Efforts towards the Synthesis of Stelliferin Natural Products

A thesis presented

by

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A.B., Chemistry (1994)
Princeton University

to

The Department of Chemistry
in partial fulfillment of the requirements
for the degree of

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at the

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Efforts towards the Synthesis of Stelliferin
# Natural Products

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ABSTRACT

Studies for this thesis involve efforts toward the synthesis of stelliferin natural product Stellettin A (2). Key steps towards this synthesis were developed using epiandrosterone (9) as a model for the stelliferin ring system. Our synthetic strategy produced new functionalized steroid compounds, including 15, as well as more efficient syntheses of various 2-pyrone derivatives. The metal-catalyzed coupling of 16 and 5 resulted in a novel steroidal compound 27. Hydrogenation of this molecule afforded the Stellettin A model 10. The methodology for synthesis of Stellettin A (2) thus has been developed, which can be utilized on the actual stelliferin ring system.

2

9

15

16

5

27

10
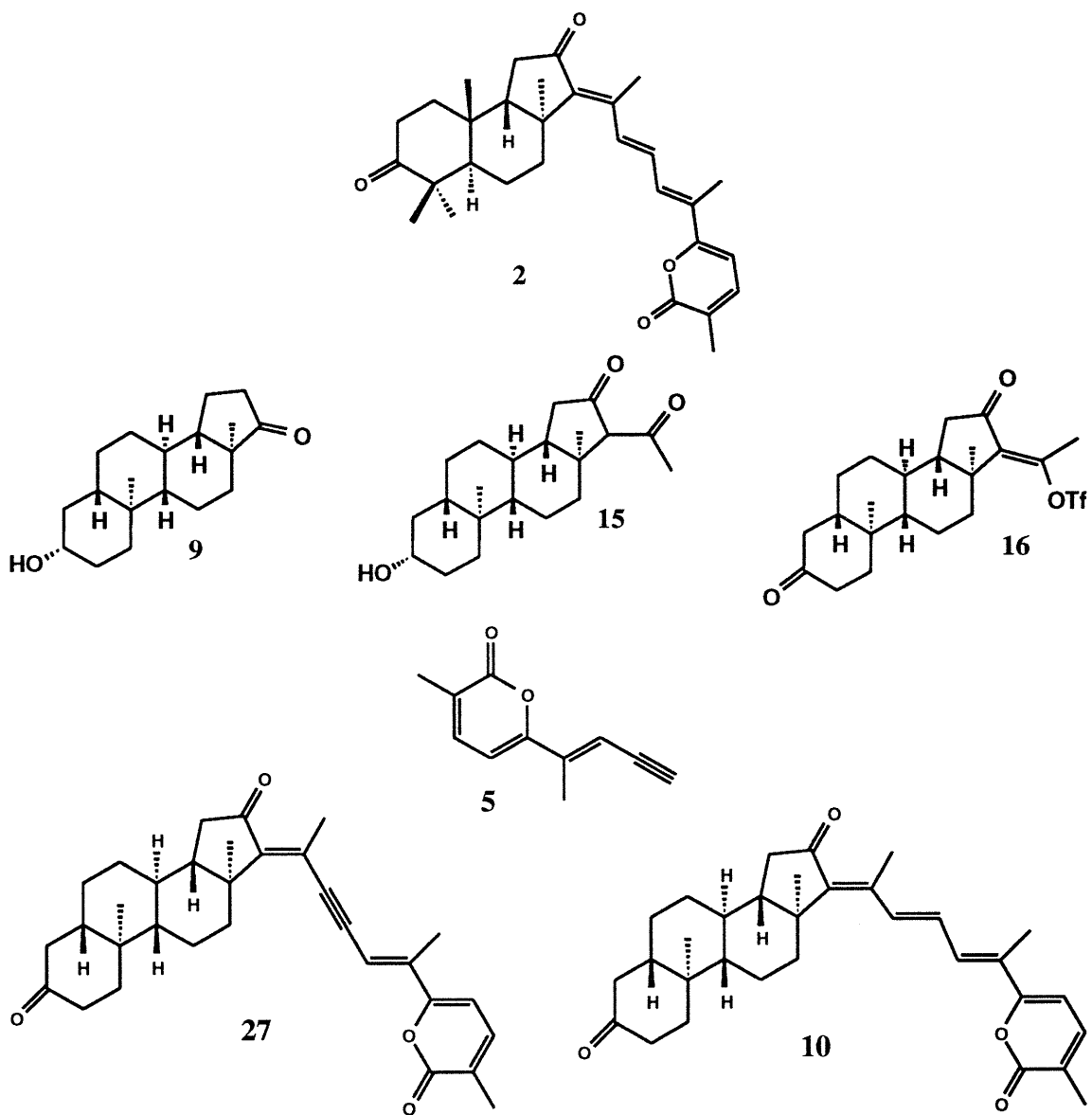
Thesis Supervisor: Scott C. Virgil

Title: Assistant Professor of Chemistry

Acknowledgments

Professor Scott Virgil has been an understanding and helpful advisor. He has a knowledge of chemistry that is extremely comprehensive, and his enthusiasm and love for science is contagious. I have learned much organic chemistry from him and feel saddened that my life path is so quickly taking me away from his lab.

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Continuous thanks and much love need to be expressed to my parents. I will never be able to fully repay them for all the support they have given me over the years. Their guidance and love has taught me dedication and given me the ability to make important life decisions, especially those that require major life changes. I hope that I can always conduct myself in a way that makes them proud. (Even in their jests, I find inspiration: *this* is where playing with those "tinker toys" brought me...)

My brother Larry is an impressive individual, by whom I am continuously amazed and of whom I am exceedingly proud. While I may not admit it that often, I have learned much from him; he is a superb role model and a great friend. Good luck in the real world, bro, as I continue on with at least five more years in school.

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Chapter 1

Introduction

Marine organisms have been the source of many terpenes with various biological activities. In 1981, Ravi, *et al.* isolated three novel triterpenes from *Jaspis stellifera*, a marine sponge collected in the Great Barrier Reef and off the coasts of Fiji, Somalia, and Japan. These stelliferin compounds were the first non-squalene triterpenes found in sponges. Based on spectral evidence, it was suggested that their ring system had the rare *trans-anti-trans* malabaricane skeleton (Figure 1).[1] A year later, McCabe, *et al.* found, using X-ray crystallography, that the 6.6.5-tricyclic system of at least one of these triterpene products was actually an isomalabaricane system.[2] In 1991, the discovery of McCabe's compound (**1**), an unstable yellow pigment, was followed by the isolation of six other stelliferin natural products (**3-8**).[3] In 1994, yet another stelliferin product, named Stellettin A (**2**), was isolated by Su, *et al.*[4] This product differs from the McCabe compound only in the stereochemistry of the side chain with respect to the triterpene ring system.
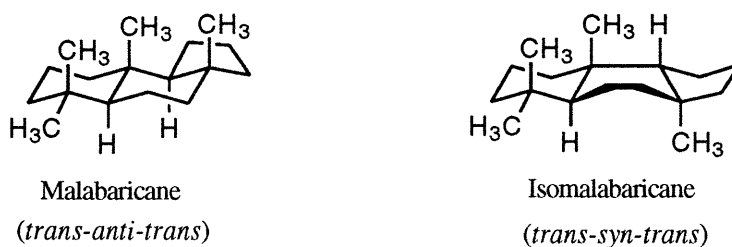
Malabaricane
(*trans-anti-trans*)

Isomalabaricane
(*trans-syn-trans*)

Figure 1

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[1]Ravi, B.N.; Wells, R.J. *J. Org. Chem.* **1981**, *46*, 1988.

[2]McCabe, T.M.; Clardy, J.; Minale, L.; Pizza, C.; Zollo, F.; Riccio, R. *Tetrahedron Lett.* **1982**, *33*, 3307.

[3]Tsuda, M.; Ishibashi, M.; Agemi, K.; Sasaki, T.; Kobayashi, J. *Tetrahedron*, **1991**, *47*, 2181.

[4]Su, J.Y.; Meng, Y.H.; Zeng, L.M.; Fu, X.; Schmitz, F.J. *J. Nat. Prod.* **1994**, *57*, 1450.
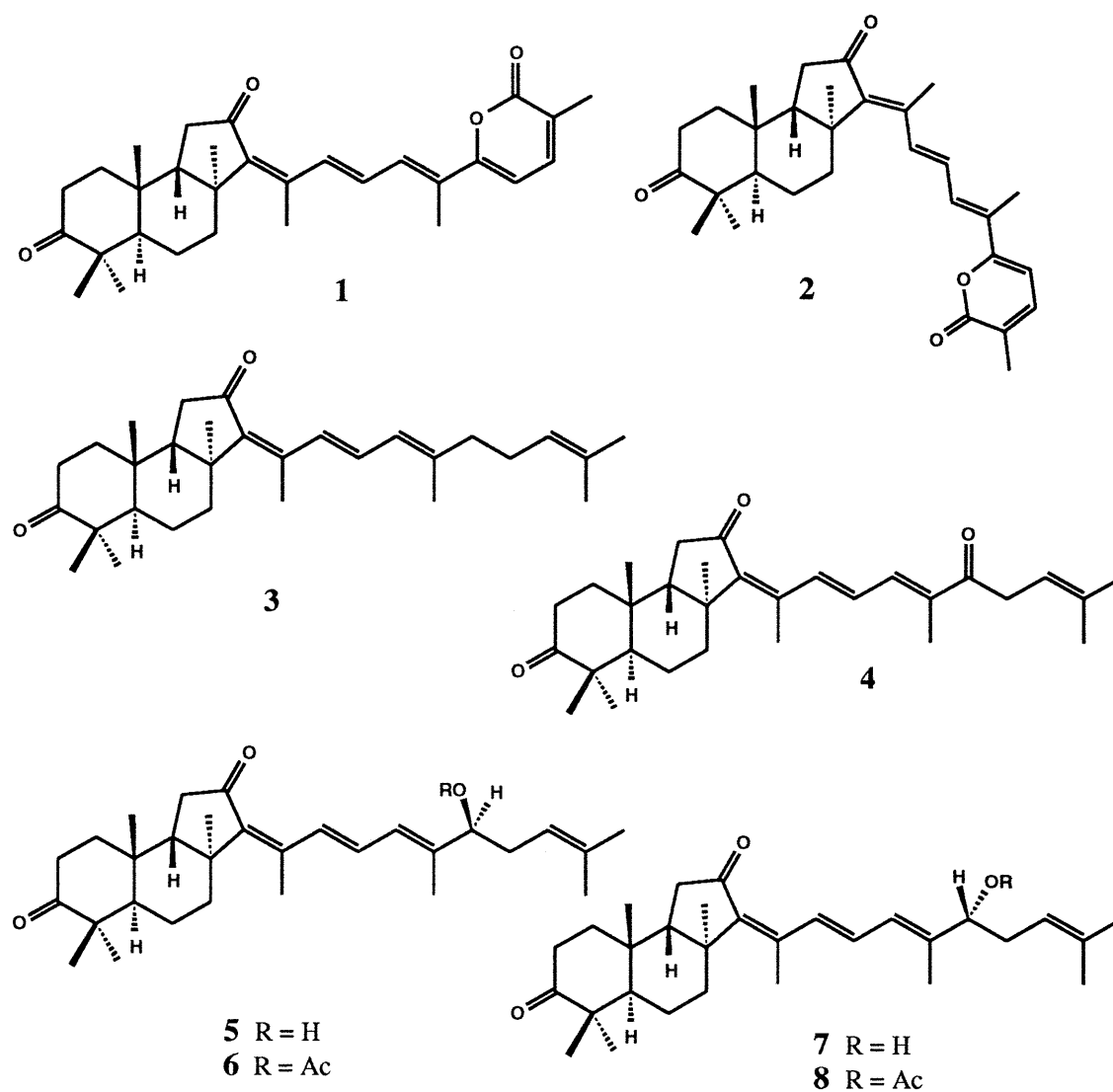
Figure 2

The biological activity of these stelliferin natural products has not been extensively researched. Stelliferins **3-8** have been reported to possess antineoplastic activity with IC$_{50}$ values ranging from 0.57 - 2.4 µg/mL and 1.4 - 6.5 µg/mL for L1210 and KB cell lines, respectively.[3] In addition, Stellettin A (**2**) was shown to be toxic to P388 leukemia cells.[4] It is likely that the observed biological activities of these natural products derives from the carbonyl in the C-ring and their polyene side chains. It is even more convincing that the

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polyene/pyrone side chain of Stellettin A (**2**) is the cause of its interesting activity, as many naturally occurring pyrones exhibit a wide-range of biological activity.[5]

Stelliferin products **1** and **2** are attractive synthetic targets due to the challenges of constructing the *trans-syn-trans* system of the isomalabaricane, as well as the novel 2-pyrone side chain. The potential of producing families of similar compounds could also be of pharmaceutical interest.
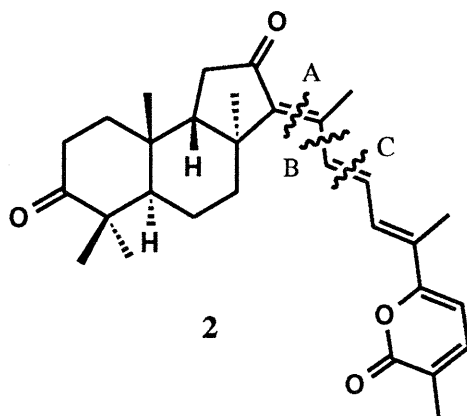
1.2 Retrosynthetic Analysis

Figure 3

Retrosynthetically, the stelliferin system can be disconnected along the polyene side chain. This produces a pyrone fragment and a functionalized isomalabaricane system to which the former would attach. There are three potential sites for this disconnection (Figure 3). It would be attractive to attempt a convergent synthesis using disconnection A, which would allow a pre-formed side chain to be attached to the ring-system in one step. However, the final coupling of the two fragments could not occur directly with a tricyclic ketone intermediate because of the difficulty of forming the sterically crowded

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[5]a) Rocca, J.R.; Tumlinson, J.; Glancey, B.M.; Lofgren, C.S. *Tetrahedron Lett.*, **1983**, *24*, 1889. b) Suh, H.; Wilcox, C. *J. Am. Chem. Soc.*, **1988**, *110*, 470. c) Liebeskind, L.S.; Wang, J. *Tetrahedron*, **1993**, *49*, 5461.

tetrasubstituted double bond. Disconnection B would provide an alternative to this problem. One attractive strategy for connecting the side chain would be a metal-catalyzed coupling of a pyrone fragment to an activated derivative of the ring system. By following this route, the double bond could be stereoselectively synthesized, allowing potential routes to either stelliferin compound **1** or **2**. The final disconnection at C would be feasible *via* a Wittig coupling; unfortunately, this route would require two stages for attachment of the side chain. We chose a strategic route employing disconnection B for this project (Scheme I).

Scheme I
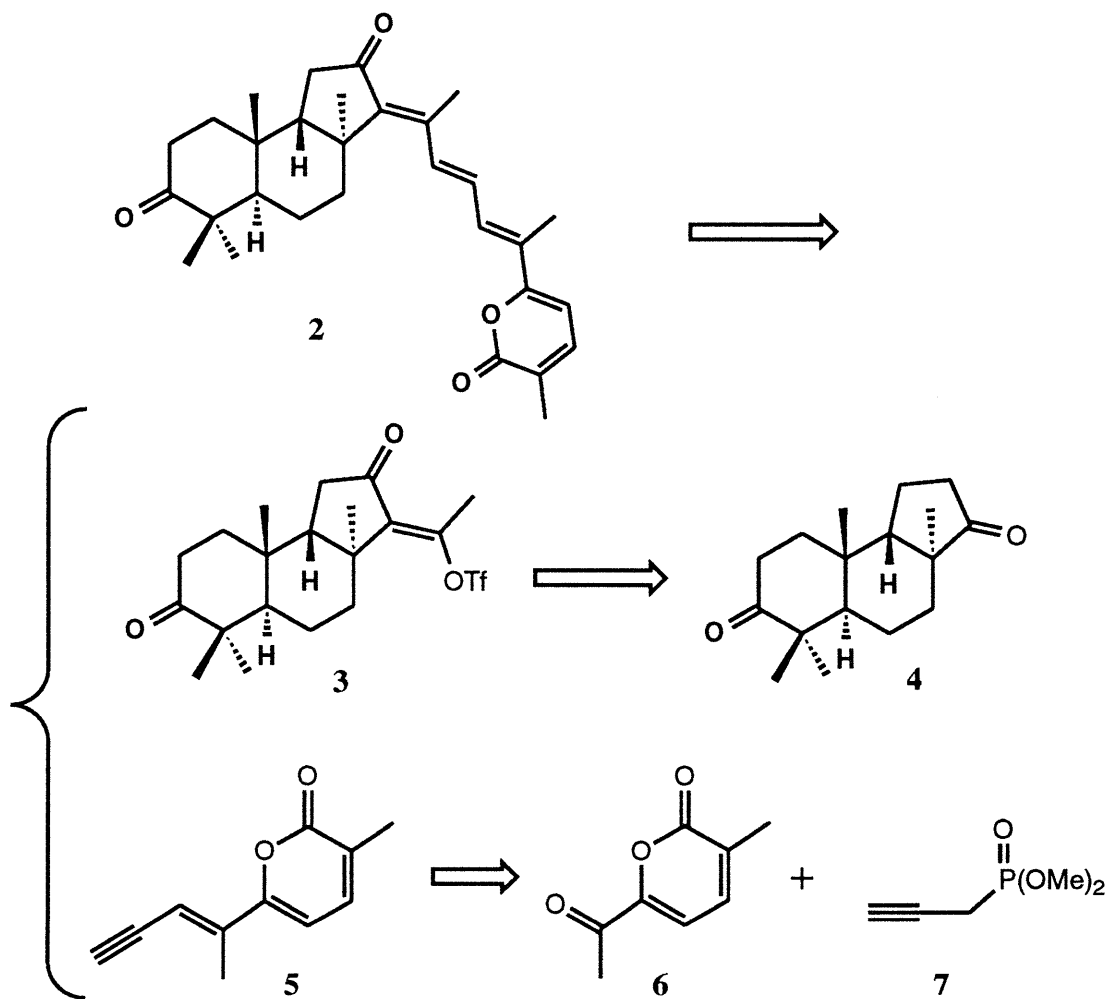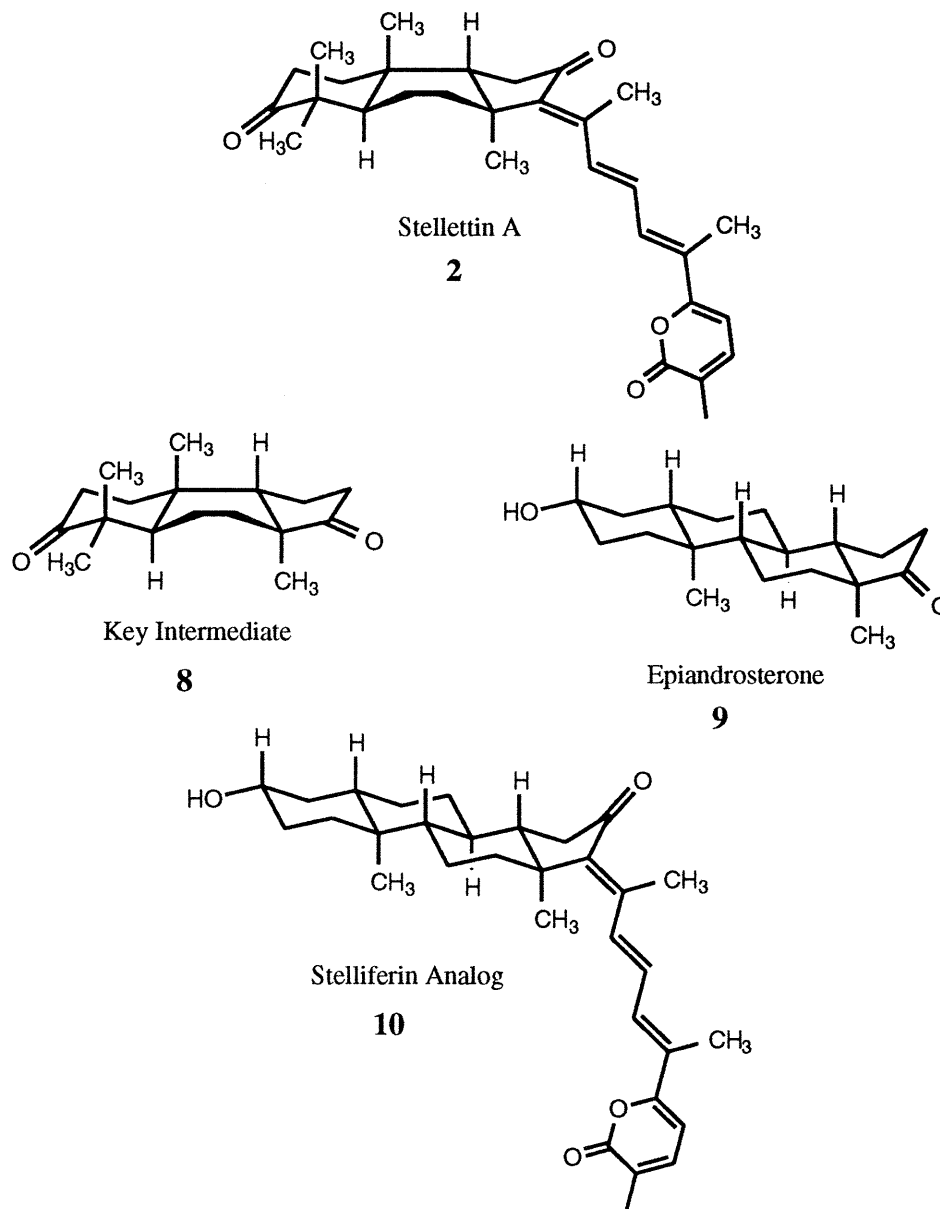
1.3 Choice of Model System

Figure 4

In an effort to synthesize the isomalabaricane skeleton of the stelliferin products, our group proposed the development of an acyclic substrate, which could be cyclized using the lanosterol cyclase found in Baker's yeast. However, original attempts at this

cyclization did not produce significant amounts of product.[6] After comparison of the structural similarities of the isomalabaricane to steroidal systems (Figure 4), epiandrosterone (**9**) was chosen as a suitable model for the stelliferin ring system and for development of a strategy for attachment of the 6-polyene-3-methyl-2-pyrone side chain to the ring system. The 6.5-*anti* ring fusion and the stereochemistry of the C-18 methyl group made this commercially available steroid an attractive model compound. Our retrosynthesis of this stelliferin analog **10** is analogous to that shown in Scheme I.

Additionally, the stelliferin analog **10** is an attractive target because it contains the pyrone side chain, which is likely the pharmacophore of the molecule. An efficient synthesis of this compound, using a relatively inexpensive steroid as the starting material, could produce large-quantities of potentially bioactive compounds.

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[6]Rosner, K.E. *Approaches to the Synthesis of Stelliferin, a Marine Isomalabaricane Triterpene*, Ph.D. Thesis, Massachusetts Institute of Technology, February 1996.

Chapter 2
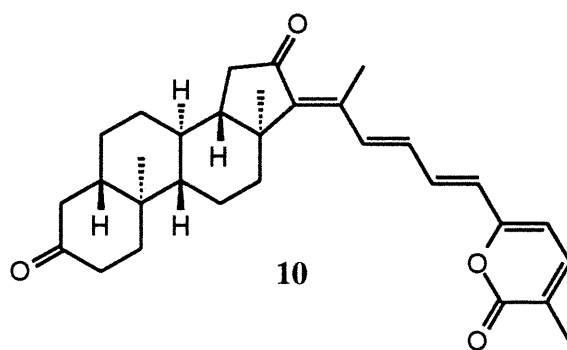
Synthesis of Stellettin Model

Figure 5

Our route to the synthesis of the Stellettin A model (**10**) is a convergent one. Before assembling our compound, the epiandrosterone steroid had to be functionalized for coordination to a metal catalyst. The side chain chemistry also needed to be developed. In addition to designing a synthesis for the pyrone, it was necessary to make the polyene side chain suitable for attachment to the steroid ring system.

2.1 Synthesis of steroid model

In the first synthetic step, epiandrosterone (**9**) was treated with trisylhydrazine in acetonitrile with a catalytic amount of concentrated hydrochloric acid (Scheme II). This was followed by protection of the alcohol with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide and methylene chloride to afford trisylhydrazone **11** in 91% yield. Our next step was a modification on the Shapiro reaction;[7] this reaction proceeds through the anion of a vinyldiimide, which decomposes to a vinyllithium reagent.

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[7]Shapiro, R.H. *Org. React.*, **1976**, *23*, 405.

We utilized this vinyllithium reagent to functionalize our compound. Treatment of the trisylhydrazone product with 2.3 equivalents of n-butyllithium in tetrahydrofuran at -78°C, followed by addition of dimethyl disulfide, and then 1.1 equivalents of n-butyllithium while warming to 0°C, produced methyl vinyl sulfide **12** in 73% yield.

Scheme II
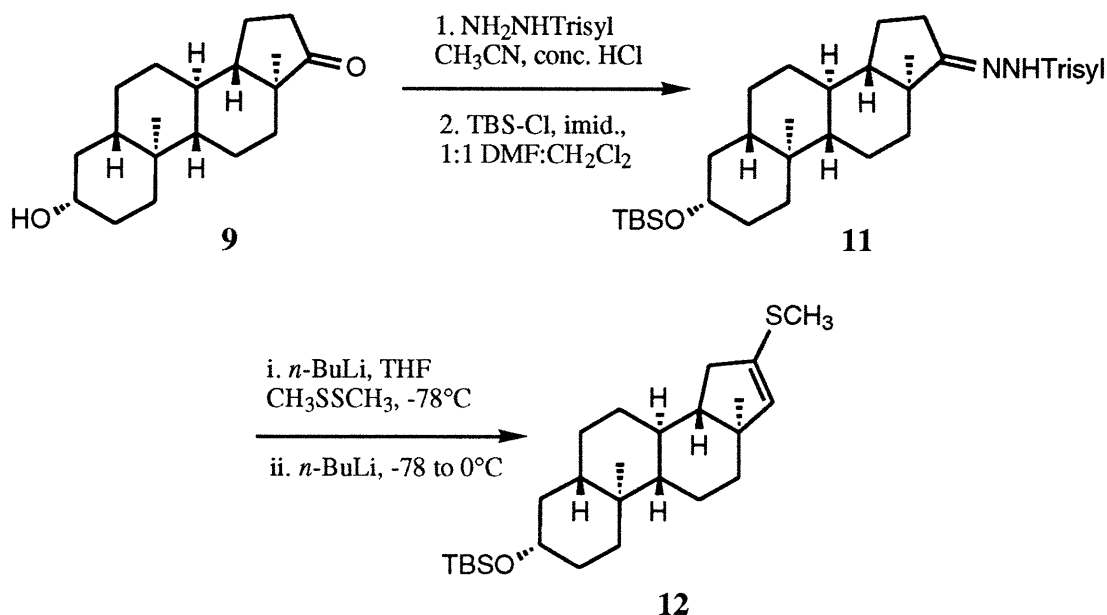
As vinyl sulfides have been successfully used in cycloaddition reactions,[8] we chose to attempt a 1,3-dipolar cycloaddition to form an isoxazoline.[9] Reductive cleavage of the isoxazoline could produce a diketone or a β-aminoenone, either of which would be one step removed from our required metal-coupling intermediate; in theory, either of these products could be activated to allow addition to a metal catalyst.

[8]a) Caramella, P.; Albini, E.; Bandiera, T.; Corsico Coda, A.; Grünanger, P.; Marinone Albini, F. *Tetrahedron*, **1983**, *39*, 689. b) Caramella, P.; Bandiera, T.; Grünanger, P.; Marinone Albini, F. *Tetrahedron*, **1984**, *40*, 441.
[9]For reviews see: a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984. b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: Weinheim, 1988.

The 1,3-dipolar cycloaddition is similar to a Diels-Alder cycloaddition. In a 1,3-dipolar cycloaddition, the dipolar lowest unoccupied molecular orbital (LUMO) and the dipolarophile highest occupied molecular orbital (HOMO) undergo a concerted, suprafacial, $\pi^4s + \pi^2s$ processes. The HOMO of the dipolarophile reacts due to the dipolarophile's electron donating group; this alkyl sulfide also controls the regiochemistry of the addition. The intermolecular addition of nitrile oxides to trisubstituted double bonds is rare. In crowded systems, the steric interactions between substituents on the dipolarophile with the dipole hinder the reaction. In such a case, the side reaction of dimerization of the nitrile oxide competes with the cycloaddition.

Scheme III

Side reaction:

14
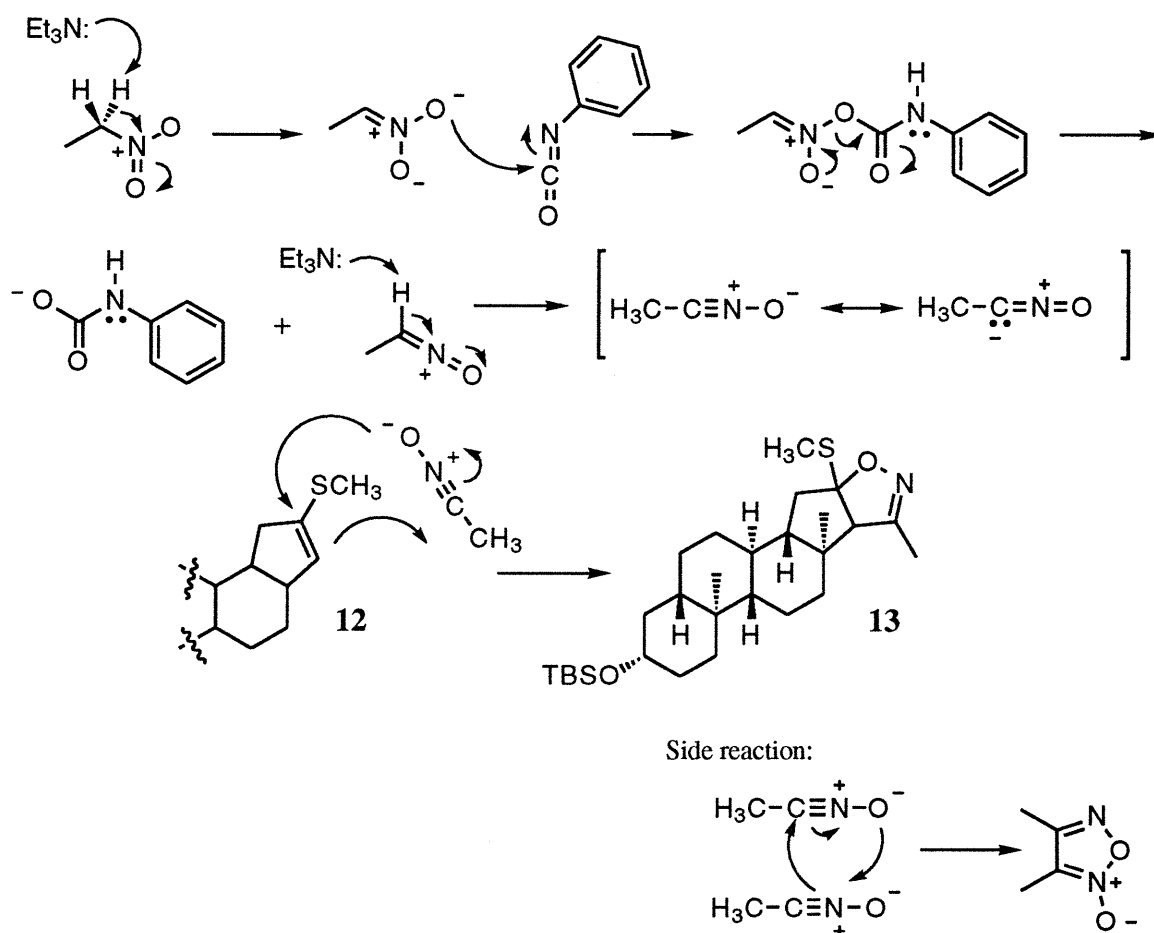
Previously, the 3-methylthio-2-isoxazoline compound **13** was obtained in only 40% yield[6] by reacting the vinyl sulfide with acetonitrile oxide, produced *in situ* using N-chlorosuccinimide, acetaldoxime and triethylamine.[10] By using a more efficient approach,[11] the yield of the isoxazoline was increased to 77%. Methyl vinyl sulfide **12** was dissolved in toluene; an excess of nitroethane and phenyl isocyanate, as well as a catalytic amount of triethylamine, were added (Scheme III). Due to dimerization of the nitrile oxide intermediate, 13 equivalents of reagents were continuously added over the course of the reaction.

The isoxazoline **13** was produced as a single isomer. While the stereochemistry of the product has not been confirmed, monosubstituted cyclopentenes with substitution at the 3-position show a strong preference for addition *anti* to the substituent.[12] Therefore, we predict that the 2-isoxazoline moiety is *syn* to the methyl group.

Scheme IV
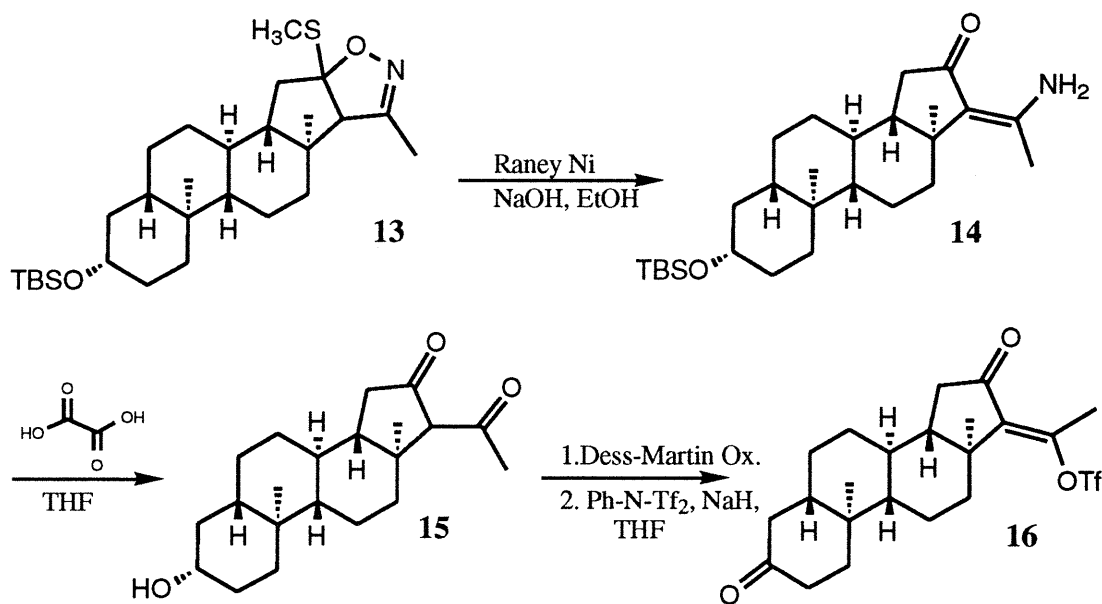
[10]Grundmann, C.; Grünanger, P. *The Nitrile Oxides*; Springer-Verlag: Berlin, 1971.

[11]Yadav, J.S.; Rao, E.S. *Syn. Comm.* **1988**, *18*, 2315.

[12]Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: Weinheim, 1988.

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Opening of the isoxazole to form β-aminoenone **14** was attempted utilizing many different methods. Initial efforts involved hydrogenation using various catalysts: molybdenum hexacarbonyl heated to reflux[13] (74% yield); hydrogen with palladium on carbon over six weeks[14] (72%); or hydrogen with Raney nickel and boric acid[15] (60%). By running the hydrogenation using 50% Raney nickel catalyst under basic conditions (10 mol% sodium hydroxide in ethanol), the reaction time was reduced to two hours, and the conversion yield was improved to 96% (Scheme IV).
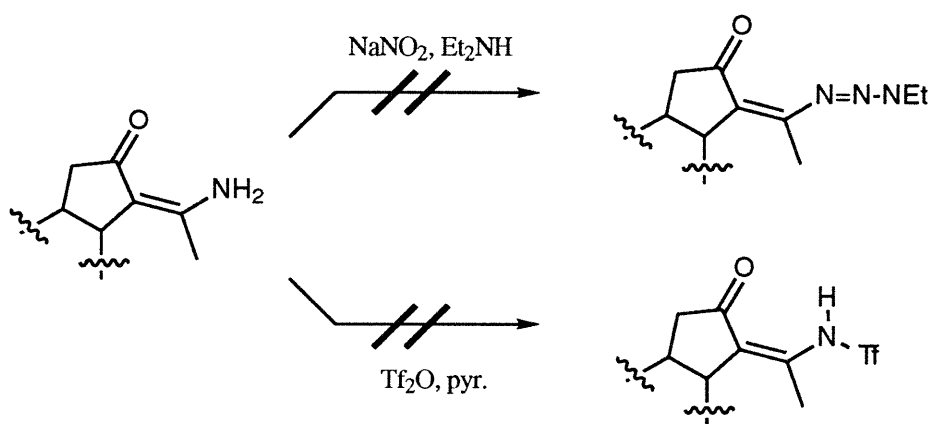
Figure 6

Initially, we wished to activate the amino group of β-aminoenone **14**, in order to allow direct metal-catalyzed coupling to the pyrone side chain. Our first strategy involved synthesizing a triazene[16] (Figure 6). Our hope was that this triazene could either be used directly in a palladium coupling, or be converted into a reactive vinyl iodide.[17] Unfortunately, after reacting the amine with sodium nitrite and diethylamine, the triazene product was not observed. Another approach was to convert the amine into a triflimide,

[13]Baraldi, P.G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis*, **1987**, 276.
[14]Scott, J.W.; Saucy, G. *J. Org. Chem.*, **1972**, *37*, 1652.
[15]a) Andersen, S.H.; Sharma, K.K.; Torssell, K.B.G. *Tetrahedron*, **1983**, *39*, 2241. b)Curran, D.P. *J. Amer. Chem. Soc.*, **1983**, *105*, 5826.
[16]a) Barrio, J.R.; Satyamurthy, N. *J. Org. Chem.*, **1983**, *48*, 4394. b) Barrio, J.R.; Ku, H. *J. Org. Chem.*, **1981**, *46*, 5239.
[17]Moore, J.S.; Weinstein, E.J.; Wu, Z. *Tetrahedron Lett.*, **1991**, *32*, 2465.

using pyridine and trifluoromethanesulfonic anhydride.[18] This intermediate also could be a suitable substrate for a metal-catalyzed cross coupling. However, our experiments were unsuccessful in producing any substituted amine.

We, therefore, chose to convert β-aminoenone **14** to diketone **15** by reaction with 10% aqueous oxalic acid in tetrahydrofuran.[19] This product, obtained in 96% yield, was confirmed by mass spectrometry and ^{1}H NMR spectroscopy, which showed clear resonances for the enol tautomer and both keto diasteriomers.

The strongly acidic conditions in this last reaction also removed the *tert*-butyldimethylsilyl protecting group on the 3β-hydroxyl group of the steroid system. As Stellettin A (**2**) contains a ketone at this position, we wished to oxidize this alcohol in the model system. Numerous attempts were made to effect this oxidation, using various chromium reagents, including PCC[20] and chromium trioxide under both acidic[21] and basic[22] conditions. However, each led to minor amounts of the desired product, the major product being diketone **15** with cleavage of the acyl group. Employing another method, Dess-Martin oxidation,[23] led to the desired product in 70% yield.
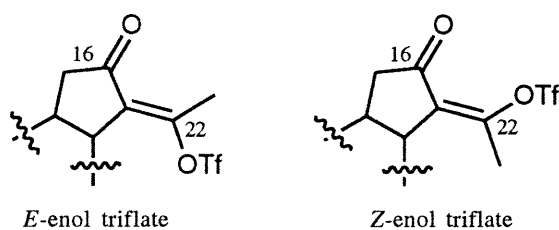

E-enol triflate   Z-enol triflate

Figure 7

As was previously the case with the β-aminoenone system, we now needed to make this intermediate capable of reacting in a metal-catalyzed cross coupling. Reacting the

[18]Beard, C.D.; Baum, K.; Grakauskas, V. *J. Org. Chem.*, **1973**, *38*, 3673.
[19]Oliver, J.E.; Lusby, W.R.; Waters, R.M. *J. Agric. Food Chem.*, **1989**, *37*, 1501.
[20]a) Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.*, **1975**, 2647. b) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis*, **1982**, 245.
[21]Bowden, K.; Heilbron, I.M.; Jones, E.R.H.; Weedon, B.C.L. *J. Chem. Soc.*, **1946**, 39.
[22]Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.*, **1970**, *35*, 4001.
[23]Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

diketone with *N*-phenyltriflimide and sodium hydride led to a mix of triflated products. The major product (66% yield) was determined to be the C-22 triflate, which could be separated from the C-3 vinyl triflate (23% yield). We had expected that the desired reaction at the C-22 position would proceed *via* a chelated *Z*-enolate intermediate, to yield the *Z*-triflate product (Figure 7). However, the ^{1}H NMR shifts for the methyl group in triflate **16** and later products were further downfield than expected, leading us to believe that the C-16 carbonyl was deshielding these protons, and suggesting that *E*-triflate **16** had been obtained. In addition, the chemical shifts for the protons on the pyrone ring and conjugated side chain of the completed Stellettin A model system **10** were in agreement with Su, *et al.*'s results for Stellettin A (**2**).[3] These results seem incongruous to us, as one would expect the triflate to form *via* the hydrogen-bound enol intermediate. Apparently, the *E*-enolate must have some greater stability. At this time, though, we have not completed any other studies to further confirm our result. An nOe experiment would give an inconclusive stereochemical assignment. And, while X-ray crystallography should be able to determine the absolute stereochemistry of the system, the triflate obtained is not crystalline.

## 2.2 Synthesis of the Pyrone and Polyene Side Chain

Having obtained triflate **16**, it was necessary to prepare the pyrone side chain in a form suitable for coupling. The pyrone nucleus was generated by dimerization of the vinyl ketene produced from tiglic acid *via* the acid chloride[24] (Scheme V). This reaction results in an approximately 1:1 mixture of 3-methyl-6-(1-methylallyl)-2-pyrone (**19**) and 3-methyl-6-(1-methylpropenyl)-2-pyrone (**20**) (combined yield, 54%). Previous attempts to isomerize the mixture to **20**, in acidic or basic conditions, resulted in either opening of the pyrone ring or recovery of the initial mixture.[6] The mixture of products, therefore, was

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[24]Rey, M.; Dunkelblum, E.; Allain, R.; Dreiding, A.S. *Helv. Chim Acta* **1970**, *53*, 2159.

oxidatively cleaved with 10 mol% osmium tetraoxide[25] and excess sodium periodate to form ketopyrone **6** in 50% yield (100% based on **20**). None of the aldehyde from **19** was observed.

Scheme V
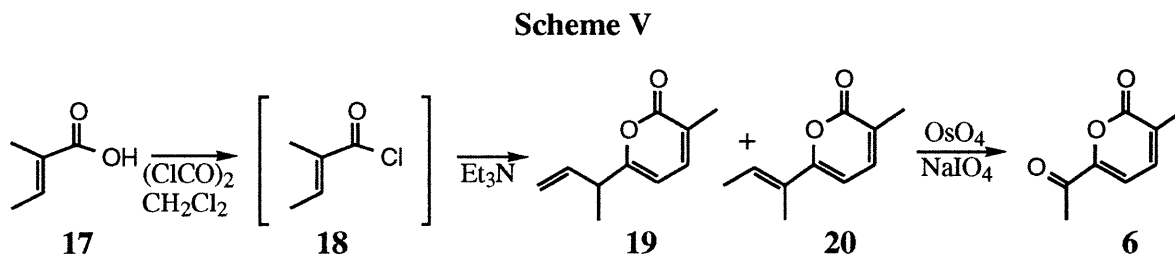
At first, we were interested in a tributyltin compound as a possible reagent for a Stille transmetallation reaction to connect the pyrone side chain to the steroid ring system. Even though tin compounds are inherently toxic, tin reagents are usually easy to prepare and handle, and we had considered this a viable route. In addition, in these reactions the vinyl groups usually retain stereochemistry at the double bond, which also was important to us. Hence, much effort was spent trying to form adduct **24** by appending 3-tributylstannyl-2-propenylphosphonate reagent **23** onto ketopyrone **6**. Coupling the resulting adduct **24** to triflate **16** would directly produce the stelliferin analog **10**.

Scheme VI
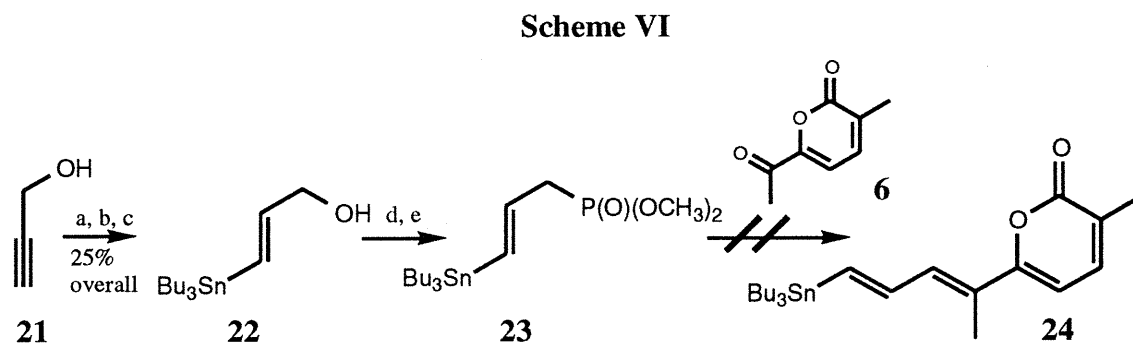
a) TBSCl, cat, DMAP, Et$_3$N, CH$_2$Cl$_2$; b) polymethylhydrosiloxane, (Bu$_3$Sn)$_2$O, cat AIBN, 90 °C; c) TBAF, THF; d) CBr$_4$, PPh$_3$, 2,6-lutidine, CH$_3$CN, 64%; e) (CH$_3$O)$_2$P(O)H, NaH, THF, 70%

[25]a) Schroder, M. *Chem. Rev.*, **1980**, *80*, 187. b) Pappo, R.; Allen Jr., D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.*, **1956**, *21*, 478. c) Wakharkar, R.D.; Deshpande, V.H.; Landge, A.B.; Upadhye, B.K. *Org. Prep. Proc.*, **1988**, *20*, 527.

Our stannyl-phosphonate reagent **23** was synthesized from propargyl alcohol (Scheme VI). The alcohol was reacted with *t*-butyldimethylsilyl ether; hydrostannated with polymethylhydrosiloxane, bis(tribuyltin) oxide and catalytic 2,2'-azobis(2-methylpropino-nitrile); and deprotected with tetrabutylammonium fluoride.[26] The resulting 1-tributylstannyl-1-propen-3-ol was converted to the bromide using carbon tetrabromide, triphenylphosphine, and 2,6-lutidine in acetonitrile in 64% yield.[27] This allylic bromide was then converted to the phosphonate with sodium hydride and dimethyl phosphite in tetrahydrofuran in 70% yield.[28] However, the necessary olefination proved unsuccessful, and starting materials were recovered. These results matched those previously obtained in our lab,[6] which are in contrast to those of Evans, *et al.*,[29] who had successfully used a similar phosphonate (Figure 8) in a Horner-Wadsworth-Emmons coupling.

Evan's Phosphonate
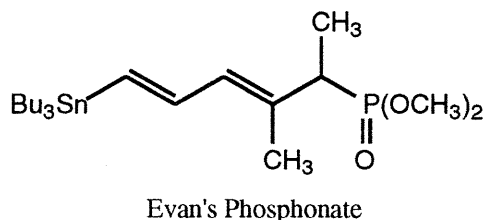
Figure 8

As an alternative to a stannyl-intermediate, we chose to make a system that could be coupled to the steroid triflate **16** *via* a Castro-Stephens reaction. In the Castro-Stephens reaction, a terminal alkyne is coupled to a vinyl or aryl halide with a palladium-copper catalyst in the presence of an amine. The mechanism for this reaction is not fully understood, but almost certainly involves oxidative addition to the triflate followed by

[26]Wedner, P.A.; Sieburth, S.M.; Petraitis, J.J.; Singh, S.K. *Tetrahedron*, **1981**, *37*, 3967.
[27]a) Axelrod, E.H.; Milne, G.M.; vanTamelen, E.E. *J. Amer. Chem Soc.*, **1970**, *92*, 2139. b) Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Amer. Chem. Soc.*, **1992**, *114*, 9434.
[28]Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Amer. Chem. Soc.*, **1992**, *114*, 9434.
[29] Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Amer. Chem. Soc.*, **1992**, *114*, 9434.

transmetallation from copper. Stereochemistry of the vinyl halide is retained.[30] The amine appears to be required both to reduce any palladium(II) precatalysts to palladium(0) and to act as a base for copper acetylide production.[31]

Scheme VII
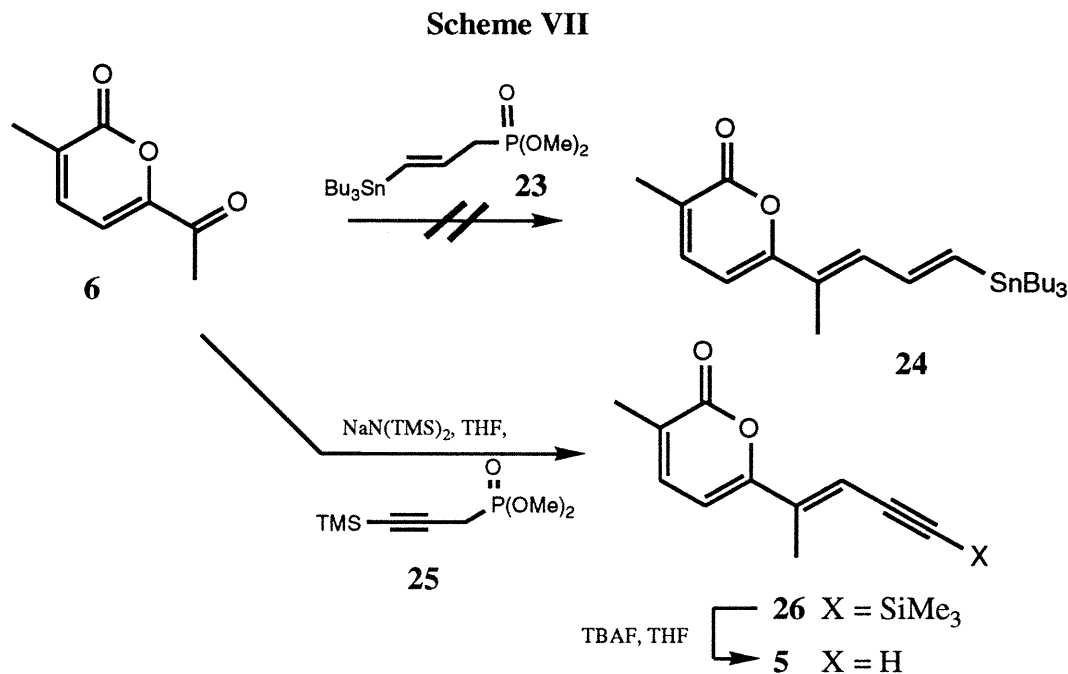
Previously in the group, enyne pyrone **26** had been obtained in 30% yield by coupling ketopyrone **6** with a propargyl triphenylphosphonium Wittig reagent. The yield in this reaction was doubled by use of phosphonate reagent **25** in a Horner-Wadsworth-Emmons reaction. The commercially available 3-bromo-1-trimethylsilylprop-1-yne was converted into phosphonate **25** using sodium bis(trimethylsilyl)amide and dimethyl phosphite[32]. This produced a mix of **26** and the corresponding Z-isomer (combined yield 76%) (Scheme VII). After removal of the trimethylsilyl protecting group with tetrabutylammonium fluoride, **5** was isolated (60% yield).

[30]a) Magnus, P.; Annoura, H.; Harling, J. *J. Org. Chem.*, **1990**, *55*, 1709. b) Butlin, R.J.; Holmes, A.B.; Mcdonald, E. *Tetrahedron Lett.* **1988**, *29*, 2989.
[31]a) Yang, Z-Y.; Burton, D.B. *Tetrahedron Lett.* **1990**, *31*, 1369 b) Crombie, L.; Horsham, M.A.; Blade, R.J. *Tetrahedron Lett.* **1987**, *28*, 4879.
[32]Gibson, A.W.; Humphrey, G.R.; Kennedy, D.J.; Wright, S.H.B. *Synthesis* **1991**, *5*, 414.

Our modified Castro-Stephens reaction,[33] using bis(triphenylphosphine) palladium dichloride and cuprous iodide in diethylamine to couple triflate **16** and enyne pyrone **5**, produced enyne **27** in moderate yield (46%). The presence of the acetylenic linkage was confirmed by IR spectrophotometry and ^{13}C NMR spectroscopy.

Scheme VIII
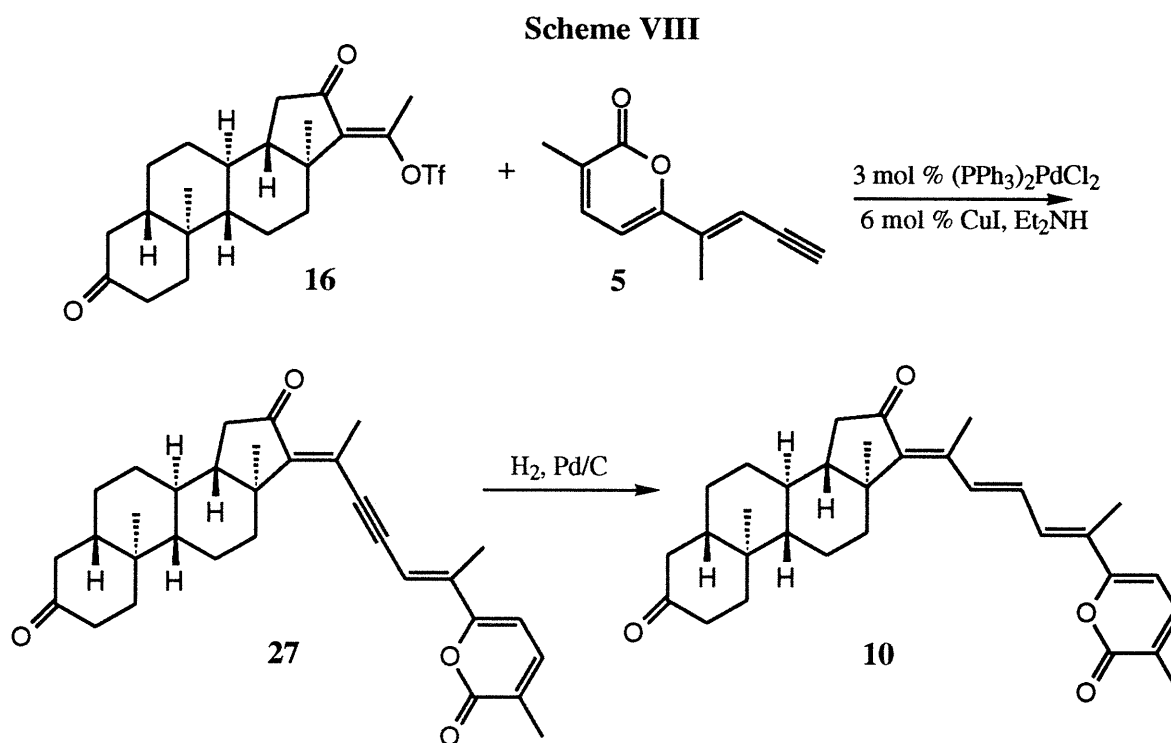
The final synthetic step requires reduction of the enyne. Attempts were made using various palladium reagents as well as chromous sulfate.[34] These reactions either resulted in recovery of starting material or over-hydrogenation. The reduction reaction of **27** was accomplished with quinoline and 1-hexene under a 60 psi hydrogen atmosphere in the presence of 5% palladium on carbon, with methanol and ethyl acetate as solvents. However, less than 5 milligrams of stelliferin model **10** were obtained (42% yield), and even after purification by column chromatography, the desired material was still slightly

[33]Sonogashira, K.; Todha, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.
[34]Constantino, M.G.; Donate, R.M.; Petragnani, N. *J. Org. Chem.* **1986**, *51*, 253.

impure by ^{1}H NMR. Due to decomposition, product **10** could not be further purified, and a more thorough analysis of the product has yet to be undertaken.

In summary, this work has accomplished the synthesis of a model system for the marine natural product Stellettin A. Further studies which can now be undertaken include production of model compound **10** in greater purity and yield. This product can then be tested for its biological activity. In addition, the synthetic pathway developed for the synthesis of model compound **10** can be adopted to other stelliferin analogs, perhaps based on different steroid systems. If the synthesis for the 6.6.5-tricyclic ring system of stelliferin can be further developed, the necessary steps for synthesis of Stellettin A (**2**) and stelliferin **1** are available.

Chapter 3

Experimental Section

General Procedures: Reaction mixtures were stirred using a magnetic stirring apparatus, unless otherwise indicated. All moisture or air sensitive reactions were carried out under a positive pressure of argon, and were performed in glassware that was oven and/or flame dried. Solvents and liquid reagents were transferred *via* syringe or cannula. Reactions were monitored by thin layer chromatography (TLC), as described below. Organic solvents were removed through concentration, using a Büchi rotary evaporator at 20-40 mm Hg.

Materials: Commercial solvents and reagents were used without further purification, with the following exceptions:

Solvents:

Benzene was distilled under argon from calcium hydride.

Deuteriochloroform was stored over granular anhydrous potassium carbonate.

Dichloromethane was distilled under nitrogen from phosphorus pentoxide.

N,N-Dimethylamine was distilled from calcium hydride.

N,N-Diisopropylamine was distilled under nitrogen from calcium hydride.

N,N-Dimethylformamide was stored over activated 4Å molecular sieves.

Ethyl ether was distilled under nitrogen from sodium benzophenone ketyl.

Hexanes were distilled under nitrogen from calcium hydride.

Pyridine was distilled under argon from calcium hydride.

Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl.

Toluene was distilled under nitrogen from calcium hydride.

Triethylamine was distilled under nitrogen from calcium hydride.

Reagents:

n-Butyllithium in hexanes was titrated prior to use with *s*-butanol in tetrahydrofuran at 0 °C using 1,10-phenanthroline as an indicator.

Lithium diisopropylamine was prepared by the addition of 2.11 *M n*-BuLi (4.74 mL) to a solution of *N,N*-diisopropylamine (1.67 mL) in tetrahydrofuran (3.59 mL) at -78 °C, followed by warming to room temperature.

Chromatography:

Flash column chromatography was performed using EM silica gel of particle size 0.040-0.060 mm. HPLC grade solvents were used.

Thin layer chromatography (TLC) was performed as an analytical tool using Baker high performance precoated glass silica gel (SiO_2, approximately 5 μm particle size) plates (200 μm thickness). The plates were assimilated with 254 nm fluorescent indicator. The procedure used was to elute using the solvent mixture indicated in the text, followed by an observation by illumination with a 254 nm ultraviolet light and staining by dipping in either an ethanolic solution of 2.5% *p*-anisaldehyde (3.5% sulfuric acid and 1.0% acetic acid) or an ethanolic solution of phosphomolybdic acid (20% wt.) followed by heating on a hot plate.

Physical Data:

Melting points were determined on a Fischer-Johns hot stage apparatus and are uncorrected.

FTIR spectra were recorded on a Perkin-Elmer spectrometer equipped with an internal polystyrene sample as a reference.

^{1}H NMR were recorded either on a Varian XL 300 MHz spectrometer, a Varian Unity 300 MHz spectrometer or a Varian VXR 500 MHz spectrometer. Chemical shifts are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane

(δ 0.0) using the residual chloroform signal (δ 7.26) as a standard. Multiplicities are reported with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), pd (pair of doublets), pq (pair of quartets), pdq (pair of a doublet of quartets, dd (doublet of doublets), ddd (doublet of doublet of doublets), *etc.*

^{13}C NMR were recorded on either a Varian 300 NMR at 75 MHz on a Varian 500 NMR at 125 MHz. The deuteriochloroform signal (δ 77.01) was used as a standard.

^{19}F NMR were recorded on a Varian 300 NMR at 282 MHz. The $CFCl_3$ signal (δ 0.0) was used as a standard.

Mass spectra and high resolution mass spectra (HRMS) were recorded on a Finnigan MAT System 8200, double focusing, magnetic sector, mass spectrometer. The spectra were recorded using either electron impact (EI), generating ($M^+ + 1$), or fast atom bombardment (FAB) with sodium iodide in 3-nitrobenzyl alcohol, generating ($M + Na^+$). Spectra were recorded in units of mass to charge (m/e).

All compounds, except **10**, were judged to be greater than or equal to 95% pure based on their ^{1}H NMR spectra.

Standard Steroid Representation
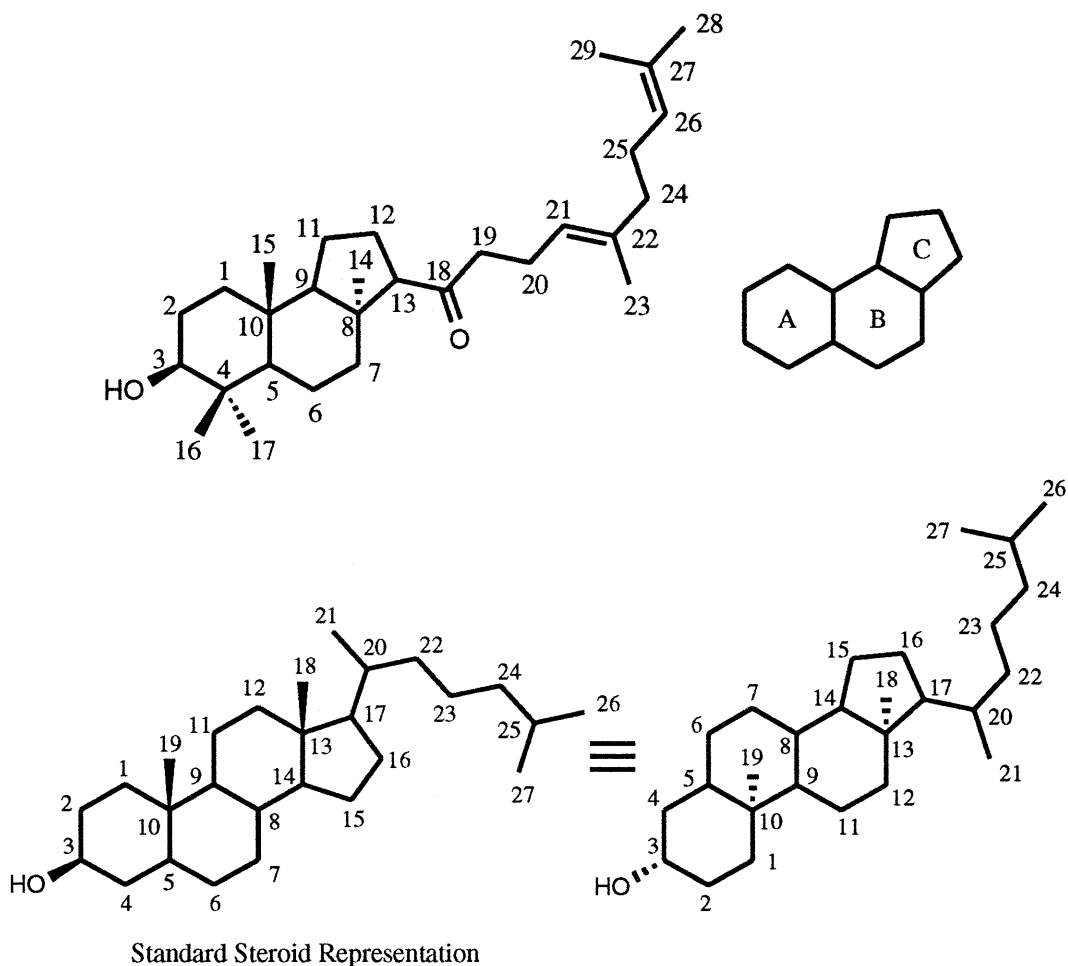
Nomenclature and physical assignments are presented in accord with the numbering for isomalabaricane skeleton and steroid structure as shown above. Hydrogen and methyl substituents attached to the isomalabaricane and steroid nucleus are designated according to the position of attachment and projection of the substituent (in the standard representations, α depicting below the plane of the page and β depicting above the plane of the page).
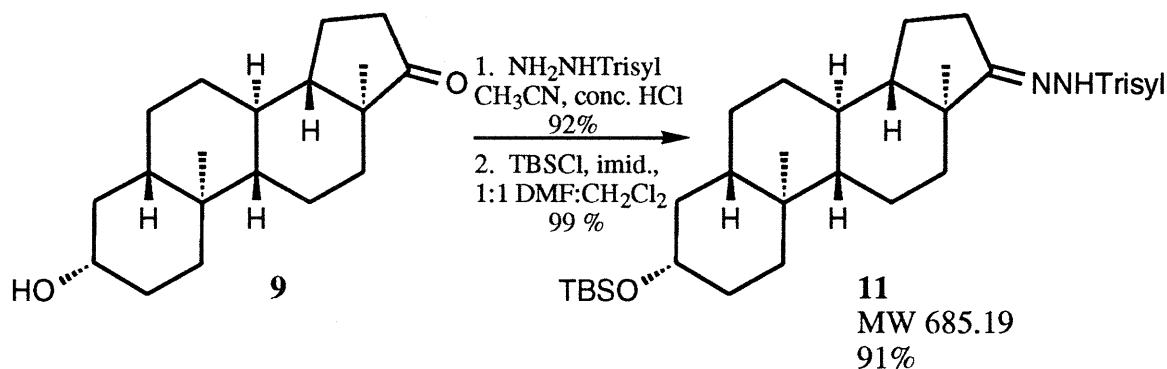
Trisylhydrazone 11:

To trisylhydrazide (5.65 g, 18.9 mmol) dissolved in acetonitrile (20 mL) was added the epiandrosterone (**9**) (4.91 g, 17.0 mmol) and concentrated hydrochloric acid (7 drops). The mixture was stirred 2 hours and then filtered. The resulting white solid was washed with cold acetonitrile and was dried under vacuum to yield a white powder (8.83 g, 92%). The crude trisylhydrazone (8.83 g, 15.5 mmol) was dissolved in a mixture of dimethylformamide and methylene chloride (1:1, 100 mL), imidazole (3.22 g, 47.3 mmol), and *t*-butyldimethylsilyl chloride (3.18 g, 21.1 mmol). The reaction mixture was stirred for 4 hours, during which additional imidazole (0.55 g, 0.80 mmol, each) and *t*-butyldimethylsilyl chloride (0.60 g, 0.40 mmol) were added. The methylene chloride was removed in vacuo and water (100 mL) was added. The mixture was extracted with 10% ether / hexanes and the combined organic layers were dried over magnesium sulfate and concentrated. Purification by column chromatography (SiO$_2$, 25% ether / hexanes) yielded **11** as a white solid (11.7 g, 99%).

11: m.p. = 180-182 °C, (dec.); FTIR (cm^{-1}, thin film) 3227, 2955, 2926, 2858, 1661, 1600, 1563, 1463, 1383, 1325, 1256, 1154, 1096, 1024, 908, 871, 836, 774, 735, 666; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14 (s, 2H), 7.04 (s, 1H, NH), 4.19 (septet, 2H, *J* = 6.8 Hz), 3.52 (ddd, 1H, *J* = 4.0, 10.5, 15.0 Hz), 2.90 (septet, 1H, *J* = 6.8 Hz), 2.22 (dd, 1H, *J* = 9.0, 17.5 Hz), 2.09 (ddd, 1H, *J* = 8.5, 8.5, 18.0 Hz), 1.82 (m, 1H), 1.75 (ddd, 1H *J* = 3.5, 3.5, 12.5 Hz), 1.68 (m, 2H), 1.55 (dddd, 1H, *J* = 3.0, 3.0, 14.0, 14.0

Hz), 1.30 (m, 10H), 1.25 (m, 18H), 1.05 (m, 2H), 0.89 (m, 2H), 0.87 (s, 9H), 0.77 (s, 3H), 0.71 (s, 3H), 0.6 (ddd, 1H, J = 5.0, 12.0, 15.0 Hz), 0.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.7, 152.9, 151.2, 131.5, 123.5, 72.0, 54.5, 53.4, 45.0, 44.8, 38.6, 37.1, 35.6, 34.9, 34.1, 33.7, 31.9, 31.4, 29.8, 28.5, 25.9, 25.8, 24.9, 24.8, 23.6, 23.3, 20.6, 18.2, 16.8, 12.3; HRMS (EI) calculated for C$_{31}$H$_{50}$N$_2$O$_3$SSi (M$^+$) 684.4720, observed 684.4712.
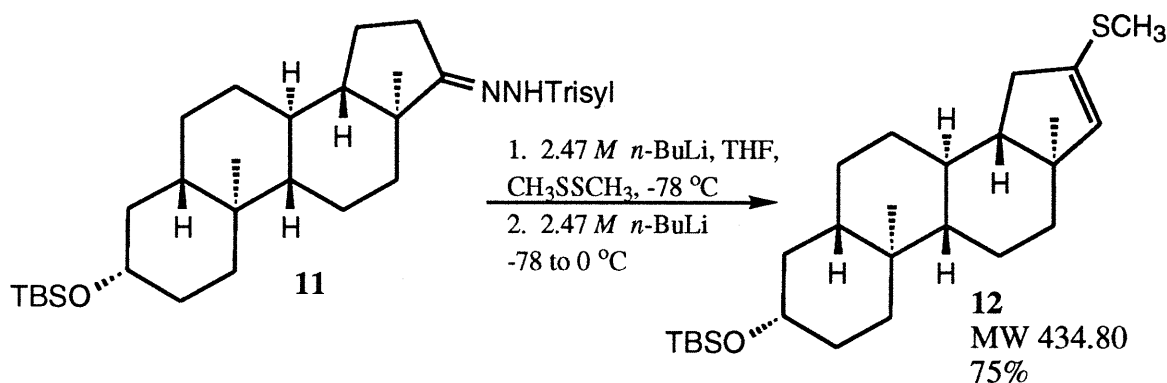
Methyl Vinyl Sulfide 12:

To a solution of trisylhydrazone **11** (1.01 g, 1.47 mmol) in tetrahydrofuran (5 mL) at -78 °C was added 2.47 M n-butyllithium in hexanes (1.4 mL, 3.5 mmol). The resulting red solution was stirred for 30 minutes, then dimethyl disulfide (159 µL, 1.76 mmol) was added via syringe. The reaction color immediately faded to yellow. The mixture was stirred for 25 minutes before 2.47 M n-butyllithium in hexanes (0.8 mL, 2 mmol) was added. The red-orange colored solution was stirred at -78 °C for 30 minutes. After warming to 0 °C and stirring for 30 minutes, the vinyl lithium anion was quenched with saturated aqueous ammonium chloride. The mixture was poured into water (10 mL) and extracted with ether. The combined organic layers were dried over magnesium sulfate, concentrated and purified by column chromatography (SiO_2, 10% methylene chloride / hexanes) to yield methyl vinyl sulfide **12** (482 mg, 75%).

12: m.p. = 116 - 117 °C; FTIR (cm^{-1}, thin film) 2928, 2854, 1569, 1462, 1373, 1251, 1092, 1069, 1005, 867, 834, 796, 774; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.37 (s, 1H), 3.54 (ddd, 1H, J = 4.9, 10.7, 15.6 Hz), 2.25 (s, 3H), 2.11 (m, 2H), 1.60 - 1.20 (m, 14H), 1.09 (m, 1H), 0.95 (m, 2H), 0.88 (s, 9H), 0.82 (s, 3H), 0.78 (s, 3H), 0.71 (m, 1H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.2, 132.8, 72.1, 56.4, 55.1, 46.1, 45.2, 38.7, 37.0, 36.3, 36.1, 35.8, 34.0, 32.0, 31.9, 28.7, 25.9, 21.1, 18.3, 17.3, 14.9, 12.4, -4.6; HRMS (EI) calculated for $C_{26}H_{46}OSSi$ (M$^+$) 434.3039, observed 434.3047.
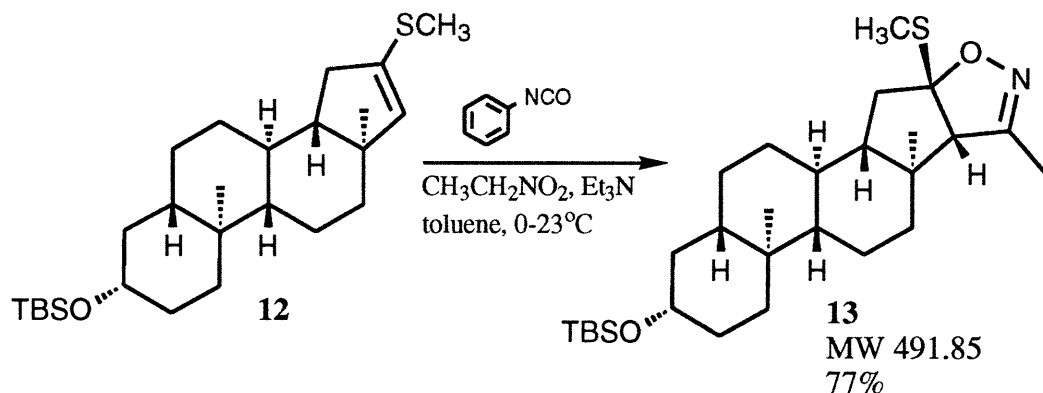
3-Methyl Sulfide-2-isoxazoline 13:

To methyl vinyl sulfide **12** (1.47 g, 3.38 mmol) in toluene (30 mL) at 0 °C was added nitroethane (0.775 mL, 10.8 mmol), phenyl isocyanate (2.3 mL, 22 mmol), and triethylamine (0.10 mL). The mixture was stirred for 2 hours and was allowed to warm to room temperature. A precipitate formed. The same quantities of nitroethane, phenyl isocyanate, and triethylamine were added four times over the course of two days. After filtering off the precipitate and rinsing it with toluene, the eluant was adsorbed onto silica gel 60. Purification by dry-loaded column chromatography (SiO$_2$, 25% ether / hexanes) yielded 3-methyl sulfide-2-isoxazoline **13** (1.44 g, 77%) as a slightly yellow off-white powder.

13: R$_f$ 0.36 (25% ether / hexanes); FTIR (cm^{-1}, thin film) 2926, 2855, 1434, 1383, 1248, 1098, 884, 836, 797, 774; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.54 (ddd, 1H, J = 4.4, 10.7, 15.6 Hz), 2.96 (s, 1H), 2.34 (dd, 1H, J = 5.9, 13.2 Hz), 2.12 (s, 3H, SCH$_3$), 1.98 (s, 3H), 1.72 (m, 1H), 1.71 (t, 1H, J = 13.2 Hz), 1.62 (m, 4H), 1.43 (m, 3H), 1.31 (m, 4H), 1.25 (m, 1H), 1.21 (m, 1H, J = 3.4, 13.2 Hz), 1.04 (m, 1H, J = 3.4, 12.2 Hz), 0.99 (s, 3H), 0.94 (m, 2H, J = 4.4, 5.4, 12.2 Hz), 0.88 (s, 9H), 0.79 (s, 3H), 0.64 (ddd, 1H, J = 4.4, 11.2, 11.2 Hz), 0.04 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.1, 101.2, 72.2, 71.8, 53.7, 50.6, 46.7, 46.1, 44.7, 41.1, 38.5, 37.0, 35.7, 35.5,

34.8, 32.1, 31.8, 28.4, 25.9, 20.8, 20.2, 18.2, 13.8, 12.2, 11.9; HRMS (EI) calculated for $C_{28}H_{49}NO_2SSi$ (M$^+$) 491.3253, observed 491.3254.
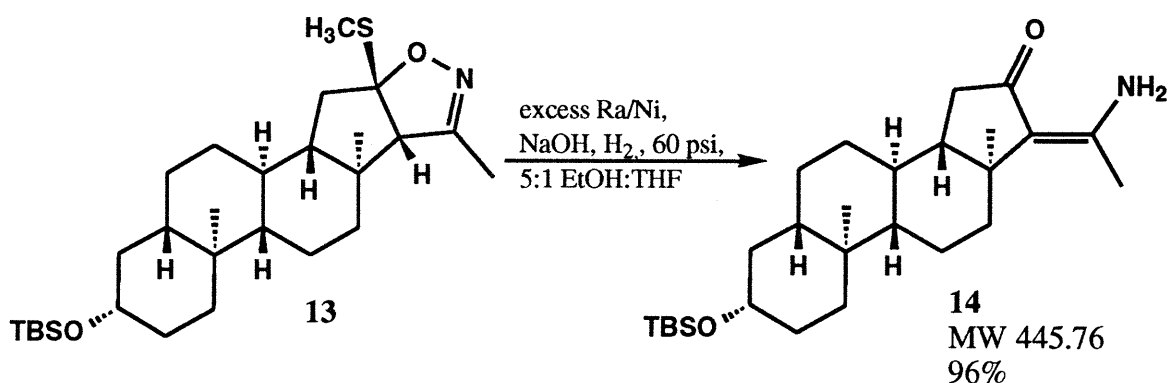
β-Amino Enone 14:

To 3-methyl sulfide-2-isoxazoline **13** (55.5 mg, 0.100 mmol) in sodium hydroxide (1.16 g, 29.0 mmol) in ethanol (50 mL) and tetrahydrofuran (12 mL) was added excess Raney nickel (commercial, 50% slurry in water, 1.58 g). The reaction was placed on a hydrogenator under a 60 psi hydrogen atmosphere. The reaction mixture was shaken for 17 hours. After filtration through magnesium sulfate and rinsing with ethyl acetate, the mixture was concentrated. β-Amino enone **14** (1.38 g, 96%) was purified by column chromatography (SiO$_2$, 5% ether / methylene chloride) to yield a white powder.

14: R$_f$0.21 (5% ether / methylene chloride), m.p. = 285 °C (dec.); FTIR (cm^{-1}, thin film) 3389, 3188, 2929, 2854, 1628 (ν$_{C=O}$), 1504, 1471, 1376, 1249, 1090, 1065, 1007, 872, 834, 772; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.56 (broad s, 1H, NH), 4.50 (broad s, 1H, NH), 3.55 (ddd, 1H, J = 4.9, 10.7, 15.6 Hz), 2.09 (m, 1H, J = 7.3, 16.1 Hz), 2.08 (dd, 2H, J = 12.8, 16.1 Hz), 1.95 (s, 3H), 1.65 (m, 4H), 1.55 - 1.25 (m, 9H), 1.07 (m, 1H), 0.98 (s, 3H), 0.93 (m, 2H), 0.88 (s, 9H), 0.82 (s, 3H), 0.76 (m, 1H), 0.04 (s, 6H); HRMS (EI) calculated for C$_{27}$H$_{47}$NO$_2$Si (M$^+$) 445.3376, observed 445.3372.
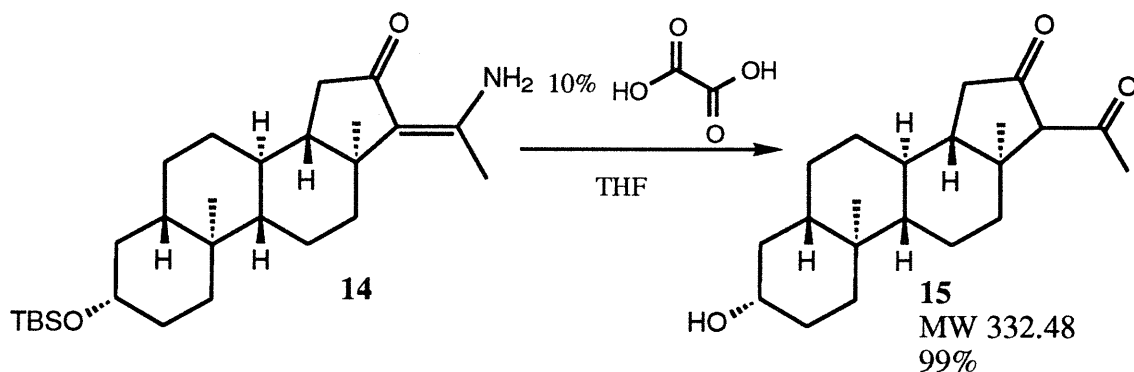
Diketone 15:

The aminoenone **14** (1.38 g, 3.09 mmol) was dissolved in tetrahydrofuran (18 mL) and treated with 10% aqueous oxalic acid (55 mL) while stirring at room temperature. Upon addition of the acid, the solution turned cloudy white. The mixture was stirred overnight, then diluted with water, and extracted with 20% ethyl acetate / hexanes. The organic layers were dried over magnesium sulfate and concentrated. Purification by column chromatography (SiO_2, 1:1 ether / methylene chloride) yielded **15** as a white powder (1.02 g, 99%), a mix of the two diketone diasteriomers and the enol tautomer.

15: R_f 0.64 (100% ether); m.p. = 156-172 $^{\circ}$C (dec.); FTIR (cm^{-1}, thin film) 3389, 2930, 2855, 1746, 1702, 1650, 1606, 1450, 1417, 1381, 1359, 1214, 1035, 916, 733, 647; ^{1}H NMR (300 MHz, CDCl$_3$) keto-1: δ 3.20 (s, 1H), 2.23 (s, 3H), 0.99 (s, 3H), 0.83 (s, 3H); keto-2: δ 2.92 (s, 1H), 1.93 (s, 3H), 0.99 (s, 3H), 0.84 (s, 3H); enol: δ 13.79 (s, 1H), 2.18 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H). For all three isomers, δ 3.59 (ddd, 1H, J = 4.4, 10.8, 15.6 Hz), 2.40-1.00 (m, 20 H); HRMS (FAB) calculated for $C_{21}H_{32}O_3$ 332.235145, observed 332.23508.

AcO OAc
     OAc
      I
       O

       O

CH2Cl2

15

28
MW 330.46
70%
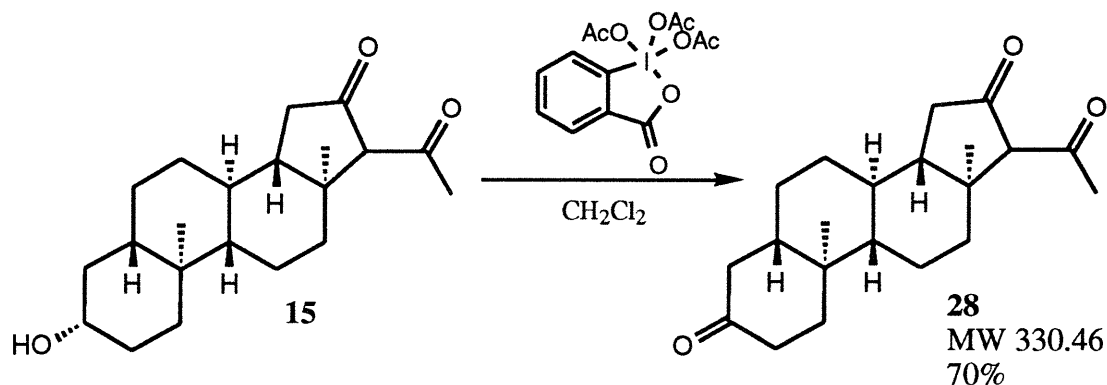
Triketone 28:

To the Dess-Martin periodate reagent (0.279 g, 0.843 mmol) was added methylene chloride (20 mL), and the resulting cloudy solution stirred under argon for 15 minutes at 0 °C. The alcohol **15** (0.200 g, 0.602 mmol), dissolved in methylene chloride, was added and the resulting mixture stirred at 0 °C. Three additional portions of the Dess-Martin reagent, each of 0.5 equivalents (0.128 g, 0.302 mmol), were added as the mixture stirred for 24 hours at 0 °C. The mixture was poured into a 1:1 saturated sodium bicarbonate:saturated sodium thiosulfate solution and extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated. Purification by column chromatography (SiO$_2$, 5% ether / methylene chloride) yielded **28** (0.140g, 70%).

28: R$_f$ 0.70 (100% ether); FTIR (cm^{-1}, thin film) 2926, 2857, 1745. 1709, 1650, 1608, 1452, 1418, 1383, 1356, 1217, 1162, 916, 733; ^{1}H NMR (300 MHz, CDCl$_3$) keto-1: δ 3.20 (s, 1H), 2.22 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H); keto-2: δ 2.92 (s, 1H), 1.98 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H); enol: δ 13.78 (s, 1H), 2.17 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H). For all three isomers, δ 2.50-1.90 (m, 3H), 1.80-1.20 (m, 10H), 1.10-0.70 (m, 7H)
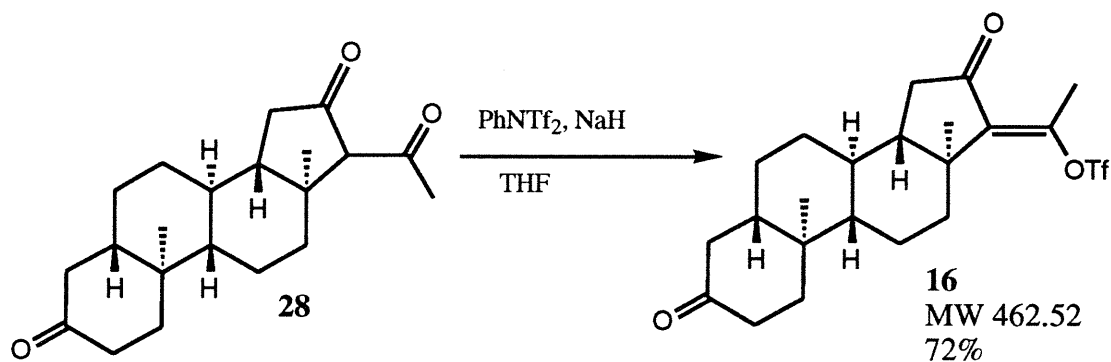
Triflate 16:

The triketone **28** (0.148 g, 0.448 mmol) was dissolved in tetrahydrofuran (15 mL) at 0 °C and sodium hydride (60% dispersion in mineral oil, 17.9 mg, equivalent to 10.8 mg NaH, 0.448 mmol) was added. The mixture was stirred at 0 °C for 90 minutes under argon with an oil bubbler, until hydrogen gas stopped evolving. The temperature was reduced to -60 °C and *N*-phenyl-trifluoromethane sulfonimide (0.18 g, 0.50 mmol) was added. The reaction mixture was stirred 10 minutes at -60 °C, then the temperature increased to -15 °C. After stirring overnight at -15 °C, water was added, and the tetrahydrofuran was removed *in vacuo*. The mixture was extracted with ether, and the combined organic layers were dried over magnesium sulfate and concentrated. Purification by column chromatography (SiO$_2$, 1% ether / methylene chloride) produced **16** (0.149 g, 72%).

16: R$_f$ 0.79 (5% ether / methylene chloride); m.p. 94-108 °C (dec.); FTIR (cm^{-1}, thin film) 2941, 2861, 1714, 1674, 1621, 1427, 1383, 1362, 1308, 1245, 1213, 1143, 1035, 973, 953, 872, 845, 832, 786, 760, 605, 514; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.52 (d, 1H, *J* = 9.3 Hz), 2.50 (d, 1H, *J* = 3.0 Hz), 2.38 (dd, 1H, *J* = 6.8, 15.6 Hz), 2.36 (s, 3H), 2.31 (m, 1H), 2.24 (m, 1H), 2.22 (ddd, 1H, *J* = 2.9, 4.4, 12.8 Hz), 2.08 (ddd, 1H, *J* = 2.2, 3.9, 14.9 Hz), 1.98 (ddd, 1H, *J* = 2.2, 6.6, 13.2 Hz), 1.71-1.60 (m, 4H), 1.54 (m, 1H), 1.47 (ddd, 1H, *J* = 4.4, 13.2, 26.4 Hz), 1.40-1.25 (m, 4H), 1.11 (s, 1H), 1.06 (s, 3H), 1.02 (s, 3H), 0.86 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 211.5, 194.3, 154.5,

36

139.2, 129.3, 125.9, 123.1, 53.7, 53.2, 46.7, 46.6, 44.5, 38.0, 35.9, 34.1, 33.0, 31.3, 31.2, 28.5, 20.9, 16.2, 11.5; ^{19}F NMR (282 MHz, CDCl$_3$, referenced to CFCl$_3$ in benzene) δ -74.2.
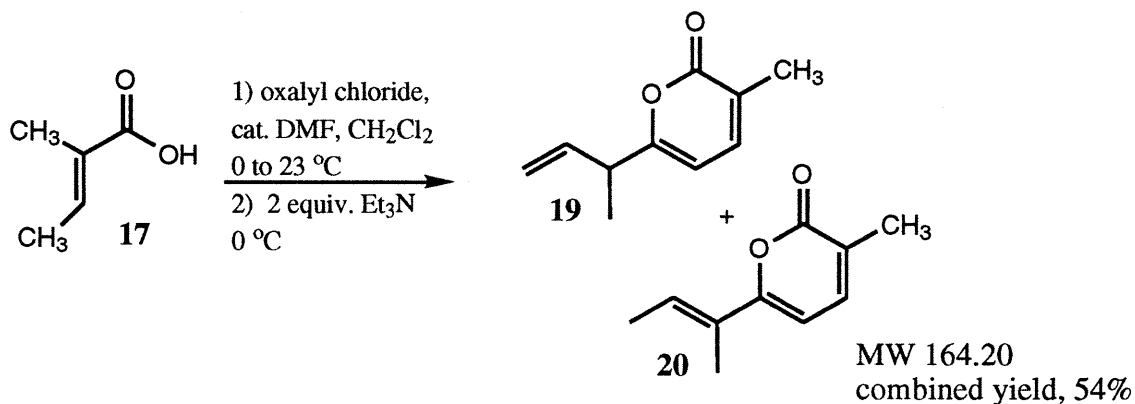
3-Methyl-6-(1-methylallyl)-2-pyrone (19) and 3-Methyl-6-(1-methylpropenyl)-2-pyrone (20):[1]

To tiglic acid (17) (9.85 g, 97.4 mmol) in methylene chloride (100 mL) at 0 °C in a 200-mL round bottom flask under argon attached to an oil bubbler was added dimethylformamide (2 drops) and freshly distilled oxalyl chloride (8.5 mL, 97.4 mmol). After 30 minutes at 0 °C the reaction mixture was warmed to room temperature for 3 hours. The crude acid chloride was recooled to 0 °C and triethylamine (28 mL, 195 mmol) was slowly added. A white precipitate formed immediately. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. It was poured into water (100 mL) and extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, concentrated and purified by column chromatography (SiO$_2$, 25% ether / hexanes) to yield 19 and 20 as a red oil (~1:1 mixture, 54%)

Mixture: R$_f$0.34 (25% ether / hexanes); FTIR (cm^{-1}, thin film) 2979, 2923, 1720, 1714, 1645, 1582, 1563, 1451, 1382, 1209, 1127, 1110, 1048, 994, 926, 805, 760.

19: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.04 (d, 1H, J = 6.7 Hz), 5.88 (d, 1H, J = 6.4 Hz), 5.87 (ddd, 1H, J = 3.4, 6.6, 10.4 Hz), 5.15 (dd, 1H, J = 1.3, 10.4 Hz), 5.10 (dd, 1H, J = 1.3, 3.4 Hz), 3.26 (m, 1H, J = 6.6, 7.0 Hz), 2.06 (s, 3H), 1.32 (d, 3H, J =

[1]Rey, M.; Dunkelblum, E.; Allain, R.; Dreiding, A. S. *Helv. Chim. Acta,* **1970,** *53,* 2159-2175.

7.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.4, 162.0, 139.6, 138.0, 122.9, 116.2, 101.5, 41.6, 17.7, 16.5.

20: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.09 (d, 1H, J = 7.1 Hz), 6.59 (q, 1H, J = 7.3 Hz), 6.02 (d, 1H, J = 7.0 Hz), 2.04 (s, 3H), 1.82 (s, 3H), 1.80 (d, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.5, 159.9, 140.0, 128.1, 126.9, 104.0, 100.4, 41.6, 14.1, 12.0.
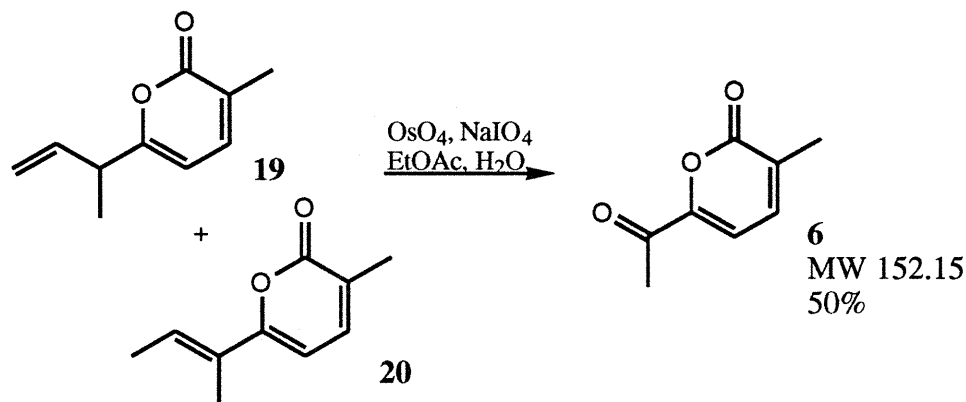
Keto Pyrone 6:

To a mixture of **19** and **20** (1:1, 218 mg, 1.33 mmol) in ethyl acetate (30 mL) and water (30 mL) was added osmium tetraoxide (34 mg, 0.13 mmol) at room temperature. The resulting black solution was stirred for 15 minutes. Sodium periodate (2.84 g, 13.3 mmol) was added portionwise over 1.5 hours. After the addition of sodium periodate was complete, the reaction mixture was stirred overnight. The ethyl acetate layer was separated and additional ethyl acetate was used to extract the aqueous phase. The combined organic layers were dried and concentrated to afford a white solid with a brown tinge (180 mg). Recrystallization from ethyl acetate / hexanes yielded **6** as white crystals (102 mg, 50%) (100% based on **20**).

6: R_f 0.39 (5% ether / methylene chloride); m.p. = 145 - 146 °C, (dec.); FTIR (cm^{-1}, thin film) 3083, 1704, 1644, 1428, 1378, 1342, 1274, 1123, 1087, 861, 754; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.23 (dq, 1H, J = 1.3, 6.8 Hz), 6.92 (d, 1H, J = 6.8 Hz), 2.47 (s, 3H), 2.14 (d, 1H, J = 1.3 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 191.2, 161.2, 153.2, 137.9, 131.8, 107.1, 25.7, 17.4; HRMS (EI) calculated for C$_8$H$_8$O$_3$ (M$^+$) 152.0473, observed 152.0473.

TMS——≡——Br + (MeO)$_2$PH (with O double bond) $\xrightarrow[\text{THF}]{\text{NaN(SiMe}_3)_2}$ TMS——≡——P(OMe)$_2$ (with O double bond)

29
MW 220.29
63%
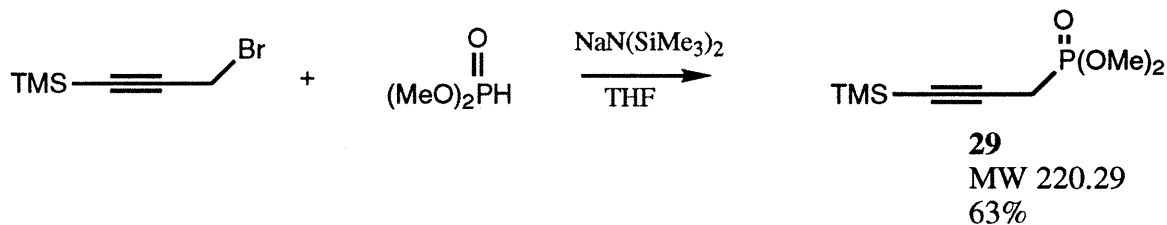
Diethyl (3-Trimethylsilyl-2-propynyl)phosphonate 29:[2]

To a stirred solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 10 mL, 10 mmol) at -10 °C under argon was added dimethyl phosphite (1.4 g, 13 mmol) in tetrahydrofuran (3 mL). The solution was stirred for 15 minutes at -10 °C, and then was treated with 3-bromo-1-trimethylsilyl-1-propyne (1.9 g, 10 mmol) in tetrahydrofuran (3 mL), maintaining the temperature at -10 °C. The mixture was stirred for one hour at -10 °C. It was then diluted with water and extracted with ethyl acetate. The extract was washed with 2 M hydrochloric acid, followed by water. The organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO$_2$, 33% ethyl acetate / hexanes) yielded **29** (1.38 g, 63%).

29: R$_f$ 0.19 (33% ethyl acetate / hexanes); FTIR (cm^{-1}, thin film) 2957, 2899, 2852, 2180, 1462, 1409, 1252, 1185, 1252, 1185, 1044, 846, 700, 641, 570; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.84 (d, 6H, J = 10.9 Hz), 2.83 (d, 2H, J = 22.3 Hz), 0.16 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 94.8 (d, J = 15.2 Hz), 86.5 (d, J = 8.0 Hz), 52.4, 17.1 (d, J = 143 Hz), -1.3.

[2]Gibson, A.W.; Humphrey, G.R.; Kennedy, D.J.; Wright, S.H.B. *Synthesis*, **1991**, *5*, 414.
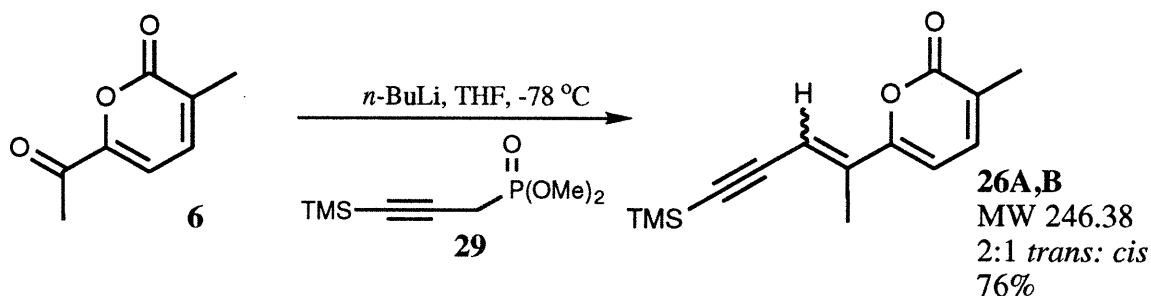
Trimethylsilyl Enyne Pyrone 26A,B:

(3-Trimethylsilyl-2-propynyl)-phosphate **29** (224 mg, 1.02 mmol) in tetrahydrofuran (5 mL) was deprotonated at -78 °C under argon with 2.11 M n-butyllithium in hexanes (0.49 mL, 1.0 mmol). The resulting orange-yellow solution was stirred for 1.5 hours at -78 °C. The solution was added via cannula at -78 °C to keto pyrone **6** (140 mg, 0.920 mmol) in dimethoxyethane (2 mL) and tetrahydrofuran (7 mL). The reaction mixture turned bright yellow. It was stirred a few minutes at -78 °C, warmed to 0 °C, and then allowed to warm slowly to room temperature. Upon warming to 0 °C, the mixture turned yellow-brown. The reaction mixture was poured into a saturated ammonium chloride solution and extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated. Crude purification by column chromatography (SiO$_2$, 20% ether / hexanes) yielded a 2:1 mixture of the *cis* isomer **26A** and the *trans* isomer **26B** (173 mg, 76%).

cis-**26A**: R$_f$ 0.36 (25% ether / hexanes); FTIR (cm^{-1}, thin film) 2959, 2133, 1714, 1634, 1541, 1423, 1387, 1335, 1246, 1101, 1037, 847, 817, 764, 674; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.15 (dq, 1H, J = 1.0, 6.8 Hz), 7.12 (d, 1H, J = 6.8 Hz), 5.74 (q, 1H, J = 1.0 Hz), 2.13 (br s, 3H), 2.09 (d, 3H, J = 1.0 Hz), 0.22 (s, 9H).

trans-**26B**: R$_f$ 0.36 (25% ether / hexanes); FTIR (cm^{-1}, thin film) 2960, 2133, 1708, 1560, 1384, 1371, 1249, 1109, 981, 840, 811, 756; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.12 (dq, 1H, J = 1.0, 6.8 Hz), 6.44 (s (broad), 1H), 6.18 (d, 1H, J = 6.8 Hz), 2.10 (br s, 6H), 0.21 (s, 9H).
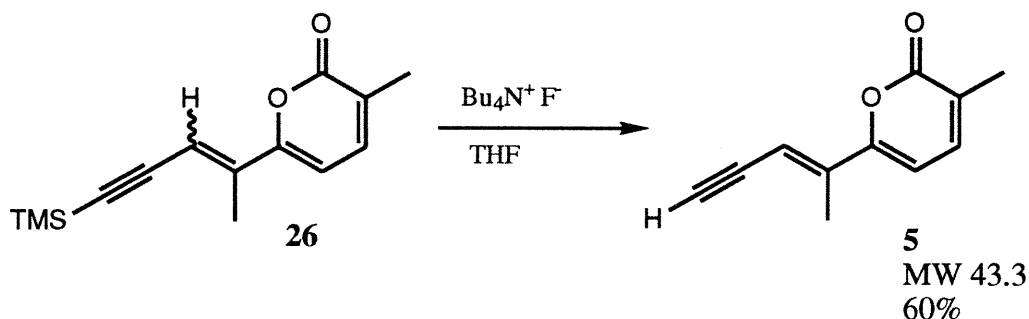
Acetylinic pyrone 5:

The trimethylsilyl-protected acetylene pyrone **26** (173 mg, 0.702 mmol) was dissolved in tetrahydrofuran (4 mL) under argon at room temperature, and 1 M tetrabutylammonium fluoride in tetrahydrofuran (0.807 mL, 0.807 mmol) was added. The dark black reaction mixture was stirred at room temperature for 90 minutes. Water was then added, and the tetrahydrofuran was removed *in vacuo*, and the mixture redissolved in methylene chloride. The mixture was washed with water, 1 M hydrochloric acid, and then again with water. The organic layers were dried over magnesium sulfate and then concentrated. Purification by column chromatography (SiO$_2$, 0.25% ether / methylene chloride) yielded *trans*- **5** (73.4 mg, 60%, 100% based on *trans* starting material) as a brown-tinged powder.

5: R$_f$ 0.27 (25 % ether / hexanes); FTIR (cm^{-1}, thin film) 3251, 1698, 1634, 1563, 1430, 1384, 1121, 1085, 811,756; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13 (dq, 1H, J = 1.0, 6.8 Hz), 6.43 (s (broad), 1H), 6.21 (d, 1H, J = 6.8 Hz), 3.48 (d, 1H, J = 2.4 Hz), 2.13 (s, 3H), 2.12 (s, 3H).

43
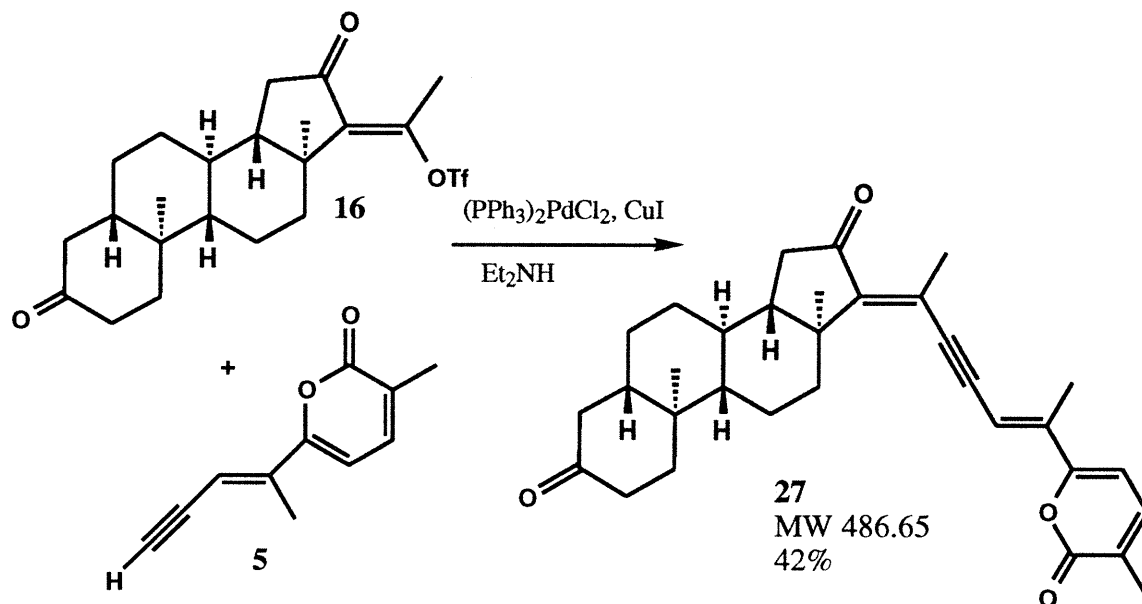
Steroid Acetylene 27:

Triflate **16** (50.9 mg, 0.110 mmol) was dissolved in diethylamine (3 mL) under argon and bis(triphenylphosphine)palladium dichloride (2.5 mg, 0.0036 mmol) and cuprous iodide (1.4 mg, 0.0074 mmol) were added. The mixture was stirred a couple minutes at room temperature, and then the acetylene pyrone **5** (20.4 mg, 0.117 mmol) dissolved in diethylamine (3 mL) was added slowly over one hour. The resulting mixture was stirred overnight. The diethylamine was removed *in vacuo*, water was added to the residue, and the product was extracted with methylene chloride. The organic layers were filtered through magnesium sulfate and silica gel and then concentrated. Purification by column chromatography (SiO$_2$, 2% ether / methylene chloride to 20% ether / methylene chloride) yielded **27** (22.3 mg, 42%) as a yellow powder.

27: R$_f$ 0.61 (5% ether / methylene chloride); m.p. 188-192 °C (dec); FTIR (cm^{-1}, thin film) 2939, 2358, 1713, 1652, 1553; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.15 (dd, 1H, J = 1.0, 6.8 Hz), 6.68 (s, 1H), 6.24 (d, 1H, J = 6.8 Hz), 2.51 (s, 3H), 2.46 (dd, 1H, J = 6.6, 15.9 Hz), 2.41-2.24 (m, 5H), 2.13 (s, 3H), 2.12 (s, 3H), 2.08 (ddd, 1H, J = 2.2, 3.7, 15.1 Hz), 2.00 (ddd, 1H, J = 2.2, 6.6, 13.2 Hz), 1.75-1.25 (m, 11H), 1.03 (s, 3H), 0.99 (s, 3H), 0.82 (ddd, 1H, J = 4.4, 10.5, 12.5 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ

211.8, 196.9, 162.4, 157.3, 156.7, 139.0, 138.4, 133.2, 126.0, 110.4, 103.7, 99.6, 97.3, 54.6, 54.0, 48.5, 46.7, 44.6, 39.1, 38.2, 38.1, 35.8, 34.7, 33.6, 31.4, 30.6, 28.7, 21.2, 16.8, 15.8, 15.4, 11.4; HRMS (FAB) calculated for $C_{32}H_{38}O_4$ 486.2770, observed 486.2771.

H_2, Pd/C

quinoline, 1-hexene

27

10
MW 488.67
42%
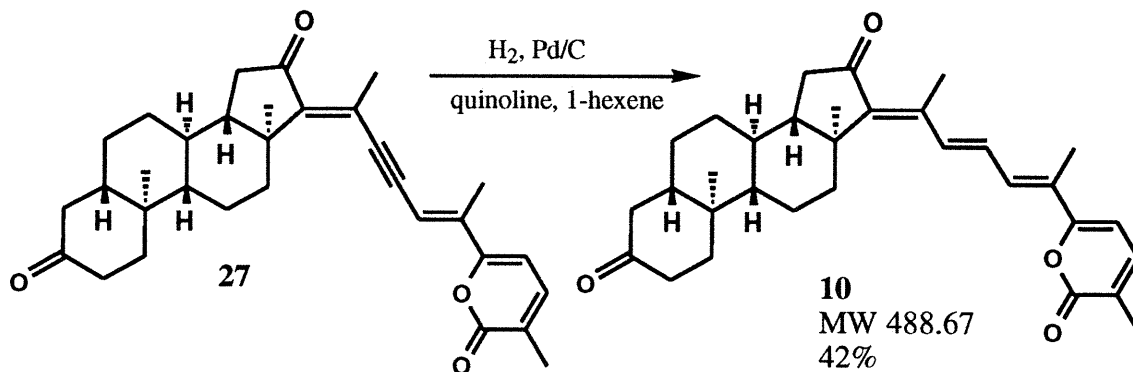
Stellettin model 10:

The steroid acetylene **27** (12 mg, 0.024 mmol) was dissolved in methanol (1.5 mL) and ethyl acetate (2.5 mL). To the solution was added 1-hexene (25 μL), quinoline (10 μL), and palladium on carbon (5% activated catalyst, 5 mg). The reaction vessel was placed on a hydrogenator and allowed to react under a 60 psi hydrogen atmosphere at room temperature. After 45 minutes, the reaction temperature was reduced to 0 °C and left stirring overnight under 60 psi hydrogen. The reaction was then re-warmed to room temperature and reacted for 3 additional hours. The mixture was filtered through magnesium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate / benzene to 20% ethyl acetate / benzene) yielded **10** (4.8 mg, 42%) as a yellow powder (still slightly impure by ^{1}H NMR).

10: R_f 0.38 (20% ethyl acetate / benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, 1H, J = 11.2 Hz), 7.14 (d, 1H, J = 6.8 Hz), 7.13 (d, 1H, J = 15.1 Hz), 6.75 (dd, 1H, J = 11.7, 15.1 Hz), 6.21 (d, 1H, J = 6.8 Hz), 2.33-2.00 (m, 8H), 2.38 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H), 1.80-1.05 (m, 11H), 1.25 (s, 3H), 1.05 (s, 3H), 0.80 (m, 1H).

11

12

7   6   5   4   3   2   1   0   ppm

1.04   1.00   0.94 3.00   6.00   3.01   0.89.813.09   5.71
              2.96   6.20 3.19.15 1.01

14

15

28

16
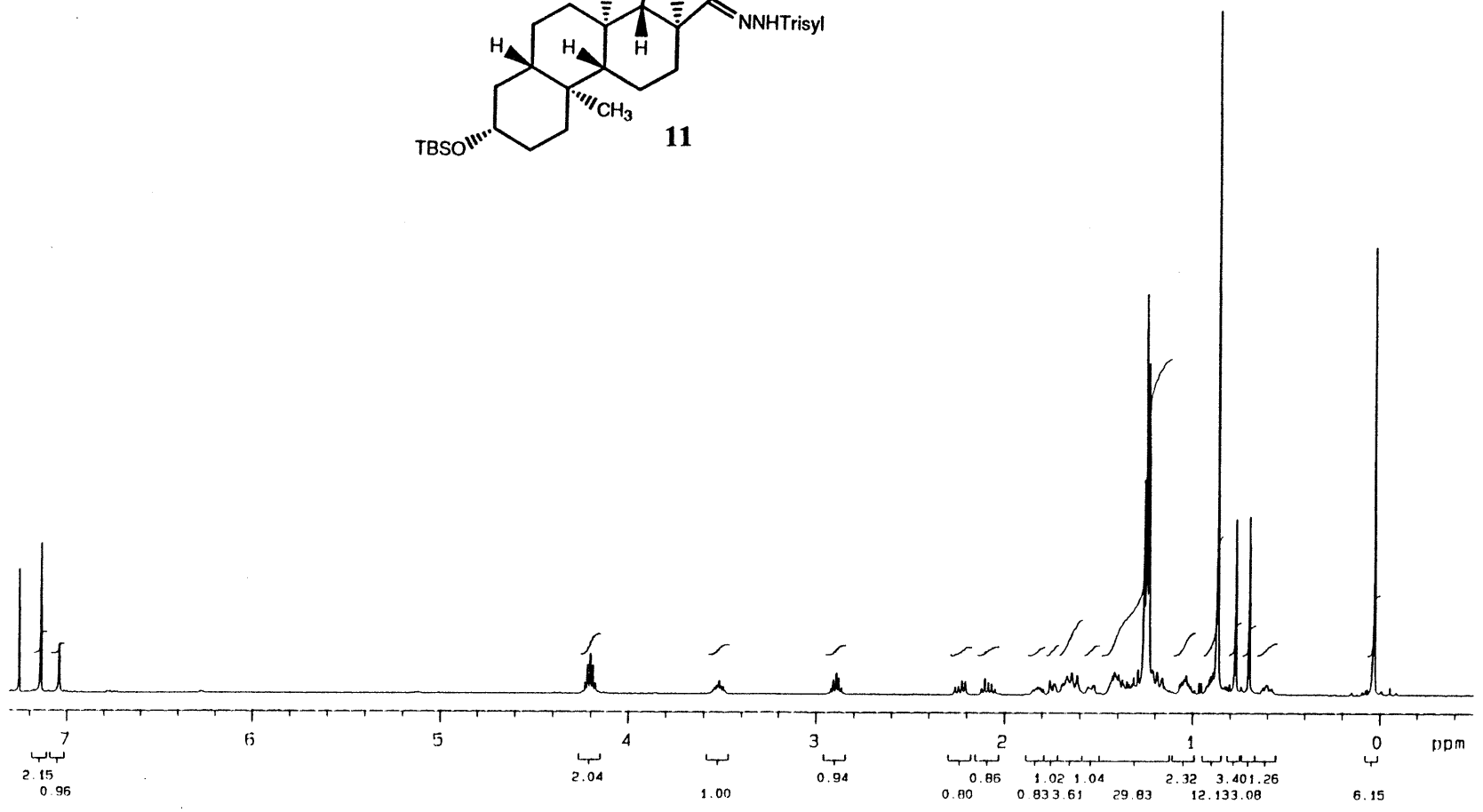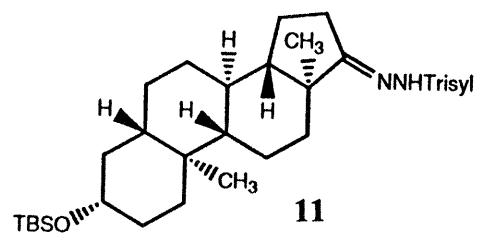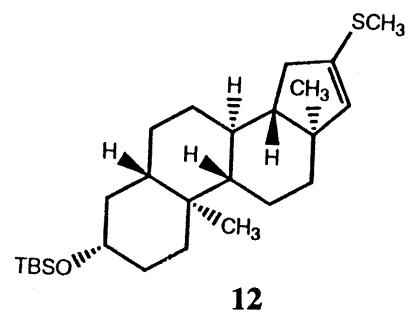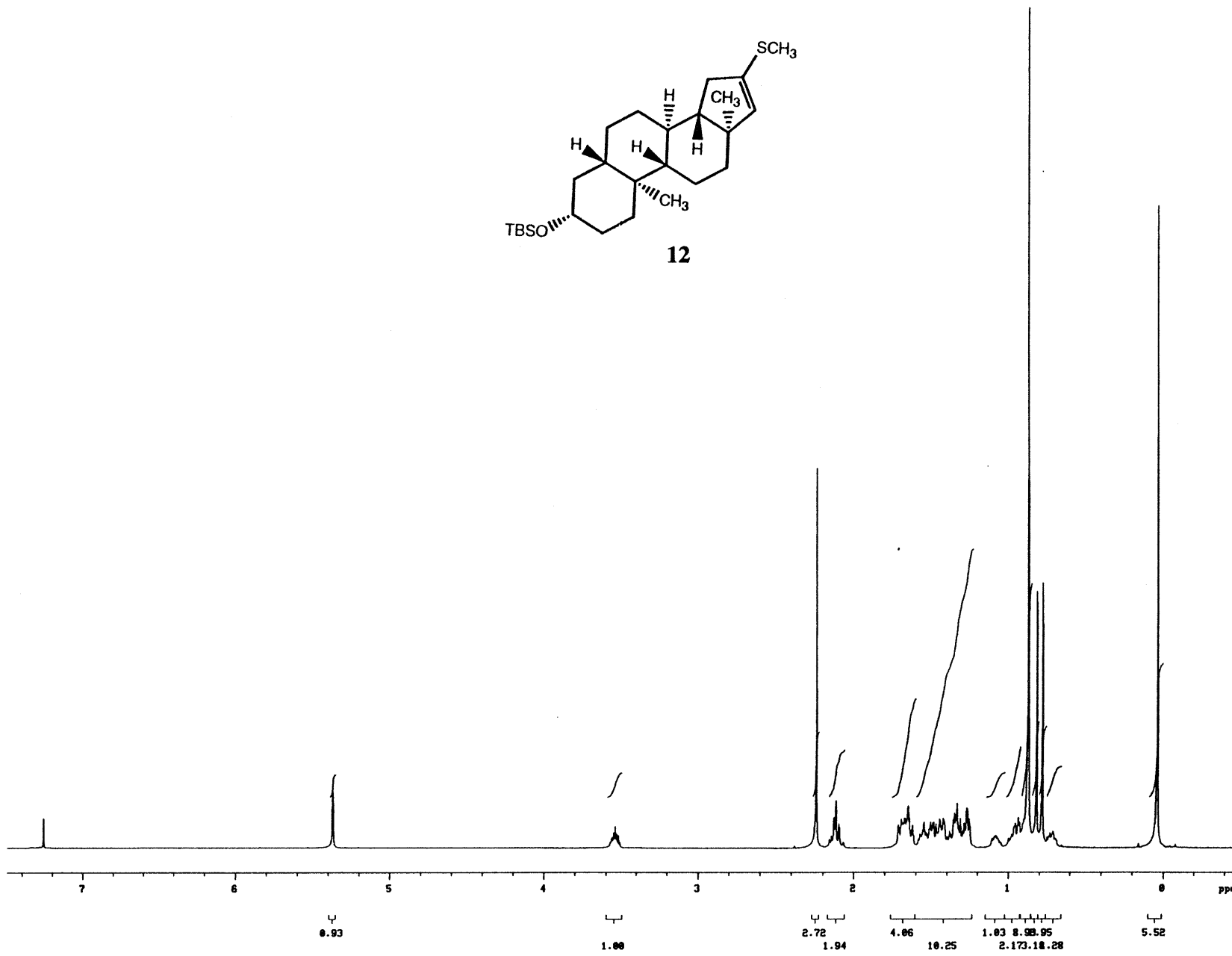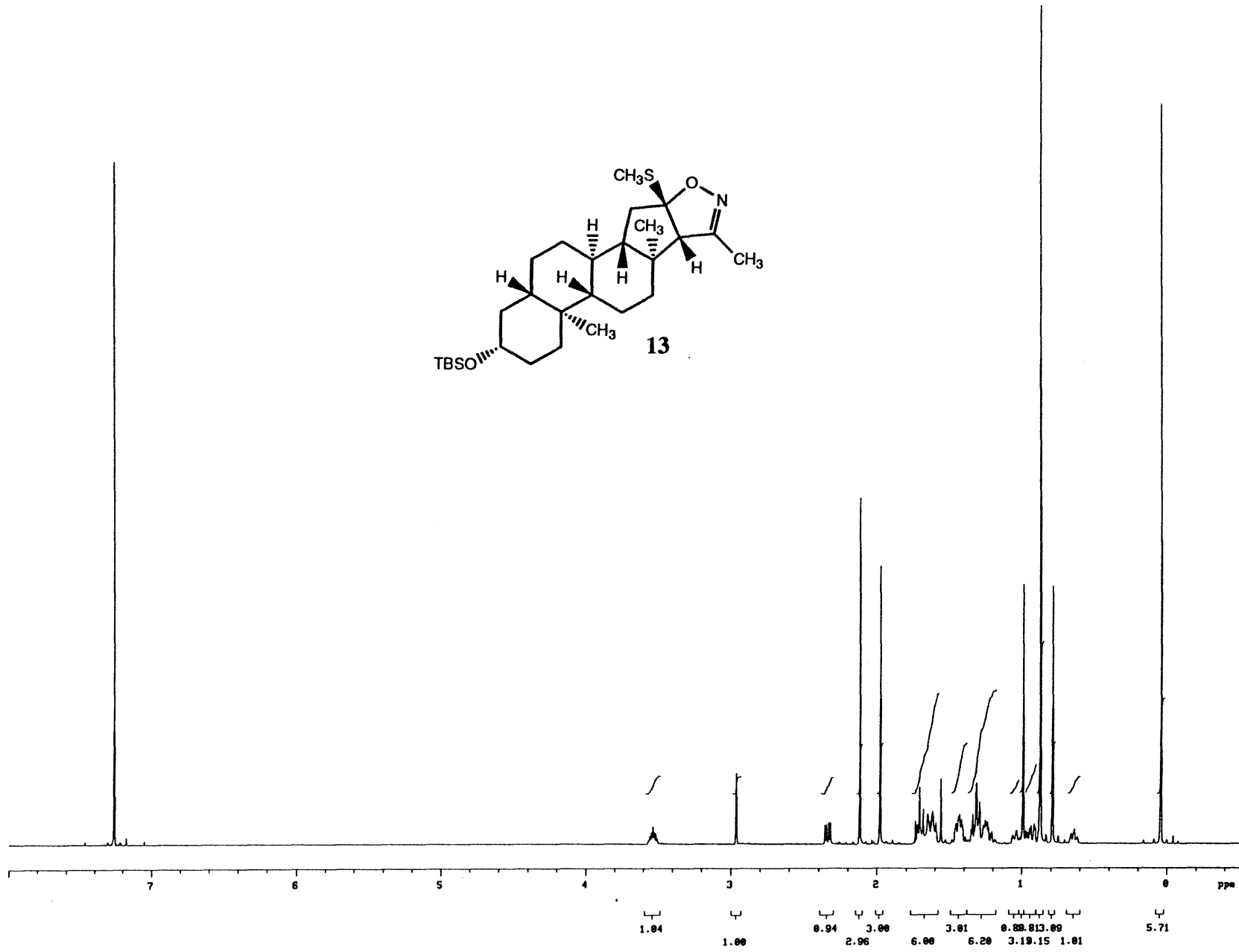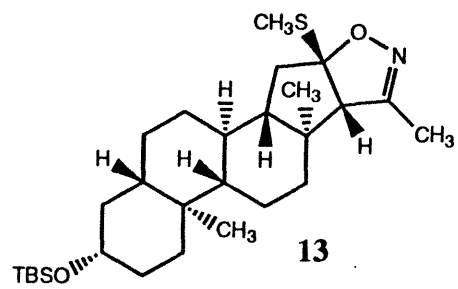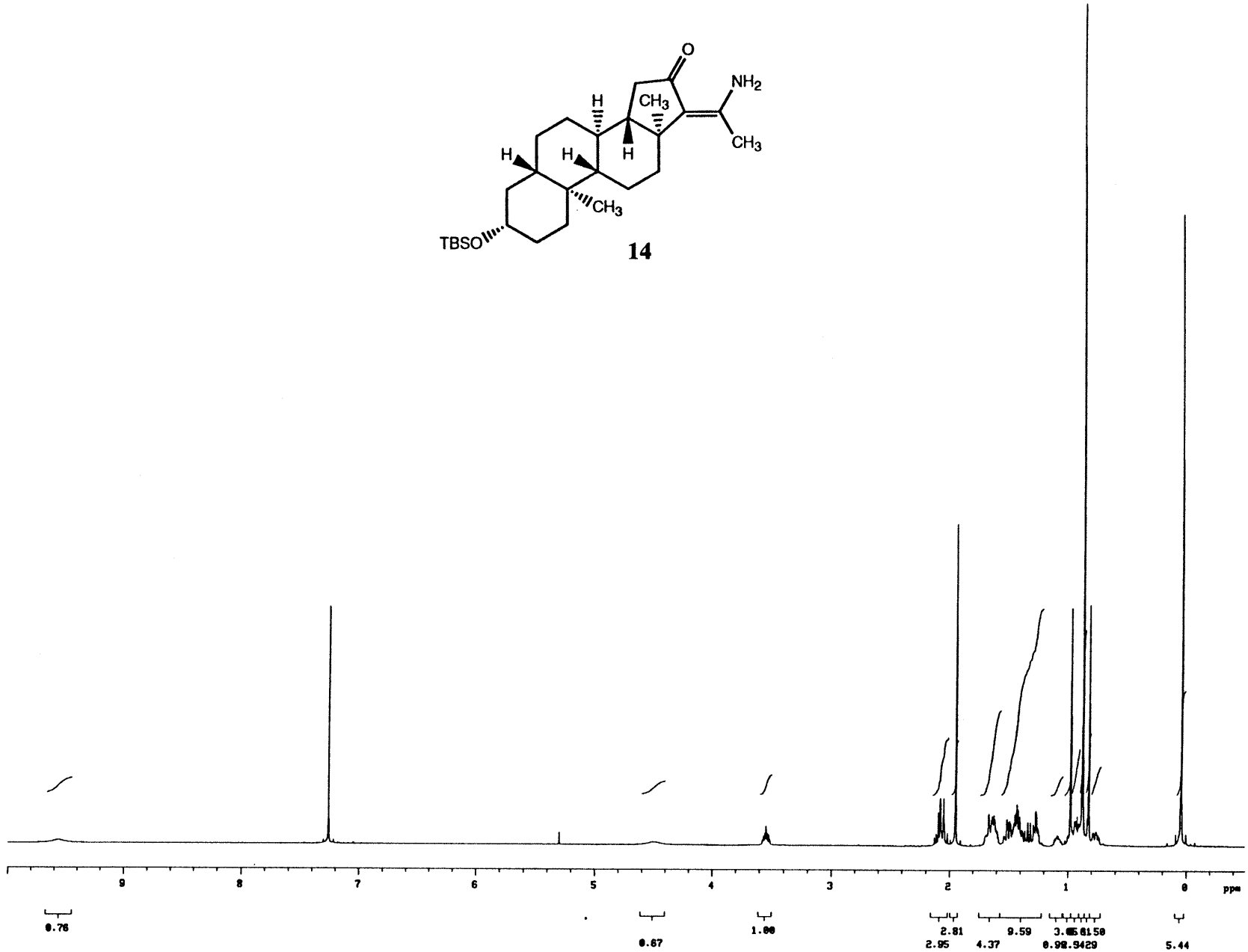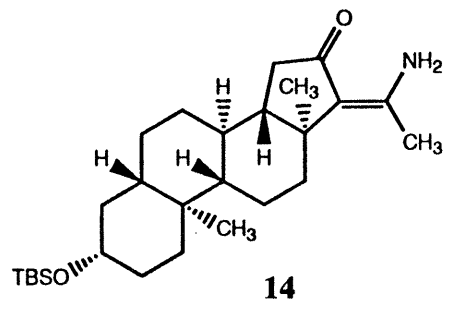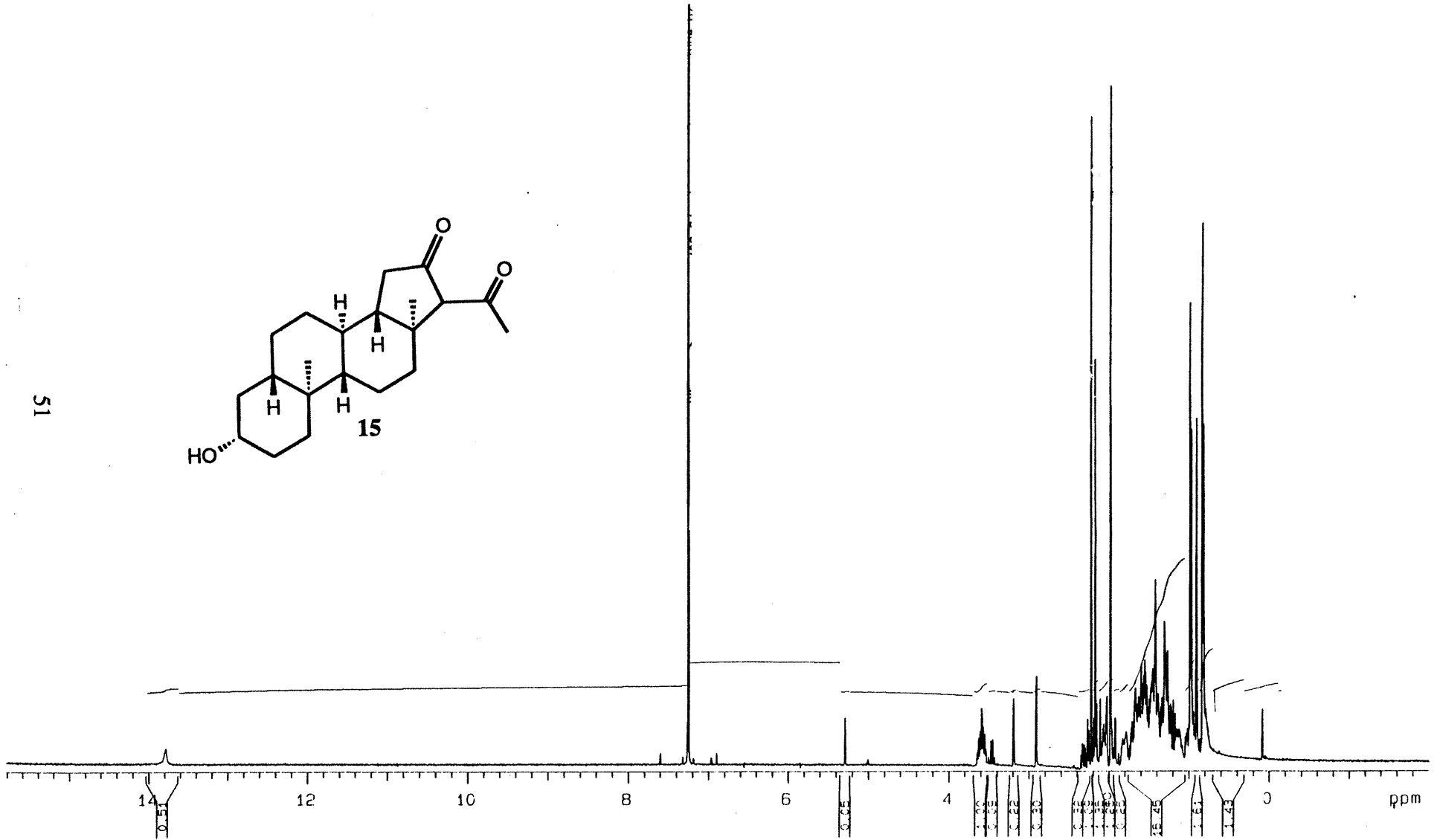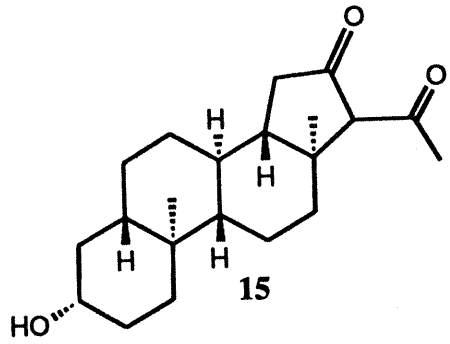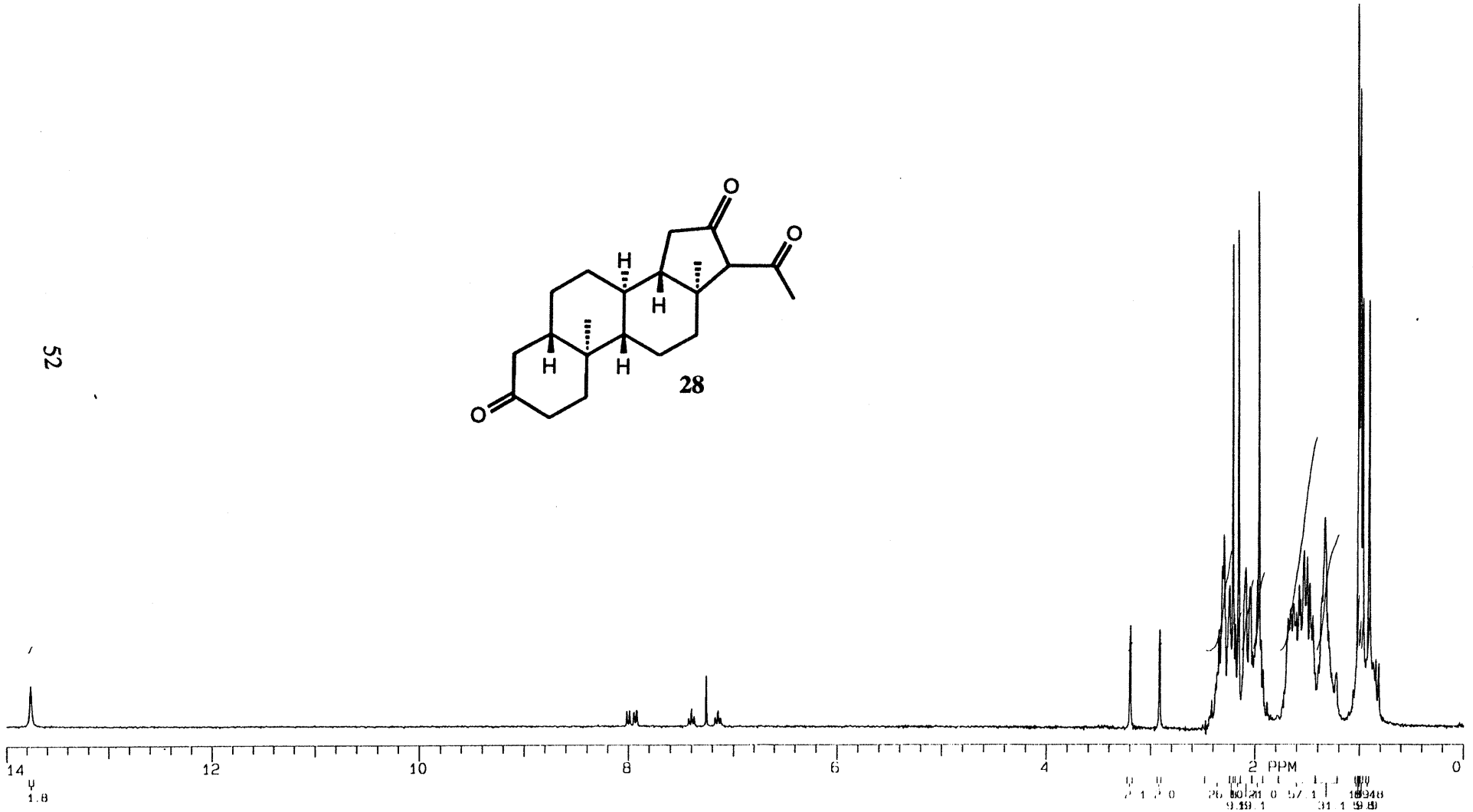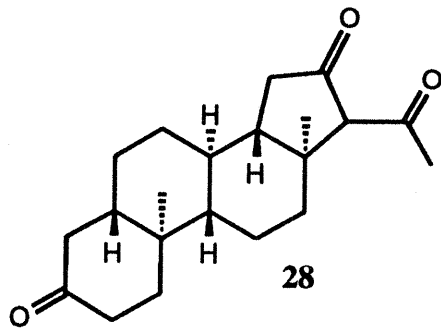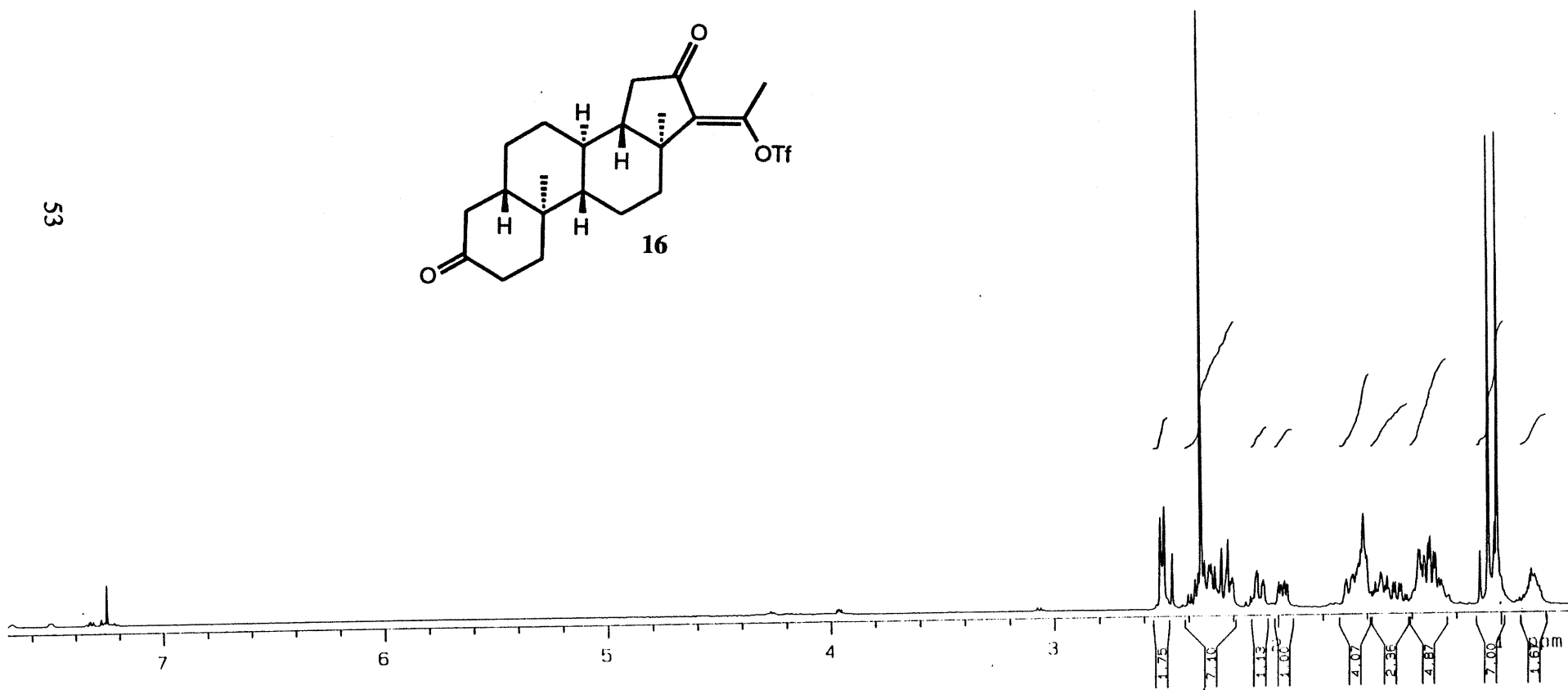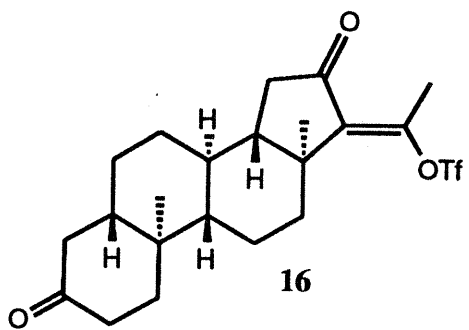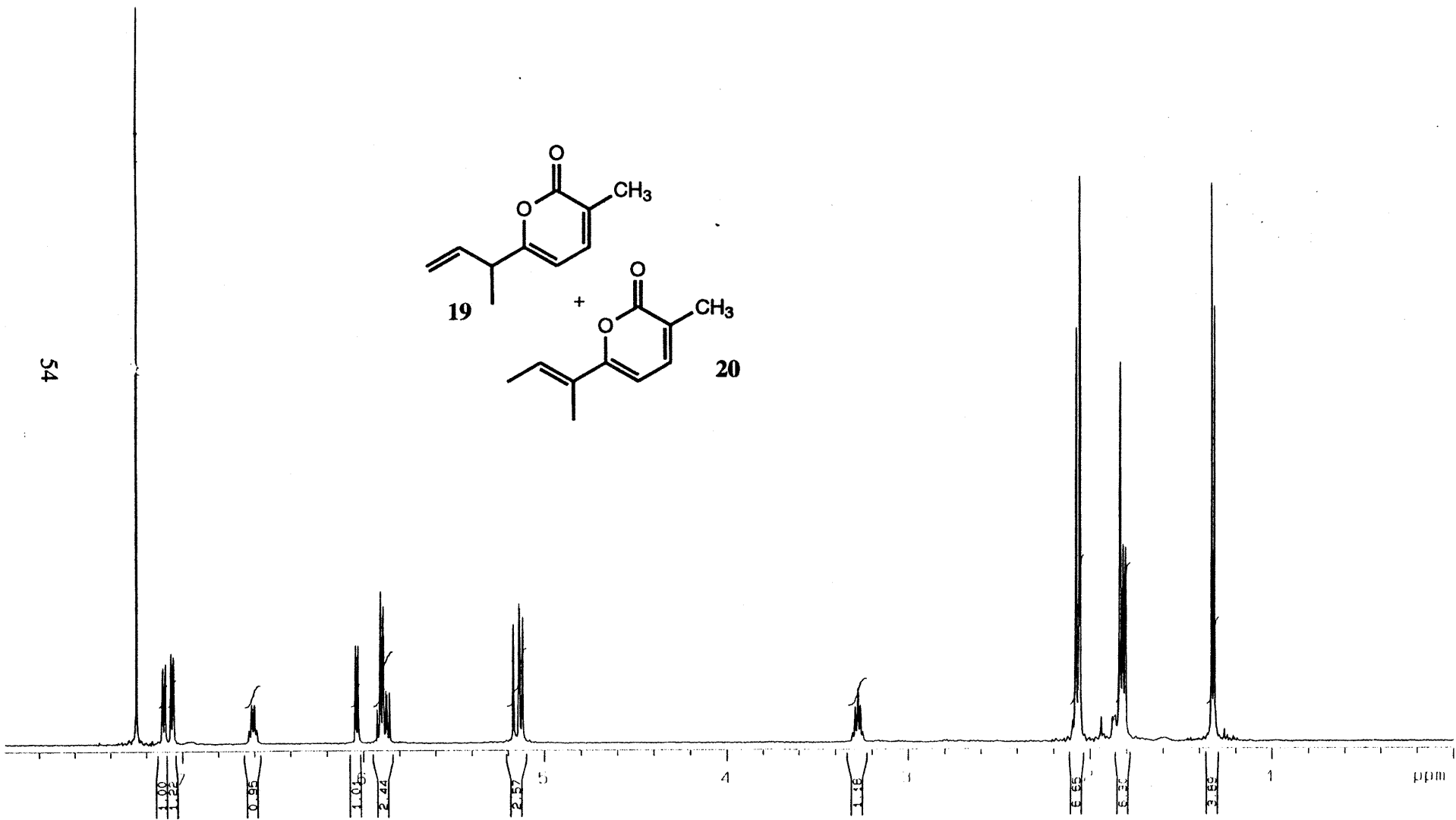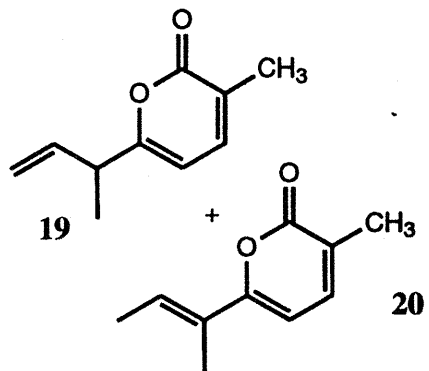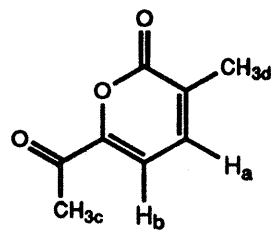
6

$J_{ab} = 6.8$ Hz
$J_{ad} = 1.3$ Hz
$J_{ba} = 6.8$ Hz
$J_{da} = 1.3$ Hz

TMS—≡—P(OMe)₂

$$\text{TMS}-\!\!\equiv\!\!-\overset{\overset{\textstyle O}{\|}}{P}(OMe)_2$$

29

TMS
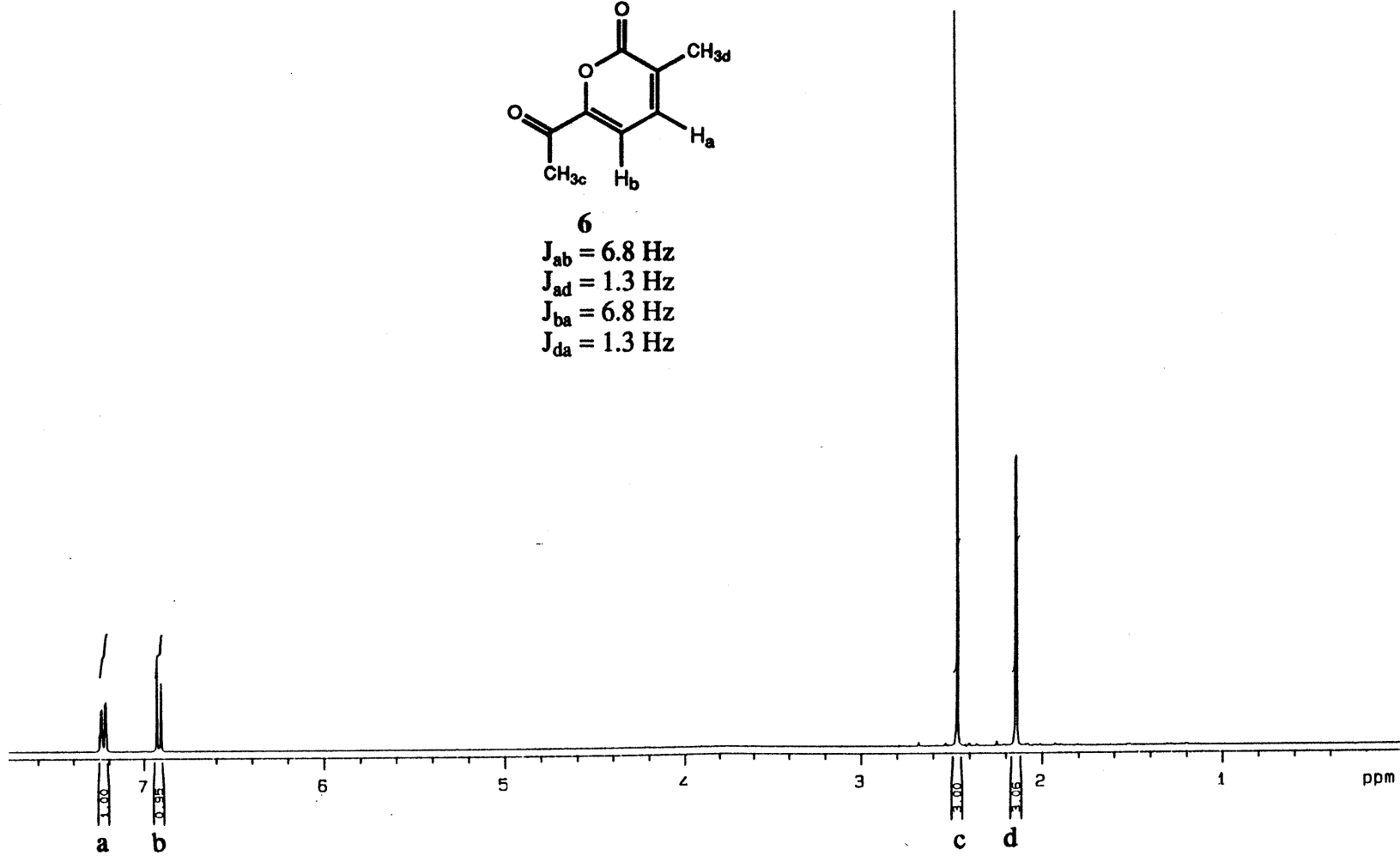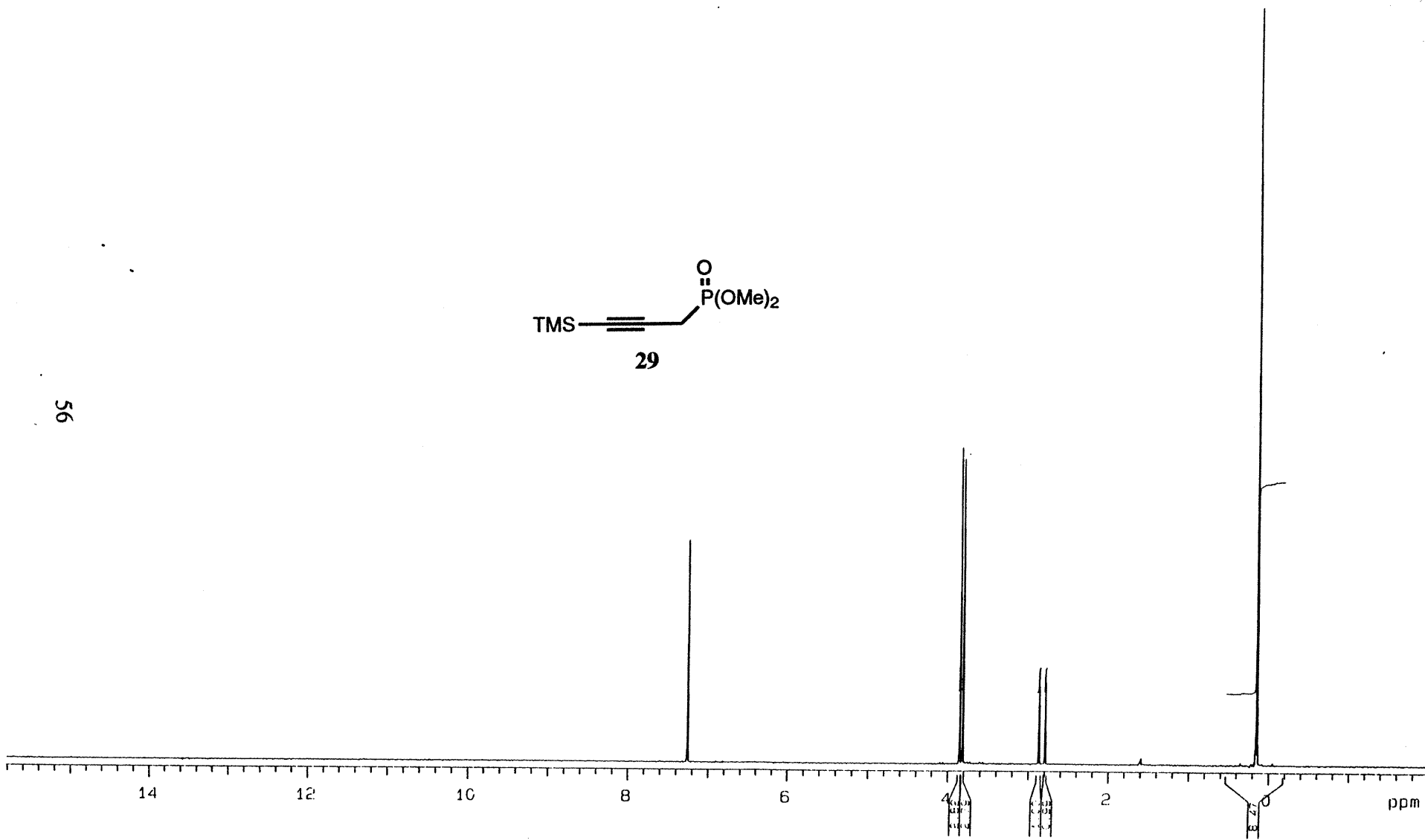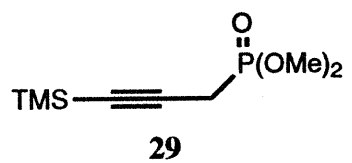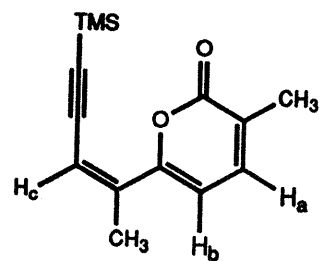
cis-26A

$J_{ab} = 6.8$ Hz
$J_{aMe} = 1.0$ Hz
$J_{ba} = 6.8$ Hz
$J_{cMe} = 1.0$ Hz
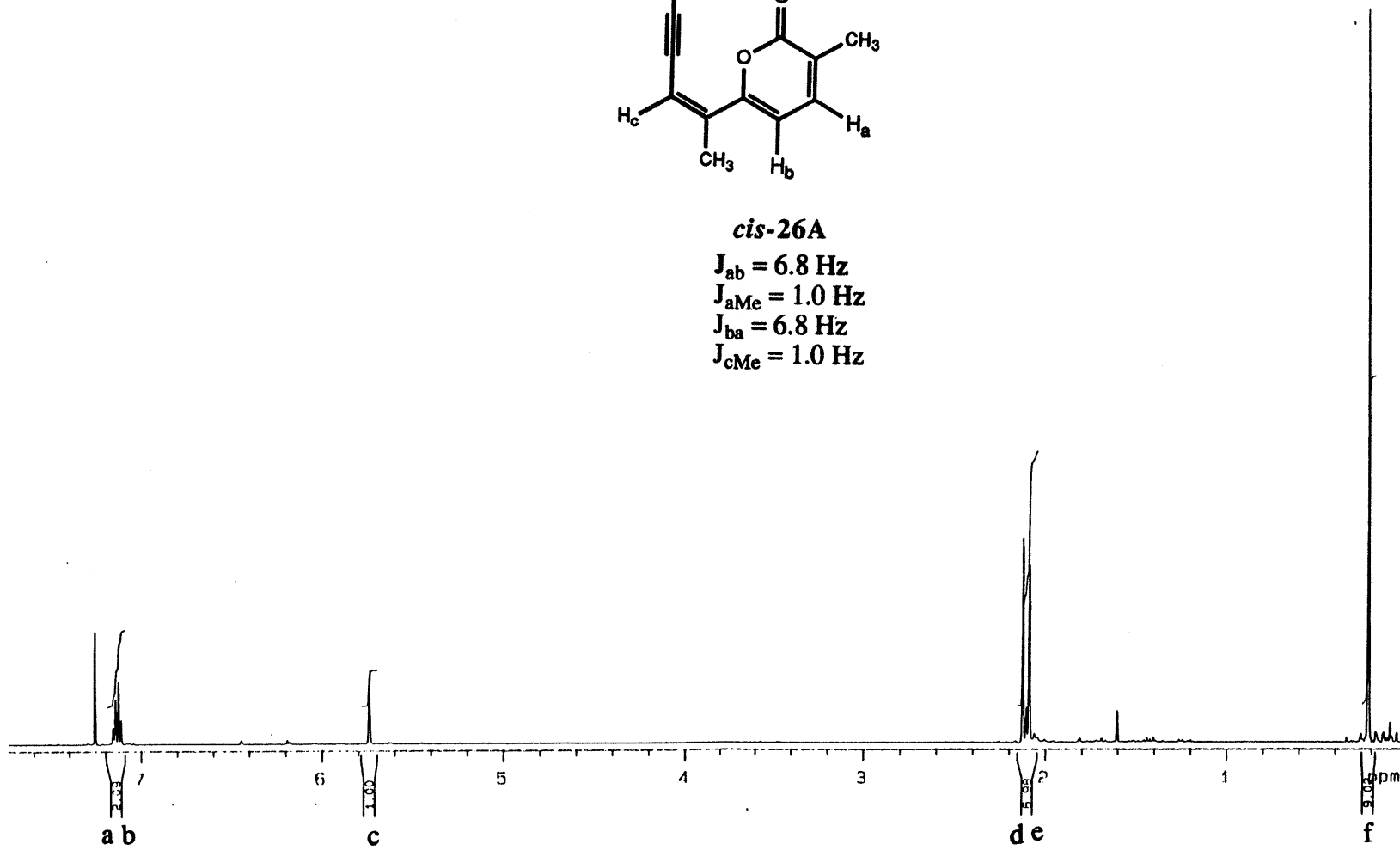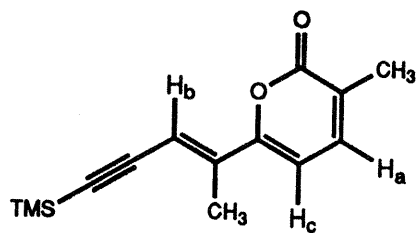
trans-26B

J_{ac} = 6.8 Hz
J_{aMe} = 1.0 Hz
J_{ca} = 6.8 Hz
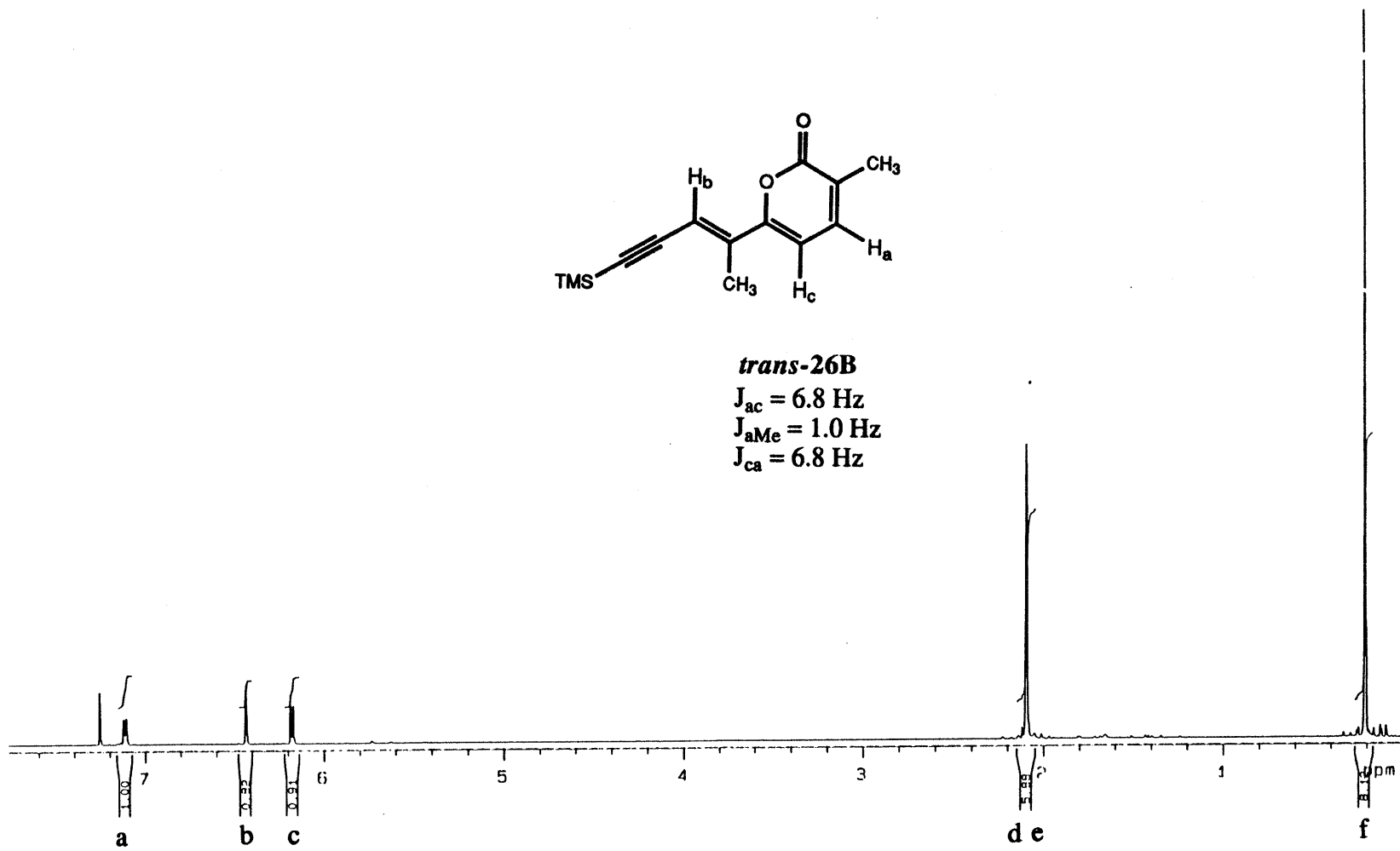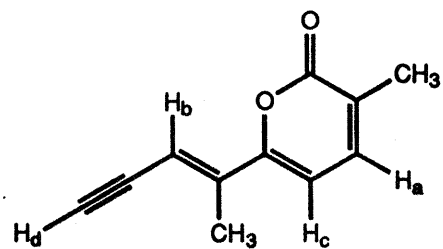
5

$J_{ac} = 6.8$ Hz
$J_{aMe} = 1.0$ Hz
$J_{ca} = 6.8$ Hz
$J_{db} = 2.4$ Hz

10