3500
3000
2500
2000
1500
1000
cm-1
500

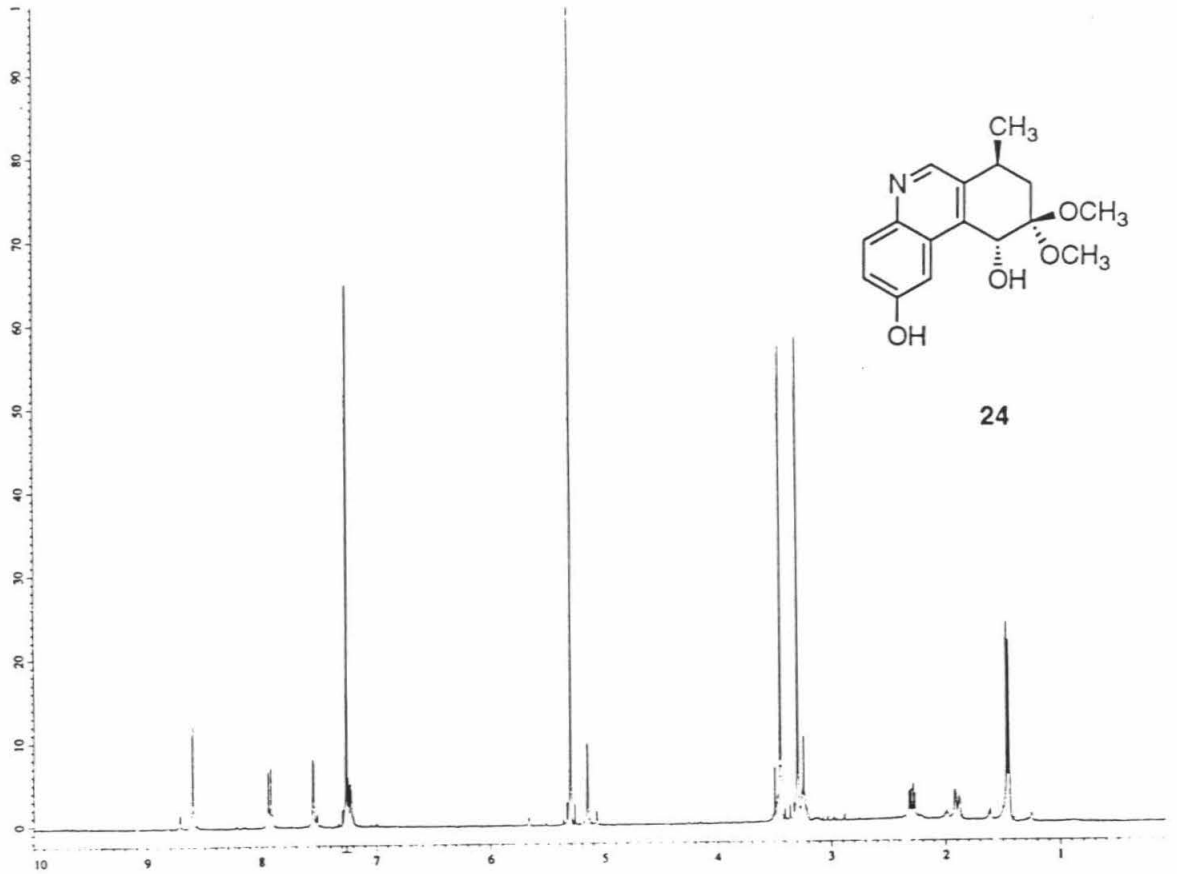



**22**

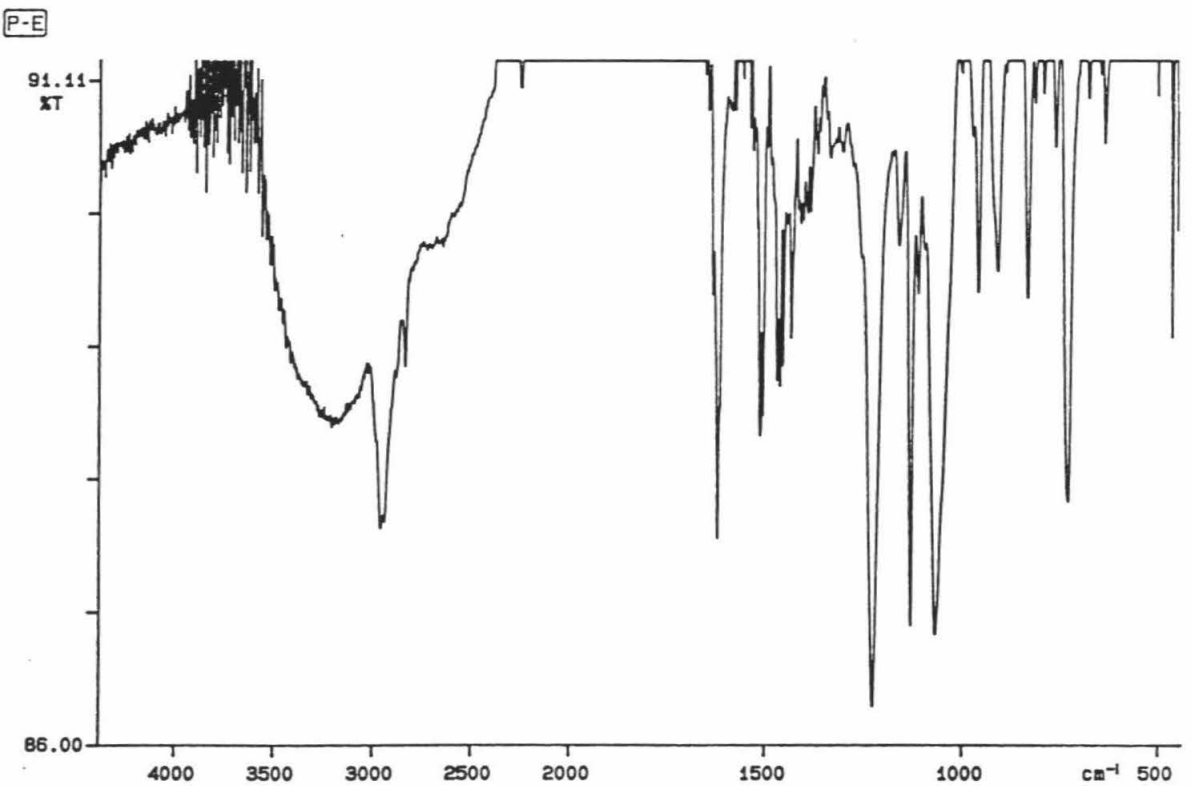

CH3
N
OCH3
OCH3
OH
OCH3

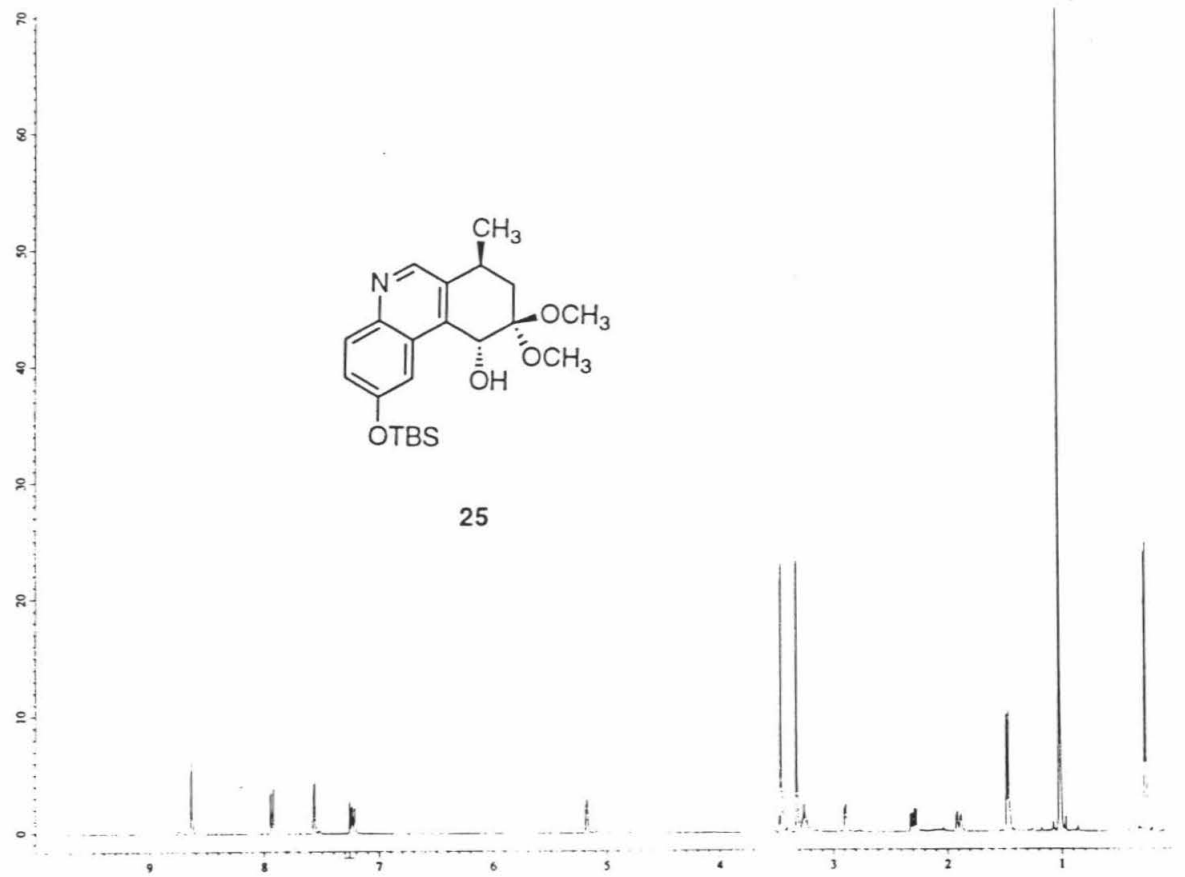
23


P-E
98.08
%T
81.84
3500
3000
2500
2000
1500
1000
cm-1
500

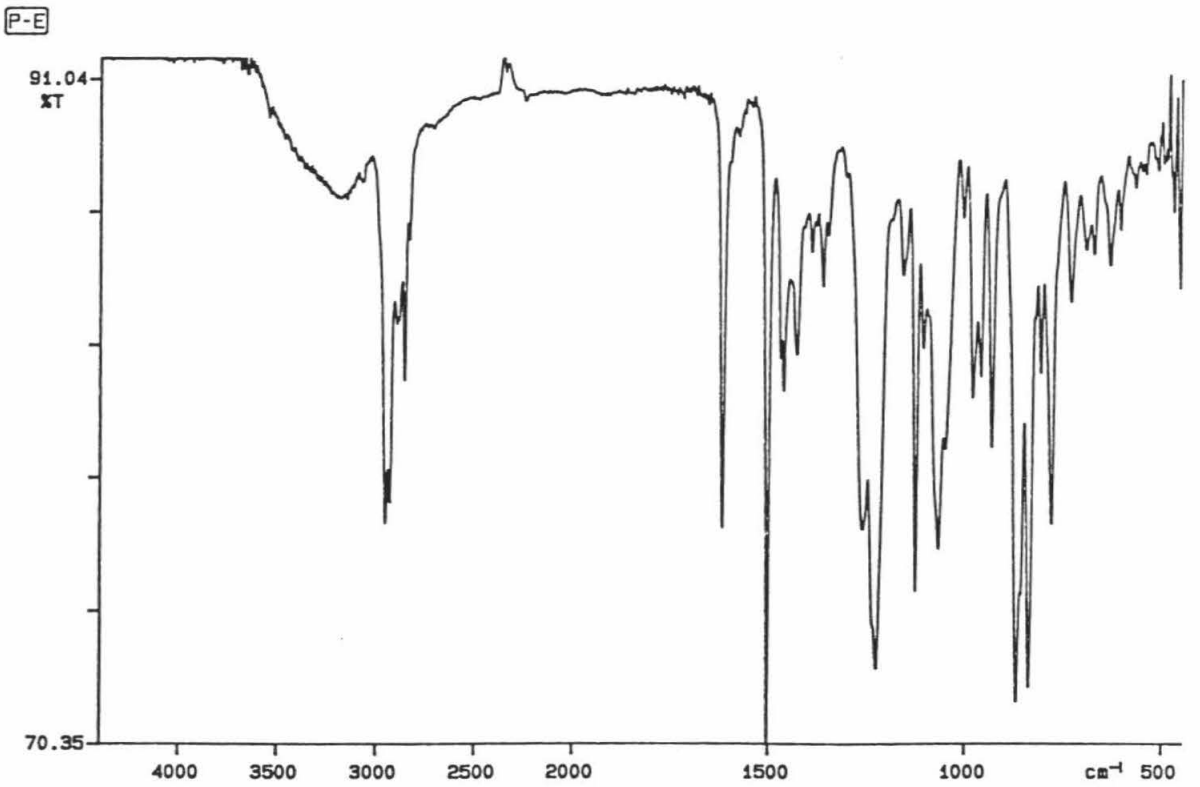

CH3
N
OCH3
OCH3
OH
OH

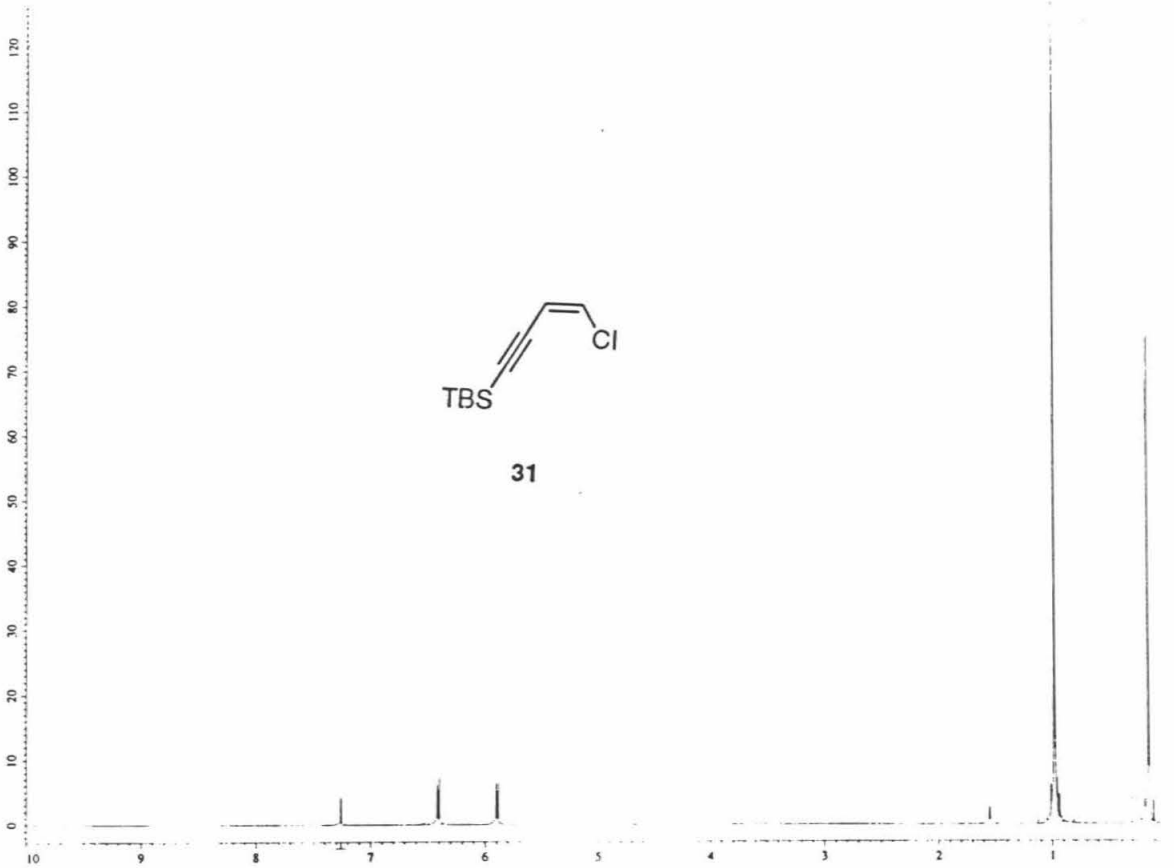
24


P-E
91.11
%T
86.00
4000
3500
3000
2500
2000
1500
1000
cm-1
500

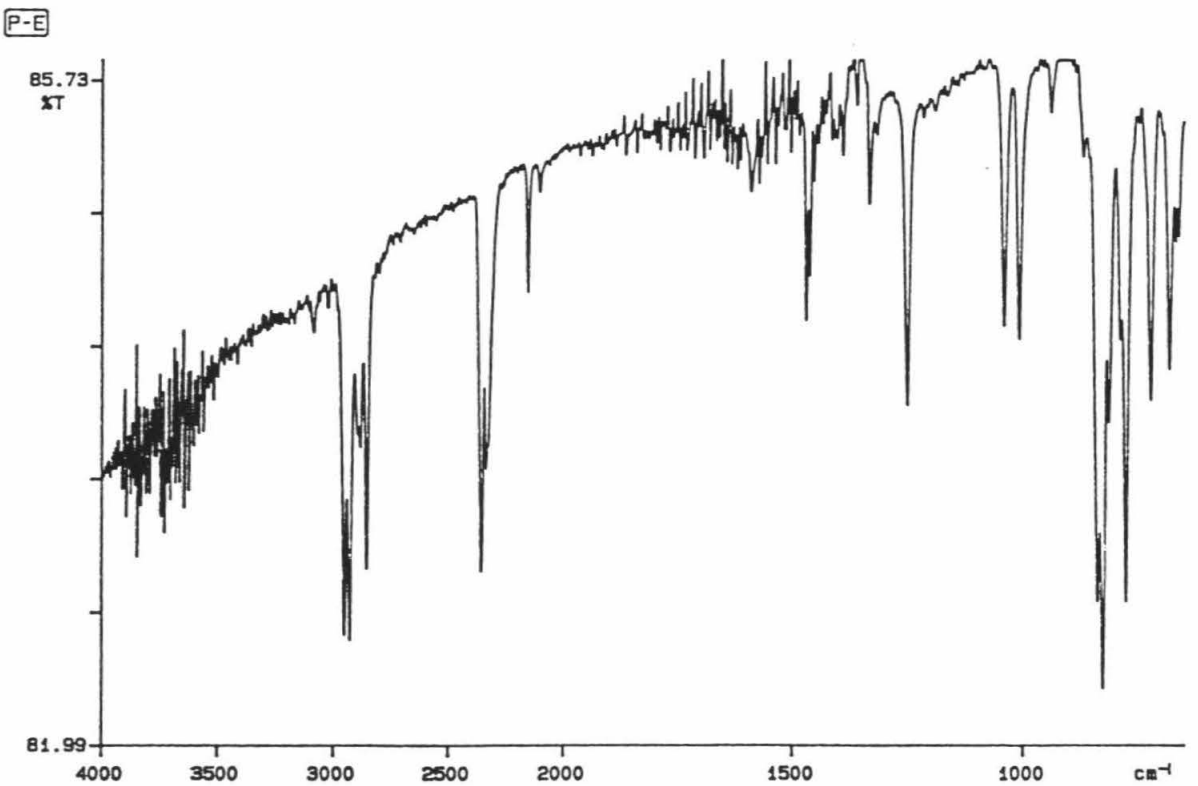

CH3
N
OCH3
OCH3
OH
OTBS

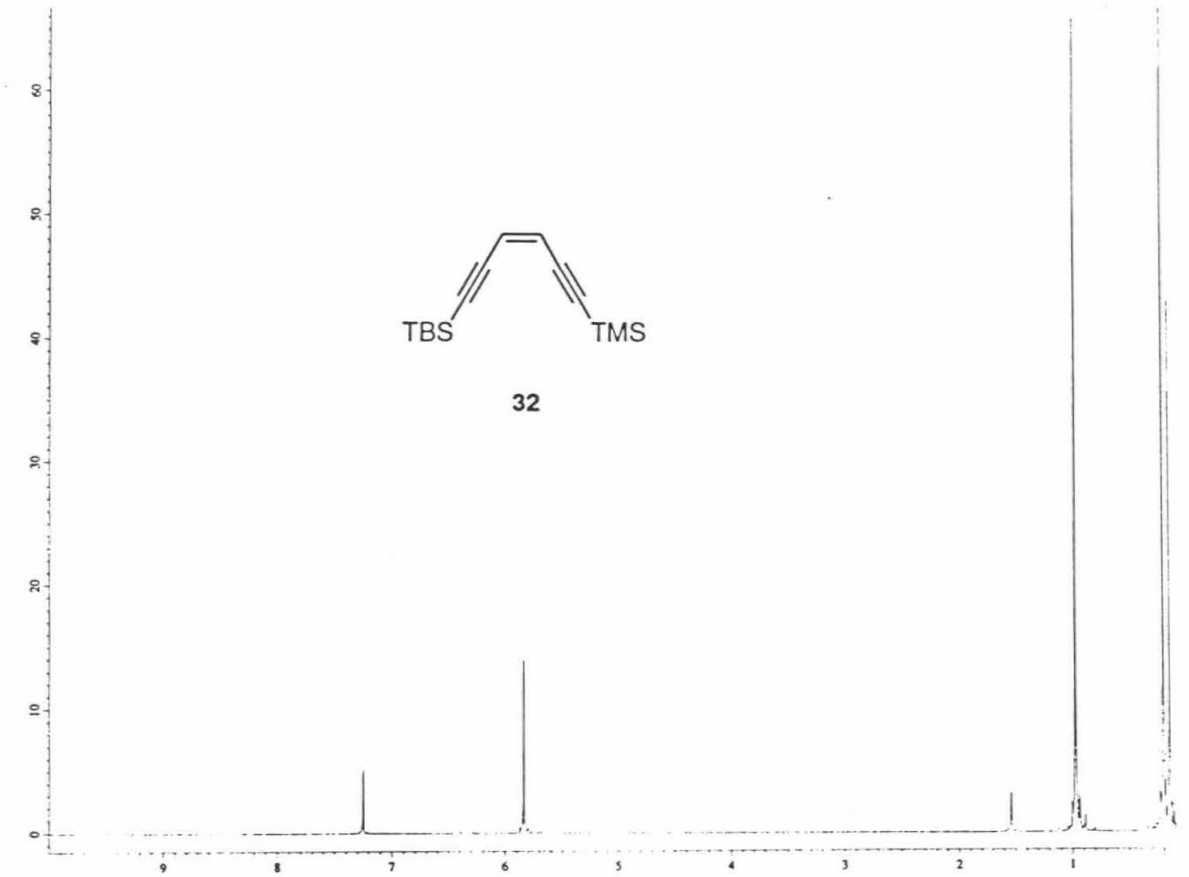
25


P-E
91.04
%T
70.35
4000
3500
3000
2500
2000
1500
1000
cm-1
500

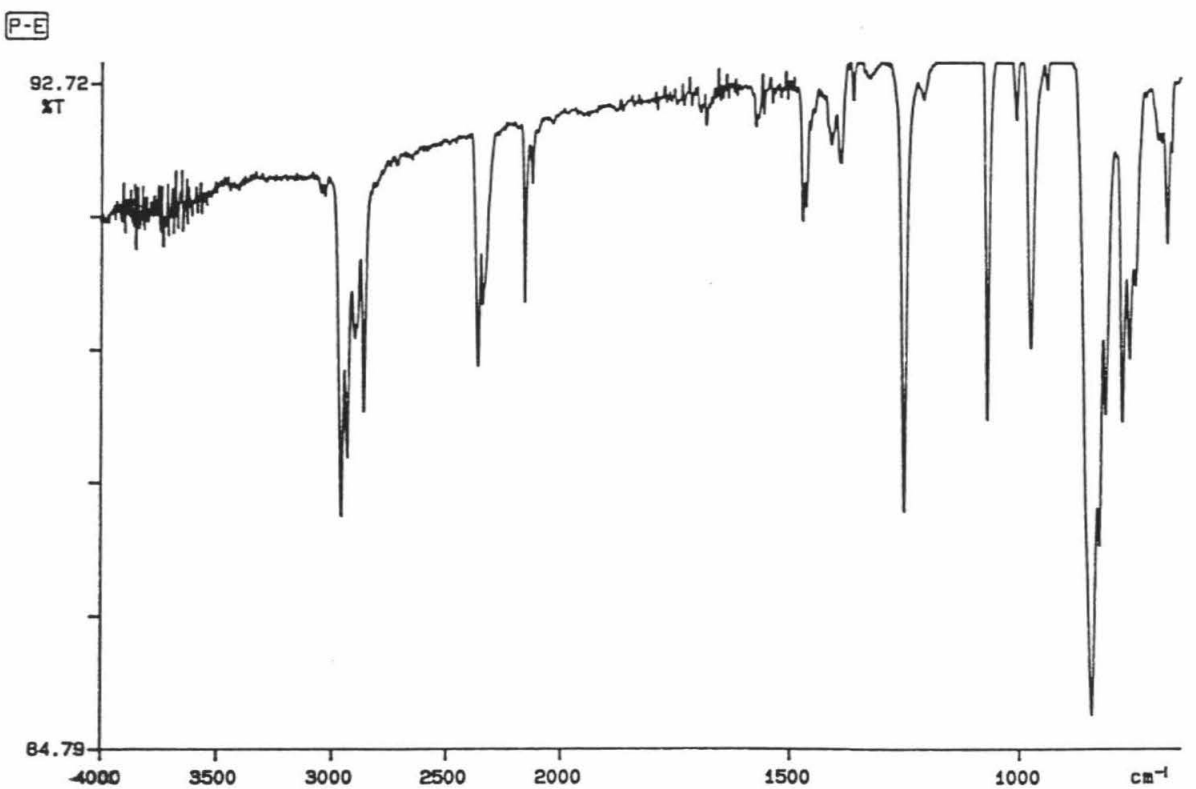


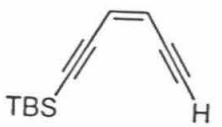

31





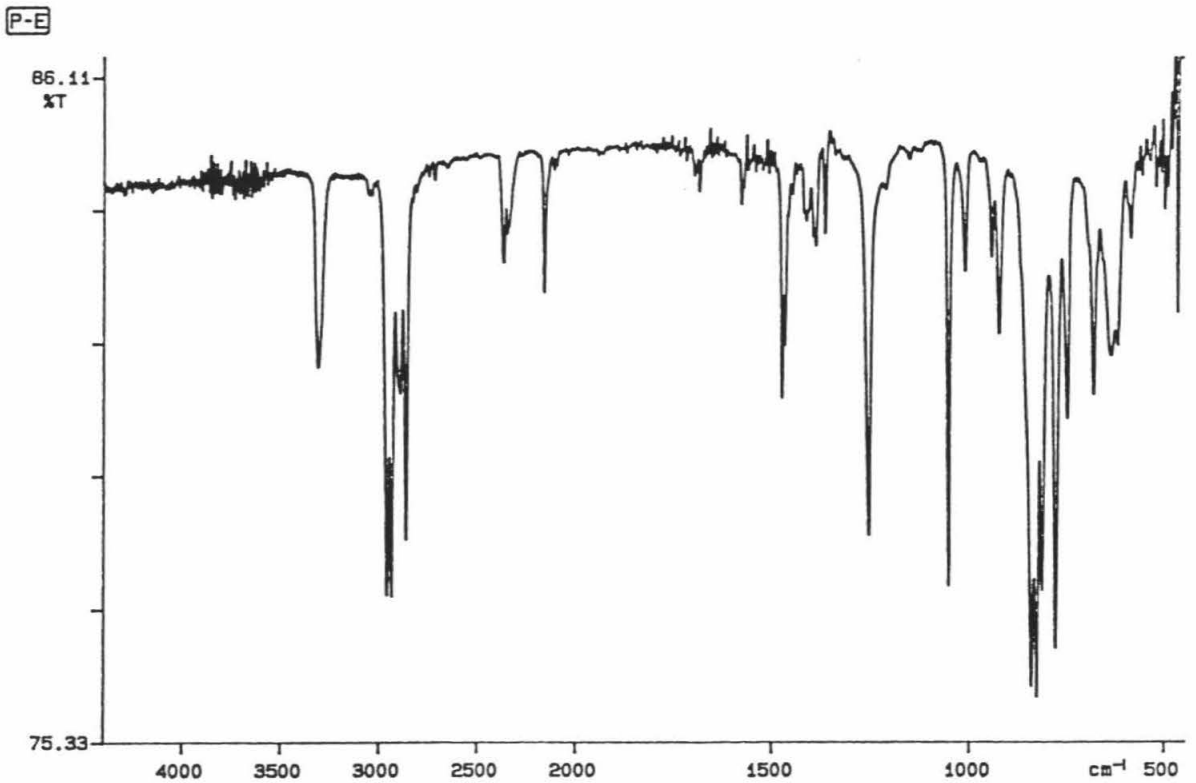

**32**

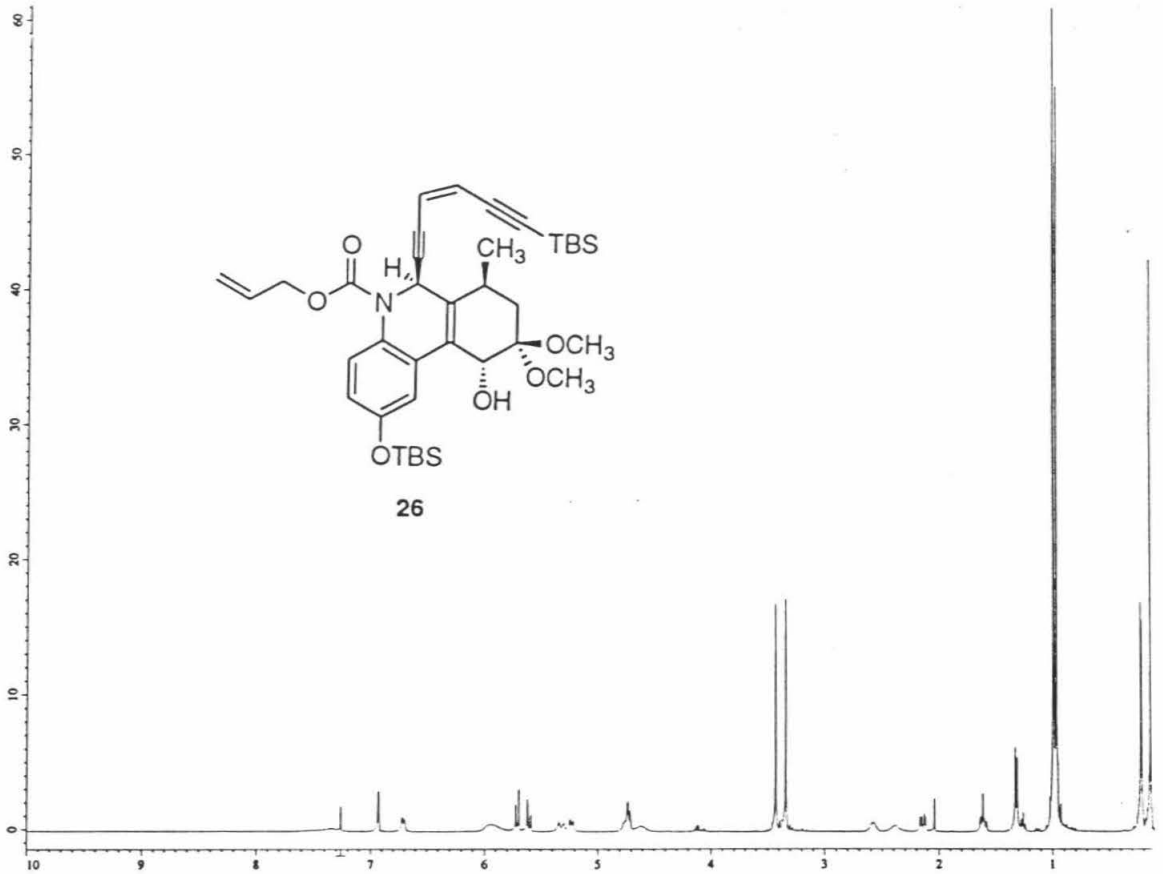



TBS
H

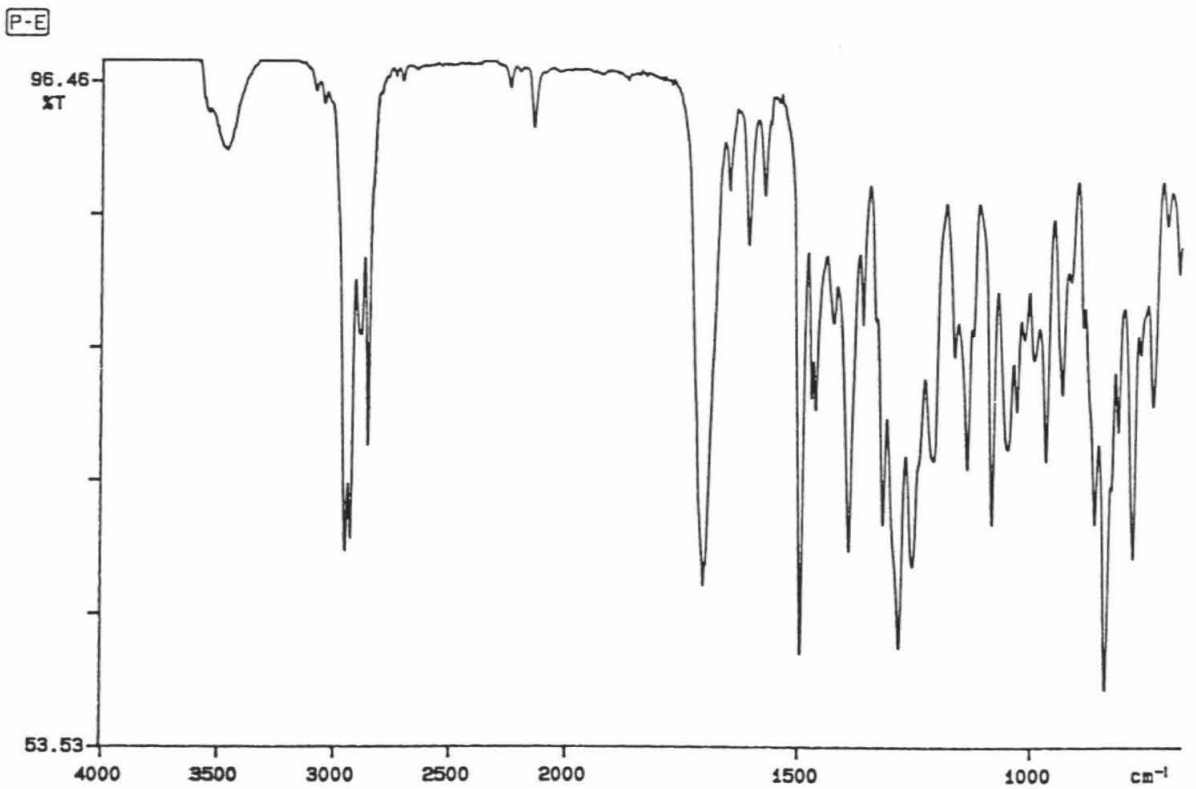
**33**

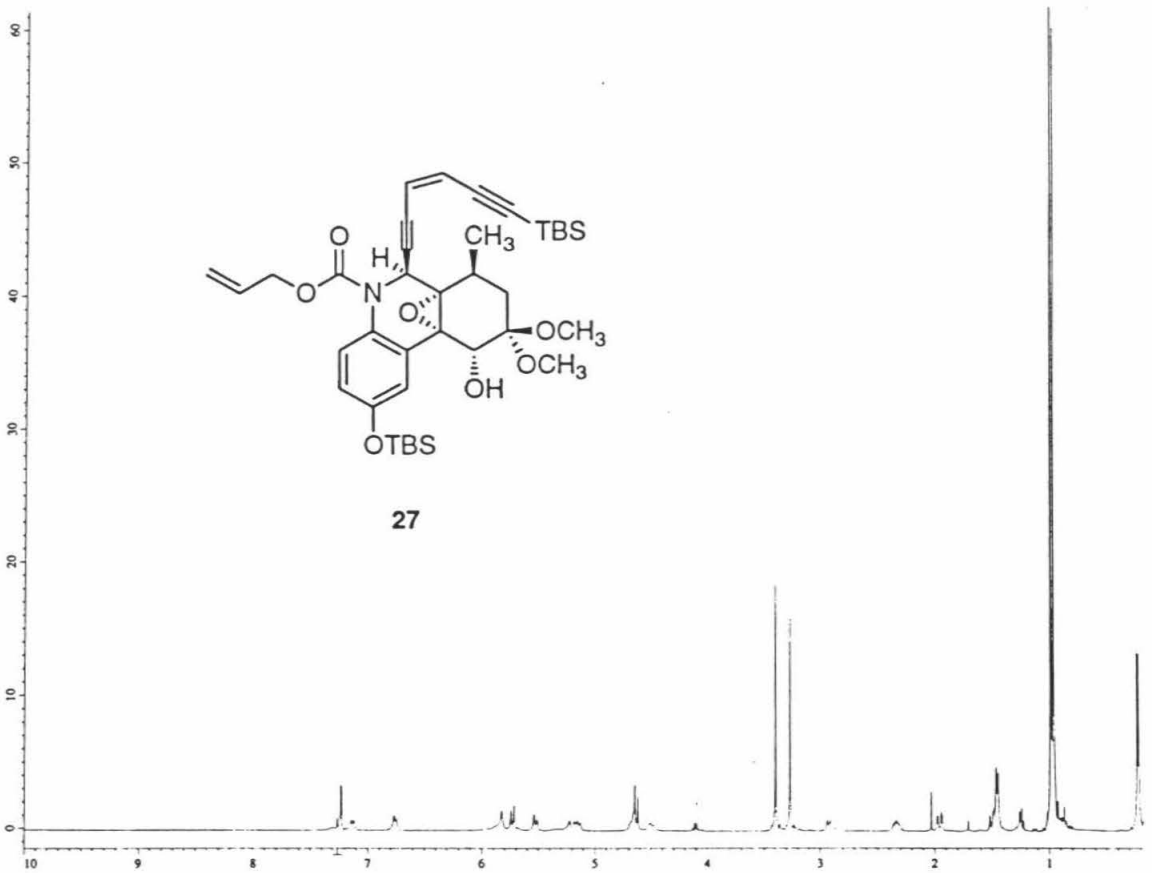

10
9
8
7
6
5
4
3
2
1
0


P-E
86.11
%T
75.33
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

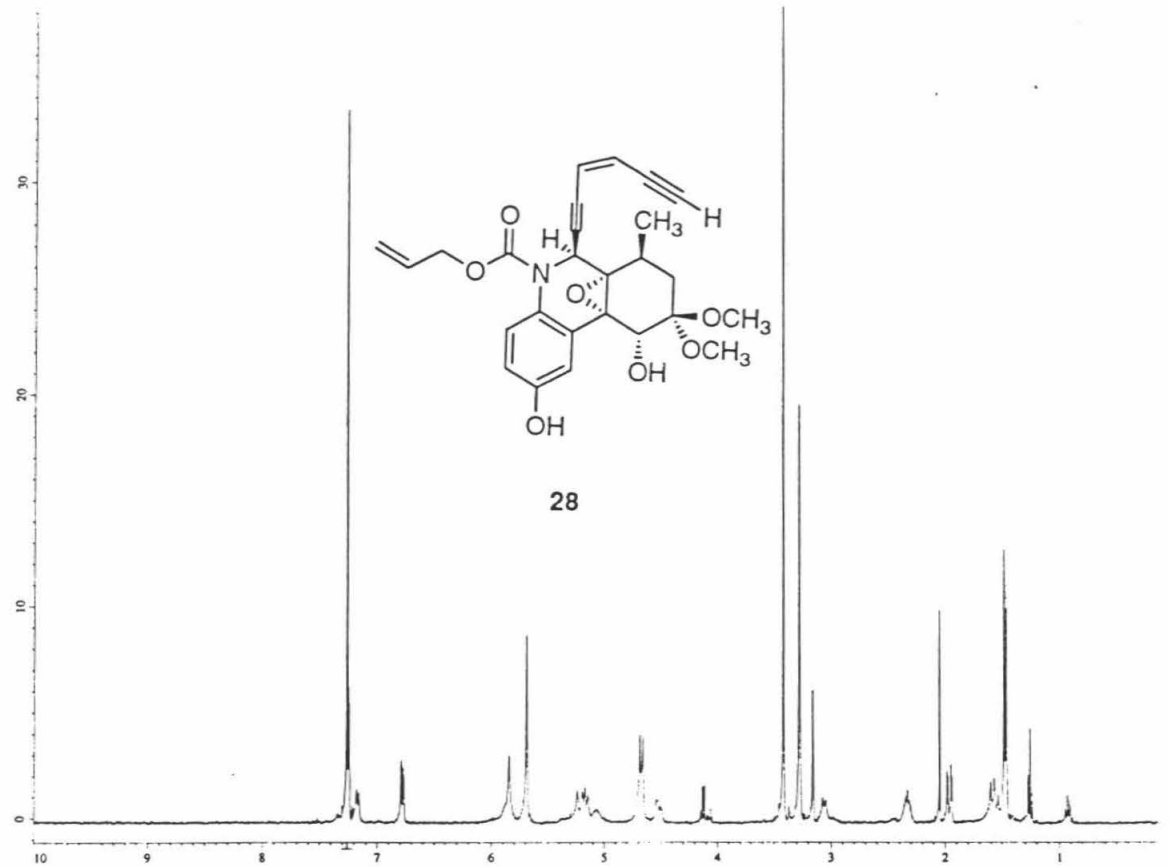

O
H
N
O
CH3
TBS
OCH3
OCH3
OH
OTBS
10
9
8
7
6
5
4
3
2
1
0

**26**

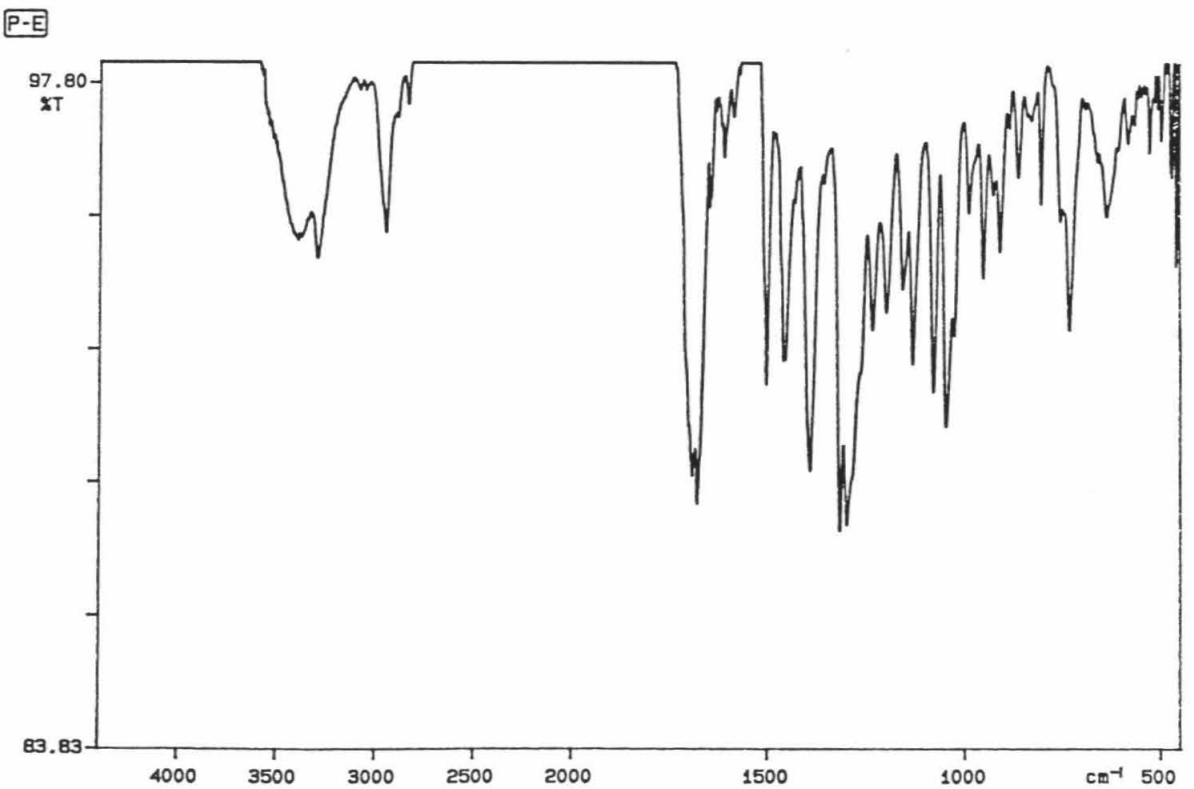

P-E
96.46
%T
53.53
4000
3500
3000
2500
2000
1500
1000
cm-1

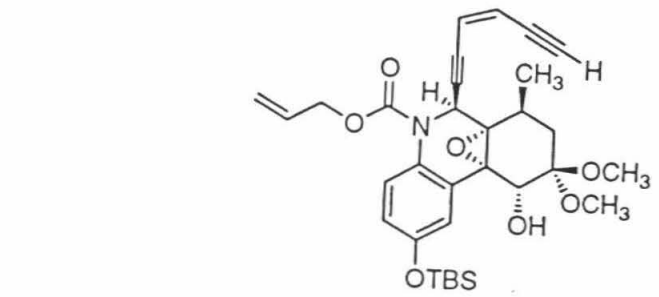



**27**

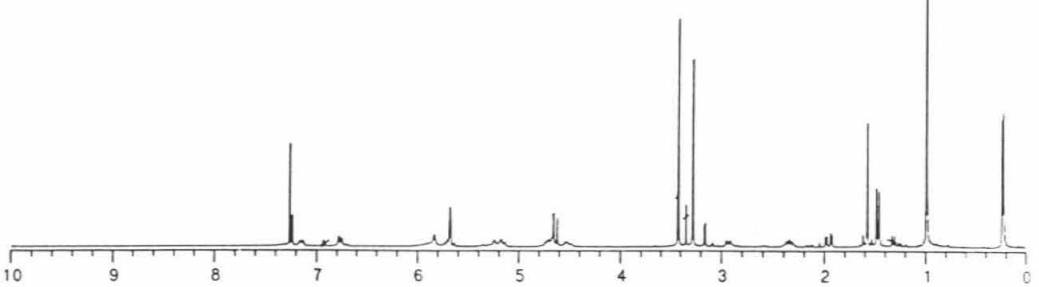

O
H
CH3
H
O
N
O
OCH3
OCH3
OH
OH
10
9
8
7
6
5
4
3
2
1
0
10
20
30

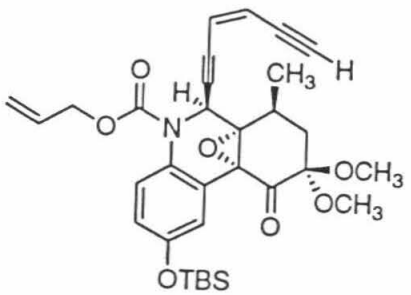
**28**


P-E
97.80
%T
83.83
4000
3500
3000
2500
2000
1500
1000
cm-1
500

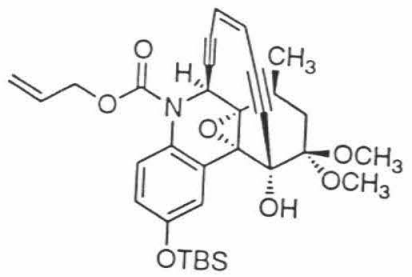



**9**



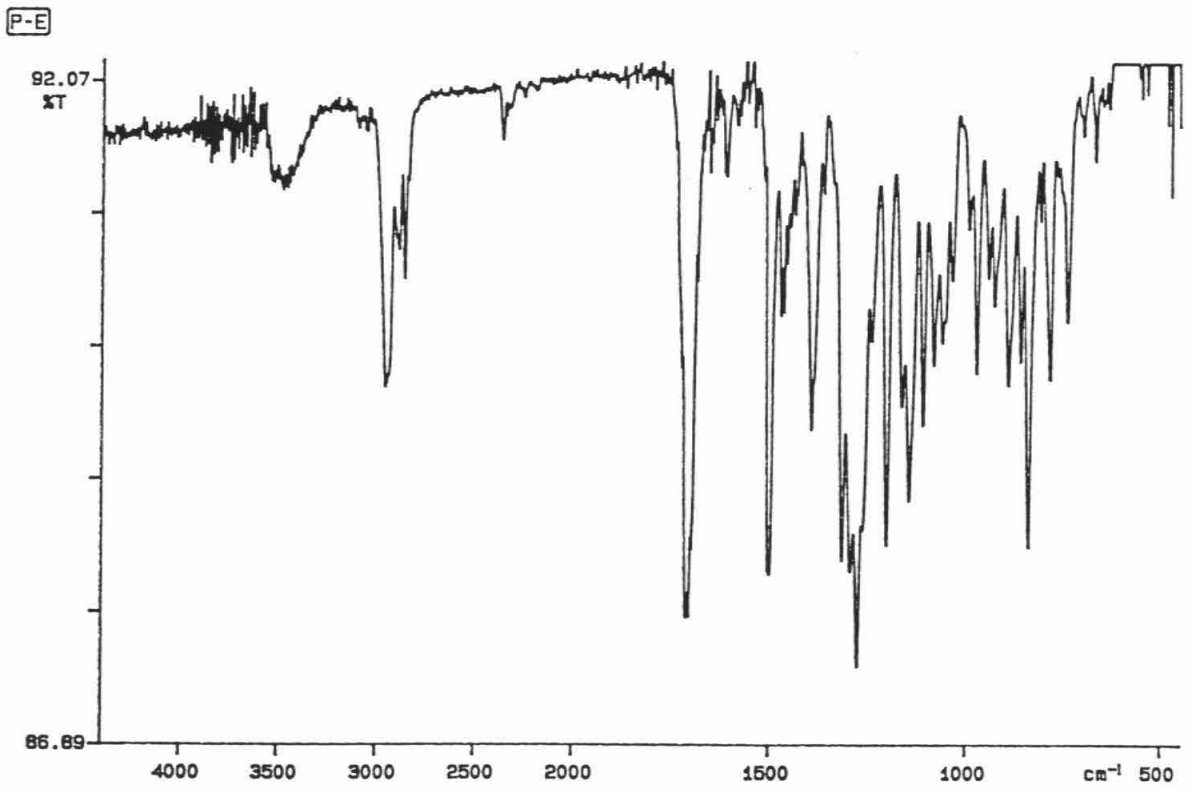


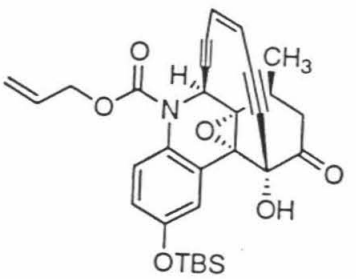

**29**


O
H
CH3
N
O
OCH3
OCH3
OH
OTBS

**30**

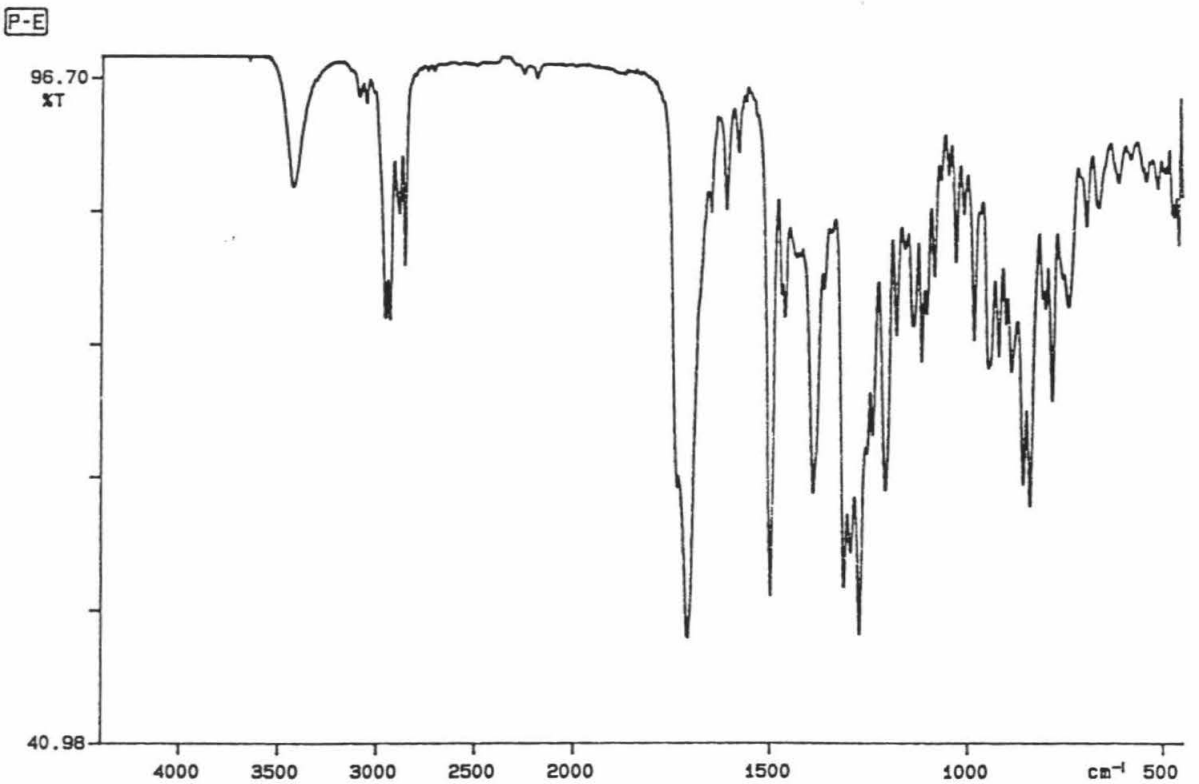

8
6
4
2
0

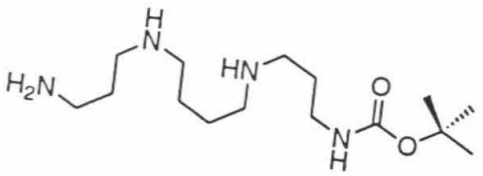

P-E
92.07
%T
86.89
4000
3500
3000
2500
2000
1500
1000
cm-1
500


O
H
CH3
O
N
O
O
OH
OTBS

**31**

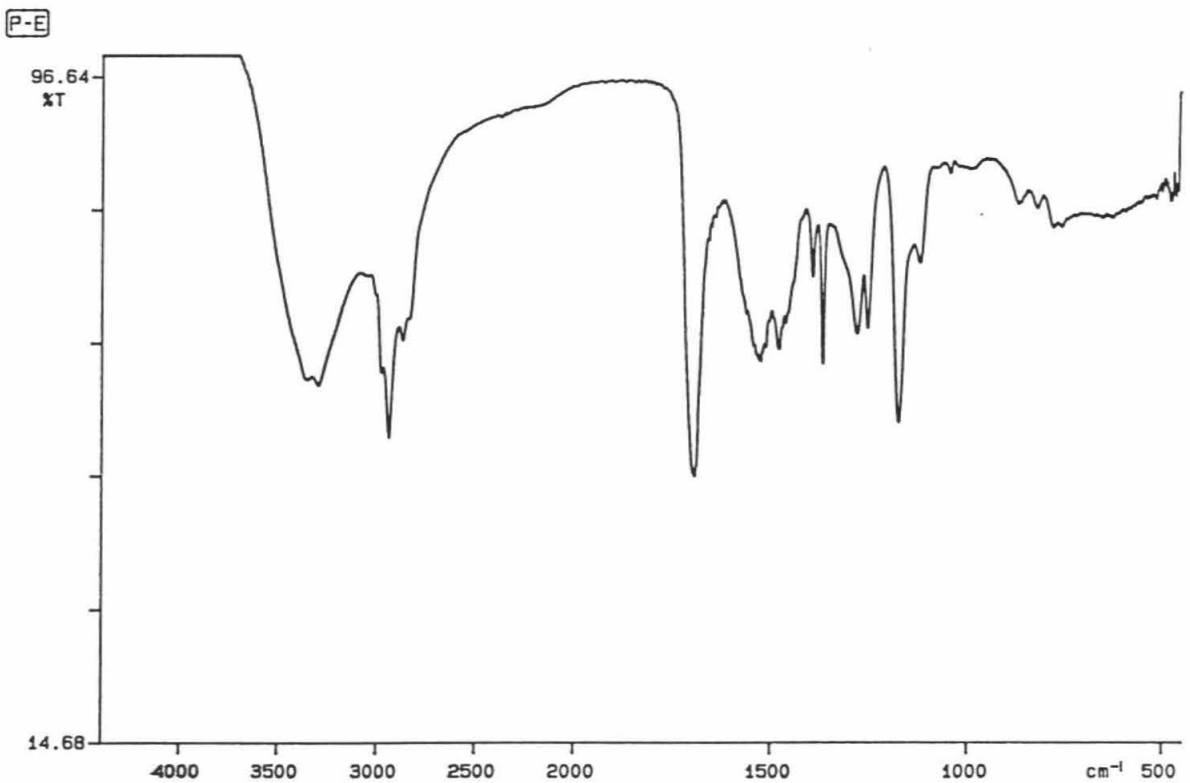

10
9
8
7
6
5
4
3
2
1
0

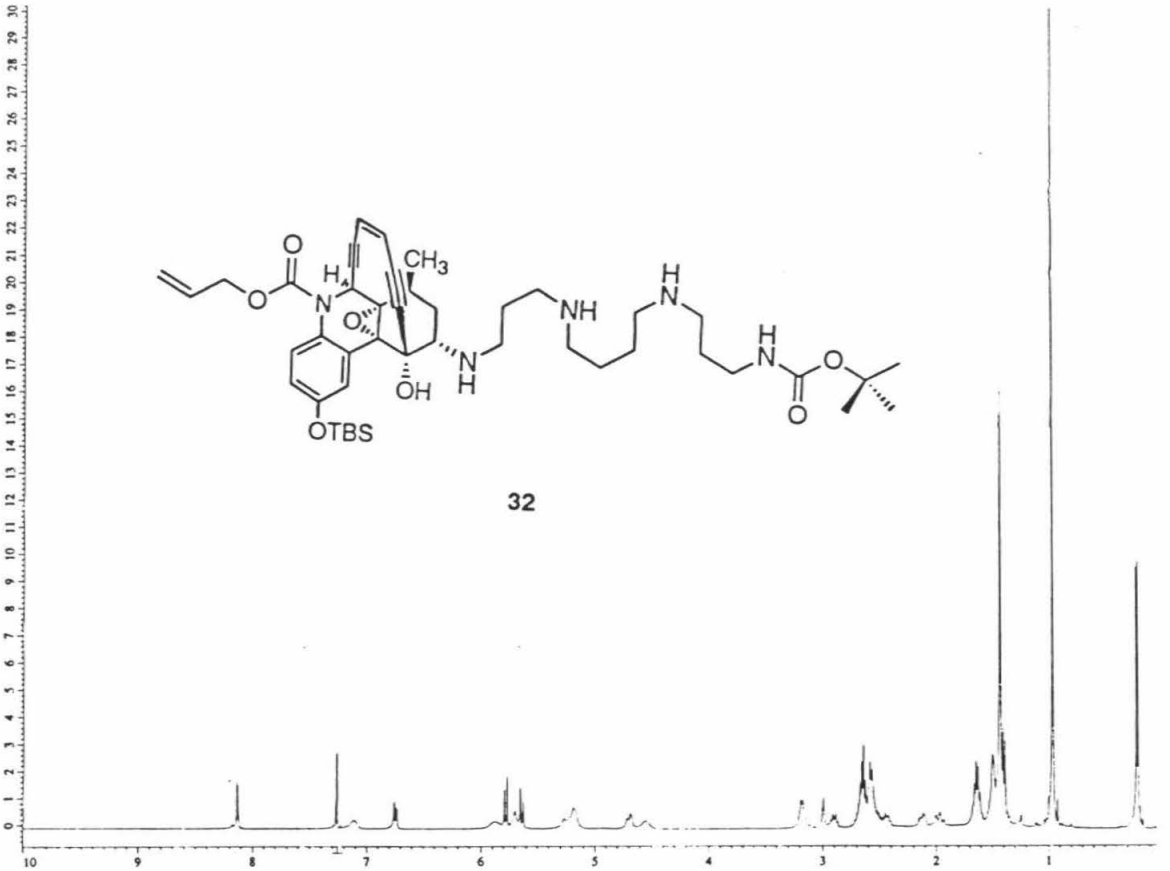

P-E
96.70
%T
40.98
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H
N
$H_2N$
HN
O
N
H
O

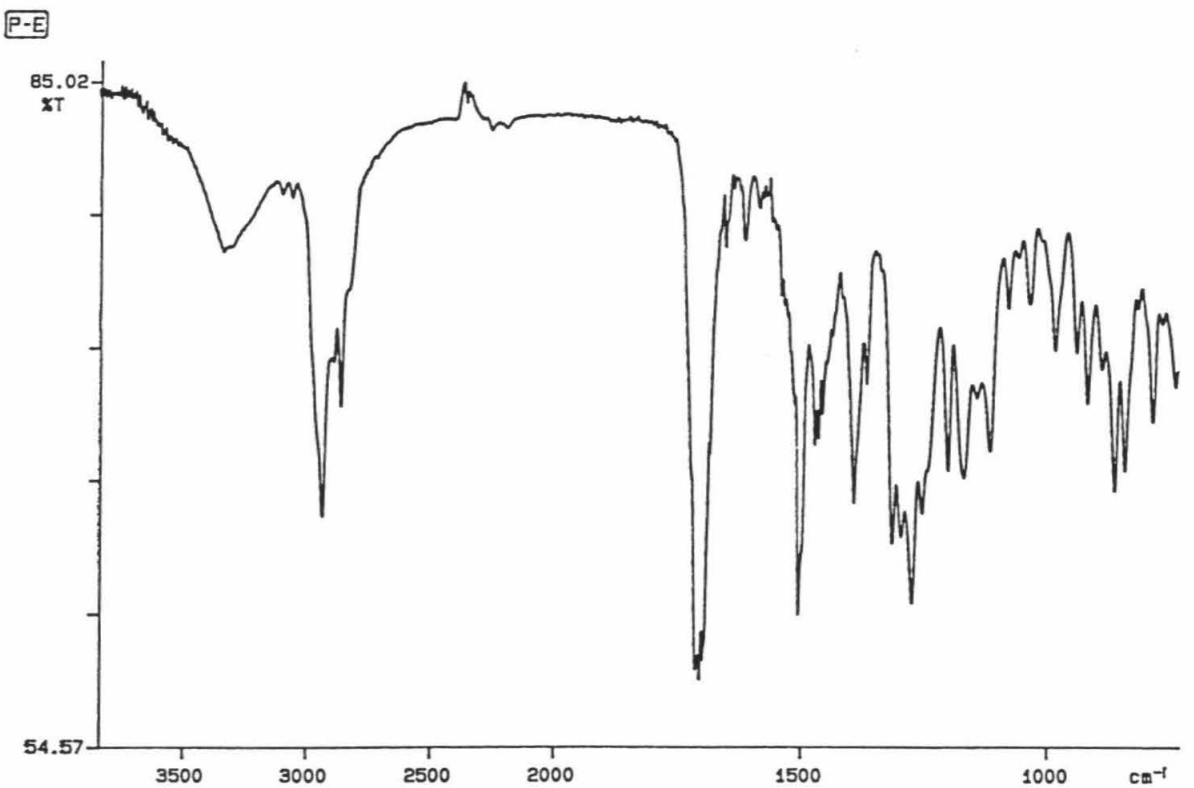
**8**

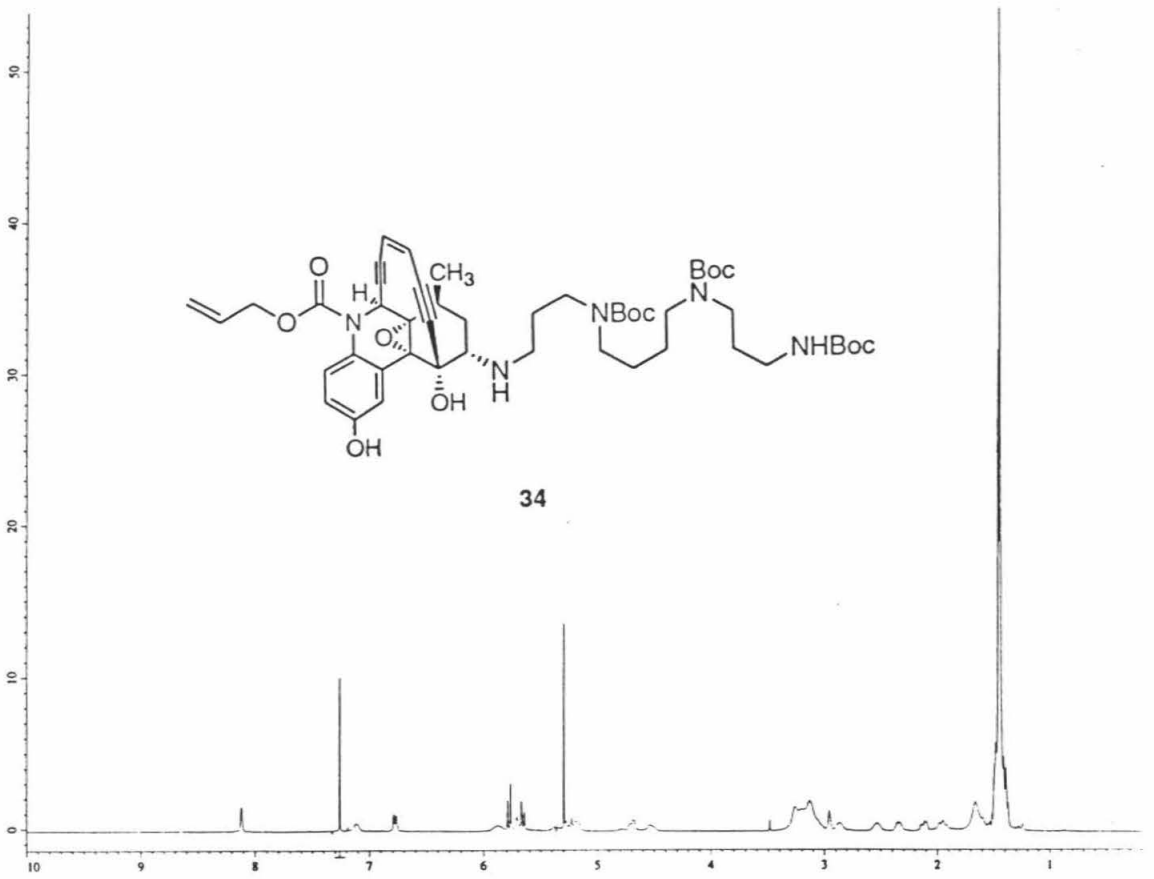

8
6
4
2
0


P-E
96.64
%T
14.68
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

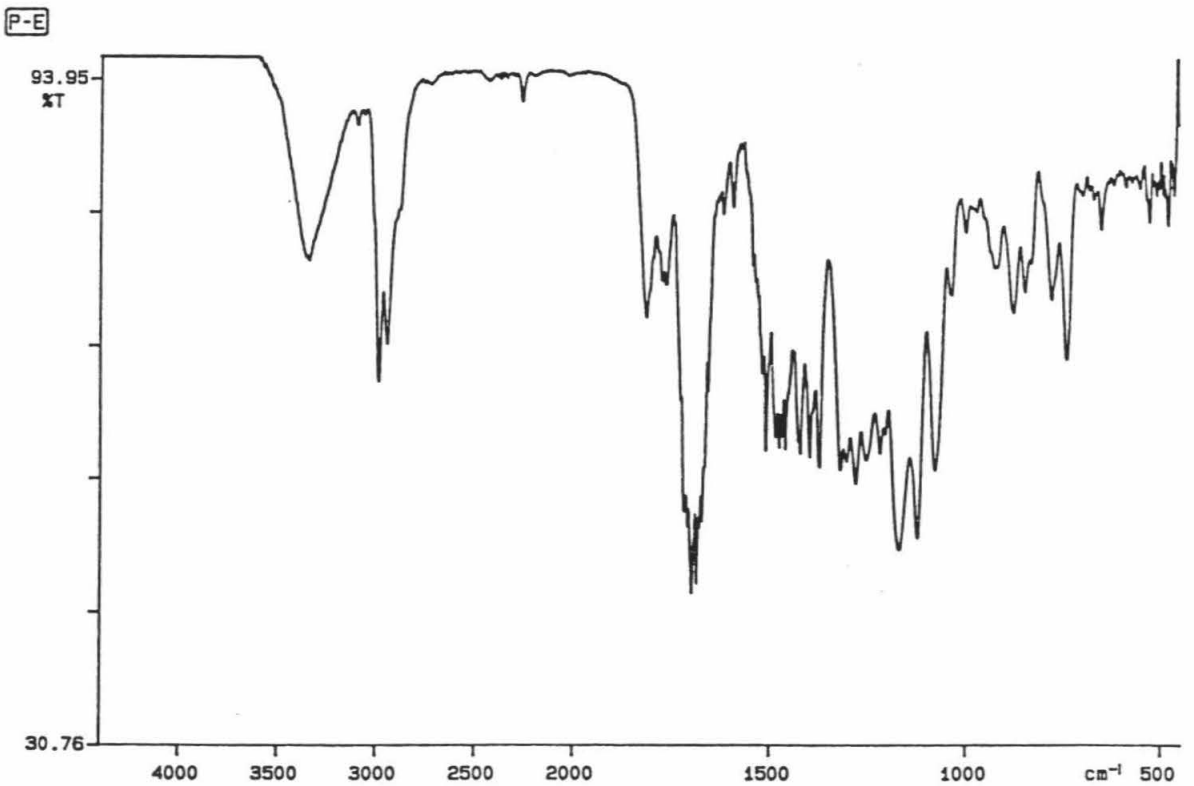

O
O
N
H
CH3
O
OH
N
H
NH
H
N
H
N
O
O
OTBS

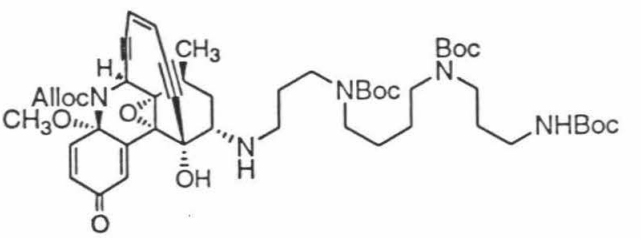
32


P-E
85.02
%T
54.57
3500
3000
2500
2000
1500
1000
cm-1


O
H
N
O
CH3
O
OH
OH
N
H
NBoc
Boc
N
NHBoc

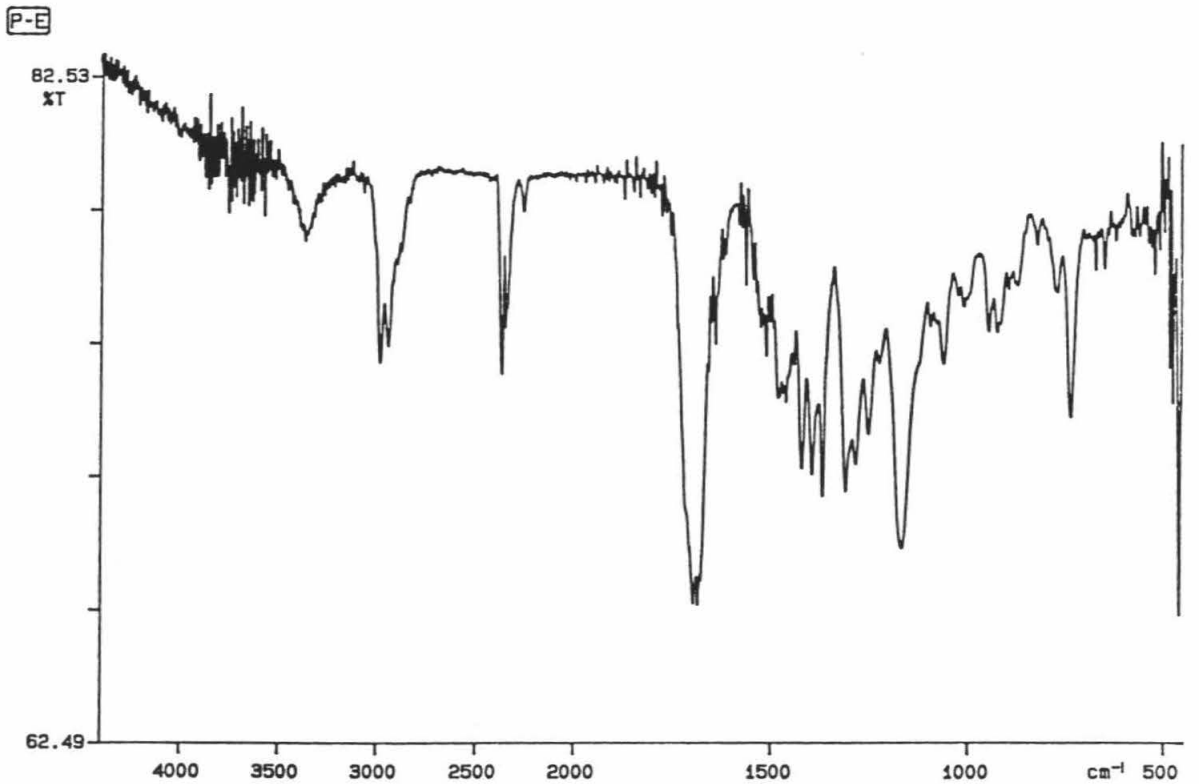
34

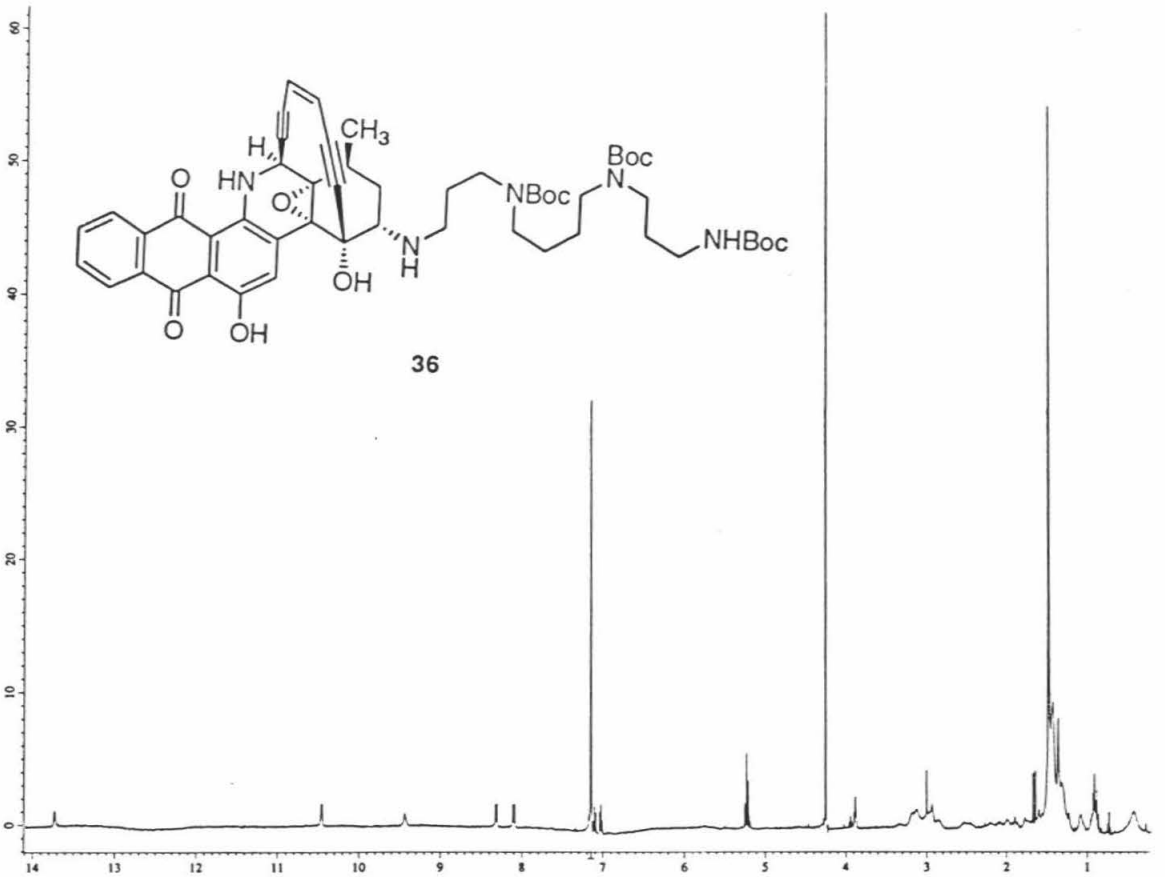

P-E
93.95
%T
30.76
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
H
AllocN
CH3O
O
OH
O
N
H
NBoc
Boc
N
NHBoc

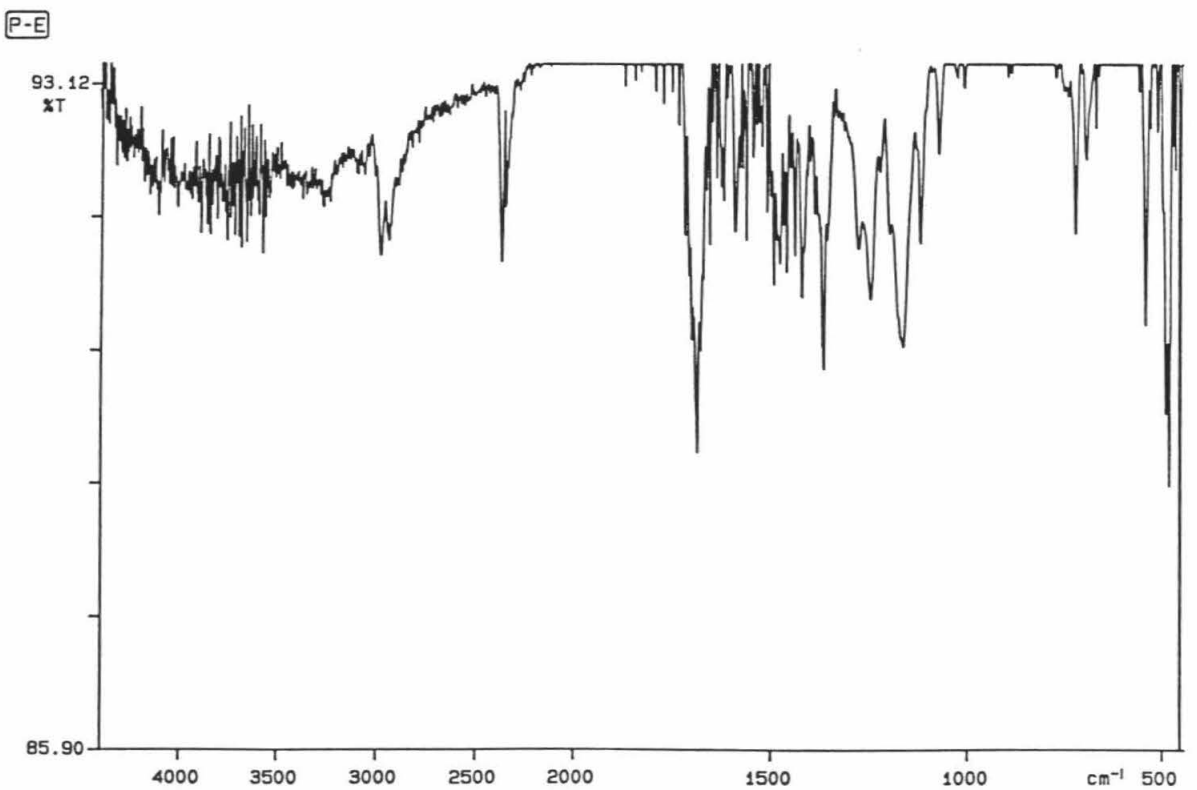
35


40
30
20
10
0
10
9
8
7
6
5
4
3
2
1


P-E
82.53
%T
62.49
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
H
HN
O
O
OH
O
OH
N
H
NBoc
Boc
N
NHBoc

36


P-E
93.12
%T
85.90
4000
3500
3000
2500
2000
1500
1000
cm-1
500