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Efforts Toward the Total Syntheses of Phorbol and CP-225917

by
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B.S. Chemistry
Furman University, 1992

Submitted to the Department of Chemistry in
Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy in Chemistry

at the

Massachusetts Institute of Technology

September 1997

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ABSTRACT

The total synthesis of complex natural products is a challenging and sometimes rewarding assignment. Progress in the routes to phorbol, a diterpene tumor promoter of the tigliane class, and CP-225,917, a potent inhibitor of the enzymes squalene synthase and farnesyl protein transferase, is presented. Both products have highly oxygenated polycyclic frameworks which offer formidable tasks to the synthetic chemist as well as an opportunity to present elegant solutions. Both projects have evolved as newer and better strategies were developed to account for problems encountered while conducting the research. Future prospects in each synthesis is also discussed.

Thesis Supervisor: Scott C. Virgil

Title: Assistant Professor of Chemistry

Acknowledgments

I wish to begin by thanking my thesis advisor Professor Scott C. Virgil for his guidance and support throughout my tenure at MIT. He has allowed me the freedom to pursue my own interests within the boundaries of the projects to which I have been assigned. With his unbridled enthusiasm for and extremely deep knowledge of the art of organic chemistry, he has led me through some difficult periods in my professional development.

The other members of the Virgil group have served as examples of how to have a life outside of chemistry, yet still strive to achieve their best in the day-to-day drudgery which is graduate school. In particular, I wish to thank Dan Allen, Paige Mahaney, Ed Licitra, Edcon Chang, and Becky Carazza for their support and concern for my well-being. To Justin Miller, I can only offer my wishes for a swift completion of the task at hand.

I am indebted to Evan Powers, Bill Kobertz, David Wang, Matt Bogyo, Martha Rook, and Ben Turk for the many years of friendship and understanding which they have provided. The lunches we have shared have served as pleasant exchanges of ideas about chemistry, volleyball, and life. Without you, I doubt that I would have made it this far.

My parents have always been a bastion of support for most of my decisions, and though I may not show it, I am very proud to be your son.

My wife Theresa, without whom I would definitely not be the person I am today, deserves special thanks for putting up with my many varied moods during these past five years. You are the main reason this has made any sense.

I would be remiss if I neglected to mention other members of the department who have aided in my graduate career. The members of the Kemp and Danheiser groups - specifically Linda Shimizu, Mike Lawlor, and Rob Niger - have been tireless sounding boards with whom I have shared much. I thank you all.

Finally, I wish to thank Merck & Co., the David and Lucile Packard Foundation, the Henry and Camille Dreyfus Foundation, and the Department of Chemistry for their financial support of my education and the research presented in this thesis.

For Theresa

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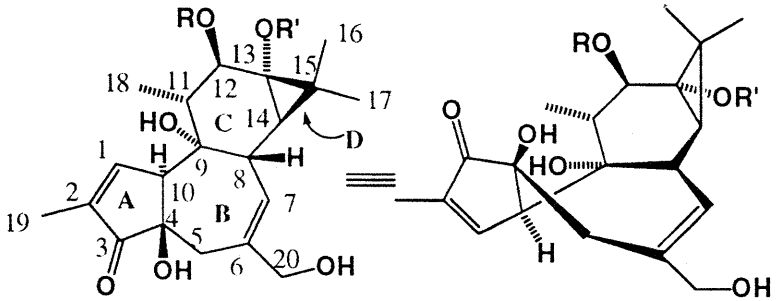
Part I: Efforts Toward the Total Synthesis of Phorbol

Chapter 1 - Introduction

When choosing natural products as targets for total syntheses, it is not only important to choose a complex structure which demonstrates biological activity, but also to establish a strategy which, through its novelty, will serve to edify both the researcher and the chemical community. Phorbol (**1b**) satisfies the first requirement wholly. As shown in Figure 1, below, the highly oxygenated core is just the initial challenge to the synthetic chemist, but the most daunting aspect has to be the *trans* ring junctures between both the AB and the BC rings. The cyclopropyl D ring offers its own challenges, not only in its construction, but also in its maintenance. Our strategies, which will be outlined later, fulfill the second requirement.



1a R=$CO(CH_2)_{12}CH_3$, R'=Ac
1b R=R'=H

Figure 1

1.1 Historical Background

Chemical carcinogenesis is a complex multistage process which often is effected through the action of a carcinogenic agent binding covalently to cellular DNA. Some chemicals, although not in themselves carcinogenic, act to accelerate tumor formation after repeated exposure following a low or insufficient dosage of a carcinogen. Such compounds are defined as tumor promoters, and their exact roles in carcinogenesis have been the subject of extensive studies.

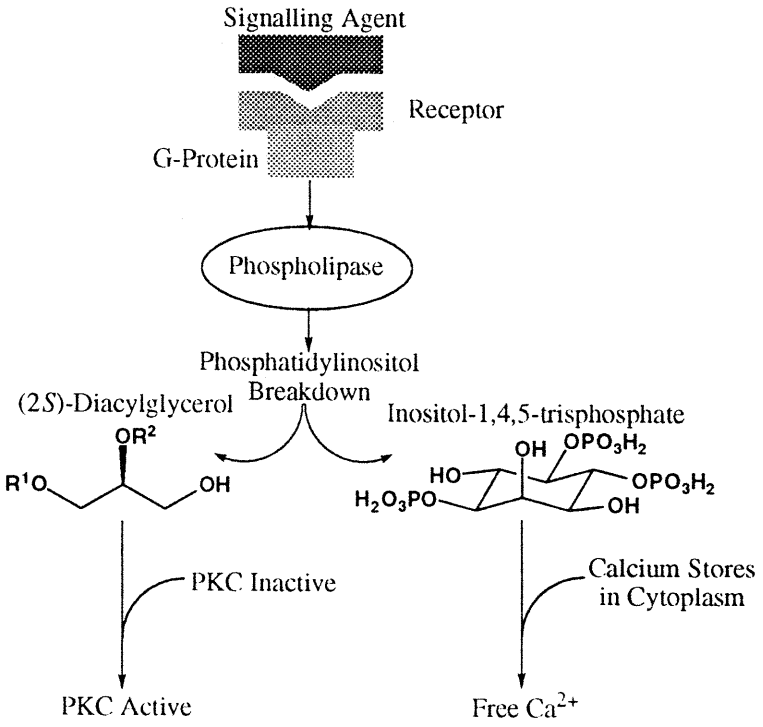


Figure 2: The Signal Transduction Pathway Leading to Protein Kinase C activation and Calcium Ion Mobilization

Many tumor promoters are known to interact with certain receptors found on cellular membranes.[1] The diterpene ester 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (**1a**), which is isolated from the seeds of the plant *Croton tiglium* and other members of the *Euphorbicae* family, is an example of a tumor promoter which binds to and activates

[1] Weinstein, I. B.; Gattoni-Celli, S.; Kirschmeier, P.; Lambert, M.; Hsiao, W.; Backer, J.; Jeffrey, A. "Molecular Mechanisms in Multistage Chemical Carcinogenesis" in *Biochemical Basis of Chemical Carcinogenesis* Greim, H.; Jung, R.; Kramer, M.; Marquardt, H.; Oesch, F. Eds. Raven Press: New York, 1984, pp 193-212.

phospholipid-dependent, Ca^{2+}-sensitive protein kinase C (PKC).[2] In order to better understand the implications of the action of **1a** on PKC, first a brief explanation of the signal transduciton pathway and the role of PKC in cell growth and differentiation is required.

Signal transduction by receptor mediated hydrolysis of phosphatidylinositol-4,5-bisphosphate (Figure 2) is accomplished by activation of specific receptors by hormones or other intercellular signaling agents which causes activation of a guanosine triphosphate (GTP) binding protein (G-protein). The activation of the G-protein results in activation of phospholipases within the plasma membrane, which, in turn, hydrolyze the glycerophosphate bond of phosphatidylinositol-4,5-bisphosphate to release 1,2-*sn*-diacylglycerol and inositol-1,4,5-trisphosphate. The latter of the two products is water soluble and acts to release calcium cations from stores in the endoplasmic reticulum.[3] Protein kinase C, which was first discovered in 1977, is a proteolytically activated protein kinase found in many tissues and organs. It requires both a calcium cation and a phospholipid, particularly phosphatidyl serine, for its activation. 1,2-Diacylglycerol, from the above hydrolysis, significantly increases the affinity of PKC for Ca^{2+} and makes it fully active without increasing the concentration of calcium cation.[3,4]

Both the inositol-1,4,5-trisphosphate and the diacylglycerol are short lived, which limits the immediate results from both pathways. Much of the calcium which is released in response to the inositol-1,4,5-trisphosphate is reabsorbed into its stores, and the diacylglycerol which activates PKC is quickly metabolized by either diacylglycerol kinase or diacylglycerol lipase. However, the long-term effects of the extracellular signal are just beginning.

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[2] Castagna, M.; Takai, Y.; Kaibuchi, K.; Sano, K.; Kikkawa, U.; Nishizuka, Y. *J. Biol. Chem.* **1982**, *257*, 7847-7851.
[3] Zeisel, S. H. *Adv. Exp. Med. Biol.* **1995**, *369 (Nutrition and Biotechnology in Heart Disease and Cancer)*, 175-183.
[4] Nishizuka, Y. *Science* **1986**, *233*, 305-312.

One major function of protein kinase C appears to be phosphorylation of a wide variety of substrate proteins, including receptor proteins and cytoskeletal proteins. Other target proteins for phosphorylation activate many cellular functions and control cell proliferation. Another crucial function of PKC is intimately related with negative feedback control of cell surface receptors, termed down-regulation.[4] It should be noted here that this signal transduction pathway is only one of many such systems active within cellular membranes.

TPA (**1a**) has been shown to have the same effect on PKC as diacylglycerol; however, unlike diacylglycerol, its complex is not short-lived. The prolonged activation of PKC causes the protein phosphorylation to proceed unregulated and diminishes intercellular communication by blocking down-regulation. Both processes have been associated with increased susceptibility to carcinogenesis.[5] Bell and Burns[6] later demonstrated that there are two binding sites for phorbol esters on PKC. Although the target of **1a** has been well established as PKC[7], there has been much discussion as to which part of the molecule is the active pharmacophore.

Beginning in 1979, Smythies[8] postulated that the tetradecanoyl side chain at O12 was responsible for association into the phospholipid membrane; however, he also postulated that the target for **1a** was phospholipase A_2. Since phorbol (**1b**) was determined to have virtually none of the activity of **1a**, Smythies claim was generally accepted. When it was shown that **1a** had a similar effect on PKC that 1,2-*sn*-diacylglycerol, where at least one of the acyl groups was a long chain fatty acid[6b], the claim was further substantiated. To support this claim, spin-labeling experiments by Pecar *et al.*, and Svetek *et al.*[9] demonstrated that, indeed, the fatty acid residue at O12 did associate

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[5] a) Symington, B. E.; Symington, F. W.; Rohrschneider, L. R. *J. Biol. Chem.* **1989**, *264*, 13258-13266. b) Hu, J.; Engman, L.; Cotgreave, I. A. *Carcinogenesis* **1995**, *16*, 1815-1824.
[6] Burns, D. J.; Bell, R. M. *J. Biol. Chem.* **1991**, *266*, 18330-18338.
[7] a) Shoyab, M.; Boaze, R. *Arch. Biochem. Biophys.* **1984**, *234*, 197-205. b) Nishizuka, Y. *Nature (London)* **1984**, *308*, 693-698. And Reference 4.
[8] Smythies, J. R. *J. Theor. Biol.* **1979**, *81*, 401-405.
[9] a) Pecar, S.; Schara, M.; Nemec, M.; Hecker, E. *Carcinogenesis* **1992**, *13*, 205-209. b) Svetek, J.; Hergenhahn, M.; Schara, M., Pecar, S.; Hecker, E. *Carcinogenesis* **1992**, *13*, 211-216.

greatly with the phospholipids in the cellular membrane. However, Jeffrey *et al.*[10], and Wender *et al.*[11], through the use of molecular modeling techniques demonstrated that the region necessary for activation of PKC, also the region which mapped onto 1,2-*sn*-diacylglycerol, was not the hydrophobic region of C12 and C13, but the hydrophilic region which included the C3 carbonyl and the hydroxyls at C4, C9, and C20 (See Figure 3, below).

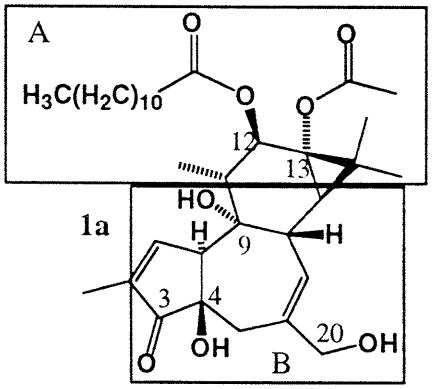
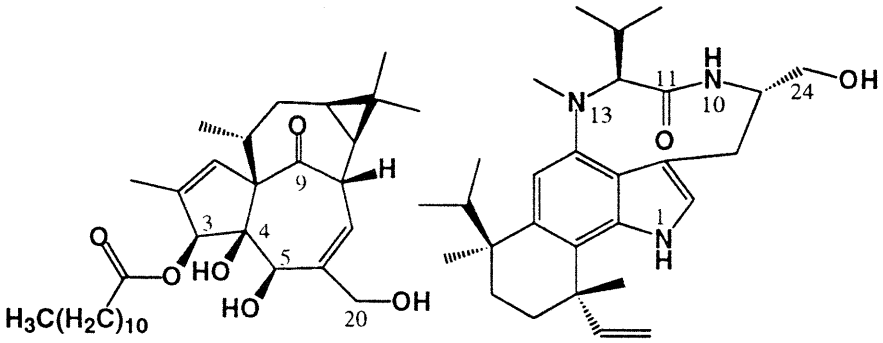


Figure 3: A is the Hydrophobic Region and B is the Hydrophilic.



2: Ingenol 3-tetradecanoate **3**: Teleocidin B

Figure 4

Both Wender and Jeffrey used the structurally similar ingenol 3-tetradecanoate (**2**) and the structurally dissimilar teleocidin B (**3**) tumor promoters (Figure 4) to substantiate their argument that the hydrophobic region present in **1a** was absent in both **2** and **3**, whereas

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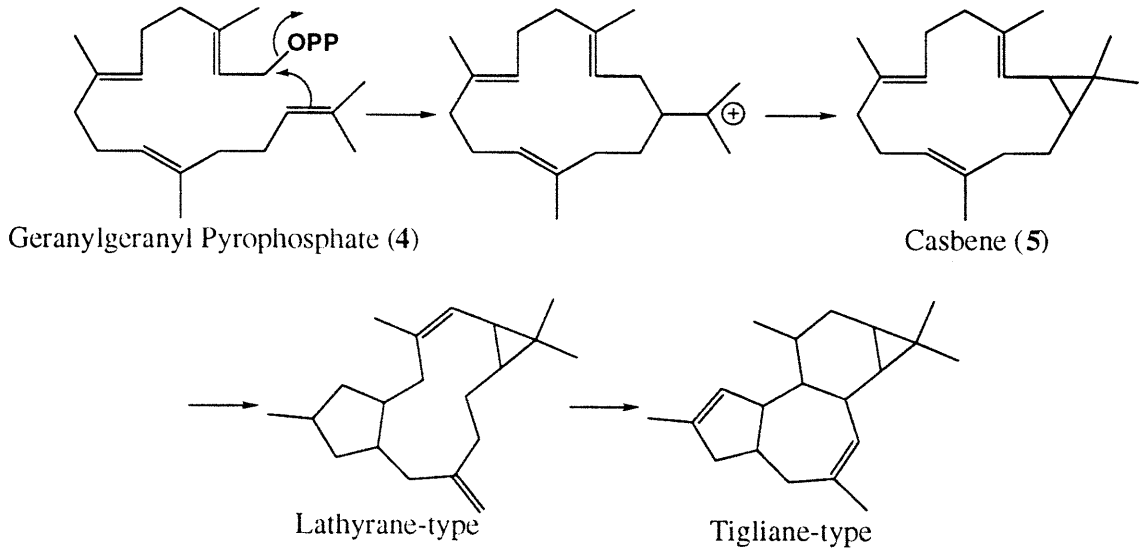
[10] Jeffrey, A. M.; Liskamp, R. M. J. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 241-245.
[11] Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 4214-4218.

all three structures had hydrophilic regions (denoted in Figure 4 by the numberings). Their claims were later substantiated by analysis of the conformations and electrostatic potential maps of **1a**, **2**, and **3**.[12] Recent analysis has also confirmed the results of Wender and Jeffrey, but it also demonstrates the necessity of the carboxyl group of the ester at O13.[13]

X-ray crystallographic analysis of the membrane bound complex of PKC and phorbol 13-acetate has demonstrated that the hydrophobic portion is necessary for intercalation of **1a** into the phospholipid membrane, but that the hydrophilic region is responsible for its interaction with PKC. In fact, the promoter binds in a groove between two strands of the protein, and caps a hydrophilic groove forming a continuous hydrophobic surface which allows for greater membrane association of PKC, resulting in its prolonged activation.[14]

1.2 Prior Synthetic Strategies

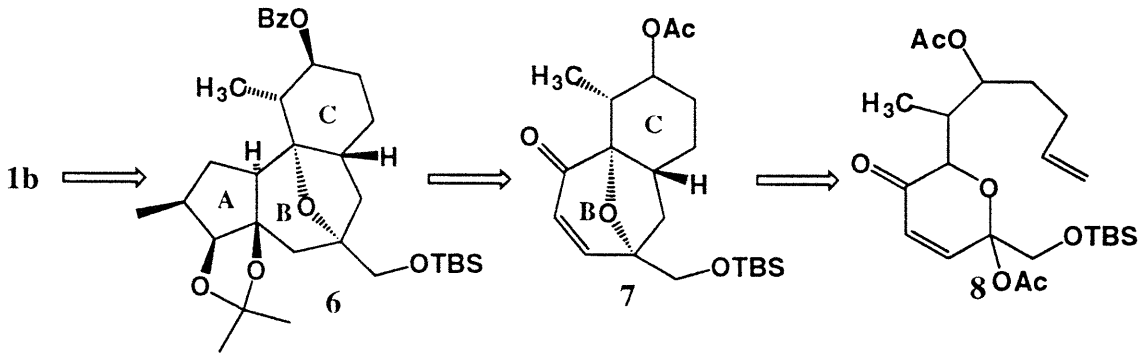


Scheme 1: Biosynthesis of the Tigliane Skeleton

[12] Thomson, C.; Wilkie, J. *Carcinogenesis* **1989**, *10*, 531-540.
[13] Krauter, G.; Von Der Lieth, C.-W.; Schmidt, R.; Hecker, E. *Eur. J. Biochem.* **1996**, *242*, 417-427.
[14] Zhang, G.; Kazanietz, M. G.; Blumberg, P. M.; Hurley, J. H. *Cell* **1995**, *81*, 917-924.

Phorbol (**1b**) is a diterpene natural product of the tigliane class which is biosynthetically derived from geranylgeranyl pyrophosphate (**4**). As shown in Scheme 1, cyclization of the C14 olefin to C1 after clevage of the carbon-oxygen bond affords a macrocyclic intermediate which further cyclizes to casbene (**5**), and further cyclizations afford the tigliane skeleton.[15]

Thus far the first and only total syntheses of **1b** have been accomplished by Wender and coworkers at Stanford University. The key retrosynthetic steps in their first synthesis are detailed in Scheme 2, below.



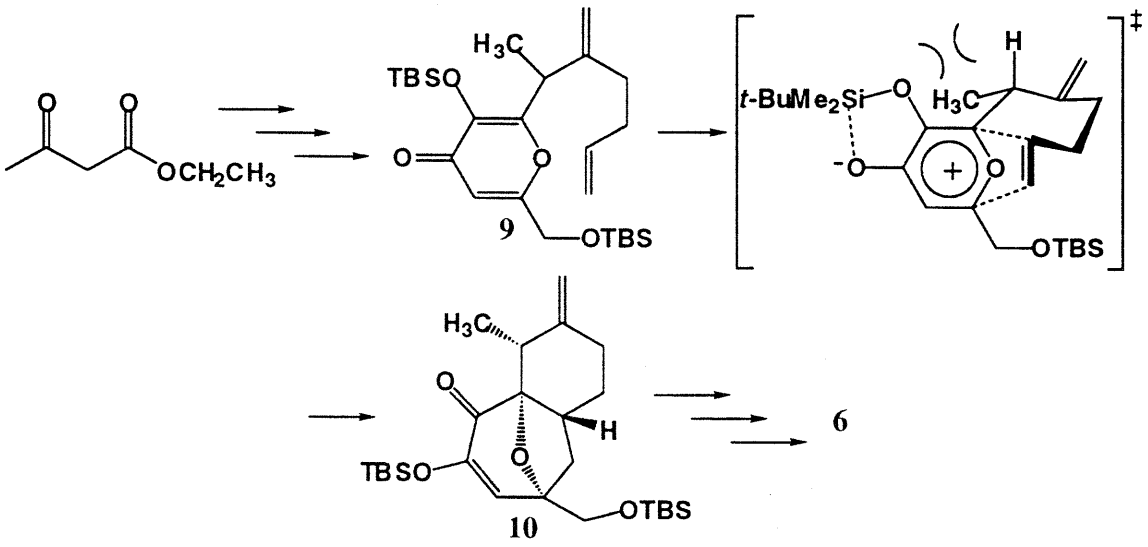
Scheme 2: Wender's Initial Retrosynthesis

Phorbol could be constructed from compound **6**, which incorporates the ABC ring system. Intermediate **6** arises through the annelation of the five membered A ring onto intermediate **7**, during which the C6-C9 oxygen bridge internally protects the hydroxyl at C9 and, conveniently, conformationally and facially biases the seven-membered B ring, which controls the generation of two new stereogenic centers at C10 and C4. Intermediate **7** is derived from **8** through an oxidopyrylium-alkene [6π+2π] cycloaddition. **8** is available in seven steps and 52% overall yield from furfuryl alcohol.[16] Wender's route to

[15] Crombie, L.; Kneen, G.; Pattenden, G.; Whybrow, D. *J. Chem. Soc. Perkin Trans. I* **1980**, 1711-1717.
[16] Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954-8957.

intermediate **6** is rather lengthy (24 steps), and the construction of **1b** is only partially complete.

A second generation synthesis of **6** based upon the oxidopyrylium-alkene [6π+2π] cycloaddition has been accomplished in 16 steps from ethyl acetoacetate through the intermediate **9** which undergoes the cycloaddition depicted in Scheme 3 to generate **10**.[17]



Scheme 3: Wender's Second-Generation Synthesis of Intermediate **6**

Conversion of **6** into **1b** has been accomplished in 28 steps through construction of the *gem*-dimethylcyclopropyl D ring and various functional group interconversions.[18] The overall number of steps in the first route is 52 and in the second is 44. Still a very long and arduous process. In a subsequent study of the oxidopyrylium-alkene [6π+2π] cycloaddition, Wender shows an improved synthesis, but to a much simpler intermediate than **6**.[19]

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[17] Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956-4958.
[18] Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D., Jr.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957-8958.
[19] Wender, P. A.; Mascareñas, J. L. *J. Org. Chem.* **1991**, *56*, 6267-6269.

Other groups have tried to make analogs to **1a** which have simplified structures in order to probe the possible biologically active substructure of the molecule[20] or to follow a possible biosynthetic pathway to natural products which have the daphnane skeleton (Figure 5)[21]. However, no one has undertaken an attempt either to improve upon Wender's routes or to offer a significantly different route.

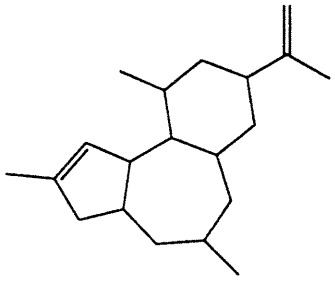


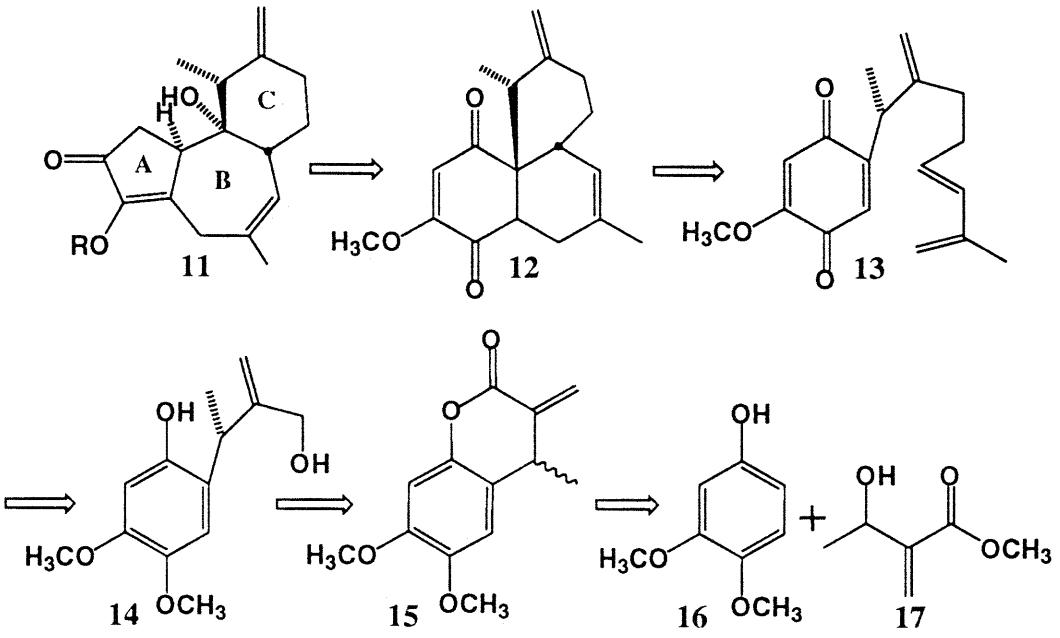
Figure 5: The Daphnane Skeleton

[20] Kerr, D. E.; Kissinger, L. F.; Shoyab, M. *J. Med. Chem.* **1990**, *33*, 1958-1962.
[21] Magar, S. S.; Dessi, R. C.; Fuchs, P. L. *J. Org. Chem.* **1992**, *57*, 5360-5369.

Chapter 2 - Initial Strategy for the ABC Skeleton

2.1 Retrosynthetic Analysis

Following the example of Wender, *et al.*[5a,c], the initial strategy was to accomplish the synthesis of the tricyclic ABC-ring core of **1b**. The target (**11**), although slightly less functionalized than Wender's intermediate (**6**), was to eventually be converted to phorbol using methodology similar to that of Wender and his group.

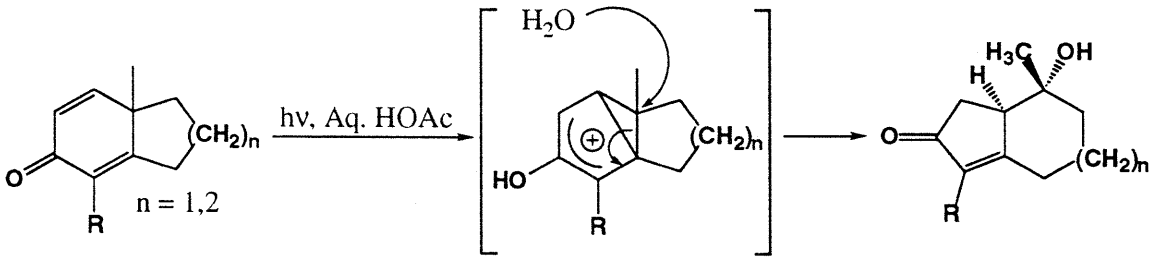


Scheme 4

The retrosynthetic analysis for **11** is shown in Scheme 4. The first disconnective transformation involves an acid catalyzed photochemical rearrangement similar to what is observed with santonin and related synthetic molecules (Scheme 5)[22]. Some simplifying

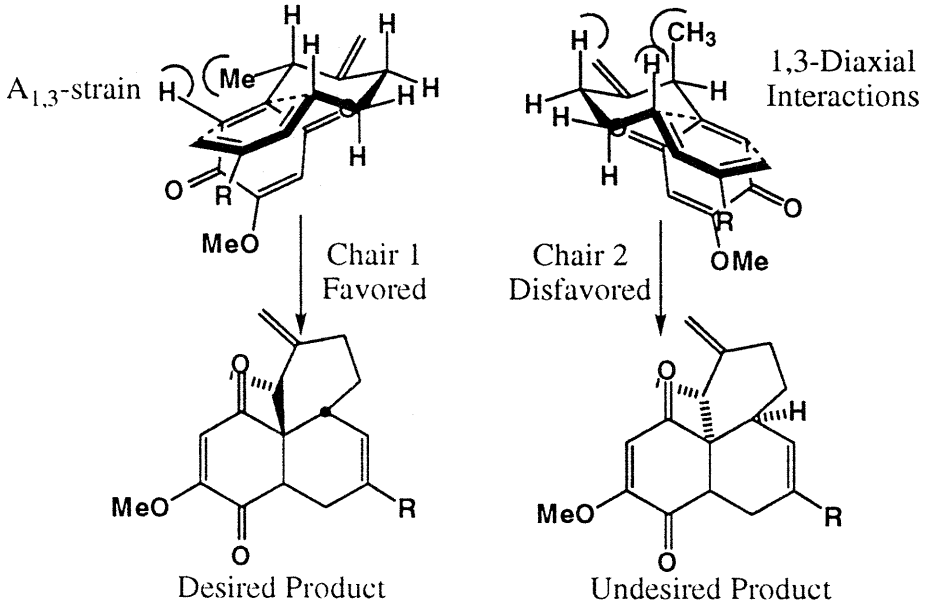
[22] a) Caine, D.; Dawson, J. B. *J. Org. Chem.* **1964**, *29*, 3108-3110. b) Kropp, P. J. *J. Org. Chem.* **1964**, *29*, 3110-3111. c) Caine, D.; Tuller, F. N. *J. Org. Chem.* **1973**, *38*, 3663-3670.

functional group interchanges arrive at **12** which is the product of an intramolecular Diels-Alder cycloaddition transformation.



Scheme 5: Acid Catalyzed Photochemical Rearrangement

An analysis of the Diels-Alder reaction of **13** using molecular models suggests two possible chair-like transition states (Scheme 6).

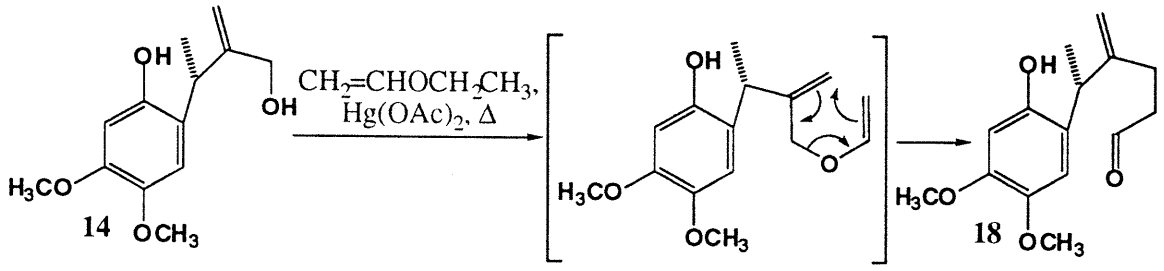


Scheme 6

Although the two conformers differ only slightly in energy, Chair 2 is less favorable due to 1,4 diaxial interactions between the methyl group and the indicated hydrogens. Thus, Chair 1, which leads to the desired product (**12**), is the preferred conformation for the

Diels-Alder reaction despite the allylic ($A_{1,3}$) strain between the methyl group and the indicated hydrogen.

Compound **13** could be derived from an olefination with the ylide of 2-methyl-2-propenyl-triphenylphosphonium bromide on aldehyde (**18**) which results from the spontaneous Claisen rearrangement of the transetherification reaction shown in Scheme 7 between the allylic alcohol moiety of **14** and ethyl vinyl ether, catalyzed by mercury(II) acetate.[23]



Scheme 7

The diol **14** is to be the result of a 1,2-reduction of the exo-methylene coumarin **15**, which is the product of a Claisen rearrangement from an allyl aryl ether constructed by the allylic displacement of the acetate derivative of **17** by the sodium salt of 3,4-dimethoxyphenol (**16**). β-Hydroxy-α-methylene ester **17** is derived from methyl acrylate and acetaldehyde by a Baylis-Hillman reaction[24]

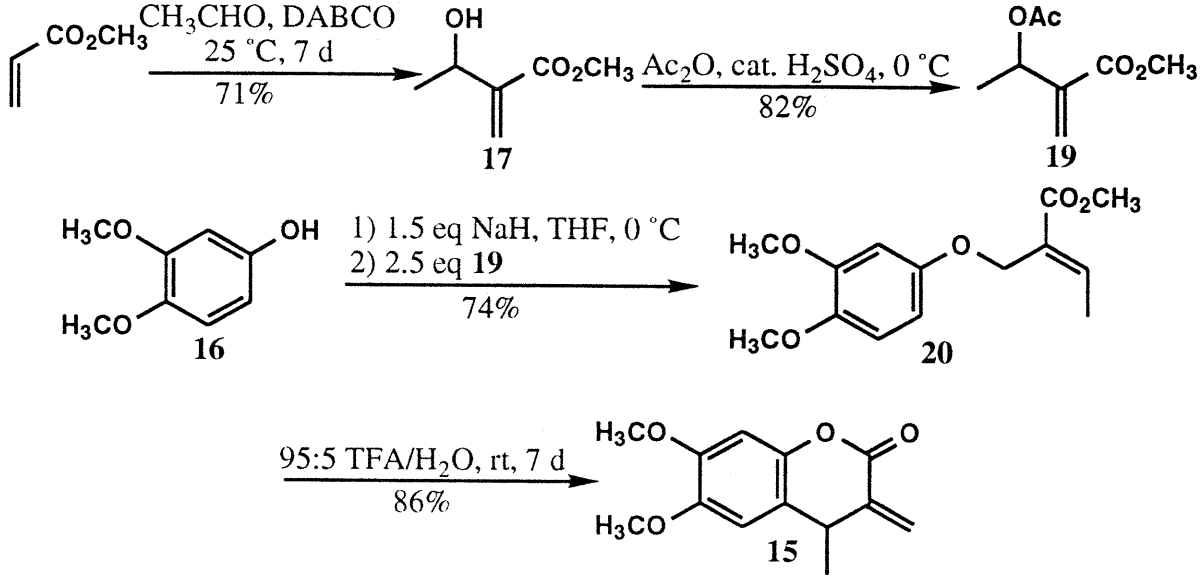
2.2 Forward Progress

The progress which has been achieved in the synthetic strategy outlined above is shown in Scheme 8, below.

---

[23] Büchi, G.; White, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2884-2887.
[24] a) Hoffman, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795-796. b) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151-2161.

The first reaction, which was alluded to in the previous section as the Baylis-Hillman reaction, is a condensation between methyl acrylate and acetaldehyde catalyzed by



Scheme 8

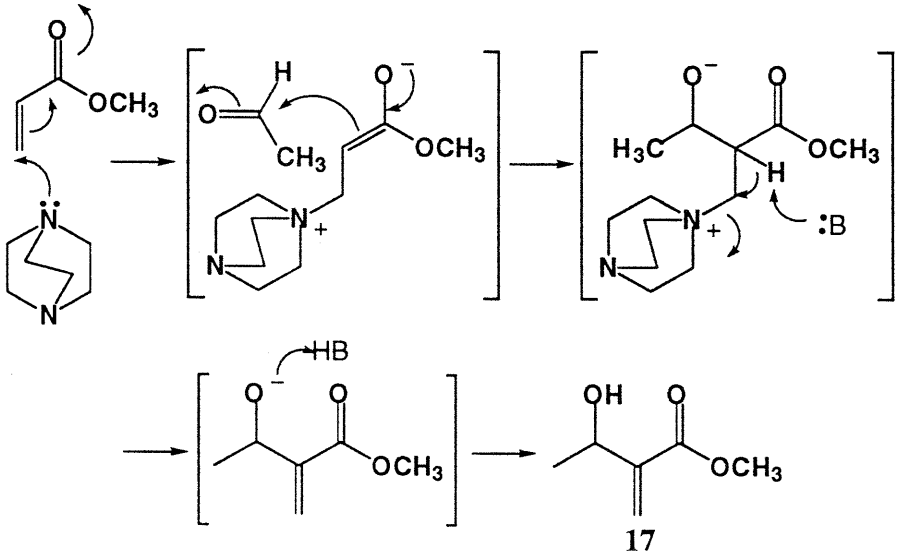
the tertiary amine diazabicyclo[2.2.2]octane (DABCO). The mechanism of the reaction has been elucidated by Hoffman and Rabe[24a] is shown in Scheme 9. The tertiary amine adds to the β position of the ester forming an enolate zwitterion intermediate. A typical aldol condensation occurs between the enolate and acetaldehyde generating the second intermediate, which undergoes an elimination of the amine and a proton transfer to generate the product **17**.

Formation of acetate **19** using standard nucleophilic techniques (4-(*N,N*-dimethyl-amino)pyridine, pyridine, acetic anhydride) was complicated through a subsequent elimination of the acetate, which generated diene **21**. This diene underwent a spontaneous Diels-Alder dimerization reaction to afford the dimethyl ester of mikanecic acid[25] (**22**)

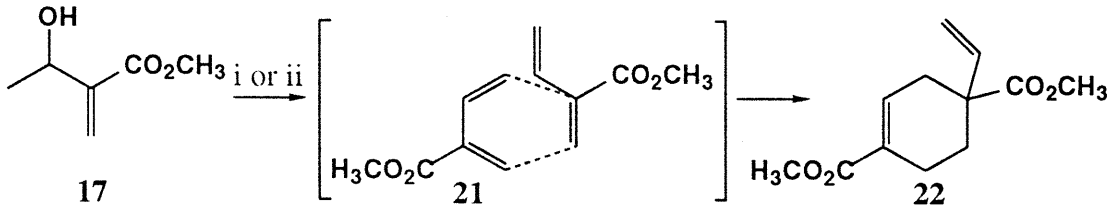
---

[25] Mikanecic Acid has been the target of a few prior syntheses. See a) Sydnes, L. K.; Skattebøl, L.; Chapelo, C. B.; Leppard, D. G.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chem. Acta.* **1975**, *58*, 2061-2073; b) Goldberg, O.; Dreiding, A. S. *Helv. Chem. Acta* **1976**, *59*, 1904-1910; and c) Hoffman, H. M. R.; Rabe, J. *Helv. Chem. Acta.* **1984**, *67*, 413-415.

(Scheme 10). Although this resulted in a two-step synthesis of **22**, it was of no use in our current synthetic plan.



Scheme 9



i) Ac_2O, Pyridine, cat. DMAP, 25 °C, 86%. ii) Ac_2O, Pyridine, 25 °C, 54%

Scheme 10

While the problems with the acetylation of **17** were occurring, it was decided that an alternate route to **20** was necessary. Toward that end, allylic bromide **23** (Scheme 11) was synthesized using a procedure described by Roush and Brown in their synthetic studies toward kijanolide[24b]. Even though the procedure worked in good yield, the result of the attempted condensation with **16** was less than optimal. Finally, the conditions for the formation of **19** using acetic anhydride and a catalytic amount of concentrated sulfuric acid[26] were found.

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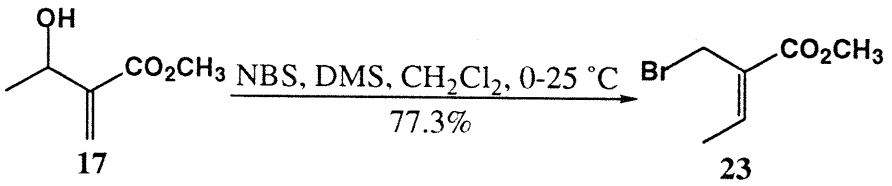
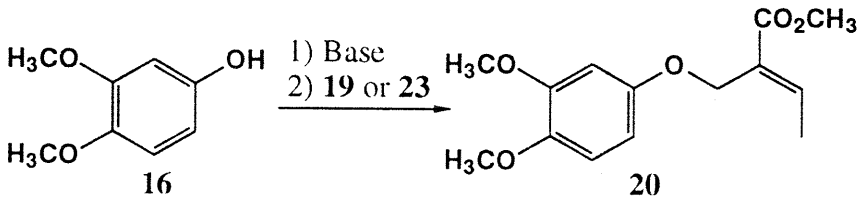
[26] Drewes, S. E.; Emslie, N. D. *J. Chem. Soc. Perkin Trans. I* **1982**, 2079-2083.



17 23

Scheme 11

Many conditions were tried for the assembly of **20**, the results shown in Table 1 demonstrated only a few of the attempts which yielded any product. Acetone and *N, N*-dimethylformamide were also used as solvents; however, no detectable amount of product was formed. In another attempt to synthesize **20**, 10 mole percent of $Pd(PPh_3)_4$ was used as a catalyst for the displacement of the acetoxy group by the phenoxide generated by deprotonation of the phenol with sodium hydride; however, only the undesired regioisomer was produced. Also, attempts to react **16** and **17** directly using Mitsunobu conditions (DEAD, PPh_3 or *n*-Bu_3P, Et_2O, -25° C)[27] were unsuccessful.



16 20

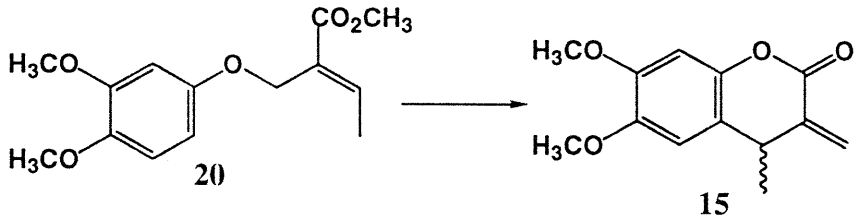
Run	Substrate	Base	Solvent	% Yield
1	**22**	NaH	Et_2O	5
2	**22**	NaH	CH_3OH	28
3	**19**	Cs_2CO_3	THF	0
4	**19**	n-BuLi	THF	22
5	**19**	NaH	THF	74

Table 1: Reaction Conditions Used to Generate **20**

[27] Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891-3898.

After the above studies, it became necessary to find an inexpensive method for generating **16**. Although it is commercially available, its cost ($99.60/10g[28]) was rather high for the amount of material needed. A procedure to make **16** from veratraldehyde (3,4-dimethoxy-benzaldehyde) and 3-chloroperoxybenzoic acid followed by treatment with aqueous sodium hydroxide[29] was utilized which was very cost effective.

With the allyl aryl ether in hand, the next task was accomplishing the Claisen rearrangement to form **15**. Catalysis by a variety of Lewis acids which were reported to effect the rearrangement on similar compounds were attempted.[30] However, the yields for the reactions were discouragingly low (see Table 2 for conditions). The best yield was obtained using trifluoroacetic acid[31] (a Brønsted acid).



Run	Acid	Solvent	Temp (° C)	Yield
1	$AlCl_3$	CH_2Cl_2	40	48%
2	BCl_3	CH_2Cl_2	-40-0	2%
3	Et_2AlCl	CH_2Cl_2	25	NR
4	CF_3CO_2H	19:1 TFA:H_2O	25	86%

Table 2

The low yields for the Lewis acid catalyzed Claisen rearrangements were especially disappointing since it was hoped that a chirally modified Lewis acid would facilitate a stereoselective rearrangement to the lactone which had its stereogenic center in the *R*

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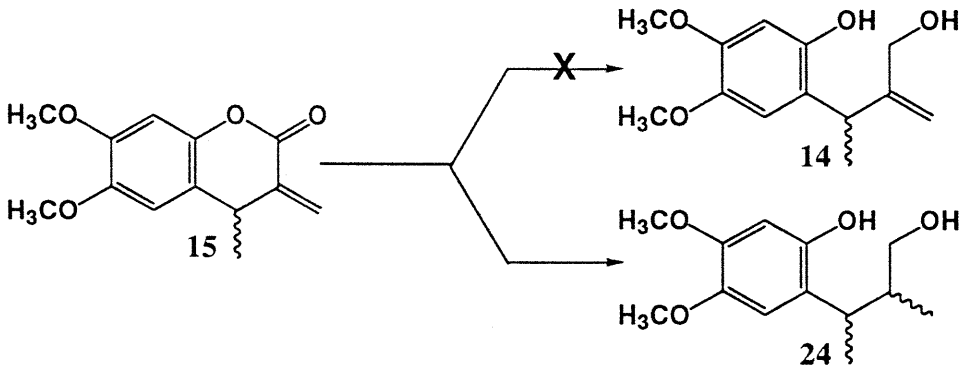
[28] *Catalog Handbook of Fine Chemicals 1996-1997*, Aldrich Chemical: Milwaukee, 1996; p 562.
[29] Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc. Perkin. Trans. I* **1974**, 1353-1354.
[30] a) Sunitha, K.; Balasubramanian, K. K.; Rajagopalan; K. *Tetrahedron Lett.* **1984**, *25*, 3125-3126. b) Fahrni, P.; Habich, A.; Schmid, H. *Helv. Chim. Acta* **1960**, *43*, 448-452. c) Sonnenberg, F. M *J. Org. Chem.* **1970**, *35*, 3166-3167.
[31] a) Svanholm, U.; Parker, V. D. *J. Chem. Soc. Chem. Commun.* **1972**, 645-647. b) Svanholm, U.; Parker, V. D. *J. Chem. Soc. Perkin Trans. II* **1974**, 169-173.

configuration. The success of the trifluoroacetic acid catalyzed rearrangement to the racemic mixture of lactones (**15**) necessitates a chiral resolution step later in the synthesis.

2.3 Strategic Limitations

The resolution of the different enantiomers of **15** from the acid catalyzed Claisen rearrangement proved to be just the tip of the iceberg of the problems with this synthetic route. Many of the problems, up to this point, were overcome through persistence and a thorough study of the relevant literature. The next obstacle would prove to be the Achilles' Heel for our first route to phorbol.



Scheme 12

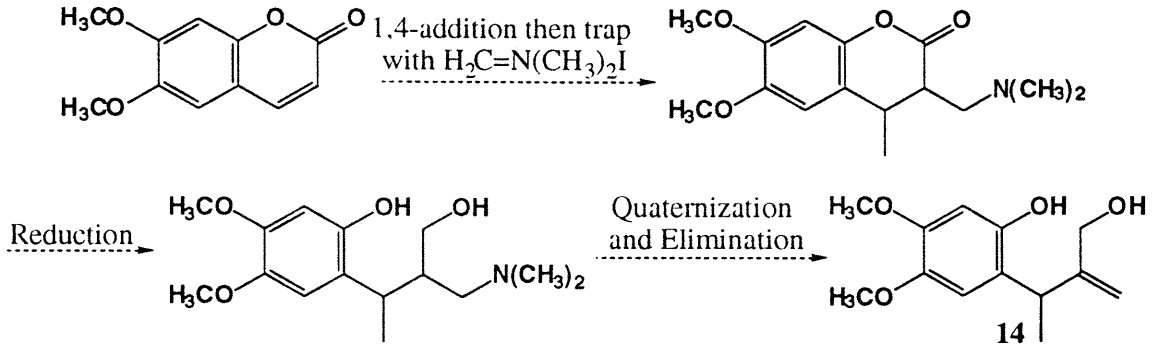
The next step in the synthetic scheme was to be a reduction of the lactone (**15**) to the corresponding diol (**14**) (Scheme 12). Thus far, three reducing agents were used: diisobutylaluminum hydride (DIBALH), lithium aluminum hydride (LAH), and lithium borohydride ($LiBH_4$). The DIBALH reduction was patterned after the procedure described by Hangauer[32] for a similar system and appeared to proceed smoothly; however, the crude product mixture decomposed upon standing. The LAH reduction proceeded less smoothly, but a stable product was isolated and characterized as a mixture of diastereomers of the overly reduced diol **24**. The final reduction method using $LiBH_4$ as reductant[33] appeared to proceed cleaner than the first two. However, the product proved to be the same as for the

[32] Hangauer, D. G. *Tetrahedron Lett.* **1986**, *27*, 5799-5802.
[33] Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702-4708

LAH reduction. Aside from the obvious problem of obtaining the wrong product, the yields of the reduction attempts were very low.

An apparent solution to the over-reduction problem was to use lanthanide salts to promote reduction of the carbonyl instead of the conjugated olefin.[34] However, attempts using $CeCl_3$ and LAH or DIBALH proved to be as fruitless as the attempts without the lanthanide salts.

The apparent demise of the route was actually a blessing in disguise, because at the time of the unsuccessful reduction attempts, we had been contemplating alternate ways to synthesize the exo-methylene coumarin (**15**). It was believed that conjugate addition of a methyl group to 6,7-dimethoxycoumarin followed by trapping the enolate intermediate with Eschenmoser's salt (via a Mannich Reaction)[35] would serve as an alternate means to produce a precursor to **15**. The reduction of the resulting saturated lactone, followed by quaternization of the amine and subsequent elimination would prove to be an efficient means to circumvent the above problem (Scheme 13).



Scheme 13: Alternate Route to **14**

Initial attempts to effect the conjugate addition of a methyl group to 6,7-dimethoxy-coumarin followed by trapping of the resulting enolate were unsuccessful. One of the

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[34] Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc. Perkin. Trans. I* **1986**, 1929-1932.

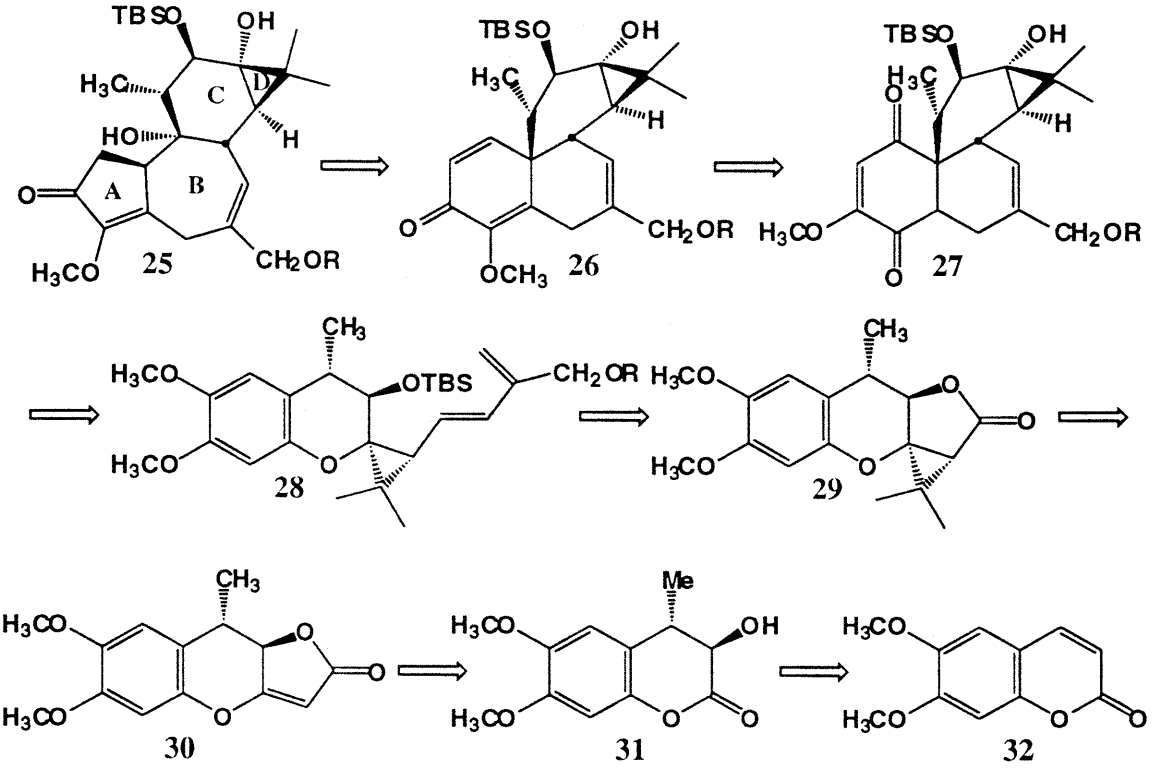
[35] Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715-6717.

problems was the insolubility of the coumarin in diethyl ether, and another problem was control of the four possible diastereomers produced in such a reaction sequence. Through these attempts, the second generation synthesis of the core ring structure of phorbol was conceived.

Chapter 3 - Final Strategy for the Complete Skeleton

3.1 Retrosynthetic Analysis

After the initial attempts which were described at the end of the previous chapter, a more stepwise approach to the construction of the complete carbocyclic framework of phorbol (**1b**) was conceived. The new synthetic strategy was to include many of the functional groups which are present in the target molecule **25**.

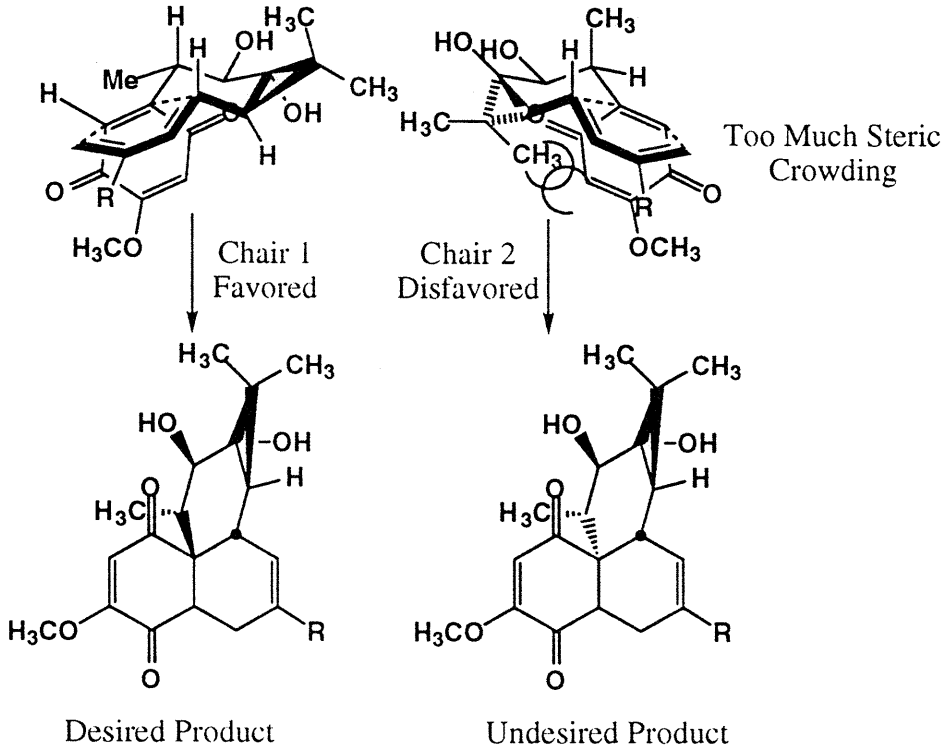


Scheme 14: Retrosynthesis of the Phorbol Skeleton

The retrosynthetic analysis for the new route, as shown in Scheme 14 above, kept some of the later steps from the initial strategy. The first disconnective transformation remained the acid catalyzed photochemical rearrangement to **26**, followed by several

functional group interconversions to achieve the product of a Diels-Alder transformation **27**.

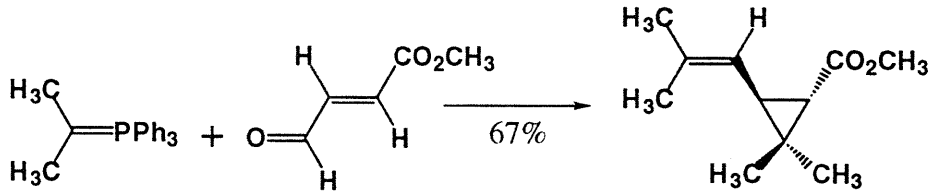
Another analysis of the possible transition states leading to the possible products of the Diels-Alder reaction demonstrated the effect of the cyclopropyl ring on the outcome of the cycloaddition. As shown in Scheme 15, the only viable transition state would lead to the desired product due to the rigidity of the molecule. The only other possible products would arise from an intermolecular cycloaddition.



Scheme 15: Analysis of the Diels-Alder Cycloaddition

The Diels-Alder precursor **28** was to arise from a Wittig-type condensation onto the lactol of the tetracyclic lactone **29**. Construction of the tetracycle was to be achieved by cyclopropanation of the vinyl ether portion of the tetronolactone **30**. The exact conditions for the cyclopropanation were to be determined. Due to the ambivalent nature of the olefin to be reacted (i.e. electron rich from the enol ether and electron poor from the α,β-

unsaturated lactone), either a nucleophilic cyclopropanation similar to what was used to construct the methyl ester of chyrsanthemic acid from methyl *E*-4-oxobutenoate[35] (Scheme 16), or a carbenoid cyclopropanation using conditions similar to the Simmons-Smith reaction[36] could be attempted.



2.4 eq. 1 eq.

Scheme 16: Cyclopropanation using a Phosphorus Ylide

The tetronolactone **30** was to arise from an aldol or Wittig condensation of an acyl substituent on the free hydroxyl of the α-hydroxy-β-methyl-3,4-dihydrocoumarin **31**. The final disconnective transformation of α-hydroxylation preceded by conjugate addition of a methyl group to 6,7-dimethoxycoumarin (**32**).

3.2 Forward Progress

Once again, the cost of the desired starting material, **32**, was rather high ($118.55/1 g)[37], so we endeavored to synthesize it from less costly starting materials. Esculin monohydrate (**33**), with a cost of only $33.15/25 g[38], was easily hydrolyzed with a dilute aqueous solution of sulfuric acid to produce esculetin (**34**). Treatment of **34** with an acetone solution of potassium carbonate and dimethylsulfate afforded **32** as a crystalline product in a total overall yield of 76% (Scheme 17)[39].

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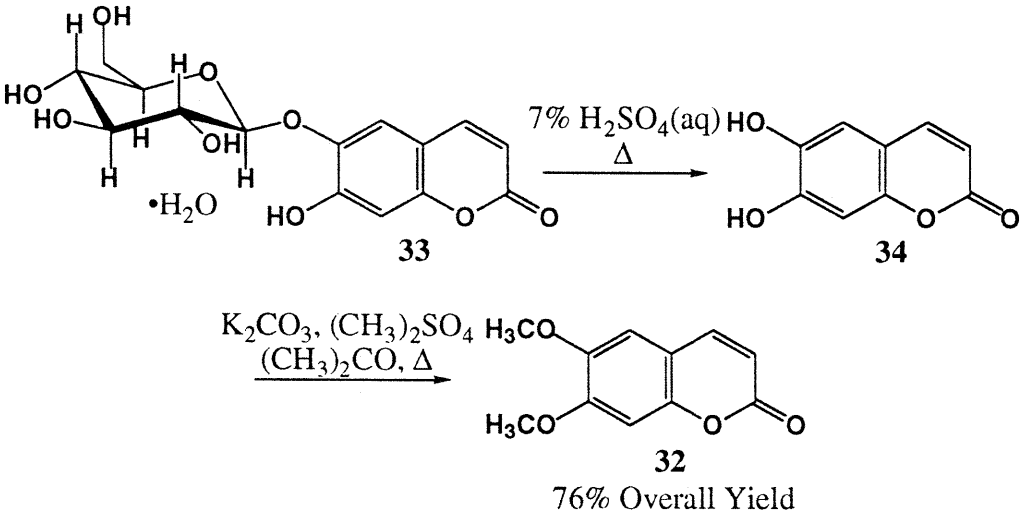
[35] Devos, M. J.; Hevesi, L.; Bayet, P.; Krief, A. *Tetrahedron Lett.* **1976**, 3911-3914.
[36] LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048.
[37] *Catalog Handbook of Fine Chemicals 1996-1997*, Aldrich Chemical: Milwaukee, 1996; p 560.
[38] *Ibid.* p 658.
[39] Merz, K. W. *Arch. Pharm.* **1932**, *270*, 476-494.



Scheme 17

With the above procedure, we were able to produce multi-gram quantities of **32** in a relatively short time with a drastic reduction in cost.

The next challenge was to effect the 1,4-addition of a methyl group to **32**. Very little information about conjugate additions to coumarins existed in the literature, and no instances of using **32**, which was a very electron rich substrate, were found. After many experiments afforded little or no reaction, conditions which optimized the addition were found (Table 3). The higher-order cuprate reagent derived from copper(I) cyanide and methyllithium was believed to be the better choice over its lower-order analog formed from copper(I) iodide, due to the increased reactivity of the higher-order species[40]. Also, the use of Lewis acidic additives such as boron trifluoride-diethyl ether complex (BF_3•OEt_2)[41] and chlorotrimethylsilane (TMSCl)[42] to increase the reactivity of the cuprate species was explored.

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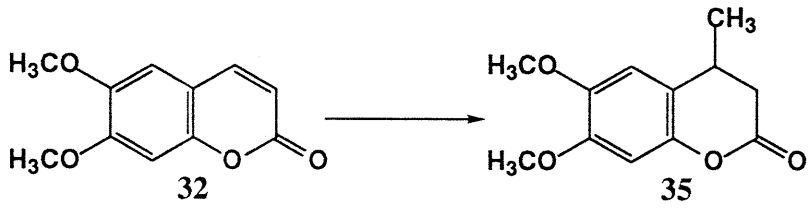
[40] Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938-3942.
[41] Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240-3241.
[42] Smith, A. B. III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, *29*, 439-442.



Cuprate	Solvent	Additive	Yield (%)
$(CH_3)_2Cu(CN)Li_2$	Et_2O	none, TMSCl	0
$(CH_3)_2Cu(CN)Li_2$	THF	TMSCl	0
$(CH_3)_2Cu(CN)Li_2$	Et_2O/THF	none, BF_3•OEt_2	0
$(CH_3)_2Cu(CN)Li_2$	Et_2O/CH_2Cl_2	TMSCl	7
$(CH_3)_2CuLi$	CH_2Cl_2	none	0
$(CH_3)_2CuLi$	Et_2O/CH_2Cl_2	TMSCl	71

Table 3: Conditions for Cuprate Addition to **32**

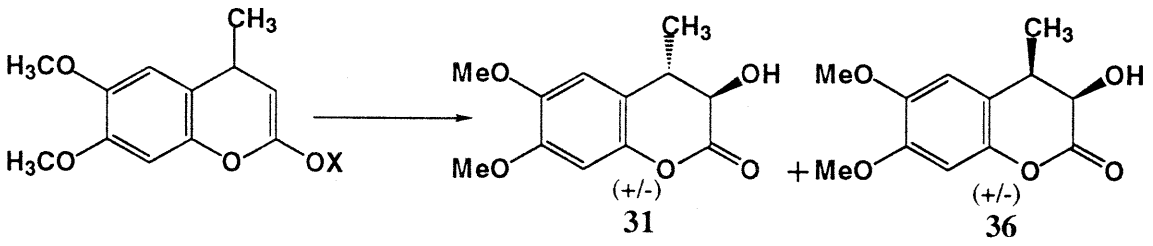
As can be seen from Table 3, above, the ideal conditions for the cuprate addition were using the lower-order cuprate with TMSCl as an additive in a mixed solvent system of diethyl ether and methylene chloride. The rationale for using the mixed solvent system was that the substrate **32** was insoluble in diethyl ether, but completely soluble in methylene chloride. The enhanced solubility permitted the reaction to occur in an appreciable yield.

The next challenge was the α-hydroxylation of the newly-formed dihydrocoumarin (**35**). A variety of electrophilic oxygenation reagents were tried under a variety of conditions (Table 4). Initially, oxidation of the enolate of **35** with dimethyldioxirane (DD)[43] afforded the desired diastereomer (**31**) exclusively; however the yield was terribly low. Next, oxidation of the same enolate with oxidoperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoO_5•Py•HMPA) (MoOPH)[44] was attempted, but only the undesired diastereomer (**36**) was formed. Next, epoxidation of the silyl ketene acetal derivative of **35** with 3-chloroperoxybenzoic acid (*m*-CPBA) in the presence of sodium

[43] a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205-211. b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187-1201. c) Guertin, K. R.; Chan, T.-H. *Tetrahedron Lett.* **1991**, *32*, 715-718.

[44] Vedejs, E.; Larsen, S. *Org. Synth. Coll. Vol. VII* **1985**, 277-282.

bicarbonate ($NaHCO_3$)[45] proved fruitless; however it did offer a modification of the DD oxidation. Oxidation of the silyl ketene acetal of **35** with DD gave a moderate yield of the desired diastereomer; however, the yield was still too low to be synthetically viable. Finally, use of the Davis' *N*-benzenesulfonyl-3-phenyloxaziridine[46], which had been prepared by the oxidation of *N*-benzylidinebenzenesulfonylamide with *m*-CPBA in chloroform catalyzed by benzyltriethylammonium chloride (BTEAC), afforded the best yield, albeit with less diastereoselection than the other methods. The diastereomers were completely separable by standard column chromatography over silica gel.



X	Oxidant	Yield (%)	Ratio of 31:36
Li	DD	10	only **31**
Li	MoOPH	64	only **36**
TMS	m-CPBA	13	only **31**
TMS	DD	47	only **31**
TMS	Oxaziridine	95	2.9:1

Table 4

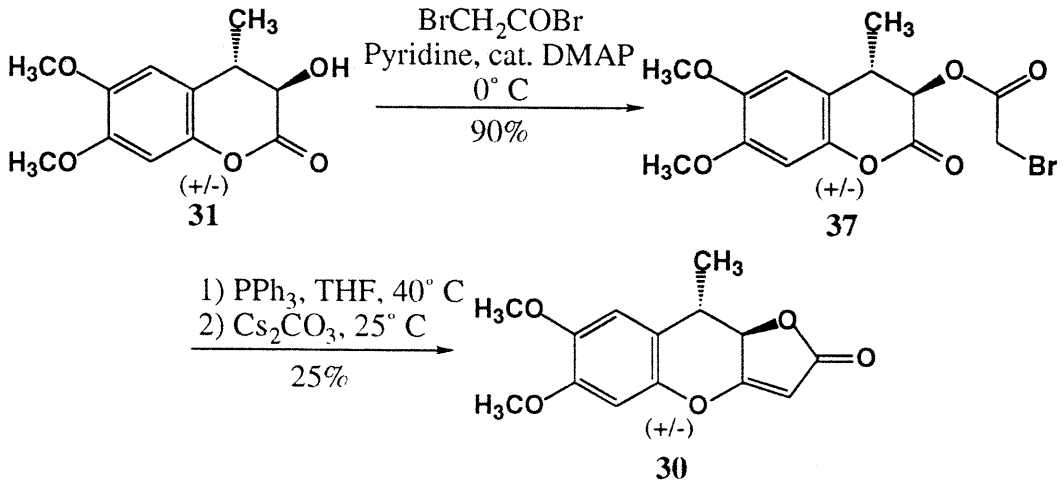
Construction of tetracyclic lactone **30** was the next formidable task. After exploring some of the literature detailing various methods[47] by which this transformation

[45] Rhubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599-1602.

[46] a) Davis, F. A.; Lamendola, J. Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R. Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000-2005. b) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774-1775. c) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241-3243.

[47] One of the methods which was embarked upon, but proved fruitless was the addition of trimethylsilyl-ketene to the free hydroxyl, which was supposed to spontaneously cyclize to form the tetronolactone. See a) Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607-3608. b) Taylor, R. T.; Cassell, R. A. *Synthesis* **1982**, 672-673. c) Kita, Y.; Sekihachi, J.; Hayashi, Y.; Da, Y.-Z.; Yamamoto, M.; Akai, S. *J. Org. Chem.* **1990**, *55*, 1108-1112.

could be accomplished, the route we chose was to first make the 2'-bromoacetyl derivative **37**, then to add triphenylphosphine (PPh_3). After generation of the ylide from the phosphonium salt, a spontaneous cyclization was to occur to form **30** (Scheme 18).[48]



Scheme 18

The largest difficulty was the generation of the ylide and cyclization, which occurred in only 25% yield. Subsequent review of the literature of the formation of tetronolactones had indicated the possibility of forming the corresponiding acetate, and effecting an aldol condensation using lithium bis(trimethylsilyl)amide as the base. Yields from similar condensations ranged from 78% to 95%.[49]

The construction of **30** was the extent of the progress on this route to phorbol. The overall yield, from esculin monohydrate, was 8.1%, largely as a result of the poor yield in the final cyclization reaction. The route, shown in Scheme 19, had a variety of points where it could have been improved; however, at this stage, the project was placed on hold in order to investigate the total synthesis of CP-225,917.

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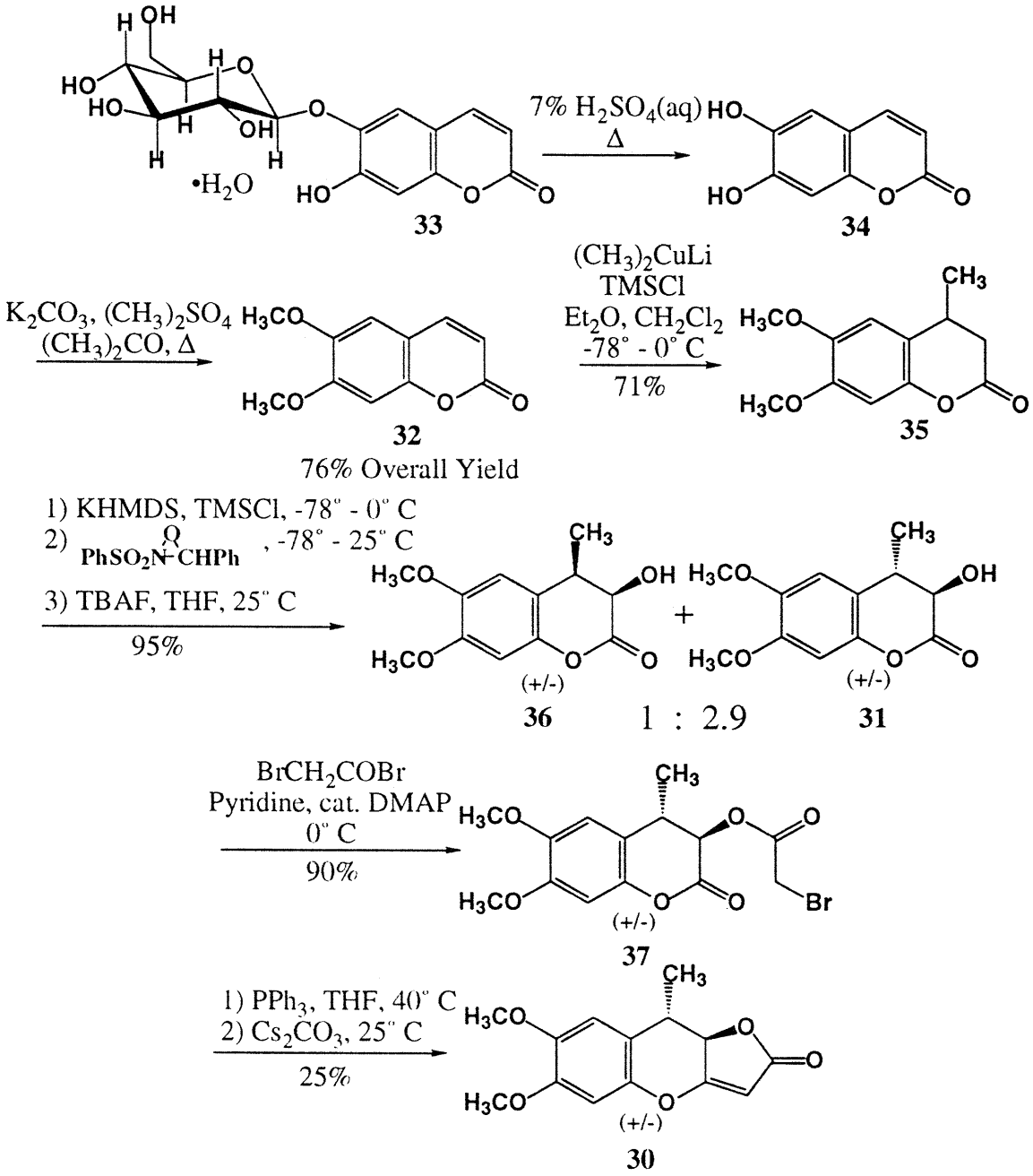
[48] Brennan, J.; Murphy, P. J. *Tetrahedron Lett.* **1988**, *29*, 2063-2066.
[49] Brandänge, S.; Flodman, L.; Norberg, A. *J. Org. Chem.* **1984**, *49*, 927-928.



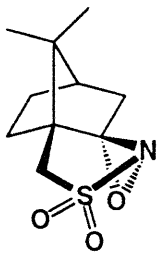
Scheme 19: Synthesis of **30**

3.3 Future Prospects for the Completion of Phorbol

Despite the problems which were encountered during the above synthetic plan, it would have been a more efficient route to **1b** than was shown by Wender. The main

obstacles for our plan to overcome were the absence of any enantioselection during the cuprate addition, which still necessitated a resolution step later in the synthesis; the moderate diastereoselection of the α-hydroxylation ; and an improvement in the yield of **30**, which was discussed at the end of the previous section.

A catalytic asymmetric hydrogenation of 4-methyl-6,7-dimethoxycoumarin using Noyori's Ru-BINAP catalyst[50] is a possible alternative to the cuprate addition, and it would allow for control of the resulting stereochemistry. Also, using a chiral ligand for the copper could possibly offer some measure of enantioselection during the 1,4-addition. The final alternative, and one which we had explored briefly, would be to use the glycal present in esculin as a chiral auxiliary for the cuprate reaction. Our attempts with the permethylated derivative of esculin have demonstrated that this last option is, perhaps, the least viable.



38

Figure 6: (-)-Camphorsulfonyloxaziridine

The most attractive solution to the mediocre diastereoselection in the α-hydroxylation reaction would be the use of (-)-camphorsulfonyloxaziridine (**38**) (Figure 6)[51].

The cyclopropanation reaction described in part 1 of this chapter was anticipated to proceed without severe difficulty. The steps leading to the Diels-Alder reaction should have been likewise. The major challenges in this sequence should have been the Diels-

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[50] Kitamura, M.; Ohkuma, T.; Inoue, S; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629-631.
[51] Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402-2404.

Alder reaction and the acid catalyzed photochemical rearrangement to form the skeleton; however, we will not have a chance to explore them.

It is with regret that I must terminate this synthetic plan. I believe it had much potential, and, by the addition of a variety of cuprates, it offered the chance to form many different analogs of **1b**.

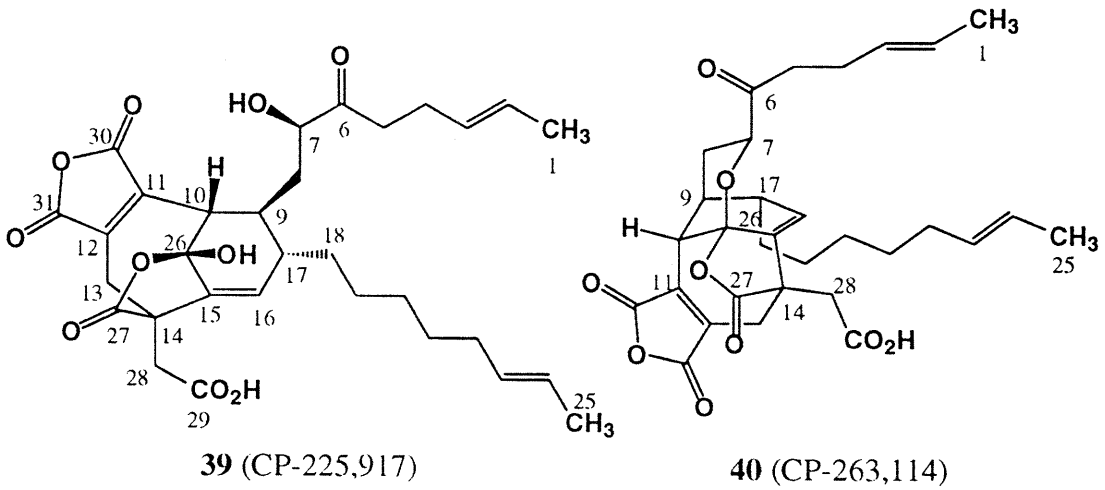
In Chapter 1, I listed the requirements necessary for a worthwhile endeavor in the total synthesis of natural products. Phorbol satisfied the first requirement for a complex, biologically active structure. I believe that our efforts described above satisfied the second requirement for a novel strategy which, had it been allowed to continue, would have contributed to the wealth of chemical knowledge.

Part II: Efforts Toward the Total Synthesis of CP-225,917

Chapter 4 - Introduction

Often, when undertaking the total synthesis of a complex structure, it becomes necessary to begin with an elementary evaluation of the structure and the means by which one hopes to accomplish its construction. After investigating the plausibility of a particular route, it may be necessary to reevaluate the scheme and begin a completely new route.

Our attempts toward the total synthesis of CP-225,917 (**39**), and its ketal analog CP-263,114 (**40**), are examples of just that kind of investigations. Both structures are novel polycyclic cage compounds with highly oxygenated frameworks and reactive functionalities. Both have biological activity, which makes them very attractive targets for total synthesis. Finally, they both possess a latent symmetry which creates an opportunity for a highly convergent and an elegant synthesis. In later chapters, our progress in the assmbly of the left-half portion of **39** will be discussed.

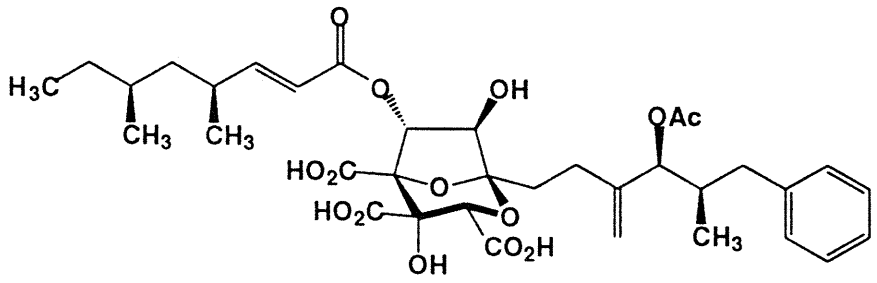


39 (CP-225,917) **40** (CP-263,114)

Figure 7

4.1 Isolation and Characterization

In 1994, a team of scientists at Pfizer Research Laboratories in Groton, Connecticut isolated the target structures while screening for inhibitors of squalene synthase. The producing organism was isolated from a juniper twig in Texas and was an unidentified fungus which was deposited in the American Type Culture Collection under accession number ATCC 74256. From 15 liters of fermentation broth, 31 mg of **39**, 18 mg of **40**, and 8 mg of zaragozic acid A (squaleastatin 1) (**41**) were isolated by reverse phase HPLC. Their novel structures were elucidated through the use of high resolution mass spectroscopy, infra-red and ultra-violet spectrophotometry, and one- and two-dimensional nuclear magnetic resonance spectroscopy.[52]



41

Figure 8: Zaragozic Acid A

Both **39** and **40** were found to inhibit squalene synthase from rat liver microsomes with IC_{50}[53] values of 43 and 160 μM, respectively. They were also found to inhibit ras

[52] a) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Kaneko, T. U. S. Patent 5 430 055, 1995. b) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1-7. c) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594-1598.

[53] The IC_{50} value is the concentration needed to inhibit the productivity of the enzyme by 50%.

farnesyl transferase with IC_{50} values of 6 and 20 μM, respectively.[52] **41**, by comparison, inhibited both enzymes with IC_{50} values of 0.5 nM and 250 nM, respectively.[54]

4.2 Inhibition of Squalene Synthase

The significance of squalene in the biosynthesis of cholesterol was demonstrated by Langdon and Bloch in 1953 when they demonstrated that rat liver produced squalene and further converted it to cholesterol.[55] Shortly thereafter, Woodward and Bloch suggested a scheme for folding squalene, such that many of its carbon atoms overlapped with those of cholesterol, and they also identified the initial product of the cyclization of squalene as lanosterol.[56]

Since that time, the biosynthetic pathway of cholesterol starting from acetic acid has been the object of extensive study. Scheme 20, below, shows some of the stages in the process. First, two molecules of acetyl-CoA condense to form acetoacetyl-CoA, which then condenses with another molecule of acetyl-CoA to form β-hydroxy-β-methyl glutaryl-CoA (HMG-CoA). HMG-CoA is reduced to mevalonic acid by the action of HMG-CoA reductase in the presence of NADPH. Double phosphorylation of the primary hydroxyl group followed by decarboxylation and elimination of the tertiary hydroxyl group produce isopentenyl pyrophosphate (IPP). After isomerization to dimethylallyl pyrophosphate (DMAPP), two molecules of IPP condense with DMAPP to form farnesyl pyrophosphate (FPP). At this stage, FPP is used in a variety of cellular processes, from formation of polyterpenoid substances such as geranylgeranyl pyrophosphate to isoprenylation of a variety of cellular proteins. The synthesis of squalene from two molecules of FPP catalyzed by squalene synthase is really the point of no return for the biosynthesis of

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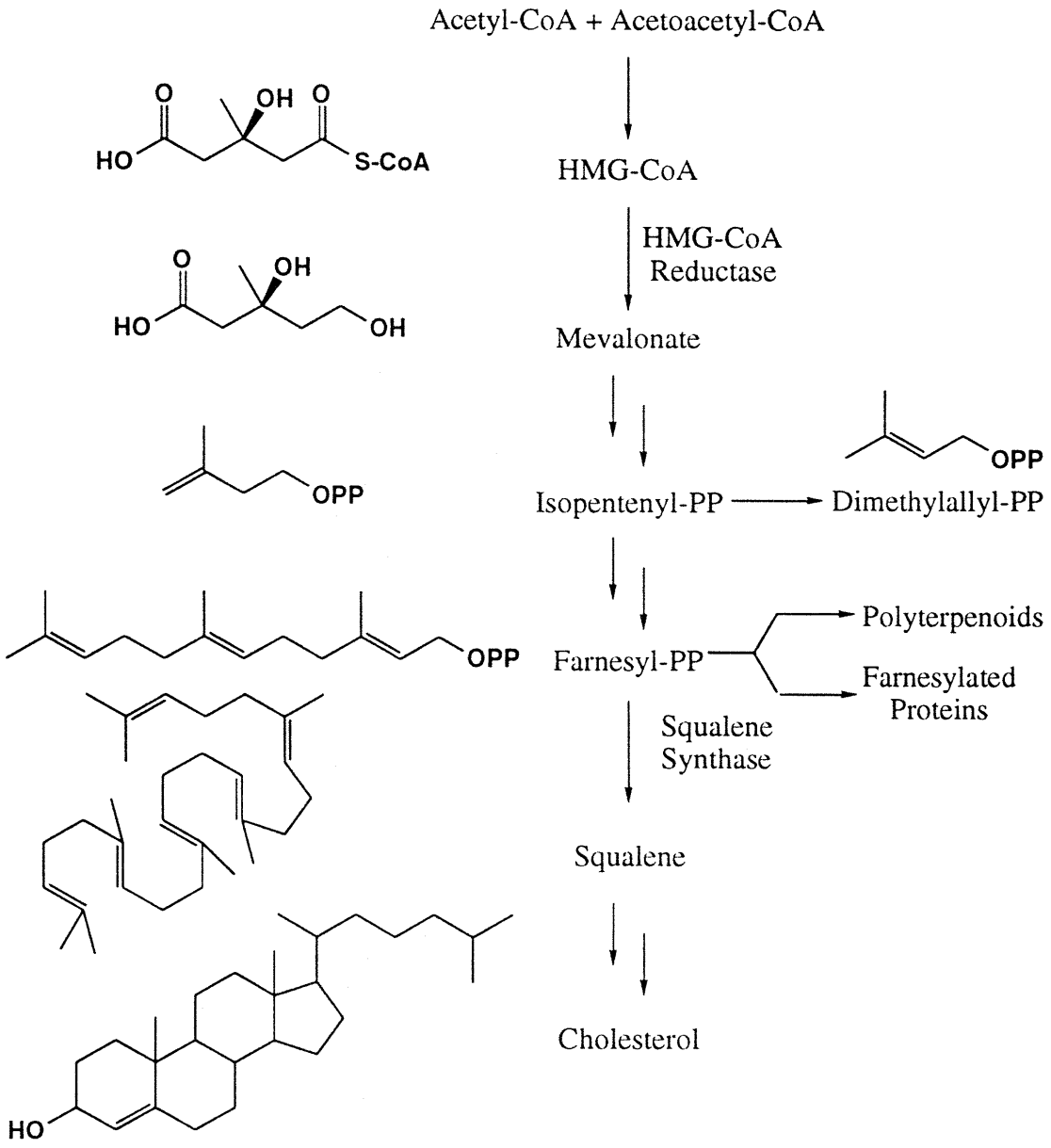
[54] For a review on the biological activity of and efforts toward the total synthesis of zaragozic acid A, see Nadin, A.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1622-1656.
[55] Langdon, R. G.; Bloch, K. *J. Biol. Chem.* **1953**, *200*, 135-144.
[56] Woodward, R. B.; Bloch, K. *J. Am. Chem. Soc.* **1953**, *75*, 2023-2024.

cholesterol. Squalene is then epoxidized and cyclized to lanosterol, which, through a series of oxidations, decarboxylations, and reductions is converted to cholesterol.[57]



Scheme 20

[57] For a review see Poulter, C. D.; Rilling, H. C. in *Biosynthesis of Isoprenoid Compounds* Porter, J. W.; Spurgeon, S. L. Eds. John Wiley and Sons: New York, 1981; Vol. 1, Chapter 8.

The two enzymes listed in Scheme 20, HMG-CoA reductase and squalene synthase, are targets for the inhibition of cholesterol biosynthesis. The first has been the main focus due to the discovery of small molecule inhibitors such as mevinolin (**42**) (marketed by Merck & Co. under the name Mevacor®), simvastin (**43**) (marketed by Merck & Co. under the name Zocor®), pravastatm sodium (**44**) (marketed by Brystol-Myers/Squibb under the name Pravachol®), and fluvastatin (**45**) (marketed by Sandoz). The second enzyme has received relatively little attention, mainly due to the fact that until the zaragozic acids were discovered virtually no small molecules were shown to inhibit its mode of action.

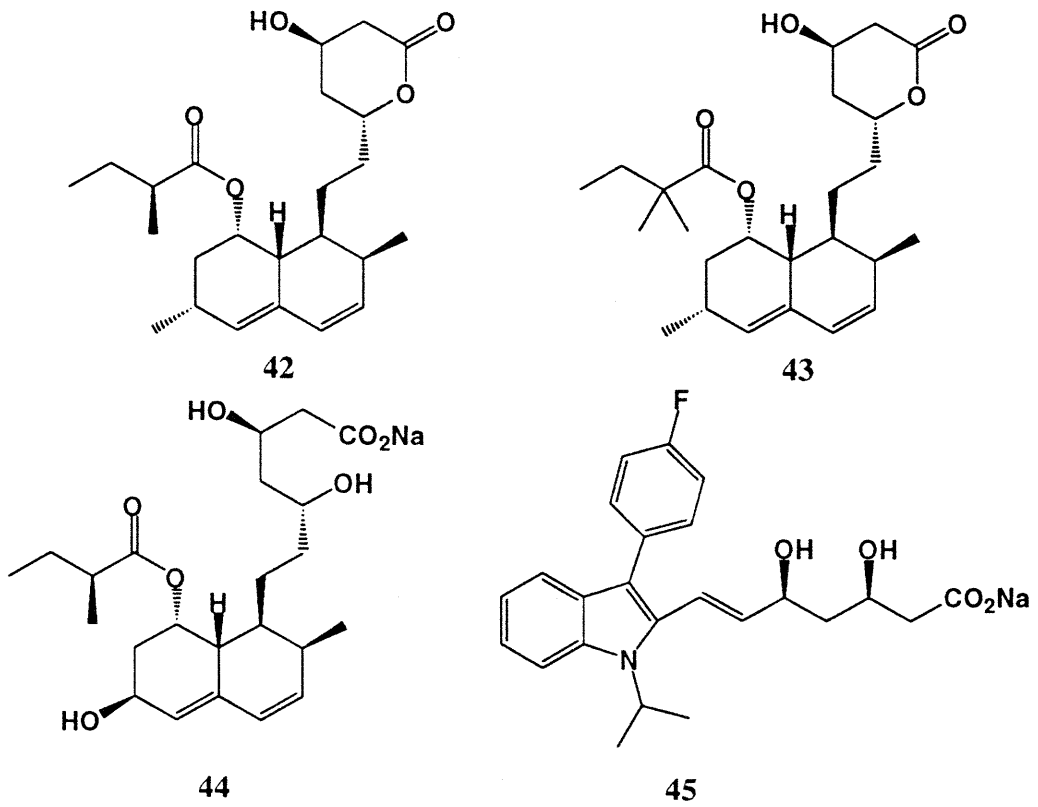
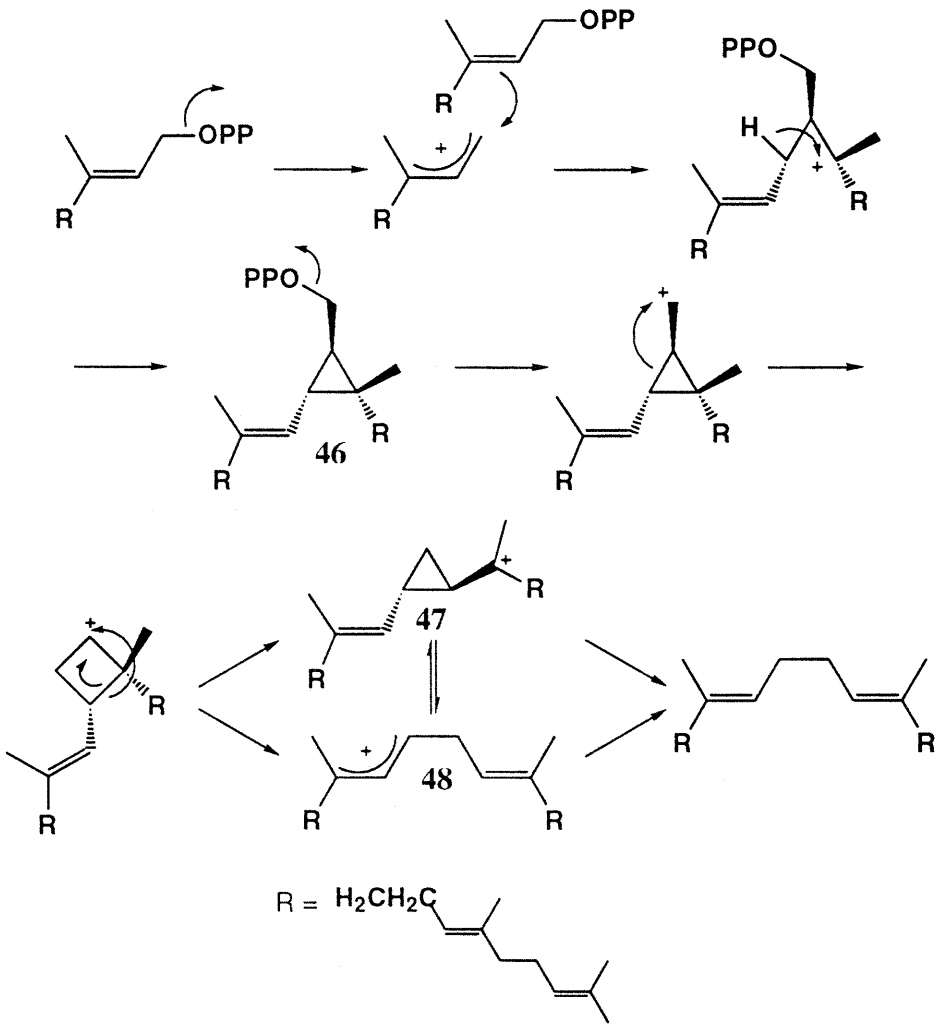


Figure 9: HMG-CoA Reductase Inhibitors

The synthesis of squalene is a two step process. The first is the formation of presqualene pyrophosphate (**46**) via a prenyl transfer step between the C1' on the first of

the farnesyl pyrophosphate molecules to the C2-C3 double bond of the second with the loss of one proton and a pyrophosphate group. The second step is either the reductive opening of the rearranged cyclopropane derivative (**47**) or the reduction of the allylic cation (**48**) formed after the loss of the second pyrophosphate group (Scheme 21).[58]



Scheme 21

Zaragozic acid A has been shown to inhibit both steps by first mimicking **46** with its long lipophilic side chains and charged core structure, and then covalently modifying the

[58] Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70-77.

enzyme.[59] The target structures have been demonstrated to inhibit only the formation of **46**, as monitored by the use of tritium labeled farnesyl pyrophosphate, and measuring the concentration of the released tritium.[53] The mode of action of **39** and **40** is presumably the same as **41**; however they do not covalently modify the enzyme which could be the reason that they are not as potent as **41**.

4.3 Inhibition of Farnesyl Protein Transferase

The role of farnesyl protein transferase (FPTase) in cell surface signal transduction has been studied in detail. It is known that post-translational modification of certain cellular proteins by FPTase is necessary for association with the cell membrane in order to participate in relaying extracellular information. A wide number of proteins are substrates for farnesylation by FPTase, however, they all have a similar C-terminal region comprising of a CAAX motif, cysteine (C) followed by two aliphatic amino acids (A) and usually ending in serine or methionine (X).[60] The isoprenylation at the cysteine residue is followed by hydrolysis of the three remaining residues by a C-terminal protease. Then, methylation of the carboxylate by a methyl transferase completes the modifications which lead to membrane association.

The Ras family of guanosine triphosphate (GTP) binding proteins is representative of the proteins which are modified as shown in Scheme 22. The Ras family is necessary for the normal function of the signal transduction pathway. In its active state, Ras proteins bind to GTP; however when the extracellular signal is no longer produced, they release guanosine diphosphate (GDP). Mutants of these proteins are locked in the GTP bound state which results in the continuous transmission of signals to the nucleus, and they have been identified with various types of carcinomas including those of the lung, colon,

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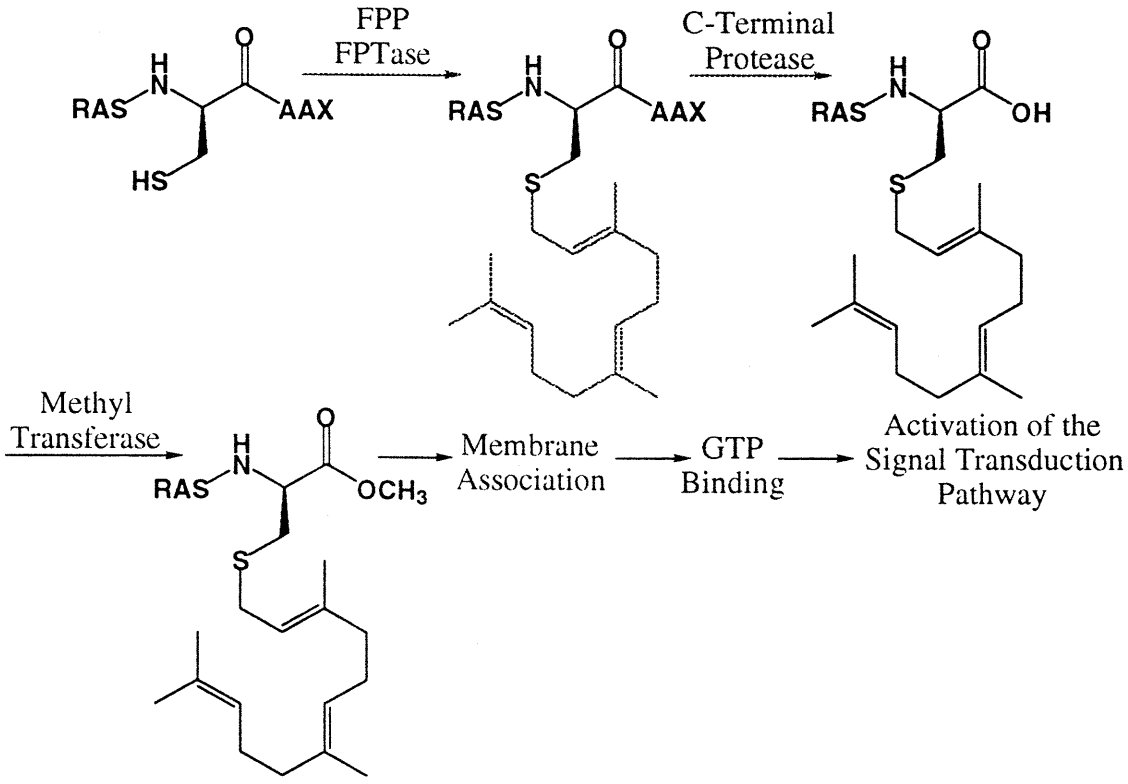
[59] Hasumi, K.; Tachikawa, K.; Sakai, K.; Murakawa, S.; Yoshikawa, N.; Kumazawa, S.; Endo, A. *J. Antibiot.* **1993**, *46*, 689-691.
[60] Maltese, W. A. *FASEB J.* **1990**, *4*, 3319-3328.

pancreas, and breast, as well as a few types of leukemia. In the absence of farnesylation, mutant Ras proteins cannot associate with the cell membrane, and, therefore, cannot transform normal cells into malignant ones.[61]



Scheme 22

Inhibition of the farnesylation of the Ras mutants offers a way to control the growth of cells which have been transformed by the carcinogenic proteins. Additionally, the inhibition of FPTase does not appear to affect the function of the normal Ras proteins, and thus produces anticancer activity without cytotoxicity to the normal cells.[62]

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[61] Siperstein, M. D. *Adv. Exp. Med. Biol.* **1995**, *369 (Nutrition and Biotechnology in Heart Disease and Cancer)*, 155-166.
[62] Gibbs, J. B.; Oliff, A.; Kohl, N. E. *Cell* **1994**, *77*, 175-178.

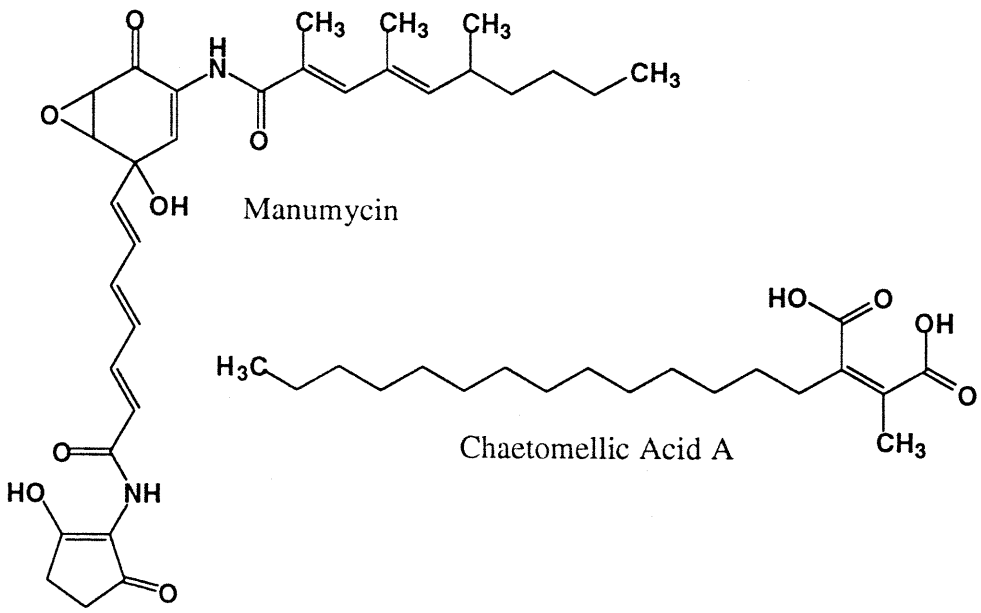

Figure 10: FPP Mimics which Inhibit FPTase

There are a wide variety of FPTase inhibitors. Some, like the zaragozic acids and the target compounds, act by associating with the farnesyl pyrophosphate binding domain of the enzyme. Two representatives are shown in Figure 10.[63] However, the bulk of the rationally designed inhibitors mimic the Ras C-terminal CAAX peptide sequence.[64]

4.4 Possible Biosynthetic Origin

Dabrah *et al.* suggested a possible biosynthetic route to **39** and **40** depicted in Scheme 23.[53b] Disconnecting the C10-C26 bond produced a nine-membered ring shown in **49**. Further disconnection of the large ring and the maleic anhydride moiety led to the virtually symmetrical **50**, which was dissected to lauric acid (**51**) and oxaloacetic acid (**52**). Through these transformations, they attempted to relate the target compounds to a

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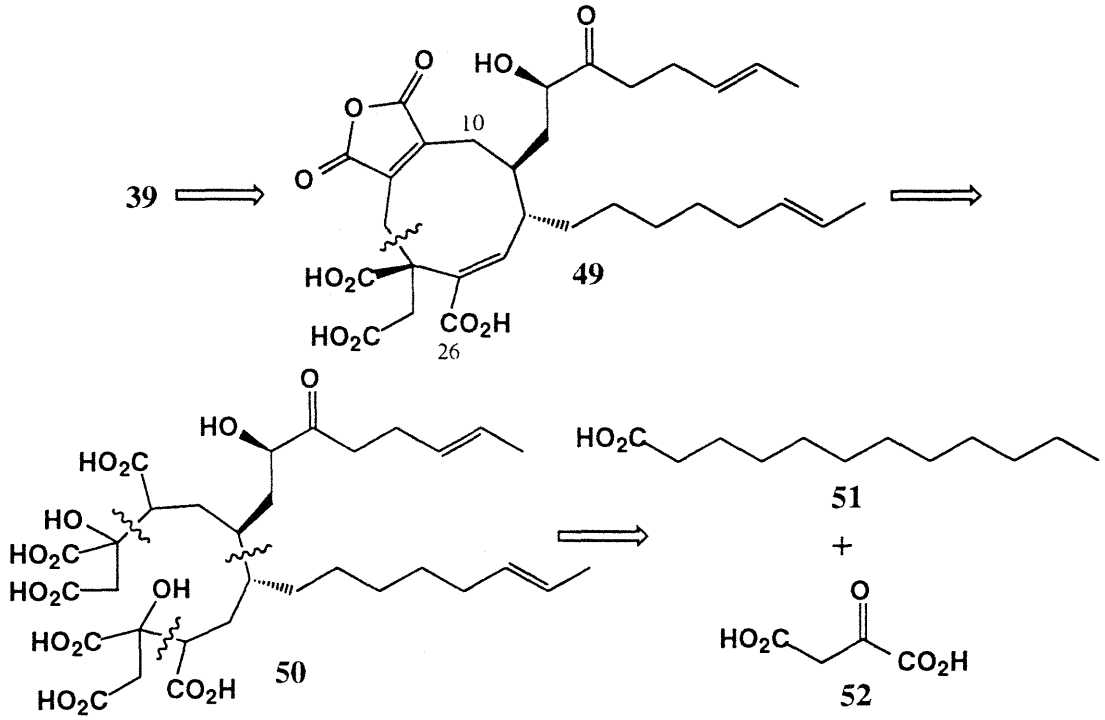
[63] Tamanoi, F. *Trends Biochem. Sci.* **1993**, *18*, 349-353.

[64] a) Koblan, K. S.; Kohl, N. E.; Omer, C. A.; Anthony, N. J.; Conner, M. W.; deSolms, S. J.; Williams, T. M.; Graham, S. L.; Hartman, G. D.; Oliff, A.; Gibbs, J. B. *Biochem. Soc. Trans.* **1996**, *24*, 688-692. b) Sebti, S. M.; Hamilton, A. D. *Biochem. Soc. Trans.* **1996**, *24*, 692-699.

class of natural products called nonadrides, so named because of the presence of a nine-membered ring in their structures.

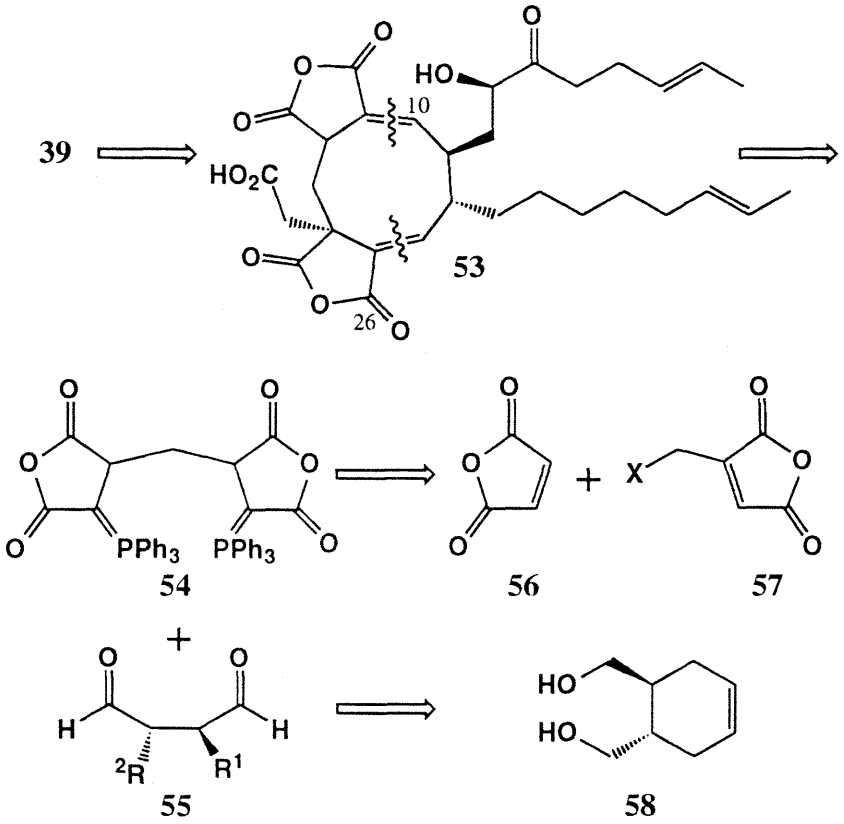


Scheme 23: Putative Biosynthetic Origins of **39** and **40**

Chapter 5 - Initial Studies

5.1 Biomimetic Strategy and Limitations

Our initial strategy for the assembly of **39** attempted to include elements of the proposed biosynthesis illustrated at the end of the last chapter. The retrosynthetic analysis depicted in scheme 24 was devised with a biomimetic strategy in mind.

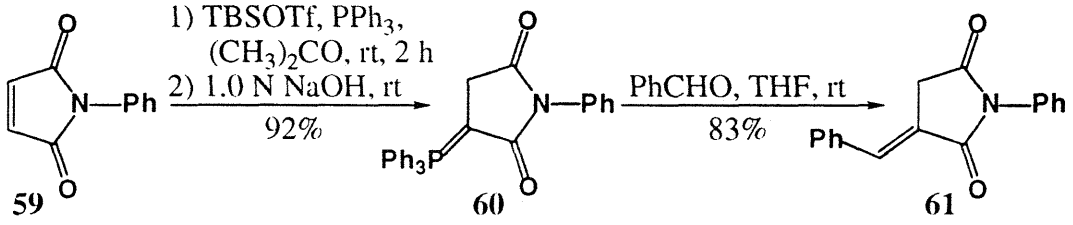


Scheme 24: Biomimetic Retrosynthesis of **39**

The first disconnective transformation was similar to that proposed by Dabrah *et al.*[53], a scission of the C10-C26 bond to give an intermediate (**53**) with a nine-membered ring; however, we proposed to keep the anhydride moieties intact. **53** was to be assembled

via a tandem Wittig condensation between the symmetrical bis(triphenylphosphonium) ylide **54** and the dialdehyde **55**. The dimer **54**, in turn, was to be constructed through an alkylation of maleic anhydride (**56**), or some synthetic equivalent, by bromocitraconic anhydride (**57**). Dialdehyde **55** was intended to be derived from the *C2* symmetric diol **58**. Investigations into the synthesis of **55** were begun by Justin Miller and will be presented in a later chapter.

The success of this route depended on the tandem Wittig condensation. To study the feasibility of this step, a few model reactions were attempted. Due to the highly reactive nature of maleic anhydride, *N*-phenylmaleimide (**59**) was chosen as a synthetic equivalent. Addition of triphenylphosphine to **59** in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) followed by treatment with a 1.0 N aqueous sodium hydroxide solution generated the triphenylphosphonium ylide **60** in very good yield. The synthetic utility of **60** was tested by condensation with benzaldehyde which produced the benzylidine **61**, also in good yield (Scheme 25).[62]

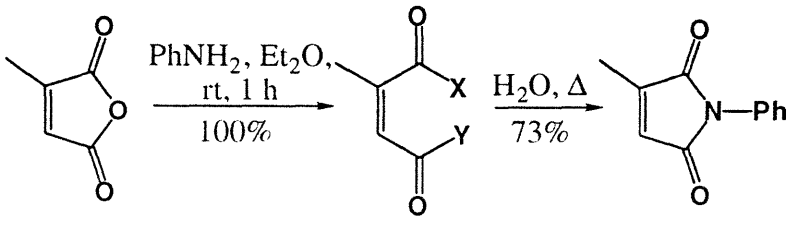


Scheme 25

With these very promising results in hand, we undertook the synthesis of 2-methyl-*N*-phenylmaleimide (**62**) (Scheme 26). The initial product of the addition of aniline to citraconic anhydride (**63**) was a mixture of regioisomeric anilic acids (**64**) in quantitative yield. Closure to the cyclic imide was more troublesome than first thought. Treatment of **64** with acetic anhydride in the presence of sodium acetate[63] produced no appreciable

[62] Heyada, E.; Theodoropulos, S. *Tetrahedron* **1968**, *24*, 2241-2254.
[63] Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J. *Org. Synth. Coll. Vol. V* **1973**, 944-???

amount of the desired product. Next, **64** was treated with thionyl chloride in the presence of a catalytic amount of *N, N*-dimethylformamide, which produced none of the desired product. The same result was obtained upon addition of *p*-toluenesulfonyl chloride to a solution of **64** in pyridine.[64] Finally, heating an aqueous solution of **64** over a steam bath (100 - 110 °C) for 38 hours, cooling the mixture, and collecting the precipitate afforded **62** in 73% yield.[65]



63 **64** **62**

64a: X = -N(H)Ph; Y = -OH
64b: X = -OH; Y = -N(H)Ph

Scheme 26

When we attempted to generate the triphenylphosphonium ylide of **62** using the same conditions for the unsubstituted case, no product was formed.

During the above investigation, we were also attempting to prepare 2-bromomethylmaleic anhydride (**57**, X=Br). Following a literature procedure[66], itaconic acid (**65**) was treated with bromine in acetic acid to form 2-bromo-2-(bromomethyl)succinic acid (**66**). The anhydride **67** was formed by heating a solution of **66** in trifluoroacetic anhydride to reflux, then removing the solvent under reduced pressure. Elimination of the tertiary bromide with 2,6-lutidine in benzene[66,67] produced **57** in 53% overall yield from **65** (Scheme 27).

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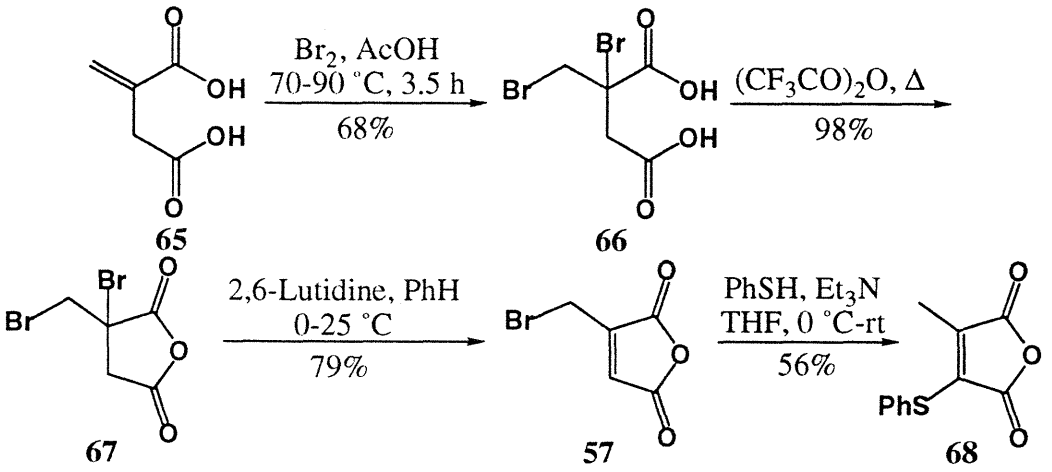
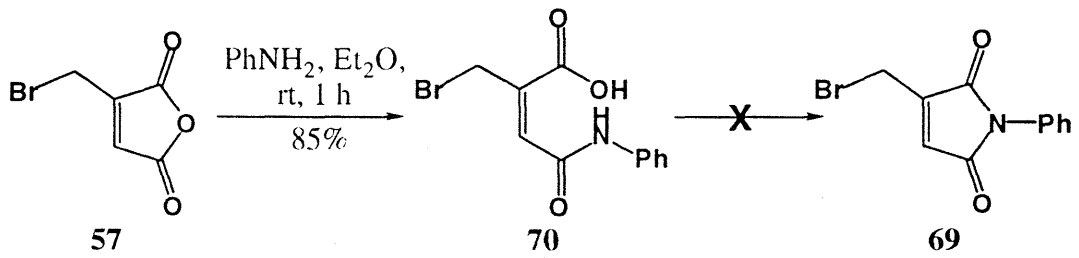
[64] Brewster, J. H.; Ciotti, C. J., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 6214-6215.
[65] Sheremeteva, T. V.; Gusinskaya, V. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1966**, 695-700; *Chem. Abstr.* **1966**, *65*, 8714f.
[66] Laursen, R. A.; Shen, W.-C.; Zahka, K. G. *J. Med. Chem.* **1971**, *14*, 619-621.
[67] Greenlee, W. J.; Woodward, R. B. *Tetrahedron* **1980**, *36*, 3367-3375.



Scheme 27

We then attempted to displace the bromide with thiophenol using triethylamine as a base[68]; however, the only product was 3-(thiophenyl)citraconic anhydride (**68**).

We next embarked upon a synthesis of 2-(bromomethyl)-*N*-phenylmaleimide (**69**), following the procedures above for the preparation of 2-methyl-*N*-phenylmaleimide. Addition of aniline to **57** proceeded in good yield to the anilic acid **70**.



Scheme 28

However, when we tried to complete the cyclization by heating an aqueous solution of **70**, none of the desired product formed. Next we attempted to use the refluxing trifluoroacetic anhydride conditions which worked to form **67**, but these also proved fruitless (Scheme 28).

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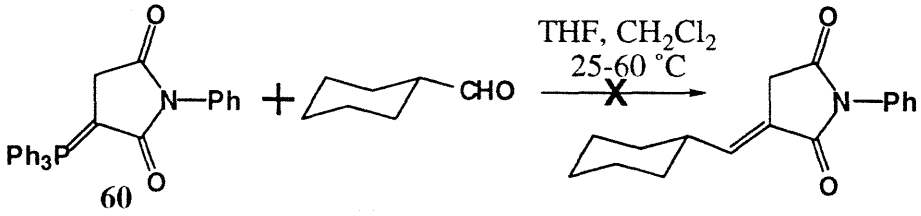
[68] Landini, D.; Rolla, F. *Synthesis* **1974**, 565-566.

We had begun to have misgivings about this route after a couple of the reactions had failed, but we wanted to test whether or not the ylide **60** would react well with an aliphatic aldehyde. To this end we attempted the condensation of **60** with cyclohexane carboxaldehyde. Under the conditions we employed, no reaction was observed, and the starting materials were re-isolated (Scheme 29).



Scheme 29

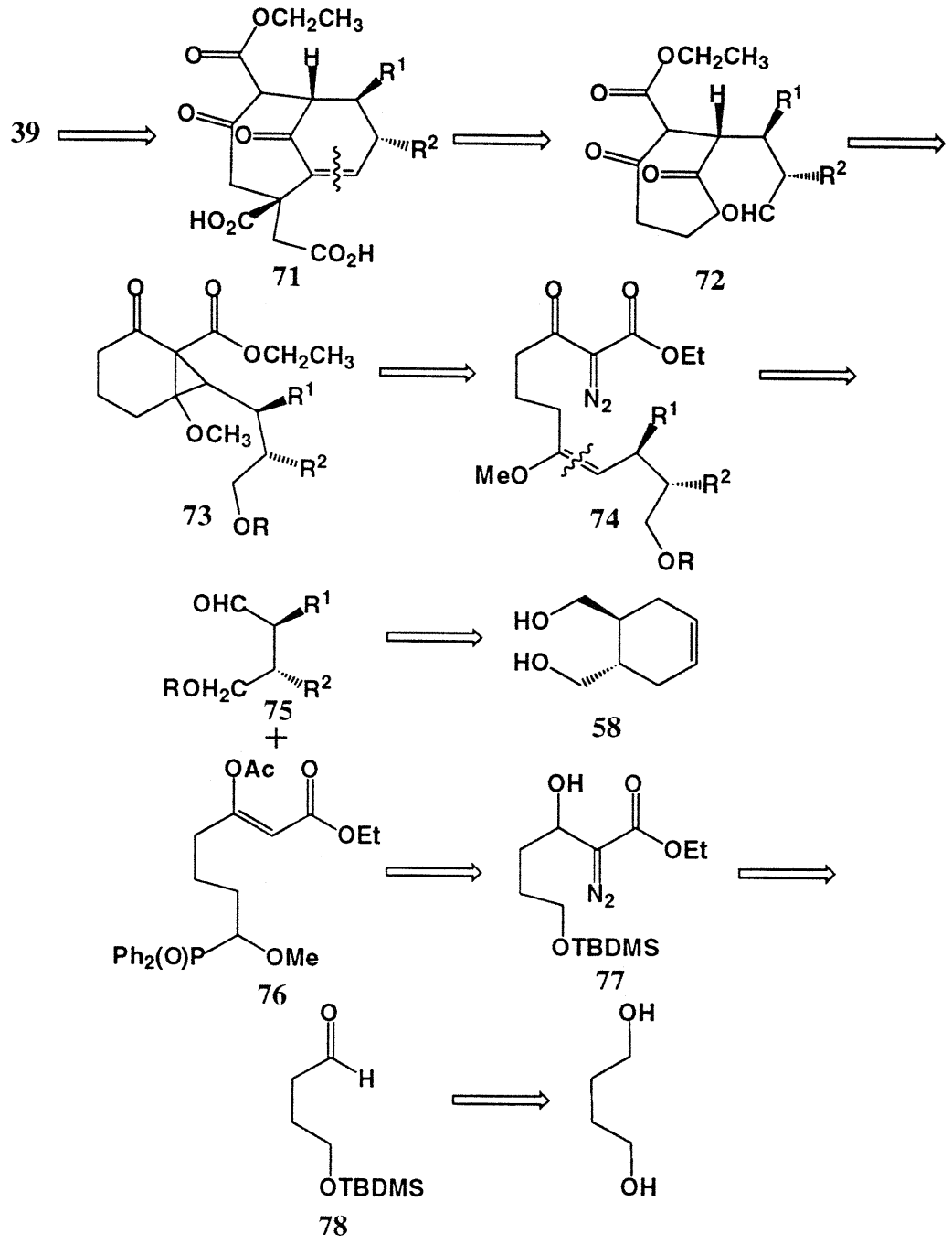
After this disappointing result, a reevaluation of the original strategy determined that this was not a feasible route to **39**. Aside from the fact that we were only able to condense **60** with benzaldehyde and that we were unable to generate the triphenylphosphonium ylide from **62**, we had not really devised a plan for incorporating the carboxylic acid moiety. Also, the final step of contracting the nine-membered ring into the carbocyclic framework required the geometry of the C15-C16 double bond to be opposite to what would have been generated from the tandem Wittig condensation.

Realizing that our biomimetic strategy was proceeding with more difficulty than we had anticipated, we were determined to devise a plan for the target molecule which still included the *C2*-symmetric diol **58**.

5.2 Linear Strategy and Limitations

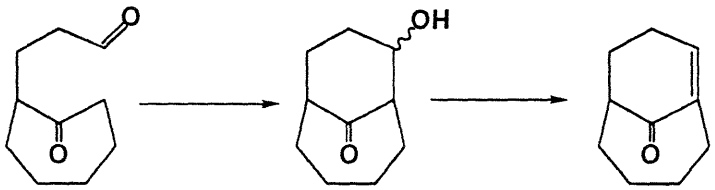
Our next strategy was entirely based upon keeping the diol **58** as a key intermediate, and we developed a more linear route to accommodate it. The revised

retrosynthetic analysis (Scheme 30) was conceived with the notion of keeping the transformations simpler, without relying on any reactions which might be too ambitious.



Scheme 30

We were planning to install the anhydride moieties at the very end of the synthesis as a way of circumventing their highly reactive nature, so our first disconnective transformation led to the bicyclic pentacarbonyl structure **71**. After a simplifying disconnection which removed the two carboxylic acid functionalities, we had planned to form the cyclohexenyl ring via an aldol condensation followed by dehydration of **72**. A similar ring system was assembled through an aldol reaction and pyrolysis of the benzoate derived from the β-hydroxy ketone (Scheme 31).[69]



Scheme 31

We had thought that the seven-membered ring of **72** could arise from an acid catalyzed ring expansion of the bicyclic [4.1.0] ring system **73**. Construction of the bicycle was to be accomplished by a rhodium catalyzed carbenoid insertion into the vinyl ether portion of **74**. A condensation between the chiral aldehyde **75** and the ylide derived from the diphenylphosphine oxide **76** was conceived to assemble **74**. **75** was to be synthesized from the *C*2-symmetric diol **58**. **76** was to arise from the α-diazo-β-hydroxy ester **77**, which was constructed by an aldol reaction between ethyl diazoacetate and the silyl protected γ-hydroxy aldehyde **78**. The precursor of **78** was 1,4-butanediol.

The assembly of **58** and subsequently **75** was charged to Justin Miller who had been working on the construction of the dialdehyde portion required for the biomimetic route. His efforts to utilize **58** in our synthetic plan will be discussed in a later chapter.

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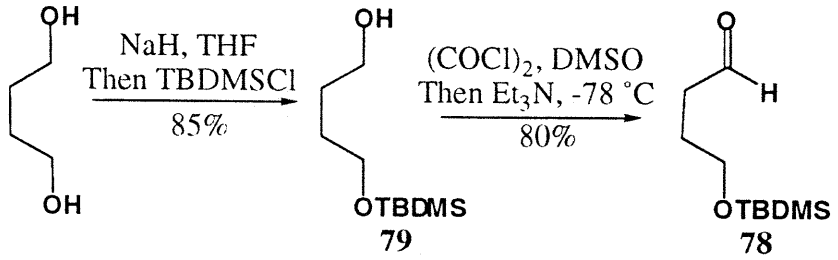
[69] a) Allan, R. D.; Cordiner, B. G.; Wells, R. J. *Tetrahedron Lett.* **1968**, 6055-6058. b) Cordiner, B. G.; Vegar, M. R.; Wells, R. J. *Tetrahedron Lett.* **1970**, 2285-2286.

The monoprotection of 1,4-butanediol was first attempted using a tetrahydropyranyl protecting group; however, using standard conditions[70], we obtained mostly the diprotected product. Likewise, using the standard conditions for silylation gave the diprotected product. Finally, using one equivalent of sodium hydride to generate the monoanionic species, and silylation with one equivalent of *t*-butylchlorodimethylsilane (TBDMSCl) gave rise to the monoprotected product **79** in very good yield.[71] Oxidation of the primary alcohol was accomplished in good yield using the conditions described by Nicolaou *et al.* to generate **78** (Scheme 32).[72]



Scheme 32

The addition of the lithium enolate of ethyl diazoacetate to carbonyl compounds using either *n*-butyllithium[73] or lithium diisopropylamide (LDA)[74] has been covered in the literature in some detail. Using the conditions of Schöllkopf *et al.*[73], we obtained the desired α-diazo-β-hydroxy ester **77** from **78**, only in low yields (25-50%). Using the modified conditions with LDA also proceeded in mediocre yields. Conversion of **77** to the β-keto ester **80** using a catalytic amount of rhodium(II) acetate dimer in dimethoxyethane (DME)[74] proceeded very cleanly (Scheme 33). However, when we tried to protect the

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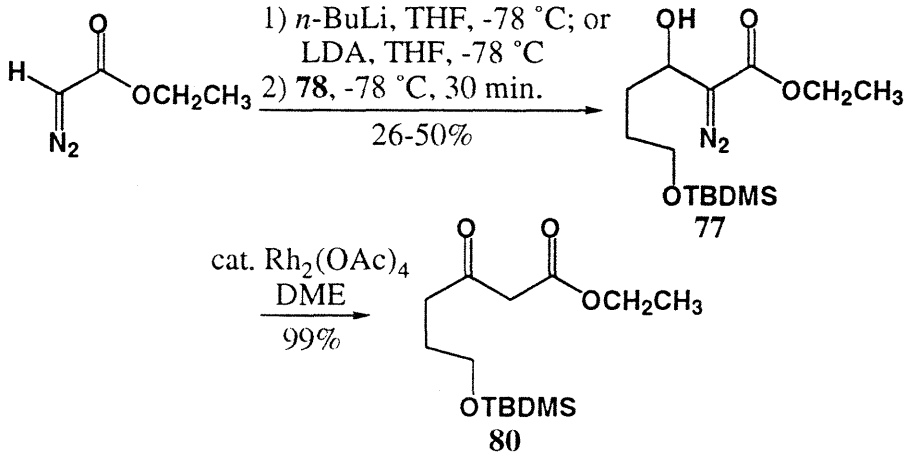
[70] Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772-3774.
[71] McDougal, P.; Rico, J.; Oh, Y.; Condon, B. *J. Org. Chem.* **1986**, *51*, 3388-3390.
[72] Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J Am. Chem. Soc.* **1989**, *111*, 5321-5330.
[73] a) Schöllkopf, U.; Fasnelli, H. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 301-302. b) Schöllkopf, U.; Bánhidai, B.; Frasnelli, H.; Meyer, R.; Beckhaus, H. *Liebigs Ann. Chem.* **1974**, 1767-1783.
[74] a) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc. Chem. Commun.* **1979**, 959-960. b) Pellicciari, R.; Fringuelli, R.; Sisani, E.; Curini, M. *J. Chem. Soc. Perkin Trans. I* **1981**, 2566-2569. c) Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis* **1983**, 197-199.

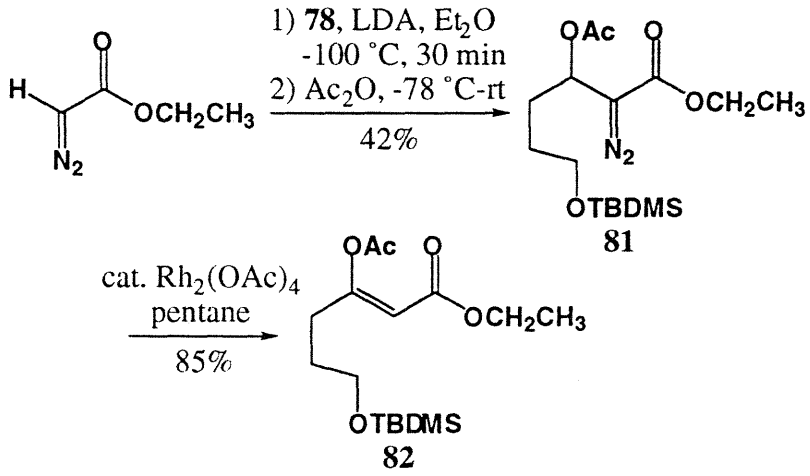
ketone portion of the molecule using either ethylene glycol and pyridinium *p*-toluenesulfonate (PPTS)[75] to generate the cyclic ketal, or diazomethane to generate the enol ether, no desirable products formed.



Scheme 33

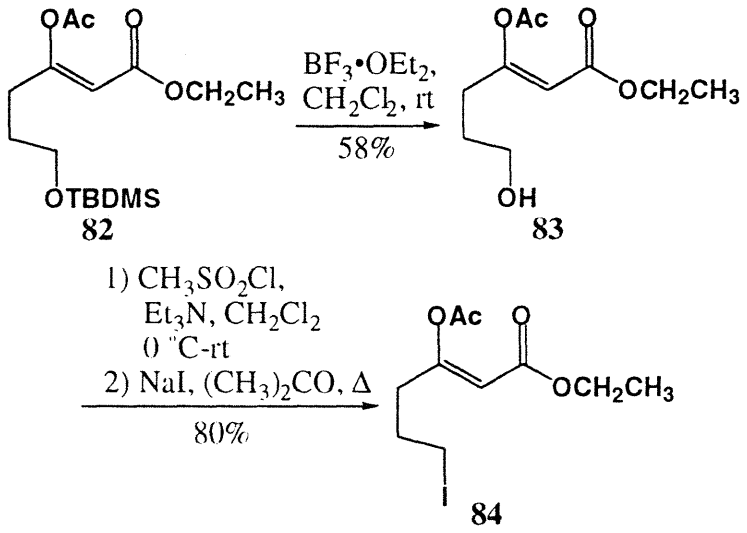
Protection of the ketone was essential for the completion of this route, so we decided to attempt to trap the alkoxide intermediate from the ethyl diazoacetate addition with acetic anhydride. Generation of the β-acetoxy-α-diazo ester **81** also proceeded in mediocre yield, but we now had the means to protect the β-keto ester as the enol acetate **82** which was formed after the rhodium(II) acetate dimer catalyzed rearrangement (Scheme 34).

[75] Sterzycki, R. *Synthesis* **1979**, 724-725.



Scheme 34

The next task was to deprotect the primary alcohol, which ordinarily would not be a problem. Standard conditions using tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran worked poorly, resulting in only a 12 percent yield of the desired alcohol.



Scheme 35

Alternative conditions which worked in a much better yield were found which called for boron trifluoride•diethyl etherate (BF_3•OEt_2) in methylene chloride.[76] The resulting primary alcohol **83** was converted to the corresponding iodide **84** after preparing the methanesulfonate derivative *in situ* (Scheme 35).[77]

The next step called for the alkylation of the ylide derived from (methoxymethyl)-diphenylphosphine oxide which was prepared from chloromethyl methyl ether, triphenyl-phosphine and sodium hydroxide.[78] Generation of the ylide with lithium diisopropylamide in tetrahydrofuran proceeded nicely, as evidenced by the appearance of a red color; however, upon addition of the iodide **84**, no reaction was observed. Even upon heating the reaction mixture to refluxing conditions, only starting material was obtained.

Repeated attempts at the alkylation were all fruitless. We had reached another dead end in the approach to **39**. Upon further review of the synthetic strategy, we had not taken into account a means of installing the carboxylate groups, and the conditions for the elimination to form the cyclohexenyl ring would not have tolerated many functional groups. This route was also getting pretty lengthy (already at seven steps). What we needed was a more convergent route which would tolerate all of the functionality which is present in the target molecule.

The first problem was that we did not want to abandon the *C2*-symmetrical diol **58**, with which Justin Miller was making much progress. The second problem was that we wanted to include as much of the functionality of the target from the outset. The third, and perhaps most daunting, problem was that we had to make the route as short and as elegant as possible. To these ends we arrived at our current strategy which will be described in the next chapter.

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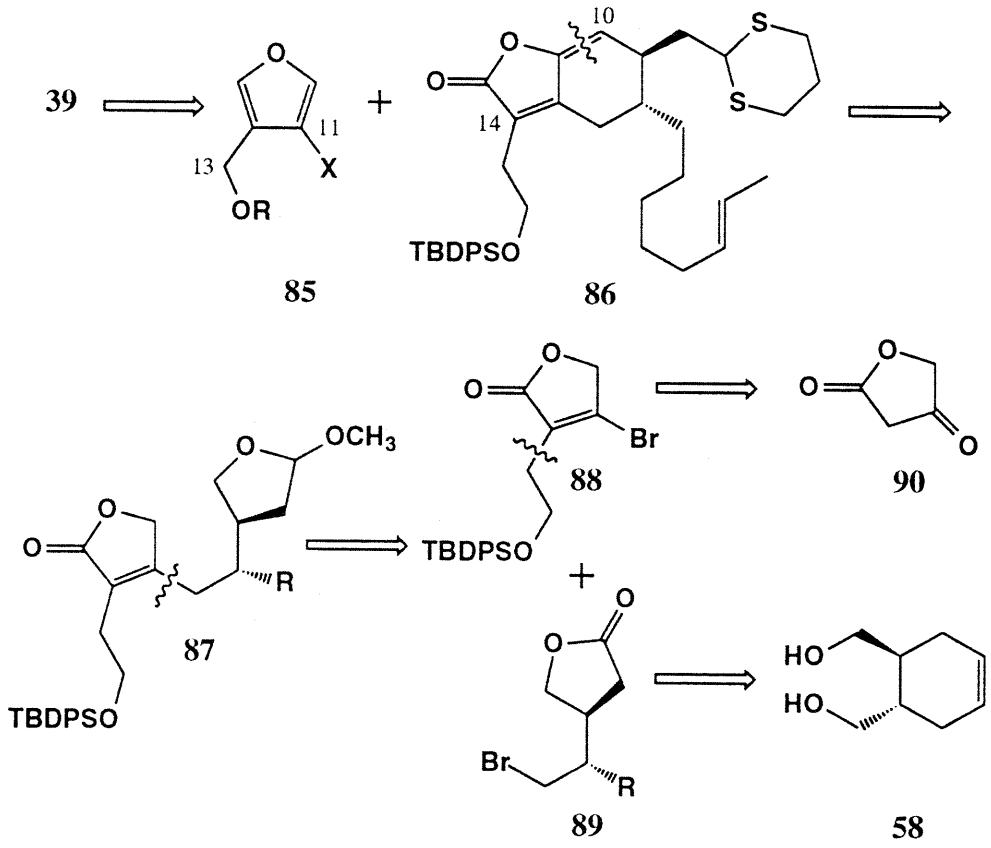
[76] Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295-299.
[77] Poss, A. J.; Belter, R. K. *J. Org. Chem.* **1987**, *52*, 4810-4812.
[78] Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc. Perkin Trans. I* **1979**, 3099-3106.

Chapter 6 - Current Strategy

6.1 Retrosynthetic Analysis

Facing the three problems listed at the end of the last chapter, we endeavored to create a simple yet elegant strategy for assembling the target compound **39**. The retrosynthetic analysis we devised still contained the *C2*-symmetric diol **58**.



Scheme 36

This time, however, instead of trying to synthesize a nine-membered ring and contracting it as in the biomimetic strategy, or trying to annulate the cyclohexenyl ring onto the seven-

membered ring in the linear strategy, we decided to start from the five-membered lactone-ketal ring and build outward (Scheme 36).

The initial disconnection for the current synthetic plan was to simplify the maleic anhydride moiety to a furan which could subsequently be oxidized to give the natural product. Then, breaking both the C10-C11 and C13-C14 bonds we arrived at the substituted furan **85** and the chiral trisubstituted dihydrobenzofuranone **86**. We envisioned closing the benzofuranone via an intramolecular aldol condensation followed by a rather mild dehydration. An oxidative transform followed by cyclization to form the acetal portion brought us to the substituted furanone **87**. Cleavage of the C15-C16 bond produced the crotonyl bromide **88** and the bromolactone **89**. **88** was to be derived from tetronic acid (**90**), and **89** was to arise from the same *C2*-symmetric diol **58**.

6.2 Concurrent Studies

As was mentioned previously, Justin Miller was charged with the synthesis of **58** and any subsequent materials derived from it. He undertook the task by first making di-(-)-menthyl fumarate (**91**) from maleic anhydride and (-)-menthol. The reaction proceeded through the di-(-)-menthyl ester of malic acid which was isomerized by piperidine to give **91**. The Diels-Alder reaction of **91** with 1,3-butadiene was catalyzed by diisobutyl-aluminum chloride in hexanes at -50 °C. This was a well established route to make the chiral diester **92**, which was subsequently reduced to the diol **58**. The above reactions proceeded in 75% overall yield from maleic anhydride with an enantiomeric excess of greater than 95% without purification until after the reduction to form **58** (Scheme 37). The literature precedents[79] for these reactions only claimed a 58% yield with the same enantiomeric excess.

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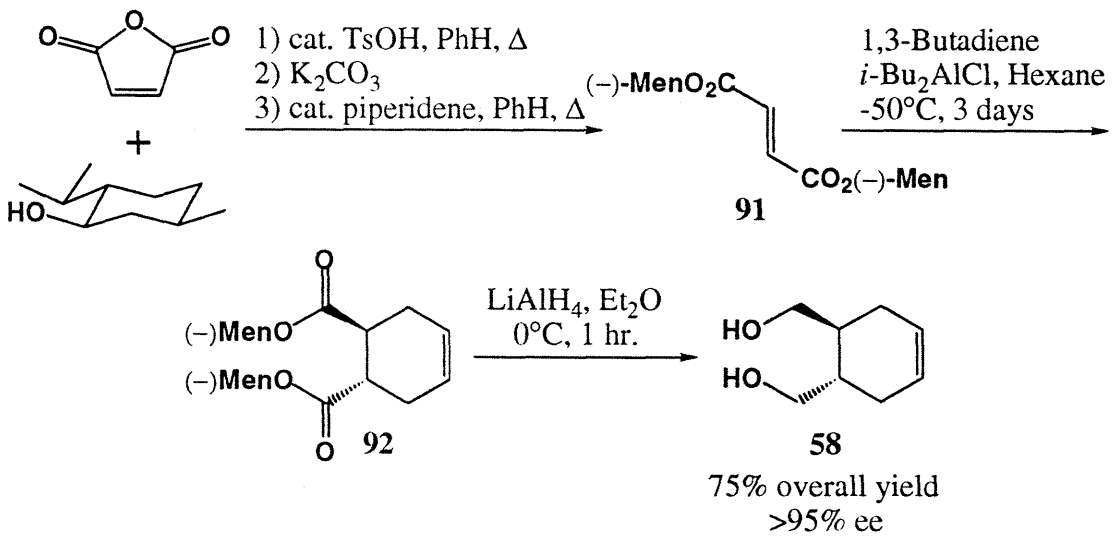
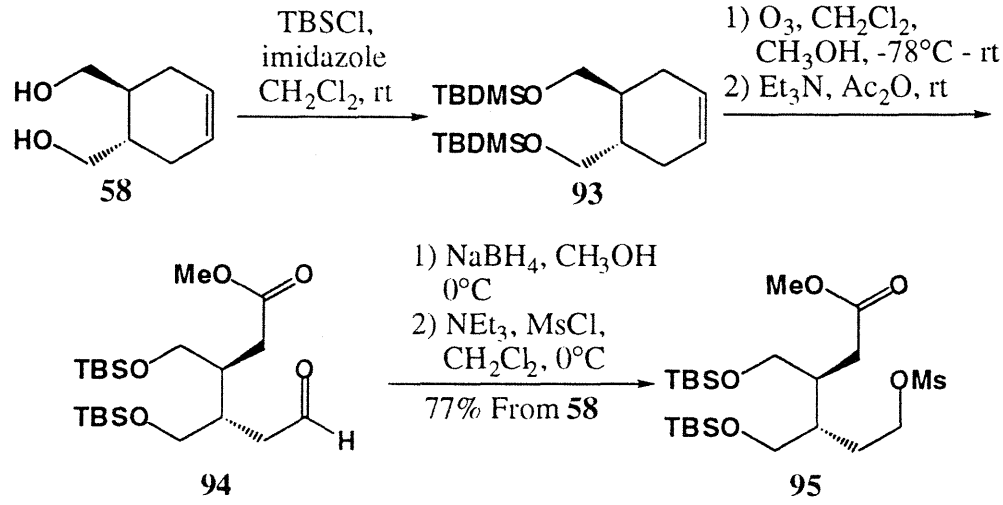
[79] (a) Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507-4510. (b) Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197-202.



Scheme 37

The diol was then diprotected with excess *t*-butylchlorodimethylsilane (TBDMSCl) in methylene chloride in the presence of an excess amount of imidazole[80] to form **93** in nearly quantitative yield.



Scheme 38

[80] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.

In order to differentiate between the two hyroxyl groups, the olefinic portion of the molecule was oxidatively cleaved with ozone in a solution of equal parts methanol and methylene chloride at -78 °C. The ozonide was warmed to ambient temperature and then treated with acetic anhydride and triethylamine which produced **94** which had one of the olefinic carbons oxidized to the methyl ester while the other remained as an aldehyde.[81] Selective reduction of the aldehyde followed by formation of the methanesulfonic ester produced **95** in excellent overall yield (Scheme 38).

In order to install the functionality of the target molecule, the sidechain moieties were synthesized by Mr. Miller and Federico Bernal. Mr. Miller was to construct the six carbon sidechain required for the C20-C25 portion of **39**, and Mr. Bernal was to construct the six carbon sidechain required for the C1-C6 portion. Mr. Bernal's task also included forming a dithioacetal moiety at the C6 portion which was to be added to an aldehyde in order to generate a protected version of the α-hydroxy ketone present in **39**. Mr. Miller began with a mercury(II) acetate catalyzed transetherification of ethyl vinyl ether with (*E*)-(+/-)-3-buten-2-ol which was followed by a spontaneous Claisen rearrangement to generate (*E*)-4-hexenal which was reduced with lithium aluminum hydride to form (*E*)-4-hexen-1-ol (**96**) in good yield. **96** was converted into the corresponding methanesulfonic ester which was displaced by lithium bromide in tetrahydrofuran to generate (*E*)-1-bromo-4-hexene (**97**). Mr. Bernal began with a dissolving metal reduction of 3-pentyn-1-ol in liquid ammonia using sodium as the reductant. The resulting (*E*)-3-penten-1-ol (**98**) was then converted to the methanesulfonic ester **99** and then to (*E*)-1-iodo-3-pentene (**100**) using standard conditions. Finally, treatment of **100** with 2-lithio-1,3-dithiane, which was generated by deprotonating 1,3-dithiane with *n*-butyllithium in tetrahydrofuran, generated the desired dithioacetal **101** (Scheme 39).

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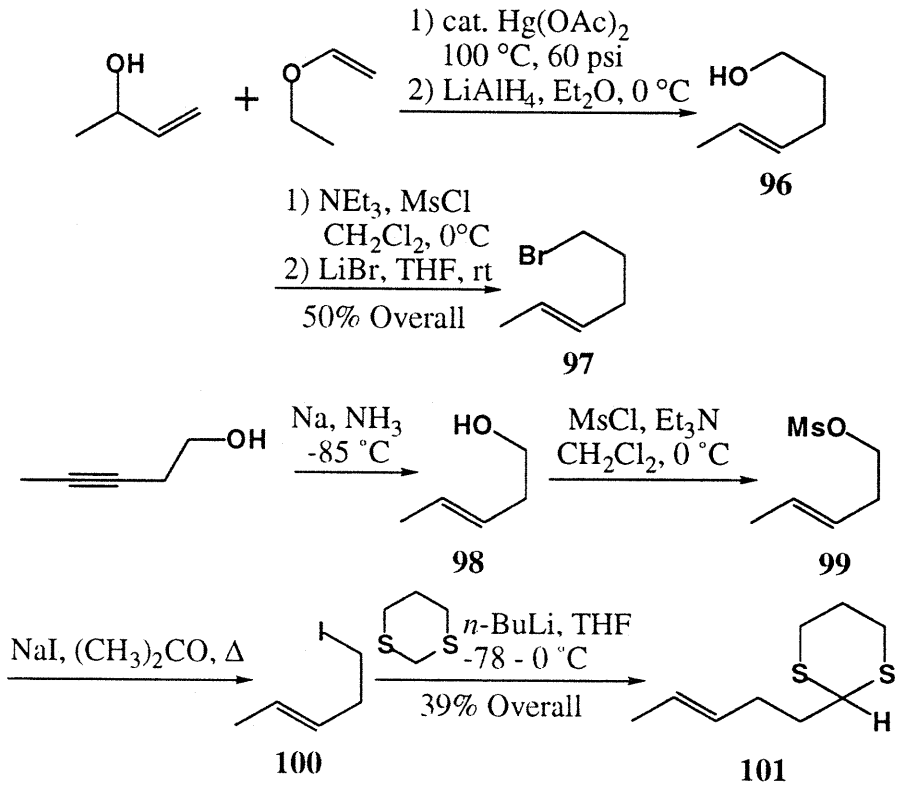
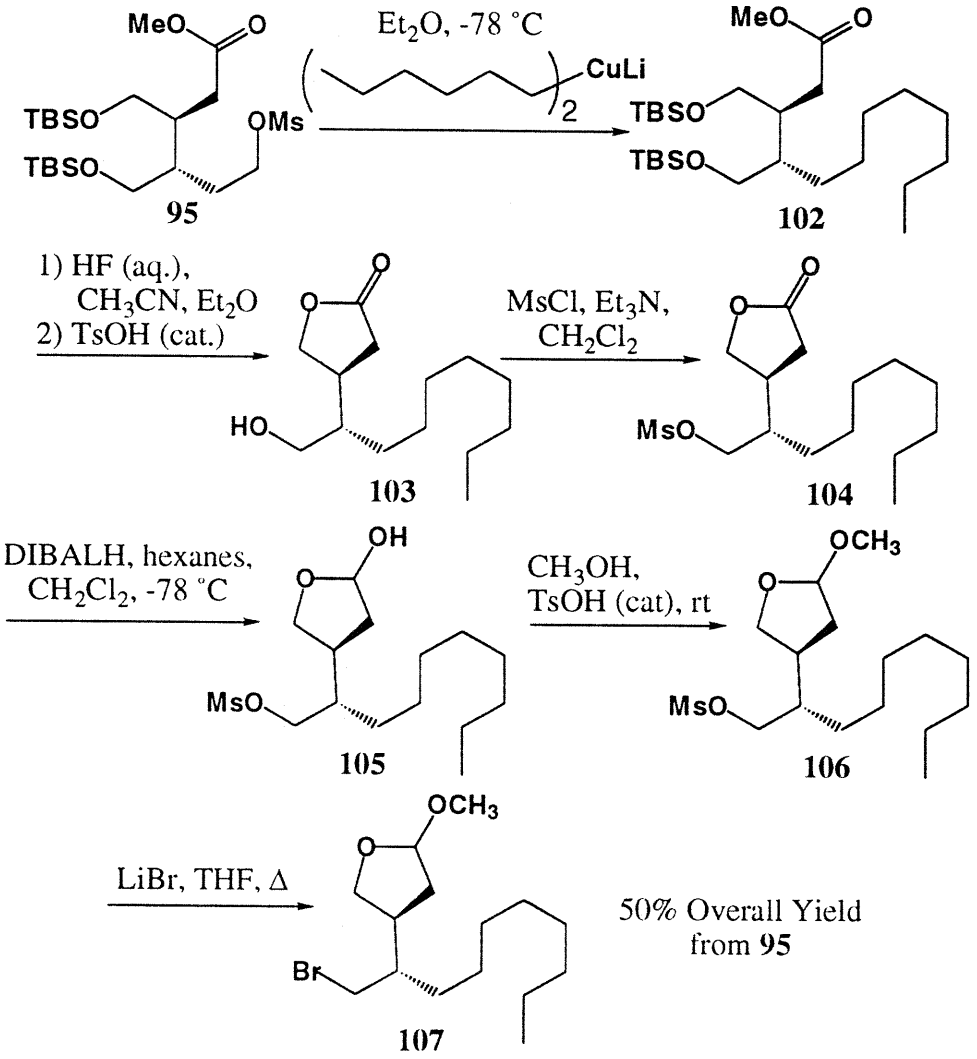
[81] Claus, R. E.; Schreiber, S. L. *Org. Synth. Coll. Vol. VII*, **1990**, 168-170.



Scheme 39: Assembly of the Alkenyl Sidechains

In order to study the effectiveness of some of the forthcoming steps in the synthetic sequence, Mr. Miller constructed a model system wherein the the six carbon C20-C25 alkenyl sidechain was replaced with a saturated analog. Treatment of **95** with lithium dihexylcuprate, which was generated from *n*-hexyllithium and copper(I) iodide, in diethyl ether resulted in the formation of the aliphatic ester **102**. Deprotection of the primary alcohols with an aqueous solution of hydrofluoric acid in acetonitrile appeared to result in a mixture of isomeric lactones which was equilibrated with a catalytic amount of *p*-toluenesulfonic acid to give only the γ-lactone **103**. The free hydroxyl group was converted to the methanesulfonic ester **104** using standard conditions. Diisobutyl-aluminum hydride reduction of the lactone portion afforded lactol **105** which was protected as the methyl acetal **106** using a catalytic amount of *p*-toluenesulfonic acid in methanol.

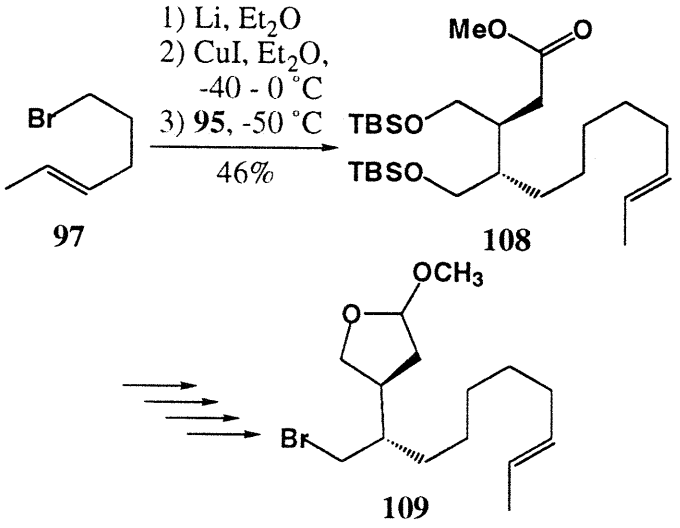
Bromoacetal **107** was formed by displacement of the primary methanesulfonic ester with lithium bromide in tetrahydrofuran (Scheme 40).



Scheme 40: Construction of the Aliphatic Model System

Although **107** was to be used to test the subsequent reactions, Mr. Miller still proceeded to generate the system for the completion of **39**. The organolithium reagent was generated from **97** and metallic lithium, and reacted *in situ* with copper(I) iodide to generate the corresponding lithium dialkylcuprate. A solution of **95** in diethyl ether was added to the cuprate solution to afford the unsaturated ester **108**. The yield of the addition reaction,

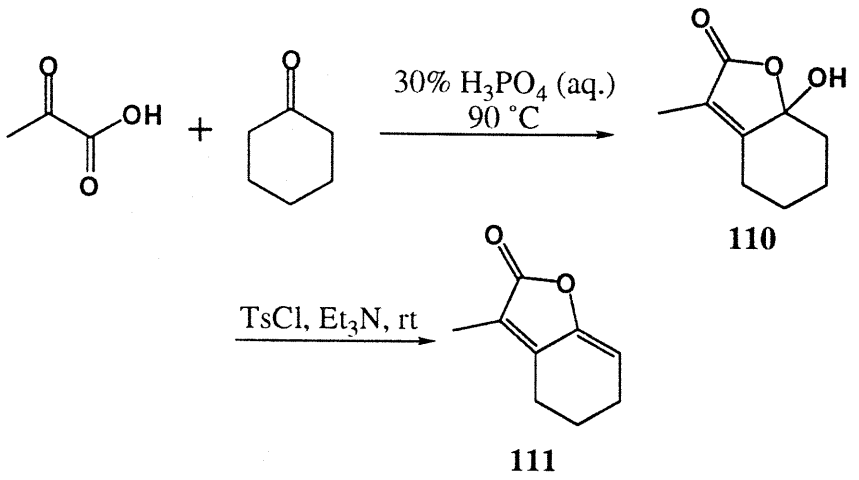
however, was only mediocre. Undaunted by this result, Mr. Miller forged ahead with the synthetic plan. Using the same procedures outlined for the construction of **107**, he was able to generate bromoacetal **109** (Scheme 41).



Scheme 41

After completing the synthesis of the alkenyl dithiane **101**, Mr. Bernal began the construction of a model dihydrobenzofuranone system in order to explore the possibility of either a 1,6-addition of an organocopper species or an alkylation at the α-position after deprotonating at the γ-position. Following a literature precedent[82], cyclohexanone and pyruvic acid were suspended in a 30% aqueous phosphoric acid solution and heated to reflux. After the hemiketal **110** was isolated, it was dehydrated using *p*-toluenesulfonyl chloride and triethylamine to generate 3-methyl-6,7-dihydrobenzofuranone (**111**) (Scheme 42).

[82] Wyss, H.; Révész, L.; Scheffold, R. *Helv. Chim. Acta* **1981**, *64*, 2272-2278..



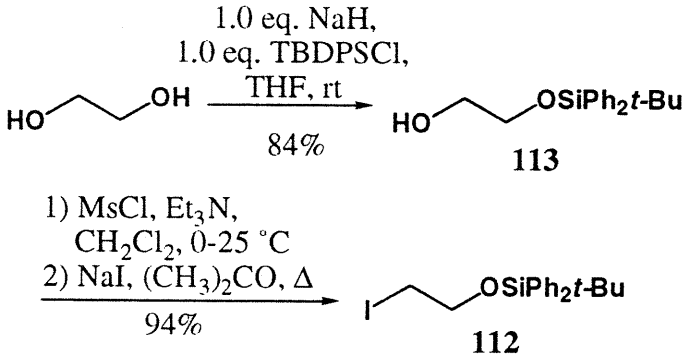
Scheme 42

To date, only the alkylation by 2-iodobenzyl bromide at the α-position after deprotonation at the γ-position has succeeded, and only in a very small yield. However, we are confident that the necessary modifications to our synthetic plan will allow for the total synthesis of **39**.

6.3 Studies Toward the Dihydrobenzofuranone Intermediate

With the assembly of the sidechains and the bromoacetal well underway, investigations into the assembly of the desired dihydrobenzofuranone **86** began with attempting to alkylate tetronic acid (**90**).

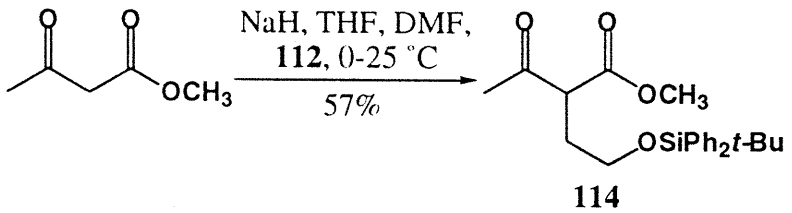
Our intention was to directly C-alkylate **90** with 2-(*tert*-butyldiphenylsiloxy)-1-iodoethane (**112**), which was prepared from ethylene glycol in two steps. The monoprotection of ethylene glycol using one equivalent each of sodium hydride and *tert*-butylchlorodiphenylsilane to afford alcohol **113** was accomplished in good yield, and conversion of the remaining primary hydroxyl group to the iodide **112** using standard procedures also proceeded nicely (Scheme 43).



Scheme 43

After **90** was deprotonated with sodium hydride in a tetrahydrofuran-*N*,*N*-dimethylformamide solution, a solution of **112** in tetrahydrofuran was added; however, only the O-alkylation product was obtained, and only in a very poor yield. Repeated attempts with a variety of conditions all had the same result.

Our next attempt to form the C-alkylated tetronic acid stemmed from the fact that one of the ways to synthesize **90** was to brominate methyl acetoacetate, which spontaneously cyclized to give **90**.[83] Methyl acetoacetate was deprotonated with sodium hydride in a tetrahydrofuran-*N*,*N*-dimethylformamide solution, and a solution of **112** in tetrahydrofuran was added to give the C-alkylated product **114** (Scheme 44). When **114** was treated with bromine in acetic acid none of the desired tetronic acid formed.



Scheme 44

[83] a) Conrad, M.; Schmidt, L. *Chem. Ber.* **1896**, *29*, 1042-1048. b) Kharasch, M. S.; Sternfeld, E.; Mayo, F. R. *J. Am. Chem. Soc.* **1937**, *59*, 1655-1657.

We had seemingly reached another dead-end, but the O-alkylation of tetronic acid held the key which opened a whole new realm of possibilities. If we could produce the O-allyl tetronic acid, then we might be able to effect a Claisen rearrangement to produce the C-alkylated product. During the investigation of the feasibility of these proposed steps, we found a literature precedents for the direct C-allylation of **90** with cinnamyl acetate or 2-cyclohexenyl acetate using tetrakis(triphenylphosphine)palladium(0) which was generated *in situ*.[84] Most of the examples resulted in the double allylation of **90** with the singly allylated species as side products. A method for producing only the singly allylated species was found[85]; however, it called for the use of a huge excess of **90** and only proceeded in 59% yield. For assembly of the target molecule, we decided to use allyl acetate[86], and instead of generating the catalyst in situ, we decided to make the catalyst separately. After much experimentation, the conditions for synthesizing 2-allyltetronic acid **115** were optimized as follows: 1 equivalent each of **90**, allyl acetate, and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU); 2 mole percent of the palladium catalyst; and heating to reflux for 2 days.

With the allylated product in hand, the next task was the functionalization of **115** to **88**, or a synthetic equivalent. Direct formation of the vinyl bromide was attempted using a Vilsmeier reagent[87]; however the conditions proved to be too harsh for the allyl group. Following another literature precedent[88], the vinyl triflate **116** was synthesized by treatment of **115** with *N,N*-diisopropylethylamine (DIEA) and trifluoromethanesulfonic anhydride (Tf_2O) in methylene chloride at -78 °C. The triflate was to serve as a synthetic equivalent for the bromide. Ozonolysis of the more electron rich double bond of the allyl group using Sudan Red III as an indicator[89] readily produced the corresponding aldehyde

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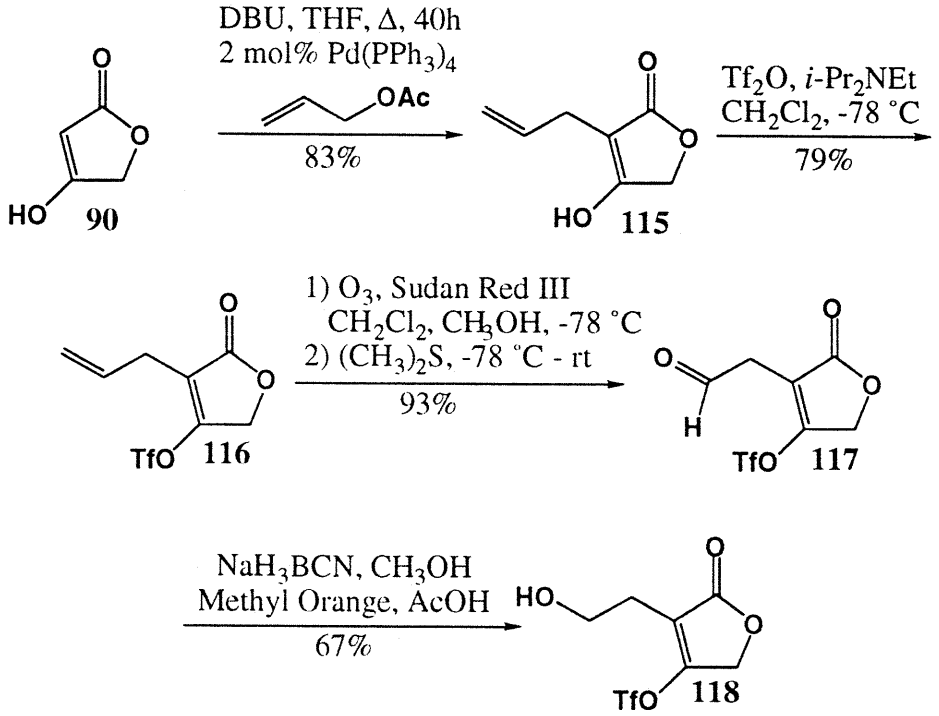
[84] a) Moreno-Mañas, M.; Prat, M.; Ribas, J.; Virgili, A. *Tetrahedron Lett.* **1988**, *29*, 581-584. b) Prat, M.; Moreno-Mañas, M.; Ribas, J. *Tetrahedron* **1988**, *44*, 7205-7212.
[85] Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron* **1994**, *50*, 8337-8346.
[86] None of the above references used allyl acetate in their examples.
[87] a) Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30*, 3753-3756. b) Jas, G. *Synthesis* **1991**, 965-966.
[88] Grigg, R.; Kennewell, P.; Savic, V. *Tetrahedron* **1994**, *50*, 5489-5494..
[89] Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis*, **1980**, 807-810.

117 without disturbing the double bond of the ring. Selective reduction of the aldehyde portion was accomplished using sodium cyanoborohydride[90] in a methanolic solution of acetic acid to generate the hydroxyethyl substituted furanone **118** (Scheme 45).

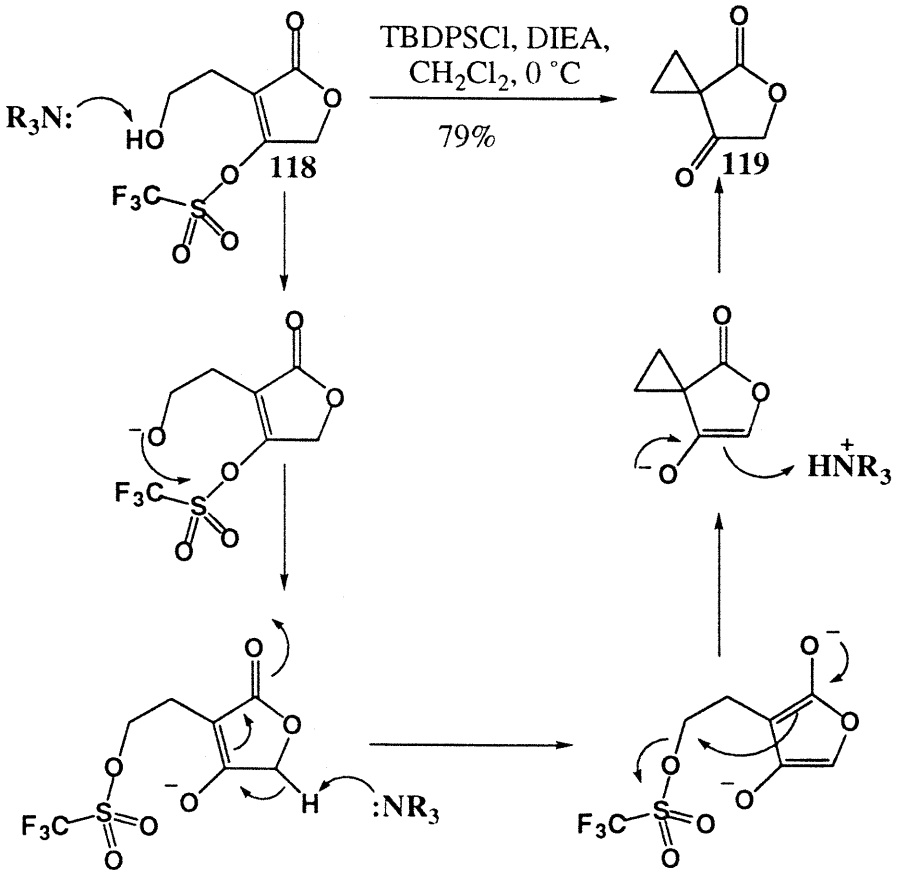


Scheme 45

The protection of the primary hydroxyl group was expected to proceed routinely; therefore, **118** was treated with *N,N*-diisopropylethylamine and *tert*-butylchlorodiphenyl-silane in methylene chloride, and a crystalline product was obtained. To our surprise, what we obtained was not the protected alcohol. The ^{1}H NMR spectrum contained none of the characteristic signals for the protecting group; in fact, the spectrum was conspicuously bare. The ^{13}C NMR spectrum contained signals for only five carbons, and the infra-red spectrum indicated the presence of two carbonyl groups in the molecule. Taking into account all of the spectral data, the product which was obtained was 5-oxaspiro-

[90] Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897-2904.

[2.4]heptane-4,7-dione. We had accidentally discovered a novel method for installing a cyclopropyl ring onto the furandione. In order to rationalize this discovery, the following mechanism was proposed (Scheme 46).

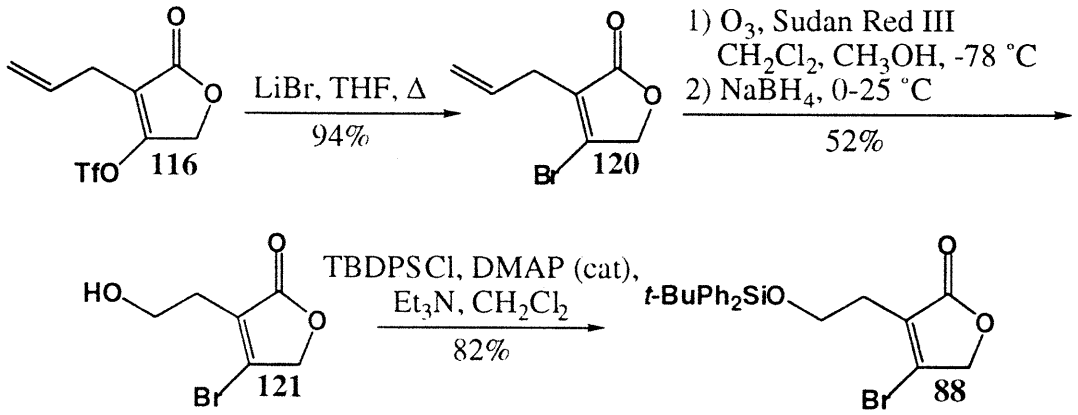


Scheme 46

The first steps in the proposed mechanism is the deprotonation of the primary hydroxyl group followed by the transfer of the trifluoromethanesulfonate group, which was thouroughly unexpected. What we failed to realize before trying this reaction was that the sulfur is activated by the vinylogous ester and was able to be transferred to the primary hydroxyl group. The next proposed step is the deprotonation of the γ-carbon to form the furan, which is probably aided by the silyl chloride present. Formation of the cyclopropane ring by alkylation of the ester enolate is likely to occur next. The remaining

enolate is then protonated either by the ammonium species present in the solution or the aqueous workup. A couple of different conditions for the protection of the primary hydroxyl group all resulted in the formation of **119**.

In order to circumvent this interesting but inconvenient process, a simple conversion of **118** to the analogous bromide **120** was sought. Standard conditions for the conversion of primary alkyl triflates to bromides were attempted and proceeded quite well. Ozonolysis of the allyl group and reduction of the ozonide to the primary hydroxyl group with sodium borohydride[91] gave **121** in a modest yield, which was comparable to the yield obtained from the two step procedure conducted with **118**. This time, when we attempted the protection of the hydoxyl group as the *tert*-butyldiphenylsilyl ether using 4-dimethyl-aminopyridine as a catalyst[92], we obtained the desired product **88** in excellent yield (Scheme 47).



Scheme 47

We now had the two pieces necessary for constructing the substituted furanone **87**, but before attempting to condense the crotonyl bromide **88** with the bromoacetal **109**, we began a model study to determine the best way to effect the coupling.

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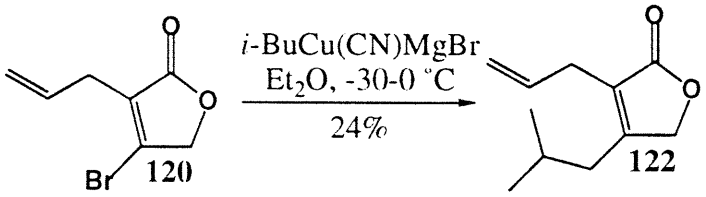
[91] Sousa, J. A.; Bluhm, A. L. *J. Org. Chem.* **1960**, *25*, 108-111.
[92] a) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975-2977. b) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99-102.

Instead of using **88** directly, **120** was used as a synthetic equivalent to test the various methods for the coupling reaction. Inspired by a couple of literature precedents, we decided to try a palladium(0) catalyzed cross coupling[93] of **120** with an alkylborane prepared *in situ* from isobutylmagnesium bromide and *B*-bromo-9-borabicyclononane. Repeated attempts to effect this coupling all resulted in the isolation of the starting bromide **120**. Following precedented methods of preparing alkylzinc halides, we attempted to form isobutylzinc bromide from 2-methyl-1-bromopropane and either a zinc-copper couple[94] or highly reactive zinc powder[95]; which was to be used in a palladium(0) catalyzed cross coupling[96] onto **120**. These attempts also resulted in no product formation.

Finally we decided to attempt the addition of an organocopper species with **120**. Since the alkyl bromide **109** was rather precious, we decided against making the dialkylcuprate; and, instead, opted for the lower-order cyanocuprate which was prepared *in situ* from isobutylmagnesium bromide and a copper(I) cyanide•lithium bromide complex[97] in tetrahydrofuran. Addition of **120** as a solution in tetrahydrofuran resulted in the formation of the desired furanone **122** (Scheme 48).



Scheme 48

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[93] Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314-321.
[94] Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149-3152.
[95] a) Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323-4324. b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445-1453.
[96] Negishi, E.; Kobayashi, M. *J. Org. Chem.* **1980**, *45*, 5223-5225.
[97] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390-2392.

After demonstrating that the cuprate additon would work, the remainder of the synthesis was placed in the capable hands of Mr. Miller, who had already done much to advance the project.

6.4 Future Prospects for the Completion of CP-225,917

Having established the viability of the formation of intermediate **88**, the total synthesis of **39** will be completed. Slight alterations in the plan may become necessary, but the groundwork described in the preceeding chapters should contribute to the final route.

Although the cuprate reaction worked, a means of improving the yield of the coupling reaction are needed. A couple of alternatives for effecting the coupling of **88** and **109** exist, including new attempts of the palladium(0) catalyzed cross coupling reaction and alkylation of an anion derived from **88** onto **109**.

With the synthetic plan is now at a stage where completion of the dihydrobenzofuranone **86** is now in sight. The synthesis of the substituted furan **85** needs to be completed to investigate the construction of the core ring system which can be tested on the model dihydrobenzofuranone **111** described earlier.

Part III: Experimental Section

Chapter 7 - Experimental Procedures and Spectral Data

7.1 General Procedures

Reaction Mixtures were stirred magnetically, unless noted otherwise. All moisture and/or air sensitive reactions were conducted in oven-dried glassware under a positive pressure of argon. Solvents and liquid reagents were transferred *via* syringe or cannula, unless noted otherwise. Reactions were monitored by thin-layer chromatography on silica coated glass plates. Organic solvents were removed through concentration on a Büchi rotary evaporator at a pressure of 20-40 mmHg.

Materials

Commercial solvents and reagents were used without further purification, unless specifically stated in the text, with the following exceptions:

Solvents:

Benzene was distilled under argon from calcium hydride.

Dichloromethane was distilled under nitrogen from phosphorous pentoxide.

Diethyl ether was distilled under nitrogen from sodium benzophenone ketyl.

1,2-Dimethoxyethane was distilled under nitrogen from sodium benzophenone ketyl.

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

Deuteriocholoroform, for spectra, was stored over anhydrous calcium chloride.

n-Hexane was 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 sodium metal.

Reagents:

n-Butyllithium was titrated prior to use with *sec*-butyl alcohol in tetrahydrofuran at 0 °C using 1,10-phenanthroline as an indicator.[98]

Chlorotrimethylsilane was distilled under argon.

Copper(I) iodide was purified by dissolving the discolored powder in a solution of potassium iodide (130 g) in water (100 mL) and treating the resulting solution with activated carbon (1 g) for a few minutes. The resulting suspension was filtered by gravity. The colorless filtrate was then diluted with water (30 mL) and the white precipitate, which had formed after dilution, was collected on a Büchner funnel and washed twice with water (10 mL) and twice with 95% ethanol (10 mL). The solid was collected and dried in a vacuum dessicator over phosphorous pentoxide.[99]

Copper(I) cyanide was stored in a drybox under nitrogen.

Lithium wire was stored under mineral oil, cut, and washed with hexanes prior to use.

Lithium bromide was stored in a drybox under nitrogen.

Diisopropylamine was distilled under nitrogen from calcium hydride.

4-(*N,N*-Dimethylamino)pyridine was recrystallized from hexanes.

Methanesulfonyl chloride was distilled at 20 mmHg.

Ozone was generated from a Welsbach ozone generator using the settings described in the text.

Tetrakis(triphenylphosphine)palladium(0) was prepared by first completely dissolving palladium(II) chloride (1.773 g, 10.0 mmol) and triphenylphosphine (13.114 g, 50.0 mmol) in dimethyl sulfoxide (120 mL) at 140 °C. 2 minutes after the oil bath was

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[98] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
[99] Kauffman, G. B.; Teter, L.A. *Inorg. Synth.* **1963**, *7*, 9-12.

removed, hydrazine hydrate (1.94 mL, 40.0 mmol) was added. The reaction mixture was allowed to cool to room temperature shielded from light for 6h. The resulting yellow crystals were collected on a fritted funnel under argon, washed successively three times each with ethanol (20 mL) and diethyl ether (20 mL), then dried overnight in a vacuum dessicator over phosphorous pentoxide to generate a yellow powder (10.665 g, 9.23 mmol, 92%). The reagent was stored in the dark under argon at -20 °C.[100]

Triethylamine was distilled under nitrogen from calcium hydride.

Triphenylphosphine was recrystallized from hexanes.

Chromatography

Column chromatography was performed using Merck 230-400 mesh silica gel. HPLC grade solvents were used.

Thin layer chromatography was conducted using Merck pre-coated, glass backed silica gel 60 plates with a 0.25 mm layer thickness , assimilated with 254-nm fluorescent indicator; J. T. Baker pre-coated, glass backed silica gel 60 plates with a 0.25 mm layer thickness, assimilated with 254-nm fluorescent indicator; or Merck pre-coated, glass backed silica gel 60 plates with a 0.5 mm layer thickness, assimilated with 254-nm fluorescent indicator. The plates were visualized by illumination with a short-wave ultraviolet lamp and by staining with an ethanolic solution of *p*-anisaldehyde (2%) with concentrated sulfuric acid (5%) and acetic acid (1.5%).

Instrumentation

Melting points were determined on a Fisher-Johns melting stage apparatus and are uncorrected.

^{1}H NMR spectroscopy was conducted on a Varian XL300 (300 MHz) spectrometer, a Varian XL301 (300 MHz) spectrometer, a Varian Unity 300 (300 MHz)

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[100] Cotton, F. A. *Inorg. Synth.* **1972**, *13*, 121.

spectrometer, or a Varian VXR500 (500 MHz) spectrometer using the specified frequencies. Chemical shifts are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane, using the residual chloroform signal (δ 7.26), methylene chloride signal (δ 5.20), acetone signal (δ 2.20), or dimethyl sulfoxide (δ 2.50) as standard. Multiplicities are reported with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), qnt (quintet), m (multiplet), bs (broad singlet), dd (doublet of doublets), *etc.*

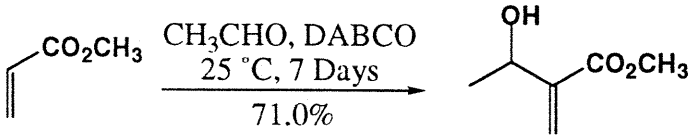
^{13}C NMR were recorded on a Varian XL300 (75 MHz) spectrometer, a Varian XL301 (75 MHz) spectrometer, a Varian Unity 300 (75 MHz) spectrometer, or a Varian VXR500 (125 MHz) spectrometer using the specified frequencies. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane, using the deuteriochloroform signal (ppm 77.0) as standard.

Infrared spectrophotometry (IR) was conducted using a Perkin-Elmer 1600 FTIR spectrophotometer. Broad absorption peaks are denoted with the letter "b" in parentheses.

High resolution mass spectra (HRMS) were recorded on a Finnigan MAT 8200 mass spectrometer using either electron ionization (EI) or fast atom bombardment (FAB) techniques by the MIT Spectroscopy Laboratory.

Elemental analyses (Anal.) were performed by Galbraith Laboratories in Knoxville, Tennessee.

7.2 Experimental Procedures for Part I

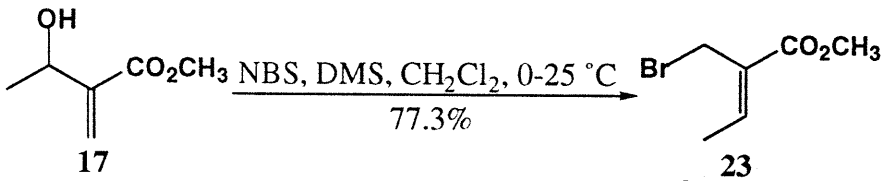


17
$C_6H_{10}O_3$
Mol. Wt.: 130.14

Methyl 3-Hydroxy-2-methylenebutanoate (17):

Diazabicyclo[2.2.2]octane (DABCO) (3.429 g, 0.0306 mol) was dissolved in methyl acrylate (39.47 g, 0.459 mol), and acetaldehyde (13.46 g, 0.306 mol) was added. The solution was shaken vigorously for 5 minutes and allowed to react at room temperature for 7 days. The solution was diluted with diethyl ether (200 mL) and washed with water (100 mL). The aqueous layer was acidified to pH 6 with 1.0 N aqueous hydrochloric acid and extracted twice with diethyl ether (50 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure to afford the Baylis-Hillman product as a colorless oil (28.27 g, 0.217 mol, 71.0 %). b.p. (10 mmHg) 90 °C (Lit.[101] 94-95 °C, 15 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.20 (s, 1 H); 5.81 (d, J = 1.3 Hz, 1 H); 4.60 (m, 1 H); 3.77 (s, 3 H); 2.62 (d, J = 3.0 Hz, 1 H); 1.37 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 167.0, 143.5, 124.1, 67.0, 51.8, 22.0.

[101]Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151-2161.

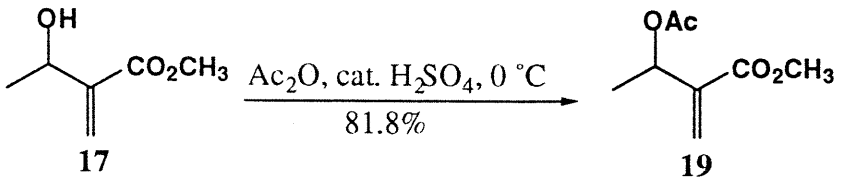


17

23
$C_6H_9BrO_2$
Mol. Wt.: 193.04

Methyl (2Z) 2-Bromomethyl-2-butenoate (23):

To a 0 °C mixture of *N*-bromosuccinimide (NBS) (3.008 g, 16.9 mmol) in methylene chloride (10 mL) under nitrogen, a solution of dimethyl sulfide (DMS) (1.142 g, 18.4 mmol) in methylene chloride (5 mL) was added. The resulting yellow solution with a white precipitate was stirred at 0 °C for 5 minutes. A solution of methyl 3-hydroxy-2-methylenebutanoate (2.00 g, 15.4 mmol) in methylene chloride (5 mL) was added dropwise. The opaque yellow mixture was allowed to warm to room temperature and stirred overnight. The now translucent yellow solution was diluted with pentane (100 mL) and poured onto an ice/brine slurry (100 mL). The organic phase was separated, and the aqueous phase was extracted three times with diethyl ether (50 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by column chromatography (5:1 hexanes-diethyl ether) afforded the bromide as a pale yellow oil (2.299 g, 11.9 mmol, 77.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (q, 1 H, J = 7.3 Hz), 4.22 (s, 2 H), 3.78 (s, 3 H), 1.90 (d, 3 H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 143.4, 130.2, 52.1, 24.0, 14.5, 12.5.

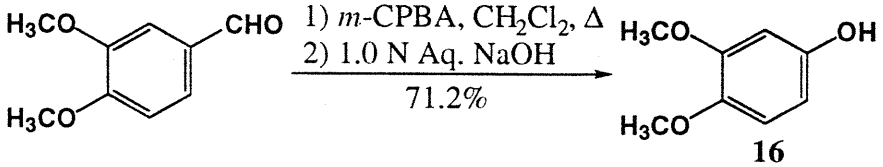


17 **19**

$C_8H_{12}O_4$
Mol. Wt.: 172.18

Methyl 3-Acetoxy-2-methylenebutanoate (19):

Methyl 3-hydroxy-2-methylenebutanoate (5.399 g, 41.5 mmol) and acetic anhydride (6.353 g, 62.2 mmol) were combined and cooled to 0 °C. A catalytic amount of sulfuric acid (2 drops) was added, and the solution stirred at 0 °C for 30 minutes, during which the solution turned a pale yellow color. The solution was poured onto water and extracted three times with diethyl ether. The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was distilled under reduced pressure to afford the product as a colorless oil (5.846 g, 33.9 mmol, 81.8 %). B.P. (0.15 mm Hg) 34 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.26 (s, 1 H); 5.80 (s, 1 H); 5.68 (q, 1 H, J = 6.8 Hz); 3.75 (s, 3 H); 2.05 (s, 3 H); 1.38 (d, 3 H, J = 6.9 Hz).

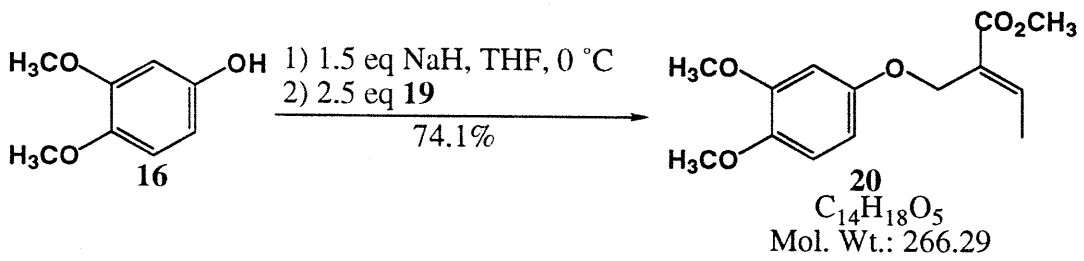


16
$C_8H_{10}O_3$
Mol. Wt.: 154.16

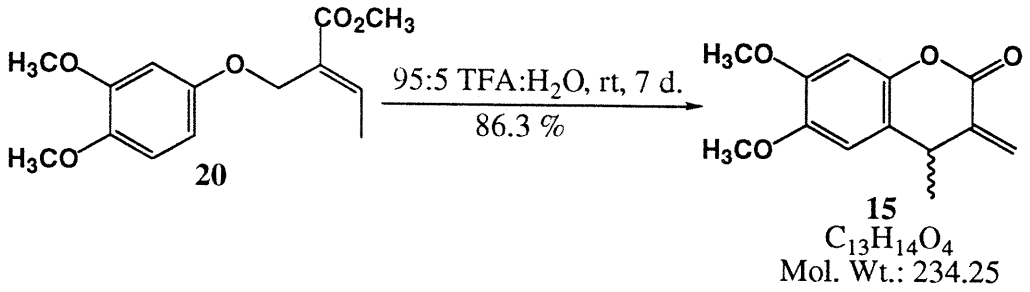
3, 4-Dimethoxyphenol (16):

Veratraldehyde (5.00 g, 30.1 mmol, recrystallized from diethyl ether) was dissolved in methylene chloride (100 mL). 3-Chloroperoxybenzoic acid (13.00 g of a 50-60% mixture, 37.7-45.2 mmol) was added, and the solution was heated to reflux for 24 hours. The mixture, which had become cloudy and turned a dark orange color, was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with a saturated aqueous sodium bicarbonate solution until bubbling ceased, and washed with brine. The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue (the crude formate ester) was dissolved in methanol (50 mL) and hydrolysed under argon with a 1.0 N aqueous sodium hydroxide solution (35 mL) for 30 minutes. The mixture was extracted four times with diethyl ether (50 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was eluted through a short plug of silica gel with diethyl ether. Removal of the solvent yielded the phenol as a mauve powder (3.305 g, 21.4 mmol, 71.2 %). m.p. 75-76 °C (Lit.[102] 79 °C) ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (d, 1 H, J = 8.5 Hz); 6.45 (d, 1 H, J = 2.7 Hz); 6.32 (dd, 1 H, J_1 = 8.5 Hz, J_2 = 2.7 Hz); 5.00 (bs, 1 H); 3.79 (s, 6 H).

[102]Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc. Perkin. Trans. I* **1974**, 1353-1354.



Methyl (2Z)-2-((3',4'-Dimethoxy)phenoxy)methyl-2-butenoate (20): 3,4-Dimethoxyphenol (50 mg, 0.324 mmol) was dissolved in tetrahydrofuran (2 mL) and cooled to 0 °C; sodium hydride (20 mg of a 60% dispersion in mineral oil, 0.486 mmol) was added. Methyl 3-acetoxy-2-methylenebutanoate (140 mg, 0.811 mmol) was dissolved in tetrahydrofuran (1 mL) and added dropwise. The resulting mixture was stirred at 0 °C for 7 days. The reaction was quenched with water, and the resulting mixture was extracted three times with diethyl ether (15 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and condensed under reduced pressure. Purification by column chromatography (3:1 hexanes-diethyl ether) yielded the allyl phenyl ether as a white crystalline solid (64 mg, 0.240 mmol, 74.1 %). m.p. 60-61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (q, 1 H, J = 7.3 Hz); 6.76 (d, 1 H, J = 8.7 Hz); 6.54 (d, 1 H, J = 2.8 Hz); 6.46 (dd, 1 H, J_1 = 8.7 Hz, J_2 = 2.8 Hz); 4.72 (s, 2 H); 3.83 (s, 3 H); 3.82 (s, 3 H); 3.75 (s, 3 H); 1.93 (d, 3 H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 167.0, 153.3, 149.8, 143.7, 128.8, 111.7, 104.4, 101.2, 62.2, 56.4, 55.8, 51.9, 14.8. FTIR (CCl_4 solution): cm^{-1}.



20

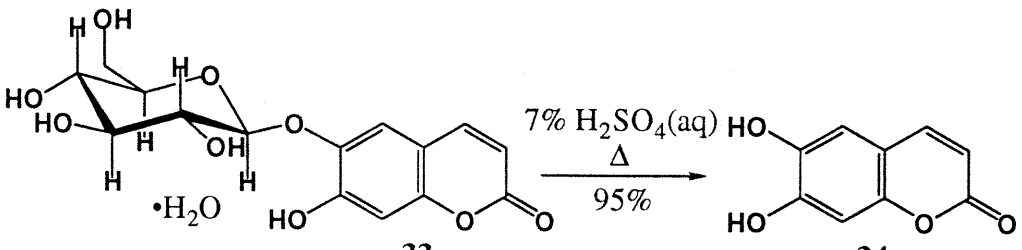
15

$C_{13}H_{14}O_4$

Mol. Wt.: 234.25

(+/-)-6,7-Dimethoxy-4-methyl-3-methylenecoumarin (15):

Methyl (2Z)-2-(3',4'-dimethoxyphenoxy)methyl-2-butenoate (**20**, 50 mg, 0.188 mmol) was dissolved in a 1:19 H_2O/TFA solution (500 μL) and allowed to react at room temperature for 7 days. The trifluoroacetic acid was removed under reduced pressure. The residue was redissolved in methylene chloride, washed once with dilute aqueous sodium hydroxide solution, once with dilute aqueous hydrochloric acid solution, and once with H_2O. The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to afford pure coumarin as a yellow powder (38 mg, 0.162 mmol, 86.3 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.62 (s, 1 H); 6.60 (s, 1 H); 6.33 (s, 1 H); 5.71 (s, 1 H); 3.85 (s, 3 H), 3.83 (s, 3 H); 3.70 (q, 1 H, J = 6.9 Hz); 1.39 (d, 3 H, J = 6.9 Hz).

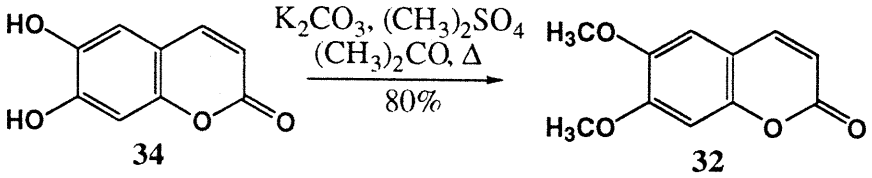


33

34
$C_9H_6O_4$
Mol. Wt.: 178.14

Esculetin (34):

Esculin monohydrate (10.00 g, 27.91 mmol) was suspended in a 7 % v/v H_2SO_4/H_2O solution (150 mL). The mixture was heated to reflux for 6 hours. After cooling to room temperature, the mixture was placed in a 4 °C refridgerator overnight to facilitate precipitation. The product was filterted and dried in a 100 °C oven overnight to afford esculetin as a light tan powder (4.711 g, 26.44 mmol, 94.7 %). ^{1}H NMR (300 MHz, d_6-DMSO): δ 10.21 (s, 1 H); 9.41 (s, 1 H); 7.87 (d, 1 H, J = 9.4 Hz); 6.97 (s, 1 H); 6.73 (s, 1 H); 6.16 (d, 1 H, J = 9.4 Hz).

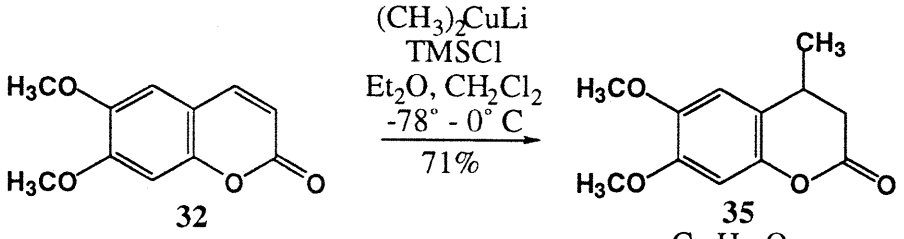


34 **32**

$C_{11}H_{10}O_4$
Mol. Wt.: 206.19

6,7-Dimethoxycoumarin (32):

Esculetin (3.000 g, 16.84 mmol) was added to dry acetone (50 mL); potassium carbonate (9.310 g, 67.36 mmol) and dimethyl sulfate (6.37 mL, 67.4 mmol) were added, and the resulting solution was heated to reflux overnight. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was recrystallized from aqueous methanol to give 6,7-dimethoxycoumarin (scoparone) as light tan needles (2.784 g, 13.50 mmol, 80.2 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, 1 H, J = 10.2 Hz); 6.83 (s, 1 H); 6.82 (s, 1 H); 6.27 (d, 1 H, J = 9.6 Hz), 3.94 (s, 3 H); 3.90 (s, 3 H).



32

35

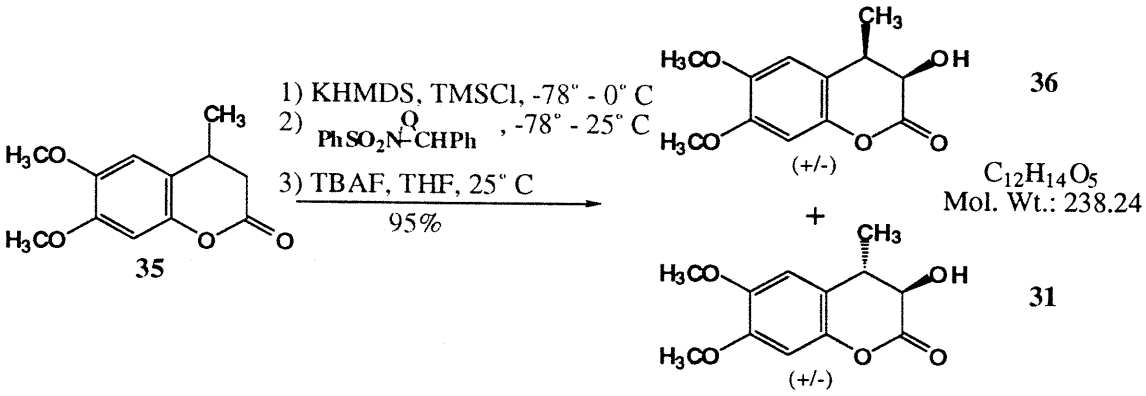
$C_{12}H_{14}O_4$

Mol. Wt.: 222.24

(+/-)-6,7-Dimethoxy-4-methylchromanone (35):

An oven-dried 500 mL round bottom flask equipped with a stirbar was charged with copper(I) iodide (5.541 g, 29.1 mmol). After capping the flask with a rubber septum, it was evacuated and filled with argon five times. Dry diethyl ether (150 mL) was added, and the resulting suspension was stirred while cooling to -78 °C (dry ice/acetone). A 1.35 M solution of methyllithium (43.11 mL, 58.2 mmol) was added dropwise over 10 minutes. The resulting mixture became a homogeneous pale yellow solution. After stirring for 5 minutes at -78 °C, the solution was warmed to 0 °C (ice/H_20) for 20 minutes to allow for the generation and dissolution of the dimethyl cuprate. The solution was recooled to -78 °C, and freshly distilled chlorotrimethylsilane (TMSCl) (3.70 mL, 29.1 mmol) was added dropwise. After stirring for 2 minutes, a solution of 6,7-dimethoxycoumarin (3.000 g, 14.5 mmol) in methylene chloride (50 mL) was added dropwise. The resulting bright orange mixture was gradually warmed to 0 °C over 4 hours. The mixture was stored in a -50 °C freezer overnight (12 hours). The brown reaction mixture was warmed to 0 °C and quenched by addition of a 10% ammonium hydroxide in saturated aqueous ammonium chloride solution (100 mL). The resulting mixture was extracted four times with methylene chloride (50 mL) until the organic layer was colorless, adding more saturated aqueous ammonium chloride solution (100 mL) to separate any emulsion which had formed. The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Column chromatography (eluent gradient from 7:1 to 1:1 hexanes-ethyl acetate) afforded (+/-)-6,7-dimethoxy-4-methyl-chromanone as an

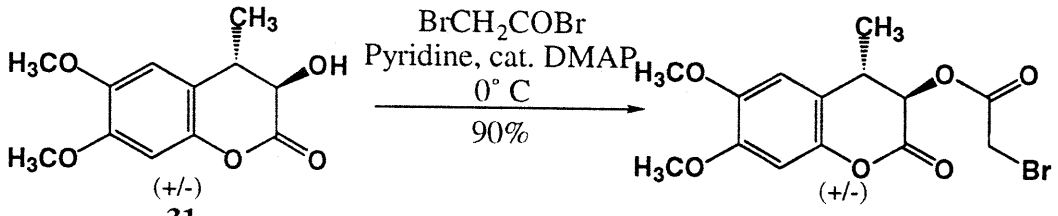
amorphous tan powder (2.285 g, 10.28 mmol, 70.7 %). m.p. 77-78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1 H); 6.59 (s, 1 H); 3.85 (s, 3 H); 3.83 (s, 3 H); 3.08 (dq, 1 H, J_1 = 13.2 Hz, J_2 = 6.7 Hz); 2.80 (dd, 1 H, J_1 = 15.8 Hz, J_2 = 5.5 Hz); 2.53 (dd, 1 H, J_1 = 15.8 Hz, J_2 = 6.8 Hz); 1.29 (d, 3 H, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 168.4, 148.6, 145.7, 144.8, 137.7, 118.6, 109.0, 56.4, 56.0, 36.9, 29.2, 20.1. FTIR (thin film): 2938, 1757, 1516, 1445, 1215, 1157, 1004 cm^{-1}. HRMS (EI) calculated for $C_{12}H_{14}O_4$ (M^+): 222.08921; observed: 222.08911. Anal. calculated for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Observed: C, 64.74; H, 6.49.



(+/-)-6,7-Dimethoxy-3-hydroxy-4-methyl-(3,4-*anti*)-chromanone (31) and (+/-)-6,7-Dimethoxy-3-hydroxy-4-methyl-(3,4-*syn*)-chromanone (36):

35 (100 mg, 0.450 mmol) was placed in a 10 mL oven-dried round bottom flask equipped with a stirbar and a rubber septum. The flask was evacuated an placed under an argon atmosphere. Tetrahydrofuran (2 mL) was added, and the solution was cooled to -78 °C (dry ice/acetone). Chlorotrimethylsilane (TMSCl) (114 μL, 0.900 mmol) was added dropwise followed by a 0.5 M potassium bis(trimethylsilyl)amide solution in toluene (990 μL, 0.495 mmol) which was also added dropwise. The solution was stirred for 1 hour while gradually warming to 0 °C. After recooling to -78 °C, a solution of *N*-benzene-sulfonyl-3-phenyloxaziridine (235 mg, 0.900 mmol) in tetrahydrofuran (3 mL) was added via cannula. The resulting mixture warmed to the ambient temperature overnight. A 1.0 M solution of tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (900 μL, 0.900 mmol) was added, and the solution was stirred at the ambient temperature for 10 minutes. The reaction mixture was quenched by addition of a 1.0 N aqueous hydrochloric acid solution (1 mL). After removal of the solvent, the residue was dissolved in methylene chloride (20 mL), washed once with saturated aqueous ammonium chloride (10 mL), and once with water (10 mL). The combined aqueous layers were extracted three times with methylene chloride (10 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Column chromatography (eluent gradient from 6:1 to 4:1 hexanes-ethyl acetate) afforded starting

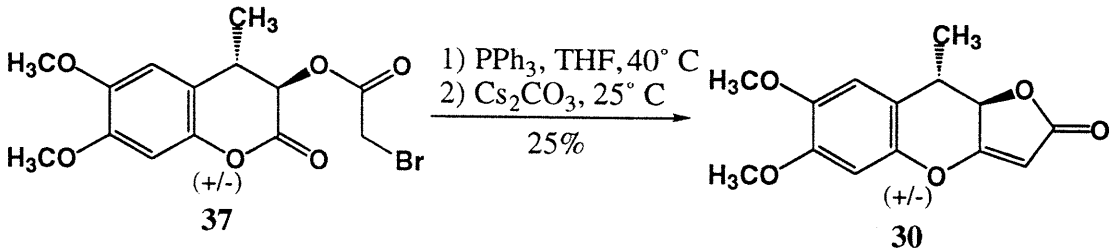
material (24 mg, 0.108 mmol, 24%), **31** (58 mg, 0.243 mmol, 54%, 71% based on recovered starting material), and **36** (20 mg, 0.084 mmol, 19%, 25% based on recovered starting material). Analytical data for **31**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1 H); 6.63 (s, 1 H); 3.97 (dd, 1 H, J_1 = 12.6 Hz, J_2 = 2.7 Hz); 3.89 (s, 3 H); 3.86 (s, 3 H); 3.34 (d, 1 H, J = 2.6 Hz); 3.05 (dq, 1 H, J_1 = 12.9 Hz, J_2 = 6.4 Hz); 1.53 (d, 3 H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 171.8, 149.2, 146.4, 143.5, 124.5, 116.5, 108.9, 70.5, 56.5, 56.1, 35.1, 14.5. Analytical data for **36**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.66 (s, 1 H); 6.62 (s, 1 H); 4.60 (dd, 1 H, J_1 = 6.4 Hz, J_2 = 2.8 Hz); 3.88 (s, 3 H); 3.86 (s, 3 H); 3.29 (d, 1 H, J = 2.8 Hz); 3.19 (qnt, 1 H, J = 6.8 Hz); 1.18 (d, 3 H, J = 8.0 Hz).



$C_{14}H_{15}BrO_6$
Mol. Wt.: 359.17

(+/-)-3-Bromoacetoxy-6,7-dimethoxy-4-methyl-(3,4-*anti*)-chromanone (37):

31 (60 mg, 0.252 mmol) and 4-dimethylaminopyridine (DMAP) (3 mg, 0.025 mmol) were dissolved in methylene chloride (4 mL). The solution was cooled to 0 °C (ice/H_2O), and bromoacetyl bromide (66 μL, 0.756 mmol) and pyridine (61 μL, 0.756 mmol) were added sequentially. The solution warmed to the ambient temperature while stirring overnight. The reaction mixture was poured onto water (10 mL), and the layers were separated. The organic layer was washed once with water (10 mL), once with brine (10 mL), and once again with water (10 mL). The combined aqueous layers were extracted three times with methylene chloride (10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Column chromatography (eluent gradient from 7:1 to 5:1 hexanes-ethyl acetate) afforded **37** as an amorphous white powder which was crystallized from diethyl ether to form colorless needles (81 mg, 0.226 mmol, 90%). m.p. 151-152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (s, 1 H); 6.64 (s, 1 H); 5.20 (d, 1 H, J = 12.7 Hz); 4.05, (d, 1 H, J = 12.2 Hz); 3.99 (d, 1 H, J = 12.2 Hz); 3.90 (s, 3 H); 3.87 (s, 3 H); 3.39 (dq, 1 H, J_1 = 12.9 Hz, J_2 = 6.6 Hz); 1.46 (d, 3 H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 166.4, 164.6, 149.5, 146.4, 143.5, 115.1, 108.6, 101.0, 72.2, 56.5, 56.2, 32.8, 24.9, 14.4. FTIR (thin film): 2972, 1779, 1518, 1443, 1406, 1226, 1192, 857, 782 cm^{-1}. HRMS (EI) calculated for $C_{14}H_{15}BrO_6$ (M^+): 358.00520; observed: 358.00519. Anal. calculated for $C_{14}H_{15}BrO_6$: C, 46.82; H, 4.21. Observed: C, 46.82; H, 4.34.



37

30

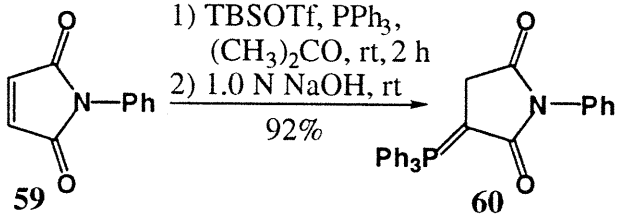
$C_{14}H_{14}O_5$

Mol. Wt.: 262.26

(+/-)-6,7-Dimethoxy-9-methyl-9,9a-dihydro-*2H*-furo[3,2-*b*]-(9,9a-*anti*)-chromen-2-one (30):

In an oven-dried 5 mL round bottom flask **37** (50 mg, 0.139 mmol) was dissolved in tetrahydrofuran (1 mL). Triphenylphosphine (73 mg, 0.278 mmol) was added, and the mixture was heated to 45 °C for 2 hours. The mixture was cooled to the ambient temperature, and cesium carbonate (181 mg, 0.557 mmol) was added. The resulting mixture was stirred overnight at the ambient temperature. After addition of water (2 mL), the mixture was extracted three times with methylene chloride (15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (methylene chloride) to yield **30** as an amorphous white powder (9 mg, 0.034 mmol, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1 H); 6.65 (s, 1 H); 5.37 (d, 1 H, J = 1.3 Hz); 4.56 (dd, 1 H, J_1 = 12.1 Hz, J_2 = 1.4 Hz); 3.89 (s, 3 H); 3.88 (s, 3 H); 2.96 (dq, 1 H, J_1 = 12.3 Hz, J_2 = 6.1 Hz); 1.58 (d, 3 H, J = 6.7 Hz).

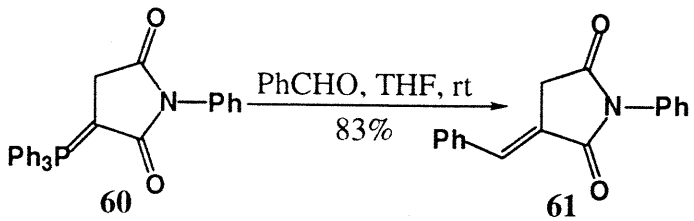
7.3 Experimental Procedures for Part II



$C_{28}H_{22}NO_2P$
Mol. Wt.: 435.45

_N_-Phenyl-2-(triphenylphosphoranylidine)succinimide (60):

_N_-Phenyl-maleimide (500 mg, 2.89 mmol) was dissolved in dry acetone (5 mL). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (730 μL, 3.18 mmol) and triphenylphosphine (833 mg, 3.18 mmol) were added sequentially. After 2 hours, the solution had turned red, and a 1.0 N aqueous sodium hydroxide solution was added (5.77 mL, 5.77 mmol), and a precipitate began to form. After stirring at room temperature overnight, the reaction mixture was neutralized by addition of a 1.0 N aqueous hydrochloric acid solution. The mixture was extracted twice with methylene chloride (20 mL). The combined organic layers were washed once with saturated aqueous sodium bicarbonate (20 mL), then dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent under reduced pressure afforded **60** as an amorphous white powder (1.161 g, 2.67 mmol, 92%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.21-7.67 (m, 20 H); 3.14 (s, 2 H).

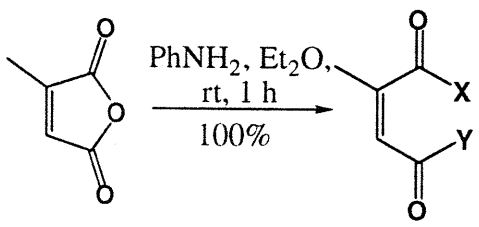


60 **61**

$C_{17}H_{13}NO_2$
Mol. Wt.: 263.29

2-Benzylidine-*N*-phenylsuccinimide (61):

The phosphonium ylide **60** (500 mg, 1.15 mmol) was suspended in tetrahydrofuran (2 mL). Benzaldehyde (175 μL, 1.72 mmol) was added, and the reaction mixture was stirred at the ambient temperature for 2 hours. The solvent was removed under reduced pressure, and the residue was triturated with methanol (5 mL). Filtration of the mixture afforded **61** as an amorphous white powder (252 mg, 0.957 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (t, 1 H, J = 2.3 Hz); 7.36-7.57 (m, 10 H); 3.78 (d, 2 H, J = 2.4 Hz).

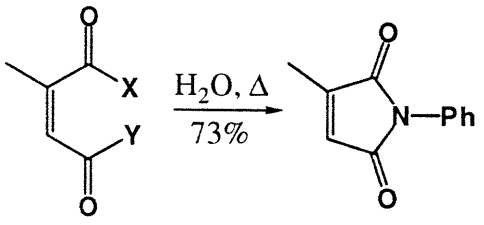


63 **64**

64a: X = -N(H)Ph; Y = -OH
64b: X = -OH; Y = -N(H)Ph
$C_{11}H_{11}NO_3$
Mol. Wt.: 205.21

(Z)-4-Anilino-2-methyl-4-oxo-2-butenoic Acid (64a) and (Z)-4-anilino-3-methyl-4-oxo-2-butenoic Acid (64b):

Citraconic anhydride (**63**) (5.000 g, 44.6 mmol) was dissolved in diethyl ether (40 mL), and a solution of aniline (4.07 mL, 44.6 mmol) in diethyl ether (10 mL) was added dropwise via a pressure equalizing dropping funnel. The reaction mixture was stirred vigorously for 1 hour at the ambient temperature. After cooling to 0 °C (ice/water) for 20 minutes, the precipitate was filtered and washed with cold diethyl ether to afford the mixture of anilic acids (**64**) as an amorphous white powder (9.166 g, 44.6 mmol, 100%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 12.64 (bs, 2 H); 10.14 (s, 1 H); 10.07 (s, 1 H); 7.60 (d, 4 H, J = 8.5 Hz); 7.30 (t, 4 H, J = 7.9 Hz); 7.05 (t, 2 H, J = 7.4 Hz); 6.09 (q, 1 H, J = 1.6 Hz); 5.80 (q 1 H, J = 1.5 Hz); 2.04 (d, 3 H, J = 1.5 Hz); 1.98 (d, 3 H, J = 1.6 Hz).



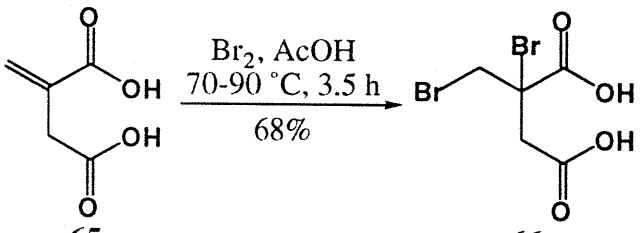
64 **62**

64a: X = -N(H)Ph; Y = -OH $C_{11}H_9NO_2$

64b: X = -OH; Y = -N(H)Ph Mol. Wt.: 187.19

2-Methyl-*N*-phenylmaleimide (62):

A mixture of the anilic acids (**64**) (1.500 g, 7.31 mmol) was dissolved in water (30 mL) and heated to reflux over a steam bath (100 - 110 °C) for 38 hours. After cooling to the ambient temperature, the precipitate was collected over a Büchner funnel and dried in a vacuum dessicator over anhydrous phosphorous pentoxide to afford **62** as a tan powder (0.992 g, 5.30 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.50 (m, 2 H); 7.32-7.38 (m, 3 H); 6.48 (q, 1 H, J = 1.8 Hz); 2.17 (d, 3 H, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 170.6, 169.5, 145.8, 131.8, 129.0, 127.6, 127.5, 125.9, 102.3, 85.6, 11.1.

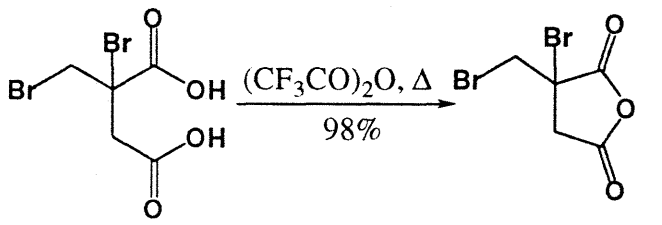


65 **66**

$C_5H_6Br_2O_4$
Mol. Wt.: 289.91

2-Bromo-2-(bromomethyl)succinic Acid (66):

Itaconic acid (**65**) (36.00 g, 0.277 mol) was suspended in glacial acetic acid (50 mL) and warmed to 70 °C (oil bath temperature) while stirring. A solution of bromine (16.0 mL, 0.313 mol) in glacial acetic acid (50 mL) was added dropwise while the solution was heated to 90 °C (oil bath temperature). After the addition was complete (2 hours), the temperature of the mixture was maintained at 90 °C for an additional 1.5 hours. After cooling to room temperature, the volatile components were removed under reduced pressure. The residue was suspended in carbon tetrachloride (50 mL) and stored in a 4 °C refridgerator overnight. The precipitate was collected over a scintered glass funnel and washed with carbon tetrachloride to afford **66** as an amorphous white powder (54.95 g, 0.190 mol, 68%). All of the material was used immediately in the following reaction.

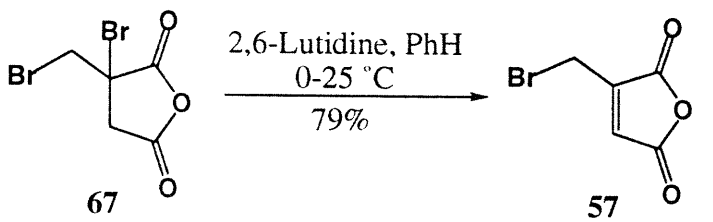


66 **67**

$C_5H_4Br_2O_3$
Mol. Wt.: 271.89

2-Bromo-2-(bromomethyl)succinic Anhydride (67):

In a 250 mL round bottom flask equipped with a stirbar and refluxing condenser topped with a drying tube filled with anhydrous sodium carbonate, **66** (54.95 g, 0.190 mol) was suspended in trifluoroacetic anhydride (60 mL), and the mixture was heated to reflux for 30 minutes. The solvent was removed under reduced pressure, and the residue was stored under high vaccuum (0.15 mmHg) overnight to remove any residual solvent. **67** was collected as colorless needles (50.53 g, 0.186 mol, 98%). The entire amount of **67** was used immediately in the following reaction. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (d, 1 H, J = 10.6 Hz); 3.90 (d, 1 H, J = 19.6 Hz); 3.89 (d, 1 H, J = 11.1 Hz); 3.45 (d, 1 H, J = 19.7 Hz).



67

57

$C_5H_3BrO_3$

Mol. Wt.: 190.98

2-(Bromomethyl)maleic Anhydride (57):

In an oven-dried 250 mL round bottom flask equipped with a stirbar and septum, **67** (50.53 g, 0.186 mol) was dissolved in benzene (100 mL) and cooled to 0 °C (ice/water). 2,6-Lutidine (2,6-dimethylpyridine) (22.0 mL, 0.189 mol) was added dropwise over 10 minutes. The resulting black mixture was warmed to the ambient temperature, and the salts were removed by filtration. Vaccuum distillation afforded **57** as a light yellow oil (28.13 g, 0.147 mmol, 79%). B.P. 75-77 °C @ 0.35 mmHg (Lit.[103] 75 °C @ 0.45 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (t, 1 H, J = 1.5 Hz); 4.22 (d, 2 H, J = 1.5 Hz).

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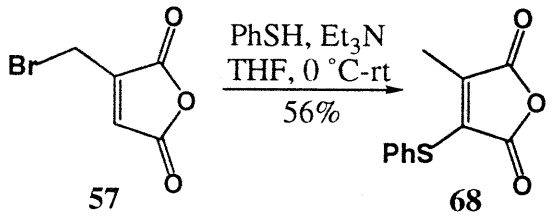
[103]a) Laursen, R. A.; Shen, W.-C.; Zahka, K. G. *J. Med. Chem.* **1971**, *14*, 619-621. b) Greenlee, W. J.; Woodward, R. B. *Tetrahedron* **1980**, *36*, 3367-3375.

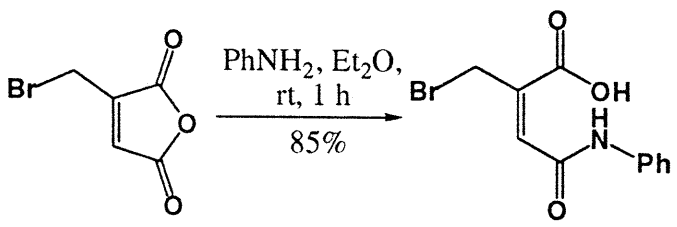


57 **68**

$C_{11}H_8O_3S$
Mol. Wt.: 220.25

3-Methyl-4-(phenylsulfanyl)-2,5-dihydro-2,5-furandione (68):

In an oven-dried 5 mL round bottom flask equipped with a stirbar and septum which was evacuated and filled with argon, **57** (100 mg, 0.524 mmol) was dissolved in tetrahydrofuran (0.5 mL) and cooled to 0 °C (ice/water). Thiophenol (54 μL, 0.524 mmol) and triethylamine (73 μL, 0.524 mmol) were added sequentially. The reaction mixture was stirred overnight while warming to the ambient temperature. After filtration to remove the ammonium salts, the solvent was removed under reduced pressure. Purification by column chromatography (7:1 hexanes-ethyl acetate) afforded **68** as a yellow oil (65 mg, 0.295 mmol, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.57 (m, 2 H); 7.38-7.48 (m, 3 H); 1.64 (s, 3 H). FTIR ($CDCl_3$ cast): 3062, 2958, 1852, 1816, 1765, 1605, 1475, 1379, 1275, 1237, 1068, 1023, 916 cm^{-1}.

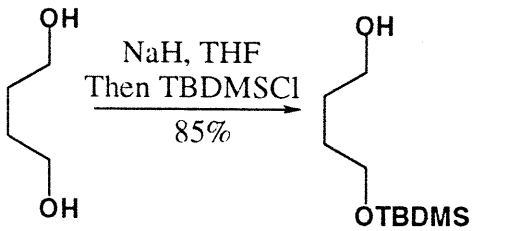


57 **70**

$C_{11}H_{10}BrNO_3$
Mol. Wt.: 284.11

(Z)-4-Anilino-2-(bromomethyl)-4-oxo-2-butenoic Acid (70):

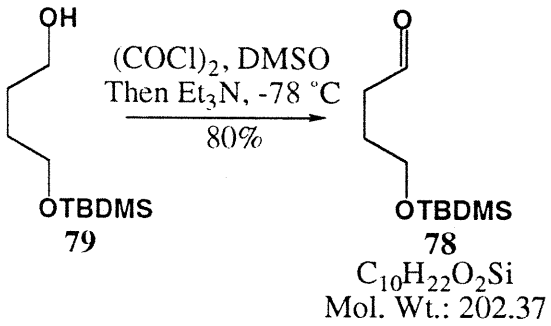
In a 300 mL 3-necked round bottom flask equipped with a stirbar, reflux condenser, and pressure equalizing addition funnel, **57** (10.00 g, 52.4 mmol) was dissolved in diethyl ether (40 mL). A solution of aniline (4.78 mL, 52.4 mmol) in diethyl ether (10 mL) was added dropwise over 30 minutes, resulting in a very exothermic reaction. After the addition was complete, the mixture was stirred for 1 hour at the ambient temperature and 1 hour at 0 °C (ice/water). The precipitate was collected over a Büchner funnel and washed twice with cold diethyl ether (20 mL). **70** was isolated as an amorphous yellow powder (12.677 g, 44.6 mmol, 85%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 10.34 (s, 1 H); 7.61 (d, 2 H, J = 8.1 Hz); 7.31 (t, 2 H, J = 7.9 Hz); 7.07 (t, 1 H, J = 7.4 Hz); 6.62 (s, 1 H), 4.37 (s, 2 H).



79
$C_{10}H_{24}O_2Si$
Mol. Wt.: 204.38

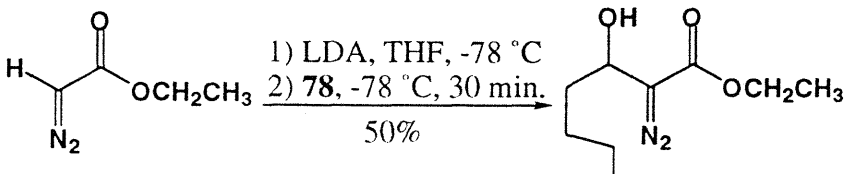
4-(*tert*-Butyldimethylsiloxy)-1-butanol (79):

In an oven-dried 500 mL round bottom flask, a 60% dispersion of sodium hydride in mineral oil (4.51 g, 0.113 mol) was washed three times with dry hexanes (20 mL), once with pentane (20 mL) and dried in vacuo. The dry powder was placed under argon and suspended in tetrahydrofuran (200 mL). A solution of 1,4-butanediol (10.00 mL, 0.113 mol) in tetrahydrofuran (20 mL) was added dropwise via cannula over 20 minutes, and the mixture was stirred vigorously for 1 hour with evolution of hydrogen and formation of a white precipitate. *tert*-butylchlorodimethylsilane (17.00 g, 0.113 mol) was added in one portion, and the reaction mixture was stirred vigorously for an additional 45 minutes. The mixture was poured onto diethyl ether (400 mL) and washed sequentially with a 10% aqueous potassium carbonate solution (200 mL) and brine (200 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in a small amount of diethyl ether, filtered over a plug of silica gel, and eluted with additional diethyl ether (200 mL) to afford the monoprotected product **79** as a colorless viscous oil (19.66 g, 0.096 mol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (t, 2 H, J = 5.6 Hz); 3.64 (t, 2 H, J = 5.8 Hz), 2.42 (bs, 1 H); 1.61-1.68 (m, 4 H); 0.90 (s, 9H), 0.07 (s, 6 H). FTIR (thin film): 3333 (b), 2955, 1388, 1256, 1101, 1063 cm^{-1}.



4-(*tert*-Butyldimethylsiloxy)butanal (78):

In an oven-dried 300 mL round bottom flask equipped with a stirbar and rubber septum under an argon atmosphere, oxalyl chloride (5.10 mL, 58.7 mmol) was dissolved in methylene chloride (90 mL) and cooled to -78 °C (dry ice/acetone). Dimethylsulfoxide (8.70 mL, 122 mmol) was added, and a rapid evolution of gas (carbon dioxide and carbon monoxide) was observed. A solution of **79** (10.00 g, 48.9 mmol) in methylene chloride (10 mL) was added dropwise, and the mixture became slightly cloudy. After 45 minutes, triethylamine (41.0 mL, 294 mmol) was added dropwise, and the resulting mixture was slowly warmed to the ambient temperature over 4 hours. The reaction mixture was diluted with diethyl ether (500 mL) and water (200 mL), and the layers were separated. The organic phase was washed once with water (100 mL), once with a saturated aqueous solution of sodium bisulfite (100 mL), and once with brine (100 mL). The combined aqueous layers were extracted once with diethyl ether (200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by filtration over a plug of silica gel and elution with hexanes. Removal of the solvent afforded **78** as a colorless oil (8.012 g, 39.6 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (t, 1 H, J = 1.6 Hz); 3.65 (t, 2 H, J = 6.0 Hz); 2.50 (dt, 2 H, J_1 = 7.1 Hz, J_2 = 1.6 Hz); 1.86 (qnt, 2 H, J = 6.5 Hz); 0.88 (s, 9H); 0.04 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 202.4, 62.1, 40.8, 25.9 (3 carbons), 25.5, 18.3, -5.4 (2 carbons). FTIR (thin film): 2943, 2866, 2717, 1728, 1463, 1383, 1106 cm^{-1}.

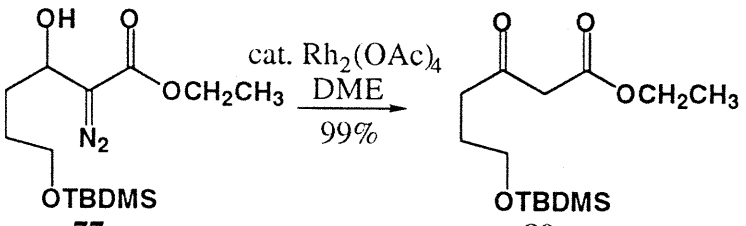


77

$C_{14}H_{28}N_2O_4Si$

Mol. Wt.: 316.47

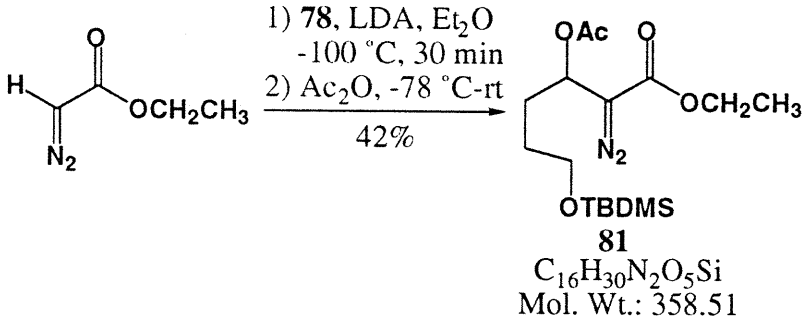
(+/-)-Ethyl 6-(*tert*-Butyldimethylsiloxy)-2-diazo-3-hydroxyhexanoate (77): In an oven-dried 50 mL round bottom flask equipped with a stirbar and rubber septum, **78** (2.005 g, 9.91 mmol) and ethyl diazoacetate (1.25 mL, 11.9 mmol) were dissolved in tetrahydrofuran (15 mL) and cooled to -78 °C (dry ice/acetone). A freshly prepared solution of lithium diisopropylamide (prepared by dissolving diisopropylamine (1.95 mL, 14.9 mmol) in tetrahydrofuran (5 mL), cooling to -78 °C, and adding a 2.2 M solution of *n*-butyllithium in hexanes (5.85 mL, 12.9 mmol)) was added dropwise via cannula. After 30 minutes, the reaction was quenched by addition of a saturated aqueous ammonium chloride solution (20 mL) and warming to the ambient temperature. The mixture was extracted with diethyl ether (100 mL), and the organic phase was washed once with a 1.0 N aqueous hydrochloric acid solution (10 mL), once with a solution of saturated aqueous sodium bicarbonate (20 mL), and once with brine (20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, filtered and concentrated under reduced pressure. Column chromatography (eluent gradient from 9:1 to 5:1 hexanes-diethyl ether) afforded **77** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (bt, 1 H, J = 6.3 Hz); 4.23 (q, 2 H, J = 7.1 Hz); 3.67 (t, 2 H, J = 5.7 Hz); 3.41 (bs, 1 H); 1.75 (m, 4 H); 1.28 (t, 3 H, J = 7.1 Hz), 0.89 (s, 9 H); 0.06 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 166.4, 66.2, 62.9, 60.8, 31.9, 31.6, 28.9, 25.9 (3 carbons), 22.6, 18.3, 14.5, 14.0, -5.4 (2 carbons). FTIR (thin film): 3437 (b), 2929, 2856, 2094, 1693, 1460, 1370, 1095 cm^{-1}.



$C_{14}H_{28}O_4Si$
Mol. Wt.: 288.46

Ethyl 6-(*tert*-Butyldimethylsiloxy)-3-oxohexanoate (80):

In an oven-dried 5 mL round bottom flask equipped with a stirbar and loosely capped with a polyethylene stopper, **77** (308 mg, 0.973 mmol) was dissolved in dimethoxyethane (1 mL). A catalytic amount of rhodium(II) acetate dimer (1 mg, 0.002 mmol, 0.2 mol %) was added in one portion. After the rapid evolution of nitrogen, the mixture was filtered over a plug of silica gel and eluted with diethyl ether (10 mL). Evaporation of the solvent afforded **80** as a pale green oil (278 mg, 0.964 mmol, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (q, 2 H, J = 7.1 Hz); 3.62 (t, 2 H, J = 6.0 Hz); 3.45 (s, 2 H); 2.62 (t, 2 H, J = 7.2 Hz); 1.81 (qnt, 2 H, J = 6.6 Hz); 1.28 (t, 3 H, J = 7.2 Hz); 0.88 (s, 9 H); 0.04 (s, 6 H). FTIR (thin film): 2955, 2857, 1746, 1716, 1256, 1098 cm^{-1}.

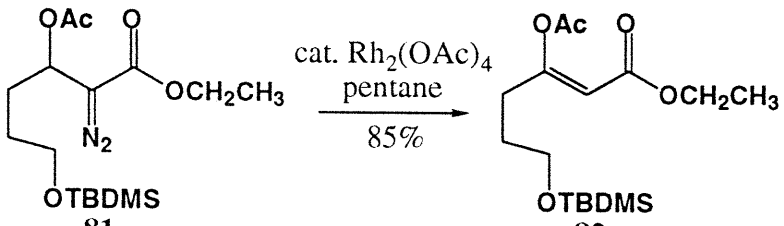


81

$C_{16}H_{30}N_2O_5Si$

Mol. Wt.: 358.51

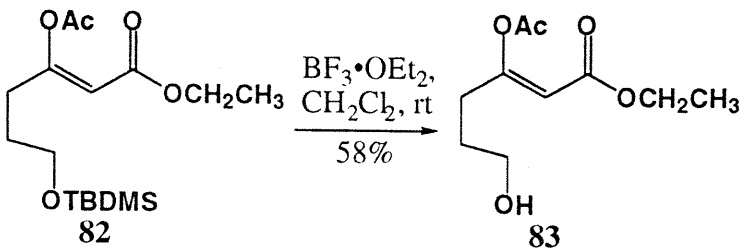
(+/-)-Ethyl 3-Acetoxy-6-(*tert*-butyldimethylsiloxy)-2-diazohexanoate (81): In an oven-dried 50 mL round bottom flask equipped with a stirbar and rubber septum, **78** (2.009 g, 9.93 mmol) and ethyl diazoacetate (1.56 mL, 14.9 mmol) were dissolved in diethyl ether (5 mL) and cooled to -100 °C (dry ice/diethyl ether). In a separate flask, a solution of lithium diisopropylamide was prepared by dissolving diisopropylamine (2.60 mL, 19.9 mmol) in diethyl ether (5 mL), cooling the solution to -78 °C (dry ice/acetone), and adding a 2.15 M solution of *n*-butyllithium in hexanes (7.85 mL, 16.9 mmol). After stirring for 5 minutes, the lithium diisopropylamide solution was transferred via cannula to the first solution. The reaction was quenched after 15 minutes by addition of freshly distilled acetic anhydride (1.87 mL, 19.9 mmol). The resulting mixture was warmed to the ambient temperature and filtered to remove any salts. After evaporation of the solvent, the residue was purified by column chromatography (eluent gradient from 10:1 to 4:1 hexanes-diethyl ether) to afford **81** as a colorless oil (1.497 g, 4.18 mmol, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.62 (t, 1 H, J = 7.5 Hz); 4.23 (q, 2 H, J = 7.1 Hz); 3.60-3.70 (m, 2 H); 2.06 (s, 3 H); 1.80-1.90 (m, 2 H); 1.50-1.60 (m, 2 H); 1.27 (t, 3 H, J = 7.2 Hz); 0.89 (s, 9 H); 0.04 (s, 6 H). FTIR (thin film): 2955, 2858, 2098, 1743, 1703, 1471, 1372, 1226, 1099, 1014 cm^{-1}.



$C_{16}H_{30}O_5Si$
Mol. Wt.: 330.49

Ethyl (*Z*)-3-Acetoxy-6-(*tert*-butyldimethylsilyl)-2-hexenoate (82):

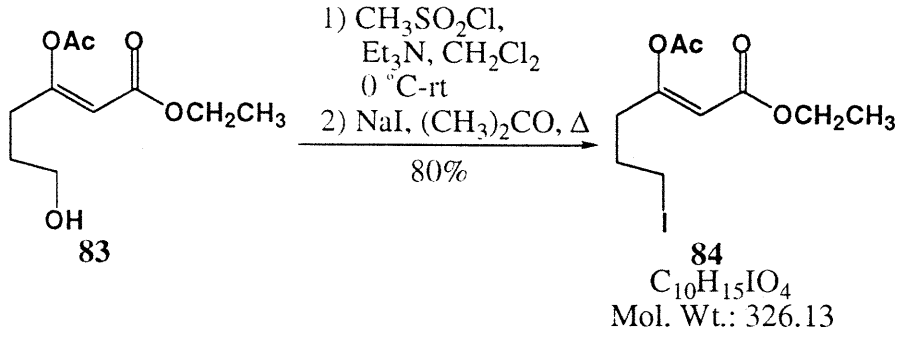
In a 50 mL round bottom flask equipped with a stirbar and loosely capped with a polyethylene stopper, **81** (1.497 g, 4.18 mmol) was dissolved in pentane (20 mL) and stirred vigorously. Rhodium(II) acetate dimer (18 mg, 0.042 mmol, 1 mol %) was added in one portion with a rapid evolution of nitrogen. After 3 hours, the mixture was filtered over a plug of silica gel and eluted first with a 4:1 hexanes-diethyl ether solution, then with diethyl ether. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (eluent gradient from 15:1 to 9:1 hexanes-diethyl ether) to afford **82** as a colorless oil (1.171 g, 3.54 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (t, 1 H, J = 7.9 Hz); 4.24 (q, 2 H, J = 7.2 Hz); 3.65 (t, 2 H, J = 6.3 Hz); 2.64 (q, 2 H, J = 7.7 Hz); 2.18 (s, 3 H); 1.68 (quintet, 2 H, J = 6.9 Hz); 1.30 (t, 3 H, J = 7.1 Hz); 0.89 (s, 9 H); 0.04 (s, 6 H).



$C_{10}H_{16}O_5$
Mol. Wt.: 216.23

Ethyl (Z)-3-Acetoxy-6-hydroxy-2-hexenoate (83):

In an oven-dried 10 mL flask equipped with a stirbar and rubber septum, **82** (50 mg, 0.151 mmol) was dissolved in methylene chloride (1 mL). Boron trifluoride•diethyl etherate complex (37 μL, 0.303 mmol) was added, and the solution stirred overnight at the ambient temperature. The mixture was diluted with methylene chloride (10 mL) and poured onto a saturated aqueous sodium bicarbonate solution (10 mL). After separation, the organic layer was washed once with a 0.5 N aqueous sodium hydroxide solution (5 mL), and the combined aqueous layers were extracted once with methylene chloride (10 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure to afford **83** as a colorless oil (19 mg, 0.088 mmol, 58%) without need for further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.93 (t, 1 H, J = 8.6 Hz); 4.24 (q, 2 H, J = 7.1 Hz); 3.67 (t, 2 H, J = 6.0 Hz); 2.68 (dt, 2 H, J_1 = 8.5 Hz, J_2 = 7.1 Hz); 2.18 (s, 3 H); 1.74 (qnt, 2 H, J = 6.5 Hz); 1.60 (bs, 1 H); 1.29 (t, 3 H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 169.7, 162.3, 138.0, 133.4, 61.4, 61.3, 31.4, 23.1, 20.3, 14.0 cm^{-1}.



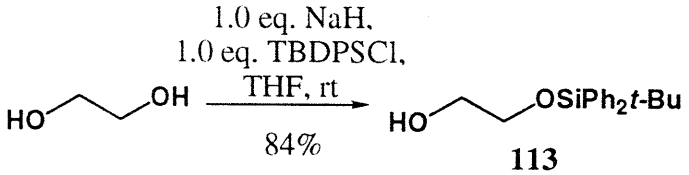
83

84
$C_{10}H_{15}IO_4$
Mol. Wt.: 326.13

Ethyl (Z)-3-Acetoxy-6-iodo-2-hexenoate (84):

In an oven-dried 25 mL round bottom flask equipped with a stirbar and rubber septum, **83** (57 mg, 0.264 mmol) was dissolved in methylene chloride (5 mL) under an argon atmosphere. After cooling to 0 °C (ice/water), methanesulfonyl chloride (31 μL, 0.395 mmol) and triethylamine (55 μL, 0.395 mmol) were added. The mixture was stirred at 0 °C for 15 minutes then warmed to the ambient temperature. After 2 hours, the reaction was incomplete as monitored by thin layer chromatography, therefore additional amounts of triethylamine (37 μL, 0.264 mmol for a total of 92 μL, 0.659 mmol) and methanesulfonyl chloride (20 μL, 0.264 mmol for a total of 51 μL, 0.659 mmol) were added. After stirring overnight at the ambient temperature, the reaction mixture was diluted with methylene chloride (10 mL) and washed, once with a 0.25 N aqueous hydrochloric acid solution (10 mL) and once with a solution of saturated aqueous sodium bicarbonate (10 mL). The combined aqueous layers were extracted once with methylene chloride (10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in dry acetone (10 mL), and sodium iodide (158 mg, 1.05 mmol) was added. The mixture was heated to reflux overnight. After removal of the solvent, the residue was suspended in water (10 mL) and extracted three times with diethyl ether (10 mL). The combined organic layers were washed once with a dilute aqueous solution of sodium bisulfite to remove any traces of iodine. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **84** as a colorless oil (69 mg, 0.212 mmol, 80%) which required no

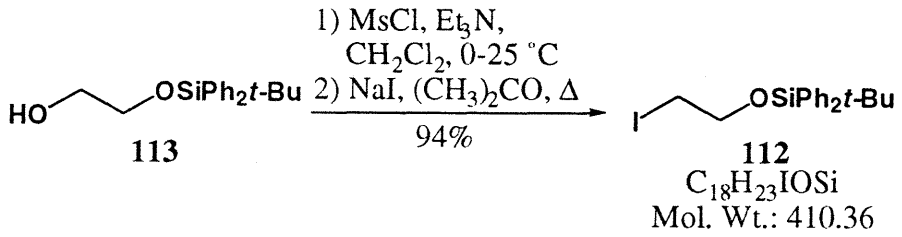
further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (t, 1 H, J = 8.1 Hz); 4.23 (q, 2 H, J = 7.1 Hz); 3.19 (t, 2 H, J = 7.0 Hz); 2.68 (q, 2 H, J = 7.6 Hz); 2.16 (s, 3 H); 1.98 (qnt, 2 H, J = 7.2 Hz); 1.29 (t, 3 H, J = 7.1 Hz).



113
$C_{18}H_{24}O_2Si$
Mol. Wt.: 300.47

2-(*tert*-Butyldiphenylsiloxy)-1-ethanol (113):

In an oven-dried 100 mL round bottom flask equipped with a stirbar, a 60% dispersion of sodium hydride in mineral oil (2.307 g, 57.7 mmol) was washed three times with hexanes (10 mL) and once with pentane (10 mL) then dried in vacuo. Tetrahydrofuran (20 mL) was added, and the resulting slurry was stirred vigorously as a solution of ethylene glycol (3.22 mL, 57.7 mmol) in tetrahydrofuran (5 mL) was added dropwise. After stirring at the ambient temperature for 30 minutes, *tert*-butylchlorodiphenylsilane (TBDPSCl) (15.00 mL, 57.7 mmol) was added dropwise over 5 minutes. The resulting mixture was stirred for an addtional 30 minutes, at which time the mixture was poured into diethyl ether (50 mL) and washed once with 10% aqueous potassium carbonate (20 mL) and once with brine (20 mL). The combined aqueous layers were extracted once with diethyl ether (20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column (eluent gradient from 9:1 to 1:1 hexanes-diethyl ether) to afford **113** as a colorless oil (14.48 g, 48.2 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.70 (m, 4 H); 7.36-7.44 (m, 6 H); 3.75-3.79 (m, 2 H); 3.66-3.71 (m, 2 H); 1.98 (bs, 1 H); 1.08 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 136.0 (4 carbons), 134.0 (2 carbons), 130.2 (2 carbons), 128.2 (4 carbons), 65.6, 64.2, 27.4 (3 carbons), 19.7. FTIR ($CDCl_3$ cast): 3383 (b), 3071, 2931, 2858, 1472, 1428, 1113, 1057 cm^{-1}.



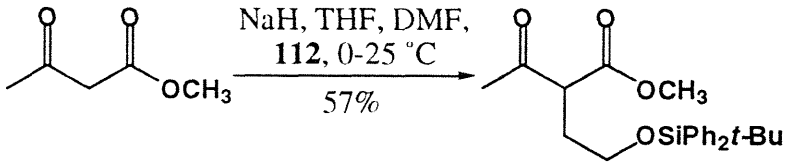
113 **112**

$C_{18}H_{23}IOSi$

Mol. Wt.: 410.36

2-(*tert*-Butyldiphenylsiloxy)-1-iodoethane (112):

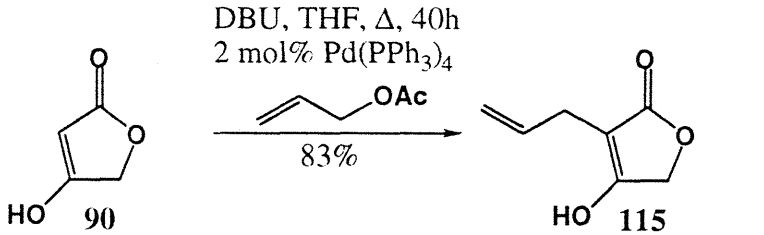
In a 250 mL round bottom flask equipped with a stirbar and rubber septum, **113** (9.184 g, 30.57 mmol) was dissolved in methylene chloride (100 mL) and cooled to 0 °C. Triethylamine (10.6 mL, 76.4 mmol) and methanesulfonyl chloride (5.90 mL, 76.4 mmol) were added sequentially, and the mixture was stirred at 0 °C for 1 hour. The mixture was warmed to the ambient temperature and stirred overnight. After diluting with methylene chloride (100 mL), the mixture was washed once with a 1.0 N aqueous hydrochloric acid solution (50 mL), once with a saturated aqueous sodium bicarbonate solution (50 mL), and once with brine (50 mL). The combined aqueous layers were extracted once with methylene chloride (50 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in dry acetone (150 mL), and sodium iodide (18.326 g, 122 mmol) was added. The solution was then heated to reflux overnight. After cooling to the ambient temperature, the solvent was evaporated,and the residue was suspended in water (150 mL). The mixture was extracted three times with diethyl ether (150 mL), and the combined organic phases were washed once with a 25% aqueous sodium bisulfite solution (50 mL) and once with water (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford **112** as a golden oil (11.863 g, 28.9 mmol, 95%) which required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.71 (m, 4 H); 7.37-7.45 (m, 6 H); 3.88 (t, 2 H, J = 6.8 Hz); 3.23 (t, 2 H, J = 6.8 Hz); 1.08 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 135.6 (4 carbons), 133.5 (2 carbons), 129.8 (2 carbons), 127.8 (4 carbons), 102.4, 64.9, 26.9 (3 carbons), 19.3.



114
$C_{23}H_{30}O_4Si$
Mol. Wt.: 398.57

Methyl 4-(*tert*-Butyldiphenylsiloxy)-2-(1-oxoethane)butanoate (114):

In a 250 mL round bottom flask equipped with a stirbar, a 60% dispersion of sodium hydride in mineral oil (1.719 g, 43.0 mmol) was washed twice with hexanes (20 mL), washed once with pentane (10 mL), and dried in vacuo. The dried powder was placed under an argon atmosphere and suspended in a solution of tetrahydrofuran (25 mL) and *N,N*-dimethylformamide (50 mL). After cooling the mixture to 0 °C, methyl acetoacetate (4.64 mL, 43.0 mmol) was added dropwise. After the rapid evolution of hydrogen had subsided, a solution of **112** (4.410 g, 10.7 mmol) in tetrahydrofuran (10 mL) was added via cannula, and the reaction mixture became homogeneous. The mixture was warmed to the ambient temperature and stirred for 10 days. Water (10 mL) was added to quench the reaction, and the mixture was extracted three times with a 1:1 hexanes-diethyl ether solution (100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and condensed. The residue was purified by column chromatography (eluent gradient from 19:1 to 15:1 hexanes-diethyl ether) to afford **114** as a colorless oil (2.413 g, 6.05 mmol, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.65 (m, 4 H); 7.35-7.44 (m, 6 H); 3.81 (t, 1 H, J = 7.1 Hz); ; 3.71 (s, 3 H); 3.67 (dt, 2 H, J_1 = 5.9 Hz, J_2 = 1.4 Hz); 2.24 (s, 3 H); 2.11 (dt, 2 H, J_1 = 7.2 Hz, J_2 = 5.9 Hz); 1.05 (s, 9 H). FTIR (thin film): 3071, 2931, 2857, 1745, 1713, 1428, 1112.

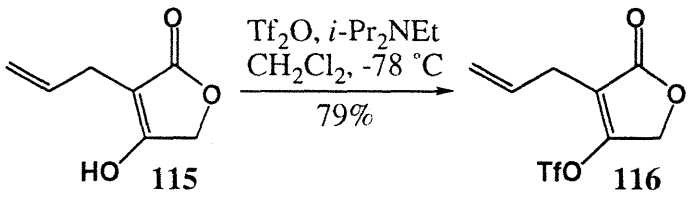


$C_7H_8O_3$
Mol. Wt.: 140.14

3-Allyl-2,5-dihydro-4-hydroxy-2-furanone (115):

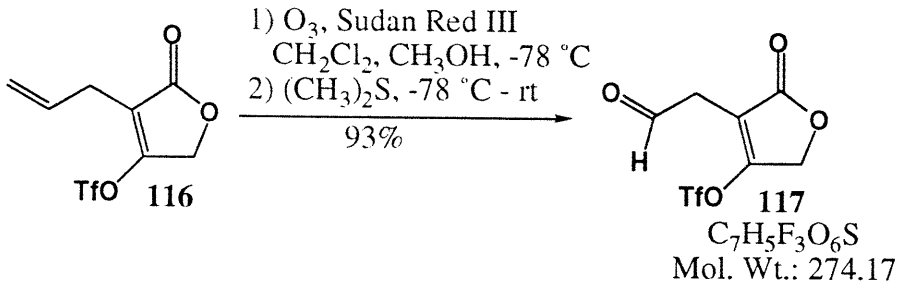
Tetronic acid (**90**) (10.000 g, 99.9 mmol) and tetrakis(triphenylphosphine)palladium(0) (2.310 g, 2.00 mmol, 2 mol %) were placed in a 500 mL round bottomed flask which was equipped with a stirbar and rubber septum under an argon atmosphere. Tetrahydrofuran (200 mL), 1,8-diaza[5.3.0]undec-7-ene (DBU) (15.00 mL, 99.9 mmol), and allyl acetate (10.80 mL, 99.9 mmol) were added sequentially. The reaction mixture was then heated to reflux for 40 hours, then cooled to the ambient temperature. The solvent was evaporated, and the residue was acidified with a 1.0 N aqueous hydrochloric acid solution (200 mL). The solution was then saturated with solid sodium chloride (~5 g) and extracted with ethyl acetate (200 mL). The organic layer was washed once with brine (100 mL), and the combined aqueous layers were extracted once with ethyl acetate (200 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent gradient from 3:2 to 2:1 ethyl acetate-hexanes) to afford **115** as an amorphous yellow solid (11.588 g, 82.7 mmol, 83%). An analytical sample was recrystallized (prisms) from 1:1 hexanes-diethyl ether. m.p. 103-104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.34 (bs, 1 H); 5.86 (tdd, 1 H, J_1 = 17.1 Hz, J_2 = 10.0 Hz, J_3 = 6.2 Hz); 5.13 (dq, 1 H, J_1 = 17.1 Hz, J_2 = 1.6 Hz); 5.07 (dq, 1 H, J_1 = 10.0 Hz, J_2 = 1.2 Hz), 4.70 (t, 2 H, J = 1.4 Hz); 2.98 (dt, 2 H, J_1 = 6.4 Hz, J_2 = 1.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 177.7, 174.5, 133.8, 116.5, 99.1, 67.7, 25.4. FTIR (thin film): 2983, 2705, 1718, 1651, 1436, 1410, 1272, 1035 cm^{-1}. HRMS (EI) calculated for $C_7H_8O_3$ (M^+): 140.04734;

observed: 140.04737. Anal. calculated for $C_7H_8O_3$: C, 60.0; H, 5.75. Observed: C, 59.9; H, 5.76.



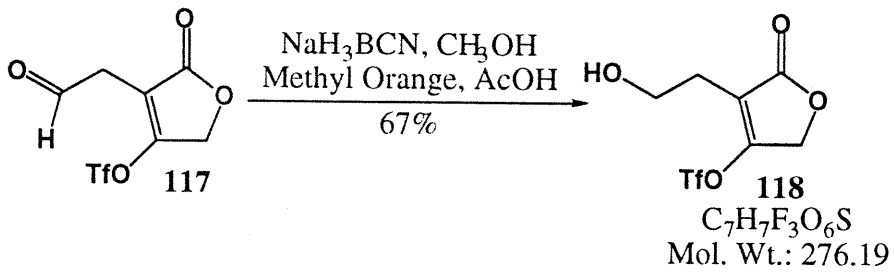
$C_8H_7F_3O_5S$
Mol. Wt.: 272.20

3-Allyl-2,5-dihydro-2-oxo-4-furanyl Trifluoromethanesulfonate (116): **115** (100 mg, 0.714 mmol) was dissolved in dichloromethane (1.5 mL) under argon in a 5 mL round bottom flask equipped with a stirbar and rubber septum. The solution was cooled to -78 °C (dry ice/acetone), and *N,N*-diisopropylethylamine (126 μL, 0.721 mmol) and trifluoromethanesulfonic anhydride (121 μL, 0.721 mmol) were added. After 45 minutes, the mixture was warmed to -20 °C and quenched by addition of a saturated aqueous sodium bicarbonate solution (1 mL). The mixture was warmed to the ambient temperature, diluted with methylene chloride (20 mL), and washed once with water (10 mL) and once with a saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (5:1 hexanes-ethyl acetate) afforded **116** as a pale yellow oil (153 mg, 0.562 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (ddt, 1 H, J_1 = 17.0 Hz, J_2 = 10.0 Hz, J_3 = 6.6 Hz); 5.19 (dq, 1 H, J_1 = 18.6 Hz, J_2 = 1.4 Hz); 5.17 (dq, 1 H, J_1 = 9.9 Hz, J_2 = 1.3 Hz); 4.94 (t, 2 H, J = 1.4 Hz); 3.11 (dqnt, 2 H, J_1 = 5.2 Hz, J_2 = 1.5 Hz).



2-Oxo-3-(2-oxoethyl)-2,5-dihydro-4-furanyl Trifluoromethanesulfonate (117):

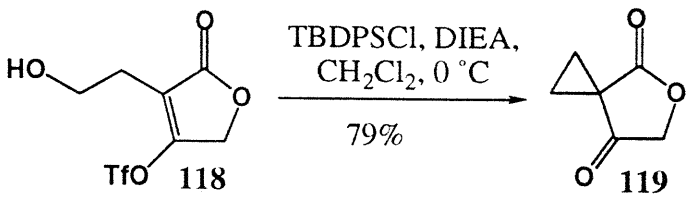
In a 100 mL round bottom flask equpped with a stirbar, **116** (500 mg, 1.84 mmol) was dissolved in a 1:1 methanol-dichloromethane solution (10 mL), and a 0.05% solution of sudan red III in methanol (200 μL) was added to provide a slight red color. Oxygen was bubbled through the solution for 5 minutes, and the solution was cooled to -78 °C (dry ice/acetone). A stream of ozone was generated (0.3 kg/cm^2, 2.5 slpm., 90 volts) and bubbled through the solution until the red color disappeared, which indicated the completion of the oxidation (approximately 10 minutes). A stream of oxygen was bubbled through the solution to purge any of the excess ozone. Dimethylsulfide (1.35 mL, 18.4 mmol) was added, and the solution warmed to the ambient temperature overnight. The solvent and any volatile materials were removed under reduced pressure, and the residue was dissolved in methylene chloride (20 mL) and washed twice with water (10 mL). The combined aqueous layers were extracted twice with methylene chloride (10 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by filtration over a plug of silica gel and elution with a 1:1 hexanes-diethyl ether solution to afford **117** as a colorless oil (468 mg, 1.71 mmol, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (s, 1 H); 5.01 (s, 2 H); 3.52 (s, 2 H).



$C_7H_7F_3O_6S$
Mol. Wt.: 276.19

3-(2-Hydroxyethyl)-2-oxo-2,5-dihydro-4-furanyl Trifluoromethane-sulfonate (118):

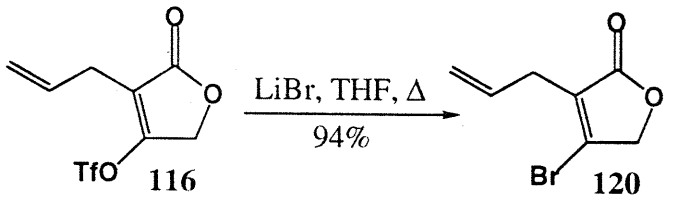
To a 95:5 methanol-acetic acid solution (10 mL) of **117** (428 mg, 1.56 mmol), sodium cyanoborohydride (98 mg, 1.56 mmol) and methyl orange indicator (10 mg) were added separately. Acetic acid (1 mL aliquots) was added periodically to maintain the deep orange color of the solution. After 1 hour, another portion of sodium cyanoborohydride (98 mg, 1.56 mmol to give a total of 196 mg, 3.12 mmol) was added, and the reaction solution was stirred for 1 more hour. Thin layer chromatography indicated the completion of the reaction, and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride (20 mL) and washed sequentially with water (10 mL), saturated aqueous sodium bicarbonate (10 mL), and brine (10 mL). The combined aqueous layers were extracted twice with methylene chloride (10 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (eluent gradient from 2:1 to 1:1 hexanes-diethyl ether) to yield **118** as a colorless oil (289 mg, 1.05 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.97 (t, 2 H, J = 1.5 Hz); 3.86 (t, 2 H, J = 6.1 Hz); 2.63 (tt, 2 H, J_1 = 6.0 Hz, J_2 = 1.3 Hz); 1.95 (bs, 1 H). FTIR (neat): 3445 (b), 2958, 1772, 1699, 1436, 1363, 1220, 1136, 1090, 1045, 961. HRMS (EI) calculated for $C_7H_7F_3O_6S$ (M^+): 275.99155; observed: 275.99187.



$C_6H_6O_3$
Mol. Wt.: 126.11

5-Oxaspiro[2.4]heptane-4,7-dione (119):

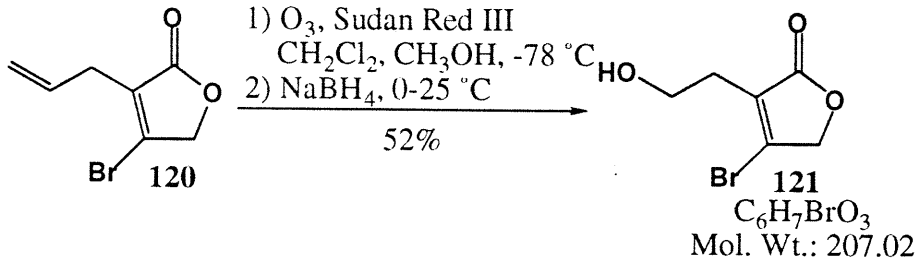
In a 10 mL round bottom flask equipped with a stirbar and rubber septum, **118** (289 mg, 1.05 mmol) was dissolved in methylene chloride (10 mL) under argon. The solution was cooled to 0 °C (ice/water), and *tert*-butylchlorodiphenylsilane (299 μL, 1.15 mmol) and *N,N*-diisopropylethylamine (200 μL, 1.15 mmol) were added separately. After warming to the ambient temperature overnight, the reaction mixture was quenched by addition of water (5 mL). After the layers were separated, the aqueous phase was extracted with methylene chloride (10 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Column chromatography (1:1 hexanes-diethyl ether) afforded **119** as needle-like crystals (104 mg, 0.825 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.75 (s, 2 H); 1.89-1.93 (m, 2 H); 1.84-1.88 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 205.5, 175.0, 73.5, 28.2, 24.1 (2 carbons). FTIR (thin film): 3107, 3006, 2952, 1790, 1746, 1436, 1362, 1339, 1309, 1149, 1076, 1033, 956. HRMS (FAB, Glycerol/NaI) calculated for $C_6H_7O_3$ ($[M+H]^+$): 127.03951; observed: 127.03951.



$C_7H_7BrO_2$
Mol. Wt.: 203.03

3-Allyl-4-bromo-2,5-dihydro-2-furanone (120):

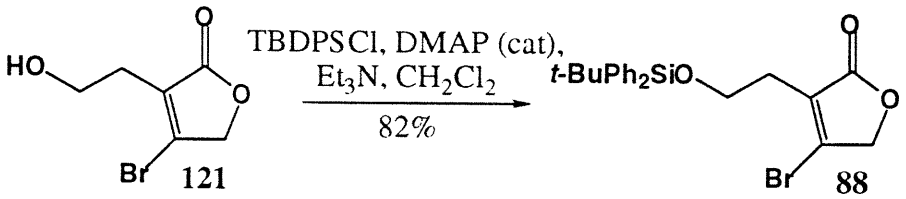
In an oven-dried 25 mL round bottom flask equipped with a stirbar and refluxing condenser fitted with an argon inlet, a solution of **116** (1.004 g, 3.69 mmol) and lithium bromide (499 mg, 5.75 mmol) in tetrahydrofuran (15 mL) was heated to reflux for 2.5 hours. After cooling to room temperature, the solution was treated with magnesium sulfate (750 mg) and silica gel (500 mg), and the resulting slurry was filtered over a plug of silica gel and eluted with diethyl ether. After removal of the solvent, the pink residue was dissolved in a 1:1 hexanes-diethyl ether solution (10 mL), filtered over another plug of silica gel, and eluted with the 1:1 hexanes-diethyl ether solution. Evaporation of the solvent yielded **120** as a colorless oil (704 mg, 3.47 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (ddt, 1 H, J_1 = 17.1 Hz, J_2 = 10.0 Hz, J_3 = 6.5 Hz); 5.16 (dq, 1 H, J_1 = 17.1 Hz, J_2 = 1.5 Hz); 5.11 (dq, 1 H, J_1 = 9.9 Hz, J_2 = 1.3 Hz); 4.80 (t, 2 H, J = 1.2 Hz); 3.10 (dqnt, 2 H, J_1 = 6.5 Hz, J_2 = 1.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): ppm 170.8, 140.3, 131.3, 130.6, 117.9, 73.2, 29.0. FTIR ($CDCl_3$ cast): 3082, 2981, 1763, 1655, 1448, 1346, 1206, 1054, 1027, 921. HRMS (EI) calculated for $C_7H_7BrO_2$ (M^+): 201.96294; observed: 201.96301.



$C_6H_7BrO_3$
Mol. Wt.: 207.02

4-Bromo-3-(2-hydroxyethyl)-2,5-dihydro-2-furanone (121):

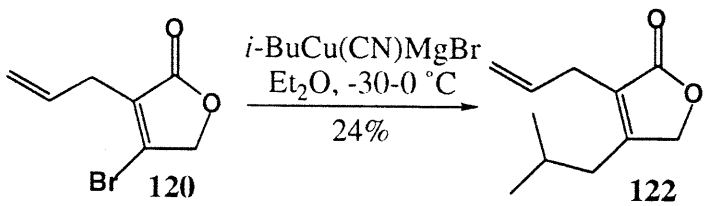
In a 50 mL round bottom flask equipped with a stirbar, **120** (100 mg, 0.493 mmol) was dissolved in a 1:1 methanol-methylene chloride solution (6 ml), and a 0.05% sudan red III in methanol solution (500 µL) was added to generate a red color. The solution was cooled to -78 °C (dry ice/acetone), and oxygen was bubbled through it for 5 minutes. A stream of ozone was generated (0.3 kg/cm^2, 2.5 slpm., 90 volts) and bubbled through the red solution until all of the color had disappeared (approximately 10 minutes). Oxygen was then bubbled through the solution in order to purge any residual ozone. The solution was warmed to 0 °C (ice/water), and sodium borohydride (149 mg, 3.94 mmol) was added, which resulted in the evolution of hydrogen. The reaction mixture warmed to room temperature overnight and was quenched by dropwise addition of a 1.0 N aqueous hydrochloric acid (approximately 1 mL). After diluting the mixture with methylene chloride (10 mL), it was washed with water (10 mL), and the aqueous phase was extracted with methylene chloride (10 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford **121** as a colorless oil (53 mg, 0.256 mmol, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.82 (t, 2 H, J = 1.5 Hz); 3.81 (t, 2 H, J = 6.4 Hz); 2.60 (tt, 2 H, J_1 = 6.1 Hz, J_2 = 1.4 Hz); 2.57 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): ppm 171.8, 141.8, 130.0, 73.4, 59.5, 28.5. FTIR (thin film): 3408 (b), 2957, 2885, 1760, 1652, 1442, 1348, 1295, 1050, 1018. HRMS (EI) calculated for C6H7BrO3 (M^+): 205.95786; observed: 205.95788.



$C_{22}H_{25}BrO_3Si$
Mol. Wt.: 445.42

4-Bromo-3-(2-*tert*-butyldiphenylsiloxyethane)-2,5-dihydro-2-furanone (88):

In an oven-dried 10 mL round bottomed flask equipped with a stirbar and capped with a polyethylene stopper, **121** (53 mg, 0.256 mmol) was dissolved in methylene chloride (5 mL), and 4-dimethylaminopyridine (1 mg, 0.010 mmol, 4 mol. %), *tert*-butylchloro-diphenylsilane (73 μL, 0.282 mmol), and triethylamine (43 μL, 0.307 mmol) were added sequentially to the solution at the ambient temperature. After 2 days, the solvent was removed under reduced pressure, and the residue was suspended in a 1:1 hexanes-diethyl ether solution (10 mL) and washed successively with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (2:1 hexanes-diethyl ether) to afford **88** as an amorphous white solid (109 mg, 0.251 mmol, 98%). An analytical sample was crystallized (prisms) from 10:1 hexanes-diethyl ether. m. p. 69.5-71.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61-7.64 (m, 4 H); 7.36-7.45 (m, 6 H); 4.73 (t, 2 H, J = 1.2 Hz); 3.87 (t, 2 H, J = 6.4 Hz); 2.62 (tt, 2 H, J_1 = 6.4 Hz, J_2 = 1.2 Hz); 1.03 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): ppm 141.2, 135.5 (4 carbons), 133.4 (2 carbons), 129.9, 129.7 (2 carbons), 127.7 (4 carbons), 73.1, 60.4, 28.3, 26.8 (3 carbons), 19.1. FTIR (thin film): 3070, 2930, 2857, 1767, 1657, 1472, 1427, 1295, 1111, 1021, 998, 823 cm^{-1}. HRMS (FAB, 3-NBA) calculated for $C_{22}H_{26}BrO_3Si$ ($[M+H]^+$): 445.08350; observed: 445.08334. Anal. calculated for $C_{22}H_{25}BrO_3Si$: C, 59.32; H, 5.66. Observed: C, 59.53; H, 5.91.



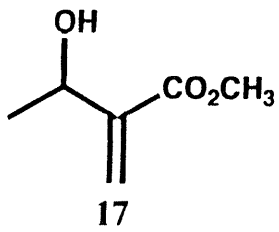
3-Allyl-4-(2-methylpropane)-2,5-dihydro-2-furanone (122):

In an oven-dried 25 mL round bottom flask equipped with a stirbar and rubber septum, copper(I) cyanide (27 mg, 0.296 mmol) and lithium bromide (51 mg, 0.591 mmol) were placed under an argon atmosphere. Tetrahydrofuran (5 mL) was added, and the solution was cooled to -30 °C. A 1.53 M solution of isobutylmagnesium bromide in diethyl ether (135 μL, 0.207 mmol), which had been titrated against iodine prior to use, was added dropwise, and the solution was allowed to warm to 0 °C. After 10 minutes, the solution became homogeneous and was recooled to -30 °C. **120** (50 mg, 0.246 mmol) was added via syringe, and the reaction mixture was stirred for 18 hours at 0 °C. A solution of 10% ammonium hydroxide in saturated aqueous ammonium chloride (5 mL) was added to quench the reaction. The mixture was diluted with water (10 mL) and extracted twice with diethyl ether (10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent gradient from 3:1 to 1:1 hexanes-diethyl ether) to afford **122** (9 mg, 0.050 mmol, 24%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (ddt, 1 H, J_1 = 17.1 Hz, J_2 = 10.0 Hz, J_3 = 6.5 Hz); 5.07 (dq, 1 H, J_1 = 17.1 Hz, J_2 = 1.5 Hz); 5.05 (dq, 1 H, J_1 = 10.0 Hz, J_2 = 1.5 Hz); 4.67 (s, 2 H); 3.03 (d, 2 H, J = 6.4 Hz); 2.30 (d, 2 H, J = 7.8 Hz); 1.83 (septet, 1 H, J = 7.0 Hz); 0.95 (d, 6 H, J = 6.8 Hz). FTIR (thin film): 2958, 1752, 1029 cm^{-1}.

7.4 Selected Spectra

Index for Spectra

Index (Continued)



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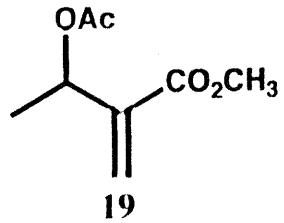

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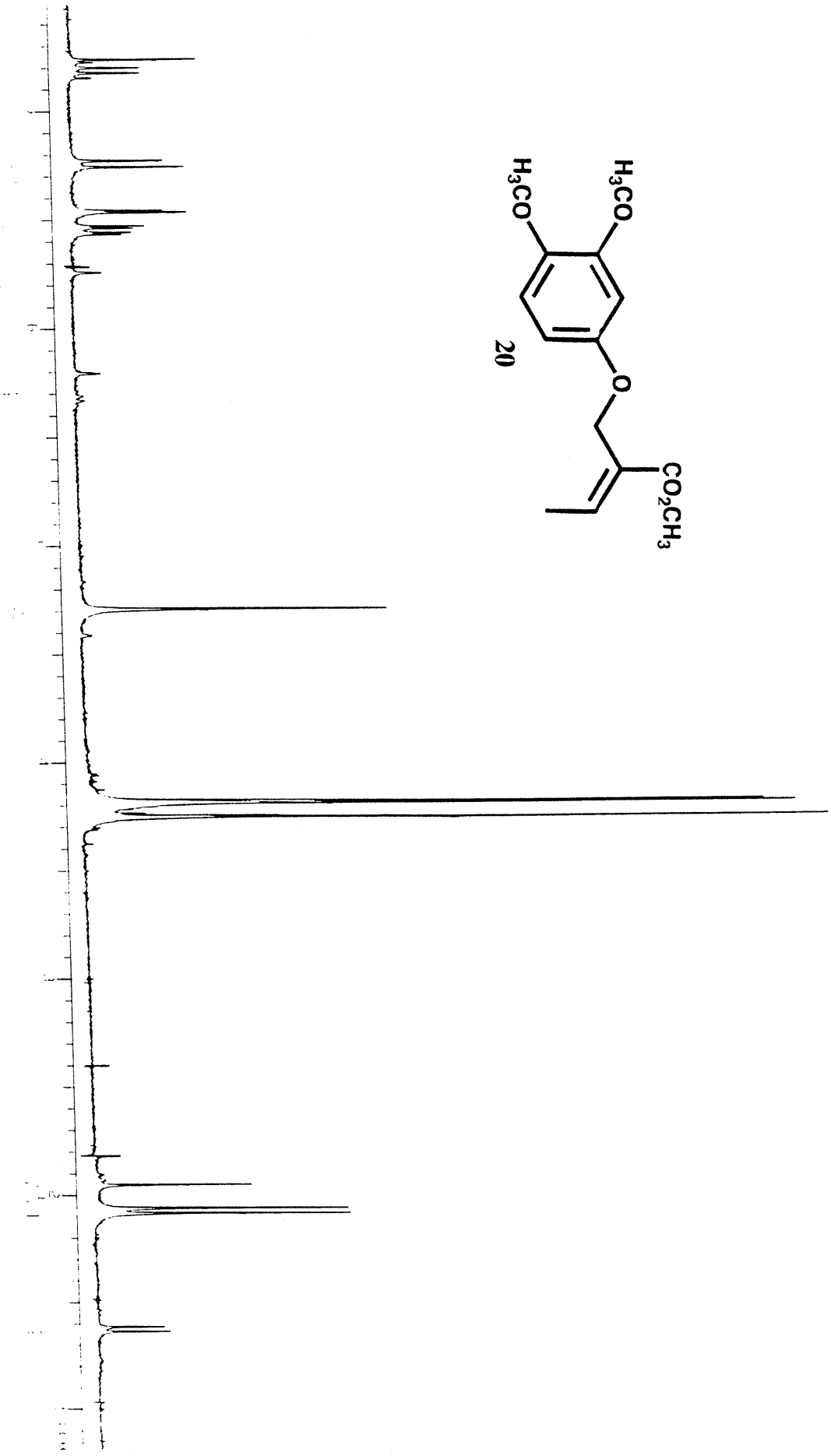

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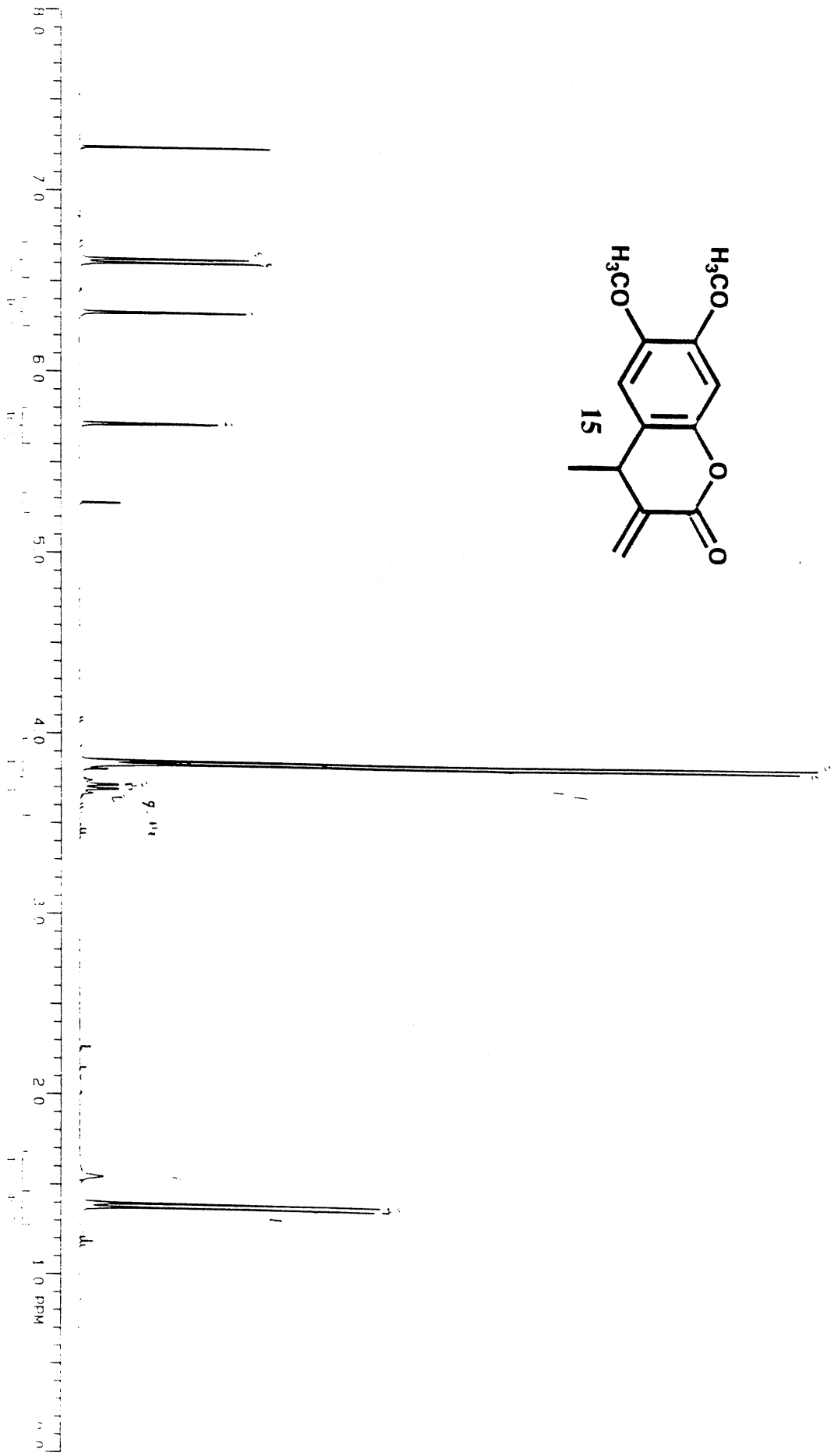
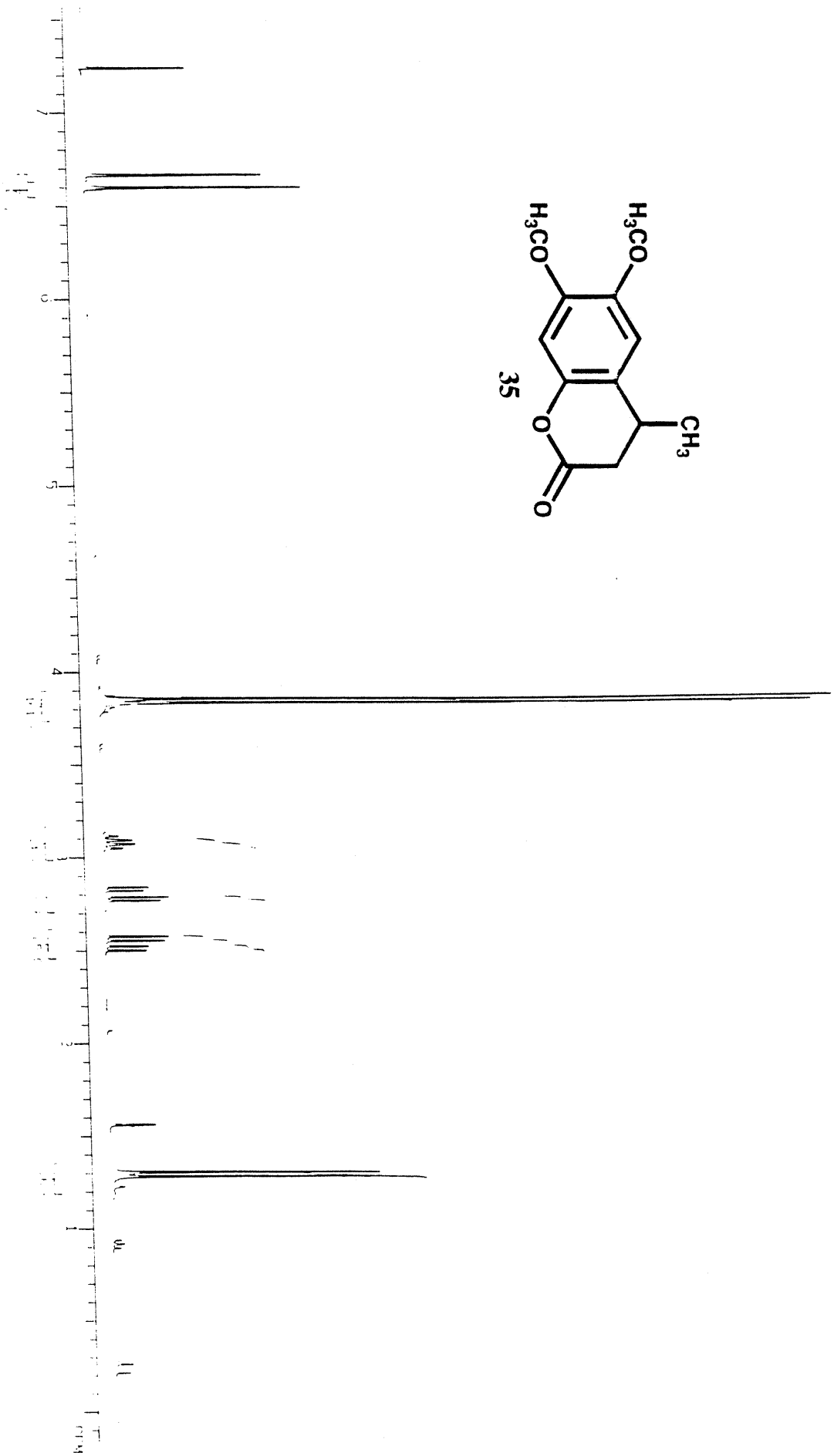
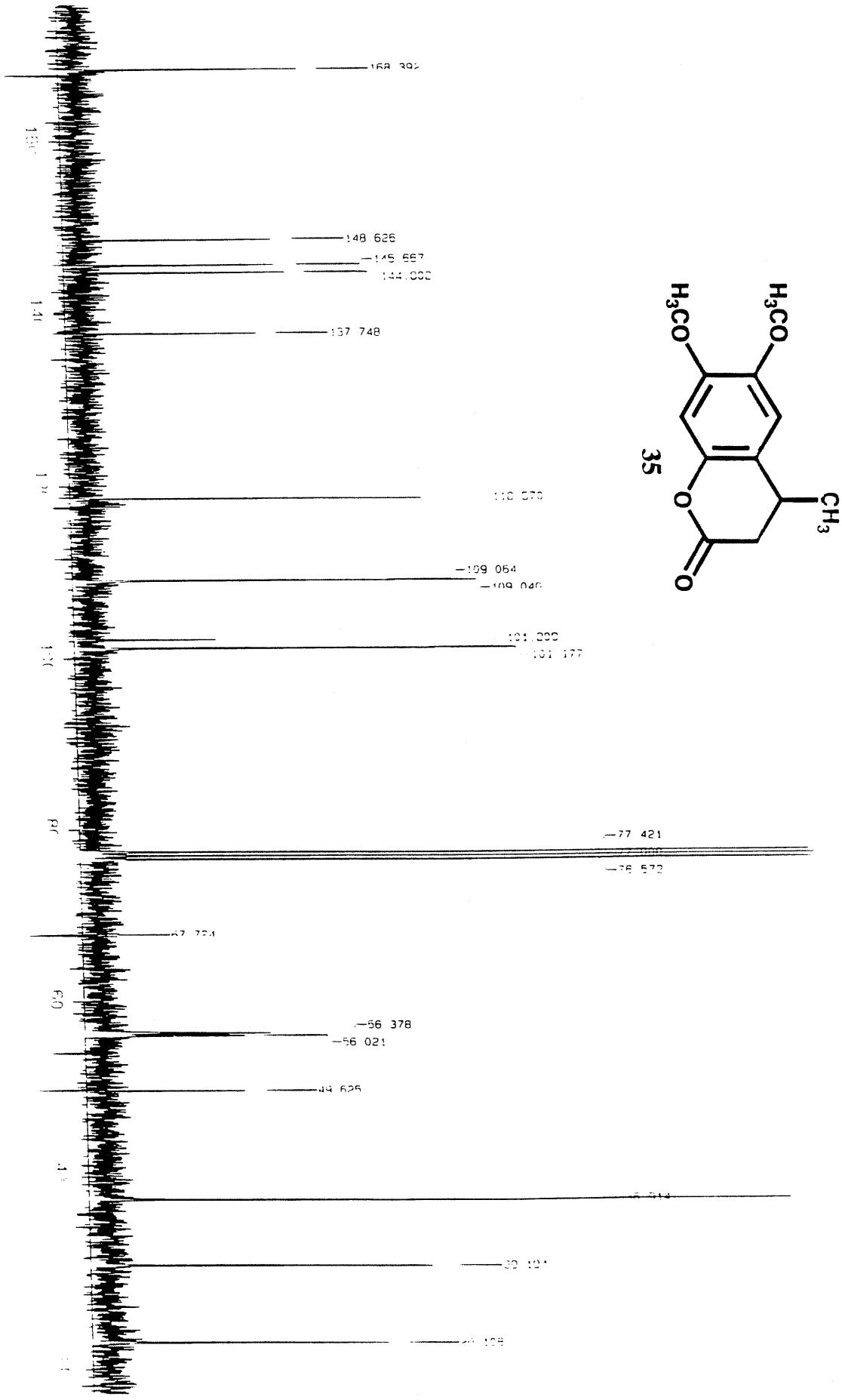
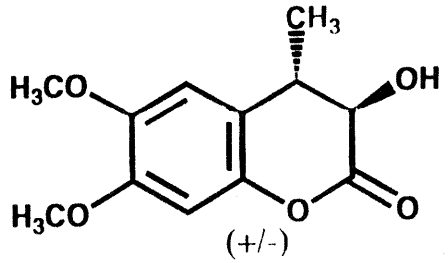

H3CO
H3CO
15
O
O
ppm

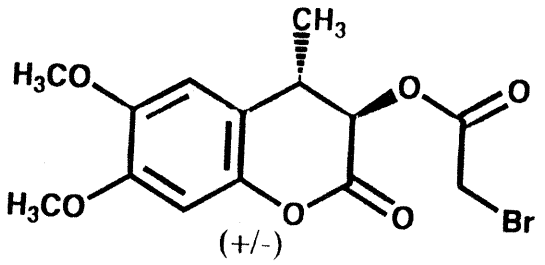

H3CO
H3CO
35
O
CH3
O


168.392
148.626
145.667
144.000
137.748
118.570
109.064
109.046
101.000
101.177
77.421
76.572
56.378
56.021
49.625
30.191
H3CO
H3CO
O
O
CH3
35



(+/-)

31



(+/-)

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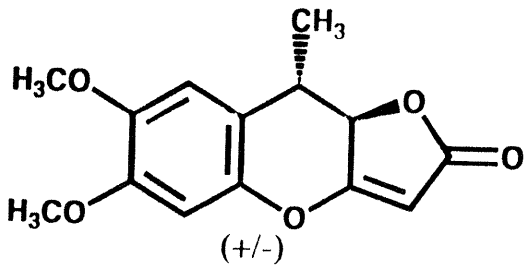

(+/-)

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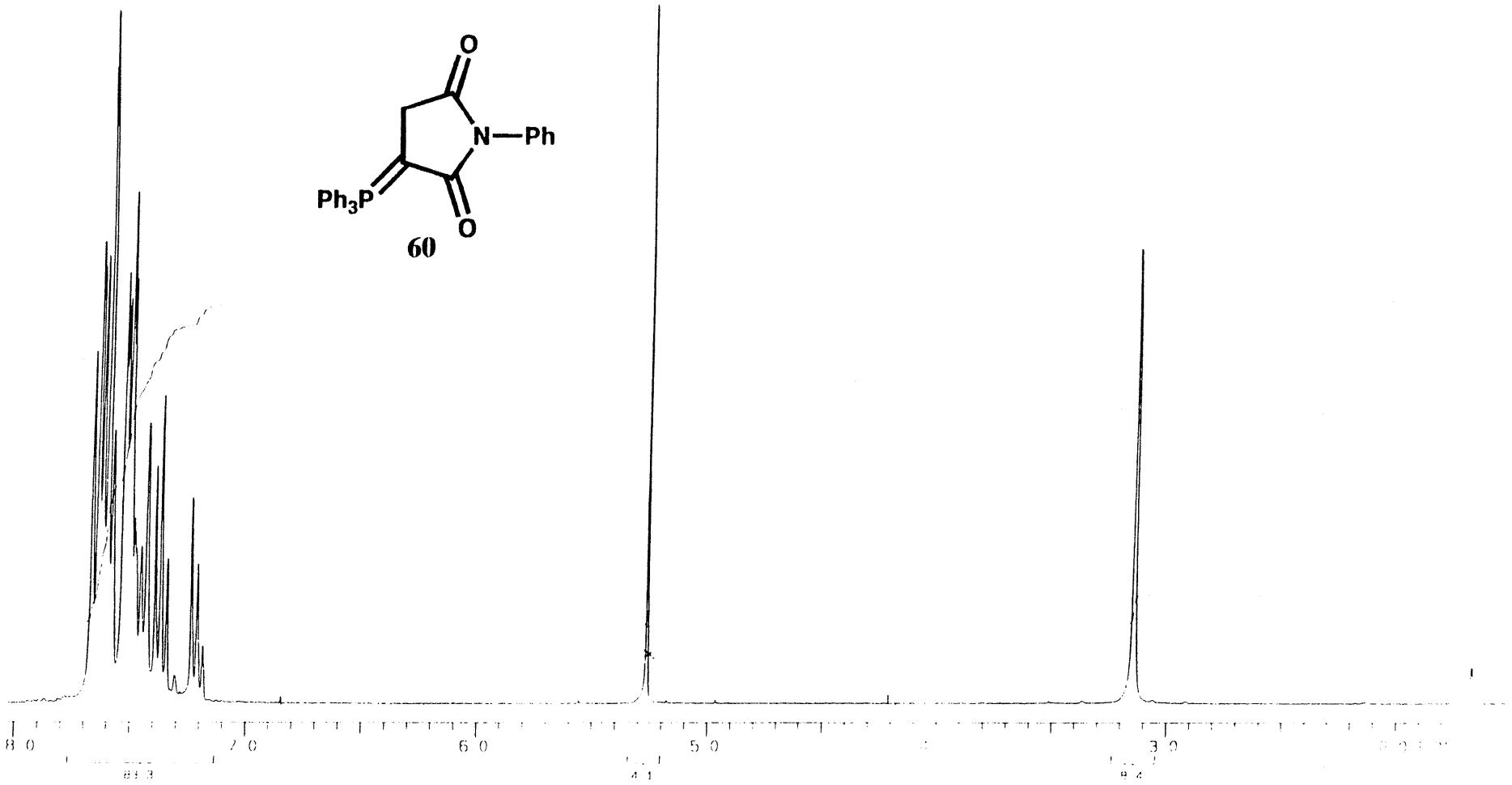

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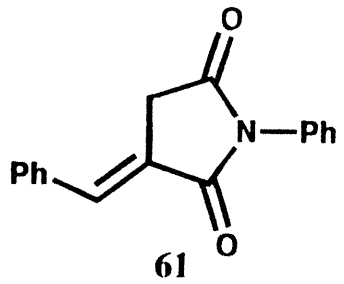

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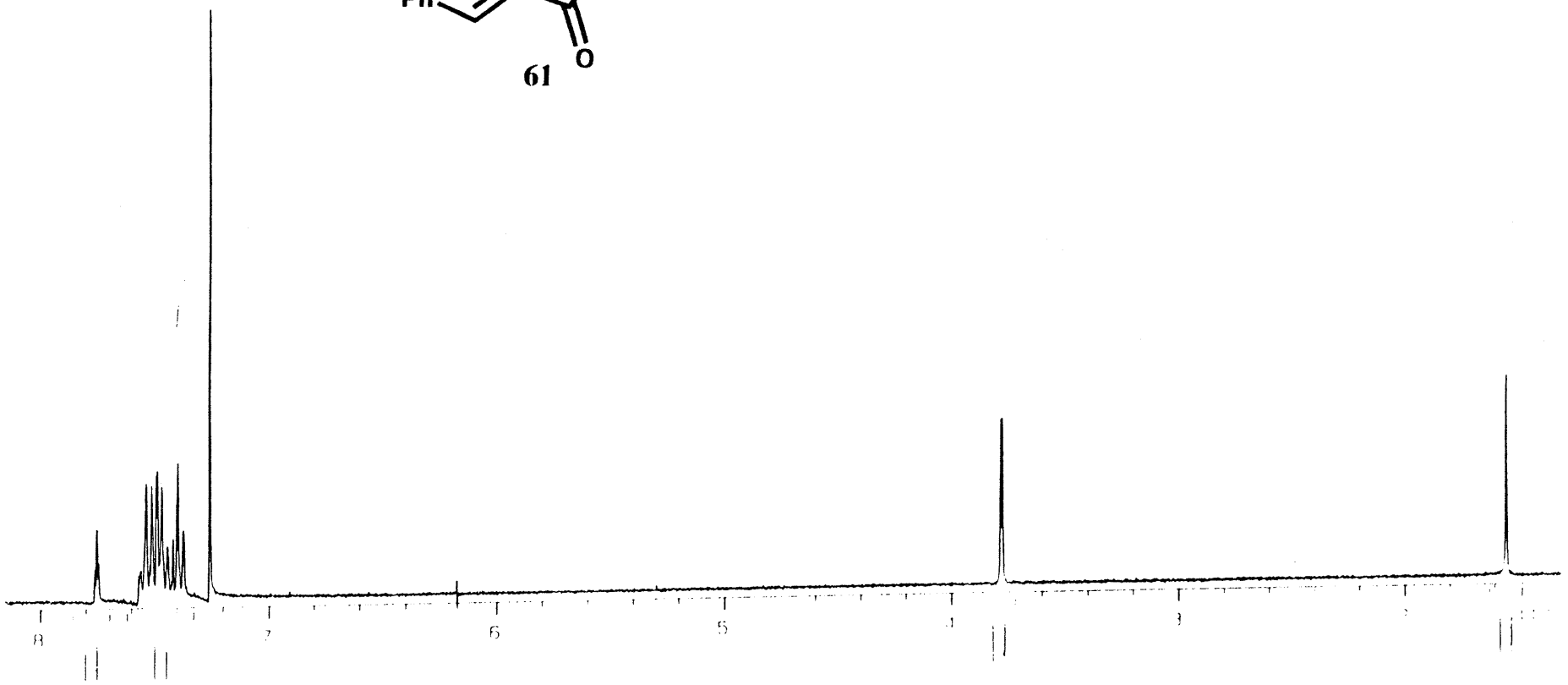
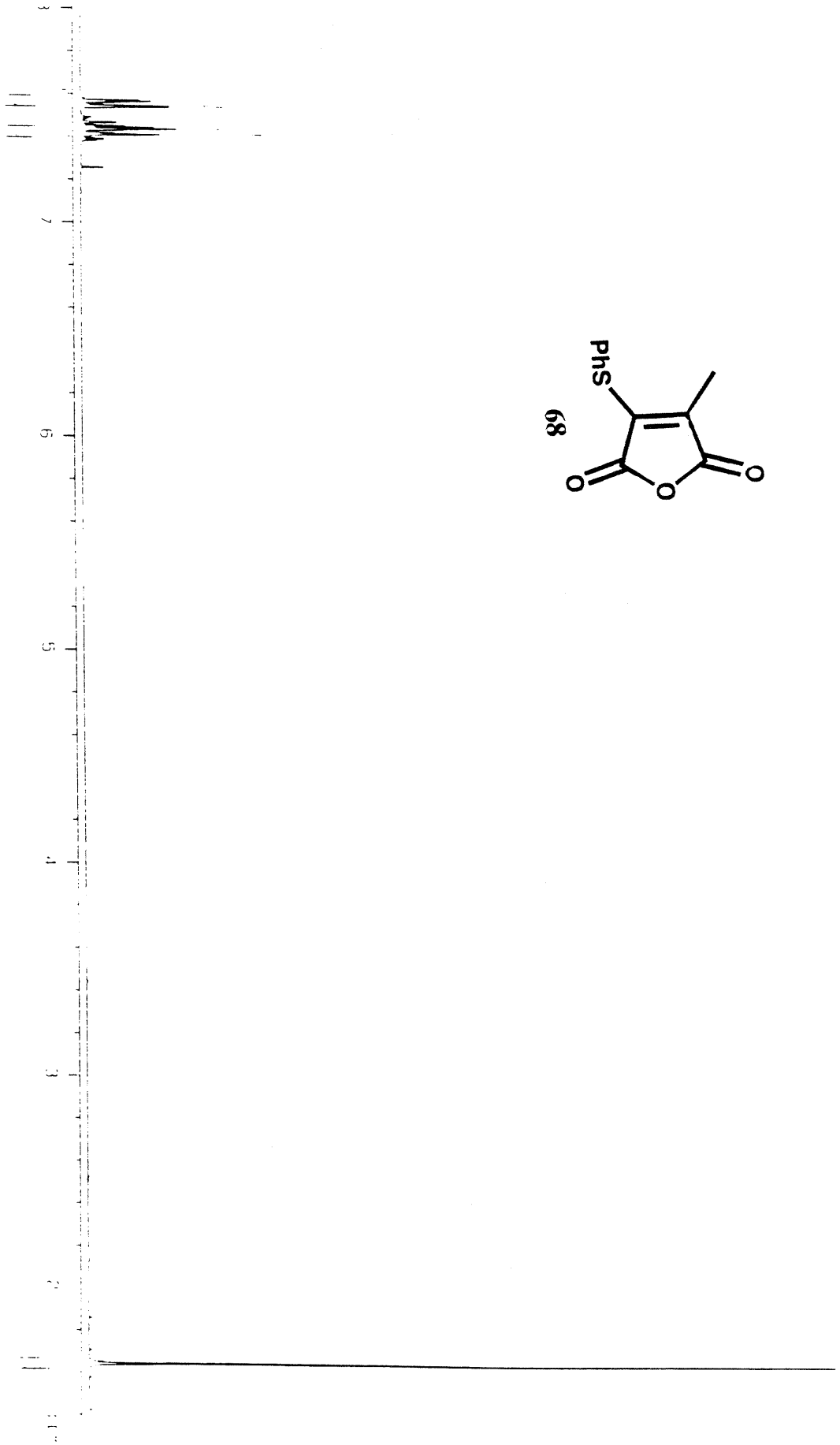
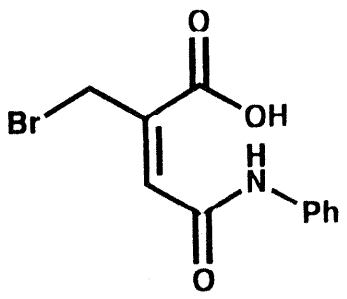




89
PhS
O
O
O



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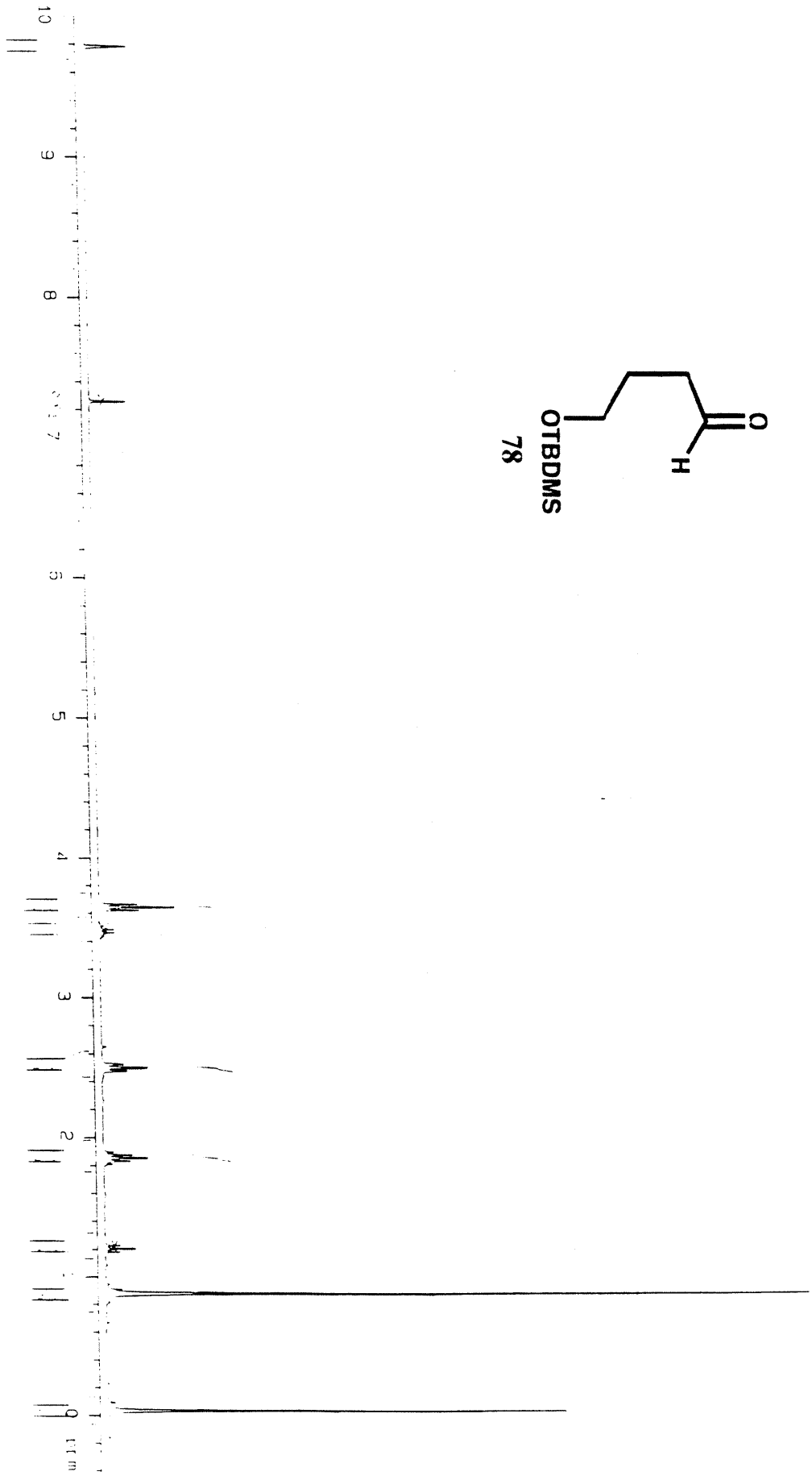
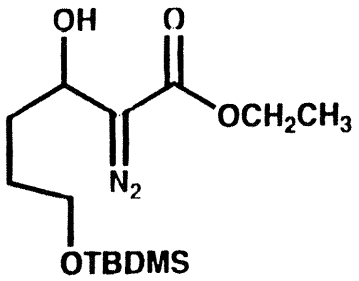

OTBDMS
78
O
H



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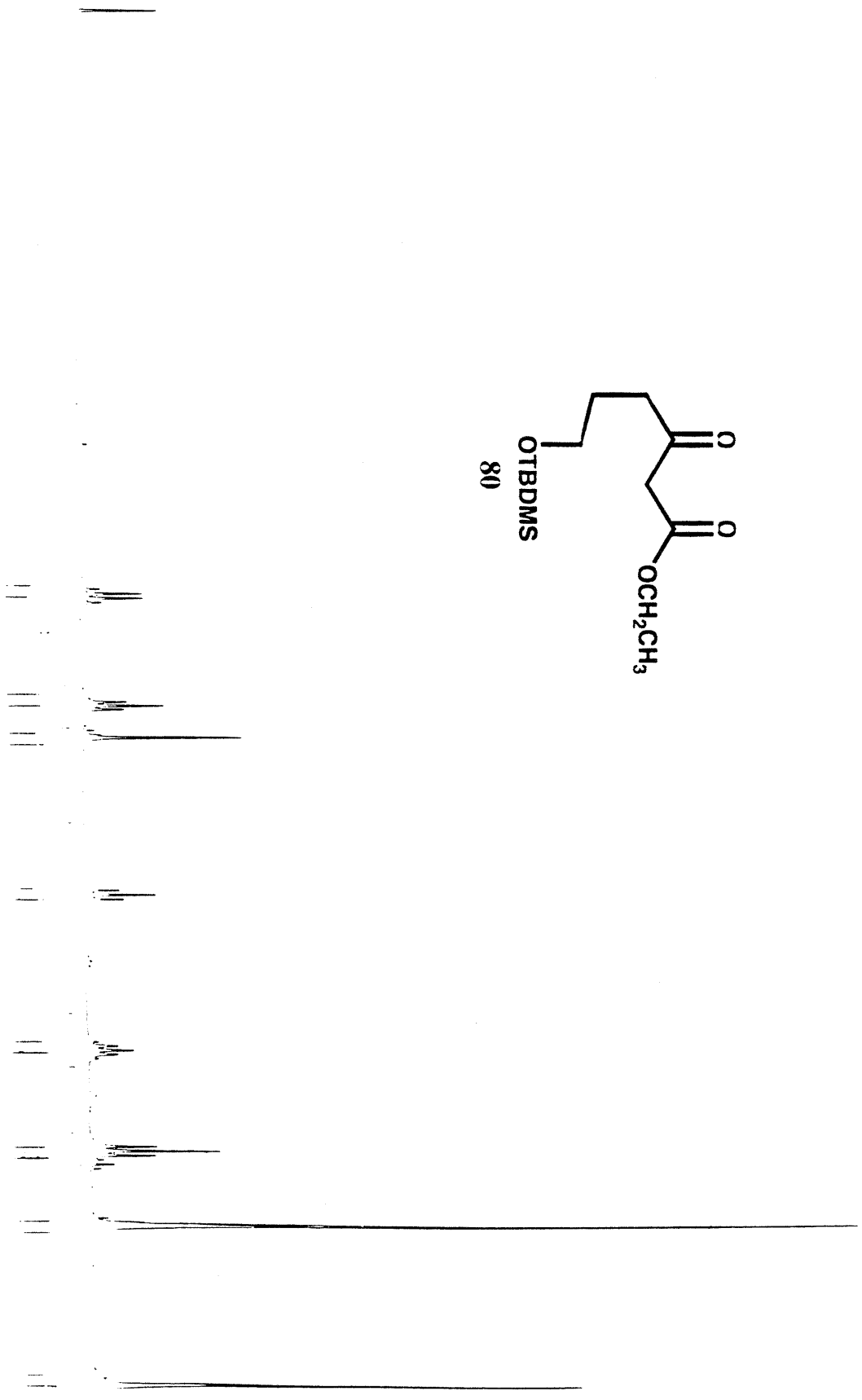
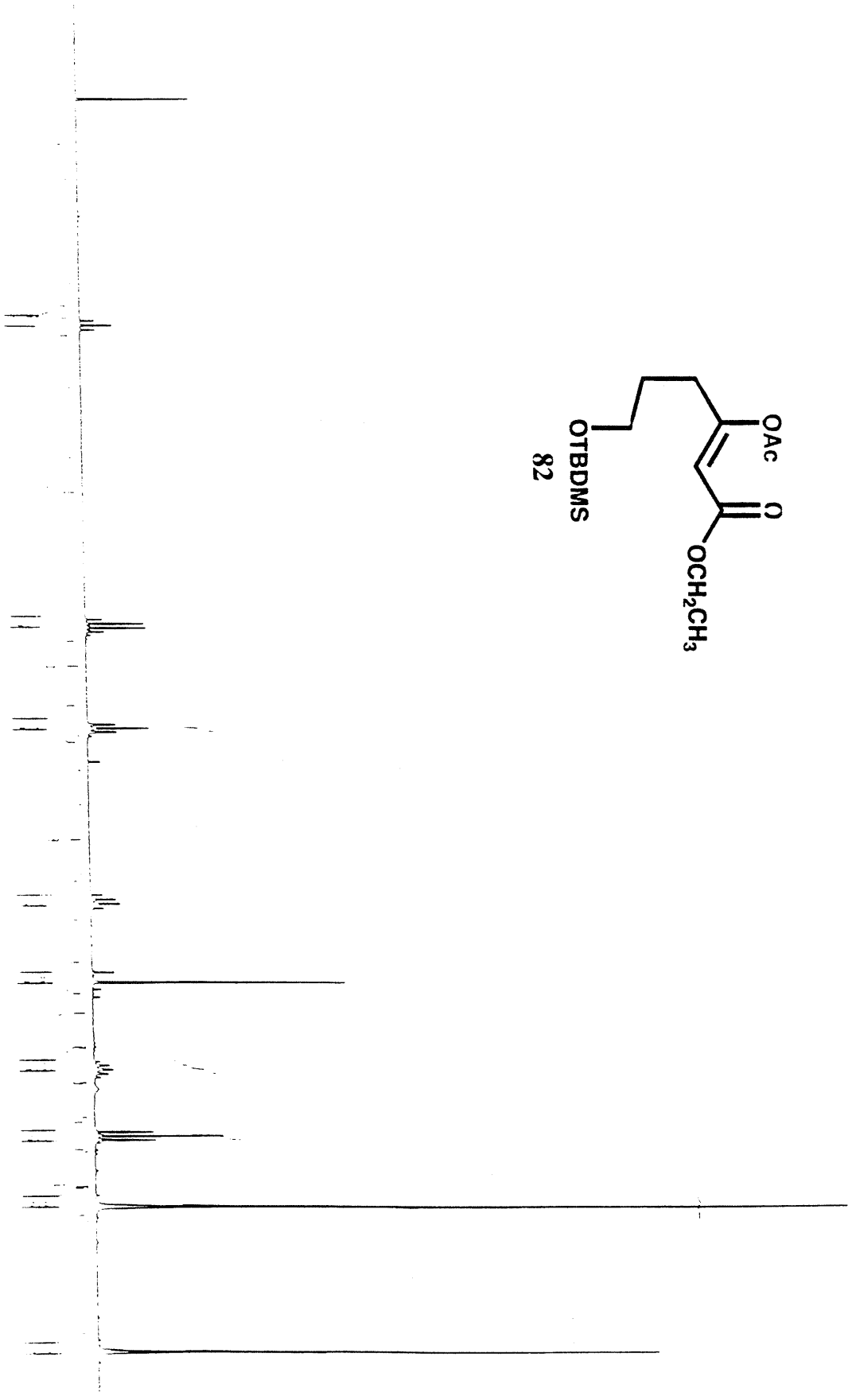

OTBDMS
80
O
O
OCH2CH3



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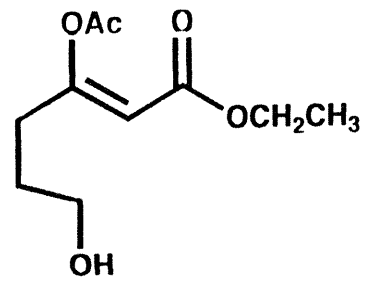

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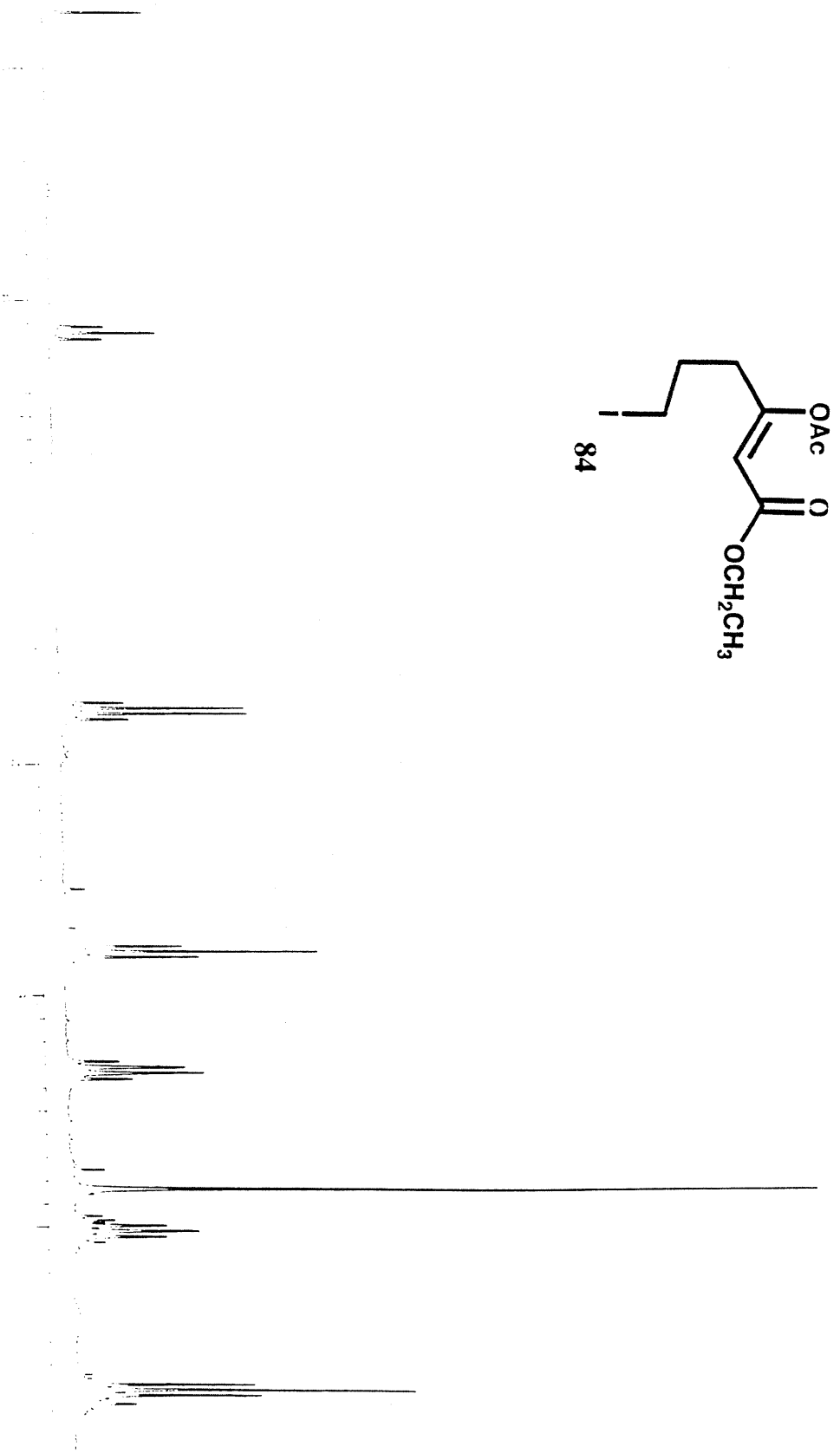

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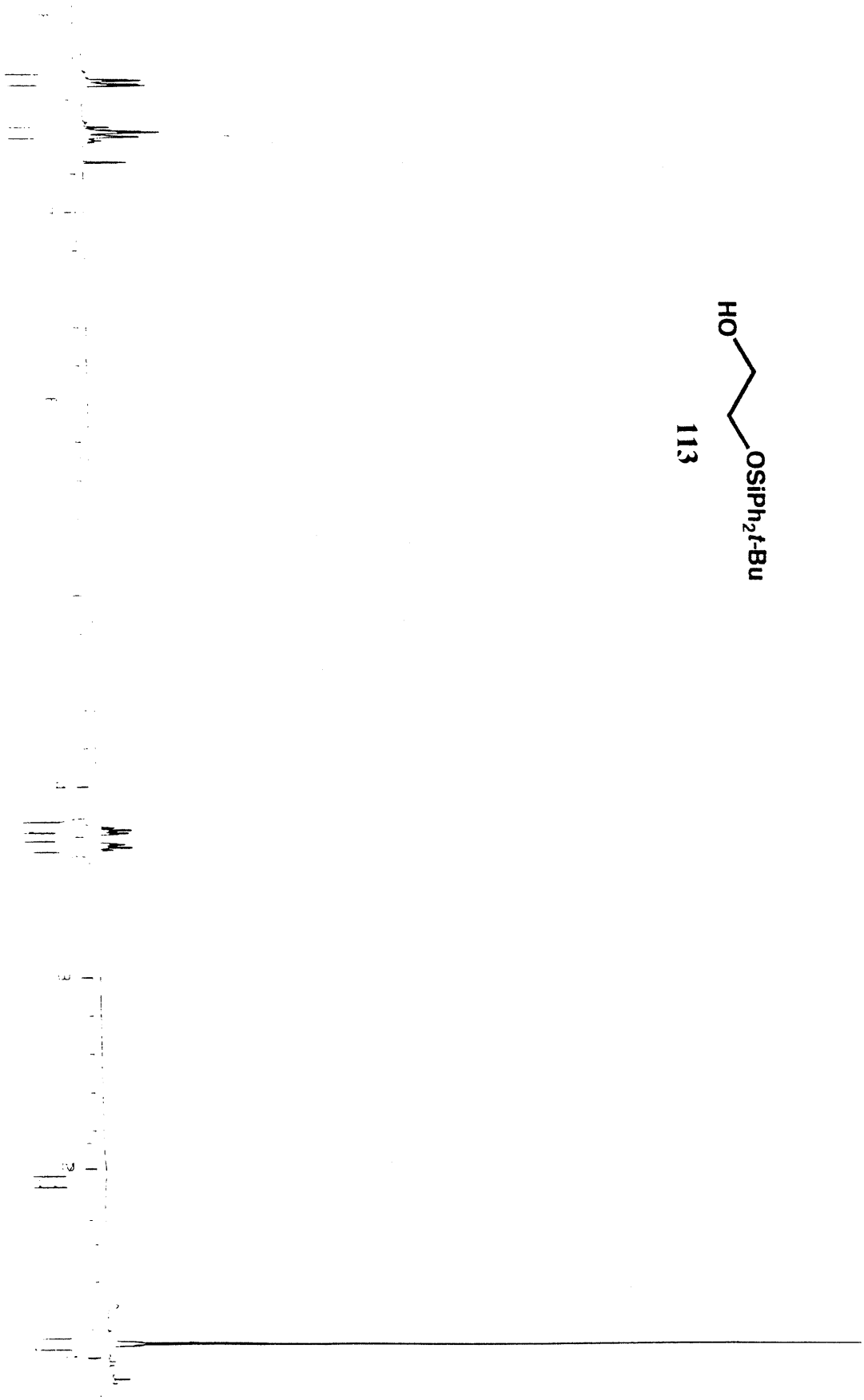
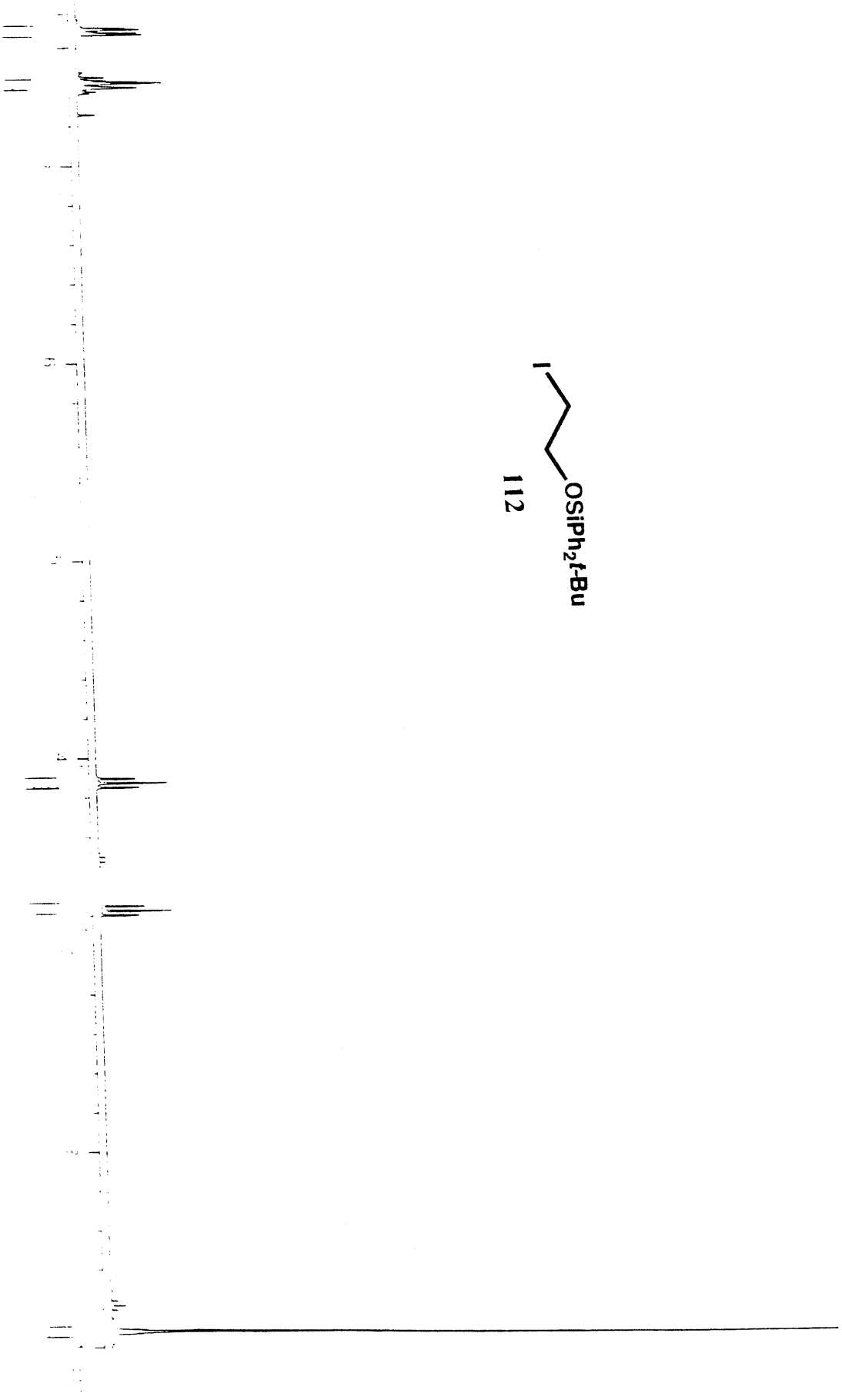


HO—OSiPh$_2$*t*-Bu

113



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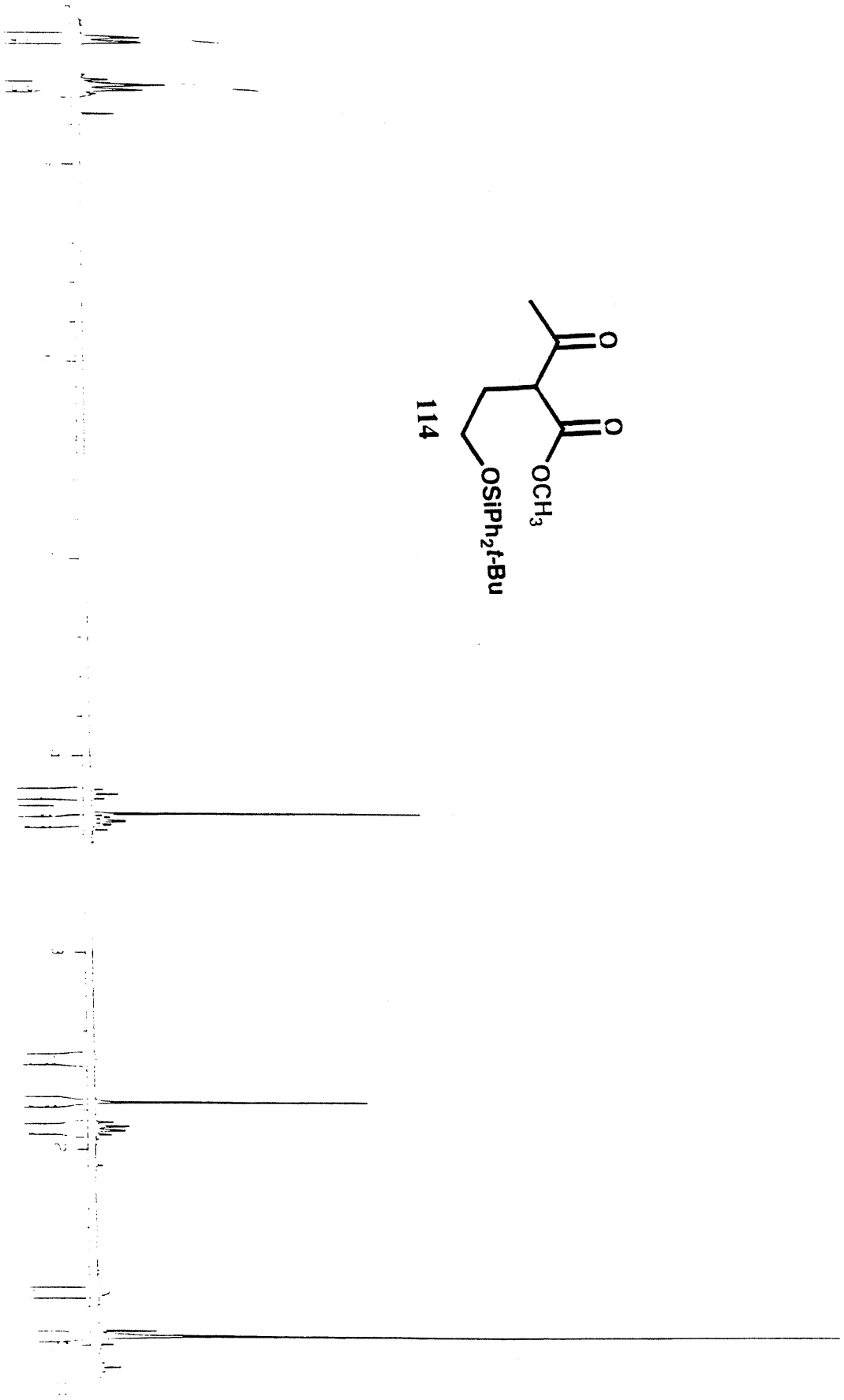

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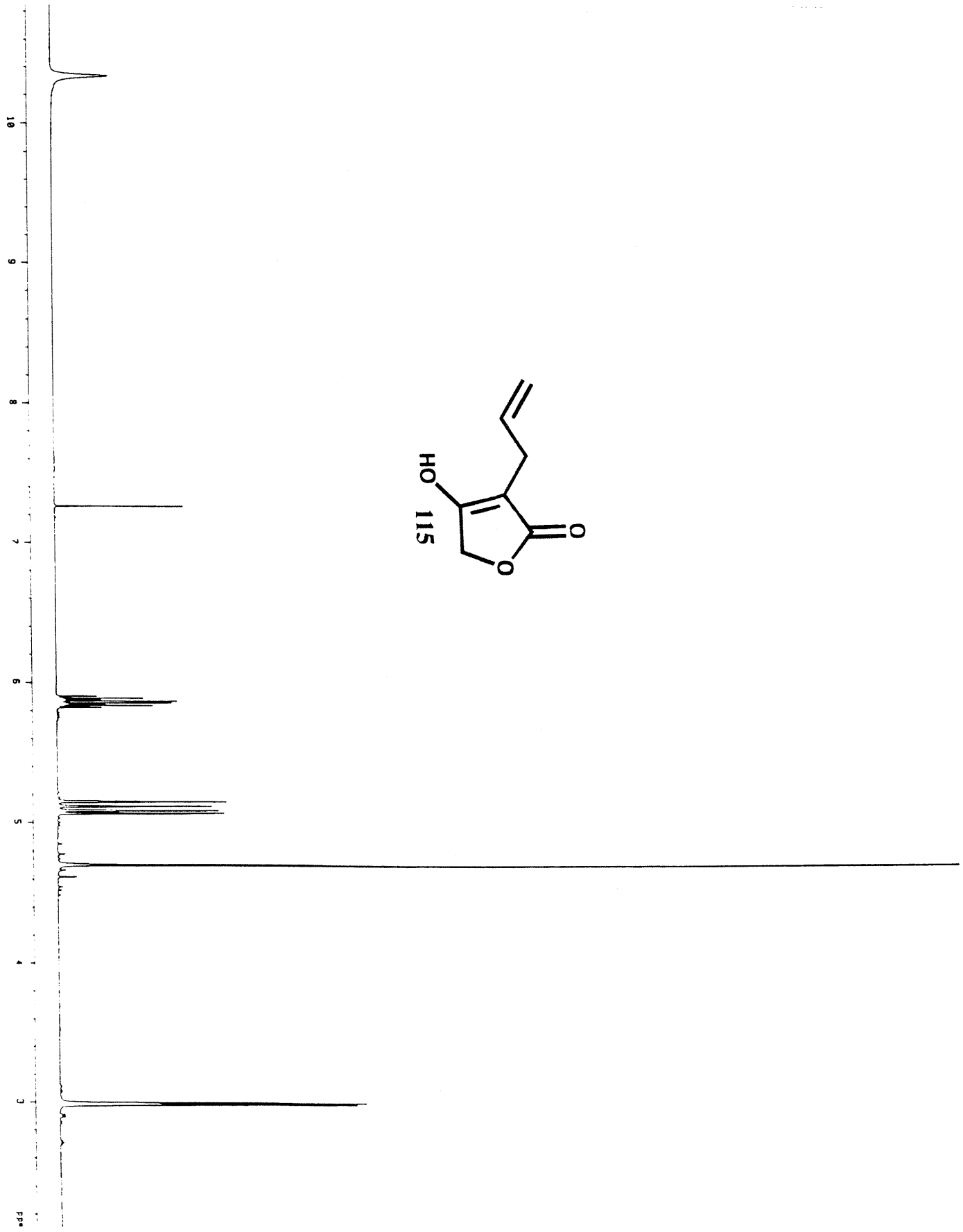
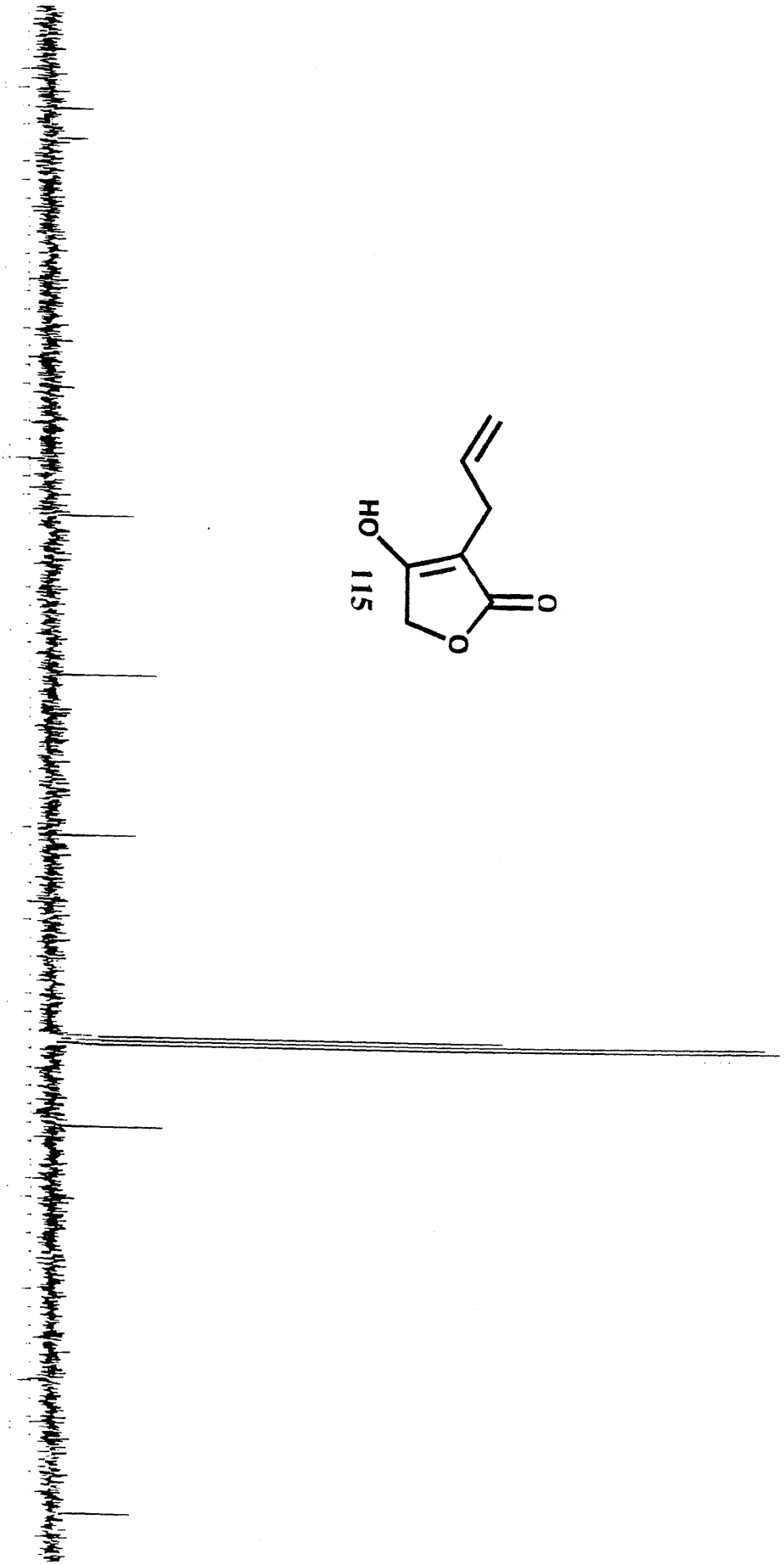
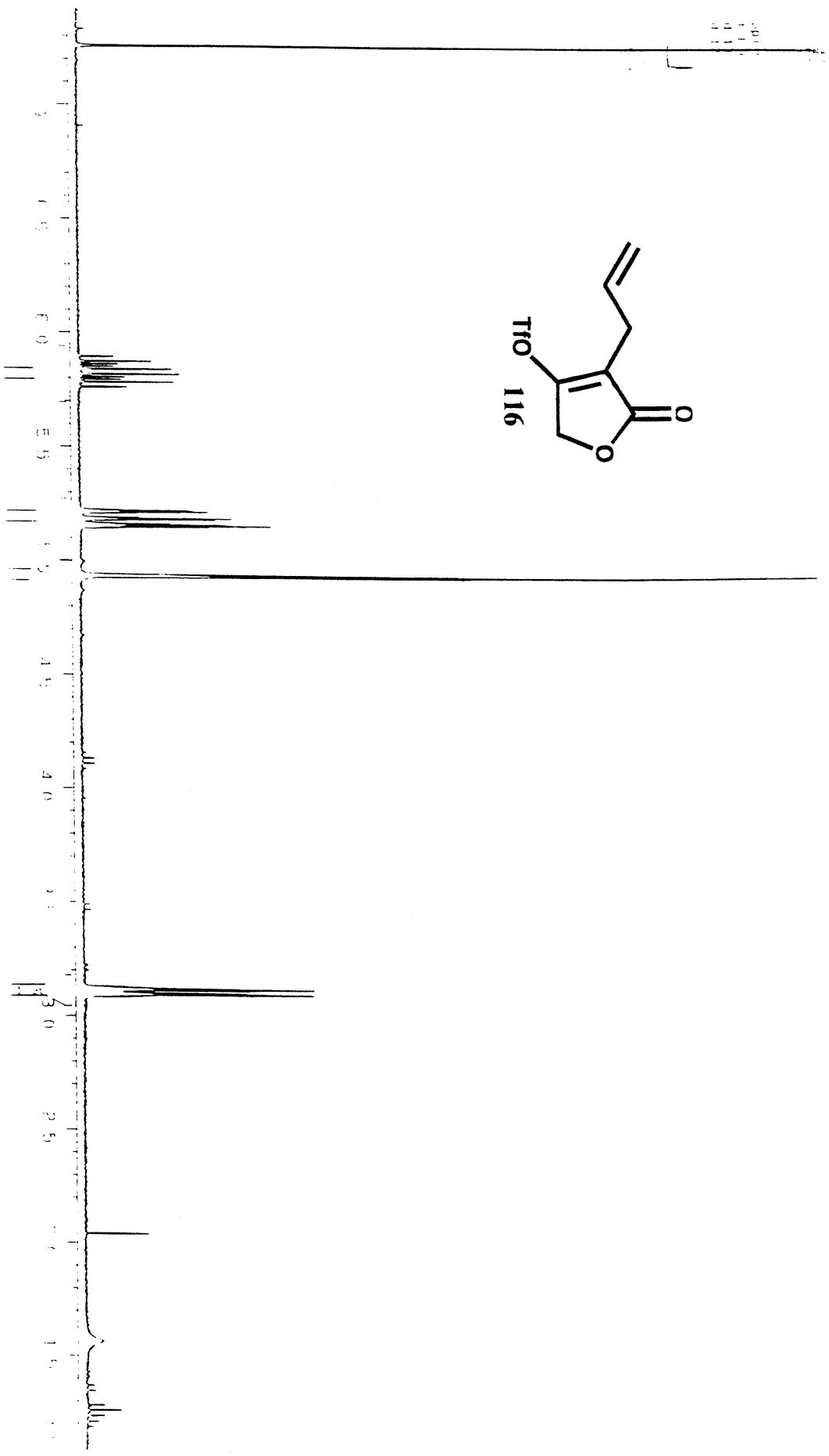
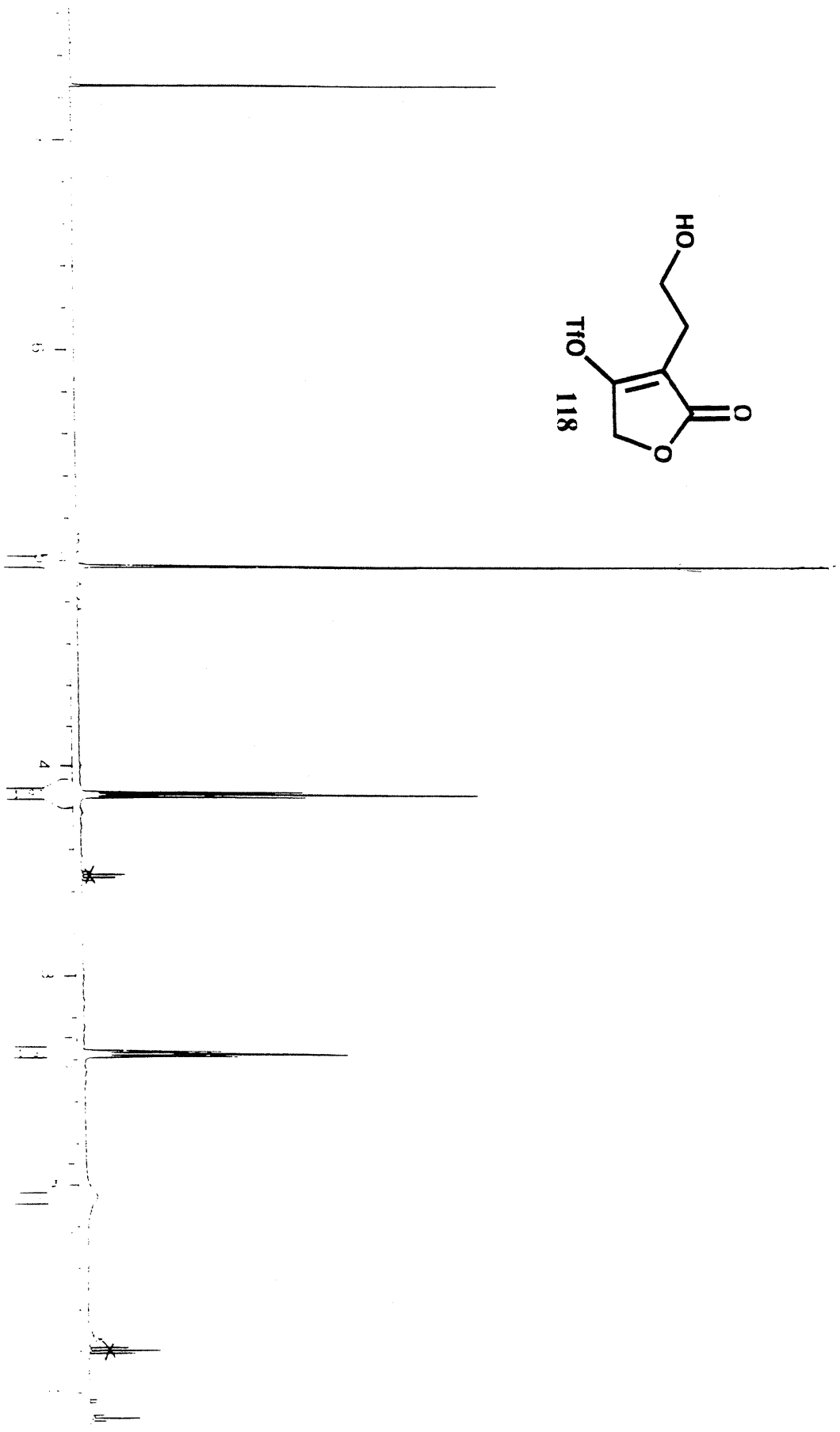
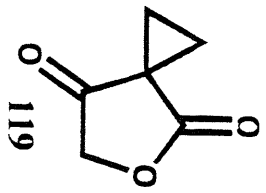

HO
O
O
115
10
9
8
7
6
5
4
3
ppm


HO
115
O
O


TfO
116
O
O


HO
TfO
O
O
118



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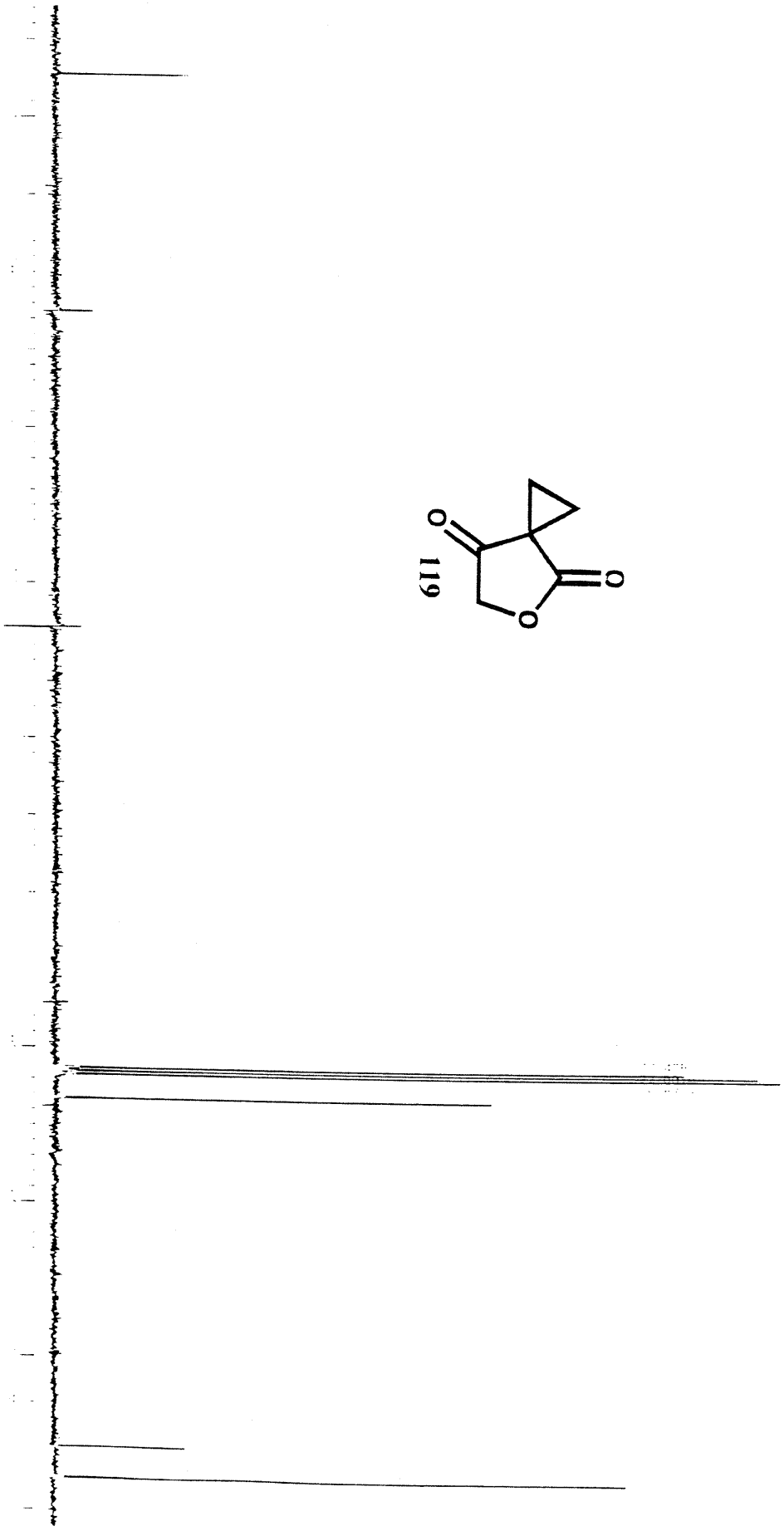

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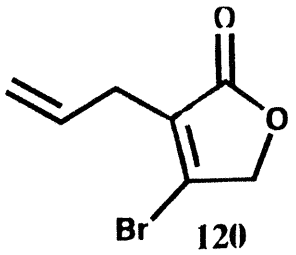
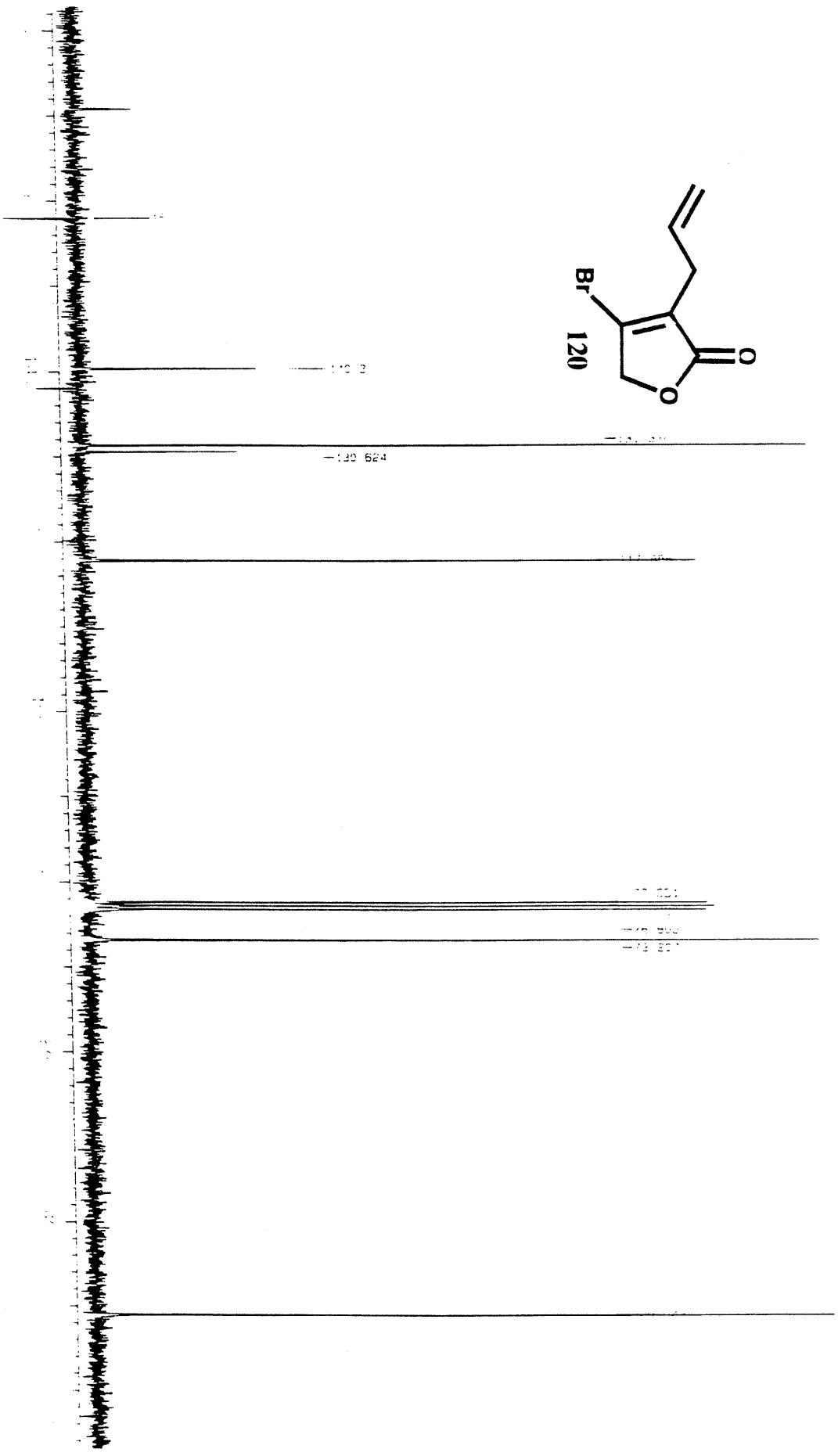
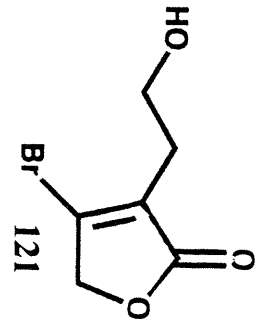
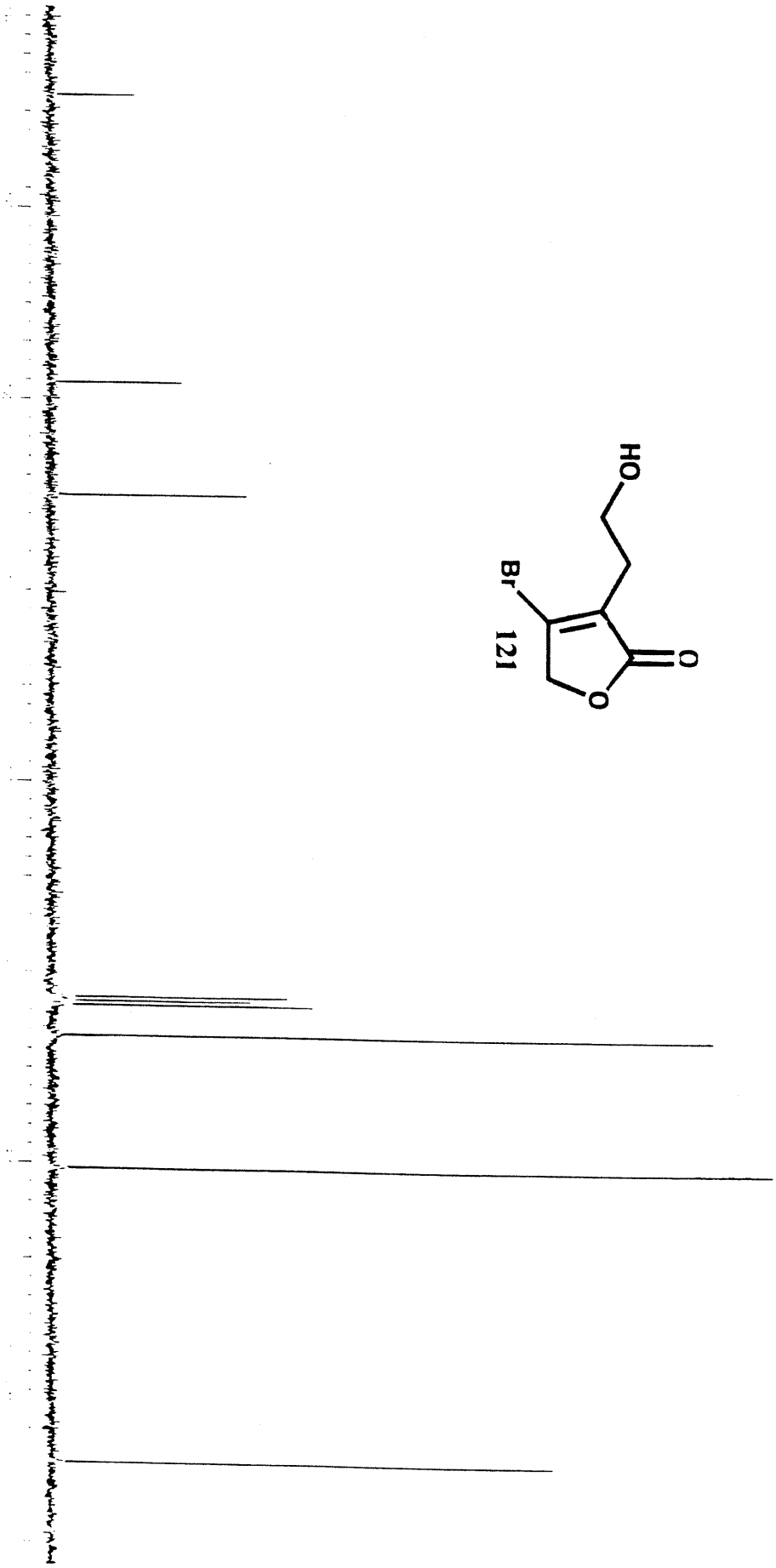

O
O
Br

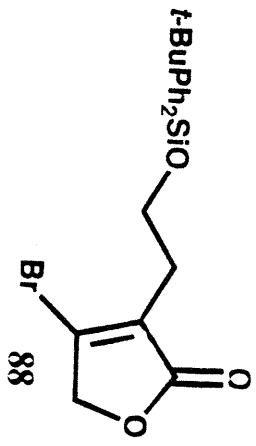
120

3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
Hz
2.19
2.35
2.32
5.47
5.16


Br
O
O
120


OH
Br
121
O
O


HO
Br
121
O
O



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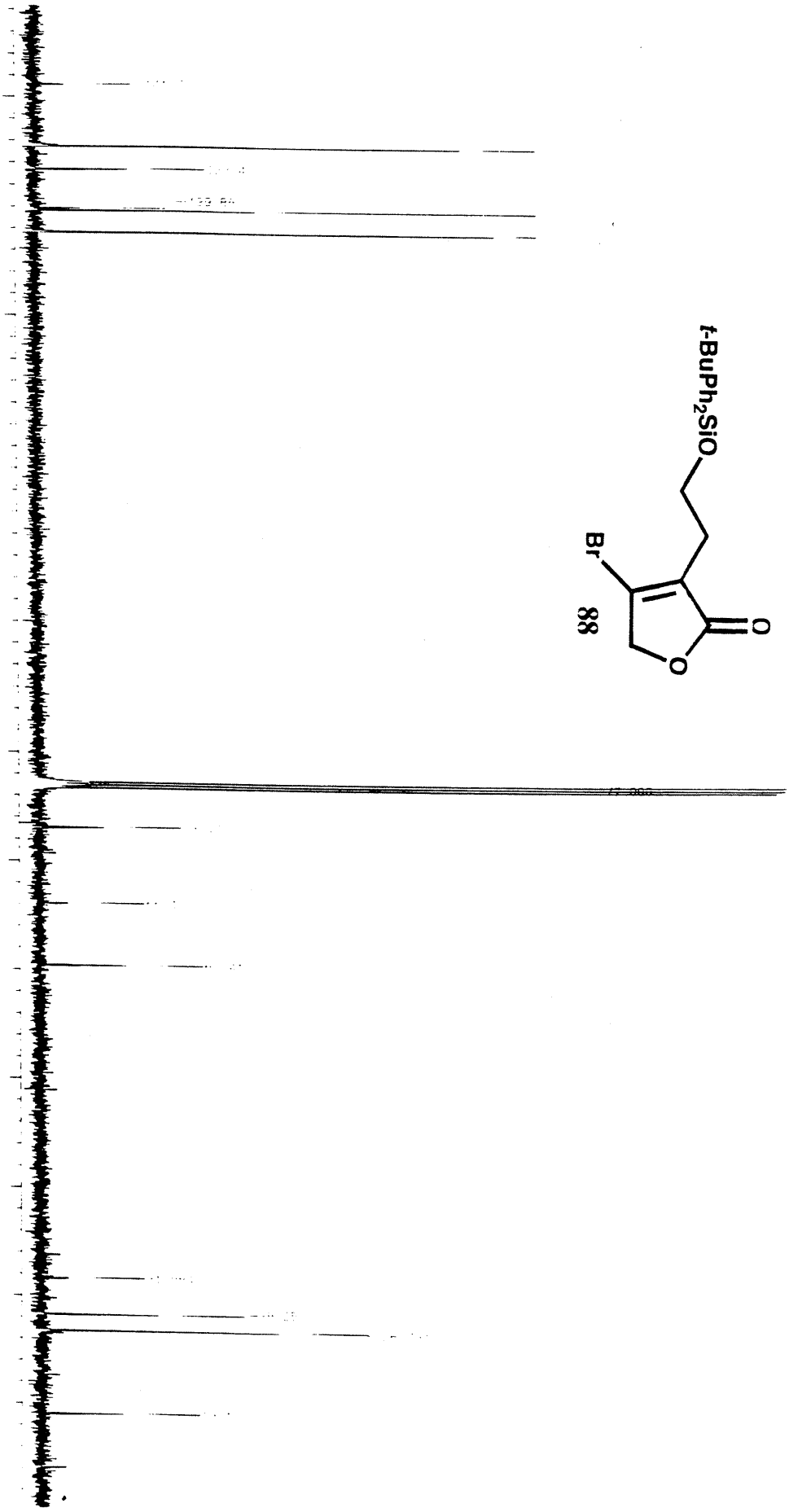
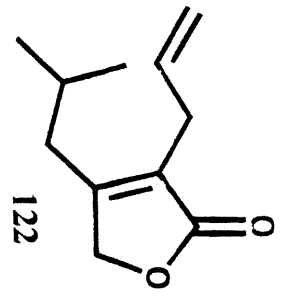

t-BuPh2SiO
Br
O
O
88



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